The expanding landscape of Immunotherapy

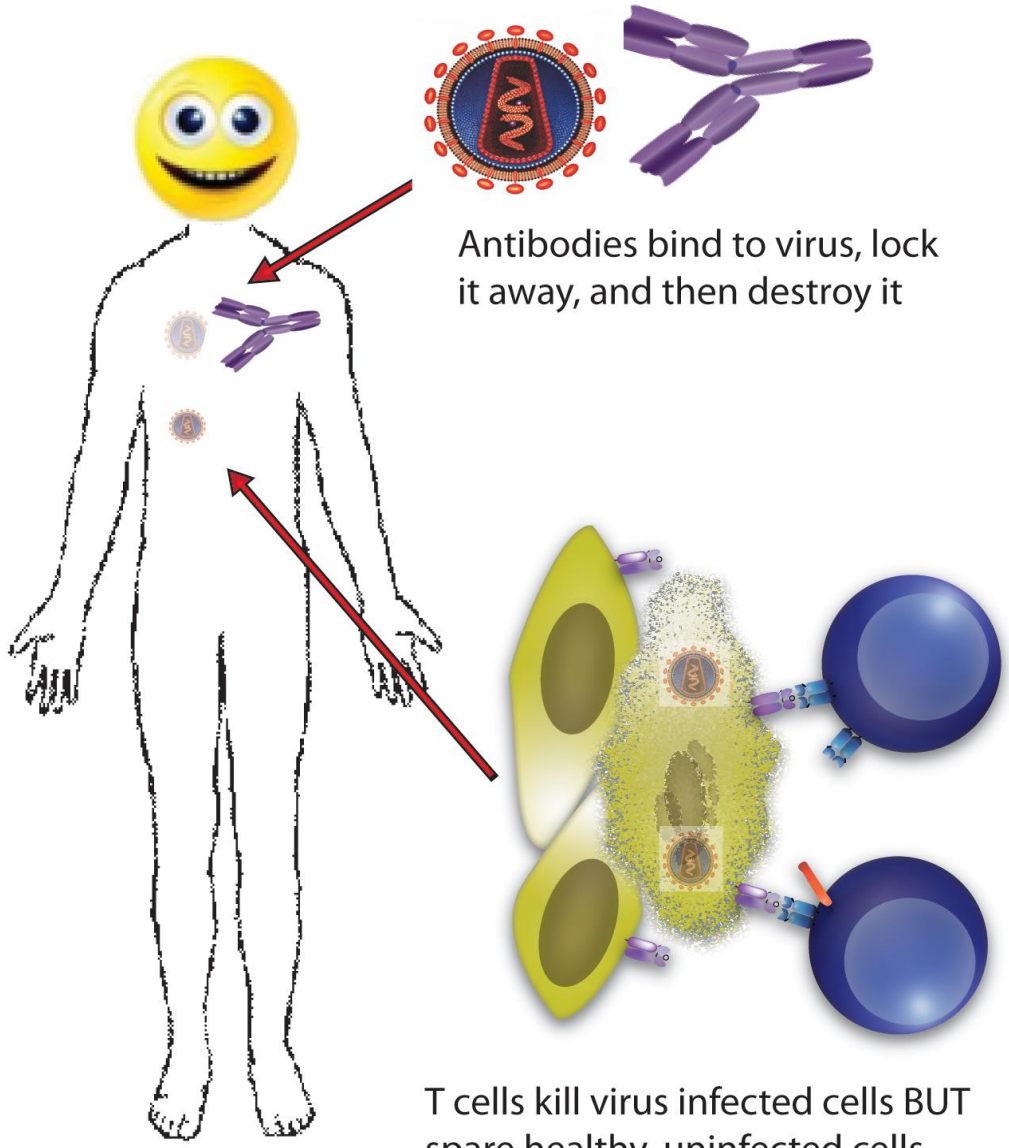
Michael A. Curran, Ph.D.

The University of Texas, MD Anderson Cancer Center

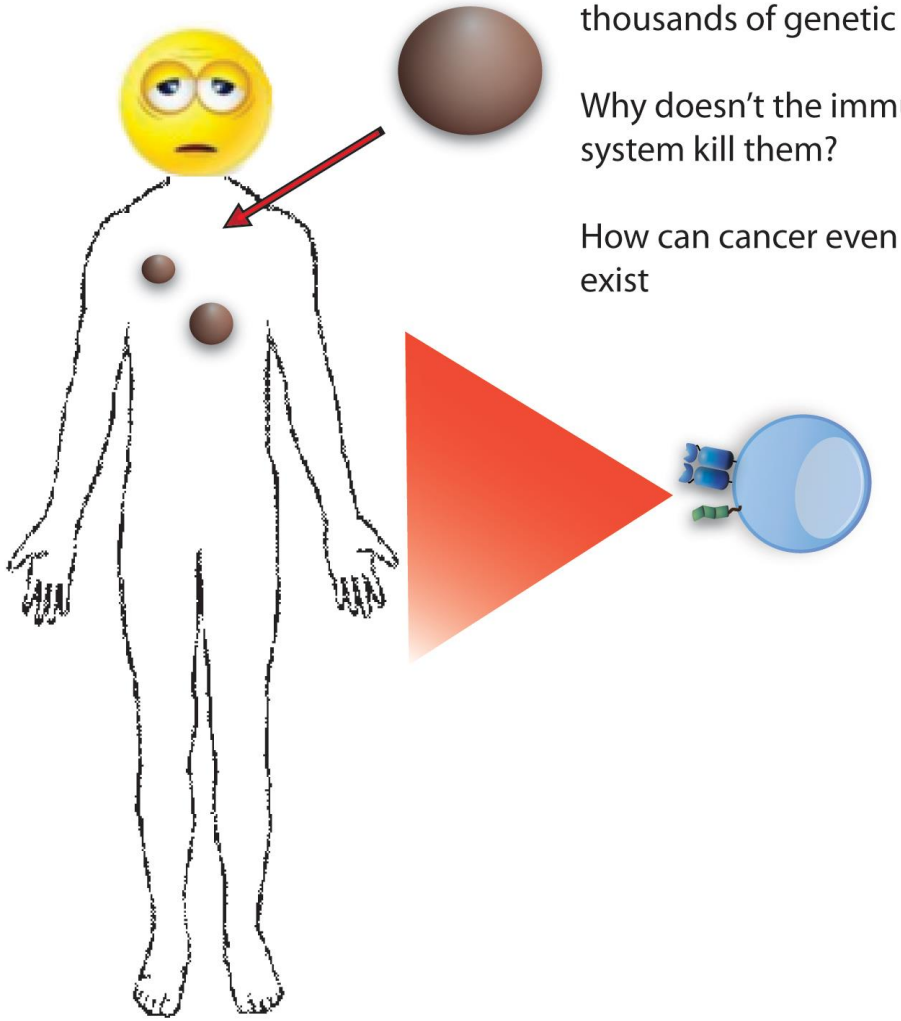
Associate Professor, Immunology
Co-Scientific Director, ORBIT Moonshot Platform

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

How does your immune system work?



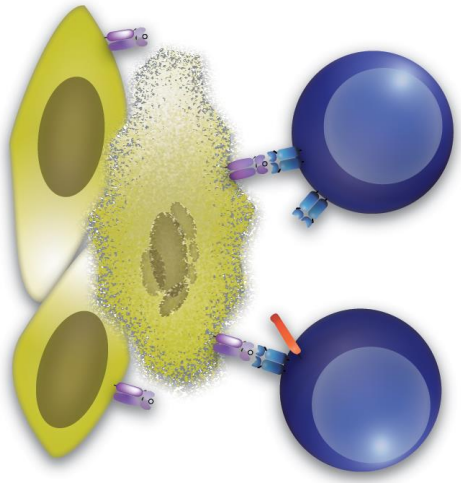
Why is there cancer?



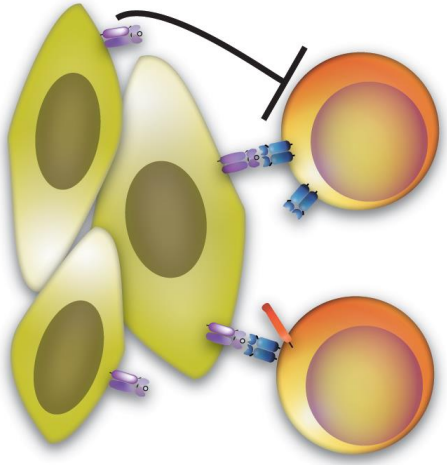
Tumors have dozens to thousands of genetic changes

Why doesn't the immune system kill them?

How can cancer even exist



The immune system has the potential to recognize and eliminate cancer, BUT...



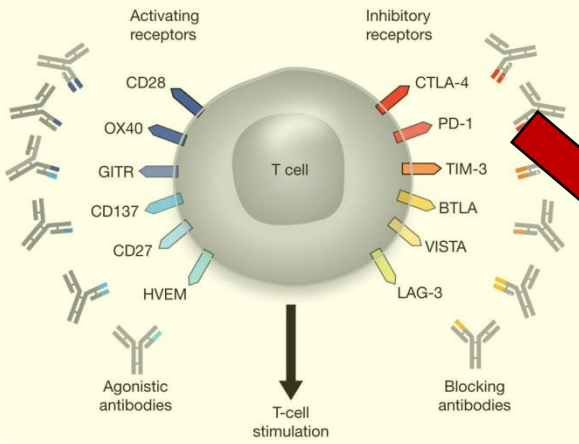
Tumors actively cripple the immune system, creating a shield against elimination.

To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

The goal of immunotherapy, then, is to restore the capacity of the immune system to recognize and reject cancer.

Types of Immunotherapy

T Cell Checkpoint Modulation



Jimmy Carter says he no longer needs cancer drug treatment

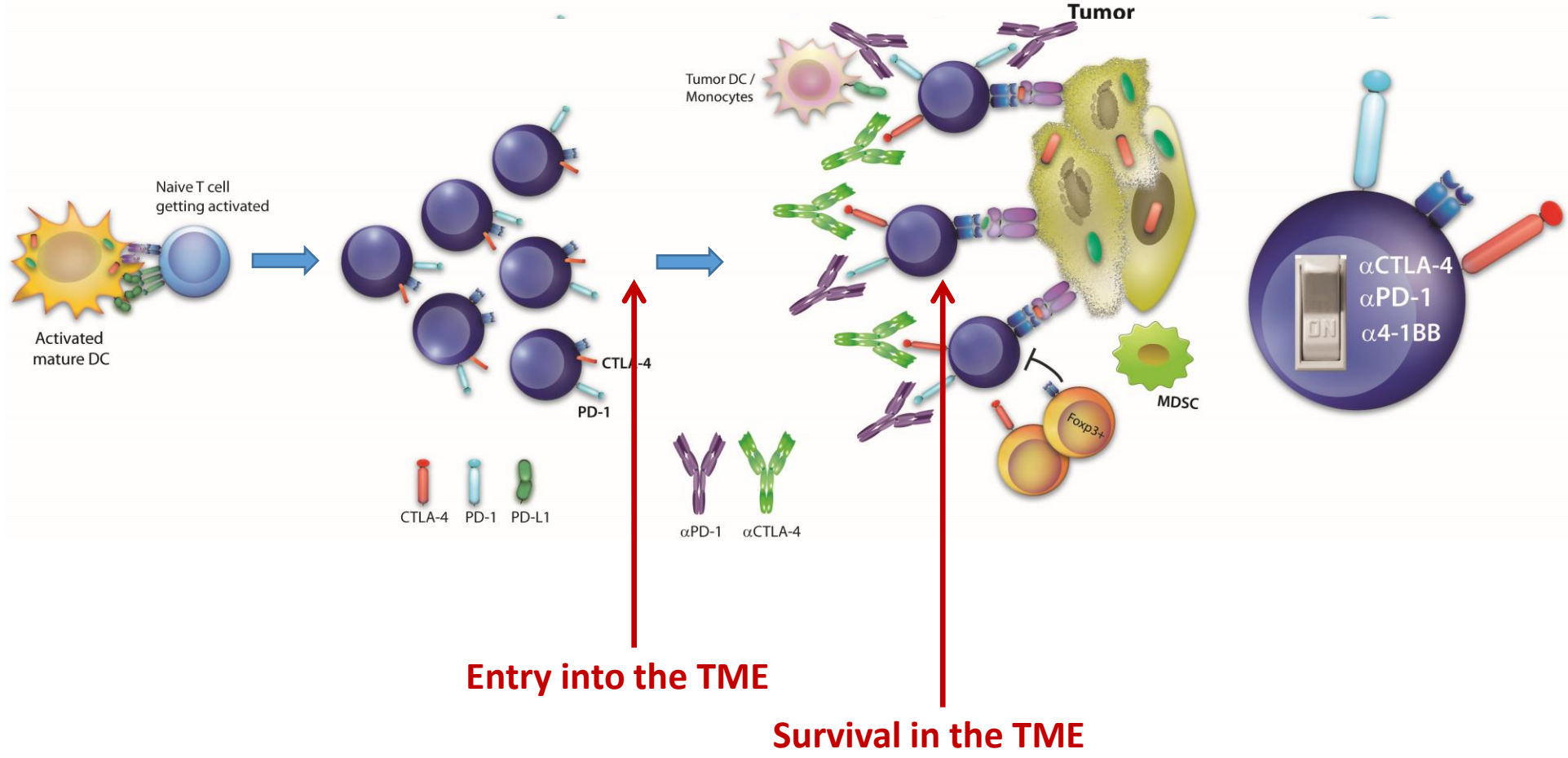
AP By KATHLEEN FOODY
March 6, 2016 6:47 PM

