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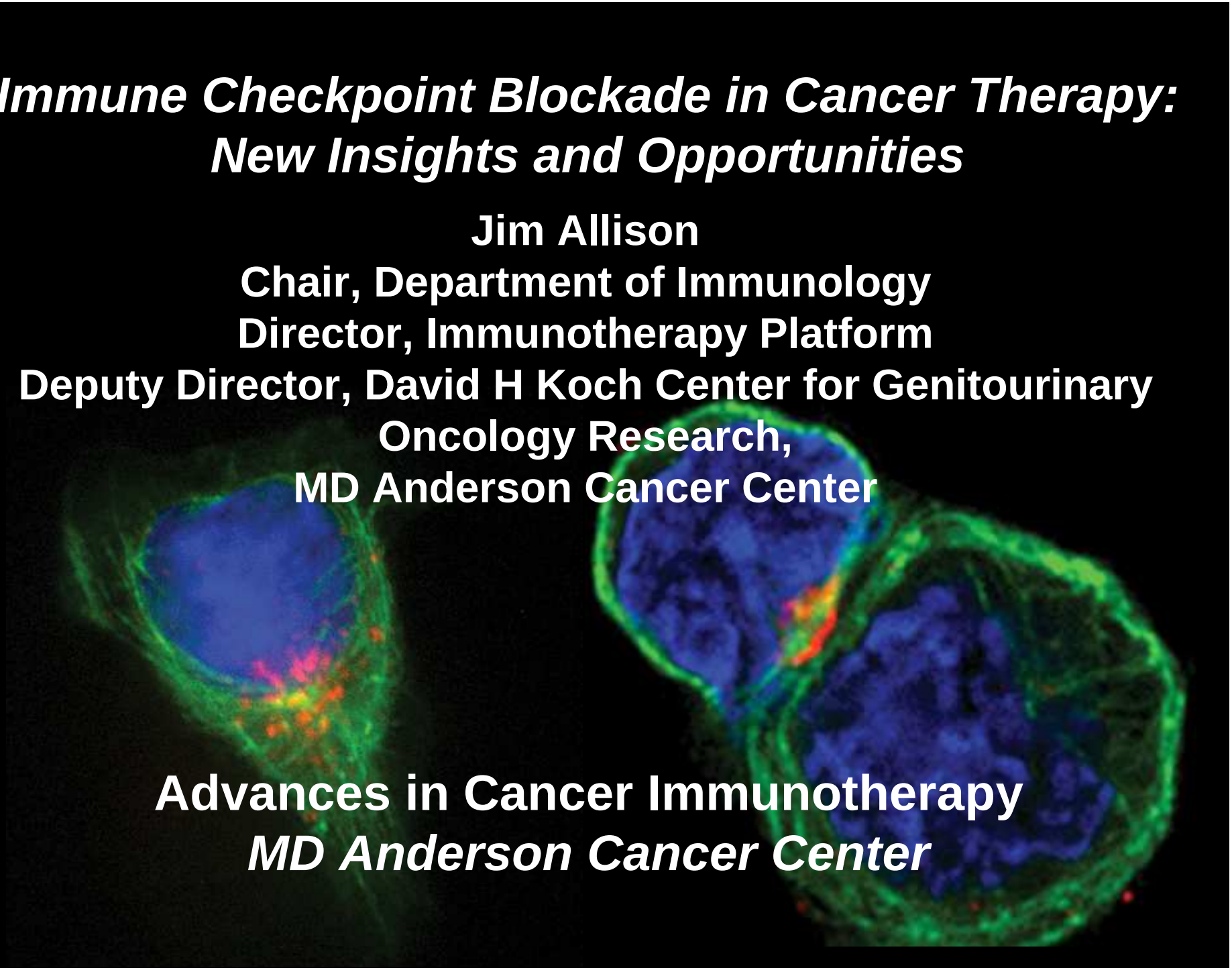
Scientific Advisory Board, Kite Pharmaceuticals

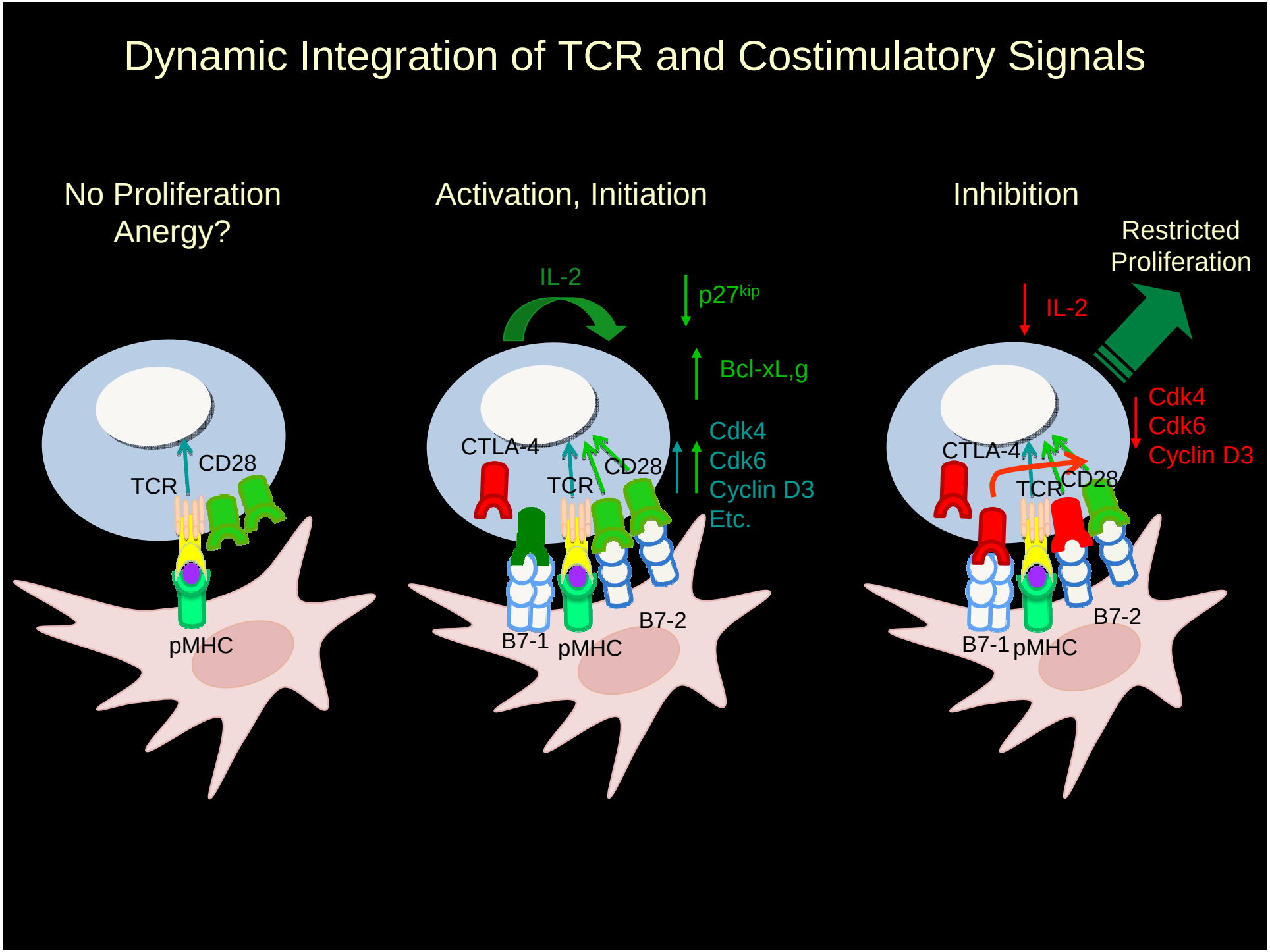
Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities

Jim Allison
Chair, Department of Immunology
Director, Immunotherapy Platform
Deputy Director, David H Koch Center for Genitourinary Oncology Research,
MD Anderson Cancer Center



Advances in Cancer Immunotherapy
MD Anderson Cancer Center

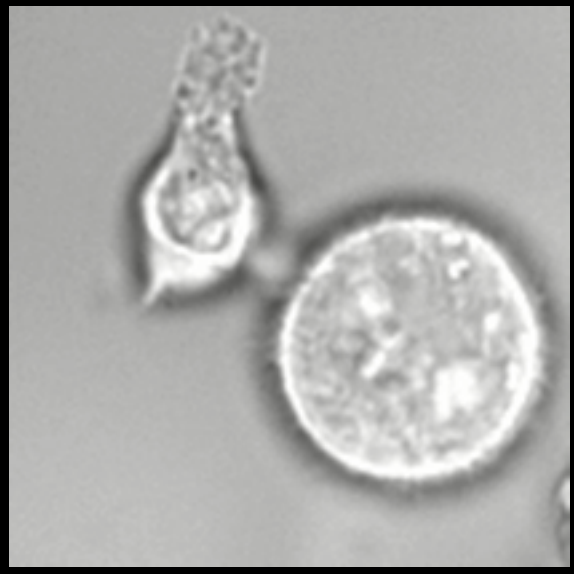
Dynamic Integration of TCR and Costimulatory Signals



