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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

- Consulting Fees: Astra-Zeneca, Pfizer, Merck, Celgene, Eli Lilly, Novartis, Takeda, Guardant
- Contracted Research: Astra-Zeneca, Pfizer, Merck, Celgene, Eli Lilly, Novartis, BMS
- I will 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.

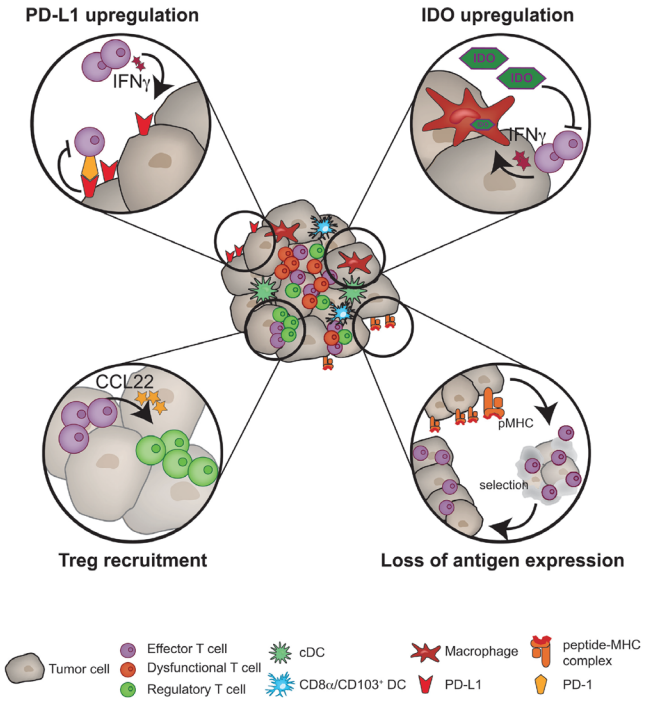
# Two major mechanisms of tumor immune escape

- **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.

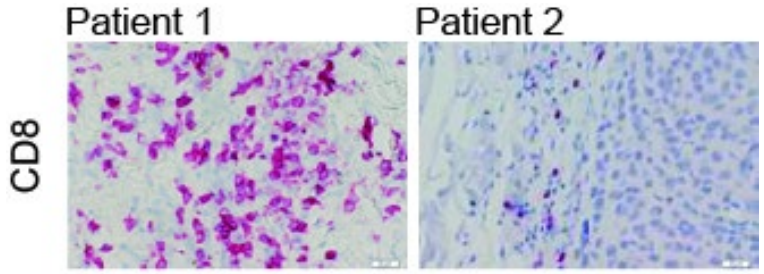
- **Avoiding an immune response:** A state in which the tumor remains invisible to the immune system. Many features of tumors can result in immune exclusion/avoidance including lack of antigens (T cells don't "see" anything on the tumor) or active immune repellents.

# Immune evasion

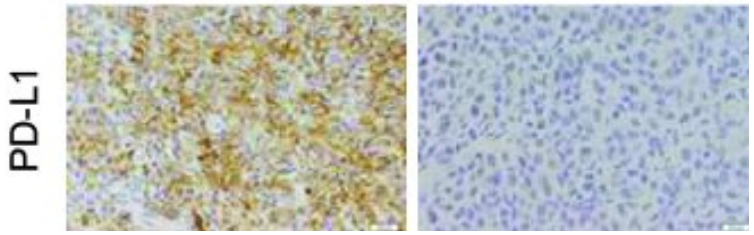
## T cell-inflamed tumor microenvironment



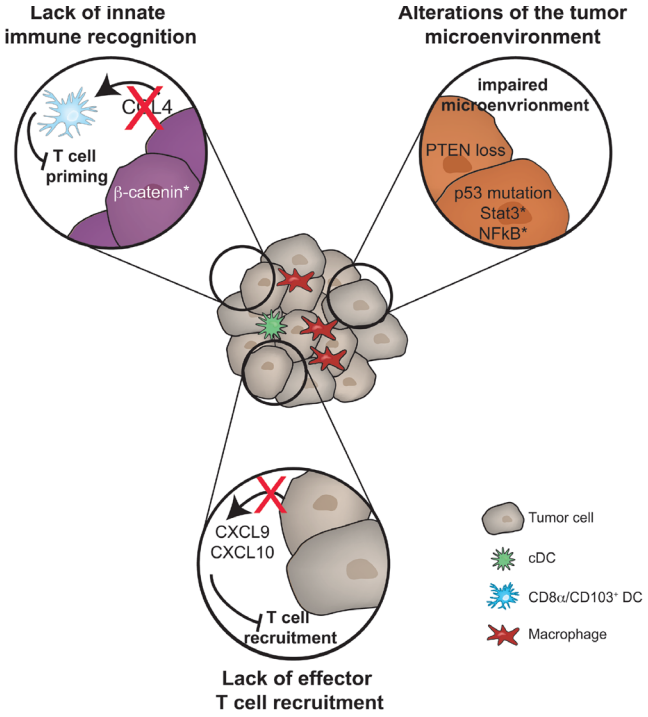

## T cells




## Immune suppression



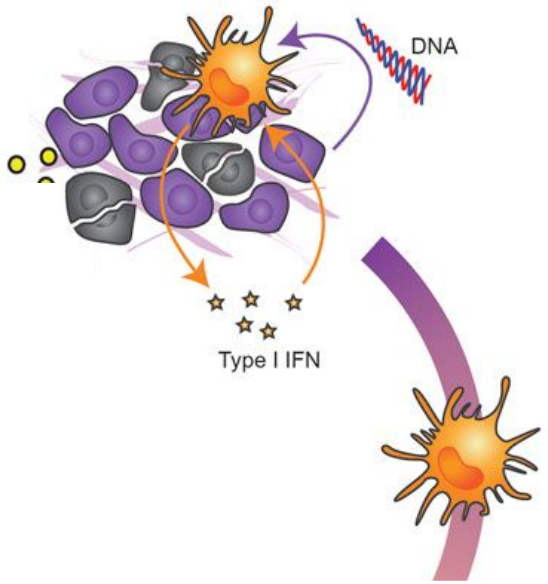

## Non-T cell-inflamed tumor microenvironment




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

# Initiation of an anti-tumor immune response

Innate immune sensing (i.e. Sting activation)




APC maturation
&
Transport to lymph node

Modified from Corrales et al. Cell Res. 2017

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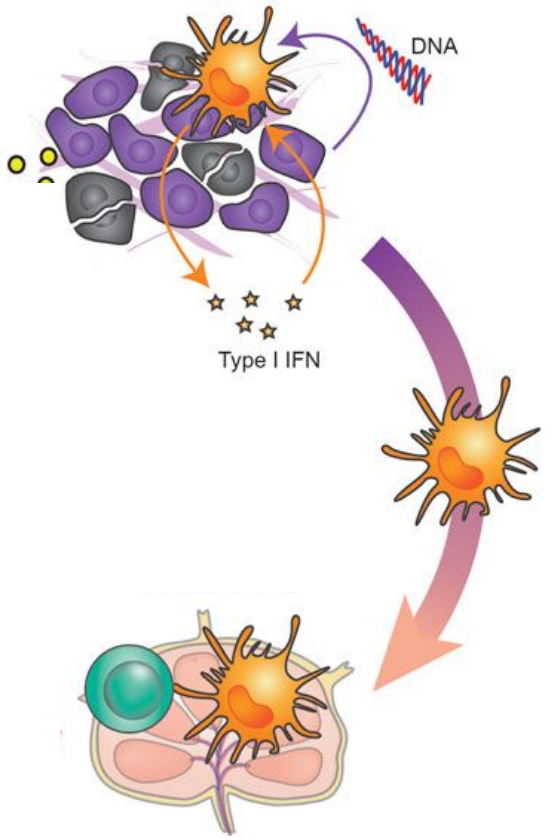



APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

# Antigen-specific T cell Activation

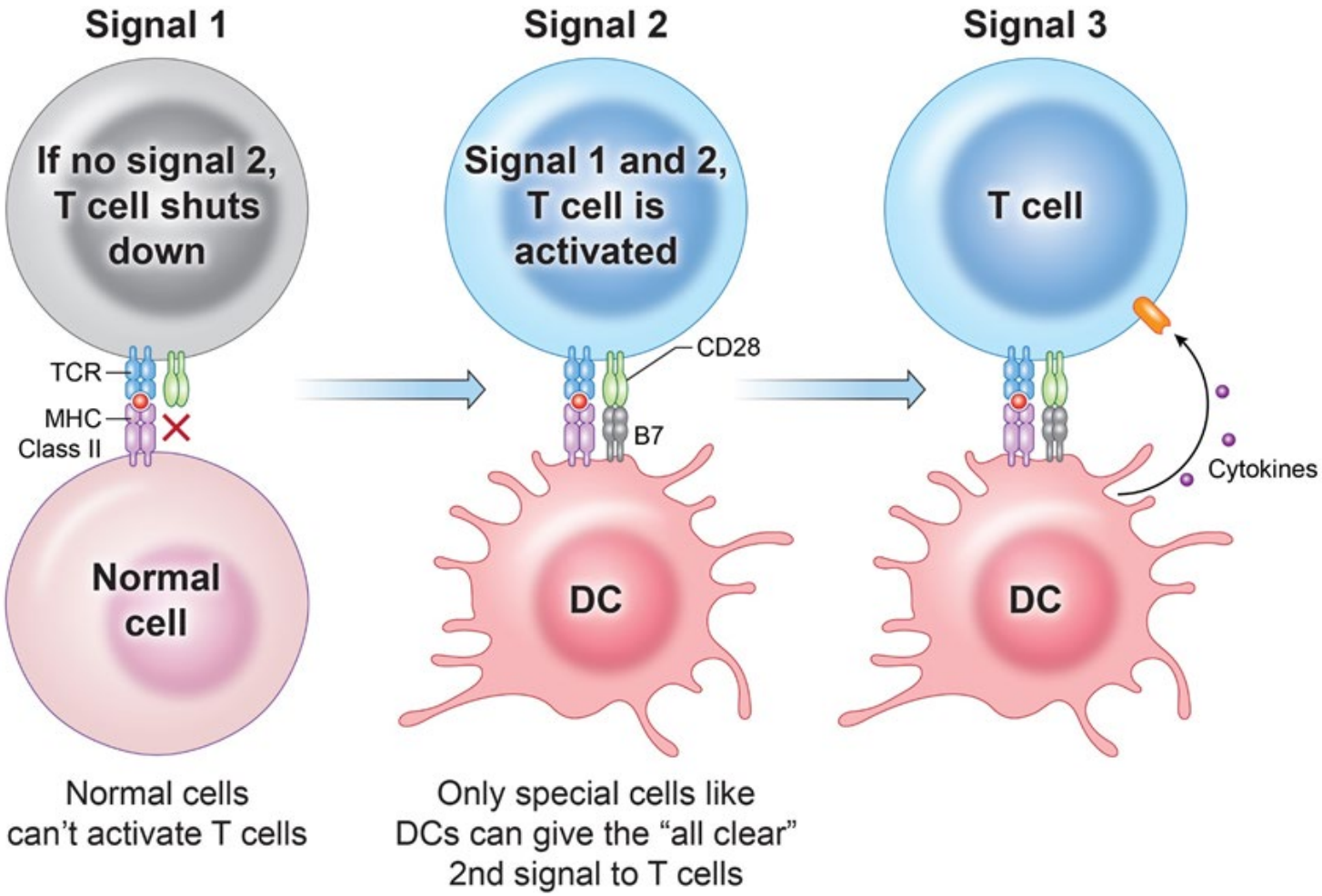
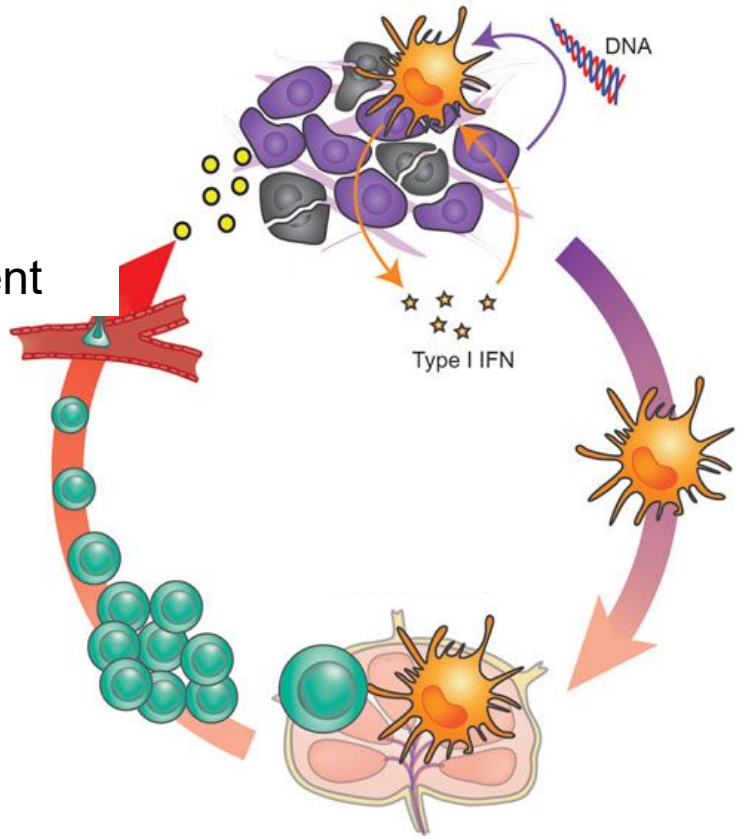



