Basic Principles of Tumor Immunotherapy

CME Disclosures

Craig L. Slingluff, Jr., MD

<u>The following relationships exist related to this presentation:</u>

IMMATICS BIOTECHNOLOGIES, Consultant, SAB member, Research Support funds,

GLAXO SMITH KLINE , Research Support, PI on funded clinical trial

POLYNOMA, Consultant, Advisory Board, Research Support funds,

3M, Clinical trial Research Support

MERCK, Clinical trial Research Support

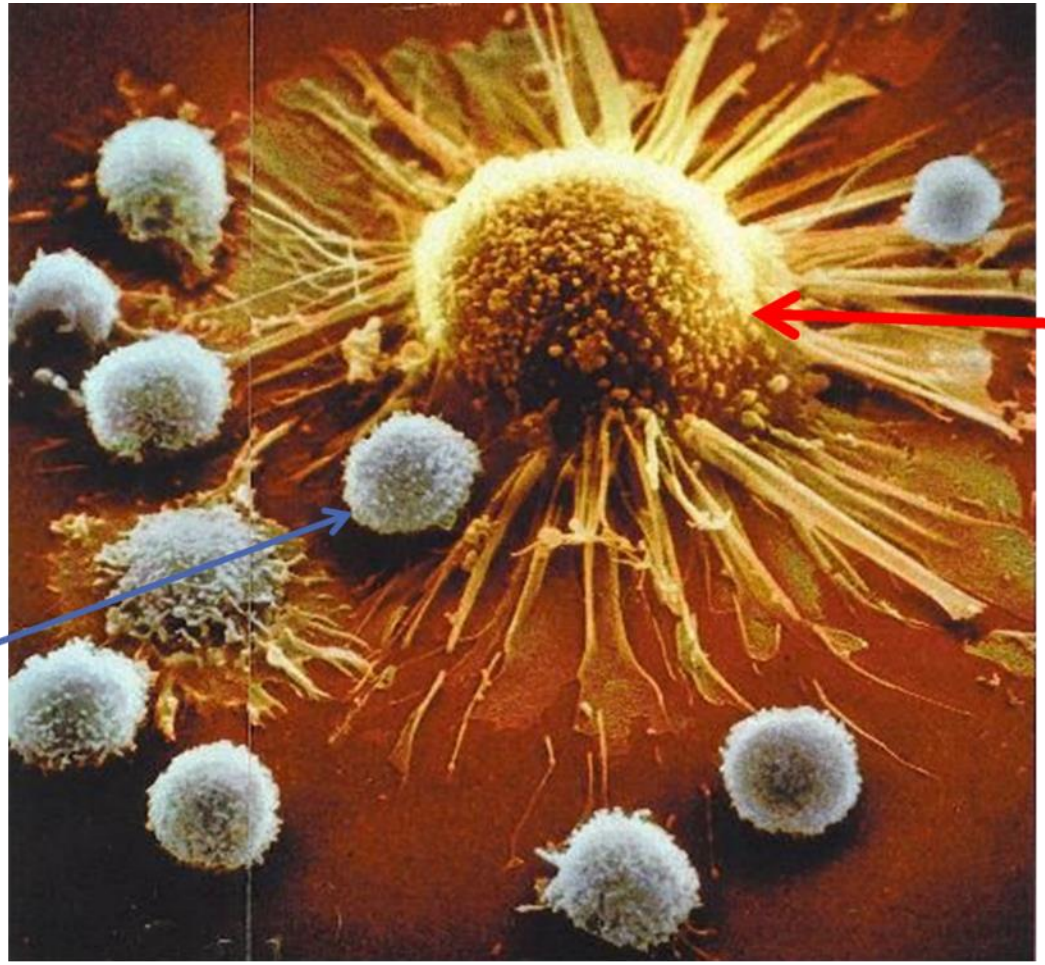
UVA LICENSING AND VENTURE GROUP, royalty/licensing fees, inventor on peptides.

Experimental use of cancer vaccines, imiquimod, interferon-gamma.

To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

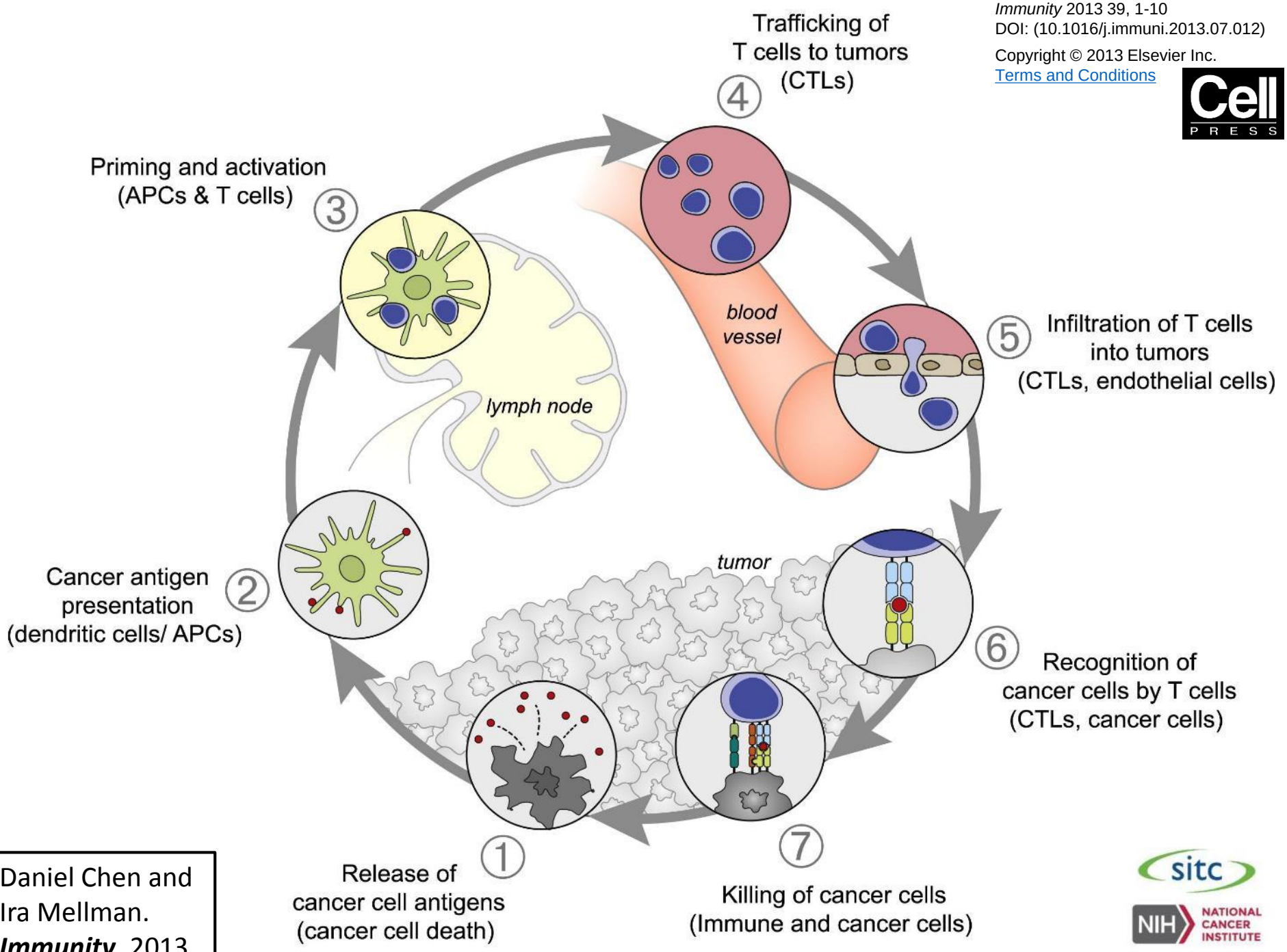
The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

T lymphocytes at the center of immune therapy



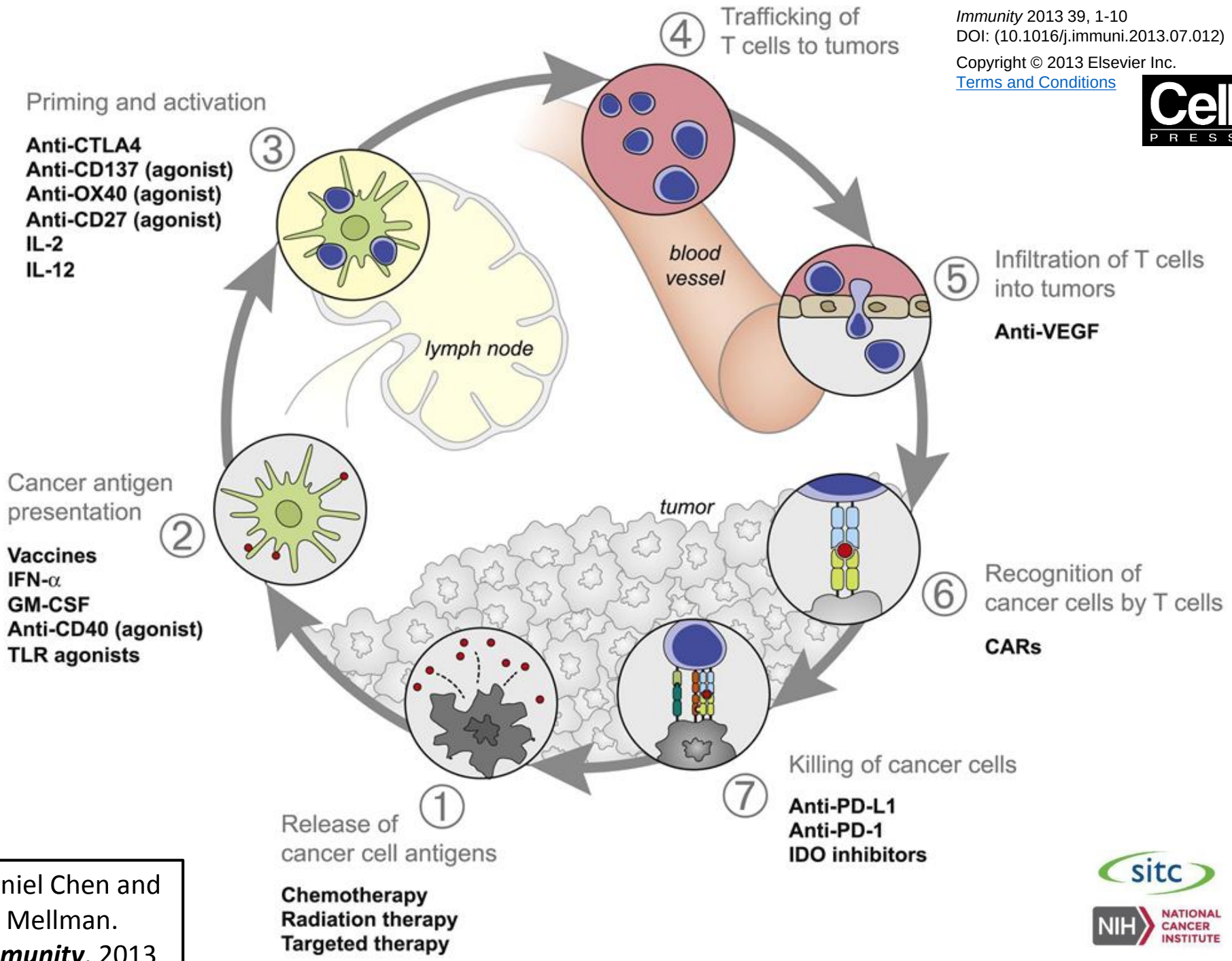
Peter Jaret "Our Immune System: The Wars Within," *National Geographic* (June 1986).

Immunity 2013 39, 1-10
DOI: (10.1016/j.immuni.2013.07.012)



Daniel Chen and Ira Mellman. ***Immunity***. 2013

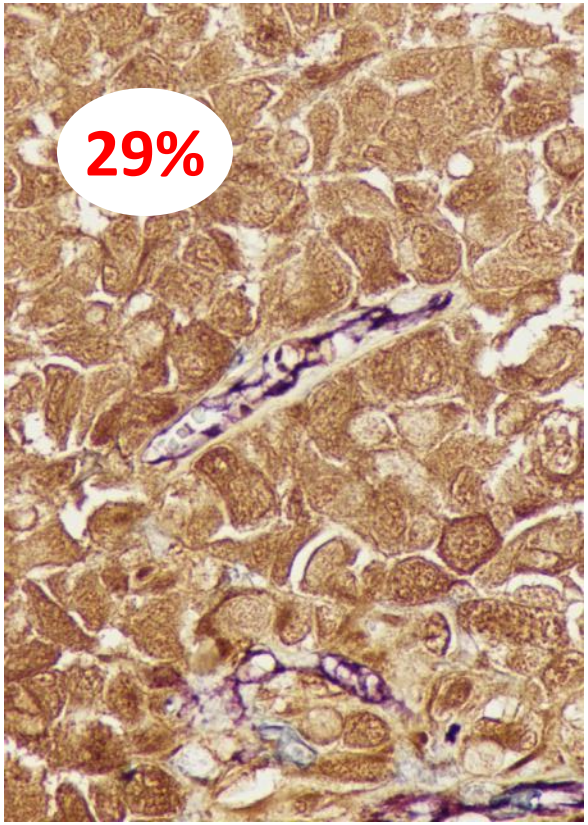
Immunity 2013 39, 1-10
DOI: (10.1016/j.immuni.2013.07.012)



