

# **T Cell Immunotherapy- Optimizing Trial Design**

## **Session I**

### **Current Status of Cancer Immunotherapy: Trials, Results, and Challenges**

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**Institution: Baylor College of Medicine**

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# Disclosure

Center for Cell and Gene Therapy has collaborative research agreement with Celgene to develop genetically modified T cells

# CAR Studies at BCM

CAR	T cell	Patients Enrolled
CD19 zeta CD19 zeta/28	Activated CD3 or CD3/28 T cell	12
CD19 zeta CD19 zeta/28	Activated CD3/28 T cell or EBV CTL	4
CD19 zeta/28	Donor multivirus CTL	9
Kappa zeta/28	Activated CD3 or CD3/28 T cell	10
CD30zeta/28	Activated CD3 or CD3/28 T cell	4
CD30zeta/28	EBV CTL	3
GD2 zeta	Activated CD3 T cell or EBV CTL	19
GD2 zeta/28/Ox40/iC9	Activated CD3 or CD3/28 T cell	
Her2Neu/28	Activated CD3 or CD3/28 T cell	34
Her2Neu/28	EBV CTL	6
<b>TOTAL</b>		<b>101</b>

# Overview of Trials

<b>Protocol number/title</b>	<b># 776: Phase I Study of CD19 Chimeric Receptor Expressing T Lymphocytes</b>	<b># 915: Phase I Study of the Administration of Peripheral Blood T Cells or EBV Specific CTLs Expressing CD19 CARs</b>
<b>Disease indication/Research Participant population</b>	<b>B-Cell Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia</b>	<b>Advanced B-Cell Non Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia</b>
<b>TCR or CAR product (ex vivo cell/vector/transgene) and Dose</b>	<b>Retrovirus CD19 CAR zeta/CD28 vs Zeta CD3 then CD3/28 activated T cells 4 x 10E7 to 4 x 10E8/m2</b>	<b>Retrovirus CD19 CAR zeta/CD28 in CD3/28 activated T cells Vs Retrovirus CD19 CAR zeta In EBV CTLs 4 x 10E7 to 4 x 10E8/m2</b>
<b>Trial initiation date/status /enrollment</b>	<b>Enrolled 12 patients – now evaluating Ipilumimab post infusion</b>	<b>Enrolled 4 patients - now closed</b>

# Overview of Trials (continued)

<b>Protocol number/title</b>	<b>PROTOCOL # 945: Phase I/II Study of the Administration of Multi-virus-specific Cytotoxic T Lymphocytes (CTLs) Expressing CD19 Chimeric Receptors</b>	<b>Protocol #941: Phase I Study Of Adoptive Transfer of Autologous T Lymphocytes Engrafted with a Chimeric Antigen Receptor Targeting the Kappa Light Chain</b>
<b>Disease indication/Research Participant population</b>	<b>ALL Or CD19 +ve CLL/NHL relapsed post transplant</b>	<b>CLL B cell lymphoma Myeloma</b>
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	<b>Retrovirus CD19 CAR zeta/CD28 in Donor Derived Trivirus specific CTLs 1.5 x 10E7 to 1.2 x 10E8/m2</b>	<b>Retrovirus kappa CAR zeta/CD28 in CD3/28 activated T cells 2 x 10E7 to 2 x 10E8/m2</b>
<b>Trial initiation date/status /enrollment</b>	<b>Enrolled 9 patients</b>	<b>Enrolled 10 patients</b>

