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

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MD Anderson Cancer Center

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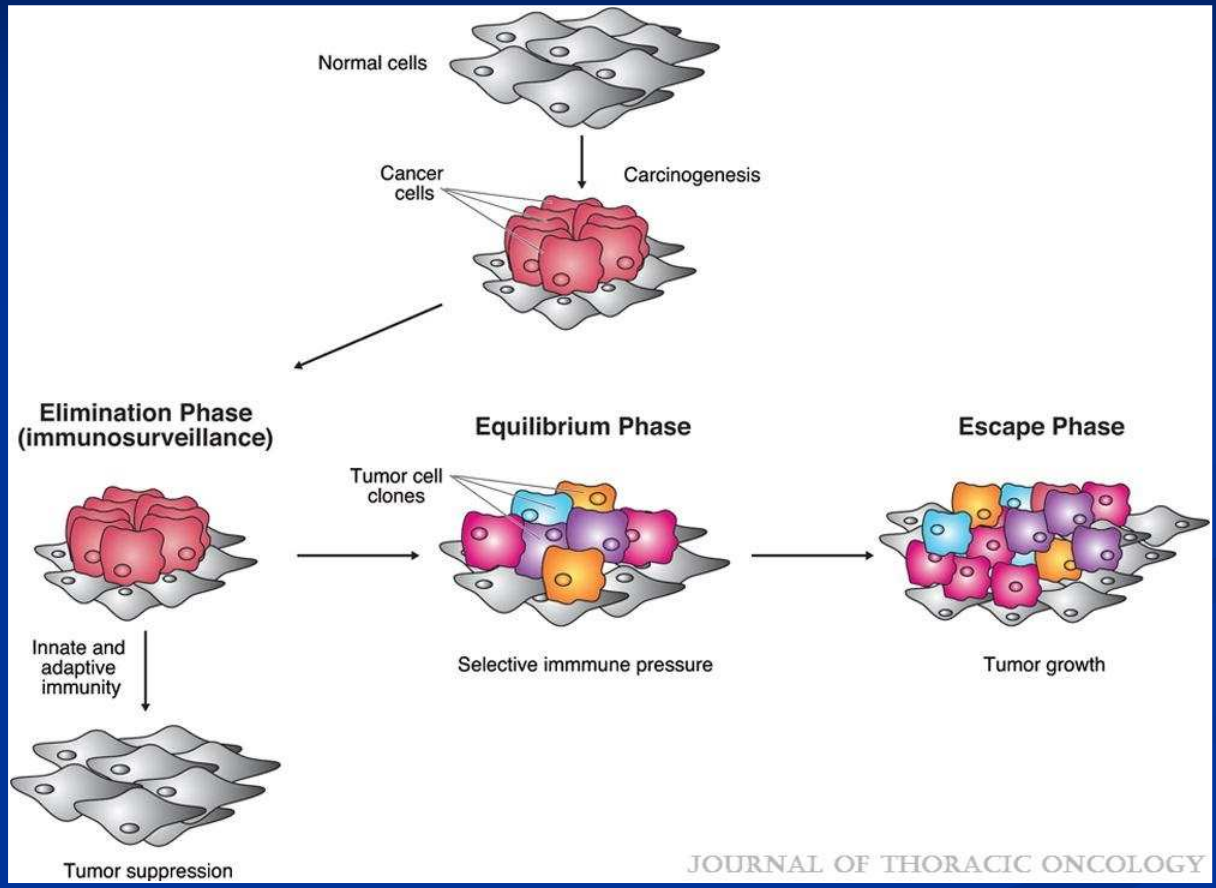
Disclosures

Pfizer, Novartis, Boehringer Ingelheim, Genentech – Consulting Fees

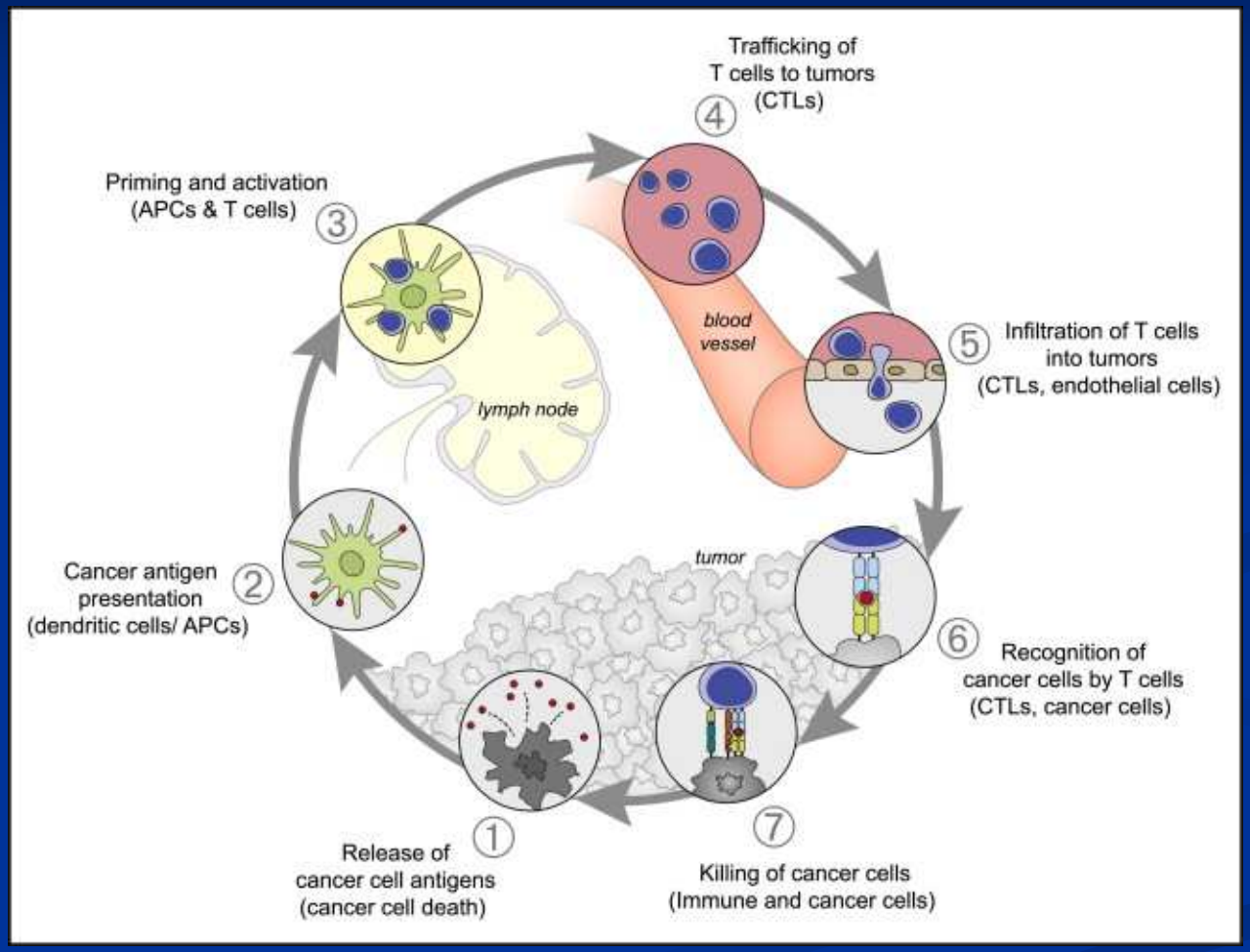
Genentech – Fees for Non-CME/CE Services Received Directly from a Commercial Interest *or their Agent*

Cancer Immunoediting



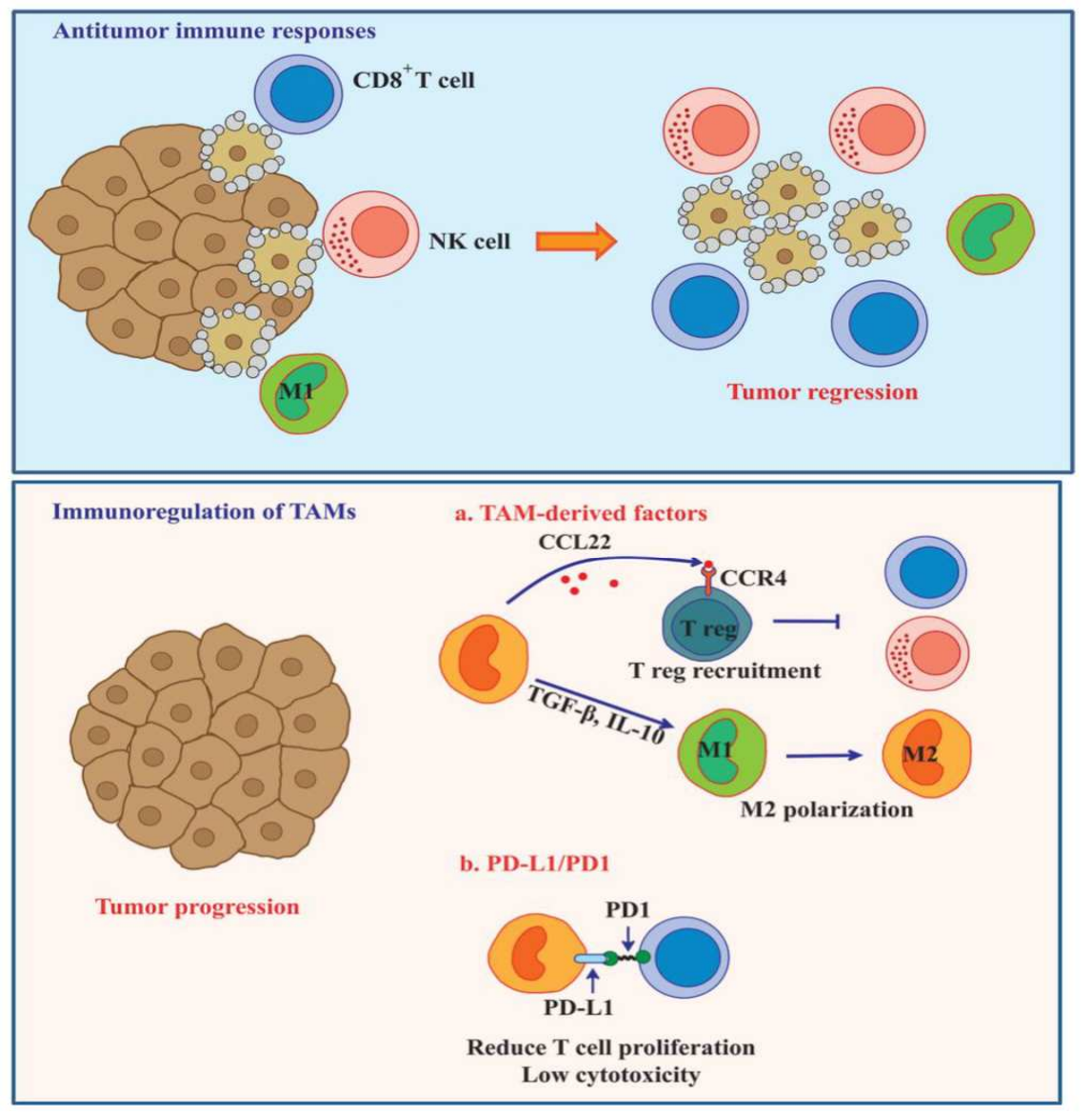
Carbone, et al Journal of Thoracic Oncology, 2015

