

## Immune Checkpoint Blockade in Cancer Therapy



THE UNIVERSITY OF TEXAS  
**MD Anderson**  
**Cancer Center**  
Making Cancer History®

**Jim Allison, PhD**

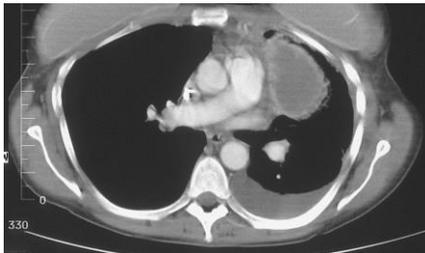
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Director, Parker Institute of Cancer Immunotherapy  
Vivian L. Smith Distinguished Chair in Immunology*

**Texas Higher Education Coordinating Board  
Austin, July 25 2019**

## The longest survivor on ipilimumab

May 2001



10 years later



Ribas

## Why Immunotherapy?

### Cancer:

- Myriad gene mutations
- High genome instability
- Many different diseases, each with distinct genetic alterations
- Targeting any single mutation often leads to disease relapse

### Immunotherapy:

- Specificity
- Memory
- Adaptability

**The immune system is a match for cancer!**

## Immune Checkpoint Blockade

**Paradigm shift in cancer therapy:**

Doesn't target tumor cells

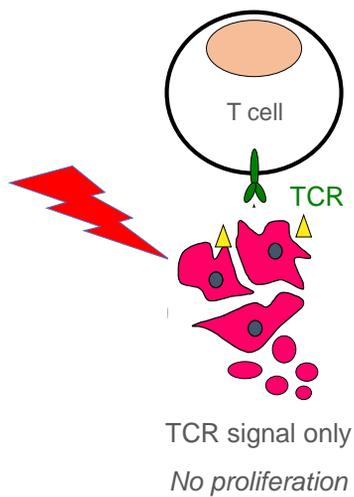
Doesn't involve vaccines or anything to turn on immune responses

*Works by blocking inhibitory pathways to unleash anti-tumor immune responses*

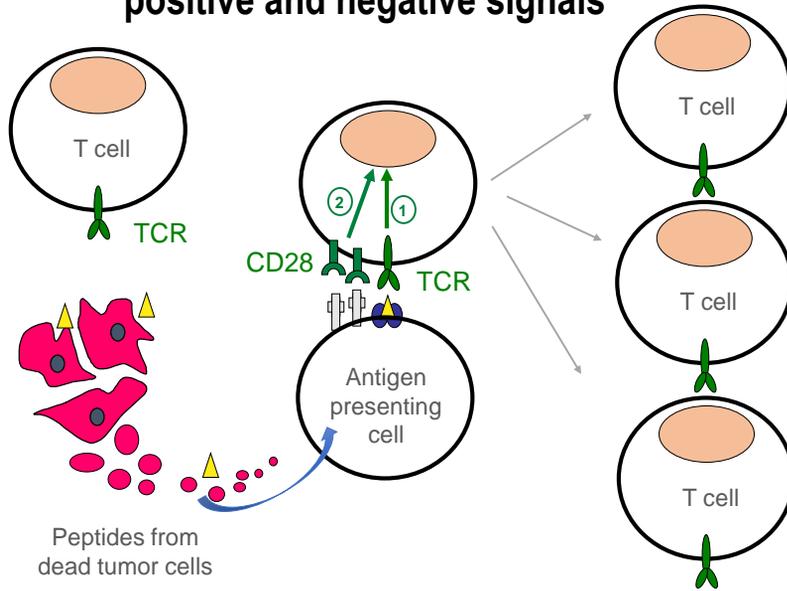
## How did we get here?

Understanding of fundamental mechanisms  
of T cell activation and regulation

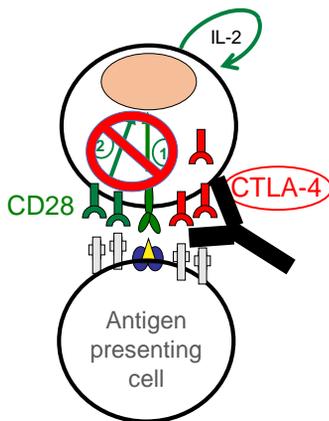
The immune system is regulated by both  
positive and negative signals



### The immune system is regulated by both positive and negative signals



### The immune system is regulated by both positive and negative signals



What would happen if we blocked the CTLA-4 signal with an antibody?