Image courtesy of NCI

# Initiation of an anti-tumor immune response

Innate immune sensing (i.e. Sting activation)

T cell recruitment




APC maturation
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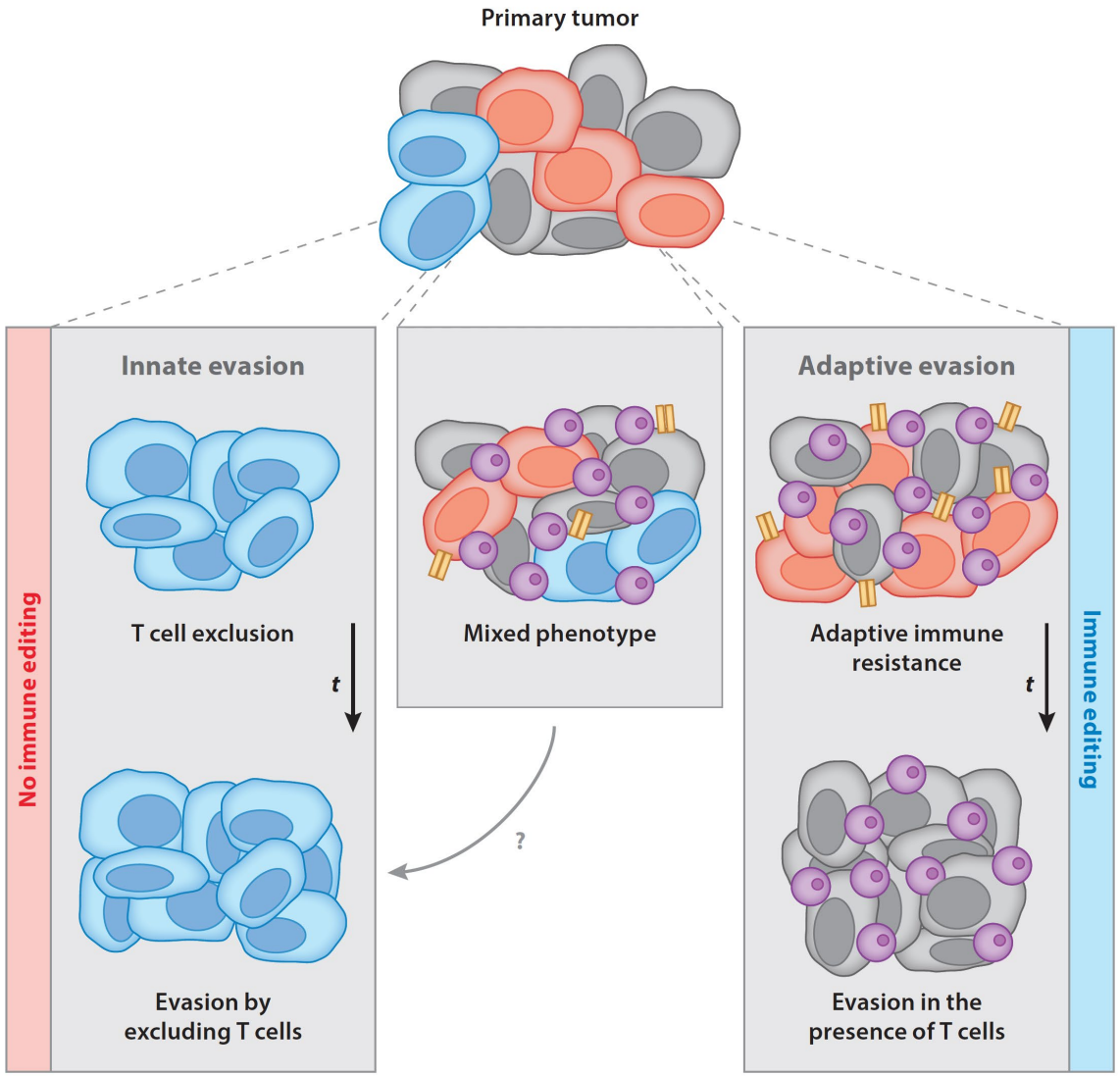
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

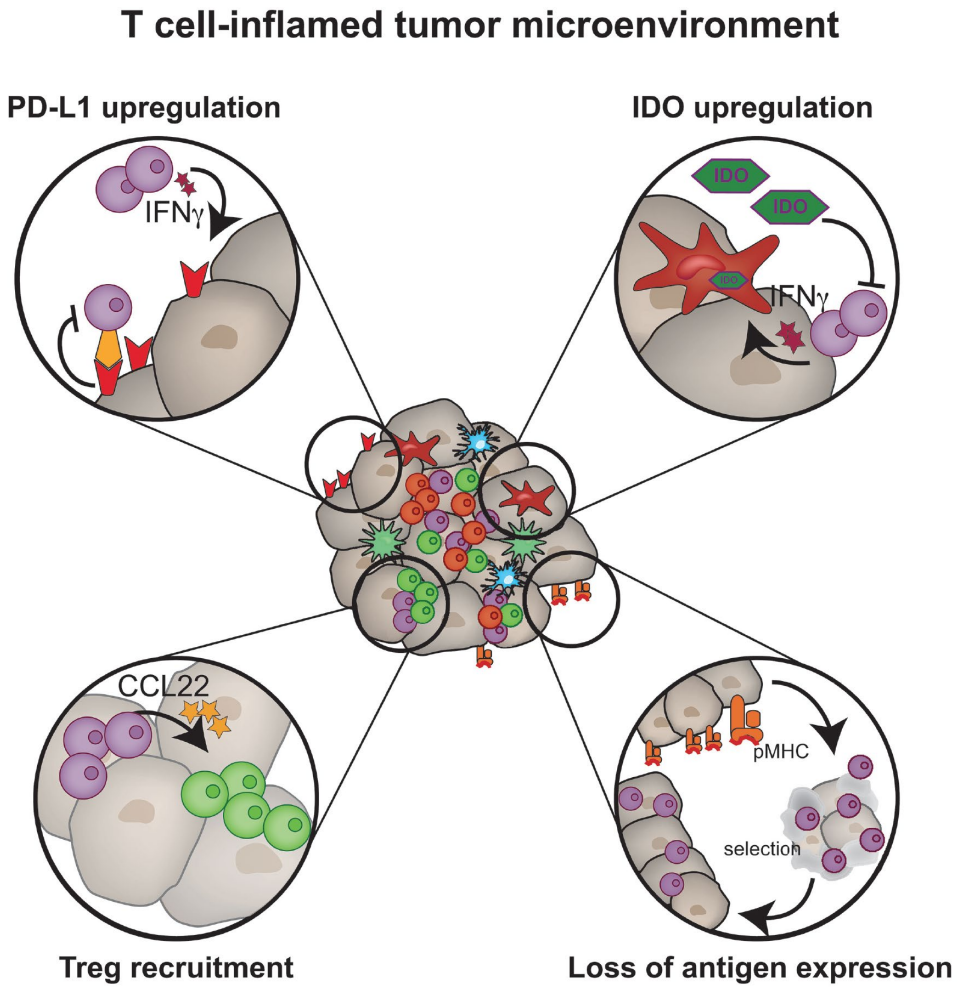
# Immune evasion occurs over time




Immunogenic tumor cell
Nonimmunogenic tumor cell
Immune-excluding tumor cell
T cell
PD-L1

