Society for Immunotherapy of Cancer (SITC)

Current Status of Chimeric and Adoptive T cell Therapy

Lawrence G. Lum, MD, DSc
Karmanos Cancer Institute and Wayne State University
Advances in Cancer Immunotherapy™
Dearborn, MI
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CAR-T Slides Generous Gift courtesy of Carl H. June and UPENN Group

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Outline

1. Tumor Microenvironment Considerations
2. Adoptive T cell Therapies
3. Clinical experience with CAR-T and BATs
4. Challenges for T cell Therapies
5. Future Directions

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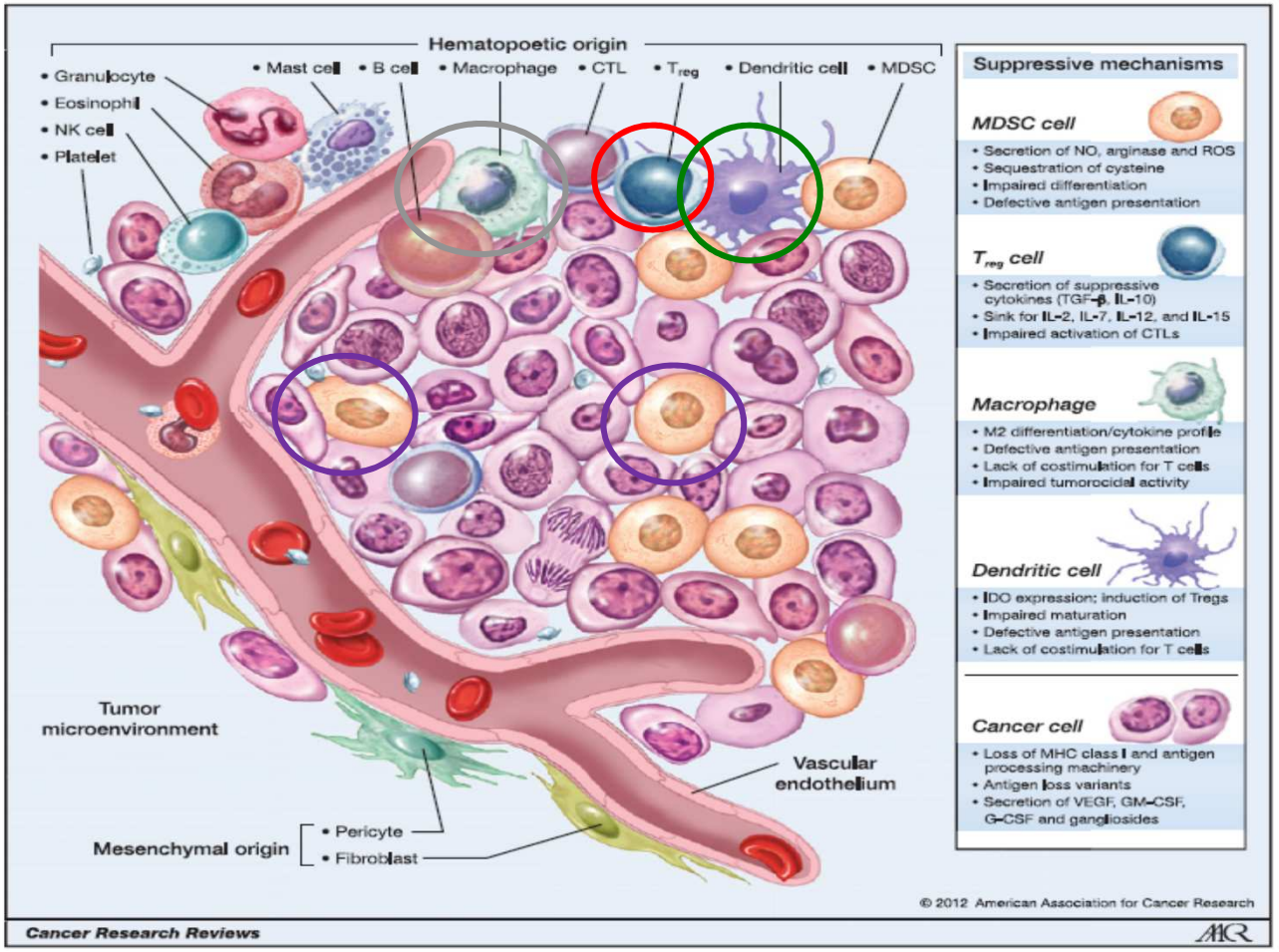
The Yin & Yan of the Tumor Microenvironment



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Challenges: Cytokines, Regulatory Factors, and Cells that Limit Immunotherapy Approaches

Immunosuppressive cytokines

- **TGF-β,**
- **IL-10**
- **IL-6**

Negative regulatory factors

- **CTLA-4**
- **PD-1**
- **TIM-3**
- **LAG-3**

Immune suppressive cells

- **T regulatory cells (Tregs)**
- **Myeloid derived suppressive cells (MDSC)**
- **Tumor associated macrophages (TAMs)**

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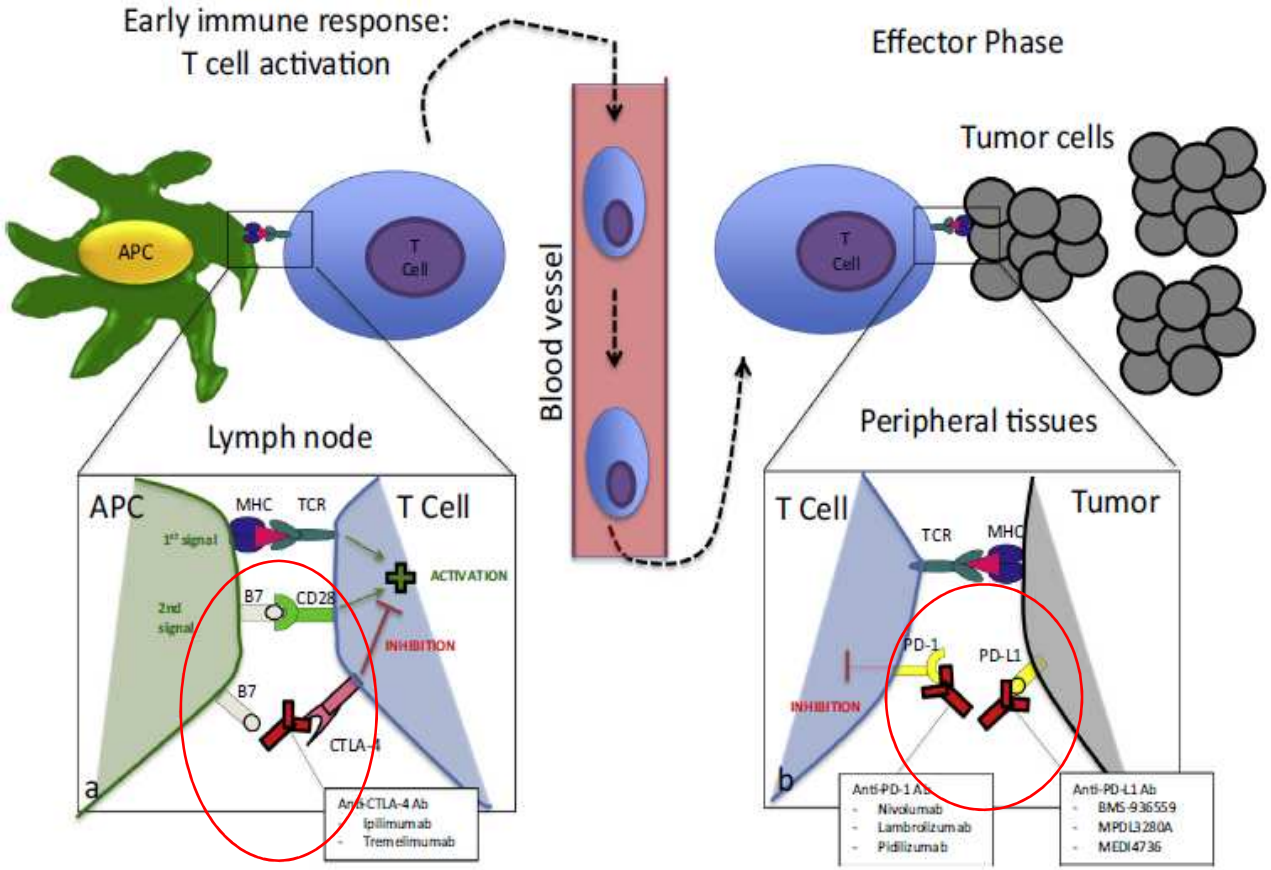
Checkpoint Inhibitors to Block Suppressive Molecules on T Cells

