Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

Chrystal M. Paulos, PhD

Co-Leader of Cancer Immunology Program

Hollings Cancer Center @MUSC

Associate Professor of Microbiology and Immunology

Second appointment in Dermatology and Dermatological Surgery

Endowed Peng Chair of Melanoma Research

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

- Ares Immunotherapy
- Obsidian Therapuetics
- Lycera Corporatin
- ThermoFisher

- I will be discussing non-FDA approved indications during my presentation.

Cancer Immunotherapy Premise

- Normally, the immune system eliminates precancerous cells

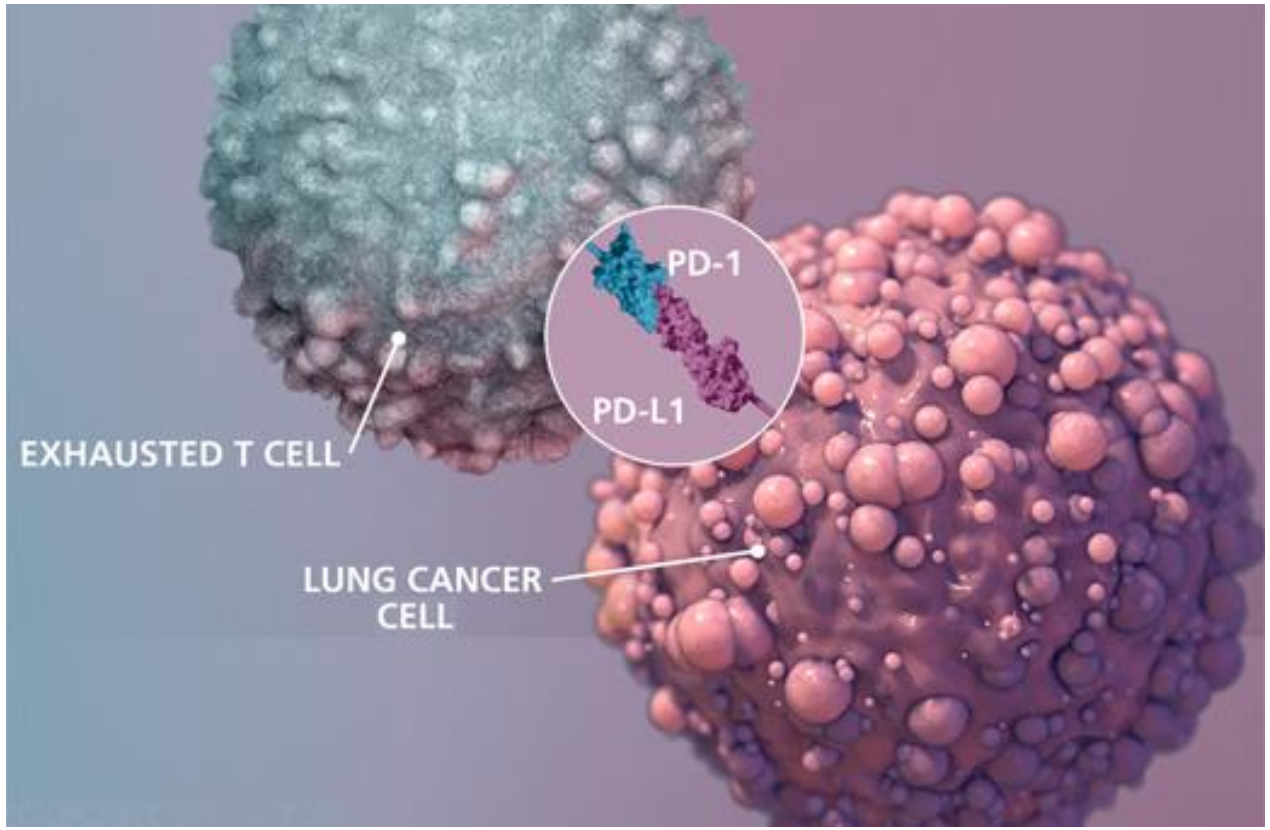
- But some tumors disable the immune system.

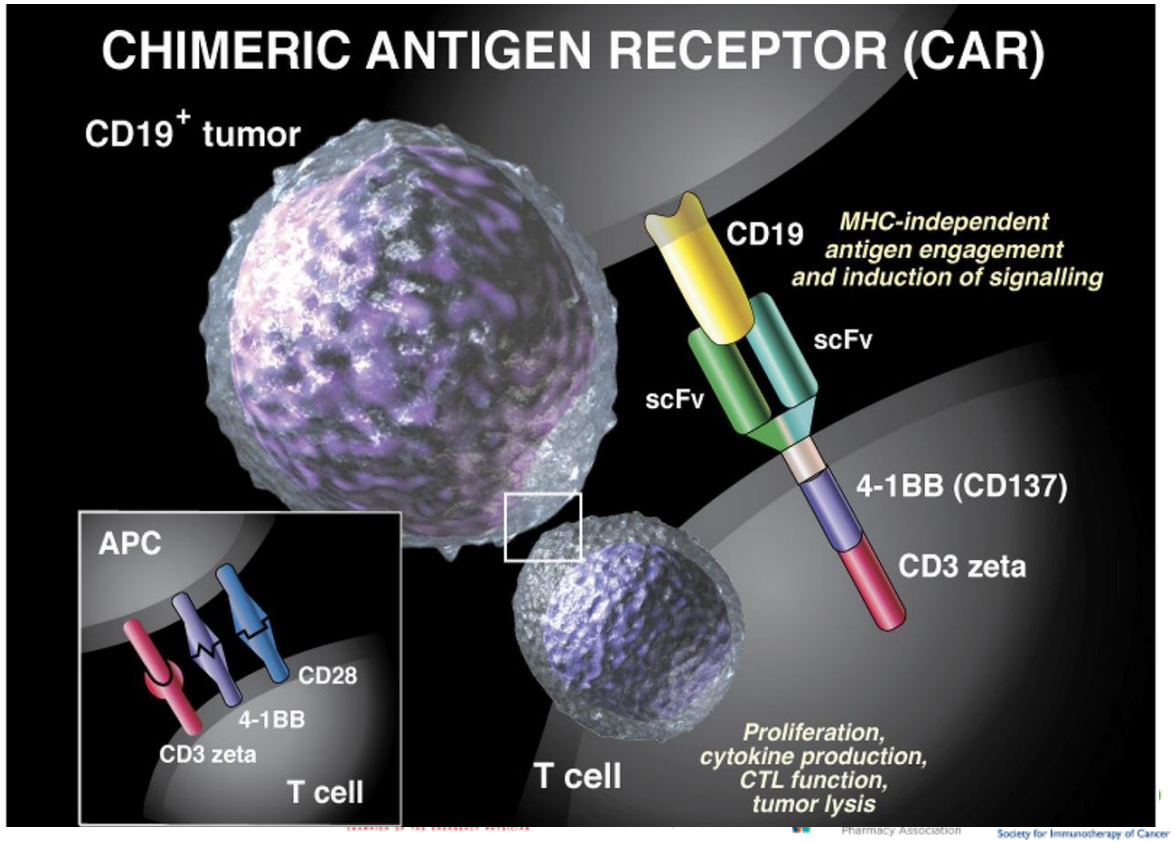
The goal of the immunotherapy field is to develop medicines that restore the capacity of the patients' immune system to recognize and kill cancer.

sitc Society for Immunotherapy of Cancer

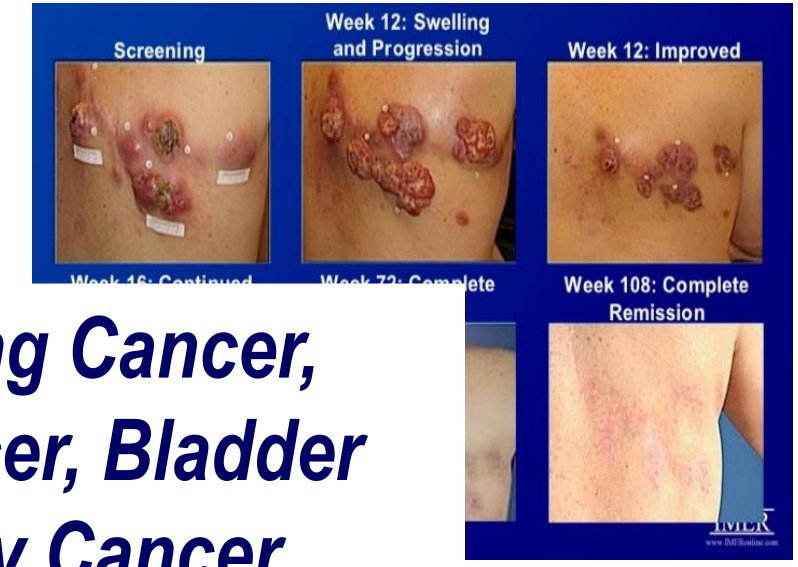
ADVANCES IN Cancer IMMUNOTHERAPY™

Science's Top Breakthrough





Remarkable Success

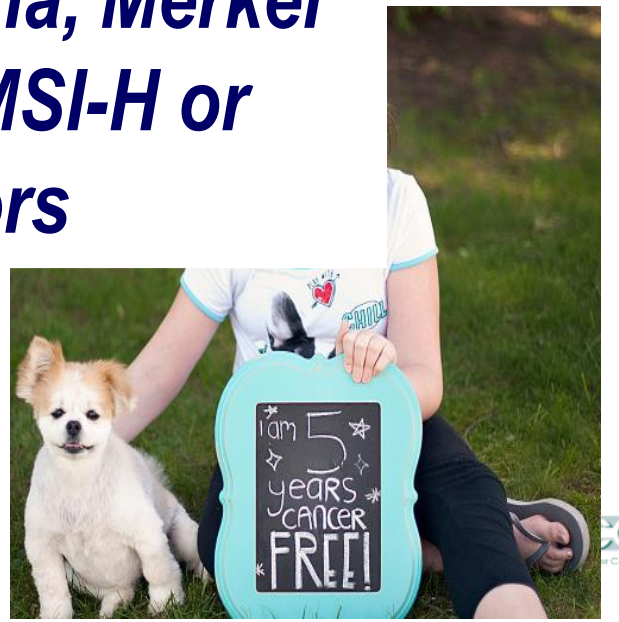


Melanoma, Lung Cancer, Head/Neck Cancer, Bladder Cancer, Kidney Cancer, Hodgkin's Lymphoma, Merkel Cell Carcinoma, MSI-H or dMMR Tumors

⬆ Anti-P

rapy

⬆ T cell therapy (natural)

