Personalized Medicine

Adoptive therapy with engineered T-cells

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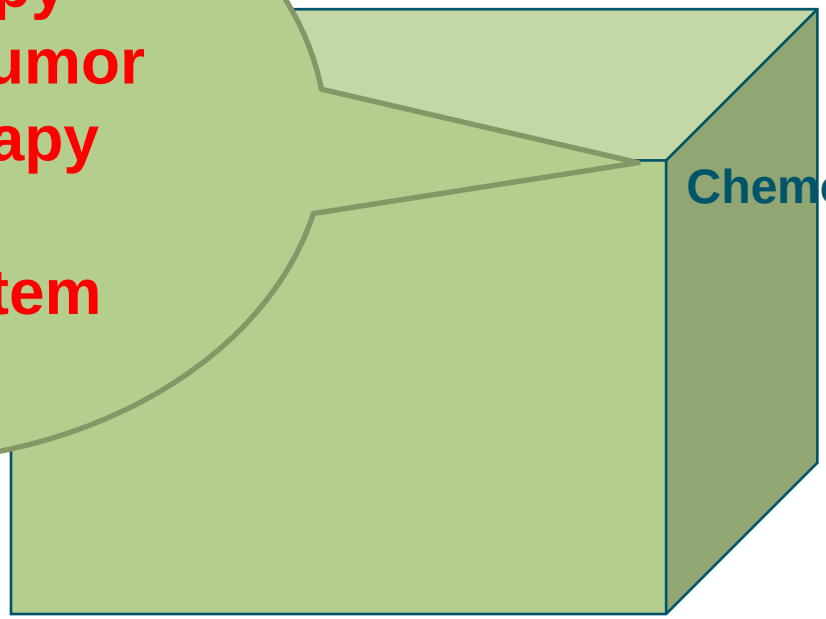
September 29, 2014

Combinatorial Cancer Immunotherapies: Many possibilities

- **Chemotherapy targets the tumor**
- **Immunotherapy targets the immune system**



