

4th MEETING ON INNOVATIVE IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

Presidents
Paolo Corradini
Marco Ruella
Pier Luigi Zinzani

Strategies to Reduce CART Toxicities

Saad Kenderian, M.D.

Mayo Clinic, Rochester, MN, U.S.A.

January 22, 2026

MILANO, STARHOTELS ROSA GRAND

January 22-23, 2026

Disclosures

➤ **Patents/royalties:** Novartis

‘managed according to an agreement between Mayo Clinic, University of Pennsylvania and Novartis’

➤ **Research Funding:**

- Novartis
- Tolero
- Humanigen
- Lentigen
- Kite, Gilead
- Morphosys
- Juno, BMS
- Sunesis
- LeahLabs
- Viracta

➤ **Patents, intellectual property and royalties:**

- Novartis
- Humanigen/Taran
- Mettaforge
- MustangBio
- Tolero
- LEAHLabs
- Sendero
- Immix Bio

➤ **Consultancy:**

- Novartis
- Kite, Gilead
- Juno, BMS
- Humanigen
- Torque
- CapstanBio

➤ **DSMB:**

- Humanigen
- Carisma

➤ **SAB:**

- Kite, Gilead
- Juno, BMS
- Humanigen
- CapstanBio
- Luminary
- Novartis
- LEAHLabs

Toxicities Post CART Cell Therapy

➤ Pathophysiology of CART Associated Toxicities

- Cytokine Release Syndrome (**CRS**)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (**ICANS**)
- Other neurological complications

➤ Management of CRS and ICANS

- Standard of Care
- Cytokine Directed Therapies
- Small Molecules to Modulate CART Cells
- CART Engineering Strategies

CRS and ICANS

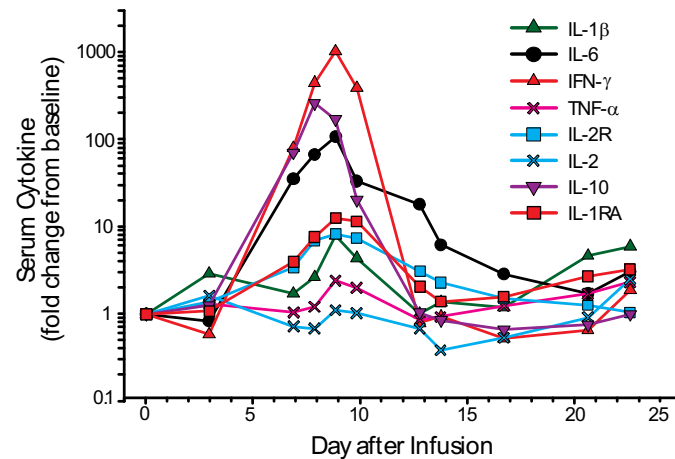
	B-ALL			DLBCL			MCL	FL	MM	
	ELIANA	ZUMA-3	FELIX	JULIET	ZUMA-1	TRANSCEND	ZUMA-2	ZUMA-5	KarMMa	CARTITUDE
CART construct	Tis-cel	Brexu –cel	Obe-cel	Tisa-cel	Axi-cel	Liso-cel	Brexu-cel	Axi-cel	Ide-cel	Cilta-cel
CRS, %	77	93	75	58	93	42	91	82	76	95
Grade ≥ 3 CRS, %	46	29	3	22	13	2	15	7	6	5
NT, %	40	78	23	21	64	30	63	77	18	17
Grade ≥ 3 NT, %	13	38	7	12	28	10	31	11	3	2

CRS and ICANS

	CRS	Neurologic AEs
Axicabtagene ciloleucel	2 (1-12)	4 (1-43)
Brexucabtagene autoleucel	3 (1-13)	6 (1-32)
Tisagenlecleucel	3 (1-51)	6 (1-359)
Lisocabtagene maraleucel	4 (3-15)	6 (5-15)
Idecabtagene vicleucel	1 (1-27)	2 (1-148)
Ciltacabtagene autoleucel	7 (1-12)	8 (7-10)

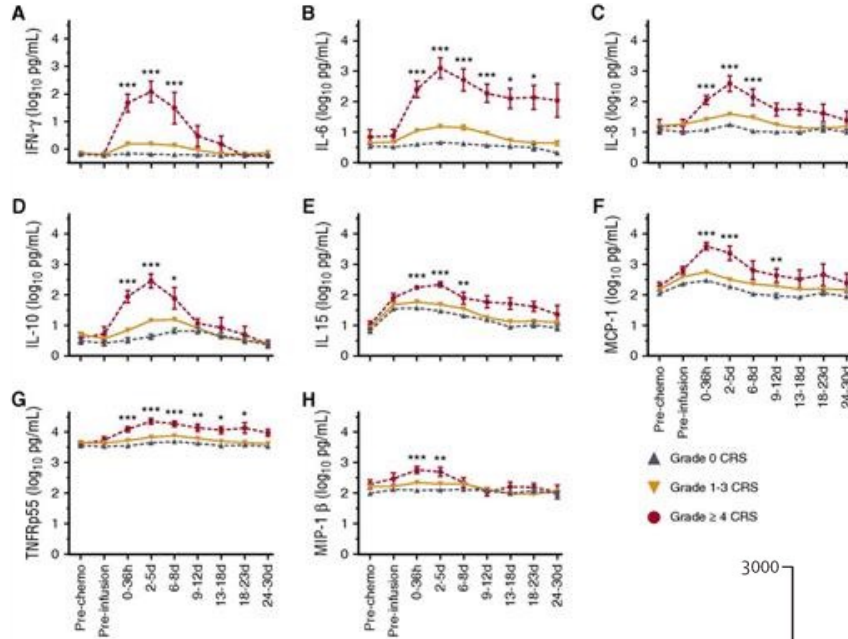
CRS: Pathophysiology

- High fevers, myalgia, nausea, hypotension, hypoxia, etc.
- Very high levels of IL6; IFN-g, modest TNF-a; Mild increases in IL-2
- Severe CRS associated with higher levels of CART19 cells
- IL-6 is produced by myeloid cells
- IL-6 and dexamethasone are the main treatment options for CRS

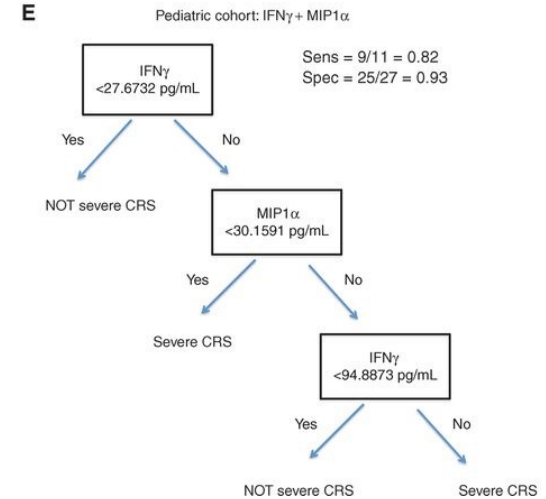


Grupp S.... June C, NEJM 2013

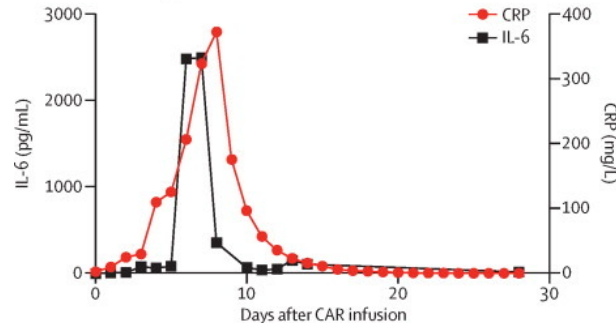
CRS: Pathophysiology – Myeloid Cytokines



Hay K.... Turtle C, *Blood* 2017

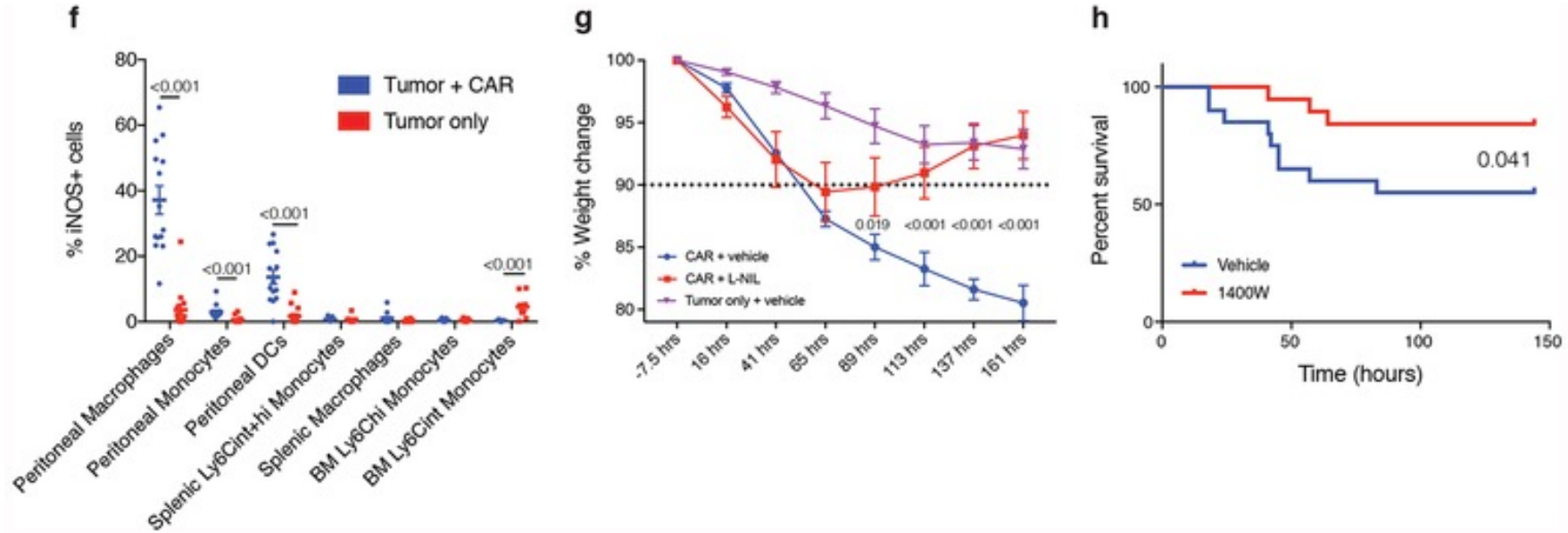


Teachey D... Grupp S, *Cancer Discov* 2015



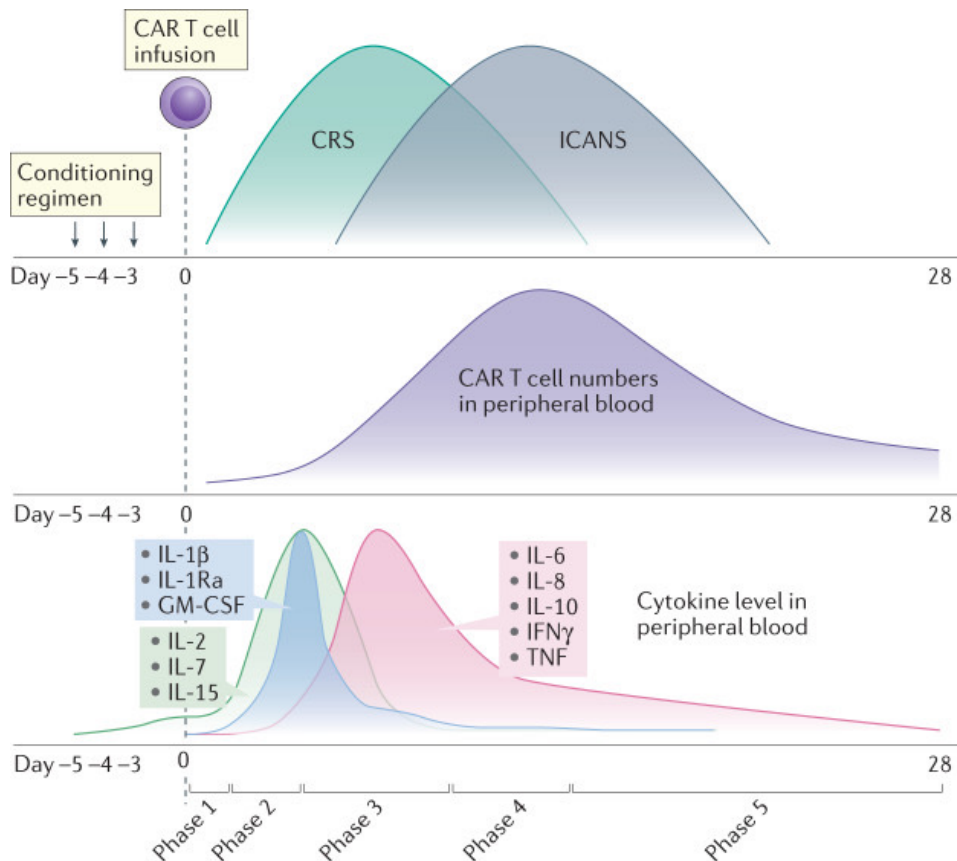
Lee D..... Mackall, *Lancet* 2015

CRS: Pathophysiology – Macrophages are Required



Giavirdis.... Sadelain M, Nat Med 2018

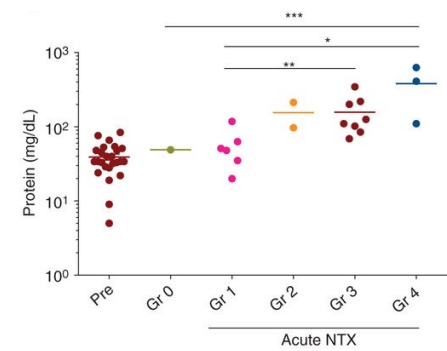
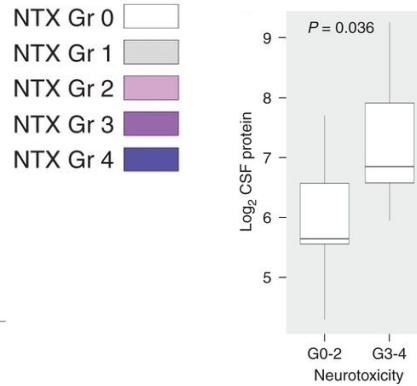
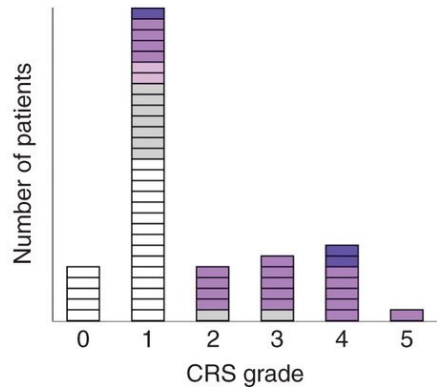
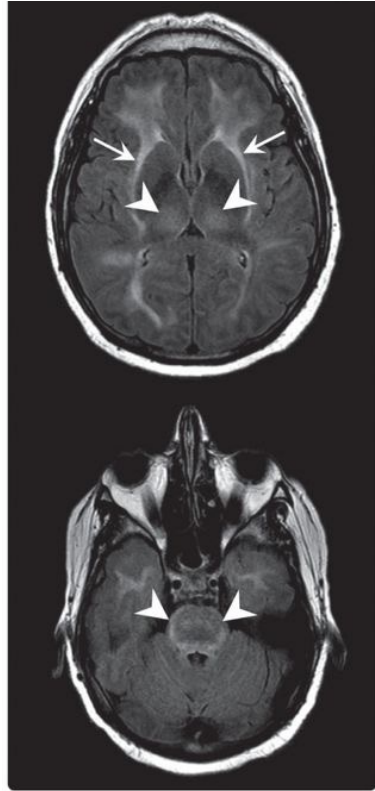
Immune Effector Cell-Associated Neurotoxicity Syndrome



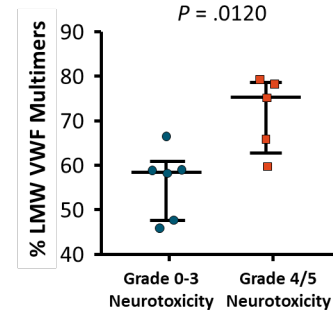
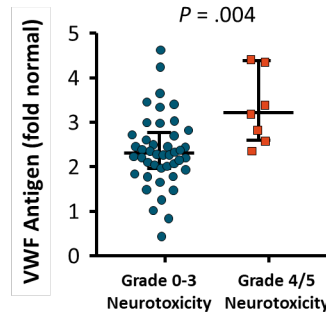
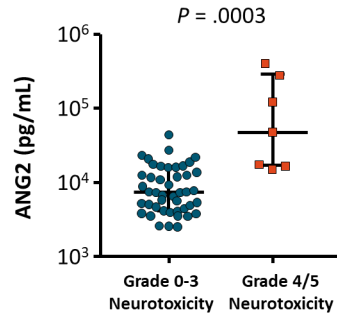
- Alterations in level of consciousness
- Confusion
- Behavioral changes
- Speech abnormalities
- Language abnormalities.
- Seizures
- Risk of diffuse cerebral edema

