

Charles G. Drake MD / PhD

Associate Professor: Medical Oncology, Immunology and Urology

Co-Director: Multi-Disciplinary Prostate Cancer Clinic



**Co-Stimulation
and
Co-Inhibition in Cancer
Immunotherapy**

Disclosure of Financial Relationships

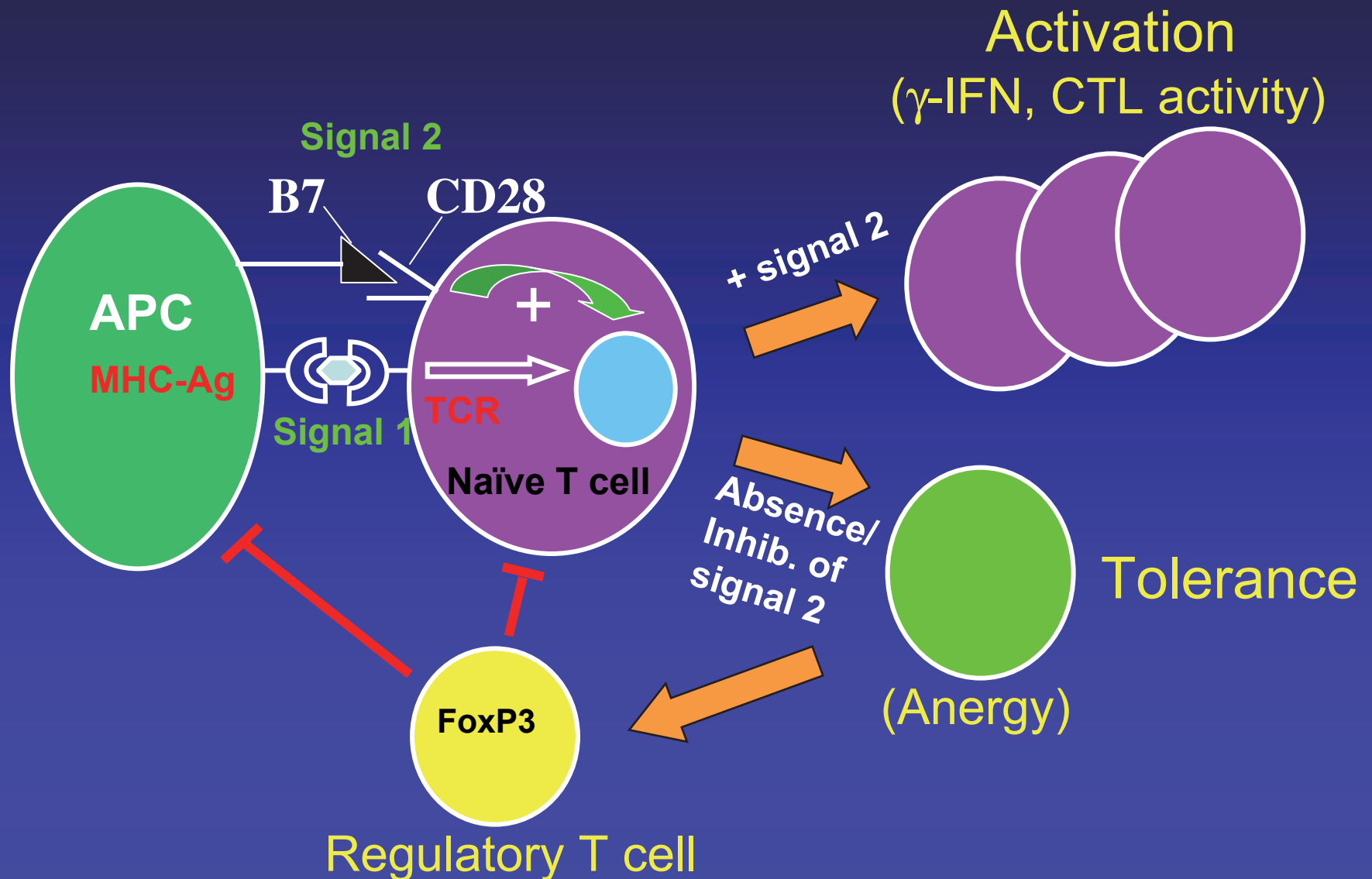
- Consulting:
Amplimmune, Bristol Myers Squibb, Janssen, Regeneron
- Patents:
Bristol Meyers Squibb, Amplimmune

NOTE: Anti-PD-1 (BMS-936558 is an EXPERIMENTAL AGENT, and is not currently FDA approved for any indication)

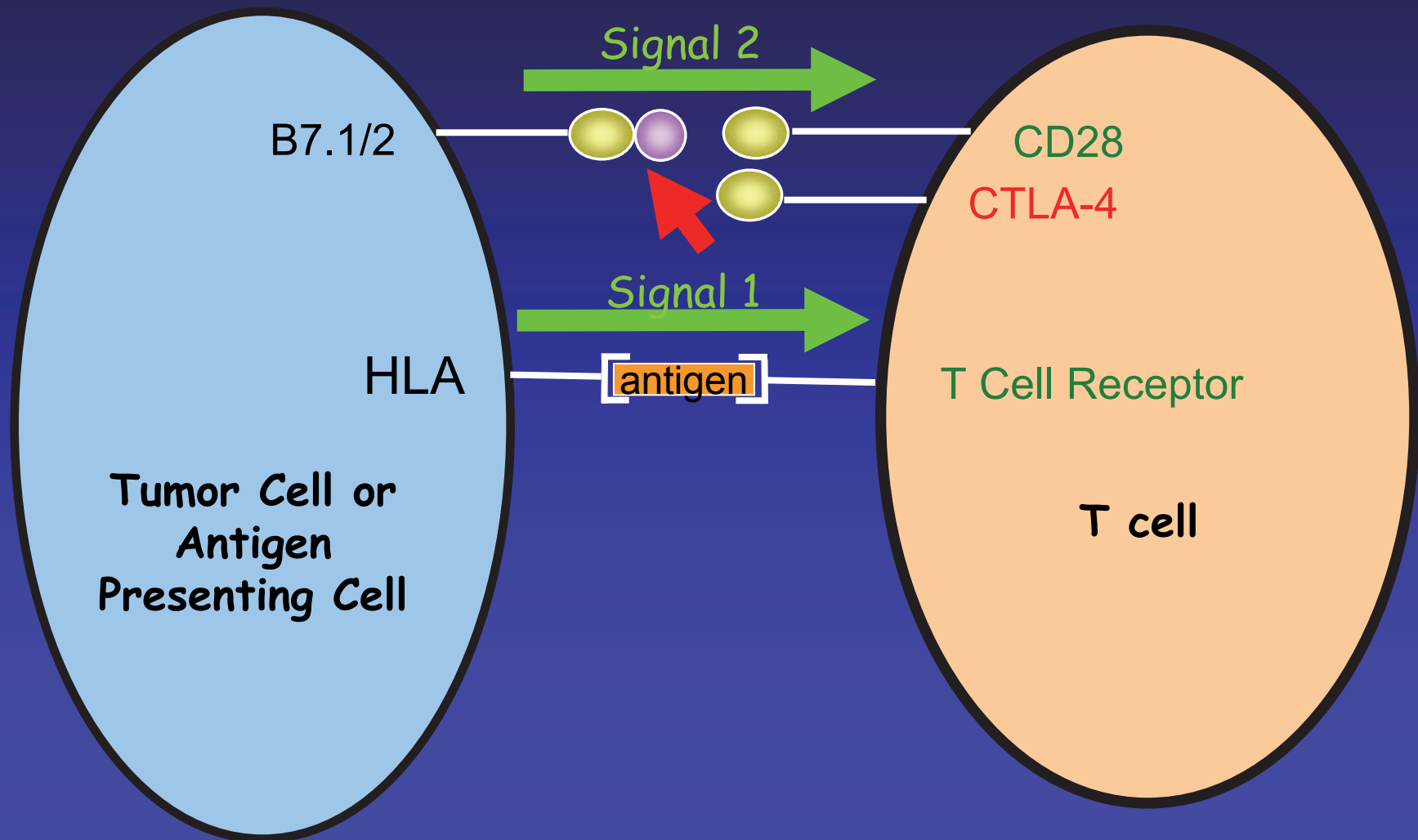
Learning Objectives

- Understand what is meant by “co-inhibition”, and define an immune “checkpoint”
- Introduce the Adaptive Immune Resistance Hypothesis
- Describe how multiple checkpoint molecules might control an anti-tumor immune response
- Discuss clinical data on PD-1 blockade
- Understand the rationale for combining immune checkpoint blockade with conventional cancer therapies

