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GD2-CAR T Cells for Diffuse Midline Gliomas

CIRM Board Meeting
January 2026

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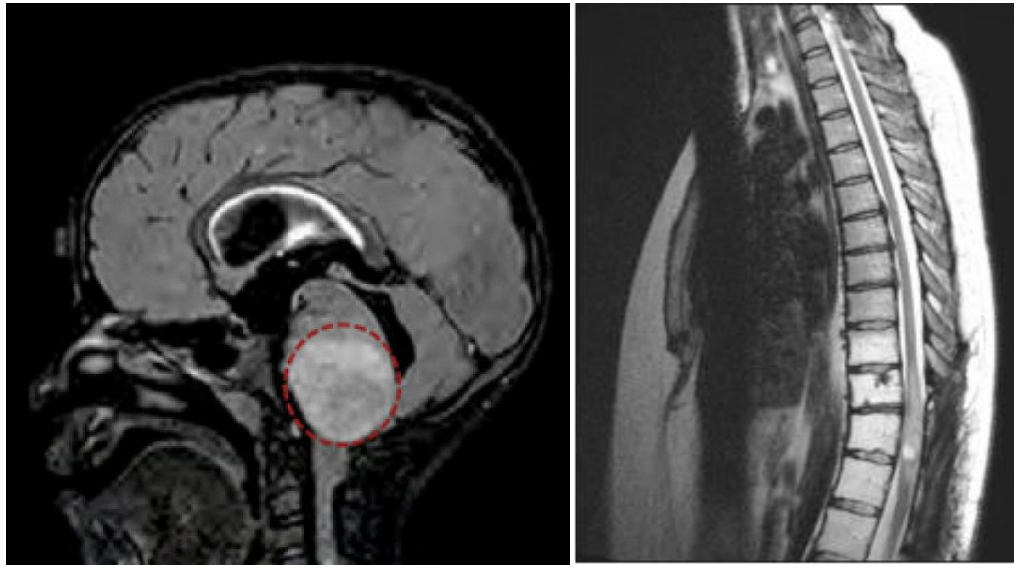
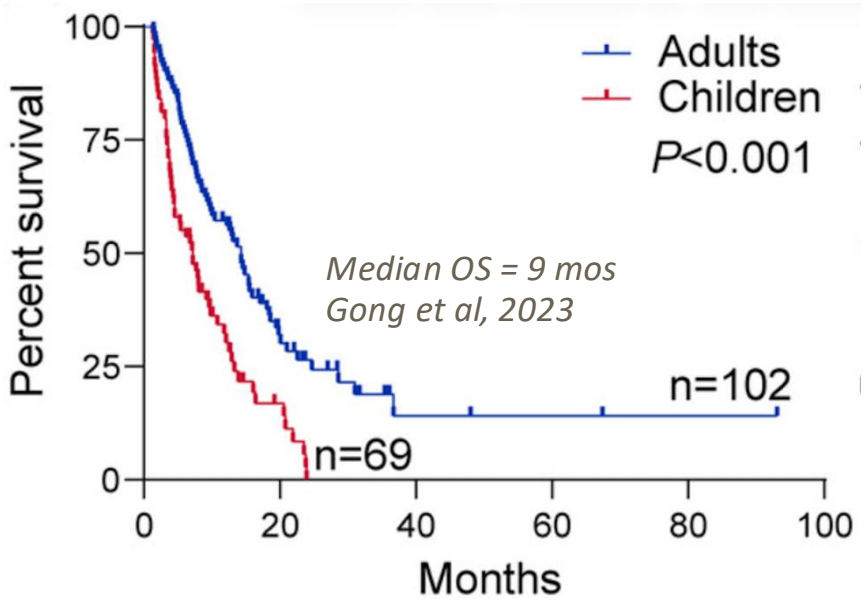
Diffuse Midline Gliomas:
Universally Lethal Cancers With No Upfront Standard Therapy Options

Midline Cancers of the Brainstem and Spinal Cord



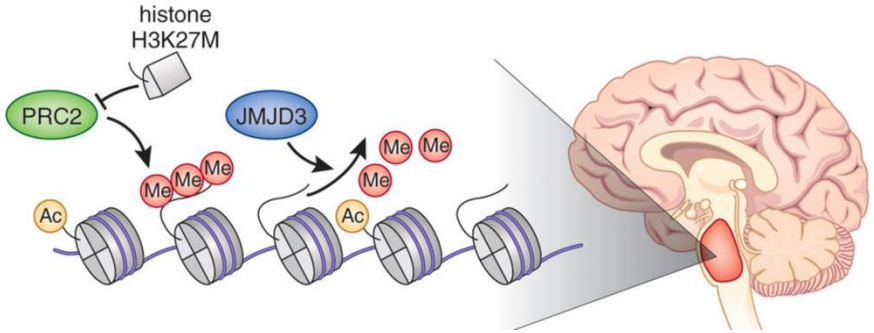
Lethal Despite Many Clinical Trials



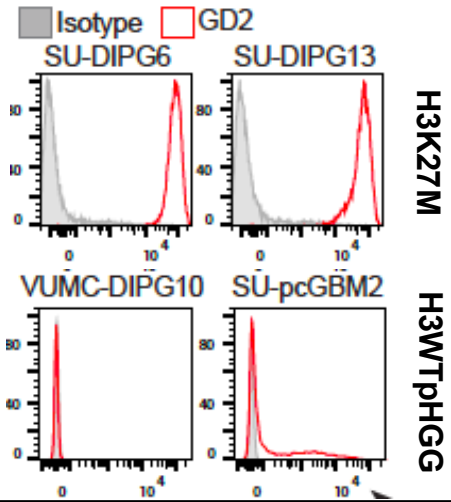
- Approximately 1000 patients/yr in the US, approximately 120 patients/yr in California
- Most common killer of children due to brain tumors.
- No standard frontline therapy except palliative radiation

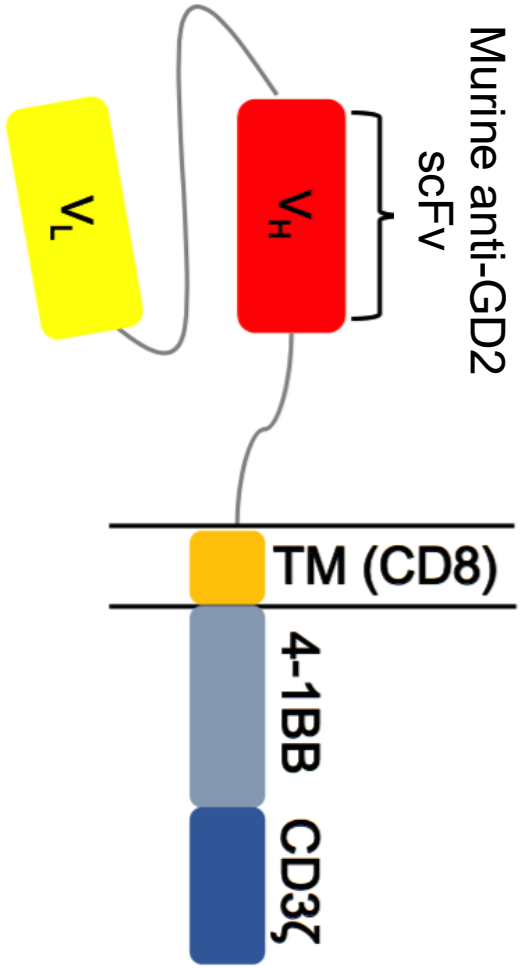
We discovered that the genetic program that causes DMGs leads to massive production of GD2, a fatty sugar that can be targeted by Chimeric Antigen Receptors (CARs)