# Overview of Trials (continued)

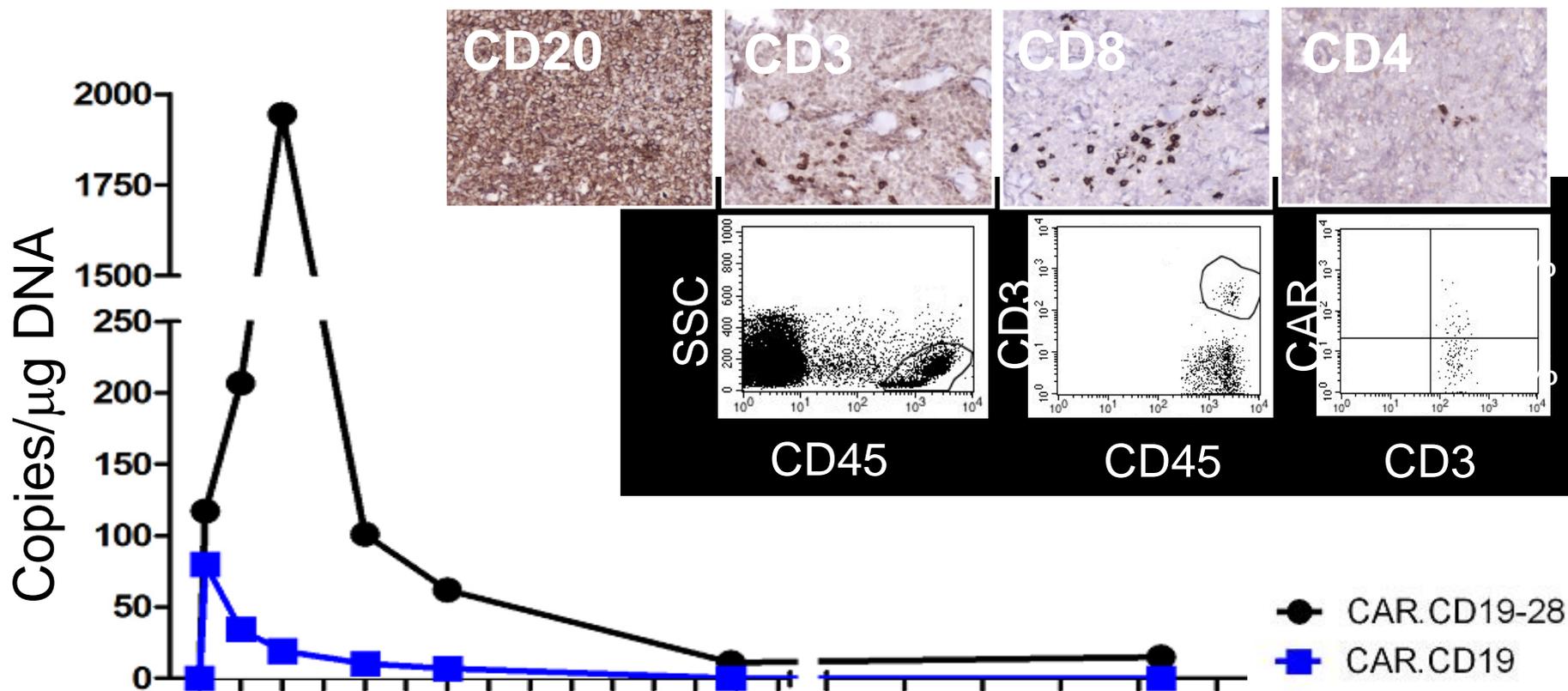
<b>Protocol number/title</b>	<b>PROTOCOL # 1034: Phase I Study of the Administration of EBV CTLs Expressing CD30 Chimeric Receptors</b>	<b>PROTOCOL # 1066: Phase I Study of the Administration of T Lymphocytes Expressing the CD30 Chimeric Antigen Receptor</b>
<b>Disease indication/Research Participant population</b>	<b>CD30+ve Hodgkin's or NHL</b>	<b>CD30+ve Hodgkin's or NHL</b>
<b>TCR or CAR product (ex vivo cell/ vector/transgene) and Dose</b>	<b>Retrovirus CD30 CAR zeta/CD28 In EBV CTLs 2 x 10E7 to 1 x 10E8/m2</b>	<b>Retrovirus CD30 CAR zeta/CD28 in CD3/28 activated T cells 2 x 10E7 to 2 x 10E8/m2</b>
<b>Trial initiation date/status /enrollment</b>	<b>Enrolled 3 patients</b>	<b>Enrolled 4 patients</b>

# Overview of Trials (continued)

<b>Protocol number/title</b>	<b>PROTOCOL # 563: : Administration of Peripheral Blood T-Cells and EBV Specific CTLs Transduced to Express GD-2 Specific Chimeric T Cell Receptors to Patients with Neuroblastoma</b>	<b>PROTOCOL # 1182: Autologous Activated T-Cells Transduced with a 3rd Generation GD-2 Chimeric Antigen Receptor and iCaspase9 Safety Switch Administered to Patients with Relapsed or Refractory Neuroblastoma</b>
<b>Disease indication/Research Participant population</b>	<b>Neuroblastoma</b>	<b>Neuroblastoma</b>
<b>TCR or CAR product (ex vivo cell/vector/transgene) and Dose</b>	<b>Retrovirus GD2 CAR zeta in EBV CTLs or CD3-activated T cells 4 x 10E7 to 4 x 10E8/m2</b>	<b>Retrovirus GD2 CAR zeta CD28-OX40-icasp9 in CD3/28-activated T cells 1 x 10E7 to 2 x 10E8/m2</b>
<b>Trial initiation date/status /enrollment</b>	<b>Enrolled 19 patients</b>	<b>Opened last week</b>

