Immunotherapy combinations: From mice to man

Michael A. Curran, Ph.D.
Department of Immunology

I have research collaborations with Bristol Myers Squibb, and am a consultant for Jounce and BD.

I receive royalties from the patent “Methods and Compositions for Localized Secretion of anti-CTLA-4 Antibodies”.

I will be talking about investigational therapeutics.

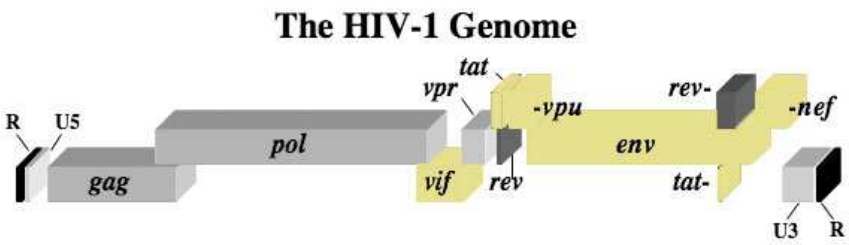
Why does the immune system fail to eliminate cancer?

Antigenic Cancer Cells Grow Progressively in Immune Hosts without Evidence for T Cell Exhaustion or Systemic Anergy

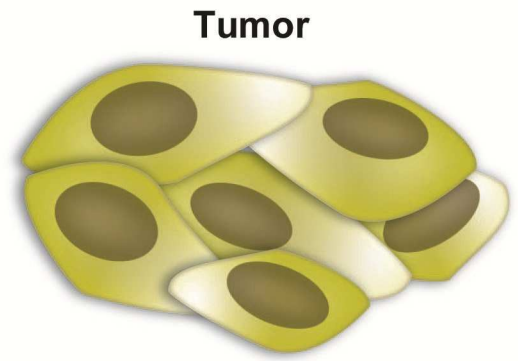
By Maresa Wick,* Purnima Dubey,* Hartmut Koeppen,* Christopher T. Siegel,‡ Patrick E. Fields,§ Lieping Chen,‖ Jeffrey A. Bluestone,§ and Hans Schreiber*

J. Exp. Med. © The Rockefeller University Press
Volume 186, Number 2, July 21, 1997 229–238

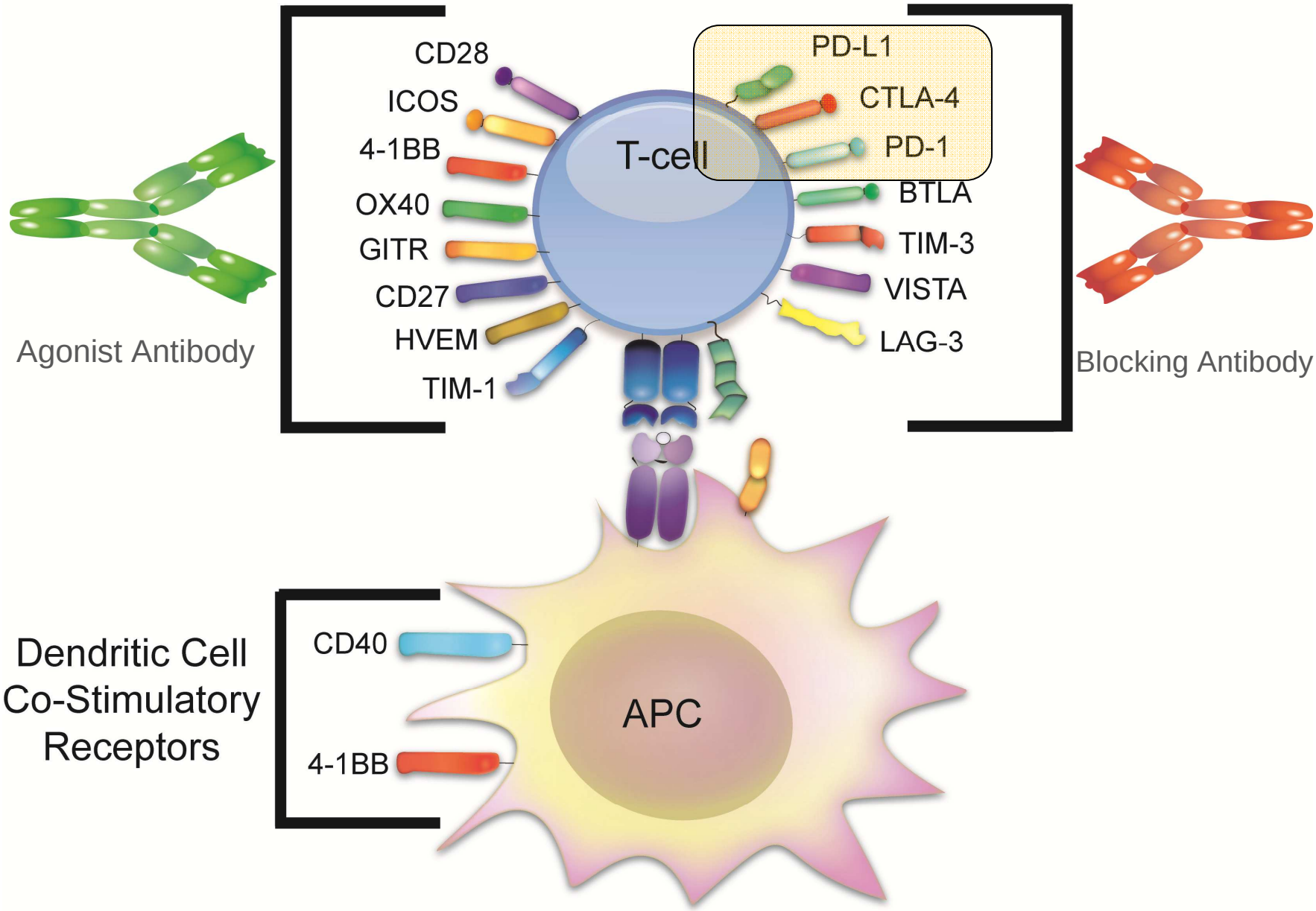
Like pathogens, tumors deploy multigenic immune evasion programs



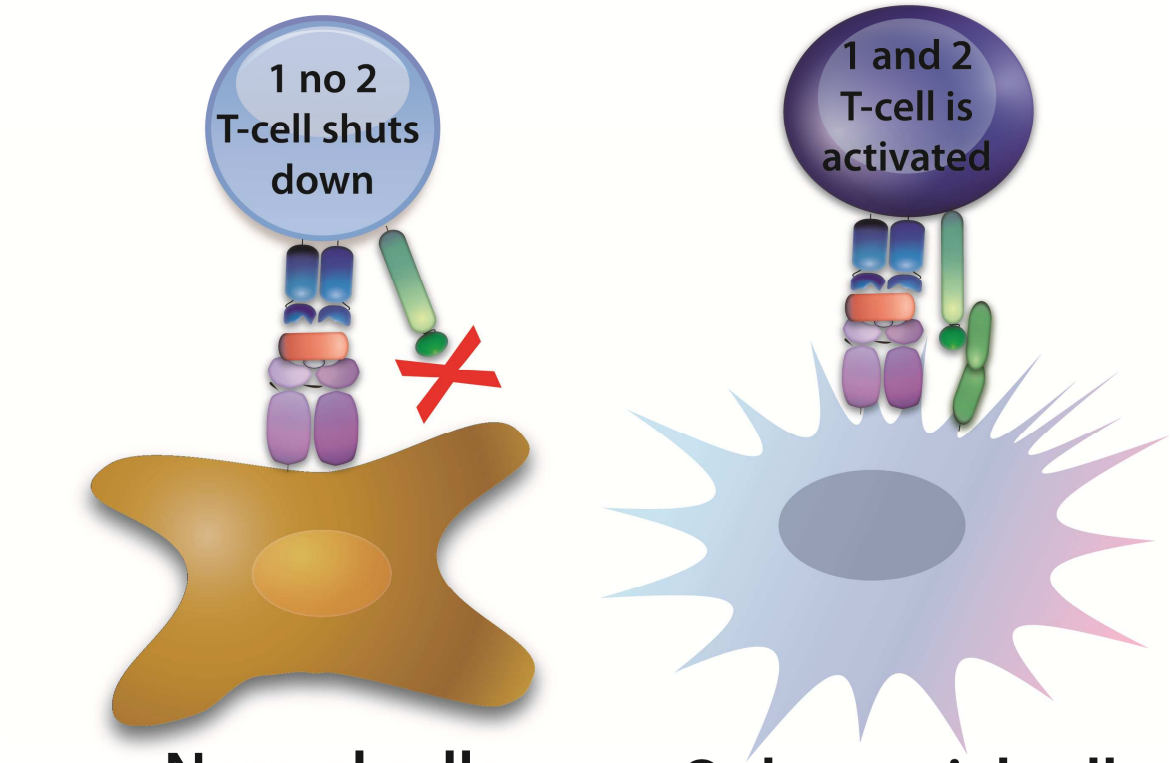
With < 9.8 kB of genome space HIV, like many other viruses devotes a large percentage of its genome to immune evasion.



Can access the entire $3x10^9$ base genome for evolutionary as well as adaptive immune evasion.


CD28
ICOS
4-1BB
OX40
GITR
CD27
HVEM
TIM-1
T-cell
PD-L1
CTLA-4
PD-1
BTLA
TIM-3
VISTA
LAG-3
Agonist Antibody
Blocking Antibody
Dendritic Cell
Co-Stimulatory
Receptors
CD40
4-1BB
APC

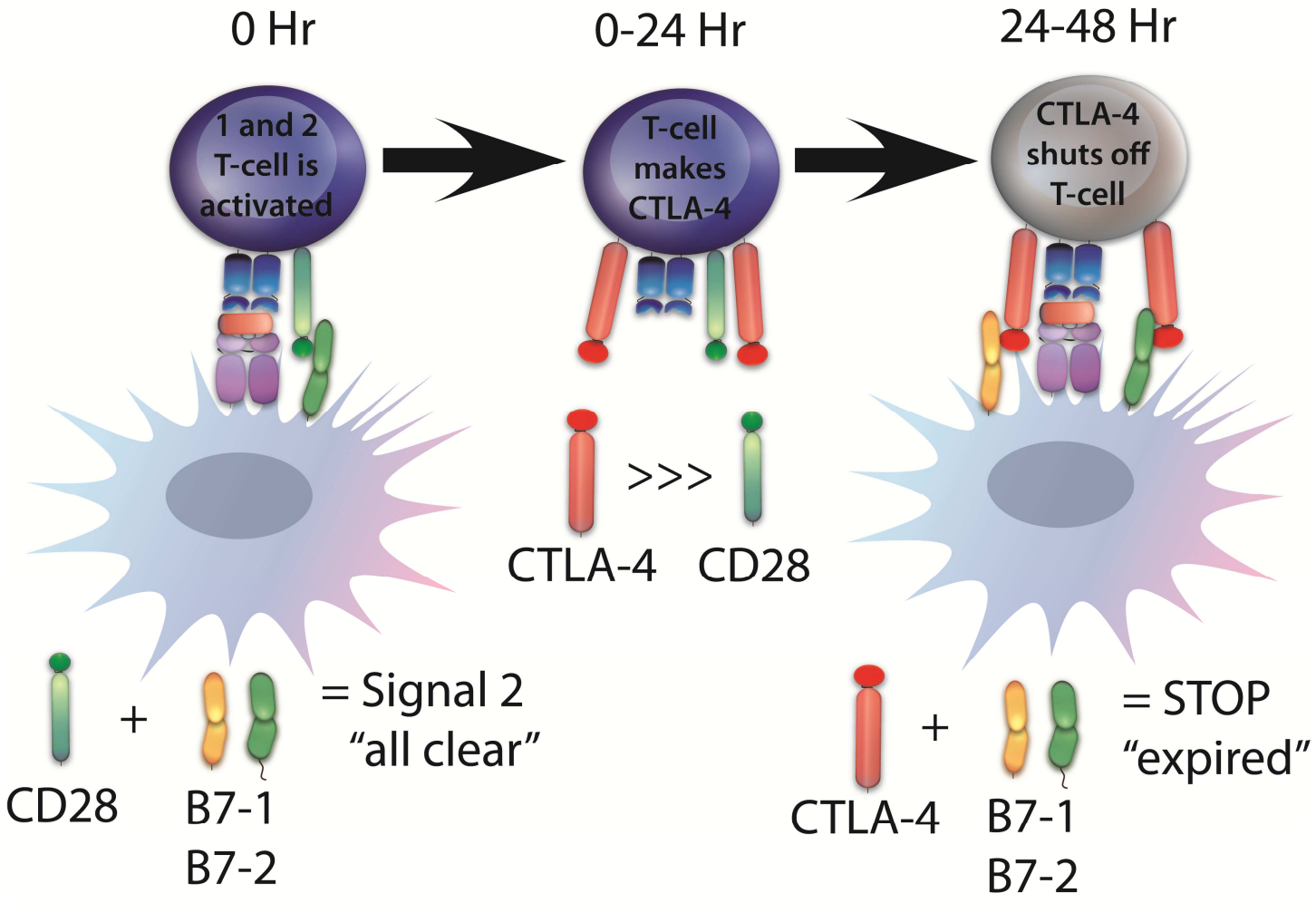
T cells are activated in two steps: T cell receptor ligation and co-stimulation



