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

Immune Checkpoint Blockade in Cancer Therapy:

New insights into therapeutic mechanisms of anti-CTLA4 and anti-PD-1

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Regental Professor and Chair, Department of Immunology
Executive Director, Immunotherapy Platform
Co-Director, Parker Institute for Cancer Immunotherapy at MDACC
Olga Keith Weiss Distinguished University Chair for Cancer Research

SITC Primer on Tumor Immunology and Immunotherapy

November 10, 2020

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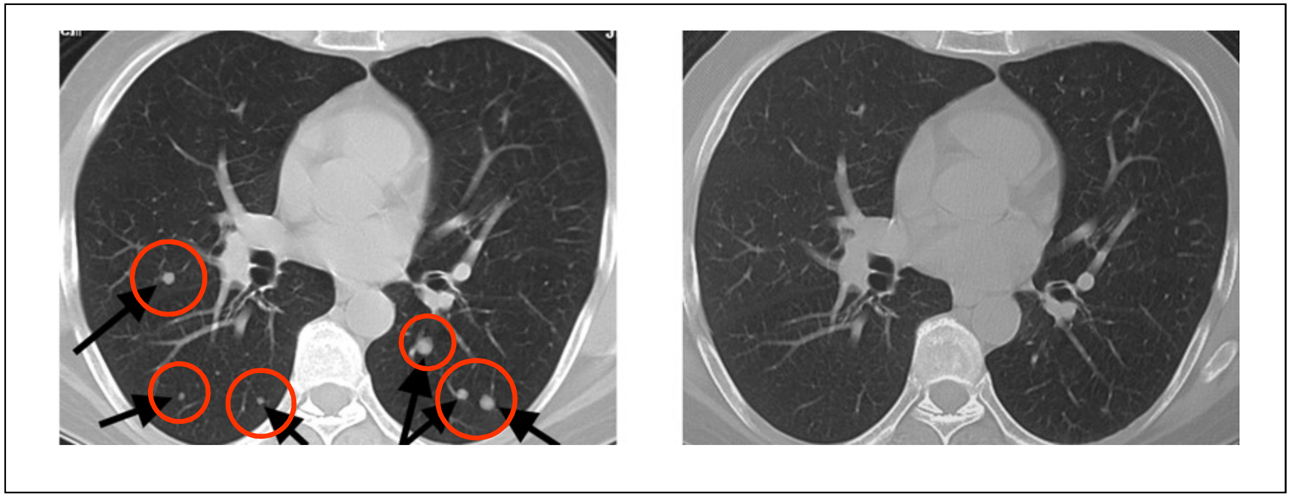
CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

Complete Responder with Anti-CTLA-4: Metastatic Melanoma

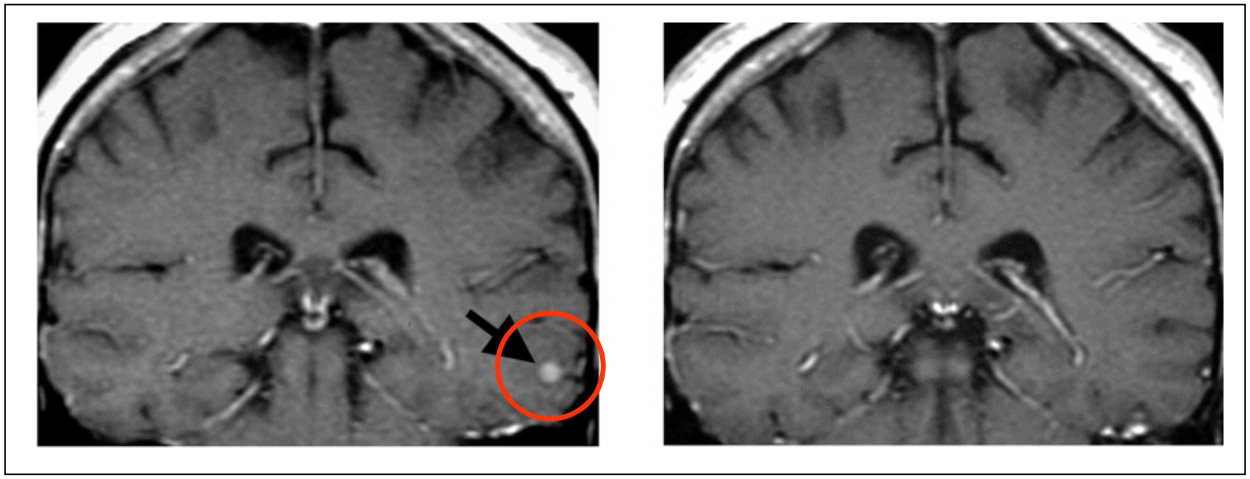
Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.



