Administration of EBV-specific Cytotoxic T cells expressing HER2 chimeric antigen receptors to subjects with advanced Osteosarcoma (ECHO)

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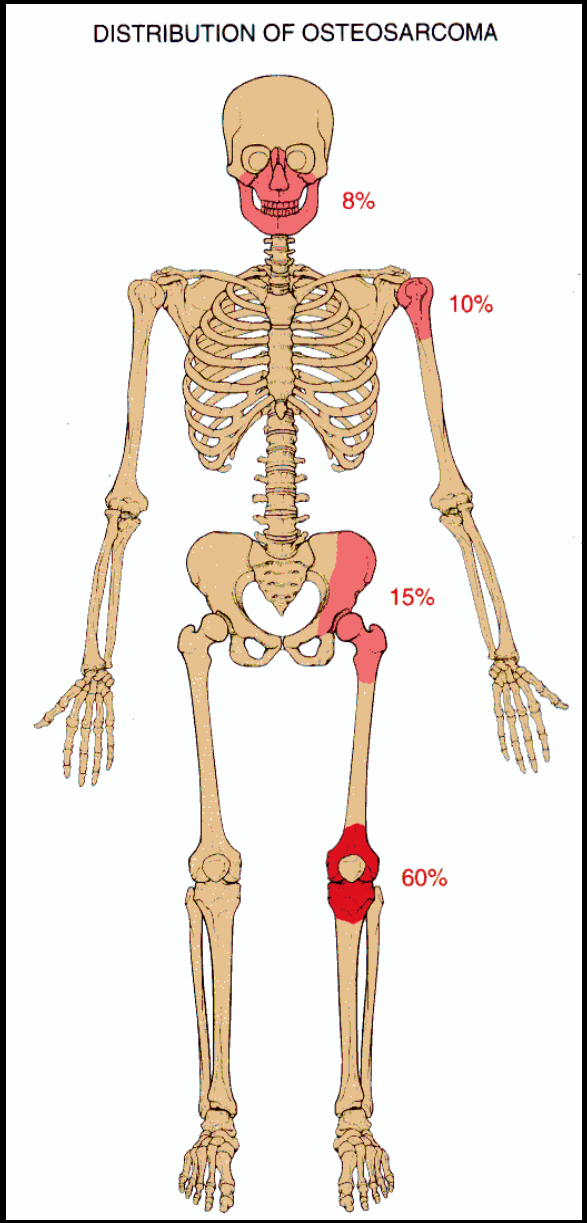
Pediatric oncologist
Head, Osteosarcoma Program

Outline

- **Osteosarcoma**
- **T cell Therapy: CAR**
- **Targeting HER2 in osteosarcoma**
- **Proposed Clinical Trial: ECHO**
  - Design
  - Subjects
  - Generation of cells
  - Monitoring plan
  - Risks
- **Questions**

Osteosarcoma (OS)

- The most common primary bone cancer
- ~ 800/year in the US
- Peak age: early adolescence
- Growing ends of long bones



http://seer.cancer.gov/publications/childhood/bone.pdf
Rodriguez-Galindo et al. *Cancer* 2007.

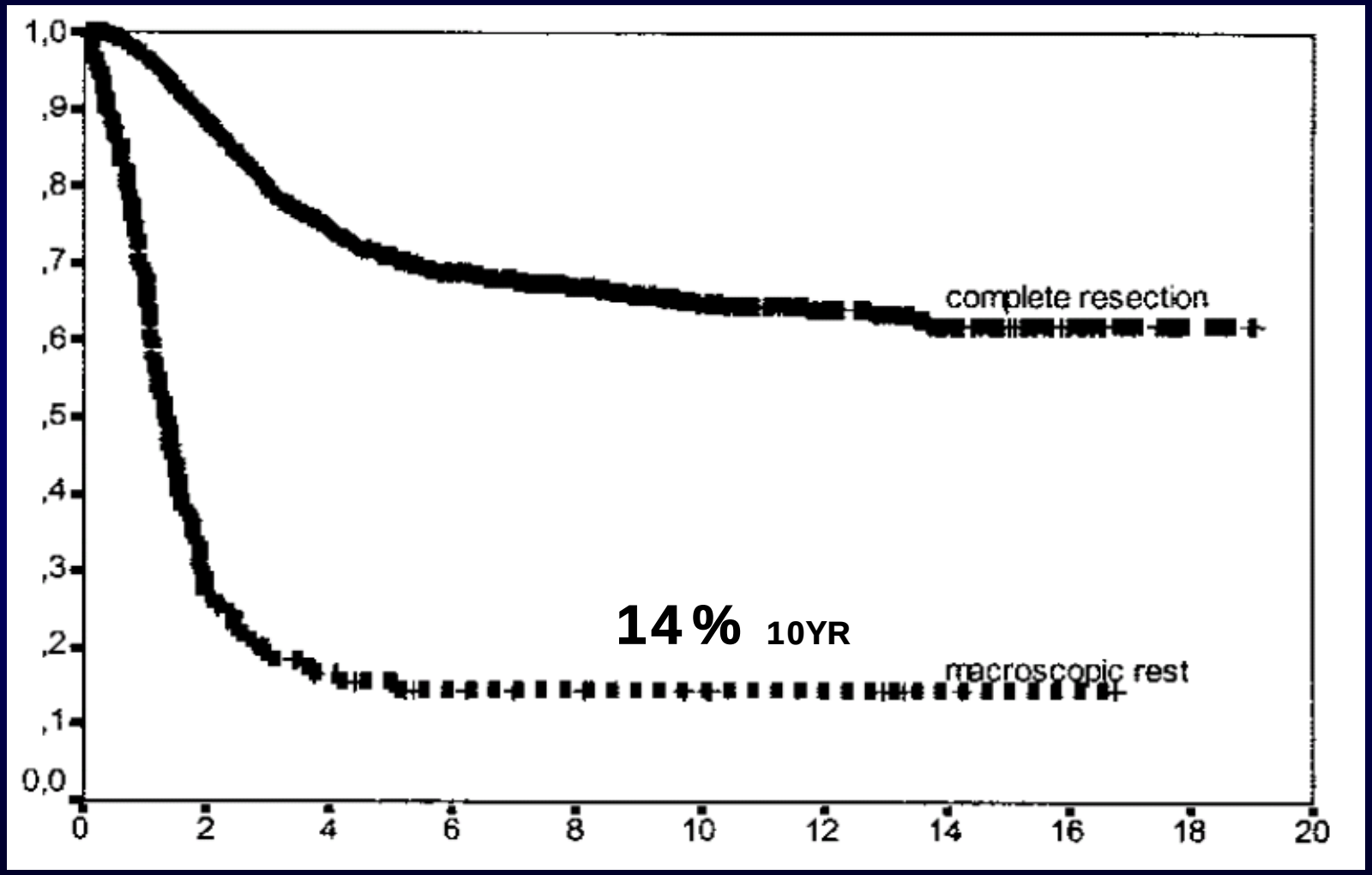
Osteosarcoma: treatment

Chemotherapy (primary) → **Amputation or limb-salvage** → **Chemotherapy** (adjuvant)

Active agents:
- Cisplatin
- Doxorubicin
- Methotrexate
- +/- Ifosfamide

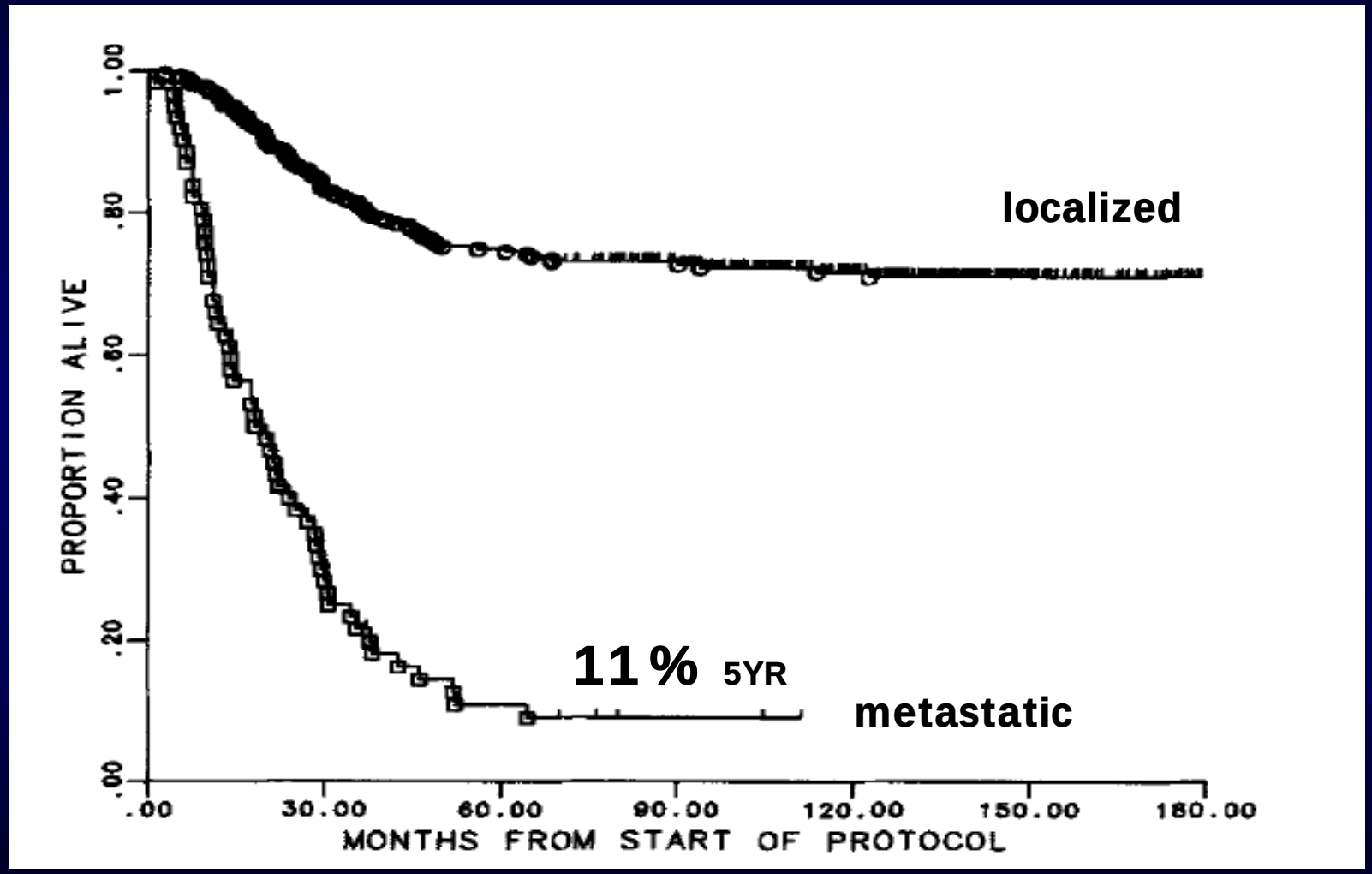
P. Pizzo and DG Poplack. P&P of Pediatric Oncology. 2009

