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

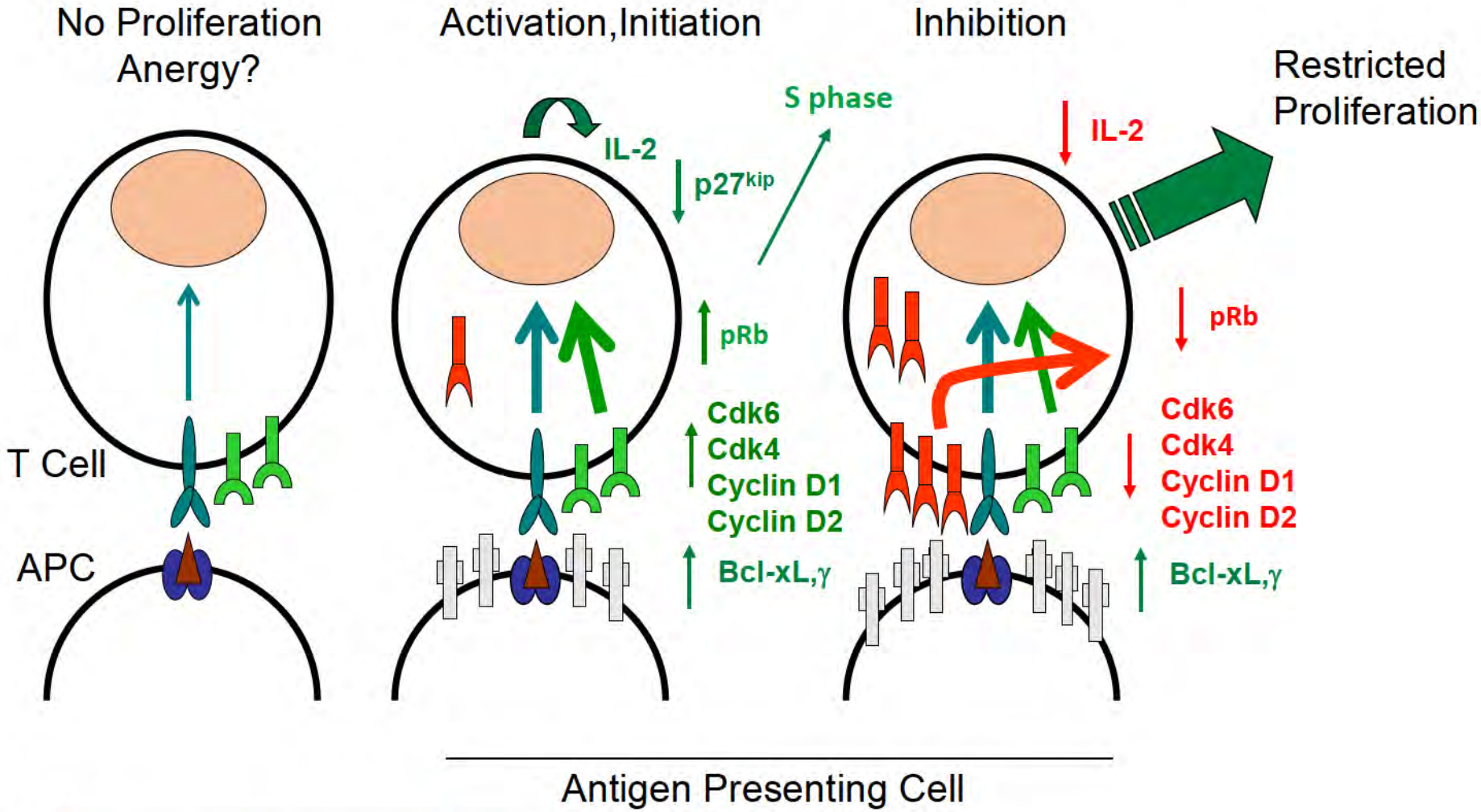
Immune Checkpoint Blockade in Cancer Therapy

Jim Allison

Nobel Prize in Physiology or Medicine Lecture 2018

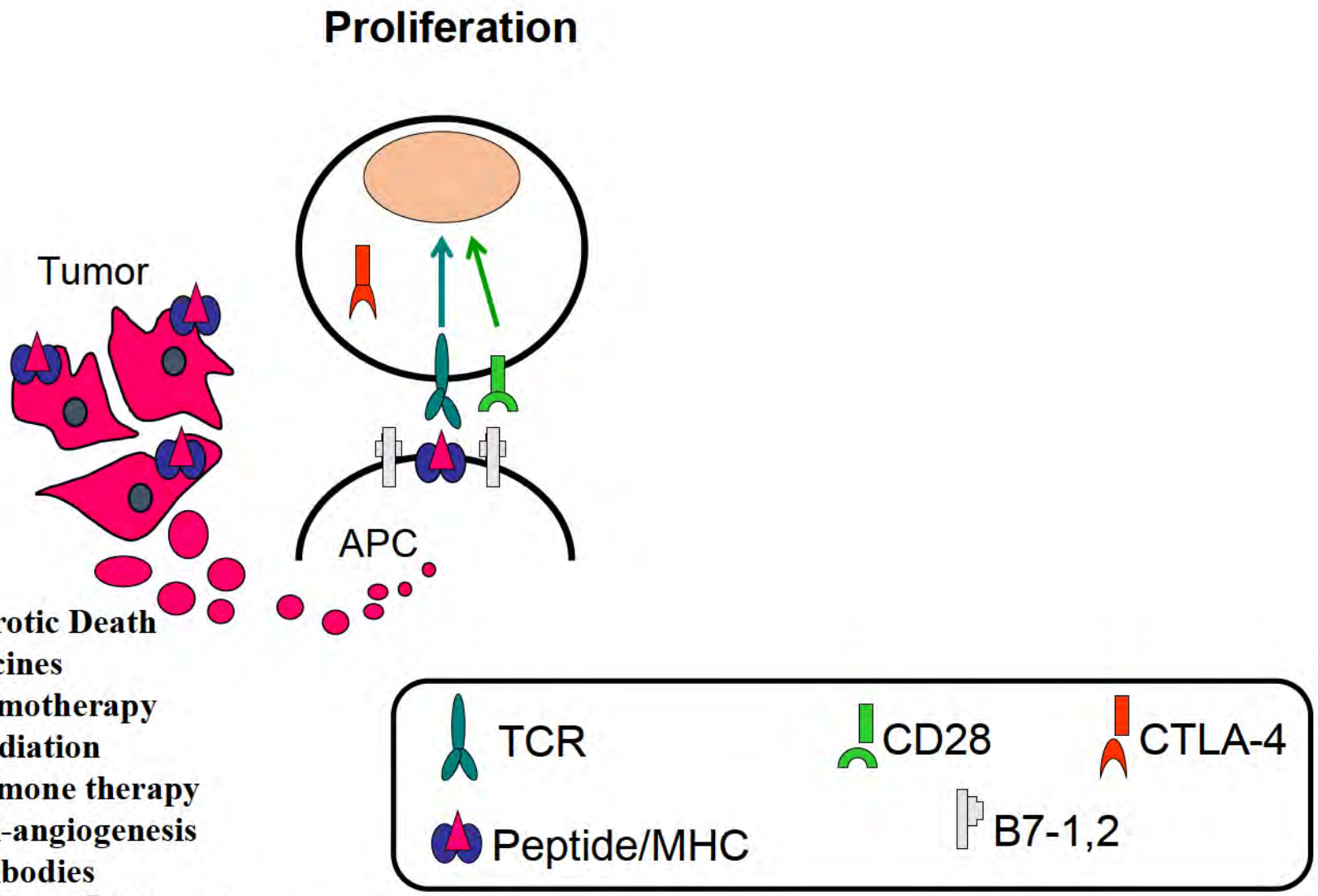
Dynamic Integration of TCR and Costimulatory Signals

circa 1996



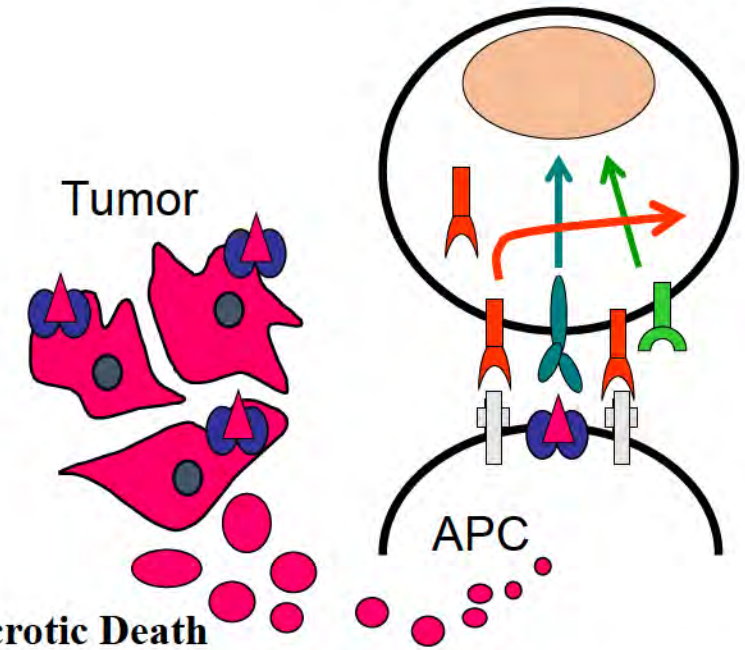
Gross, Harding,
Krummel, Chambers, Brunner, Egen, Kuhns

CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses

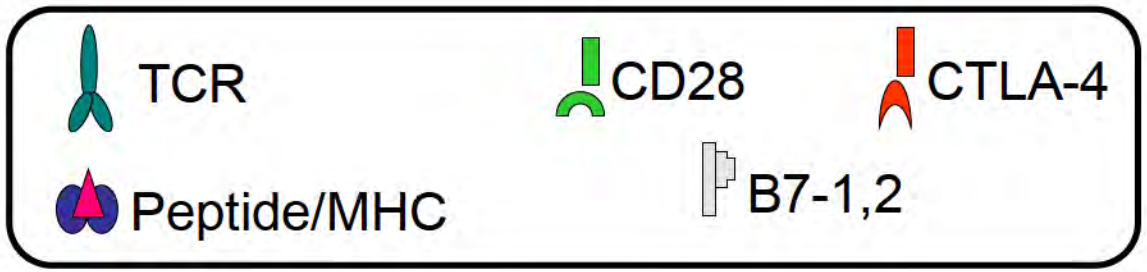


CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation



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



CTLA-4 Blockade
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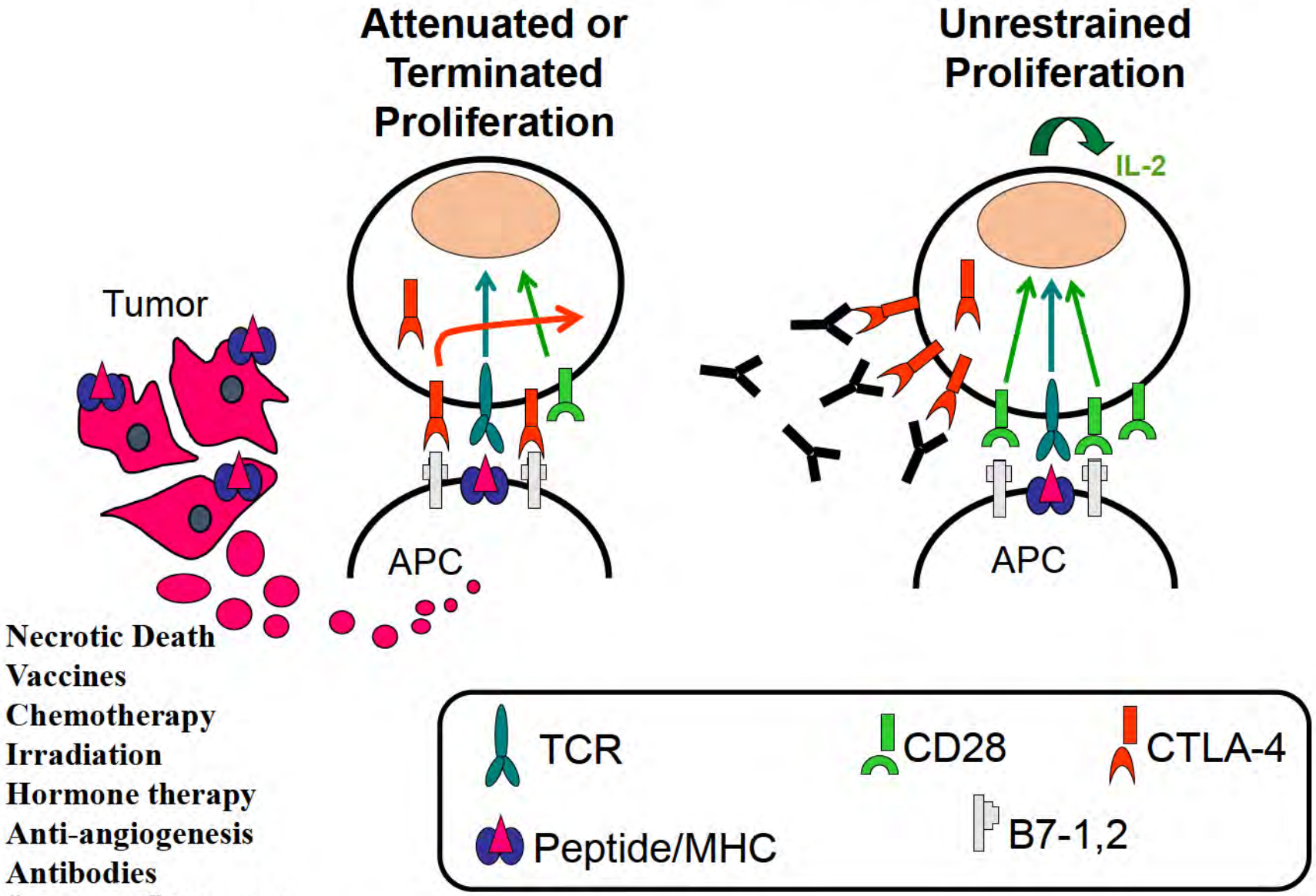
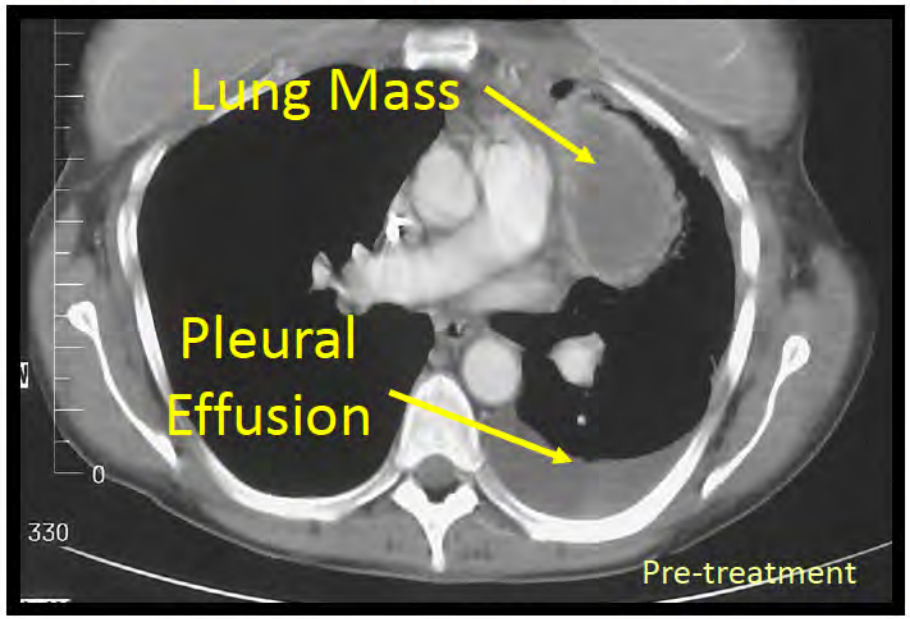
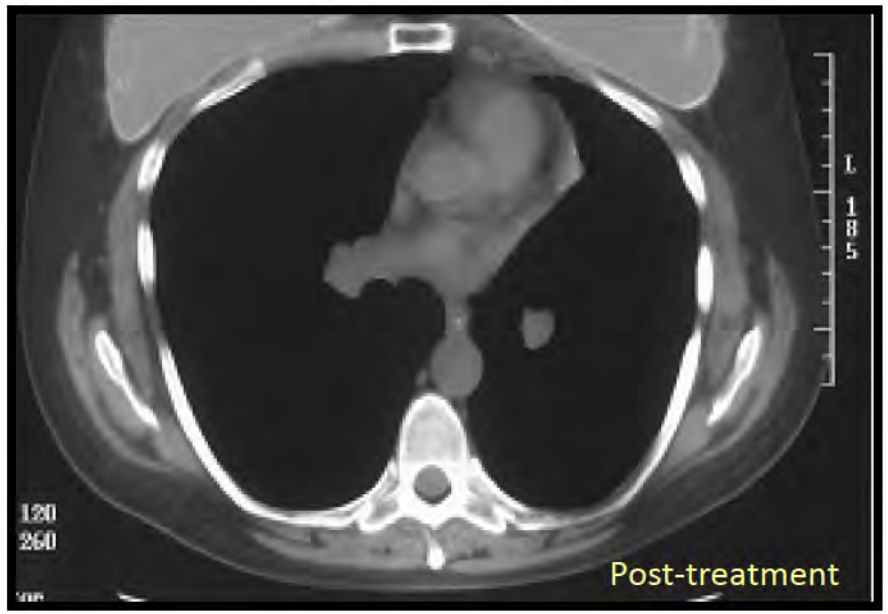


