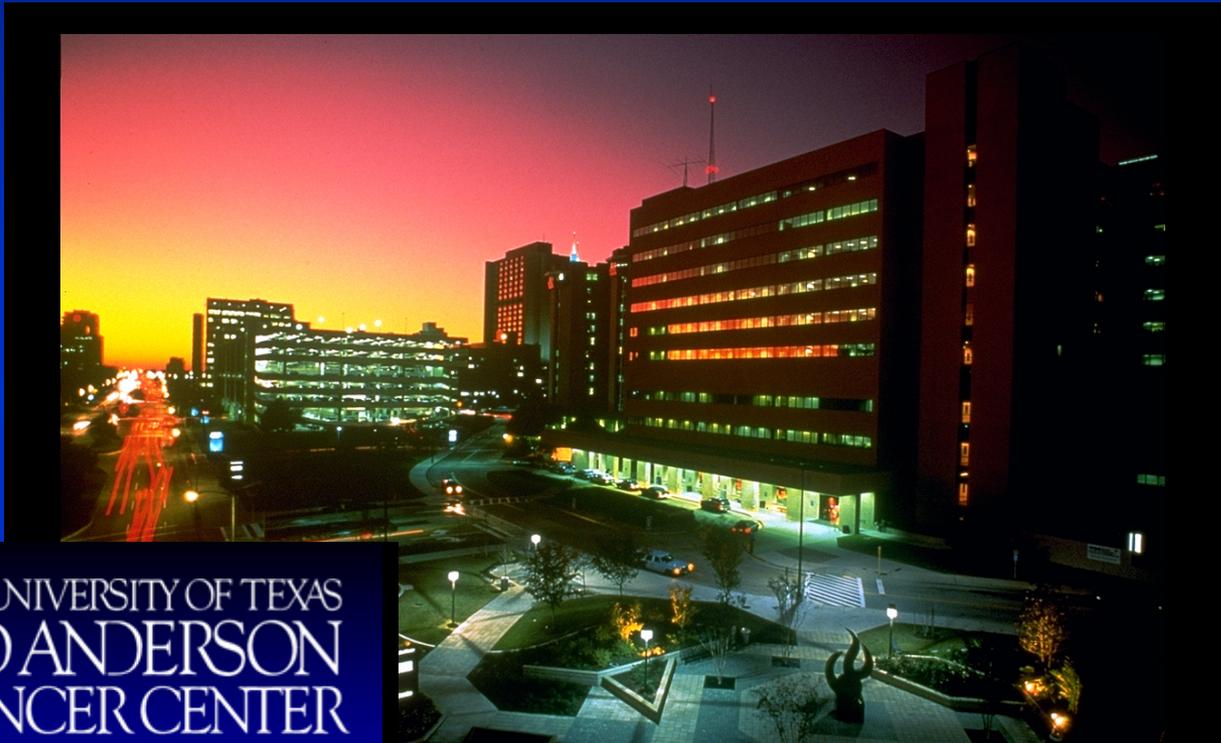


Therapy of Melanoma with CXCR2 Transduced T-cells

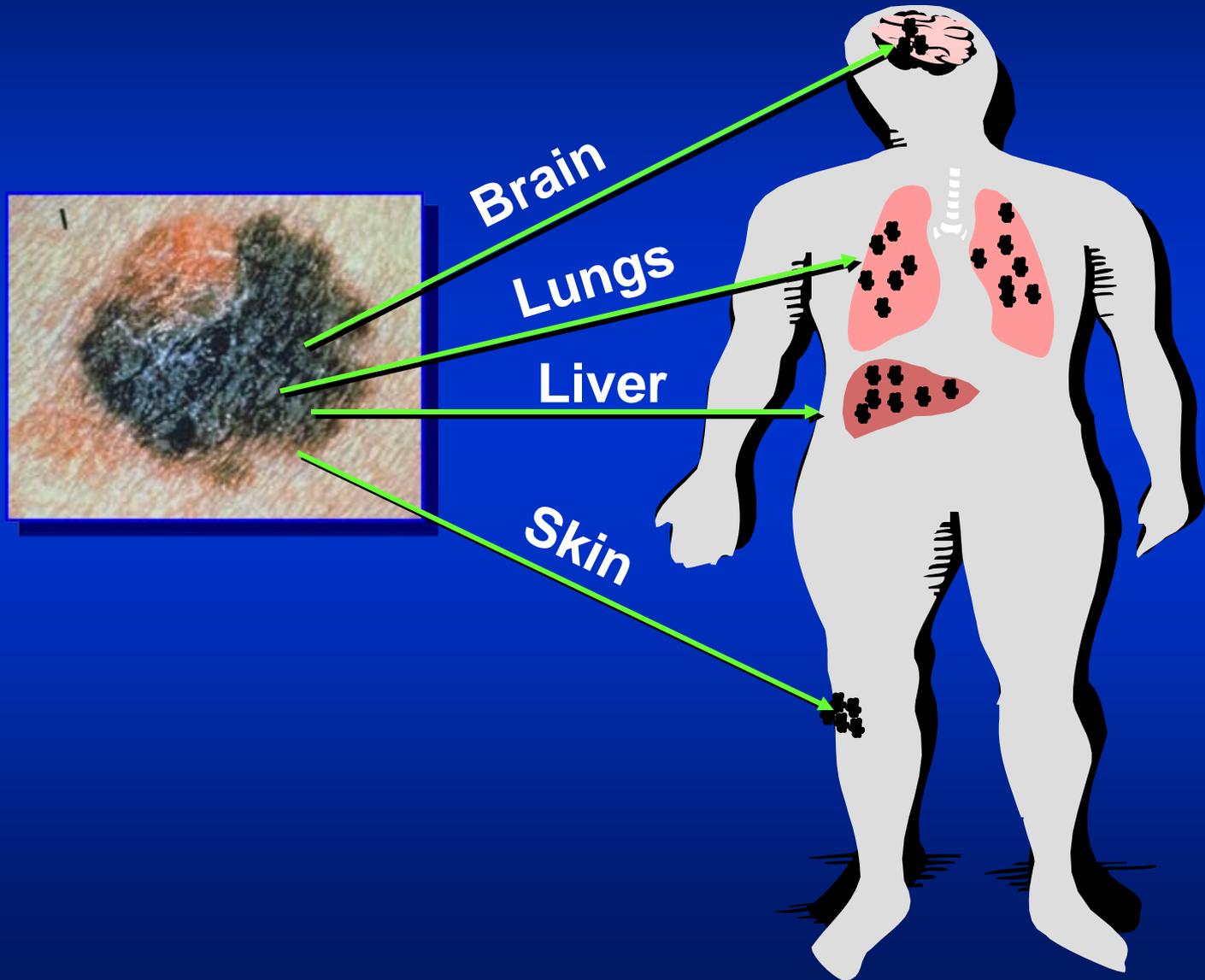


THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

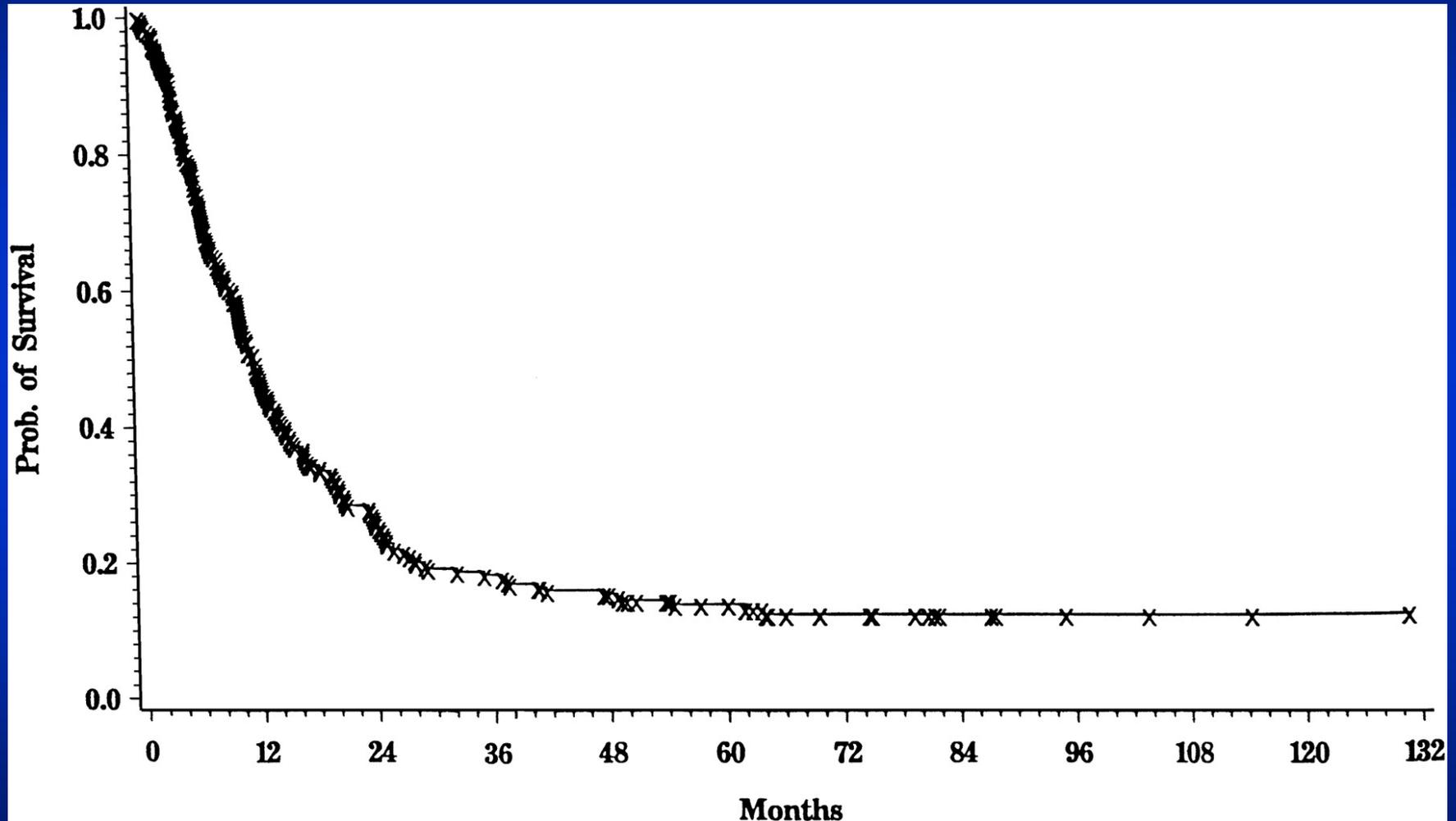
Patrick Hwu, M.D.