C. Kyi, M.A. Postow/FEBS Letters 588 (2014) 368–376



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Key Principles and Approaches

1. 1 kg of tumor = 10^{12} cells; 1 gram = 1 billion tumor cells or T effector cells

2. It is unrealistic to expect tumor eradication unless the cytotoxic effectors equal tumor cells (E:T of 1)

3. Failure to achieve critical mass of T cells and functional T cell type to overcome tumor microenvironment limitations partially explains trials with disappointing results

4. Potential solutions:
   a. Infuse huge numbers of T cells: TILs
   b. Infuse small numbers of T cells programmed to divide: CAR T cells
   c. Multiple infusions of armed T cells (BATs)

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Goals Adoptive T Cell Therapy

- Direct effector cells to tumor targets
- Create better T effector cells
- Optimize in vivo expansion and survival of effector cells
- Shift tumor microenvironment to a Th1 pattern
- Establish long-term memory responses
- Recruit endogenous immune cells against their own tumors by overcoming tolerance

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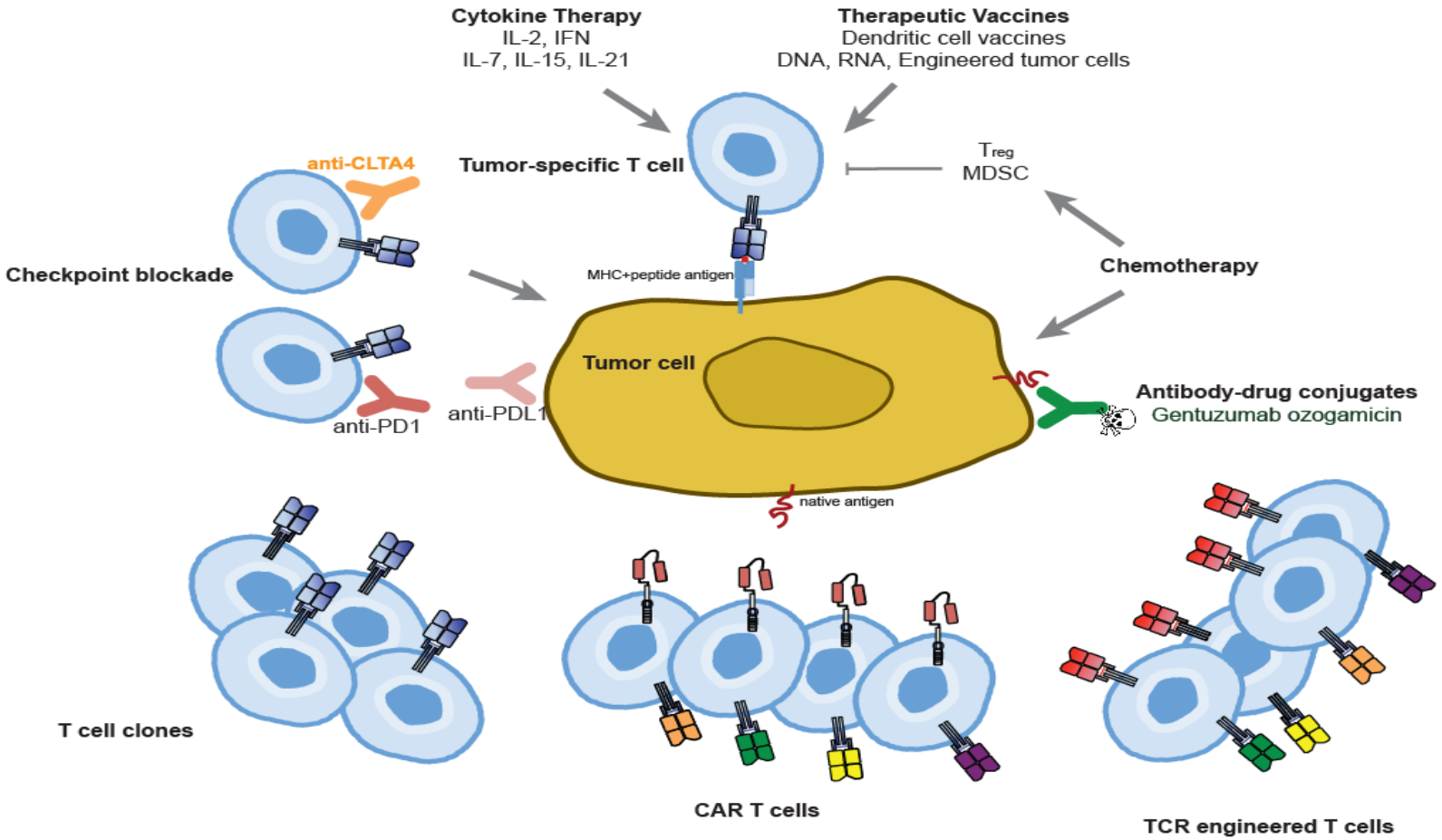
Approaches to Overcome Cancer Tolerance



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

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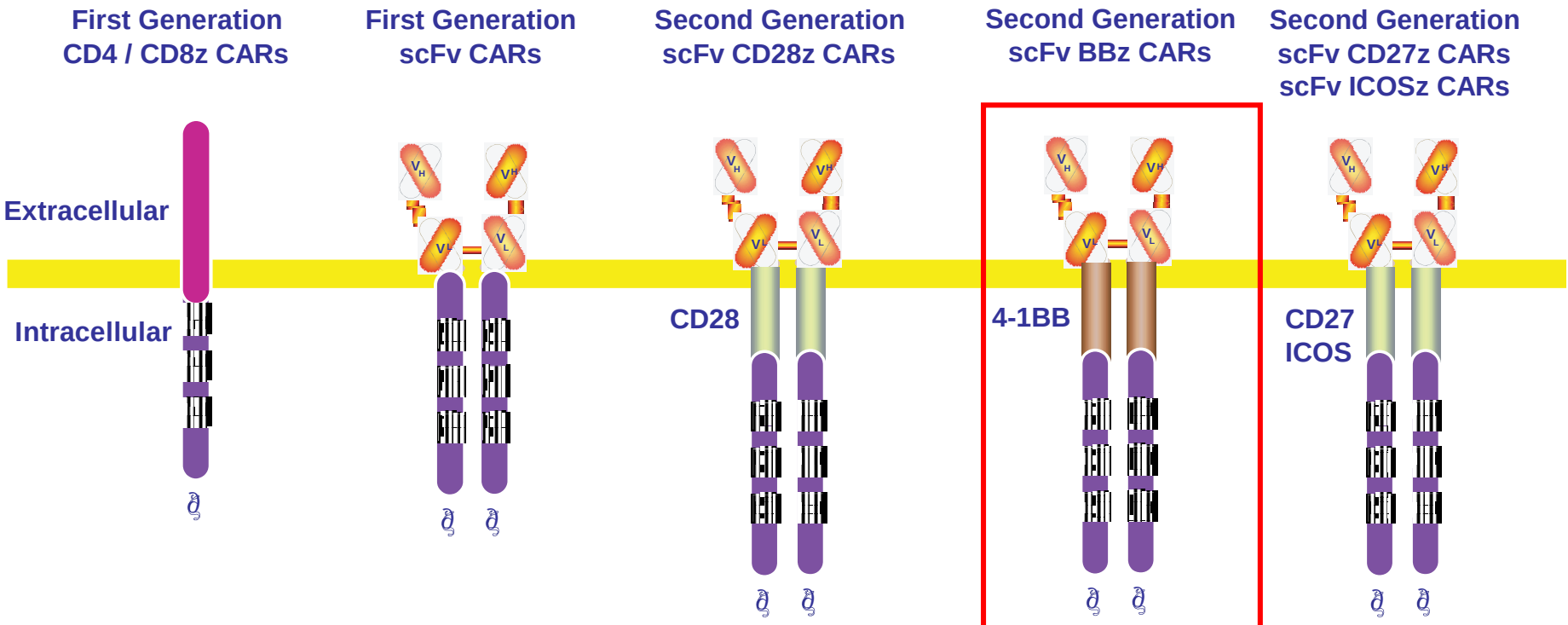
Design of CAR T Cells



