AUTOLOGOUS ACTIVATED T-CELLS TRANSDUCED WITH A 3rd *G*ENERATION GD-2 CHIMERIC ANTIGEN *R*ECEPTOR *A*ND *i*CASPASE9 SAFETY SWITCH ADMINISTERED TO PATIENTS WITH RELAPSED OR REFRACTORY *N*EUROBLASTOMA (GRAIN)

RAC Update

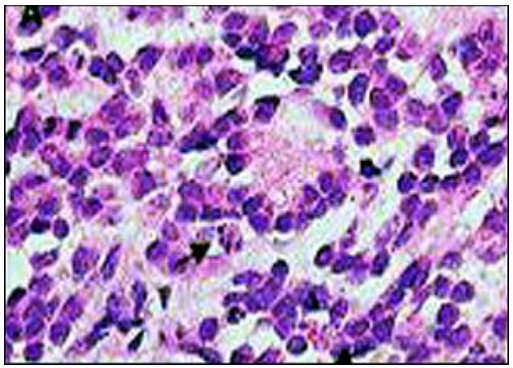
December 5th, 2012

Center for CAGT Cell and Gene Therapy

BCM Baylor College of Medicine | Methodist The Methodist Hospital | Texas Children's Hospital

Neuroblastoma

- Most common extracranial solid tumor in children
- Neoplasm of neural crest origin
- Incidence of 10.5 per 1 million children < 15 years
  - 1.2:1 male to female ratio
  - No difference based upon race or geography
  - Median age at diagnosis is 23 months



Park et al 2010

Current Survival Rates

- Accounts for 8-10% pediatric cancers
  - 15% cancer deaths
- Survival is very good for low and intermediate risk disease
  - 5 yr survival rate ~ 85-95%
- High risk disease requires multimodal therapy
  - 5 yr survival rate ~ 30-40%

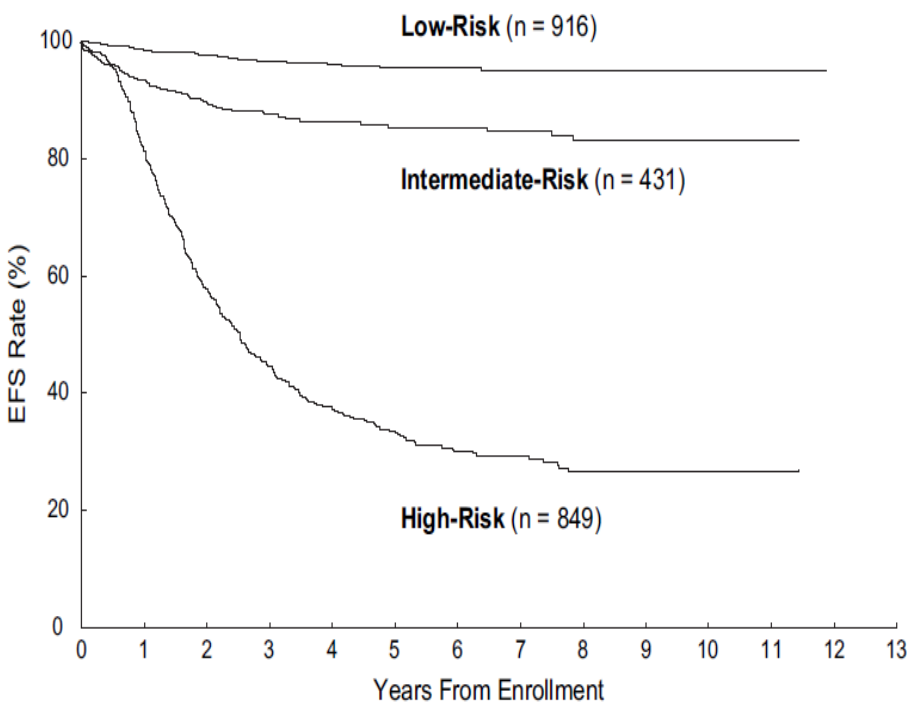


Fig. 3. Analysis of event free survival by risk stratification. (*Courtesy of* W.B. London, PhD, Children's Oncology Group Statistical Office.)

Park et al 2010

The What, When and Why of Immunotherapy

- What is it?
  - Using the immune system to help eliminate cancer or disease
- Why use it?
  - Target specific parts of the tumor (i.e. antigens) not commonly seen on normal cells
  - Should be associated with fewer side effects

