Understanding Checkpoint Inhibitors: Approved Agents, Drugs in Development and Combination Strategies

Michael A. Curran, Ph.D.

MD Anderson Cancer Center

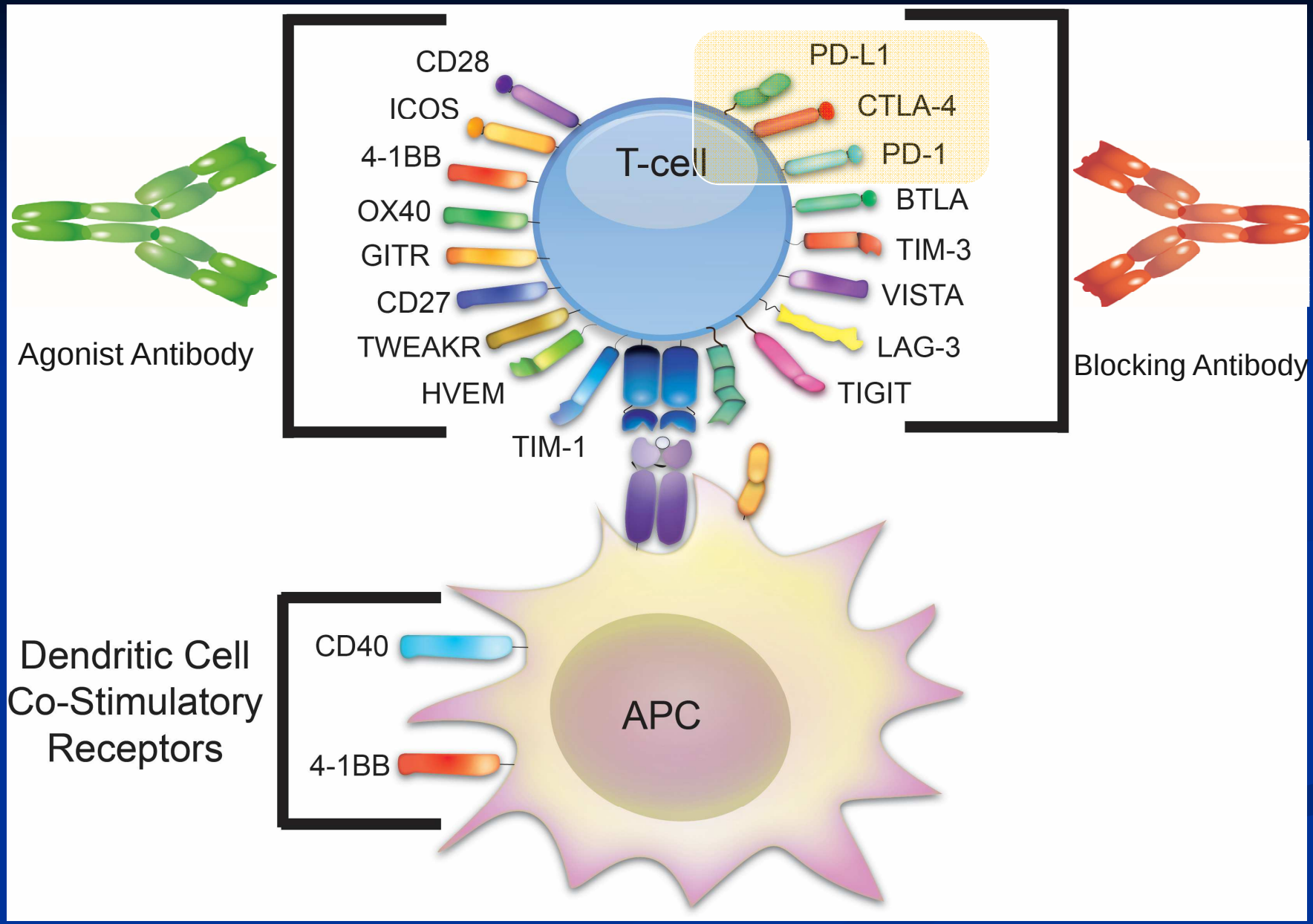
Department of Immunology

Disclosures

I have research collaborations with Bristol Myers Squibb, Astrazeneca, Adimab, Kairos and Threshold.

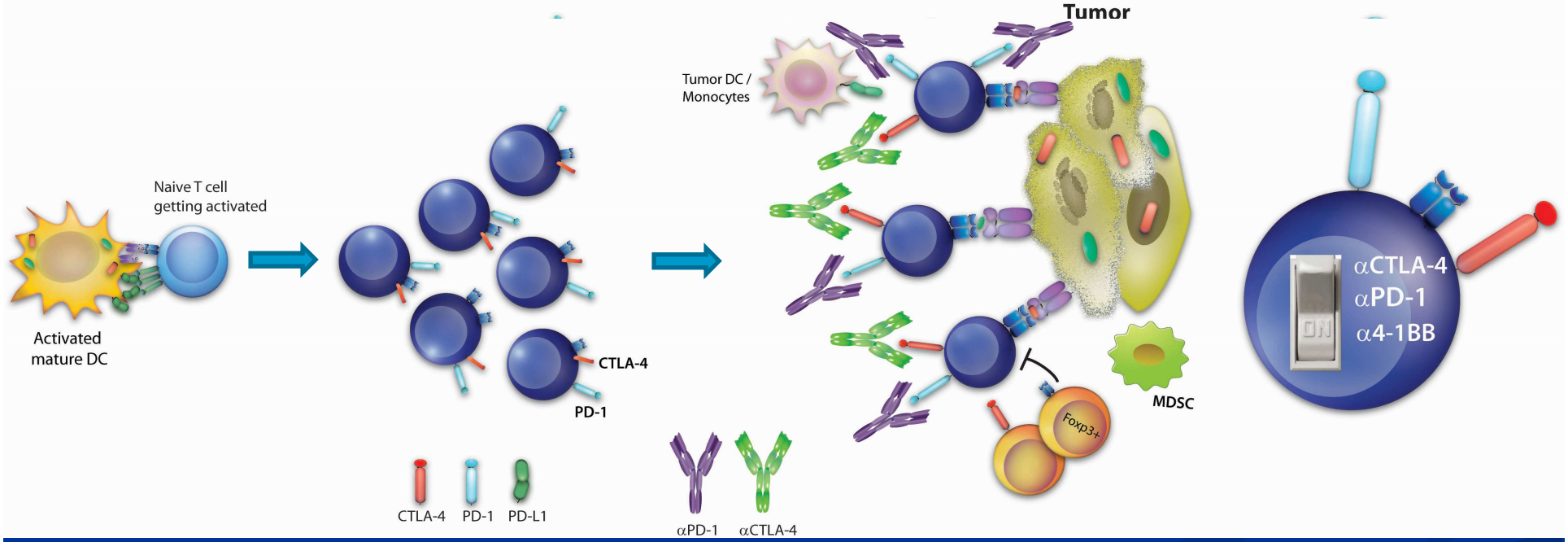
I receive royalties from the patent "Methods and Compositions for Localized Secretion of anti-CTLA-4 Antibodies".

I will be talking about investigational therapeutics.



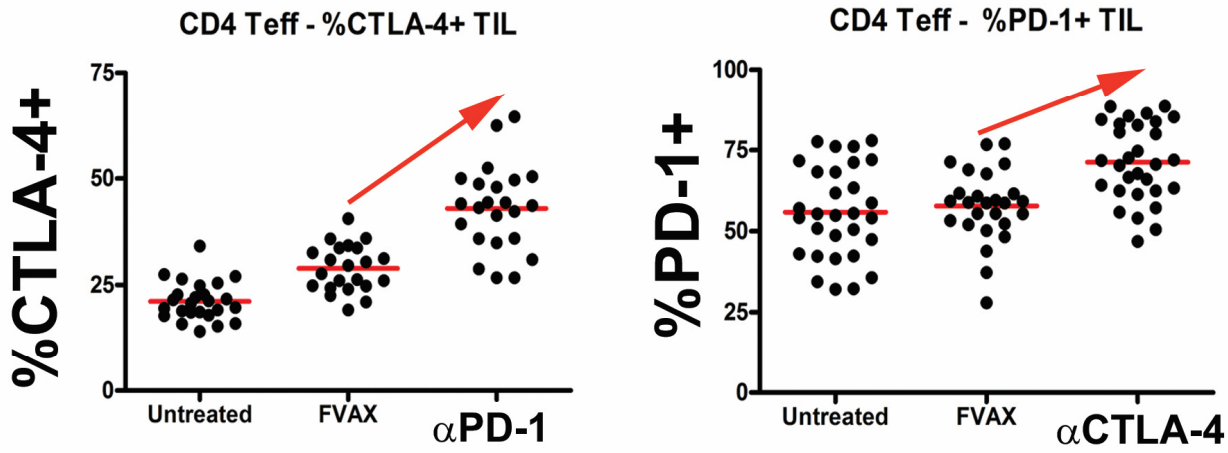
Ai M., **Curran M.** Immune checkpoint combinations from mouse to man.
Cancer Immunology Immunotherapy, 2015.

How do "immune checkpoint" antibodies like αCTLA-4 (Ipilimumab) and αPD-1 treat cancer?