The longest survivor on ipilimumab

May 2001, after progression on IL-2



10 years later

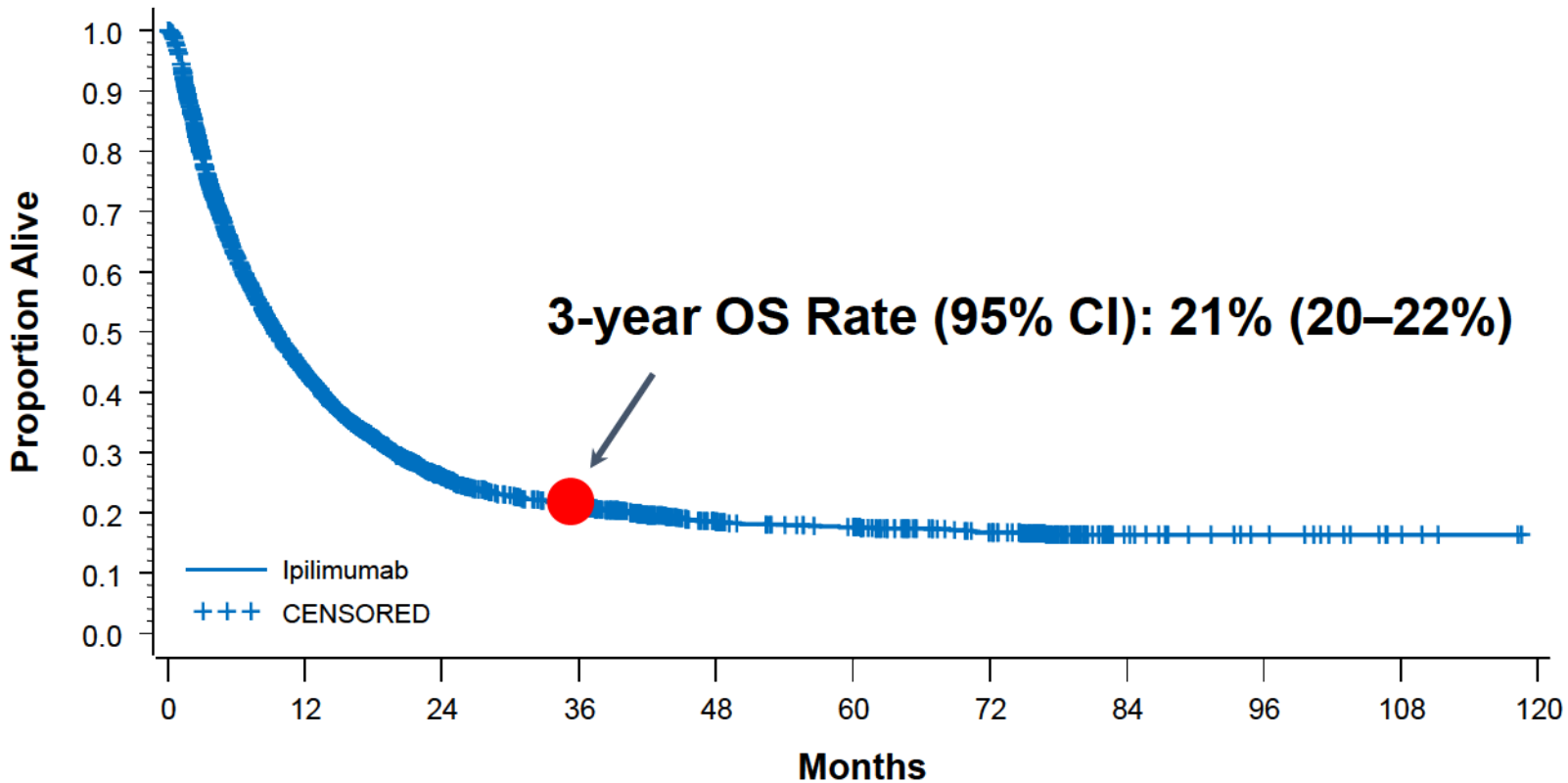


Baseline and post-MDX-010 treatment CT scans of patient with metastatic melanoma (status post dendritic cell vaccine) who experienced regression of all known sites of disease. The patient continues without relapse at last reported follow-up visit.

Ribas

Ipilimumab in Metastatic Melanoma

(pooled data from 4846 patients)

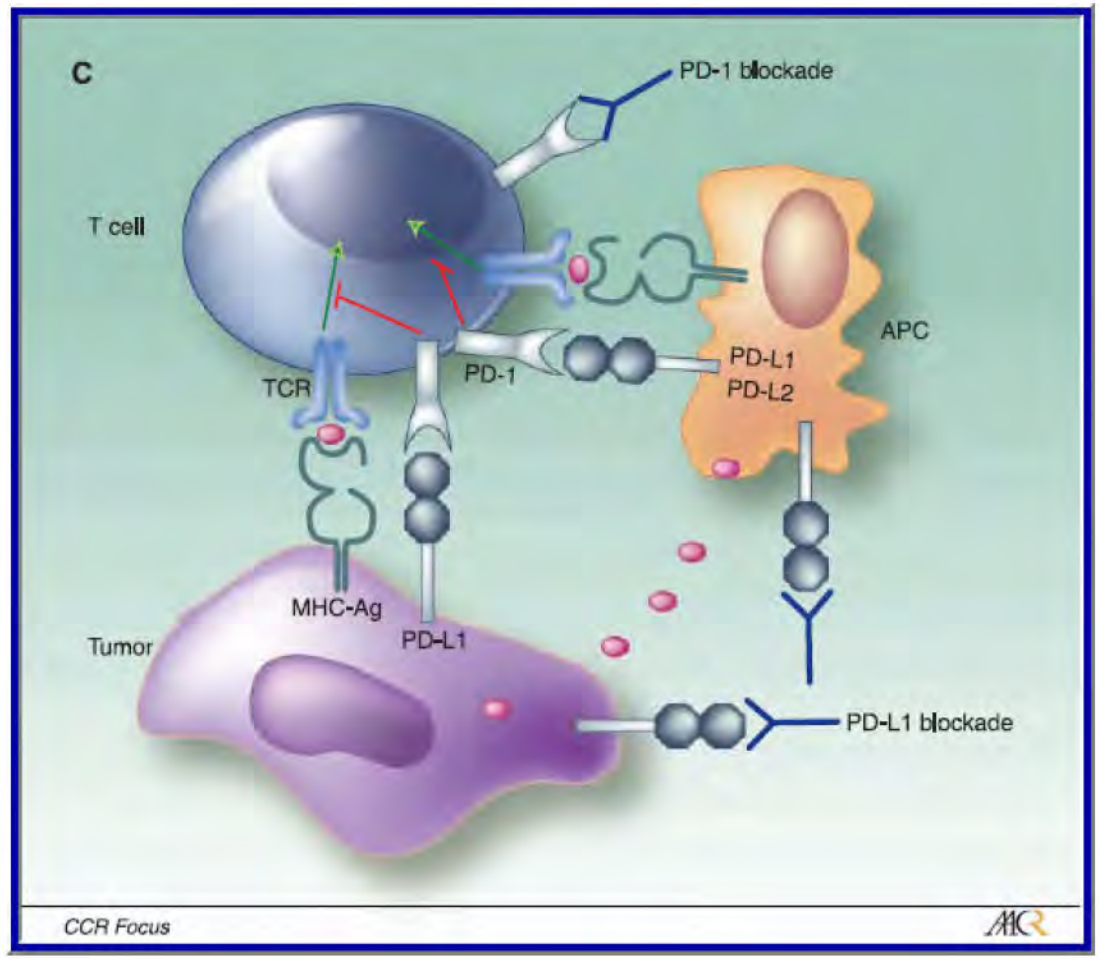


Patients at Risk

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:

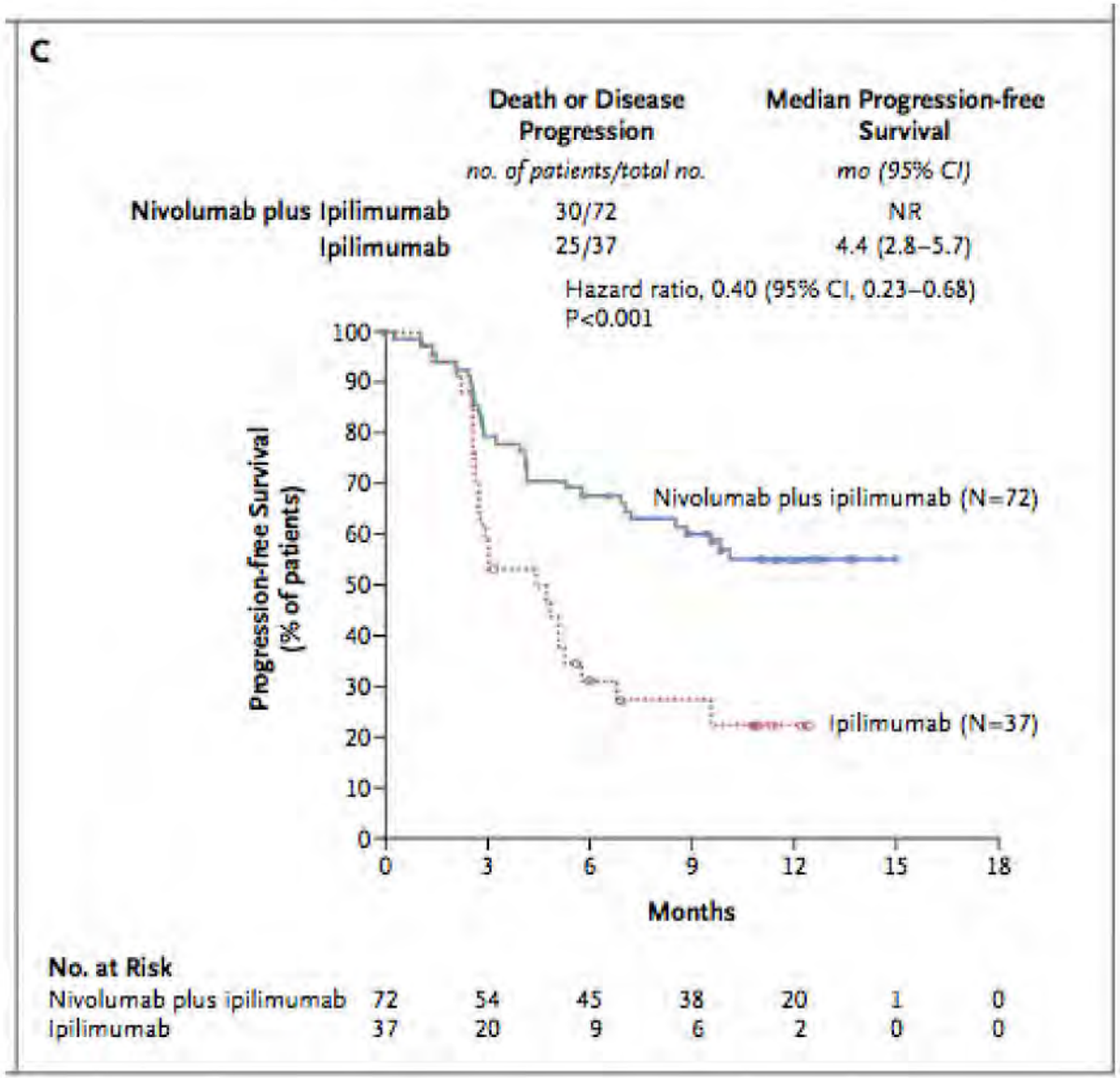
Melamona (n= 94): 28% CR/PR, 6% SD
NSCLC (n=76): 18% CR/PR, 7% SD
RCC (n= 33): 27% CR/PR, 27% SD
CRC (n=19), CRPC (n=13): No responses

Topalian ASCO, NEJM 2012

Where do we go from here?