Immune Cycle

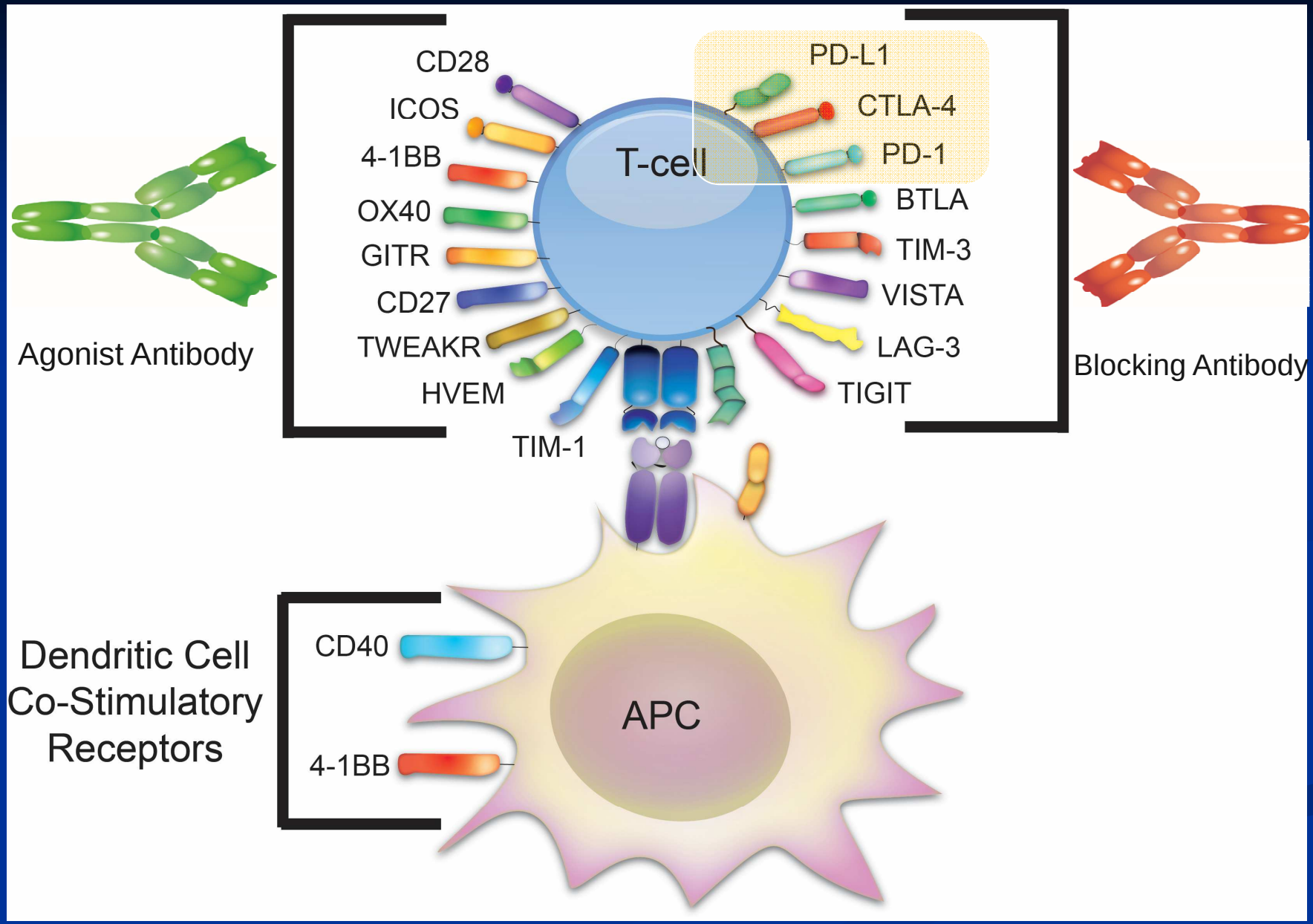


Chen, Immunity 2013

Immune Suppression Tumor Microenvironment

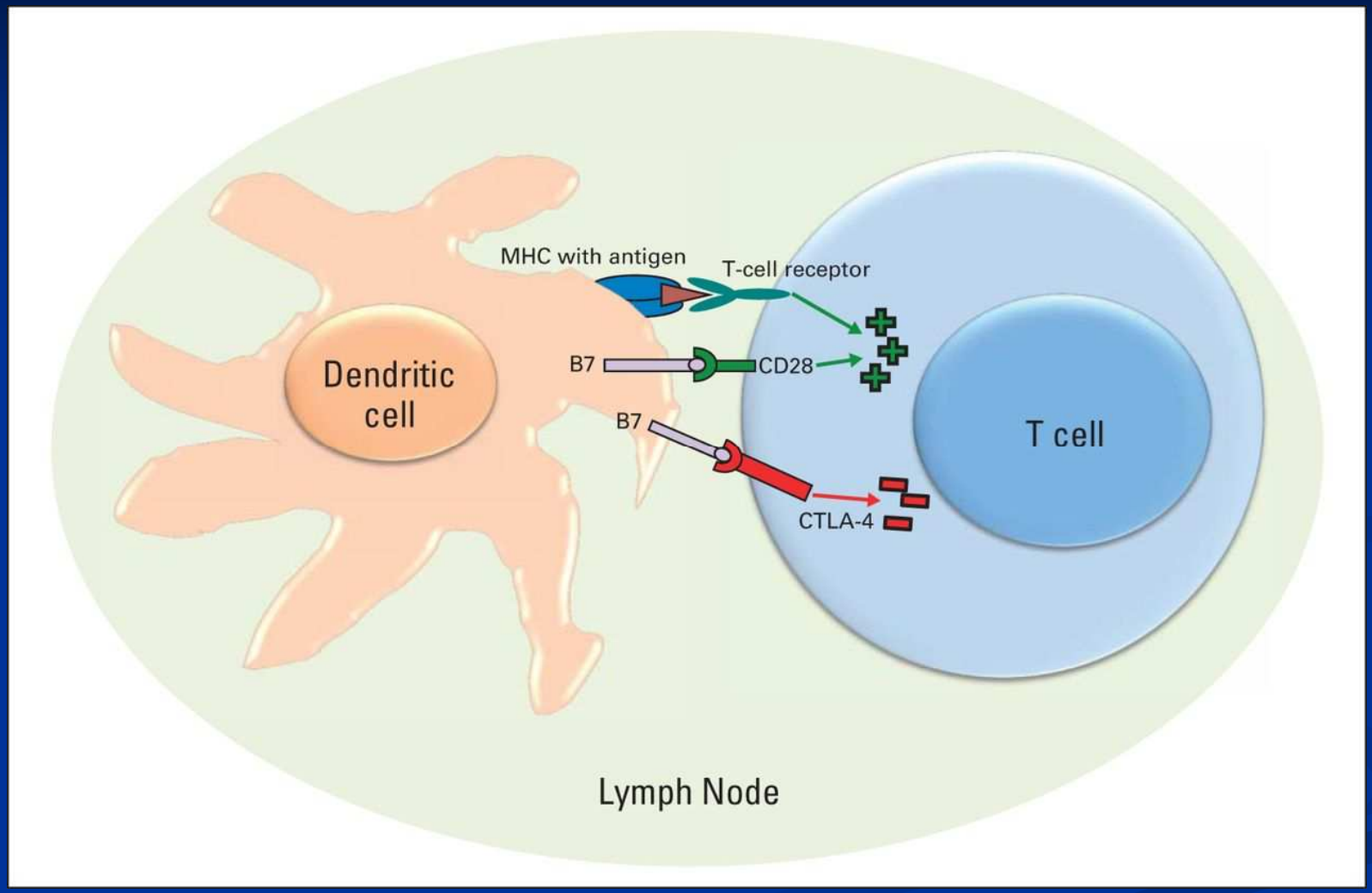


Chanmee T, Cancers 2014



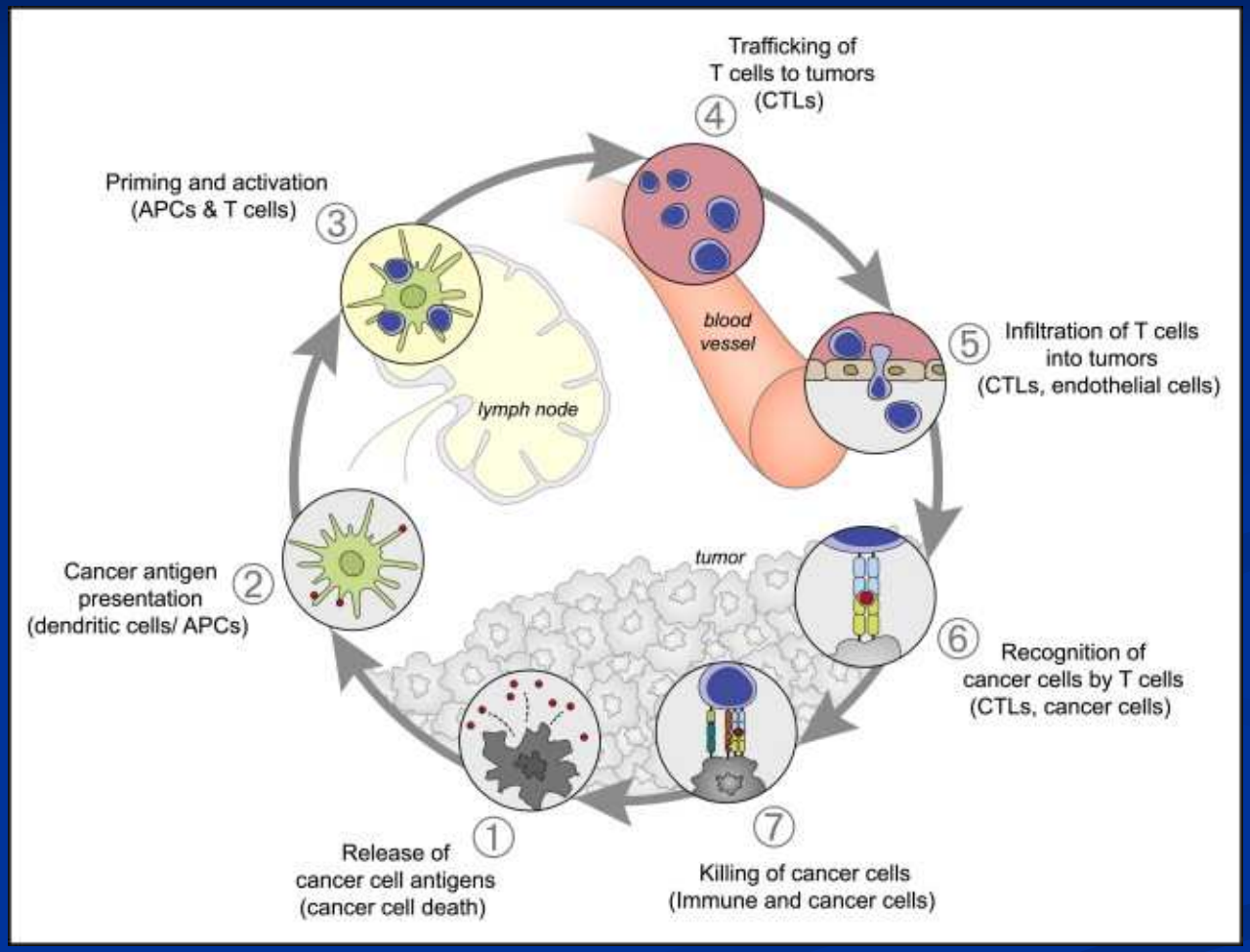
Ai M., **Curran M.** Immune checkpoint combinations from mouse to man.
Cancer Immunology Immunotherapy, 2015.

The cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) immunologic checkpoint.



Michael A. Postow et al. JCO 2015;33:1974-1982

Immune Cycle



Chen, Immunity 2013

CTLA-4 Immune Checkpoint Pathway Inhibition Using Ipilimumab: Pooled OS Data From Melanoma Patients

- In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients

Patients at risk

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

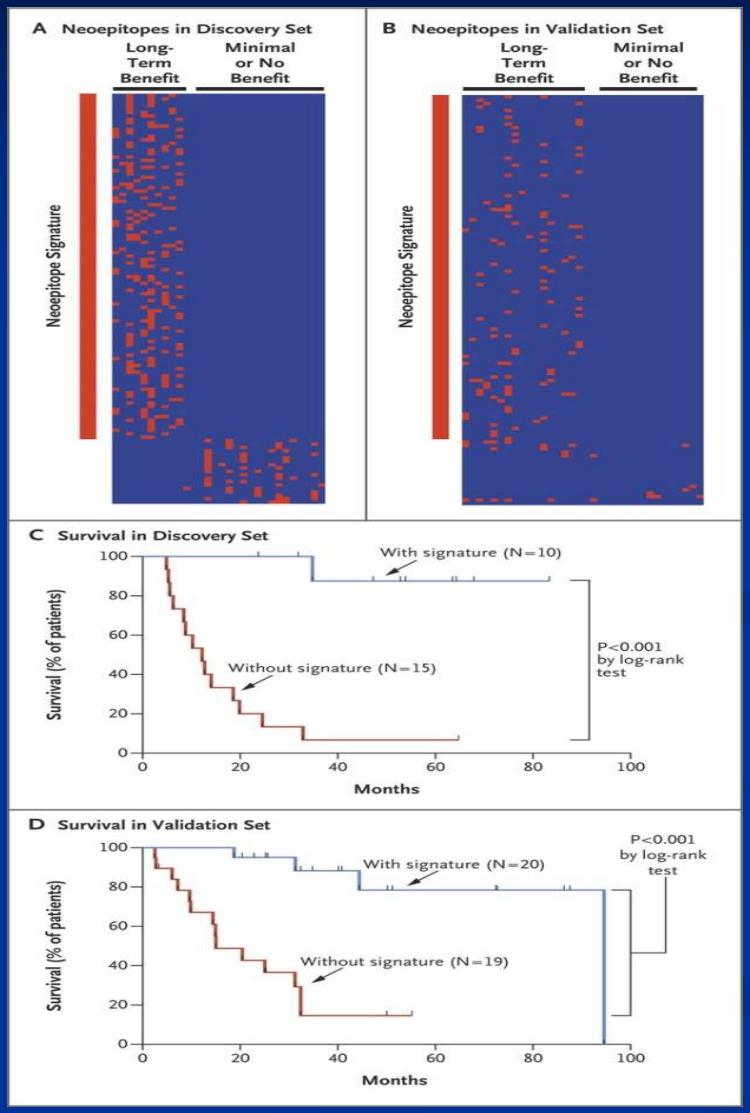
[a]Ipilimumab was given at different doses and lines of therapy, and using different schedules across the 12 studies

Schadendorf D, et al. ECC Congress 2013 Abs 124LBA

Biomarkers of Efficacy

- An early increase in lymphocyte and eosinophil count was associated with improved survival in melanoma patients.
  - Delyon J, Ann Oncol 2013.
- Increase number of T regulatory cells in the tumor was associated with response to Ipilimumab.
  - Ji RR, Cancer Immunol Immunother, 2012.

