Relevant Disclosures

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Neon Therapeutics: **Founder and scientific advisory board member**

Kite Pharmaceuticals: **Scientific advisory board member**

Immune Checkpoint Blockade in Cancer Therapy: New insights, opportunities, and prospects for cures

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

Jim Allison

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Executive Director, Immunotherapy Platform

Lilian H. Smith Distinguished Chair of Immunology

30th Annual Meeting SITC

(formerly ISBTC)

November 6, 2015

Thanks to:

Allison Lab & Alumni

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The Docs
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CPRIT
SU2C/CRI

Immune Checkpoint Blockade

Paradigm Shift in Cancer Therapy:

Doesn't target tumor cells

Doesn't involve vaccines or cytokines to turn "on" immune responses

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

FDA approval of antibodies targeting immune checkpoints

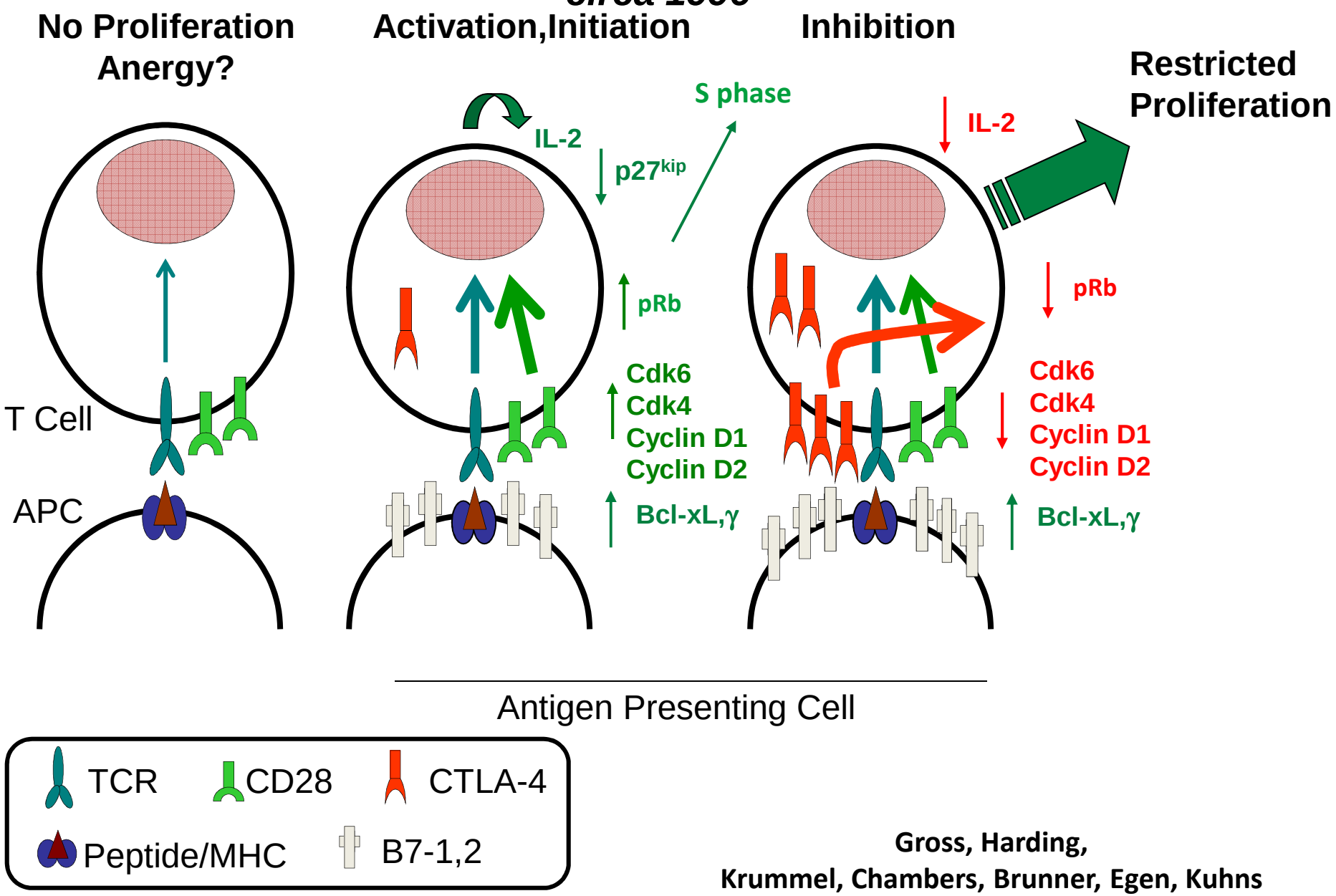
- 2011 Ipilimumab (BMS) - Melanoma
- 2014 Pembrolizimab (Merck) – Melanoma
- 2014 Nivolumab (BMS) – Melanoma
- 2015 Nivolumab (BMS) – Lung
- 2015 Ipilimumab + Nivolumab (BMS) – Melanoma
- 2015 Pembrolizumab (Merck) – Lung
- 2015 Ipilimumab (BMS) – Adjuvant melanoma
- 2015 - ????

How did we get here?

Understanding of fundamental mechanisms
of T cell activation and regulation

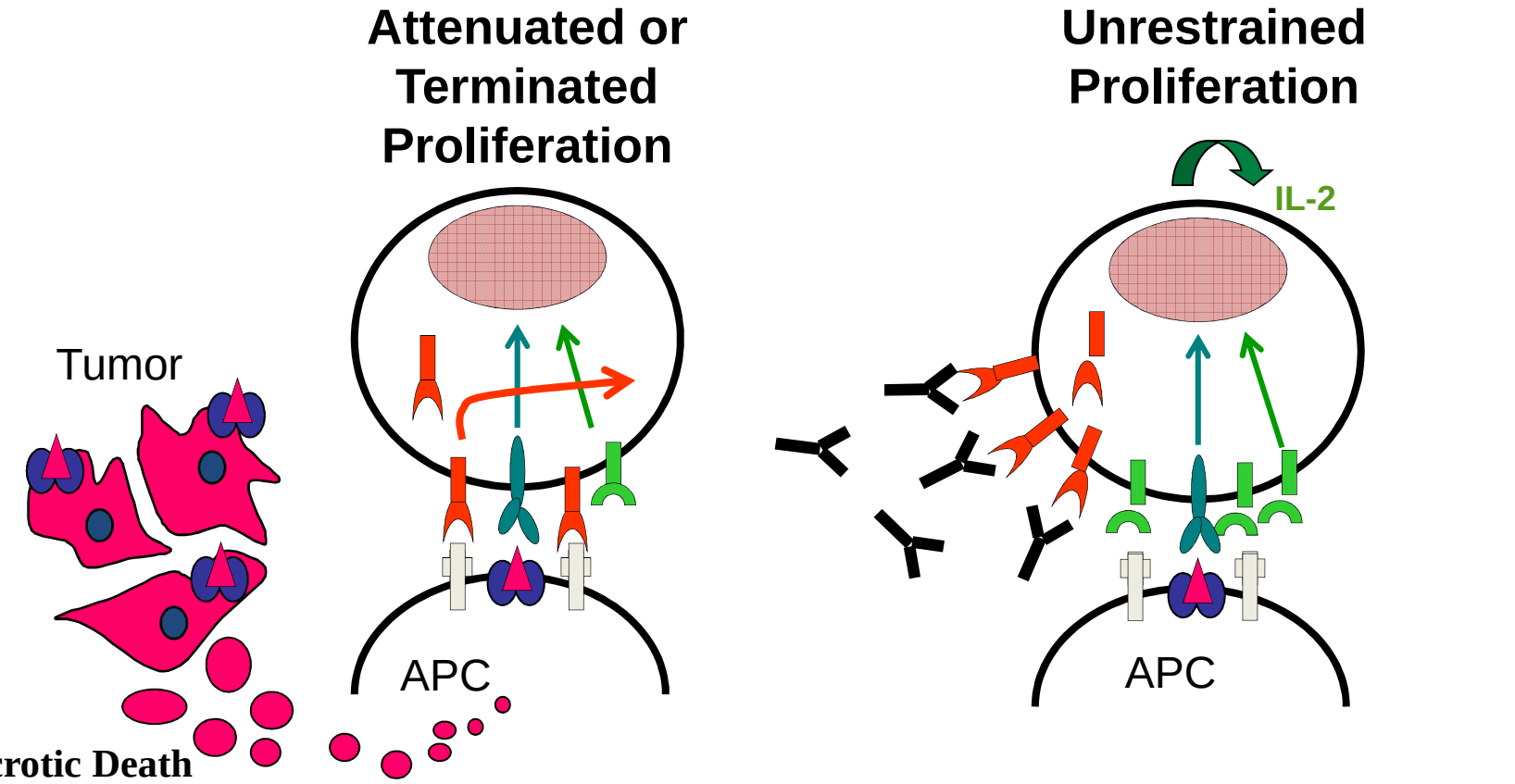
Dynamic Integration of TCR and Costimulatory Signals

circa 1996



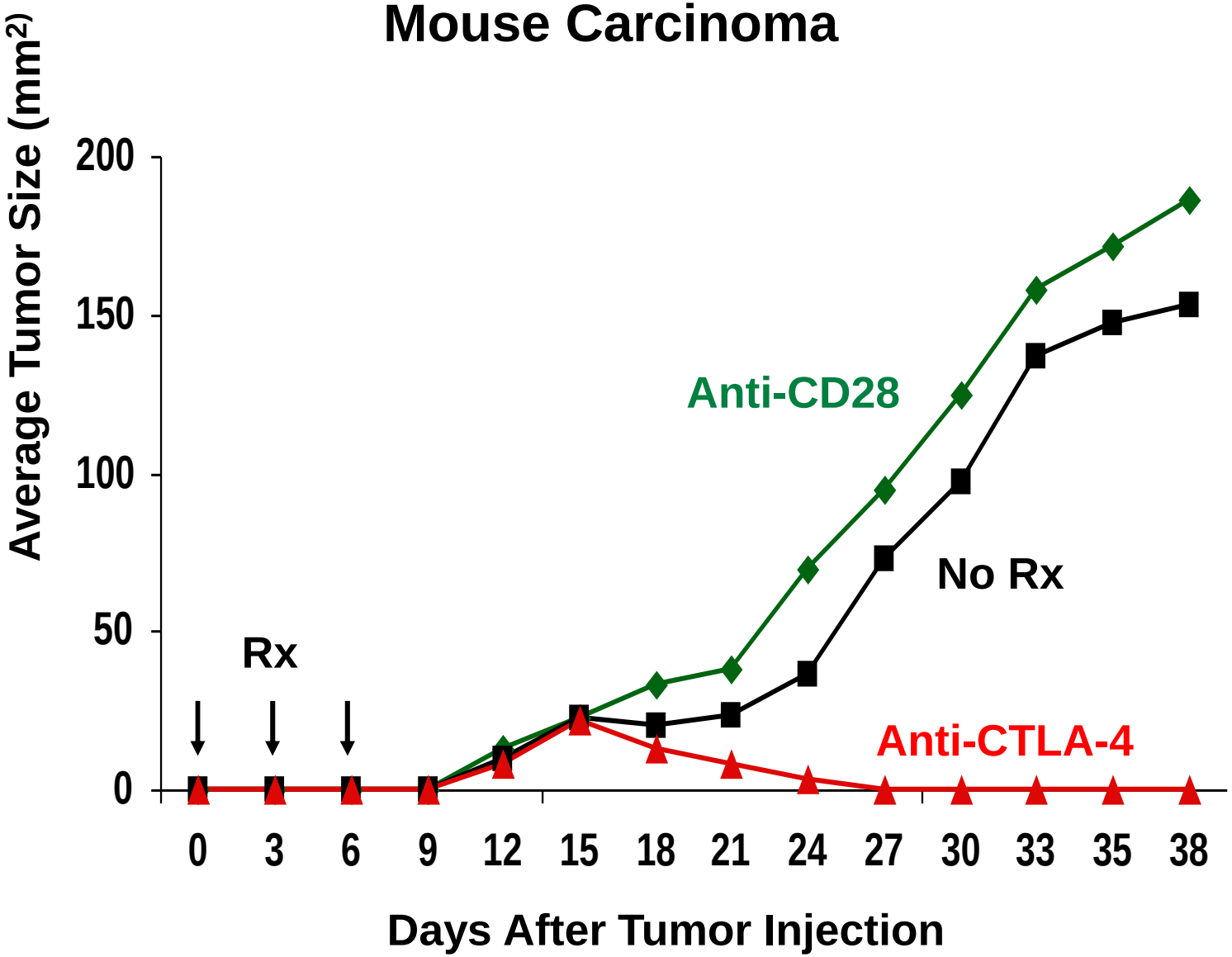
Gross, Harding,
Krummel, Chambers, Brunner, Egen, Kuhns

CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses



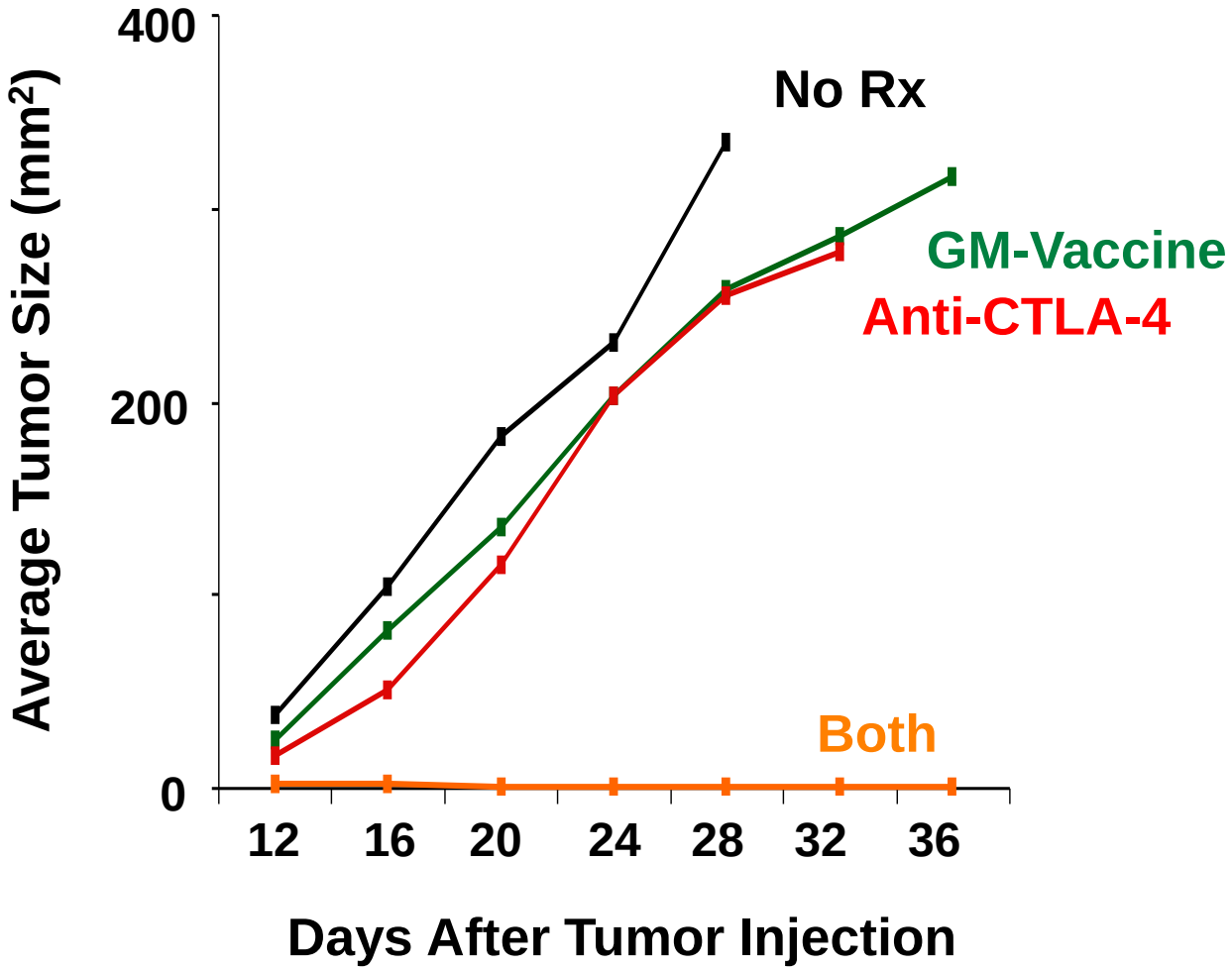
Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
"Targeted" Therapies