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

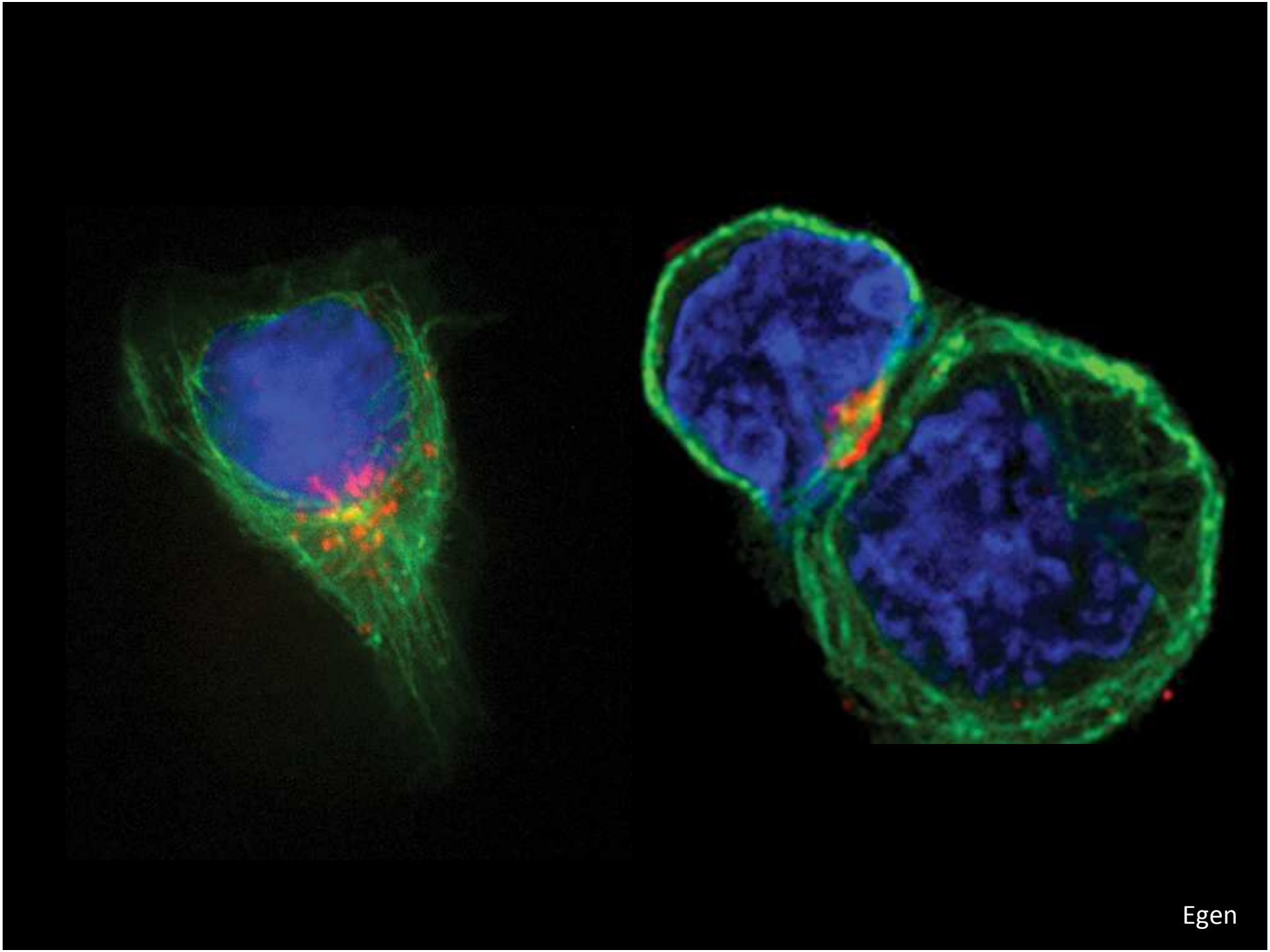
CD28

CTLA-4

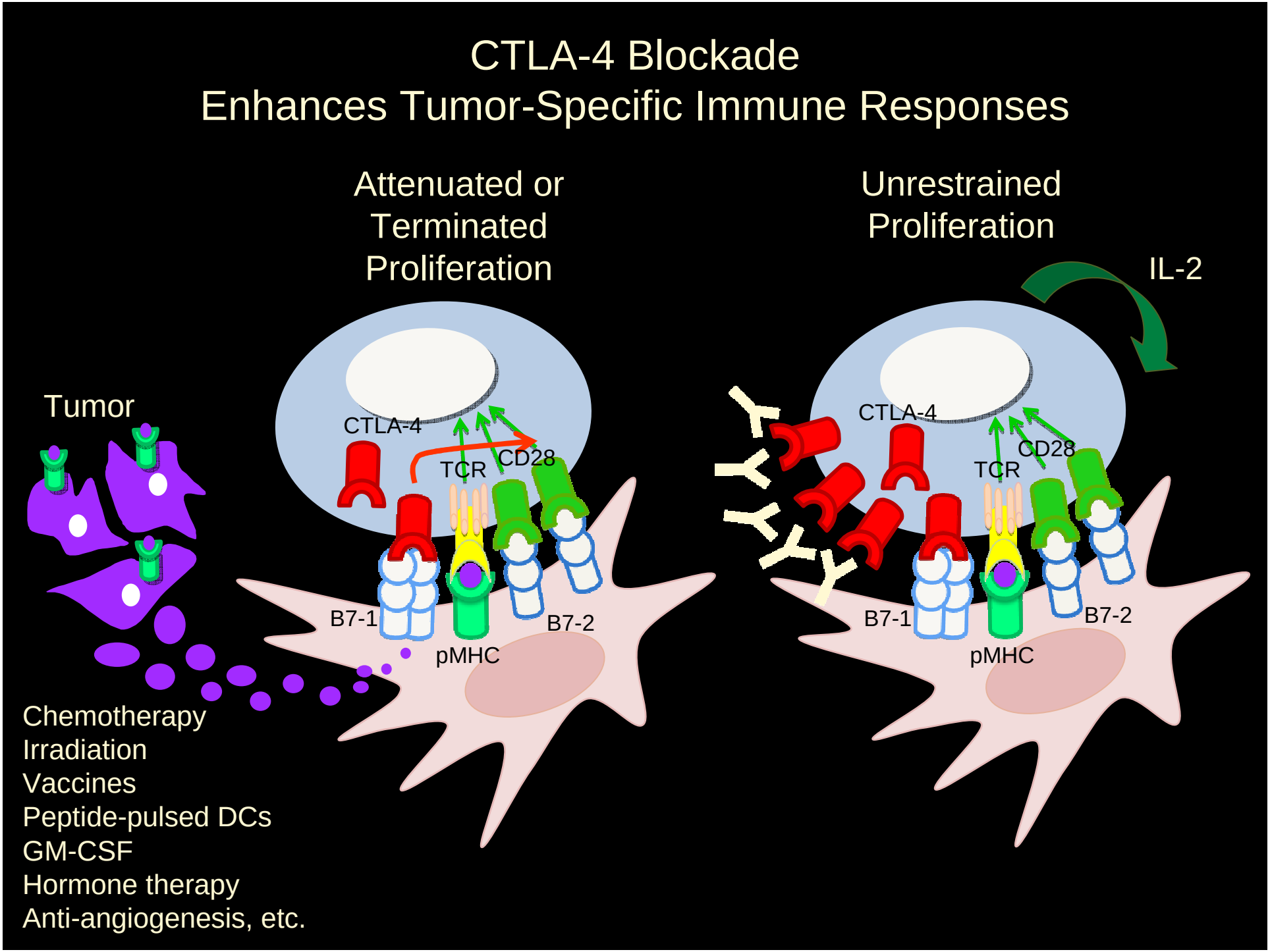


~ 5 minutes

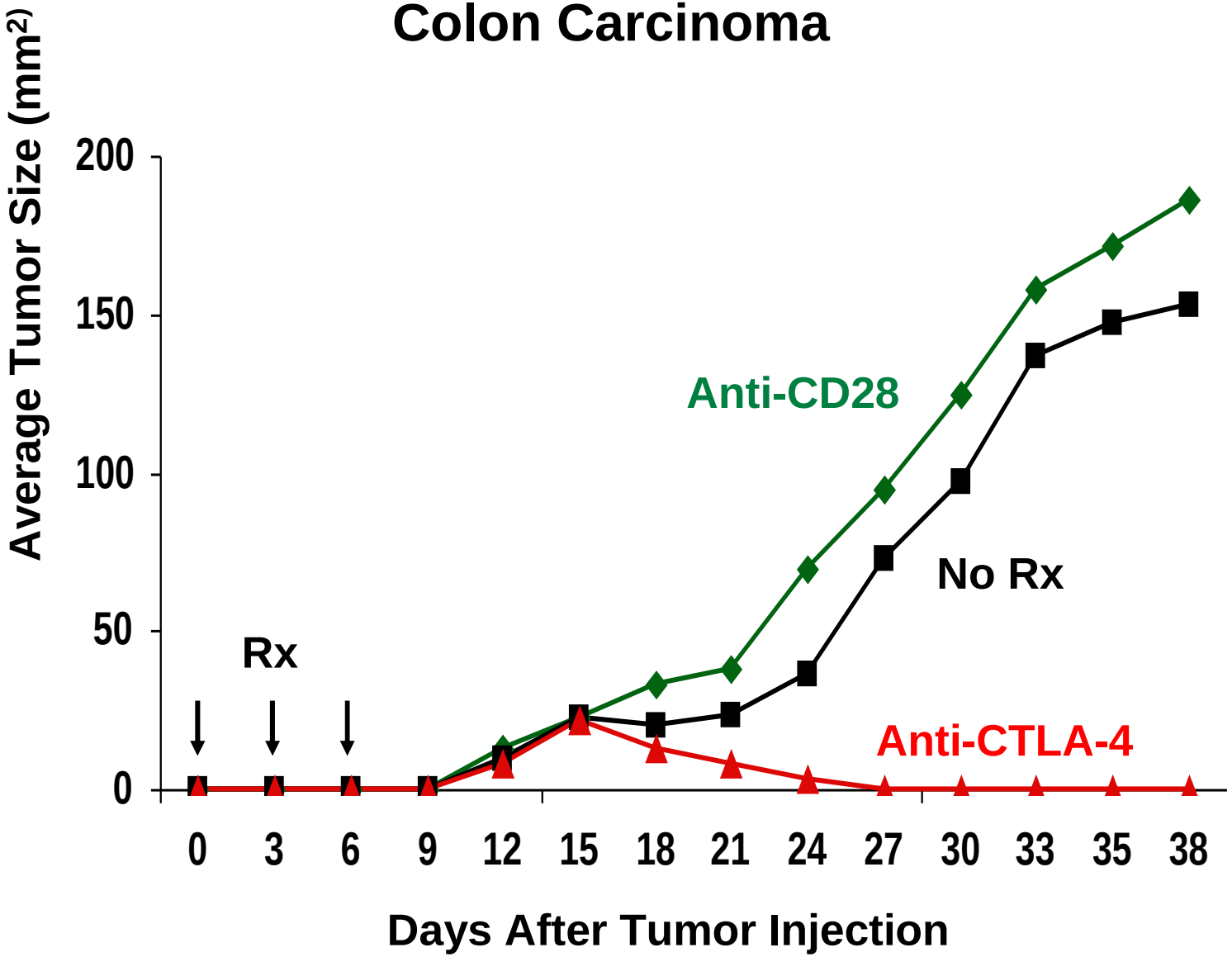
Egen


Egen

CTLA-4 Blockade Enhances Tumor-Specific Immune Responses



Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

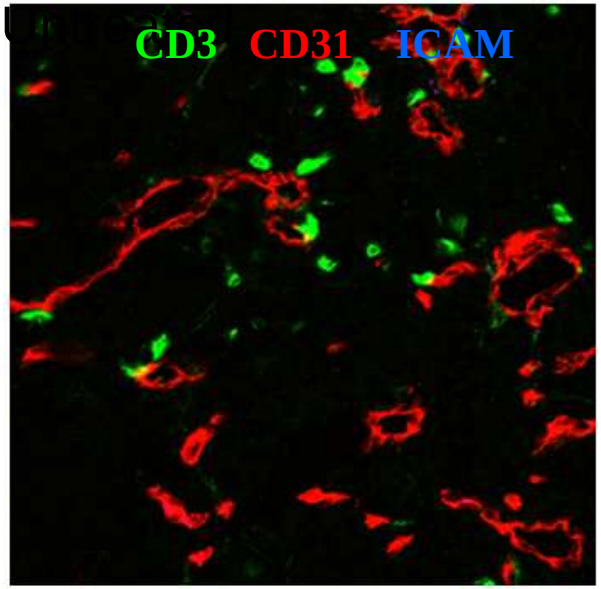


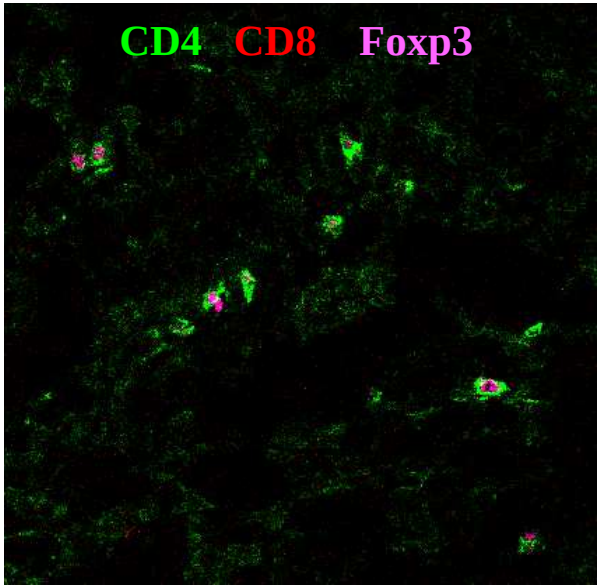
Leach

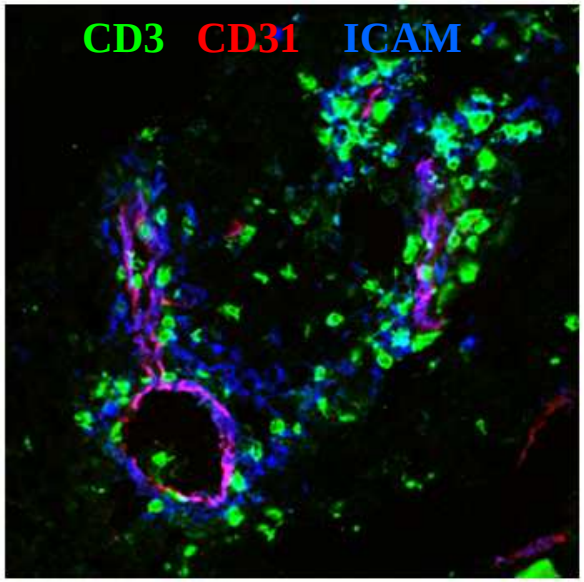
anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

