

# Μια γνωριμία με τους αναστολείς των checkpoints

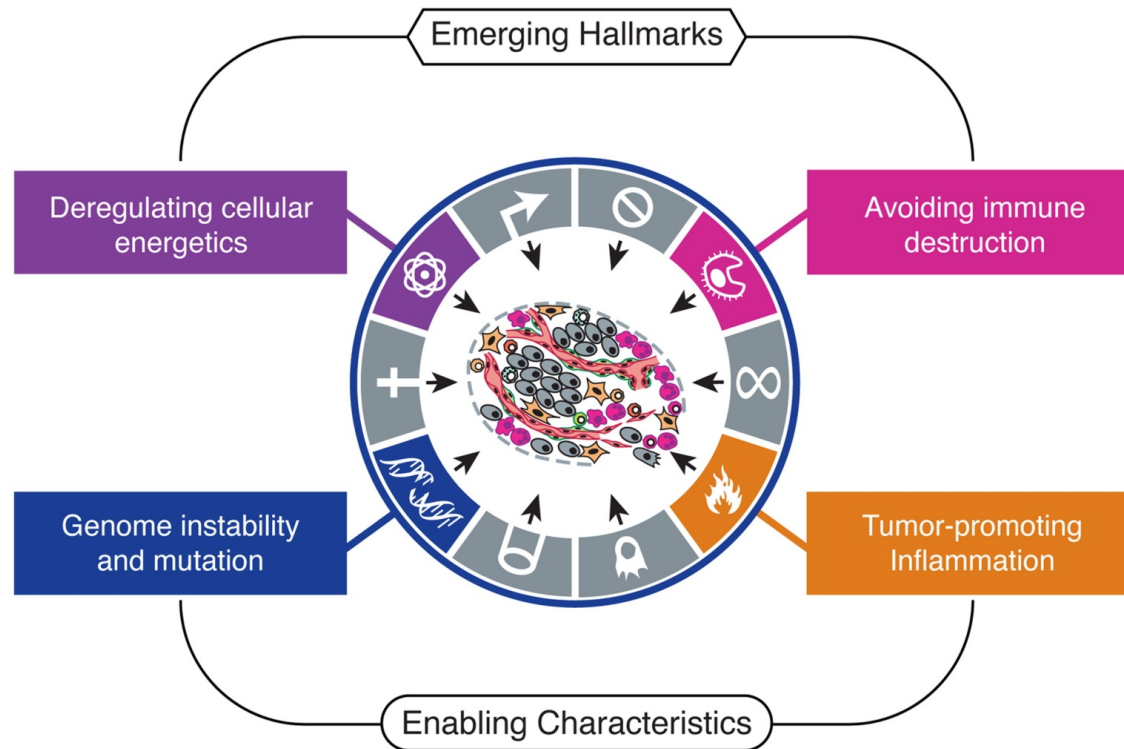
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Medical School, University of  
Ioannina, Greece.



# Disclosures

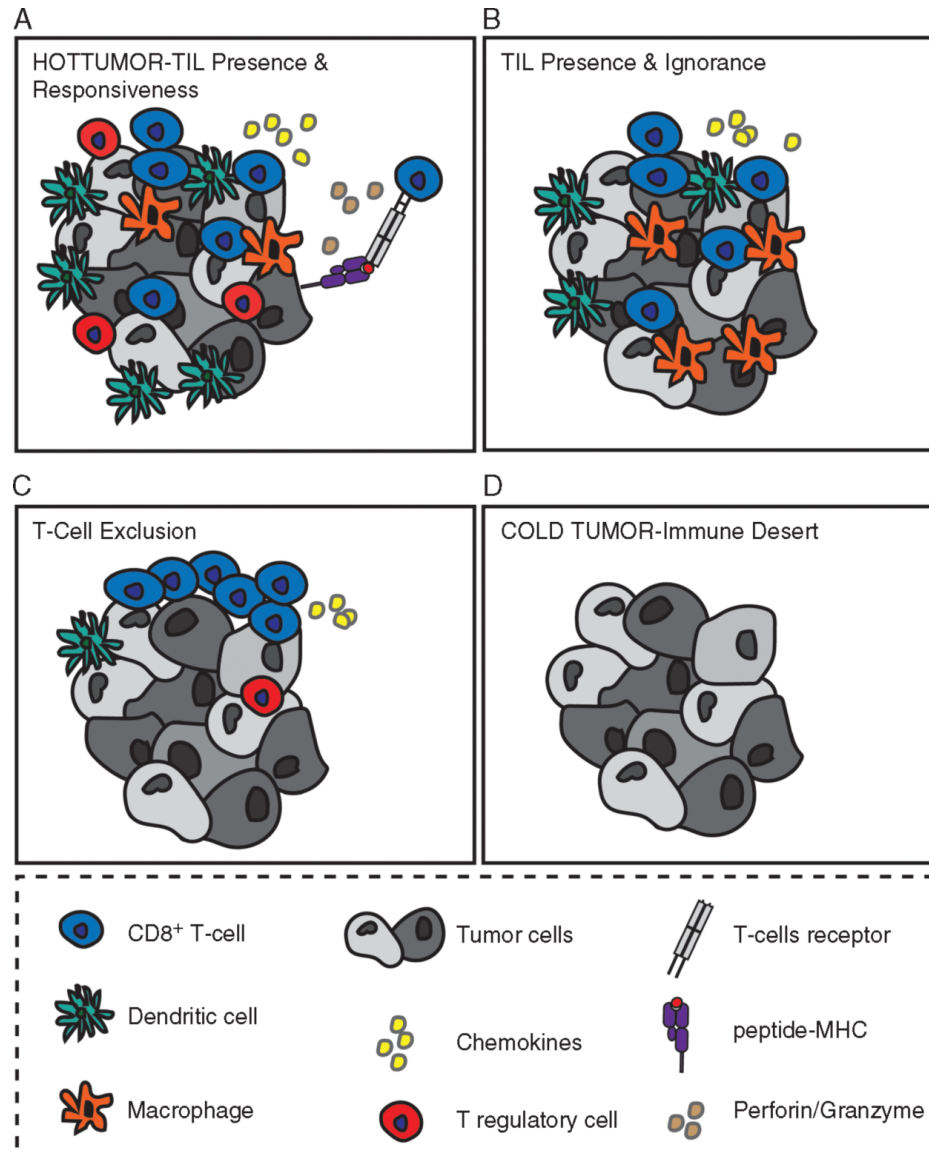
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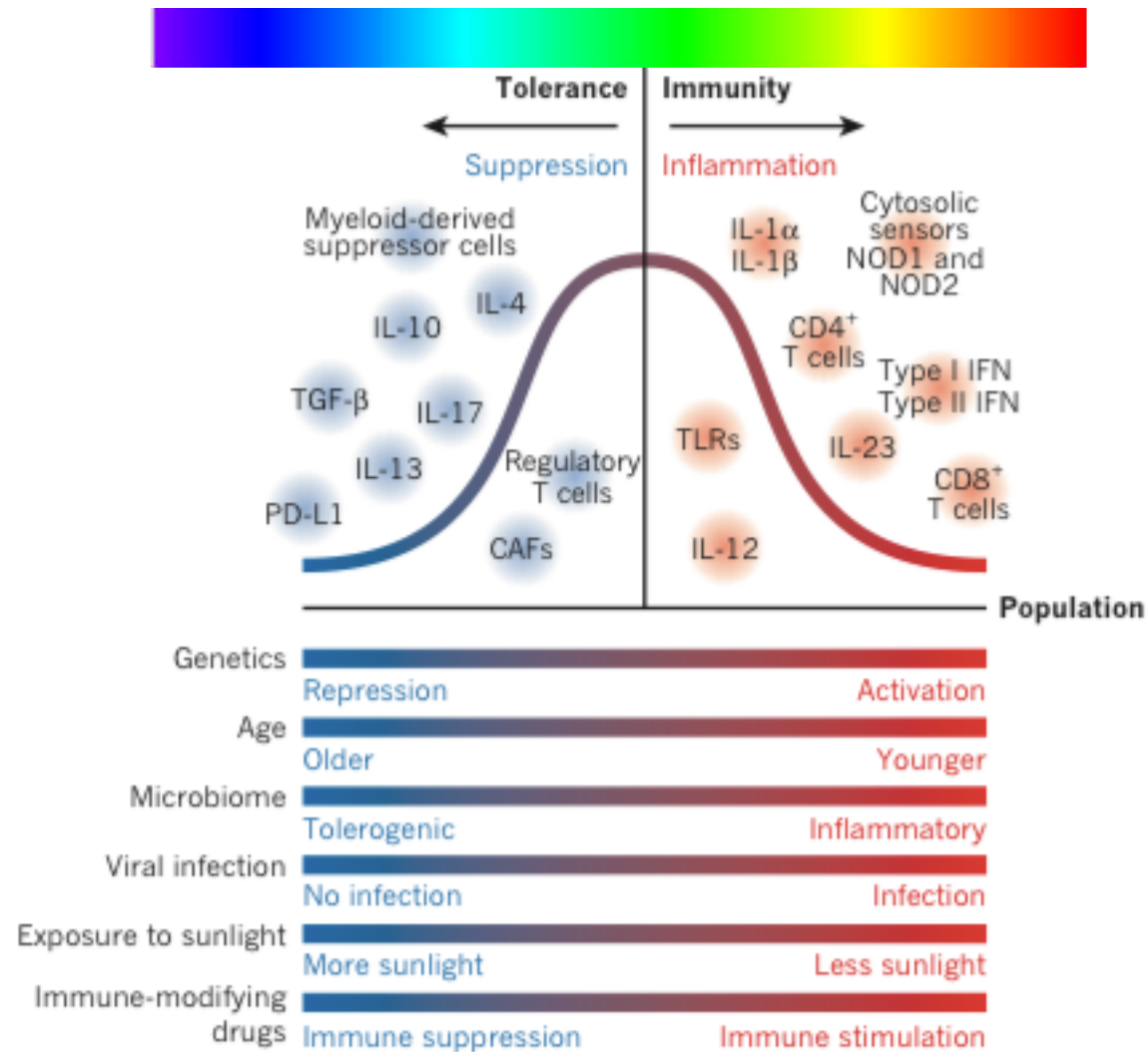


