# Μια γνωριμία με τους αναστολείς των checkpoints

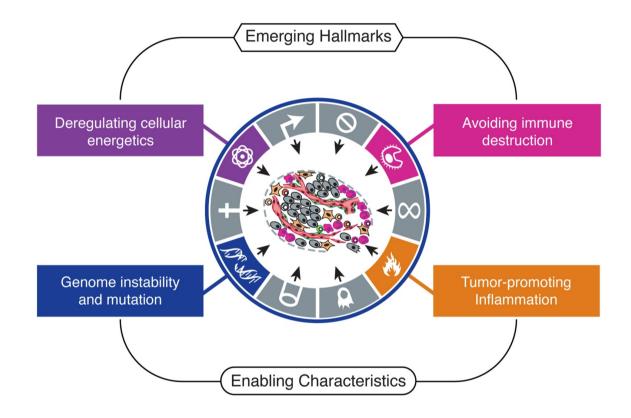


## **Davide Mauri**

Assoc Professor of Oncology, Medical School, University of Ioannina, Greece.

# **Disclosures**

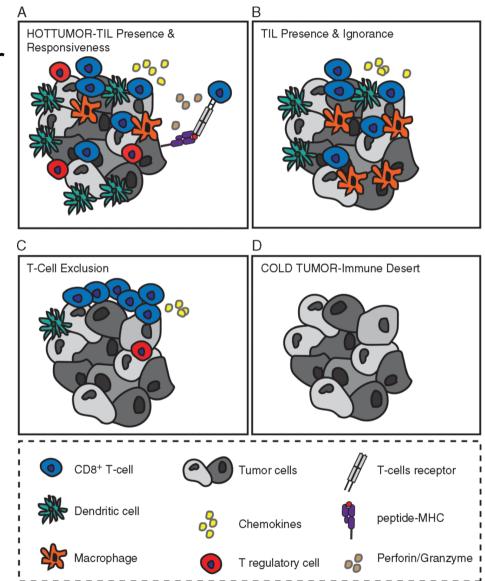
• none



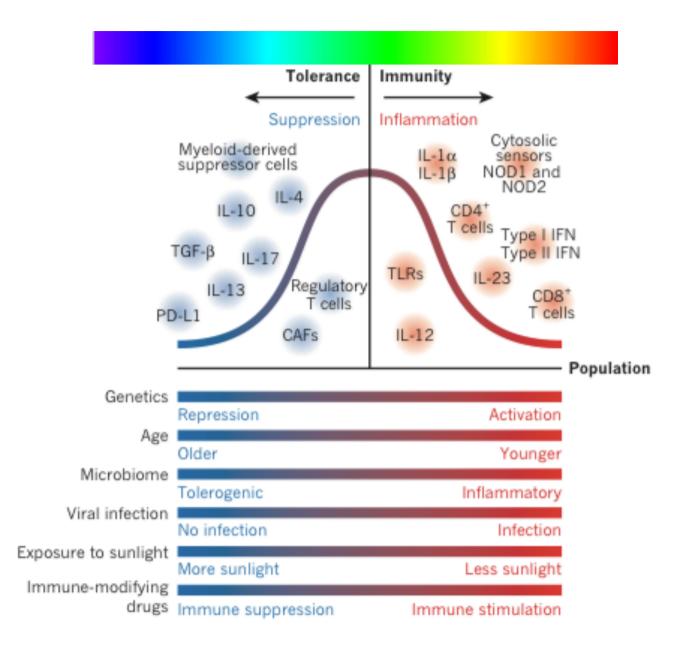
#### Cell 2011 144, 646674DOI:(10.1016/j.cell.2011.02.013)