Spranger, AR Cancer 2018

# T cell inflamed tumor microenvironment is immune suppressive

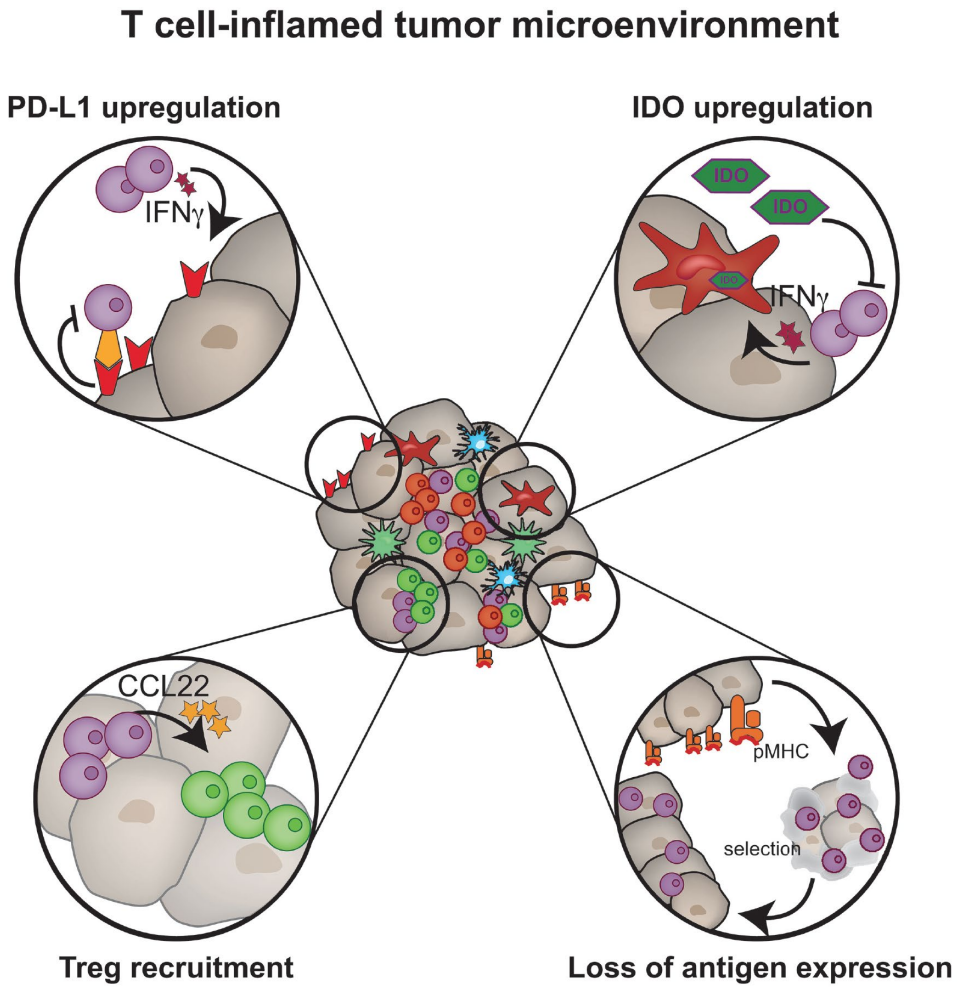



**T cell-inflamed tumors escape by suppressing T cell function**

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

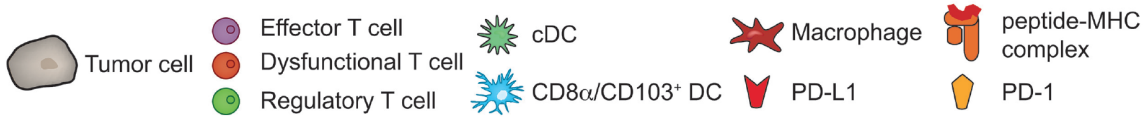
Spranger, Internat Immunol. 2016

# T cell inflamed tumor microenvironment is immune suppressive




T cell-inflamed tumors escape by suppressing T cell function

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




Spranger, Internat Immunol. 2016

# Types of Immunotherapy

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

# The CTLA-4 Checkpoint

**C**ytotoxic **T**-**L**ymphocyte **A**ssociated Protein **4**

Up-regulated in response to T cell activation

Limits positive stimulation by competition

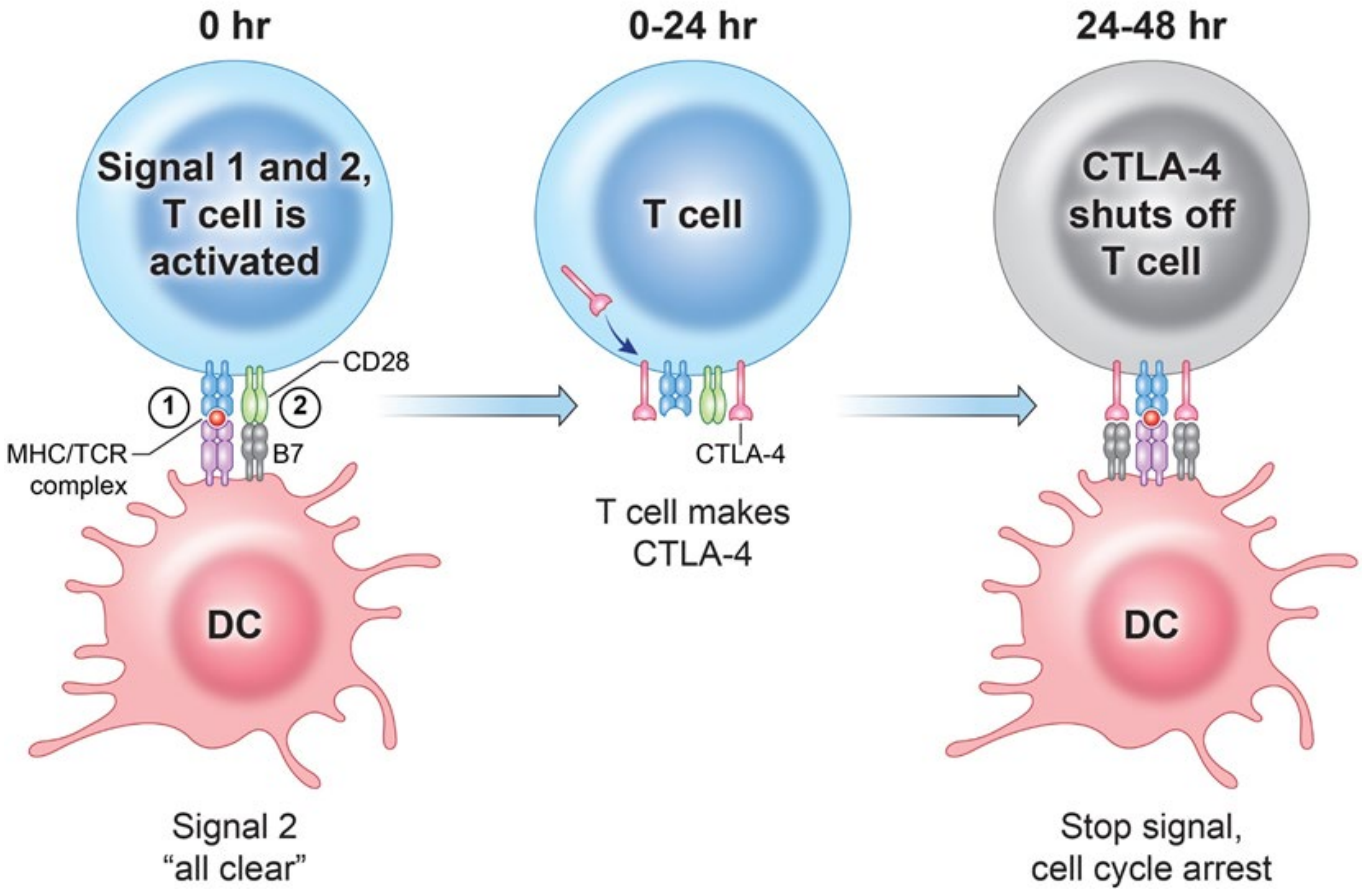



Image courtesy of NCI

# The PD-1/PD-L1 Checkpoint

**P**rogrammed **D**eath **1**

Up-regulated in response to T cell activation

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

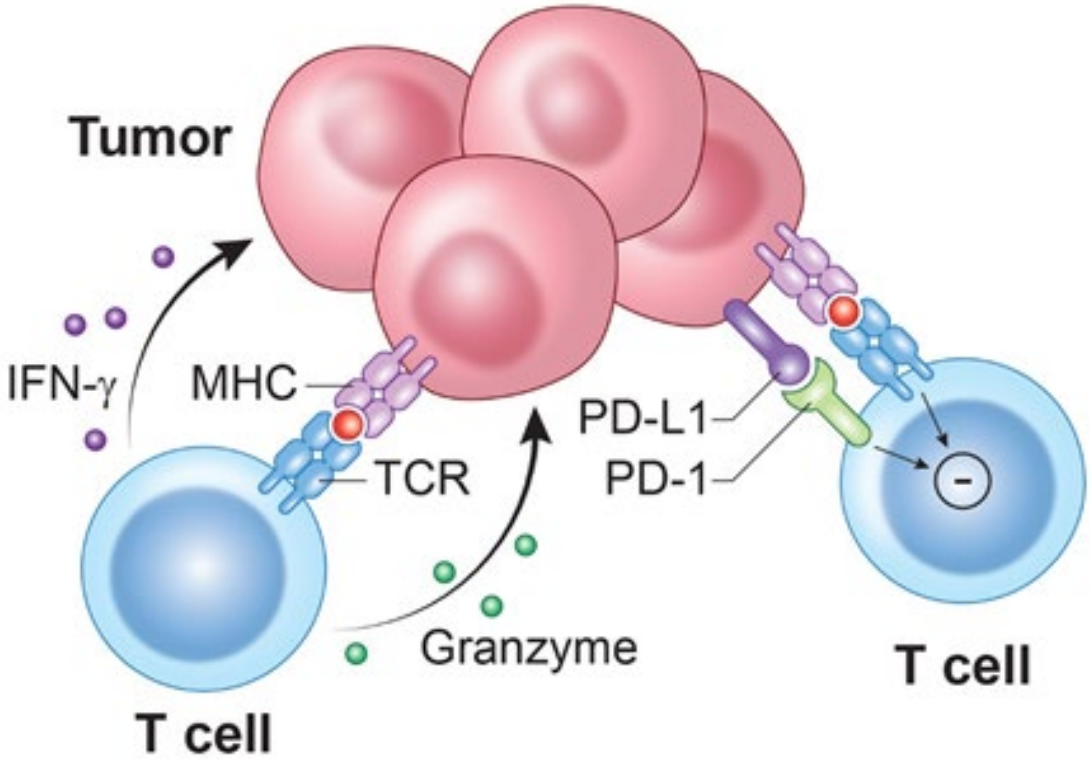
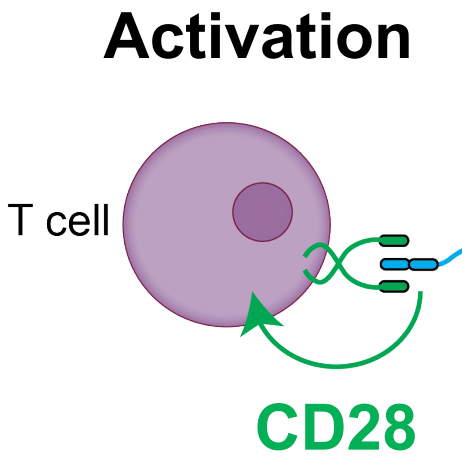


