ADVANCES IN Cancer IMMUNOTHERAPY™

Basic Principles of Cancer Immunotherapy

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

No relevant financial relationships to disclose

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

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Why does the immune system fail to eliminate cancer?

Cancer cells grow progressively in immunocompetent hosts without evidence of systemic T cell exhaustion or anergy.

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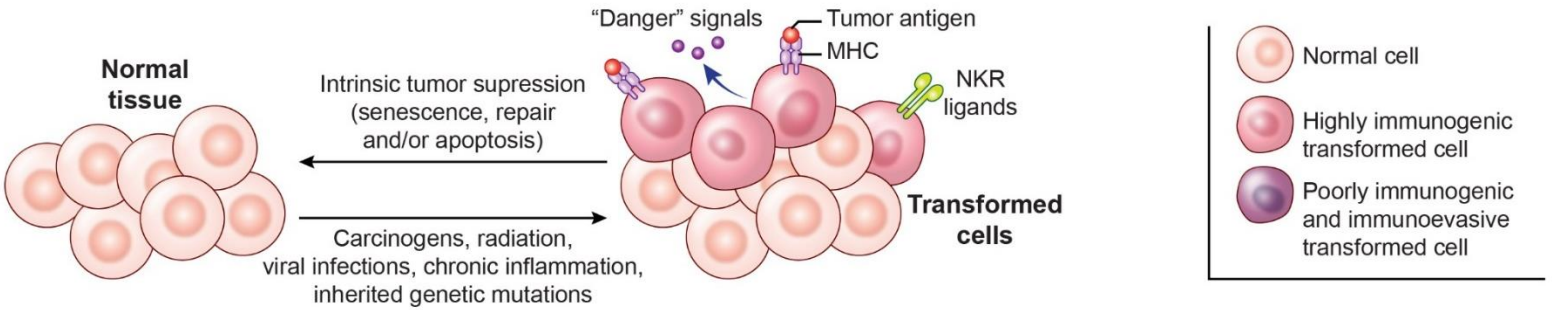
The 3 Es of cancer immunoediting



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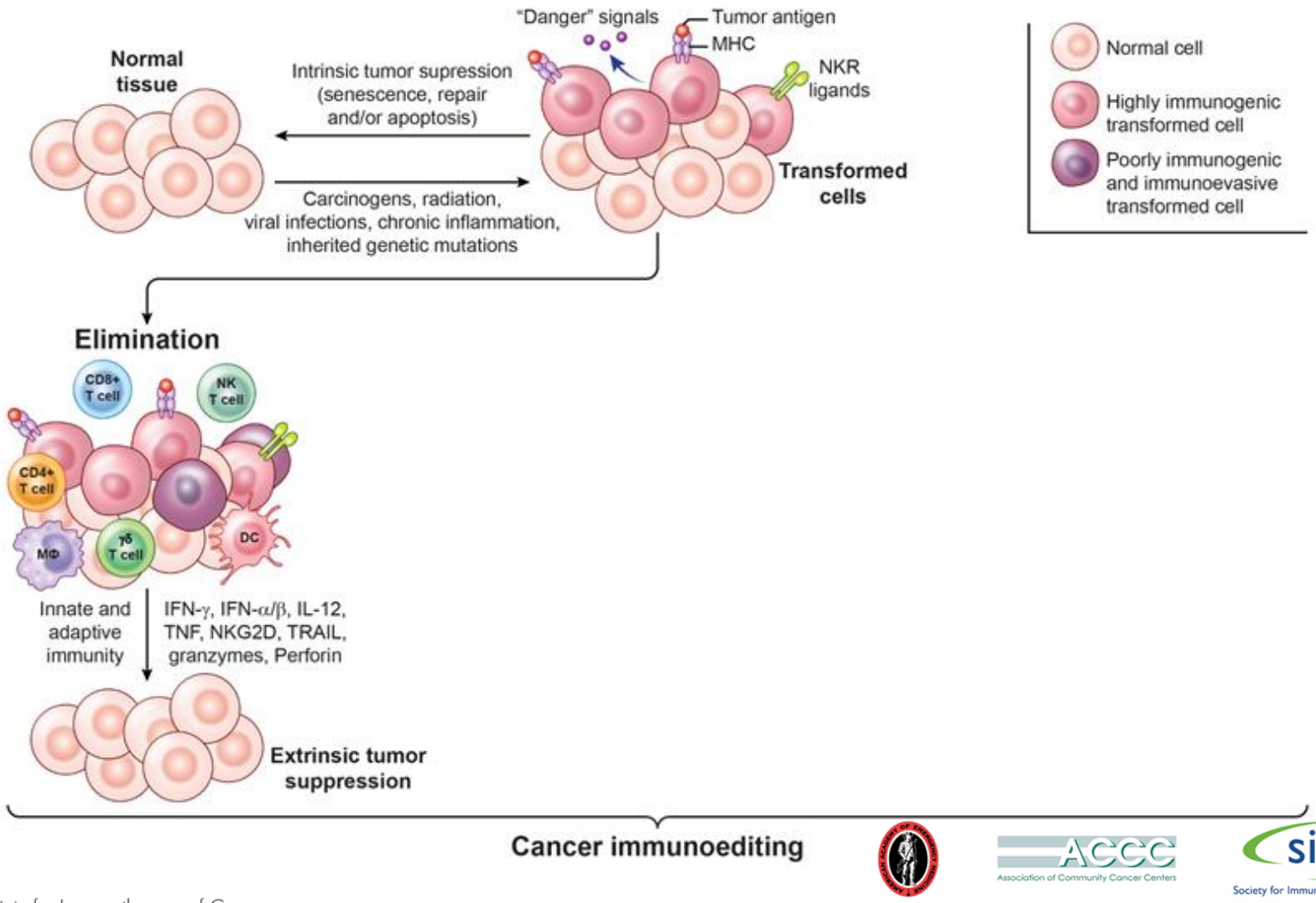
The 3 Es of cancer immunoediting