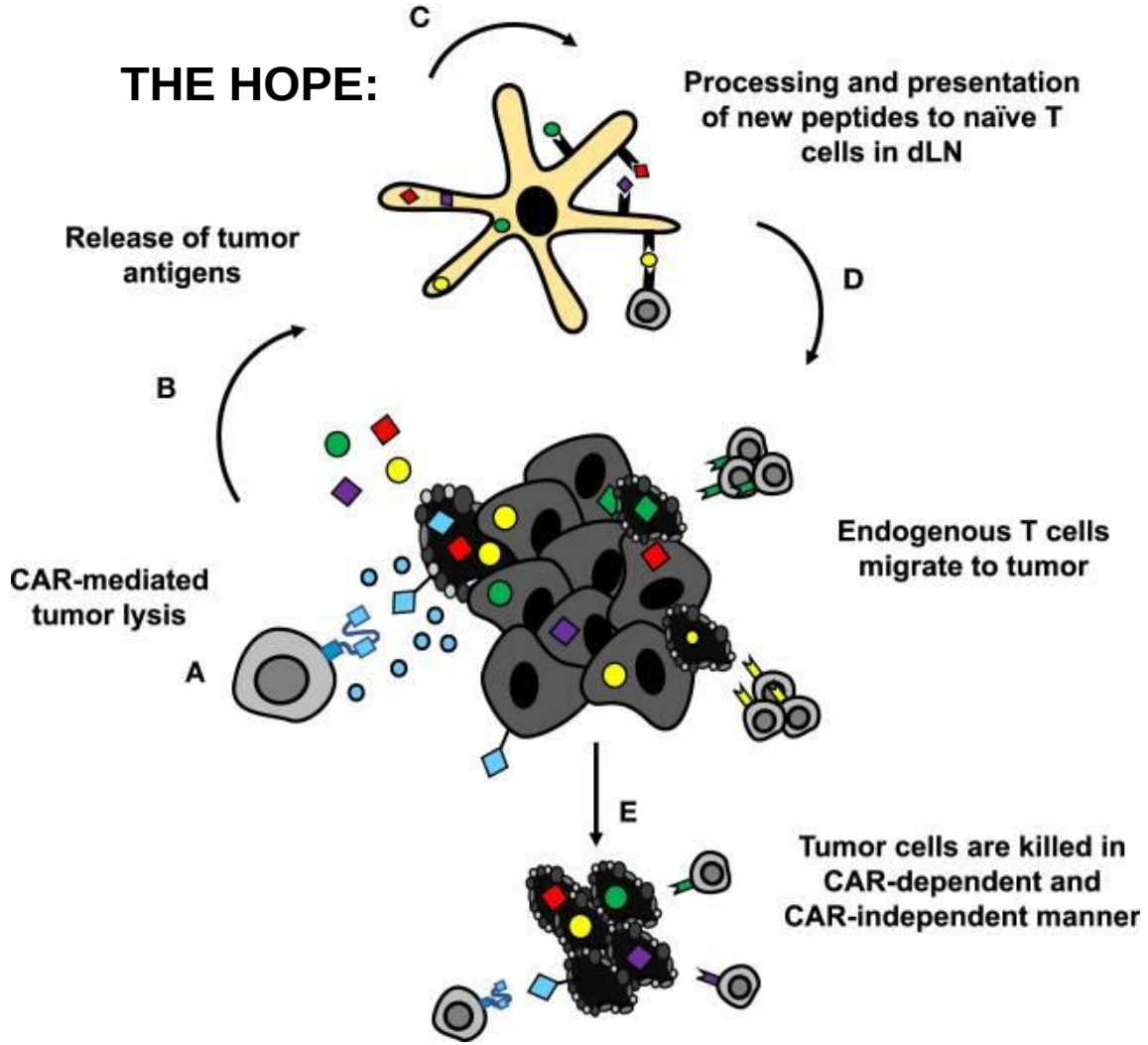


CAR-T cell therapy (T cell with synthetic receptor) FDA APPROVED

Slide made by

Zihai Li, MD PhD
Founding Dir. of PIIO @ OSU

Two mechanisms of tumor immune escape



1: Render immune dysfunction:

-T cells become exhausted via chronic stimulation

-Tumors upregulate molecules that cause T cell dysfunction.

2: Avoiding an immune response:

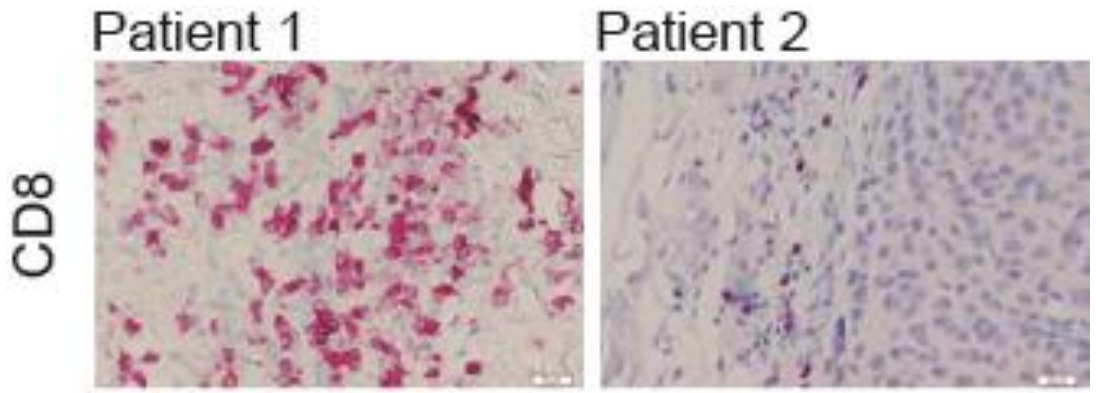
-Tumor remains invisible

-Lack of antigens (T cells don't "see" tumor)

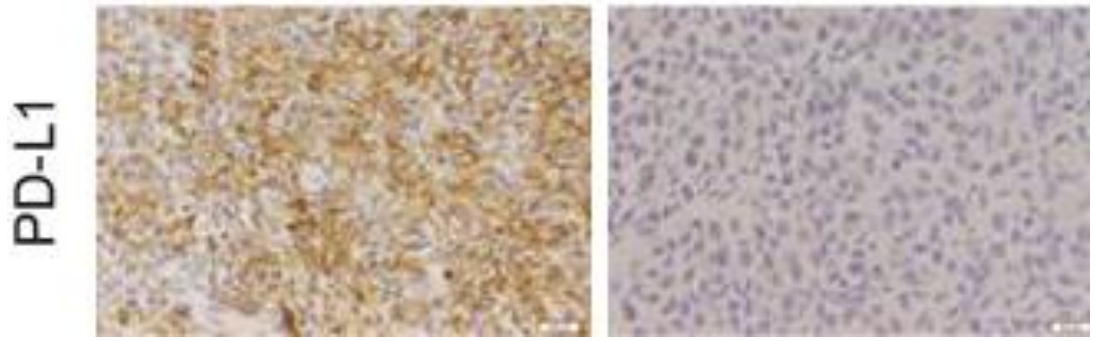
Knochelmann HM, et al. Frontiers in Immunol 2018

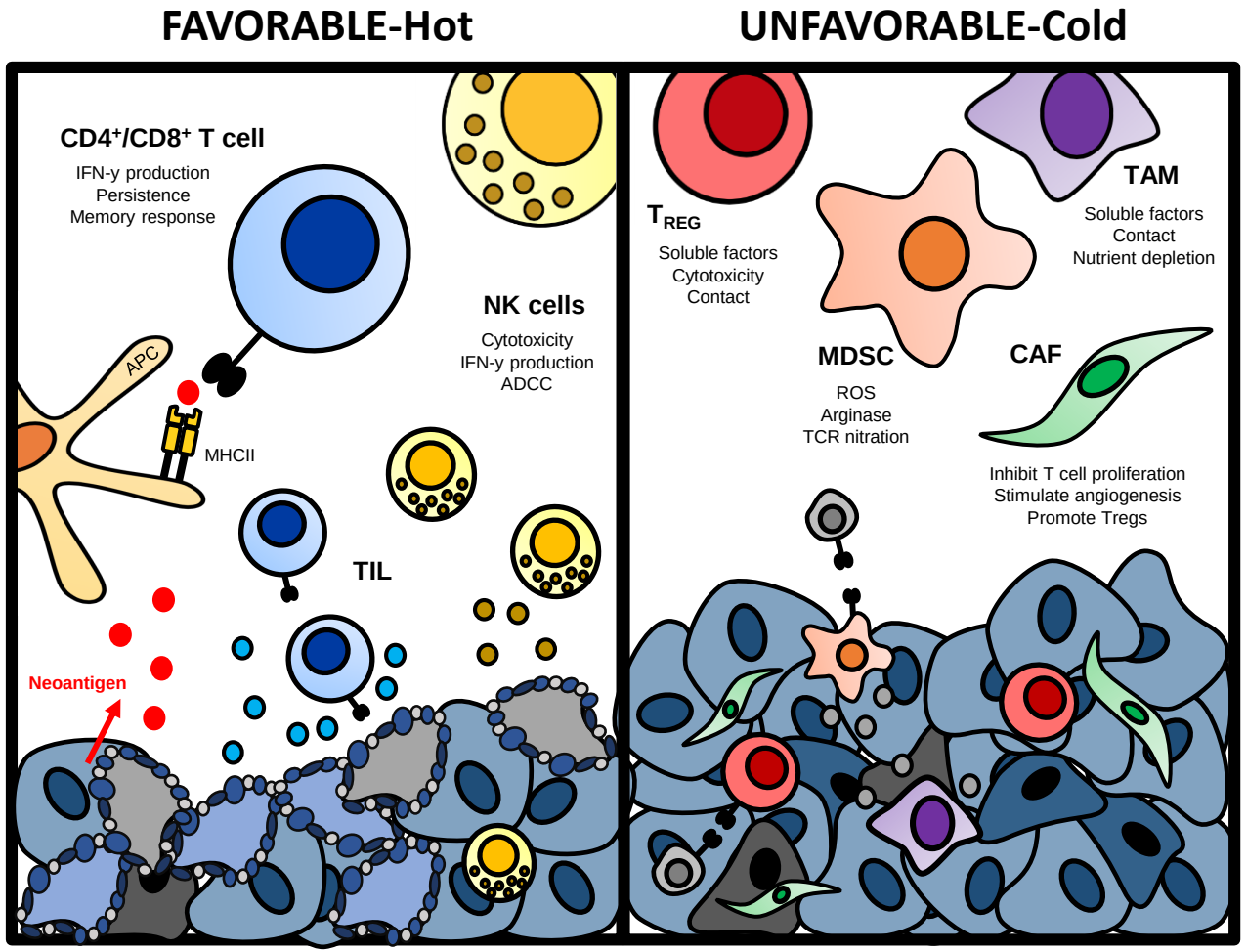
Immune evasion – Hot *vs.* cold tumors

TILs



Suppression



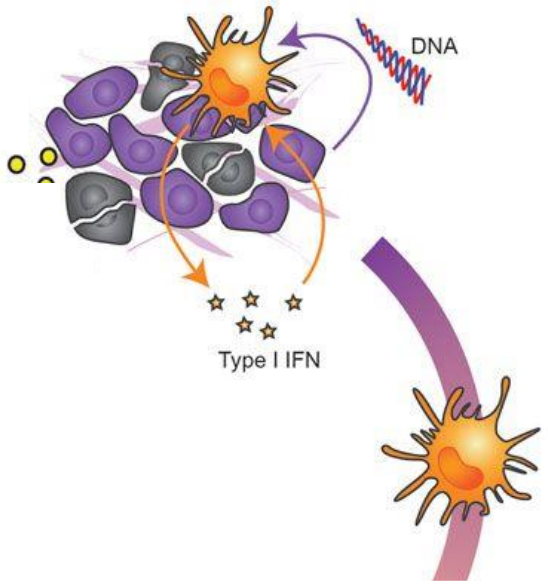


Made by Hannah Knochelmann

Ascierto P.A., Paulos CM, JITC 2019
Horton J, Knockelmann HM, et al. Trends in Cancer 2018

Initiating innate immunity

Innate immune sensing (i.e. Sting activation)

