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ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Speaker Bureau/Advisory Board:

  BMS, Merck, Regeneron, BioArray, Exelixis, Novartis

- Contracted Research:

  BMS, Merck

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

Principles of Cancer Immunotherapy

- Generation of the anti-tumor immune response
- Immunotherapy approaches
- Immune escape mechanisms
- Overcoming immune suppression
- Biomarkers – predicting response
- Tumor assessment after immunotherapy
- Optimal duration of therapy?

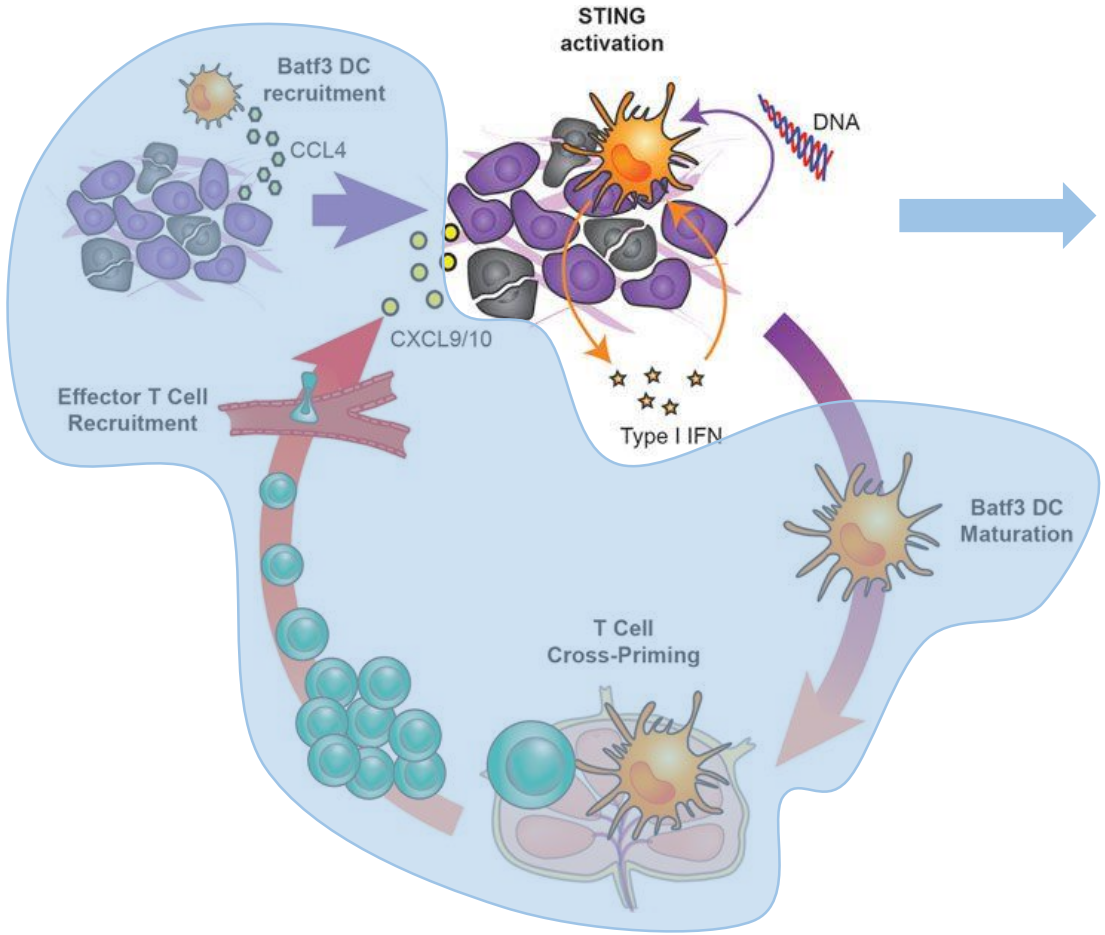
The Premise of Cancer Immunotherapy

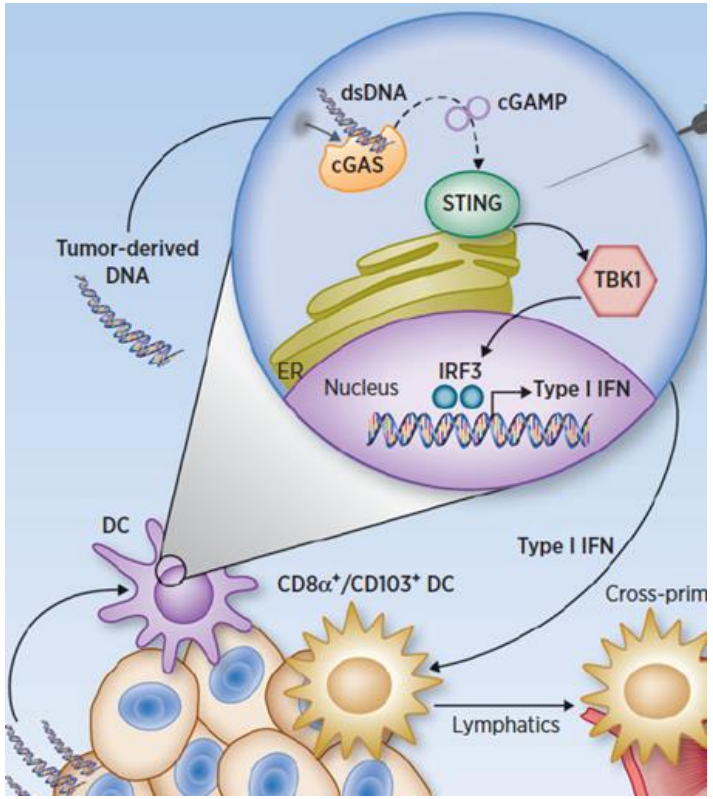
- Normally, the immune system eliminates damaged cells, including precancerous and cancer cells

- 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.

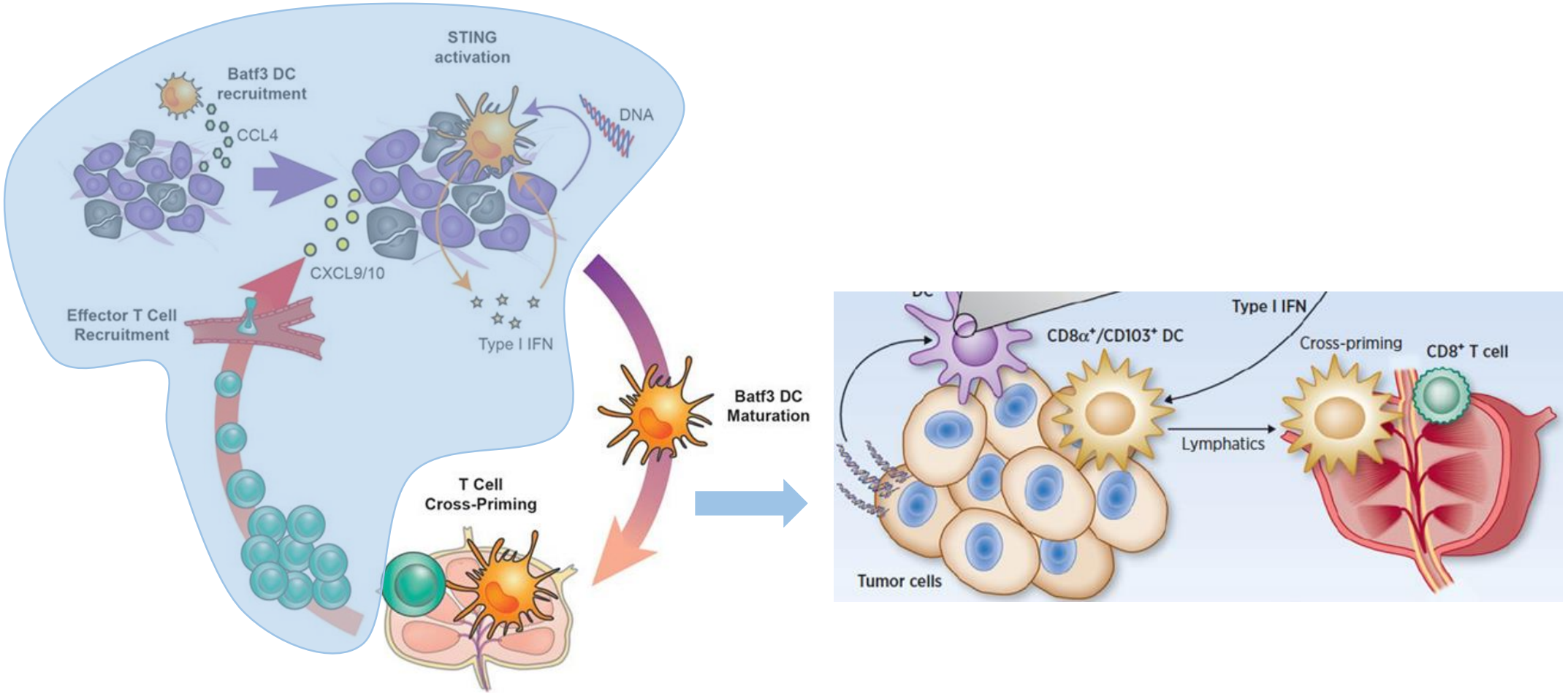
Initiation of an anti-tumor immune response - Innate immune sensing



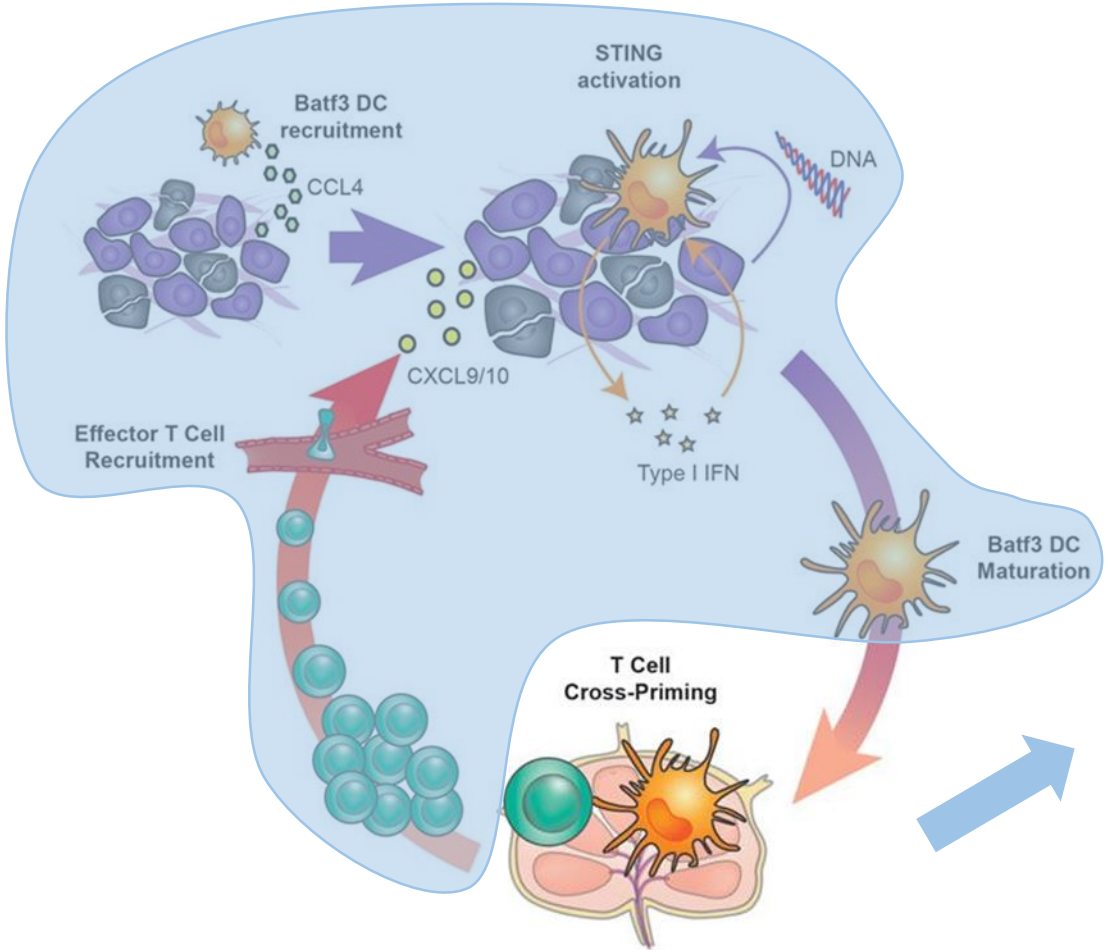


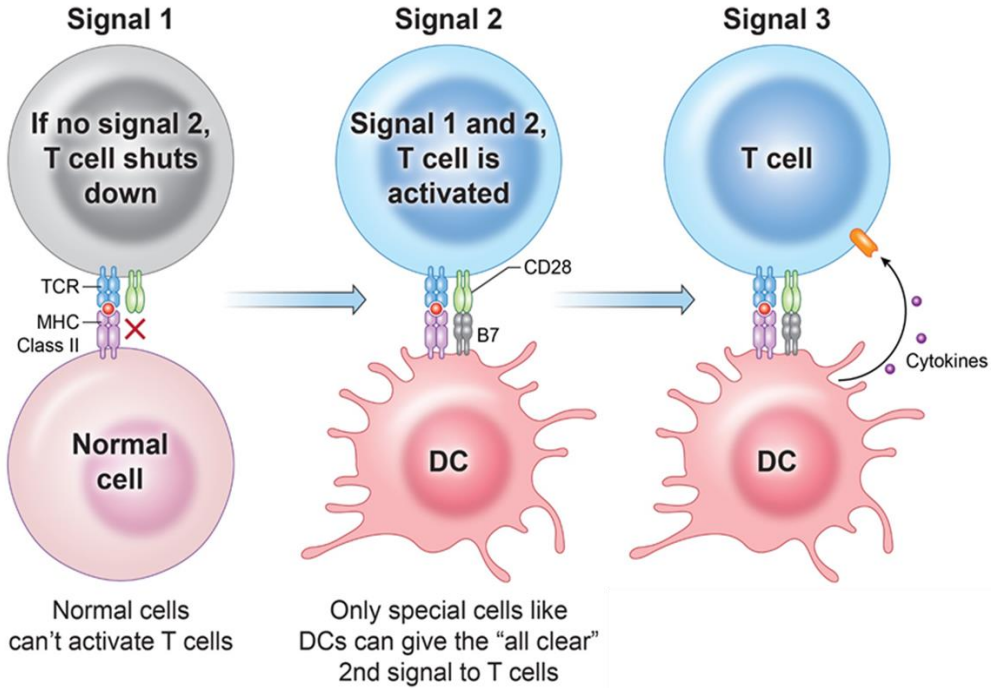
Modified from Corrales et al. Cell Res. 2017

