CENTER FOR CANCER RESEARCH

Connecting the Cancer Community

Adoptive Immunotherapy in Translocation-driven sarcomas Synovial Sarcoma Model

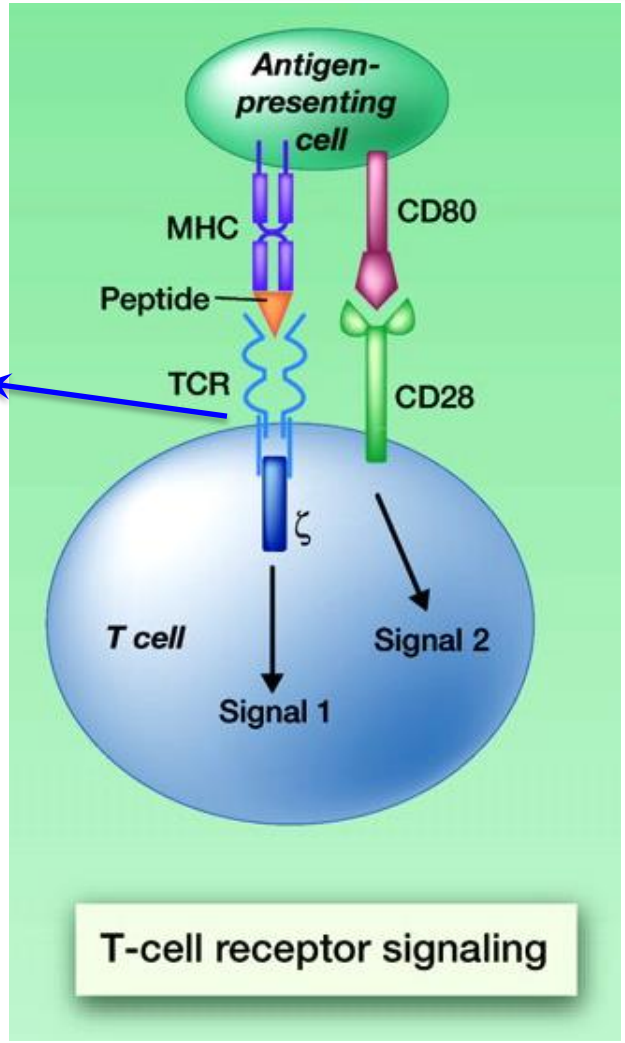
Lee J. Helman, M.D.

NATIONAL CANCER INSTITUTE

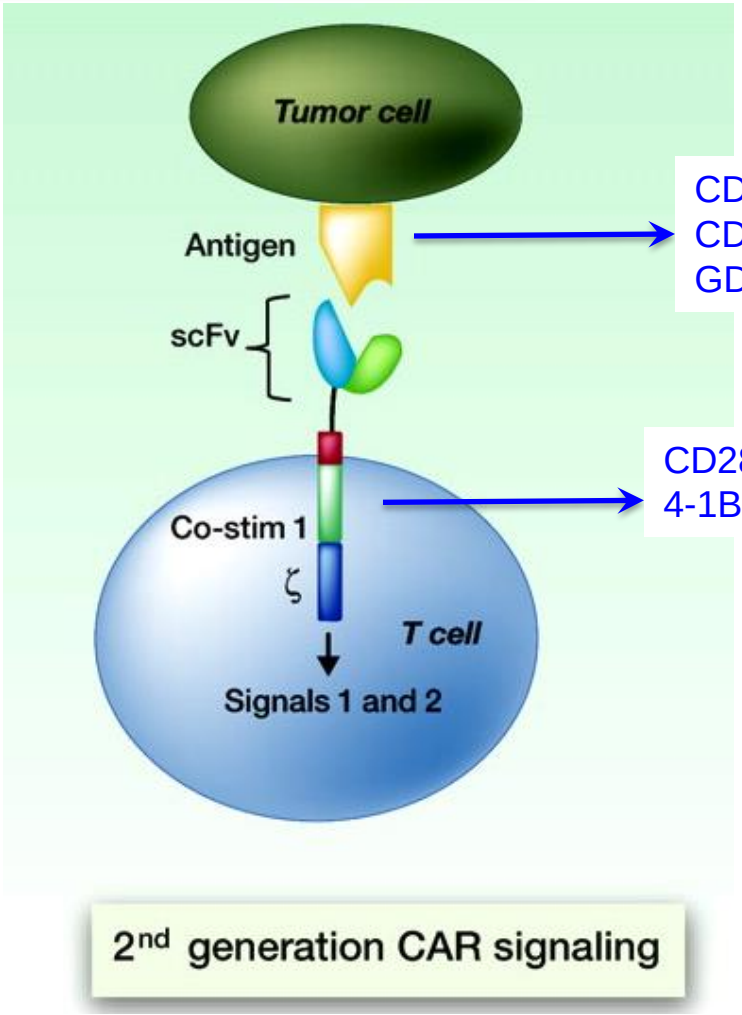
DISCLOSURE SLIDE

I work for the US Federal Govt and have nothing to disclose

Engineered T Cells: T Cell Receptors vs. Chimeric Antigen Receptors



NY-ESO-1



CD19
CD22
GD2

CD28
4-1BB (CD137)

