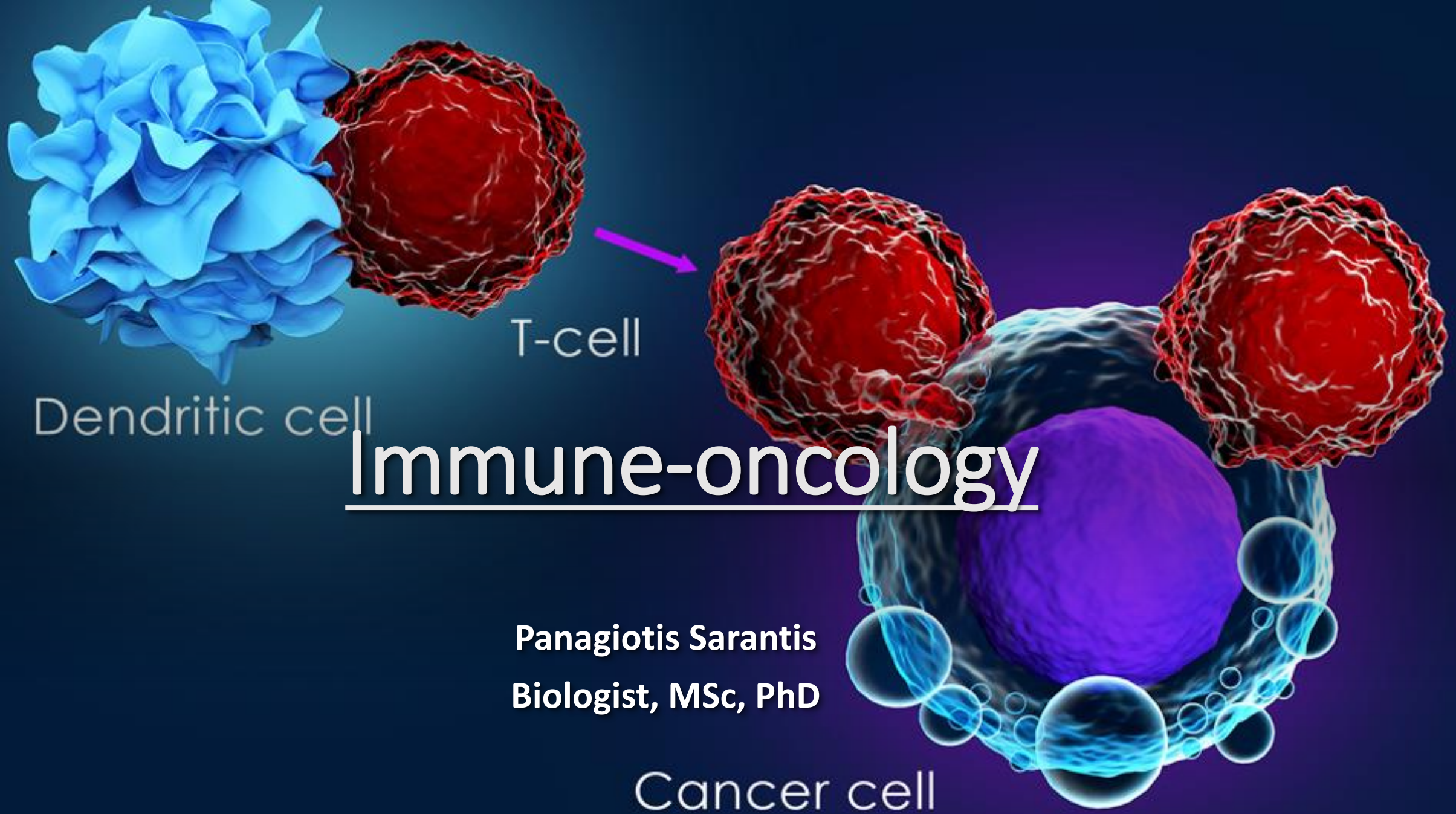



# Immune-oncology

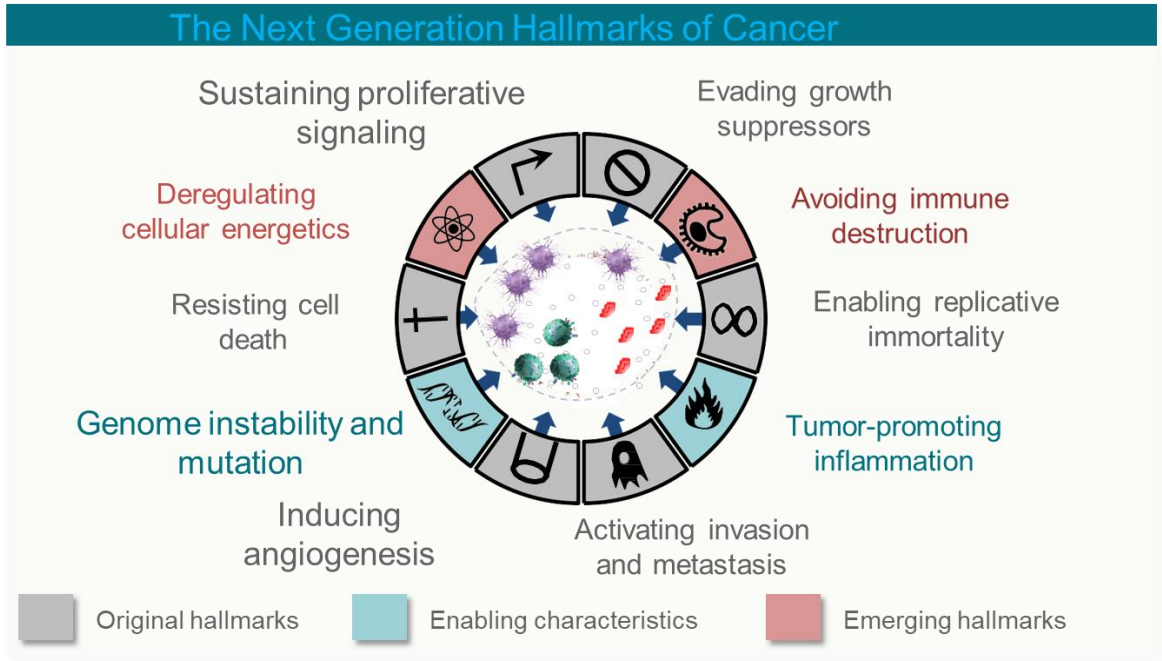
**Panagiotis Sarantis**

**Biologist, MSc, PhD**

# Educational Aims

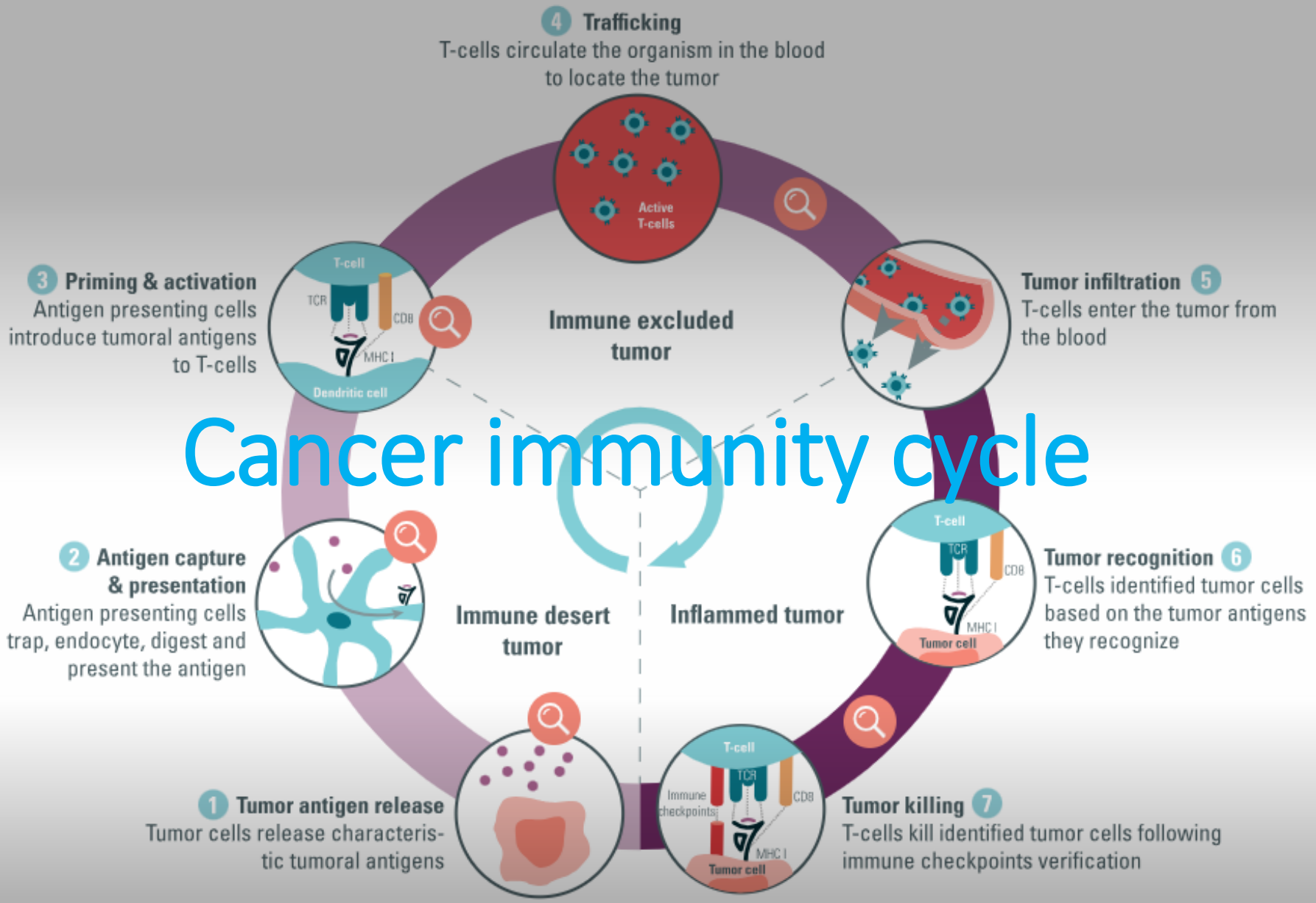
- Immune system and cancer
- **Cancer immunity cycle**
- Immune Checkpoints
- **Immunotherapy options in Cancer**

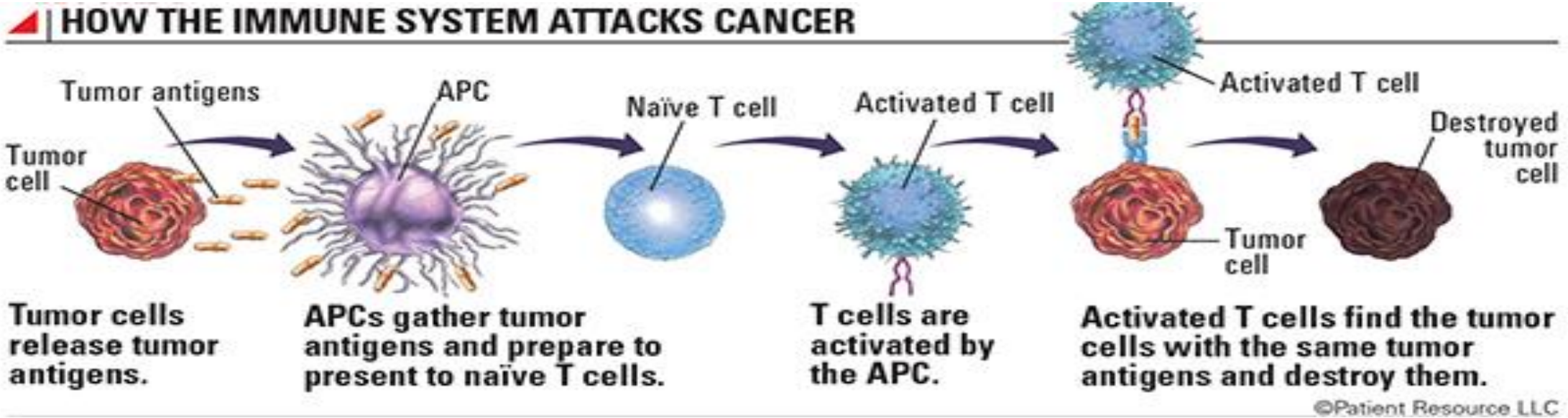