ASTCT Grading

ICANS: BBB Disruption and Endothelial Activation

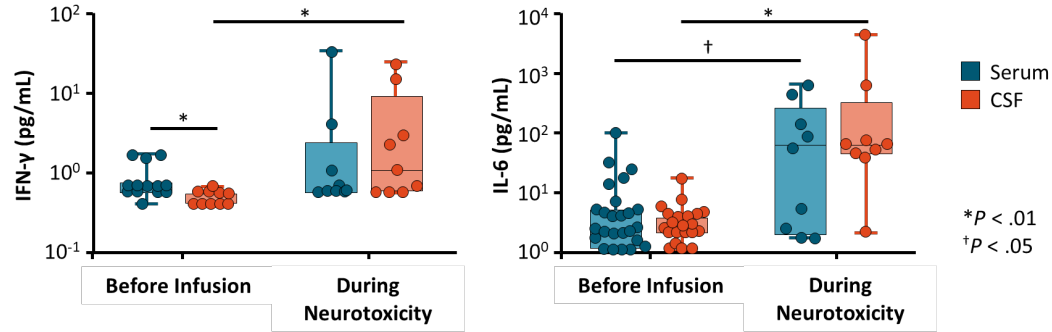


Santomasso B....Brentjens R, Cancer Discov 2018

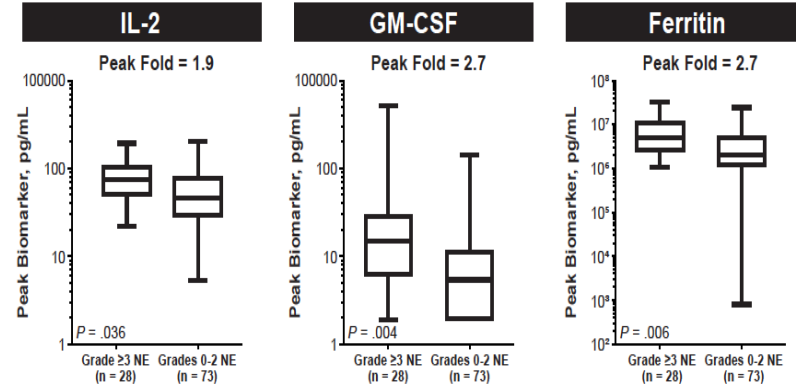


Gust J.... Turtle C, Cancer Discov. 2017

ICANS: Myeloid Cells and Cytokines

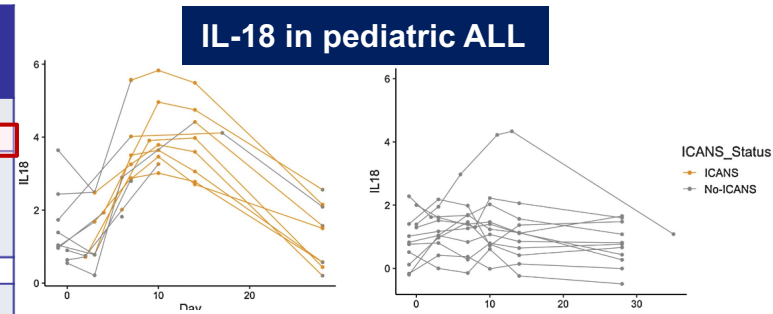


Gust J.... Turtle C, *Cancer Discov.* 2017



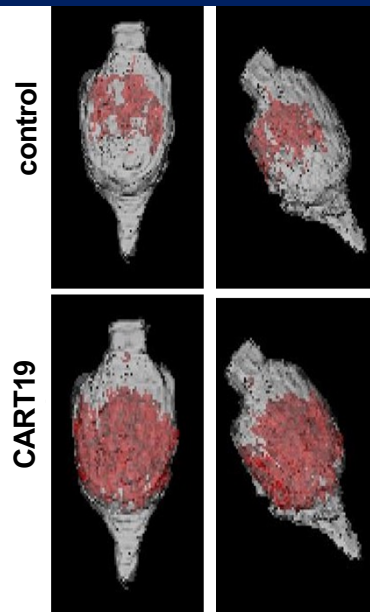
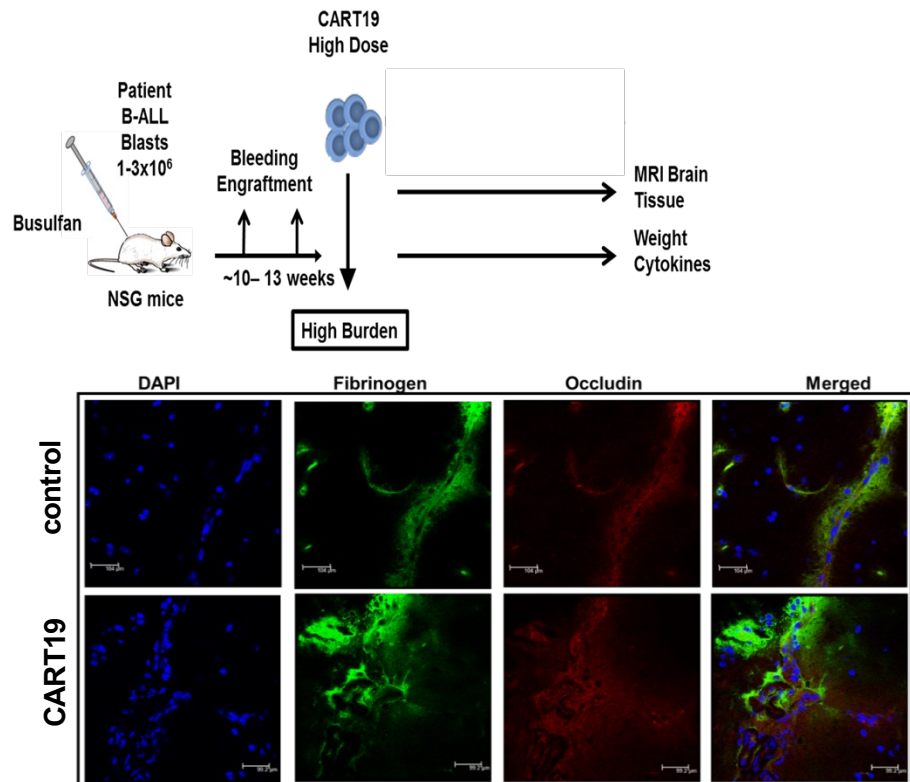
Neelapu S.... Go W, *NEJM* 2017

Cell Populations	NE Grade 0-2 (N = 15) Median cells/mL (Q1, Q3)	NE Grade ≥ 3 (N = 10) Median cells/mL (Q1, Q3)	NE Grade ≥ 3/ Grade 0-2 Ratio
CD45+ (leukocytes)	166 (18, 1504)	570 (170, 1700)	3.4
CD14+ (myeloid cells)	18 (11, 436)	306 (125, 1063)	17
CAR+ T cells			
CD3+	35 (6, 324)	79 (47, 81)	2.3
CD4+	26 (3, 213)	52 (34, 65)	2
CD8+	17 (1, 85)	15 (10, 34)	0.9
CD4/CD8 T cell ratio	2 (1, 5)	3 (2, 5)	1.6
CAR+ CD4/CAR CD8 T cell ratio	9 (8, 53)	17 (11, 22)	2



Diorio C.... Teachy D, *Clin Cancer Res* 2022

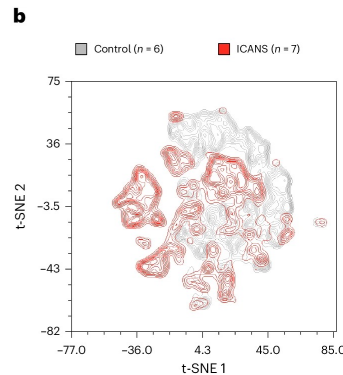
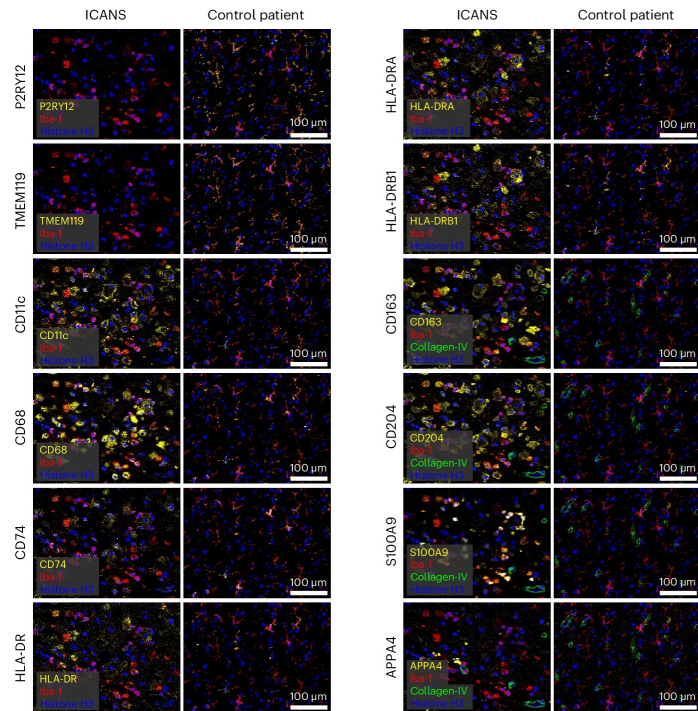
ICANS: BBB Disruption and Endothelial Activation



CART19 in humanized ALL PDX model:

- Brain inflammation
- BBB disruption
- Microglial activation

ICANS: BBB Disruption and Endothelial Activation

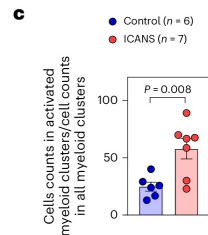


CART19 in mouse models:

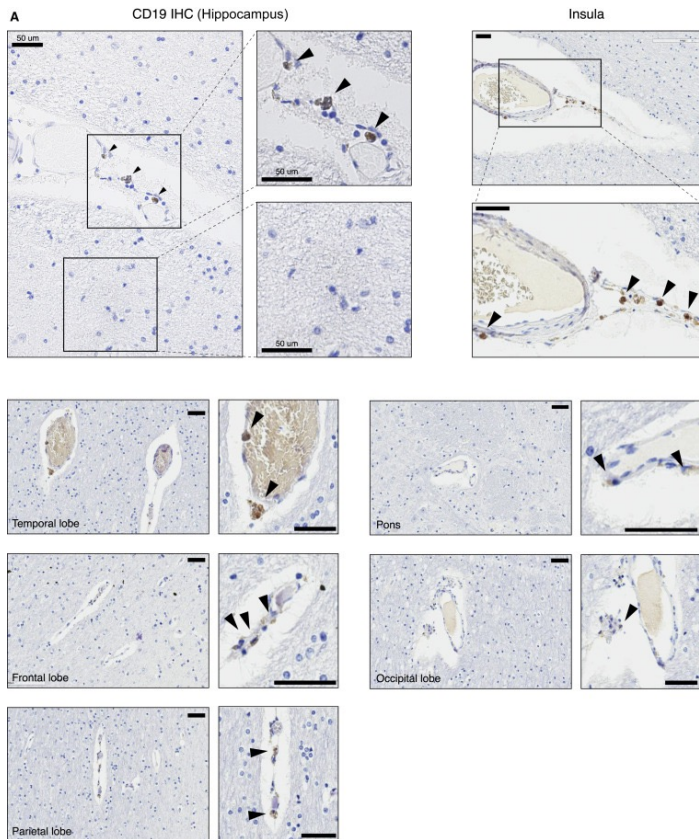
- Microglial activation
- TGF β mediated
- Activated MAPK pathways
- Ameliorated by Tak1 deletion

Patients with ICANS

- Microglial activation
- Shift from resting state



ICANS: Target Expression on the Brain



CD19 Expression on Human Brain/Pericytes

- CD19 expression on murine and human brain
- May explain toxicity following CART19 cell therapy
- Does not explain neurotoxicity after non CD19 CART cell therapy

CRS and ICANS: Risk Factors

CAR construct

- CD28 costimulated CART (axi-cel and brexu-cel)
- High affinity scFv (Obe-cel < other CART19)
- Higher CART cell dose

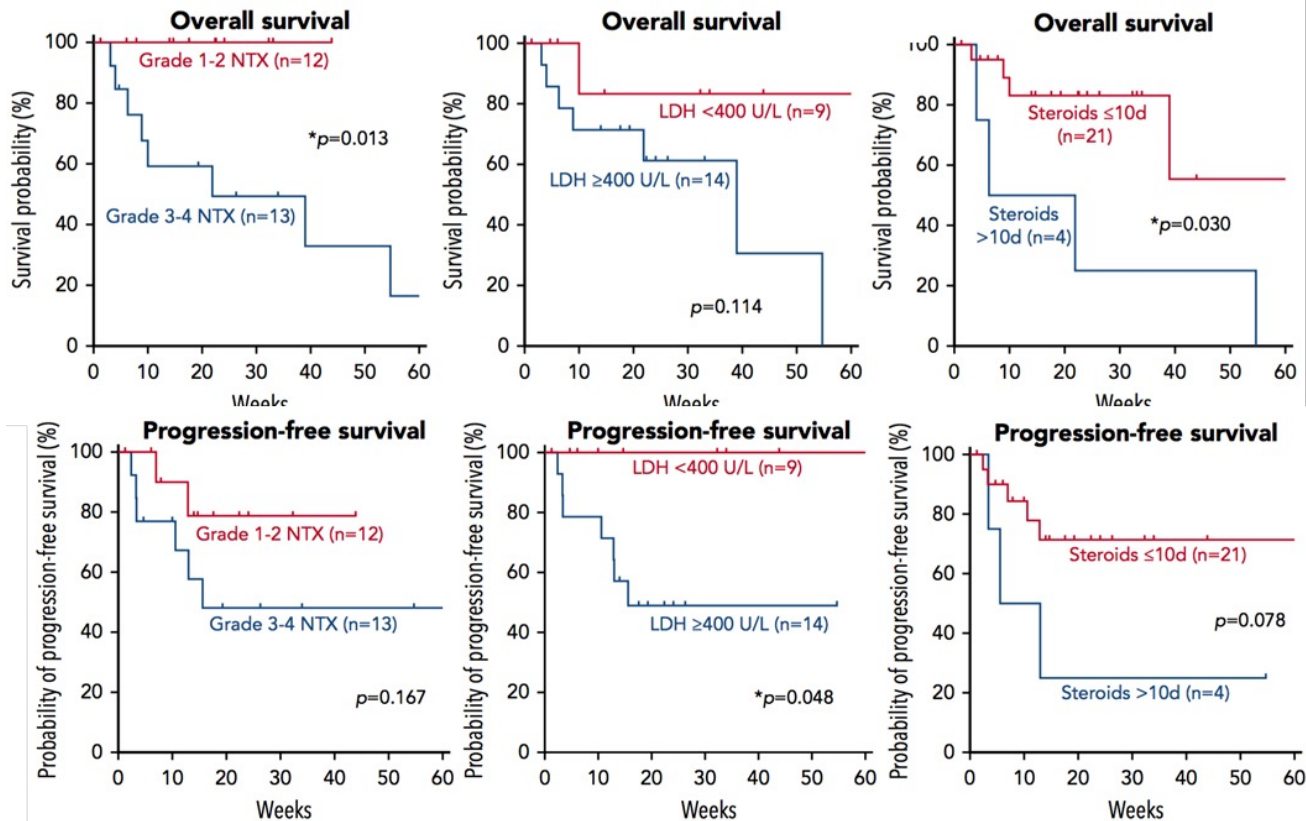
Disease

- Disease (ALL>MCL>DLBCL)
- High disease burden

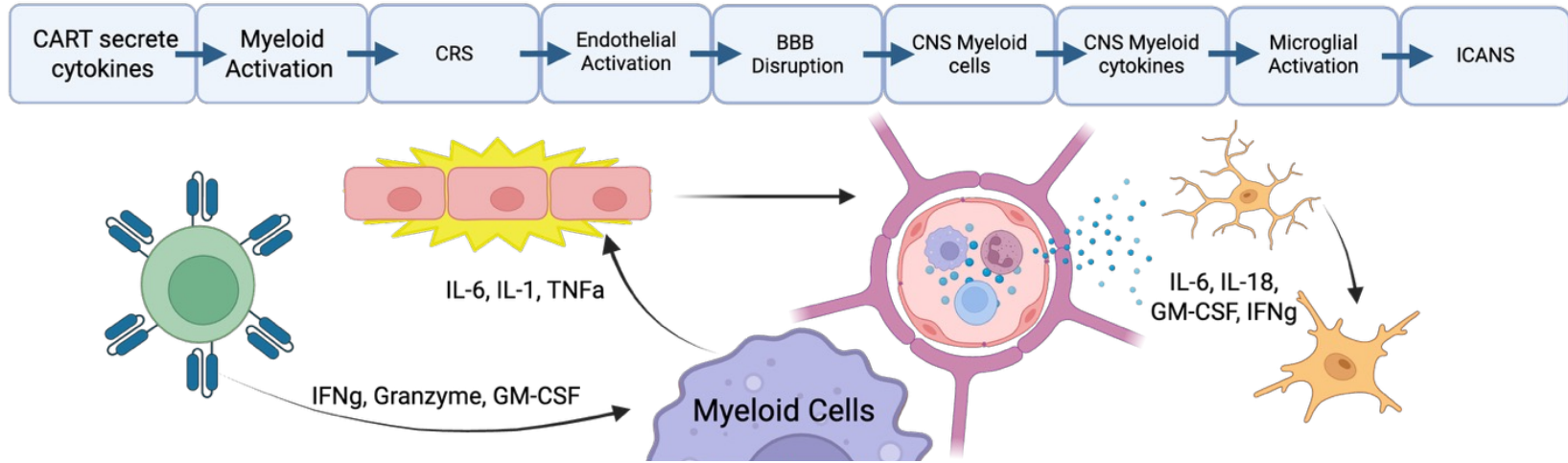
Host

- Early onset CRS (ICANS)
- Pre-existing neurological diseases (ICANS)
- Increased lymphodepletion
- Highly inflammatory state

Neurotoxicity: Implication on Overall Survival?

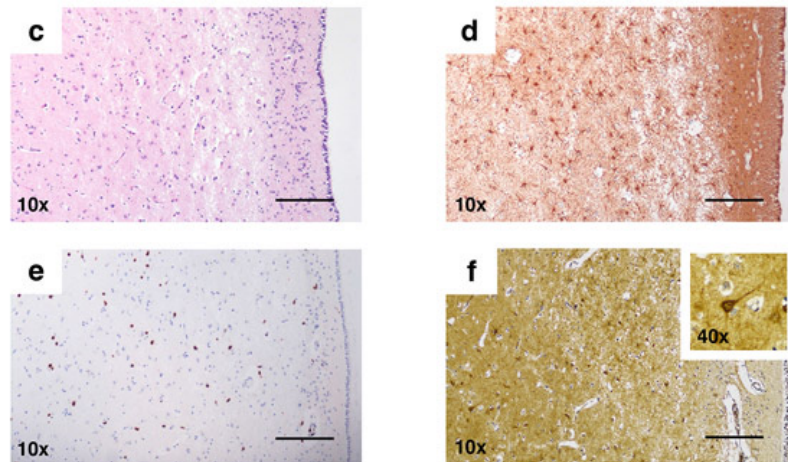
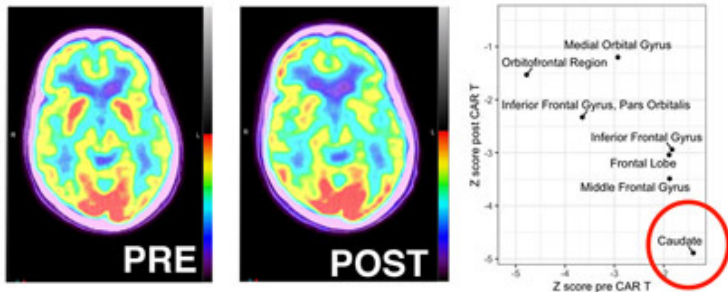


Neurotoxicity: Pathophysiology



CART Associated Parkinsonism

- Unresponsive bradykinesia, postural instability, hypomimia, hypophonia, micrographia, and impaired short-term memory.
- Weeks to months after BCMA directed T cell therapy
- CARTITUDE-1: 6%
- KarMMA-2: 2 cases
- Off tumor targeting of BCMA express



Tumor Inflammation Associated Neurotoxicity (TIAN)

- Proposed as a separate mechanism
- Mostly after CART19
- About 20% following CNS lymphoma treated with CART19
- Correlated with higher response rates to CART19 therapy (90% vs 50%)

CRS and ICANS: Management

Standard of Care

- Tocilizumab
- Dexamethasone

➤ CAR Engineering Strategies

Refractory CRS/ICANS

- **Cytokine blockade**
 - IL-1
 - IFN- γ
 - GM-CSF
 - TNF
 - IL-5
- **Small molecules to modulate T cell response**
 - Ibrutinib/BTK inhibitors
 - Dasatinib
 - JAK/STAT inhibitors

CRS and ICANS: Earlier Interventions

- ZUMA-1 cohort 4 (N=41):
 - **Steroid** intervention **starting at Grade 1 NE/CRS** when no improvement after 3 days of supportive care
 - **Grade ≥ 3 CRS (2%) and NE (17%)** (vs. 11% and 32% of pts, respectively, in ZUMA-1)
 - Tocilizumab use 76%
- ZUMA-1 cohort 6 (N=40):
 - **Prophylactic steroid** intervention on days 0-3
 - **Grade 2 CRS (45%), Gr 3 CRS (0%) and $\geq$ Gr3 NE (13%)**
 - Tocilizumab use 58%

Original AE Mgmt		AE Grade			
		1	2	3	4
CRS		Tocilizumab: No Corticosteroid: No	Tocilizumab: Yes* Corticosteroid: Yes*	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes
	NE	Tocilizumab: No Corticosteroid: No	Tocilizumab: Yes Corticosteroid: No	Tocilizumab: Yes Corticosteroid: Yes†	Tocilizumab: Yes Corticosteroid: Yes
Cohort 6 AE Mgmt	CRS	Tocilizumab: Yes‡ Corticosteroid: Yes§	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes, HD
	NEs	Tocilizumab: No Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes	Tocilizumab: Yes Corticosteroid: Yes, HD	Tocilizumab: Yes Corticosteroid: Yes, HD

Table III. Incidence, severity, onset, and duration of CRS and NEs.

