

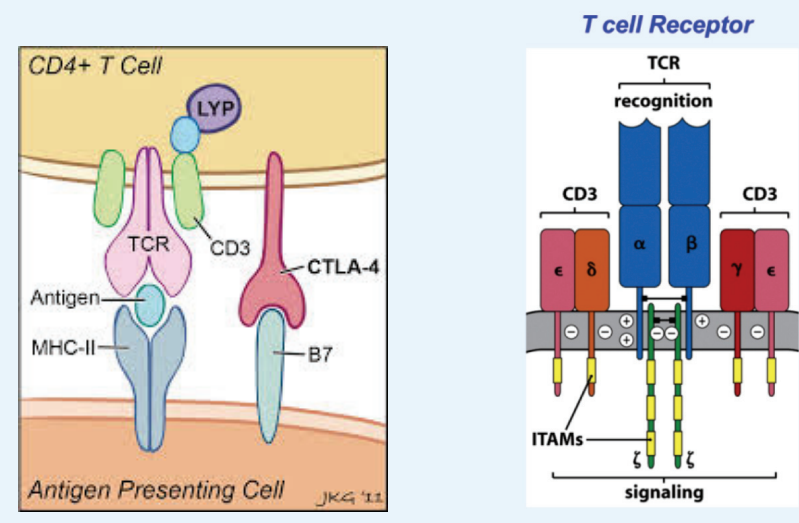
Personalized Immune Therapy For Cancer A Potential Game-Changing Treatment

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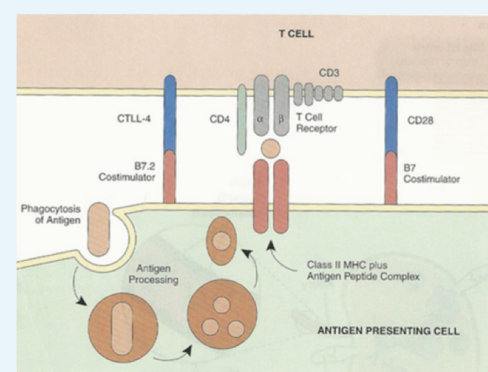
T-CELL RECEPTOR, NORMALLY

T-cell receptors reside on the surface of T-cells, and recognize a specific antigen presented by an MHC molecule
Next, the T-cells become either CD4 or CD8 cells
Co-stimulation is a key step in activating the T-cell; B7 proteins on the surface of antigen-presenting cells interact with CD28/CTLA-4 receptors on the T-cell.



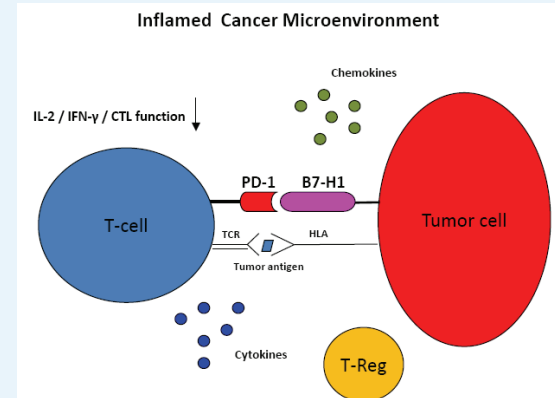
WHAT IS THE T-CELL'S JOB?

T-cells are upregulated in chronic inflammatory states, and cytotoxic T-cells recognize and destroy virally infected cells and tumor cells, Normally, a type of antigen-presenting cells, called dendritic cells, bring information about invaders to the T-cells, and using co-stimulator molecules such as B7, influence T-cells to respond appropriately to the invader. Dendritic cells play a role in orchestrating response to certain cancers. T-cells are trained at an early stage to avoid responding to "self" antigens, a process called immune tolerance.



