

# Cancer Immunotherapy Patient Forum

New approaches to immunotherapy

for the Treatment of Melanoma, Leukemia, Lymphoma,  
Lung and Genitourinary Cancers - November 7, 2015



# Presenter Disclosure Information

*Craig Slingluff, MD*

The following relationships exist related to this presentation:

- Scientific adv boards (Funds to Institution)
  - Immatics (cancer vaccines)
  - Polynoma (cancer vaccines) – PI for MAVIS trial
- Funded clinical trials:
  - Glaxo-Smith Kline: Cancer vaccine
- Support by provision of drug for clinical trials
  - Merck, Celldex, 3M, Oncovir
- Patent holder for peptides used in cancer vaccines, via UVA Licensing and Ventures Group
- Off-label or experimental use of:
  - Cancer vaccines, Adoptive T cell therapy, Intralesional therapies, CD27 antibody

# Personalized cancer immunotherapy

- Adoptive T cell therapy
  - TIL therapy
    - CAR-T cell therapy
- Personalized Cancer Vaccines
  - In situ vaccination
- Personalized selection of immune therapies
  - Effective therapies / toxicity / cost
  - Combination with standard therapies
  - Personalized assessment of tumor to guide therapy

# Training your own body to win



Shannon Miller

## Shannon Miller (Gymnast): most decorated gymnast, male or female, in U.S. history

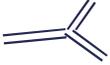
- Olympic Gold 1996 x 2; 1992: 5 medals
- Ovarian cancer 2011
- In remission after surgery and chemotherapy
- President of Shannon Miller Lifestyle: Health and Fitness for Women,
- Autobiography *It's Not About Perfect* 2015



## Mario Lemieux (Hockey): "The Magnificent One"

- Hodgkin's lymphoma in 1993.
- Olympic gold 2002
- In remission after radiation therapy.
- Founded the Mario Lemieux Foundation, which raises funds for cancer research.