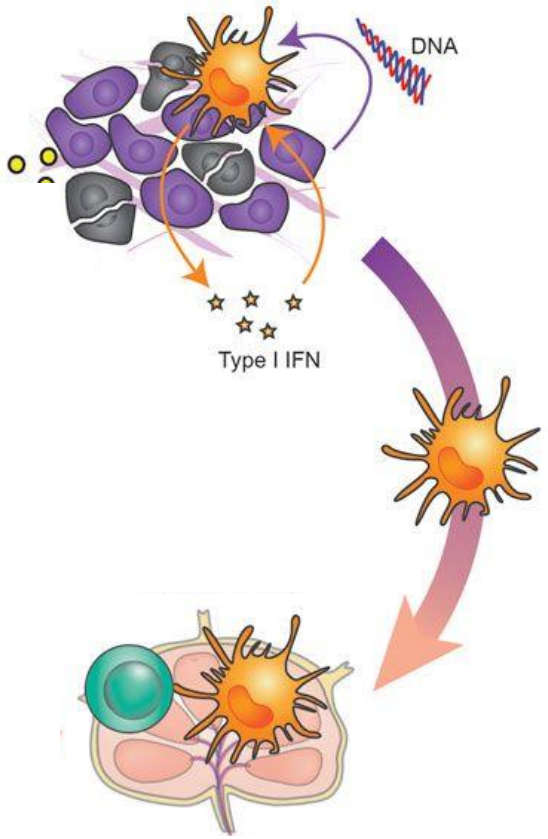


APC maturation
&
Transport to lymph node

Modified from Corrales et al. Cell Res. 2017

Results in T cell activation

Innate immune sensing (i.e. Sting activation)



APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

T cell are activated if there are 3 signals

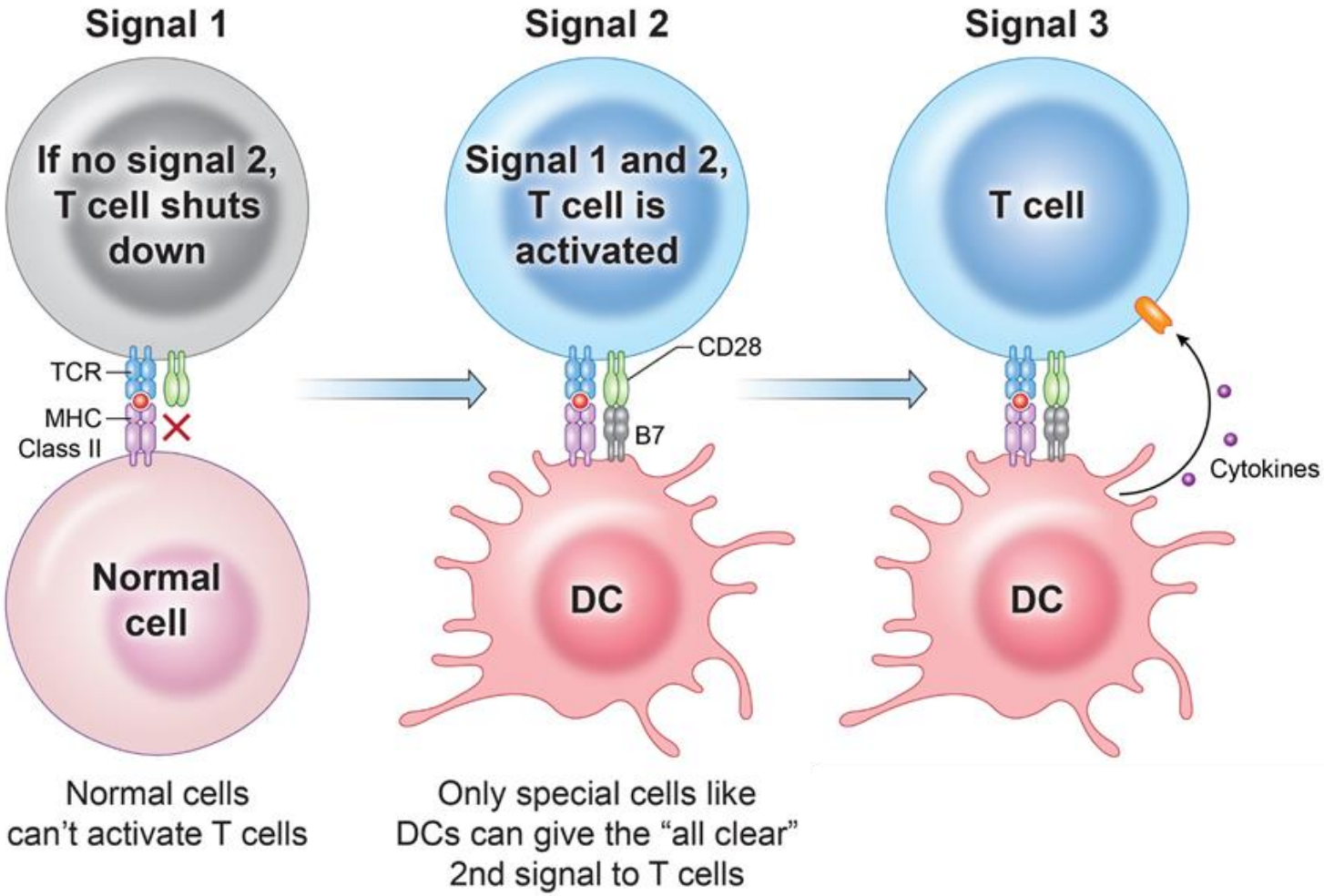
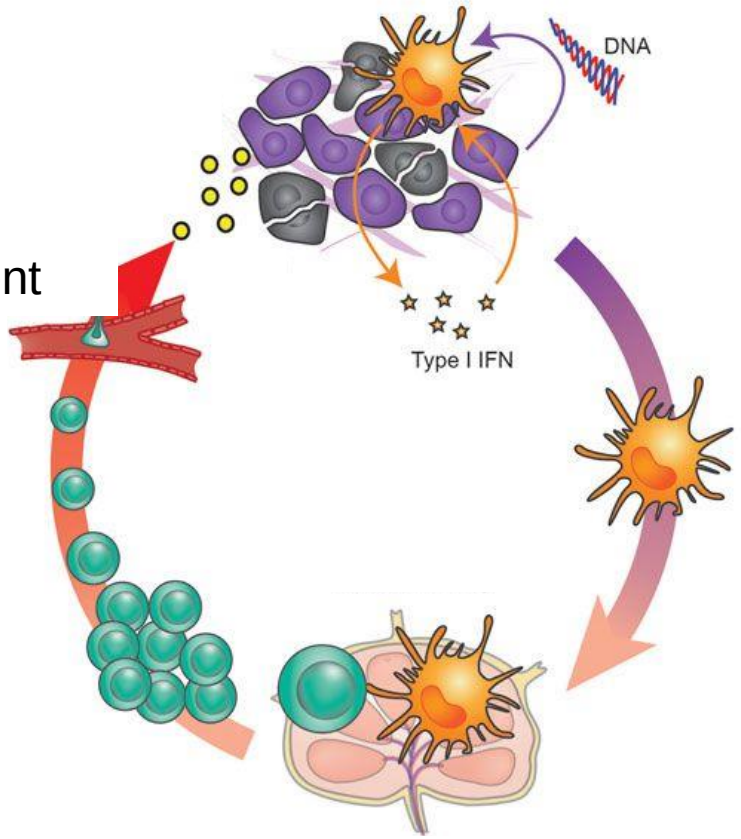


Image courtesy of NCI

Mediating T cell proliferation & migration to tumor

Innate immune sensing (i.e. Sting activation)

