Society for Immunotherapy of Cancer

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

Society for Immunotherapy of Cancer

Disclosures

- Consulting Fees:
  - BMS, Alkermes

- 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 cancer cells

- To escape, tumors must 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.

Immunotherapy for Cancer: Induce inflammation
A 18th and 19th Century Paradigm

1768: G. White: Use of poultice made from decaying toads for breast cancer

1844: S. Tanchou: Treatise on breast cancer:
spontaneously or induced Gangrene as a therapeutic agent in cancer

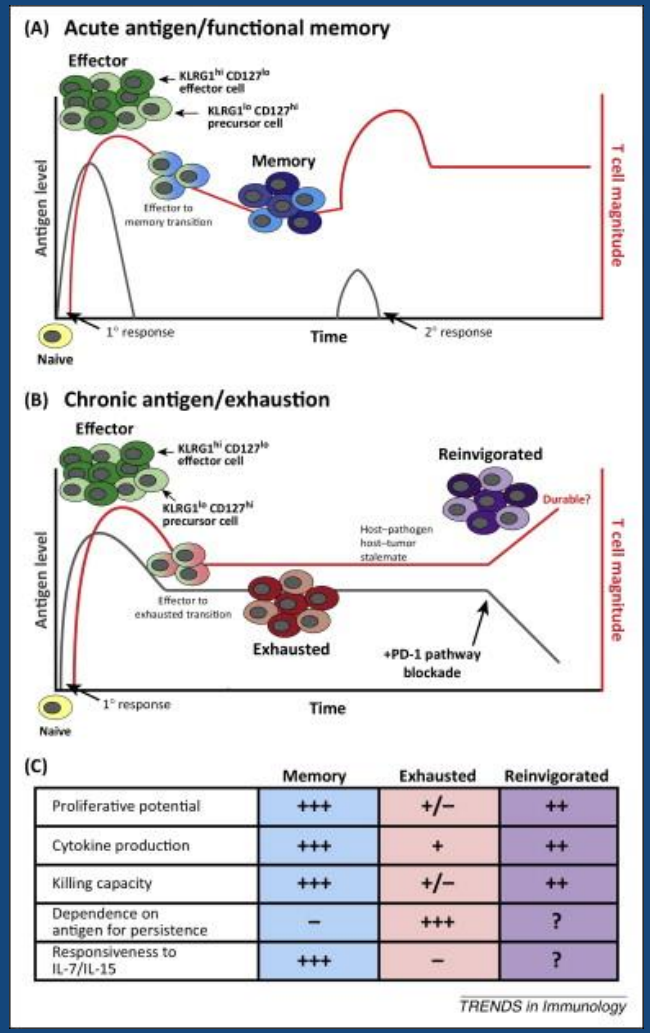
1886: A. Verneuil: Suppuration after surgery; Congress of Surgery Paris

1891: W.B.Coley: Annals of Surgery describing Toxins:
Initially used deliberate infection and in 1893 he began combining killed *Streptococcus pyogenes* and *Serratia marcescens* ---- *1985 mammalian TLR*

Immunotherapy for Cancer: "Modern" Foundation for Cancer Immunotherapy
20th Century Discoveries

	1868: P. Langerhans: Skin Dendritic Cells
NOBEL 1908	1909: P. Ehrlich: immune system control of cancer and the Magic Bullet
NOBEL 1960	1949: F. Burnet: Proposes acquired tolerance to tumors verified by in 1953 by B. Medawar
	1954: Y. Nagano described Interferon
	1956: B. Glick: B cell discovery reported in Poultry Science, significance by M. Cooper & R. Good in 1965
	1957: A. Isaacs and J Lindenmann identify Interferon
	1958: J. Dausset, B. Benacerraf, and G.D. Snell HLA discovered
	1959: L. Thomas: Immune Surveillance
	1965: M. Cooper: description of T cells
	1969: R. Gershon & K. Kondo Regulatory T cells
	1970: P. Bretscher and M. Cohn Two-signal model of T cells
NOBEL 2011	1973: R. Steinman and Z. Cohn: DC
	1976: F. Ruscetti, D. Morgan, R. Gallo: IL-2 discovered
	1985: Nusslein-Vulhard TLRs
	1995: S. Sakaguchi Mouse CD4 Regulatory cells followed by identification in humans in 2001
NOBEL 2018	1996: J. Allison identification of CTLA4 immune check point
NOBEL 2018	2000: T. Honjo idenfication of PD1 immune check point

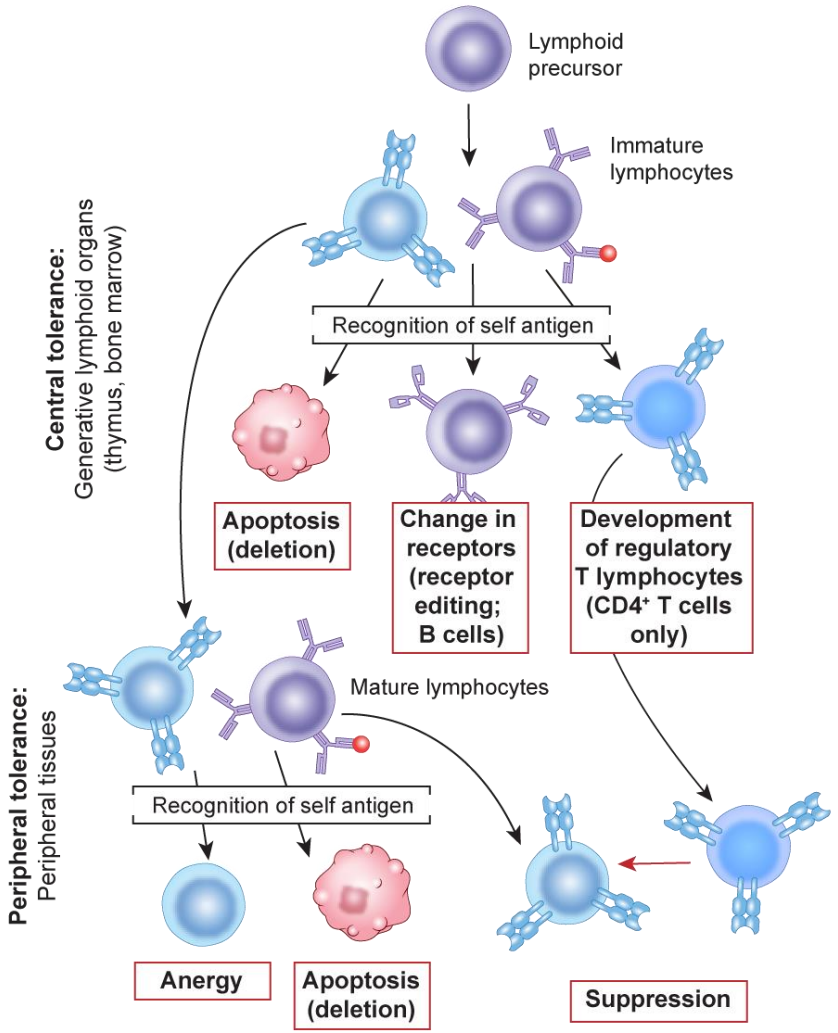
IRAE MECHANISM
Basic Immunology: Immune Response Kinetics



	Memory	Exhausted	Reinvigorated
Proliferative potential	+++	+/–	++
Cytokine production	+++	+	++
Killing capacity	+++	+/–	++
Dependence on antigen for persistence	–	+++	?
Responsiveness to IL-7/IL-15	+++	–	?

Pauken & Wherry
Trends in Immunology
2015

Central and Peripheral Tolerance



Central Tolerance

- For T cells it occurs in the thymus
- Some survive as regulatory (suppressor) T cells while others escape to peripheral tissues

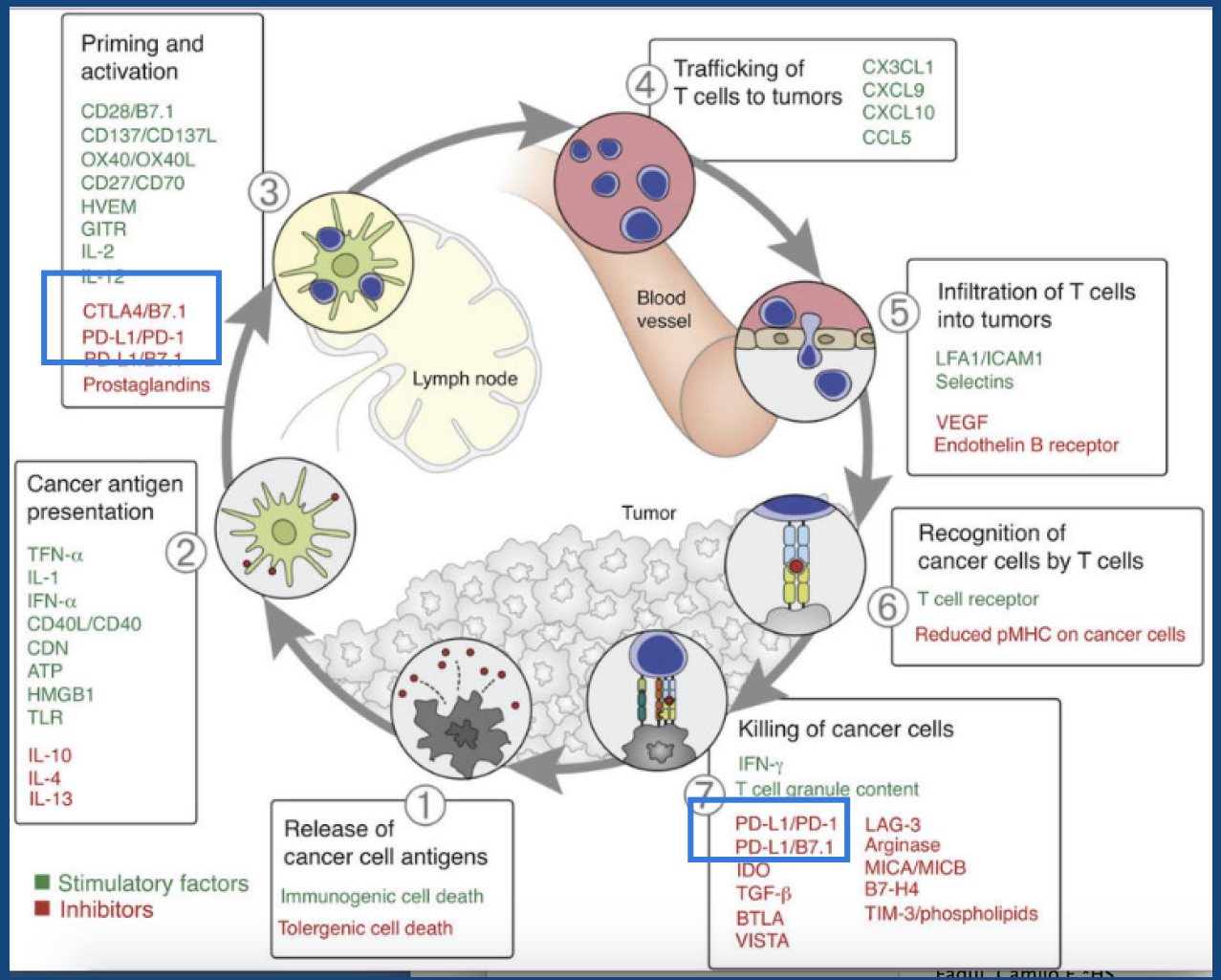
Peripheral Tolerance

- Self-reactive T cells are suppressed by regulatory T cells
- CTLA-4 and PD-1, among other molecules play a role in maintaining self-reactive T cells from becoming activated (anergic)