**Professor & Chairman, Melanoma Medical Oncology
Associate Director, Center for Cancer Immunology Research (CCIR)**

Melanoma Can Spread Throughout the Body

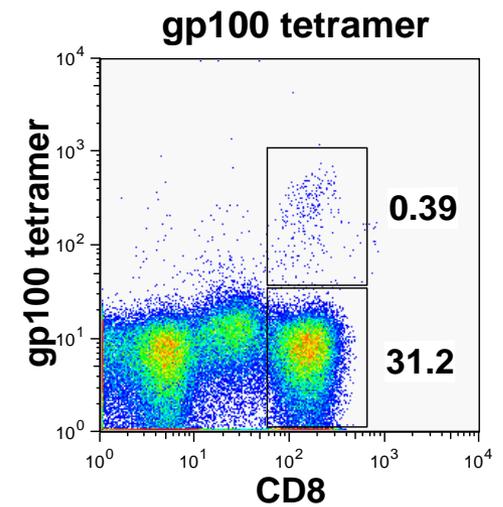
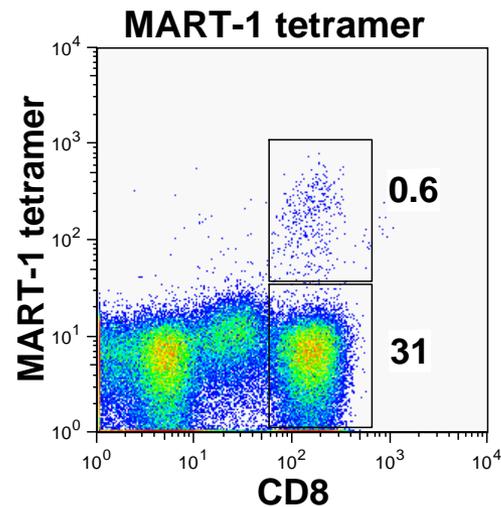
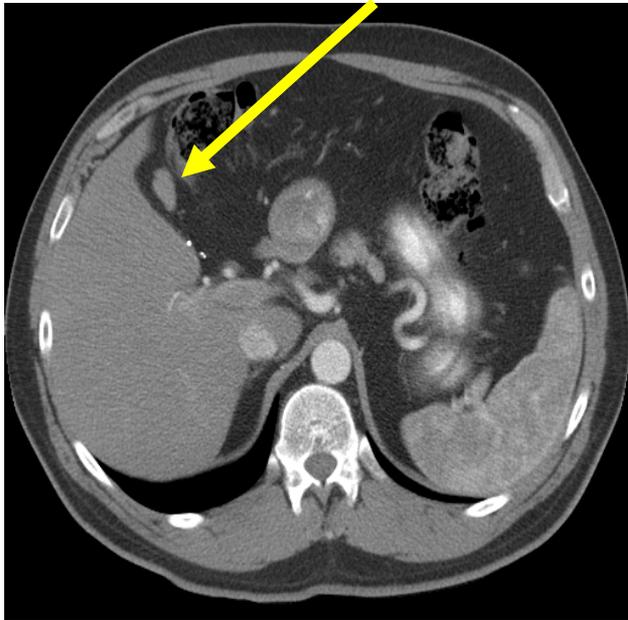


Survival of Patients Receiving High Dose IL-2



(Atkins et al, J of Clin Oncol 17(7):2105 – 2116, Jul 1999)

Tumor-reactive T-cells are Present in Some Melanomas: Are These the Patients that Respond to Immunotherapies?



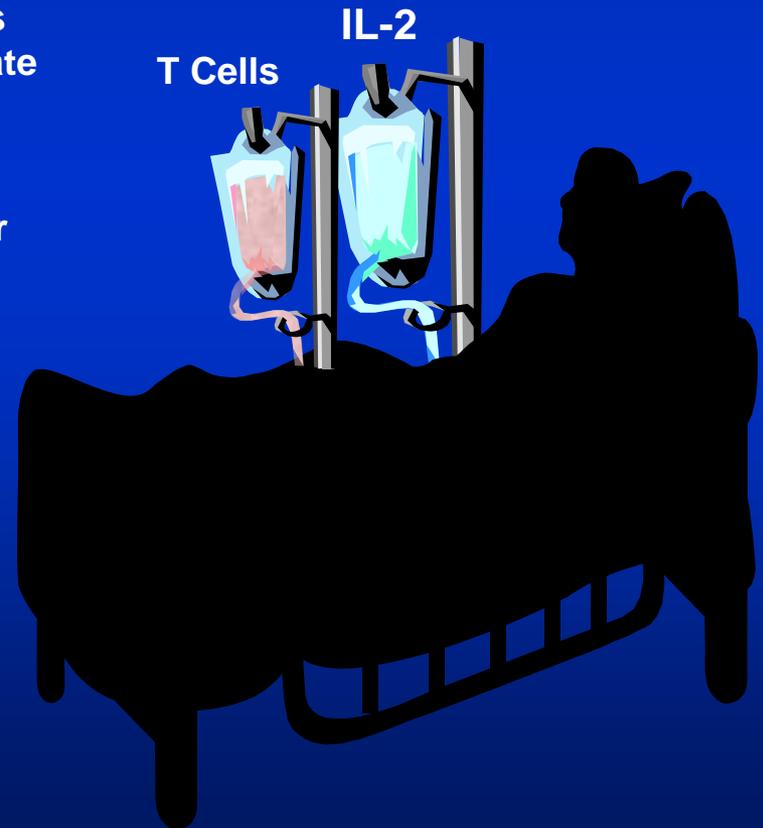
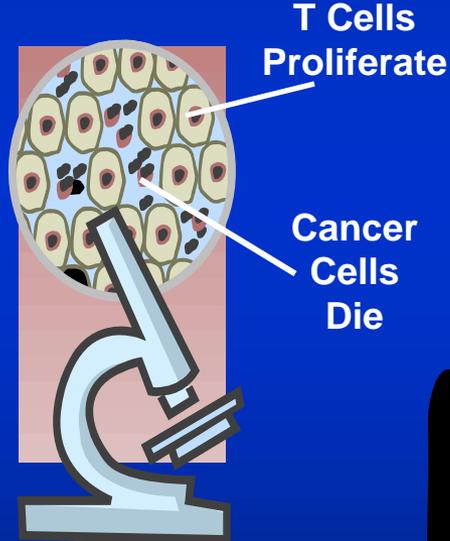
M. Ross; L. Radvanyi

Adoptive Cell Therapy (ACT) with Antigen Specific T-cells

Surgical
Removal of
Cancer Nodule



Single Cell
Suspension
Incubated with IL-2

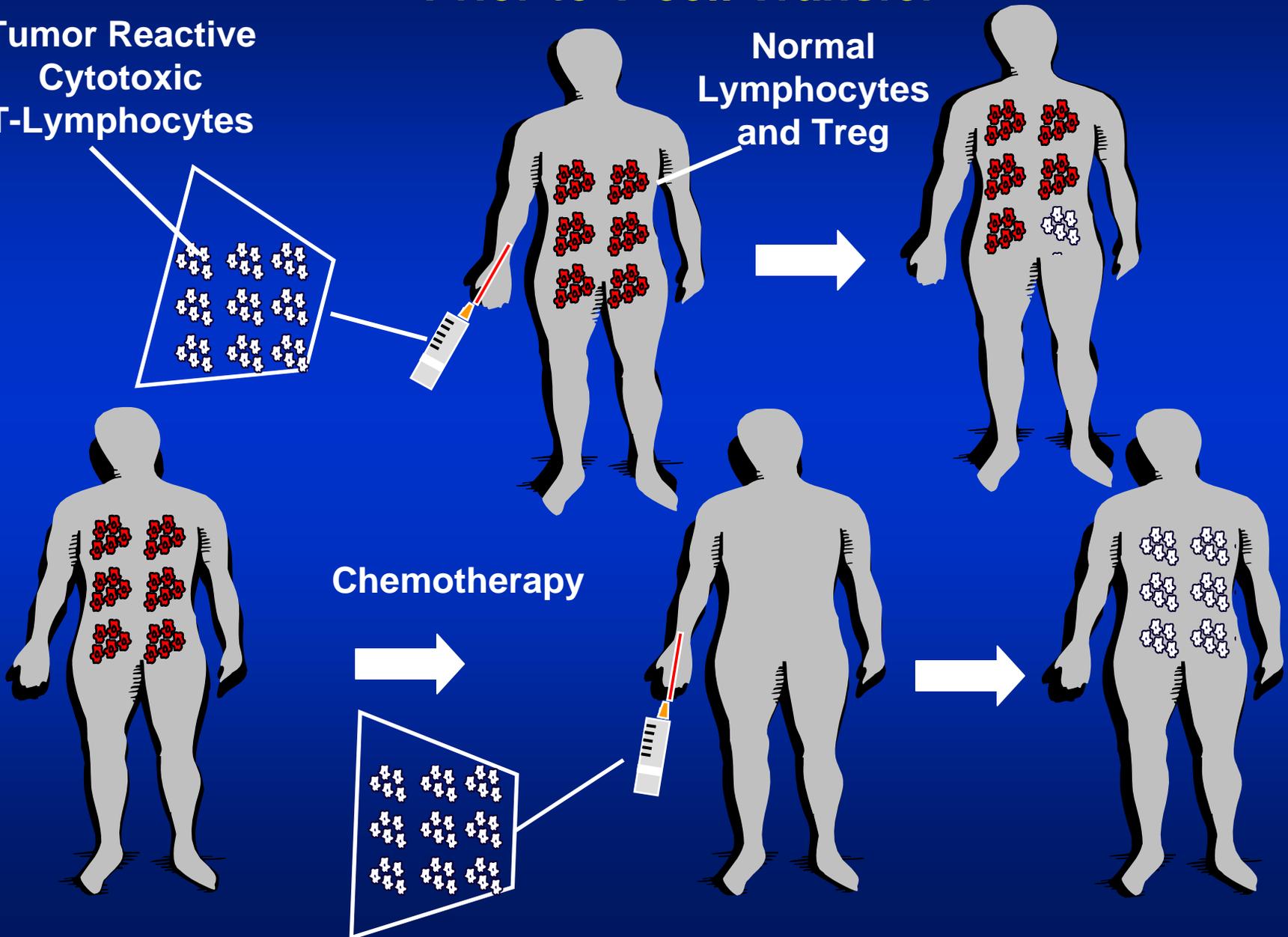


Elimination of Regulatory Cells with Chemotherapy Prior to T-cell Transfer

Tumor Reactive
Cytotoxic
T-Lymphocytes

Normal
Lymphocytes
and Treg

Chemotherapy



Clinical Response following Lymphodepletion Plus T-lymphocyte Infusion

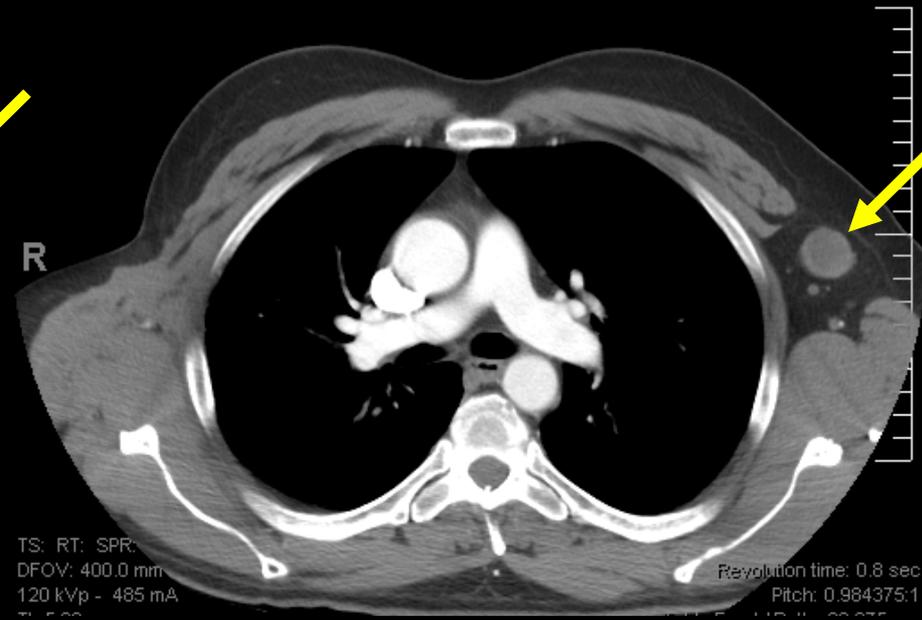
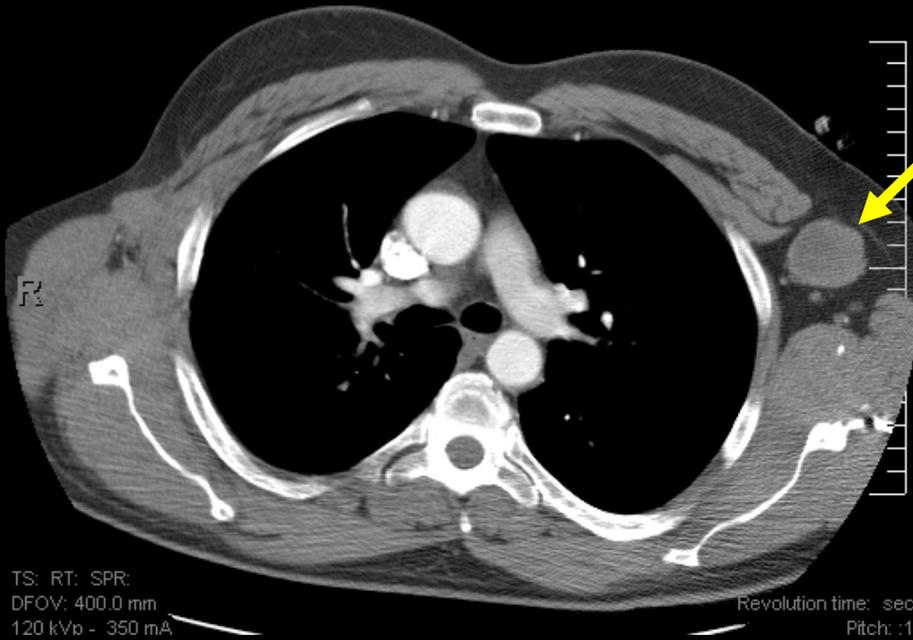
# Patients Enrolled	CR	PR	Total
35	4	14	18 (51%)