# Multiple arms of the immune system: T cells and their targets

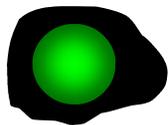
  
*Antibody*

 carbohydrates  
and proteins



 MHC Class I  
+ peptide

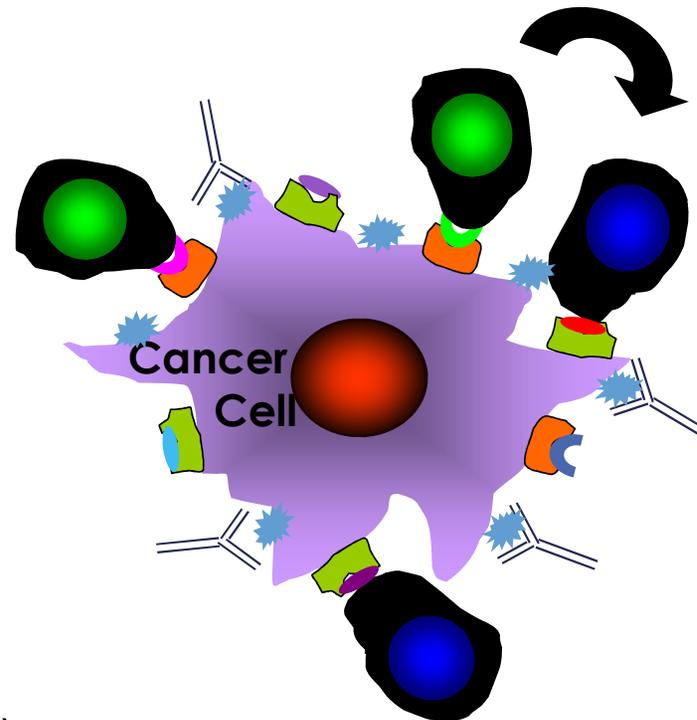
*CD8 killer T-cells*



 MHC Class II  
+ peptide

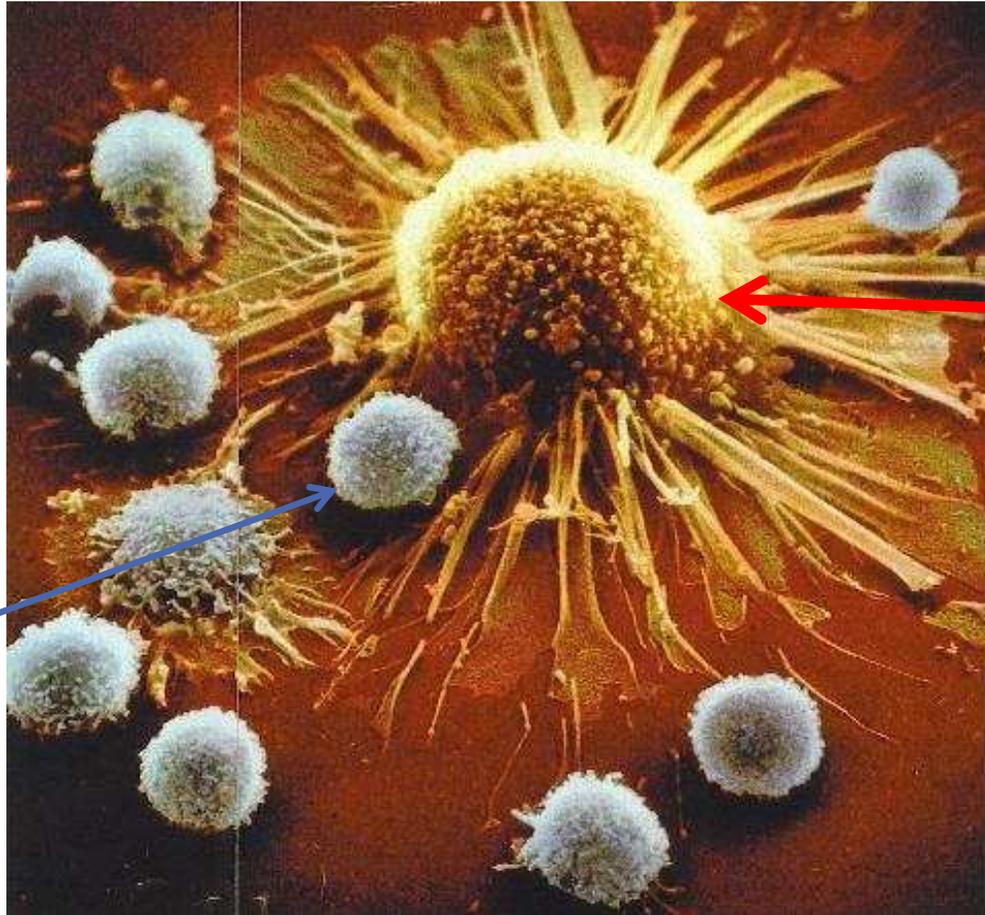
*CD4 helper T-cells*

Innate Immunity (eg: NK, TLR)



# T lymphocytes at the center of immune therapy

Killer T cell:  
(immune  
system cell)