### TURNING OFF T CELLS

## Ipilimumab

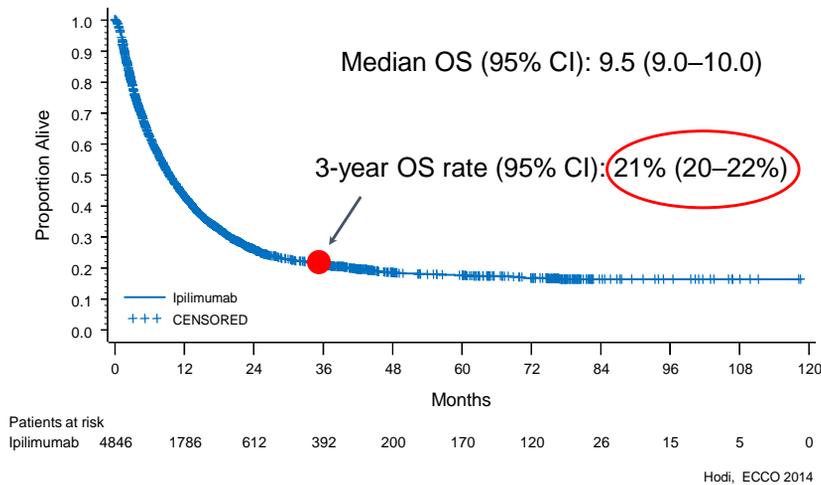
(Medarex, Bristol-Myers Squibb)

Fully human antibody to CTLA-4:

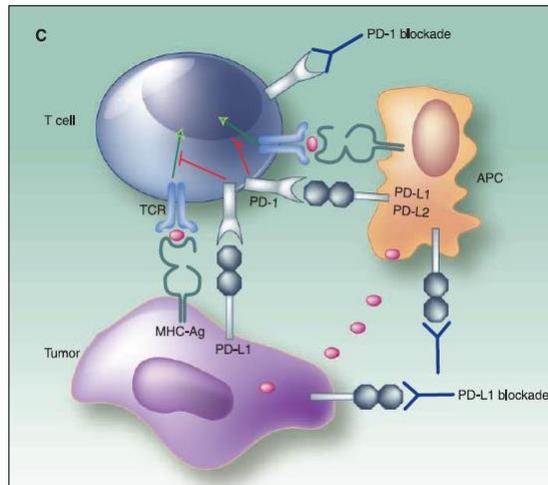
Objective responses in many tumor types,  
including melanoma, prostate, kidney, bladder,  
ovarian and lung cancer, etc.

Adverse events (colitis, hepatitis, hypophysitis, etc.)  
serious, but generally manageable

### Ipilimumab in metastatic melanoma: Pooled Survival analysis (4846 patients)



## Another T cell OFF switch: Programmed death 1 (PD-1)



<http://www.melanoma.org/community/mpip-melanoma-patients-information-page/video-how-anti-pd-1-therapy-works-immune-system>

### Anti-PD-1 Phase I (Nivolumab, BMS)

296 Patients with Metastatic Cancer  
1, 3, 10 mg/kg, MTD not reached

Safety: Adverse events similar to Ipilimumab, but 4%  
pneumonitis

#### Clinical Activity:

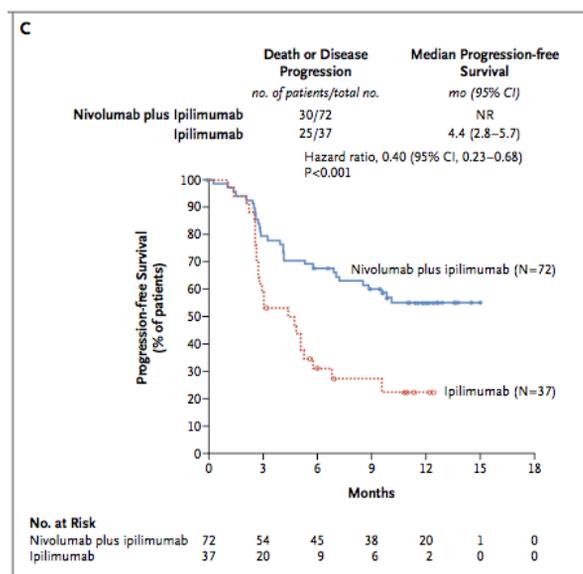
Melanoma (n= 94): 28% CR/PR, 6% SD  
NSCLC (n=76): 18% CR/PR, 7% SD  
RCC (n= 33): 27% CR/PR, 27% SD  
CRC (n=19), **CRPC (n=13)**: No responses