T cell recruitment

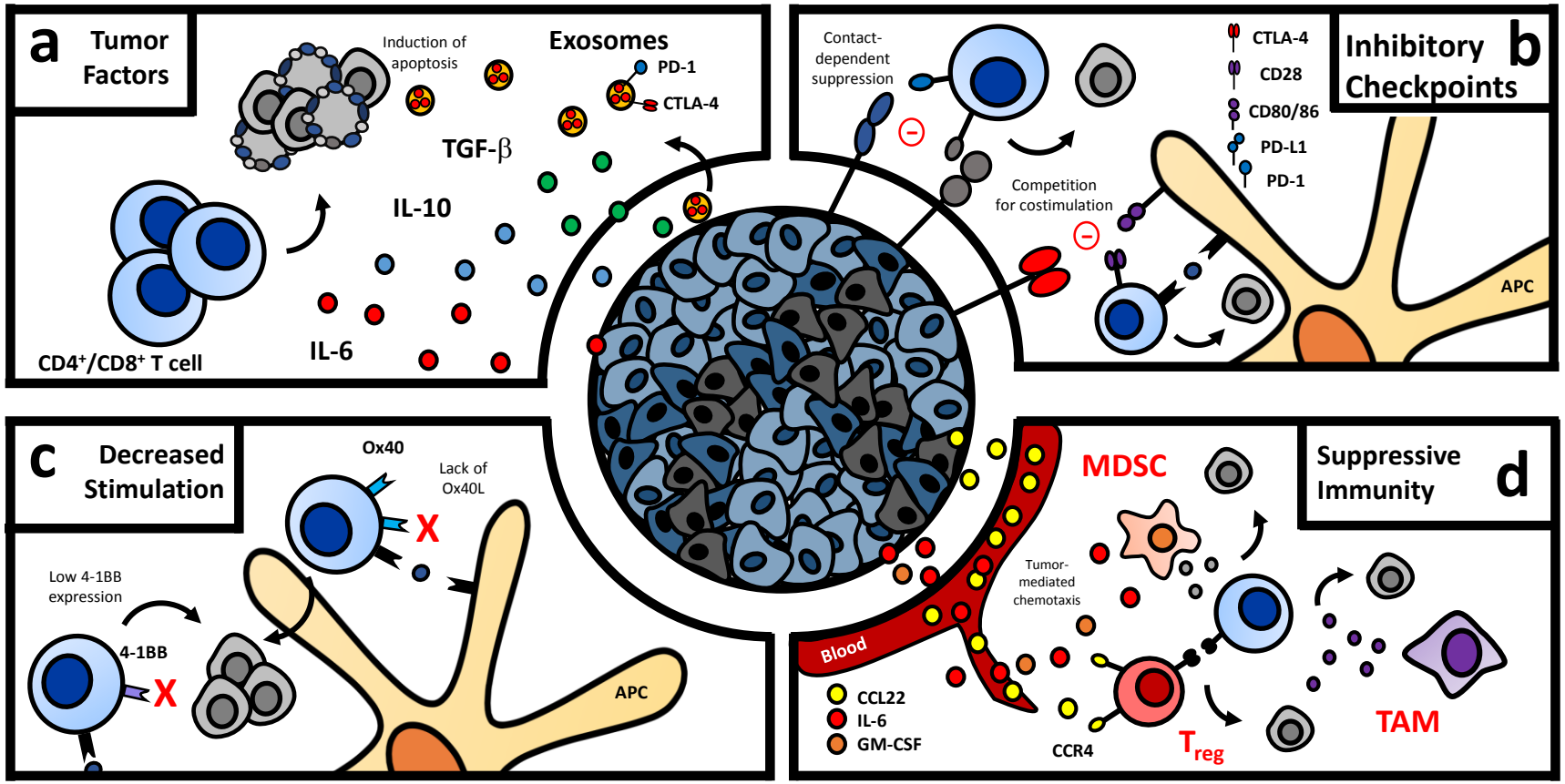


APC maturation
&
Transport to lymph node

Cytotoxic T cell activation

Modified from Corrales et al. Cell Res. 2017

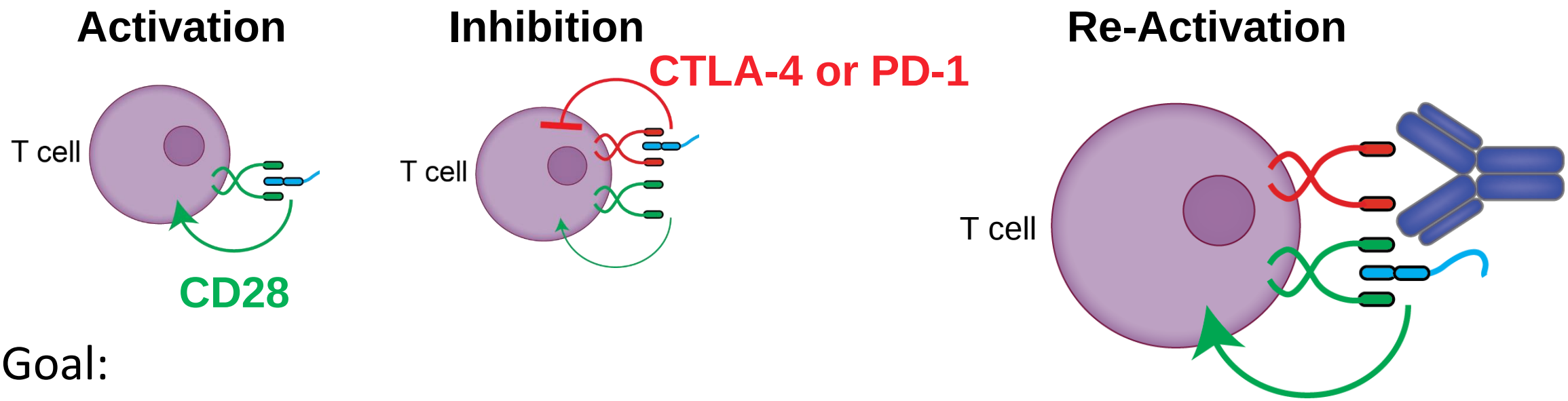
Many problems remain….



But there are some solutions…

- Checkpoint blockade
- Cancer vaccines
- Adoptive T cell transfer therapy
- Oncolytic viruses

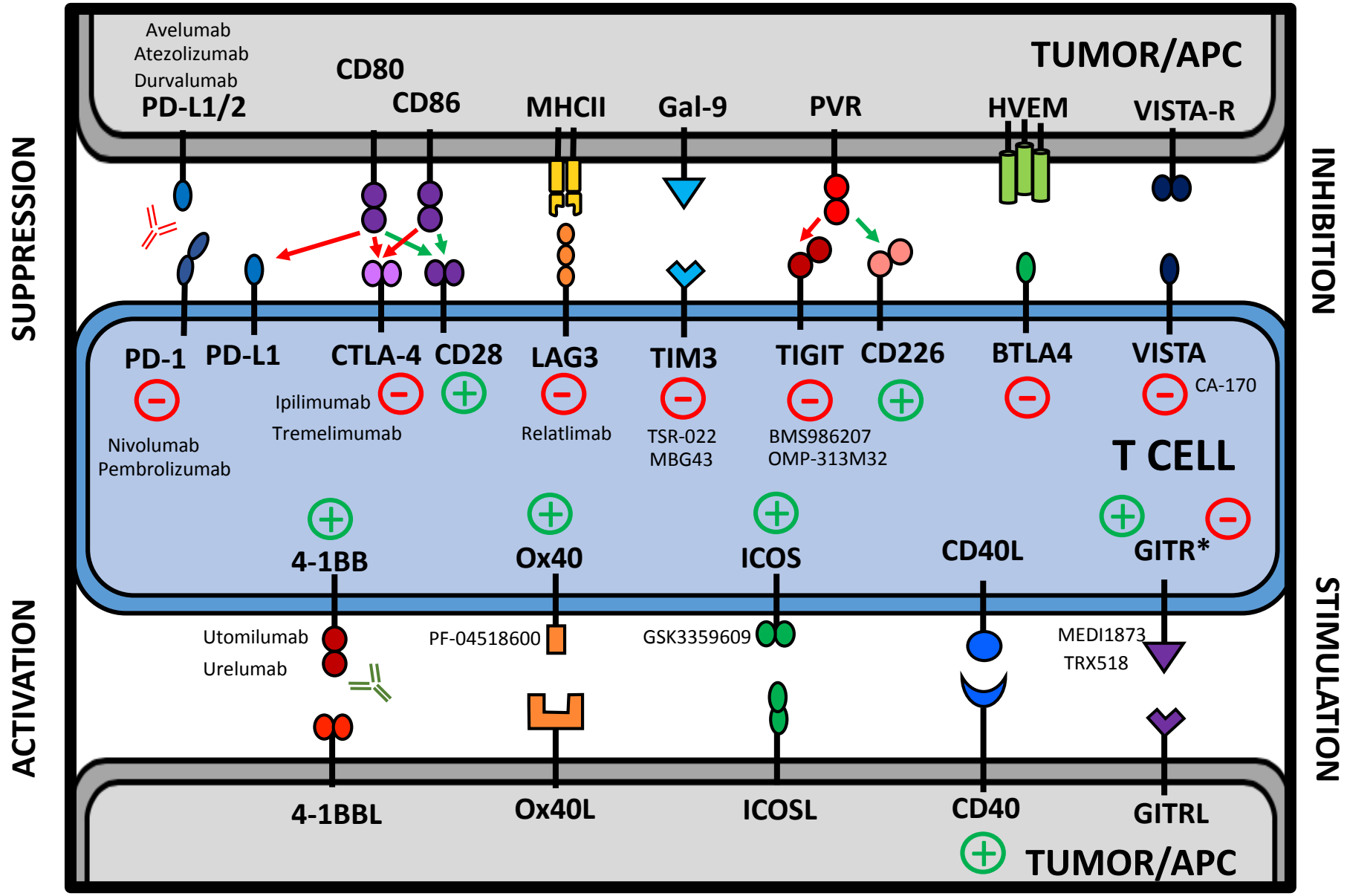
Checkpoint blockade unleashes the “brakes”



Goal:

Regain effector T cell activity by reducing inhibitory signals and/or enhance stimulatory signals

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™



Cancer Vaccines

Goal:

To increase the immunogenicity of antigens to generate T cells with activity against tumor.

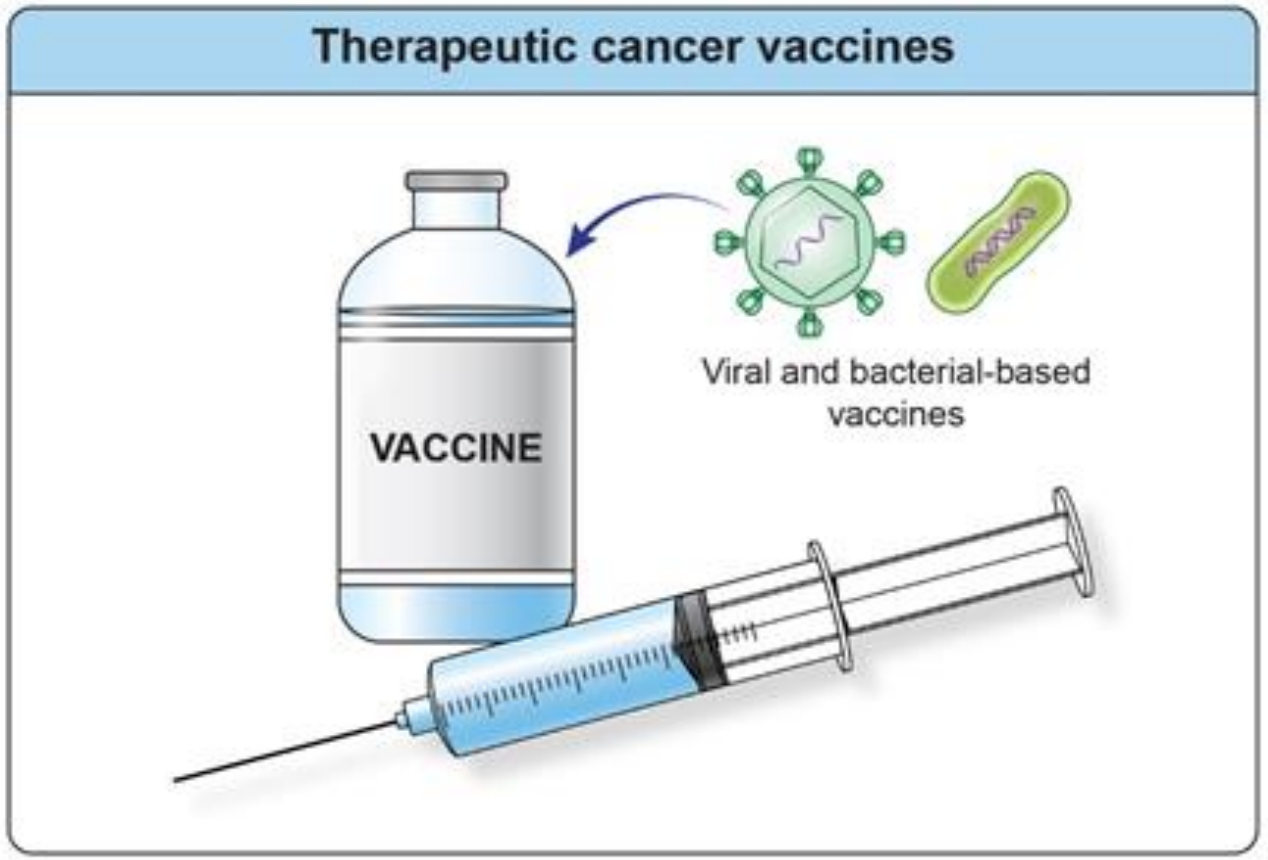
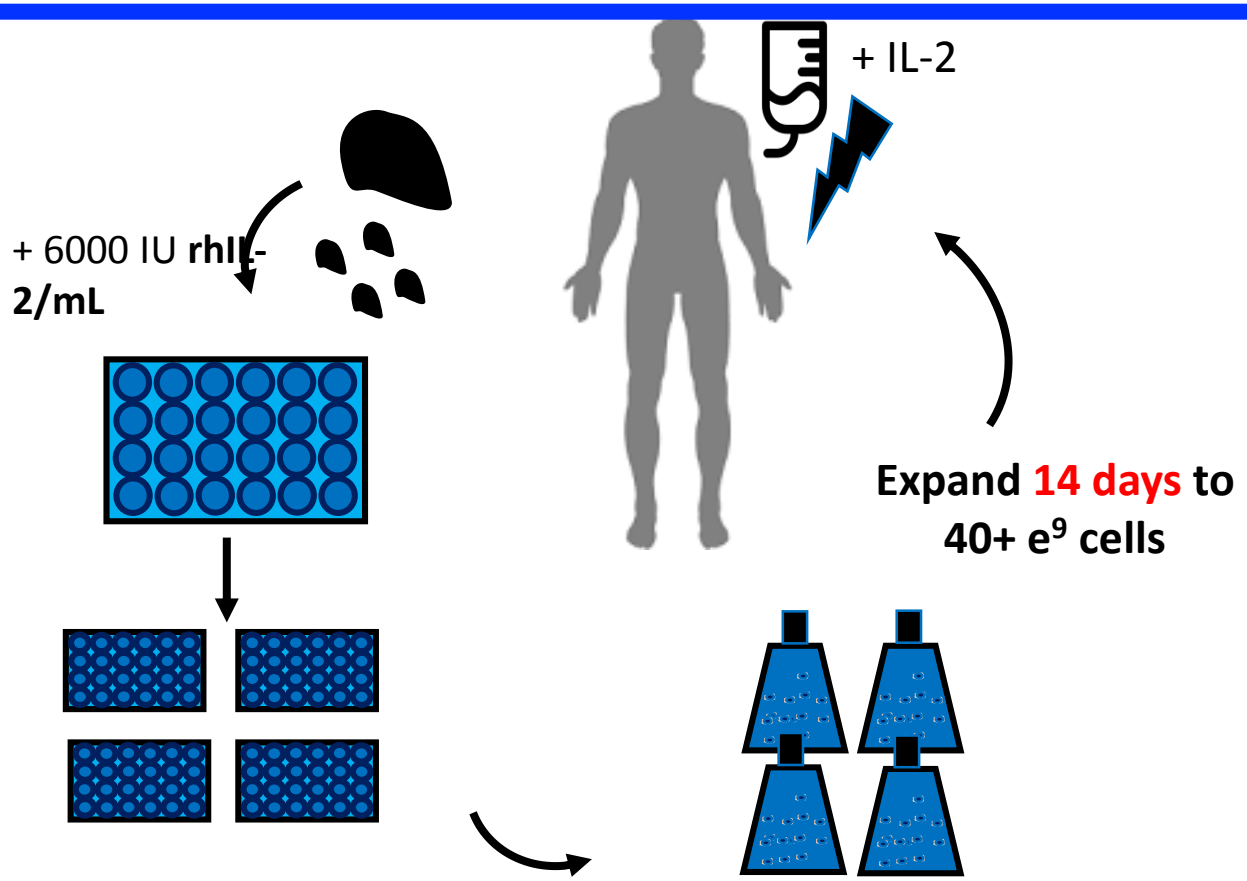
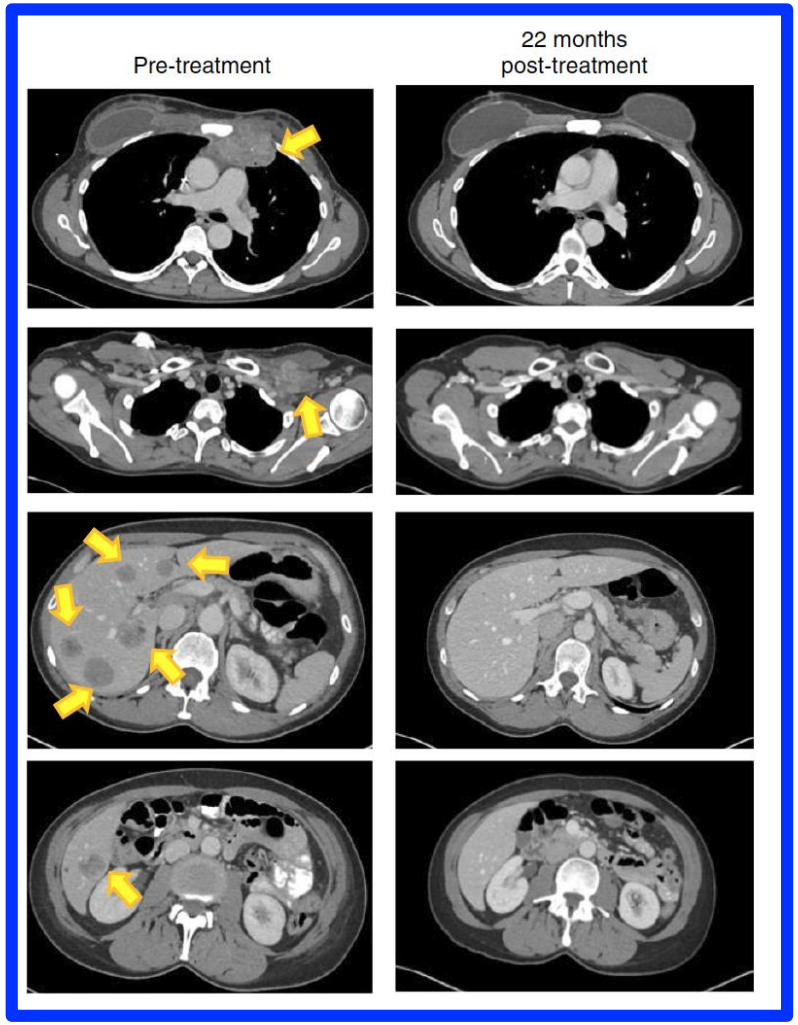


