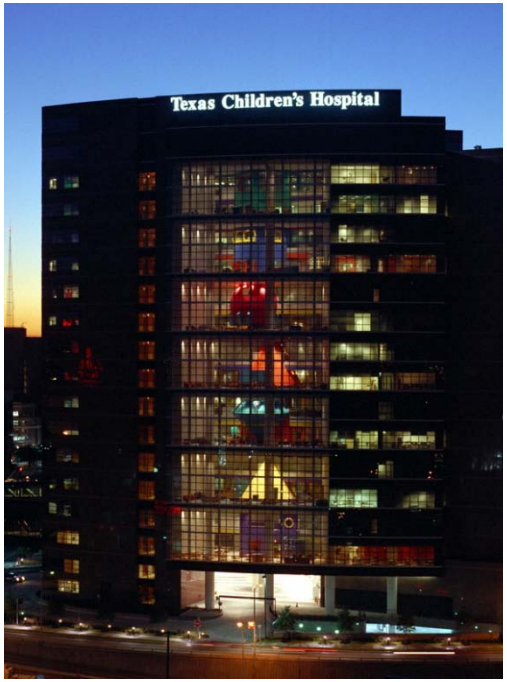
HER2-targeted T-cell Therapies

Stephen Gottschalk



Outline

- What criteria were used in choosing the target?
- What approach was employed in evaluating potential off target effects?
- How did that data inform the starting cell dose?
- Were there unexpected toxicities?

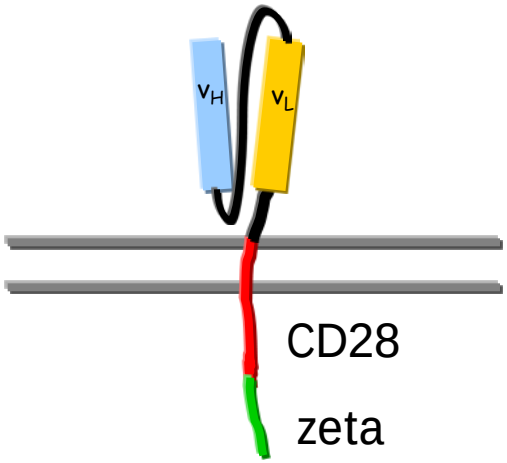
Why HER2-CAR T cells?

- HER2 is among the ‘top 10’ immunotherapy targets
  (NCI consensus panel; Cheever et al; Clin Can Res 2009)
- Gene amplified in 20 to 25% of breast cancer
  - HER2 antibodies and tyrosine kinase inhibitors effective
- Overexpressed in broad range of malignancies at low levels
  - Brain tumors, sarcomas, 20 – 30% of breast cancer, lung cancer
  - HER2 antibodies and tyrosine kinase inhibitors **ineffective**

HER2-CAR T cells for HER2 low expressing malignancies

- Completed preclinical studies for
  - Medulloblastoma (Ahmed et al Cancer Res 2007)
  - Osteosarcoma (Ahmed et al Mol Therapy 2009)
  - Glioblastoma multiforme (Ahmed et al Clin Cancer Res 2010)

