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Immune Checkpoint Inhibitors: mechanism of action and implications in clinical practice

Lorenzo Belluomini

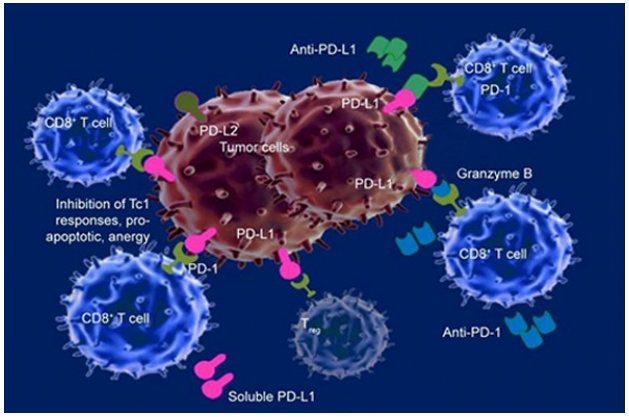
Oncologia Medica

IRCCS Ospedale Sacro Cuore Don Calabria – Negrar (VR)

Immune Checkpoint Inhibitors (ICIs)

Immune checkpoint therapy, which targets regulatory pathways in T cells to enhance antitumor immune responses, has led to important clinical advances and provided a powerfull weapon against cancer.

This therapy has elicited **durable clinical responses** and, in a fraction of patients,
long-term remissions
where patients exhibit no clinical signs of cancer for many years.



Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56–61.

FDA approved ICIs

Since the 2011 **FDA approval** of ***Ipilimumab*** (anti-CTLA4) for the treatment of metastatic melanoma, 5 additional checkpoint blockade therapies, all targeting the PD-1/PD-L1 axis, have been approved for the treatment of a broad range of tumor types.

Tumor type	Therapeutic agent	FDA approval year
Melanoma	Ipilimumab	2011
Melanoma	Nivolumab	2014
Melanoma	Pembrolizumab	2014
Non-small cell lung cancer	Nivolumab	2015
Non-small cell lung cancer	Pembrolizumab	2015
Melanoma (BRAF wild-type)	Ipilimumab + nivolumab	2015
Melanoma (adjuvant)	Ipilimumab	2015
Renal cell carcinoma	Nivolumab	2015
Hodgkin lymphoma	Nivolumab	2016
Urothelial carcinoma	Atezolizumab	2016
Head and neck squamous cell carcinoma	Nivolumab	2016
Head and neck squamous cell carcinoma	Pembrolizumab	2016
Melanoma (any BRAF status)	Ipilimumab + nivolumab	2016
Non-small cell lung cancer	Atezolizumab	2016
Hodgkin lymphoma	Pembrolizumab	2017
Merkel cell carcinoma	Avelumab	2017
Urothelial carcinoma	Avelumab	2017
Urothelial carcinoma	Durvalumab	2017
Urothelial carcinoma	Nivolumab	2017
Urothelial carcinoma	Pembrolizumab	2017
MSI-high or MMR-deficient solid tumors of any histology	Pembrolizumab	2017
MSI-high, MMR-deficient metastatic colorectal cancer	Nivolumab	2017
Pediatric melanoma	Ipilimumab	2017
Hepatocellular carcinoma	Nivolumab	2017
Gastric and gastroesophageal carcinoma	Pembrolizumab	2017
Non-small cell lung cancer	Durvalumab	2018
Renal cell carcinoma	Ipilimumab + nivolumab	2018

Spencer C. Wei et al.
Fundamental Mechanisms of Immune Checkpoint Blockade Therapy, Cancer Discovery 2018

ICIs

These drugs represent
a radical and disruptive change
in cancer therapy in **two ways**.

