Basic Principles of Cancer Immunotherapy

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Disclosures

- Nothing to disclose

- I will not be discussing non-FDA approved indications during my presentation.

The Premise of Cancer Immunotherapy

- Normally, the immune system eliminates damaged cells, including precancerous and cancer cells

- To escape, tumors evolve mechanisms to locally disable the immune system.
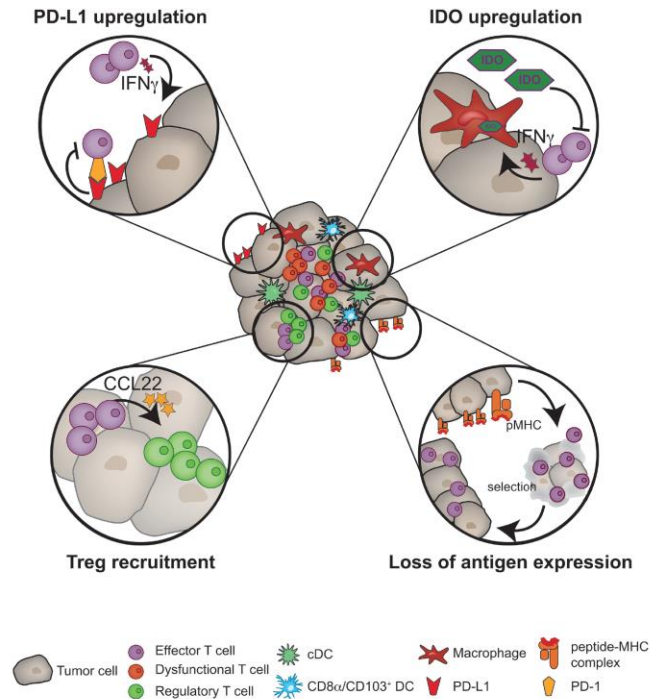
The goal of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.

# Two major mechanisms of tumor immune escape

- **Render the immune response dysfunctional:** Cytotoxic (CD8+) T cells often become dysfunctional or exhausted during chronic stimulation (chronic viral responses or responses against tumors). To enhance T cell dysfunction, the tumor microenvironment upregulates a suite of suppressive molecules.

- **Avoiding an immune response:** A state in which the tumor remains invisible to the immune system. Many features of tumors can result in immune exclusion/avoidance including lack of antigens (T cells don't "see" anything on the tumor) or active immune repellents.

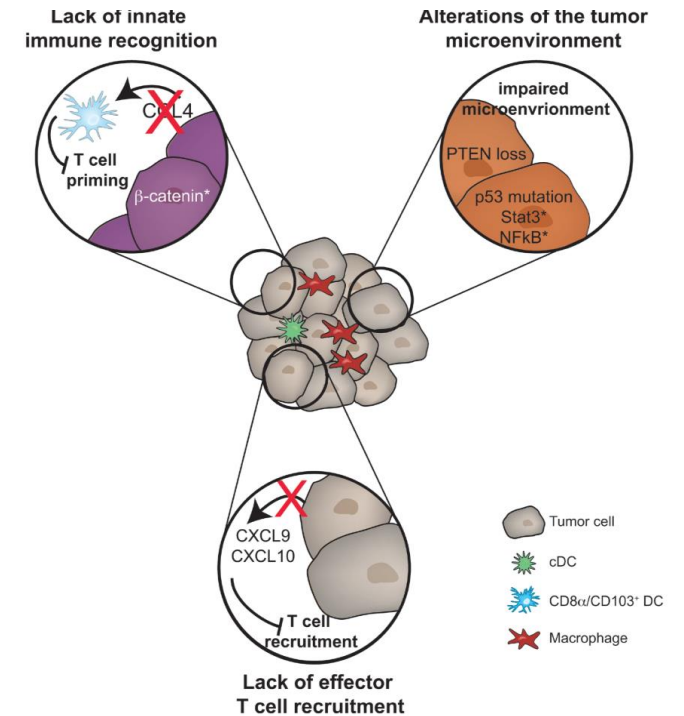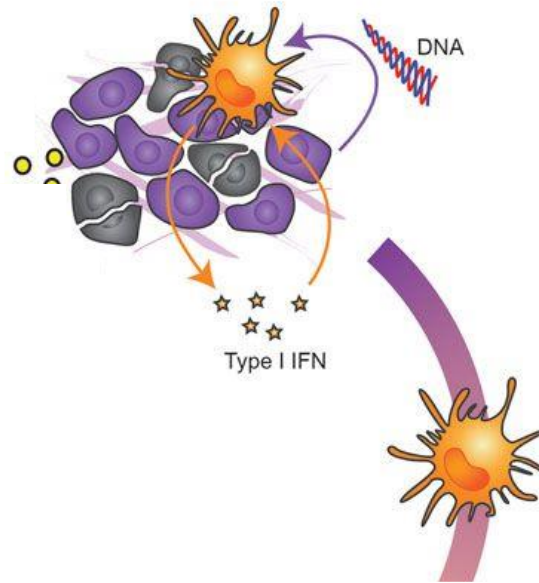# Immune evasion

T cell-inflamed tumor microenvironment
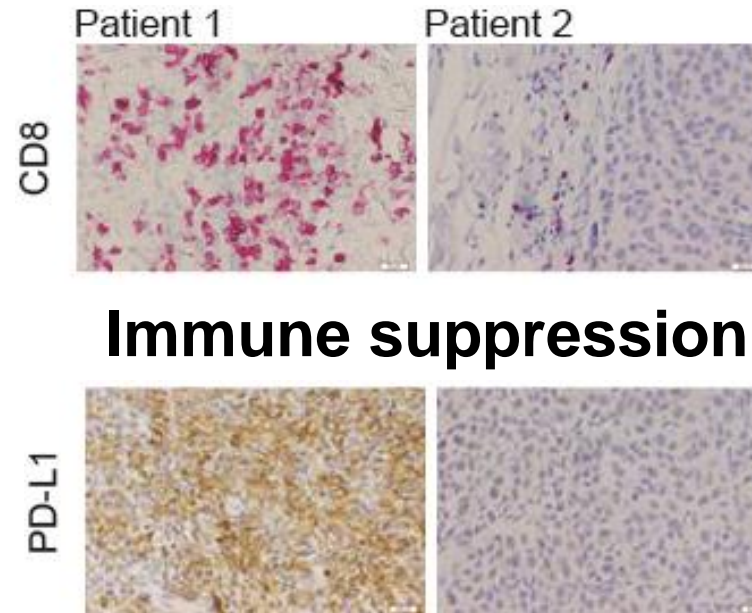
Non-T cell-inflamed tumor microenvironment

T cells

Immune suppression

Spranger *et al.*, STM 2013
Spranger, Internat Immunol. 2016

Initiation of an anti-tumor immune response

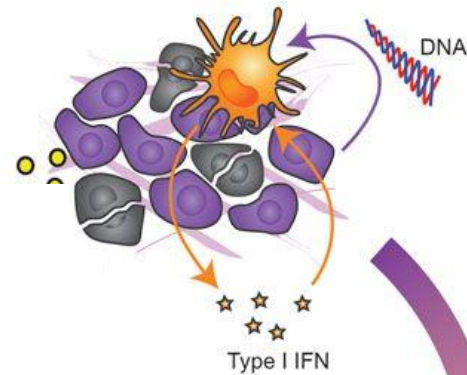Innate immune sensing (i.e. Sting activation)

DNA

Type I IFN

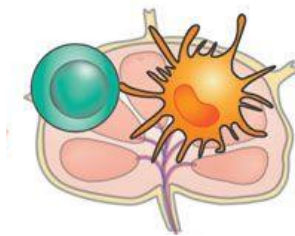APC maturation
&
Transport to lymph node

Shanker *et al*. J Immunol 2007
Modified from Corrales *et al*. Cell Res. 2017

Initiation of an anti-tumor immune response
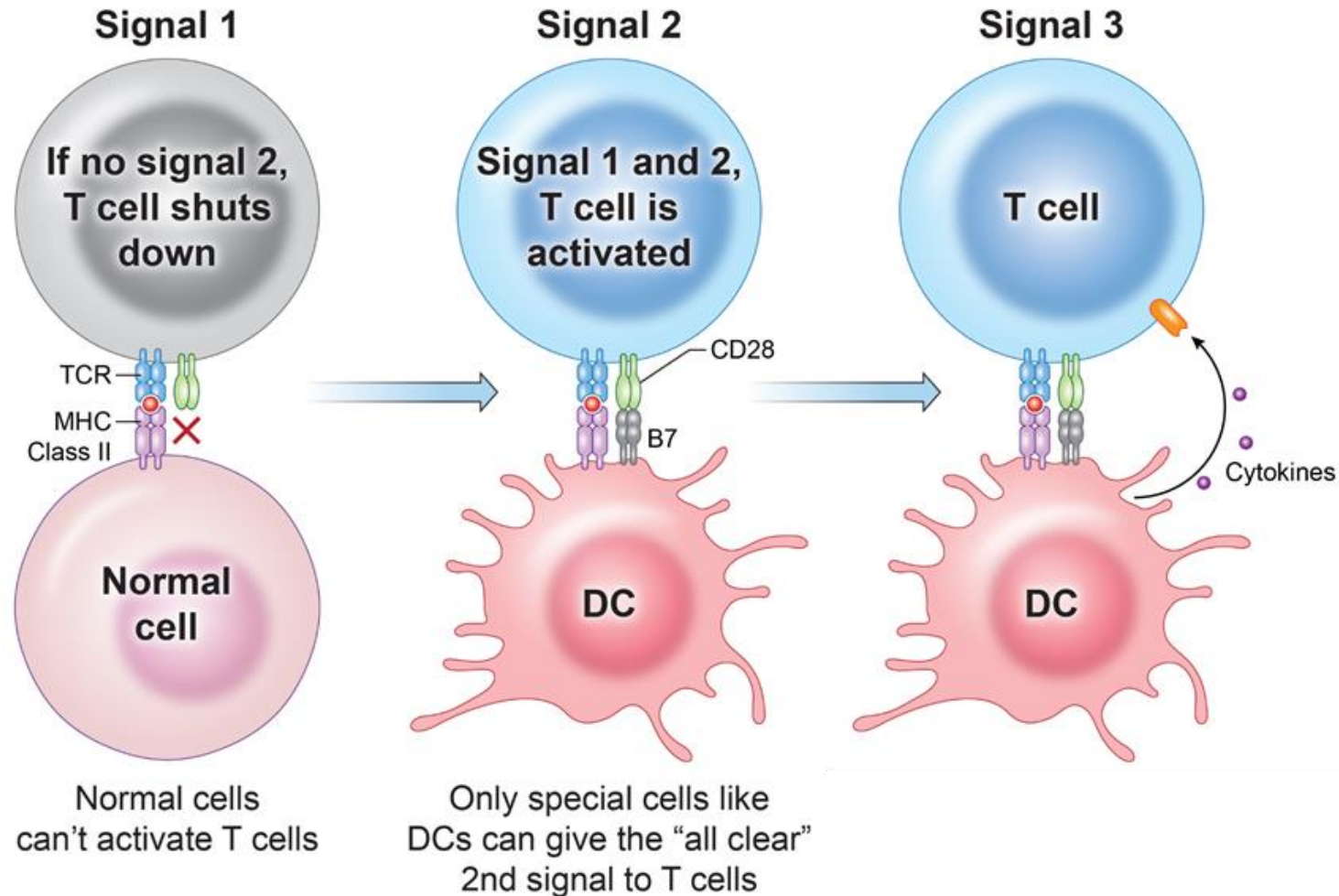
Innate immune sensing (i.e. Sting activation)
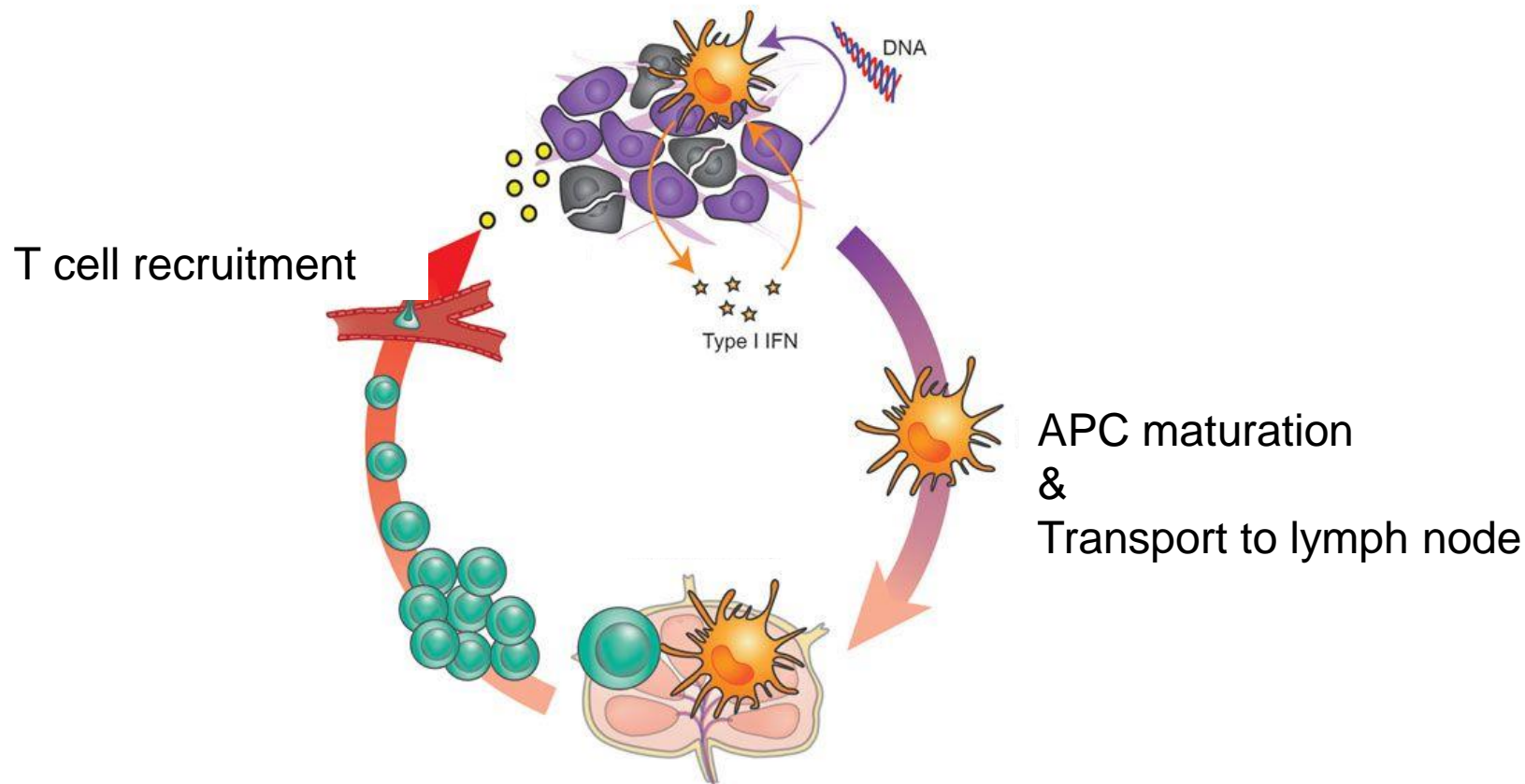