Image courtesy of NCI

Adoptive T cell transfer therapy induces durable responses in some patients





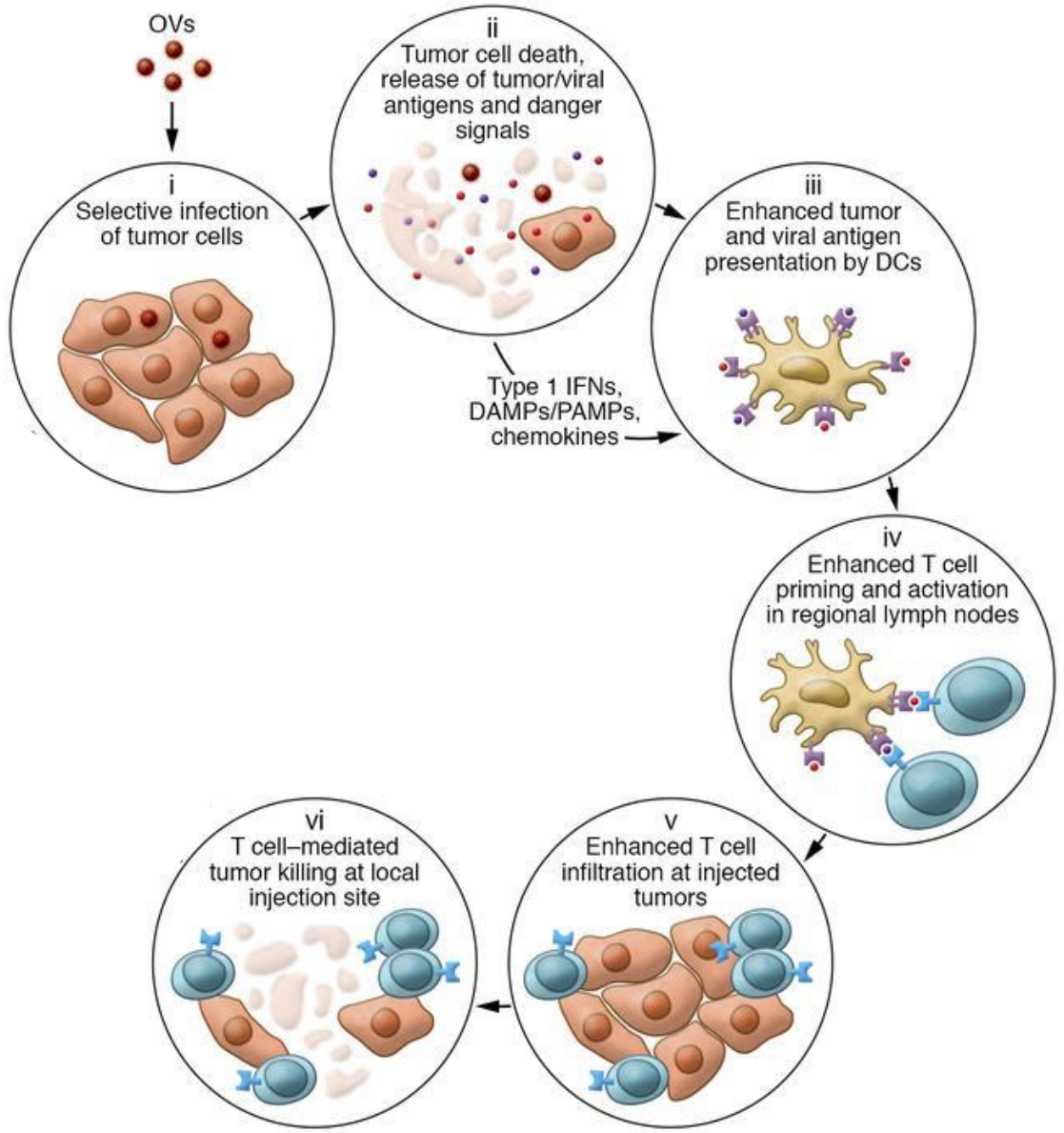
Model by Hannah Knochelmann

Dudley et al, *J Immunother*, 2003
Wu et al, *Cancer J* 2012
Zacharakis et al, *Nat Med*, 2018

Oncolytic Viruses

Goal:

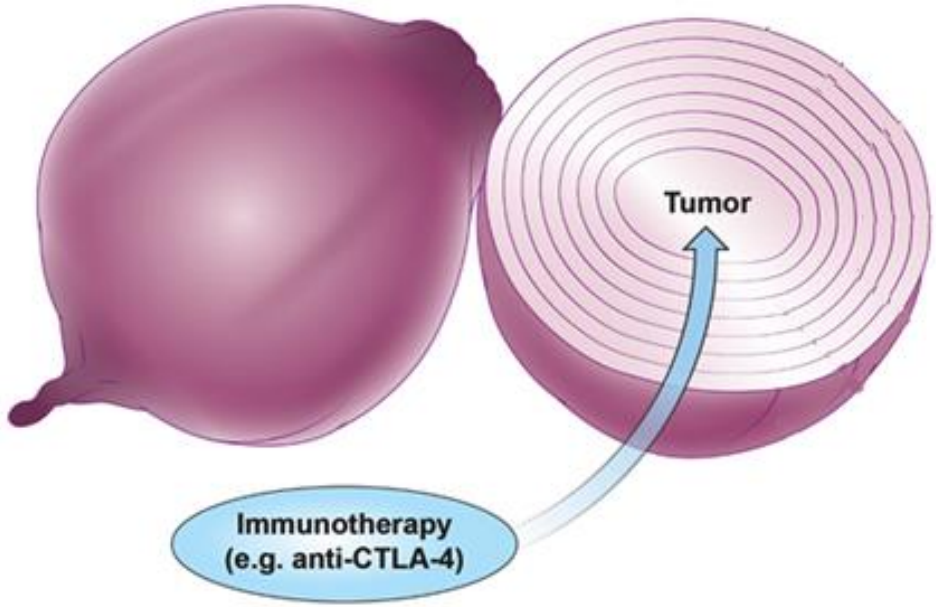
Target and kill tumors via viral replication & release innate immune activators and tumor antigens