Science. 298:5594 (2002); and Dudley et al, *J Clin Oncol* 23(10):2346-57 (2005)

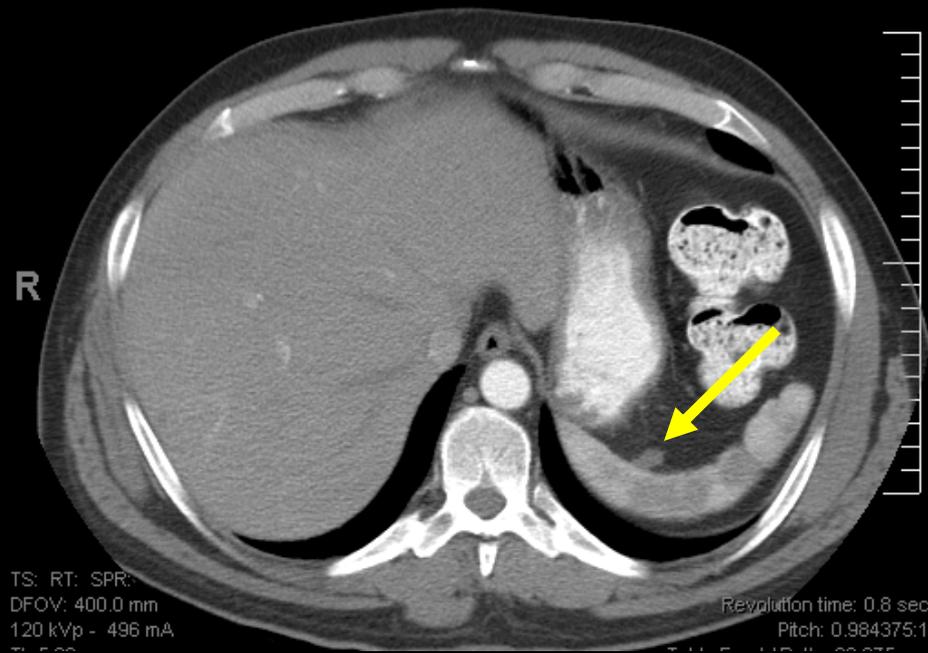
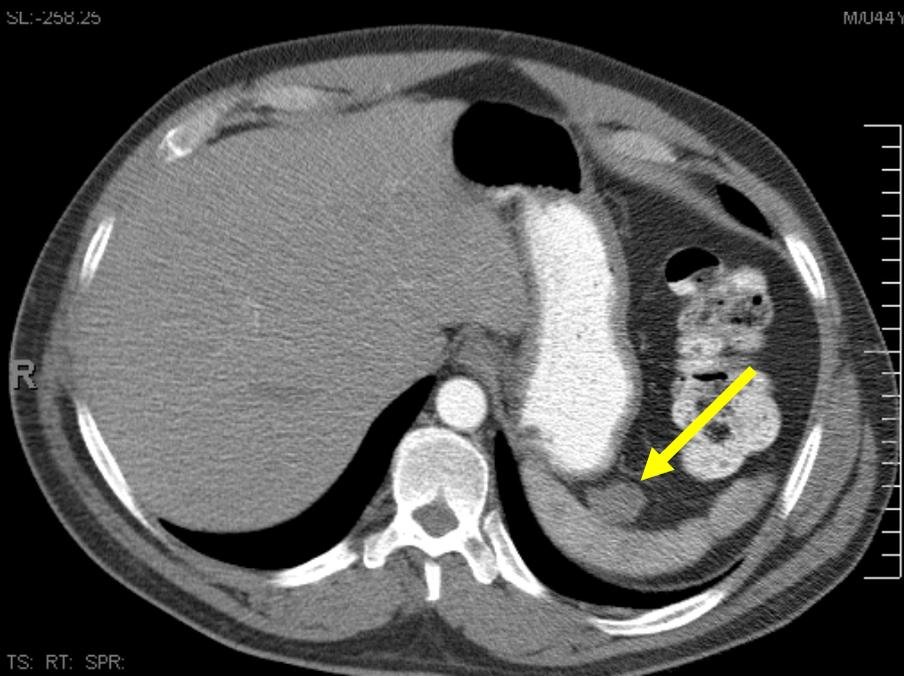
Initial Goals of MDACC TIL Trial

- **Determine if clinical results could be reproduced outside of the NIH intramural program**
- **Understand the characteristics between responders and non-responders**

Clinical Response to TIL



Clinical Response to TIL



Development of Vitiligo – Patient #2



Patient #3 TIL Response



Pre-treatment



Post-treatment

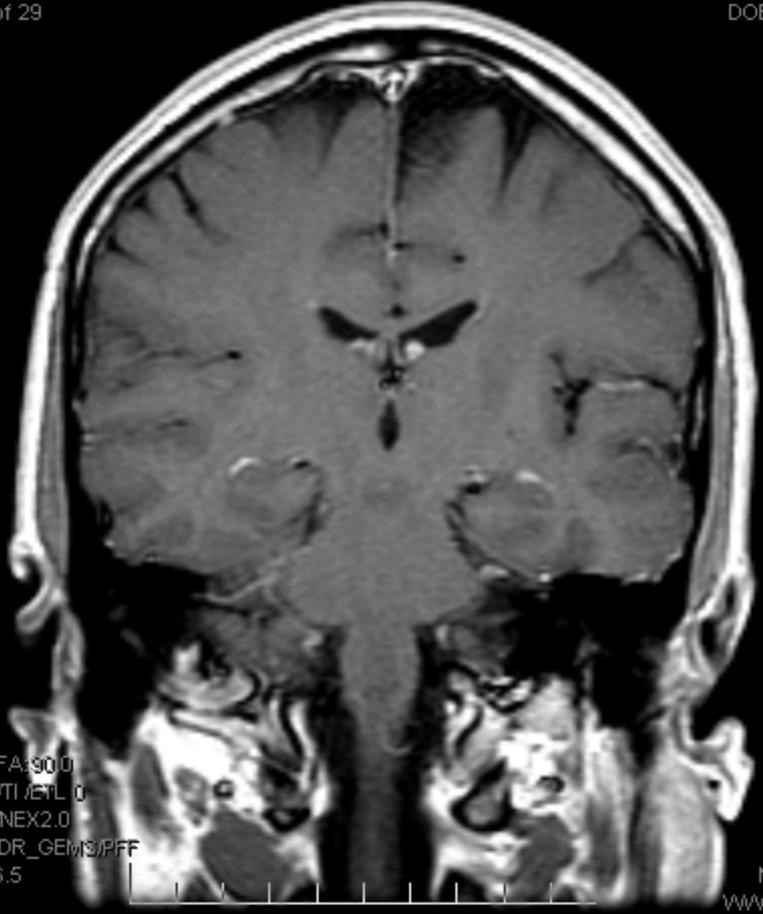
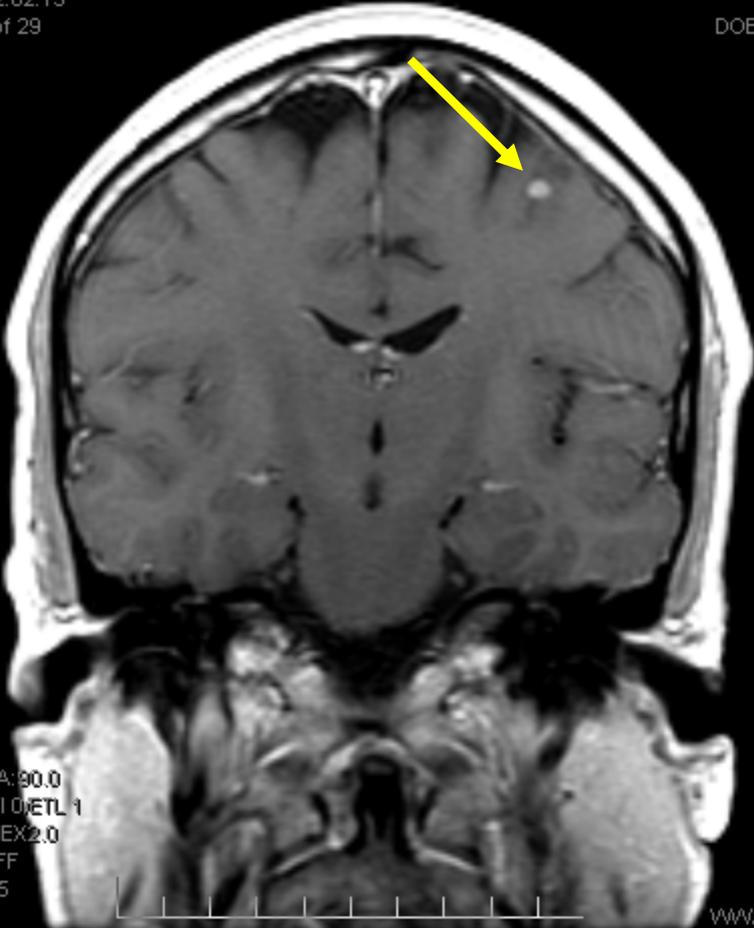
Response of Brain Metastasis to TIL Therapy

38 22:02:13
:15 of 29
38

MR:
DOB: 1C

3 14:47:02
6 of 29
385

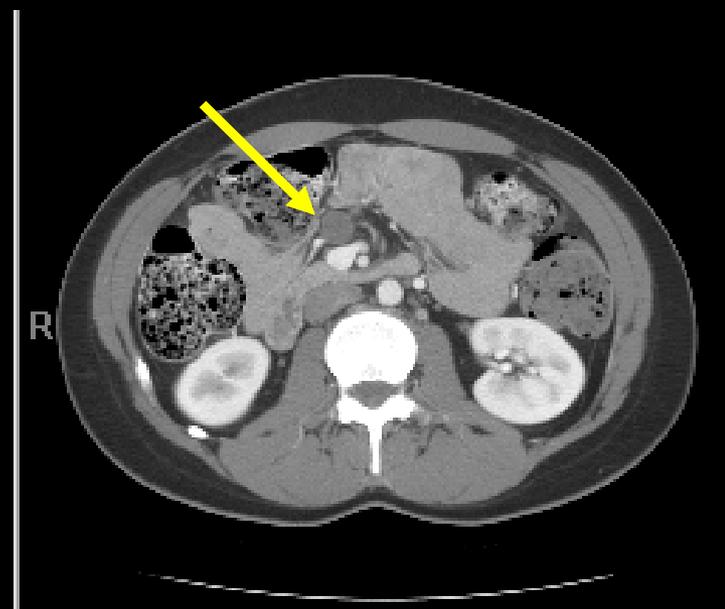
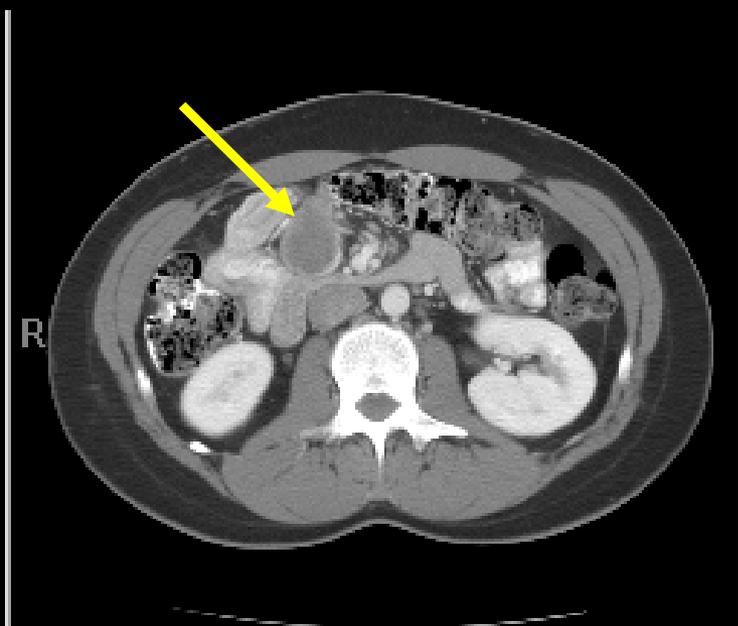
M
DOB: 1