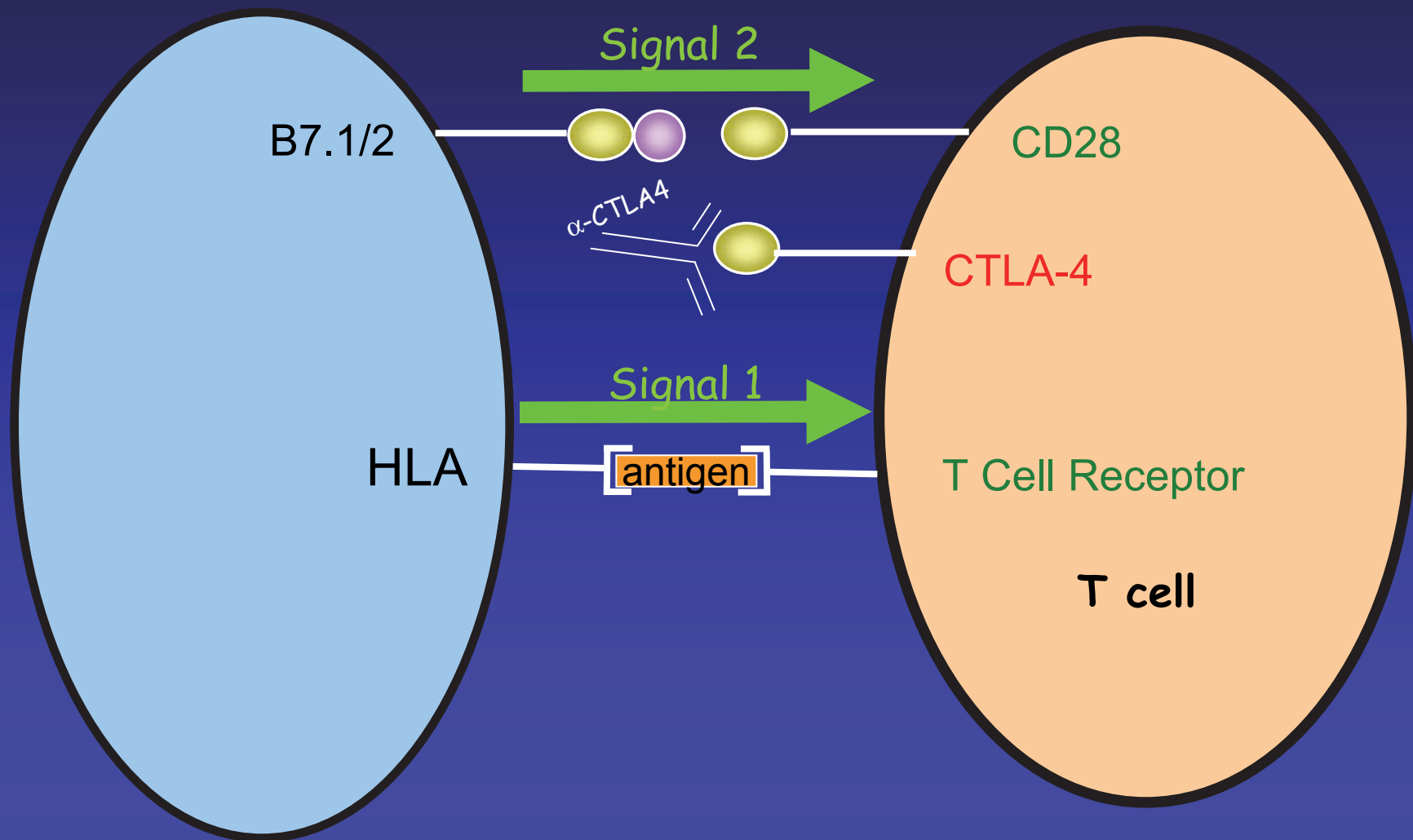
Absence or Inhibition of Signal 2 leads to Peripheral T cell Tolerance



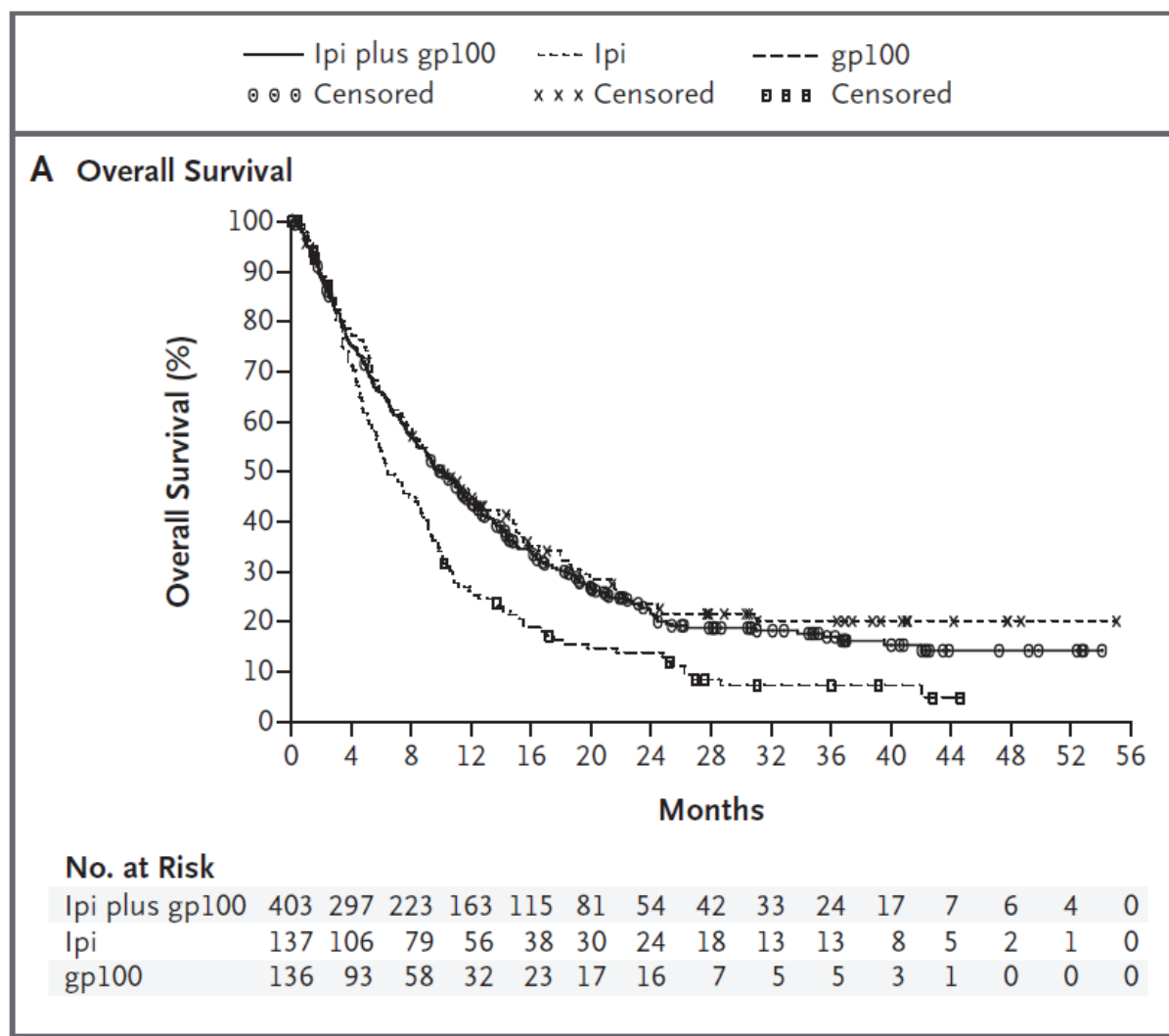
Co-Stimulation Co-Inhibition



Blocking Co-Inhibition: Anti-CTLA-4



Clinical Proof of Concept: A Survival Benefit in Metastatic Melanoma (anti-CTLA-4 = ipilimumab = Yervoy)

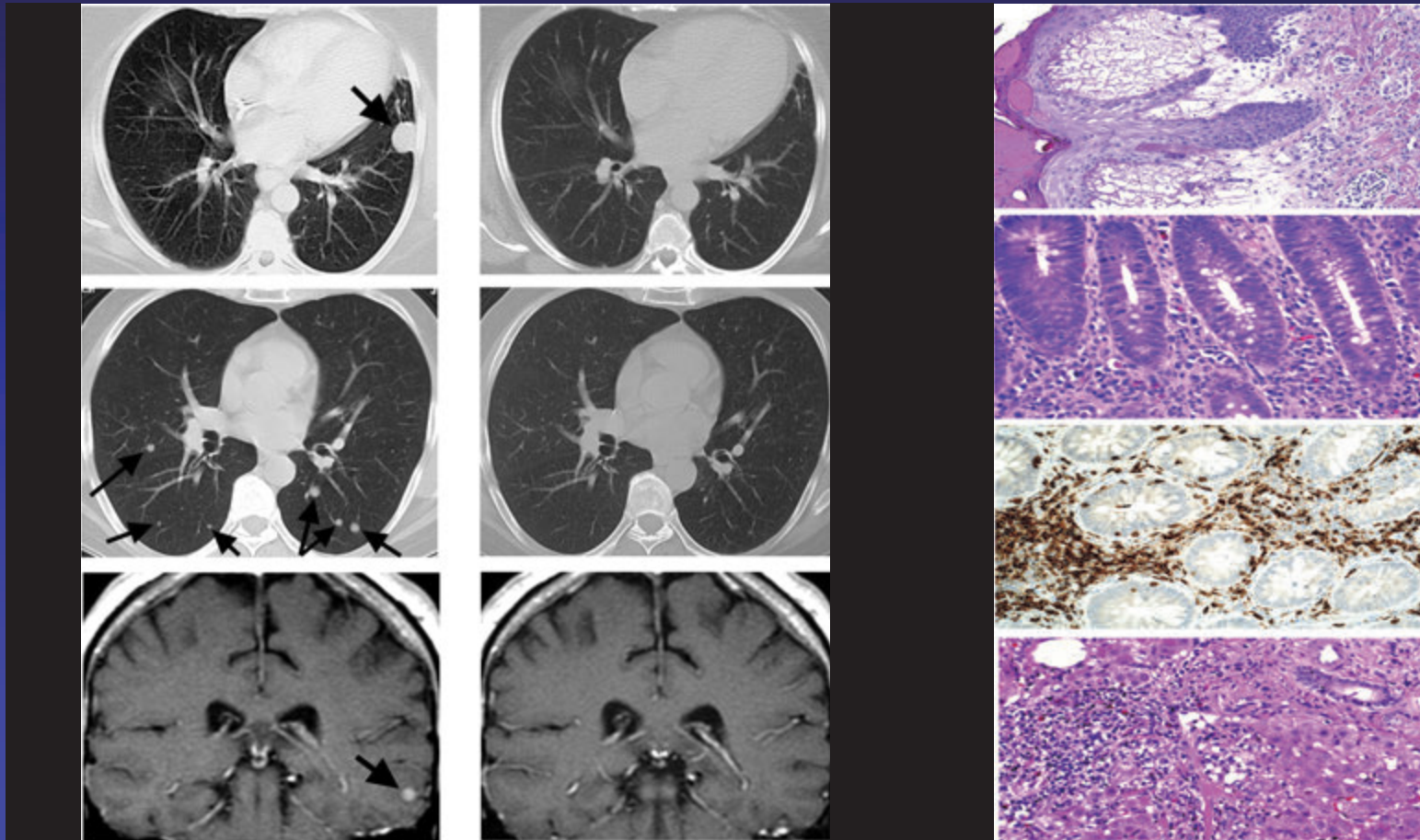


Adverse Events with Anti-CTLA-4

- 12 % objective response rate (Mel and RCC)
- 23-33% grade 3/4 autoimmune toxicities