Daniel Chen and Ira Mellman. ***Immunity***. 2013

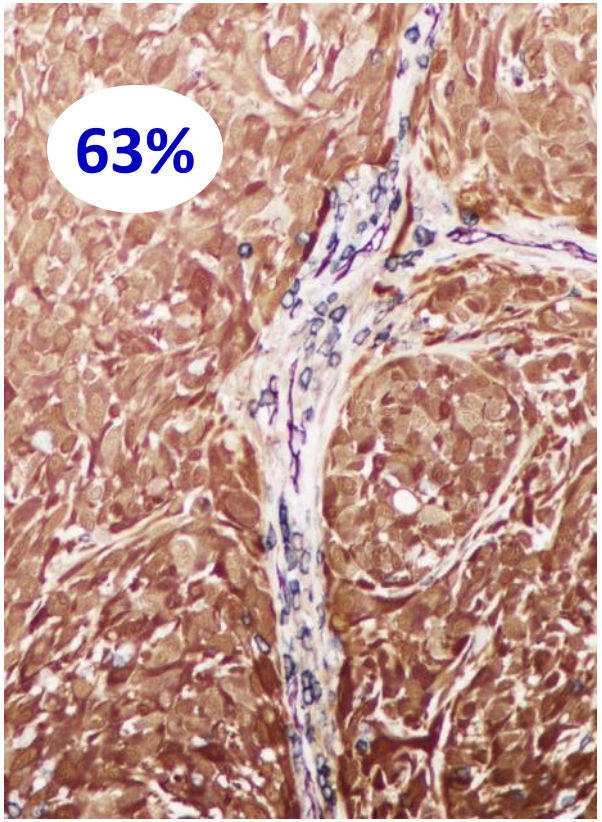
Immunotypes in Metastatic Melanoma

purple = CD31; blue = CD45; brown = S100



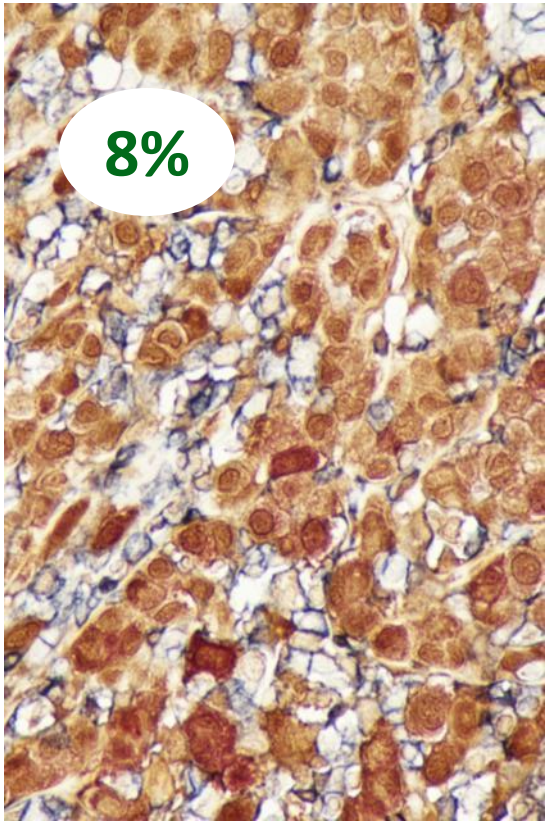
A

None



B

Cuffing

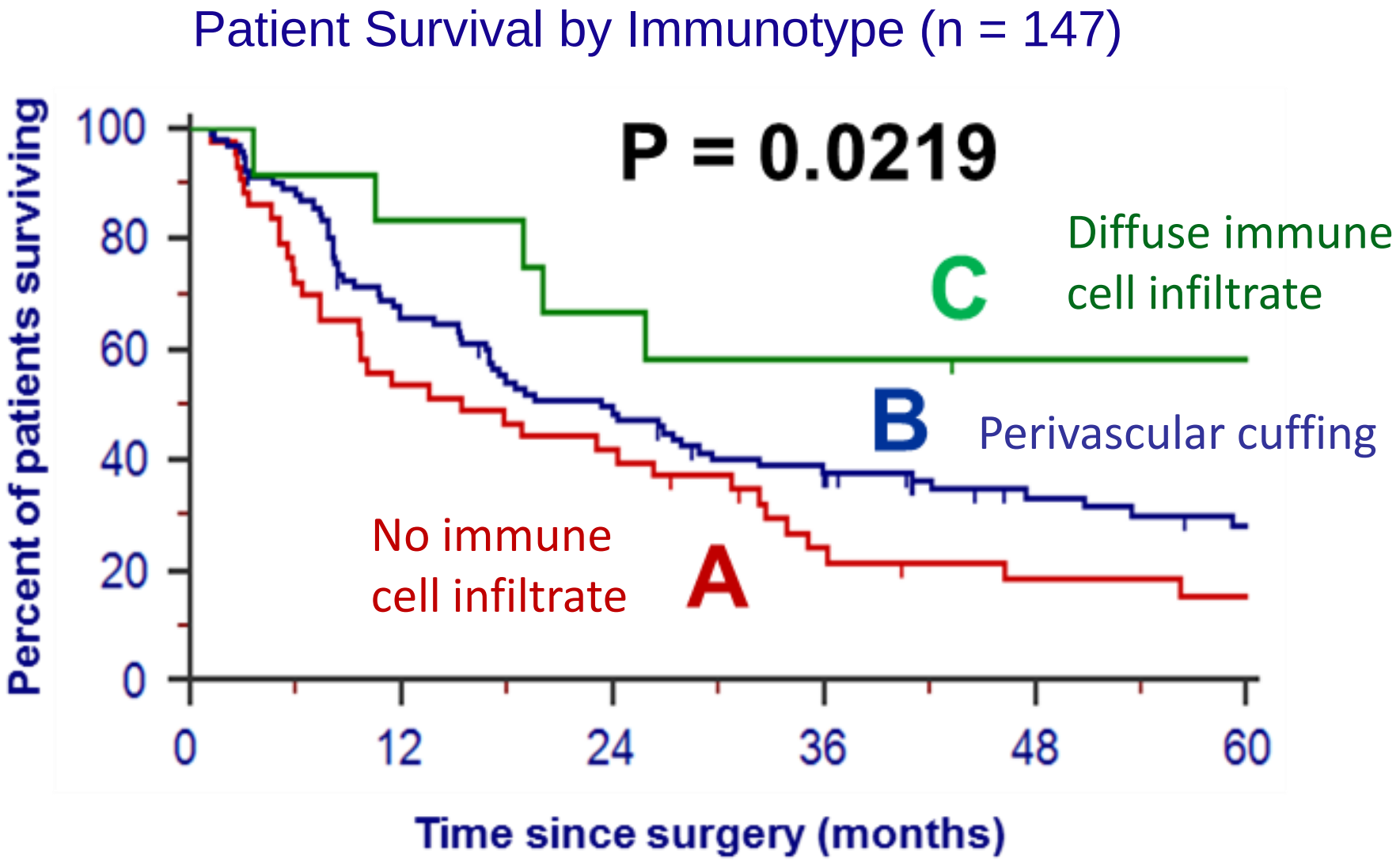


C

Diffuse

Erdag G, et al. Cancer Res 2012

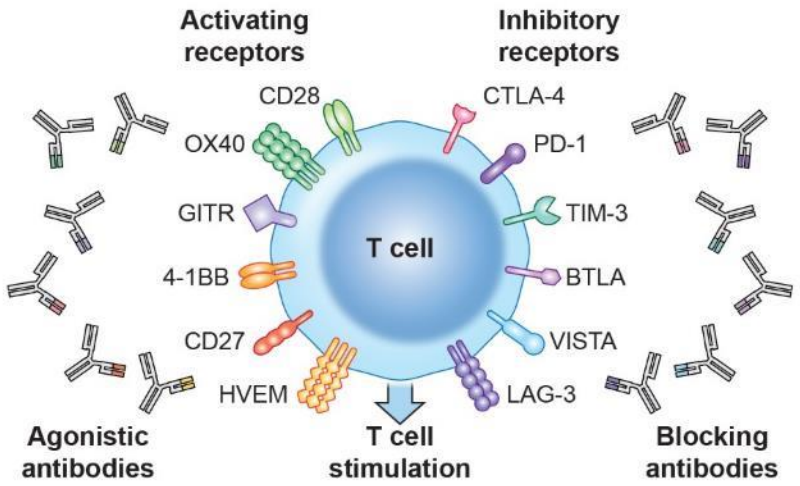
Survival is associated with the ability of T cells to infiltrate metastases



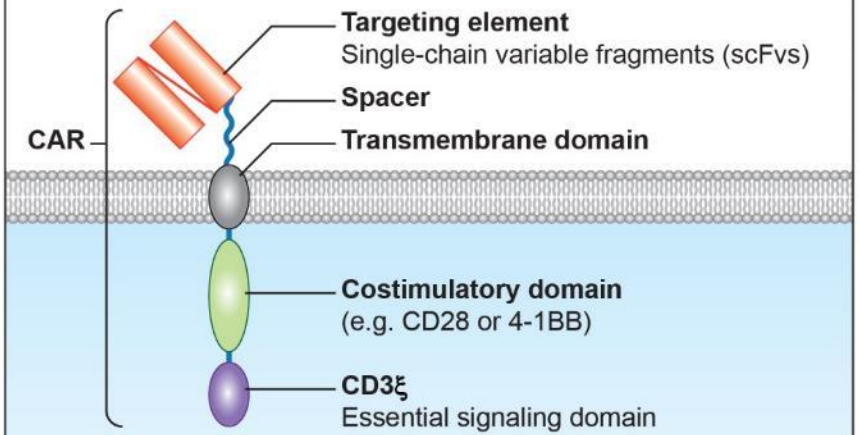
Erdag G, et al. Cancer Res 2012

Types of immunotherapy

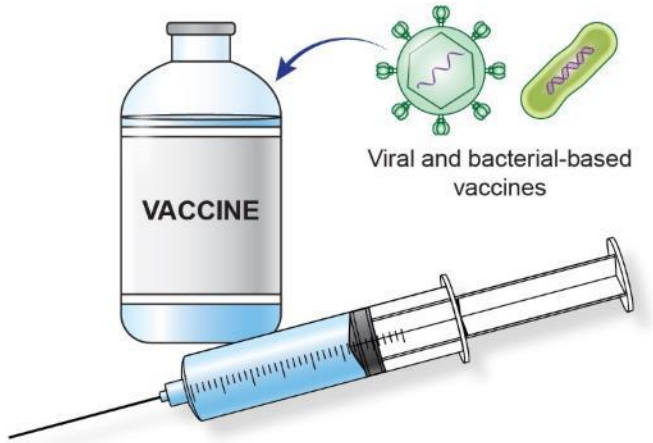
T cell checkpoint modulation



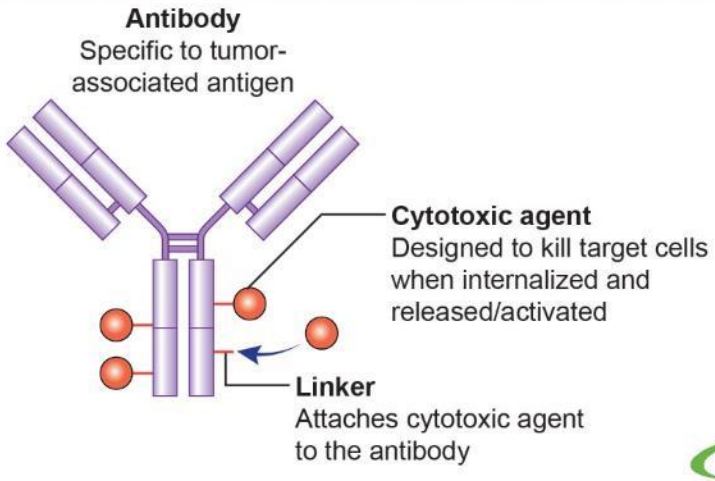
T cell adoptive transfer



Therapeutic cancer vaccines



Effector antibodies and antibody-drug conjugates



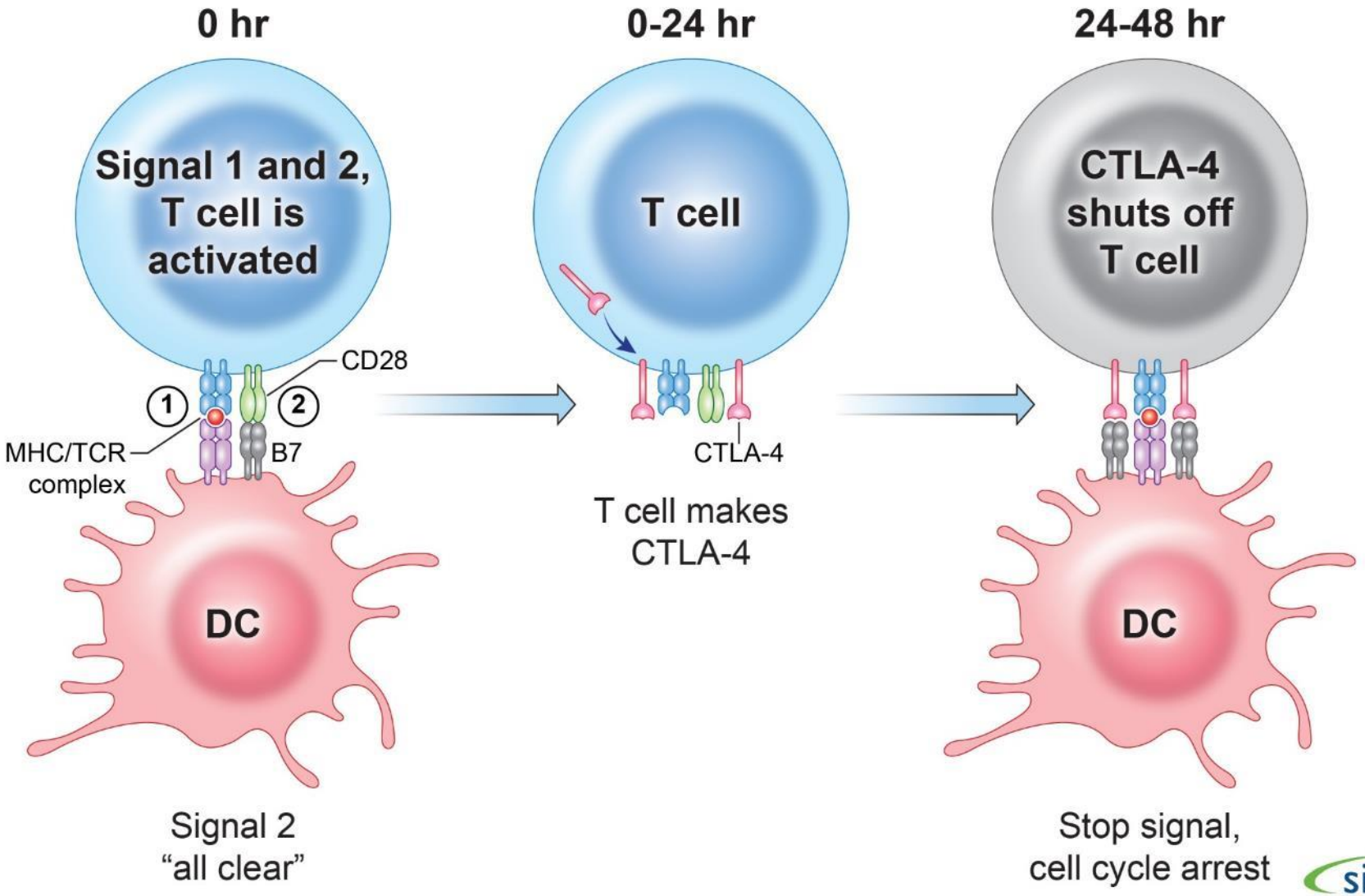
sitc

NIH NATIONAL CANCER INSTITUTE

Checkpoint blockade therapy

The goal of T cell checkpoint blockade is to make T cell “off-switches” inaccessible to tumor cells, thus restoring tumor-specific immunity.