Association of a Neoepitope Signature with a Clinical Benefit from CTLA-4 Blockade.



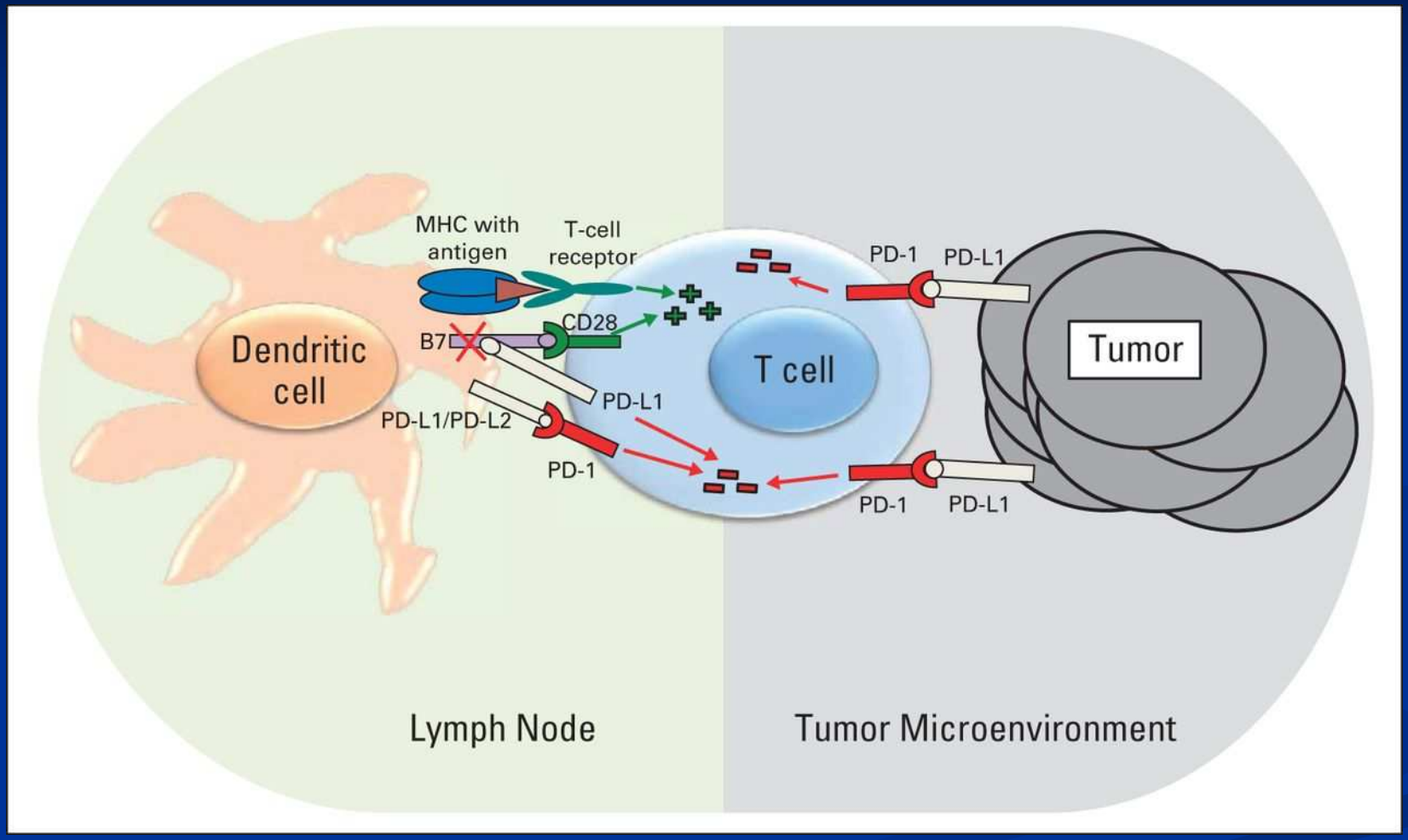
Snyder A et al. N Engl J Med 2014;371:2189-2199.

The NEW ENGLAND JOURNAL of MEDICINE

Ipilimumab in Other Tumors

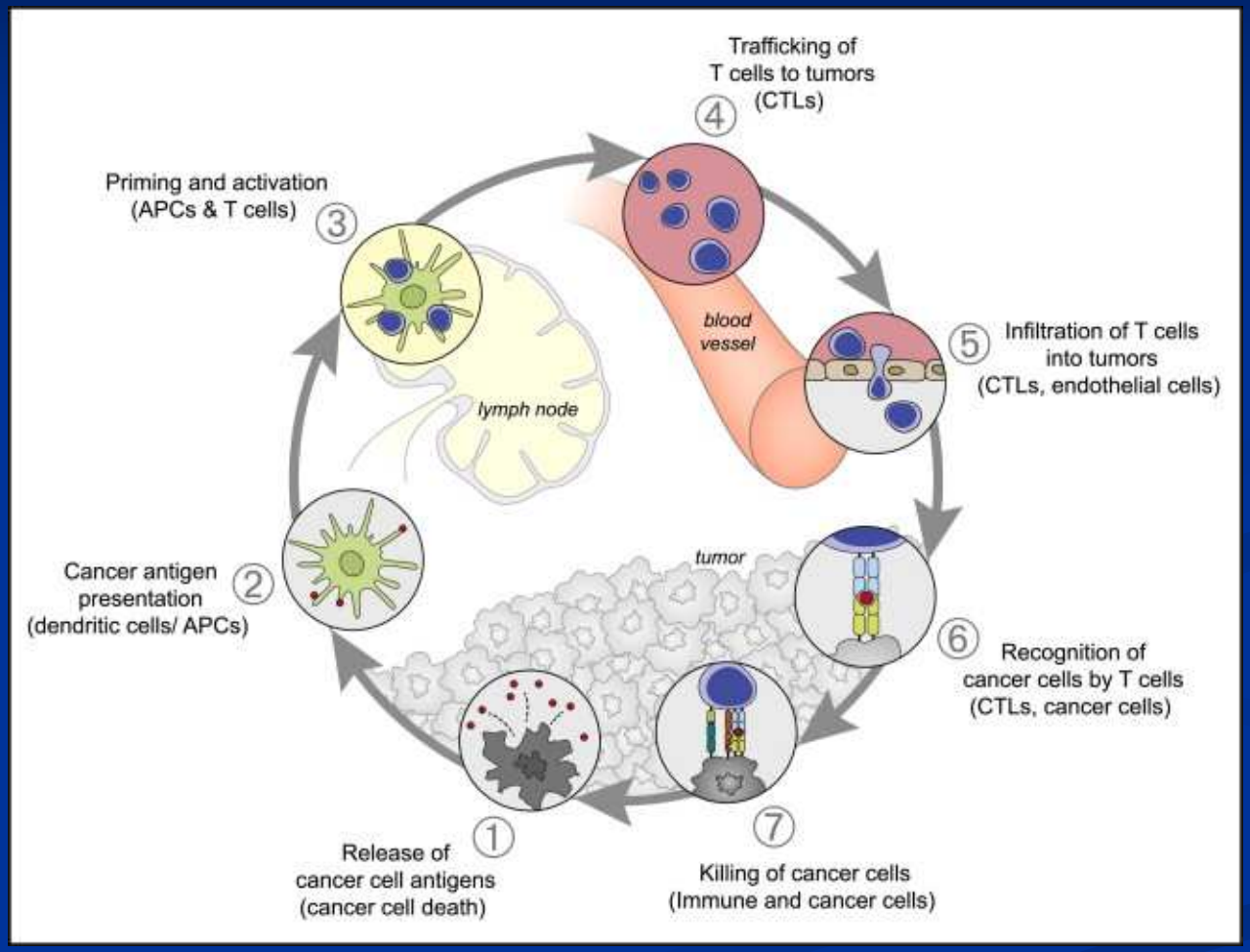
- Randomized Phase II trial of carboplatin and paclitaxel with ipilimumab in NSCLC
  - Lynch, J Clin Oncol 2012
- Ipilimumab with GVAX vaccine in Pancreatic Cancer
  - Le, J Immunother 2013.
- Castration resistant Prostate Cancer- Study was negative. Subgroup analysis- Benefit in patients without visceral metastases.
  - Kwon, Lancet Oncol, 2014
- Tremelimumab showed promising results in Mesothelioma
  - Calabron, Lancet Oncol, 2013

The programmed cell death protein 1 (PD-1) immunologic checkpoint.



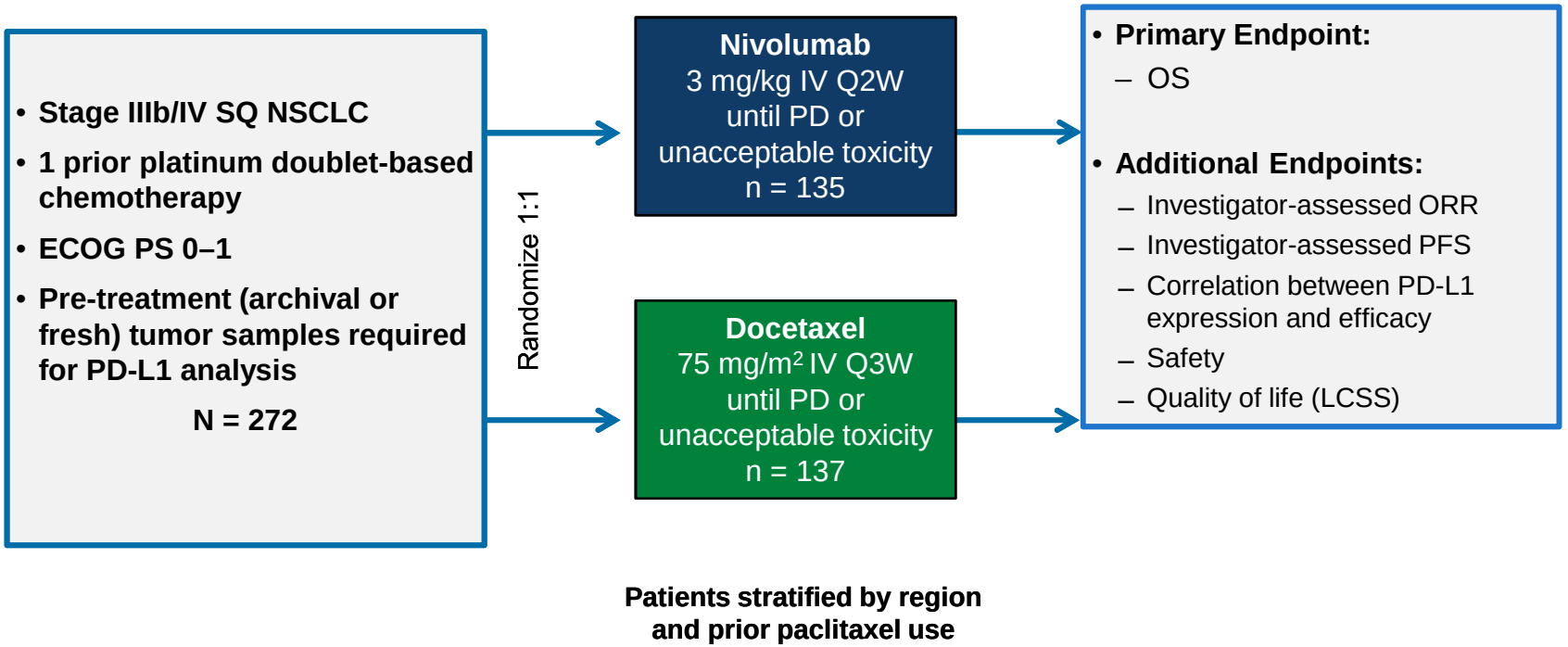
Michael A. Postow et al. JCO 2015;33:1974-1982

