

Session I

Update on Current Approaches and Trials

MDACC EXPERIENCE

**Laurence J.N. Cooper, M.D., Ph.D.
MD Anderson Cancer Center**

**September 10, 2013
Session begins 8:40 AM**



MDACC's approach

- Treat patients with B-cell malignancies at high risk of relapse recognizing that:
 - Infusing CAR⁺ T cells in patients with minimal residual disease (MRD) will avoid cytokine storm and concomitant toxicities
 - Such patients should receive CAR⁺ T cells after HSCT since the latter is standard-of-care and thus likely needed at this stage in the development of CAR-based therapies

MDACC's approach (cont.)

- To reduce the burdens and costs of T-cell therapies
 - Avoid cost and complexity of recombinant viral vectors
 - Propagate T cells *ex vivo* in a physiologic CAR-dependent manner
 - Simplify manufacturing and delivery including infusion of cryopreserved products

Implementation of T-cell trials

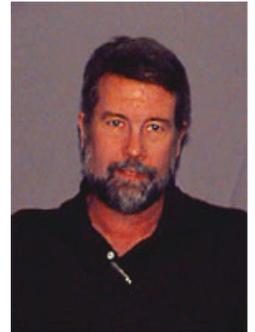
Begun by testing three new technologies in humans

1. Our CD19-specific CAR (designated CD19RCD28) that co-activates T cells via chimeric CD3- ζ and CD28 to deliver signal 1 and signal 2, respectively
2. The genetic modification of T cells to express CAR from DNA plasmids derived from *Sleeping Beauty* (SB) system
3. Selective activation and propagation of CAR⁺ T cells on γ -irradiated engineered artificial antigen presenting cells (aAPC)

A new approach to manufacturing CAR⁺ T cells

Combining two platform technologies we adapted for human application

- *Sleeping Beauty* (SB) transposon/transposase system
 - Non-viral approach to gene therapy using DNA plasmids
 - Inexpensive
 - Facile
- Engineered artificial antigen presenting cells (aAPC)
 - Selective propagation of CAR⁺ T cells



Dr. Perry Hackett
University of Minnesota

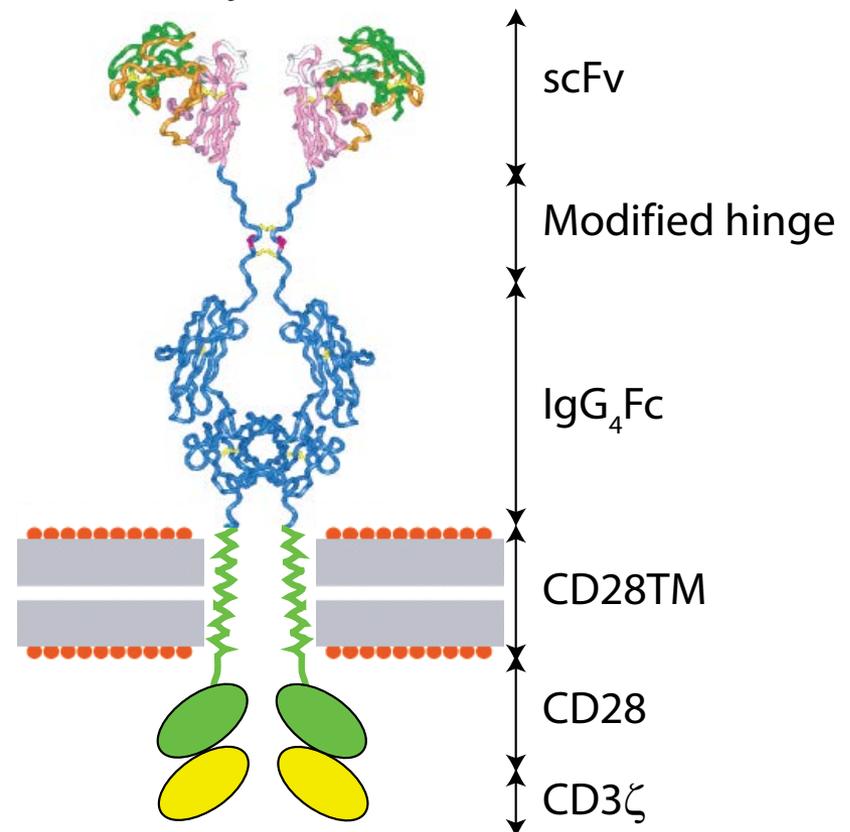


Dr. Carl June
University of Pennsylvania

SB system to genetically modify T cells to target CD19

- T cells targeting CD19 feasible gene therapy approach
 - Successful infusions of genetically modified T cells
 - Tolerable “on target” side-effects
- Compelling patient population
 - Patients with advanced B-cell malignancies high rate of relapse despite hematopoietic stem-cell transplantation (HSCT)