Irving & Weiss, 1991
Letourneur, 1991
Romeo, 1991

Eshhar, 1993

Roberts, 1995
Finney, 1998
Maher, 2002

Finney, 2003
Imai, 2004
Milone, 2009
Carpenito, 2009

Song, 2012
Guedan, 2014
Duong, 2013

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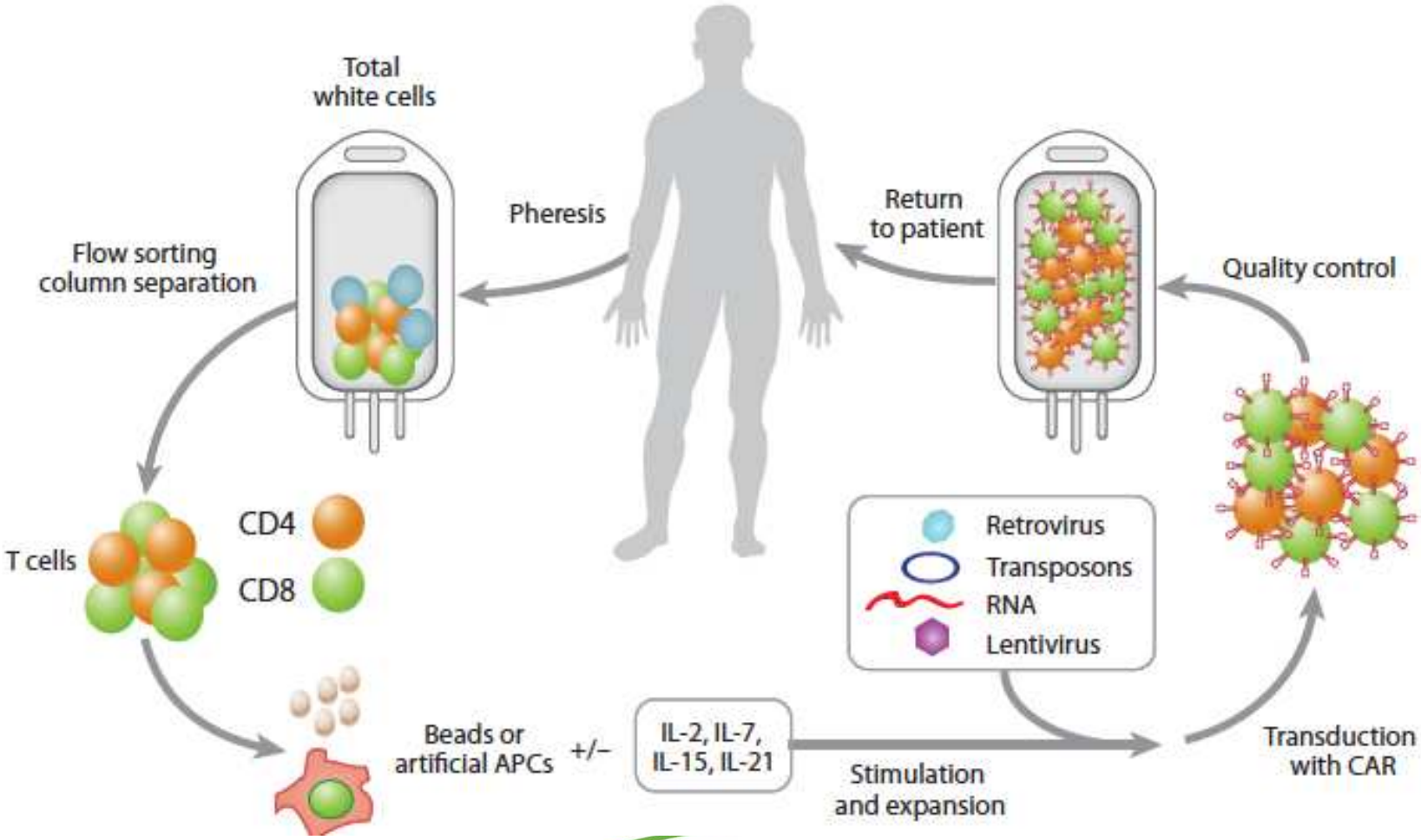
Chimeric Antigen Receptor T Cells



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scFv CARs For Cancer: Background

- Redirected T cell concept pioneered in vitro by Eshhar and colleagues: (Gross et al, PNAS 86: 10024, 1989)
  Despite strong pre-clinical rationale, technical difficulties have prevented clinical translation until recently:
  Efficient T cell culture systems
  Efficient gene transfer systems
- First clinical experiences in cancer:

  Lamers et al. *J Clin Oncol*. 24:e20, 2006
  Kershaw et al. *Clin Cancer Res*. 12: 6106, 2006
  Park et al. *Mol Ther*. 15:825-833, 2007
  Pule et al. *Nat Med*, 14:1264, 2008
  > Trials disappointing due to poor T cell engraftment

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Relapsed / Refractory ALL in Adults

Reference	Year	Therapy	N Pts	CR Rate	Survival
1st Salvage				**31-44%**	
Thomas et al	1999	Various	314	31%	6%
Tavernier et al	2007	Various	421	44%	8%
Fielding et al	2007	Various	609	44%	7%
Vives et al	2008	Various	198	42%	5%
Gökbuget et al	2012	Various	547	42%	24%
2nd Salvage				**18-33%**	
O'Brien et al	2008	Various	288	18%	3mo
Gökbuget et al	2012	Various	82	33%	13%
Relapse after SCT				**23%**	
Gökbuget et al	2012	Various	48	23%	15%

N. Goekbuget, German Multicenter ALL.

Number Pts	**> 2000**
Survival	**< 10% at 2 yrs**

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CD19: An Ideal Tumor Target in B-Cell Malignancies

- CD19 expression is generally restricted to B cells and B cell precursors[1]
  - CD19 is not expressed on hematopoietic stem cells
- CD19 is expressed by most B-cell malignancies
  - B-ALL, CLL, DLBCL, FL, MCL
- Antibodies against CD19 inhibit tumor cell growth