# Classification of tumors based on their immune cell infiltrate

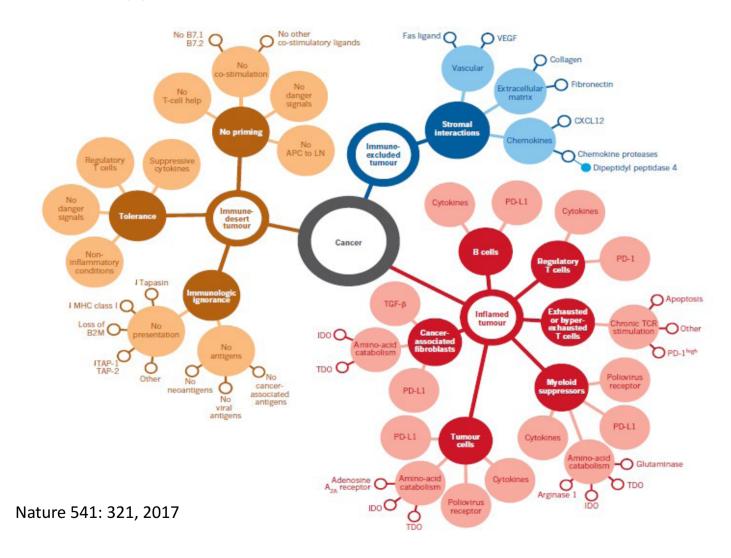
- A. T-cell-inflamed tumors (Hot tumors) infiltrated by T cells respond to checkpoint blockade therapies.
- B TIL Presence and Ignorance (Hot tumors) not respond to checkpoint blockade.
- C. T-Cell Exclusion
  immune cells are excluded at the periphery (C), as well as tumors that are, and having a so-called
- D Cold tumor immune desert landscape completely devoid of immune infiltrate



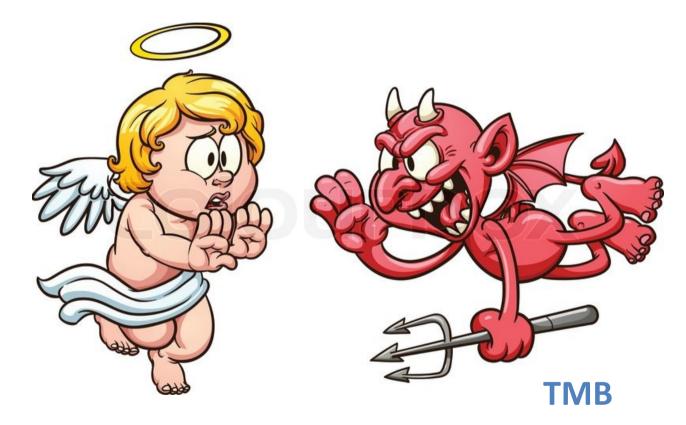
Ann Oncol 28 (Supp.12): xii18–xii32, 2017



## **Types of Cancers & Immune Function**



# Many players involved



CD8+ cytotoxic T-lymphocytes

# E Contraction of the second se

CD8+ cytotoxic T-lymphocytes (CTLs) are directly capable of killing tumour cells.

