

T Cell Immunotherapy- Optimizing Trial Design

Session I

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

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NCI 12-C-0112

Phase I Study of T Cells Expressing an Anti-CD19 Chimeric Receptor in Children and Young Adults with B Cell Malignancies

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PATIENT POPULATION:

- Age 1-30
- Refractory CD19+ B cell malignancy
- two strata—no hx of alloBMT, hx of alloBMT

REGIMEN/PRODUCT:

- Cyclophosphamide (900mg/m²)/fludarabine (75 mg/m²)
- Fresh or frozen T cells
 - anti-CD3/CD28 beads plus rhIL2
 - anti-CD19.zeta.28 CAR (Kochendorfer designed; supplied by S. Rosenberg)
 - Retrovirus (MSGV)
- No interleukin-2
- Dose Escalation: 1 x 10⁶/kg; 3 x 10⁶/kg

PROTOCOL OPENED: APRIL, 2012

Enrollment: 10 patients

Status: open to accrual

NCI Pediatric Trial (FMC63-CAR.28.z)

67% CR Rate Overall; 75% CR Rate in ALL

Pt.	Age/Sex	Disease	Prior Allo BMT	CAR Dose (x10 ⁶ /kg)	% marrow blasts		Response	Status
					PRE-	POST		
Dose Level 1								
1	13M	ALL	Yes	1	30%	0.6%	CRi	DOD
2	16F	ALL	Yes	.04	8%		PD	DOD
3	10F	NHL	Yes	1	-	-	PD	DOD
4	11F	ALL	No	1	30%	<0.01%	CR	NED s/p BMT
8	18M	ALL	Yes	1	0.04%	<0.01%	CR	NED d56
Dose Level 2								
5	10M	ALL	No	0.4	10%	<0.01%	CR	NED s/p BMT
6	10M	ALL	No	3	40%	72%	PD	AWD
7	23M	ALL	No	3	50%	0.3%	CR	s/p 2 nd dose
9	13M	ALL	Yes	3	0.18%	<0.01%	CR	Preparing for BMT
10	5M	ALL	No	3	0.04%	n/a		

MRD negative is defined as <0.01% blasts

Lessons Learned

- 75% CR rate in Acute Lymphoblastic Leukemia
 - Intent-to-Treat analysis
 - No preselection for ability for cells to expand:
 - Includes 2 patients in whom T cells expanded poorly
 - Antitumor effects observed even with doses $\ll 1 \times 10^6/\text{kg}$
 - CR in patient with primary refractory ALL confirms activity in chemoresistant disease
- CD19-CAR traffic to tissues and mediate antitumor effects
 - Observed CD19-CAR mediated clearance of CSF blasts
 - Expansion in malignant effusion with no evidence for lymphoblasts
- Toxicity
 - Overall well tolerated with Gr \leq I-II Cytokine Release in 9/10 patients treated
 - One dose limiting cytokine release syndrome
 - Hypotension treated successfully with anti-IL6r mAb
 - Anti-IL6R therapy resulted in rises in serum IL-6 levels
 - Persistent hallucinations x 5-6d, IL-6 levels present in CSF
 - Retreatment at lower disease burden with same cells resulted in no toxicity
 - ? relationship between tumor burden and toxicity
- Evidence for B cell recovery observed in all patients

NCI 11-C-0113

**A Pilot Study of Genetically Engineered NY-ESO-1 Specific (c259) T cells in HLA-A2+ Patients with Synovial Sarcoma
NCI/Children's Hospital of Philadelphia/MSKCC (pending)**

Patient Population:

- **HLA-A2+ Synovial Sarcoma, NY-ESO-1+**
- **Unresectable, metastatic, progressive or recurrent**
- **must have already received doxorubicin and/or ifosfamide**
- **must have measurable disease**

Product:

Cyclophosphamide/fludarabine preparative regimen

Cryopreserved T cells

-activated using anti-CD3/CD28 beads plus rhIL2

-NY-ESO-1 (c259) T cell receptor

-Lentivirus (pELNS backbone vector)

-EF-1 alpha promoter, 2A cleavage between TCR alpha and beta

NO interleukin-2

Cell dose: 1 x 10⁹/kg (max 4 x 10¹⁰ cells)