A. Unresectable OS



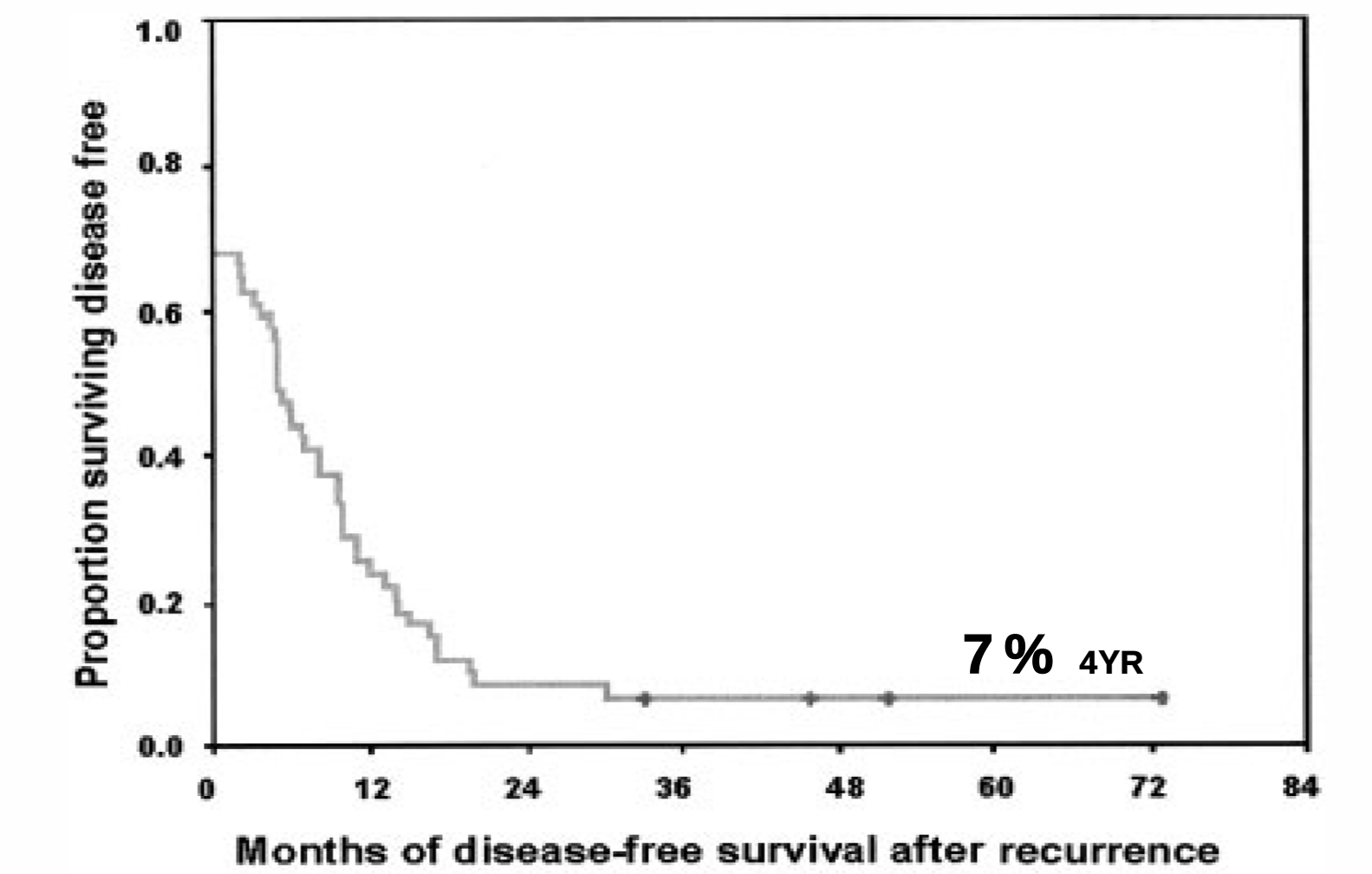
Bielack et al. *JCO* 2002

B. Metastatic OS



Myers et al. *JCO* 1993

C. Recurrent OS



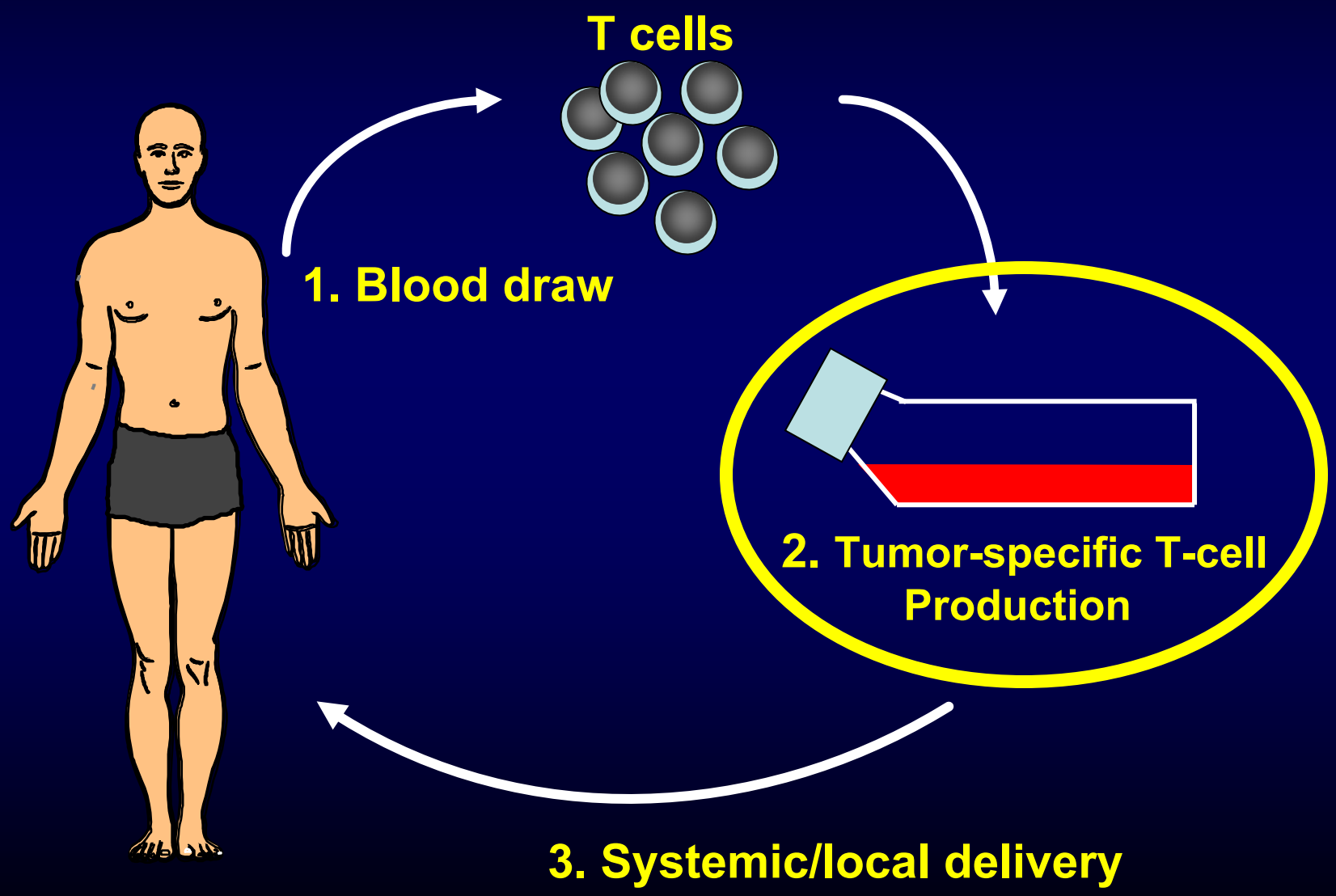
Hawkins et al. *Cancer* 2003

Rationale for Immunotherapy

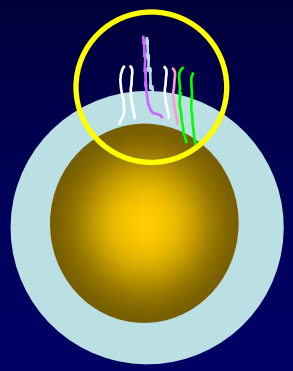
- **Prognosis remains poor** for patients with
  - Metastatic disease
  - Un-resectable
  - Recurrent/ resistant
- **Significant acute toxicities**
- **Long-term effects**
  - Disability after surgery

Barker et al. *JCO* 2005. Cangir et al. *Cancer* 1990. Rodriguez-Galindo et al. *Cancer* 2007.
http://seer.cancer.gov/publications/childhood/bone.pdf