Immune Cycle



Chen, Immunity 2013

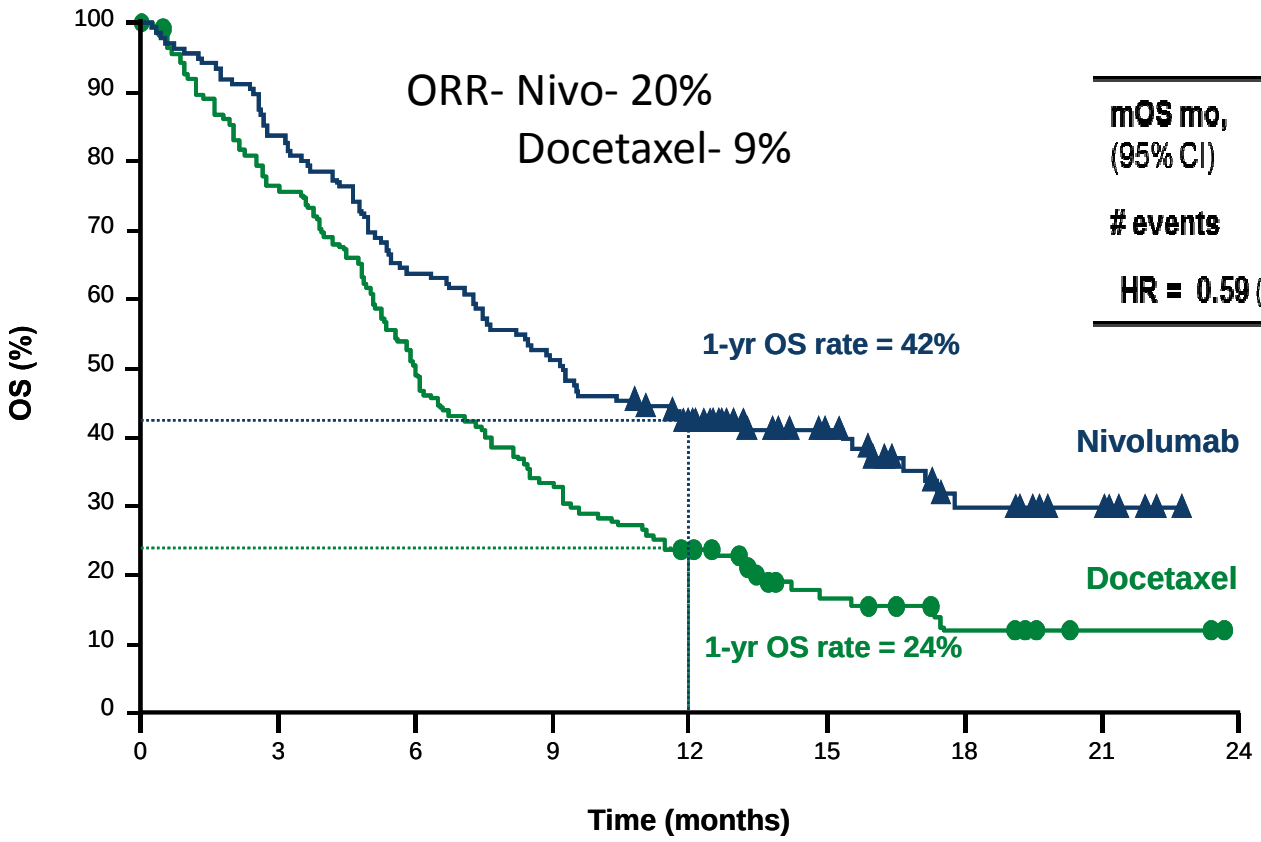
CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was *P* <0.03

LCSS = Lung cancer symptom scale

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

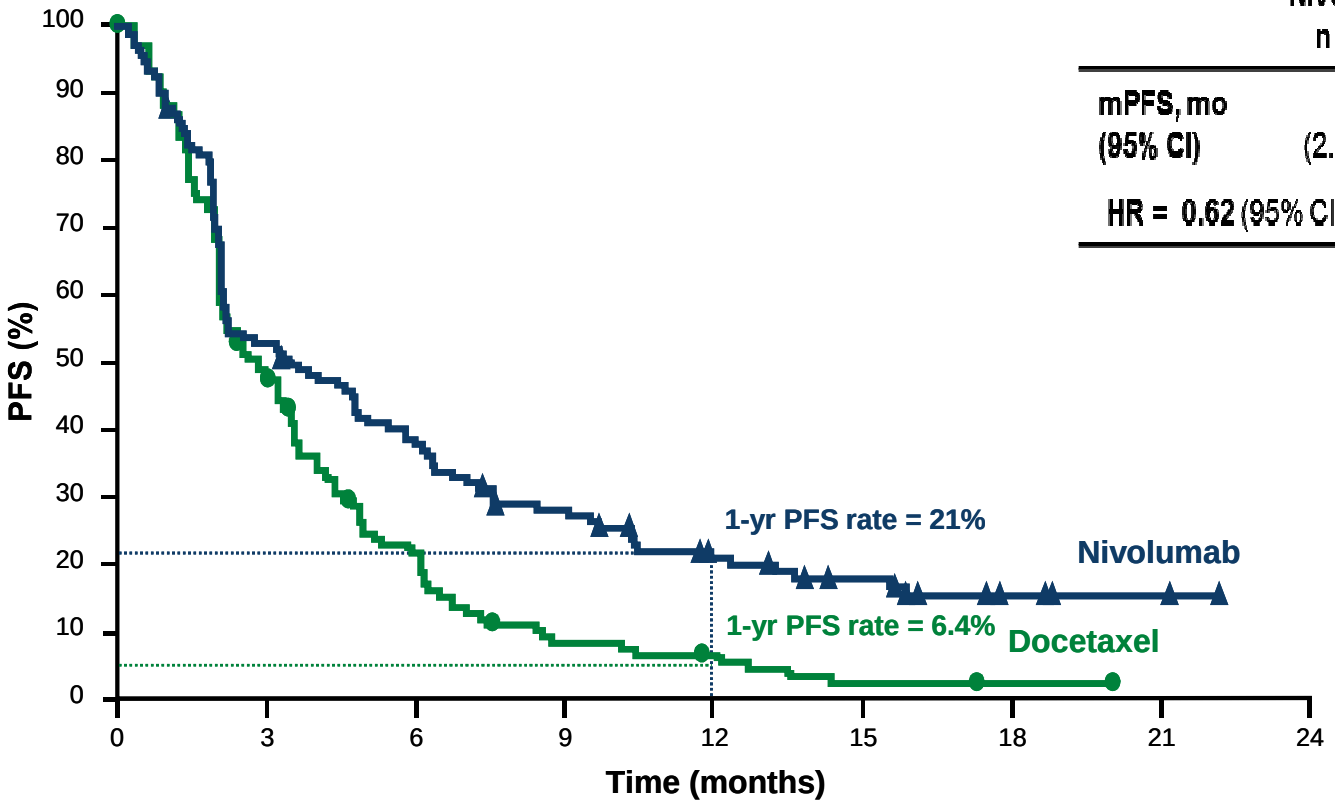
HR = 0.59 (95% CI: 0.44, 0.79), ***P*** **= 0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Symbols represent censored observations

Progression-free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

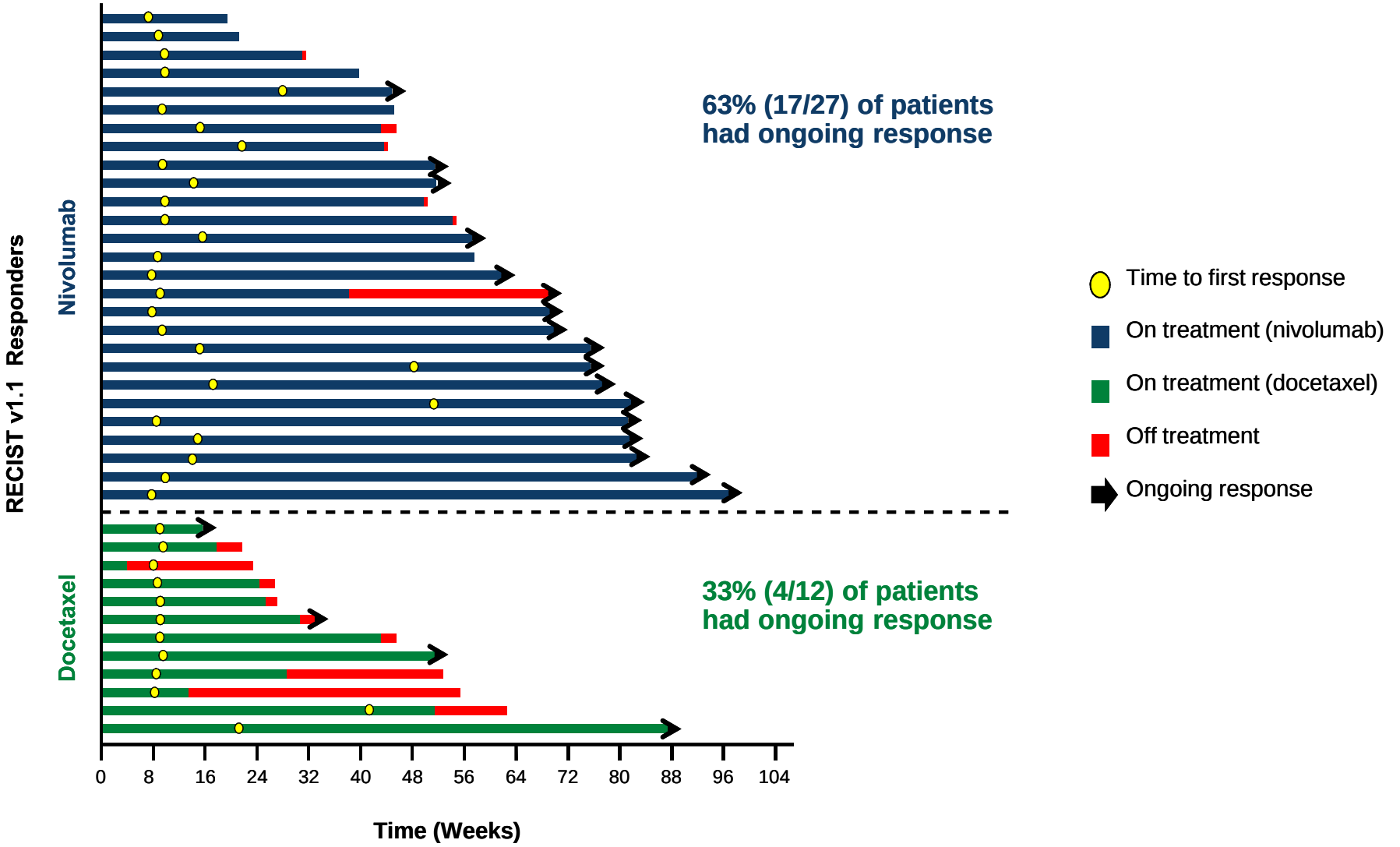
HR = 0.62 (95% CI: 0.47, 0.81); *P* = 0.0004

Number of Patients at Risk

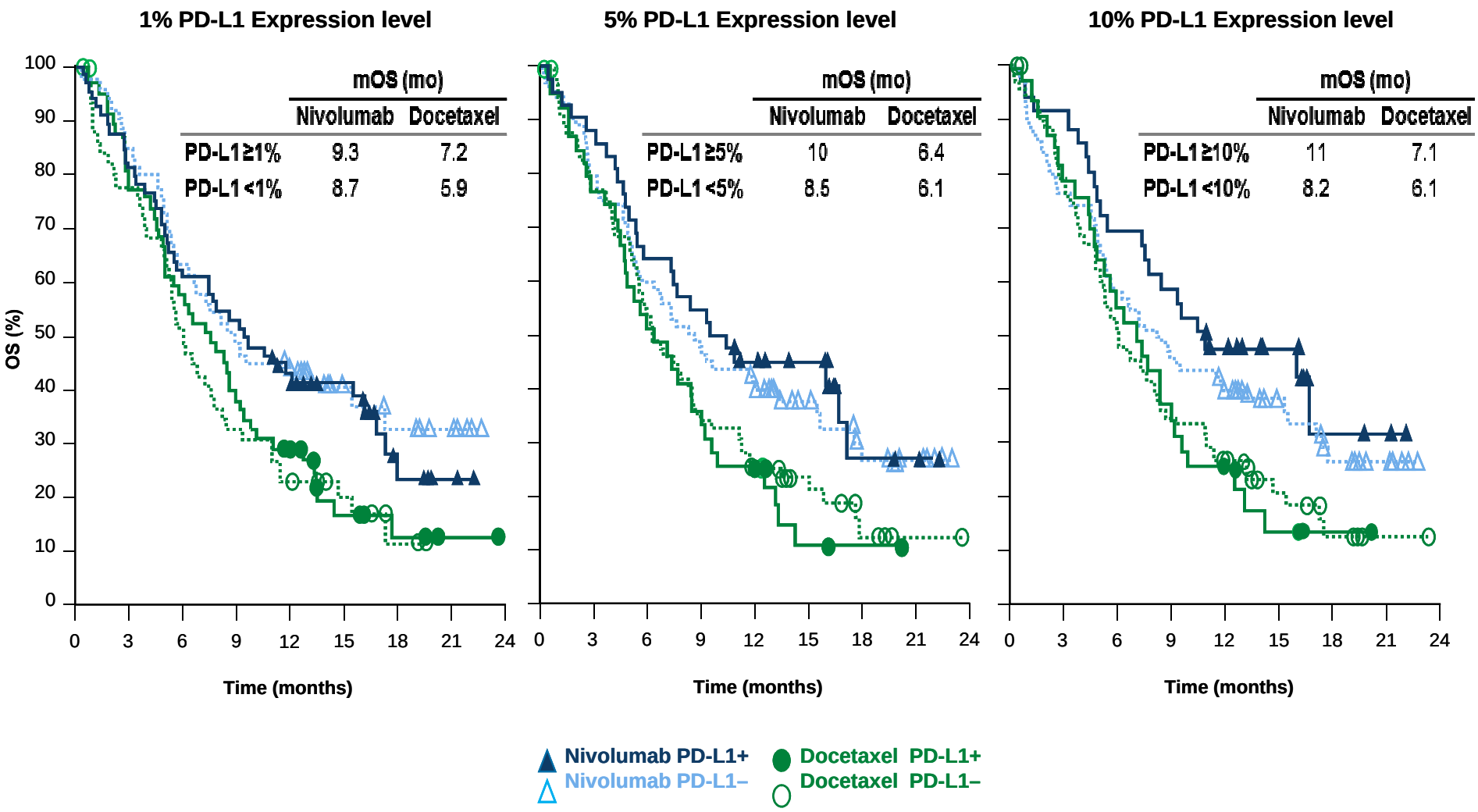
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

