Treatment of cancers with genetically modified cells: “the future is now”

OECI meeting, 2023 June 15th

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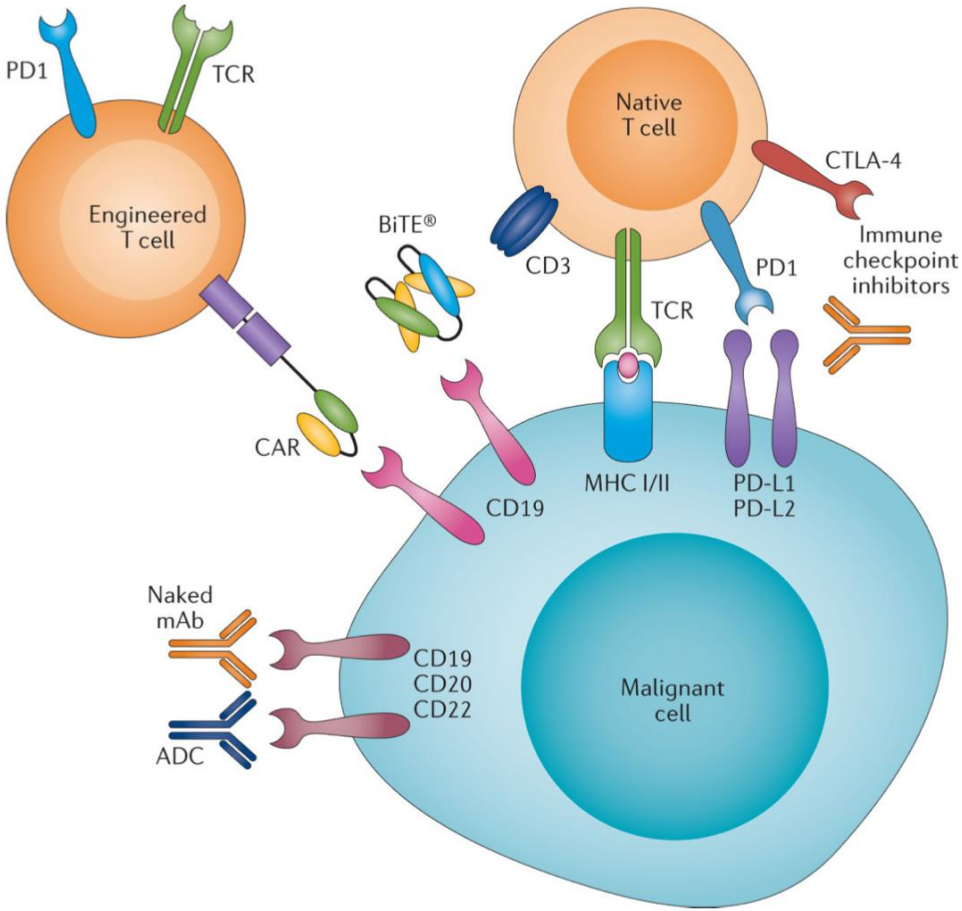
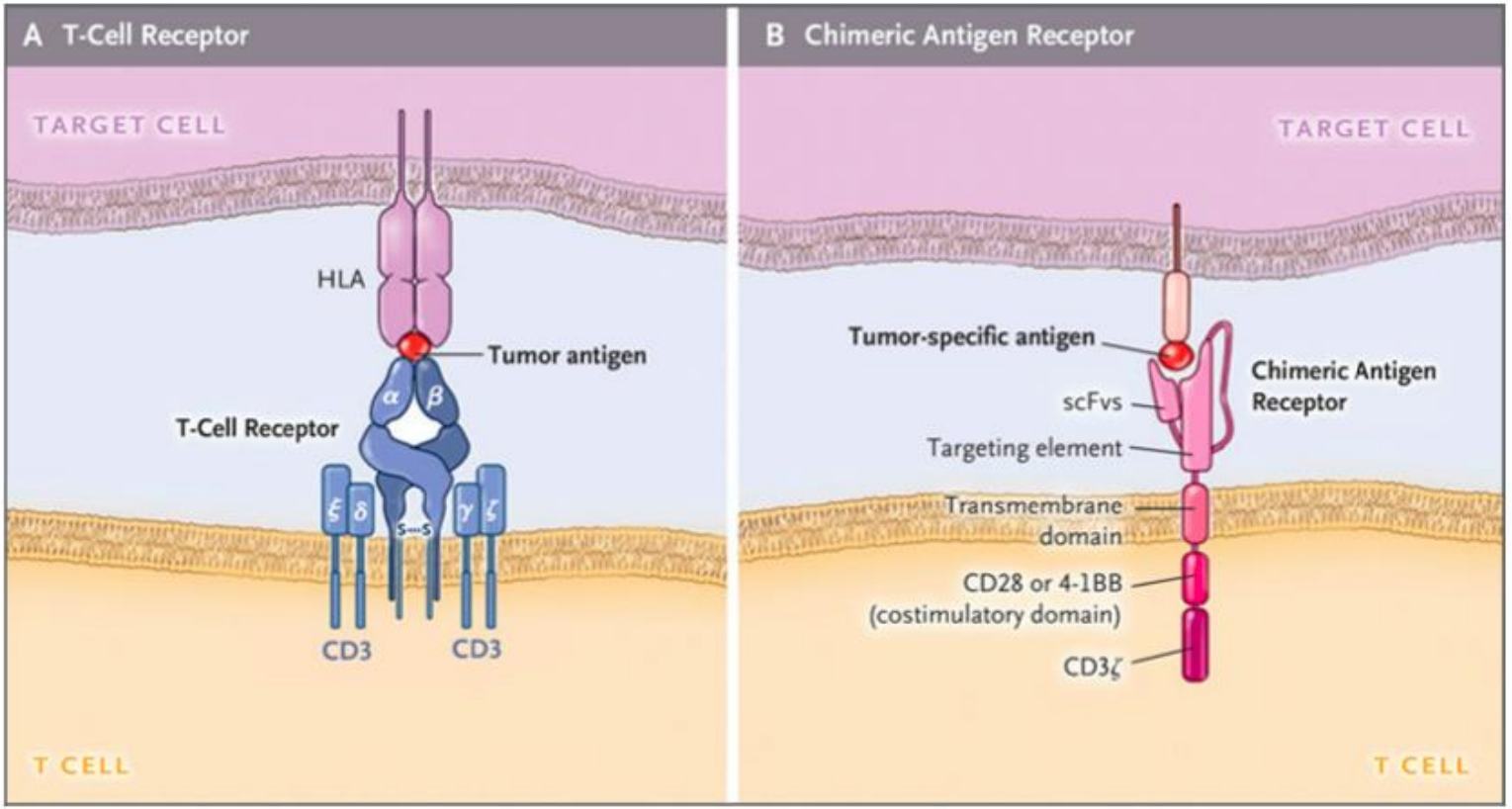
Introduction