2004

Anti-CTLA-4 immunotherapy treats brain metastases

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

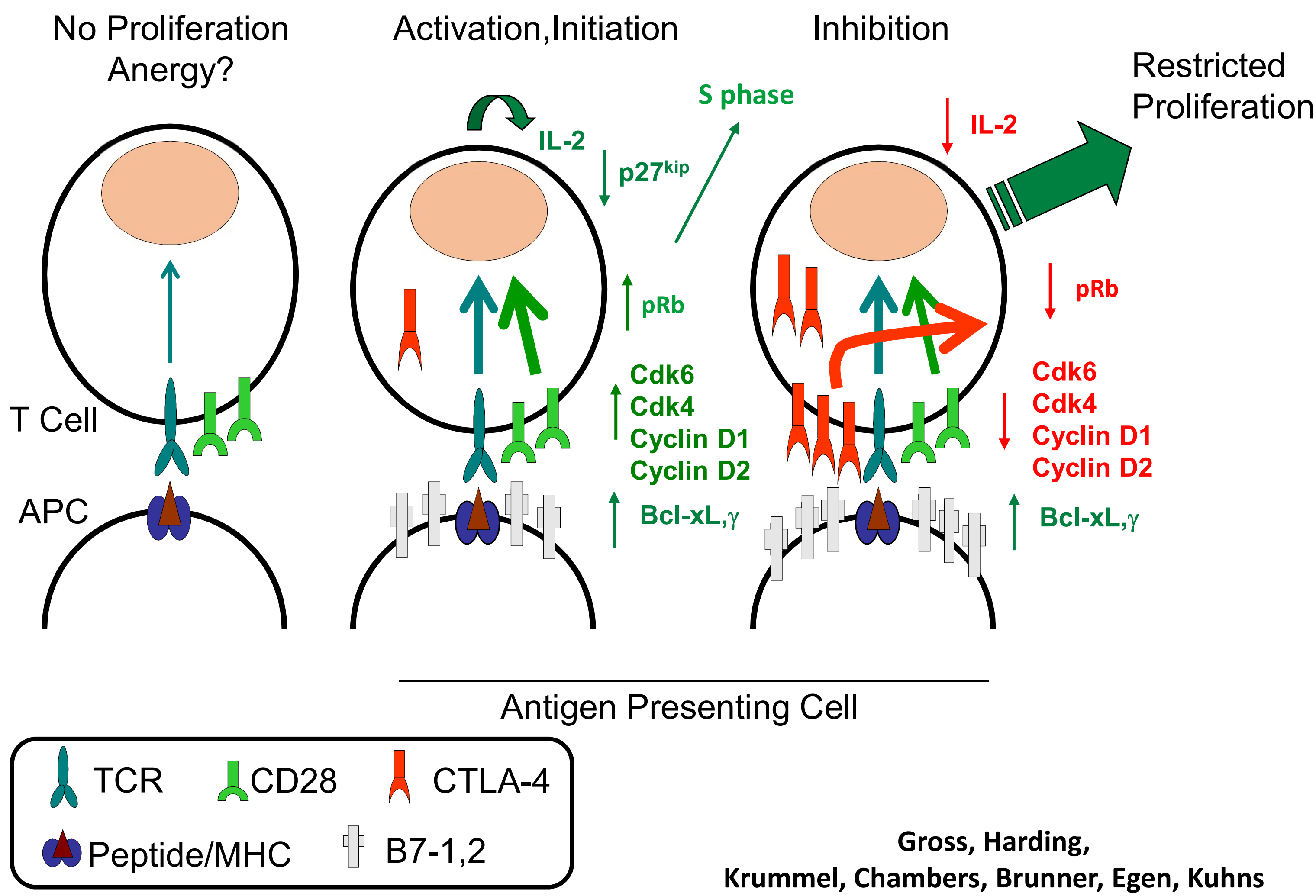


2004

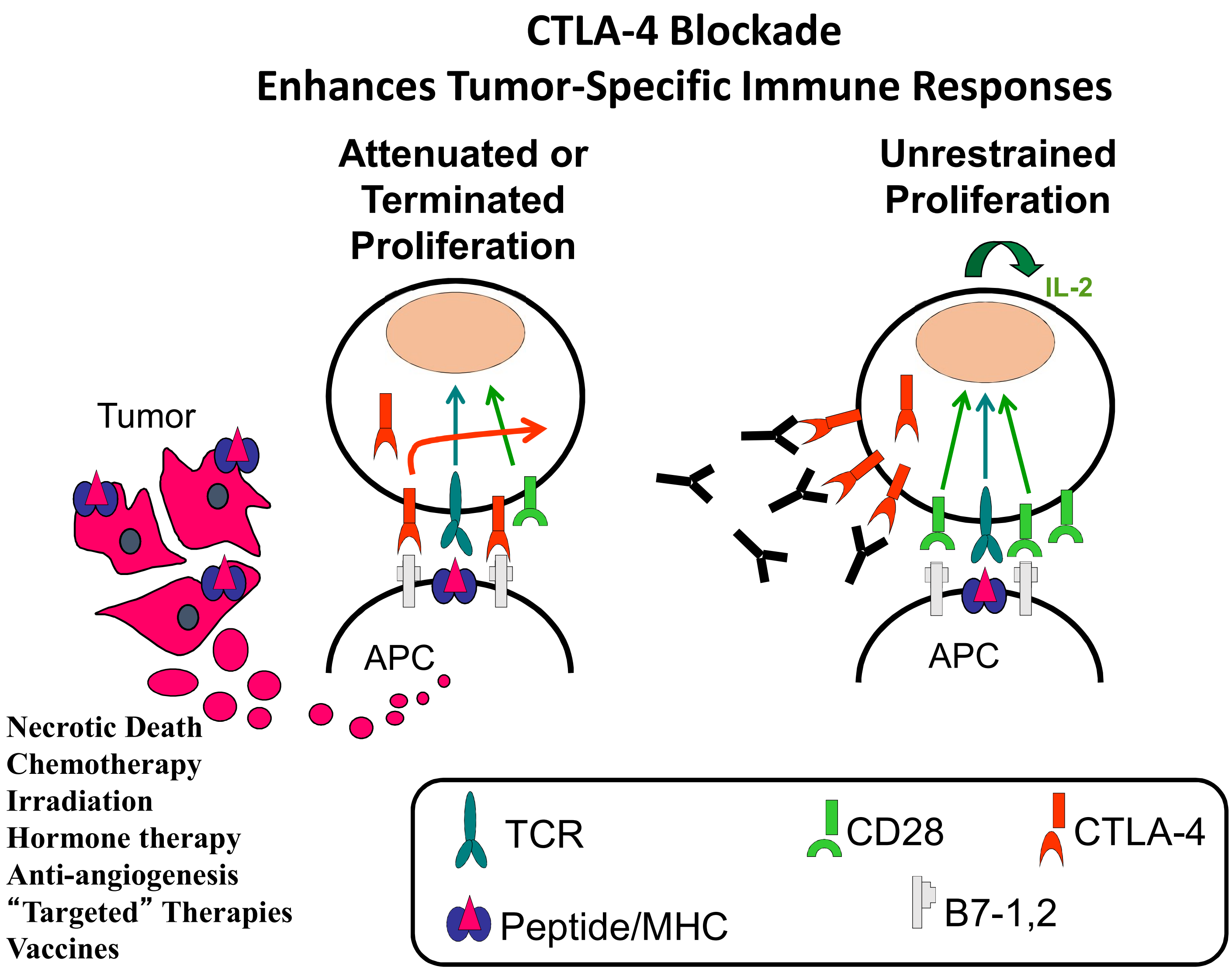

2016

Dynamic Integration of TCR and Costimulatory Signals

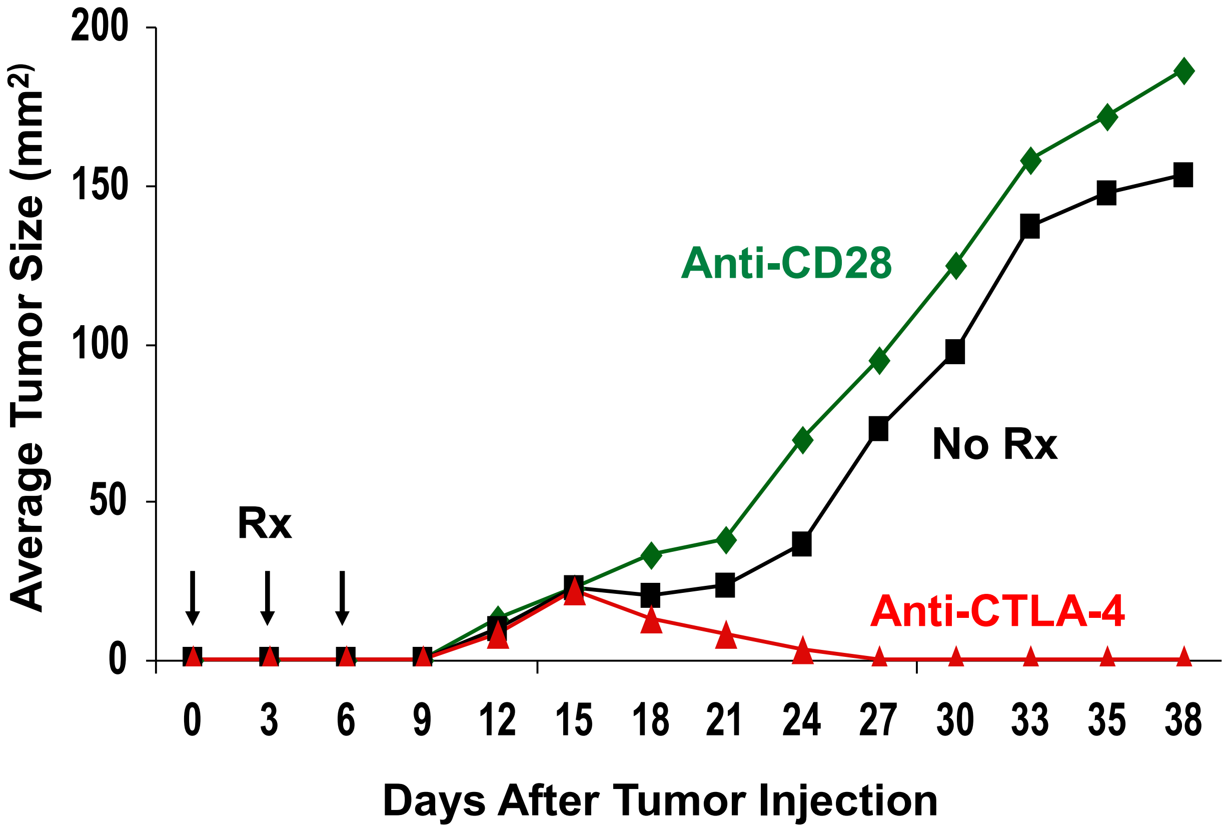
circa 1996



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


CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses
Attenuated or Terminated Proliferation
Unrestrained Proliferation
IL-2
Tumor
APC
APC
Necrotic Death
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
"Targeted" Therapies
Vaccines
TCR
CD28
CTLA-4