Adopted from SITC

Immune Cycle
Locations of Immune Checkpoint Control

Central

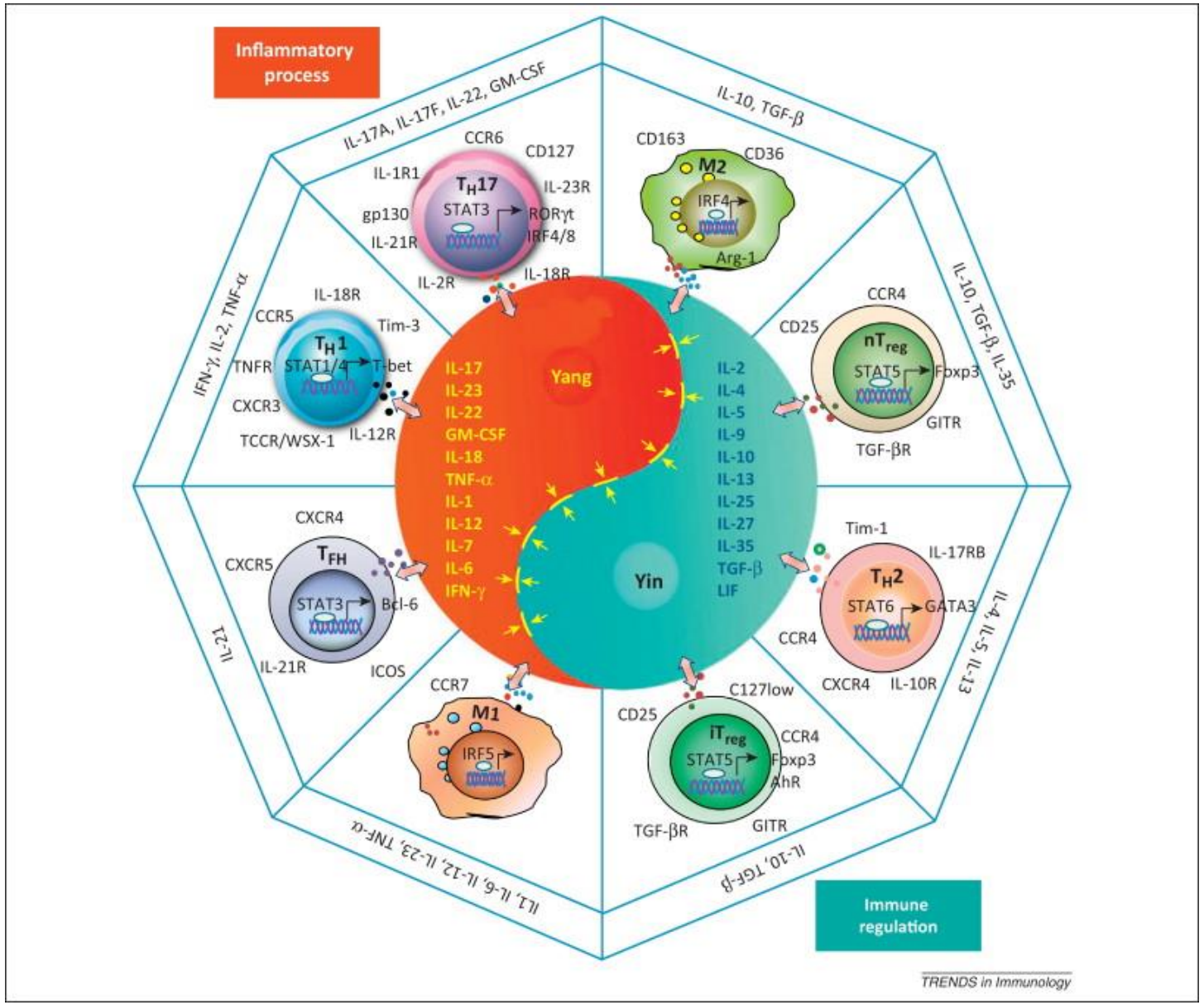


From Chen & Mellman Immunity 2013

Peripheral

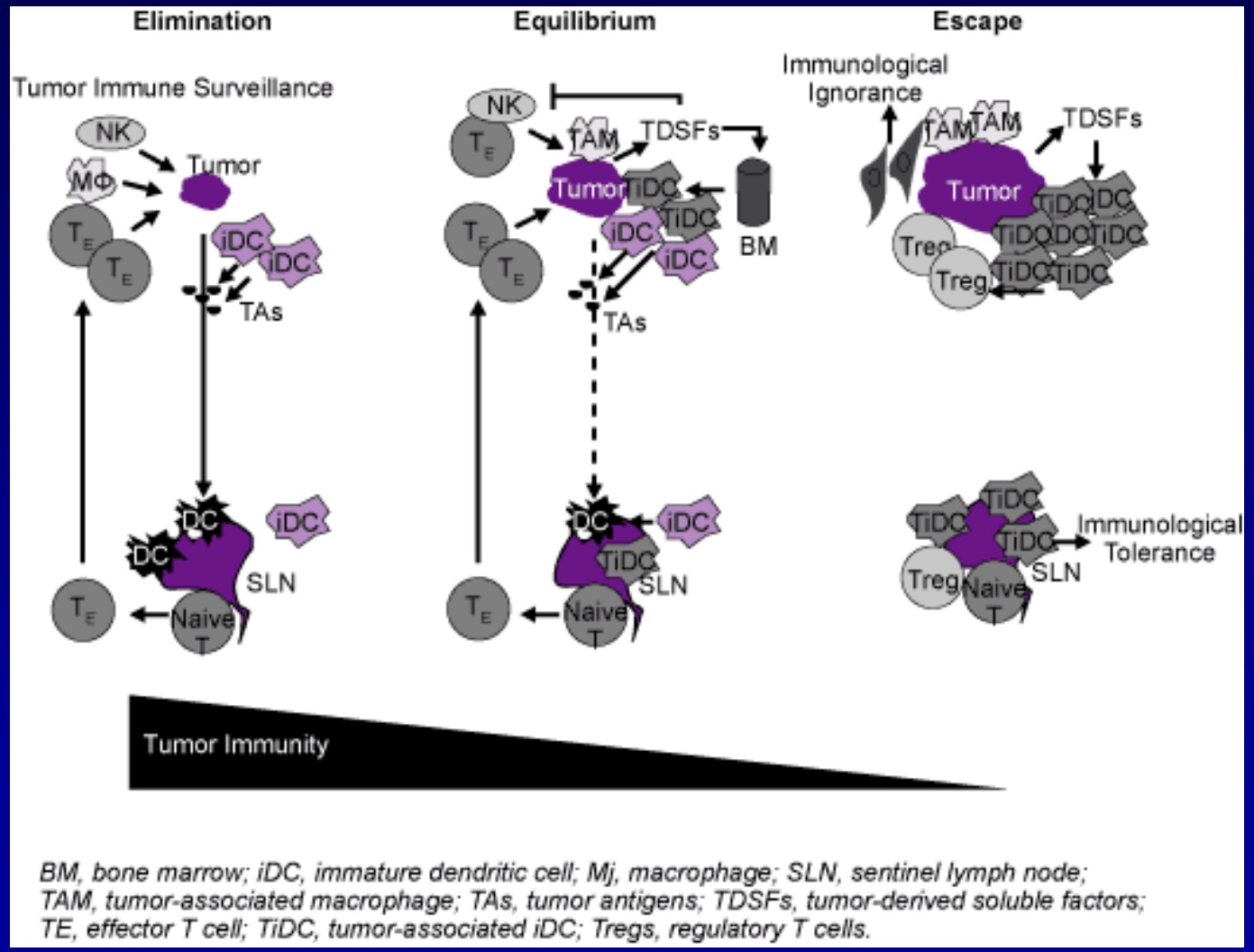
ROSWELL PARK CANCER INSTITUTE

Systemic and TME Components



Tumor Immungenicity: Immune Surveillance & Immunoediting

Ehrlich 1909
Burnet and Thomas 1957
Schreiber 2002



BM, bone marrow; iDC, immature dendritic cell; Mj, macrophage; SLN, sentinel lymph node; TAM, tumor-associated macrophage; TAs, tumor antigens; TDSFs, tumor-derived soluble factors; TE, effector T cell; TiDC, tumor-associated iDC; Tregs, regulatory T cells.

From FS Hodi

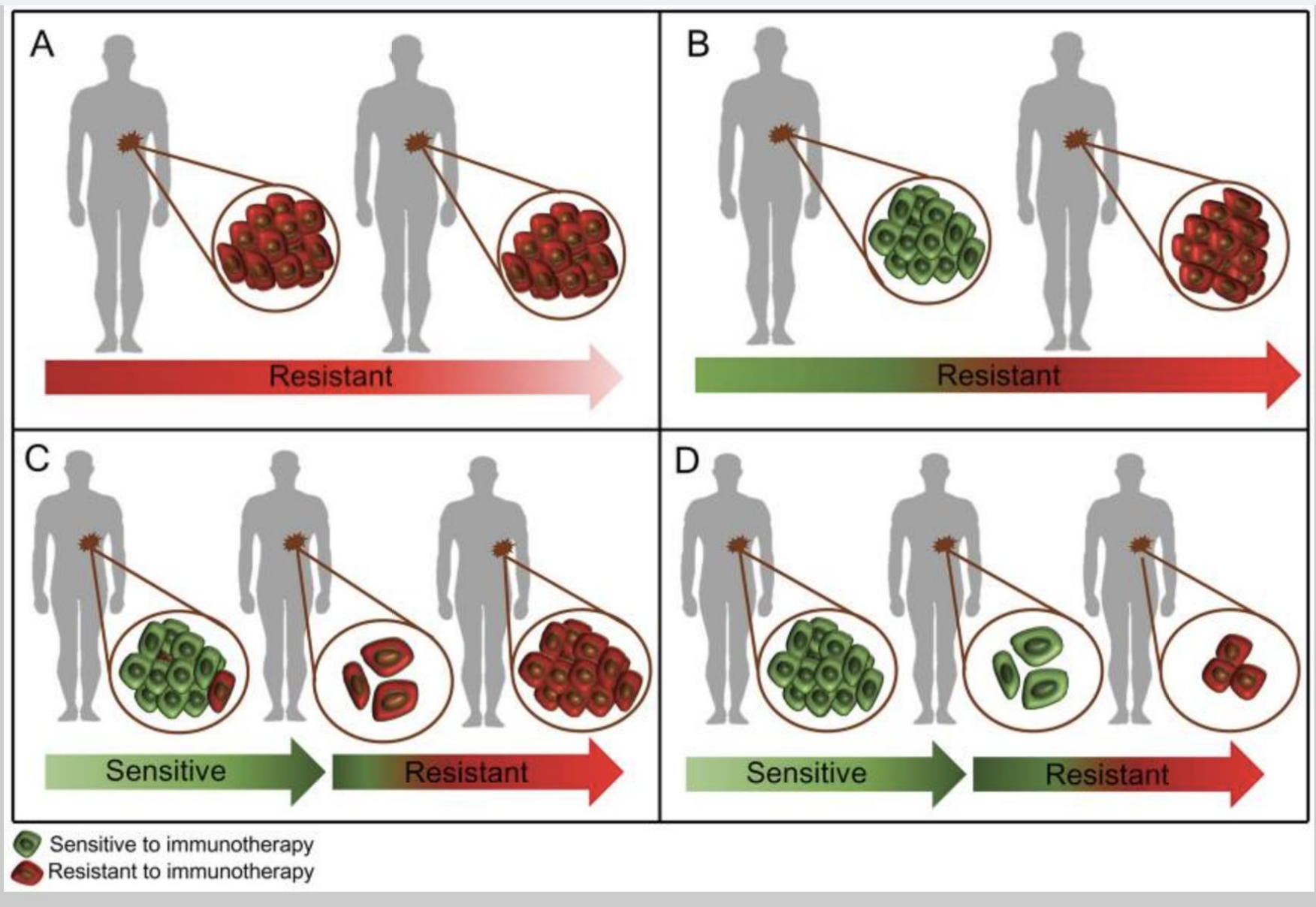
Two major mechanisms of tumor immune escape

- **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 unviable 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.

Resistance Mechanisms

Sharma et al 2017 Cell



A: No immune response

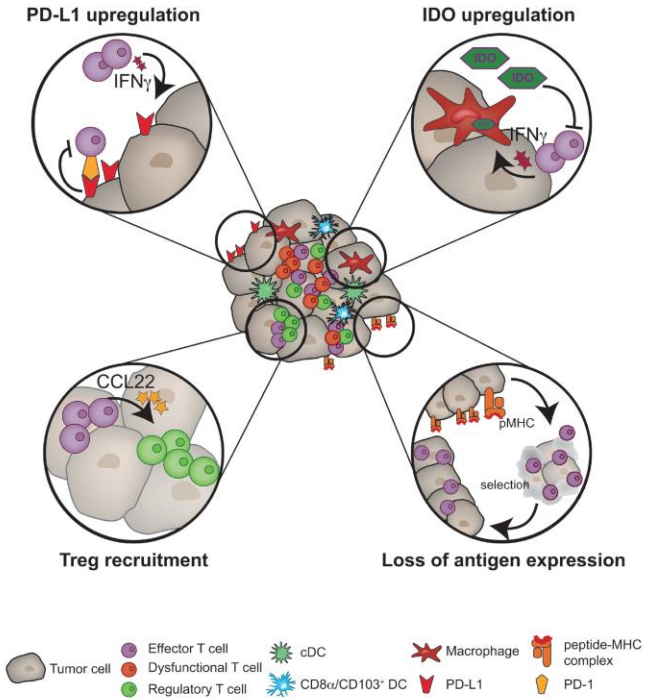
B: Immune response
No Clinical Response

C: Resistant clones

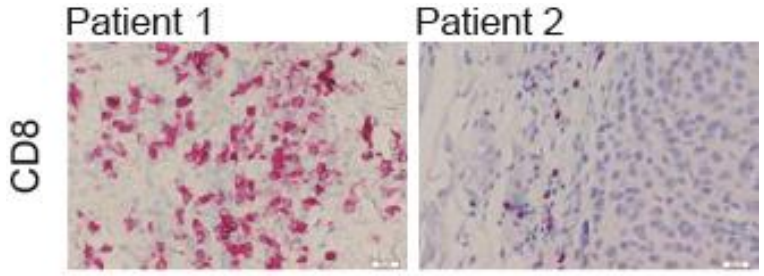
D: Acquired immune resistance

Immune evasion

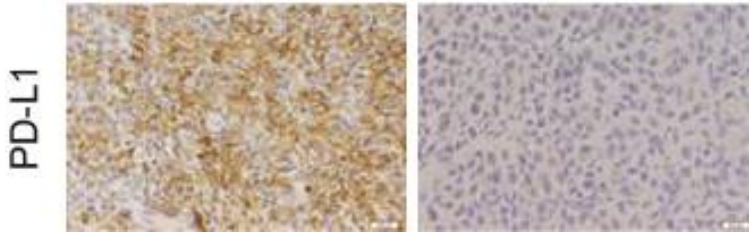
T cell-inflamed tumor microenvironment



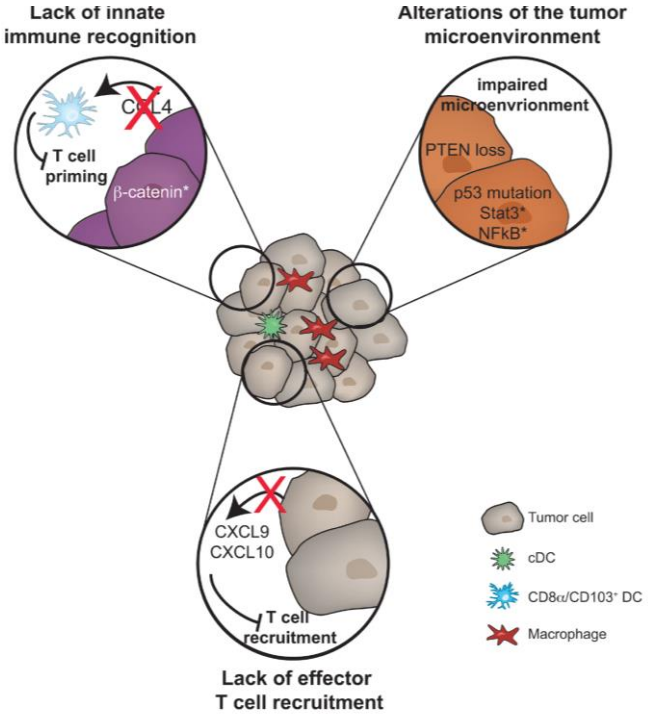
T cells



Immune suppression



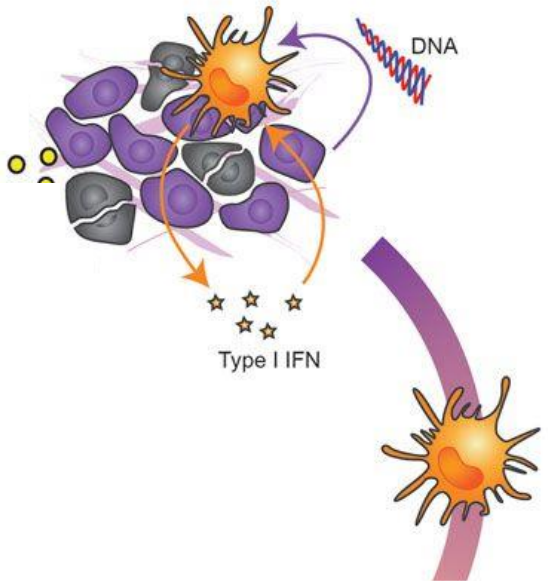
Non-T cell-inflamed tumor microenvironment



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

Initiation of an anti-tumor immune response

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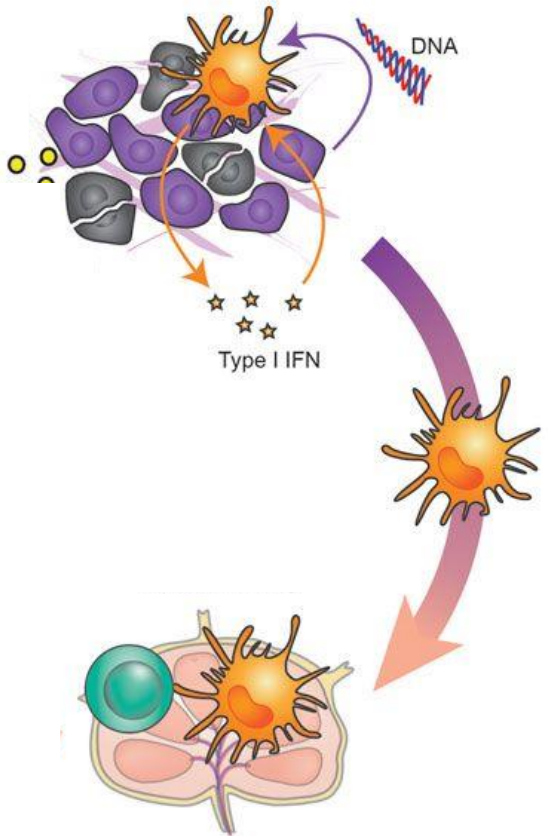


APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

Antigen-specific T cell Activation

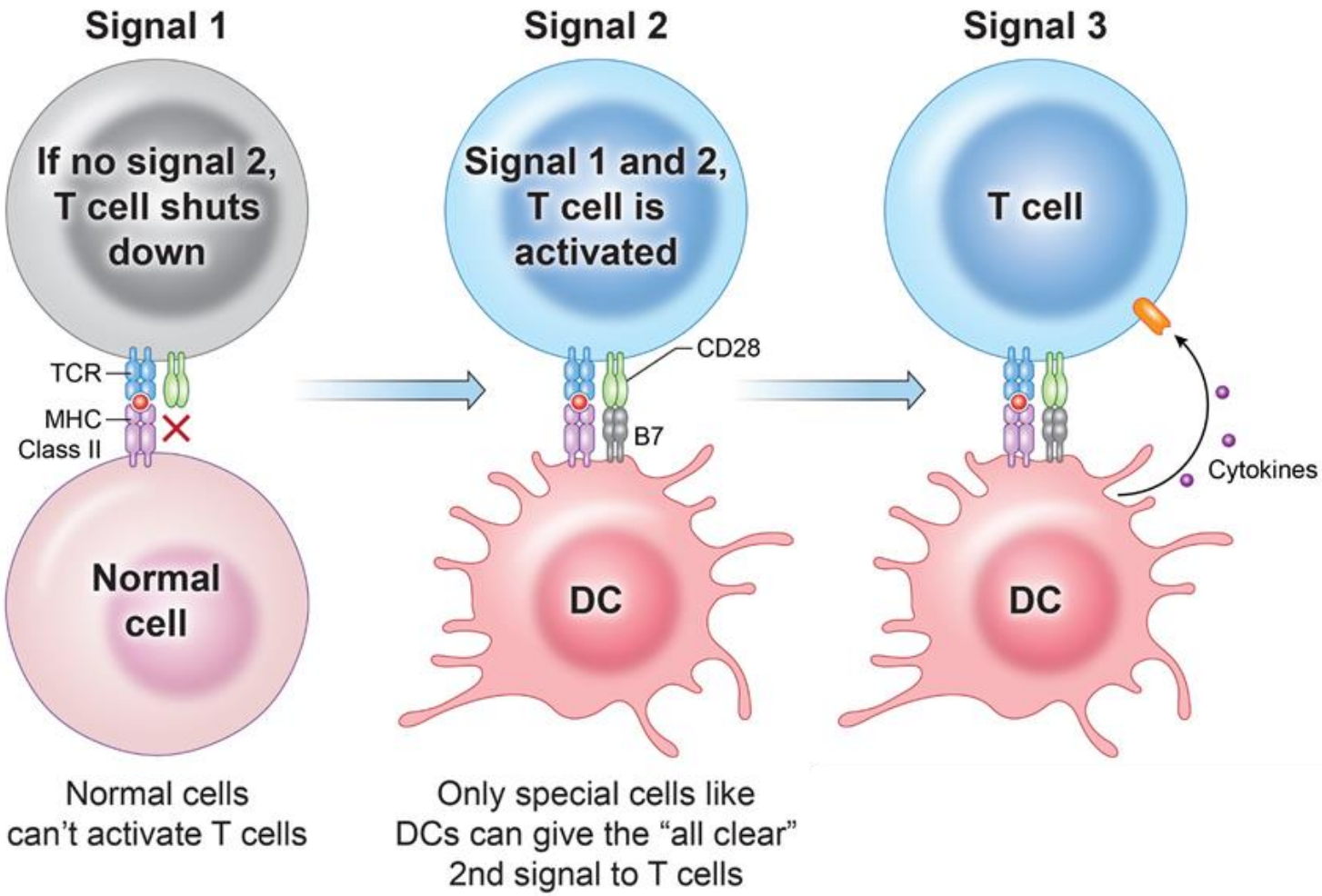
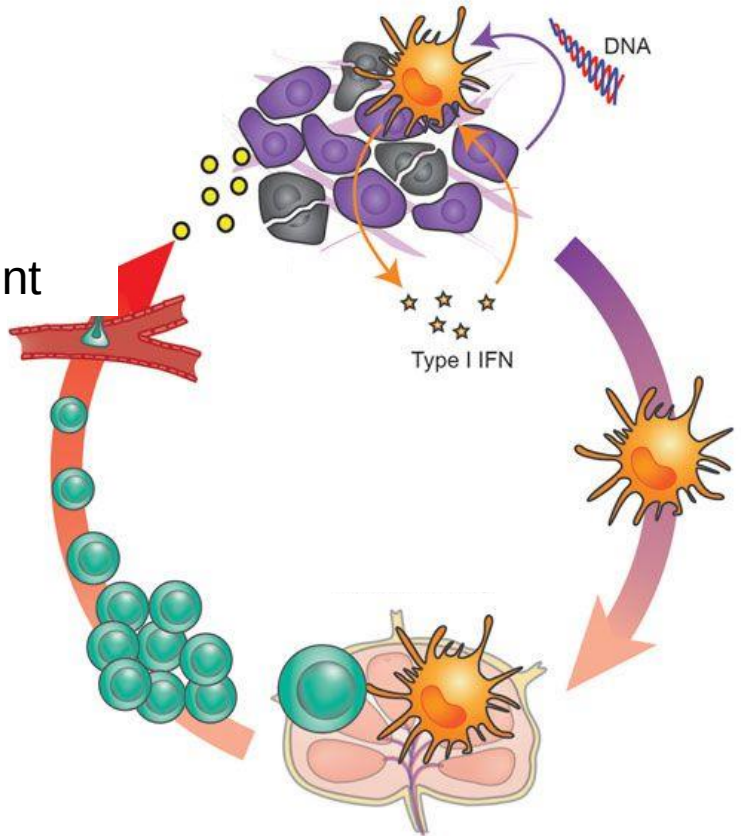


Image courtesy of NCI

Initiation of an anti-tumor immune response

Innate immune sensing (i.e. Sting activation)

T cell recruitment

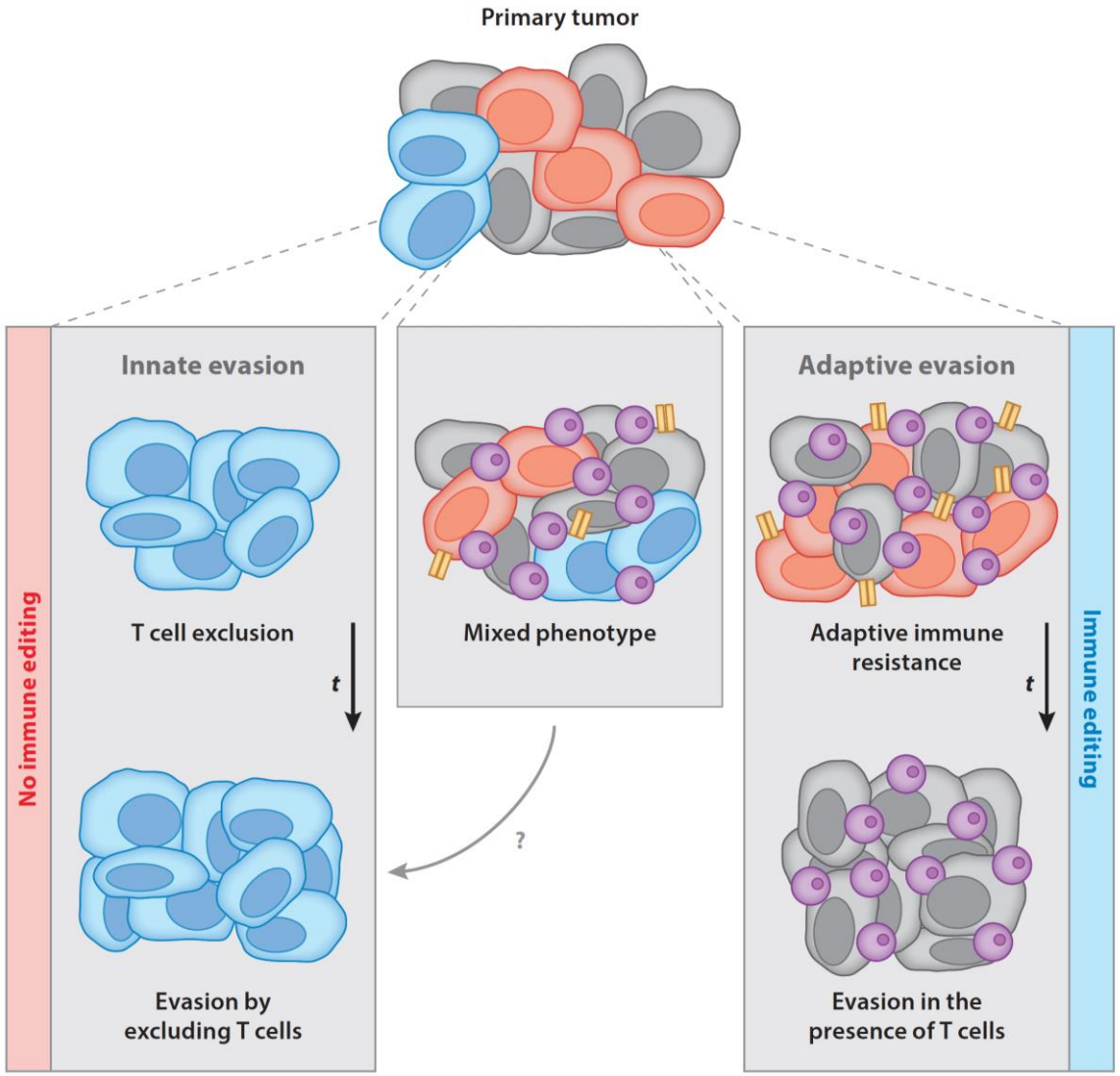


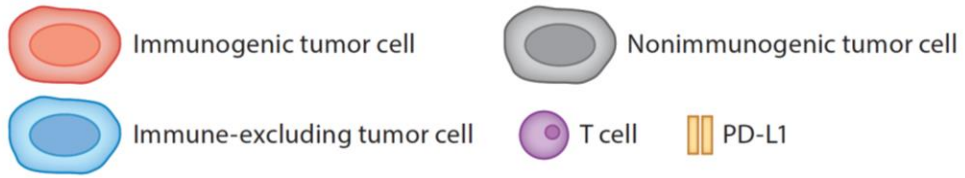
APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

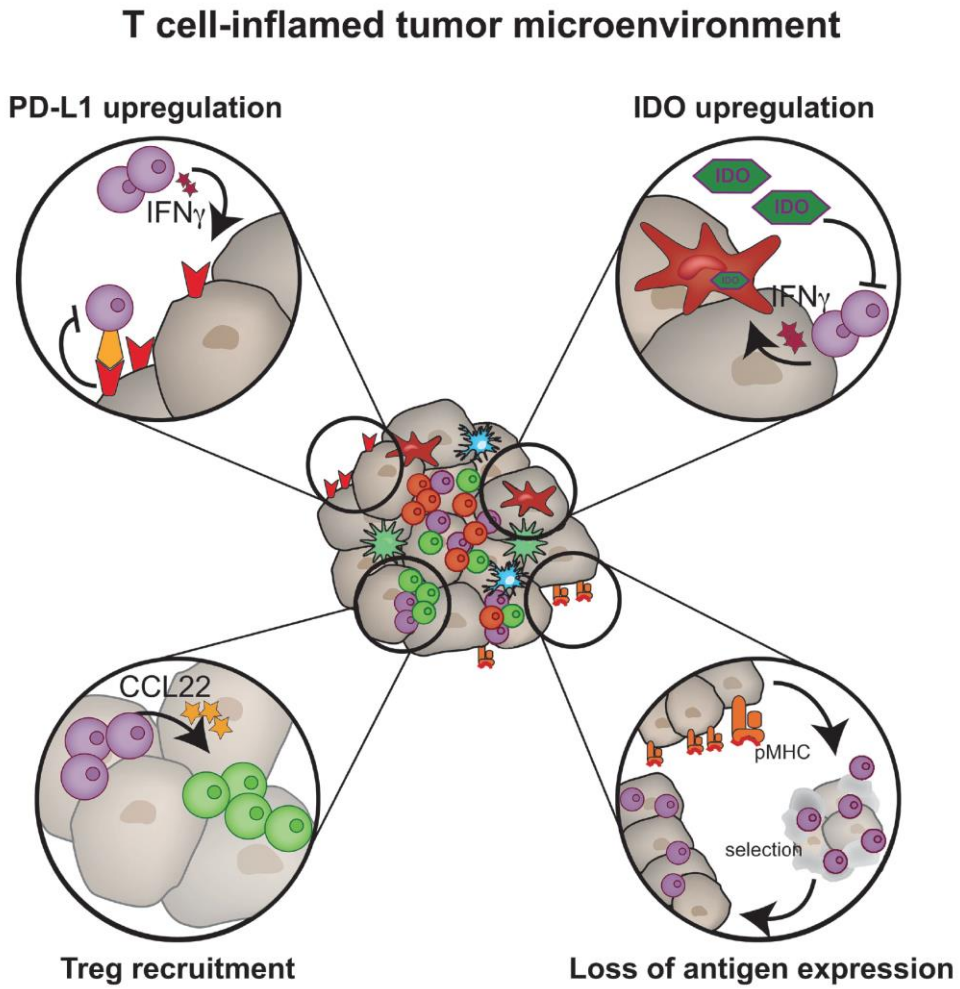
Immune evasion occurs over time





Spranger, AR Cancer 2018

T cell inflamed tumor microenvironment is immune suppressive

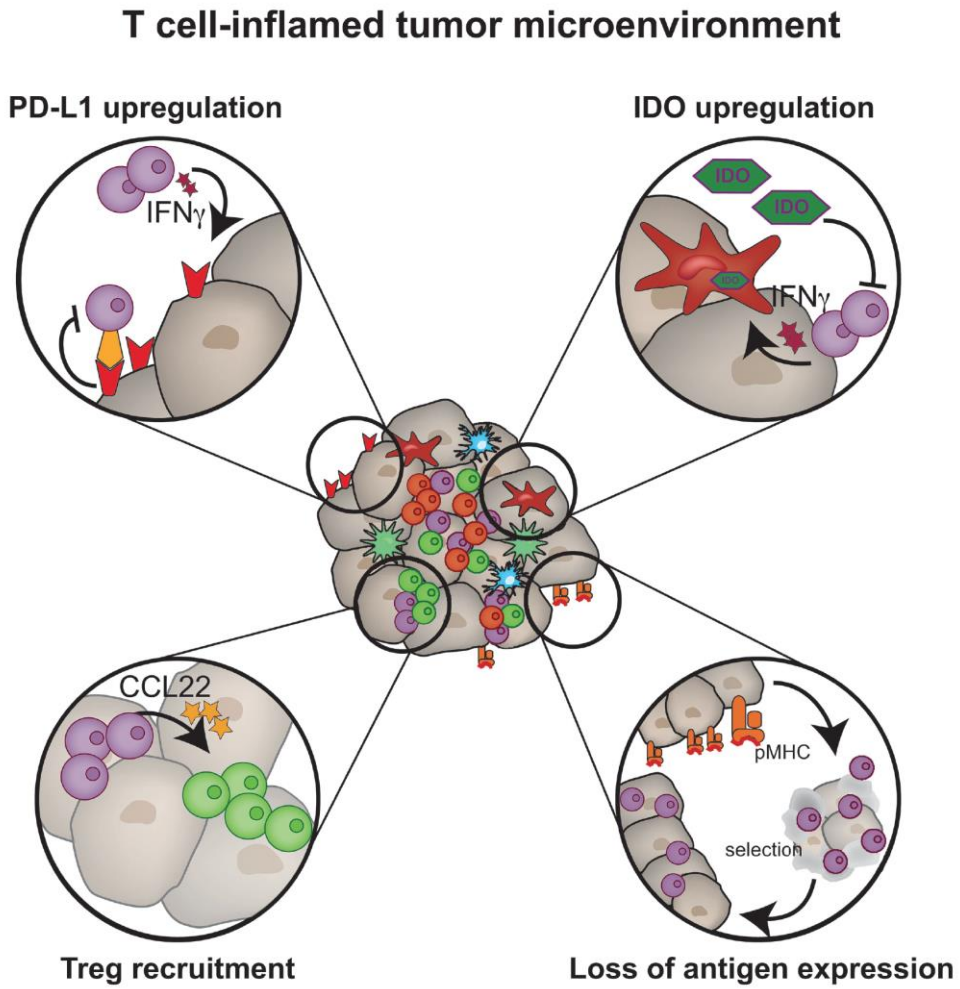


T cell-inflamed tumors escape by suppressing T cell function

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
- Cytokines
- TLRs
- Chemokines

