Adoptively transferred T cells for primary and secondary CNS malignancies

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Disclosure

I have no conflicts of interest to disclose

NCI Surgery Branch CRADA: Kite Pharma
Iovance Biotherapeutics
Ziopharm Oncology

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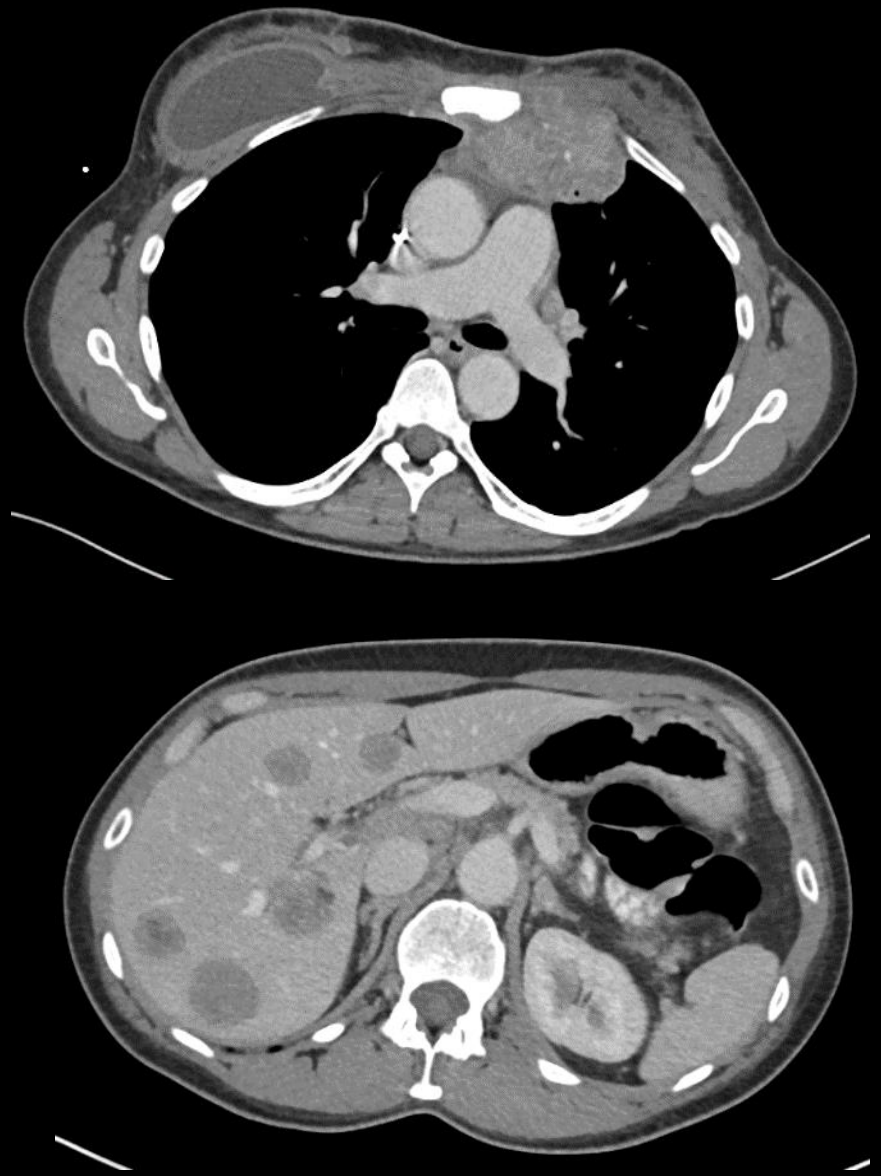
Baseline 12/2015



49 YO Woman with advanced BrCa ER+PR+ her2-

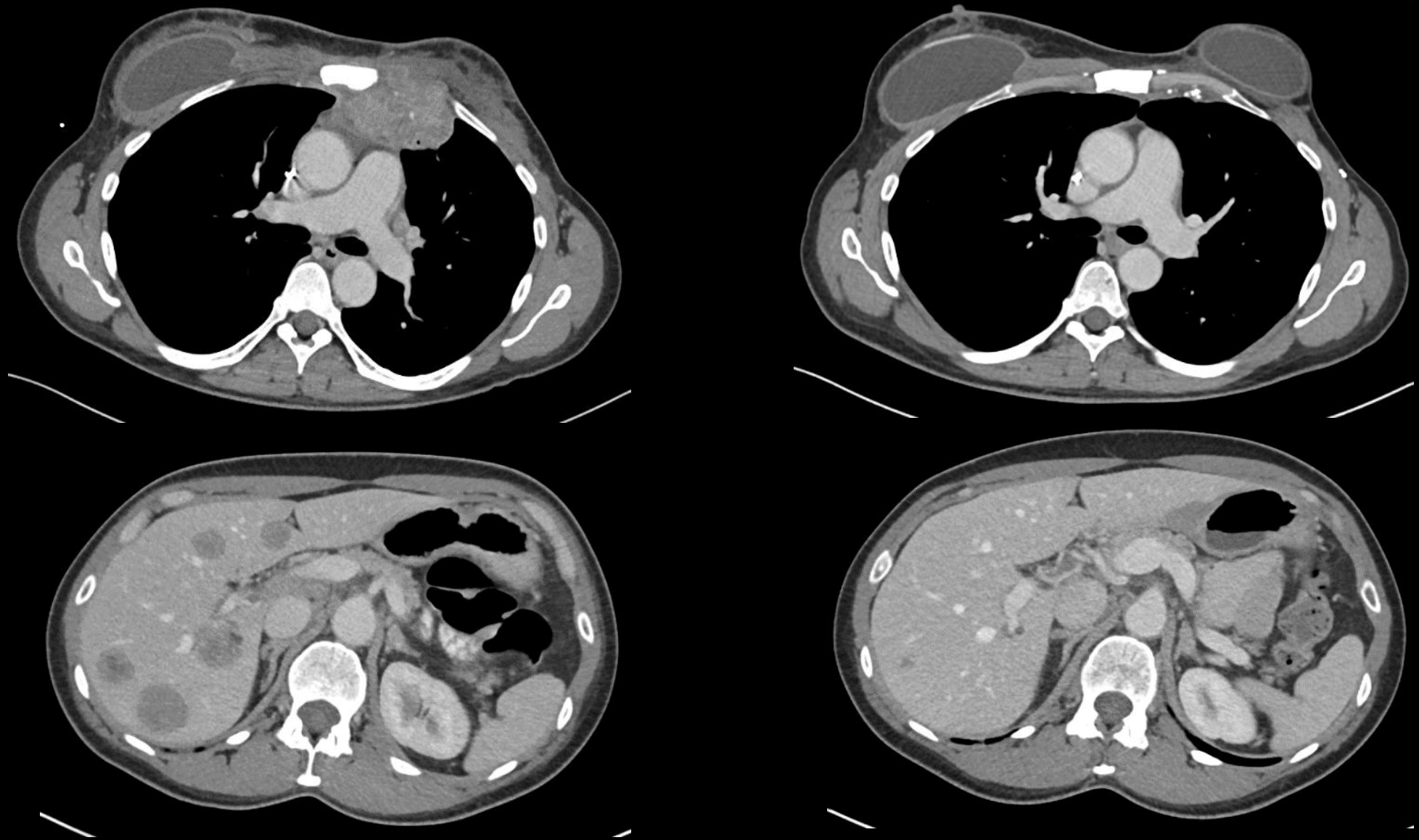
S/p multiple hormonal therapies

S/p 6 different lines of Chemotherapy

Received TIL *selected* for *somatic mutation* reactivity
(And 4 doses Pembro)

Baseline 12/2015

F/U 5/2019 (+40)



Zacharakis et al. Nature Medicine June 4, 2018

Adoptively transferred T cells for primary and secondary CNS malignancies

ACT Background and Principles

Can infused Lymphocytes effectively traffic to the brain and cause cancer regression ?