Peptide/MHC
B7-1,2

Anti-CTLA-4 Induces Regression of Transplantable Murine Tumor



Leach et al *Science* 1996

Ipilimumab

(Medarex, Bristol-Myers Squibb)

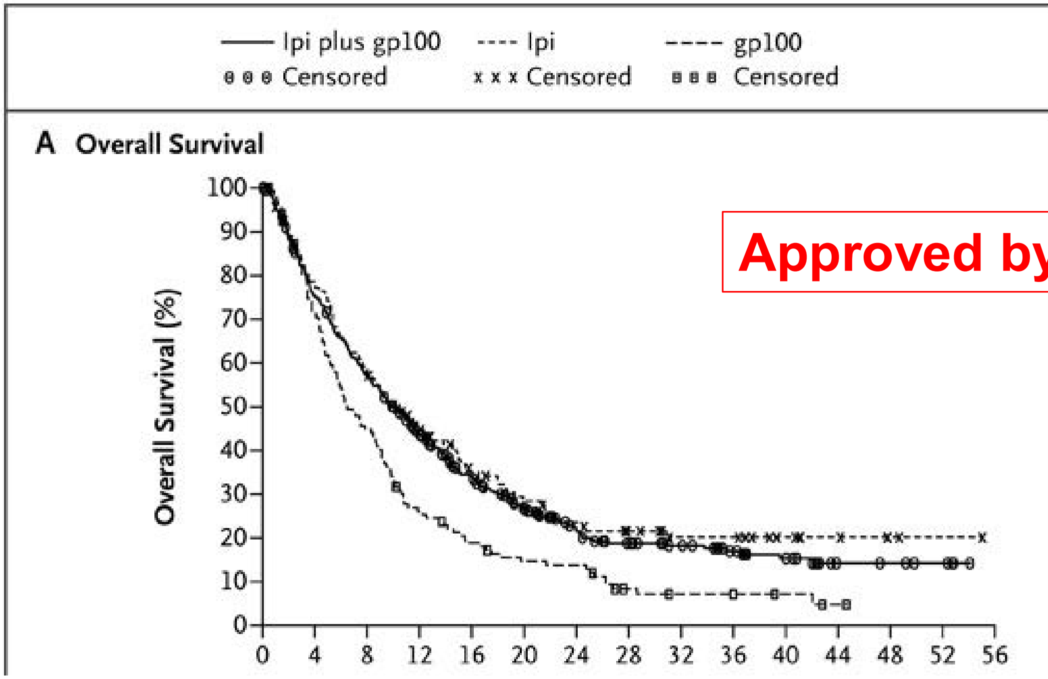
Fully human antibody to CTLA-4

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

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

Very rare: Type I diabetes, myocarditis

Survival Data: Phase III clinical trial

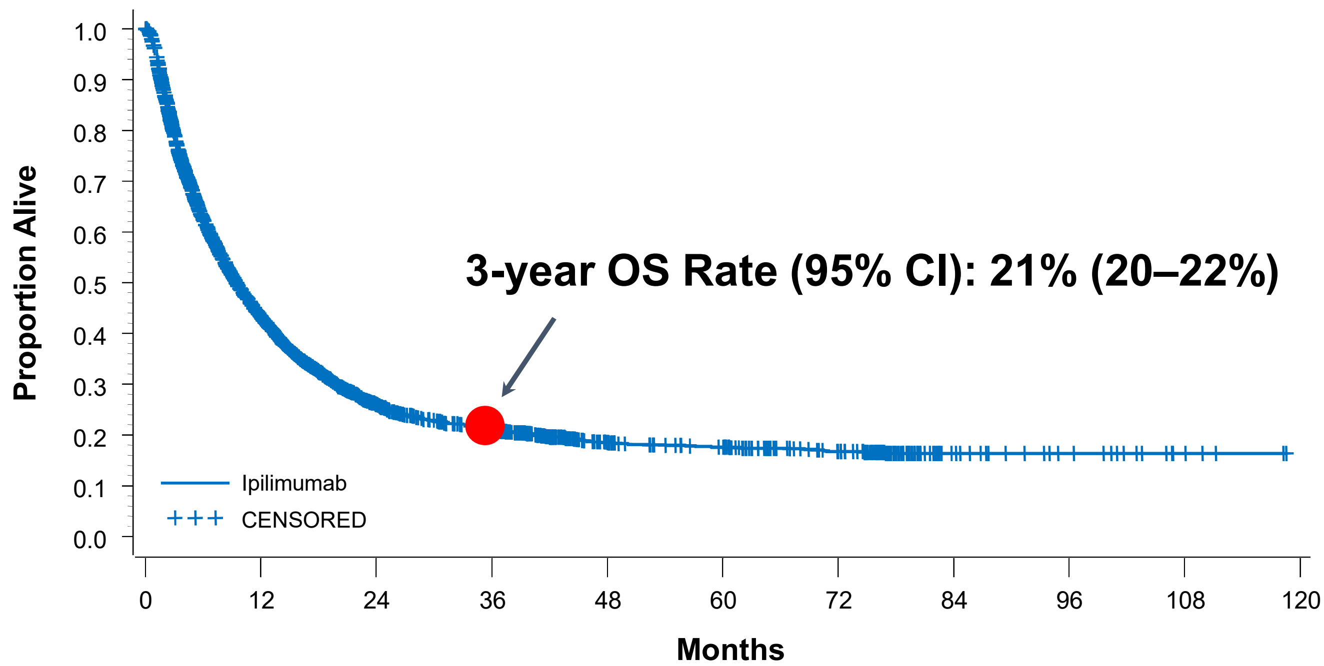


Approved by FDA 2011

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

Ipilimumab (anti-CTLA-4) in Metastatic Melanoma

(pooled data from 4846 patients)