Combinations

Ipi/Nivo vs. Ipi in Metastatic Melanoma



Hodi NEJM 2015

Immune checkpoint blockade FDA approvals

Melanoma – *Ipilimumab, Pembrolizumab, Nivolumab, Ipilimumab + Nivolumab*

Melanoma (adjuvant) – *Ipilimumab, Nivolumab*

Pediatric melanoma – *Ipilimumab*

Non-small cell lung cancer - *Nivolumab, Pembrolizumab, Atezolizumab*

Renal cell carcinoma – *Nivolumab*

Hodgkin's lymphoma – *Nivolumab, Pembrolizumab*

Bladder cancer – *Atezolizumab, Nivolumab, Durvalumab, Avelumab, Pembrolizumab*

Head and neck cancer – *Nivolumab, Pembrolizumab*

Merkel cell carcinoma – *Avelumab*

MSI-H, dMMR – *Pembrolizumab (any histology), Nivolumab (colorectal)*

Gastric/gastroesophageal cancer – *Pembrolizumab*

Hepatocellular carcinoma - *Nivolumab*

Critical issues for further clinical development of immune checkpoint targeting

- Determination of the cellular and molecular mechanisms involved in the anti-tumor effect

- Determination of the impact of other therapeutic agents on the immune system

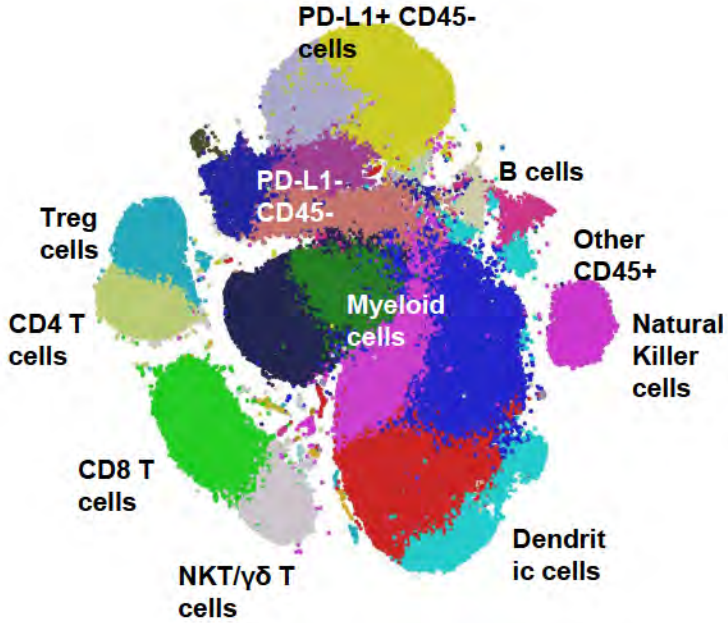
- Combining the best standard-of-care therapies with immune checkpoint agents

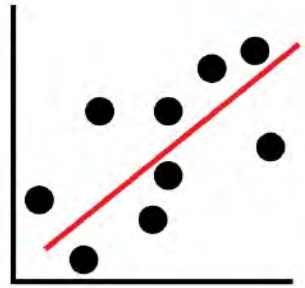
- Targeting new molecules to improve efficacy

- Identification of predictive, prognostic or pharmacodynamic biomarkers

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

Can we identify checkpoint blockade responsive T cell populations?





CyTOF analysis of murine TILs (43 Parameters)

+/- checkpoint blockade

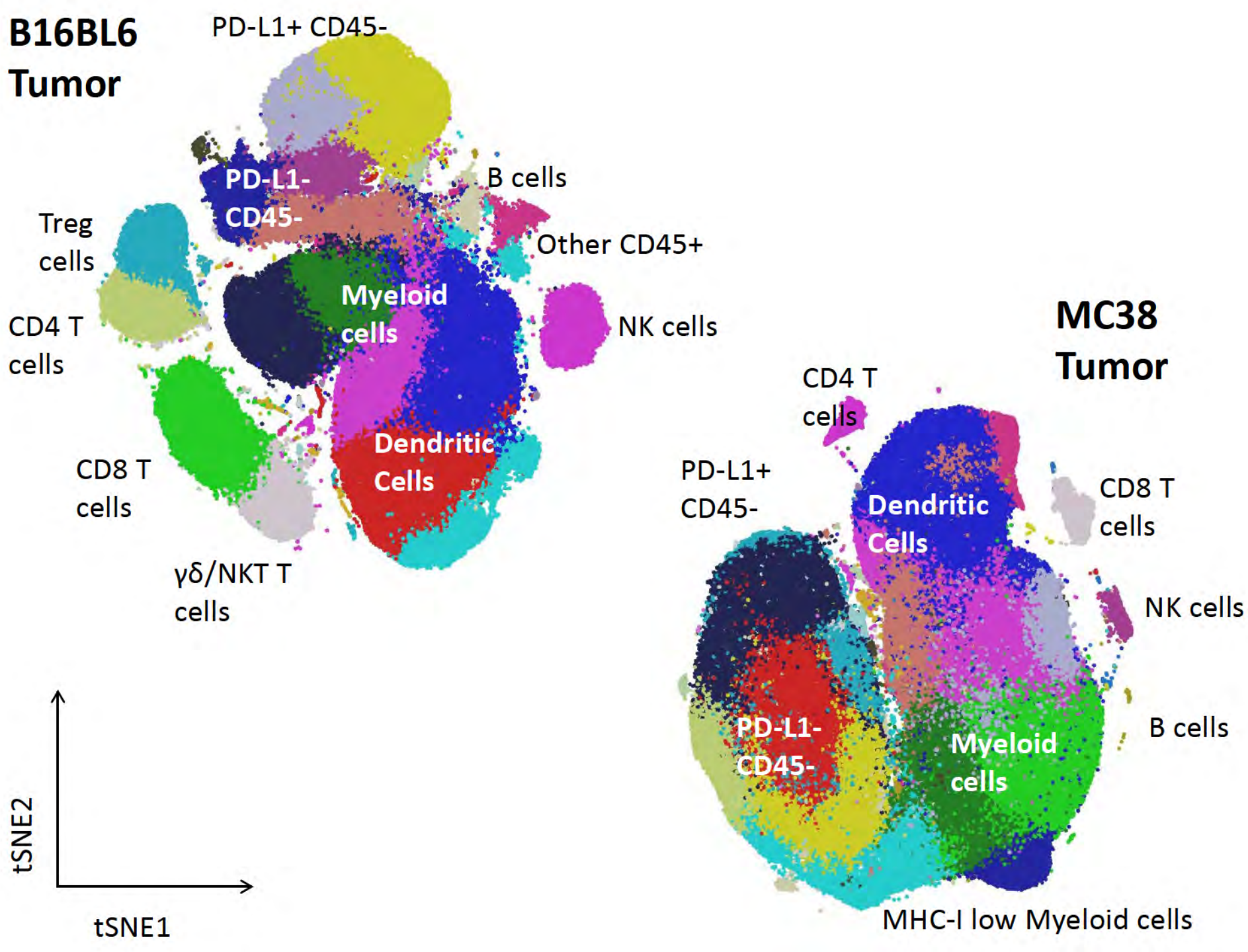
→

Unsupervised population identification

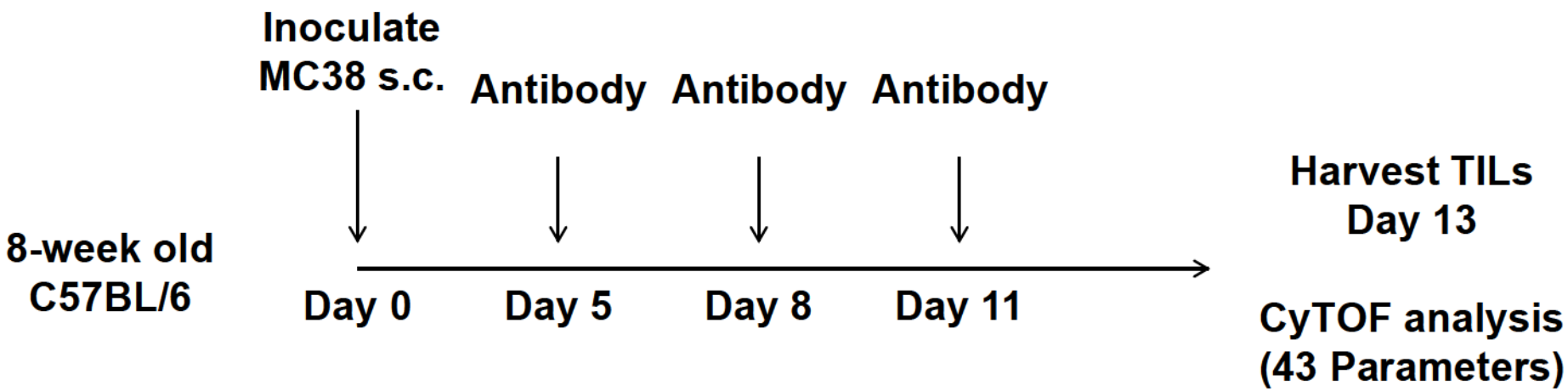
→

Identify associations with treatment and outcome

Spencer Wei

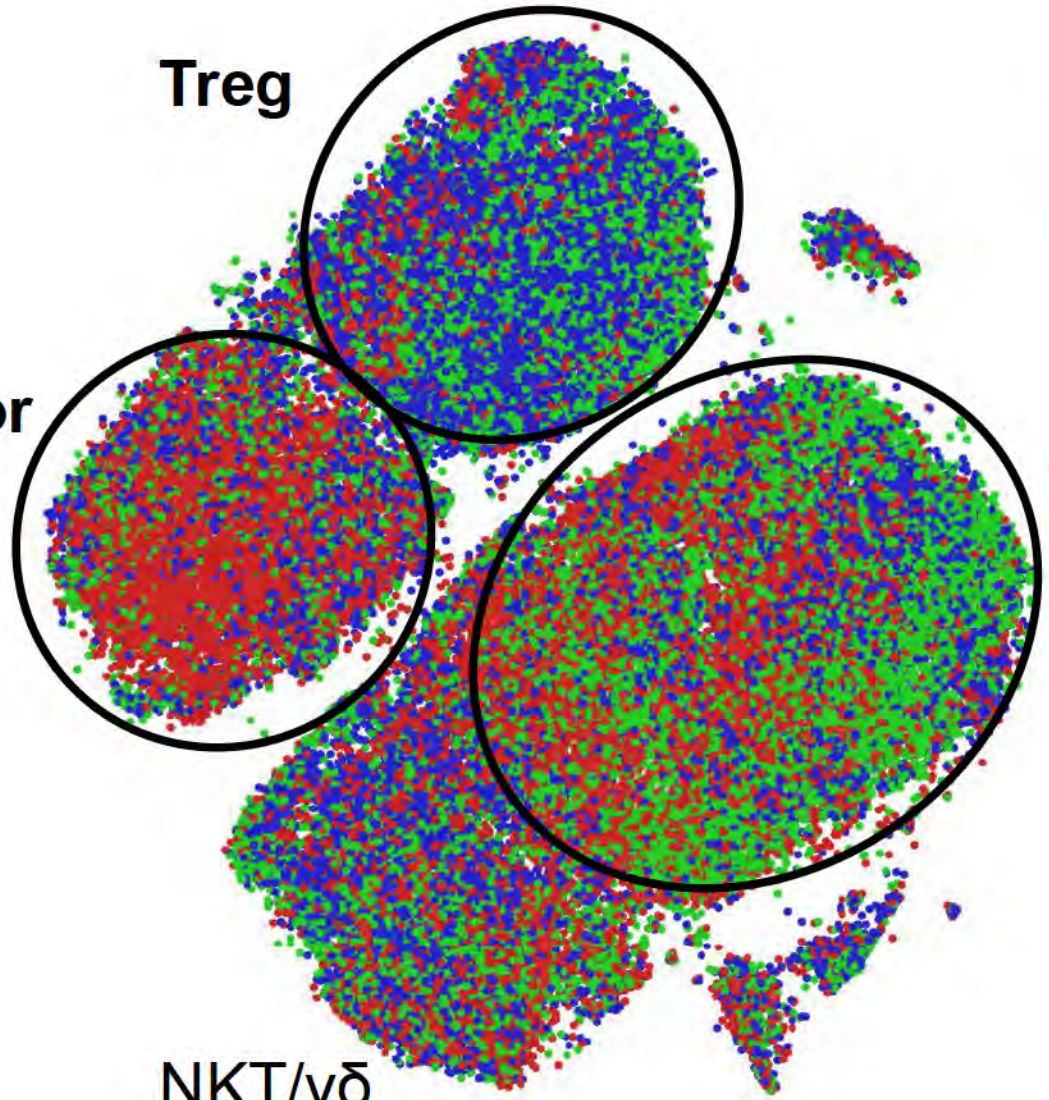

B16BL6
Tumor
PD-L1+ CD45-
PD-L1-
CD45-
B cells
Treg
cells
Other CD45+
Myeloid
cells
CD4 T
cells
NK cells
Dendritic
Cells
CD8 T
cells
γδ/NKT T
cells
tSNE2
tSNE1
MC38
Tumor
CD4 T
cells
PD-L1+
CD45-
Dendritic
Cells
CD8 T
cells
NK cells
PD-L1-
CD45-
Myeloid
cells
B cells
MHC-I low Myeloid cells