PRE-RX

POST-RX



Dermatitis

Colitis

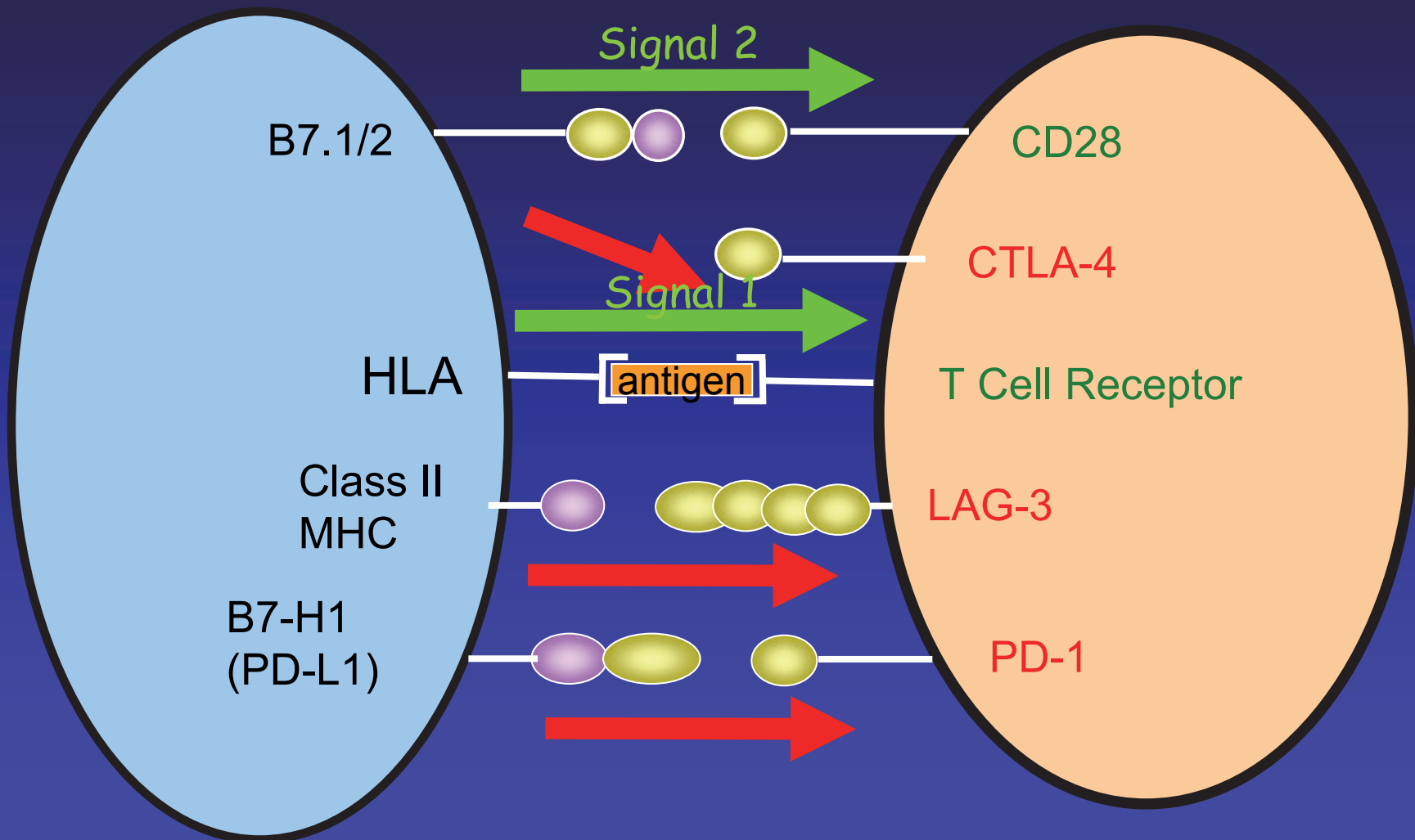
Hypopyhsitis

Hepatitis

It Takes a Village to Control a T Cell?

Tumor Cell or
Antigen Presenting Cell

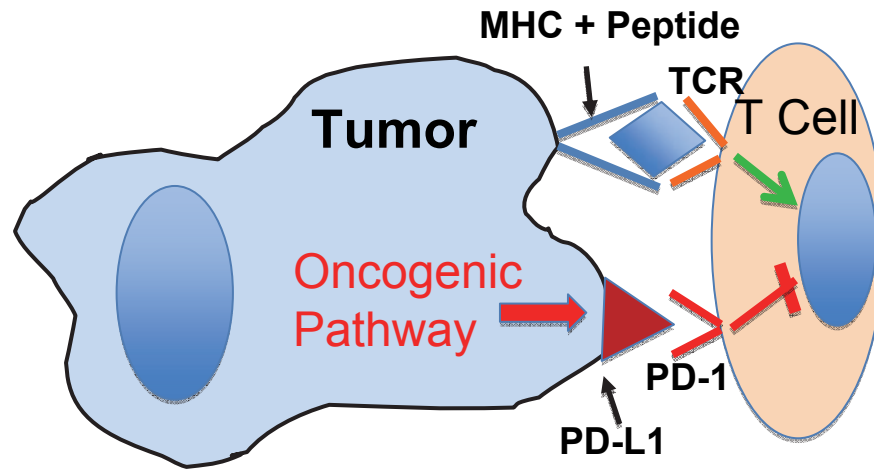
T cell



Others: ICOS, GITR, Tim-3

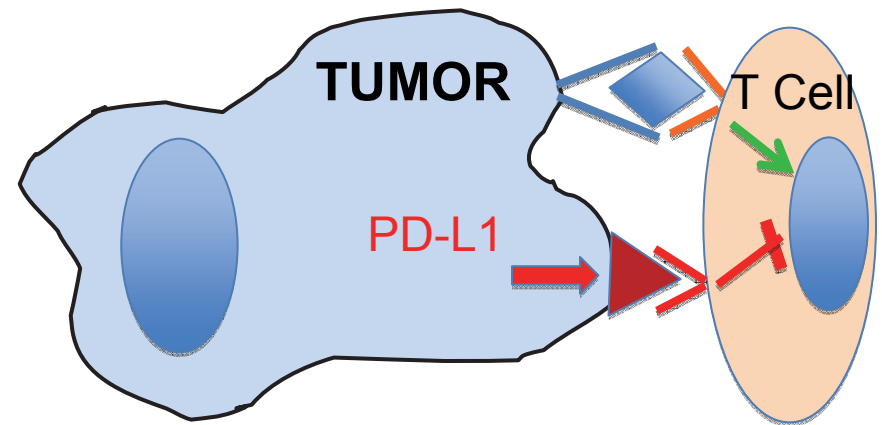
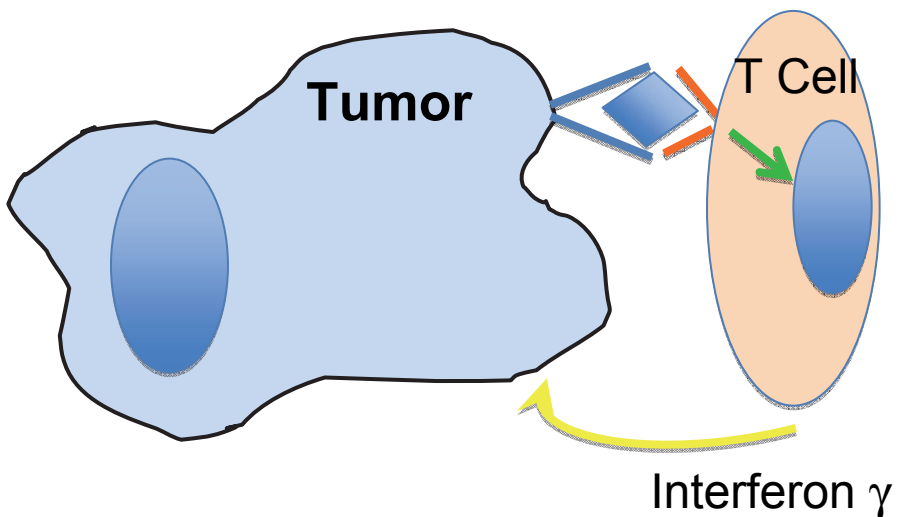
PD-1

