

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.

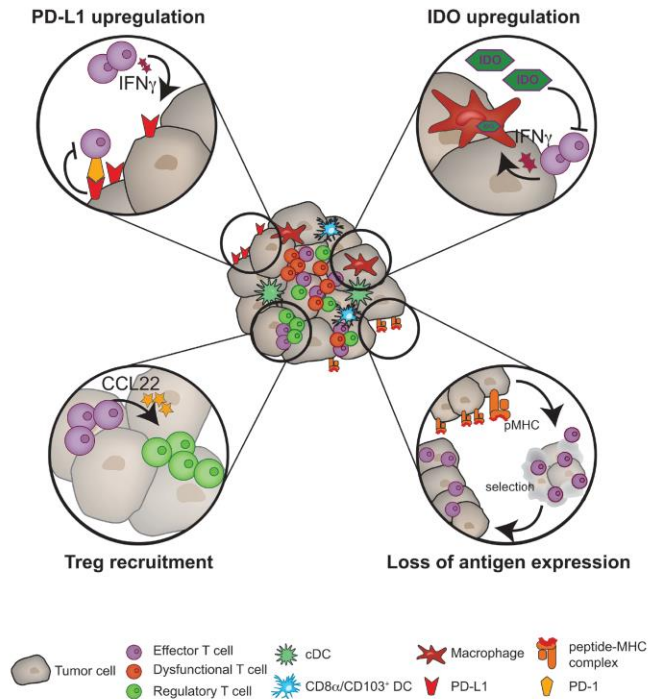
The goal of immunotherapy is to restore the capacity of the immune system to recognize and eliminate cancer.

Two major mechanisms of tumor immune escape

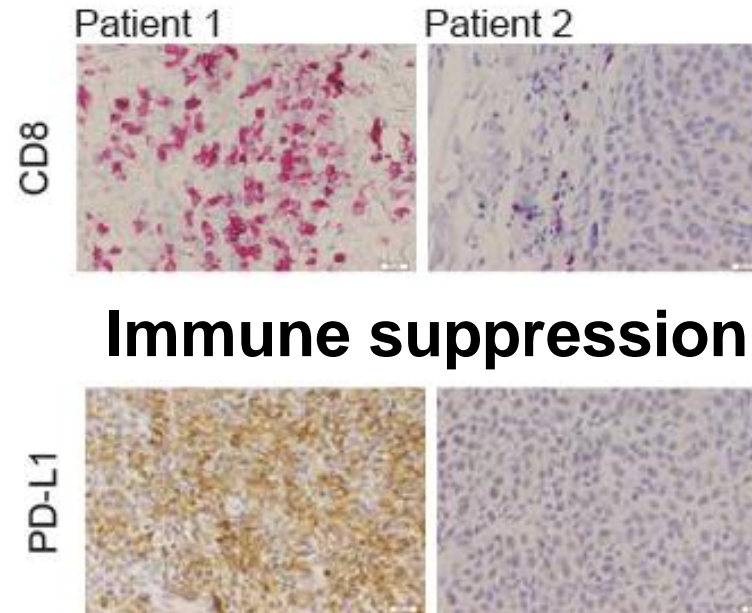
- **Render the immune response dysfunctional:** cytotoxic (CD8+) T cells often become dysfunctional or exhausted during chronic stimulation (chronic viral responses or responses against tumors). To enhance T cell dysfunction, the tumor microenvironment upregulates a suite of suppressive molecules.
-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

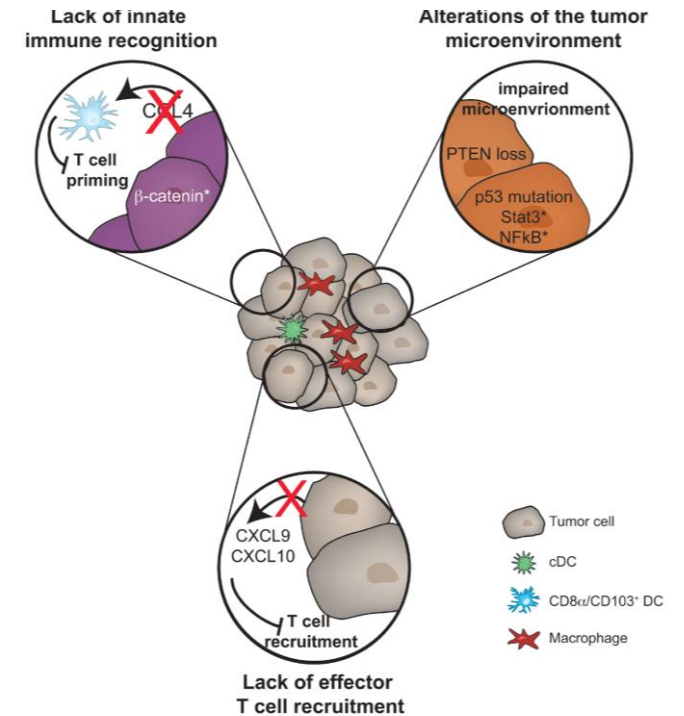
T cell-inflamed tumor microenvironment



T cells

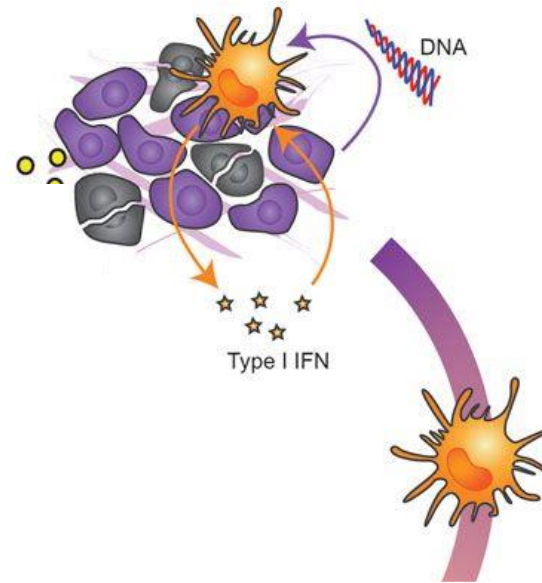


Non-T cell-inflamed tumor microenvironment



Initiation of an anti-tumor immune response

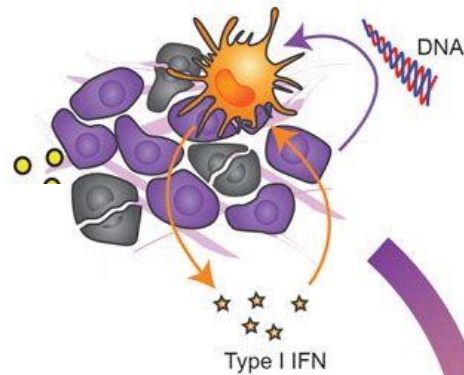
Innate immune sensing (i.e. Sting activation)



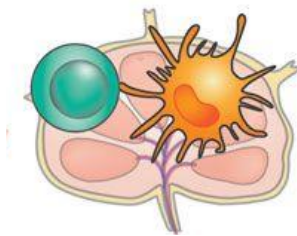
APC maturation
&
Transport to lymph node

Initiation of an anti-tumor immune response

Innate immune sensing (i.e. Sting activation)