Study or subgroup	Log[Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% Cl	Hazard ratio IV, random, 95% CI
Overall survival					
Adams 2009	-0.53	0.26	4.6%	0.59 (0.35, 0.98)	
Barnett 2010	-0.46	0.1B	6.9%	0.63 [0.44, 0.90]	
Clarke 2009	-0.17	0.06	10.9%	0.84 [0.72, 0.99]	-
Galon 2006	-0.82	0.16	7.6%	0.44 [0.32, 0.60]	
Gao 2007	-0.17	0.15	8.0%	0.84 [0.63, 1.13]	
Hinsoka 2006	0.21	0.3	3.8%	1.23 (0.69, 2.22)	
Jensen 2009	0.2	0.24	5.1%	1.22 [0.76, 1.95]	
Jordanova 2008	-0.07	0.43	2.2%	0.93 [0.40, 2.17]	
Kasajima 2010	-0.74	0.25	4.9%	0.48 [0.29, 0.78]	
Lee 2008	-0.54	0.25	4.9%	0.58 (0.36, 0.95)	-
Nosho 2010	-0.3	0.15	8.0%	0.74 [0.55, 0.99]	
Ruffini 2009	-0.25	0.11	9.7%	0.78 [0.63, 0.97]	
Sato 2005	-0.67	0.27	4.4%	0.51 [0.30, 0.87]	
Shen 2010	-0.22	0.33	3.3%	0.80 [0.42, 1.53]	
Zingg 2010	-0.84	0.24	5.1%	0.43 (0.27, 0.69)	
Zobec 2007	-0.15	0.09	10.5%	0.66 (0.72, 1.03)	
Subtotal (95% CI)			100.0%	0.71 [0.62, 0.82]	٠
	$04; \chi^2 = 36.85, df = 15$ Z = 4.84 (P < 0.00001)		001); 7 <sup>e</sup> = 8	19%	
Disease-specific surv	Mali				
Al Shibii 2008	-0.44	0.19	13.8%	0.64 [0.44, 0.93]	
Chiba 2004	-0.89	0.18	14.1%	0.41 [0.29, 0.58]	
De Jong 2009	-1.17	0.28	10.9%	0.31 [0.18, 0.54]	
Jensen 2009	0.36	0.27	11.2%	1.43 [0.84, 2.43]	
.effers 2008	-0.39	0.2	13.5%	0.68 (0.46, 1.00)	
Nosho 2010	-0.49	0.19	13.8%	0.61 [0.42, 0.89]	
Prall 2004	-0.62	0.29	10.6%	0.54 (0.30, 0.95)	
Sorbye 2011	-0.05	0.24	12.1%	0.95 [0.59, 1.62]	
Subtotal (95% CI)			100.0%	0.63 [0.47, 0.84]	•
Heterogeneity: r <sup>0</sup> = 0. Test for overall effect	$12; \chi^2 = 24.63, df = 7$ ( Z = 3.14 (P = 0.002)	P = 0.0	000); i <sup>d</sup> = 7	2%	
Progression / disease	/ relapse-free survival				
De Jong 2009	-0.6	0.26	18.2%	0.55 [0.33, 0.91]	
Galon 2008	-0.77	0.17	20.2%	0.46 [0.33, 0.65]	
Gao 2007	-0.24	0.16	20.6%	0.79 [0.57, 1.08]	
lensen 2009	0.25	0.24	17.1%	1.28 (0.80, 2.06)	
Nedergiaard 2007	-0.89	0.34	13.0%	0.41 [0.21, 0.80]	
Profit 2004	-0.84	0.34	13.0%	0.43 [0.22, 0.84]	
Subtotal (95% CI)			100.0%	0.62 [0.44, 0.87]	•
A CONTRACTOR OF A CONTRACT	$13: \chi^2 = 17.10, df = 5$ ( Z = 2.73 (P = 0.006)	P = 0.0			5.55
					ALC: 14

Br J Cancer 2011 Jun 28; 105(1): 93–103.



## TMB (tumor mutational burden)

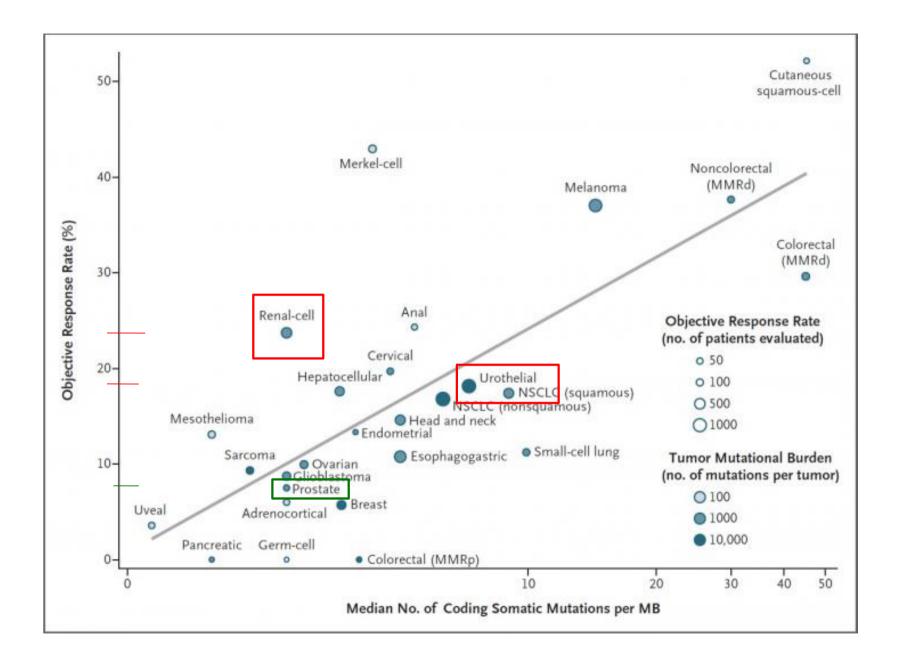


high frequency of DNA mutations  $\rightarrow$  abnormal antigens  $\rightarrow$  better immunotherapy target

• **MMR ("spell-checker"):** mismatch repair enables cells to correct mistakes in their DNA code that sometimes occur during DNA replication.