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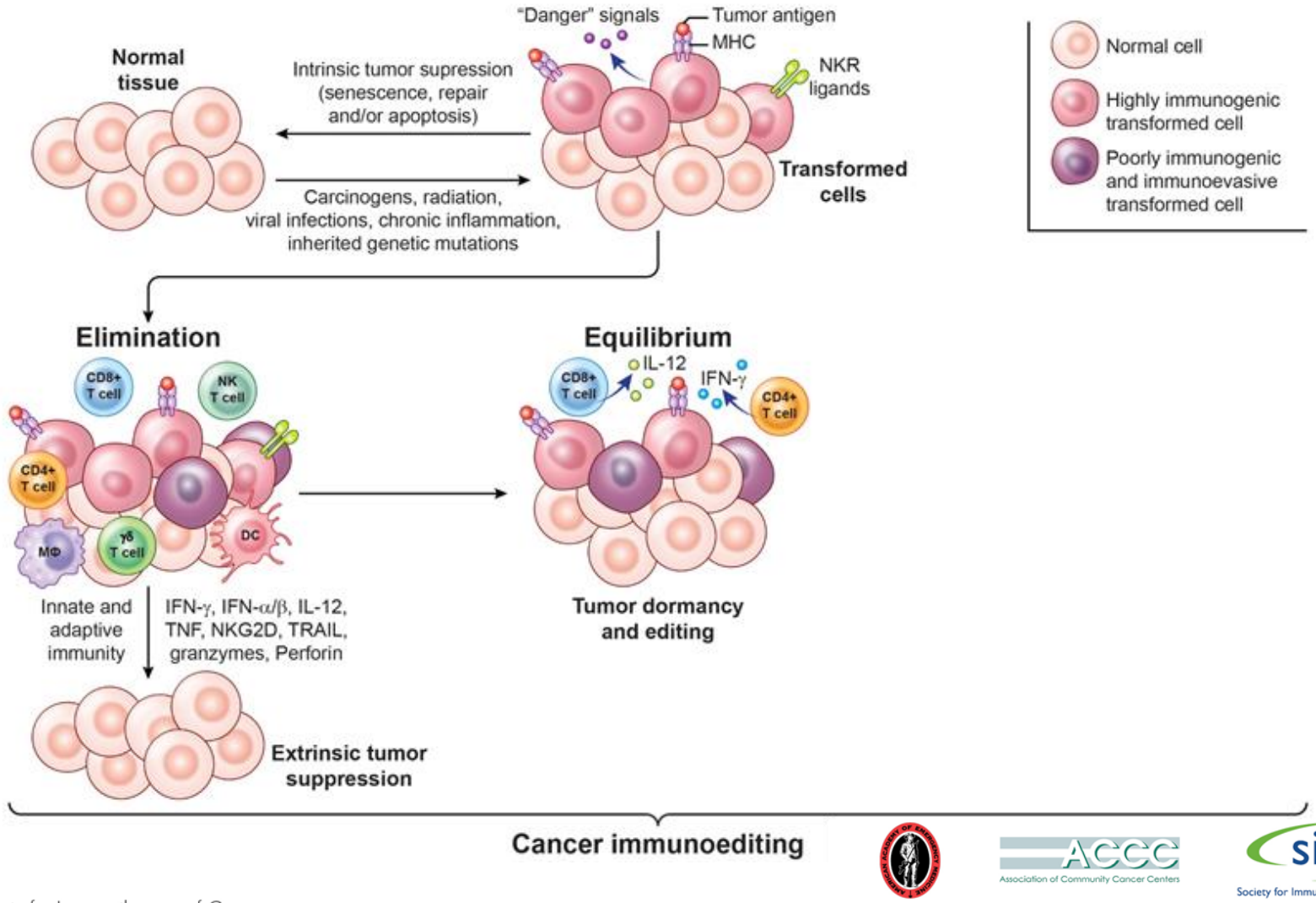

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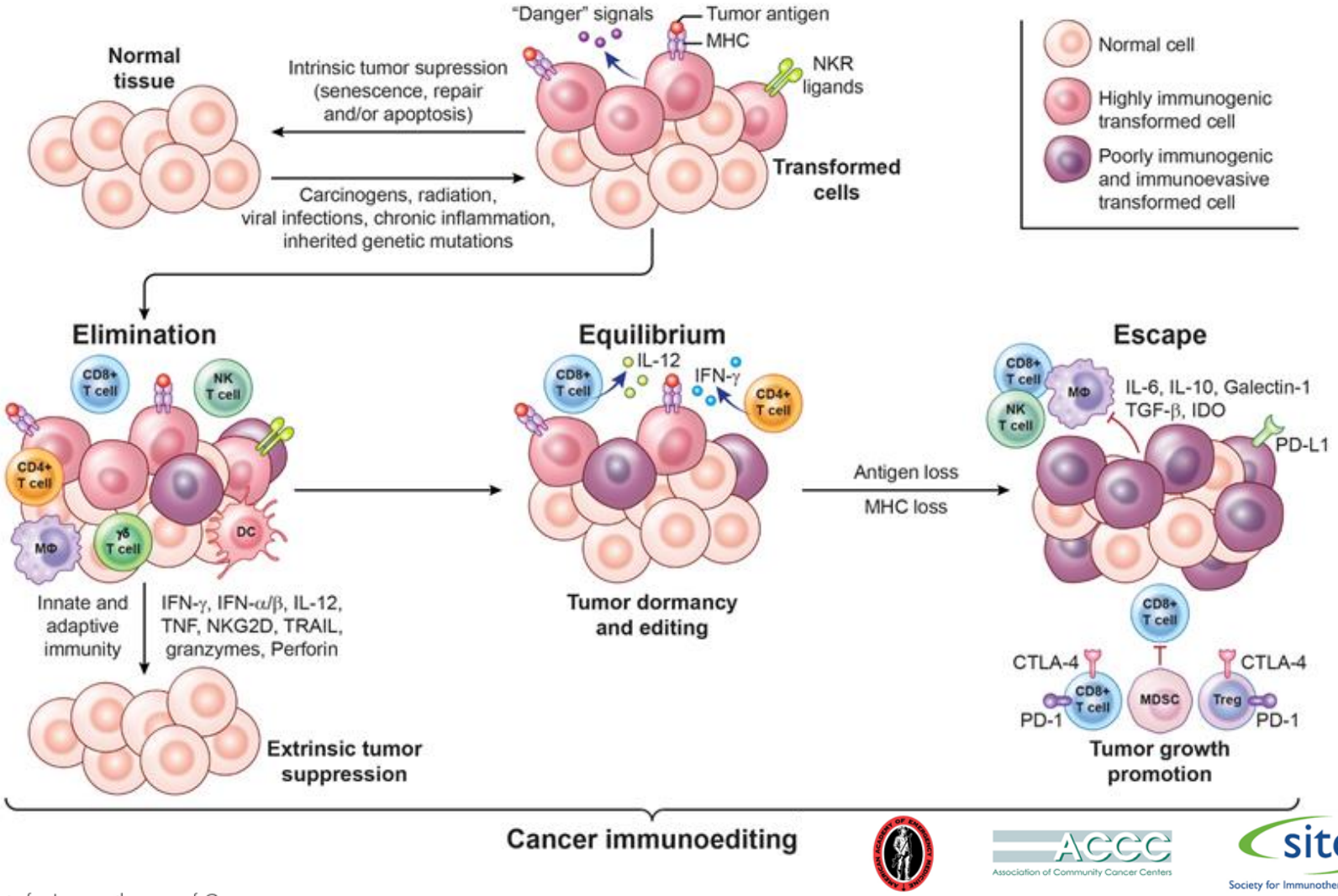
The 3 Es of cancer immunoediting