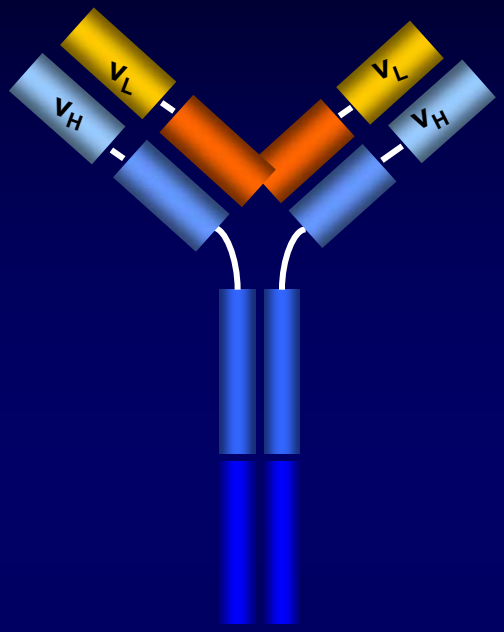
Tumor-specific T-cell Therapies



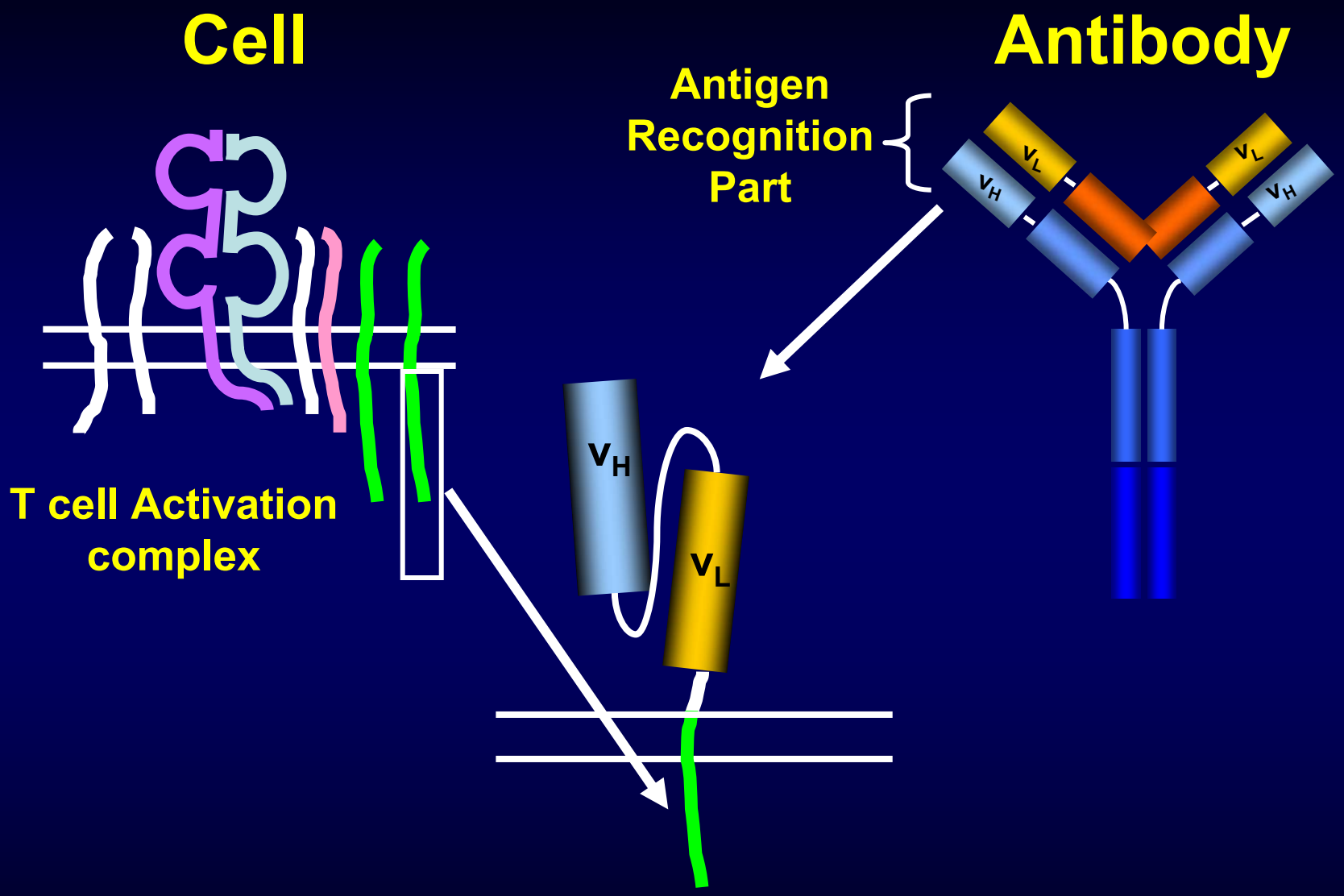
Cell



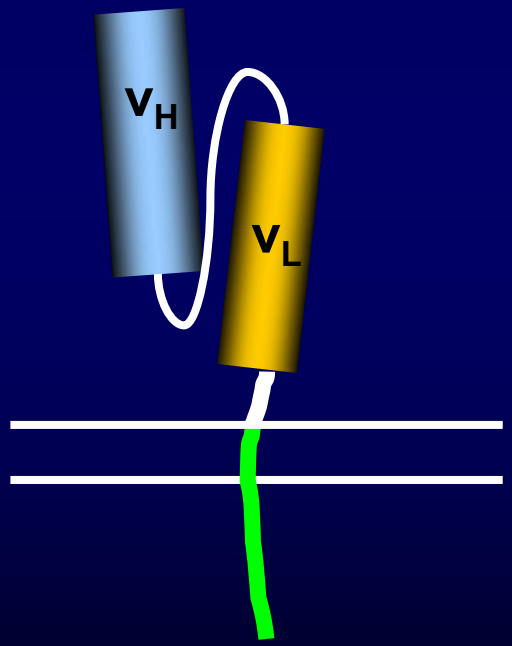
Antibody



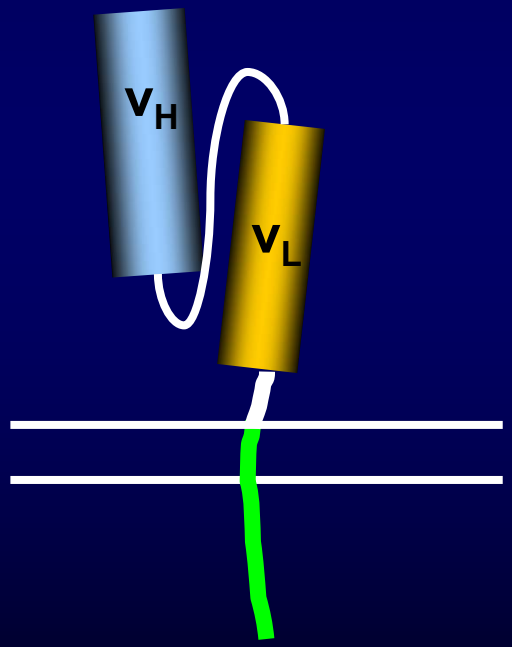
Chimeric Antigen Receptor



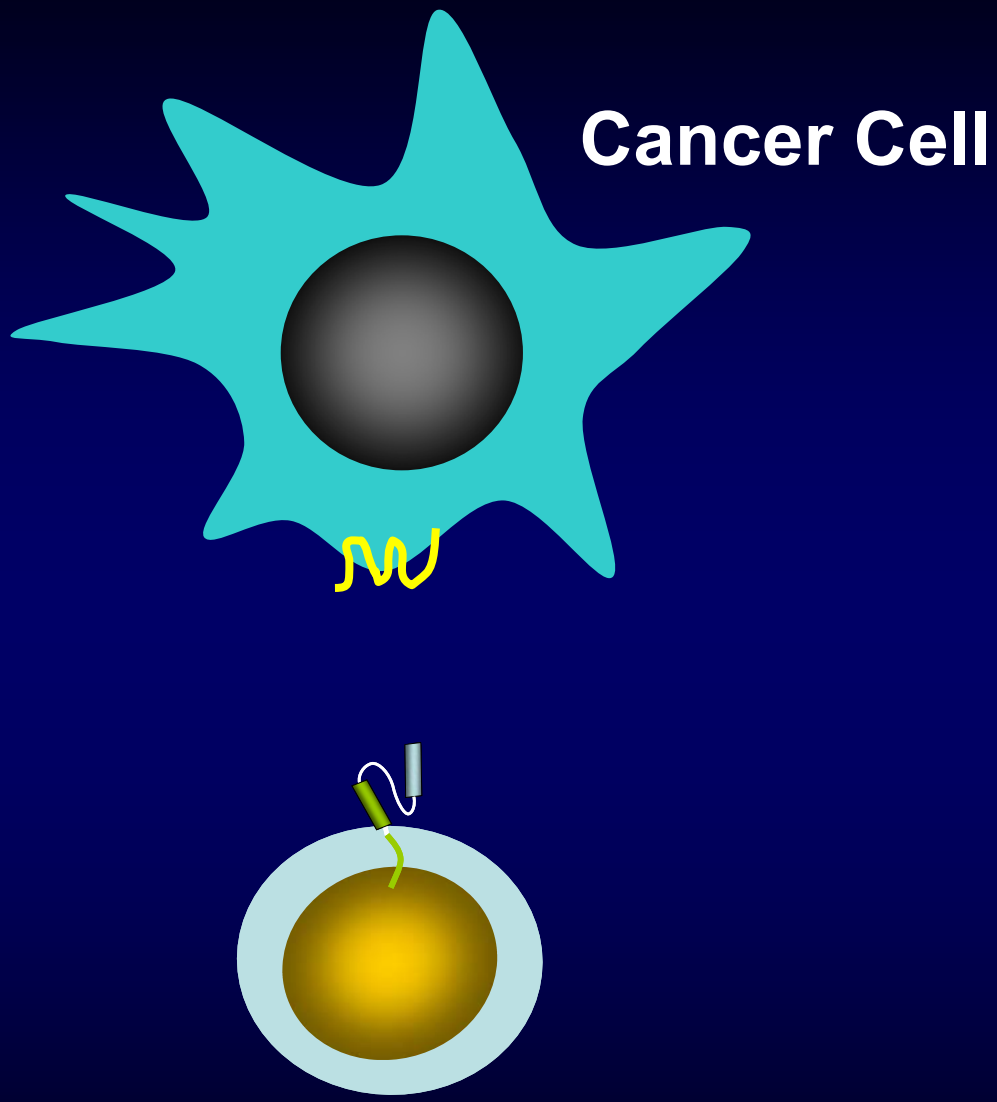
Chimeric Antigen Receptor



Chimeric Antigen Receptor

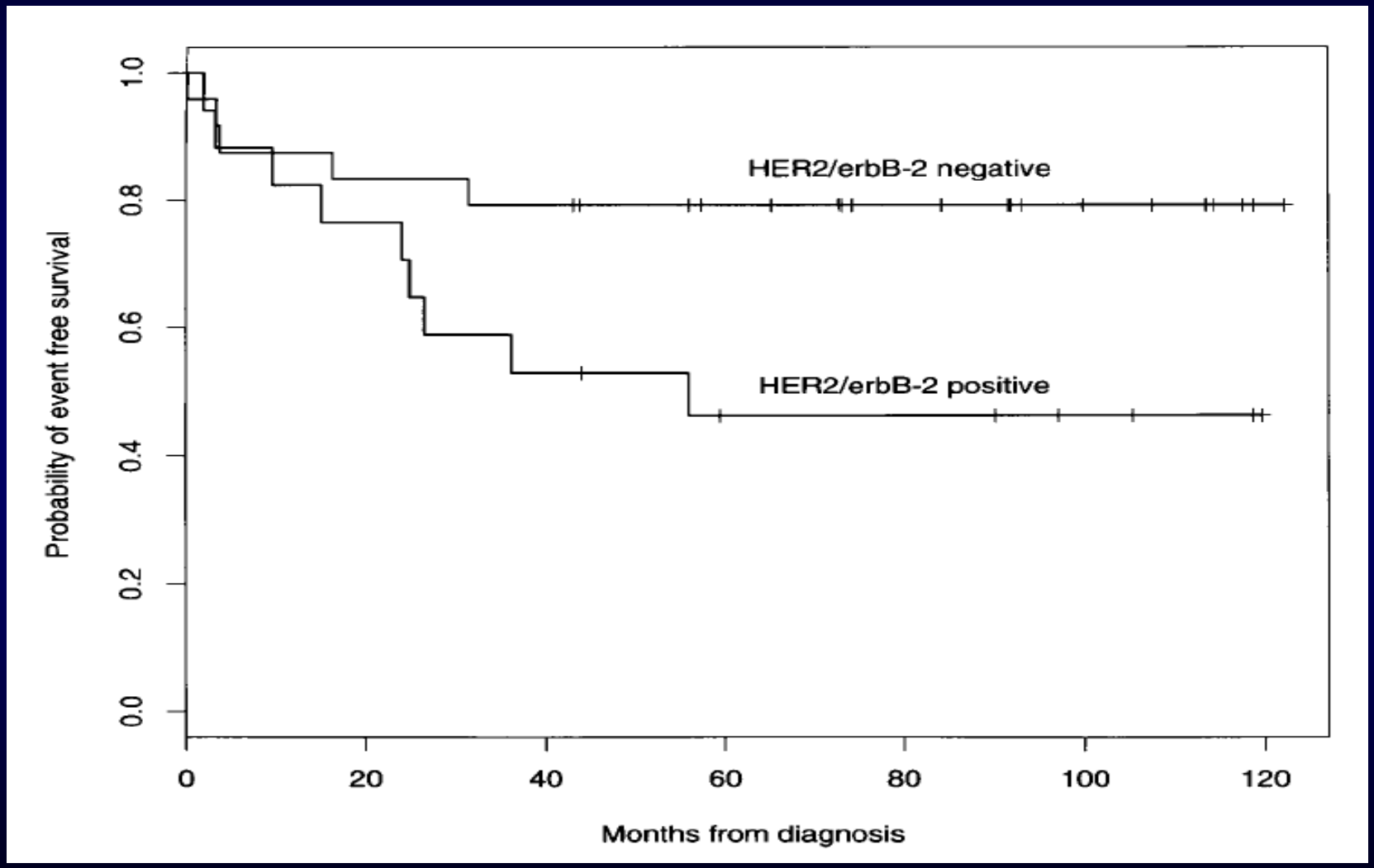


CAR



CAR T cell

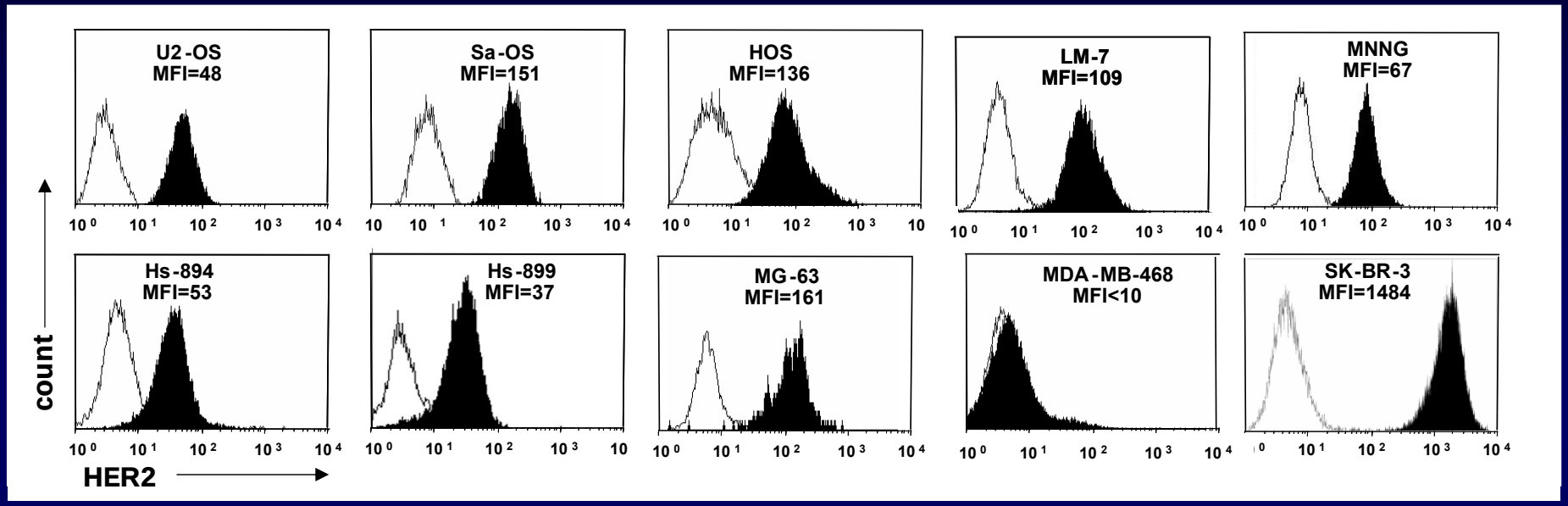
HER2 expression and prognosis



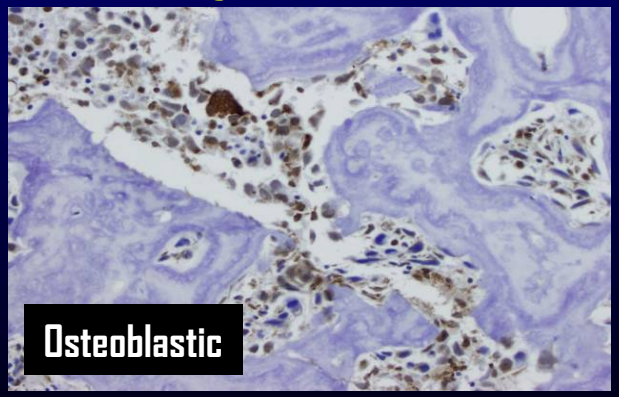
Gilbertson RJ. *Oncologist.* 2005; Scotlandi et al. *Eur. J. Can.* 2005; Gorlick et al. *JCO* 1999