Anti-tumor immune response - APC maturation and transport to TdLN



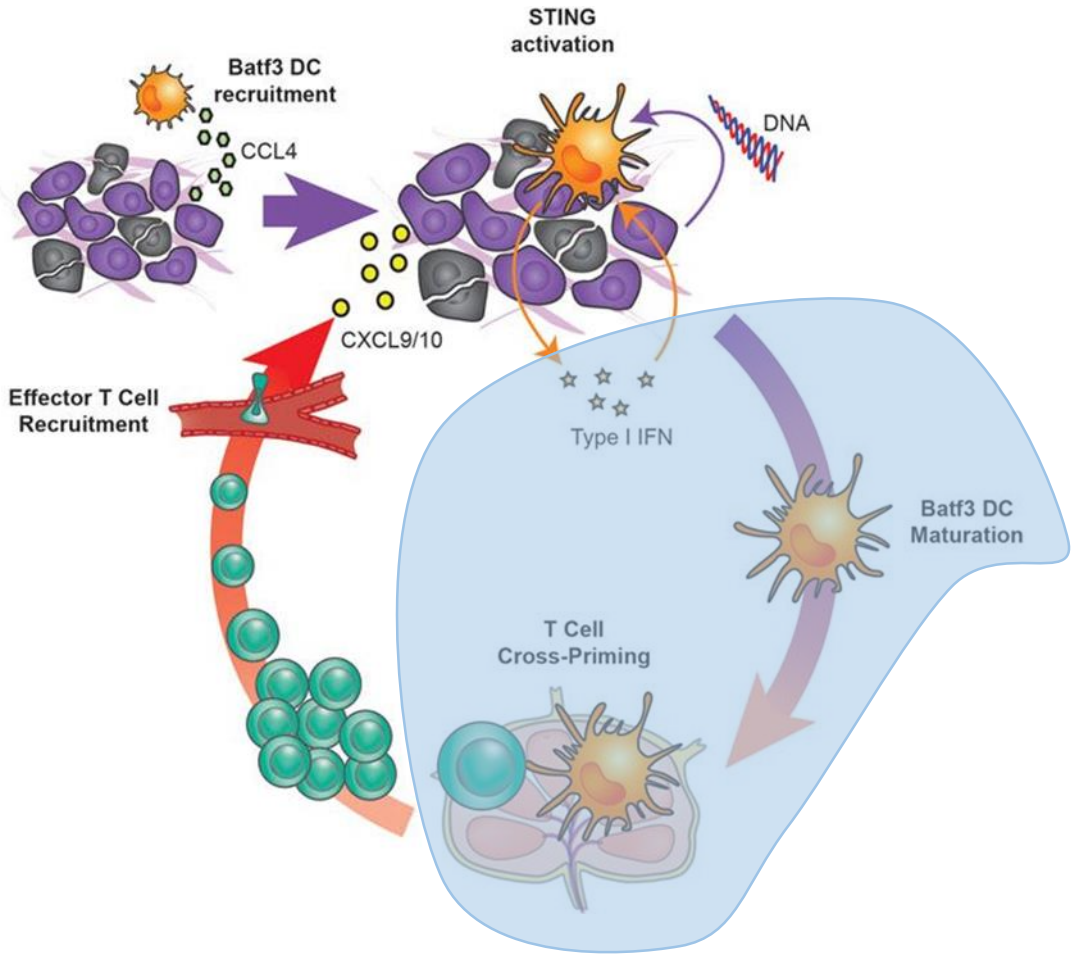
Initiation of an anti-tumor immune response - Cytotoxic T cell activation





Modified from Corrales et al. Cell Res. 2017

Initiation of an anti-tumor immune response - T cell recruitment



Modified from Corrales et al. Cell Res. 2017

Types of Immunotherapy

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

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

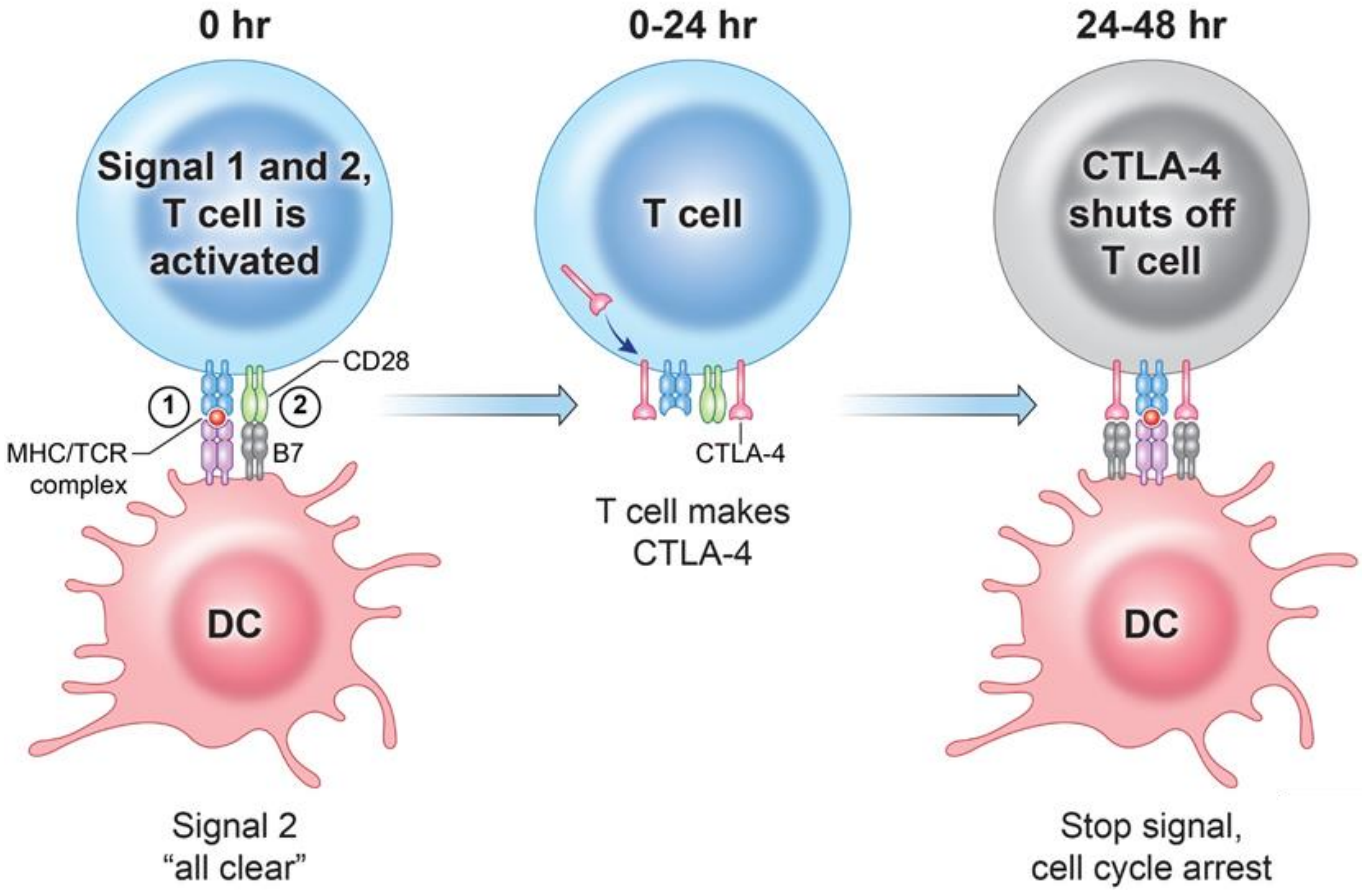
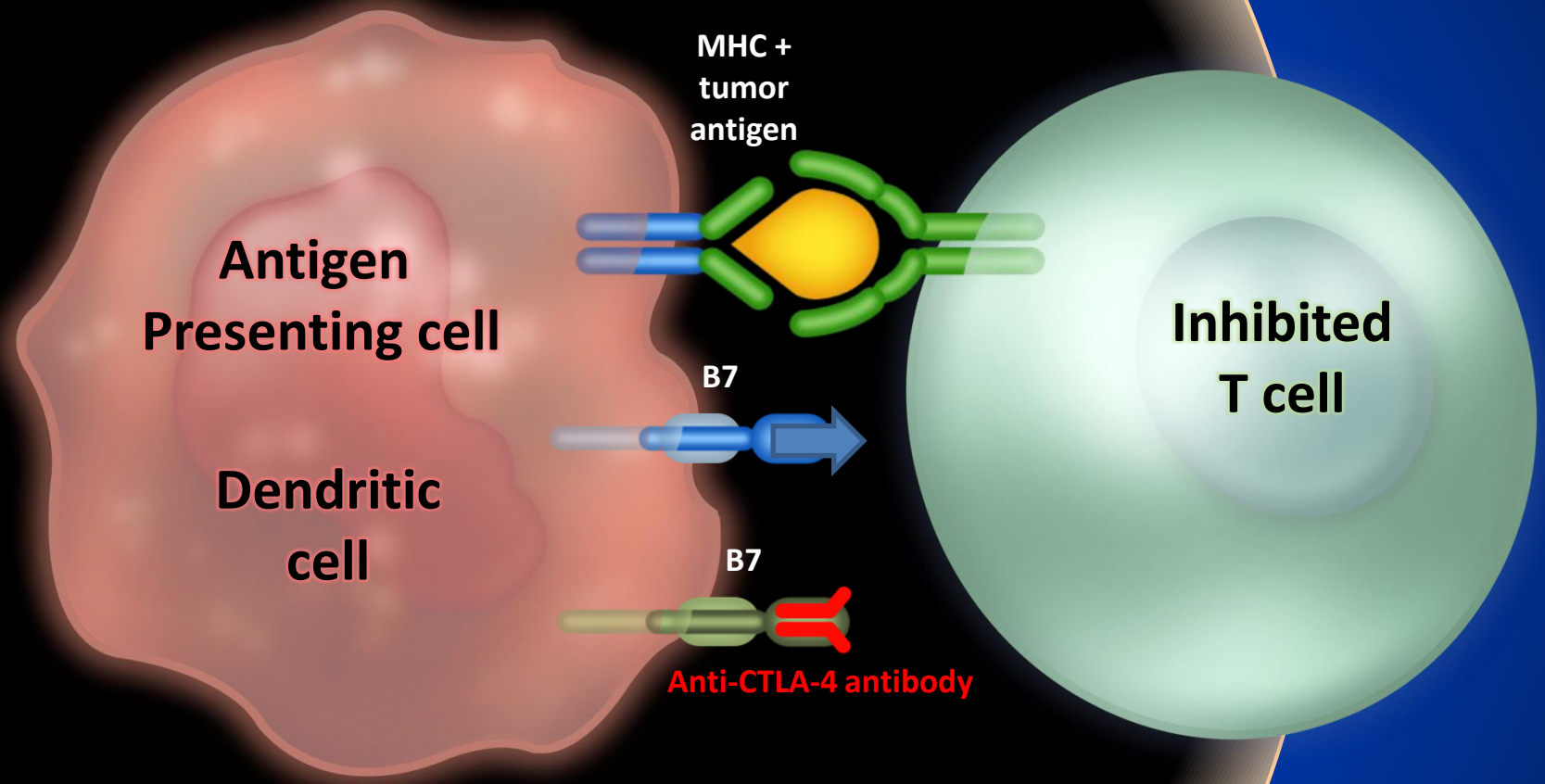


Image courtesy of NCI

CTLA-4 Blockade unleashes the “brakes” on T cells



Central Immune Event

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)