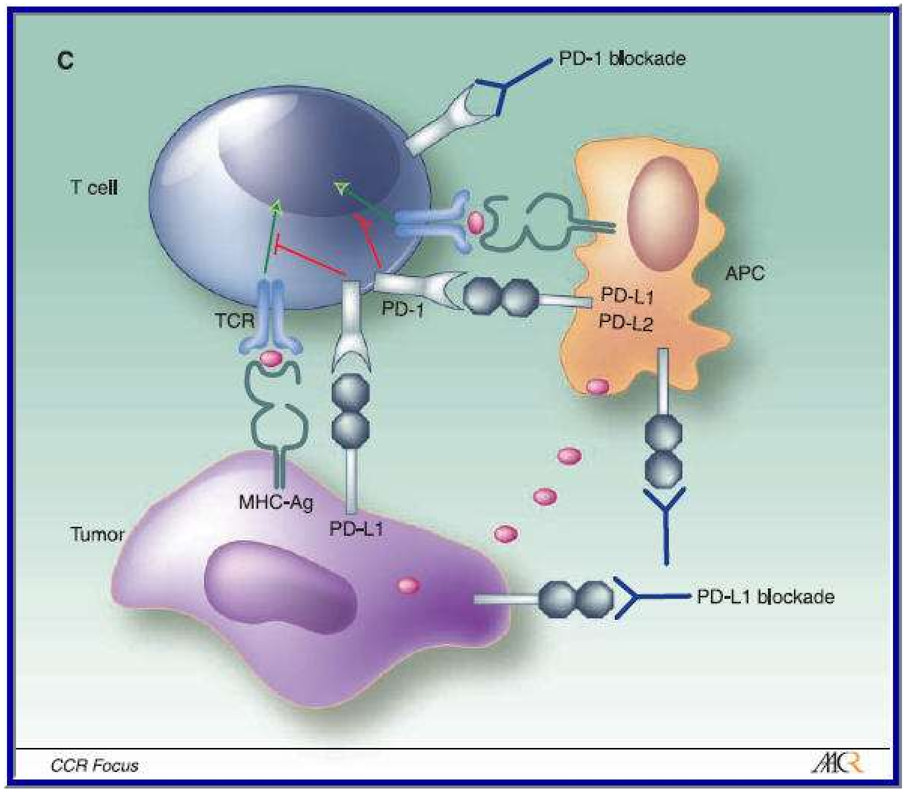


Patients at Risk

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

Schadendorf JCO 2015

Programmed Death 1
(PD-1)



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:

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

Clinical responses can occur after prior ICT failure

Ipilimumab therapy ➡ Progression ➡ Nivolumab Therapy
38% ORR

Nivolumab therapy ➡ Progression ➡ Ipilimumab Therapy
56% ORR

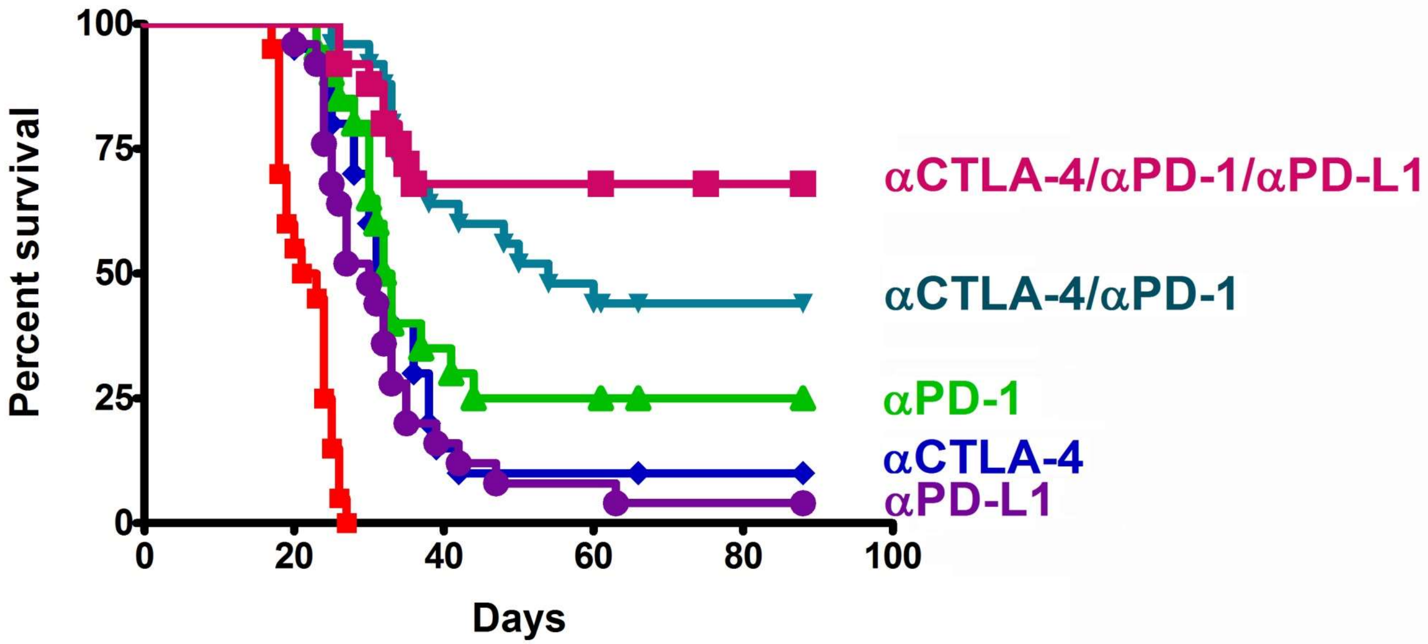
Weber et al. *Lancet Oncology* 2015
Weber et al. *Lancet Oncology* 2016

Where do we go from here?