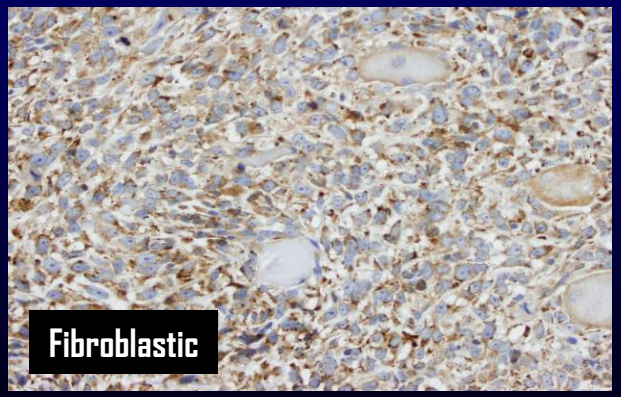
HER2 *expression*

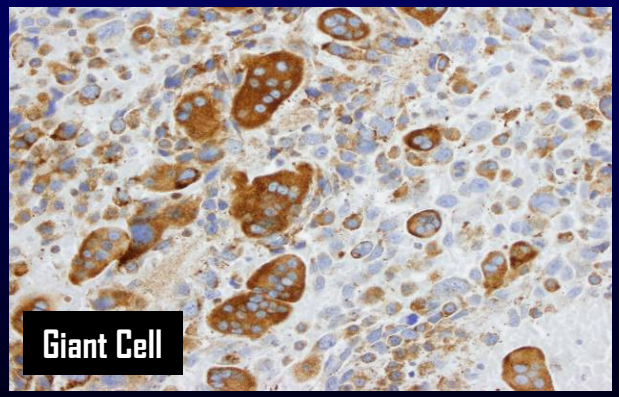
Osteosarcoma cell lines



Primary osteosarcoma

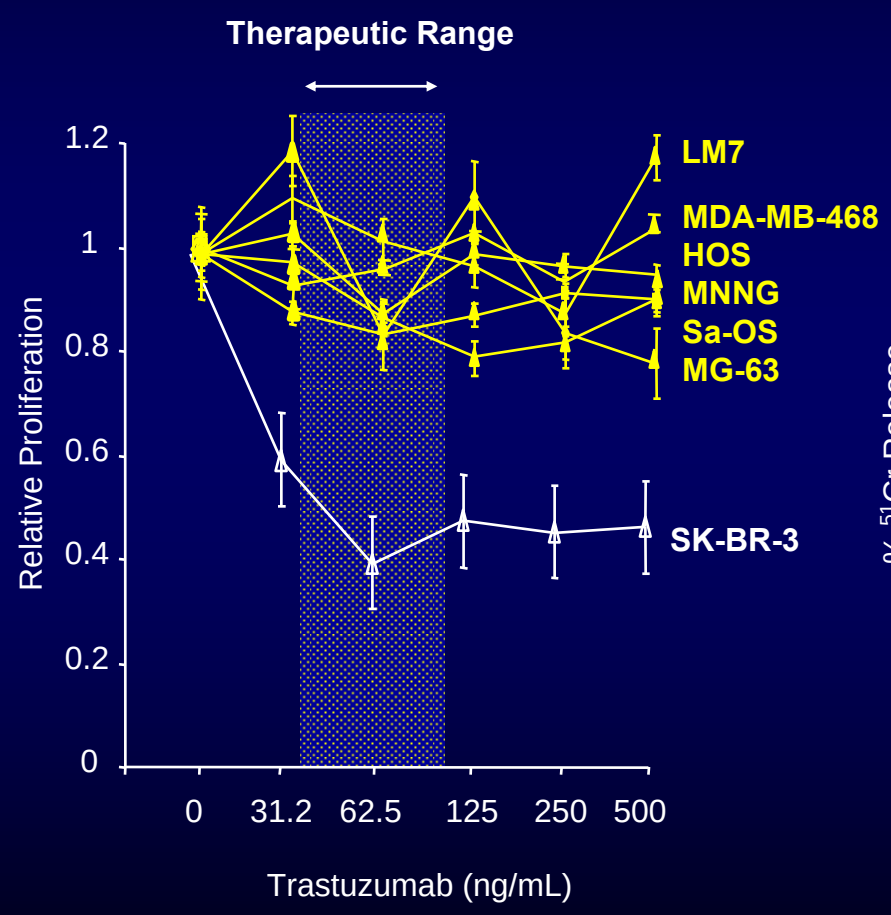




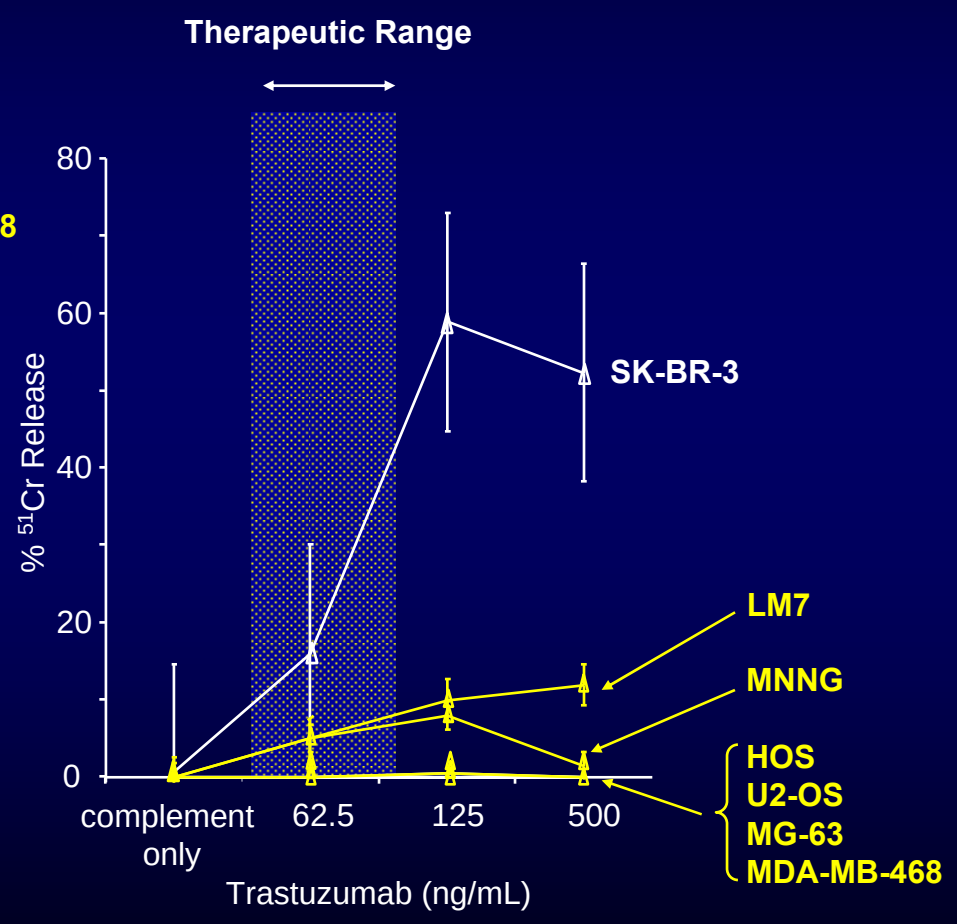


Ahmed et al. *Molec Therapy 2009*

Trastuzumab fails to lyse or inhibit proliferation of Osteosarcoma

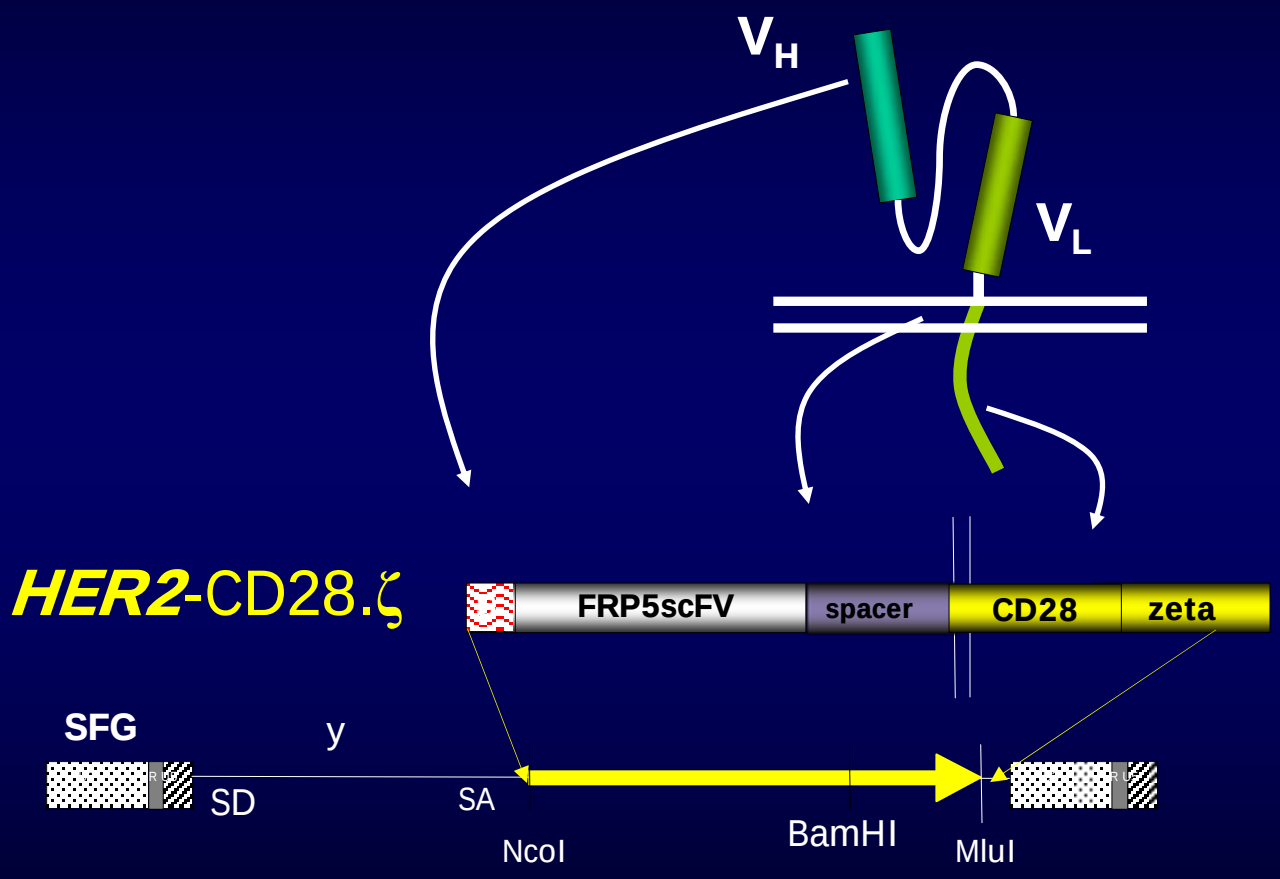


Inhibition of Proliferation

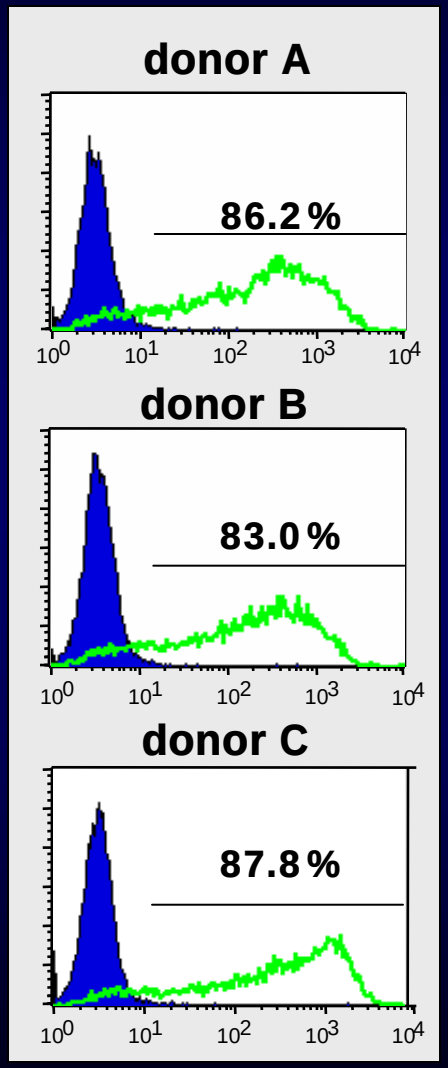


Complement Cytotoxicity

HER2 CD28.ζ CAR

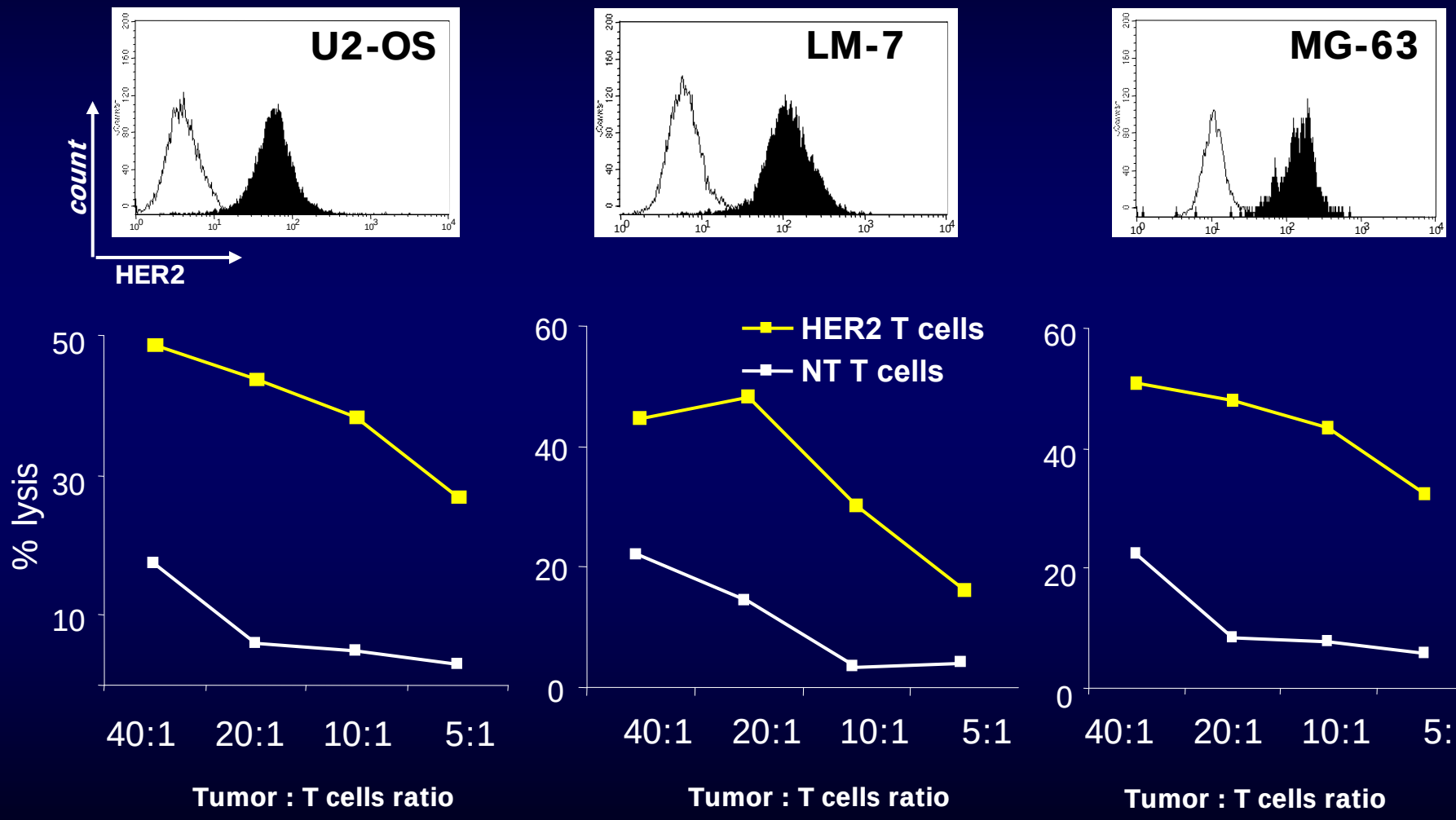


RD114
envelope endogenous feline retrovirus



Wels et al. *Biotech (NY).* 1992

HER2.CAR T cells Kill HER2+ OS



Ahmed et al. *Molec Therapy 2009*