APC maturation
&
Transport to lymph node

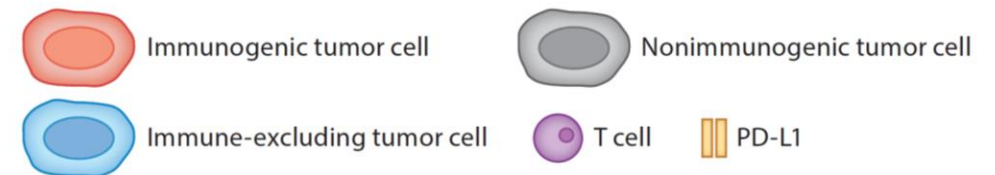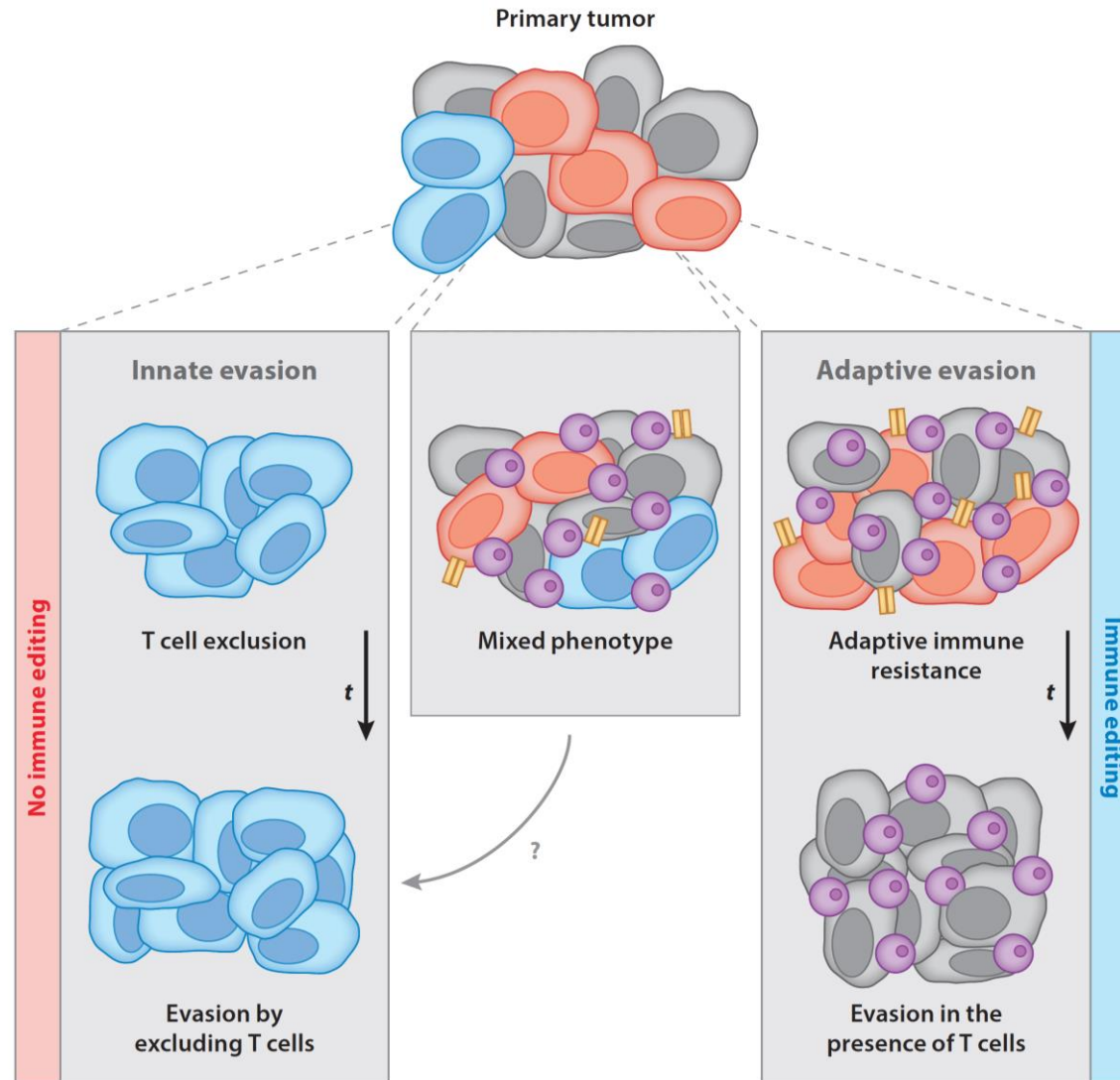Cytotoxic T cell activation

Antigen-Specific T cell Activation

Initiation of an anti-tumor immune response

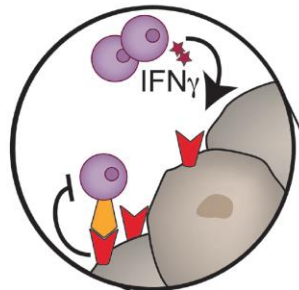Innate immune sensing (i.e. Sting activation)

T cell recruitment

APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Immune evasion occurs over time

Spranger, AR Cancer 2018

T cell inflamed tumor microenvironment is immune suppressive

T cell-inflamed tumor microenvironment
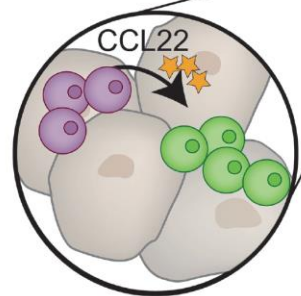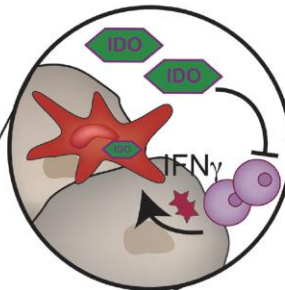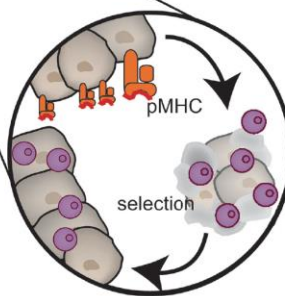
T cell-inflamed tumors escape by suppressing T cell function

Spranger, Internat Immunol. 2016

Tumor immune evasion in a non-T cell-inflamed tumor microenvironment

Non-T cell-inflamed tumor microenvironment
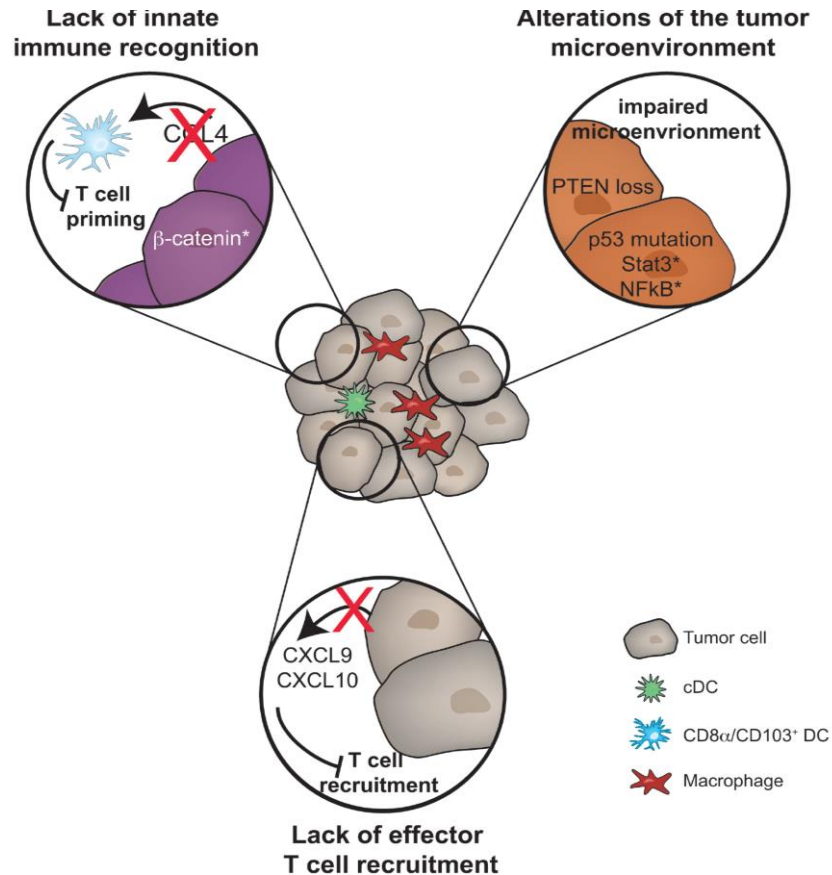
Non-T cell-inflamed tumors are a result of a malfunctioning cancer immunity cycle