Targeted Small Molecule Drugs

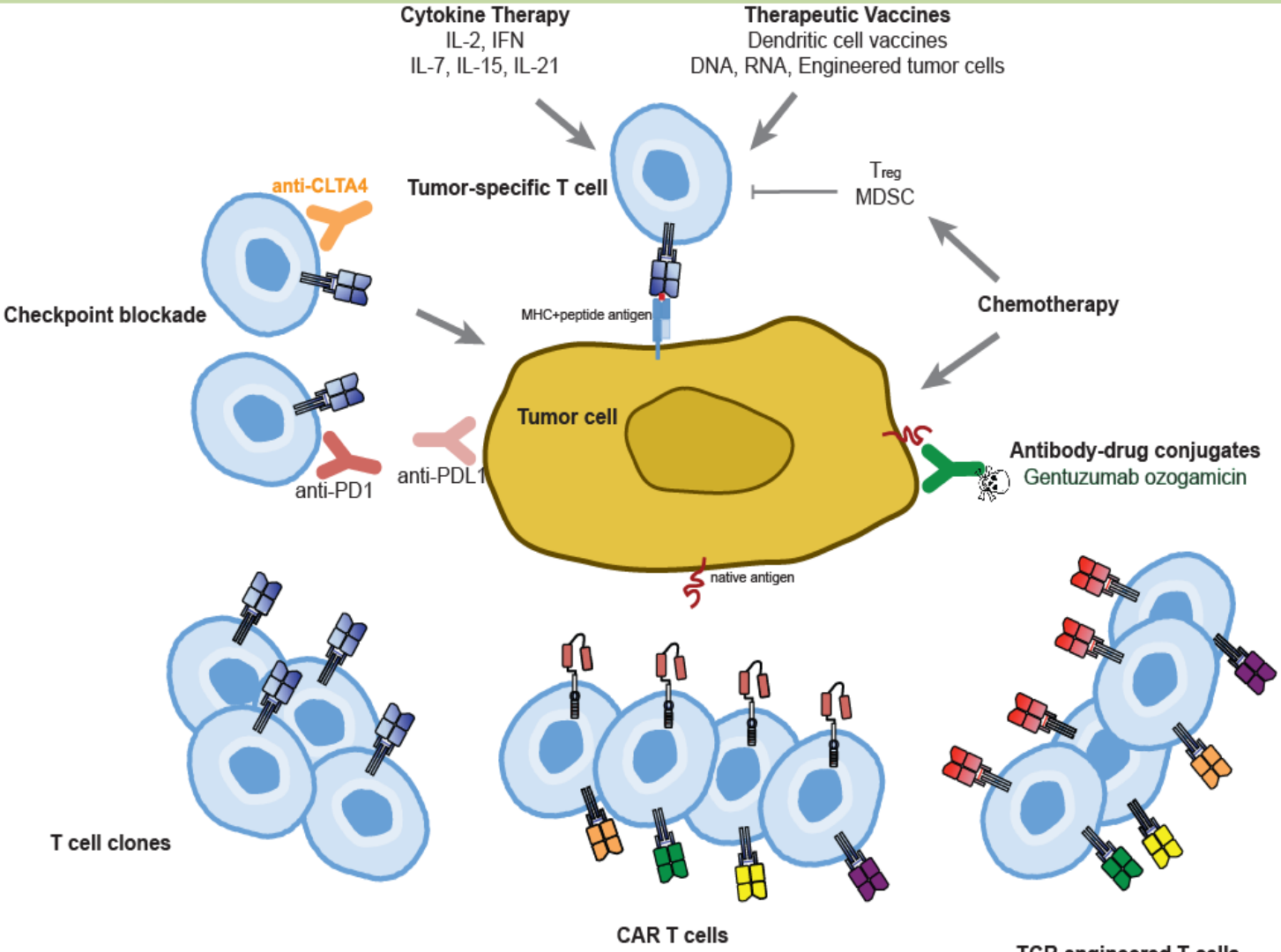
Chemotherapy

Radiation

Antibodies

Cell Based Therapies

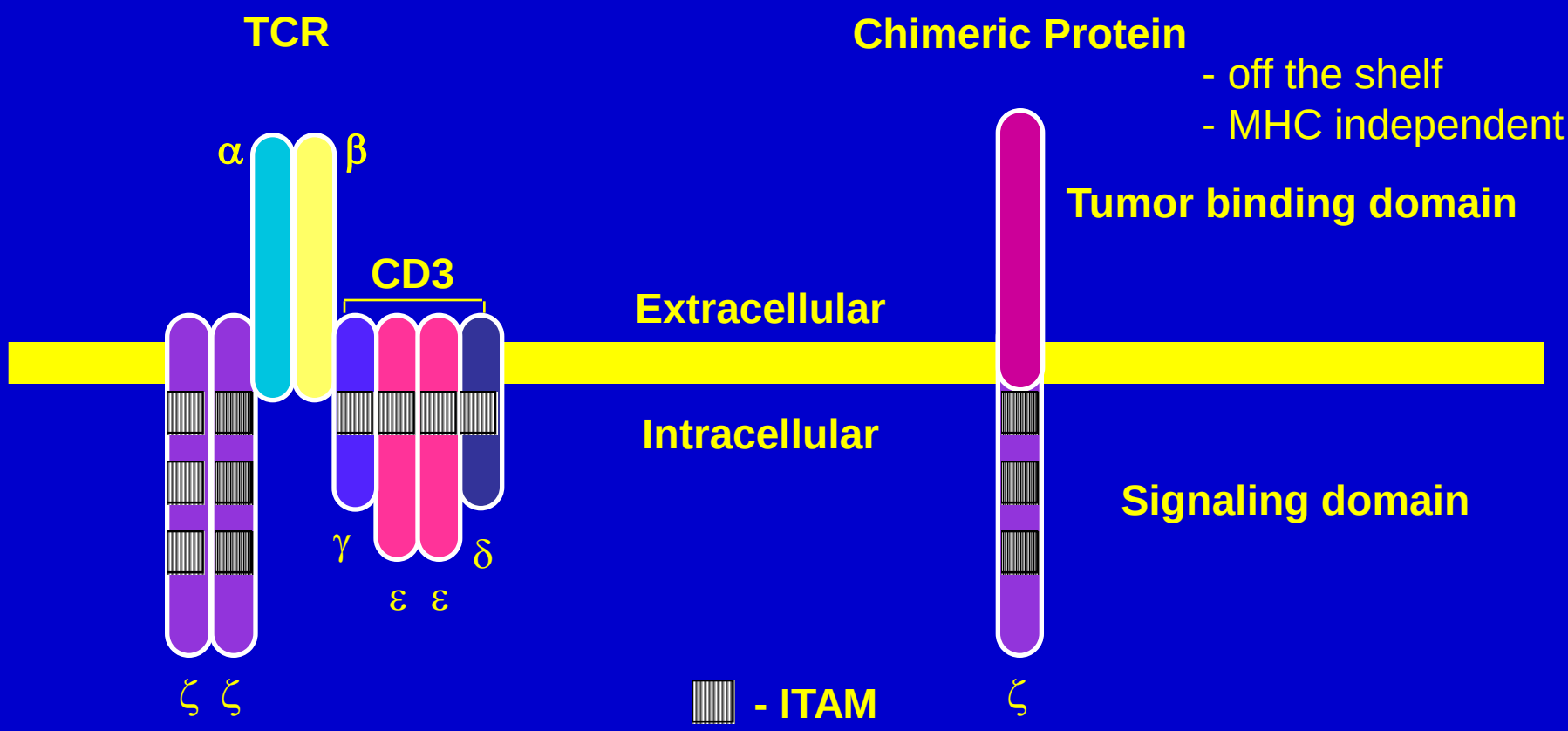
Approaches to Overcome Tolerance



Maus MV et al. Blood. 2014;123:2625-2635.