Driven by a Mutation in the H3 Histone



Massive GD2 Production

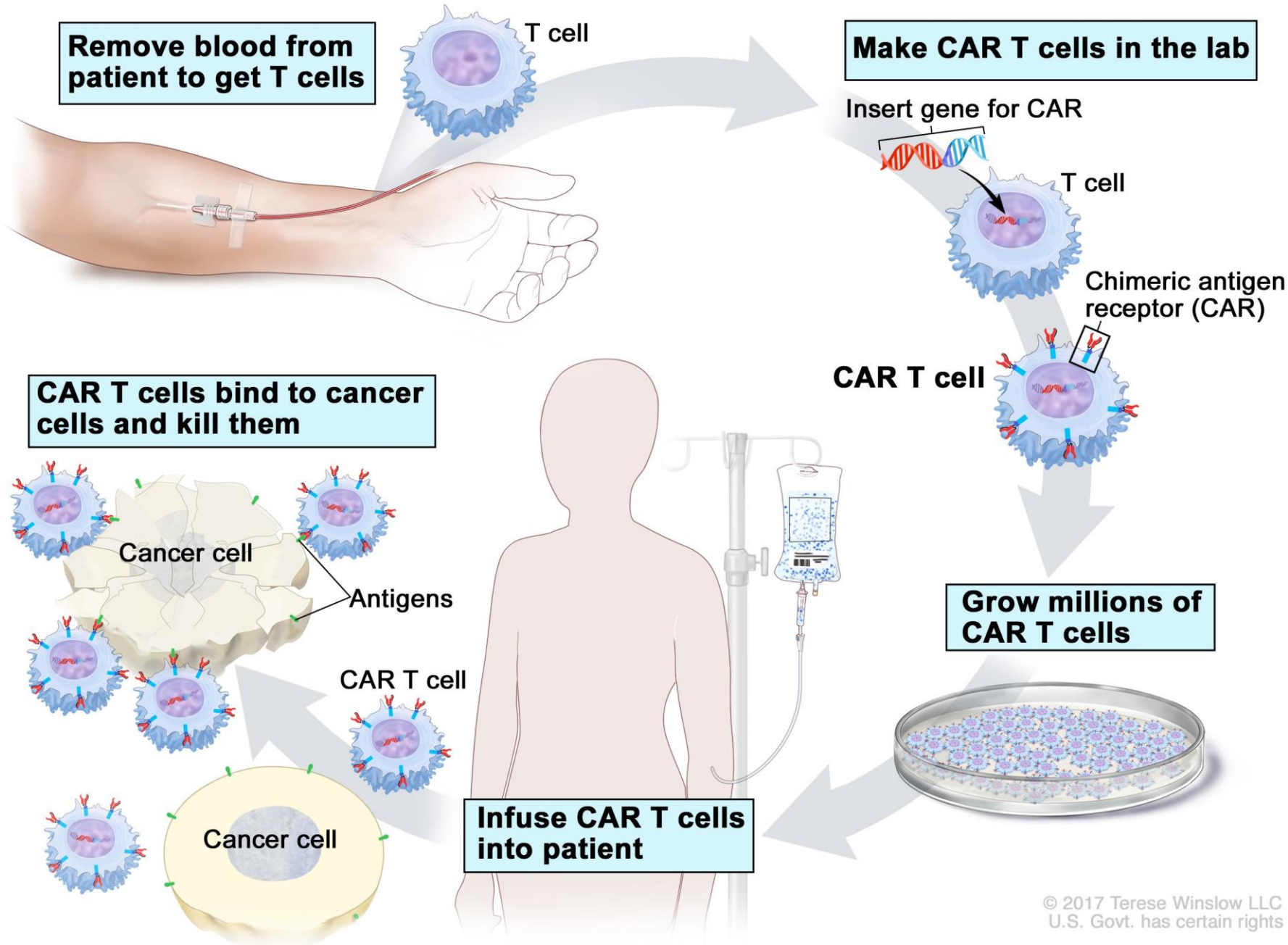




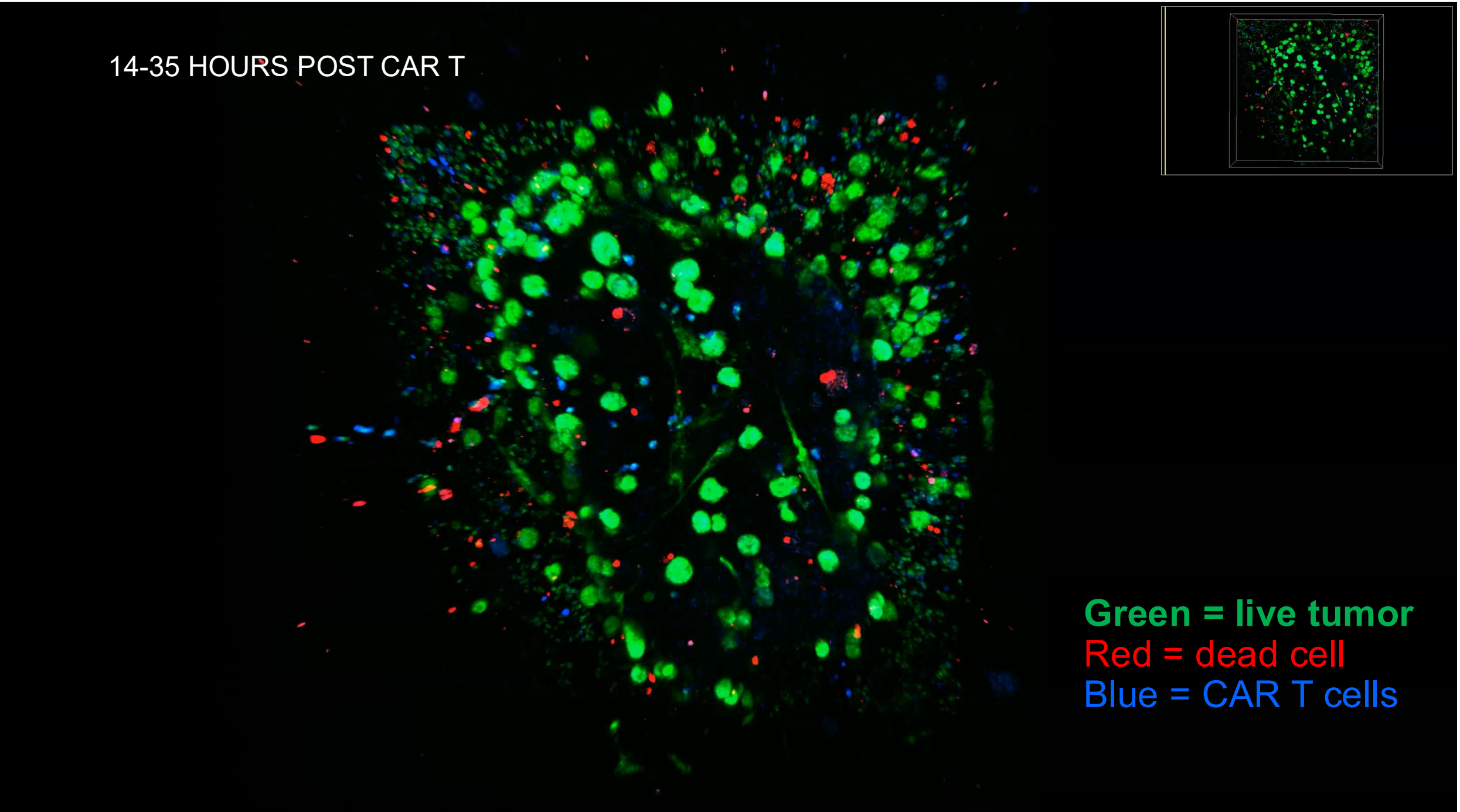
GD2-CAR

Mount, Majzner….Monje, Mackall. Nat Med 2018

CAR T-cell Therapy



14-35 HOURS POST CAR T



Green = live tumor
Red = dead cell
Blue = CAR T cells

Opportunity: Systemic and/or Intracranial Delivery of GD2-CAR T Cells for a Lethal Pediatric Brain Tumor

