

Targeting Immune Checkpoints in Cancer Therapy: New Insights and Opportunities

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Applied Research of Genitourinary Cancers**

MD Anderson Cancer Center

SITC Primer 2014

Why immunotherapy?

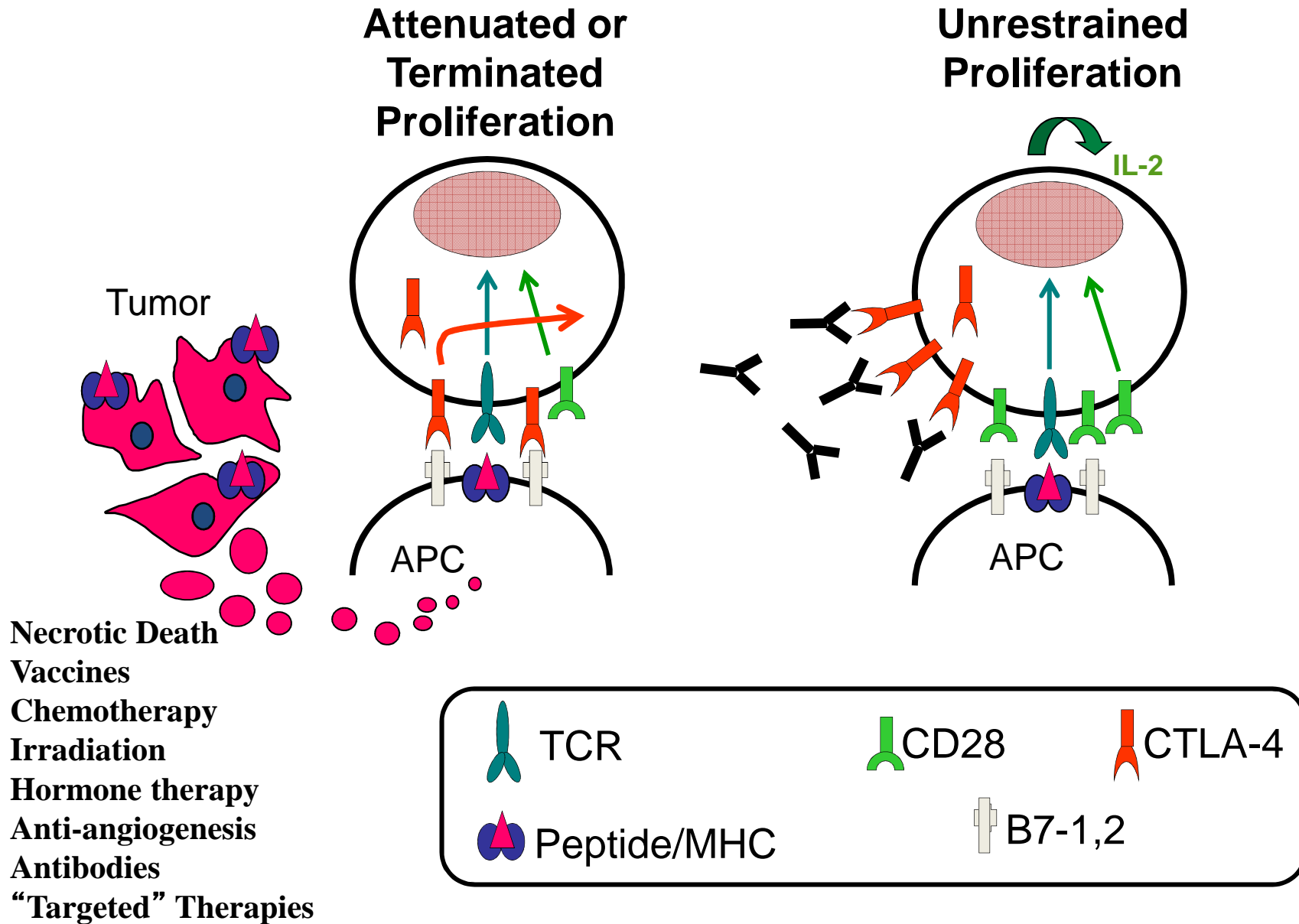
Specificity

Memory

Adaptability

CTLA-4 Blockade

Enhances Tumor-Specific Immune Responses

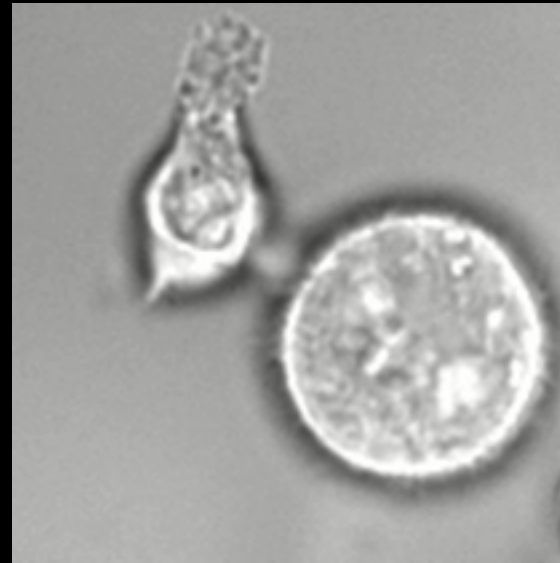


Localization of CD28 and CTLA-4 to the T Cell-APC Interface

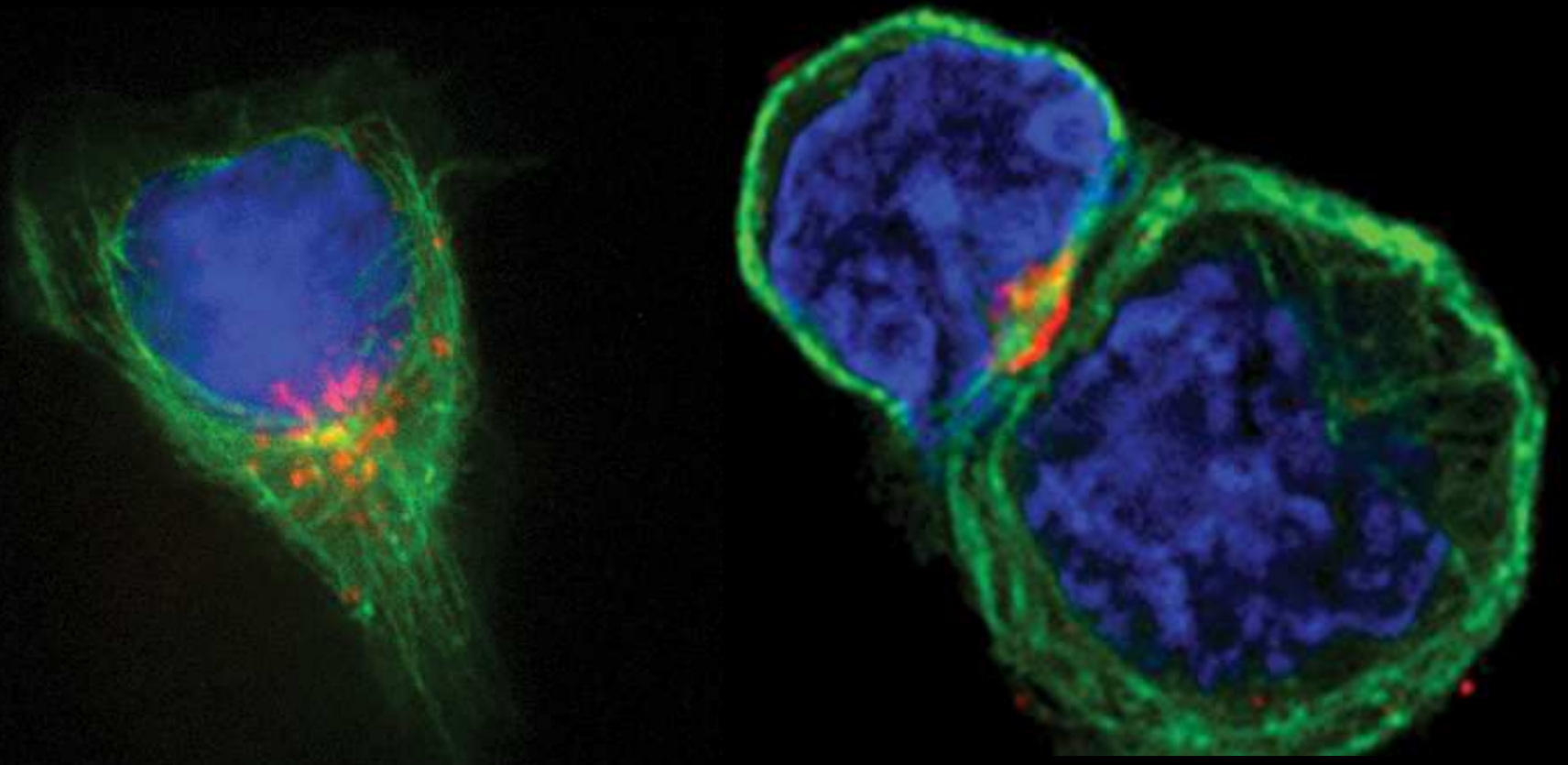
CD28



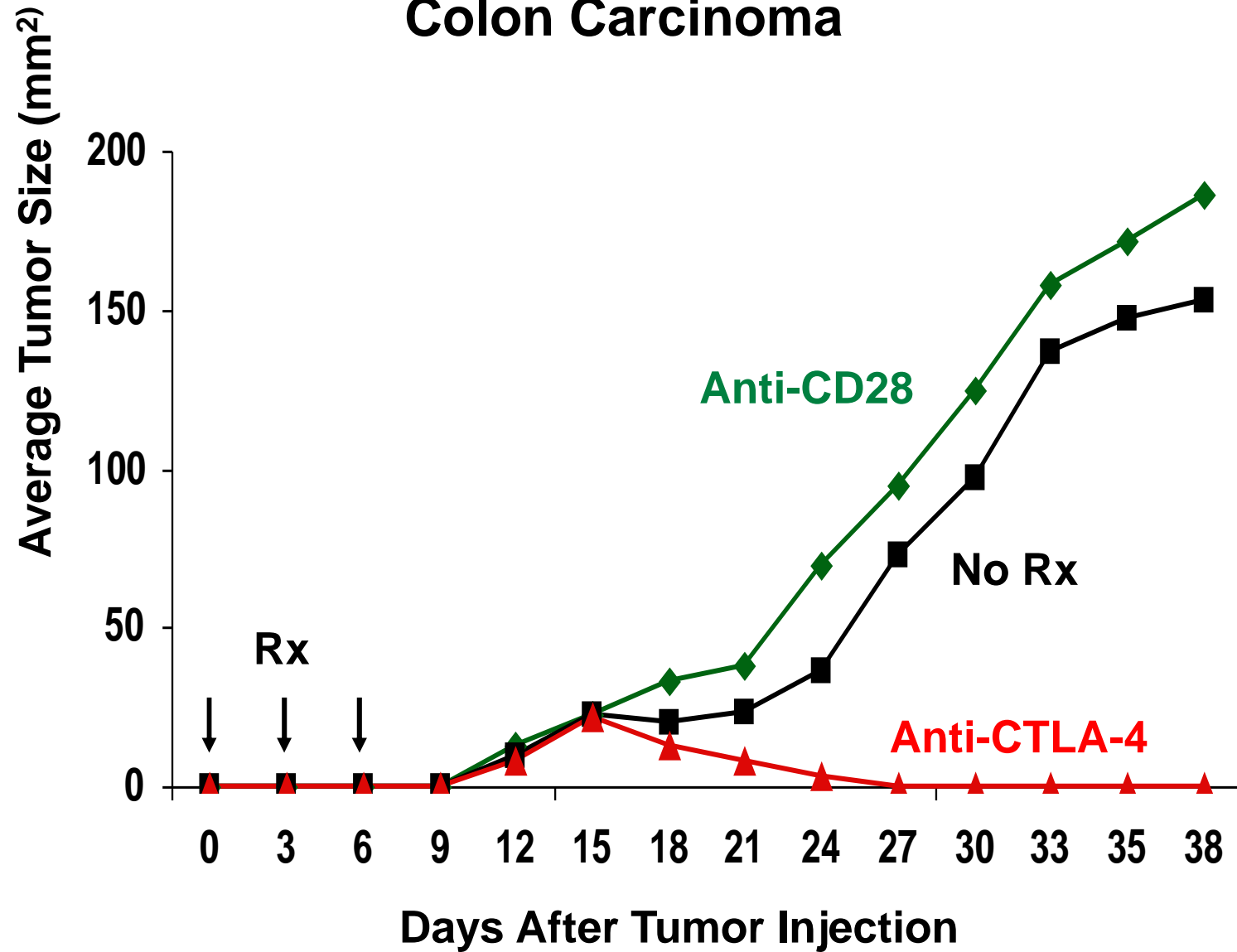
CTLA-4



~ 5 minutes

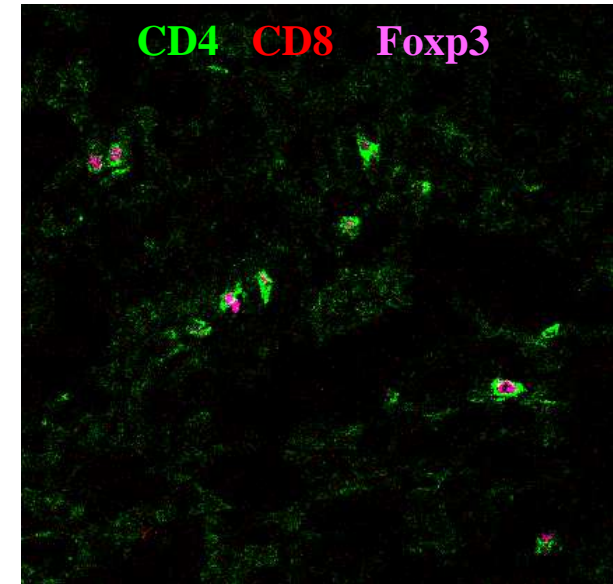
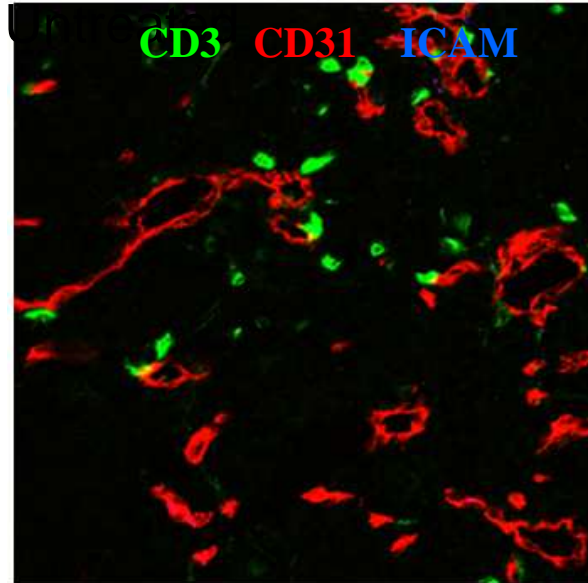


Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma



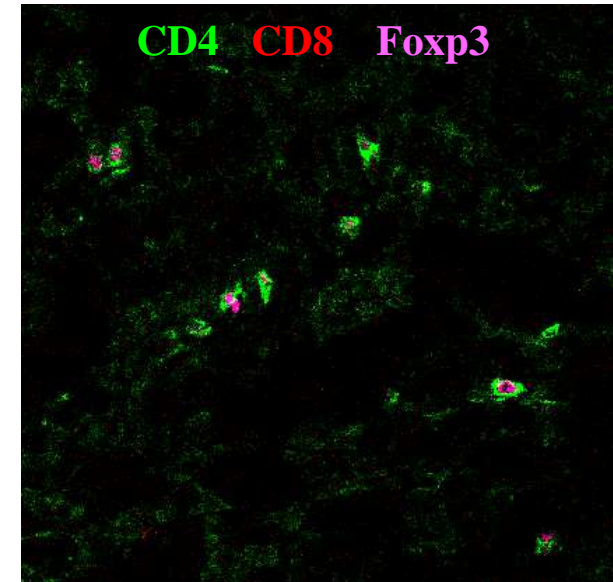
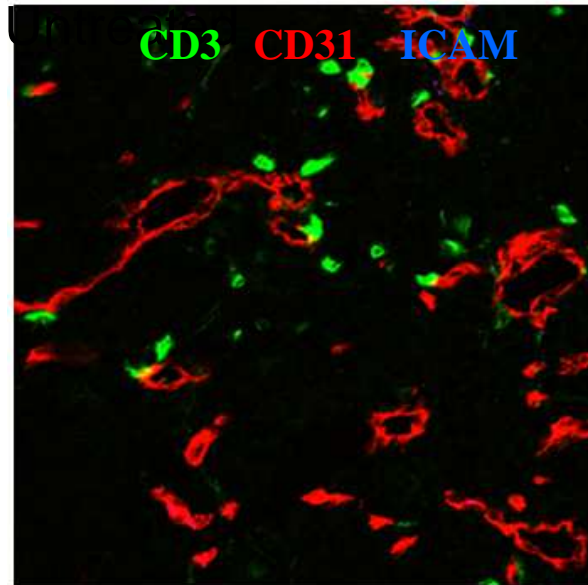
Anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

Untreated

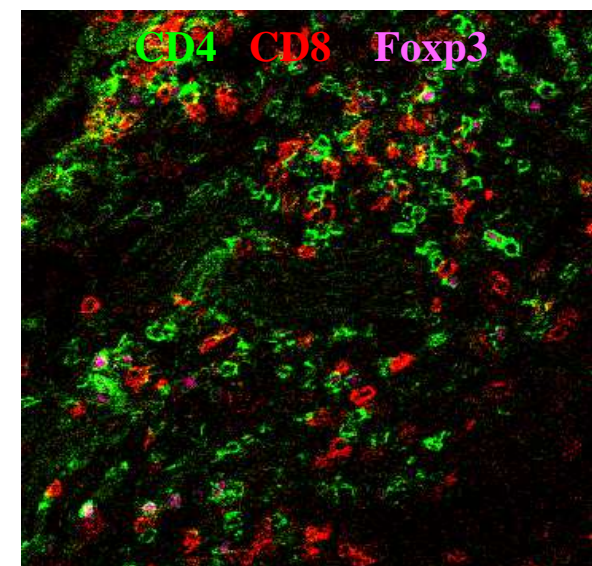
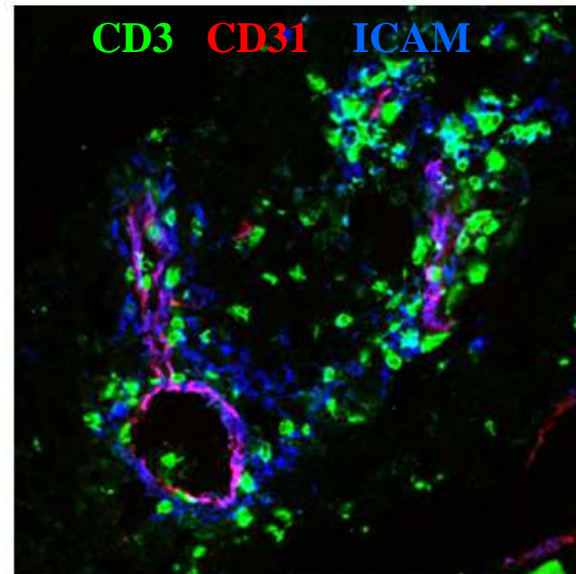


anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

Untreated

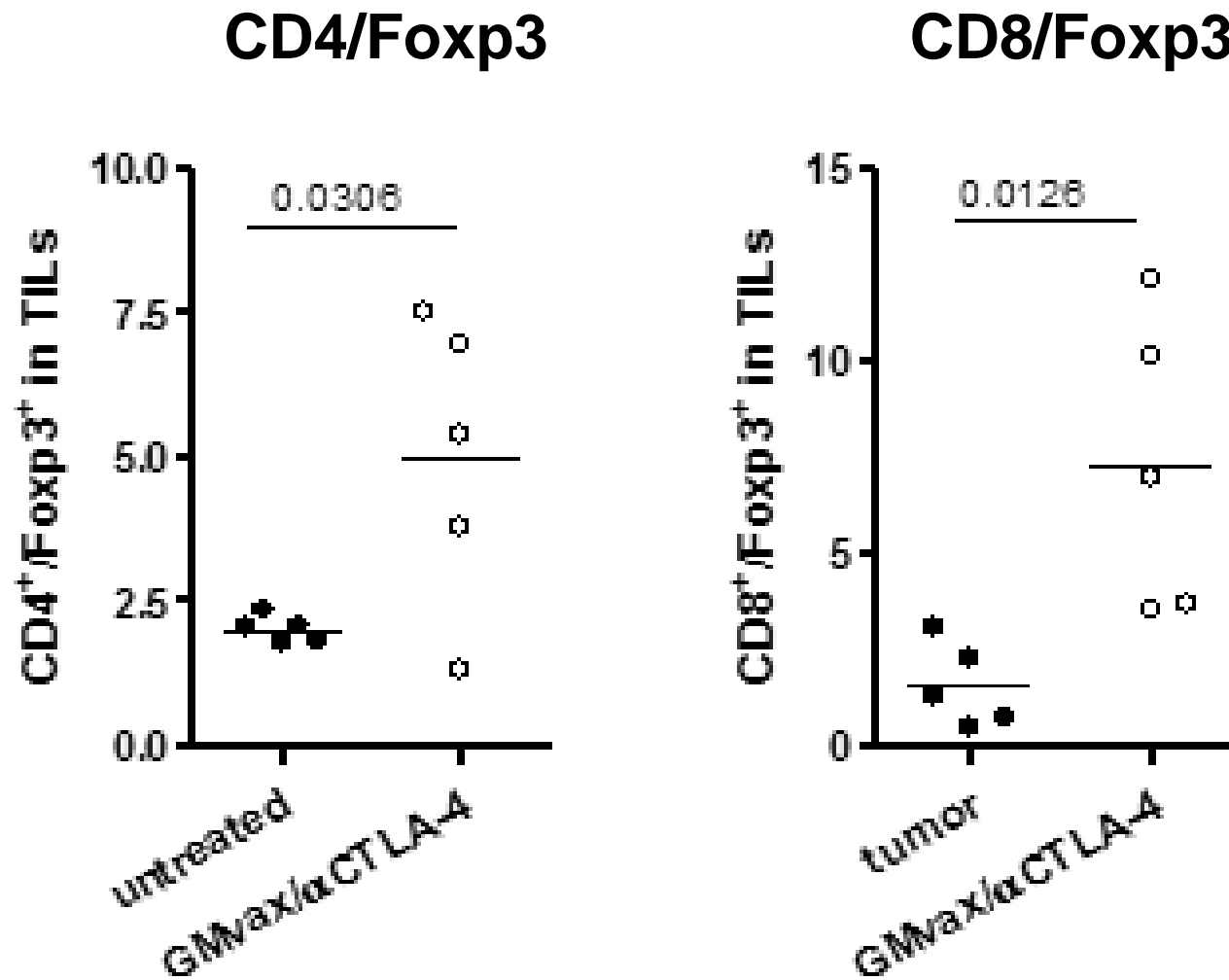


α CTLA-4/GVAX



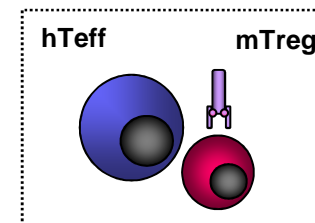
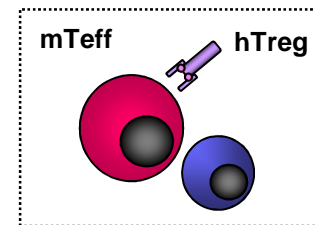
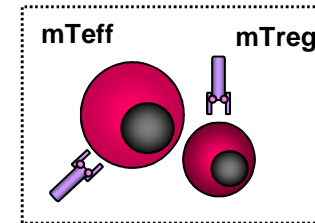
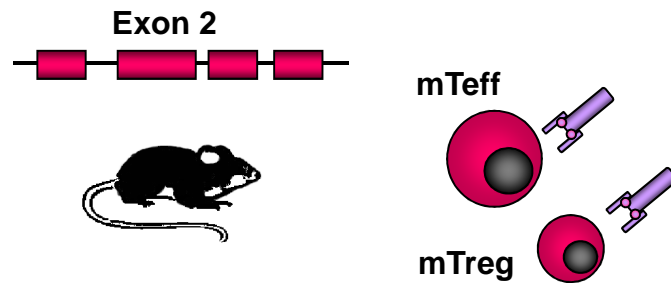
Quezada

α CTLA-4/GVax **Increases** Teff/Treg Ratio In Tumor

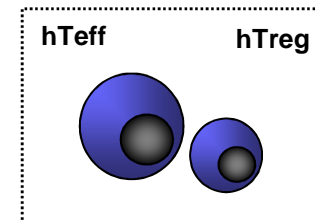
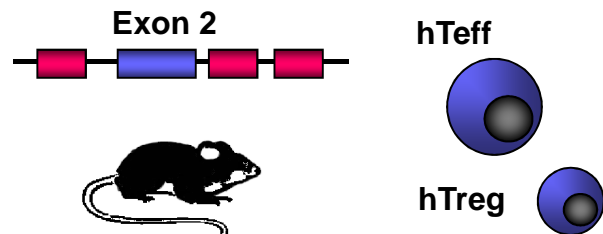


Uni-compartmental CTLA-4 blockade:

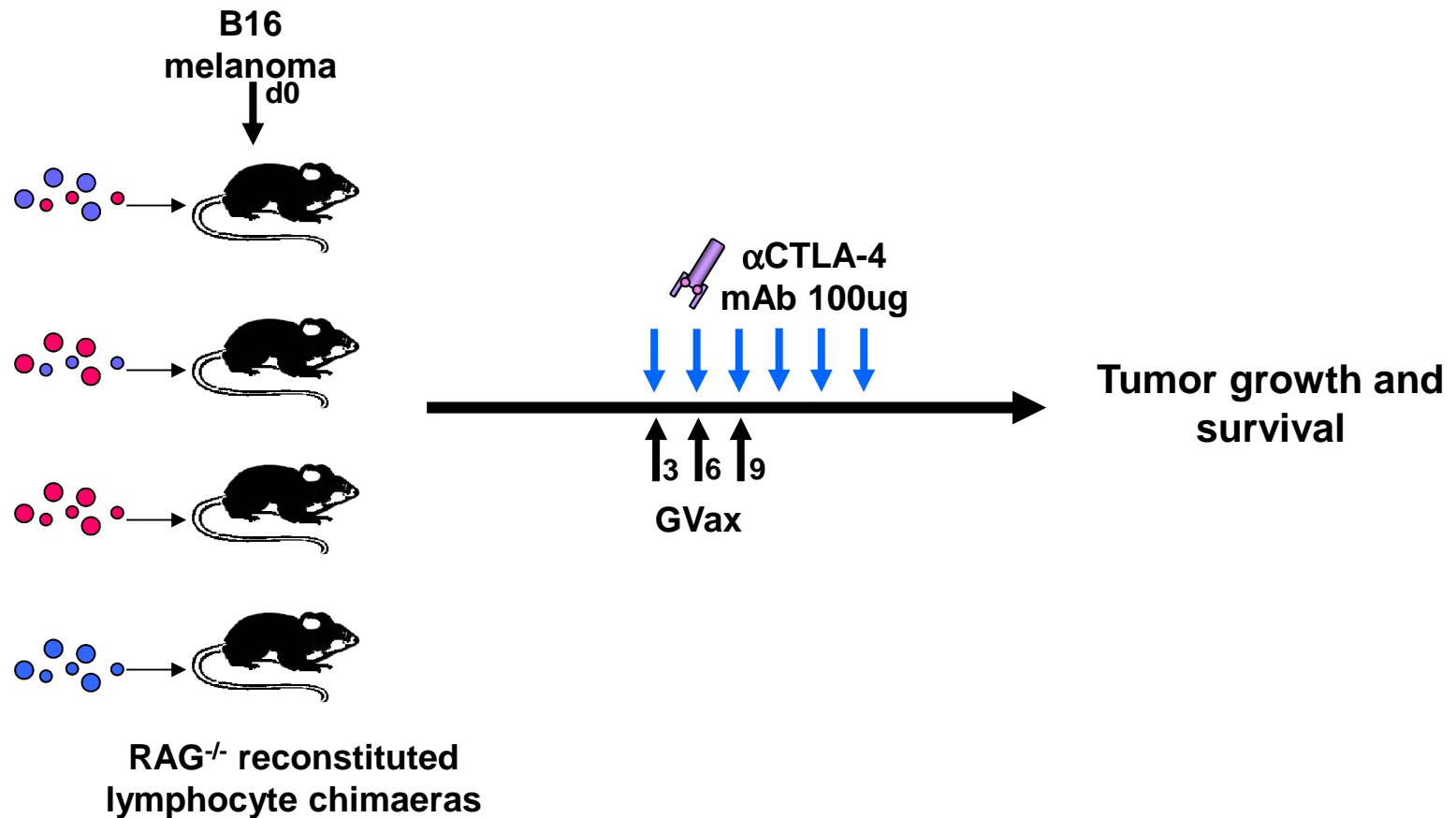
Wild type CTLA-4:



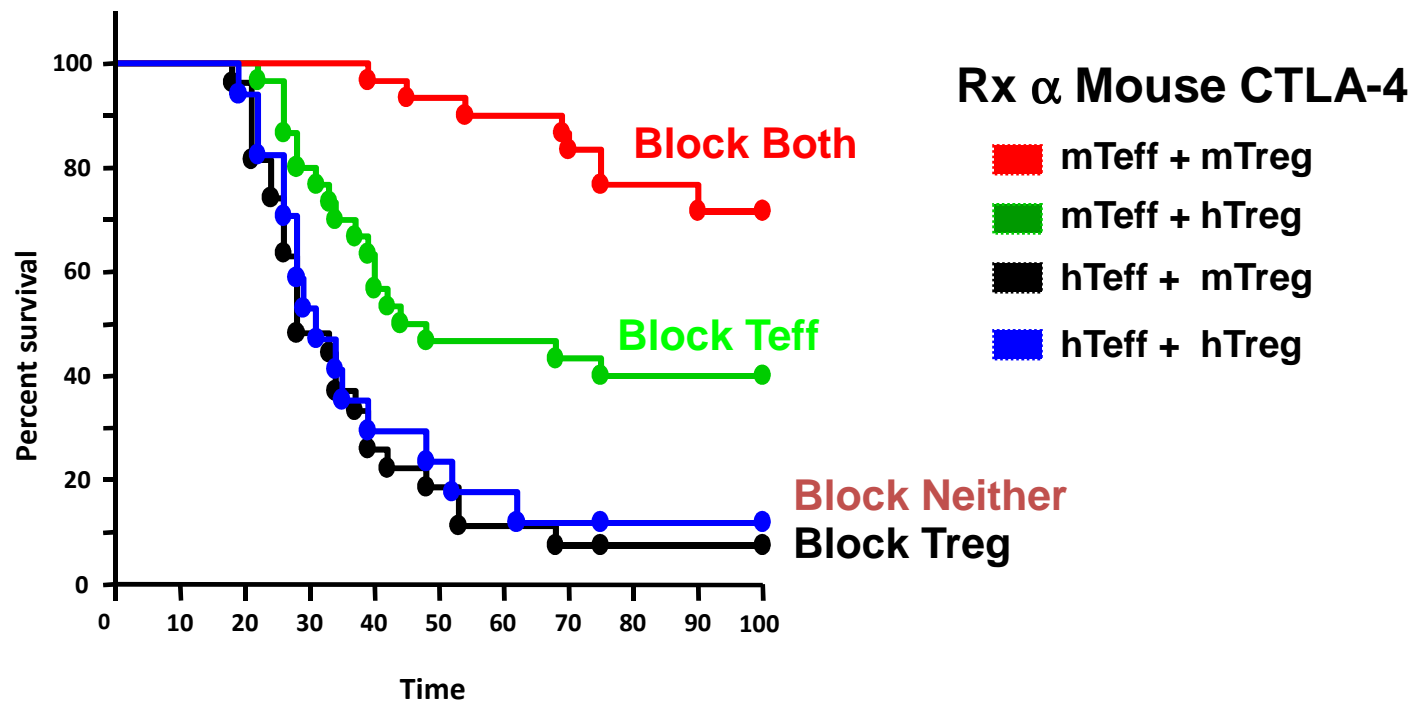
Human tg CTLA-4:



