

Basic Principles of Cancer Immunotherapy

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Disclosures

- SAB - Alector, Ascend Biopharmaceuticals, SBI Biotech, Avipep, Avidbiotics, Five Prime Therapeutics, Atreca, Nkarta, Virtuoso, Valitor, Dragonfly, Obsidian
- Ad hoc consulting – Nohla, Novartis, Merck, Pulse
- Ownership Interest less than 5%: Vivance, Valitor, Dragonfly, Avidbiotics, Nkarta, Five Prime, AviPep, Ascend, Pulse. And some stock in Alector, Five Prime, Atreca, and Merck
- I will not be discussing non-FDA approved indications during my presentation.

The Premise of Cancer Immunotherapy

- Normally, the immune system can eliminate damaged cells, including pre-cancerous and cancer cells
- To escape, tumors evolve mechanisms to locally disable the immune system

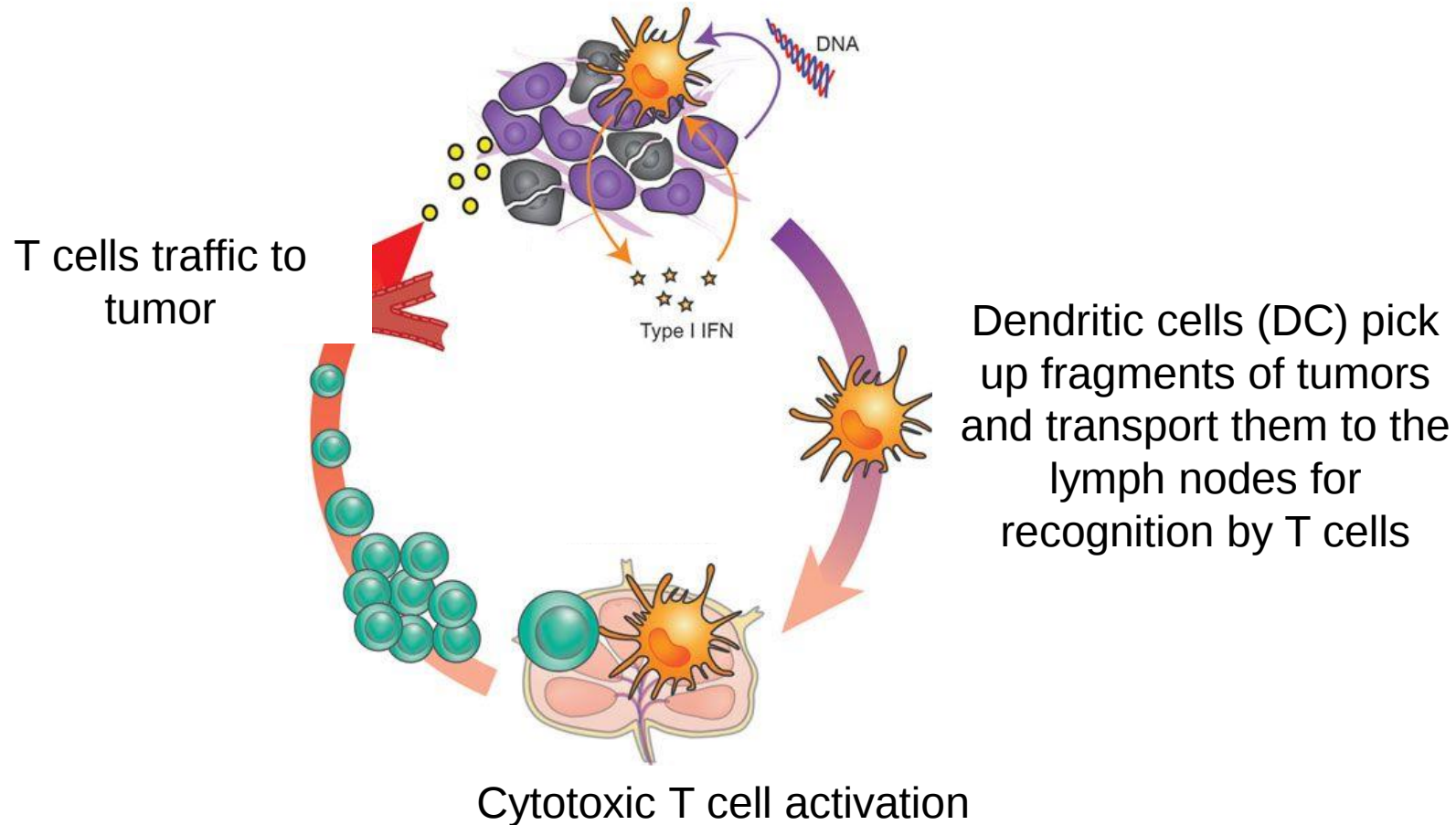
The goal of immunotherapy is to generate or restore the capacity of the immune system to recognize and eliminate cancer

Two major mechanisms of tumor immune escape

- **Cancer renders immune cells dysfunctional**
chronic stimulation by tumors or factors they secrete can “exhaust” or suppress immune cells
- **Tumors hide from the immune system**
tumors become resistant to the immune system by lacking or losing molecules that immune cells recognize to become activated

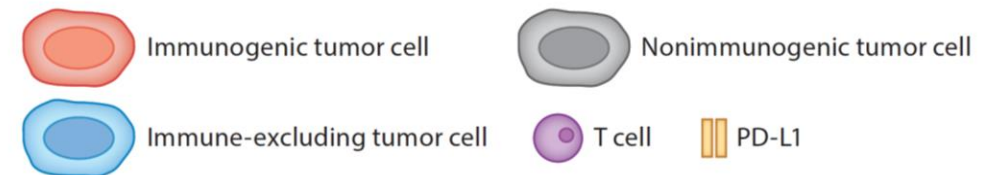
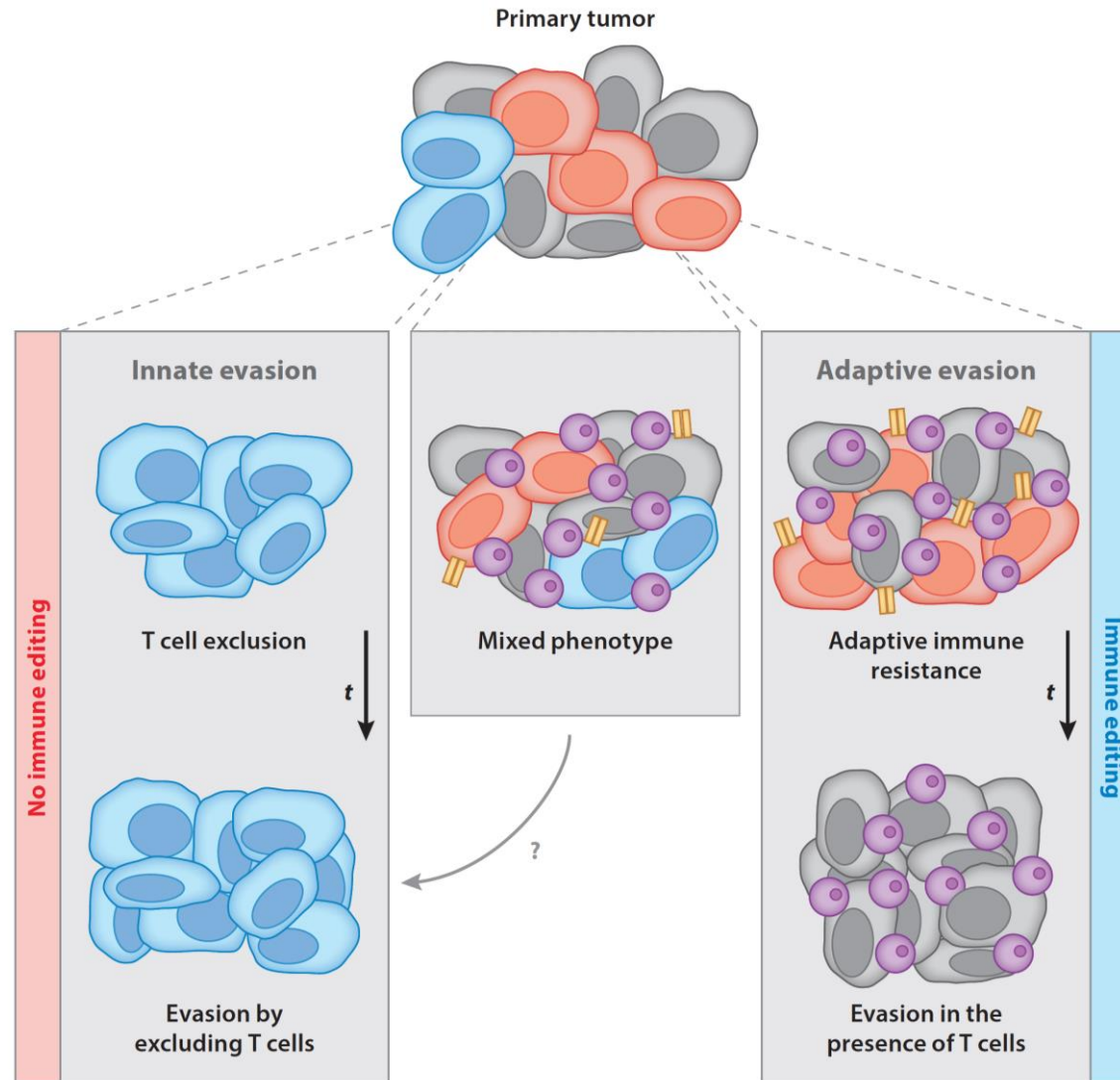
Initiation of an anti-tumor immune response