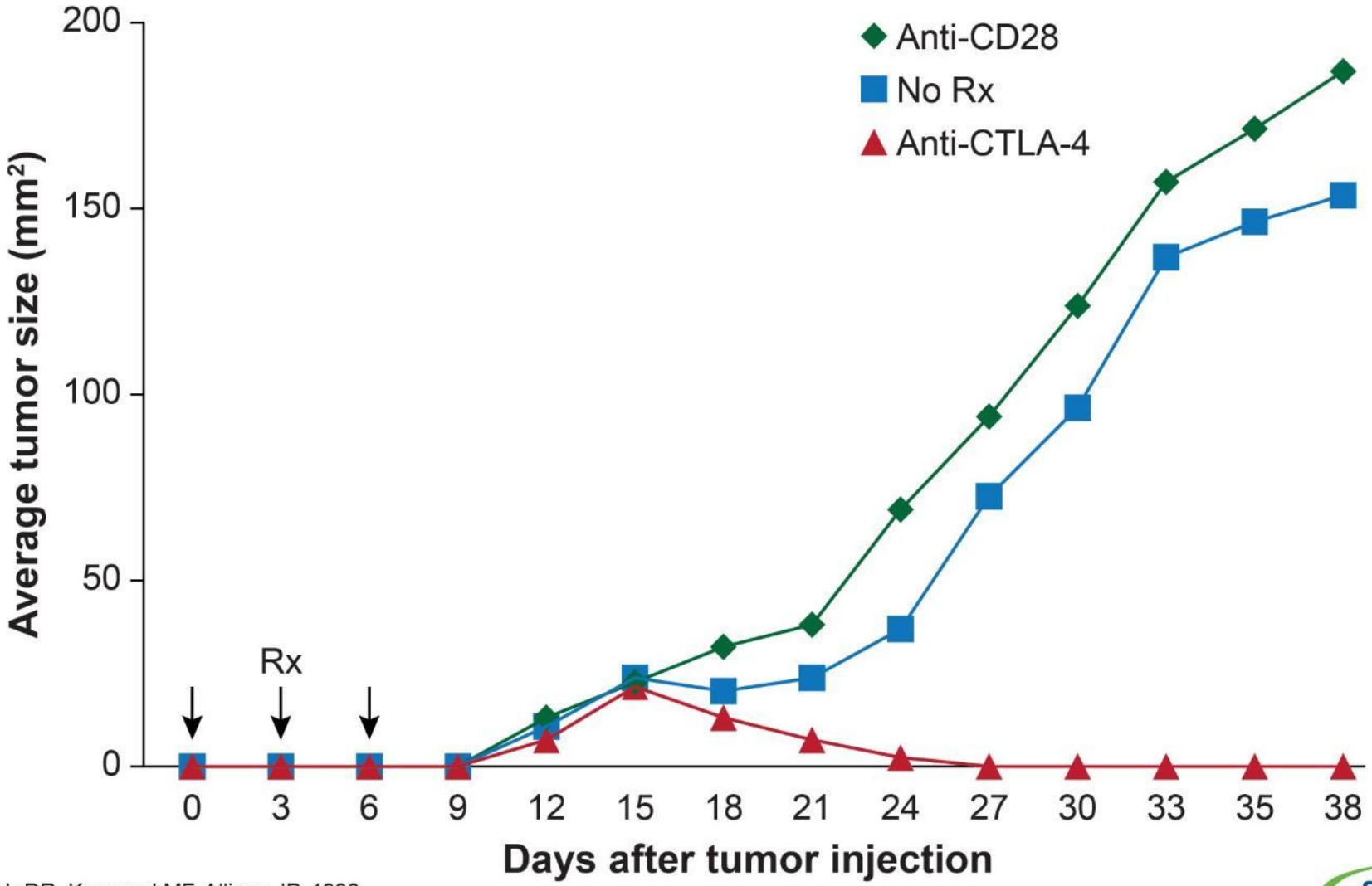
CTLA-4, a negative regulator of T cell activity, limits the responsiveness of activated T cells



sitc

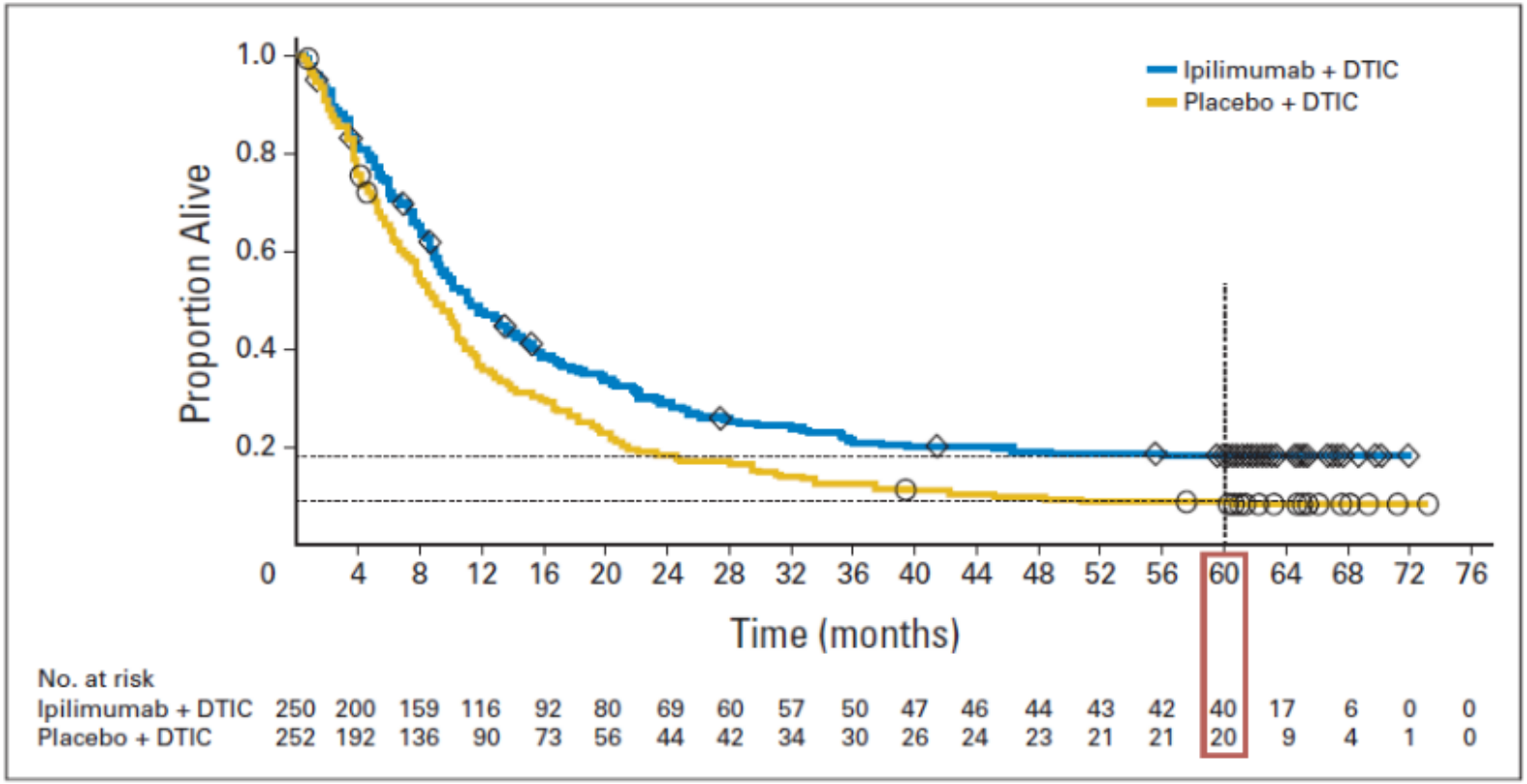
NIH NATIONAL CANCER INSTITUTE

Anti-CTLA-4 induces regression of transplantable colon carcinoma



Leach DR, Krummel MF, Allison JP. 1996.
Enhancement of antitumor immunity by CTLA-4 blockade.
Science. 217(5256): 1734-6.

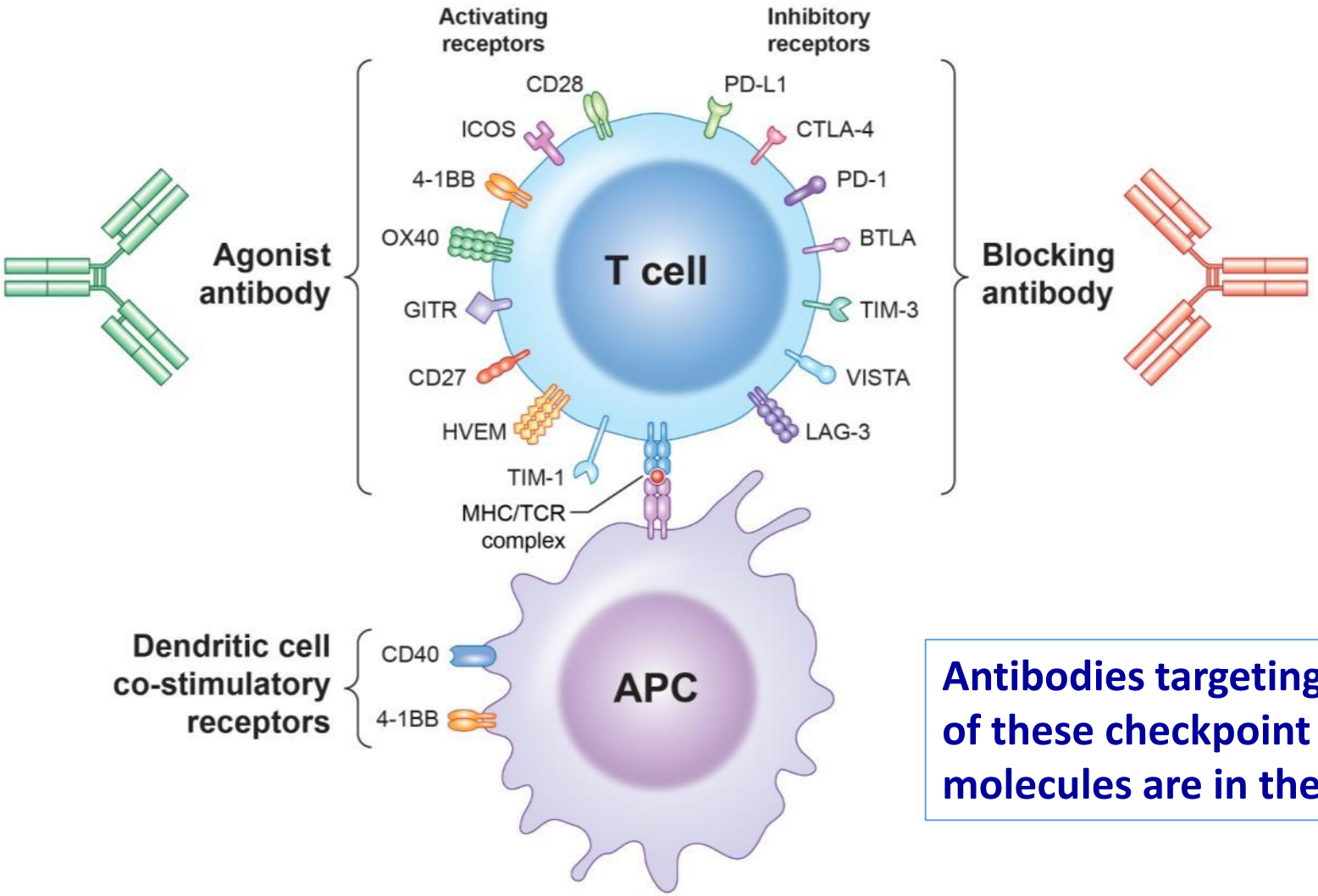
Durable improved survival with CTLA4 blockade in melanoma



Kaplan-Meier estimates of overall survival in patients treated with ipilimumab plus dacarbazine (DTIC) or placebo plus DTIC in phase III CA184-024 study. Symbols indicate censored observations. Red box highlights updated 5-year survival data

Maio M, et al. J Clin Oncol 2015

T cell checkpoint modulation



Antibodies targeting many of these checkpoint molecules are in the clinic

sitc

NIH NATIONAL CANCER INSTITUTE

Summary significance of checkpoint blockade

Checkpoint blockade antibodies have no direct anticancer effect.