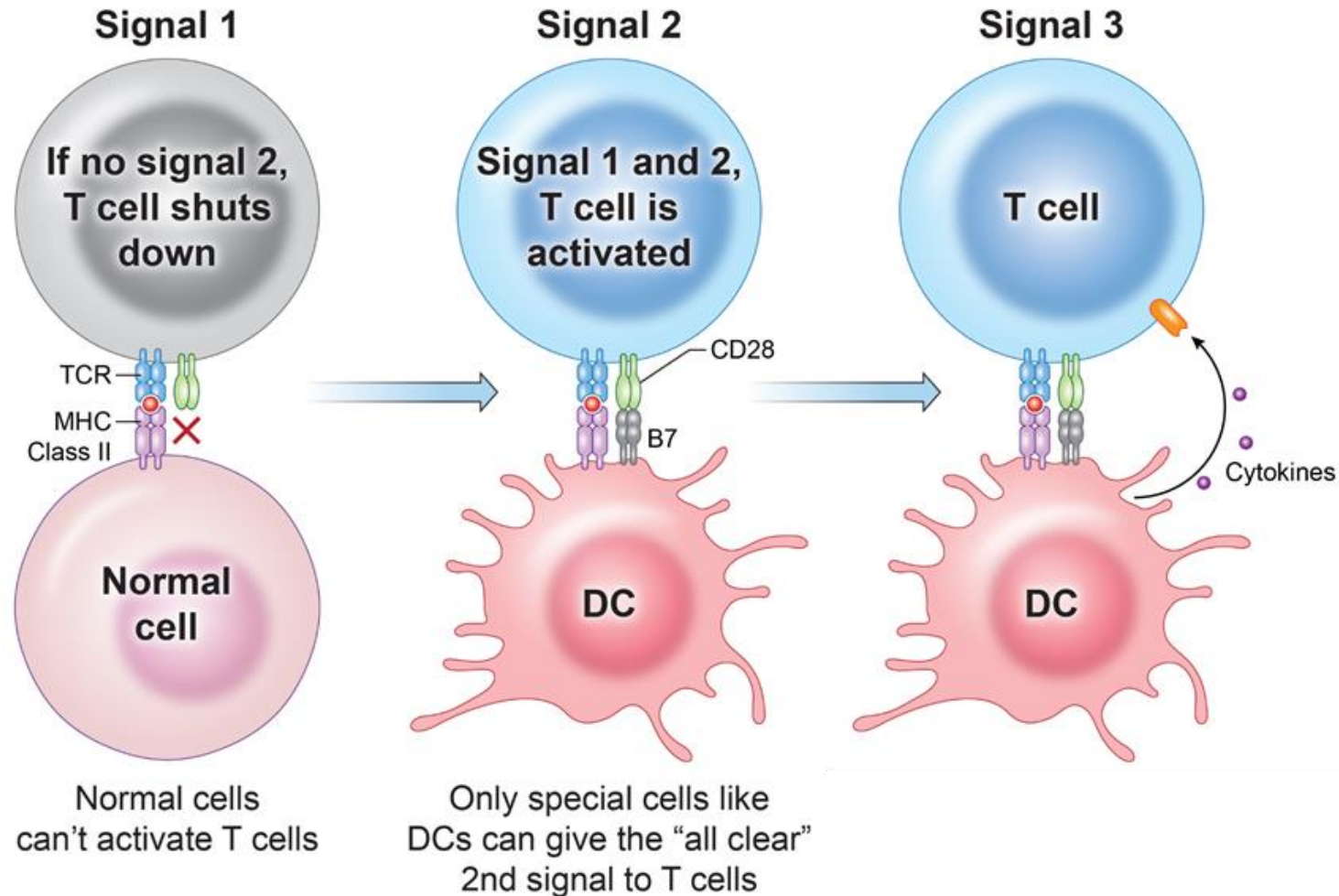


APC maturation
&
Transport to lymph node



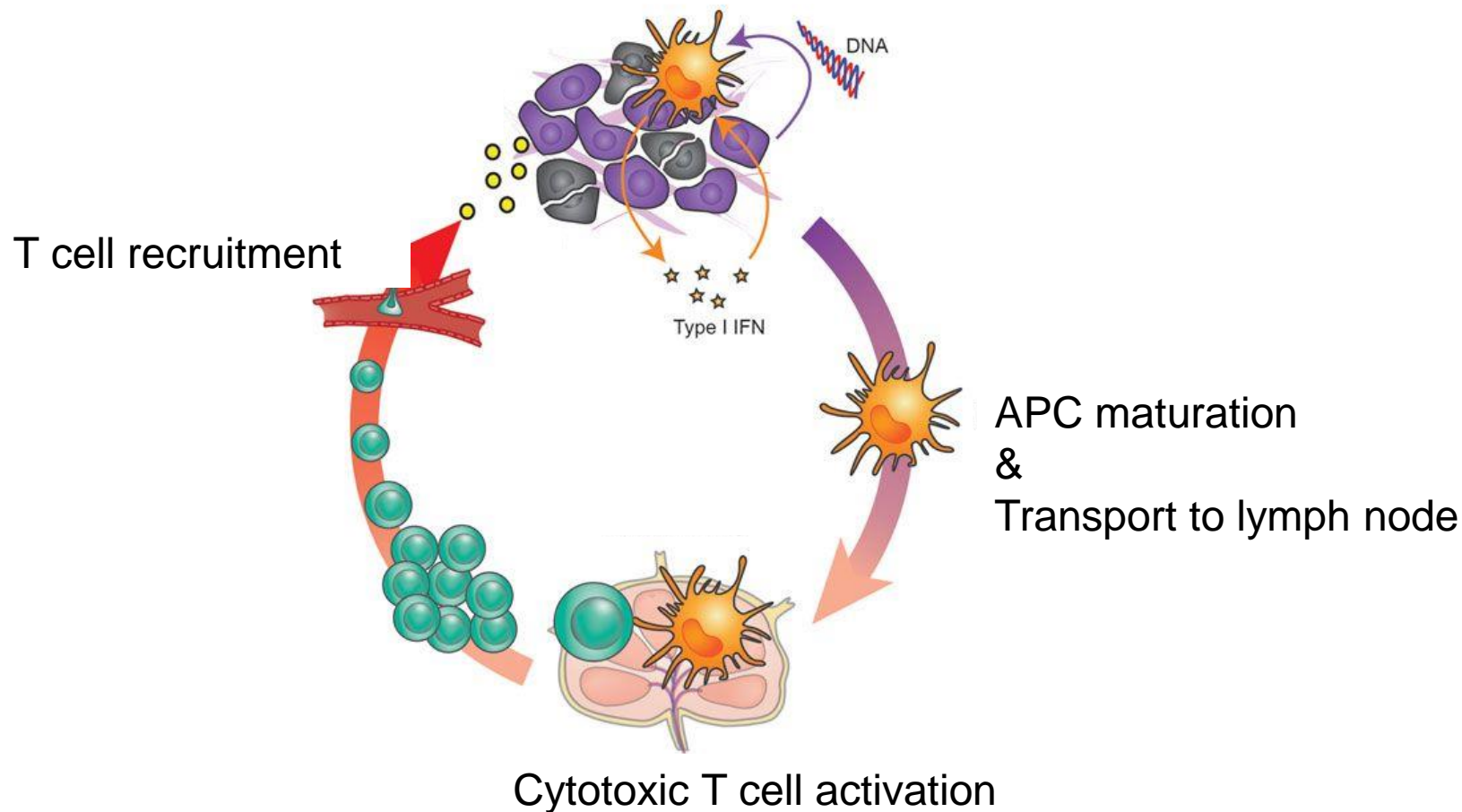
Cytotoxic T cell activation

Antigen-specific T cell Activation



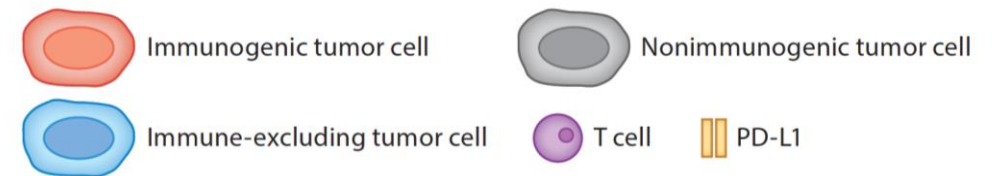
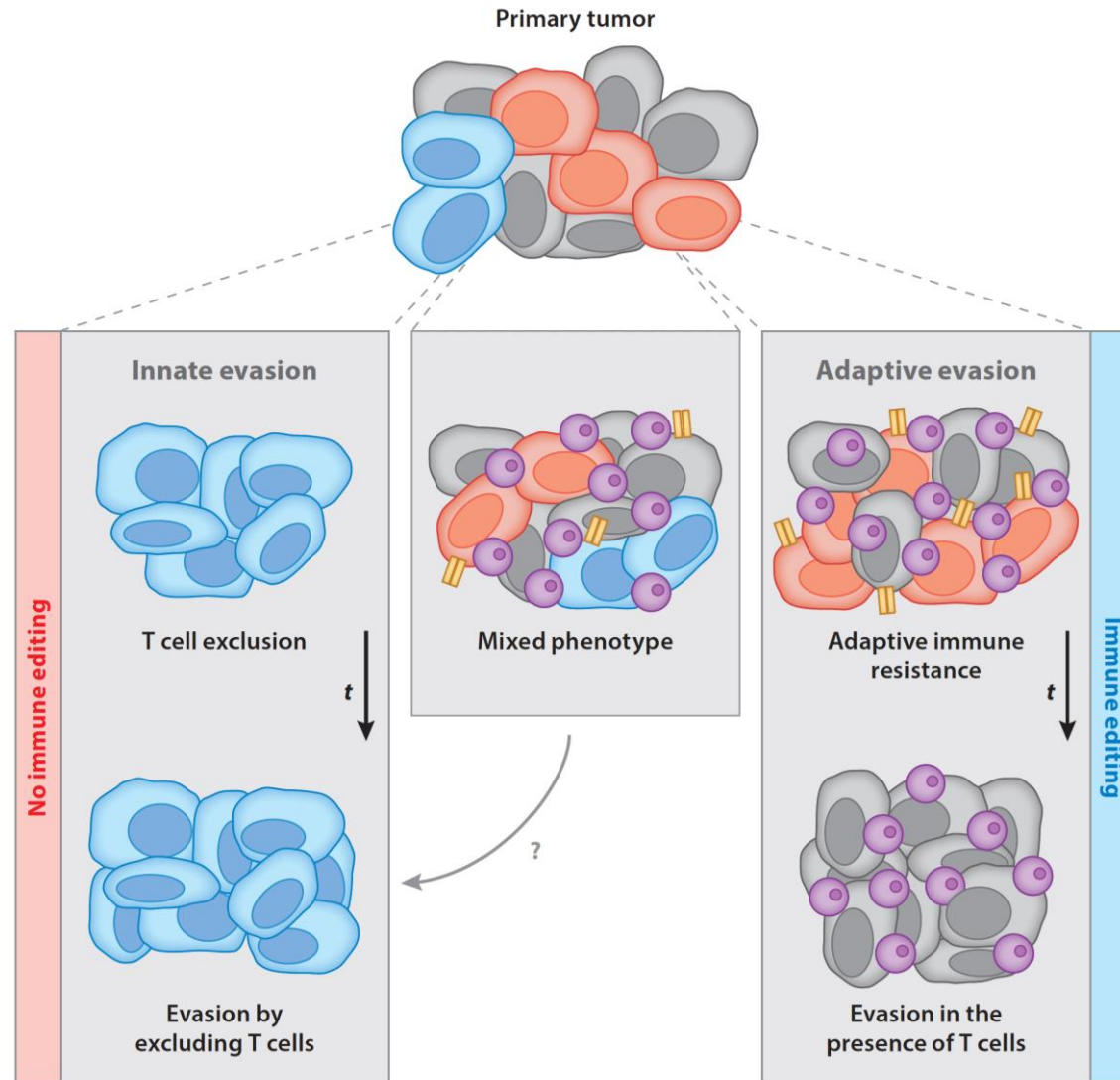
Initiation of an anti-tumor immune response

Innate immune sensing (i.e. Sting activation)