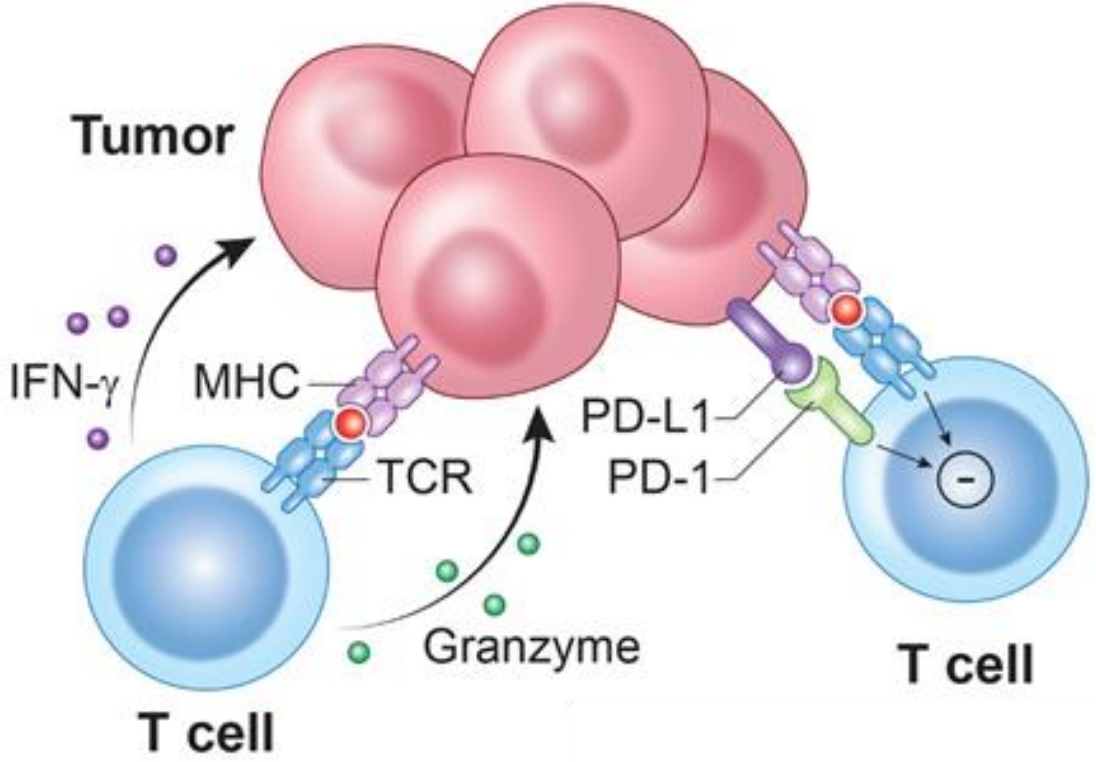
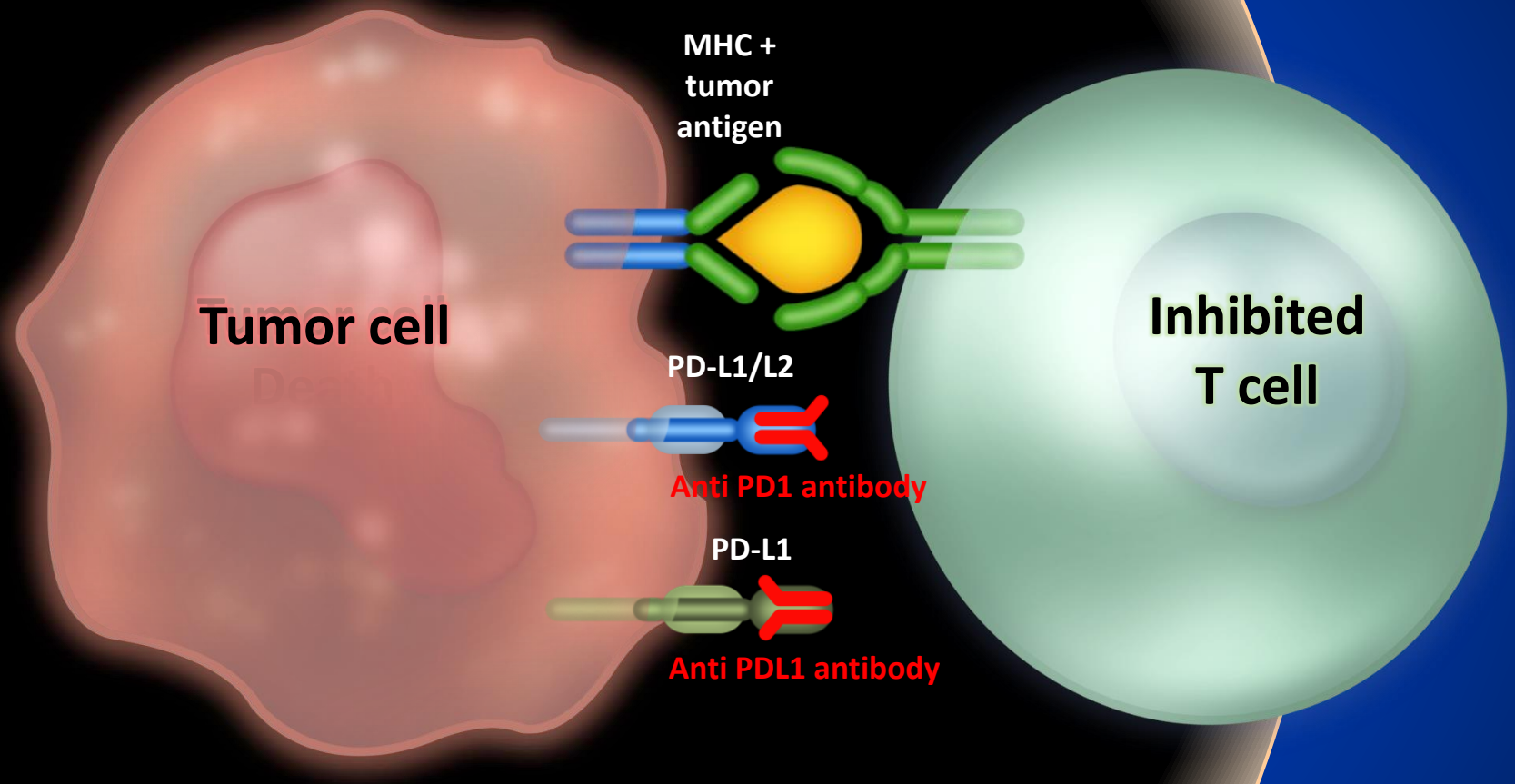