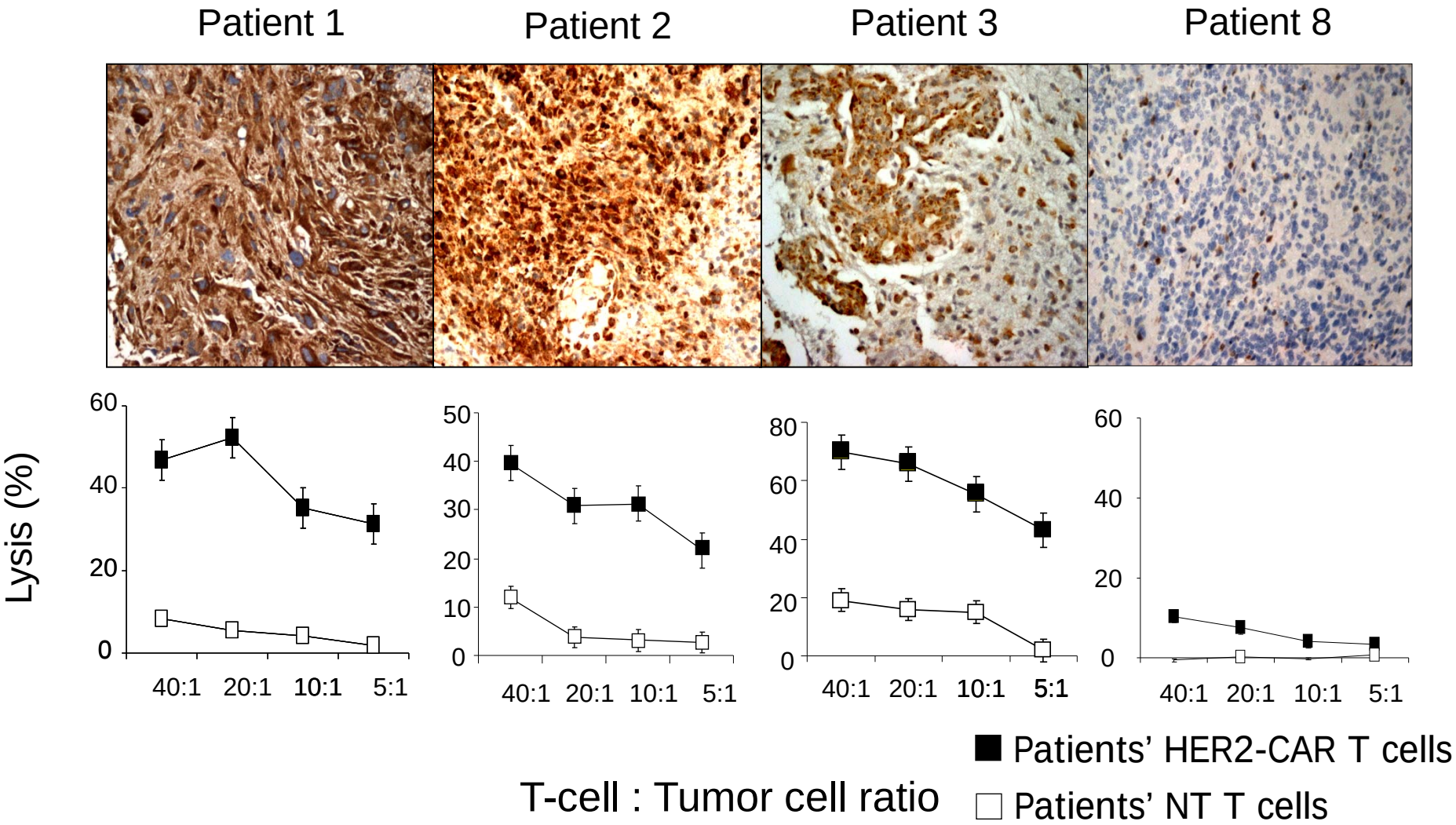
2nd Generation HER2-specific CAR



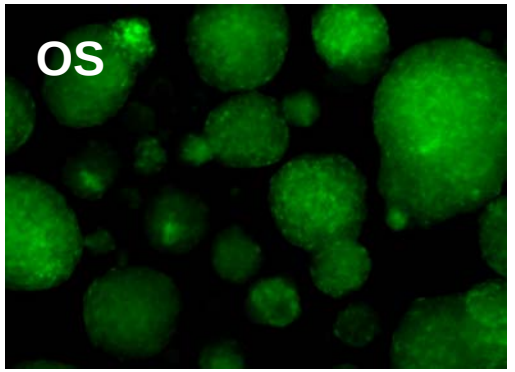
GALV or RD114 pseudotyped retroviral particles

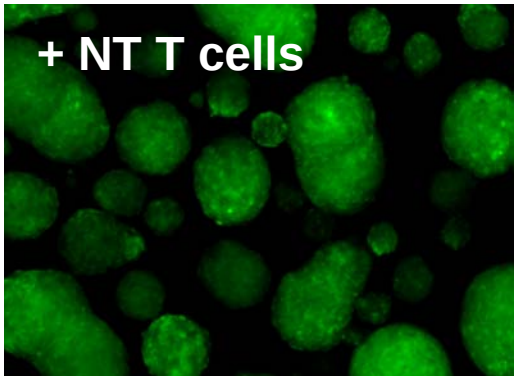
(Moritz et al, PNAS 1994; Pule et al, Mol Thr 2005; Ahmed et al, Mol Thr 2009)