Response Characteristics of Confirmed Responders



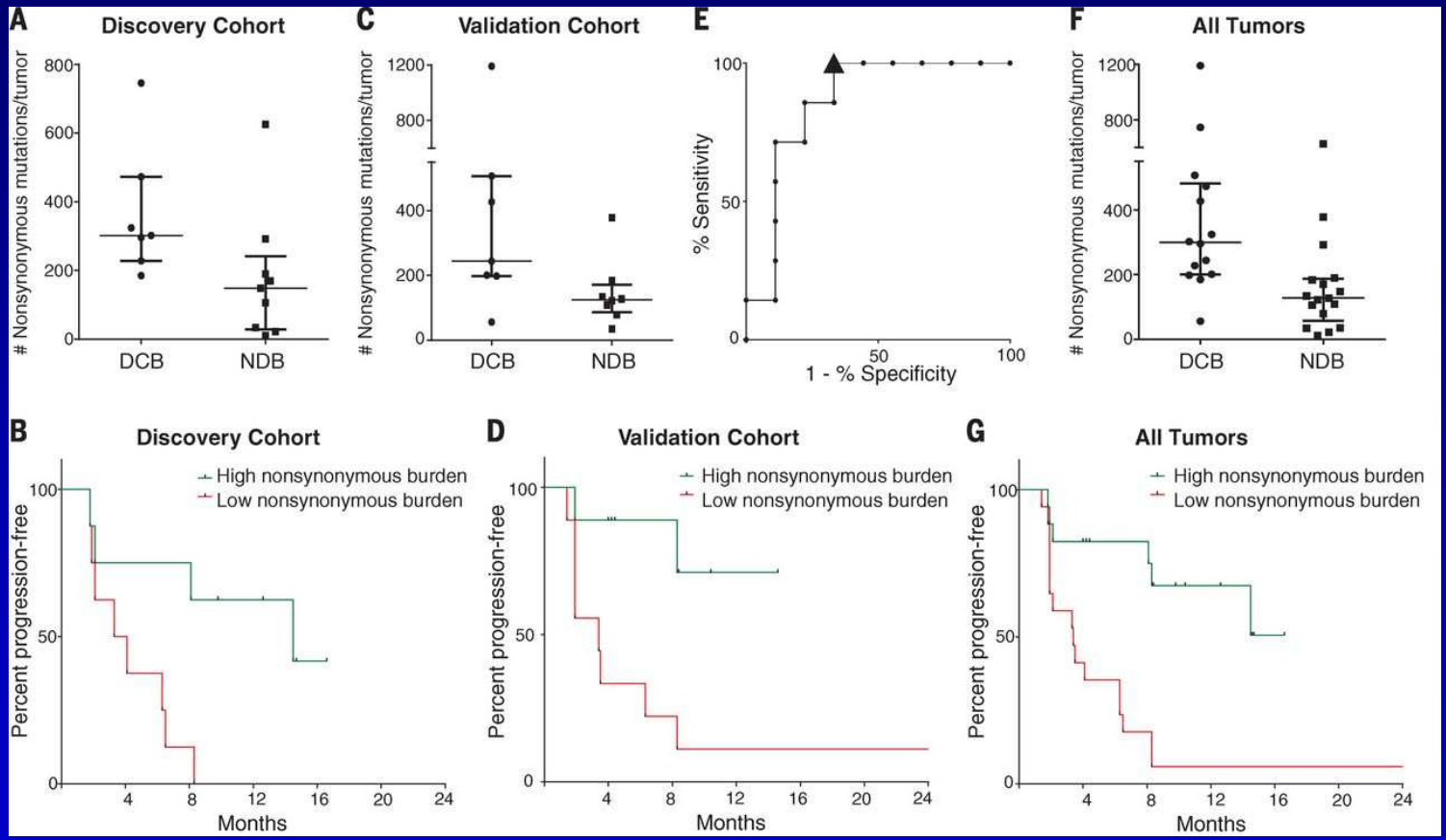
OS by PD-L1 Expression



PD-L1 expression as a biomarker

- Generally patients with tumors that have PD-L1 expression have higher likelihood of benefit
- Inconsistent results.
  - Expression of PD-L1 is heterogenous- patchy vs. diffuse, tumor cell vs. stroma, archival vs. fresh
- 10% of the patients with PD-L1 negative tumors derived benefit. Duration of benefit in these patients is similar to the duration of benefit in PD-L1 positive patients.
- Maybe used to select patients in select situations- first line, never smokers.

Higher Mutation Burden Correlates With Benefit from Anti-PD-1



Rizvi, Science 2015

Patients with MMR deficient are more likely to benefit from anti-PD-1
Le, ASCO 2015, abstract LBA 100

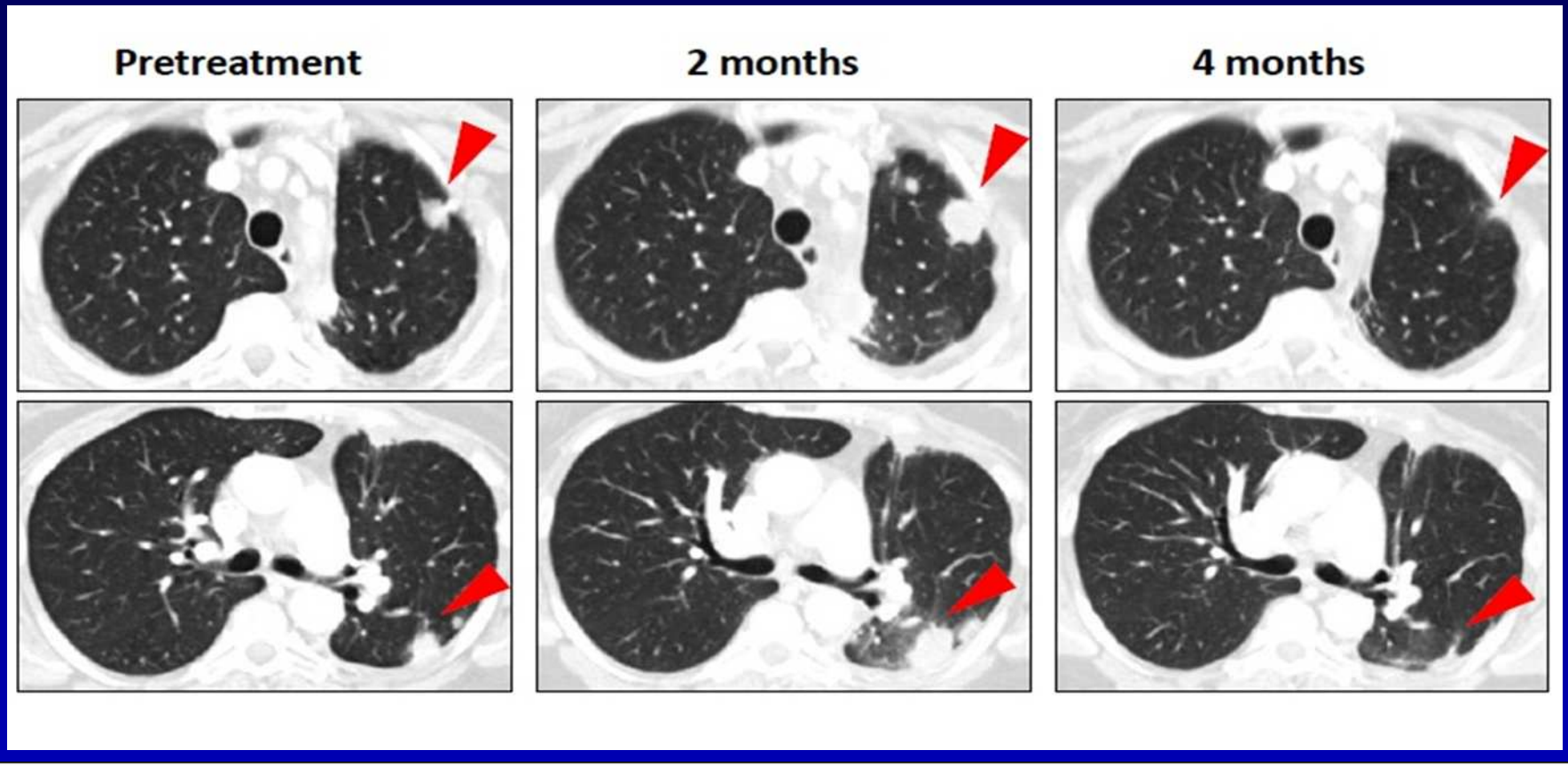


Table 2. Differences Between RECIST (version 1.1) and irRC

Factor	RECIST	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Complete response	Disappearance of all target and nontarget lesions; lymph nodes must regress to < 10-mm short axis; no new lesions; requires confirmation	Same as for RECIST
Partial response	≥ 30% decrease in tumor burden compared with baseline; requires confirmation	≥ 50% decrease in tumor burden compared with baseline; requires confirmation
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir; progression of nontarget lesions and/or appearance of new lesions (at any single time point)	≥ 25% increase in tumor burden compared with most recent prior evaluation; new lesions added to tumor burden; requires confirmation
Stable disease	Any response pattern that does not meet criteria for complete response, partial response, or progressive disease	Same as for RECIST

Abbreviation: irRC, immune-related response criteria.