Image courtesy of NCI

PD1 Axis Blockade prevents T cells from switching OFF



Tumor Microenvironment

T Cell Checkpoint Modulation

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

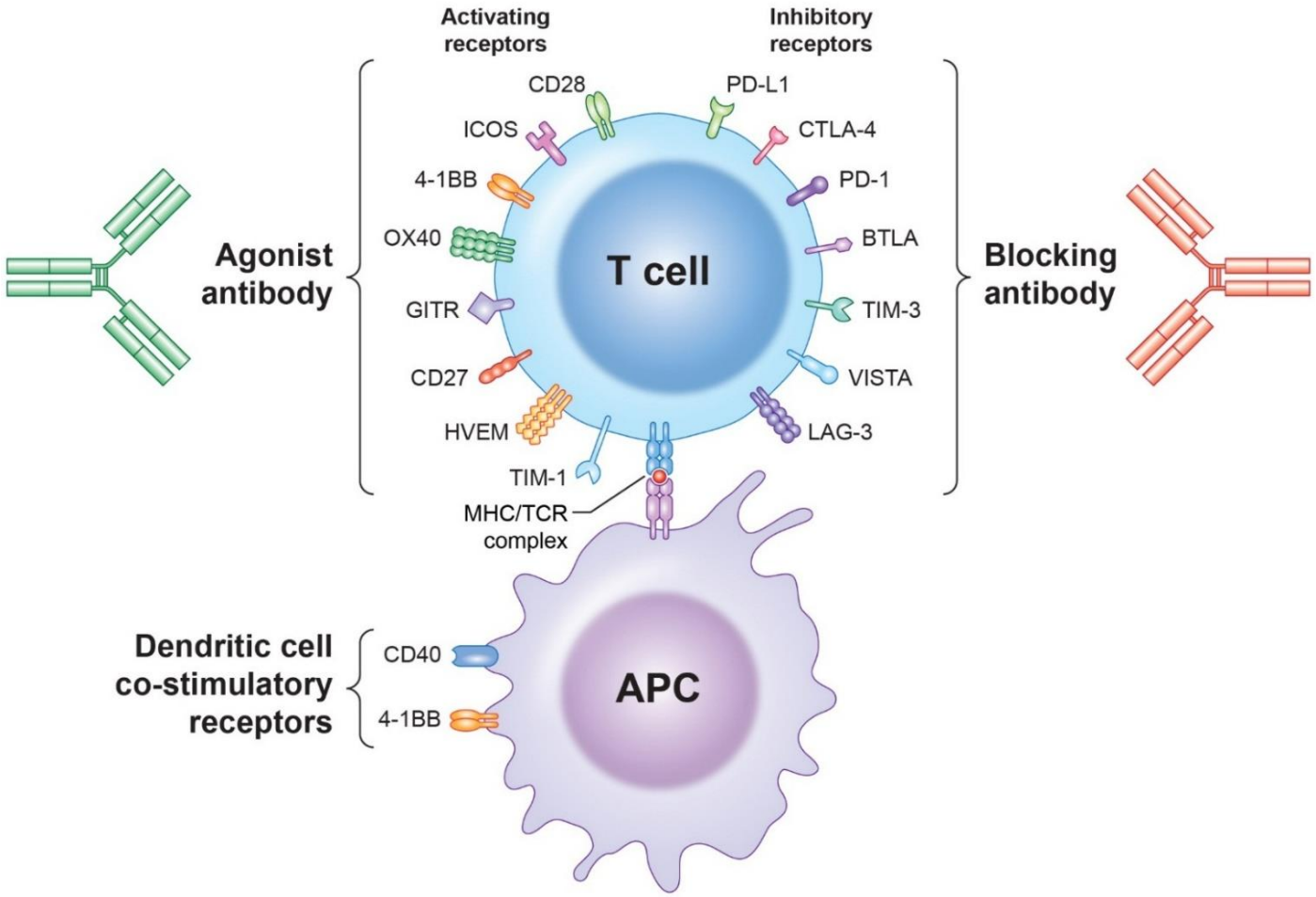


Image courtesy of NCI

Therapeutic Cancer Vaccines

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

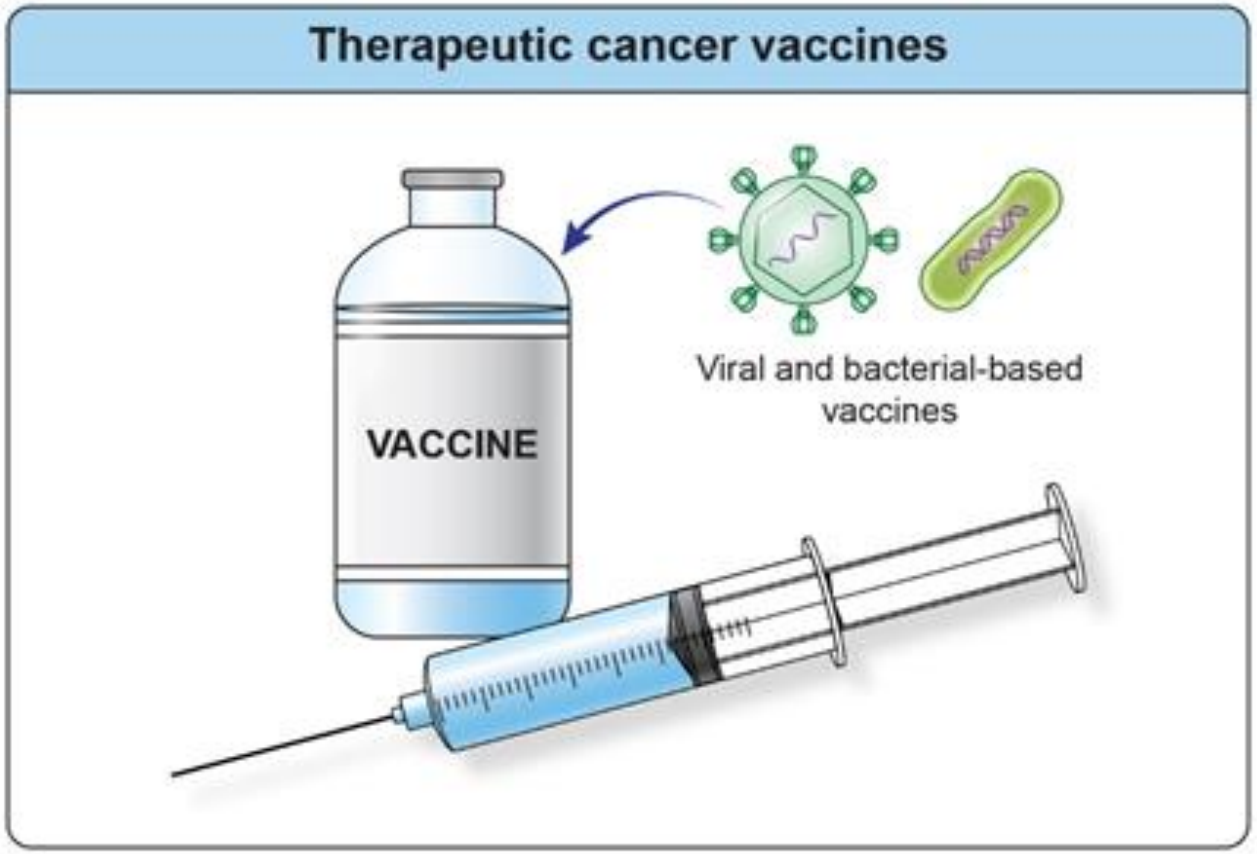


Image courtesy of NCI

Adoptive Cell Therapy

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

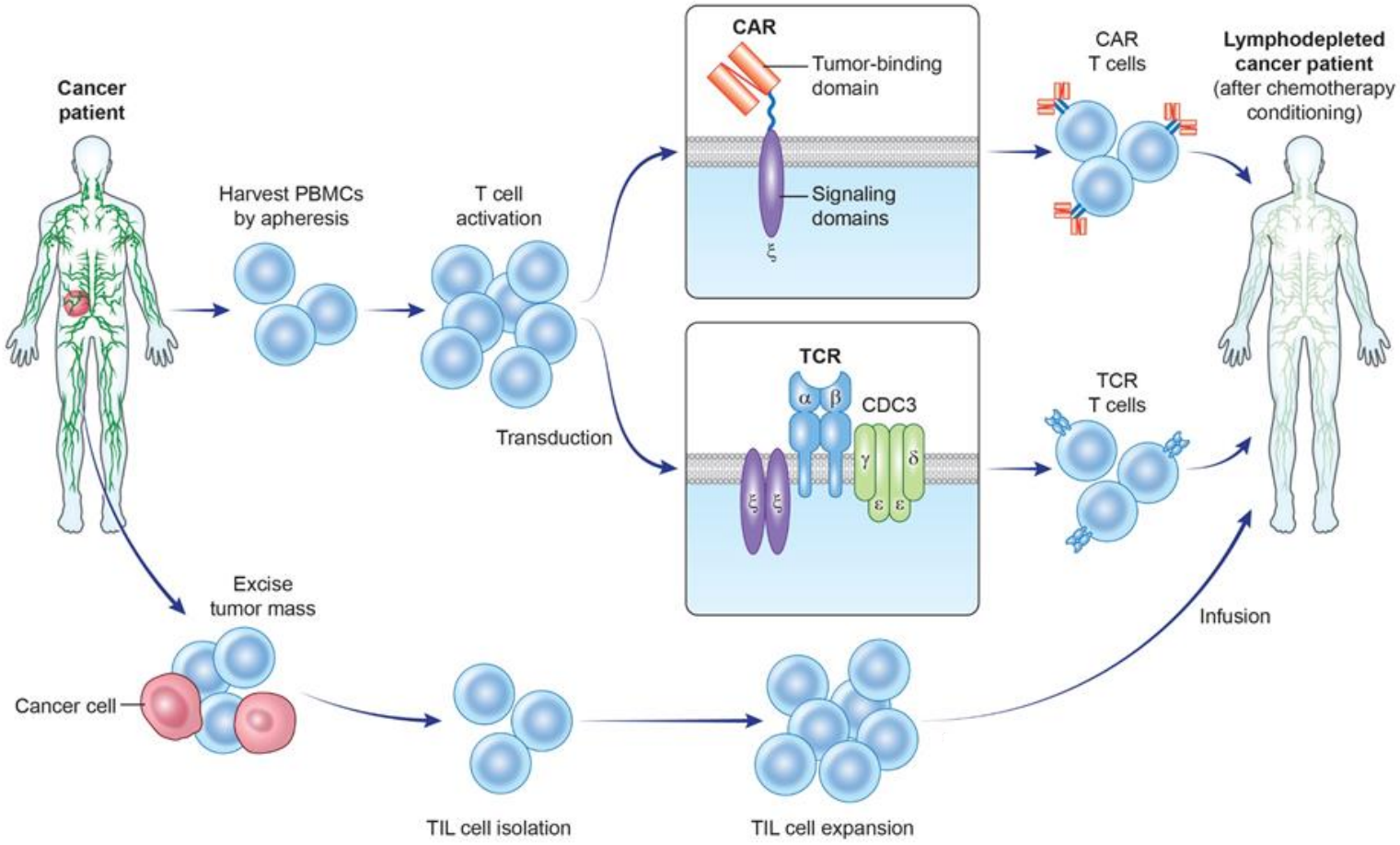


Image courtesy of NCI

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

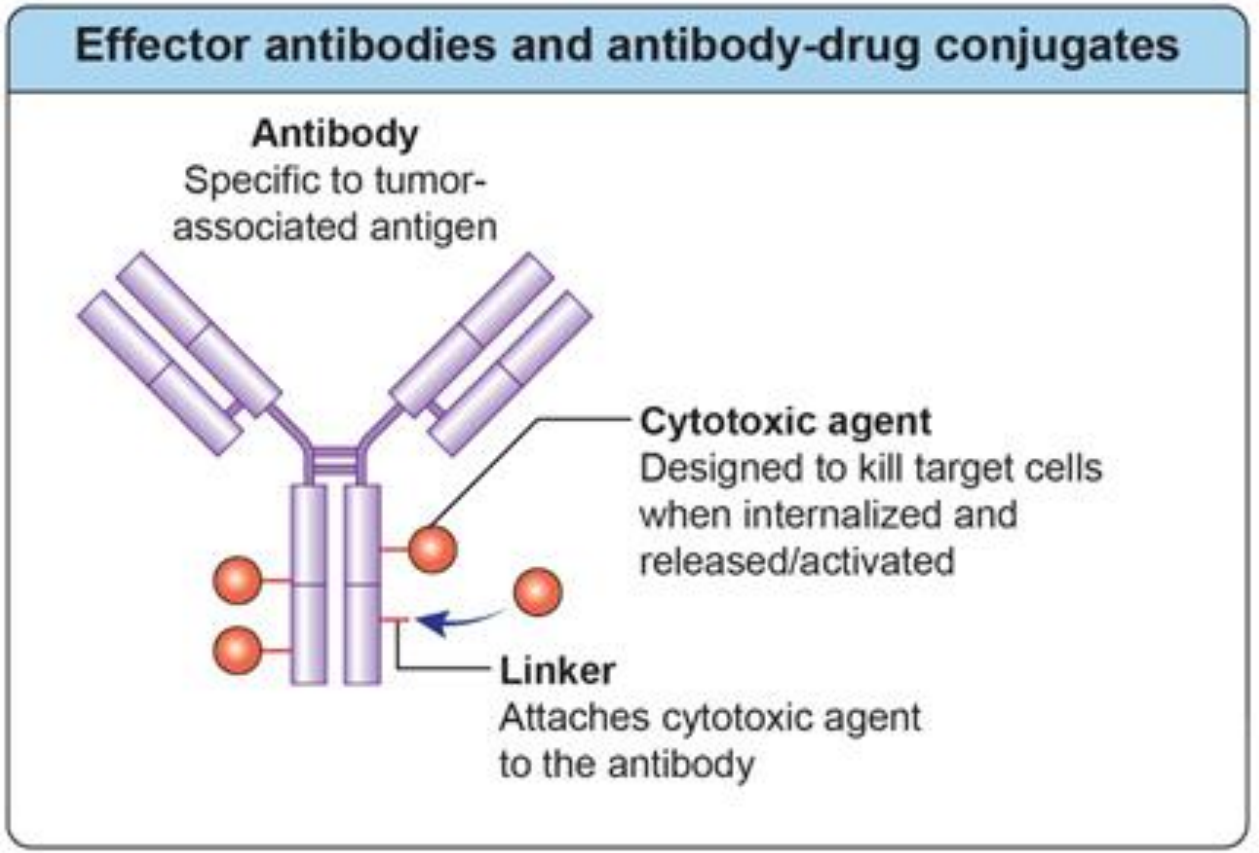
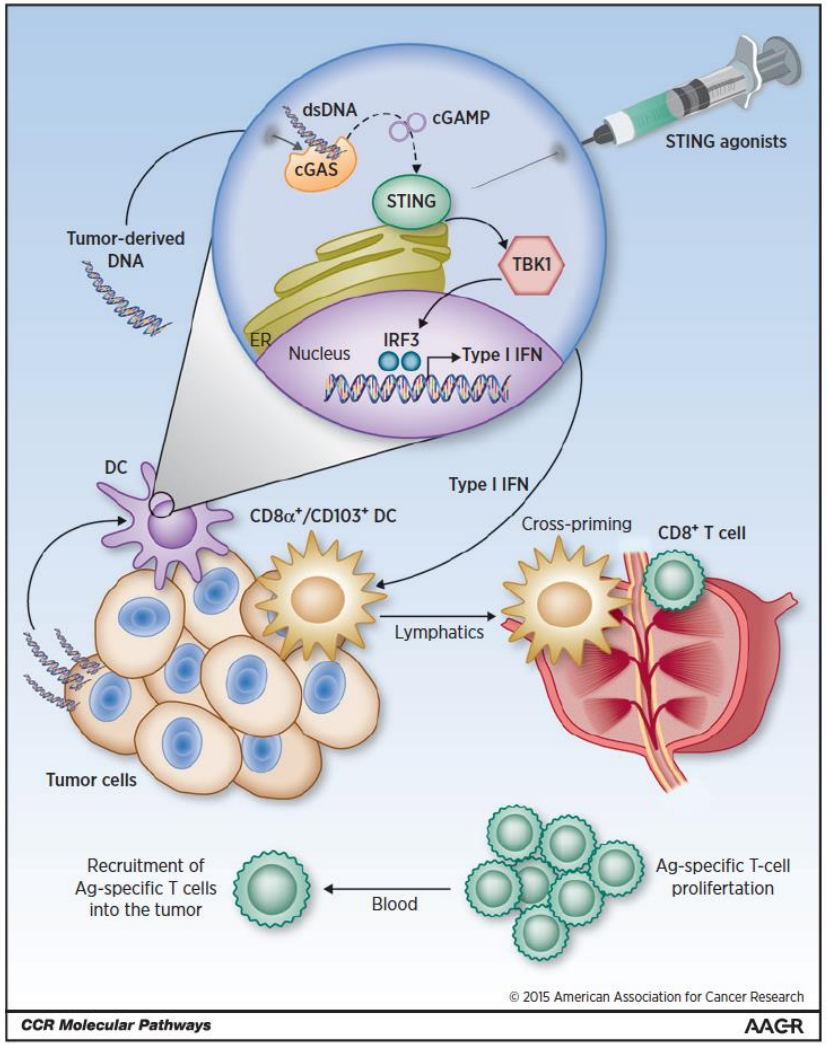


Image courtesy of NCI

Innate immune activation

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



Agents:

Sting agonists

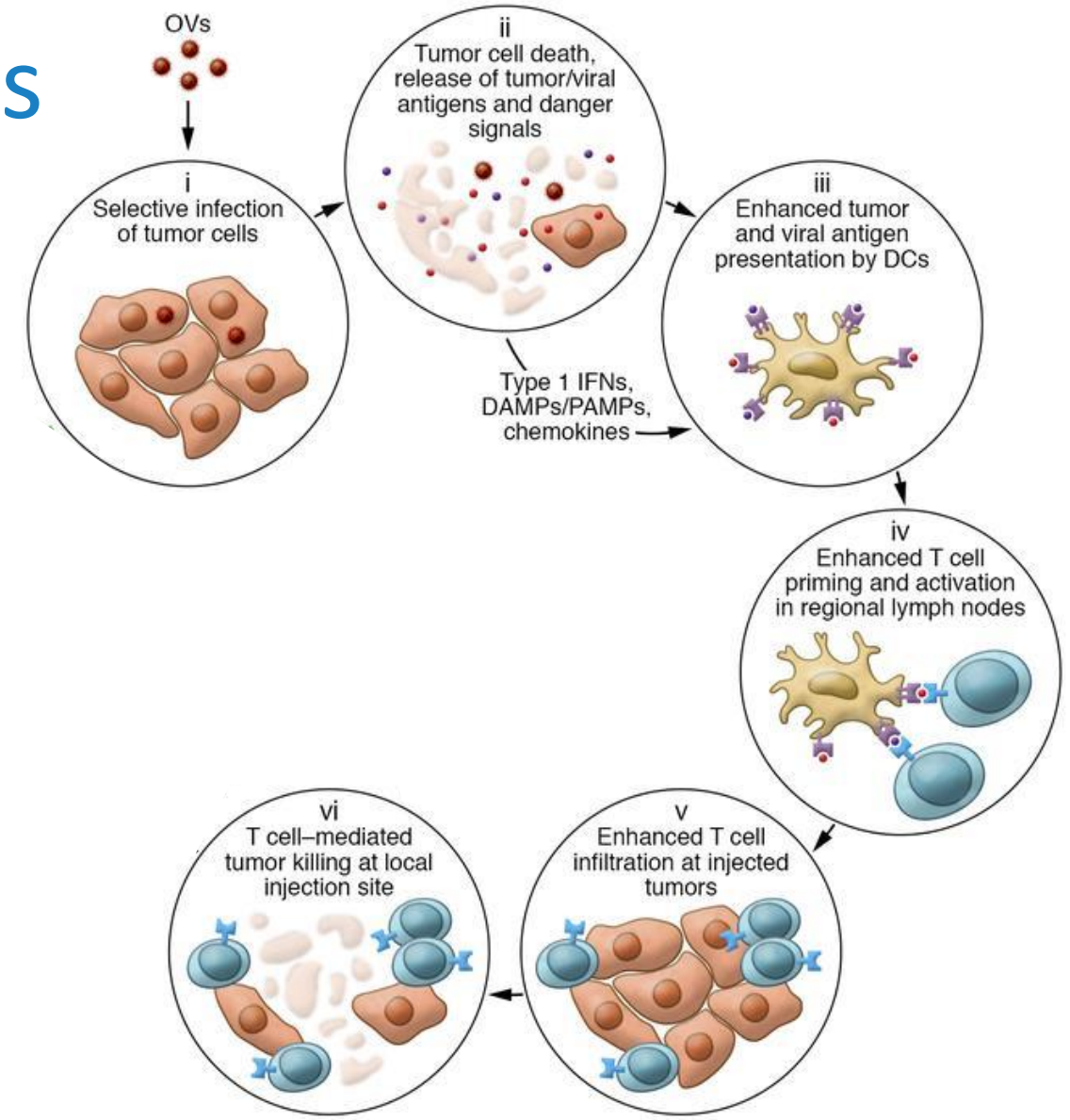
TLR agonists

Immunogenic RNA

Corrales, Clin Can Res 2015

Oncolytic Viruses

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



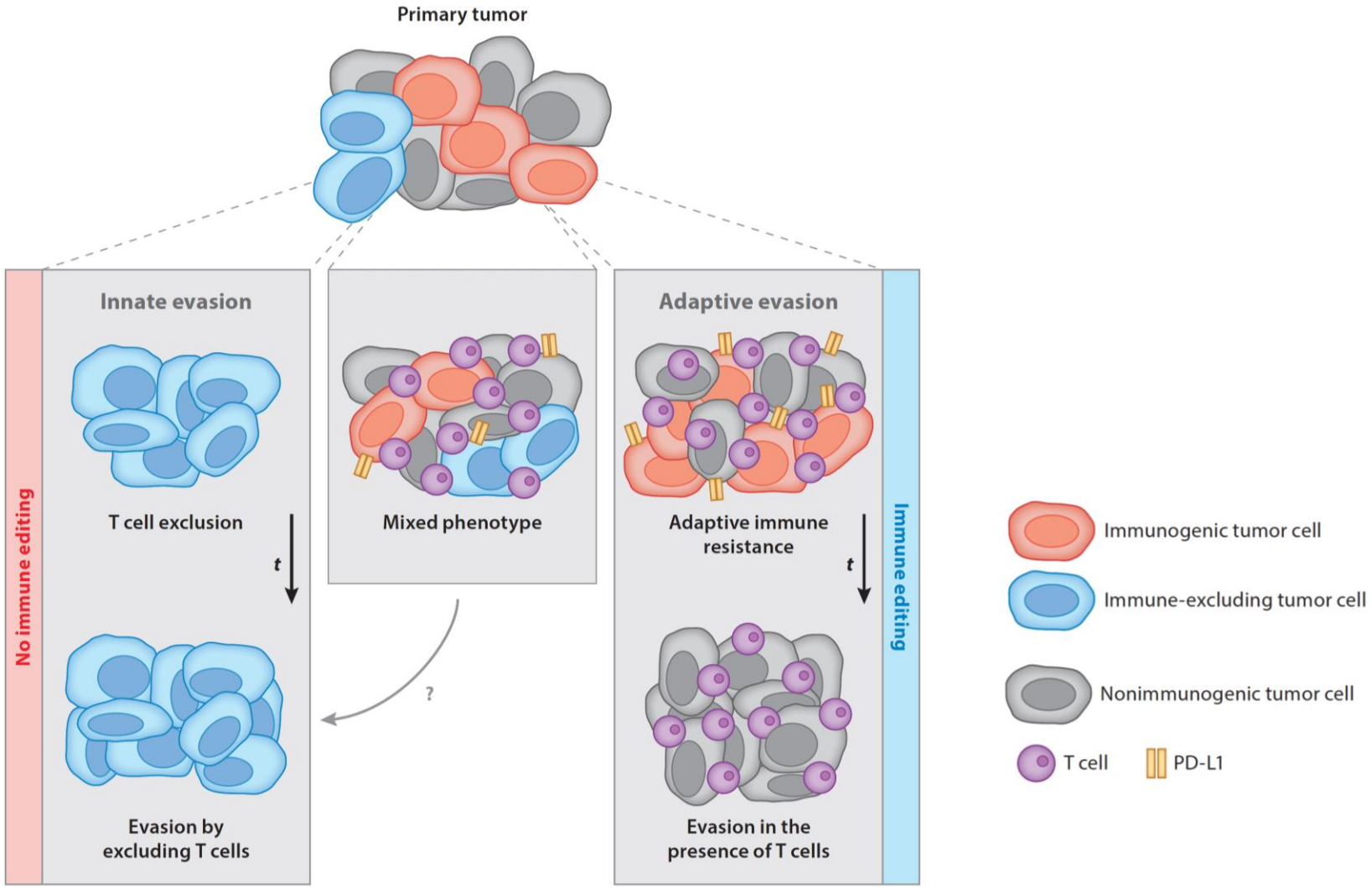
Modified from Bommereddy et al. JCI 2018

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.