Uni-compartmental CTLA-4 blockade during anti-tumor responses



Blockade of CTLA-4 on both Teff and Treg compartments is necessary for optimal anti-tumor activity



Ipilimumab

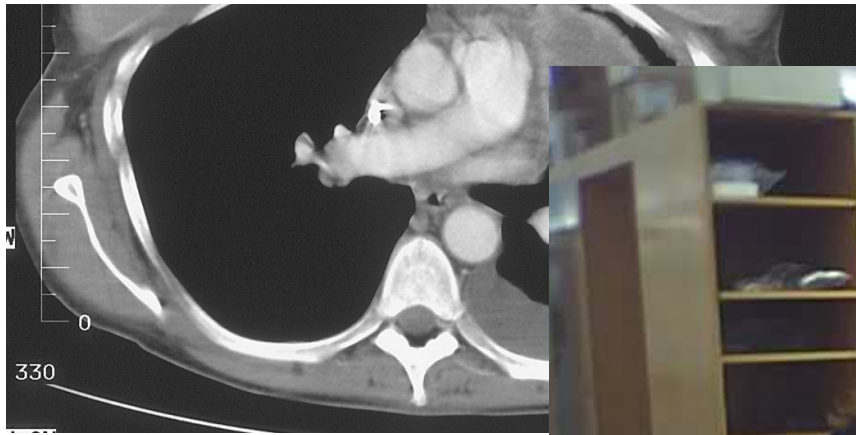
Fully human antibody to CTLA-4

>17,000 patients treated to date:

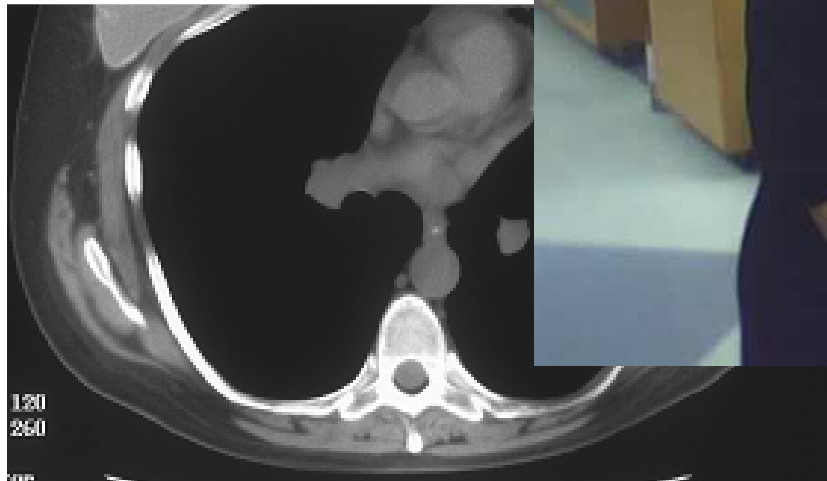
- **Objective responses in melanoma, prostate, ovarian, lung, & kidney cancer, glioblastoma**
- **Adverse events: colitis, rashes, hepatitis, hypophysitis. Manageable with systemic steroids**

The longest survivor on ipilimumab

May 2001, after progression on IL-2

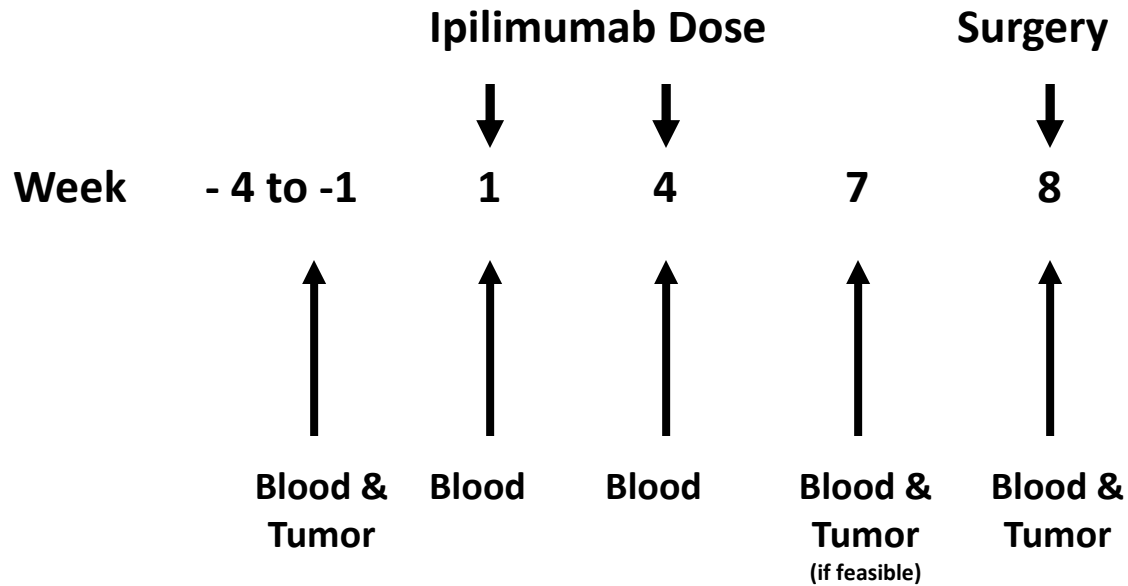


10 years later

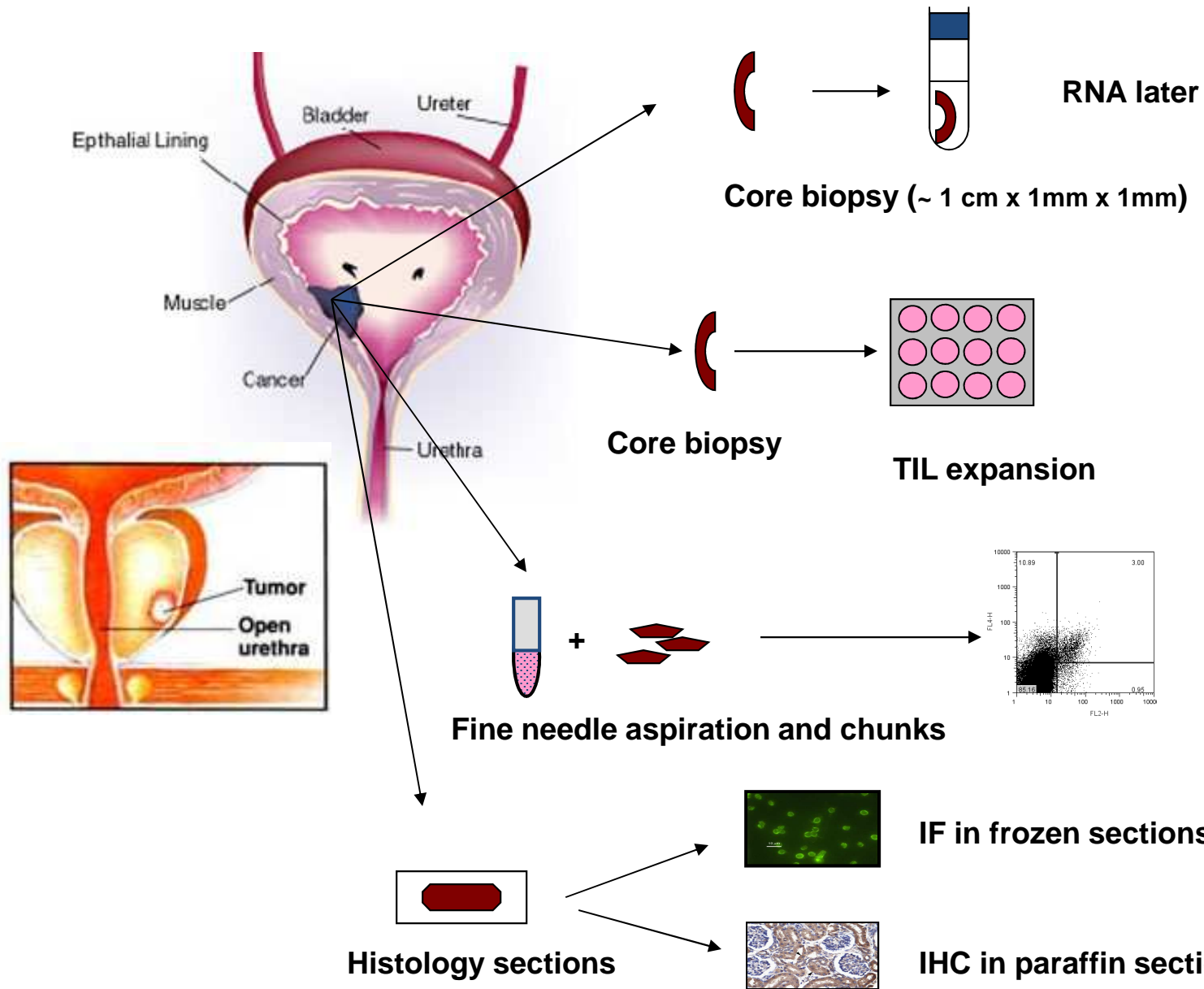


Ribas

Pre-surgical anti-CTLA-4 trial in bladder cancer



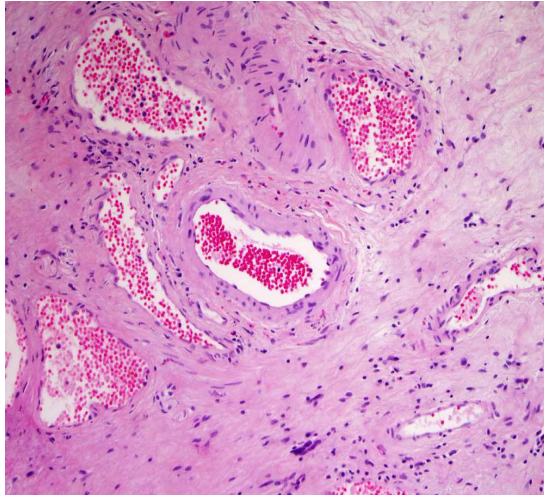
Tissue Analysis



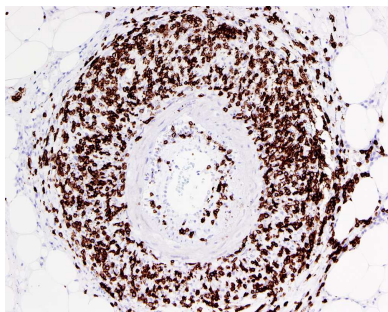
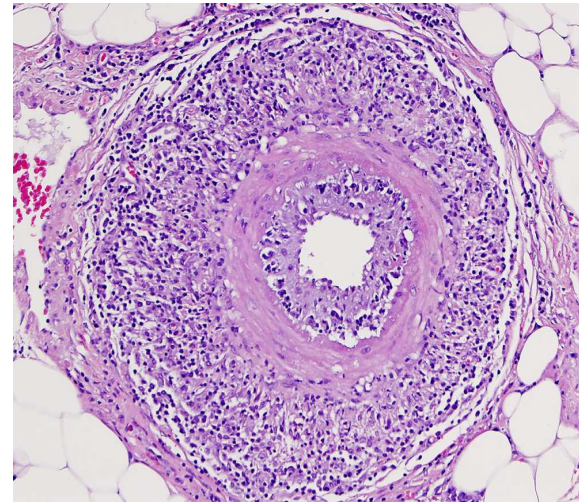
Sharma, MDACC