Therapeutic Cancer Vaccines

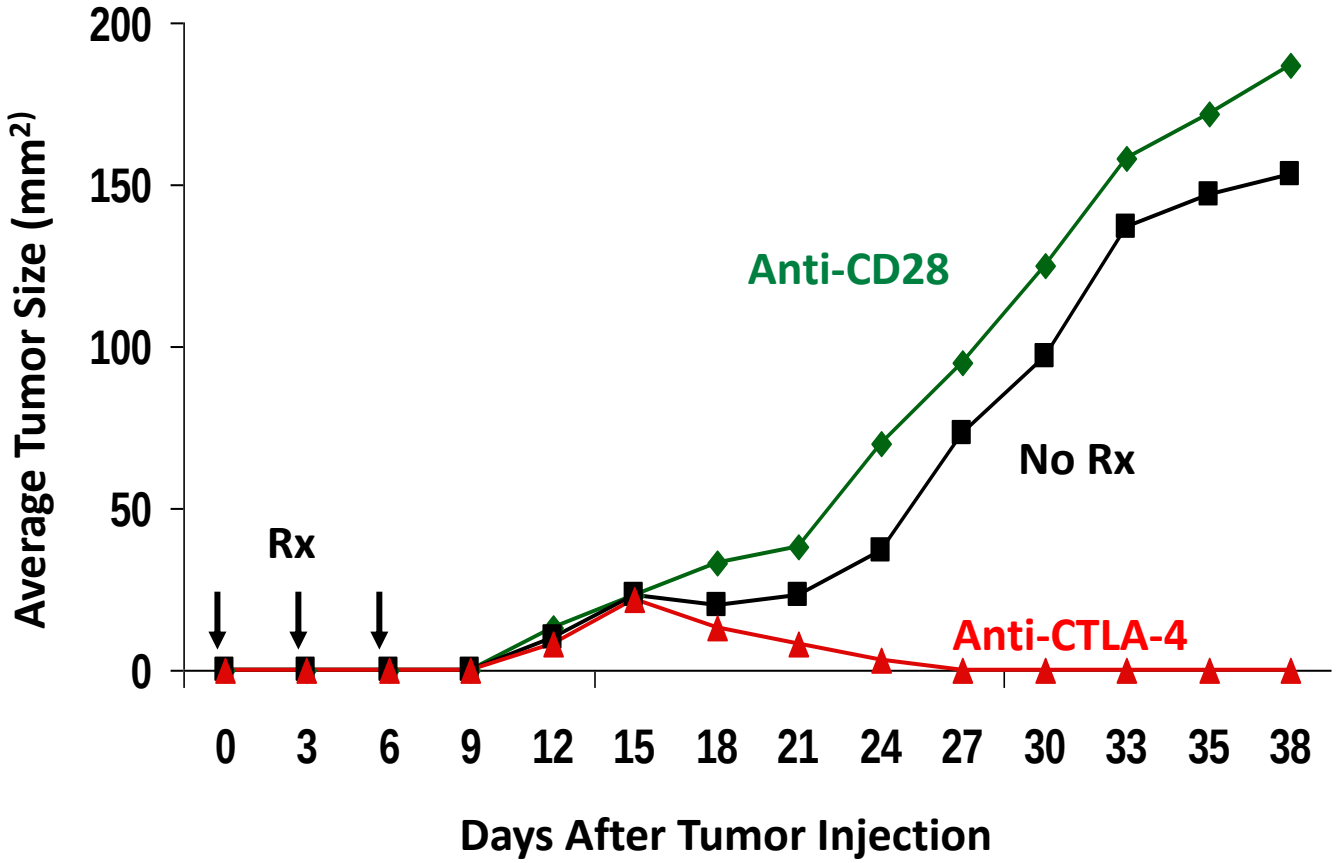
Me

DCs

How do immune checkpoint antibodies like αCTLA-4 (Yervoy) and αPD-1 (Keytruda/Opdivo) treat cancer?



Antibodies that block immune checkpoints can cure murine cancers.

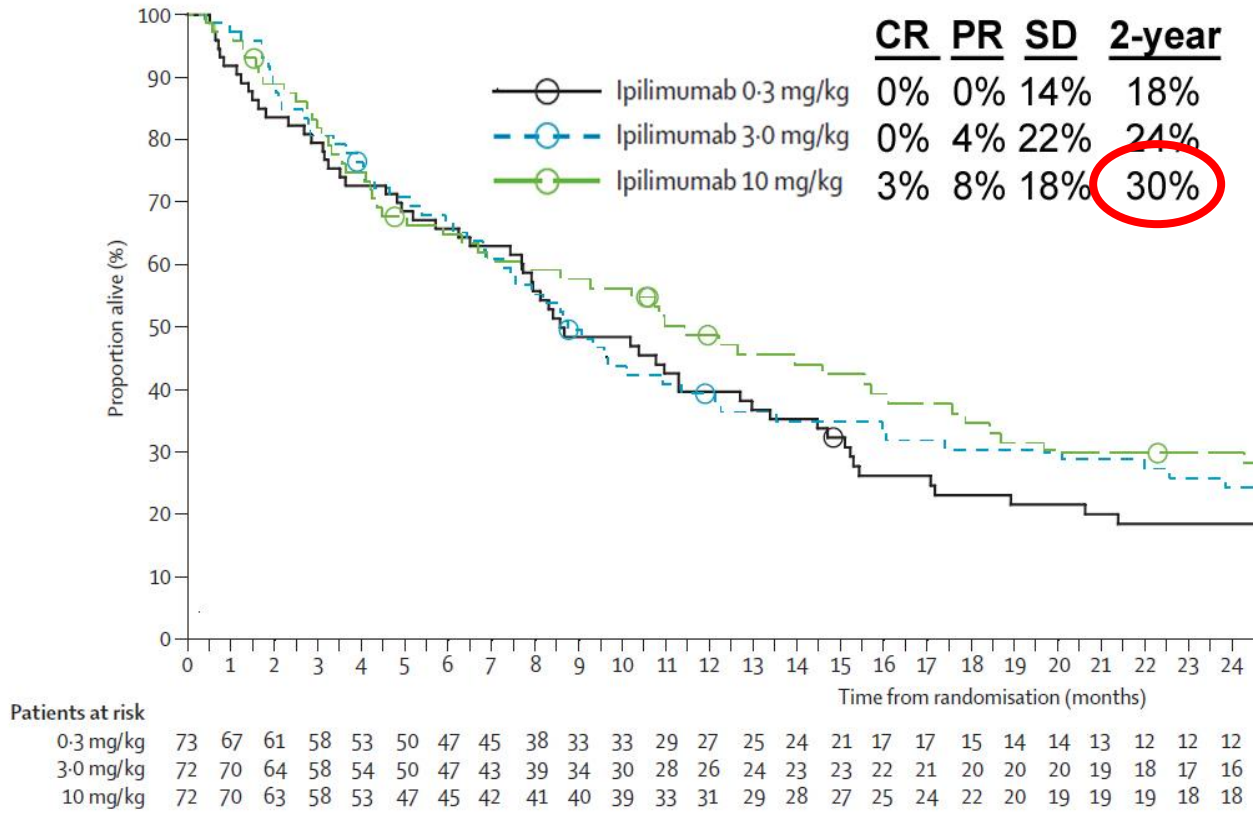


Science. 1996 Mar 22;271(5256):1734-6.

Enhancement of antitumor immunity by CTLA-4 blockade.

Leach DR[1], Krummel MF, Allison JP.

Ipilimumab (αCTLA-4) was the first checkpoint antibody approved by the FDA in 2010.



Wolchok et al, *Lancet Oncol*, 2010

Temodar:

CR: 2.5%

PR: 11%

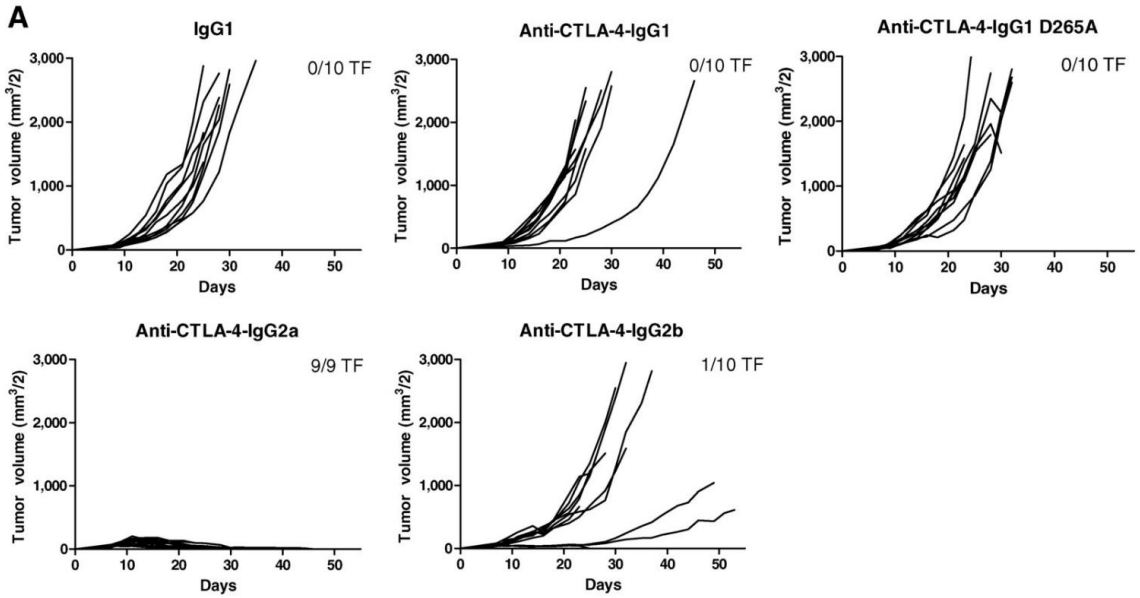
SD: 18%

2yr: 18%

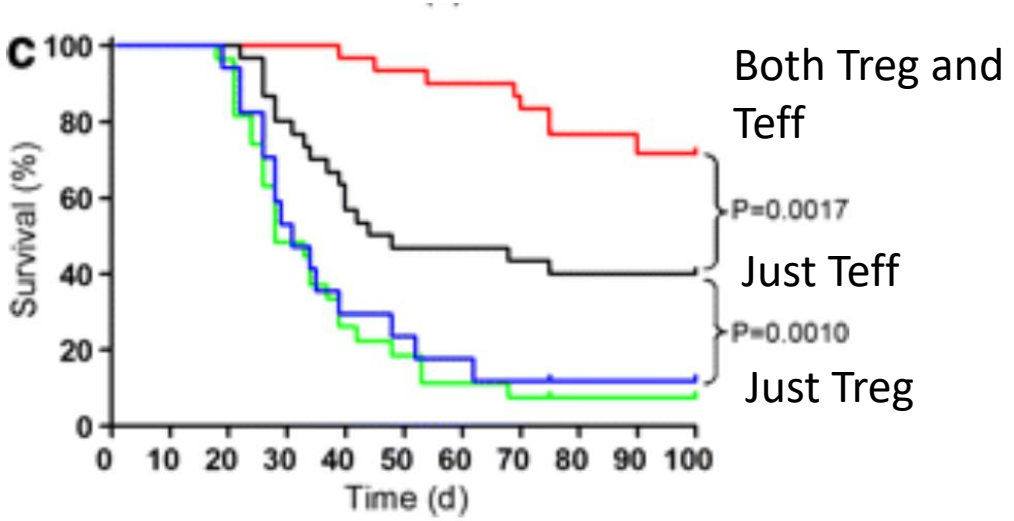
Middleton et.al,
***J Clin Oncol*, 2000**

How do CTLA-4 antibodies potentiate tumor immunity?