Table 1 Incidence of Immune-Related Adverse Events Associated With Ipilimumab and Pembrolizumab

	Ipilimumab (n = 1,498)[8] (%)		Pembrolizumab (n = 411)[39] (%)	
Toxicity	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
GI (eg, enterocolitis)	33	9.1	1	< 1
Pneumonitis	< 1	< 1	2.9	< 1
Hepatitis	1.6	1.1	< 1	< 1
Dermatologic	45	2.6	11–30	0
Hypophysitis	2.7	2.1	< 1	< 1
Thyroiditis	1.8	< 1	9.5	< 1
Nephritis	< 1	< 1	< 1	< 1

Postow, et al JCO 2015

Treatment-related AEs (≥10% of patients)

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Total patients with an event, %	**58**	**7**	**86**	**55**
Fatigue	16	1	33	8
Decreased appetite	11	1	19	1
Asthenia	10	0	14	4
Nausea	9	0	23	2
Diarrhea	8	0	20	2
Vomiting	3	0	11	1
Myalgia	2	0	10	0
Anemia	2	0	22	3
Peripheral neuropathy	1	0	12	2
Neutropenia	1	0	33	30
Febrile neutropenia	0	0	11	10
Alopecia	0	0	22	1

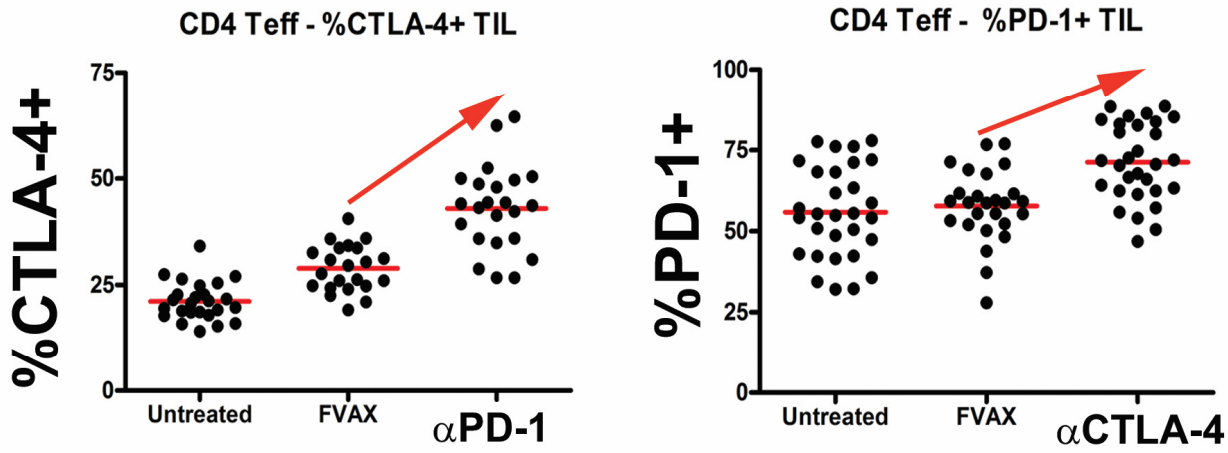
Table 1. PD-1 and PD-L1 Antibodies in Clinical Development

Target and Agent	Class
PD-1	
Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
Pidilizumab (CT-011)	IgG1 humanized Ab
PD-L1	
BMS935559 (MDX-1105)	IgG4 fully human Ab
MPDL3280A	IgG1 engineered fully human Ab
MEDI4736	IgG1 engineered fully human Ab
MSB0010718C	IgG1 fully human Ab
PD-1–positive T cells	
AMP-224	Fc of human IgG–PD-L2 fusion

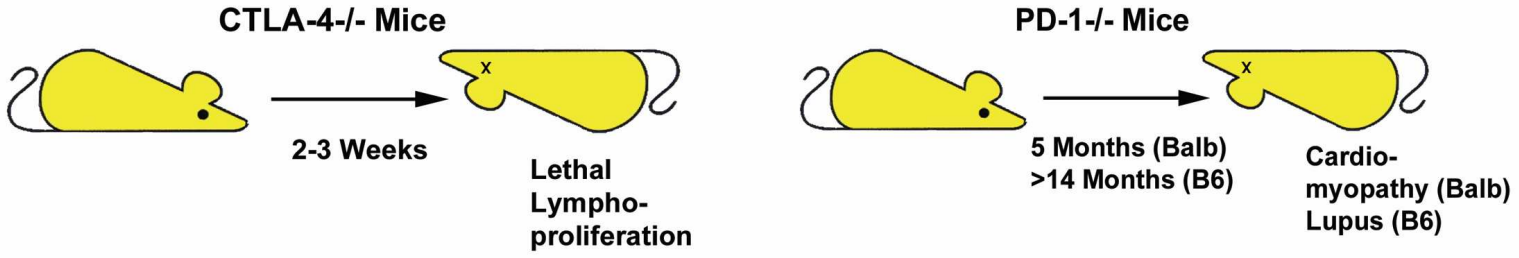
Abbreviations: Ab, antibody; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand.

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.

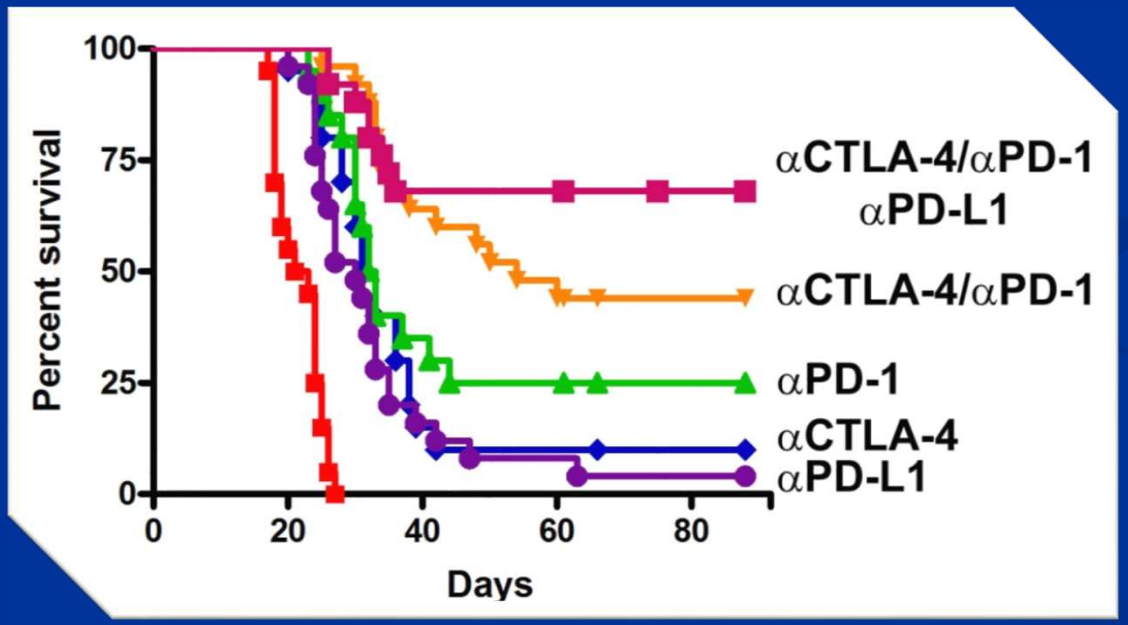
PNAS

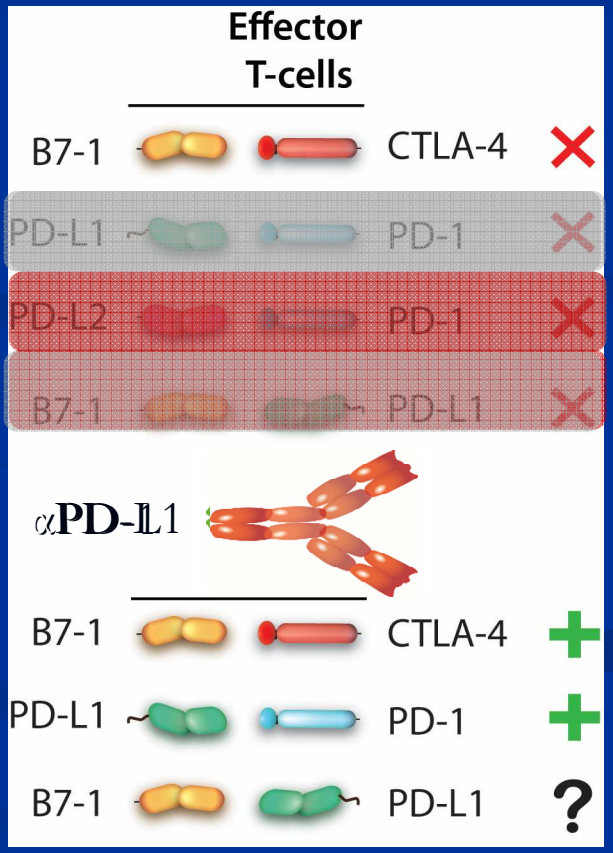
PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

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

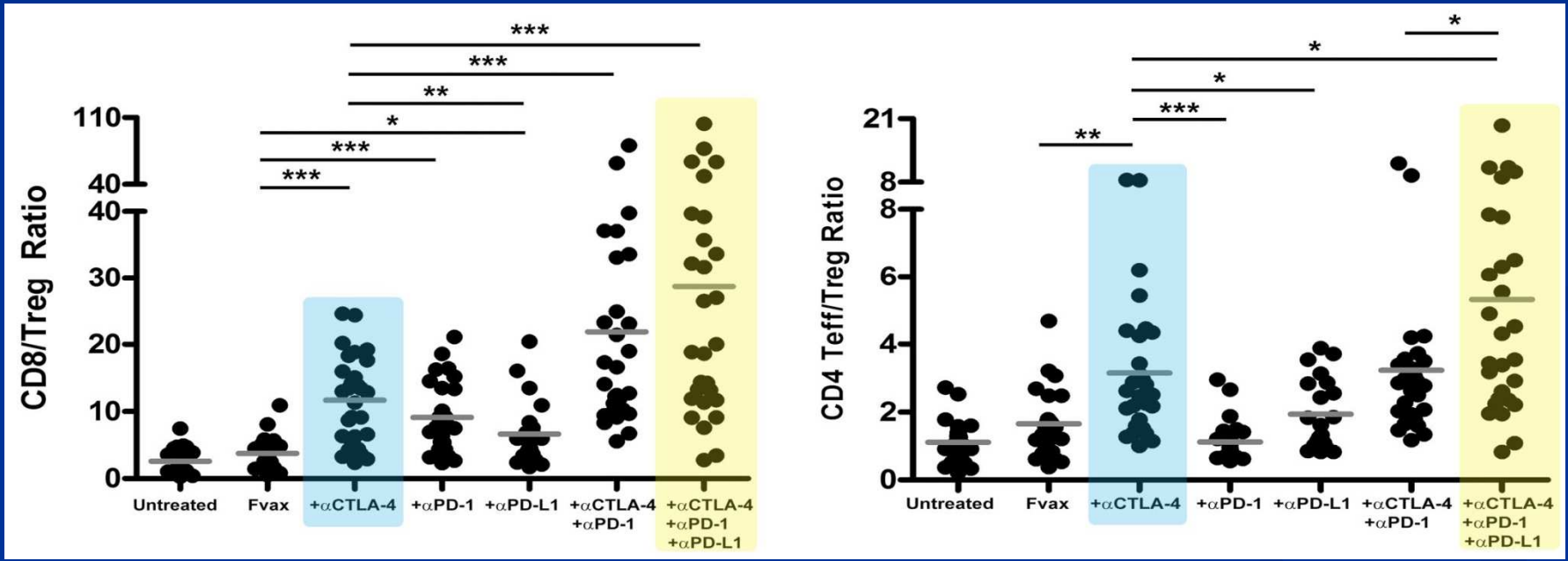
Contributed by James P. Allison, January 19, 2010 (sent for review December 17, 2009)





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

Conversion of the tumor micro-environment from suppressive to inflammatory



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

Objective response rates in malignant melanoma with checkpoint blockade

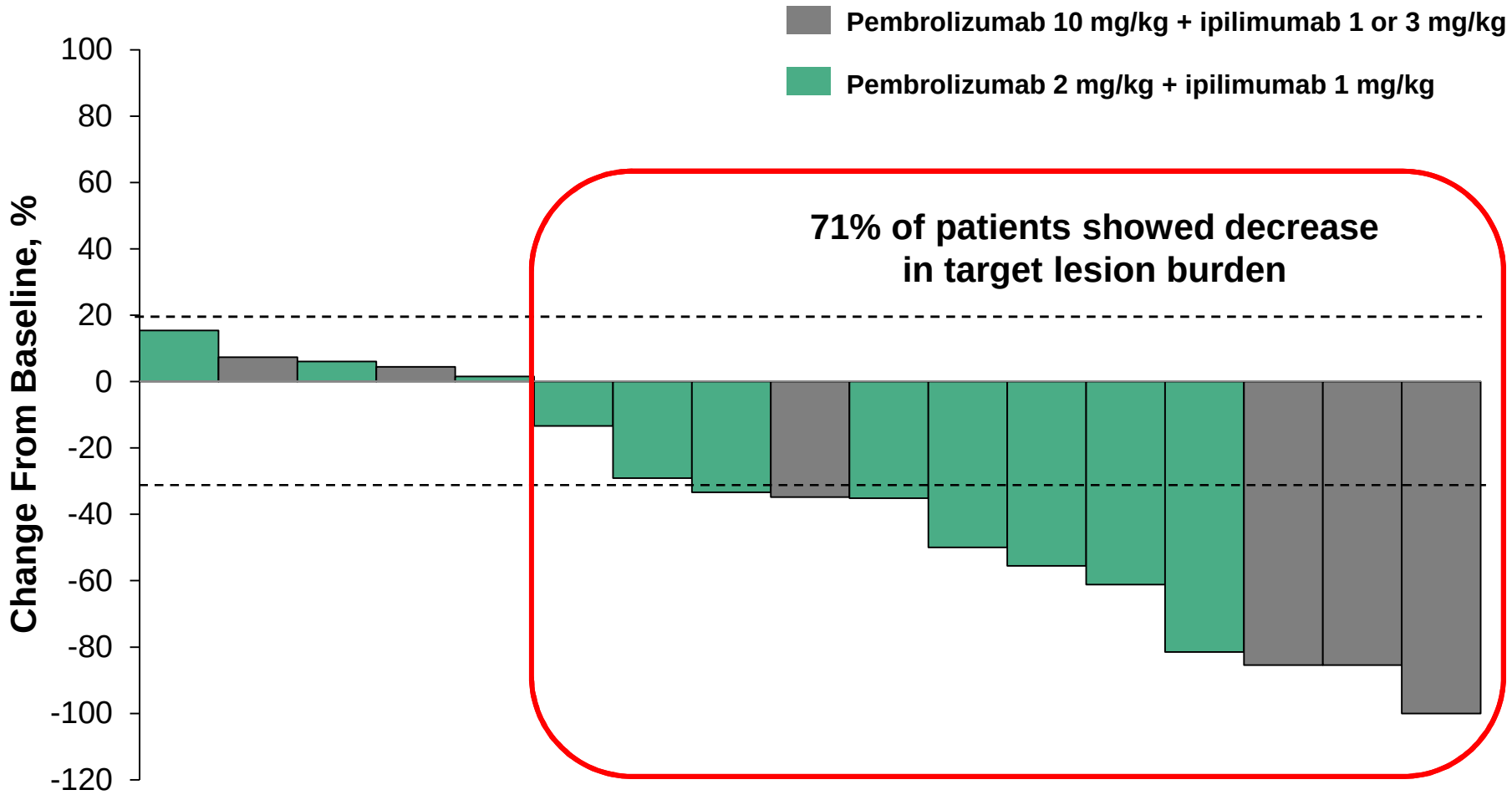
	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs IPI	<0.001	<0.001	--
Best overall response — %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive 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.