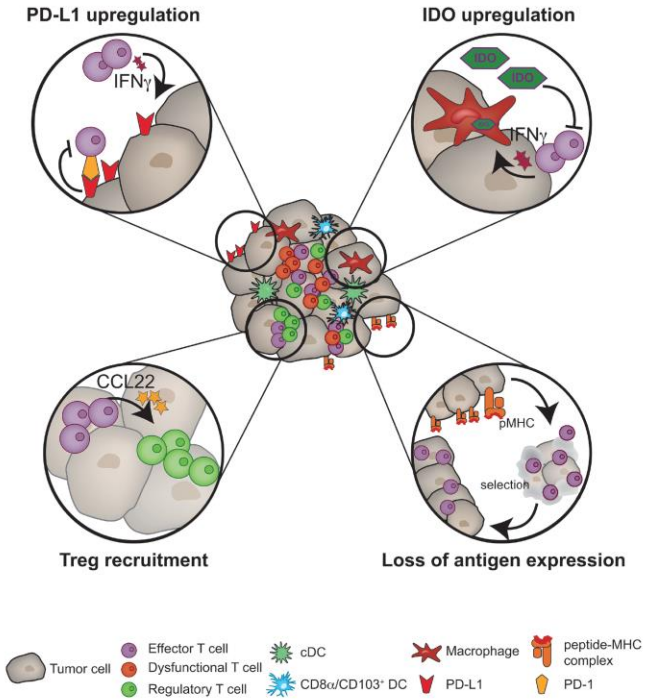
Immune evasion



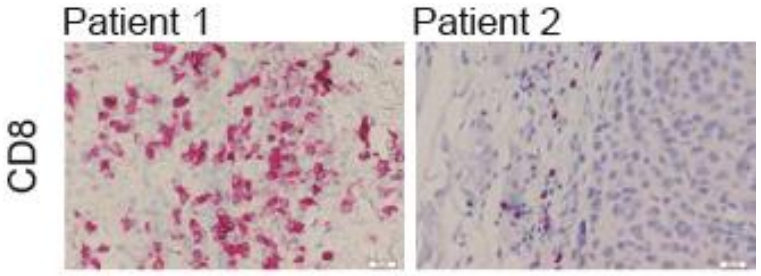
Spranger, AR Cancer 2018

Immune evasion

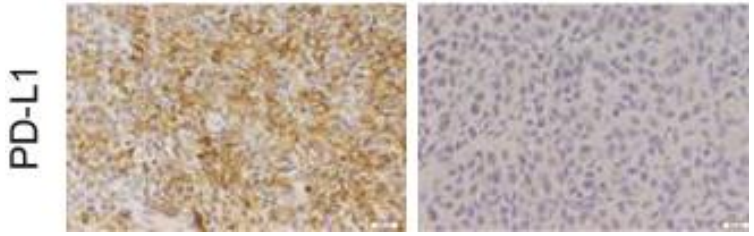
T cell-inflamed tumor microenvironment



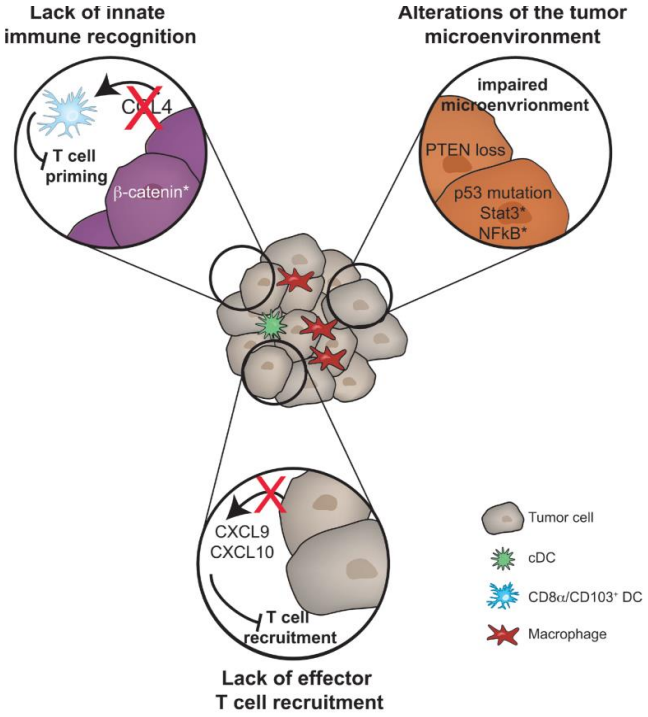
T cells



Immune suppression

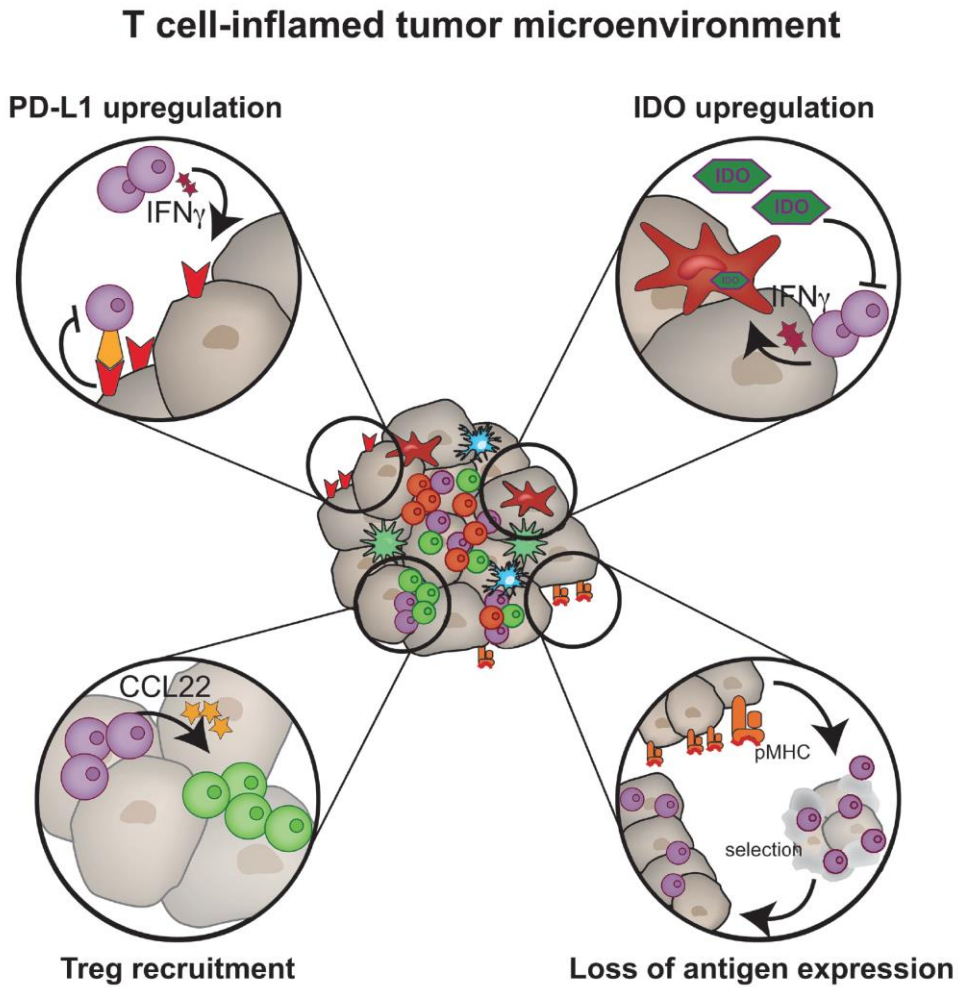


Non-T cell-inflamed tumor microenvironment



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

T cell inflamed tumor microenvironment is immune suppressive



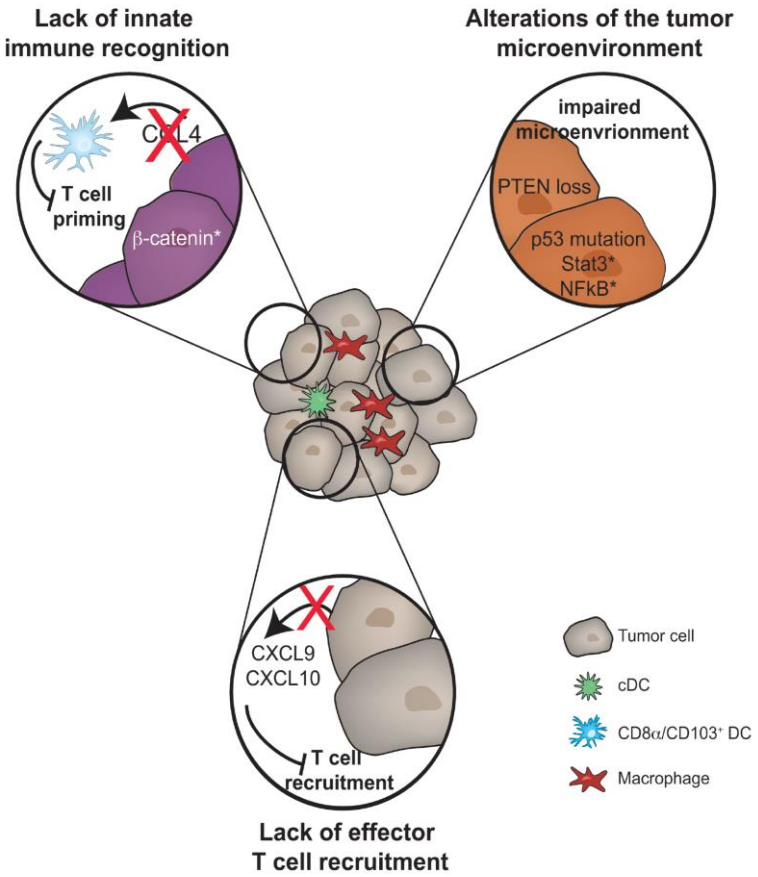
T cell-inflamed tumors escape by suppressing T cell function

Tumor cell
Effector T cell
Dysfunctional T cell
Regulatory T cell
cDC
CD8α/CD103⁺ DC
Macrophage
PD-L1
peptide-MHC complex
PD-1

Spranger, Internat Immunol. 2016

Non-T cell inflamed tumor microenvironment is ‘deserted’

Non-T cell-inflamed tumor microenvironment

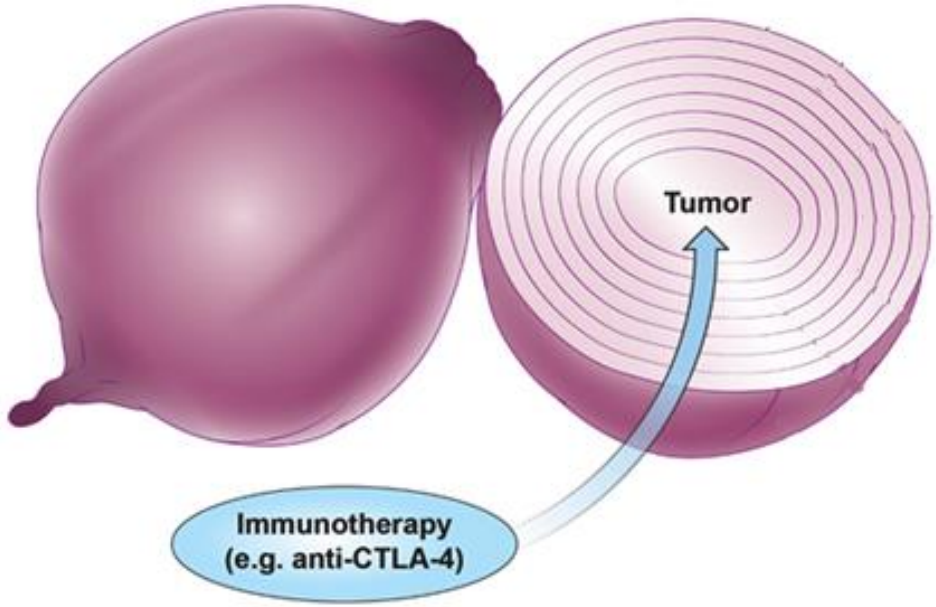


Non-T cell-inflamed tumors are a result of a malfunctioning cancer immune cycle

Spranger, Internat Immunol. 2016

Multi-layered Immunosuppression

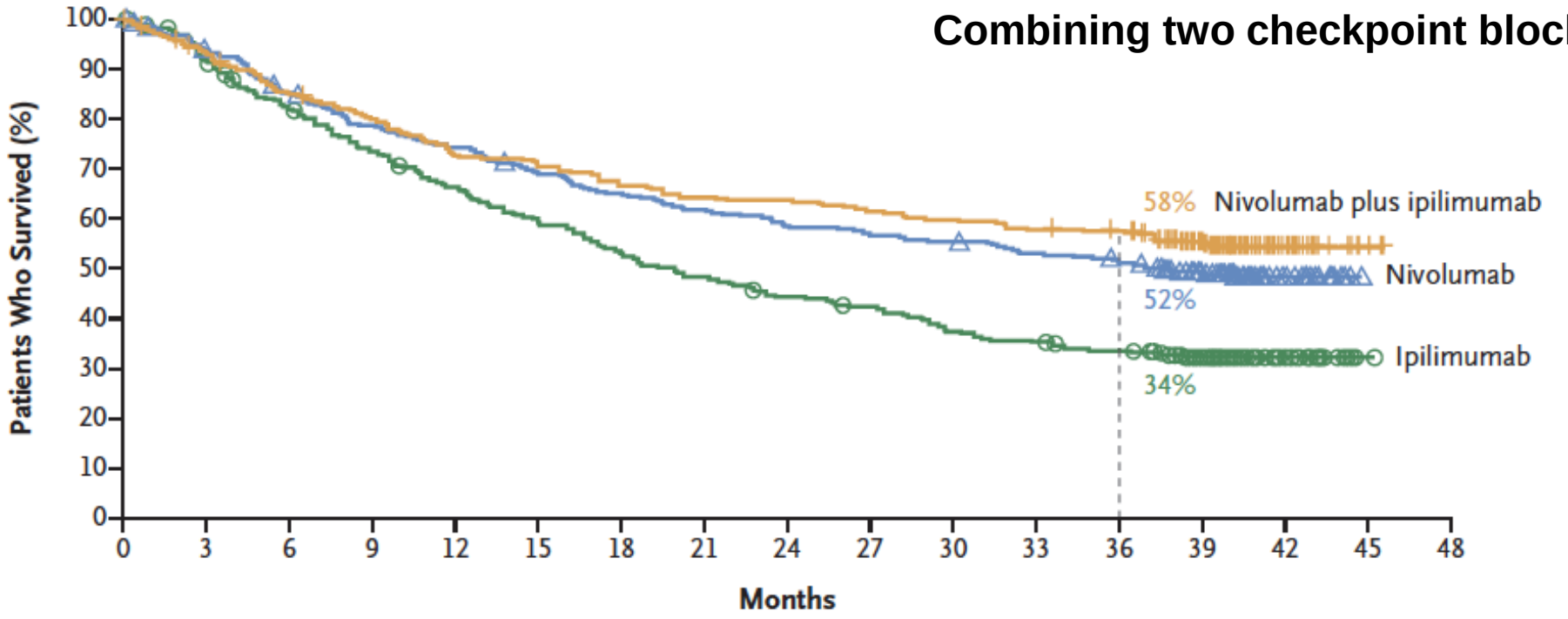
- Tumors insulate themselves with dense layers of immune-suppression
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression
- Combination therapy might be needed to overcome all layers



