Cancer immunity and immunotherapy

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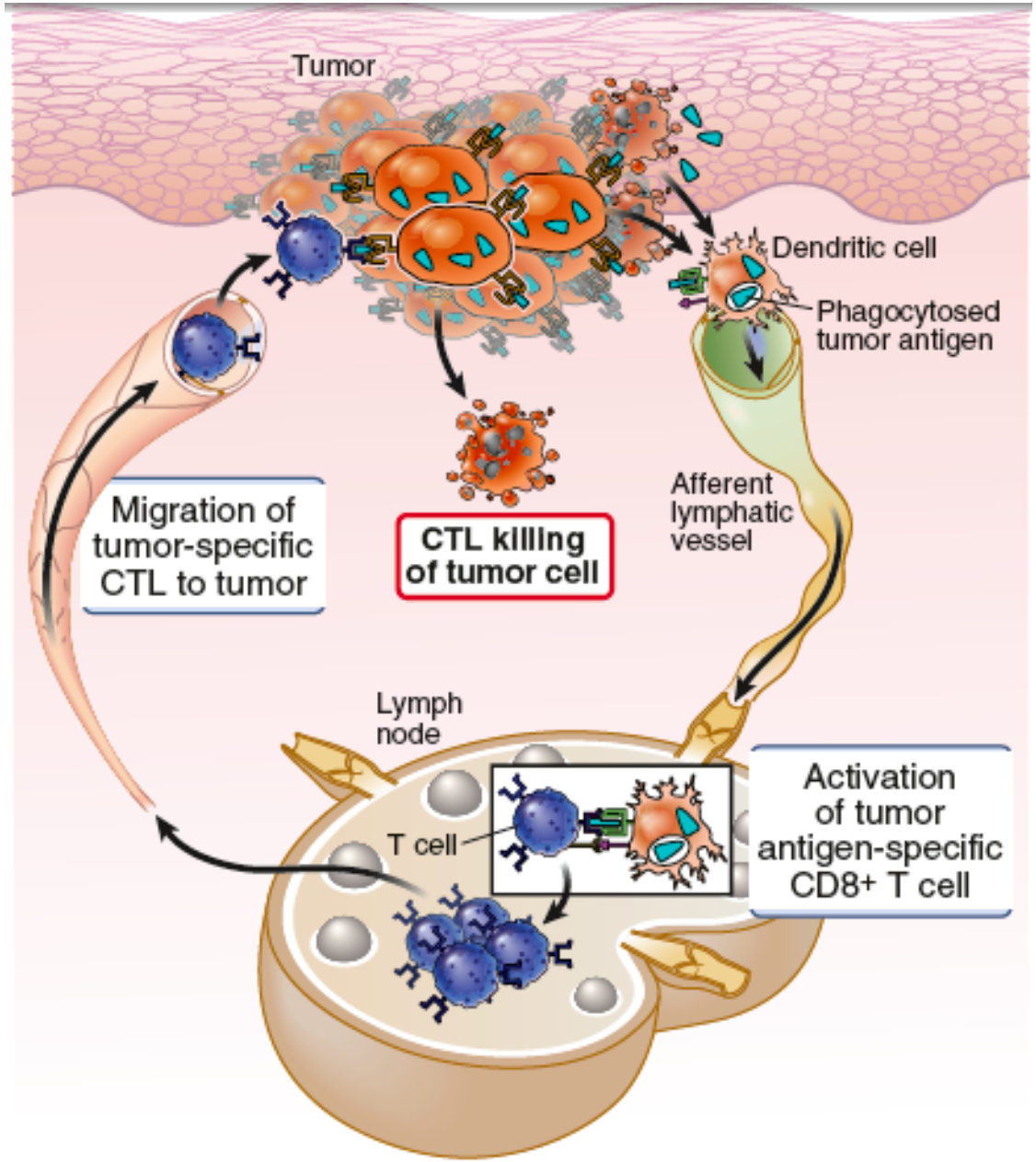
General principles

- The immune system recognizes and reacts against cancers
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer
- Some immune responses promote cancer growth
- Defining the immune response against cancers will help in developing new immunotherapies