Mass cytometry analysis of MC38 TILs



Wei et al *Cell* 2017

MC38 infiltrating T cell populations

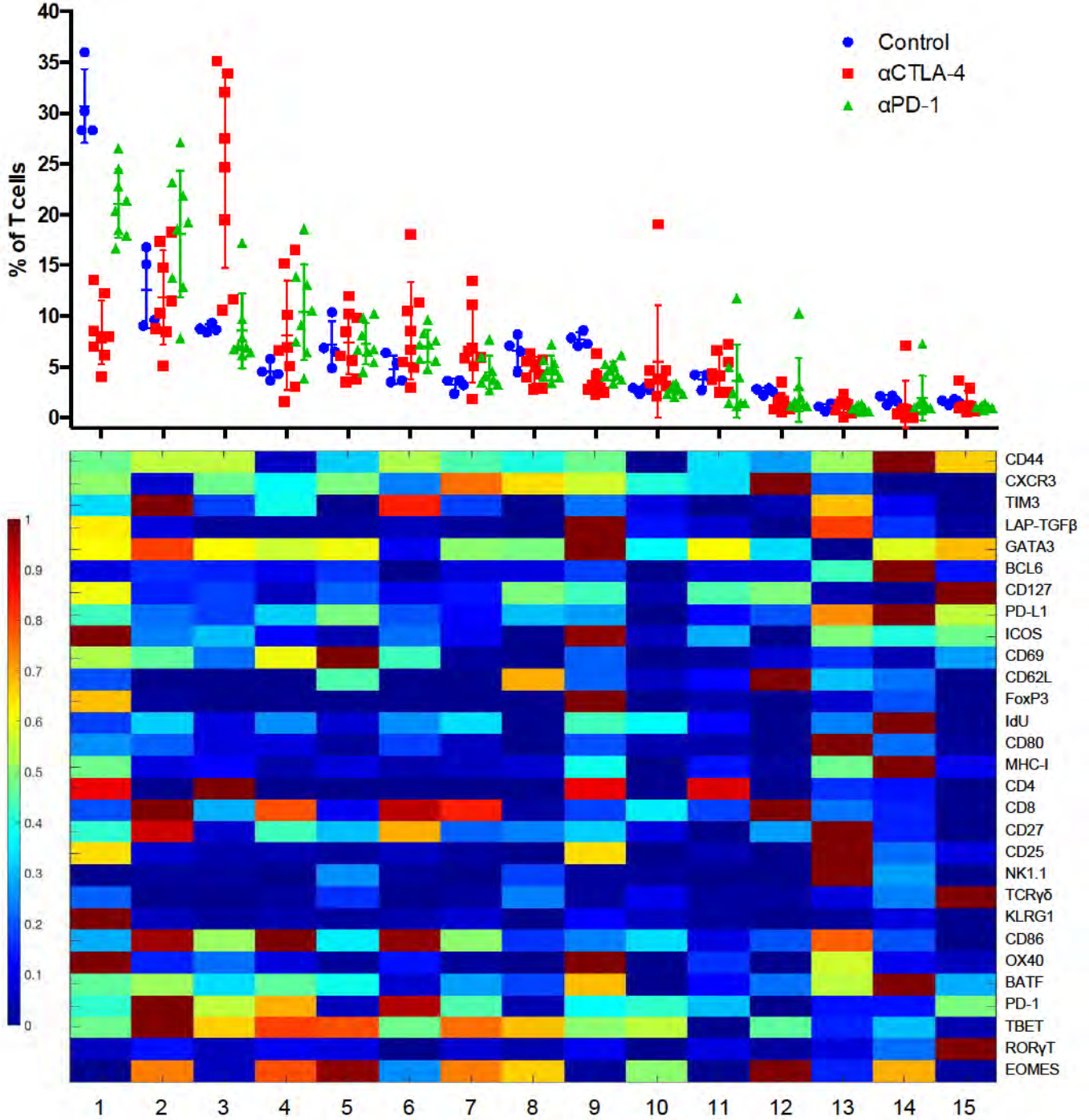


Control
αCTLA-4
αPD-1

Gated for
CD45+, CD3ε+

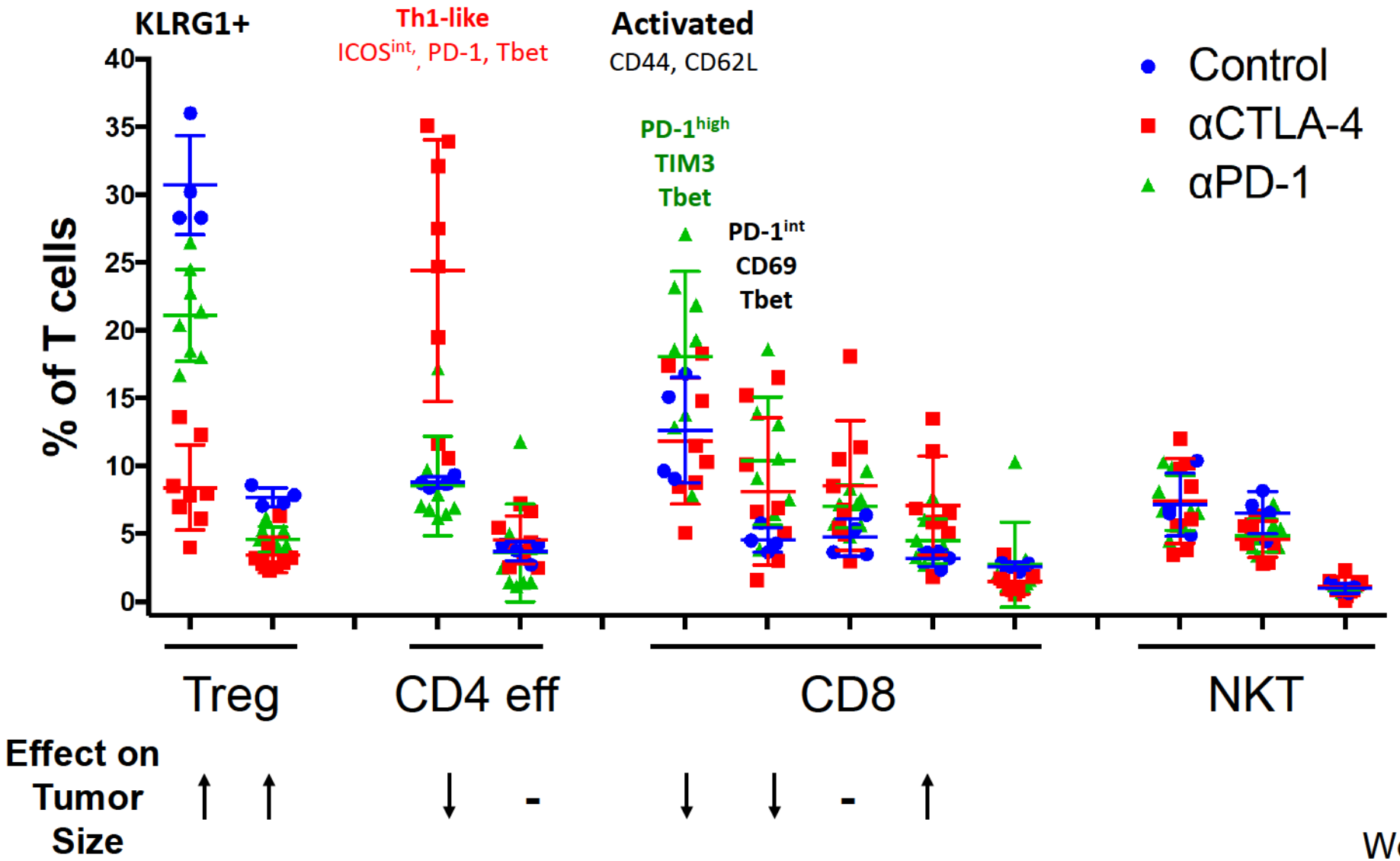
Wei et al *Cell* 2017

MC38 TIL



Wei et al *Cell* 2017

Checkpoint blockade modulates MC38 infiltrating T cell population frequencies



Wei et al *Cell* 2017

Summary

- The therapeutic mechanisms of αCTLA-4 and αPD-1 are distinct
- These mechanisms are the same in a highly immunogenic and a poorly immunogenic tumor
- These distinct mechanisms may explain why the combination is so effective
- Specific CD4 and CD8 T cell subtypes contribute to the therapeutic effects in both therapies
- Monitoring these subtypes rather than total CD4 or CD8 cells correlates better with outcome and may be much predictive of outcome

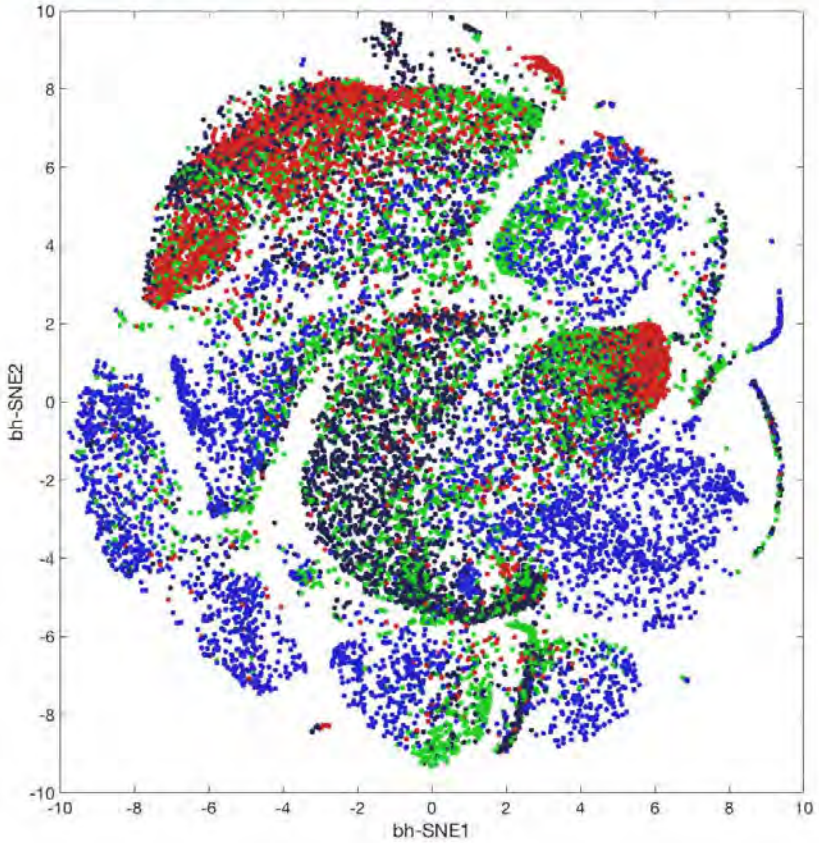
Are similar mechanisms involved in patients?

TILS from treated melanoma patients

Normal PBMC Ipilimumab (αCTLA-4)