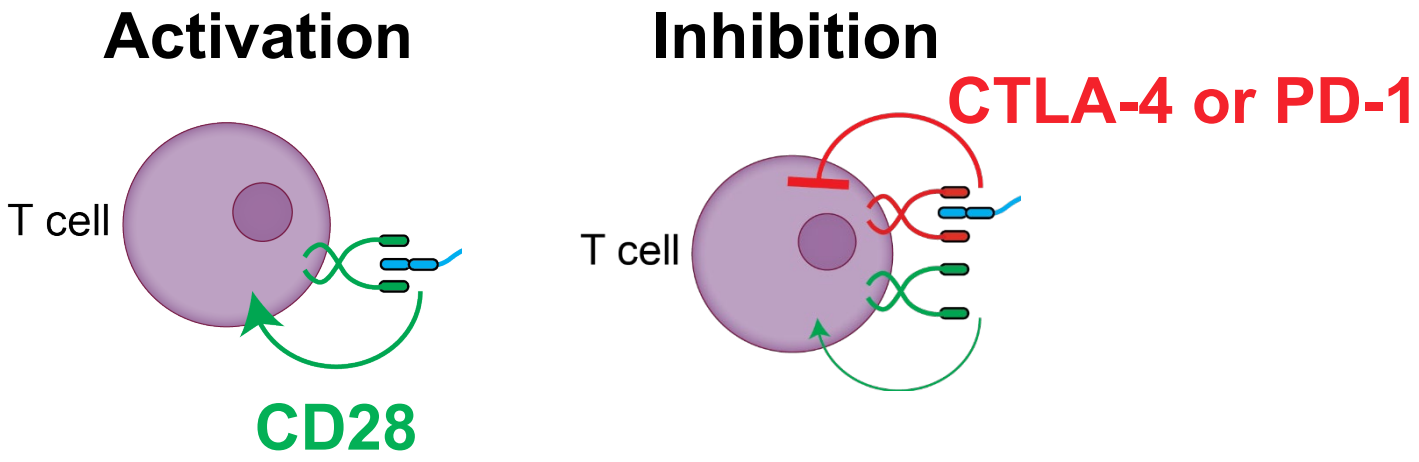

Image courtesy of NCI

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



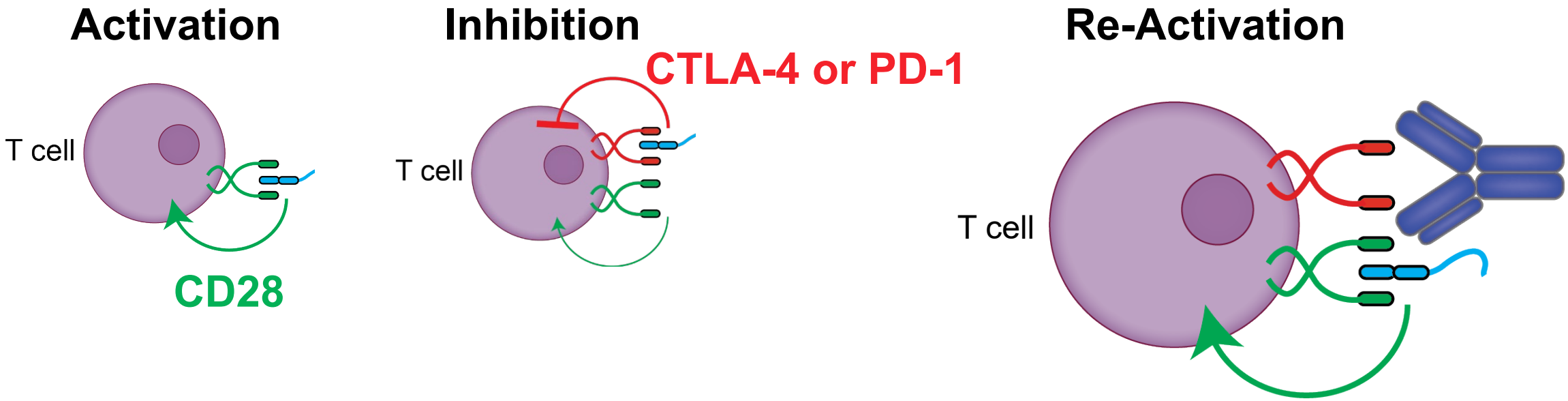

Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

# 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.

# 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

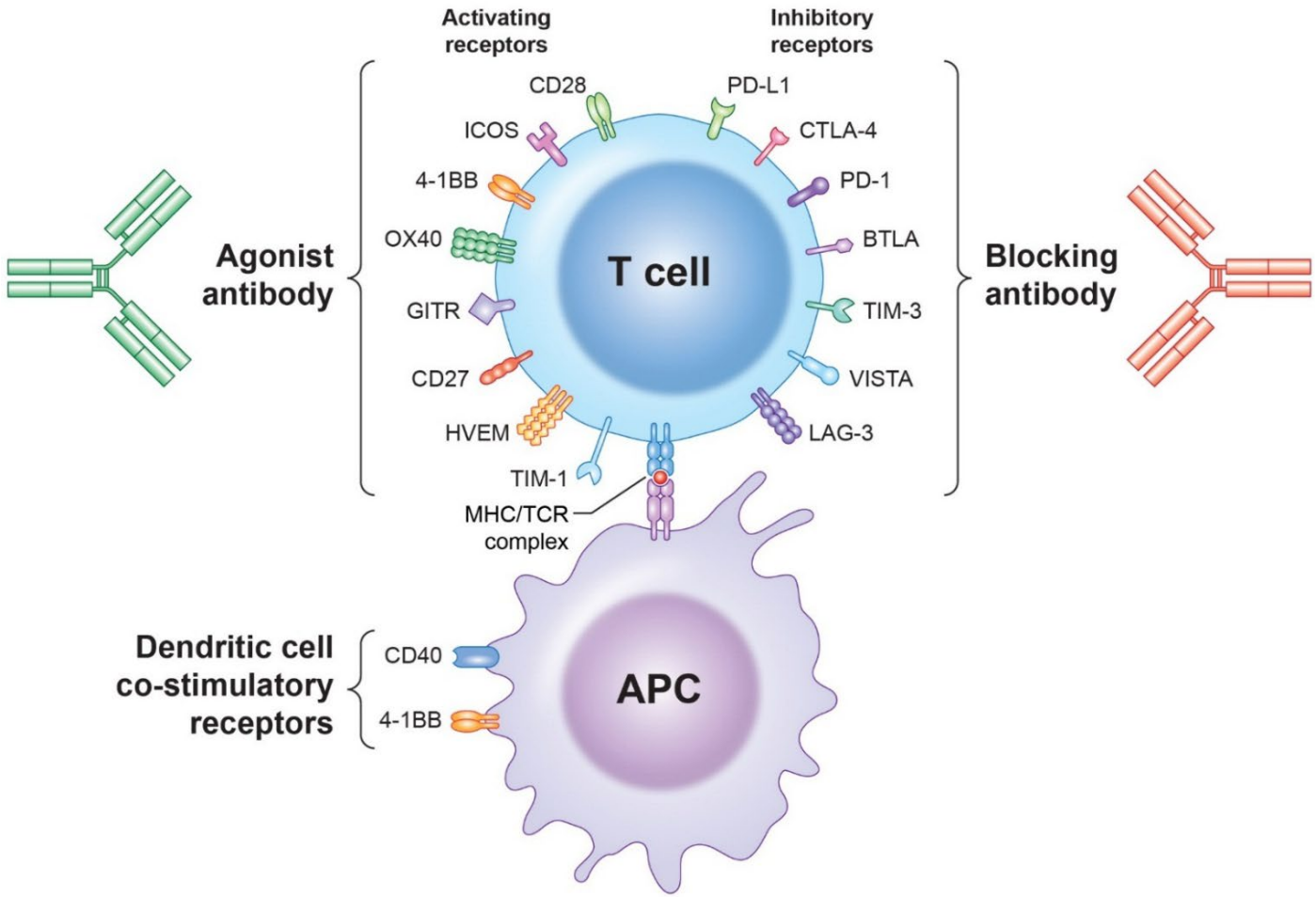



Image courtesy of NCI

# Therapeutic Cancer Vaccines

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

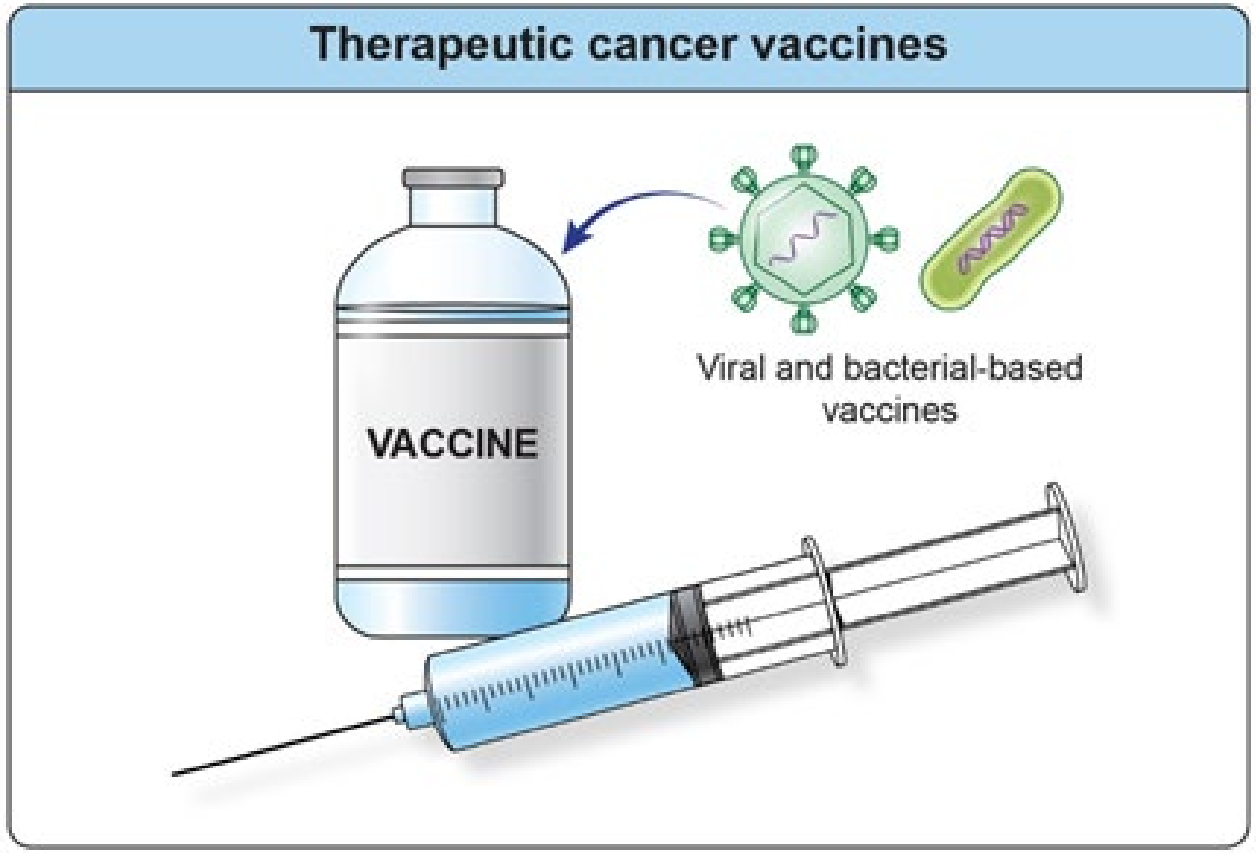



Image courtesy of NCI

# Adoptive Cell Therapy

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