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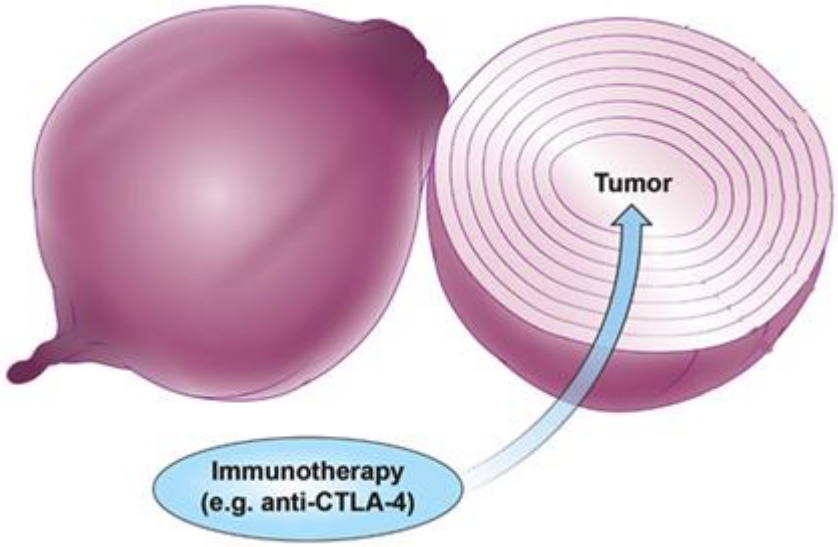
Multi-layered immunosuppression

- Tumors insulate themselves with layers of different immunosuppression
- Overcoming these multiple layers represents a daunting challenge for tumor-specific T cells
- **The goal of Immunotherapy is to overcome these layers restoring the capacity of T cells to eradicate the tumor**



Fundamental types of immunotherapy

Positive

Turning the immune system on so it can punch through the inhibitory layers better

‘Negative’

Making the immune response more effective by removing Layers of inhibition

Targeting

Keeping the immune Response specific to tumor tissue

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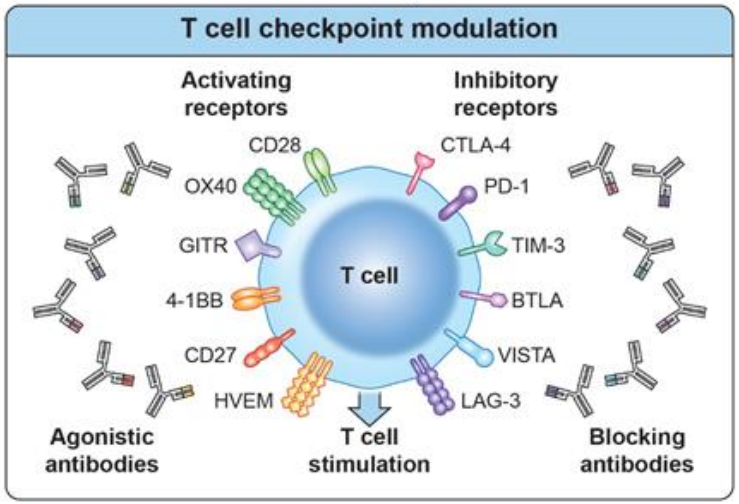
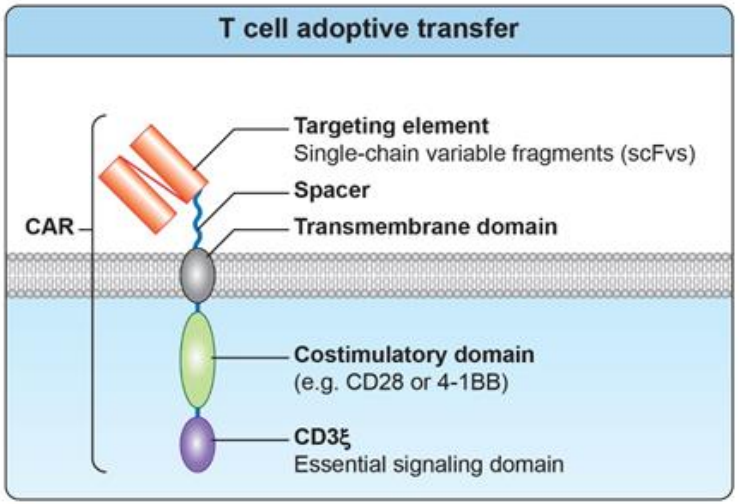
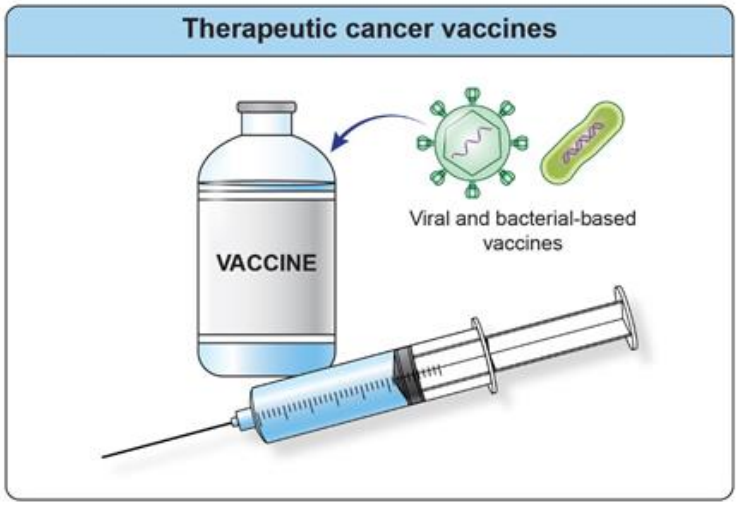
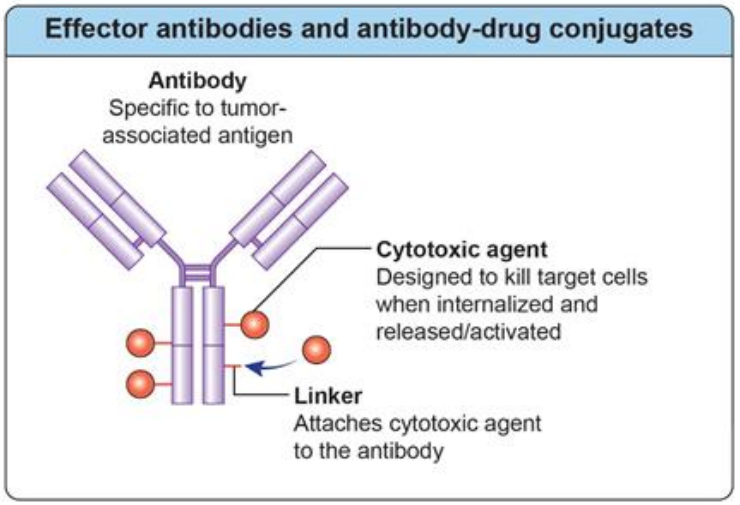
Major methods to achieve immunotherapy