Mechanisms of action of immunotherapy



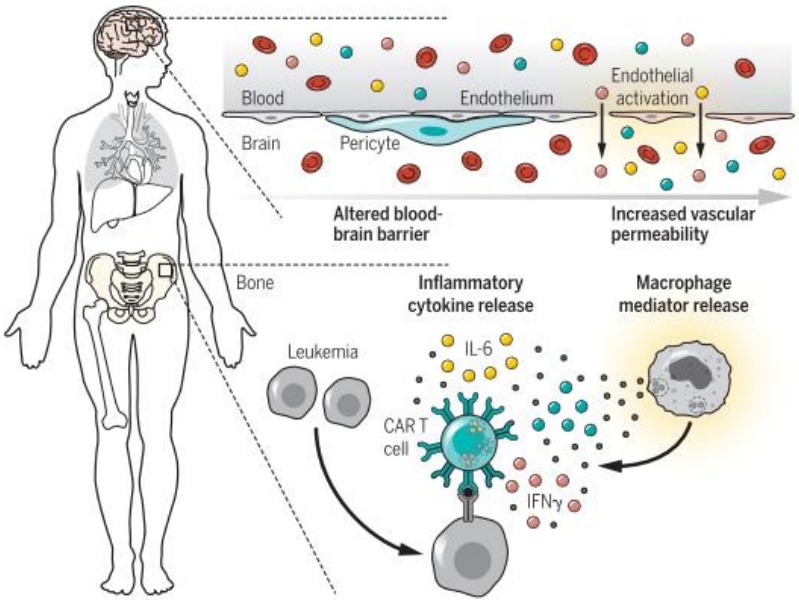
Batlevi et al, Nat Rev Clin Oncol. 2016

CAR *versus* TCR-T cells



June and Sadelain, NEJM 2018

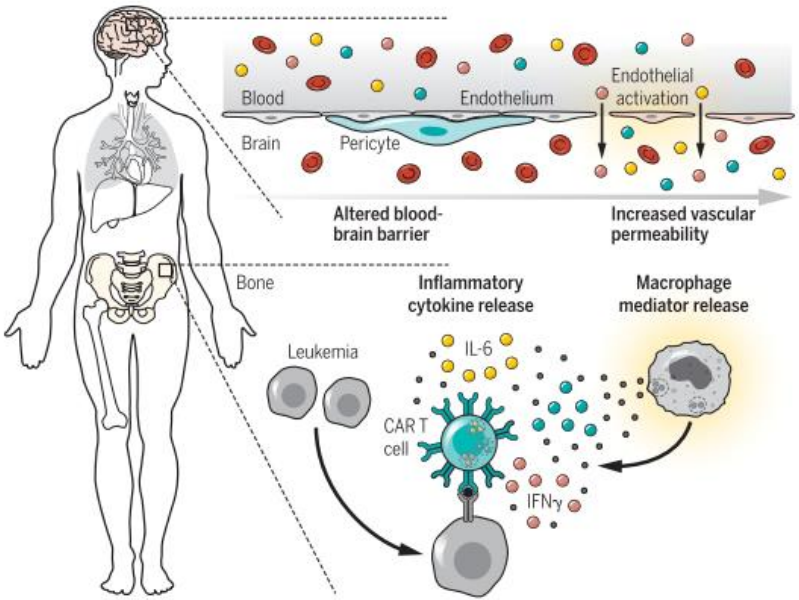
CAR-T toxicity



Cytokine release syndrome

Fever
Hypotension
Tachycardia
Capillary leak syndrome
Respiratory failure
Organ dysfunction

CAR-T toxicity

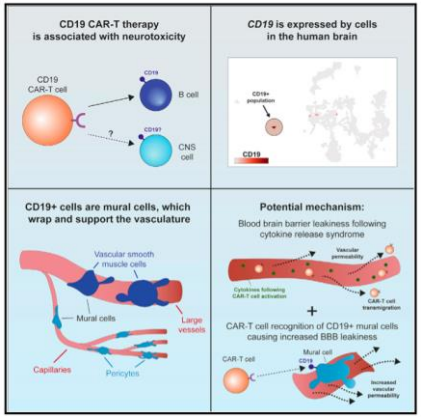


Neurotoxicity: ICANS

Immune effector cell-associated neurotoxicity syndrome

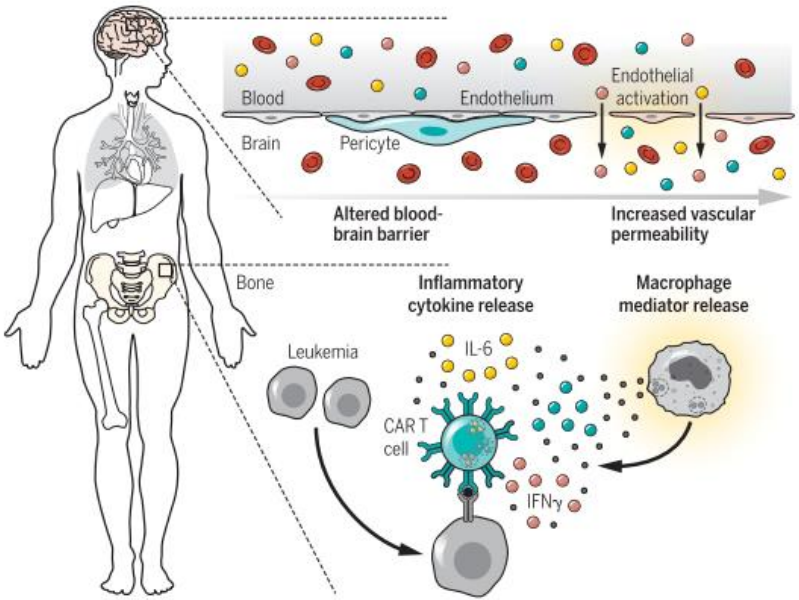
Impaired handwriting
Confusion
Cognitive impairment
Aphasia
Motor deficit
Seizures
Cerebral edema

On-target, off-tumor?



June et al, Science 2018
Parker et al, Cell 2020

CAR-T toxicity



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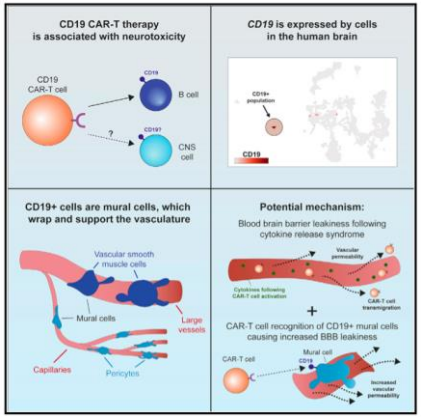

Treatment

- Symptomatic
- Tocilizumab (anti-IL6R)
- Corticosteroids

June et al, Science 2018
Parker et al, Cell 2020

Today's CAR-T cells

- **CD19**
  - B cell acute lymphoblastic leukemia (B-ALL)
    L3+ or relapse after allotransplant
  - Diffuse large B cell lymphoma (DLBCL)
    L3+, L2 patients eligible for ASCT
  - Mantle cell lymphoma (MCL)
    L3+, including a BTK inhibitor
  - Follicular lymphoma (FL)
    L3+
- **BCMA**
  - Myeloma
    L4+ including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody

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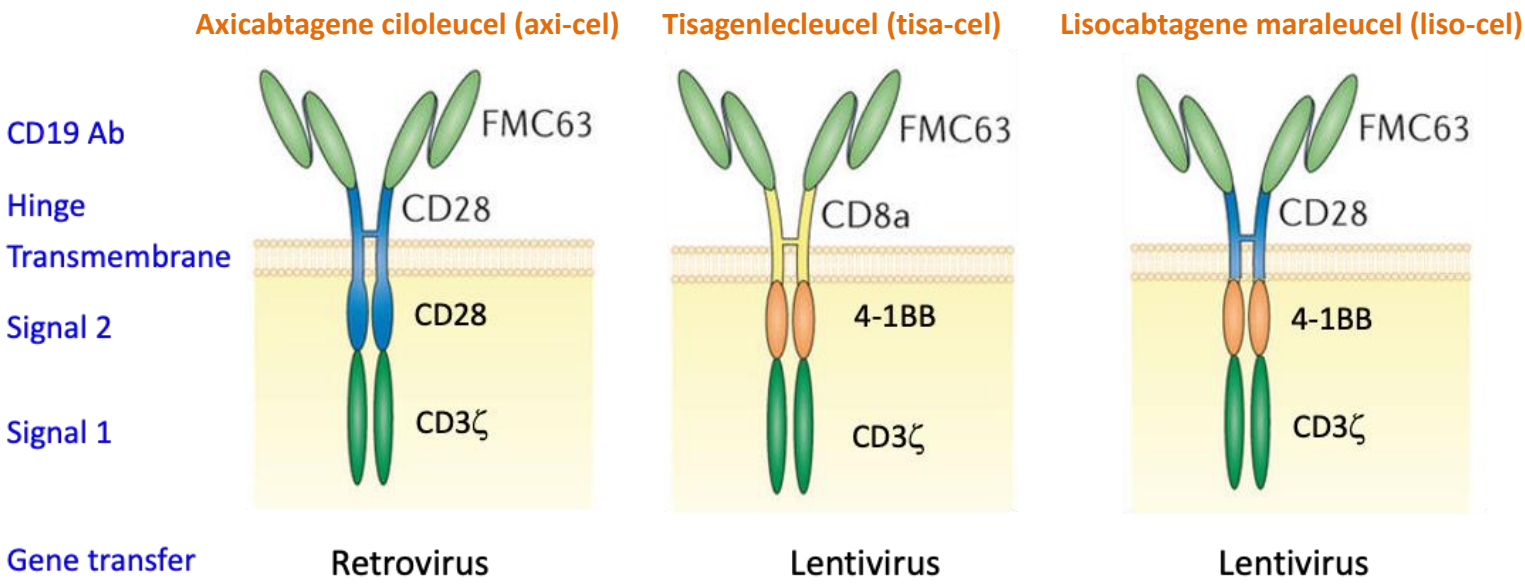
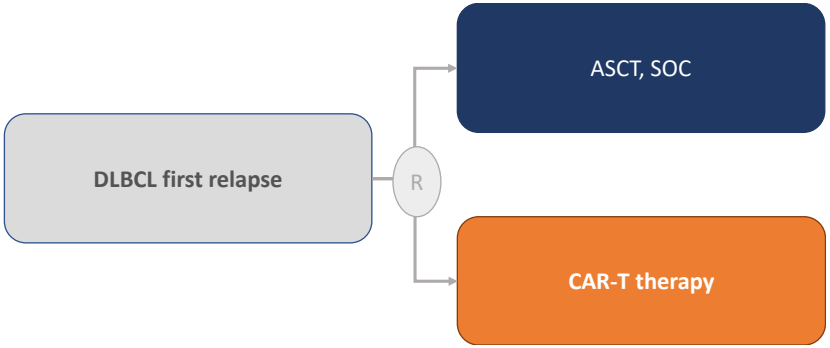
CAR-T cell constructs