Innate immune cells interact with tumor



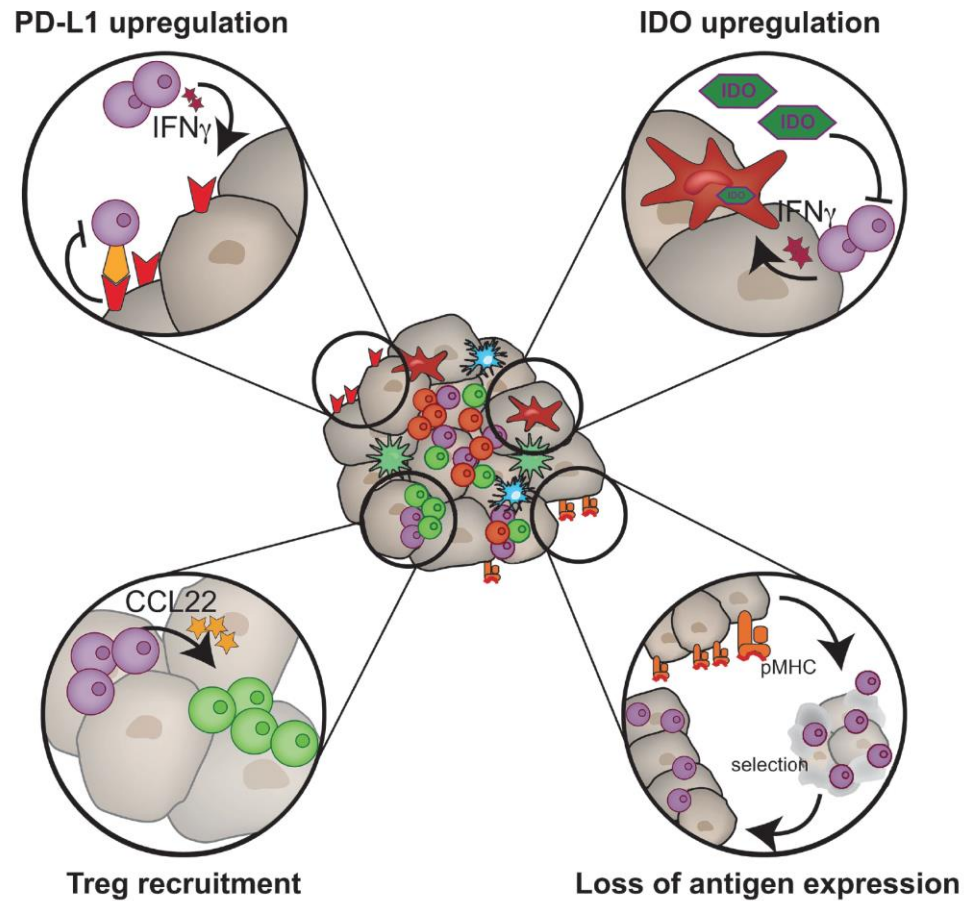
Cytotoxic T cell activation

Immune system “edits” tumors – some are detected and killed – others invisible to immune cells escape



Tumor microenvironment is immune suppressive

T cell-inflamed tumor microenvironment



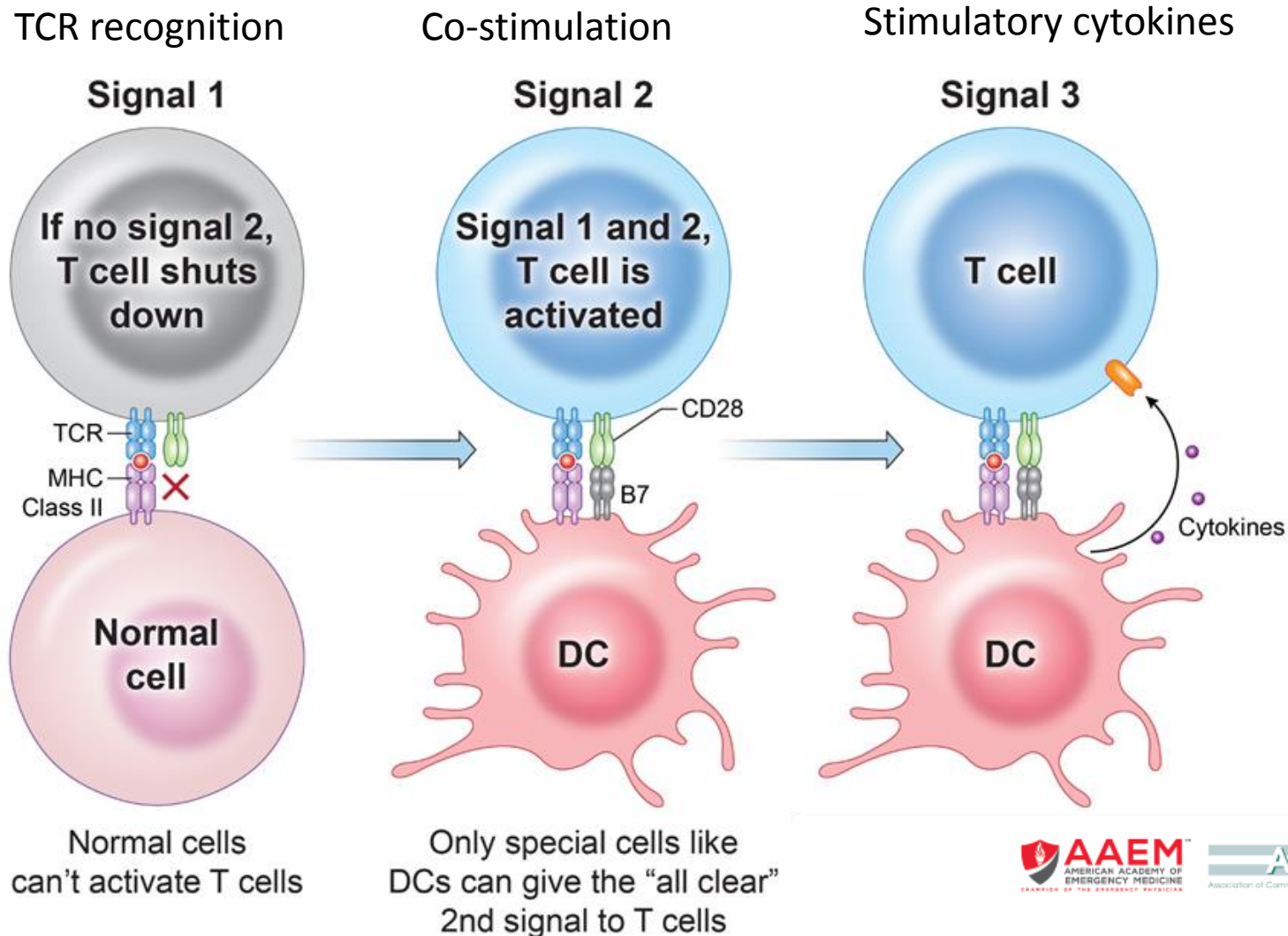
Tumors escape by suppressing T cell function or by losing molecules that immune cells recognize to become activated