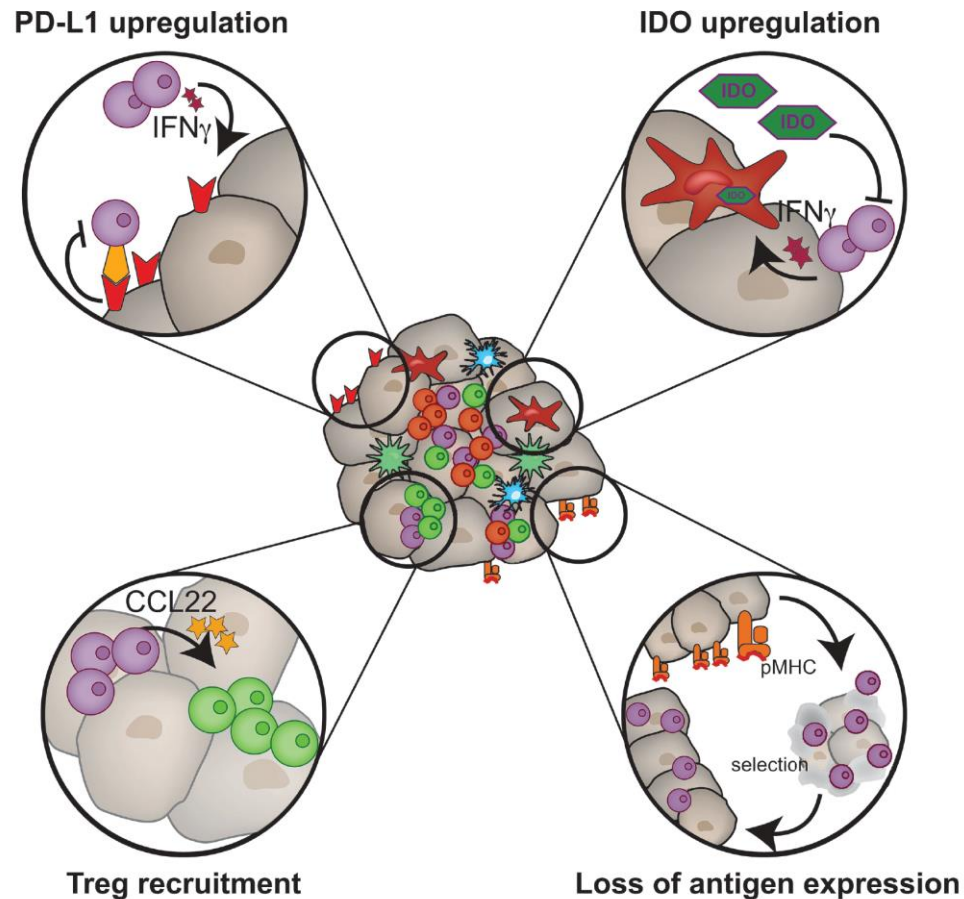
Cytotoxic T cell activation

Immune evasion occurs over time



T cell inflamed tumor microenvironment is immune suppressive

T cell-inflamed tumor microenvironment

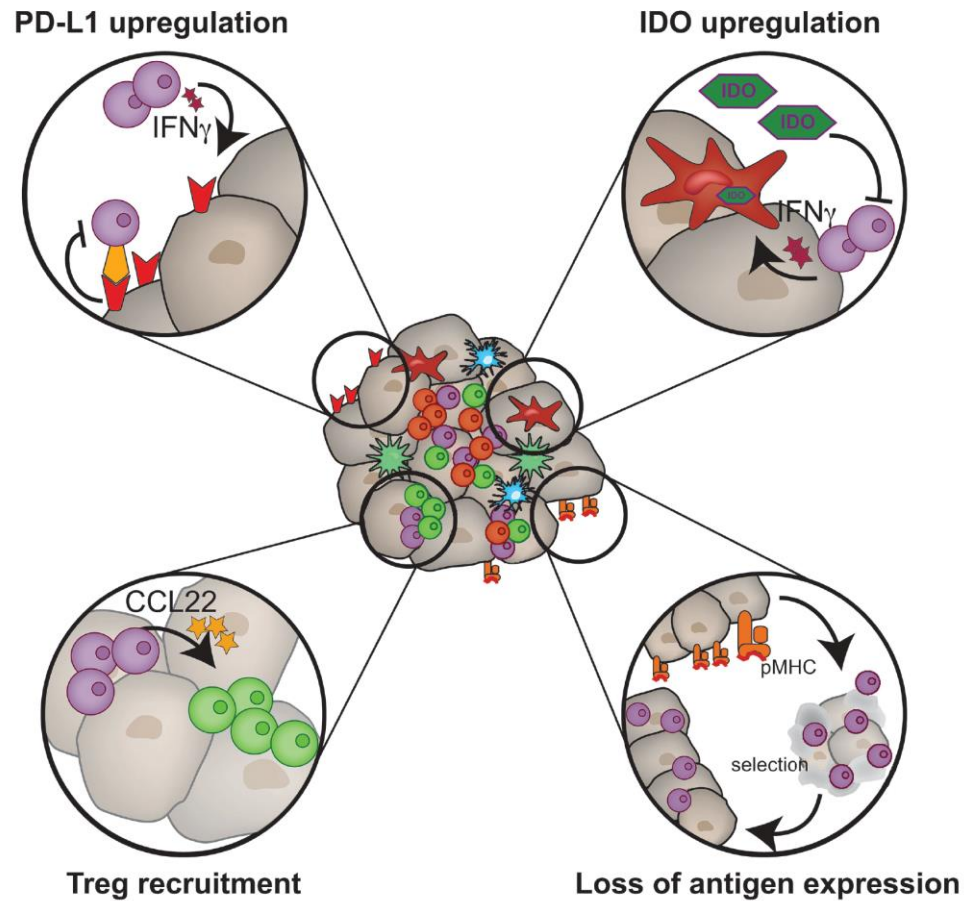


T cell-inflamed tumors escape by suppressing T cell function



T cell inflamed tumor microenvironment is immune suppressive

T cell-inflamed tumor microenvironment



T cell-inflamed tumors escape by suppressing T cell function

Non-T cell-inflamed tumors are a result of a malfunctioning cancer immune cycle



Types of Immunotherapy

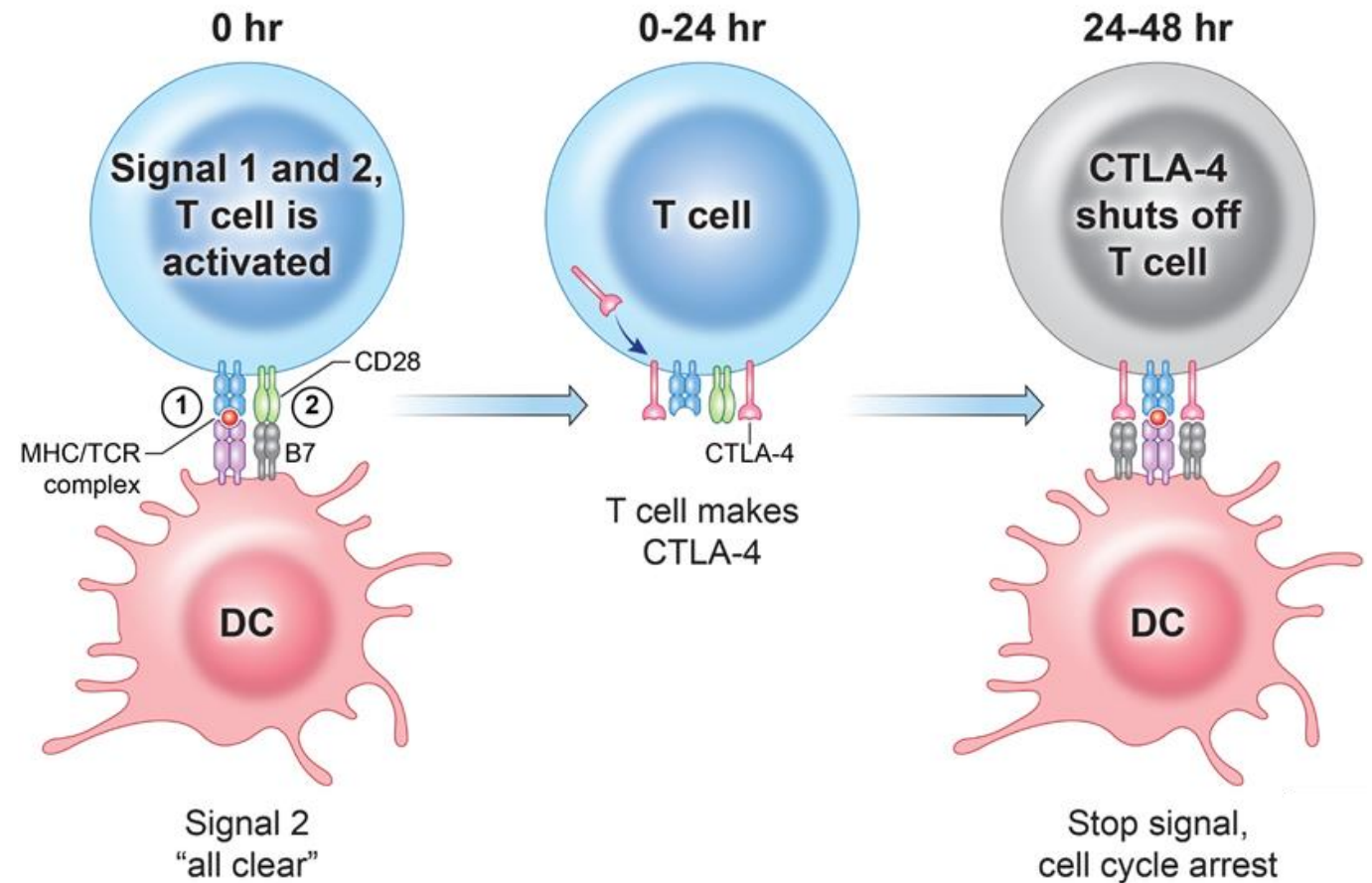
- Checkpoint blockade immunotherapy
- Cancer vaccines
- Adoptive cell transfer
- Effector antibodies
- Innate immune activation

The CTLA-4 Checkpoint

Cytotoxic T-Lymphocyte Associated Protein 4

Up-regulated in response to T
 cell activation

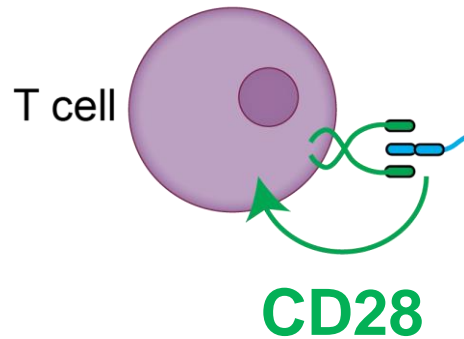
Limits positive stimulation by
 competition



Up-regulated in response to T cell activation

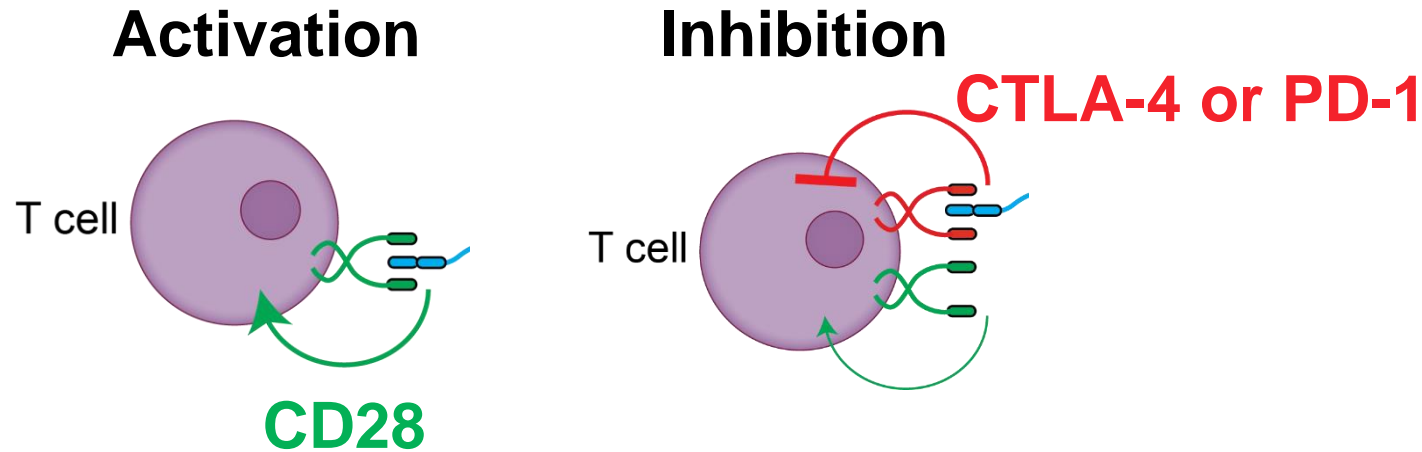
Checkpoint blockade therapy unleashes the “brakes” on T cells

Activation



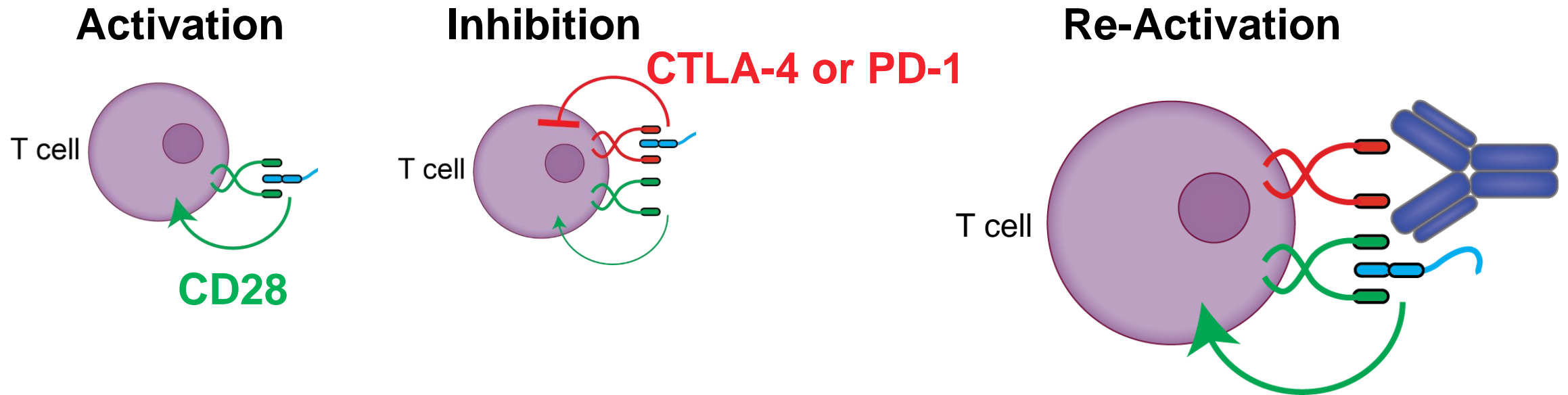
Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint 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.