Adapted from Van Der Steegen et al, Nat Rev Drug Discov 2015

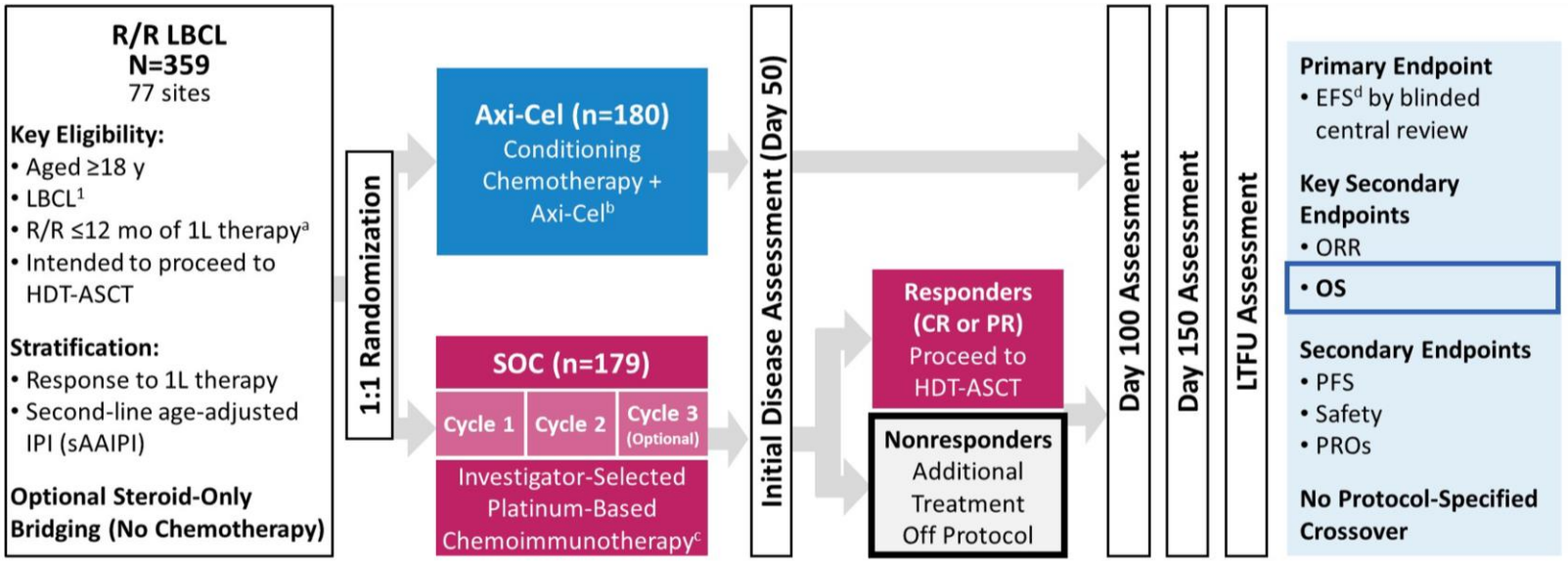
CAR T-cells as a second-line therapy for large B-cell lymphoma: a paradigm shift?



- Three randomized, international, multicentric studies
- Primary end-point: EFS
  - ZUMA-7: 8.3 *versus* 2 months
  - TRANSFORM: NR *versus* 2.4 months

	ZUMA-7 Axi-Cel (Yescarta®) ★ Locke FL et al. NEJM 2022	BELINDA Tisa-Cel (Kymriah®) Bishop MR et al. NEJM 2022	TRANSFORM Liso-Cel (Breyanzi®) ★ Kamdar M et al. Lancet 2022
N patients	179 + 180	160 + 162	92 + 92
Definition of specific events	Salvage switch (R-DHAP => R-ICE)	No	No
Bridging allowed	No (only corticosteroids)	Yes	Yes
Lymphodepletion (Fludarabine/Cyclophosphamide)	30/500	25/250	30/300
Cross-over	No	Yes	Yes
Median time from leukapheresis to CAR-T infusion	29 days	52 days	36 days
Median follow-up	24.9 months	?	6.2 months

ZUMA-7: study schema and endpoints



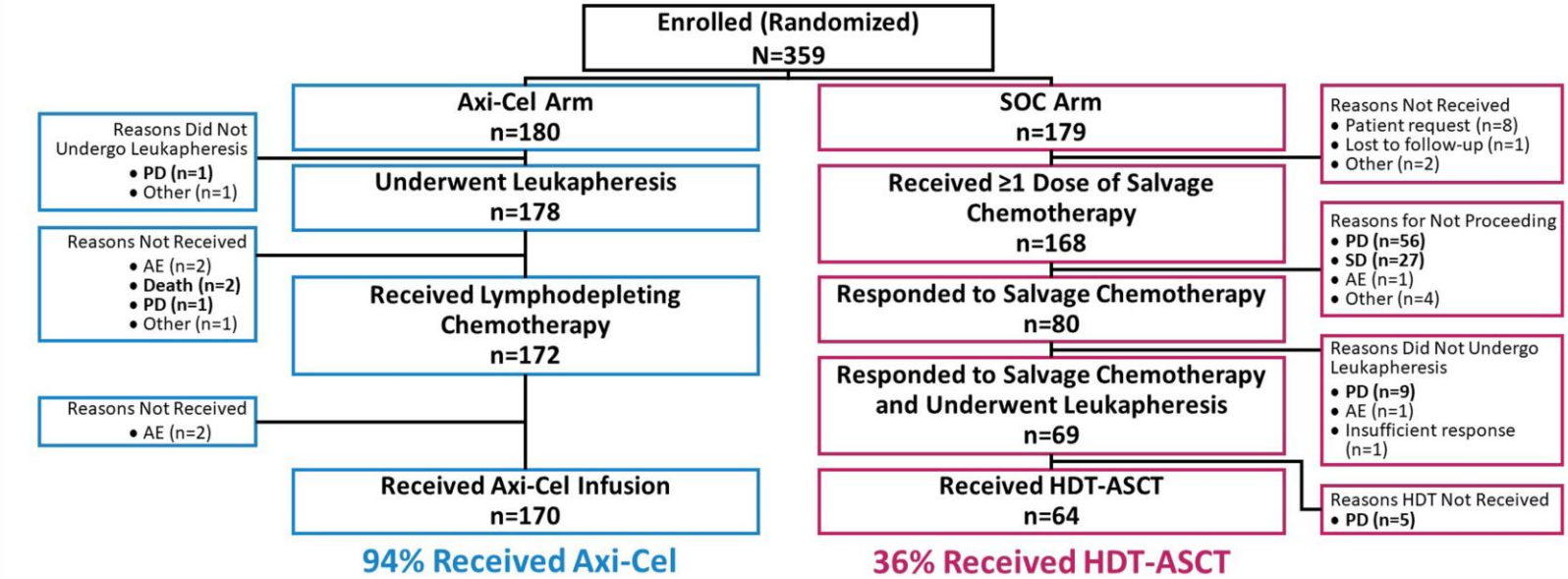
Westin et al, LBA107, ASCO 2023
Westin et al, NEJM 2023

ZUMA-7: baseline characteristics of the patients

Characteristic	Axi-Cel n=180	SOC n=179	Overall N=359
Median age (range), years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 years, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
sAAIPI of 2-3[a], n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy[a], n (%)			
Primary refractory	133 (74)	131 (73)	264 (74)
Relapse ≤12 mo of 1L therapy	47 (26)	48 (27)	95 (26)
Prognostic marker per central laboratory, n (%)			
HGBL (including double-hit lymphomas)	32 (18)[b]	25 (14)	57 (16)[b]
Double expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH level[c]	101 (56)	94 (53)	195 (54)