Anti-CTLA-4 Induces Regression of Transplantable Mouse Carcinoma



Leach

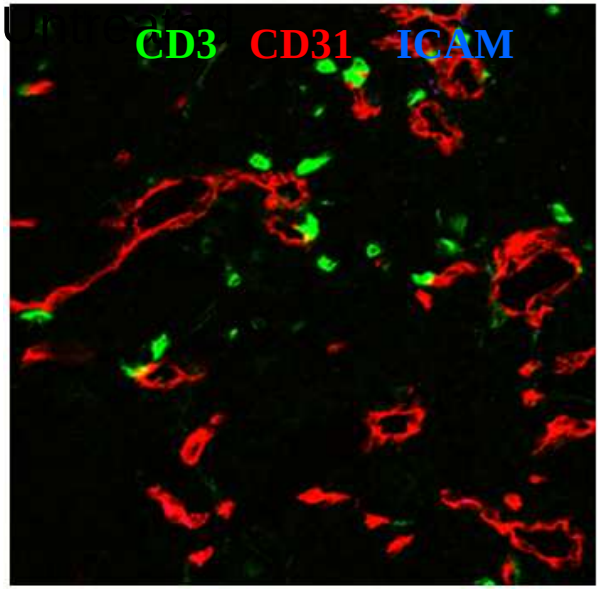
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

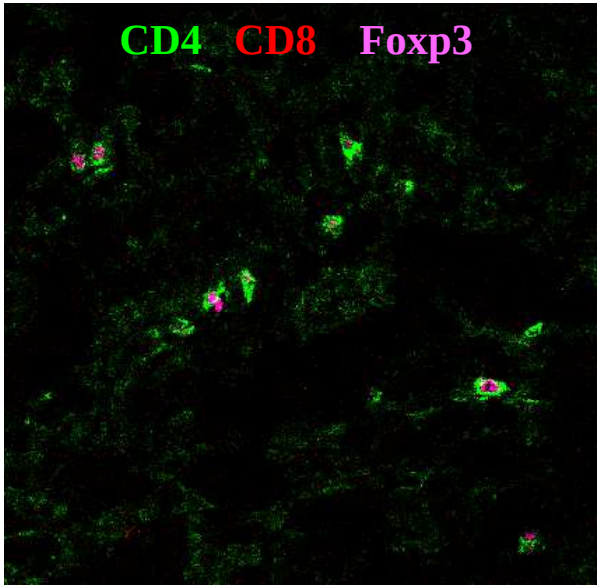


van Elsas,Hurwitz

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

Untreated



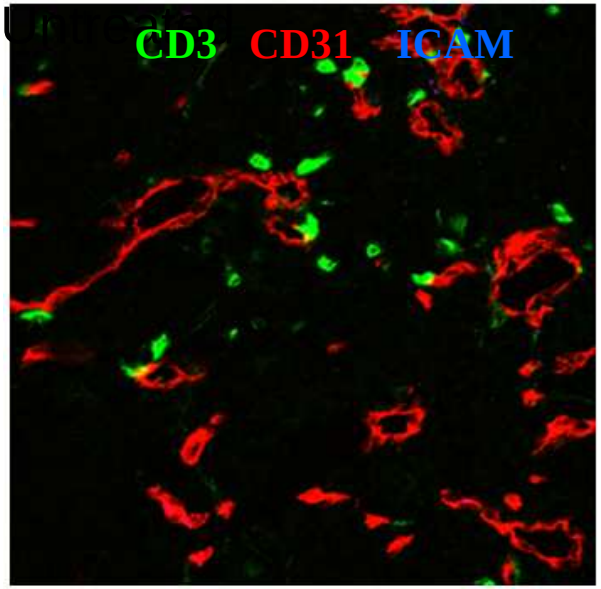


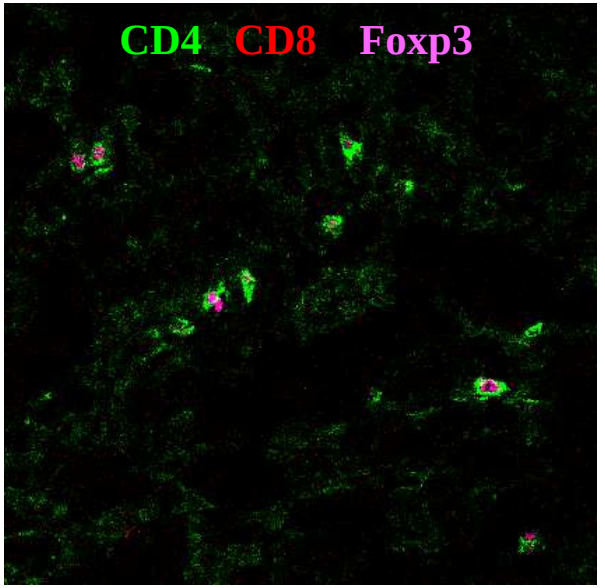
Quezada

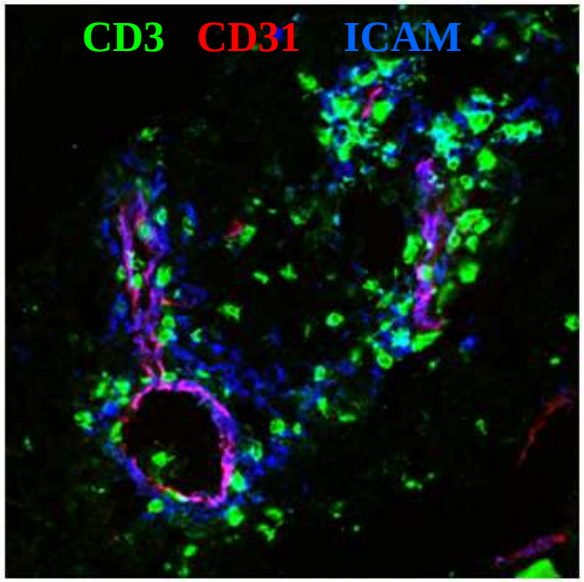
anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

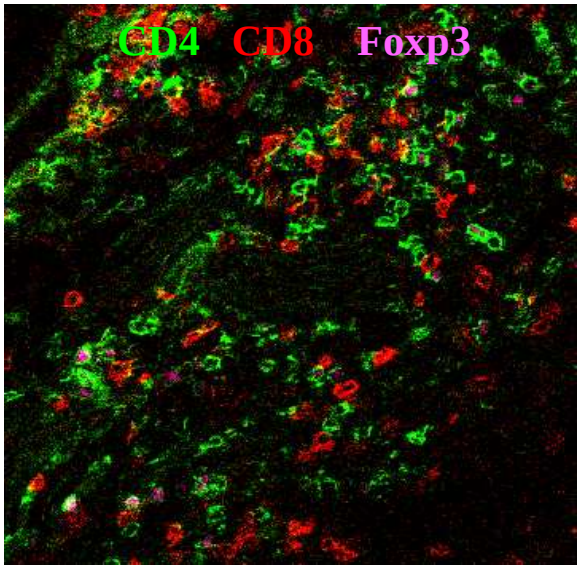
Untreated

αCTLA-4/GVAX









Quezada

Mechanisms involved in tumor rejection by CTLA-4 blockade

- **Major impact results from effects on cell intrinsic inhibitory pathway of CTLA-4 in Teff**

- **Optimal effect in some settings requires effects on CTLA-4^{Hi} Treg**
  - **ADCC mediated deletion of Treg by myeloid cells**

Quezada, Peggs, Simpson

Ipilimumab
(Medarex, Bristol-Myers Squibb)

Fully human antibody to CTLA-4

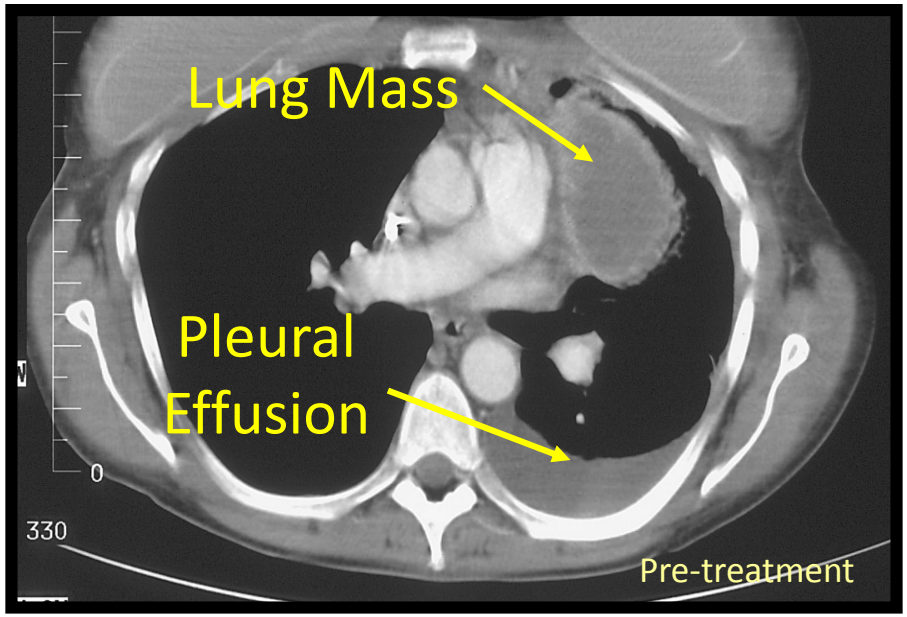
>70,000 patients treated to date:

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

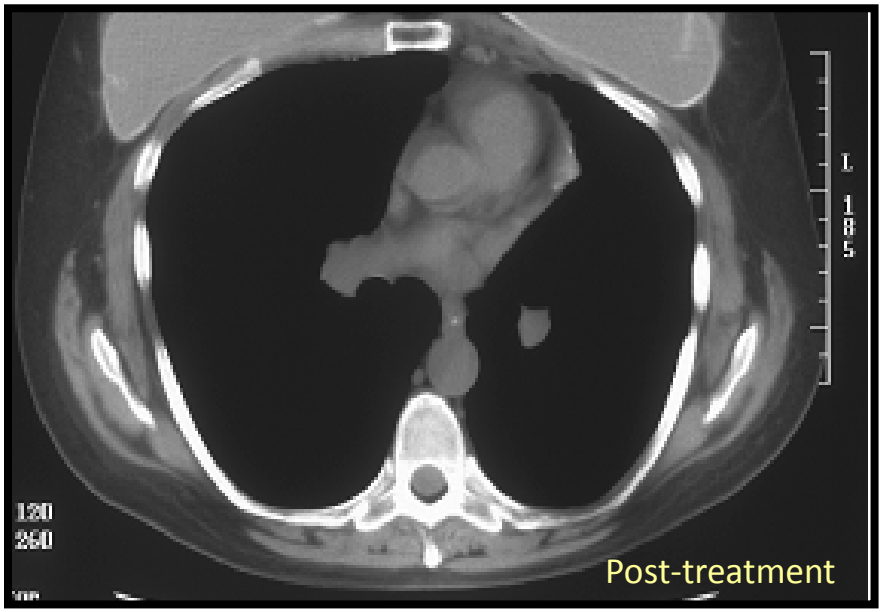
Adverse events (colitis, hepatitis, hypophysitis, etc) serious but generally mangageable

The longest survivor on ipilimumab?

May 2001, after progression on IL-2



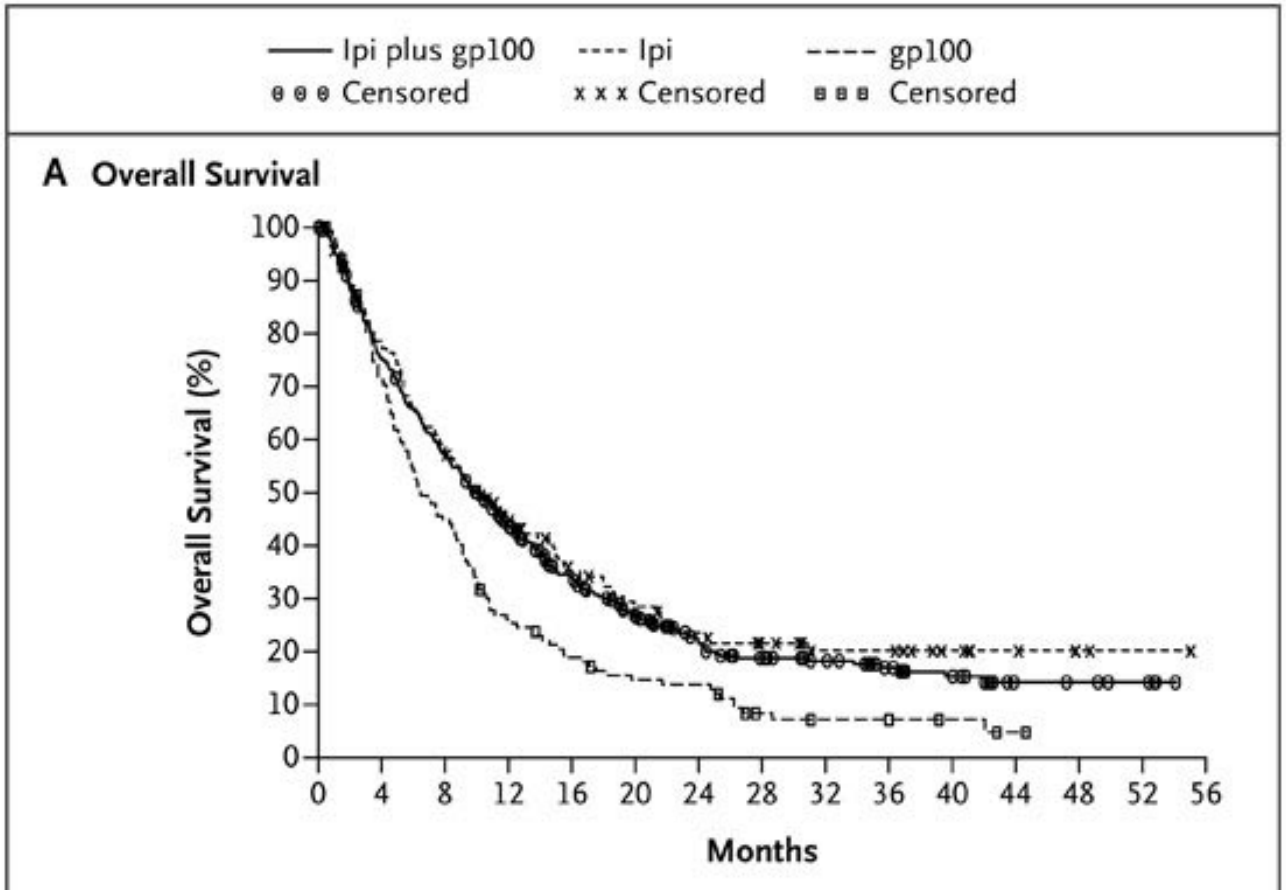
10 years later



Baseline and post-MDX-010 treatment CT scans of patient with metastatic melanoma (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.