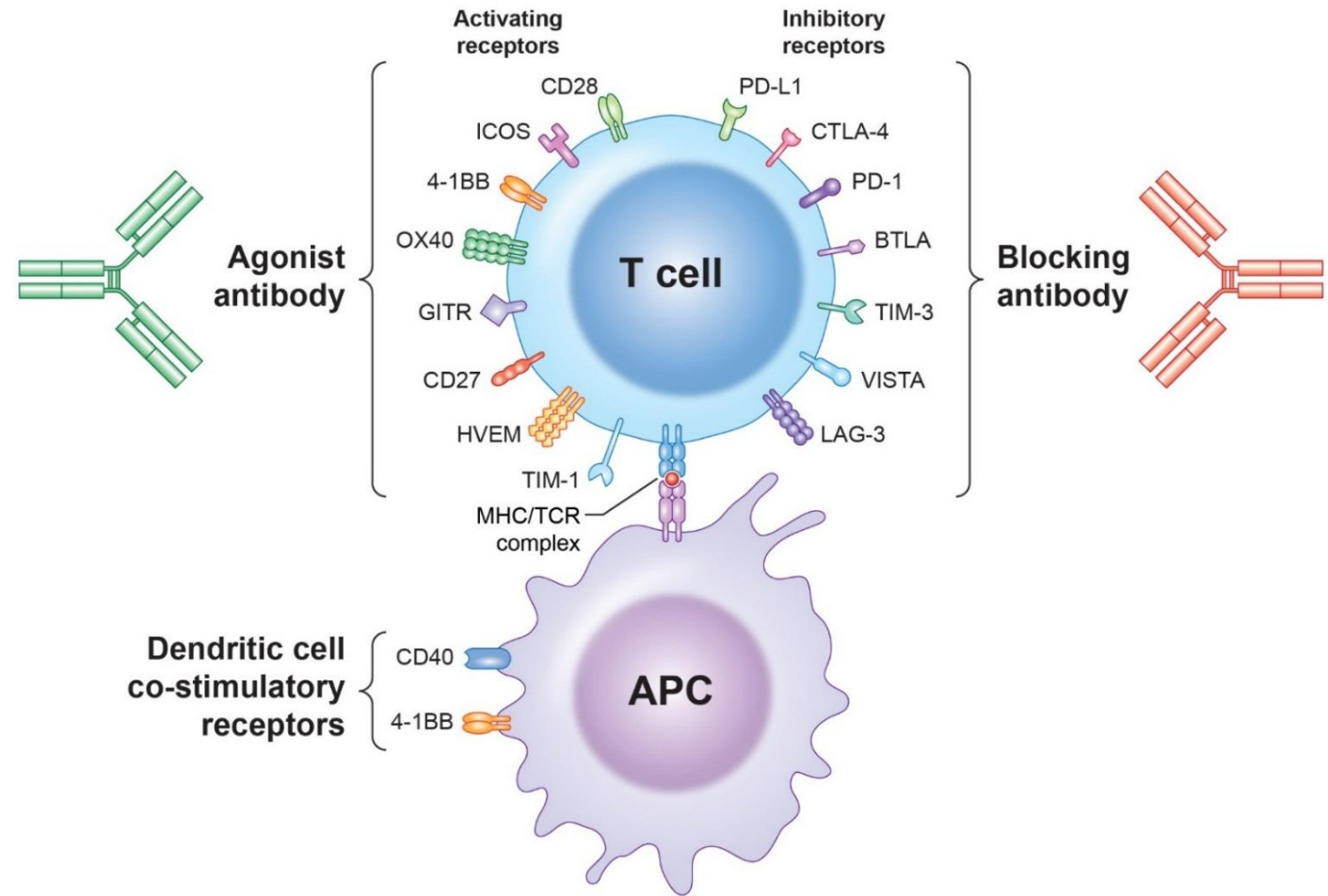
Checkpoint blockade therapy unleashes the “brakes” on T cells



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

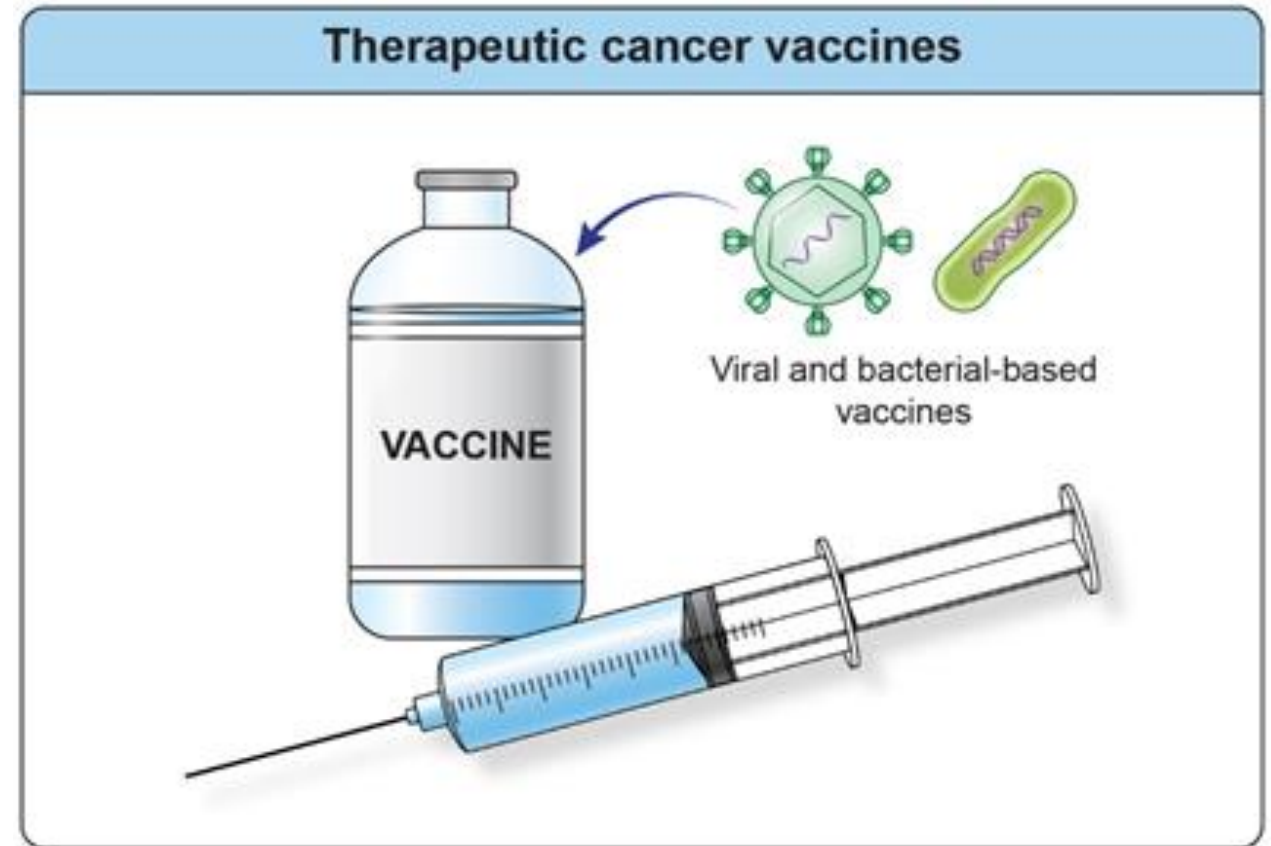
T Cell Checkpoint Modulation

- First generation of checkpoint modulation: blocking inhibitory checkpoints
- Second generation of checkpoint modulation: activating stimulatory checkpoints