# Lessons Learned- CD19 CAR Studies

## Better expansion and persistence with CD28

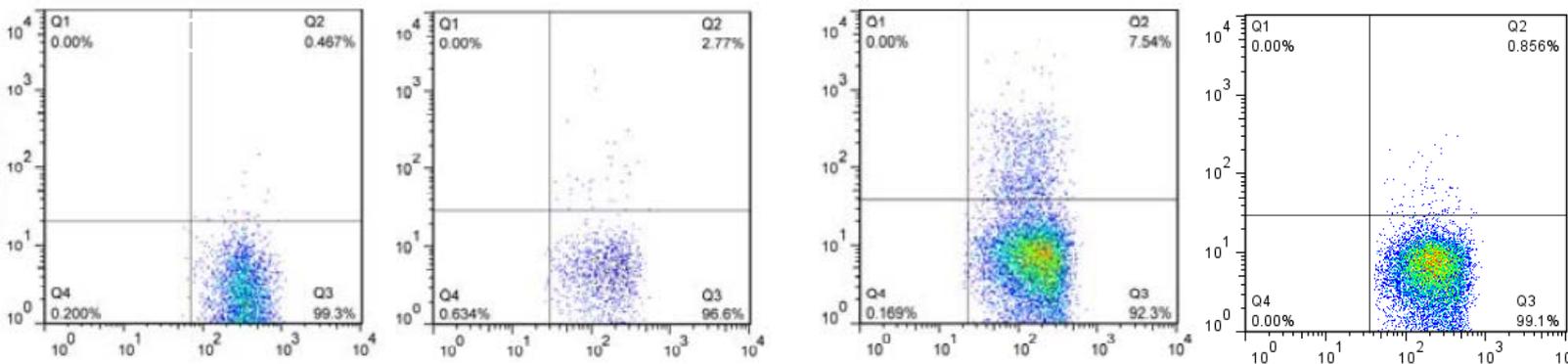
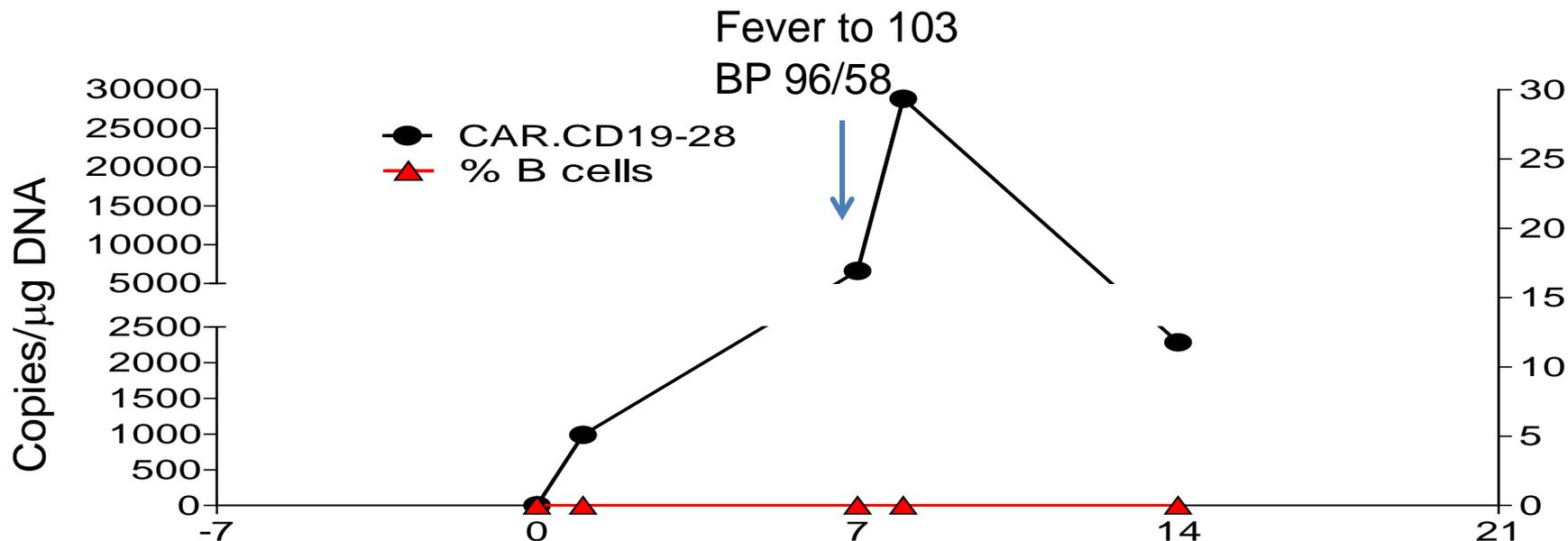


CAR+ T cells  $1 \times 10^8 / m^2$

*Savoldo et al JCI 2011*

# Lessons Learned – CD19

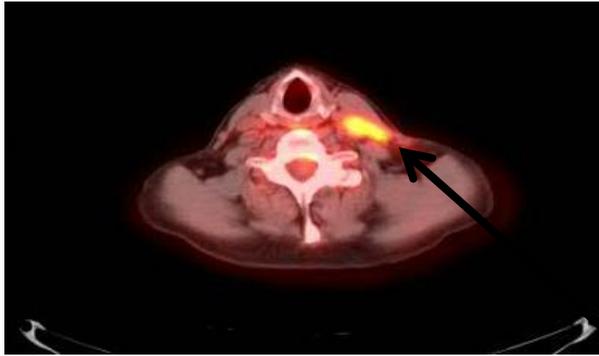
## Mantle cell lymphoma post autograft



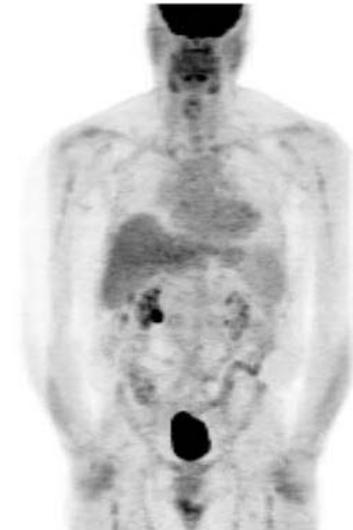
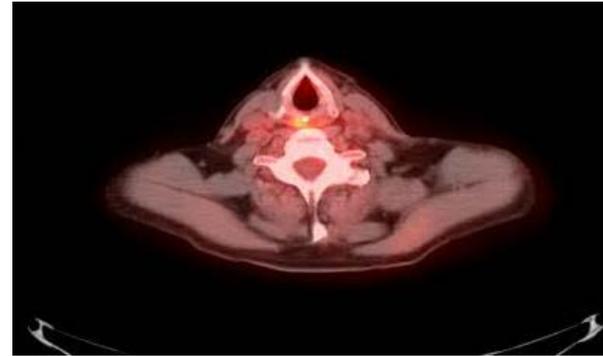
# Kappa CAR

## DLBCL in 5<sup>th</sup> relapse

Pre-T cell infusion (25 days after bendamastine)