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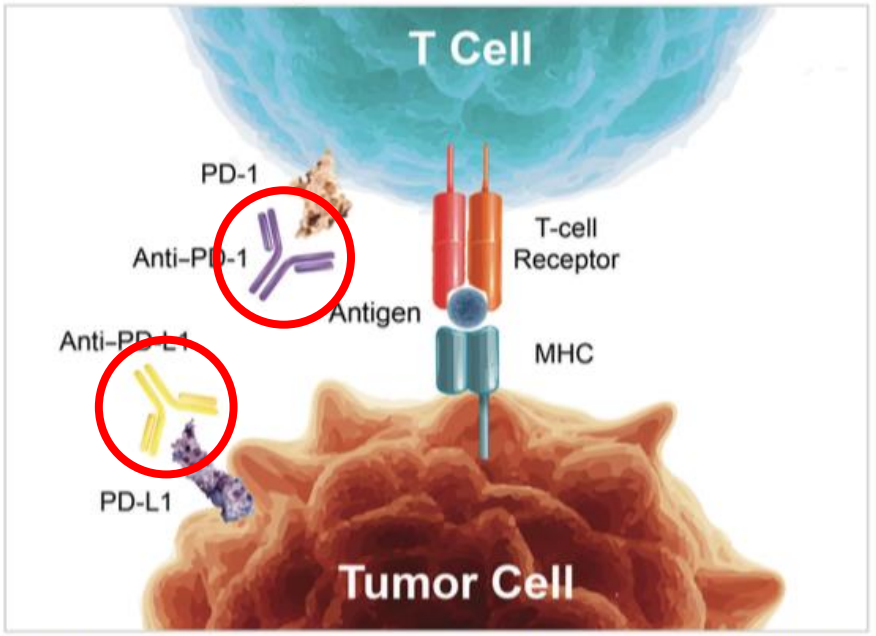
T cell checkpoint modulation/blockade

- T cell function is modulated by a large number of pathways in both **positive** and **negative** directions
- These pathways can be altered by addition of inhibitory or agonistic antibodies
- Checkpoint blockade typically works by taking the brakes off existing immune responses

FIGURE. Immune Checkpoint Blockade



MHC indicates major histocompatability complex. A major checkpoint, mediated by the interaction between PD-1 on T cells and its ligand, PD-L1, on tumor cells, has been the focus of many clinical trials. Immune checkpoint blockade has changed the treatment landscape of several solid tumors. Source: Drake CG, Lipson EJ, Brahmer JR. Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer.
Source: *Nat Rev Clin Oncol.* 2014 Jan;11(1):24-37.

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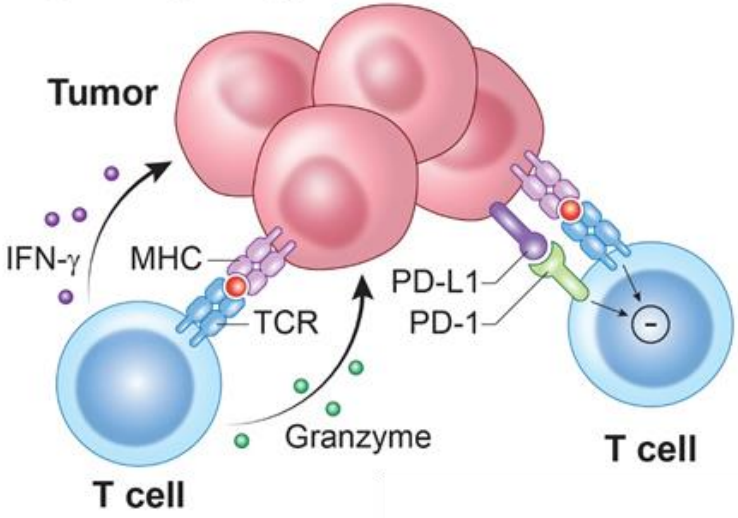
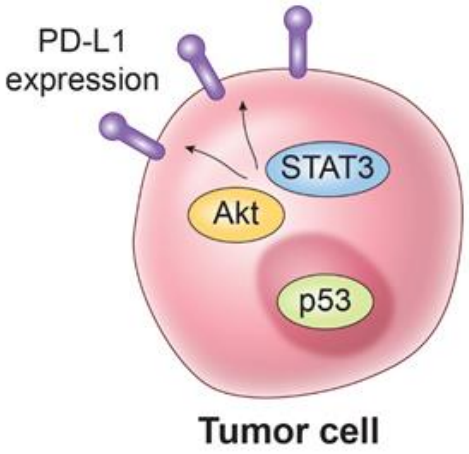
PD-1: PD-L1 inhibitory pathway

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
- Many cells within the tumor microenvironment express PD-L1/PD-L2 allowing for the suppression of T cell activation
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. TIL production of IFN-γ
  2. Oncogenic signaling pathways





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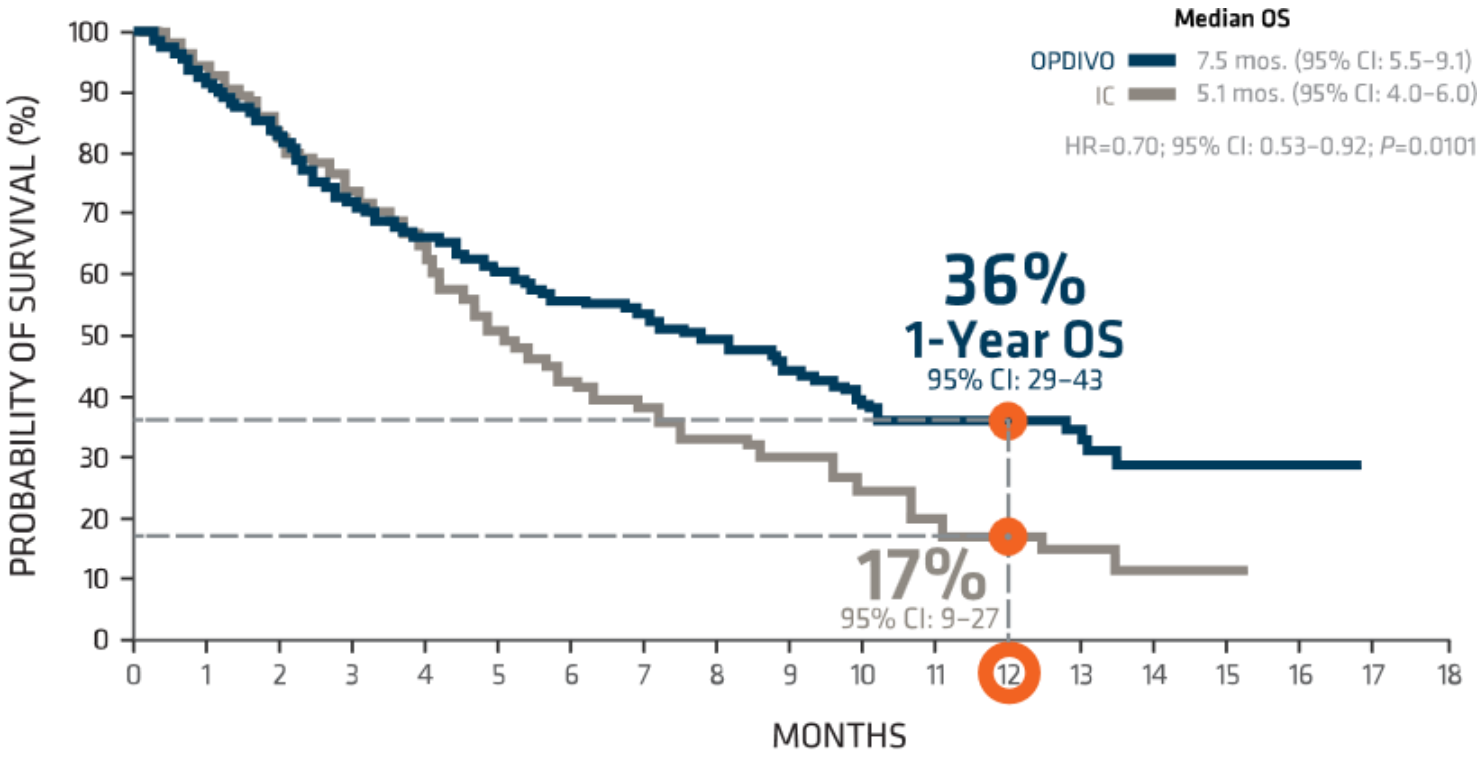
Anti-PD1 antibodies were approved for metastatic melanoma in 2014