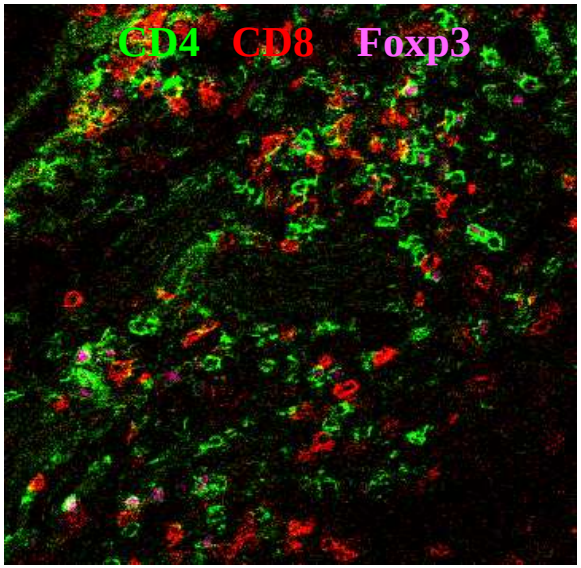
Untreated

αCTLA-4/GVAX





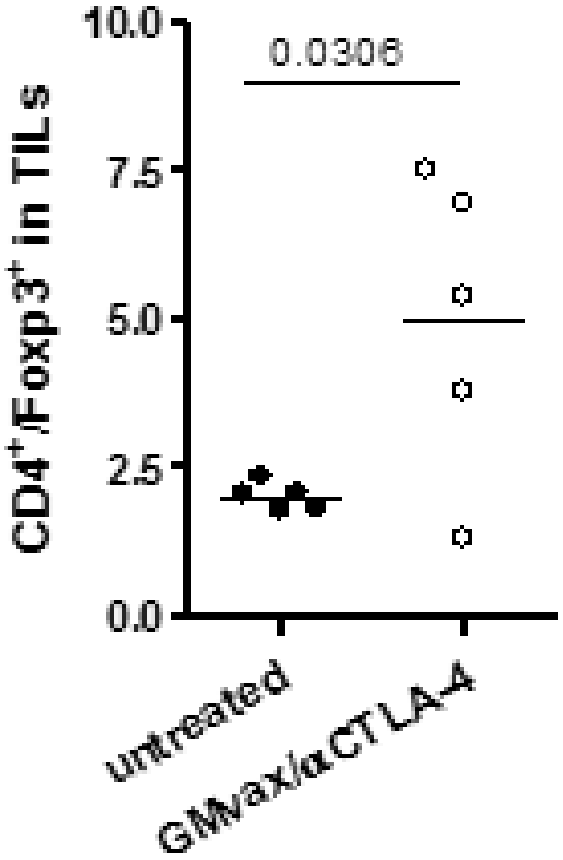




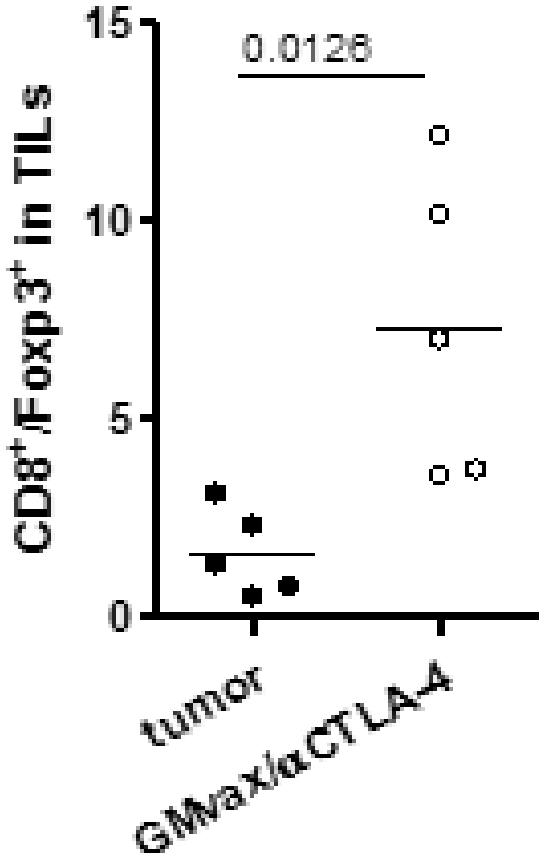
Quezada

αCTLA-4/GVax Increases Teff/Treg Ratio In Tumor

CD4/Foxp3

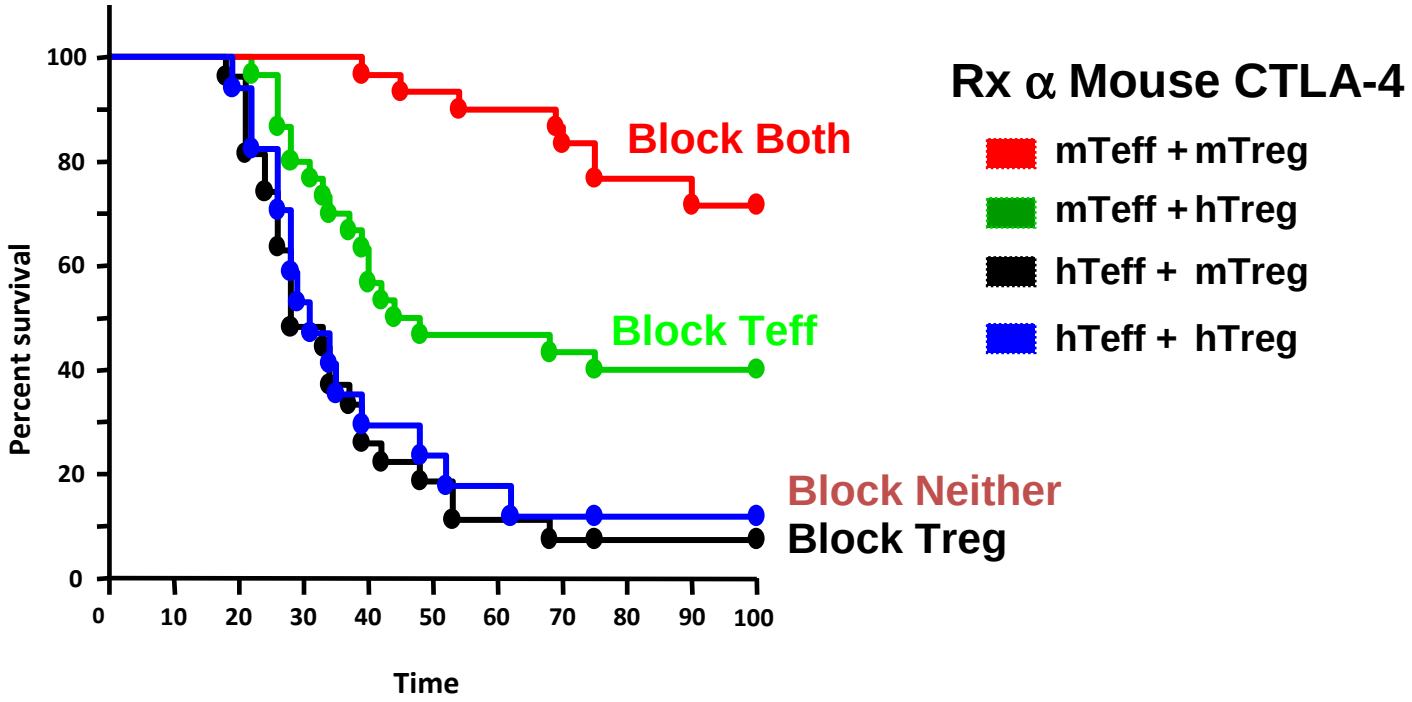


CD8/Foxp3



Quezada

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



Peggs & Quezada

Effects of αCTLA-4 on Treg

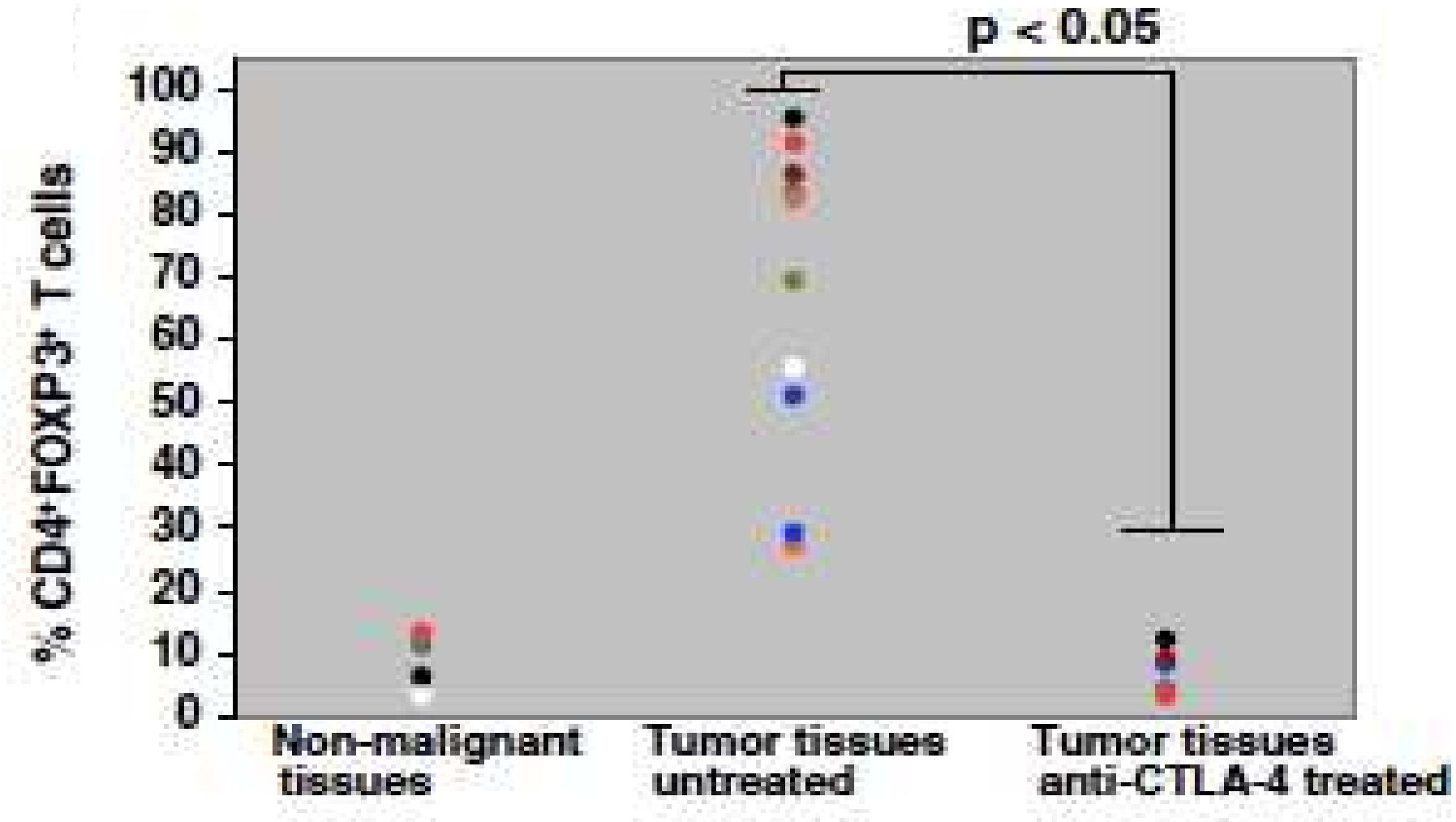
Peripheral Lymph Nodes

- **Expand due to blockade of cell intrinsic inhibition of proliferation by CTLA-4**

Tumor

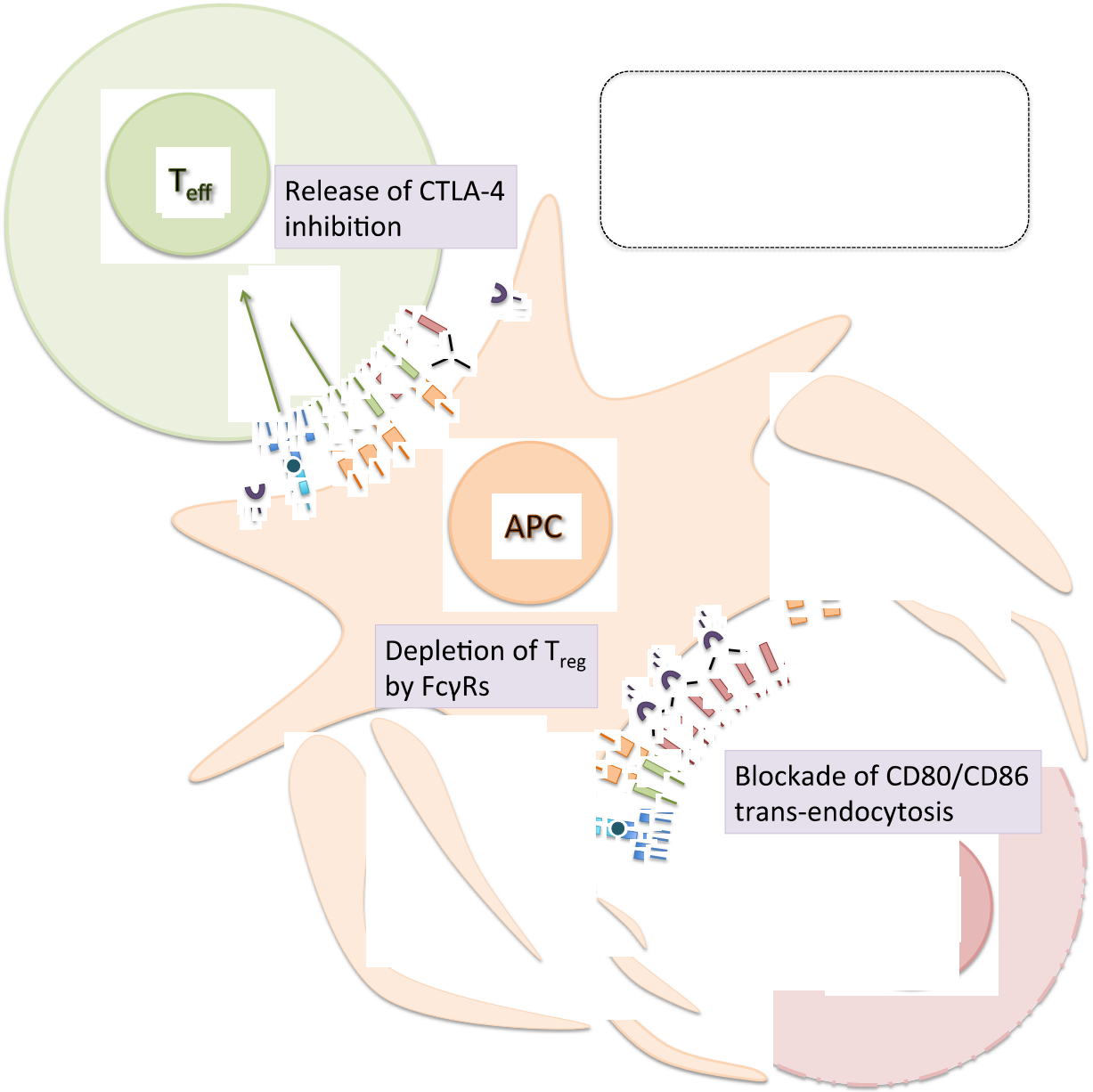
- **Killed by ADCC by FcγR-IV on macrophages due to higher expression of CTLA-4 on Treg than Teff and higher levels of macrophages in tumor**

Ipilimumab Rx reduces Foxp3+ T cells in bladder cancer patients



Laikou and Sharma, 2008

α-CTLA-4 antibody functions by multiple mechanisms



Ipilimumab

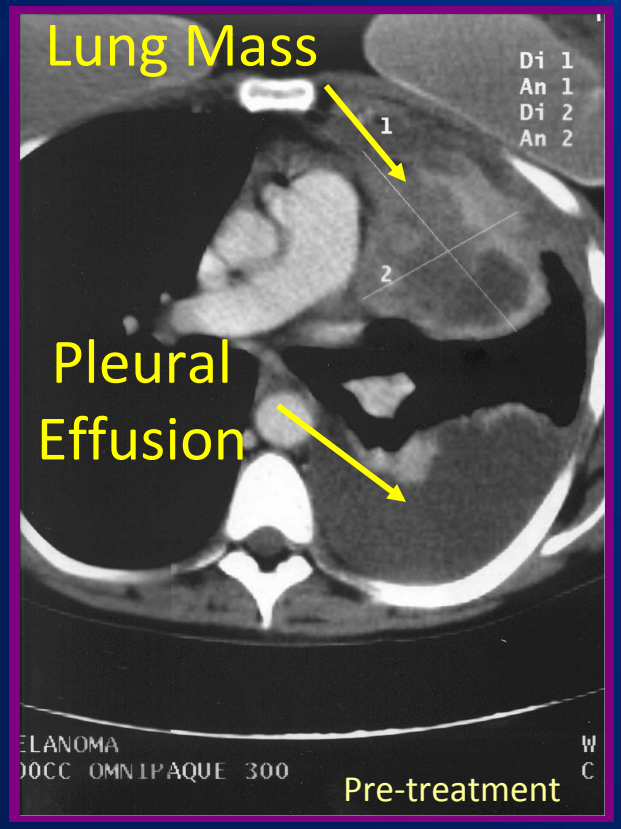
(Medarex, Bristol-Myers Squibb)

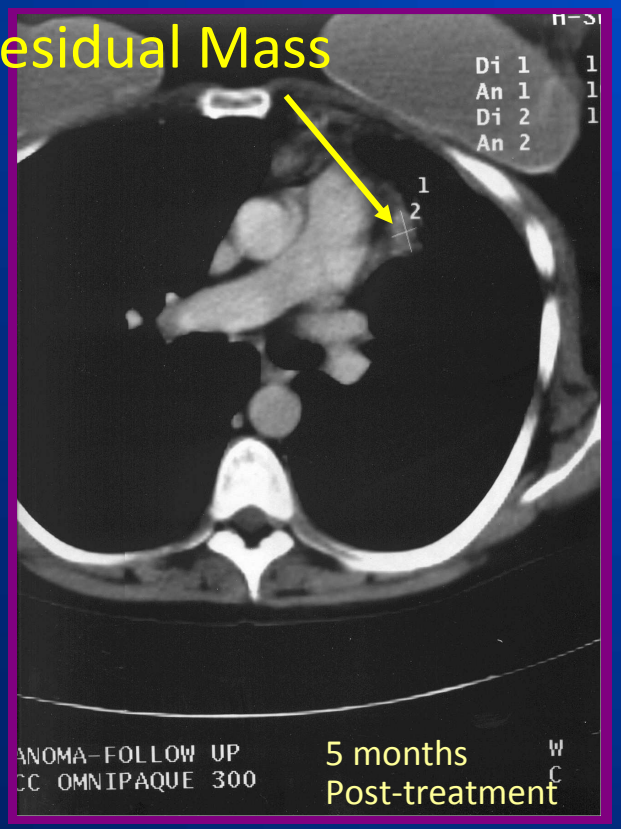
Fully human antibody to CTLA-4

>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**

Clinical Response - Melanoma



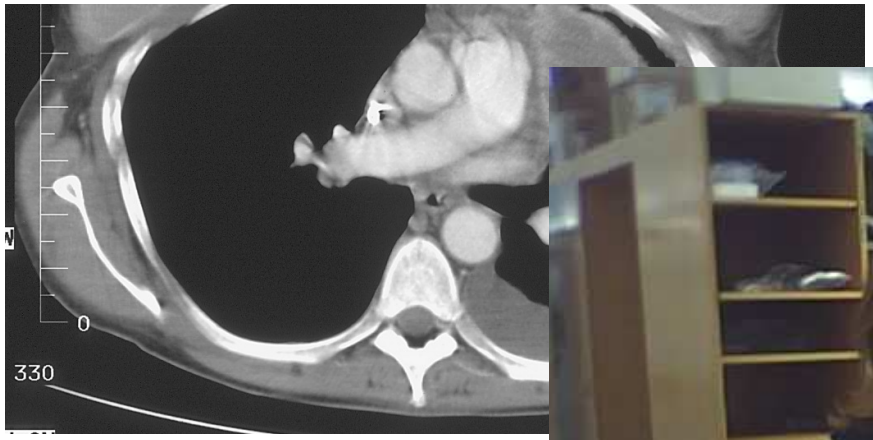


Baseline and 5 months post-MDX-010 treatment CT scans of patient with metastatic melanoma (1 month status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit

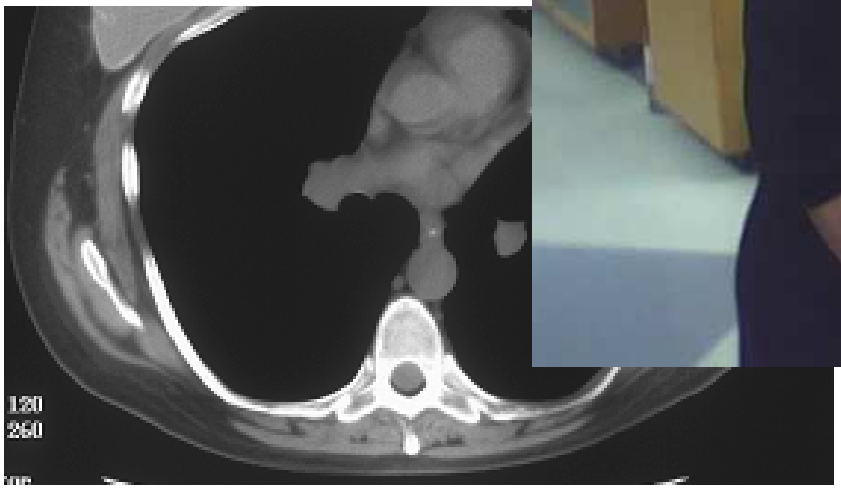
MEDAREX

The longest survivor on ipilimumab

May 2001, after progression on IL-2



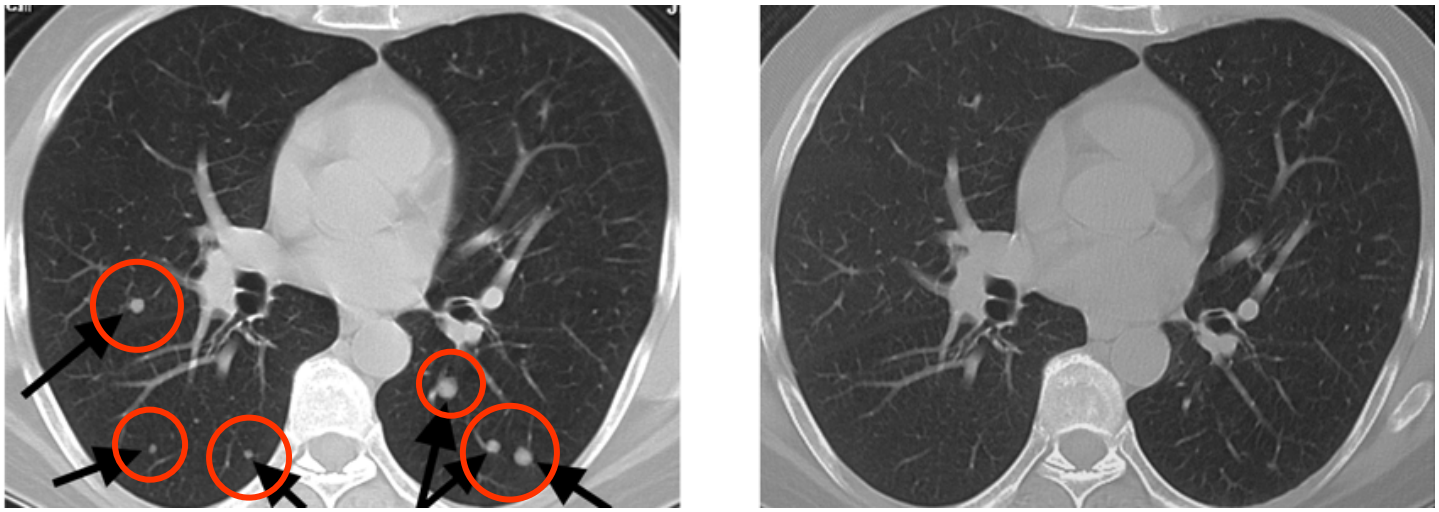
10 years lat



Ribas

Complete Responder: Melanoma

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



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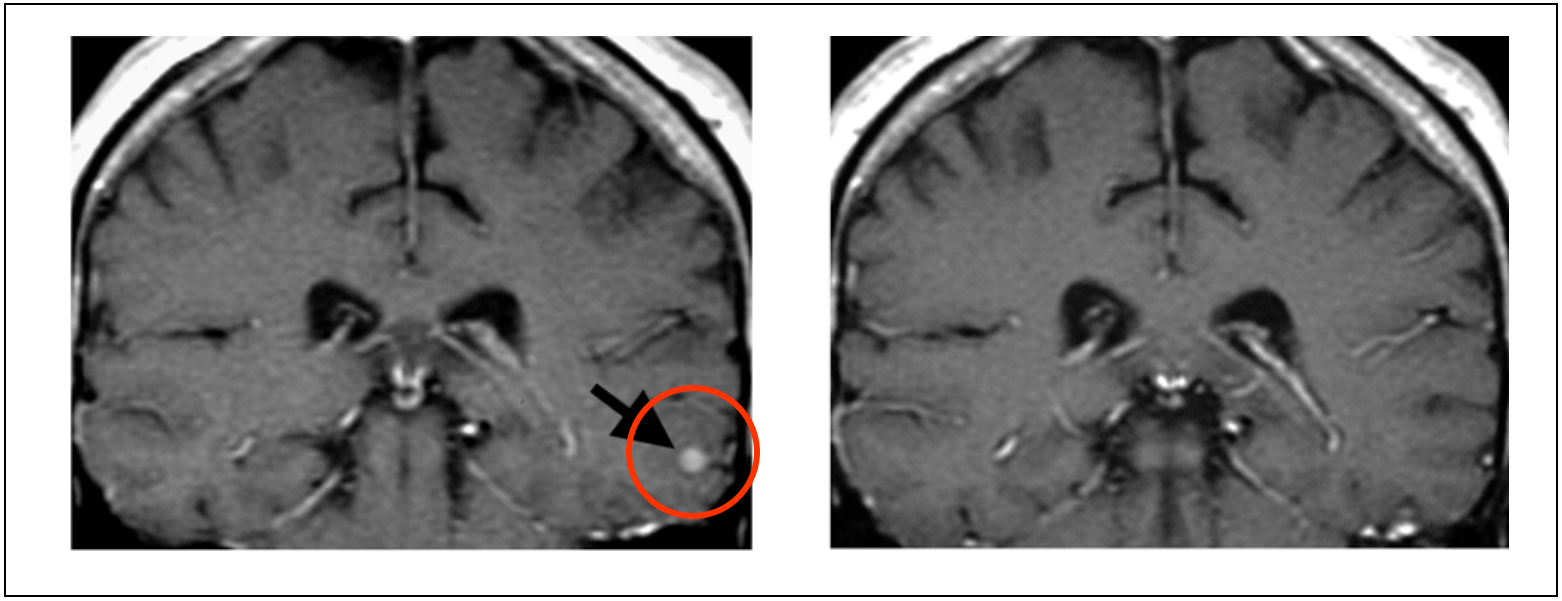
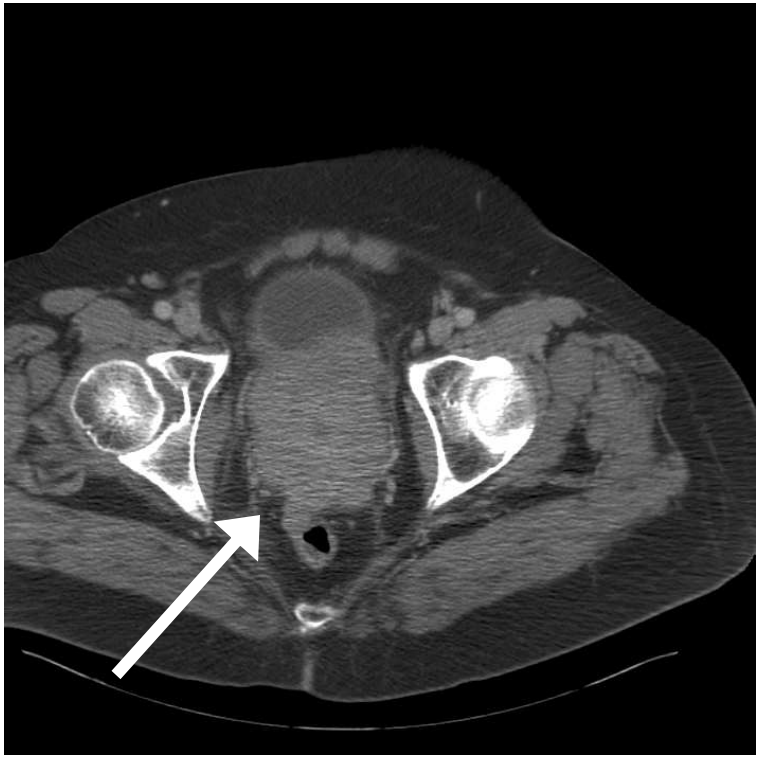
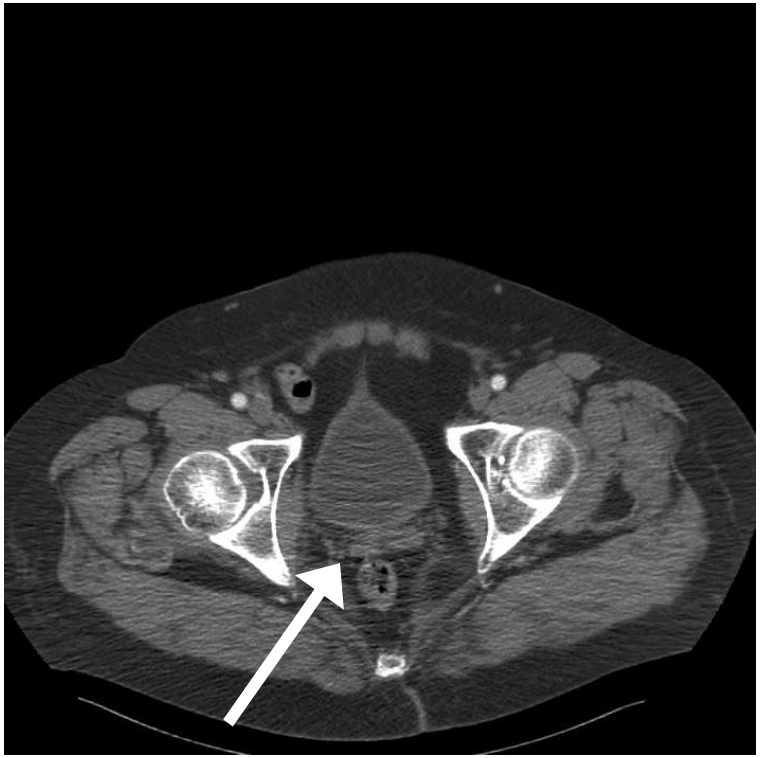


Complete Responder: Prostate Cancer

Screening



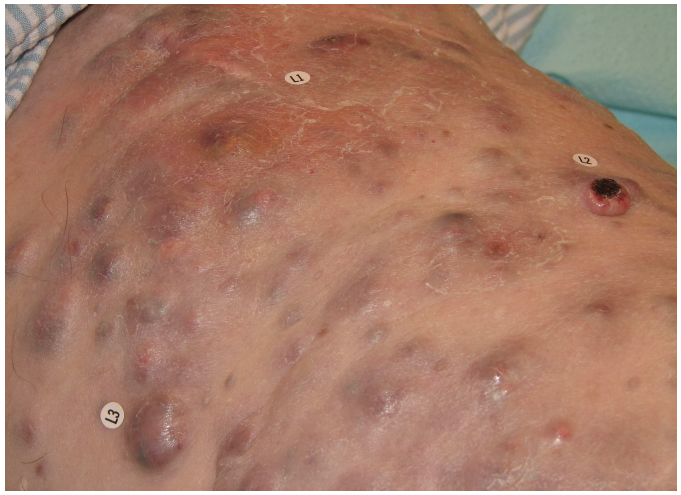
14 months



Phase III trials ongoing

BMS

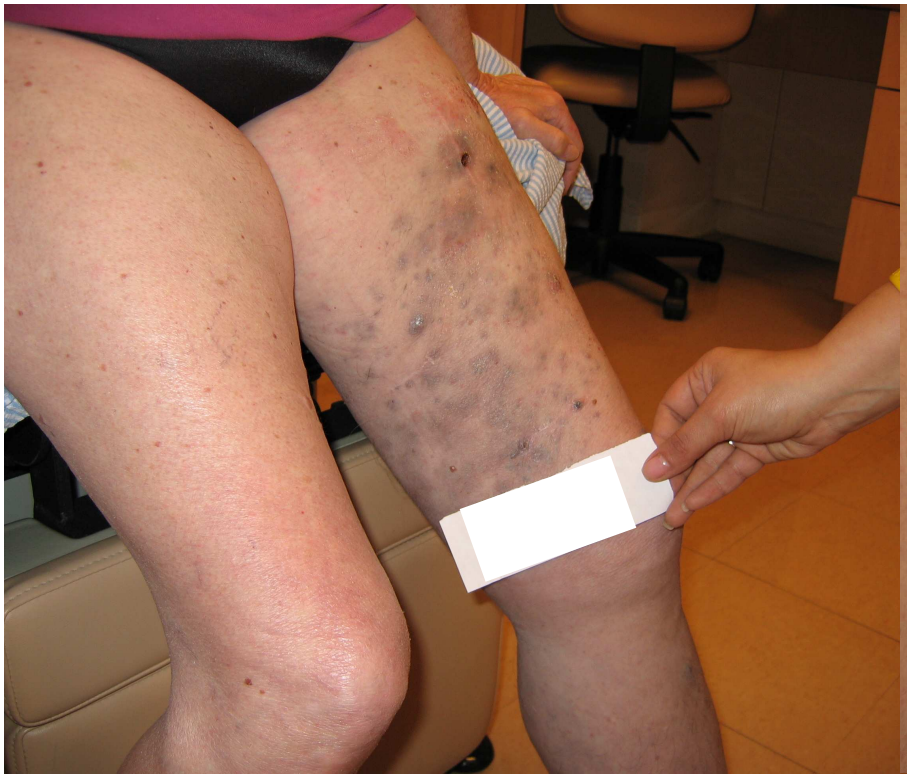
Baseline 11/28/06



Wolchok (MSKCC)