# Avoiding "immuno-surveillance" is a key feature of cancer cells




Hanahan & Weinberg, Cell 2011;144:646

# Cancer immunity cycle






Cancer cells are created by the body

In early stages, cancer cells may shed proteins into the body

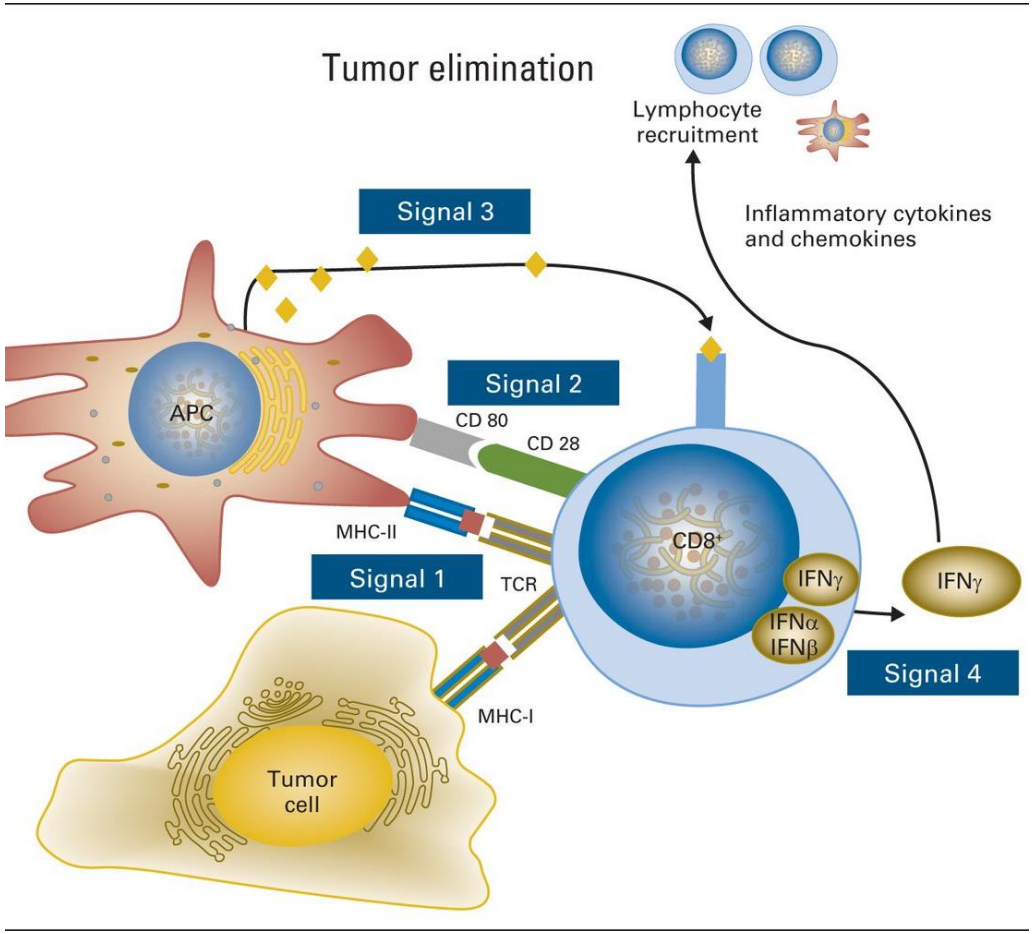
The DNA changes (mutations) that cause the cancer may be different enough to stimulate an immune response similar to the response for invading virus cells