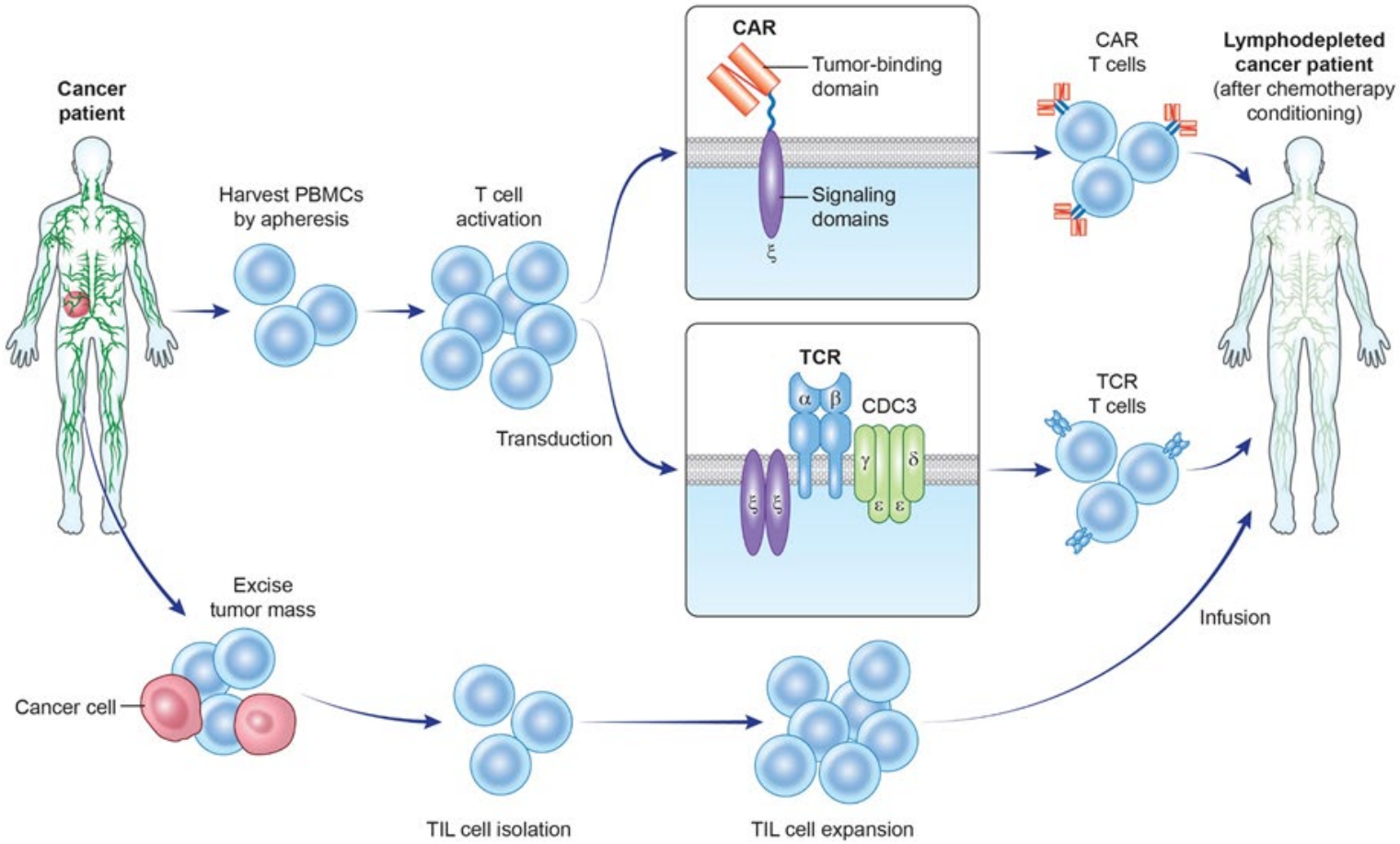



Image courtesy of NCI

# 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

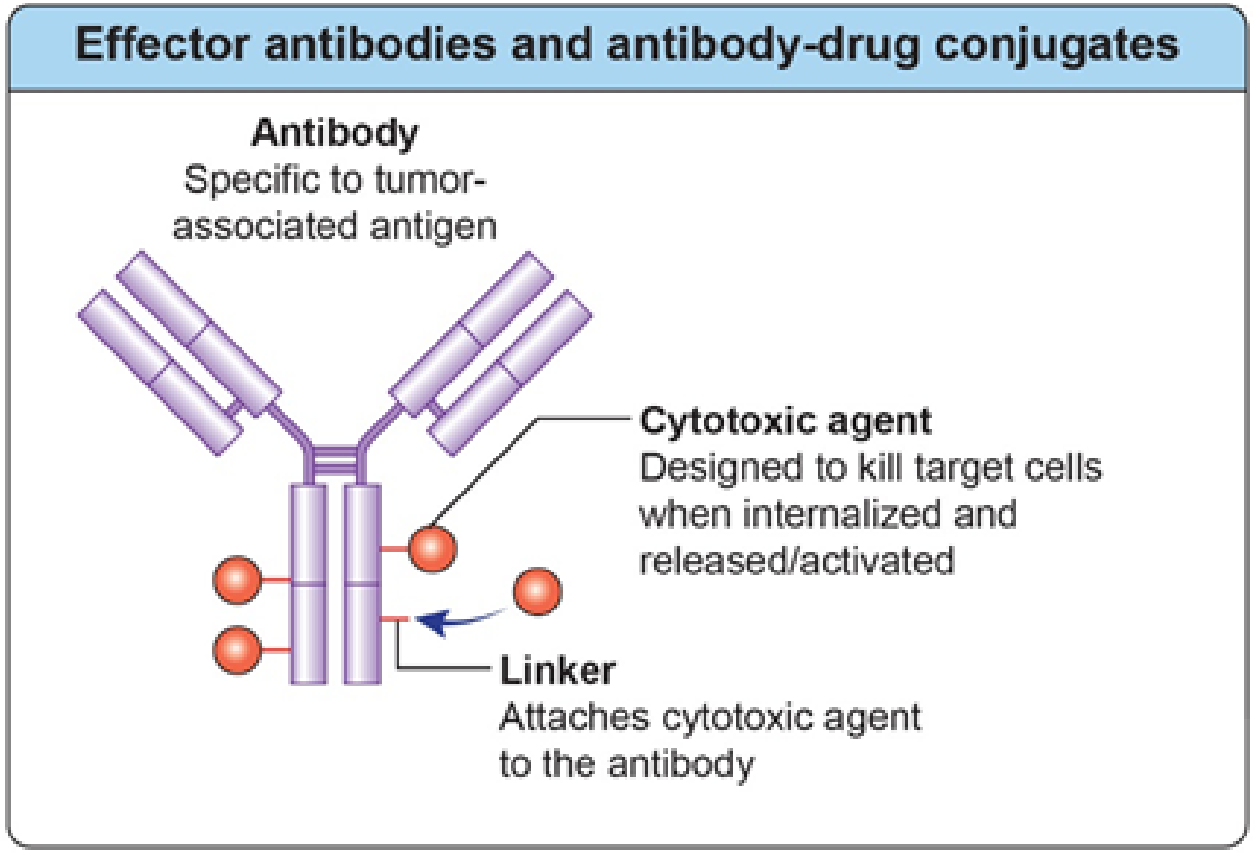
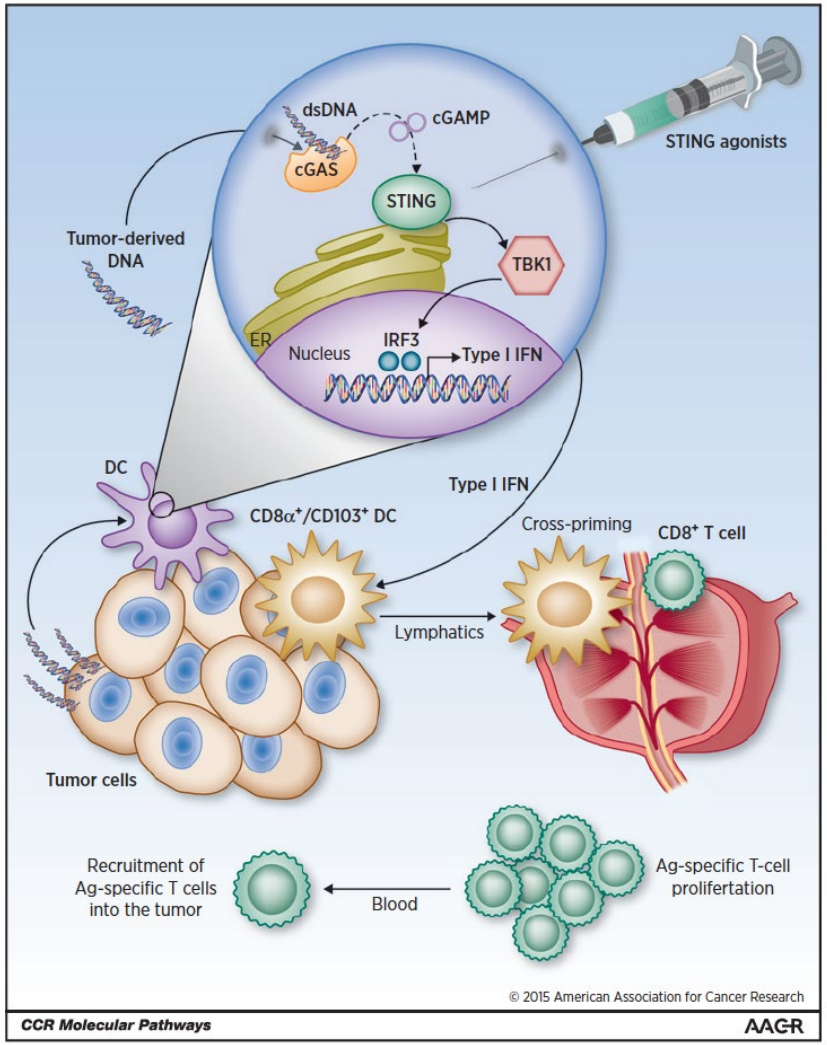



Image courtesy of NCI

# Innate immune activation

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




Agents:

Sting agonists

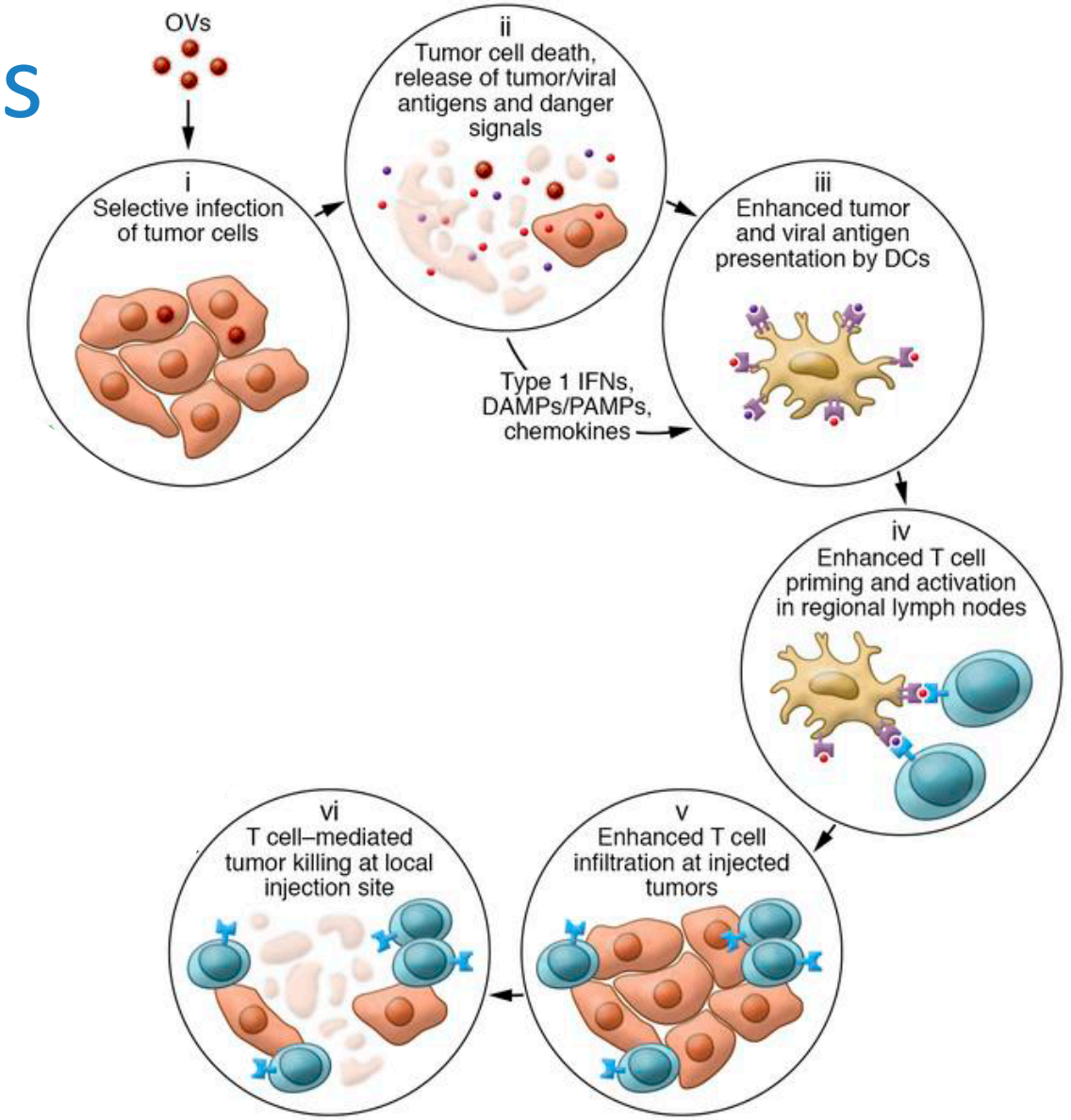
TLR agonists

Immunogenic RNA

Corrales, Clin Can Res 2015

# Oncolytic Viruses

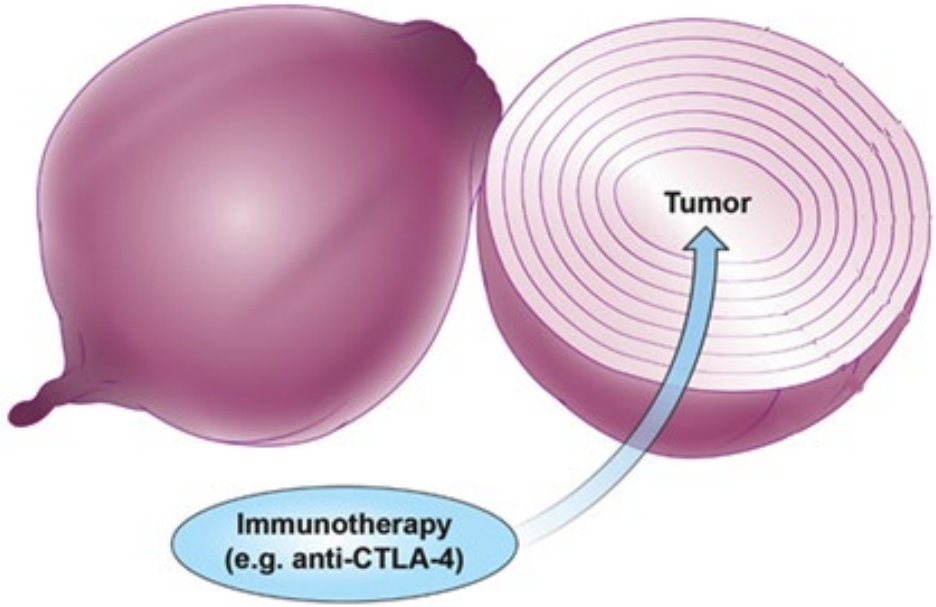
Goal: specifically target and kill tumor cells through viral replication AND release innate immune activators and tumor antigens