T cell infiltration into tumor tissues after anti-CTLA-4 therapy

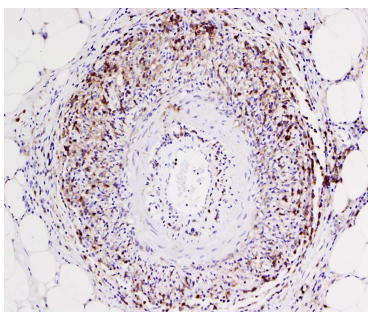
Pre-therapy



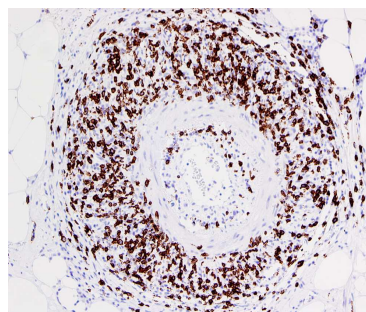
Post-therapy



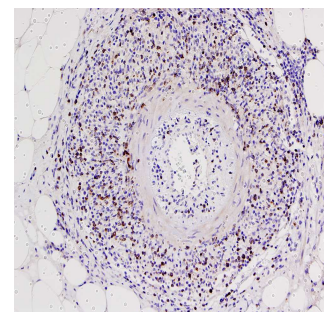
CD3



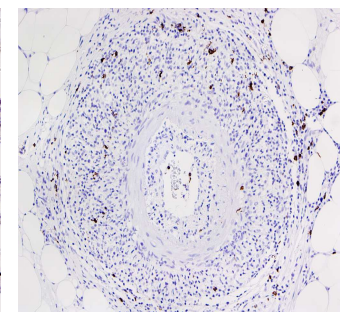
CD4



CD8

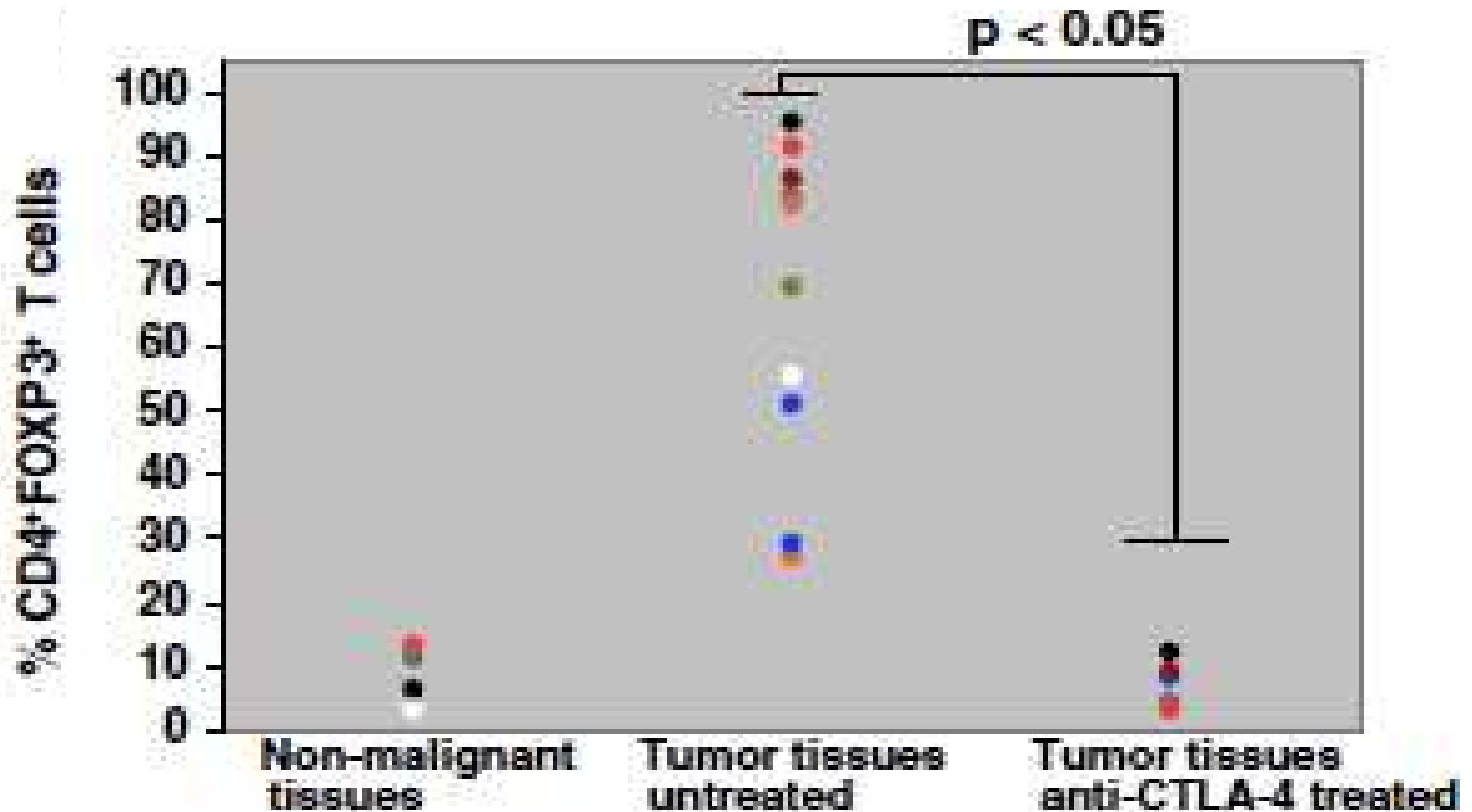


Granzyme



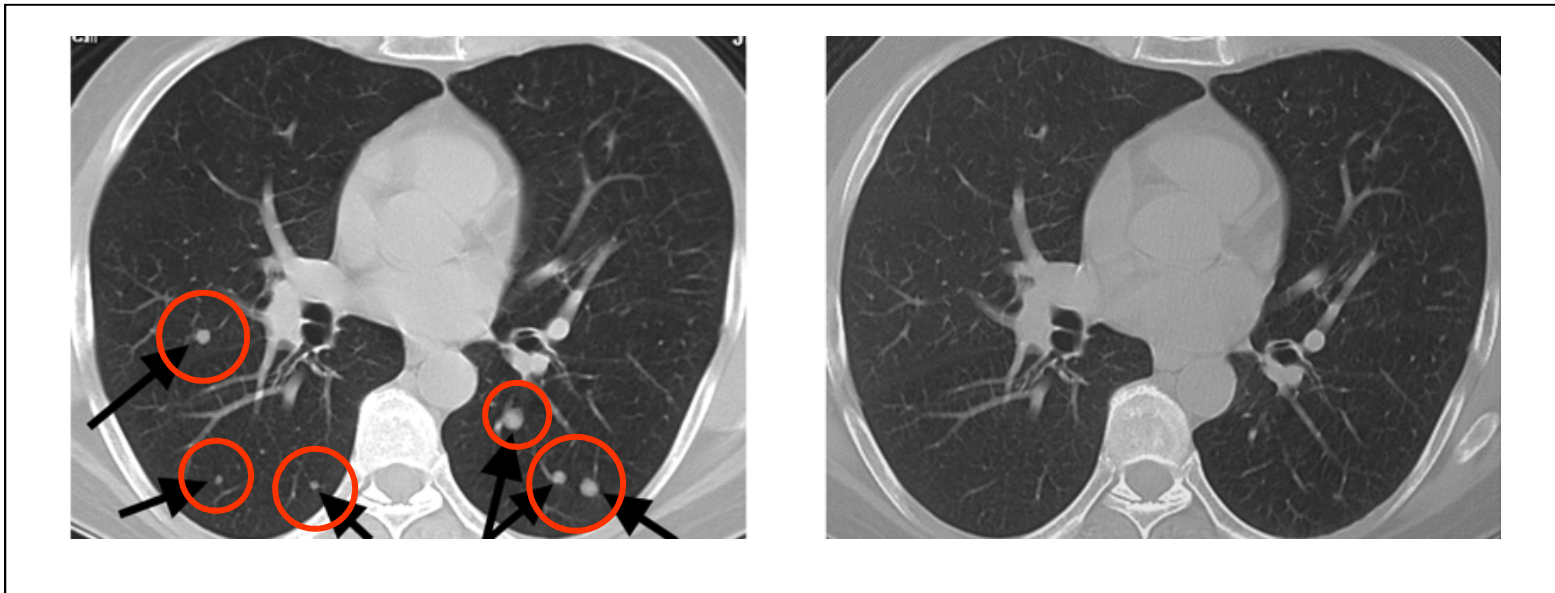
CD20

Ipilimumab Rx reduces Foxp3+ T cells in bladder cancer patients



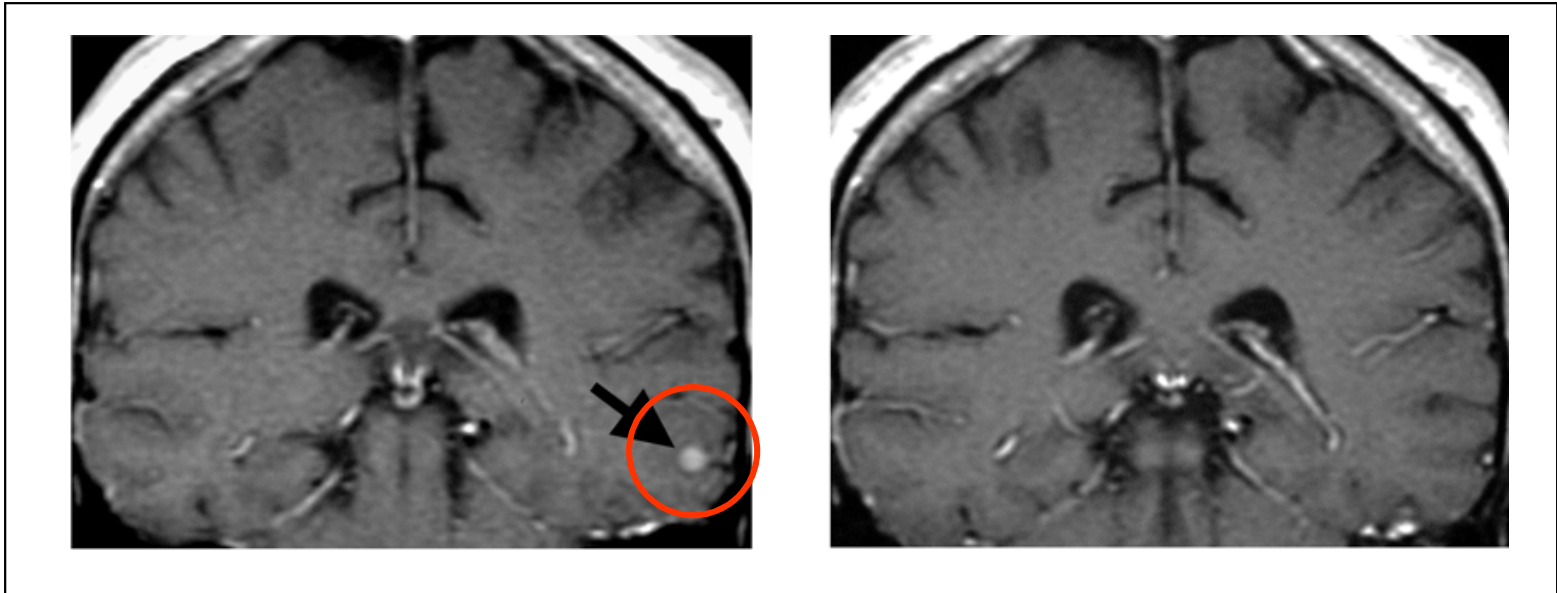
Complete Responder: Melanoma

Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.



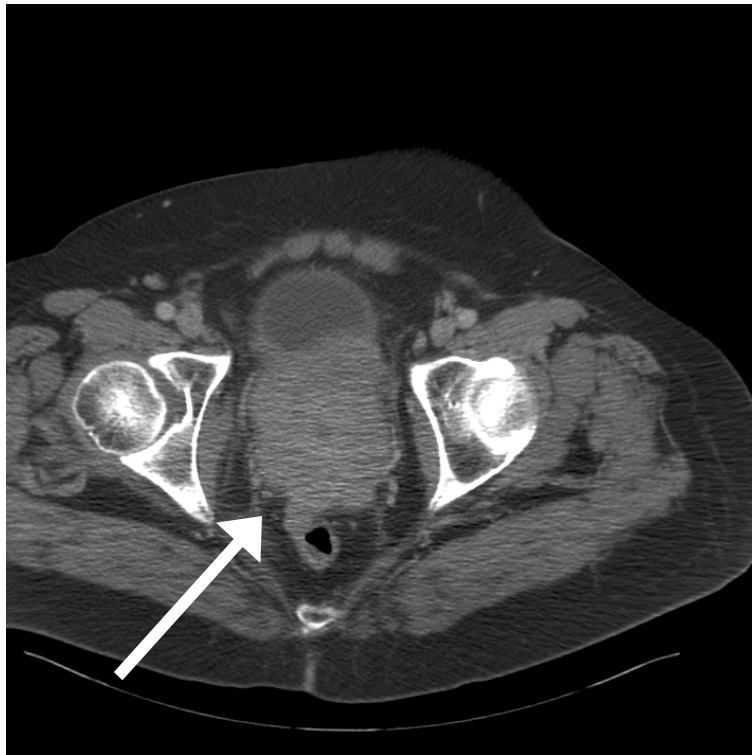
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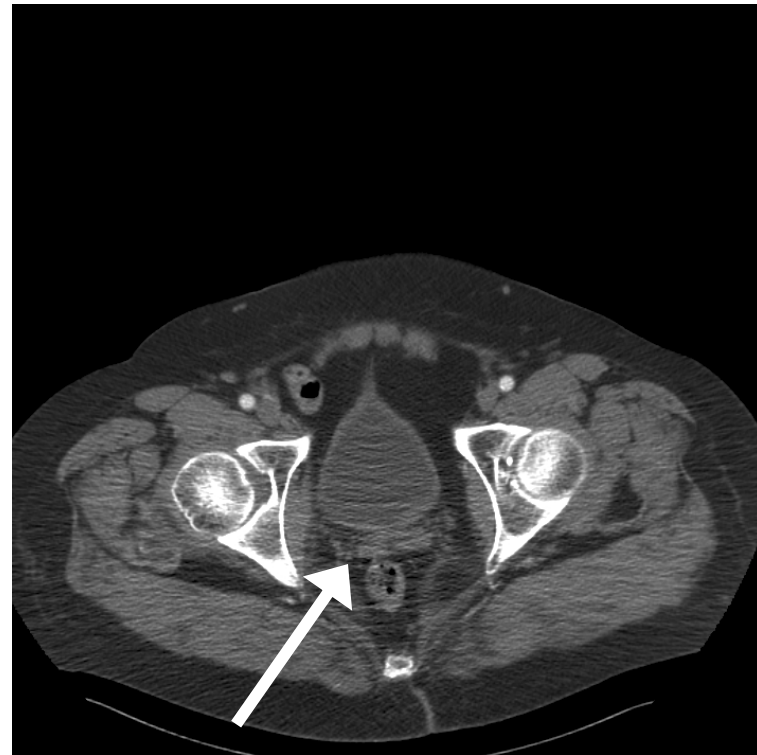


Complete Responder: Prostate Cancer

Screening

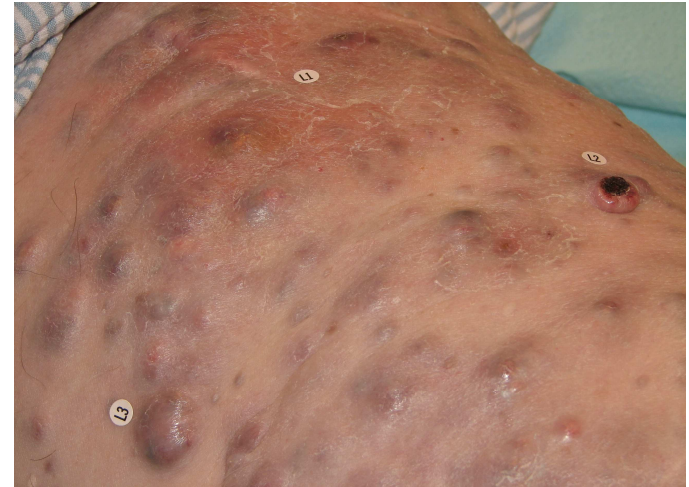


14 months



Phase III trials ongoing

Baseline 11/28/06



Wolchok (MSKCC)

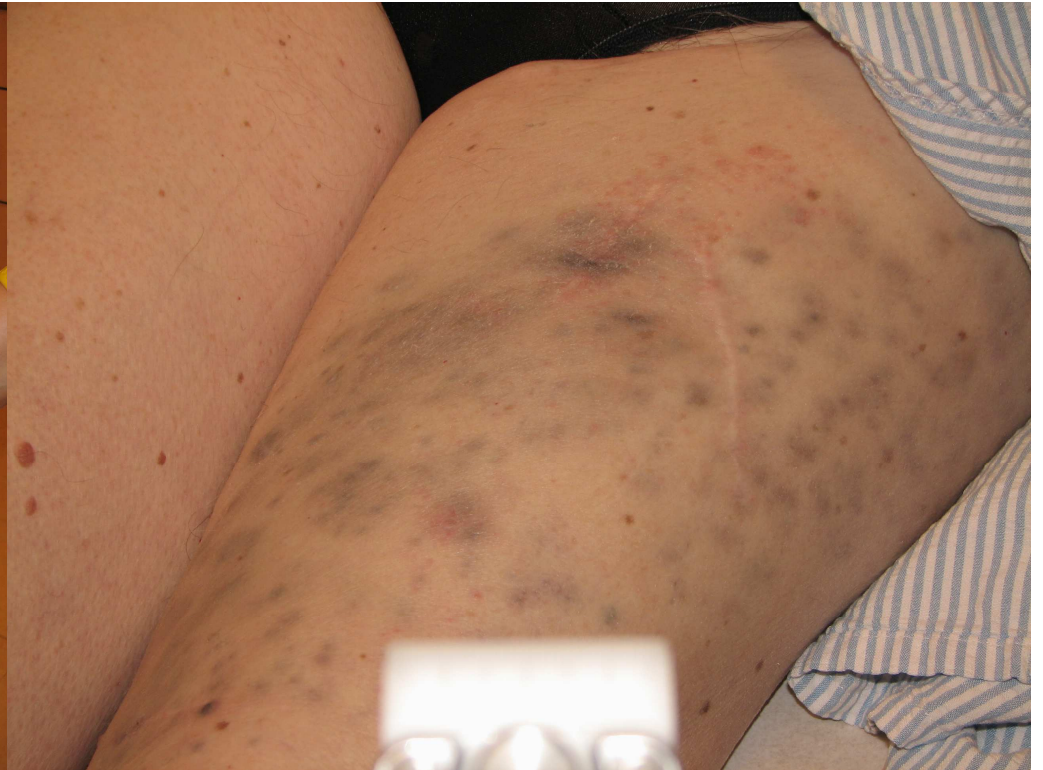
1/9/07

6 Weeks



2/12/07

10 Weeks



Wolchok (MSKCC)