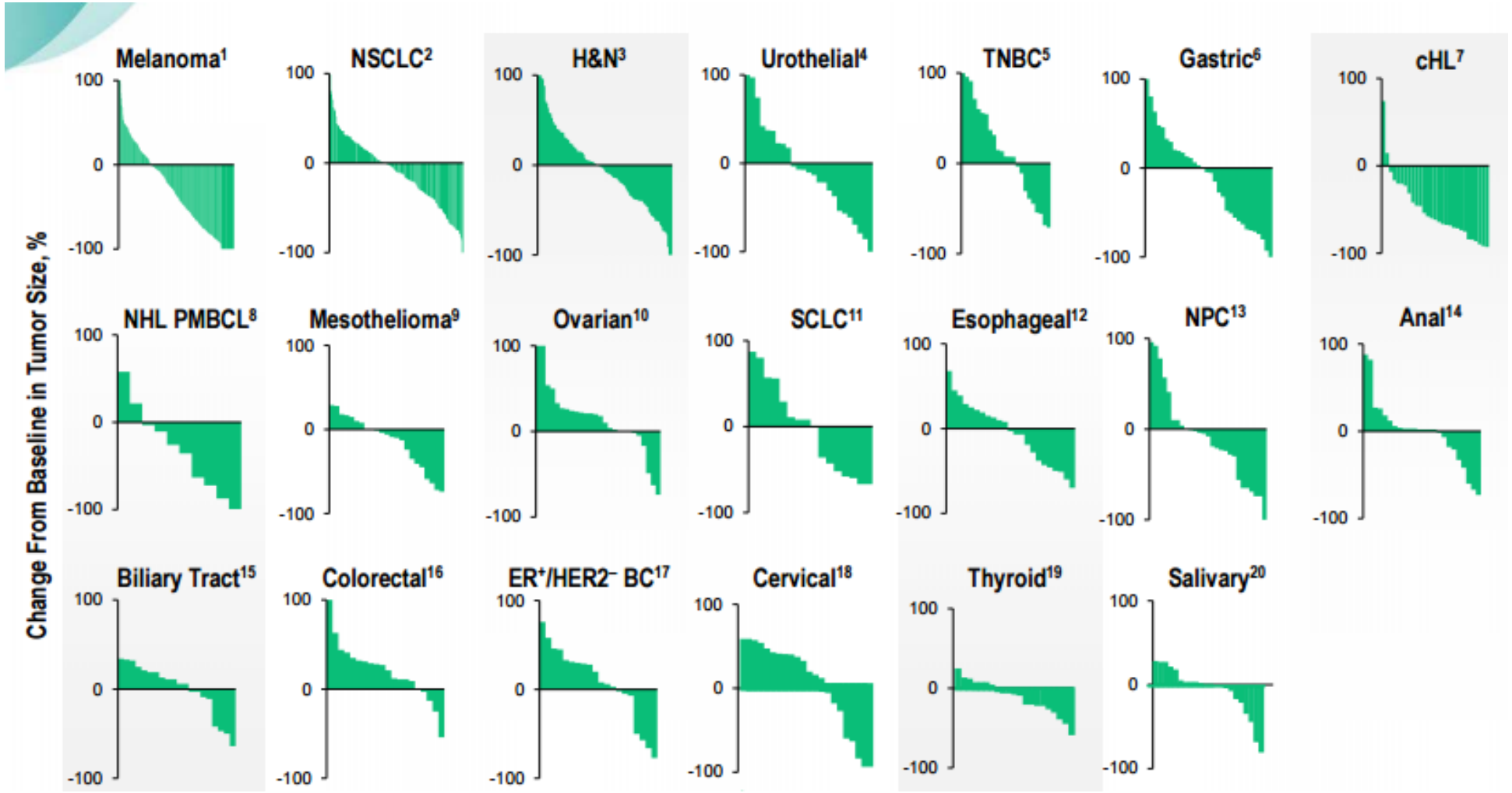
Treg depletion is critical



But blockade is also important

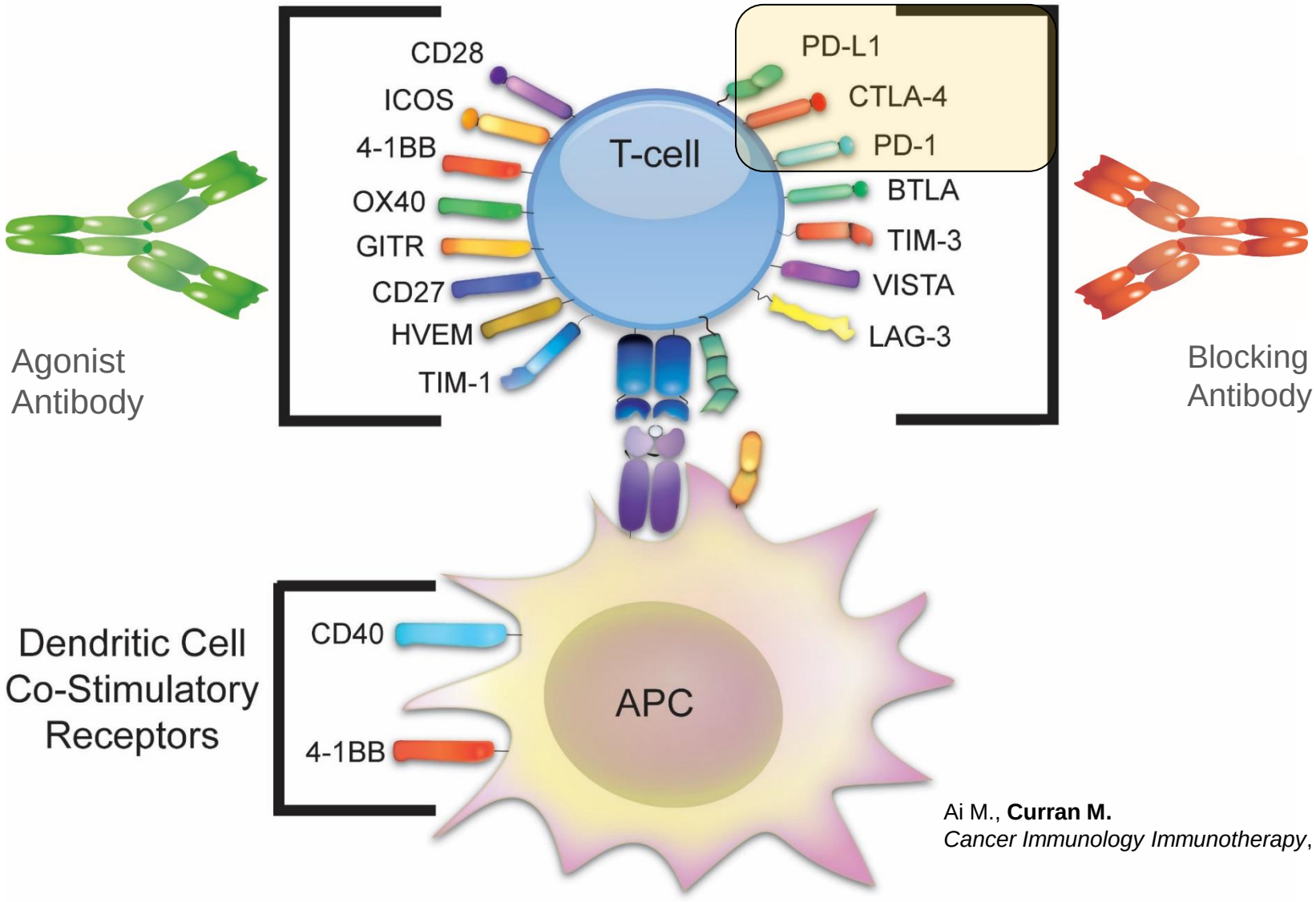


PD-1 blocking antibodies are approved for treatment of more than 20 types of cancer.



ASCO 2016

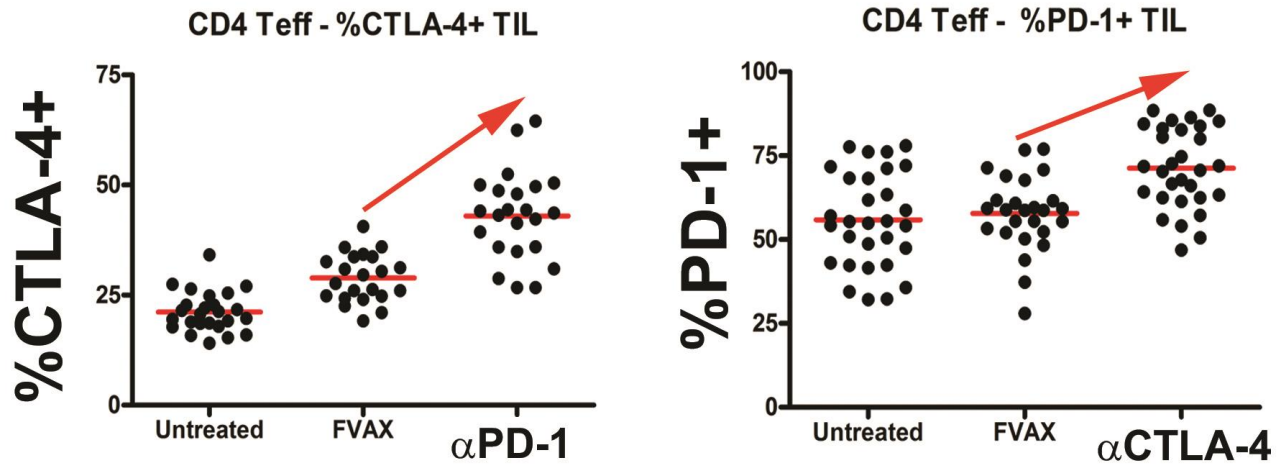
T cell co-stimulatory and co-inhibitory receptors



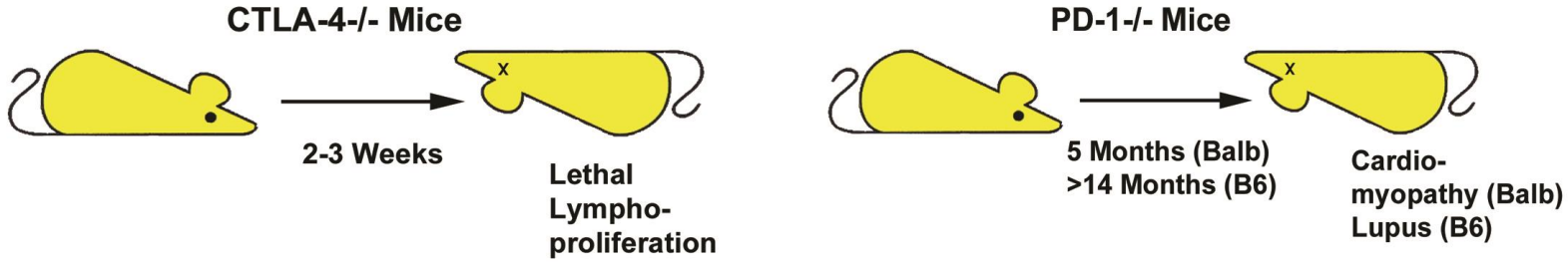
Ai M., **Curran M.**
Cancer Immunology Immunotherapy, 2015.

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

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



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



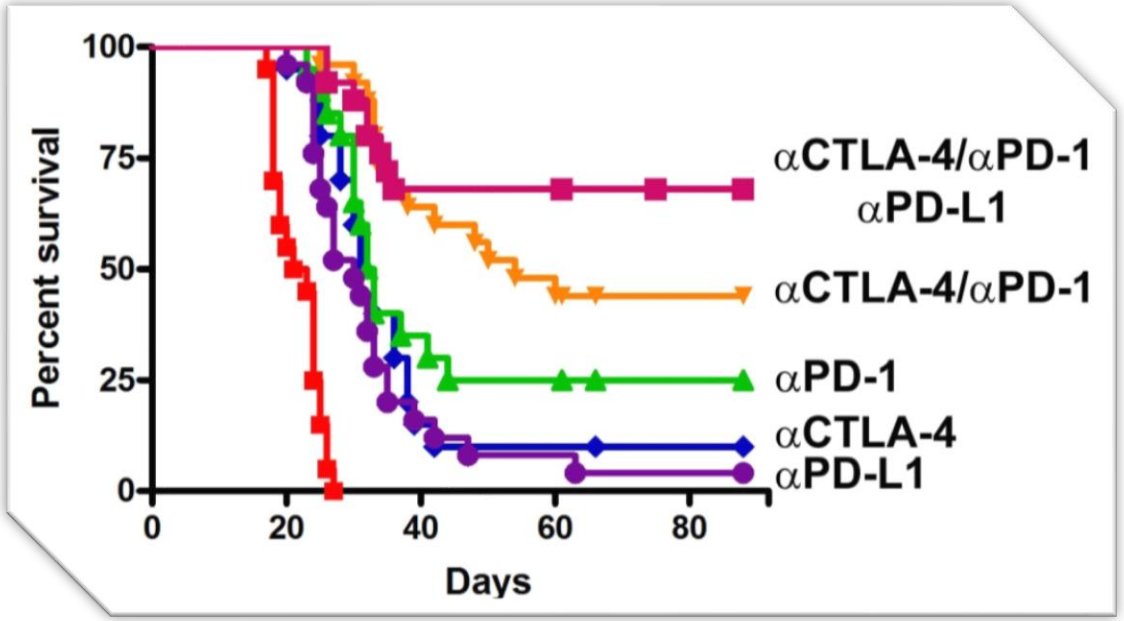
Curran M A et al. PNAS 2010; 107(9):4275-80.

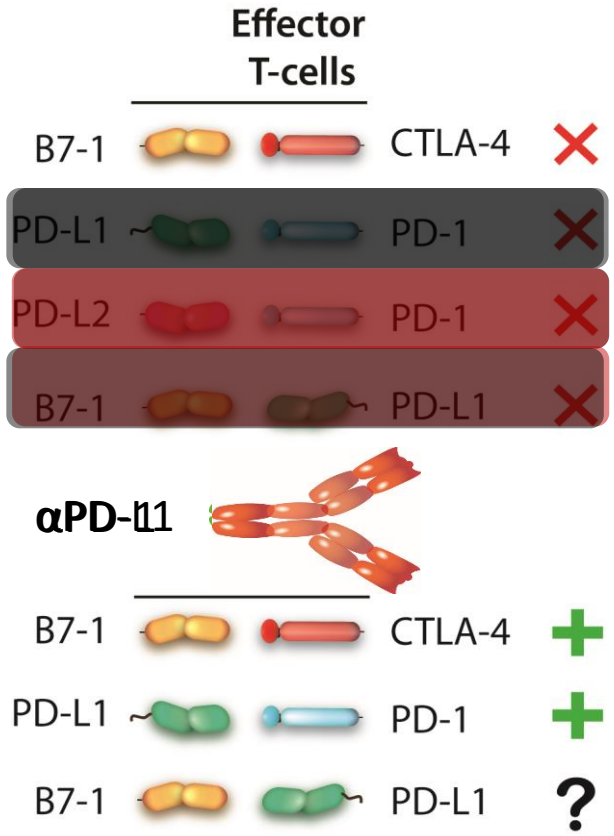
PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

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

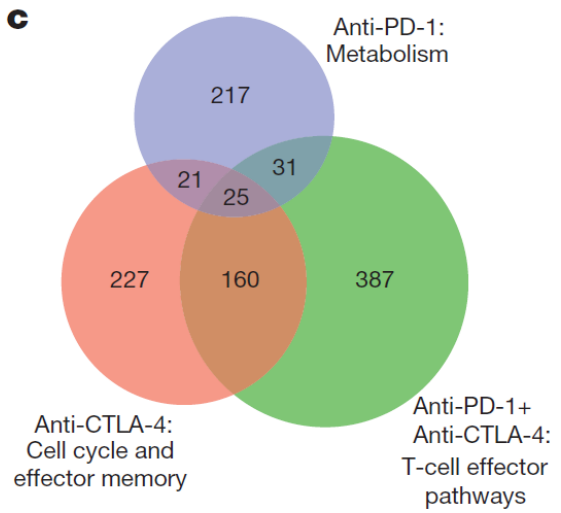
Contributed by James P. Allison, January 19, 2010 (sent for review December 17, 2009)

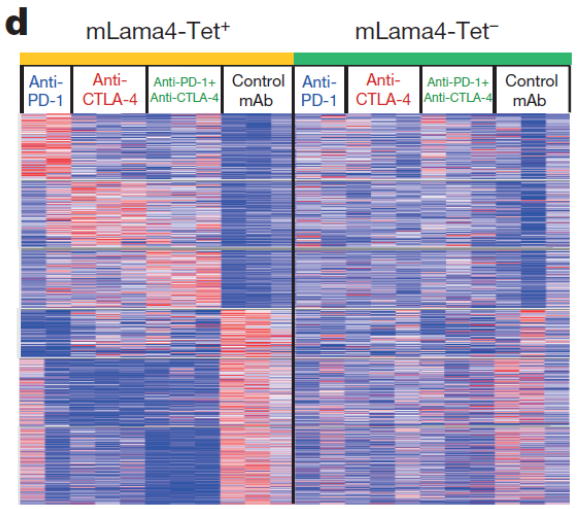




Curran M A et al. PNAS 2010; 107(9):4275-80.