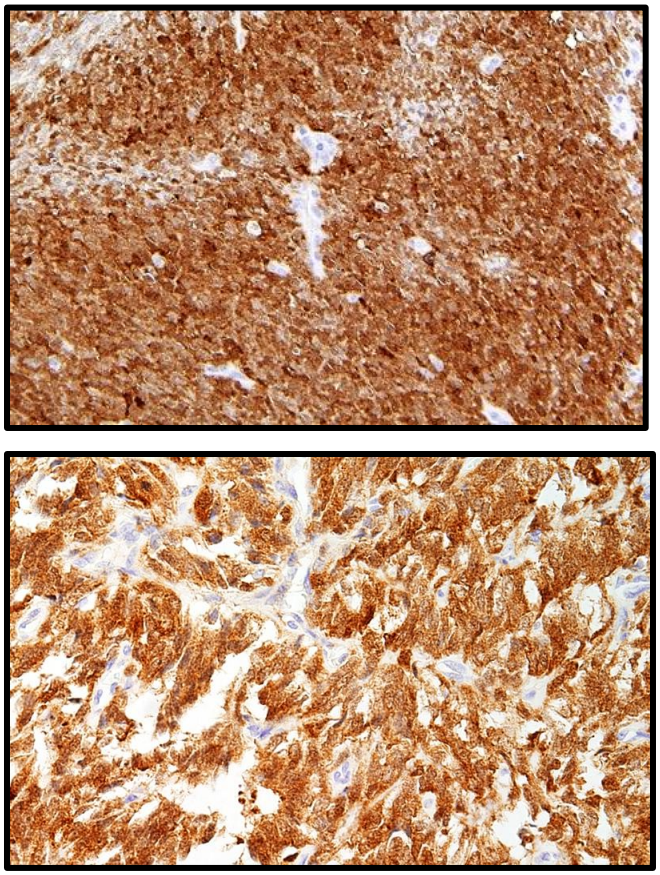
- *recognize processed peptides (intracellular or cell surface antigen)*
- *MHC restricted*
- *requires co-stimulation from APC or tumor*

- *recognize intact cell surface antigens*
- *non- MHC restricted*
- *costimulatory signal provided coincident with antigen recognition*

NY-ESO-1: A Targetable Antigen in Synovial Sarcoma

- **NY-ESO-1 is a Cancer-Testis Antigen** identified by Chen et al (1997)
- **Highly Expressed in synovial sarcomas**
  - 76% of synovial sarcomas express strong staining
- A **T cell receptor (TCR)** recognizing **NY-ESO-1** in the context of **HLA:A0201** was cloned from a patient with cancer, then modified for higher affinity Zhao, J Immunol, 2007

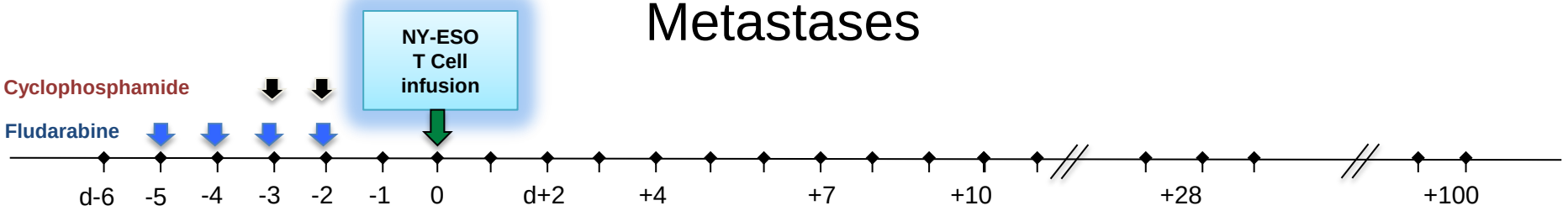
NY-ESO IHC screening on Synovial Sarcomas