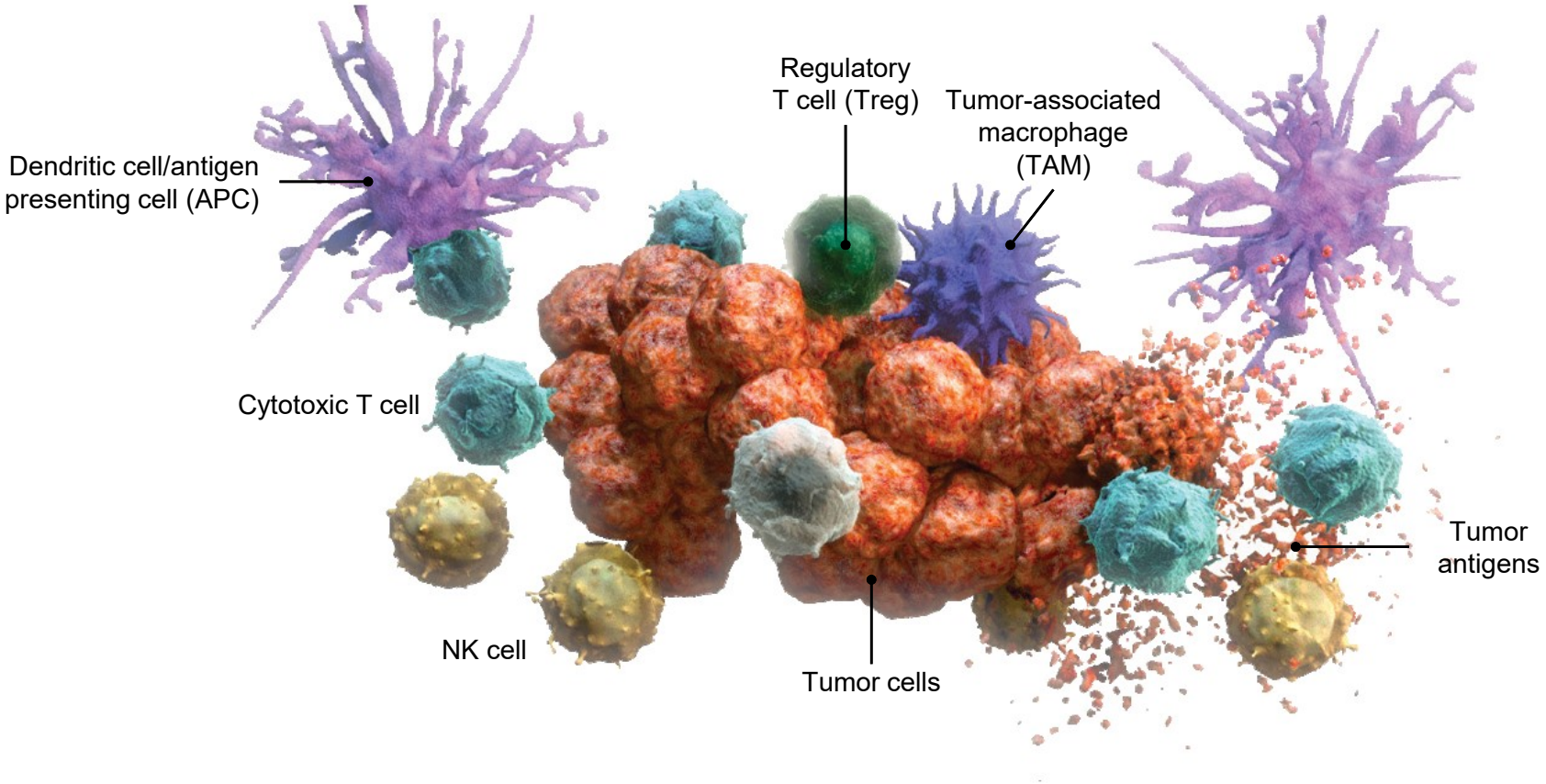
1 They do *not target the tumor cell*, but target molecules involved in regulation of T cells, the soldiers of the immune system.

2 The goal of the therapy is not to activate the immune system to attack particular targets on tumor cells, but rather *to remove inhibitory pathways* that block effective antitumor T cell responses

Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56–61.

Tumor microenvironment and immune system

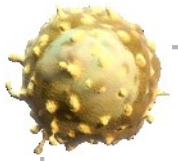
The immune system is capable of recognizing and eliminating tumor cells in the tumor microenvironment. **Innate** and **adaptive** immunity act as a complementary network of self-defense against foreign threats.



Tumors can use various mechanisms to escape detection and enable growth.

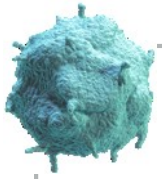
Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56–61.

Immune system



Innate immune response

The first line of defense, it identifies and attacks tumor cells without antigen specificity. **Natural killer (NK) cells** are the main effector cells of innate immunity.



Adaptive immune response

A durable response that attacks tumor antigens. Once activated, it can be sustained through a memory response.[7] **Cytotoxic T cells** are the main effector cells of adaptive immunity.