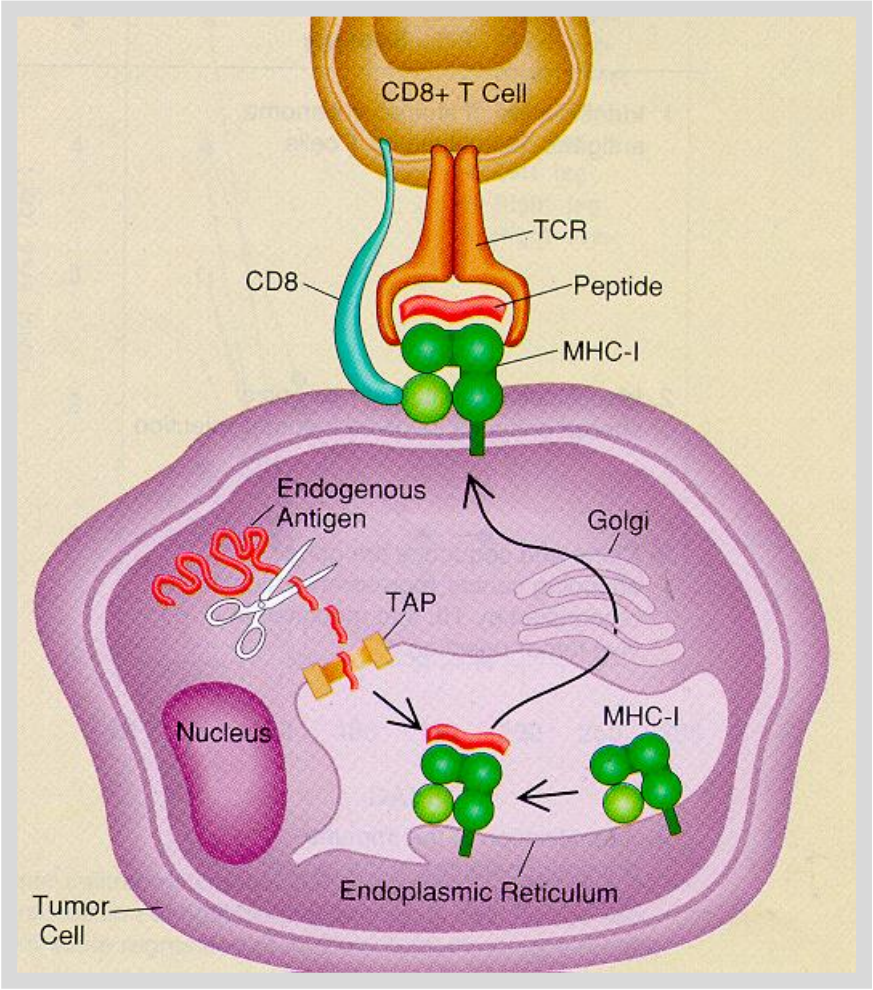
Anti-EGFRvIII CAR for patients with GBM

J Immunother 42(4):126, 2019

Adoptive Cellular Therapy (ACT) for Cancer

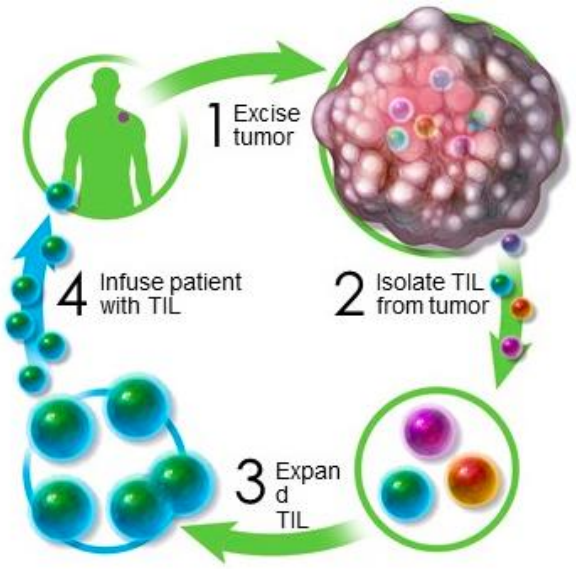
- Infusion of tumor specific T Cells in combination with lymphodepleting chemotherapy given to eliminate cancer.

- Depends on the isolation, identification, or de novo generation of appropriate effector T-Cells.