CTLA-4 and PD-1 blockade synergize at a transcriptomic level to drive superior T cell activation.

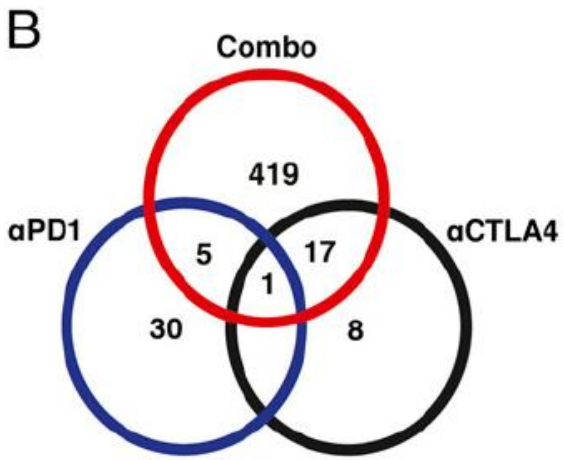




doi:10.1038/nature13988

Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

Matthew M. Gubin[1], Xiuli Zhang[2], Heiko Schuster[3], Etienne Caron[4], Jeffrey P. Ward[1,5], Takuro Noguchi[1], Yulia Ivanova[1], Jasreet Hundal[6], Cora D. Arthur[1], Willem-Jan Krebber[7], Gwenn E. Mulder[7], Mireille Toebes[8], Matthew D. Vesely[1], Samuel S. K. Lam[1], Alan J. Korman[9], James P. Allison[10], Gordon J. Freeman[11], Arlene H. Sharpe[12], Erika L. Pearce[1], Ton N. Schumacher[8], Ruedi Aebersold[4,13], Hans-Georg Rammensee[3], Cornelis J. M. Melief[7,14], Elaine R. Mardis[6,15], William E. Gillanders[2], Maxim N. Artyomov[1] & Robert D. Schreiber[1]

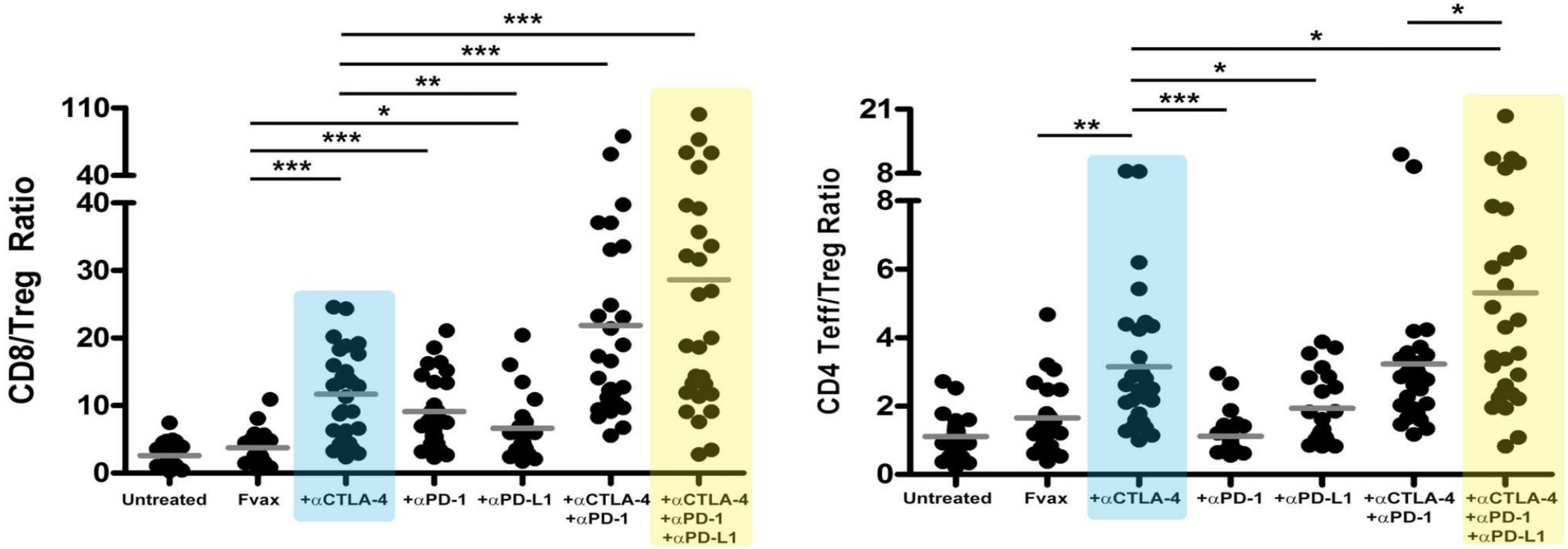


The Journal of Immunology

Combination Therapy with Anti–CTLA-4 and Anti–PD-1 Leads to Distinct Immunologic Changes In Vivo

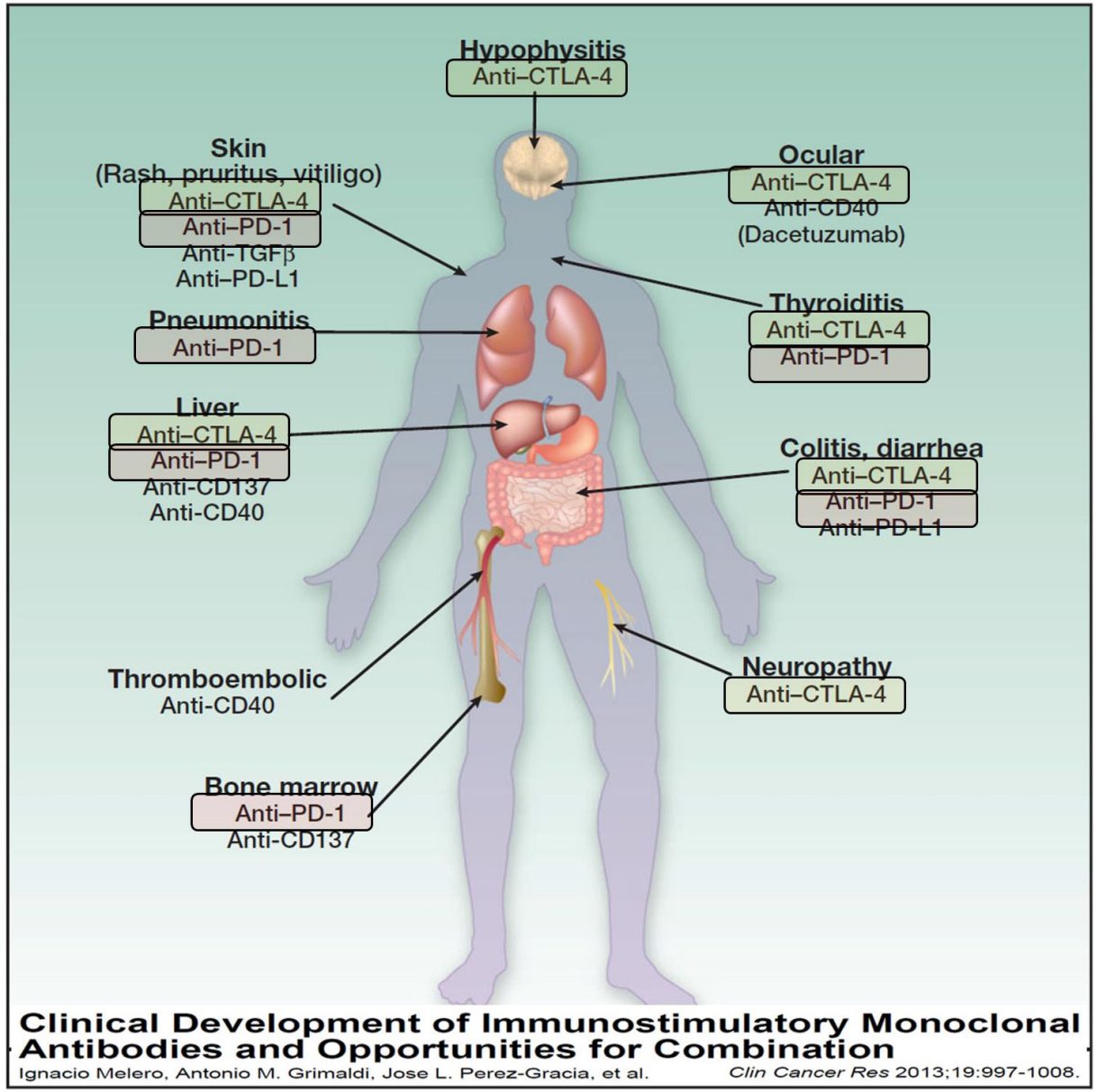
Rituparna Das, Rakesh Verma, Mario Sznol, Chandra Sekhar Boddupalli, Scott N. Gettinger, Harriet Kluger, Margaret Callahan, Jedd D. Wolchok, Ruth Halaban, Madhav V. Dhodapkar and Kavita M. Dhodapkar

Conversion of the tumor microenvironment from suppressive to pro-inflammatory.



Curran M A et al. PNAS 2010; 107(9):4275-80.

Risk of increased iRAE severity vs frequency?

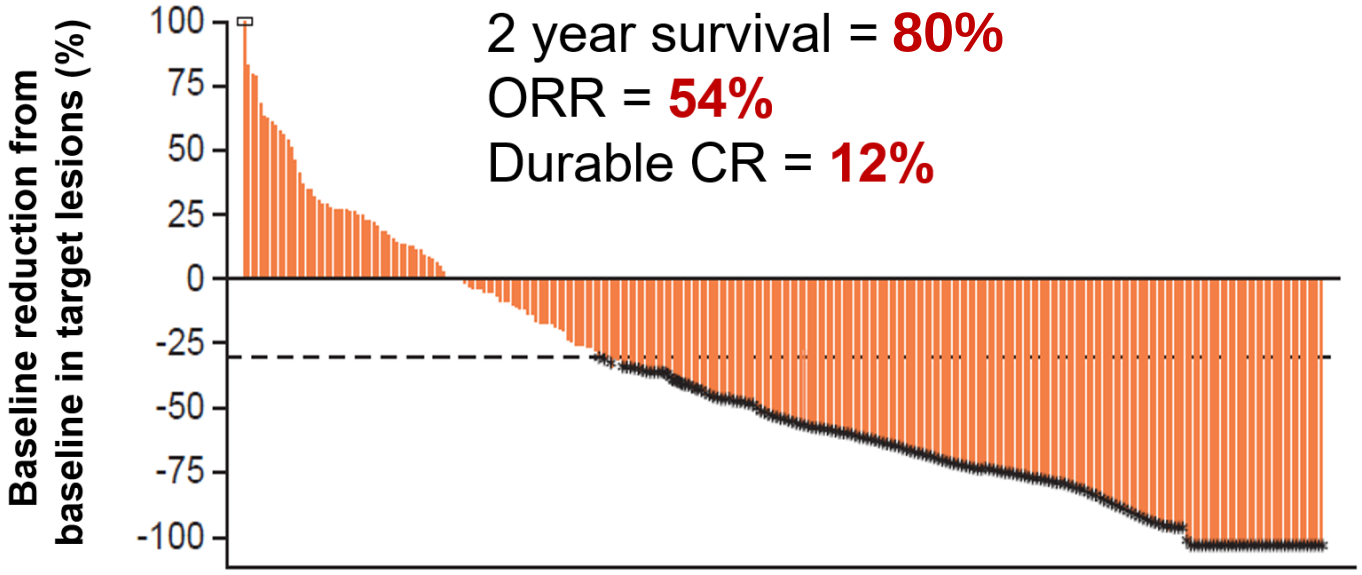


Clinical Development of Immunostimulatory Monoclonal Antibodies and Opportunities for Combination

Ignacio Melero, Antonio M. Grimaldi, Jose L. Perez-Gracia, et al. *Clin Cancer Res* 2013;19:997-1008.

Transformative improvement in outcome for metastatic melanoma patients.