T cell responses to tumors

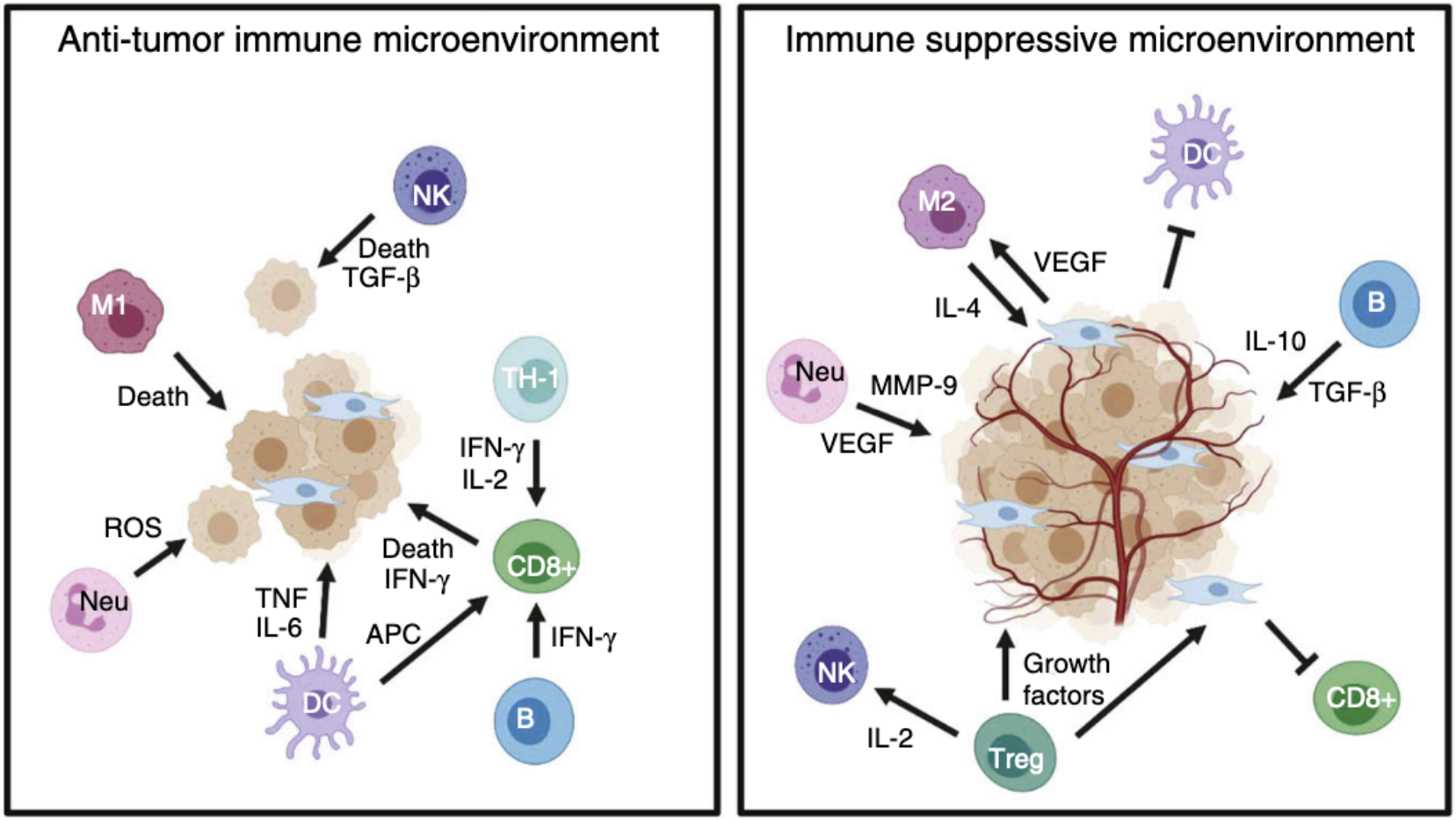


The tumor microenvironment (TME)

- Collection of cells around the tumor that kill tumor cells or promote tumor growth
  - Consists of lymphoid and myeloid cells, stromal cells (fibroblasts), vascular cells
  - Promote tumor growth by providing growth factors and nutrients and suppressing host immunity

- Challenges in targeting the TME
  - Heterogeneity (varies even in the same tumor at different sites)
  - Lack of good markers for different cell types, e.g., MDSCs
  - Risks of systemic depletion of cells (Tregs, macrophages)

Opposing roles of the tumor microenvironment (TME)