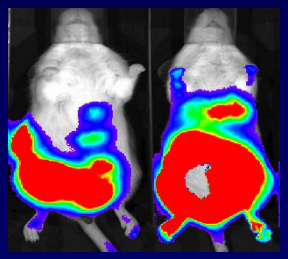
Animal Models

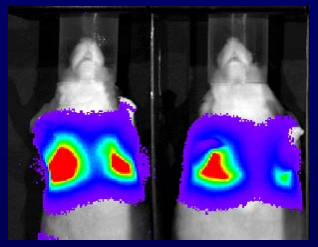
Cancer Cells +

IP

IV

locoregional model

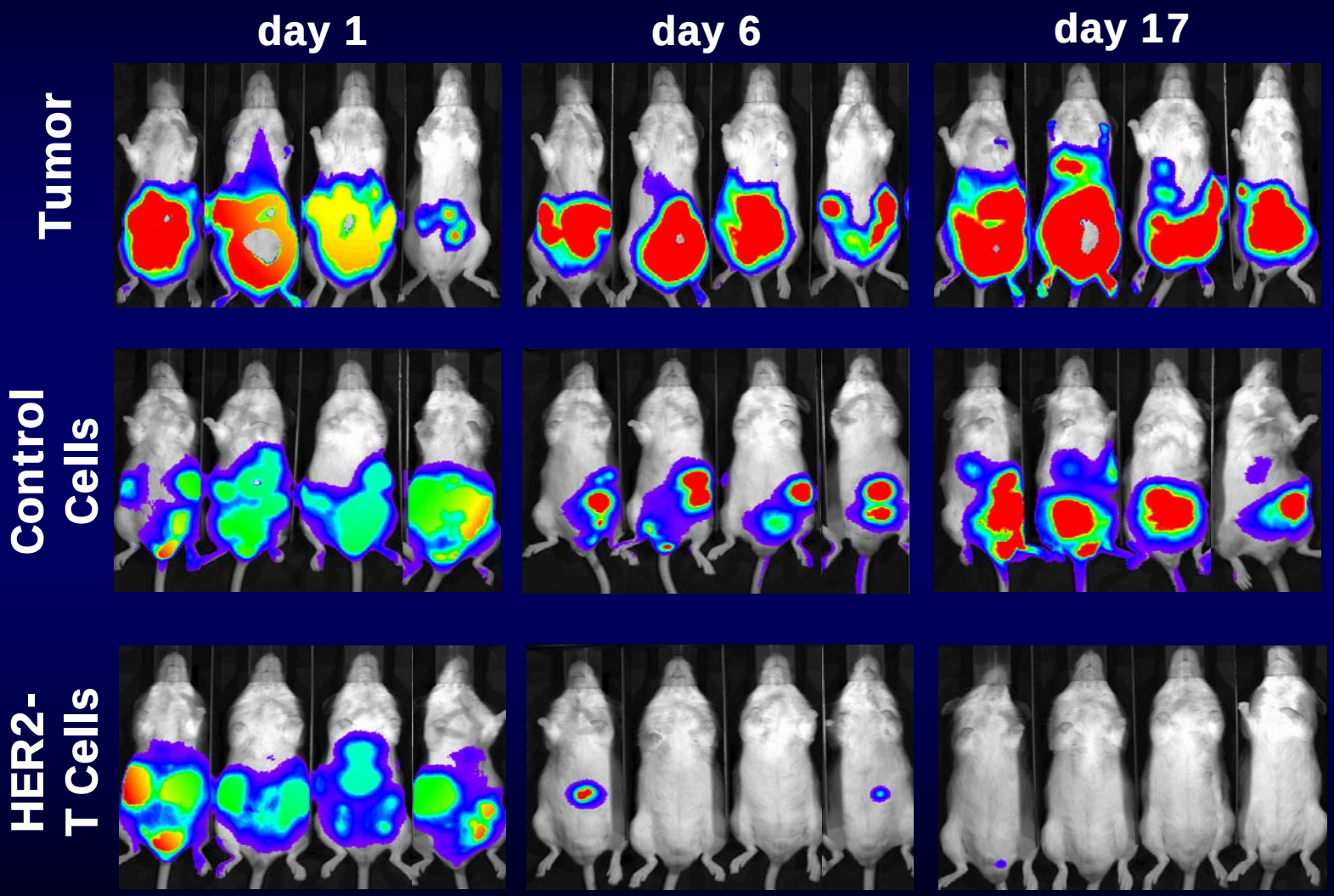




lung metastasis model

Ahmed et al. *Molec Therapy 2009*

Locoregional Model



Ahmed et al. *Molec Therapy 2009*

Lung Metastasis Model

Wk

Control

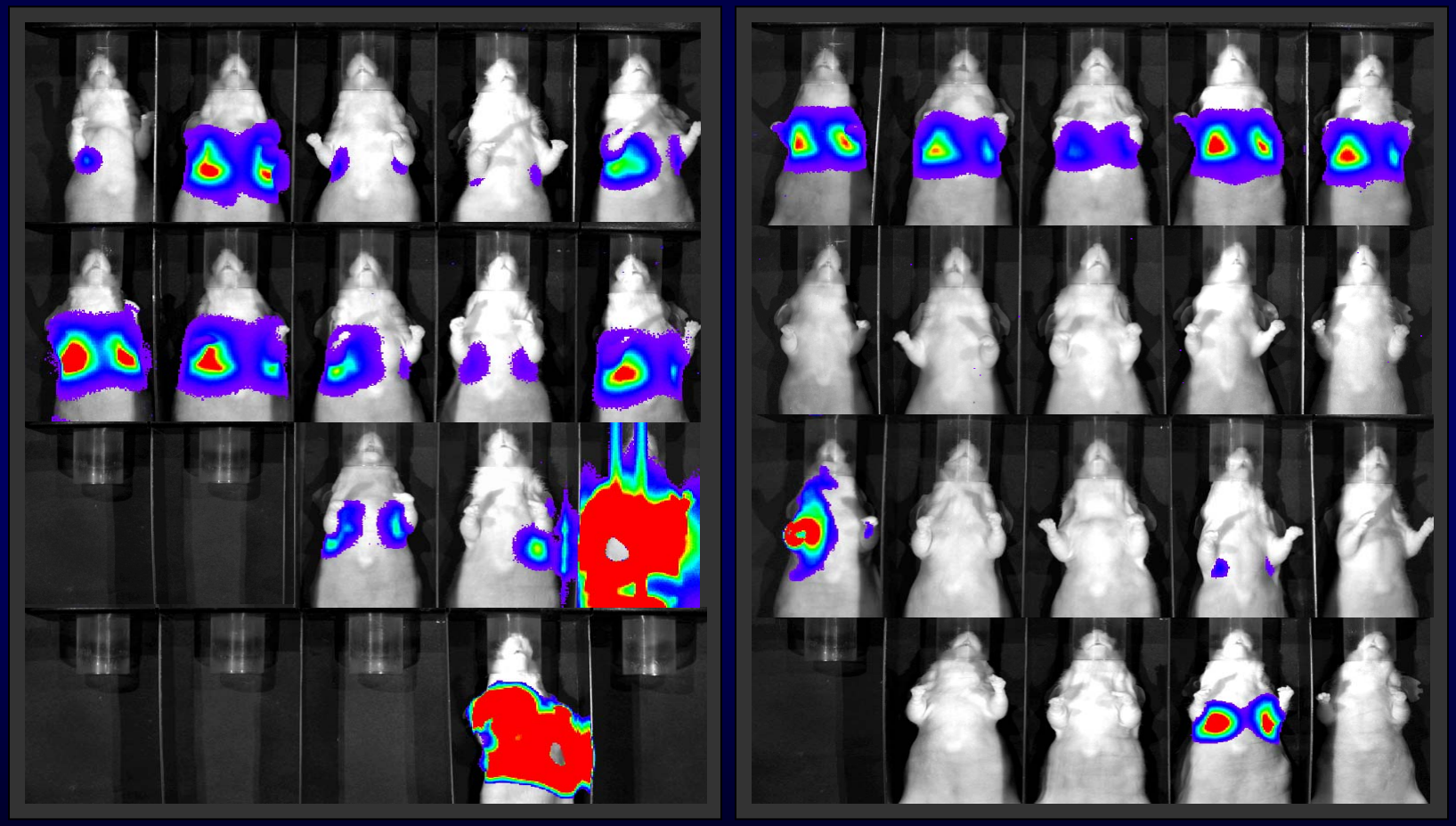
HER2.CD28.ζ T cells

2

4

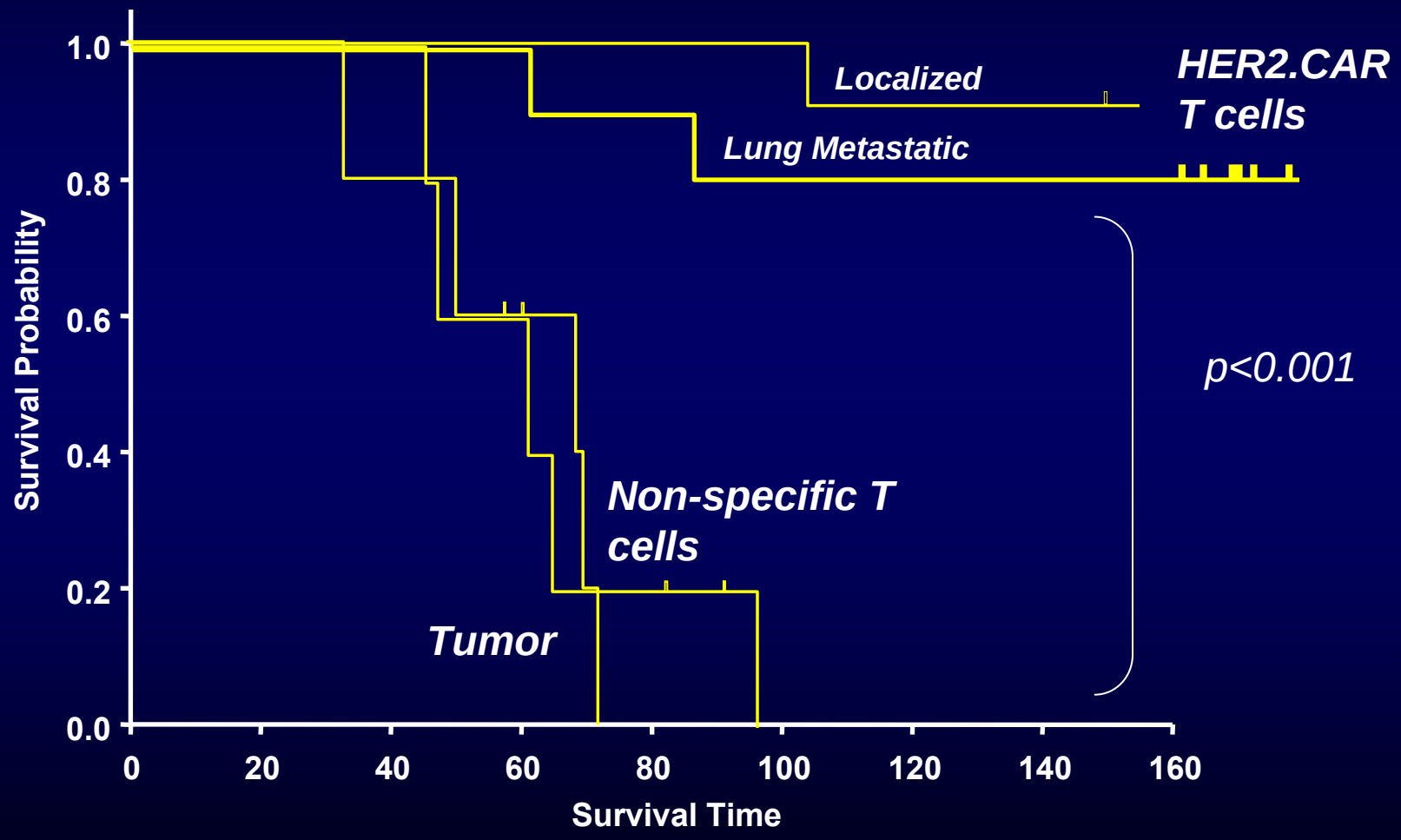
8

10



Ahmed et al. *Molec Therapy 2009*

Survival



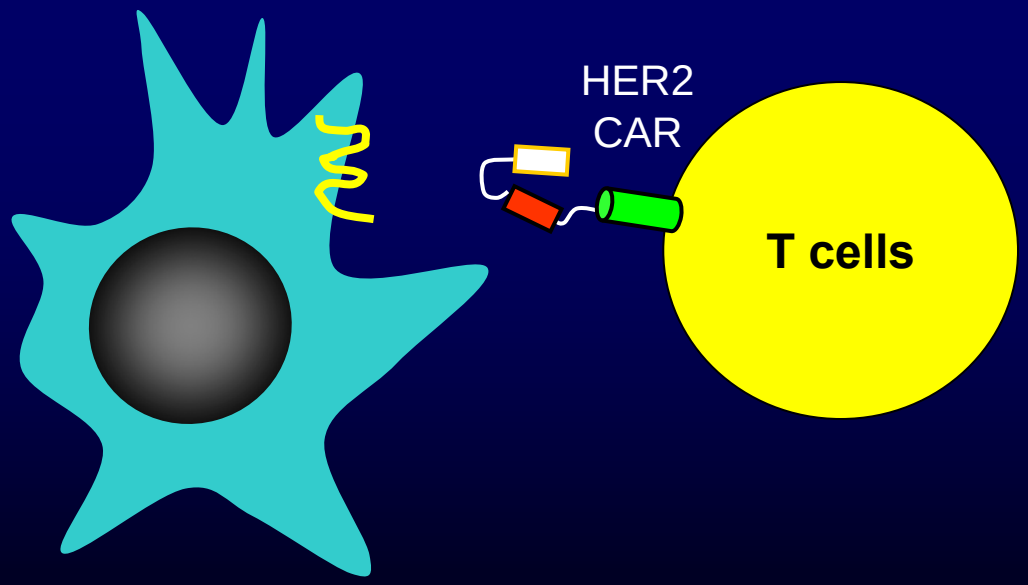
Ahmed et al. *Molec Therapy 2009*

HEROS

HER2 chimeric antigen Receptor expressing T cells for subjects with advanced OSteosarcoma