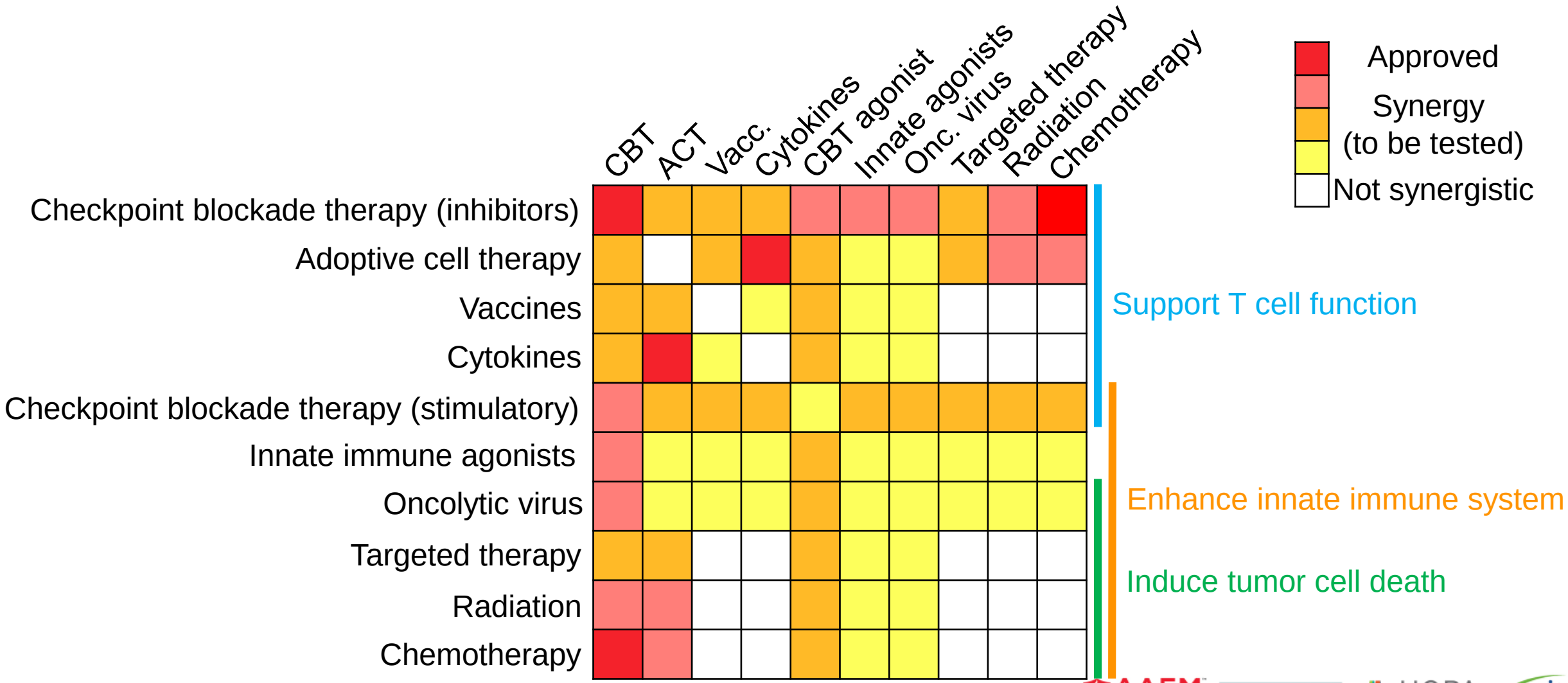
Modified from Bommereddy et al. JCI 2018

Multi-layered Immunosuppression

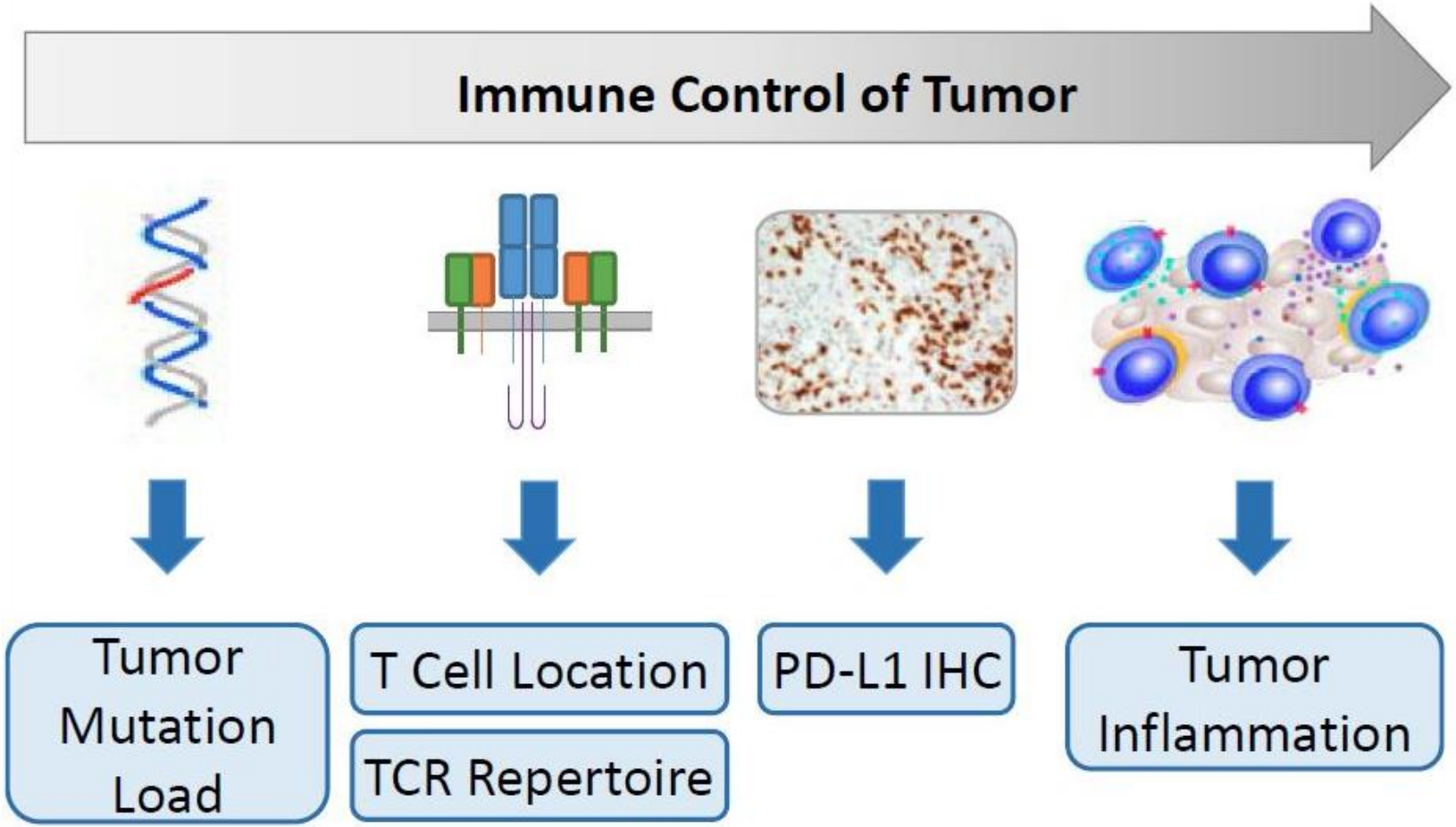
- Tumors insulate themselves
- Overcoming suppressive mechanisms in the tumor is a daunting for T cells
- Immunotherapy can “peel back” the layers
- Combination therapy might be needed