Benefits of T cell Therapy

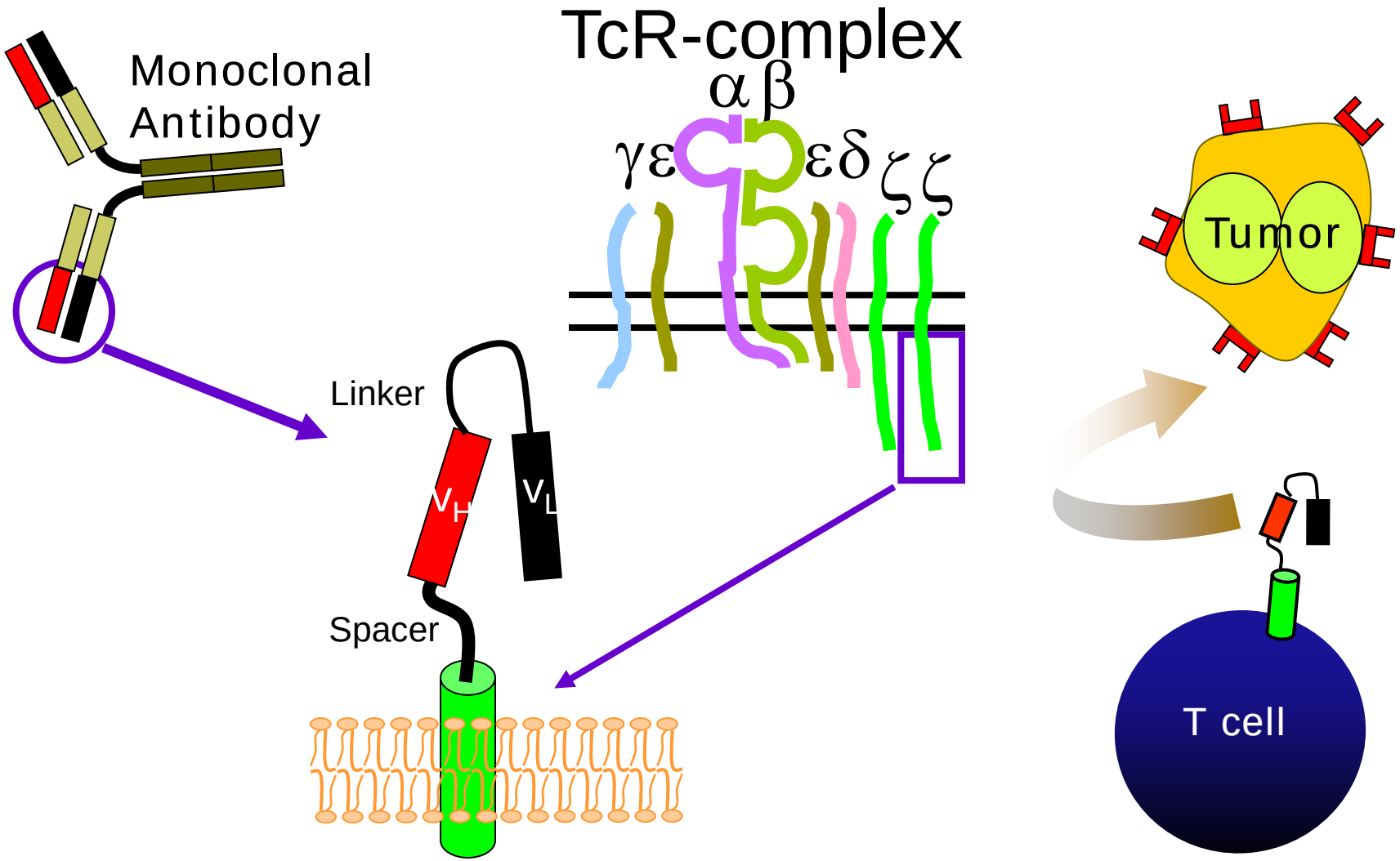
- Bio-distribution into tumor tissue
  - Traffic through multiple tissue planes
- Known efficacy against solid tumors
  - NPC
  - Bulky disease
- Self amplifying

CAR-specific T cell Therapies

Modify T lymphocytes to express a chimeric antigen receptor (CAR)

Target GD2 for patients with neuroblastoma

Chimeric Antigen Receptor Generation



Phase I Study with CAR-redirected T cells in Neuroblastoma (2004-2009)

- Primary objective
  - Safety of GD2 CAR T cell administration to patients with high-risk neuroblastoma
- Secondary objective
  - Evaluate the persistence and efficacy of adoptively transferred GD2 CAR T cells

Patient Details

- 19 patients were treated
  - 10 on dose level 1 ($2x10^7/m^2$)
  - 6 on dose level 2 ($5x10^7/m^2$)
  - 3 on dose level 3 ($1x10^8/m^2$)
- Median age of 7 years (range 2-20)
- 22 infusions (44 lines)
  - 3 patients received 2 infusions
  - No dose limiting toxicities identified

Patient Details

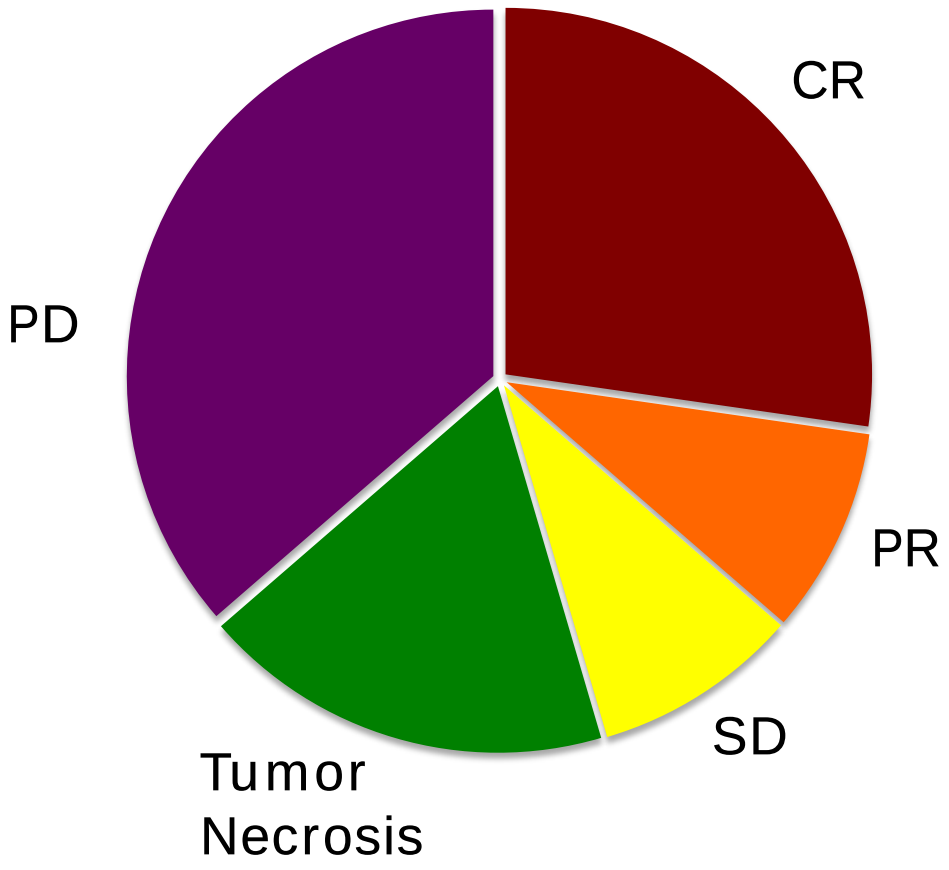
- At the time of infusion
  - 8 with no evidence of disease (NED)
    - 3 after HR therapy
    - 5 with history of relapse, but NED
  - 4 relapsed with active, limited disease
    - 3 with solitary bone lesions
    - 1 with bone marrow disease
  - 7 relapsed with bulky disease