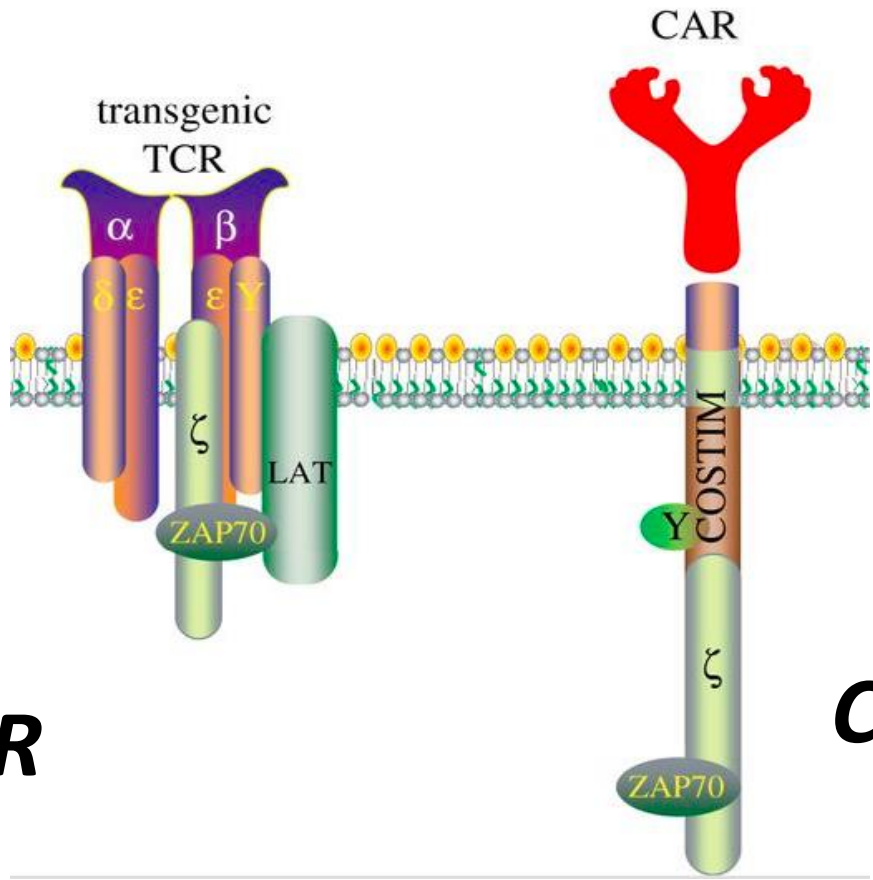
Adoptive T Cell Therapy for Cancer

TIL



Naturally occurring autologous lymphocytes derived from tumor

*Gene modified PBL**

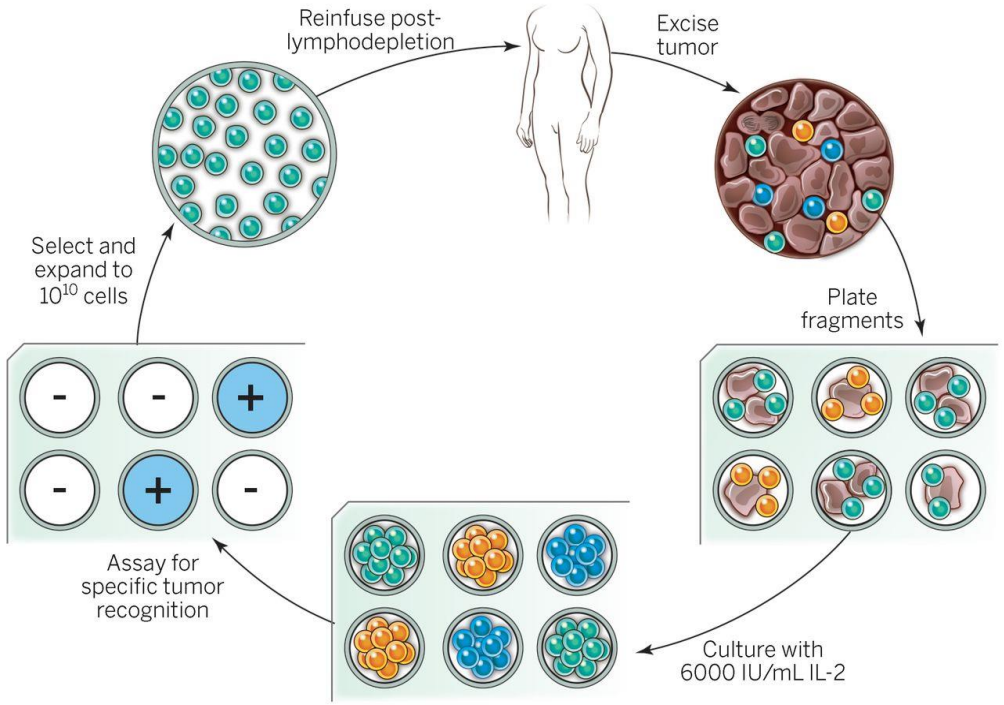


TCR ***CAR***

Insertion of target receptor

* Peripheral Blood Lymphocytes

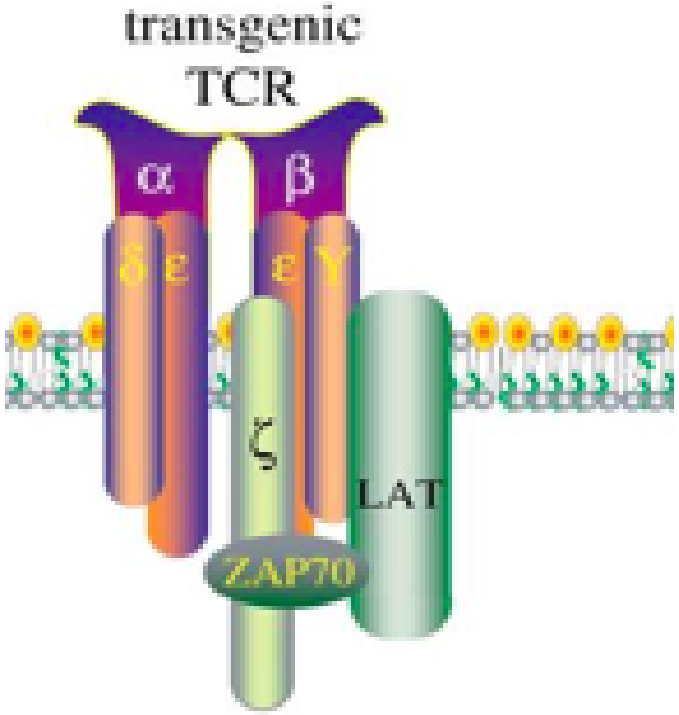
TIL



Naturally occurring autologous lymphocytes derived from tumor

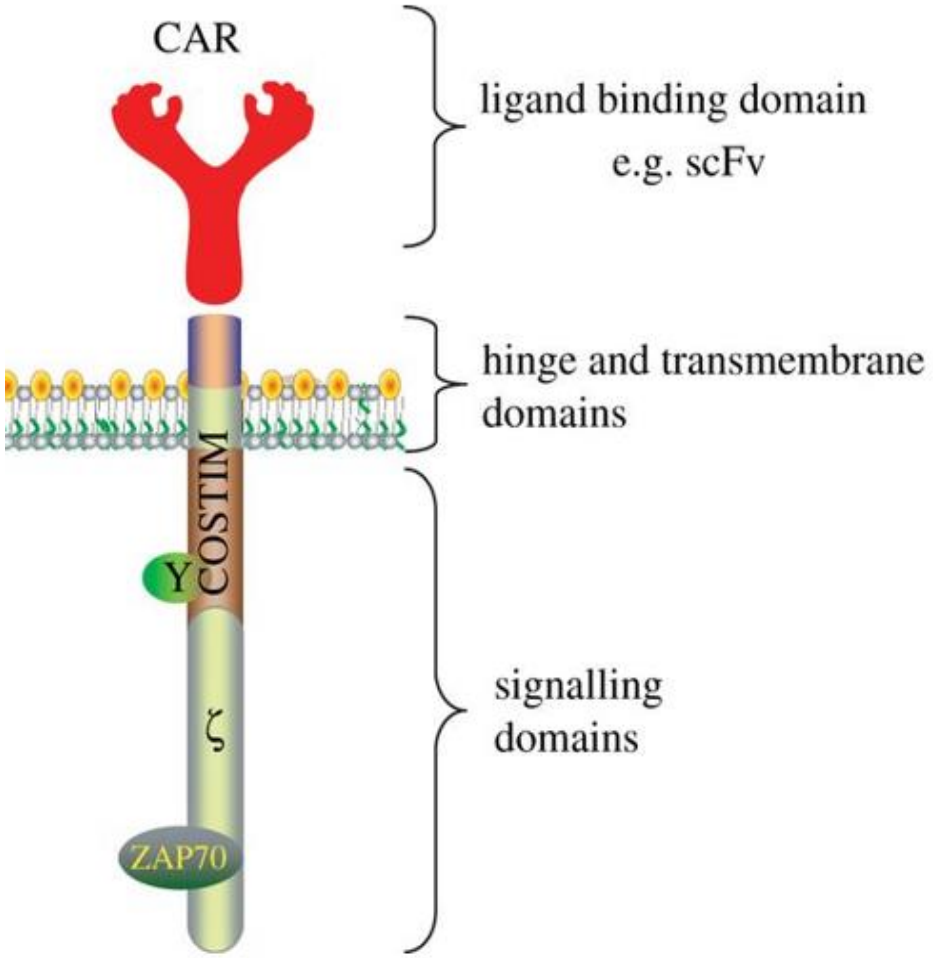
- Polyclonal
- TCR have had normal selection in the thymus
- *TCRs recognize unique mutated peptide products expressed on the cancer cell surface on HLA*

TCR



- Autologous PBL Transduced with TCR
- TCR inserted randomly into an "open repertoire"
- Each T Cells has its native unique TCR *and* the transduced TCR
- HLA presentation required

CAR



- Autologous PBL Transduced with CAR
- Each T Cell has its unique native TCR *and* the Transduced CAR
- CAR inserted randomly into an “open repertoire”
- Recognizes selected cell surface protein without HLA presentation

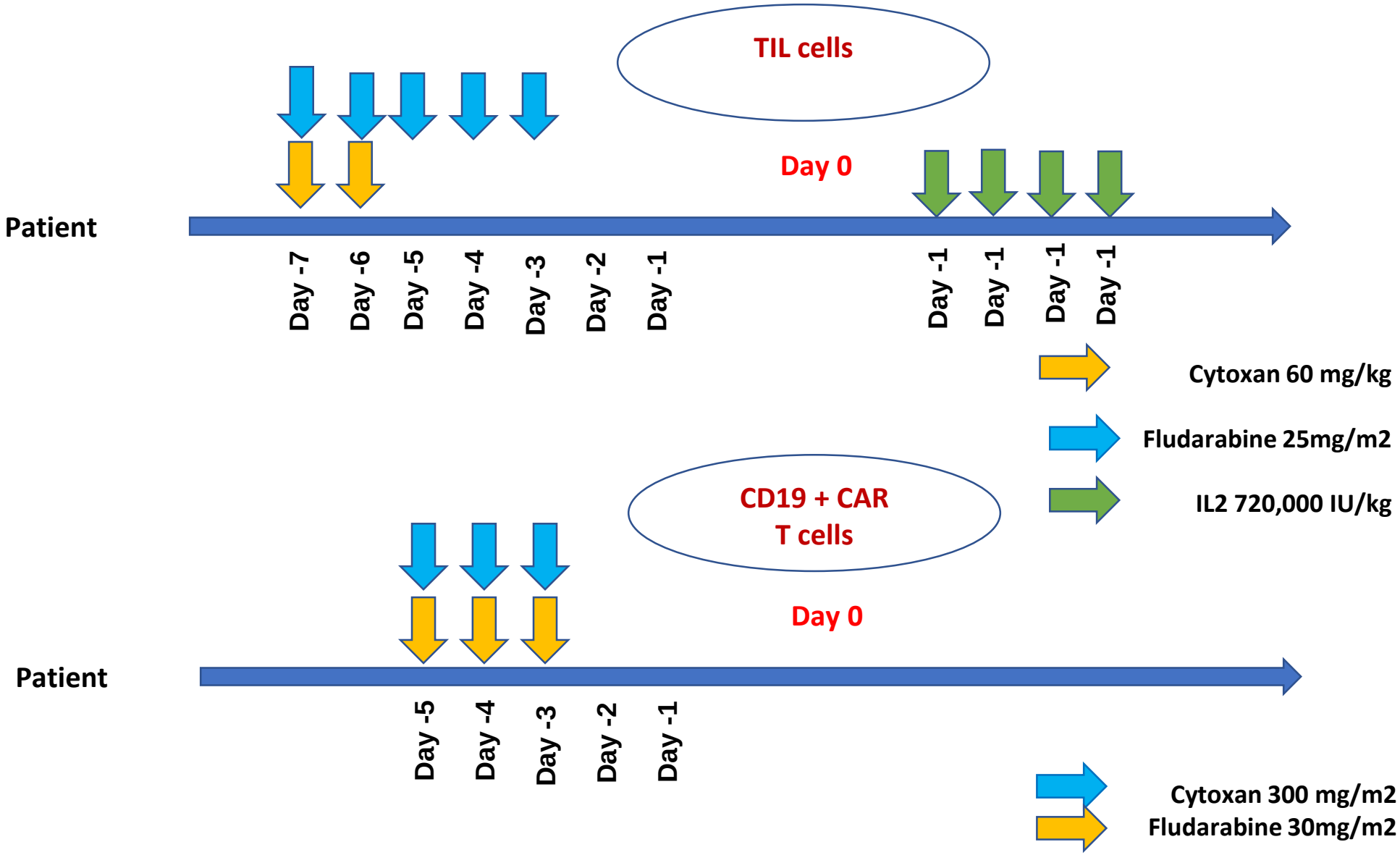
Adoptive Cell Transfer 2019

- *The T Cell*
  Number of Cells impacts efficacy and toxicity
  Phenotype of Cells? (CM, EM, N)
  Persistence?