Evolution of Response: Patient Example

Screening

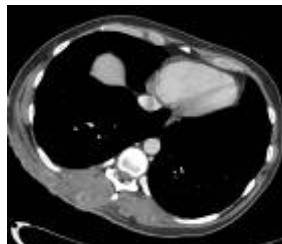


Week 12

**Initial increase in
total tumor burden (mWHO PD)**



Week 16
Responding

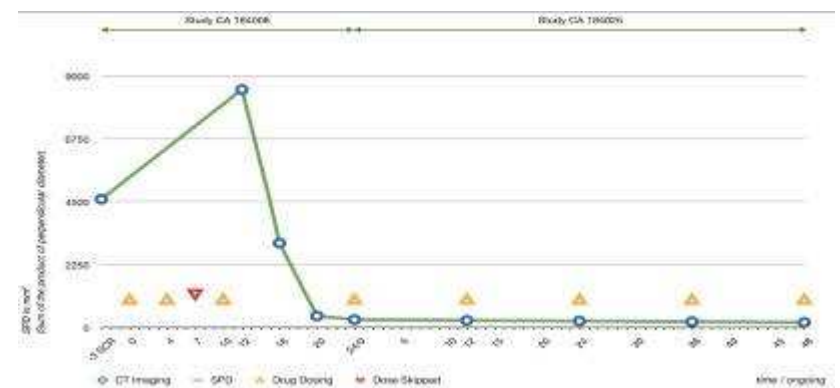


Week 72

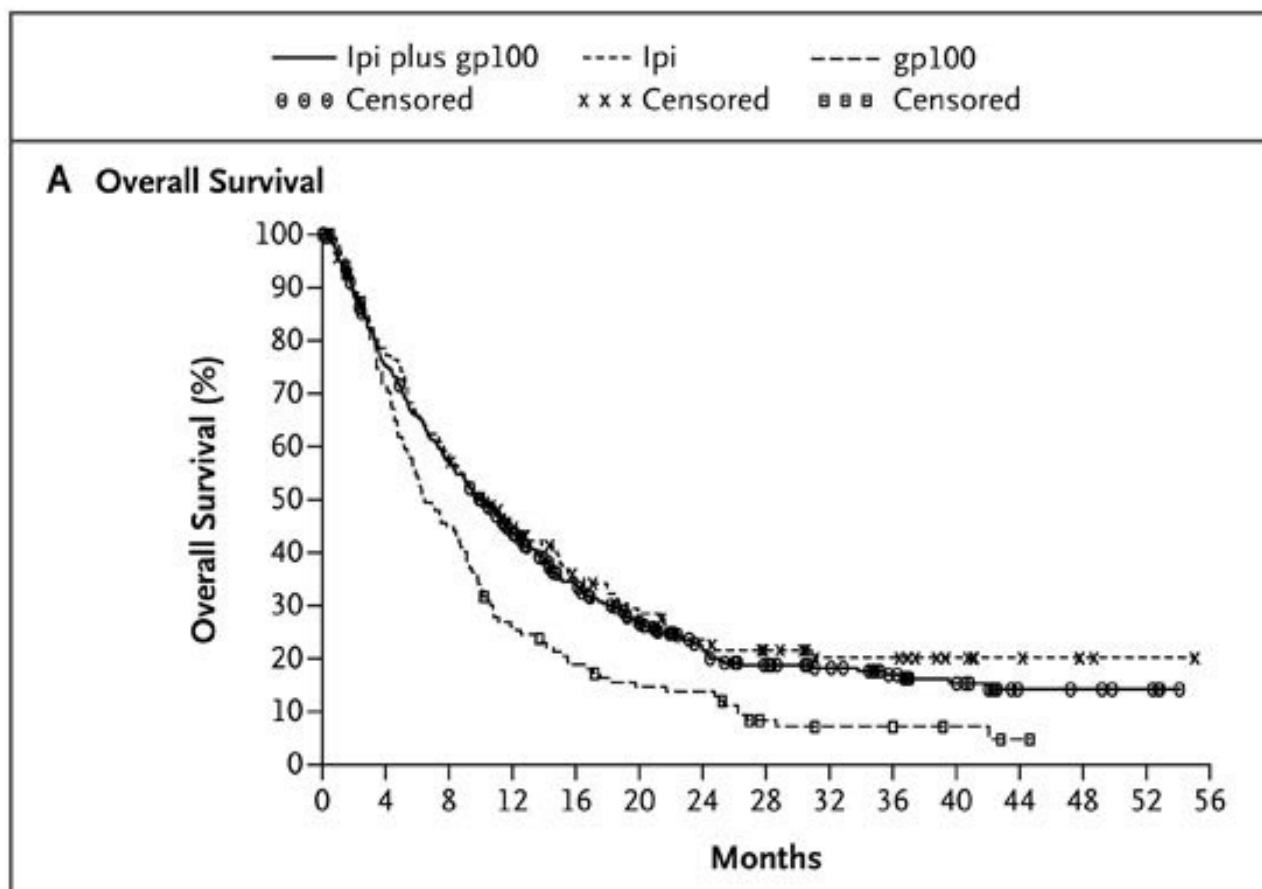
**Durable & ongoing response
without signs of IRAEs**



20006



Kaplan-Meier Analysis of Survival



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Ipilimumab

- **Metastatic Melanoma**
 - **Ipilimumab was approved by FDA in 2011 for second and front line therapy.**
 - **Trial of ipilimumab plus dacarbazine showed enhanced survival over dacarbazine alone.**
- **Castrate-resistant Prostate Cancer**
 - **Randomized Phase III registration trails ongoing of ipilimumab following palliative radiation**

Critical Issues for Further Clinical Development of anti-CTLA-4

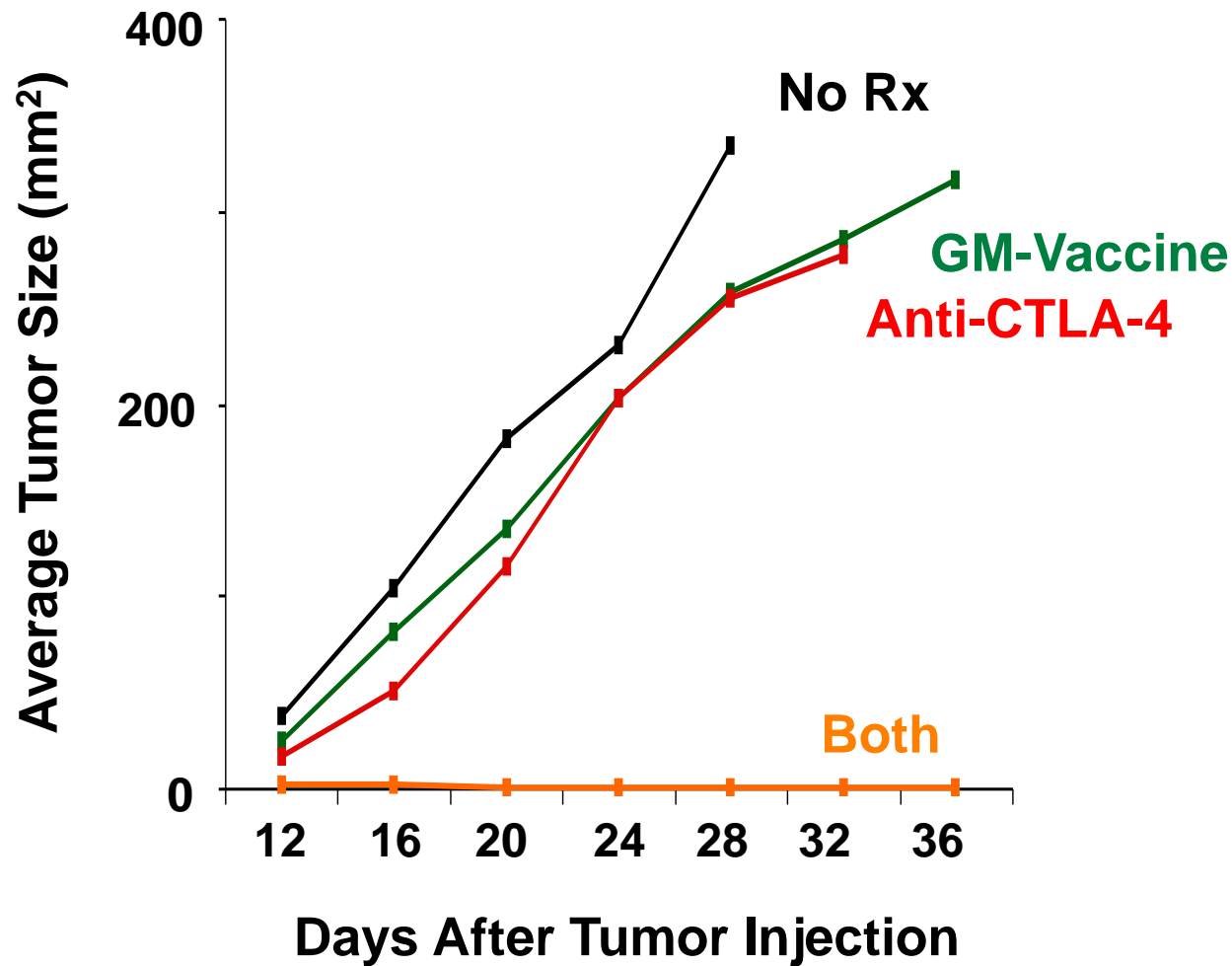
- **What are the cellular and molecular mechanisms involved in the anti-tumor effect?**
- **What distinguishes between responders and non-responders?**
- **What are the best conventional therapies or vaccines to be used combinatorially?**

How can we increase the response rate?

Combinations to Increase Efficacy of CTLA-4 Blockade

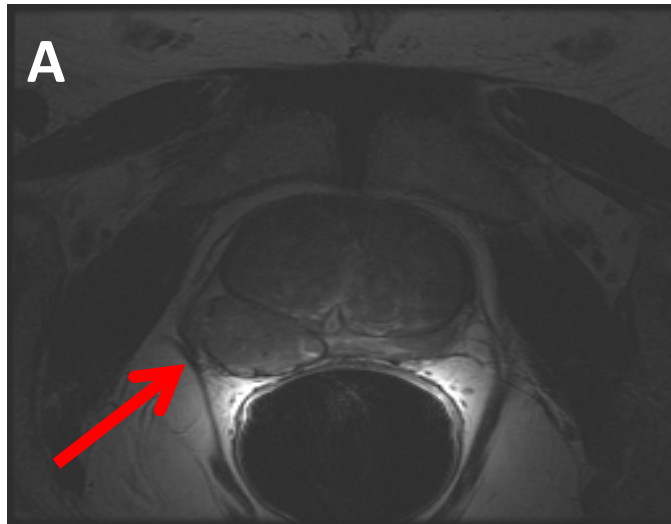
- **Vaccines**
- **Conventional Therapies**
- **Targeted Therapies**

Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

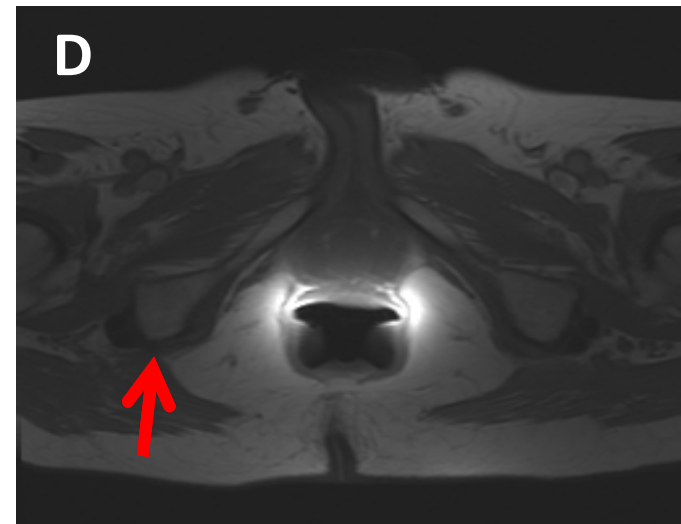
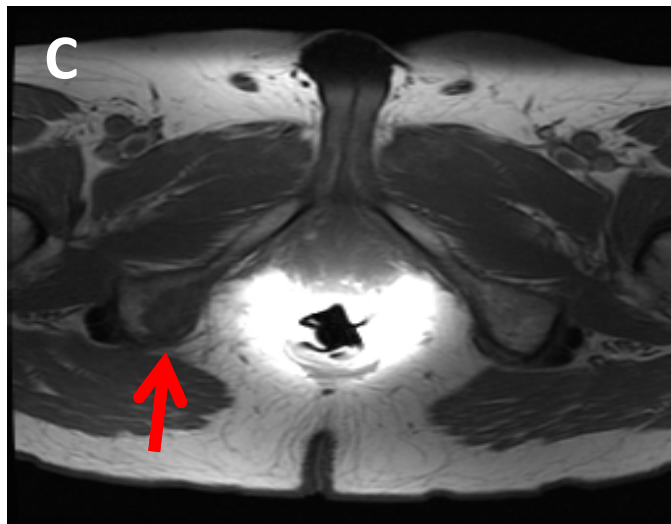
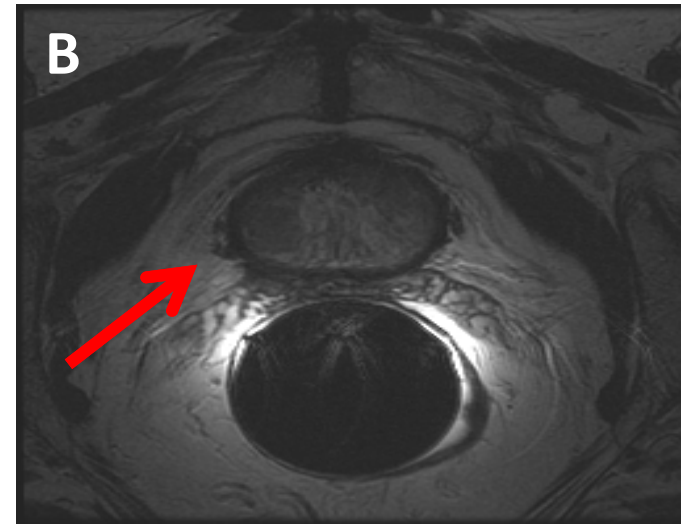


Regression of metastatic disease after ipilimumab plus androgen deprivation

Pre



Post



Aparicio and Sharma (MDACC)

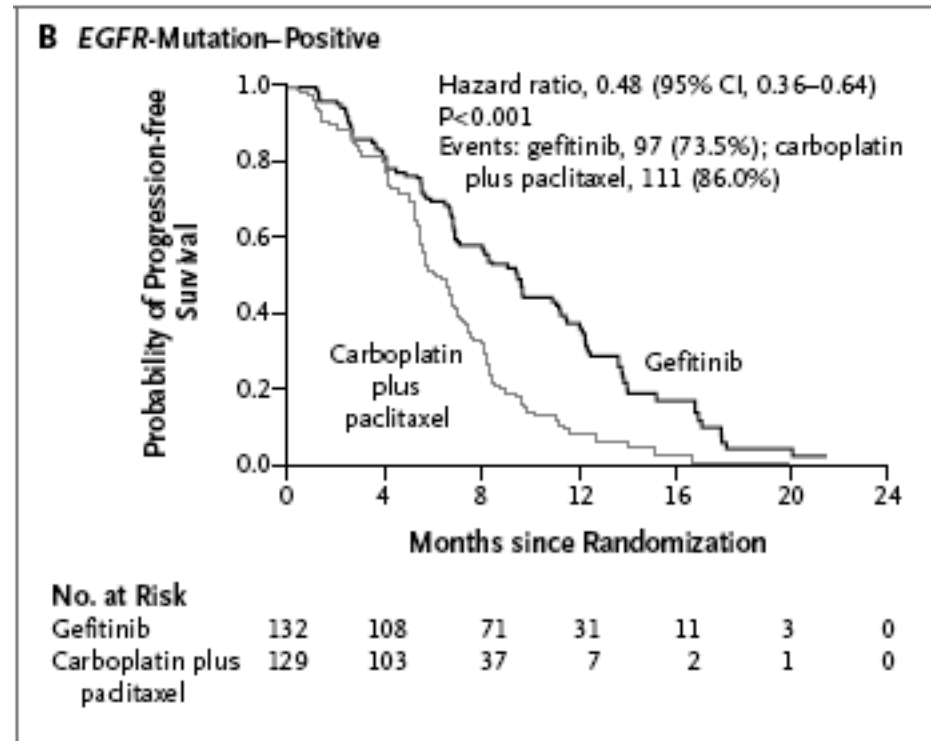
Combinations to Increase Efficacy of CTLA-4 Blockade

- **Vaccines**
- **Conventional Therapies**
- **Targeted Therapies**

Targeted Therapies

- High response rates, rapid tumor regression in patients with target**
- Responses are often of short durability, not necessarily associated with overall survival**
- Recurrence is associated with drug resistance**
- Success may require iterative identification of targets, development of additional drugs**