TEAE	Cohort 4 (N = 41)
CRS	
Any, n (%)	38 (93)
Worst grade 1, n (%)	13 (32)
Worst grade 2, n (%)	24 (59)
Worst grade 3, n (%)	1 (2)
Worst grade 4, n (%)	0
Worst grade 5, n (%)	0
Median (range) time to onset of any grade CRS, days	2.0 (1.0–8.0)
Median (range) duration, days	6.5 (2.0–16.0)
NEs	
Any, n (%)	25 (61)
Worst grade 1, n (%)	14 (34)
Worst grade 2, n (%)	4 (10)
Worst grade 3, n (%)	7 (17)
Worst grade 4, n (%)	0
Worst grade 5, n (%)	0
Median (range) time to onset of any grade NE, days	6.0 (1.0–93.0)
Median (range) duration, days	8.0 (1.0–144.0)

CRS, cytokine release syndrome; NE, neurologic event; TEAE, treatment-emergent adverse event.

CRS and ICANS: Earlier Interventions

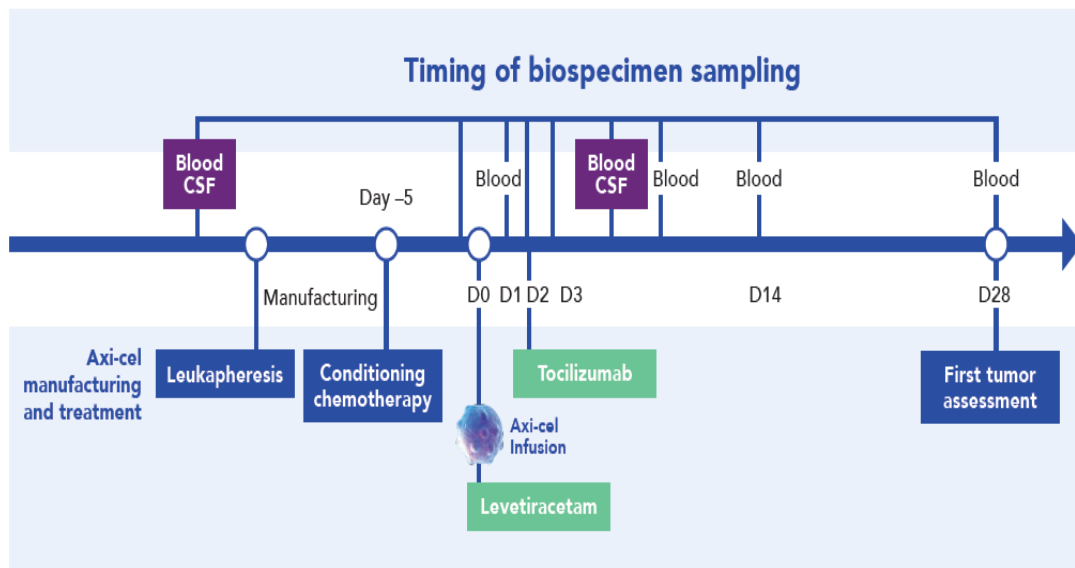


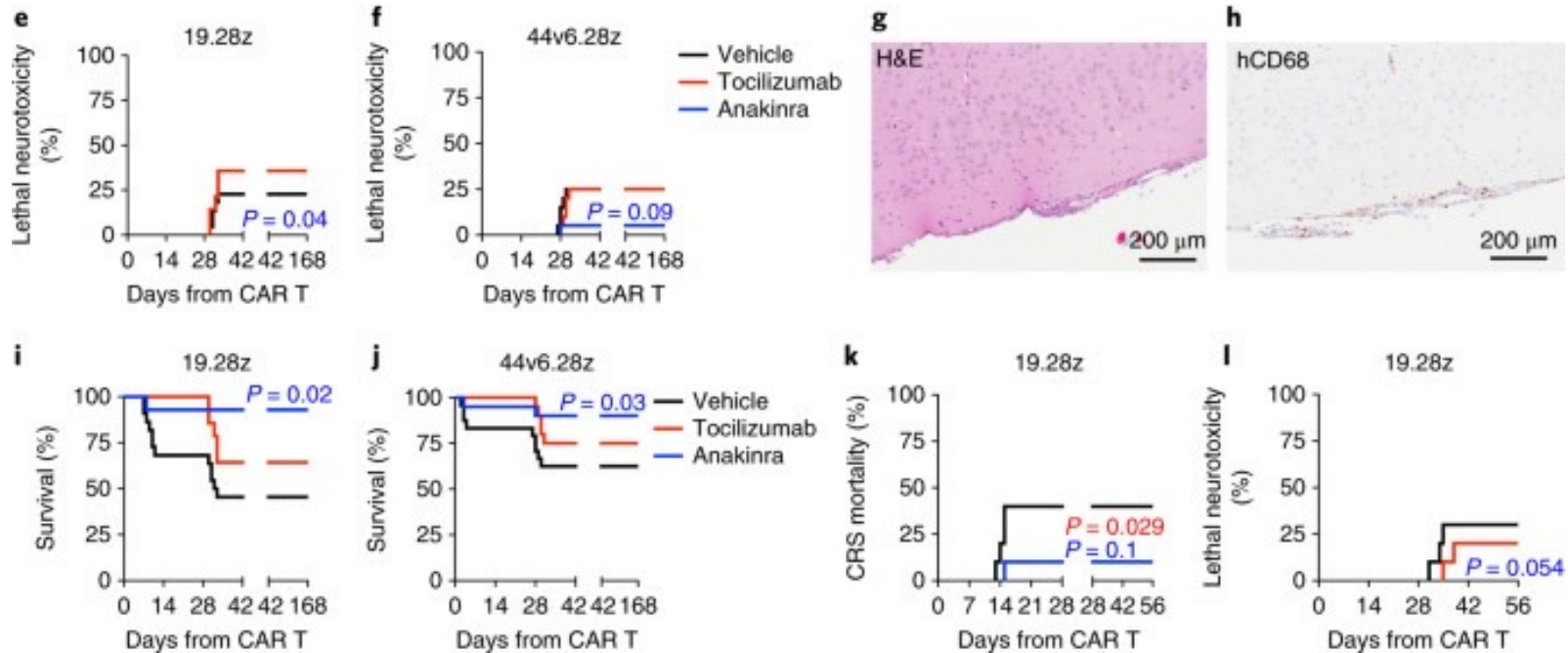
Table 3

Incidence, Severity, Onset, and Duration of CRS and NEs

TEAE	Cohort 3 n = 38
CRS	
Any, n (%)	35 (92)
Worst Grade 1, n (%)	13 (34)
Worst Grade 2, n (%)	21 (55)
Worst Grade 3, n (%)	0
Worst Grade 4, n (%)	1 (3)
Worst Grade 5, n (%)	0
Median time to onset of any-grade CRS, days (IQR)	2.0 (2.0–4.0)
Median duration, days (IQR)	6.5 (5.0–11.0)
NEs	
Any, n (%)	33 (87)
Worst Grade 1, n (%)	9 (24)
Worst Grade 2, n (%)	8 (21)
Worst Grade 3, n (%)	14 (37)
Worst Grade 4, n (%)	1 (3)
Worst Grade 5, n (%)	1 (3)
Median time to onset of any-grade NE, days (IQR)	7.0 (5.0–8.0)
Median duration, days (IQR)	15.0 (6.0–34.0)

CRS indicates cytokine release syndrome; IQR, interquartile range; NE, neurologic event; TEAE, treatment-emergent adverse event.

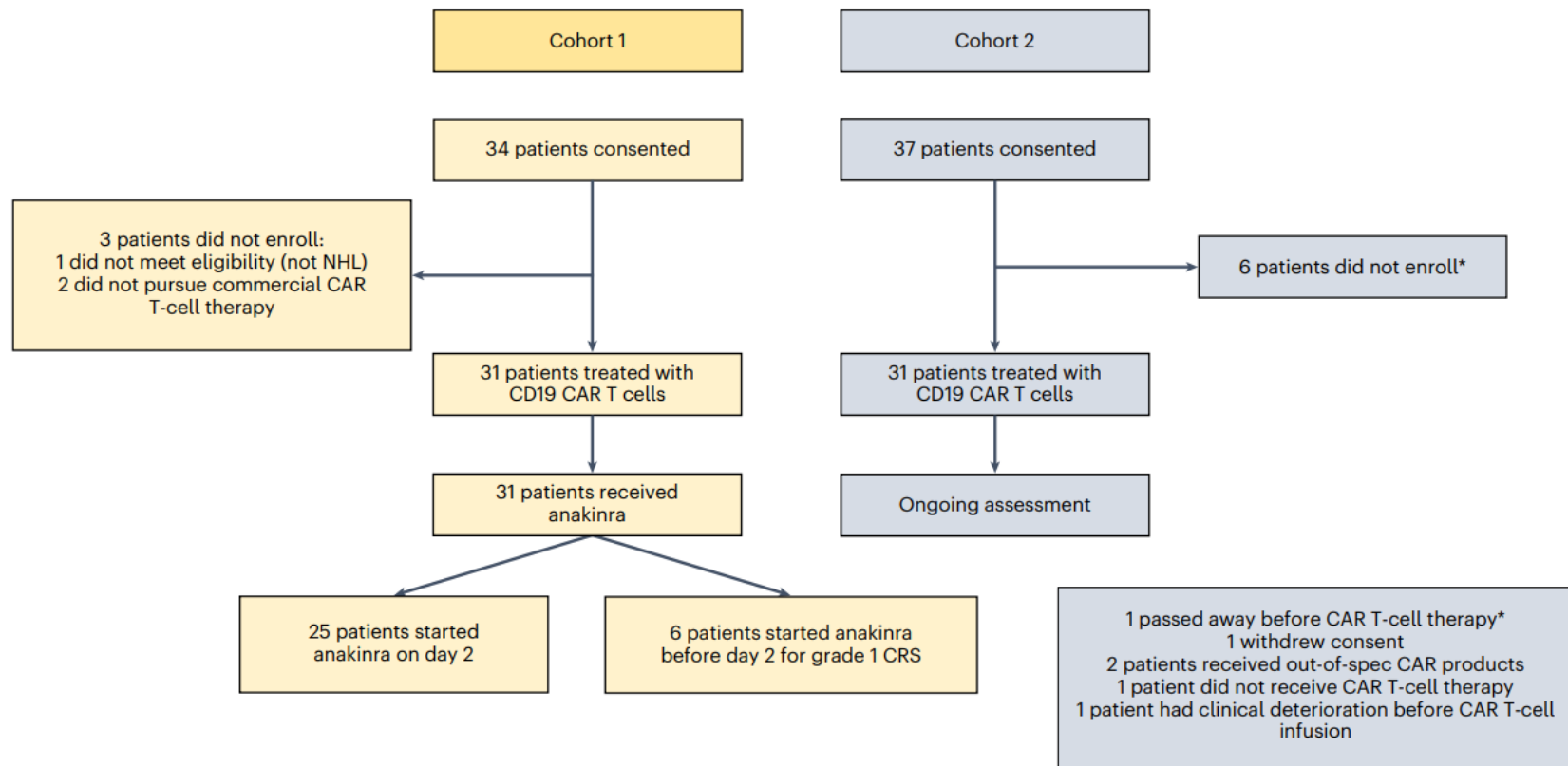
IL-1: Prevents Neuroinflammation in a Humanized Mouse Model



Summary:

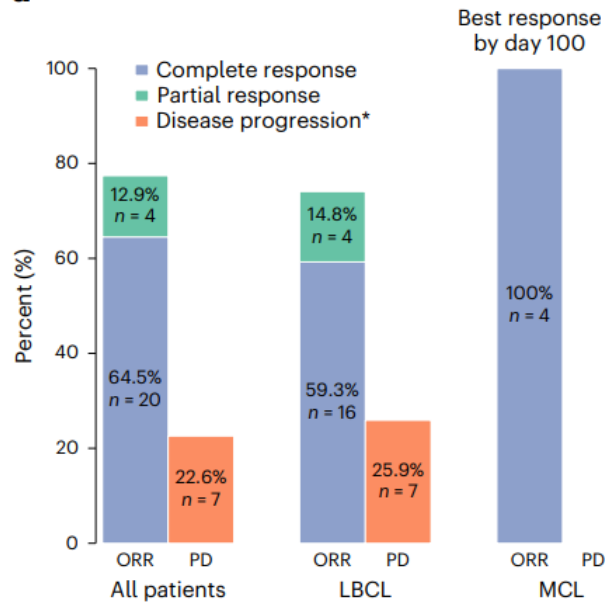
- CD44v6 CART cells in humanized model
- Neurotoxicity developed late during CART

IL-1: Phase II Trial of Anakinra Combination with CART Cells

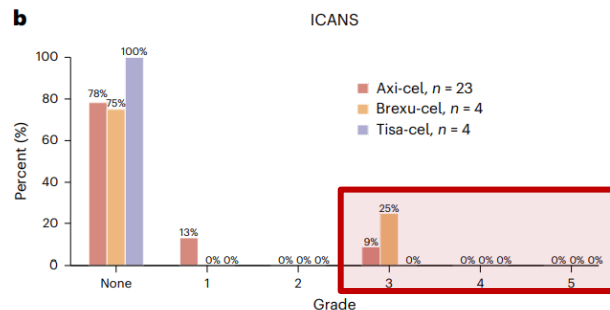


IL-1: Phase II Trial of Anakinra Combination with CART Cells

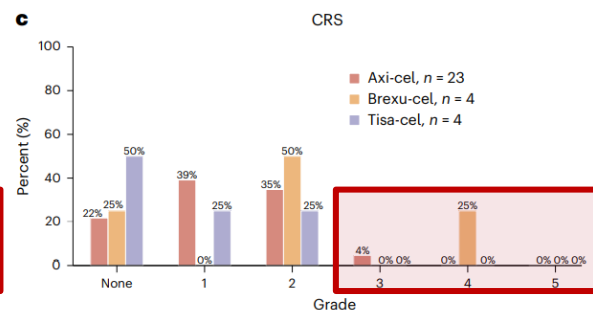
a



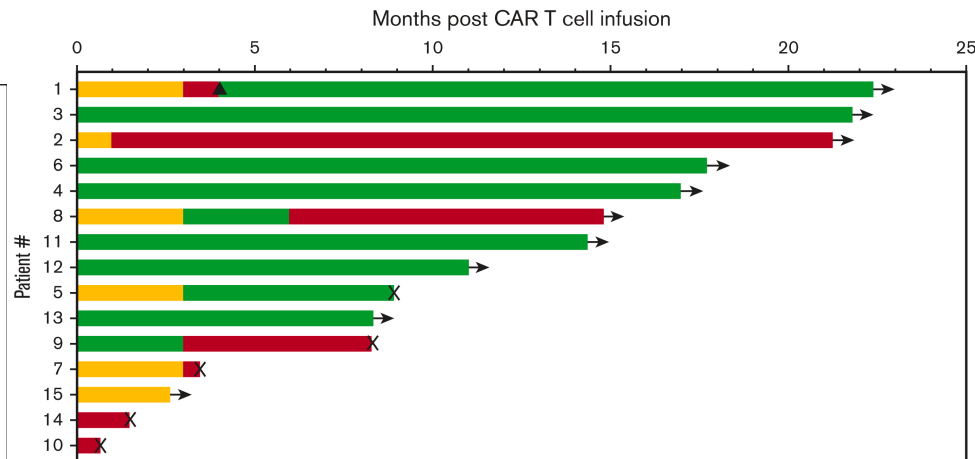
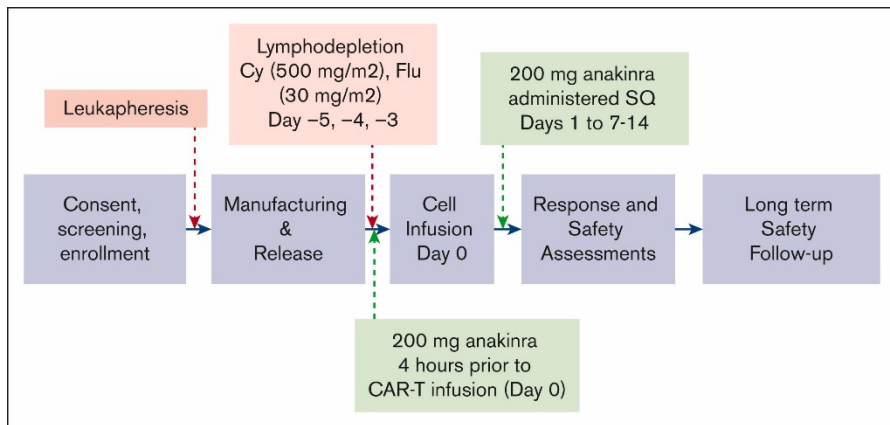
b



c



IL-1: Phase II Trial of Anakinra Combination with CART Cells

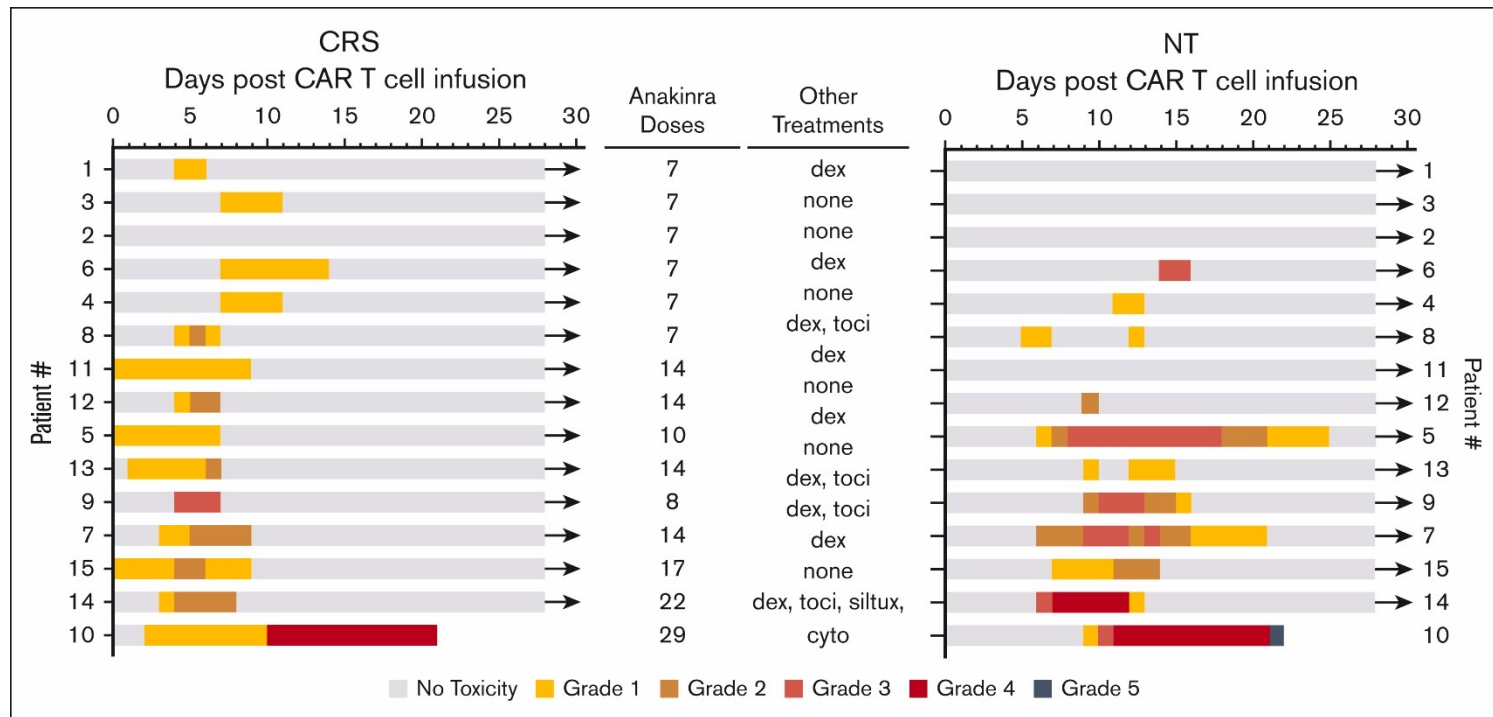


Month 1	N = 15*	PFS at 6 months (95% CI)	58.2% (29.4 – 78.7)
ORR	13/15 (87%)	PFS at 12 months (95% CI)	42.4% (16.9 – 66.1)
CR	7/15 (47%)	OS at 6 months (95% CI)	79.4% (48.8 – 92.9)
PR	6/15 (40%)	OS at 12 months (95% CI)	64.2% (33.9 – 83.4)

*two patients included were deceased prior to M1 assessments.