They only work by unleashing *pre-existing* antitumor immunity.

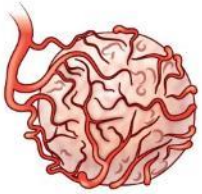
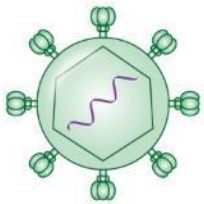
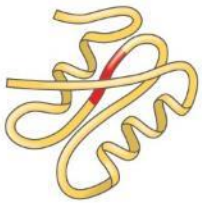
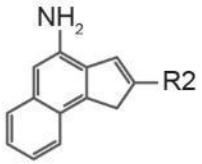
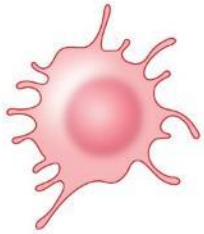
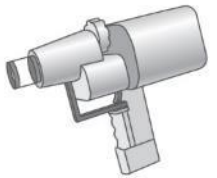
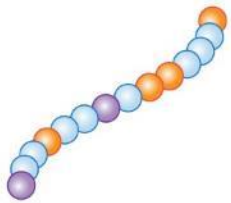
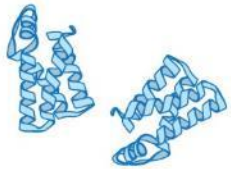
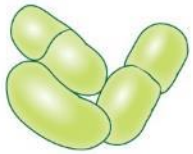
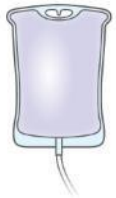
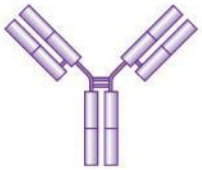
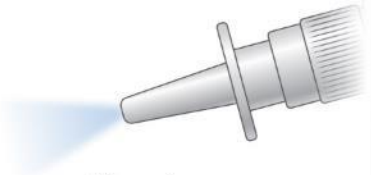
Thus, the success of checkpoint blockade (anti-CTLA4 and anti-PD-1) proves that spontaneous antitumor immunity exists and can be therapeutic.

However, the failure of checkpoint blockade antibodies in some patients highlights the need to induce antitumor immunity or to modulate other checkpoints.

Cancer Vaccines

The goal of therapeutic cancer vaccination is to increase the immunogenicity of tumor antigens which are poorly presented by the tumor in order to generate a high frequency of tumor-specific T cells.

Therapeutic cancer vaccines - composition

Antigen	Adjuvant	Vector	Vehicle
 Whole tumor	 Emulsifiers	 Viral vectors	 Injection
 Protein antigen	 Innate agonists	 Dendritic cells	 Gene gun
 Antigenic peptide(s)	 Cytokines	 Attenuated bacteria	 Systemic infusion
	 Antibodies		 Nasal spray

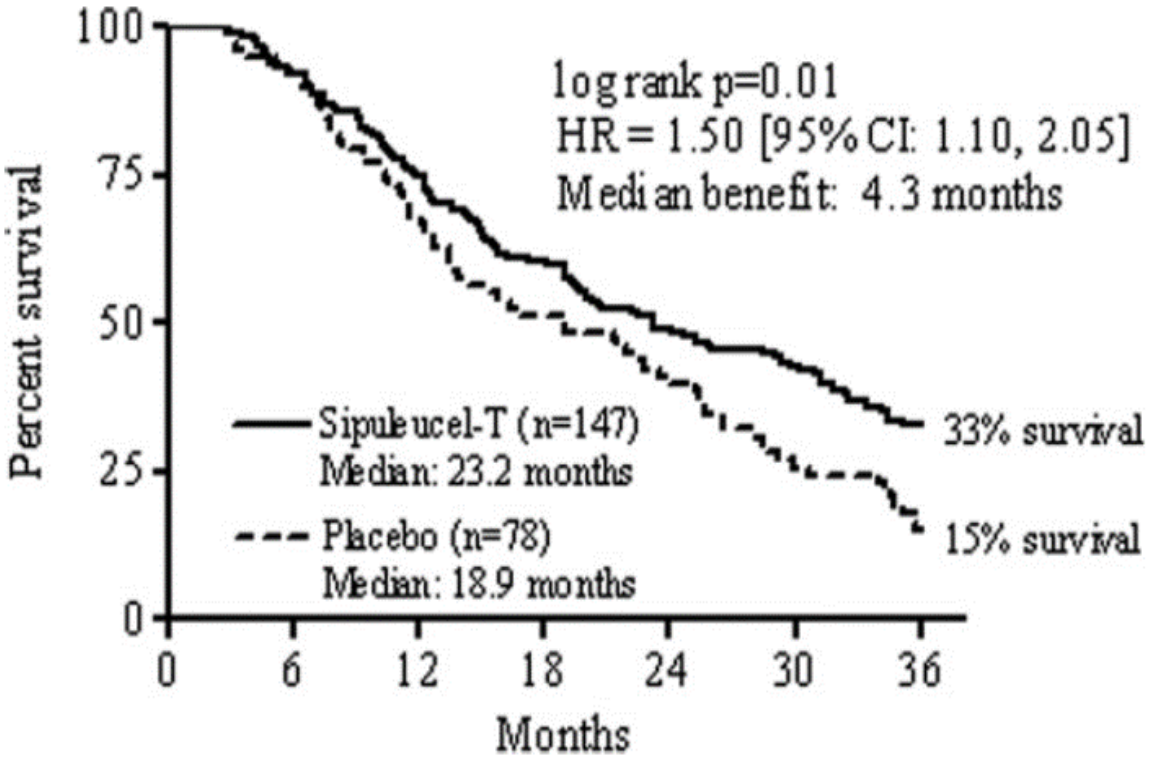
sitc

NIH NATIONAL CANCER INSTITUTE

Prostate cancer vaccine

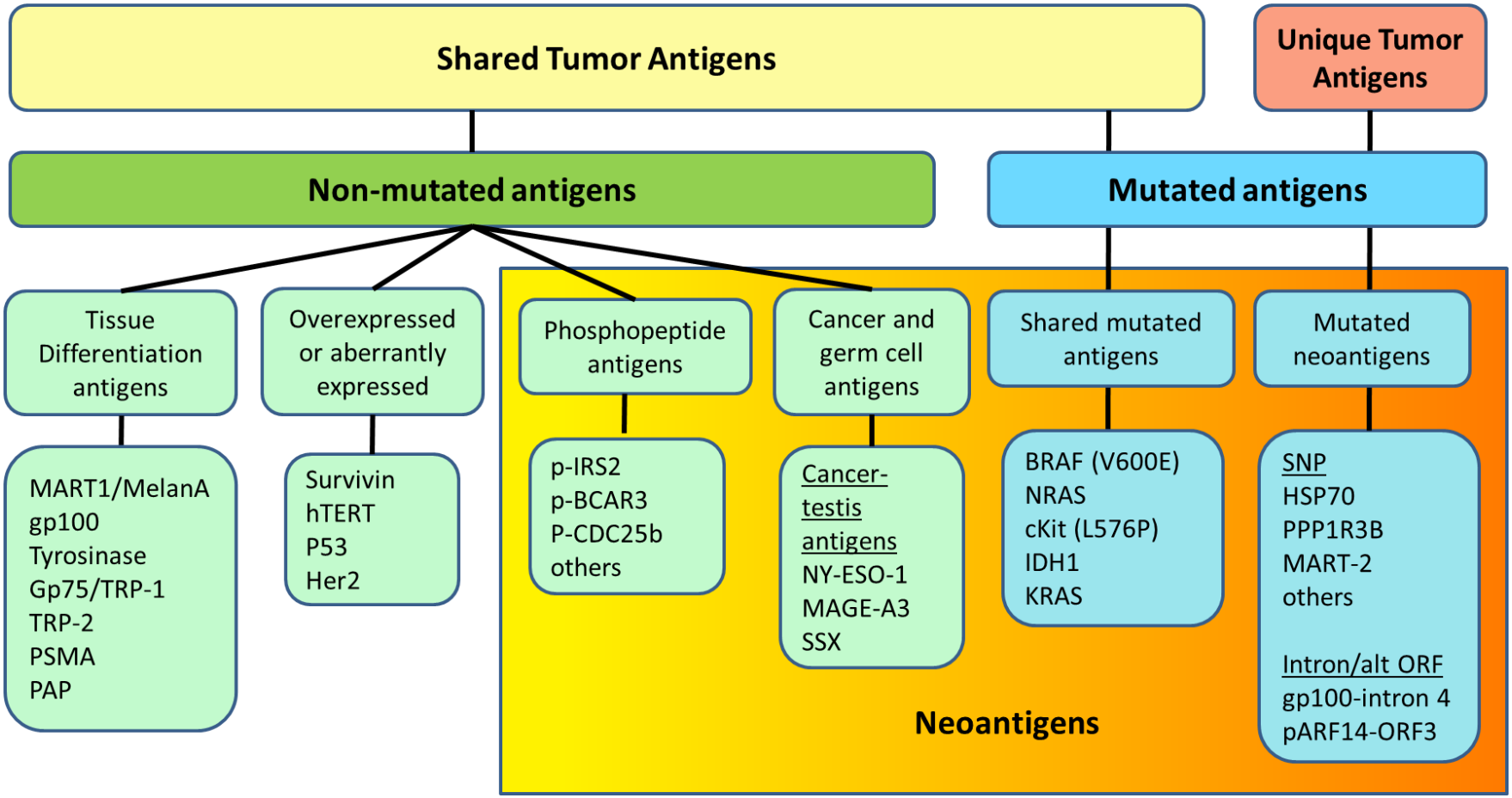
- **Cancer vaccine FDA approved for hormone-refractory prostate cancer:**

- Sipuleucel-T: PAP/GM-CSF/dendritic cells and T cells[1]
- Integrated data from 2 randomized phase III trials



1) Higano CS. *Cancer* 2009.

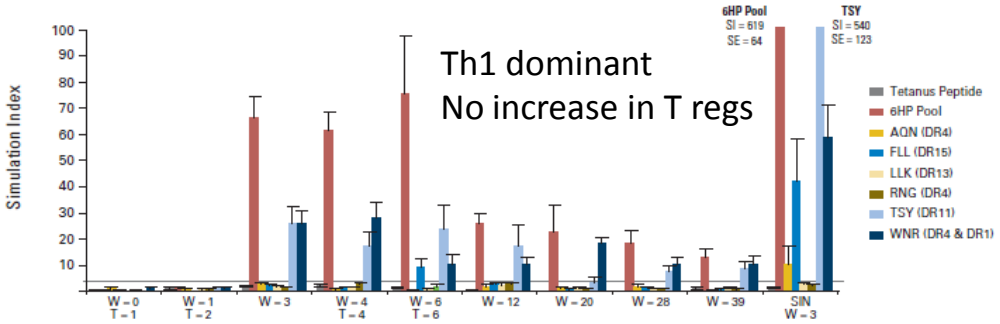
Shared and mutated antigens for T cells in human melanoma and other cancers



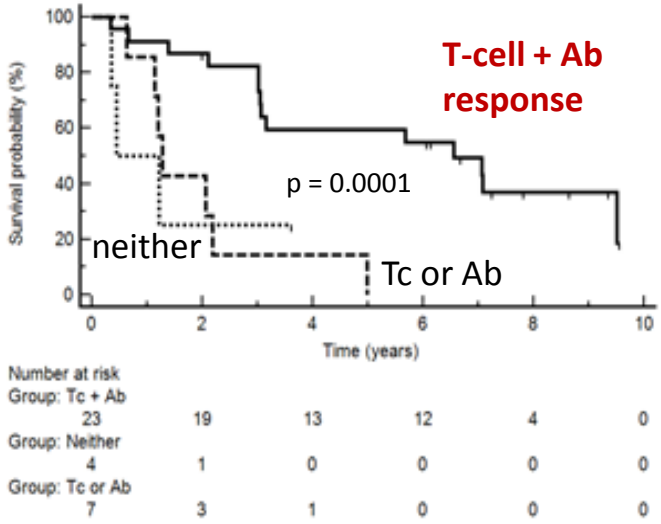
Targeting shared peptide antigens in melanoma

6 Class II-MHC Restricted Melanoma Peptides (6MHP)

Protein (residues)	Allele	Peptide Sequence
Tyrosinase $_{56-70}$	DR4	(A)QNILLSNAPLGPQFP (Topalian)
Tyrosinase $_{388-406}$	DR15	FLLHHAFVDSIFEQWLQRHRP (Kobayashi)
MelanA $_{51-73}$	DR4	RNGYRALMDKSLHVGTQCALTRR (Zarour)
MAGE-3 $_{281-295}$	DR11	TSYVKVLHHMVKISG (Manici)
MAGE-1-3, $6_{121-134}$	DR13	LLKYRAREPVTKAE (Chaux)
gp100$_{44-59}$	DR1, DR4	WNRQLYPEWTEAQRLD (Halder/Li)

