SITC 2018 NOVEMBER 7–11 • WASHINGTON, D.C.

Infusion of TGFβ-resistant EBV-specific T cells post cytoreductive chemotherapy is safe and associated with clinical benefit in patients with recurrent/metastatic NPC

Christopher DeRenzo, Mamta Kalra, Carlos Ramos, Catherine Robertson, Huimin Zhang, Claudia Gerken, Olga Dakhova, Melinda Mata, Meng-Fen Wu, Hao Liu, Catherine Bollard, Zhuyong Mei, Adrian Gee, Bambi Grilley, Gianpietro Dotti, Helen Heslop, Malcom Brenner, Cliona Rooney, Stephen Gottschalk

CAGT CENTER FOR CELL AND GENE THERAPY

Baylor College of Medicine · Texas Children's Hospital · Houston Methodist

sitc Society for Immunotherapy of Cancer

#SITC2018

St. Jude Children's Research Hospital®

Finding cures. Saving children.

ALSAC • DANNY THOMAS, FOUNDER

Presenter Disclosure Information

Christopher DeRenzo, MD

The following relationships exist related to this presentation:

No Relationships to Disclose

CAGT CENTER FOR CELL AND GENE THERAPY

Baylor College of Medicine | Texas Children's Hospital | Houston Methodist

sitc

Society for Immunotherapy of Cancer

#SITC2018

St. Jude Children's Research Hospital®

Finding cures. Saving children.

ALSAC • DANNY THOMAS, FOUNDER

Aim: phase I clinical trial

Evaluate autologous TGFβ-resistant EBVSTs +/- cytoreductive chemotherapy for patients w/ NPC

Clinicaltrials.gov identifier NCT02065362

EBVST = Epstein-Barr virus specific T cells; NPC = Nasopharyngeal carcinoma

EBVSTs for NPC: Rationale

- Poor outcomes for relapsed NPC
  - Salvage regimens not curative for majority of patients
- Frontline chemoradiotherapy causes morbidity
  - Hormone deficiencies, pulmonary fibrosis, & others
- NPC is EBV associated malignancy
  - ~90% EBV positive

EBVSTs for NPC: previous experience

- Up to $3x10^8/m^2$ EBVSTs
  - Safe
  - Limited T cell expansion & antitumor activity

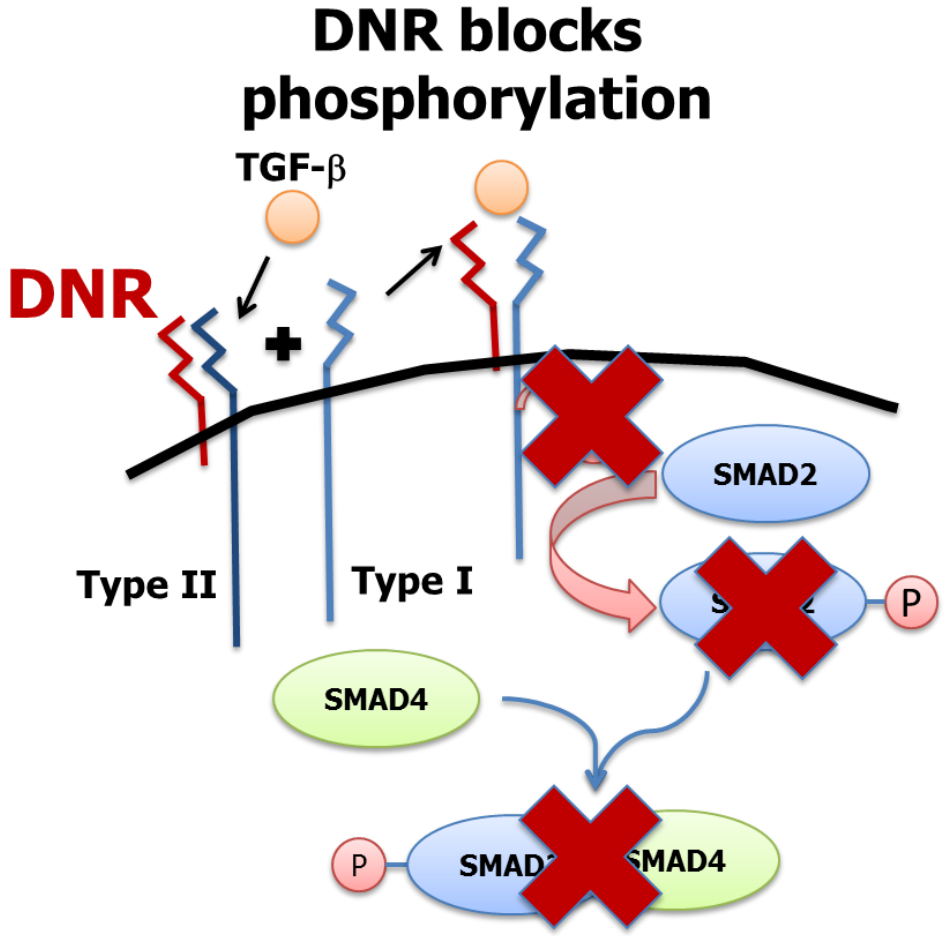
- Strategies to improve antitumor activity
  - Overcome immunosuppressive tumor microenvironment
    - TGFβ
  - Improve T cell expansion