Westin et al, LBA107, ASCO 2023
Westin et al, NEJM 2023

ZUMA-7: nearly 3X patients received axi-cel *versus* HDT-ASCT



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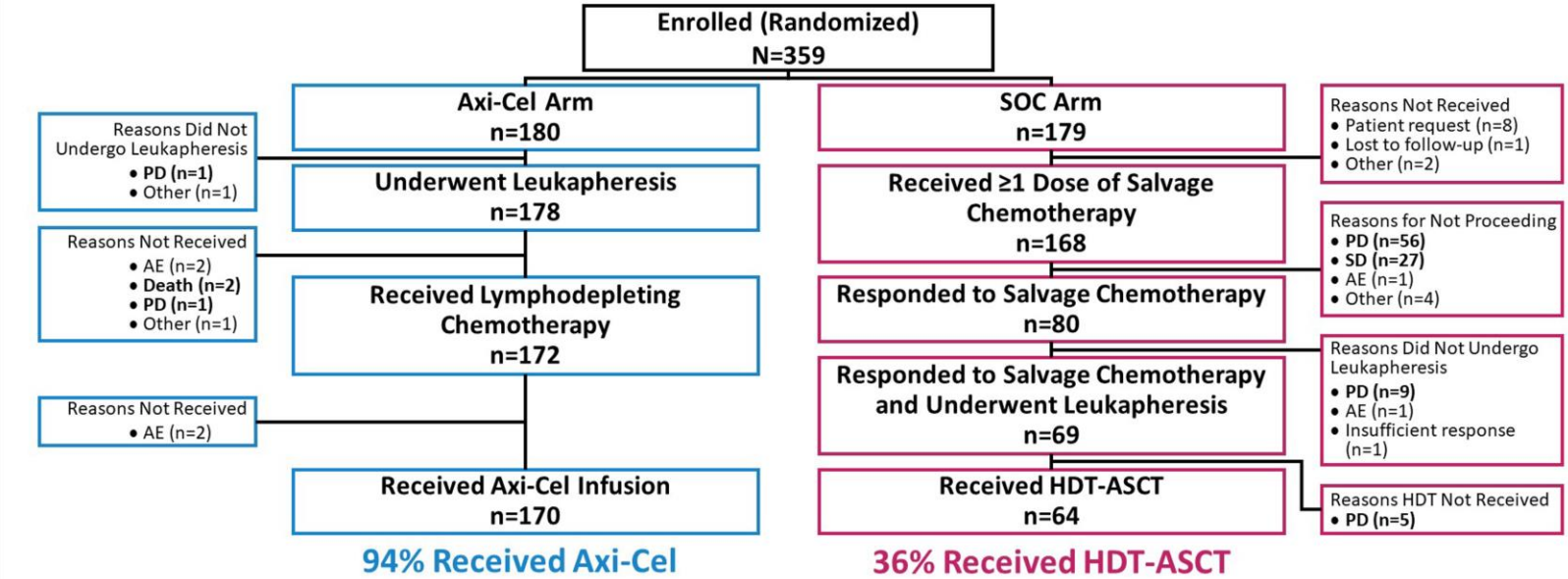


Westin et al, LBA107, ASCO 2023
Westin et al, NEJM 2023

ZUMA-7: key safety data

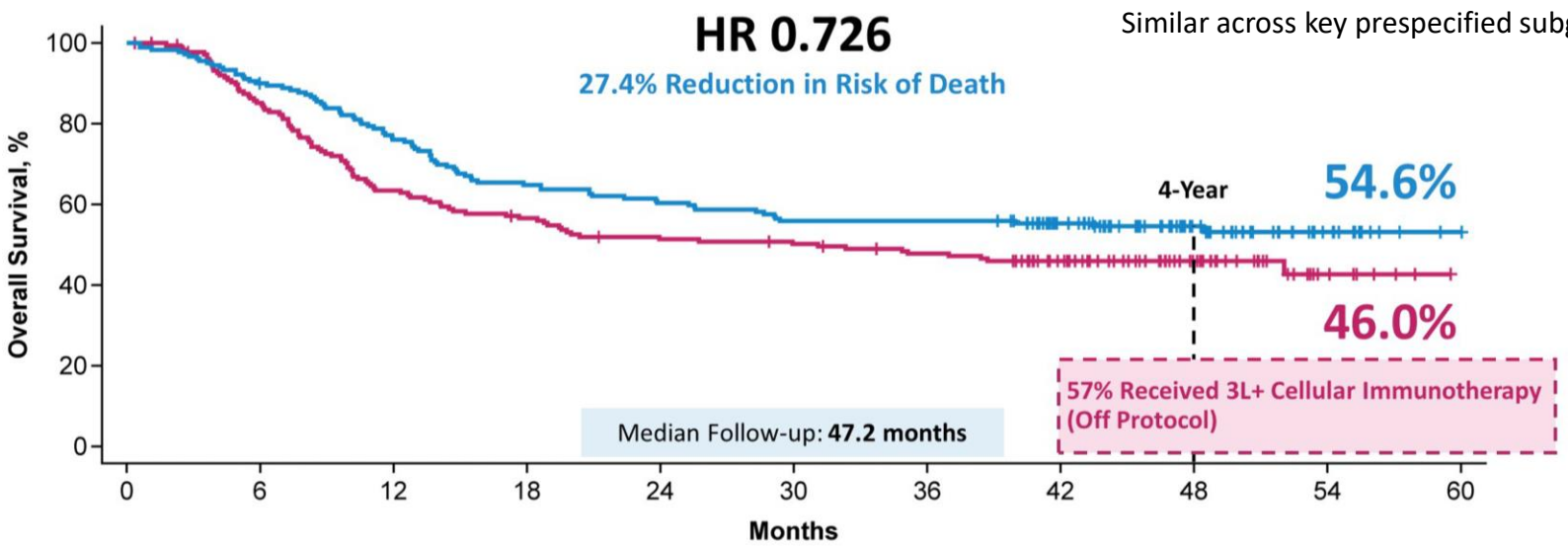
AEs of Interest, %	Axi-Cel n=170		SOC n=168	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
CRS	92%	6%	–	–
Neurologic event	61%	21%	20%	1%
Hypogammaglobulinemia	11%	0%	1%	0%
Cytopenia	80%	75%	80%	75%
Infections	45%	16%	32%	12%

- No changes in cumulative treatment-related serious or fatal AEs occurred since the primary EFS analysis

Reason for Death	Axi-Cel n=170	SOC n=168
Progressive disease, n (%)	51 (30)	71 (42)
Grade 5 AE during protocol-specific reporting period, n (%)	8 (5)[a]	2 (1)[b]
New or secondary malignancy, n (%)	2 (1)[c]	0
Other reason for death,[d] n (%)	13 (8)	18 (11)
Definitive therapy-related mortality,[e] n/N (%)	1/170 (1)[f]	2/64 (3)[g]

Westin et al, LBA107, ASCO 2023
Westin et al, NEJM 2023

ZUMA-7: axi-cel improved OS *versus* SOC



- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Historical SOC trials had 3-year OS rates of ~30%[a] and <40%[b] in similar patient populations

Westin et al, LBA107, ASCO 2023
Westin et al, NEJM 2023

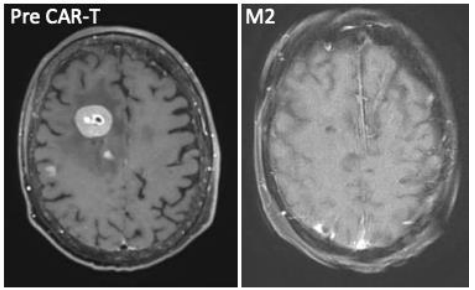
Tomorrow’s CAR-T cells

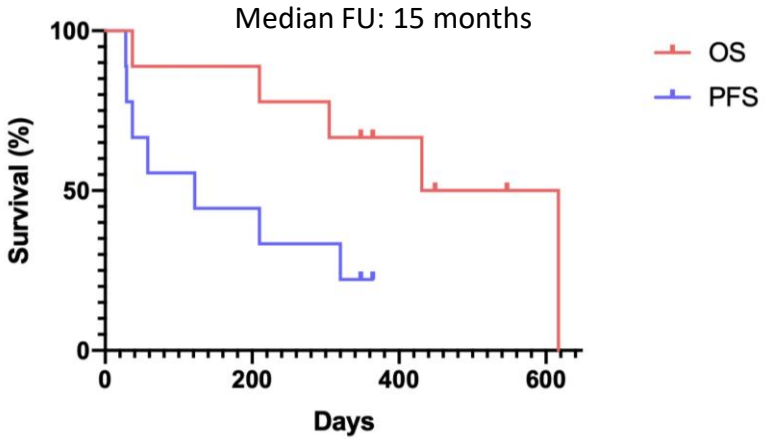
- **Other hematologic malignancies**
  - Primary central nervous system lymphoma (PCNSL)
  - Chronic lymphocytic leukemia (CLL)
  - Hodgkin lymphoma (HL)
  - T-cell non Hodgkin lymphoma (T-NHL)
- **Solid tumors**
- **Earlier in the course of the disease**

CD19 CAR-T in PCNSL : The clinical experience of the French LOC network

- Primary central nervous system lymphoma
- B-cell derived cancer
- Localized in the CNS (brain, eye, spinal cord, CSF)
- Physiopathology not fully understood
- 300 new cases/year in France
- Poor prognosis

- 9 patients
  - Median age 67 years
  - 3 prior lines of therapy (median)
  - 7 tisa-cel, 2 axi-cel
- ORR: 67%
  - CR: 5/9
  - PR: 1/9
- No unexpected toxicity
  - 1 CRS grade 3
  - 2 ICANS grade ≥ 3