■ CR ■ PR ■ PD → In follow-up ▲ Retreatment ✕ Death

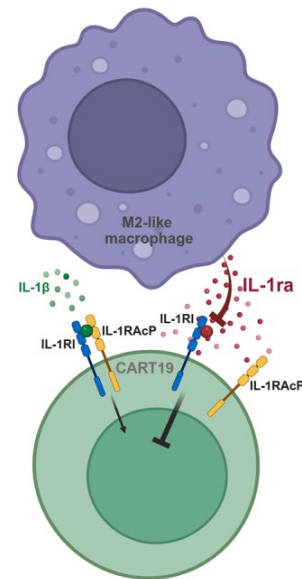
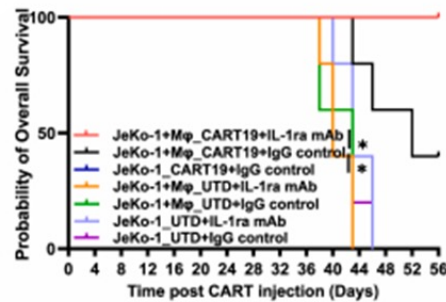
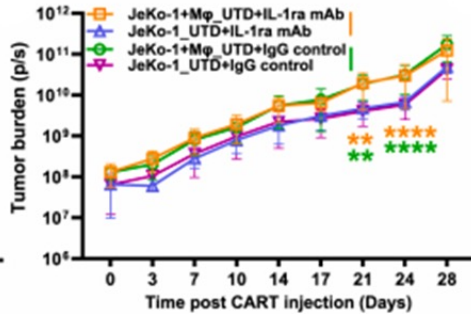
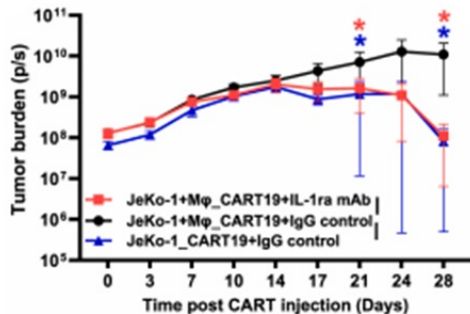
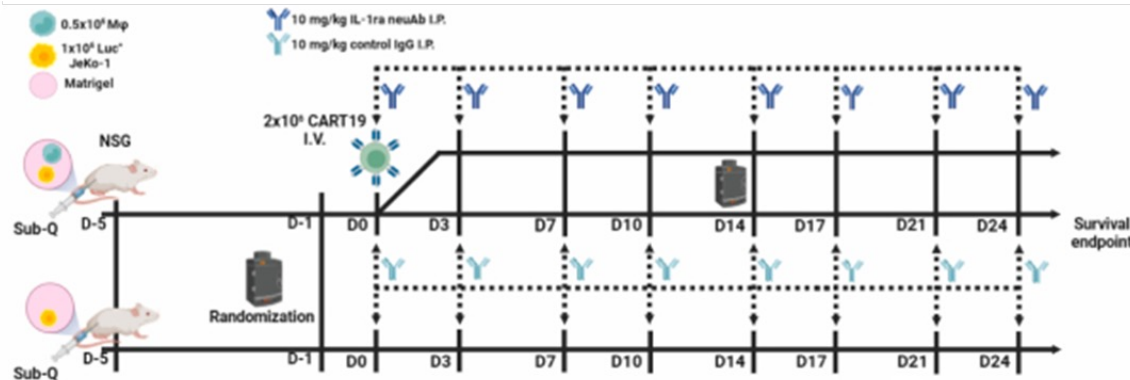
IL-1: Phase II Trial of Anakinra Combination with CART Cells



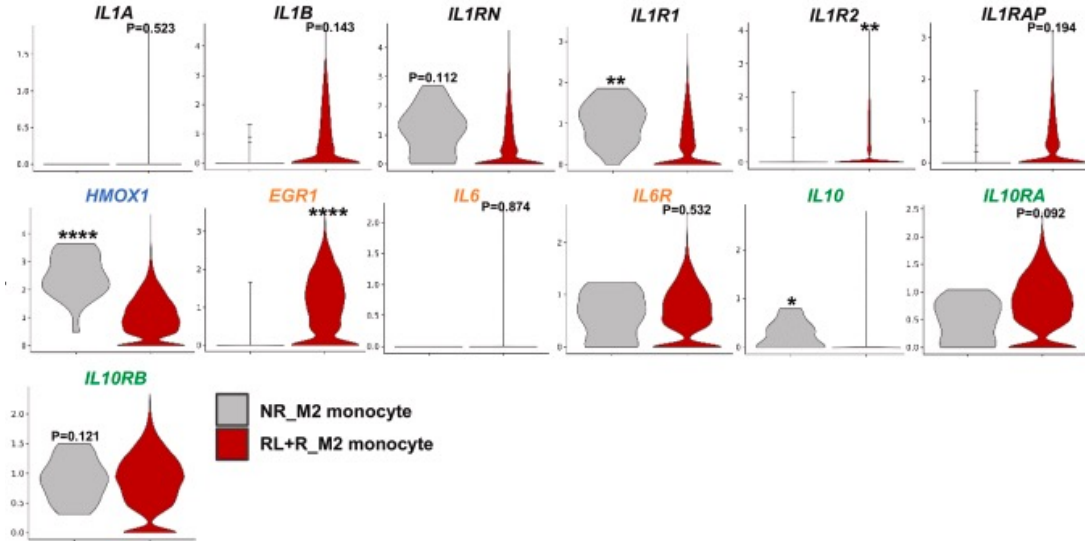
IL-1: IL-1 Pathway Blockade May Impair CART Cell Activity

CART19 in xenograft mouse models

- Continuous IL-1 blockade impairs IL-1 β mediated CART19 antigen specific proliferation
- Continuous IL-1 blockade impairs CART19 antitumor activity
- Continuous IL-1 blockade reduced overall survival



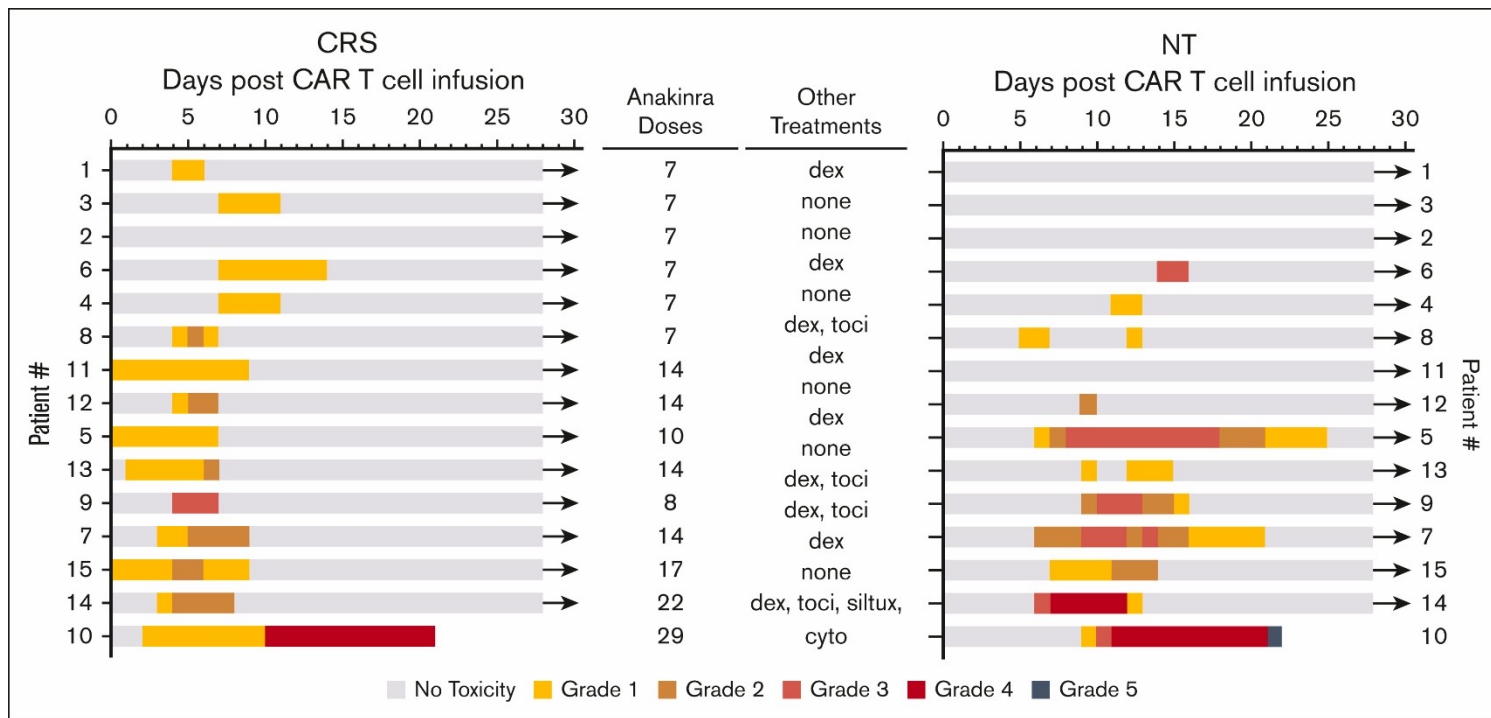
IL-1: IL-1 Pathway Blockade May Impair CART Cell Activity



MCL patients treated with brexu-cel on the ZUMA-2

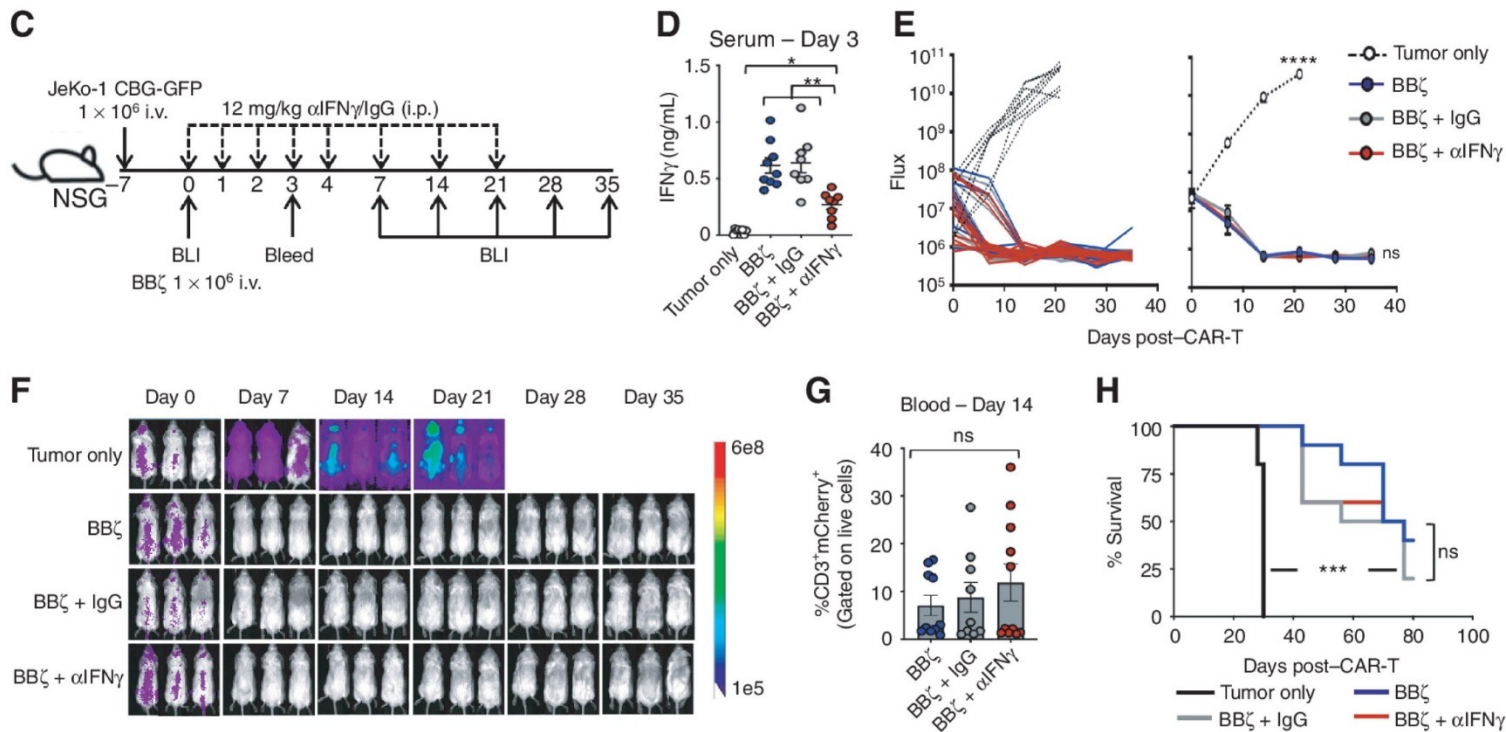
- Higher IL-1ra in baseline monocytes from non responders
- Decreased IL-1 signaling in baseline CART19 cell in non responders

IL-1: Phase II Trial of Anakinra Combination with CART Cells

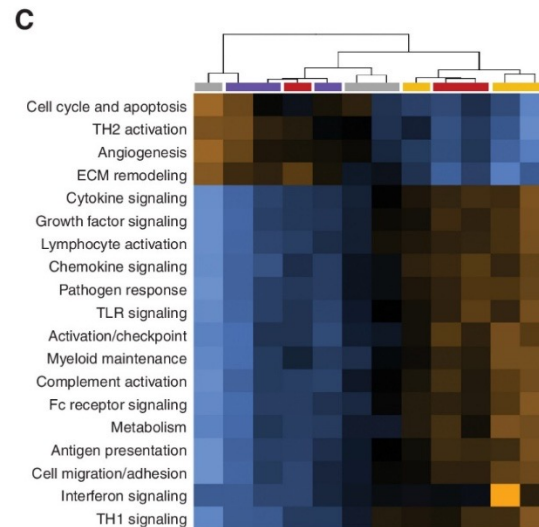
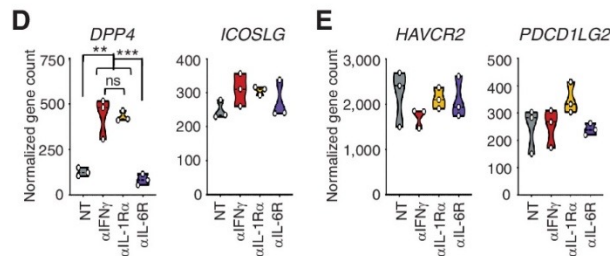
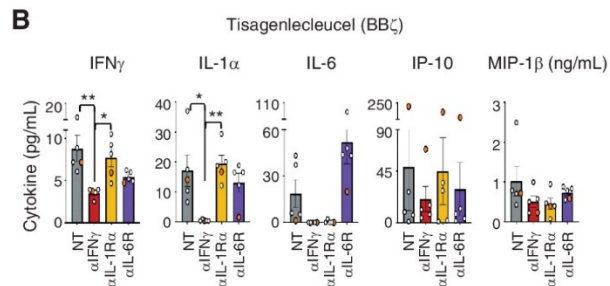
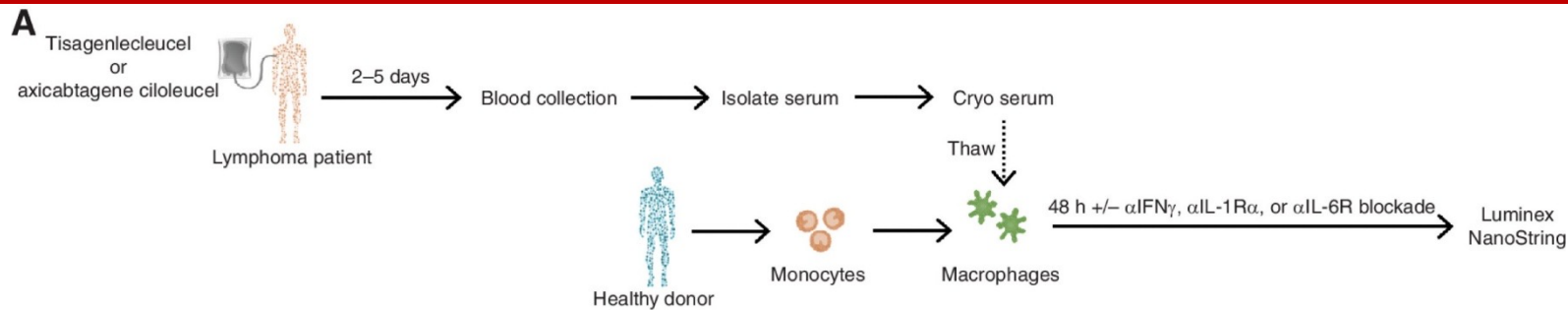


Single-cell RNA sequencing of immune cells identified IFN- γ as a potential mechanism for escape