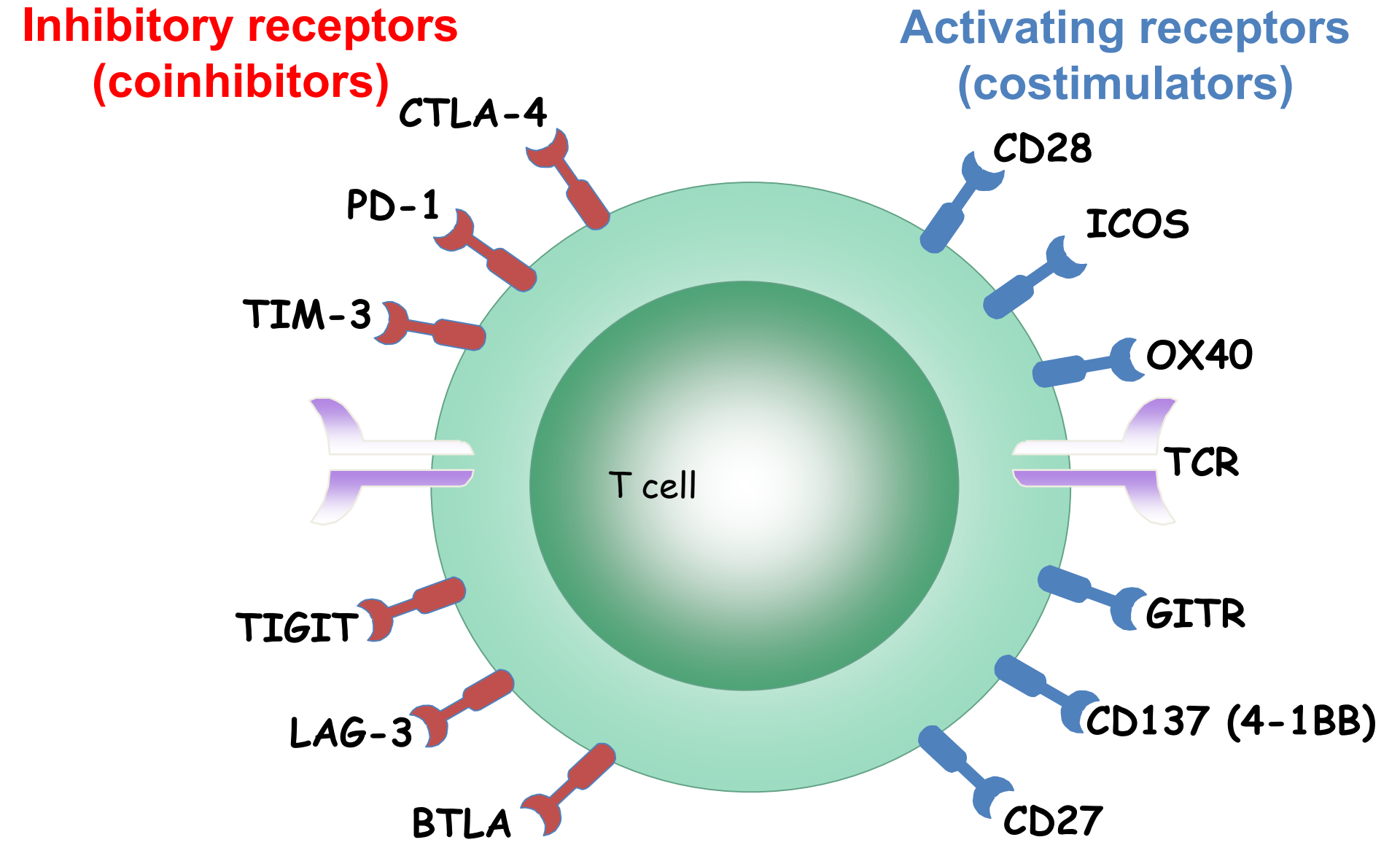
The antitumor activity of NK cells and cytotoxic T cells is regulated through a network of **activating** and **inhibitory** signaling pathways:

ACTIVATING
Stimulating pathways trigger immune responses

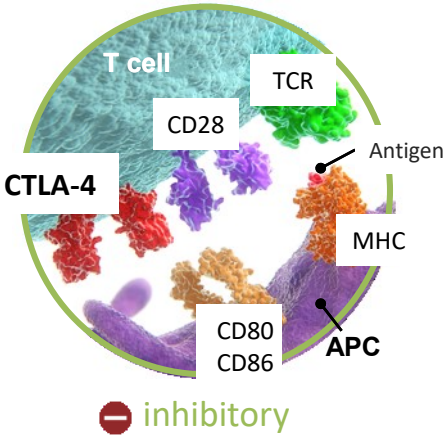
INHIBITORY
Pathways that counterbalance immune activation such as checkpoints

Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56–61.