- *The Target*
  Must be on the Tumor cell surface
  Antigen must be processed and presented by HLA
  Tumor heterogeneity?, normal tissue expression?, Ag loss?

- *Lymphodepletion*

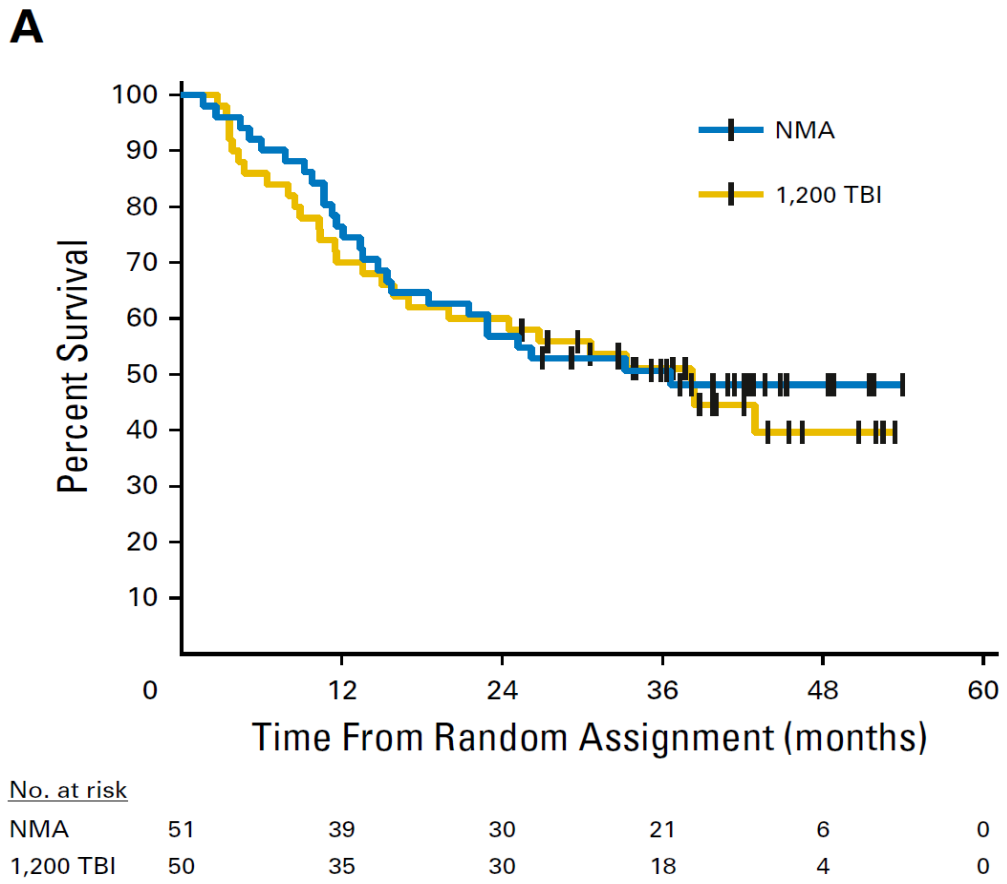
Typical Conditioning Regimens



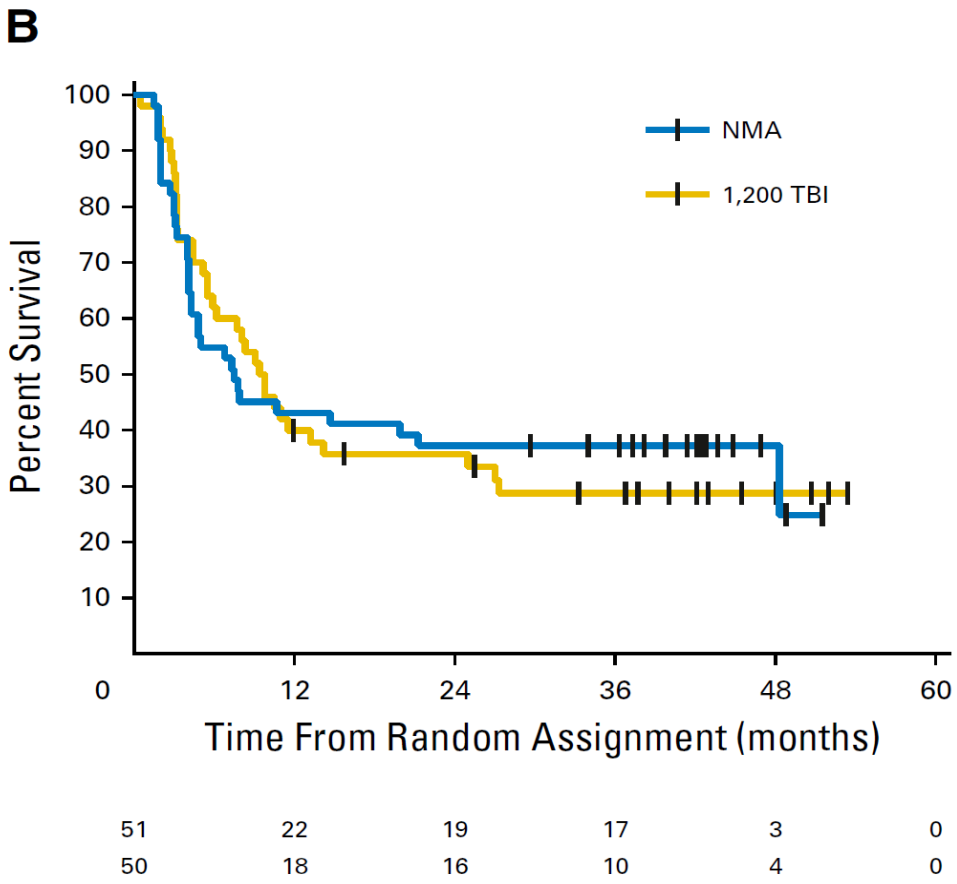
Importance of lymphodepletion on ACT

1998	2016
20 Patients advanced MM	101 Patients Advanced MM
TIL (2 E11)	TIL (5 E10)
HD IL-2	HD IL-2
Cytoxin 25 mg/kg X 1	Cytoxin 60 mg/kg X2 Fludarabine 25 mg/m2 X5
40 % ORR	**56% ORR**
Durable CR 5%	**Durable CR/PR 36%**
Responses not durable	**Responses durable**

Adoptive Cell Therapy with Autologous Tumor-infiltrating Lymphocytes for Patients with Metastatic Melanoma