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

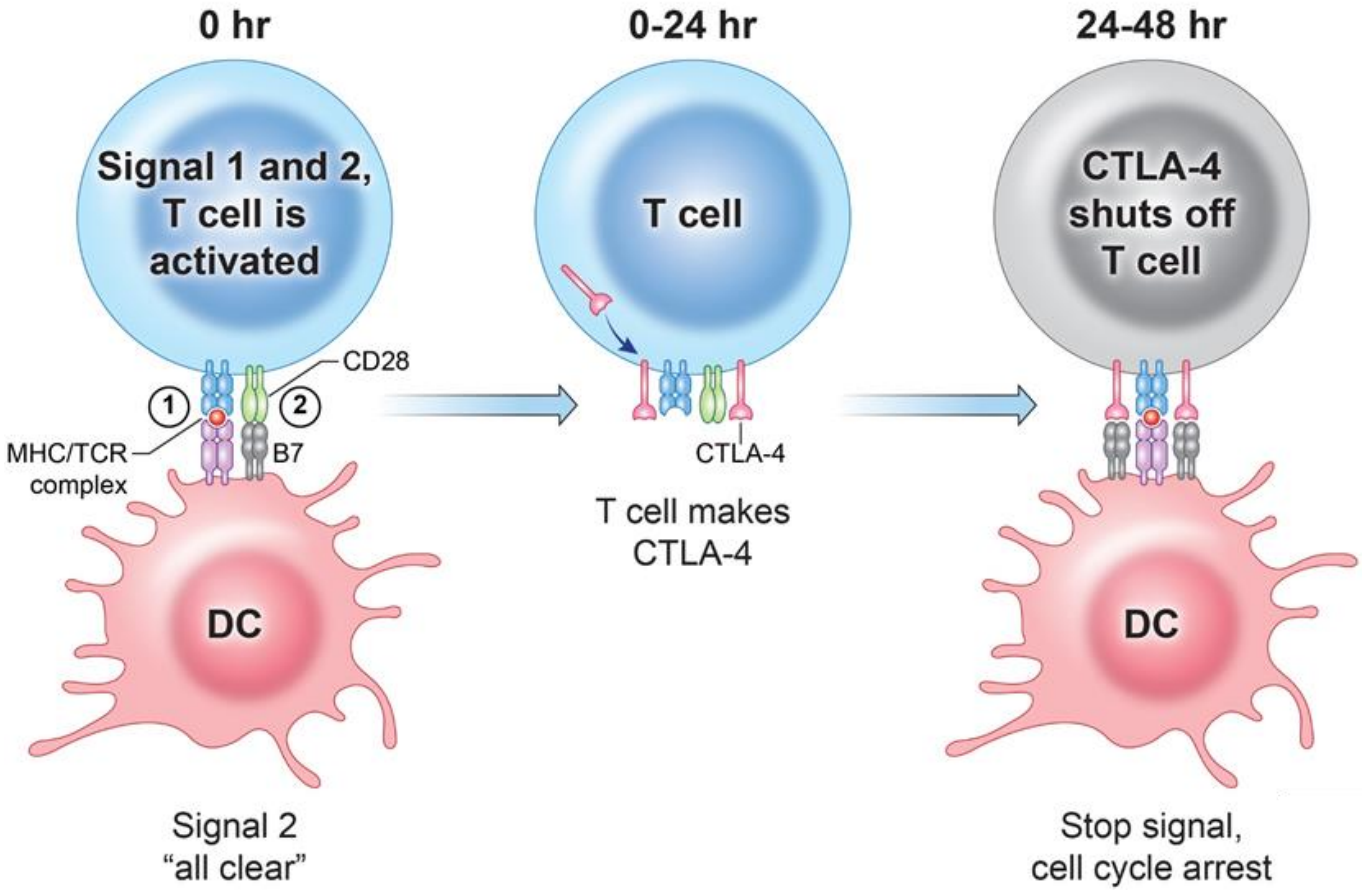


Image courtesy of NCI

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)

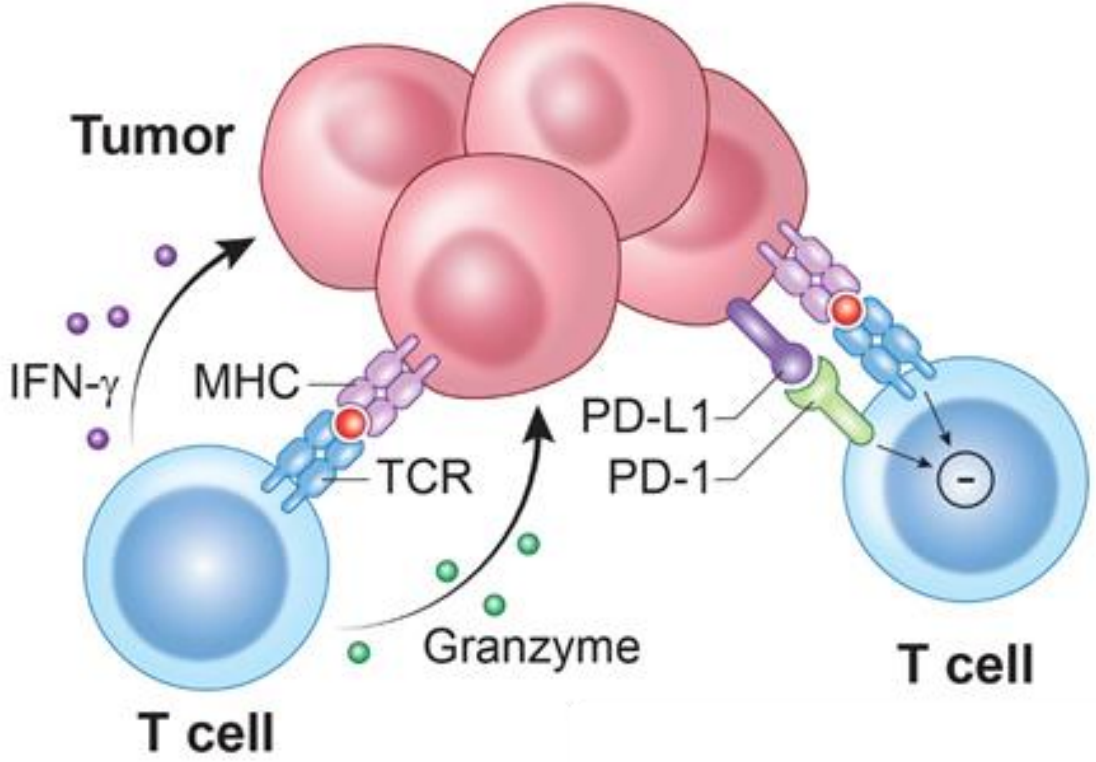
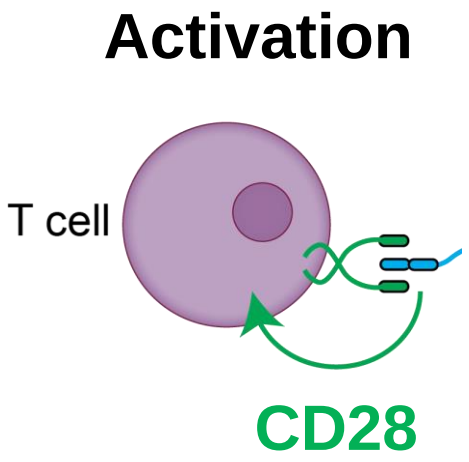


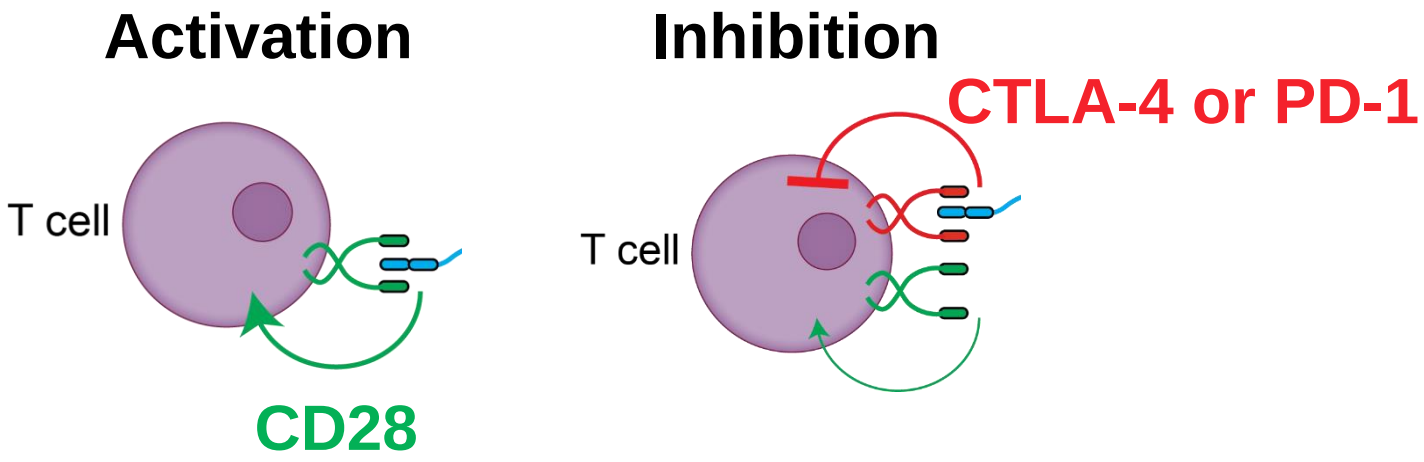
Image courtesy of NCI

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.

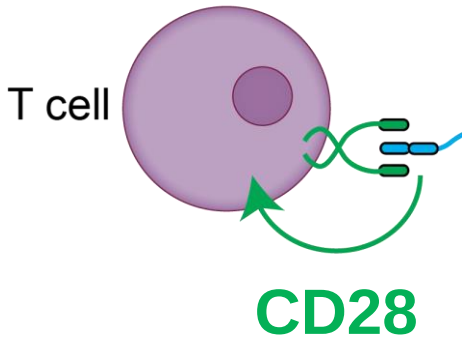
Checkpoint blockade therapy unleashes the “brakes” on T cells



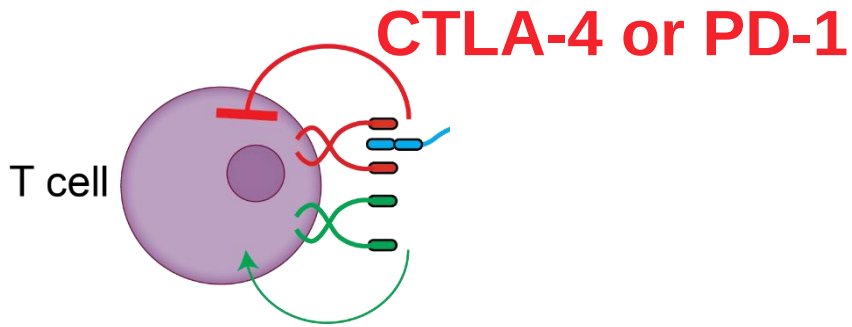
Goal: to reduce immune inhibitory signals and/or enhance stimulatory signals to allow T cells to regain effector functions.