The landscape of T cell activating and inhibitory receptors



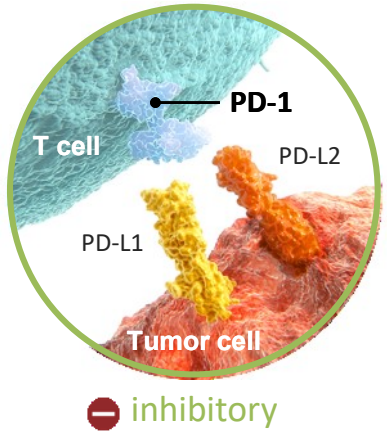
Pathways that modulate adaptive immune response



CTLA-4 is an immune checkpoint receptor on T cells that plays a key role in preventing T-cell overactivation.

Tumor cells use the CTLA-4 pathway to suppress initiation of an immune response, resulting in decreased T-cell activation and ability to proliferate into memory T cells.

Preclinical data suggests that treatment with antibodies specific for CTLA-4 can restore an immune response through increased survival of memory T cells and depletion of regulatory T cells.



PD-1 is an immune checkpoint receptor on cytotoxic T cells that plays a key role in T-cell exhaustion and prevention of autoimmunity.

Preclinical data suggests that PD-1 blockade reinvigorates exhausted T cells and restores their cytotoxic immune function. Inhibiting both PD-1 ligands (PD-L1 and PD-L2) may be more effective at reversing T-cell exhaustion than inhibiting PD-L1 alone.

Molecular mechanism of CTLA4 and PD-1

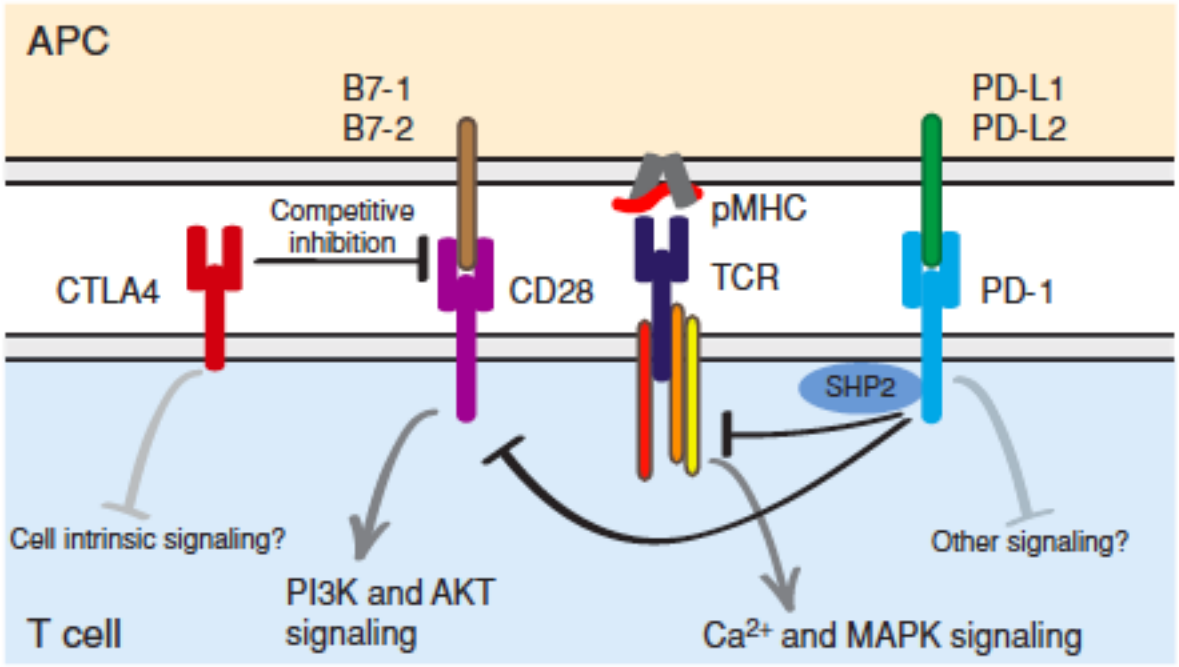
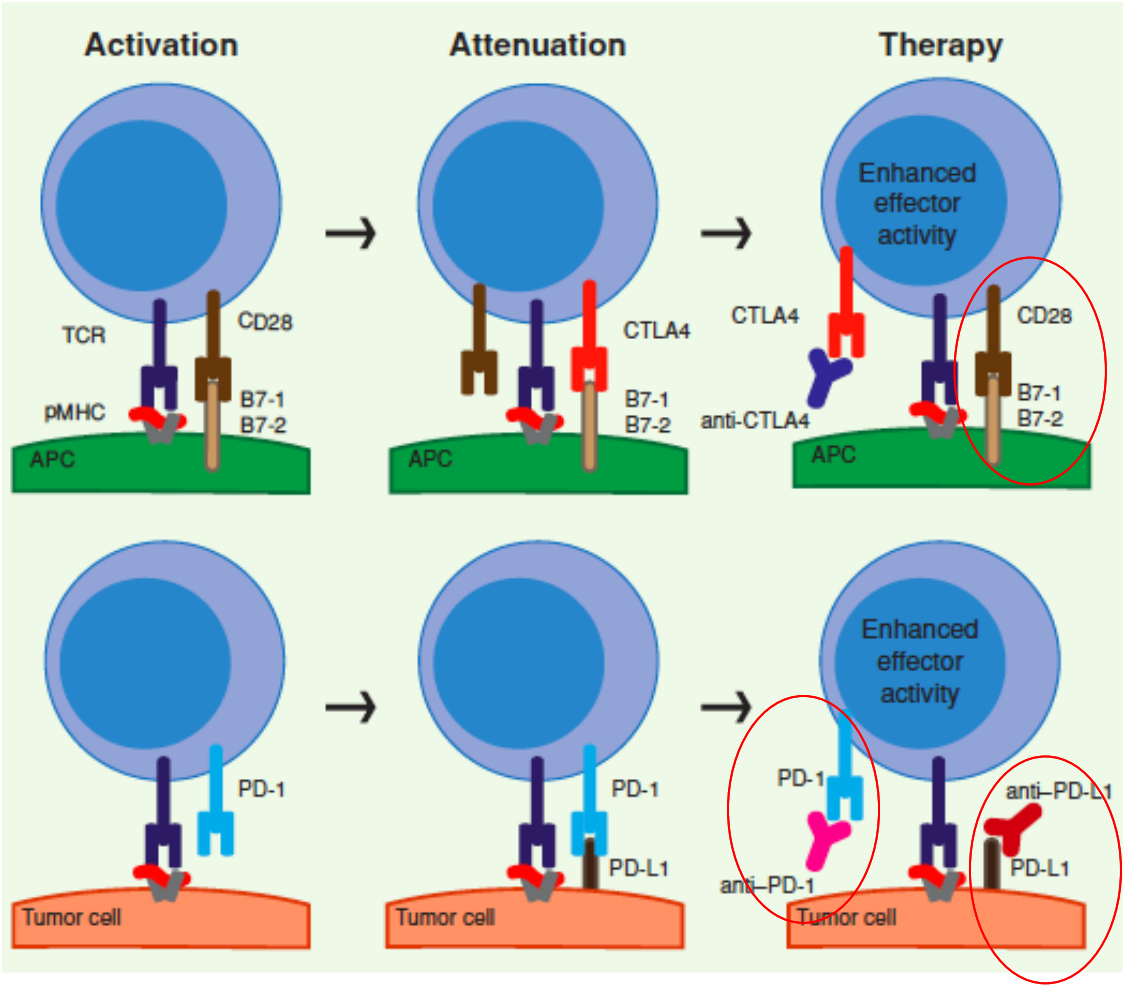