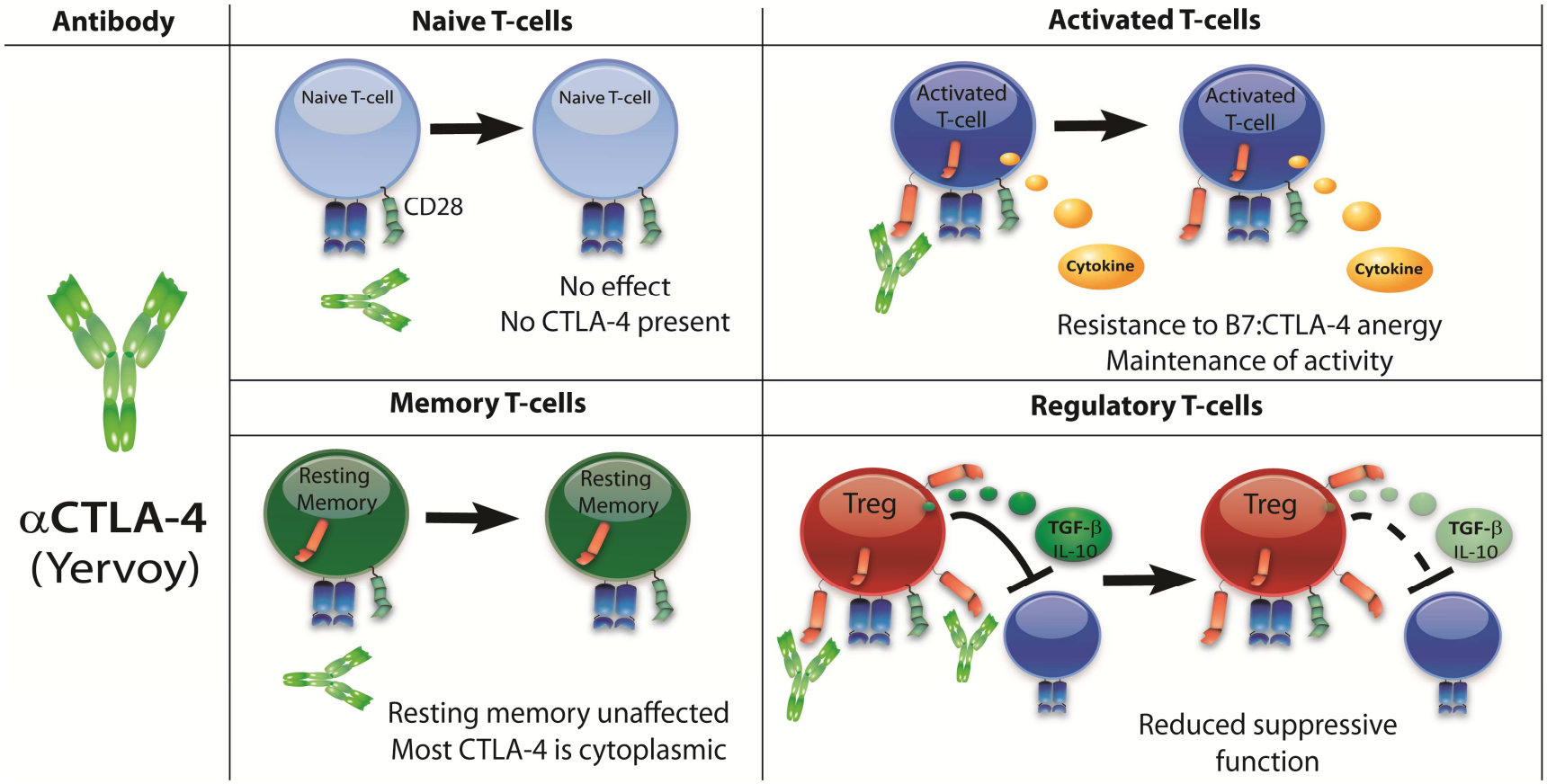
Normal cells can't activate T-cells

Only special cells like DCs can give the "all clear" 2nd signal to T-cells

CTLA-4, a negative regulator of T cell activity, limits the lifespan of activated T-cells



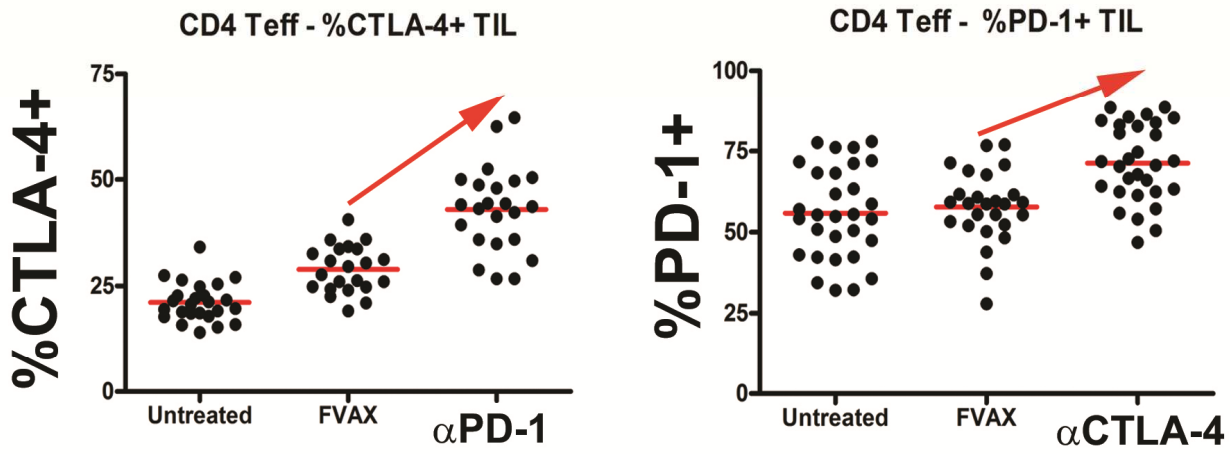
Which T-cells are affected by Ipilimumab(αCTLA-4)?



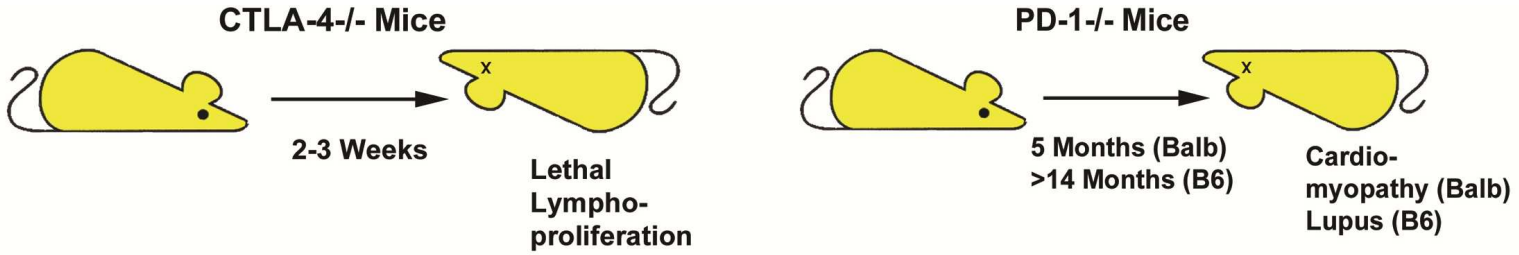
The greater the percentage of active T-cells in a patient targeting the tumor when αCTLA-4 is initiated, the greater the efficacy and selectivity should be.

Why choose to block the PD-1 and CTLA-4 pathways in combination?

Blocking one co-inhibitory receptor leads to reciprocal upregulation of the other



CTLA-4 and PD-1 inhibitory signals are non-redundant



Evidence of CTLA-4 induction and subsequent progression?

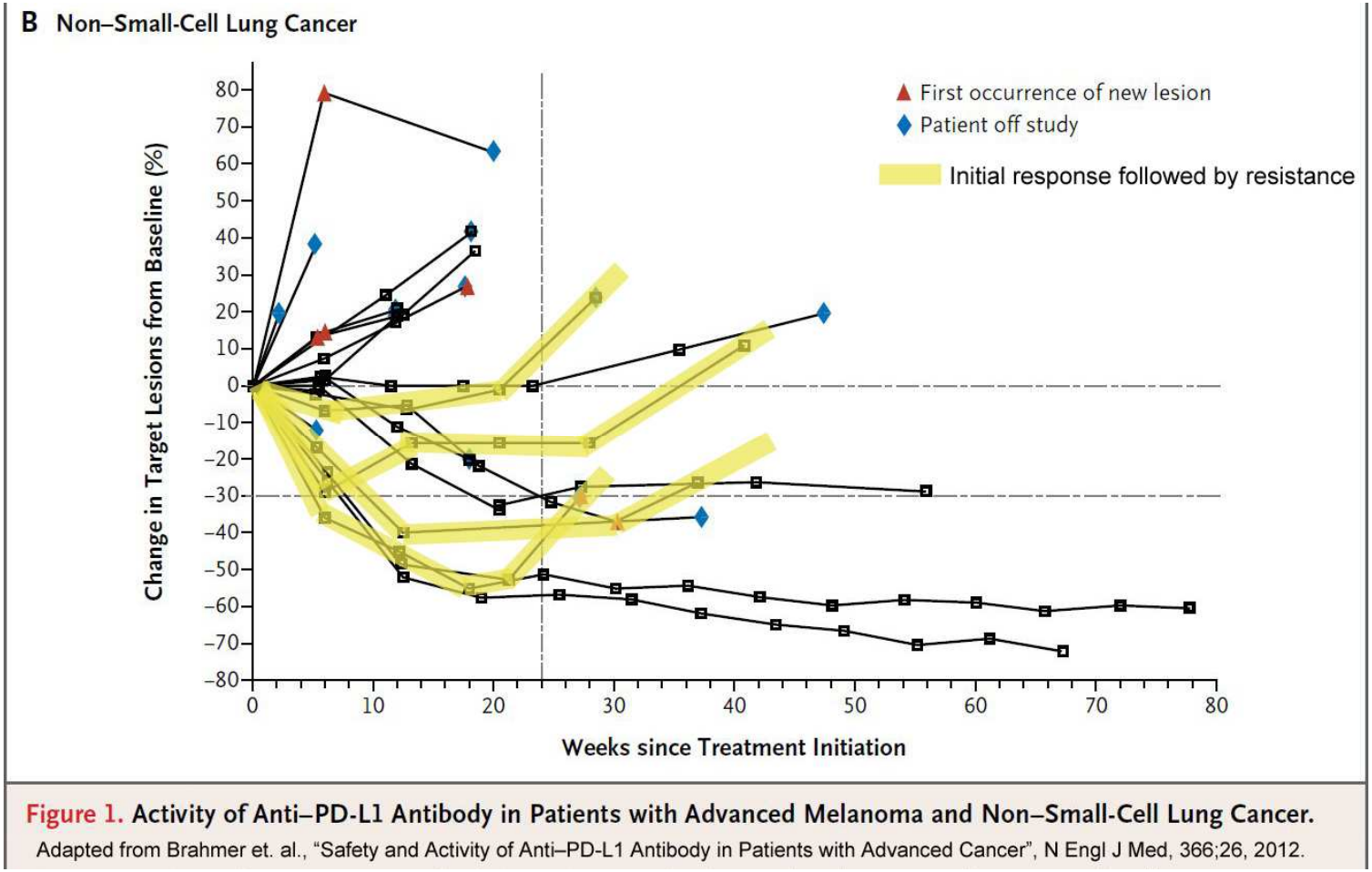


Figure 1. Activity of Anti–PD-L1 Antibody in Patients with Advanced Melanoma and Non–Small-Cell Lung Cancer.

Adapted from Brahmer et. al., "Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer", N Engl J Med, 366;26, 2012.