Types of Immunotherapy

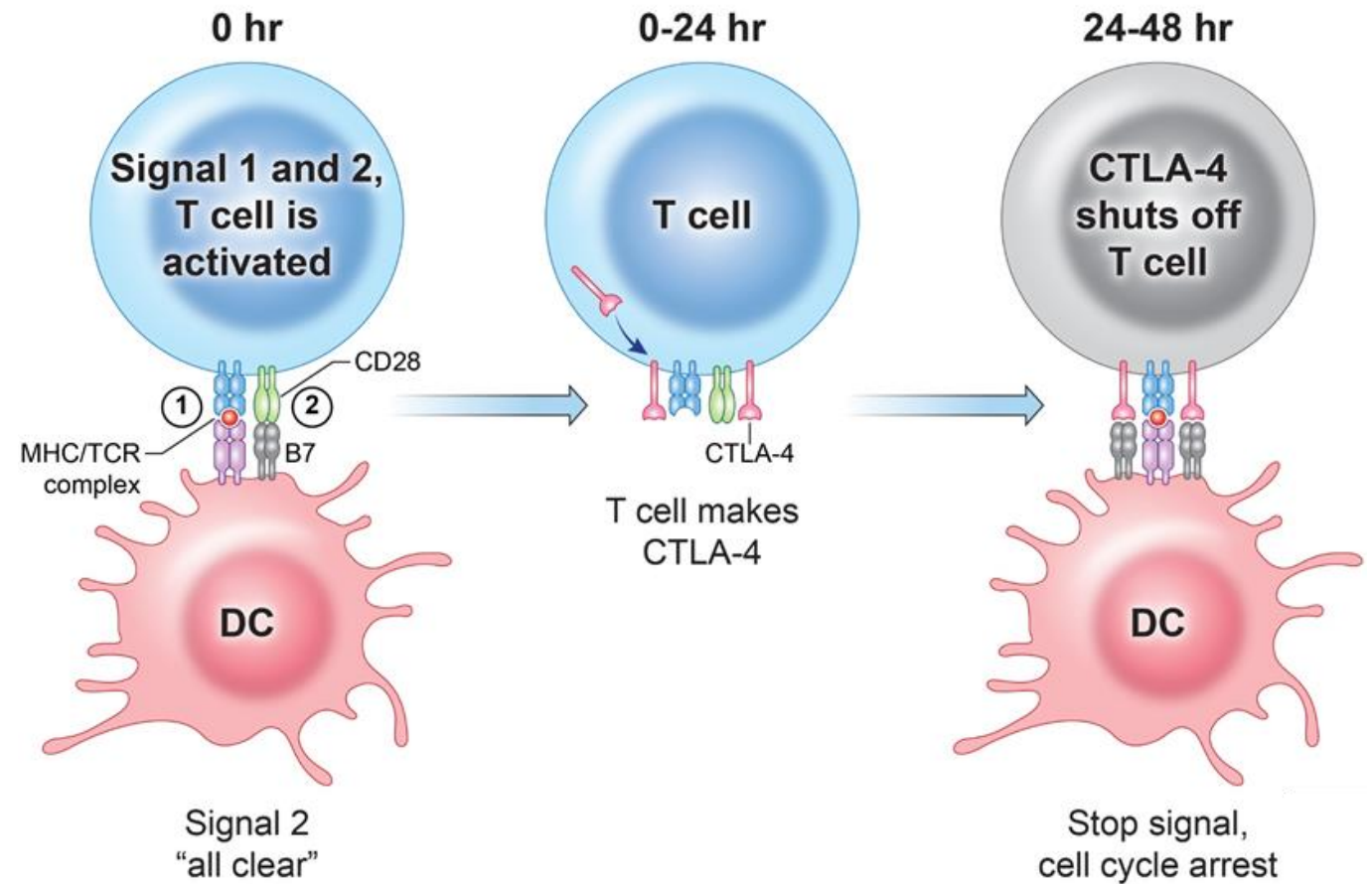
- Checkpoint blockade immunotherapy
- Cancer vaccines
- Adoptive cell transfer
- Effector antibodies
- Innate immune activation

T cells need 3 signals to respond – no response if these are absent



CTLA-4 checkpoint blocks the 2nd signal for T cells

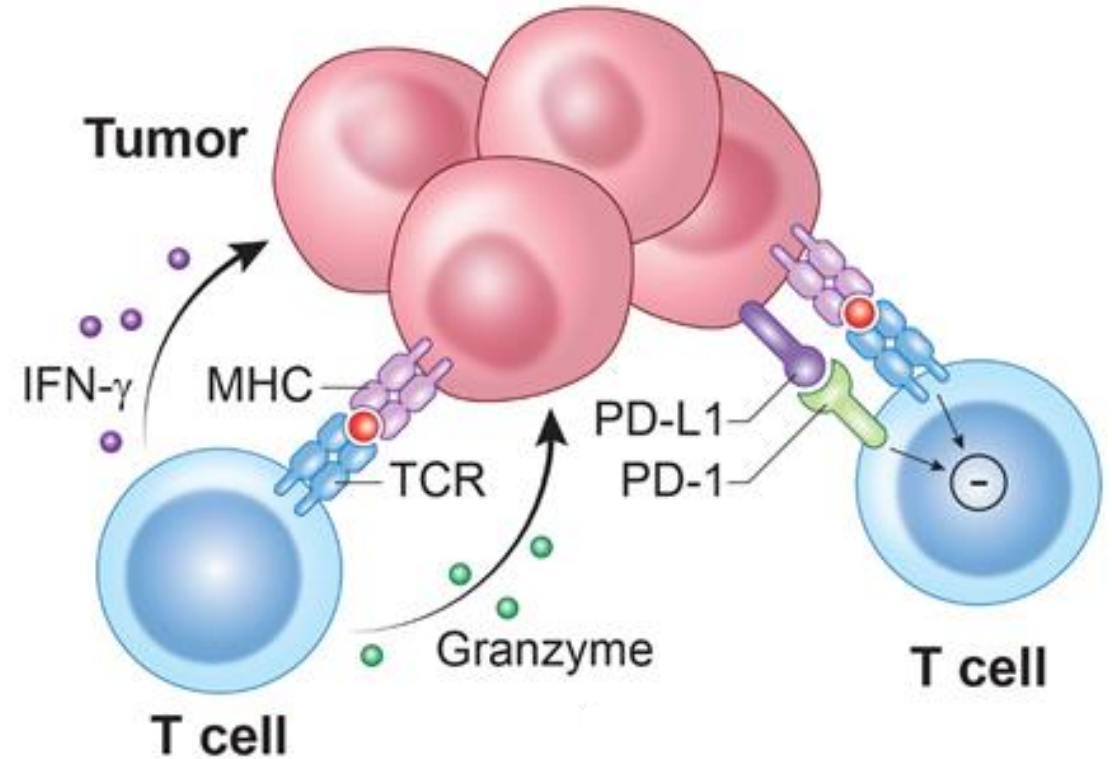
TCR stimulation up-regulates the CTLA-4 inhibitory receptor – that blocks co-stimulation by the 2nd signal



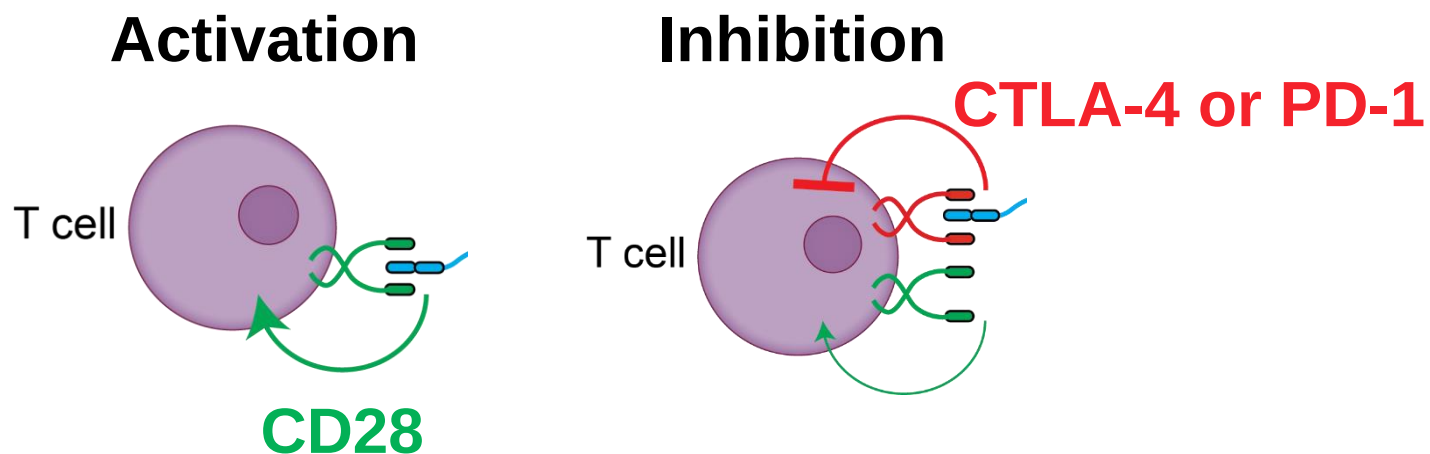
PD-1 checkpoint blocks T cell function at the tumor site

TCR stimulation also up-regulates the PD-1 inhibitory receptor on T cells

At the tumor site, PD-1 engages its ligands (PD-L1 or PD-L2) to suppress function of the T cells



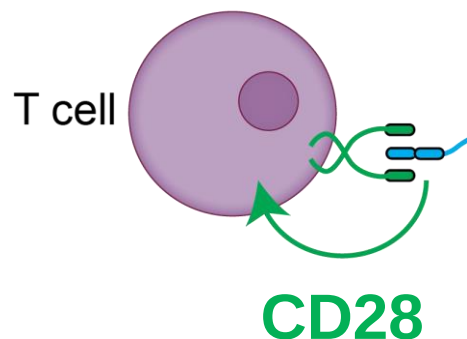
Checkpoint antibody blockade therapy unleashes the “brakes” on T cells