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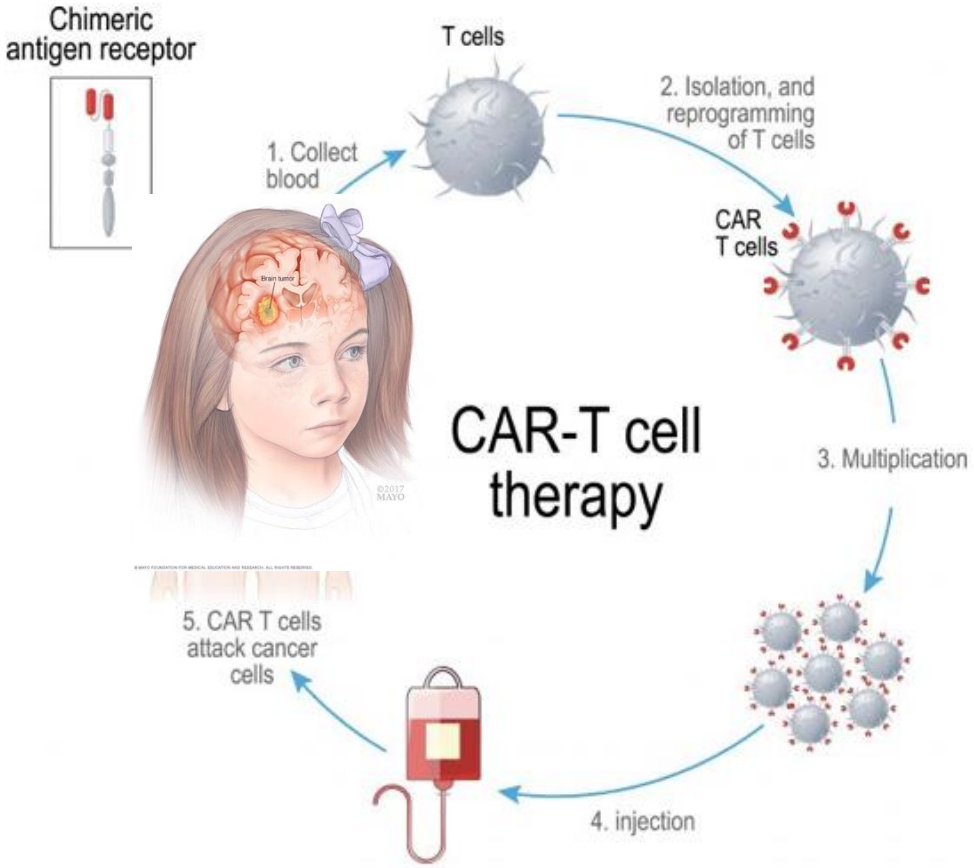
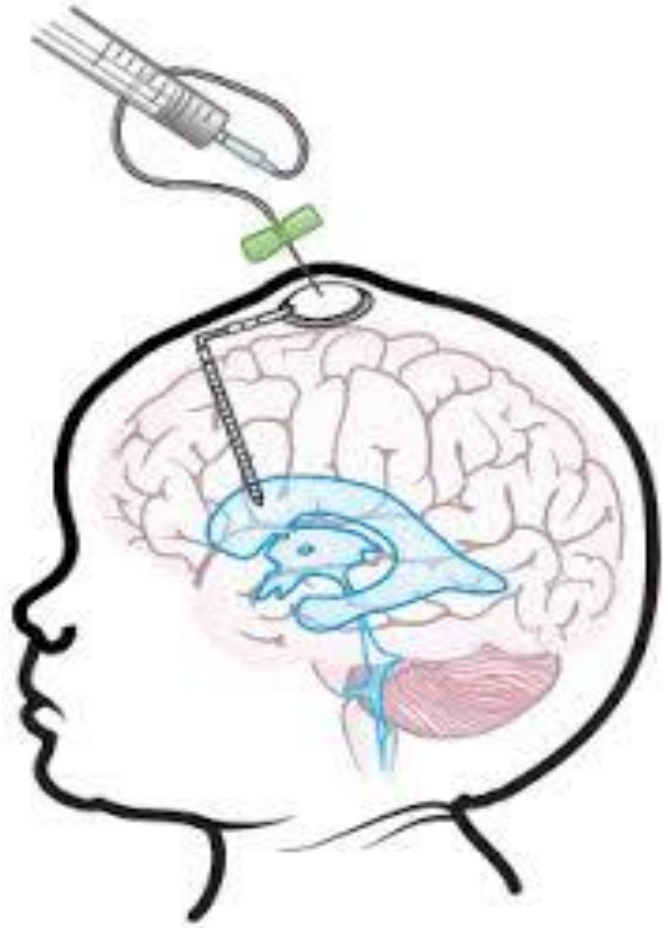
Intravenous Delivery (IV)



Delivery Into the CNS (ICV)



CLIN2-12595: CIRM Funded Phase 1 trial to assess feasibility and safety of GD2.41BB.z CAR T cells in H3K27M DMG

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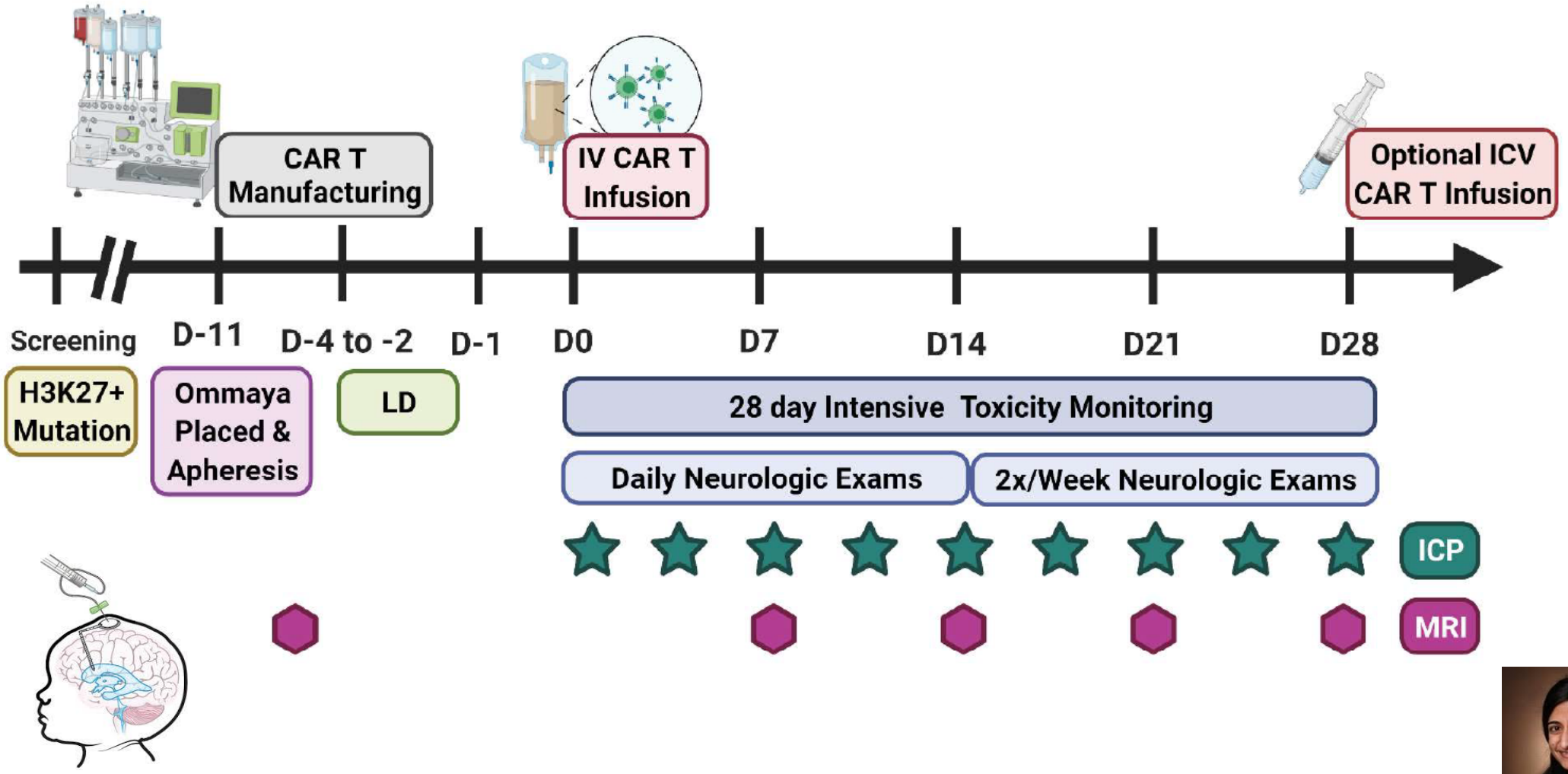
Arm A, Trial opened June 2020