If the immune system detects the cancer, the APCs must share the information with the T cells, which are the primary players in the fight against cancer

Tumor cells can create cytokines, which means that cancer cells can communicate with and confuse other immune cells, allowing the cancer to take control of certain parts of the process that the body uses to regulate the immune response. So, even if the immune system recognizes the cancer, it may not be able to successfully start or maintain an attack long enough to kill the cancer cells

https://www.youtube.com/watch?v=K09xzIQ8zsg

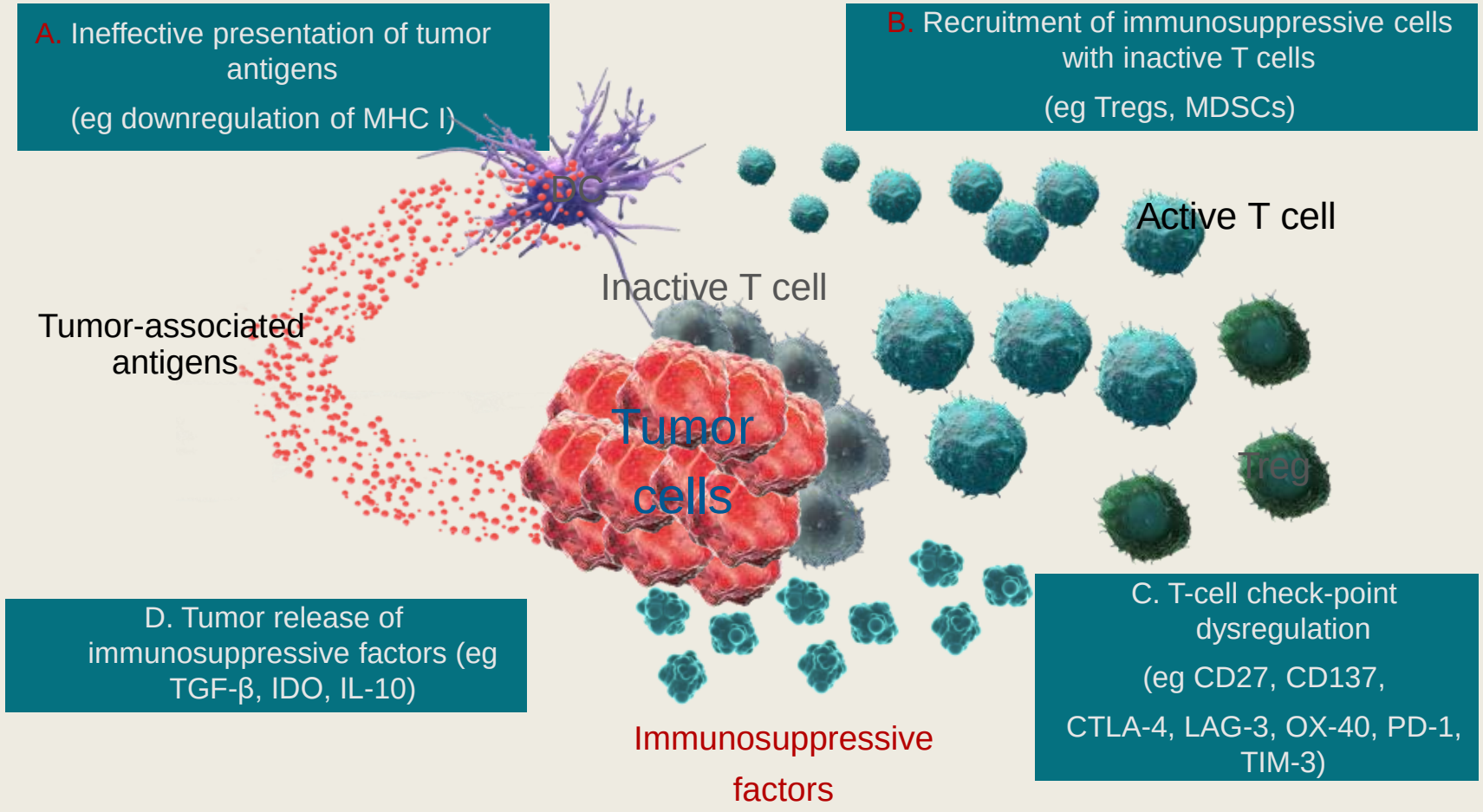
# Steps required for the development of strong antitumor immunity



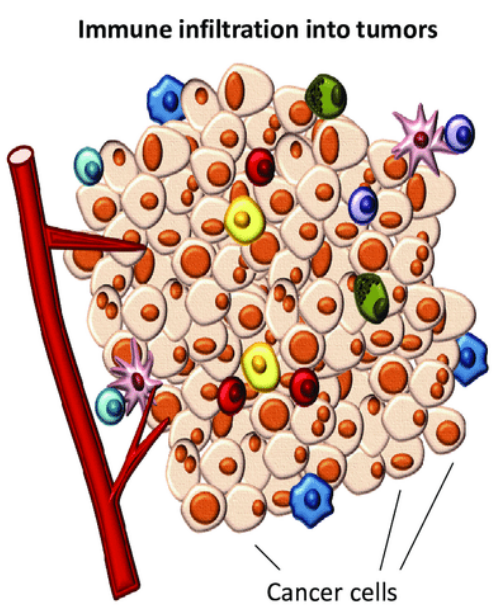

- **Signal 1 represents TCR:HLA-peptide antigen interactions, Signal 2 represents co-stimulatory (or co-inhibitory) signals, Signal 3 indicates cytokine secretion, which may be proinflammatory, type 1 (Th1) antitumor mediators, or tumor-permissing type 2 (Th2) cytokines. Signal 4 represents cell extrinsic attracting chemokine signals to recruit cellular immune populations into the tumor microenvironment and augment/amplify or suppress antitumor immunity.**