IRB approval: 2/25/2011

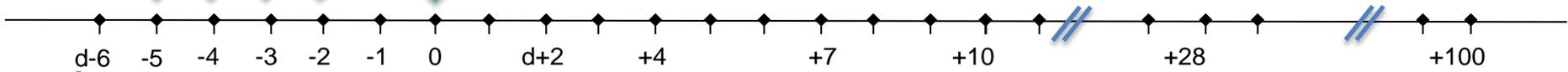
Enrollment: 2 patients

Status: open to accrual

NY-ESO
T Cell
infusion:
34 x 10⁹

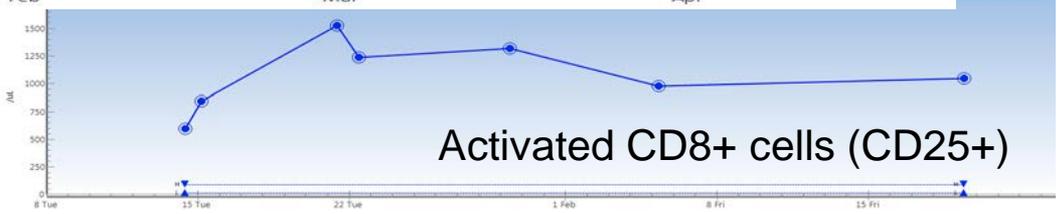
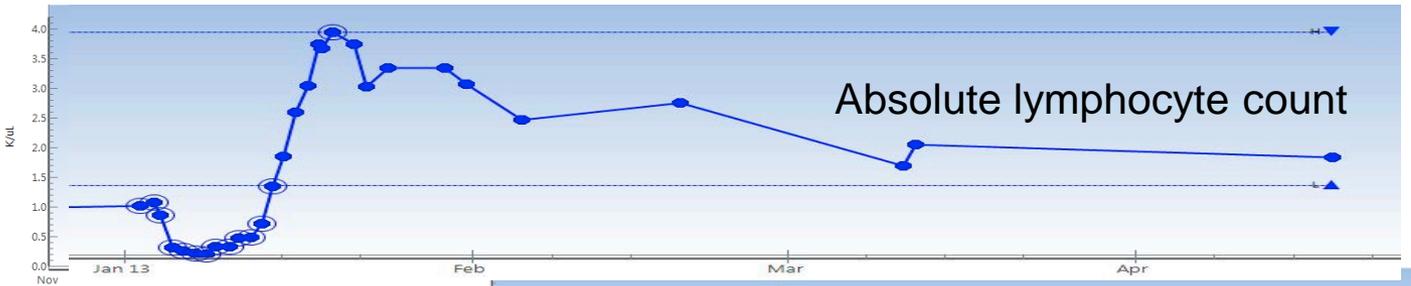
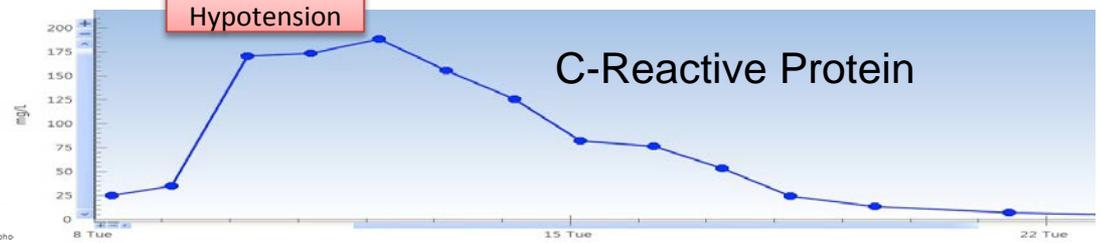
Cyclophosphamide