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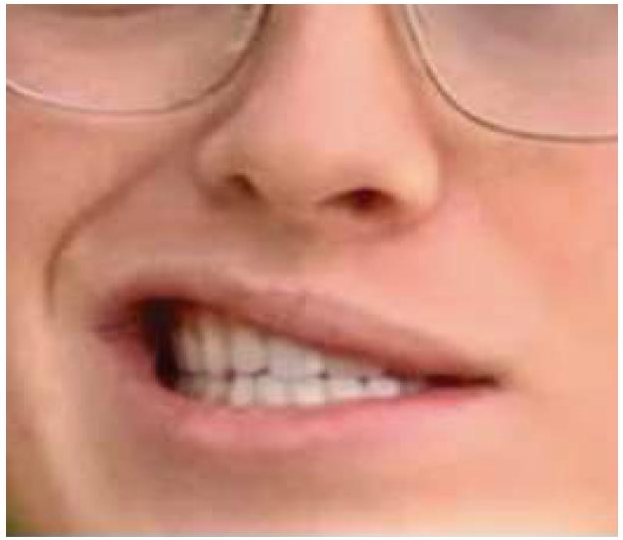
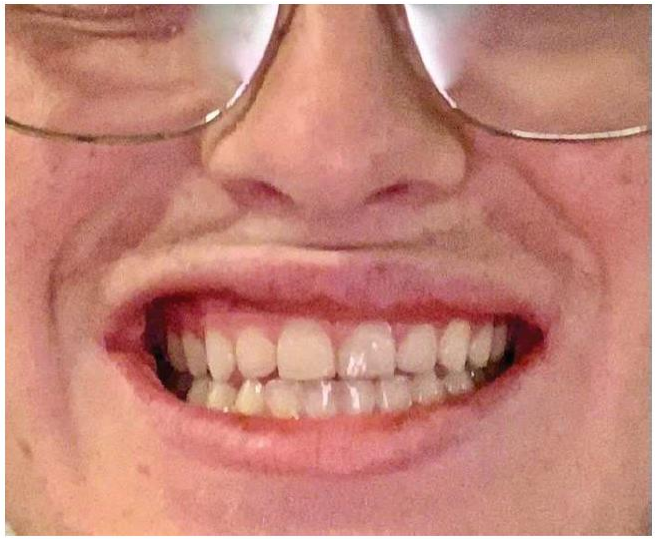
Pt. #3: Remarkable Clinical Response to ICV GD2-CART

Pre ICV GD2-CAR



Post ICV GD2-CAR



Videos with patient's consent

Pre ICV GD2-CAR

2 weeks post ICV GD2-CAR

Majzner, Ramakrishna*…Mackall^, Monje^ Nature, 2022*

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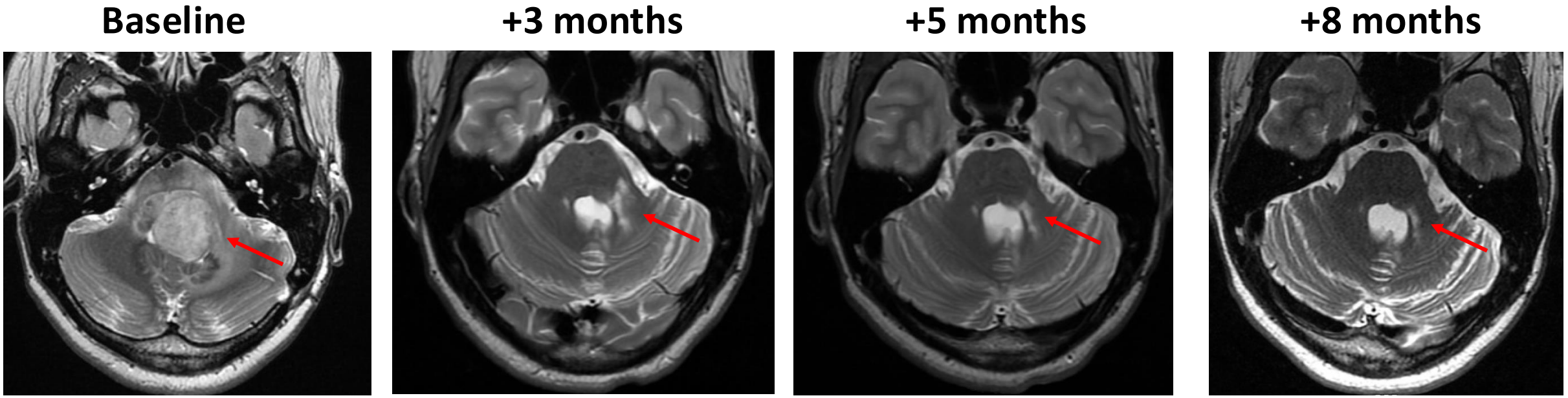
Pt. #10: 17-year-old male with DIPG achieved a CR over 6 infusions, response ongoing 5 years from diagnosis



Major clinical improvements:

- *Wheelchair with any distance to independent walking*
- *Homebound at treatment entry in high school, in college and living independently, traveled Europe in summer 2024*

Monje….Mackall, Nature, 2024

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Pt #10: Complete Radiographic Clearance Associated with Durable Clinical Benefit

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Videos with patient's consent