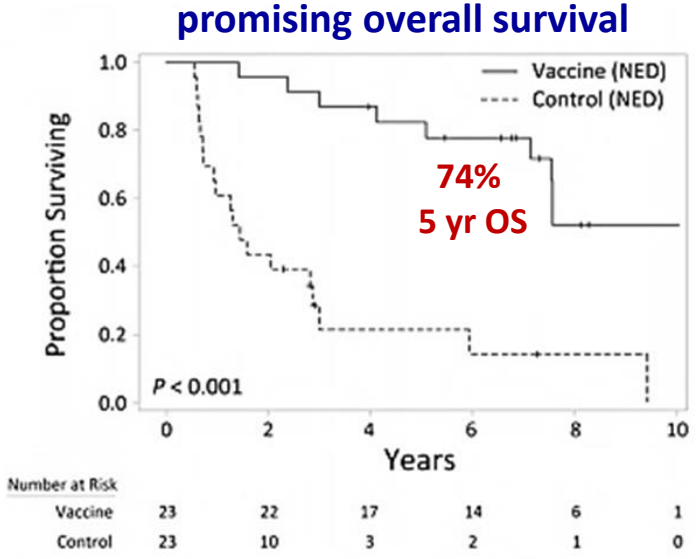


Immune response rate: 57% PBMC, 81% Node



Strong correlation between immune response and survival

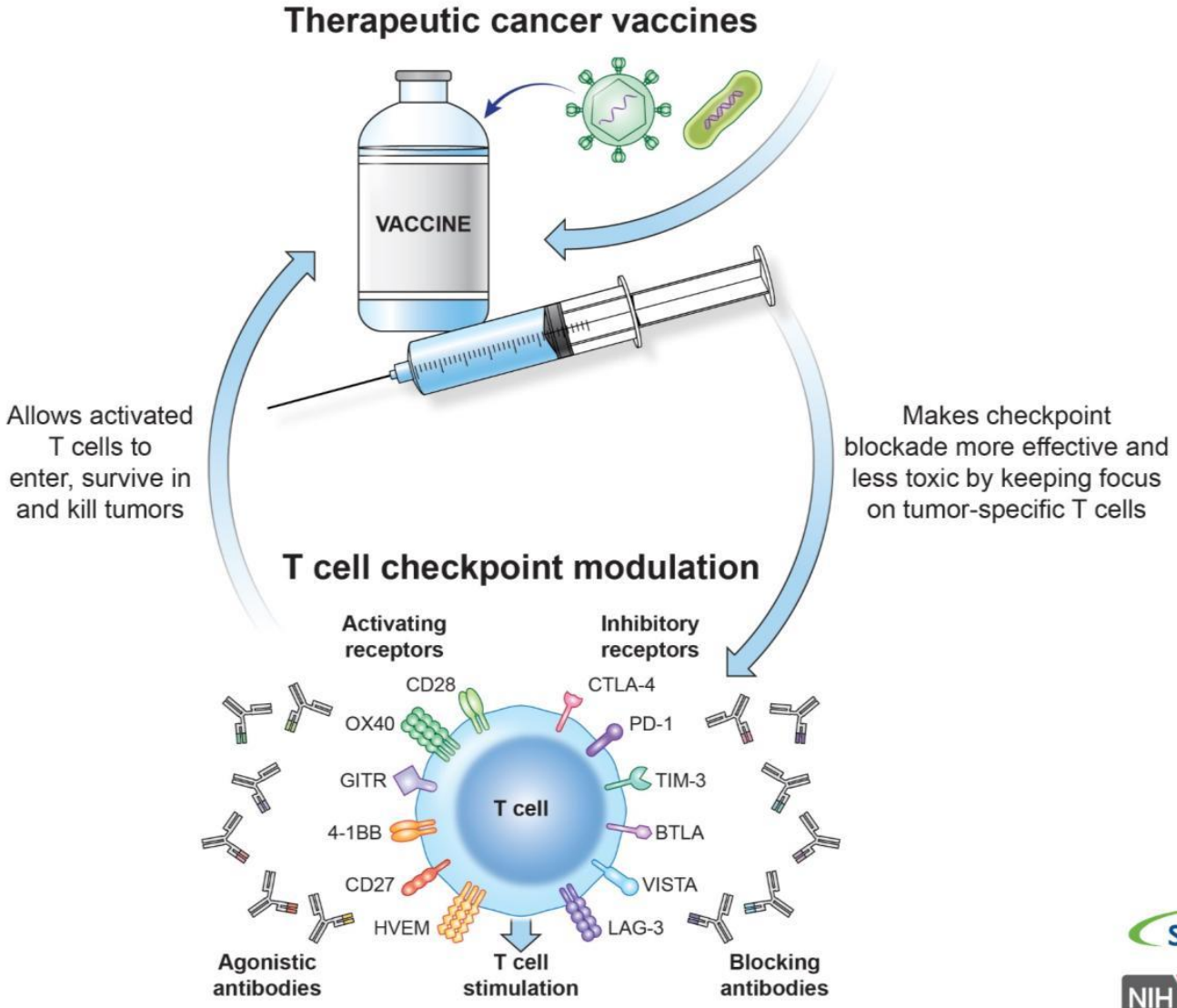
Resected stage IV melanoma: promising overall survival



Advanced melanoma: 2PR, 2SD of 17 patients, durable 1-7 years

Reed, CCR 2015
Hu, Ann Surg 2015
Dillon, JITC 2014
Slingluff, CCR 2013
Slingluff, JCO 2008

Combinations with checkpoint blockade may enhance outcomes with vaccines



sitc

NIH NATIONAL CANCER INSTITUTE

Clinical trials of combination immunotherapies with 6MHP vaccines for melanoma

CTLA4 blockade NCT02385669	• Expands T cell responses to tumor Ag • Mediates effects initially through CD4+ T cells (Allison) • Induces T cell infiltration of metastases
PD-1 blockade NCT02515227	• depends on T cell reactivity to tumor antigens • can increase T cell infiltration of metastases
BRAFi/MEKi NCT02382549	• induce MHC and antigen expression (J Wargo) • increase T cell infiltration

- 6MHP vaccines plus systemic therapy in advanced melanoma with biopsies of tumor and vaccine-draining nodes.

J Clin Oncol 2008; Dillon PM. JITC 2014; Hu, Y. CII 2014; Reed, C. Clin Ca Res 2015

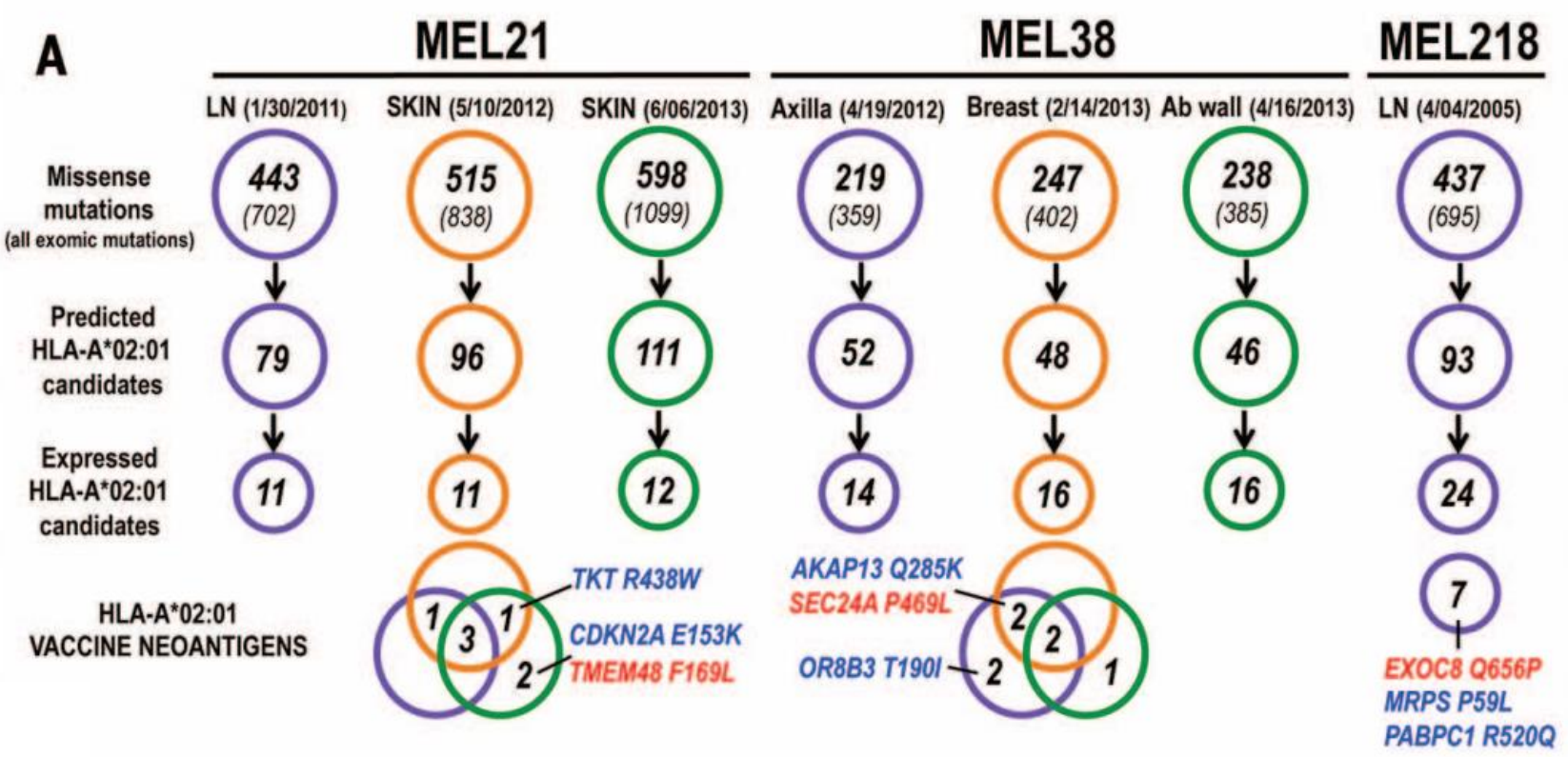
Mutated neoantigen vaccines

A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells

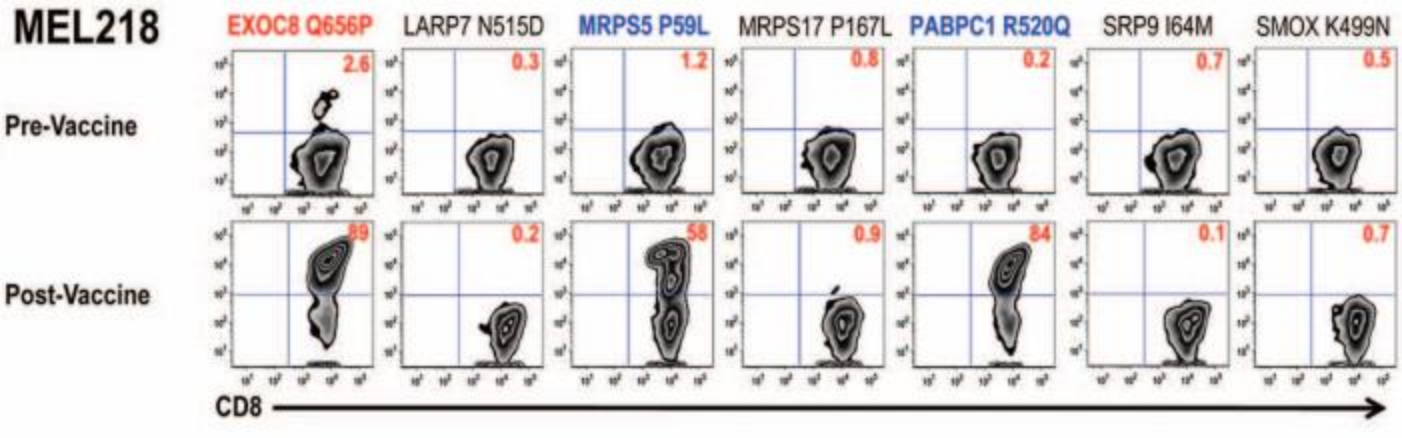
Beatriz M. Carreno,[1]* Vincent Magrini,[2] Michelle Becker-Hapak,[1] Saghar Kaabinejadian,[3] Jasreet Hundal,[2] Allegra A. Petti,[2] Amy Ly,[2] Wen-Rong Lie,[4] William H. Hildebrand,[3] Elaine R. Mardis,[2] Gerald P. Linette[1]

Science
May 2015

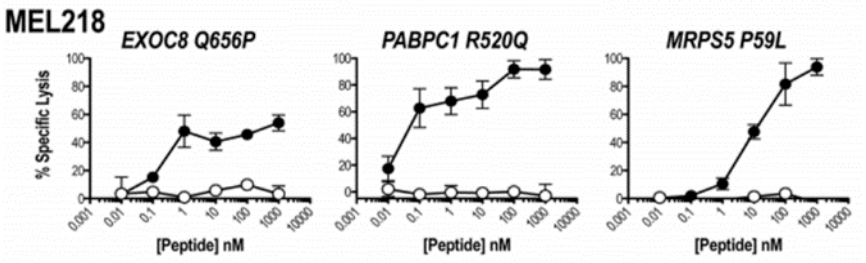
Mutated neoantigens selected in silico for 3 patients with resected stage III melanoma



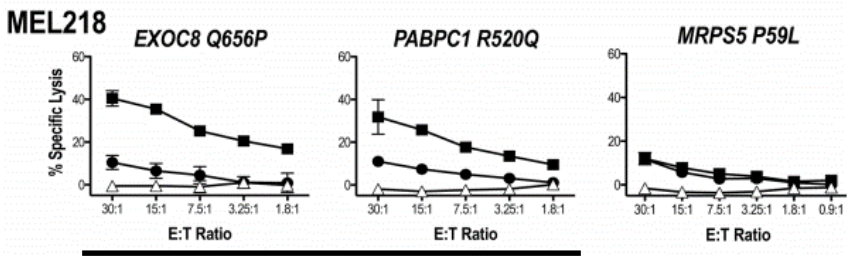
T cell responses to mutated peptides pulsed on dendritic cells



Specificity for mutant peptide: Vaccine-induced T-cells expanded from each patient recognize mutated peptide > wild-type peptide (8/9).



Natural processing of epitope: Vaccine-induced T-cells expanded from each patient recognize HLA-A2+ melanoma cells transfected with tandem minigene construct encoding mutated peptide, vs controls. (6/9).