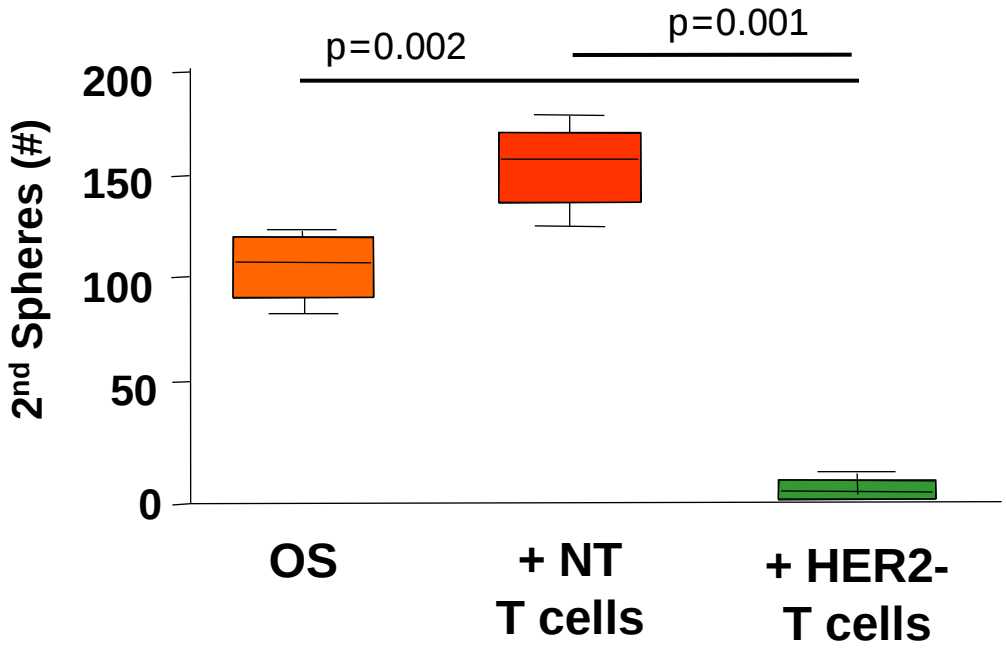
HER2-CAR T cells kill primary HER2+ gliomas