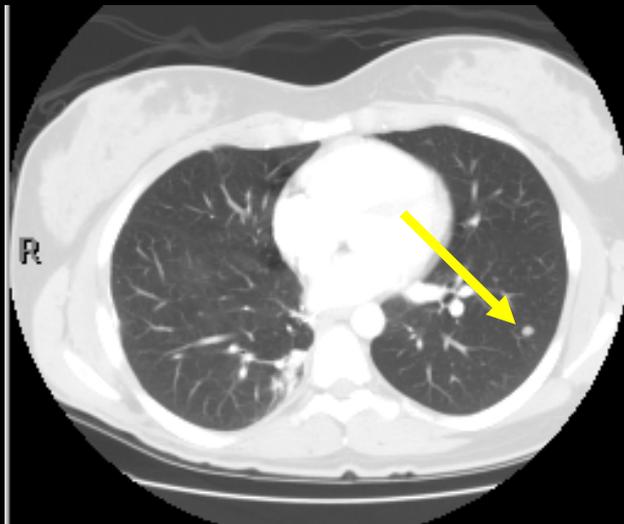
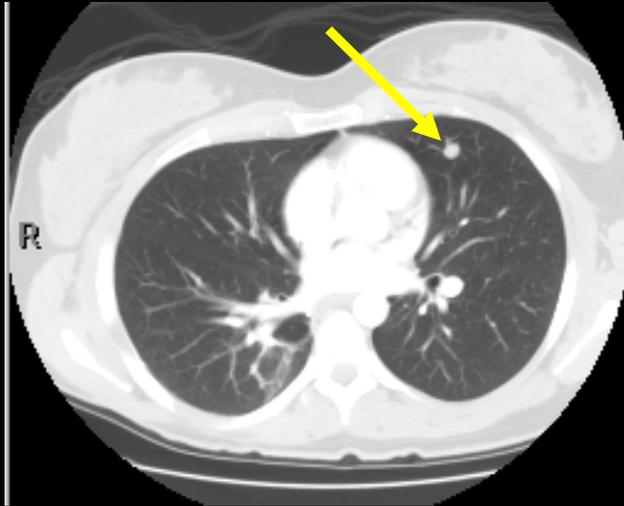
Patient #10 TIL Response



Patient #10 TIL Response



Patient #10 TIL Response

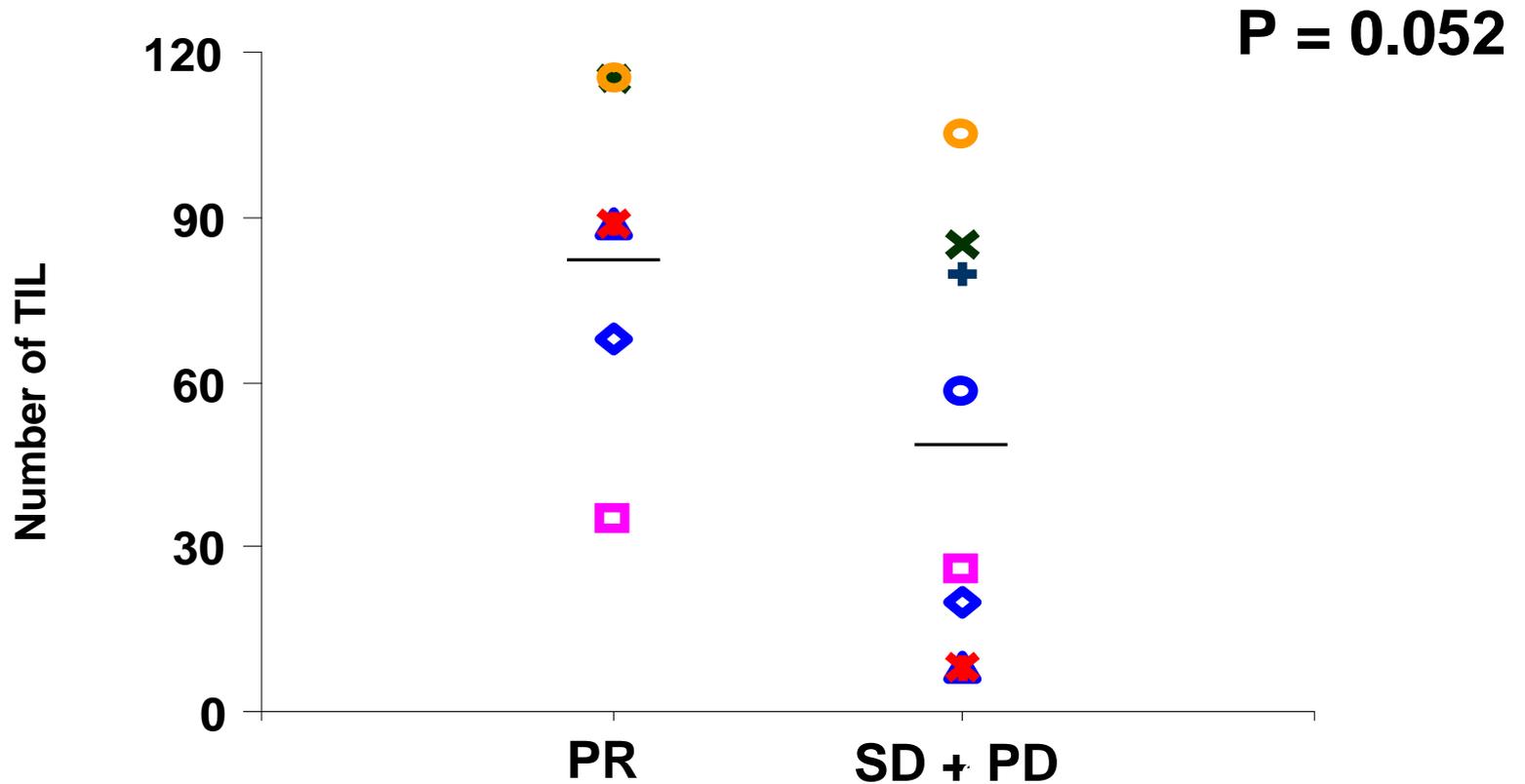


**M. D. Anderson Cancer Center
Clinical Response Rate
Lymphodepletion Plus TIL
(as of December 2009)**

Clinical Response Rate (RECIST criteria):

# of evaluable patients	PR*	CR*	Total
21	8 (38%)	1 (5%)	9 (43%)

Number of TIL Infused in Responders vs Non-responders (43% response)



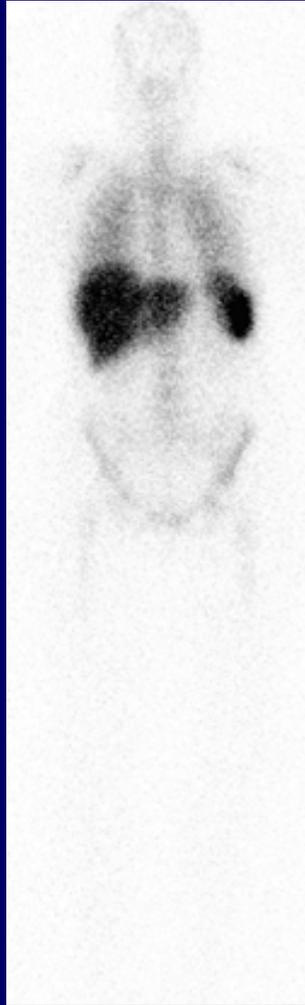
T-cell Therapy: Goals

- **Follow response duration (7 of 9 responders are still responding; longest duration 13 months as of 1/10)**
- **Improve clinical outcome**

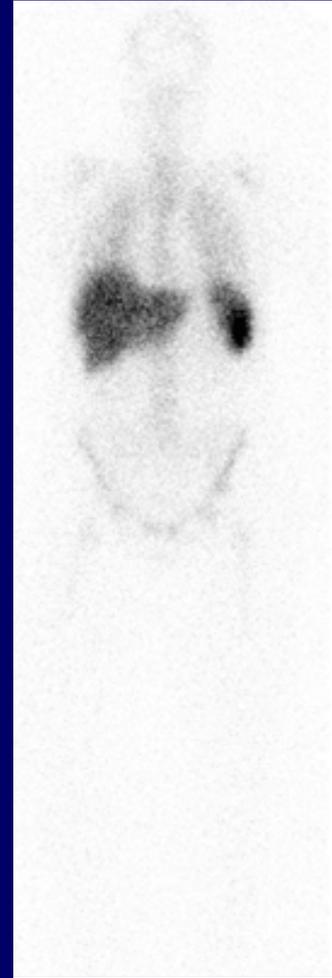
T-cell Trafficking to Tumor is Inefficient