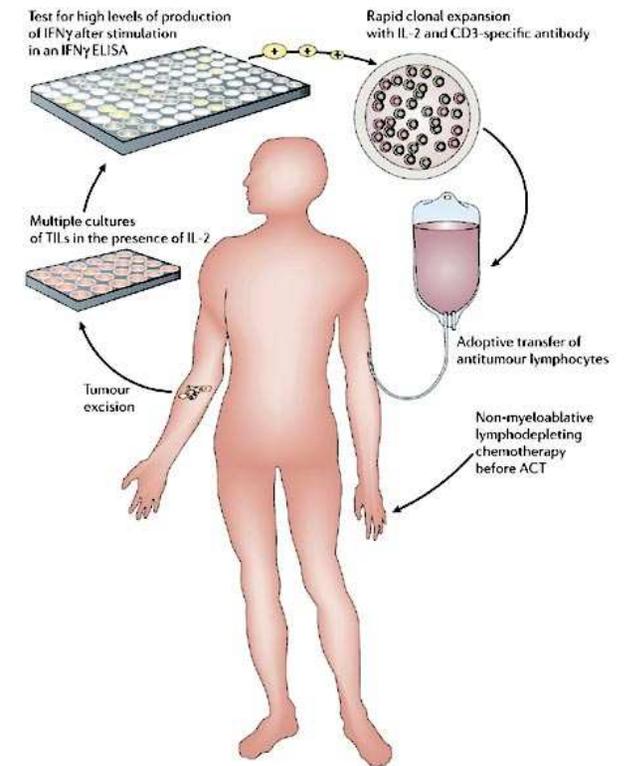


Cancer  
Cell

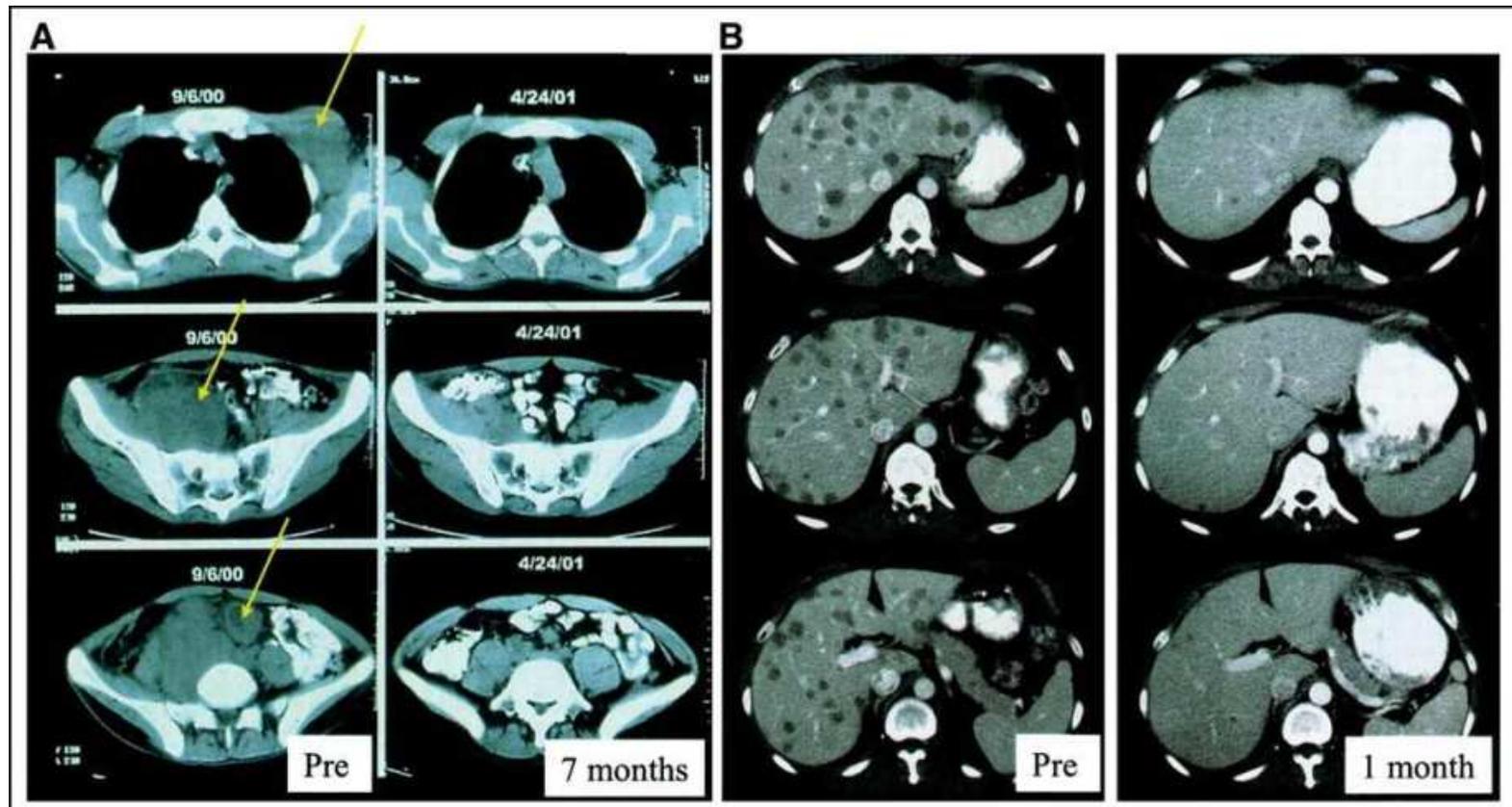
Peter Jaret "Our Immune System: The Wars Within,"  
*National Geographic* (June 1986).