2nd generation CD19-specific CAR (**CD19RCD28**) signaling through CD28 and CD3- ζ



Shown as a homo-dimer

Investigator-initiated Gene Transfer Trials under 4 INDs at MD Anderson Cancer Center

MDACC / NCI #	Agent	Dose of CD19RCD28 ⁺ T cells	Enrolled	Products made	Infused
2007-0635/00968760	CD19-specific T cells derived from patient combined with autologous HSCT	$5 \times 10^7/\text{m}^2$ to $5 \times 10^9/\text{m}^2$ (IL-2 last 2 cohorts)	9 (all NHL)	7	5
2009-0525/01497184	CD19-specific T cells derived from donor combined with allogeneic HSCT	$10^6/\text{m}^2$ to $10^8/\text{m}^2$	18 (ALL, n=11; NHL, n=6; CLL, n=1)	14	5
2010-0835/0136452	CD19-specific T cells derived from umbilical cord blood (UCB) donor combined with UCB transplantation	$10^6/\text{m}^2$ to $10^8/\text{m}^2$	4 (ALL, n=3; NHL, n=1)	4	1
2011-1169/01653717	CD19-specific T cells from CLL patients after chemotherapy (non-HSCT)	$10^7/\text{m}^2$ to $5 \times 10^{10}/\text{m}^2$	1	1	0