04

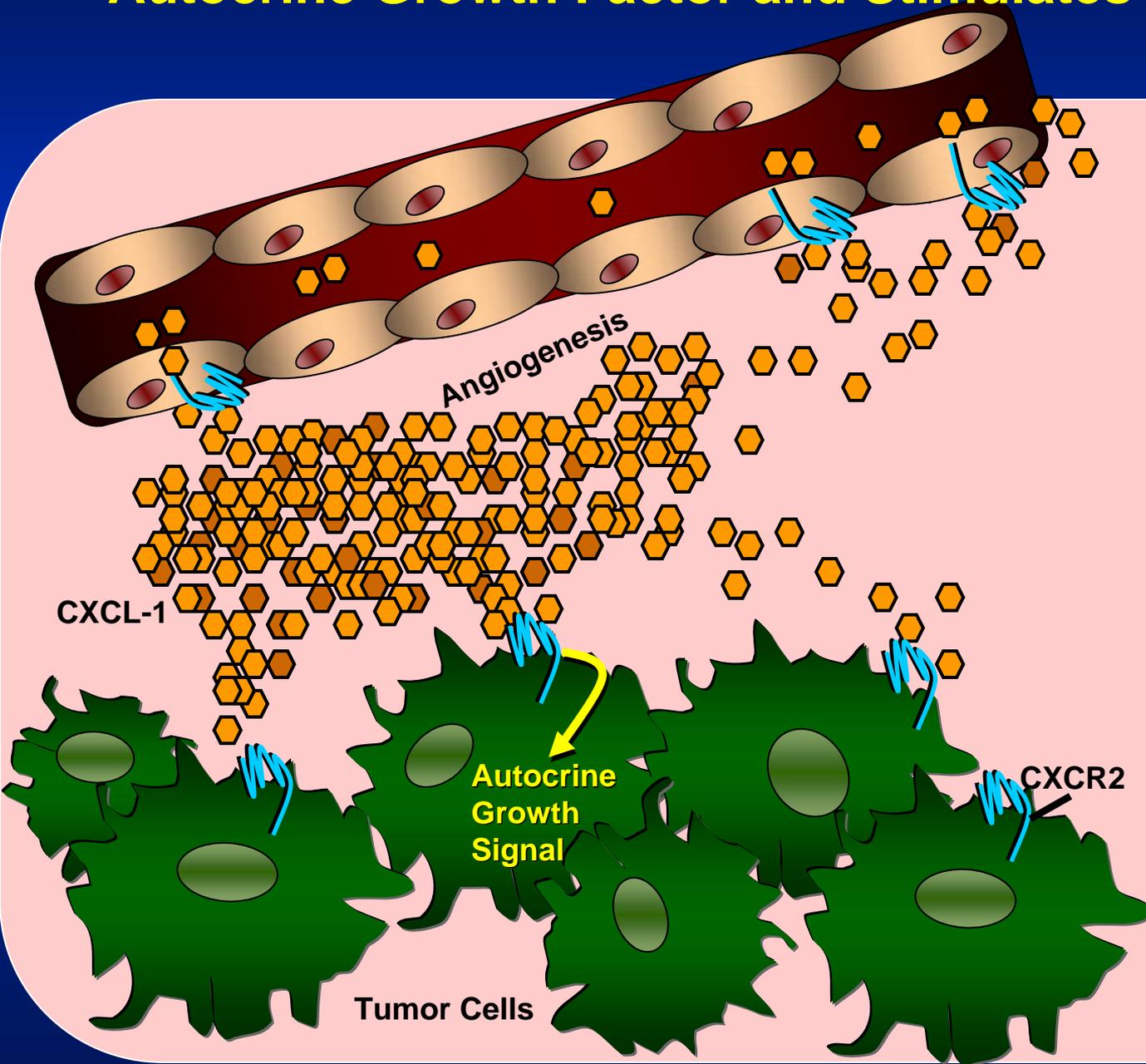


24

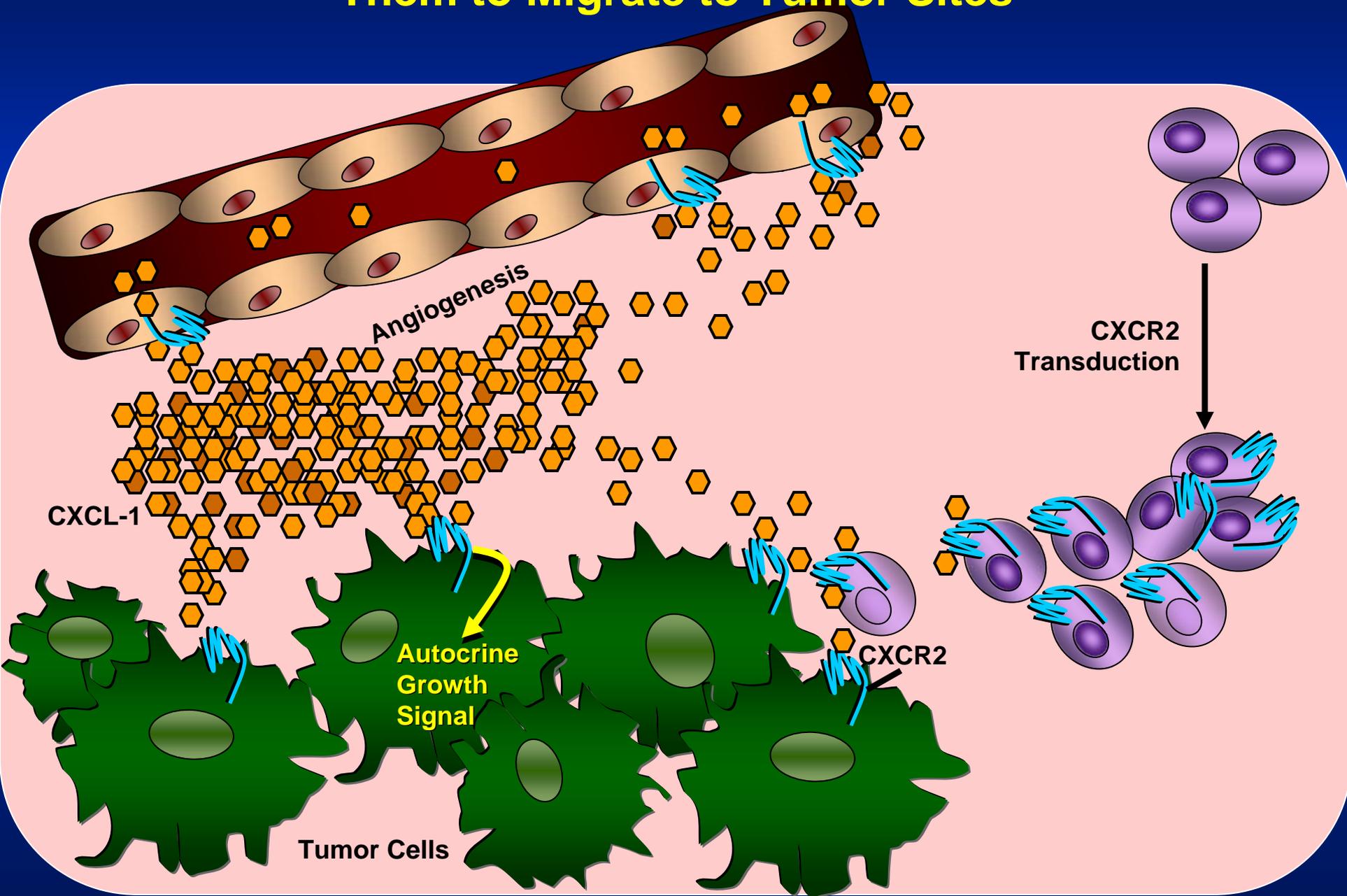


48

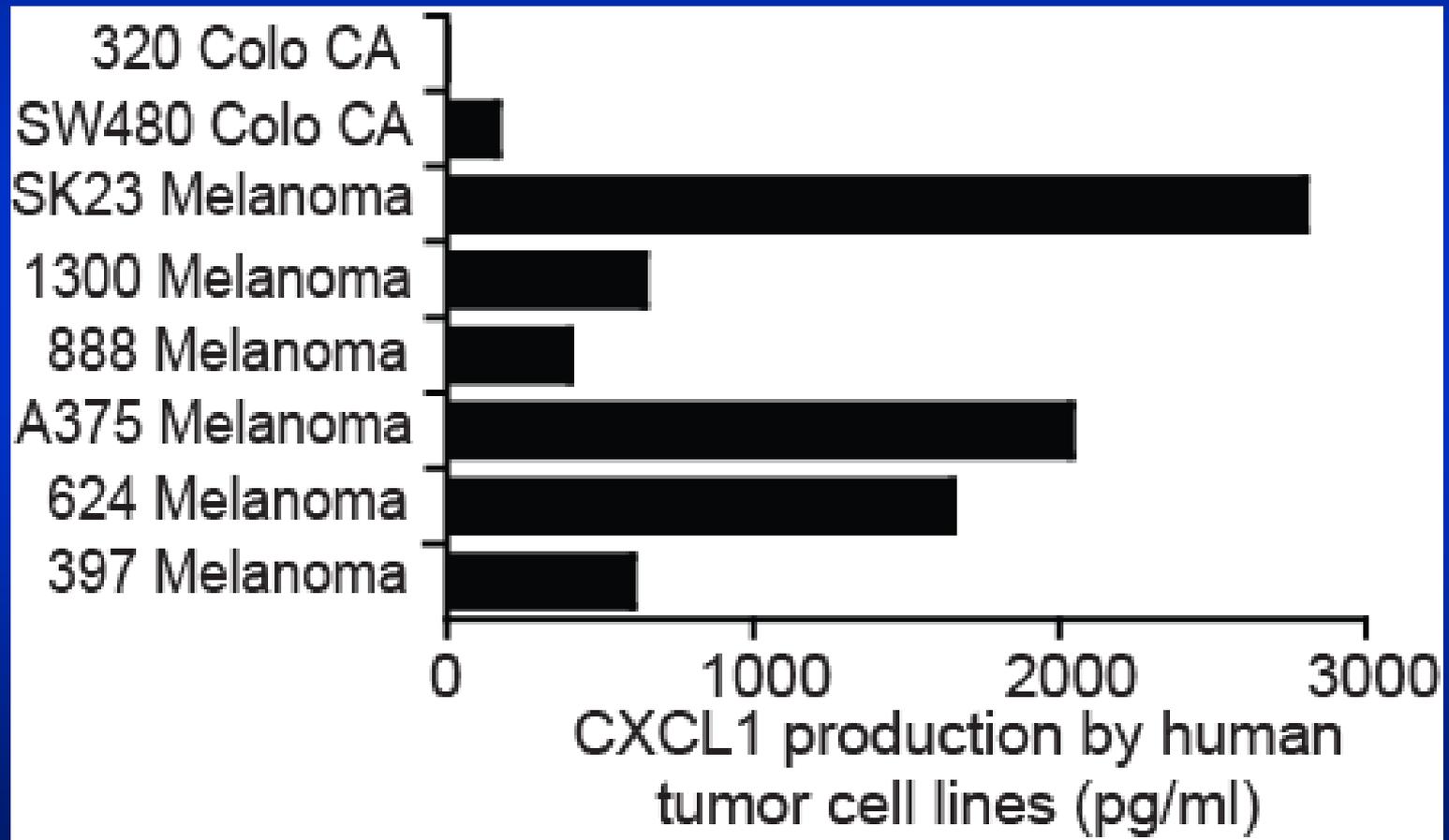
Melanoma Cells Produce CXCL1 which Serves as an Autocrine Growth Factor and Stimulates Angiogenesis



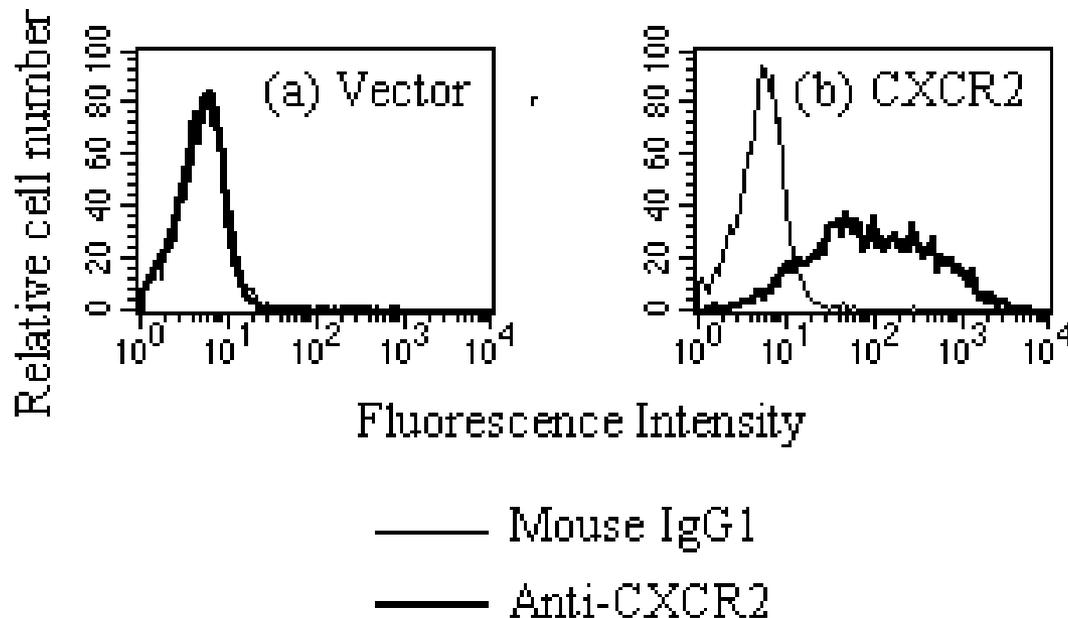
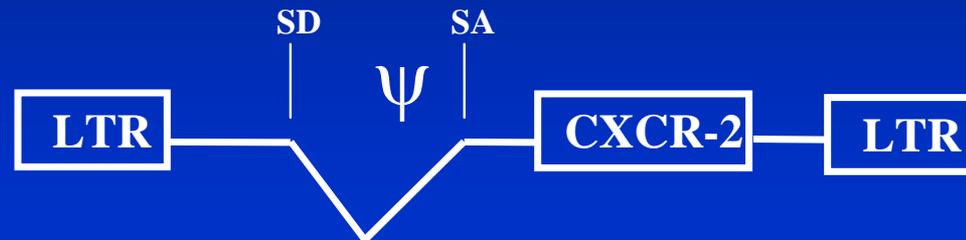
Transduction of T-cells with CXCR2 May Allow Them to Migrate to Tumor Sites