Modified from Bommereddy et al. JCI 2018

# Multi-layered Immunosuppression

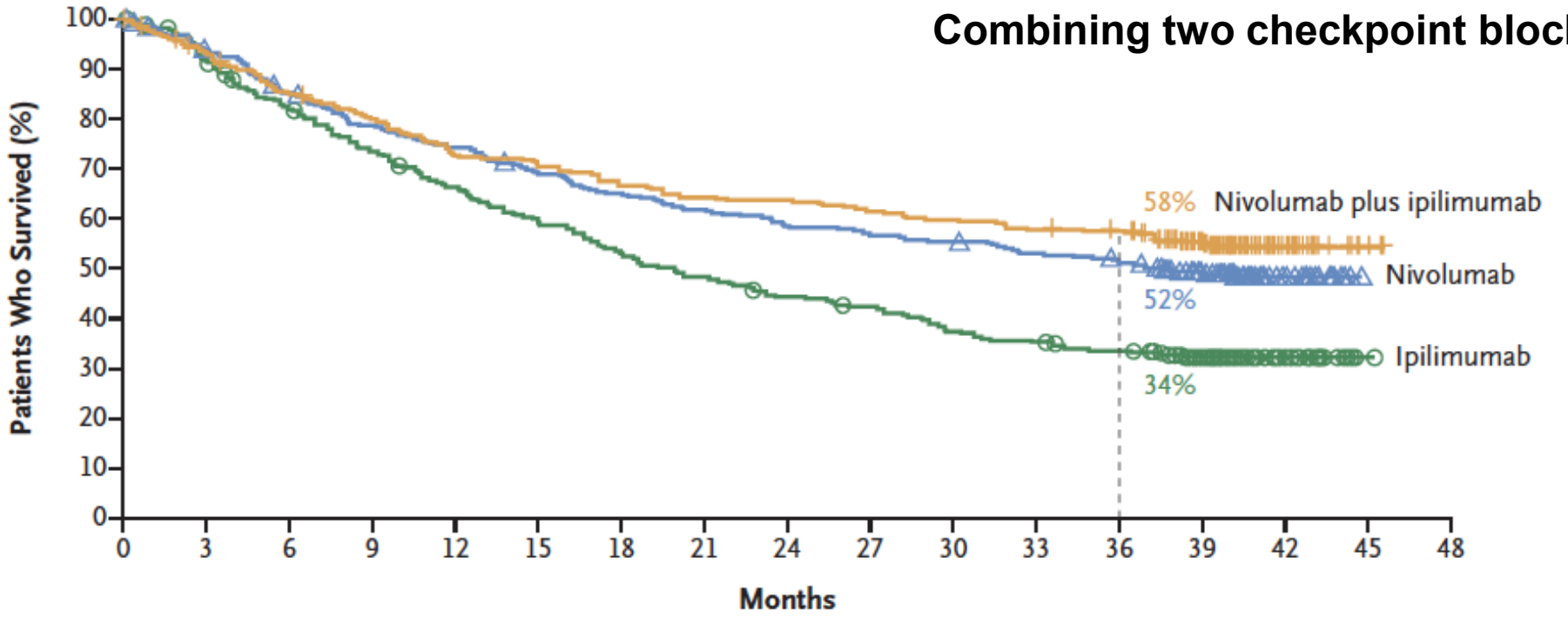
- Tumors insulate themselves with dense layers of immune-suppression
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression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