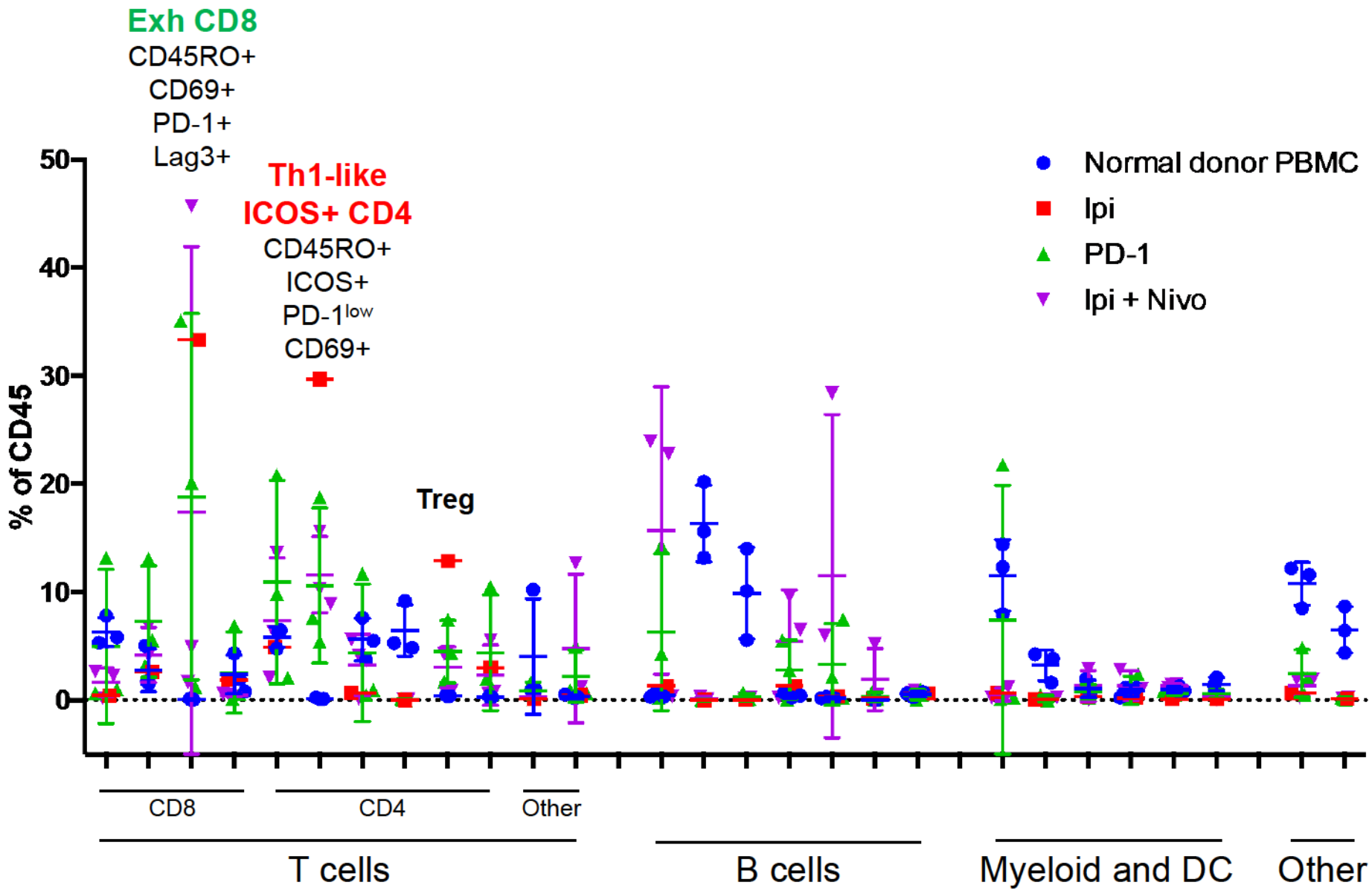
Nivolumab (αPD-1) Ipi + Nivo

Total CD45+ cells



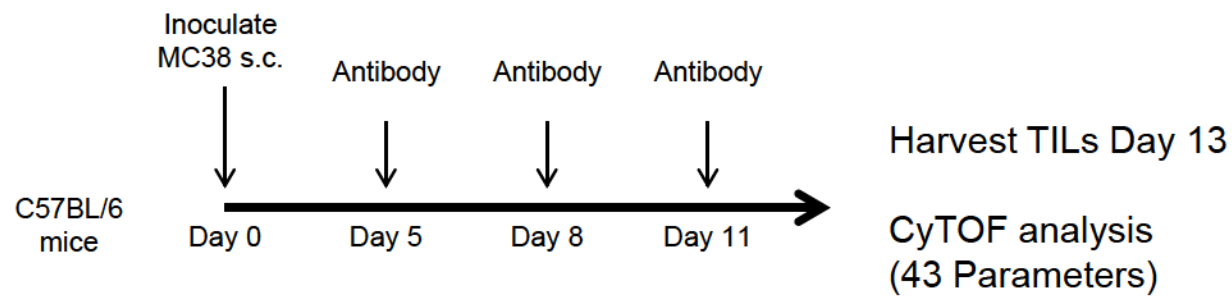
Wei et al *Cell* 2017

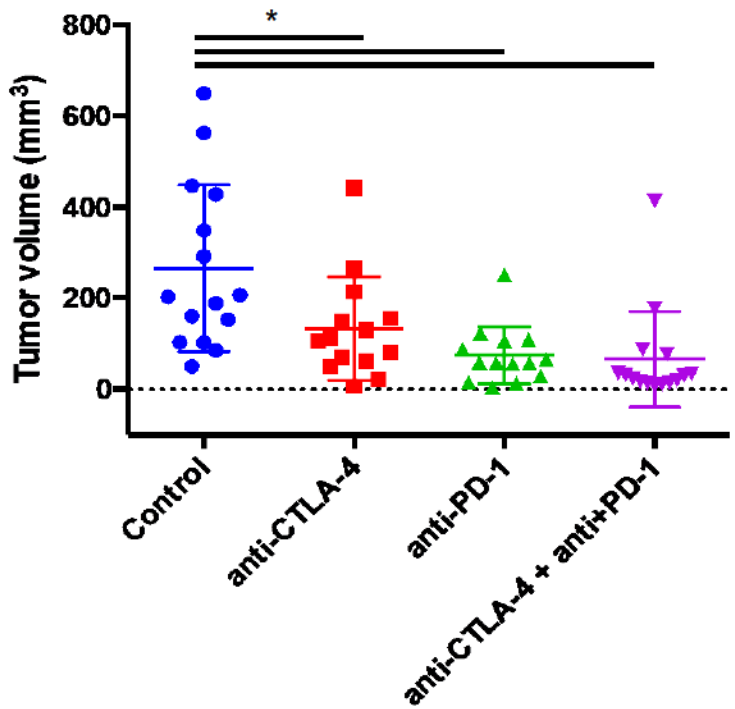
Checkpoint blockade modulates the frequency of specific TIL populations in melanoma patients



How do these cellular mechanisms interact?

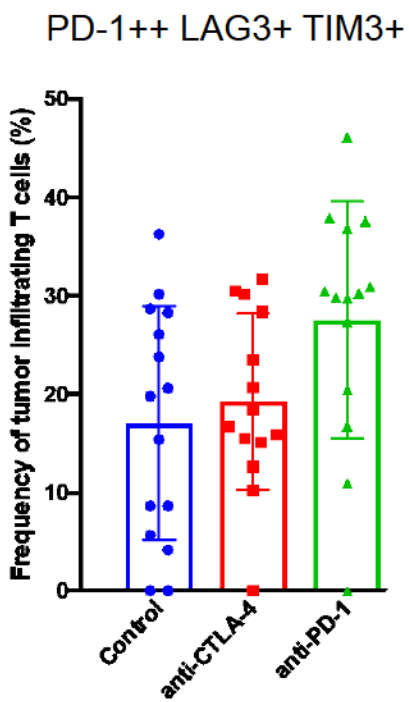
Mass cytometry analysis of MC38 TILs





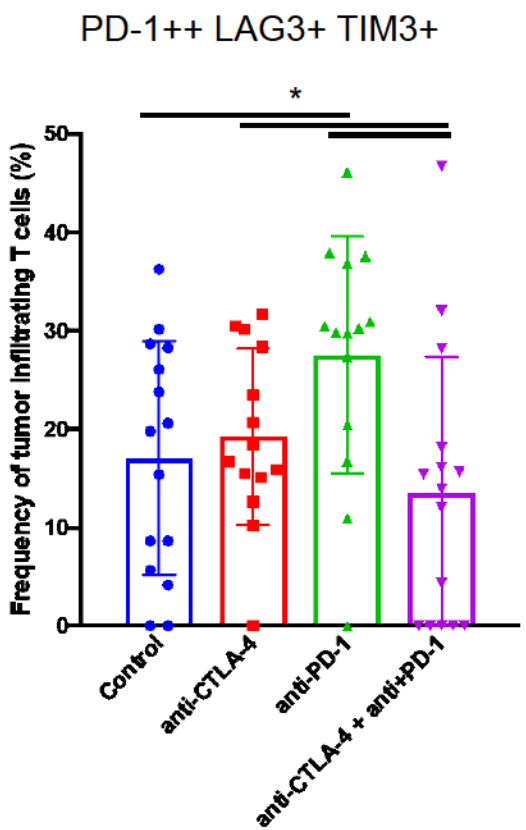
Wei et al *unpublished*

Expansion of phenotypically exhausted CD8 T cells



Wei et al *unpublished*

Combination therapy differentially affects CD8 subsets



Wei et al *unpublished*

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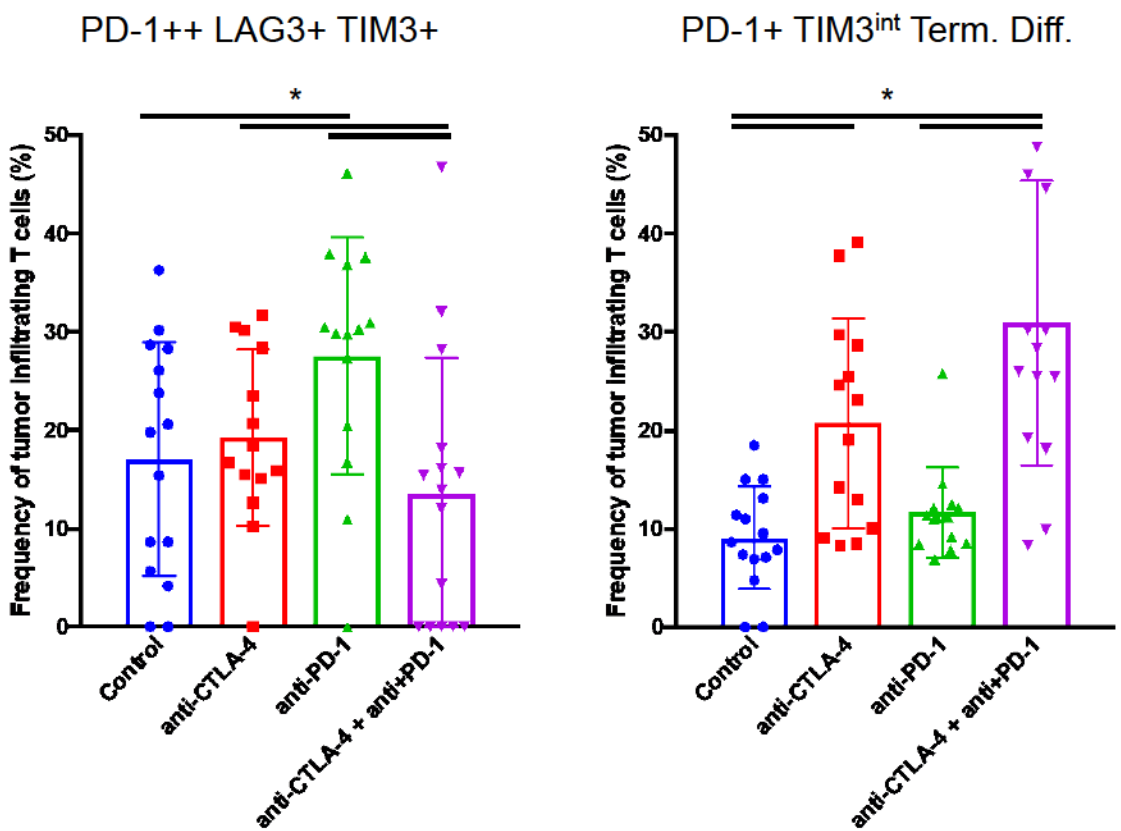
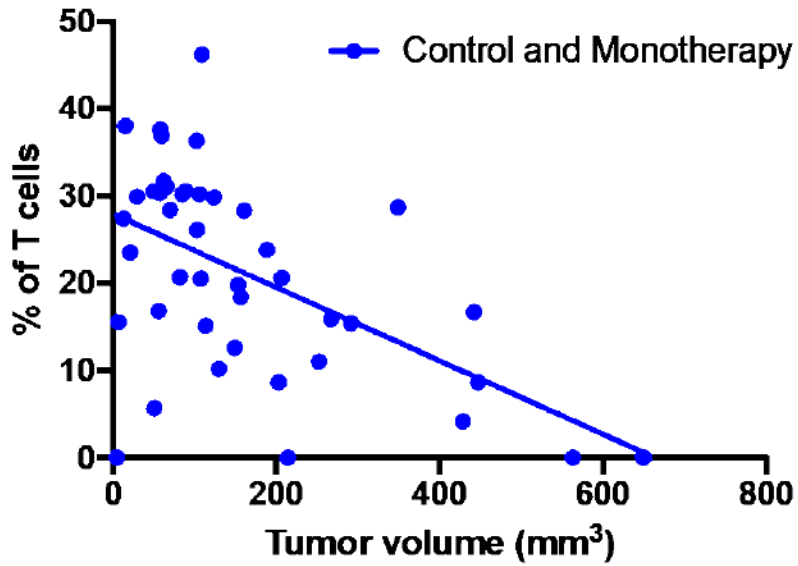


Wei et al *unpublished*

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



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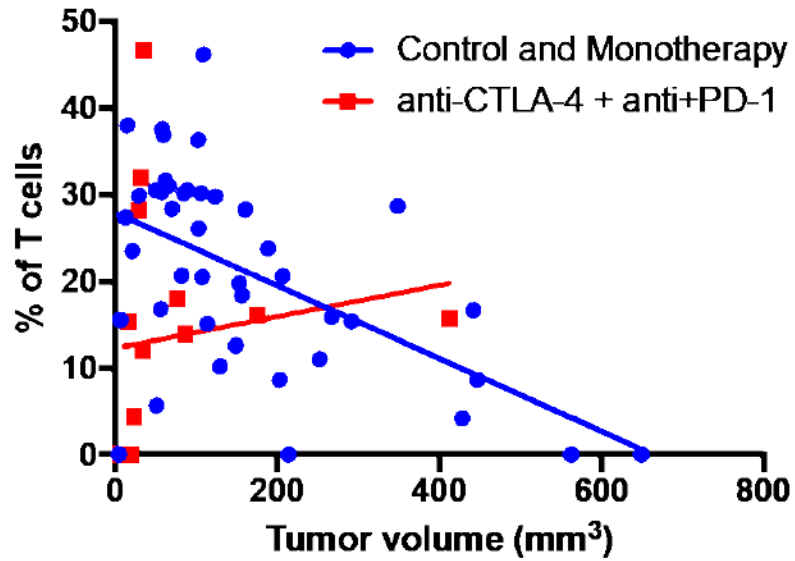


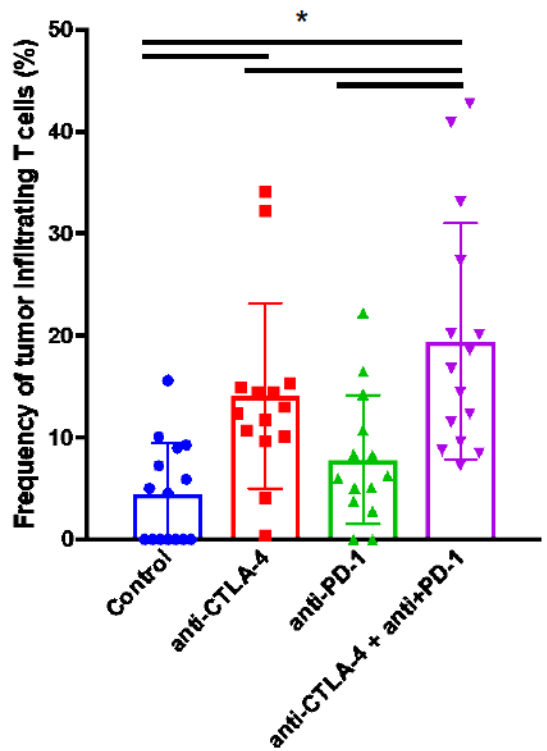
Wei et al *unpublished*

Effects on the CD4 effector compartment?