Using Synthetic Biology to Overcome Tolerance
Creation of Bi-specific T cells

TCR heterodimer approach "CAR" or T body approach

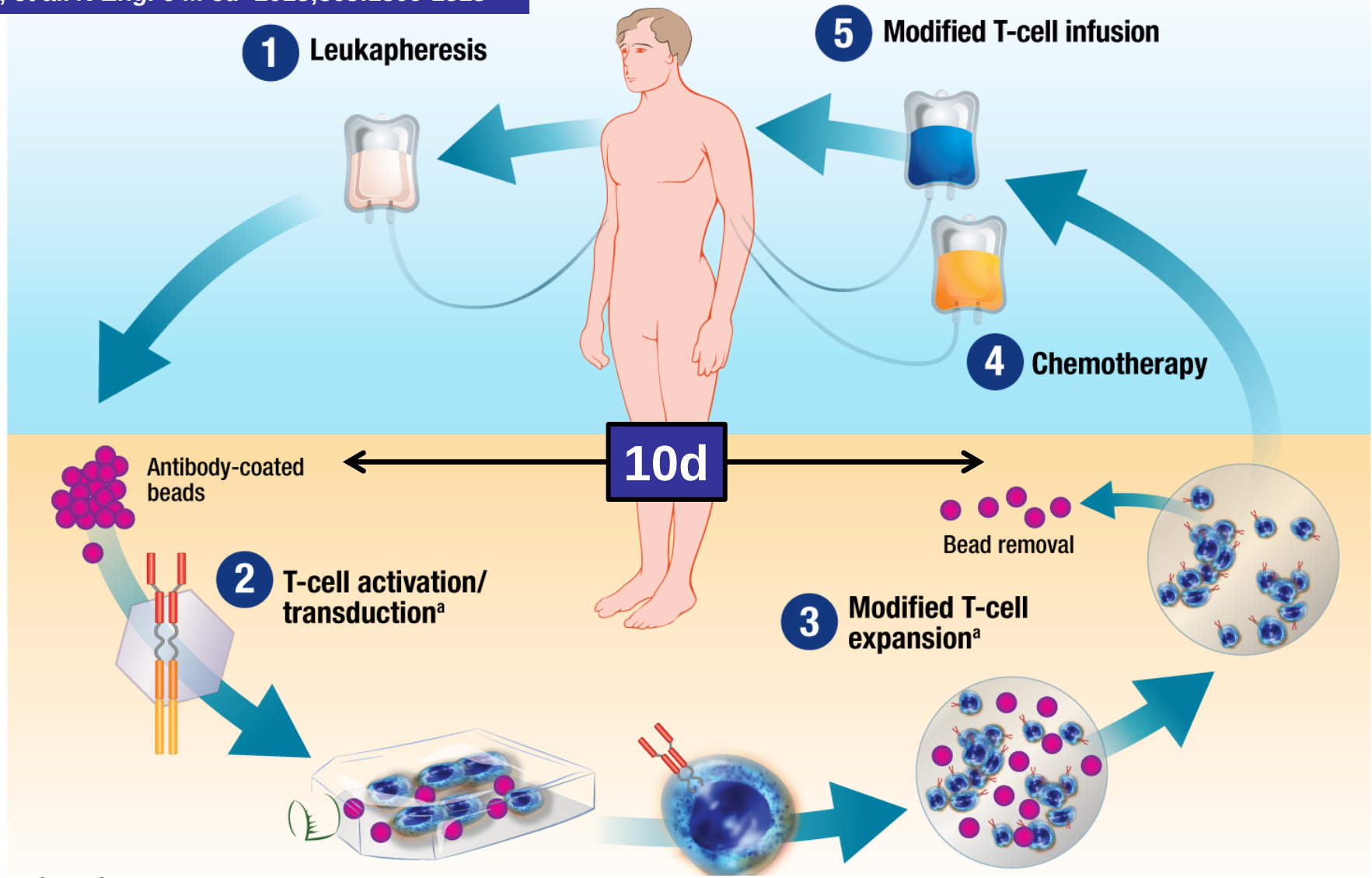


Considerations for T Cell Therapy

- 1 kg of tumor = 10^12 cells
- Our first 3 patients had 3 to 7 lbs of tumor!
- It is not realistic to expect tumor eradication unless the killing machinery (T, NK, macrophage) is equivalent to tumor burden. i.e. "E:T" ratio ~= 1
- Failure to achieve critical mass of T cells explains previous trials with disappointing results
- Two potential solutions:
  - Infuse huge numbers of T cells (TILs)
  - Infuse small numbers of T cells programmed to divide

CART19 CLL Study Overview*

Porter DL, et al. *N Engl J Med*. 2011;365(8):725-733
Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73
Grupp S, et al. *N Engl J M ed* 2013;368:1509-1518



* ClinicalTrials.gov #NCT01029366

CART19 CLL: Generalities on First 3 Treated Patients

- All 3 patients had Chronic Lymphocytic Leukemia (CLL)
  - ✓ Late stage incurable leukemia
  - ✓ 3.5-7 pounds of tumor/patient
- Each infused CAR T cell or its progeny

  killed more than 1000 tumor cells: CARs are “Serial Killers”
- Remissions durable to date
- Sustained antibody delivery with a single infusion

  of engineered T cells (beyond 3+ yrs)

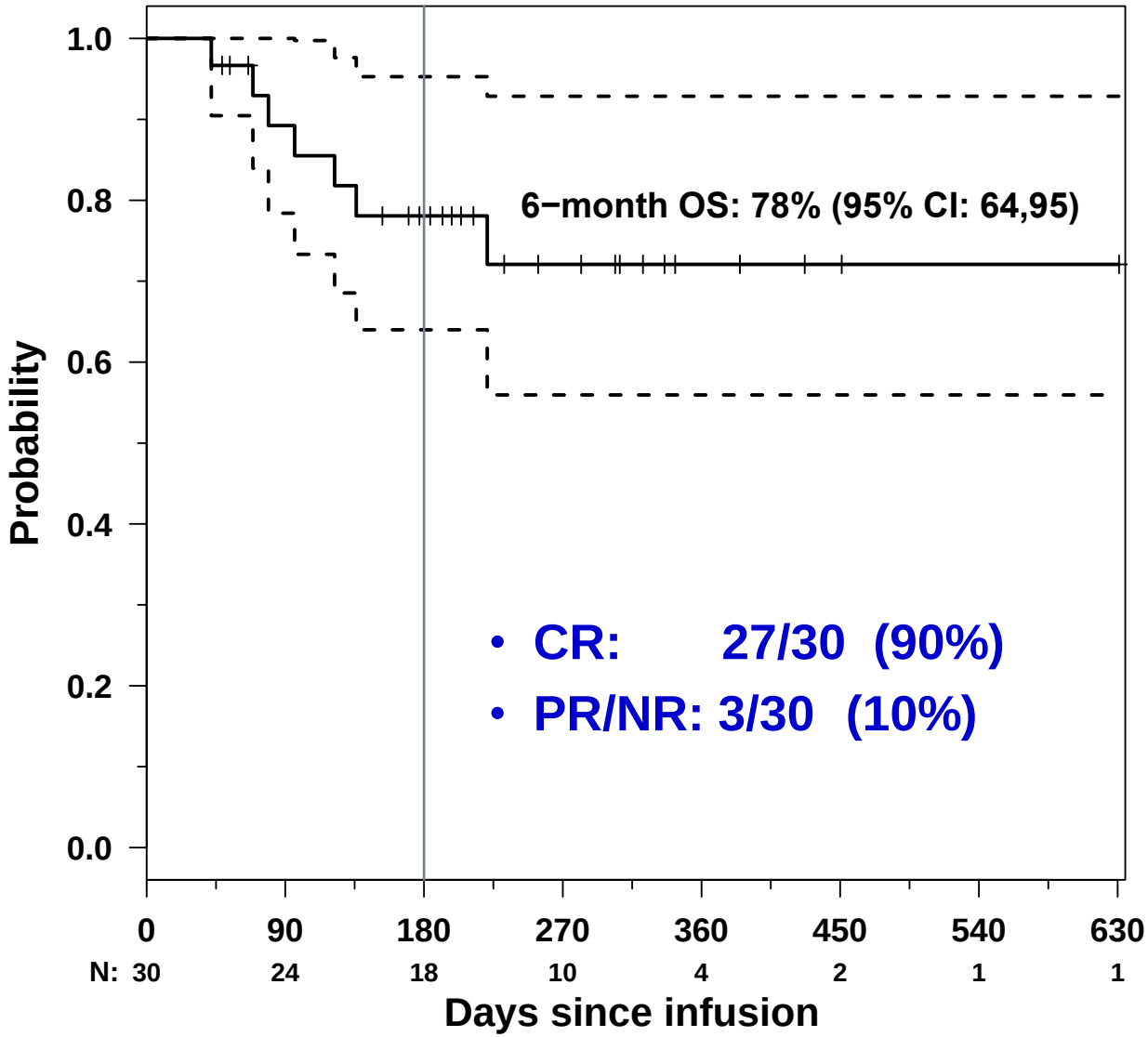
Porter, D.L. et al.. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia New England Journal of Medicine 365:725-733.