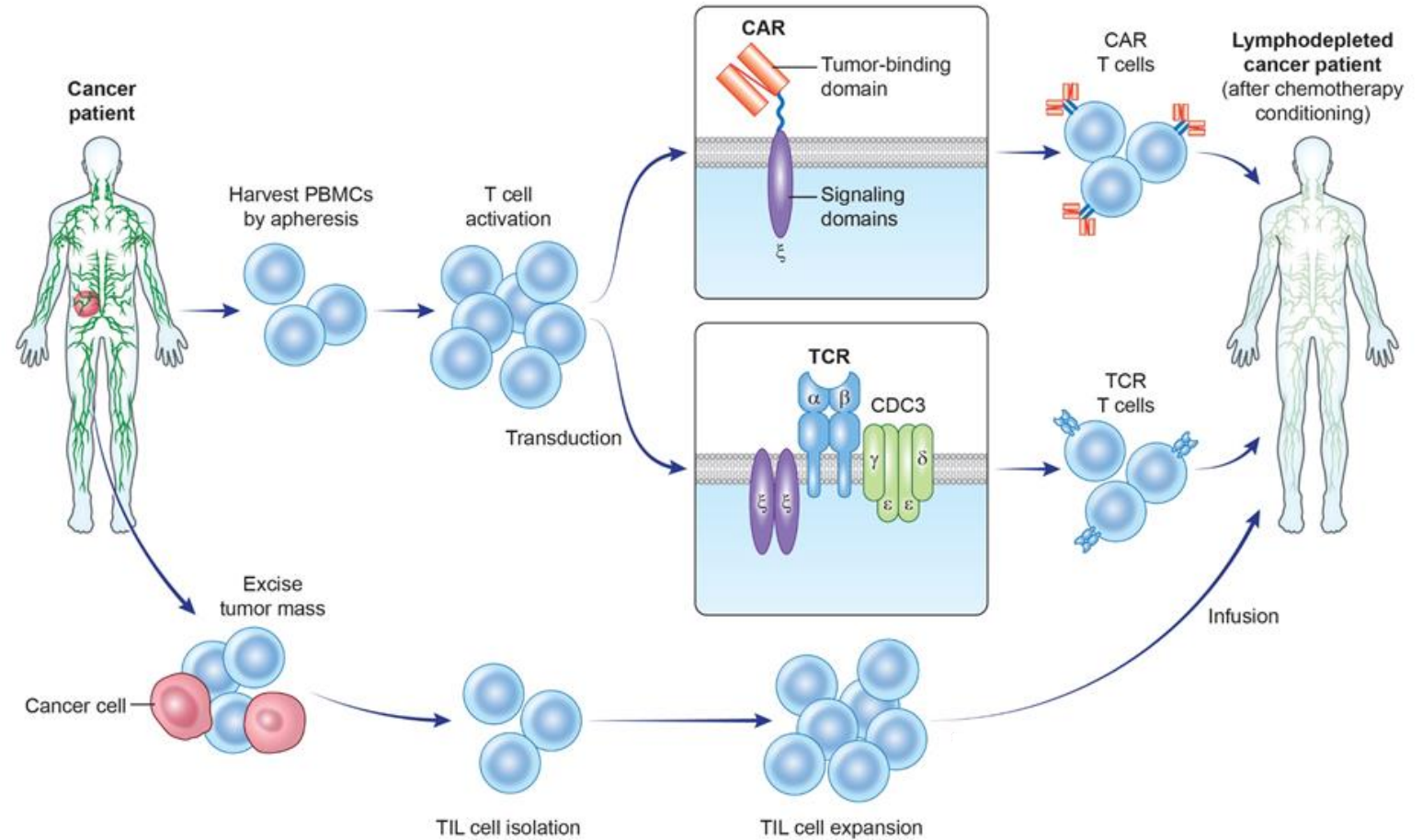
Therapeutic Cancer Vaccines

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



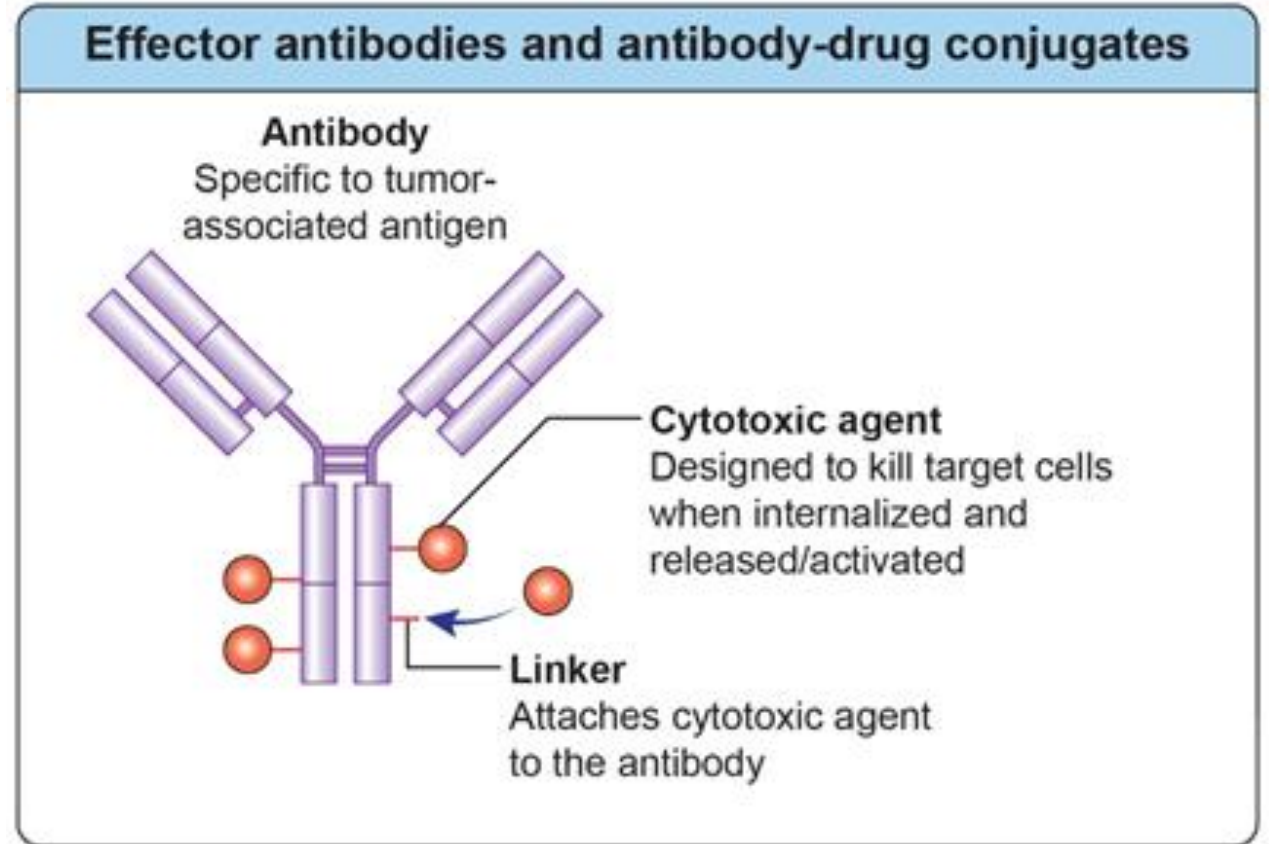
Adoptive Cell Therapy

Goal: overwhelm the tumor with a higher frequency of tumor-specific immune cells and/or engineer immune cells to target cancer.



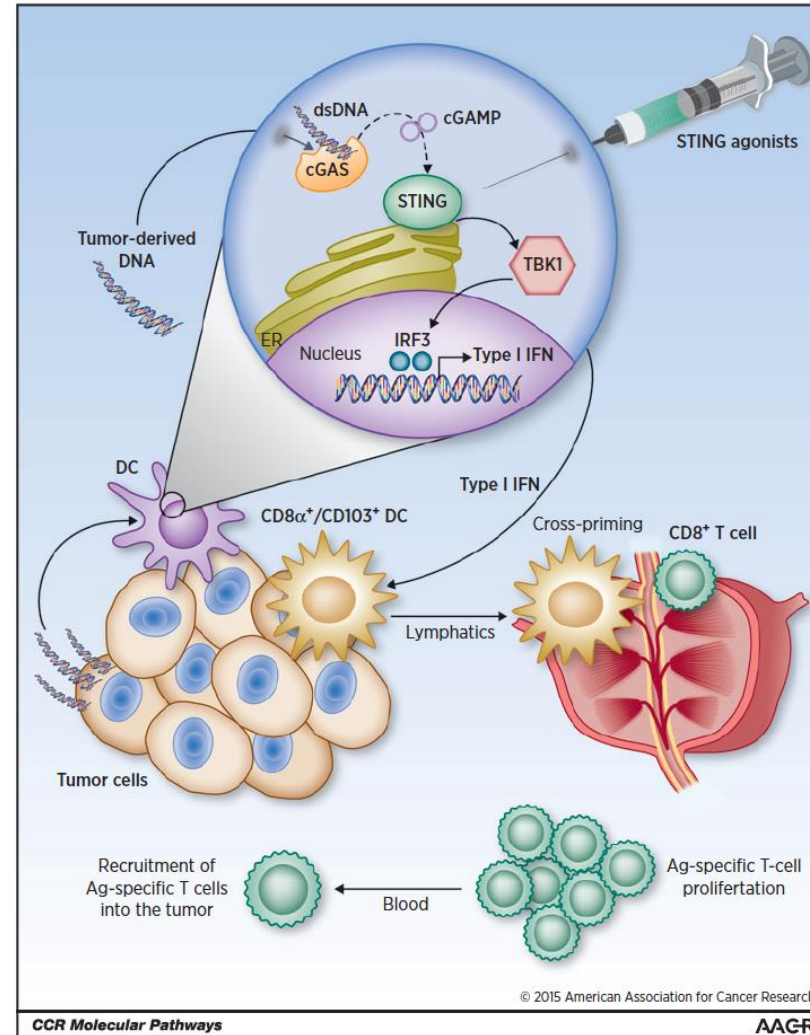
Effector Antibodies and Antibody-Drug Conjugates (ADCs)

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



Innate immune activation

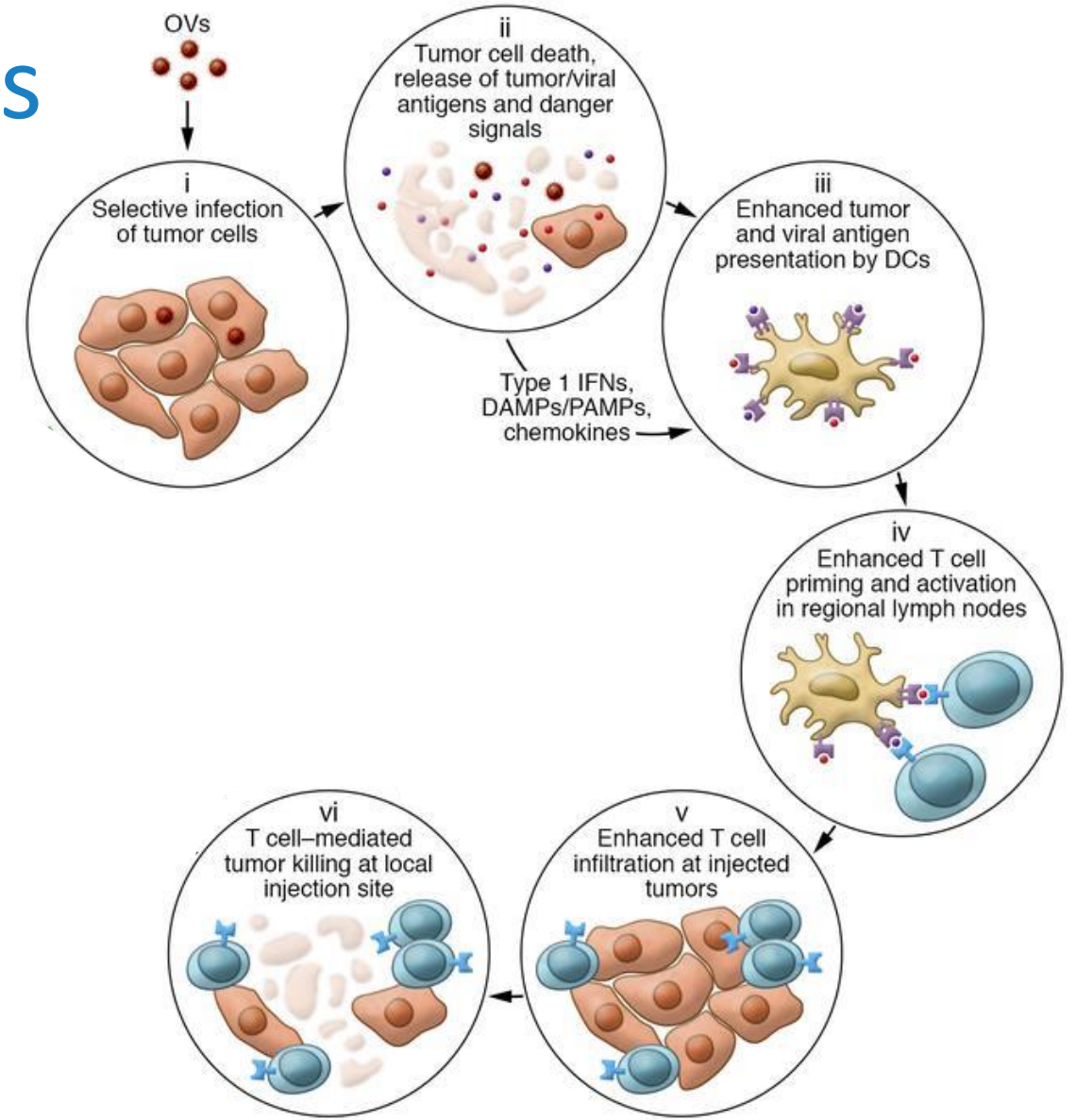
Goal: enhance innate immune sensing by providing stimulatory agents (frequently into the tumor itself)