Ribas

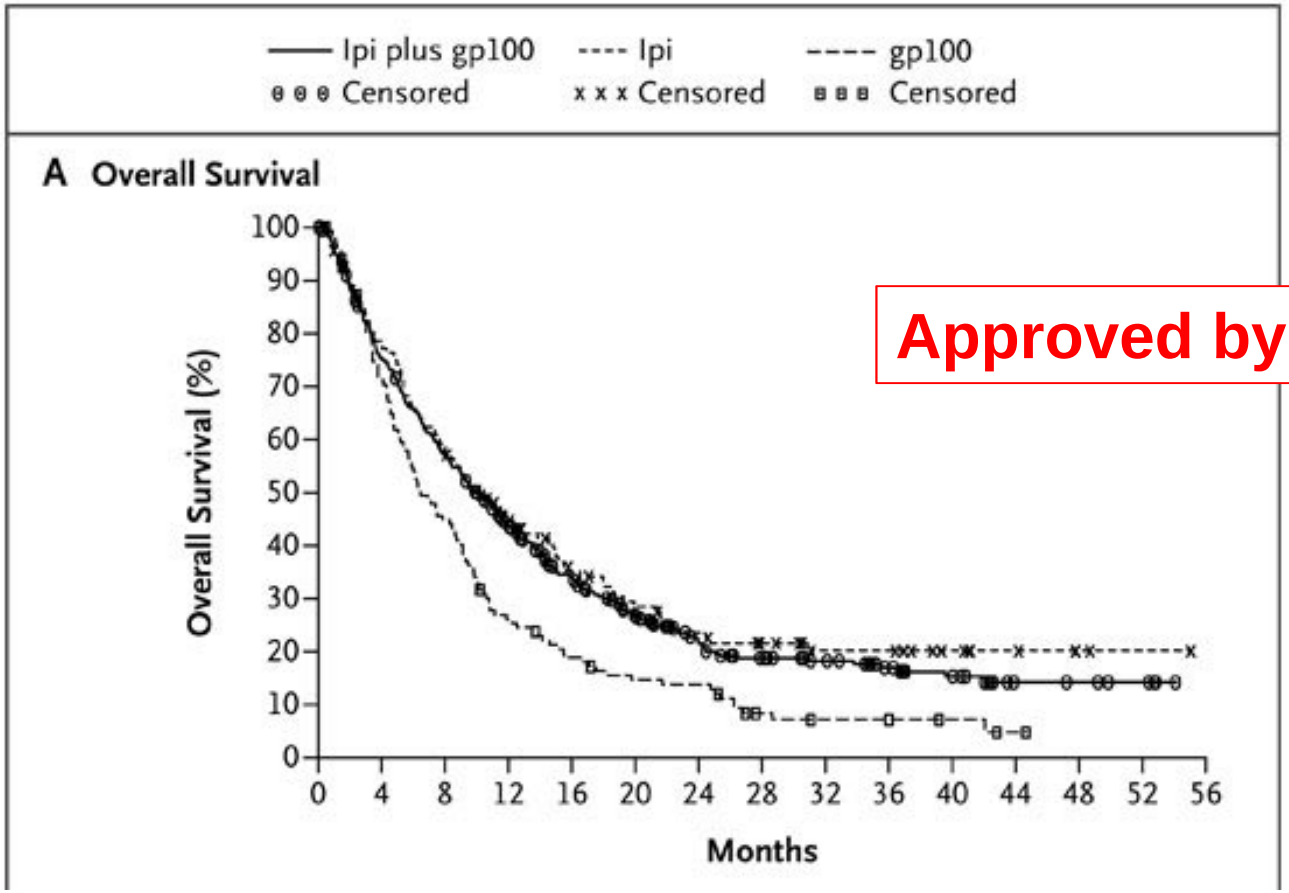
Kaplan-Meier Analysis of Survival



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

Survival Data: Phase III clinical trial

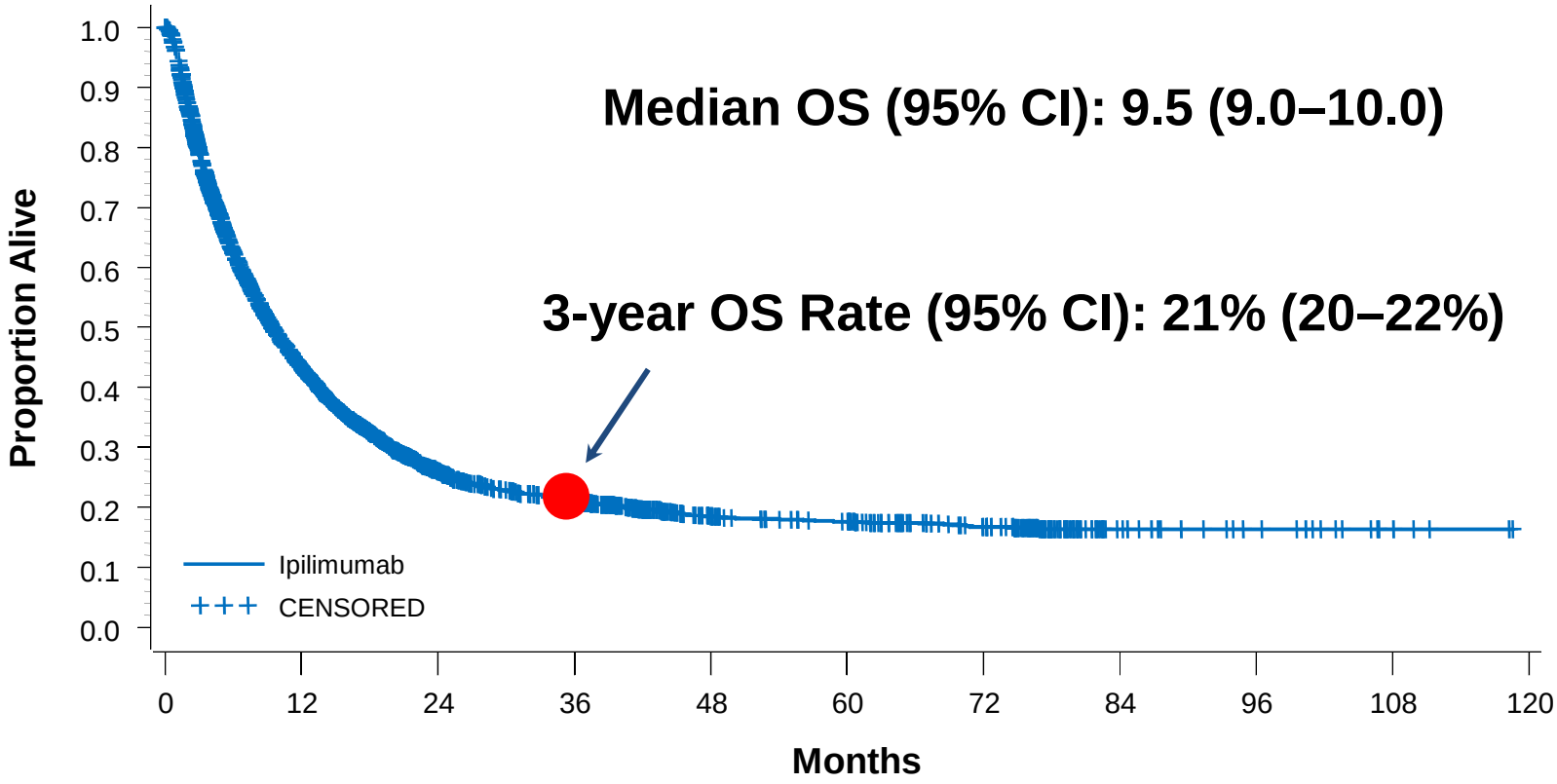


Approved by FDA 2011

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 in Metastatic Melnoma:Pooled OS Analysis Including EAP Data (4846 Patients)

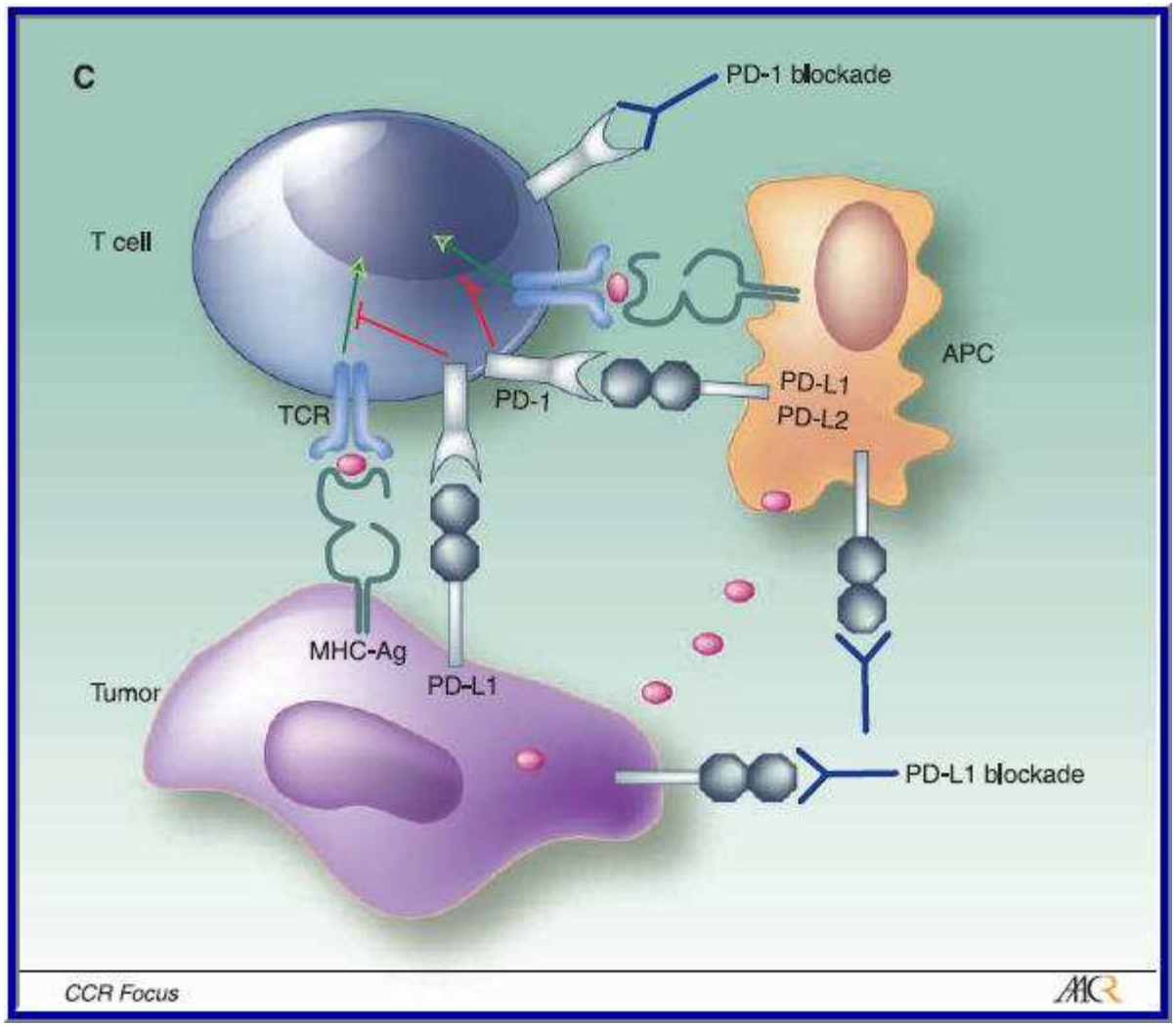


Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Hodi, ECCO 2014

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

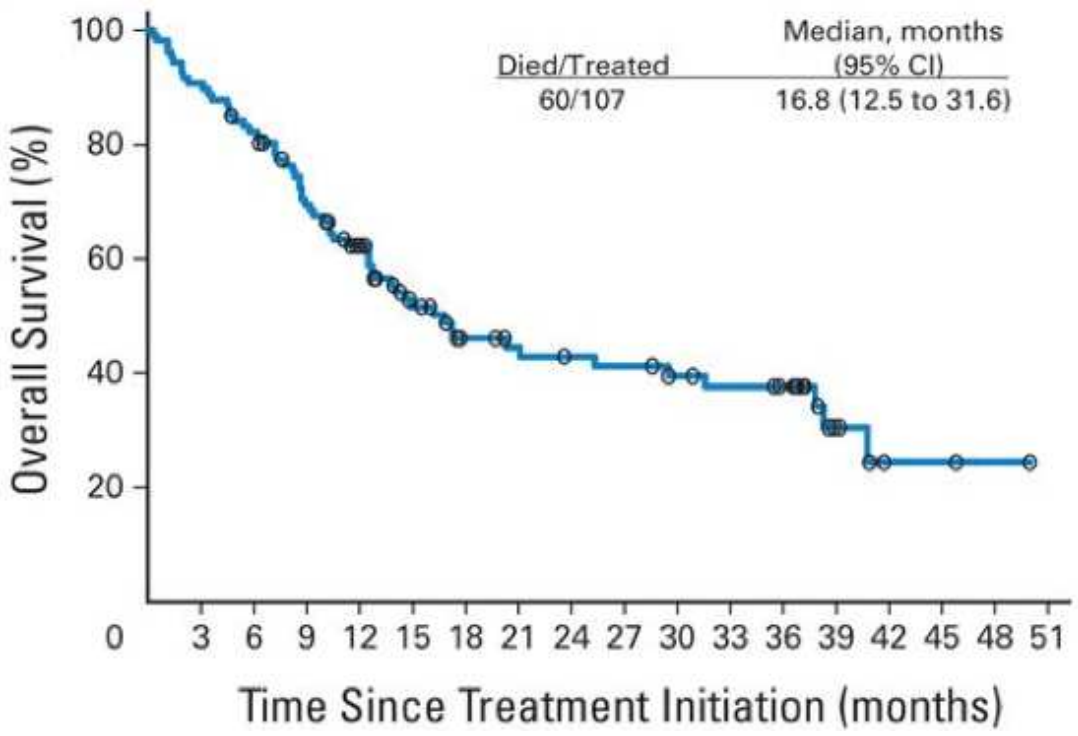
Safety: Adverse events similar to Ipilimumab, but 4% pneuomonitis (3 deaths)

