XVIII JORNADAS DE FARMÁCIA HOSPITALAR

Terapias Avançadas em Oncologia

A Realidade da Hematologia

JM Mariz, MD

Serviço de Hematologia e Transplante de Medula Óssea – IPO Porto

“Declaração de interesses”

- Não tenho conflito de interesses… nem interesse em promover conflitos!

- Participei em vários “advisory boards” com diferentes companhias:
  - Gilead, Novartis, Amgen, Roche, Pfizer, Takeda, Abbvie, Eusapharma, Janssen, MSD, BMS, Incyte, Astellas, AstraZeneca

Terapias Avançadas: definição

- As Terapias Avançadas consistem na utilização de medicamentos inovadores os ATMPs (Advanced Therapy Medicinal Products) criados a partir de genes, células ou tecidos.

- A Hematologia tem sido pioneira em avanços terapêuticos, incluindo a introdução e utilização de ATMPs

Terapias Avançadas em Hematologia
1º "Avanço Terapêutico" - 1956
- Alotransplante de Medula Óssea -"o 1º ATMP"

- O alotransplante de medula óssea, realizado com sucesso pela primeira vez em 1956, representou a primeira utilização de um "ATMP" na prática clínica

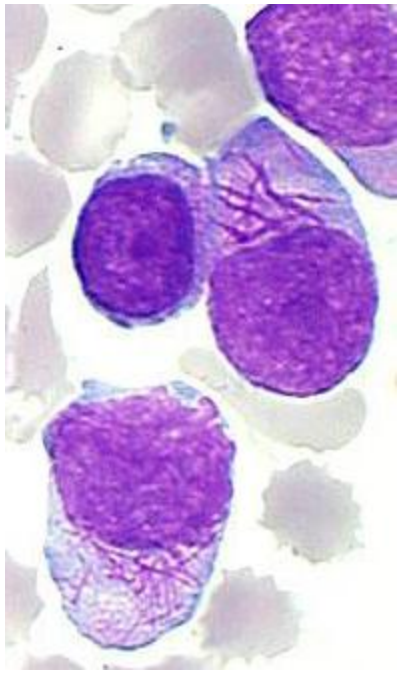
- E. Donnall Thomas foi o pioneiro da introdução dos ATMPs o que lhe valeu o prémio Nobel da Medicina em 1990

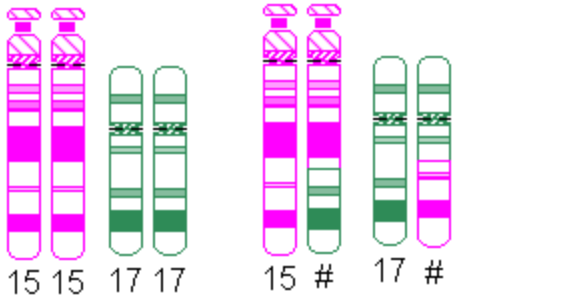
Edward Donnall Thomas, prémio Nobel da Medicina em 1990

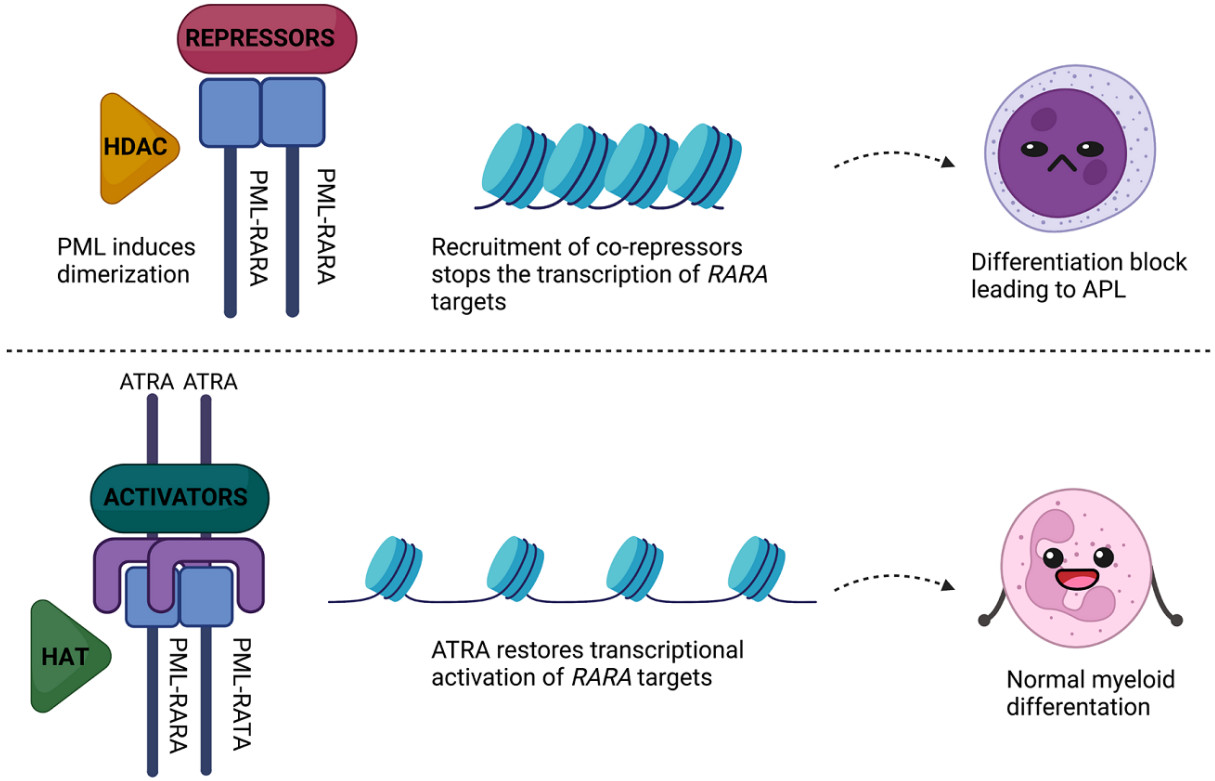
Terapias Avançadas em Hematologia

2º "Avanço Terapêutico" - 1988

- ácido all trans retinoico na LMA promielocítica





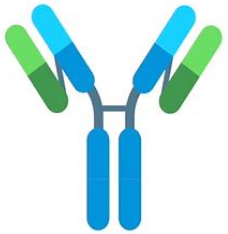


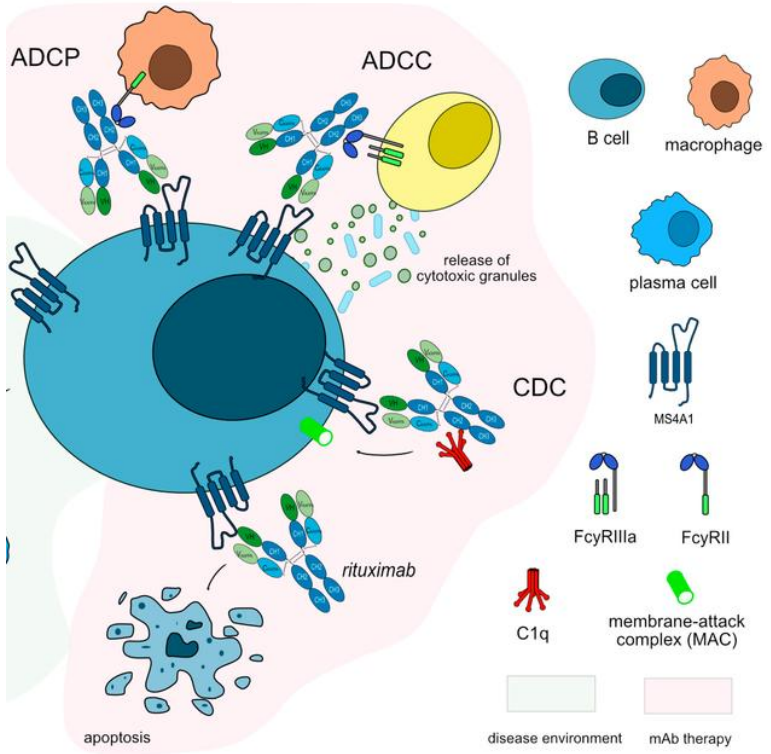
Huang Meng-er, Shanghai Institute of Hematology, Blood, Vol 72. No 2 (August). 1988: pp 567-572

Terapias Avançadas em Hematologia

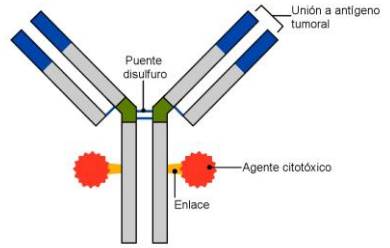
3º “Avanço Terapêutico” - 1997

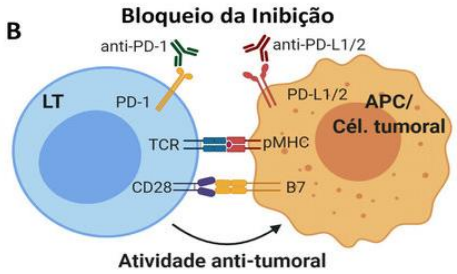
Rituximab - atc monoclonal simples anti CD20