FDA IND 14050

RAC 0903-969



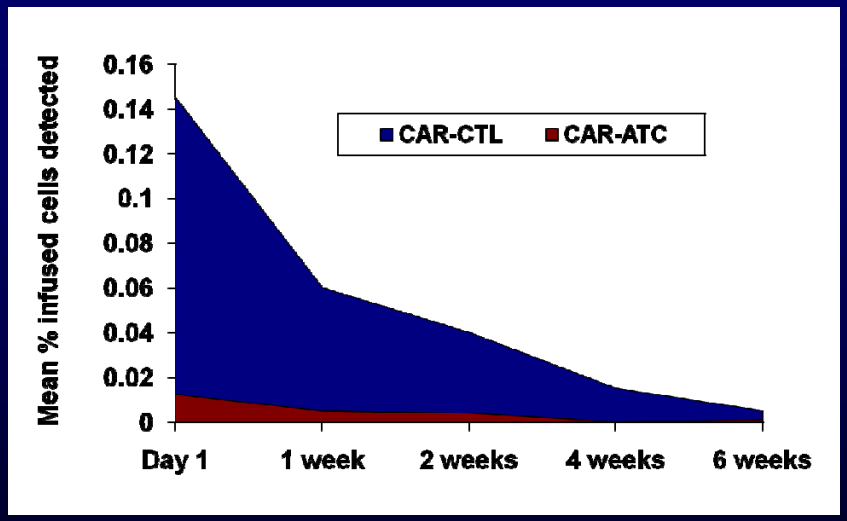
NESTLES

Peripheral blood T-cells and EBV-CTLs expressing GD2 specific CARs to subjects with Neuroblastoma

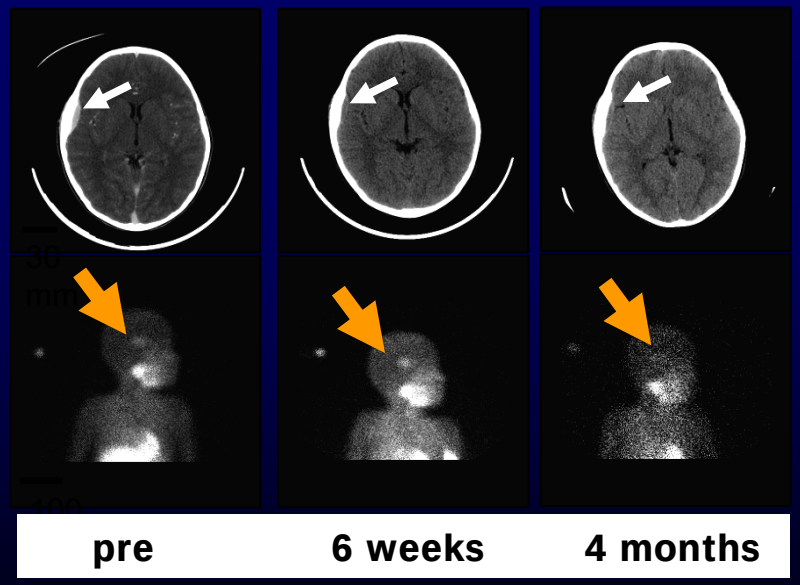
FDA IND 11217

RAC 0212-563

Better short-term persistence of CTLs than activated T cells (ATC)



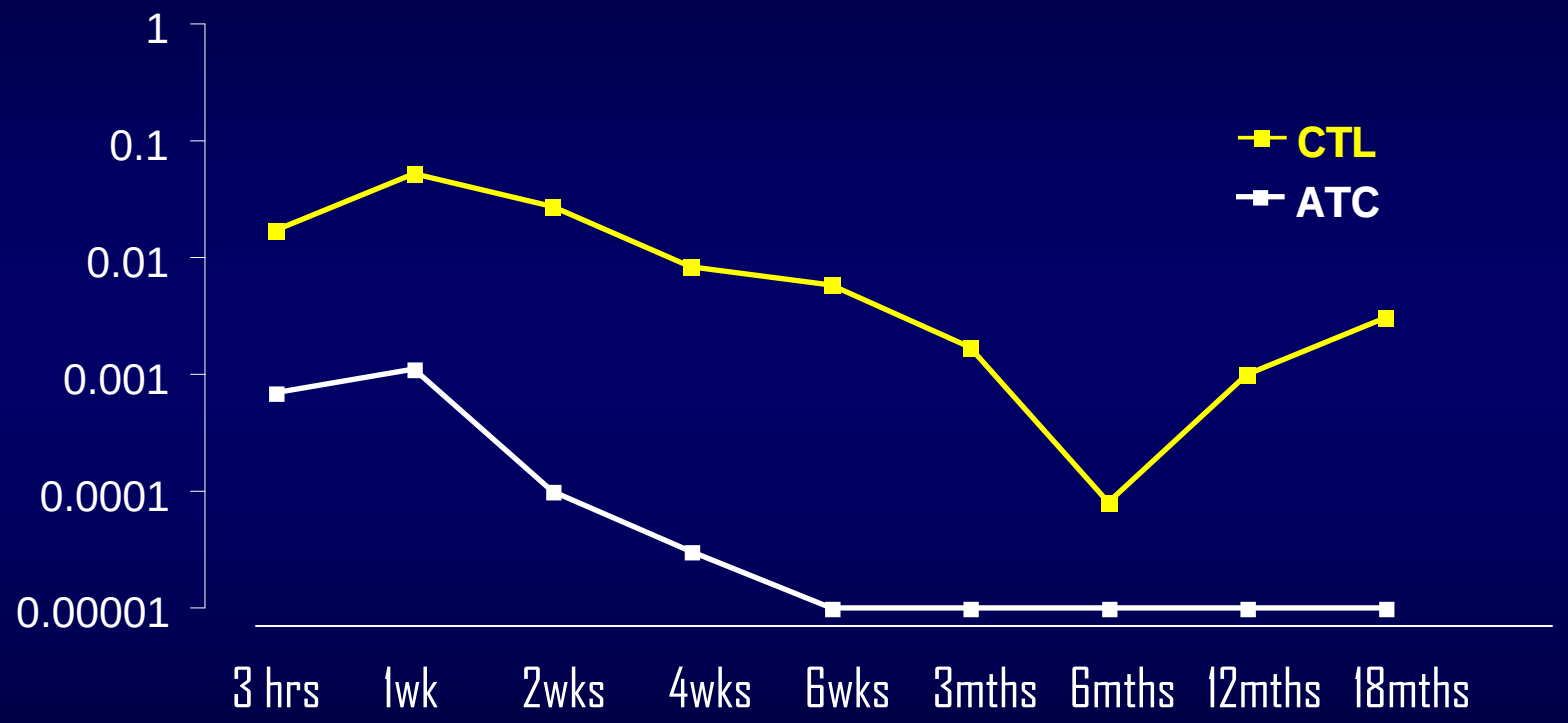
5/10 with evaluable tumors had tumor necrosis or regression; **2CR**



Pule et al. *Nat Med* 2008

NESTLES

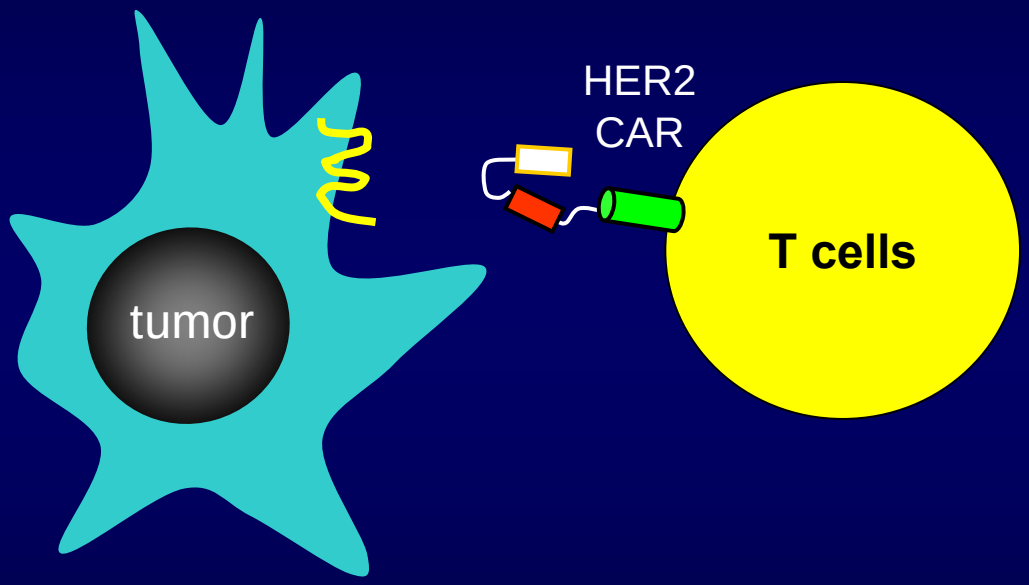
9 year old with relapsed neuroblastoma: remains in CR 18 months post T cell infusions



Now extended to 19 patients

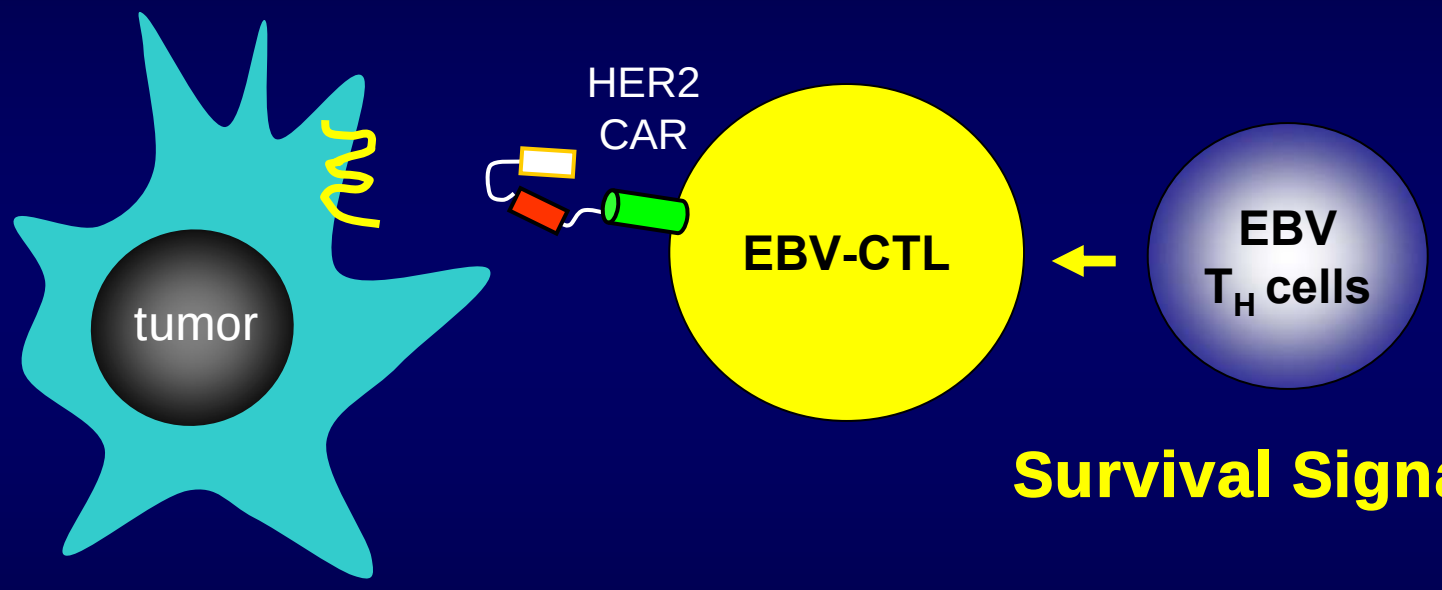
Pule et al. *Nat Med* 2008

Improving the persistence of HER2.CAR T cells



Rossig et al. *Blood* 2002; Savoldo et al. *Blood* 2007; Pule et al. *Nat Med* 2008

Improving the persistence of HER2.CAR T cells

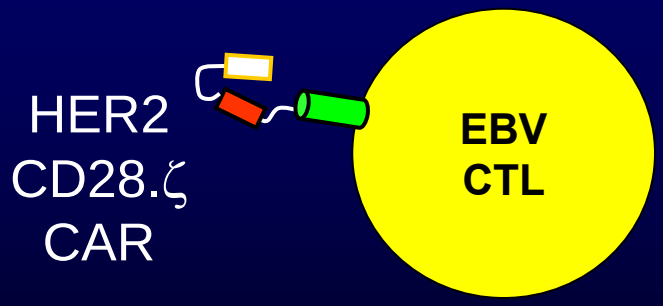


Survival Signal

Rossig et al. *Blood* 2002; Savoldo et al. *Blood* 2007; Pule et al. *Nat Med* 2008

Proposed Clinical Trial: ECHO

Administration of EBV-specific cytotoxic T cells expressing HER2 chimeric antigen receptor to subjects with advanced Osteosarcoma



ECHO: monitoring

Primary Objective:

Safety

Secondary Objectives:

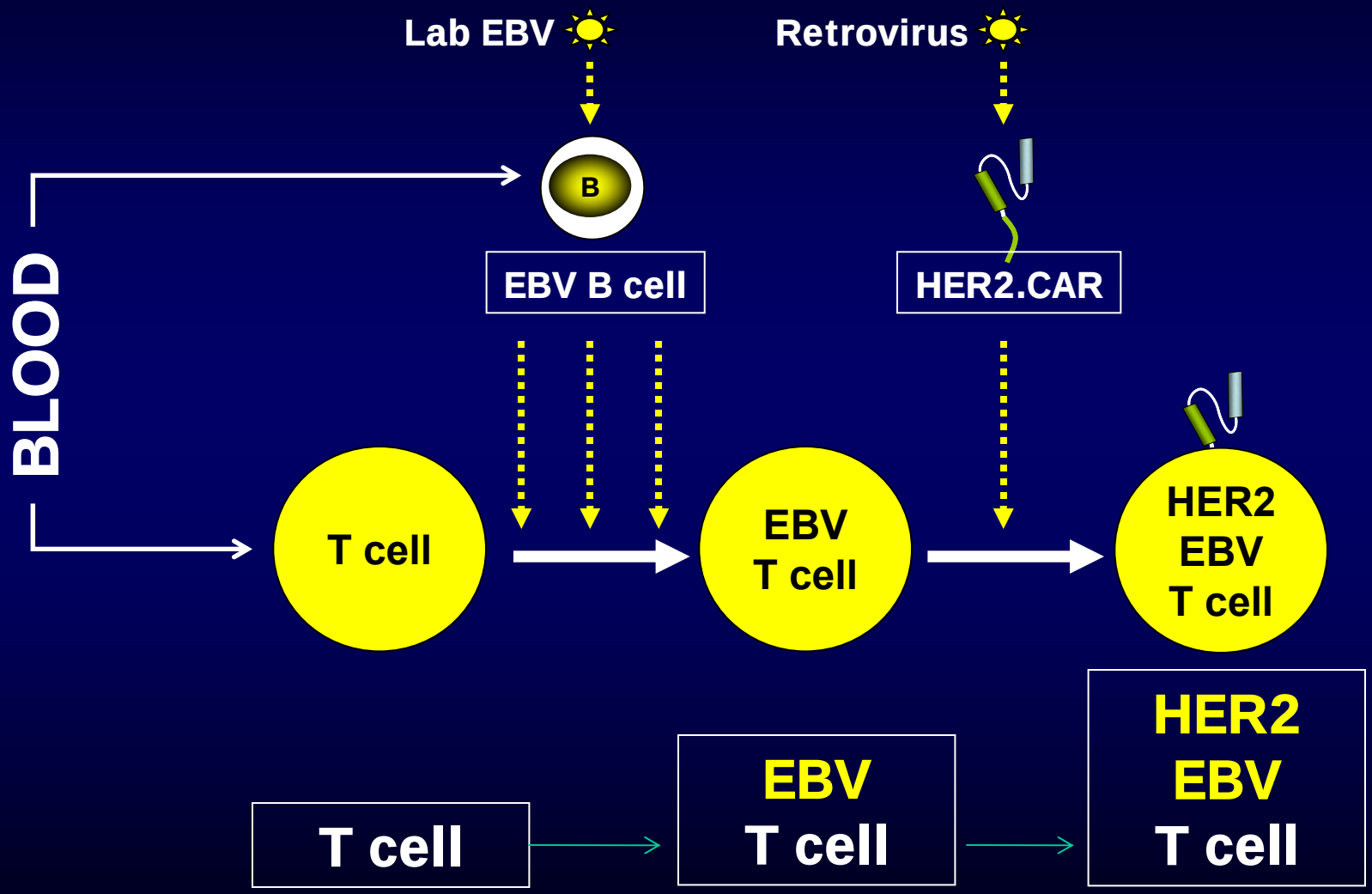
Persistence of infused cells

Anti-tumor activity of infused cells

ECHO: subjects

- **HER2-positive osteosarcoma**
  - Metastatic
  - Unresectable
  - Resistant/ recurrent
- **Failed conventional therapy**
- **EBV seropositive**
- **Performance** (Lansky/Karnofsy≥50)
- **Informed consent**

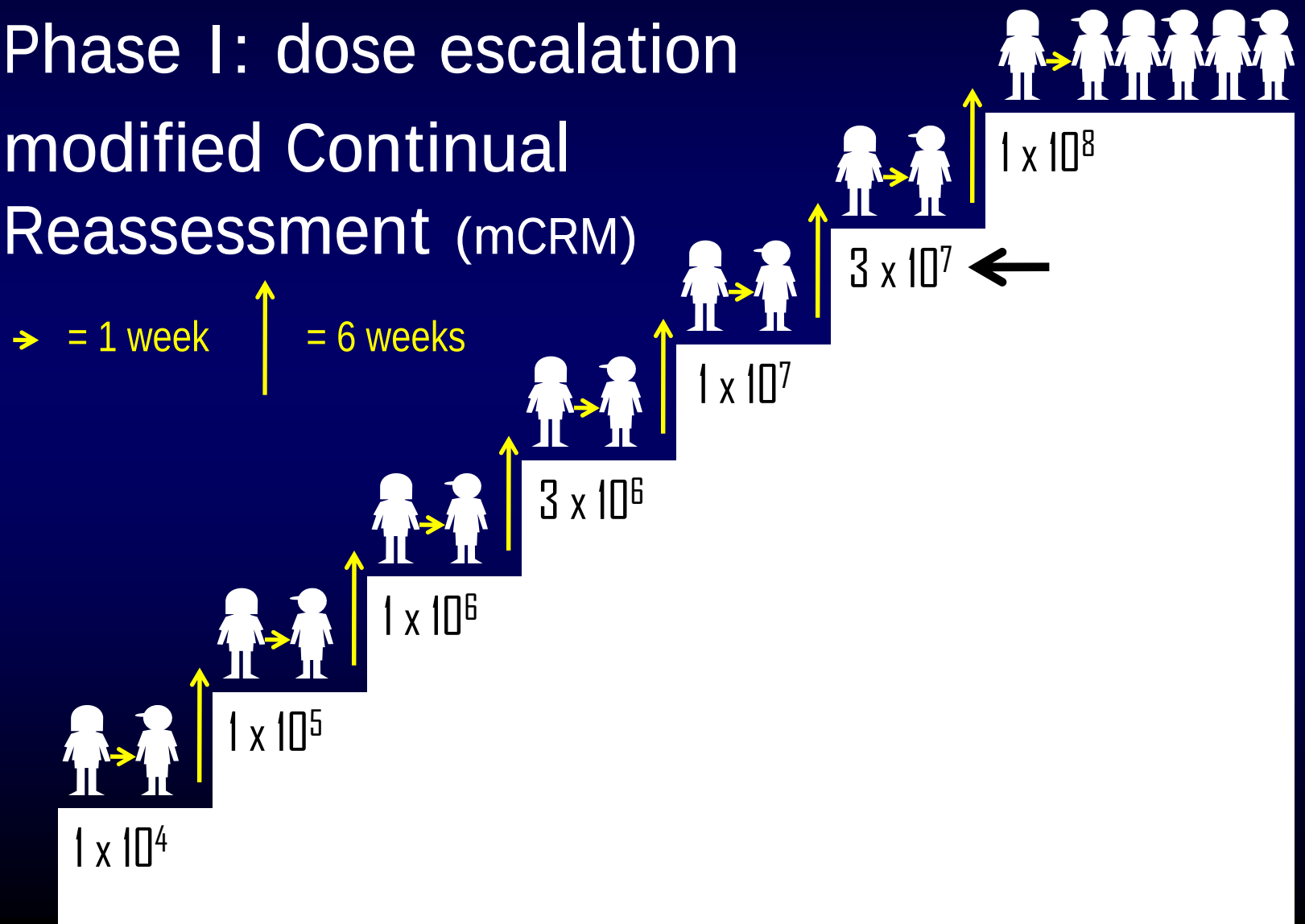
ECHO: generation of cells



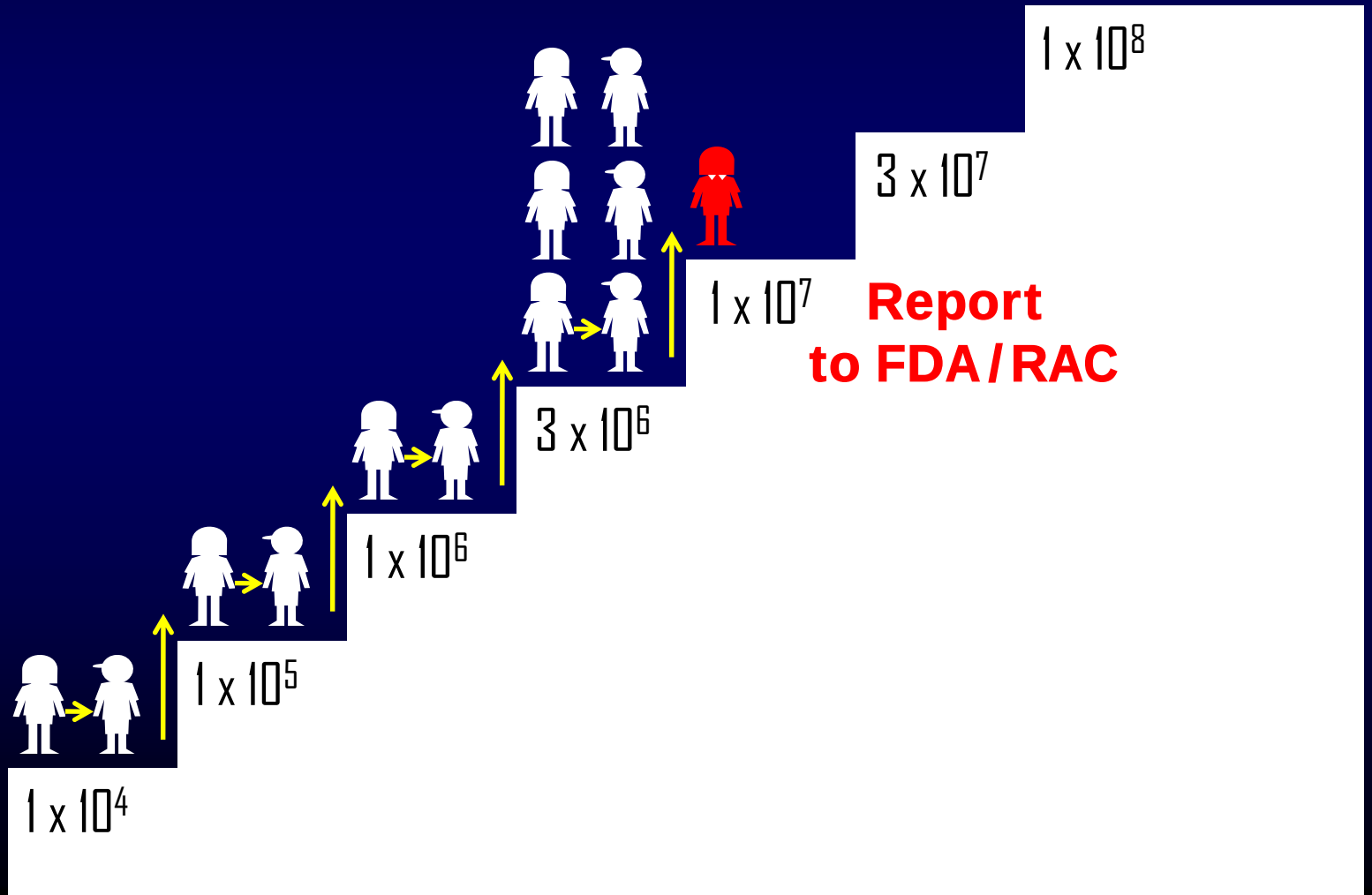
Rooney et al. *The Lancet* 1995

ECHO: trial design

- Phase I: dose escalation
- modified Continual Reassessment (mCRM)



ECHO: trial design



ECHO: Monitoring

	Study	INFUSION					Follow-up					
		Wk 0	Wk 1	Wk 2	Wk 4	Wk 6	Mth 3	Mth 6	Mth 9	Mth 12	Every 6 months x 4 years	Annually x 15 years (total)
	T cell Infusion	X										
safety	Hx	X		X	X	X	X	X	X	X	X	X
safety	PE	X		X	X	X						
safety	Performance	X		X	X	X						
safety	CBC	X	X	X	X	X	X	X	X	X	X	X
safety	Electrolytes, BUN, Cr	X	X	X	X	X						
safety	AST, Bili, Alb	X	X	X	X	X						X
safety	Pregnancy	X										
tumor and immune monitoring	T cell Function and Persistence	X	X	X	X	X	X	X	X	X	X	X
tumor and immune monitoring	RCR testing	X					X	X		X	X	X
tumor and immune monitoring	Cytokines and Chemokines	X	X	X	X	X	X					
tumor and immune monitoring	HAMA	X				X						
tumor and immune monitoring	ECHO	X				X						
tumor and immune monitoring	CT/MRI/PET	X				X						

ECHO: Risks

- **Retroviral Transduction**
  - >500 subjects received genetically modified T cells
  - No adverse effects due to gene transfer reported
- **Tumor swelling**
- **Targeting HER2**