EBVSTs for NPC: Questions

- Does rendering T cells resistant to TGFβ improve outcome?
- Is cytoreduction required for expansion of TGFβ resistant EBVSTs?

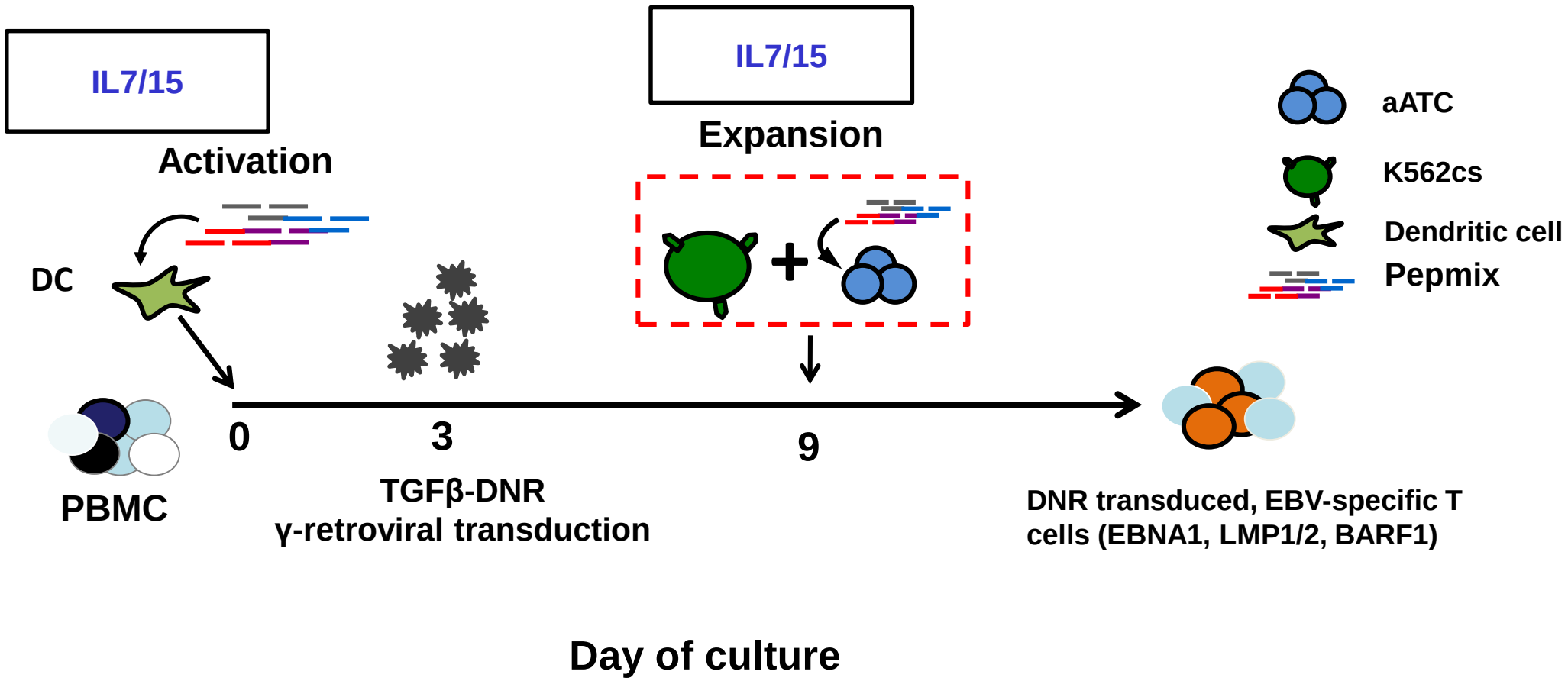
TGFβ-DNR overcomes inhibitory signal

- TGFβ-dominant negative receptor
  - Ø SMAD phosphorylation
  - Enhanced EBVST function vs lymphoma
    - Pre-clinical (Bollard et al. 2002)
    - Clinical benefit & long term safety (Bollard et al. 2018)