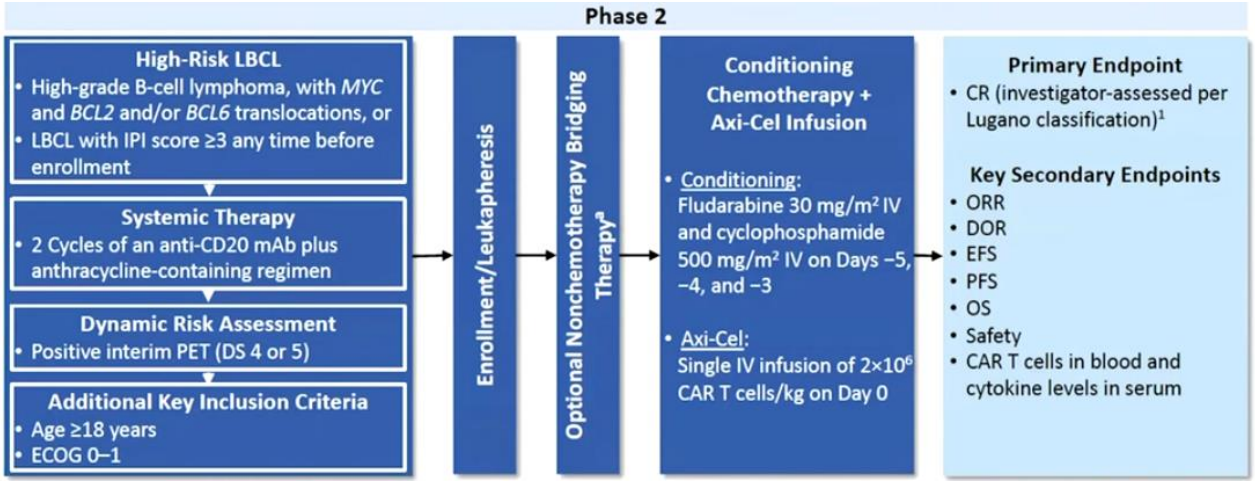




- 1-year OS: 67%
- Median OS: 17 months
- 1-year PFS: 22%
- Median PFS: 4 months
  - Responders : 9 months
  - Non responders : 1 month

Alcantara et al, Blood 2021

Axi-Cel in 1st line treatment of DLBCL

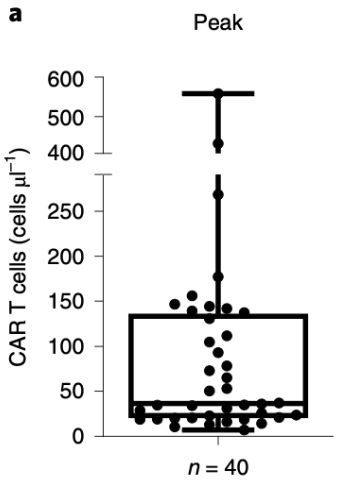


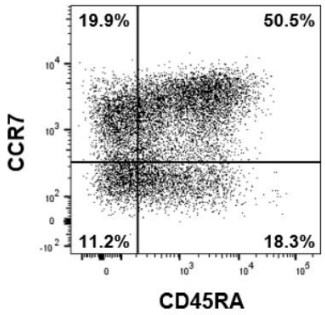
- N = 40 patients
  - Median age: 61 yo (23 – 86)
- Median FU: 15.9 months
- Best ORR: 89%
- **Best CR: 78%**
- Median DOR: NR
- 1-y PFS: 75%
- 1-y OS: 91%
- Grade ≥ 3 CRS: 8%
- Grade ≥ 3 ICANS: 23%

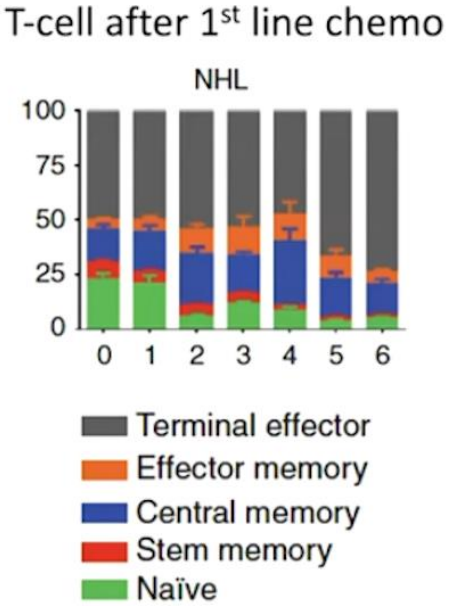
Neelapu et al, Nature Med 2022

Axi-Cel in 1st line treatment of DLBCL

- Compared to ZUMA-1
  - **Higher expansion** of CAR-T
  - **Higher number of naïve** CAR-T

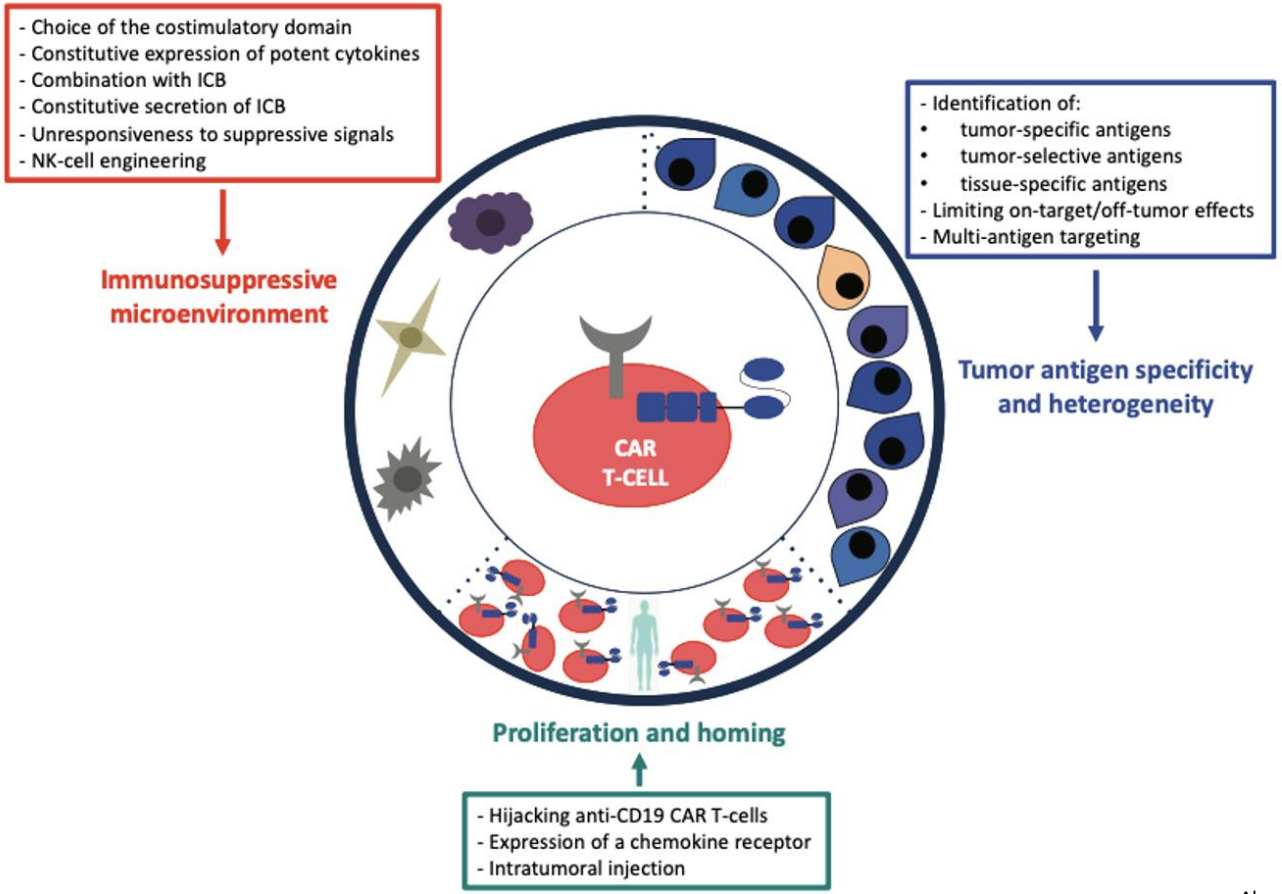






Neelapu et al, Nature Med 2022
Das et al, Cancer Discov 2019

Solid tumors are much more challenging!