Figure 1. Molecular mechanisms of CTLA4 and PD-1 attenuation of T-cell activation. Schematic of the molecular interactions and downstream signaling induced by ligation of CTLA4 and PD-1 by their respective ligands. The possibility of additional downstream cell-intrinsic signaling mechanisms is highlighted for both CTLA4 and PD-1.

Spencer C. Wei et al.
Fundamental Mechanisms of Immune Checkpoint Blockade Therapy, Cancer Discovery 2018

Mechanism of action - 1



CTLA4 blockade primarily acts at sites of priming in which CD28-positive costimulation is involved (e.g., tumordraining lymph nodes) whereas **PD-1 blockade** primarily acts in inflamed peripheral tissues (e.g., tumor)

Spencer C. Wei et al.
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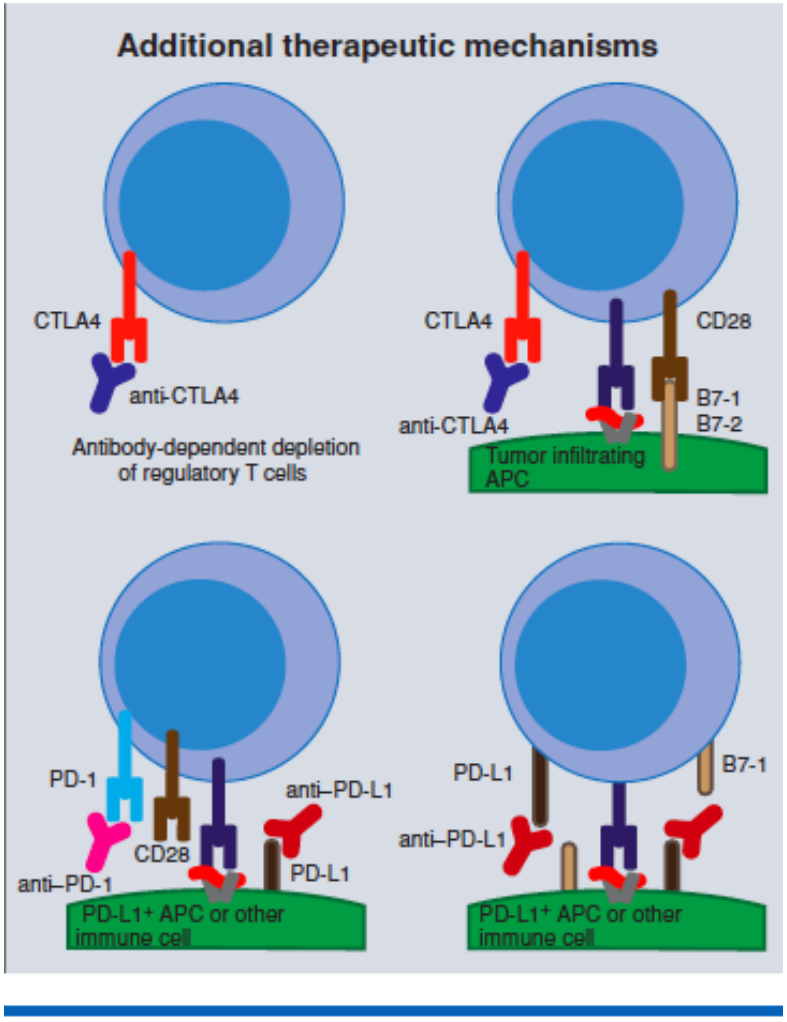
Mechanism of action - 2

CTLA4

antibody-mediated depletion of Tregs

PD-1

blockade of host-derived PD-L1 signals from nontumor cells in the microenvironment (as opposed to tumor cell–derived PD-L1)



enhancement of T-cell positive costimulation within the tumor microenvironment

blockade of interactions between PD-L1 and B7-1

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Neoantigens

Recent technological innovations have made it possible to dissect the immune response to patient-specific neoantigens that arise as a consequence of tumor-specific mutations, and emerging data suggest that recognition of such neoantigens is a major factor in the activity of clinical immunotherapies.