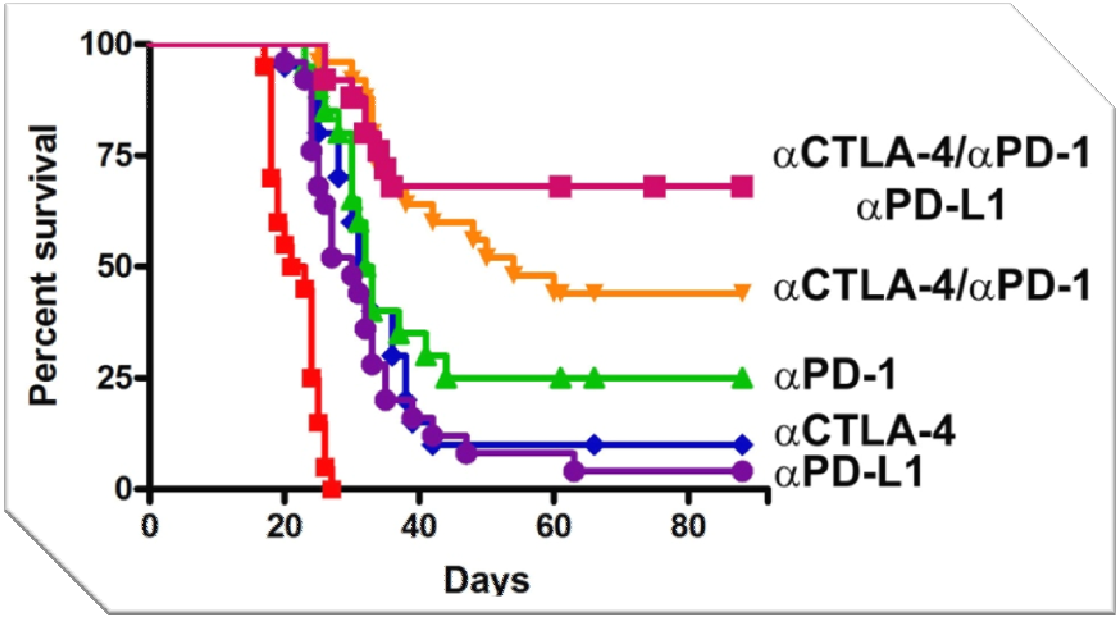
PNAS

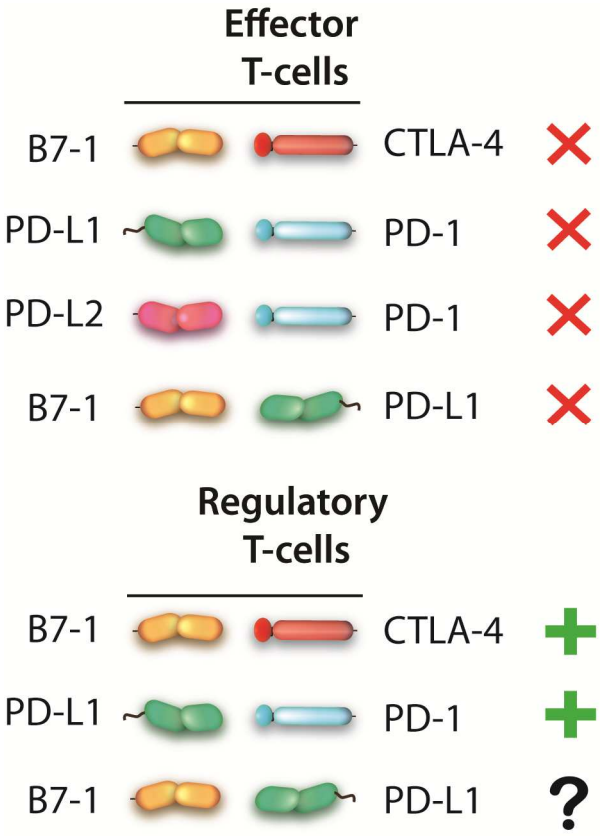
PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

Michael A. Curran[a], Welby Montalvo[a], Hideo Yagita[b], and James P. Allison[a,1]

[a]Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065; and [b]Department of Immunology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

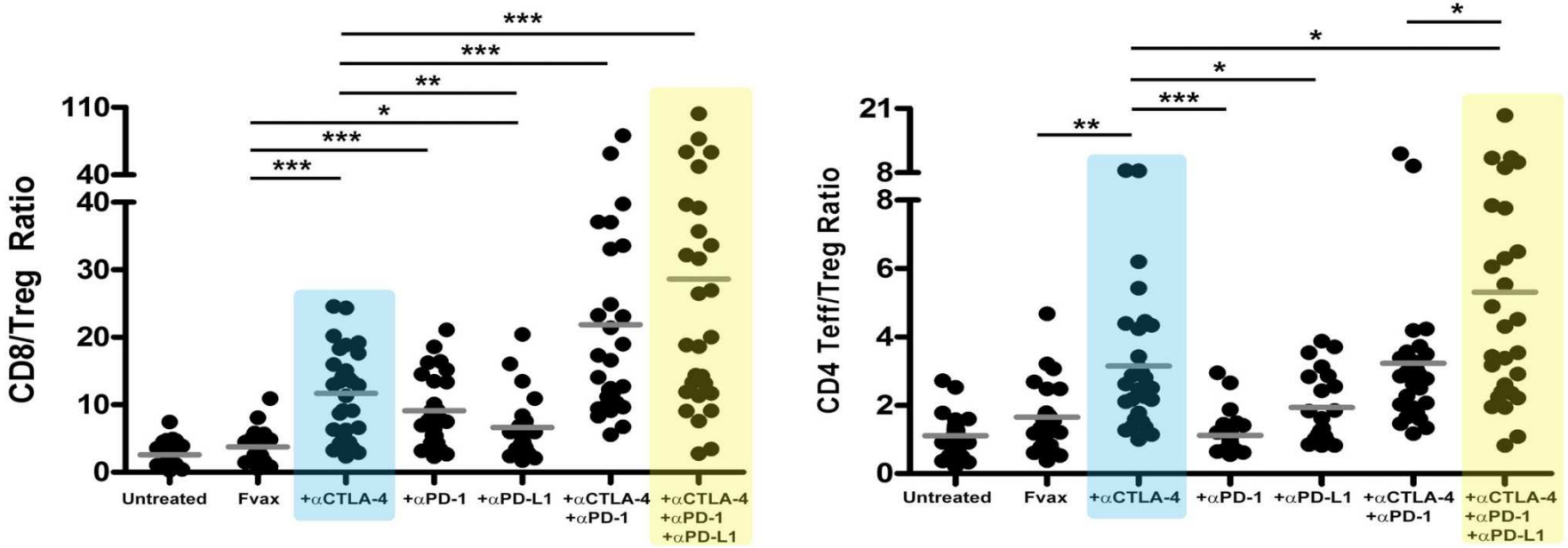
Contributed by James P. Allison, January 19, 2010 (sent for review December 17, 2009)



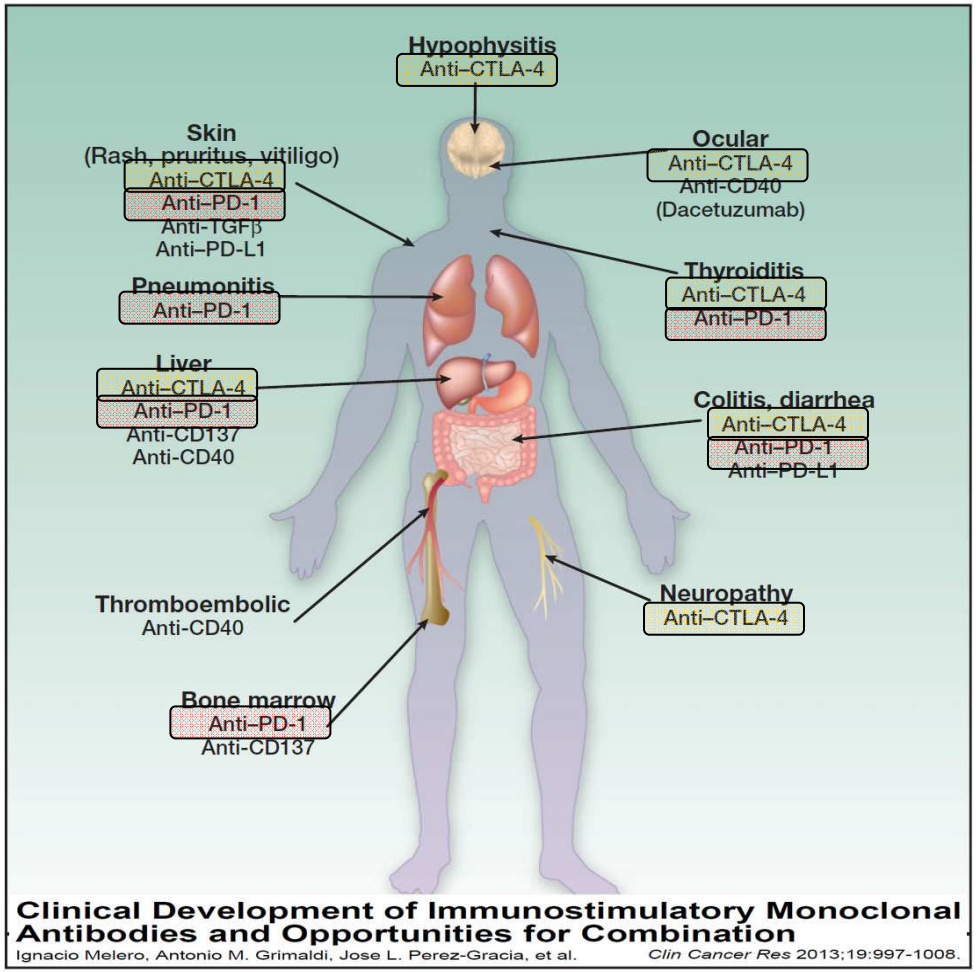


	B7-1  CTLA-4 B7-2  CTLA-4	PD-L1  PD-1 PD-L2  PD-1	B7-1  PD-L1
Inhibits T cell proliferation	+++	++	++
Reduces cytokine production	+	+++	++
Reduces cytotoxicity	+	+++	?
Reduces APC co-stimulation	++	--	--
Induces T cell apoptosis	-/+	++	?
Ligand expressed on tumor	--	++	+/-
Ligand in microenvironment	++	++	++
Supports Treg suppresion	++	++	+
Supports Teff to Treg conversion	+++	++	++

Conversion of the tumor micro-environment from suppressive to inflammatory

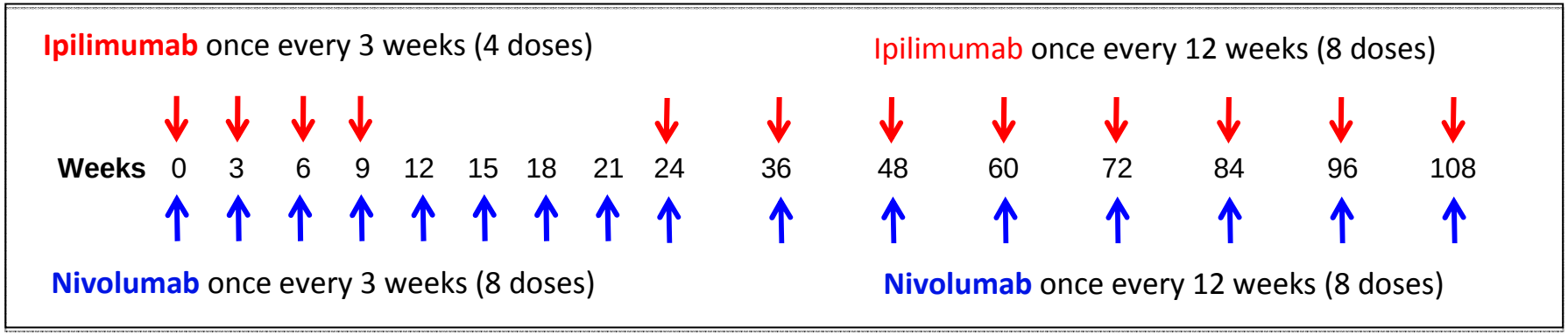


Risk/Benefit: αPD-1 monotherapy IrAE were less severe but largely overlapping with αCTLA-4