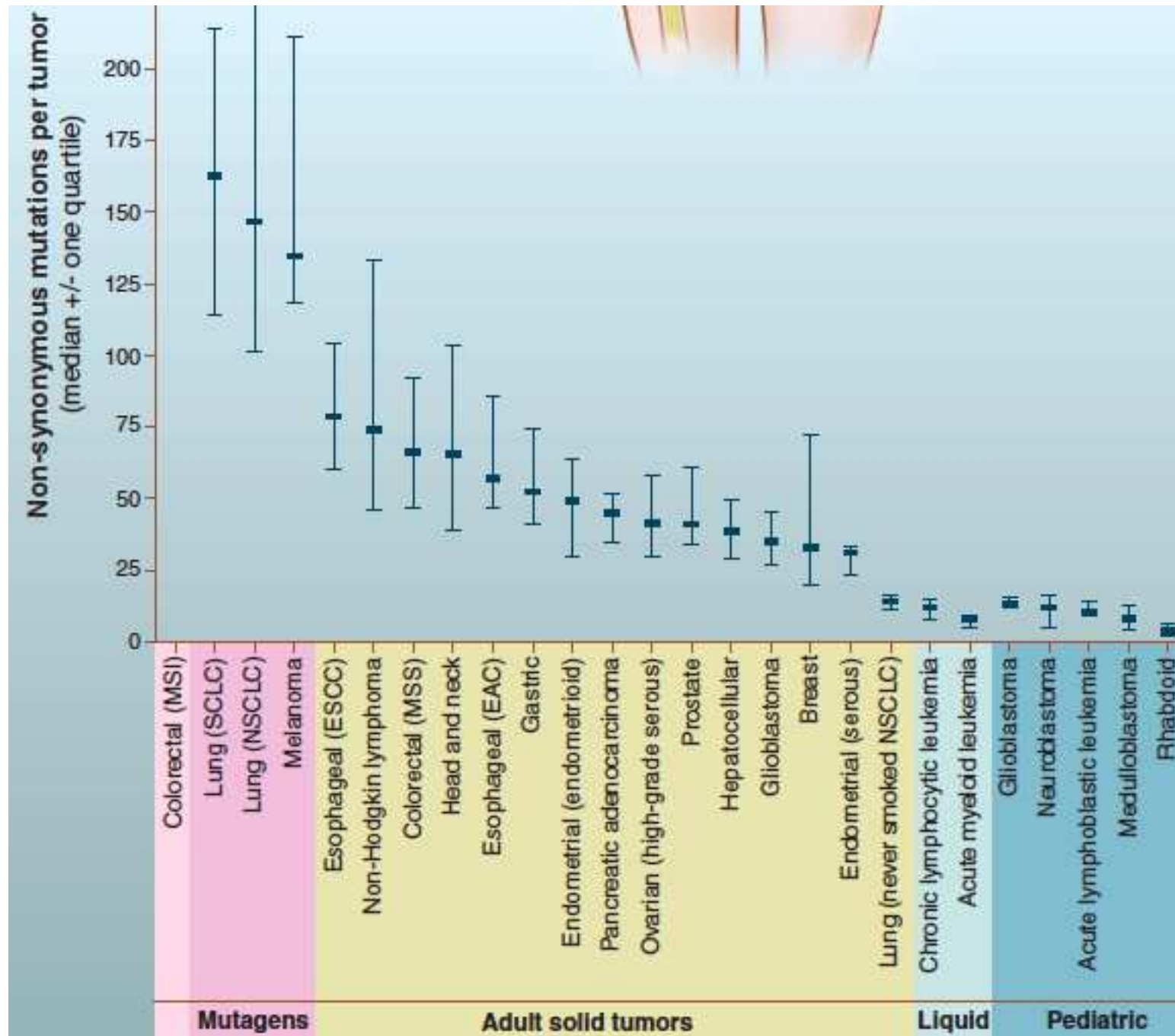
Targeted Therapy and Survival (PFS) in Non-small Cell Lung Cancer



Improved progression free survival in NSCLC patients with EGFR mutation

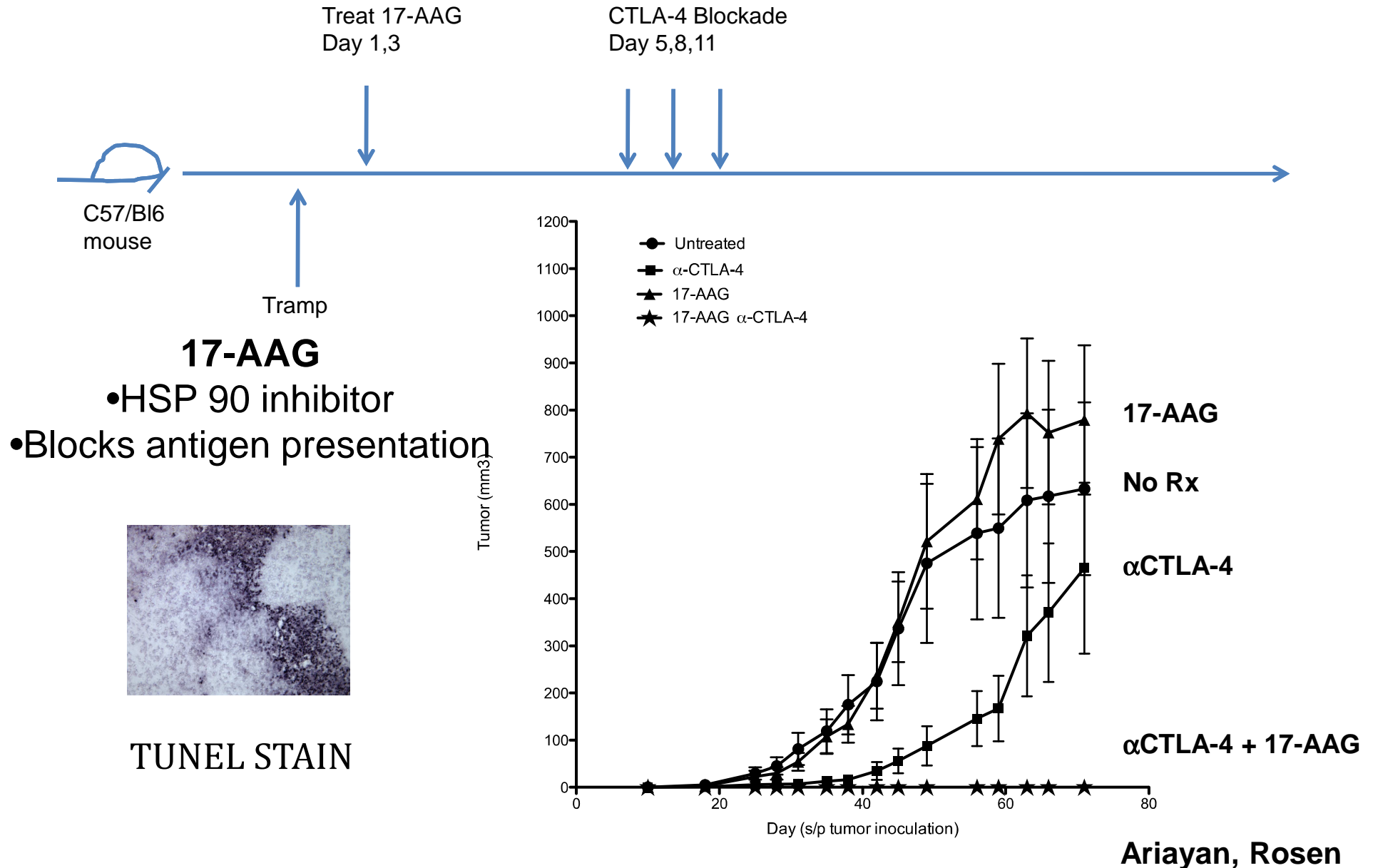
Targeting Neoantigens: Drugs as Vaccines

- **Breast and colorectal tumors contain ~100 missense mutations/cell (Vogelstein)**
- **Many of these (~50%) may be neoantigens (Segal and Allison)**
- **Exome Sequencing shows varying numbers of missense mutations in different tumors:**
 - **Prostate: 30-70**
 - **Glioblastoma: 30-50**
 - **Melanoma: 400-500**
- **Killing tumor cells should release multiple neoantigens and prime multiple T cell responses**
- **Sustaining these responses by immune checkpoint blockade may result in durable responses**



Vogelstein et al *Science* 2013

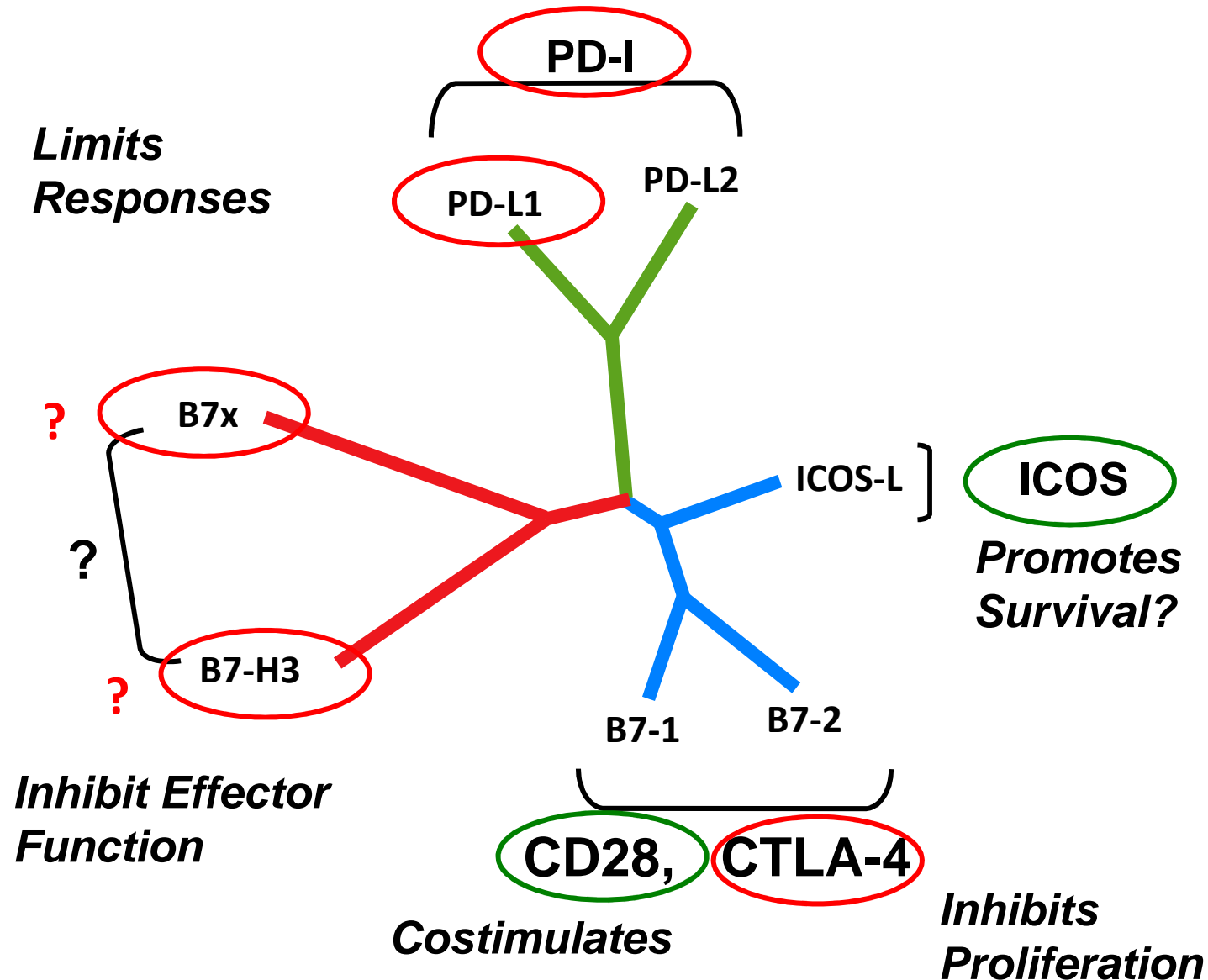
HSP90 Inhibitor Enhances Efficacy of CTLA-4 Blockade in Rx of TRAMP-C2 Prostate Tumors



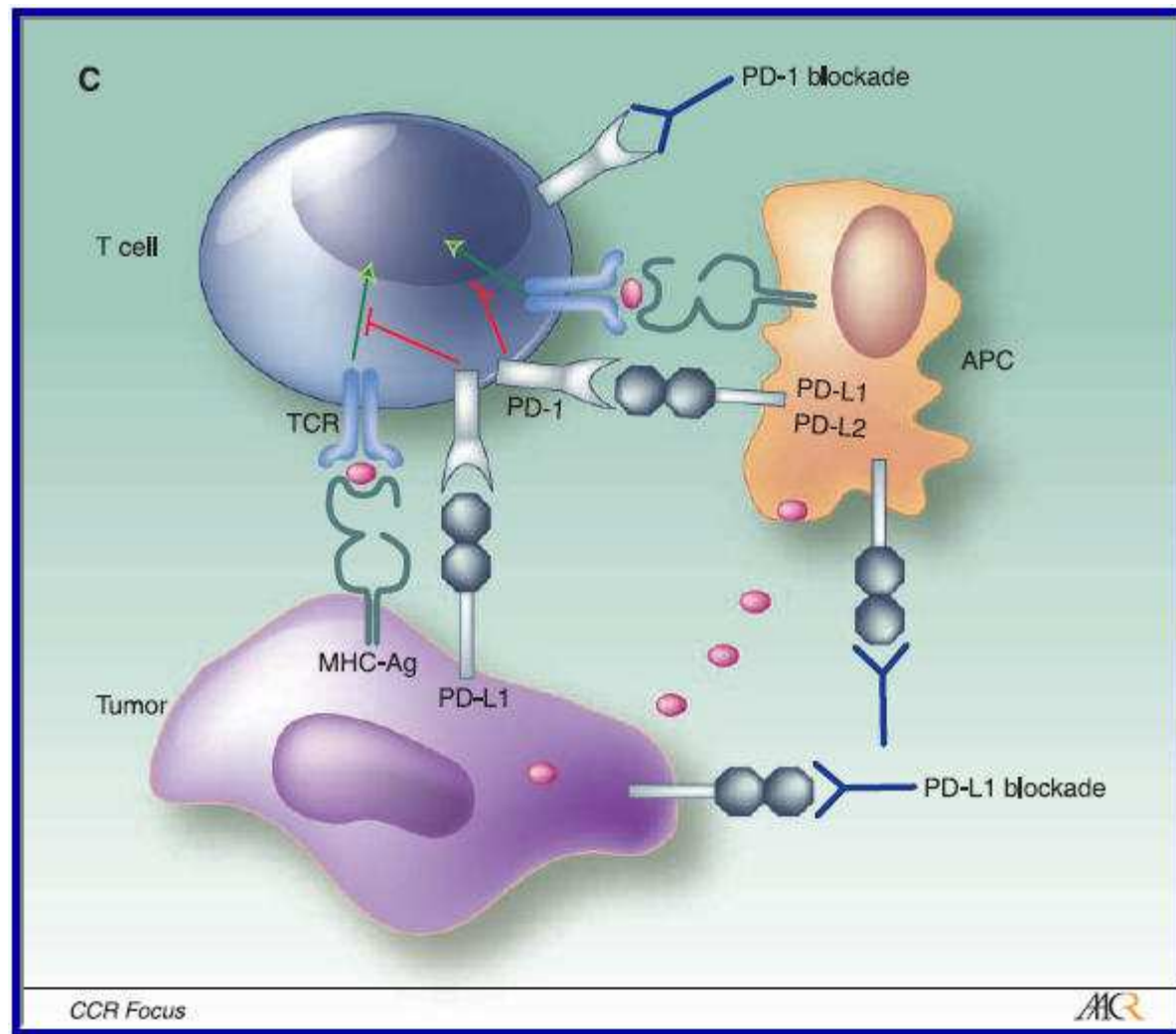
Combinations to Increase Efficacy of CTLA-4 Blockade

- **Vaccines**
- **Conventional Therapies**
- **Targeted Therapies**
- **Combinations of Checkpoint Inhibitors**
PD-1, PD-L1, B7-H3, B7-H4,
Vista, Tim-3, Lag-3