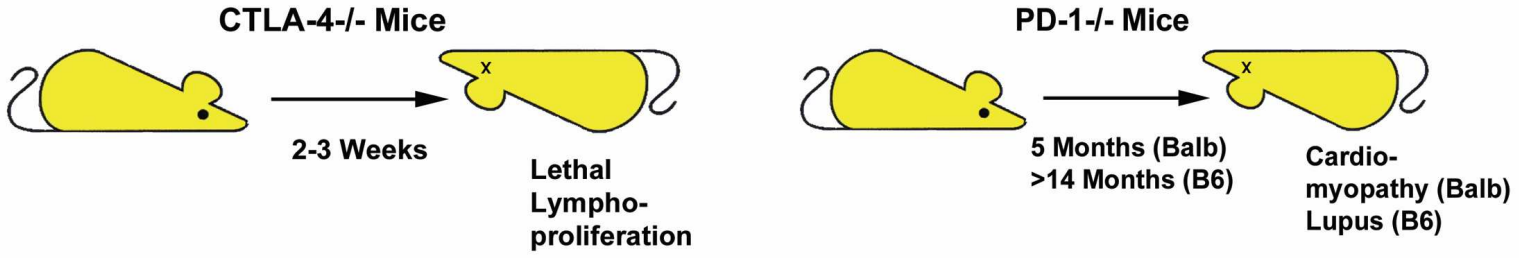


Why choose to block the PD-1 pathway in addition to CTLA-4?

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



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



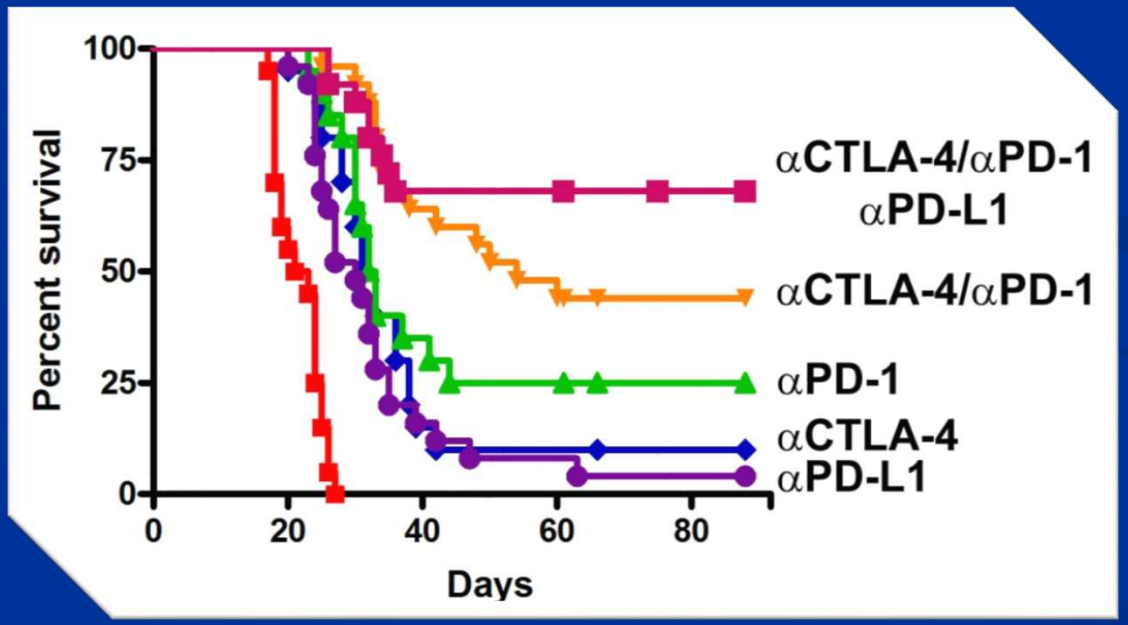
Curran M A et al. PNAS 2010; 107(9):4275-80.

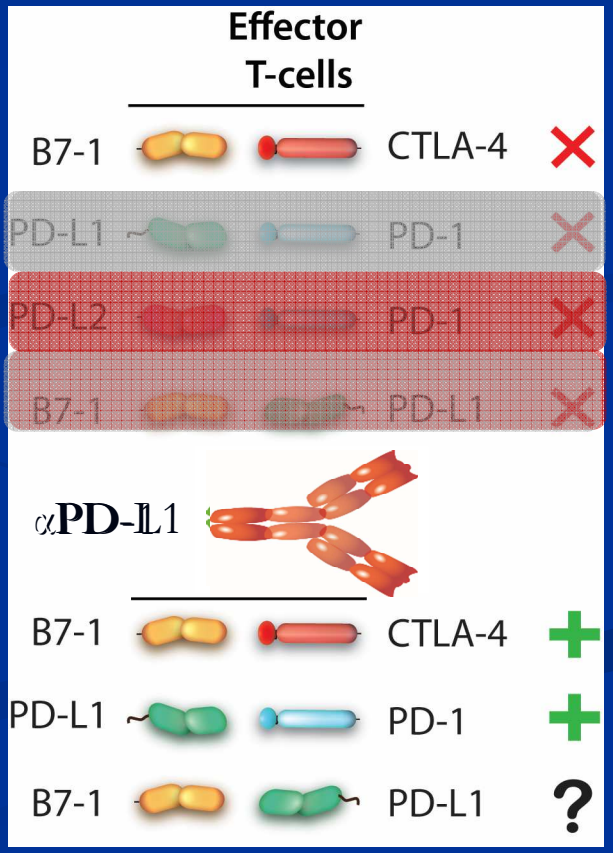
PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

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.

Objective response rates in malignant melanoma with checkpoint blockade

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2
Duration of response (months)			
Median (95% CI)	NR (13.1, NR)	NR (11.7, NR)	NR (6.9, NR)

*By RECIST v1.1.
NR, not reached.

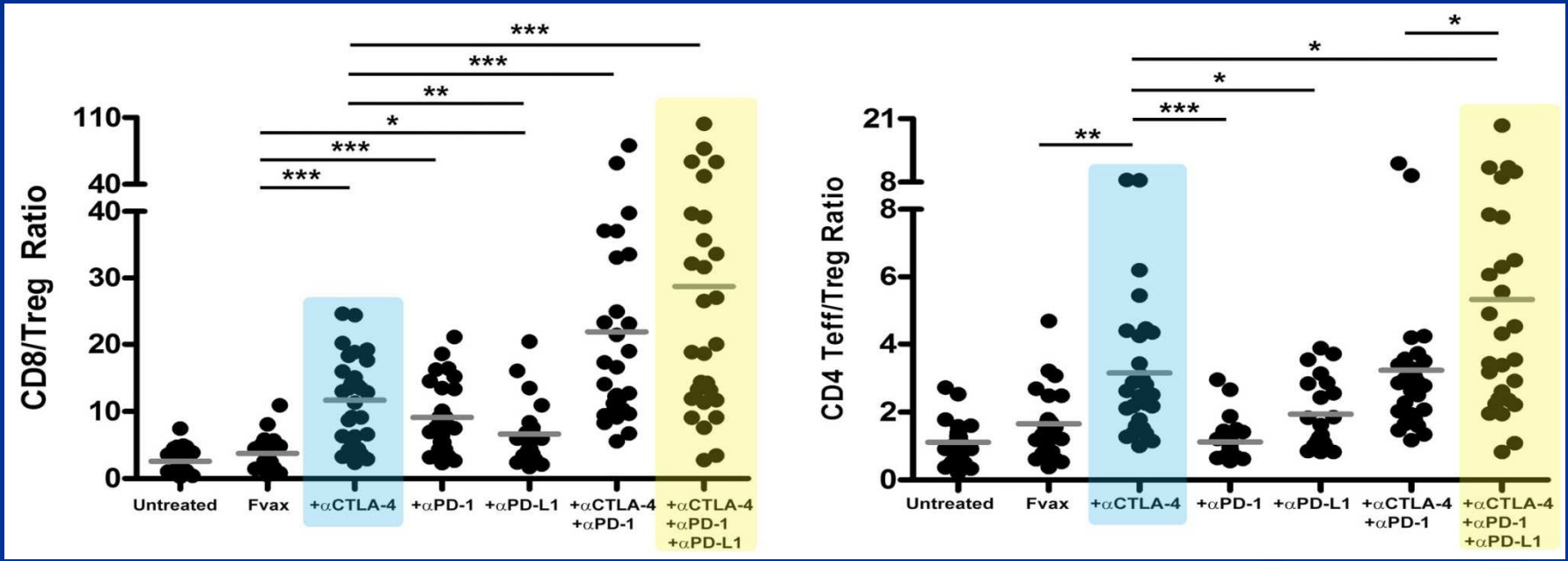
Wolchok et al. ASCO 2015

Two year survival: 2010 – standard of care – 18%
Ipilimumab (FDA 2010) – 30%
Nivolumab (FDA 2014) – 43%
Ipi/Nivo (FDA 2015?) - ~90%