# Classification of tumors based on their immune cell infiltrate

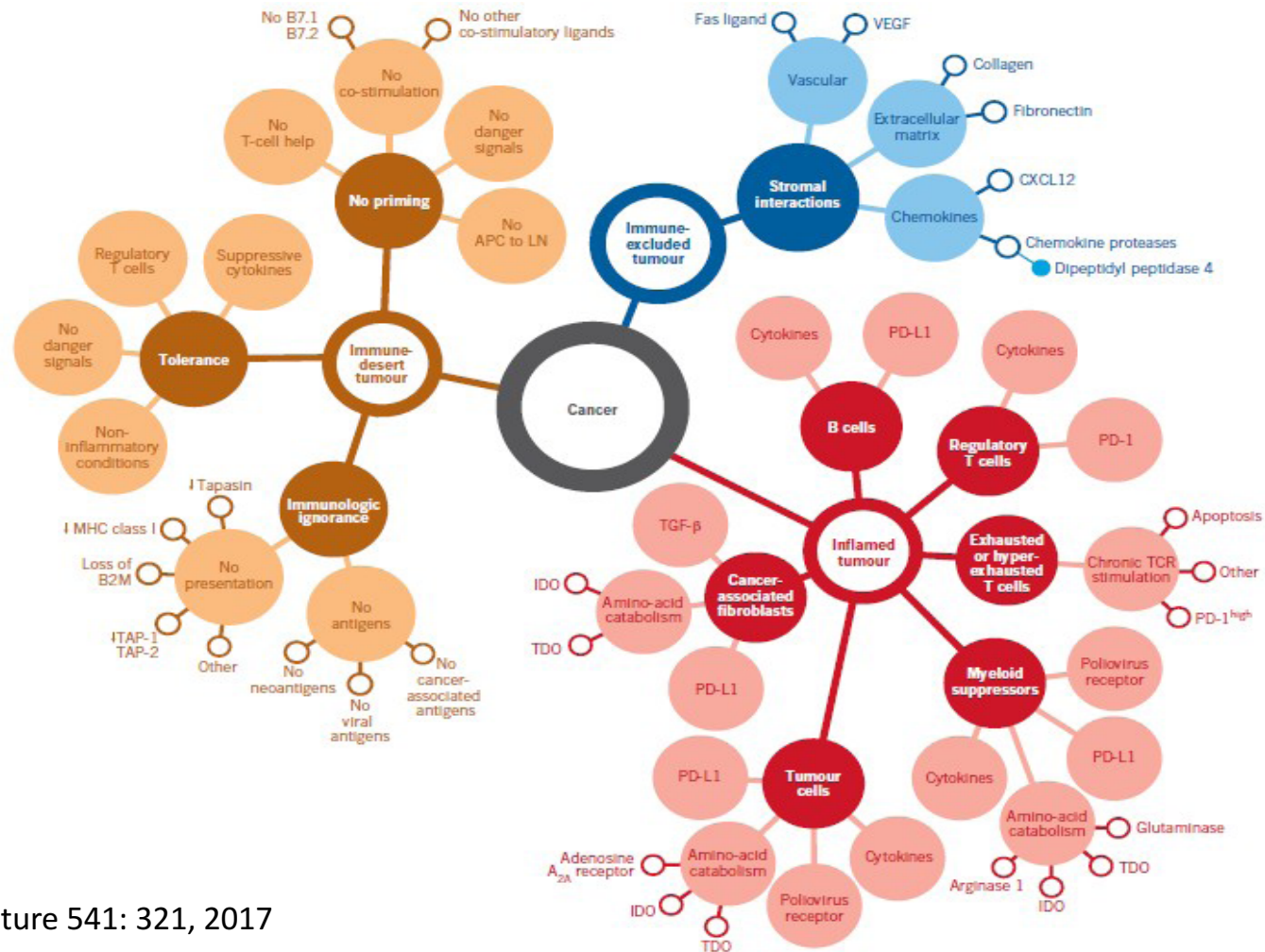


- A. T-cell-inflamed tumors (Hot tumors)**  
 infiltrated by T cells respond to checkpoint blockade therapies.
- B TIL Presence and Ignorance (Hot tumors)**  
 not respond to checkpoint blockade.
- C. T-Cell Exclusion**  
 immune cells are excluded at the periphery (C), as well as tumors that are, and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