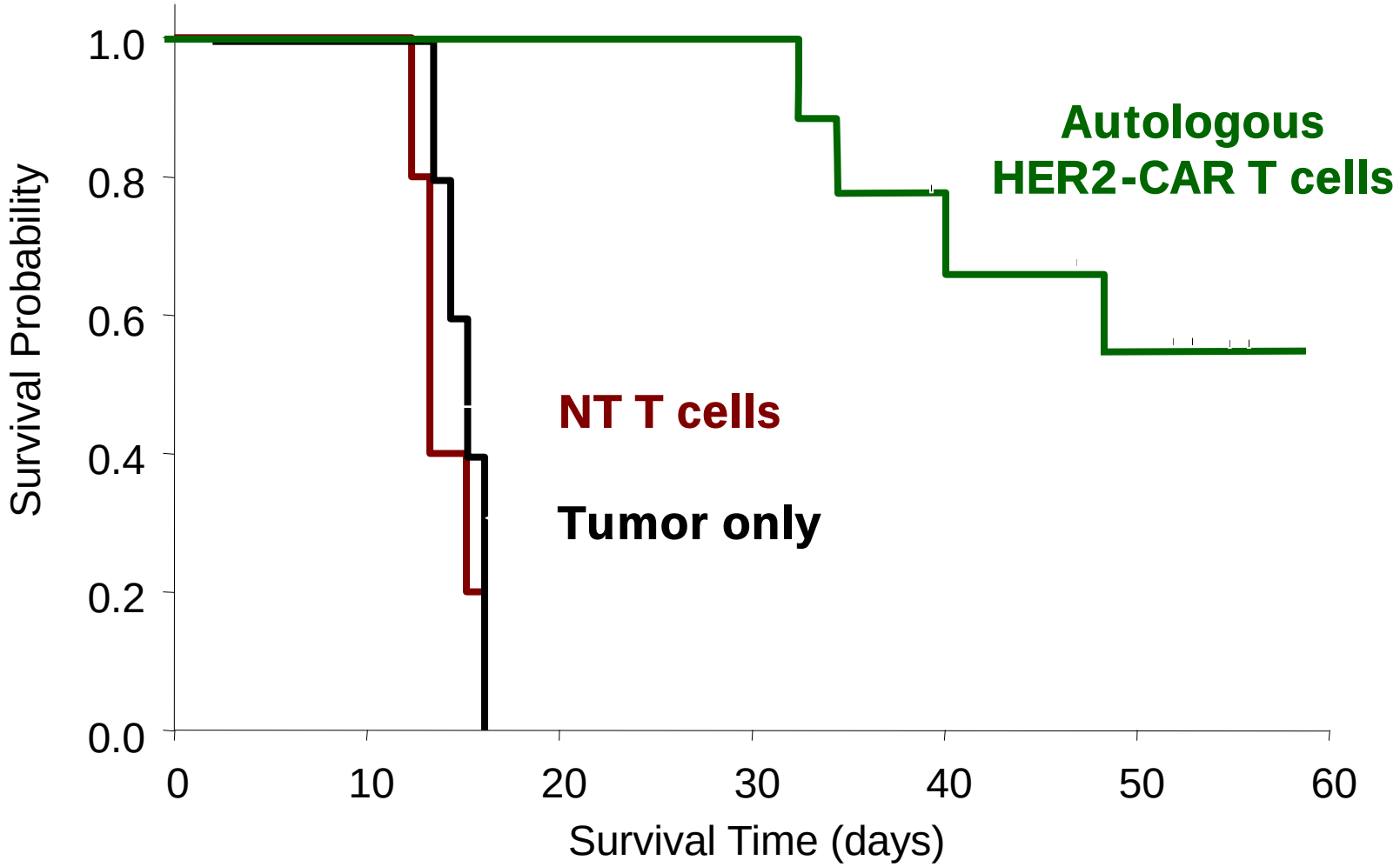
HER2-CAR T cells inhibit 2nd Sarcosphere formation







Mice treated with HER2-CAR T cells have survival advantage



(Ahmed et al, Clin Can Res 2010)