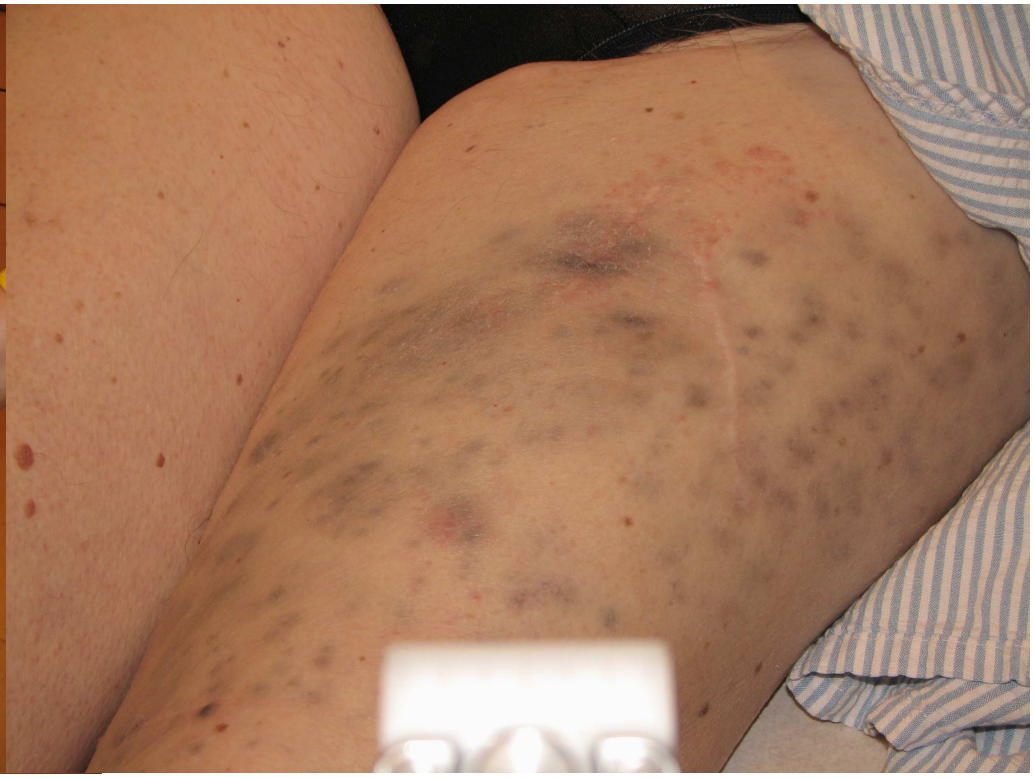
1/9/07

6 Weeks



2/12/07

10 Weeks



Wolchok (MSKCC)

Evolution of Response: Patient Example

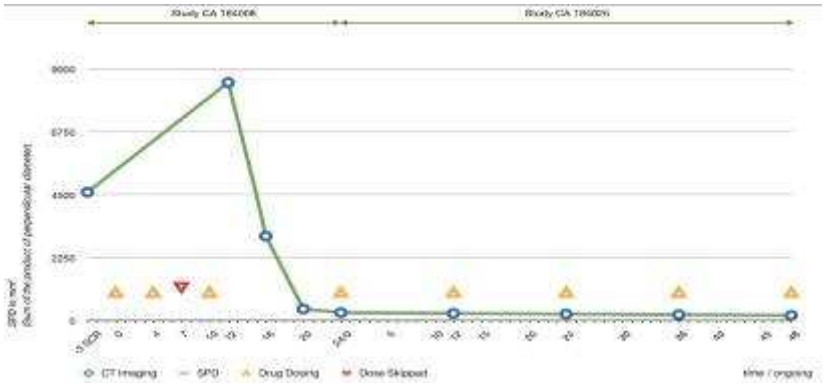
Screening


Week 12
Initial increase in
total tumor burden (mWHO PD)


Week 16
Responding

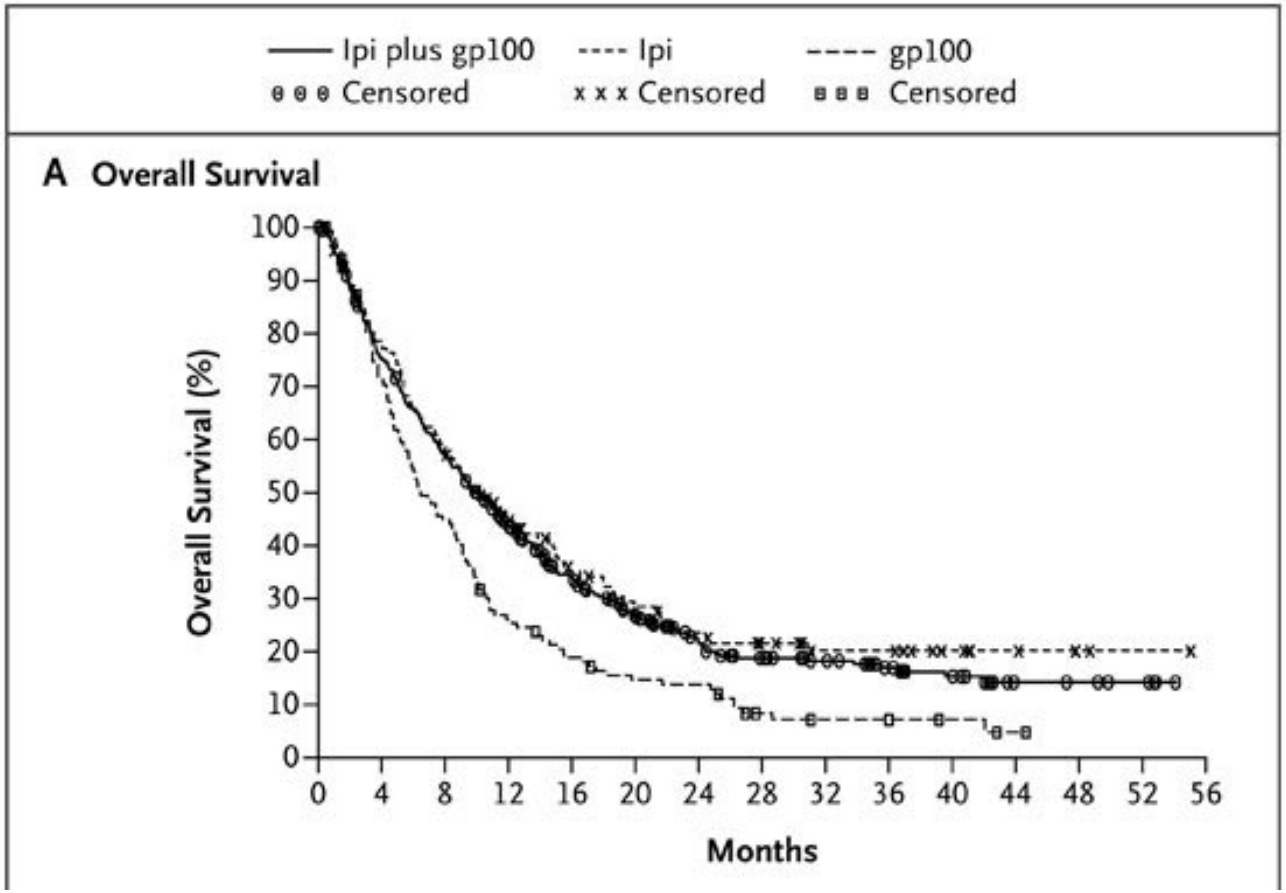

Week 72
Durable & ongoing response
without signs of IRAEs


20006



Harmankaya

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%

Hodi et al. NEJM 2010

Ipilimumab
(Bristol-Myers Squibb)

- **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?

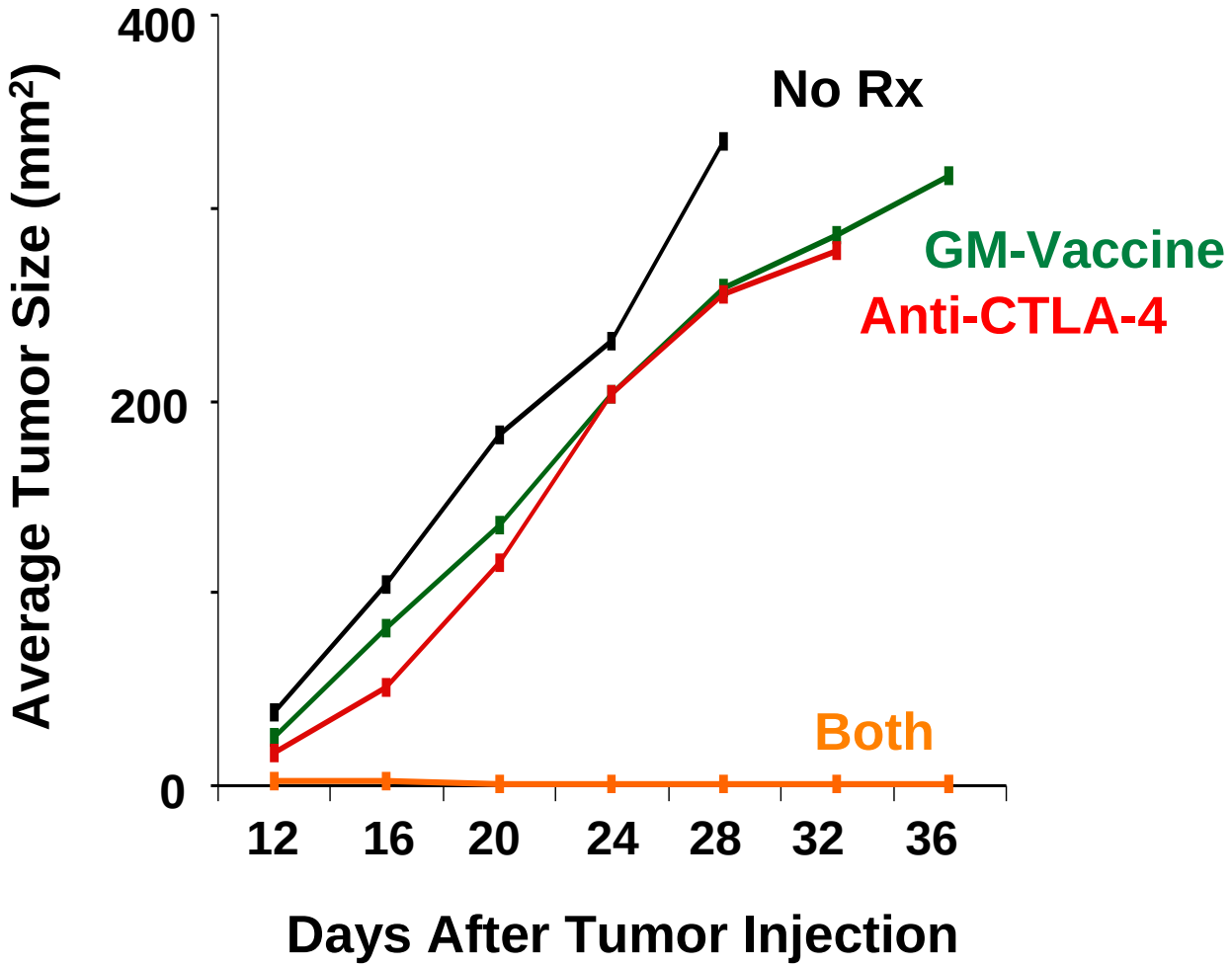
Combinations to Increase Efficacy of CTLA-4 Blockade

- **Vaccines**

GVAX, DNA, Protein

(But *not* minimal Class I MHC restricted peptides)

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



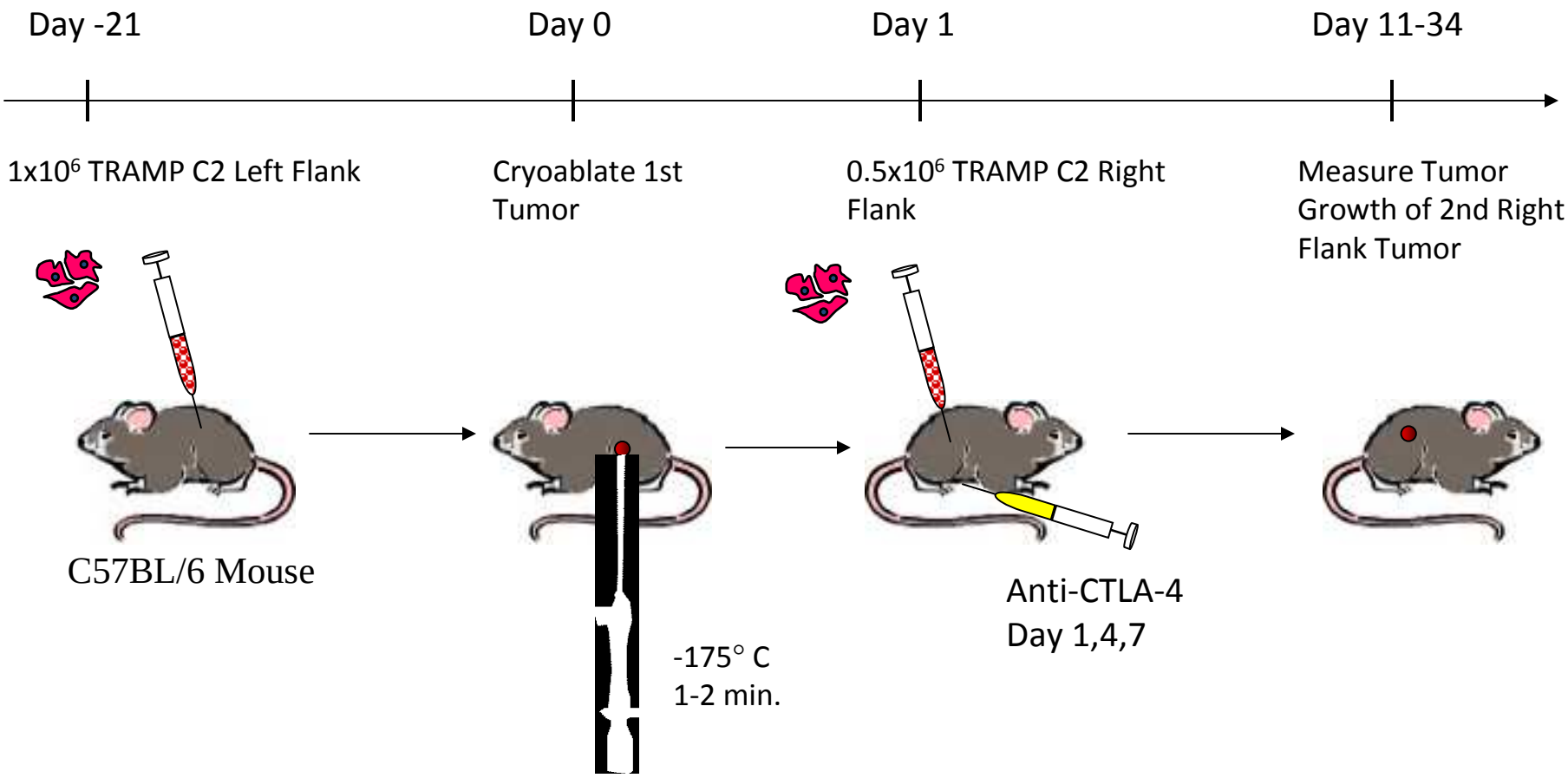
van Elsas,Hurwitz

Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- **Conventional Therapies**