Wei et al *unpublished*

Expansion of Th1-like CD4 T cells following combination therapy

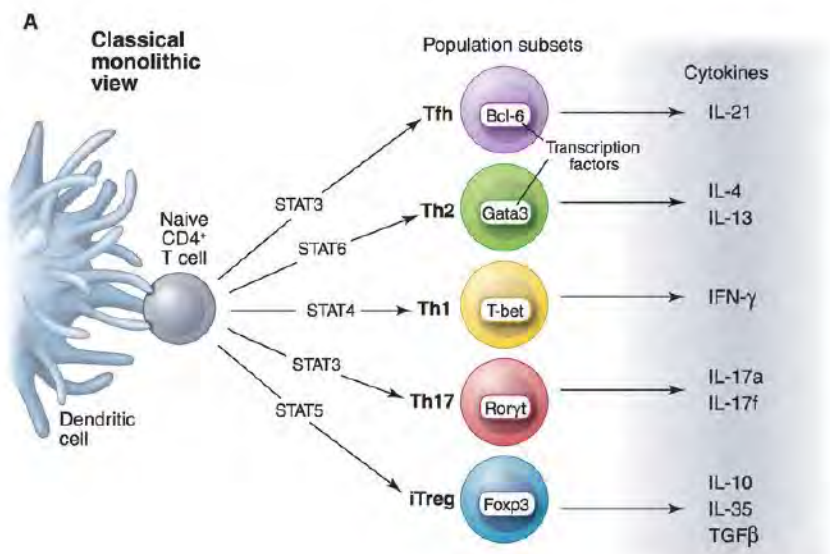
PD-1^{+} ICOS^{int} TBET^{+}
Th1-like CD4 effector

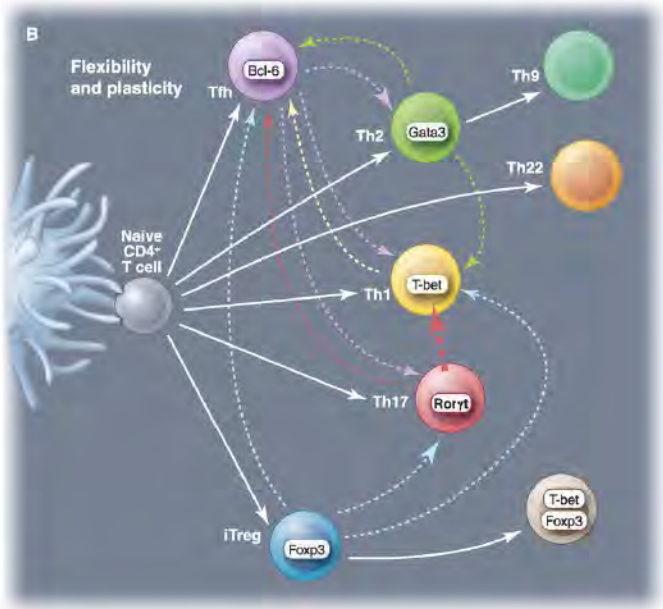


Wei et al *unpublished*

What is the role of costimulation in the regulation of T cell differentiation?

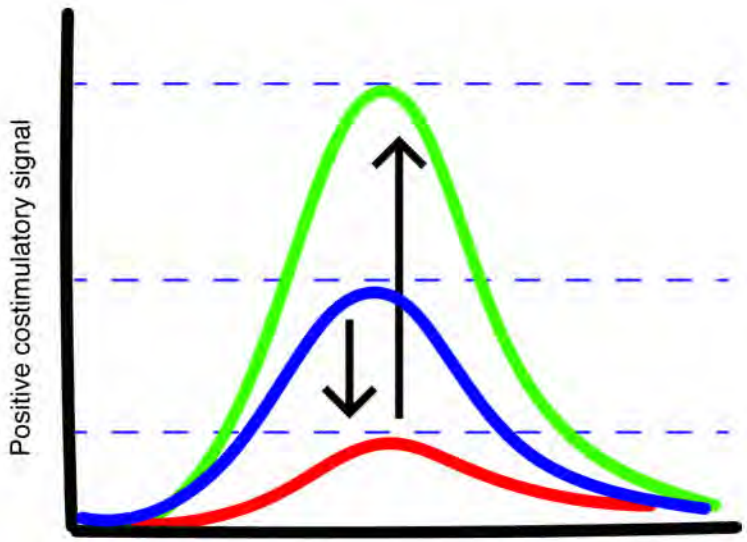
T cell differentiation is complex
How are phenotypes, lineages, and boundaries defined?





O'Shea and Paul. *Science* (2010)

Does negative costimulation regulate T cell differentiation?



Maximum in the absence of CTLA-4?

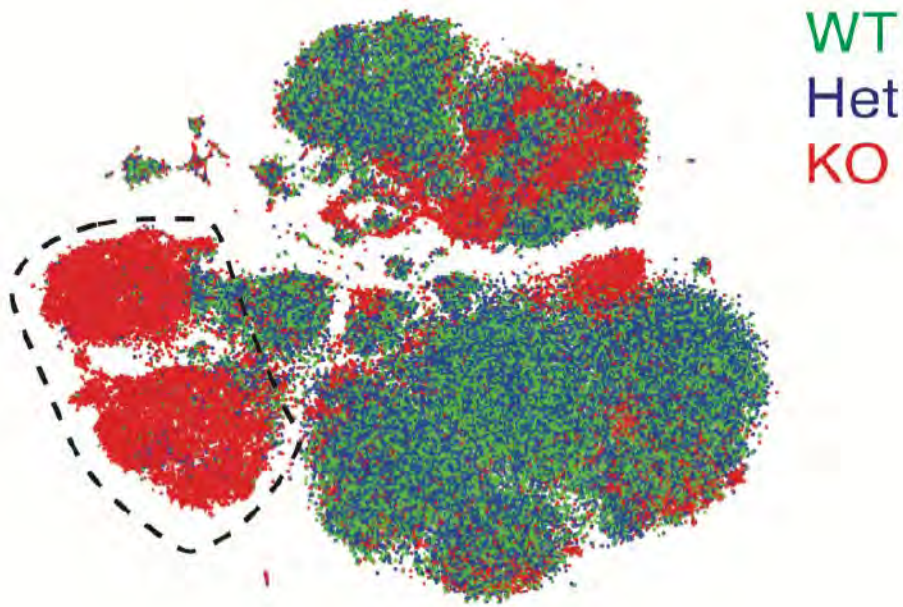
⟶ **Effect on differentiation?**

Maximum signal under normal conditions

Attenuated signal due to CTLA-4 regulation

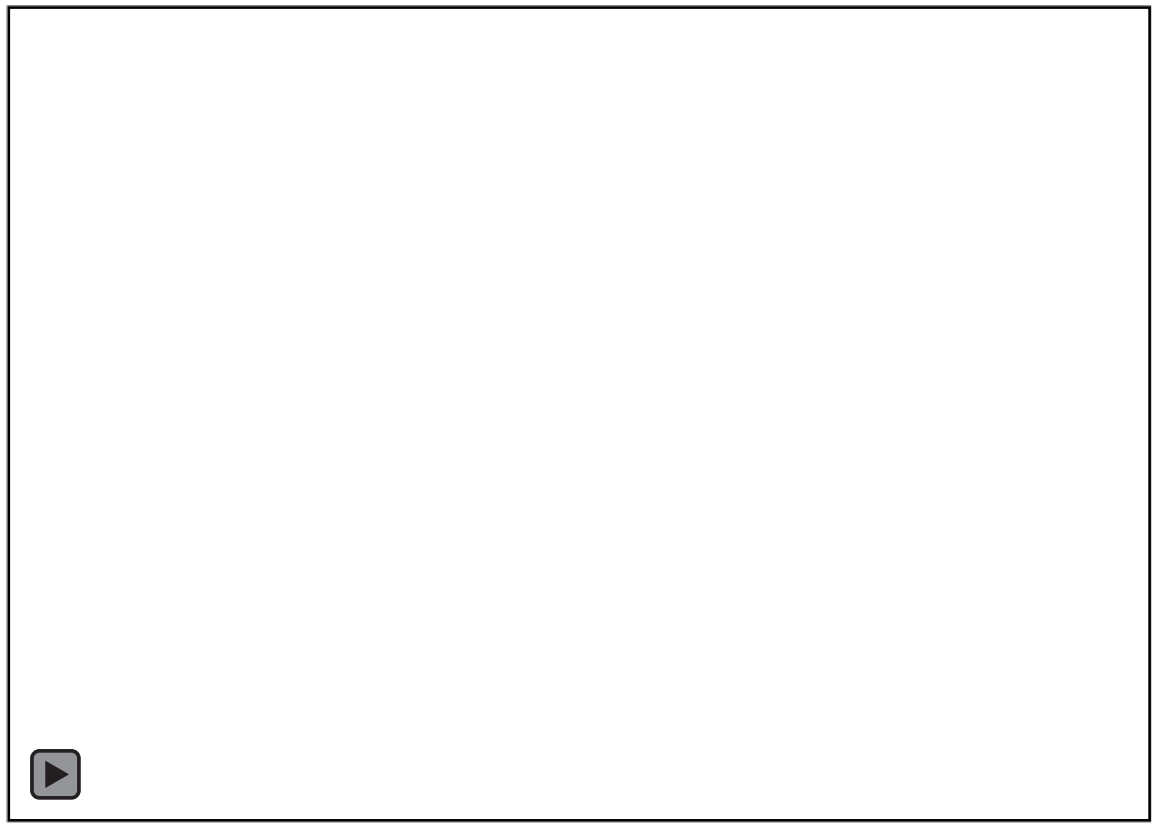
Ctla-4$^{-/-}$ T cells display distinct phenotypes

Lymph node
CD3ε^{+} T cells



Wei et al *unpublished*

New T cells phenotypes arise in the absence of CTLA-4

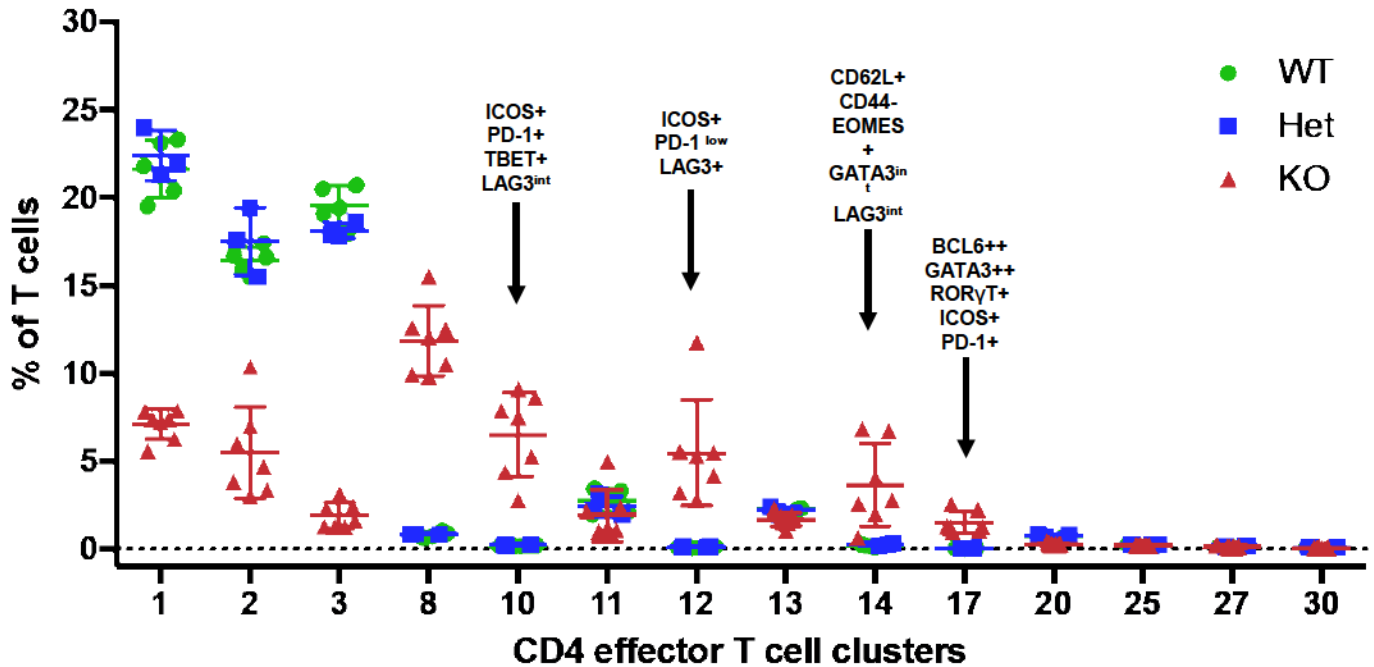


T cells gated

WT
Het
KO

Wei et al *unpublished*

Specific expansion of CD4 T cell subsets



Wei et al *unpublished*

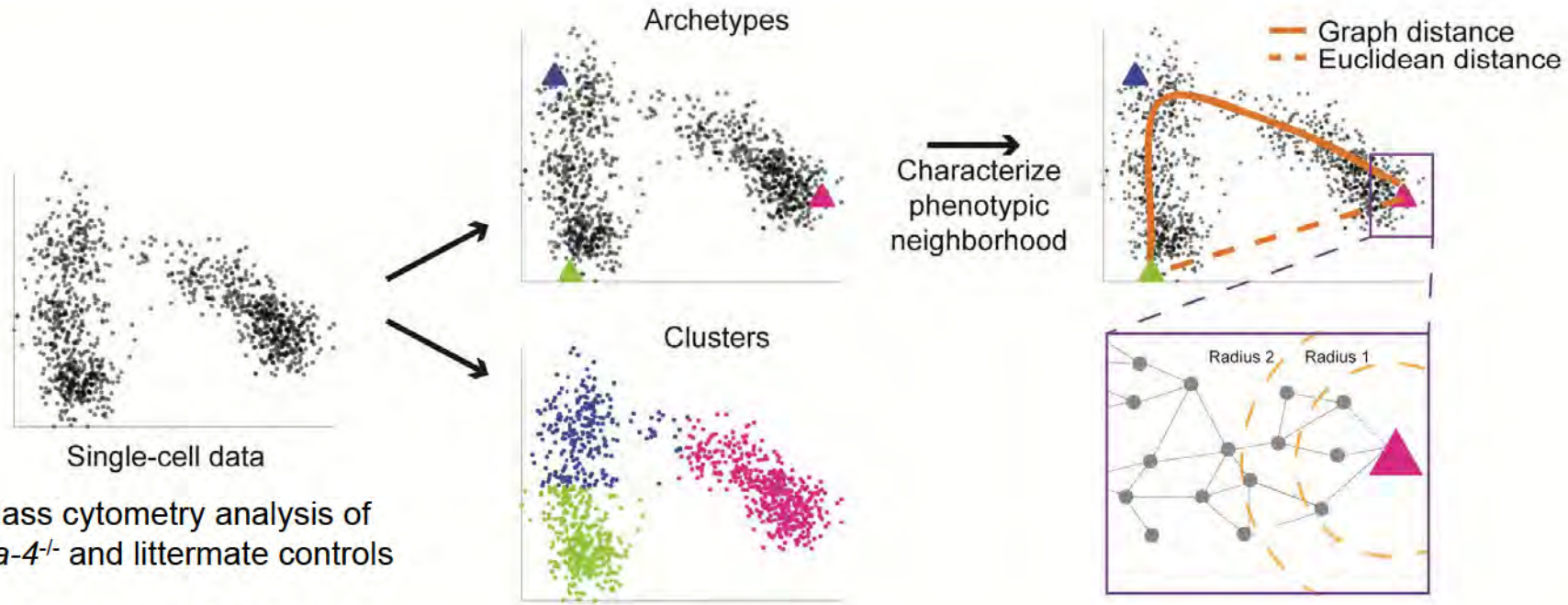
What underlies the generation of these subsets?