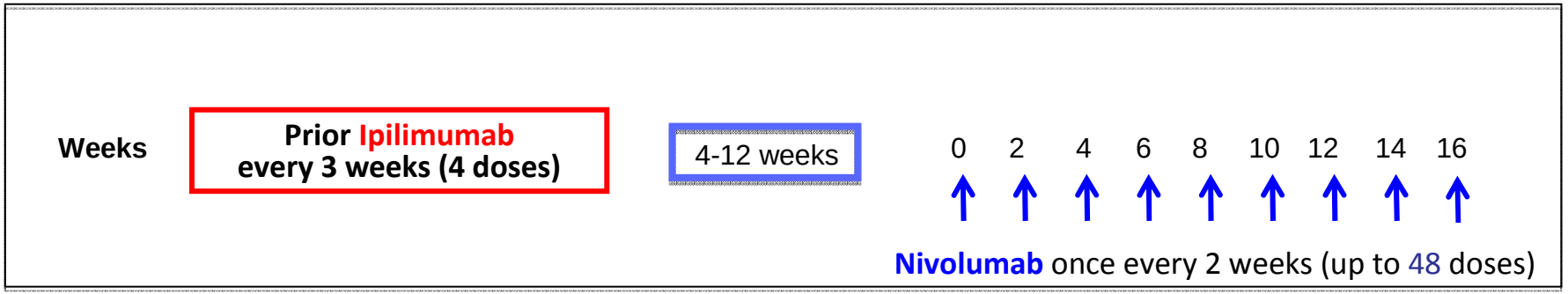


Phase I study: Concurrent and sequenced nivolumab and ipilimumab in melanoma

Concurrent Cohorts

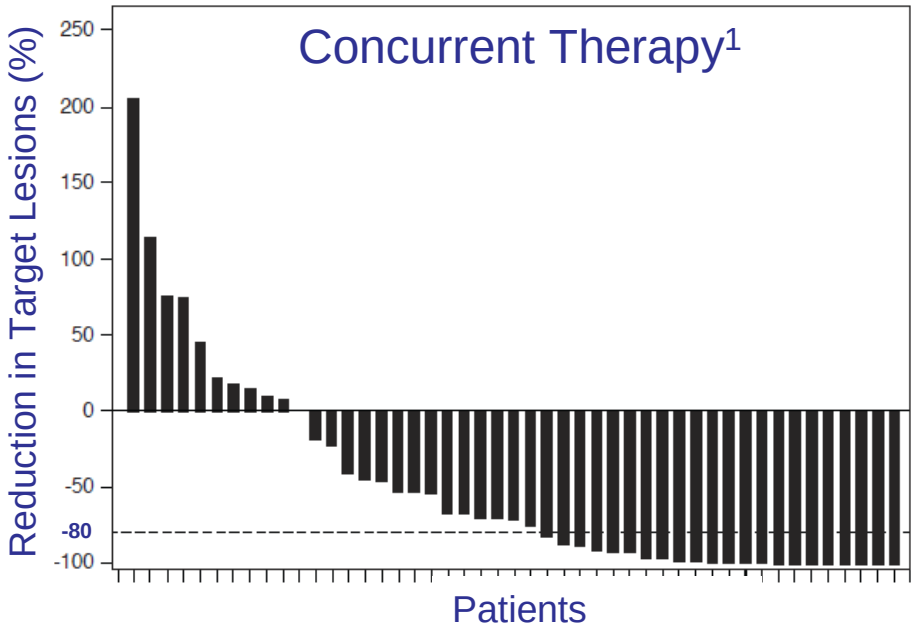


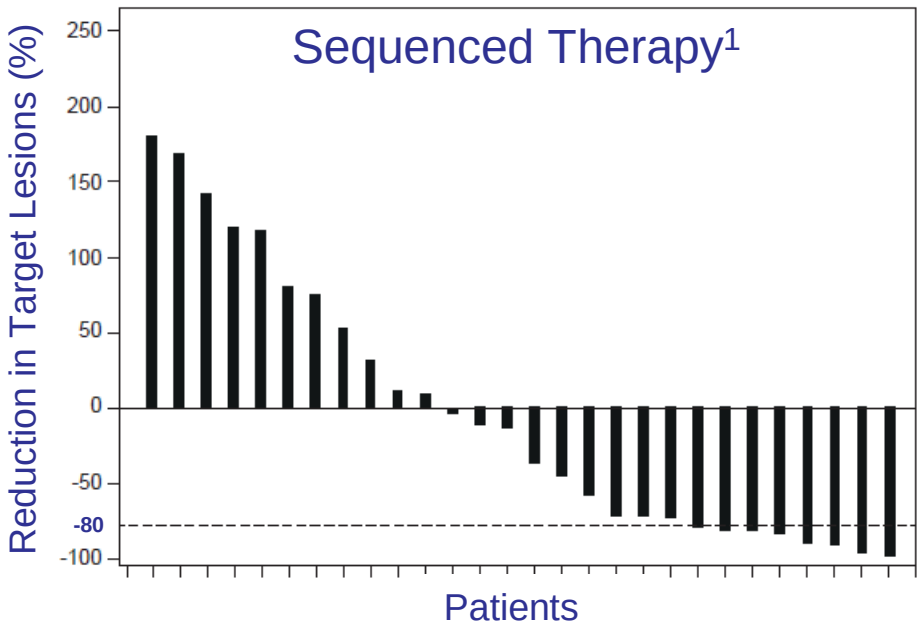
Sequenced Cohorts



- Tumor assessments by mWHO and immune-related mWHO criteria
- Data as of Feb 2013 for 86 patients are reported for the ongoing study

Clinical activity: combination of nivolumab and ipilimumab therapy



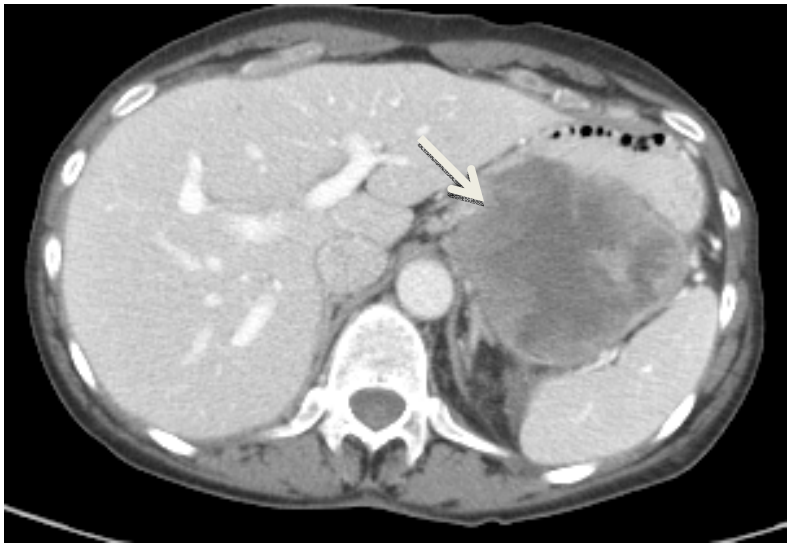


	n	ORR	Patients with ≥80% Tumor Reduction at 12 Wk
Ipilimumab (3 mg/kg)[2]	137	11%	<2
Nivolumab (3 mg/kg)[3]	17	41%	<3
Concurrent therapy[1] (3 mg/kg ipilimumab + 1 mg/kg nivolumab)	17	53%	41%

Wolchok et al. ASCO 2013, abs 9012, oral presentation. Hodi et al. N Engl J Med 2010;363:711-23. Topalian et al. N Engl J Med 2012;366:2443-54.

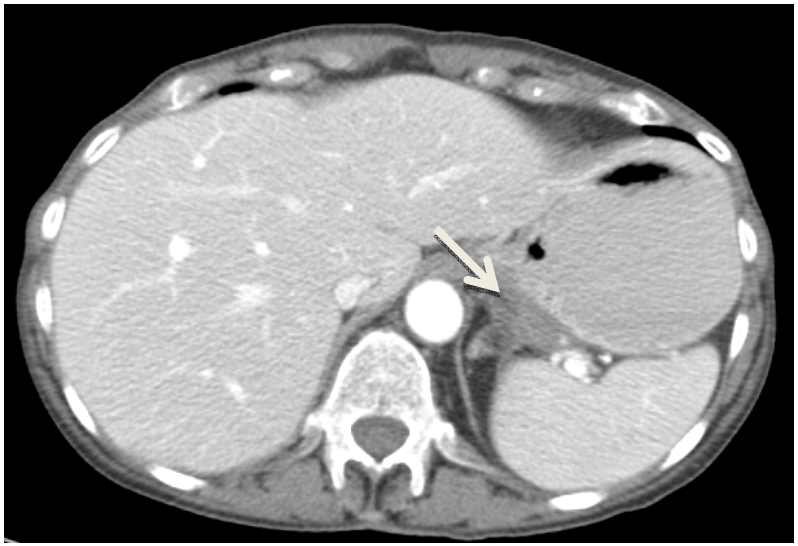
Patient 011 (MSKCC) – Dramatic Response

Pre-treatment

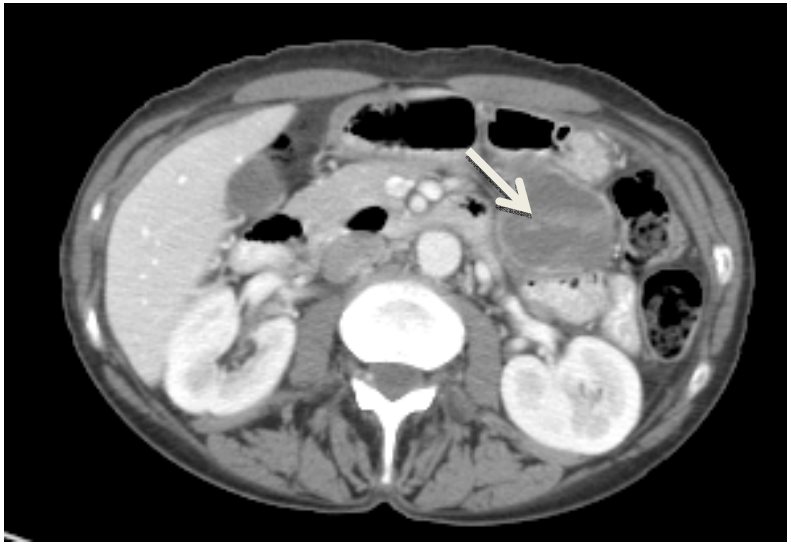


10 cm gastric mass

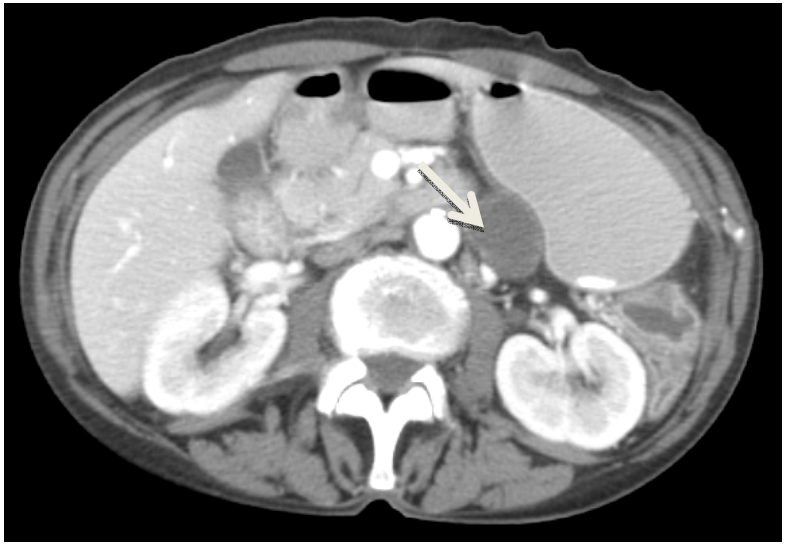
12 weeks



3.7 cm gastric mass



5 cm peripancreatic mass



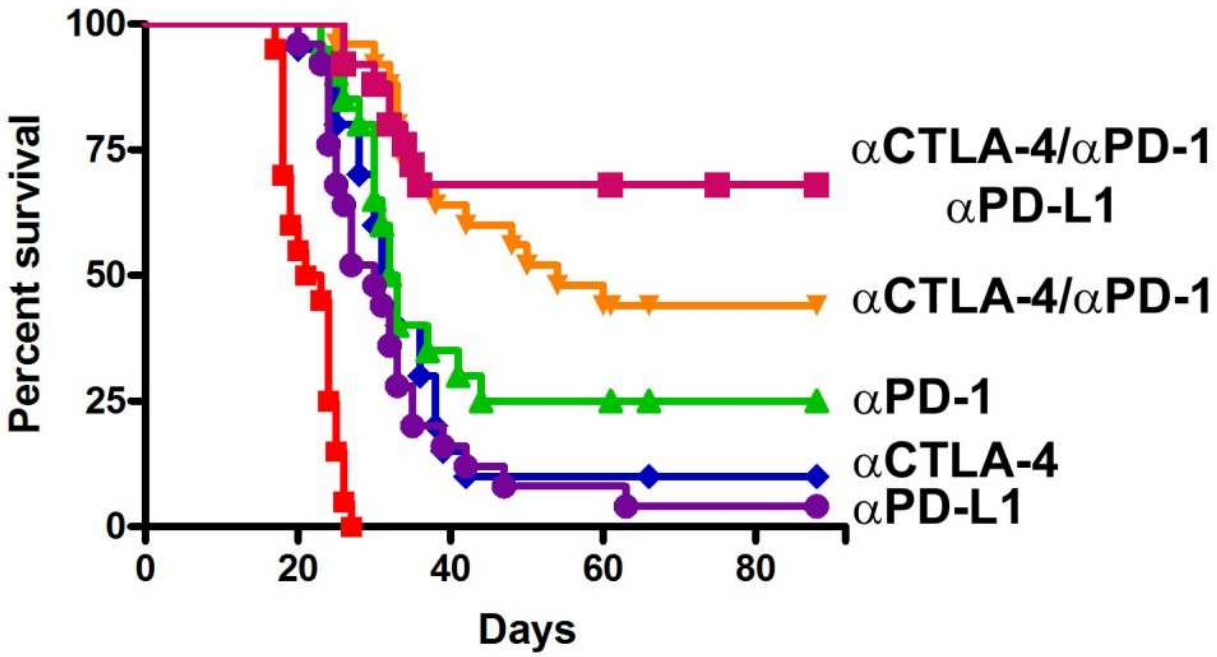
3.2 cm peripancreatic mass

Using what we know from the murine studies, what potential biomarkers should we monitor?