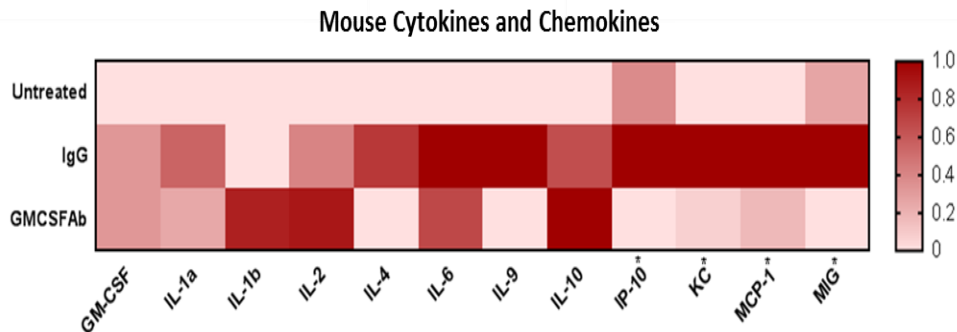
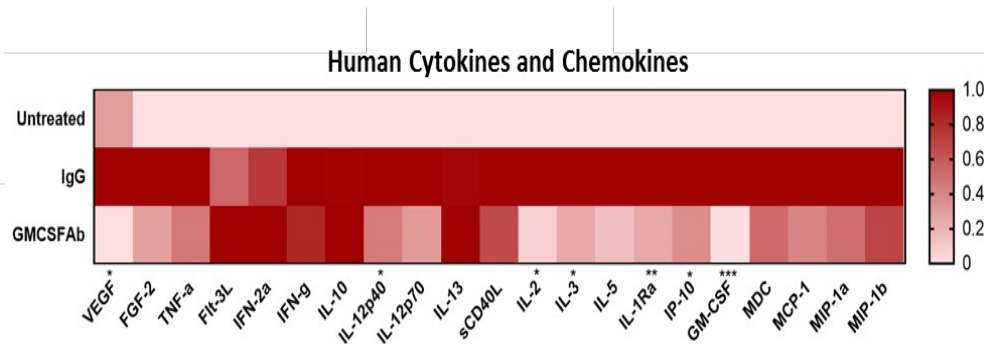
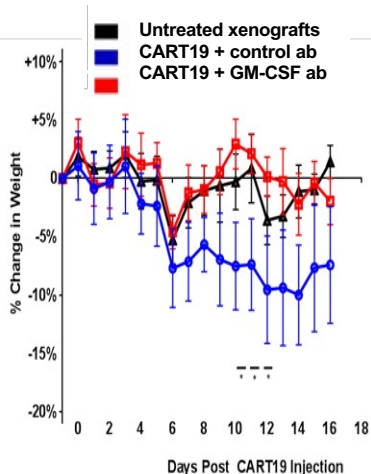
IFN- γ : Blockade Does Not Impair CART Cell Activity



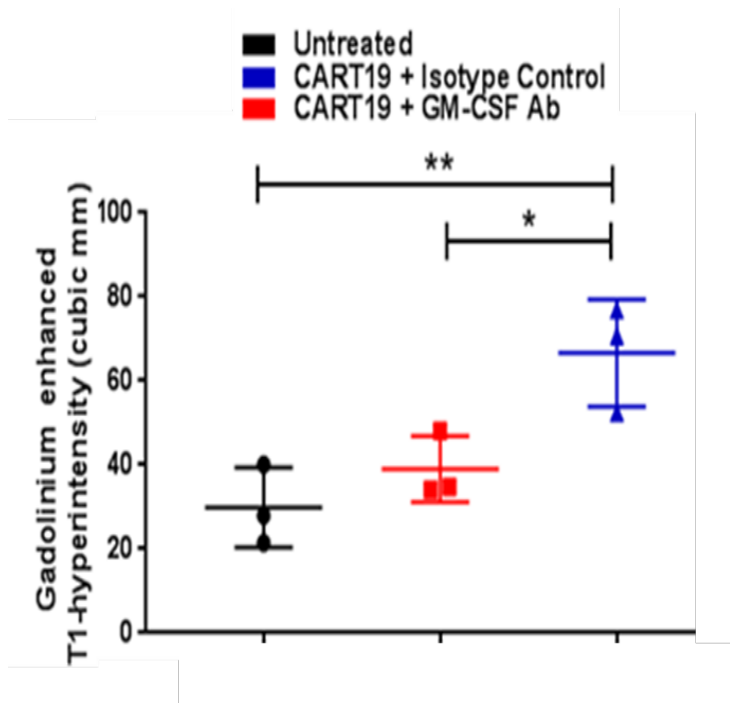
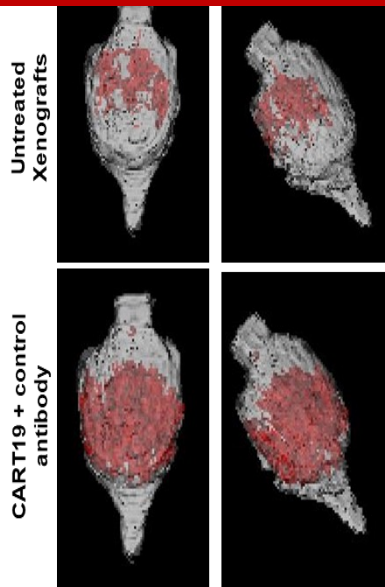
IFN- γ : Blockade Reduces Macrophage Activation



GM-CSF: Neutralization in vivo Prevents CRS After CART19 Therapy

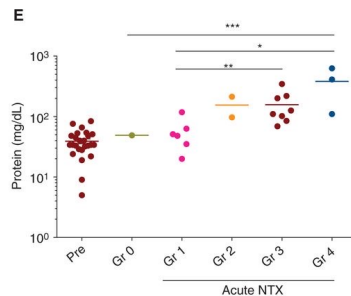
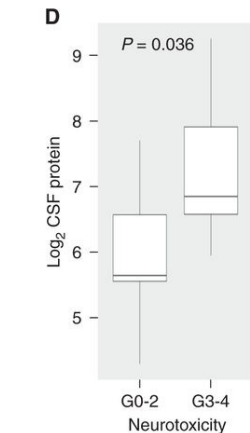


GM-CSF: Neutralization in vivo Prevents CRS After CART19 Therapy

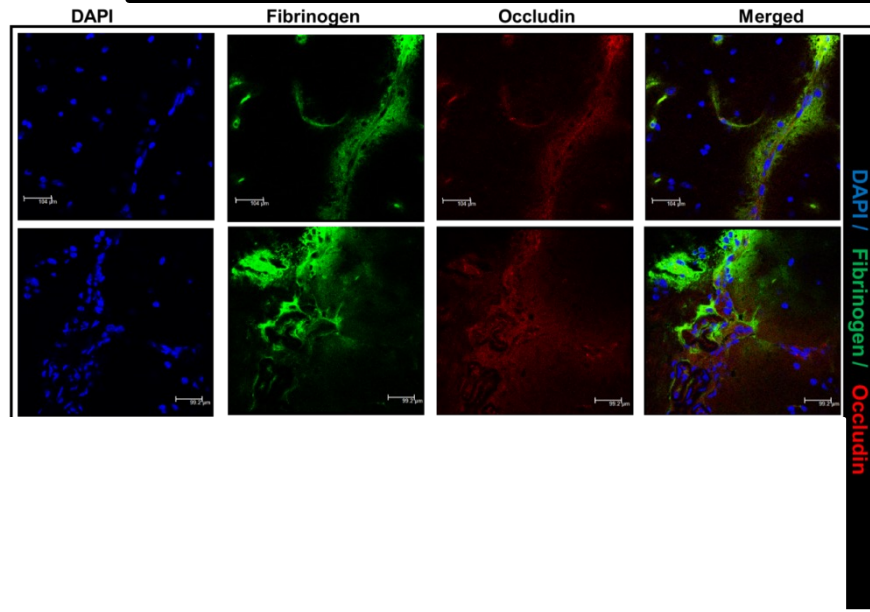


GM-CSF: Neutralization Prevents Blood Brain Barrier Disruption After CART19 Therapy

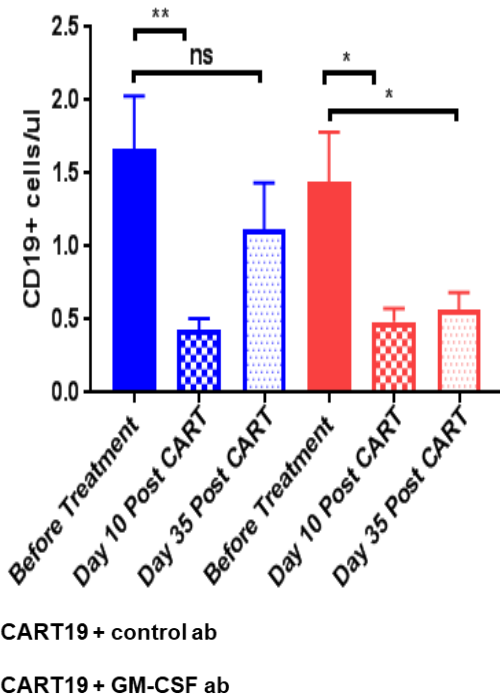
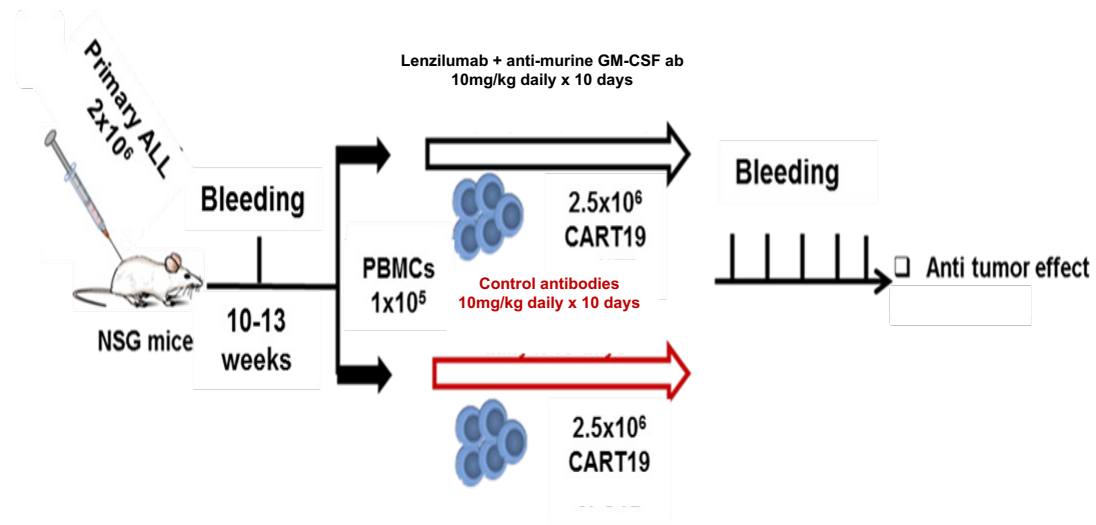
CART Toxicity – Disruption of BBB



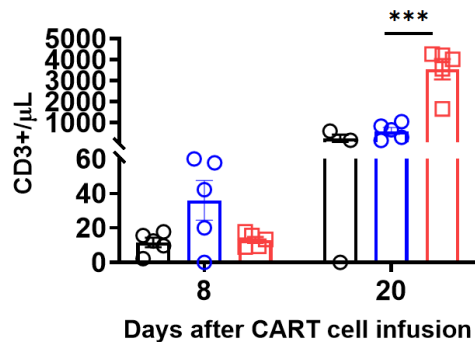
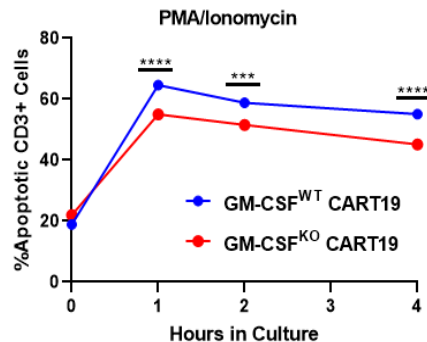
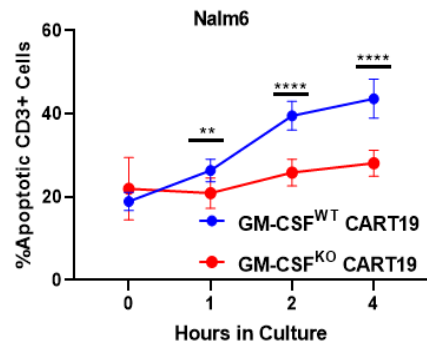
CART Toxicity Model – Xenografts



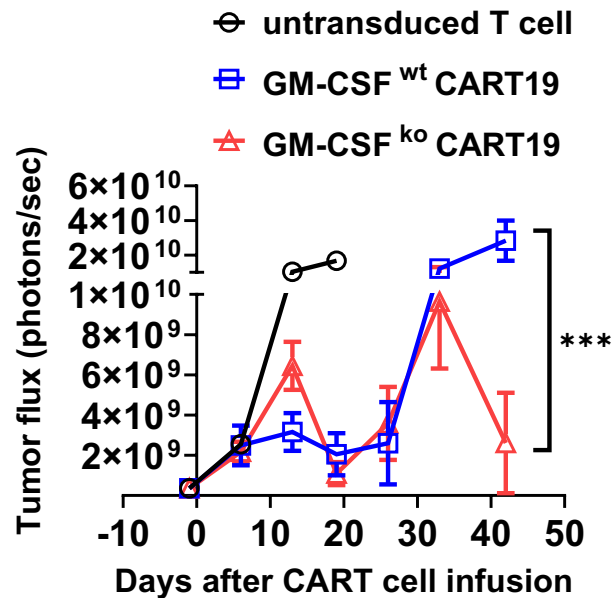
GM-CSF: Neutralization Enhances CART Cell Effector Function in a Humanized Patient Derived Xenograft Model



GM-CSF: Disruption Reduces Early CART Cell Activation and Enhances Expansion



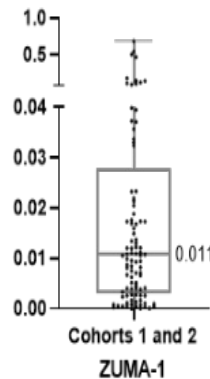
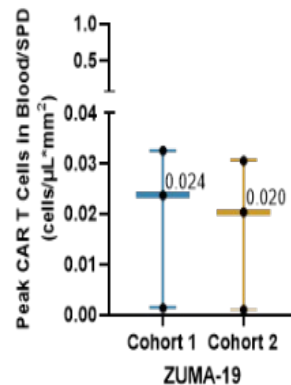
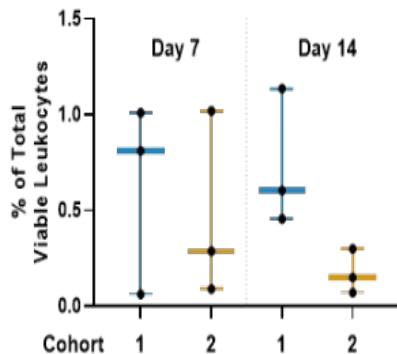
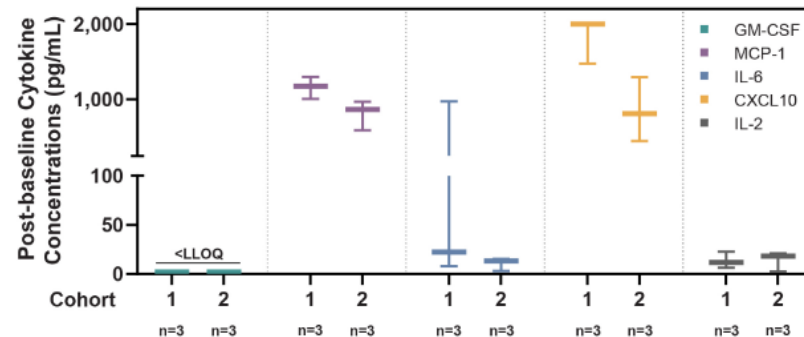
⊖ Untransduced T cell
⊖ GM-CSF^{WT} CART19
⊖ GM-CSF^{KO} CART19



ZUMA-19: GM-CSF Neutralization in Combination with Axi-Cel CART19 in Patients with Lymphoma

- 6 patients treated on two cohorts
- Phase I is reported
- Safety of combination
- Cytokine/CART correlatives

Figure: Post-baseline Cytokine Concentrations in Patients Treated With Axi-cel Plus Lenzilumab 600 mg (Cohort 1) or 1,800 mg (Cohort 2)



GM-CSF^{k/o} CART Cell Therapy in The Clinic

Table 1. Characteristics of the treated patients. * details provided in abstract.							
Pt #	Type	GM-CSF/TCR	IFNG(IL6) (pg/mL)	Response	CRS grade	Neurotoxicity	Tocilizumab
1	DCB-CL	WT	2.63(UD)	NR	None	None	No
2	MM	KO	3.3(1.5)	CR	None	None	No
3	ALL	WT	5.48(3.15)	CR	None	None	No
4	NHL	KO	20.21(6.43)	CR	None	None	No
5	MM	WT	50.85(97.41)	CR	1	None*	No
6	ALL	WT	124.89(2.93)	CR	2	None	No
7	MM	KO	1343.21(4.76)	CR	2	None	No
8	CLL	WT	2014.2(49.85)	CR	3	None	No
9	ALL	WT	2979.29(16.34)	CR	3	None	No
10	ALL	WT	3812.54(8.56)	CR	3	None	No
11	ALL	WT	4118.03(16.36)	CR	2	None	No

TNF Blockade in CART Cell Toxicity

- **Three patients with MM received etanercept for severe CRS post BCMA-CART**
- **One patient with ALL treated with etanercept for severe CRS**
- **Lack of preclinical studies**
- **Not recommended to date**

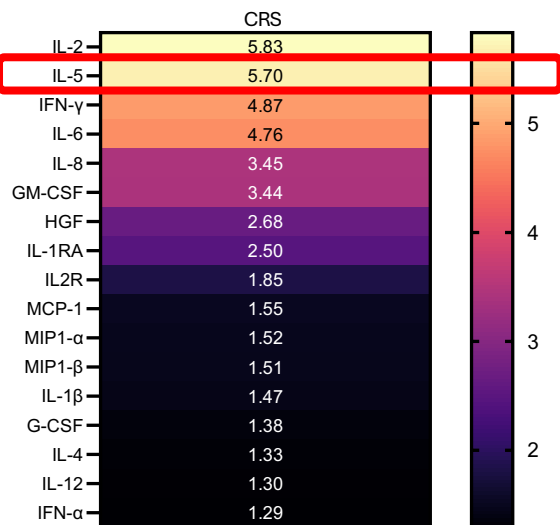
IL-5: Associated with CART Toxicities

CTL019 UPCC #13413

n=24 LBLC, 14 FL
(Schuster et al., 2017, NEJM)