Patient Details: Clinical Outcome

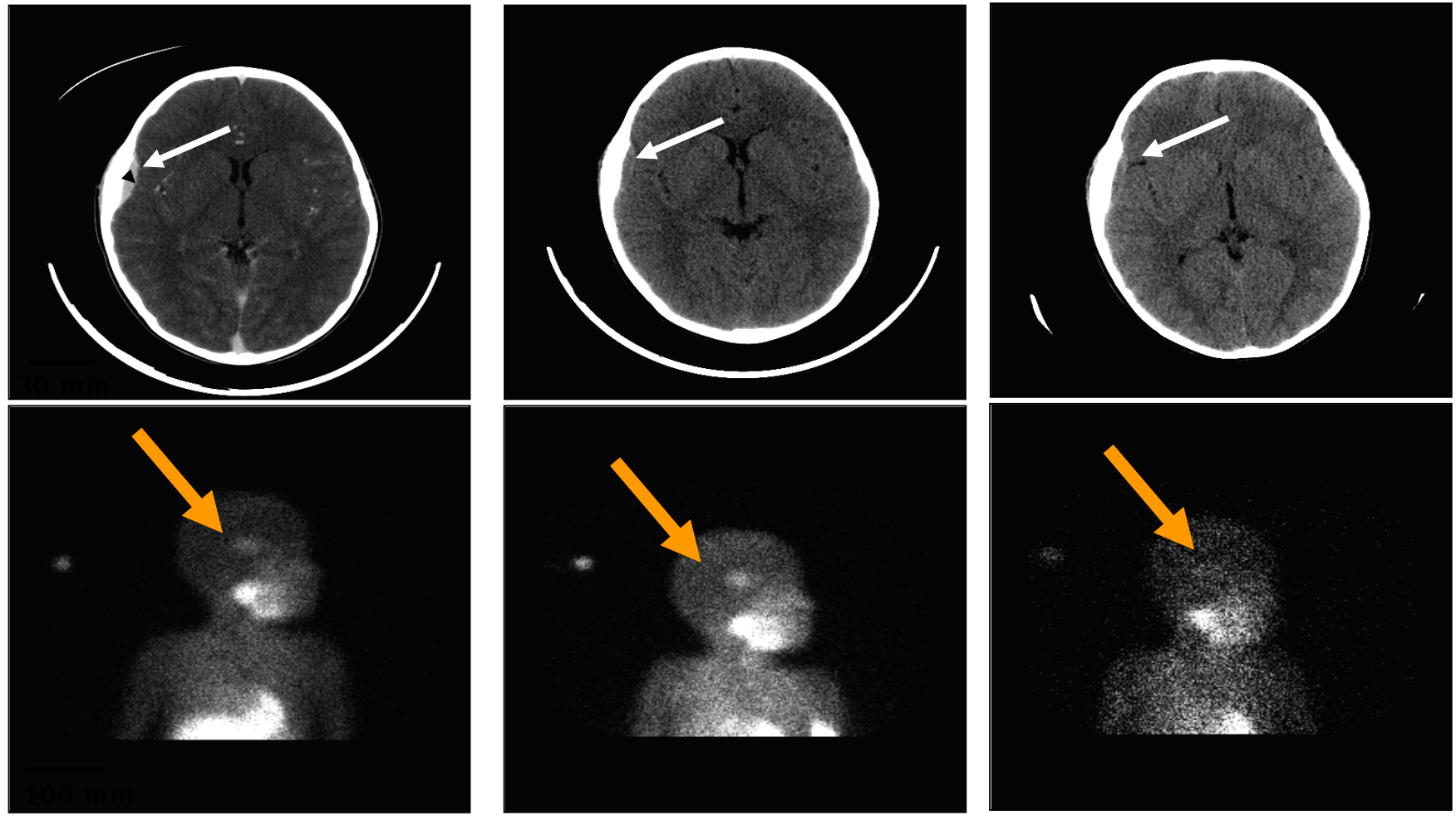
- 8 with NED
  - Median time to relapse was 411 days (142-NA)
- 4 relapsed with active, limited disease
  - 3 CR
    - 2 with solitary bone lesions
    - 1 with bone marrow disease
- 7 relapsed with bulky disease
  - 1 AWD

Best Response: Patients with Active Disease at Time of GD2 T cell Infusion (N=11)

- 3 CR (27%)
  - Bone marrow resolution
  - Resolution of spinal lesion
  - Resolution of skull lesion
- 1 PR (9%)
- 1 SD (9%)
- 2 tumor necrosis (18%)
  - Scapular lesion
  - Liver lesion