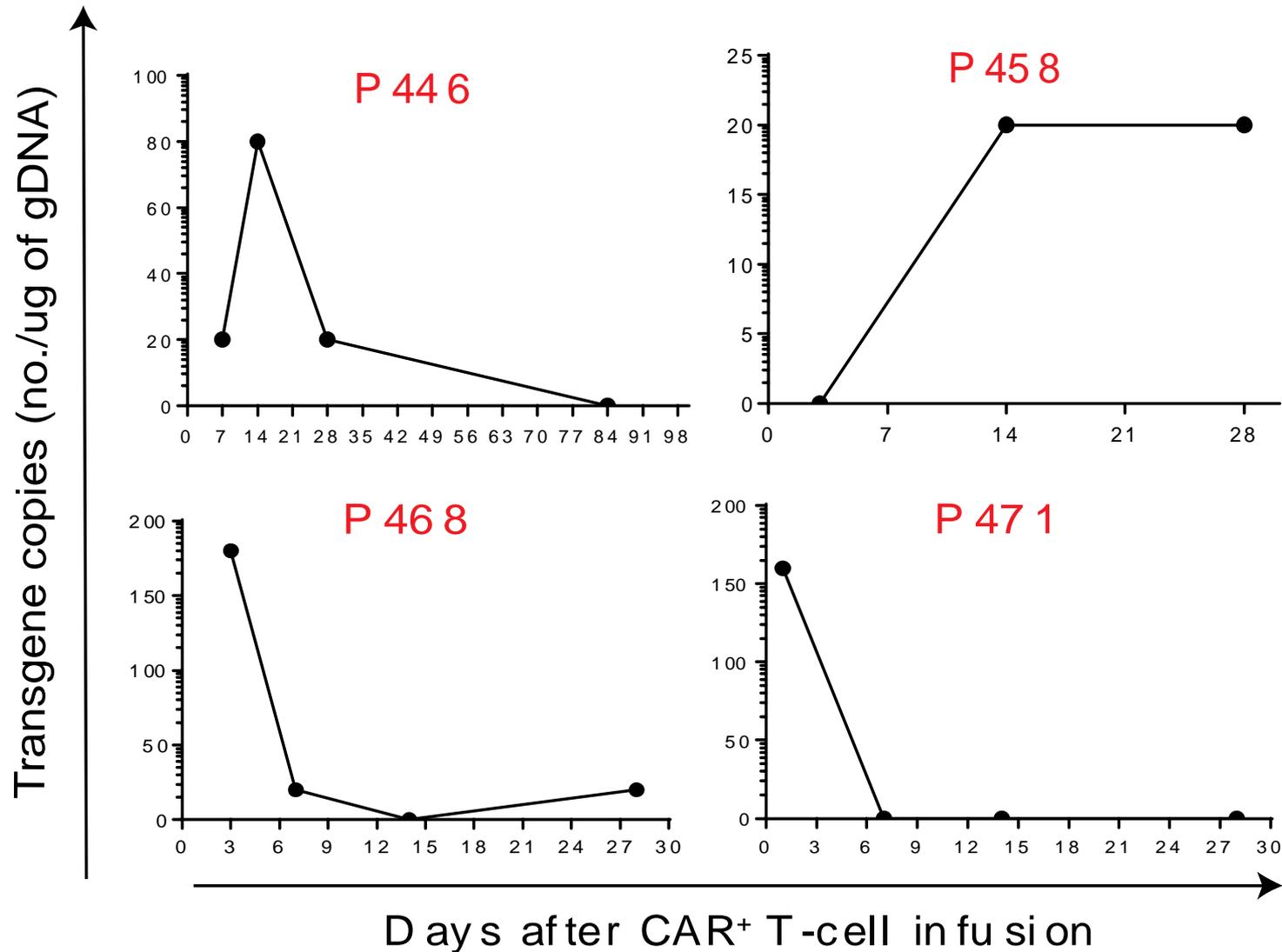
2007-0635: Autologous CAR⁺ T cells

Initial clinical data. Trial is accruing and scheduled dose escalations are planned

UPN	Age	Histology at Diagnosis	Stage at SCT	Dose Level	T cells Infused (x10 ⁸)	CAR expression (%)	Response	Toxicity
*P446	61	Follicular, mixed	Transformed DLBL, CR2	5x10 ⁸ /m ²	10.0	87.5	CCR, 6 mo.	None
P458	58	Nodular pred. HL	Transformed DLBL, CR2	5x10 ⁸ /m ²	10.6	77.2	CCR, 4 mo.	None
P468	48	Follicular, mixed	Follicular, mixed, Rel1	5x10 ⁸ /m ²	11.4	85.5	CR, 4 mo.	None
P471	55	DLBL	DLBL, Rel1	5x10 ⁸ /m ²	11.1	90.4	CR, 3 mo.	None
P509	58	CNS NHL	CR2	5x10 ⁸ /m ²	2.2	95.9	Too Early	None

* Rituximab omitted in conditioning therapy due to recent atrial fibrillation in patient