**Mismatch repair deficient (dMMR)** cells acquire multiple DNA mutation. (eg. alterations in short, repetitive DNA sequences called microsatellite (MSI-H).

• large number of genetic mutations stimulate immune response.



TMB (tumor mutational burden)



## Large number of genetic mutations $\rightarrow$ immune response.

but

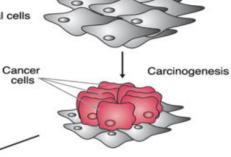
Native immune response may be too weak to reject the tumor.

#### 3 distinct phases:

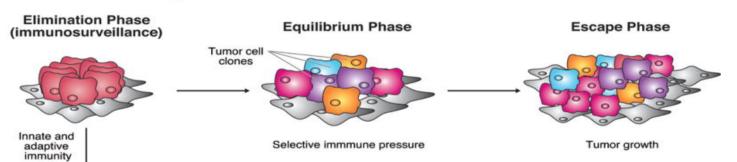
#### 1) Elimination

(immunosurveillance): innate and lormal cells adaptive immune responses recognize and destroy cancer cells suppressing tumor development.

Tumor suppression



## Cancer immunoediting

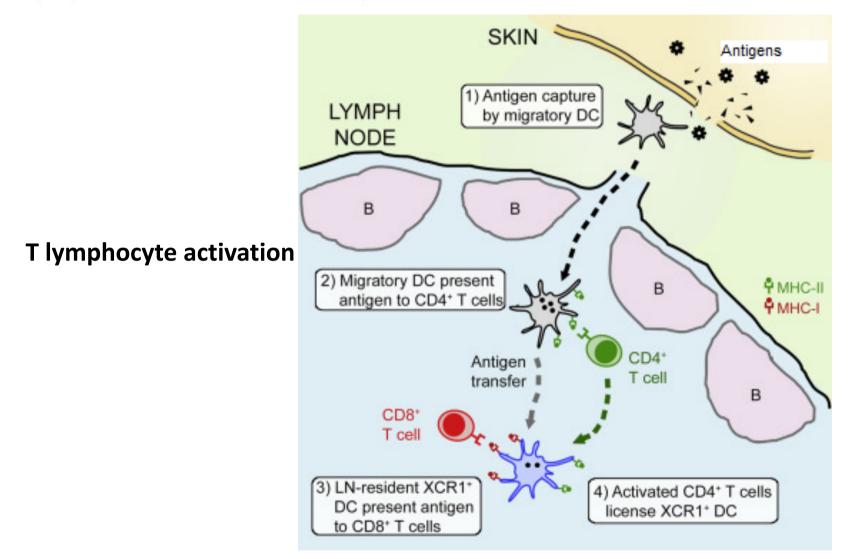


2) Equilibrium: tumor clones that escape the elimination phase remain dormant, during which tumor growth does not occur but the immunogenicity of the tumor cells continues to be shaped by selective immune pressure.

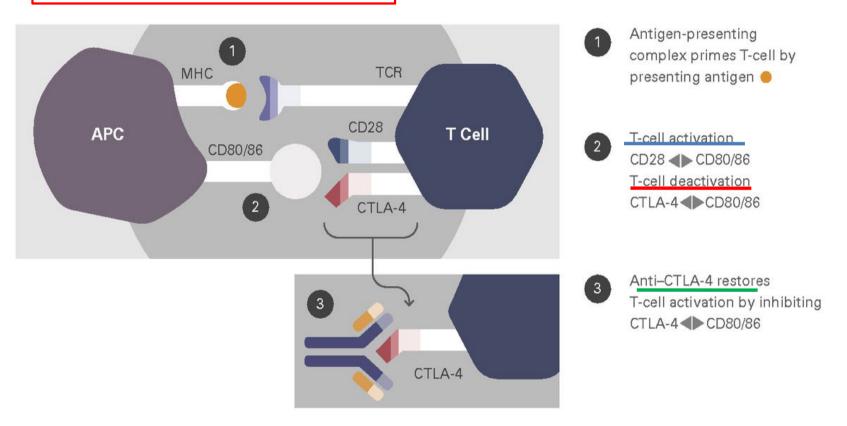
3) **Escape:** tumor cell clones that are resistant to the immune system proliferate unchecked. Adapted with permission from:

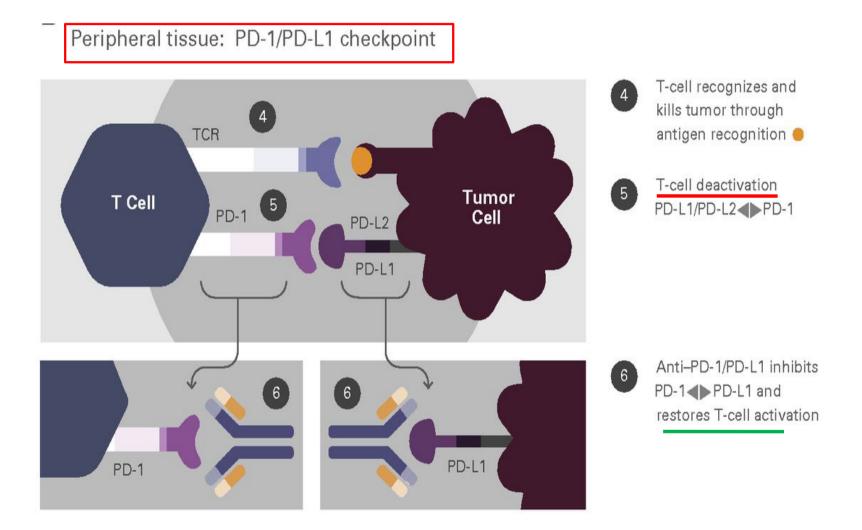
Annu Rev Immunol 2011;29:235–271

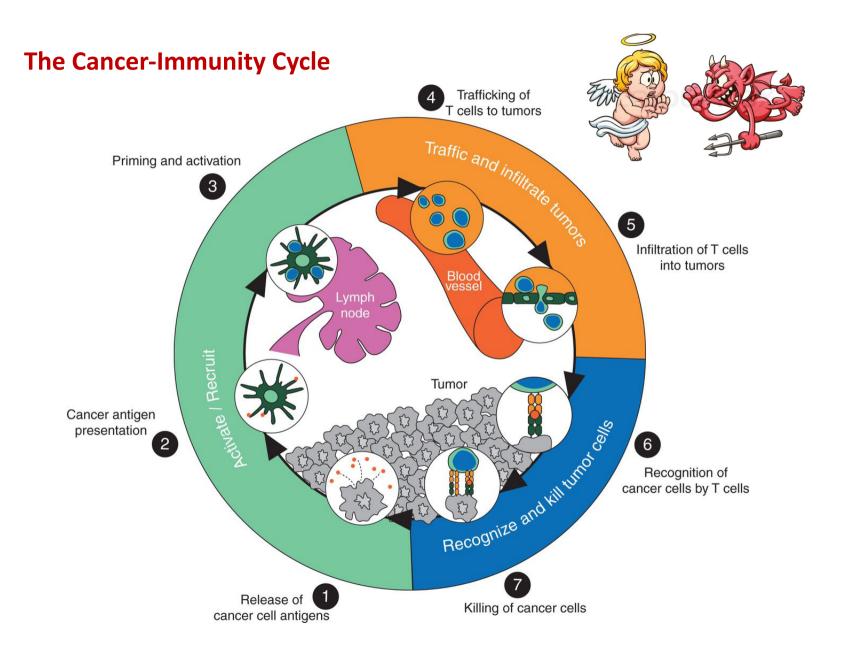
Lymphatic tissue: CTLA-4 checkpoint



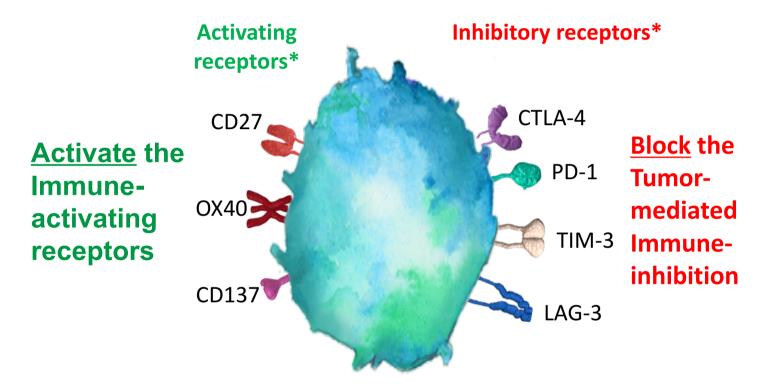
Lymphatic tissue: CTLA-4 checkpoint



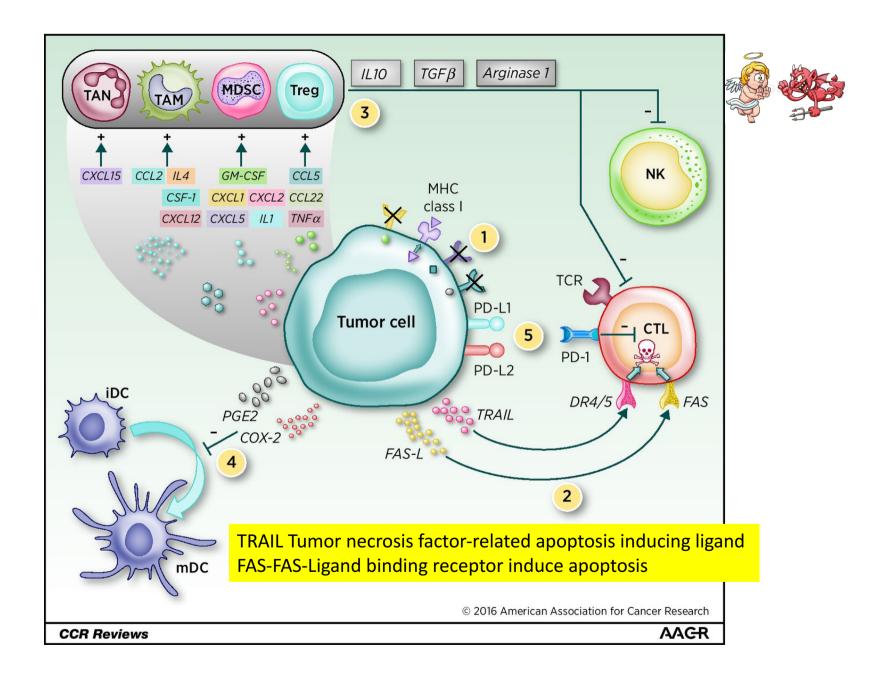




Tumors may exploit immune checkpoint signals to