Types of Immunotherapy

I. Checkpoint blockade immunotherapy

II. Cancer vaccines

III. Adoptive cell transfer

IV. Effector antibodies

V. Innate immune activation

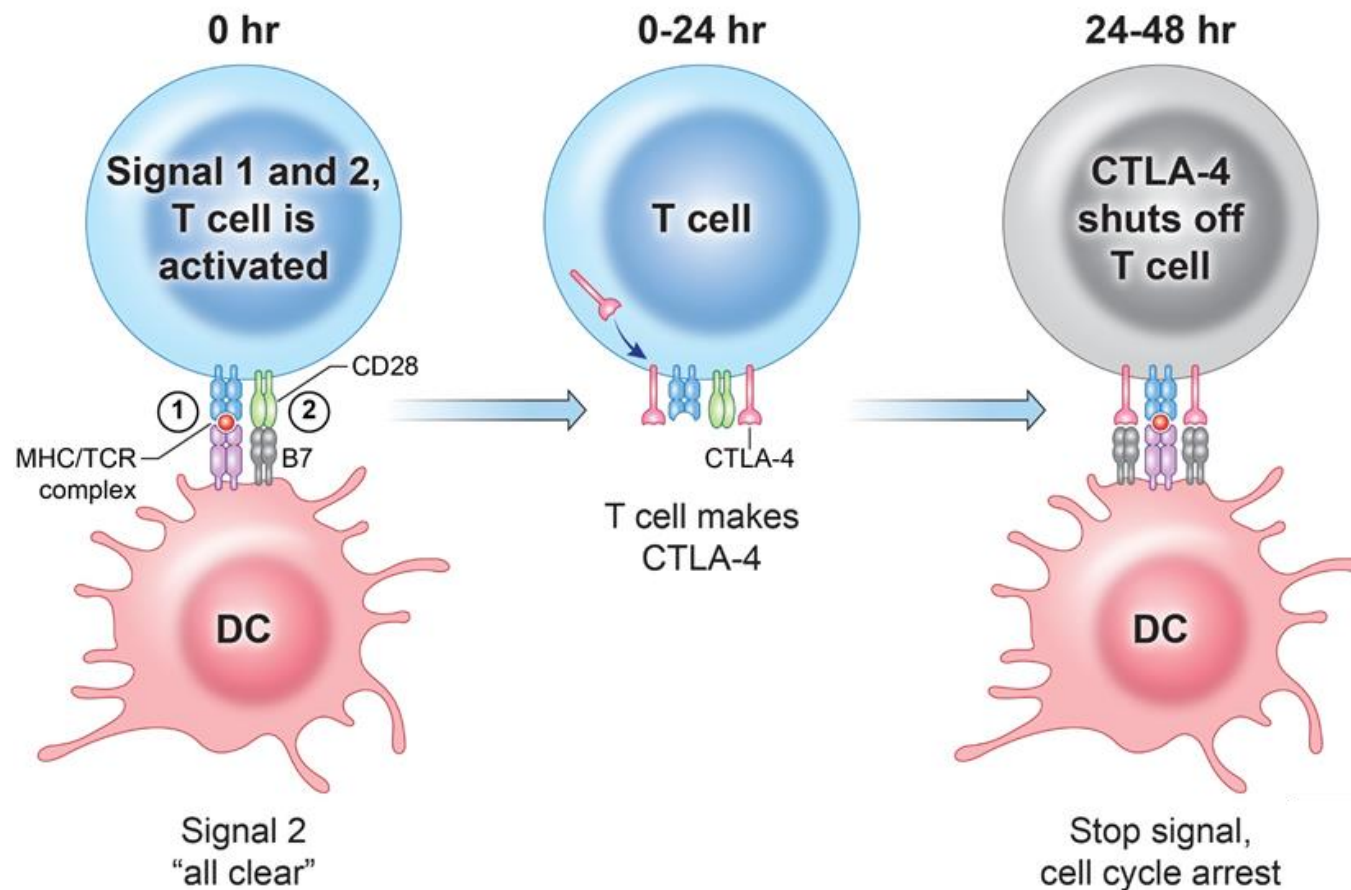# I. Checkpoint Blockade Immunotherapy

The CTLA-4 Checkpoint

Cytotoxic **T**-**L**ymphocyte **A**ssociated Protein **4**

Up-regulated in response to T cell activation

Limits positive stimulation by competition
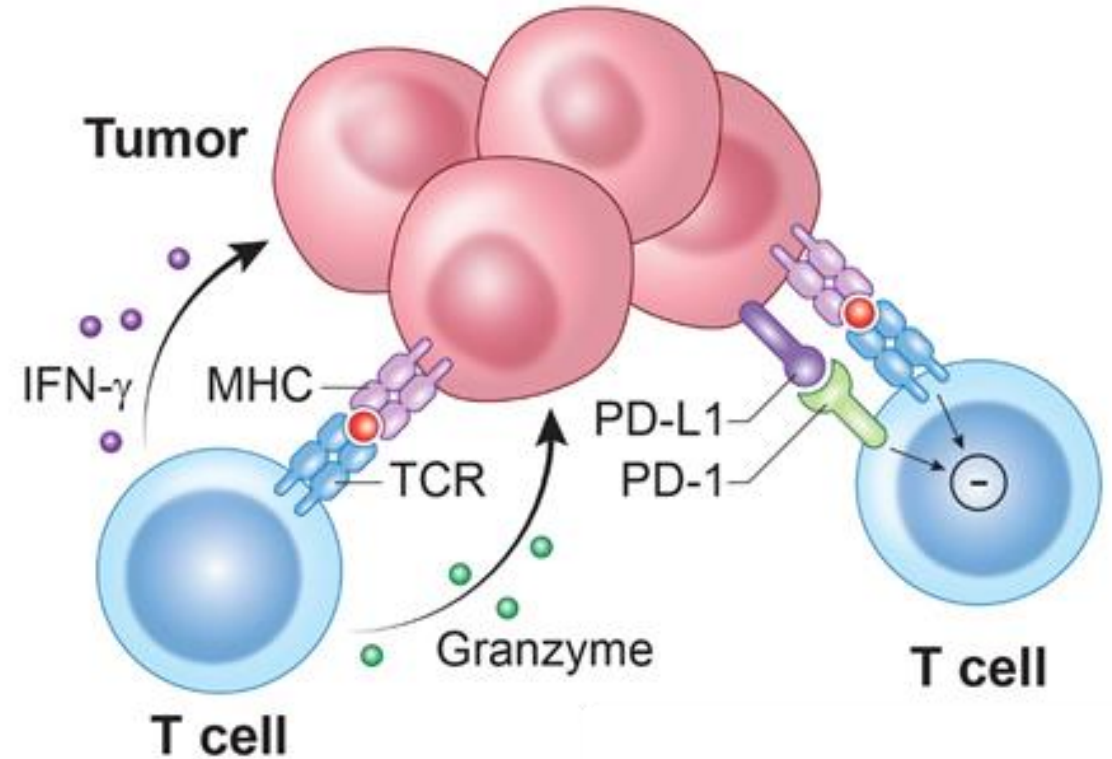

Image courtesy of NCI
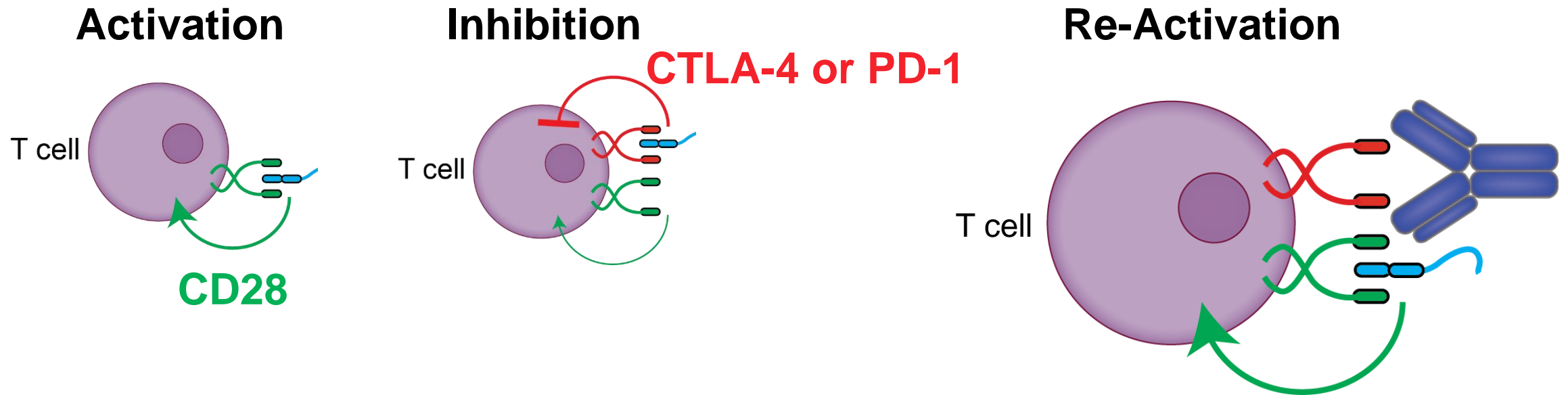
The PD-1/PD-L1 Checkpoint

Programmed **D**eath **1**

Up-regulated in response to T cell activation

Ligands PD-L1 and PD-L2 are up-regulated following inflammation (IFNγ)