Persistence of autologous CAR⁺ T cells

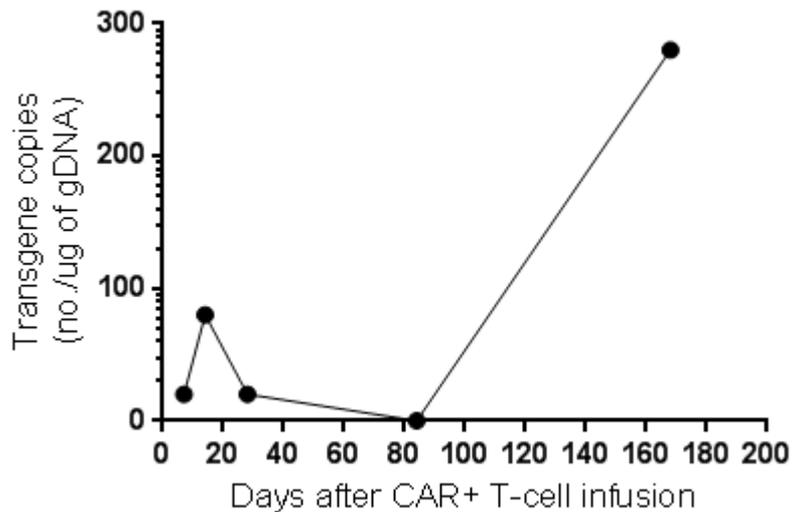


P446: No circulating CD19⁺ B cells at 6 months

CAR⁺ T cells emerged at 6 months after infusion

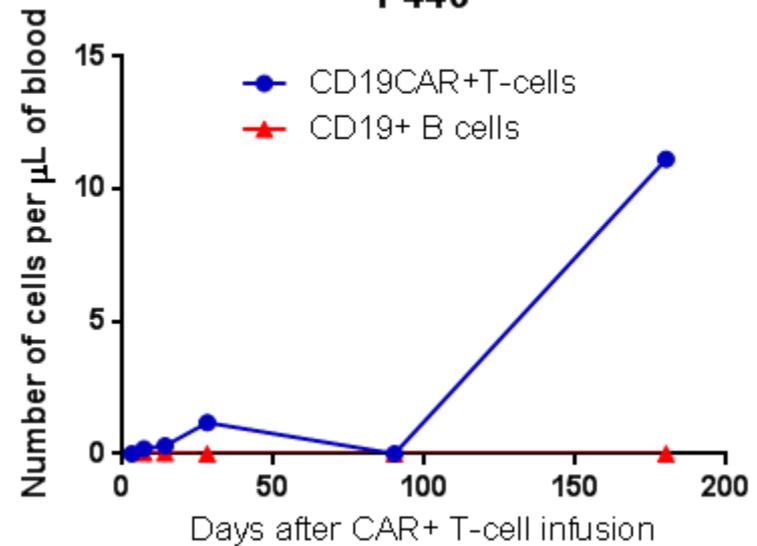
Q-PCR

P446



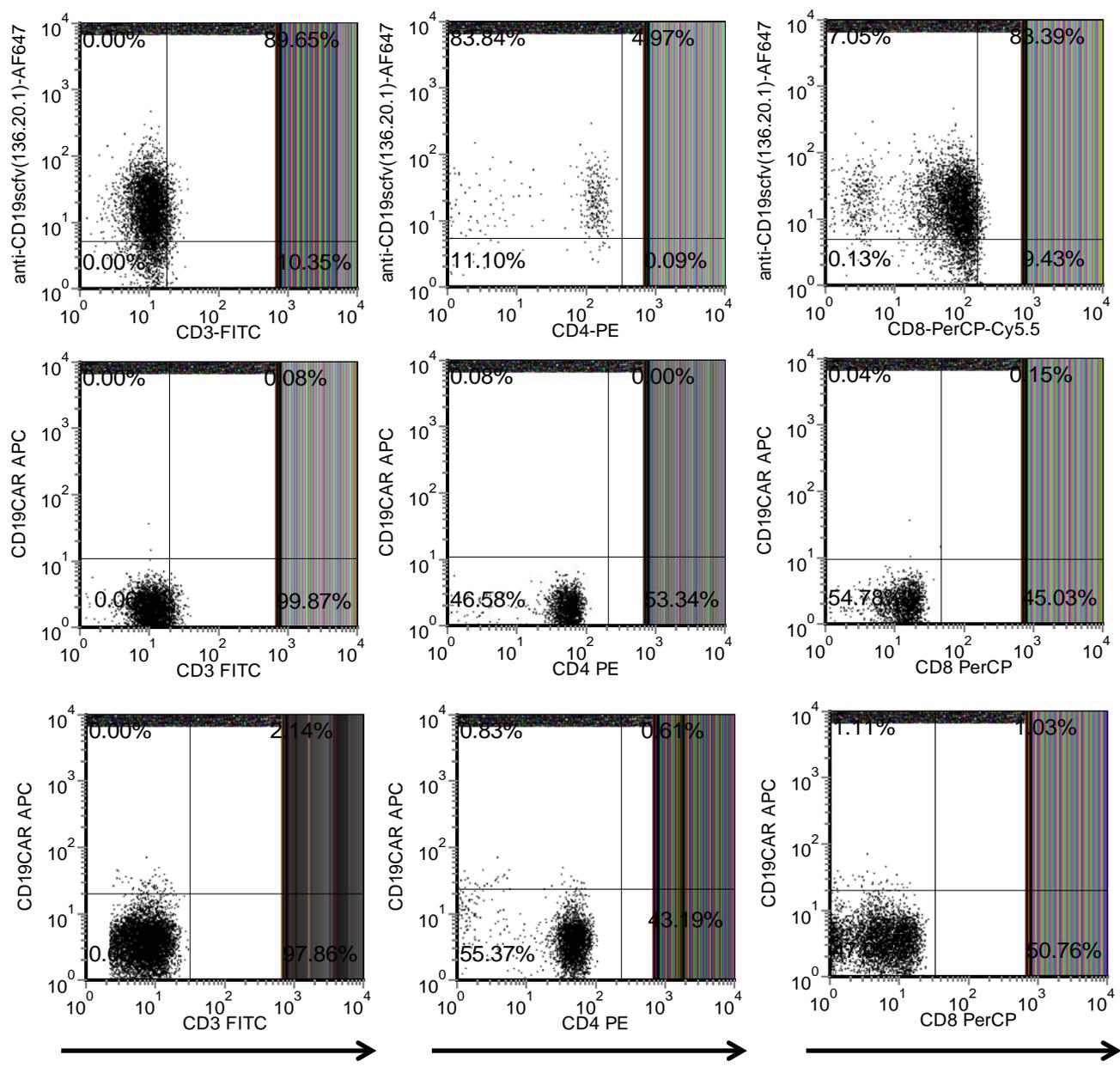
Flow cytometry

P446



P446

CAR (anti-scFv)



Infused
CAR⁺ T cells

1 week post
infusion

6 months
post infusion

Gated on CD3⁺ population

CD3

CD4

CD8

2009-0525: Allogeneic CAR⁺ T cells

Initial clinical data. Trial is accruing and scheduled dose escalations are planned

UPN	Age	Histology at Diagnosis	Stage at SCT	Dose Level	CAR-T source	T cells Infused (x10 ⁸)	CAR expression (%)	Response	Toxicity
P396	23	B-ALL	CR2, *MRD ⁺	10 ⁶ /m ²	MSD donor	0.02	96.5	Progressed	None
P411	50	DLBL	Refractory, 8 lines Rx	10 ⁶ /m ²	MSD donor	0.03	70.5	Progressed	None
P410	21	B-ALL	CR3, MRD ⁺	10 ⁶ /m ²	MSD donor	0.02	96.8	Progressed	None
P459	25	B-ALL	CR2, MRD ^{neg}	10 ⁷ /m ²	MSD donor	0.28	90.5	CCR at 6 mo.	GVHD?
P513	25	B-ALL	Refractory, auto-SCT	10 ⁶ /m ²	Haplo donor	0.02	93.3	Too Early	None