Kalos, M., et al . 2011. T cells expressing chimeric receptors establish memory and potent antitumor effects in patients with advanced leukemia. Science Translational Medicine 3:95ra73.

Clinical Update of Pediatric and Adult ALL Patients Treated with CART19

	Pediatric Cohort N=25	Adult Cohort N=5	Total N=30
Sex			
Female	11 (44%)	1 (20%)	12 (40%)
Male	14 (56%)	4 (80%)	18 (60%)
Age at Infusion	11 (5, 22)	47 (26, 61)	14 (5 ,61)
Median (range)			
Race			
African American	1 (4%)	1 (20%)	2 (6.7%)
Asian	2 (8%)		2 (6.7%)
Caucasian	21 (84%)	4 (80%)	25 (83.3%)
Pacific Islander	1 (4%)		1 (3.3%)
Post Allogeneic Transplant			
Yes	18 (72%)	0 (0%)	18 (60%)

Summary of CART19 Efficacy in ALL (n=30)
Case mix on phase I: 25 pediatric and 5 adult
NEJM 2014 (in press)



Potential Roles of CAR T Cells for ALL

- Consolidate patients with MRD
- Reinduce remission
- Produce MRD (-) state prior to allo SCT
- “Bridge” to SCT
- Multicenter phase II trials in pediatric ALL (Novartis): NCT02228096

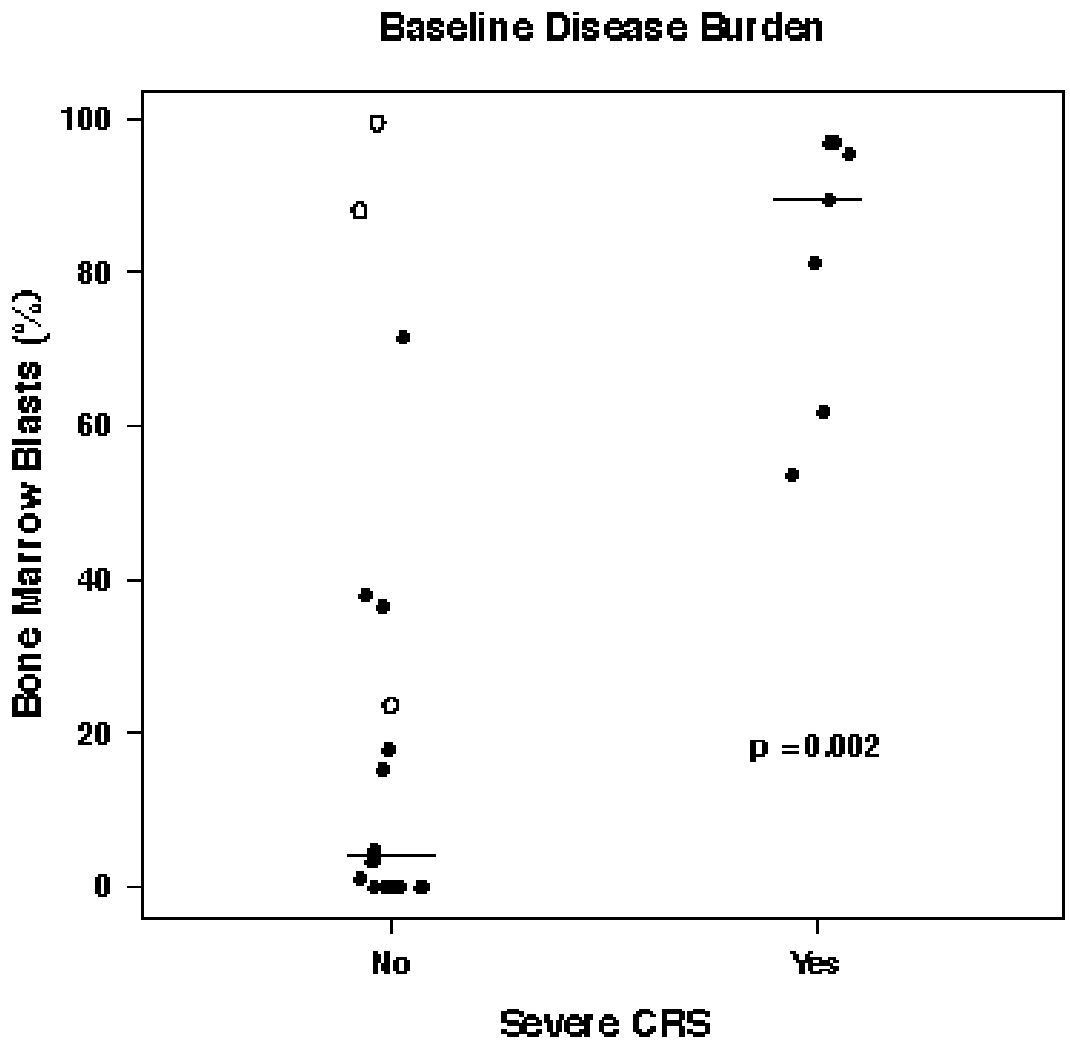
- With adequate persistence, CAR T cells may replace bone marrow transplants:

  - cancer “stem” cells can persist >1 decade

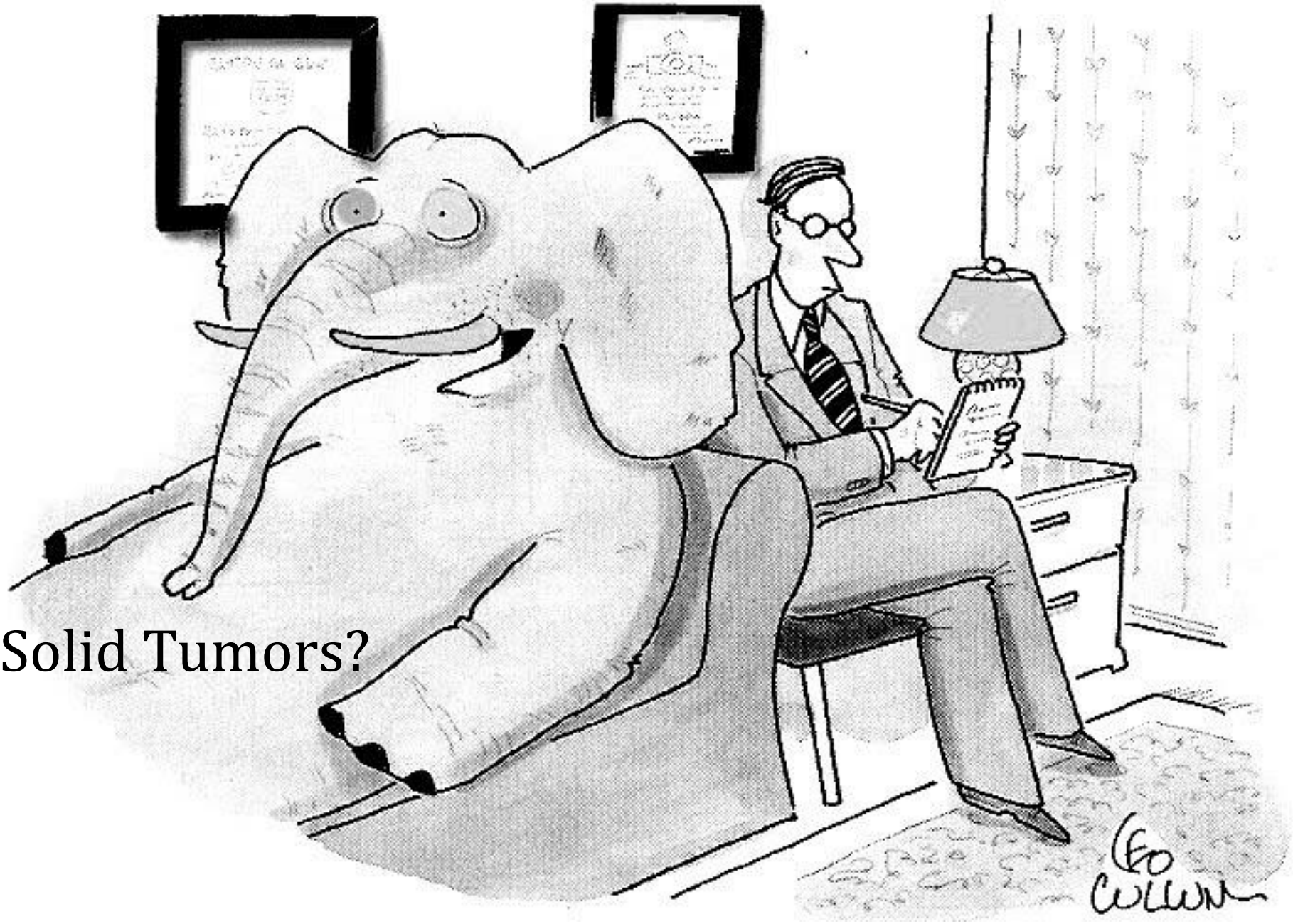
CART19 Toxicities

- **B cell aplasia**
  - **observed in all responding patients to date**
  - **managed with replacement therapy**
- **Tumor lysis syndrome (TLS)**
  - **may be delayed for 20 to 50 days post infusion**
- **Cytokine release syndrome (CRS)**
  - **reversible, on-target toxicity**
  - **Severity related to tumor burden: Treat MRD as outpatient?**
- **Macrophage activation syndrome (HLH / MAS)**
  - **elevated serum ferritin (>500,000 ng/ml), CRP, D-dimer**
  - **elevated cytokines: IL-6, IFN-gamma**
  - **Reversed with tocilizumab**

Disease burden is well-correlated with grade 4 CRS (r/r pre-B cell ALL)



Maude et al, NEJM 2014, in press



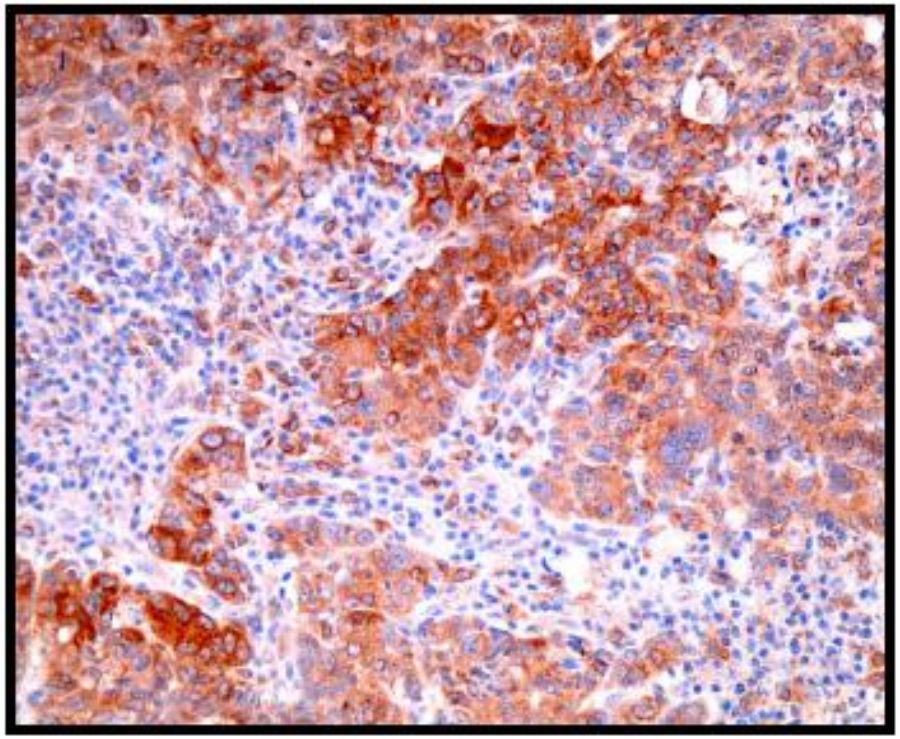
I'm right there in the room, and he doesn't even acknowledge me