Complete Response: MRI and MIBG



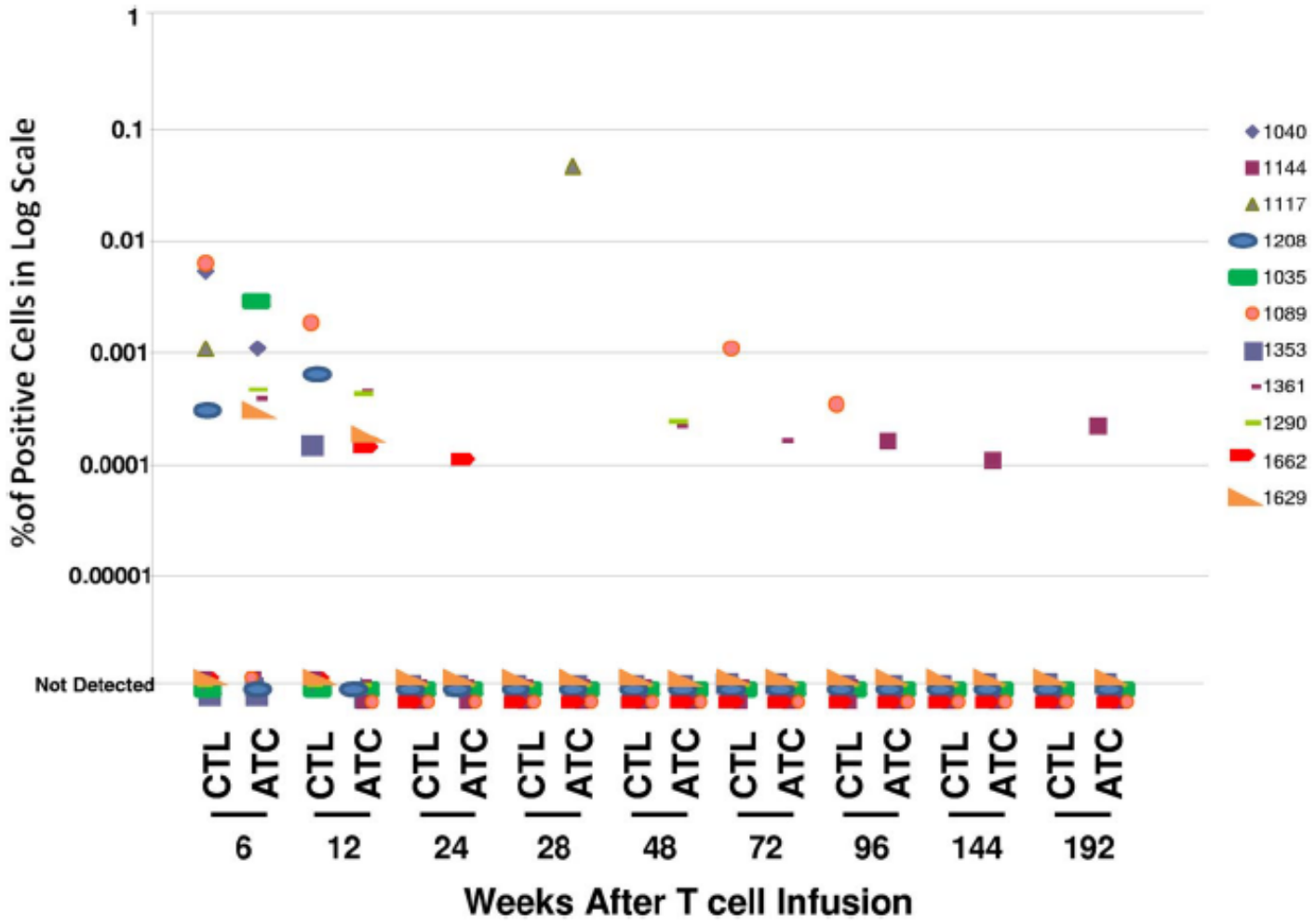
Before infusion

6 weeks

4 months

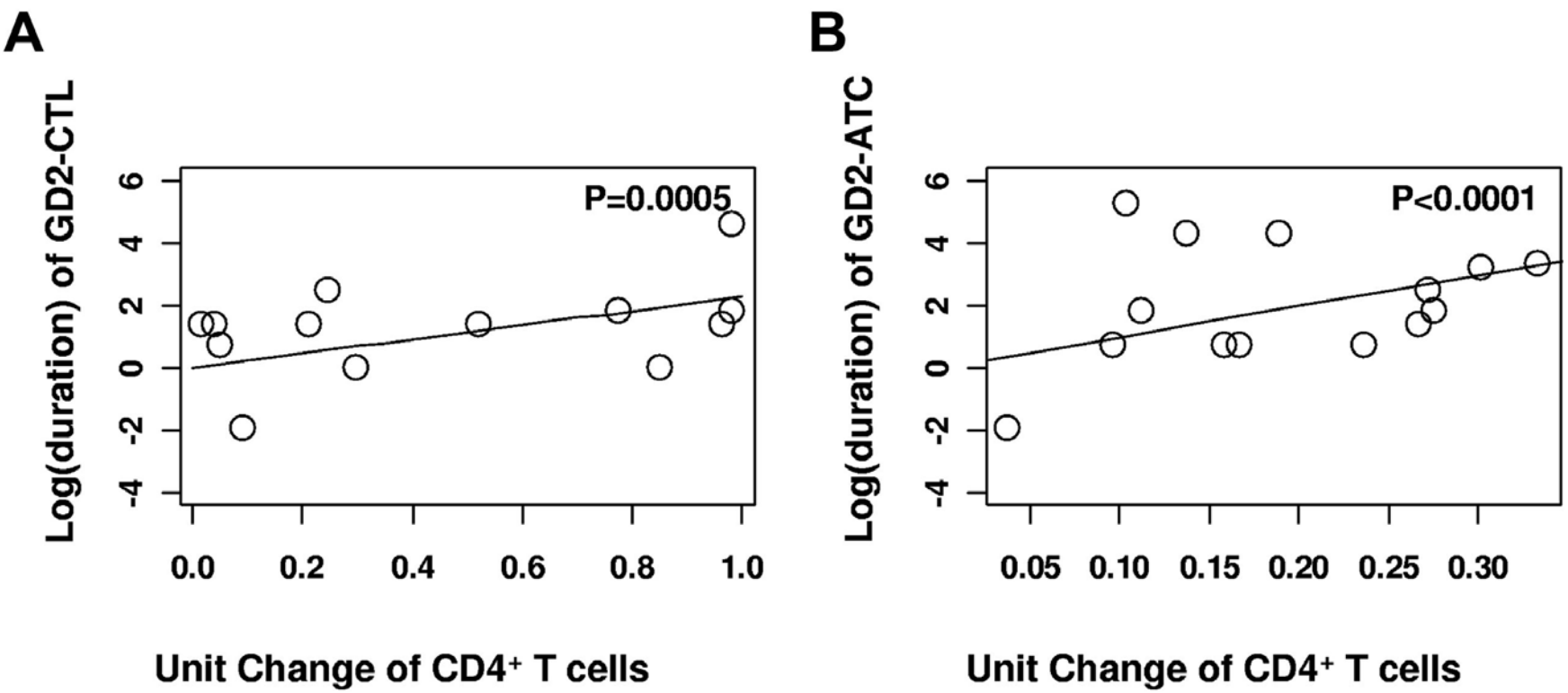
Pule et al 2008

Prolonged Detection of GD2 CAR T-cells



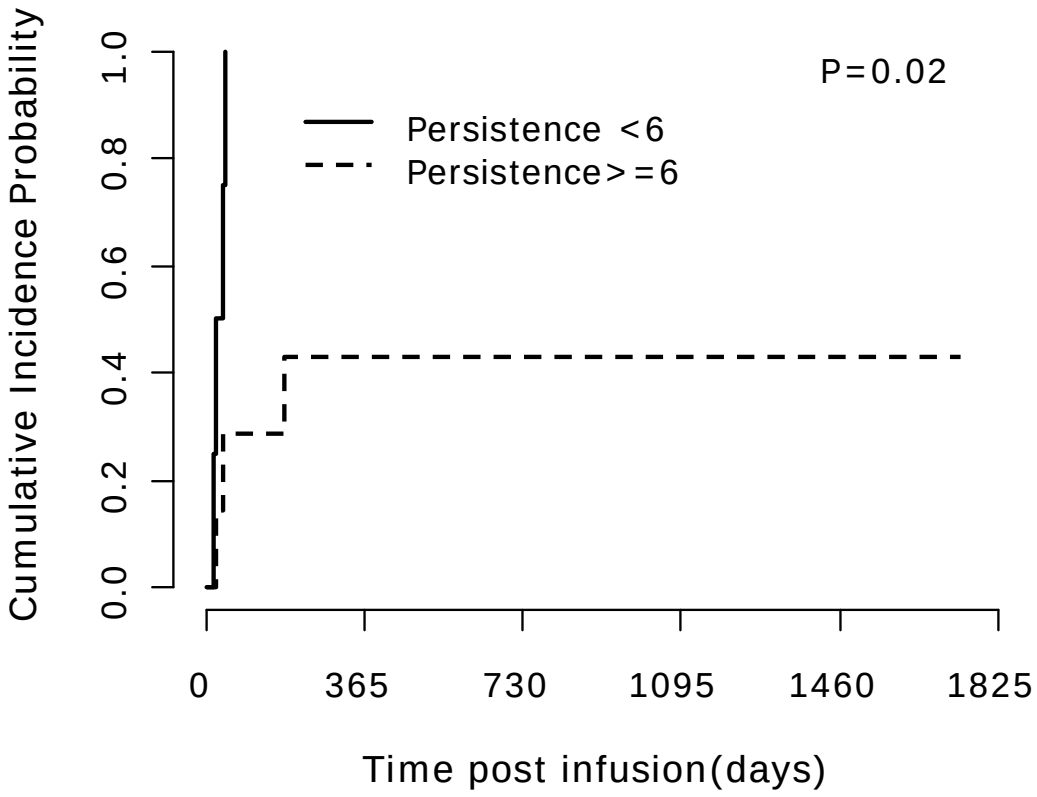
Louis et al 2011

Persistence Associated with the Percentage of CD4+ T cells in the Product



Louis et al 2011

Progression delayed if GD2 T Cells Persist ≥ 6 weeks



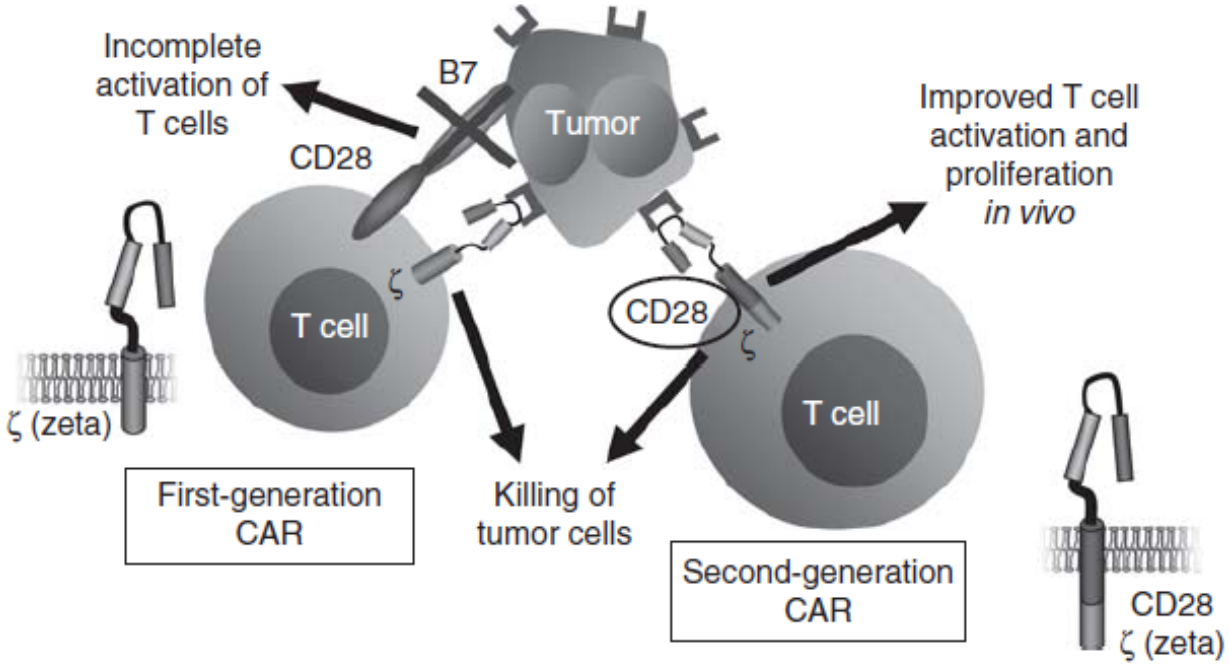
Louis et al 2011

Conclusions: 1st Generation GD2 CAR T-cells

- No severe or dose limiting toxicities
- 1st generation GD2 CAR T cells may be detected at low levels for extended time
  - Percentage of $CD4^+$ cells within the product affects persistence
- Clinical responses, including resolution of active disease, seen after infusion
  - 45% (CR, PR, SD) response rate
  - Persistence associated with increases time to progression