Outline

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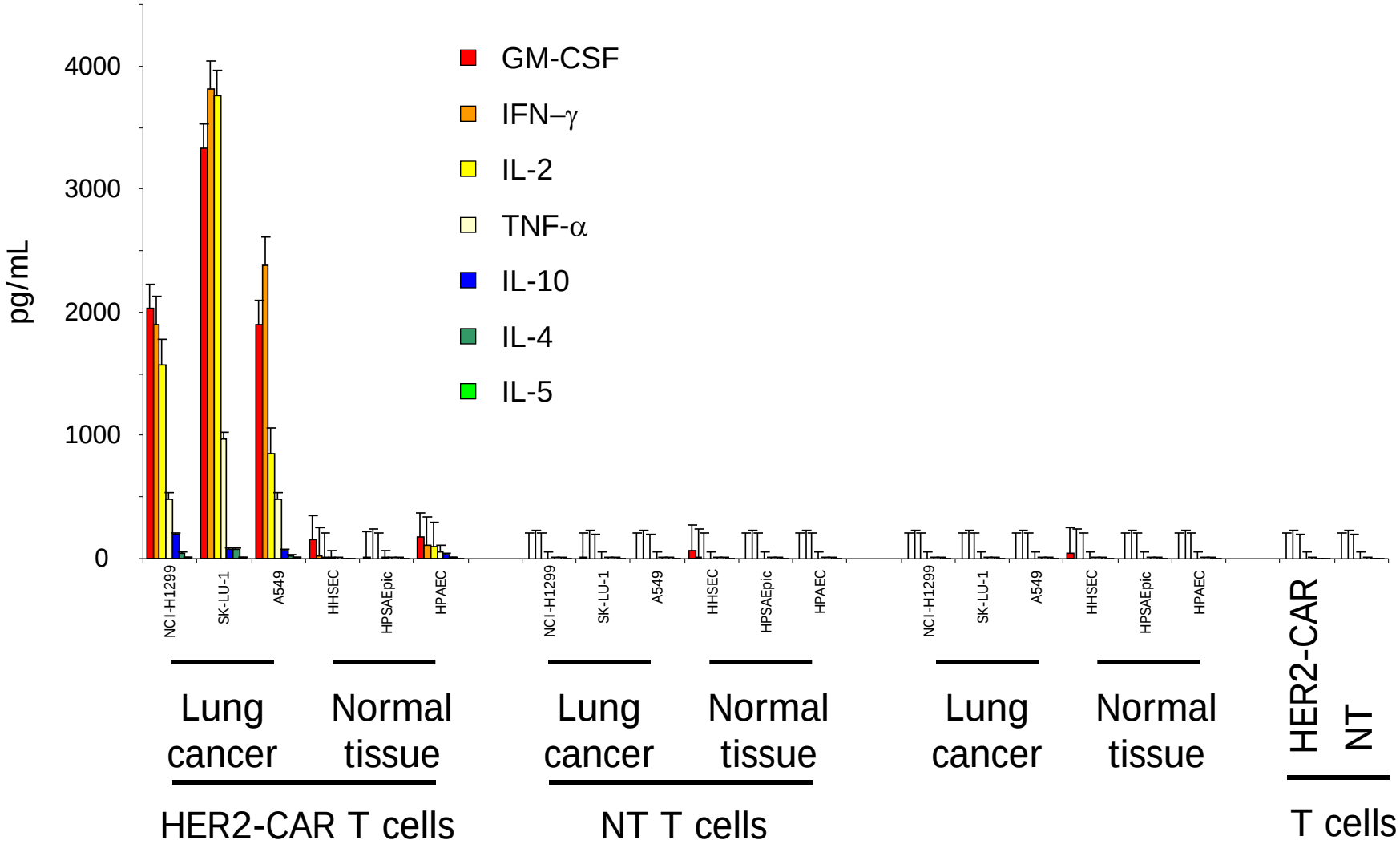
Initial IND application

- Proposed starting cell dose: $2x10^7/m^2$
  - Relied on clinical experience with HER2 monoclonal antibody (trastuzumab, Herceptin®)

HER2-CAR T cells do not recognize primary endothelial and epithelial cells



Do HER2-CAR T cells recognize primary pulmonary cells?

- **NCI: Yes** **BCM: No**
- Differences:
  - Single chain variable fragment: Trastuzumab vs. FRP5
  - Costimulatory domains: 4-1BB.CD28 vs. CD28

Approved IND

- Cell dose: $1x10^4/m^2$ to $1x10^8/m^2$
- 9 dose levels
- mCRM: 2 patients per dose level
- At least 6 weeks between dose levels
- At least one week between patients

Status of HER2-CAR T-cell studies at CAGT

- 2 clinical studies approved
  - Lung cancer, osteosarcoma
  - One patient received 3 cell doses
    - $1x10^4/m^2$, $3x10^4/m^2$, $1x10^5/m^2$
    - no toxicity (cardiac, cytokines)

What is a safe starting cell dose?

- Donor Lymphocyte Infusions for matched related or unrelated donors

  (Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation):

  – Analysis of 298 patients: The 1st cell dose should not exceed $2x10^7$ cells/kg ($6x10^8/m^2$) cells

(Guglielmi et al, Blood 2002)

What is a safe starting cell dose?

- Minor histocompatibility-specific T-cell experience:
  - CTL doses: $3.3 \times 10^7/m^2$, $3.3 \times 10^8/m^2$, $3.3 \times 10^9/m^2$
  - Lung toxicity in 3/7 patients at $3.3 \times 10^9/m^2$
  - Antigen expression in lung tissue did not predict lung toxicity

(Warren et al, Blood 2010)

Immunotherapy with HER2-specific CTLs

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Lung Cancer: Shanda Blockman (TMH, Houston)