RL Ferris JCO 2015;33:3293

# Mechanisms to avoid "immuno-surveillance" by cancer cells

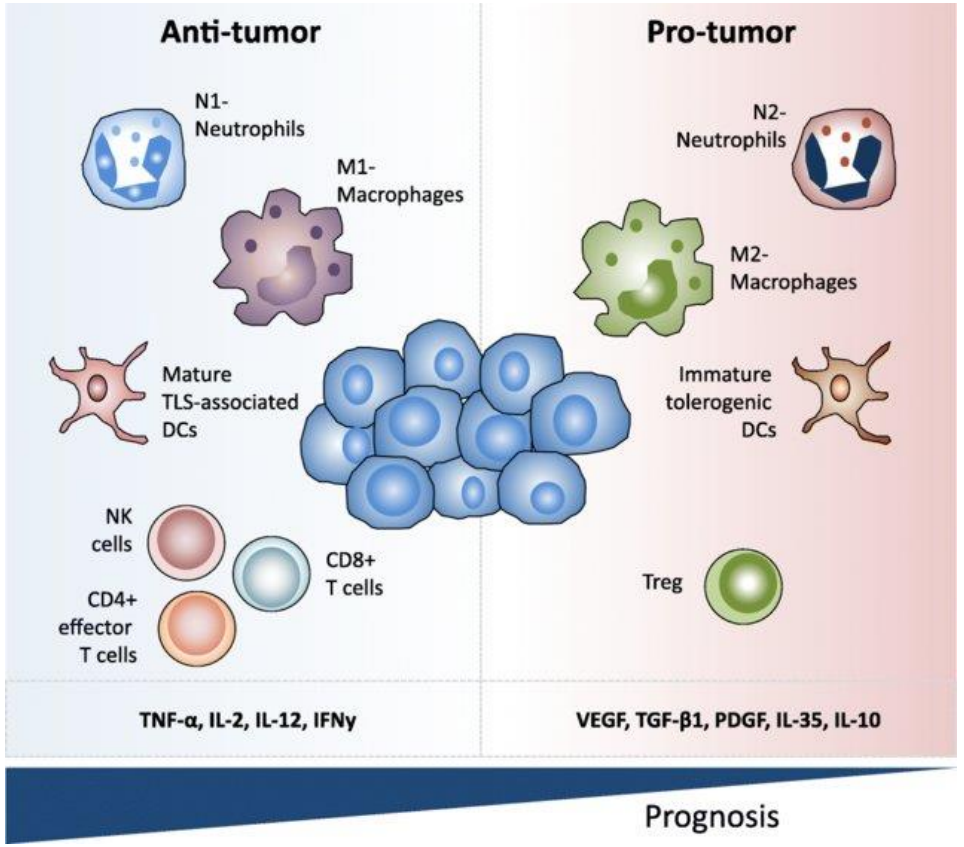


# The double-edged sword of the tumor immune microenvironment




| Immune Cell | | Roles in cancer |
|---|---|---|
| | Dendritic cell (DC) | Release cytotoxic cytokines<br>Antigen presentation to T cells |
| | | Suppress T cell functions<br>Promote tumor growth and progression |
| | T cell (CD8+, CD4+) | Directly lyse cancer cells<br>Release cytotoxic cytokines |
| | | Release tumor promoting cytokines |
| | Treg | Restore homeostasis to reduce chronic inflammation |
| | | Suppress anticancer immune responses<br>Stimulate inflammatory cytokine production |
| | Macrophage | Release cytotoxic cytokines<br>Antigen presentation to T cells |
| | | Promote angiogenesis, tumor proliferation, chemotaxis, invasiveness, and metastasis |
| | Myeloid derived suppressor cell (MDSC) | Limited |
| | | Suppress T cell functions<br>Recruit immunosuppressive immune cells |
| | NK cell | Release cytotoxic cytokines<br>Directly cytotoxic to cancer cells |
| | | Limited |

| |
|---|
| Anti-tumorigenic |
| Pro-tumorigenic |



# 5 Types of Cancer Immunotherapy Treatments

VS Hospitals™
Care. Cure. Compassion.

## Monoclonal Antibodies (MABS)

01

- Immune system can recognize cancer cells that it wasn't able to previously.
- Over 75 drugs approved to date.

## Immune - Checkpoint Inhibitors

02

- Releases immune system's molecular brakes called "checkpoints".
- At least 6 drugs approved so far.

## Cancer Vaccines

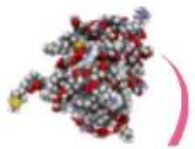
03

- Two types; Preventative and treatment.
- Possibly will use artificial intelligence for personalized medicine.

## Adoptive Cell Transfer (ACT)

04

- Pretty new with only two drugs approved.
- Uses gene editing.