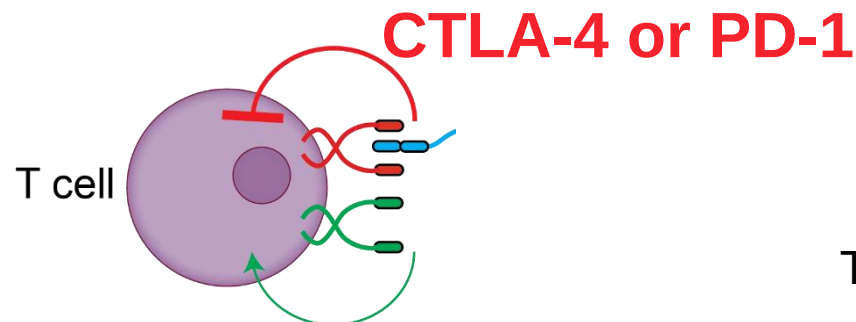
Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint antibody blockade therapy unleashes the “brakes” on T cells

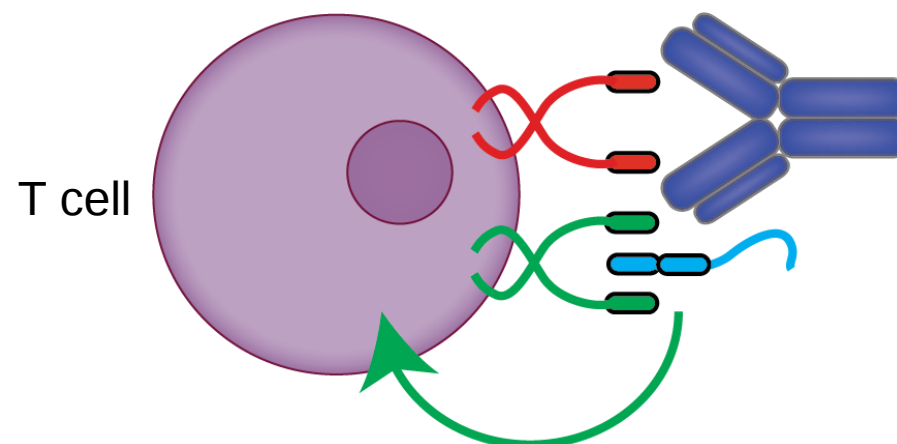
Activation



Inhibition



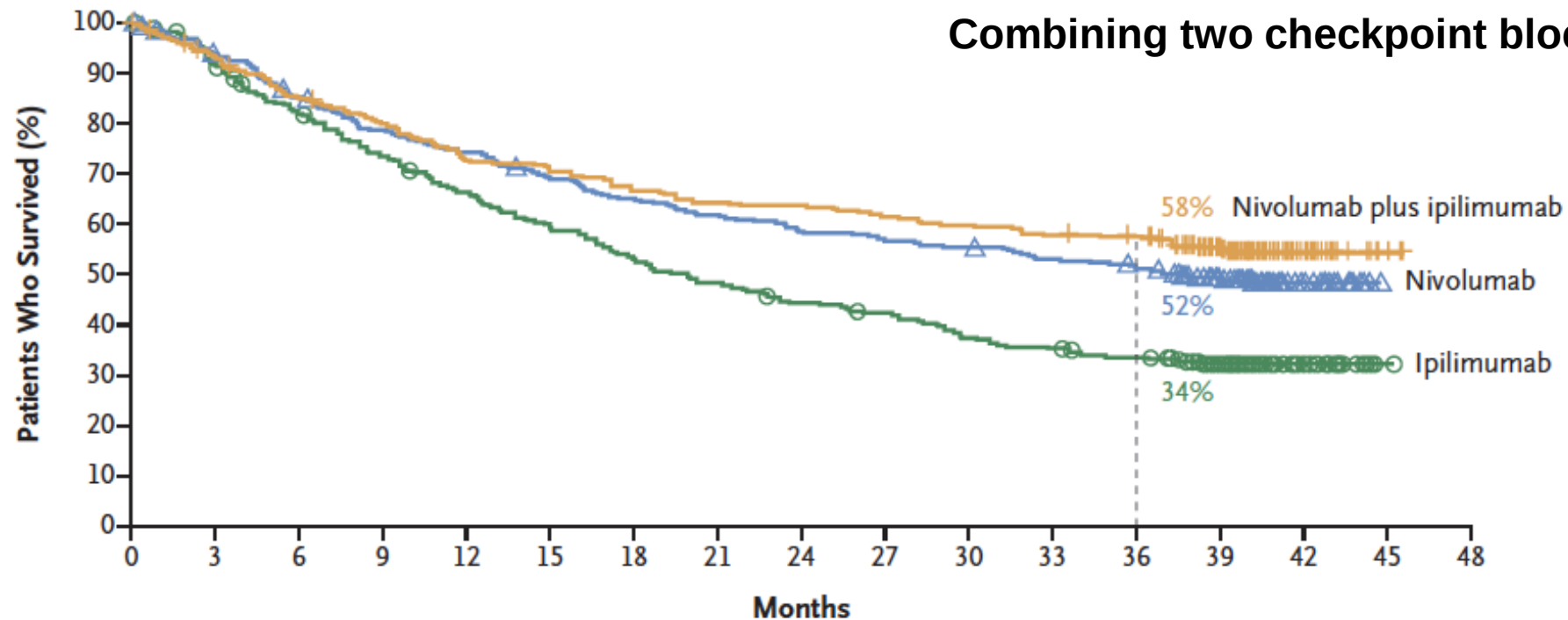
Re-Activation with anti-PD-1 or anti-CTLA-4 antibodies



Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions

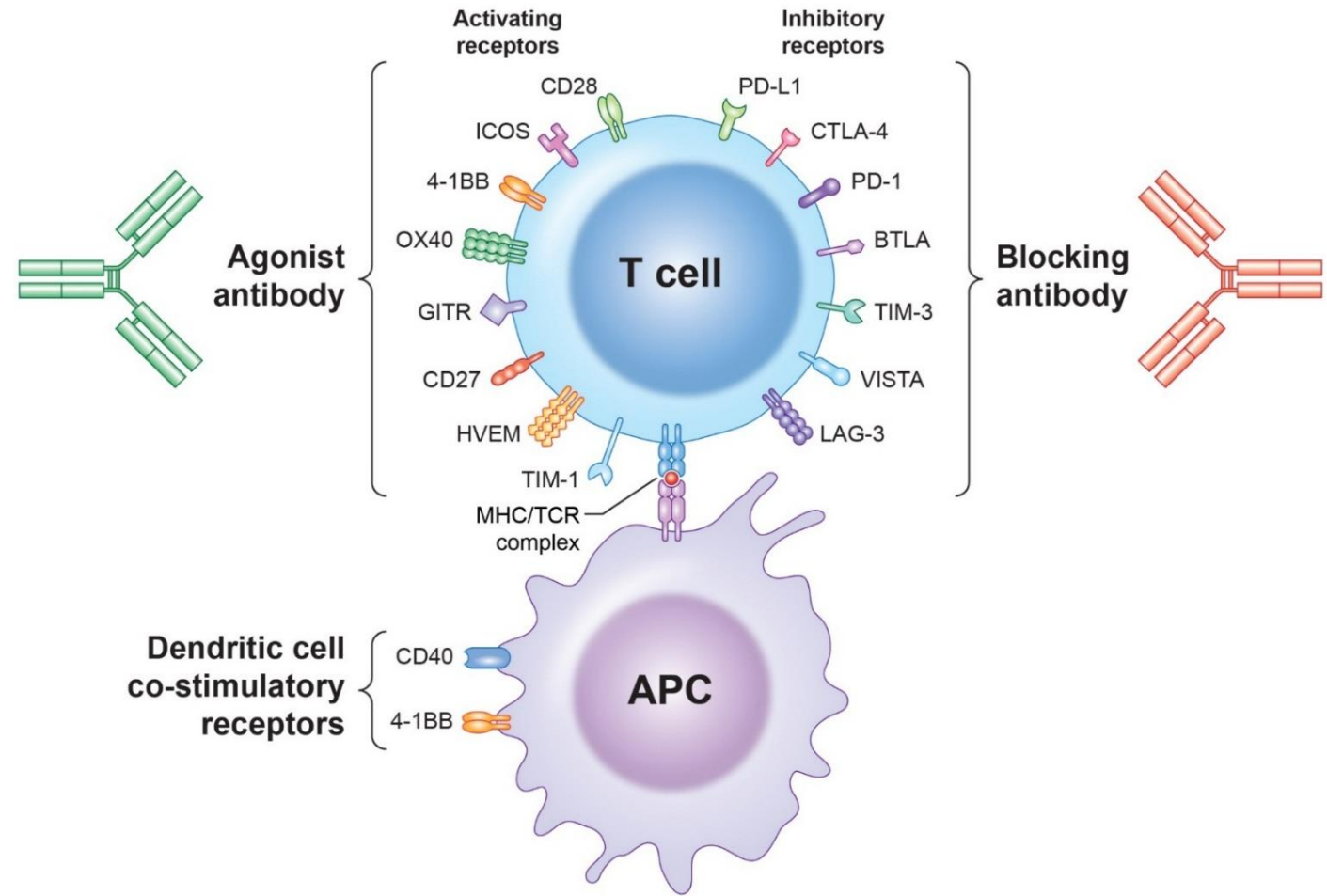
Combination Immunotherapies

Dual CTLA-4 and PD-1 inhibition



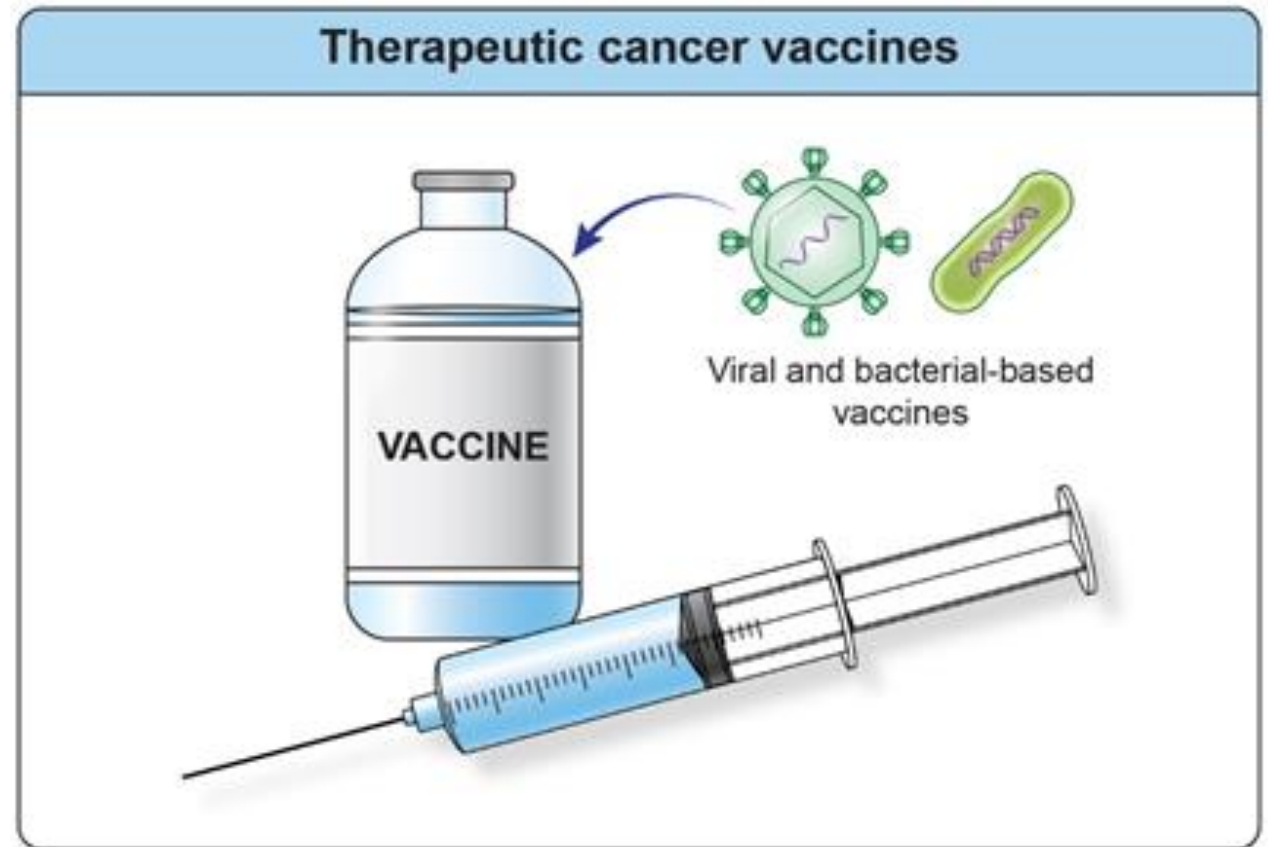
Block the inhibitors or boosting the activators