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***

Topalian ASCO, NEJM 2012

Overall Survival: Nivolumab (aPD-1) in Metastatic Melanoma



Topalian et al. JCO 2014

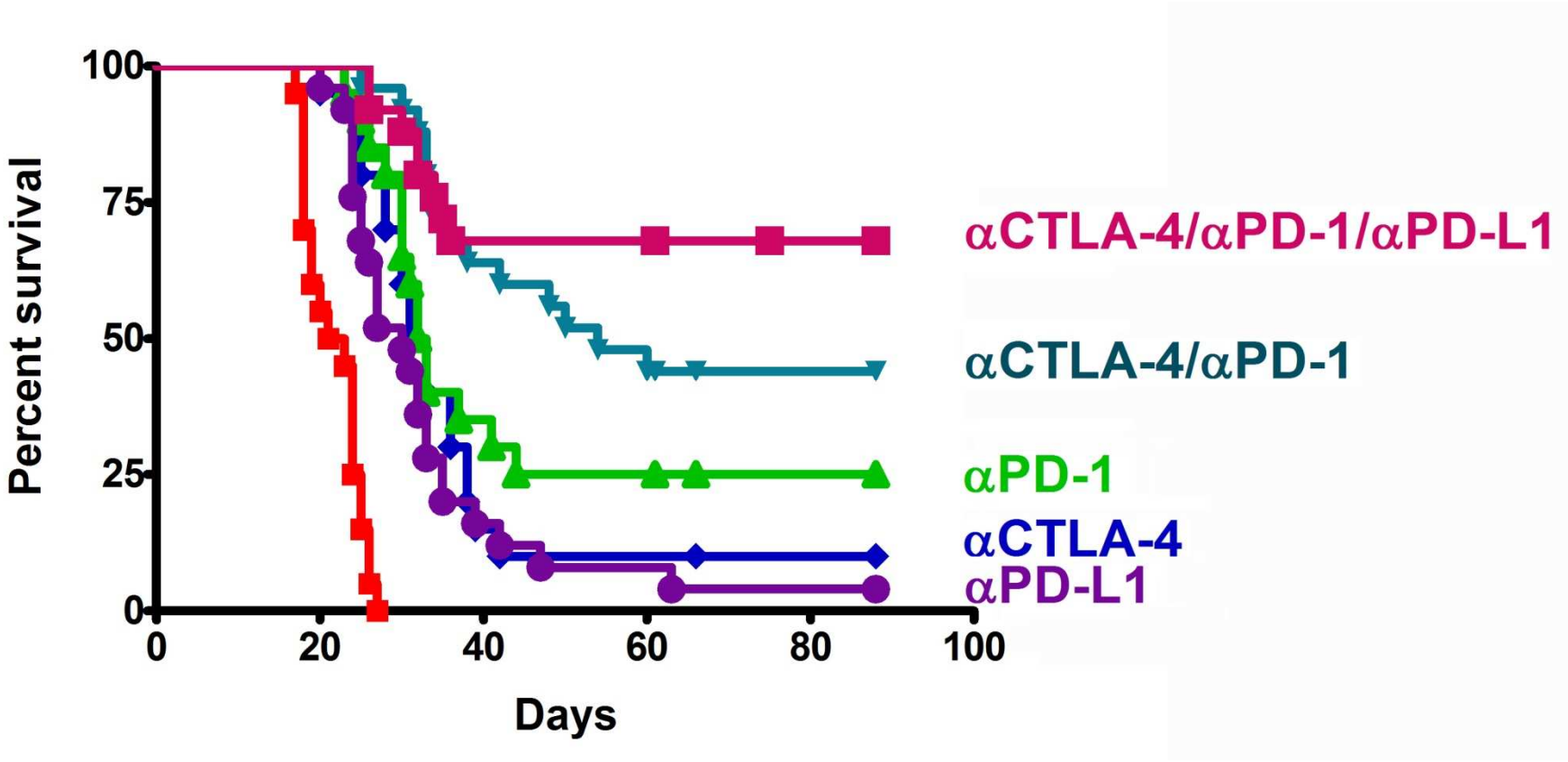
Anti-CTLA-4	Anti-PD-1
• Hard wired • Targets CD28 pathway • Expands clonal diversity • Can move T cells into tumor • Disease recurrence after response is rare	• Induced resistance • Targets TCR pathway • Does not expand clonal diversity • Does not move T cells into tumors • Disease recurrence after response is significant

Where do we go from here?

Combinations

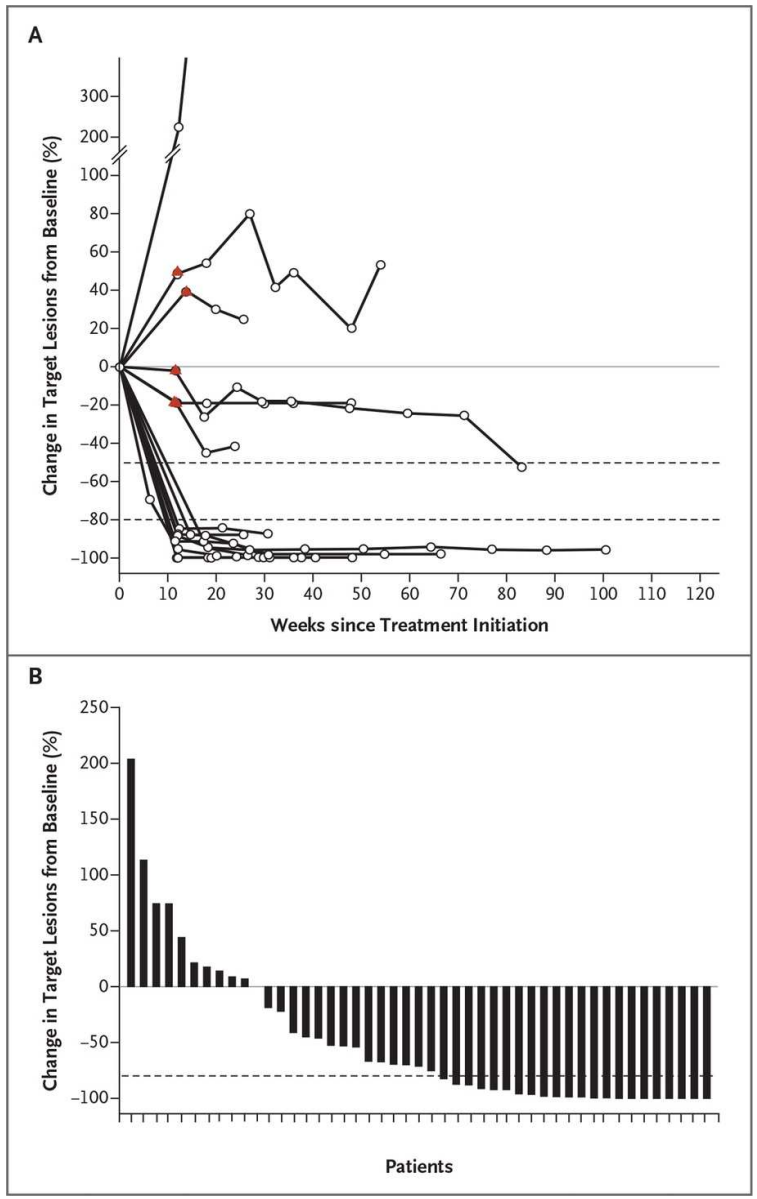
Combination blockade of the CTLA-4 and PD-1 pathways promotes rejection of B16 melanoma

Combination FVAX (B16-Flt3-ligand)+ Antibody



Curran

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

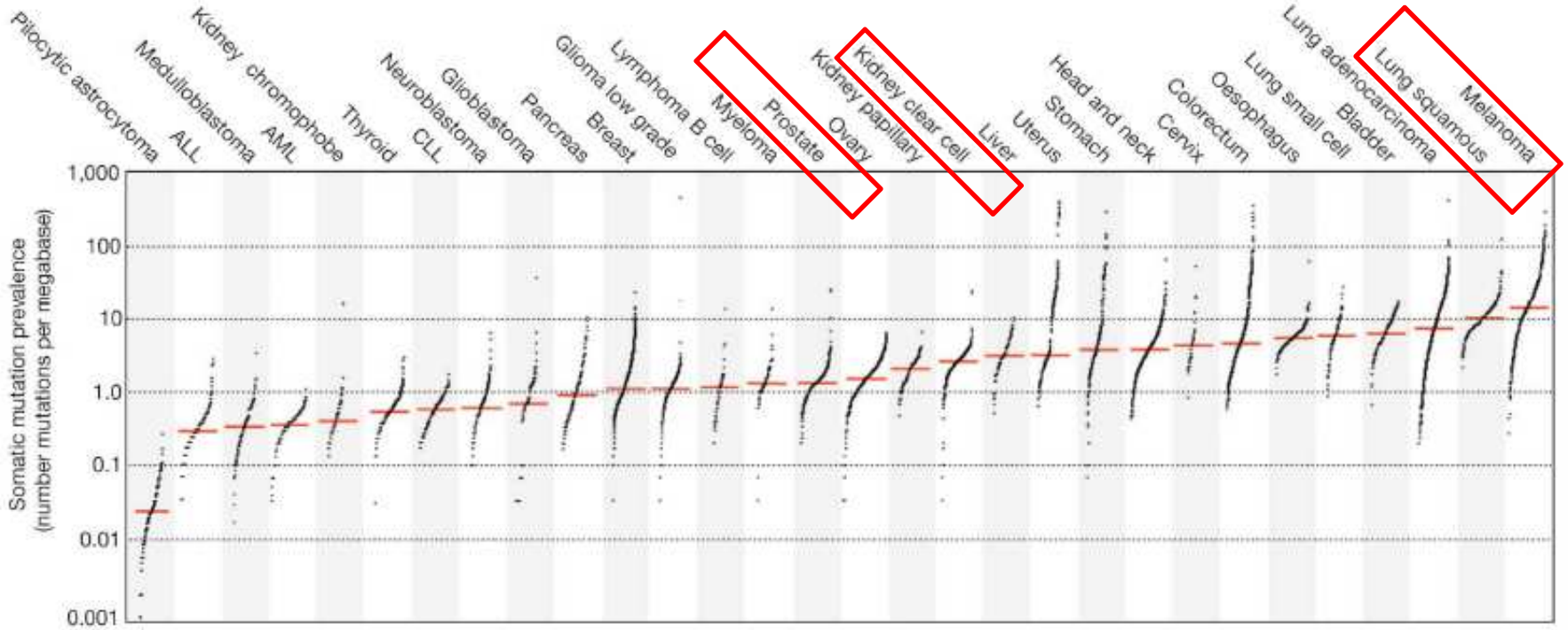


65% Clinical Activity

~50% Objective CR+PR

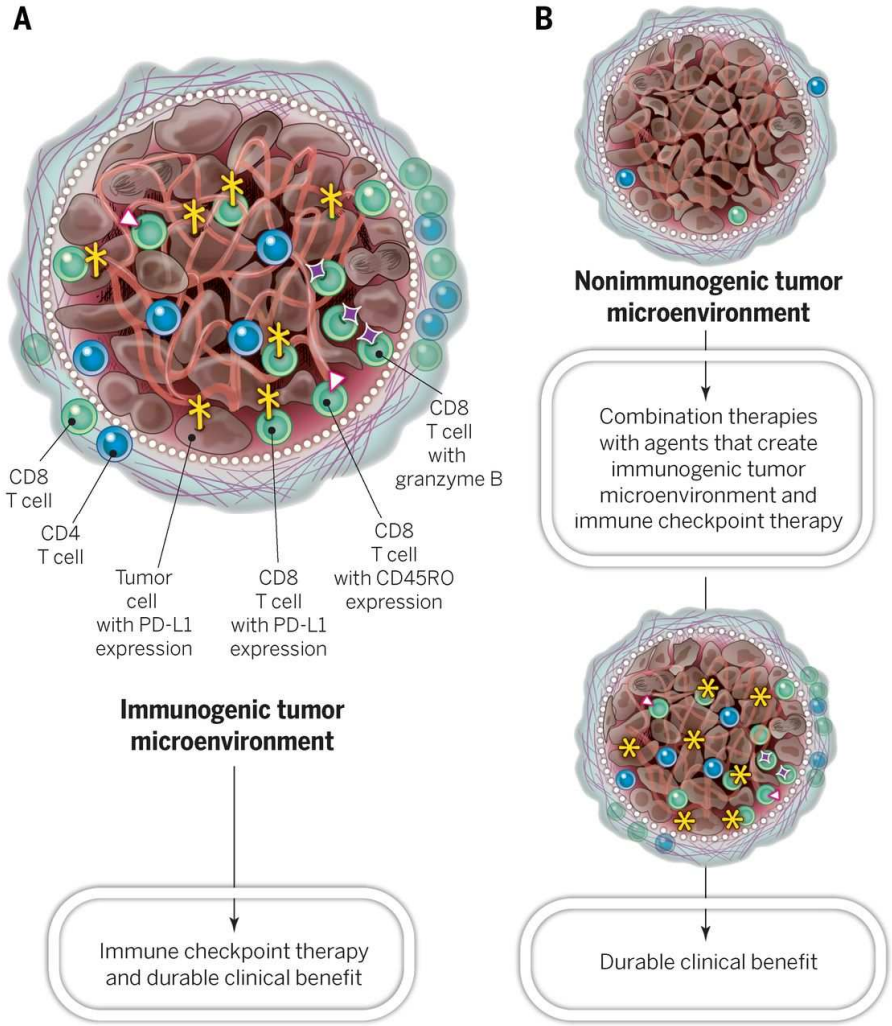
ASCO 2013
NEJM 6/2/2013

Prevalance of somatic mutations In human cancer



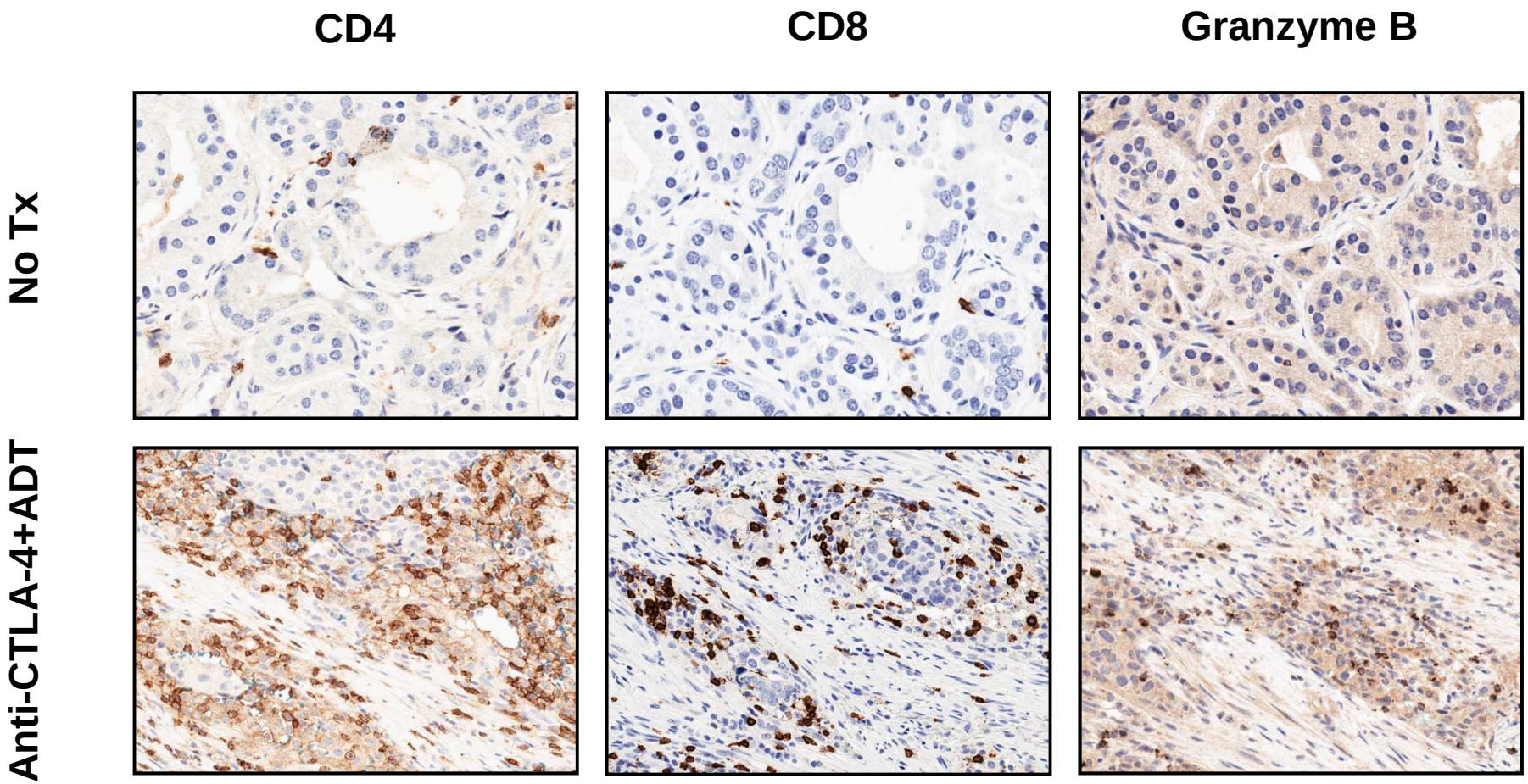
Signatures of mutational processes in human cancer Alexandrov et al.
Nature Volume: 500,Pages:415–421Date published:(22 August 2013)DOI:doi:10.1038/nature12477

Potential characteristics of immunogenic and nonimmunogenic tumors.