(Weiser et al. Mol Cell Bio 1993; Bollard et al. Blood 2002; Bollard et al. JCO 2018)

TGFβ-DNR, EBVST cell manufacture



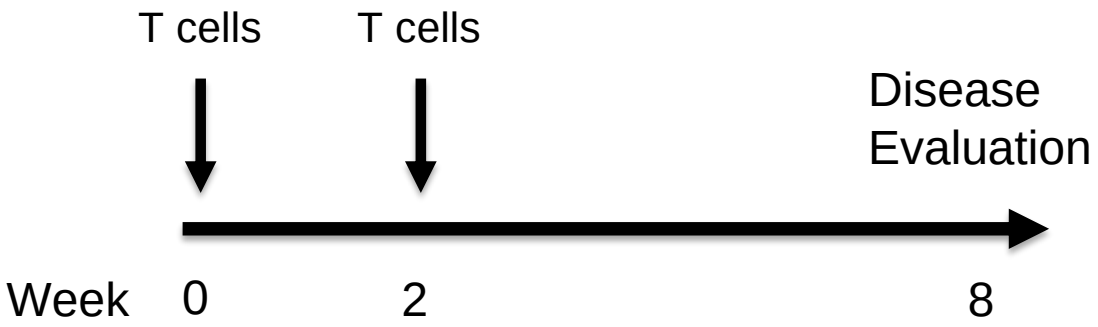
RESIST-NPC: objectives

- Phase I clinical trial
  - Determine safety
  - Assess T cell expansion & persistence
  - Assess antitumor activity & patient outcomes (PFS, OS)

Ethics Statement: The study was approved by Baylor College of Medicine internal review board

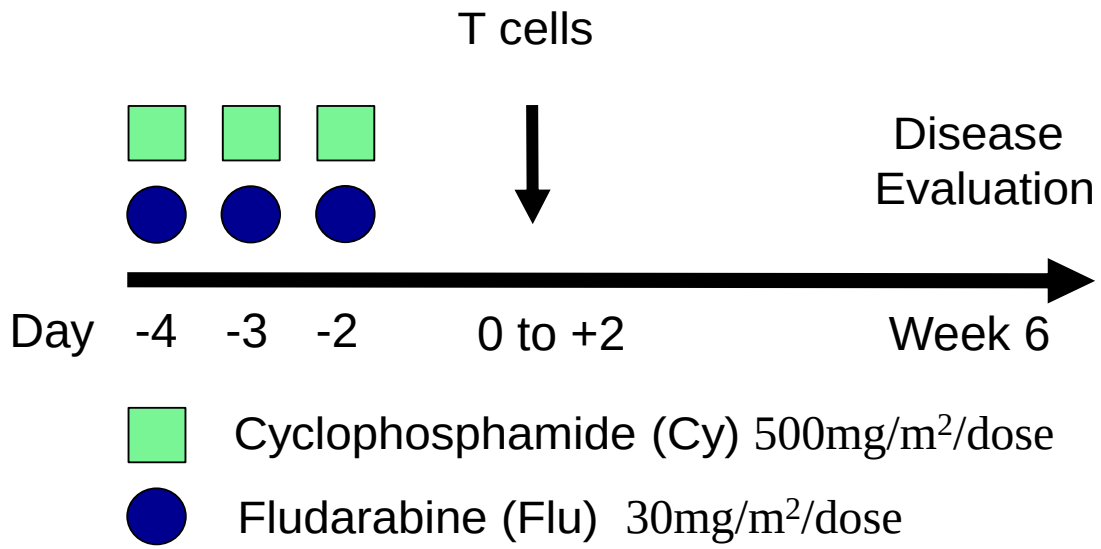
Treatment schema

Dose level 1 (no cytoreduction)