Beyond leukemia and lymphoma: engineered T cells for other cancers

- Numerous CARs targeting various surface molecules are being developed for many cancer histologies
- Examples:
  - EGFRviii for glioblastoma
  - PSMA for prostate cancer
  - Mesothelin for ovarian, pancreatic cancer and mesothelioma
  - C-Met phase 0 trial for TNBC
  - Her2/neu (c-erB2) for breast and other carcinomas
  - FAP to target tumor stroma
- Key challenges and solutions

Expression of c-Met in Triple Negative Breast Cancer (TNBC)

C-Met expression on tumor cells (%)	TNBC (n=38)		ER+ BC (n=18)	
	n	%	n	%
0	11	29	8	36
3-5	3	8	0	0
10-25	9	24	1	5
30-40	5	13	2	9
50-90	10	26	7	32

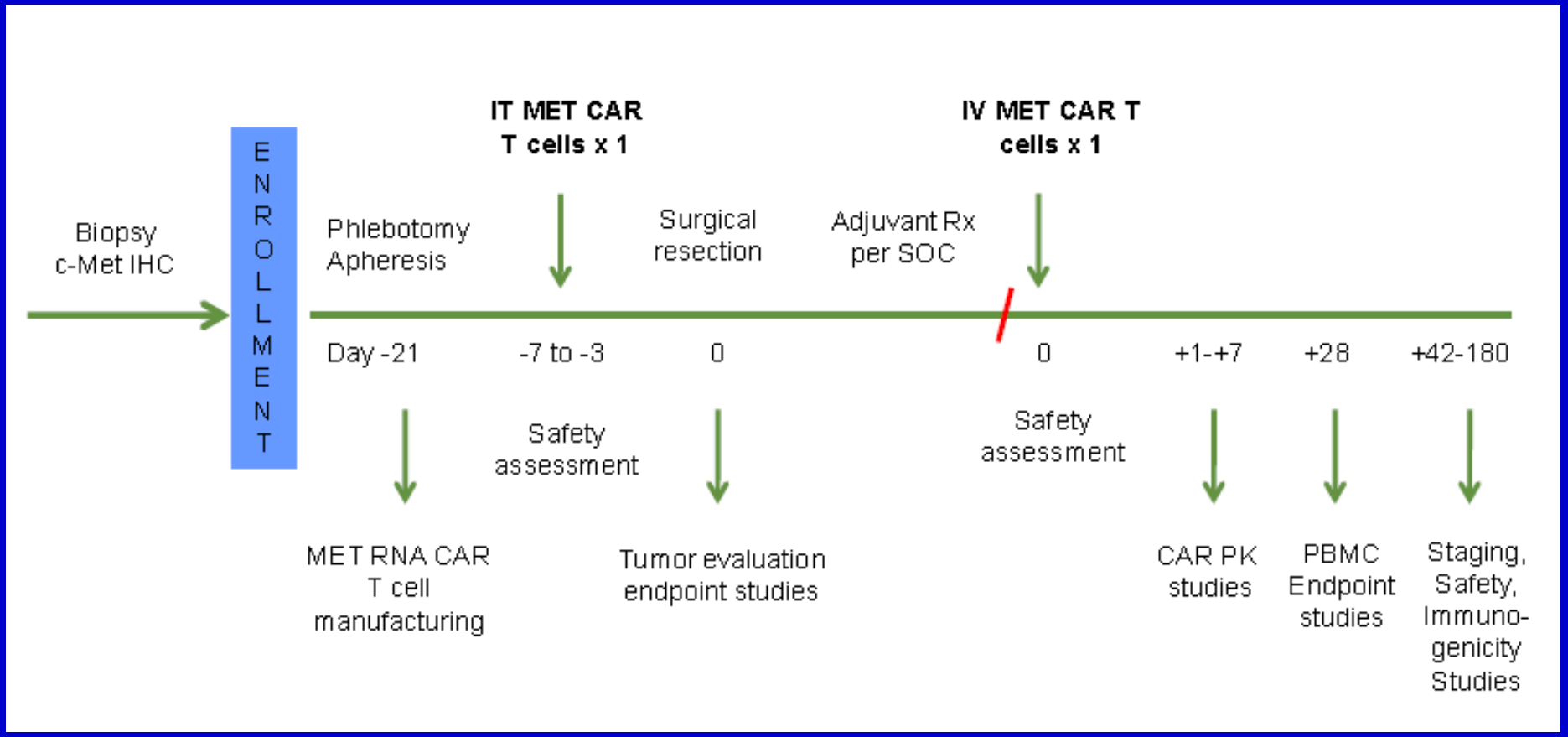


c-Met+ TNBC

* IHC performed on paraffin sections

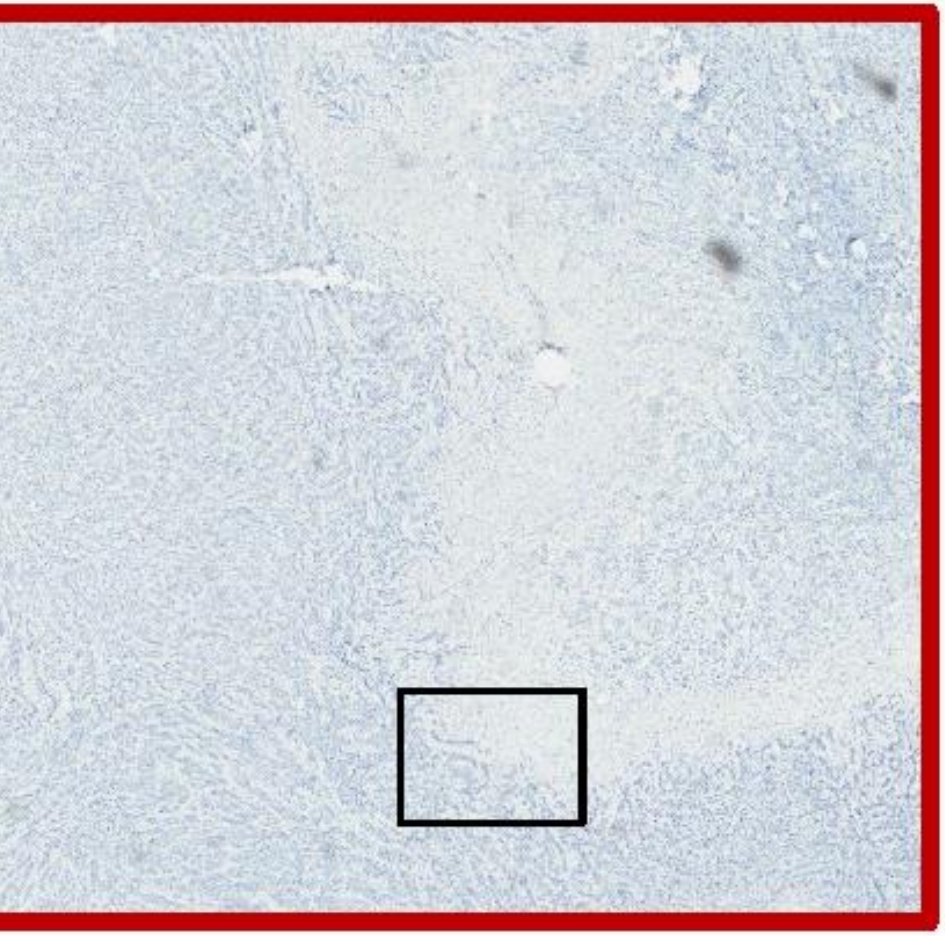
39% of TNBC are strongly c-Met+

Phase 0 CAR T Cell Protocol for Triple Negative Breast Cancer (TNBC)

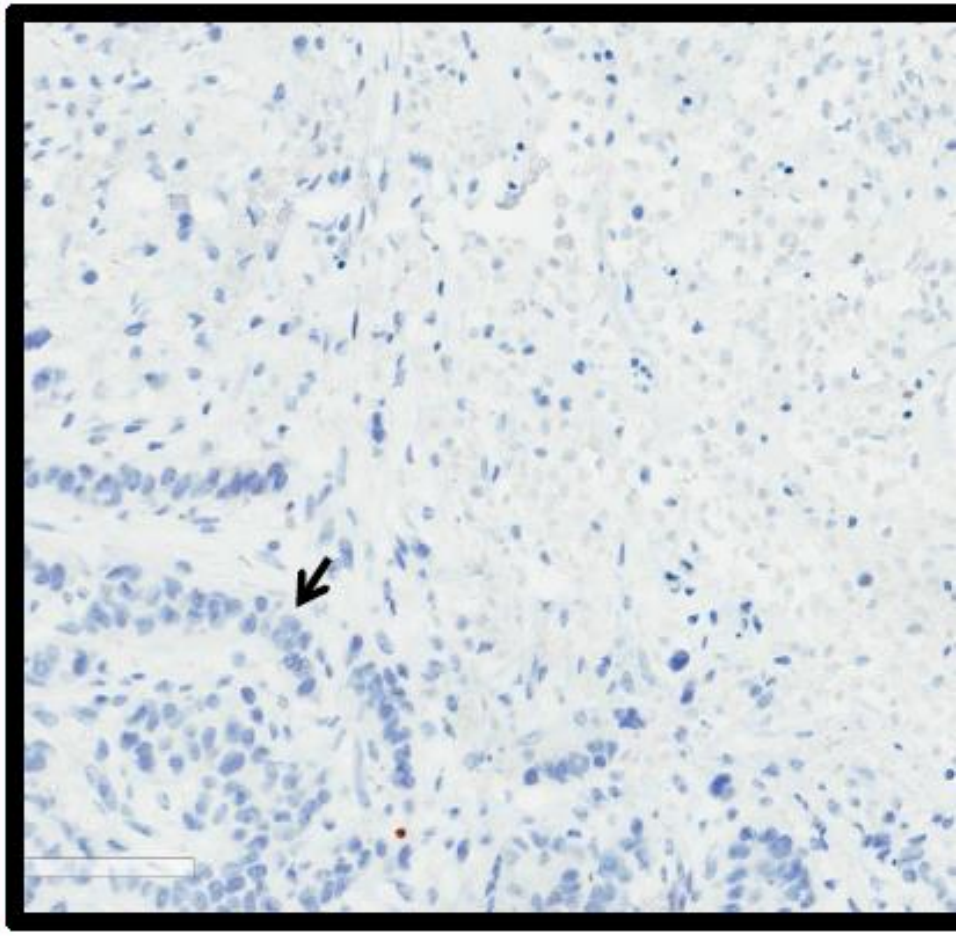


Breast cancer tissue histology 2 days post intratumoral (IT) injection with c-met RNA CAR T cells