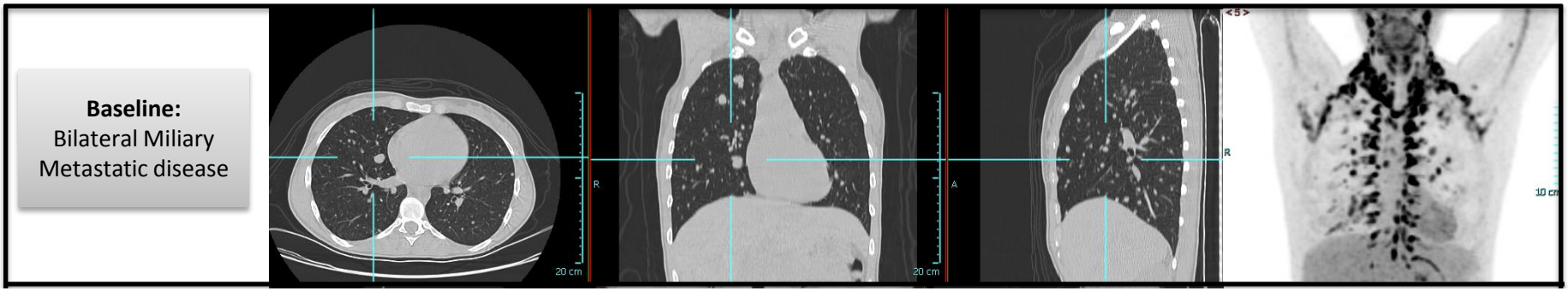


Genetically Engineered TCRs Recognizing NY-ESO-1 to Target Synovial Sarcoma

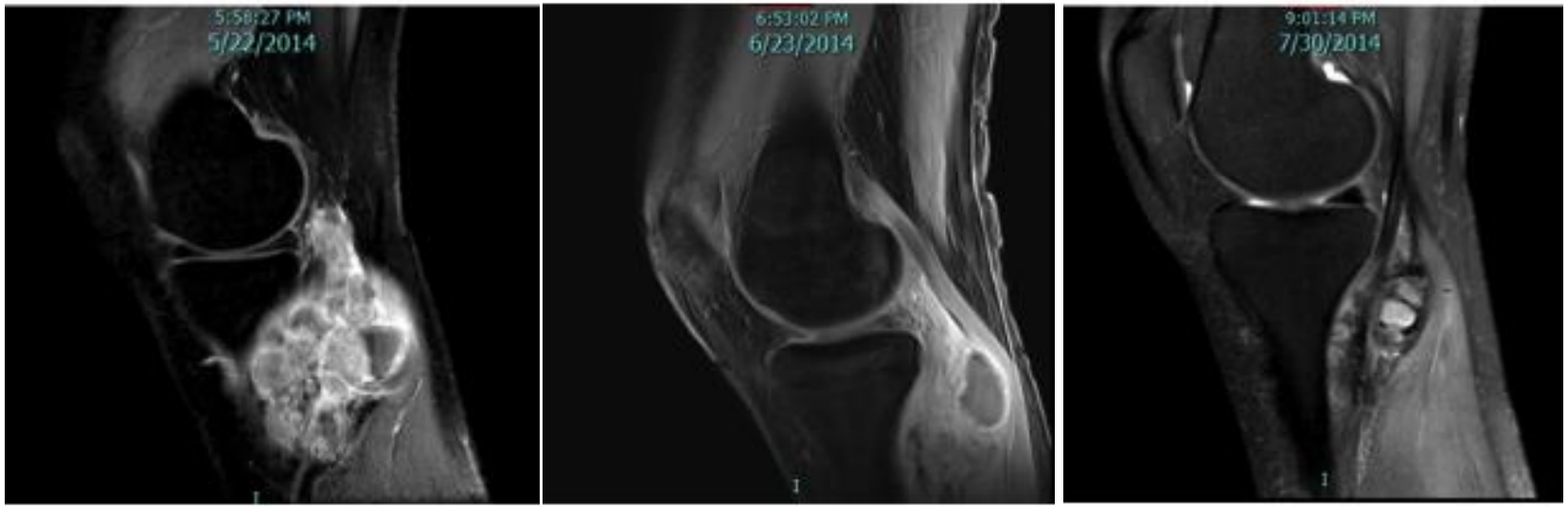
- Published clinical trial of NY-ESO-1 autologous lymphocytes in melanoma and synovial sarcoma *Robbins et al, JCO 2011*
  - Lymphodepletion + NY-ESO TCR cells + HD IL2
  - Promising results with partial response in 4 of 6 patient with synovial sarcoma
- NCI POB 11-c-0113: Seeks to test efficacy of NY-ESO-1 TCR Expressing Lymphocytes in Synovial Sarcoma with specific changes to improve safety and exportability
  - Determine the response rate following NY-ESO-1 Specific T cells (**without HD IL2**)
  - Lentivirus vector
  - Central manufacturing site and multi-center trial (Adaptimmune)

Radiographic Pseudoprogression and Response of Lung Metastases





Very Good Partial Response of Chemorefractory, Unresectable, Primary Progressive Sarcoma following NY-ESO-1 T Cells