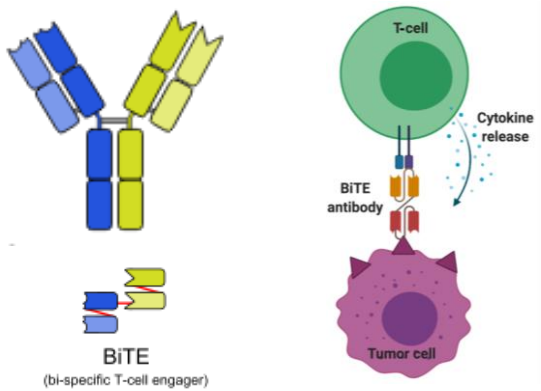




- Anticorpos Monoclonais conjugados
  - Gentuzumab, Brentuximab, etc
- Anticorpos Monoclonais Inibidores do “Checkpoint”
  - Ipilimumab, Pembrolizumab,etc
- Anticorpos Monoclonais “biespecíficos”
  - Blinatumumab, Glofitamab, etc



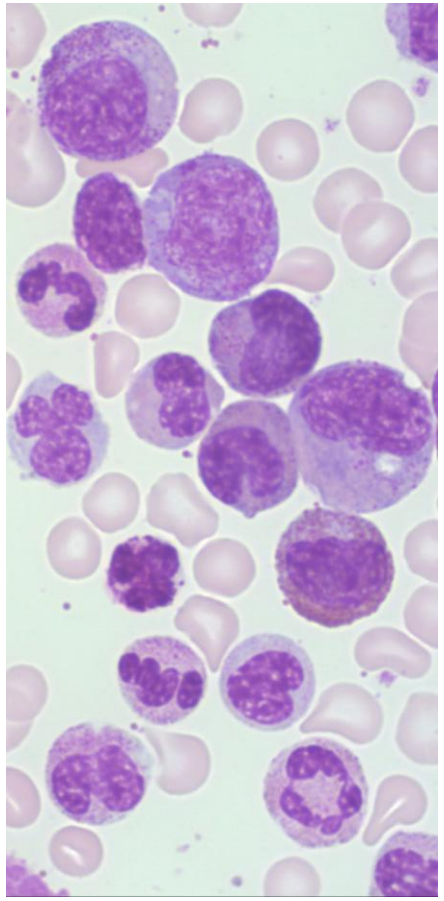


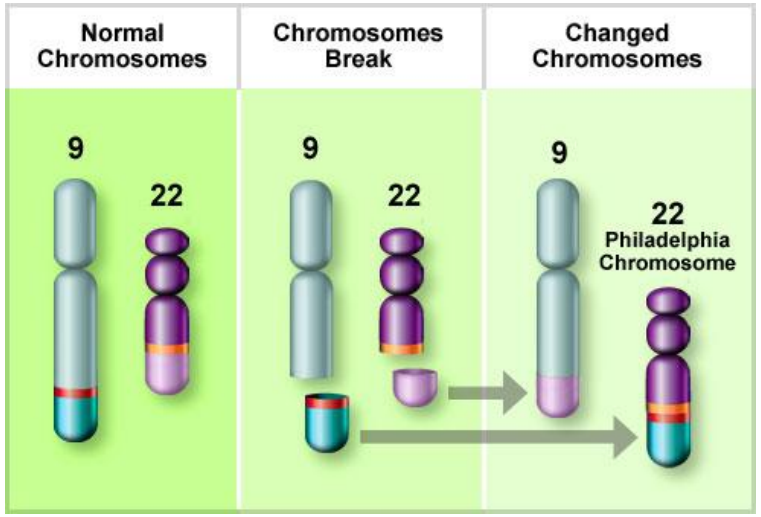


Terapias Avançadas em Hematologia

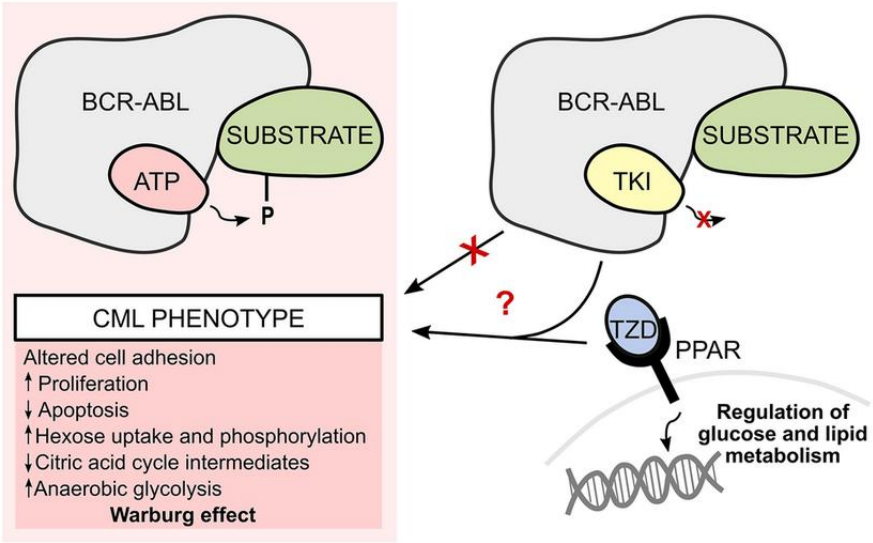
4º "Avanço Terapêutico" - 2001

Imatinib – Leucemia Mielóide Crónica Ph+



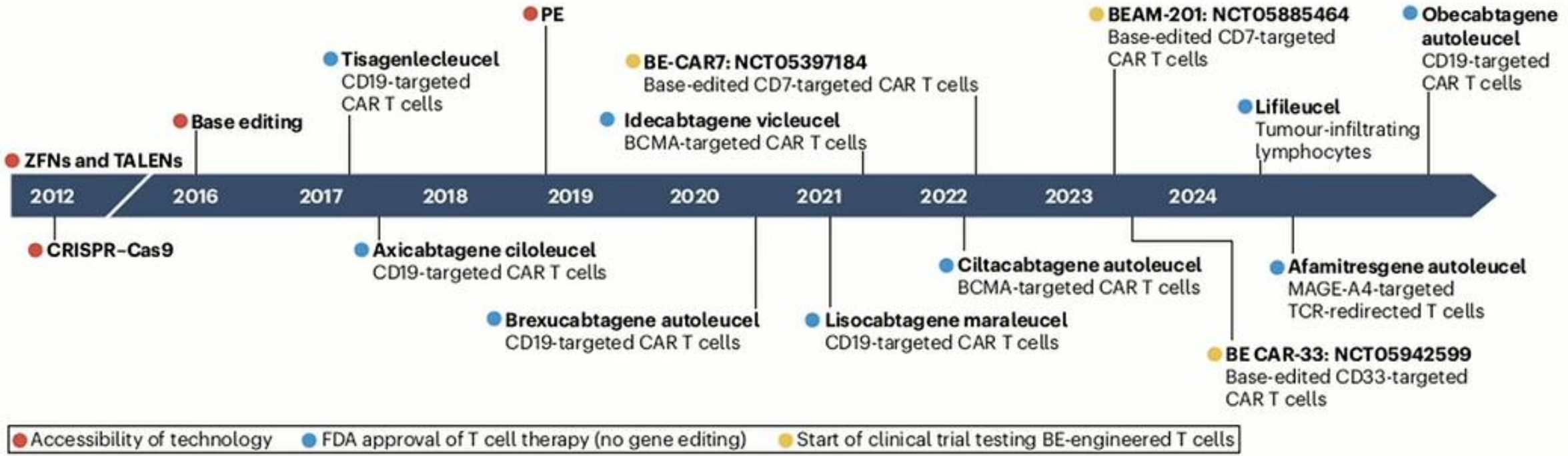


"O conceito de terapêutica alvo"



Cohen, *Clin Cancer Res* 2002;8:935-942

Evolução das Terapêuticas Avançadas (ATMP)



Base editing (BE)
Prime editing (PE)