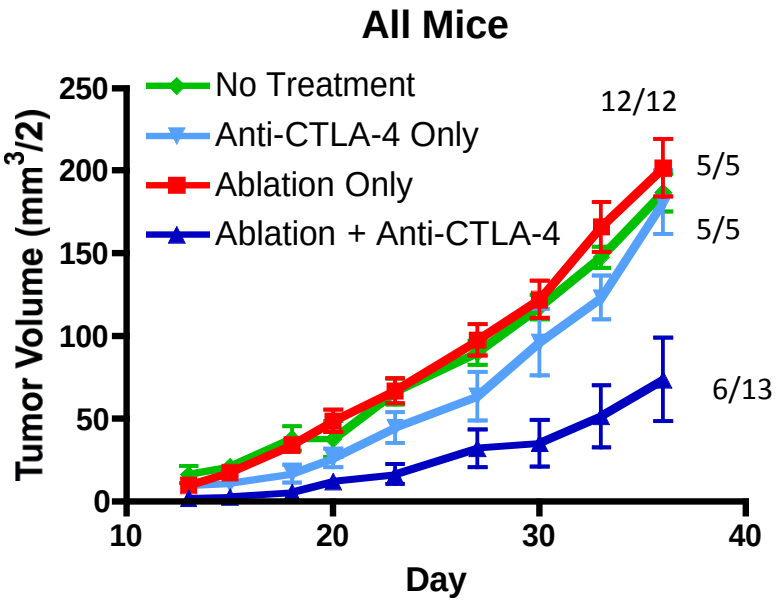
Chemotherapies, Local radiation, Cryoablation

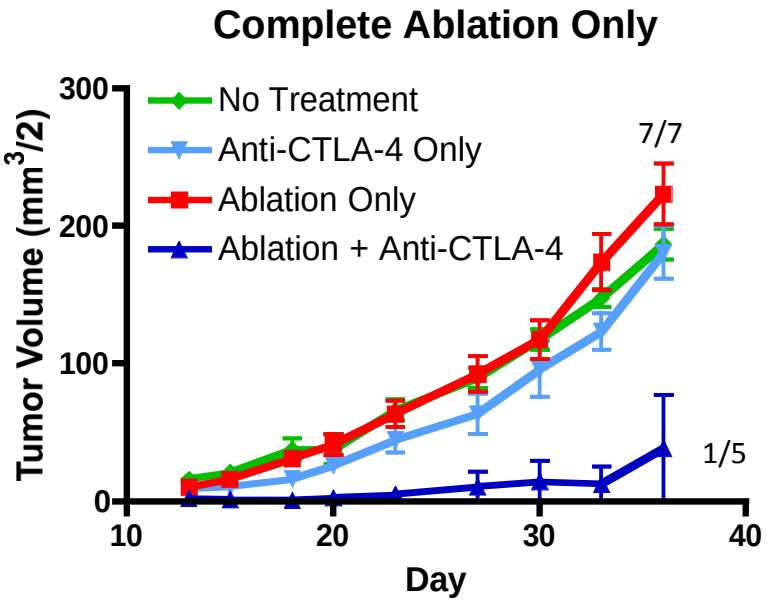
Combining Cryoablation with Anti-CTLA-4

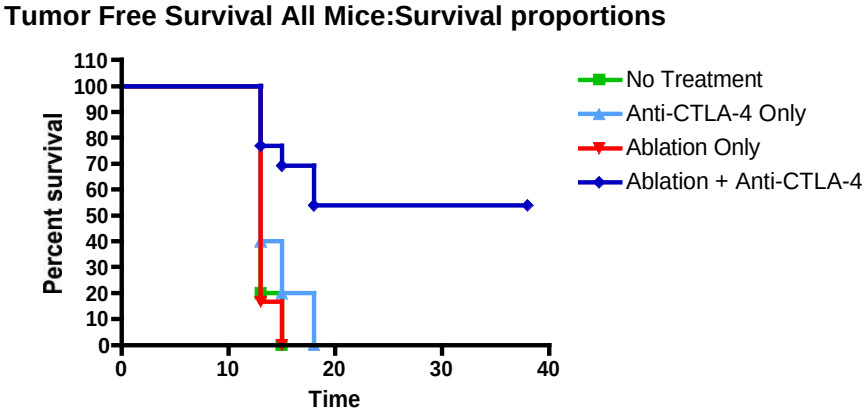


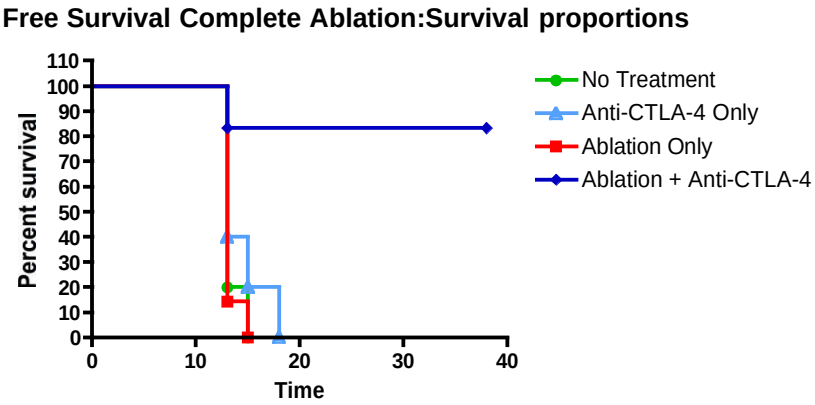
Waitz, Solomon, Norton

TRAMP C2 Cryoablation +/- Anti-CTLA-4







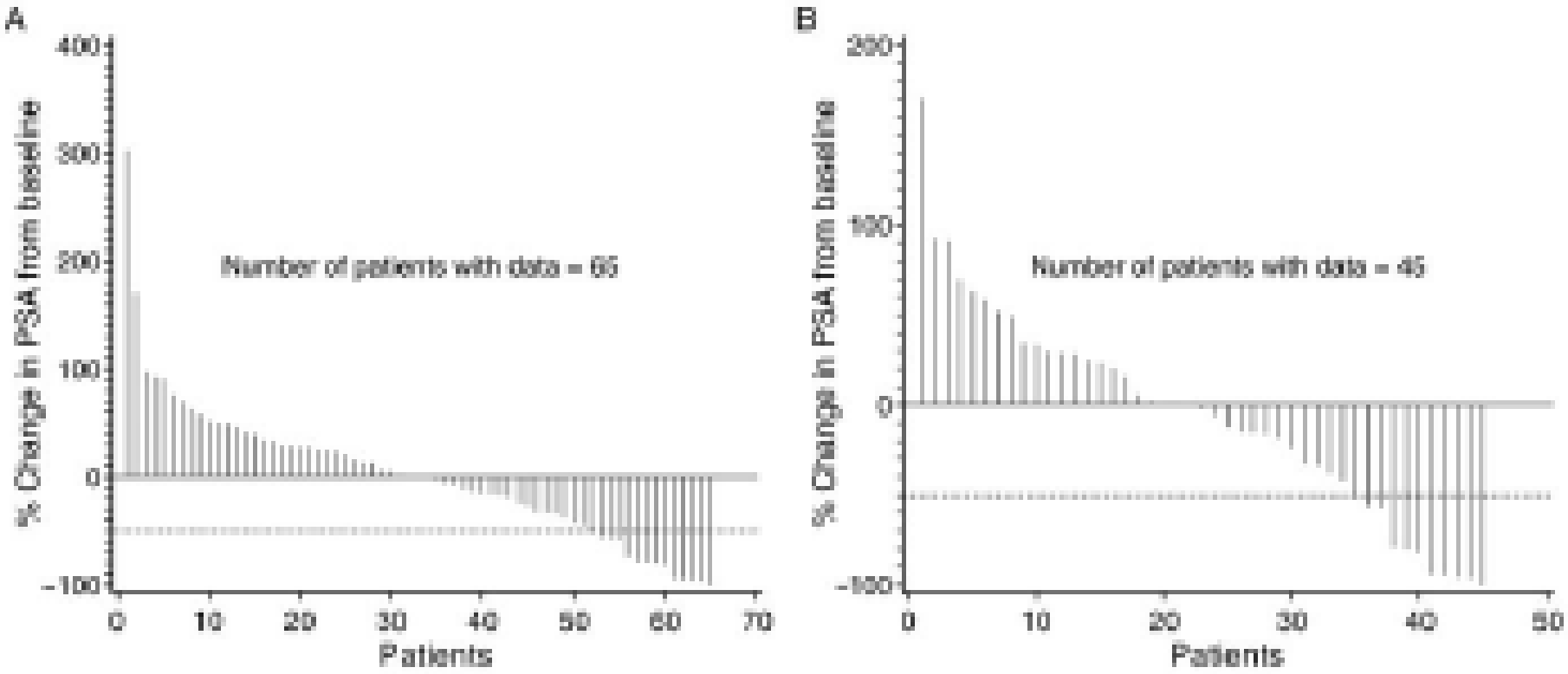


Waitz, Solomon, Norton

Ipi +/- XRT in CRPC

All Cohorts

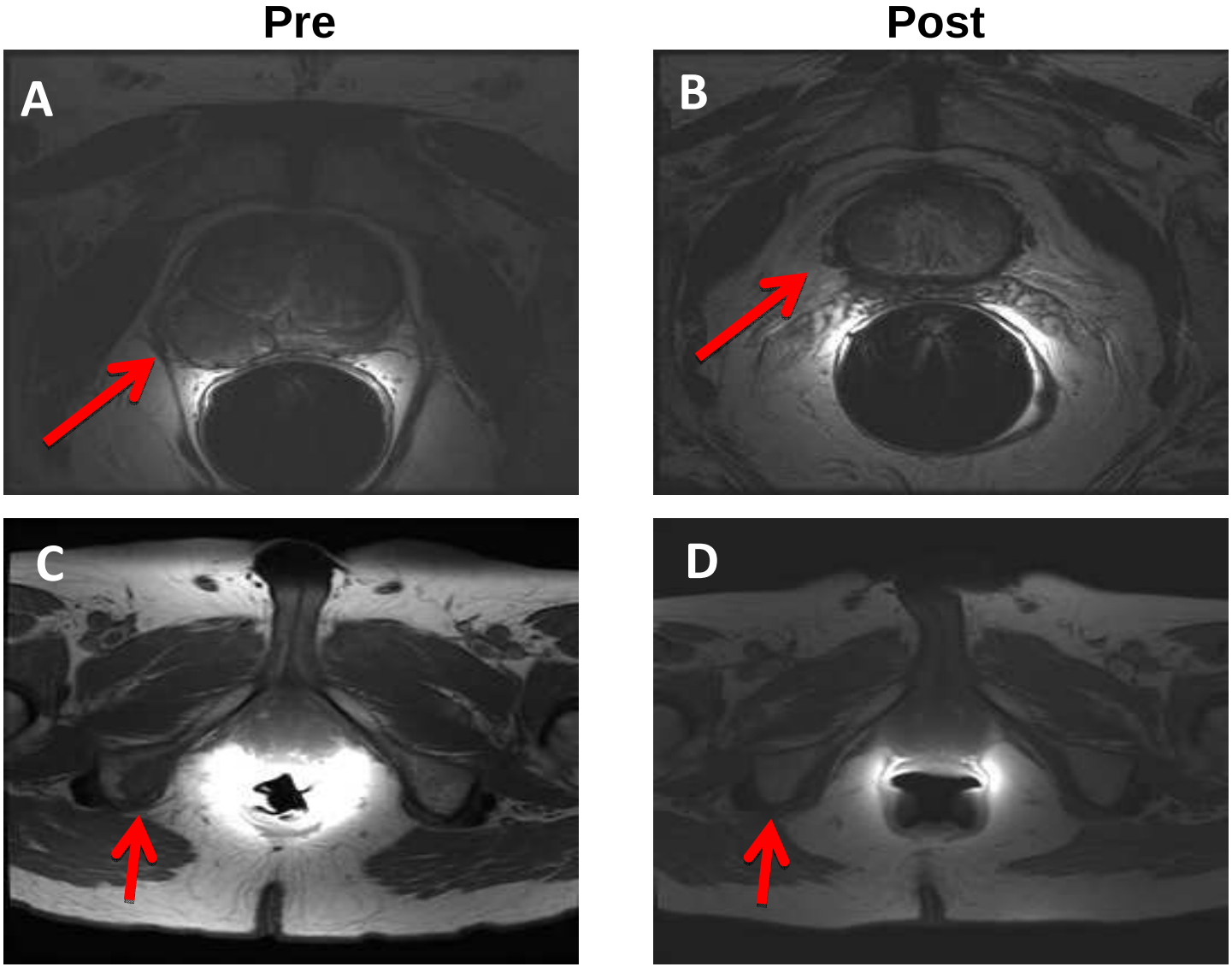
10mg/kg +/- XRT



(Greatest change in PSA by day 85 of study)

Slovin et al. Annals Oncol. 2013

Regression of metastatic disease after ipilimumab plus androgen deprivation



Aparicio and Sharma (MDACC)

Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
- Targeted Therapies

Targeted Therapies

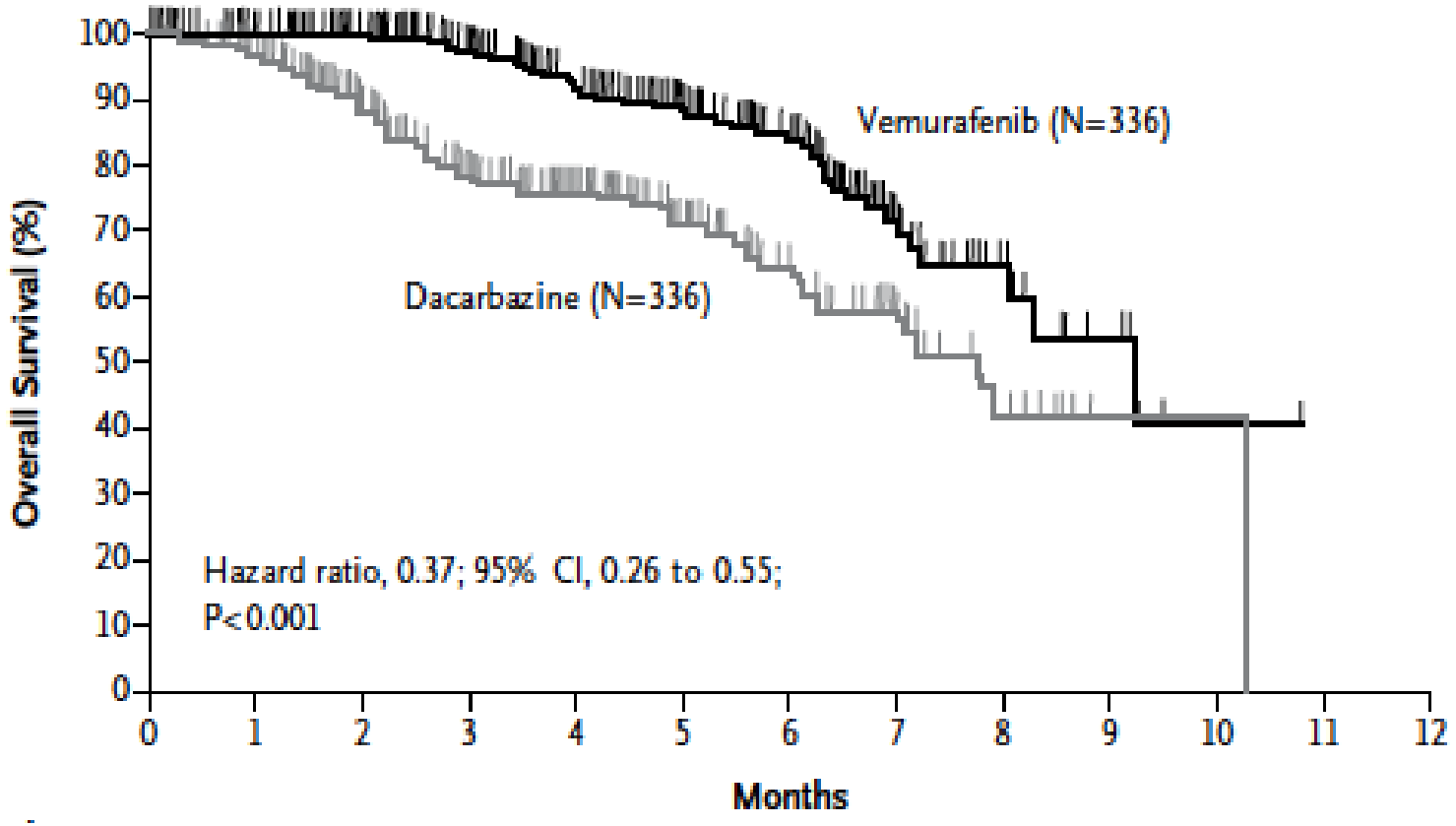
- **High response rates, rapid tumor regression in patients with target**

- **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**

Efficacy of Vemurafunib in V600E+ Melanoma



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:

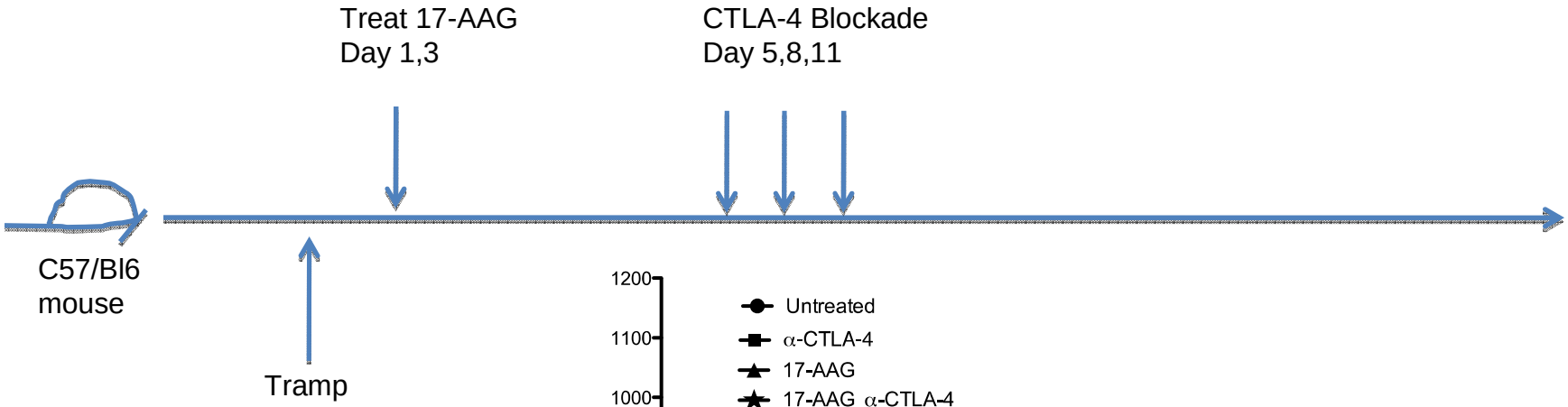
- **Prostate: 30-70**
- **Glioblastoma: 30-50**
- **Melanoma: 400-500**

•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

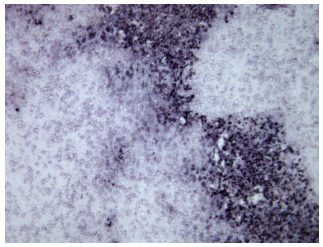
Vogelstein et al *Science* 2013

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

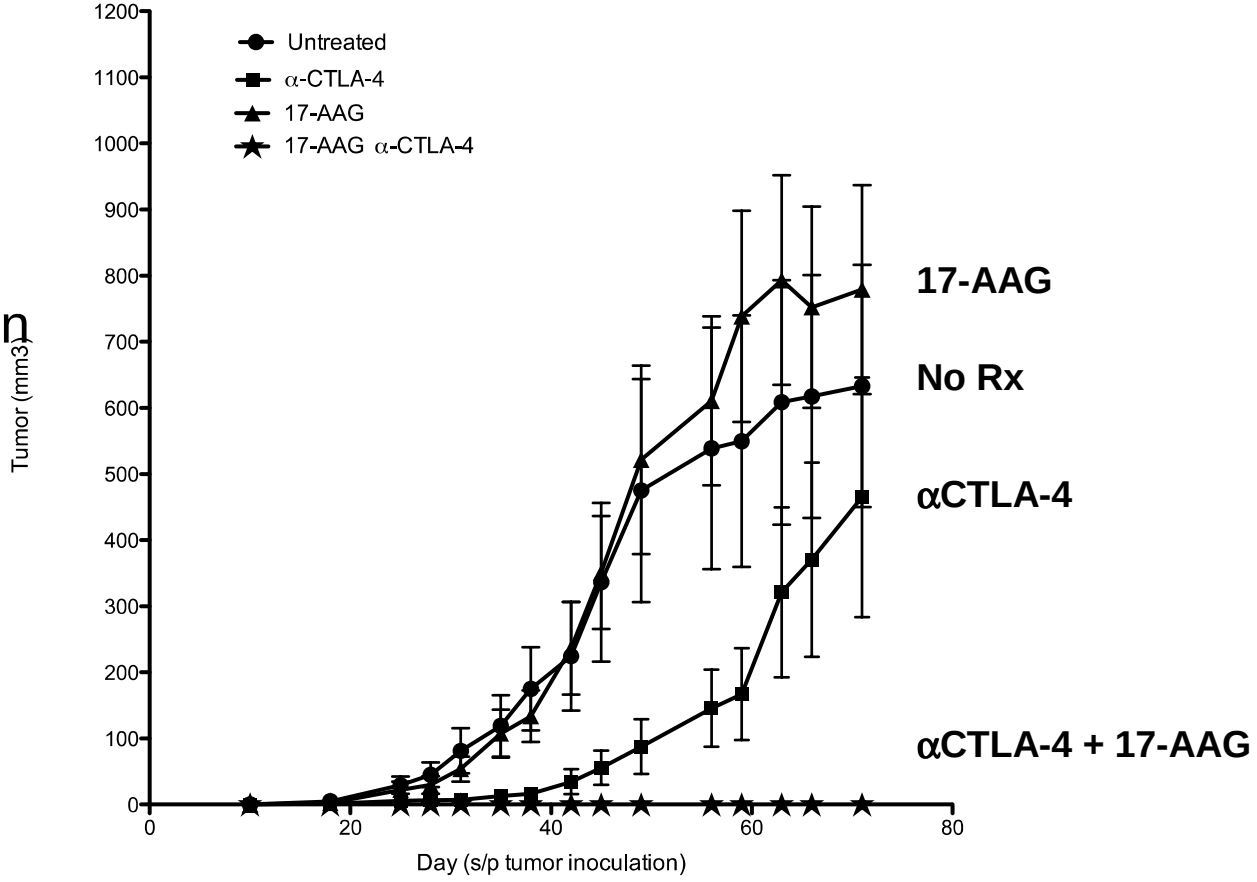


17-AAG

- HSP 90 inhibitor
- Blocks antigen presentation



TUNEL STAIN



Ariayan, Rosen

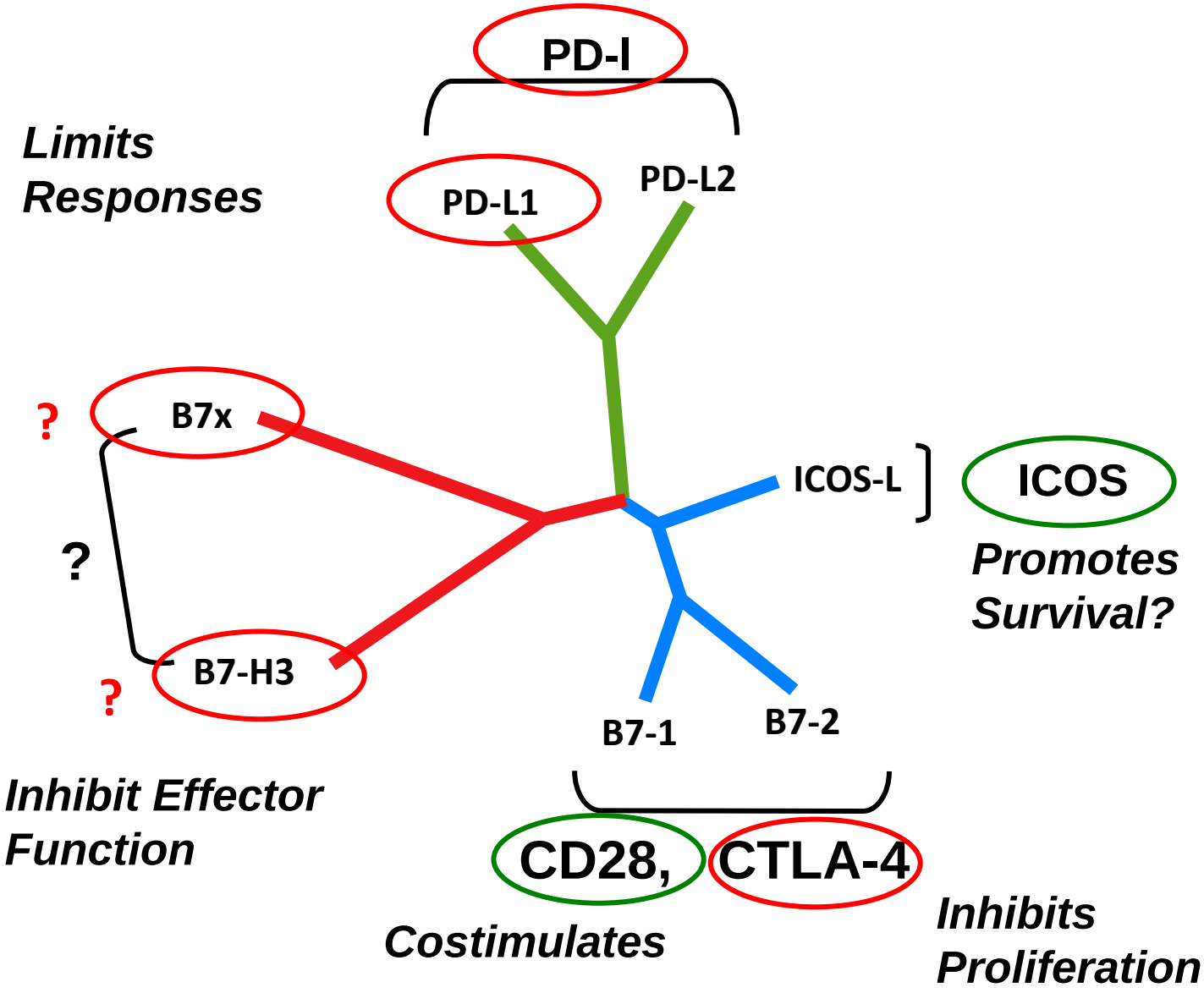
Combinations to Increase Efficacy of CTLA-4 Blockade

- Vaccines
- Conventional Therapies
- Targeted Therapies
- **Combinations of Checkpoint Inhibitors**