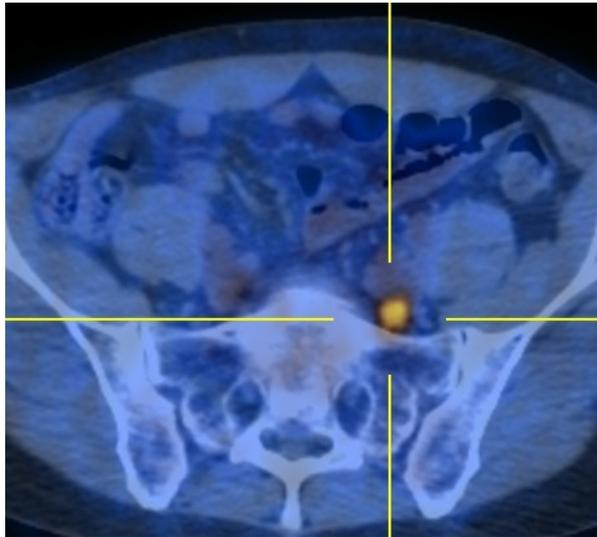
2 months post Infusion



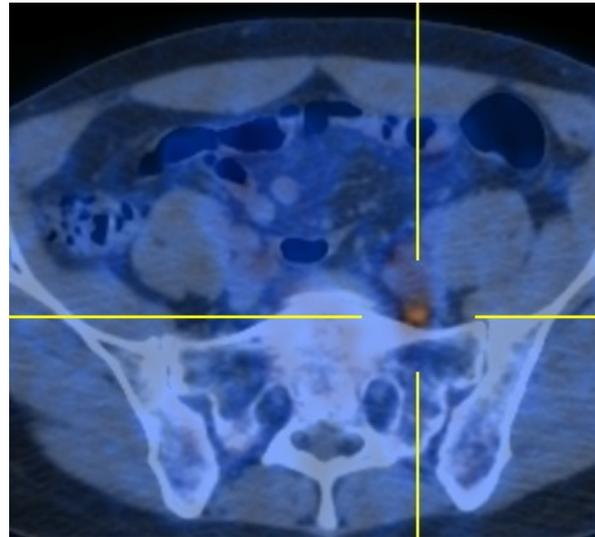
# Kappa CAR

## Follicular lymphoma in 3<sup>rd</sup> relapse

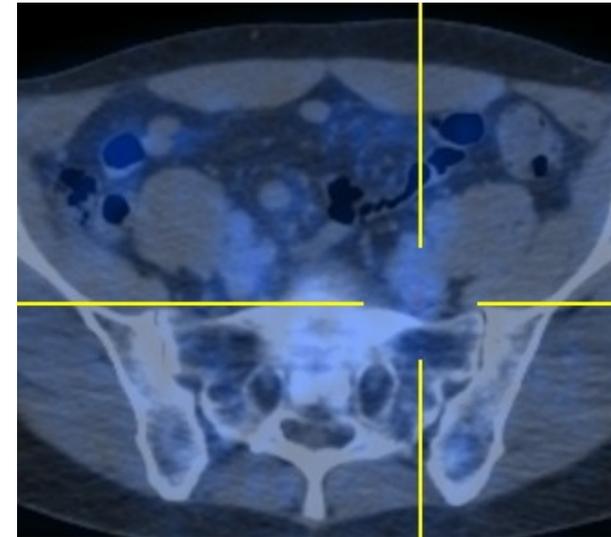
Pre



6 weeks post



12 weeks post



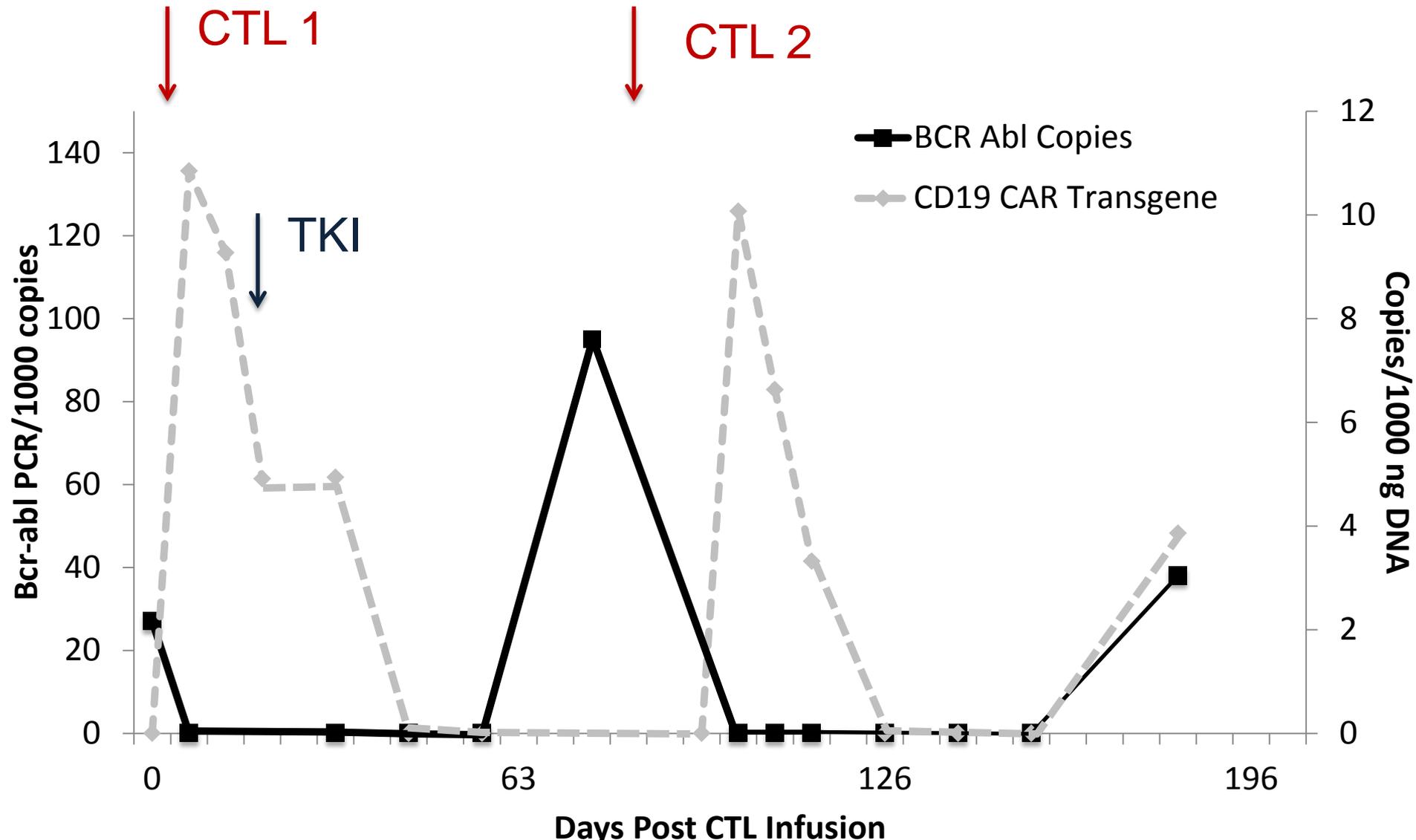
# Lessons Learned – CD19 and Kappa CAR

- Transfer of CAR transduced T cells is safe
- CAR.CD19-28<sup>+</sup> T cells expand better and persist longer than CAR.CD19<sup>+</sup> T cells
- CAR T cells home to tumor sites
- Overall response in NHL 20-40%
  - Clinical responses including CR in DLBCL, mantle cell lymphoma and FL