Checkpoint blockade therapy unleashes the “brakes” on T cells

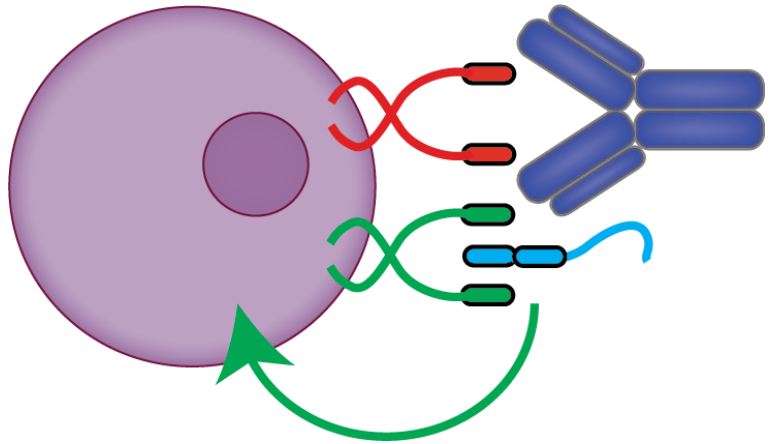
Activation



Inhibition



Re-Activation



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

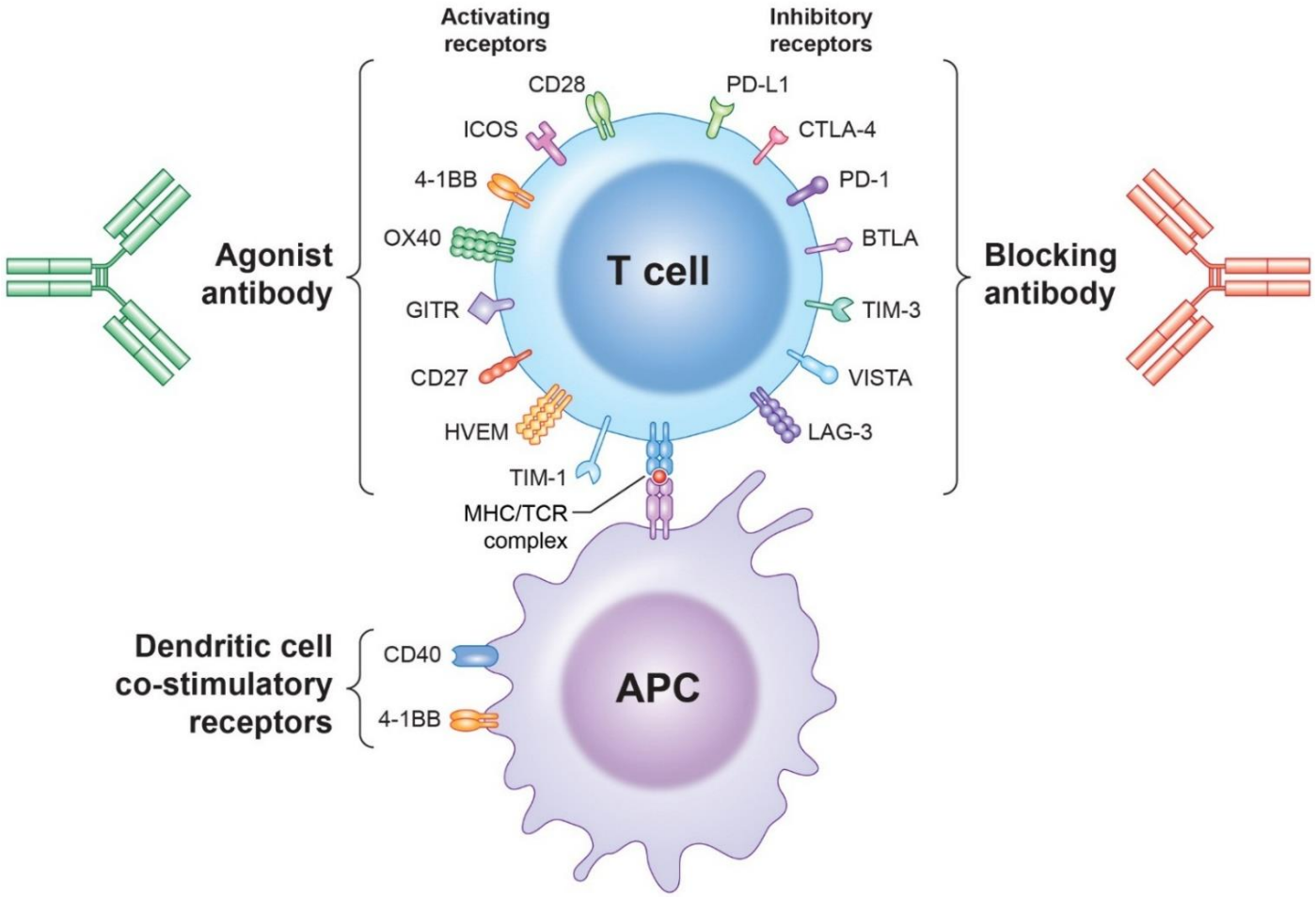


Image courtesy of NCI

Therapeutic Cancer Vaccines

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

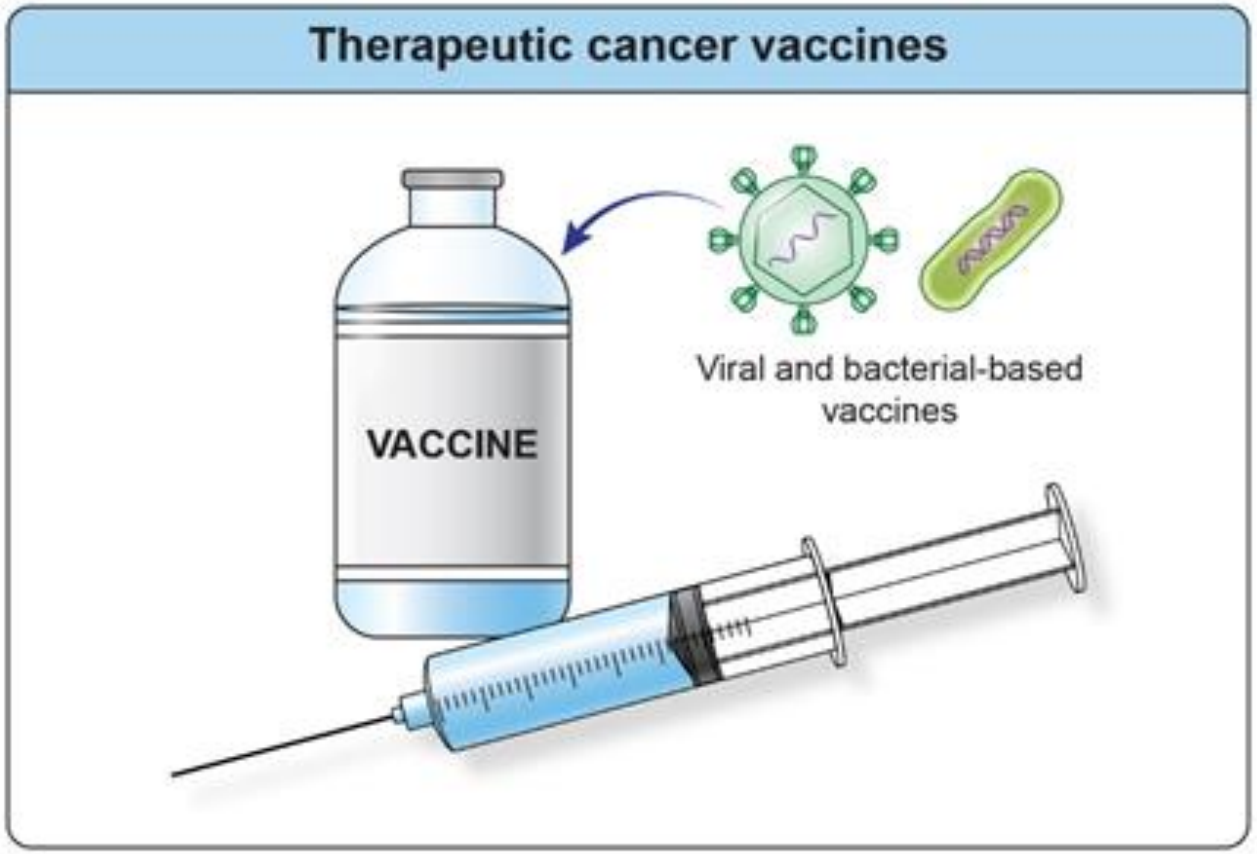


Image courtesy of NCI

Adoptive Cell Therapy

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

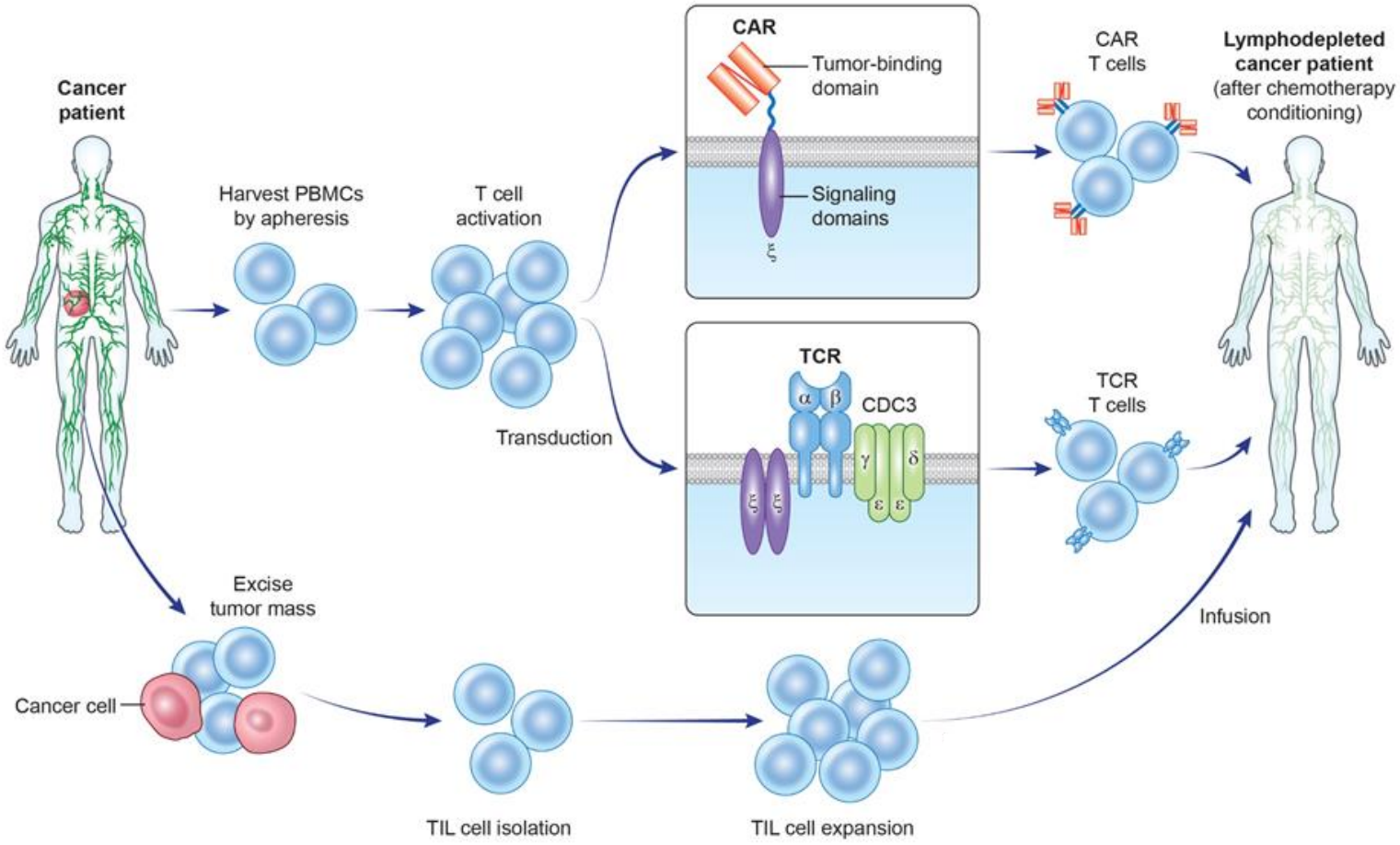


Image courtesy of NCI

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

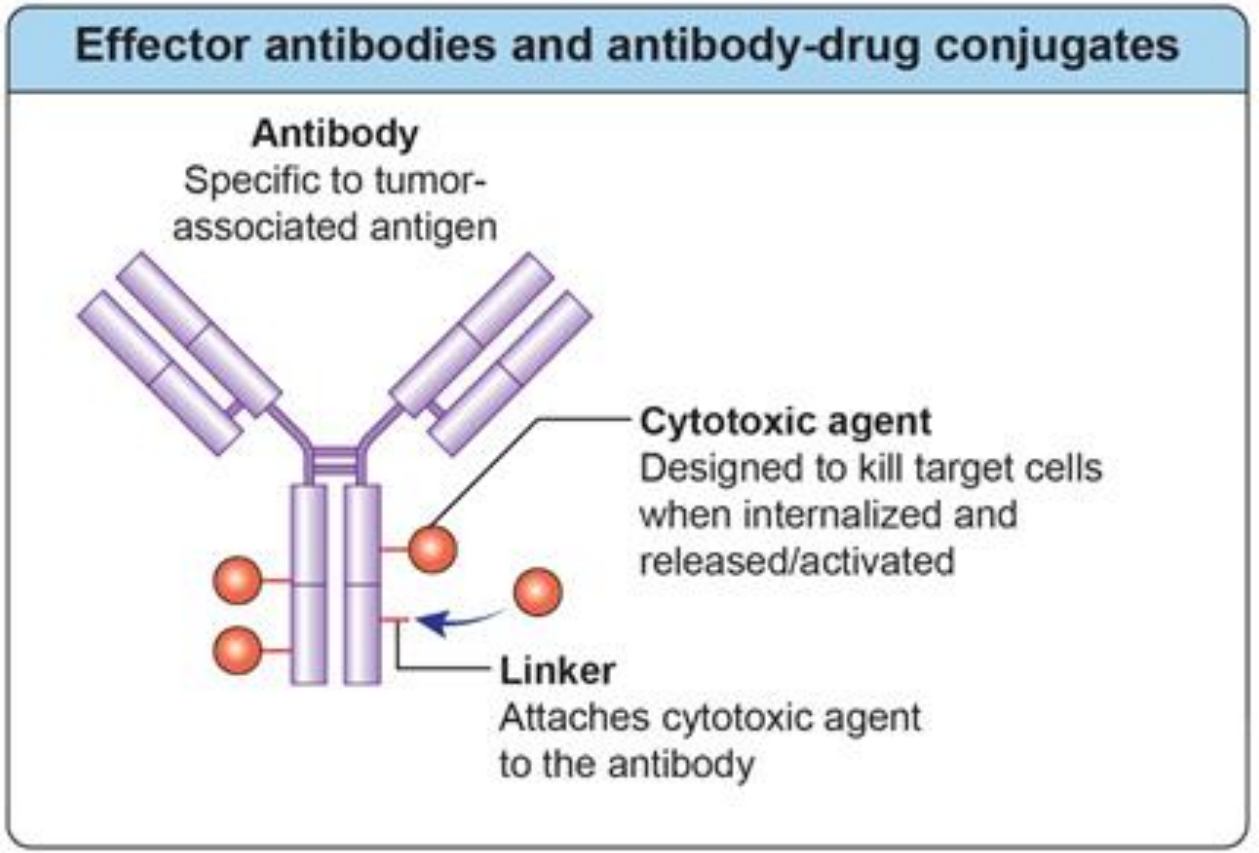
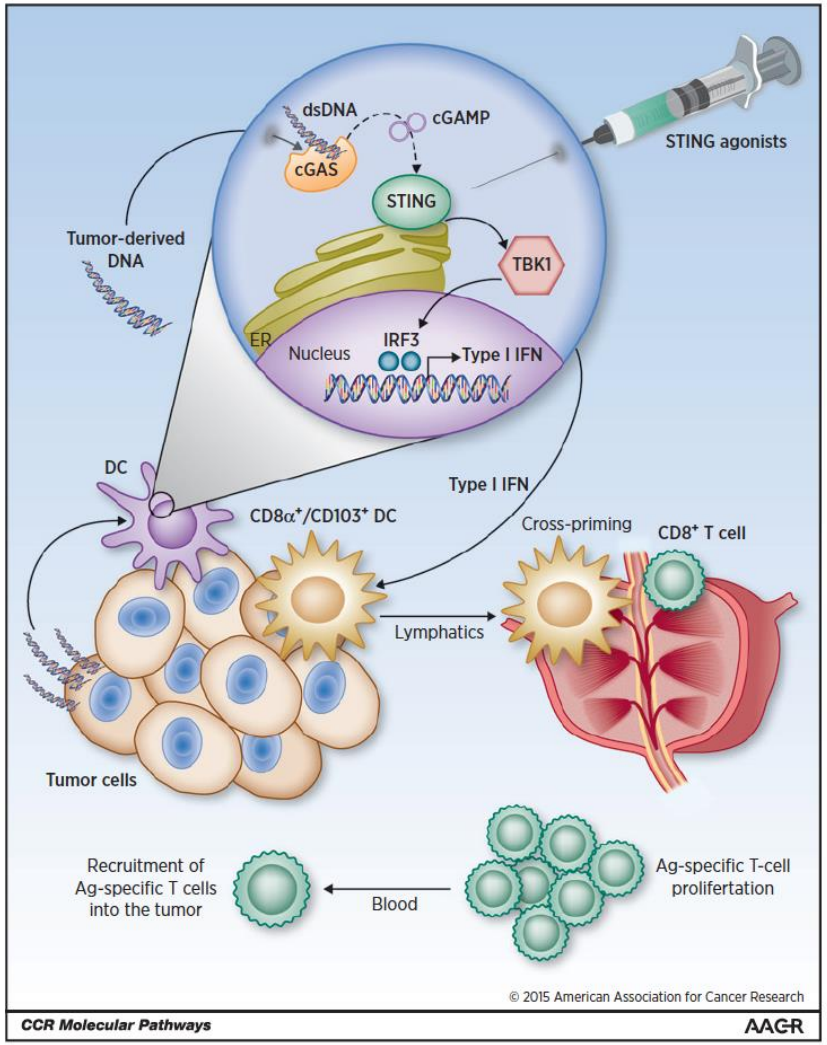