Ipilimumab / Nivolumab Combination Monitoring Panel

T-cell Gating:	Inhibitory:	Activation:	PD-1 Monitoring:
Live/Dead	CTLA-4	Icos	αhIgG4 (detects α PD-1)
CD3, CD8	Tim-3	Ki-67	αPD-1 MIH4 (total surface)
CD4, FoxP3	LAG-3	Granzyme B	αPD-1 EH12 (total unblocked)

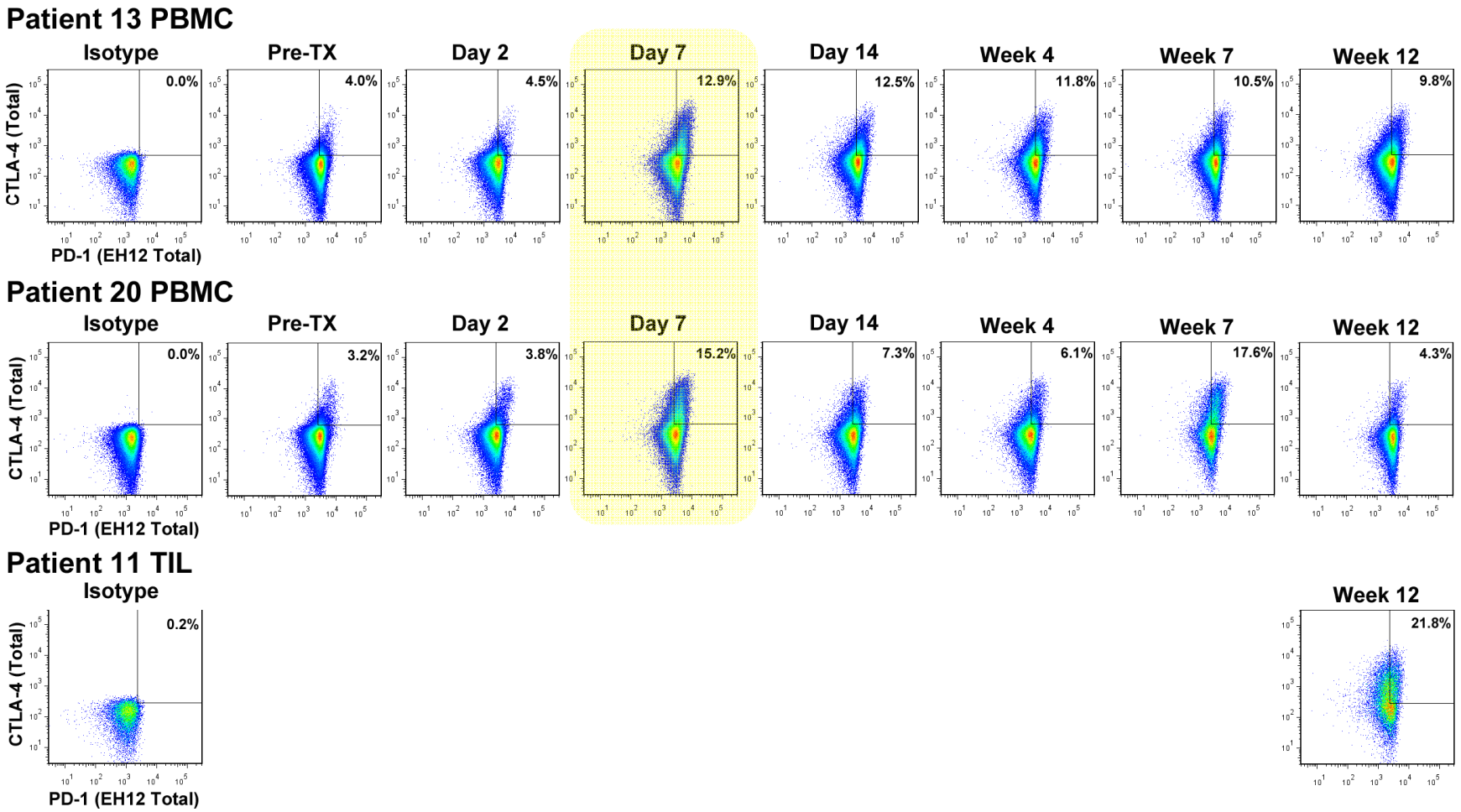
In the mouse, accumulation of CTLA-4 / PD-1 double positives in TIL correlates with tumor rejection



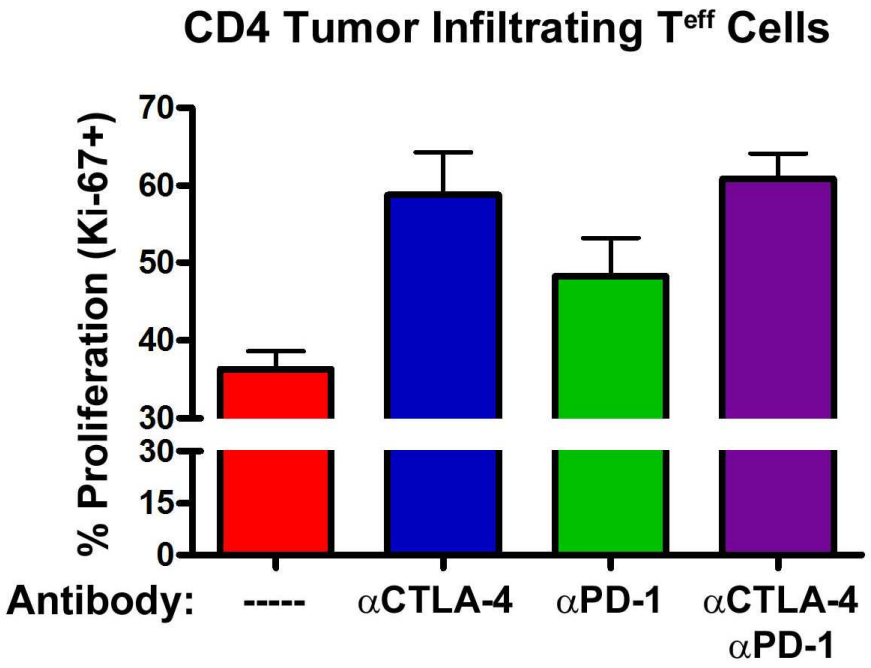
32%/25%

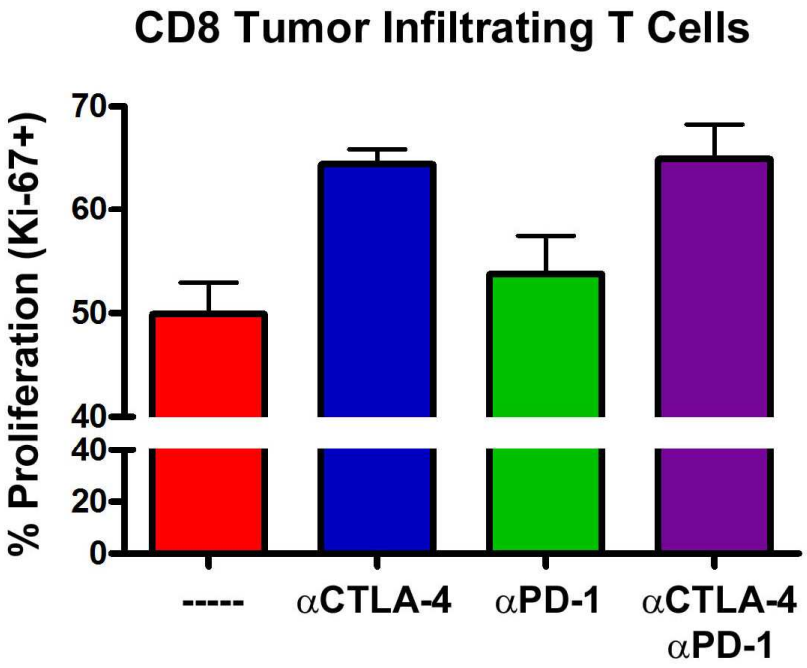
	%CTLA4/PD1+ CD8 T-cells	%CTLA4/PD1+ CD4 T-eff
αCTLA-4/αPD-1 αPD-L1	80%	62%
αCTLA-4/αPD-1	77%	51%
αPD-1	70%	41%
αCTLA-4	54%	38%
αPD-L1	54%	36%

Increase in circulating CTLA-4+/PD-1+ CD4 T^{eff} following treatment

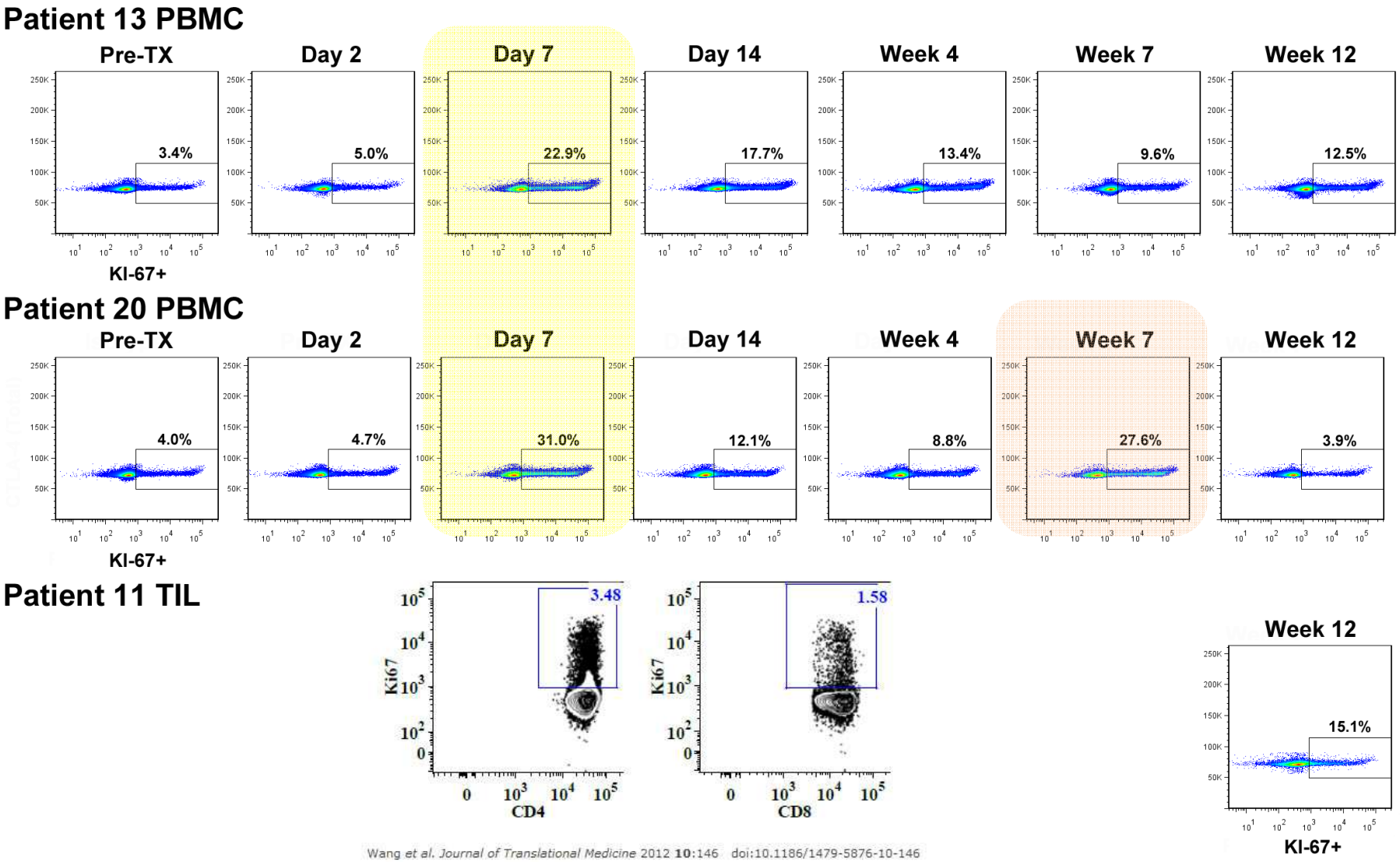


In the mouse combination co-inhibitory blockade leads to increased proliferation of TIL but offers little benefit over αCTLA-4 alone