Combination of Multiple Immune Checkpoint Blockers



Programmed Death 1



Anti – PD-1

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

**Safety: Adverse events similar to Ipilimumab, but
4% pneumonitis (3 deaths)**

Clinical Activity:

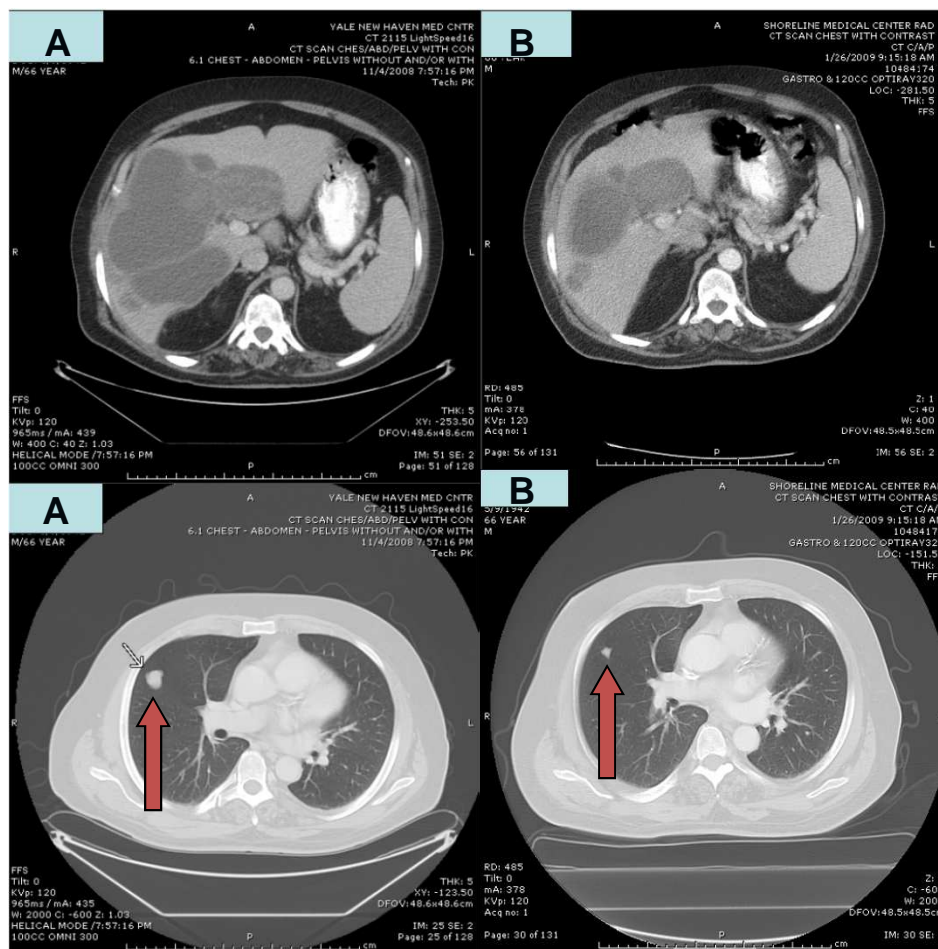
Melanoma (n= 94): 28% CR/PR, 6% SD

NSCLC (n=76): 18% CR/PR, 7% SD

RCC (n= 33): 27% CR/PR, 27% SD

CRC (n=19), CRPC (n=13): No responses

OBJECTIVE RESPONSE IN MELANOMA: 1 MG/KG



M. Sznol, Yale University

History:

66 yr/male patient

- diagnosed in 2001
- Progression on HD IL-2
- Presented with pulmonary and bulky liver lesions

A: Baseline (11/4/2008)

B: Cycle 1 assessment (1/26/2009)

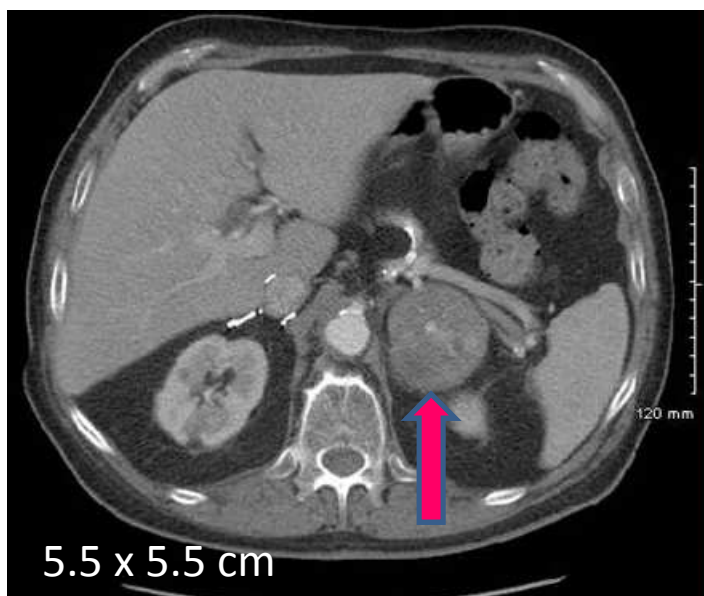
Pt. met PR criteria after 3 cycles (12 bi-weekly doses)

Pt. currently in cycle 10, response ongoing at 12+ months

Clinical Response with α PD-1: Non-small cell Lung Cancer

History: 72 yr/male with progressive disease after
right adrenalectomy,
chemotherapy, bevacizumab.

Screening: 2/23/09



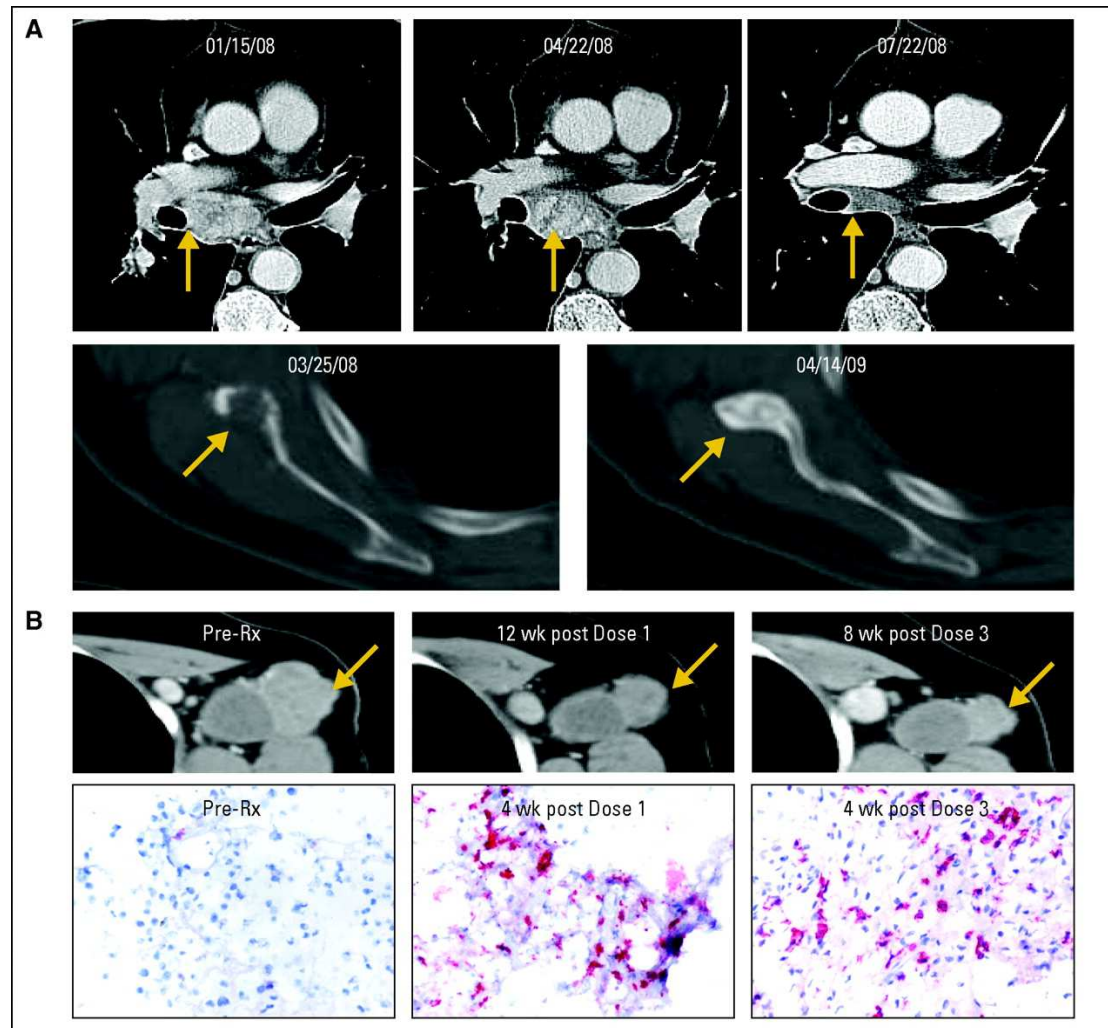
Cycle 1 Eval*: 5/2/09



J. Powderly, Carolina BioOncology Institute

*PR at 12+ months

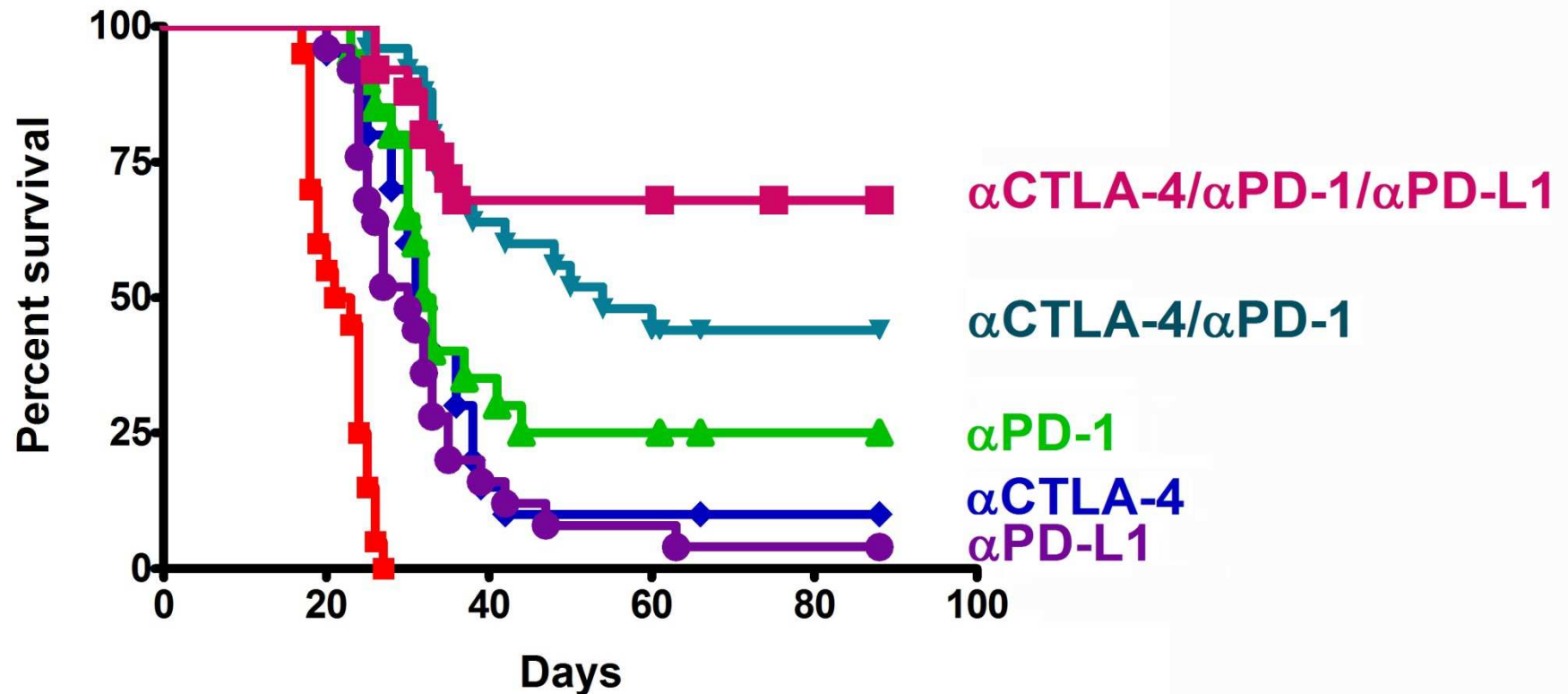
Clinical Response with α PD-1: Metastatic Renal Cell Cancer



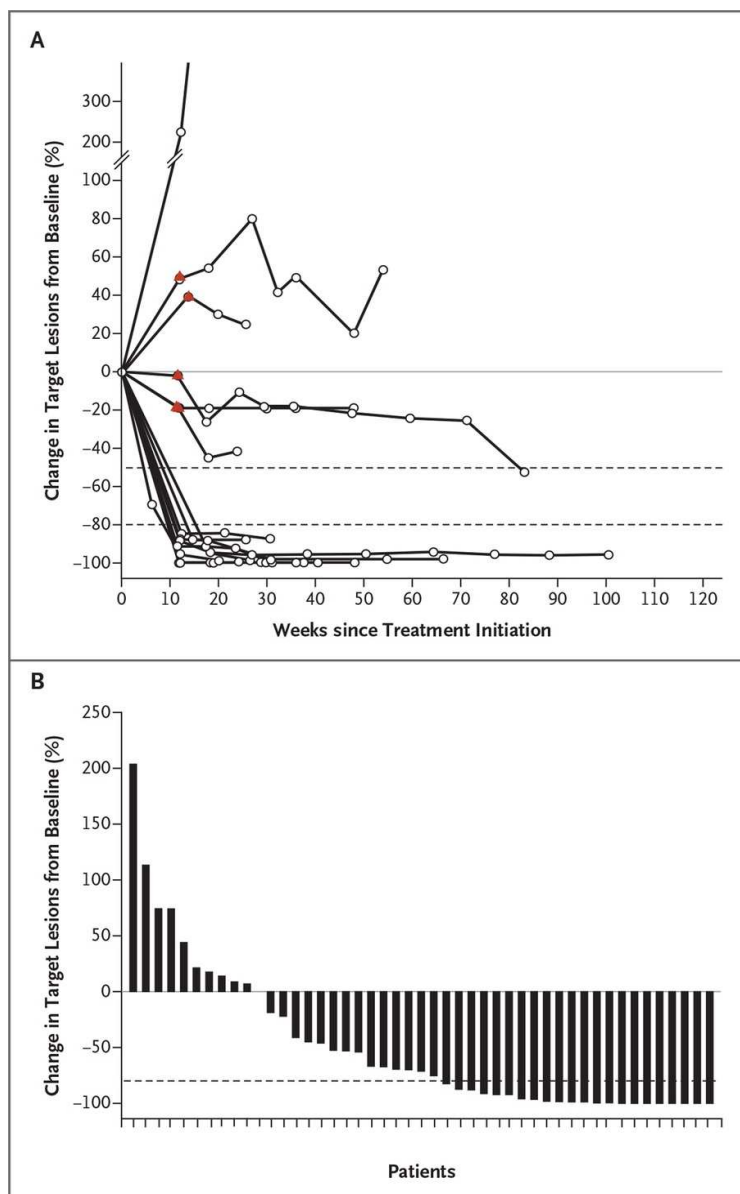
Brahmer J R et al. JCO 2010;28:3167-3175

Combination blockade of the CTLA-4 and PD-1 pathways promotes rejection of B16 melanoma

Combination FVAX (B16-Flt3-ligand)+ Antibody



Clinical Activity in Melanoma Patients Receiving Ipilimumab (α CTLA-4) and Nivolumab (α PD-1)