# 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)



# Melanoma Regression with T cell therapy

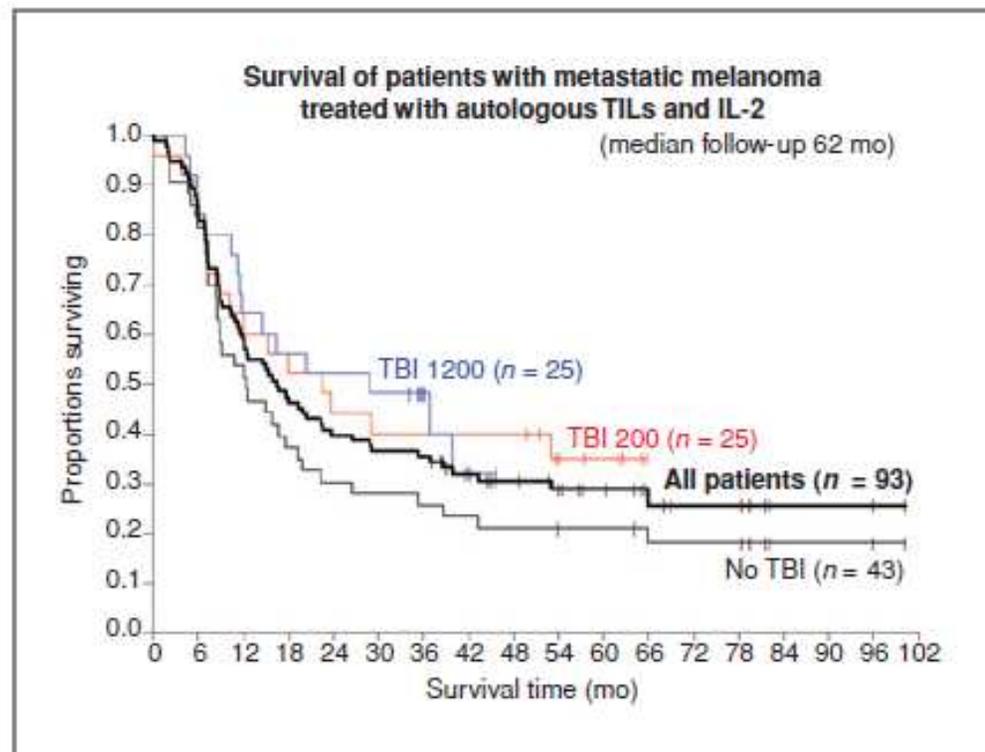


TIL after lymphodepletion. [Dudley, J Clin Oncol 2005](#)

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

Surgery Branch, NCI (SA Rosenberg)

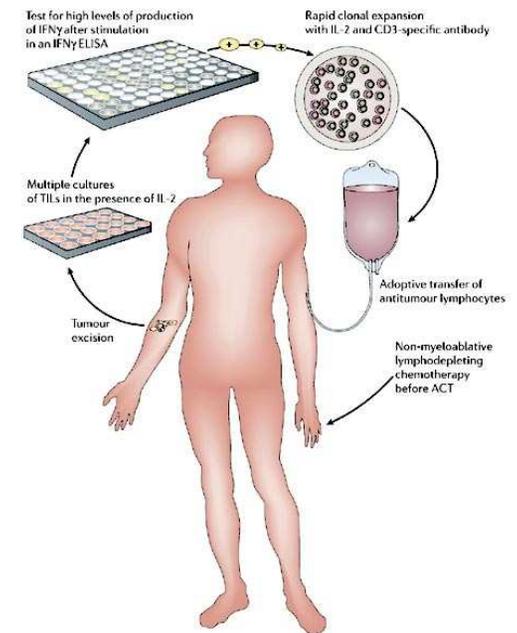
Overall survival of patients receiving TILs with the chemotherapy preparative regimen alone (no TBI) or plus 2 or 12 Gy TBI