Combination Immunotherapies

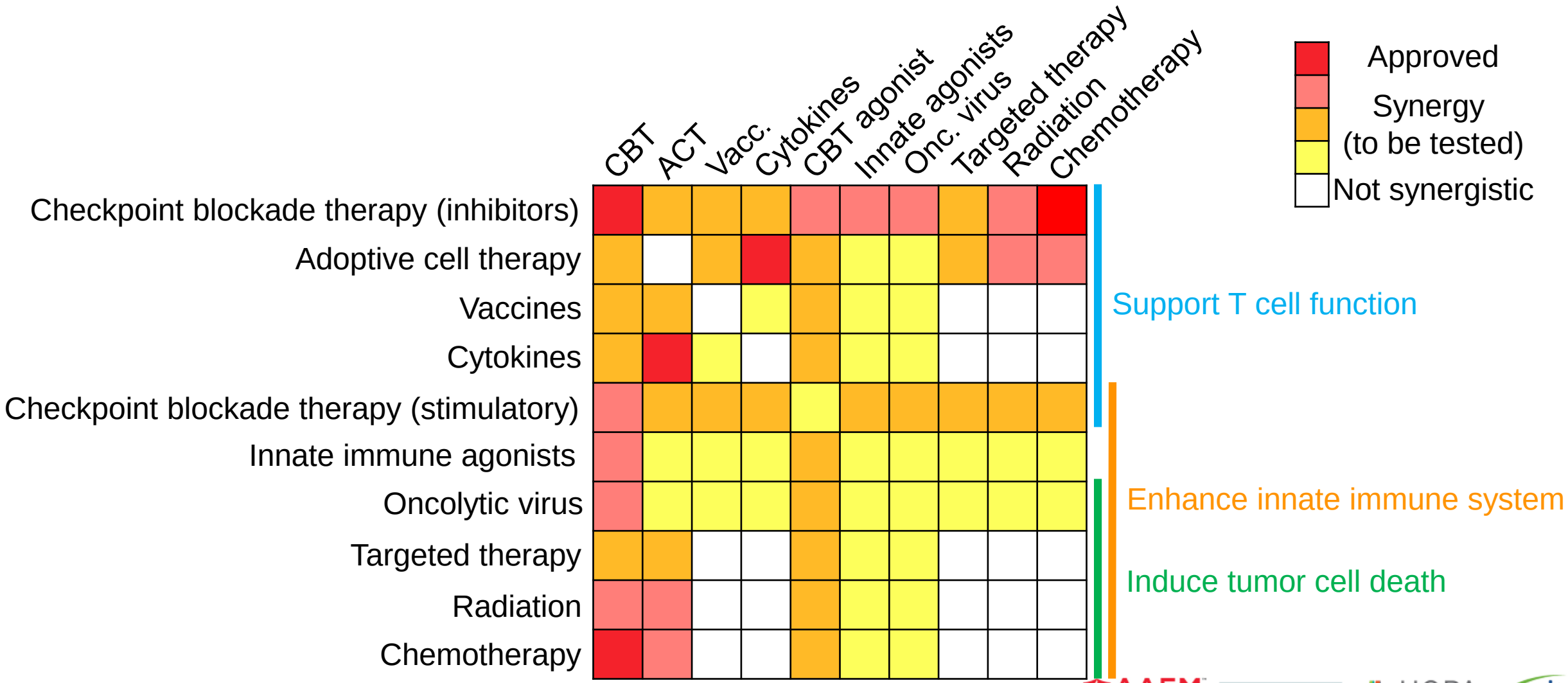
Dual CTLA-4 and PD-1 inhibition

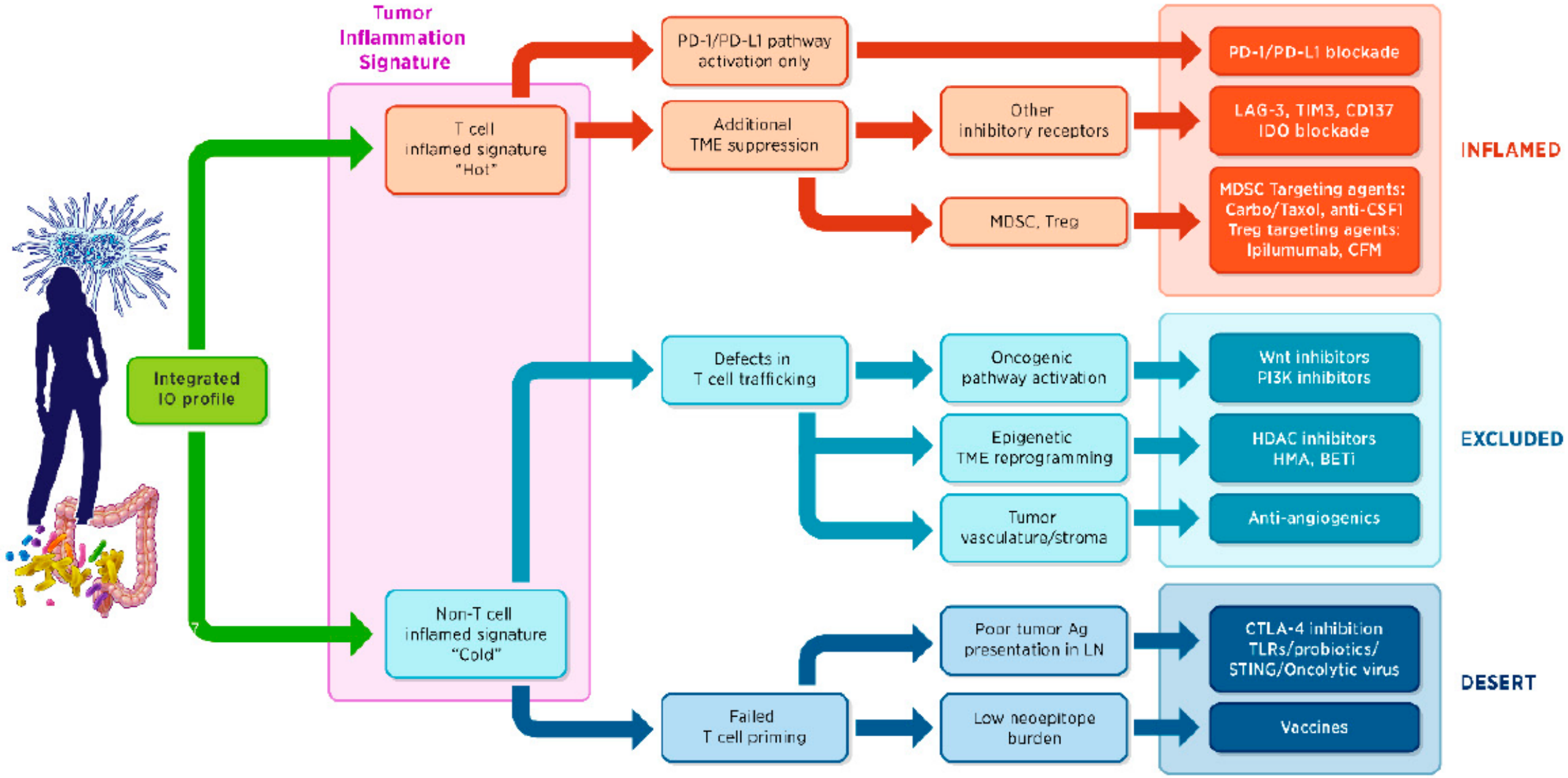
Combining two checkpoint blockade agents



Wolchok et al., NEJM 2017

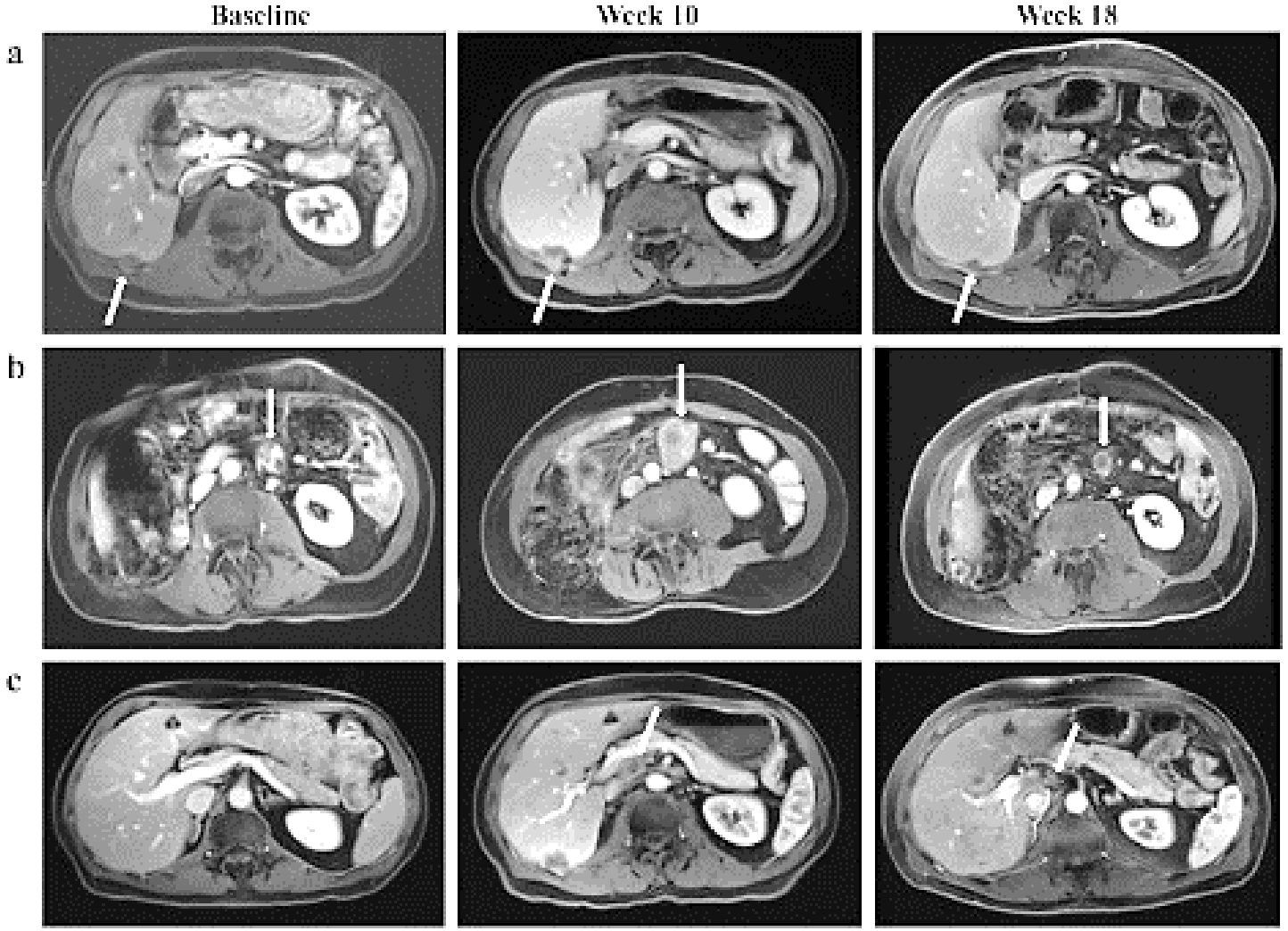
Combination Immunotherapies





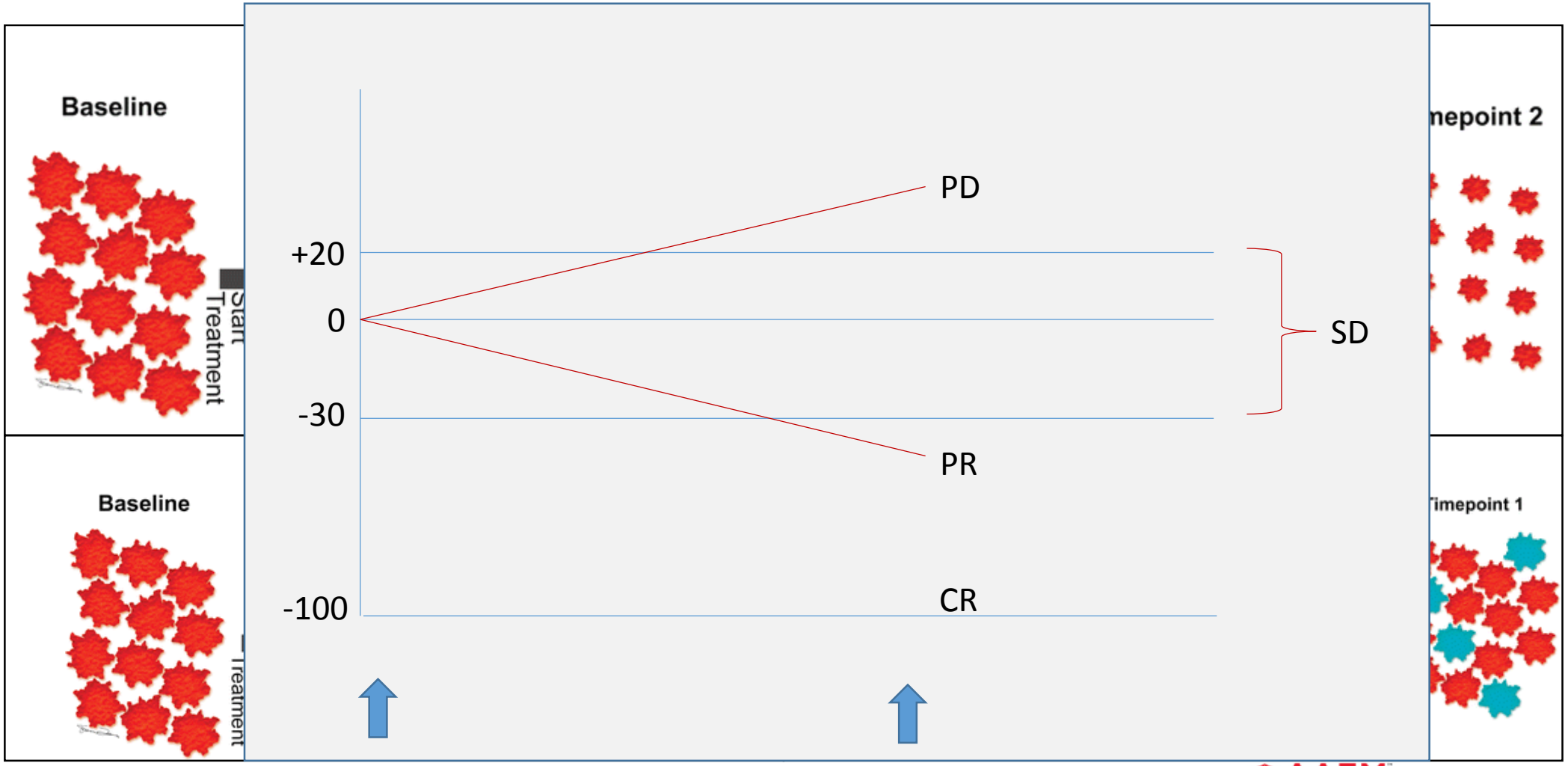
Cesano et al. Biomedicines 2018

Assessment of response



Chae, Oncotarget 2017.