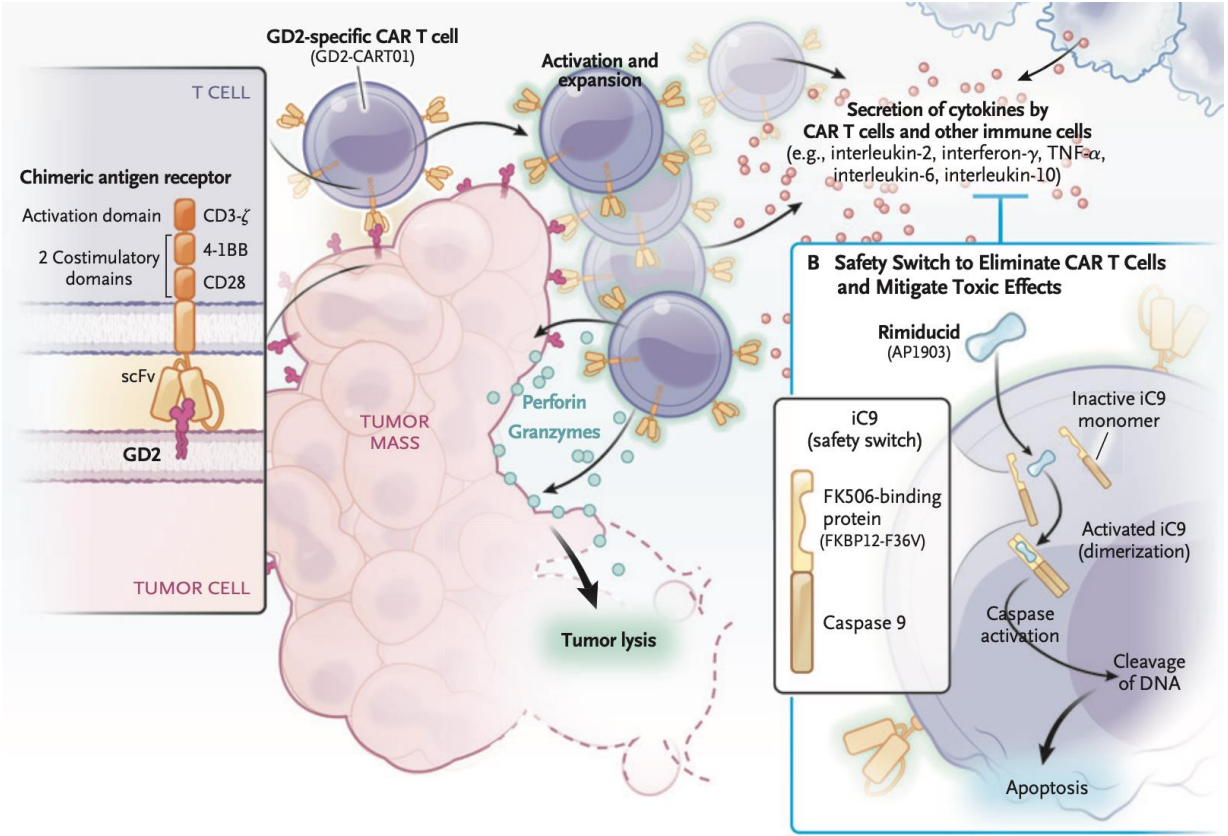


Alcantara et al, Oncoimmunology 2020

Solid tumors are much more challenging!

- Historically limited activity
- Interesting results for CAR-T cells targeting
  - Claudin18.2, PSMA, mesothelin, HER2, GD2
- High levels of activity in TCR-T cells
  - MAGE-A4, -10, NY-ESO-1
  - Synovial sarcoma, myxoid/round cell liposarcoma

GD2 CAR-T cells for high-risk neuroblastoma



GD2: member of the ganglioside family of glycolipids
Tumor-associated antigen, low expression in healthy tissues

Yeku et al, NEJM 2023

GD2 CAR-T cells for high-risk neuroblastoma

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=27)
Sex — no. (%)	
Male	18 (67)
Female	9 (33)
Median age (range) — yr	6.7 (2.7–18.6)
Median no. of previous treatments (range)	3 (1–6)
Disease status at enrollment — no. (%)	
Refractory	12 (44)
Relapsed	14 (52)
No evidence of disease after NB-HR01 first-line treatment†	1 (4)
Previous treatment with anti-GD2 monoclonal antibody — no. (%)	14 (52)
MYCN status — no. (%)	
Amplification	7 (26)
Gain	5 (19)
Normal	10 (37)
Unknown	5 (19)
Site of disease involvement — no. (%)	
Bone	21 (78)
Bone marrow	12 (44)
Lymph nodes	11 (41)
Abdomen	4 (15)
Paravertebral area	7 (26)
Thorax, pleura	2 (7)
Liver	1 (4)
Result of ^{123}I-labeled MIBG scan before infusion — no. (%)‡	
MIBG score ≤7	18 (67)
MIBG score >7	9 (33)

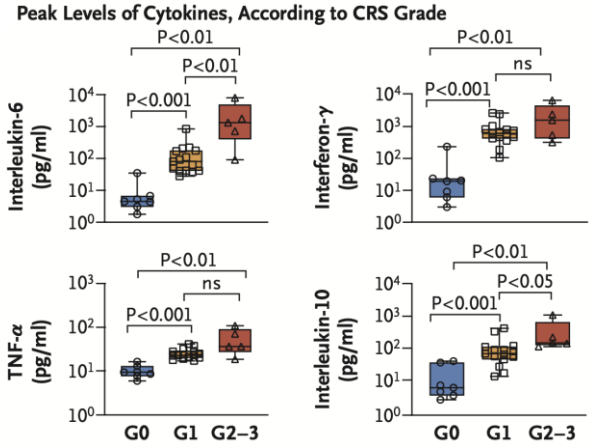
Table 2. Adverse Events in 27 Patients after the First Infusion of GD2-CART01.*

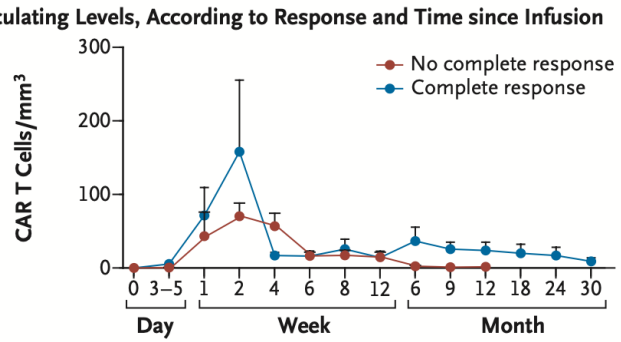
Event	Grade 1 or 2	Grade 3	Grade 4
		number of patients	
Cytokine release syndrome	19	1	0
Central neurotoxic effects	0	0	0
Peripheral neurotoxic effects or pain	6	0	0
Hematologic toxic effects			
Anemia	8	19	0
Neutropenia	0	0	27
Thrombocytopenia	1	4	19
Abnormal laboratory values			
Elevated alanine aminotransferase level, aspartate aminotransferase level, or both	13	7	0
Elevated bilirubin level	3	1	0
Electrolyte abnormalities	4	2	0
Miscellaneous			
Clostridium difficile infection	0	1	0
Rash	3	0	0
Dysuria	2	0	0
Brain hemorrhage	0	0	1

- 27 patients
  - No DLT
  - RP2D: $10x10^6$ CAR-T/kg

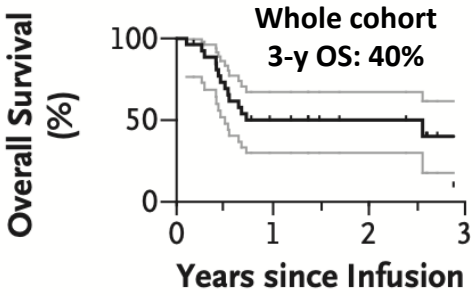
Del Bufalo et al, NEJM 2023

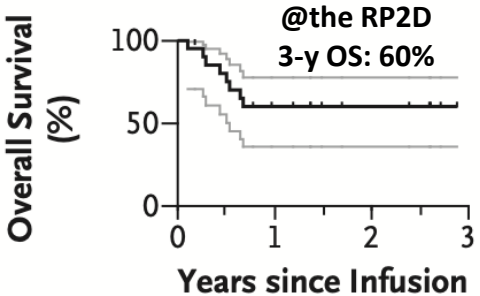
GD2 CAR-T cells for high-risk neuroblastoma