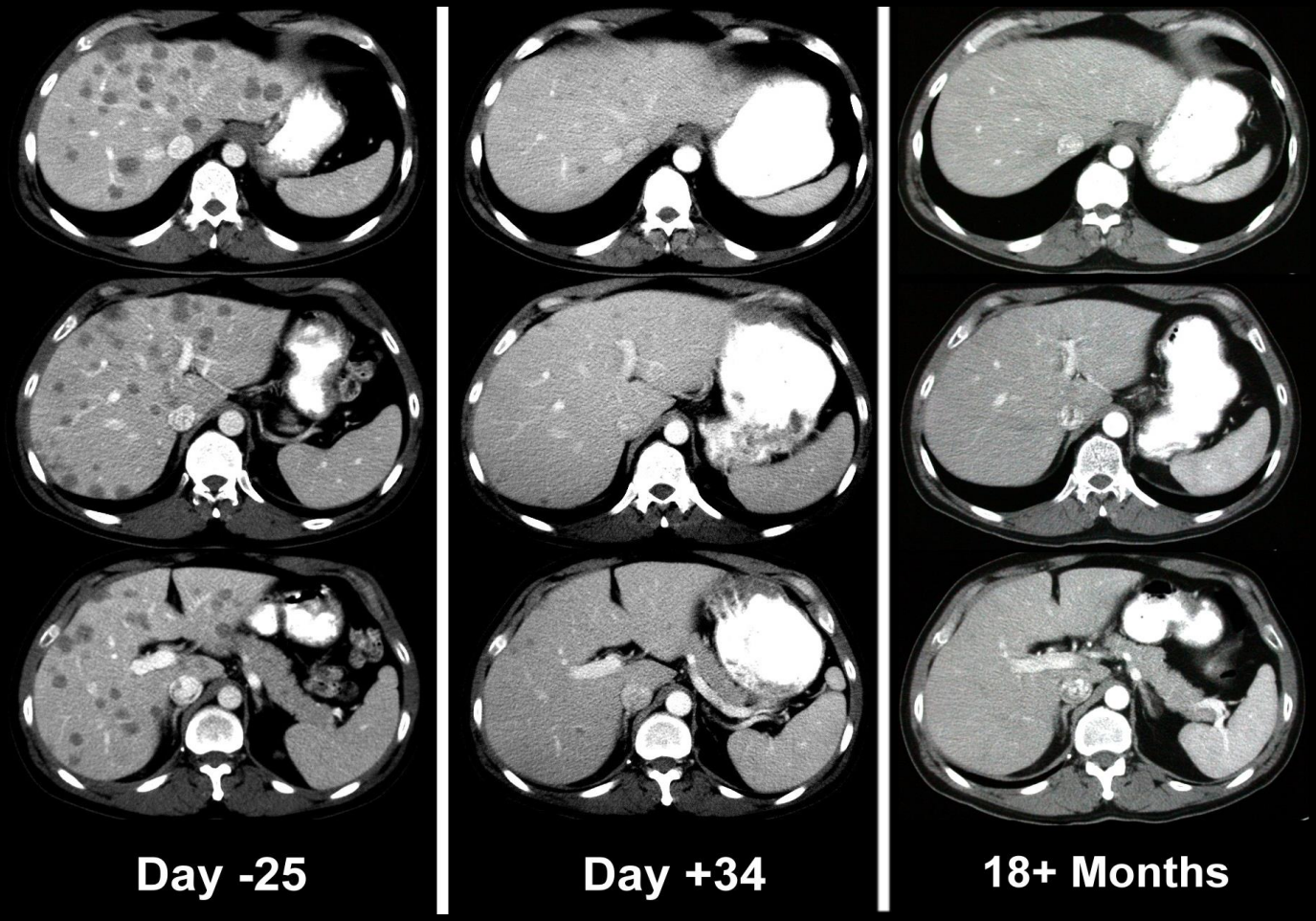


OS



PFS

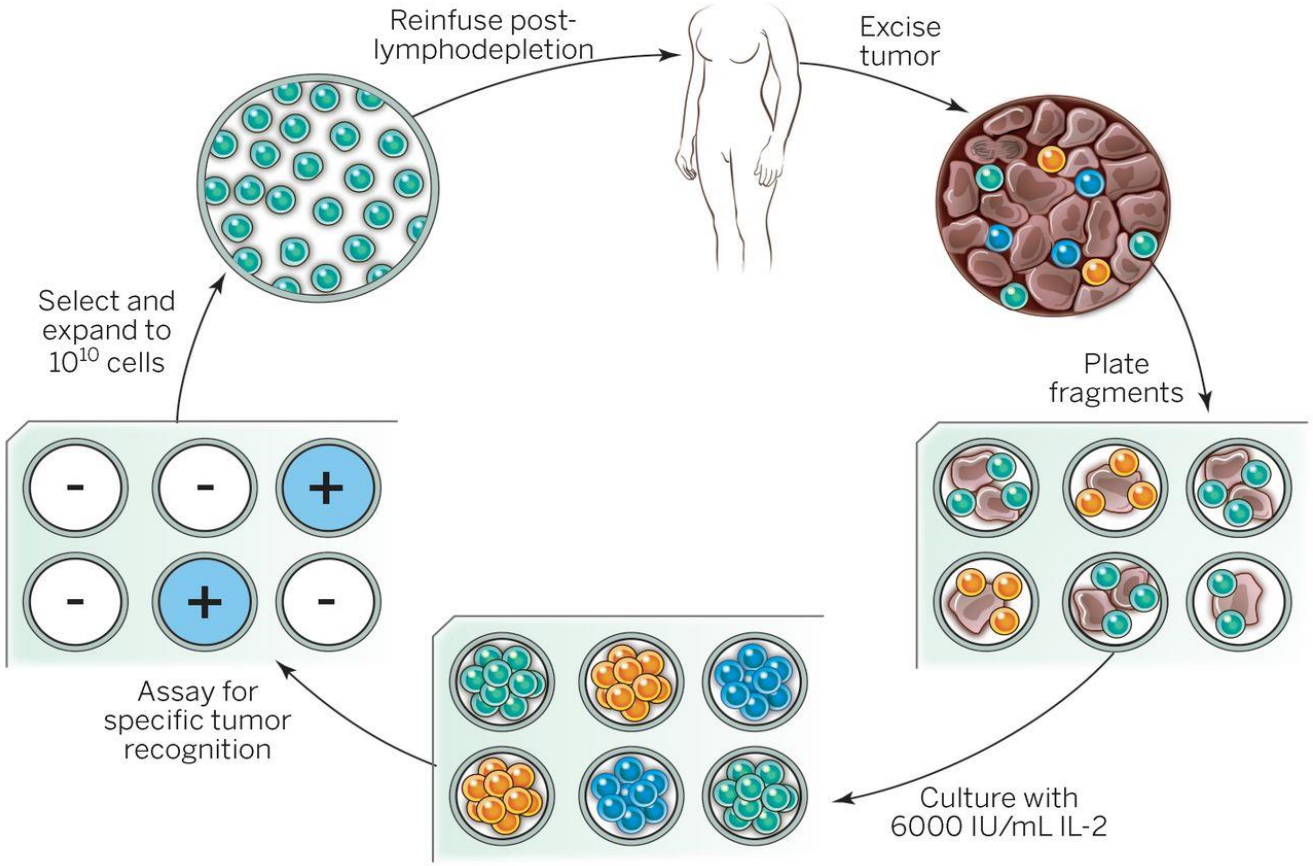
(JCO 2016 34:2389)



Resolution of liver disease in a patient treated with TIL and IL-2 after preparative lymphodepleting regimens of Cy/Flu

What is the evidence that ex vivo manipulated tumor specific lymphocytes can be infused and then traffic to the brain to mediate cancer regression ?

Melanoma TIL production takes weeks



Treatment of melanoma brain metastasis with Tumor infiltrating lymphocytes

Standard eligibility criteria for ACT *Plus*

Synchronous evaluable non CNS disease

≤ *3 brain lesions*

≤ *10 mm*

*(E*xcluded protocol exemptions)

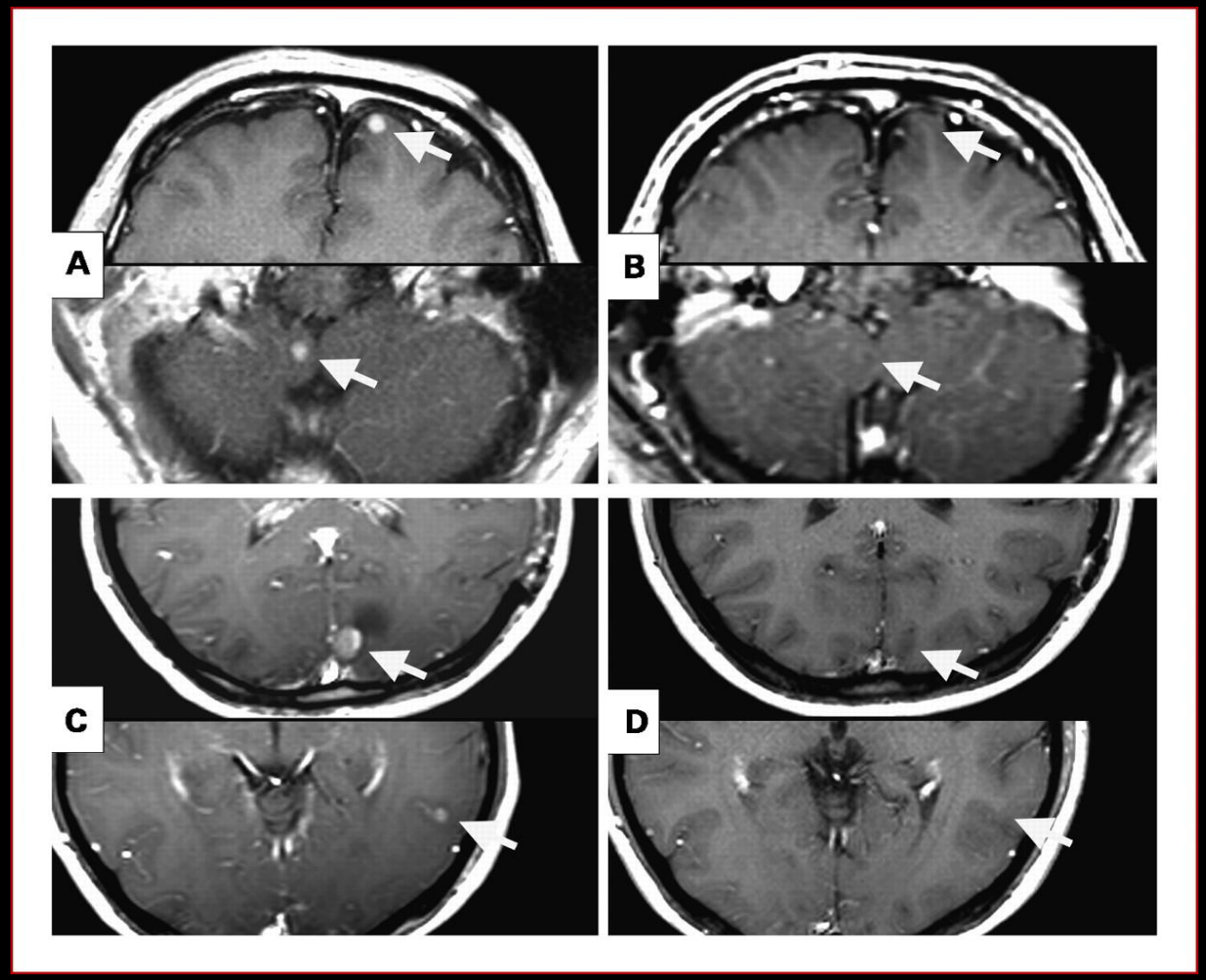
371 patients with advanced melanoma treated with TIL 2001-15