Checkpoint blockade therapy unleashes the "brakes" on T cells

Activation

Inhibition

CTLA-4 or PD-1

Re-Activation

T cell

CD28

T cell

T cell

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

T Cell Checkpoint Modulation

- **First generation of checkpoint modulation:** Blocking inhibitory checkpoints

- **Second generation of checkpoint modulation:** Activating stimulatory checkpoints
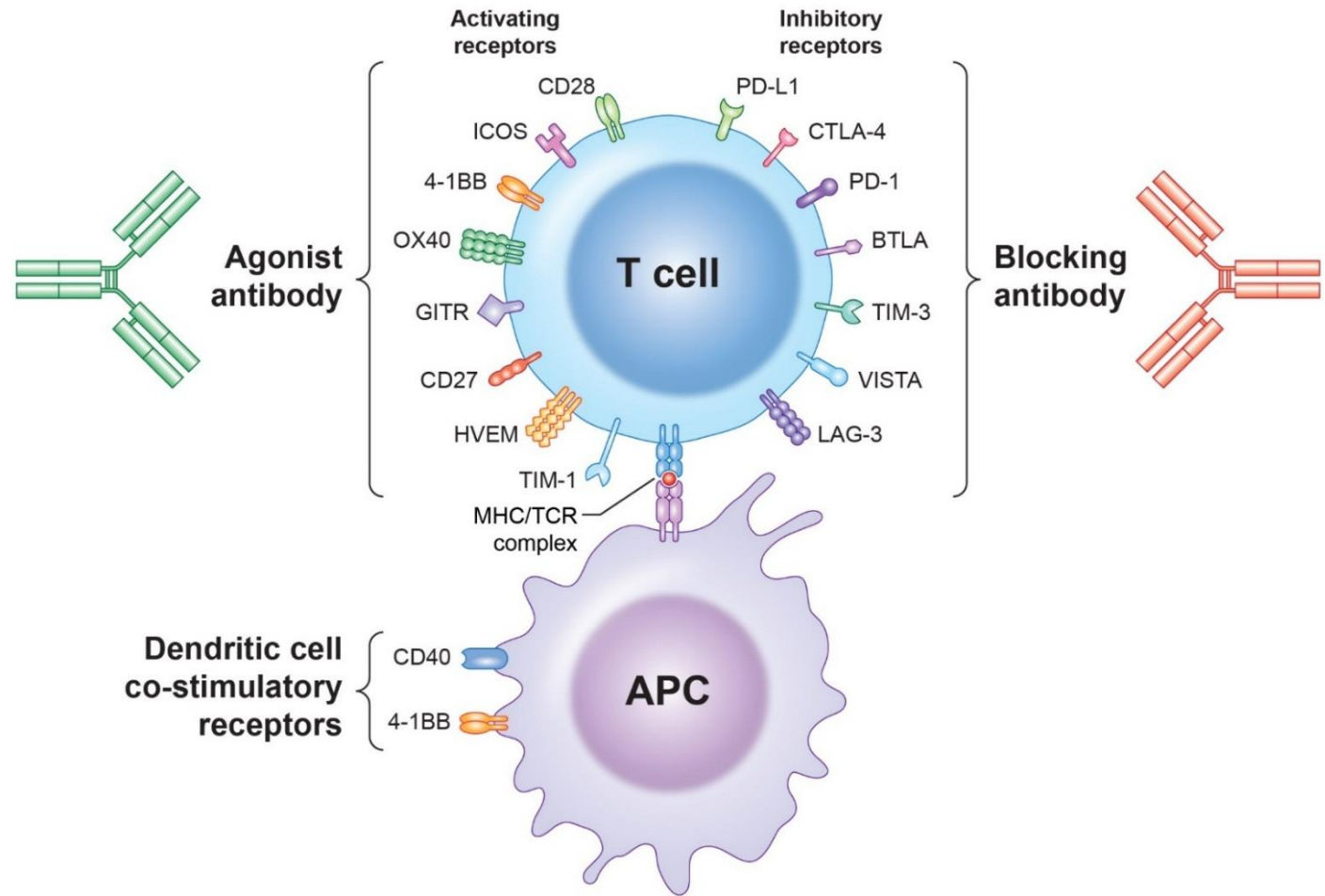
II. Therapeutic Cancer Vaccines

Goal: Increase the immunogenicity of tumor antigens to generate a high frequency of tumor-specific T cells.

Therapeutic cancer vaccines
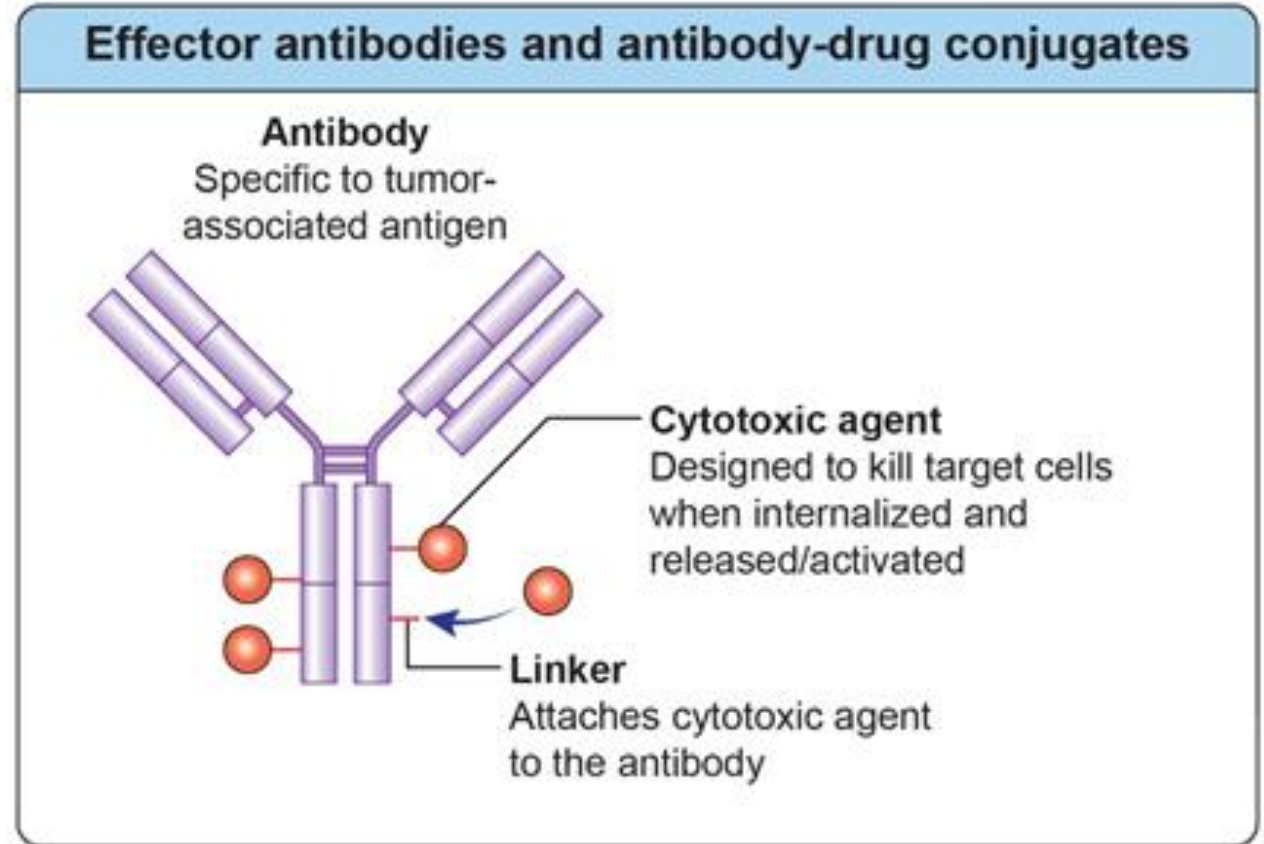
VACCINE

Viral and bacterial-based vaccines
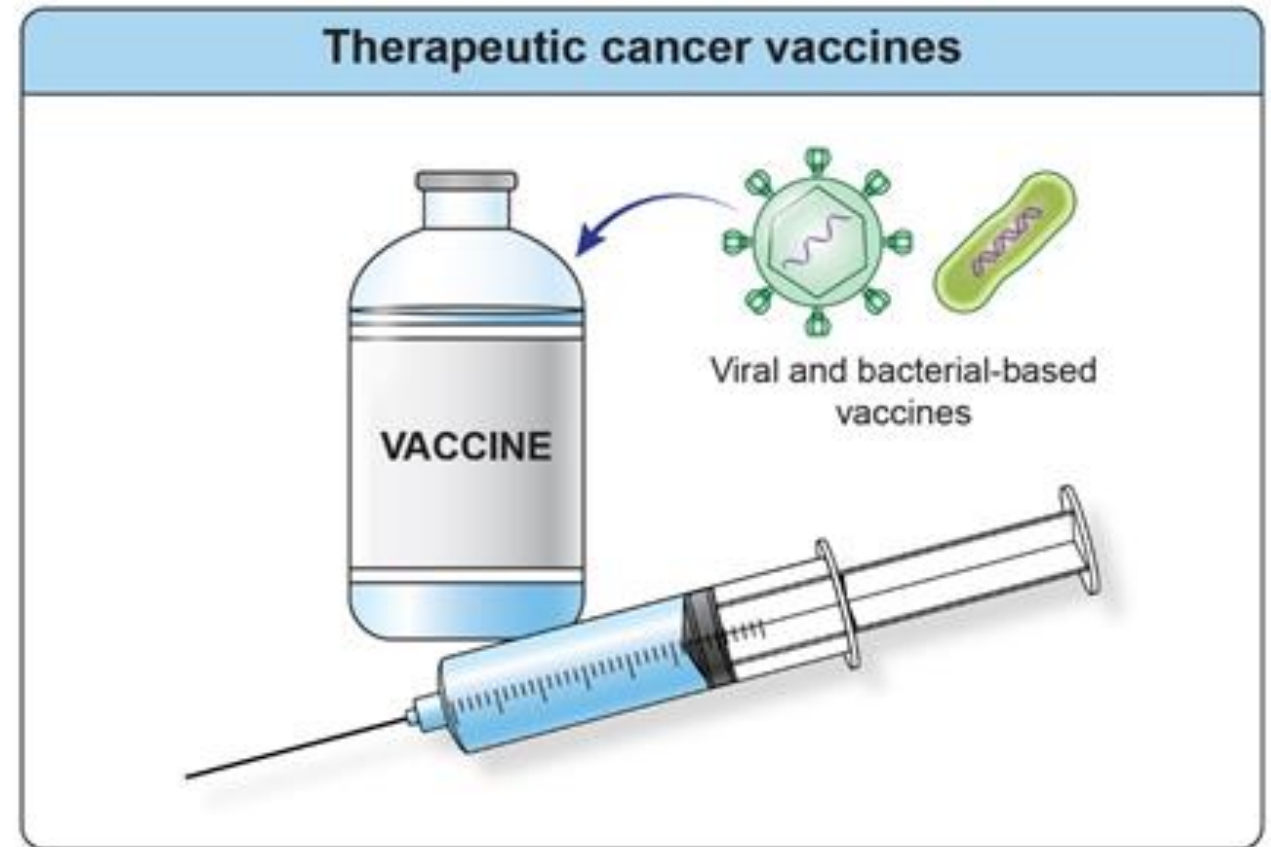
III. Adoptive Cell Transfer Therapy