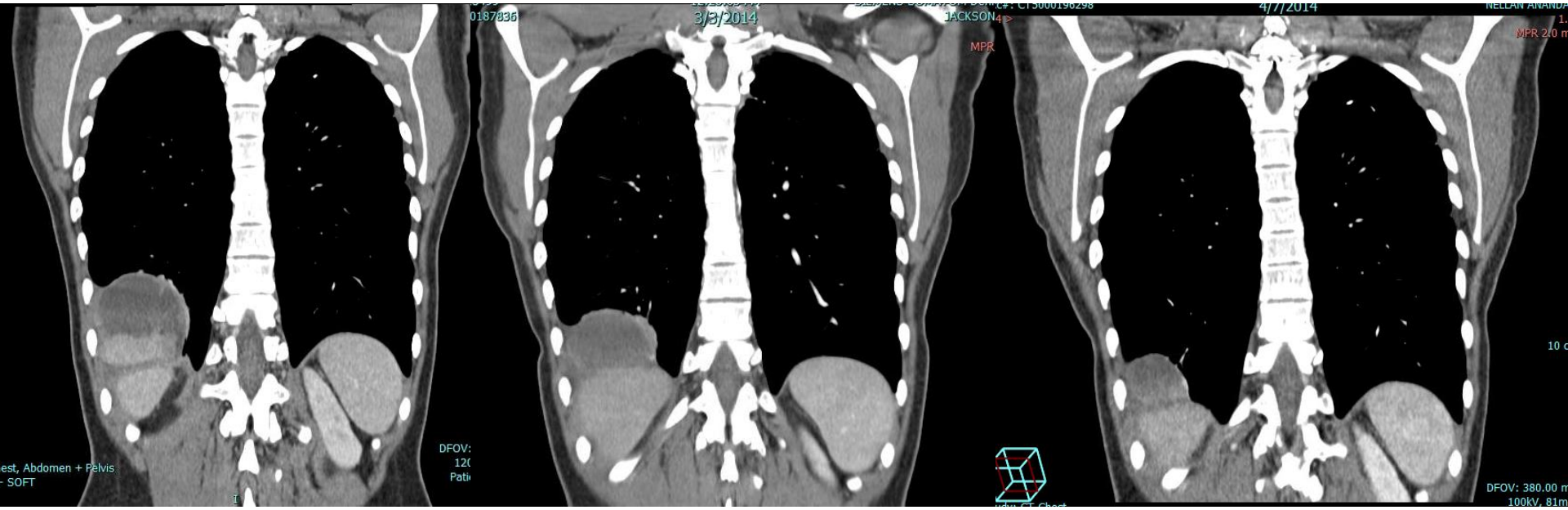


Baseline

1 month post treatment

2 months post treatment

Prolonged PR of Unresectable Metastasis

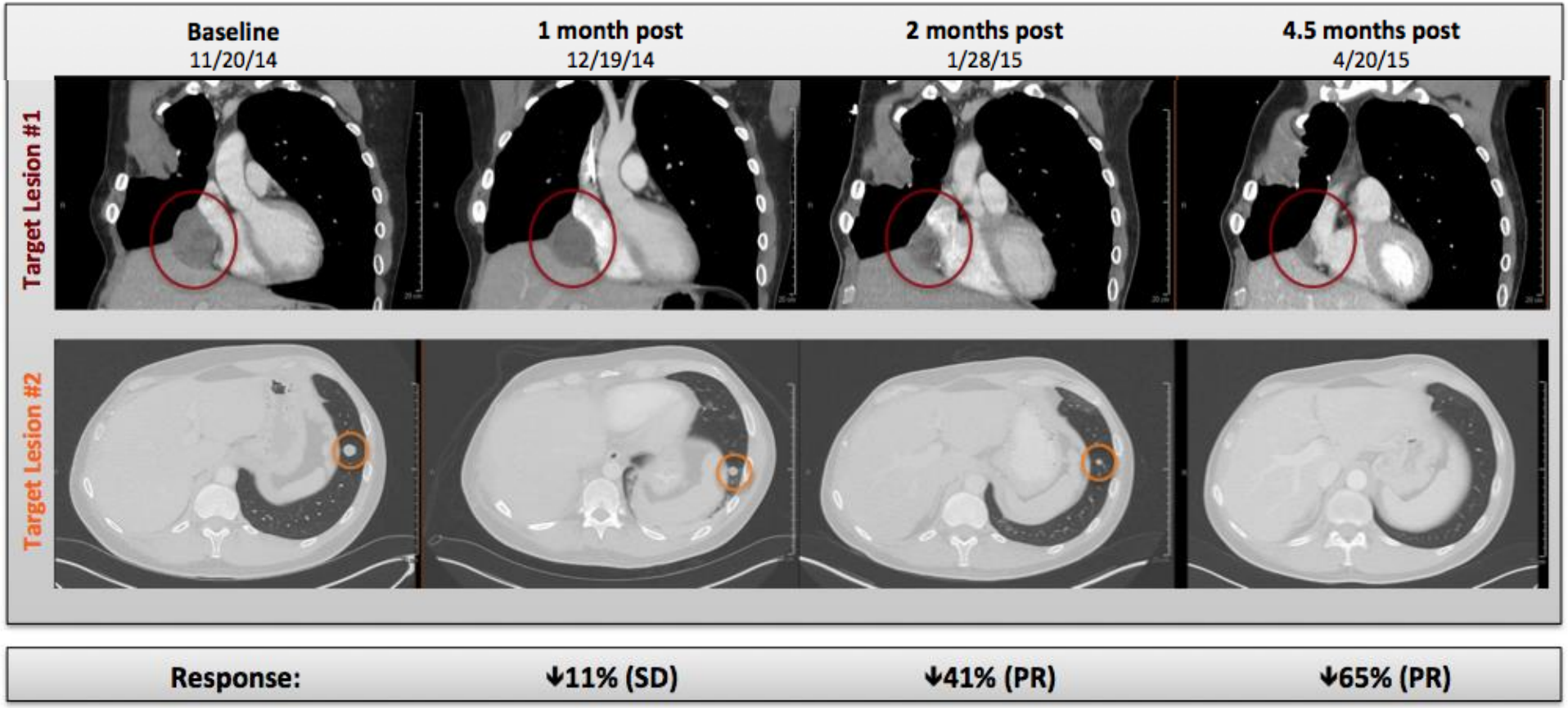