Metastatic Melanoma



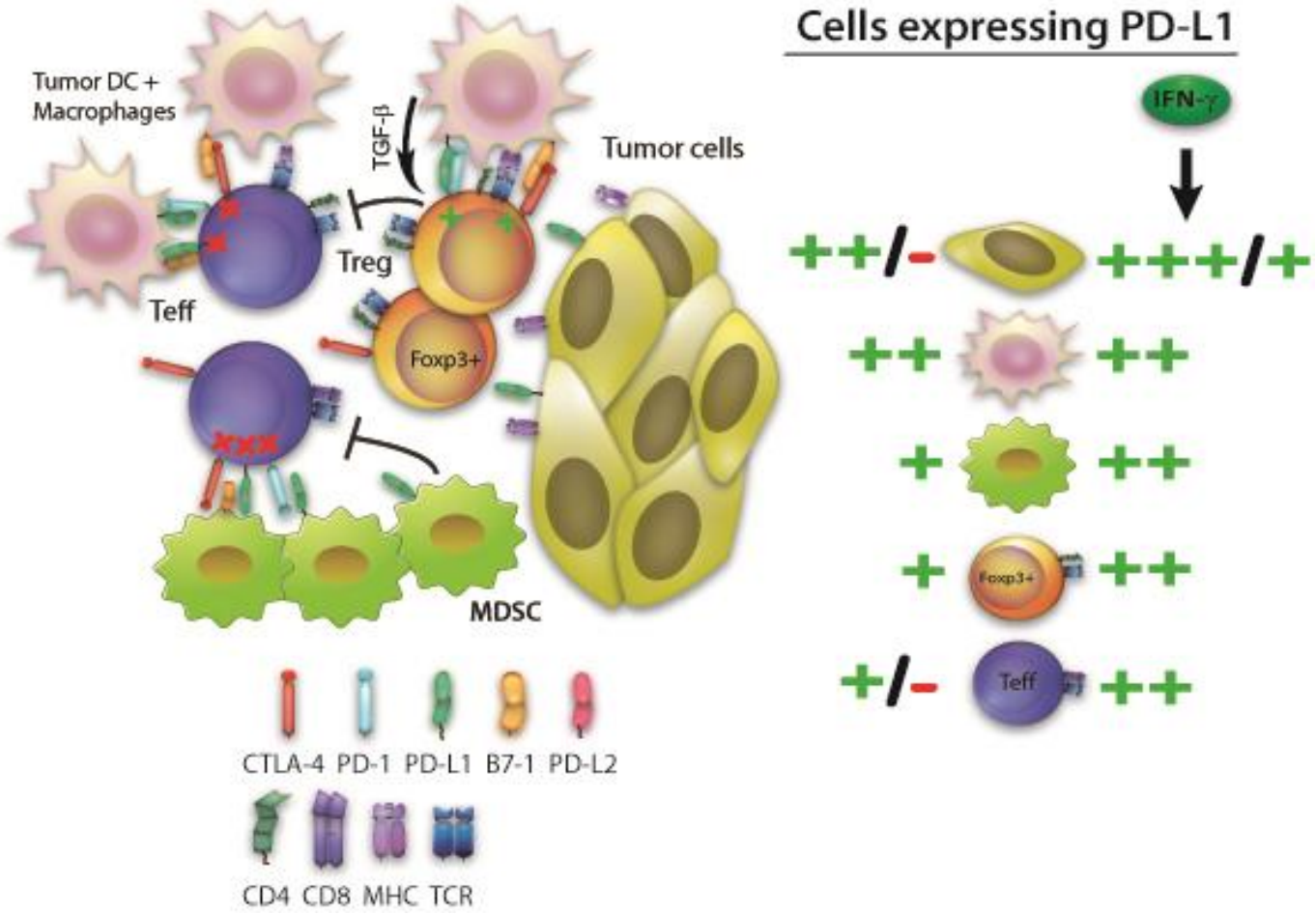
Wolchok et al. ASCO 2015 and NEJM

Non-Small Cell Lung Cancer

Outcome	NIVO 1 + IPI 1 q3w	NIVO 1 q2w + IPI 1 q6w	NIVO 3 q2w + IPI 1 q12w	NIVO 3 q2w + IPI 1 q6w
Treatment-related AEs leading to discontinuation, any grade, %	13	8	5	10
Treatment-related AEs leading to discontinuation, grade 3–4, %	10	8	3	10
Confirmed overall response, %	13	25	39	31
Median PFS, months	10.6	4.9	8.0	8.3

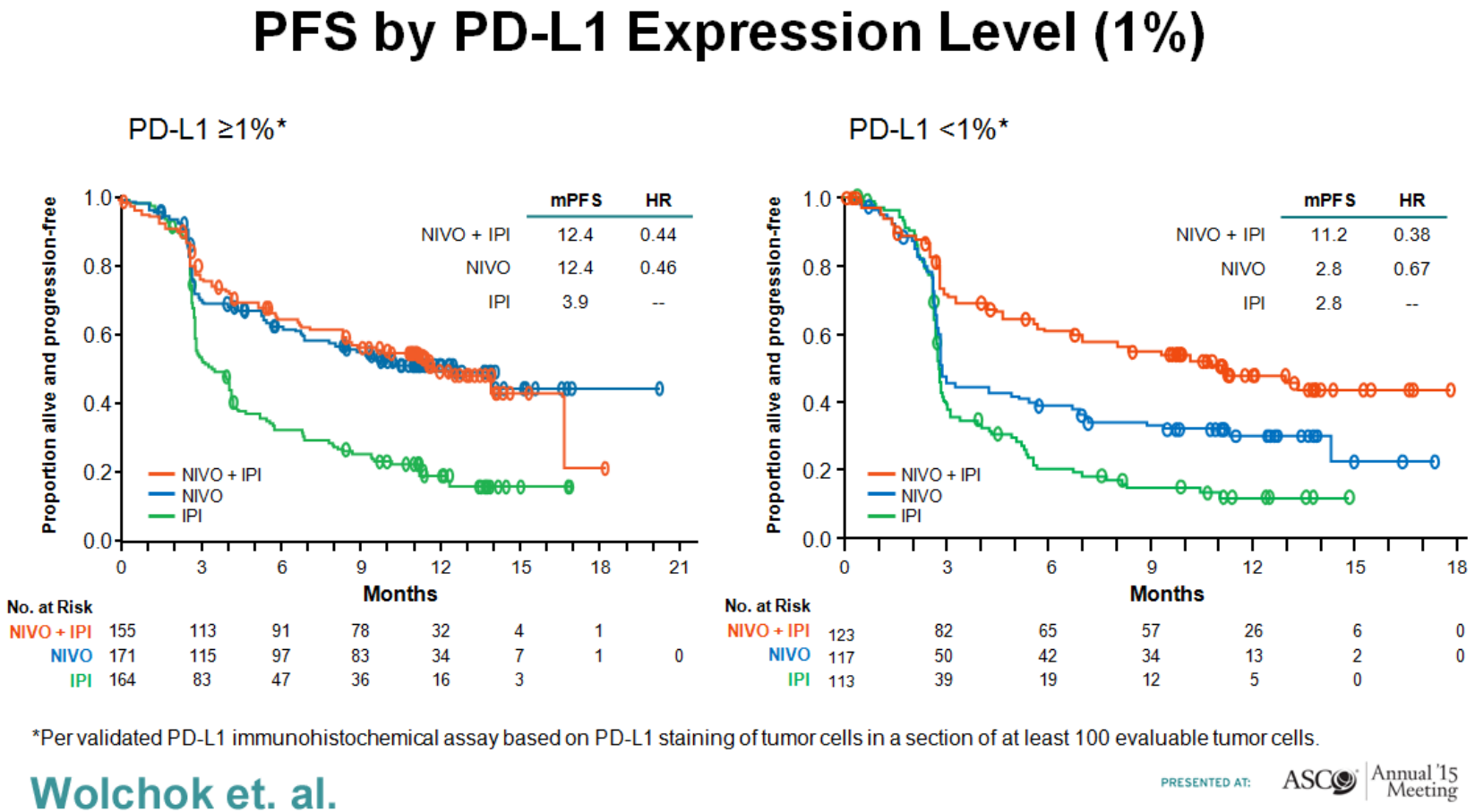
Rizvi et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL02.05

Predictive biomarkers for response to checkpoint blockade.



Idea: To expect benefit from αPD-1/αPD-L1 treatment, there must be PD-L1 expressed.

PD-L1 is a biomarker for response to αPD-1 but not combination blockade of CTLA-4 and PD-1.



*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

Wolchok et. al.

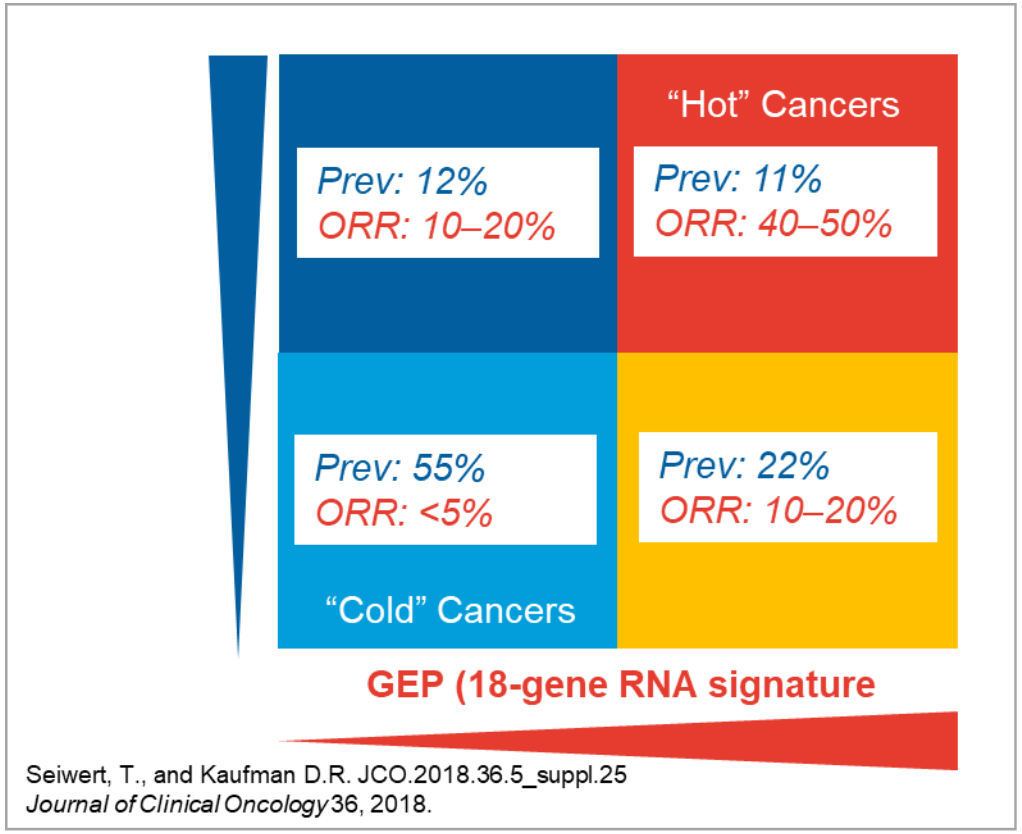
PRESENTED AT: ASCO Annual '15 Meeting

Note: Absolute Lymphocyte Count (ALC) < 1000 predicts no response to Ipilimumab but is also not predictive in the context of combination blockade of CTLA-4 and PD-1.

With the exception of MSI-high cancers, Hodgkin's lymphoma, and cutaneous melanoma, most patients still fail to respond to T cell checkpoint blockade.

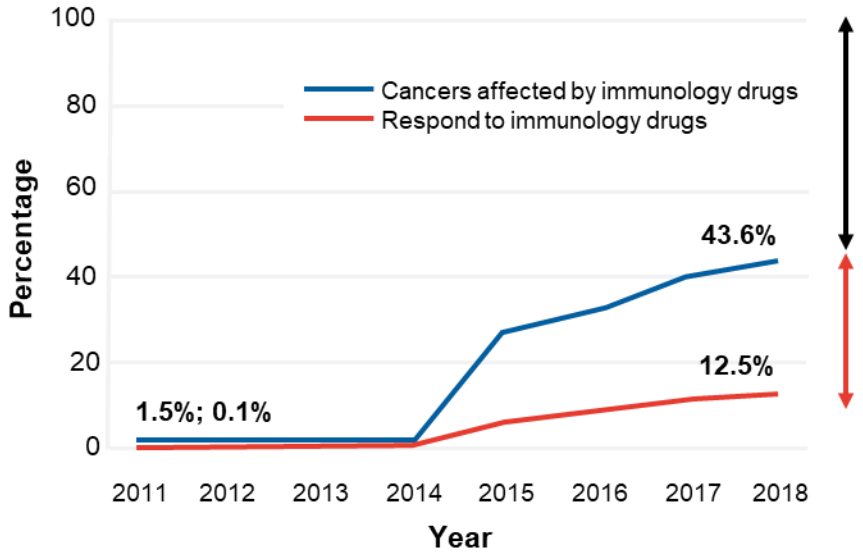
A major challenge in the field to understand the factors governing immunotherapy resistance.

Tumors with little infiltration and low neoantigen are "cold" and IO resistant



Seiwert, T., and Kaufman D.R. JCO.2018.36.5_suppl.25
Journal of Clinical Oncology 36, 2018.

Percentage of U.S. patients with cancer who may benefit from and respond to Checkpoint Inhibitor immunology drugs (2011-2018)



Overall, most tumors are cold and checkpoint non-responsive.