	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	+++	++	++

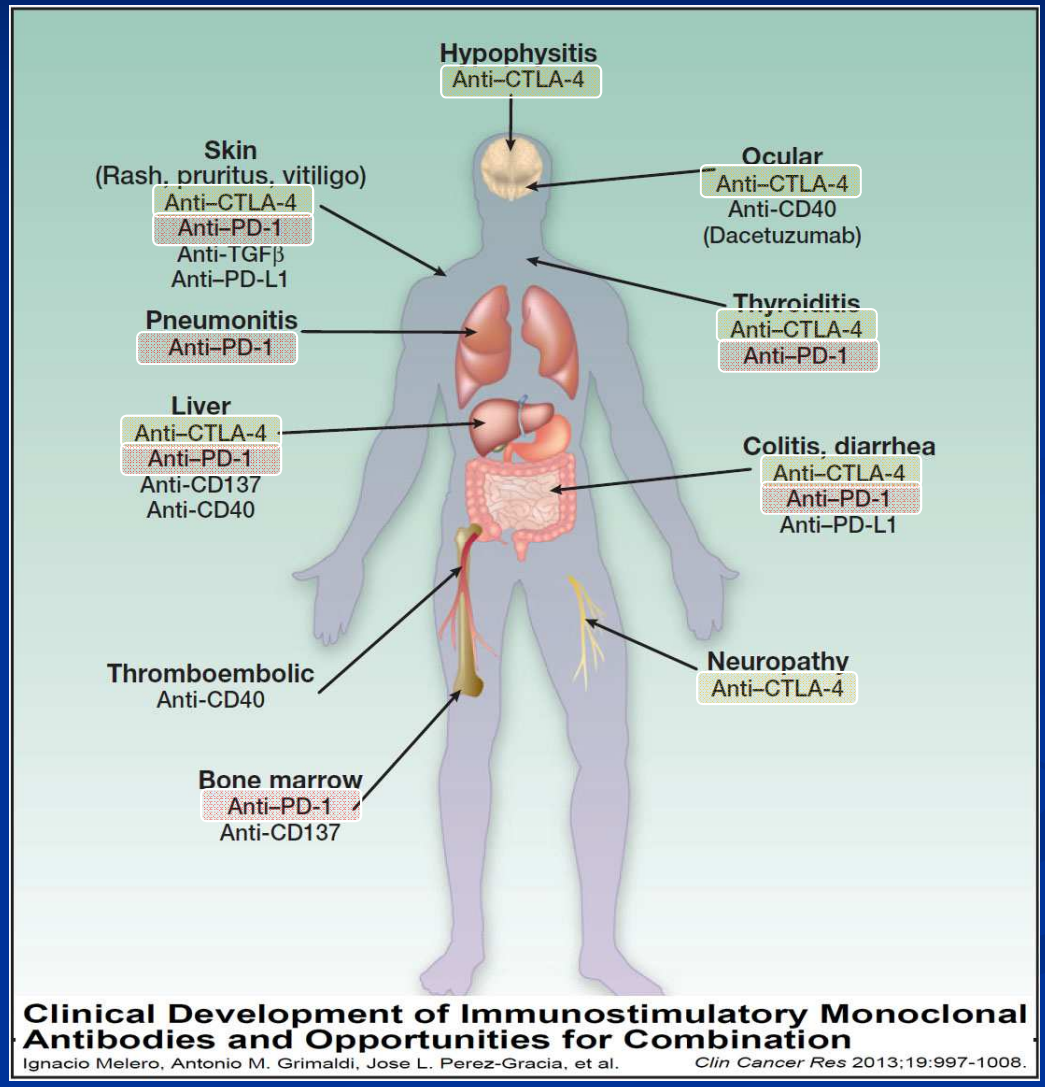
Michael A. Curran, Ph.D.

Conversion of the tumor micro-environment from suppressive to inflammatory



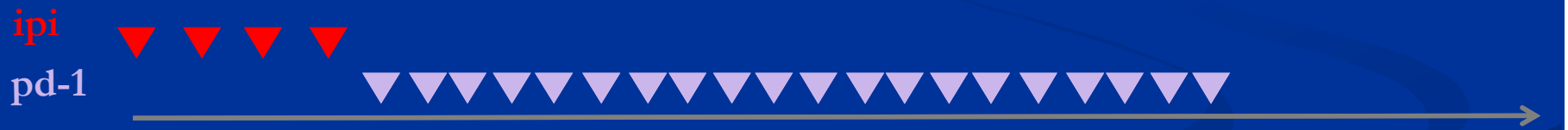
Curran M A et al. PNAS 2010; 107(9):4275-80.

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



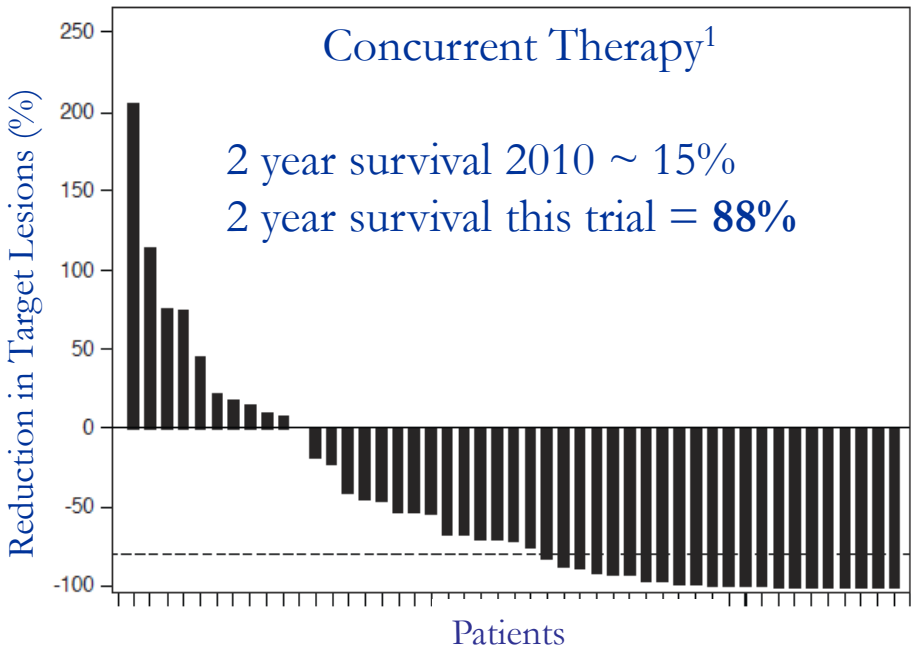
Phase I study: Concurrent and sequenced nivolumab and ipilimumab in melanoma

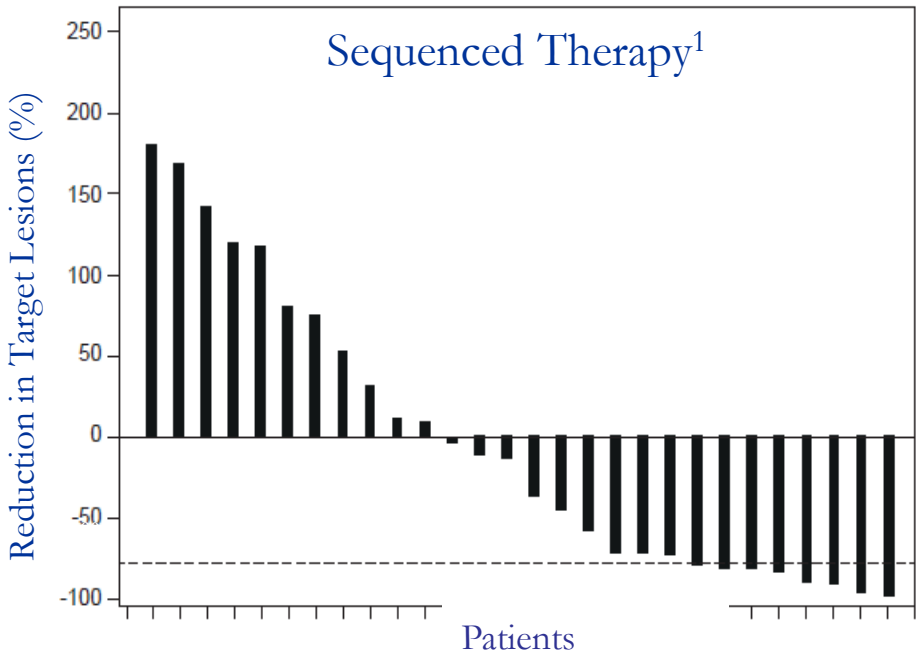
Cohort	MDX1106	Ipilimumab
1	0.3 mg/kg	3 mg/kg
2	1 mg/kg	3 mg/kg
2A	3 mg/kg	3 mg/kg
3	3 mg/kg	1 mg/kg