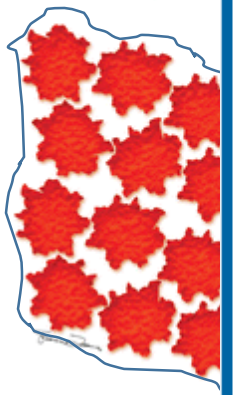
Many possible imaging findings

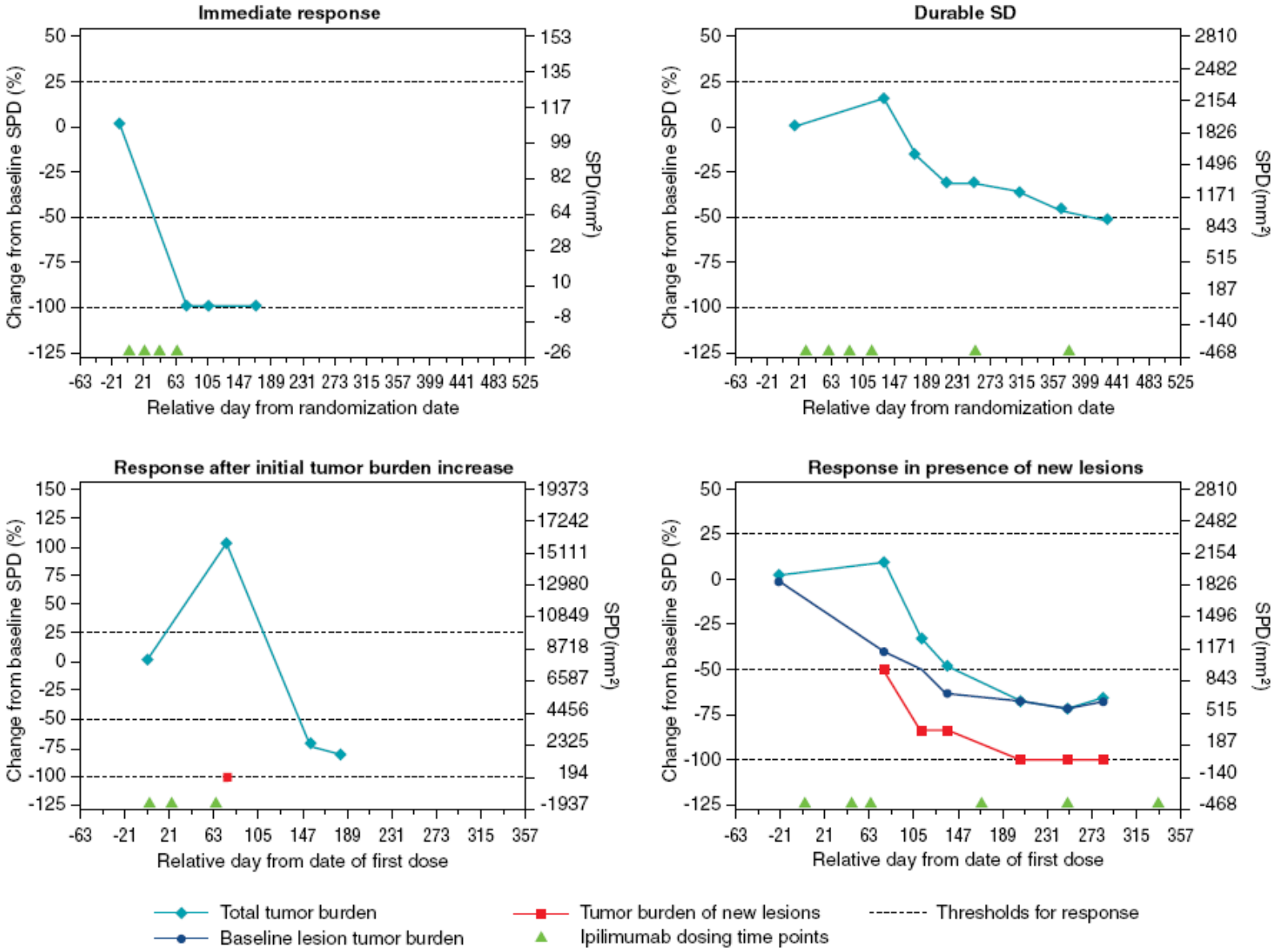


Wang, RadioGraphics 2017.

Pseud

Baseline

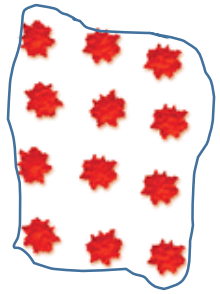




SPD= sum of perpendicular diameters

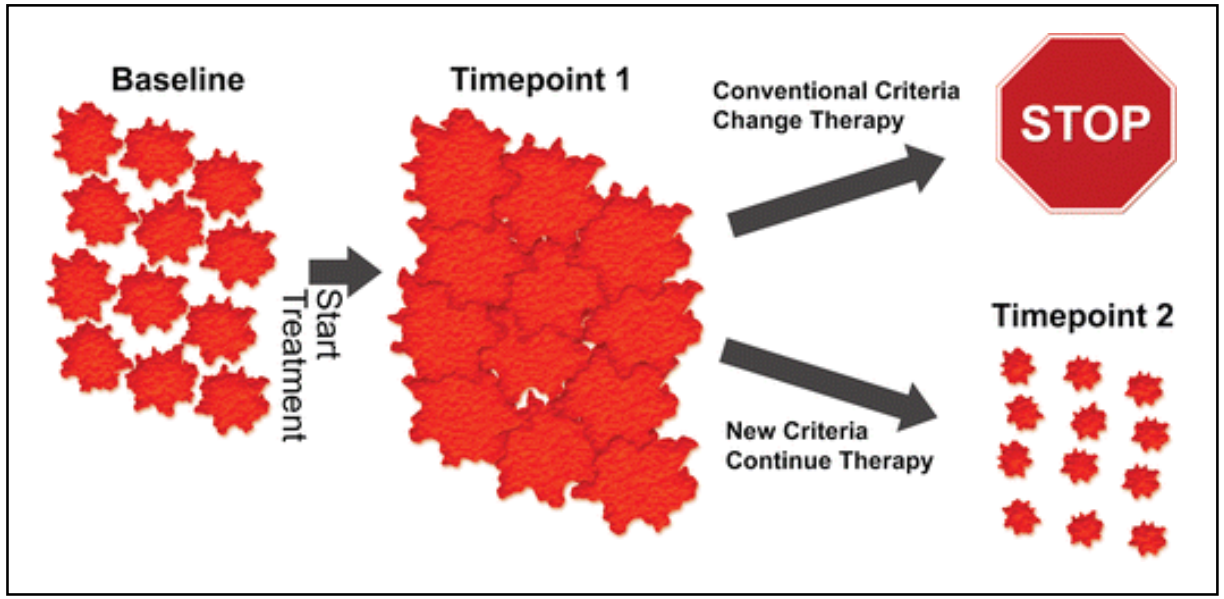
g Lesions

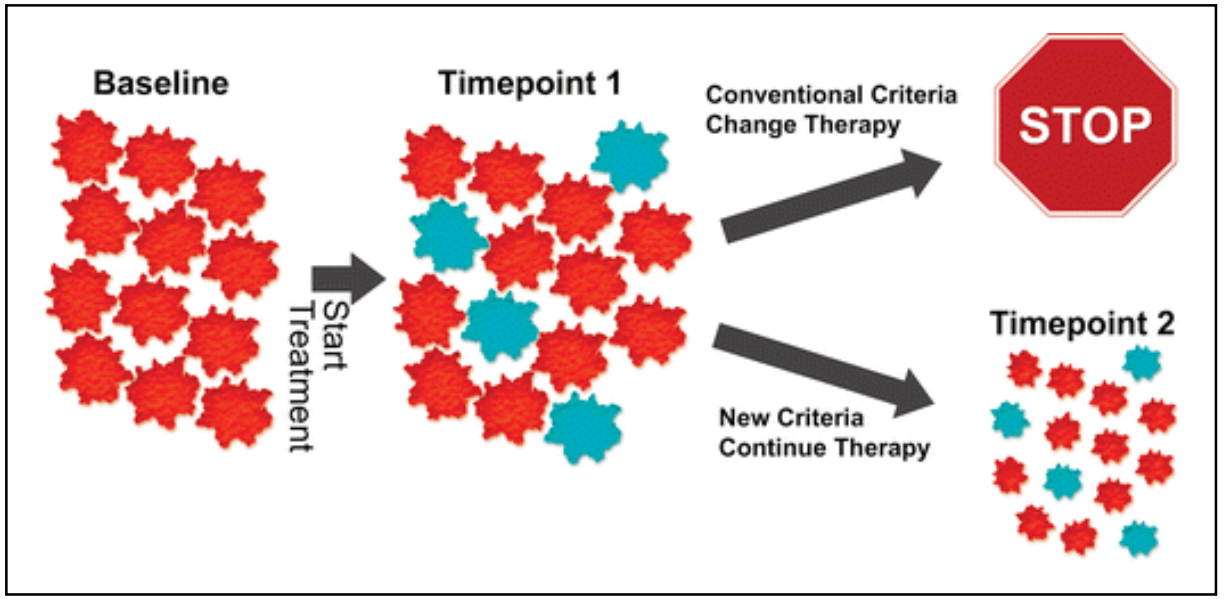
Timepoint 2



Wang, RadioGraphics 2017.

Assessment of response – unique considerations for immunotherapy





Wang, RadioGraphics 2017.

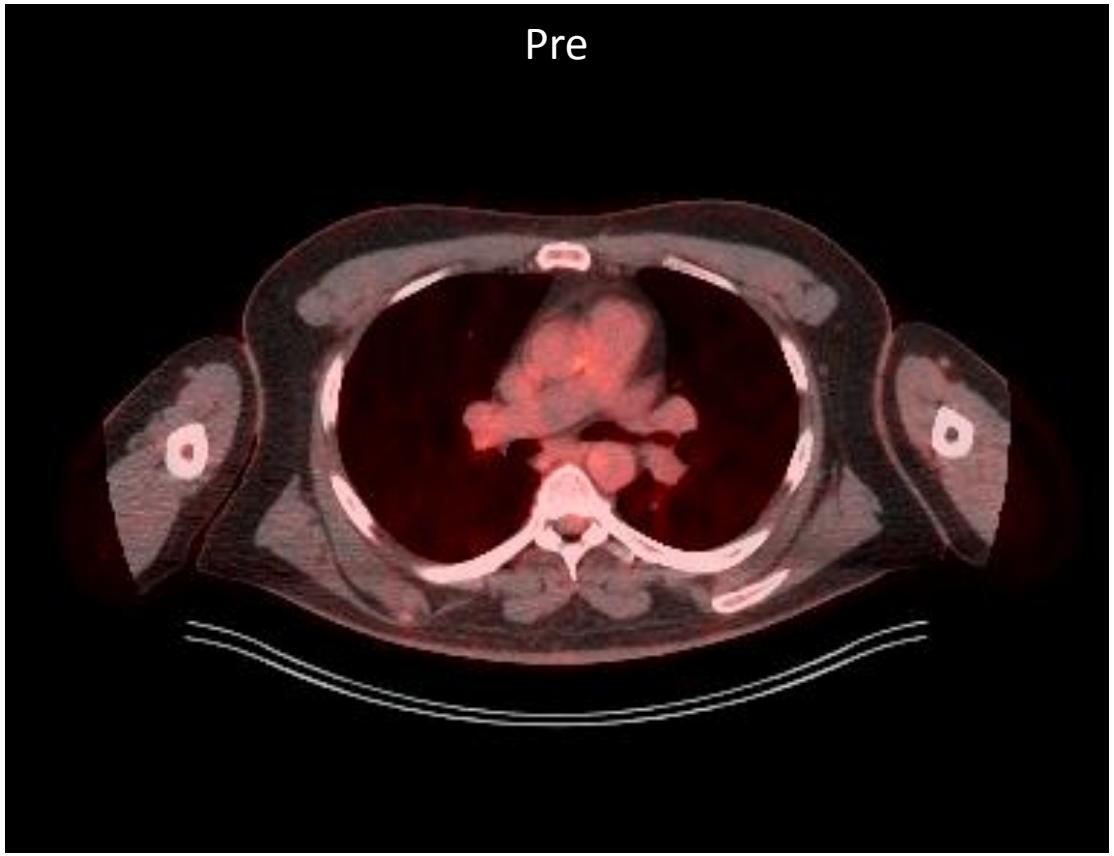
Comparison of disease progression by conventional and immune-related criteria