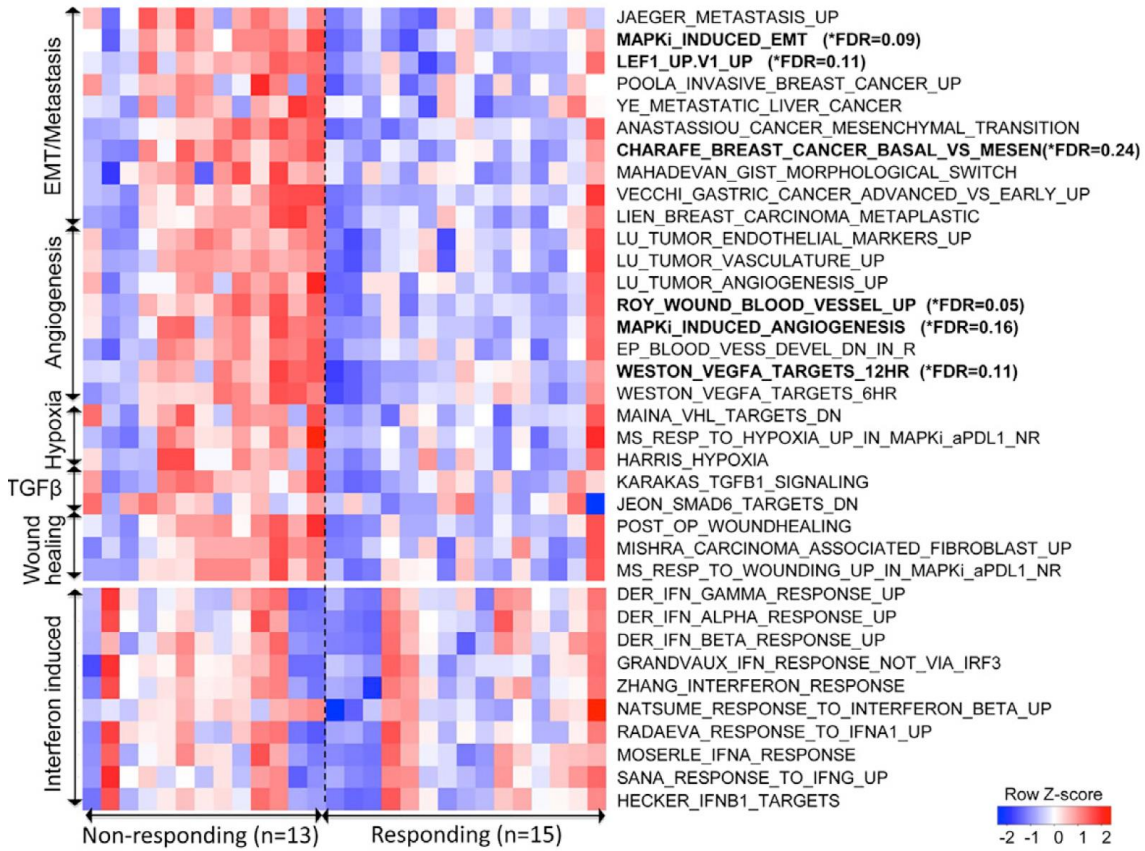
EMT, Hypoxia, TGF-beta, and lack of IFN response can all promote PD-1 resistance

Article

Cell

Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma

Willy Hugo,[1,6,9] Jesse M. Zaretsky,[2,6,9] Lu Sun,[1,6] Chunying Song,[1,6] Blanca Homet Moreno,[3] Siwen Hu-Lieskovan,[3] Beata Berent-Maoz,[3] Jia Pang,[3] Bartosz Chmielowski,[3] Grace Cherry,[3] Elizabeth Seja,[3] Shirley Lomeli,[1,6] Xiangju Kong,[1,6] Mark C. Kelley,[7] Jeffrey A. Sosman,[8] Douglas B. Johnson,[8] Antoni Ribas,[2,3,4,5,6] and Roger S. Lo[1,2,5,6,*]



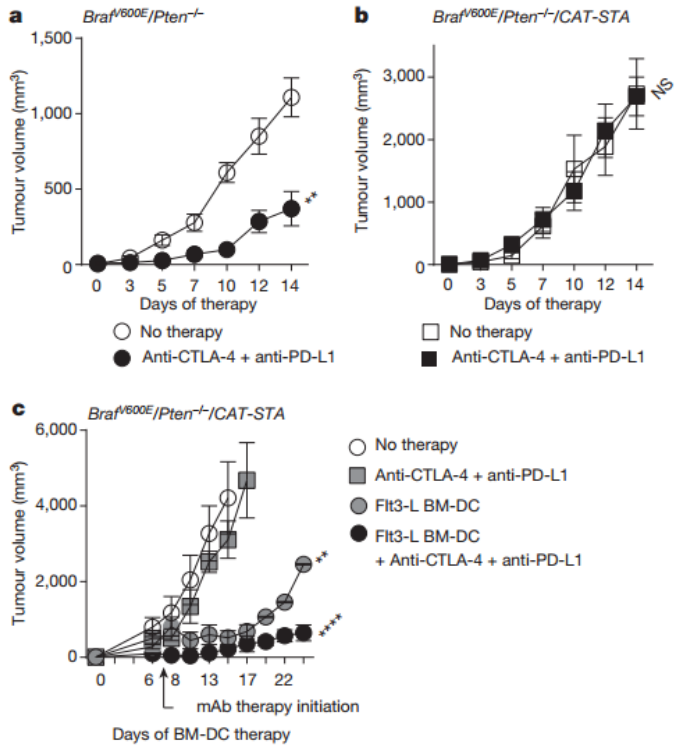
Understanding why some "cold" tumors lack T cell infiltration

LETTER

doi:10.1038/nature14404

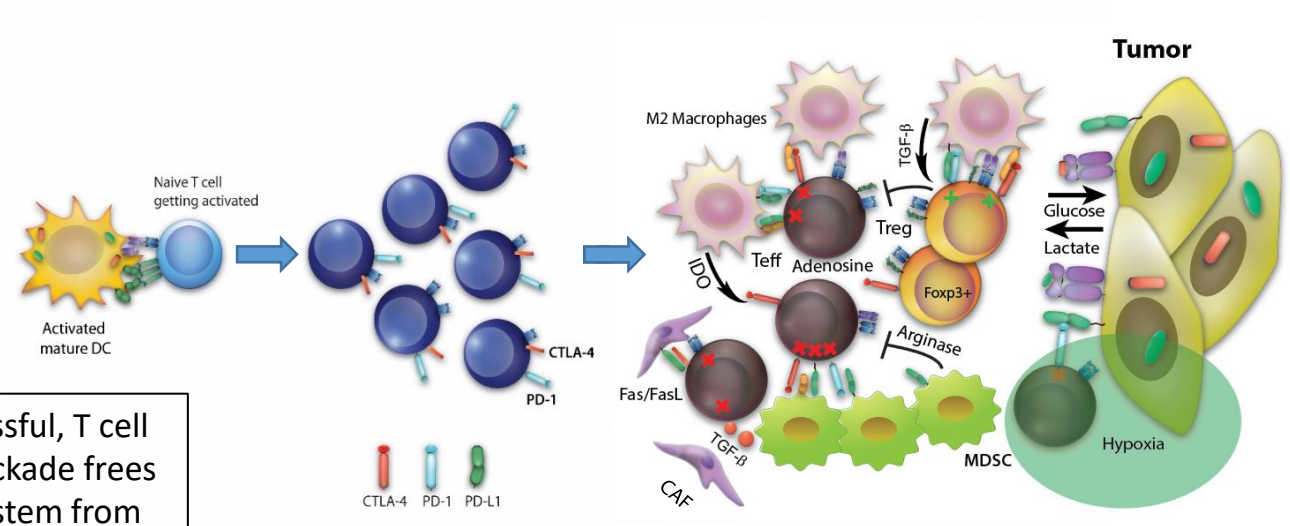
Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity

Stefani Spranger[1], Riyue Bao[2] & Thomas F. Gajewski[1,3]



After β-catenin, PTEN loss is next most Associated with "cold" melanoma.

Extrinsic suppression can be dominant over T cell checkpoint blockade

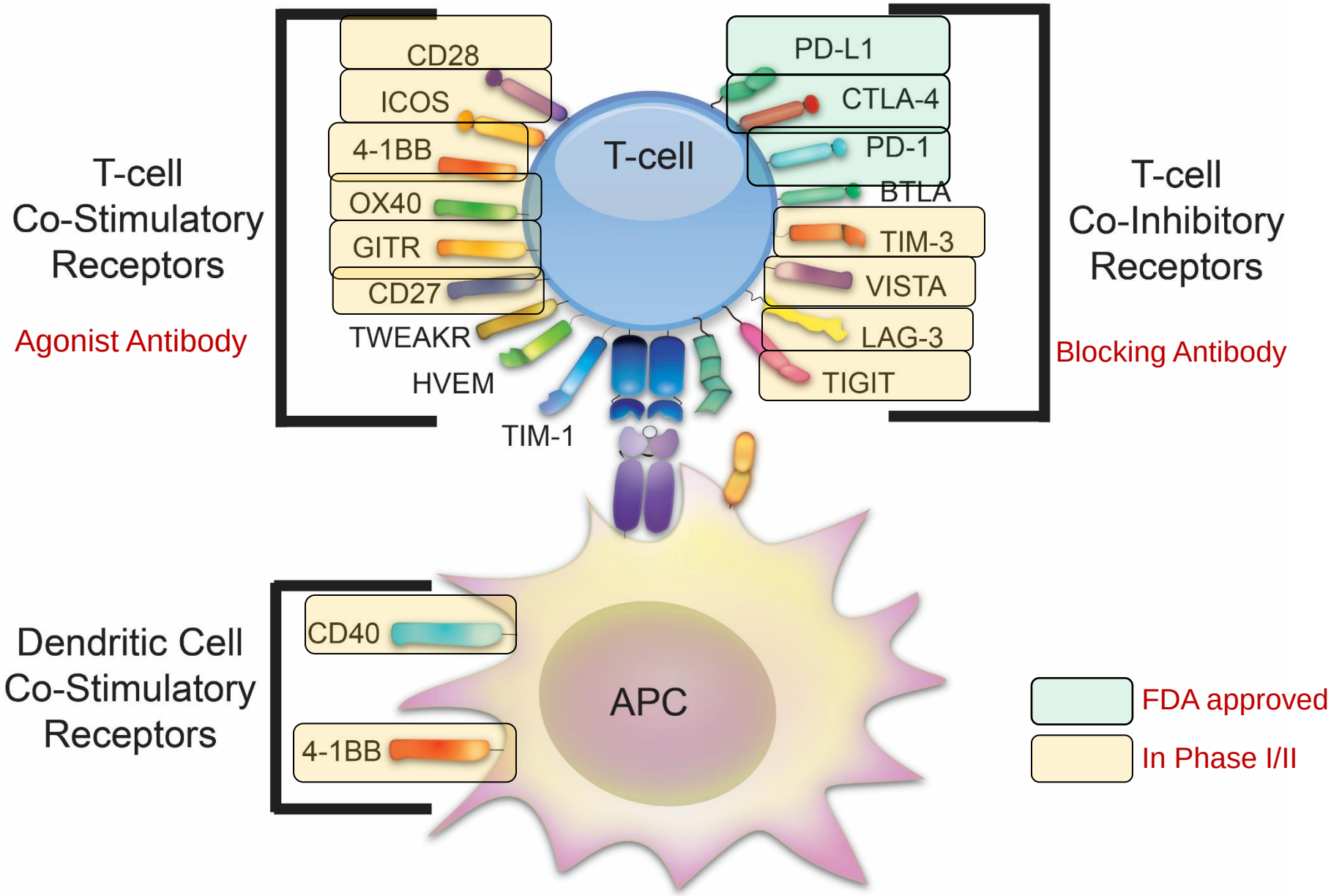


1) When successful, T cell checkpoint blockade frees the immune system from repression in the tumor eliciting durable regression of even widespread cancer.

2) Multiple mechanisms of immune suppression can repress T cells and prevent tumor regression even in the presence of checkpoint blocking antibodies.

PD-1 and CTLA-4 blockade potently impact T cell function, but no other modulators of T cell co-stimulation have reached clinical approval.

A second challenge is to identify T cell modulating antibodies with the capacity to expand the depth and frequency of immunotherapy responses.

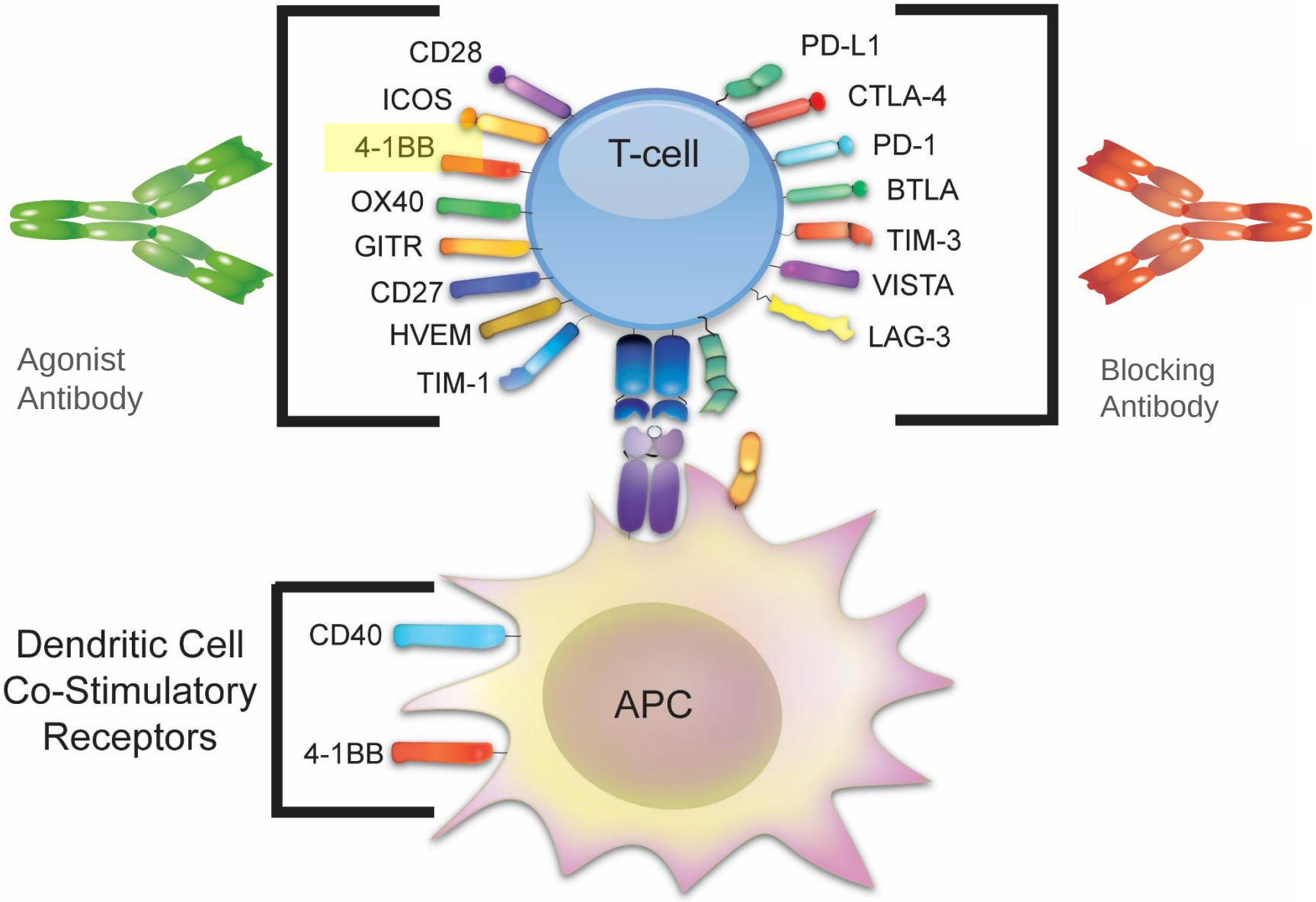


Ai M., **Curran M.A.** Immune checkpoint combinations from mouse to man. *Cancer Immunology Immunotherapy*, 2015.