- 27 patients
  - **9 CR (33%)**
  - 8 PR (30%)
- Median FU: 1.7 years



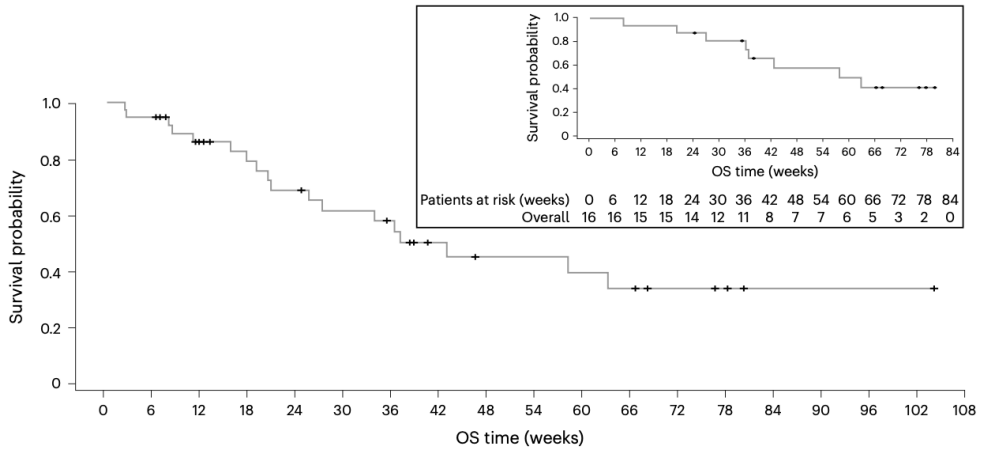


Del Bufalo et al, NEJM 2023

Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients

- Afami-cel
- First-in-human phase 1 trial
- Favorable safety profile
- ORR: 24% (all PR)
- Disease control rate (including SD): 74%
- Durable responses
  - mDoR: 25.6 months
- mOS: 42.9 weeks
  - In metastatic SS patients: 58.1 weeks

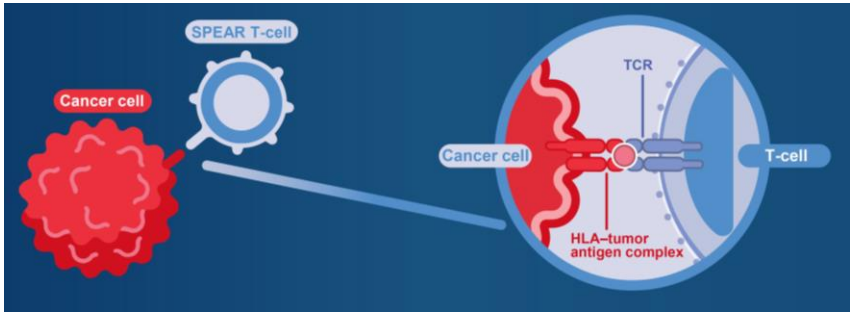
Primary tumor type	Esophageal	*n* (%)	2 (5.3)
	Gastric	*n* (%)	1 (2.6)
	Head and neck	*n* (%)	3 (7.9)
	Melanoma	*n* (%)	1 (2.6)
	NSCLC	*n* (%)	2 (5.3)
	Ovarian	*n* (%)	9 (23.7)
	Urothelial	*n* (%)	2 (5.3)
	MRCLS	*n* (%)	2 (5.3)
	SS	*n* (%)	16 (42.1)

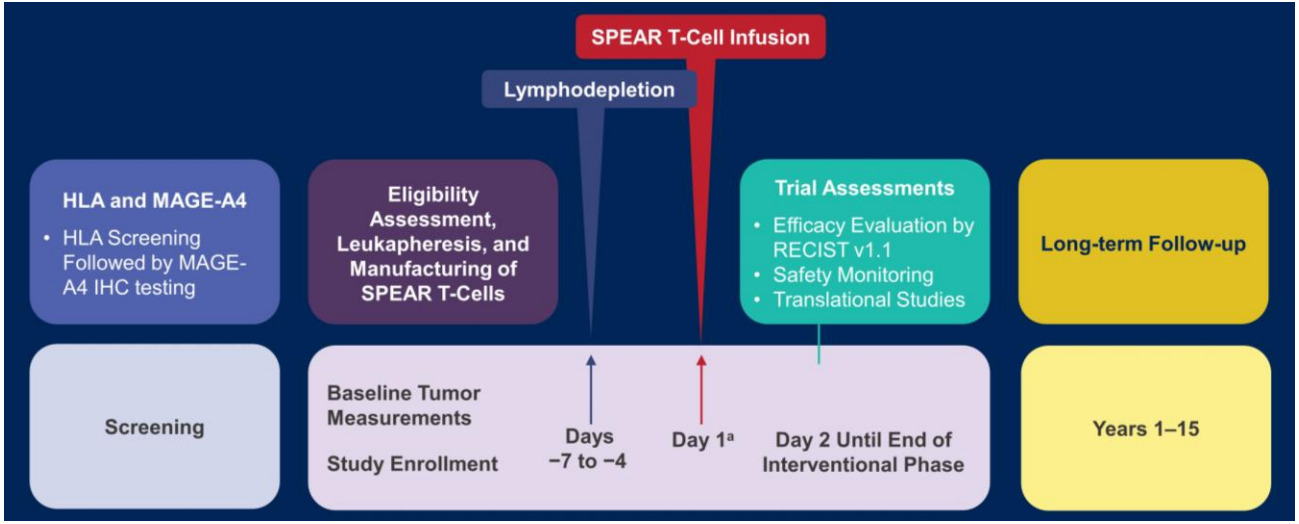


Hong et al, Nature Med 2023

SPEARHEAD-1: a phase 2 trial of anti-MAGE-A4 SPEAR T cells

- Advanced **synovial sarcoma** or **myxoid/round cell liposarcoma**
- SPEAR T cells target MAGE-A4+ tumors
- Highly expressed in synovial sarcoma and MRCLS in the context of HLA-A02





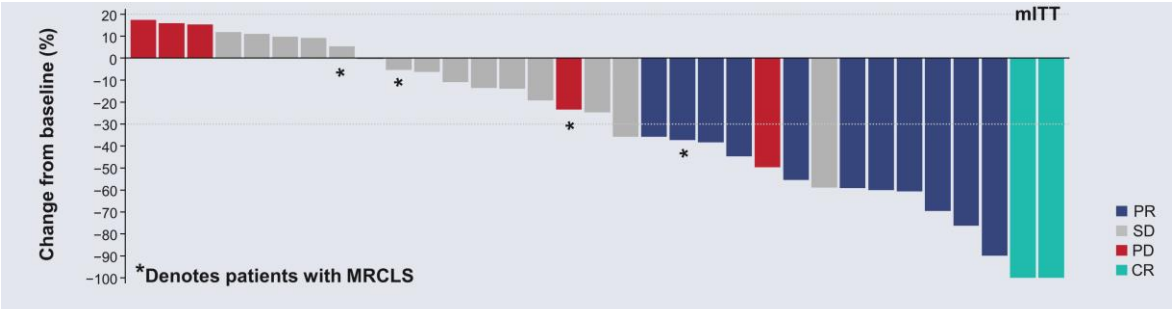
SCREENING[a]

Screened for HLA-A*02, n (%)	N=330
HLA-A*02 positive	176 (53.3)
Screened for MAGE-A4, n (%)	**N=176**
MAGE-A4 positive	106 (61.6)

D'Angelo et al, #11504, ASCO 2021

SPEARHEAD-1: main results

- 59 included patients, 37 received SPEAR T cell treatment
- Median DOR: NR (4.3 – 38 weeks)



- **Two CRs in patients with synovial sarcoma**
- **ORR of 39.4% (13/33)[a]: synovial sarcoma 41.4% (12/29) and MRCLS 25.0% (1/4)**
- **Disease control rate of 84.8% (28/33)**

Cytokine Release Syndrome, mITT, n (%)	N=37
Any grade	22 (59)
≥ Grade 3	1 (3)
Median time to onset, days (range)	3 (1–9)
Median time to resolution, days (range)	3 (1–34)
Tocilizumab use	12 (55)
Grade ≥ 3 Prolonged Cytopenia at Week 4 Post-infusion, mITT, n (%)	**N=37**
Neutropenia	2 (5)
Thrombocytopenia	1 (3)
Anemia	3 (8)