Rosenberg et al. *Clinical Cancer Research* 2011

# ACT: Successes and Future Directions

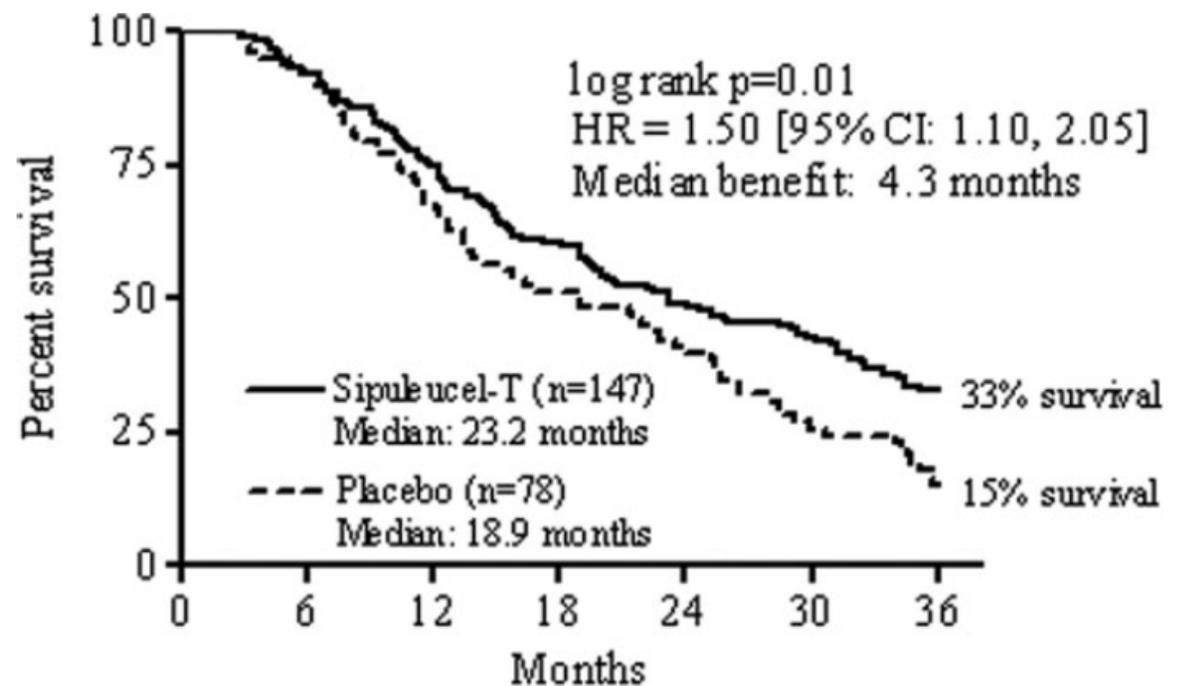
- TIL therapy:
  - 50-70% response; 25% durable survival - melanoma
- CAR-T cells:
  - 90% response in ALL (acute lymphoblastic leukemia)
  - CD19 CARs for: ALL, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia (CLL),
- T-cell receptor-transduced T cells
  - Dramatic benefit in selected cancers
- 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)?