Confirmed sequence by mass spectrometry

Carreno…Linette. Science May 2015

DC vaccine + neoantigen peptides in melanoma patients: Summary

- Neoantigen peptides selected in silico for high binding:
  - May have differential expression among different metastases of the same patient
- Vaccination with these peptides + $IL12^{+}$ DC have high rates of immunogenicity
  - Is safe (patients remain alive)
  - Induces durable T cell responses that can recognize naturally-processed antigen
  - Expands T cell repertoire
- Challenges:
  - T cell responses were demonstrated after 1 in vitro stimulation (not ex vivo)
  - Peptides must be selected for each patient
  - Antitumor activity not known

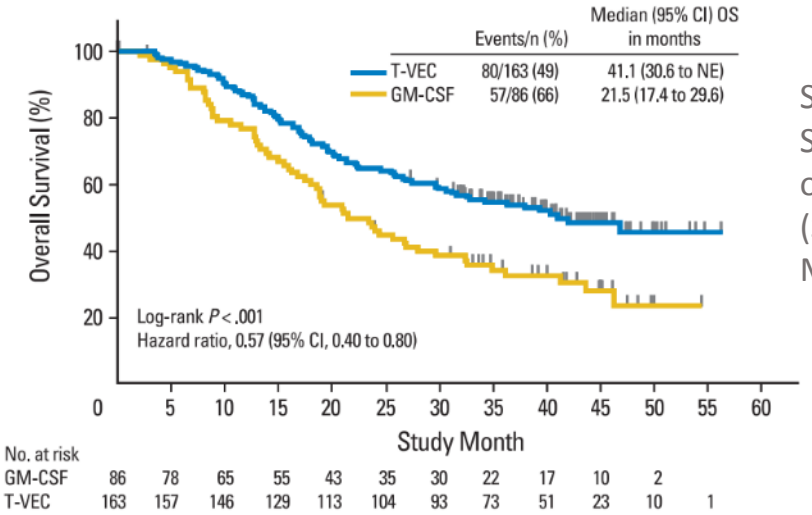
Carreno…Linette. Science May 2015

IN SITU VACCINATION:
Making a vaccine of a patient's own tumor

Randomized phase III trial of Talimogene laherparepvec (T-vec, IMLYGIC) vs systemic GM-CSF

	CR	PR
T-VEC	10.8%	15.6%
GM-CSF	0.7%	5.0%

	Durable RR
T-VEC	16.3%
GM-CSF	2.1%



Skin, Subcutaneous or Lymph node: (Stage IIIB, IIIC, IV M1a)

*FDA Advisory meeting (*April 29, 2015). Does talimogene laherparepvec have an overall favorable benefit-risk profile to support traditional approval for the treatment of injectable, regionally or distantly metastatic melanoma? Voted Yes: 22 to 1.

IMLYGIC Indicated for the Local Treatment of Unresectable Cutaneous, Subcutaneous and Nodal Lesions in Patients With Melanoma Recurrent After Initial Surgery - November 2015

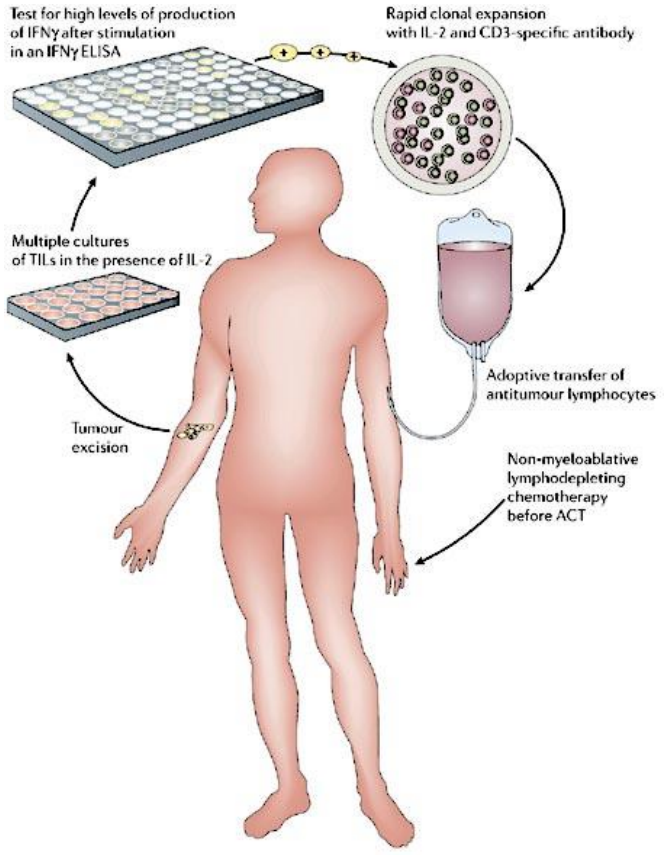
Andtbacka RH. *J Clin Oncol* 2015; http://www.fda.gov/AdvisoryCommittees/Calendar/ucm433807.htm .

Adoptive T cell therapy

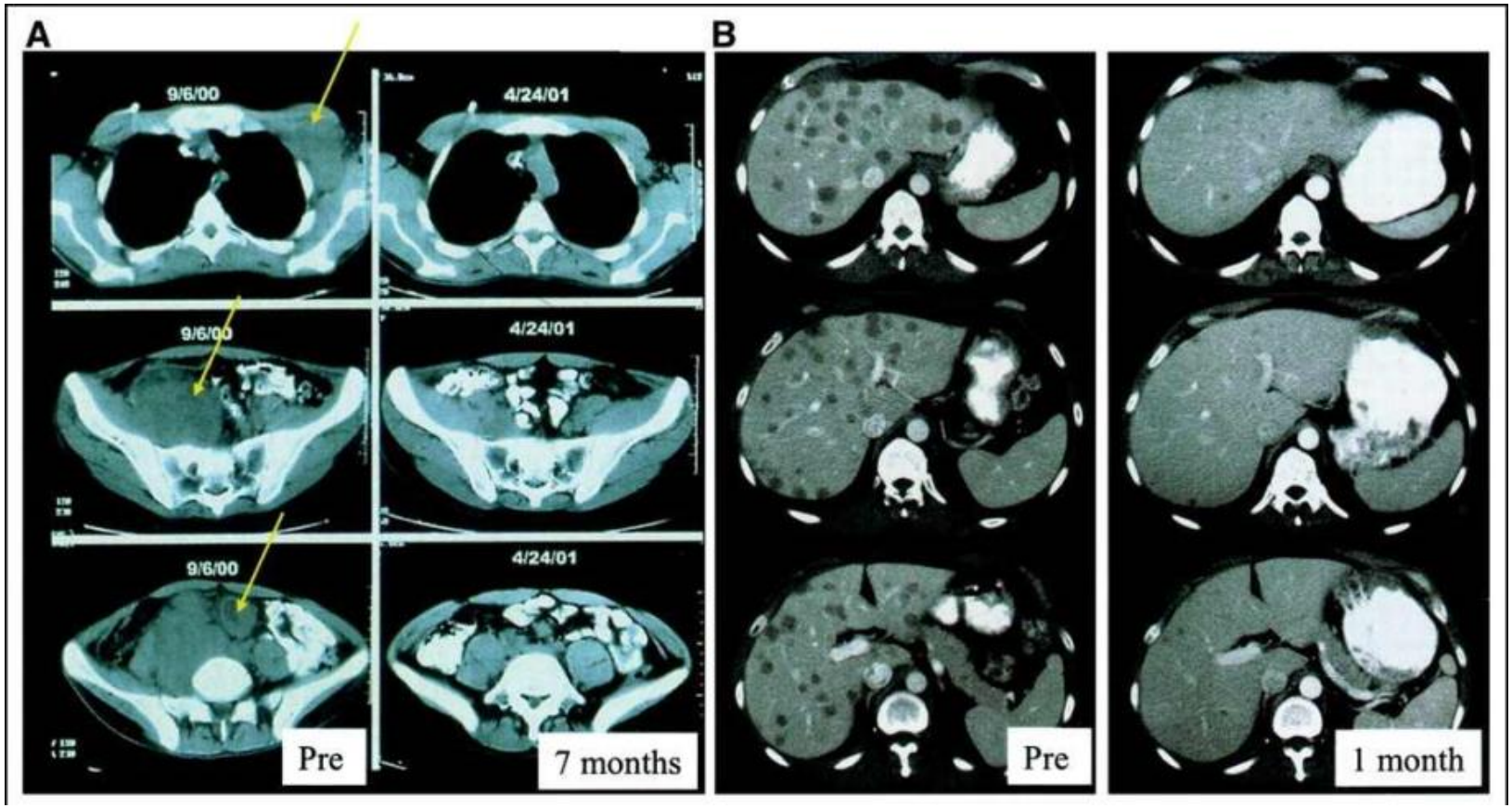
The goal of T cell adoptive transfer is to win the numbers game and overwhelm the tumor with a higher frequency of tumor-specific T cells than it is capable of suppressing.

Adoptive Cellular Therapy: Rehabilitating a patient's own T cells to destroy cancer

- Expansion of T cells outside the body, that target cancer antigens
  - Tumor infiltrating lymphocytes (TIL)
- Adding a missing gene – to recognize a specific target on cancer
  - T-cell receptor for tumor antigens
  - Chimeric antigen receptor (CAR-T)
- Arm T cells with antibody
- Bispecific antibody-armed T-cell (BAT) immunotherapy



Melanoma Regression with T cell therapy

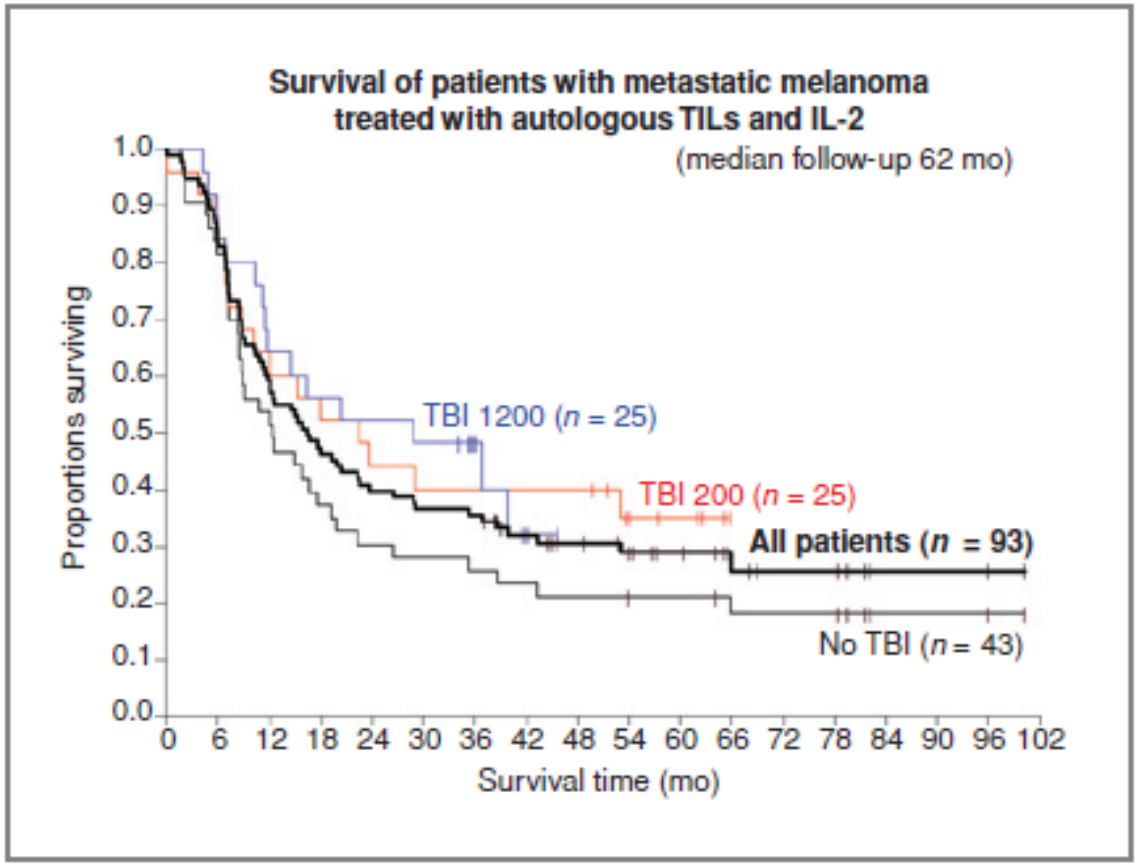


TIL after lymphodepletion. Dudley, J Clin Oncol 2005

Durable benefit with adoptive T cell transfer of tumor-infiltrating lymphocytes.