Image courtesy of NCI

Innate immune activation

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



Agents:

Sting agonists

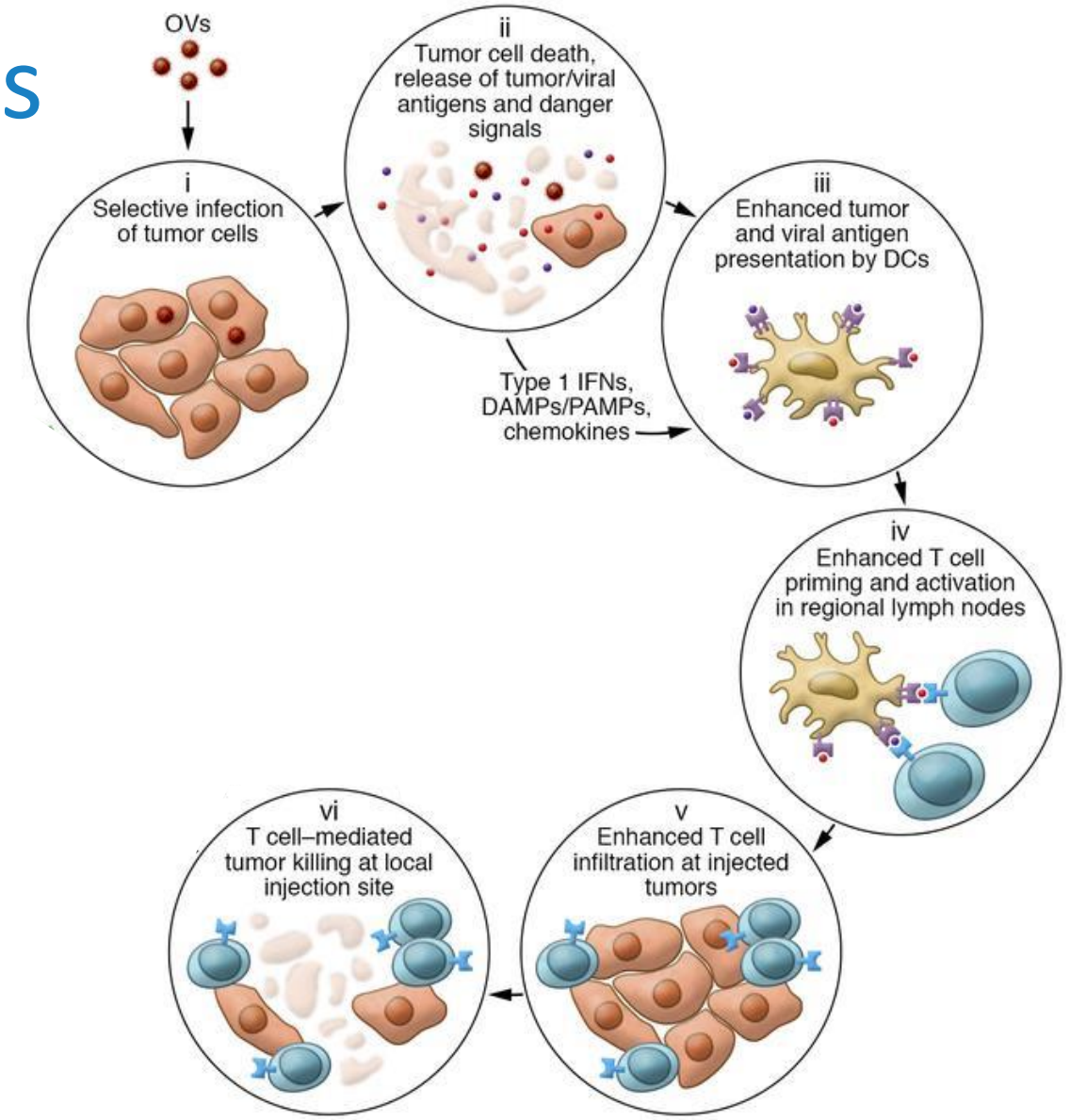
TLR agonists

Immunogenic RNA

Corrales, Clin Can Res 2015

Oncolytic Viruses

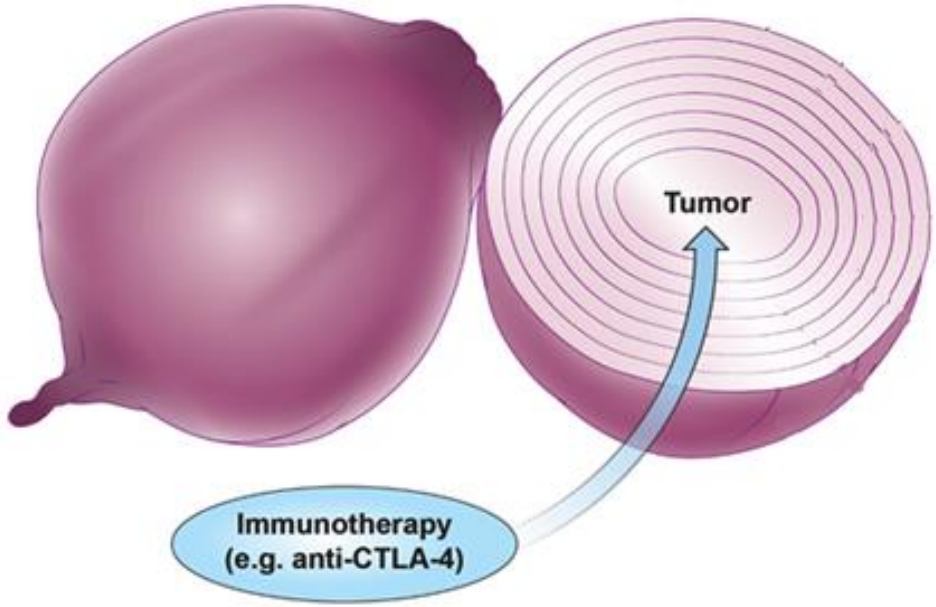
Goal: specifically target and kill tumor cells through viral replication AND release innate immune activators and tumor antigens



Modified from Bommereddy et al. JCI 2018

Multi-layered Immunosuppression

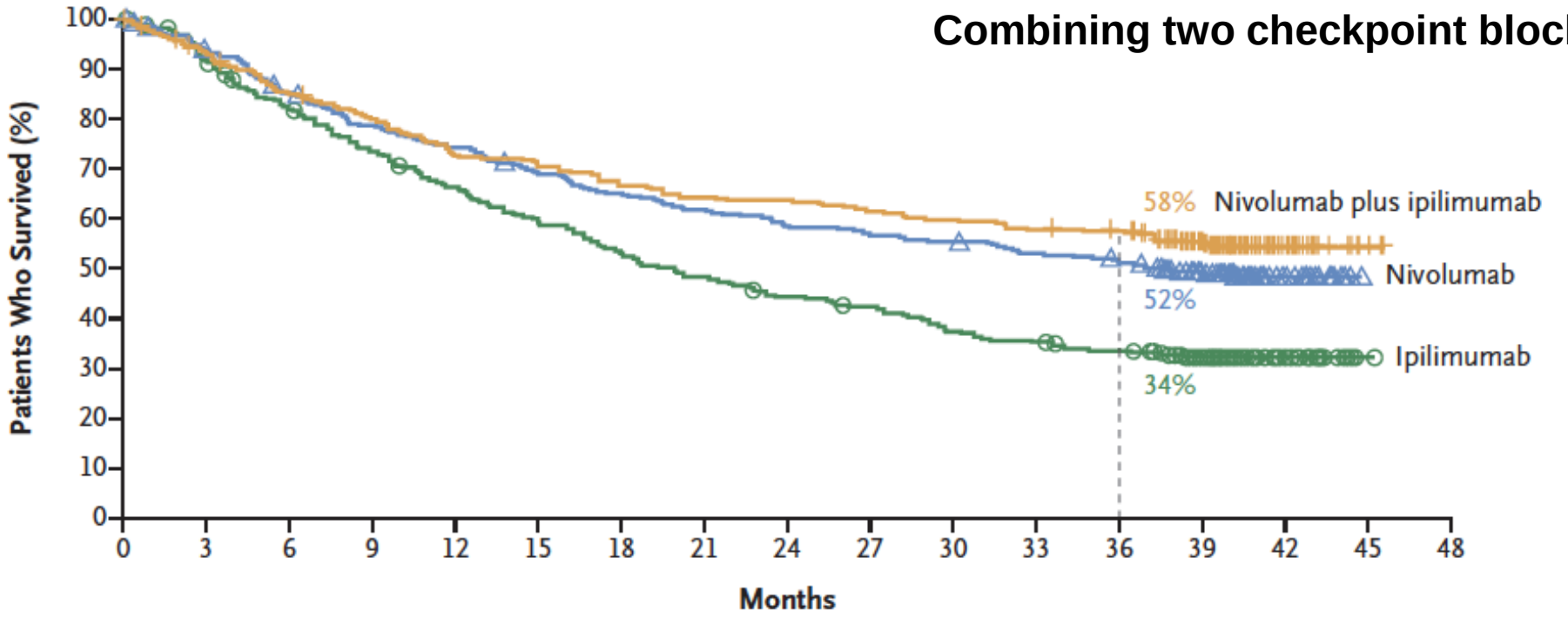
- Tumors insulate themselves with dense layers of immune-suppression
- Overcoming the many layers of interconnected and often functionally redundant immune suppressive mechanisms represents a daunting challenge for tumor-specific T cells
- Immunotherapy can “peel back” the layers of local immune suppression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