evade immune detection Potential Immuno-Oncology Targets

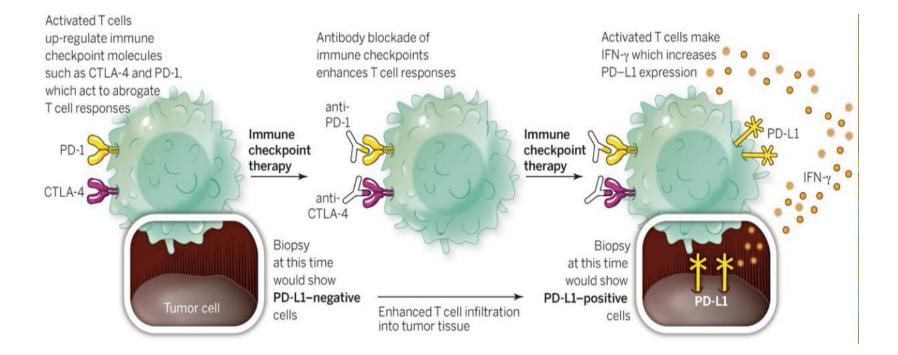


CD137, cluster of differentiation 137; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death receptor-1; CD27 cluster of differentiation 27; LAG-3; lymphocyte activation gene-3; TIM-3, T-cell immunoglobulin and mucin domain-3.