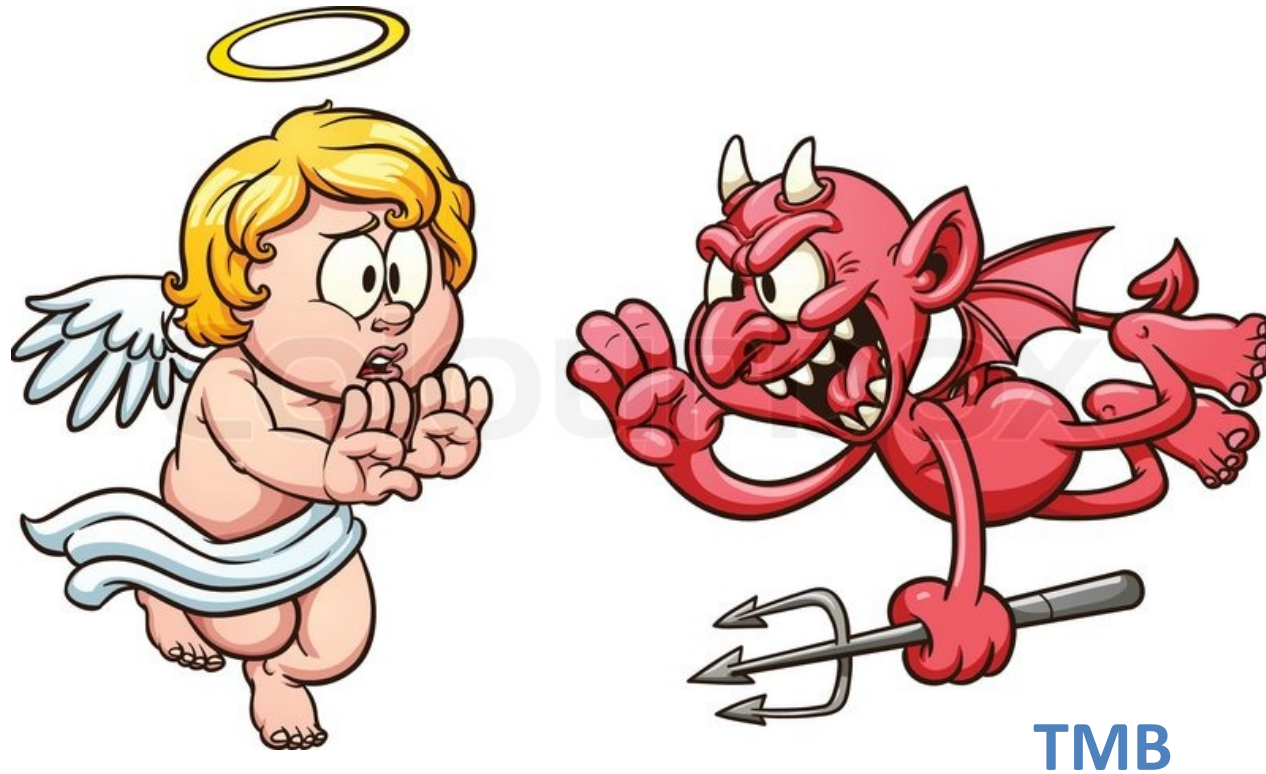


# Types of Cancers & Immune Function



Nature 541: 321, 2017

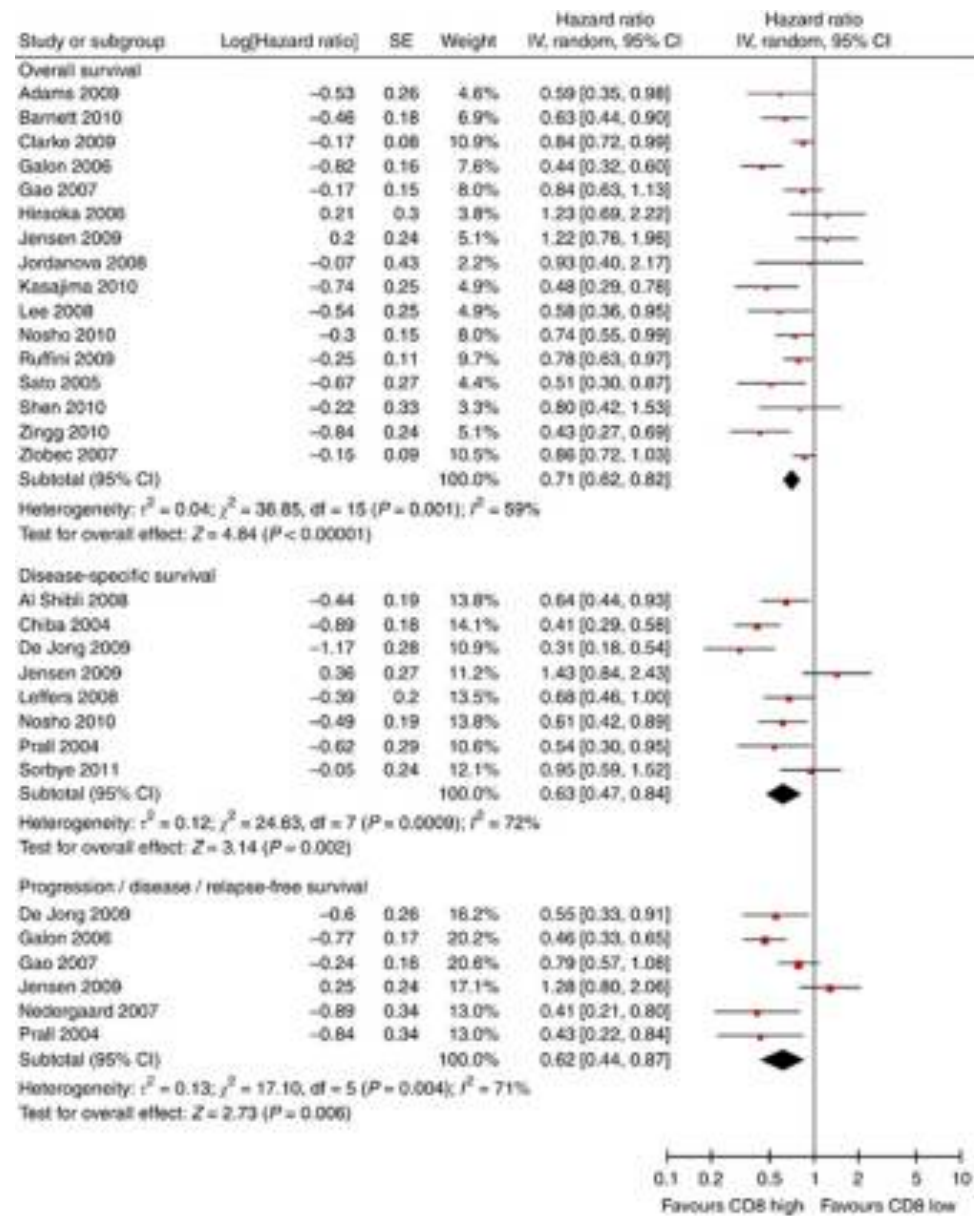
# Many players involved



CD8+ cytotoxic T-lymphocytes



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



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

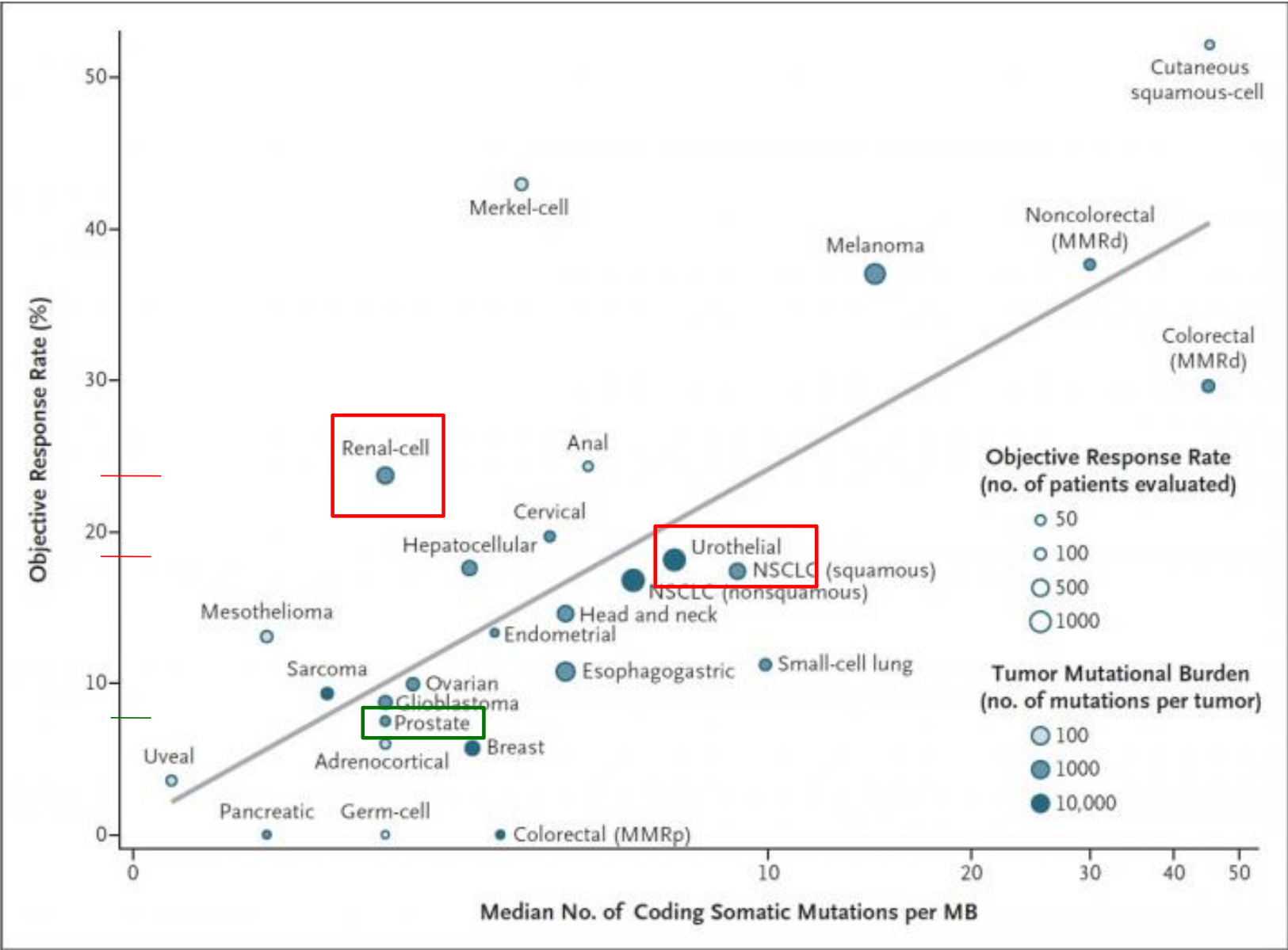


## TMB (tumor mutational burden)



high frequency of DNA mutations → abnormal antigens → 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 → immune response.**