Innate Immune Resistance



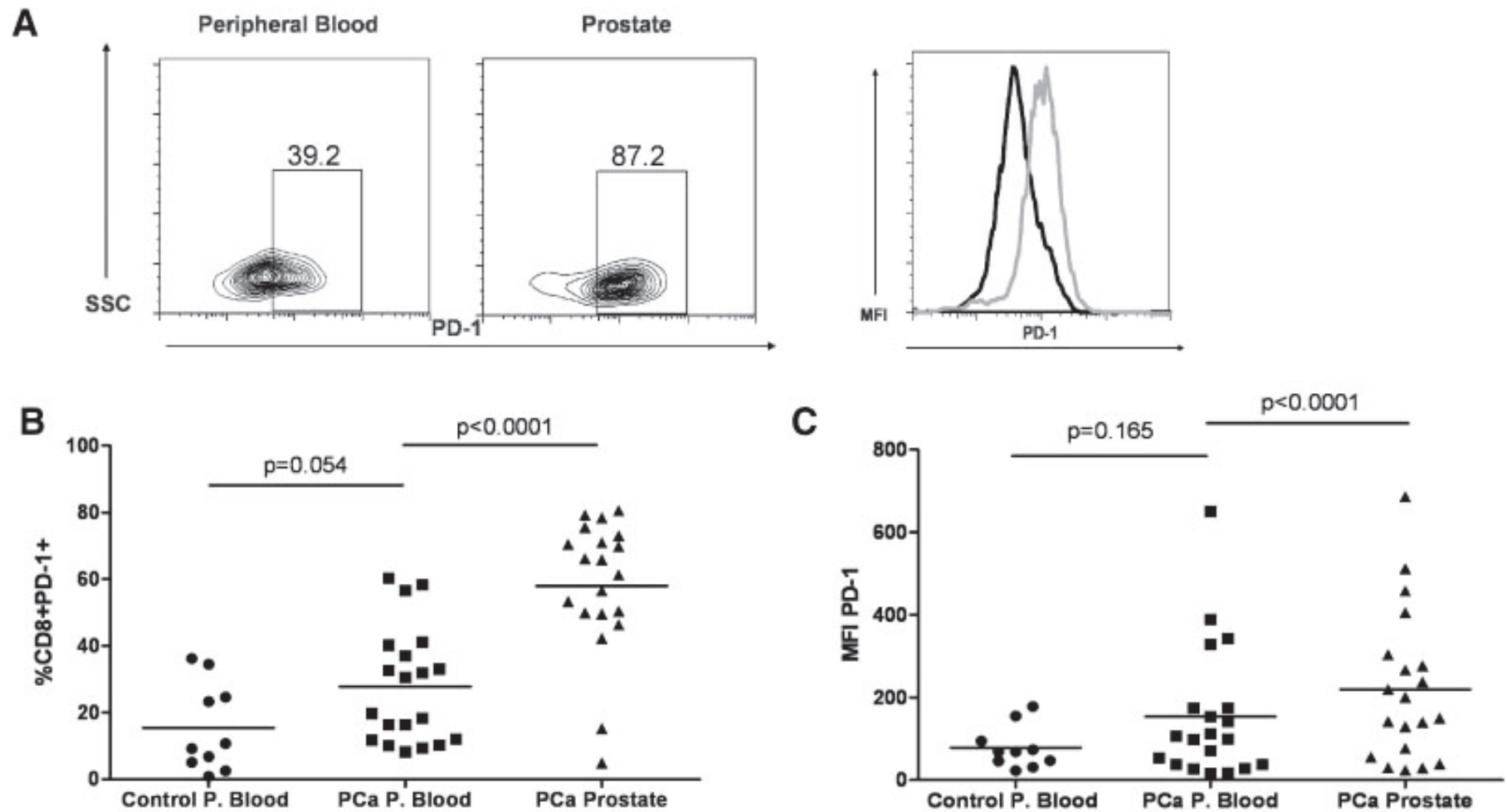
Oncogene- Driven PD-L1 Expression

Adaptive Immune Resistance

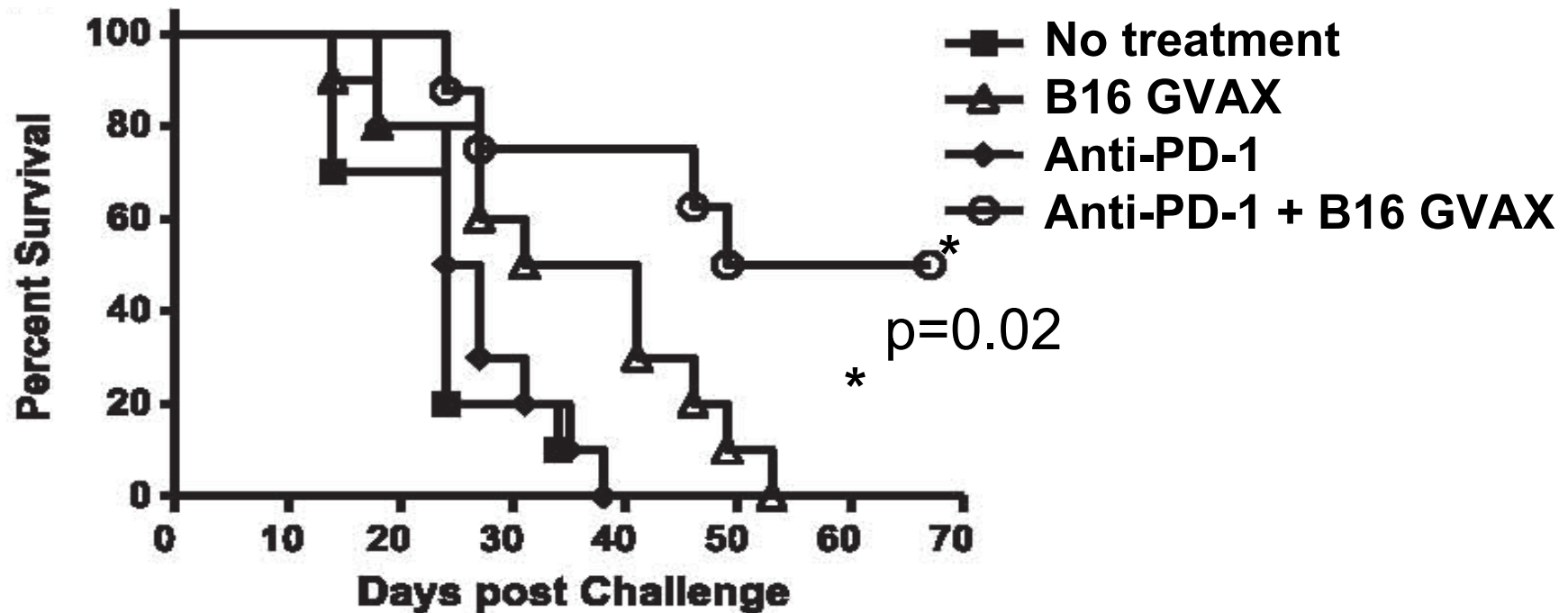


Adaptive Up-Regulation Of PD-L1 Turns T Cell OFF

High expression of PD-1 on Prostate cancer Infiltrating T cells



Synergy of PD-1 blockade with a melanoma vaccine: Prolonged survival of tumor-bearing mice receiving combinatorial therapy



Anti-PD-1 Phase I

Toxicities (39 patients)

- Grade 1: pruritis, rash, fatigue
- Grade 2:
 - Polyarticular arthropathy, 2 pts (1 mg/kg and 10 mg/kg), treated with oral steroids
 - TSH elevation, 4 pts (1 pt requiring levothyroxine)
- **Grade 3: colitis, 1 pt after multiple doses at 1 mg/kg**

Responses

- 1 MR: melanoma
- 1 transient response (>50% reduction): NSCLC
- 2 PR – melanoma, renal ca
- 1 CR - colon ca

66 year old with RCC

2001 nephrectomy at JHU = (T3b, NX, MX)

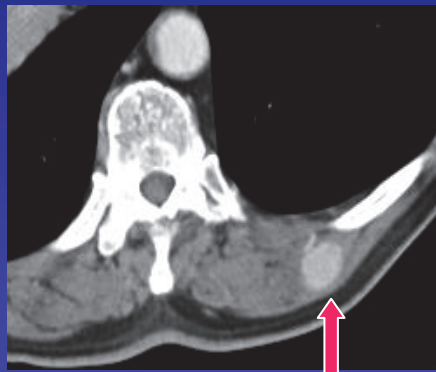
2003F/U CT Scan = Multiple Pulmonary Nodules

2004CEP 7055 (Oral TKI)
MGCD 0103 (HDACi)
Sunitinib (Oral TKI)

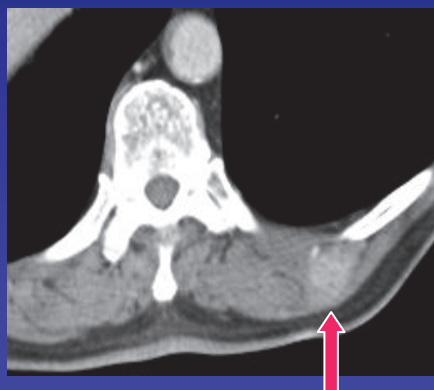
2007Progression

2008 Phase I clinical trial (New checkpoint blocking antibody, anti-PD-1)

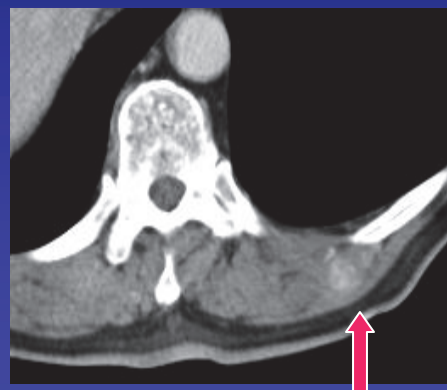
01/15/08 (pre-Rx)



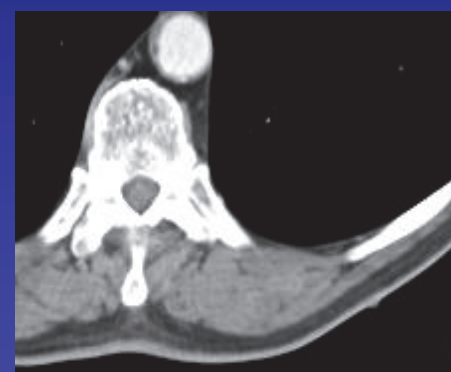
03/25/08



04/22/08



07/22/08

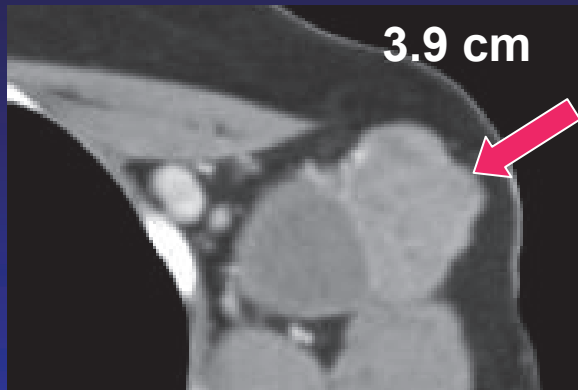


**US-guided biopsy:
No viable tumor**

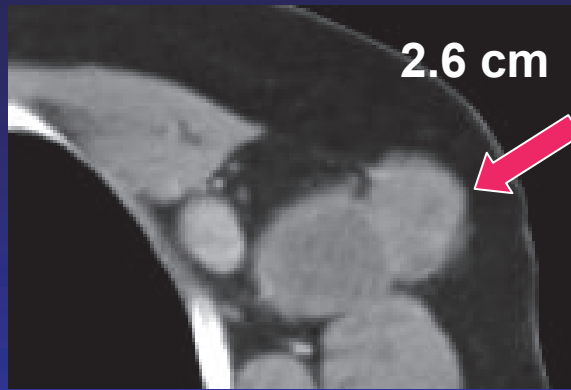
- Received 2 additional on-study treatments (10 mg/kg)
- Stable PR -> off study