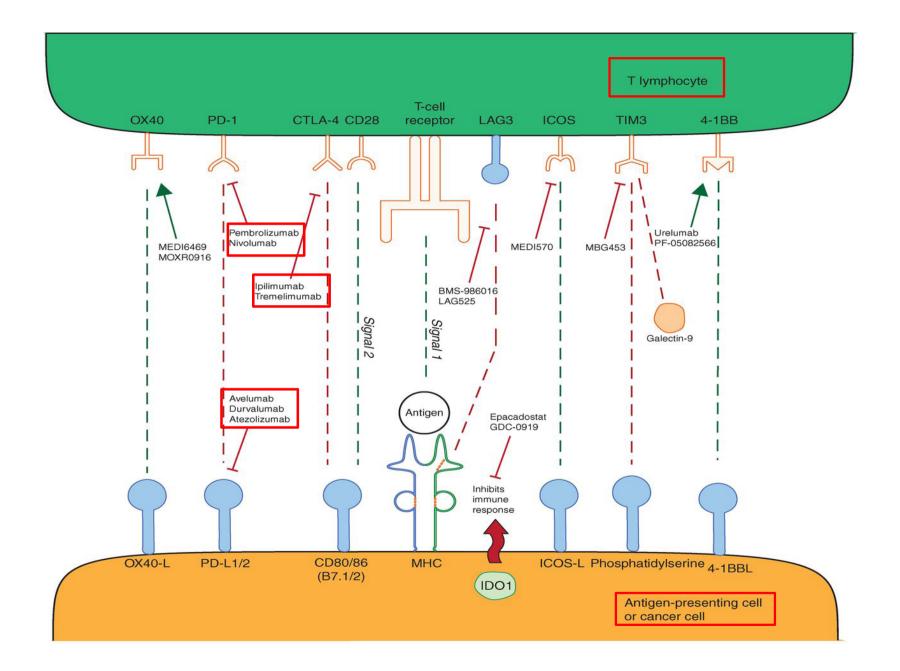


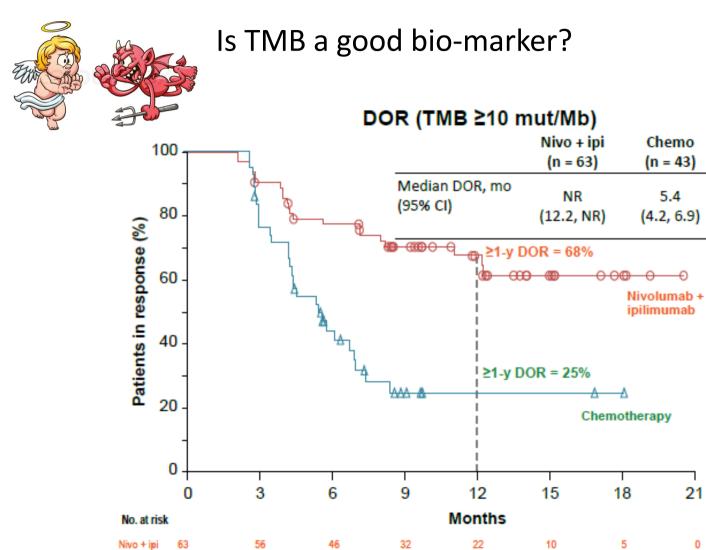


# Enhancement of T Cell Responses by Immune Checkpoint Blockade on Lymphocytes



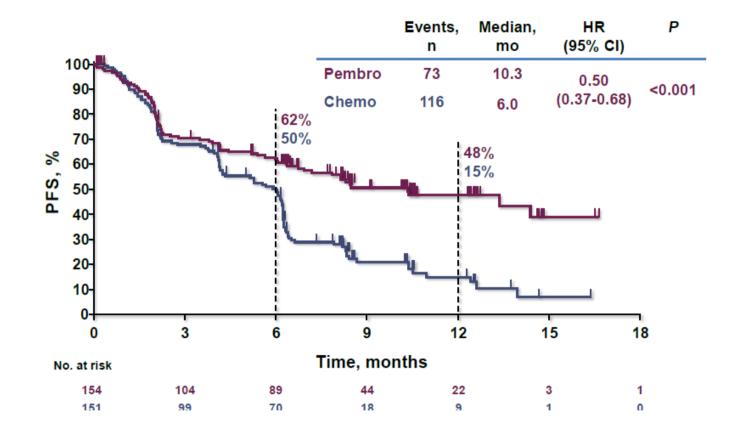
Science 348: 56, 2015



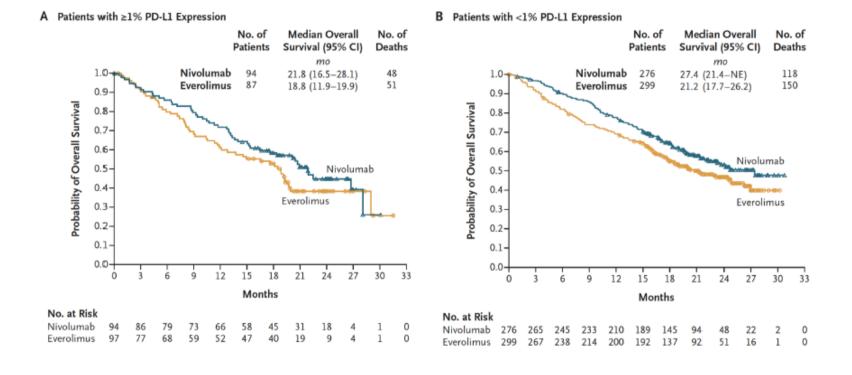