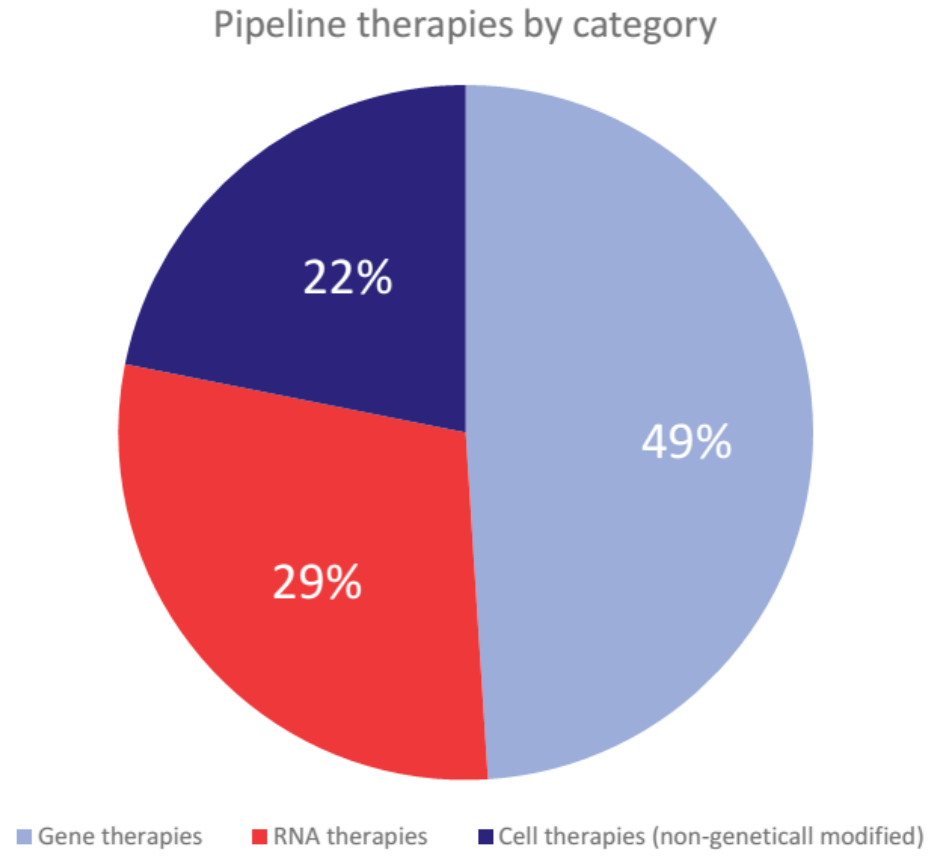
Petri K, D`Ippolita E, Künkele A, Köhl U, Busch D, Einsele H, Hudecek M. Nature Reviews Clin. Oncol. 2025

Fraunhofer

Pipeline of gene, cell, and RNA therapies

4,238 therapies are in development, ranging from preclinical through pre-registration

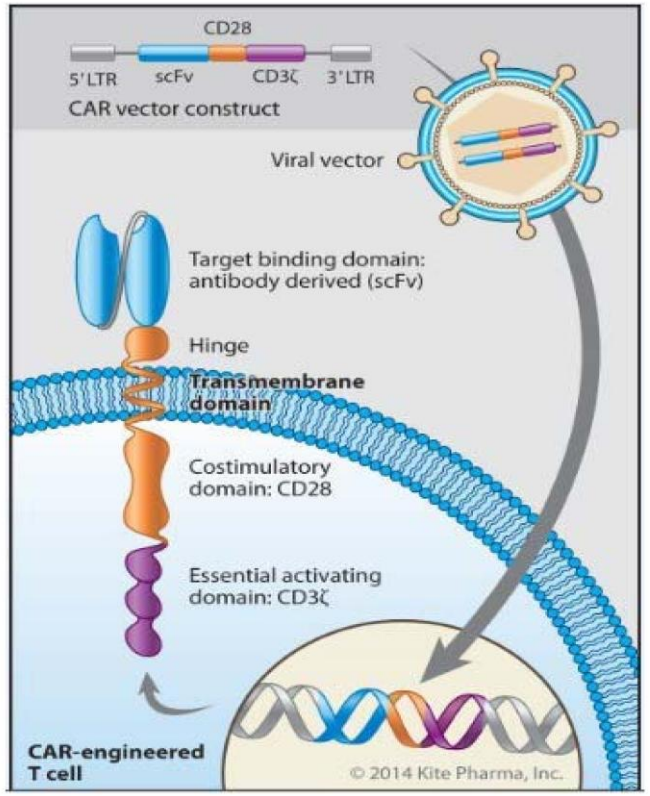
- 2,117 gene therapies (including genetically modified cell therapies such as CAR-T cell therapies) are in development, accounting for 49% of gene, cell, and RNA therapies
- 944 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies

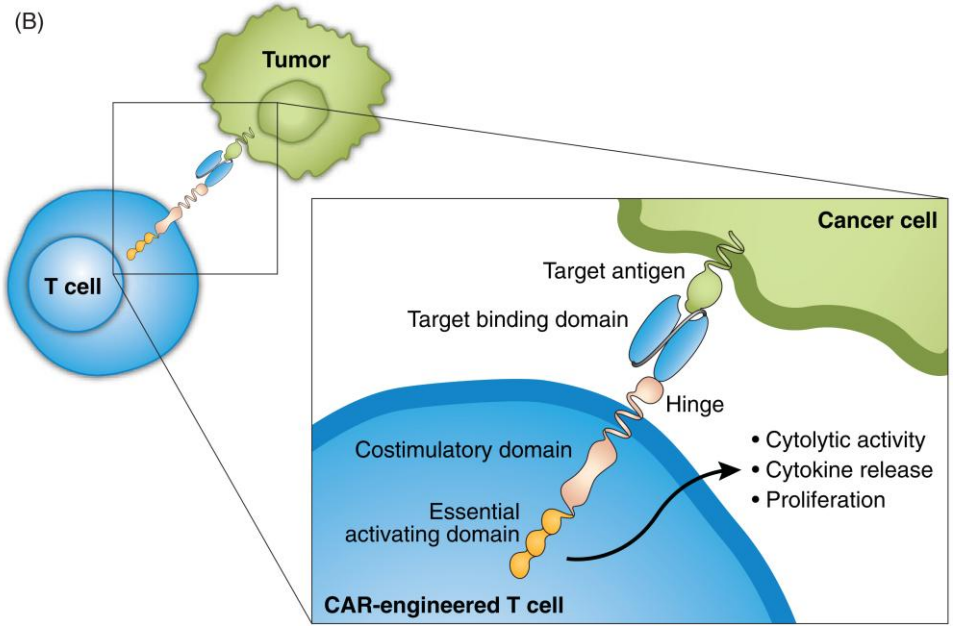


Gene, Cell, & RNA Therapy Landscape Report
Q4 2024 Quarterly Data Report
American Society of Gene + Cell Therapy

Terapias Avançadas em Hematologia
5º "Avanço Terapêutico"
Células CAR T na LLA e LNH DGCB (2º ATMPs)

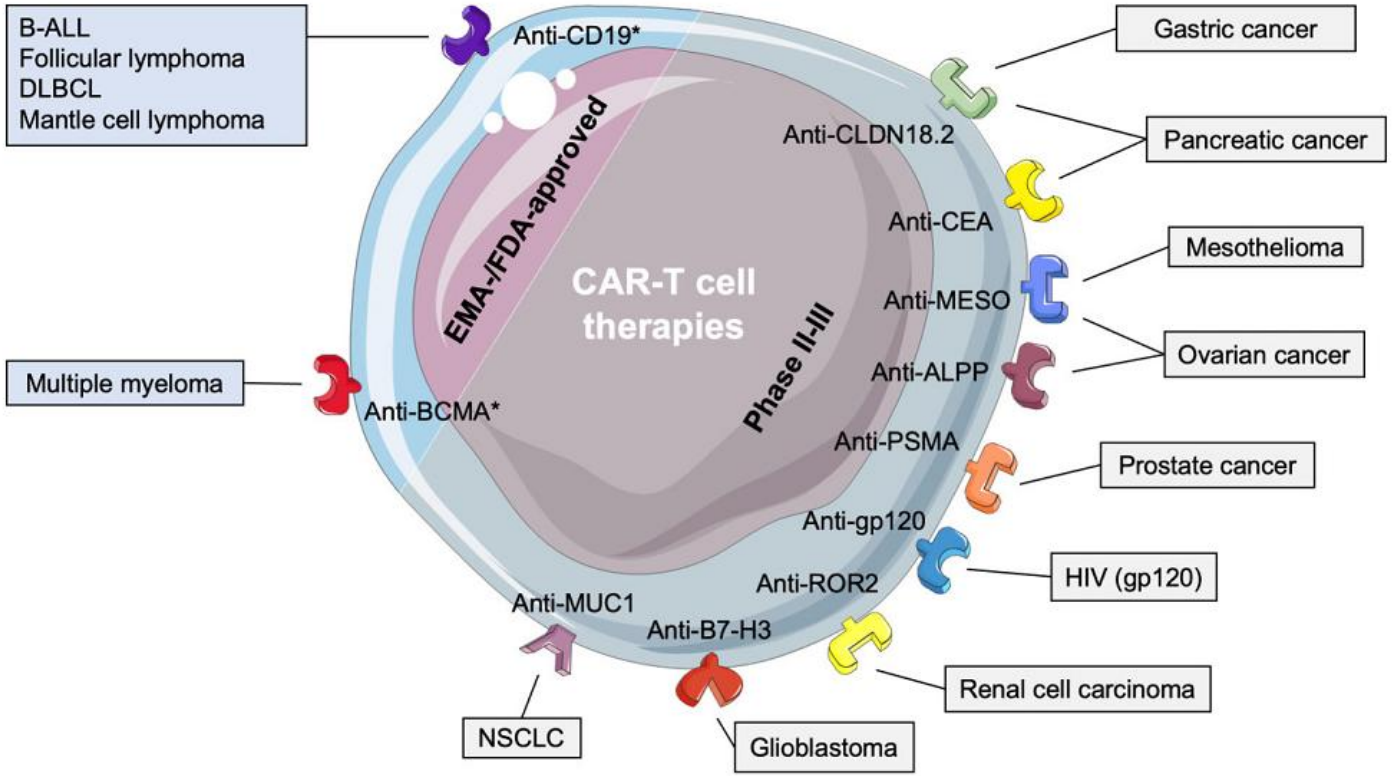
As células CAR T são linfócitos T geneticamente modificados através da introdução de um receptor quimérico (**C**himeric **A**ntigen **R**eceptor **T** cells)