Median of [peak_cytokine] in all grades CRS

Median of [peak_cytokine] in NO CRS

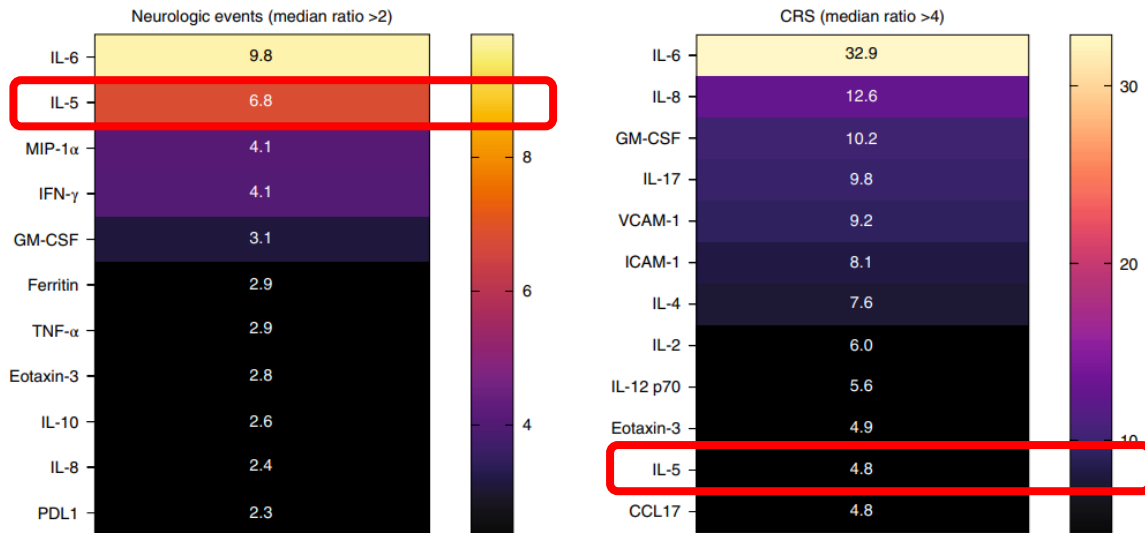


ZUMA-12

n=40 high-risk LBCL
(Neelapu S. et al., 2022, Nature Medicine)

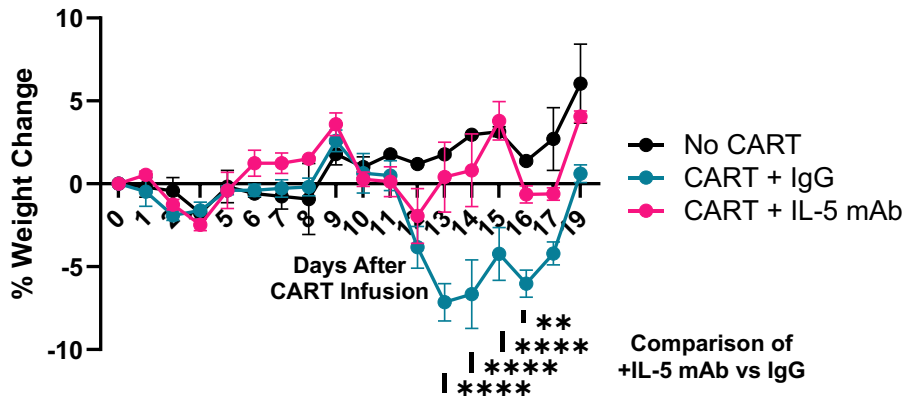
Median of [peak_cytokine] in grade ≥ 3 CRS/ICANS

Median of [peak_cytokine] in grade < 3 CRS/ICANS

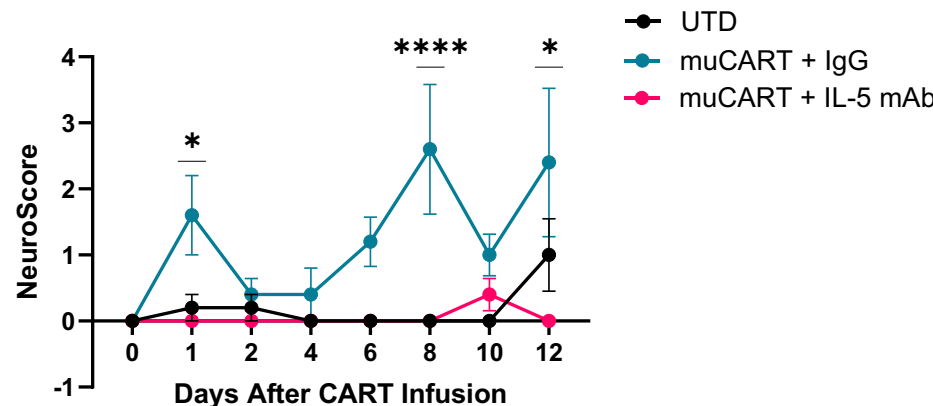


IL-5 Blockade Reduces CART Toxicity in Mouse Models

IL-5 Blockade Reduces CRS in humanized mouse models

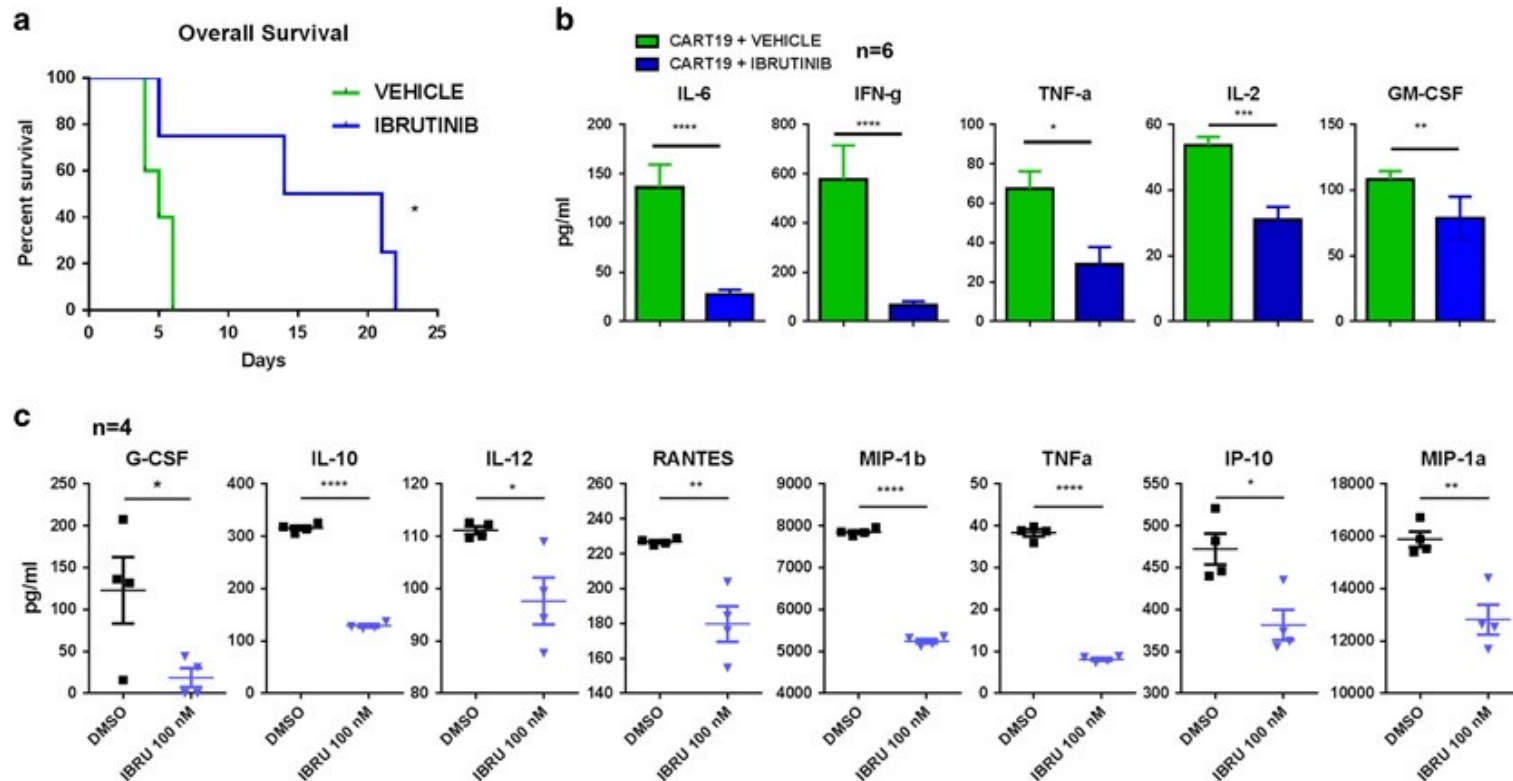


IL-5 Blockade Reduces CRS in immunocompetent mouse models

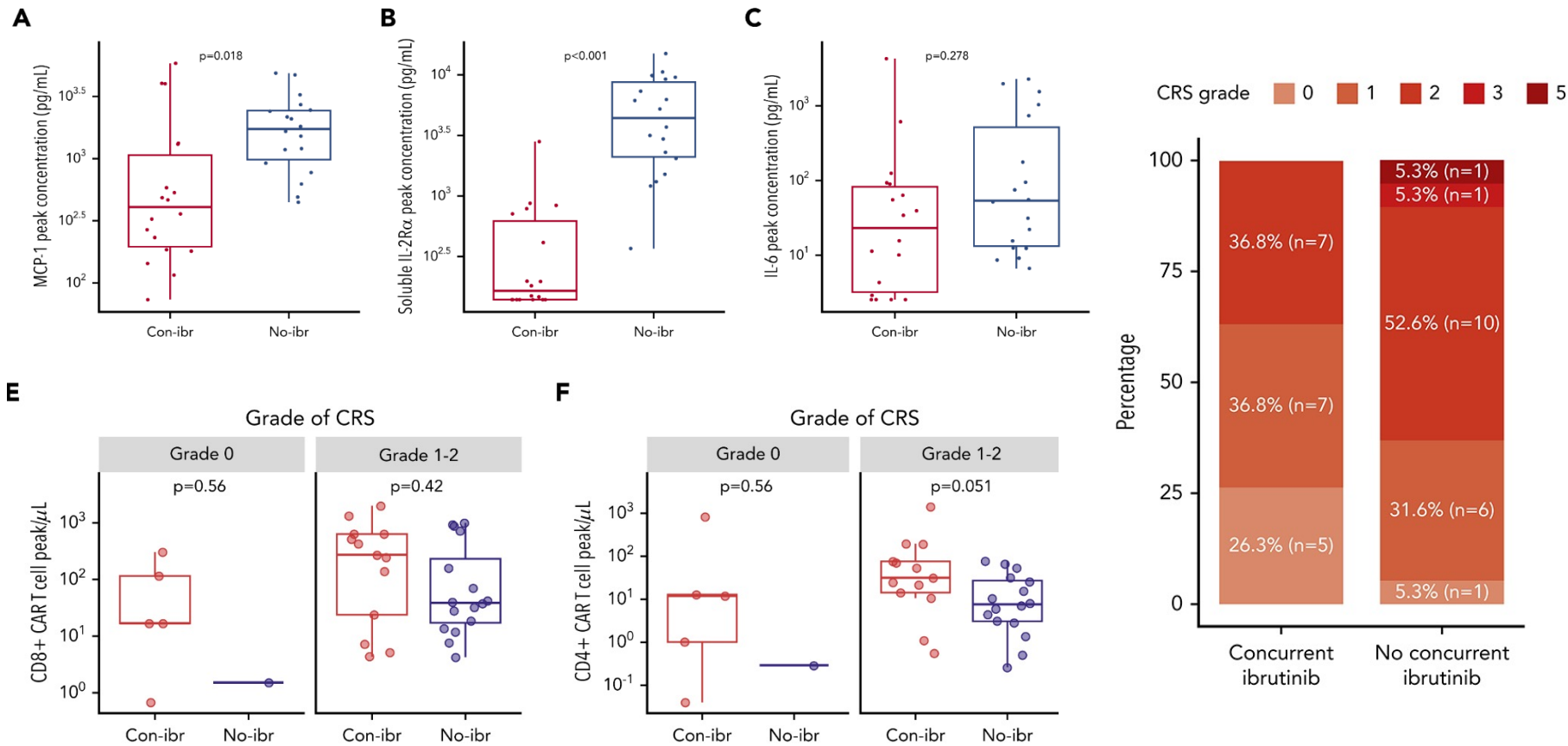


- IL-5 depletion or knockout reduces CART cell toxicities
- Enhanced activity after IL-5 depletion
- Direct effect on eosinophils

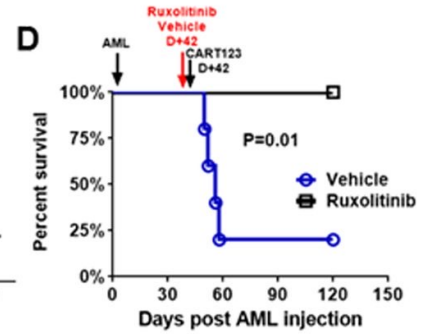
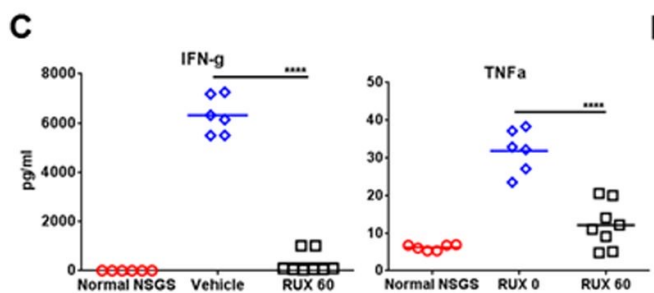
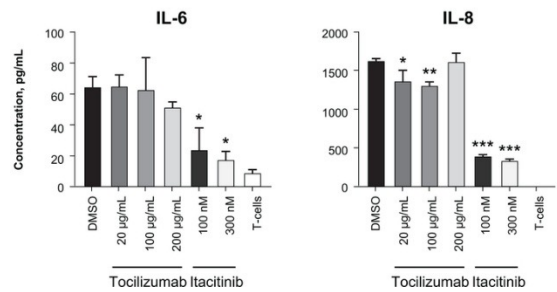
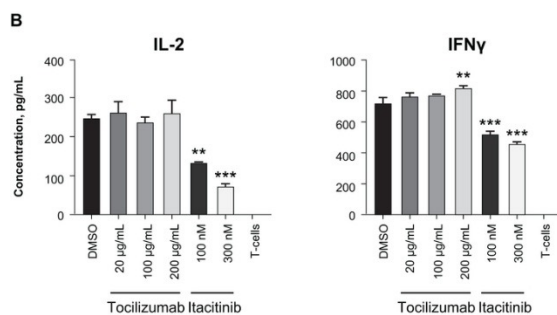
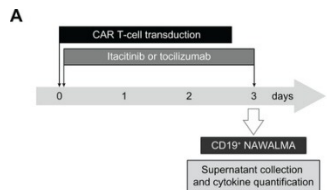
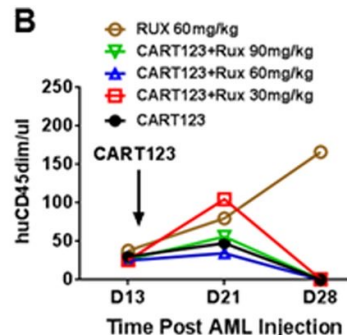
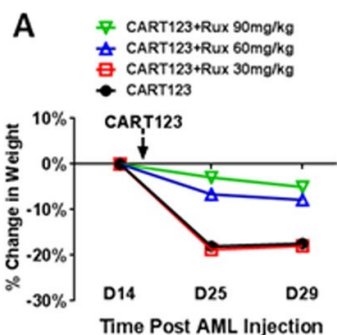
Ibrutinib: Ameliorates CRS in Preclinical Models



Ibrutinib: Combination with CART in the Clinic



JAK/STAT Inhibition: Prevents CRS in Preclinical Models

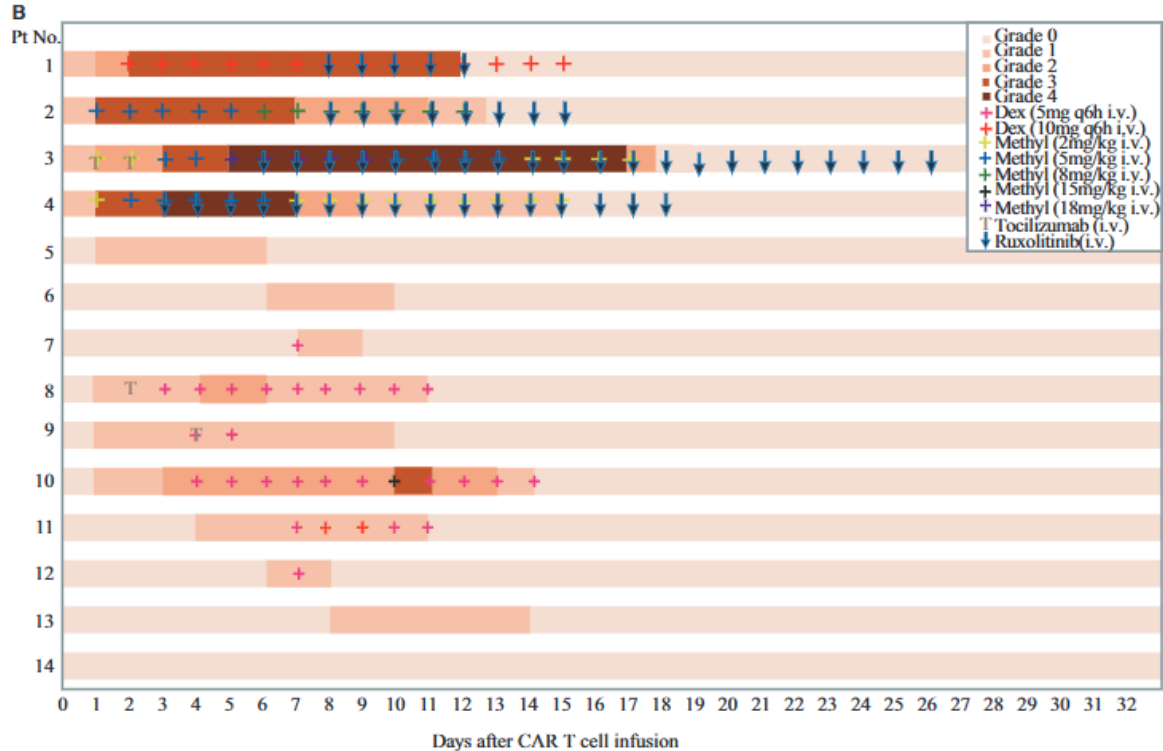


Kenderian S, Ruella M..... Gill S, ASH 2017

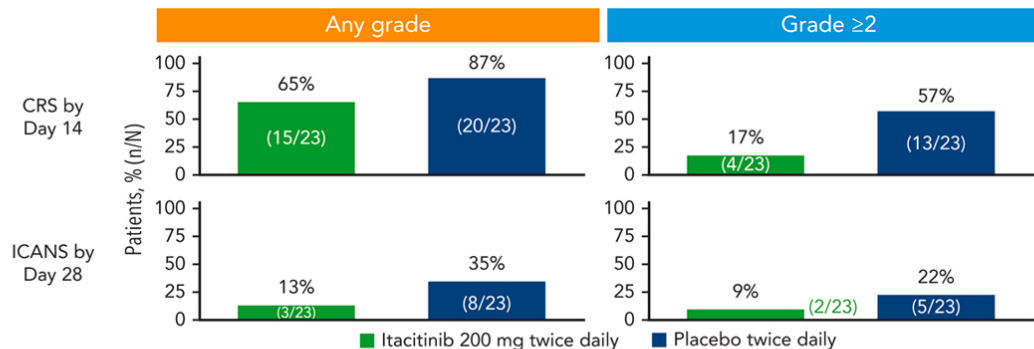
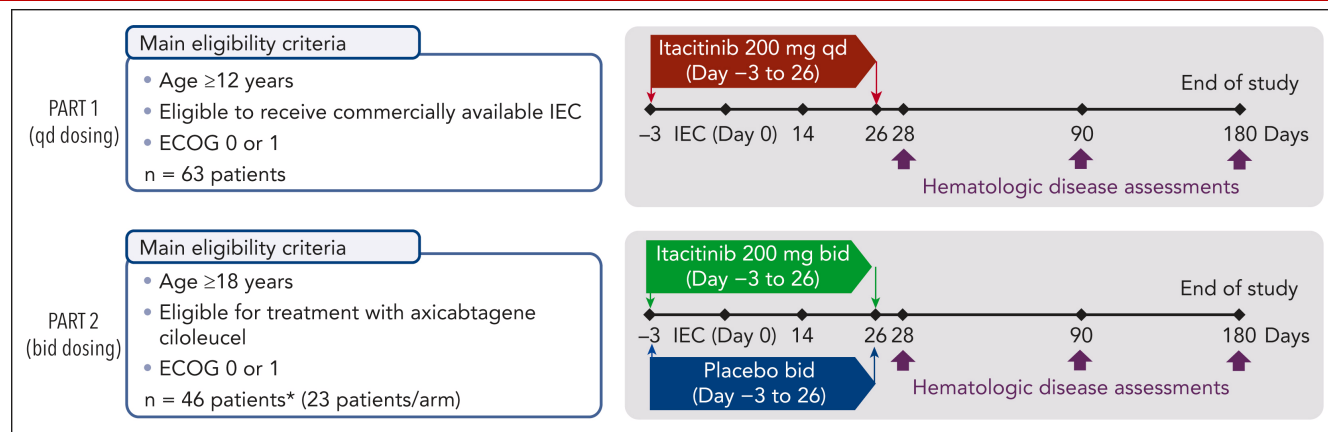
Huarte E.....Smith P, Clin Cancer Res 2020