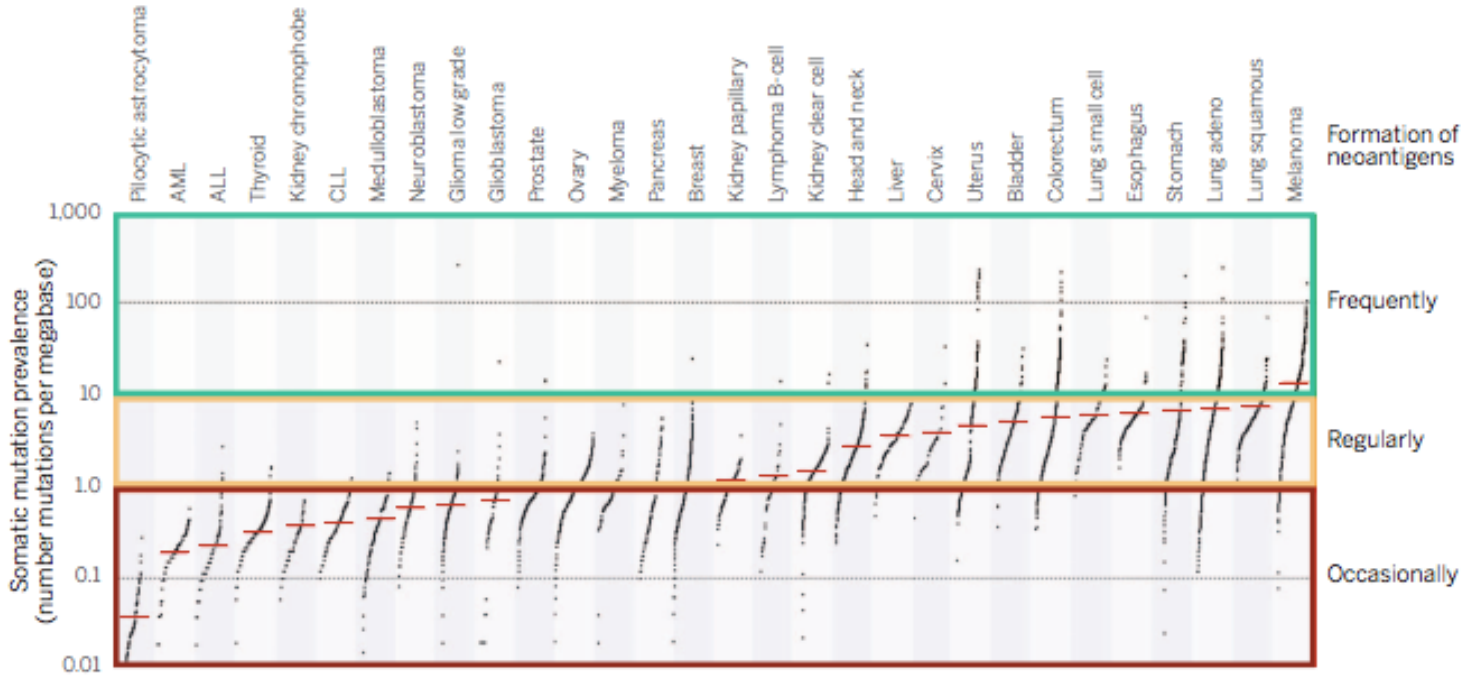

Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Schumacher, T. N., & Schreiber, R. D. (2015). Neoantigens in cancer immunotherapy. Science

Tumor Mutational Burden (TMB) and Neoantigens formation

Nonsynonimous mutations have the potential to generate neoantigens recognized by the host immune system, leading to an antitumor immune response.

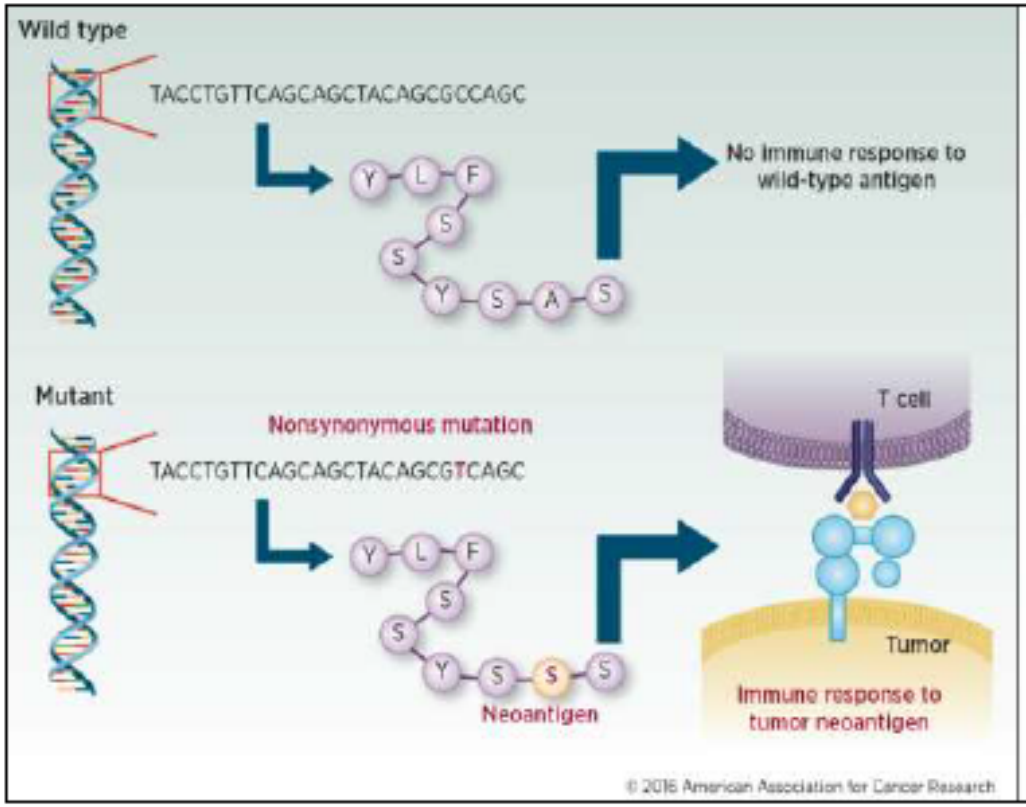

Figure 2.
Generation of neoantigens. Wild-type antigens are recognized as "self" and do not generate an immune response. Nonsynonymous mutations may lead to an altered peptide sequence that is ultimately presented on MHC molecules. This altered peptide sequence, therefore, produces a new or "neoantigen," which may then be recognized by the host immune system, leading to an antitumor immune response.

From Braun DA et al. Clin Cancer Res 2016 22(23): 5642-5650

TMB

TMB or TML: total number of somatic/acquired mutations per coding area of a tumor genome (Mut/Mb)

The number of mutations can vary across different tumor types.