Dose Level 1	**2x10^7 cells/ m^2 + 2x10^7 cells/m^2**
Dose Level 2	**Cy/Flu + 4x10^7 cells/m^2**
Dose Level 3	**Cy/Flu + 1x10^8 cells/m^2**

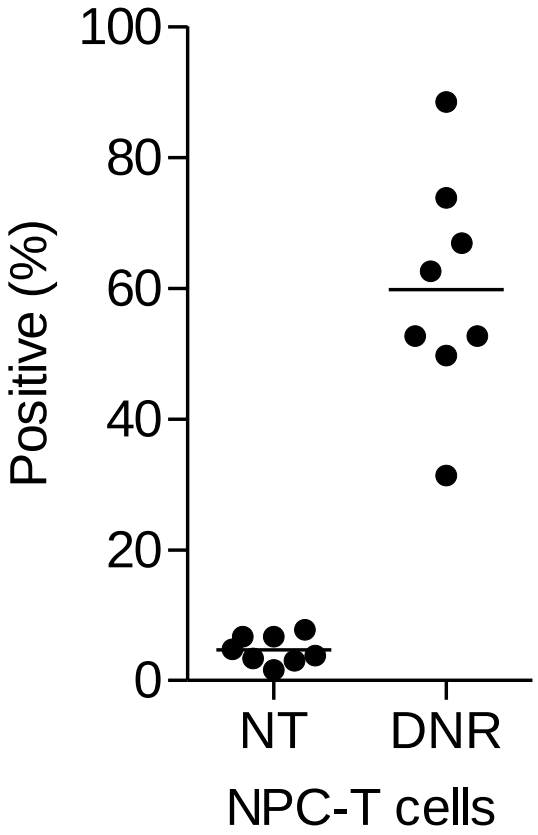
Dose levels 2 & 3 (with cytoreduction)

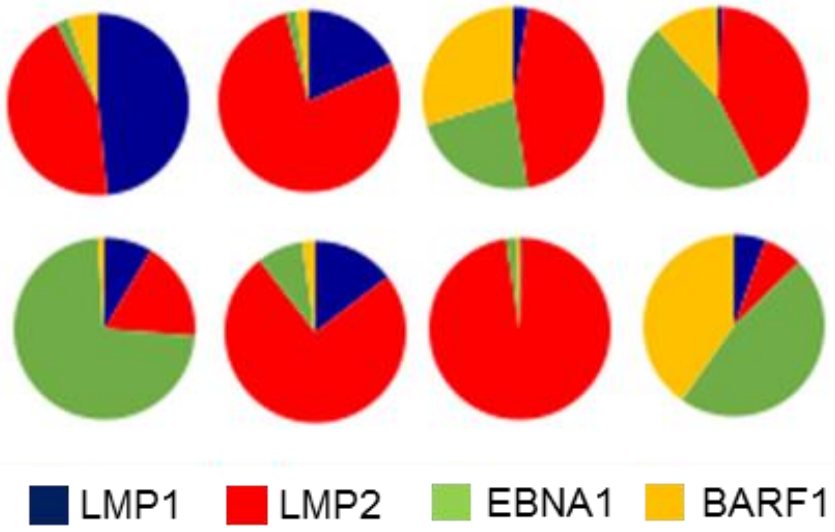


Patients heavily pre-treated pre-enrollment

	Patient	Age at Enrollment	Gender	Race	Site(s) of disease	# Chemo Pre-Enrollment	# Radiation Pre-Enrollment
Dose level 1	1	23	M	White	Lymph node	3	2
	2	17	M	White	Liver	3	1
	3	47	F	Asian	Brain/Skull	4	2
	4	50	F	Asian	Liver/Bone	4	1
Dose level 2	5	27	M	Black	Lung/Nodes	2	1
	6	17	M	Black	Bone/Nodes	2	1
Dose level 3	7	17	M	Black	Bone	2	2
	8	38	M	Asian	Lung	1	2