Goal: Overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer.
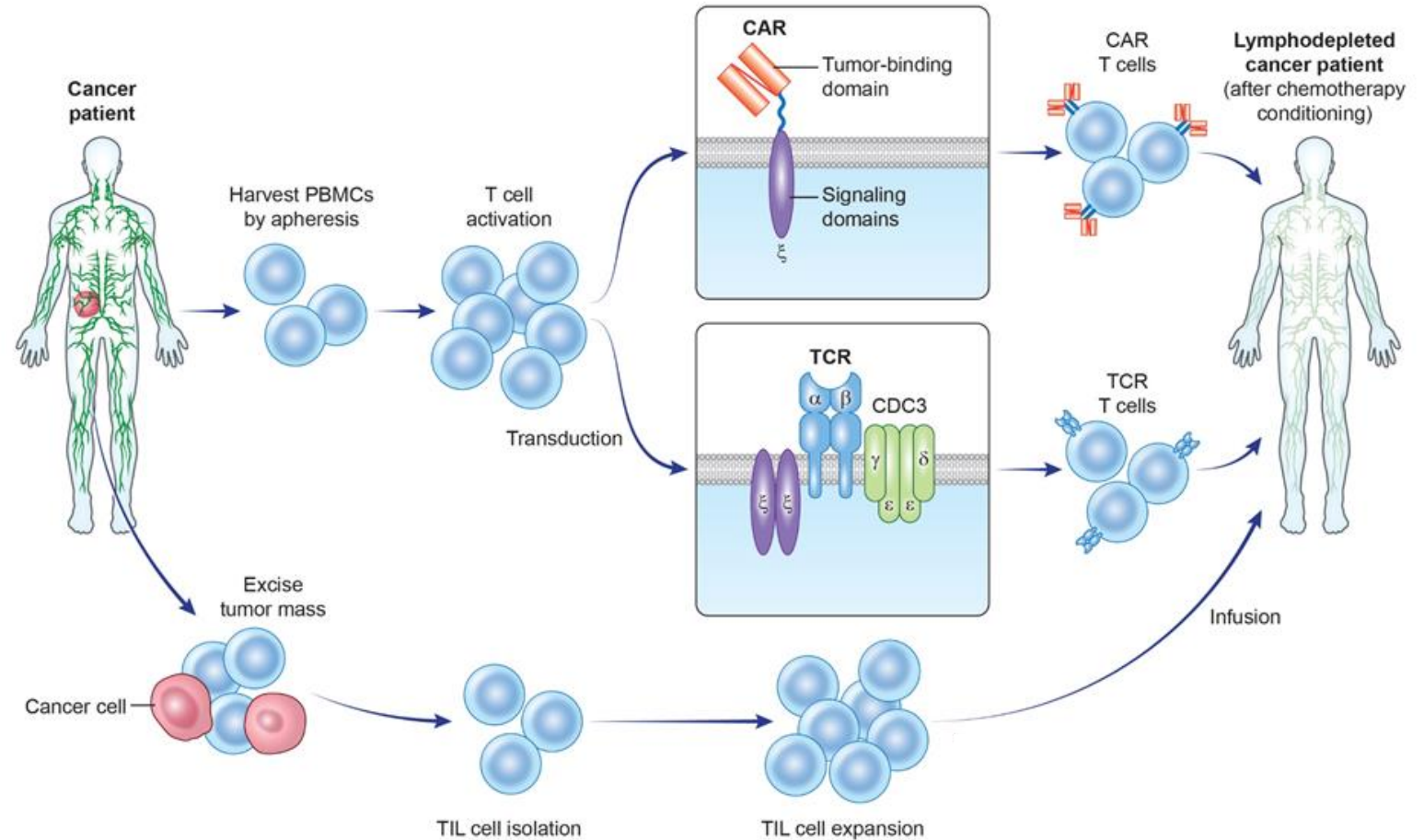
IV. Effector Antibodies and Antibody-Drug Conjugates (ADCs)

Goal: Specifically target and kill tumor cells using innate mechanisms, which are difficult to evade or suppress, and/or through delivery of cytotoxic agents.

Effector antibodies and antibody-drug conjugates

Antibody
Specific to tumor-associated antigen

Cytotoxic agent
Designed to kill target cells when internalized and released/activated

Linker
Attaches cytotoxic agent to the antibody

V. Innate Immune Activation

Goal: Enhance innate immune sensing by providing stimulatory agents (frequently into the tumor itself).
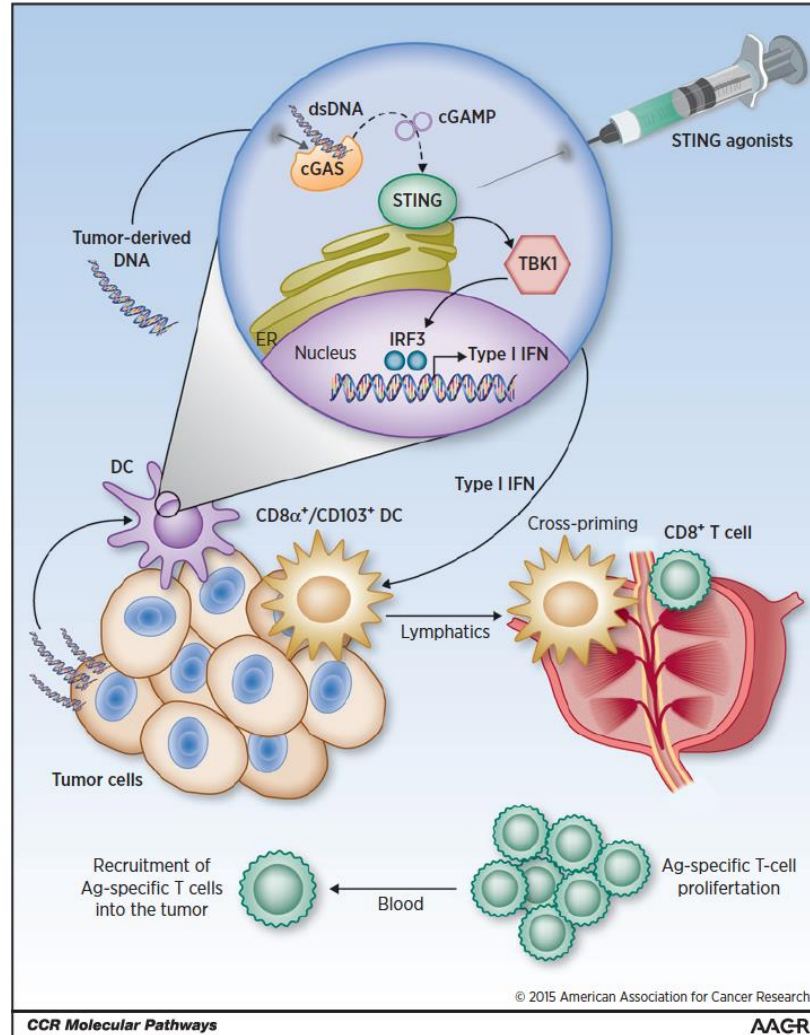
## Agents:
Sting agonists
TLR agonists
Immunogenic RNA

Corrales, Clin Can Res 2015

Oncolytic Viruses

Goal: Specifically target and kill tumor cells through viral replication AND release of innate immune activators and tumor antigens.
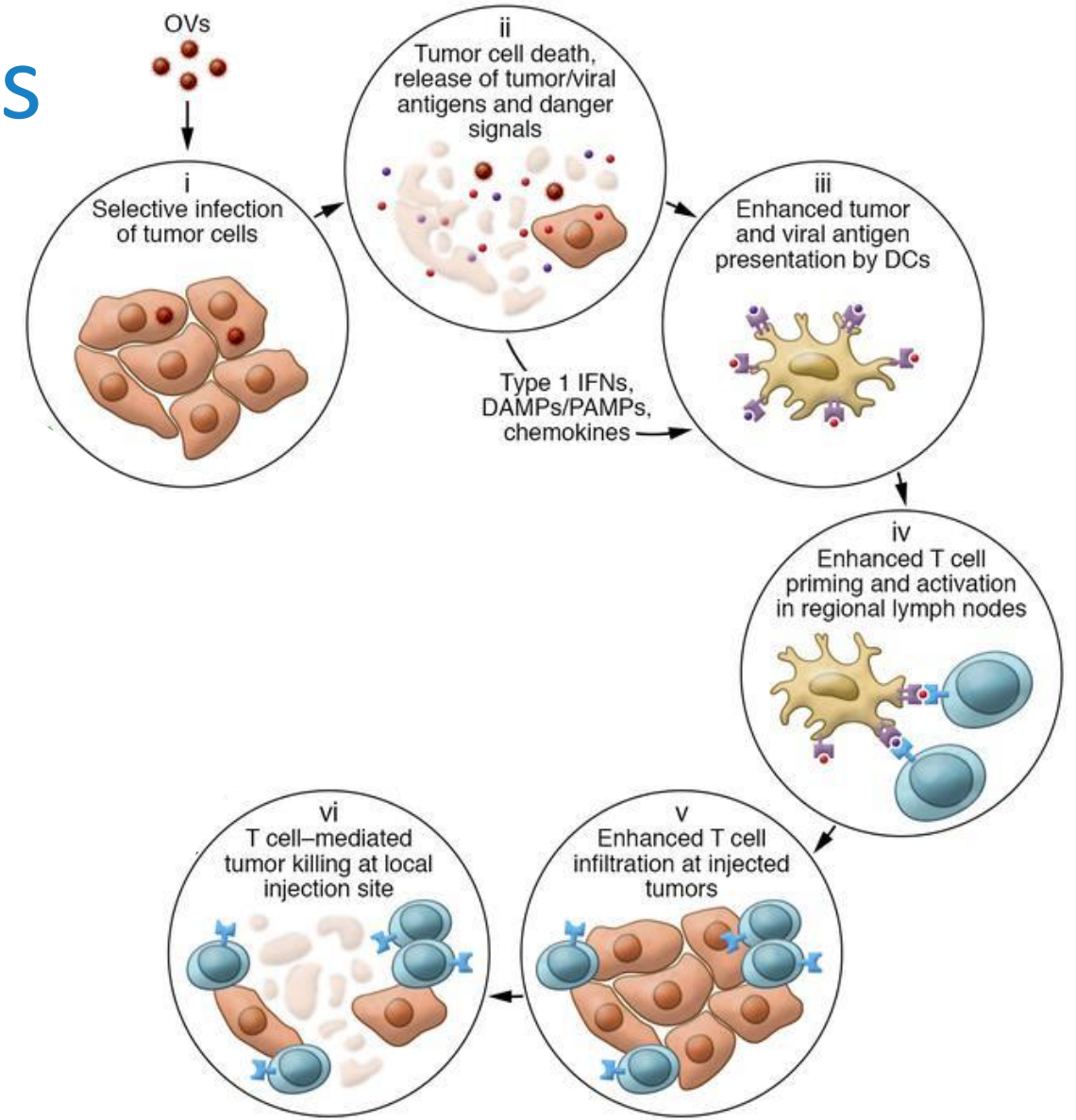
Multi-layered Immunosuppression

- Tumors insulate themselves with dense layers of immune-suppression

- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells

- Immunotherapy can "peel back" the layers of local immune suppression

- Combination therapy might be needed to overcome all layers
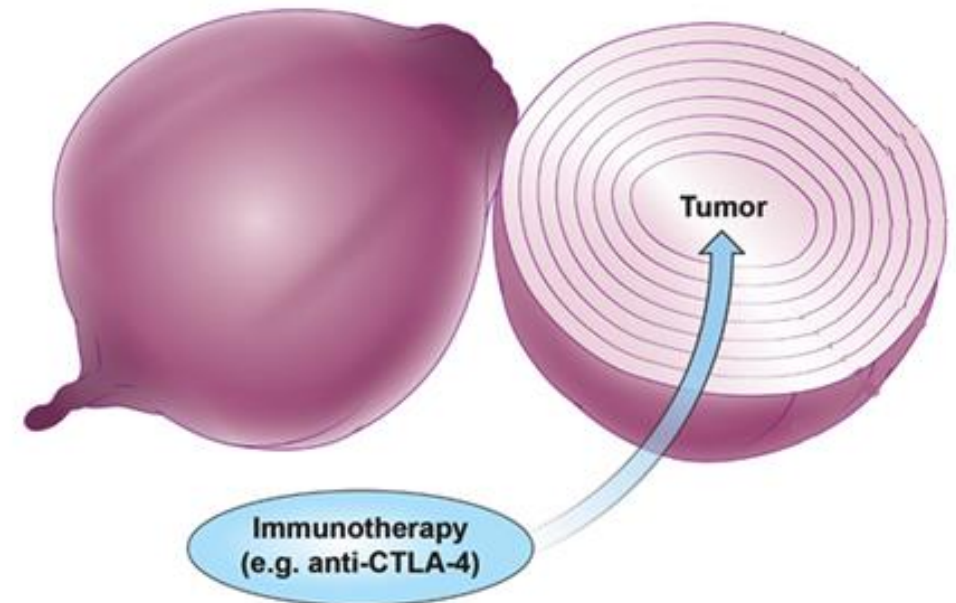
Combination Immunotherapies
Dual CTLA-4 (Ipilimumab) and PD-1 (Nivolumab) inhibition