- Not due to differences in T cell proliferation
- Not due to differences in T cell activation
- Not due to defects in thymic development

Do these populations represent new types of T cells?

Wei et al *unpublished*

Comprehensive profiling of peripheral T cells in the absence of CTLA-4

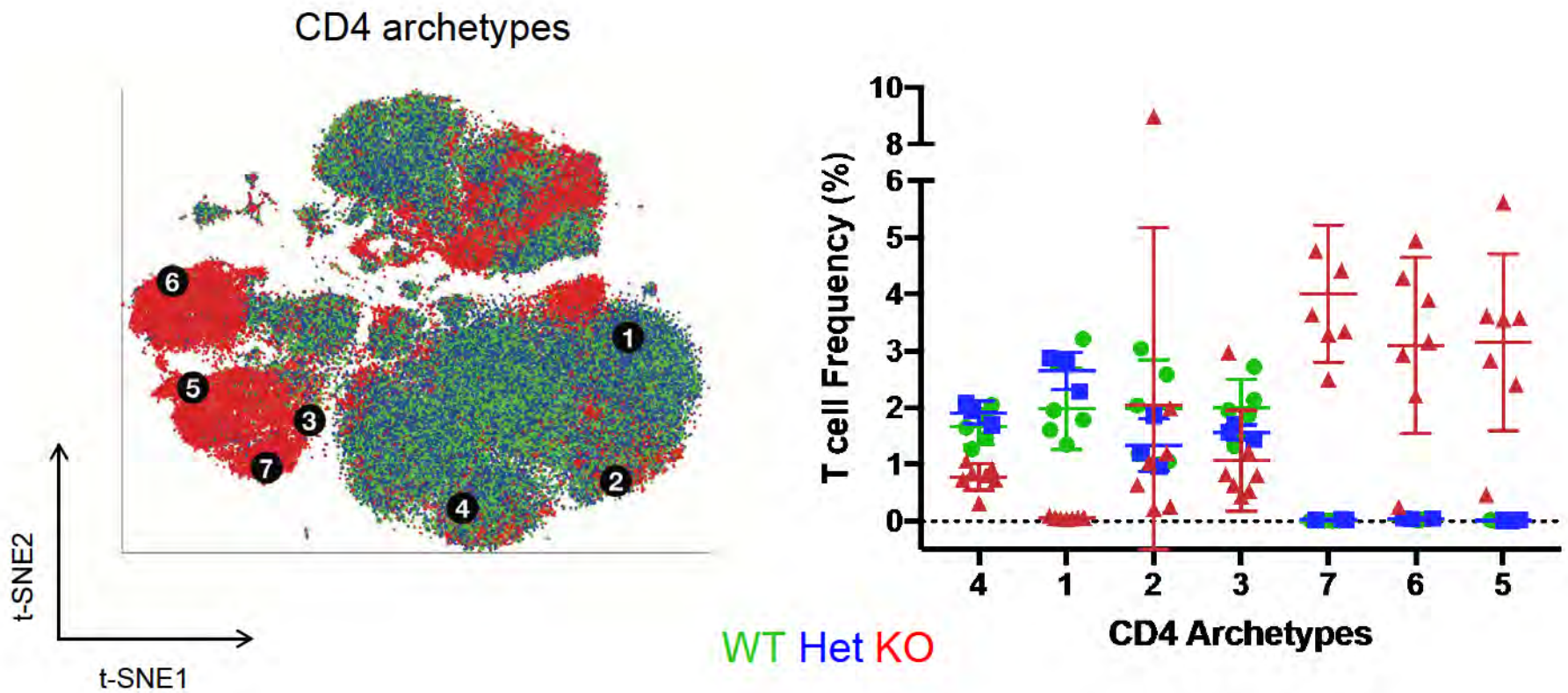


Mass cytometry analysis of
Ctla-4$^{-/-}$ and littermate controls

<u>39 Parameter T cell panel</u>
Activation, surface, lineage markers
Lineage transcription factors

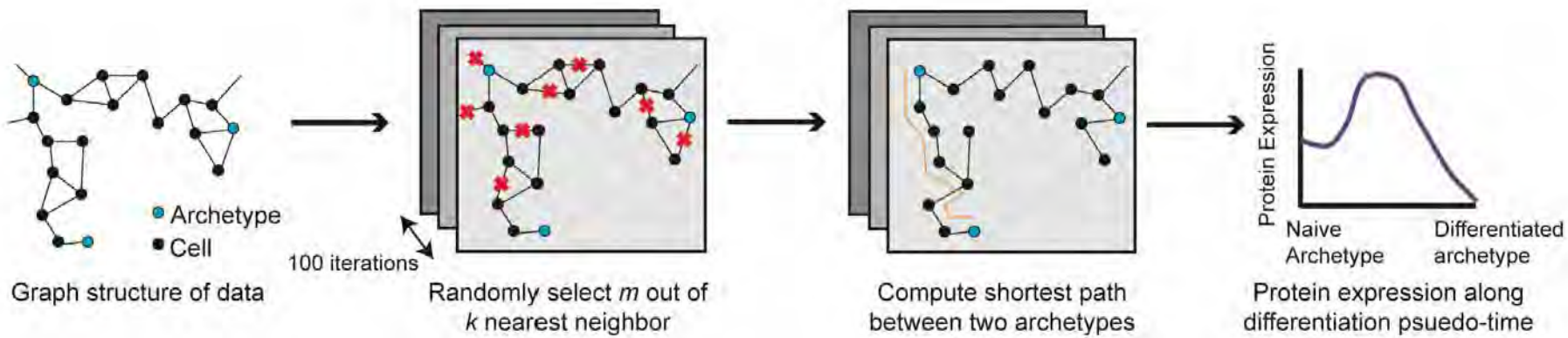
Wei et al *unpublished*

CD4 archetypes reside in *Ctla-4*$^{-/-}$ specific regions

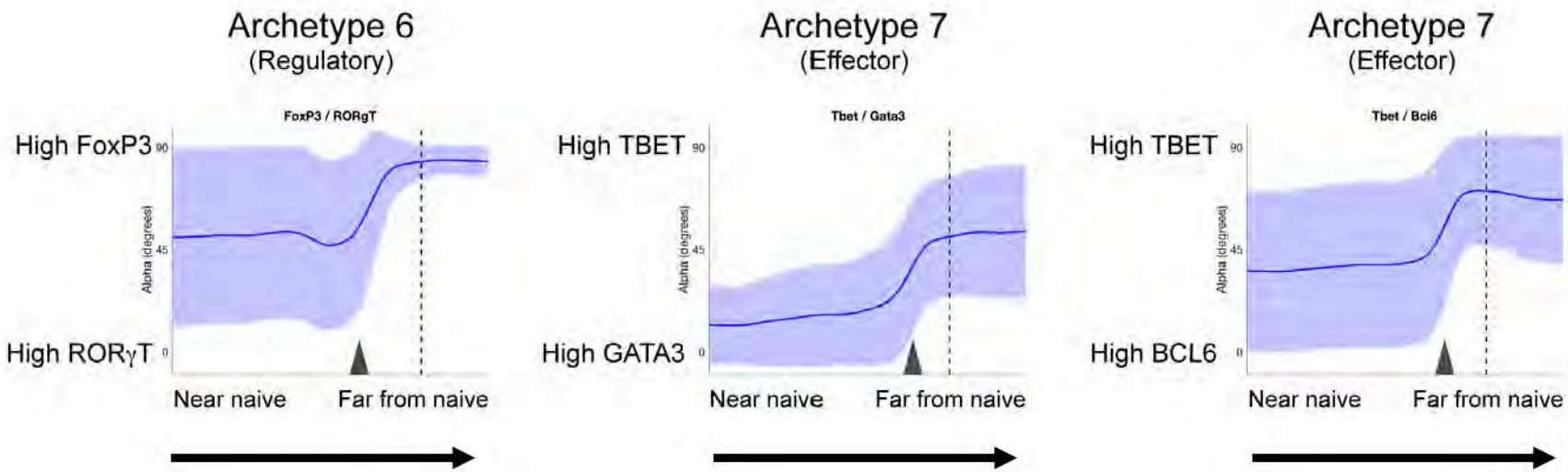


Wei et al *unpublished*

Reconstruction of CD4 T cell differentiation paths



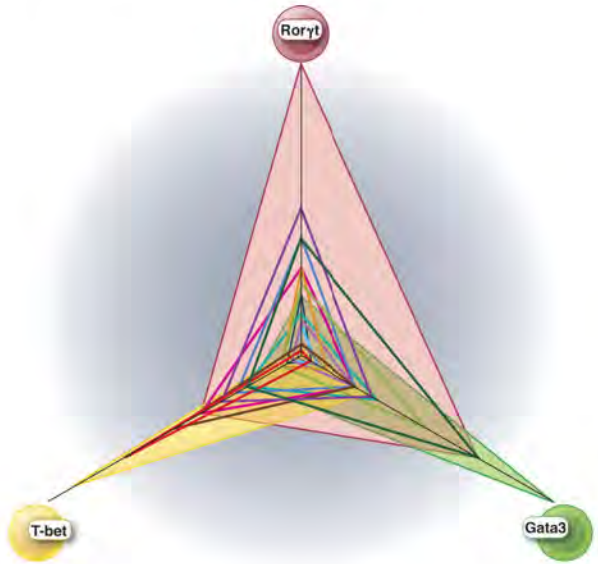
Transcription factor ratios identify lineage commitment events



Wei et al *unpublished*

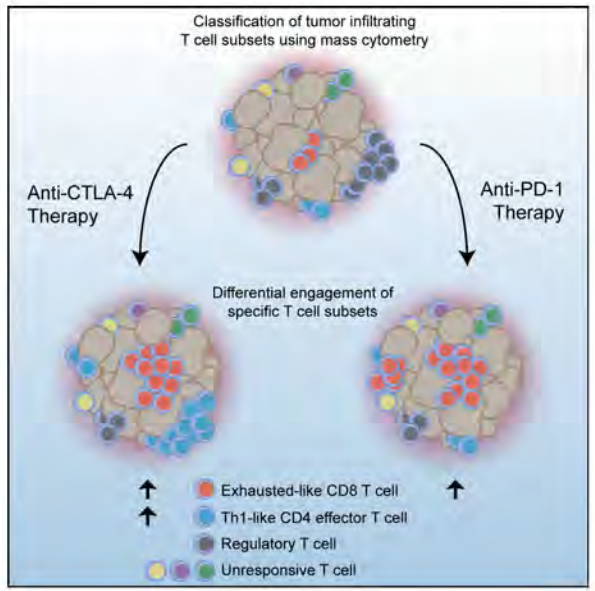
Potential implications

Evidence for a ‘nuanced model’ of T cell differentiation



O’Shea and Paul. *Science* (2010)

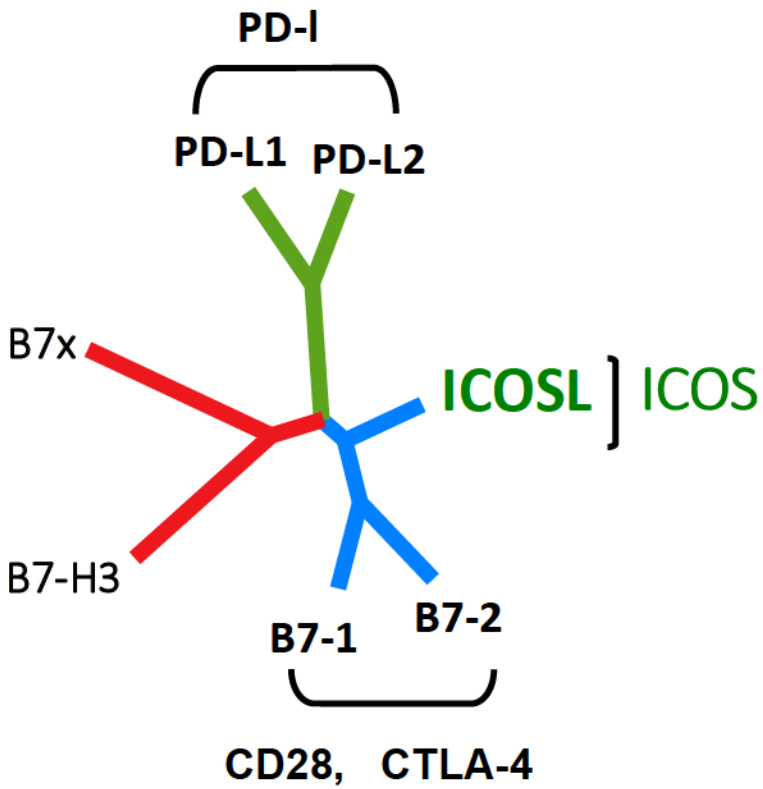
Role of T cell differentiation in mechanisms of immunotherapies



Wei et al. *Cell* (2017)

Inducible Costimulator (ICOS)

- Member of CD28/CTLA-4 superfamily
- Usually associated with Tfh or Treg
- Role in cancer
  (Sharma 2008)



Identification of unusual ICOS+ Th1-like CD4 cells that arise after CTLA-4 Blockade

Clinical Studies

- 2-10 fold increase in tumor and blood after Ipi
- Contains tumor specific IFNγ– & TNFα–producing CD4 cells
- Increase associated with longer survival
- Pharmacodynamic marker of Ipi activity