One month after first infusion

8 months after first infusion

Arm A: IV followed by Sequential ICV Infusions of GD2-CAR For DMGs

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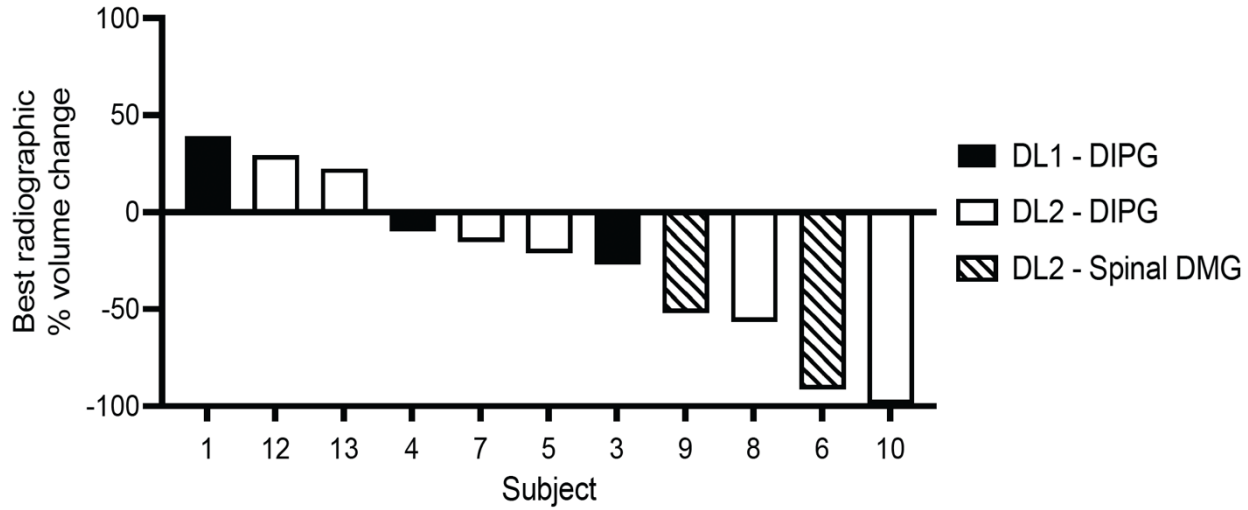
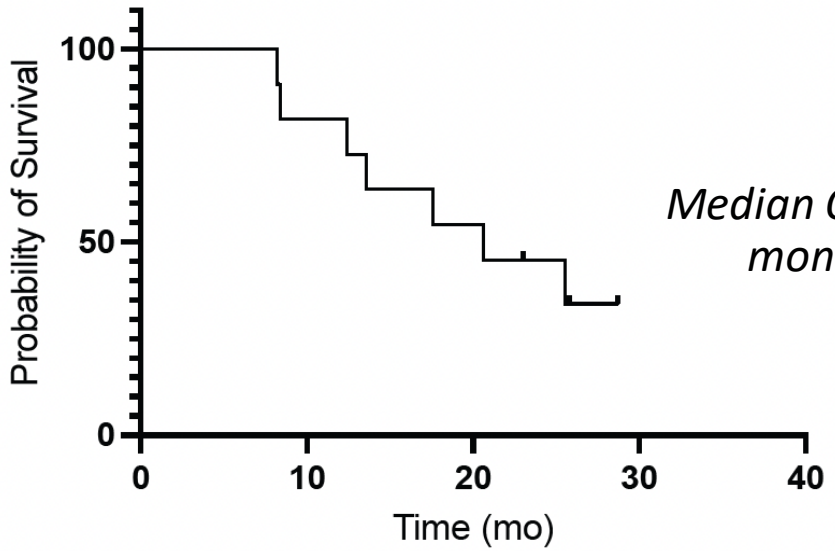




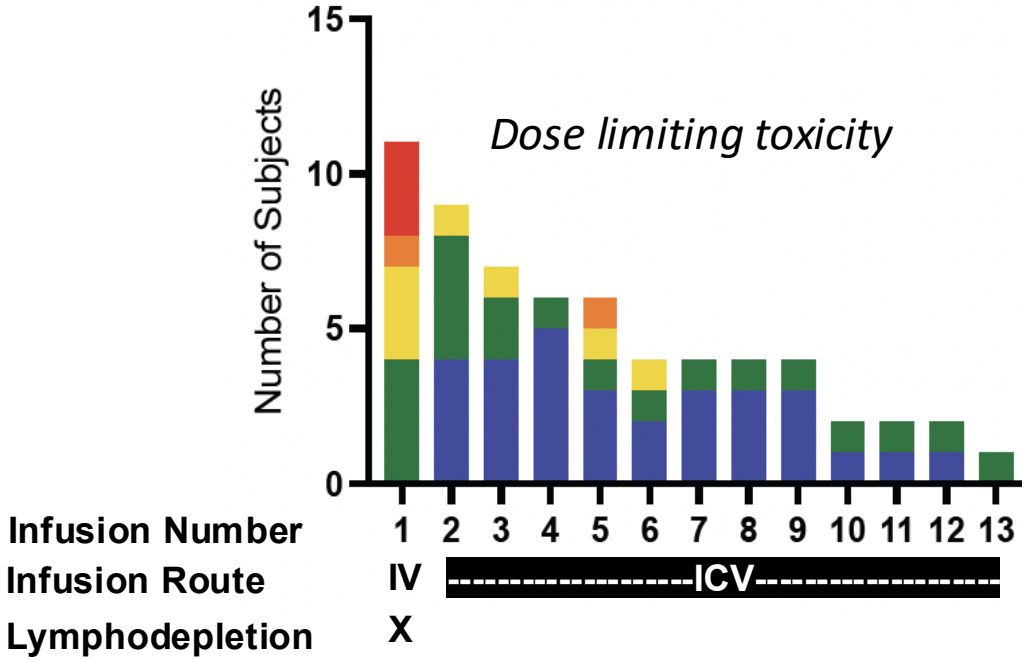
Median OS 20.6 months

- *13 patients enrolled, 11 patients treated*
- *Substantial clinical benefit measured by neurologic improvement*
- *Significant numbers of patients had major tumor shrinkage*
- *Higher median overall survival compared to historical controls (20.6 months vs. 9-11 mos)*