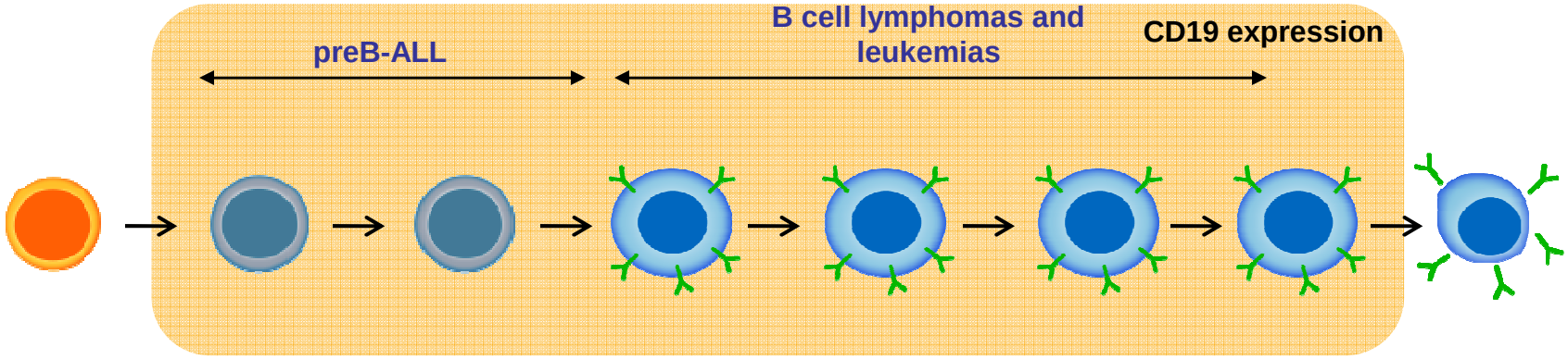
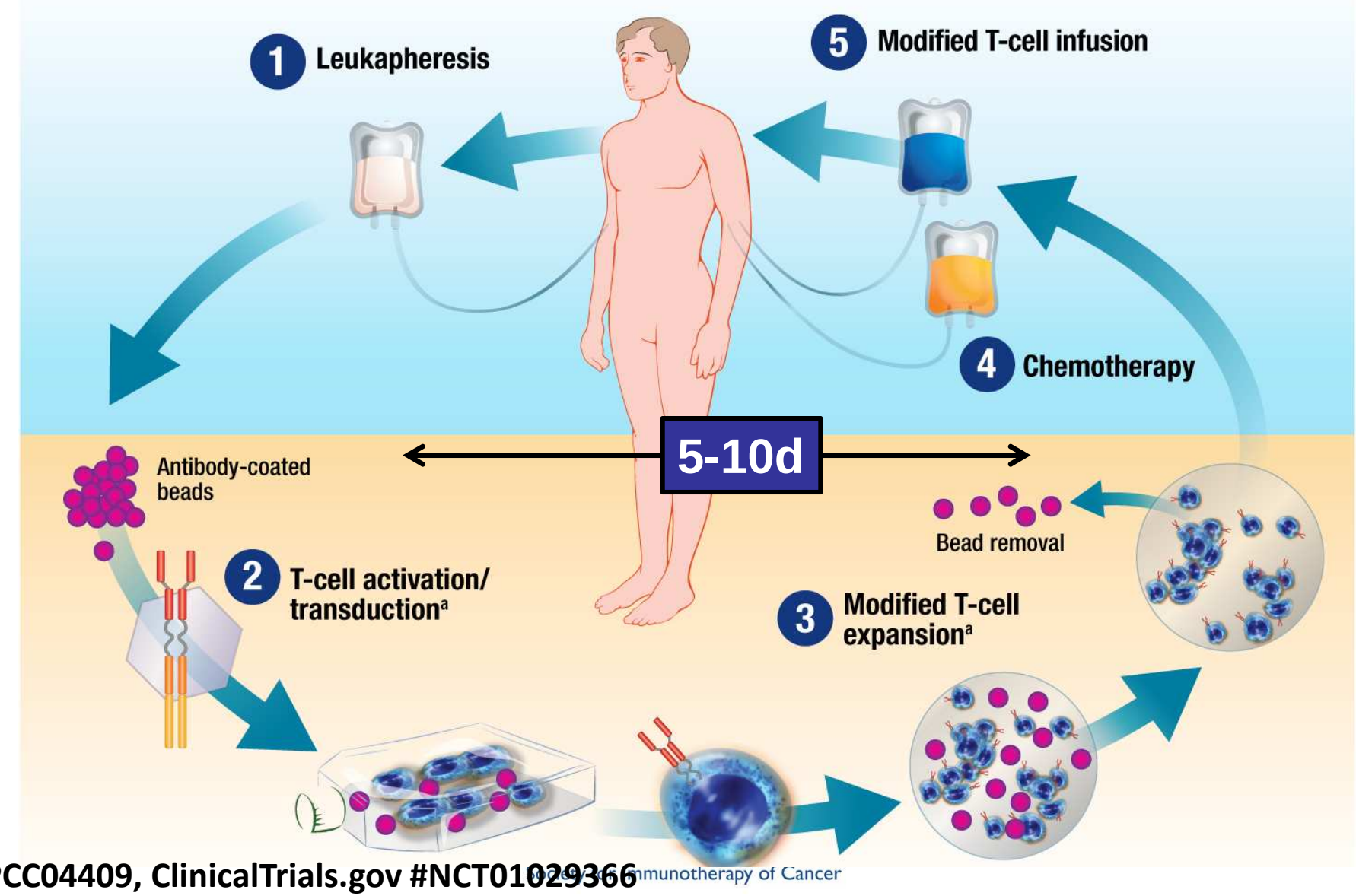


Image adapted from Janeway CA, Travers P, Walport M, et al. *Immunobiology*. 5th ed. New York, NY: Garland Science; 2001:221-293; Scheuermann RH, et al. *Leuk Lymphoma*. 1995;18:385-397; and Feldman M, Marini JC. Cell cooperation in the antibody response. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 6th ed. Maryland Heights, Missouri: Mosby;2001:131-146.