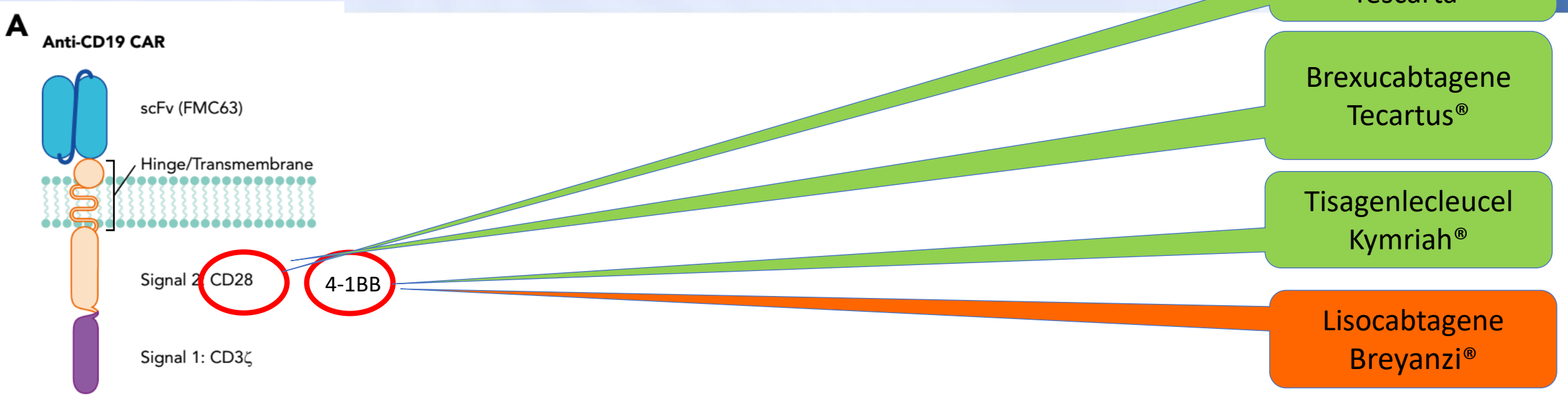
Titov et al. Cell Death and Disease (2018) 9:897

Potenciais alvos terapêuticos das células CAR T



Matthias Totzeck, European Heart Journal (2022) 00, 1–13

CAR Ts em hematologia: anti - CD19



- **Kymriah:** Tratamento de adultos c/ LNH agressivo de células B resistentes a pelo menos 2 linhas de QT. Tratamento de crianças e adultos jovens até aos 25 anos com LLA refratária ou em recidiva.

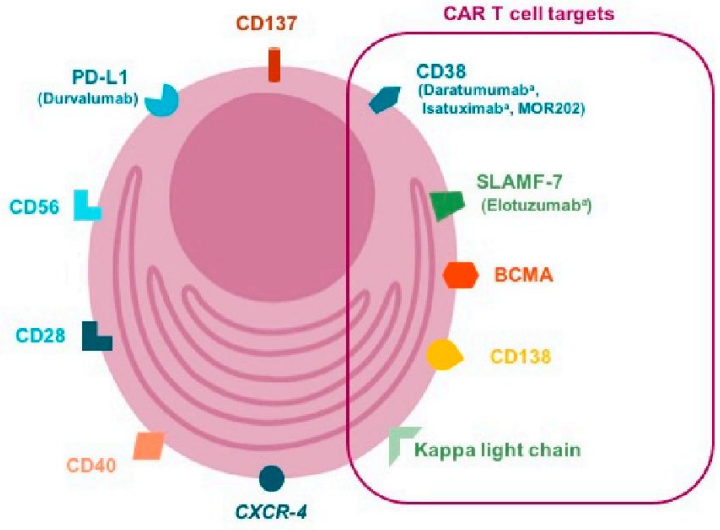
- **Yescarta:** Tratamento de adultos c/ LNH agressivo de células B resistentes a pelo menos 1 linha de quimioterapia e linfoma não Hodgkin primário do mediastino.

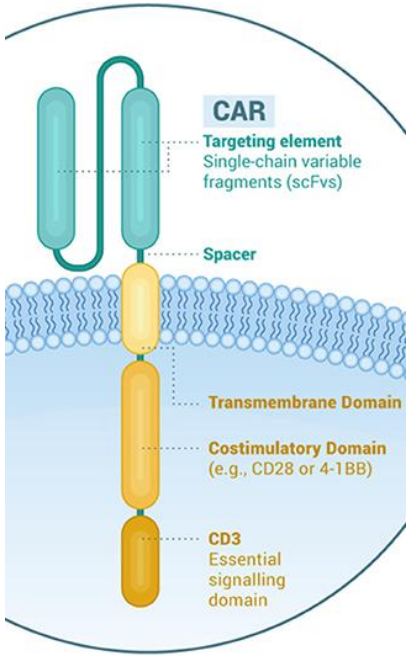
- **Tecartus:** Tratamento de adultos com LNH de células do manto em recidiva após 2 linhas e LLA