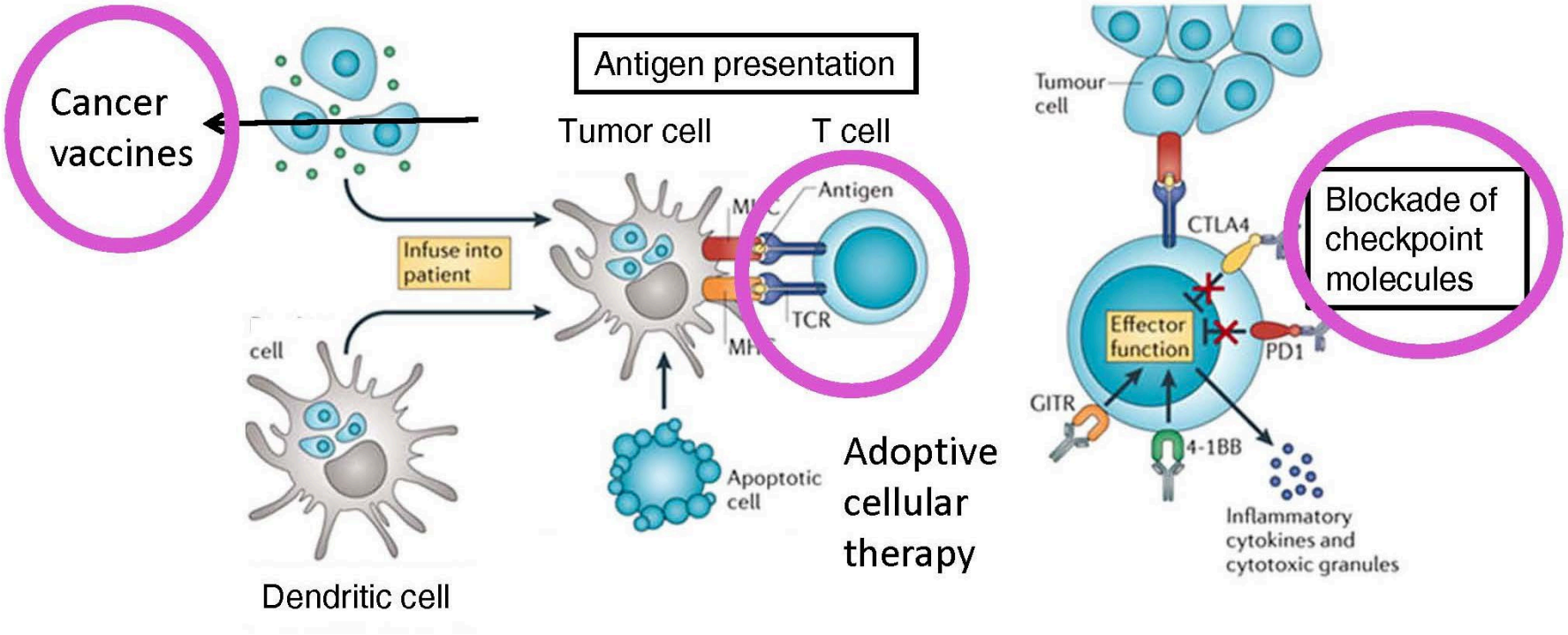
Current Biology

Anderson and Simon. Current Biology 2020

How cancers evade immune destruction

- Avoiding immune recognition
  - Loss of MHC molecules, tumor antigens
- Inhibiting immune responses
  - Engaging mechanisms that block immune activation (CTLA-4, PD-1)
  - Secreting immunosuppressive cytokines (e.g. TGF-β)
  - Activating regulatory T cells

Harnessing the immune system to combat cancer



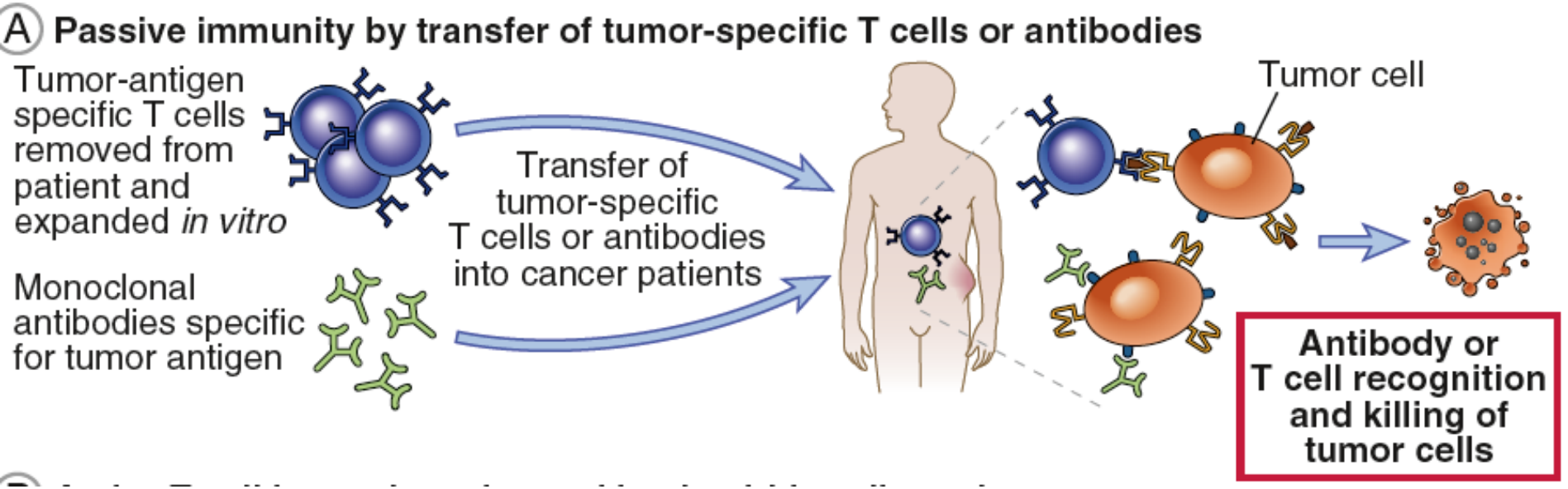
Vanneman and Dranoff, Nat Rev Can, 2012

Cancer vaccines

- Attempts to generate antibodies against antigens expressed on many tumors
  - Generally unsuccessful because the antigen is expressed on normal cells (hence induces tolerance), and antibodies do not provide effective protection

- Future attempts have to rely on generating CTLs specific for tumor-specific neoantigens
  - Identifying neoantigens in each tumor (personalized medicine): phase 3 trial of mRNA vaccine targeting mutations in melanoma launched recently
  - Challenges:
    - Preventing escape mutants
    - Have to overcome immune evasion mechanisms of tumor