PD-1 Blockade: Results in Increased CD8 T Cells in Tumors

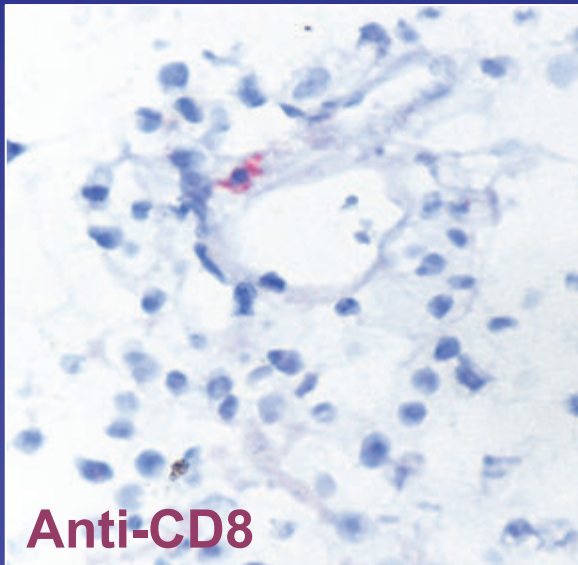
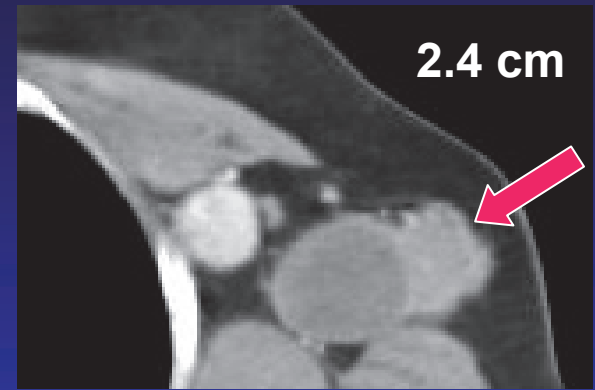
Pre-Rx



12 wk post Dose 1

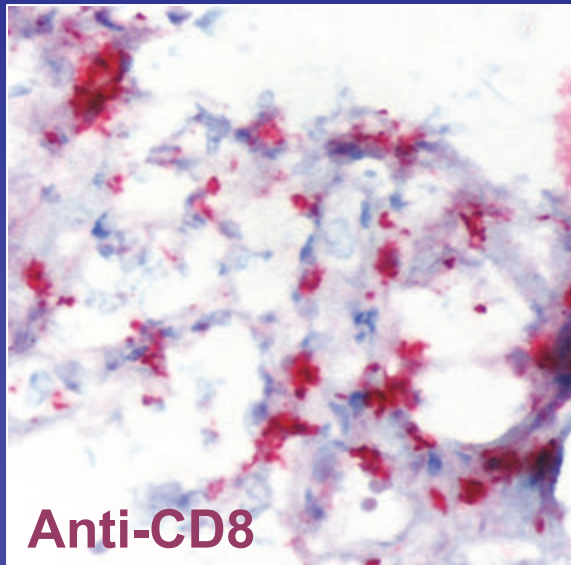


8 wk post Dose 3



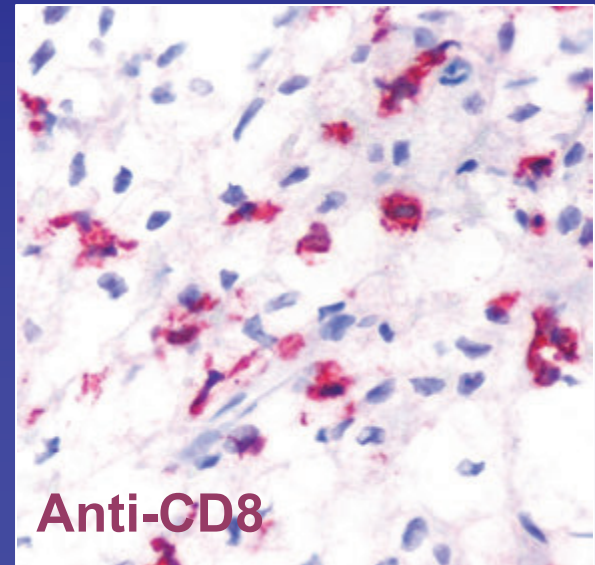
Anti-CD8

Pre-Rx



Anti-CD8

4 wk post dose 1



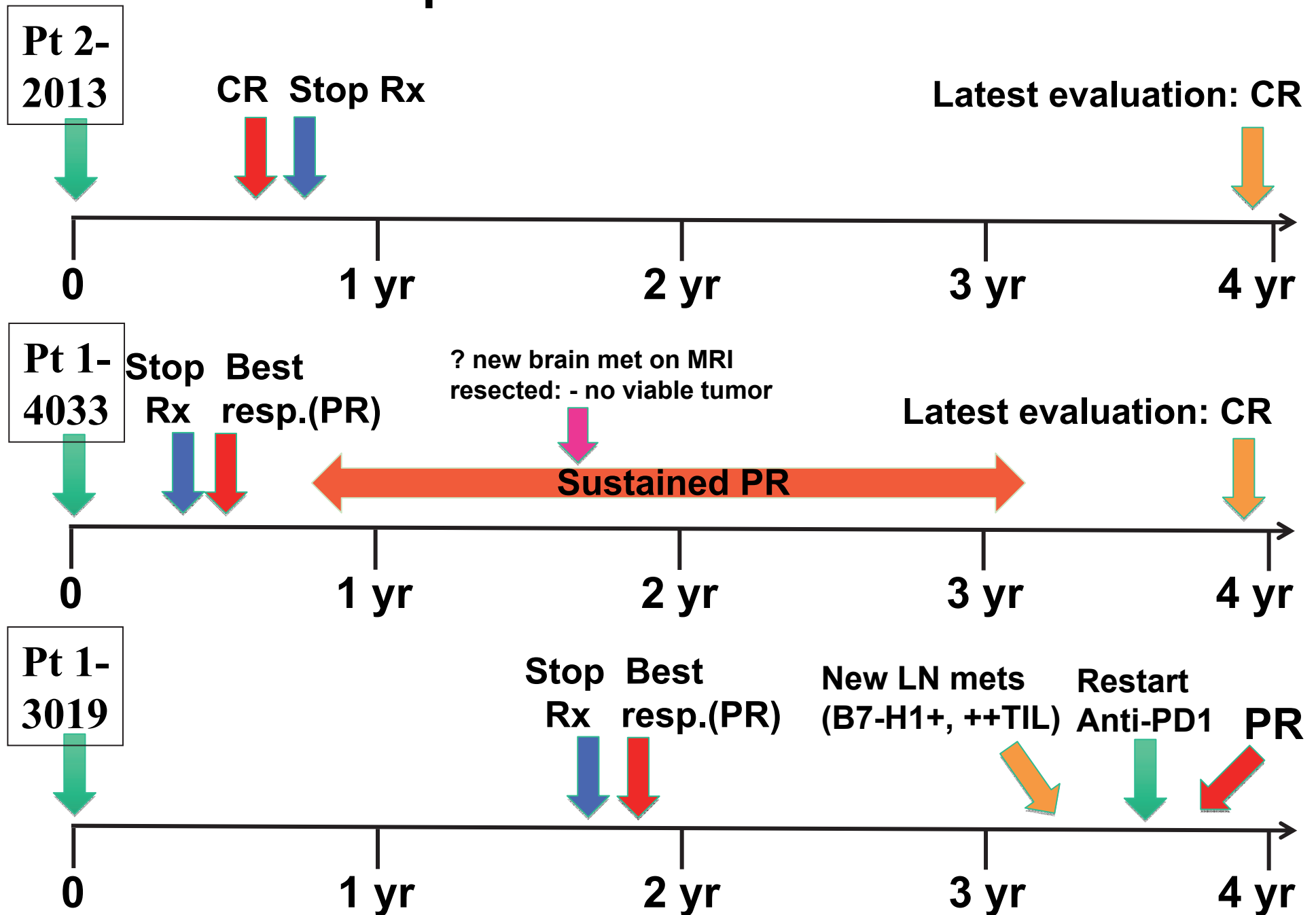
Anti-CD8

4 wk post dose 3

RCC Pt: Follow-up

- 2/10/2009 CT – New subcentimeter hyperdense mass in R frontal lobe, C/W metastatic lesion
- 2/24/2009 Right fronto-orbital craniotomy, with resection of mass
Pathology: “BRAIN, RIGHT FRONTAL LESION (EXCISION): BRAIN PARENCHYMA WITH PROMINENT MACROPHAGES, CHRONIC INFLAMMATION AND PROMINENT CAUTERY ARTIFACT. **NEGATIVE FOR TUMOR.**”
- Ongoing F/U – (latest = 4/2012)
 - CR by PET scan
 - No treatment > 4 years

Durable Responses to Anti-PD-1 *OFF THERAPY*



Co-Inhibitors: Run in Packs

Volcano plot showing Log₂ Fold Change (Y-axis) versus Relative Intensity (X-axis). The plot displays a large number of genes, with several highlighted in yellow and red boxes, indicating significant changes or specific gene sets. The Y-axis ranges from -8 to 6, and the X-axis ranges from 2 to 14. The plot shows a dense cluster of genes around the center, with a few genes showing high fold change and high relative intensity.