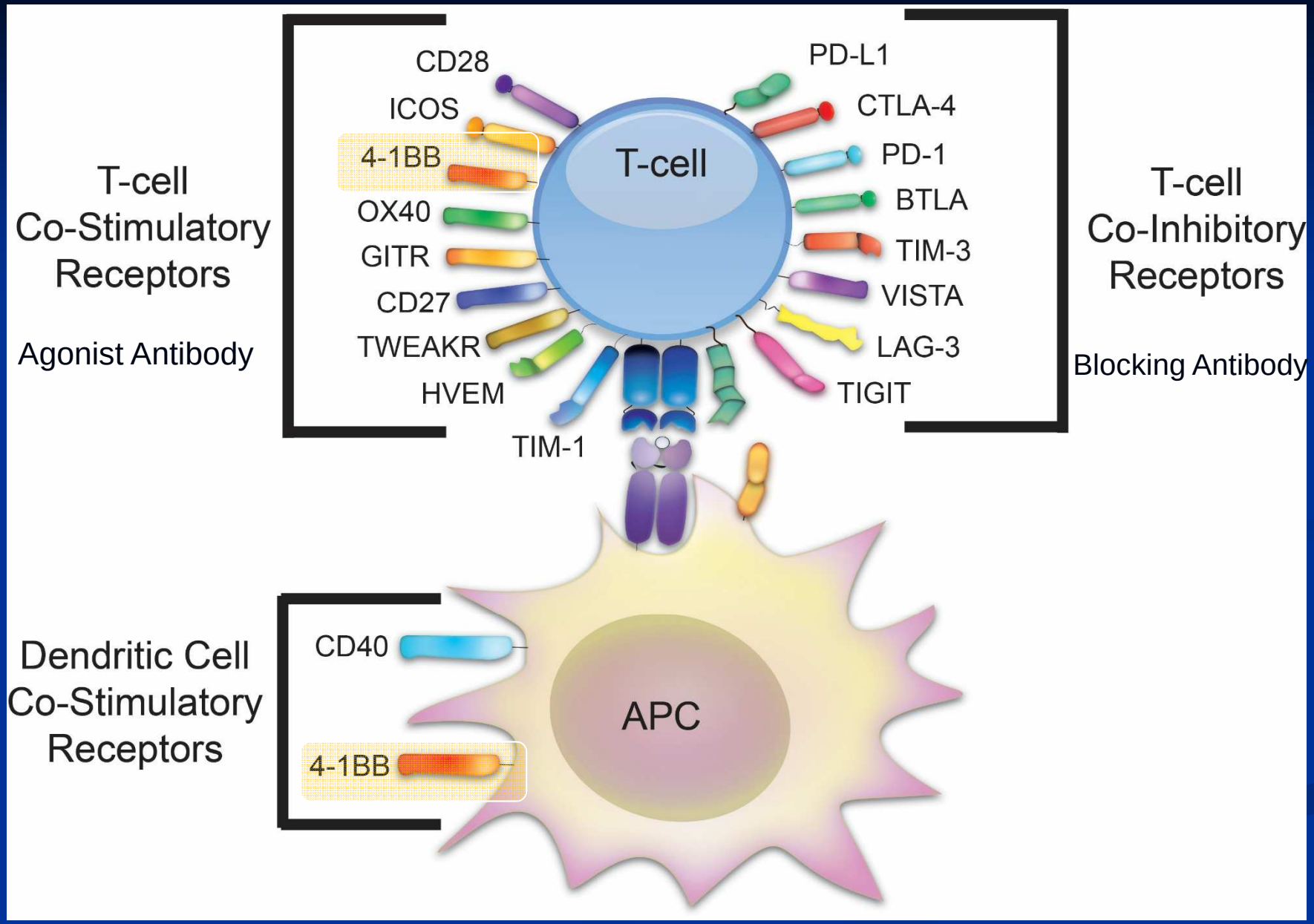
Wolchok et al. ASCO 2015

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

Change From Baseline in Tumor Size
(RECIST v1.1, Investigator Review)



Change from baseline was evaluated in patients with ≥1 postbaseline tumor assessment.
Analysis cutoff date: March 31, 2015.



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

4-1BB : Favorable expression profile for immunotherapy

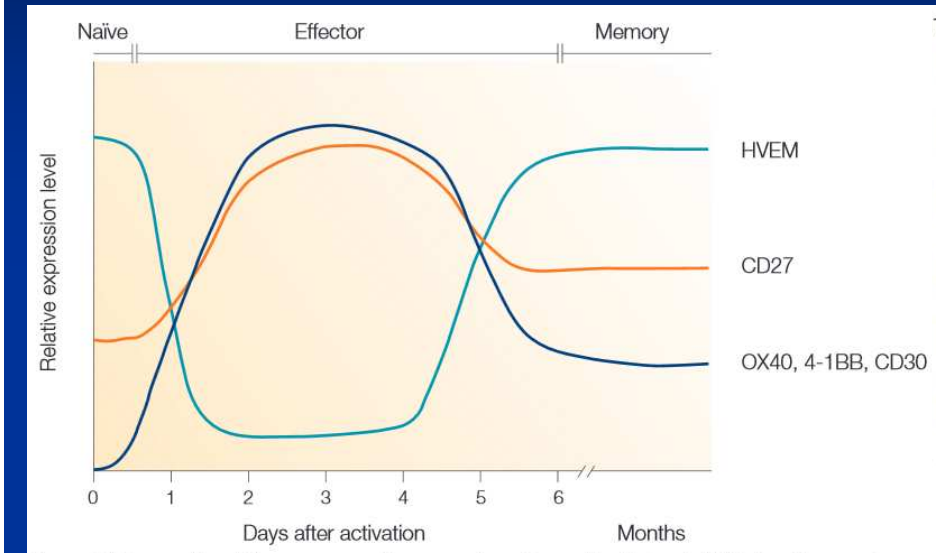


Figure 2 | **Generalized time course of expression of co-stimulatory TNFR-family members.**

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**

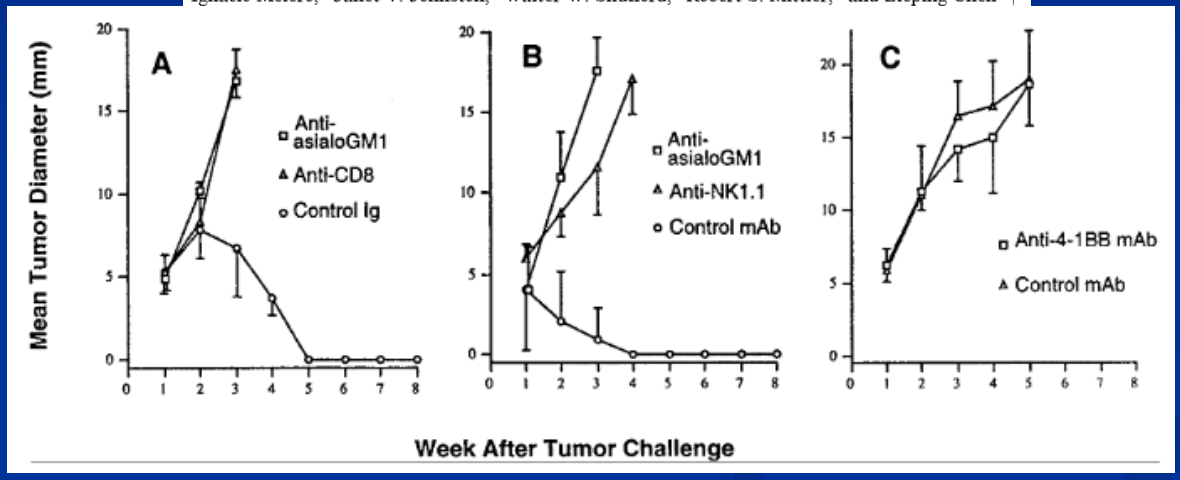
Lieping Chen & Dallas B. Flies *Nature Reviews Immunology* **13**, 227-242 (April 2013)

4-1BB activates NK Cells

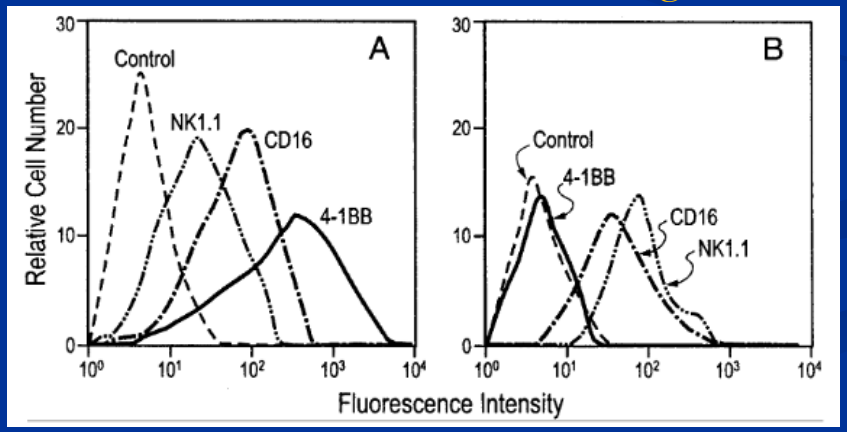
CELLULAR IMMUNOLOGY **190,** 167–172 (1998)
ARTICLE NO. CI981396