Cohort	MDX1106
6	1 mg/kg
7	3 mg/kg

Clinical activity: combination of nivolumab and ipilimumab therapy

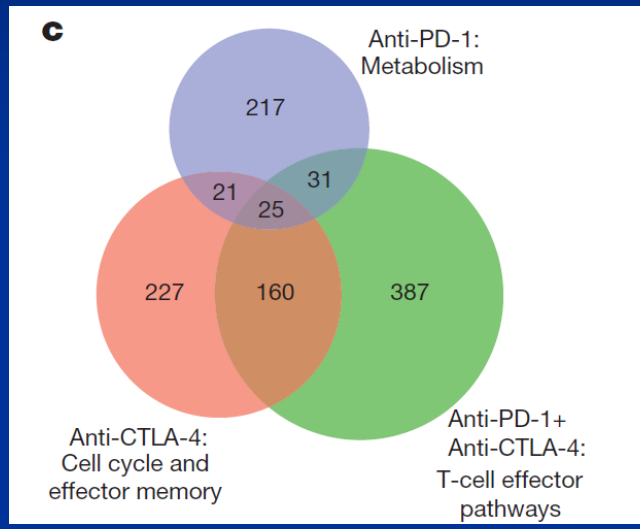


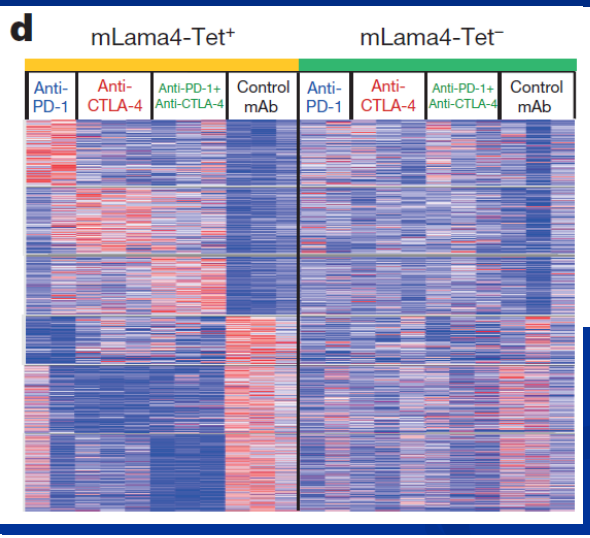


	n	ORR	Patients with ≥80% Tumor Reduction at 12 Wk
Ipilimumab (3 mg/kg)[2]	137	11%	<2
Nivolumab (3 mg/kg)[3]	17	41%	<3
Concurrent therapy[1] (3 mg/kg ipilimumab + 1 mg/kg nivolumab)	17	**53%**	**41%**

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.

Combination checkpoint blockade = More than the sum of the parts

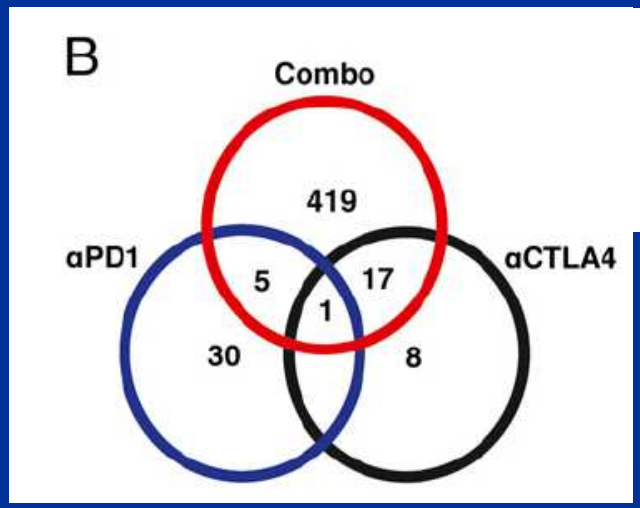




doi:10.1038/nature13988

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[3], 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]

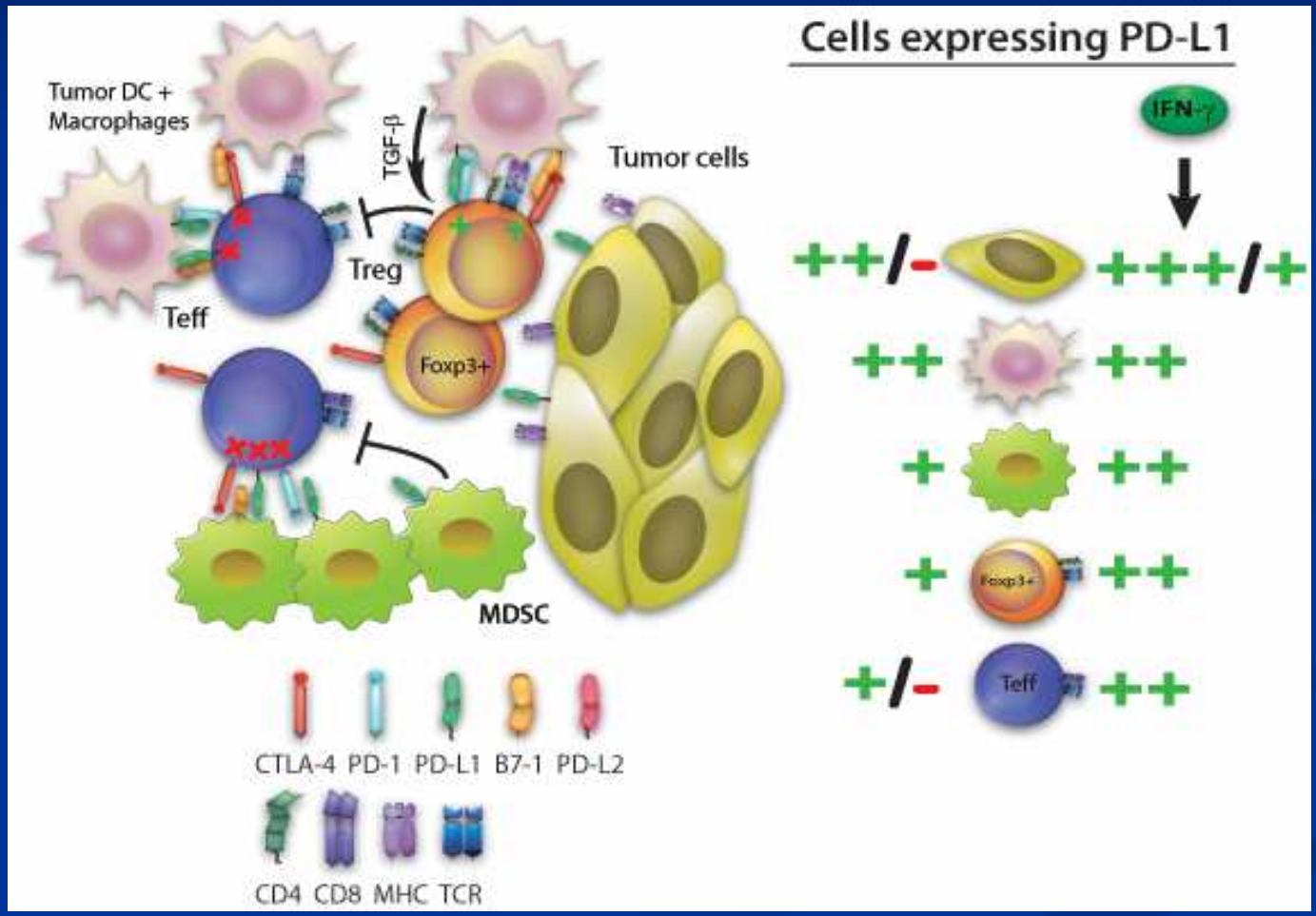


The Journal of Immunology

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

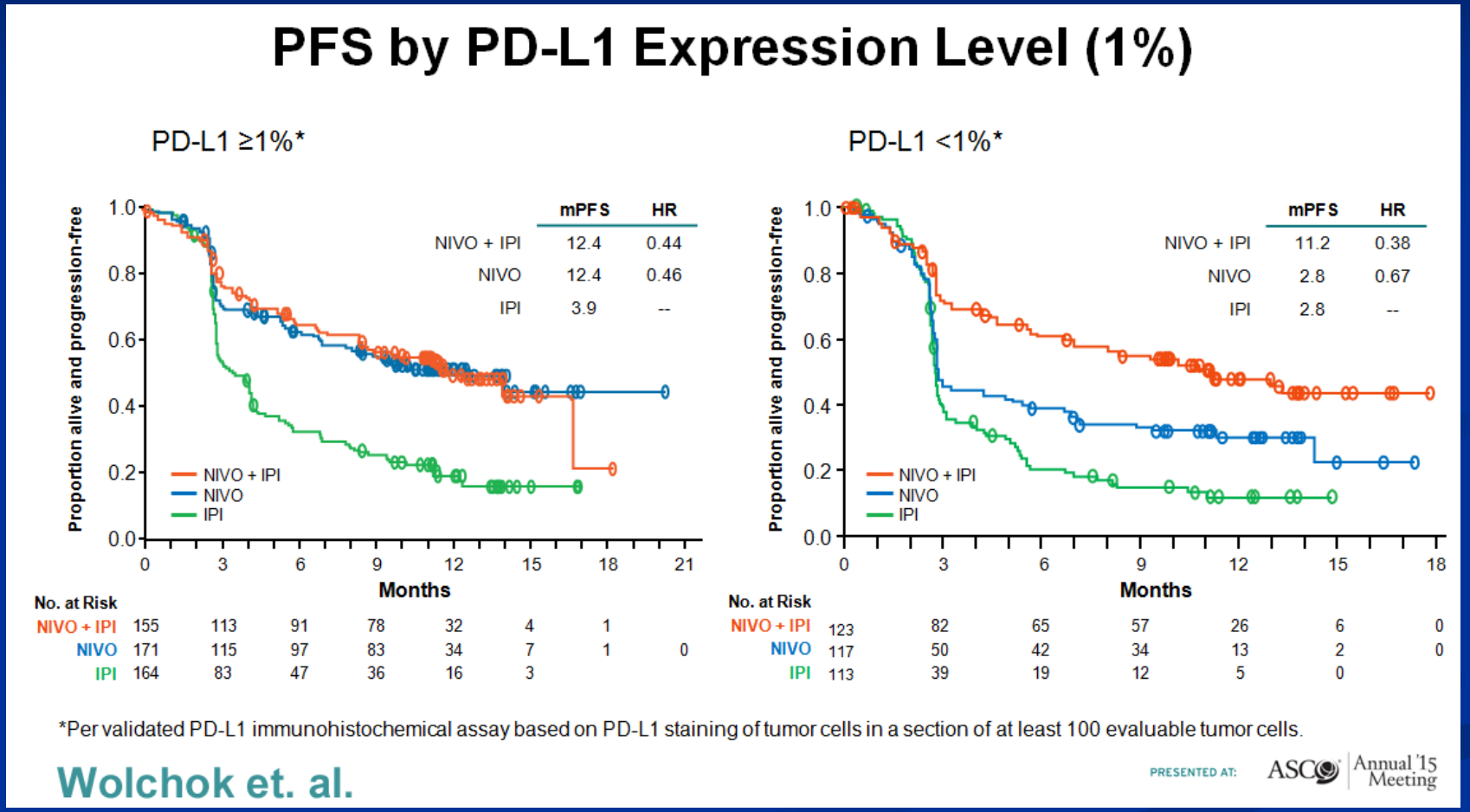
Rituparna Das, Rakesh Verma, Mario Sznol, Chandra Sekhar Boddupalli, Scott N. Gettinger, Harriet Kluger, Margaret Callahan, Jedd D. Wolchok, Ruth Halaban, Madhav V. Dhodapkar and Kavita M. Dhodapkar