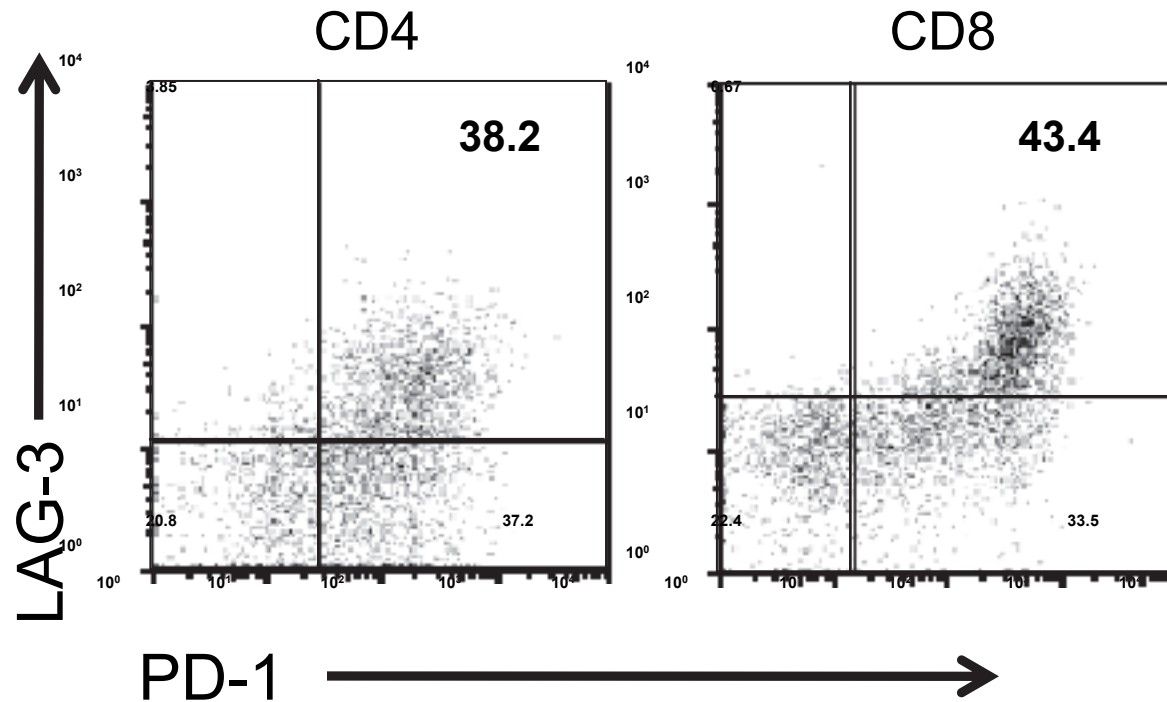
Key genes highlighted in yellow boxes (top right):

- Nrn1
- Tnfsf11
- Cd200
- Fcrl4
- Ikzf2
- Nrp1
- Lag3
- Ccr2
- Epas1
- Ccr5
- Anxa1
- Il2ra
- Mt1

Key genes highlighted in red boxes (bottom right):