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

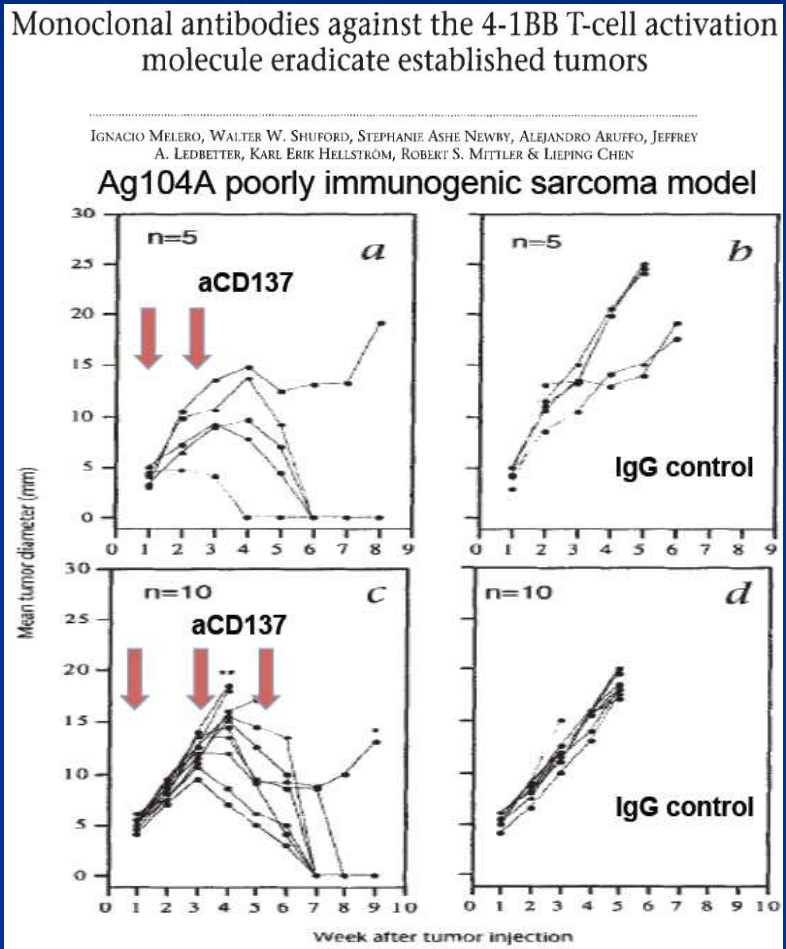


Table 1. Suppression of various tumors by targeting the 4-1BB–4-1BBL pathway

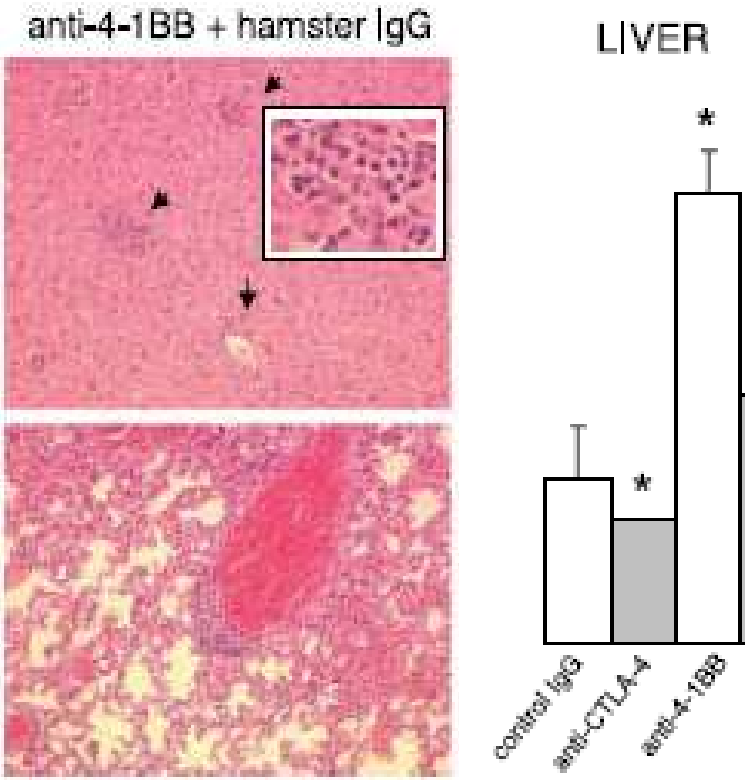
Agent	Cancer type suppressed
Anti-4-1BB mAb	Ag104A sarcoma
	MCA205, GL261 glioma
	C3 tumors, TC1 carcinoma
	J558 tumors
	A549 tumors
Variants of anti-4-1BB	K1735 melanoma
	M108 tumors
	K562 erythroleukemia
	FRα tumors
Anti-4-1BB combination therapy	B16 melanoma
	Renal cell carcinoma
	K1735 melanoma
	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 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.

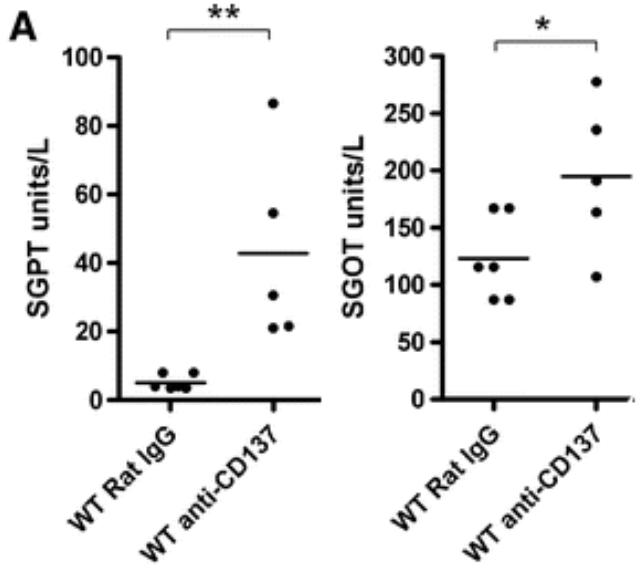
Kocak E[1], Lute K, Chang X, May KF Jr, Exten KR, Zhang H, Abdessalam SF, Lehman AM, Jarjoura D, Zheng P, Liu Y.



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

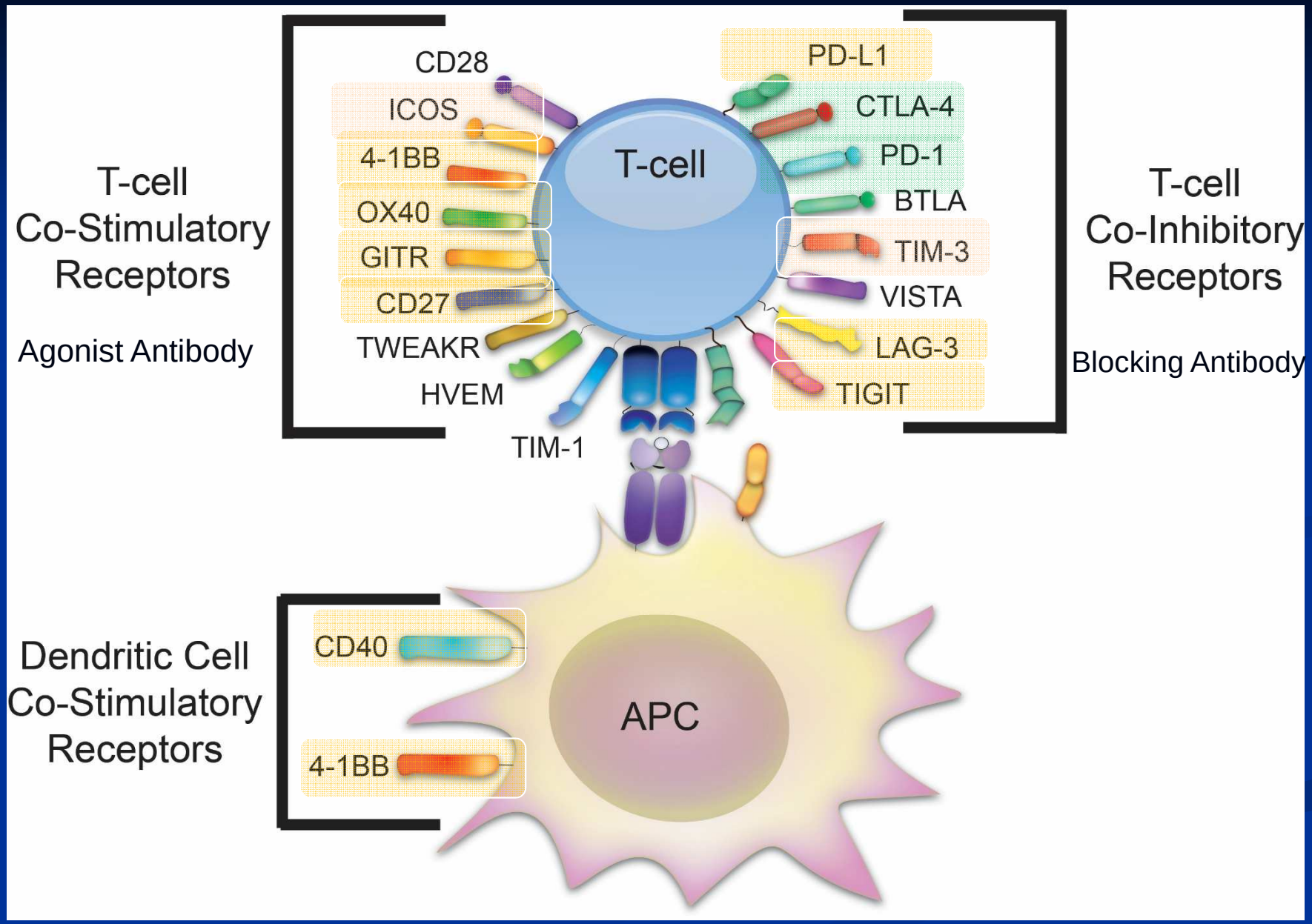
Treatment with anti-CD137 mAbs causes intense accumulations of liver T cells without selective antitumor immunotherapeutic effects in this organ.

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



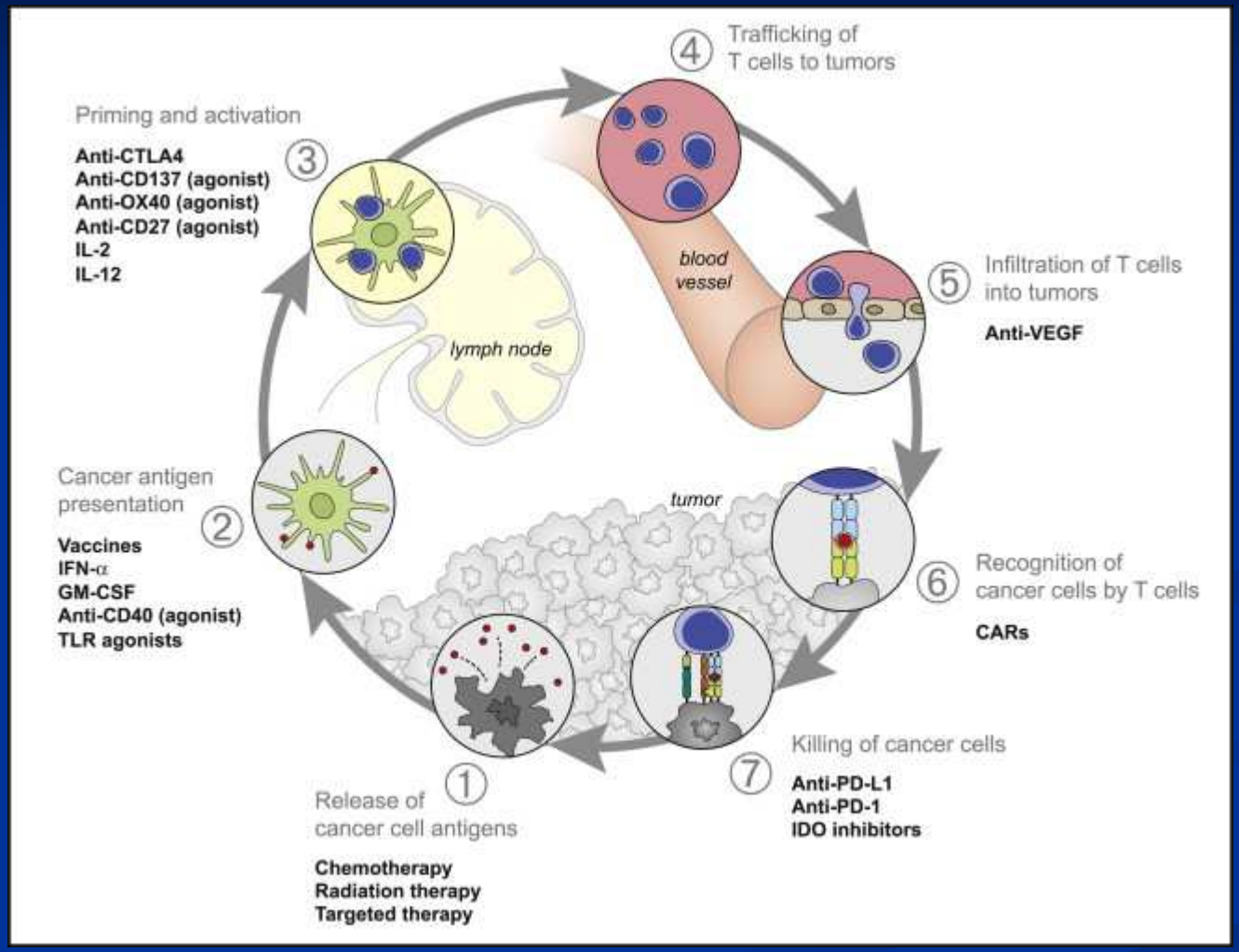
Ai M., **Curran M.A.** Immune checkpoint combinations from mouse to man.
Cancer Immunology Immunotherapy, 2015.

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.


4 Trafficking of T cells to tumors
Priming and activation
Anti-CTLA4
Anti-CD137 (agonist)
Anti-OX40 (agonist)
Anti-CD27 (agonist)
IL-2
IL-12
3
blood vessel
5 Infiltration of T cells into tumors
Anti-VEGF
lymph node
Cancer antigen presentation
Vaccines
IFN-α
GM-CSF
Anti-CD40 (agonist)
TLR agonists
2
tumor
6 Recognition of cancer cells by T cells
CARs
7 Killing of cancer cells
Anti-PD-L1
Anti-PD-1
IDO inhibitors
1 Release of cancer cell antigens
Chemotherapy
Radiation therapy
Targeted therapy

Conclusions

- Immune check point inhibitors have shown benefit in several tumors as single agents.
- Benefit occurs only in a proportion of patients but is sustained for a long time.
- Unique adverse events
- Biomarkers still not defined
  - PD-L1 expression, Genomic analysis?
- Combinations being explored
  - Both with other check point inhibitors and cytotoxic agents