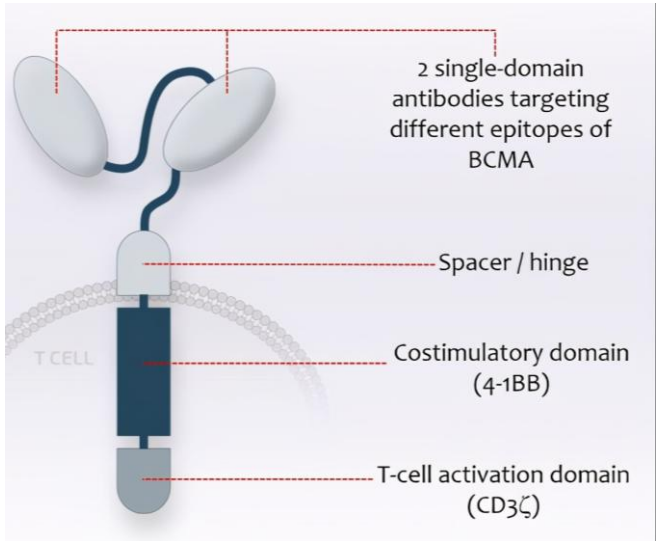
nejm 377;26 December 28, 2017

Blood advances 9 MAY 2023 • VOLUME 7, NUMBER 9

CAR Ts em hematologia: anti - BCMA







Idecabtagene Vicleucel - Abecma®

Ciltacabtagene autoleucel - Carvykti®

J. Clin. Med. **2020**, *9*, 3577

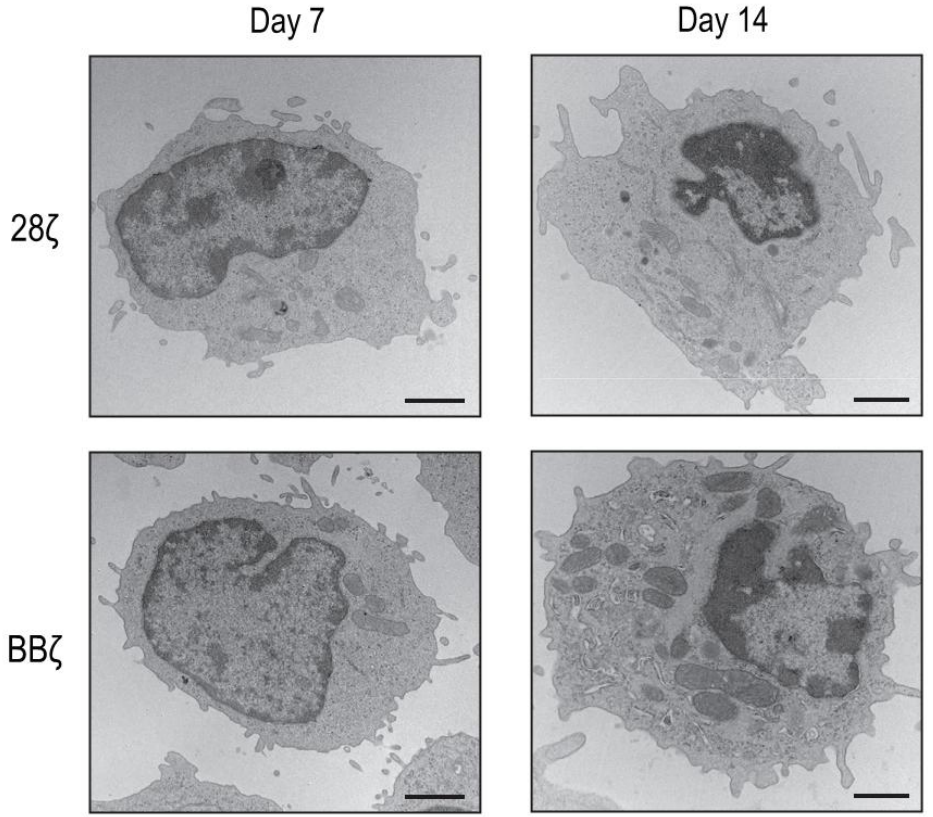
Diferenças entre CAR T CD-28 e 4-1BB

O CD28 promove o crescimento de células T CD8+ de memória efectoras

- metabolismo glicolítico
- mais rápido, 4h para destruir a célula tumoral
- menor persistência no tempo

O 4-1BB favorece o crescimento de células T CD8+ de memória central

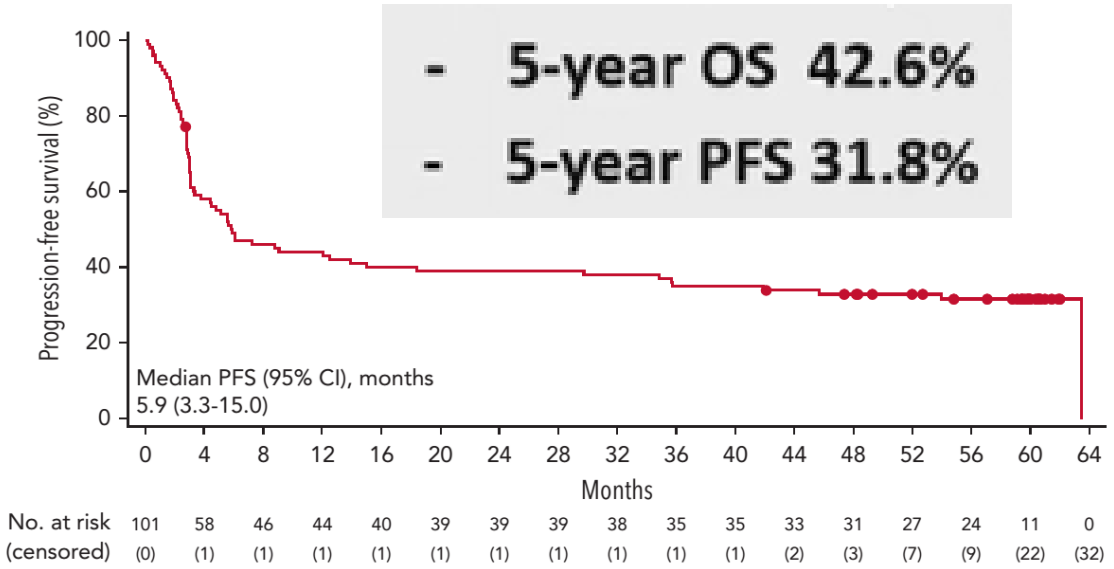
- metabolismo respiratório (ciclo de Krebs)
- mais lento, 9h para destruir a célula tumoral
- maior persistência no tempo



Omkar U. Kawalekar, Immunity 44, 380–390, February 16, 2016

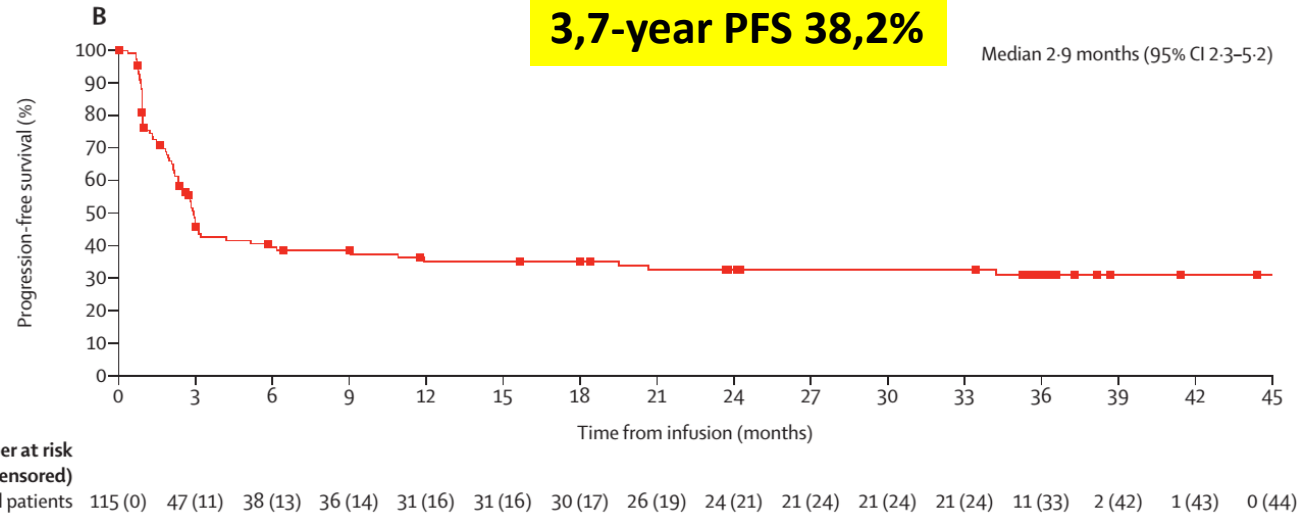
Eficácia do CAR T a longo prazo (potencial de cura):
LNH difuso de grandes células B

Axicabtagene



Tisagenlecleucel

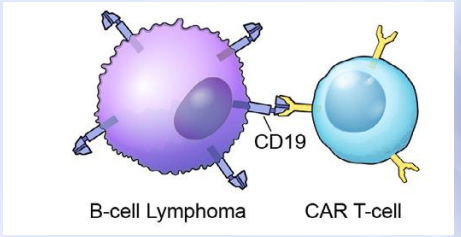
3,7-year OS 49,1%
3,7-year PFS 38,2%

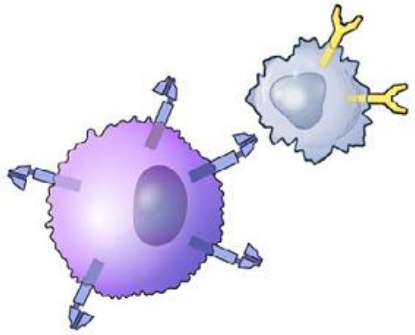


Sattva S. Neelapu, Blood 11 MAY 2023 | VOLUME 141, NUMBER 19

***Lancet Oncol* 2021; 22: 1403–15**

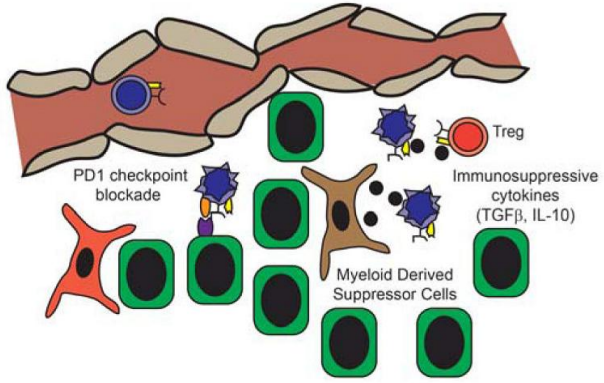
Mecanismos de resistência ao CAR T





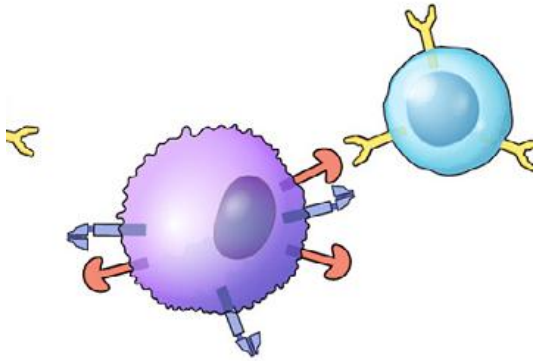
T cell Specific Factors

Inadequate central memory and/or stem central memory CAR T cells; pre-manufacture T cell dysfunction due to disease or prior therapy; inadequate cytokine profile; paucity of CD4 CAR T cells; insufficient CAR T cell expansion or persistence.