**but**

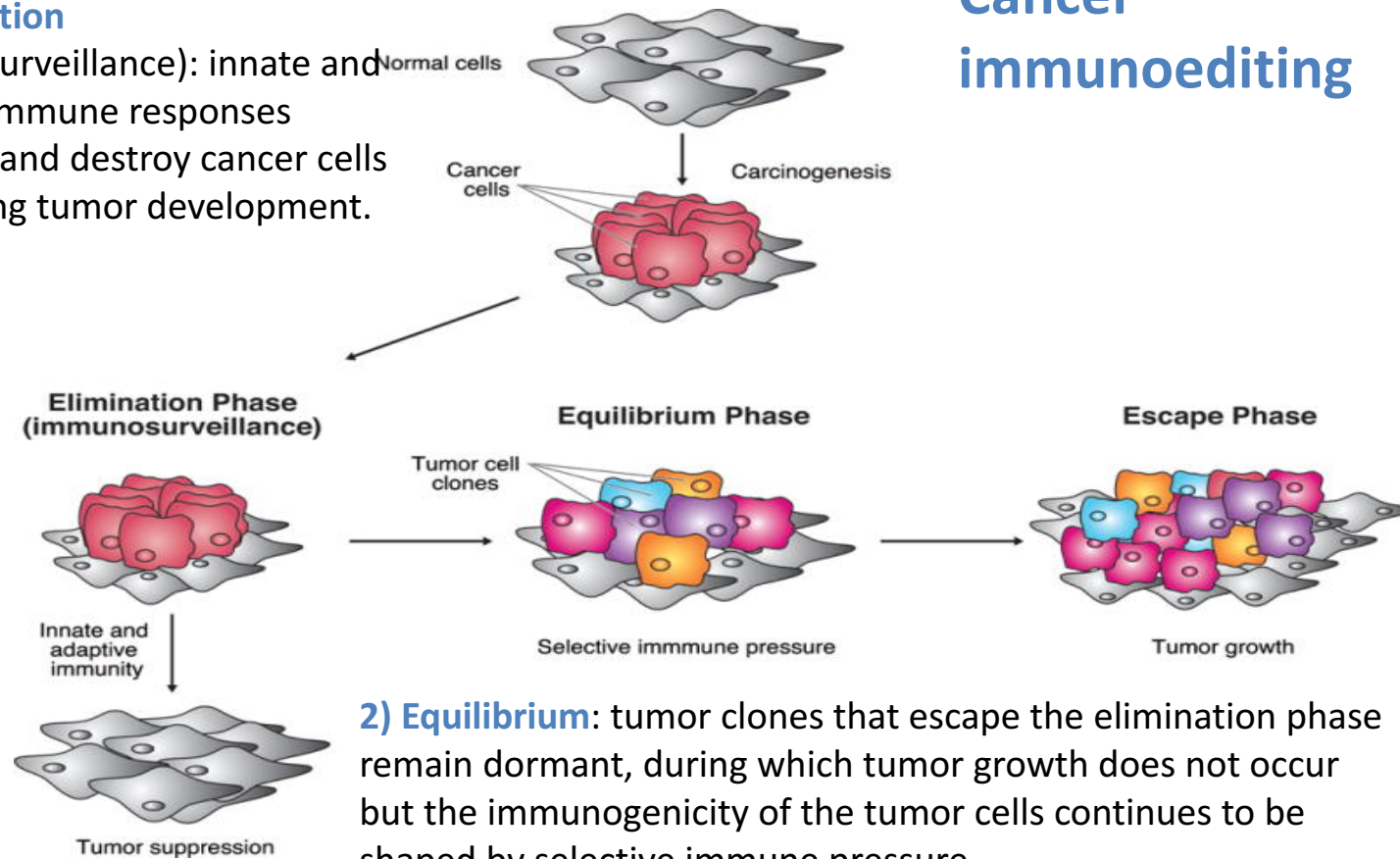
**Native immune response may be too weak to reject the tumor.**

# Cancer immunoediting

## 3 distinct phases:

### 1) Elimination

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

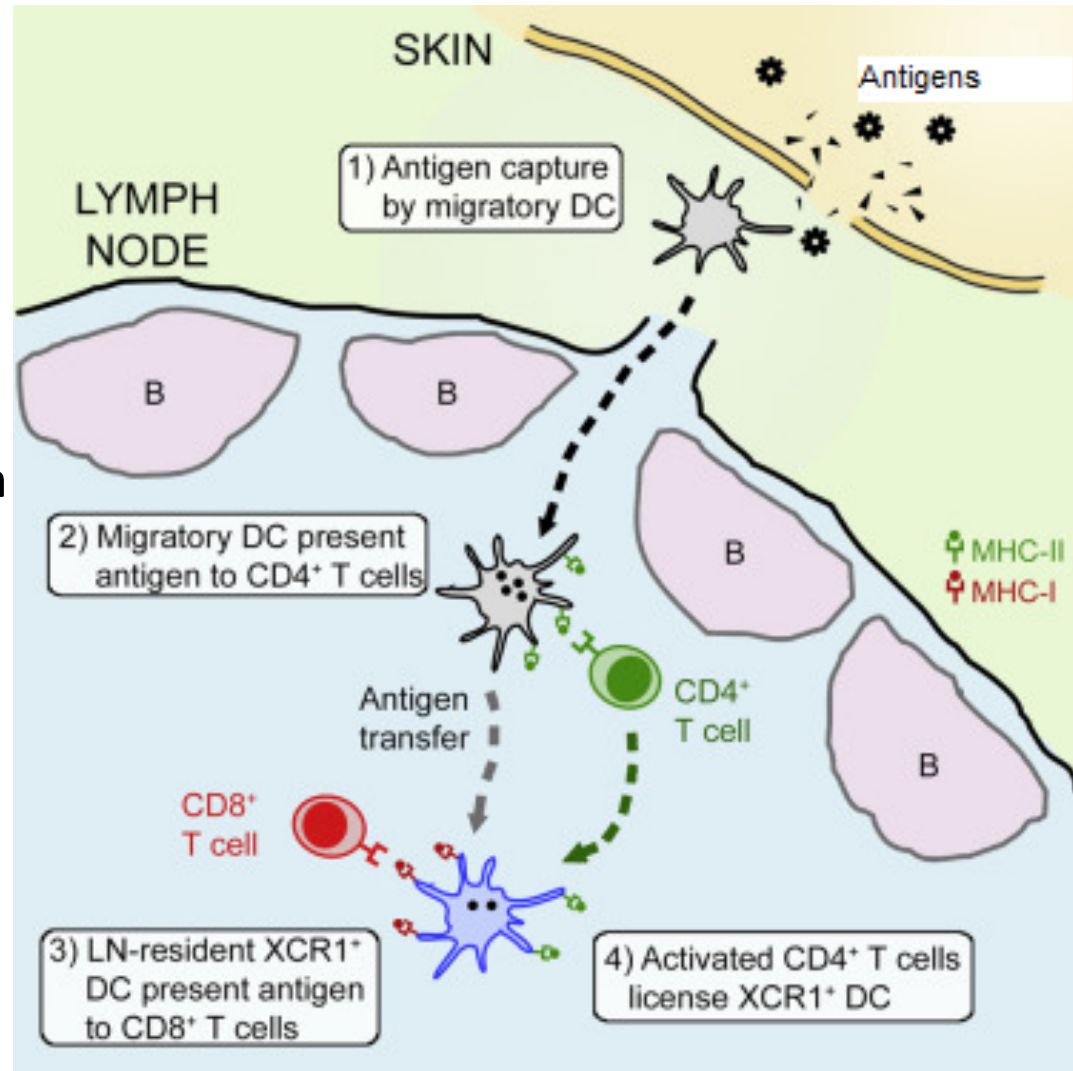


2) **Equilibrium**: tumor clones that escape the elimination phase remain dormant, during which tumor growth does not occur but the immunogenicity of the tumor cells continues to be shaped by selective immune pressure.

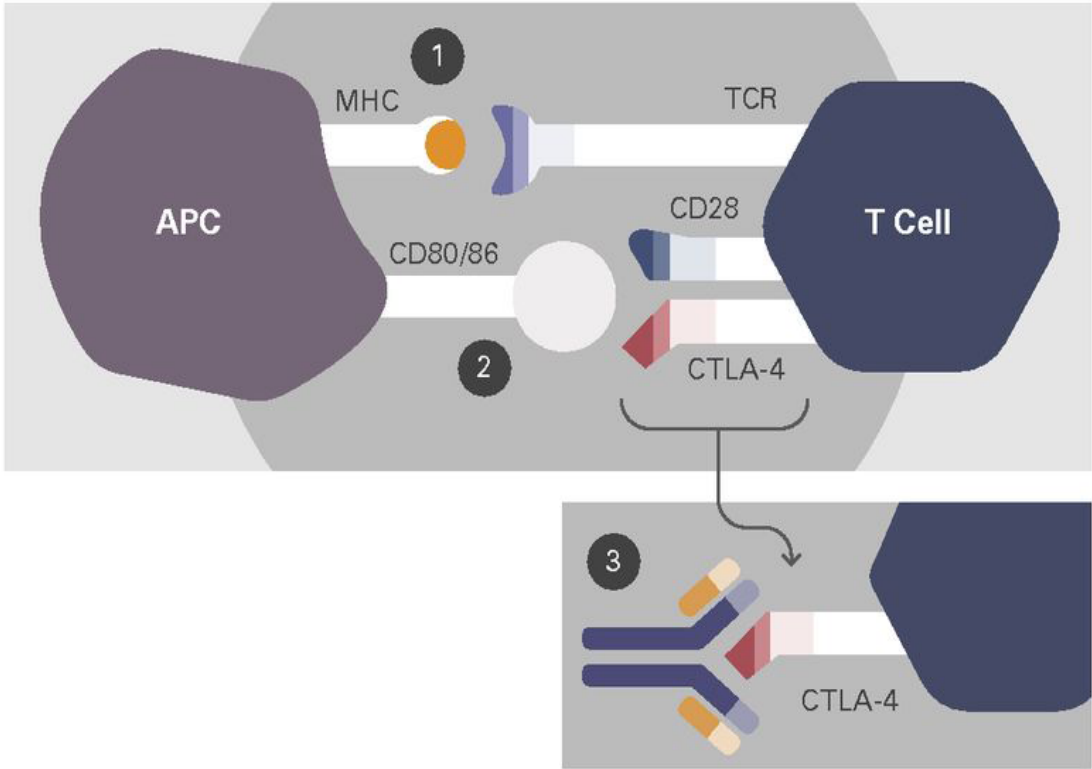
3) **Escape**: tumor cell clones that are resistant to the immune system proliferate unchecked. Adapted with permission from:

# Lymphatic tissue: CTLA-4 checkpoint

## T lymphocyte activation



Lymphatic tissue: CTLA-4 checkpoint

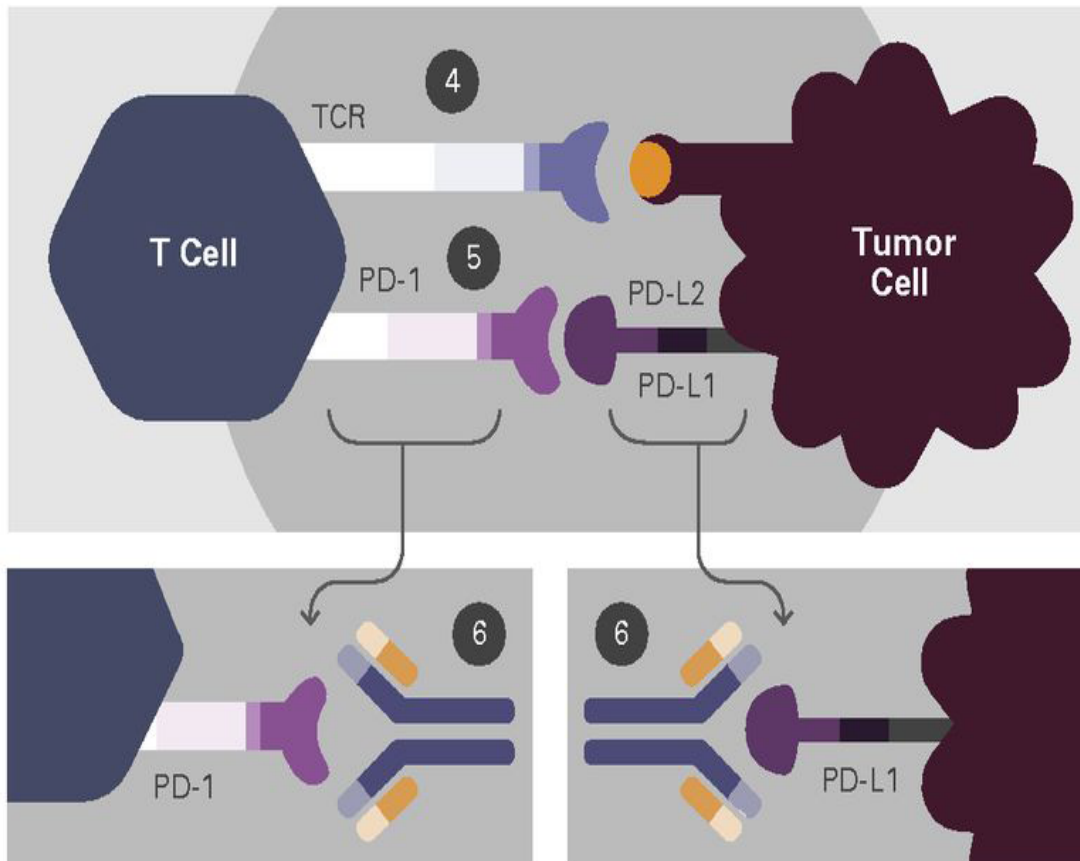


1 Antigen-presenting complex primes T-cell by presenting antigen ●

2 T-cell activation  
 CD28 ◀▶ CD80/86  
T-cell deactivation  
 CTLA-4 ◀▶ CD80/86

3 Anti-CTLA-4 restores  
T-cell activation by inhibiting  
 CTLA-4 ◀▶ CD80/86

Peripheral tissue: PD-1/PD-L1 checkpoint

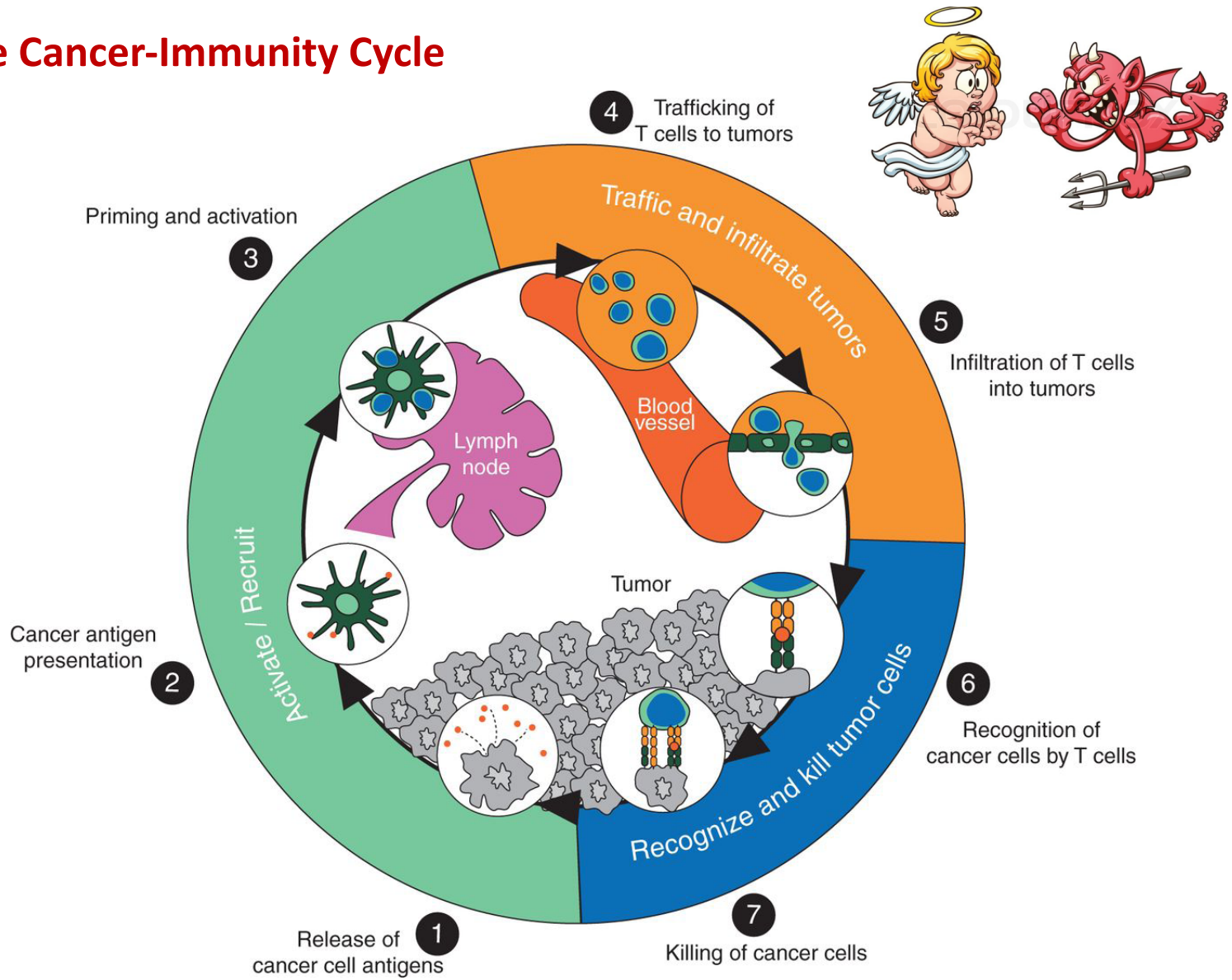


4 T-cell recognizes and kills tumor through antigen recognition ●

5 T-cell deactivation  
PD-L1/PD-L2 ◀▶ PD-1