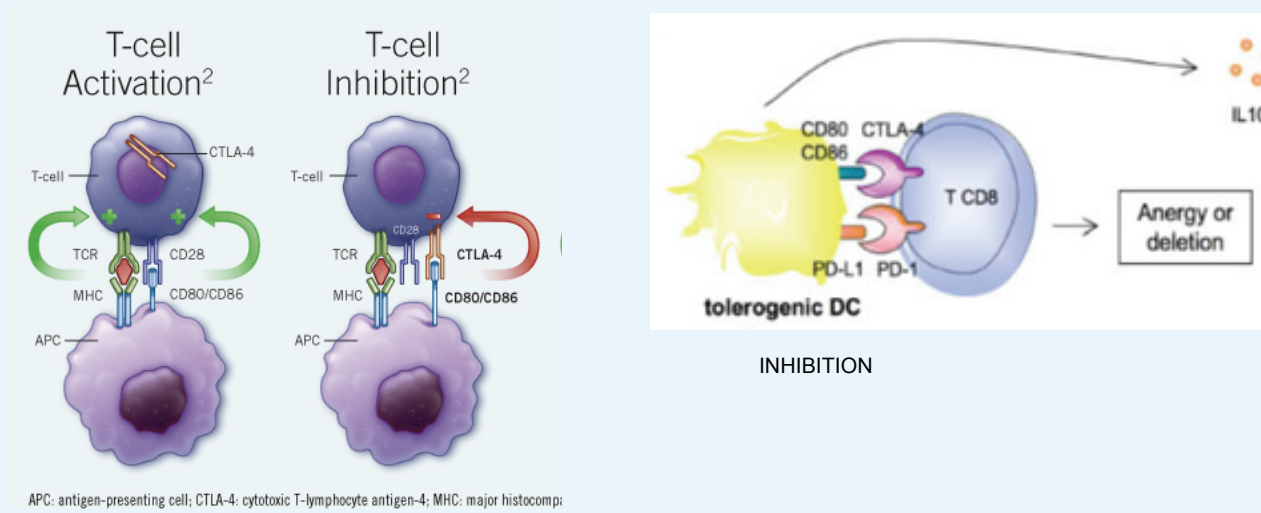
IMMUNE-CHECKPOINT

PD-1 is an immune-checkpoint receptor expressed by activated T-cells, functioning mainly in peripheral tissues where T-cells encounter tumor and stromal cells.



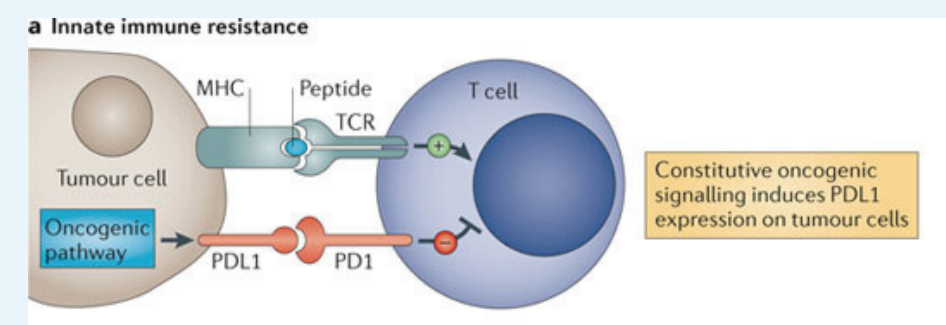
HOW TUMOR CELLS EVADE IMMUNITY

Tumor cells have mechanisms to take advantage of the immune system's intrinsic ability to overcome autoimmunity, hiding from the immune system and avoiding destruction. One of these mechanisms is the hijacking of immune-cell-intrinsic checkpoints that are induced on T-cell activation. These checkpoints include the cytotoxic T-lymphocyte-associated antigen, CTLA-4, whose ligand, B7/CD80 is upregulated on tumor cells. Another inhibitory T-cell receptor is the programmed death 1 receptor, PD-1R, whose ligands PD-L1 and PD-L2 are expressed on tumor cells.



PD-1 RECEPTOR AND PD-1 LIGAND

PD-1 inhibitory receptor is expressed by T-cells during long-term antigen exposure and results in negative regulation upon ligation with PD-1 and 2 ligands. This interaction occurs primarily in inflamed tissues and the tumor microenvironment. PD-1R:PD-1L interactions maintain peripheral tolerance, and are exploited by tumors to evade immune eradication.