- Blocking inhibitory receptors
- Boosting the activating receptors



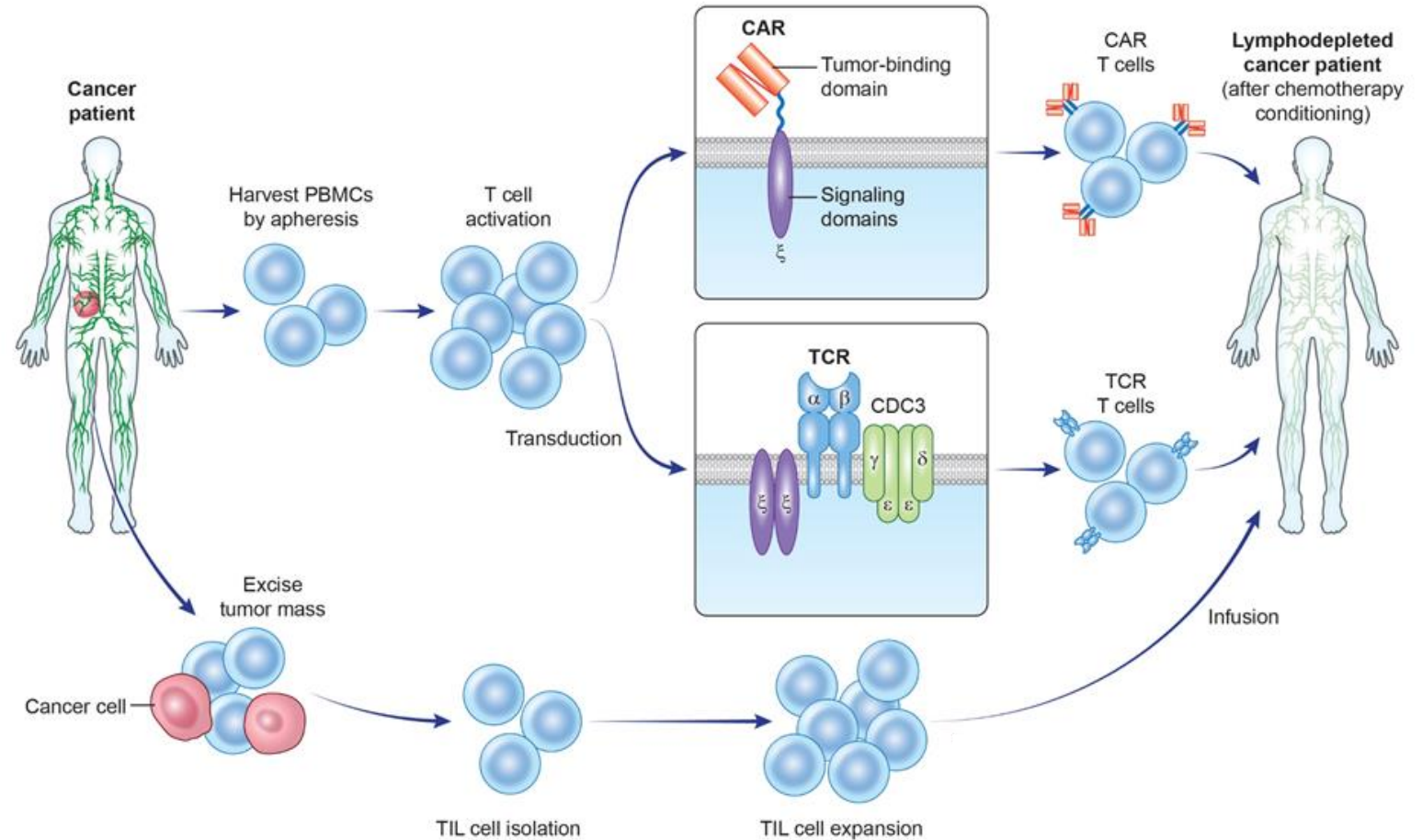
Therapeutic Cancer Vaccines

Goal: induce or boost
immune response against
tumor-specific antigens



Adoptive Cell Therapy

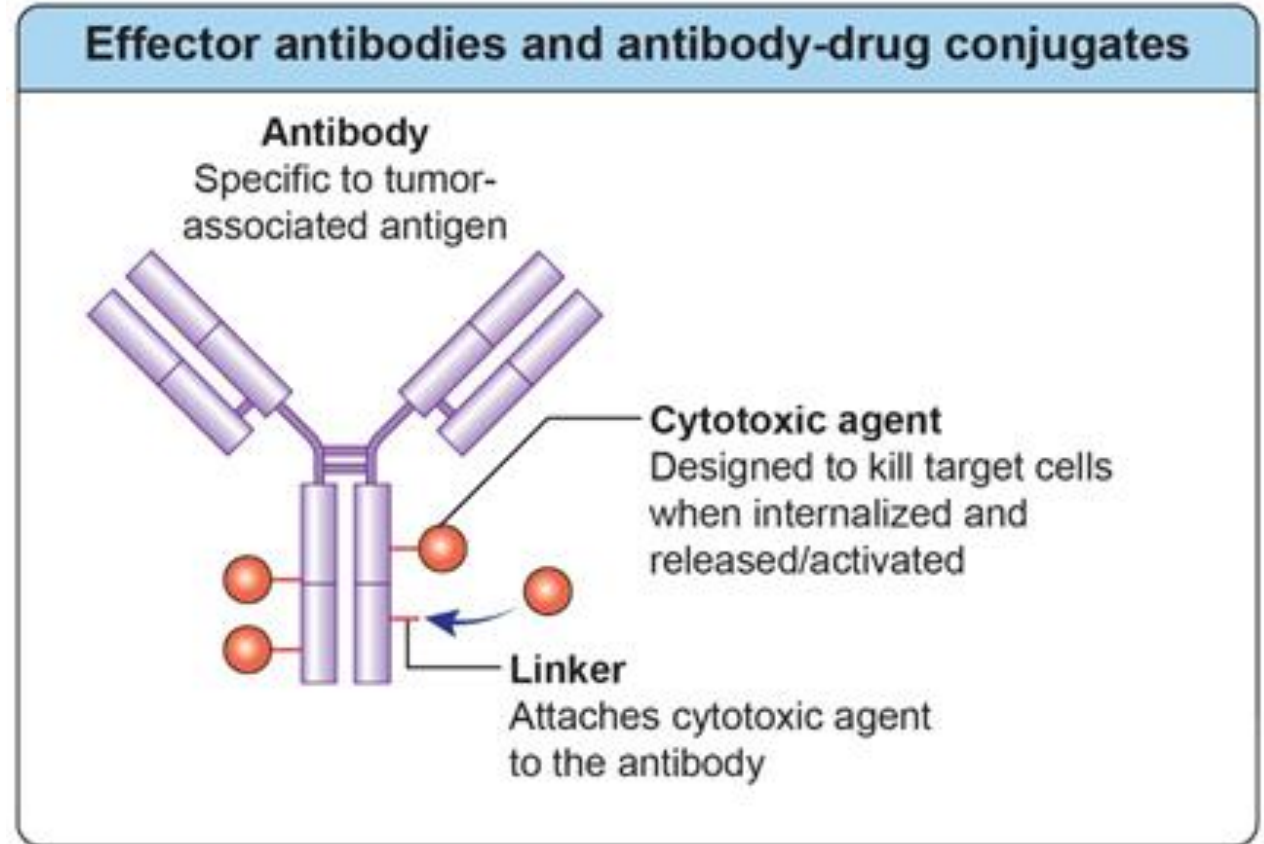
Goal: Expand or engineer tumor-specific T cells and re-infuse for more efficient anti-tumor responses



Antibodies and Antibody-Drug Conjugate (ADCs) Therapy

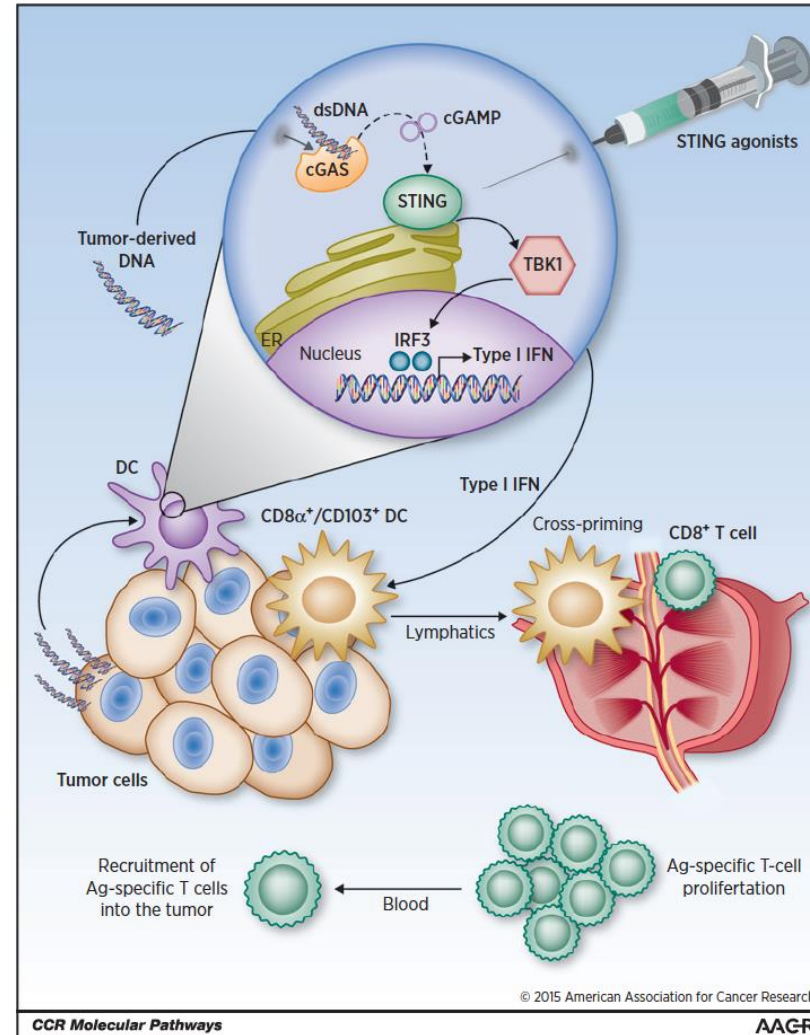
Goal: treat with
tumor-specific
antibodies to allow
innate immune cells to
kill tumors

or deliver
chemotherapeutics
directly to the tumor



Innate immune activation

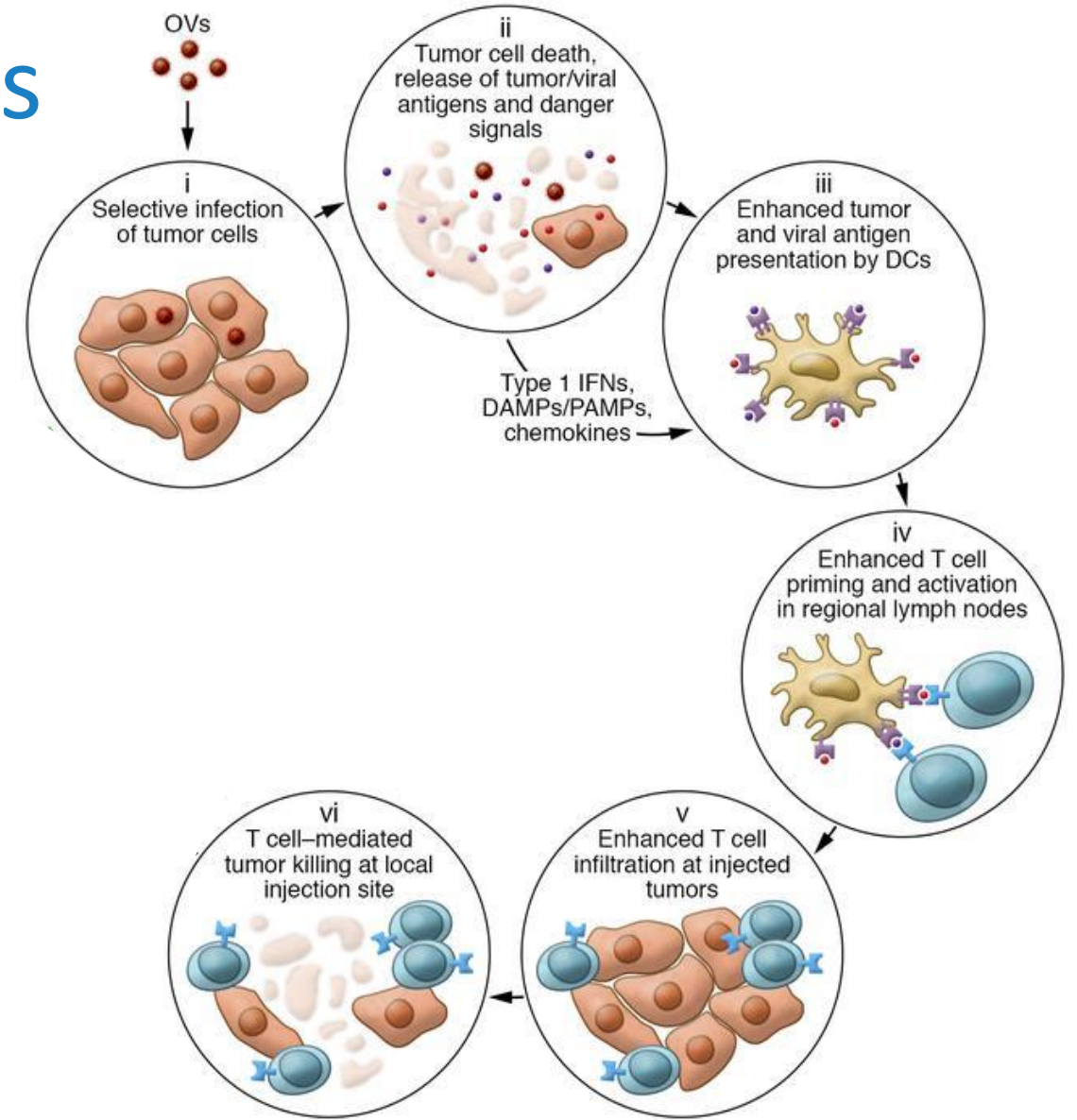
Goal: enhance innate immune sensing by providing stimulatory agents (frequently into the tumor itself)