Combinations

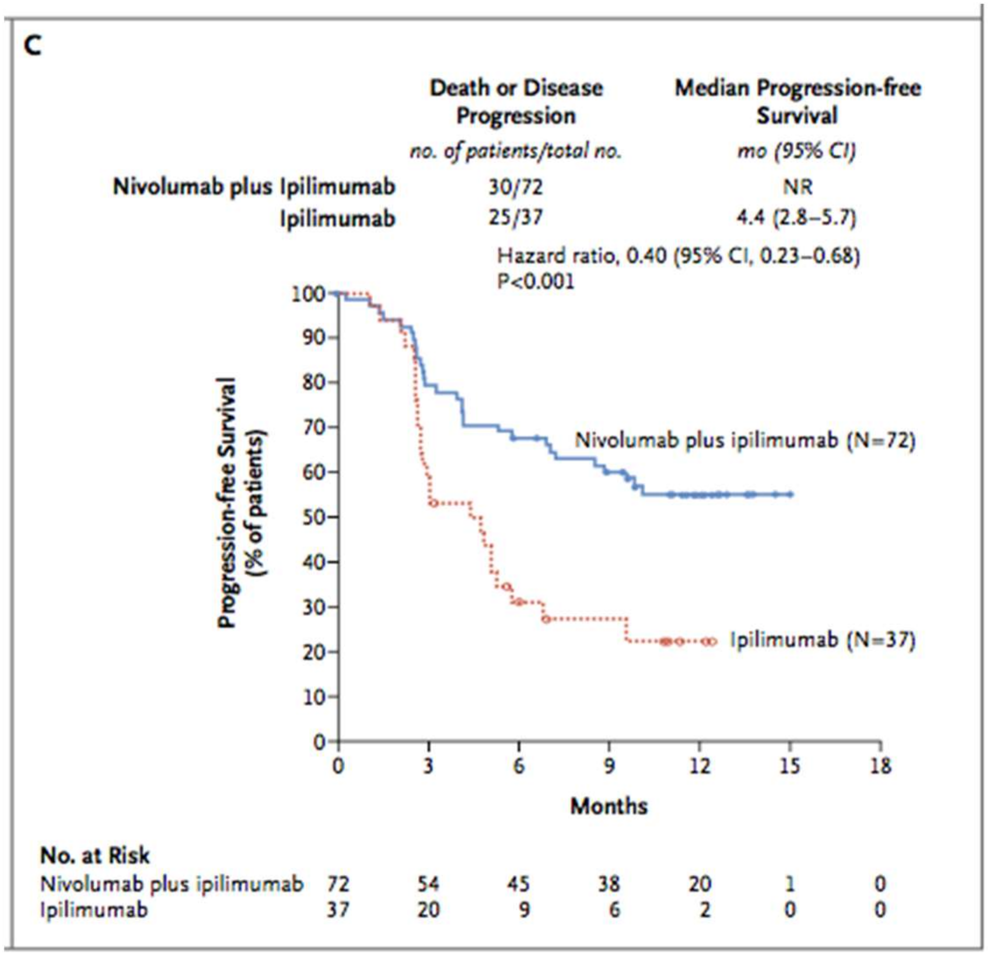
Combination blockade of CTLA-4 and PD-1 pathways promotes rejection of B16 melanoma

Combination FVAX (B16-Flt3-ligand)+ antibody



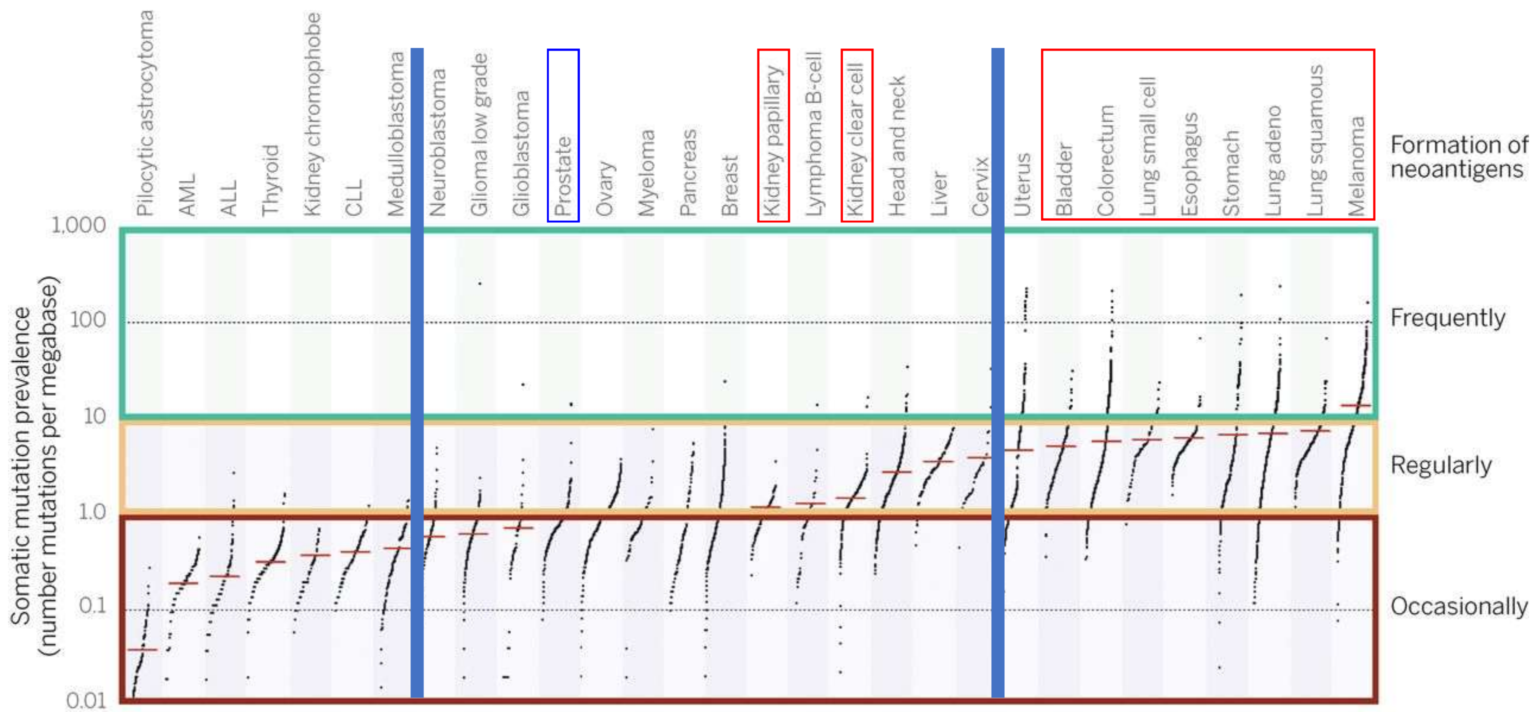
Curran et al PNAS 2011

Ipi/Nivo vs. Ipi in Metastatic Melanoma



Hodi NEJM 2015

Frequency of somatic mutations across cancer types



Modified from Schumacher TN and Schreiber RD, *Science,* 2015

FDA-Approvals of Immune Checkpoint Inhibitors
(by cancer type)

Melanoma
- Ipilimumab (2011)
- Nivolumab (2014)
- Ipilimumab + Nivolumab (2015)
- Pembrolizumab (2019)

Lung Carcinoma
- Nivolumab (2015)
- Pembrolizumab (2015)
- Atezolizumab (2016)
- Durvalumab (2018)

Renal Cell Carcinoma
- Nivolumab (2015)
- Ipilimumab + Nivolumab (2018)
- Avelumab (2019)

Colorectal Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2017)
- Ipilimumab + Nivolumab (2018)

Head and Neck Squamous Cell Carcinoma
- Nivolumab (2016)
- Pembrolizumab (2016)

Lymphoma
- Nivolumab (2016)
- Pembrolizumab (2017)

Hepatocellular Carcinoma
- Nivolumab (2017)
- Pembrolizumab (2018)

Merkel Cell Carcinoma
- Avelumab (2017)
- Pembrolizumab (2018)

Gastric/Gastroesophageal Adenocarcinoma
- Pembrolizumab (2017)

Cervical Carcinoma
- Pembrolizumab (2018)

Breast Carcinoma
- Atezolizumab (2019)

Cutaneous Squamous Cell Carcinoma
- Cemiplimab (2018)