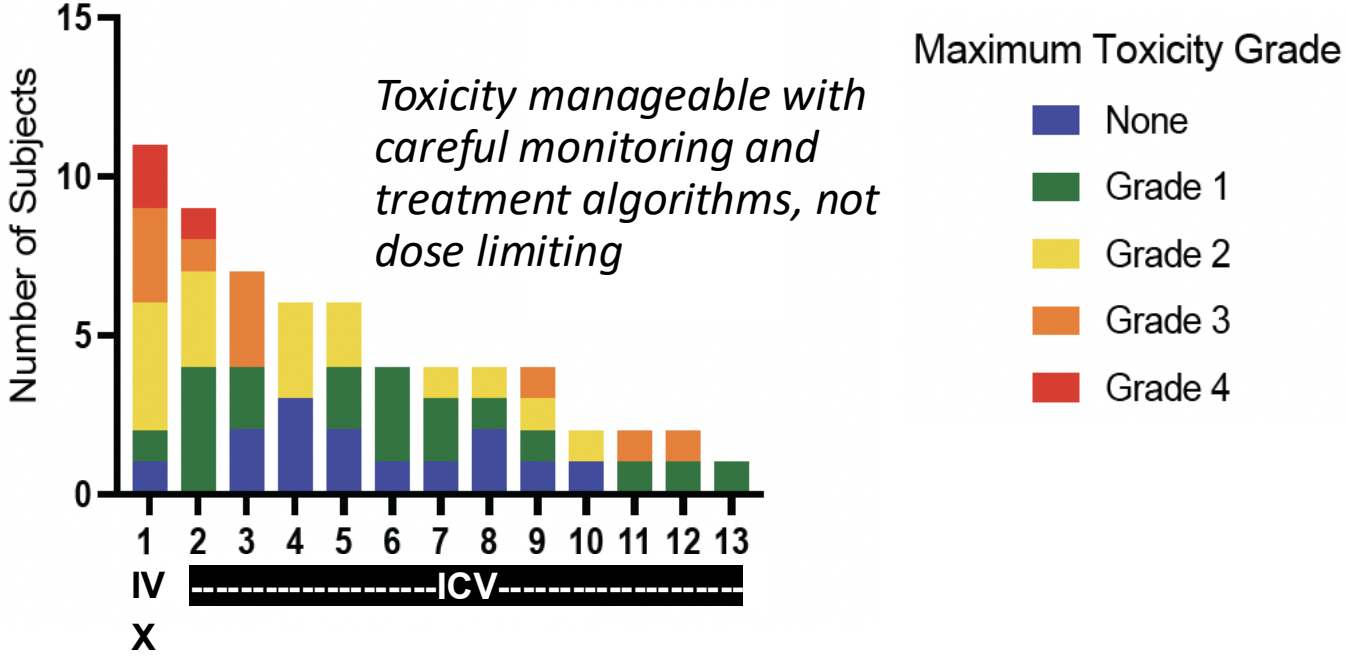
Monje….Mackall, Nature, 2024

Arm A Toxicity:
-IV infusion: Dose Limiting High-Grade Cytokine Release Syndrome
-ICV infusions: no Dose Limiting Toxicity

CRS = Cytokine Release Syndrome



TIAN = Tumor Inflammation Associated Neurotoxicity



Majzner, Ramakrishna*…Mackall^, Monje^ Nature, 2022*

Monje….Mackall, Nature, 2024

Mahdi….Monje, Nature Med, 2023

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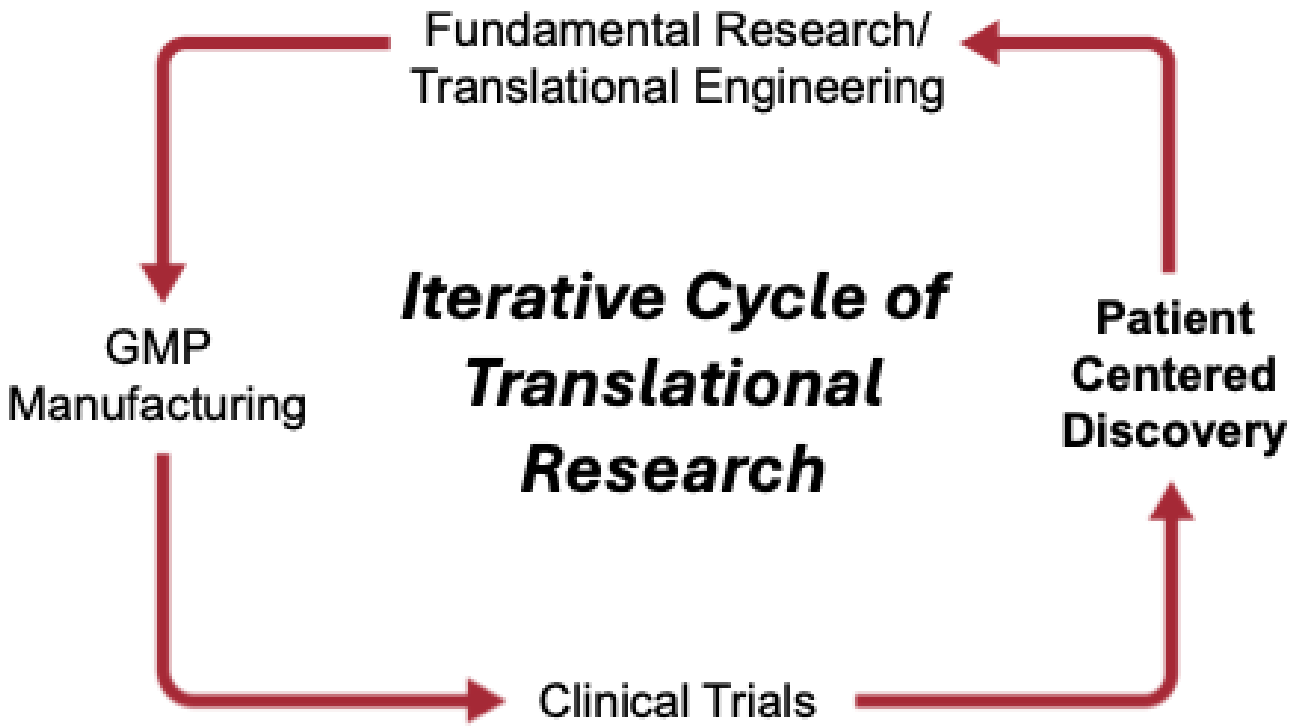
CIRM Funding Accelerates Progress by Enabling Patient Centered Discovery Research



Why do some patients experience better outcomes than others?

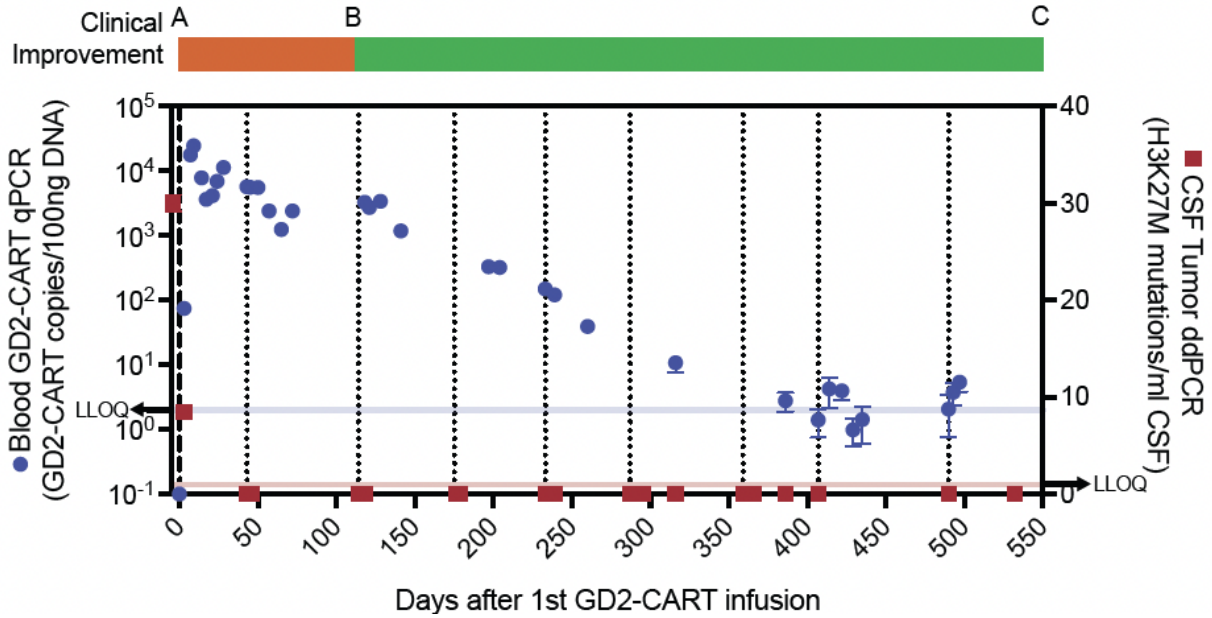
How do the therapies fail?

What are the mechanisms of resistance?