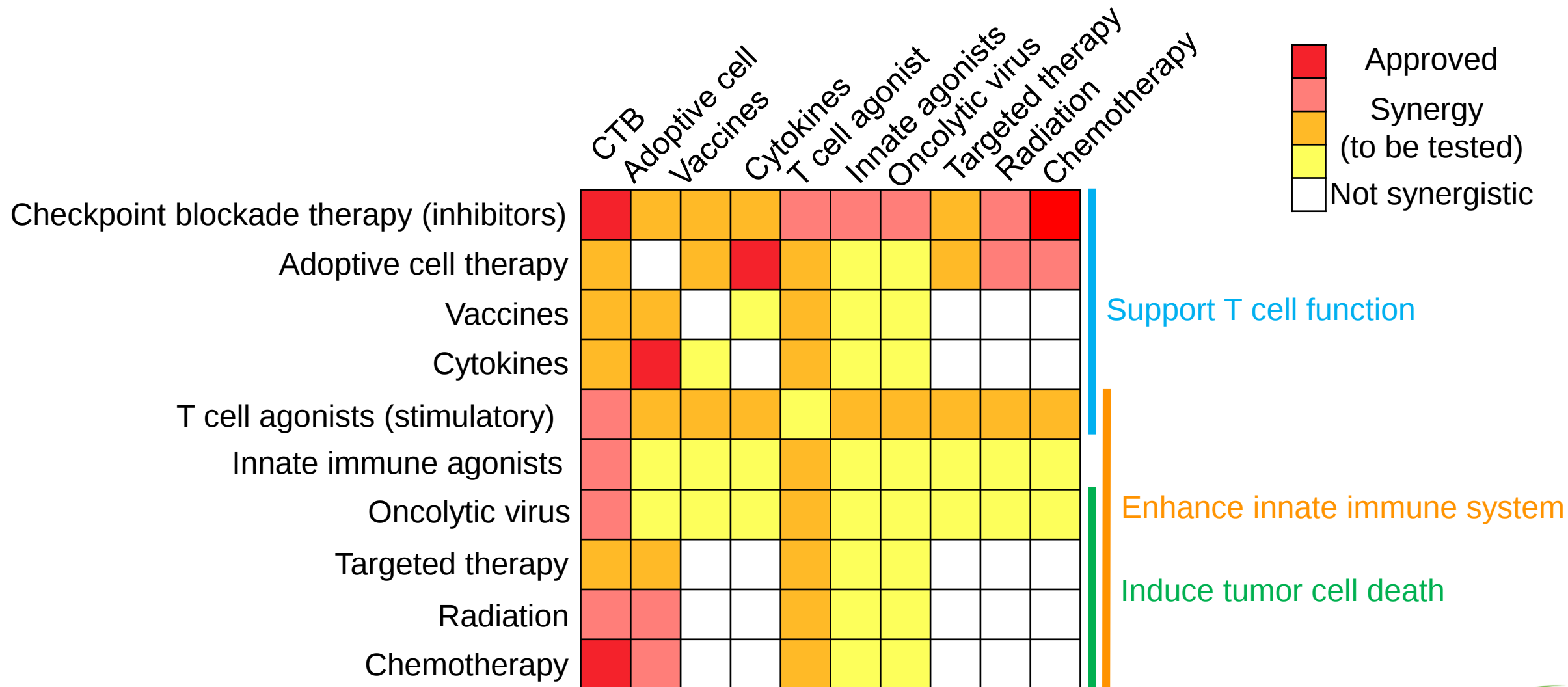
Agents:
 Sting agonists
 TLR agonists
 Cytokines
 Antibodies

Oncolytic Viruses

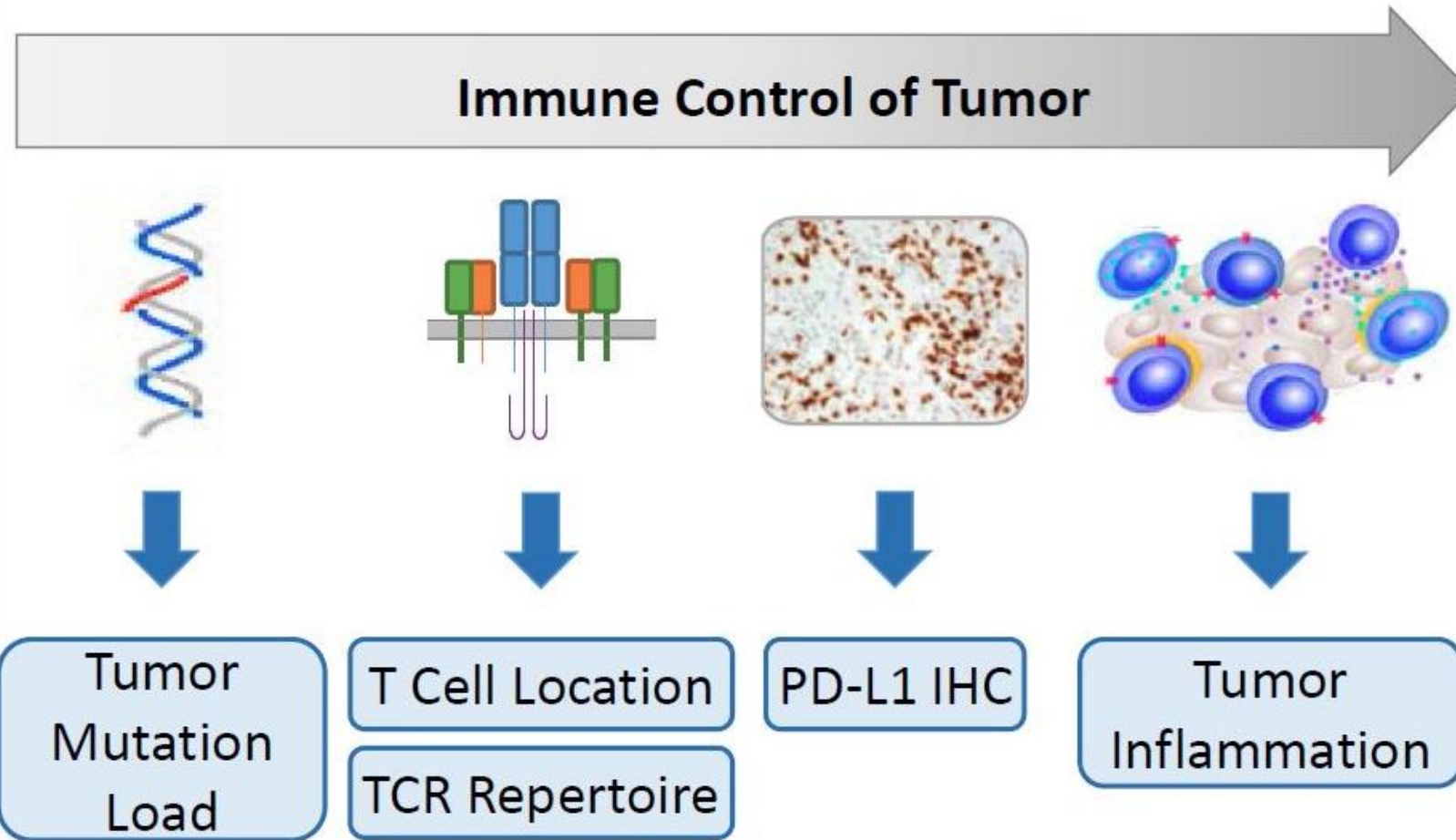
Goal: target and kill tumor cells through viral replication
 AND release innate immune activators and tumor antigens