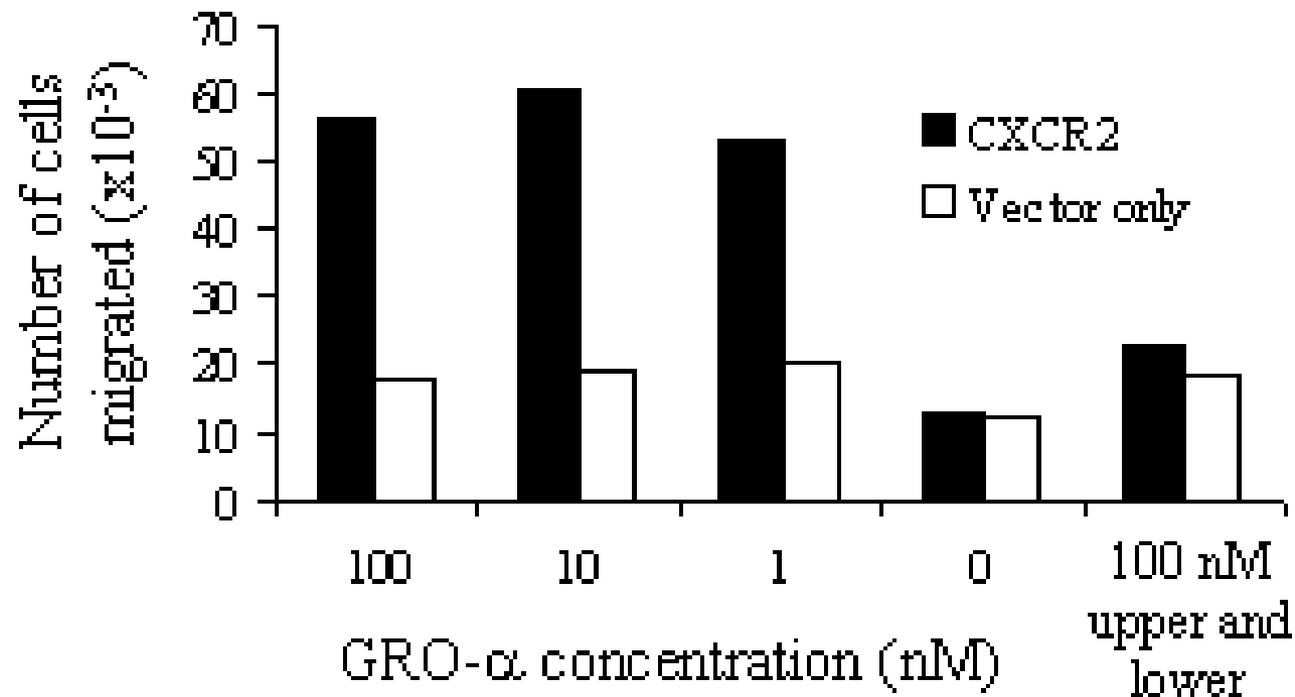
CXCL1 is Produced by Melanoma Cells



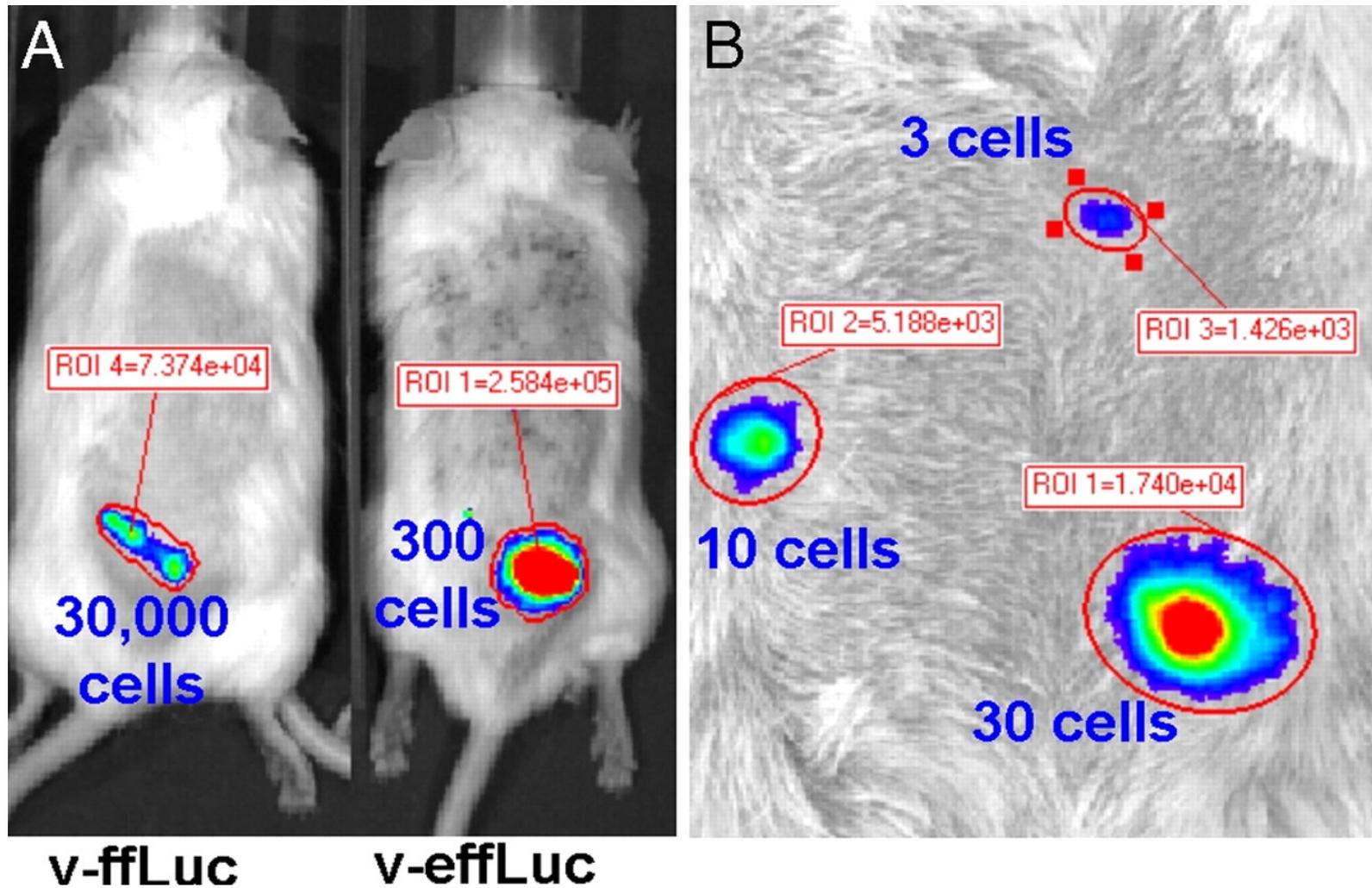
Can CXCR2 Transduction of T-cells Confer Responsiveness to CXCL1?



Chemotaxis of CXCR2 Transduced T-cells to CXCL1 (Gro- α)

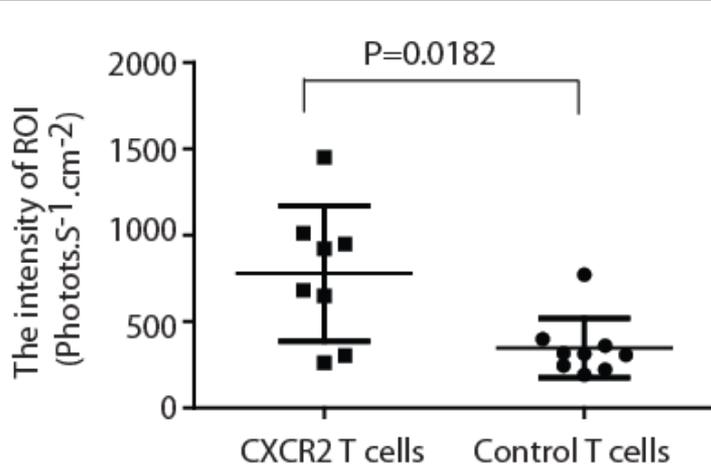
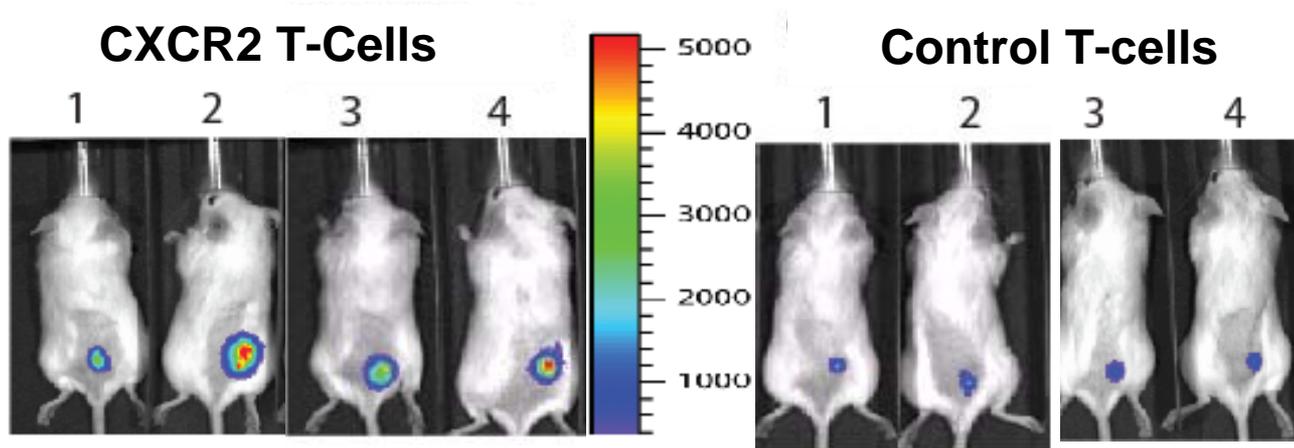