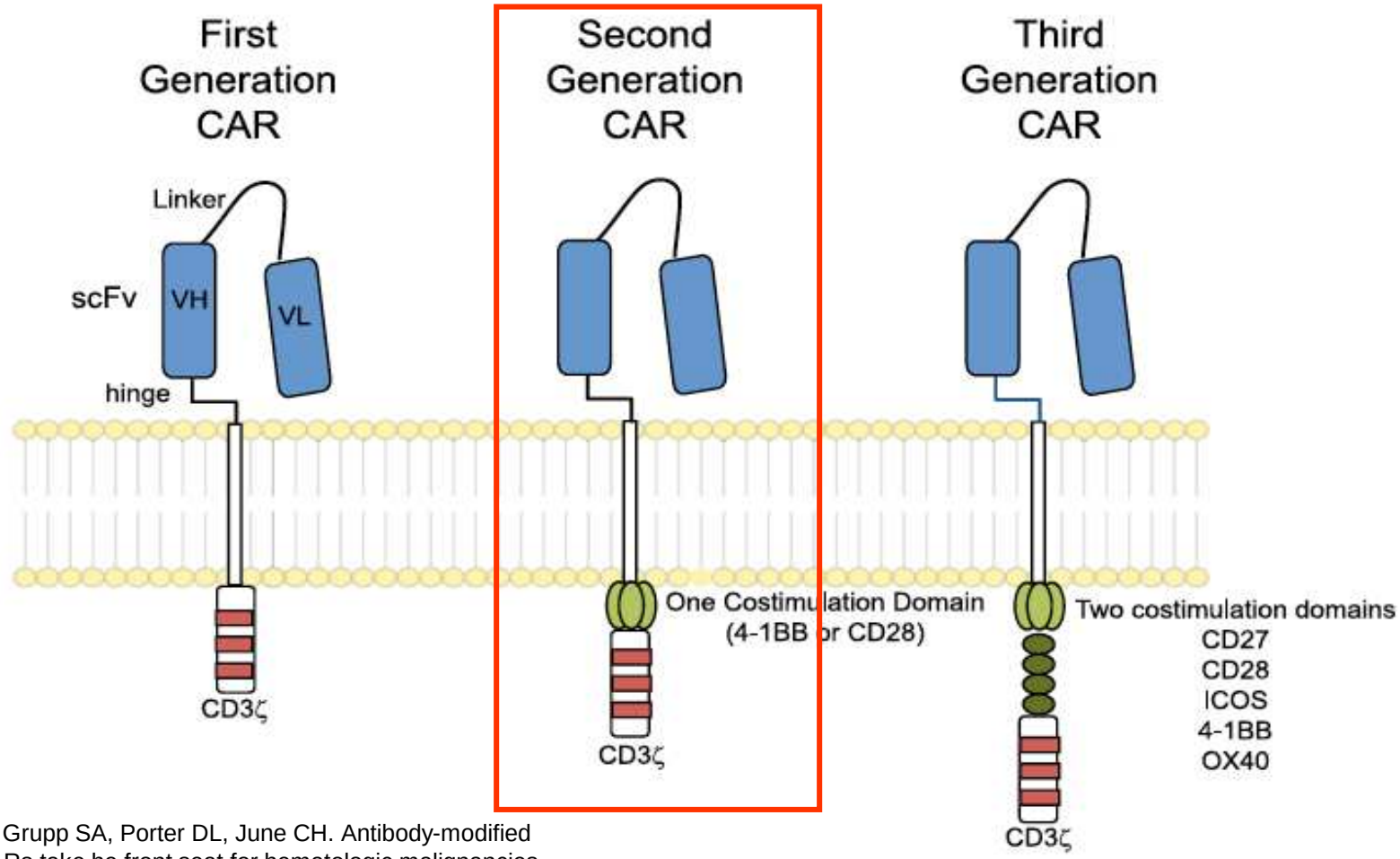
CTL019 CLL Study Overview*

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



UPCC04409, ClinicalTrials.gov #NCT01029366

Chimeric Antigen Receptor T Cells



Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take he front seat for hematologic malignancies Blood. 2014 Apr 24;123(17):2625-35..

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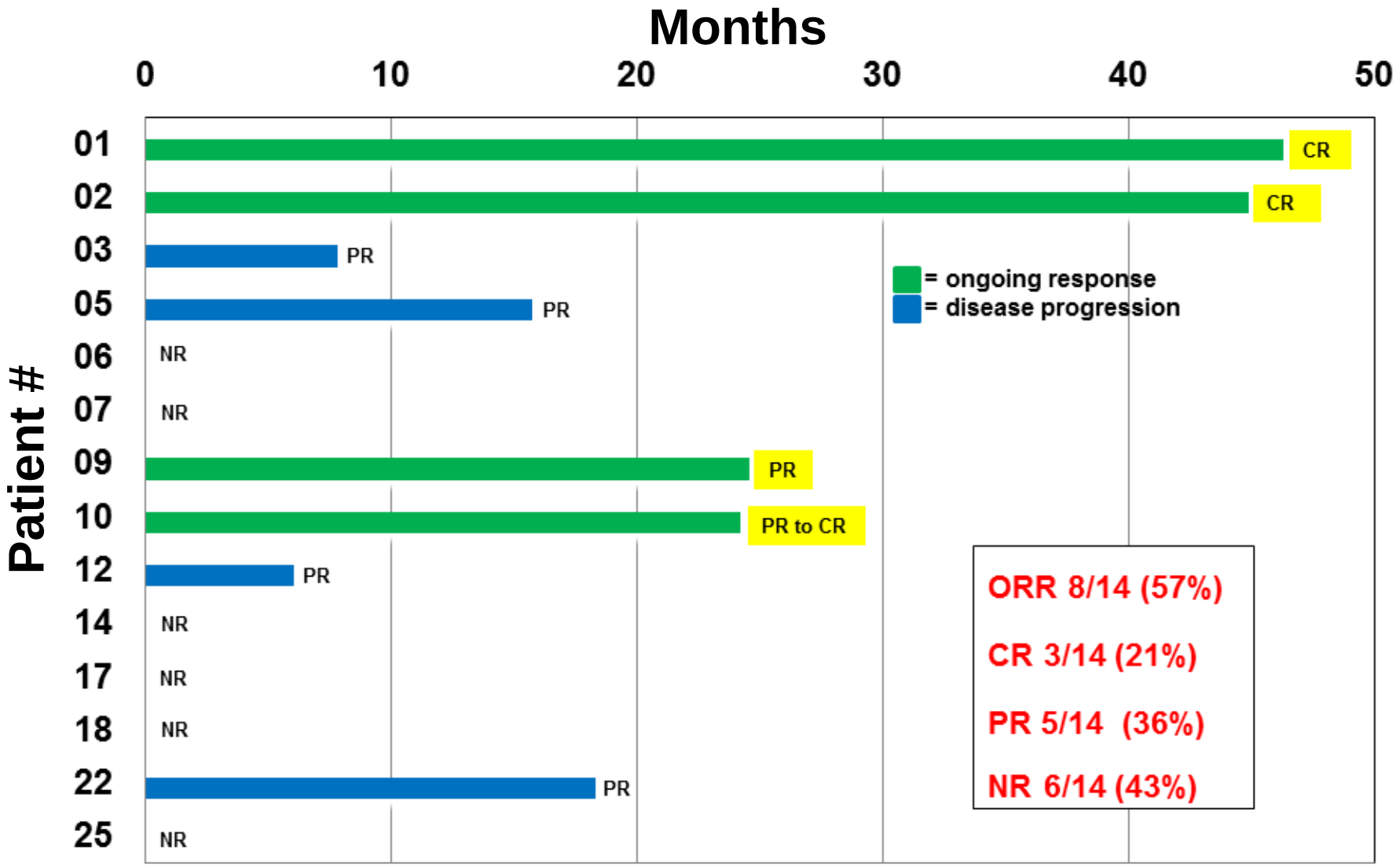
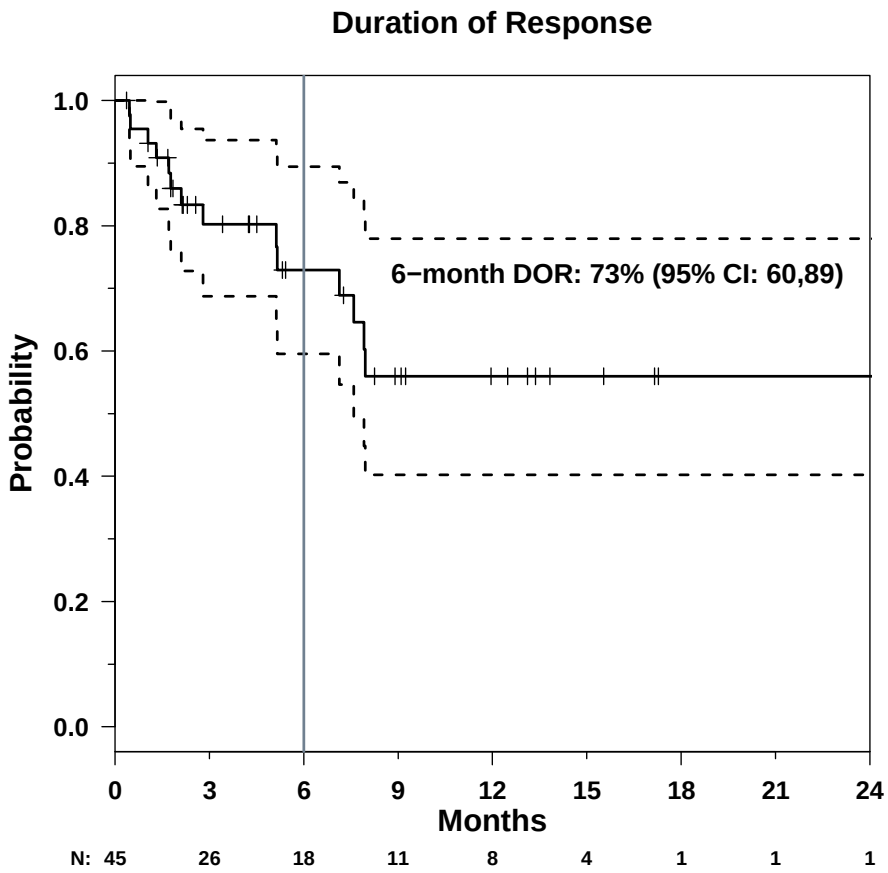
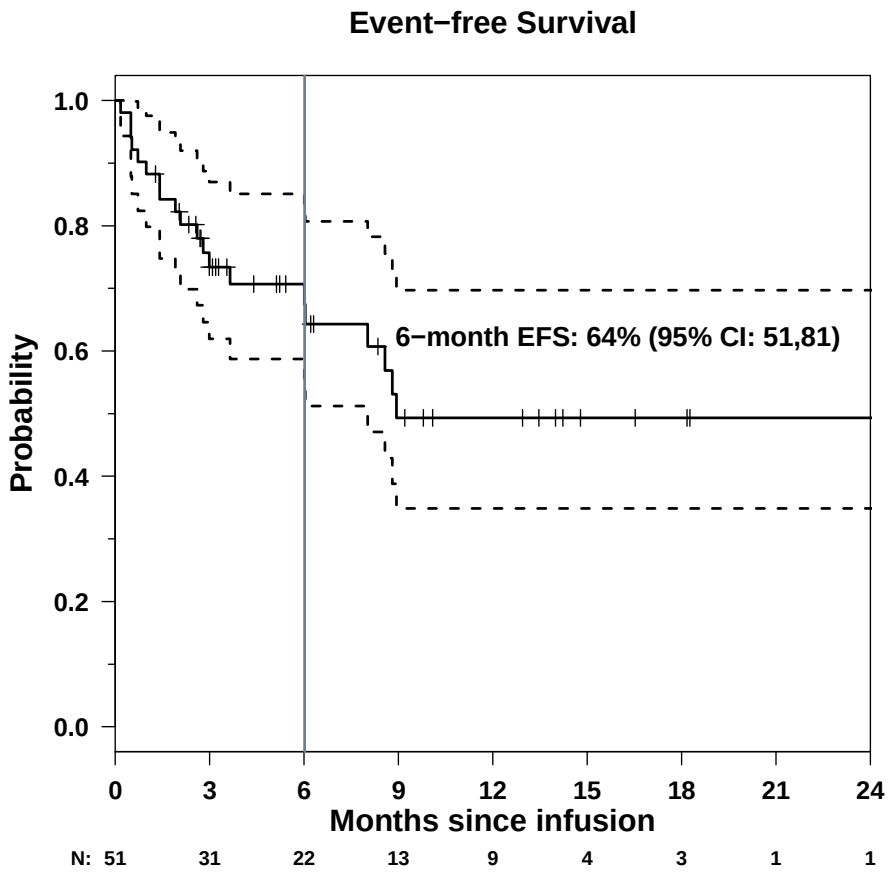
CTL019 for R/R CLL: Durable Responses in Phase I