Passive immunotherapy



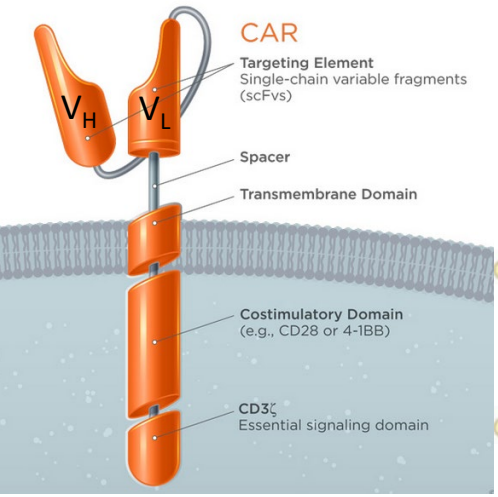
Antibody therapies

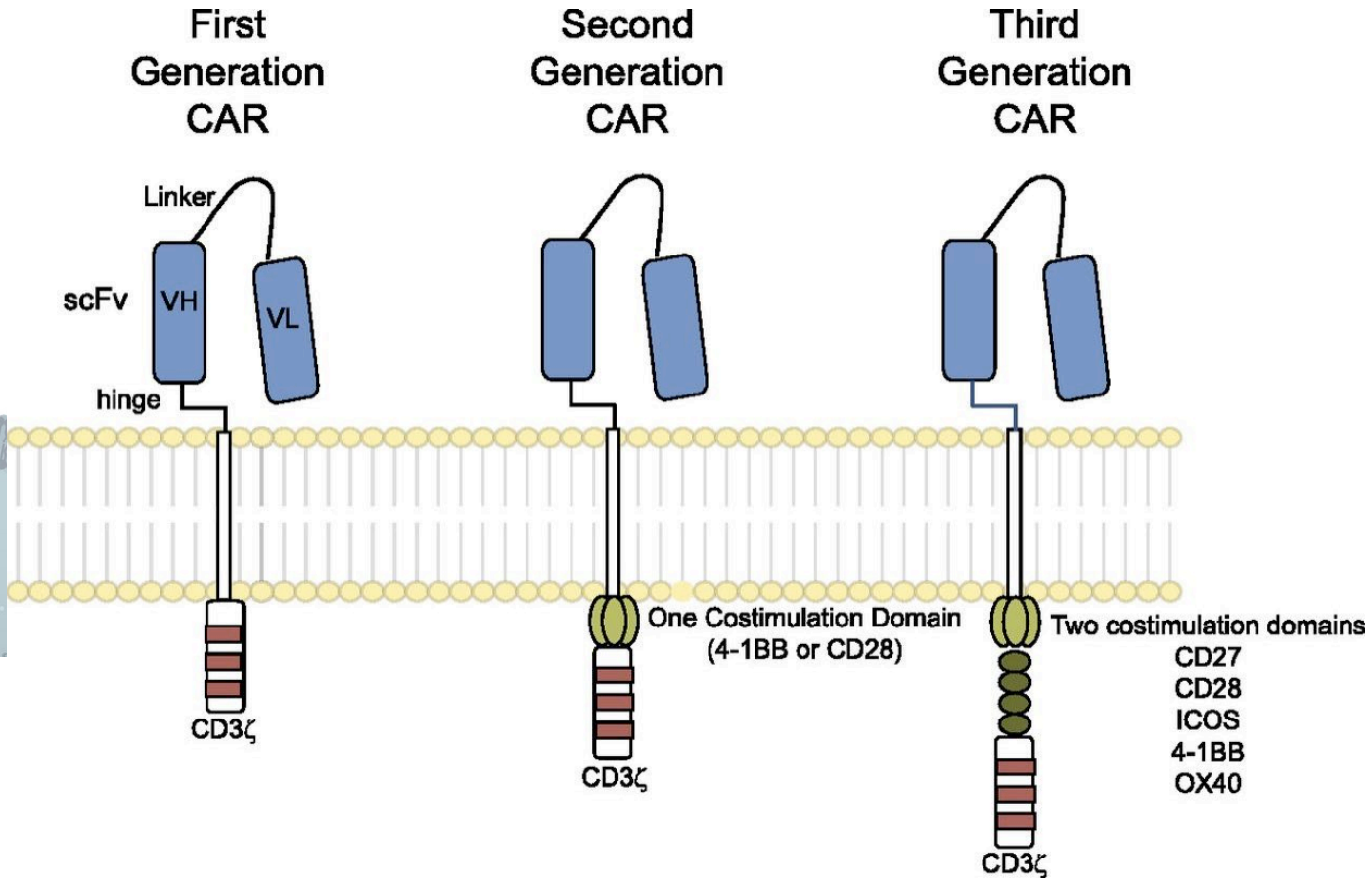
- Anti-tumor antibodies
  - Effective for many cancers (anti-CD20, -Her2)
- Antibody-drug conjugates
  - Payload is most often a drug that interferes with the cell cycle; limited by toxicities
- BiTE antibodies (bispecific T cell engagers)
  - Some approved; many in clinical development

Adoptive cell therapy

- Purify T cells (NK cells?) from blood or tumor infiltrate, expand in vitro, transfer into patients
- Major problem is low frequency of T cells specific for tumor antigens
- Attempts to overcome the problem by introducing tumor-specific antigen receptor into patient T cells
  - Problems with introducing TCR
  - Tumors often lose MHC expression