Chemo

### Is PDL-1 a good bio-marker?

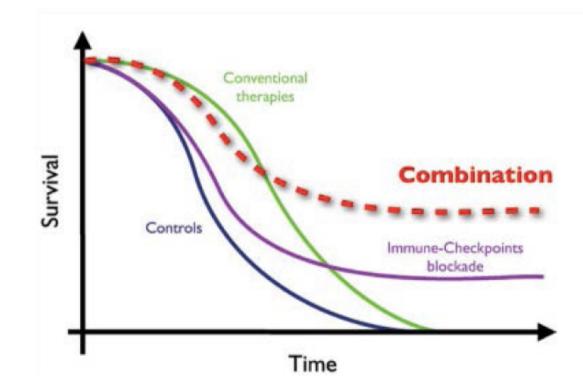


## Renal cancer - Nivolumab (OS by PD-L1)

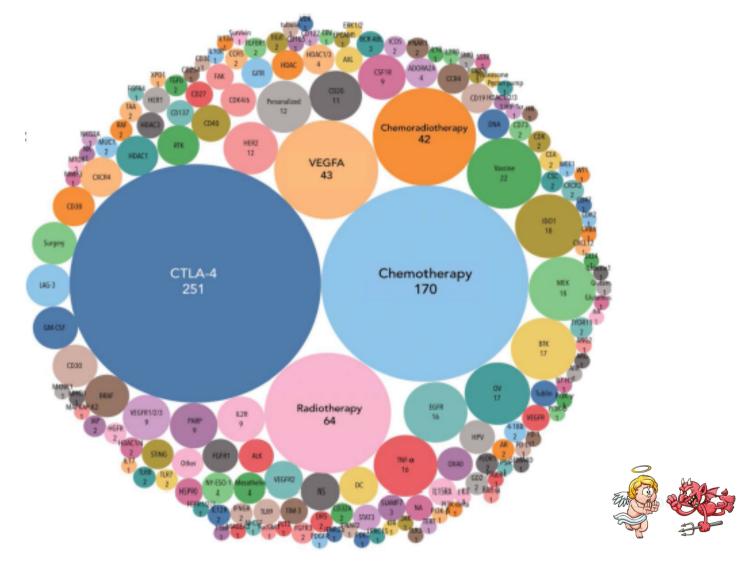




# Past- Present –Next future?



# How to combine anti-PD1/PDL1 treatment?



# Thank You