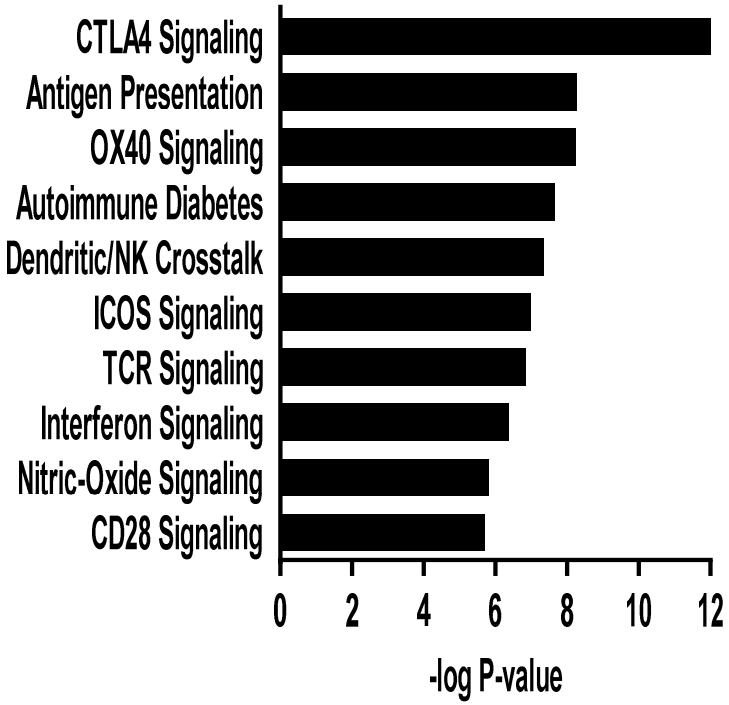
Padmanee Sharma, and James P. Allison Science 2015;348:56-61

Converting a “cold” prostate tumor microenvironment to “hot”

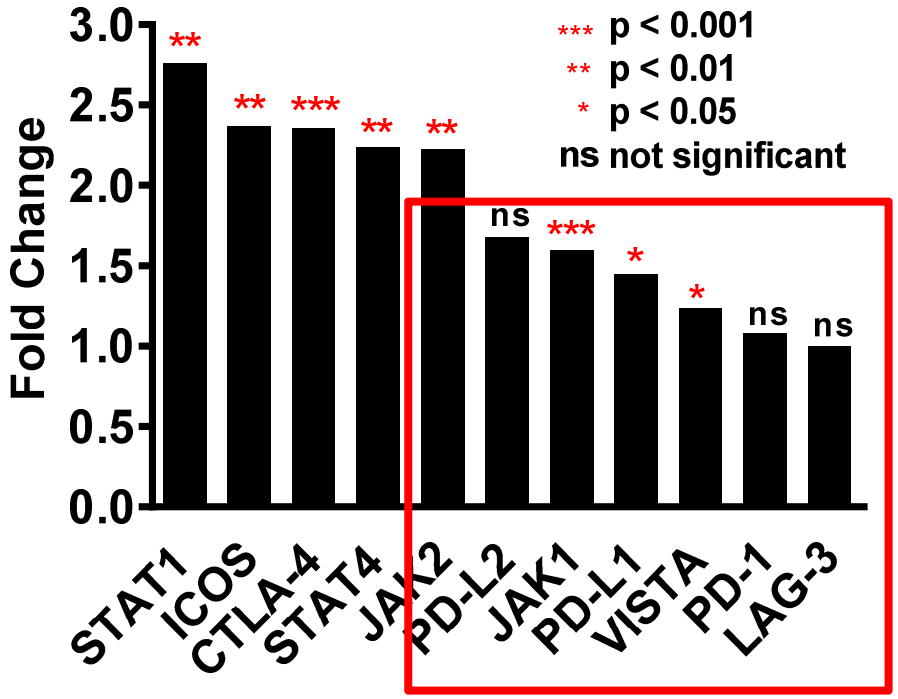


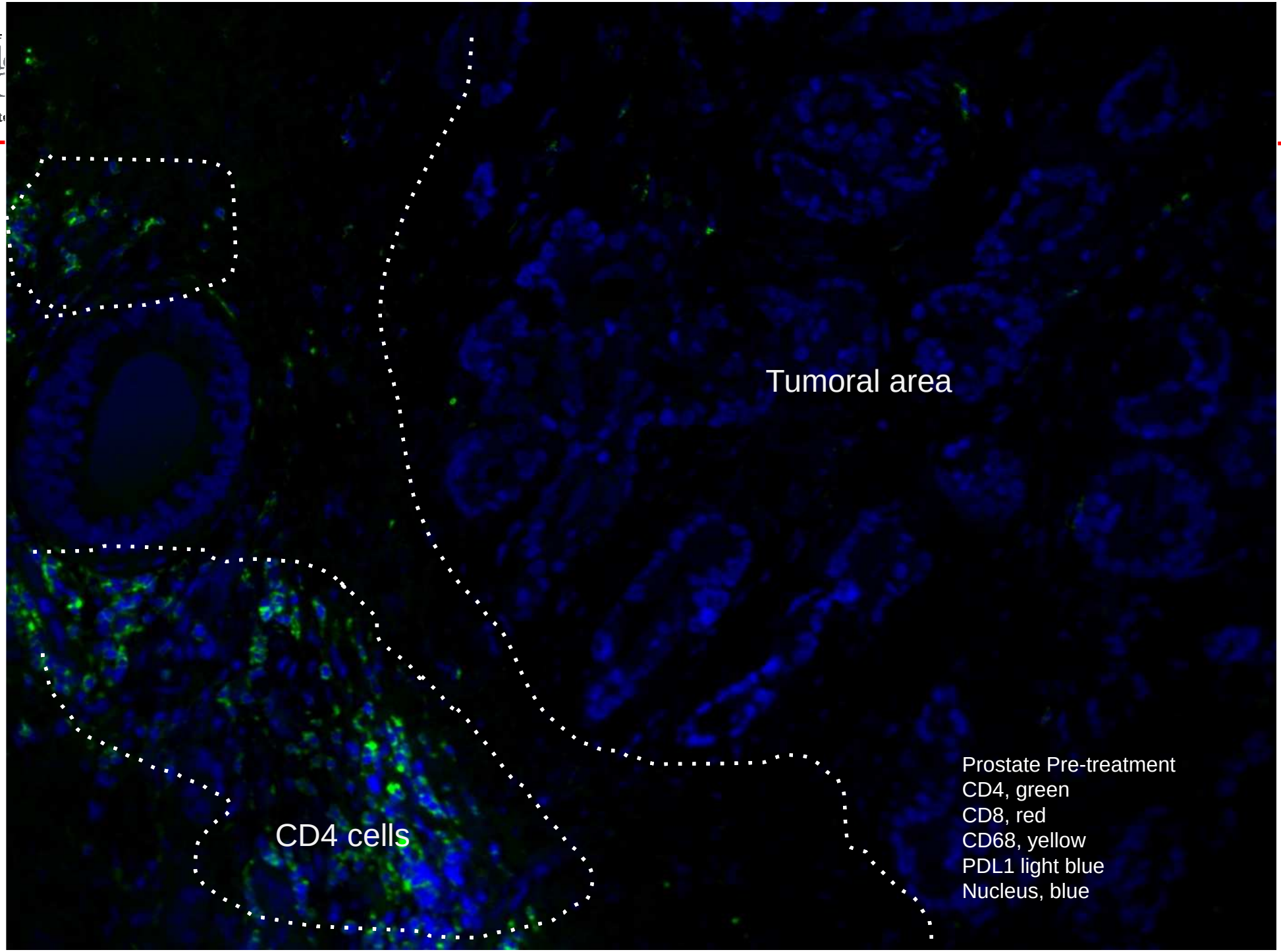
What else changes after anti-CTLA-4 therapy?

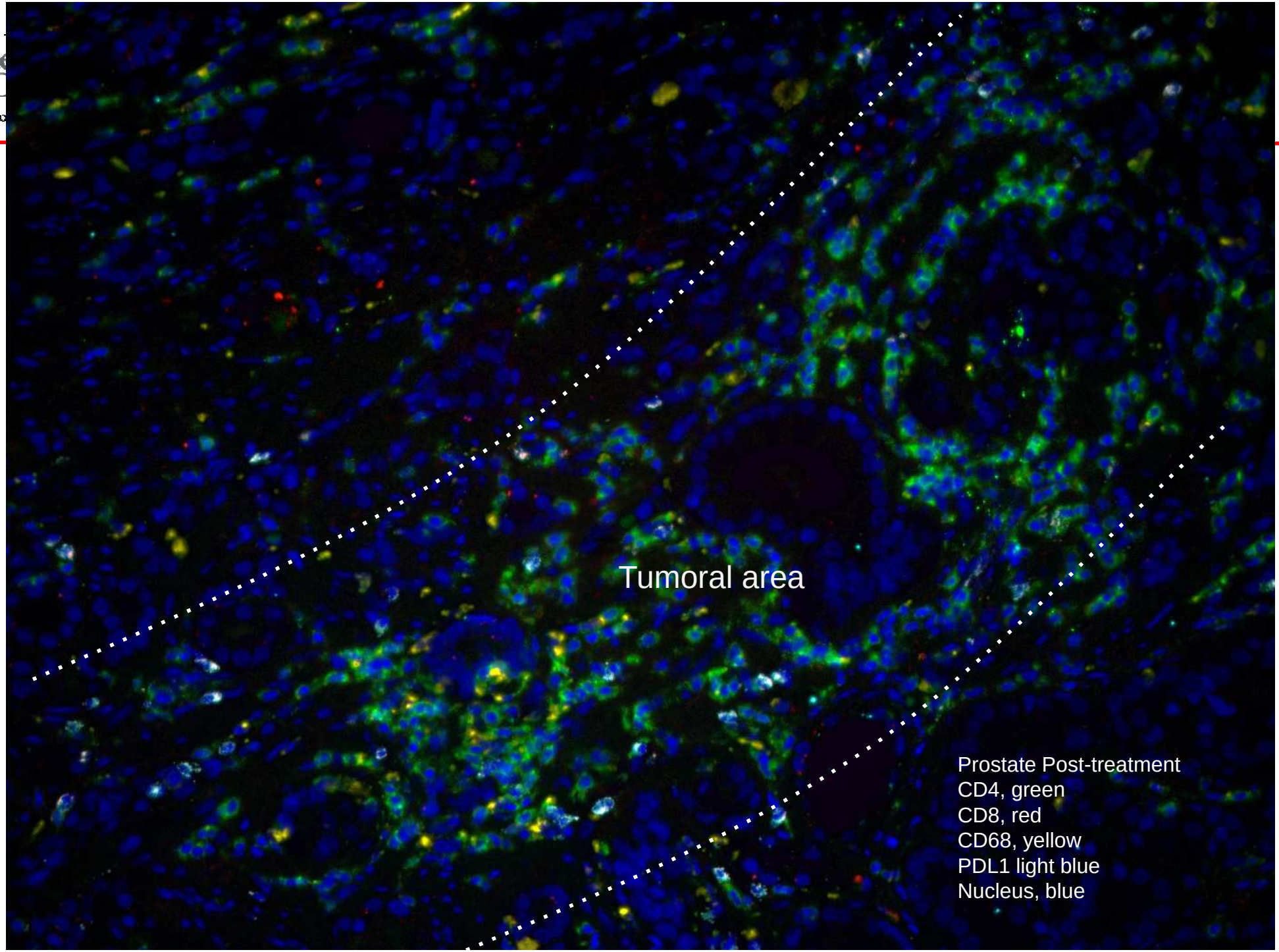
A. Top 10 signaling pathways in response to ADT + ipilimumab treatment