Summary of CTL019 Efficacy in ALL (n = 51) Case Mix on phase I: 39 Pediatric and 12 Adult





Maude, et al, *NEJM* 2014, results updated to November 30.

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Durable Responses with CTL019 for R/R ALL

- 135 patients have been treated with CART19 for CLL, ALL, lymphoma, and myeloma (Penn, CHOP, Novartis)
- Update ALL cohort (N = 64) as of November 2014:
  - 41 pediatric cases treated (28 post-allo)
  - 35 of 39 CR, 2 pending evaluation
  - 3 (of 4) responded after being refractory to blinatumomab
  - 8 electively retreated at 3-6 months for waning CARs or robust B cell recovery (2)
  - 5 off-study for alternate therapy (3 SCT)

CTL019 Toxicities

- **B cell aplasia**
  - **observed in all responding patients to date**
  - **managed with IVIg replacement therapy**
- **Cytokine release syndrome (CRS)**
  - **reversible, on-target toxicity**
  - **Controlled with anti-IL-6 therapy (tociluzumab)**
  - **Severity related to tumor burden: Treat MRD as outpatient?**
- **Macrophage activation syndrome (HLH / MAS)**
- **Neurotoxicity**
  - **Significant confusion, aphasia**
  - **Occurs in a small number of patients and after CRS**

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CTL019 Key Take Home Points

1. Persist in blood

2. CTL019 expansion after infusion

3. Five 5-log tumor reduction following CART19 without chemotherapy and at 6 months for all tumor (molecular remissions)

4. Safety profile with >1000 patient years of exposure to lentiviral and retroviral vector in 236 patients (Levine)

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CAR T Cells: Key Points

- **CD19 CARs have potent anti-leukemic effects in ALL and CLL with durable responses >4 years.**
  - **CD19 CARs induce B cell aplasia. Need IVIG**
  - **CRS: related to tumor burden. (anti-IL-6, tocilizumab).**
  - **Multicenter trials underway (Novartis)**
- **CTL019 has robust activity in DLBCL and triple-refractory Follicular Lymphoma**
- **CTL019 in refractory myeloma has acceptable safety and promising efficacy**
- **Robotic manufacturing is required for widespread use**

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Challenges and Limitations of Adoptive T Cell Therapy

***Ex vivo* expansion of specific T cells**

- **Labor intensive**
- **Time consuming**
- **Costly**
- **Limited Quantity of CTL**
- **Variable Quality of CTL**

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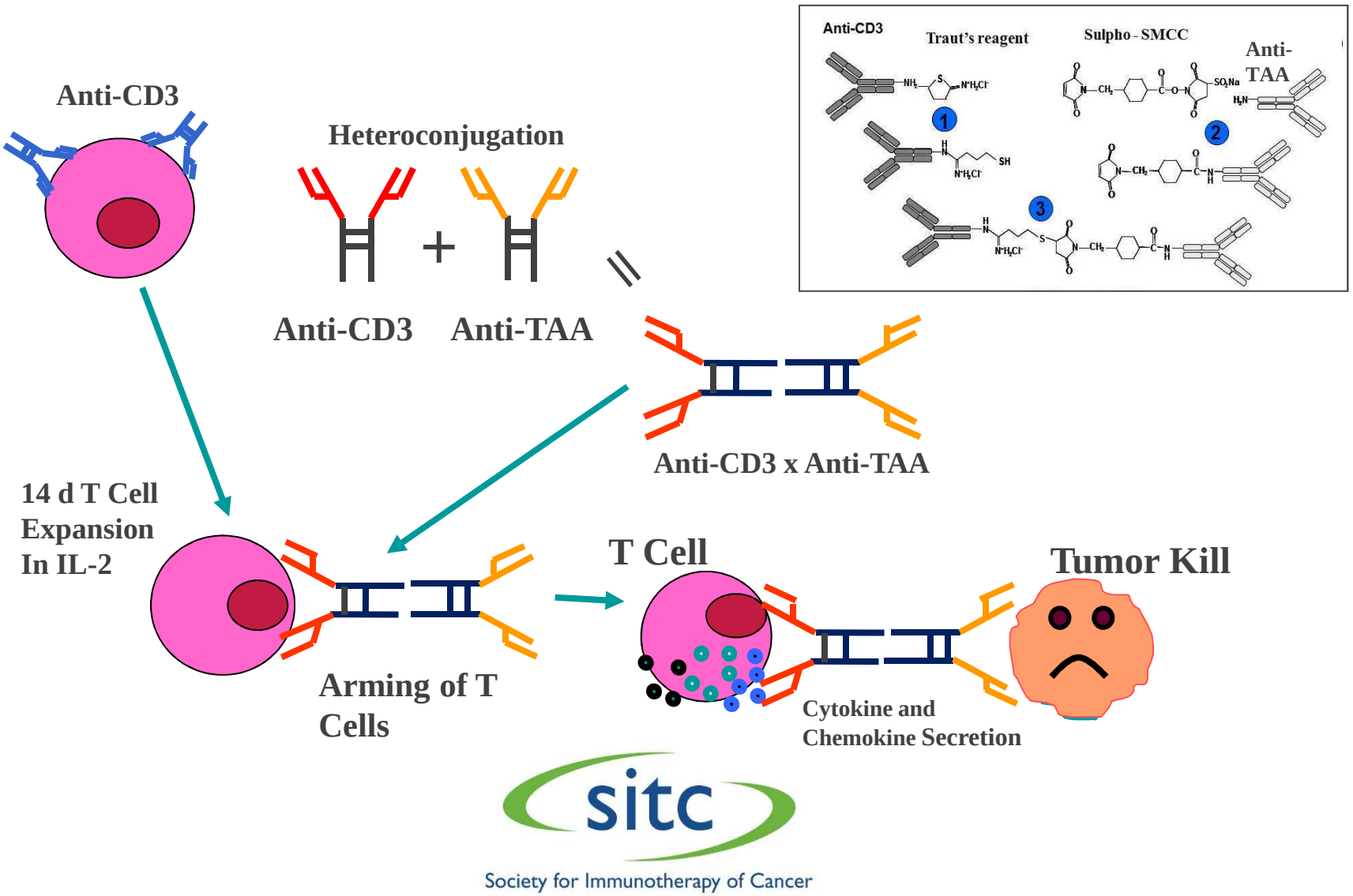
Bispecific Antibody Re-Directed T Cells