45 pts identified with **untreated** melanoma brain metastasis

Treatment of melanoma brain metastasis with Tumor infiltrating lymphocytes

45 pts with untreated melanoma brain metastasis
and synchronous evaluable non CNS disease

	Overall Systemic Response	***In Brain Response***
ORR	15 (33%)	11 (24%)
PR	*14*	1
CR	1	10 (22%)



Resolution of multiple brain lesions in two patients treated with TIL and IL-2 after preparative lymphodepleting regimens of Cy/Flu

Cancer regression and neurologic toxicity following anti-MAGE-A3 TCR gene therapy

Richard A. Morgan[1,*], Nachimuthu Chinnasamy[1], Daniel D Abate-Daga, Alena Gros[1], Paul F. Robbins[1], Zhili Zheng[1], Steven A. Feldman[1], James C. Yang[1], Richard M. Sherry[1], Giao Q. Phan[1], Marybeth S. Hughes[1], Udai S. Kammula[1], Akemi D. Miller[1], Crystal J. Hessman[1], Ashley A. Stewart[1], Nicholas P. Restifo[1], Martha M. Quezado[2], Meghna Alimchandani[2], Avi Z. Rosenberg[2], Avindra Nath[3], Tongguang Wang[3], Bibiana Bielekova[3], Simone C. Wuest[3], Akula Nirmala[4], Francis J. McMahon[4], Susanne Wilde[5], Barbara Mosetter[5], Dolores J. Schendel[5,6], Carolyn M. Laurencot[1], and Steven A Rosenberg[1]

J Immunother 36(2):133, 2013

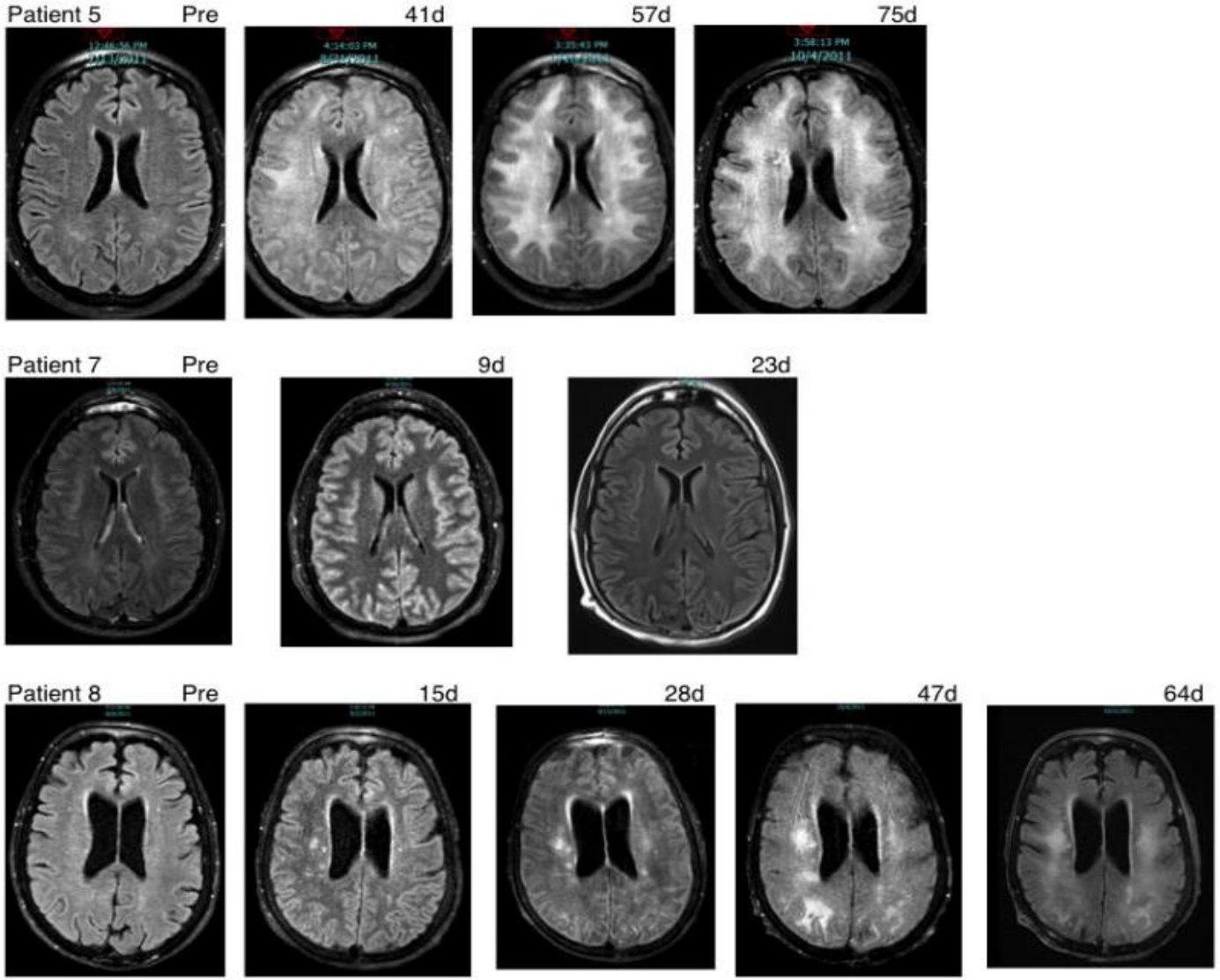
Cancer regression and neurologic toxicity following anti-MAGE-A3 TCR gene therapy

Anti-Mage-A3 TCR

Recognized Epitope	KVAELVHFL (Mage A3 protein)
AND	
Recognized Epitope	KMAELVHFL (Mage A12 protein)

J Immunother 36(2):133, 2013

Figure 5



Neurological imaging studies. Shown are MRI scans for patients 5, 7 and 8, with the timing of the images as listed.

BRIEF REPORT | SEPTEMBER 12, 2019

Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma

Clinical Trials & Observations | Brief Report

Matthew J. Frigault, Jorg Dietrich, Maria Martinez-Lage, Mark Leick, Bryan D. Choi, Zachariah DeFilipp, Yi-Bin Chen, Jeremy Abramson, Jennifer Crombie, Philippe Armand, Lakshmi Nayak, Chris Panzini, Lauren S. Riley, Kathleen Gallagher, Marcela V. Maus

Blood (2019) 134 (11): 860-866.

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

Phase I Study (NCT01454596)

NCI IRB approved	All patients signed informed consent Opened 2011
Primary end points:	Maximum safe dose Determine 6 month PFS
Secondary end points:	CAR persistence Radiologic response

(*Goff et al. J Immunother; 42:126, 2019)*

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

Epidermal growth factor receptor (EGFR)

The most frequent genetic alteration associated with GBM

The most frequent variant is EGFRvIII (25-64%)

Driver mutation

Extracellular ligand binding domain is truncated and is constitutively active

EGFRvIII is not present in normal tissue and is tumor specific

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

Protocol

Nonmyeloablative preparative chemotherapy

Cell infusion (1 E7 total cell starting dose)

Low dose IV IL-2 (72,000 IU/kg) q 8 to tolerance

MRI follow up at monthly intervals

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

Eligibility

Recurrent GBM following surgery , XRT , and chemo

18-70 years of age

Karnosfsky performance status $\geq$ 60%

Steroids allowed if on a stable dose

EGFRvIII + Determination based on a two step PCR on RNA from in-house or submitted samples (NCI Path Department)

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

Anti-EGFRvIII CAR T Cell Production and Analysis (139-28BBZ)

Single chain human scFV (139)
3rd Generation (CD28 costimulation, CD3Z, 4-1BB costimulation)

Diagram of retroviral construct detailing location of single chain variable fragment of Hu monoclonal Ab 139 CD8 linker domain, CD28 and 4-1BB costim domains and CD3zeta signaling domain

Morgan RA et al.