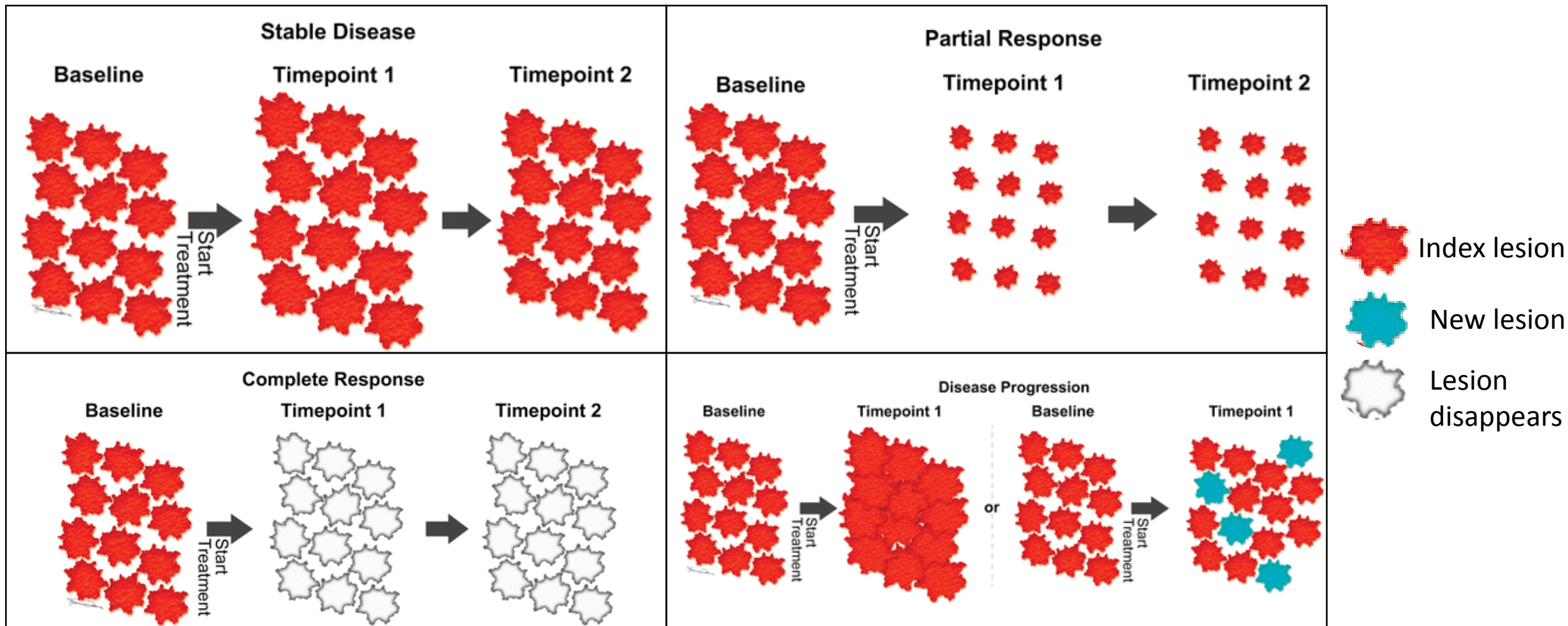
Combination Immunotherapies



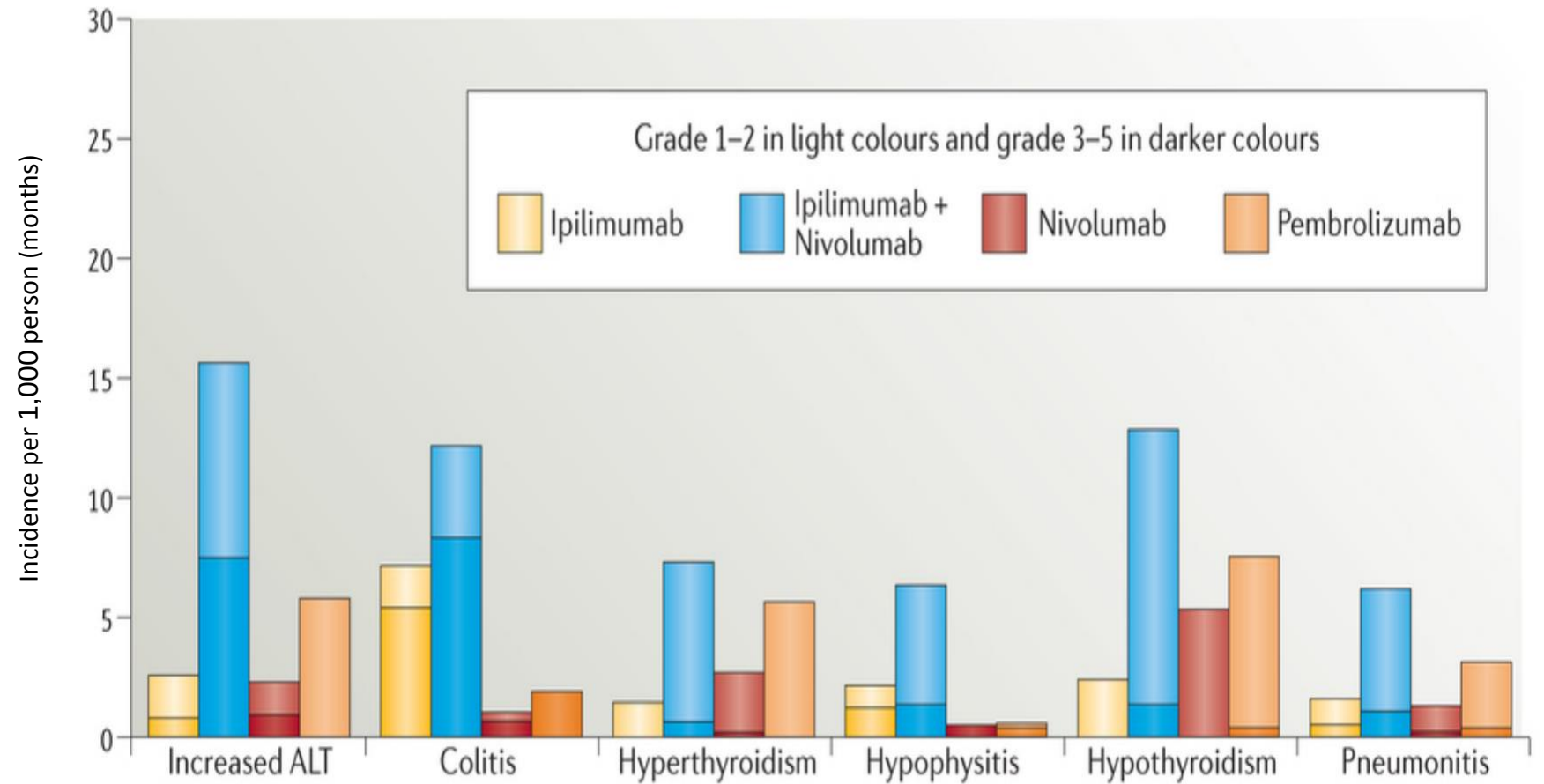
Immunotherapy Biomarkers



Many possible outcomes

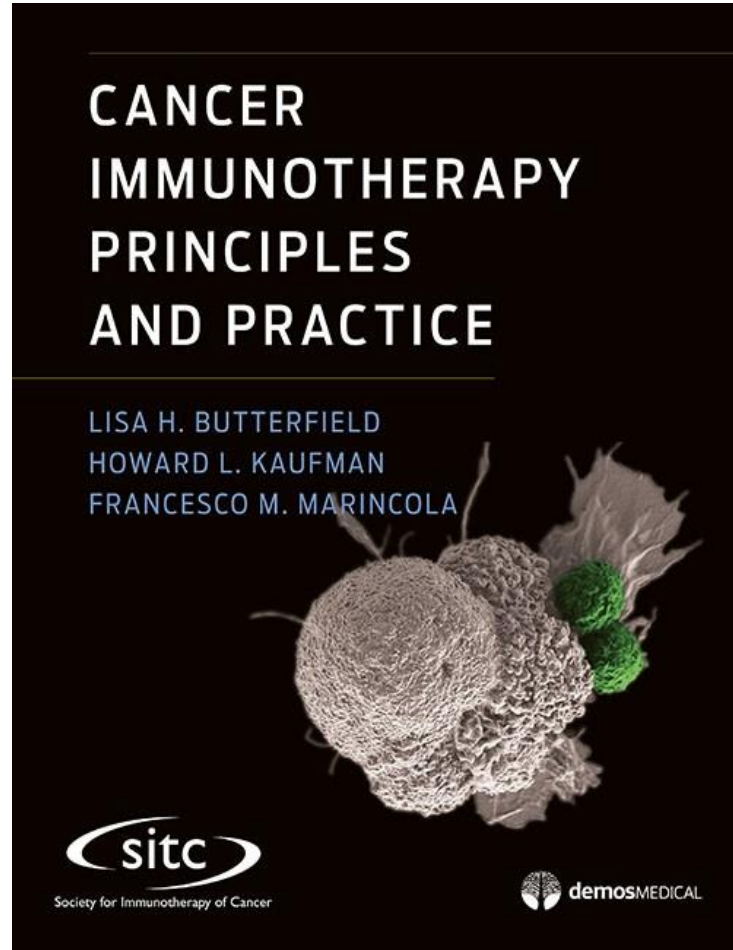


Immune-related Adverse Events Associated with Checkpoint Inhibitor Combinations



Boutros et al., *Nature Reviews Clinical Oncology*, 2016

Further Resources



SOCIETY FOR IMMUNOTHERAPY OF CANCER