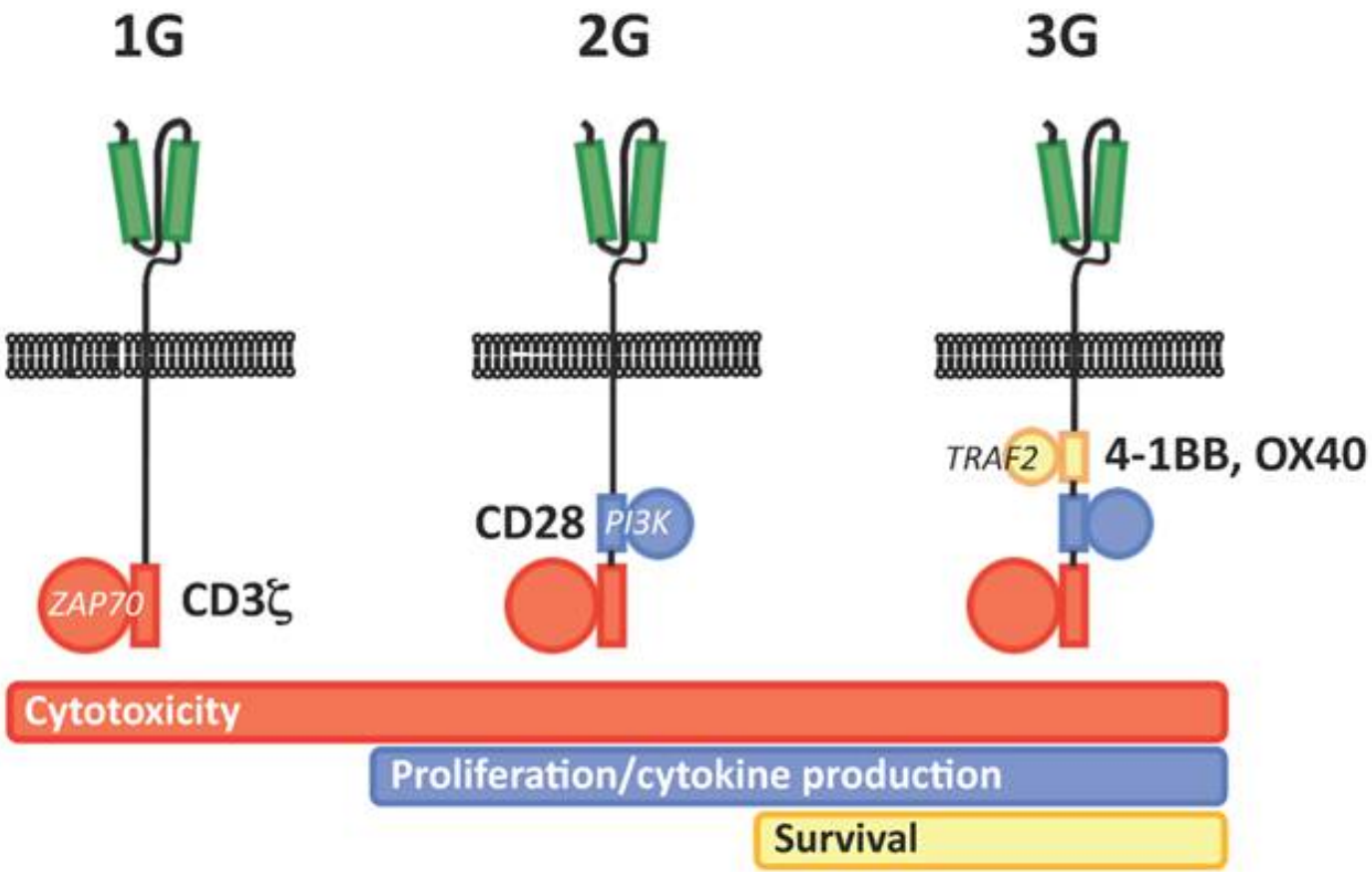
Current Limitations

- Improve anti-tumor effects of GD2 CAR T-cells
  - Proliferation
  - Cell survival after infusion



Ramos et al 2011

Next Generation CARs



Casucci et al 2011

3rd Generation CAR with OX40

- OX40 and 4-1BB endodomains
  - Belong to the TNF receptor superfamily
  - Co-expressed with CD28 to produce 3rd generation CARs
- CD28-OX40
  - Improved regulation and proliferation of **$CD4^+$** cells versus effects of 4-1BB on **$CD8^+$** T cells
- SAE after infusion with a HER2 (ERB) CAR containing both CD28 and 4-1BB
  - Death secondary to T cell activation which caused a "cytokine storm"