Combining two checkpoint blockade agents

Wolchok et al., NEJM 2017
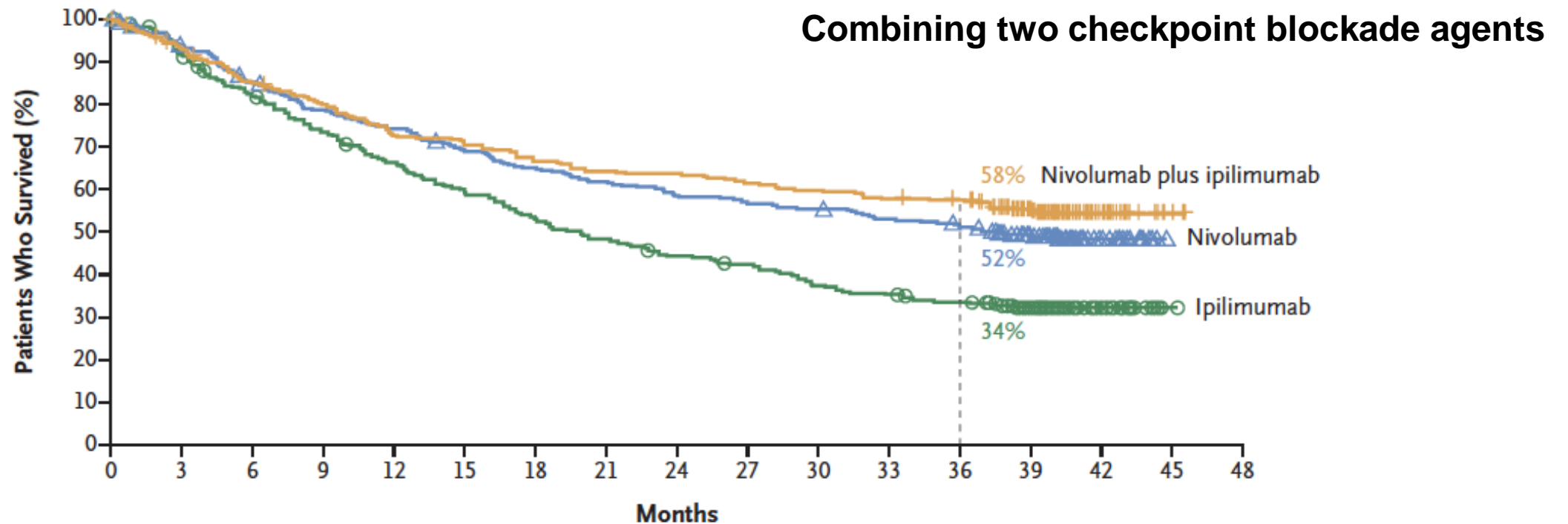
Combination Immunotherapies

|	CBT	ACT	Vaccines	Cytokines	CBT agonist	Innate agonists	Onc. virus	Targeted therapy	Radiation	Chemotherapy
Checkpoint blockade therapy (inhibitors)										
Adoptive cell therapy										
Vaccines										
Cytokines										
Checkpoint blockade therapy (stimulatory)										
Innate immune agonists										
Oncolytic virus										
Targeted therapy										
Radiation										
Chemotherapy										

Legend:
- Approved
- Synergy (to be tested)
- Not synergistic

Support T cell function

Enhance innate immune system

Induce tumor cell death

Immunotherapy Biomarkers

Cesano et al. Biomedicines 2018
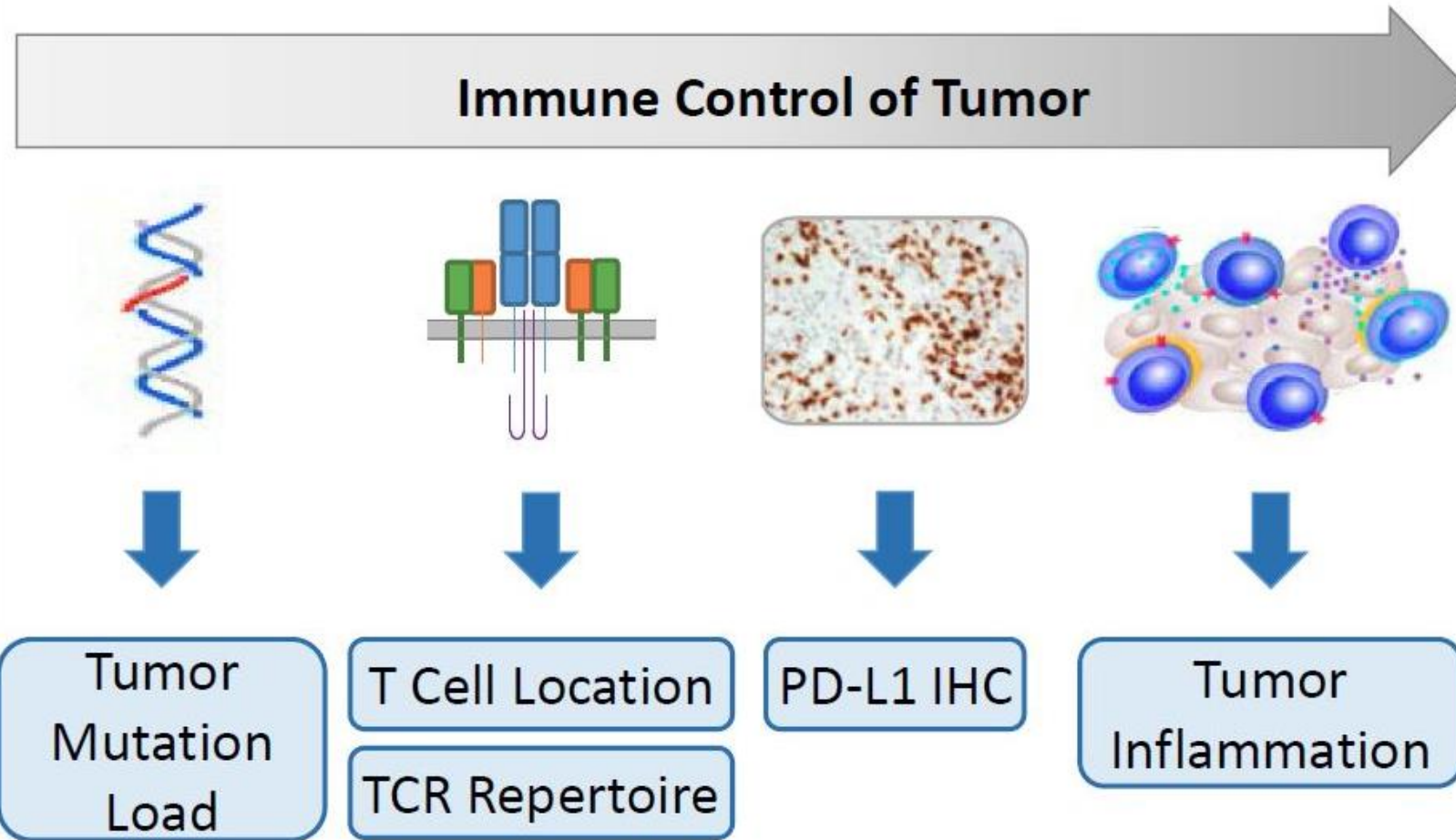
Assessment of response to combined OX-40 agonist and PD-L1 antagonist
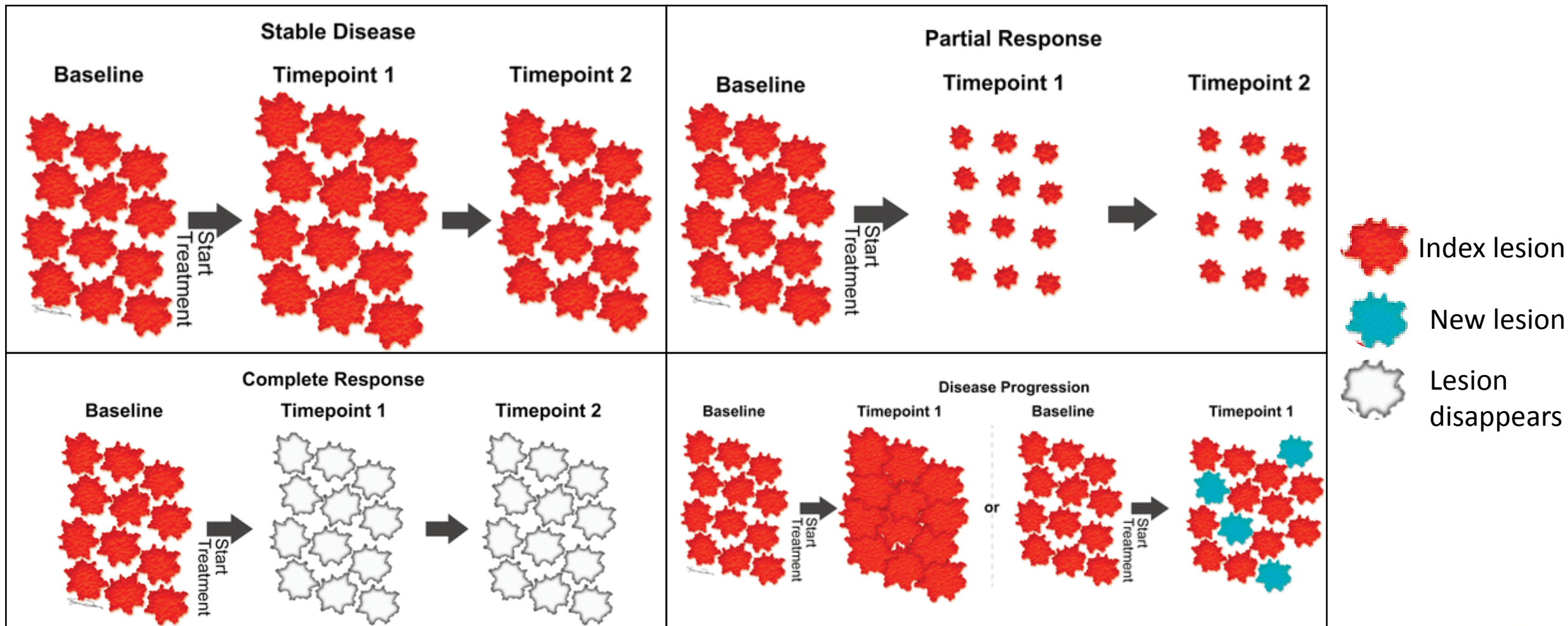