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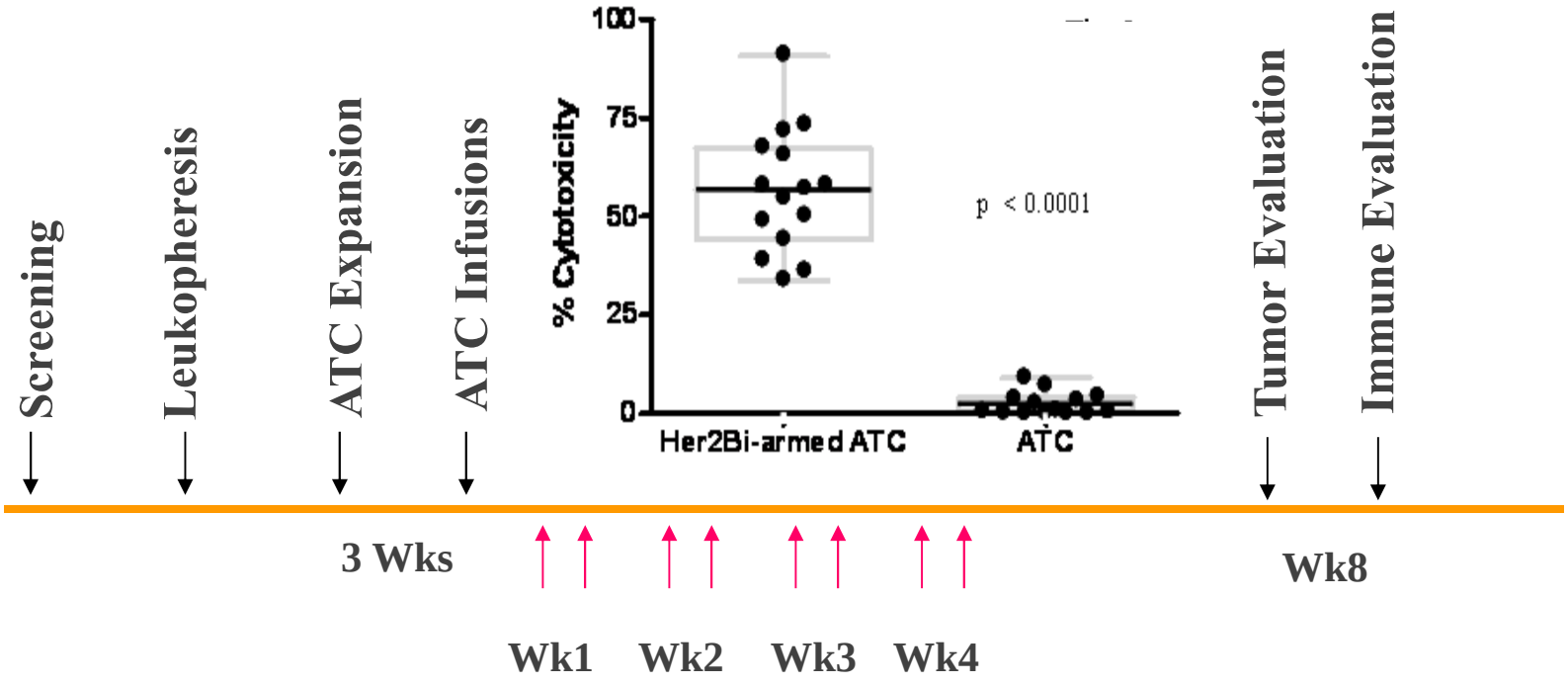
Treatment Schema for Stage IV Breast Cancer



GM-CSF 250 ug/m^2/dose

IL-2 300,000 IU/m^2/day

Dose escalation:
5, 10, 20, 40 in standard 3+3 design

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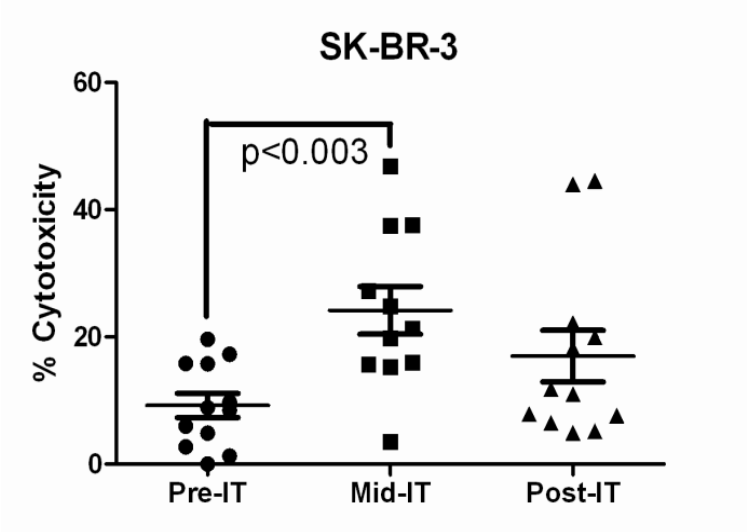
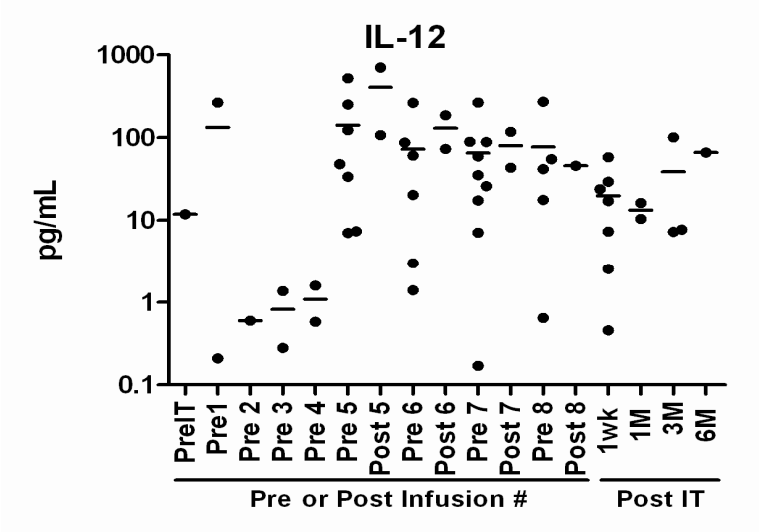
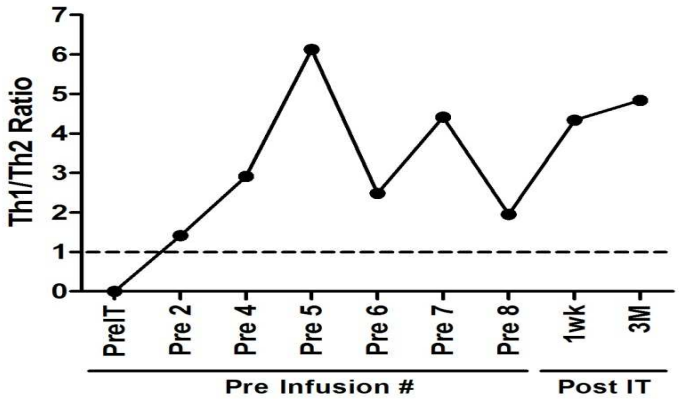
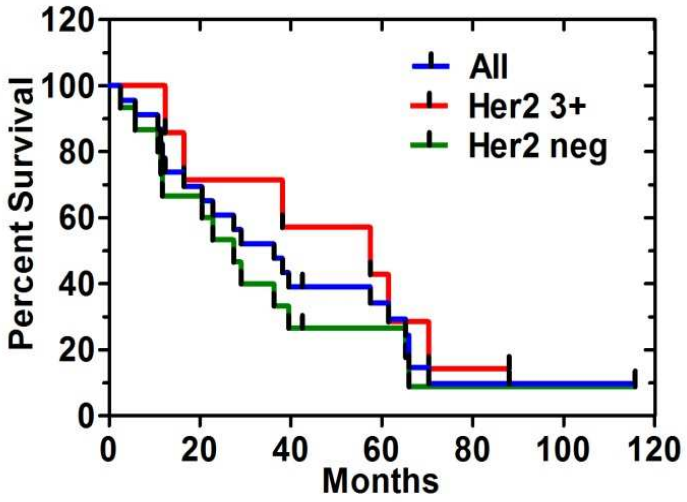
Induced Immune Responses and Overall Survival for MBC