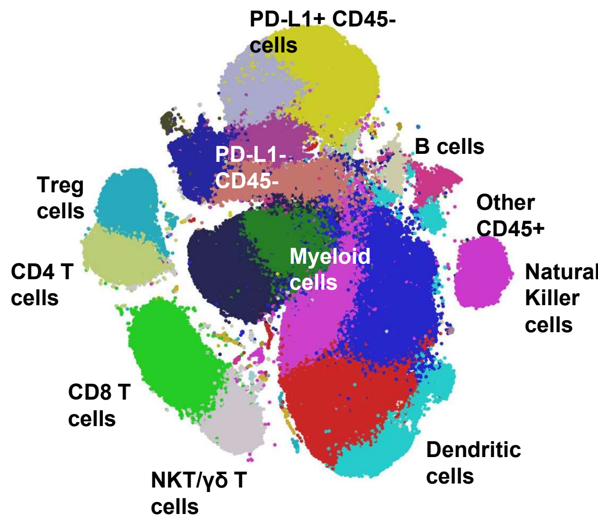
Esophageal Carcinoma
- Pembrolizumab (2019)

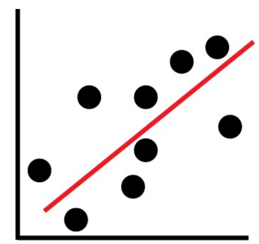
Uterine Carcinoma
- Pembrolizumab (2019)

Urothelial Carcinoma
- Atezolizumab (2016)
- Avelumab (2017)
- Durvalumab (2017)
- Nivolumab (2017)
- Pembrolizumab (2017)

Anti-CTLA-4	Anti-PD-1
• Hard wired • Targets CD28 pathway • Works during priming • Expands clonal diversity • Responses often slow • Primarily effects CD4 T cells • Can move T cells into “cold” tumors • Adverse events relatively frequent • Disease recurrence after response rare	• Induced resistance • Targets TCR pathway • Works on differentiated T cells • Does not expand clonal diversity • Responses usually rapid • Only effects CD8 T cells • Does not move T cells into tumors • Adverse events less frequent • Disease recurrence after response significant

Can we identify checkpoint blockade responsive T cell populations?





CyTOF analysis of murine TILs (43 Parameters)