Antibody engineering may be critical to optimally drug the best targets.

Target Molecule	Expression	Activity	Toxicity
	Checkpoint Blockade		
LAG-3	High	Low	Low
TIGIT	**Med/High**	**Med/High**	**Low**
TIM-3	Med	Low/Med	Low
VISTA	High	High??	High
BTLA	Med/High	None/Low	Low
CEACAM1,6	Low	???	Low??
	Co-Stimulatory Agonist		
4-1BB	**High**	**High**	**Med/High**
OX-40	Med/High	Low/Med	Low
ICOS	Med/High	Med??	Low??
CD27	Med/High	Low	Low
GITR	Med/High	Med??	Med/High
CD40	**High**	**High**	**Med/High**

Can T cell agonist antibodies work in patients?



4-1BB: favorable expression profile for immunotherapy

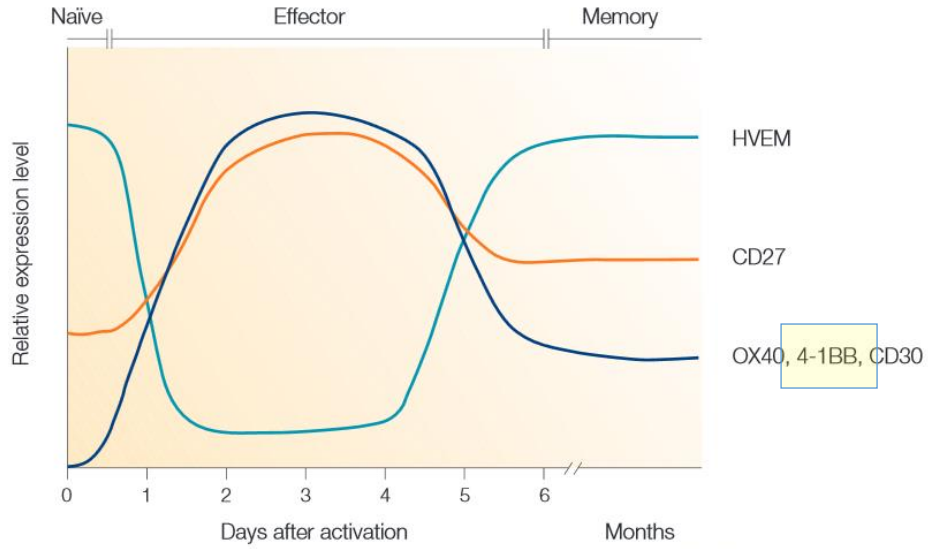


Figure 2 | **Generalized time course of expression of co-stimulatory TNFR-family members.**

Table 1 | **Expression characteristics of TNFR and TNF molecules by T cells and APCs**

Molecule	T cells			APCs	
	Naïve	*Effector*	*Memory*	*Resting*	*Activated*
CD27	++	+++	++/–	–	B*
CD70	–	+++*	–	–	B, DC, MØ
HVEM	+++	+	+++	B, DC*	B, MØ*
LIGHT	–	+++	–	DC	–
OX40	–	+++	+/–	–	B, DC*
OX40L	–	+++*	–	–	B, DC, MØ
4-1BB	–	+++	+/–	–	B, DC*
4-1BBL	–	+++*	–	–	B, DC, MØ
CD30	–	+++	+/–	–	–
CD30L	–	+++*	–	–	B, MØ

Nature Reviews Immunology **3**, 609-620 (August 2003) | doi:10.1038/nri1148

Co-stimulatory members of the TNFR family: keys to effective T-cell immunity?

Michael Croft[1] About the author

Table 1 | **Co-stimulatory and co-inhibitory receptor function in stages of T cell differentiation**

Receptor	T cell type	Priming	Cell growth	T_H cell differentiation	Effector function	Survival	Memory
4-1BB	$CD4^+$	ND	(+)	ThEO	(+)	(+)	(+)
	$CD8^+$	ND	(+)	TcEO	(+)	(+)	(+)

Adapted from: **Molecular mechanisms of T cell co-stimulation and co-inhibition**

Lieping Chen & Dallas B. Flies *Nature Reviews Immunology* **13**, 227-242 (April 2013)

4-1BB activation targets multiple arms of the immune system.

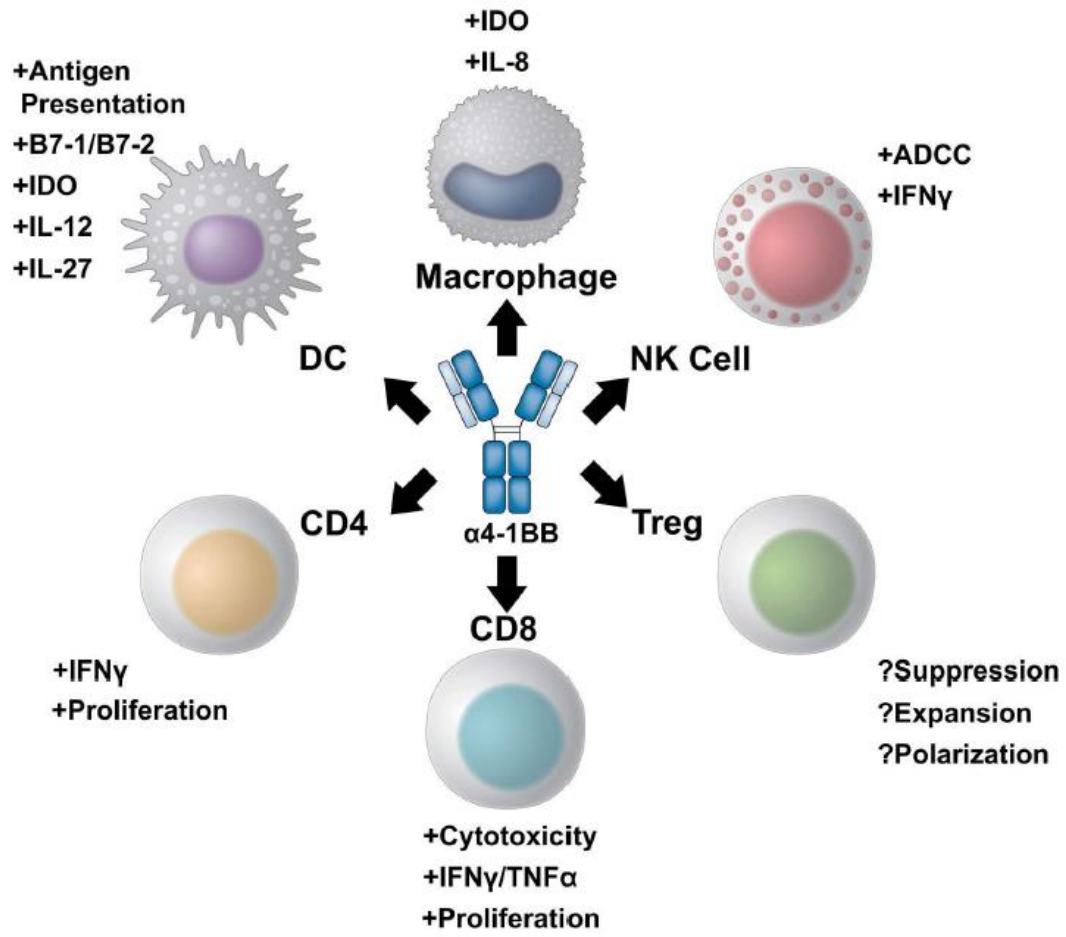


FIGURE 1 | A multi-potent role for 4-1BB targeted immunotherapy.

4-1BB Agonists: Multi-Potent Potentiators of Tumor Immunity.

Bartkowiak T, **Curran** MA.

Front Oncol. 2015 Jun 8;5:117. doi: 10.3389/fonc.2015.00117. eCollection 2015. Review.

4-1BB antibodies cure murine cancers.

Monoclonal antibodies against the 4-1BB T-cell activation molecule eradicate established tumors

Ignacio Melero, Walter W. Shuford, Stephanie Ashe Newby, Alejandro Aruffo, Jeffrey A. Ledbetter, Karl Erik Hellström, Robert S. Mittler & Lieping Chen

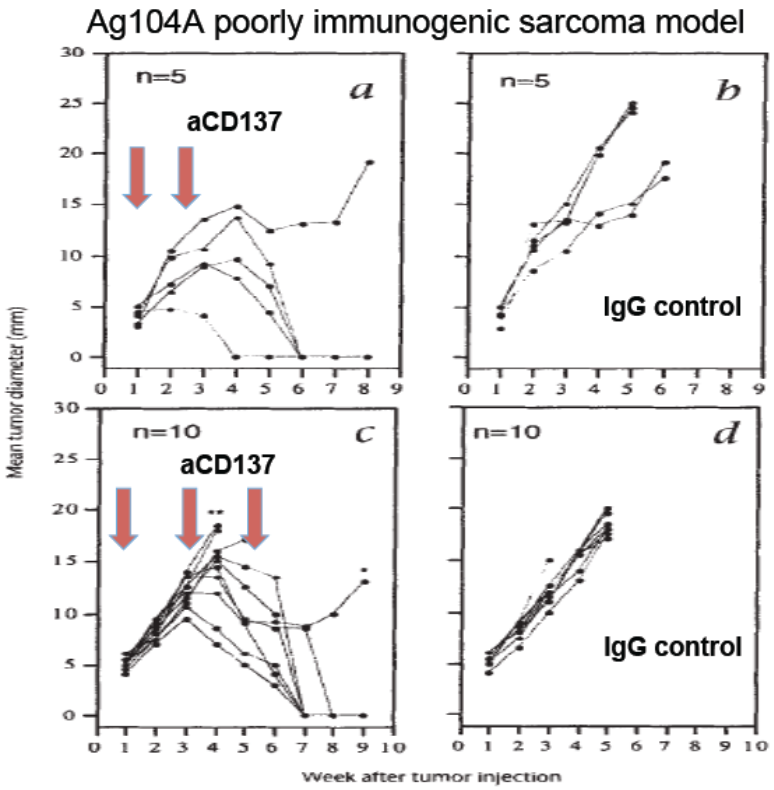


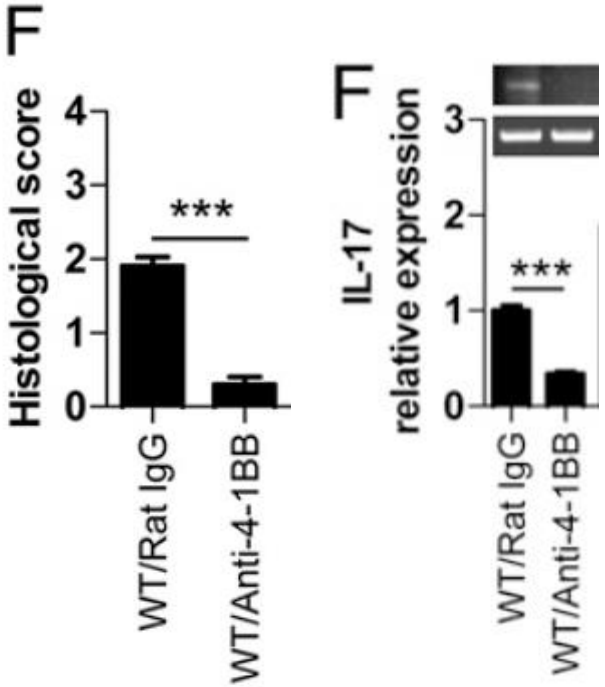
Table 1. Suppression of various tumors by targeting the 4-1BB–4-1BBL pathway

Agent	Cancer type suppressed
Anti-4-1BB mAb	Ag104A sarcoma
	MCA205, GL261 glioma
	C3 tumors, TC1 carcinoma
	J558 tumors
	A549 tumors
Variants of anti-4-1BB	K1735 melanoma
	M108 tumors
	K562 erythroleukemia
	FRα tumors
Anti-4-1BB combination therapy	B16 melanoma
	Renal cell carcinoma
	K1735 melanoma
	CT26 colon carcinoma
	MCA205 tumors
	MC38 tumors
	M109, EMT6 tumors
4-1BBL and its variants	Liver metastases
	Cholangiosarcoma
	Neuroblastoma
	AML, Wilms tumor 1
	Colon 2A and 26 tumors
	P815 plasmacytoma
	K562/AO2 tumors
	Mouse forestomach carcinoma

4-1BB antibodies can suppress autoimmune disease.