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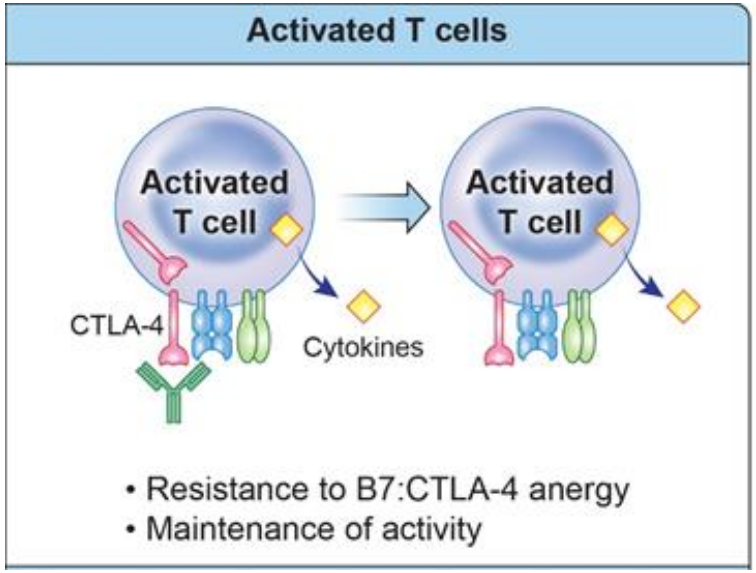
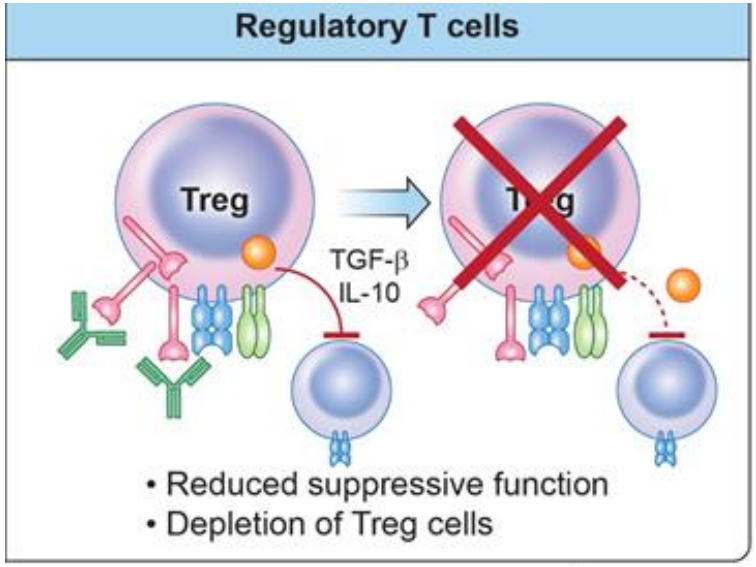
CTLA-4 inhibitory pathway





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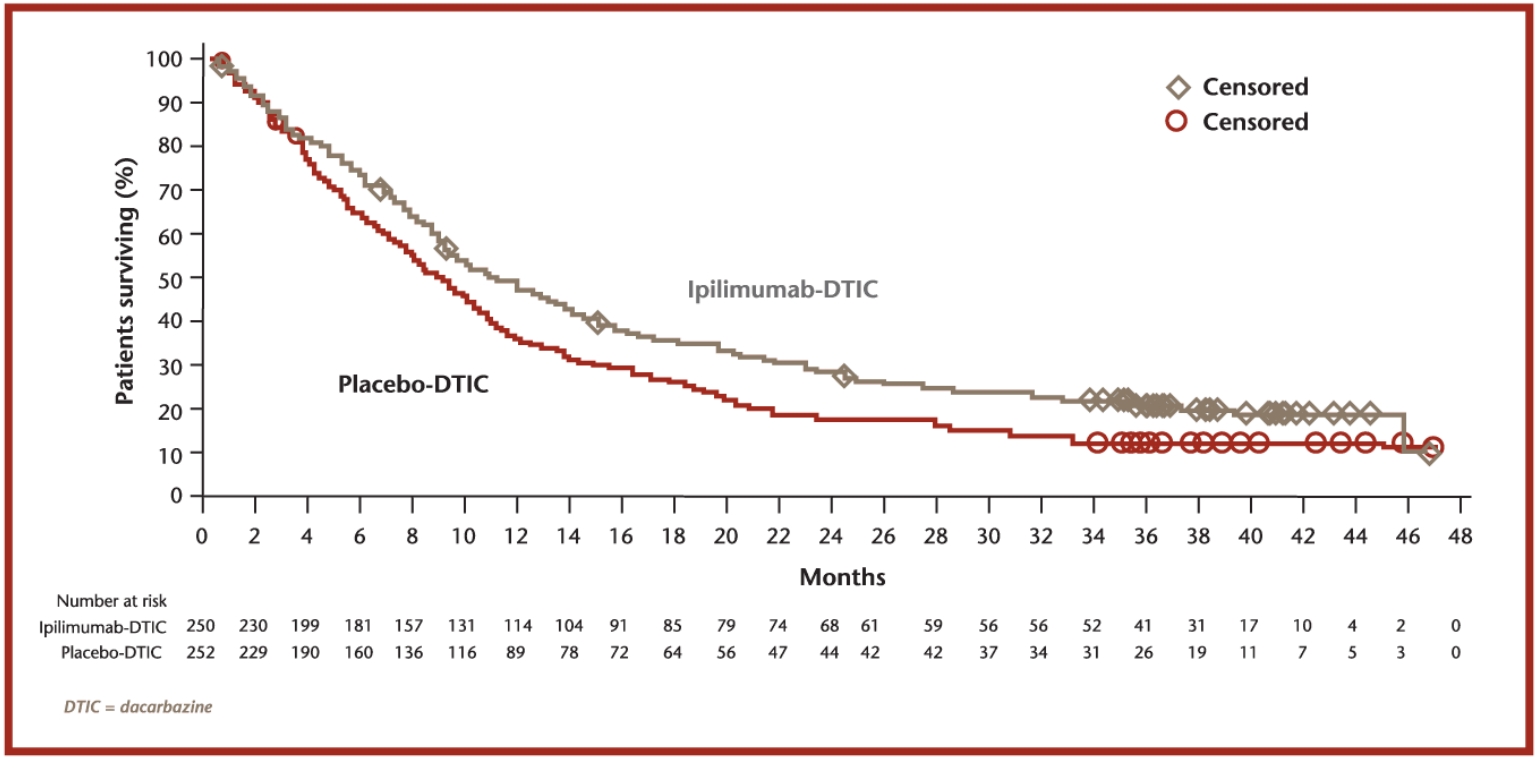
Ipilimumab (human anti-CTLA-4) was approved for the treatment of metastatic melanoma by FDA in 2010