An Added Level of Safety: iC9

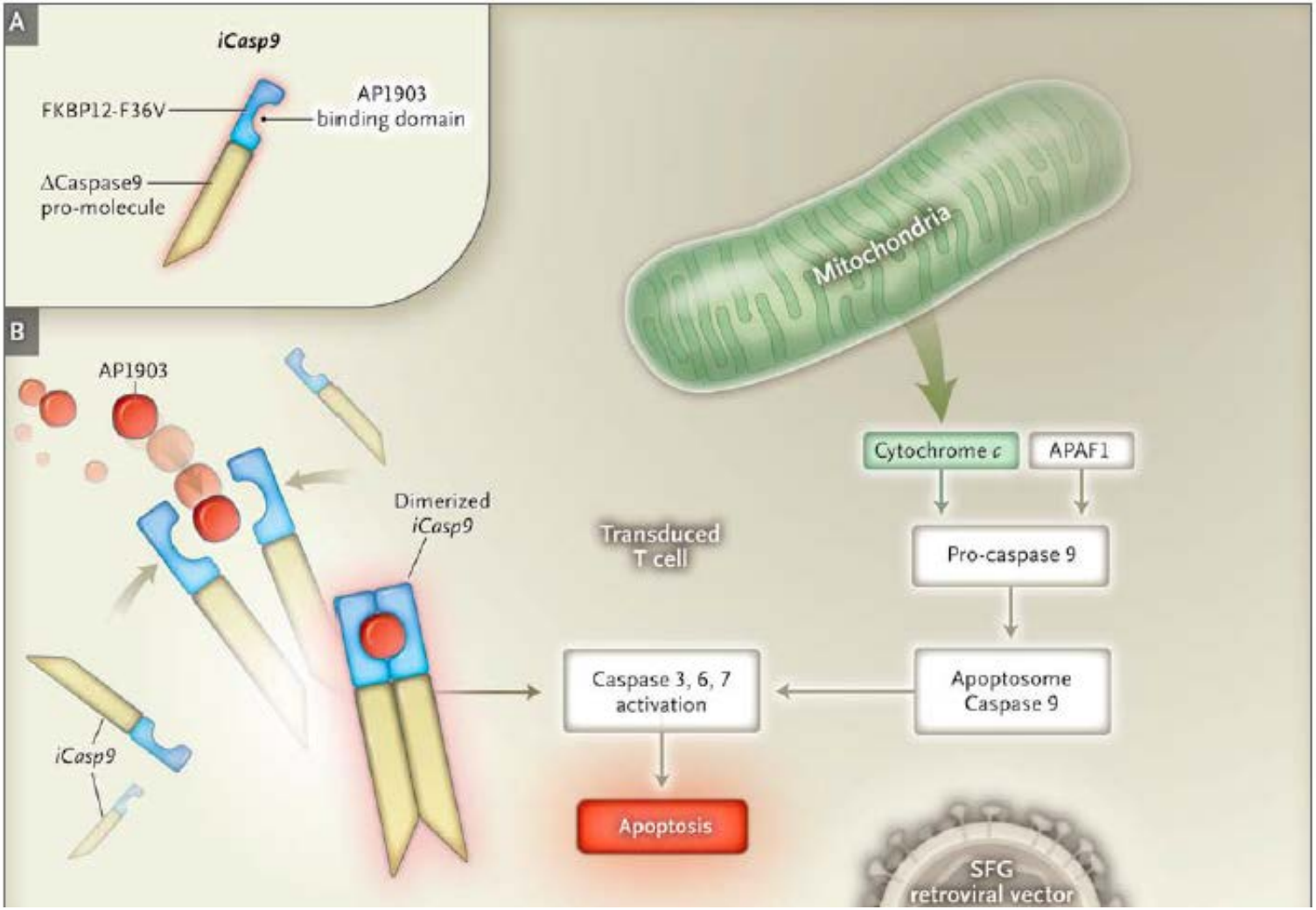
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

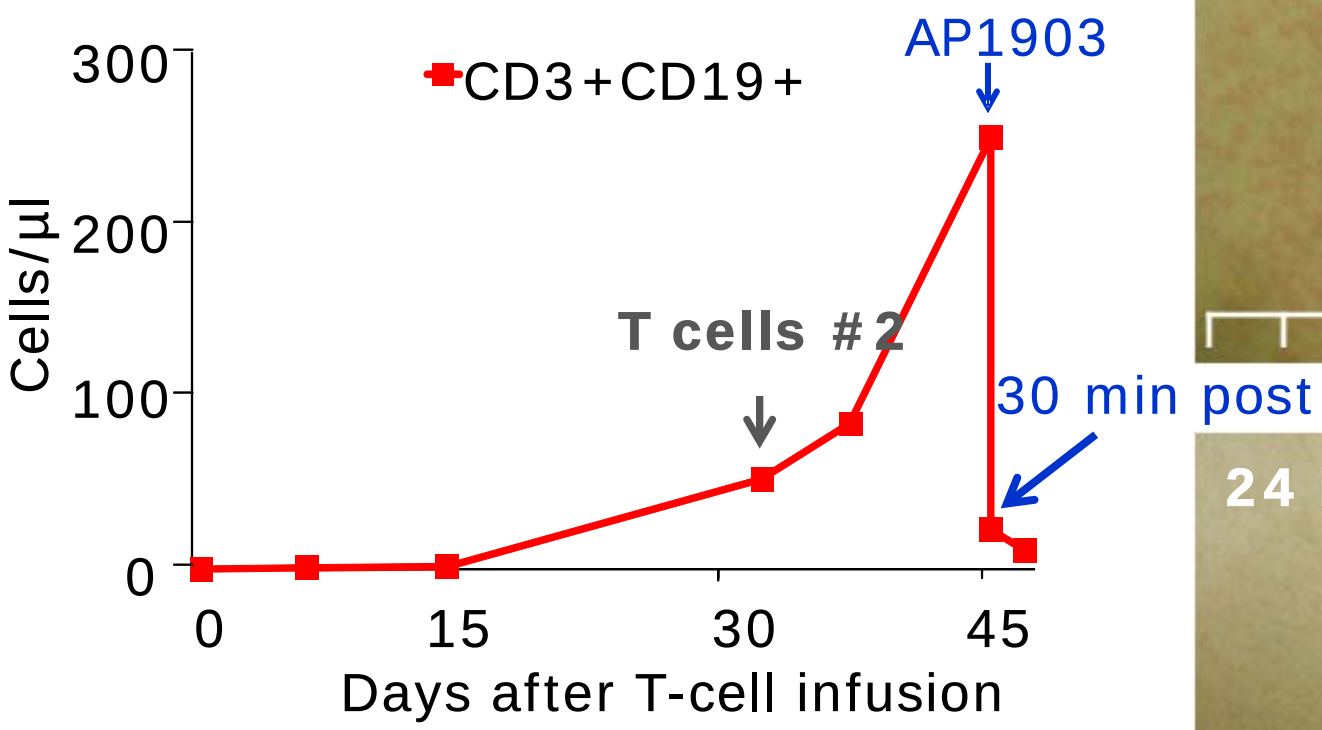
Inducible Apoptosis as a Safety Switch for Adoptive Cell Therapy