Successful transduction & generation multi-antigen specific T cells



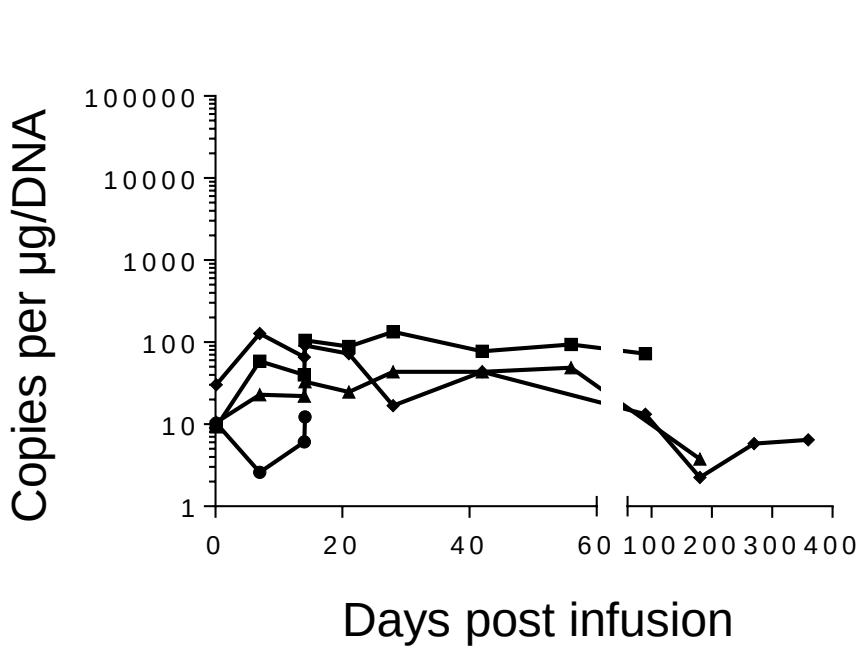


Safety

- No DLTs at any level
- No toxicity due to EBVST
  - No cytokine release syndrome
  - No neurotoxicity

Limited expansion despite DNR

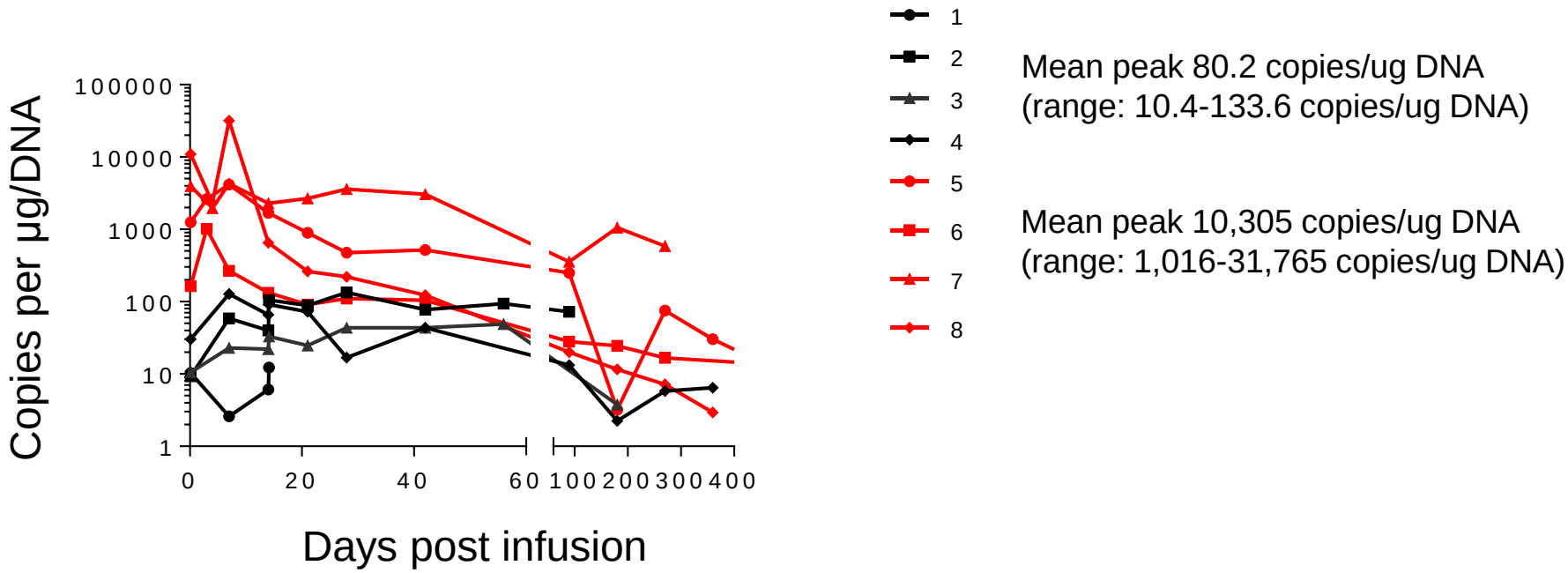
Without cytoreduction DNR.EBVSTs w/ limited expansion