# Lessons Learned – CD19 CAR

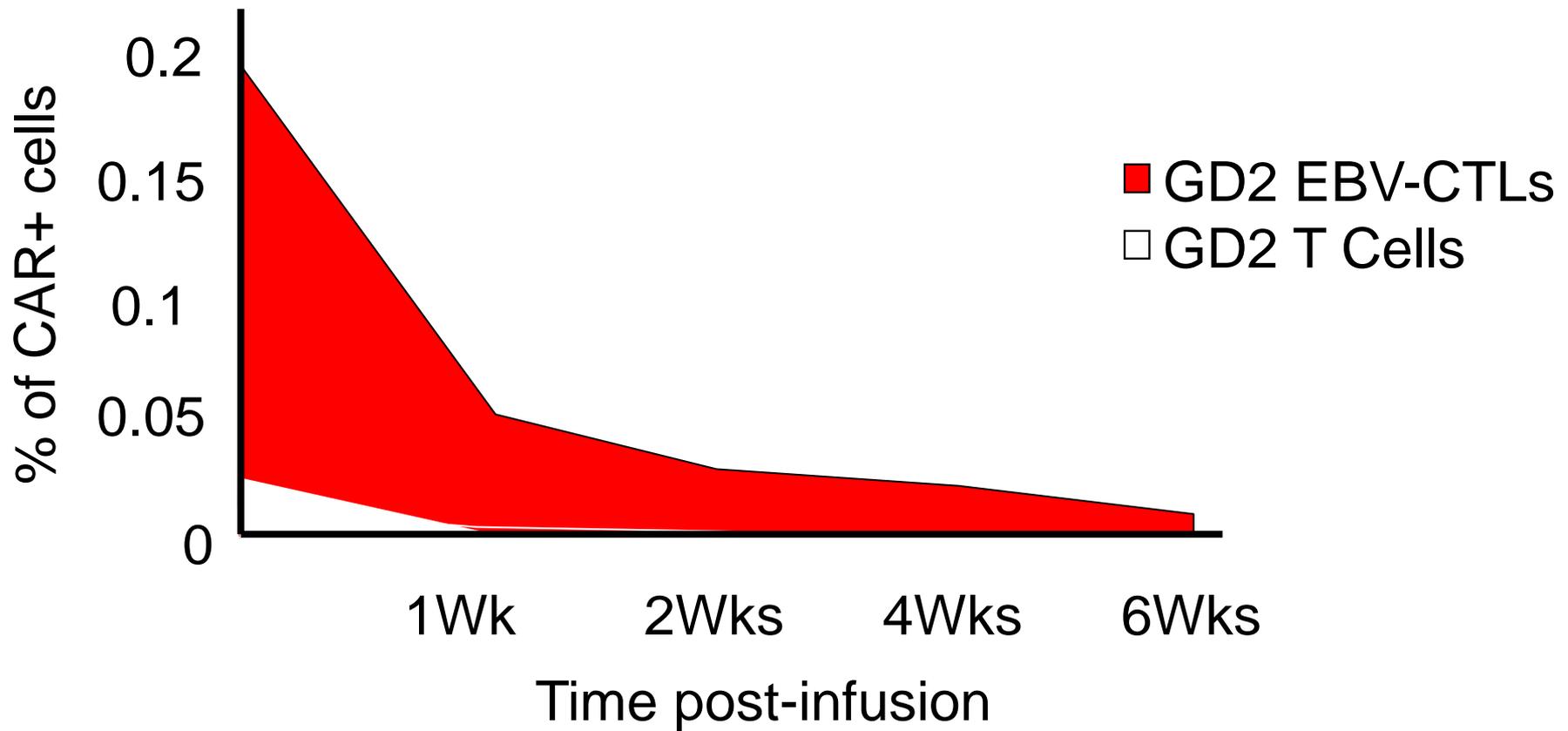
We should have targeted ALL sooner

# Multivirus CD19 CAR for Relapse Post Allograft



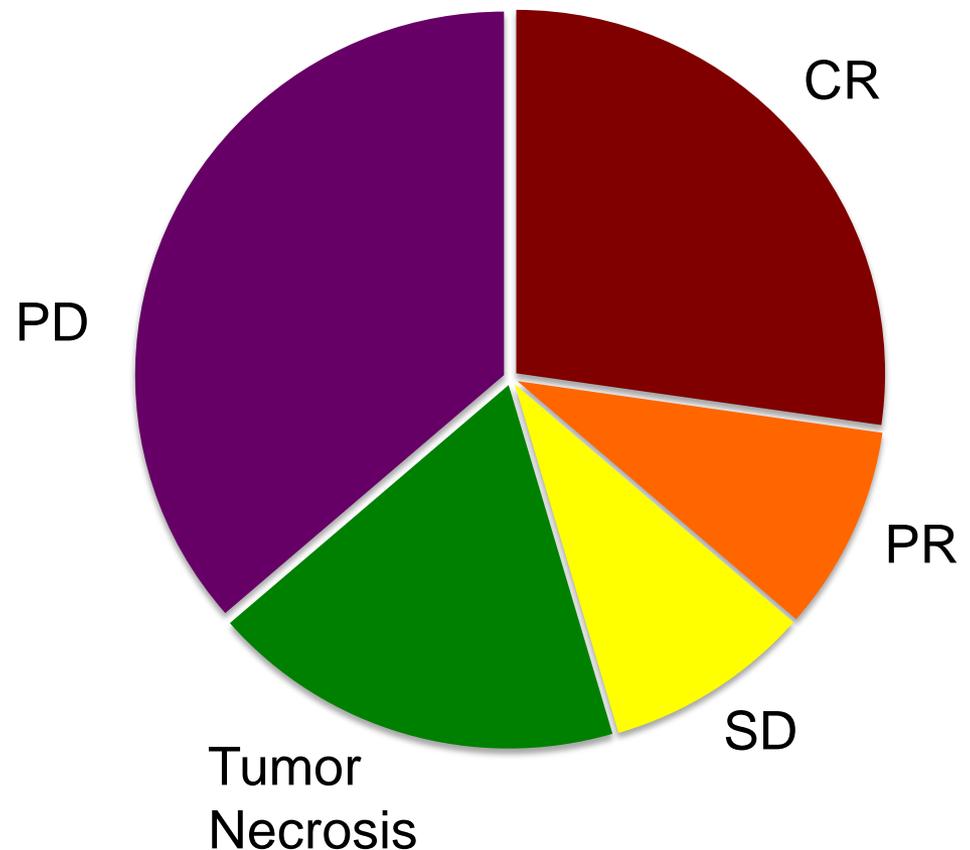