Agents:
 Sting agonists
 TLR agonists
 Immunogenic RNA

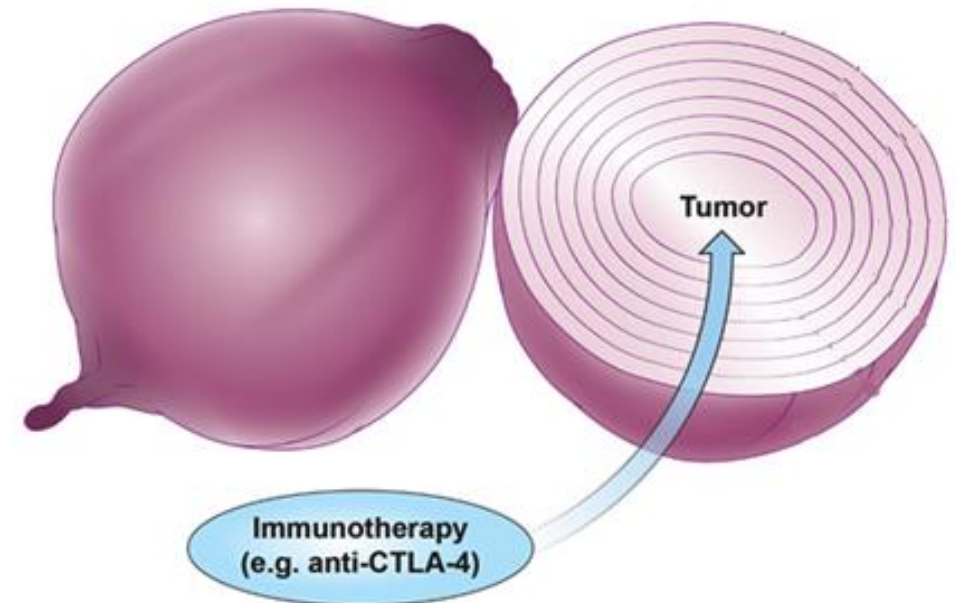
Oncolytic Viruses

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



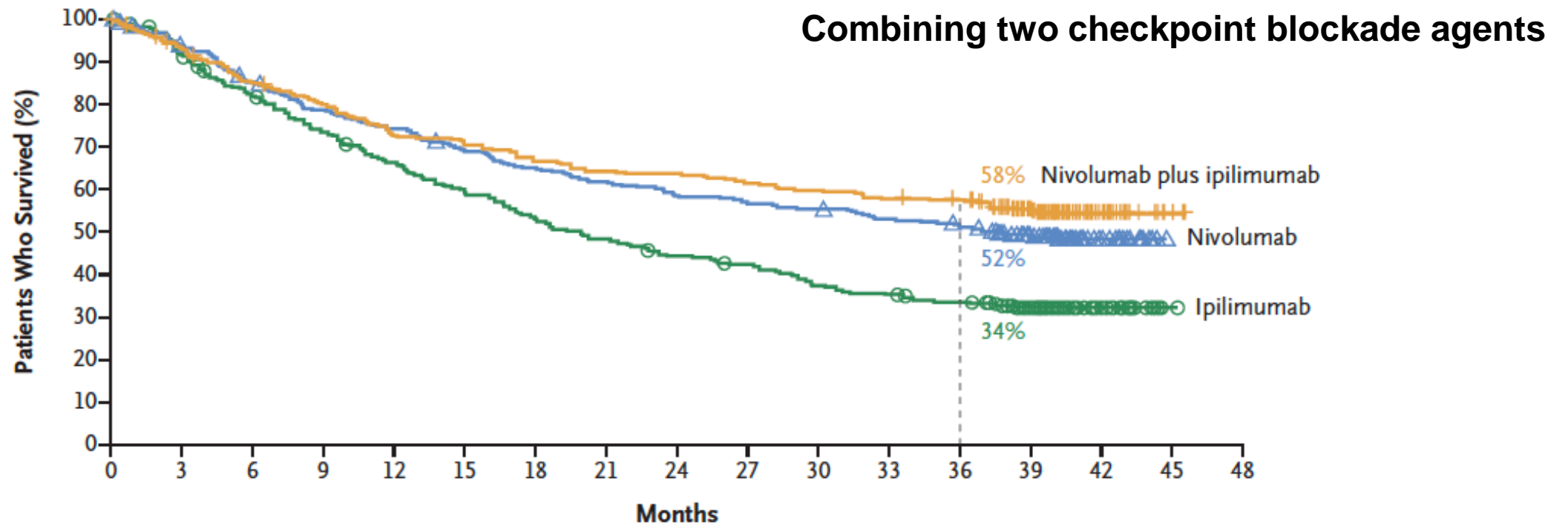
Multi-layered Immunosuppression

- 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 and PD-1 inhibition



Combination Immunotherapies

	CBT	ACT	Vacc.	Cytokines	CBT agonist	Innate agonist	Onc. virus	Targeted therapy	Radiation	Chemotherapy	
Checkpoint blockade therapy (inhibitors)	Approved	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy	Synergy	Synergy	Synergy (to be tested)	Synergy	Approved	Support T cell function
Adoptive cell therapy	Synergy (to be tested)	Not synergistic	Synergy (to be tested)	Approved	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy	Synergy	
Vaccines	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Not synergistic	
Cytokines	Synergy (to be tested)	Approved	Synergy (to be tested)	Not synergistic	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Not synergistic	Enhance innate immune system
Checkpoint blockade therapy (stimulatory)	Synergy	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	
Innate immune agonists	Synergy	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	
Oncolytic virus	Synergy	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Induce tumor cell death
Targeted therapy	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Not synergistic	
Radiation	Synergy	Synergy	Not synergistic	Not synergistic	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Not synergistic	
Chemotherapy	Approved	Synergy	Not synergistic	Not synergistic	Synergy (to be tested)	Synergy (to be tested)	Synergy (to be tested)	Not synergistic	Not synergistic	Not synergistic	

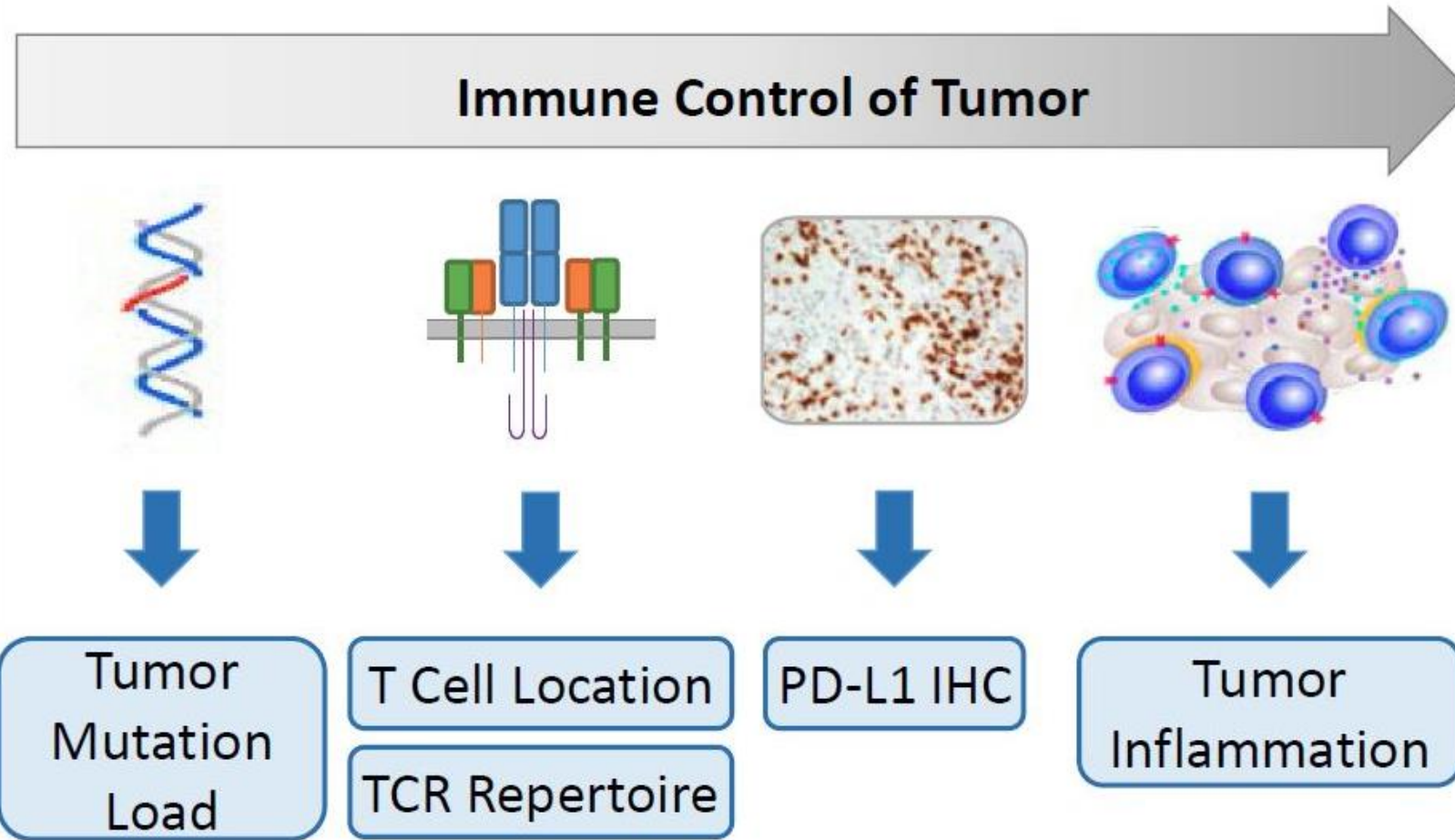
 Approved
 Synergy
 (to be tested)
 Not synergistic