1/22/14 3/3/14 4/7/14

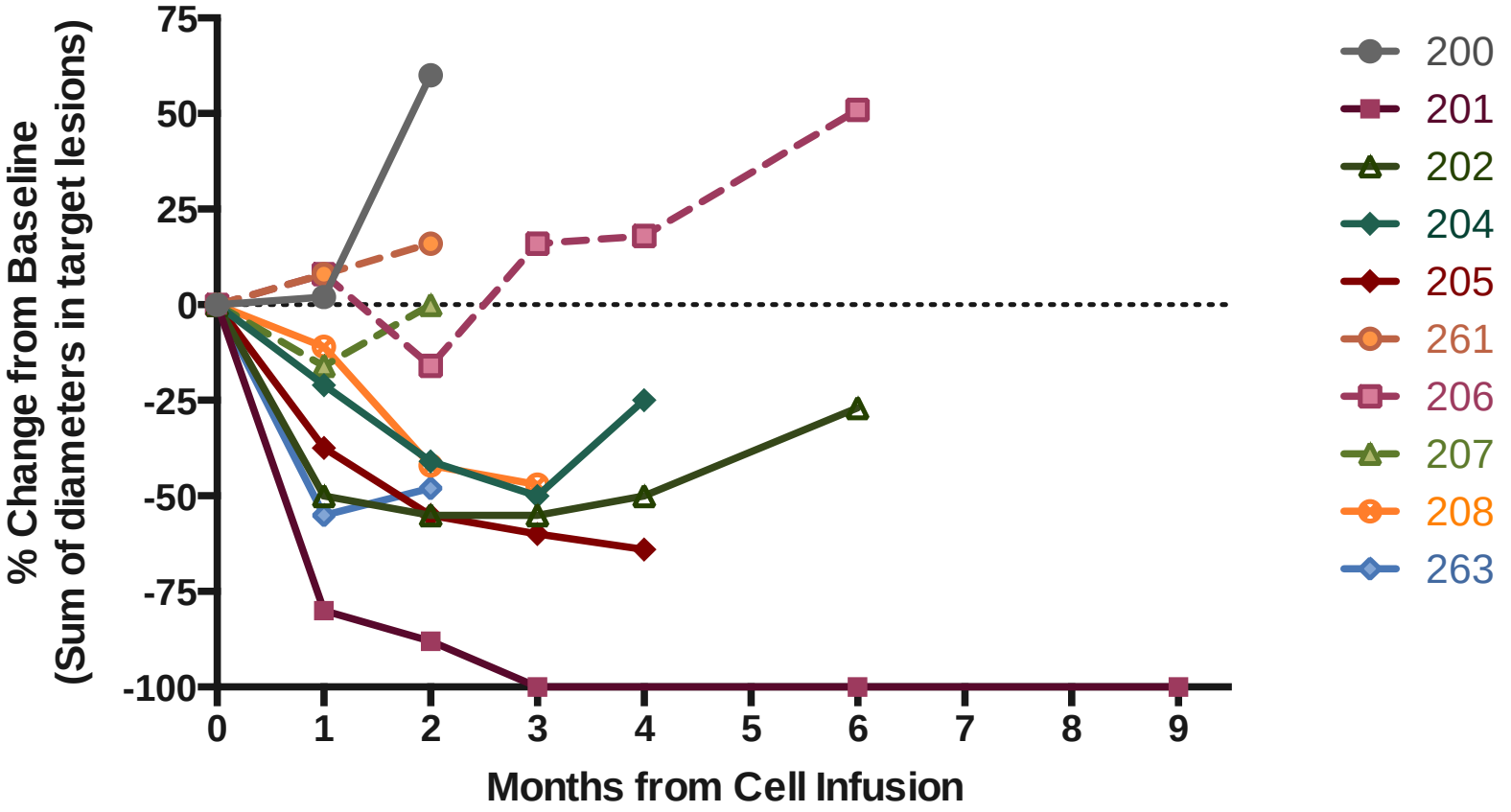
- Mass began to show regrowth ~6 months
- Surgically resected at 7 months
- Patient remains NED 21 months from initial therapy