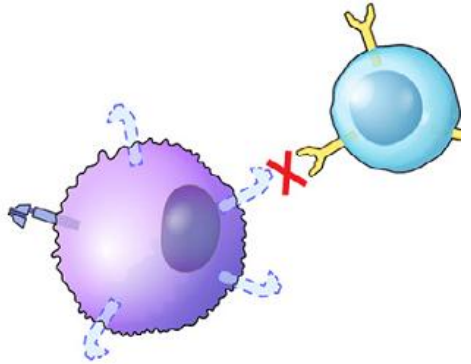
Disorganized tumor vasculature

In patients with large masses, it is difficult for CAR T to migrate into the tumor.



Host or Tumor Factors

Upregulation of negative regulatory receptors on CAR T cells or ligands on tumor or microenvironment; high tumor burden and inadequate target to effector ratio.



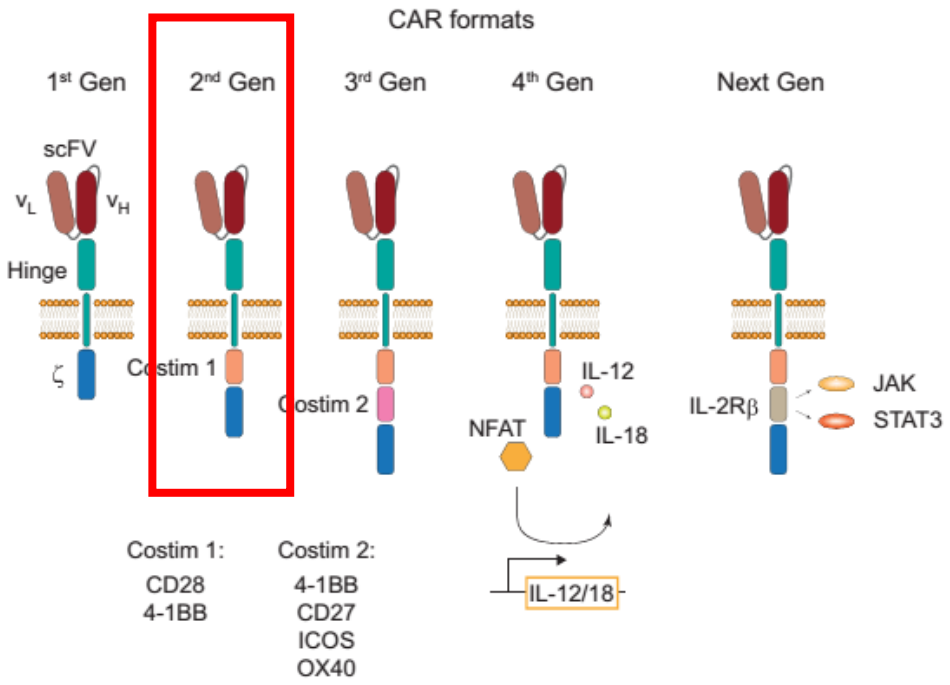
CD19 Epitope Loss

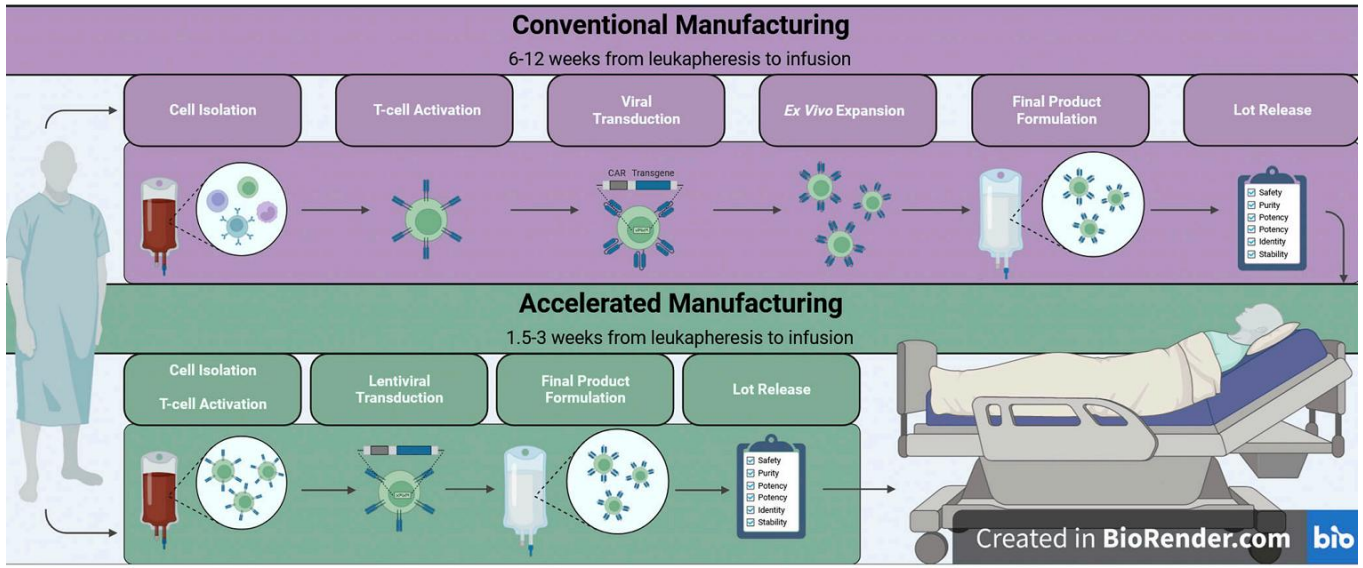
Loss of CD19 epitope by uncertain mechanisms in lymphoma.

Michael Spiotto, Sci Immunol. 2016 September ; 1(3)

Michael Byrne, Biol Blood Marrow Transplant 25 (2019) e344e351,

Como aumentar a eficácia do CAR T?



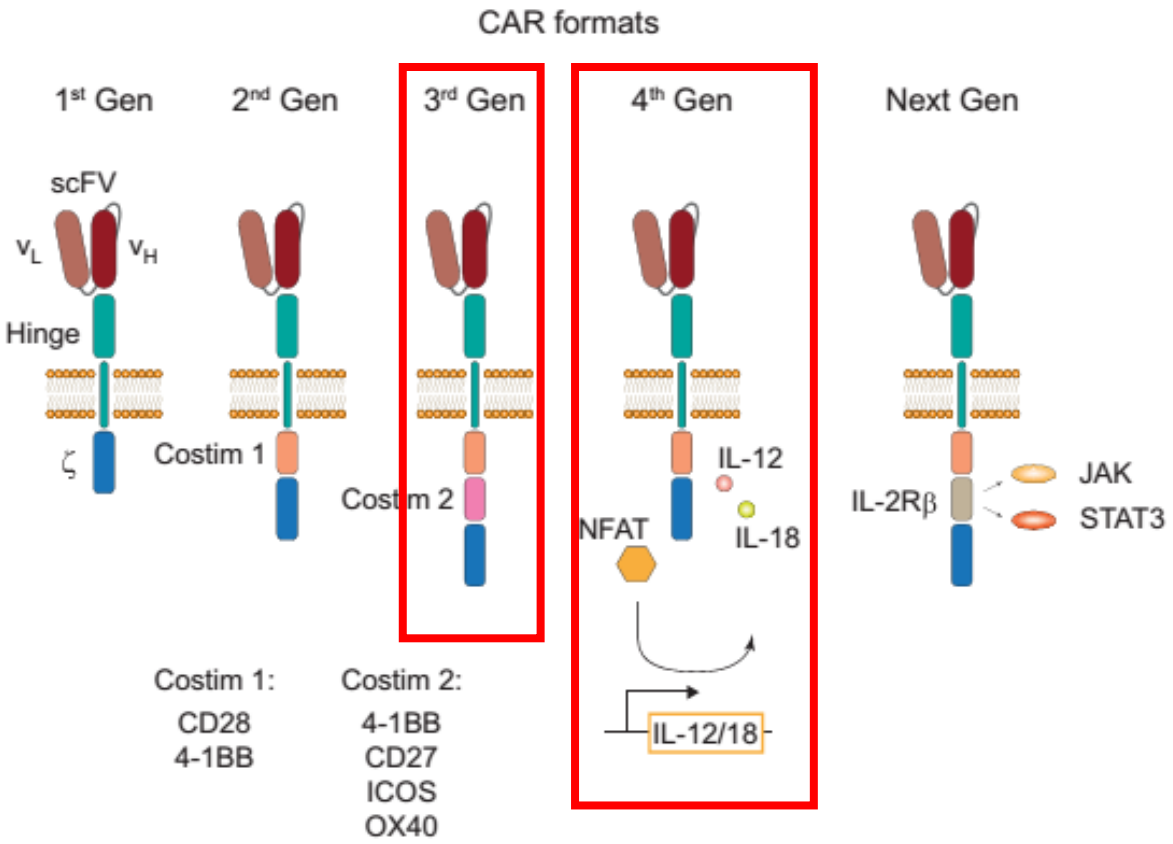


- Processo simplificado < tempo de cultura “ex vivo” (24h), < tempo de produção final para < 2 dias