Figure 5. Overall survival for a phase III study of DTIC plus ipilimumab versus DTIC plus placebo in previously untreated metastatic melanoma patients[52]



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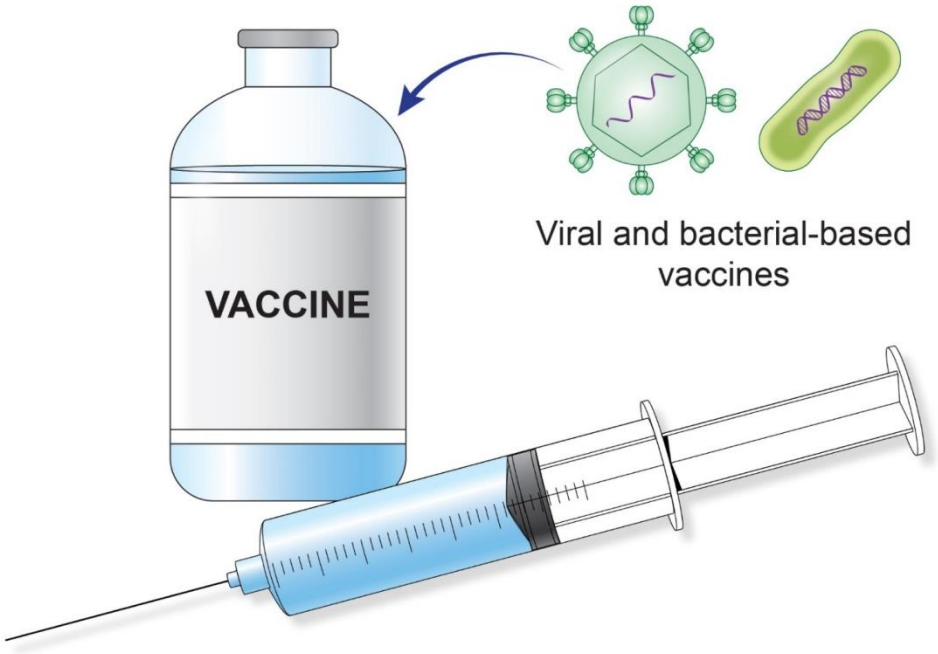
Therapeutic cancer vaccines

- Not all tumors have existing anti-tumor immune responses
- In these immunologically silent tumors, 'negative' immunotherapeutic methods typically fail
- The goal of therapeutic cancer vaccines is to induce new anti-tumor immunity



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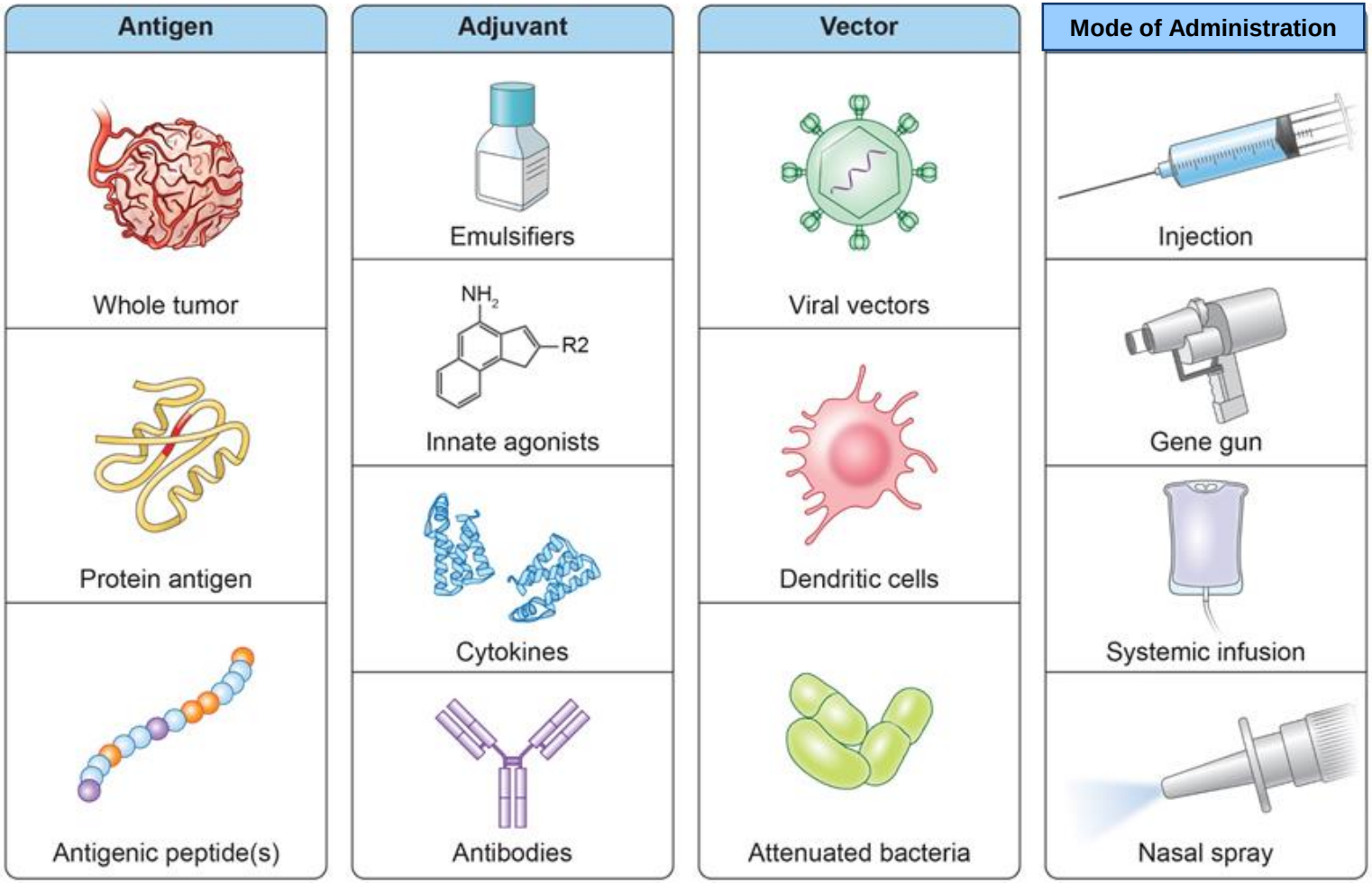
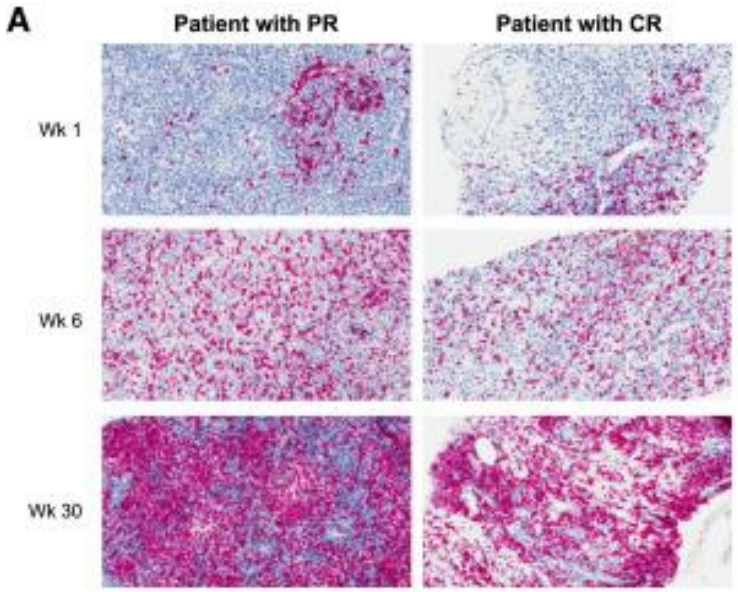
Components of a cancer vaccine