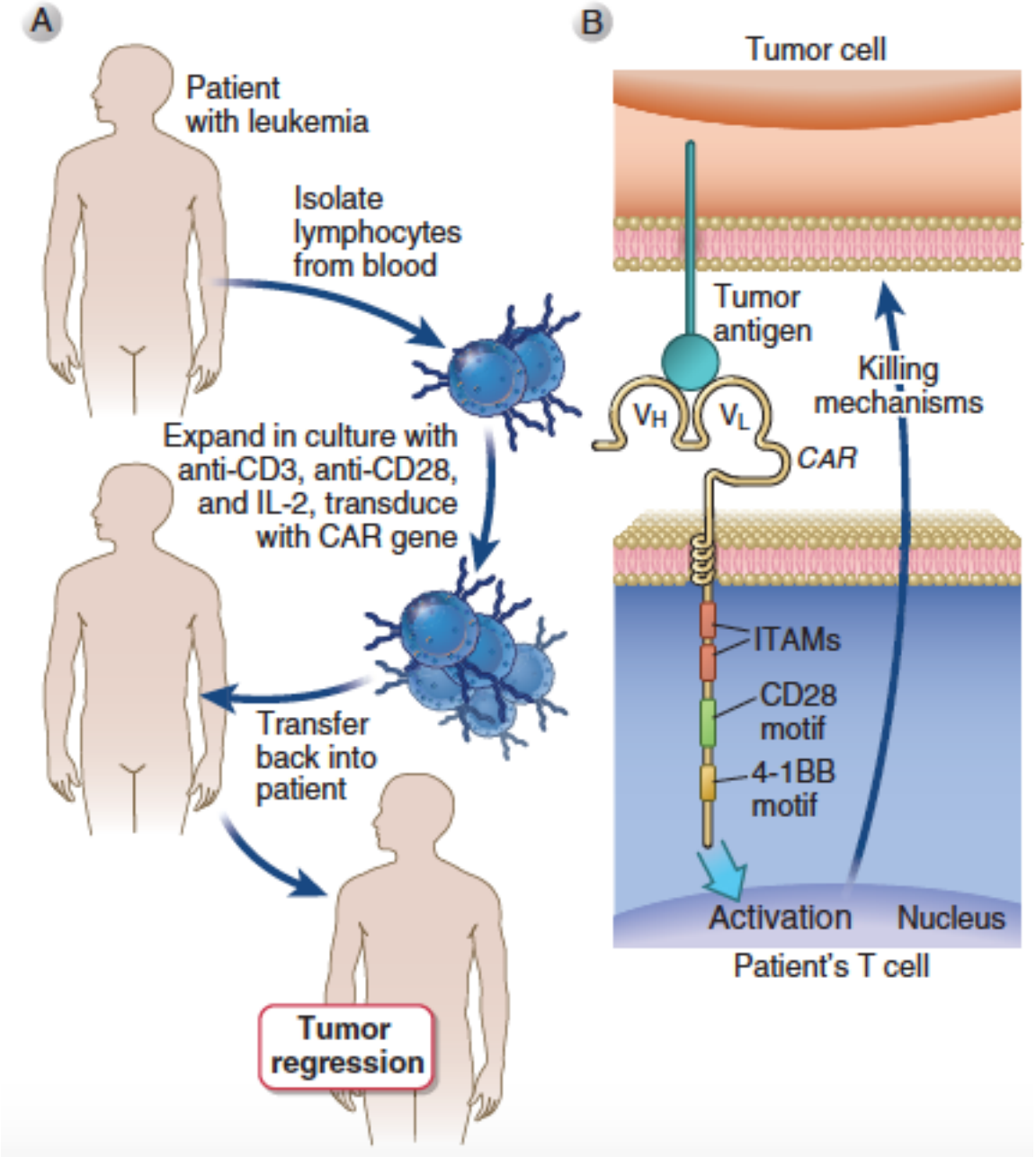
Development of chimeric antigen receptors





Attaching costimulatory signaling domains (CD28, 4-1BB) increases survival of CAR-T cells in vivo

Chimeric antigen receptor-T cell (CAR-T) therapy



- *Remarkable success in blood cancers: B cell leukemia (targeting CD19 or CD20), lymphomas, myeloma.*
- *CAR-T cells that target CD19/CD20 will deplete all B cells*
- *Not effective in solid tumors*

Limitations and challenges of CAR-T cell therapy

- Cytokine storm – many T cells respond to target antigen
  - Requires anti-inflammatory therapy (IL-6 + IL-1 blockade)
  - Unexplained neurotoxicity
- Resistance due to loss of target antigen
  - Simultaneous introduction of two CARs