Combination Immunotherapies

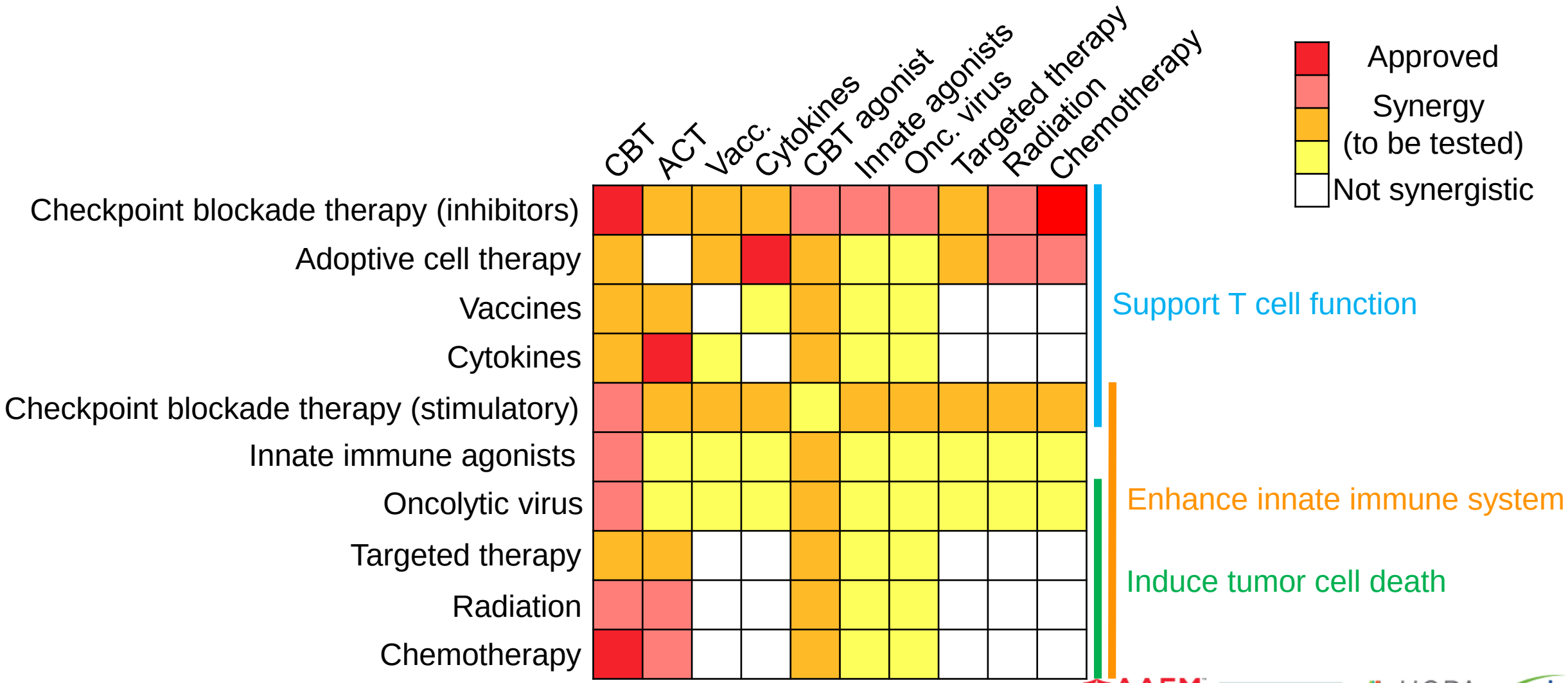
Dual CTLA-4 and PD-1 inhibition

Combining two checkpoint blockade agents

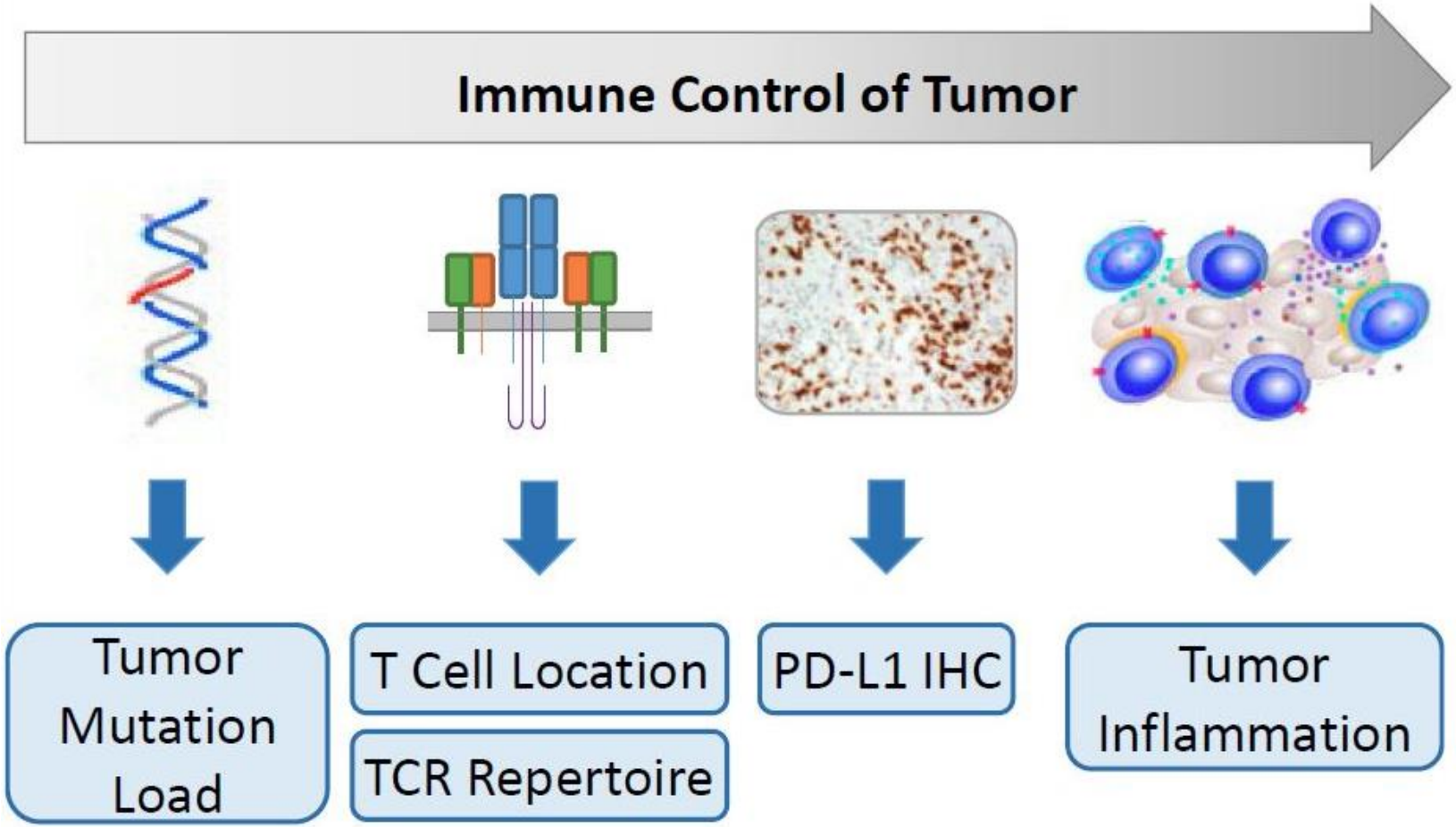


Wolchok et al., NEJM 2017

Combination Immunotherapies

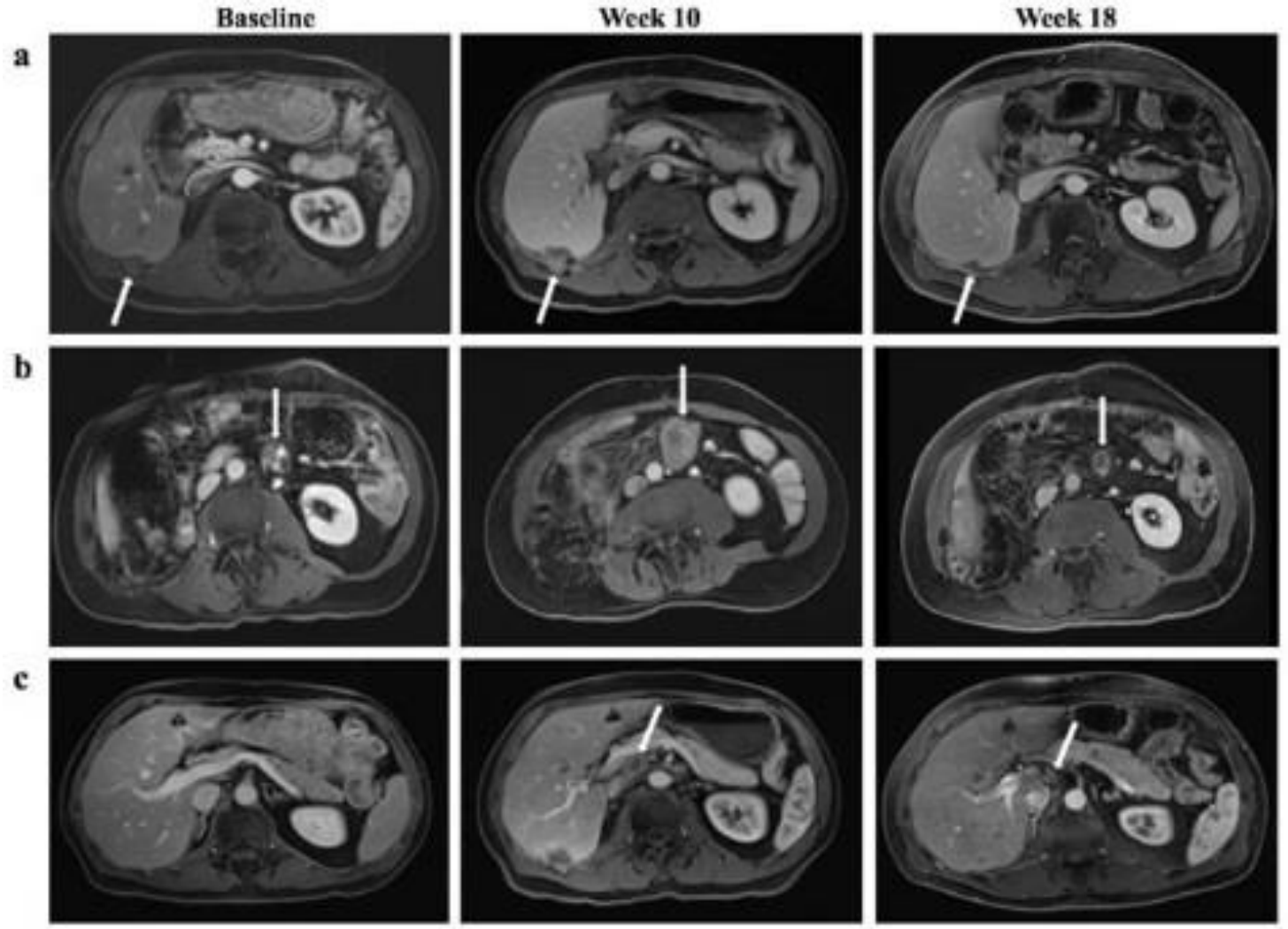


Immunotherapy Biomarkers



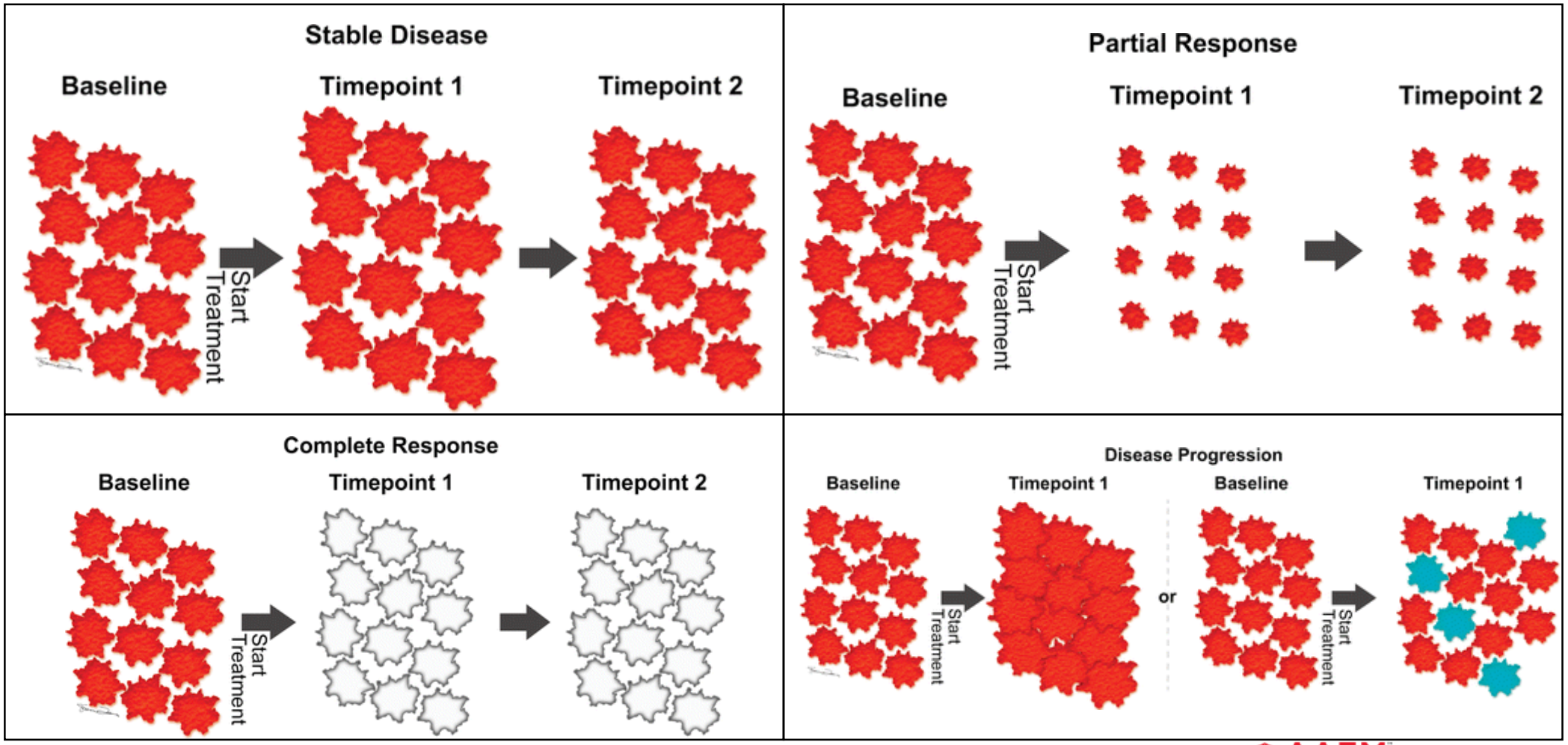
Cesano et al. Biomedicines 2018

Assessment of response



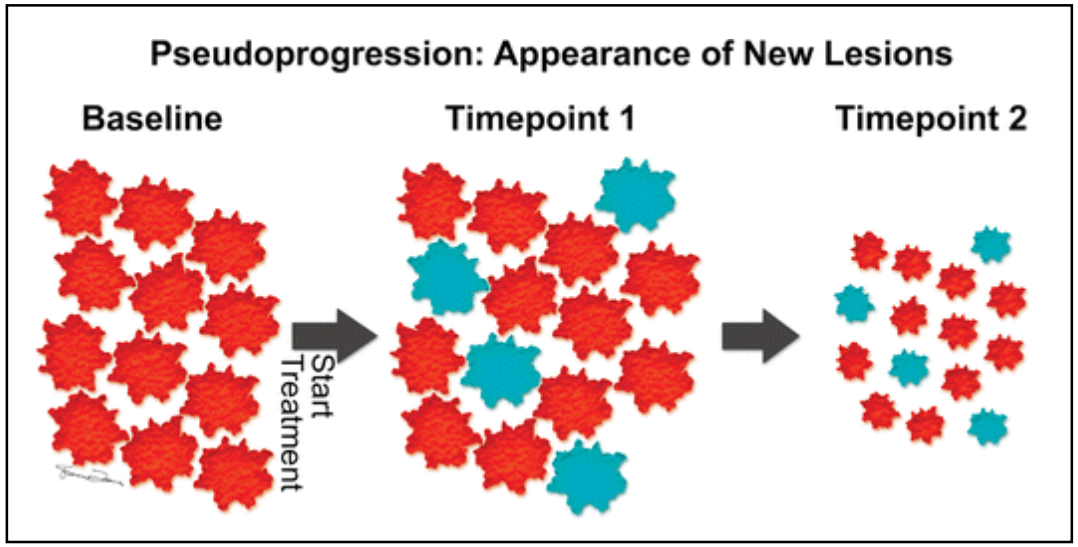
Chae, Oncotarget 2017.

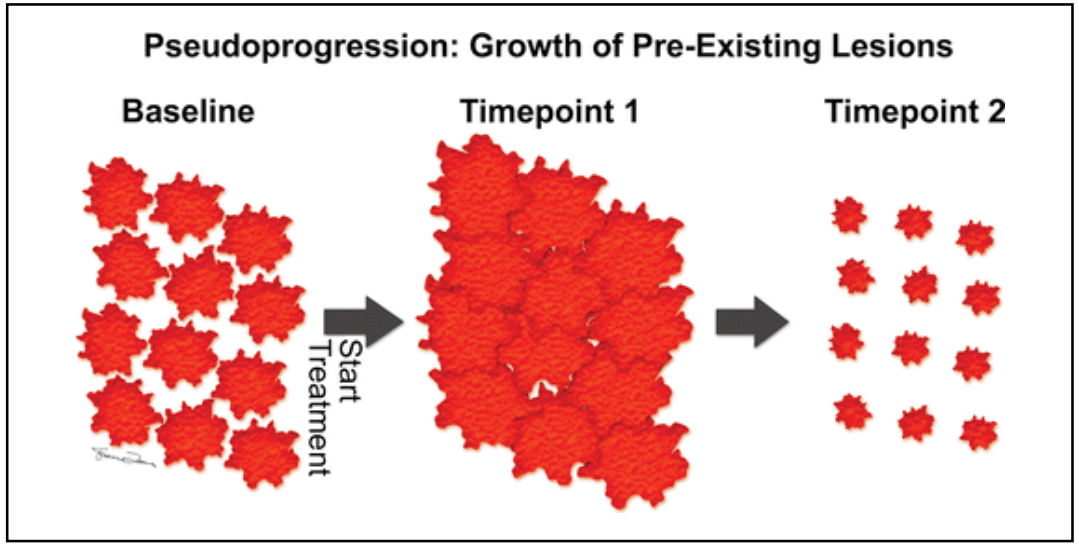
Many possible imaging findings



Wang, RadioGraphics 2017.