Combination Immunotherapies

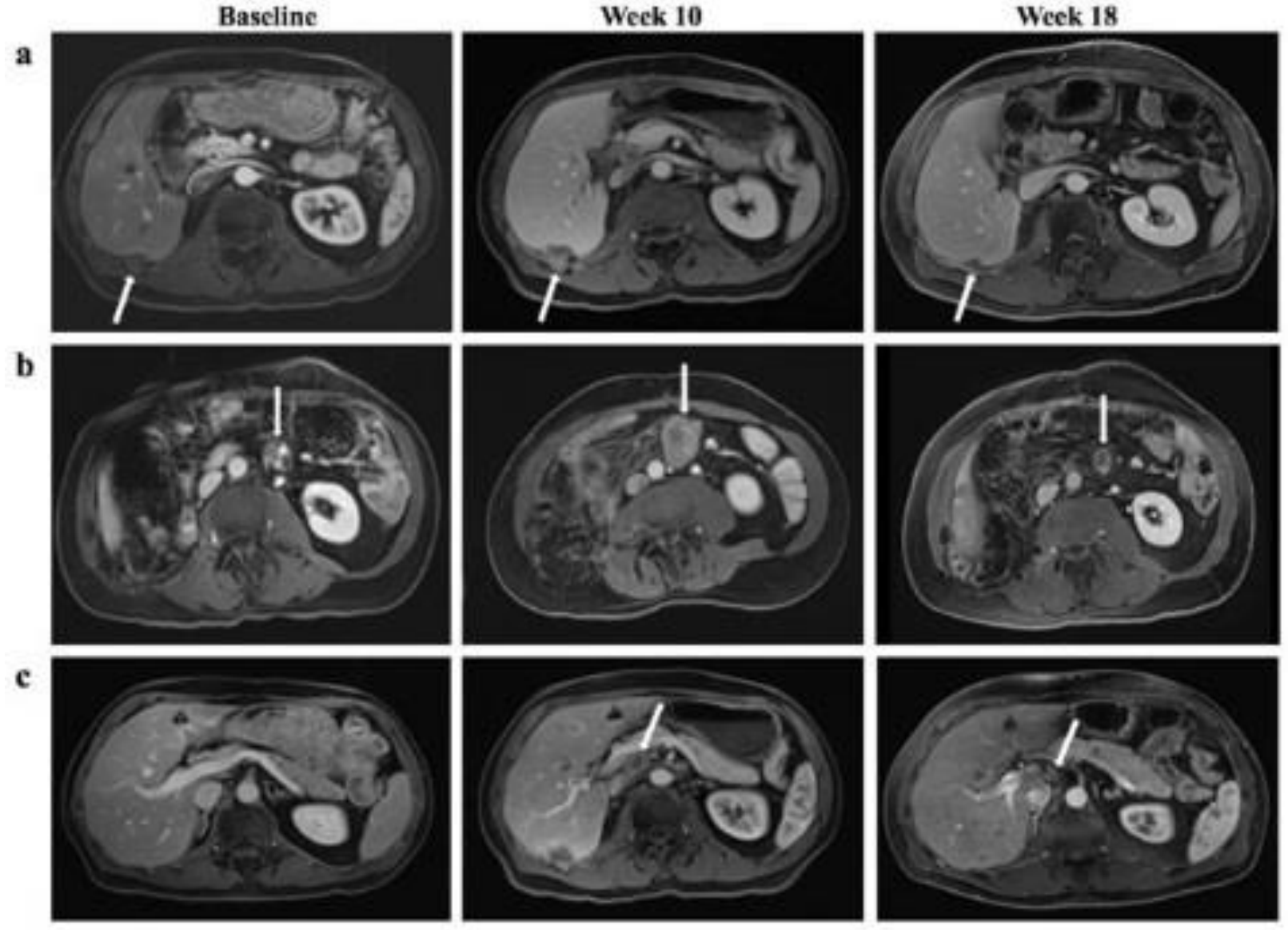


Immunotherapy Biomarkers



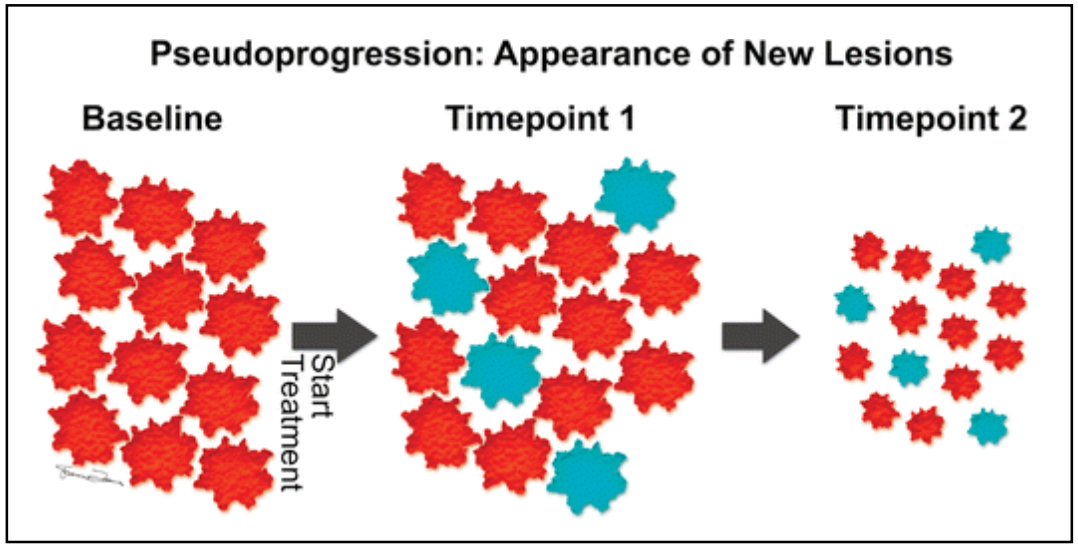
Cesano et al. Biomedicines 2018

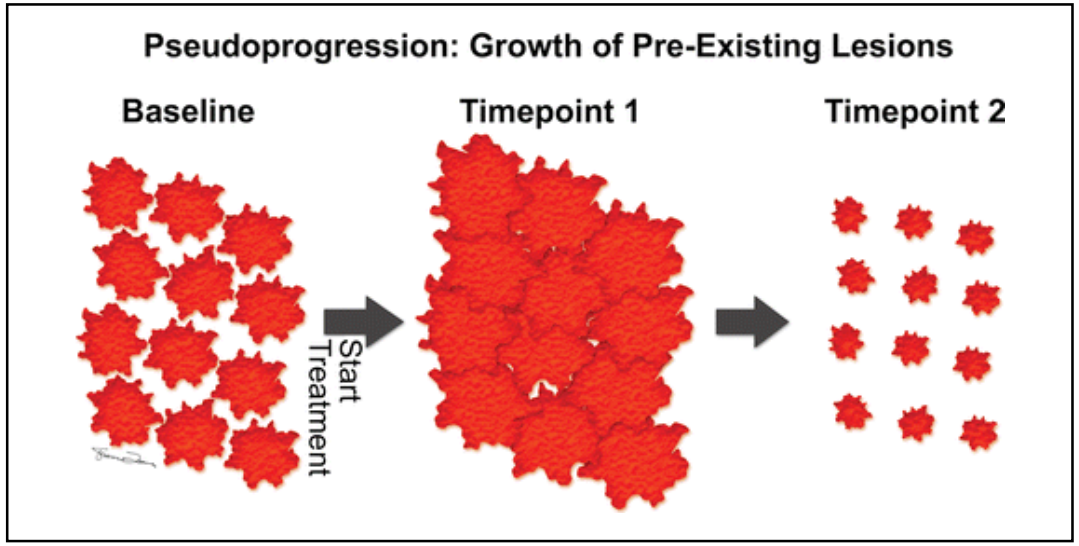
Assessment of response



Chae, Oncotarget 2017.

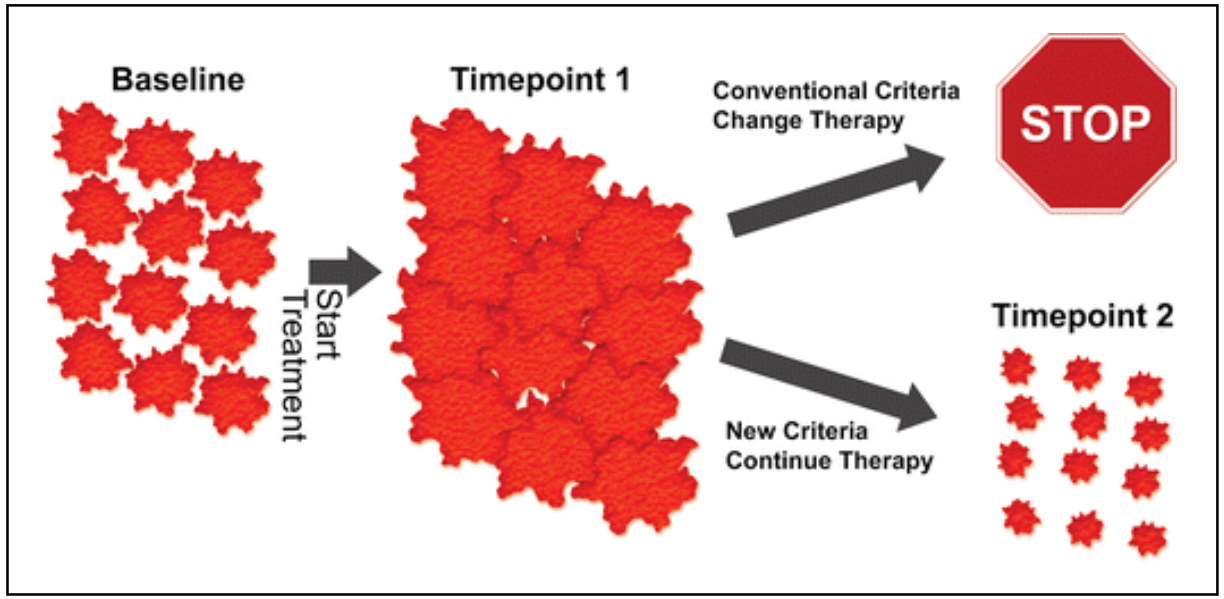
Many possible imaging findings

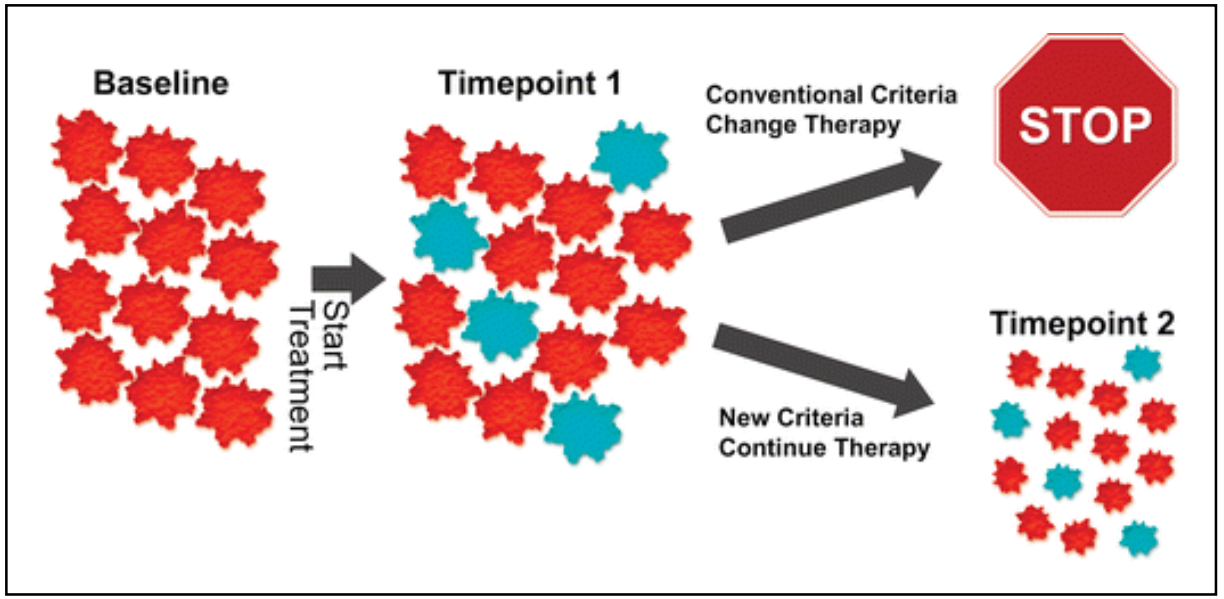




Wang, RadioGraphics 2017.

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[+] *vs.* nadir in two consecutive observations ≥4 weeks apart
New measurable lesions[#]	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

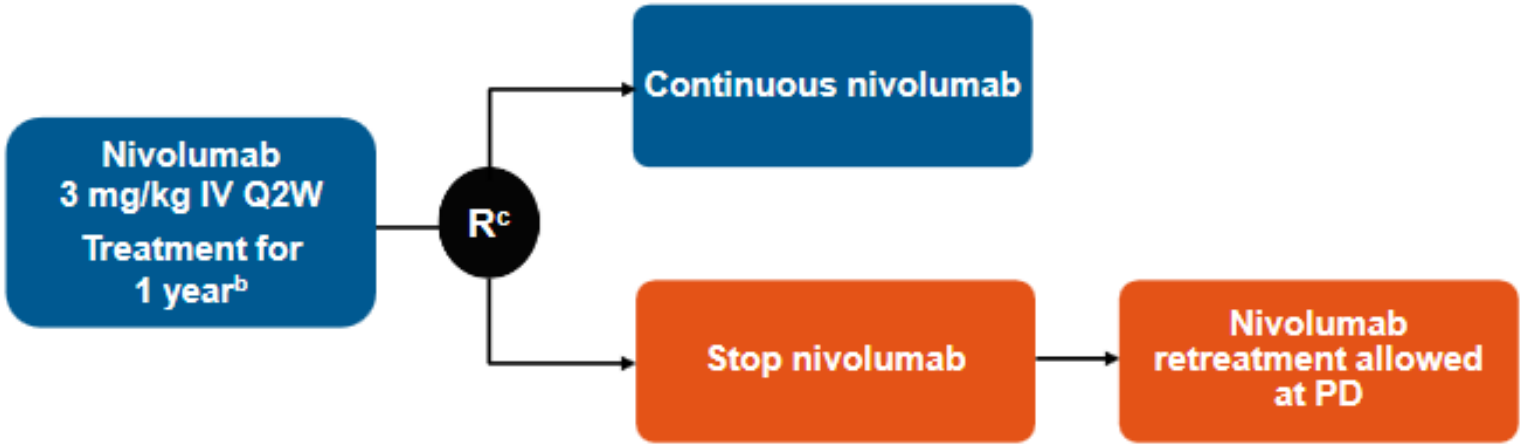
*Sum of lesion diameters: sum of the longest diameter in the plane of measurement for non-nodal target lesions and short-axis diameter for target nodal lesions.
[+]Based on the sum of the products of the two largest perpendicular diameters of all index lesions.
[#]Measurable lesion for RECIST1.1 is ≥10mm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

Wang, RadioGraphics 2017.