# Personalized cancer vaccines

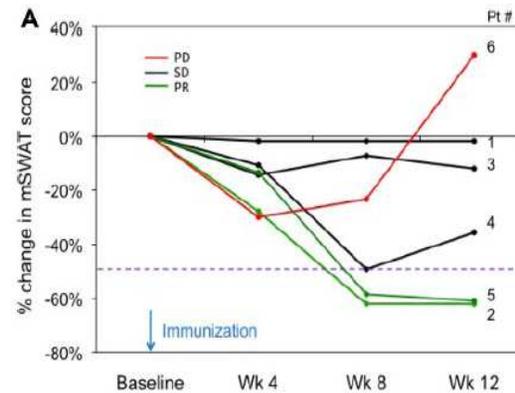
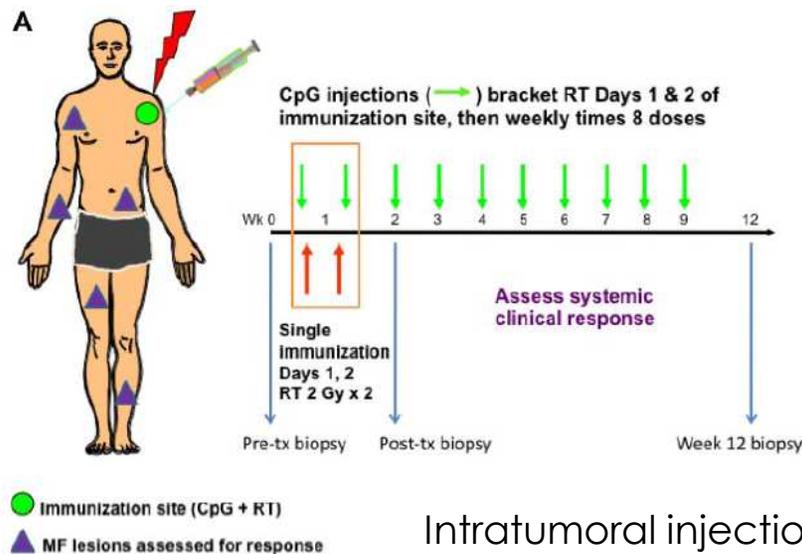
## Cancer vaccine FDA approved for hormone-refractory prostate cancer:

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



1) Higano CS. Cancer 2009.

# In situ vaccination with a TLR9 agonist in cutaneous T-cell lymphoma



Intratumoral injection of TLR9 agonist (CpG) plus RT into one lesion (thigh in example), with evaluation of overall clinical response at systemic sites (calf in example).

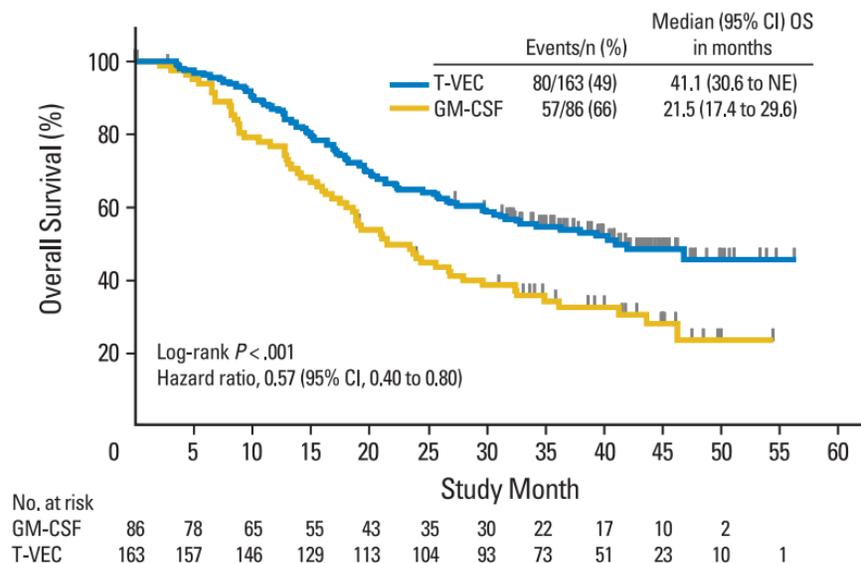
Open to enrollment: NCT02254772. TLR9 Agonist SD-101, Ipilimumab, and Radiation Therapy in Treating Patients With Low-Grade Recurrent B-cell Lymphoma

Kim YH...Levy RL, 2012 (Blood)