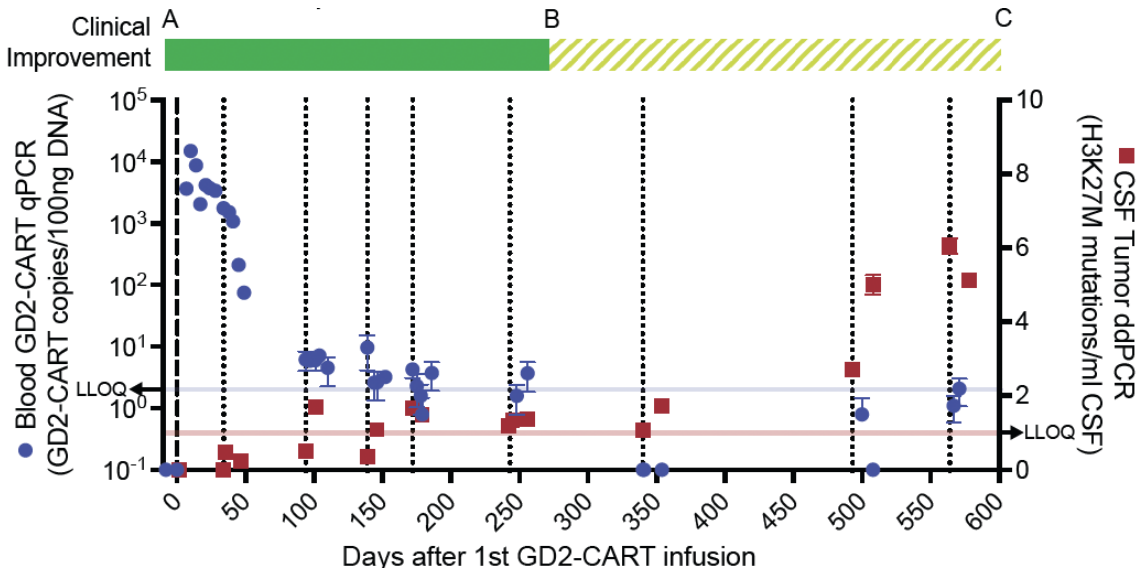
What are the most important steps needed to improve the therapy?

Arm A: Durability of Response to GD2-CART Appears to Correlate with Durability of CAR T Cell Persistence?

Patient 10: Durable Complete Response & Durable Persistence



Patient 6: Near Complete Response Followed by Progression Temporally Associated with Loss of CAR T cells



Clinical worsening

Clinical improvement

Mixed response

Monje….Mackall, Nature, 2024

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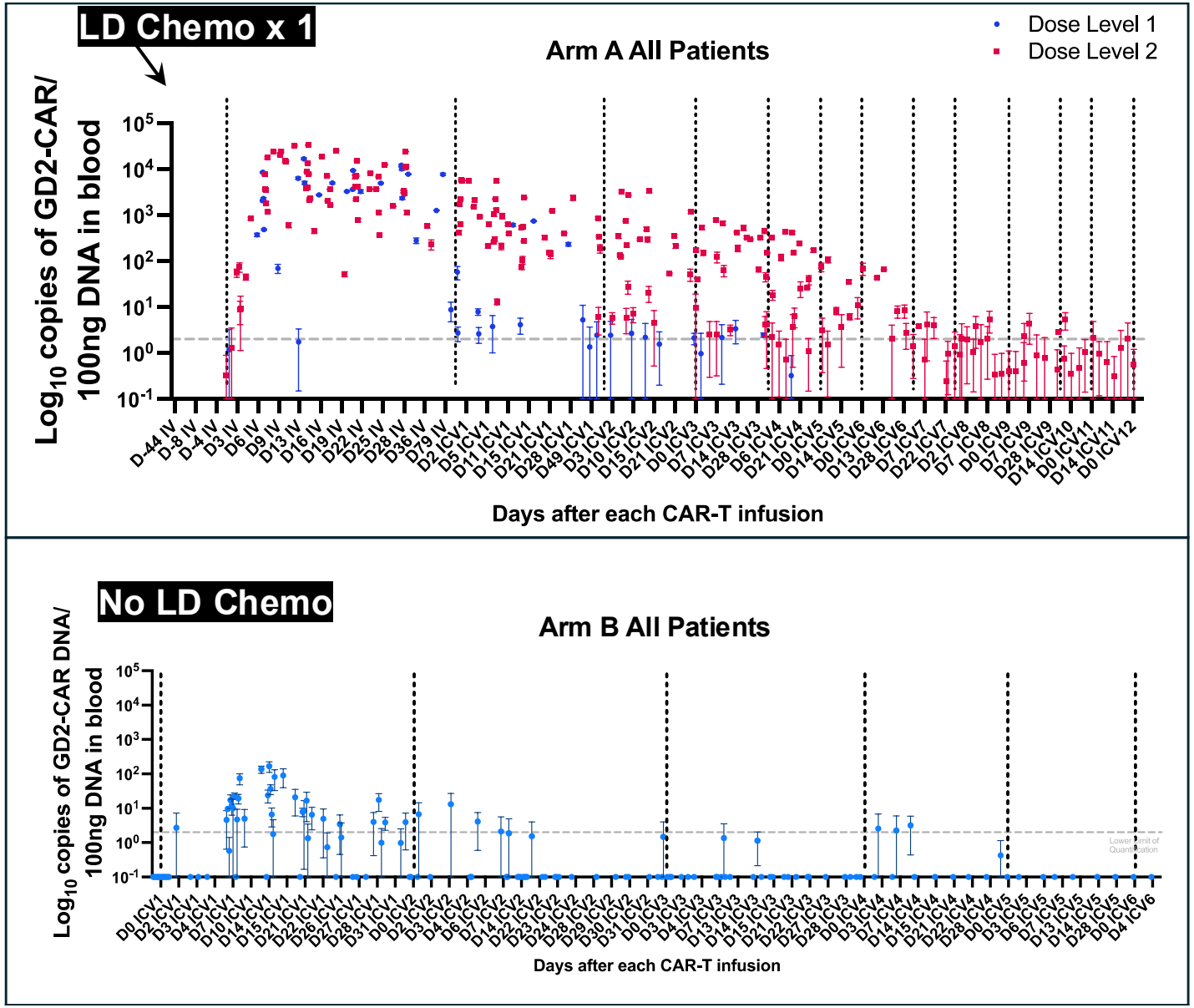
Evolution of the Treatment Regimen to Diminish Toxicity Resulted in Diminished Efficacy

Arm A (n=13)				
Regimen	**Outcomes**	**Toxicity**	**Correlates**	
Lymphodepletion x 1 IV infusion x1 Sequential ICV	**OS 20.6 mos, Sustained clinical benefit**	**Dose limiting CRS**	Some patients with excellent persistence, ?better outcomes	

Based upon these results, we modified the protocol to open Arm B

Arm B (n=18)				
Regimen	**Outcomes**	**Toxicity**	**Correlates**	
No lymphodepletion Sequential ICV	**OS 14.8 mos, Transient clinical benefit**	Non-Dose limiting	Very poor CAR persistence	

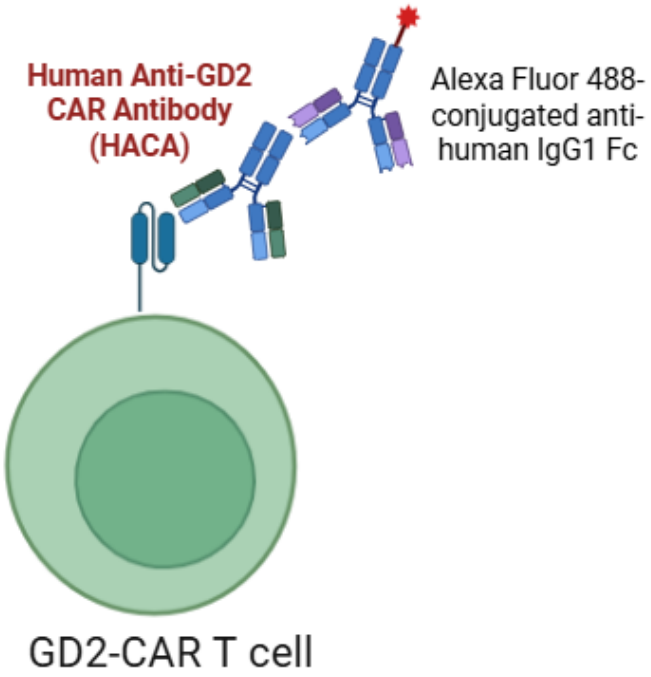
GD2-CAR Persistence Much Greater on Arm A Than Arm B