High TMB vs Low TMB

Tumors with high mutation burden have the potential to generate a larger number of neoantigens, making them more immunogenic.

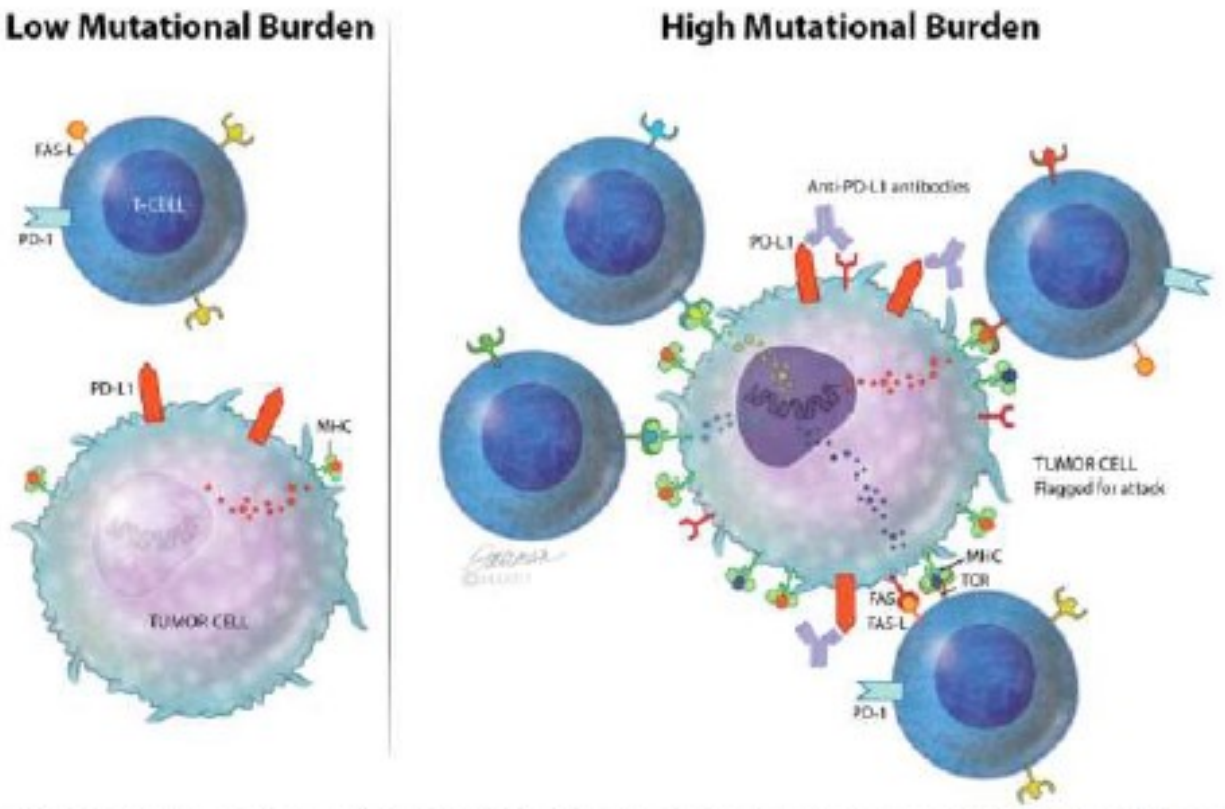

Figure 2. Schematic diagram of tumor cell with high mutational burden and enhanced immune cell recognition compared with tumor cell with low mutational burden.
Abbreviations: FAS-L, Fas ligand; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T-cell receptor.

From Sharabi et al The Oncologist 2017, 22:631–637

ASCO 2019

Tumor mutational burden (TMB) and PD-L1 expression as predictors of response to immunotherapy (IO) in NSCLC.

PD-L1 level	Negative	Low	High
TMB (mut/Mb)			
1	21 (11 - 38)	13 (4 - 39)	43 (29 - 59)
5	25 (15 - 39)	22 (10 - 42)	47 (35 - 60)
10	30 (19 - 44)	39 (24 - 56)	52 (41 - 62)
15	36 (23 - 51)	53 (36 - 70)	56 (44 - 67)
20	41 (25 - 59)	58 (38 - 77)	60 (46 - 73)
30	51 (28 - 73)	51 (21 - 81)	69 (46 - 85)

TMB and PD-L1 expression are independent markers that, when combined, have increased predictive power for response to IO. High TMB + low/neg PD-L1 behaved similarly to low TMB + high PD-L1, and high TMB + high PD-L1 predicted the highest real-world tumor response.

Emily Castellanos et al. , 2019 ASCO Annual Meeting

Grazie per l’attenzione