# 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> .

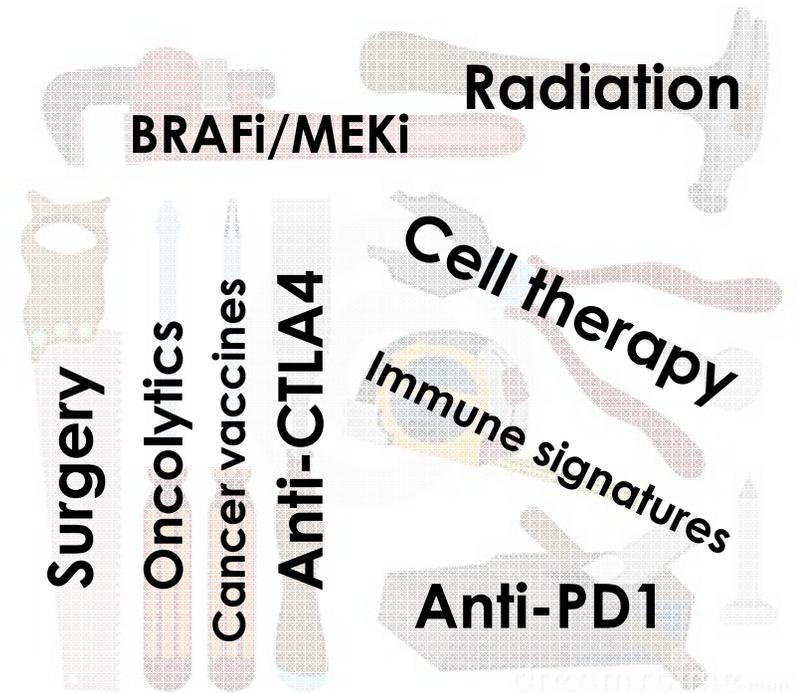
# Personalized cancer vaccines

- In situ vaccination:
  - Treat a tumor with immune activators, radiation, or chemotherapy
  - Activate immune response to that patient's tumor
- Personalized target antigen discovery
  - For each patient,
    - define known targets (antigens) on her/his own cancer cells
    - Identify modified (eg mutated) targets on her/his own cancer cells
    - Create a cocktail of peptides or RNA to give as a vaccine
    - Administer vaccines to prevent recurrence or to treat advanced cancer
  - Regulatory hurdles, cost
  - Early proof of principle
- Clinical trials testing optimal vaccine approaches alone and in combinations.