Tumor Shrinkage of Unresectable Metastasis Over Several Months Following NY-ESO-1 TCR for Synovial Sarcoma

Multiply Recurrent, Unresectable Pulmonary Mass

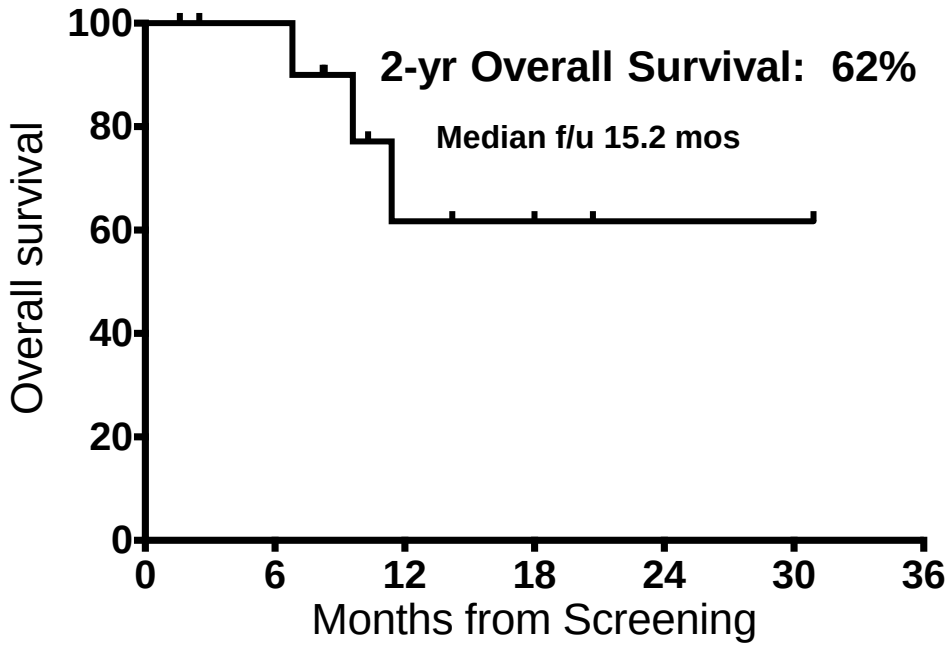


Clinical Trial of NY-ESO-1 Affinity Matured TCR in Patients with Synovial Sarcoma: 60% Response Rate (Merchant AACR, 2015)