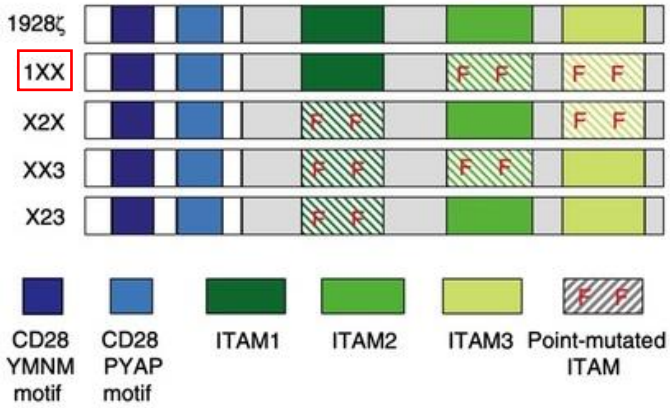
D'Angelo et al, #11504, ASCO 2021

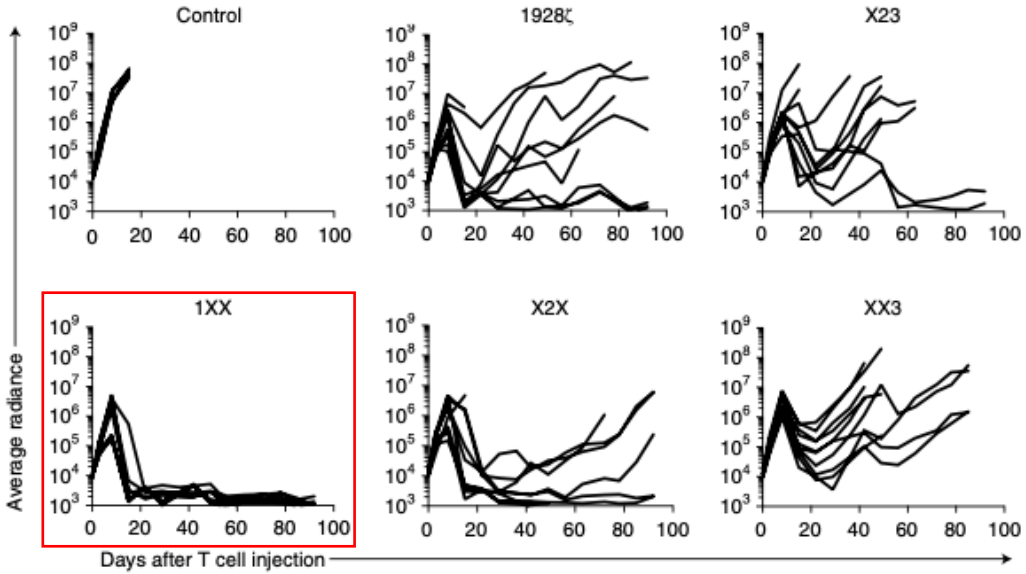
After tomorrow's CAR-T cells

- Combinations
  - Immune checkpoint inhibitors
  - Radiation therapy
  - Targeted therapies (ibrutinib, lenalidomide)
- CAR design improvements
- Bispecific CAR
- Allogeneic cell therapies
- …

Calibrating CAR Activation Potency to Increase Persistence

1XX CAR: sequential mutation of the intracellular ITAM domains of the CAR CD3ζ

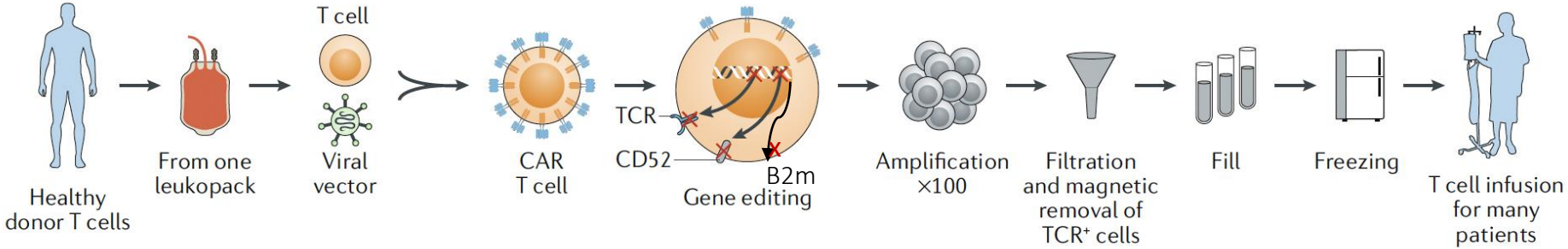




- **Balancing effector and memory programs**
- **Enhanced therapeutic efficacy**
  - Phase I dose-escalation study (MSKCC)
  - 25 patients (DLBCL, HGBCL, tFL)
  - RP2D **25x10^6 CAR-T**
  - ≥ Grade 3 CRS 11%, ICANS 0%
  - ORR 89%, CR 78%

Feucht et al, Nature Med 2019
Park et al, #163, ASH 2022

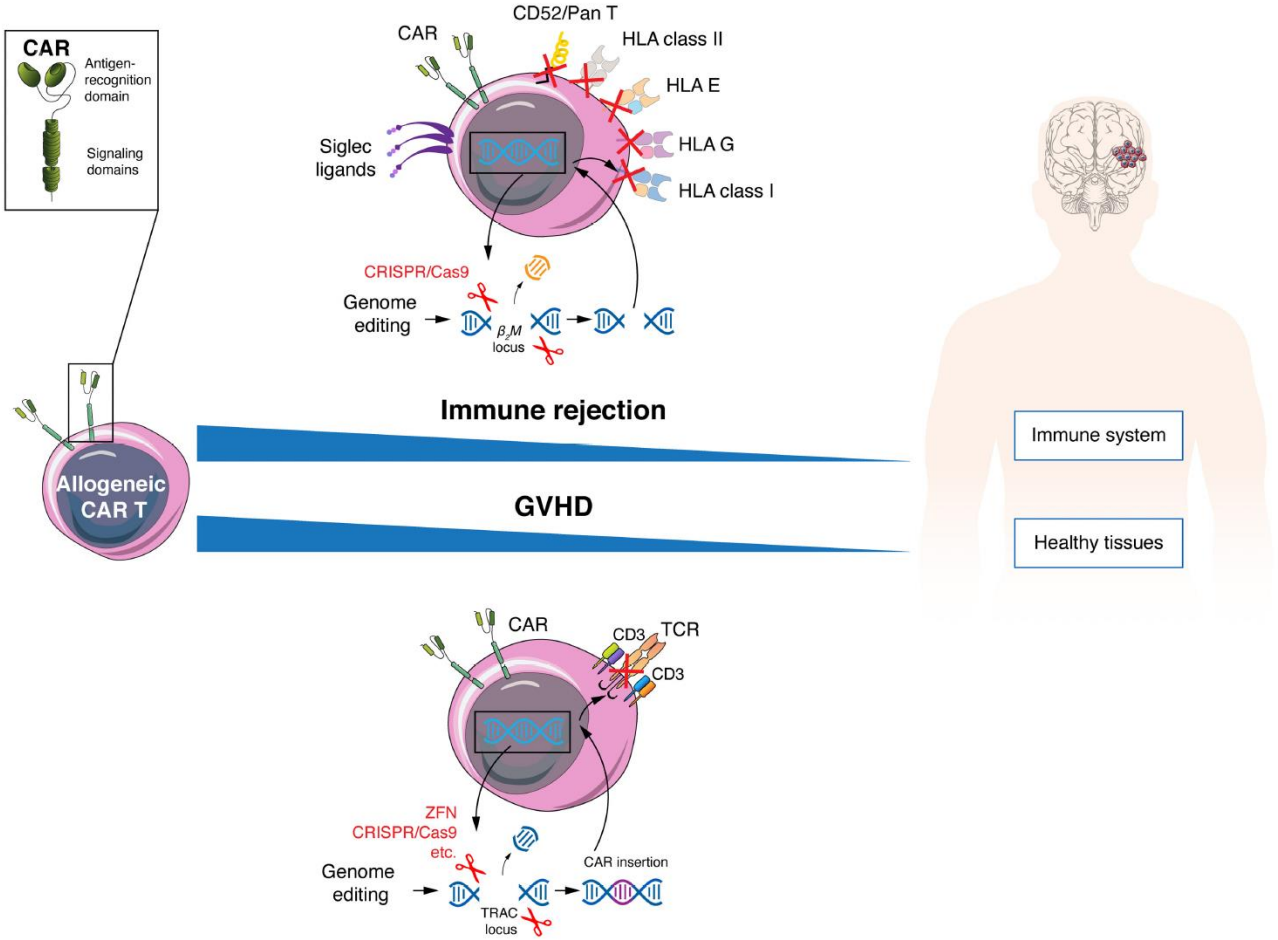
Advantages of allogeneic CAR-T cell therapy



- Immediate availability of cryopreserved batches
- Time for multiple cell modifications
- Standardization of the CAR T-cell product
- Amenable to repeat dosing
- Reduced cost
- Reduced risk of manufacturing failure

Depil et al, Nat Rev Drug Disc 2020

Challenges for Allogeneic CAR T-cell therapy



- Disrupt $\alpha\beta$TCR
- Silence MHC-I and/or class-II; overexpress ligands to inhibit NK cell cytotoxicity (HLA-E, G); CD52 lymphodepletion (UCART19)
- Use of alternative cell sources: NK cells; iNKT cells; γδT cells; EBV-reactive αβT cells; iPSC; MAIT cells
- 41BBL-CD3ζ CAR delete activated host T and NK cells

Bedoya et al, Front Imm 2022

Conclusion: “the future is now”

- CAR T-cells
  - CD19, BCMA
    - Standard of care
      - B-cell hematologic malignancies
    - Increasingly growing number of indications
- Challenges to be overcome in solid tumors
  - But the first convincing results are here
- Next steps
  - Earlier in the course of the disease
  - Randomized studies (solid tumors ++)
  - Improvements in CAR technologies, manufacturing…