# What to do with all these tools?



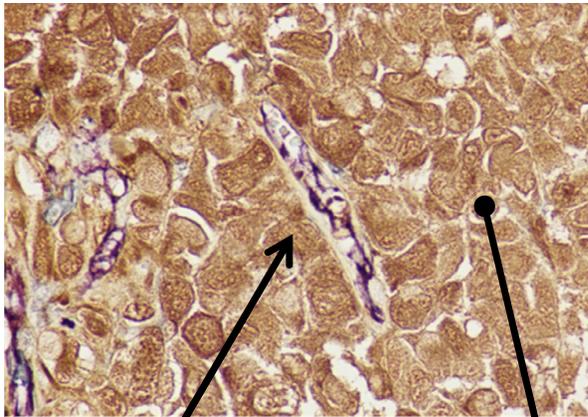
Until 2010



2015

# Immunotherapy limited by ability of T cells to infiltrate metastatic disease

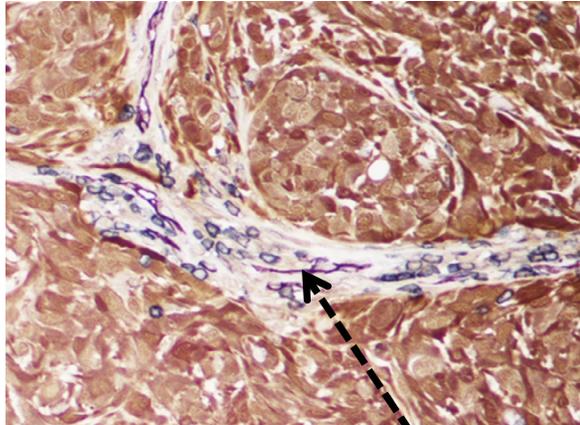
Immunotype A



Blood vessel  
purple = CD31

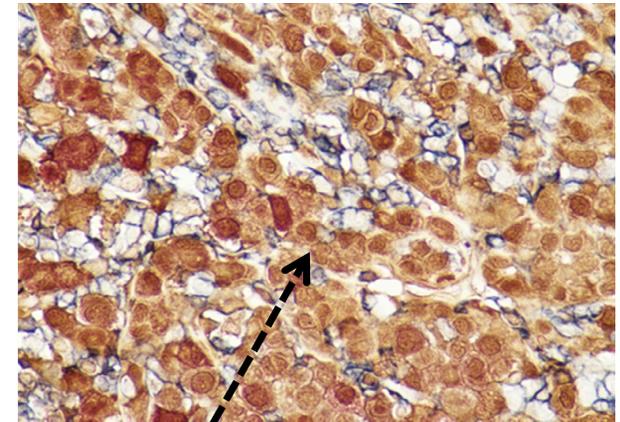
Melanoma cells:  
brown = S100

Immunotype B



Cuffing blood  
vessels only

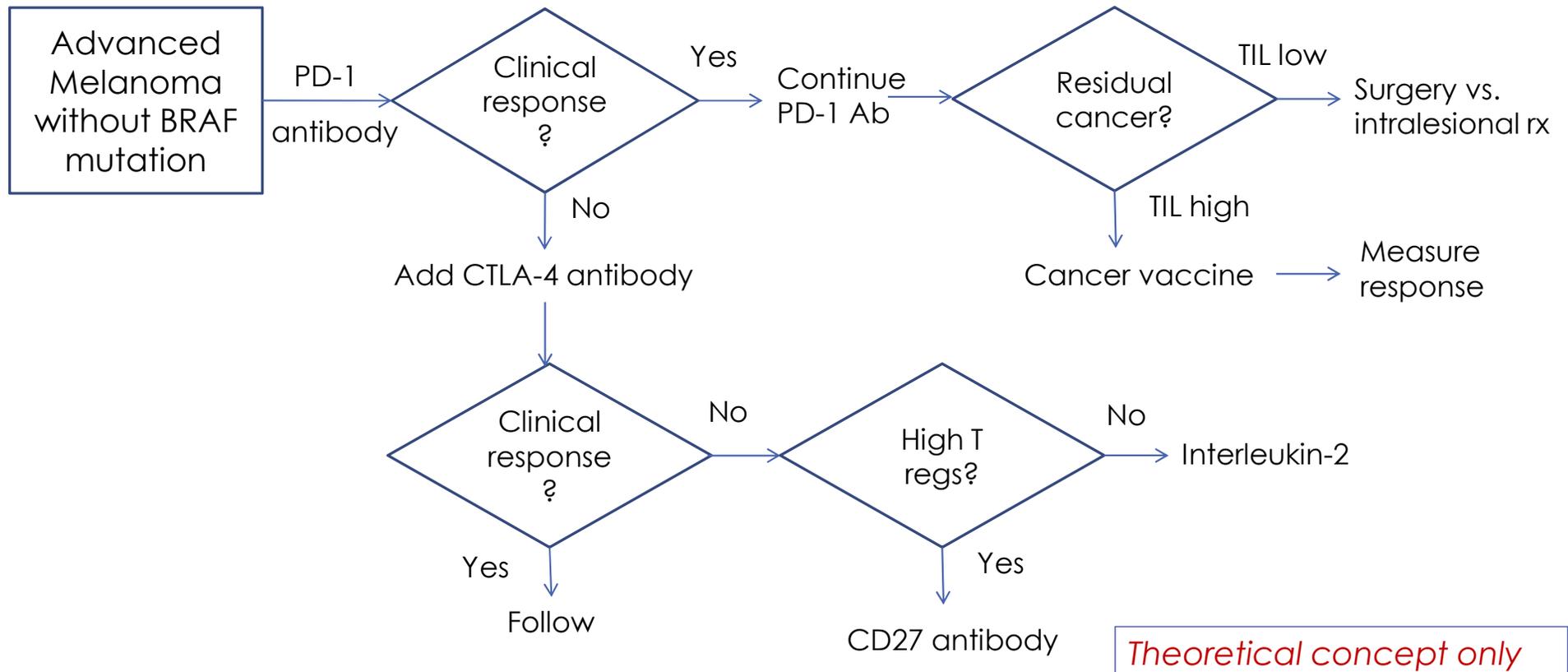
Immunotype C



Diffuse  
immune infiltrate

Immune cells  
blue = CD45

# Concept for personalized approach to response-modified combination immune therapy for cancer



# 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.