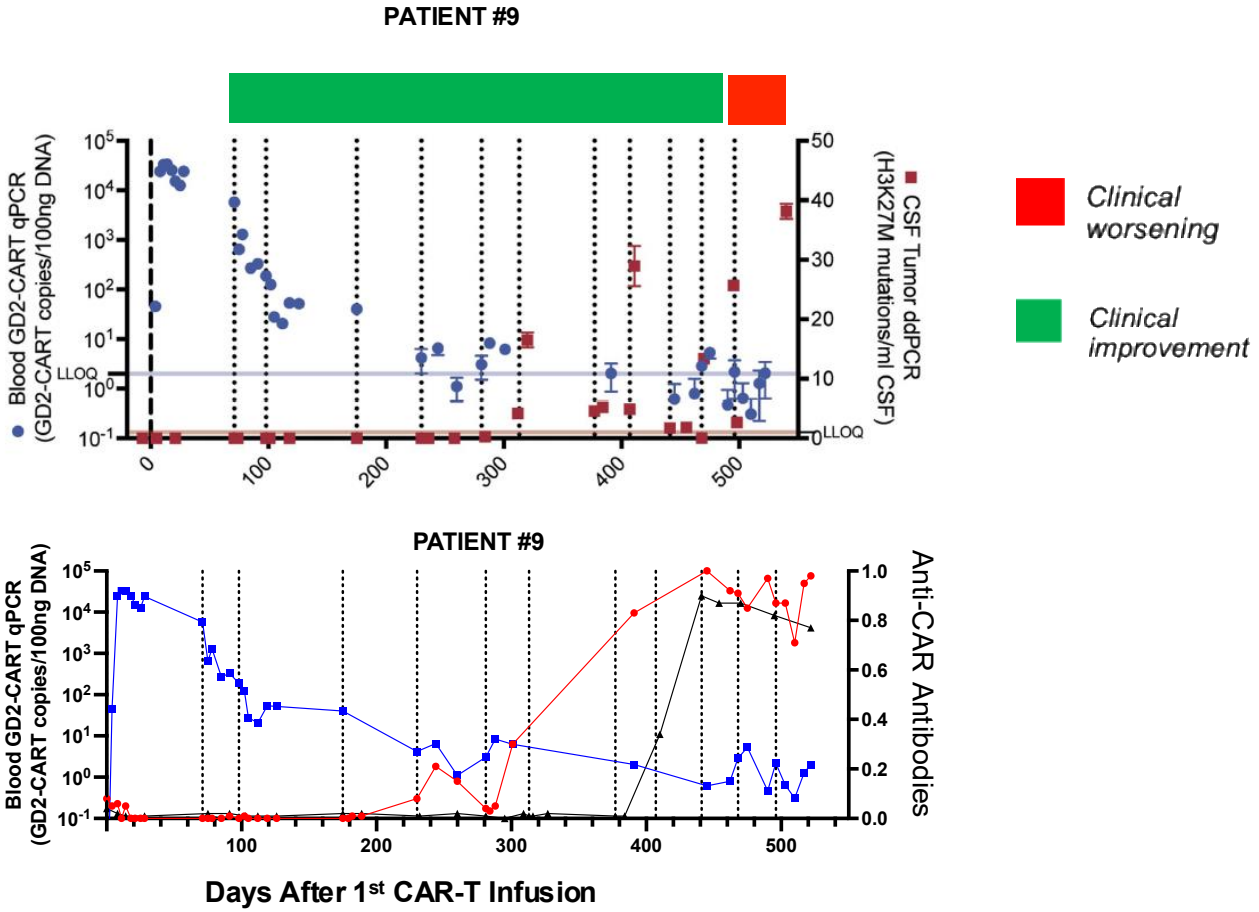


Anti-GD2-CAR Antibodies:

--Emerged in most patients on Arm A and temporally correlated with loss of GD2-CART persistence and tumor progression

--Emerged early on Arm B in all patients





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Hypothesis: Immune responses to the CAR T cells are limiting CAR persistence and preventing disease control. Lymphodepletion reduced these immune responses on Arm A.

Evolution of the Treatment Regimen Has Identified an Important Role for Lymphodepletion in Efficacy

Regimen	Outcomes	Toxicity	CAR Persistence	Anti-CAR immune responses
Arm A (n=13)				
Lymphodepletion x 1 IV infusion x1 Sequential ICV	**Median OS 20.6 mos,** **Sustained benefit**	Dose limiting CRS	Greater persistence correlates with better outcomes	Many patients, occur late
Arm B (n=18)				
No lymphodepletion Sequential ICV	**Median OS 14.8 mos,** **Transient benefit**	Non-Dose limiting	Very poor CAR persistence	All patients, occur early
Arm C (n=11)				
Sequential lymphodepletion Sequential ICV	**Median OS not reached**	Non-Dose limiting	Better CAR persistence	Preliminary data shows lower levels but still present
Arm D (now enrolling)				
Sequential lymphodepletion + rituximab, Sequential ICV	**Too early**	Non-dose limiting thus far	Pending	Pending

Current Status and Next Steps

- **CLIN2-12595** Demonstrated safety and significant clinical efficacy of GD2-CAR T cells for a universally lethal brain tumor for which no standard upfront therapies are available beyond palliative radiation.
  - Patients appear to be living longer and are experiencing better quality of life following GD2-CART
- We have learned that the target product profile requires sequential intracerebral infusions and sequential lymphodepleting chemotherapy, likely with rituximab (mirror Arm D).
- Based upon these promising results, this therapy has been designated an Regenerative Medicine Advanced Therapeutic by the US FDA.
- We have completed a Comprehensive RMAT Type B Meeting with the US FDA, which has provided critical details regarding steps necessary for pivotal testing:
  - Clinical manufacturing and controls
  - Primary and secondary endpoints
- Next steps
  - Completion of the current Phase I single institution trial funded by the CLIN2-12595
  - Conduct a (small) multisite Phase I to ensure reproducibility of results and train non-Stanford investigators regarding toxicity management
  - Launch multisite potentially pivotal single arm Phase II to demonstrate efficacy
  - File Biological License Application
- This success has emphasized a critical need for to bring active cell/gene therapies for market for rare diseases.

nature medicine

Perspective

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Enhancing pediatric access to cell and gene therapies

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Check for updates

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ACCESSforKIDS

A not-for-profit 501c3 with a nested Public Benefit Corporation (B Corp) for-profit subsidiary designed to bridge the pharma valley of death and expand access for children by developing and commercializing life-saving advanced medicines for pediatric oncology indications

Our approach will disrupt the typical cell therapy and not-for-profit landscapes to create a sustainable organization

Mission-driven approach

Lean, virtual biotech

Subsidiary for-profit public benefit corp.

Low-cost IP acquisition

Development and commercialization cost reduction

De-risked asset portfolio

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Our patients and families!

Stanford MEDICINE | Center for Cancer Cell Therapy

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