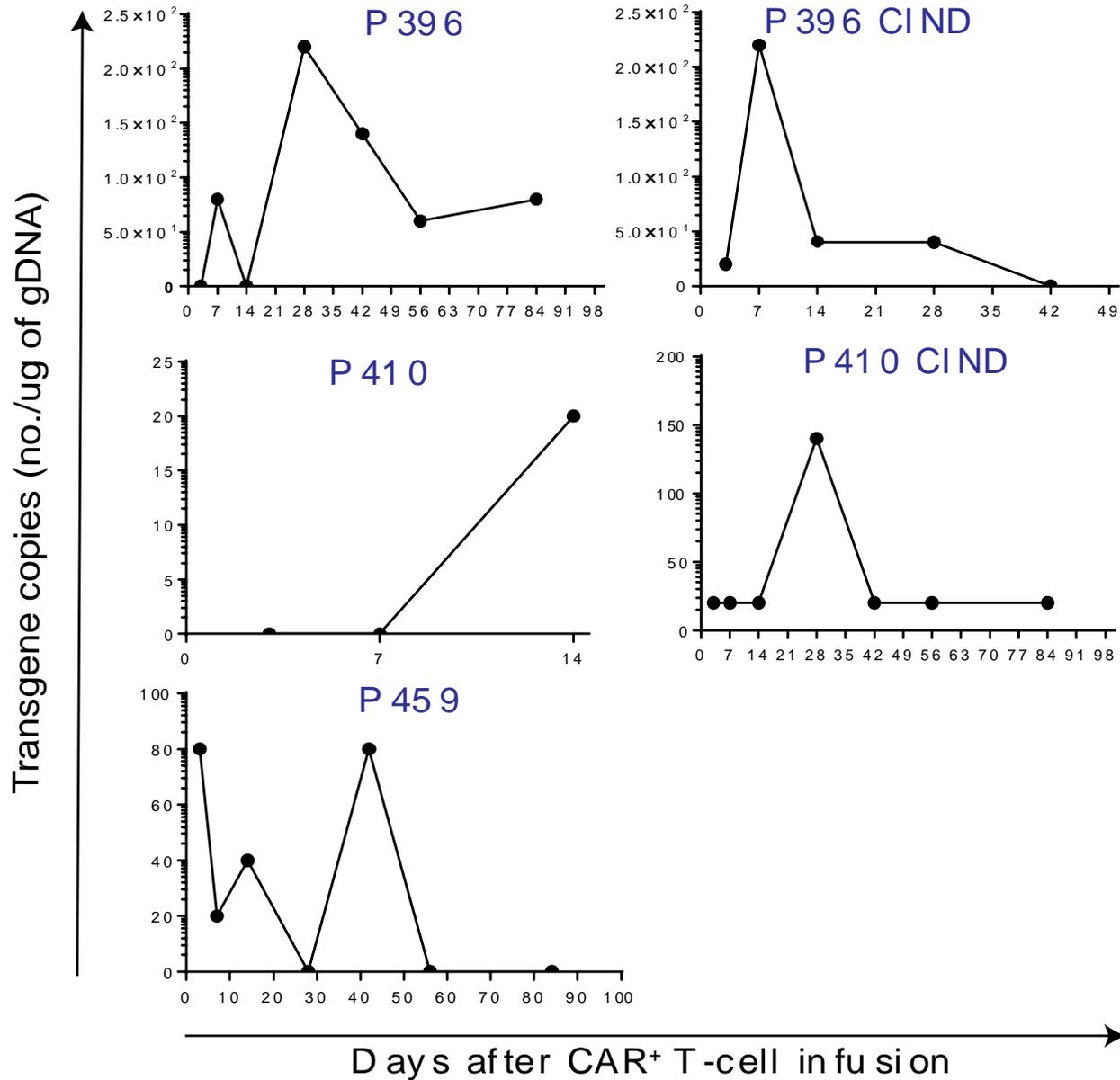
2009-0525: Allogeneic CAR⁺ T cells

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UPN	Age	Histology at Diagnosis	Stage at SCT	Dose Level	CAR-T source	T cells Infused (x10 ⁸)	CAR expression (%)	Response	Toxicity
P396	23	B-ALL	CR2, *MRD ⁺	10 ⁶ /m ²	MSD donor	0.02	96.5	Progressed	None
P396-CIND	23	B-ALL	CR3, MRD ⁺	5x10 ⁷ /m ²	MSD donor	0.95	96.5	Progressed	None
P410	21	B-ALL	CR3, MRD ⁺	10 ⁶ /m ²	MSD donor	0.02	96.8	Progressed	None
P410-CIND	21	B-ALL	CR4, MRD ^{neg}	10 ⁷ /m ²	MSD donor	0.17	96.8	CCR, relapse 9 mo.	None

P410 relapsed only in calf ←

Persistence of allogeneic CAR⁺ T cells



Lessons Learned infusing patients in MRD

- Summary of Adverse Events
 - No infusion-related toxicity
 - One patient developed acute GVHD of liver, steroid refractory, in setting of concurrent drug-induced liver injury

Lessons Learned

- Patient-derived T cells can be generated from autologous blood of heavily pre-treated recipients
- Donor-derived T cells can be generated from allogeneic blood, including umbilical cord blood
- Successfully infuse patient-and donor-derived CD19-specific T cells after autologous and allogeneic HSCT, respectively
- Initial clinical data infusing SB-modified and aAPC-propagated CAR⁺ T cells demonstrate safety, feasibility, and persistence

Lessons Learned (cont.)

- Successfully manufacture T-cell products from:
 - Small fraction of umbilical cord blood at time of transplantation
 - 200 mL of peripheral blood and avoid costs and inconvenience of apheresis
 - From heavily pre-treated patients
- No immediate or late toxicities
 - T cells now administered as outpatient infusions
 - No GVHD attributed to infused allogeneic T cells
- Can safely re-infuse CAR⁺ T cells from patient-specific cryopreserved banks

Summary to date

- First-in-human application of SB system
- Human application of K562-derived aAPC
- Human application of CD19RC28 CAR
- Infusions after autologous and allogeneic HSCT, including umbilical cord blood transplantation
- Persistence of CAR⁺ T cells in peripheral blood
- Increase in presence of CAR⁺ T cells in peripheral blood months after infusion

Plans

- Low costs of SB system enable:
 - Change of CAR design and specificity
 - Co-expression of co-stimulatory molecules with CAR
- Use aAPC to propagate CAR⁺ T cells with specificity other than CD19

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Thank You

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