Optimized Luciferase Allows *in vivo* Detection of a Small Number of T-cells

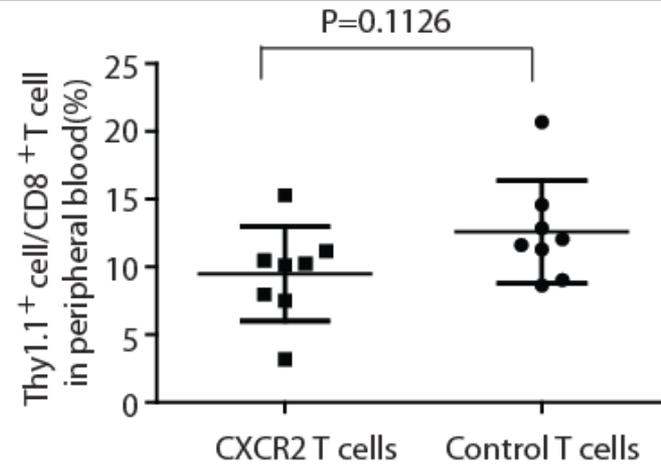


Rabinovich...Hwu. PNAS 2008;105:14342-14346

CXCR2-expressing T-cells Display Enhanced Accumulation in Tumor Site

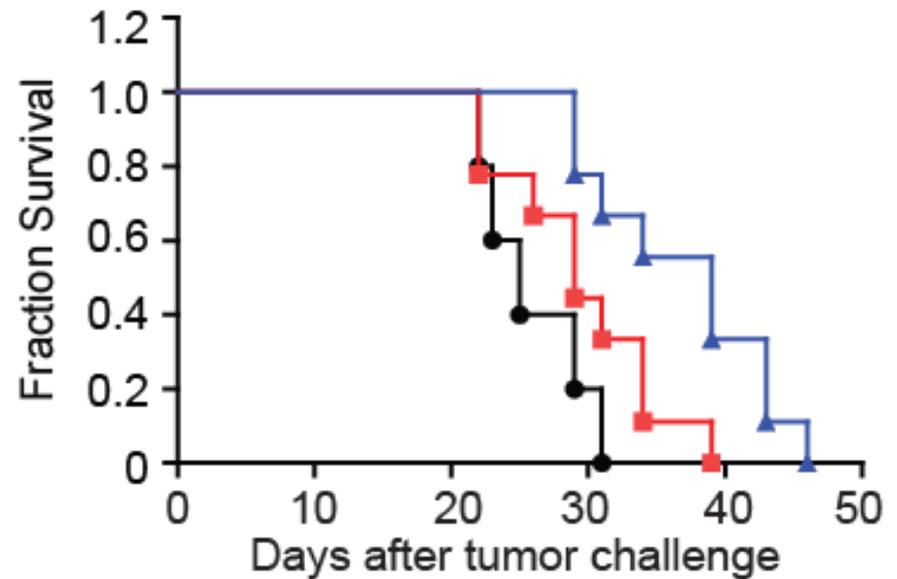
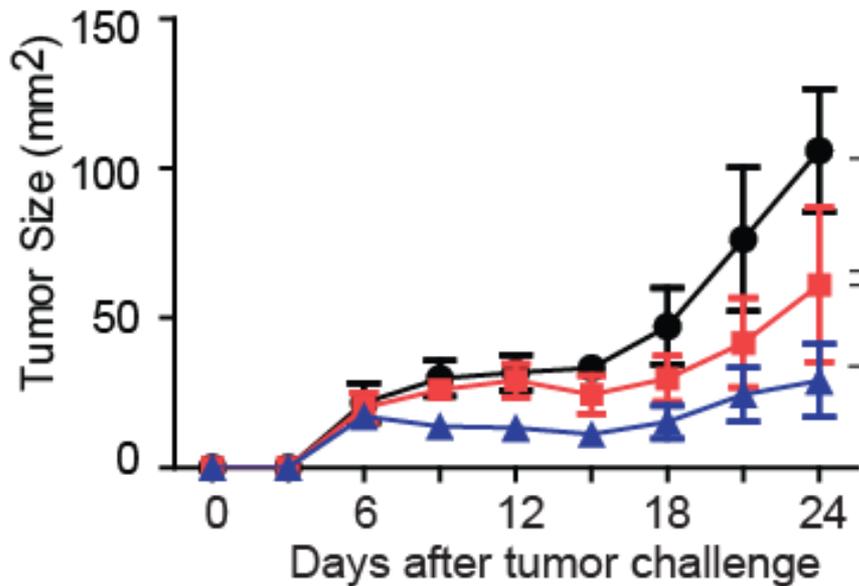


Tumor site



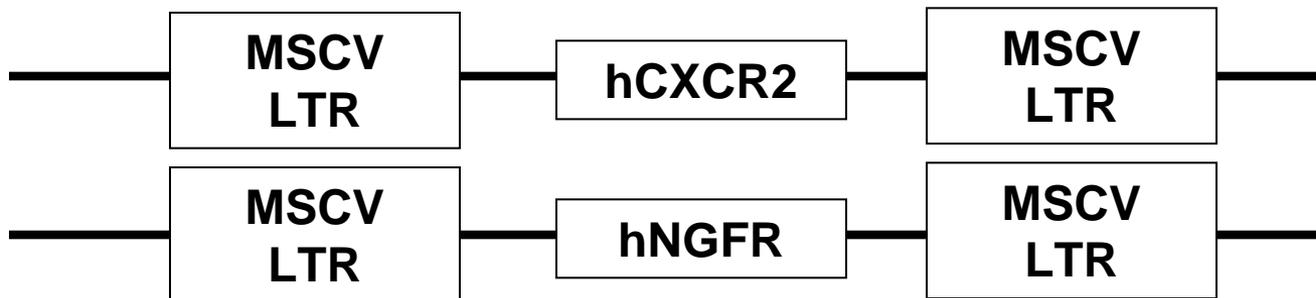
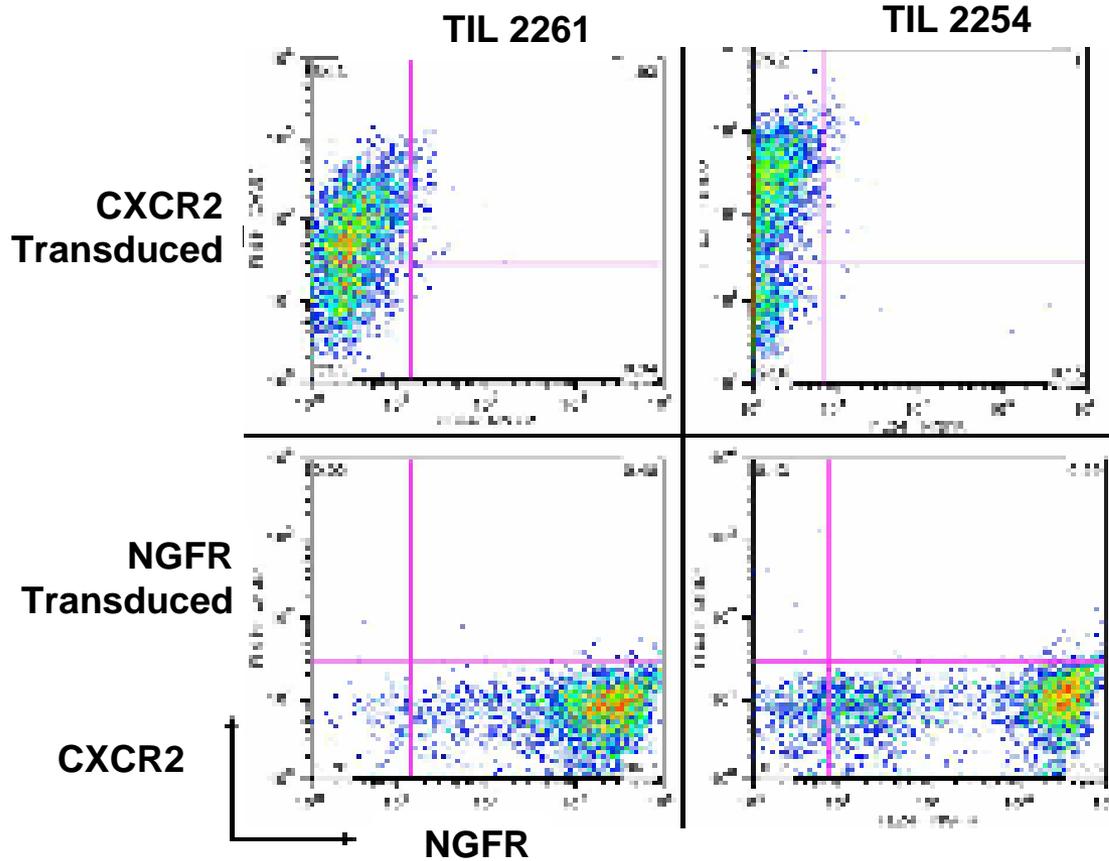
Peripheral blood

The Expression of CXCR2 in Pmel T-cells Delays Tumor Growth and Improves the Survival of Tumor-bearing Mice