Mean peak 80.2 copies/ug DNA
(range: 10.4-133.6 copies/ug DNA)

Cytoreduction enhances expansion

- 128-fold greater* T cell expansion w/ cytoreduction
- T-cell expansion at median 7 days (range: 4-7 days)

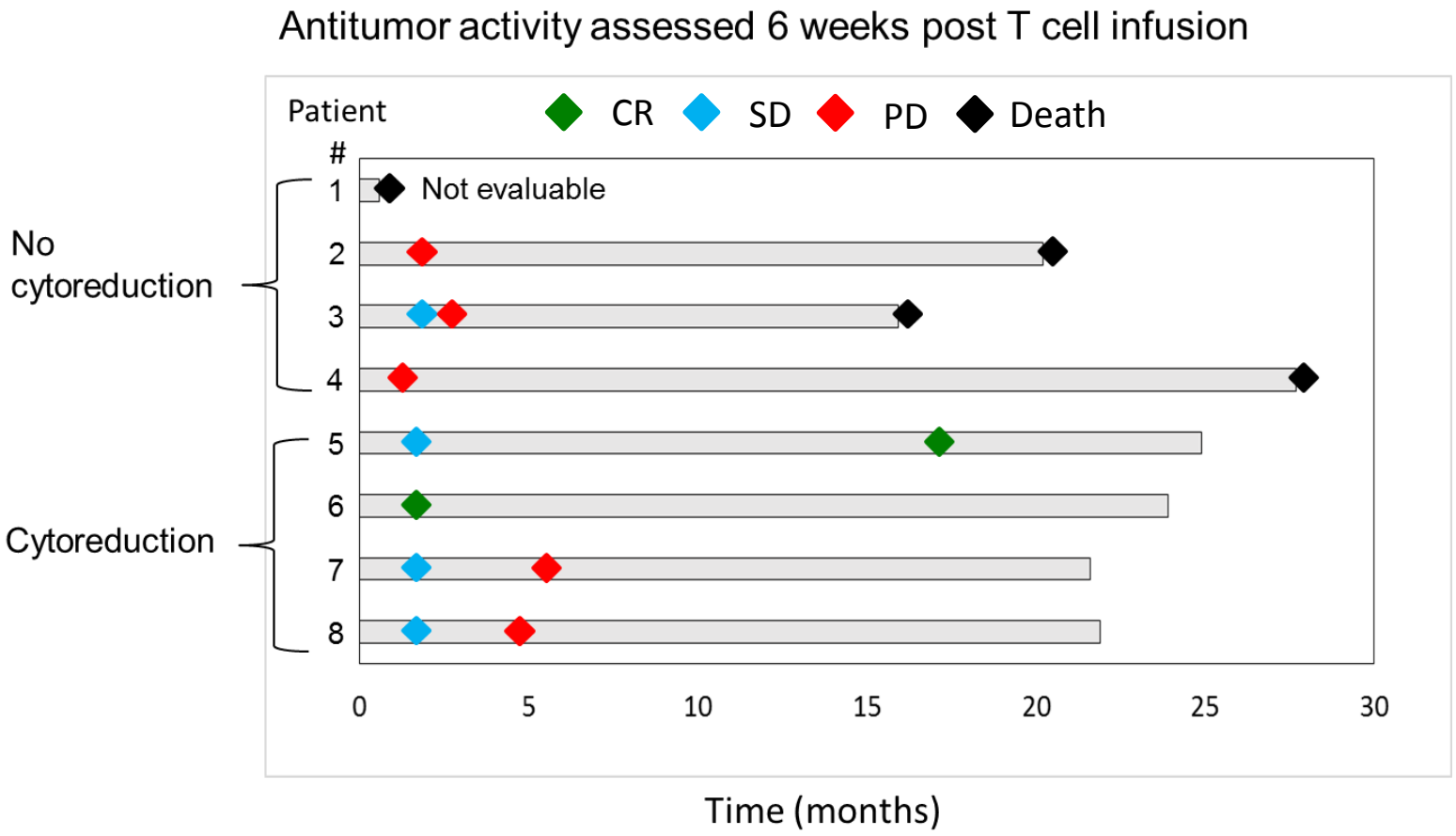


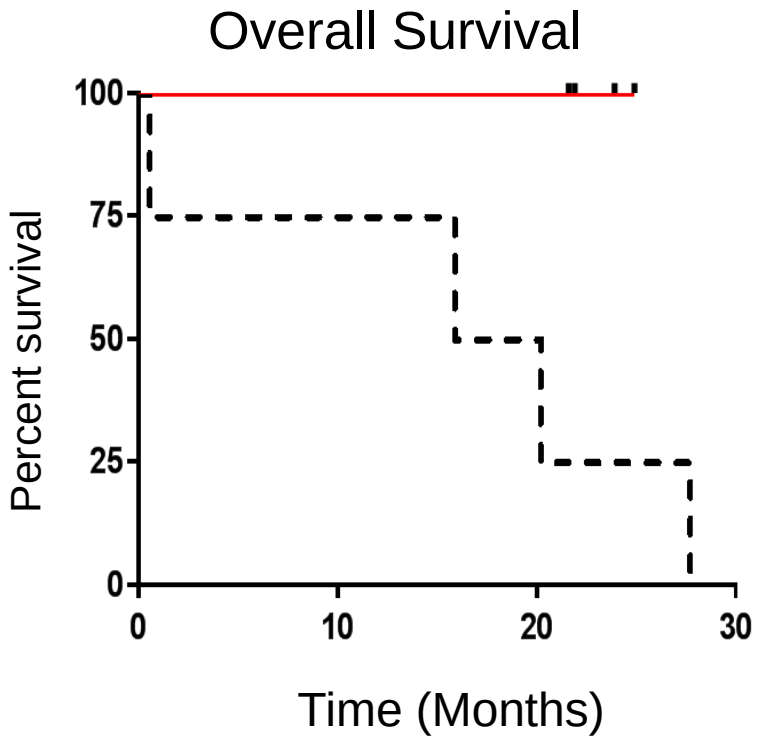
Mean peak 80.2 copies/ug DNA
(range: 10.4-133.6 copies/ug DNA)

Mean peak 10,305 copies/ug DNA
(range: 1,016-31,765 copies/ug DNA)

*P<0.05

Clinical outcomes





Conclusions

- DNR.NPC-specific T cells after cytoreductive chemo:
  - Safe
  - Results in robust T cell expansion
  - Associated with objective clinical benefit
  - Cytoreduction necessary for EBVST expansion

Acknowledgements

Stephen Gottschalk
Helen Heslop
Cliona Rooney
Malcom Brenner
Mamta Kalra
Bambi Grilley
Carlos Ramos
Catherine Robertson
Huimin Zhang
Olga Dakhova
Adrian Gee
Melinda Mata
Gianpietro Dotti
Meng-Fen Wu
Hao Liu
Catherine Bollard
Zhuyong Mei

Patients & Families
Nurses
Physicians/providers at outside centers

Funding

NIH P01CA094237
P30CA1250123
K12CA0904335

Questions?


CAGT
CENTER FOR
CELL AND GENE THERAPY
Baylor
College of
Medicine
Texas Children's
Hospital
Houston
Methodist


St. Jude Children's
Research Hospital
Finding cures. Saving children.
ALSAC • DANNY THOMAS, FOUNDER

Eligibility

Inclusion criteria

First or subsequent relapse or primary refractory disease

EBV-positive

Life expectancy ≥ 6 weeks

Bilirubin ≤3x upper limit of normal

AST ≤ 5x upper limit of normal

Hgb >8.0g/dl (can be transfused)

Creatinine ≤ 2x upper limit of normal for age

Pulse oximetry of > 90% on room air

Off investigational therapy for 4 weeks prior to study entry

Karnofsky or Lansky score of ≥ 50%

Exclusion criteria

Known HIV positivity

Pregnant or lactating

Severe intercurrent infection.