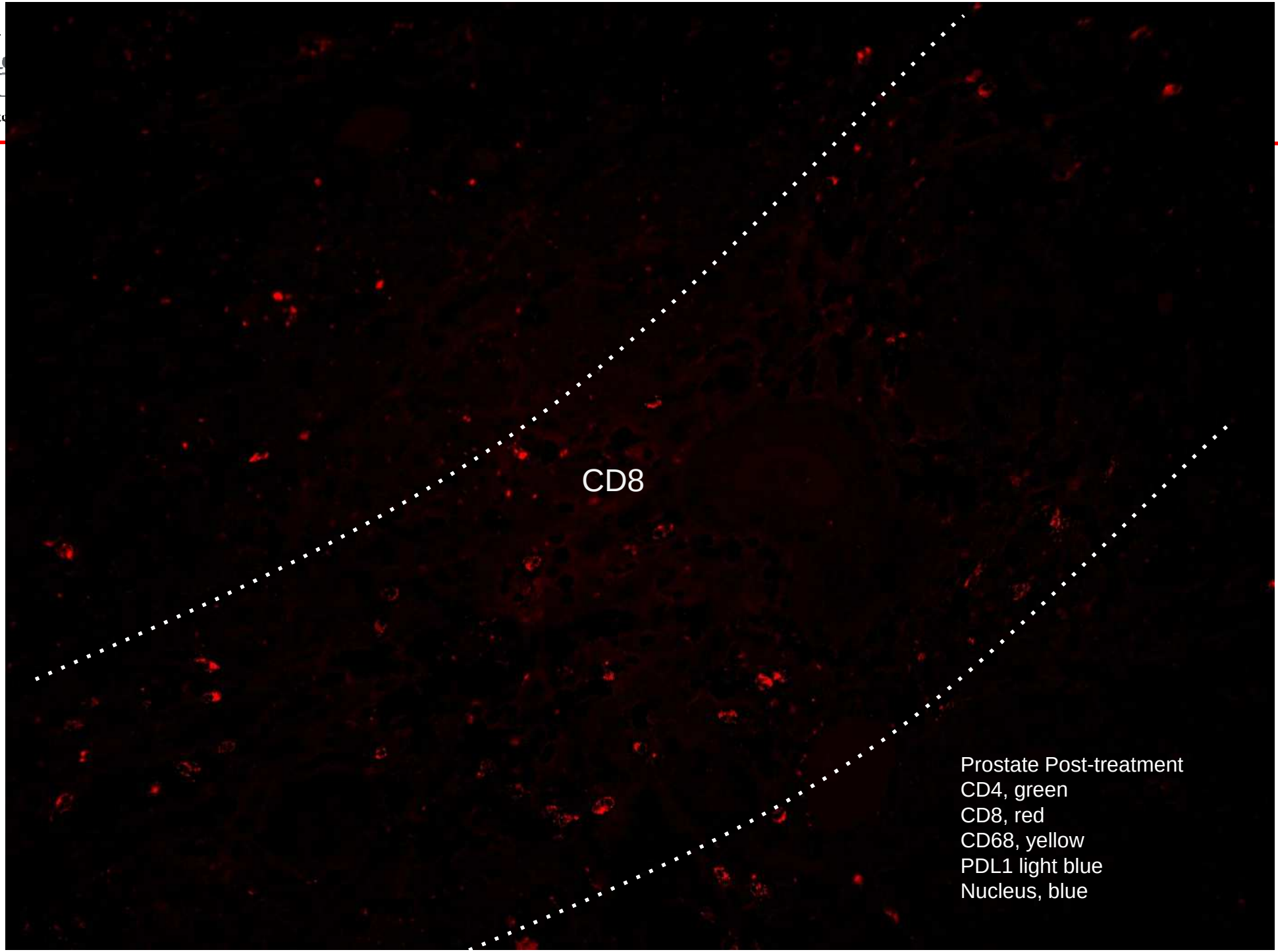


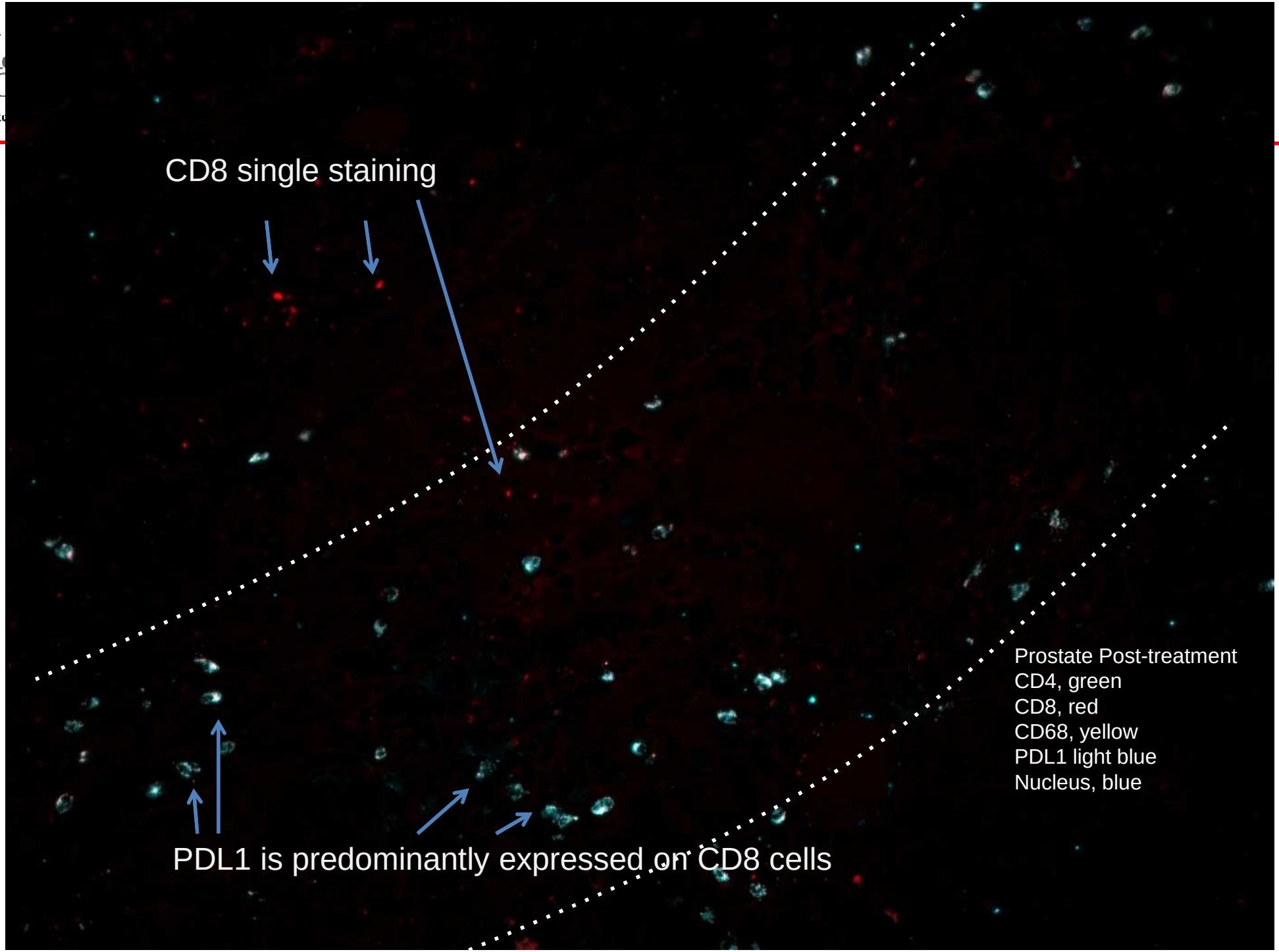
B. Selected immune gene expression after ADT + ipilimumab treatment




Tumoral area
CD4 cells
Prostate Pre-treatment
CD4, green
CD8, red
CD68, yellow
PDL1 light blue
Nucleus, blue

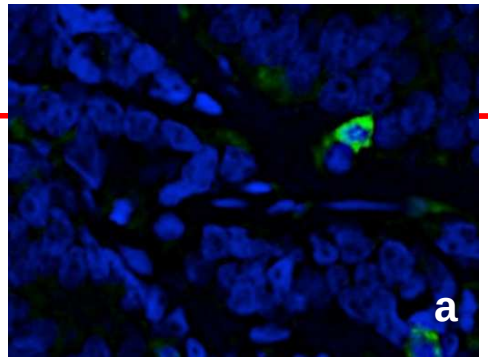

Tumoral area
Prostate Post-treatment
CD4, green
CD8, red
CD68, yellow
PDL1 light blue
Nucleus, blue


CD8
Prostate Post-treatment
CD4, green
CD8, red
CD68, yellow
PDL1 light blue
Nucleus, blue

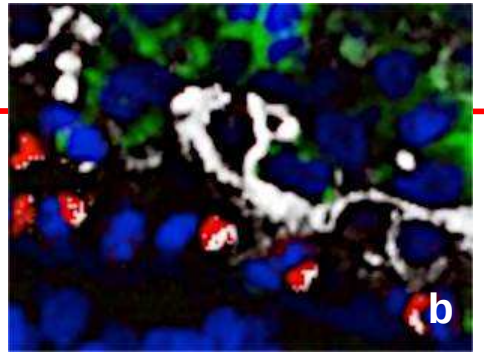

CD8 single staining
PDL1 is predominantly expressed on CD8 cells
Prostate Post-treatment
CD4, green
CD8, red
CD68, yellow
PDL1 light blue
Nucleus, blue

PD-L1 expression

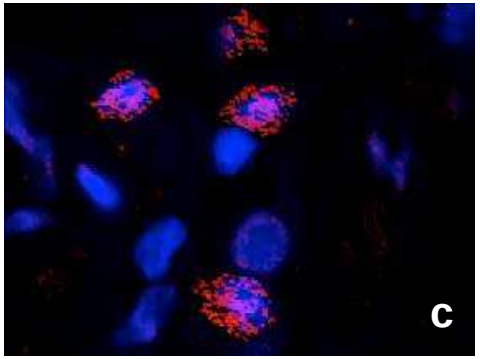
Pre-treatment



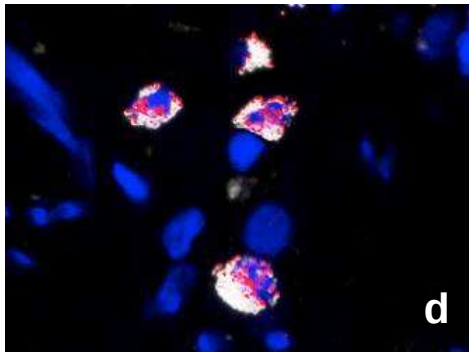
Post-treatment
(Merge all collors)



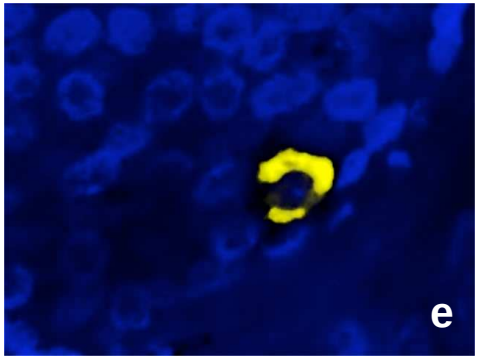
Post-treatment, CD8



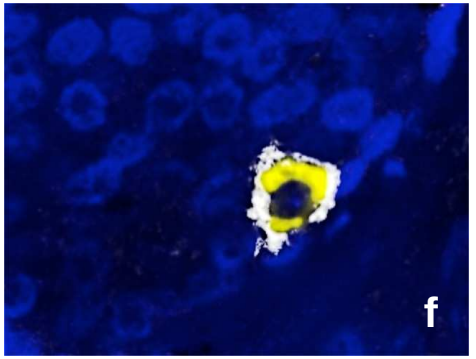
Post-treatment, CD8/PD-L1



Post-treatment, CD68



Post-treatment, CD68/PD-L1

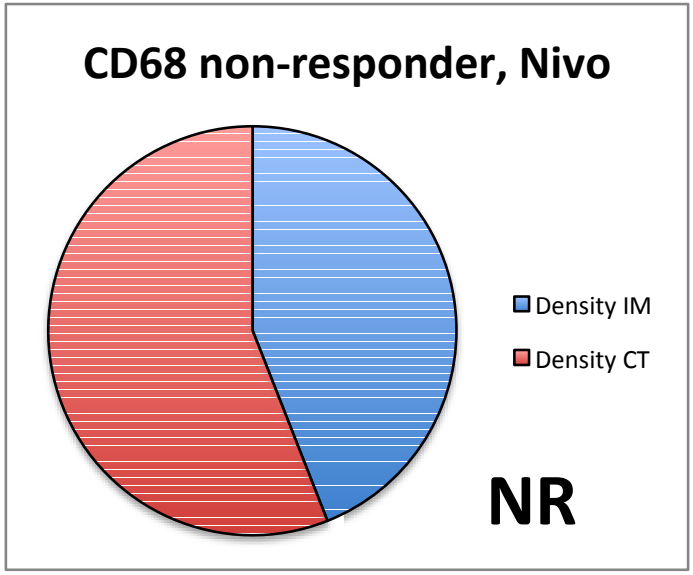


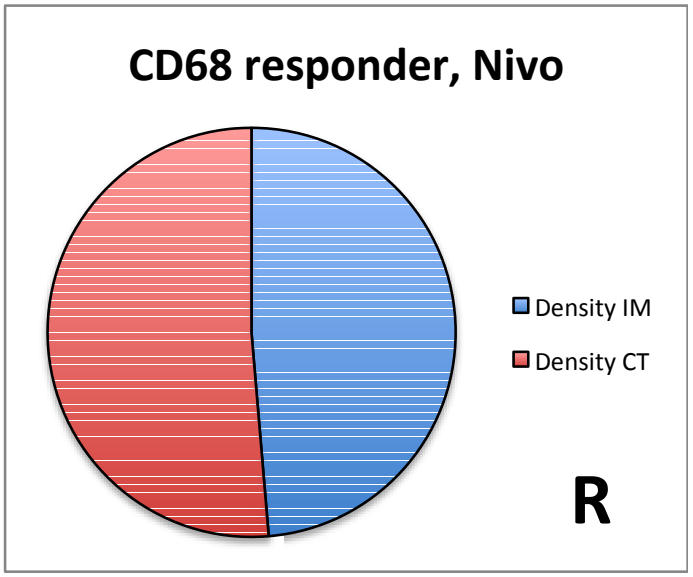
CD4, Green
CD8, Red
CD68, Yellow
PD-L1, White
Nucleus, Blue

SITY OF TEXAS
nderson
er Center
cer History

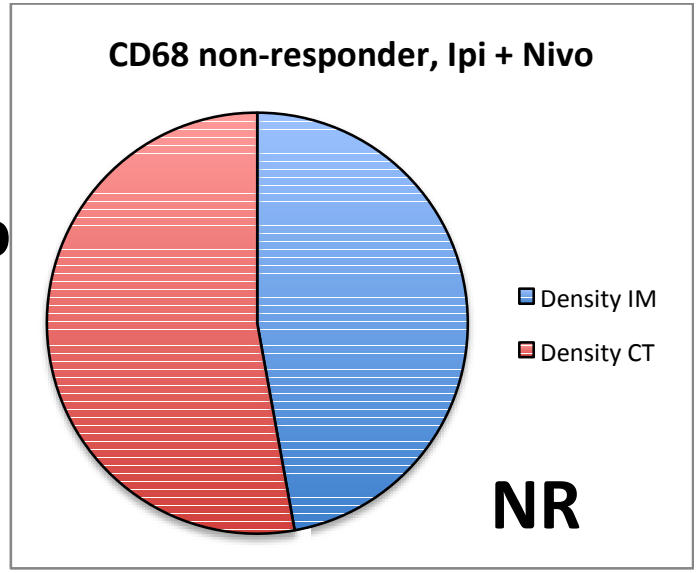
Renal Cell Carcinoma
Evaluating Baseline Tumor Tissues: CD68

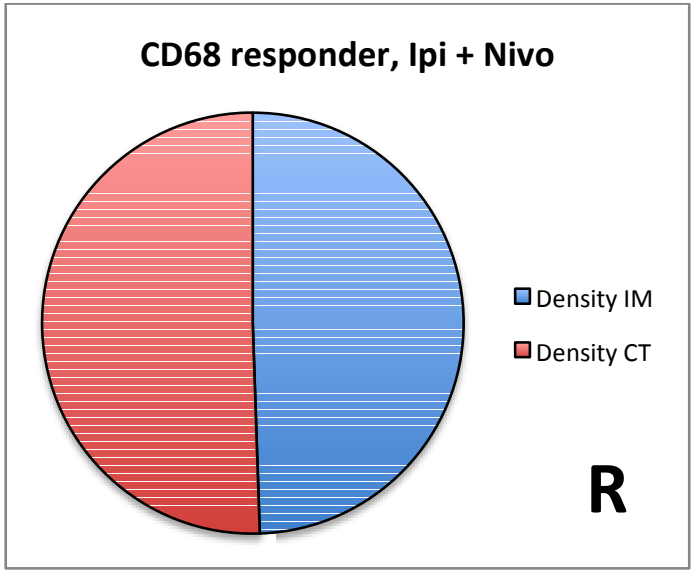
Nivo





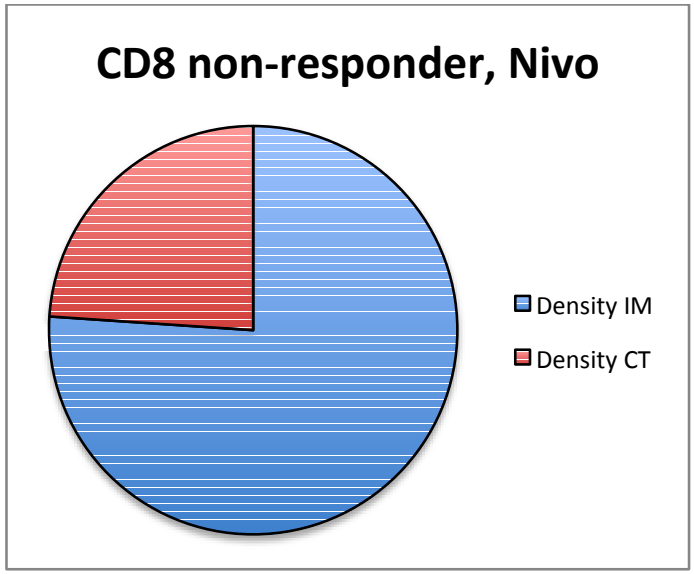
Ipi+Nivo

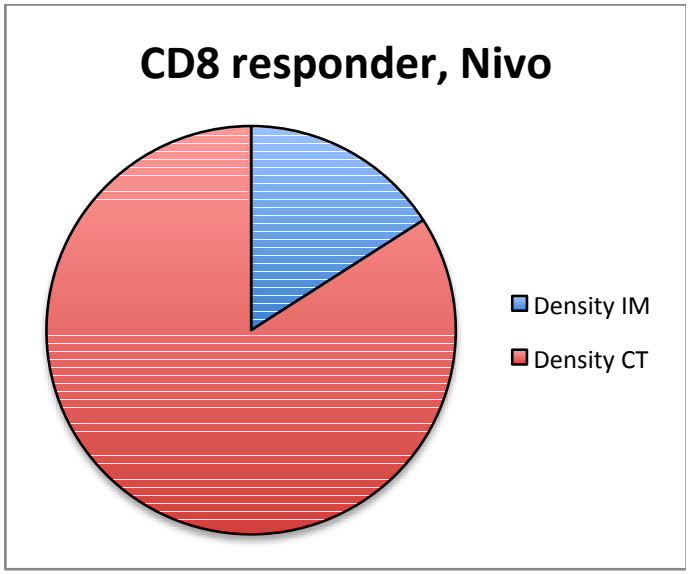




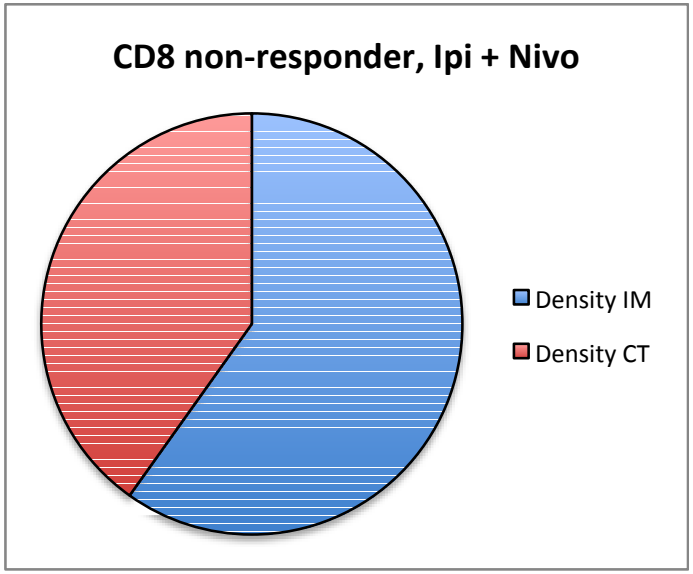
Effect of baseline distribution of CD8 cells and clinical outcome in mRCC