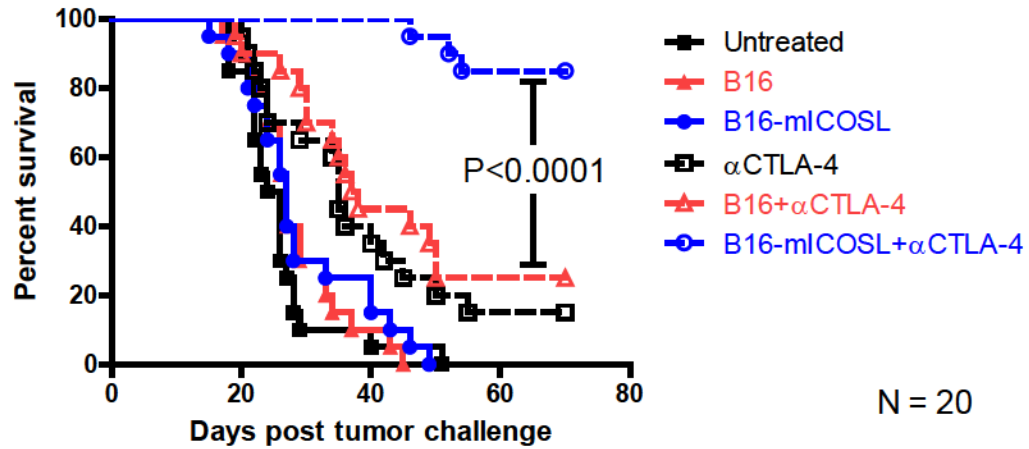
Mouse Studies

- Essential for optimal efficacy of CTLA-4 blockade
- Signaling via PI3K binding motif enhances Tbet expression
- Can be targeted to enhance efficacy of CTLA-4 blockade

Sharma and Allison

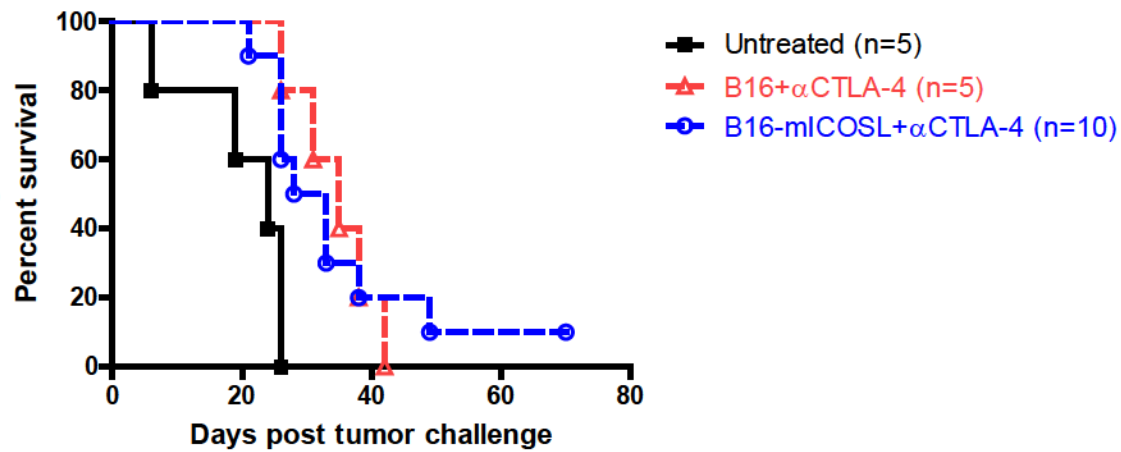
Engaging the ICOS pathway with agonist vaccine increases efficacy of anti-CTLA-4

WT



N = 20

ICOS KO

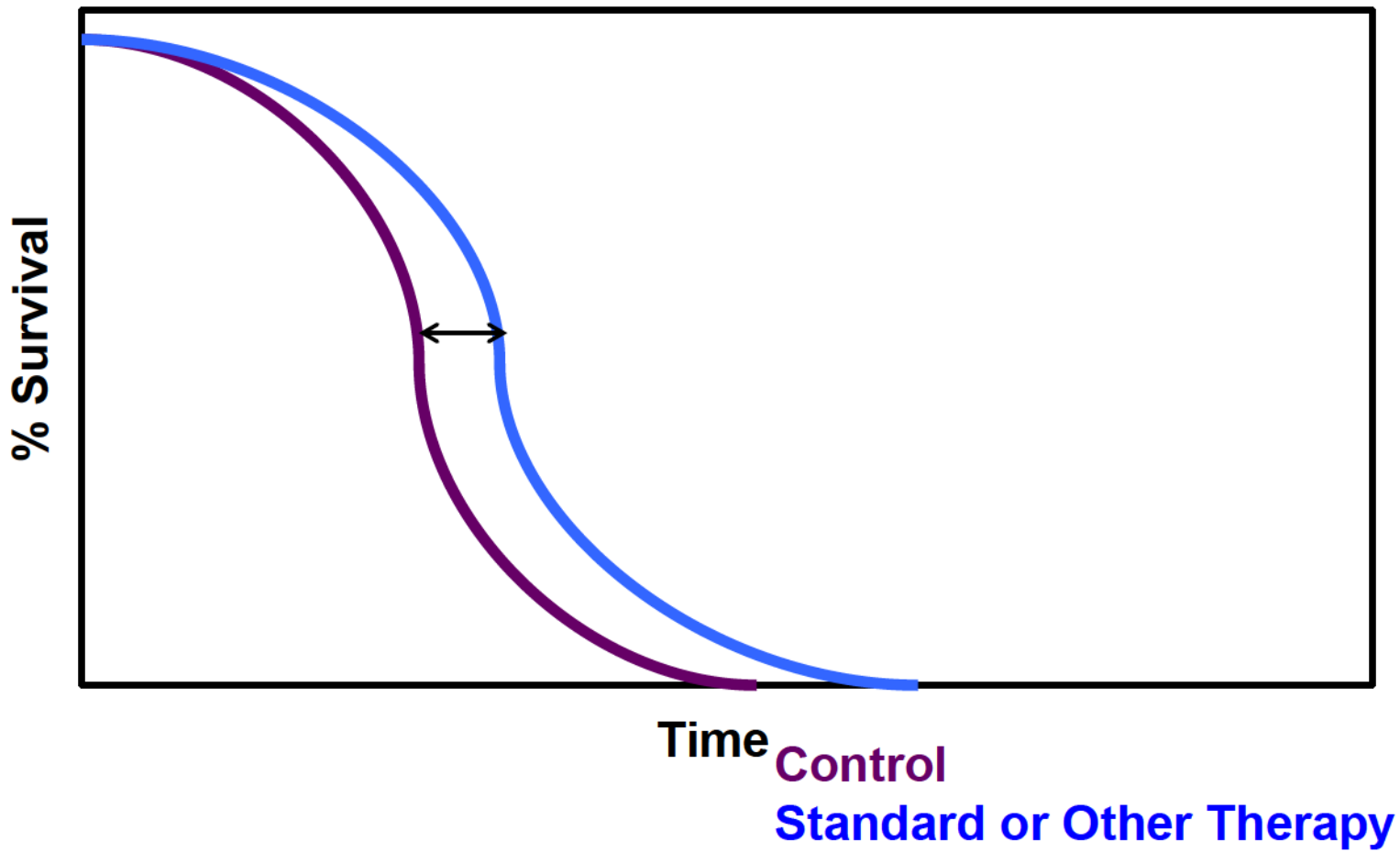


Fan et al. J Exp Med 2014

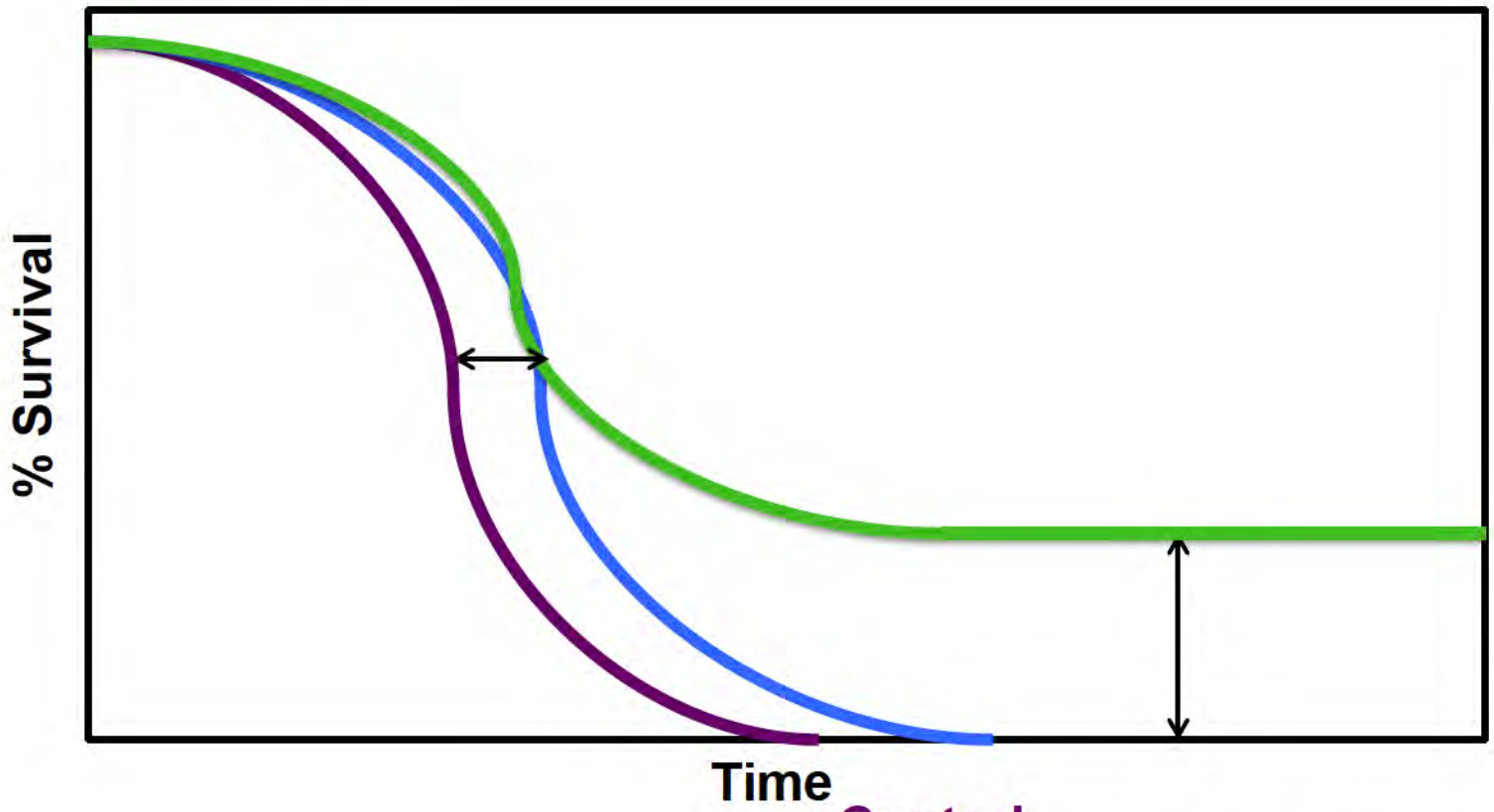
Combinations to enhance immune checkpoint targeting resulting in *CURES*

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

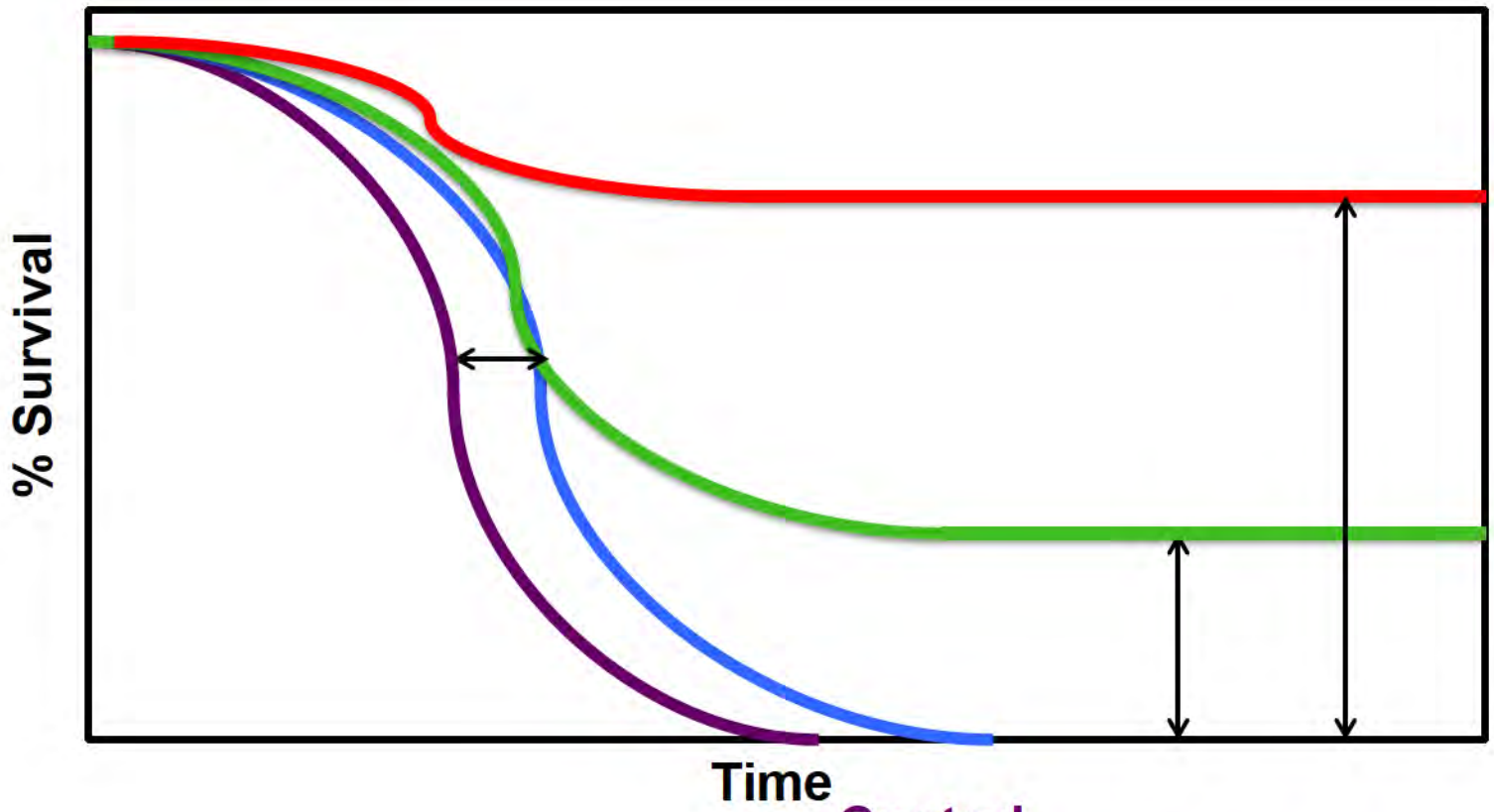
Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



Improving Survival with Combination Therapy



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