Predictive biomarkers for response to checkpoint blockade

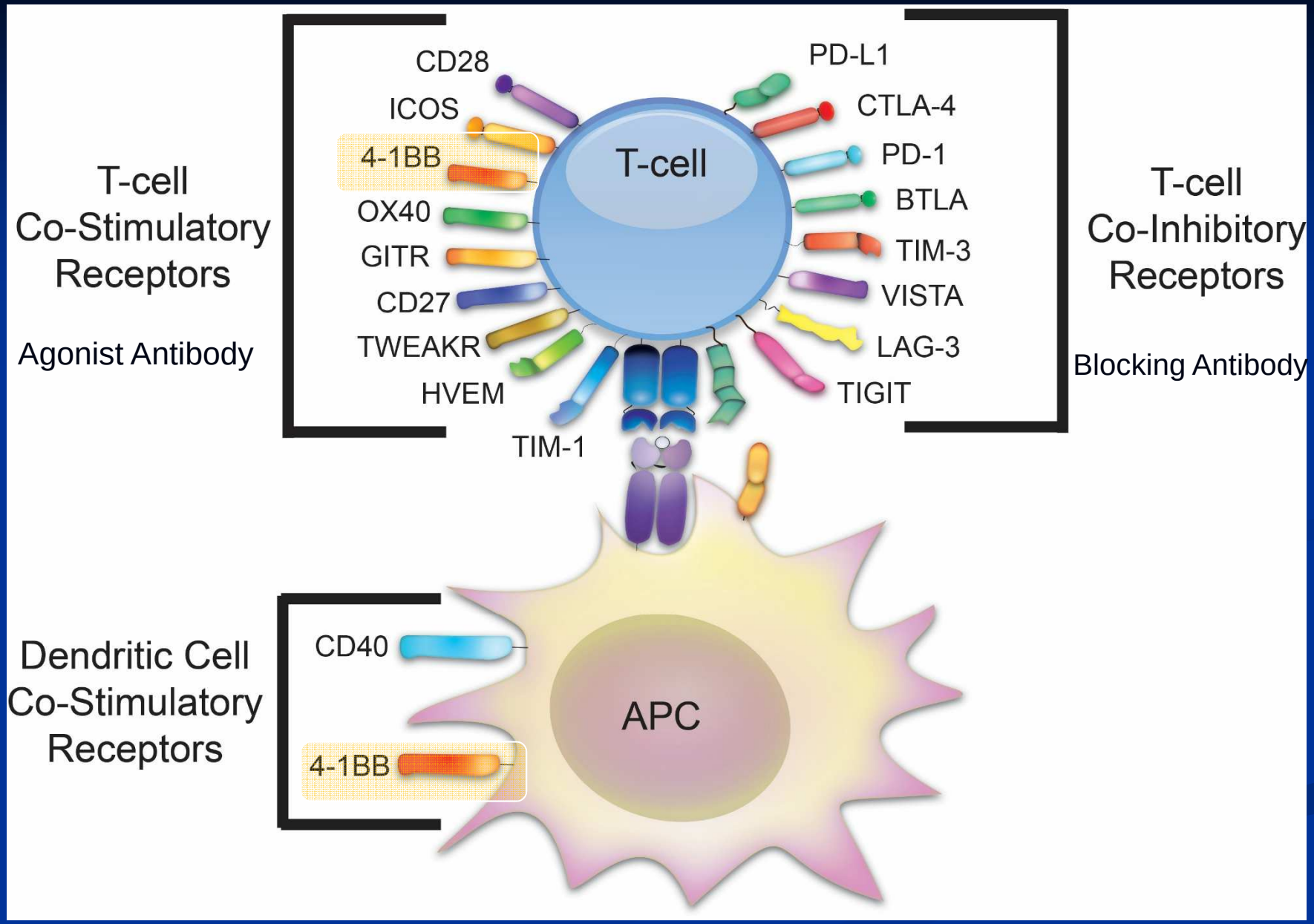


Idea: To expect benefit from αPD-1/αPD-L1 treatment, there must be PD-L1 expressed.

PD-L1 is a biomarker for response to αPD-1 but not αPD-1 + αCTLA-4



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.



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

4-1BB : Favorable expression profile for immunotherapy

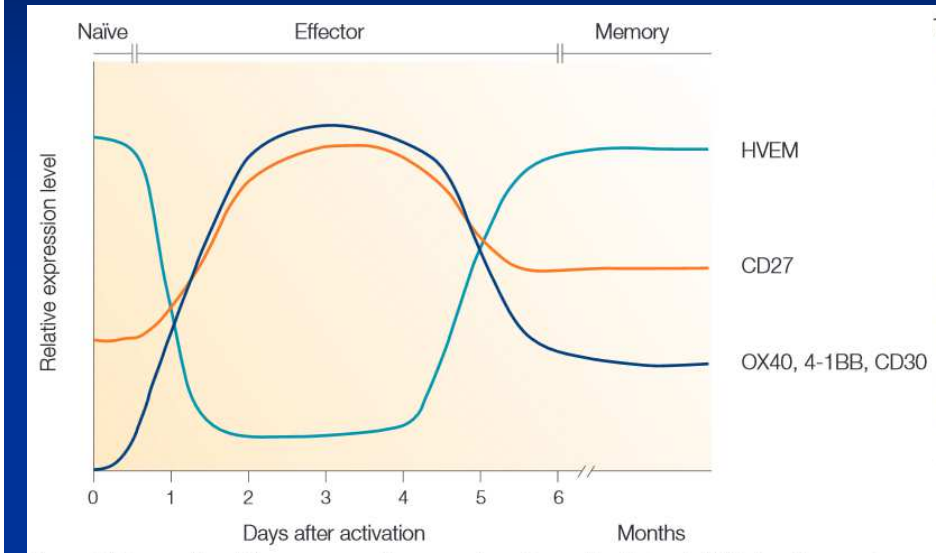


Figure 2 | **Generalized time course of expression of co-stimulatory TNFR-family members.**

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**

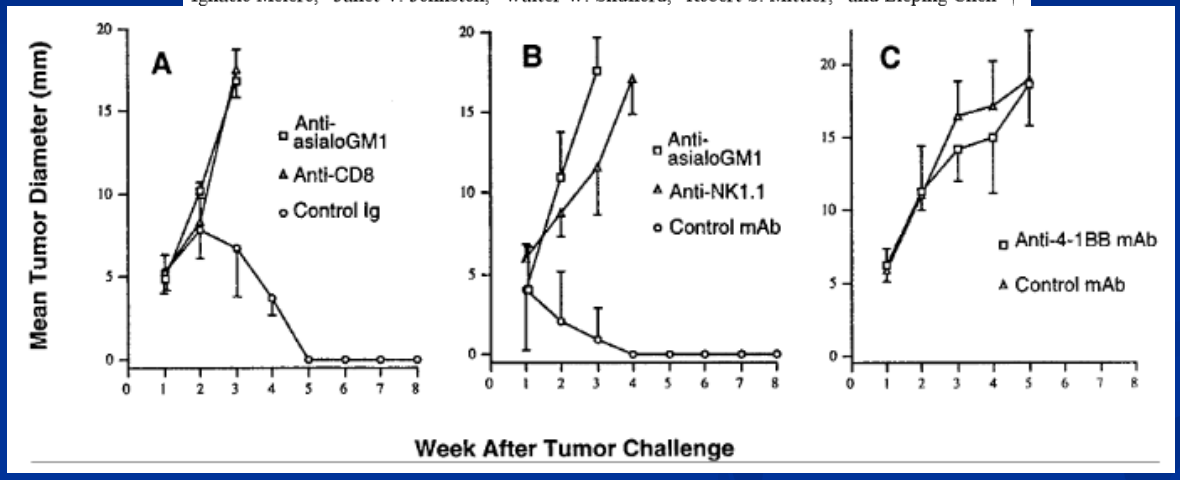
Lieping Chen & Dallas B. Flies *Nature Reviews Immunology* **13**, 227-242 (April 2013)