13111-003 – hematoxylin stained



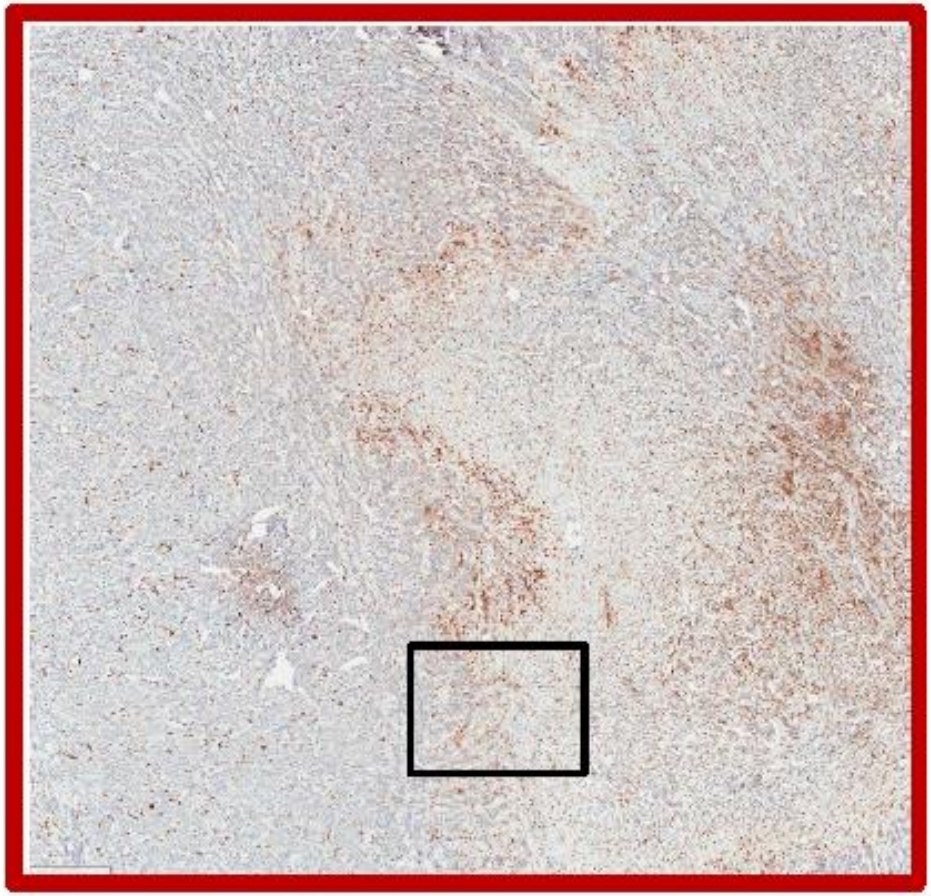
Hematoxylin stain, 2X; note representative IT injection site/tumor interphase in inset area



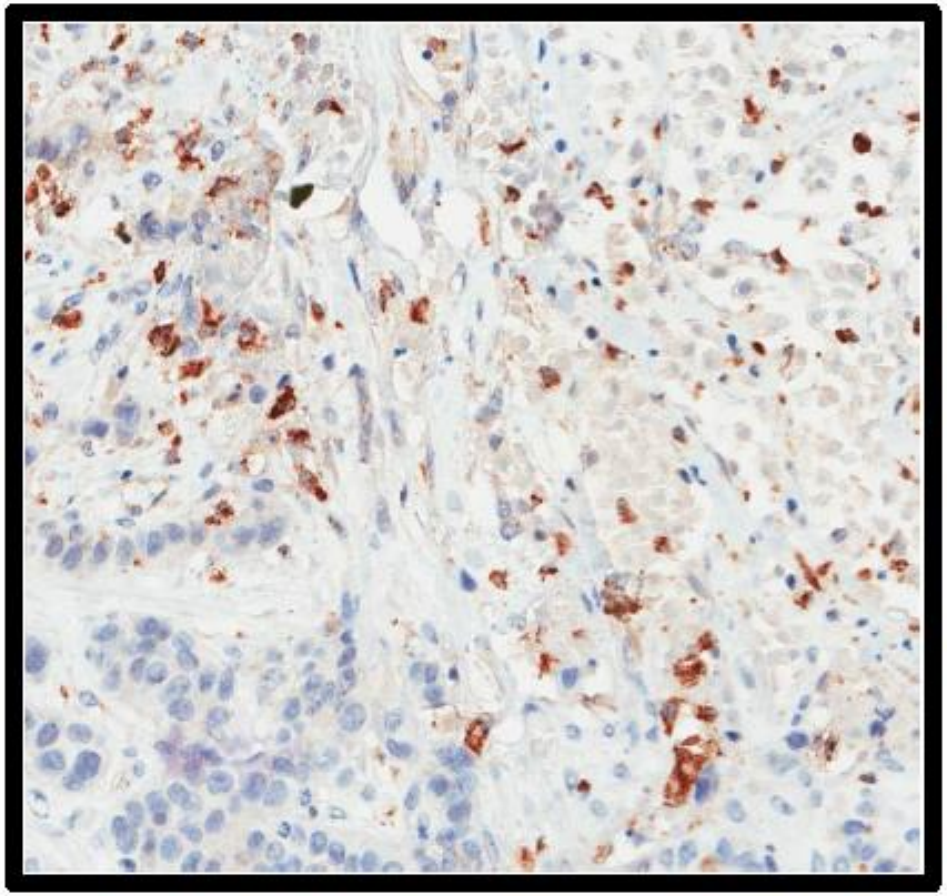
Inset, 20x magnification; note necrotic tumor in upper portion while intact tumor cells are noted in lower left as marked by arrow

Breast cancer tissue histology 2 days post intratumoral injection with c-met RNA CAR T cells

13111-003 – CD68 IHC stain



CD68 IHC stained tumor tissue, 2X; inset: IT injection site/tumor interphase



Inset, 20x magnification; note abundant CD68 (+) cells within injection site (arrow). Rare CD68 (+) cells are also noted within adjacent tumor tissue.

CAR T Cells: Summary

- CAR T cells have potent antitumor effects in leukemia and lymphoma. Multicenter trials are underway
- Numerous CARs targeting various surface molecules are being developed for many cancer histologies:
  - EGFRviii for glioblastoma
  - PSMA for prostate cancer
  - Mesothelin for ovarian, pancreatic cancer and mesothelioma
  - C-Met phase 0 trial for TNBC

CAR Trials: Colleagues and Collaborators

ACC Translational Research

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ACGT ALLIANCE FOR CANCER GENE THERAPY
National grants for cancer research

The Leukemia & Lymphoma Society®
Fighting Blood Cancers