Pule et al. *Nat Med* 2008; Bonini et al. *Nat Med* 2003

Reported Fatal Adverse Event

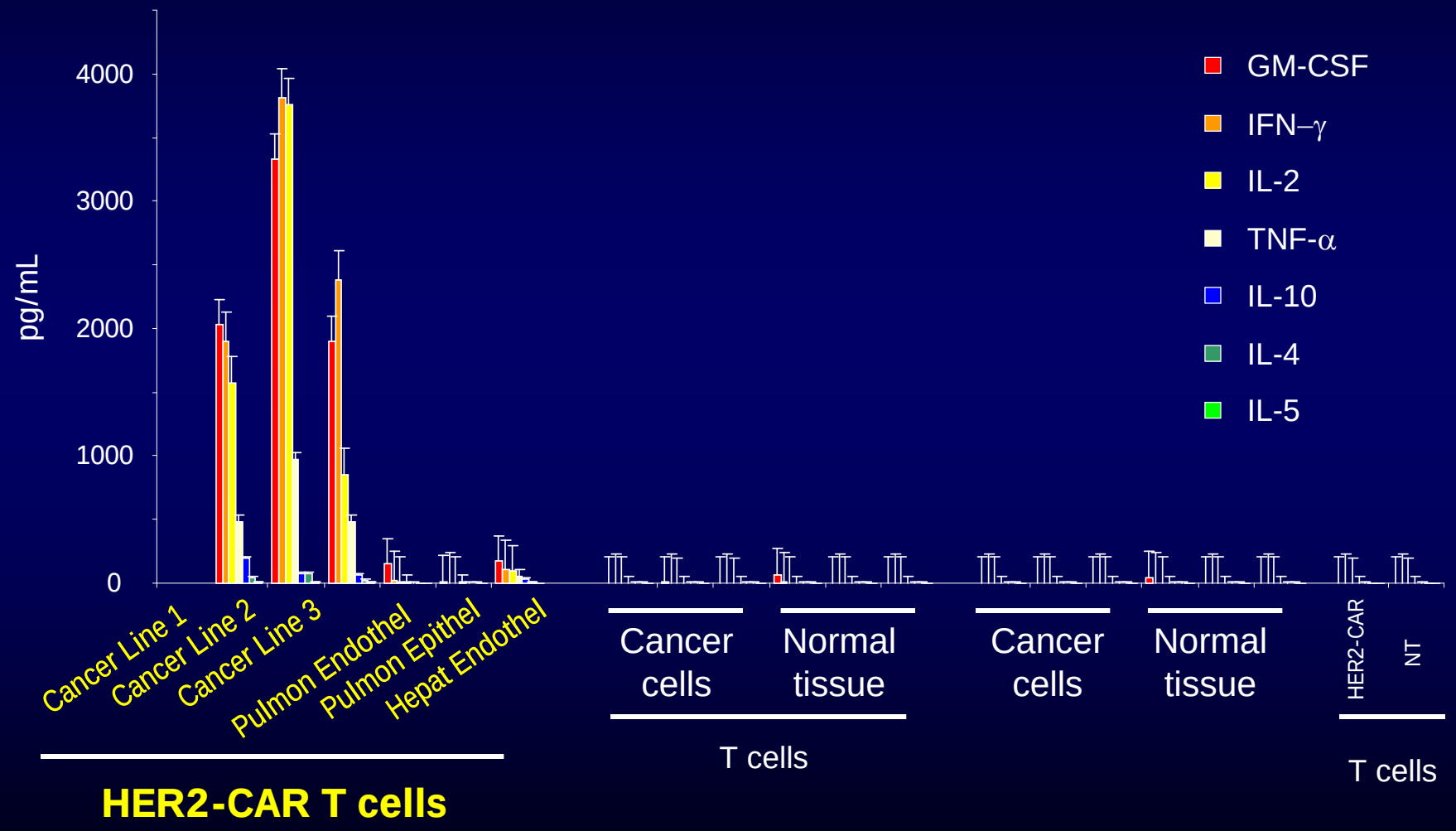
- **Patient:** 39-year-old female with colon cancer metastatic to the lungs and liver
- **Lymphodepletion:** CTX and FLUD
- **Autologous CAR T cells:**
  - CAR based on Trastuzumab (Herceptin®)
  - CD28+4-1BB+CD3.ζ signaling moieties; 79% CAR(+)
  - Intravenous infusion: $1x10^{10}$
- **Adverse Event:** severe dyspnea ~15 min; pulmonary edema; acute respiratory failure; died day+5 despite intensive medical management
- **Cytokine storm:** IFNγ, GM-CSF, TNFα, IL-6, IL-10

RAC webcast, 12.2009; Morgan et al. Mol Ther 2010

ECHO: a different risk profile

- **Cell dose:** starting at 1,000,000 fold less ($1x10^4$-$1x10^8$)
- **Trial design:** mCRM escalation
- **CAR:** CD28+CD3.ζ signaling moieties (no 41BB)
- **No lymphodepletion**

Preclinical Safety Studies



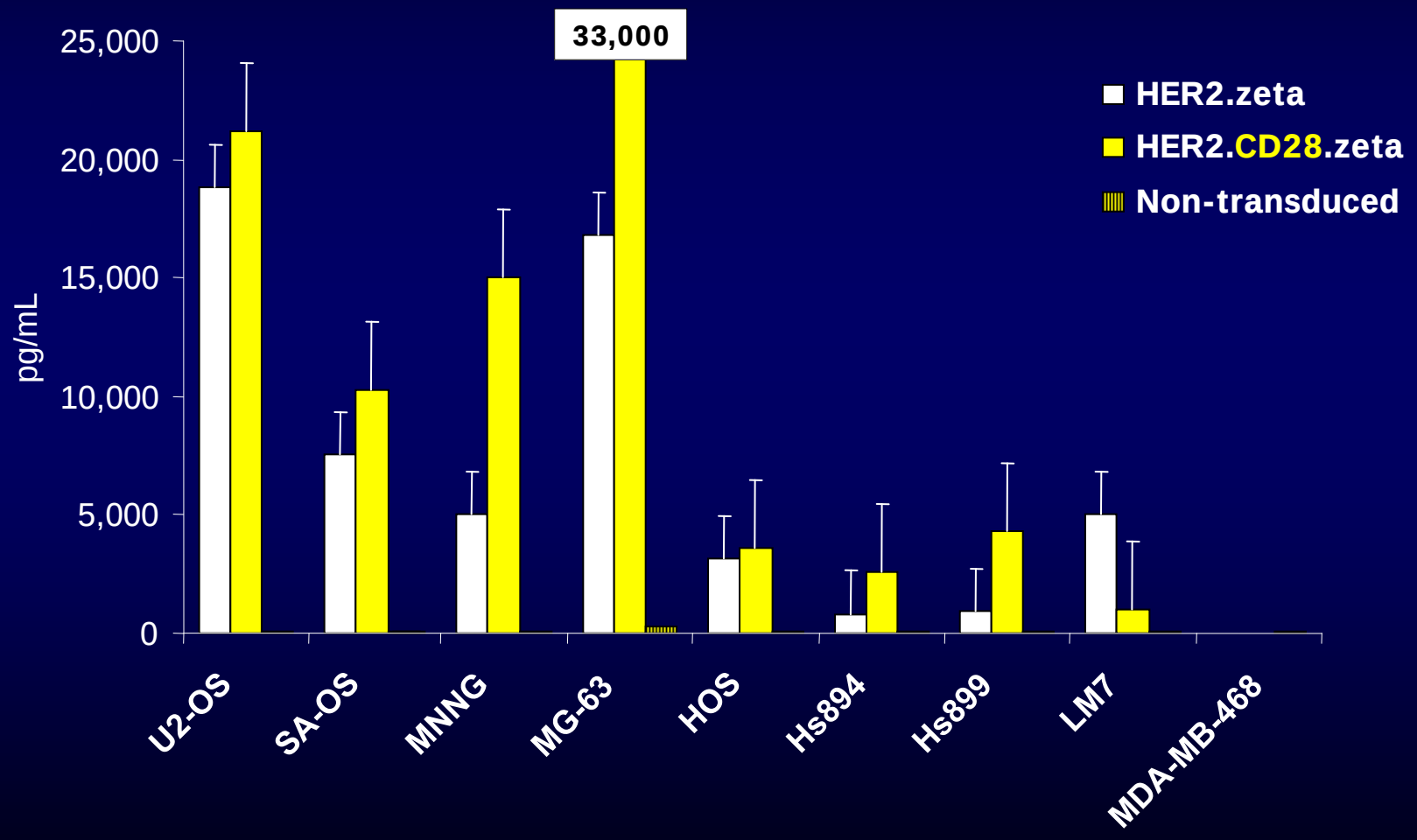
HERCREEM
HER2.CAR and TGFβ DNR for HER2-positive Lung Malignancy

FDA IND 14036
RAC 0903-971

- PI: Stephen Gottschalk, MD
- Treated 2 patients
- Dose: $1x10^4$-$1x10^7$
- No immediate toxicity observed

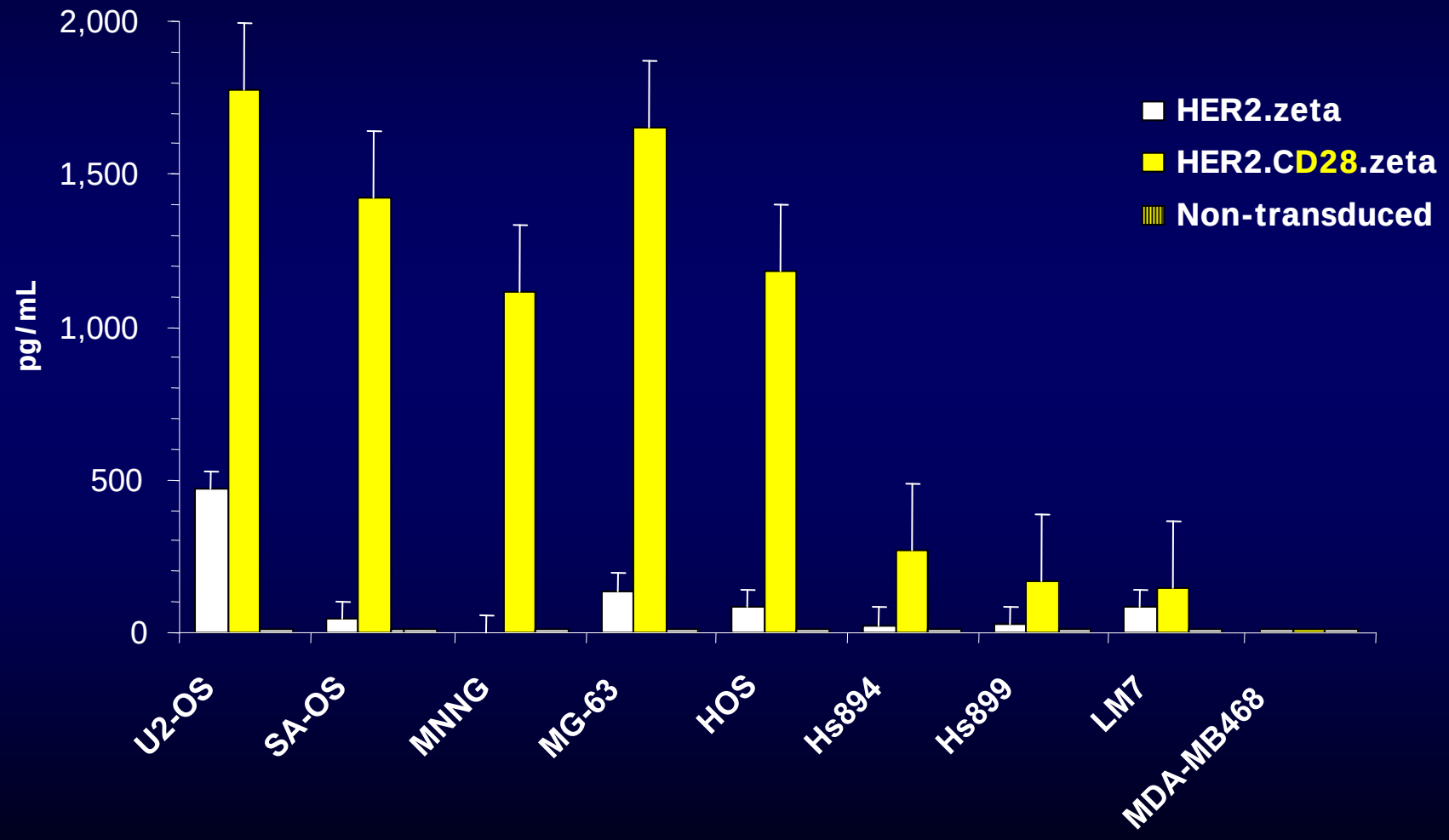
Questions

HER2-T cells are activated: secrete IFN-γ*



* 3 experiments; two donors

Better IL-2 secretion with 2nd Generation HER2 CAR*



* 3 experiments; two donors

ECHO: consent and assent

- IRB: Baylor College of Medicine
- Experimental nature
- No efficacy is guaranteed
- Toxicities may occur
- Right to withdraw
- Full confidentiality

ECHO: assent

- **Appropriately solicit for the child's assent**
- **Capability** age, cognitive and psychological maturation
- **Amount and complexity of information** will depend on age group
- **Documented in consent** "If your child is the one asked to take part in this study, you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that your child understands and agrees to take part in this study according to his or her understanding"
- **The child will not sign**

HER2-specific T cell Reports

- HER2 **vaccine** studies, which included more than 180 subjects
- Adoptive transfer of **HER2-specific T cells** has been reported in seven patients
  - $1x10^4x10^{10}$ cells
  - Six patients had no side effects
  - One lethal AE: 10^{10} cells

Mittendorf EA et al. Can Imm Immunother. 2008; Bernhard H et al. Cancer Immunol Immunother 2008; Disis M et al. JCO 2009; Rosenberg SA. : RAC webcast, 12.2009; Morgan et al. Mol Ther 2010