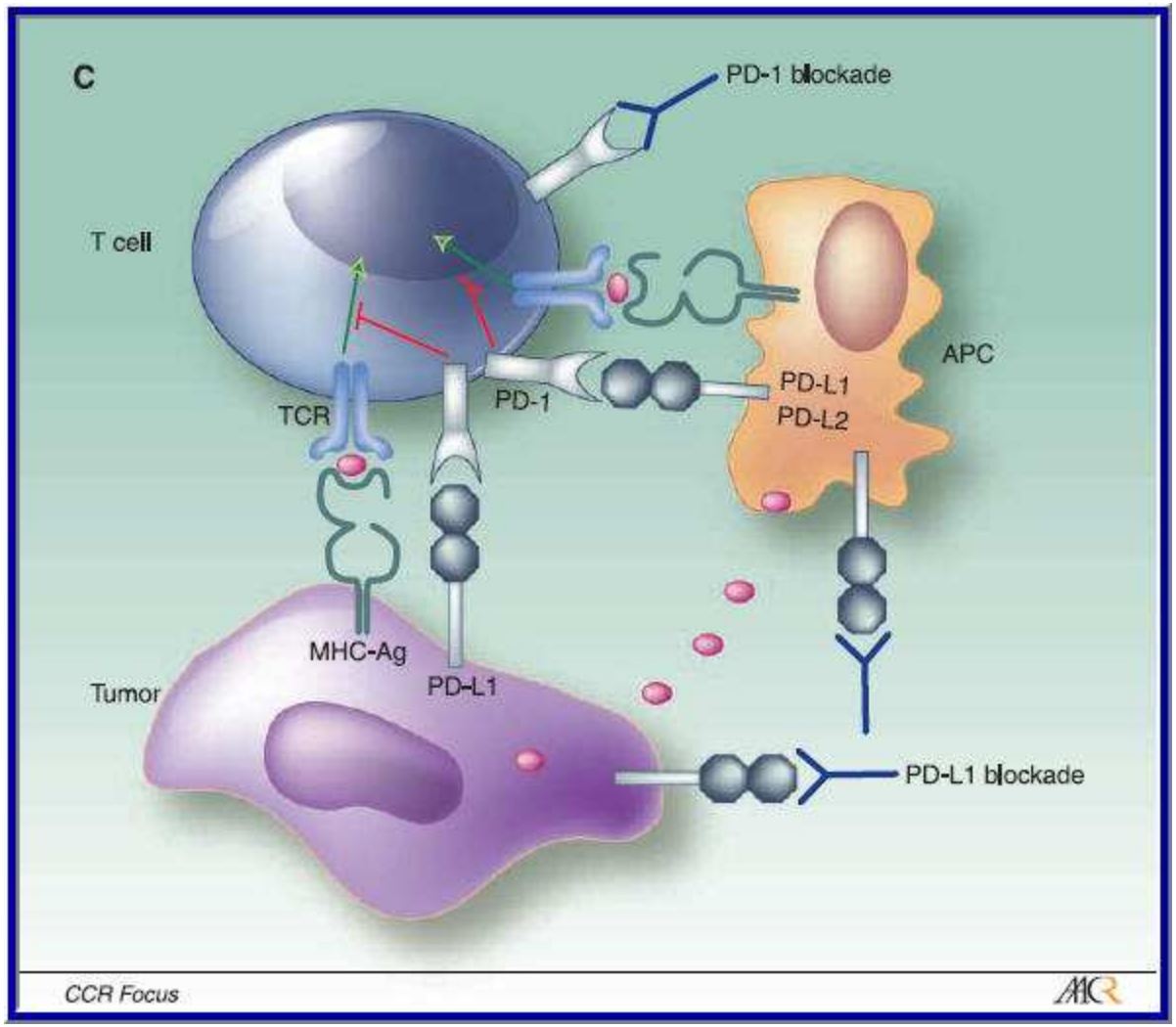
PD-1, PD-L1, B7-H3, B7-H4,

Vista, Tim-3, Lag-3

Combination of Multiple Immune Checkpoint Blockers



Programmed Death 1



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

Anti – PD-1 (BMS-936558)

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

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

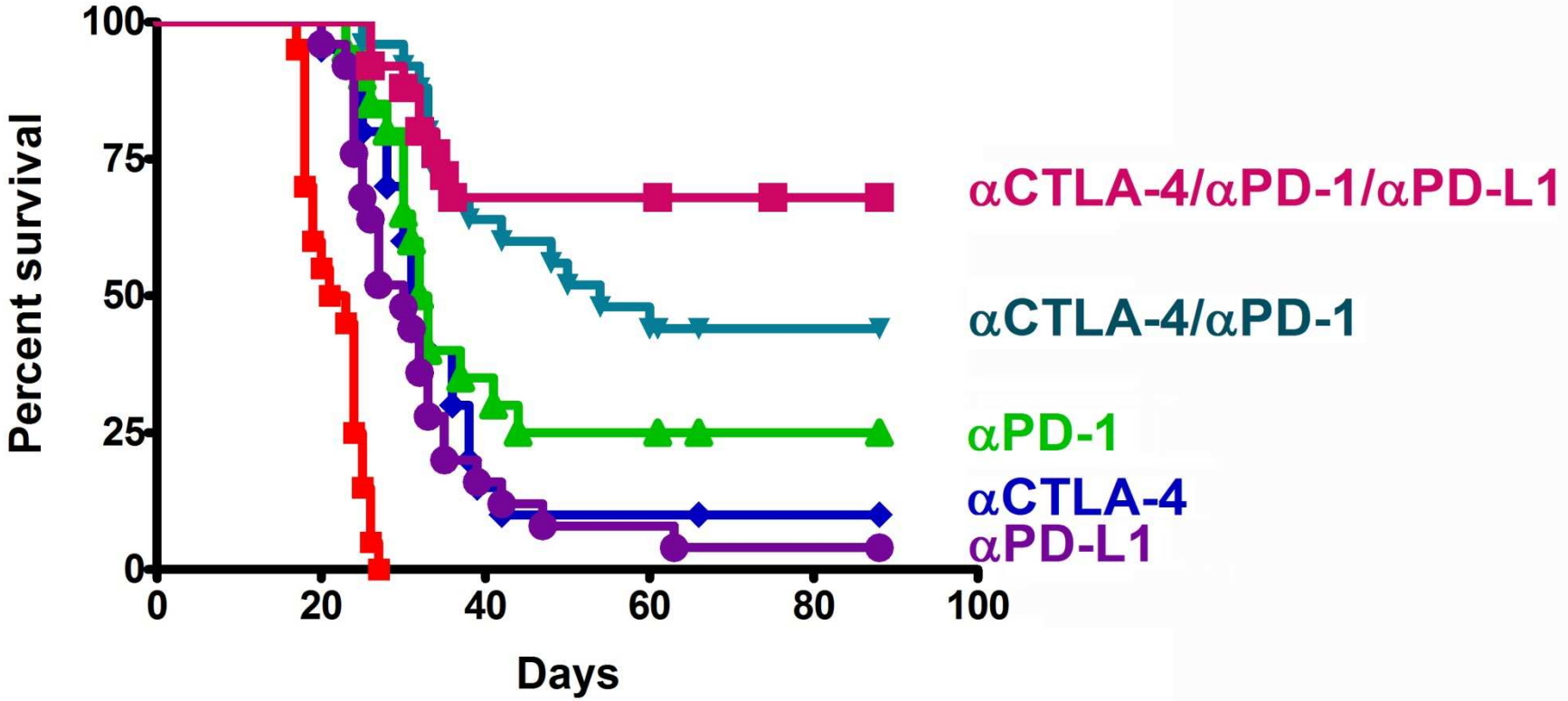
Clinical Activity:

- **Melamona (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***

ASCO, NEJM 2012

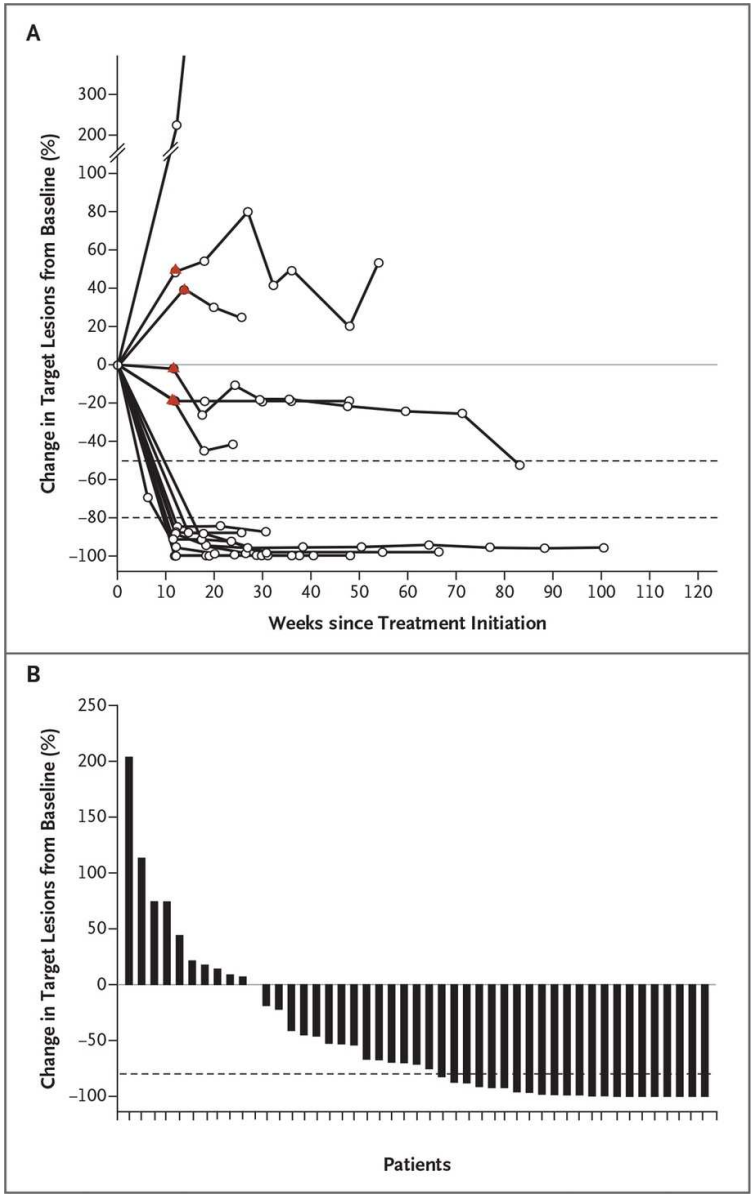
Combination blockade of the CTLA-4 and PD-1 pathways promotes rejection of B16 melanoma

Combination FVAX (B16-Flt3-ligand)+ Antibody



Curran

Clinical Activity in Melanoma Patients Receiving Nivolumad (αPD-1) and Ipilimumab (αCTLA-4)



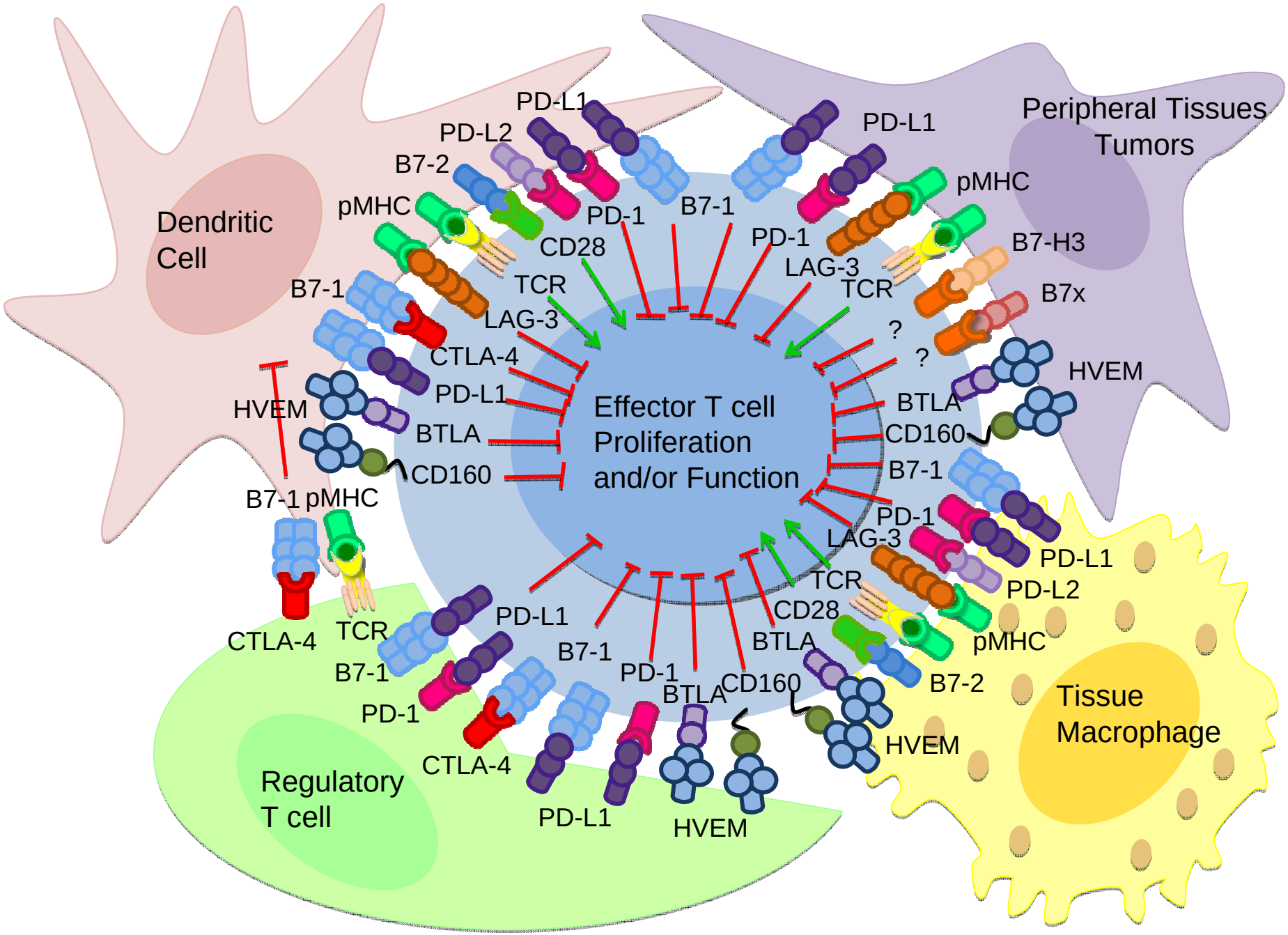
40% Objective CR+PR
65% Clinical Activity

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


Dendritic Cell
Peripheral Tissues Tumors
Effector T cell Proliferation and/or Function
Regulatory T cell
Tissue Macrophage
PD-L1
PD-L2
B7-2
pMHC
CD28
TCR
LAG-3
PD-1
B7-1
CTLA-4
HVEM
BTLA
CD160
B7-H3
B7x
?
?

Improving Survival with Combination Therapy