Pseudoprogression — Shrinkage
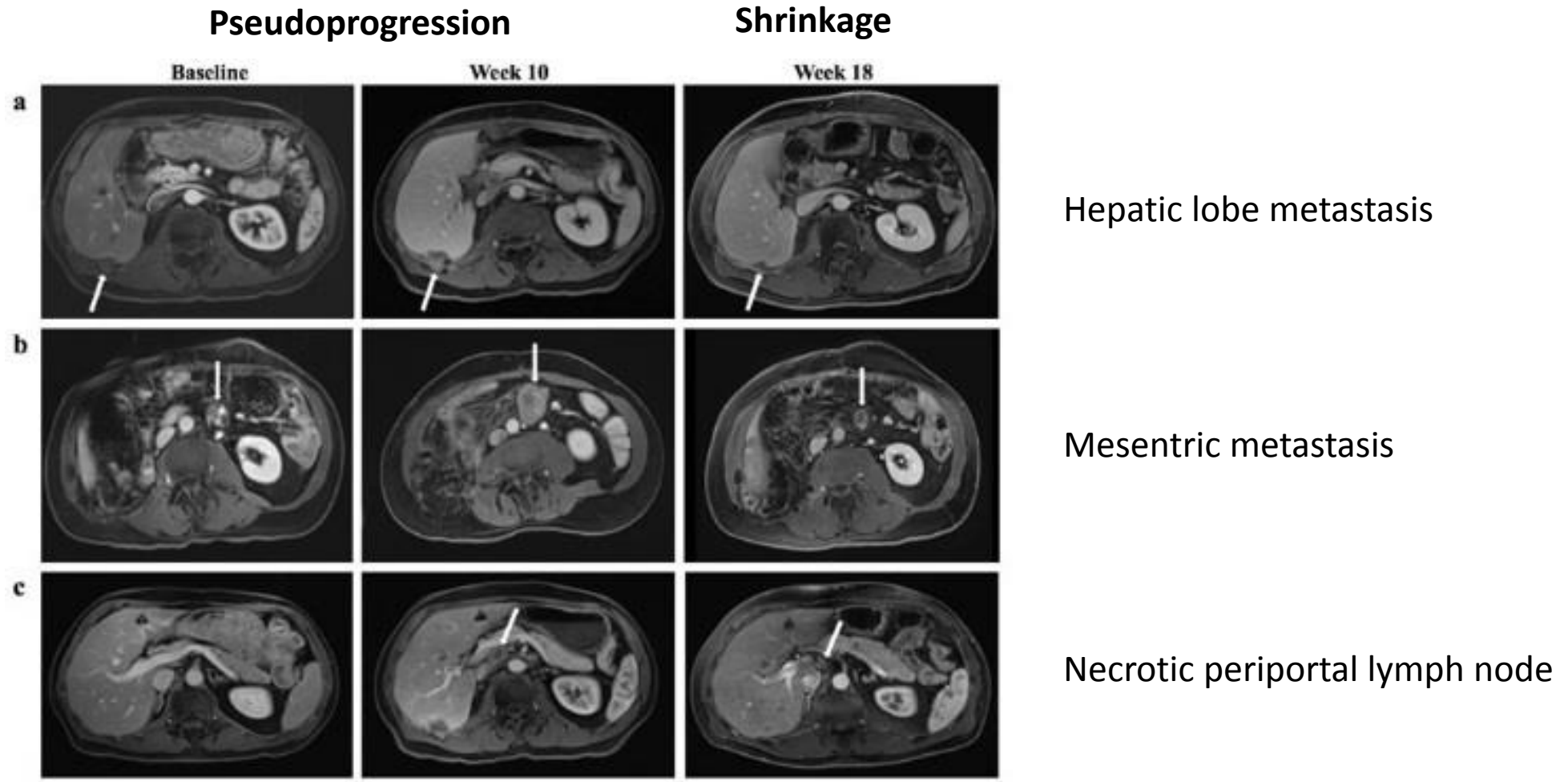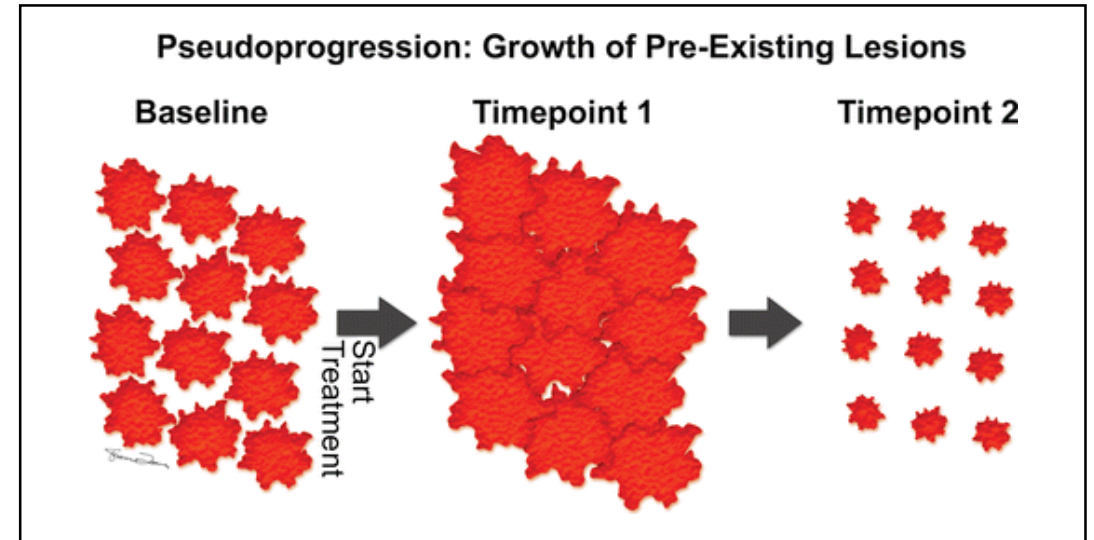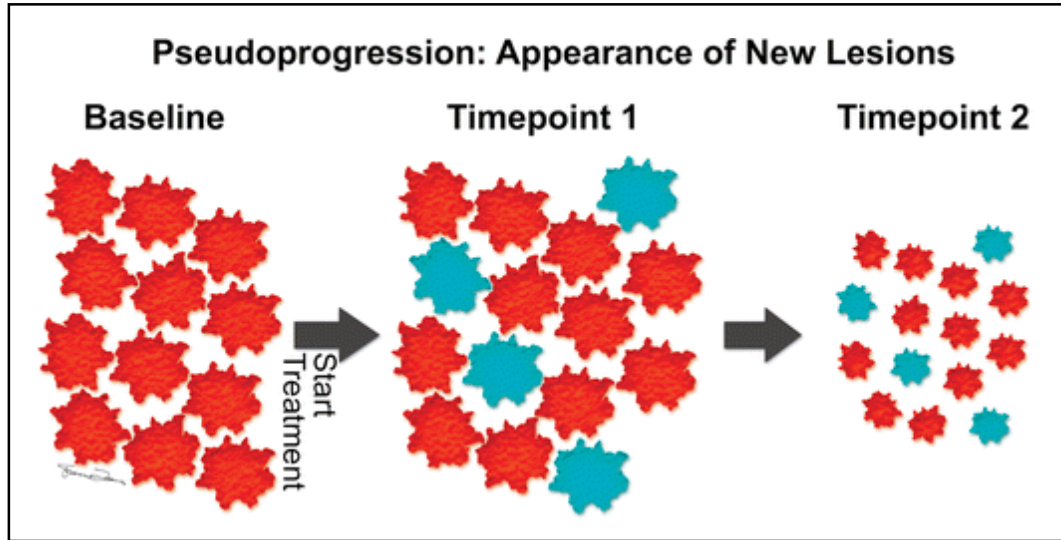
Hepatic lobe metastasis

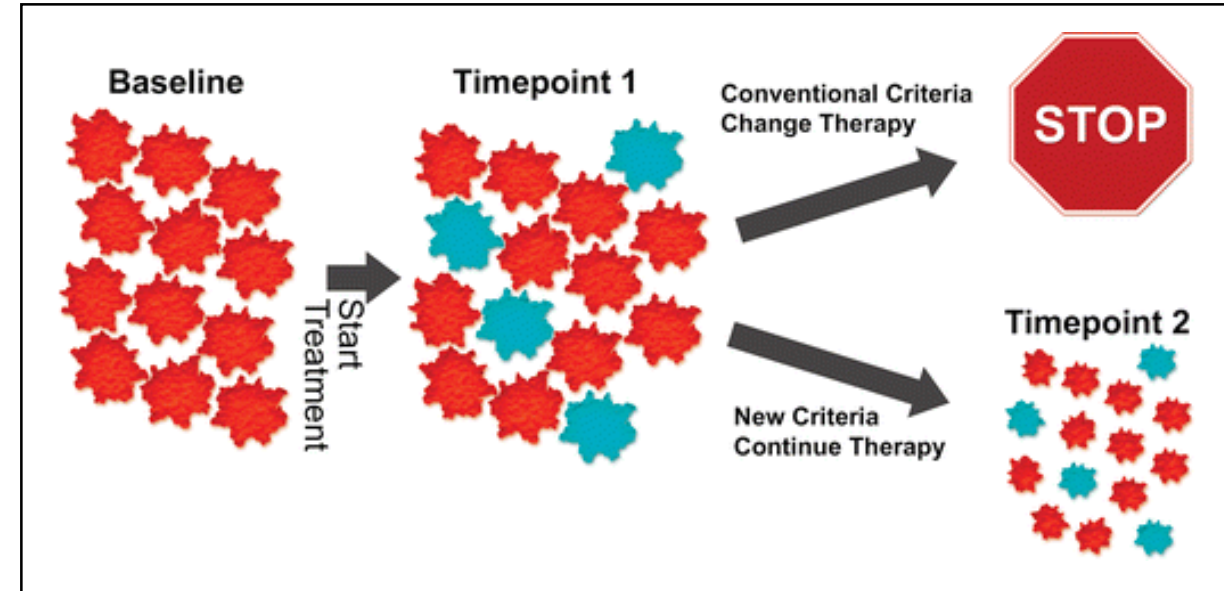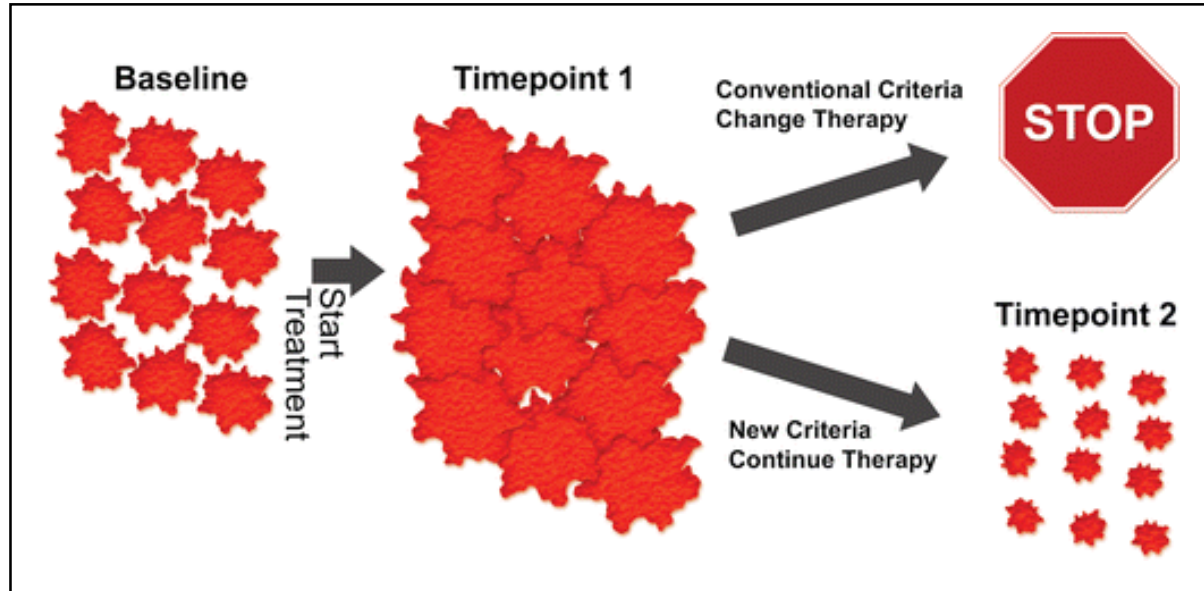Mesentric metastasis

Necrotic periportal lymph node

Many possible imaging findings

Many possible imaging findings

Assessment of response – unique considerations for immunotherapy

Comparison of disease progression by conventional and immune-related criteria

Treatment Response	RECIST 1.1 Response Evaluation Criteria in Solid Tumors	irRC Immune-related Response Criteria
Progressive disease	≥20% increase in lesion sum* (absolute size increase ≥5 mm) or 1+ new lesions at any single observation	≥25% increase in tumor burden[+] versus nadir in two consecutive observations ≥4 weeks apart
New measurable lesions[#]	Always represent progressive disease	Incorporated into disease burden
New non-measurable lesions	Considered equivocal; followed at future examinations to clarify whether it is truly new disease	Does not define progression but precludes complete response

Wang, RadioGraphics 2017.