When to stop?: Checkmate 153

Key eligibility criteria:

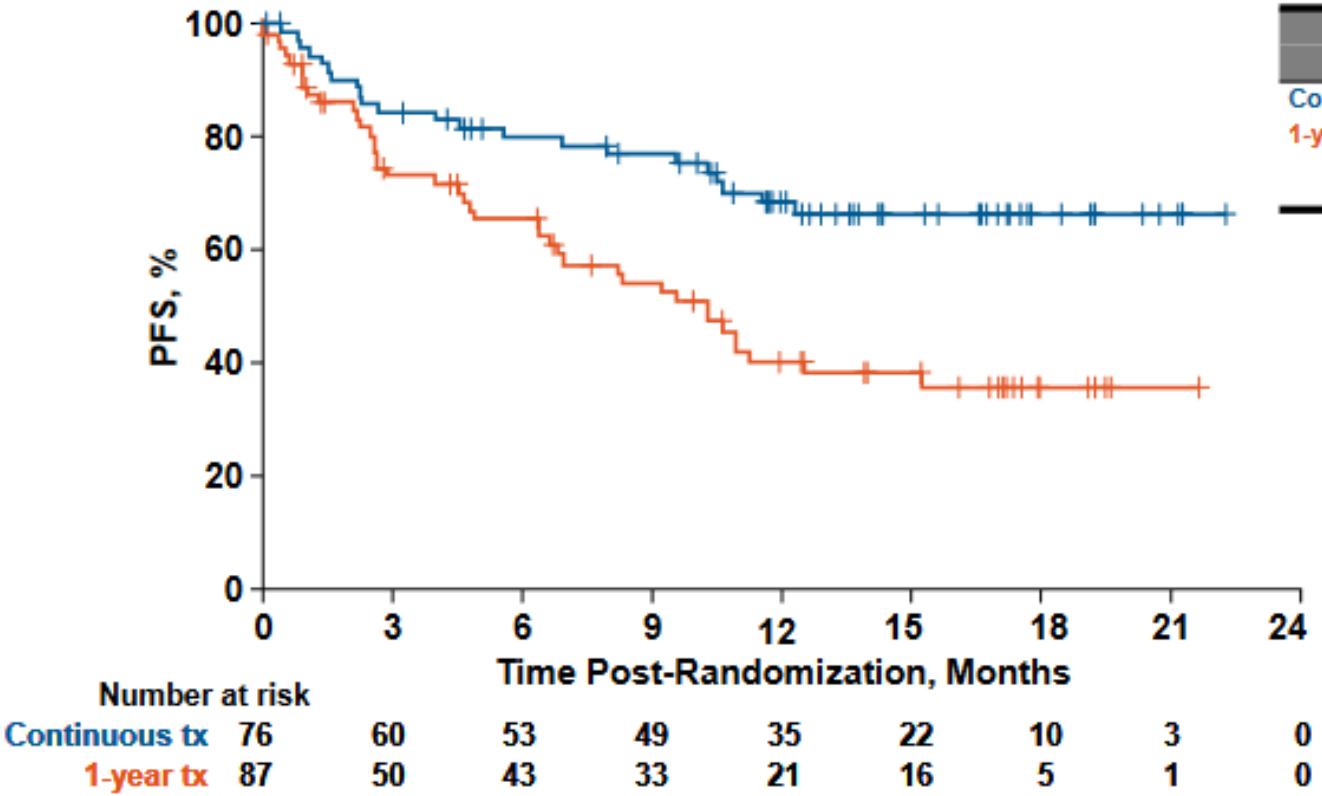
- Advanced/ metastatic NSCLC
- ≥1 prior systemic therapy[a]
- ECOG PS 0-2
- Treated CNS metastases allowed



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

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)

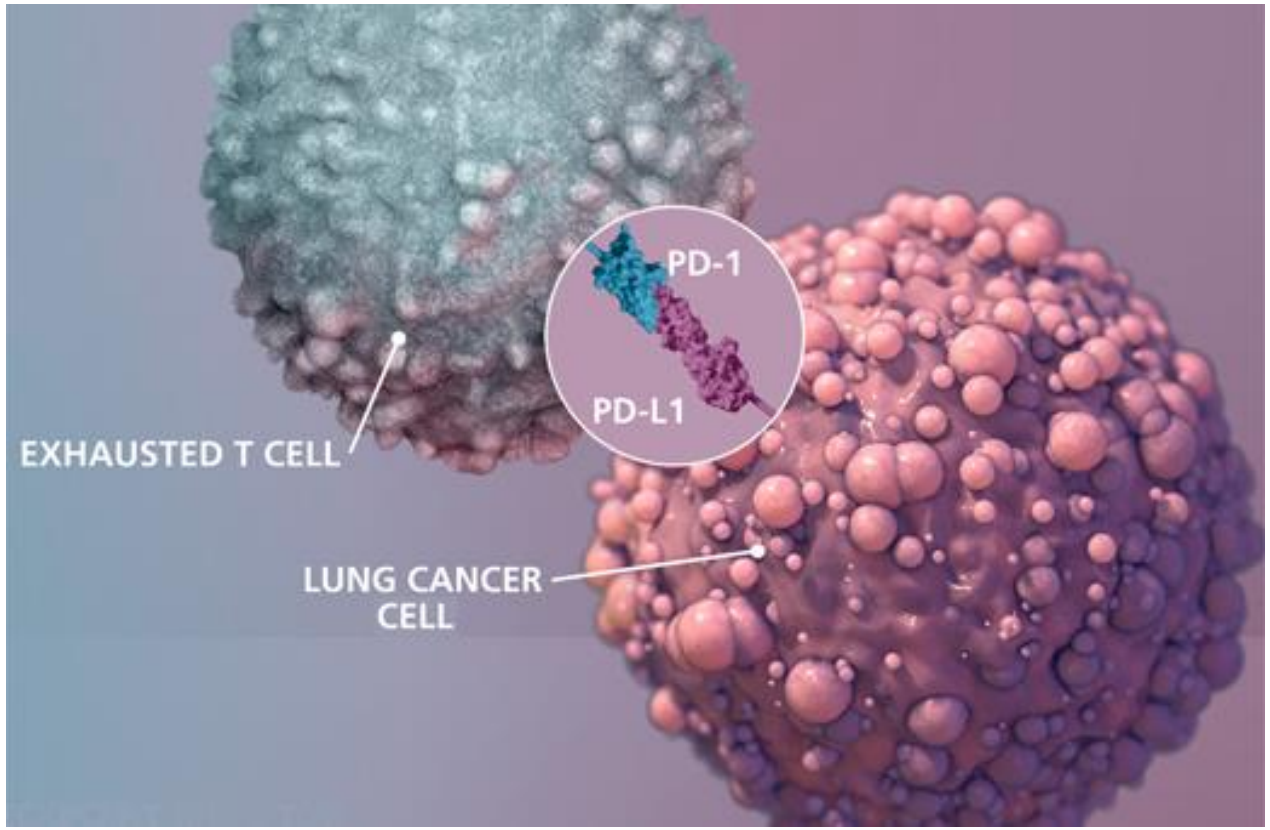
Conclusion: >1 year of treatment may be necessary

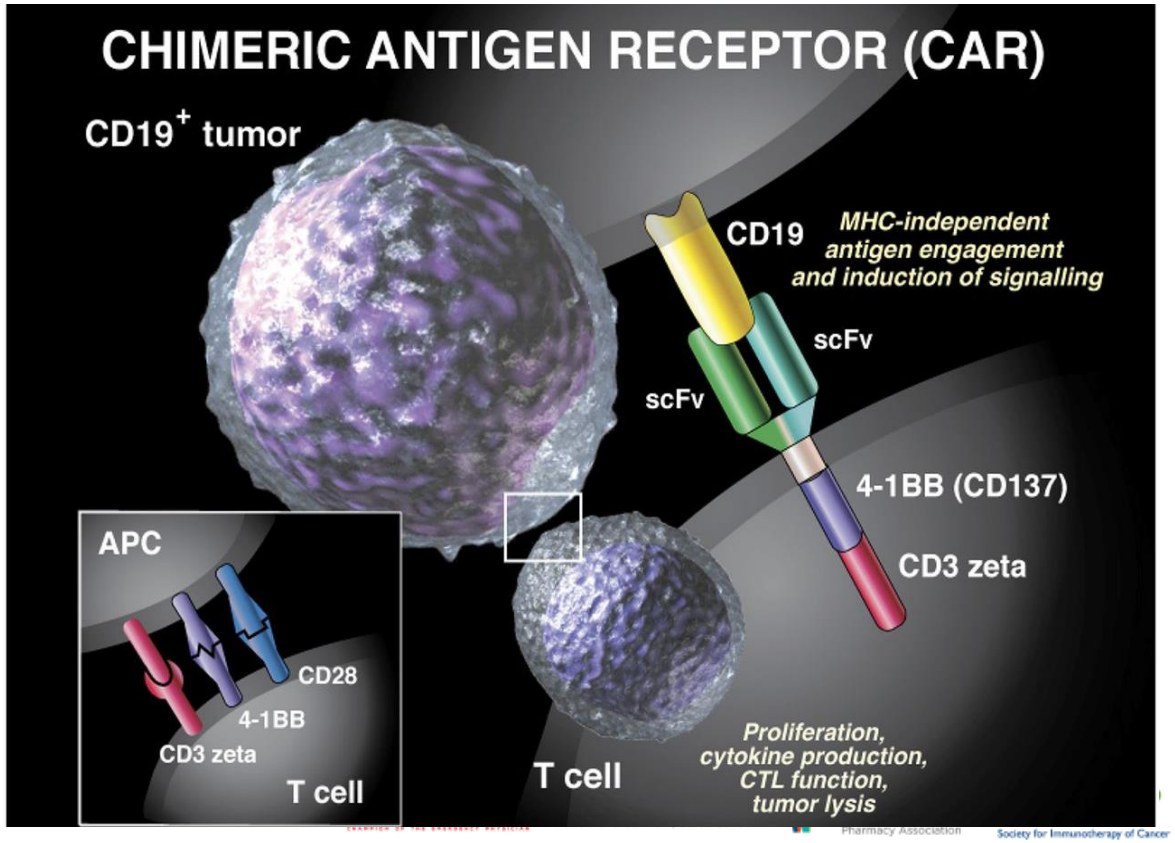
Spigel, Ann Oncol 2017.

sitc Society for Immunotherapy of Cancer

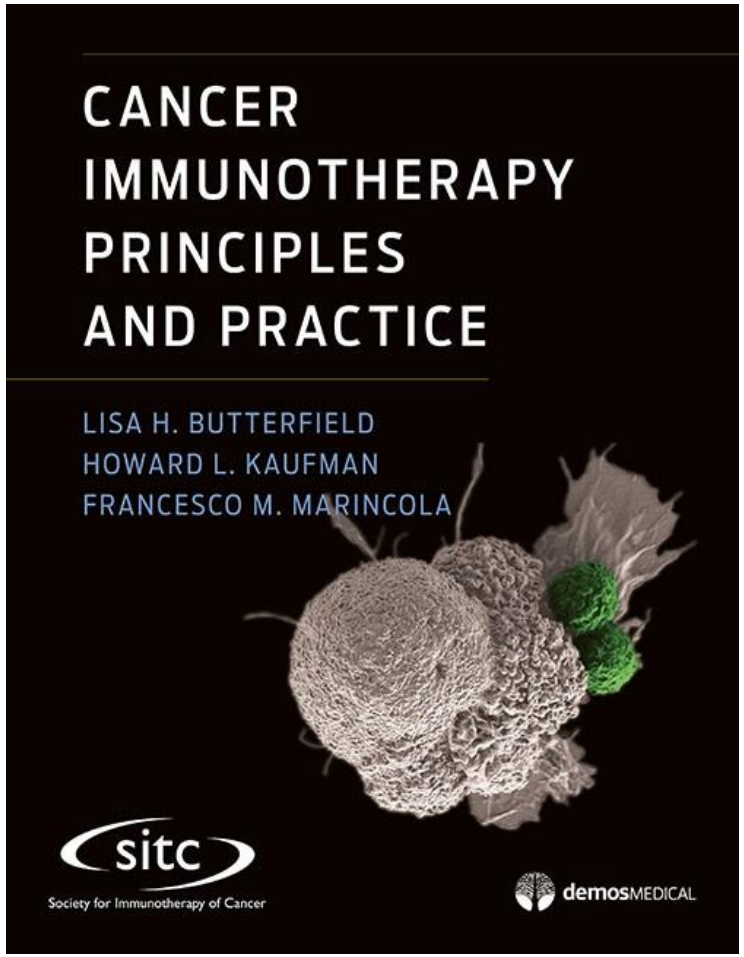
ADVANCES IN Cancer IMMUNOTHERAPY™

Science's Top Breakthrough





Further Resources



SOCIETY FOR IMMUNOTHERAPY OF CANCER

Cancer Immunotherapy CONNECT