# GD2 CAR Lessons Learned

## Better early persistence EBV CTLs



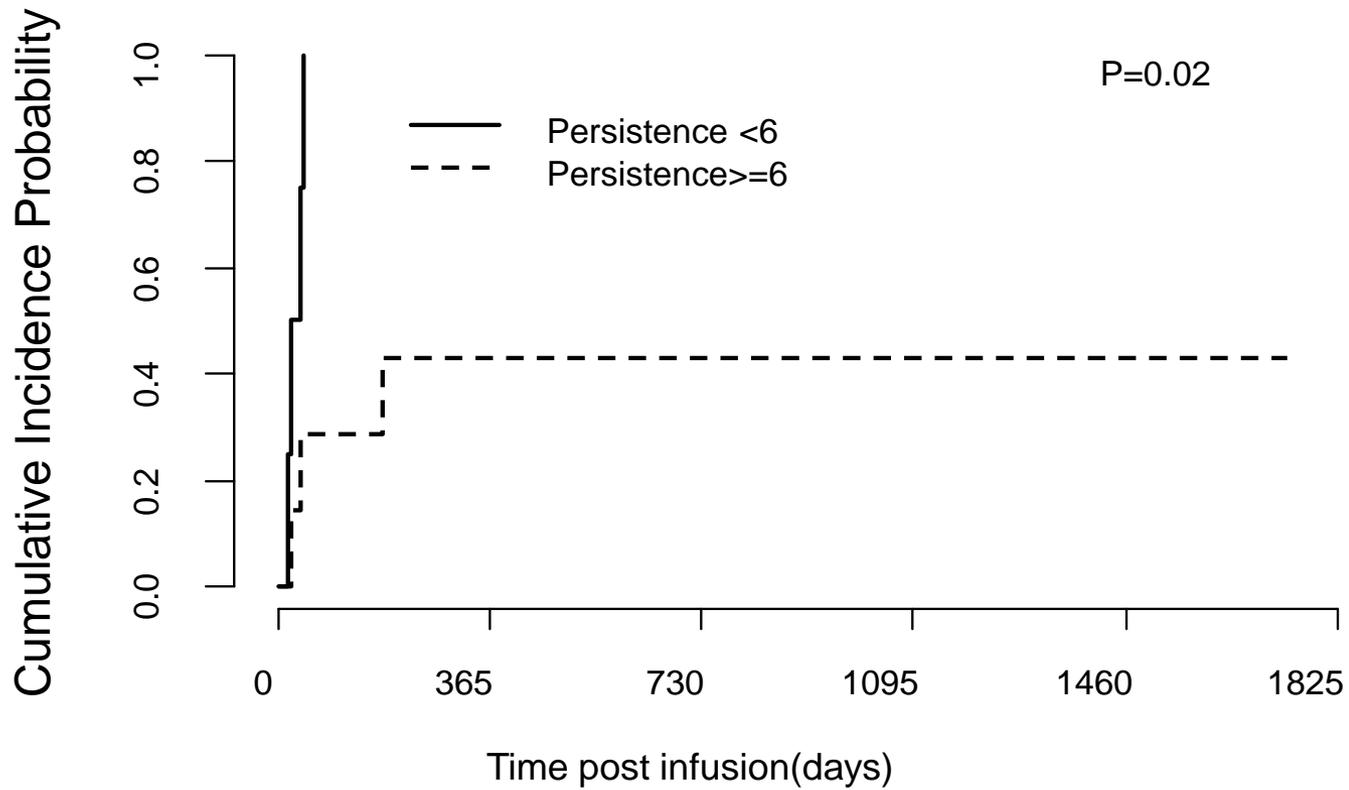
# Best Response: Patients with Active Disease at Time of GD2 T cell Infusion (N=11)