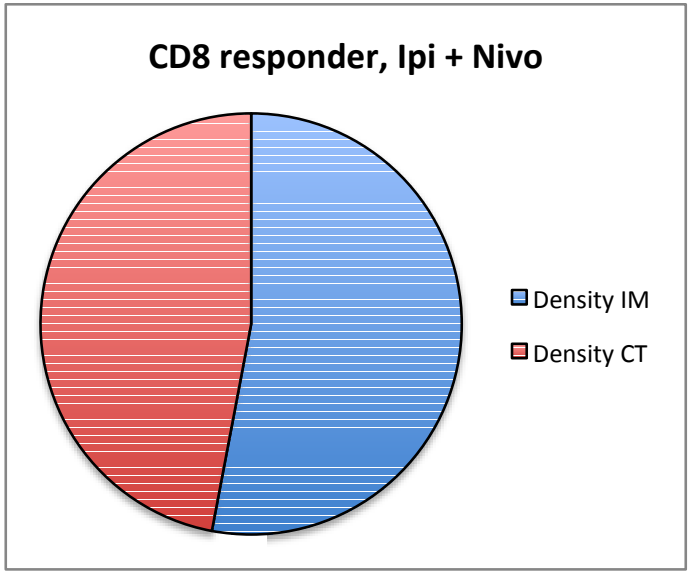
Nivo





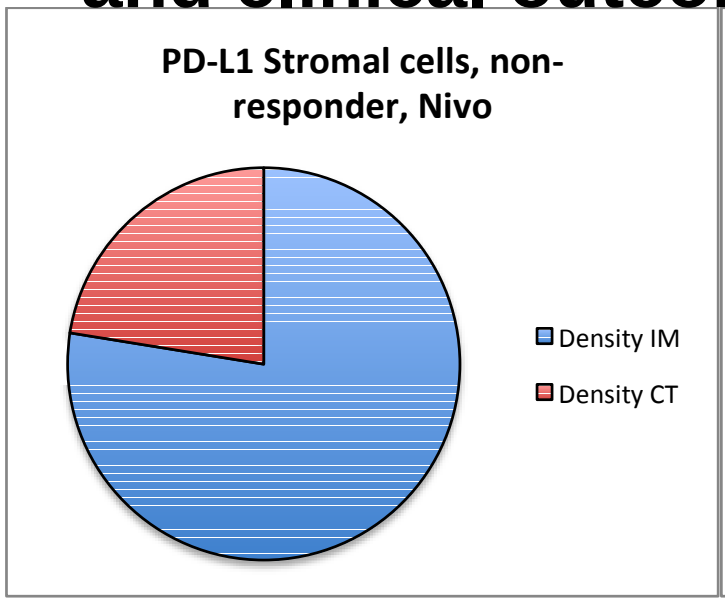
Nivo + Ipi

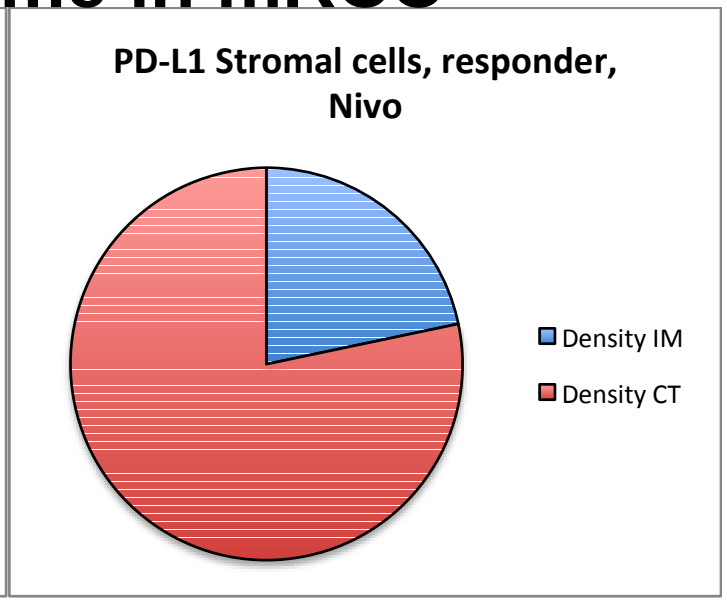




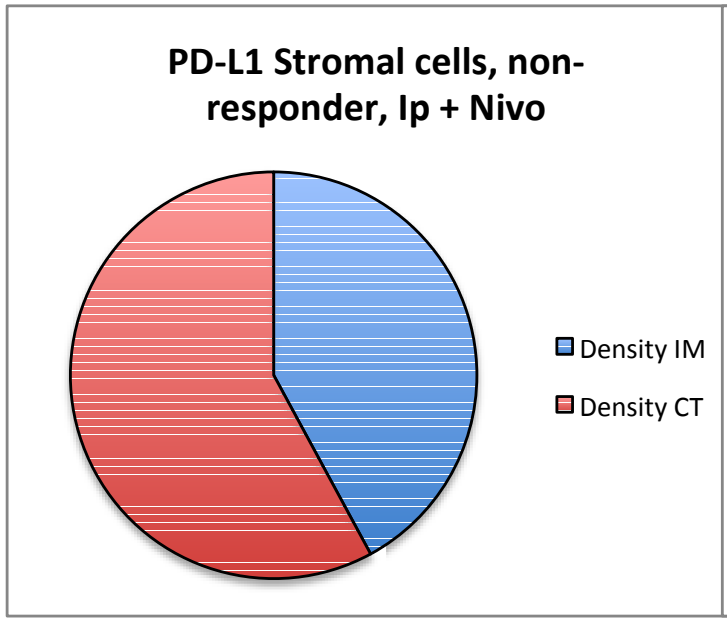
Effect of baseline distribution of PD-L1 expression and clinical outcome in mRCC

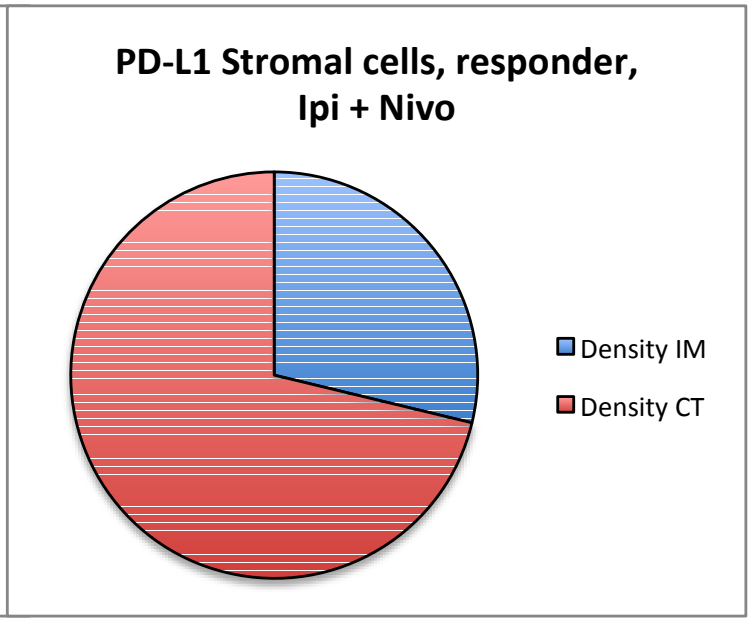
Nivo





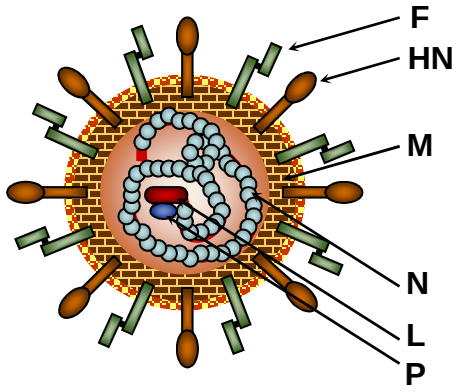
Nivo + Ipi





Engaging the Innate Immune System

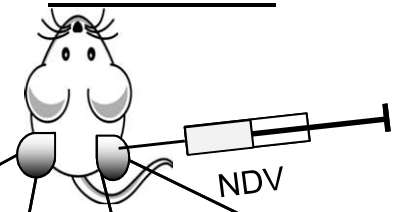
Newcastle disease virus (NDV)as an oncolytic agent



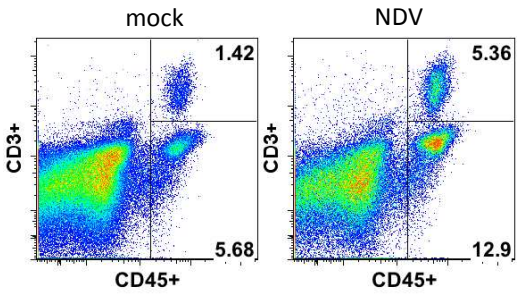
- Does not integrate into human genome
- Humans do not have pre-existing immunity to the virus

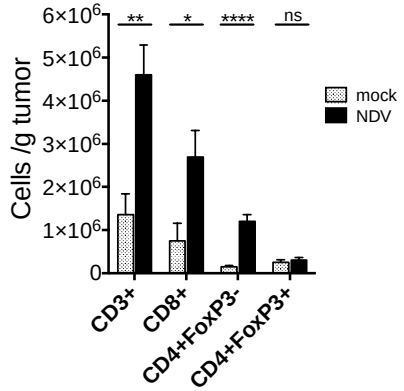
- Readily infects the majority of cancer cells
- Demonstrated safety and clinical benefit in humans
- Viral RNA detected by RIG-I, TLR3, and TLR7 leading to production of Type I interferons that enchance cross priming of T cells.

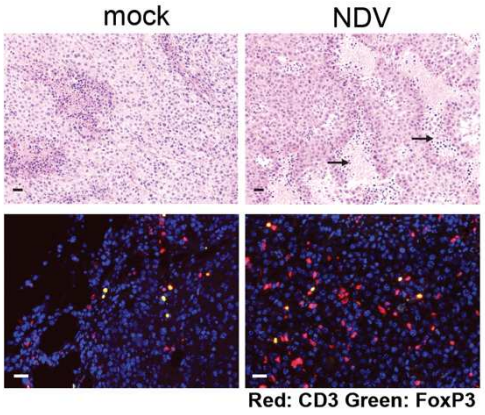
NDV treatment leads to lymphocytic infiltration of B16 and decreases the frequency of Tregs in both virus-injected and distant tumors