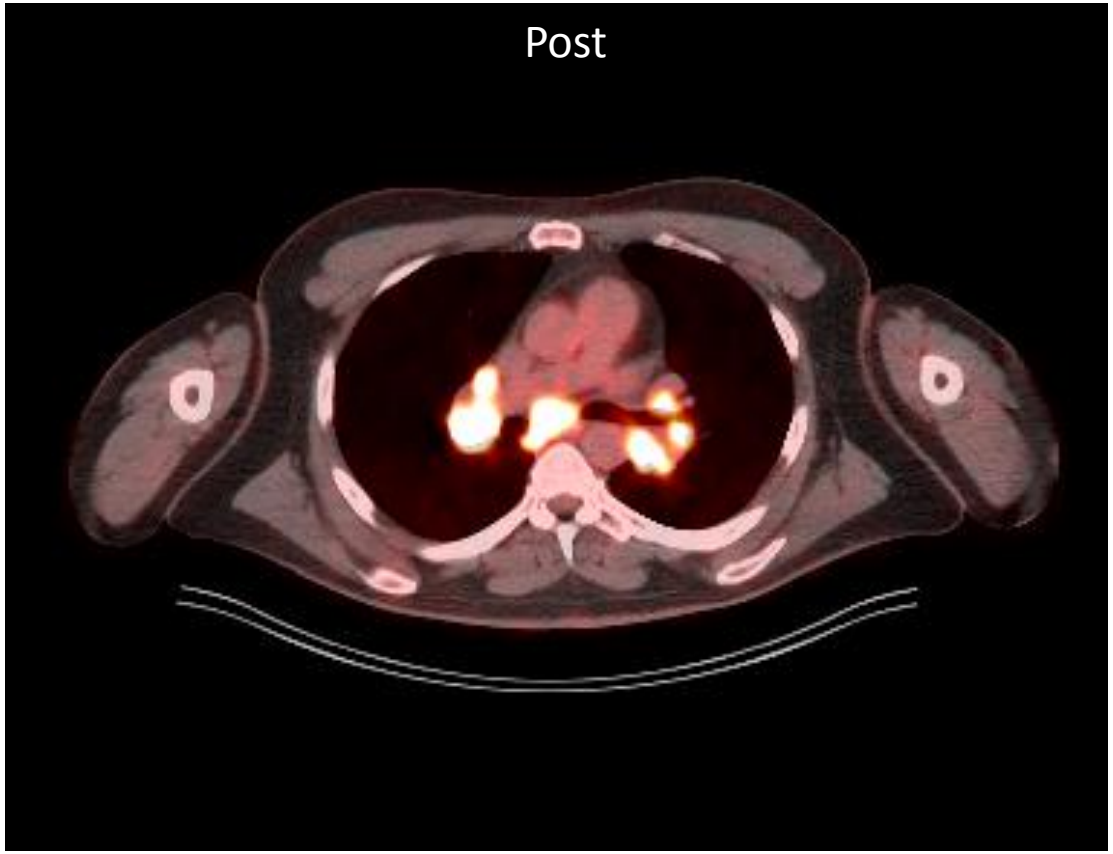
Treatment Response	RECIST 1.1	irRC
Progressive disease	≥20% increase in lesion sum* (absolute size increase ≥5 mm) or 1+ new lesions at any single observation	≥25% increase in tumor burden[+] versus nadir in two consecutive observations ≥4 weeks apart
New measurable lesions[#]	Always represent progressive 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.

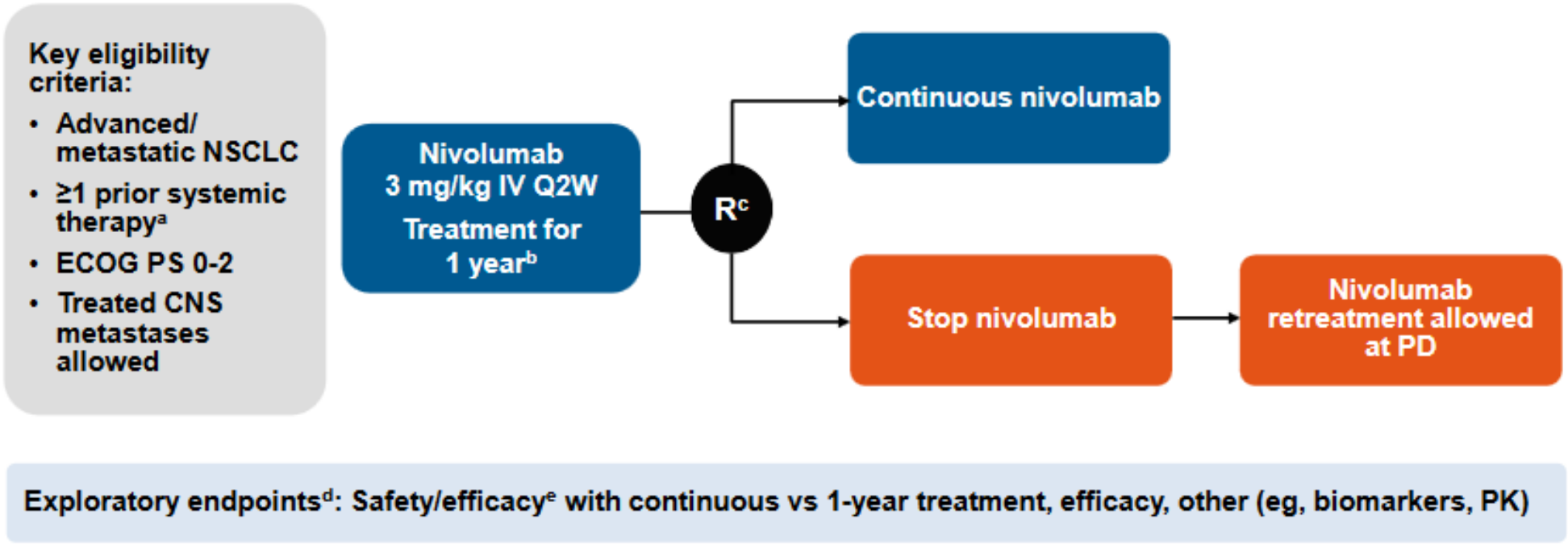
*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm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

Imaging Pitfalls after Immunotherapy



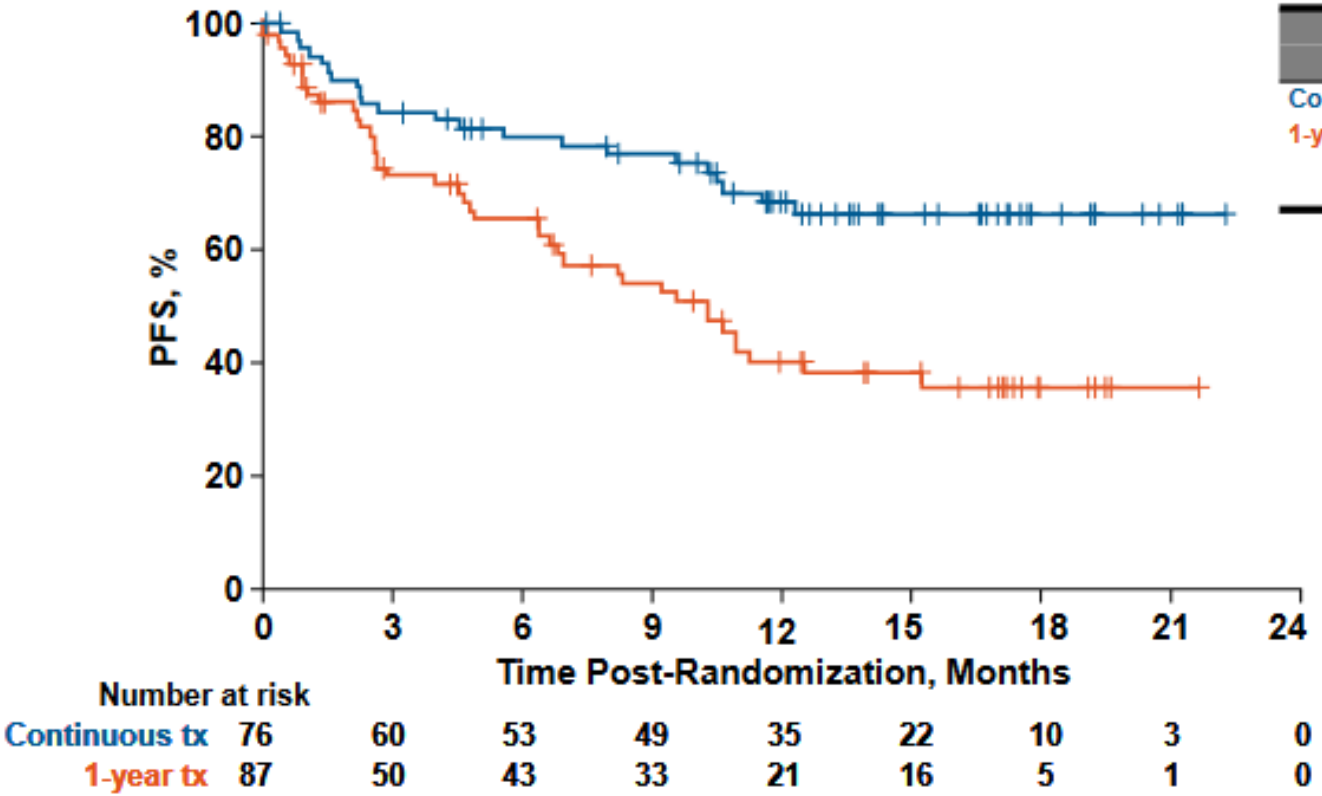


When to stop immunotherapy: Checkmate 153



Spigel, Ann Oncol 2017.

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

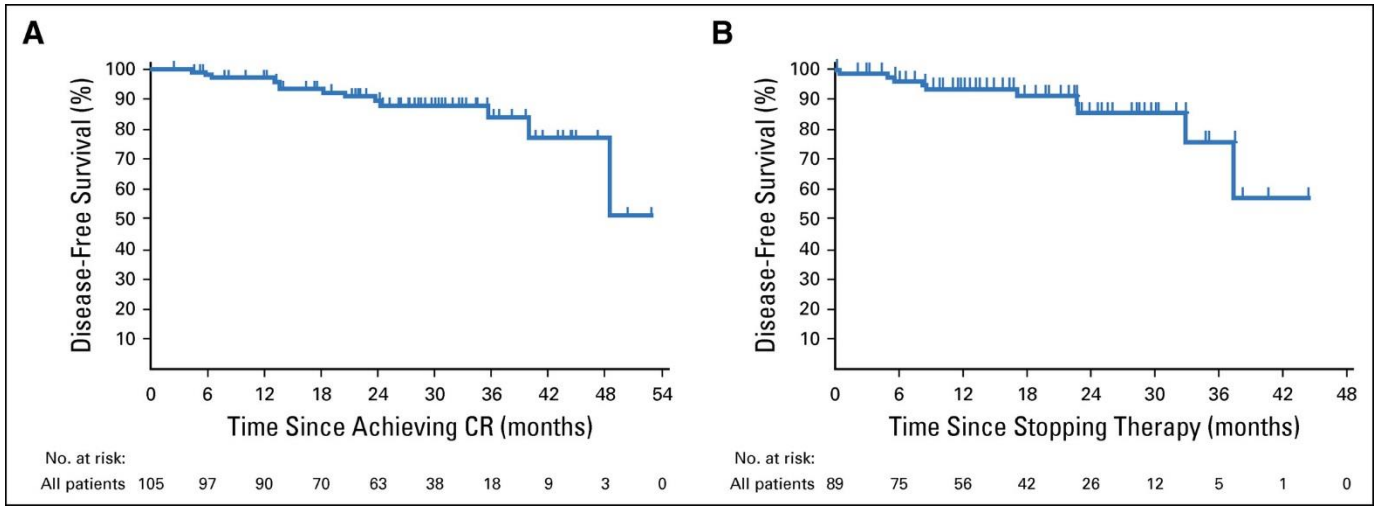
Spigel, Ann Oncol 2017.

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%

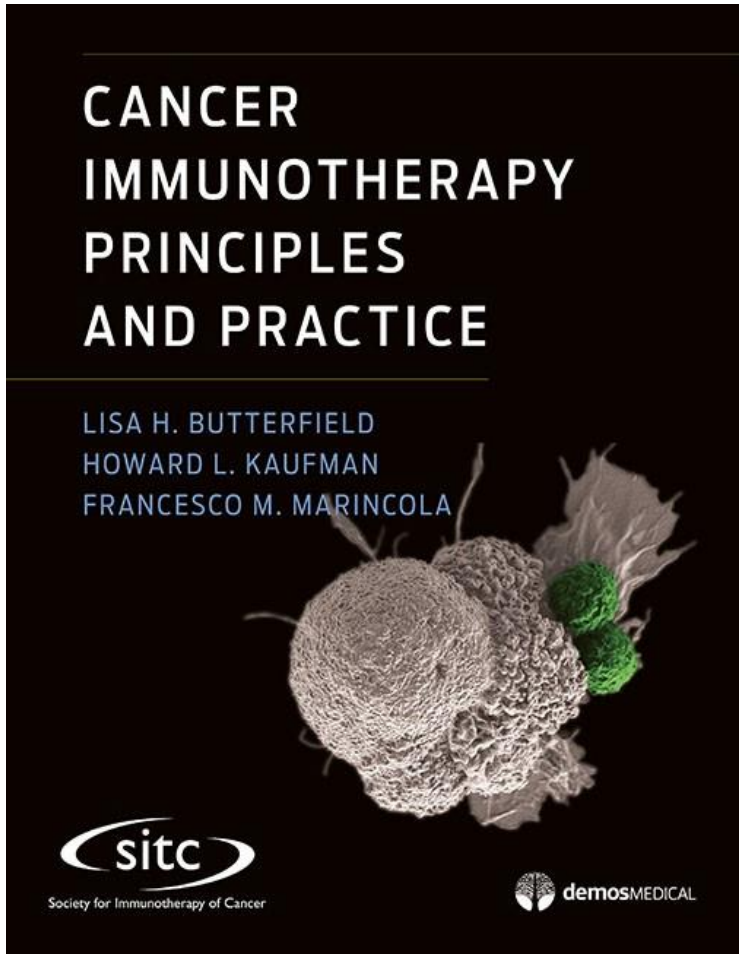


Robert, J Clin Oncol 2018.

When to stop immunotherapy: clinical measures

- Achievement of CR
- Completed 2 years of treatment
- PR or stable disease for > 6 months
- PET-based metabolic response after immunotherapy – interpretation

Further Resources



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Cancer Immunotherapy CONNECT