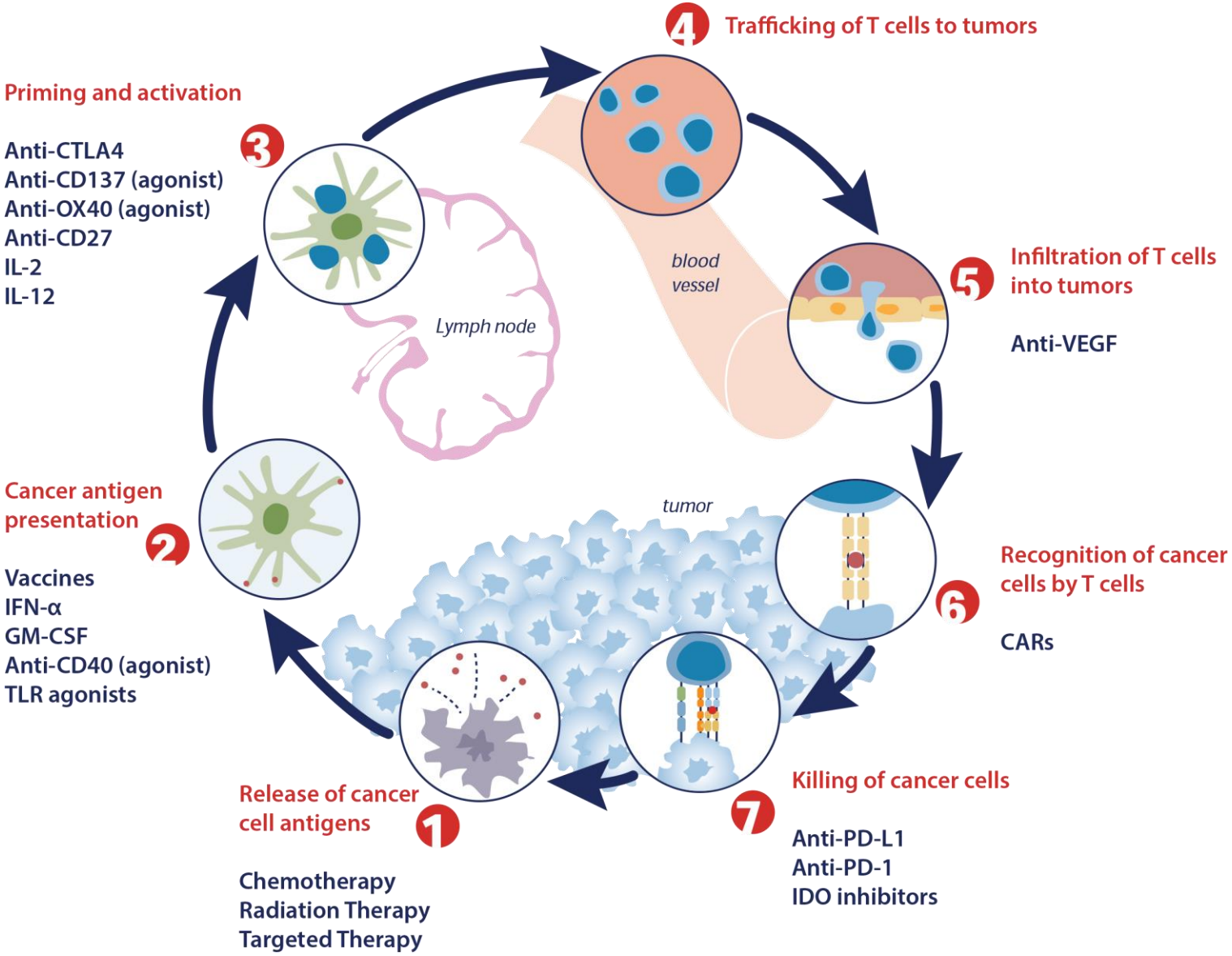


## Cytokines

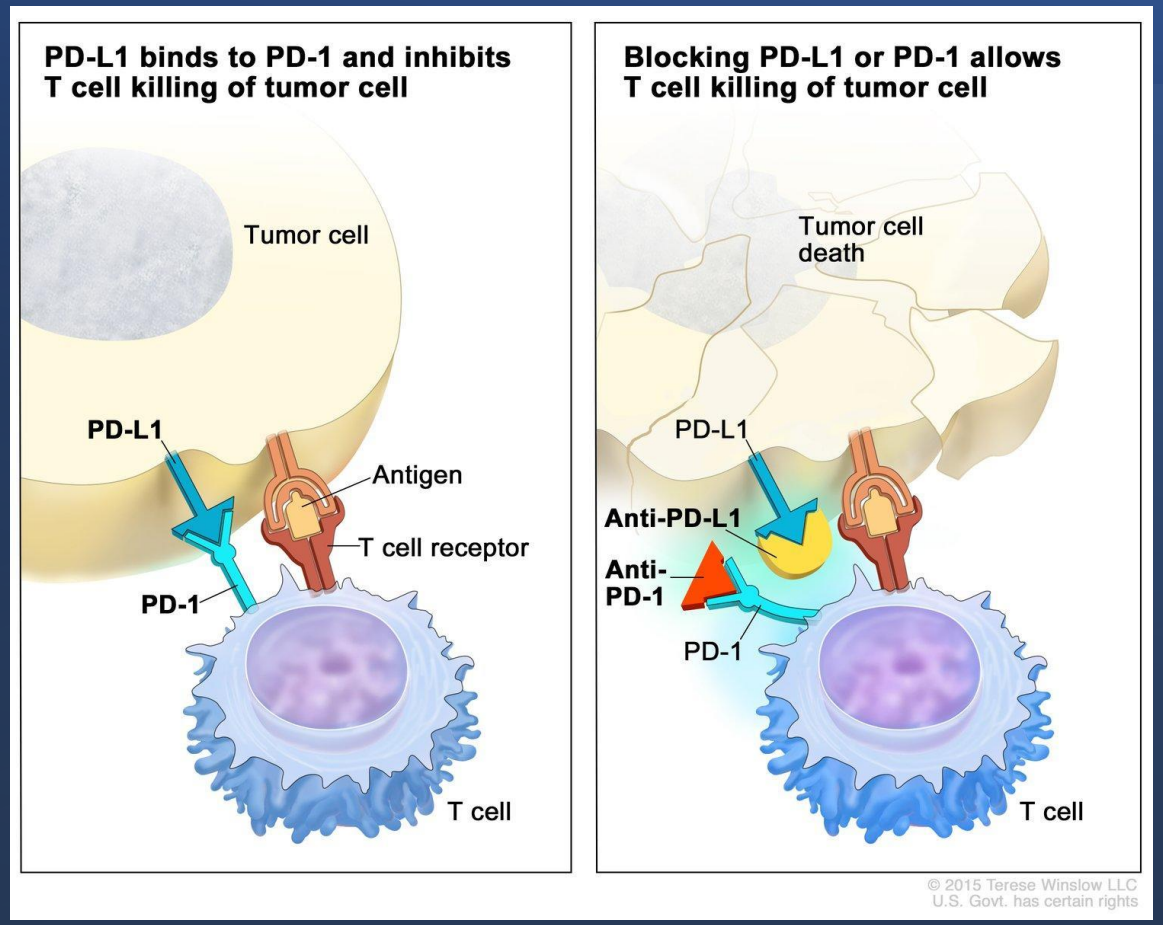
05

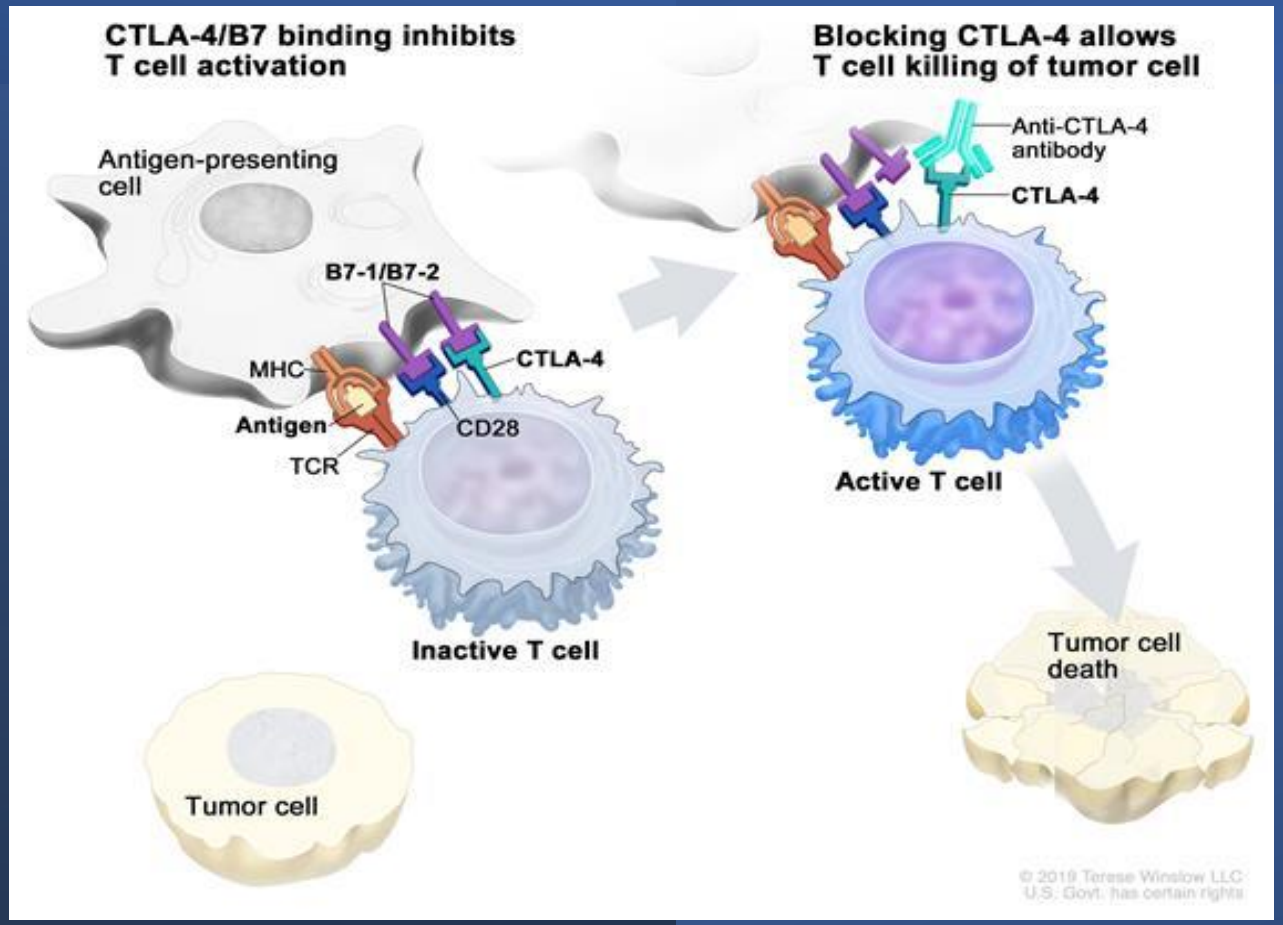
- Man made versions of some proteins that boost immune system.
- Kind of complicated stuff.