# Combination Immunotherapies

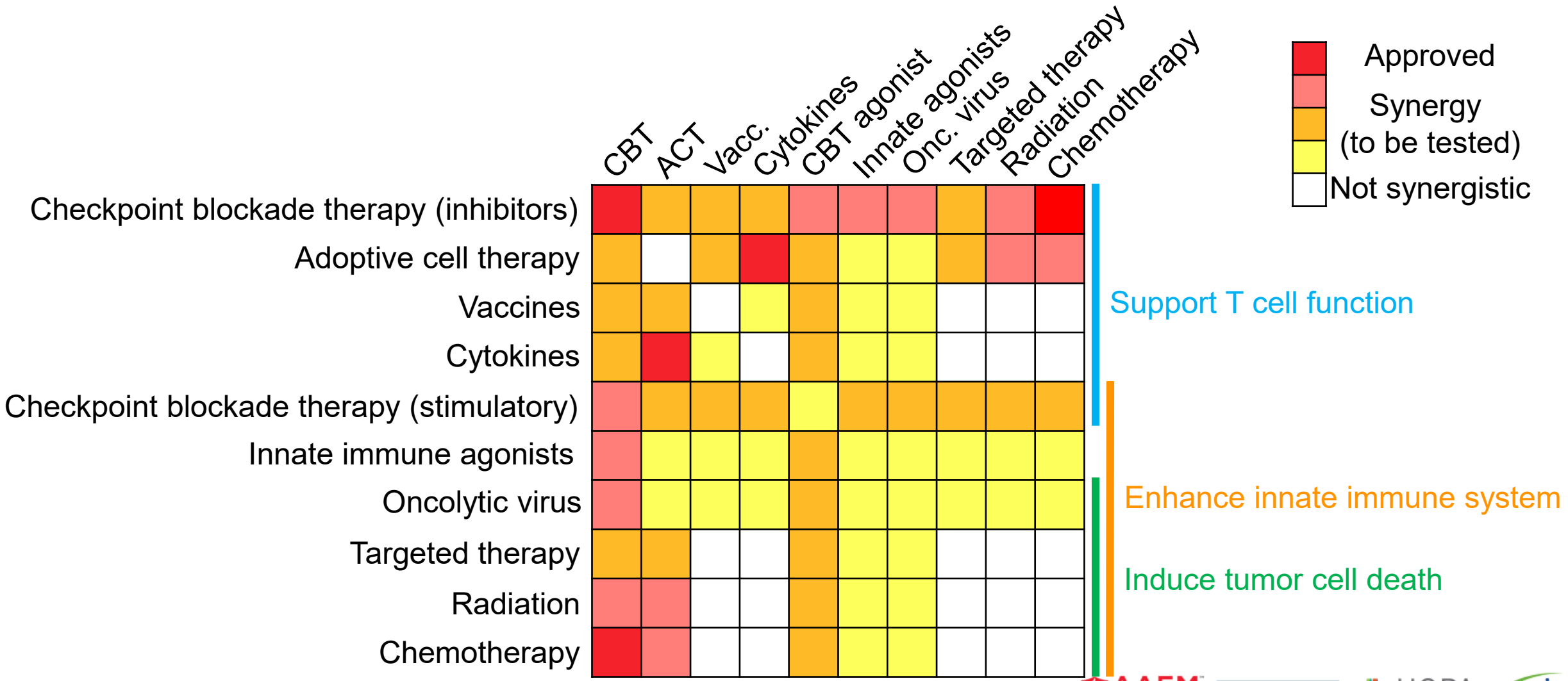
## *Dual CTLA-4 and PD-1 inhibition*

**Combining two checkpoint blockade agents**

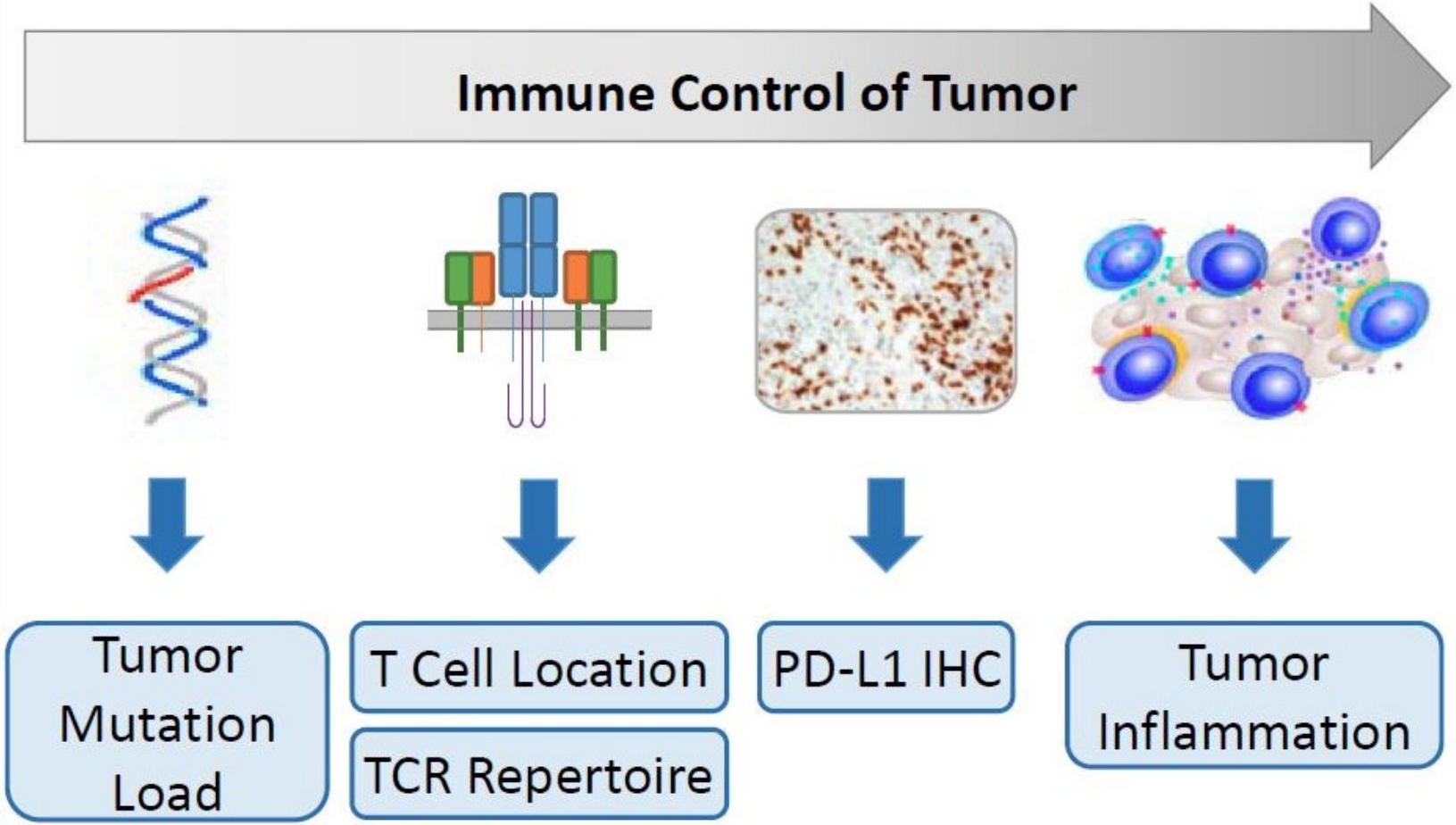



Wolchok et al., NEJM 2017

# Combination Immunotherapies

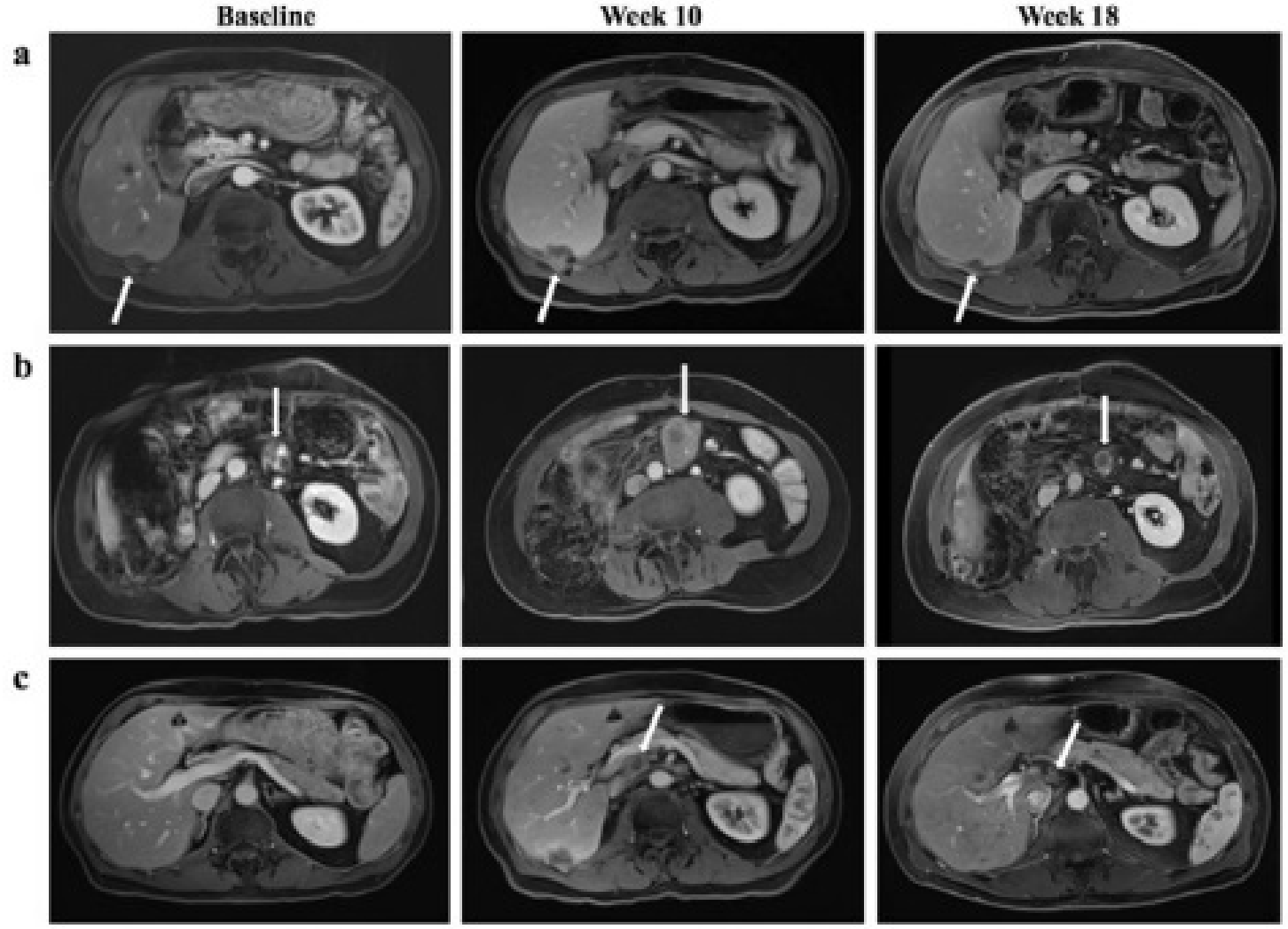


# Immunotherapy Biomarkers



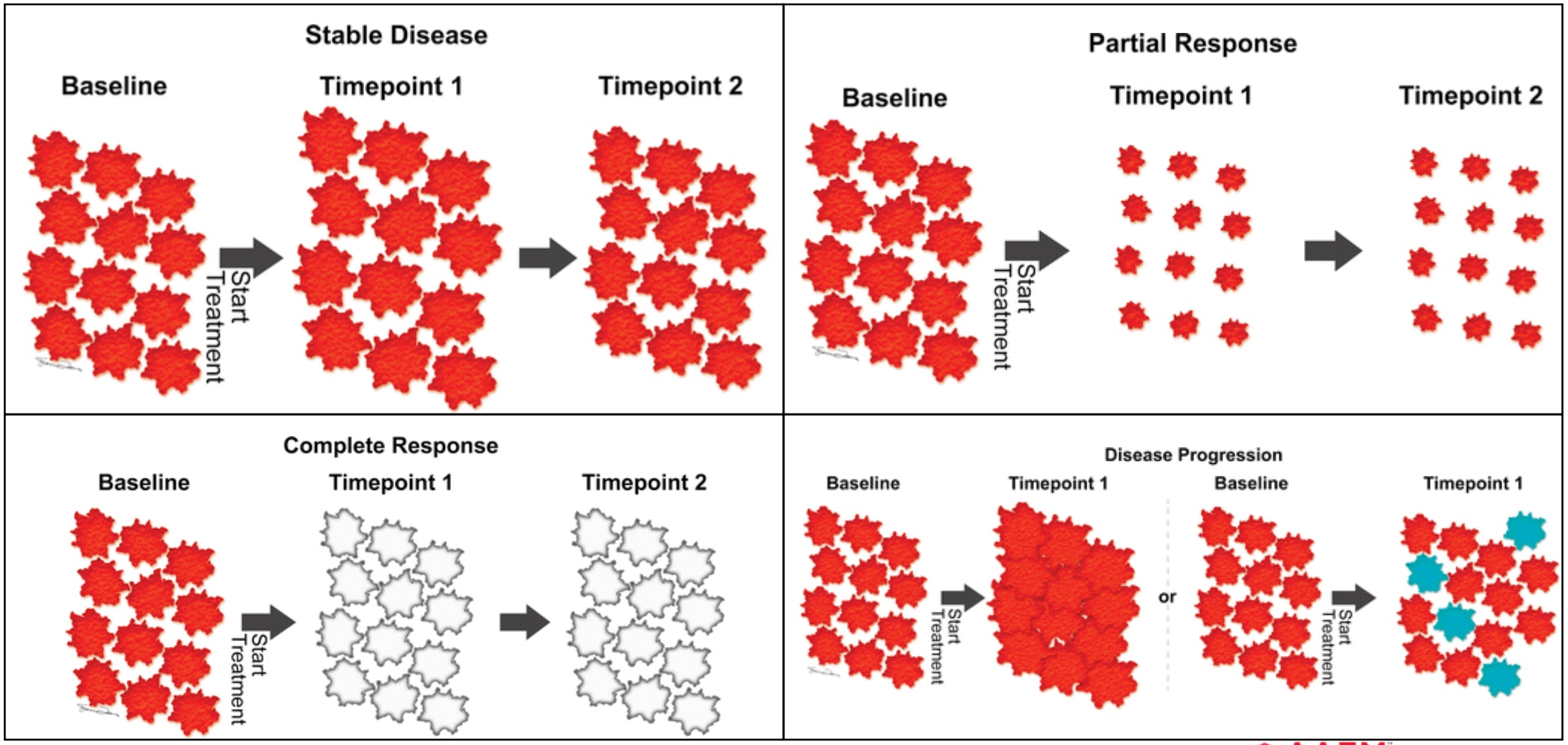

Cesano et al. Biomedicines 2018

# Assessment of response



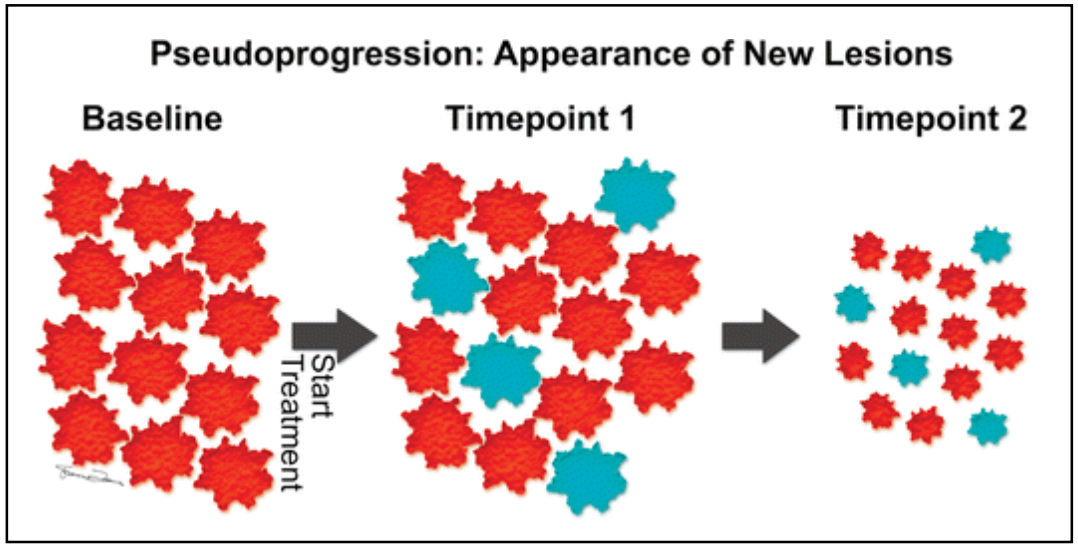

Chae, Oncotarget 2017.

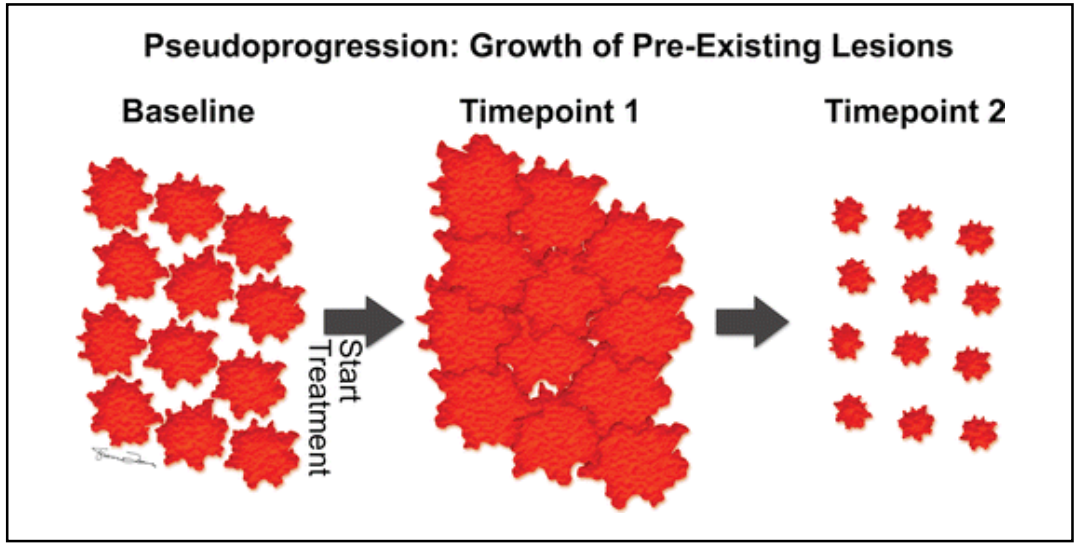
# Many possible imaging findings




Wang, RadioGraphics 2017.

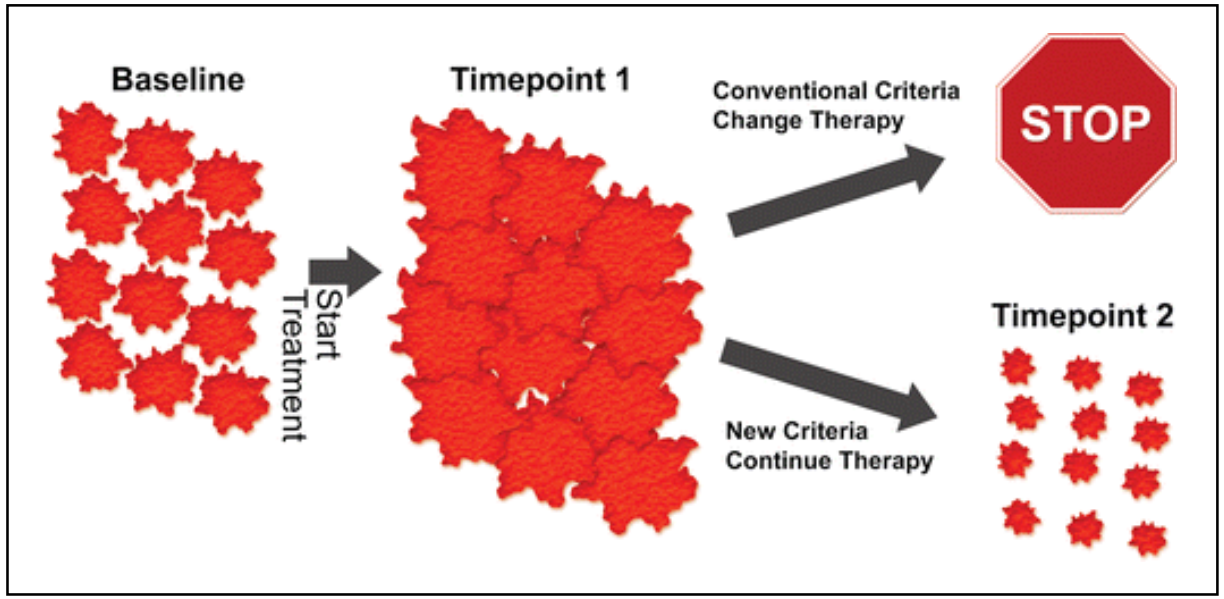
# Many possible imaging findings

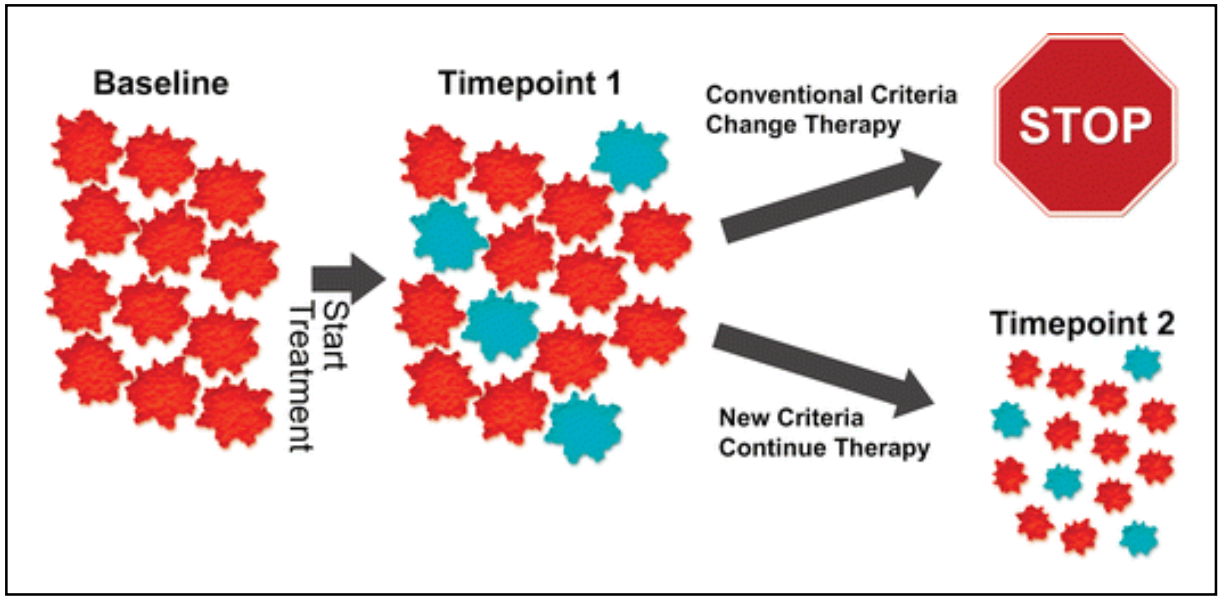



Wang, RadioGraphics 2017.