4-1BB activates NK Cells

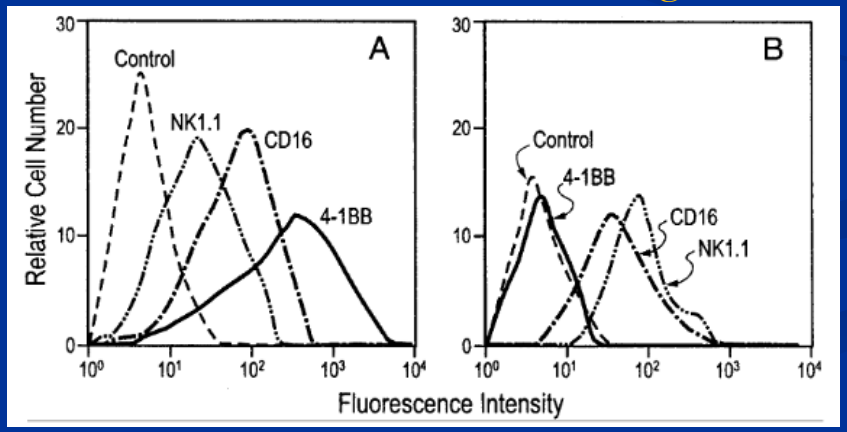
CELLULAR IMMUNOLOGY **190,** 167–172 (1998)
ARTICLE NO. CI981396

NK1.1 Cells Express 4-1BB (CDw137) Costimulatory Molecule and Are Required for Tumor Immunity Elicited by Anti-4-1BB Monoclonal Antibodies

Ignacio Melero,* Janet V. Johnston,* Walter W. Shufford,* Robert S. Mittler,* and Lieping Chen*,†,[1]



Activated NK Resting NK



4-1BB antibodies cure many types of cancer in mouse models

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

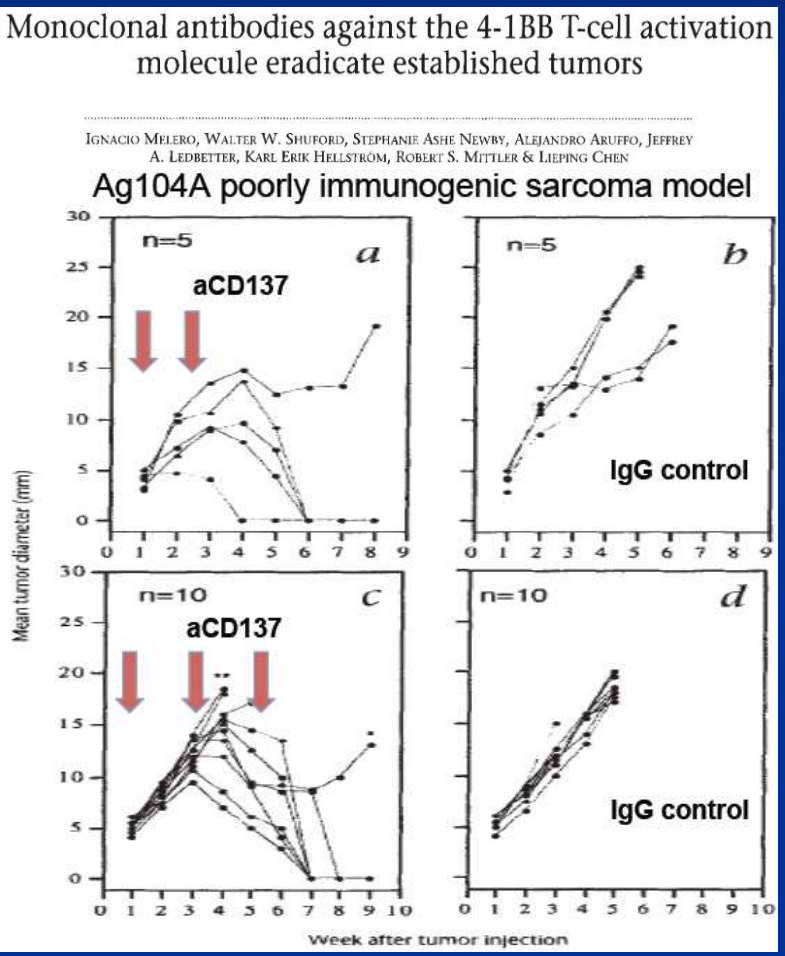


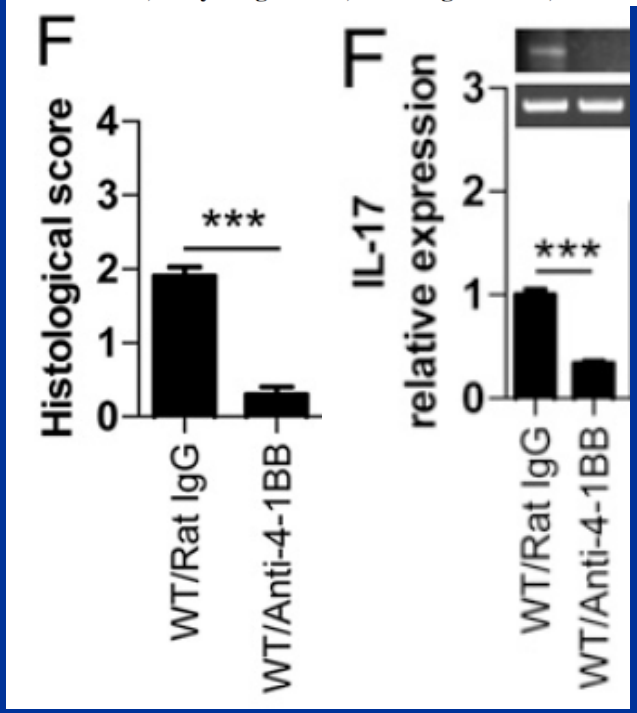
Table 1. Suppression of various tumors by targeting the 4-1BB–4-1BBL pathway

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*,†

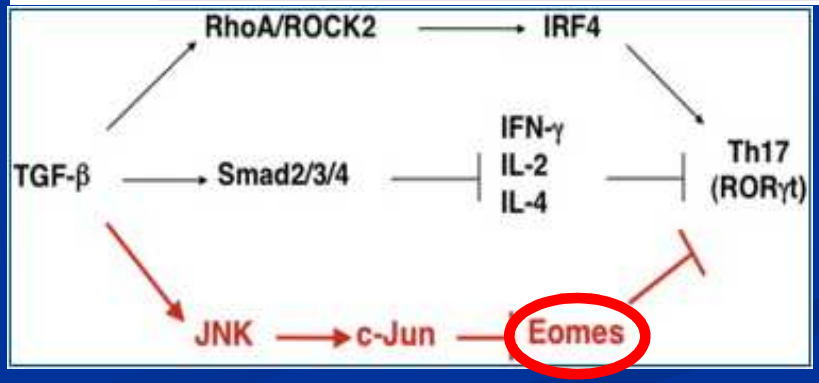


Published April 1, 2013
JEM

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]



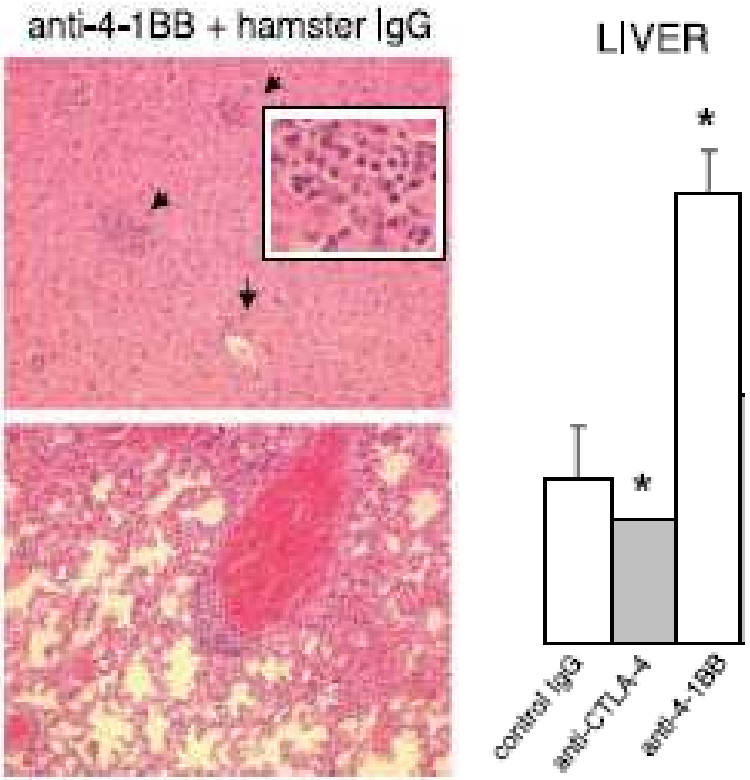
IL-27

4-1BB agonist antibodies cause liver inflammation

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.