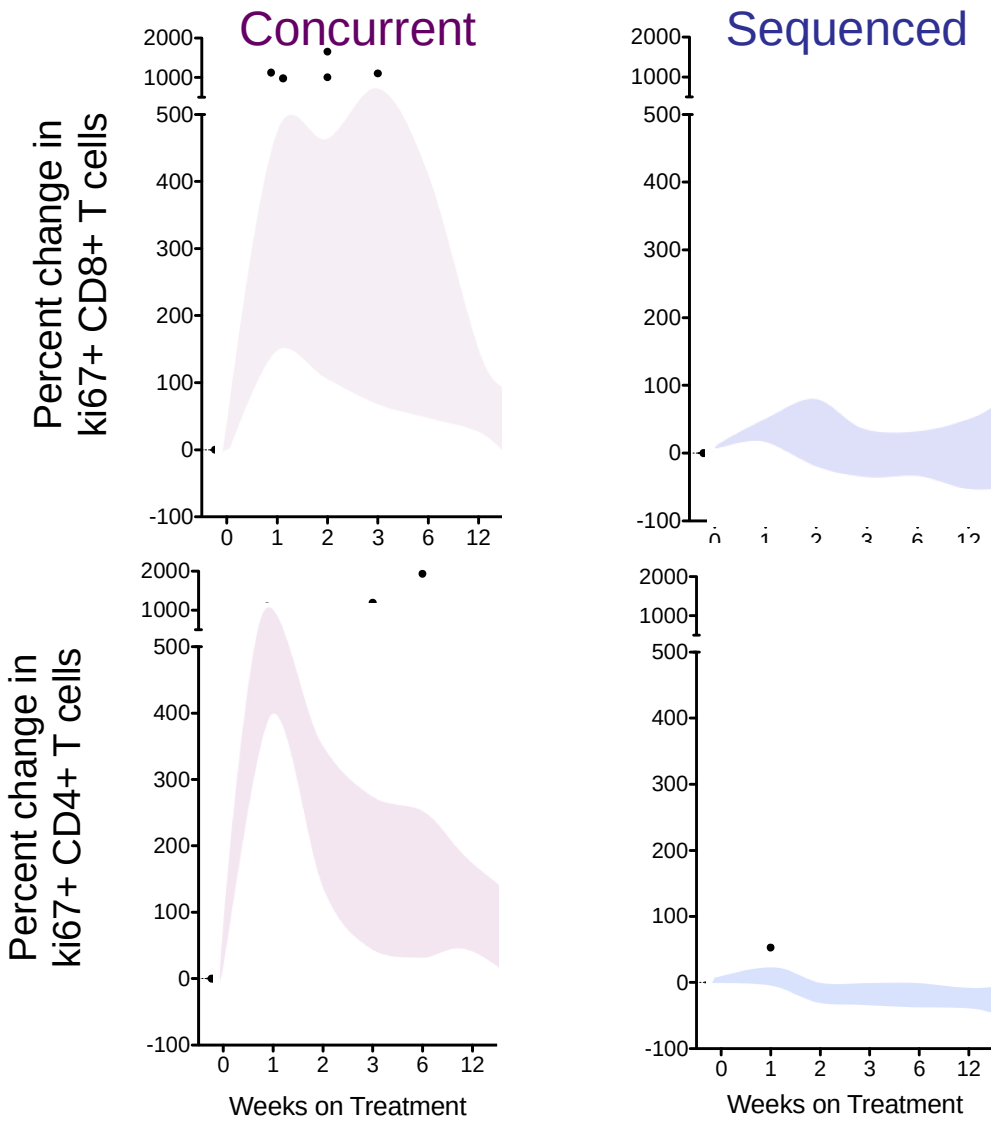
Durable increases in CD4 T^{eff} proliferation following treatment



Wang *et al. Journal of Translational Medicine* 2012 **10**:146 doi:10.1186/1479-5876-10-146

LS25

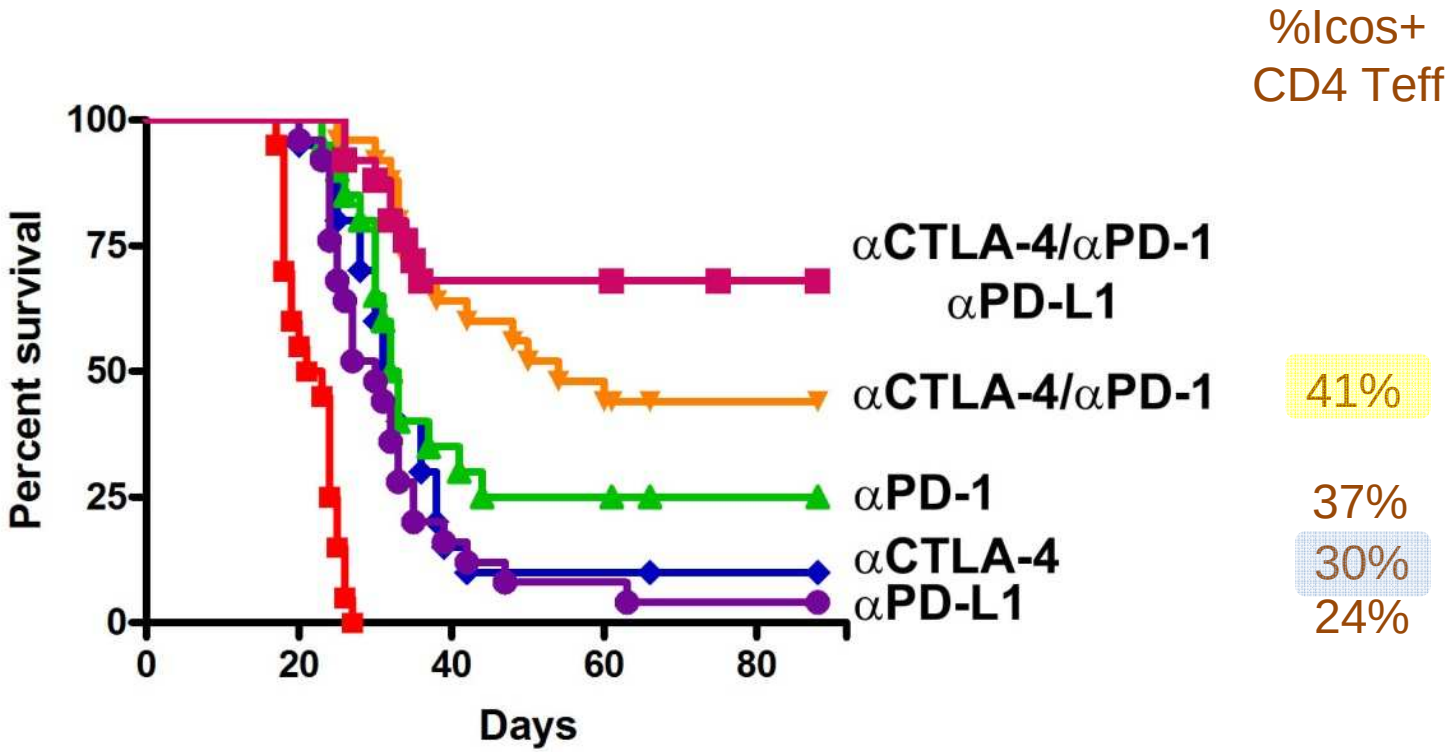
Increased frequency of activated **(ki67+)** CD4 and CD8 T cells with concurrent nivolumab + ipilimumab



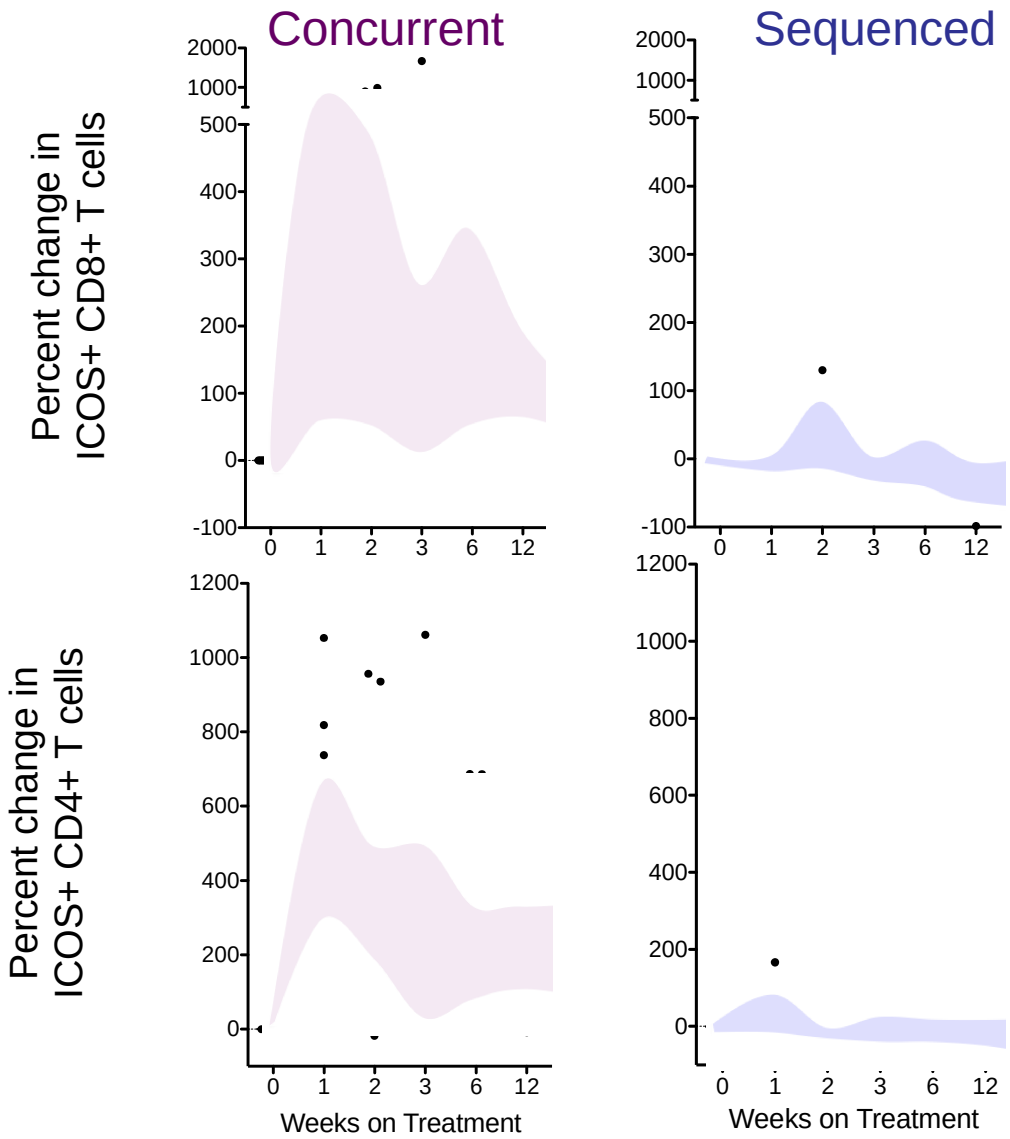
Slide 23

LS25 Christian suggests that this slide be deleted and only the ICOS data on the next slide be presented.
Or show CD4 data for ICOS and ki67 and at the bottom of the slide state
"A similar effect was seen for ICOS + and ki67+ CD8 T cells"
Leinbach, Susan, 5/14/2013

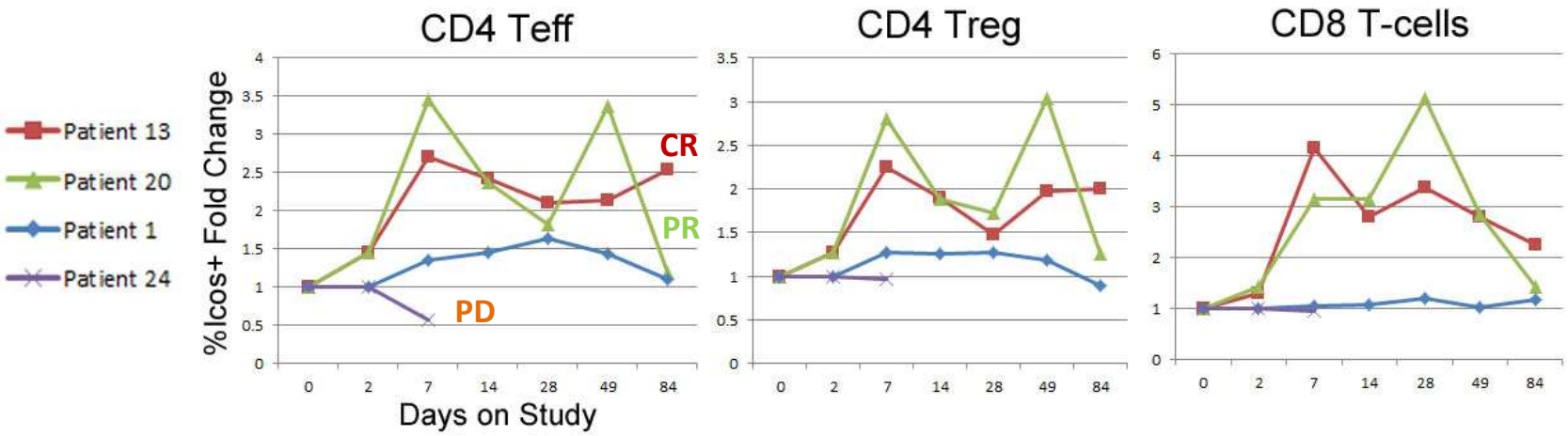
In the mouse, increased Icos expression on CD4 T-cells, especially Tregs, correlates with response to αCTLA-4/αPD-1 blockade