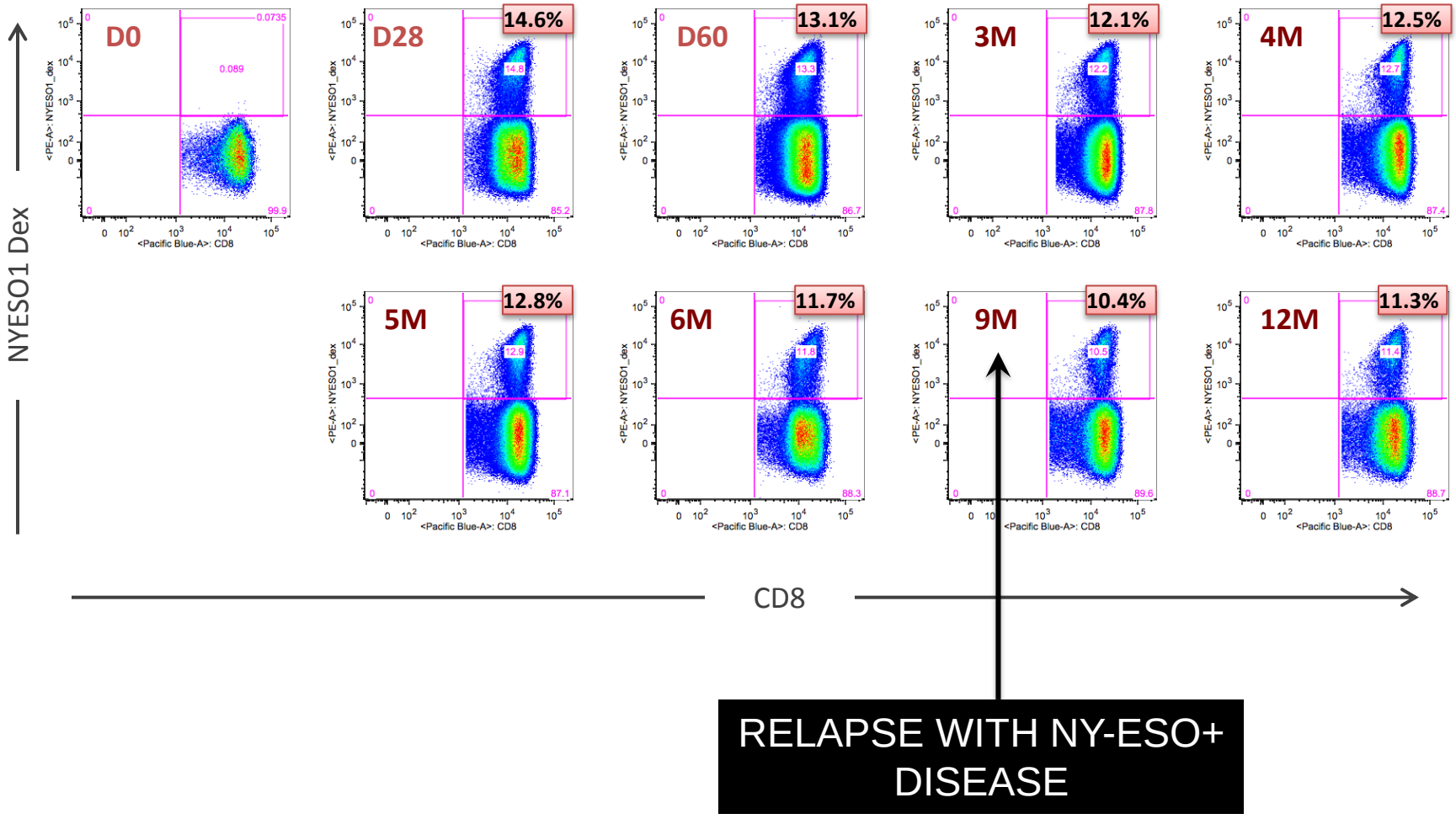


60% Objective Response Rate Favorable Overall Survival for Patients Treated on NY-ESO-1 Trial