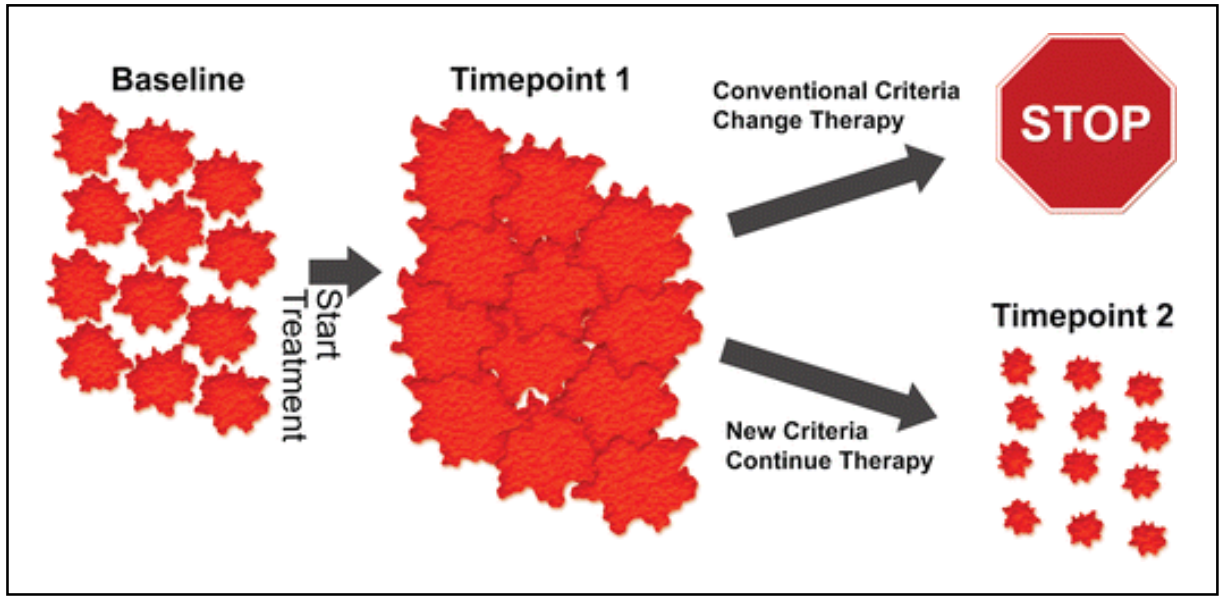
Many possible imaging findings

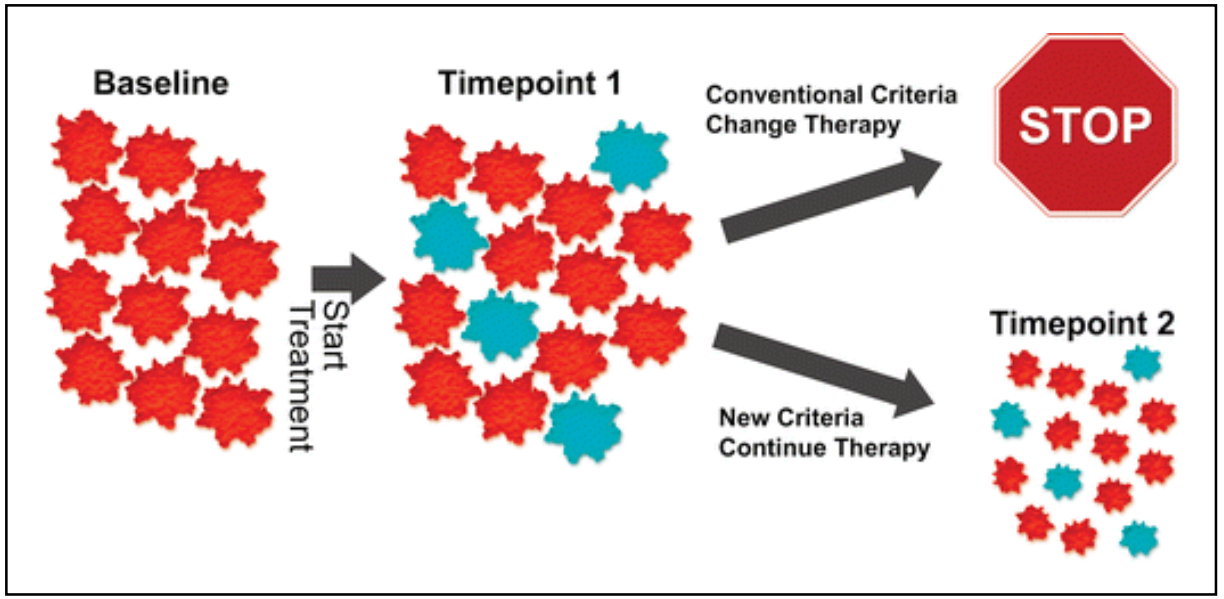




Wang, RadioGraphics 2017.

Assessment of response – unique considerations for immunotherapy





Wang, RadioGraphics 2017.

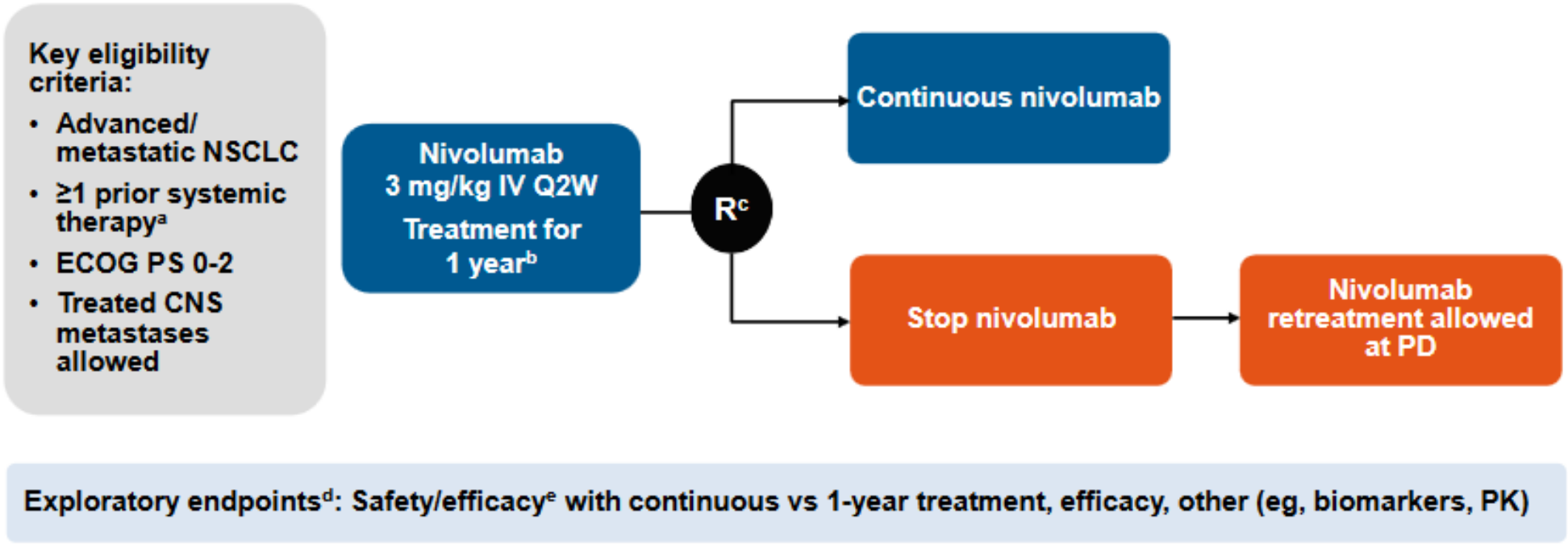
Comparison of disease progression by conventional and immune-related criteria

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.

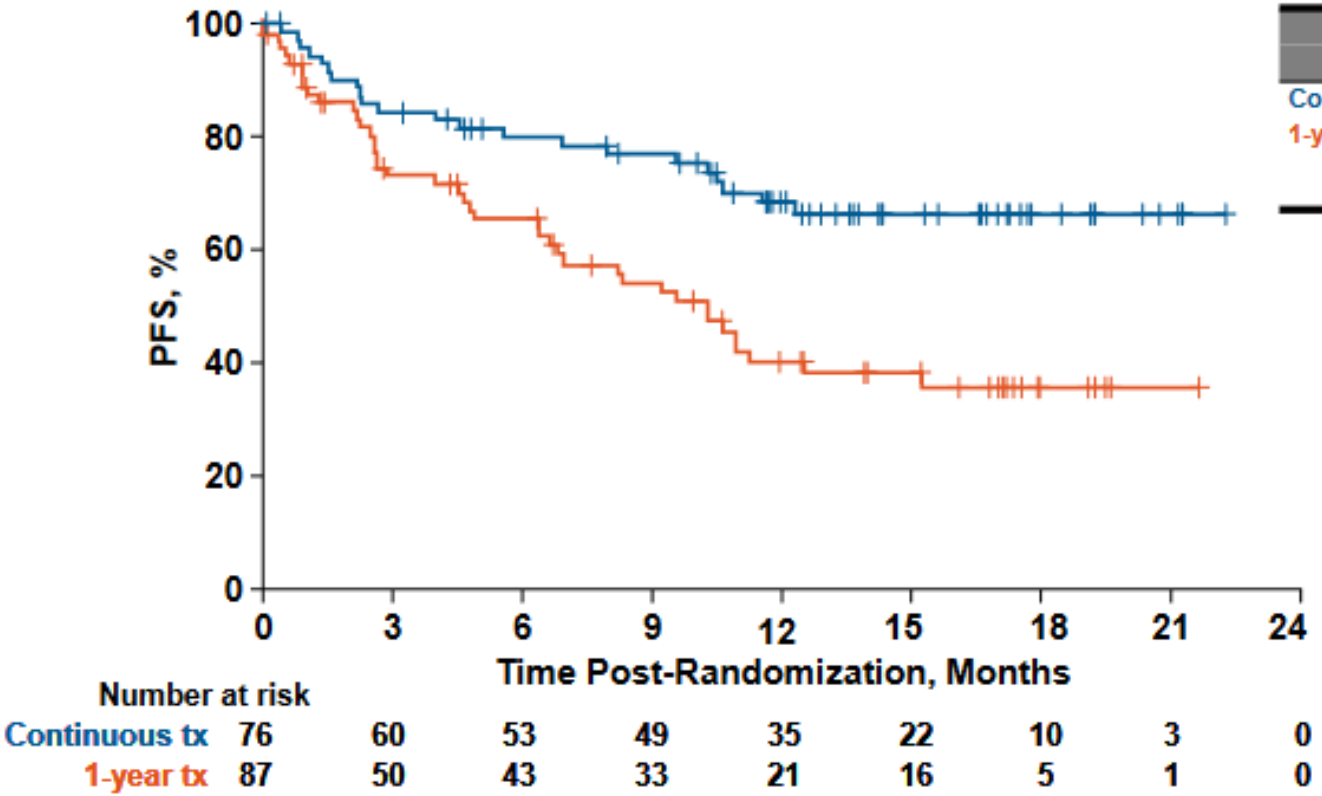
*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm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

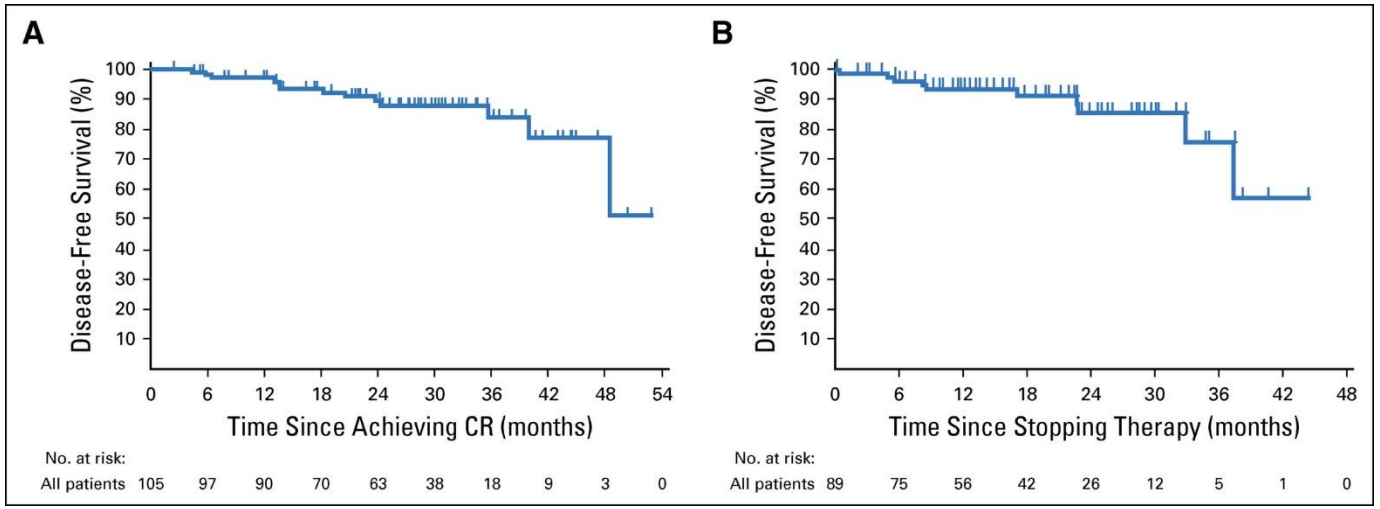
Spigel, Ann Oncol 2017.

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%

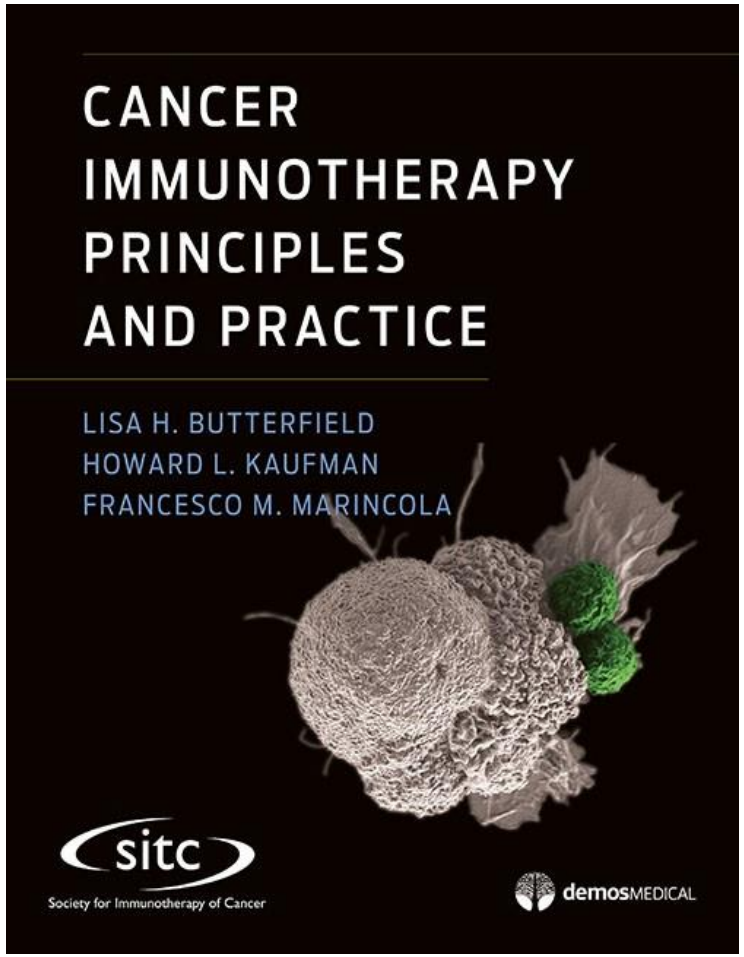


Robert, J Clin Oncol 2018.

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



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