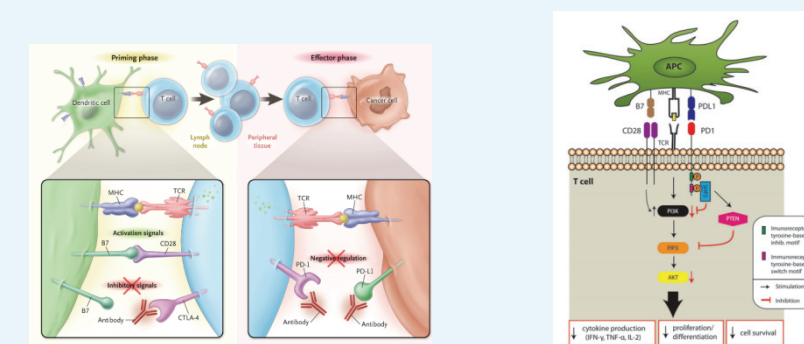


TUMOR MARKERS SERVING AS TREATMENT TARGETS

Her2neu is an abnormal and over-expressed neoantigen in certain tumor cells, namely in Her2+ breast cancers. Trastuzumab is a monoclonal antibody that targets Her2 and kills the expressing cell. Vascular endothelial growth factor is a normal protein that is over-expressed in various tumors. Bevacizumab attaches to this protein and prevents formation of new blood vessels in the tumor

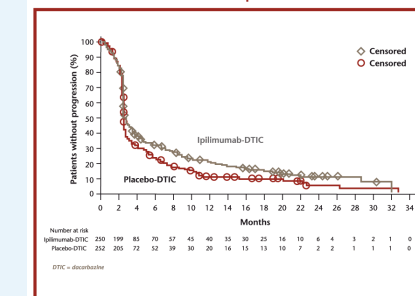
DOWNREGULATION OF PD-1R OR ITS LIGAND

A novel treatment for metastatic melanoma takes advantage of this PD-1 receptor and its ligand that directly deliver immune suppressive signals. Anti-PD-1 and anti-PD-L1 monoclonal antibodies are used to prevent the inhibition of T-cells that can then go on to eliminate tumor cells. Two antibodies have been studied: nivolumab (anti-PD-1R) and lambrolizumab (anti-PD-1R).

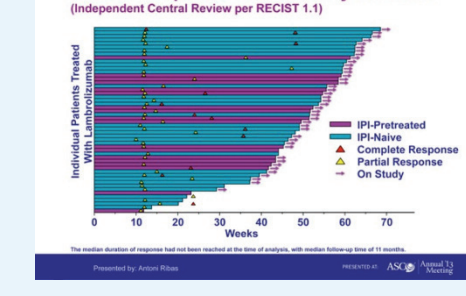


A COMPARISON TO PREDECESSORS

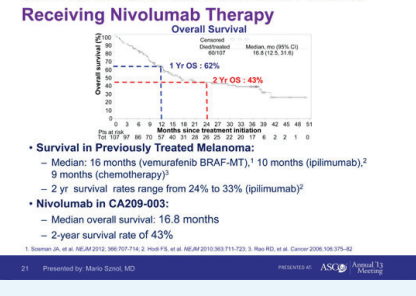
Figure 6. Progression-free survival for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients²²



Time to Response and On-Study Duration (Independent Central Review per RECIST 1.1)



Survival in Advanced Melanoma Patients Receiving Nivolumab Therapy



WHY THIS WILL "CHANGE THE GAME"

PD-1 and PD-L1 antibodies have been named "Drug of the Year" by the European Journal of Cancer. The highly tumor-selective immune suppressive signals, along with PD-1 regulation primarily in the effector phase of T-cell response, have allowed for decreased side effects and improved anti-tumor activity compared to CTLA-4 inhibition. Anti-PD1 and anti-PDL1 have broken the previous ceiling of durable tumor response rates of 10-15%, and have yielded responses in advanced melanoma, refractory non-small cell lung cancer, and renal cancer. It has shown anti-tumor activity in liver, lung, lymph node, and bone metastases.

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