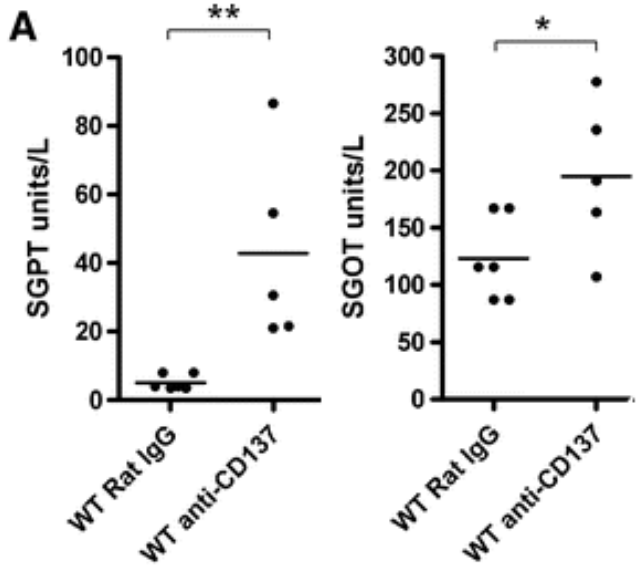
Kocak E[1], Lute K, Chang X, May KF Jr, Exten KR, Zhang H, Abdessalam SF, Lehman AM, Jarjoura D, Zheng P, Liu Y.



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.

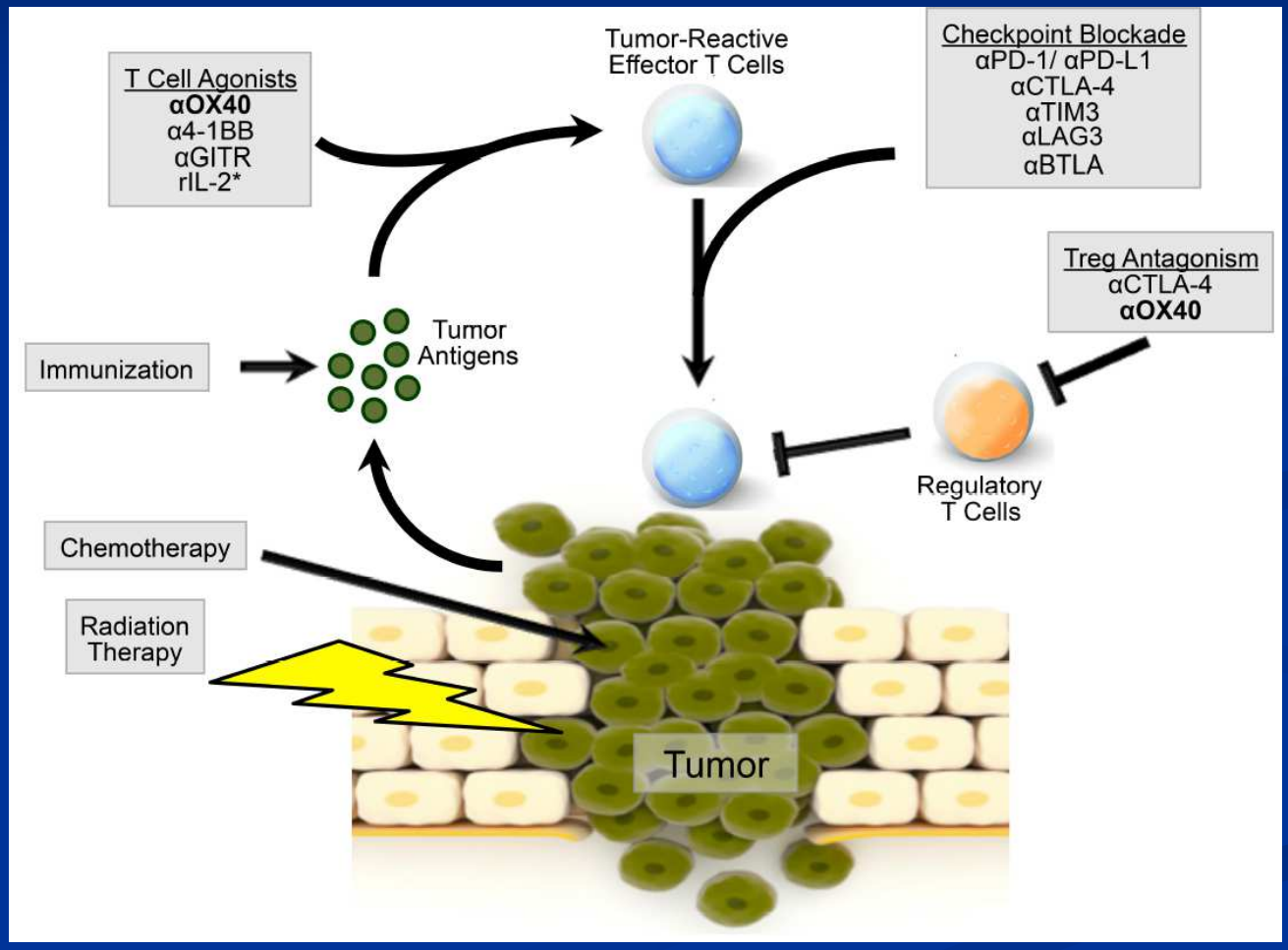
Dubrot J[1], Milheiro F, Alfaro C, Palazón A, Martinez-Forero I, Perez-Gracia JL, Morales-Kastresana A, Romero-Trevejo JL, Ochoa MC, Hervás-Stubbs S, Prieto J, Jure-Kunkel M, Chen L, Melero I.



4-1BB/CD137 agonist antibody clinical summary

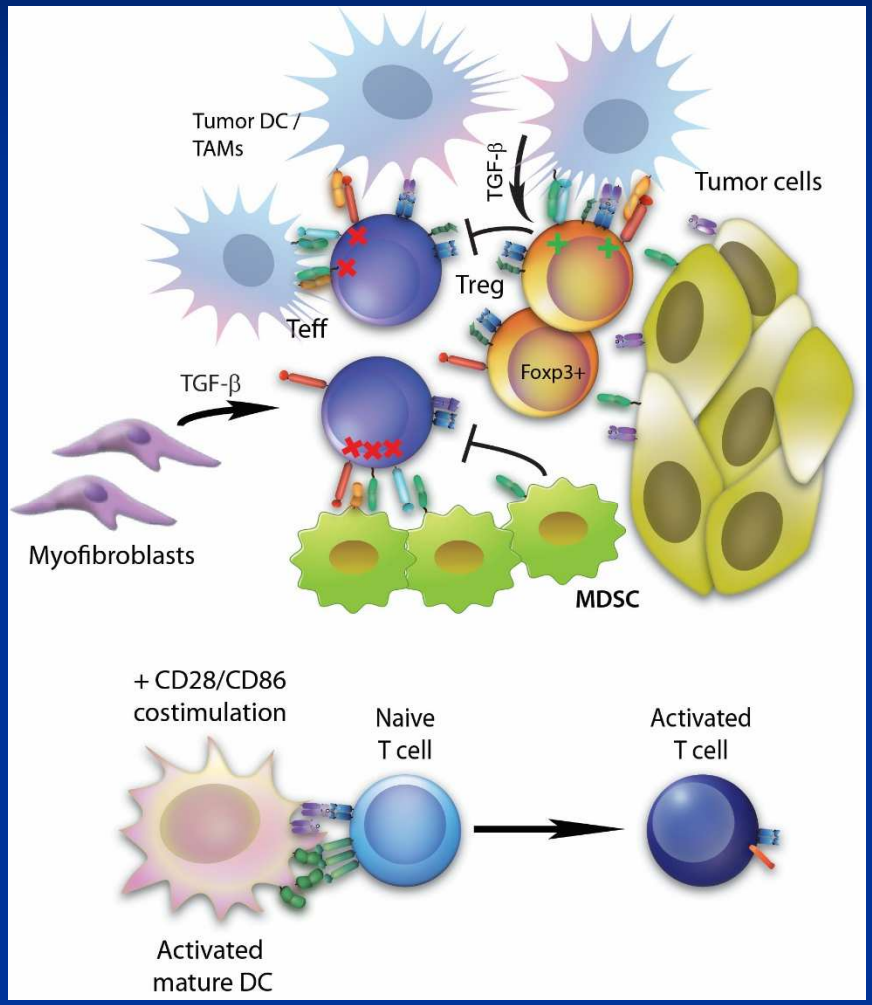
- Used as a monotherapy to treat solid tumors in some trials with PR and SD reported
- Used to activate NK (and myeloid) cells to mediate improved ADCC in combination with tumor-specific antibodies like Rituximab and Cetuximab (EGFR)
- BMS antibody is IgG4, does not block binding of 4-1BB-ligand but causes liver toxicity even at 0.3mg/kg
- Pfizer antibody is IgG2, does block 4-1BB-ligand, but does not cause severe liver toxicity even at 10mg/kg
- Combination trials with PD-1 have begun and with CTLA-4 are being planned

OX-40 antibodies augment effector T cells and deplete Tregs and are not known to cause substantial IRAE



Citation: Linch SN, McNamara MJ and Redmond WL (2015) OX40 agonists and combination immunotherapy: putting the pedal to the metal. *Front. Oncol.* 5:34. doi: 10.3389/fonc.2015.00034

There are many potential targets for immuno-therapeutic antibodies in the microenvironment