Hum Gene Ther. 2012,23(10):1043

Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Glioblastoma Expressing EGFRvIII

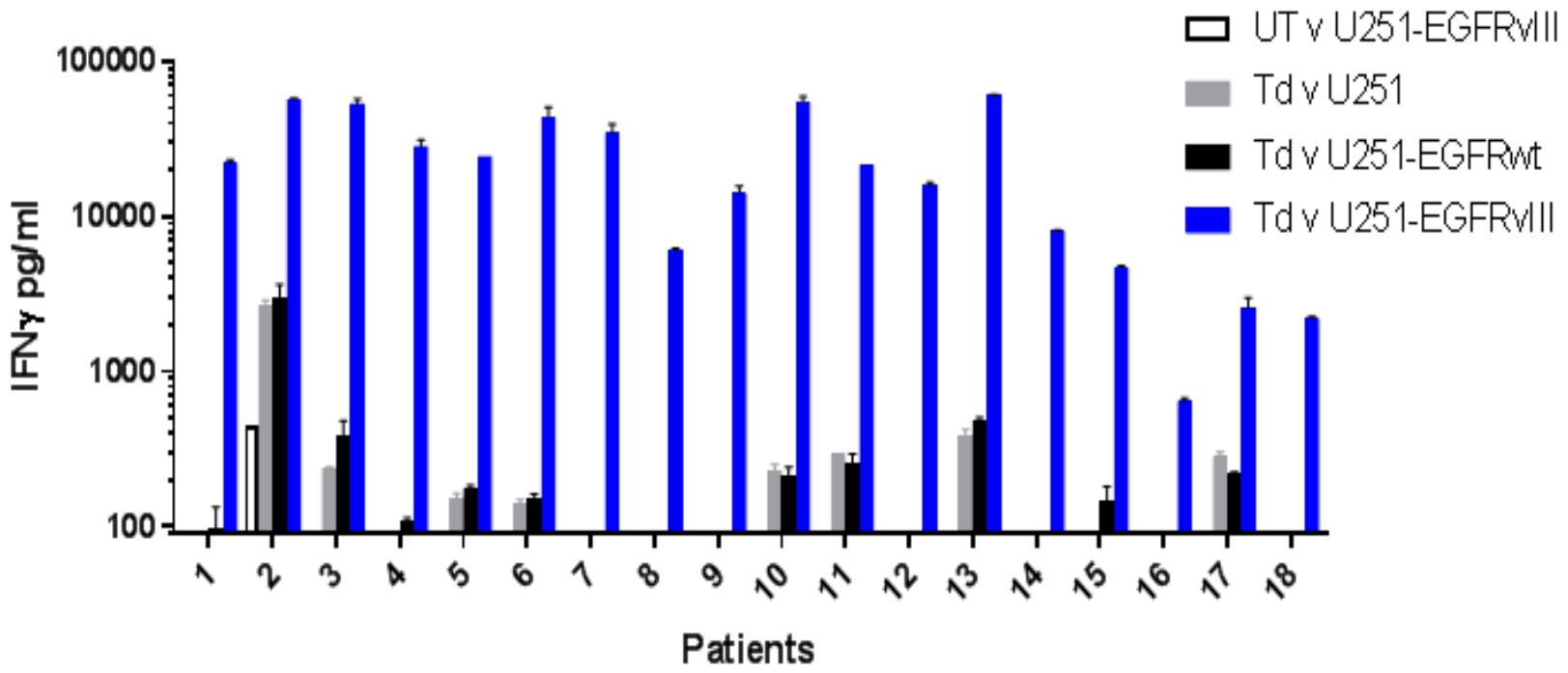
Anti-EGFRvIII CAR T Cell Production and Analysis (139-28BBZ)

OKT3 stimulated PBL transduced with a gamma-retroviral vector encoding the EGFRvIII CAR

COA included ≥ 10% CAR+ CD3 Cells
Specific INF-g release to EGFRvIII+ cell lines

(≥ 3 E 10 cells required additional rapid expansion)

B.



EGFRvIII-specific cytokine release of infused cell product as measured by interferon-γ ELISA.
UT: untransduced PBL, Td: PBL transduced with CAR-28BBZ, U251: glioblastoma cell line ± transduction to express EGFRwt or EGFRvIII

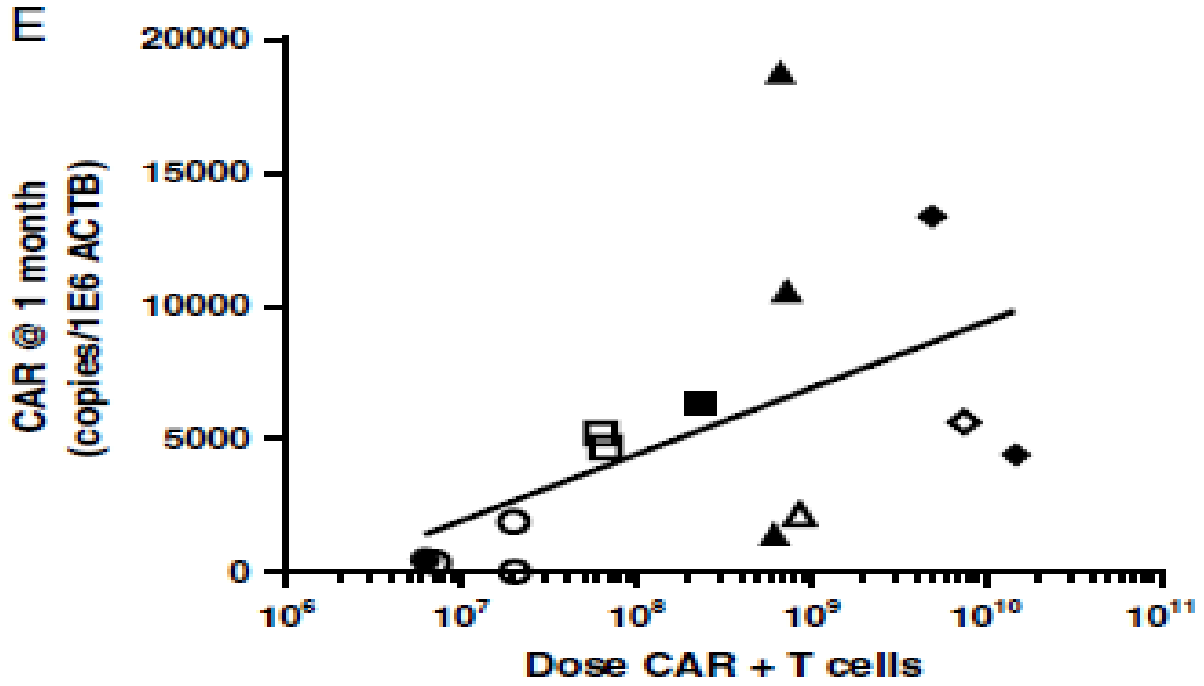
ID	AGE	SEX	PRIOR TREATMENTS
1	45*	M	Surgery, XRT, TMZ, bevacizumab, BCNU
2	43	M	Surgery, XRT, TMZ, bevacizumab
3	52*	M	Surgery, XRT, TMZ, bevacizumab
4	46	M	Surgery, XRT, TMZ
5	55	M	Surgery, XRT, TMZ
6	57*	M	XRT, TMZ, bevacizumab
7	53	M	Surgery, XRT, TMZ
8	56	M	Surgery, XRT, TMZ, AZD7451
9	55	F	Surgery, XRT, TMZ, bevacizumab
10	55	M	Surgery, XRT, TMZ
11*	61*	F	Surgery, XRT, TMZ
12*	66*	M	Surgery, XRT, TMZ, veliparib, bevacizumab
13	60*	M	Surgery, XRYT, TMZ, bevacizumab, EGFRvIII vaccine
14*	64	F	Surgery, XRT, TMZ, IMA950 vaccine
15	61*	M	Surgery, XRT, TMZ, EGFRvIII vaccine vs. placebo trial, bevacizumab, trebananib
16	43*	M	Surgery, XRT, TMZ carotuximab, bevacizumab
17	47*	M	Surgery, XRT, TMZ, EGFRvIII vaccine vs placebo trial, bevacizumab
18*	57	M	Surgery, XRT, TMZ