6 Anti-PD-1/PD-L1 inhibits PD-1 ◀▶ PD-L1 and restores T-cell activation

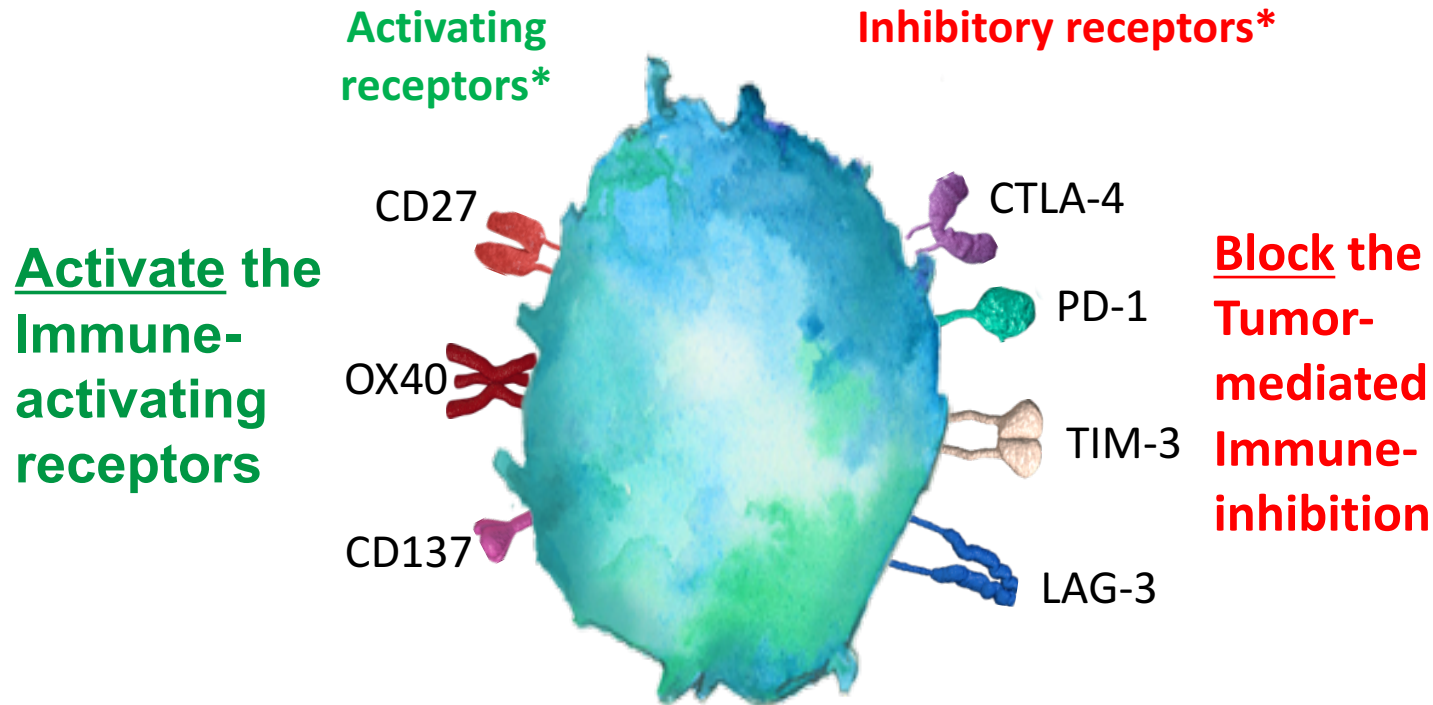
# The Cancer-Immunity Cycle





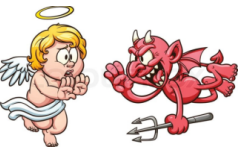
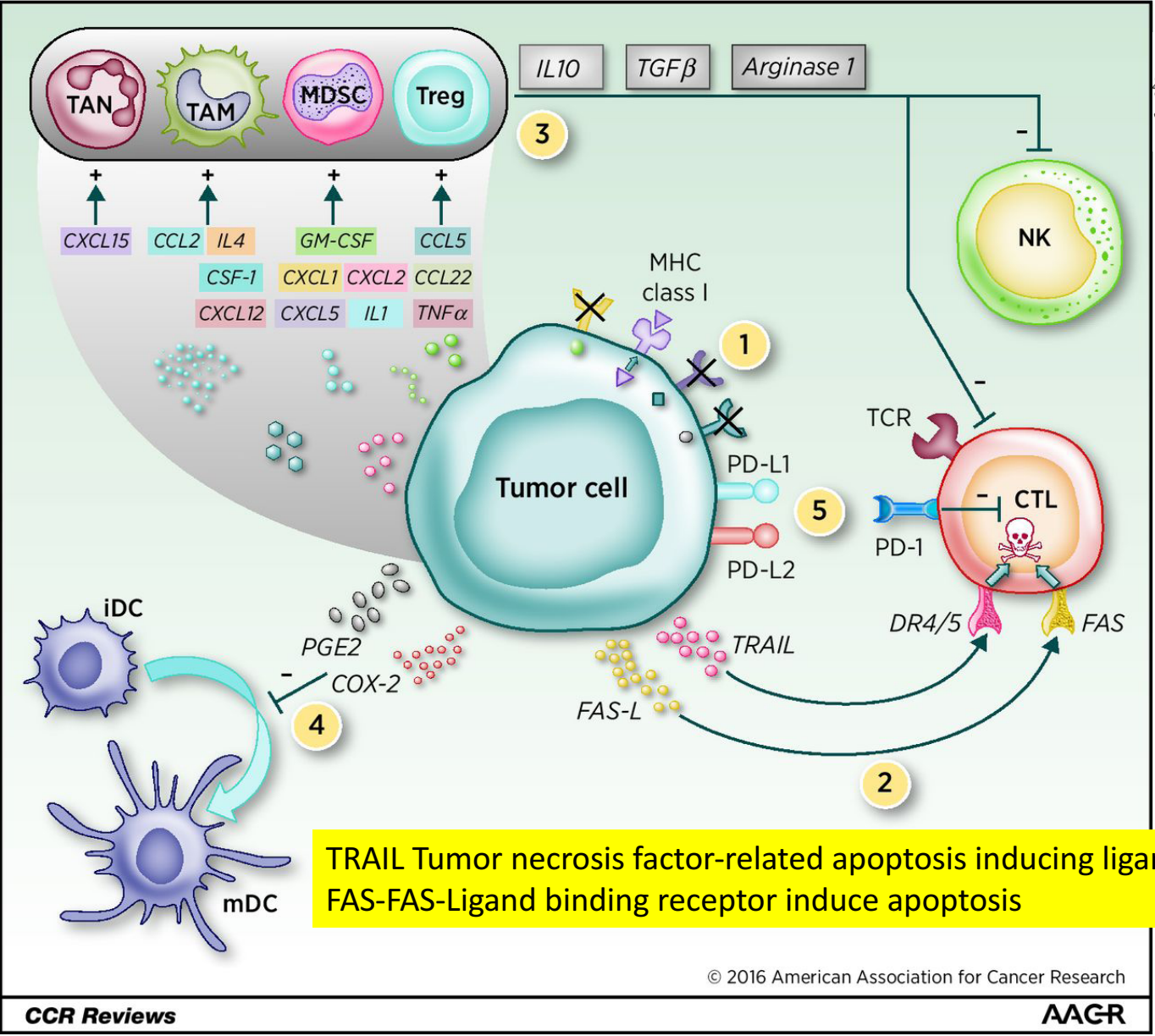
Tumors may exploit immune checkpoint signals to evade immune detection

➔ Potential Immuno-Oncology Targets



CD137, cluster of differentiation 137;  
CTLA-4, cytotoxic T-lymphocyte antigen-4;  
PD-1, programmed death receptor-1;

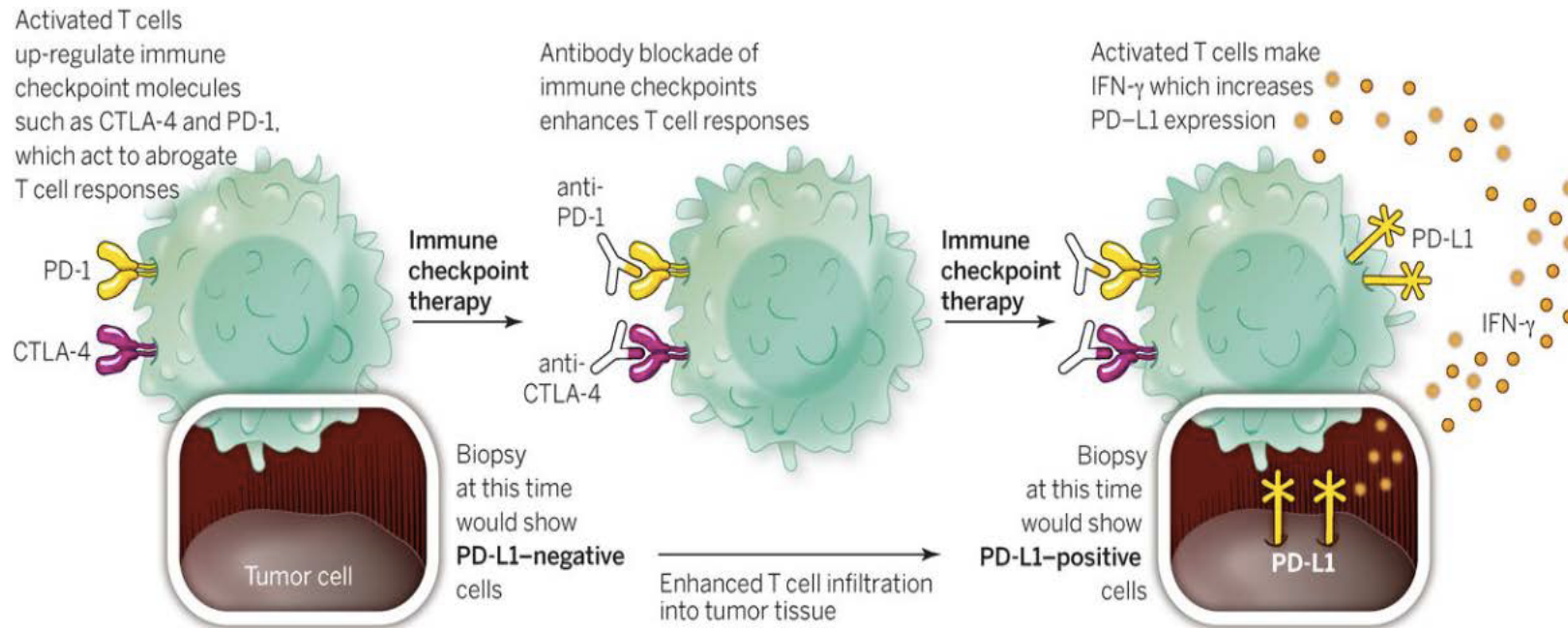
CD27 cluster of differentiation 27;  
LAG-3; lymphocyte activation gene-3;  
TIM-3, T-cell immunoglobulin and mucin  
domain-3.