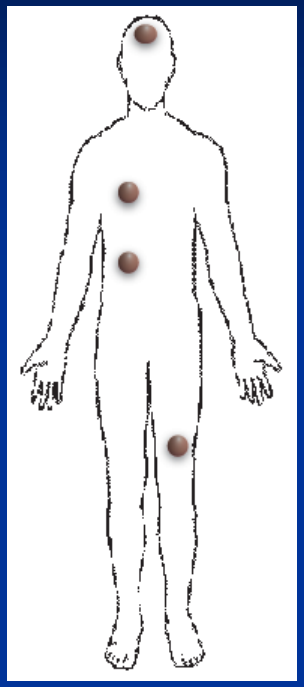


1) Blockade of T cell immune checkpoints (PD-1)
2) Activation of T cell co-stimulation (4-1BB)
3) Activation of myeloid cells (TLR, CD40)
4) Blockade of immunosuppressive cytokines (IL-10)
5) Blockade of stromal chemoattraction (CXCR4)
6) Blockade of angiogenesis (VEGFR2)
7) ADCC of tumor (CD20)
8) Depletion of suppressive cells (CTLA-4)
9) Killing of tumor with payloaded mAB (T-DM1)
10) Killing of suppressive stromal populations
11) Targeted delivery of stimulatory cytokines (IL-12)
12) Augmentation of tumor antigen presentation

All targets are not created equal

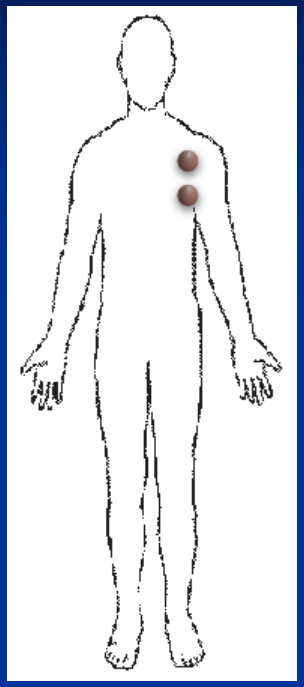
- Tier 1(monotherapy efficacy in multiple tumors)
  - PD-1, CTLA-4, 4-1BB, CD40, PD-L1
  - Rituximab, Trastuzumab, Cetuximab
- Tier 2 (limited monotherapy efficacy, strong complementary function in combination)
  - OX-40, TIGIT, (maybe TIM3, KIR, CD27, GITR)
  - erbB3, Mesothelin
- Tier 3 (no monotherapy efficacy, potential for combination efficacy in multiple tumors)
  - LAG3, VISTA, ICOS, other TNFR, PS
- Tier 4 (combination efficacy in some models)
  - LAIR, other highly tissue-specific targets

One (combination) shoe doesn't fit all



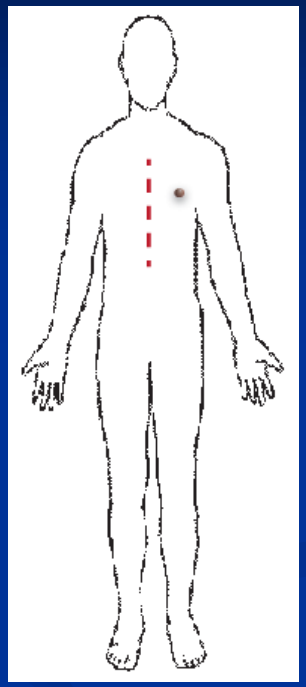
Advanced Metastatic disease

αCTLA-4/αPD-1
+Rad or drug or
Anti-stromal therapy
or STING



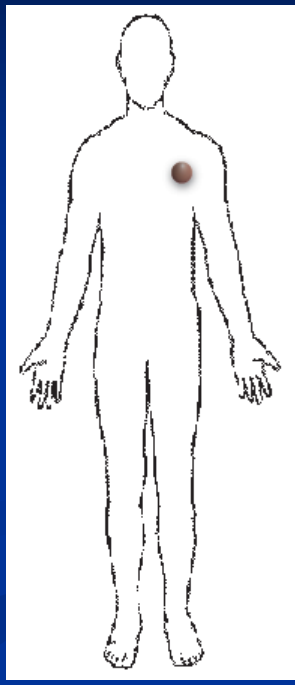
Locally advanced disease

αPD-1 or αPD-L1
+Rad or drug or
Anti-stromal therapy
or STING



MRD post-surgery

αOX40/αPD-L1
or
αOX40/αMDSC
or
αOX-40/TLR



Localized, accessible disease

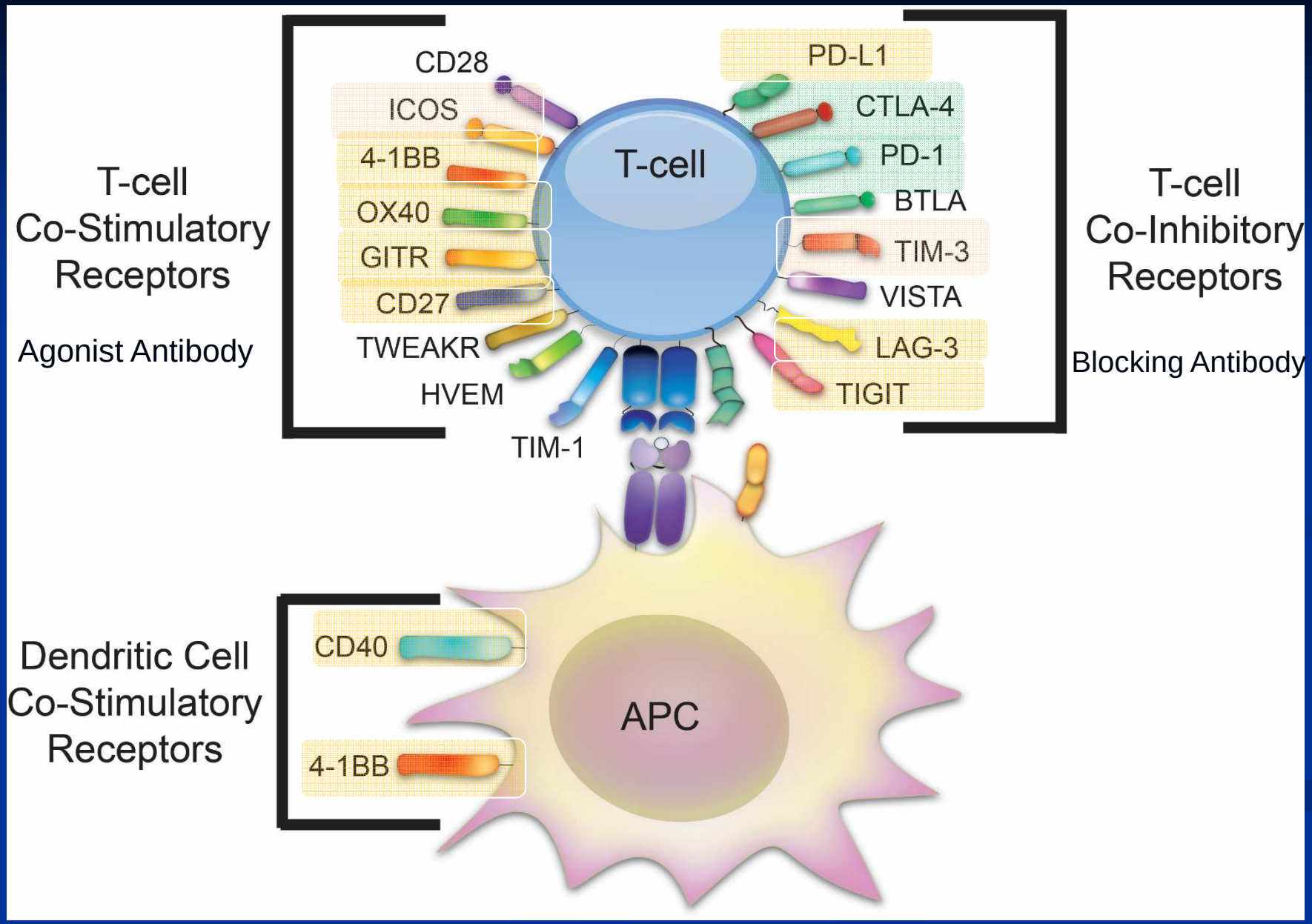
Local αCTLA-4,
α4-1BB or αCD40
or
Local STING/TLR

Immune checkpoint modulating antibodies currently in the clinic

Table 1: T cell immune checkpoint modulating antibodies in the clinic

Target Molecule	Drug	Company	Development Stage
CTLA-4	Ipilimumab	Bristol-Myers Squibb	FDA Approved
	Tremelimumab	Medimmune/Astrazeneca	Phase III Trial
PD-1	Pembrolizumab	Merck	FDA Approved
	Nivolumab	Bristol-Myers Squibb	FDA Approval Pending
	AMP-514/MEDI0680	Medimmune/Astrazeneca	Phase I Trial
PD-L1	MPDL3280A	Genentech/Roche	Phase III Trial
	MEDI4736	Medimmune/Astrazeneca	Phase III Trial
	MSB0010718C	EMD Serono	Phase II Trial
	BMS-936559	Bristol-Myers Squibb	Phase I Trial
4-1BB	Urelumab	Bristol-Myers Squibb	Phase I Trial
	PF-05082566	Pfizer	Phase I Trial
OX-40	MEDI6469	Medimmune/Astrazeneca	Phase I Trial
	MEDI6383 (rOX40L)	Medimmune/Astrazeneca	Phase I Trial
	MOXR0916	Genentech/Roche	Phase I Trial
GITR	TRX518	Tolerx	Phase I Trial
CD27	CDX-1127	Celldex	Phase I Trial
CD40	CP-870,893	Genentech/Roche	Phase I Trial
LAG3	BMS-986016	Bristol-Myers Squibb	Phase I Trial

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



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