- 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



Louis et al 2011

# Progression delayed if GD2 T Cells Persist $\geq 6$ weeks

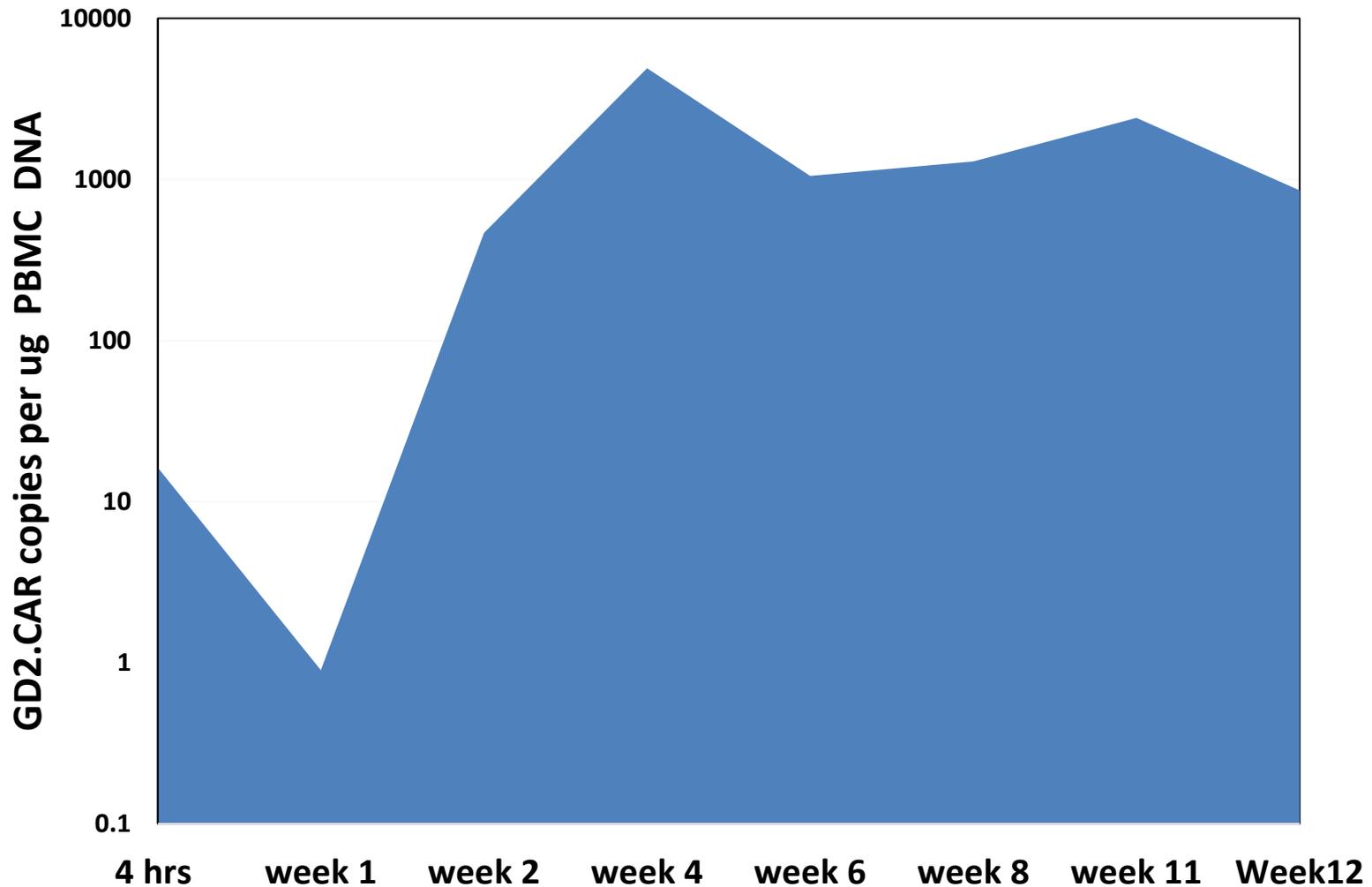


# Lessons Learned

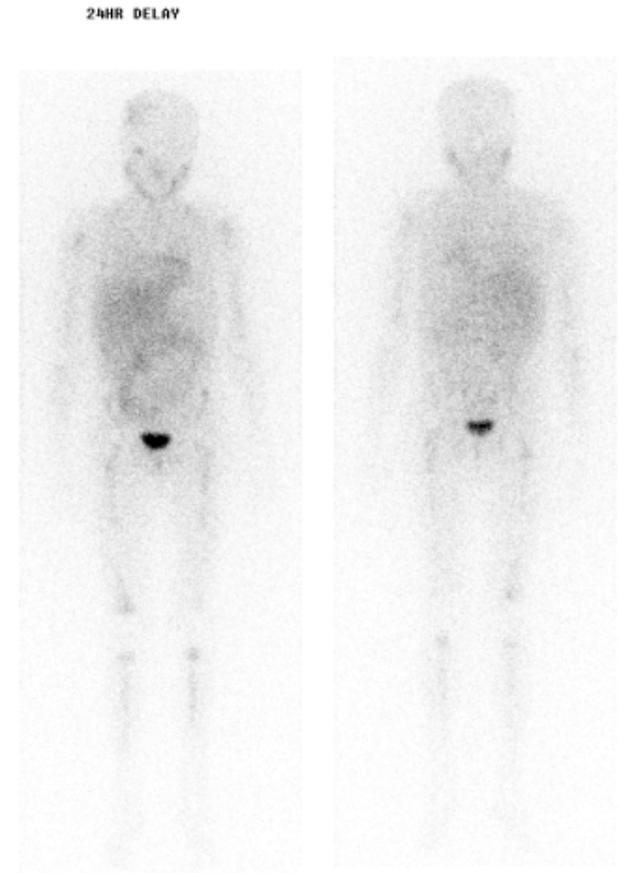
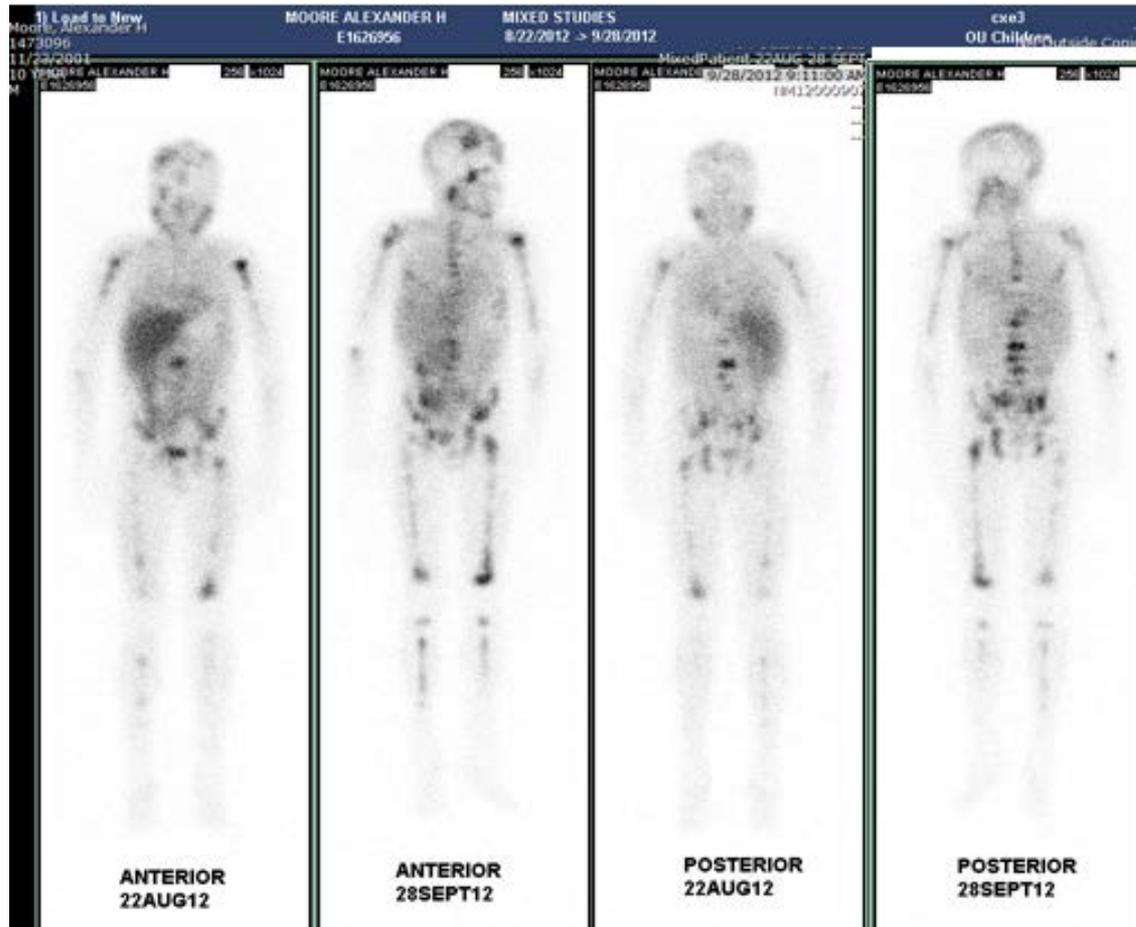
## GD2 ATCs and CTLs

- 1<sup>st</sup> generation GD2 CAR T cells may be detected for extended time after transfer to patients with high risk neuroblastoma
- Prolonged detection of GD2 EBV-CTL
  - Associated with the presence of both **CD4<sup>+</sup> and CD8<sup>+</sup> T cells** in the infused product
- Prolonged detection of GD2 ATC