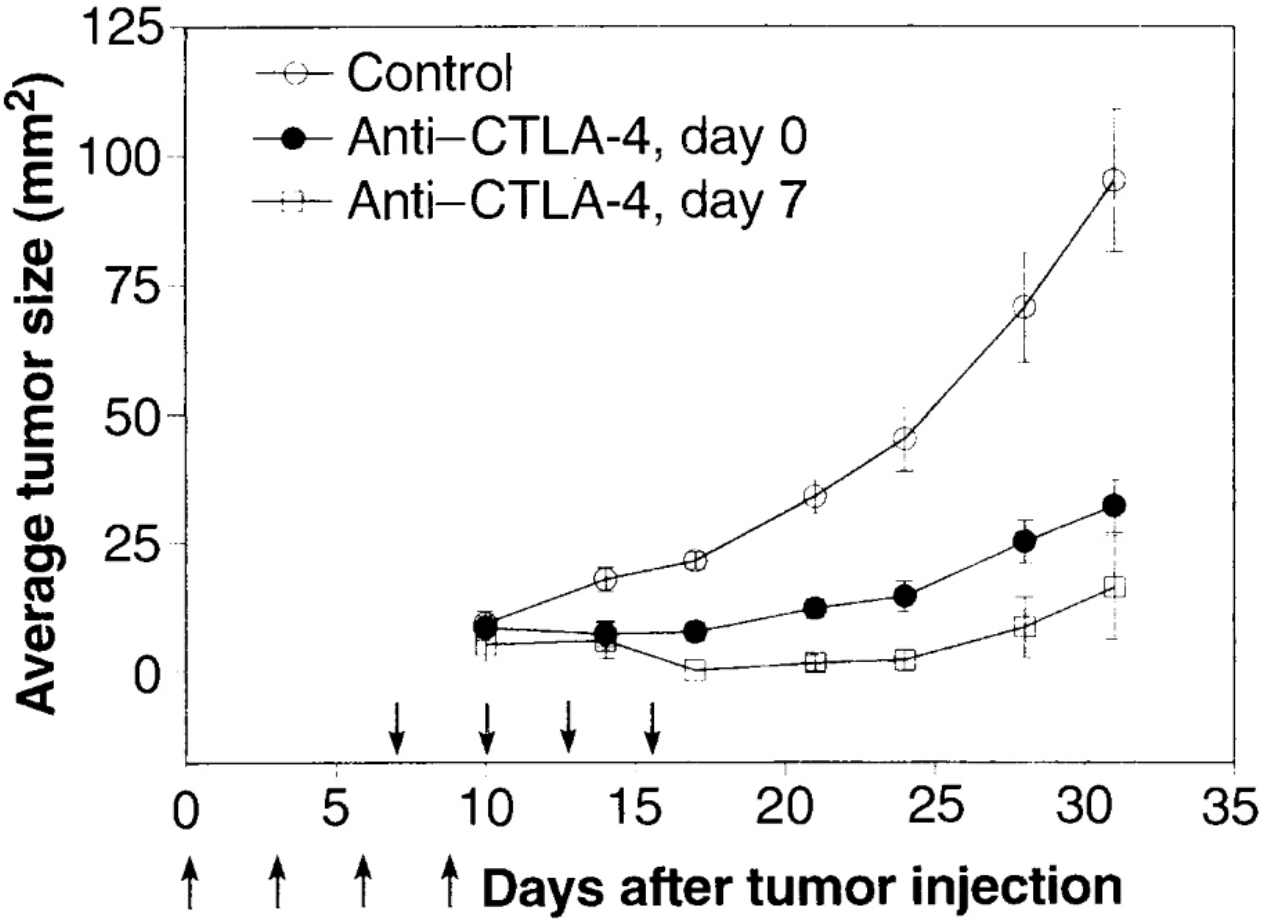
Limitations and challenges of CAR-T cell therapy

- Cytokine storm – many T cells respond to target antigen
- Resistance due to loss of target antigen
- T cells acquire inhibitory receptors
  - Phenomenon of "exhaustion"
  - May be overcome with anti-PD1 antibody or gene editing
- Not yet successful in solid tumors
  - Selection of tumor antigen
  - Problem of T cells entering tumor site
- Technical challenges, high cost

Immune checkpoints

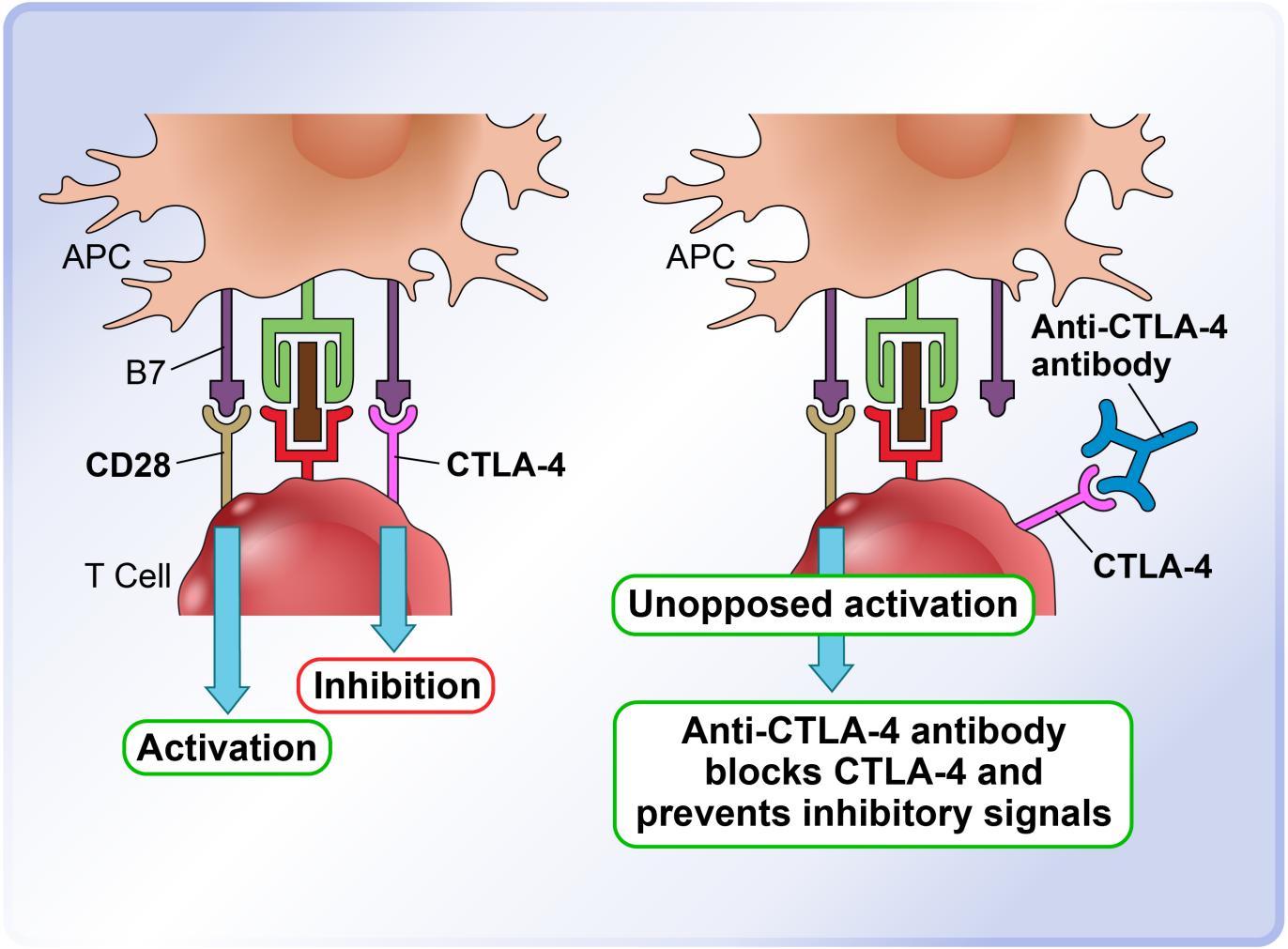
- Inhibitory receptors on T cells block activation
- CTLA-4: competes with CD28, reduces costimulation
- PD-1: activates phosphatase, blocks kinase-dependent signals from CD28 and TCR
- Many others described