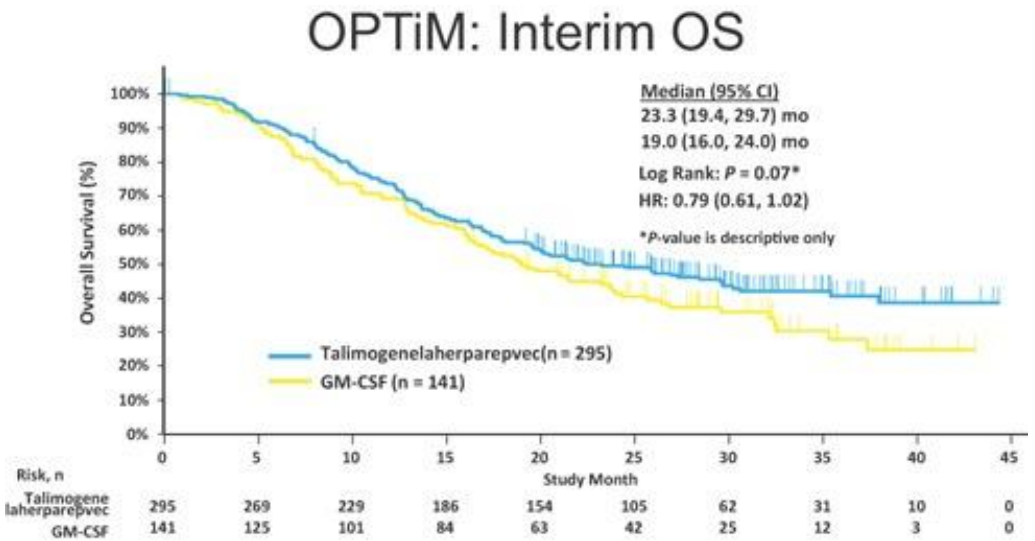


Oncolytic Herpes Simplex was approved for late stage melanoma in 2015



= CD8 T cells

Rivas et al Cell 2017



Corrales L and Gajewski TF

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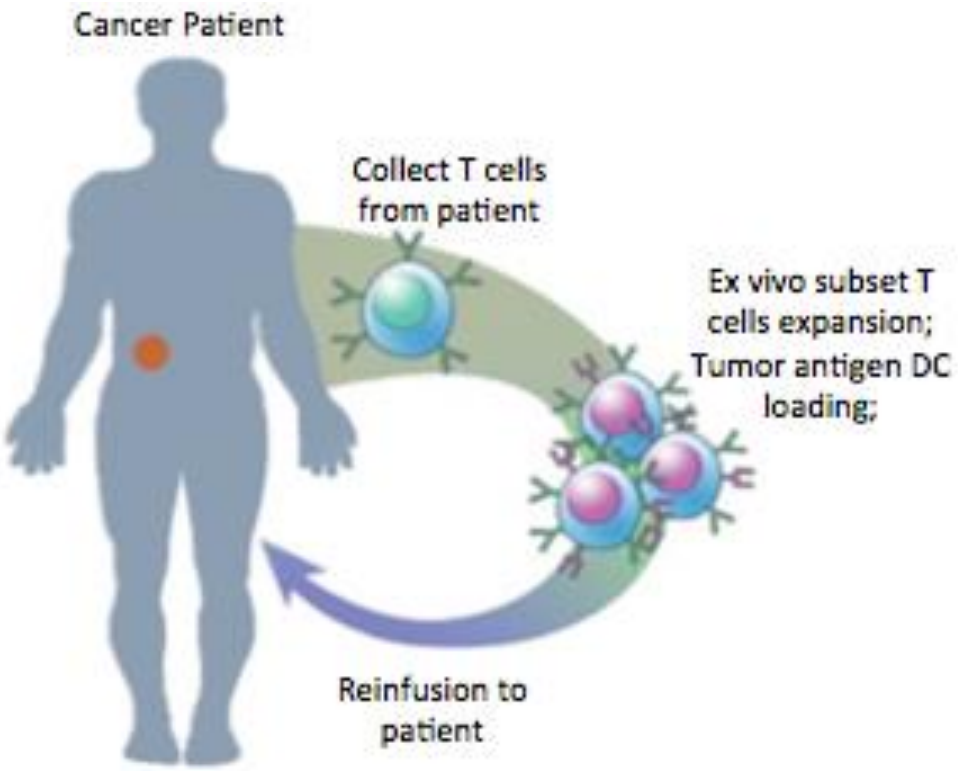
T cell Adoptive Transfer Therapy (ACT)

- ACT takes T cells from a patient, expands them to large numbers *ex vivo*, and then reinfuses them back into the patient to elicit anti-tumor effects

- The goal of ACT is to win the numbers game and overwhelm the tumor with massive numbers of T cells