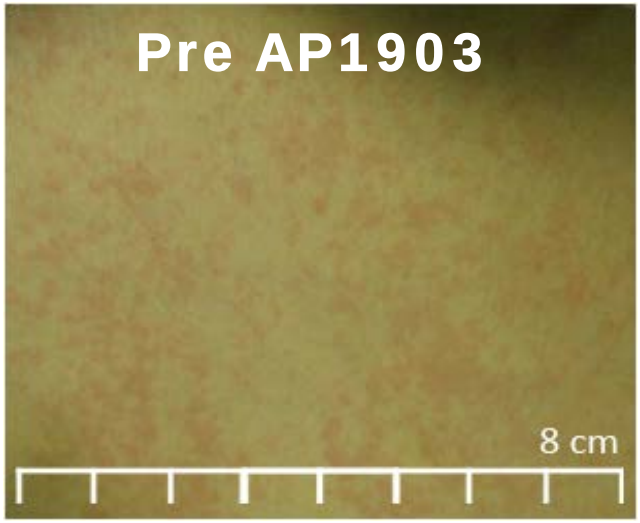
Antonio Di Stasi, M.D., Siok-Keen Tey, M.D., Gianpietro Dotti, M.D., Yuriko Fujita, M.D., Alana Kennedy-Nasser, M.D., Caridad Martinez, M.D., Karin Straathof, M.D., Enli Liu, M.D., April G. Durett, M.Sc., Bambi Grilley, R.Ph., Hao Liu, Ph.D., Conrad R. Cruz, M.D., Barbara Savoldo, M.D., Adrian P. Gee, Ph.D., John Schindler, Ph.D., Robert A. Krance, M.D., Helen E. Heslop, M.D., David M. Spencer, Ph.D., Cliona M. Rooney, Ph.D., and Malcolm K. Brenner, M.D.

Dimerized iC9 Leads to Cell Death



Prompt Resolution of Skin GvHD after a Single Dose of AP1903 (Patient 2)





Study Hypothesis

- Infusion of 3rd generation GD2 CAR T-cells, modified with an iC9 safety switch, will lead to sustained proliferation and persistence of GD2 T cells in the peripheral blood of patients with relapsed or refractory neuroblastoma
- Adverse effects will be controlled by dimerizer drug

GRAIN: Clinical Trial Objectives

- Primary
  - To determine the maximum tolerated dose (**MTD**) and **safety profile** of autologous iC9 GD2 T cells administered to patients with relapsed or refractory neuroblastoma

- Secondary
  - To evaluate the **immunologic and anti-tumor response** to autologous 3rd generation iC9 GD2 T cell administration in patients with relapsed or refractory neuroblastoma
  - To assess the effects of dimerizing drug in patients with product related toxicity

Phase I Dose Levels

- Dosing will be based on the actual number of transduced cells. **All doses are per m^2.**
  - Dose Level 1 = 1×10^7
  - Dose Level 2 = 1×10^8
  - Dose Level 3 = 2×10^8

Additional Doses

- No additional cells can be administered until the 6 week safety profile is completed
  - Patients with neither DLT nor PD after the prior infusion
  - Patient who demonstrated at least SD AND had no evidence of a DLT with any infusion and subsequently develop PD not responsive to chemotherapy and/or other investigational agents
- Max of 2 additional doses per situation
  - If cells are available

iC9-GD2 T cell Administration

- Short stay admission into the CRC
- Premedication
  - Diphenhydramine up to 1mg/kg IV (max 50 mg)
  - Acetaminophen 10mg/kg PO (max 650 mg)
- T cells will be given by IV over 5 to 10 min
- 4 hour observation period prior to discharge
- Follow-up
  - Weeks 1, 2, 4, 6, and 8
  - Months 3, 6, 9, 12 and then every 6 months until year 15

Administration of AP 1903

- Gr 3 or greater toxicity attributed to T cell infusion
  - 0.4 mg/kg IV over 2 hrs
  - Blood will be sampled at 2, 24 and 48 hrs
- Response will be evaluated 48 hr intervals
  - No response or worsening symptoms
    - Grade 3 non-hematologic toxicity: Up to 3 additional doses
    - Grade 4 or greater toxicities: Up to 3 additional doses in combination with steroids
  - Patients with severe persistent or worsening symptoms will be treated with high dose steroids

Statistical Design (2-14 Patients)

- Modified continual reassessment method (mCRM) using a cohort of size 2
  - In order to obtain additional safety data, we will treat a total of 6 patients at the MTD level
- Simulation studies showed that mCRM obtained better estimates of the MTD
  - Higher probability of declaring the appropriate dose level as the MTD
  - Smaller number of patients accrued at lower and likely ineffective dose levels
  - Lower average total number of patients required for the trial

Trial Oversight

- Monitored in accordance with the DSMB for investigator-initiated Phase I and II studies in the Center for Cell and Gene Therapy at BCM
- Conduct of the trial will be evaluated in accordance with the TCCC and CAGT Quality Assurance Policy and Procedure Plan and Quality Control Policy and Procedure Plan

Conclusions

- 1st generation GD2-CAR T cells
  - Safe
  - Low level of detection
  - Anti-tumor effects
- 3rd generation GD2-CAR T cells
  - Sustained proliferation and persistence
  - Safety
    - iC9 safety switch
    - mCRM statistical plan
    - Scheduled follow-up and trial oversight

Acknowledgements

TRL Laboratories

Helen Heslop
Cliona Rooney
Malcolm Brenner

Gianpetro Dotti
Barbara Savoldo
Stephen Gottschalk
Ann Leen
Eric Yvon
Nabil Ahmed
Catherine Bollard

Texas Children's Cancer Center

David Poplack

Clinical Research

Bambi Grilley
Bridget Medina
Florence Noel
Yu-Feng Lin
Catherine Perera
Vicky Torrano

GMP Laboratory

Adrian Gee
Oumar Diouf
Joyce Ku
Huimin Zhang
Enli Liu
Rong Cai

NIH

Gillson Longenbaugh Foundation

Anderson Foundation

Cure Kids' Cancer Foundation

Solving Kids' Cancer Foundation