ENROLLED ON STUDY
N=12

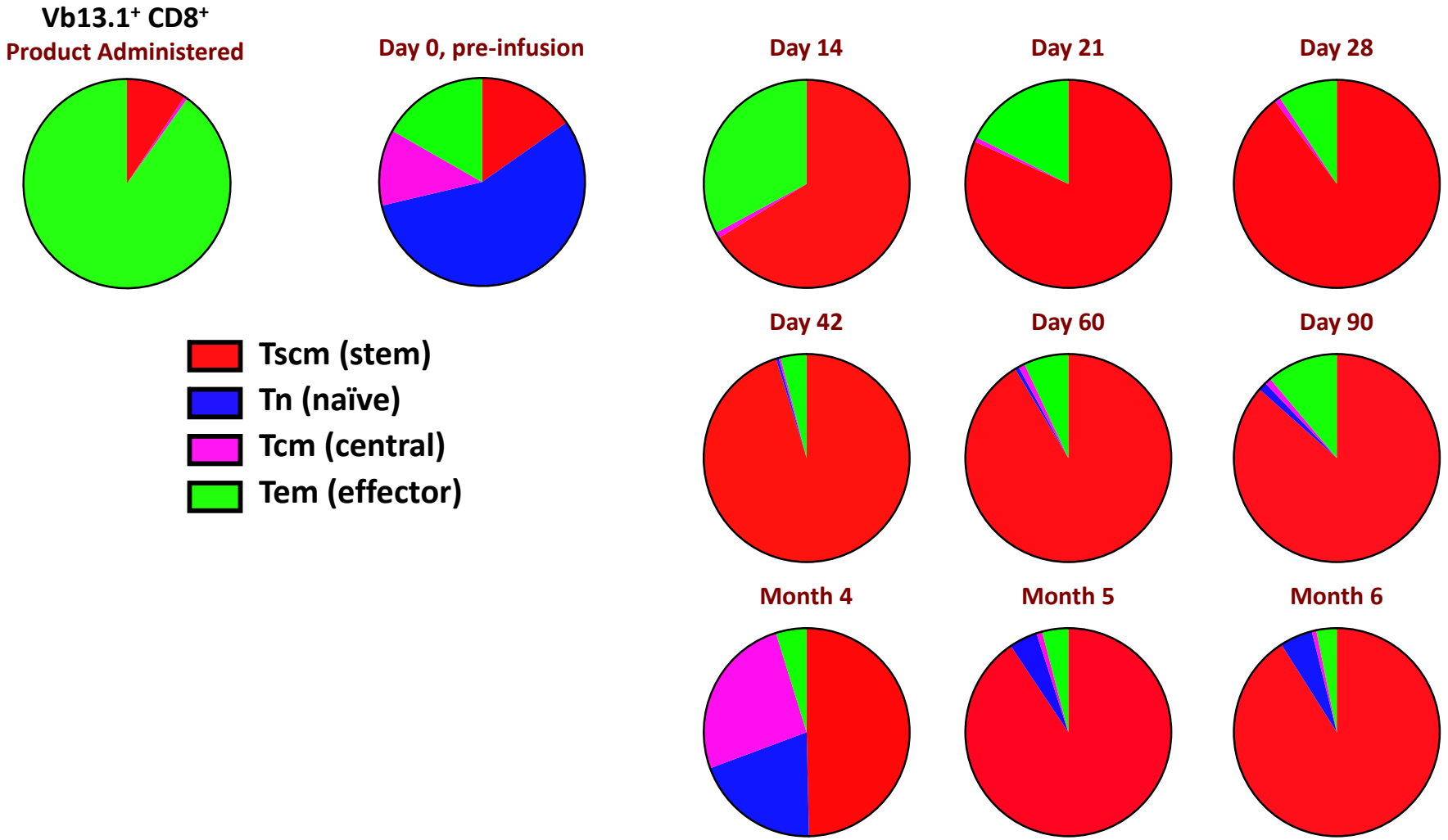


Remarkable Persistence of NY-ESO TCR+ T Cells in Patient Experiencing a Complete Response



Patient 201 NY-ESO

CD8+ T cells: Administered Product Is Predominantly Effector CD8 T cells but **Persisting cells are Predominantly Tscm CD8 T cells**



Patient 202

NY-ESO-1 TCR for Synovial Sarcoma: Proof-of-Principle of Efficacy of Cell Therapy for Solid Tumors

- 60% Response Rate in Patients with Chemorefractory Disease
  - Responses occurs over several months (distinct from leukemia)
  - Most responses are Partial Responses but persist for several months and translate into clinically meaningful benefit
  - Mechanism responsible for persistent or recurrent disease not yet defined
- Toxicity
  - No Grade IV Cytokine Release Syndrome observed
  - Generally well tolerated
- Provides basis for believing that commercial manufacturing of complex, engineered cell therapies is possible
- Associated with impressive T cell persistence despite lack of embedded costimulatory domains

Conclusions

- Responses in an “epigenetic” driven tumor (SWI/SNF) BAF driver mutation
  - Hope for other tumors without high mutational load
- Ongoing studies: treatment of patients with lower NY-ESO-1 expression
- Future plans require careful study of mechanisms of recurrence

Adaptimmune
TRANSFORMING T CELL THERAPY

U.S. Food and Drug Administration Grants Breakthrough Therapy Designation for Adaptimmune's Affinity Enhanced T-cell Therapy Targeting NY-ESO in Synovial Sarcoma

PHILADELPHIA, Pa. and OXFORD, UK, February 9, 2016 – Adaptimmune Therapeutics plc (Nasdaq: ADAP), a leader in the use of TCR engineered T-cell therapy to treat cancer, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for the company's affinity enhanced T-cell therapy targeting NY-ESO in synovial sarcoma for HLA-A*201, HLA-A*205 or HLA-A*206 allele-positive patients with inoperable or metastatic synovial sarcoma who have received prior chemotherapy and whose tumor expresses the NY-ESO-1 tumor antigen.

"We are committed to investigating the potential of our NY-ESO-1-T cell therapy across a variety of cancers. We are pleased that the FDA has granted Breakthrough Therapy designation for our T-cell therapy in synovial sarcoma, recognizing both the unmet need for patients suffering from this disease as well as the promise of these early data," said Dr. Rafael Amado, Adaptimmune's Chief Medical Officer. "We look forward to working closely with the FDA to expedite the clinical development of this therapeutic candidate."

Acknowledgements

- Crystal Mackall/Carl June
- Melinda Merchant
- Adaptimmune
- Patients