*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
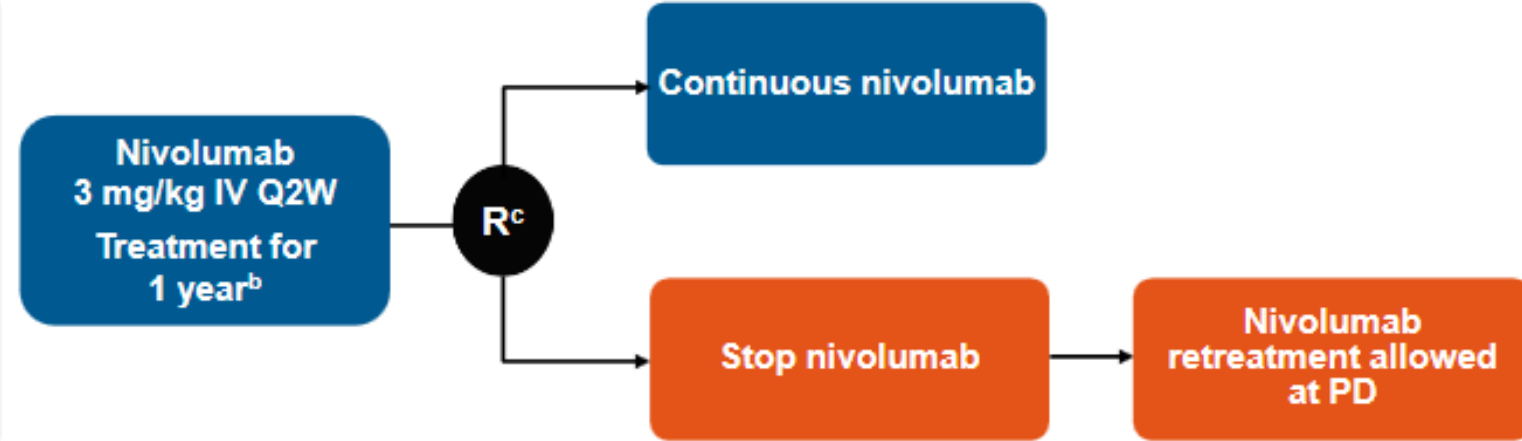[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm at CT; irRC is ≥10x10mm at CT. Smaller lesions are considered non-measurable.

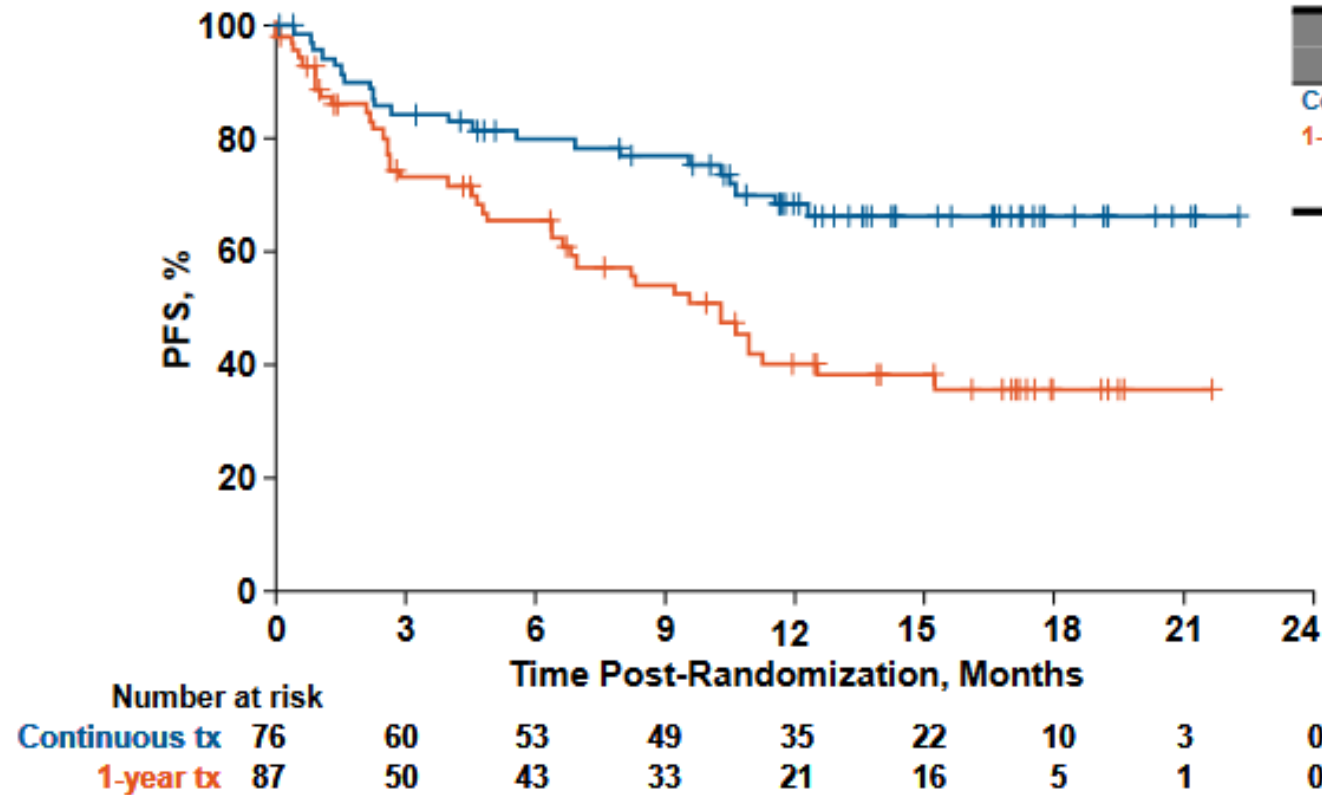# When to stop immunotherapy: CheckMate 153 trial

When to stop immunotherapy: CheckMate 153

|	Median, Months (95% CI)	PFS Rate, %	
		6-Month	1-Year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40
HR: 0.42 (95% CI: 0.25, 0.71)			

Conclusion: >1 year of treatment may be necessary

When to stop immunotherapy: KEYNOTE-006 trial

- Pembrolizumab 10 mg/kg Q2W or Q3W or ipilimumab 3 mg/kg Q3W for 4 doses

- Could stay on pembrolizumab for up to 2 years

- Of patients who completed 2 y pembro treatment, **86%** did not progress after 20 months follow-up

- More responders with pembrolizumab, but duration of response was similar for pembrolizumab and ipilimumab

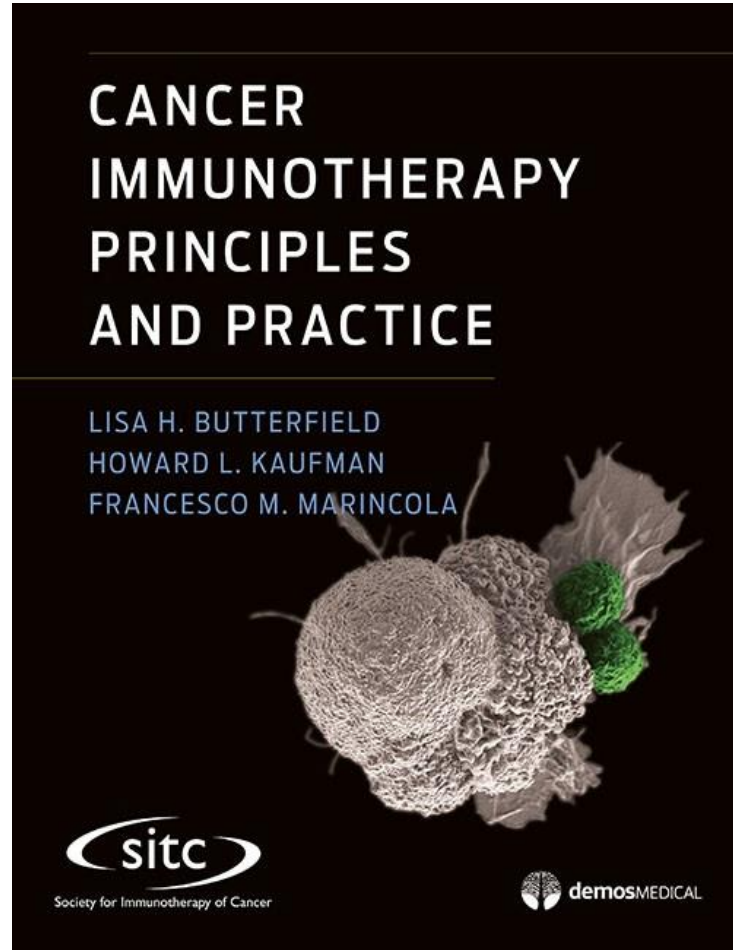# When to stop immunotherapy: KEYNOTE-001 trial

- 16% of patients achieved complete response

- Disease-free survival at 24 months after complete response:
  - In all complete response (CR) patients: 90.9%
  - In patients who discontinued cancer therapy: 89.9%

Robert, J Clin Oncol 2018
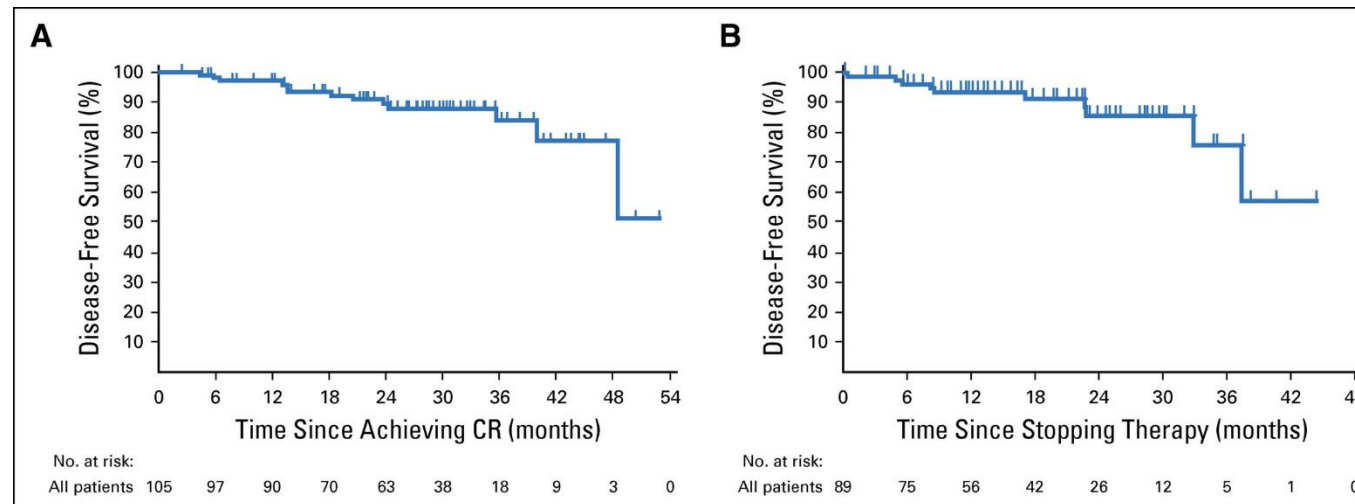
When to stop immunotherapy: clinical measures

- Positron emission tomography (PET)-based metabolic response
  - Metabolic response may precede anatomical changes on CT or MRI
- Achievement of complete response

Further Resources