4-1BB Triggering Ameliorates Experimental Autoimmune Encephalomyelitis by Modulating the Balance between Th17 and Regulatory T Cells *The Journal of Immunology*, 2011, 187: 1120–1128.

Young H. Kim,* Beom K. Choi,* Su M. Shin,* Chang H. Kim,* Ho S. Oh,* Sang H. Park,* Don G. Lee,* Myoung J. Lee,* Kwang H. Kim,* Dass S. Vinay,† and Byoung S. Kwon*,†

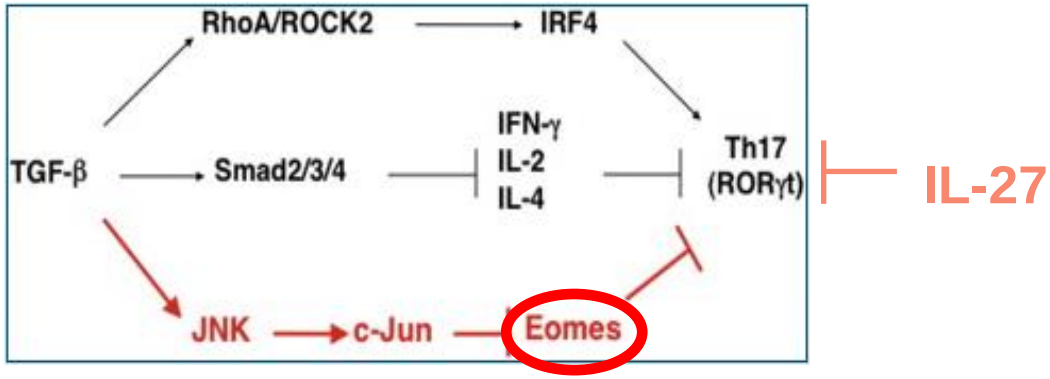


Published April 1, 2013
JEM

Article

Systemic 4-1BB activation induces a novel T cell phenotype driven by high expression of Eomesodermin

Michael A. Curran,[1] Theresa L. Geiger,[2] Welby Montalvo,[2] Myoungjoo Kim,[2] Steven L. Reiner,[3,4] Aymen Al-Shamkhani,[5] Joseph C. Sun,[2] and James P. Allison[1,2]

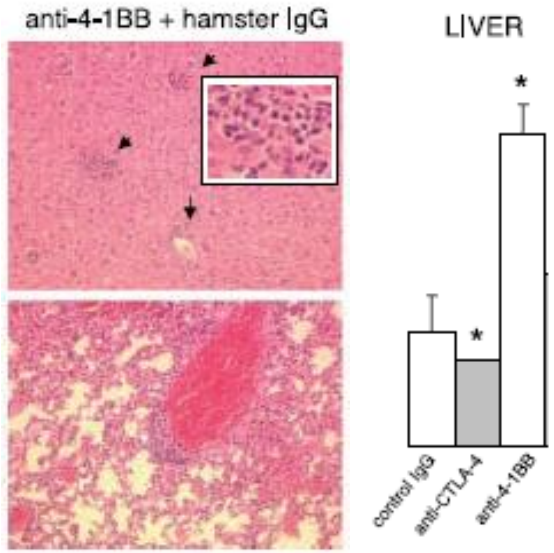


4-1BB agonist antibodies cause liver toxicity.

Cancer Res. 2006 Jul 15;66(14):7276–84.

Combination therapy with anti-CTL antigen-4 and anti-4-1BB antibodies enhances cancer immunity and reduces autoimmunity.

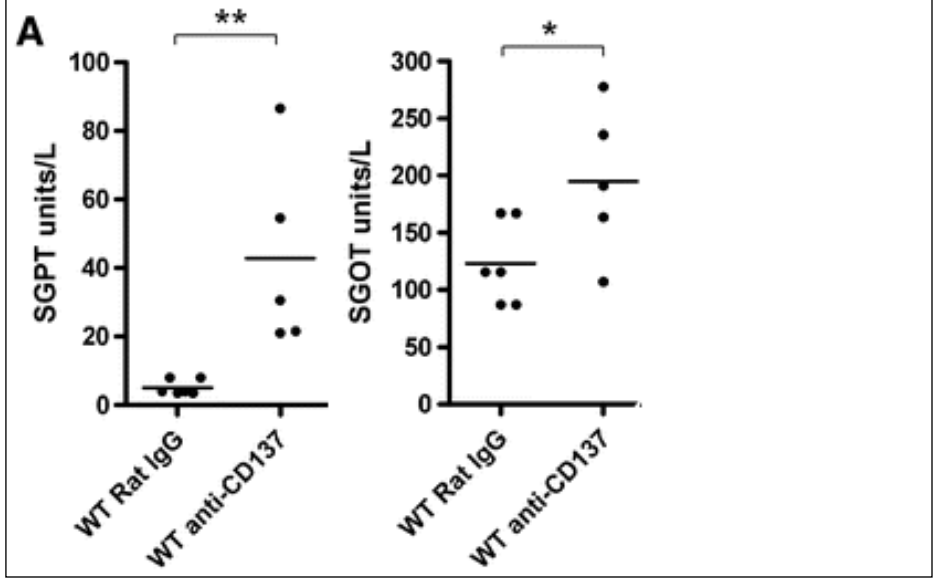
Kocak E[1], Lute K, Chang X, May KF Jr, Exten KR, Zhang H, Abdessalam SF, Lehman AM, Jarjoura D, Zheng P, Liu Y.

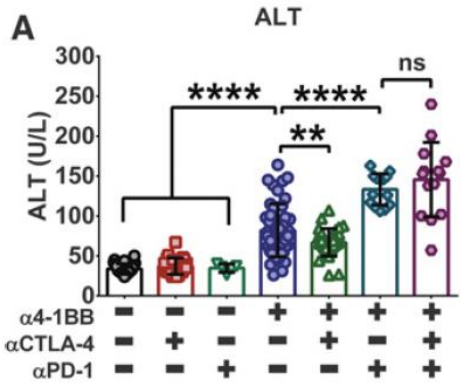


Cancer Immunol Immunother. 2010 Aug;59(8):1223-33. doi: 10.1007/s00262-010-0846-9. Epub 2010 Mar 25.

Treatment with anti-CD137 mAbs causes intense accumulations of liver T cells without selective antitumor immunotherapeutic effects in this organ.

Dubrot J[1], Milheiro F, Alfaro C, Palazón A, Martinez-Forero I, Perez-Gracia JL, Morales-Kastresana A, Romero-Trevejo JL, Ochoa MC, Hervás-Stubbs S, Prieto J, Jure-Kunkel M, Chen L, Melero I.





Cancer Therapy: Preclinical

Clinical Cancer Research

Activation of 4-1BB on Liver Myeloid Cells Triggers Hepatitis via an Interleukin-27–Dependent Pathway

Todd Bartkowiak[1,2], Ashvin R. Jaiswal[1,2], Casey R. Ager[1,2], Renee Chin[1], Chao-Hsien Chen[1,2], Pratha Budhani[1], Midan Ai[1], Matthew J. Reilley[3], Manu M. Sebastian[4], David S. Hong[5], and Michael A. Curran[1,2]

Clinical 4-1BB agonists: opposite ends of the spectrum

Urelumab : High efficacy, high toxicity (Superagonist)

1. In an open label, dose escalation study, Urelumab (BMS) achieved monotherapy Recist PR in melanoma (10-15%) and SD > 6m in 17% of melanoma and 14% of RCC (2005).
2. During a Phase II follow-up trial in melanoma, multiple instances of Grade 4/5 liver toxicity led to an FDA hold (2009).
3. Urelumab "safety dosing" is below the threshold for efficacy (10x lower than best dose from Phase I).

Utomilumab : Very low efficacy, low toxicity (Fc dependent, ligand-blocking agonist)

1. Pfizer developed Utomilumab at a time when Urelumab was on FDA hold – their primary criteria was to find a 4-1BB agonist with minimal liver toxicty.
2. Utomilumab has an excellent safety profile but very low efficacy – no PR in melanoma; PR/CR as monotherapy only in Merkel Cell.

Neither of these will be FDA approved as monotherapy and only Utomilumab is advancing in combinations.

How can you make a 4-1BB agonist that is both safe and effective?

Novartis
Compass
Alligator

Cytomx/BMS

Pieris (Ph. I)
Roche
Numab
Aptevo
Mabimmune
F-Star
Servier

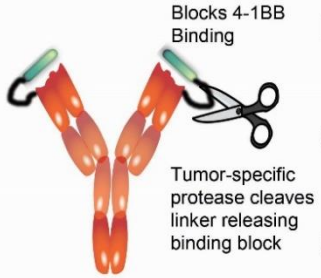
4-1BB Agonist

Pros: Activation in the LN and tumor
Easy to produce and test

Cons: Toxic 4-1BB activation in liver
Bell-shaped dose response curve

Safety: Combine w/αCTLA-4 or αCCR2
Find a selective target epitope?

4-1BB Probody

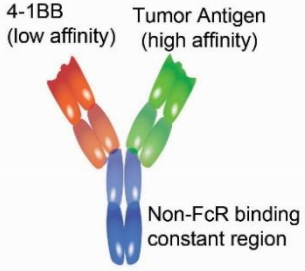


Pros: Specific activation in the tumor
No/minimal liver toxicity

Cons: No amplification in LN
Variability in activation

Safety: Should be safe at effective doses

4-1BB BiSpecific



"Tumor antigen" can be on the tumor (e.g. Her2) or in the TME (e.g. FAP, PD-L1).

Pros: Specific Activation in the tumor
No/minimal liver toxicity

Cons: Heterogenous expression of "anchor" antigen
No amplification in LN

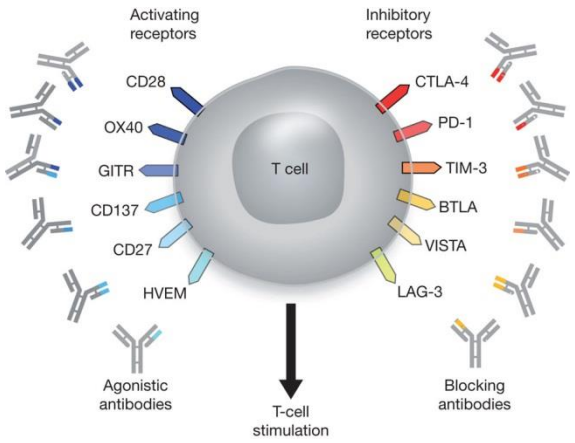
Safety: Should be safe at effective doses
Early data suggests lack of bell curve

To exist, tumors must evolve mechanisms to locally disable and/or evade the immune system.

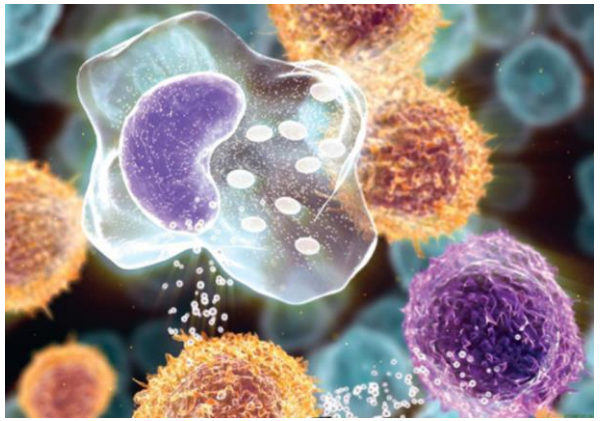
The goal of T cell checkpoint blockade is block the switches on T cells being engaged by the tumor to shut them down and in so doing to restore tumor-specific immunity.

Types of Immunotherapy.

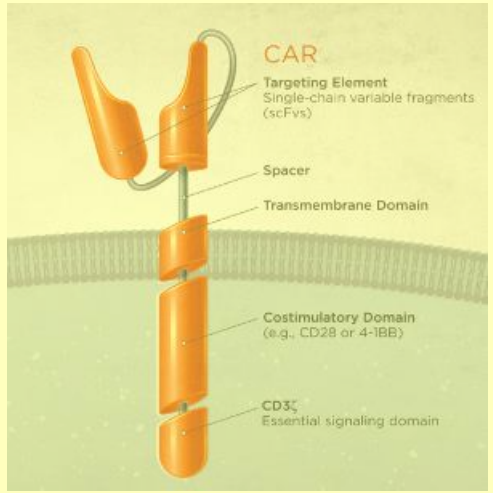
T Cell Checkpoint Modulation



Cytokine Therapy

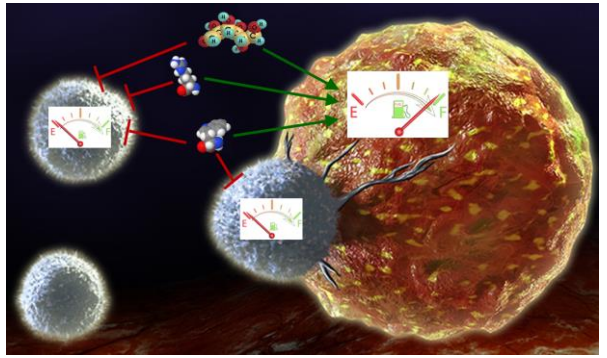


T Cell Adoptive Transfer



Therapeutic Cancer Vaccines

Metabolic Modifiers



Effector antibodies and ADCs