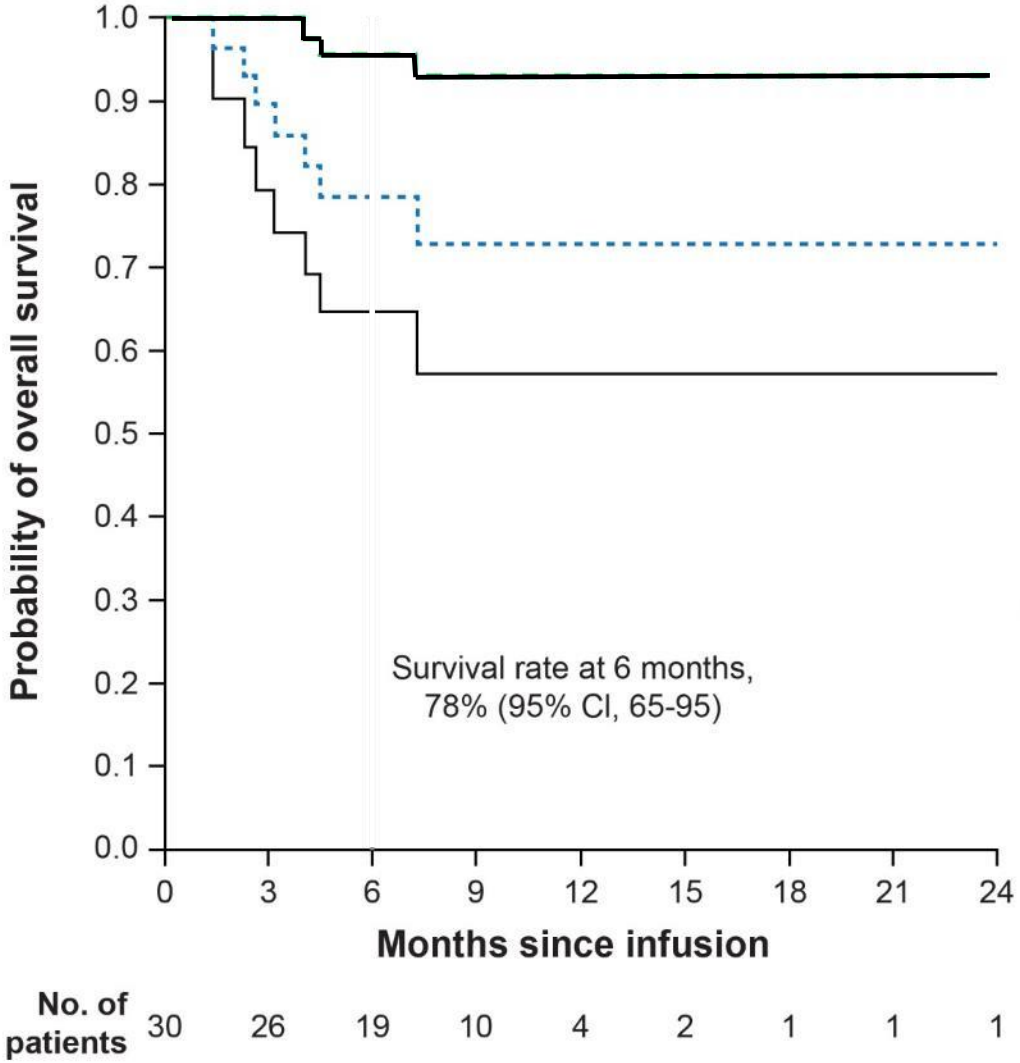
Surgery Branch, NCI (SA Rosenberg)

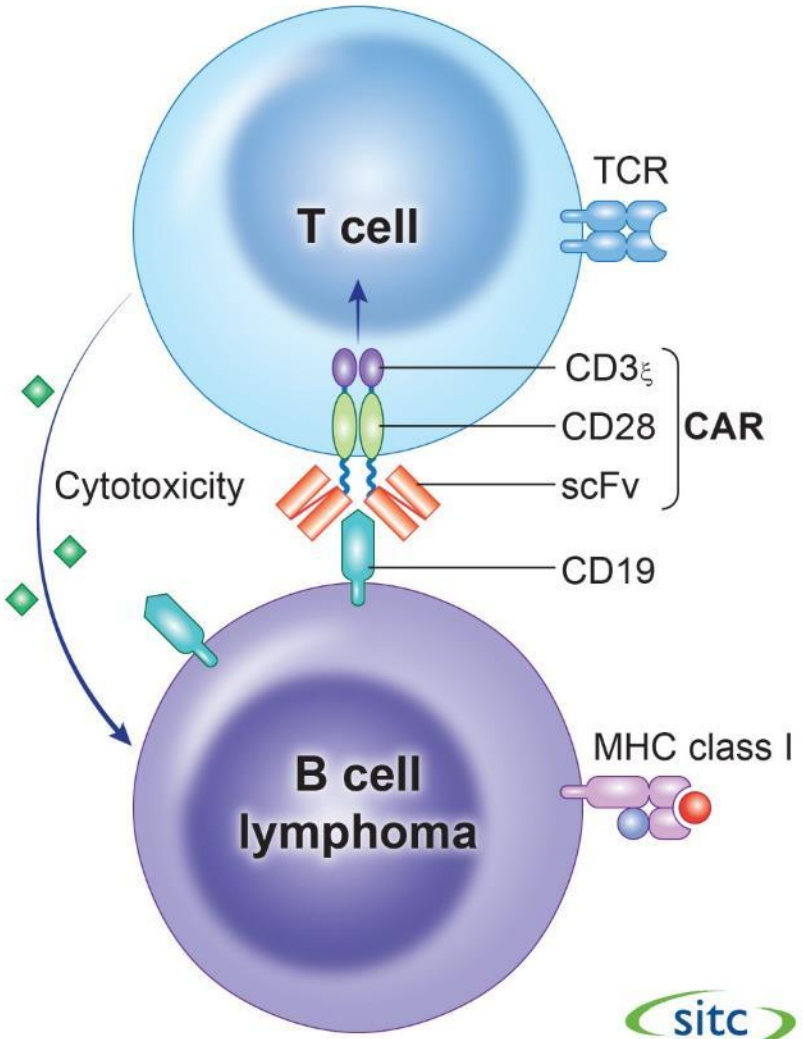
Overall survival of patients receiving TILs with the chemotherapy preparative regimen alone (no TBI) or plus 2 or 12 Gy TBI



Rosenberg et al. Clinical Cancer Research 2011

Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy





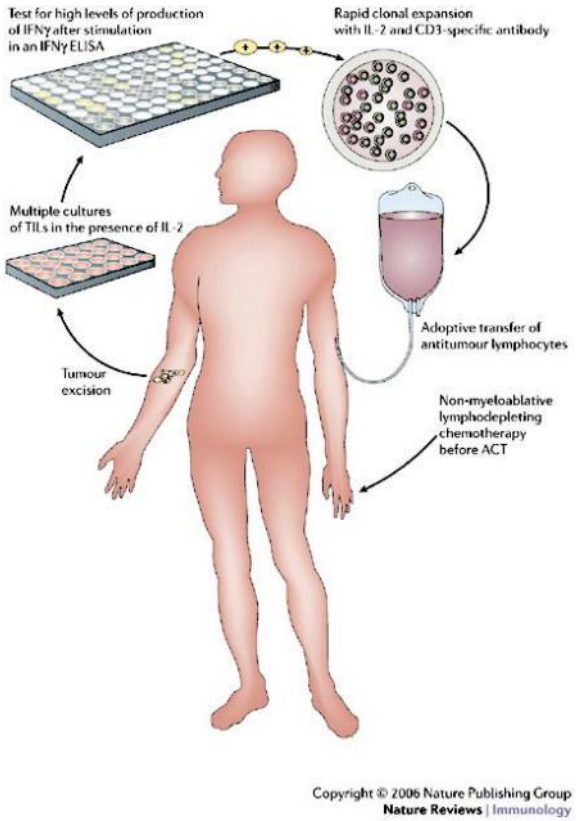
Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2016.
Chimeric antigen receptor T cells for sustained remissions in leukemia.
The New England Journal of Medicine. 374(10): 998.

sitc

NIH NATIONAL CANCER INSTITUTE

ACT: Successes and Future Directions

- TIL therapy:
  - 50-70% response; 25% durable survival - melanoma
- CAR-T cells:
  - 90% response in ALL (acute lymphoblastic leukemia
  - CD19 CARs for: ALL, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia (CLL),
- T-cell receptor-transduced T cells
  - Dramatic benefit in selected cancers
- BAT cells: promising clinical outcomes in a range of solid tumors
- Can they be effective in more patients by adding therapy that makes the tumors more receptive to infiltration by T cells (eg: PD-1 antibody)?

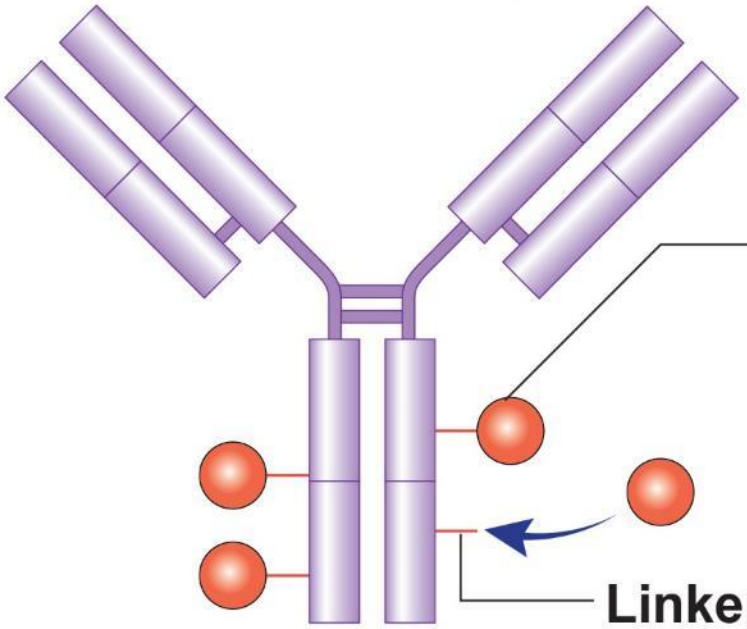


Effector Antibodies and ADC

The goal of effector antibodies is to utilize the exquisite sensitivity of antibodies to specifically target and kill tumor cells using mechanisms which are difficult to evade or suppress.

Effector antibodies and antibody-drug conjugates (ADCs)

Antibody
Specific to tumor-associated antigen



Cytotoxic agent
Designed to kill target cells when internalized and released or activated

Linker
Attaches cytotoxic agent to the antibody

sitc

NIH NATIONAL CANCER INSTITUTE

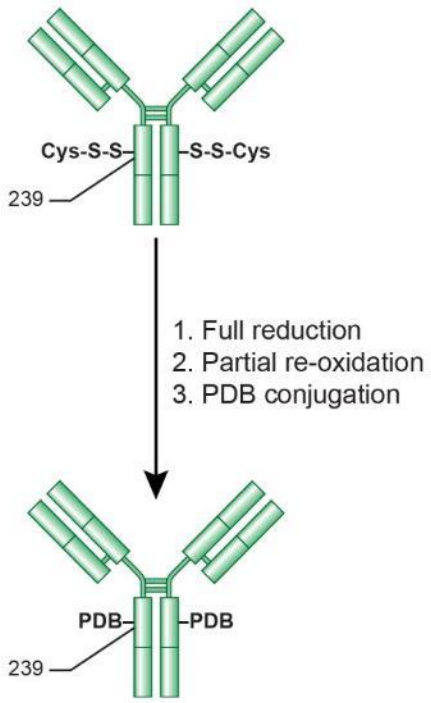
Key ADC/antibody principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity

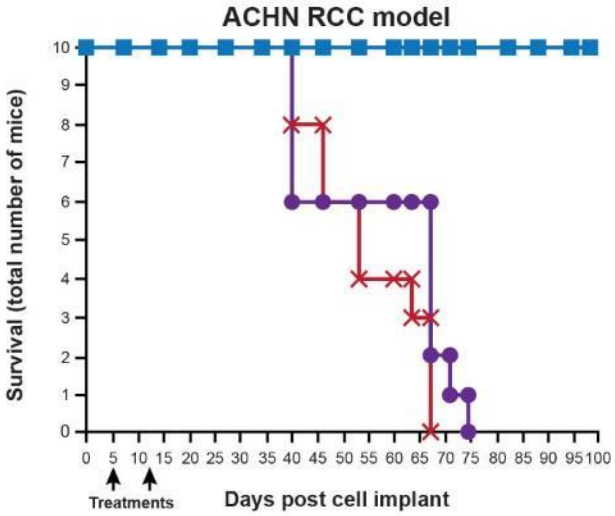
- **Internalization:** The target tumor surface protein must internalize to deliver the toxin - it should do so frequently and to a suitable endosomal compartment.

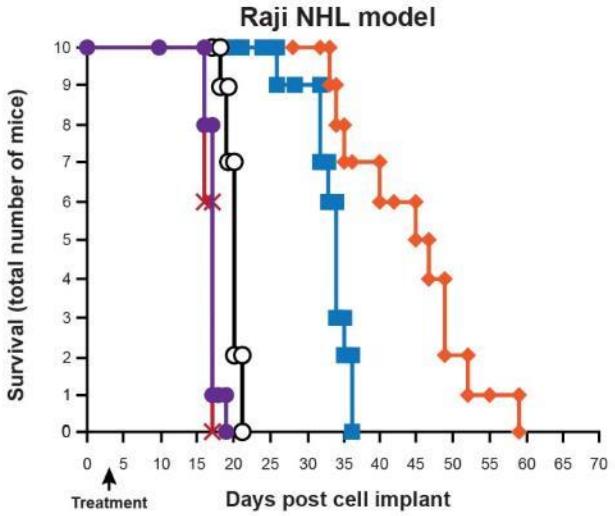
- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.