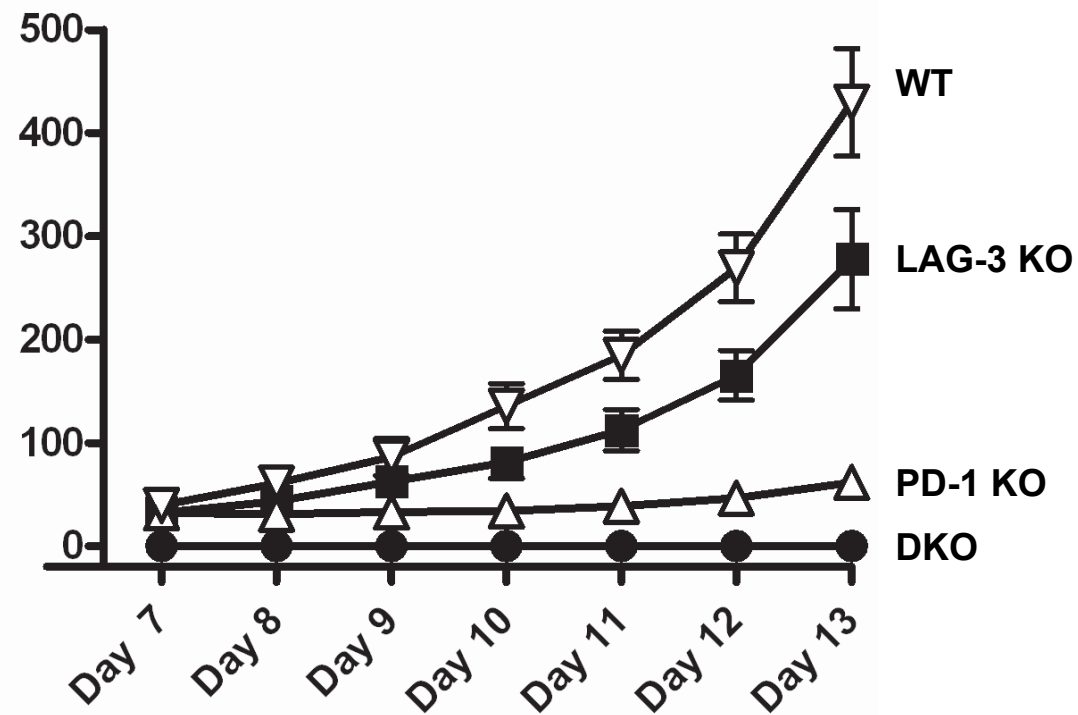
- Pdc1
- Gzma
- Gzmb

PD-1 and LAG-3 Are Co-Expressed on Tumor Infiltrating Lymphocytes

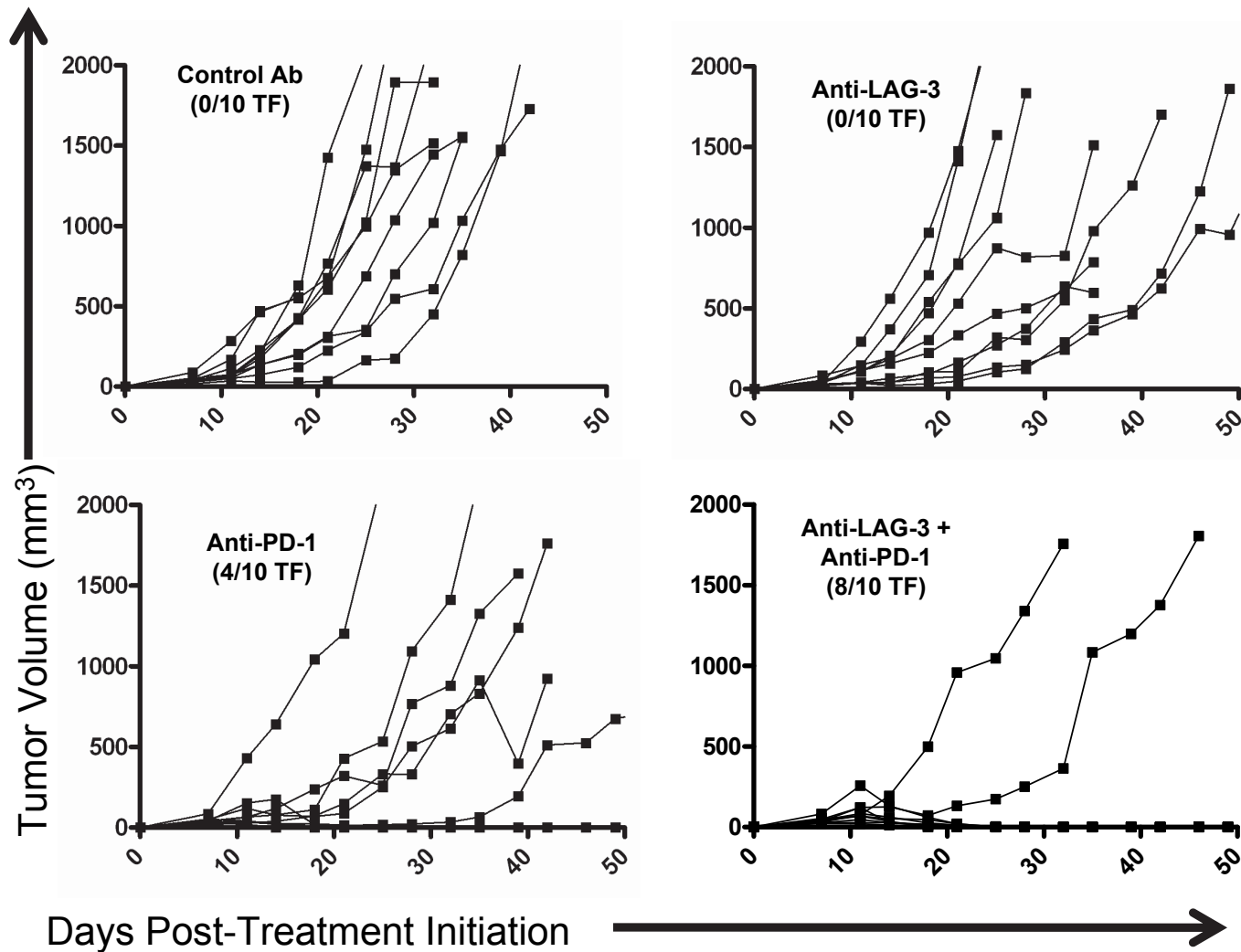


LAG-3 / PD-1 DKO Mice

Spontaneously Reject Poorly Immunogenic B16 Tumors



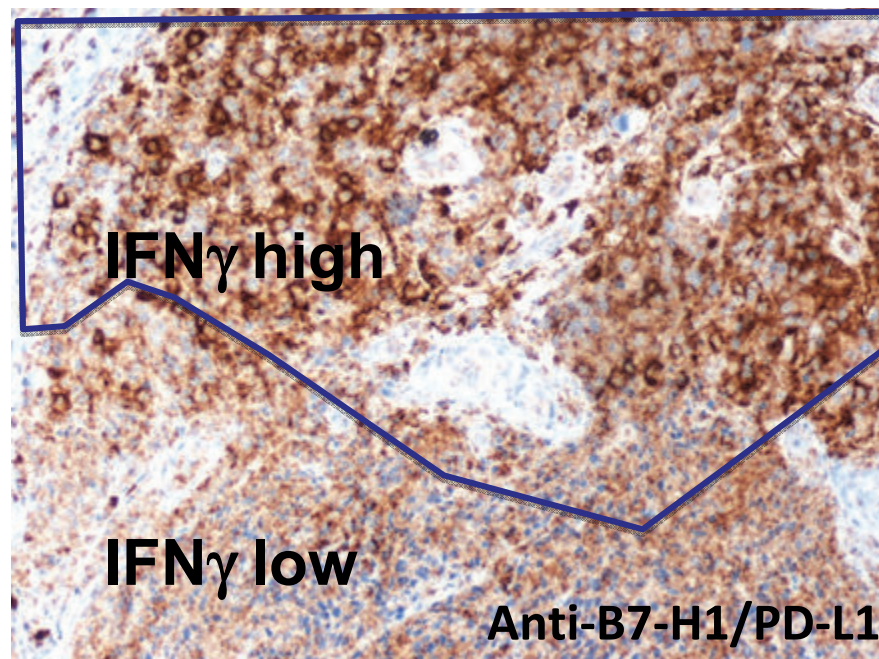
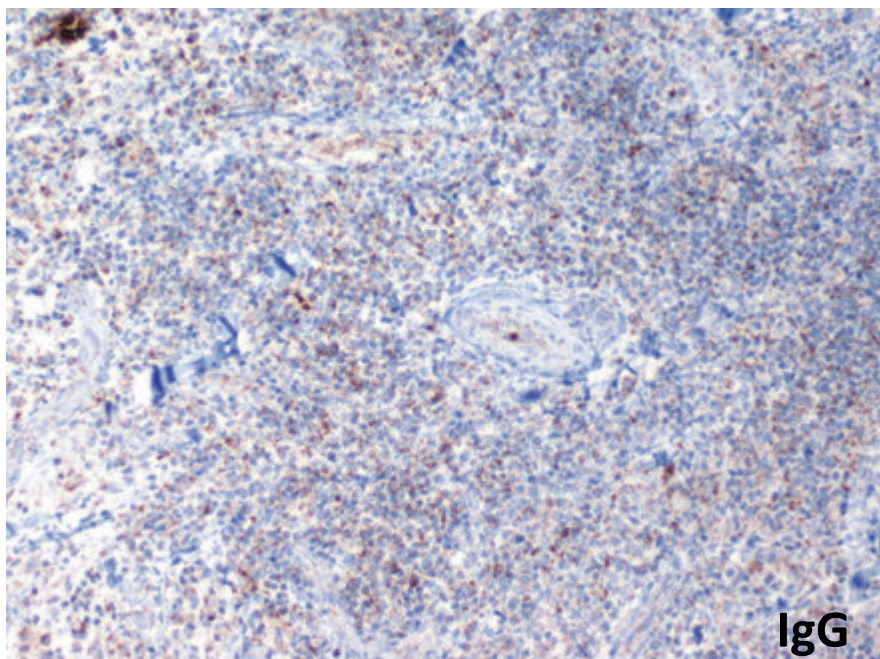
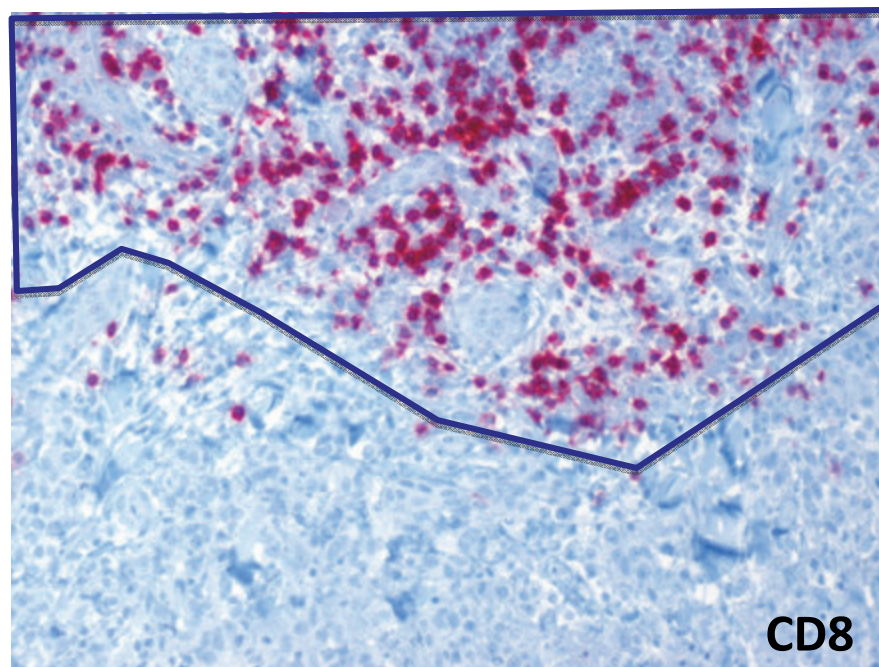
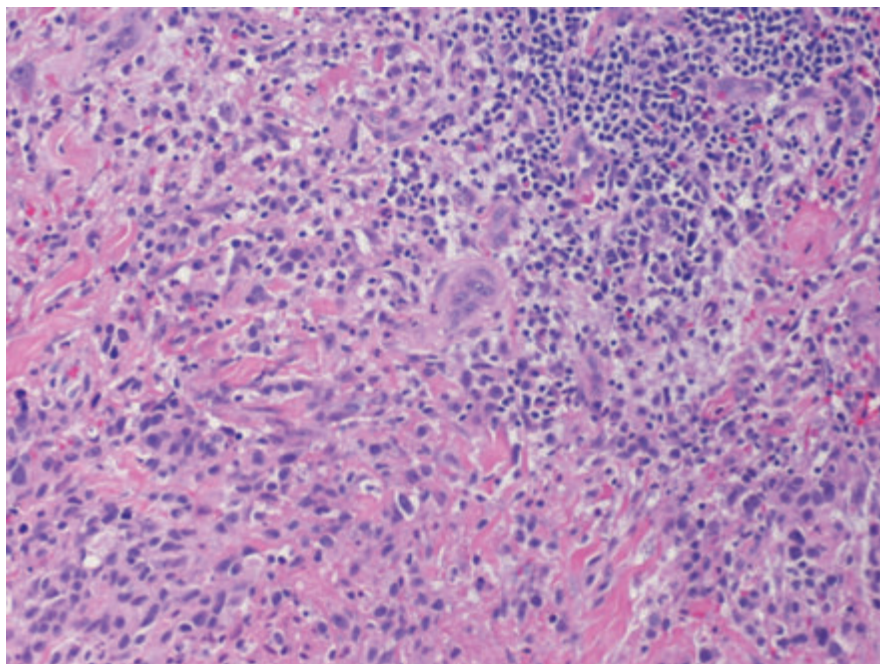
Combining PD-1 Blockade with LAG-3 Blockade



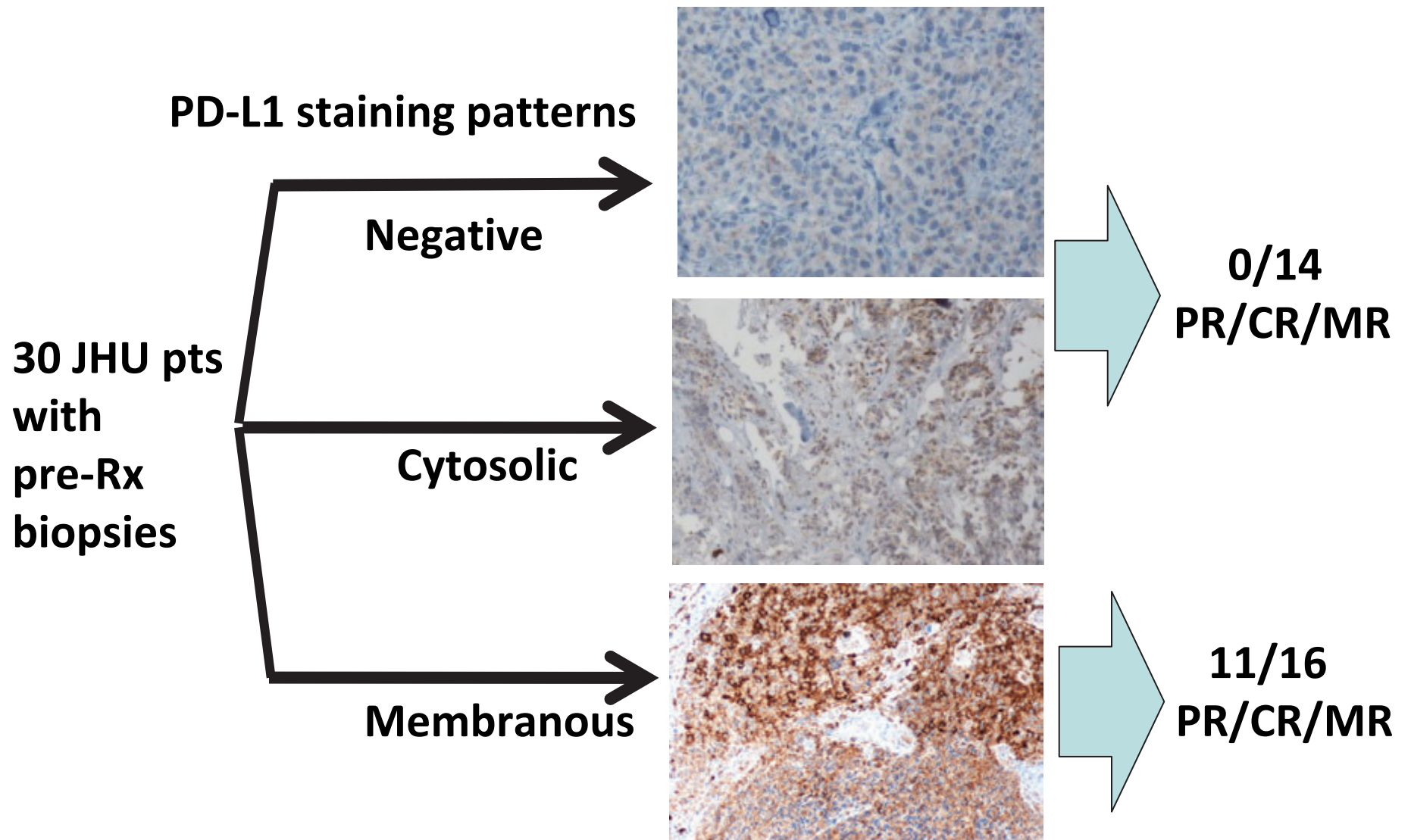
Day 7 Staged MC38 – Similar Results in Staged SA1N