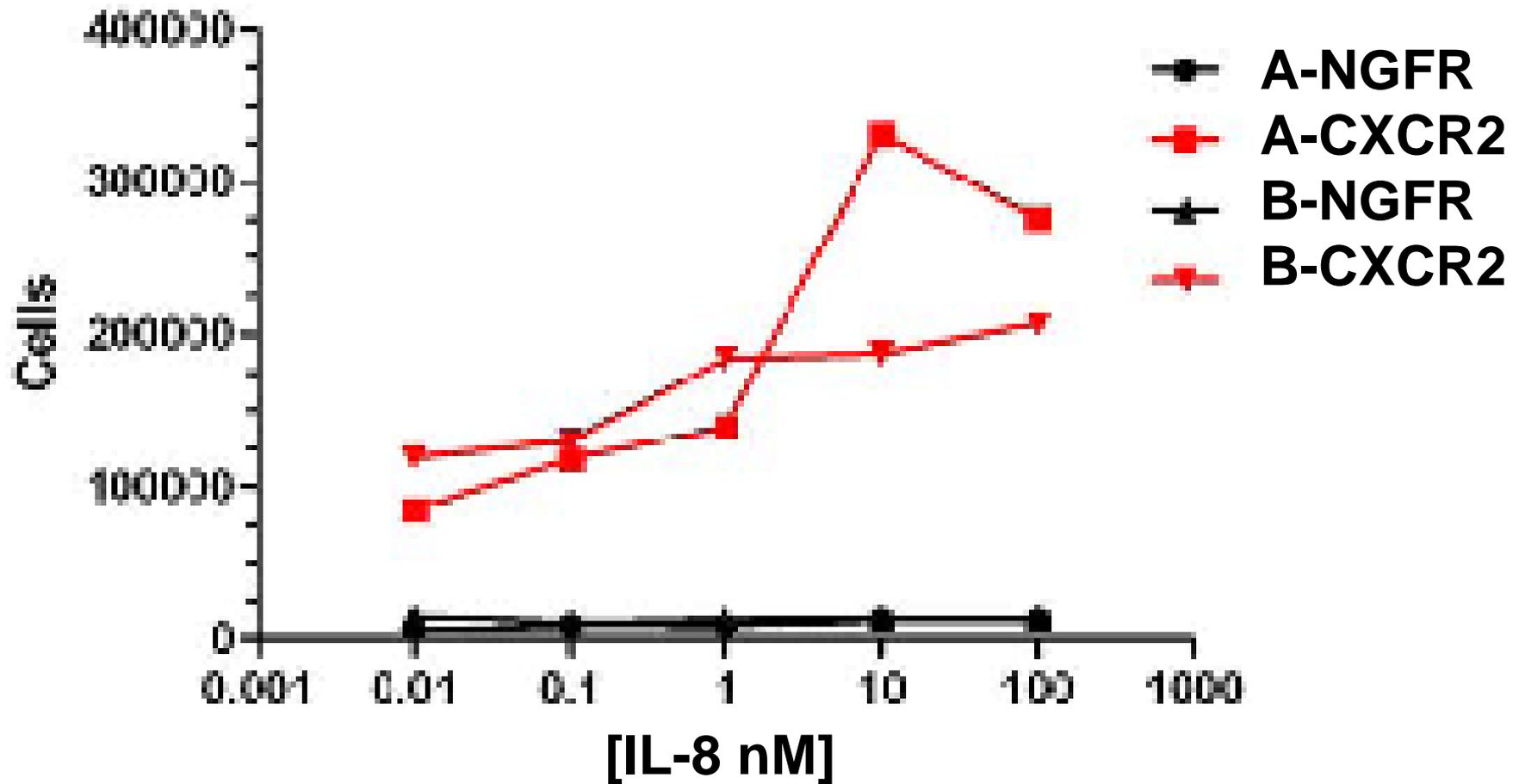


- Tumor only
- OFL T
- ▲ CXCR2 T

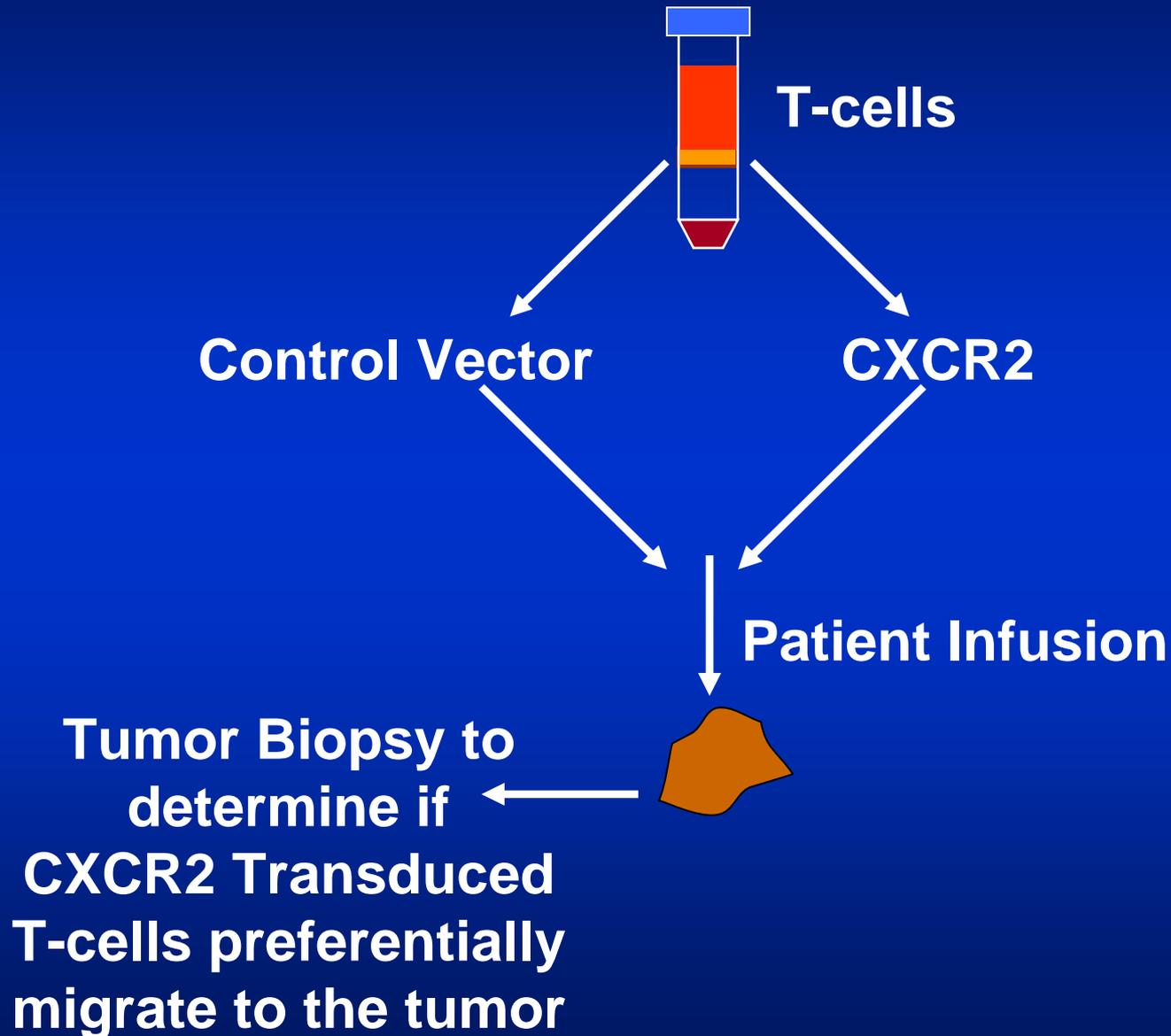
Human TIL Transduced to Express CXCR2 and NGFR



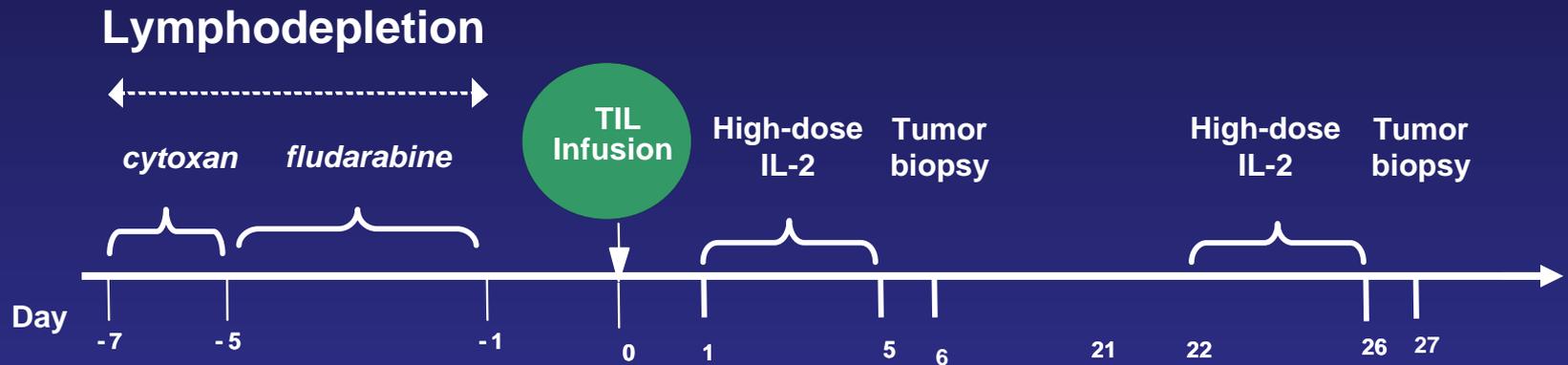
Migration of Transduced T-cells



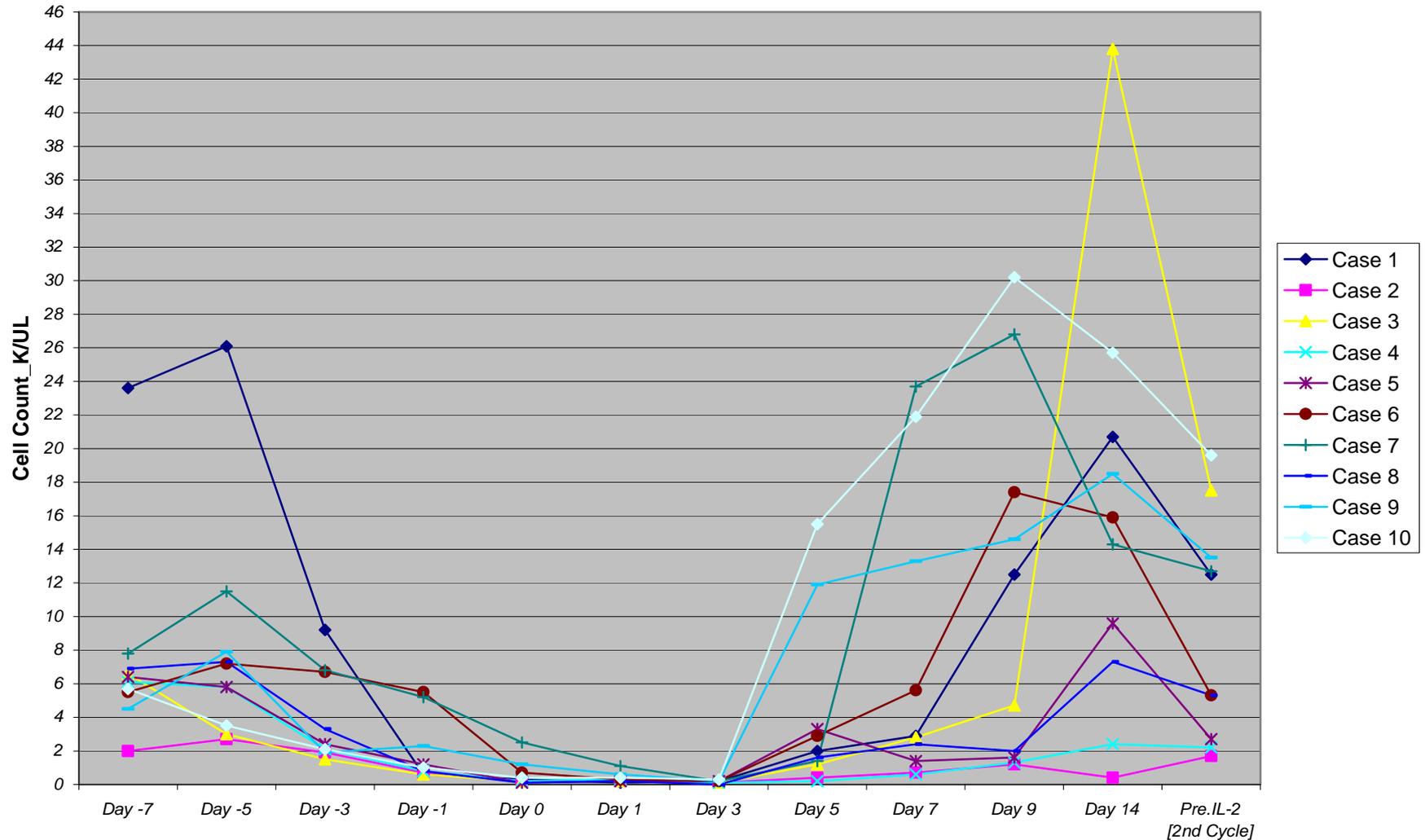
Clinical Trial Plans



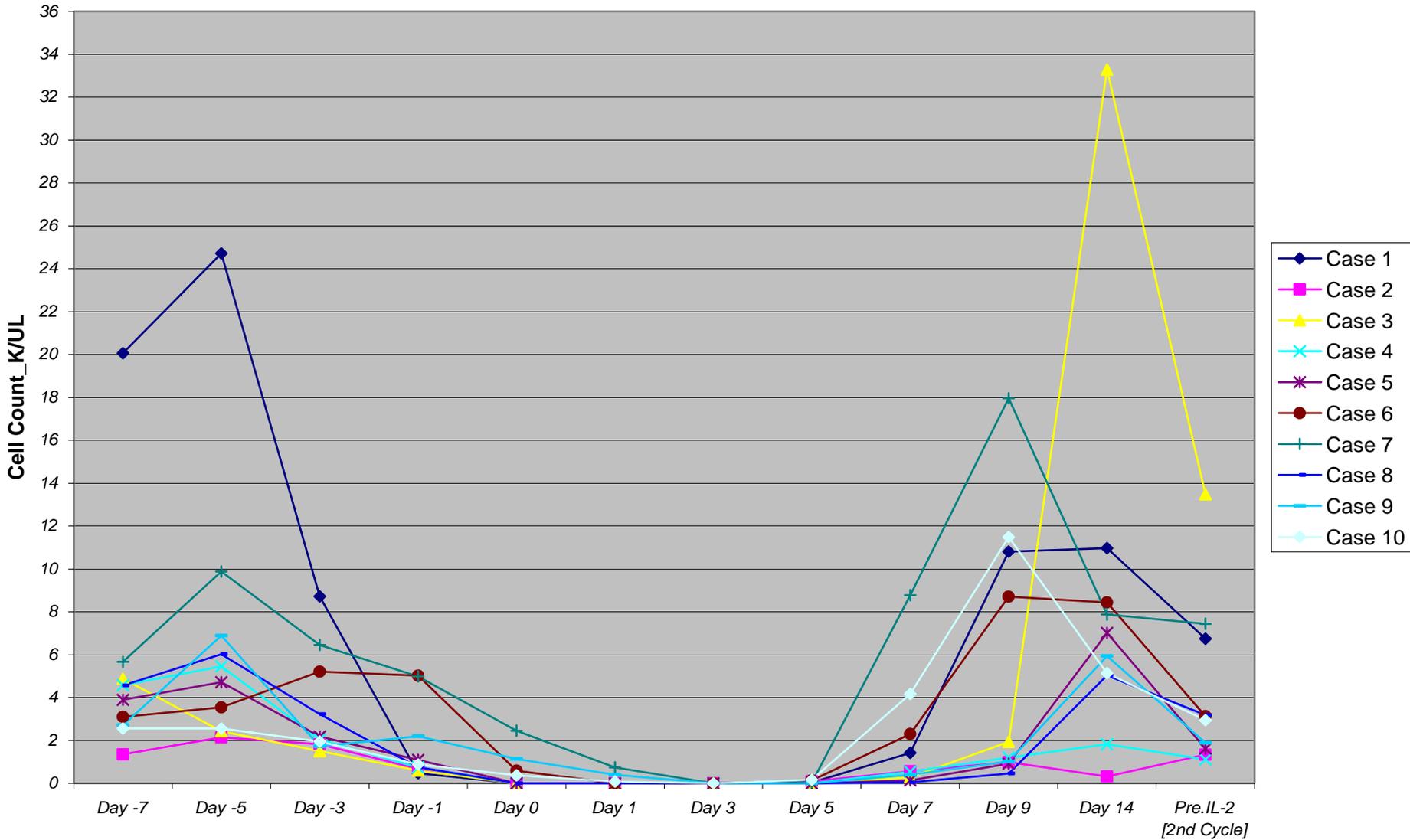
CXCR2 Study Schema



Total White Blood Cell Count



Absolute Neutrophil Count



Dose Escalation

Cohort 1: 15 billion CXCR2 transduced TIL

Cohort 2: 45 billion CXCR2 transduced TIL

Cohort 3: 75 billion CXCR2 transduced TIL

- **Equal number of truncated NGFR-transduced control TIL will be administered**
- **Non-transduced TIL will be infused in each patient for up to a total number of 150 billion TIL**