Support T cell function

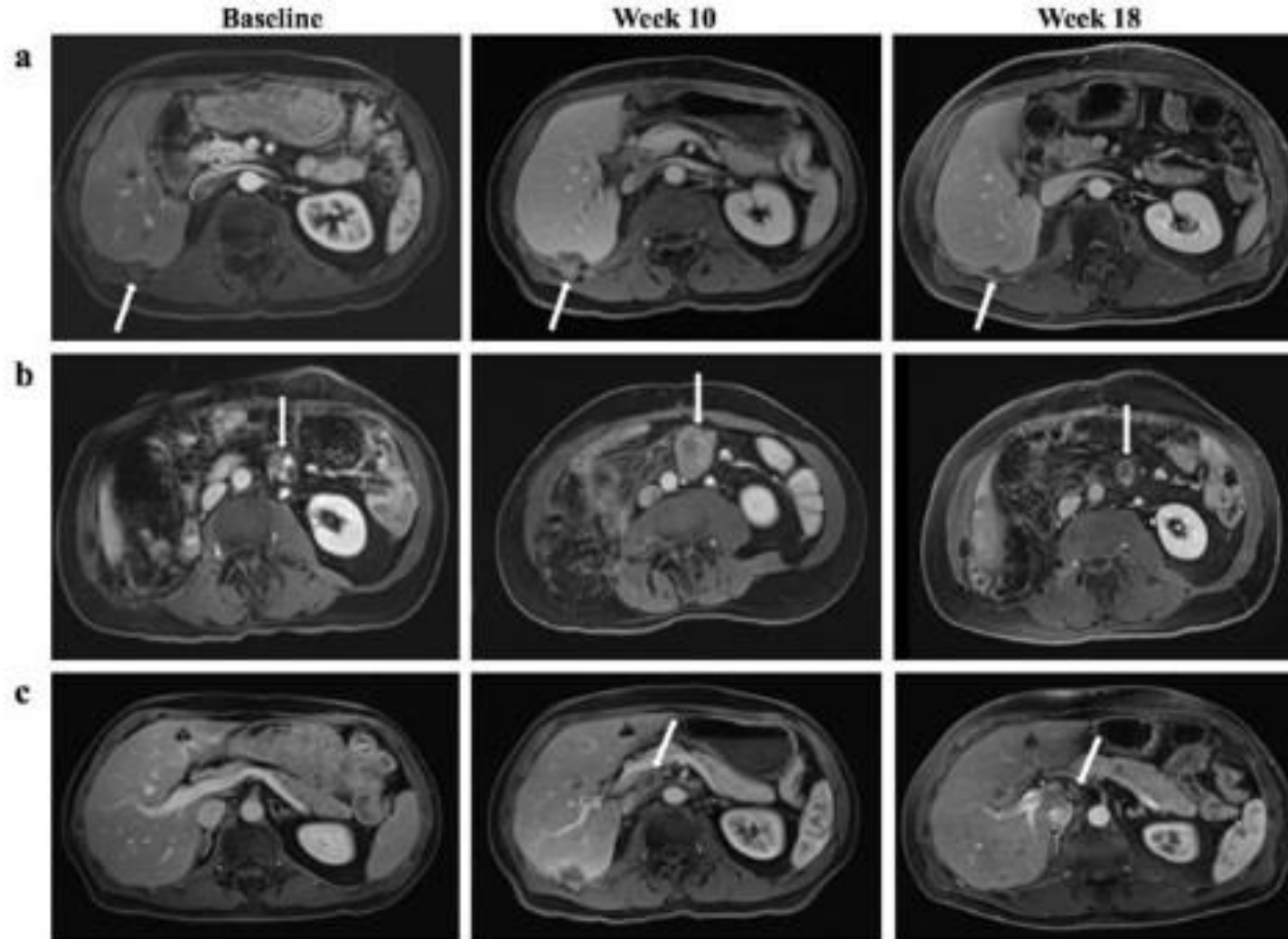
Enhance innate immune system

Induce tumor cell death

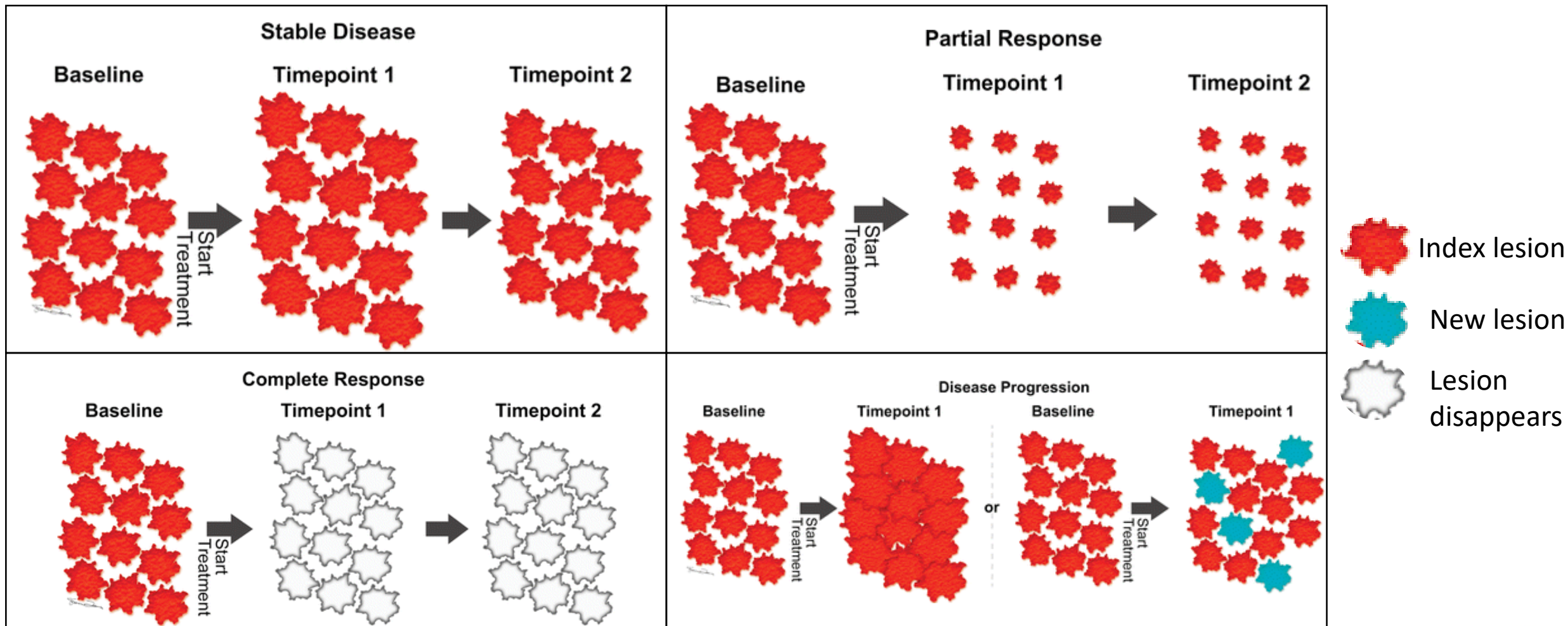
Immunotherapy Biomarkers



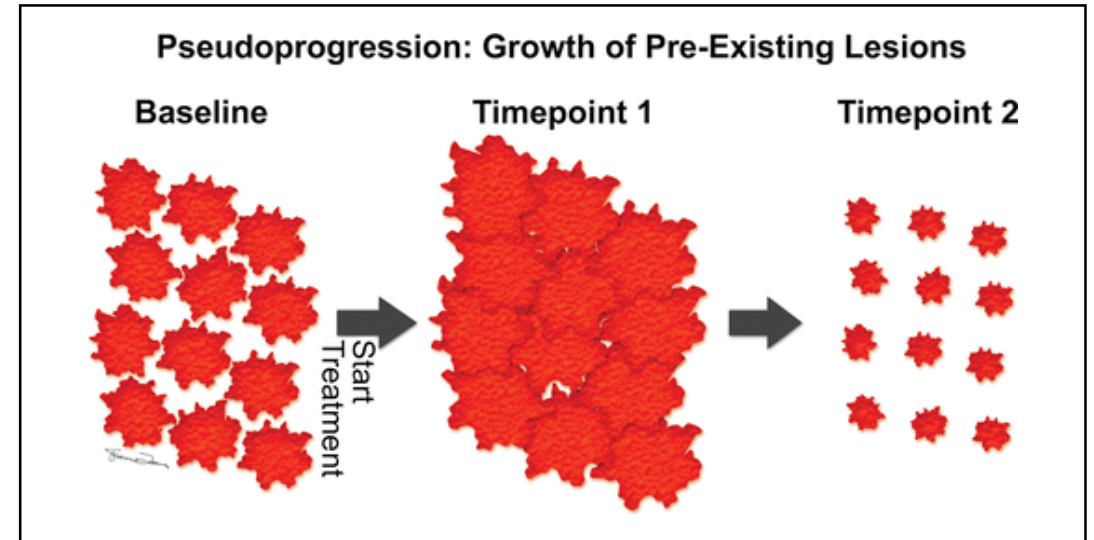
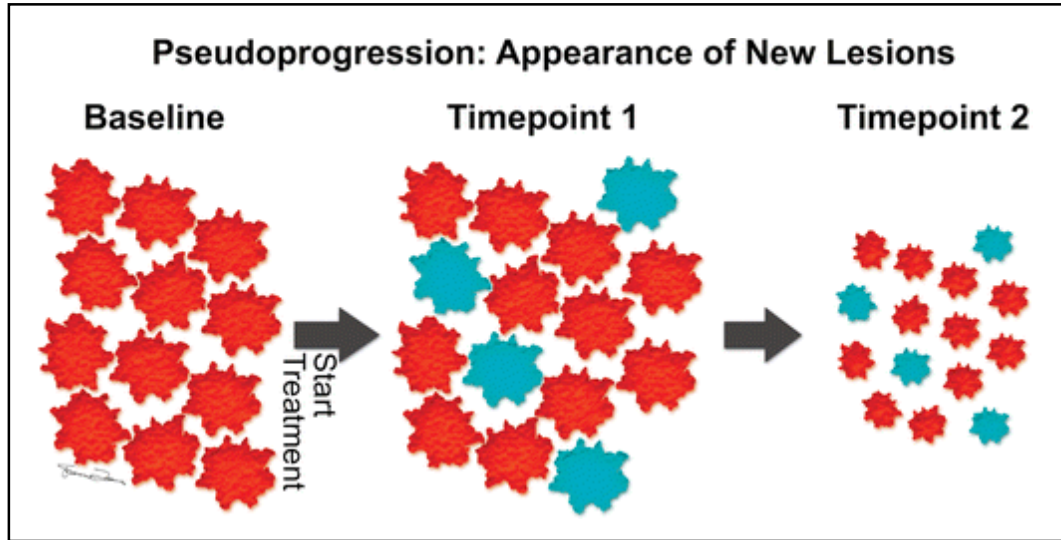
Assessment of response



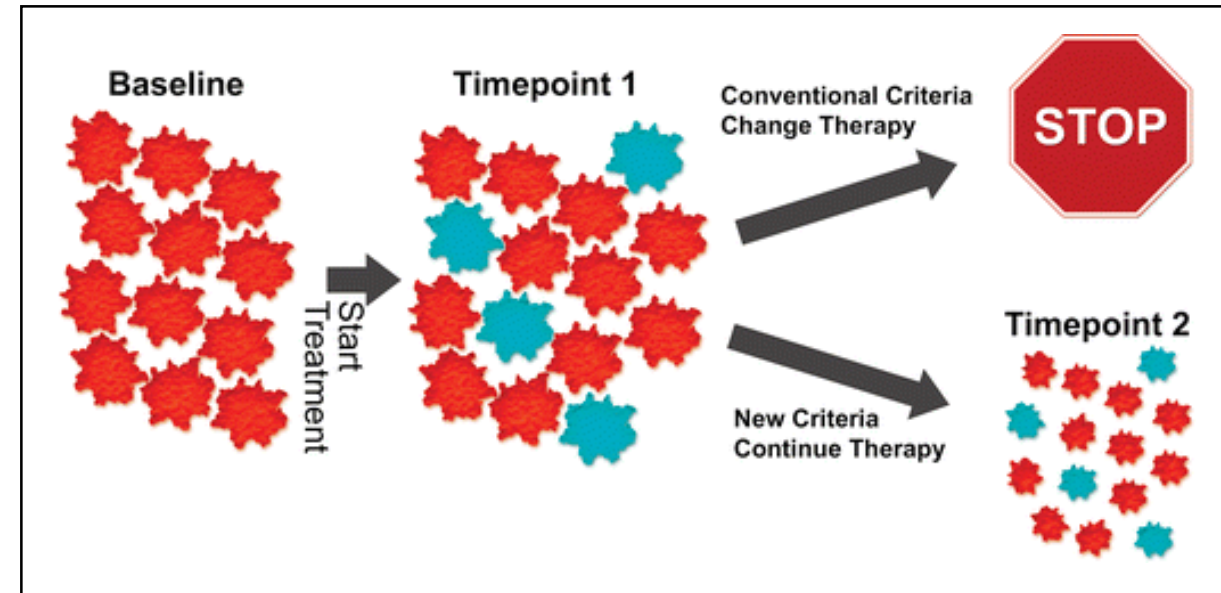
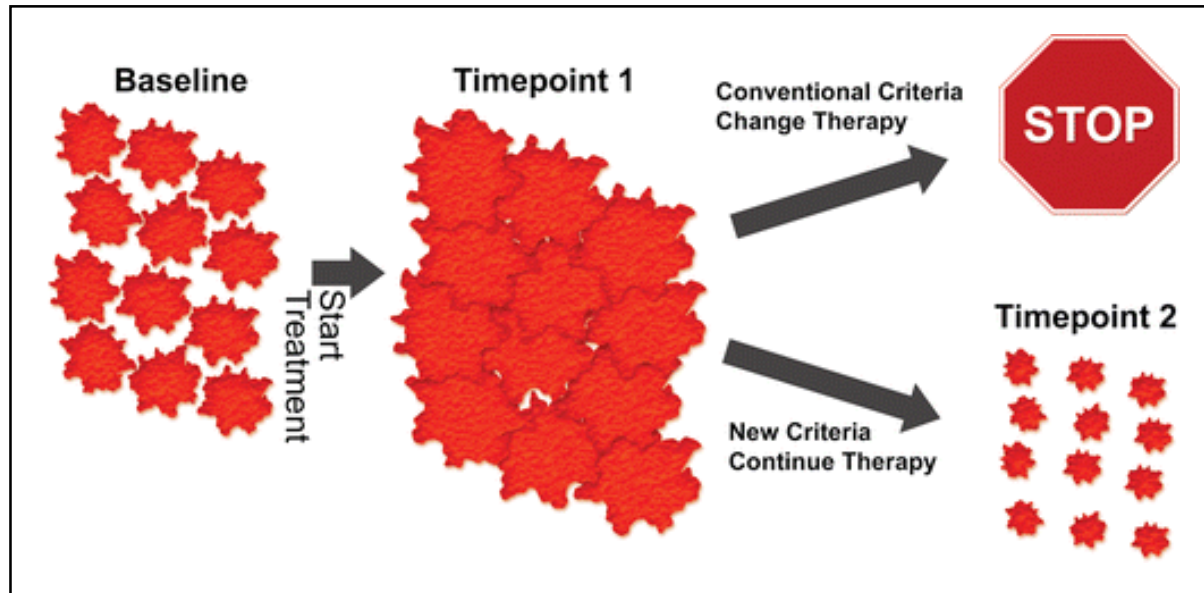
Many possible imaging findings



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	irRC
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.