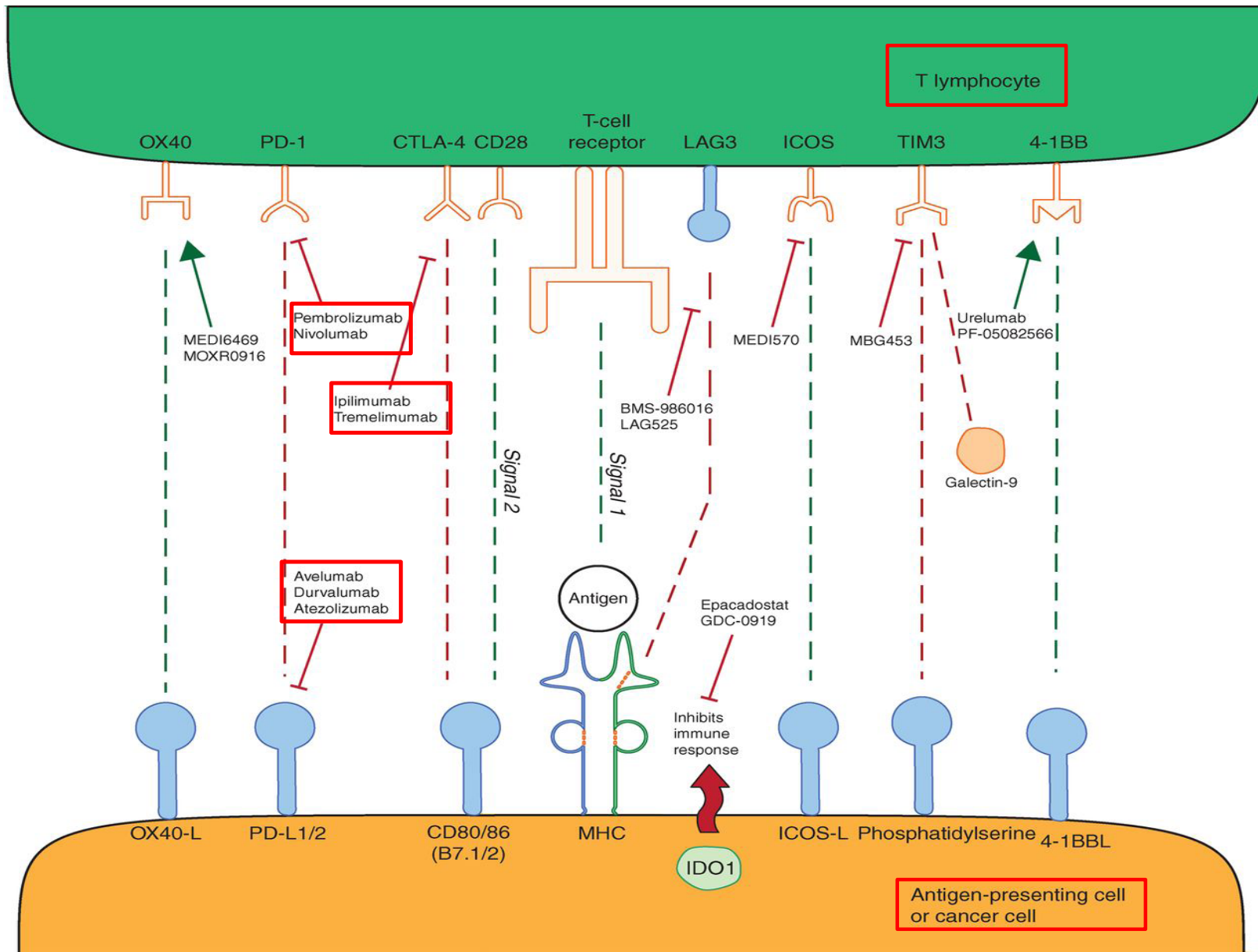


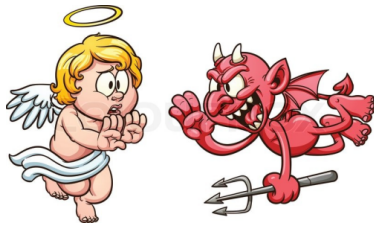
TRAIL Tumor necrosis factor-related apoptosis inducing ligand  
 FAS-FAS-Ligand binding receptor induce apoptosis



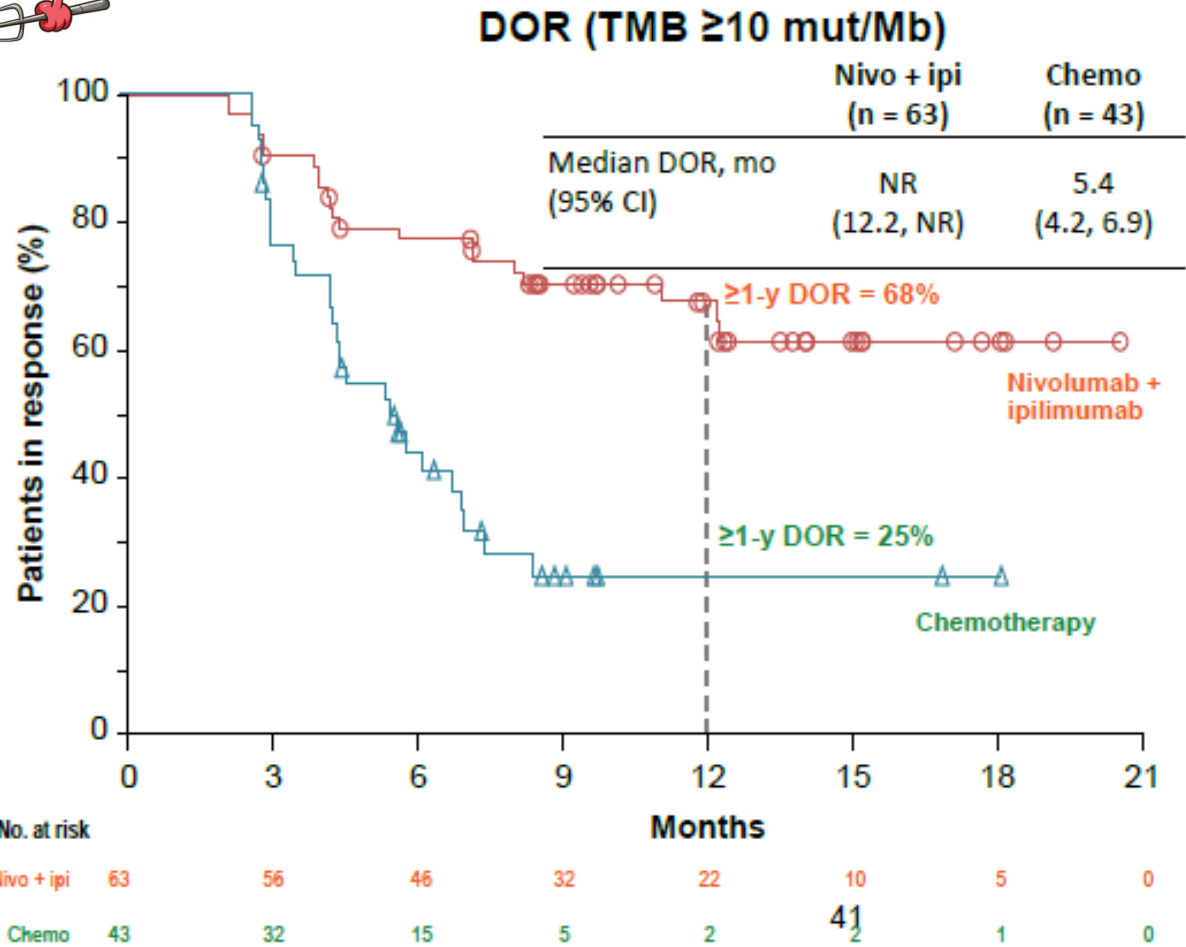
# Enhancement of T Cell Responses by Immune Checkpoint Blockade on Lymphocytes