			ADMINISTERED CELLS						SURVIVAL (MONTHS)	
ID	AGE		DOSE	% CAR (+)	# CAR (+)	# IL-2 DOSES		RESP	PFS	OS
1	45*	M	1.00E+07	71.0%	7.10E+06	7		NR	1.1	2.2
2	43	M	1.00E+07	62.6%	6.26E+06	10		NR	1.9	13.1
3	52*	M	3.00E+07	67.6%	2.03E+07	8		NR	1.1	4.5
4	46	M	3.00E+07	66.5%	2.00E+07	4		NR	2.0	11.1
5	55	M	1.00E+08	67.5%	6.75E+07	7		NR	1.5	9.0
6	57*	M	1.00E+08	62.9%	6.29E+07	6		NR	0.0	6.9
7	53	M	3.00E+08	76.5%	2.30E+08	8		NR	1.2	9.7
8	56	M	1.00E+09	62.0%	6.20E+08	6		NR	0.9	10.1
9	55	F	1.00E+09	67.6%	6.76E+08	6		NR	1.1	2.0
10	55	M	1.00E+09	73.3%	7.33E+08	5		NR	1.3	4.4
11*	61*	F	2.48E+09	35.0%	8.68E+08	3		NR	12.5	46.8+
12*	66*	M	3.00E+09	67.9%	2.04E+09	5		NR	0.9	2.1
13	60*	M	3.00E+09	79.3%	2.38E+09	1		NR	2.7	4.5
14*	64	F	1.00E+10	49.4%	4.94E+09	5		NR	1.6	8.9
15	61*	M	1.00E+10	66.0%	6.60E+09	0		NR	1.1	1.4
16	43*	M	1.00E+10	75.3%	7.53E+09	1		NR	1.1	6.9
17	47*	M	6.00E+10	43.2%	2.59E+10	0		NE	TRM	TRM
18*	57	M	3.00E+10	49.9%	1.50E+10	0		NR	2.0	13.6

Grade 3 and 4 Serious AEs
(excludes CY/Flu Aes)

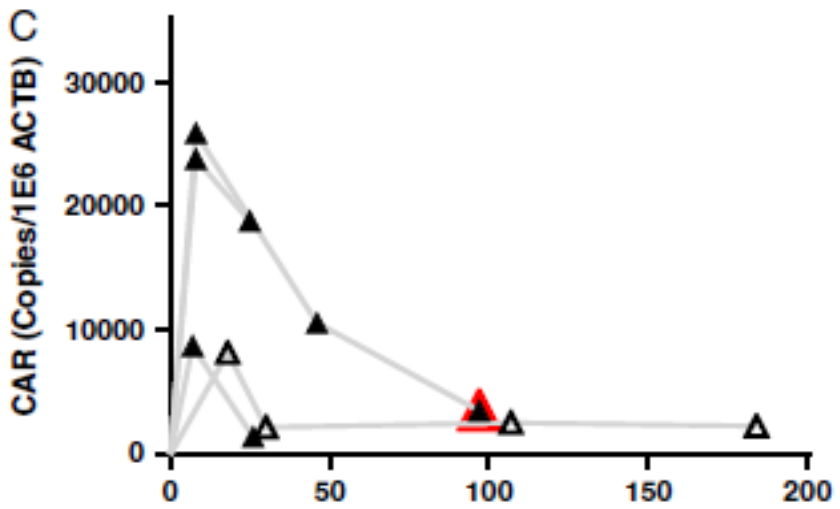
Cardiopulmonary	***Dyspnea/Hypoxia***	***2***
	Hypotension(non septic)	2
	Capillary leak	1
Infectious	Febrile Neutropenia	2
	Bacteremia	8
Neurologic	transient motor weakness	1
	transient urinary incontinence	1
Coagulation	Prolonged PTT	1
	DVT	1
	PE	1

Persistence of infused CAR+ cells as measured by qPCR

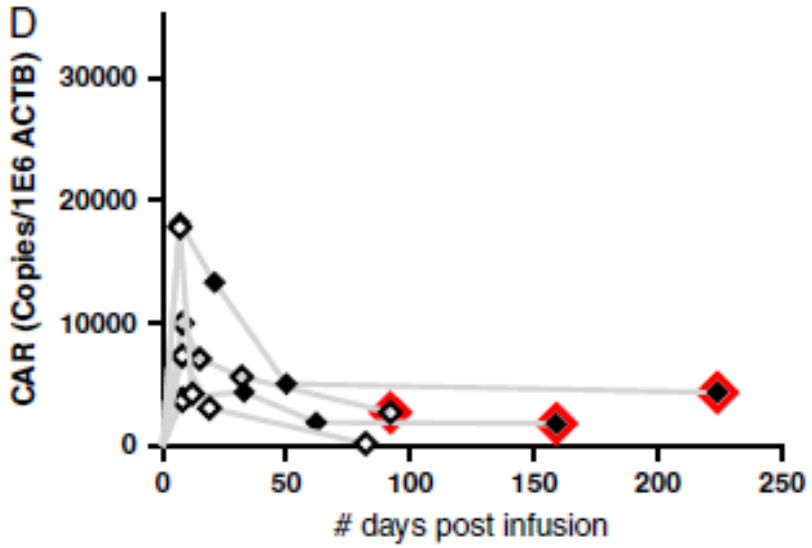


Persistence at one month (median day 32, n=14) was correlated with CAR+ cell dose (r=0.6615, p=0.0121), but not survival (not shown).

Persistence of infused CAR+ cells as measured by qPCR



Patients who received <3x10^{7} CAR+ cells



Patients who received >3x10^{8} CAR+ cells

The Safety and Feasibility of Administering T Cells Expressing Anti-EGFRvIII Chimeric Antigen Receptor to Patients with Malignant Gliomas Expressing EGFRvIII

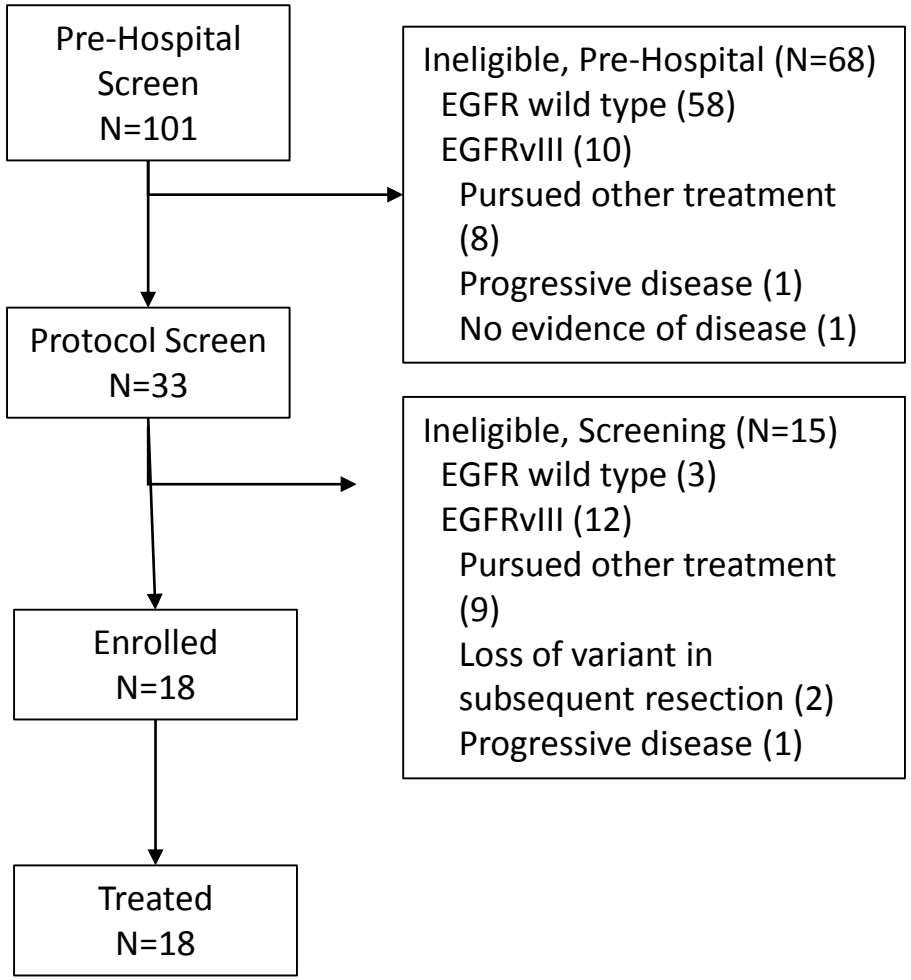
Conclusions

Safe cell dose (1 -3 E 10 total cells)
Patients with GBM can tolerate CAR T-Cells/NMA/LD IL-2
Persistence of CAR T cells appeared to be dose related
Low level CAR T cells could be detected months following infusion
CAR Persistence did not correlate with survival

Administration of anti-EGFRvIII Car T cells did not mediate a clinically meaningful effect in patients with GBM in this Phase 1 Study

(*Goff et al. J Immunother; 42:126, 2019)*

NCI Surgery Branch



CONSORT Diagram of Trial Enrollment.