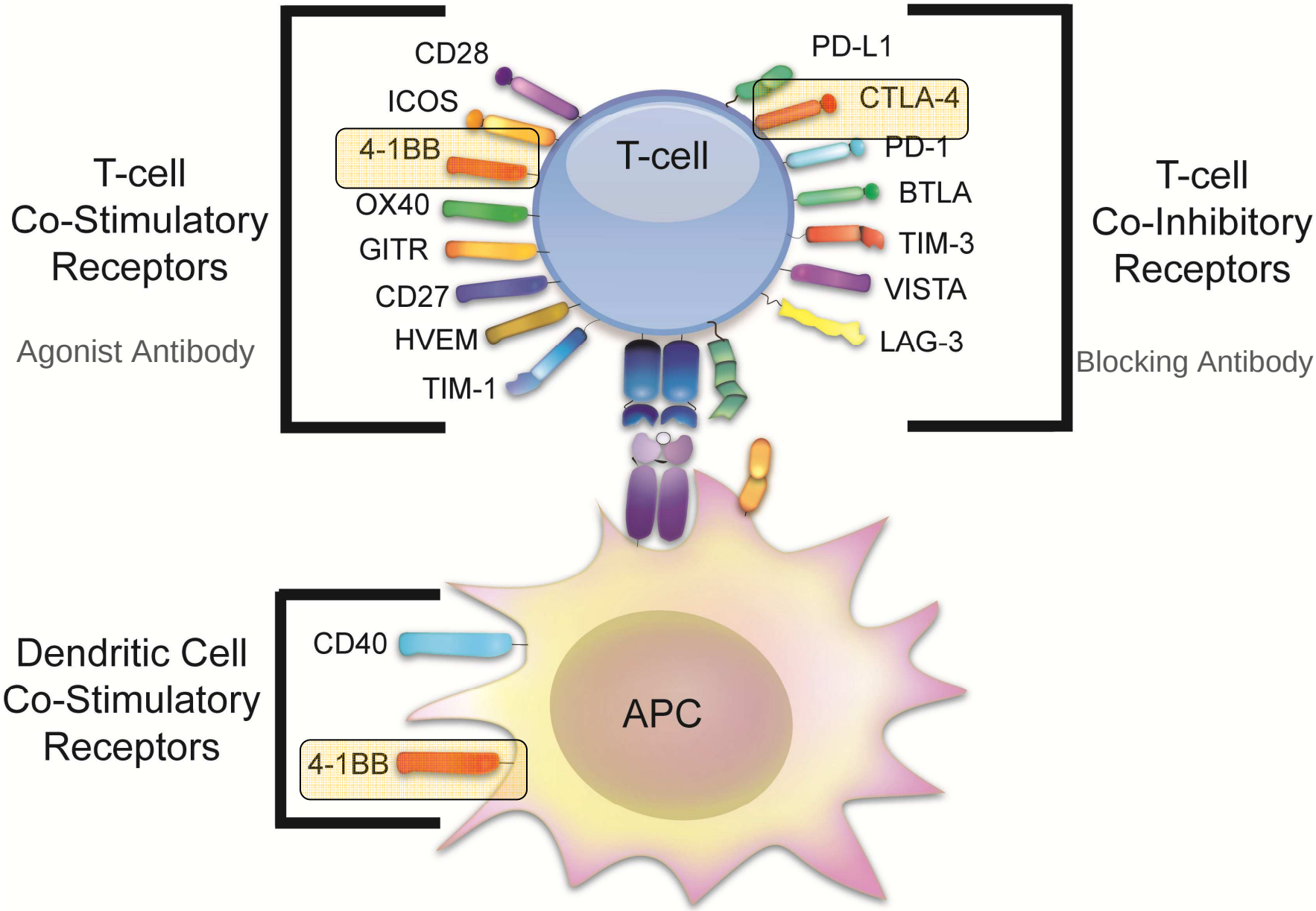


Increased frequency of activated **(ICOS+)** CD4 and CD8 T cells with concurrent nivolumab + ipilimumab



In some patients Icos upregulation correlates with clinical response




T-cell
Co-Stimulatory
Receptors
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CD28
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T-cell
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TIM-3
VISTA
LAG-3
T-cell
Co-Inhibitory
Receptors
Blocking Antibody
Dendritic Cell
Co-Stimulatory
Receptors
CD40
4-1BB
APC

Tumor infiltrating T-cells from α4-1BB treated mice upregulated KLRG1 on most CD8s and ~50% of CD4s

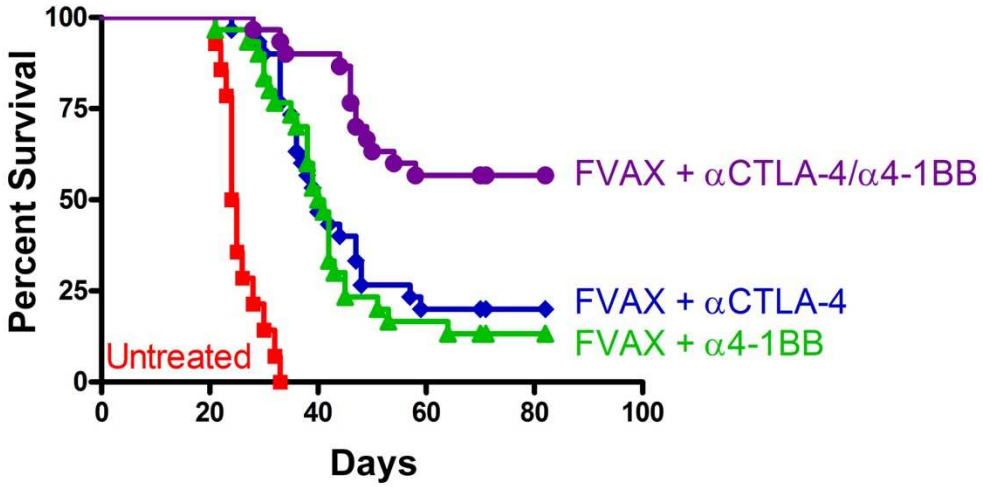
OPEN ACCESS Freely available online

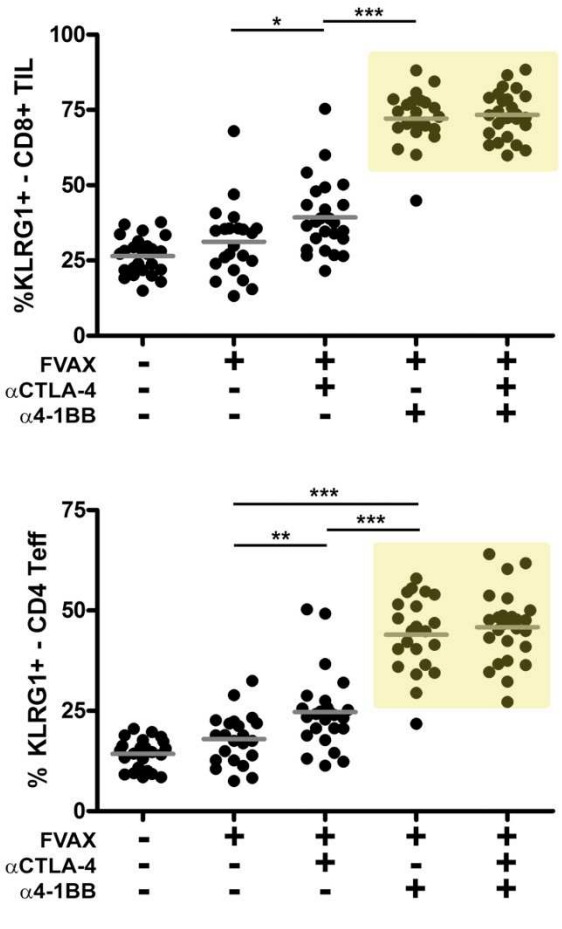
PLoS one

Combination CTLA-4 Blockade and 4-1BB Activation Enhances Tumor Rejection by Increasing T-Cell Infiltration, Proliferation, and Cytokine Production

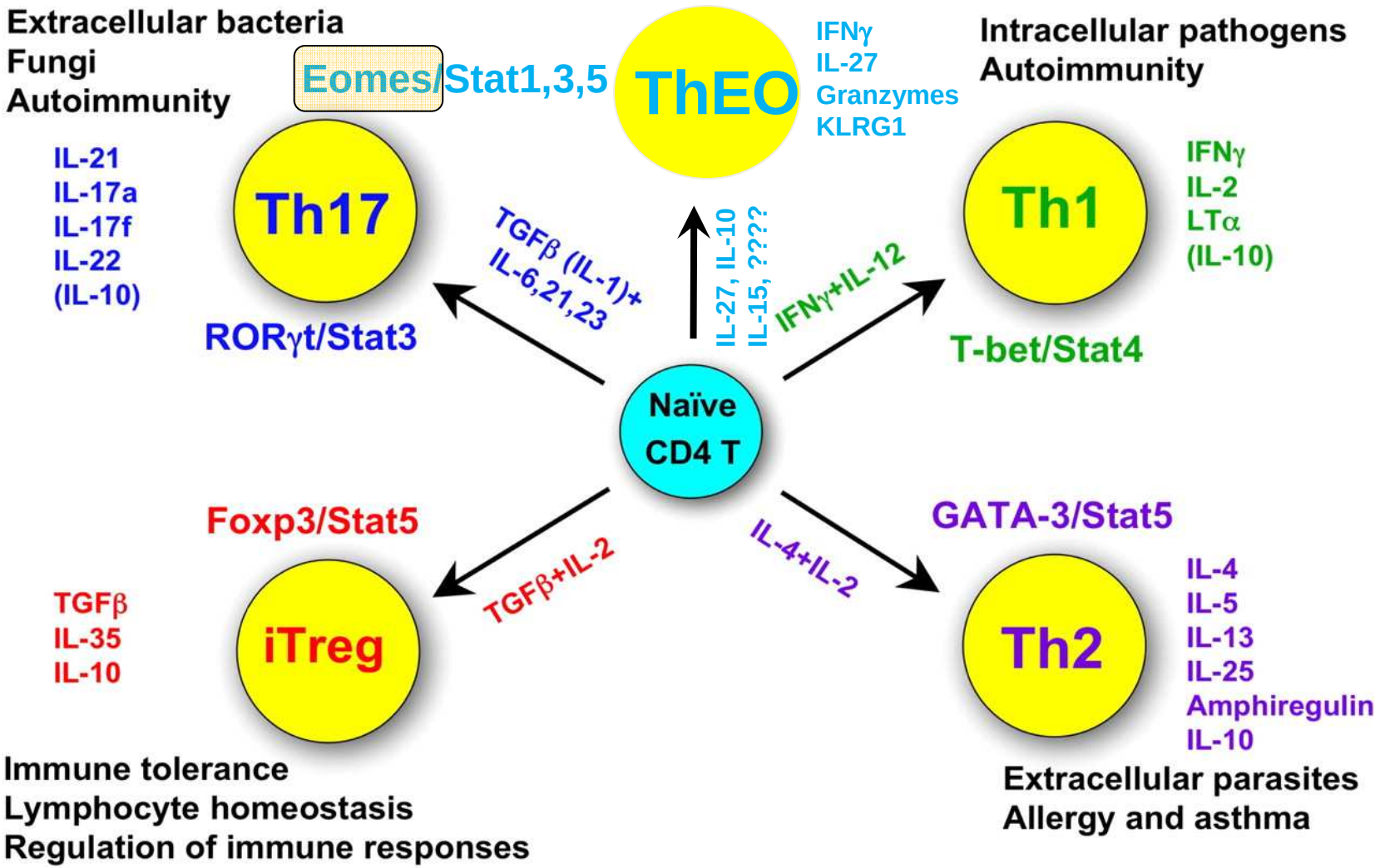
Michael A. Curran[1], Myoungjoo Kim[1], Welby Montalvo[1], Aymen Al-Shamkhani[2], James P. Allison[1]*

Received November 29, 2010; **Accepted** April 7, 2011; **Published** April 29, 2011





We have termed this CD4+ T-cell phenotype ThEO and the corresponding CD8 phenotype TcEO