Topalian ASCO, NEJM 2012

# Where do we go from here?

## COMBINATIONS

### Ipi/Nivo vs. Ipi in Metastatic Melanoma



Hodi NEJM 2015

**Immune checkpoint therapy: FDA approvals**

**Melanoma – Ipilimumab, Pembrolizumab, Nivolumab, Ipilimumab + Nivolumab**

**Melanoma (adjuvant) - Ipilimumab**

**Non-small cell lung cancer - Nivolumab, Pembrolizumab, Atezolizumab**

**Renal cell carcinoma – Nivolumab**

**Hodgkin lymphoma – Nivolumab, Pembrolizumab**

**Bladder cancer – Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab**

**Head and neck cancer – Nivolumab, Pembrolizumab**

**Merkel cell carcinoma – Avelumab**

**MSI-H, dMMR – Pembrolizumab (any histology), Nivolumab (colorectal)**

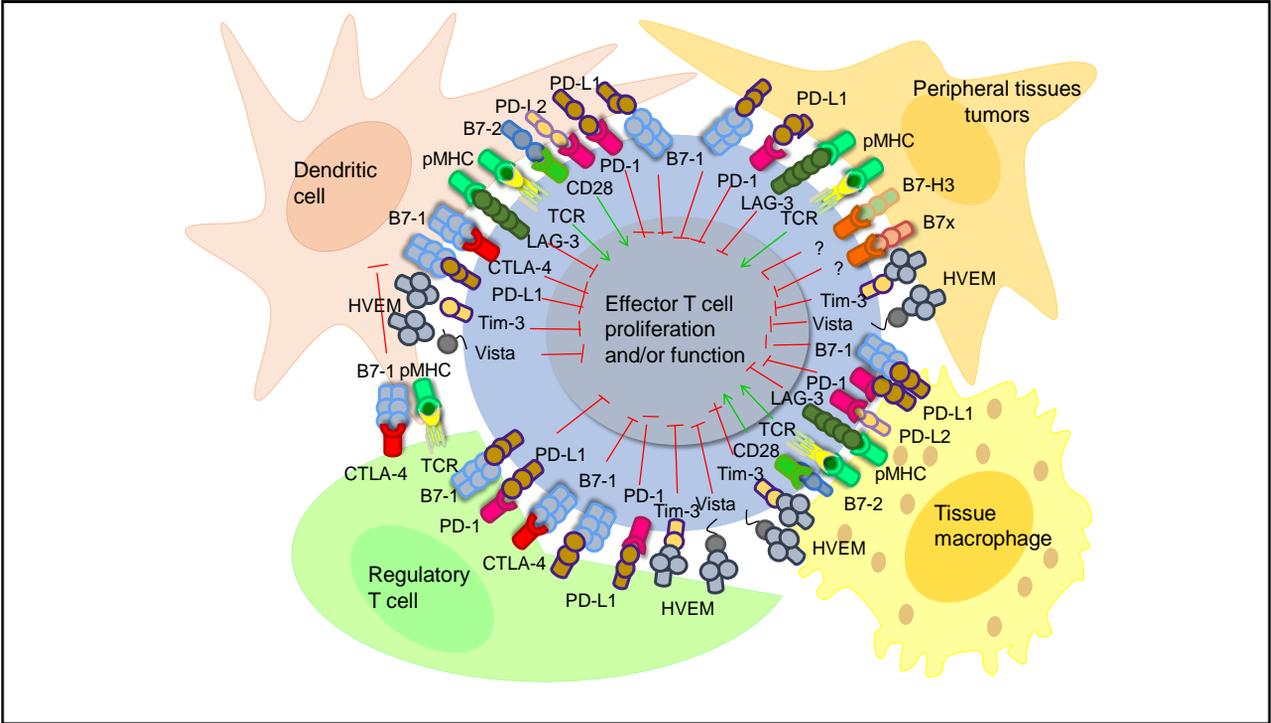
**Pediatric melanoma – Ipilimumab**

**Gastric/gastroesophageal cancer – Pembrolizumab**

**Hepatocellular carcinoma - Nivolumab**

**Combinations to enhance immune checkpoint targeting  
resulting in CURES**

- Blocking multiple checkpoints (both negative and positive)
  - Conventional therapies (chemotherapy, radiation)
    - Therapeutic vaccines
    - Targeted therapies



### Improving survival with combination therapy