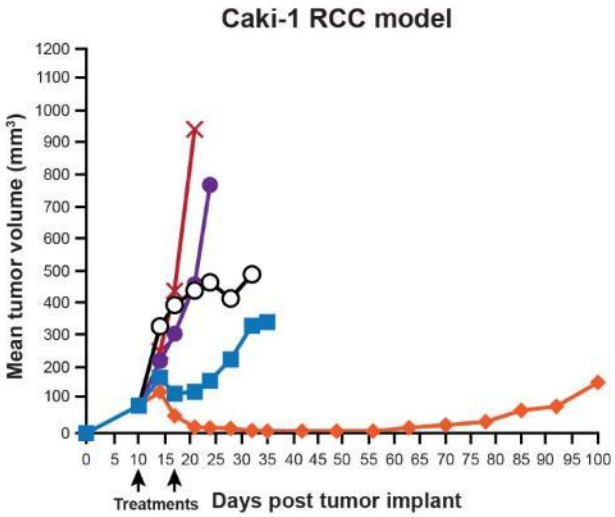
SGN-70A in the clinic for NHL and RCC

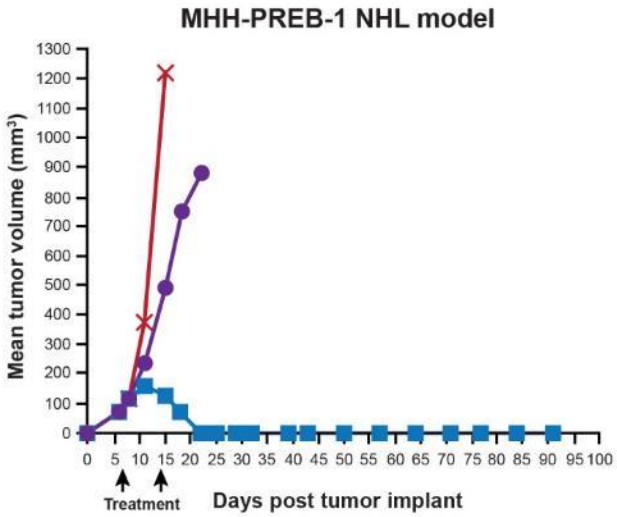


Conjugation process for the 239C antibody format. The engineered antibody, expressed in CHO cells, was isolated as the cysteine disulfide at position 239. The antibody was fully reduced with TCEP and partially reoxidized with dehydroascorbic acid. The resulting free cysteines at position 239 were conjugated to the PDB-linker to give the PDB ADC with nominally 2 drugs/mAb.









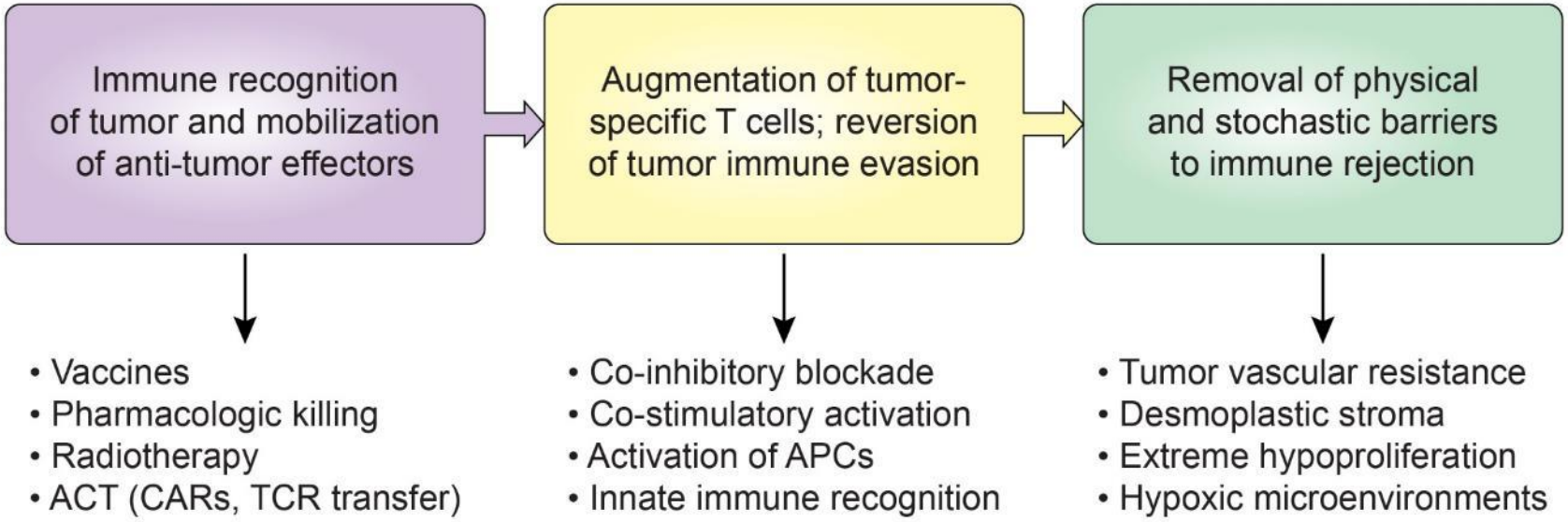
Untreated
h1F6239C-PDB 0.3 mg/kg
h1F6239C-PDB 0.1 mg/kg
hIgG239C-PDB 0.3 mg/kg
hIgG239C-PDB 01. mg/kg

Jeffrey SC, Burke PJ, Lyon RP, Meyer DW, Sussman D, Anderson M, Hunter JH, Leiske CI, Miyamoto JB, Nocholas ND, et al. 2013. A potent anti-CD70 antibody-drug conjugate combining a dimeric pyrrolobenzodiazepine drug with site-specific conjugation technology. Bioconjug Chem. 24(7): 1256-63.

sitc

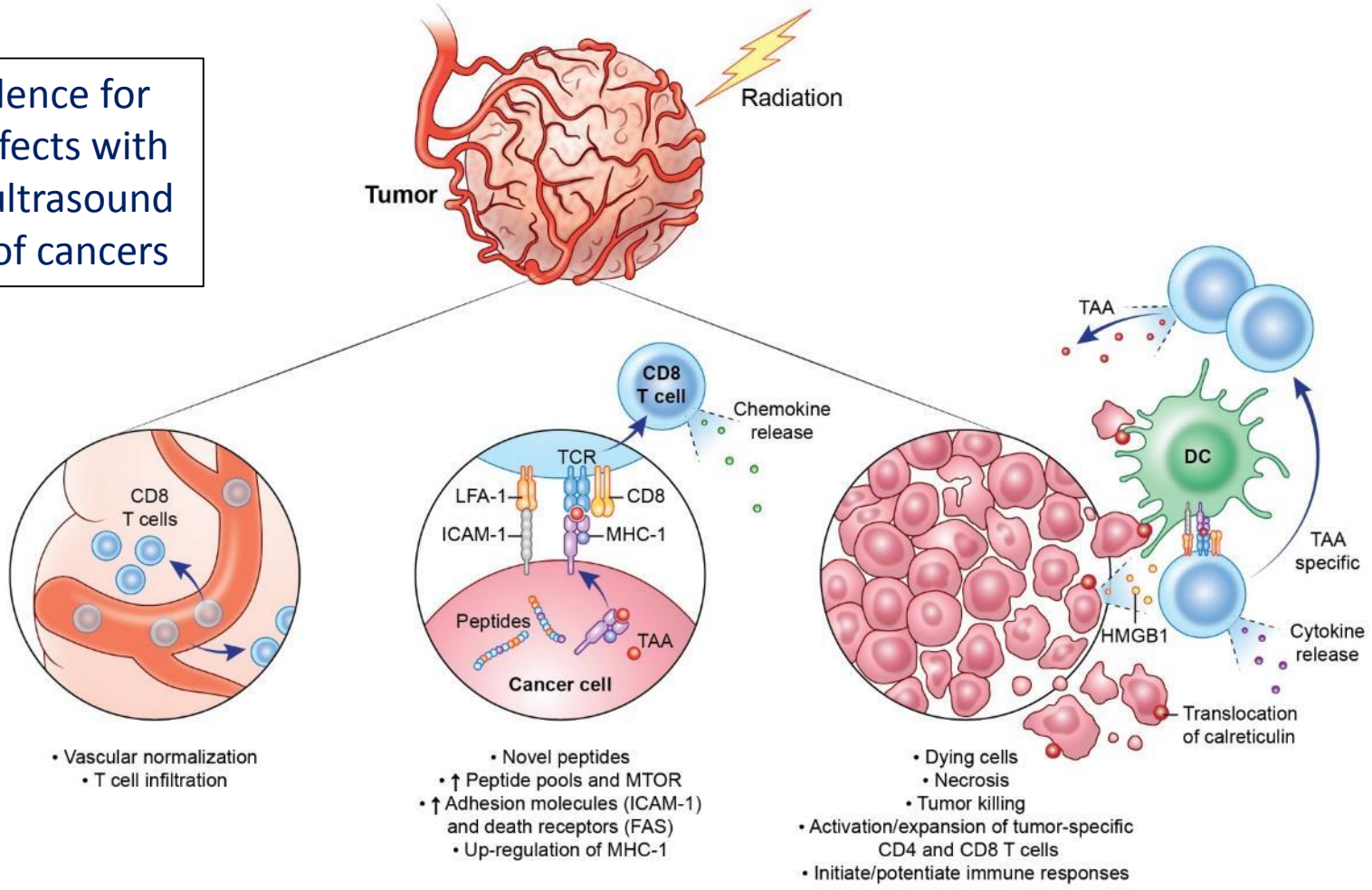
NIH NATIONAL CANCER INSTITUTE

Seeking combinations outside of T cell checkpoint immunotherapy



Radiation therapy: A potent adjuvant for tumor immunity

Early evidence for similar effects with focused ultrasound ablation of cancers



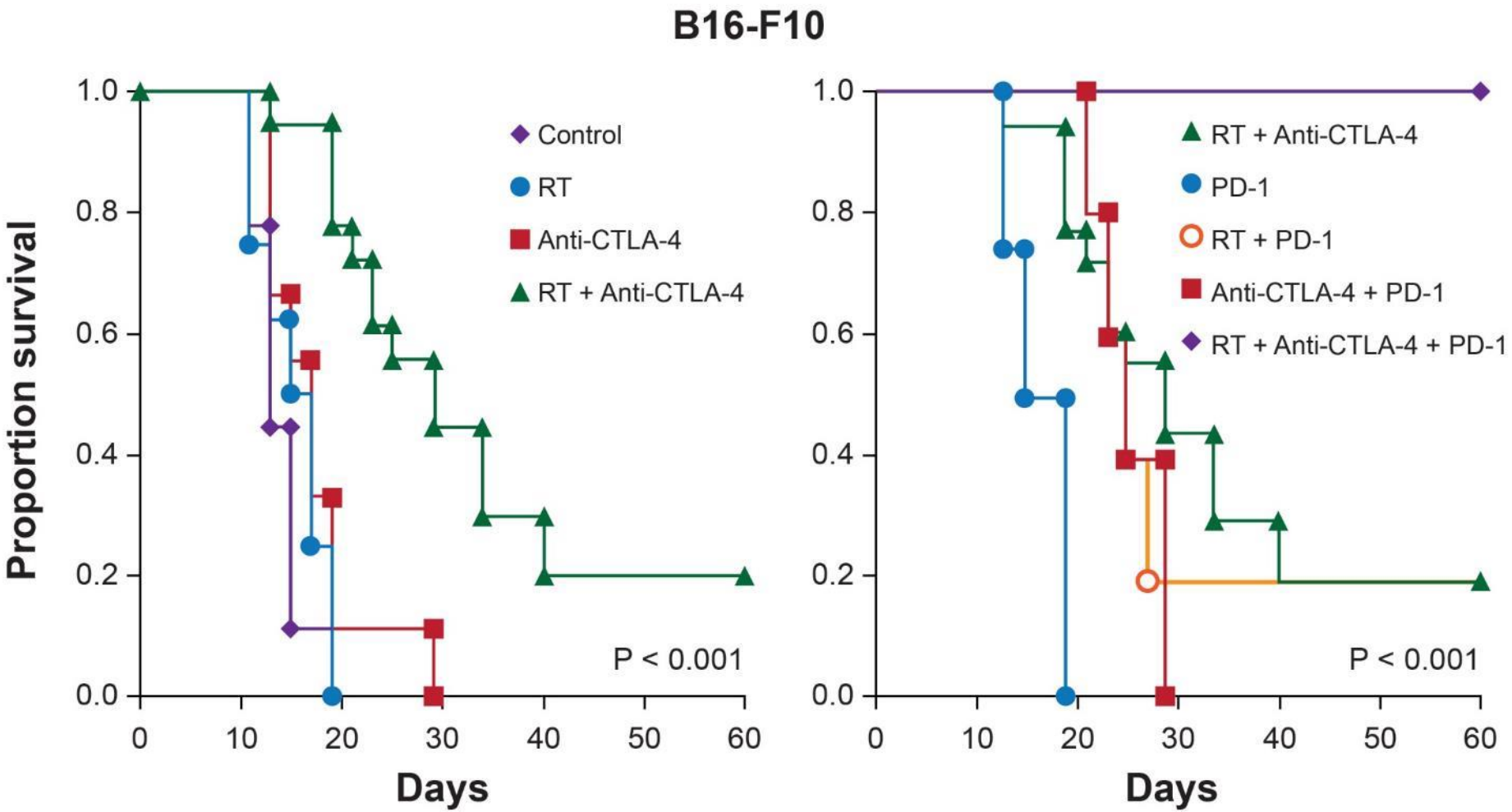
Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

http://www.ncbi.nlm.nih.gov/pubmed/18777956

sitc

NIH NATIONAL CANCER INSTITUTE

Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



Victor CT, Rech A, Maity A, Rengan R, Pauken K, Stelekati E, Benci J, Xu B, Dada H, Odorizzi P, et al. 2015. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 520: 373-377.

sitc

NIH NATIONAL CANCER INSTITUTE

UVA Clinical trials: investigator-initiated at UVA and in clinical trial networks

- Cancer vaccines
- Adoptive cell therapy
- Focused ultrasound ablation
- Checkpoint blockade combinations with IL-2 and other immune therapies
- Intratumoral therapies with checkpoint blockade and TLR agonists
- Personalized immune therapies

Lessons and Take-Home Messages

- Key Points and Lessons Learned
  - As a cancer evolves in a patient, there is a constant battle between the cancer and the patient's immune system
  - Different cancers have different weaknesses
  - Cancer immunotherapy has enabled new tools to rehabilitate a patient's immune system or to equip it to overcome a growing cancer
- Potential Impact on the Field
  - The future of cancer immunotherapy includes new combinations and new therapies that are tailored to a patient's own cancer and immune system and their response to each treatment.
  - Clinical trials offer options for patients now and promise to improve therapy for future patients.