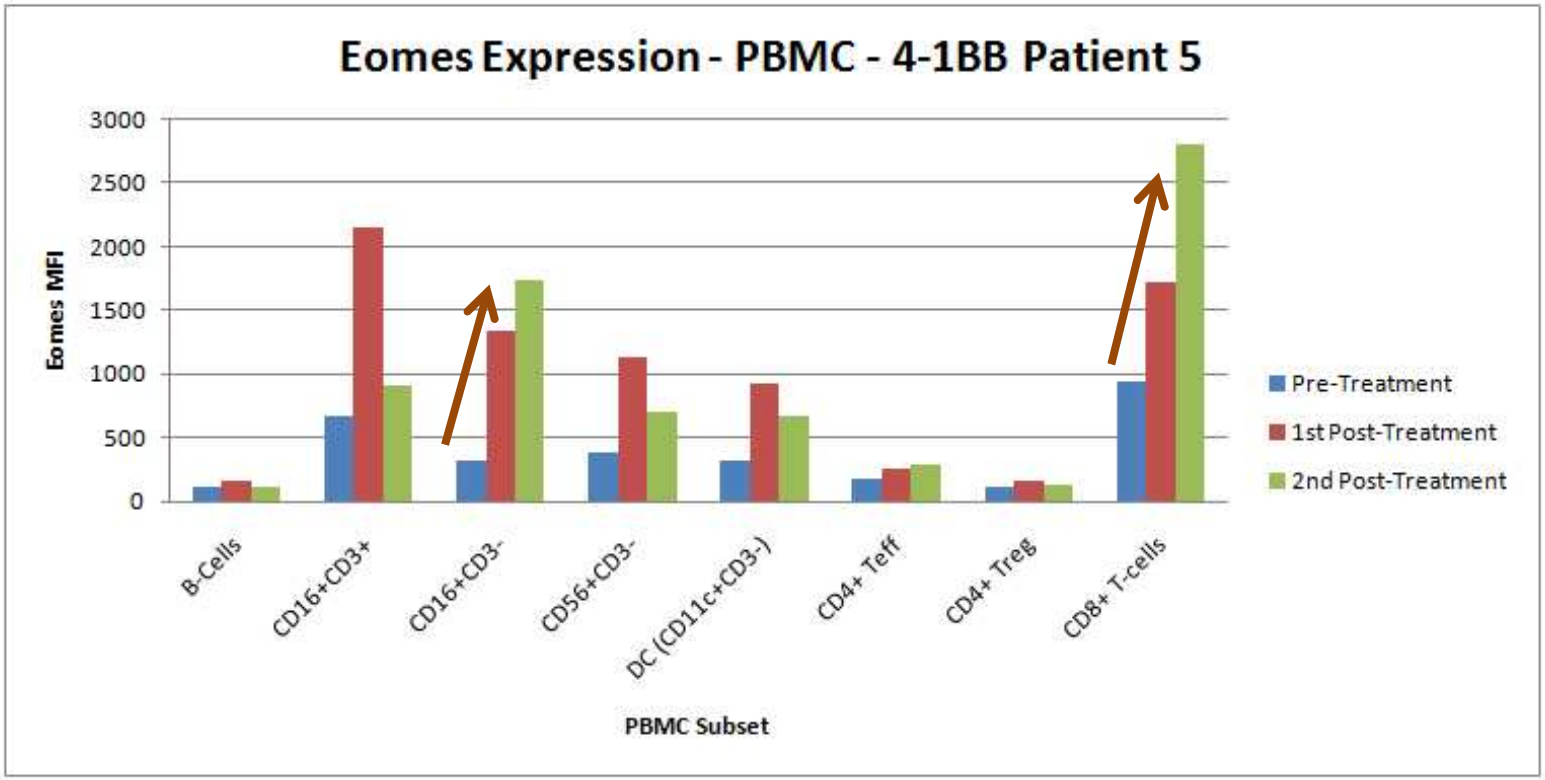


Using what we know from the murine studies, what potential biomarkers should we monitor?

Urelumab (α4-1BB/αCD137) Patient Monitoring Panel

Population Gating:	ThEO Phenotype:	Activation:	Inhibitory:
Live/Dead, CD3	Eomes, KLRG1	Icos	CTLA-4
CD8, CD4, FoxP3	Granzyme A, B, K	Ki-67	PD-1
CD16, CD56, CD11c			

Preliminary data suggests αCD137 treatment evokes Eomes upregulation in patient PBMC



1) Is Eomes upregulation in PBMC a marker of pharmacologic response to the antibody?

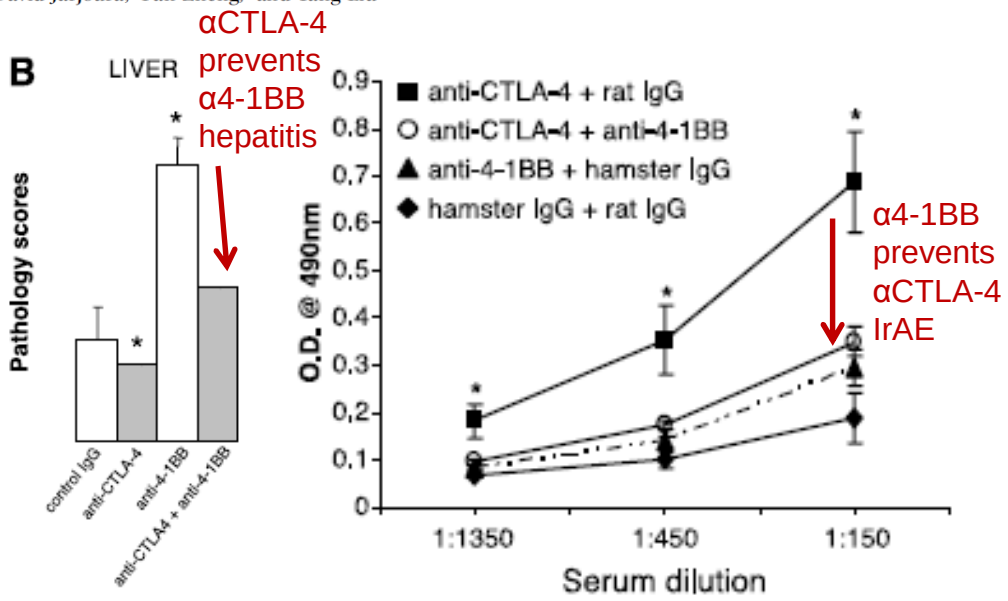
2) Does Eomes (and KLRG1) upregulation on PBMC correlate with clinical response?

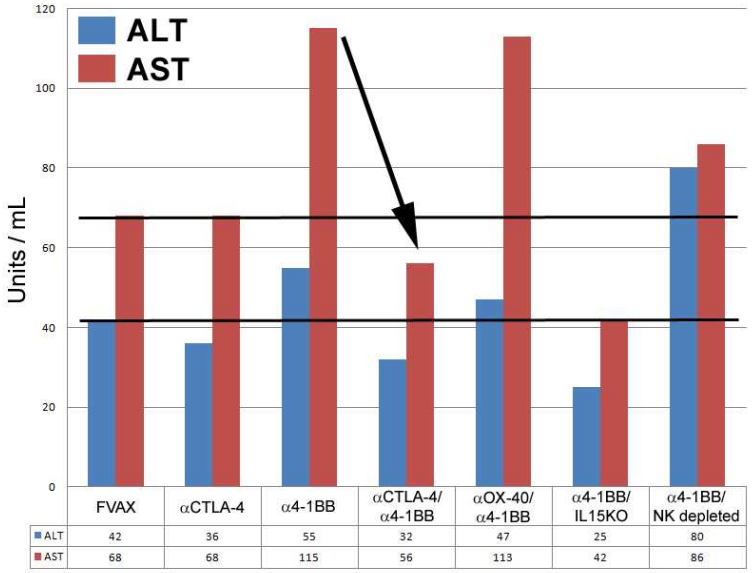
What is the root of 4-1BB induced liver inflammation and how is it ameliorated by αCTLA-4?

Research Article

Combination Therapy with Anti–CTL Antigen-4 and Anti-4-1BB Antibodies Enhances Cancer Immunity and Reduces Autoimmunity

Ergun Kocak,[1,2] Kenneth Lute,[1] Xing Chang,[1] Kenneth F. May, Jr.,[1] Katie R. Exten,[1] Huiming Zhang,[1] Shahab F. Abdessalam,[2] Amy M. Lehman,[3] David Jarjoura,[3] Pan Zheng,[1] and Yang Liu[1]





4-1BB agonist and CTLA-4 blocking antibodies were able to mutually ameliorate each others' side affects in the mouse.

Combination of Anti-CD137 & Ipilimumab in Patients With Melanoma

This study has been withdrawn prior to enrollment.

Sponsor:
Bristol-Myers Squibb

Information provided by:
Bristol-Myers Squibb

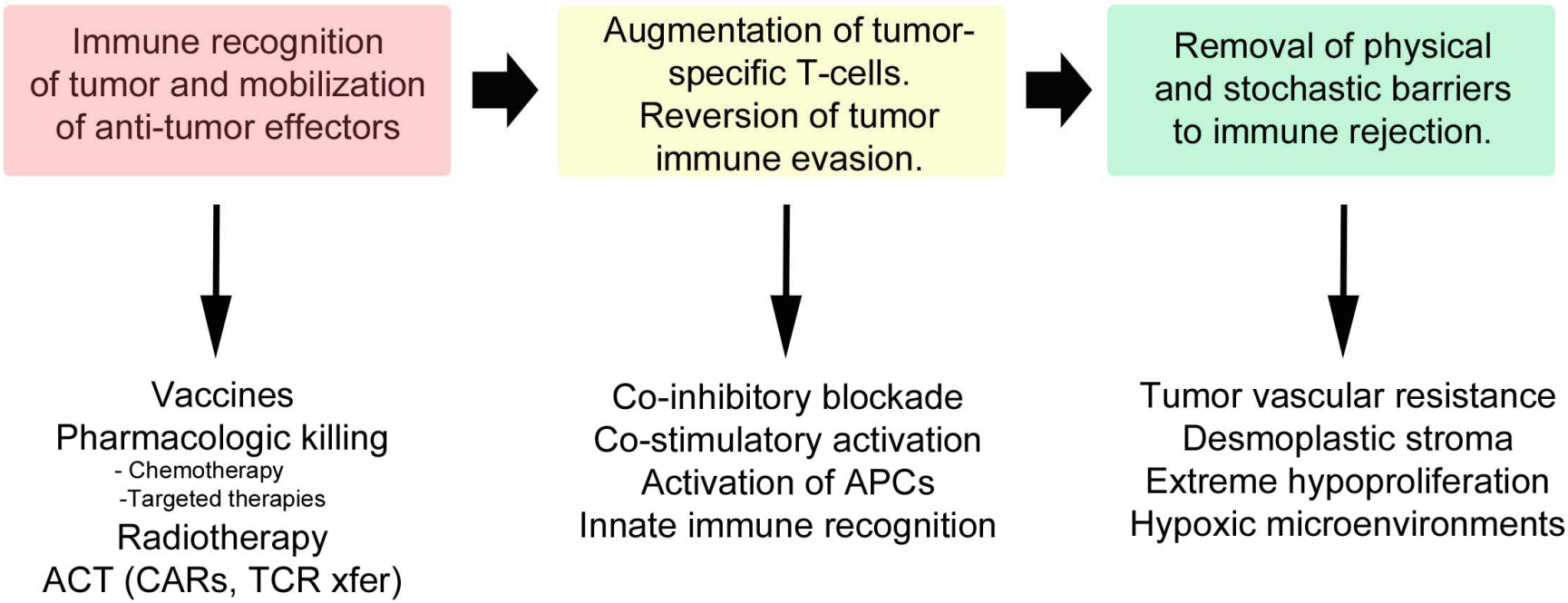
ClinicalTrials.gov Identifier:
NCT00803374

First received: December 4, 2008
Last updated: November 18, 2011
Last verified: November 2011
History of Changes

Why this trial should happen.

1. Therapeutic synergy between Ipilimumab and Urelumab (αCD137) in multiple tumor models
2. Mutual amelioration of each agents IrAE by the other
3. Potential to expand the pool of patients eligible to receive and remain on Ipilimumab

Seeking combinations outside of immunotherapy



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-MSKCC

Aymen Al-Shamkhani (α 4-1BB)
-University of Southhampton

Steve Reiner (Eomes-*flox*)
- Columbia University

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Maggie Callahan

Jedd Wolchok

MSKCC IMF:
Jedd Wolchok
Jianda Yuan
Matthew Adamow

Wolchok Lab:

David A. Schaer

Bristol-Myers Squibb:
Maria Jure-Kunkel
Stacie Goldberg
John Kurland
Christine E. Horak

MD Anderson Immunotherapy Platform

James P. Allison Ph.D, Padmanee Sharma M.D.,Ph.D., Patrick Hwu M.D.