JAK/STAT Inhibition: Prevents CRS in Preclinical Models

Case Series of Ruxolitinib in Severe CRS

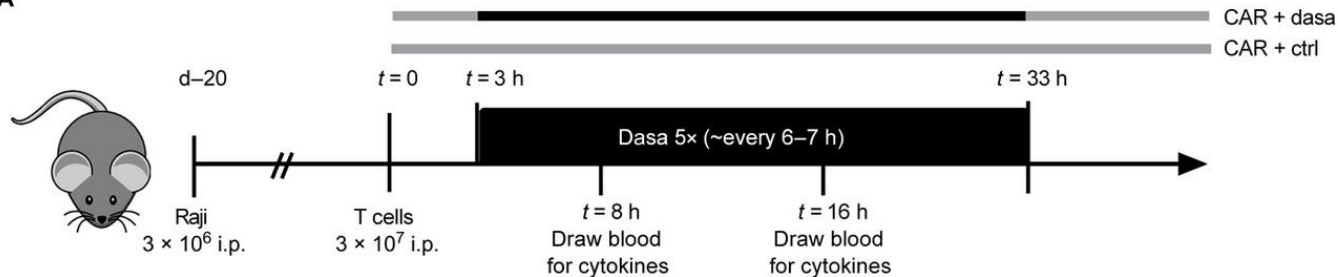


JAK/STAT Inhibition: Itacitinib for the Prevention of CART Toxicities - Phase II Placebo-Controlled Trial

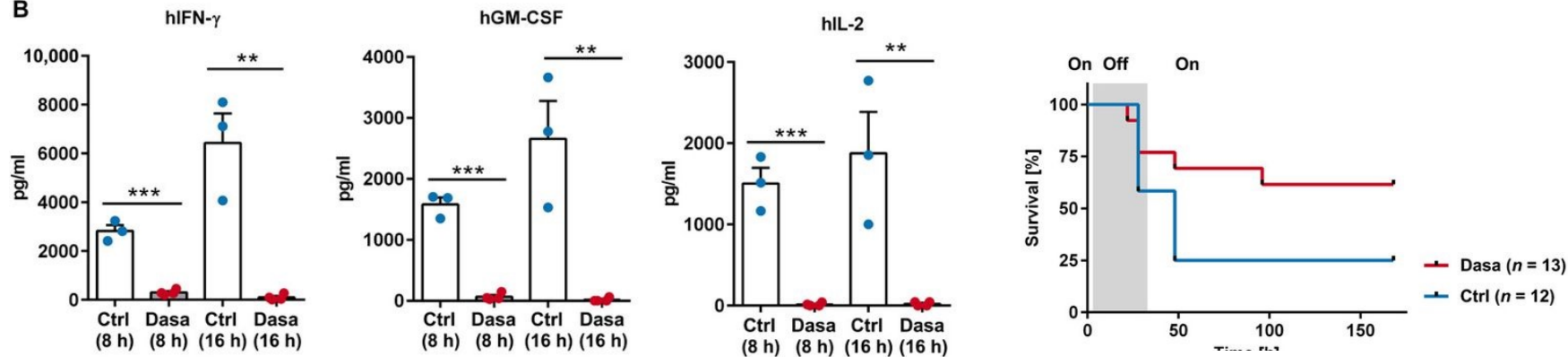


Dasatanib: SRC Pathway Inhibition as a Pharmacological On/Off Switch

A



B



T Cell Engineering (Kenderian Lab)

Ismail Can
Grace DeFranco
Jennifer Feigin
Sara Foote
Sophia Goldberg
Omar Gutierrez Ruiz
Mehrdad Hefazi
Truc Huynh
Lionel A. K. Fonkoua
Brooke Kimball
Saad Kenderian
Long Mai
Claudia Manriquez-
Roman
Ekene Ogbodo
Michael Ruff
Ateka Saleh
Leo Sakemura
Elizabeth Siegler
Olivia Sirpilla
Dominic Skeelee
Carli Stewart
Yoh Yamaguchi
Kun Yun
Hong Xia

Lab Alumni

Mohamad Adada
Evandro Bezerra
Michelle Cox
Karan Chohan
Cynthia Forsman
James Girsch
Paulina Horvei
Wannakorn Khohanlert
Makena Rodriguez
Kendall Schick
Rosalie Sterner
Erin Tapper
Nan Yang

Ruella Lab

Marco Ruella
Alberto Carturan

Kite Pharma

Simone Filosto
Sao-Mai Nguyen-
Mau
Mike Mattie
Justin Budka

MorphoSys

Tolero/Sumitomo

Humanigen

Cameron Durrant

FUNDING

Federal

- DOD CA201127
- NIH R37CA266344
- NIH R01AI179974
- NIH R01 CA251801
- NIH K99 CA273304
- NIH K12CA090628
- NIH KL2 TR002379
- NSF-GRFP 2021321972
- NIH P50CA186781

State

- RMM 091620 TR 012
- RMM 012819 EPC 003
- MNP 22.10
- MNP 32
- RMM 072523 TR 004
- RMM 20240311 TR 006

Foundation

- Exact Sciences
- NCCN
- Gilead Foundation
- ECOG
- Brains Together For Cure
- Eagles Cancer Telethon
- GI Research Foundation
- Michelson Foundation
- Falk Medical Trust
- Riney Foundation

FUNDING

Industry

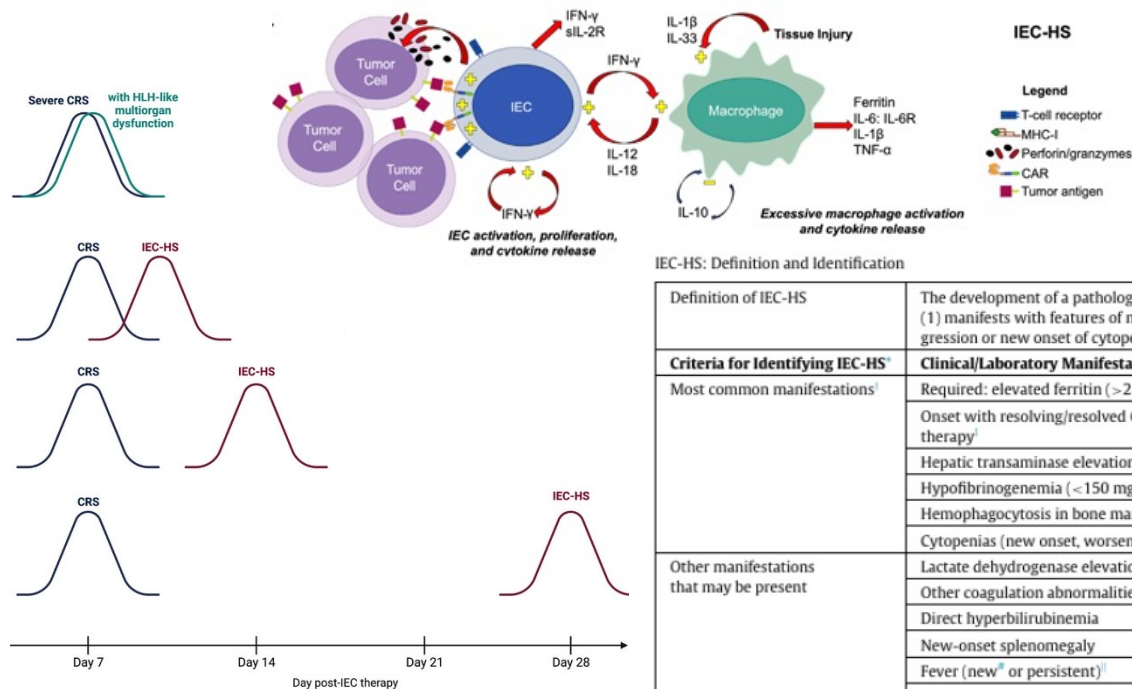
- Novartis
- Kite/Gilead
- Juno/BMS
- Lentigen
- Humanigen
- Sunesis/Viracta
- Morphosys
- Leahlabs
- Tolero

Mayo

- Center for Individualized Medicine
- Predolin Foundation
- Schulze Foundation
- Mayo Clinic Cancer Center
- Center for Biomedical Discovery
- Office of Translation to Practice
- Department of Medicine
- Division of Hematology
- Center for Reg. Biotherapeutics
- Mayo Clinic Ventures



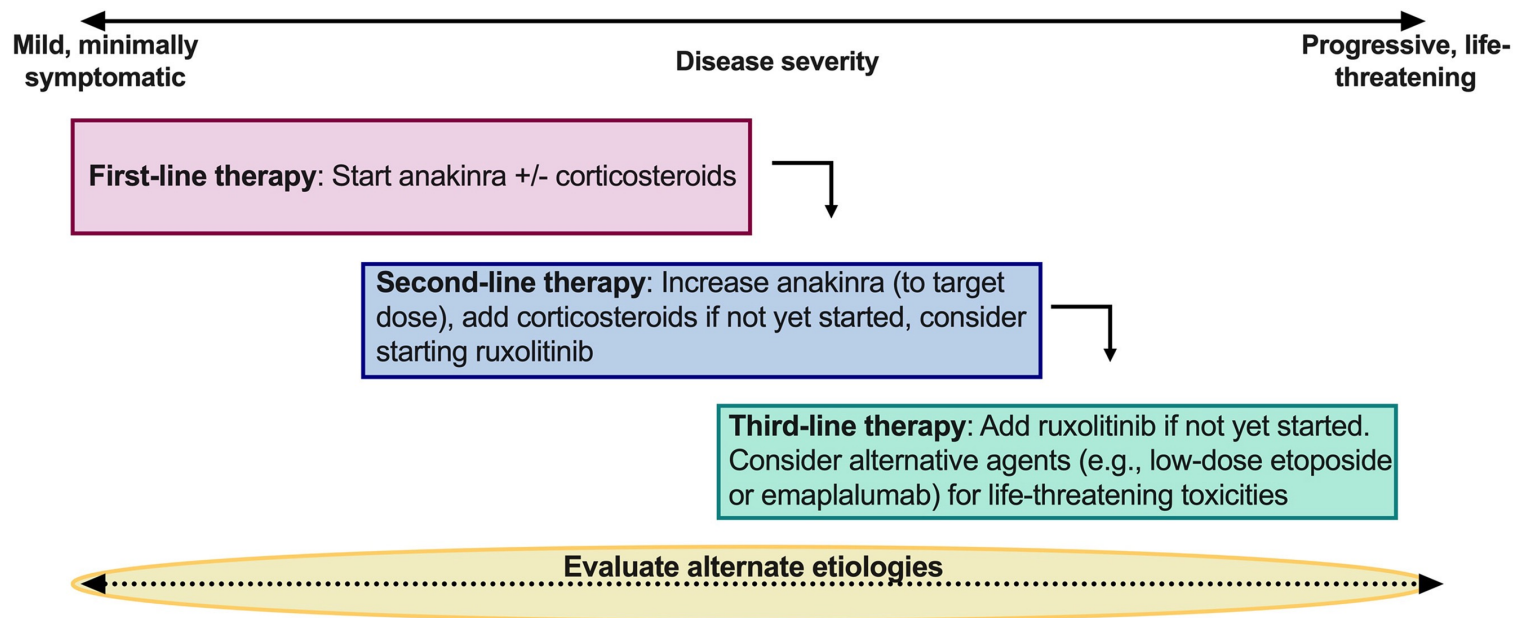
Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome



IEC-HS: Definition and Identification

Definition of IEC-HS	The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis
Criteria for Identifying IEC-HS ¹	Clinical/Laboratory Manifestations
Most common manifestations ¹	Required: elevated ferritin ($>2 \times$ ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment) Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS-directed therapy ¹ Hepatic transaminase elevation ¹ ($>5 \times$ ULN (if baseline was normal) or $>5 \times$ baseline if baseline was abnormal) Hypofibrinogenemia (<150 mg/dL or $<LLN$) ¹ Hemophagocytosis in bone marrow or other tissue ¹ Cytopenias (new onset, worsening, or refractory ¹)
Other manifestations that may be present	Lactate dehydrogenase elevations ($>ULN$) Other coagulation abnormalities (eg, elevated PT/PTT) Direct hyperbilirubinemia New-onset splenomegaly Fever (new ¹ or persistent) ¹ Neurotoxicity Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, pulmonary edema) Renal insufficiency (new onset) Hypertriglyceridemia (fasting level, >265 mg/dL ¹)

IEC-HS: Management Algorithm



Prolonged Cytopenia and ICAHT

Early Cytopenia (< 30 days)

Delayed Cytopenia (> 30-90 days)

LD Chemotherapy

Disease Burden/BM Suppression

IEC-HS

Infections

Immune/cytokine mediated

HSC apoptosis

PNH/LGL clones

secondary Myeloid neoplasms

Pre existing CHIP

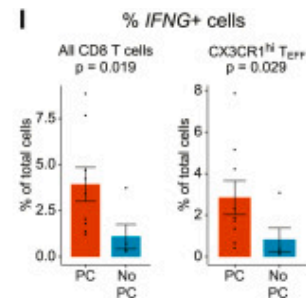
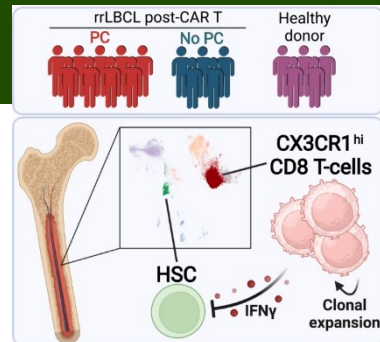
Risk Factors:

High disease burden
Prior therapies
BM infiltration
Pre-existing cytopenia
CD28 CART
Severe CRS
Infections

Treatment:

Treatment:

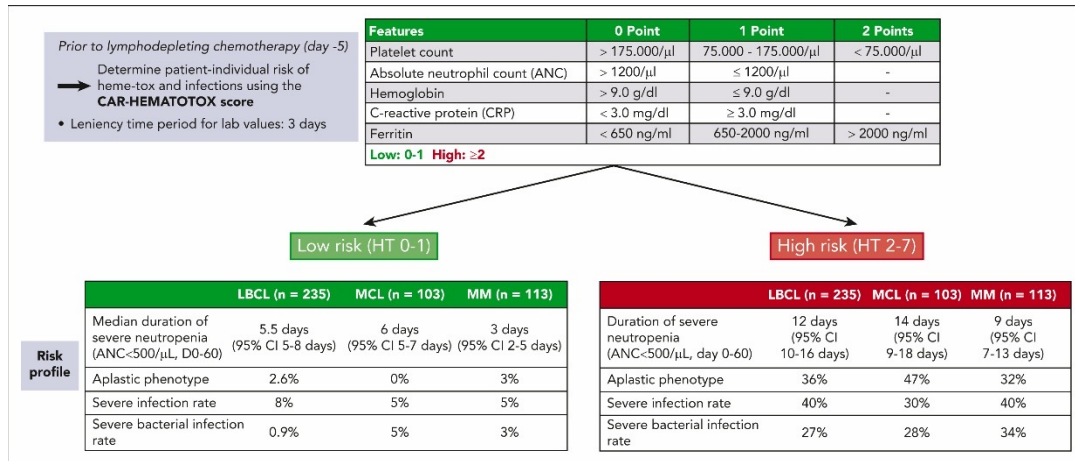
Etiology (infections, IEC-HS, myeloid malignancy)
Growth factors
Stem cell boost



Strati P..... Green M, Cell Rep Med 2023

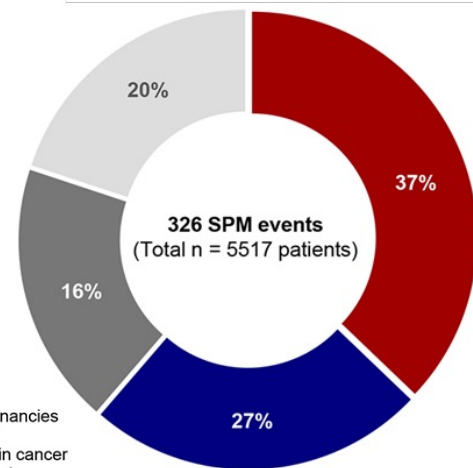
Prolonged Cytopenia and ICAHT

	Early (<30 d from infusion)	Prolonged (30-90 d from infusion)	Late (>90 d from infusion)
CD19-directed CAR T-cells, pediatrics ELIANA ¹²	Neutropenia: 53% Thrombocytopenia: 41%		Neutropenia: 34% Thrombocytopenia: 27%
CD19-directed CAR T-cells, adults ZUMA-1 ^{13,14}	Neutropenia: 78% Thrombocytopenia: 38% Anemia: 43%		Neutropenia: 11% Thrombocytopenia: 7% Anemia: 3%
JULIET ¹⁵	Neutropenia: 33% Thrombocytopenia: 28% Anemia: 39%	Neutropenia: 24% Thrombocytopenia: 41%	Grade 3-4 neutropenia: 0% Thrombocytopenia: 38%
TRANSCEND ¹⁶	Neutropenia: 60% Thrombocytopenia: 27% Anemia: 37%		Neutropenia: 7% Thrombocytopenia: 22% Anemia: 2%
ZUMA-2 ¹⁷	Neutropenia: 85% Thrombocytopenia: 51% Anemia: 50%		Neutropenia: 16% Thrombocytopenia: 16% Anemia: 12%
ZUMA-3 ¹⁸	Neutropenia: 27% Thrombocytopenia: 30% Anemia: 49%	Neutropenia: 25% Thrombocytopenia: 18% Anemia: 7%	
ZUMA-5 ¹⁹	Neutropenia: 33% Thrombocytopenia: 15% Anemia: 25%		
BCMA-directed CAR T-cells, adults KartMMA ²⁰	Neutropenia: 89% Thrombocytopenia: 52% Anemia: 60%	Neutropenia: 41% Thrombocytopenia: 48%	
CARTITUDE-1 ²¹	Neutropenia: 95% Thrombocytopenia: 60% Anemia: 68%	Neutropenia: 29% Thrombocytopenia: 27% Anemia: 27%	