# Treatments- Cancer immunity cycle



# Immune Checkpoint Inhibitors






https://www.youtube.com/watch?v=23O8rRHgluA

https://www.youtube.com/watch?v=pWaHAxZUmFY&list=LL&index=1

- **PD-1 inhibitors**

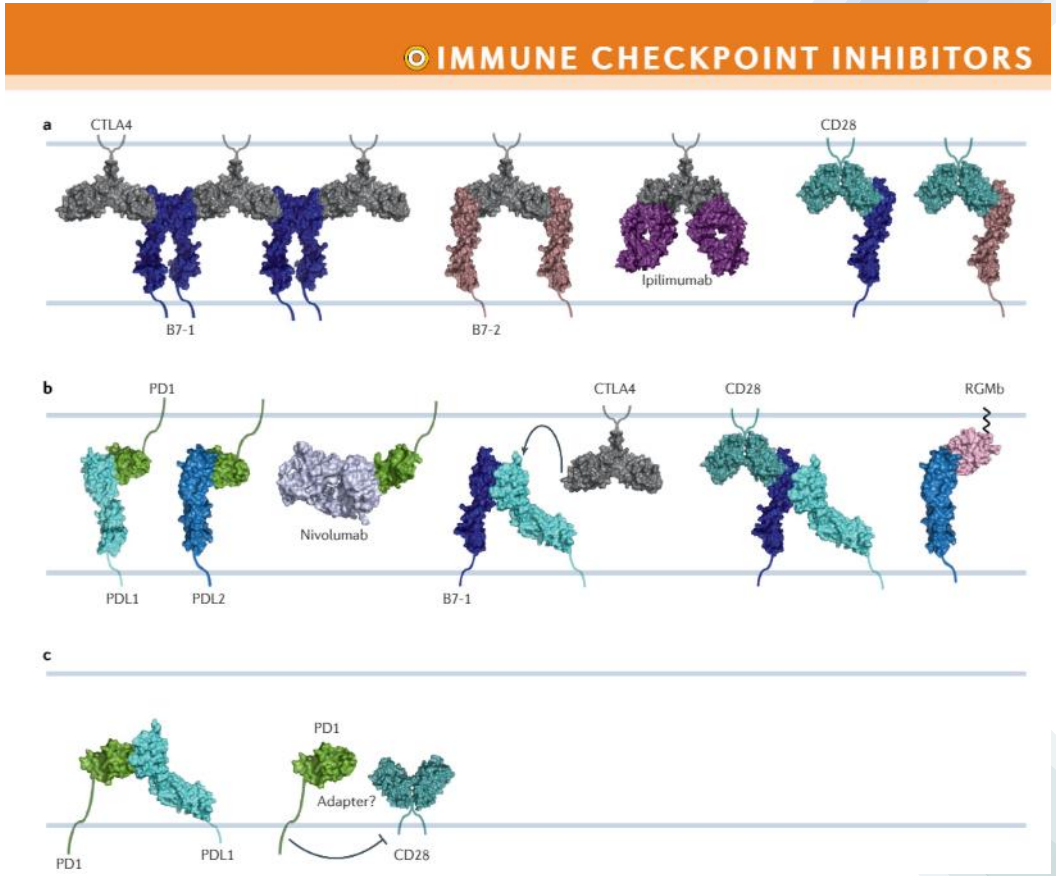
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Cemiplimab (Libtayo)