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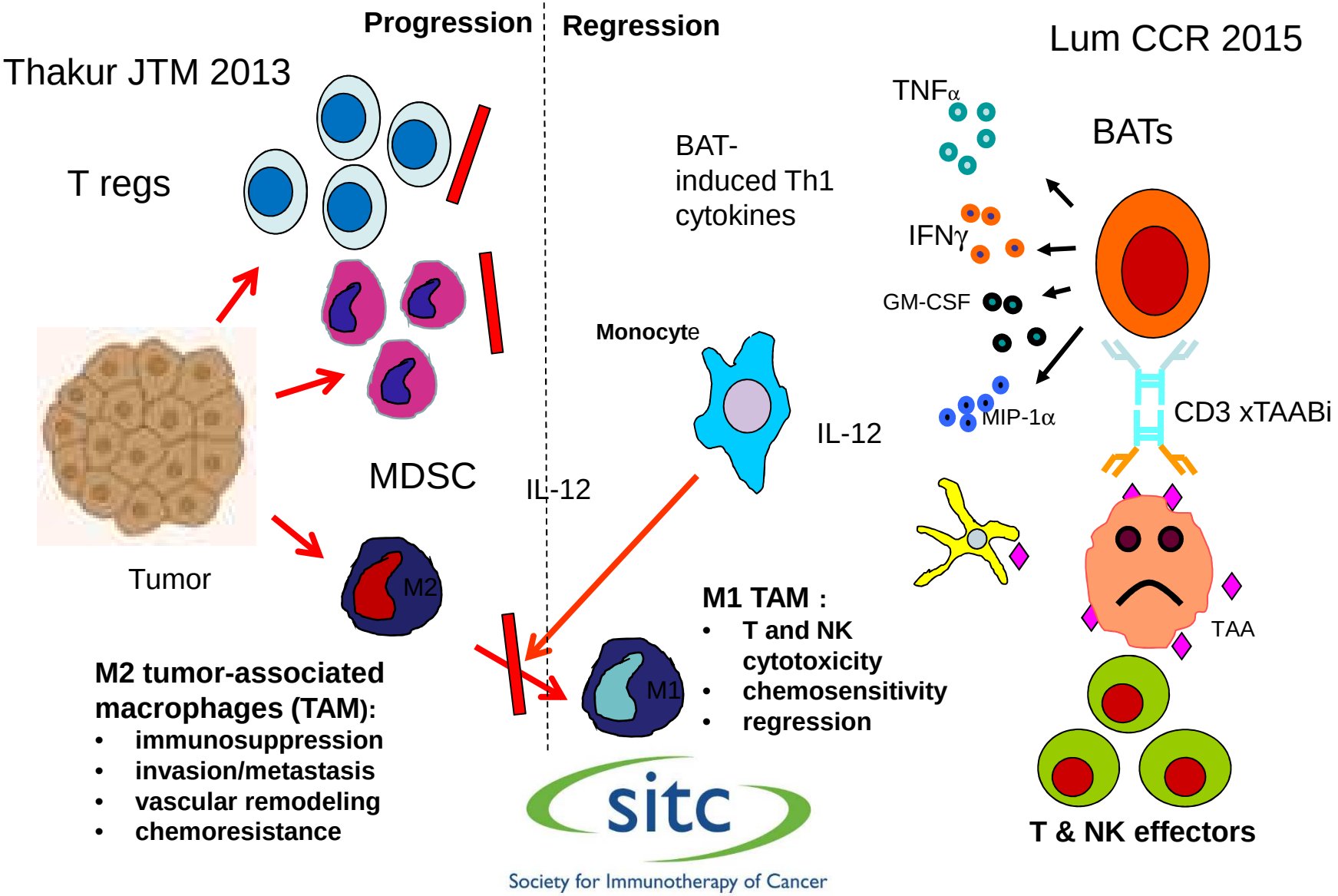
Mechanisms for BATs Overcoming Tumor Induced Suppression



BATs induce Clinical and Immune Responses without toxicities

- ATC armed with BiAb ex vivo – no BiAb infused
- Controlled Dose and frequency
- Confirmed safety profile > 120 pts
- Induces T and B cell responses directed tumor antigens
- Evidence for anti-tumor effect in solid tumors
- Clinical effect: Improved survival or suggested anti-tumor activity in metastatic or adjuvant high breast 5/9 NED with median OS of 103 mos, hormone refractory prostate (1 PR and 2 MR), NHL, Multiple myeloma, and pancreatic cancer (median OS of 14.5 mos)

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CARs in Development

Academic CAR T cells	
Academic Institute (US)	**Target(s)**
Fred Hutchinson Cancer Center	CD19, CD20, ROR1
Baylor College of Medicine	GD-2, Her2, CD30, kappa Ig
National Cancer Institute (NCI)	CD19, CSP4, GD-2, EGFRvIII , mesothelin, VEGFR2
Roger Williams Medical Center (RI)	CEA, PSMA
University of Pennsylvania	CD19, mesothelin, BCMA, EGFRvIII PSMA
Children's Mercy Hospital Kansas City	GD-2
Academic Institute (non-US)	**Target(s)**
Chinese PLA General Hospital	CD19, CD20, CD33, CD138, HER2
Christie Hospital NHS Foundation Trust	CD19
Peter MacCallum Cancer Centre, Australia	LewisY
University of Zurich	FAP

Ongoing and Future BATs

- Neuroblastoma/Osteosarcoma GD2 BATs NCI Funded
- Pancreatic Cancer Phase II
- Breast Cancer Phase II
- TNBC Phase II clinical trial ongoing (NCI Funded)