Fludarabine

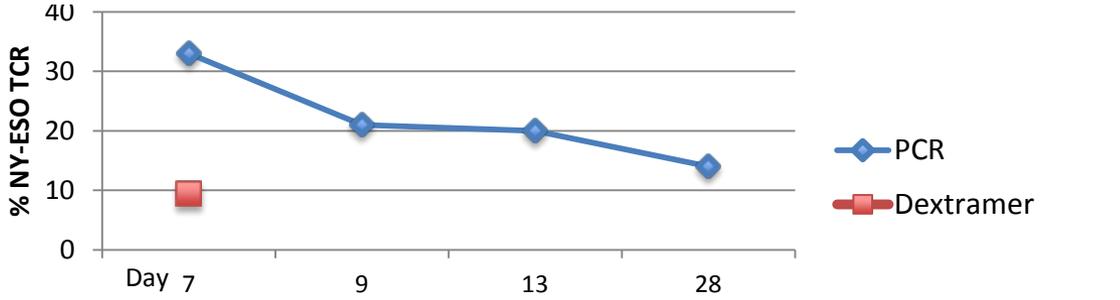


Coronavirus

Fever, SOB,
Hypotension



Recurrent Synovial Sarcoma:
Metastatic to lung
Miliary pattern

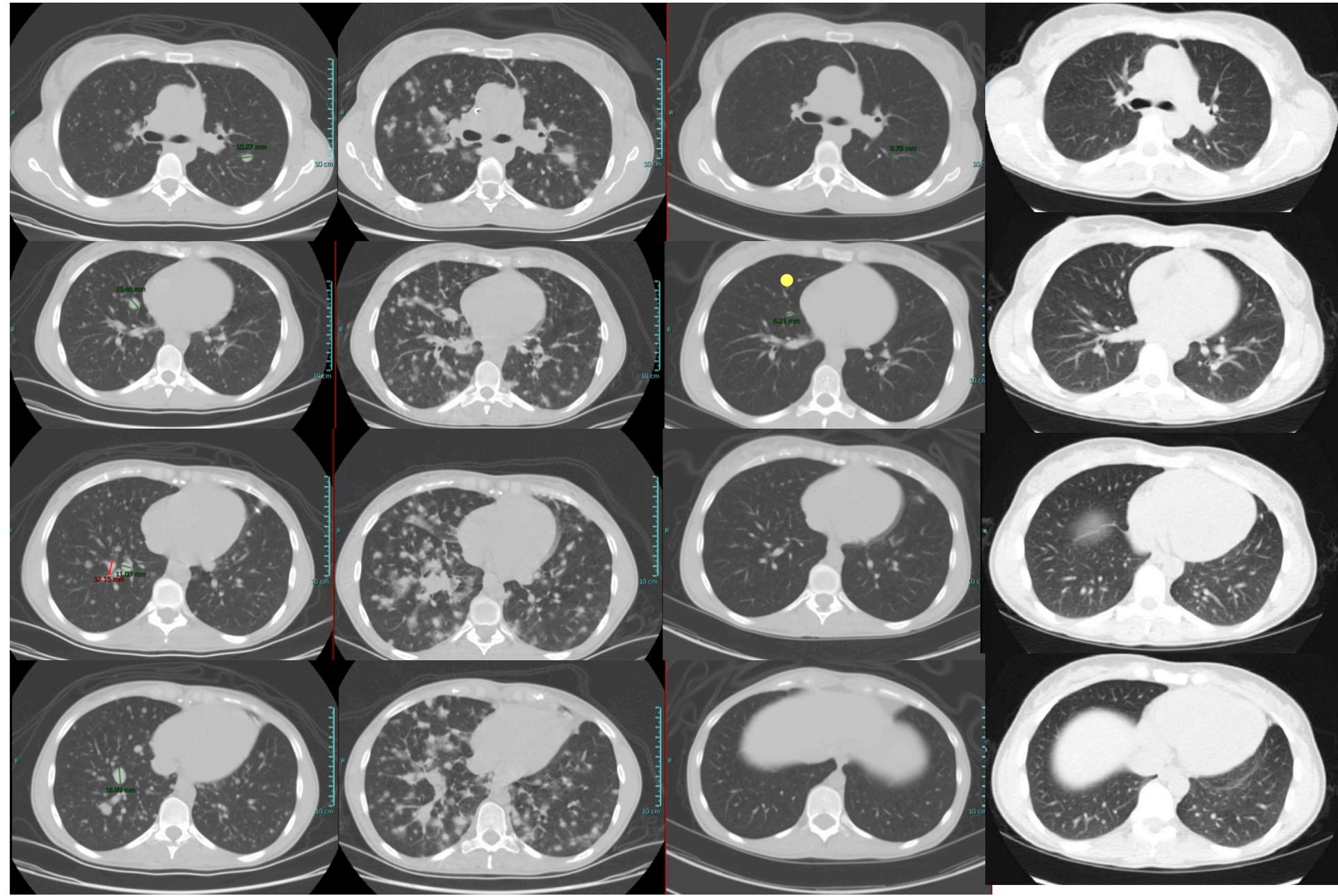


Baseline
1/2/13
“miliary disease”

Day +2
1/10/13
“pseudoprogression”