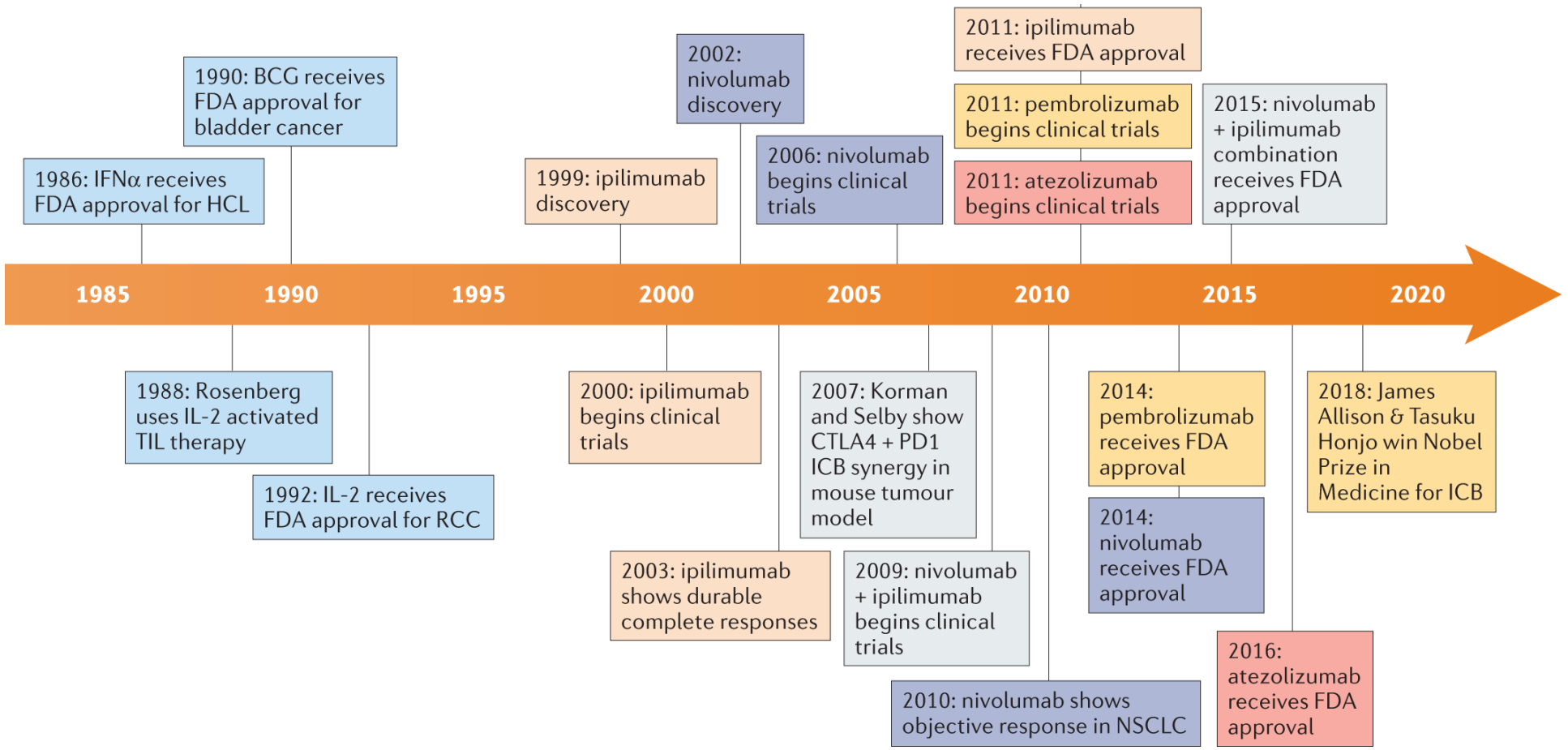
- **PD-L1 inhibitors**

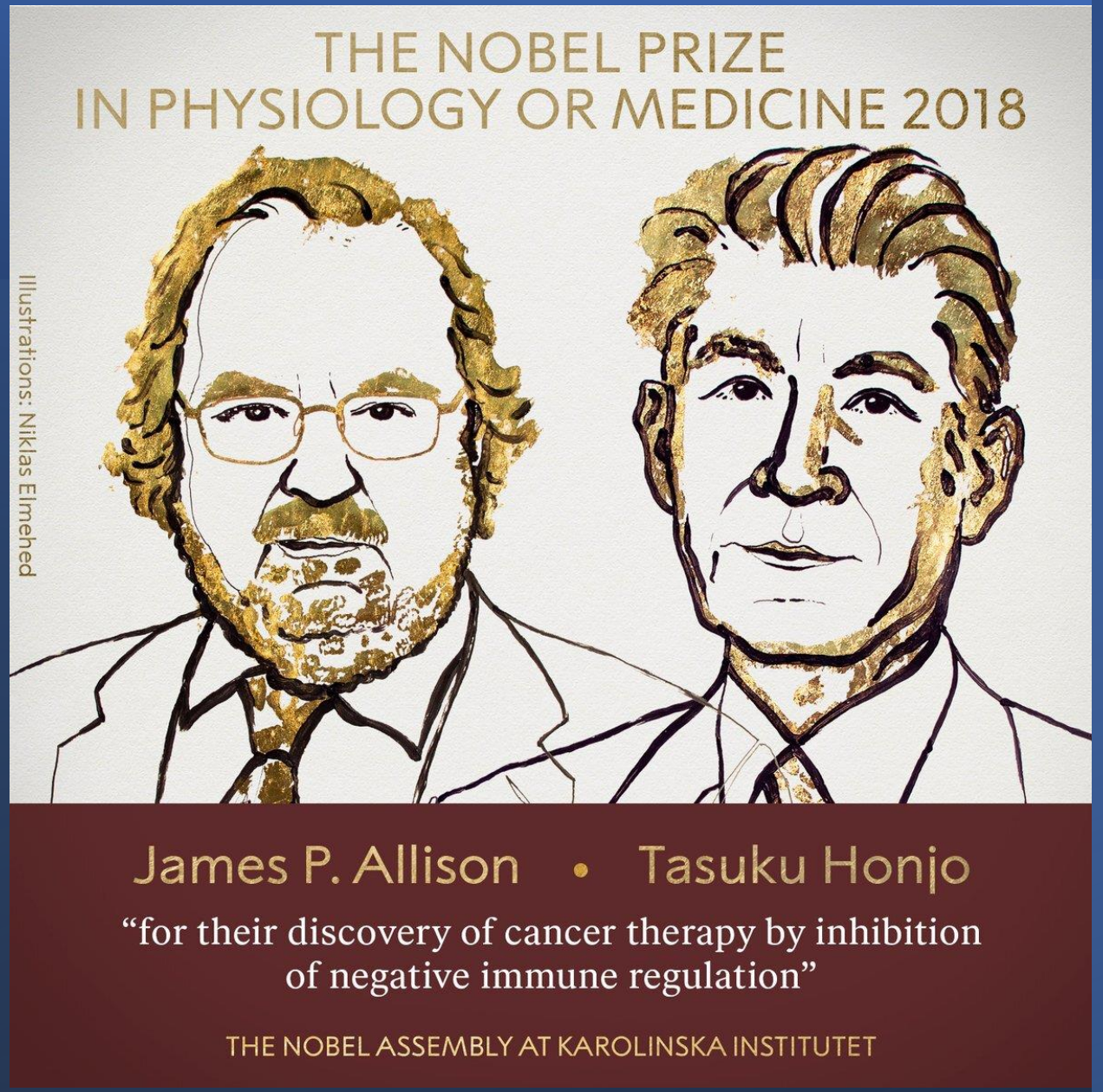
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

- **CTL-4 inhibitors**

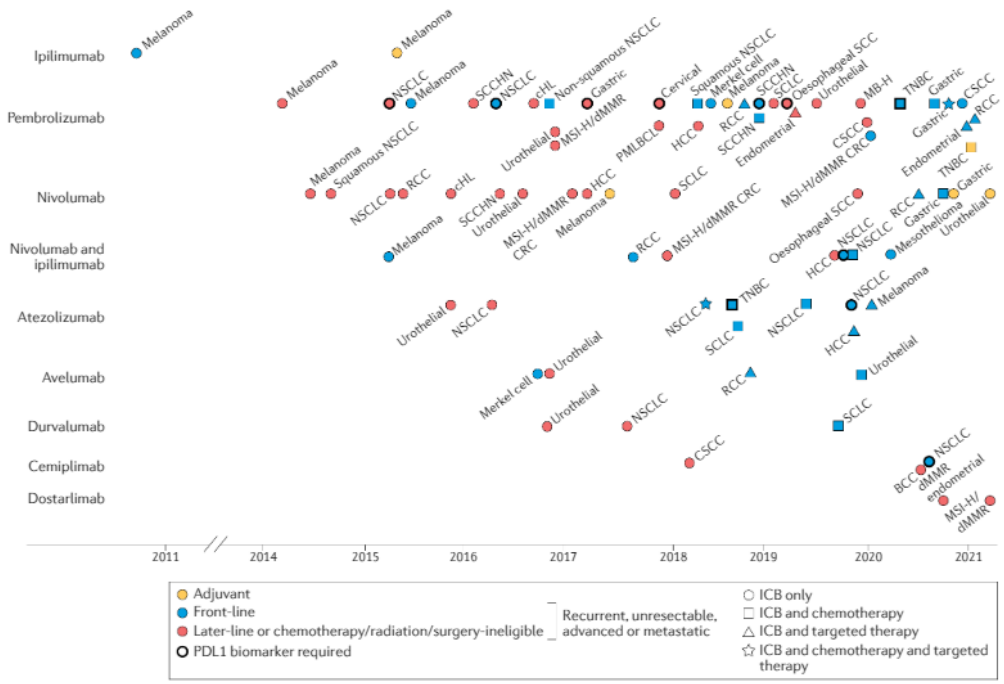
- Ipilimumab (Yervoy)
- Tremelimumab (Imjuno)