- A Plataforma T-Charge ™ preserva as células T naive e “stem cell memory T” (T_{scm}) cells no produto final, aumentando a resposta e a persistência no tempo

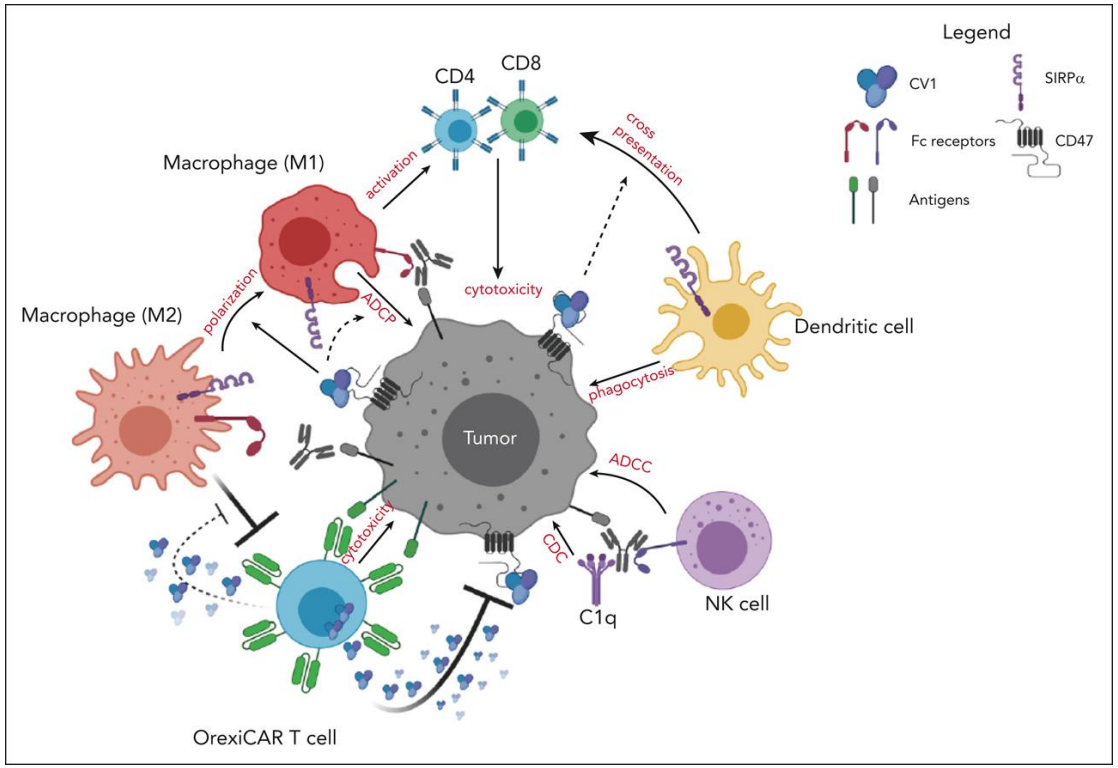
Frontiers in Immunology, 06 March 2023

CAR T mais complexos, 3ª e 4ª geração
"Armed trucks"



Frontiers in Immunology, 06 March 2023

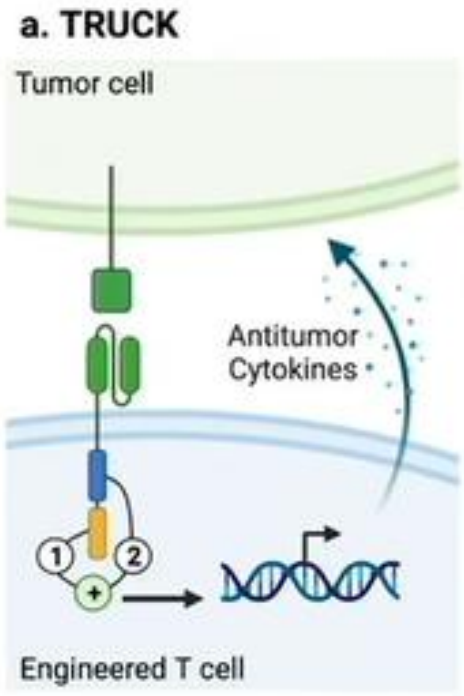
CAR T cells secreting CD47-SIRPα checkpoint blocker



Blood (2023) 141 (16): 2003–2015.

Phase I Trial of huCART19-IL18 Cells

Presented by Carl June, Strasbourg #CAR T25



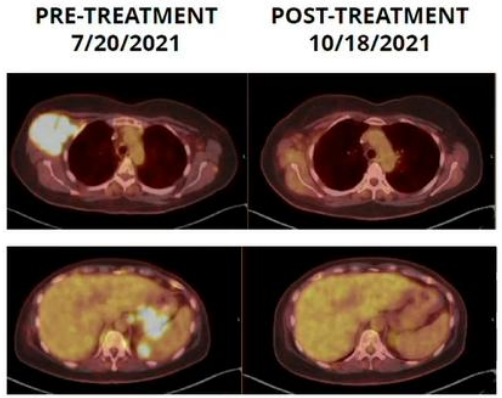
Sustained Complete Response At A Micro-Dose Of 3 Million Cells

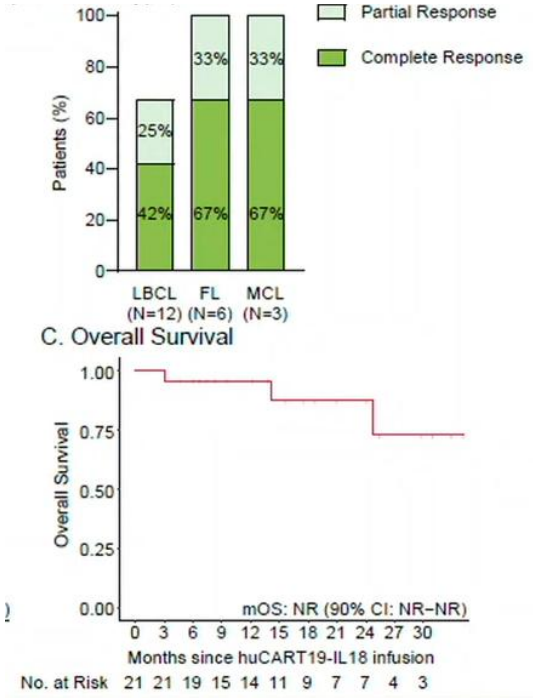
56 y.o. woman
Dx: follicular lymphoma/DLBCL
Prior lines of therapies: 9 including BEAM auto-transplant (PD), **axi-cel** (PD), blinatumomab (SD)

huCART19-IL18 treatment c/b transient grade 1 CRS, but no need for toci or steroids

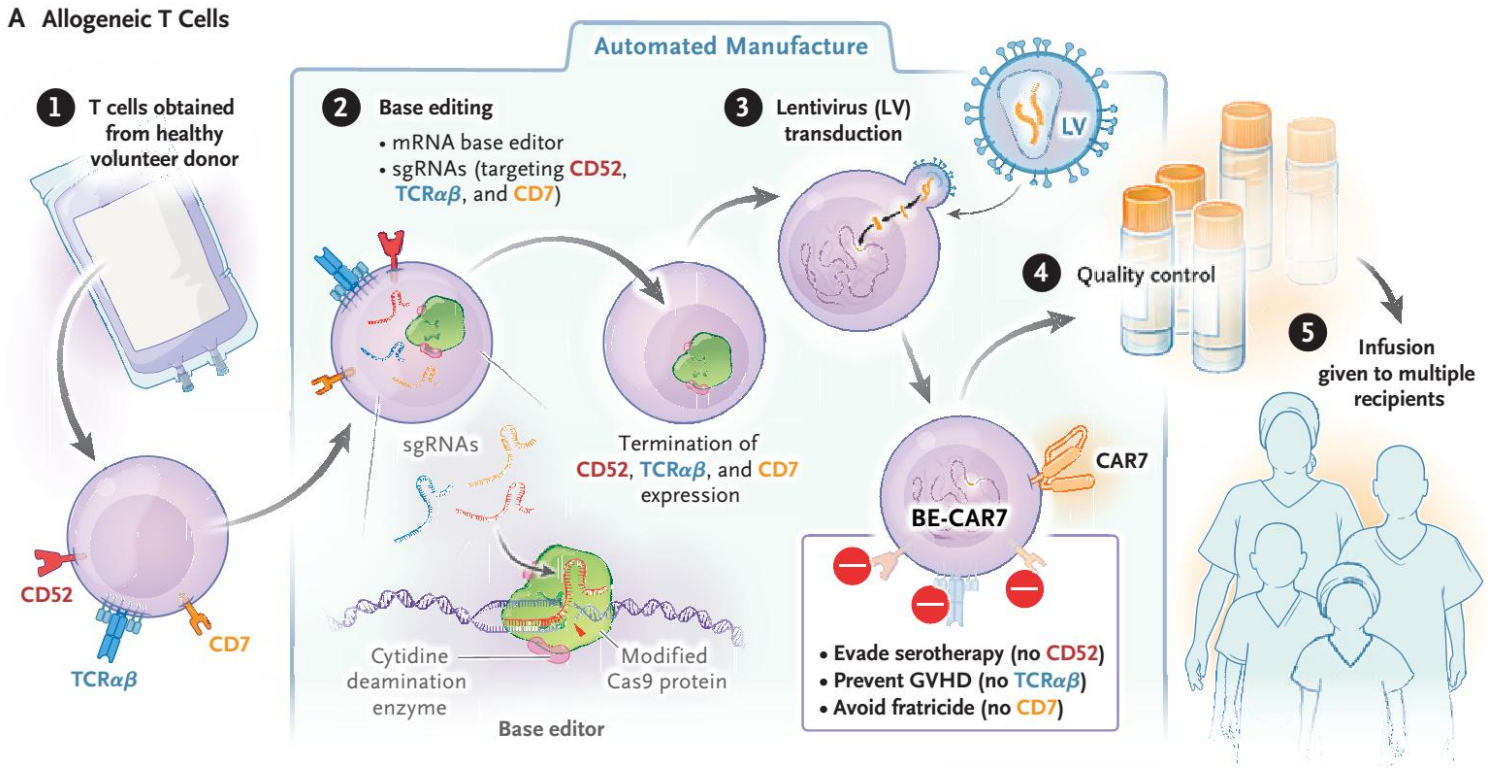
Response: **Continued CMR on M3, M6, M9 & M12 by PET/CT**