# Assessment of response – unique considerations for immunotherapy




Wang, RadioGraphics 2017.

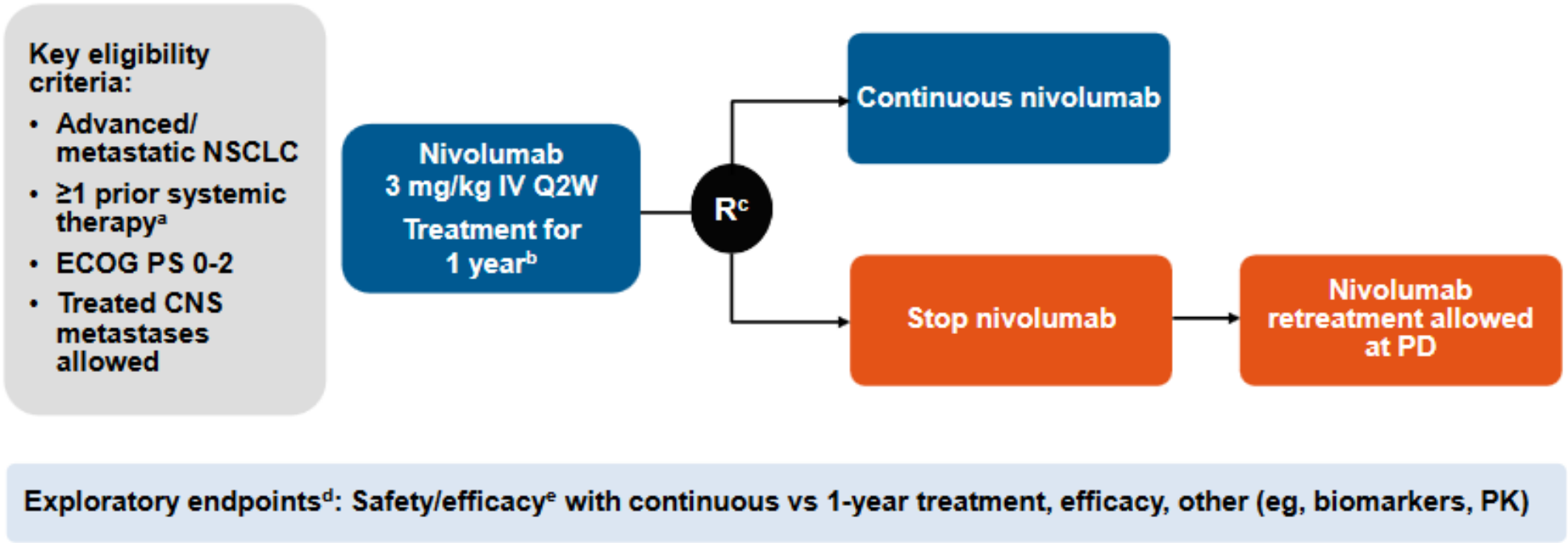
# Comparison of disease progression by conventional and immune-related criteria

| 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.

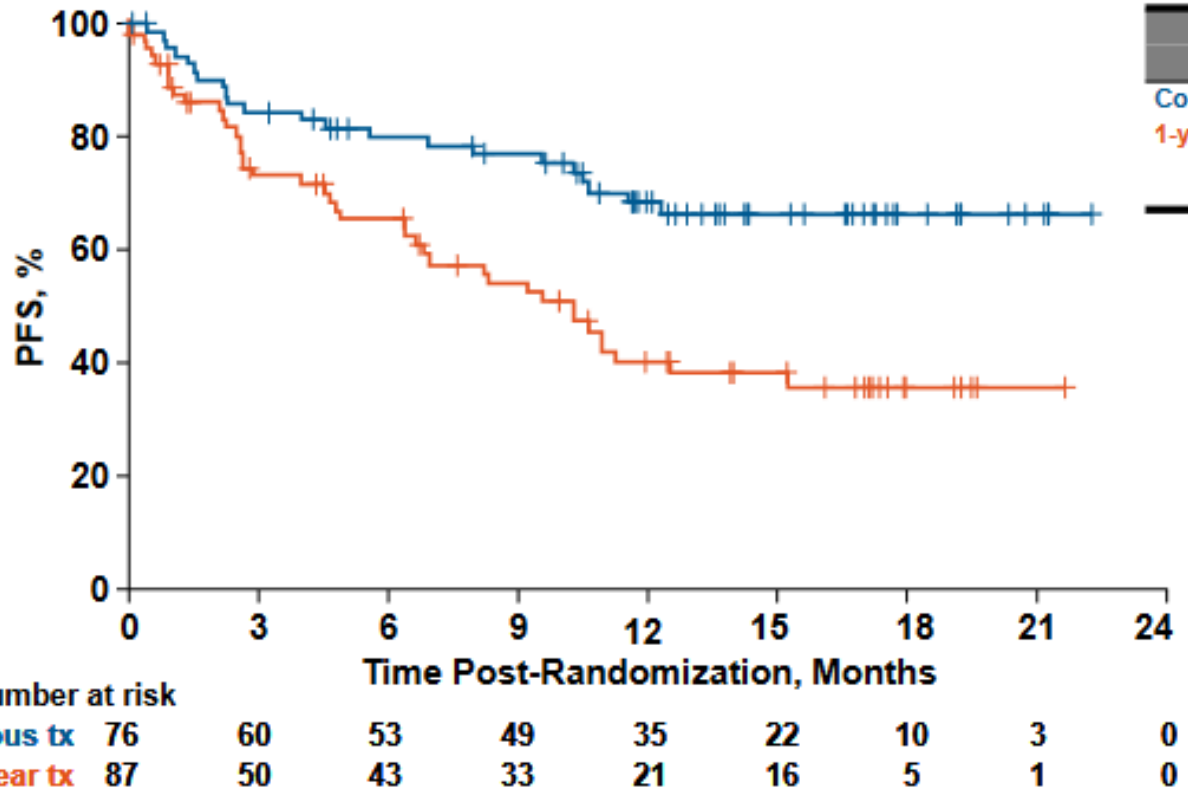
*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm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

# 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

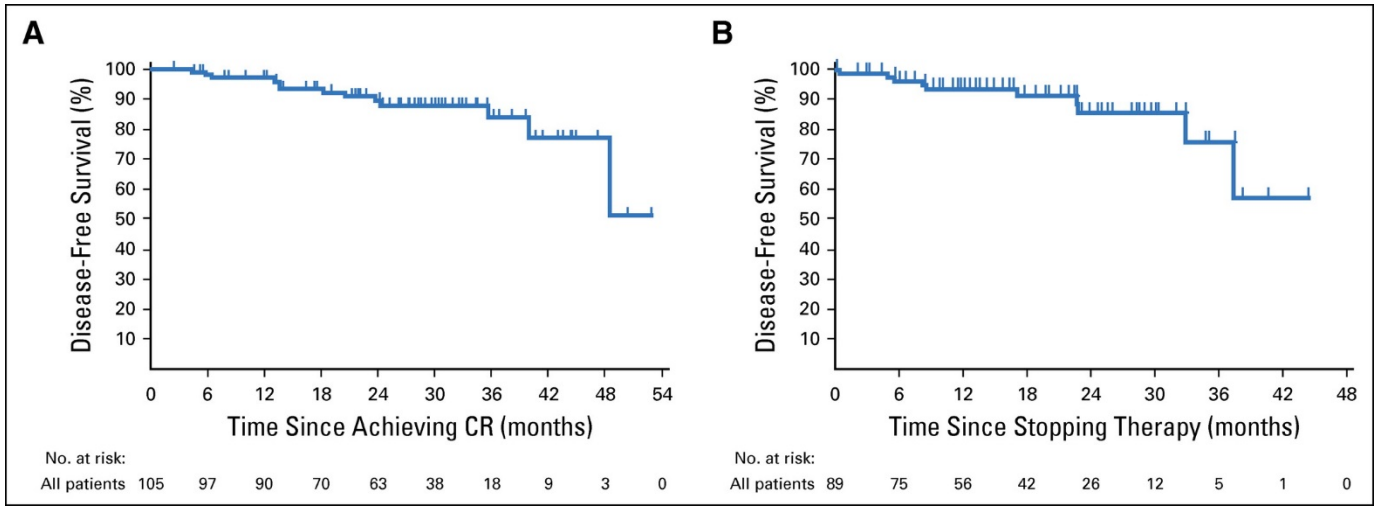
Spigel, Ann Oncol 2017.

# 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%

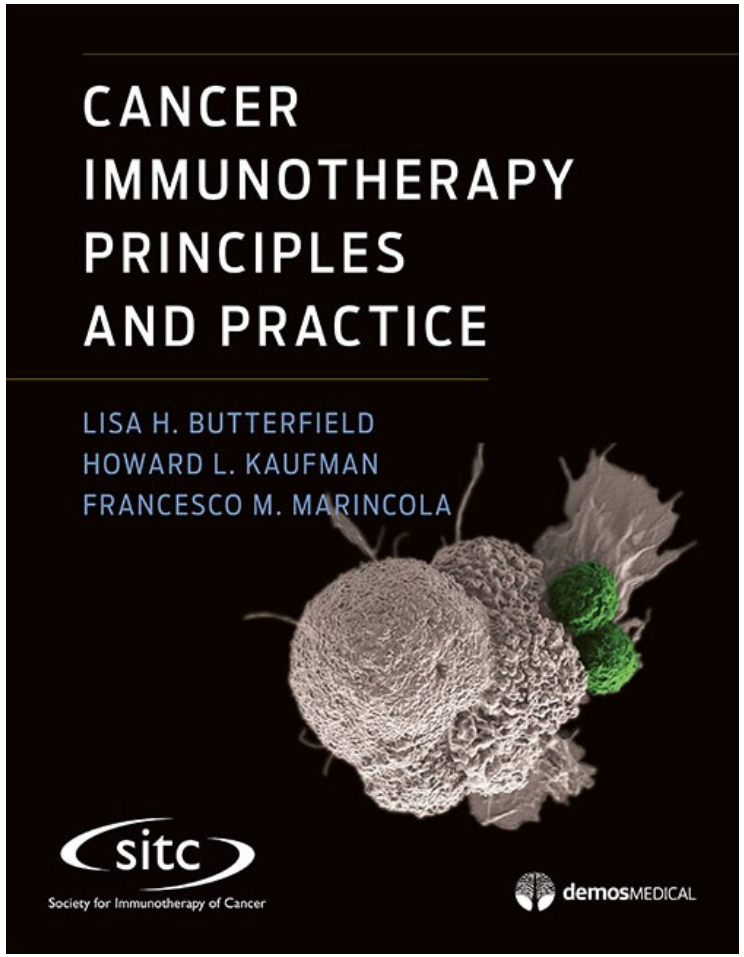



Robert, J Clin Oncol 2018.

# When to stop immunotherapy: clinical measures

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

# Further Resources




SOCIETY FOR IMMUNOTHERAPY OF CANCER

Cancer Immunotherapy CONNECT