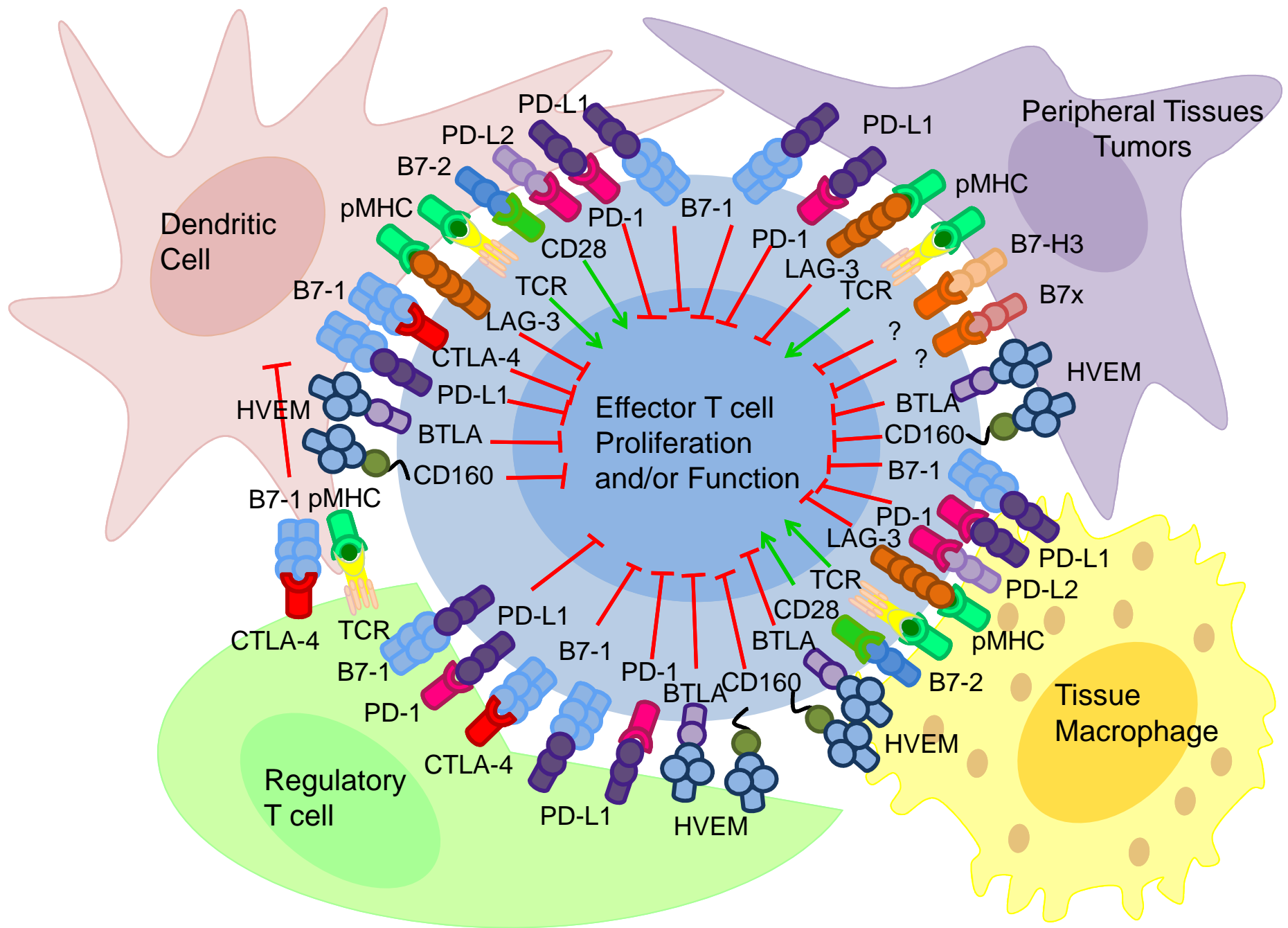


40% Objective CR+PR
65% Clinical Activity

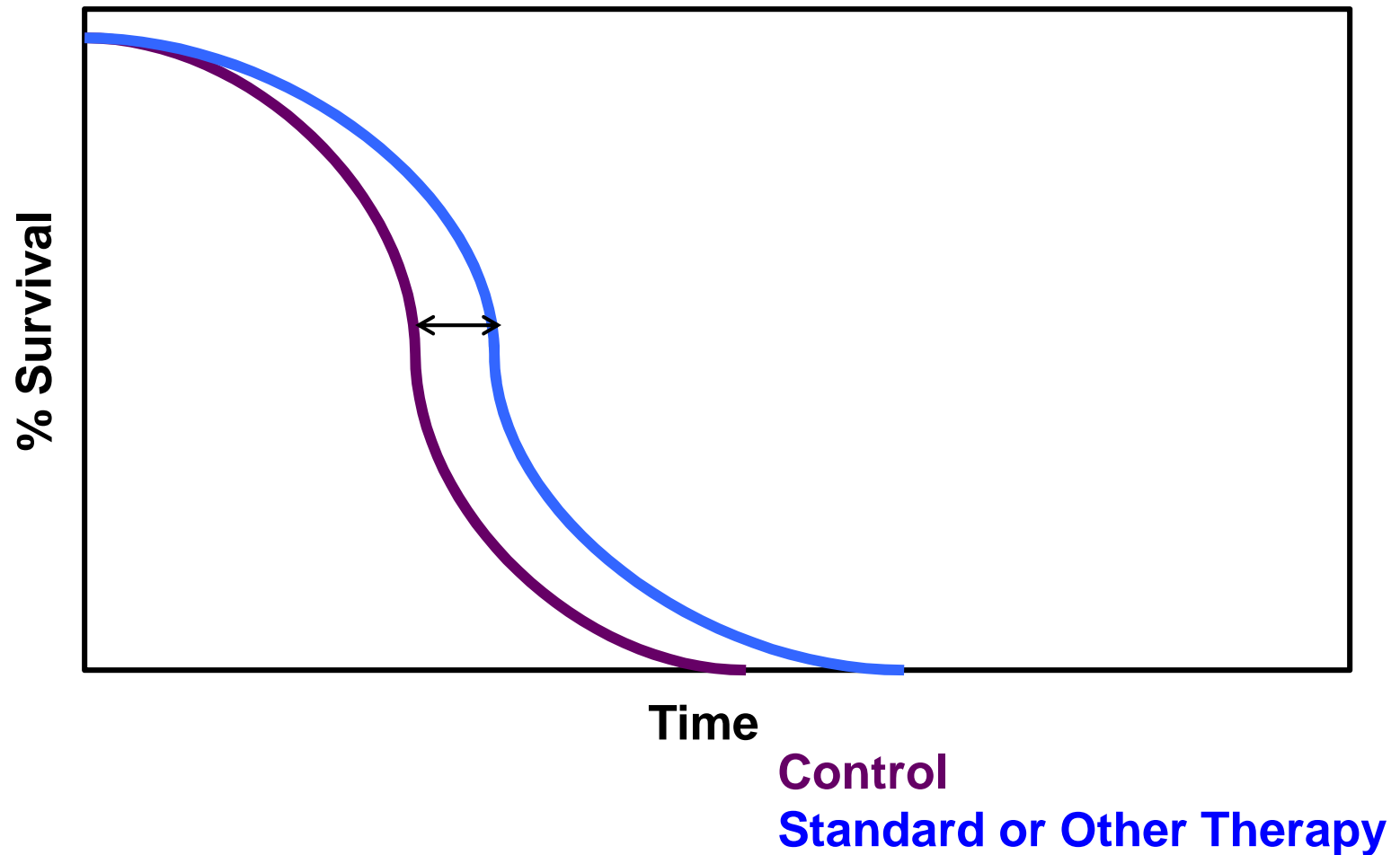
ASCO 2013
NEJM 6/2/2013

Combinations to Increase Efficacy of CTLA-4 Blockade

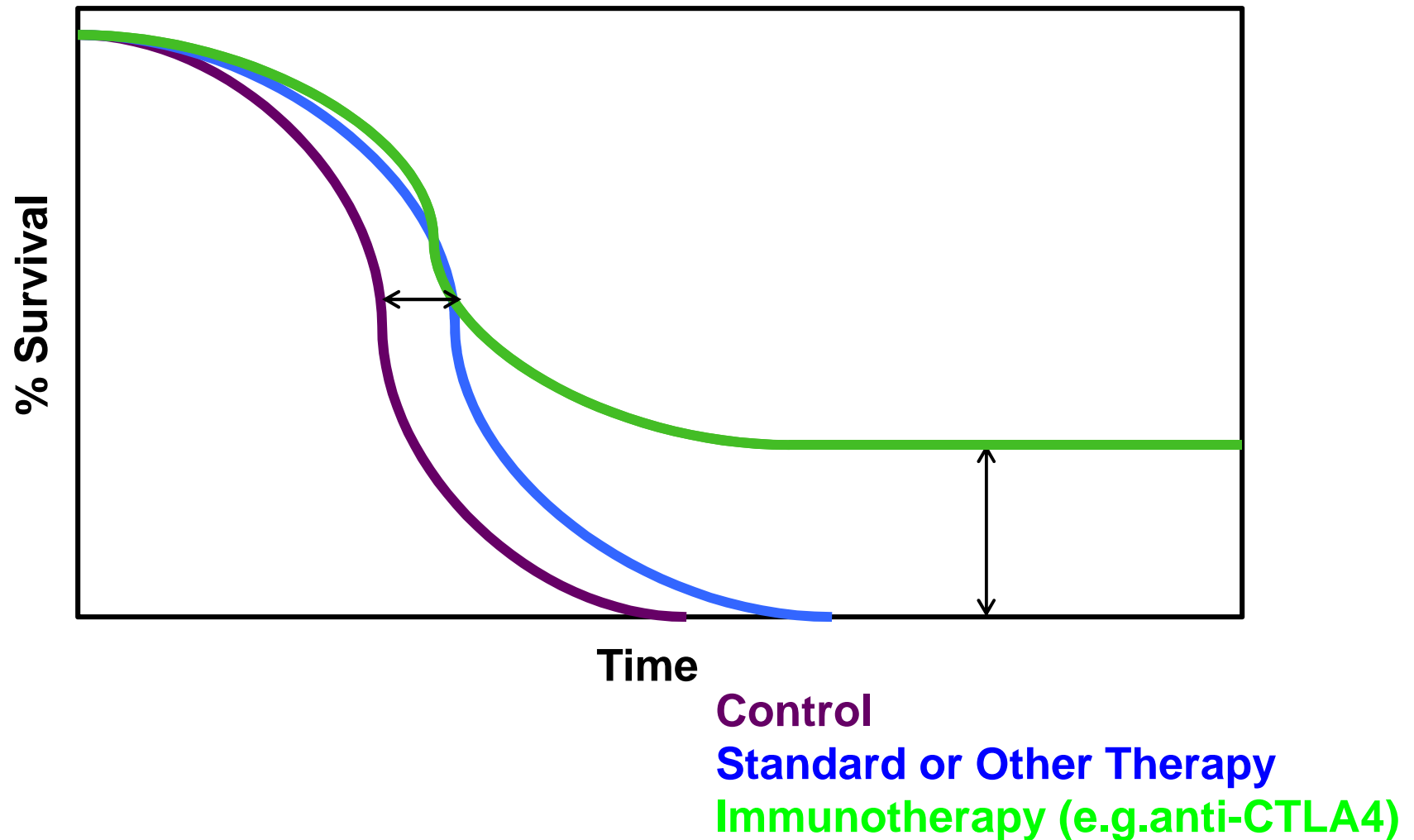
- **Vaccines**
- **Conventional Therapies**
 - **Targeted Therapies**
- **Combinations of Checkpoint Inhibitors**
- **Stimulation of Additional Costimulatory
Pathways**
OX40, CD137, ICOS



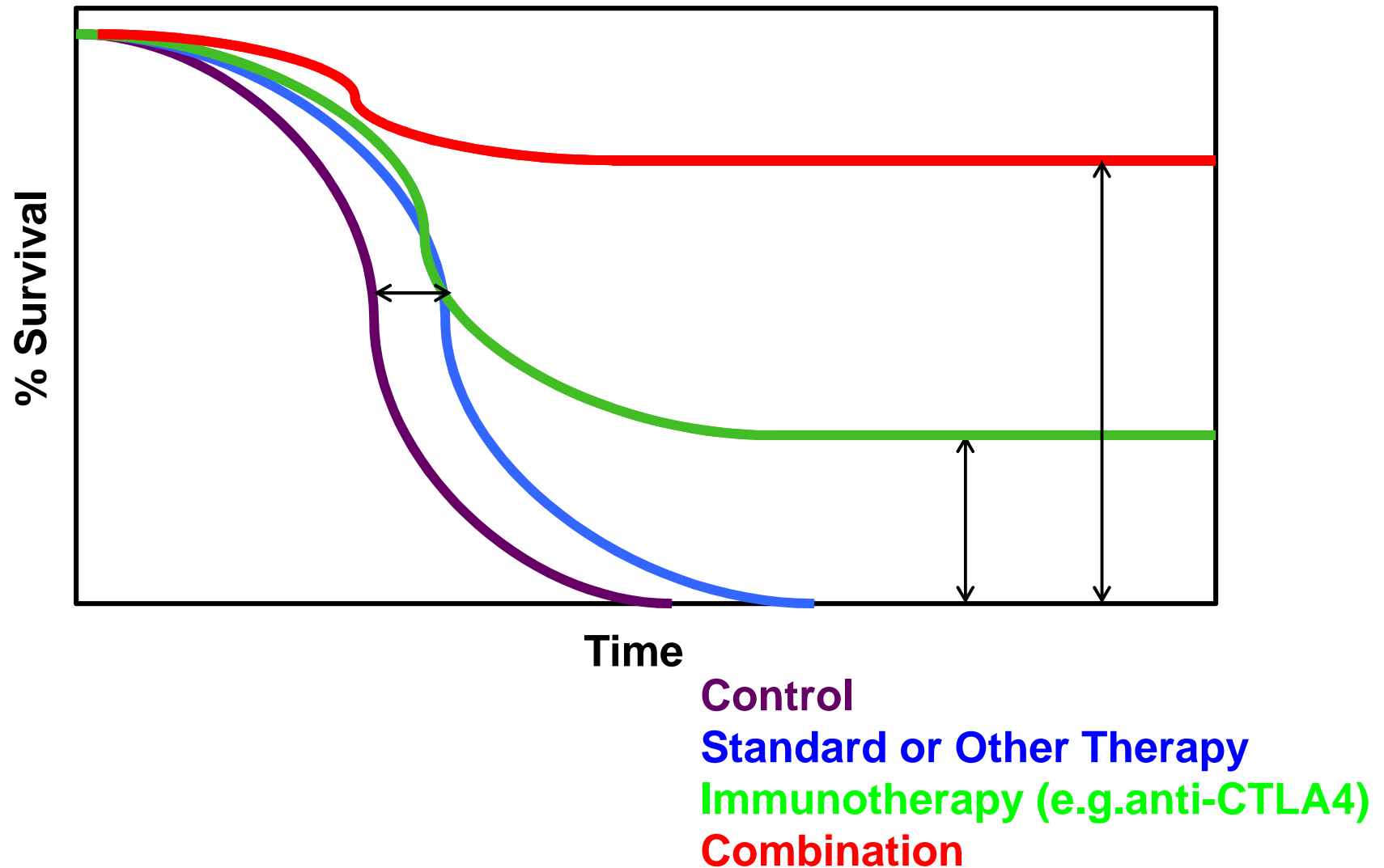
Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Allison Lab

Michael Curran

Xiaozhou Fan

Tyler Simpson

Welby Montalvo

Emily Corse

Sumit Subhudi

Tsvetelina Hoang

Joyce Wei

Nina Kreymborg

Rikke Holmgard

Charlotte Ariyan

Dimitry Zamarin

Virginia Pedicord

Anne Trumble

Collaborators

UCL Cancer Institute

Sergio Quezada

Karl Peggs

Rockefeller U

Jeff Ravetch

Fubin Li

DFCI

Gordon Freeman



Collaborators

Padmanee Sharma



Lloyd Old



**Howard Hughes Medical Institute
Ludwig Trust
National Cancer Institute
David H Koch Foundation
Prostate Cancer Foundation
Melanoma Research Alliance
Cancer Prevention Research Institute of Texas**