A Potential Biomarker for PD-1 Blockade

PD-L1 Expression and Relation to Lymphocyte Infiltration – J. Taube



Correlation of PD-L1 expression patterns with α PD-1 clinical response

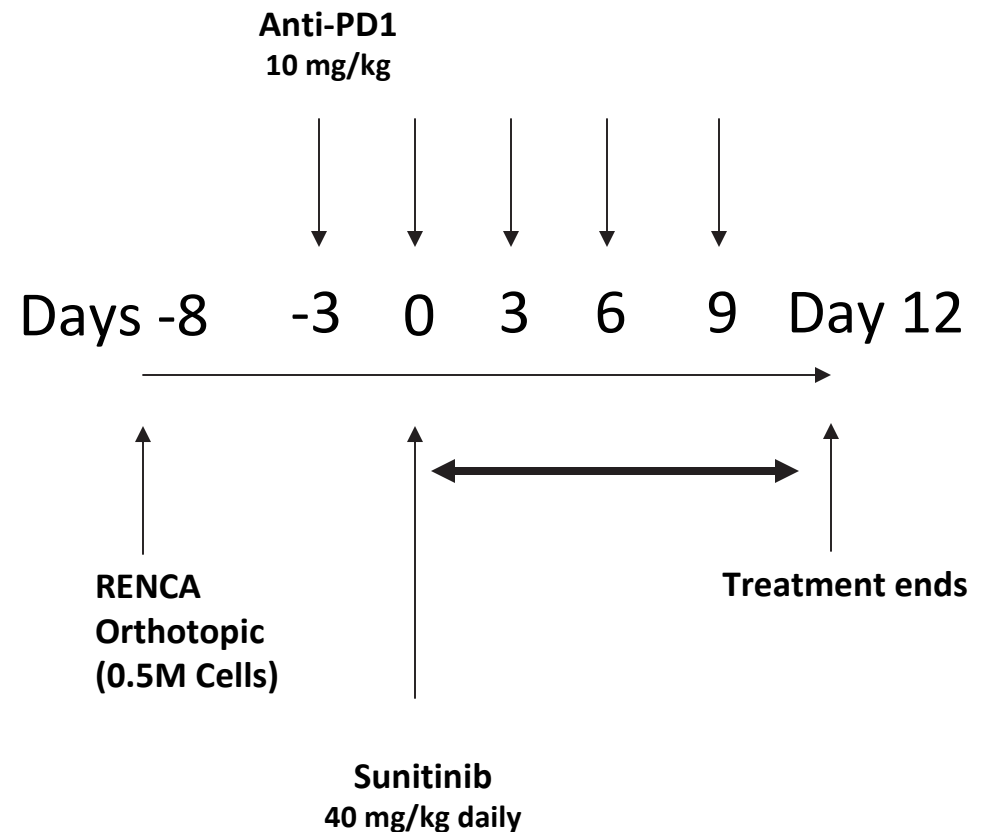


Combining Immune Checkpoint Blockade with Conventional Therapy

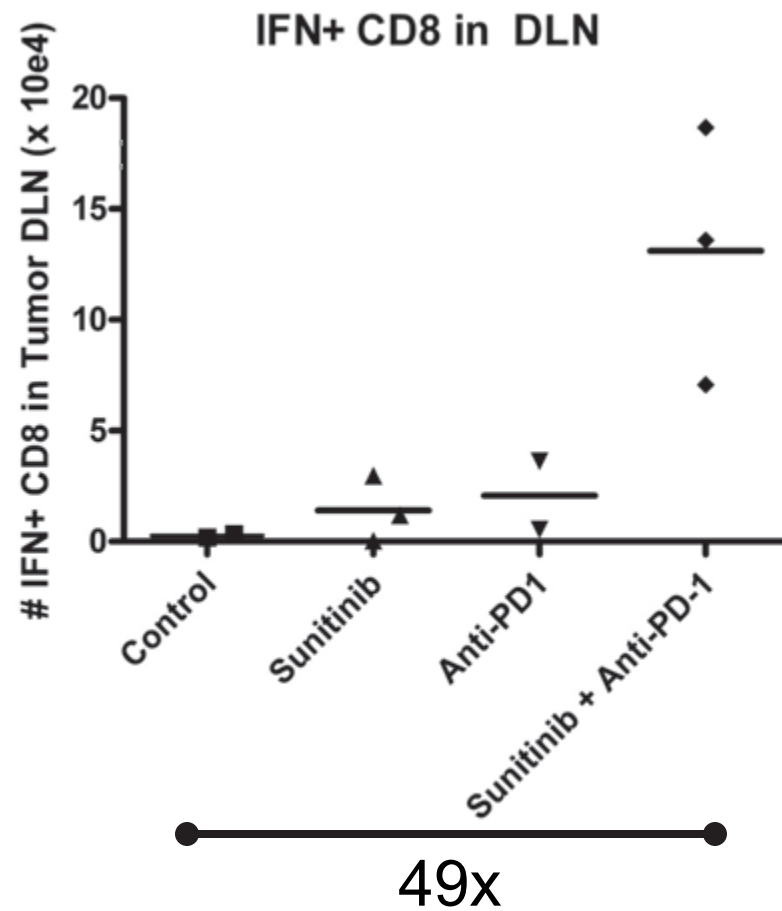
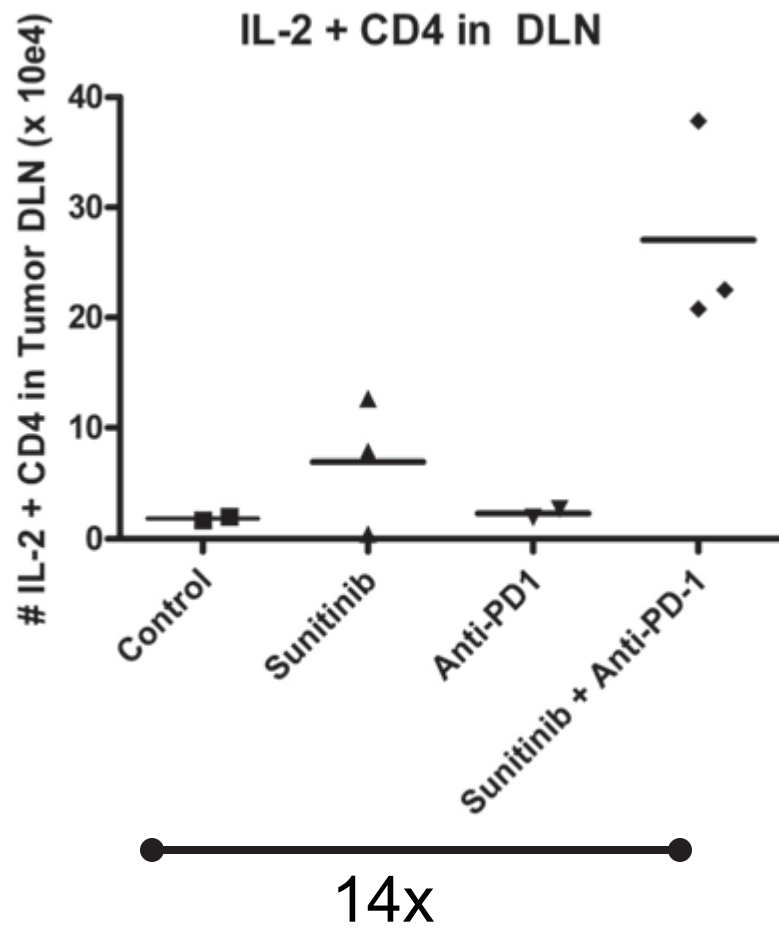
PD-1 Blockade With Tyrosine Kinase Inhibitors in Renal Cell Carcinoma

Orthotopic RENCA Model

- Hypoxia
- High VEGF Levels
- Growth Inhibition with Sunitinib







Combination Immunotherapy: Components

↑ Ag Presentation By
Appropriately Activated
DCs + ↑ Costimulation



Blockade of
Immunologic
Checkpoints



Manipulation of
Tumor
Microenvironment

Cancer Vaccines:
Dendritic Cell
Protein / Peptide
Cell Based
Viral Vector
DNA
Microbial (LM)

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

Radiation Therapy
TKI's
Chemotherapy

PD-L1 (B7-H1)
PD-L2 (B7-DC)
B7-H3
B7-H4

Summary:

- Single Agent Checkpoint Blockade
 - Clinical Lesson:
 - Meaningful responses with single-agent checkpoint blockade
 - Scientific Lesson – “one grain of rice”
- Combination Regimens
 - Block multiple checkpoint molecules
 - Combine checkpoint blockade with
 - Cancer Vaccines
 - Tyrosine Kinase Inhibitors
 - Radiation Therapy
 - Conventional Chemotherapy

HOPKINS PD-1 TEAM