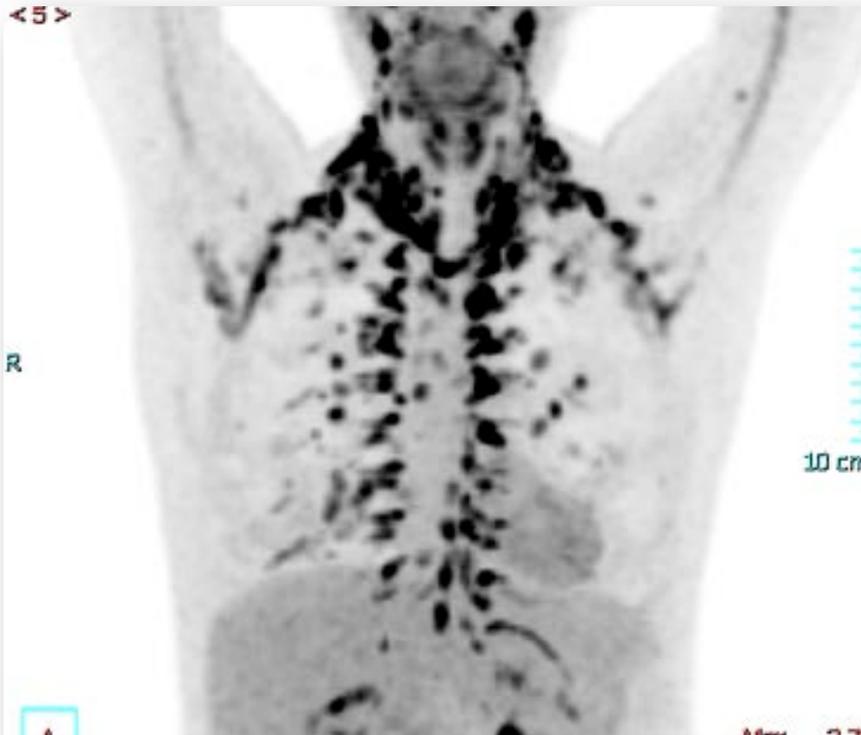
Day +28
2/6/13
VGPR

6 months
7/18/13
Sustained CR

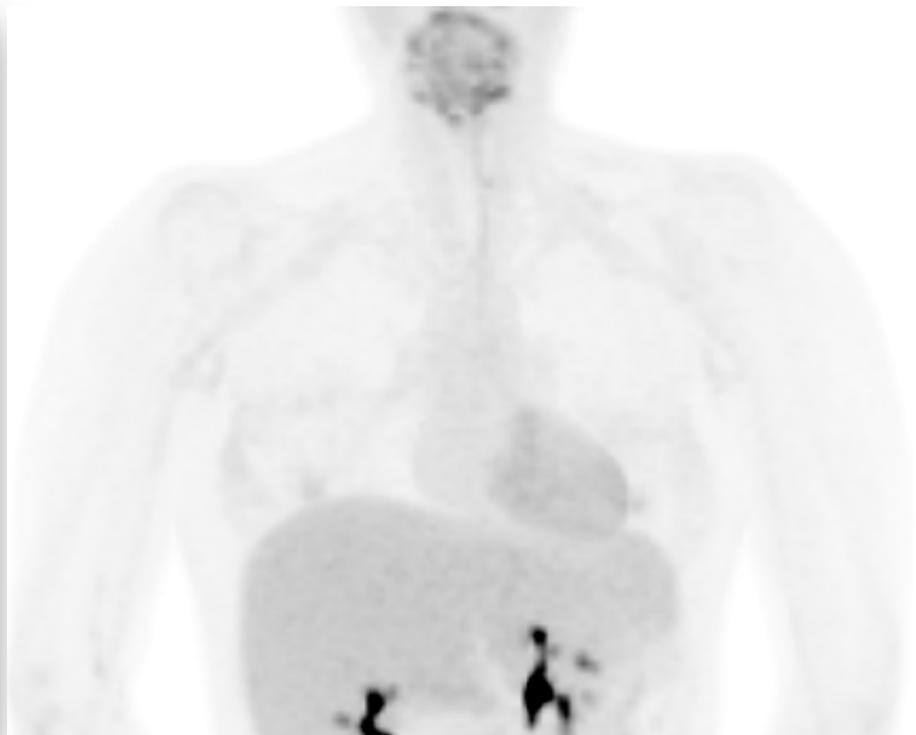


Complete Response to Adoptive Therapy with NY-ESO-1 Engineered T Cells

Baseline
January 2, 2013



6 months
July 19, 2013



Lessons Learned

- Proof-of-principle for efficacy of NY-ESO TCR therapy in synovial sarcoma
 - First sustained CR observed in synovial sarcoma treated with adoptive cell therapy
 - Factors determining response for individual patients remain unclear
 - Did the viral infection render the T cells more potent in patient #2?
- IL-2 is not necessary for antitumor effects using this approach
- Widespread T cell activation is associated with “inflammatory” toxicity
 - Pseudoprogression: The tumor appears worse before it appears better
 - Similar results seen with checkpoint inhibitors
- Major challenge is applying this therapy across the range of HLA-alleles present in the population
 - Many patients screened who do not meet the A2+/NYESO1+ eligibility criteria