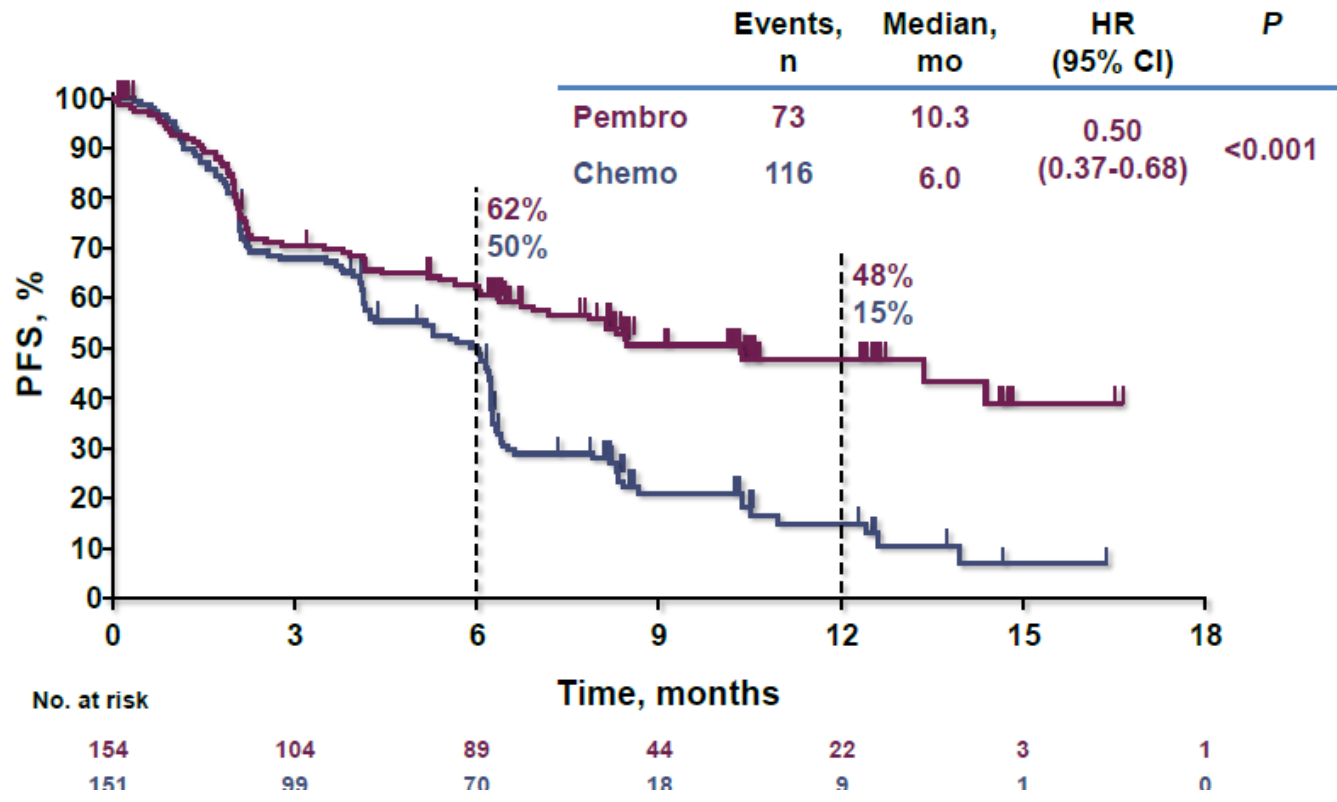




# Is TMB a good bio-marker?

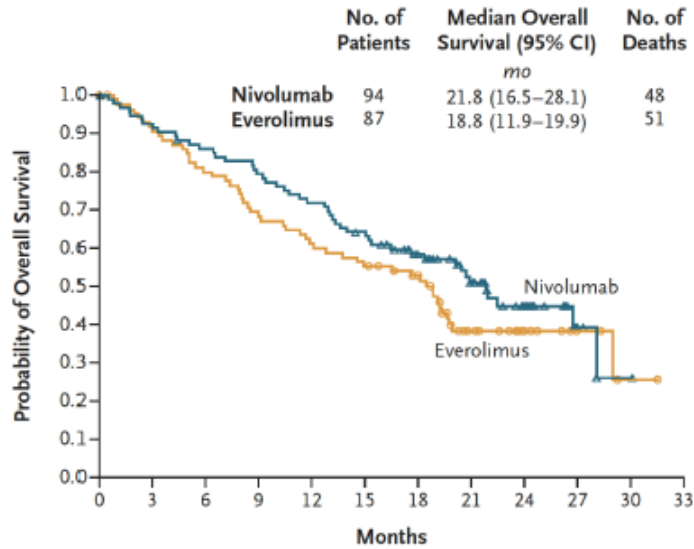


# Is PDL-1 a good bio-marker?



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

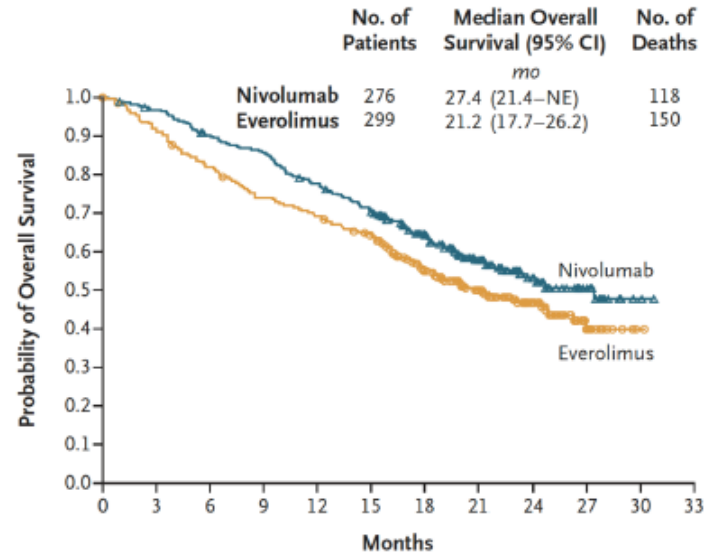
**A Patients with  $\geq 1\%$  PD-L1 Expression**



**No. at Risk**

Nivolumab	94	86	79	73	66	58	45	31	18	4	1	0
Everolimus	97	77	68	59	52	47	40	19	9	4	1	0

**B Patients with  $< 1\%$  PD-L1 Expression**



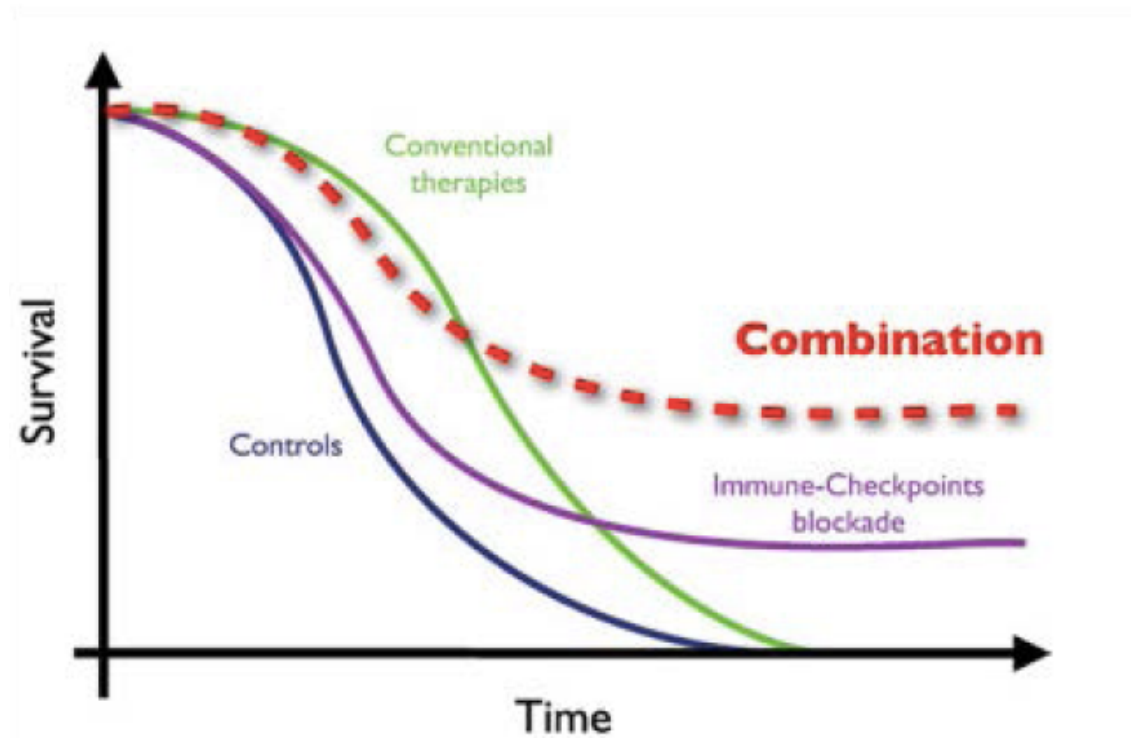
**No. at Risk**

Nivolumab	276	265	245	233	210	189	145	94	48	22	2	0
Everolimus	299	267	238	214	200	192	137	92	51	16	1	0





# Past- Present –Next future?





Thank You