Blocking CTLA-4 promotes tumor rejection: CTLA-4 limits immune responses to tumors



Administration of antibody that blocks CTLA-4 in tumor-bearing mouse leads to tumor regression

Checkpoint blockade: Removing the brakes on the immune response



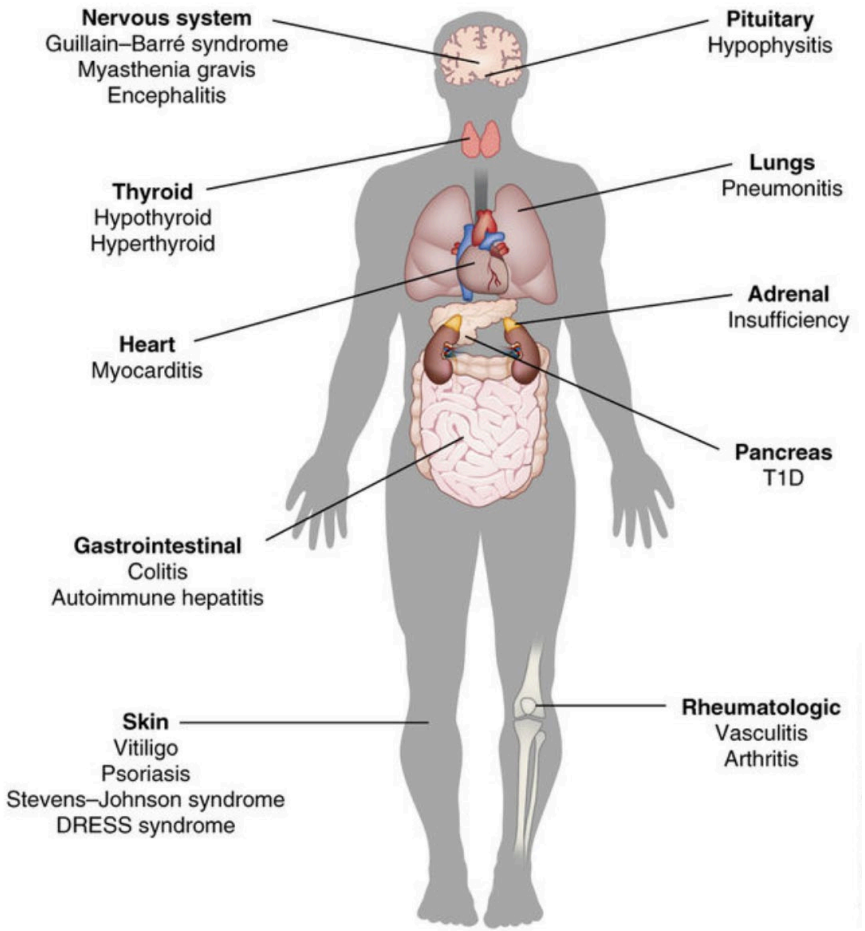
Even more impressive results with anti-PD-1 in cancer patients

Adverse effects of checkpoint blockade

- Inevitable consequence of blocking essential mechanisms of self-tolerance:

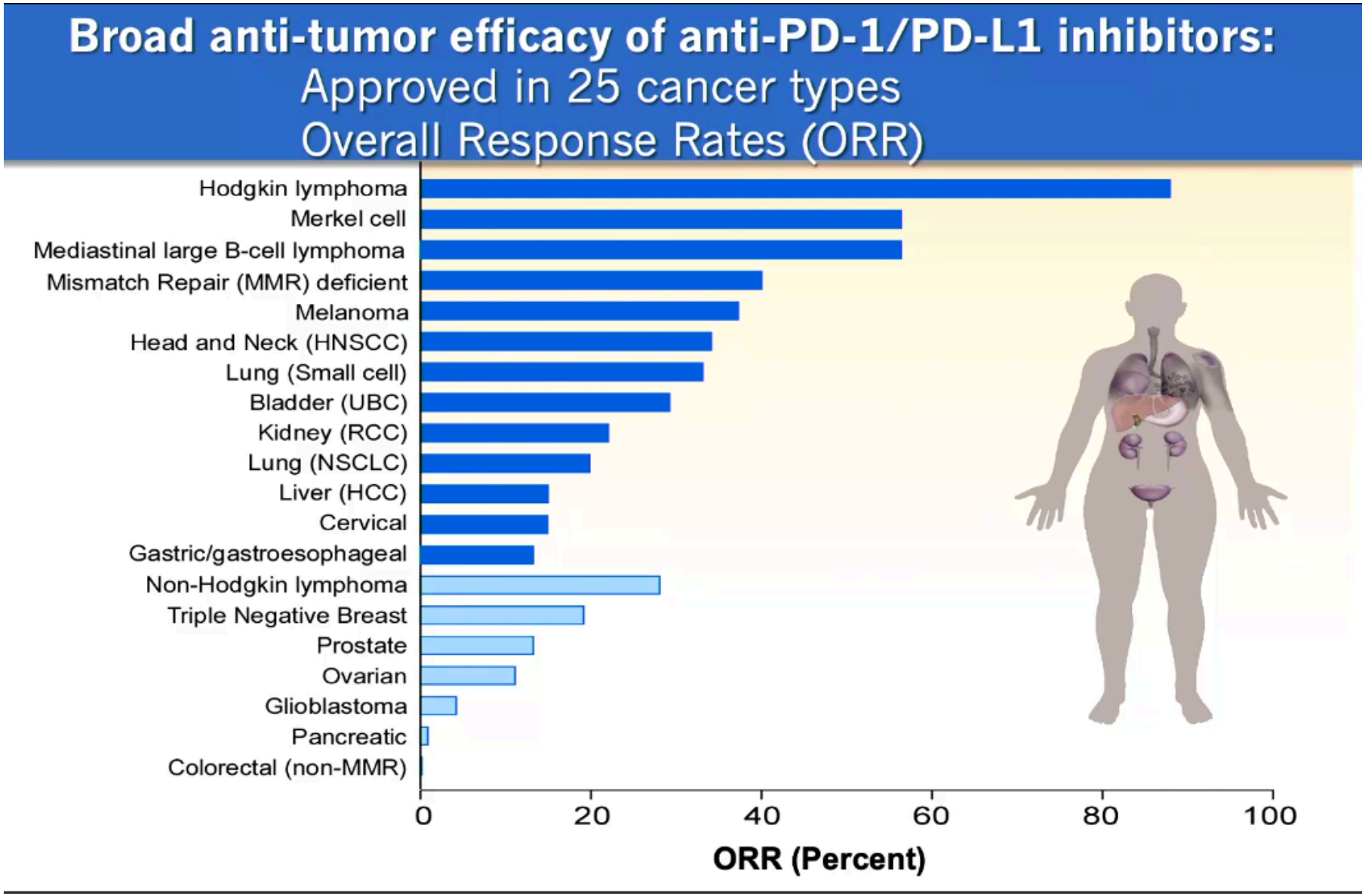
Adverse effects of checkpoint blockade

- **Inevitable consequence of blocking essential mechanisms of self-tolerance:**
  - **Autoimmune reactions**



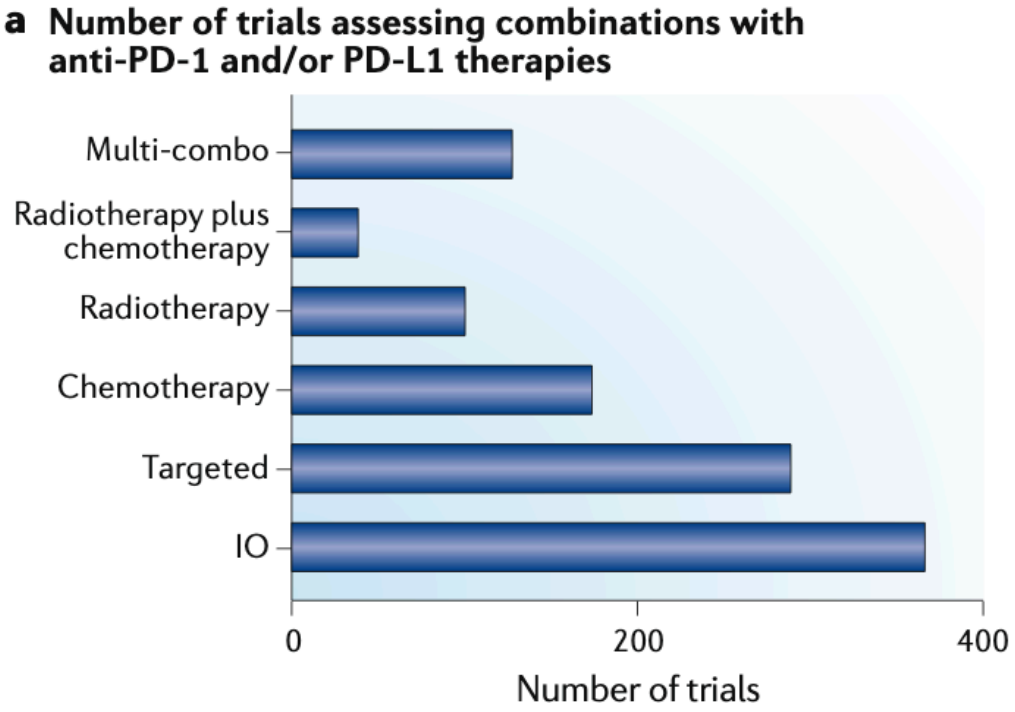
From: June, Warshauser and Bluestone Nat Med 2017

Response to checkpoint blockade



Combination strategies for cancer immunotherapy

- Combinations of checkpoint blockers or one checkpoint blocker with another cancer treatment



From Galon and Bruni. Nat Rev Drug Discov 18:197, 2019