Svoboda UNPUBLISHED





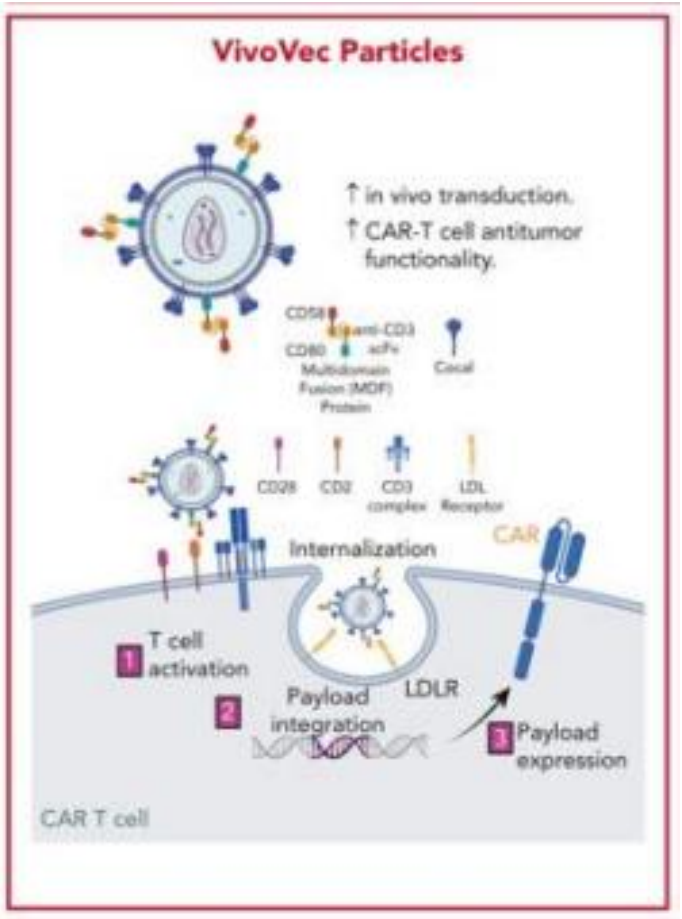
CAR T alogénico
“O desafio das patologias de células T”

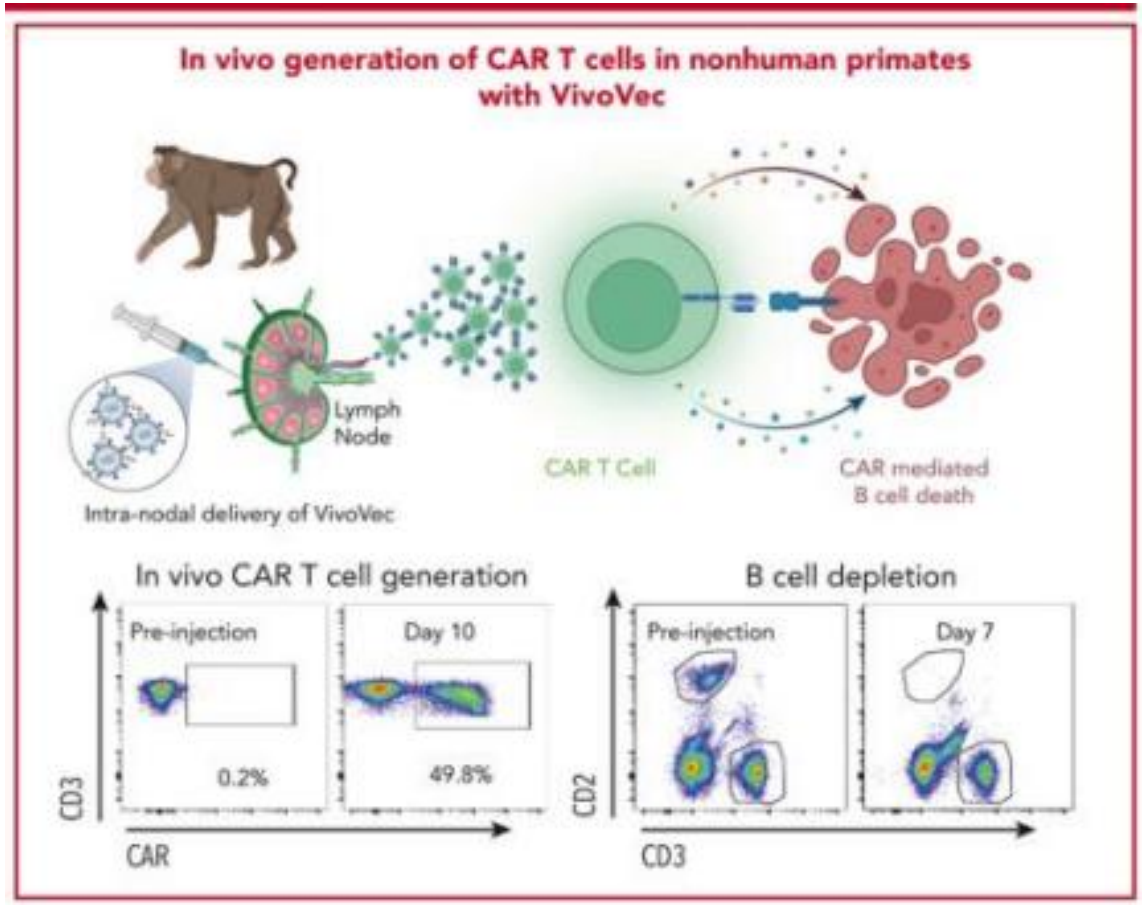


Robert Chiesa, **N Engl J Med 2026;394:152-65.**

CAR T “in vivo”

Sem necessidade de aférese ou linfodepleção





Christopher J. Nicola, Blood, 29 AUGUST 2024 | VOLUME 144, NUMBER 9

Conclusão

- Os ATMPs constituem mais um importante passo no tratamento das doenças oncológicas
- Não são solução para todos os casos, mas têm ainda um potencial enorme de evolução
- A classificação como medicamento introduz uma carga burocrática no processo de regulamentação/aprovação que os torna extremamente dispendiosos
- O elevado custo dos ATMPs vai exercer forte pressão no SNS e difficultar o acesso

Median cost 355.160,00€*
(97% is the price of CAR T)

The Economist 2017

*S. Chacim, published 09 Dec 2022 PLOS ONE

Serviço de Hematologia e Transplante de Medula Óssea
JM Mariz, Luisa Viterbo, Angelo Martins, Isabel Oliveira, Nelson Domingues, Ana E Santo, Claudia Moreira, Dulcineia Pereira, Catarina C Costa, Pinho Vaz, Rosa Branca, Luis Leite, Catarina Dantas, Manuel Guerreiro, Rita Coutinho, Delfim Duarte, Mário Pimenta, Inês Marques

Serviço de Terapia Celular
Susana Roncon, Ana, Lucia, Sara
Serviço de Cuidados Intensivos
Filomena Faria
Fernando Coelho
Serviço de Radioncologia
Carla Castro
Joana Gonçalves
Todos os Enfermeiros, Técnicos e Auxiliares
Todos os outros Serviços do IPO
Todos os Hospitais que referenciaram os doentes