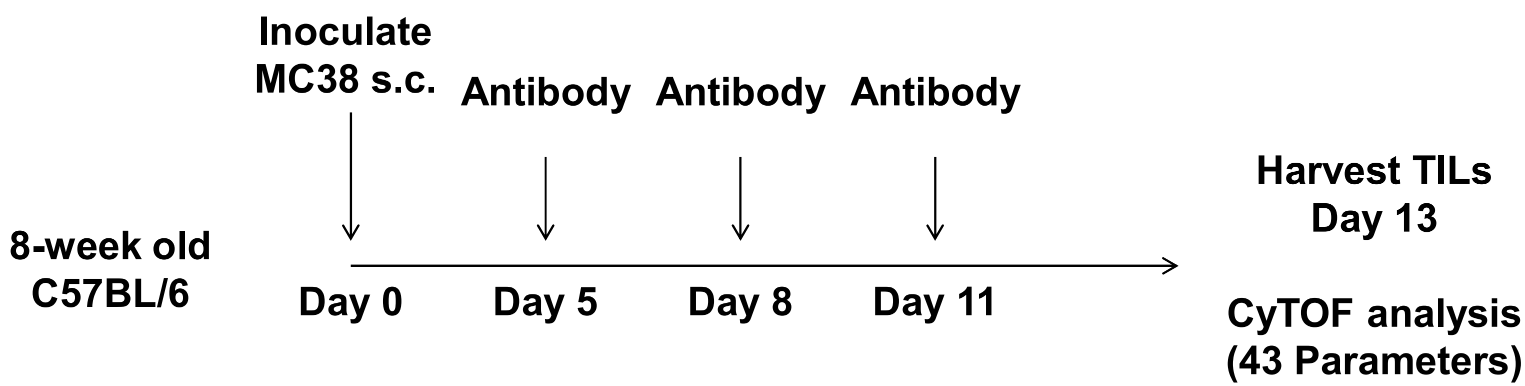
+/- checkpoint blockade

Unsupervised population identification

Identify associations with treatment and outcome

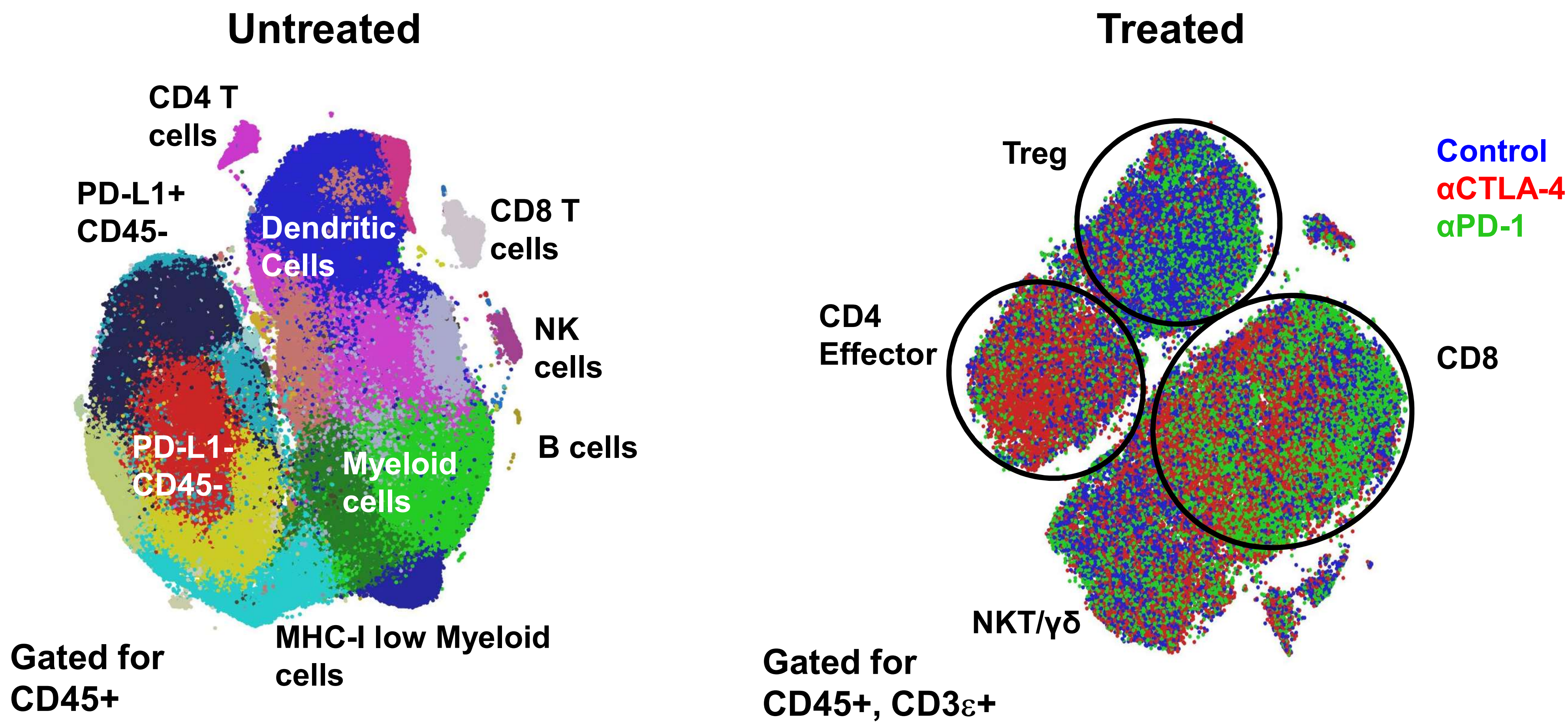
Spencer Wei

Mass cytometry analysis of MC38 TILs

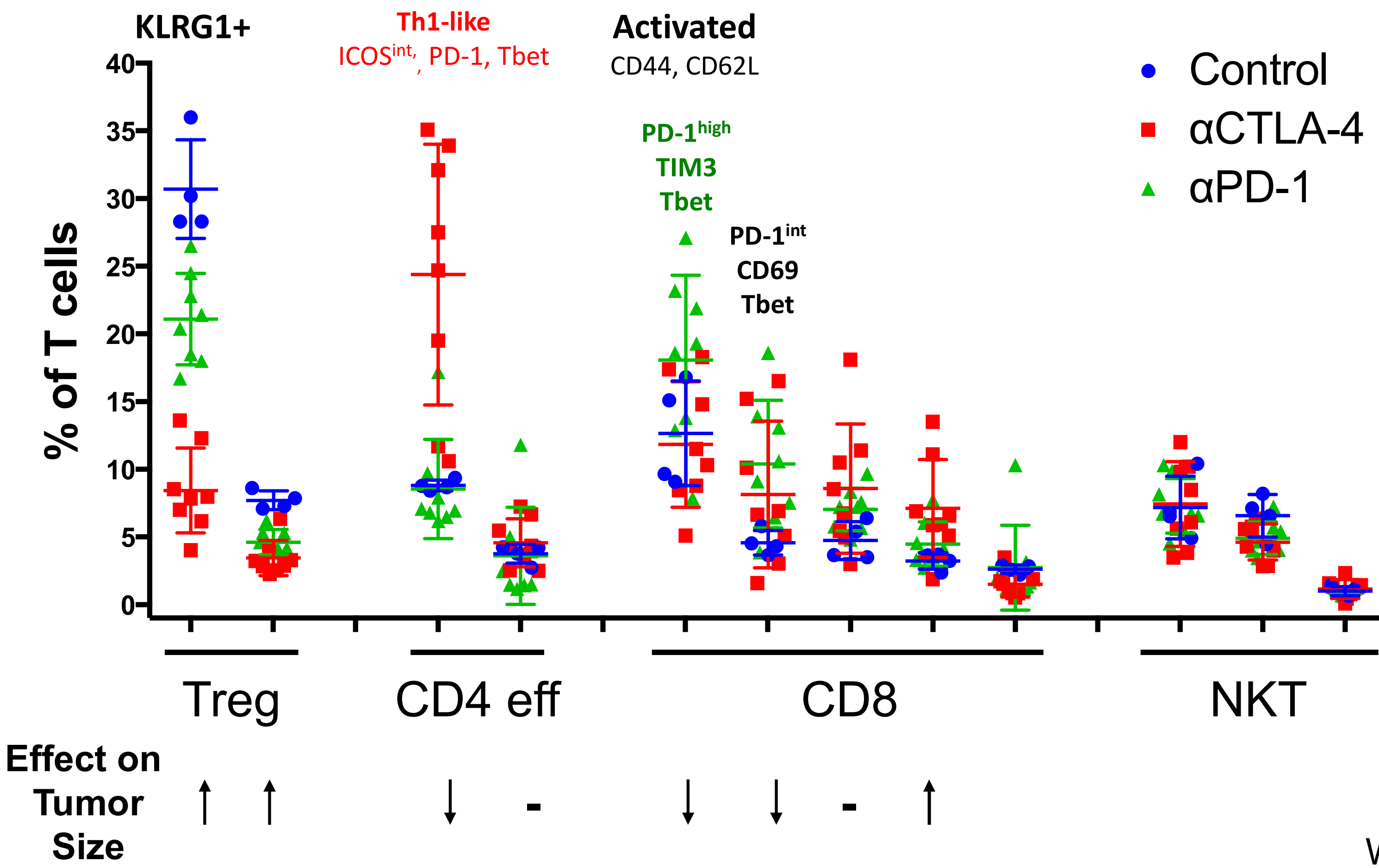


Wei et al *Cell* 2017

Mass Cytometry Analysis of MC38



Checkpoint blockade modulates MC38 infiltrating T cell population frequencies



Wei et al *Cell* 2017

CELLULAR TARGETS OF CHECKPOINT BLOCKADE

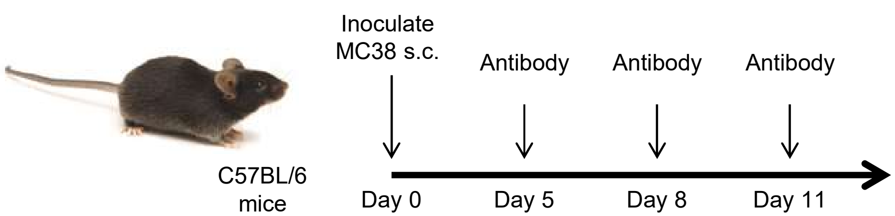
Monotherapy:

- CTLA-4
  - CD4 ICOS+ Tbet+Th1-like Effector
  - CD8 Tbet+ EOMES+ Effector
- PD-1
  - CD8 Tbet+ EOMES+ Effector
  - CD8 Tbet+ PD-1++ Lag2++ Tim3++ “Exhausted”

How do the cellular mechanisms of checkpoint blockade by the combination of CTLA-4 and PD-1 interact?

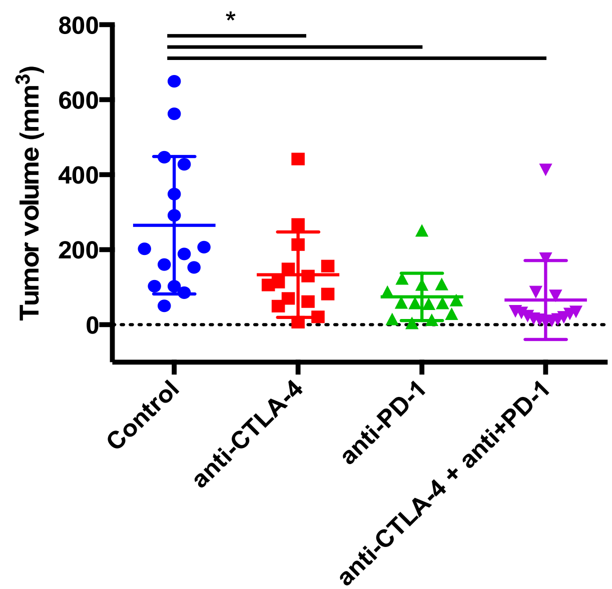
$$A + B = AB \quad \textit{or} \quad A + B = C$$

Mass cytometry analysis of MC38 TILs



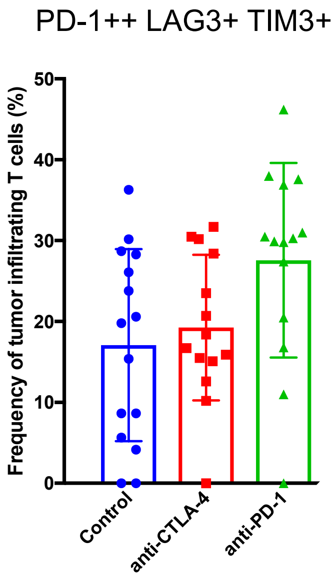
Harvest TILs Day 13

CyTOF analysis
(43 Parameters)