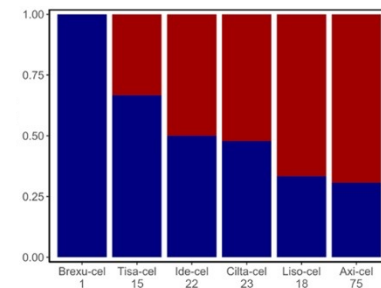
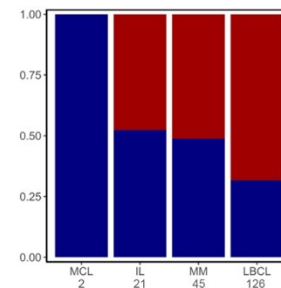


Secondary Myeloid Malignancies Post CART Cell Therapy

SPM Risk: 5.8%

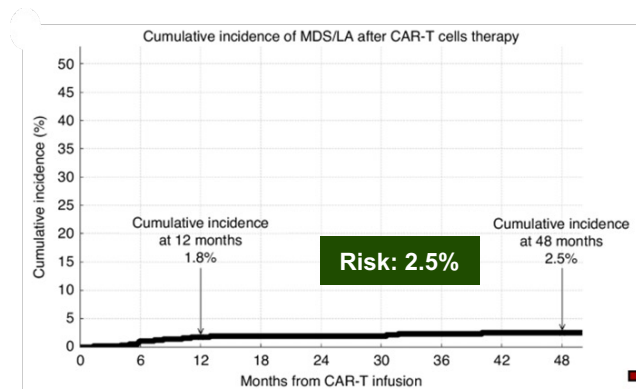


■ Hematologic malignancies
■ Solid tumors
■ Non-melanoma skin cancer
■ Not further specified

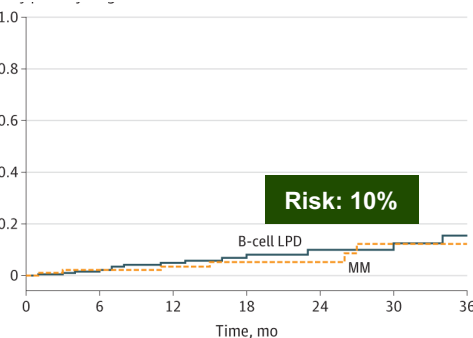


Tix T.... Rejeski K, Clin Cancer Res 2025

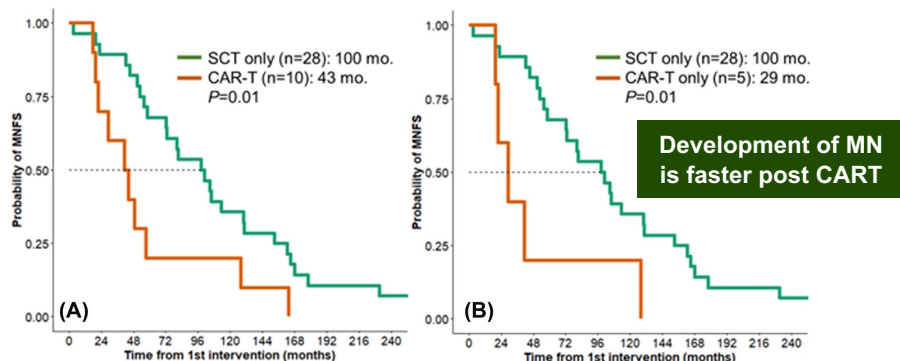
Pre-existing CHIP 2 cases of MDS U2AF1 and TP53



Farina M.... Russo D, BMT 2025



Gurney M.... Shah M, JAMA Oncology 2024



Alkhateeb H.... Shah M, Blood Cancer Journal 2022

CHIP and CART

➤ Higher incidence of CHIP at baseline in patients treated with CART

➤ 35-50% vs 5-10% in matched cohorts

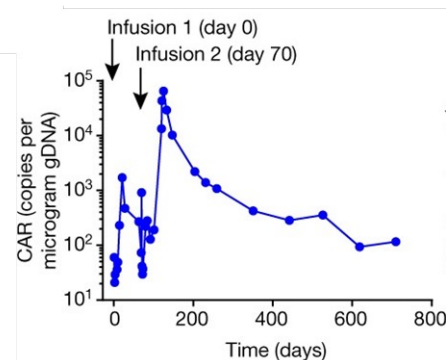
➤ Associated with increased risk of side effects

- Severe Neurotoxicity

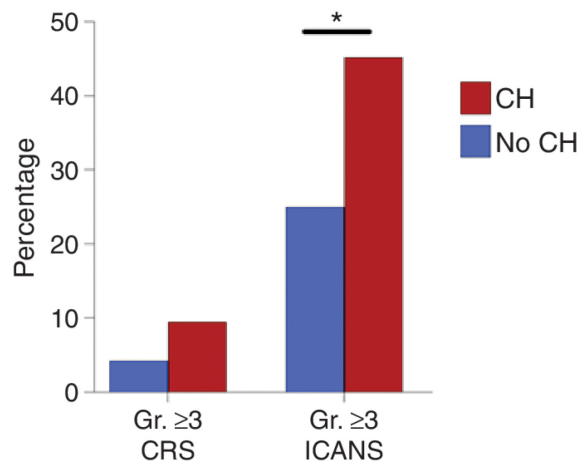
- Severe CRS

➤ ? Pre-existing high inflammatory status

➤ TET-2 CAR insertion

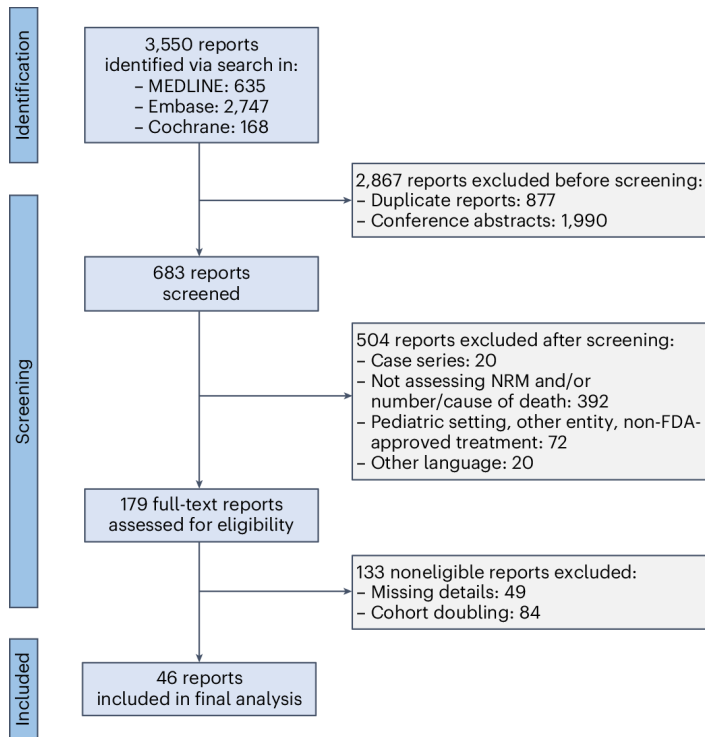


Fraietta J..... Melenhorst J, Nat 2018



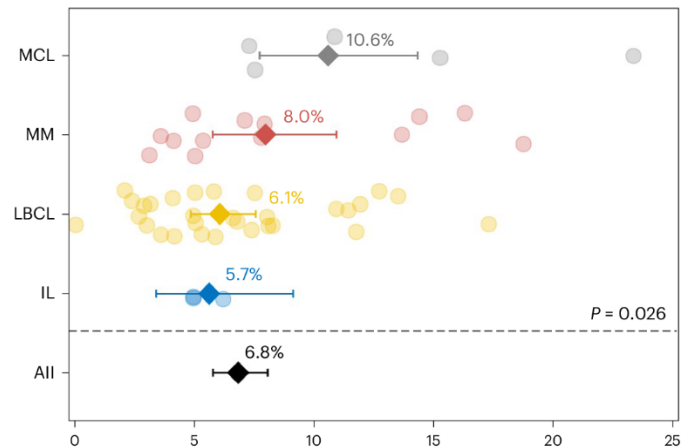
Saini N..... Takahashi K, Blood Cancer Discov 2022

Non-Relapse Mortality After CART Cell Therapy

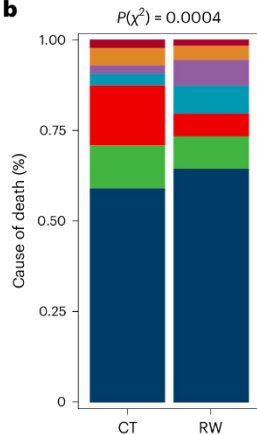


Cordas dos Santos..... Rajeski, Nat Med 2024

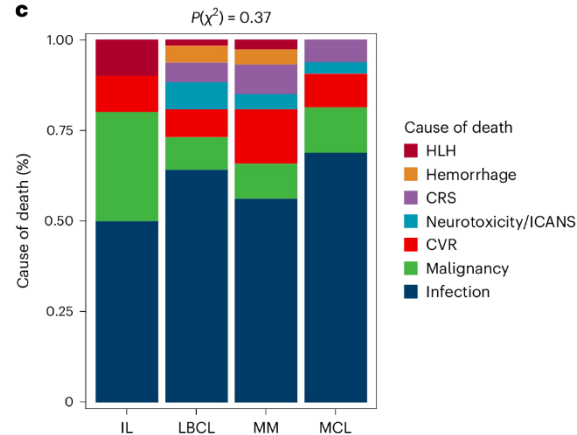
b



b



c



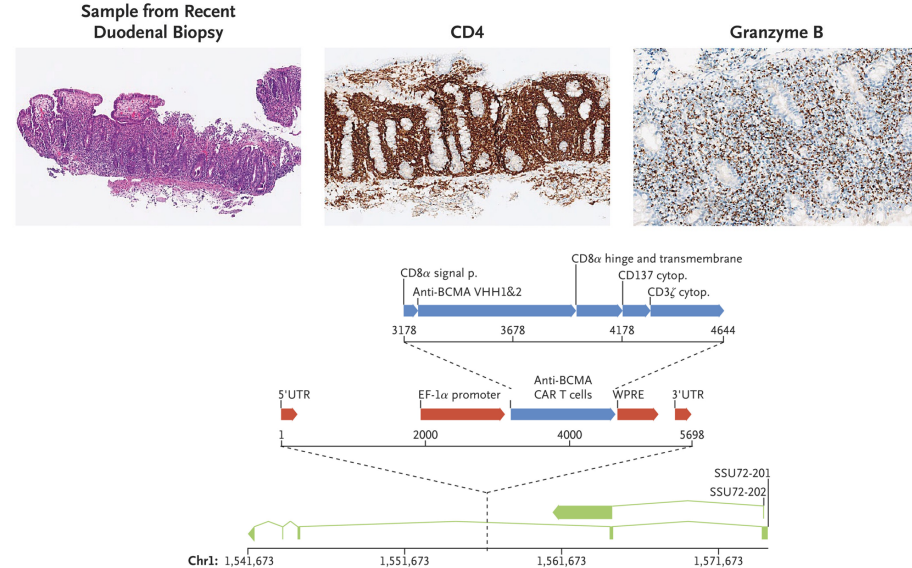
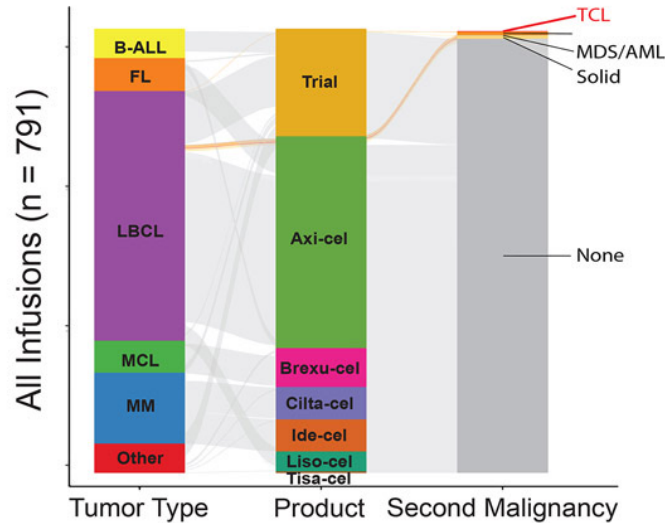
T Cell Malignancies Post CART Cell Therapy

Author (Ref)	Year of publication	Study type	CAR-T cell product prescribed	Diagnosis	No. total patients analyzed	No. patients with T cell neoplasm	Time from CAR-T cell to T cell malignancy, months	CAR transgene integration and expression confirmed
Bishop et al. [53]	2021	Clinical trial	<i>piggyBac</i> -modified CD19	B-ALL, DLBCL, Burkitt	10	2 (20%)	11.5-15	No
Verdun and Marks [20]	2024	FDA surveillance	Various	Various	>27,000	22 (~0.08%)	1-19	Yes*
Willyard [21]	2024	FDA surveillance	Various	Various	~30,000	33 (~0.11%)	NR	NR
Ghilardi et al. [25]	2024	Retrospective	Various	B cell NHL, B cell ALL, MM	449	1 (0.22%) ^y	3	No
Abramson et al. [36]	2024	Clinical trial	Liso-cel	DLBCL	270	1 (0.4%) ^l	1	No
Melody et al. [37]	2024	Retrospective	Various	Various	582	1 (0.17%) ^{l,l}	4	NP
Cliff et al. [38]	2024	Database	B cell lymphoid	Various	1542	1 (0.06%)	NR	NR
Jadlowsky et al. [23]	2025	Retrospective, single institution	Various	Various	783	1 (0.13%) ^{**}	~12	No
Harrison et al. [64]	2025	Clinical trial	Cilta-cel	MM	208 ^{***}	2 (1%)	5-16	Yes
Dulery et al. [63]	2025	Registry	Various	Various	3,066	1 (0.03%) ^{y,y}	36	Yes

Mohty R.....Kharfan Dabaja M, TCT 2025

Rate of T cell lymphoma is 0.03% - 1%

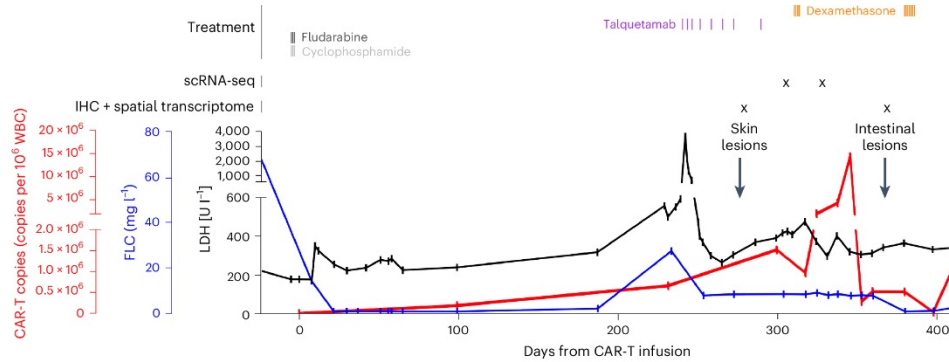
T Cell Malignancies: Linked to CART Cells?



- T cell lymphoma after DLBCL
- Both DLBCL and TCL were positive for DNMT3 and TET2

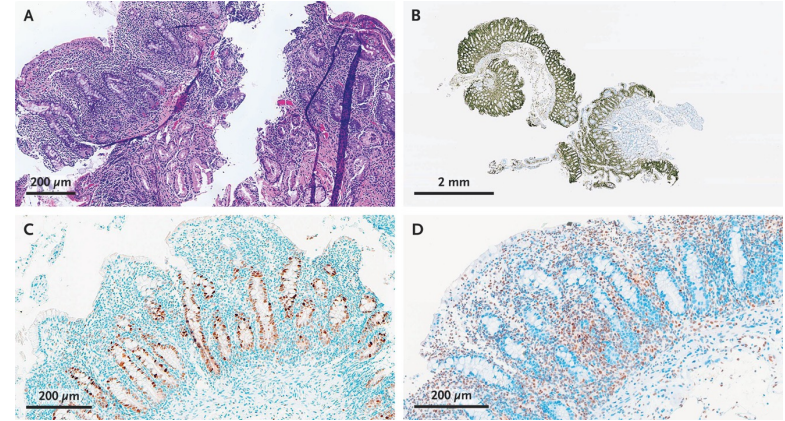
- Indolent GI T cell lymphoma
- SSU72 intron integration

T Cell Malignancies: Linked to CART Cells?



- Cutaneous and Intestinal T lymphoma after Cilta-Cel
- Distinct integration sites: ZGPAT, KPNA4 and clonal expansion of TET+ CAR+ T cells

Bruan T.....Richardson T, Nat Med 2025

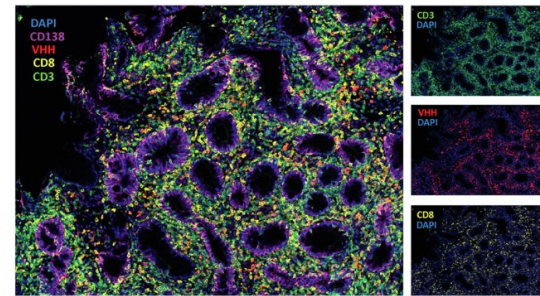


- TP53 integration after BCMA CART cell therapy

Perica K.....Mailankody S, NEJM 2025

Immune Effector Cell Associated Colitis

- 1-2% of BCMA CART cell therapy (Cilta-cel > Ida-cel)
- T cell infiltration and CART infiltration into the gut
- Unclear etiology: possibly related to BCMA expression
- Poor outcomes
- Treatment: Vedolizumab, infliximab



Fortuna G..... Hansen D, *Blood Cancer J* 2024

On-Target Off-Tumor Toxicity

Target	Products	Off Tumor Toxicity
CD19	CART19 cells (tisa-cel, axi-cel, liso-cel, brexu-cel, Obe-cel) BiTE (blinatumomab)	➤ B cell aplasia ➤ ? CD19 targeting in the brain
CD20	BiTE (Mosunetuzumab, Glofitamab, Epcoritamab)	➤ B cell aplasia
BCMA	BCMA-CART cells (ida-cel, cilta-cel) BiTE (Teclistamab, Linvoseltamab, Elranatamab)	➤ Plasma cell aplasia ➤ Caudate nucleus/basal ganglion ➤ BCMA⁺ cells in the GI mucosa
DLL3	Taraltamab	➤ DLL3⁺ cells in brain - higher rates of neurotoxicity ➤ Pulmonary toxicity
GPRC5D	Talquetamab	➤ Skin toxicity
gp100	Tebentafusp	➤ Skin toxicity