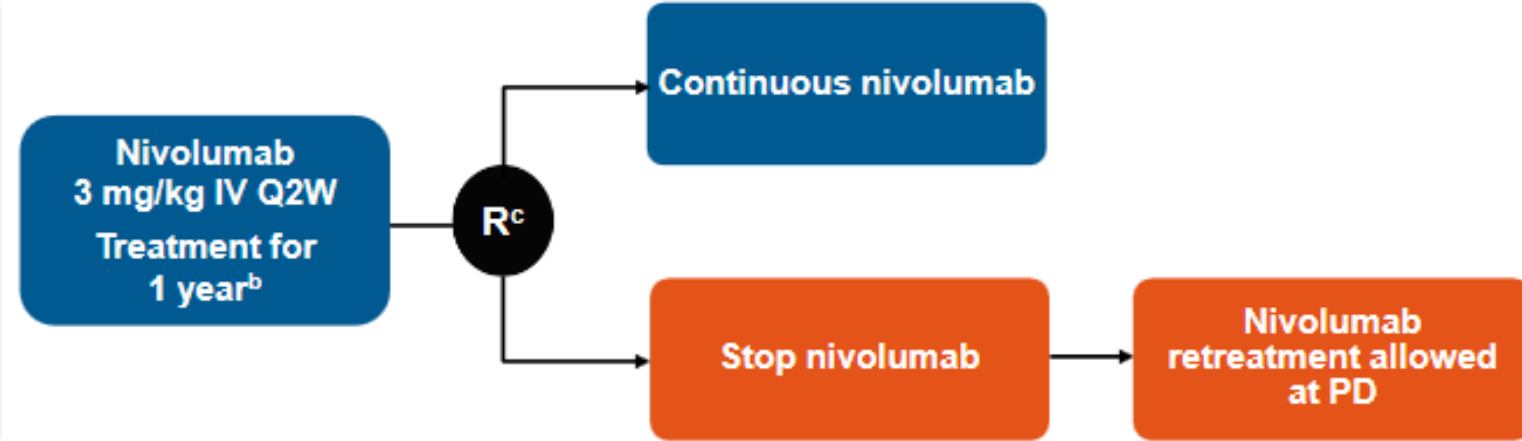
⁺Based on the sum of the products of the two largest perpendicular diameters of all index lesions.

[#]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

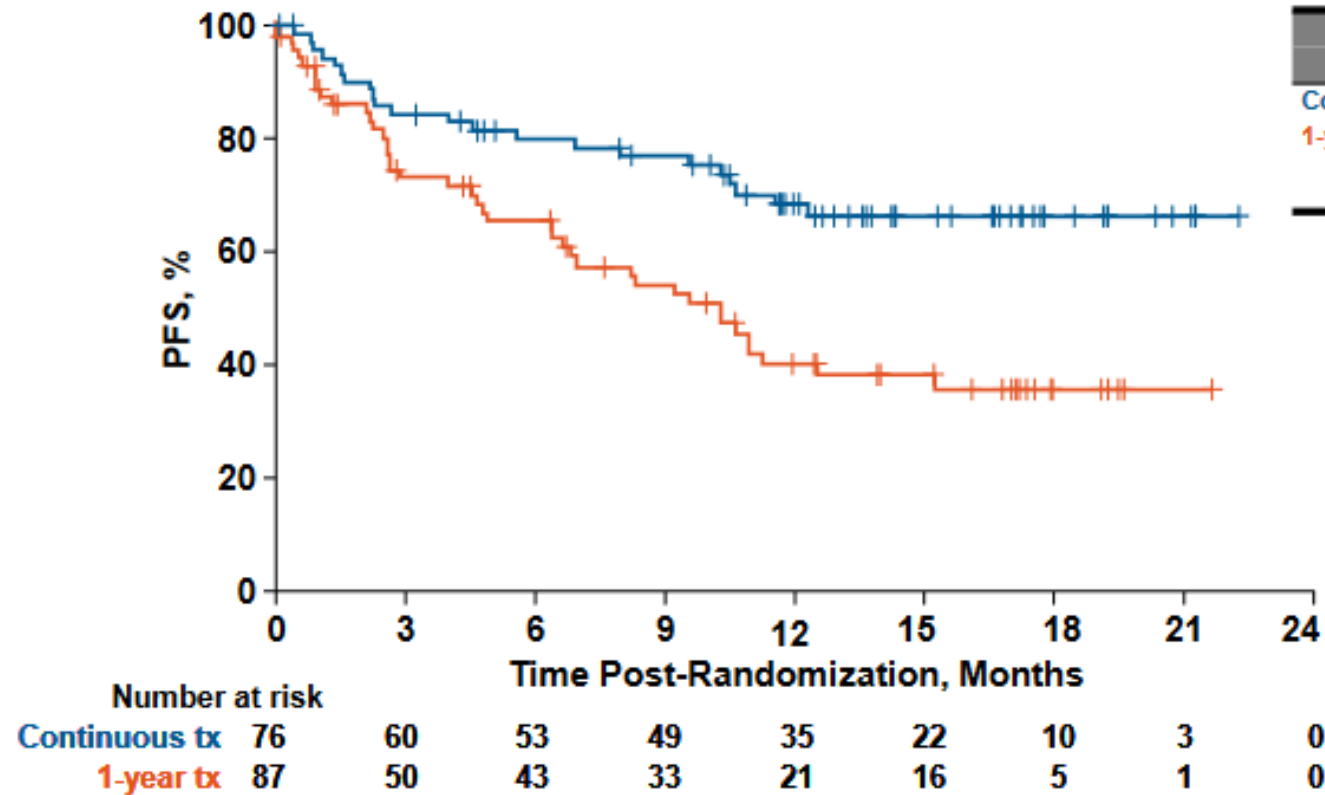
Key eligibility criteria:

- Advanced/metastatic NSCLC
- ≥1 prior systemic therapy^a
- ECOG PS 0-2
- Treated CNS metastases allowed



Exploratory endpoints^d: Safety/efficacy^e with continuous vs 1-year treatment, efficacy, other (eg, biomarkers, PK)

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)			

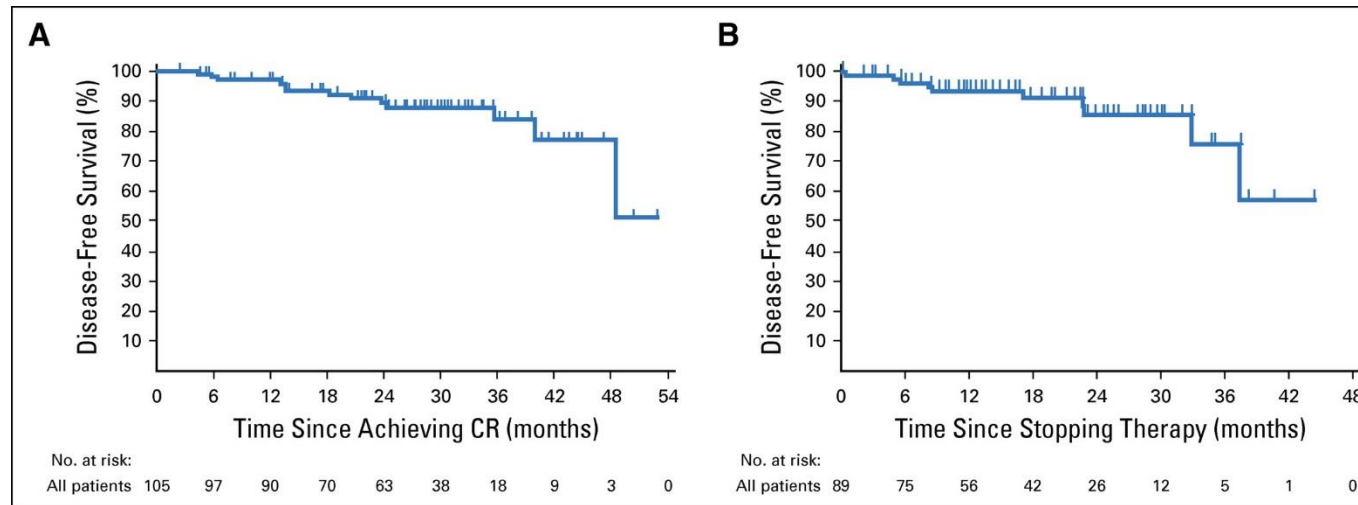
Conclusion: >1 year of treatment may be necessary

When to stop immunotherapy: KEYNOTE-006

- 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

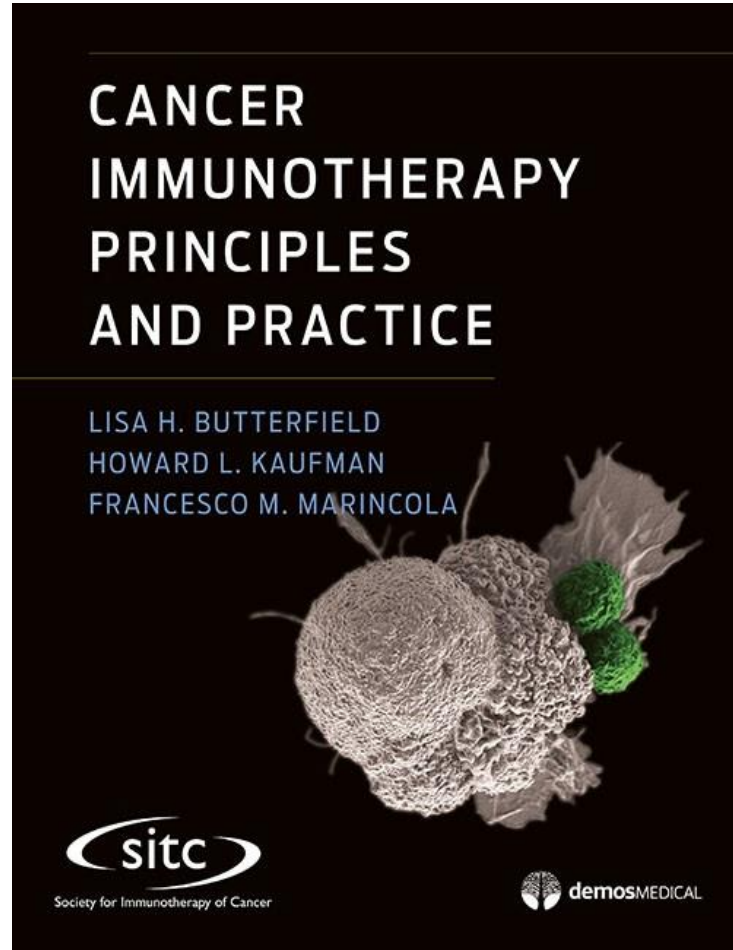
- 16% of patients achieved complete response
- Disease-free survival at 24 months after complete response:
 - In all CR patients: 90.9%
 - In patients who discontinued cancer therapy: 89.9%



When to stop immunotherapy: clinical measures

- PET-based metabolic response
 - Metabolic response may precede anatomical changes on CT or MRI
- Achievement of CR

Further Resources



SOCIETY FOR IMMUNOTHERAPY OF CANCER