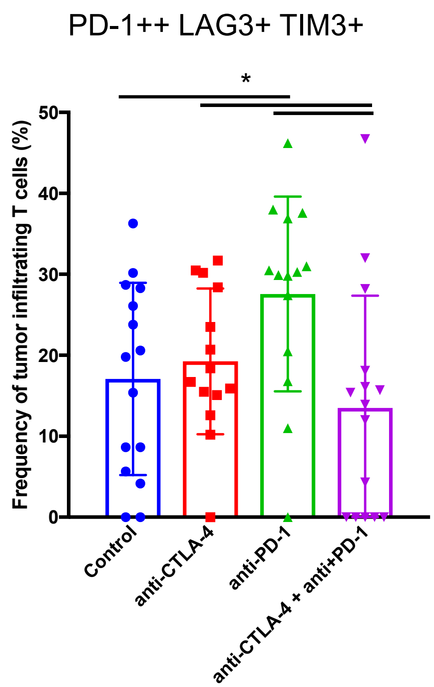
Wei et al *PNAS* 2019

Expansion of phenotypically exhausted CD8 T cells



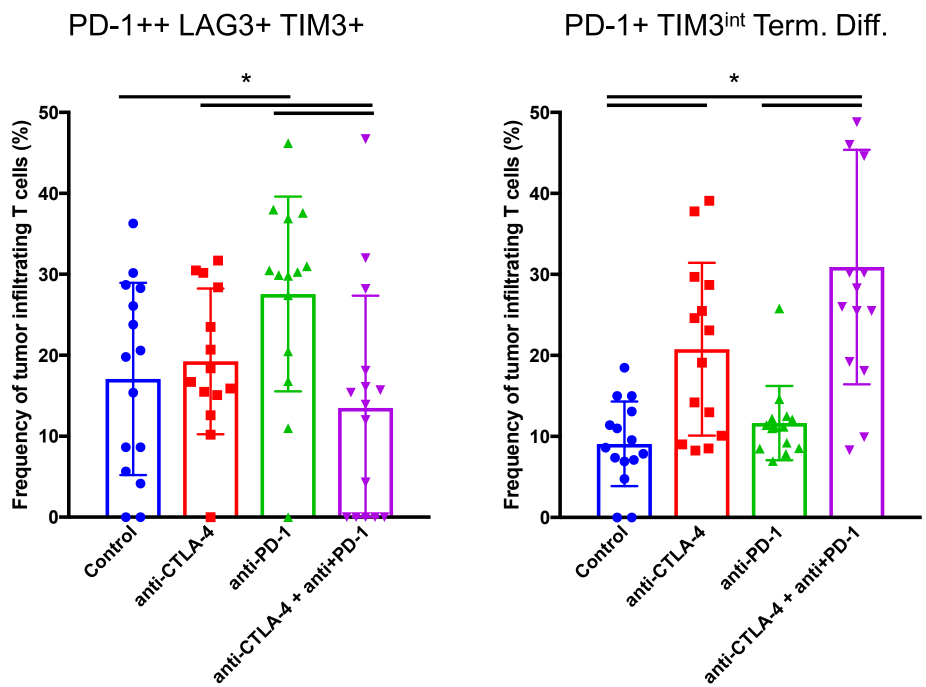
Wei et al *PNAS* 2019

Combination therapy differentially affects CD8 subsets



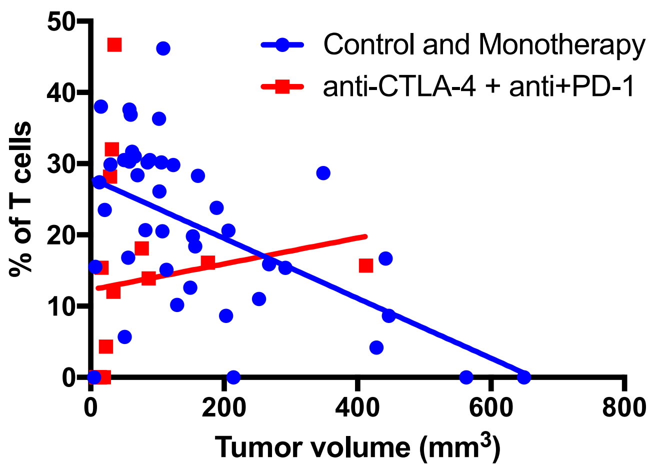
Wei et al *PNAS* 2019

Combination therapy differentially affects CD8 subsets



Wei et al in press *PNAS* 2019

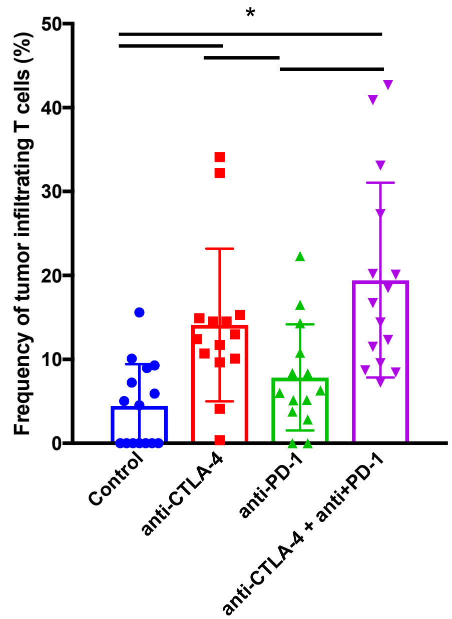
Do phenotypically exhausted CD8 T cells have
the same function in the context of combination therapy?



Wei et al in press *PNAS* 2019

Expansion of Th1-like CD4 T cells following combination therapy

PD-1^{+} ICOS^{int} TBET^{+}
Th1-like CD4 effector



Cellular Targets of Checkpoint Blaockade

Monotherapy:

- CTLA-4
  - CD4 ICOS+ Tbet+Th1-like Effector
  - CD8 Tbet+ EOMES+ KLRG-1+ Effector
- PD-1
  - CD8 Tbet+ EOMES+ KLRG-1+ Effector
  - CD8 Tbet+ PD-1++ Lag2++ Tim3++ “Exhausted”

Combination Therapy:

- CD4 ICOS+ Tbet+Th1-like Effector
- CD8 Tbet+ EOMES+ KLRG-1+ Effector

Cellular Targets of Checkpoint Blockade

What happens to “Exhausted” ($PD1^{hi}Lag3^{hi}Tim3^{hi}$) CD8 cells in presence of combination blockade of PD-1 and CTLA-4?

- Converted into CD8 effector T cells? *Unlikely, epigenetically fixed*
- Exhaustion of effectors prevented in presence of continued CD28 costimulation allowed by CTLA-4 blockade?

Combinations to enhance immune checkpoint targeting resulting in CURES

- Blocking multiple checkpoints (negative and positive)
- Conventional therapies (Chemo, Radiation)
- Targeted therapies

Improving survival with combination therapy