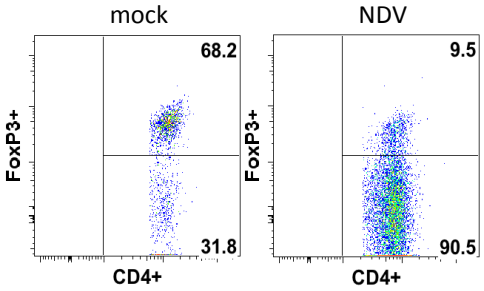


Distant tumor

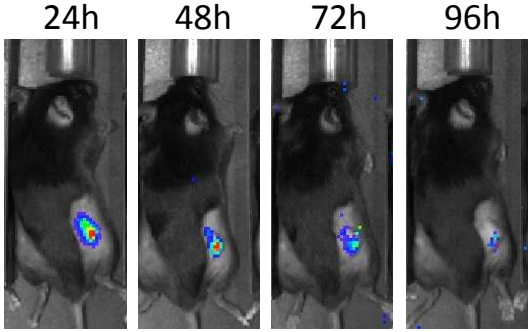




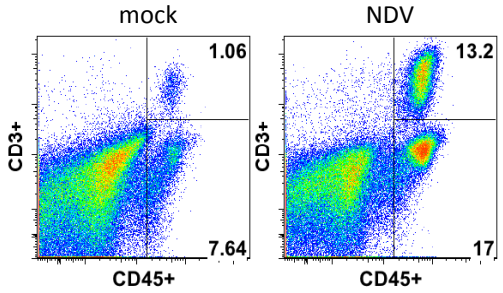




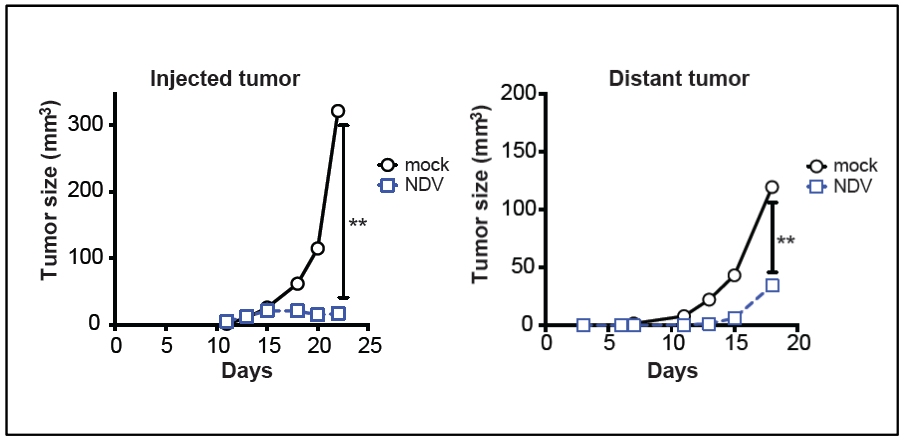
Virus-treated tumor

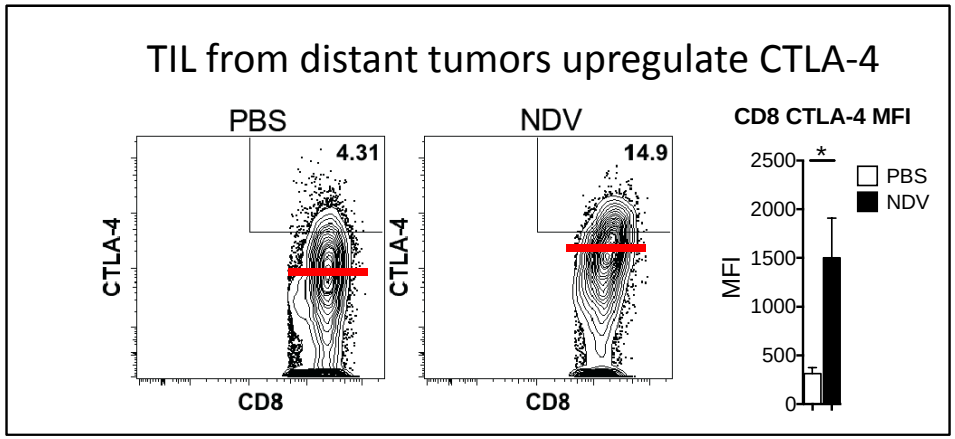


NDV-luciferase replicates only within treated tumors



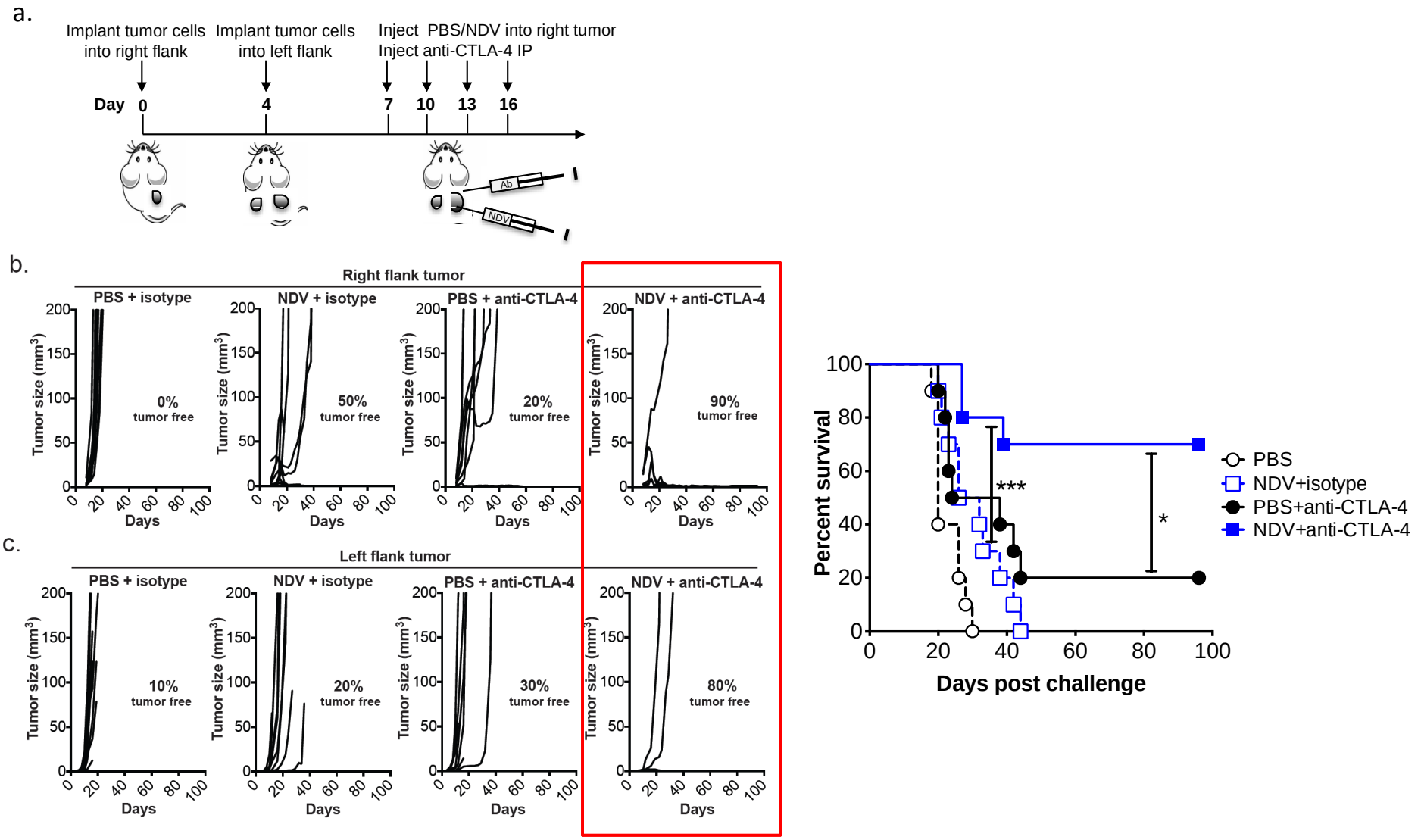
NDV induces distant tumor growth delay, but few complete regressions



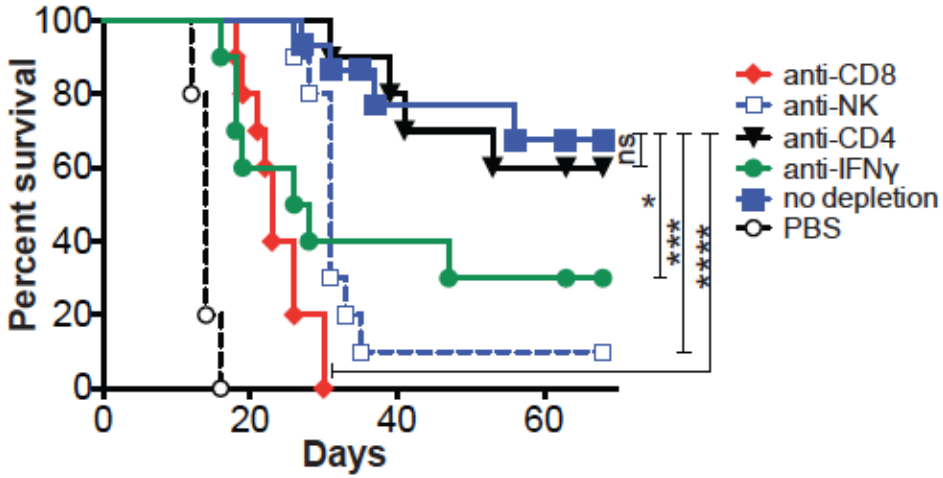


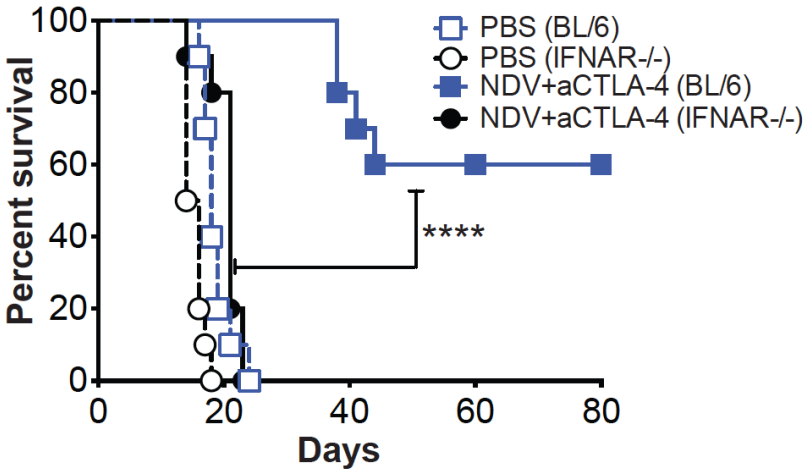
Can NDV-induced tumor inflammatory response increase tumor sensitivity to CTLA-4 blockade?

Combination therapy with NDV and CTLA-4 blockade leads to rejection and long-term survival of injected and distant B16-F10 tumors



Anti-tumor activity of NDV combination therapy is dependent on CD8 cells, NK cells, and type I and II interferons

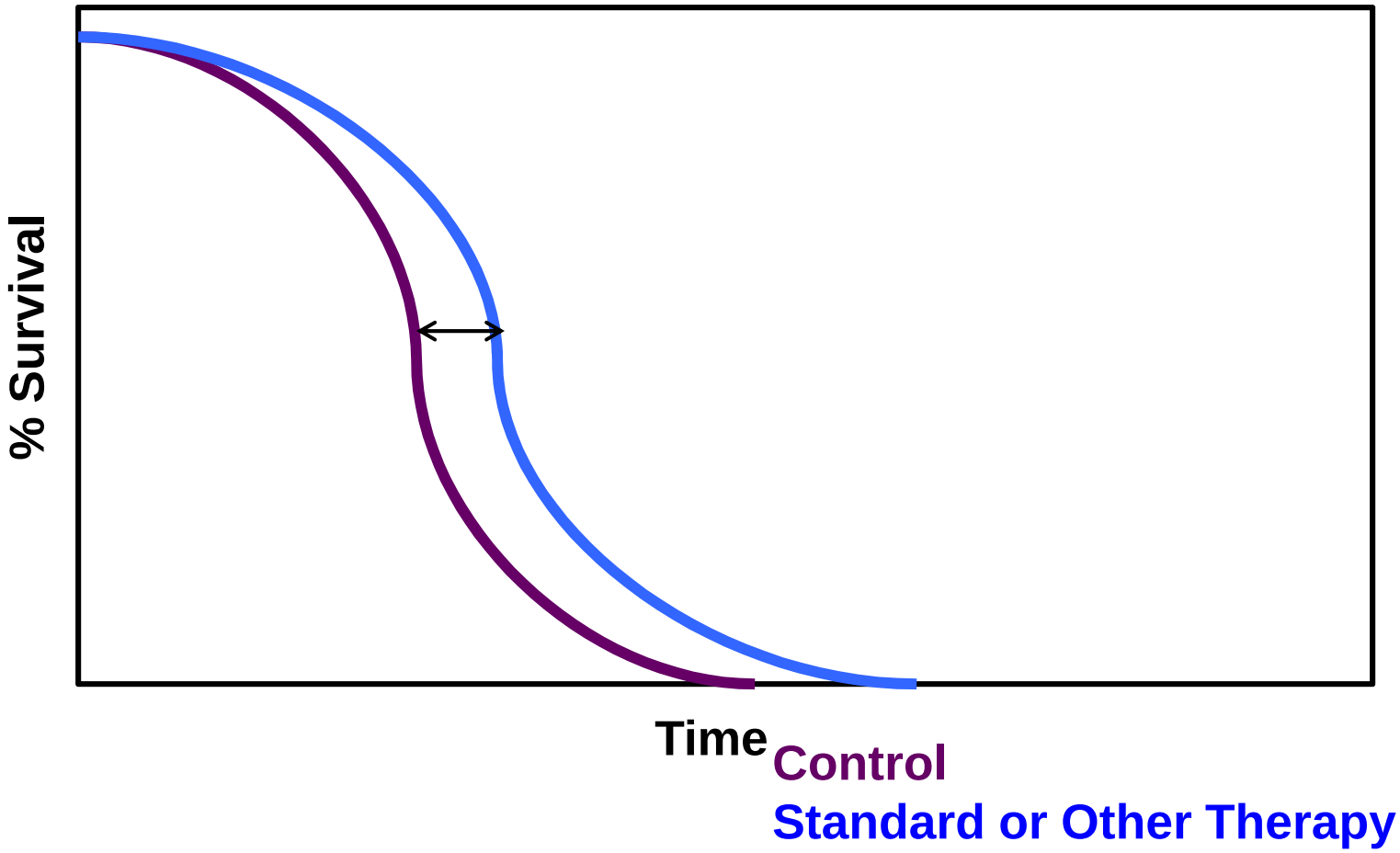




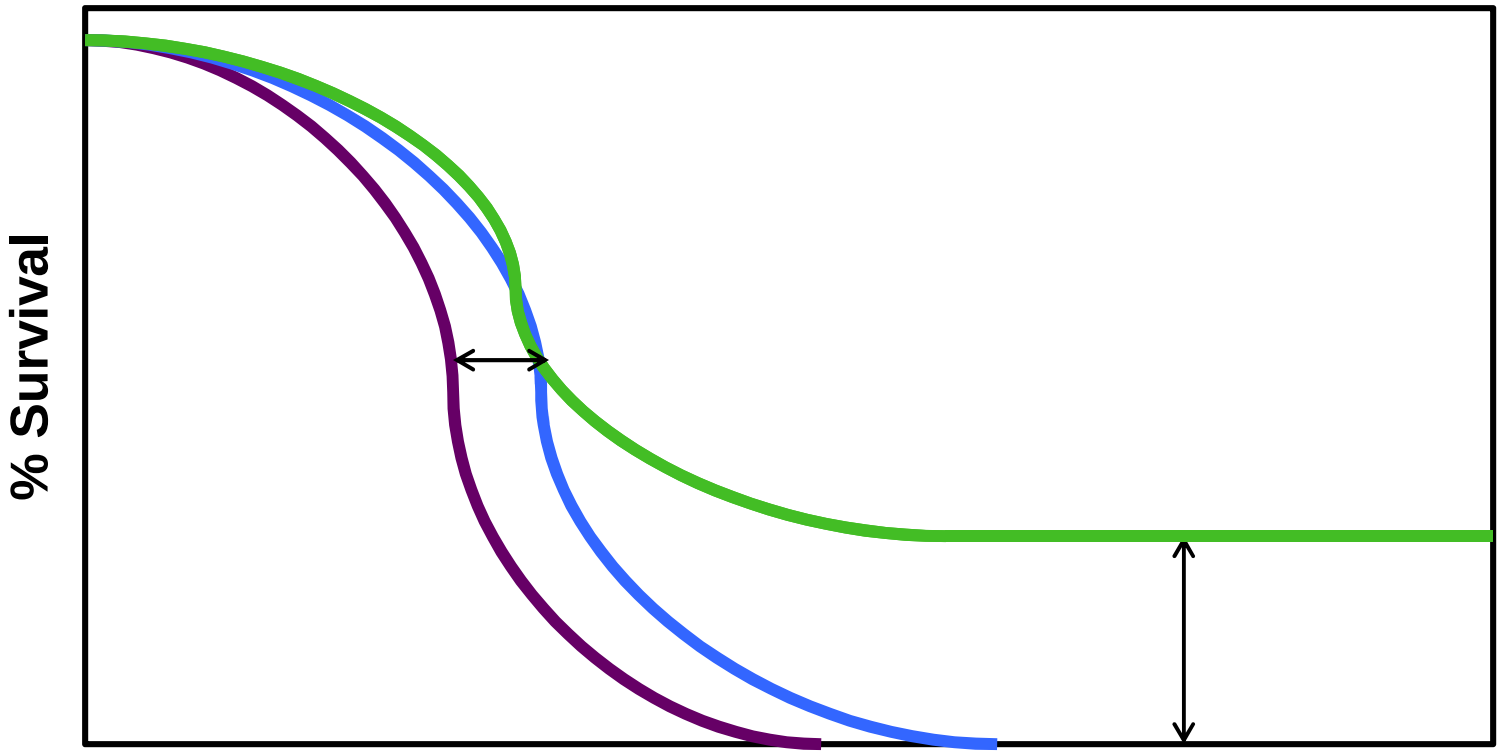
Combinations to enhance immune checkpoint targeting

- Blocking multiple checkpoints (negative and positive)
- Conventional therapies
- Blocking other immunosuppessive factors
- Local ablation
- Enhancing innate immunity
- Genomically targeted therapies
- Vaccines, shared and individual

Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Improving Survival with Combination Therapy