  - Associated with the presence of **central memory T cells** in the infused product
- What cells should be used in the future?

# GD2.CAR-Trivirus-Specific T cells after Allo HSCT in Neuroblastoma Patient



# MIBG (Neuroblastoma) Response to Allo-HSCT and GD2.CAR-EBV-CTL



# Lessons Learned: SIRS can rarely occur with Native TCRs (2/176 cases)

- 18 year old with extensive PTLD refractory to Rituximab received donor EBV CTLs
- 2 weeks later, fever and hypotension requiring 2 inotropes
- Rapid resolution after steroids and Entanercept

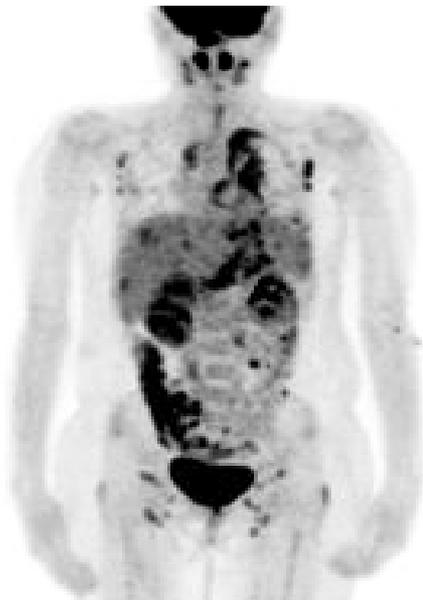


Figure 4