1985
1990
1995
2000
2005
2010
2015
2020
1986: IFNα receives FDA approval for HCL
1990: BCG receives FDA approval for bladder cancer
1988: Rosenberg uses IL-2 activated TIL therapy
1992: IL-2 receives FDA approval for RCC
1999: ipilimumab discovery
2002: nivolumab discovery
2000: ipilimumab begins clinical trials
2003: ipilimumab shows durable complete responses
2006: nivolumab begins clinical trials
2007: Korman and Selby show CTLA4 + PD1 ICB synergy in mouse tumour model
2009: nivolumab + ipilimumab begins clinical trials
2010: nivolumab shows objective response in NSCLC
2011: ipilimumab receives FDA approval
2011: pembrolizumab begins clinical trials
2011: atezolizumab begins clinical trials
2014: pembrolizumab receives FDA approval
2014: nivolumab receives FDA approval
2015: nivolumab + ipilimumab combination receives FDA approval
2016: atezolizumab receives FDA approval
2018: James Allison & Tasuku Honjo win Nobel Prize in Medicine for ICB


THE NOBEL PRIZE
IN PHYSIOLOGY OR MEDICINE 2018
Illustrations: Niklas Elmehed
James P. Allison • Tasuku Honjo
“for their discovery of cancer therapy by inhibition of negative immune regulation”
THE NOBEL ASSEMBLY AT KAROLINSKA INSTITUTET

# ICI and Cancers




| Drug (Trade name) | Company | Date of approval | Indication |
|---|---|---|---|
| ***CTLA-4 inhibitors*** | | | |
| Ipilimumab (Yervoy®) | Bristol-Myers Squibb | 2011 | Melanoma<br>colorectal cancer<br>Renal cell carcinoma |
| ***PD-1 inhibitors*** | | | |
| Nivolumab (Opdivo®) | Bristol-Myers Squibb | 2014 | Melanoma<br>Hodgkin's lymphoma<br>Diffuse large B-cell lymphoma<br>Urothelial cancer<br>Colorectal cancer<br>Hepatocellular carcinoma<br>Non-small cell lung cancer<br>Small cell lung cancer<br>Renal cell carcinoma<br>Squamous cell carcinoma |
| Pembrolizumab (Keytruda®) | Merck | 2014 | Melanoma<br>Cervical cancer<br>Hodgkin's lymphoma<br>Diffuse large B-cell lymphoma<br>Gastric cancer<br>Urothelial cancer<br>Colorectal cancer<br>Hepatocellular carcinoma<br>Non-small cell lung cancer<br>Small cell lung cancer<br>Renal cell carcinoma<br>Squamous cell carcinoma<br>Esophageal cancer<br>Merkel cell carcinoma |
| Cemiplimab (Libtayo®) | Sanofi | 2018 | Cutaneous squamous cell carcinoma |
| ***PD-L1 inhibitors*** | | | |
| Atezolizumab (Tecentriq®) | Roche, Genentech | 2016 | Non-small cell lung cancer<br>Triple negative breast cancer |
| Avelumab (Bavencio®) | Merck, Pfizer | 2017 | Merkel cell carcinoma<br>Renal cell carcinoma<br>Urothelial cancer |
| Durvalumab (Imfinzi®) | AstraZeneca | 2017 | Bladder cancer<br>Non-small cell lung cancer |

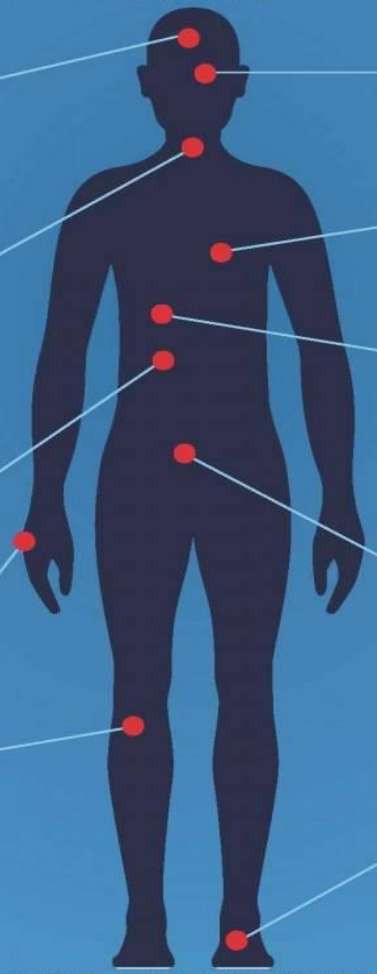
National Comprehensive Cancer Network®

# UNDERSTANDING IMMUNOTHERAPY SIDE EFFECTS

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY MAKING A WORLD OF DIFFERENCE IN CANCER CARE

Immune checkpoint inhibitors (a type of immunotherapy) offer a promising new way to treat cancer for some patients. But these medicines can occasionally cause your immune system to attack normal organs and tissues in your body, affecting the way they work. Serious side effects typically occur in less than **5%** of patients, but certain mild side effects can occur in up to **30% – 50%** of patients.

**Contact your health care professional right away if you think you may be experiencing . . .**



**Brain inflammation (encephalitis)**
Fever; confusion; changes in mood or behavior; neck stiffness; seizures; extreme sensitivity to light.

**Hormone gland problems (especially the thyroid, pituitary, adrenal glands, pancreas)**
Persistent or unusual headaches; extreme tiredness; weight loss or gain; rapid heartbeat; increased sweating; hair loss; constipation; dizziness or fainting.

**Kidney problems**
Decrease in the amount of urine; blood in the urine.

**Skin problems**
Rashes; itching; blistering; painful sores or ulcers.

**Joint or muscle problems**
Severe or persistent muscle or joint pain; severe muscle weakness.

**Eye problems**
Blurry or double vision or other vision problems; eye pain or redness.

**Lung problems (pneumonitis)**
New or worsening cough; shortness of breath.

**Liver problems (hepatitis)**
Yellowing of the skin or the whites of the eyes; severe nausea or vomiting; pain on the right side of the stomach area; dark urine; bleeding or bruising more easily than normal.

**Intestinal problems (colitis)**
Diarrhea or more bowel movements than usual; stools that have blood or are dark, tarry, or sticky; severe stomach-area pain.

**Nerve problems**
Numbness or tingling in hands or feet; unusual weakness in legs, arms, or face.

# Learning Objectives

1. Understanding the role of the immune system in cancer development and progression.
2. Understanding the signaling pathways involved in immune oncology
3. Understanding how these pathways are altered in cancer
4. Understanding the mechanisms underlying the interaction between cancer cells and the immune system.
5. Understanding the challenges and opportunities associated with the development of immunotherapeutic agents and their clinical implementation.

# Questions

- Tregs have:

a) Anti-tumor activity

b) Pro-tumor activity

# Questions

- CTLA-4 is involved in the connection:

a) T-cell/cancer cell
b) APC/cancer cell
c) APC/T-cell

# Questions

- Anti-PDL1 used in the stage:

a) Killing of cancer cells
b) Priming and activation
c) Release of neoantigens
d) Cancer antigen presentation


University of Athens

- Thank you for your attention!