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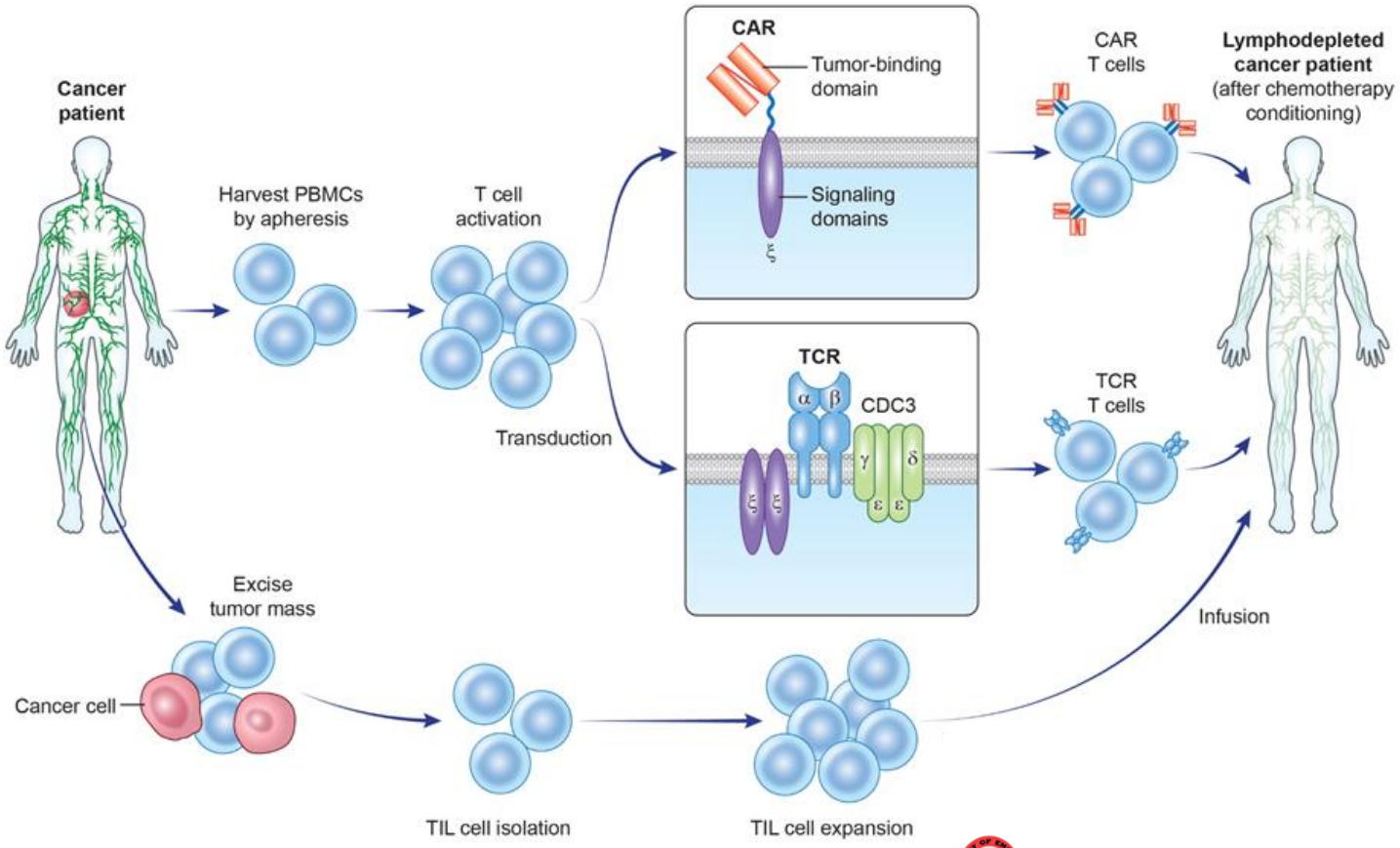
Adoptive T cell therapy can involve engineered (CAR, TCAR) or patient-derived (TIL, PBMC) T cells



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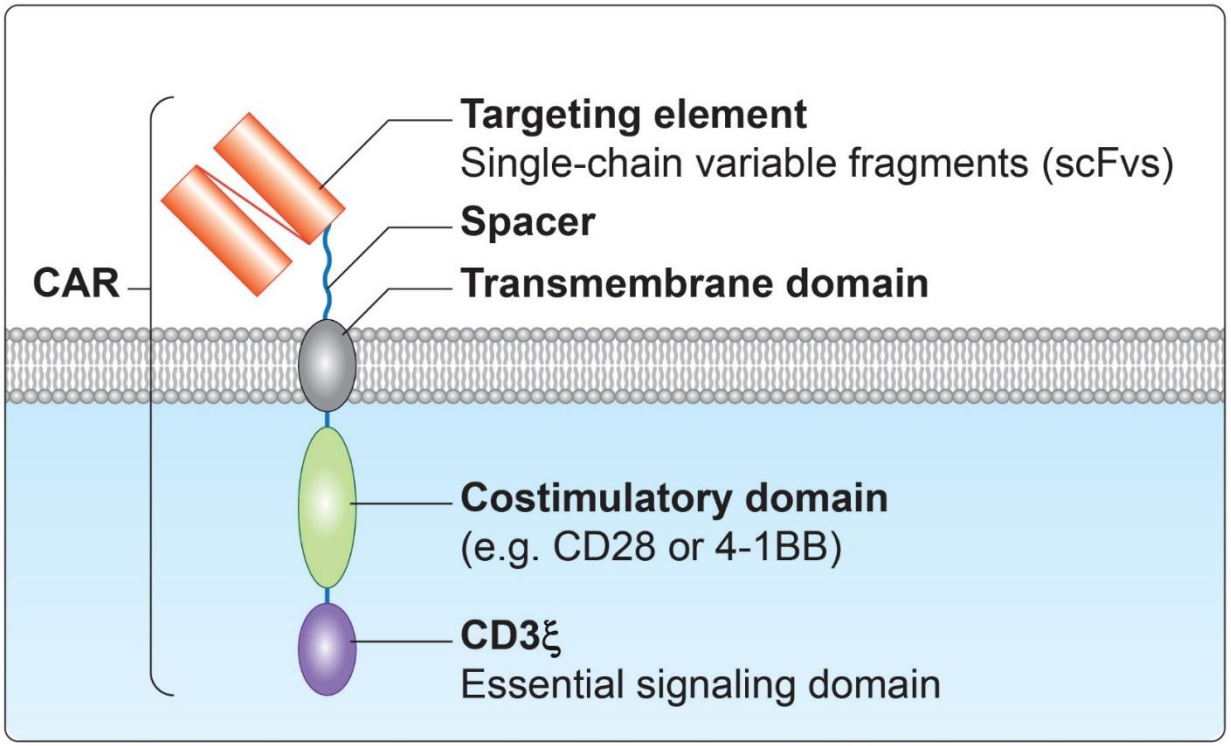
CAR based T cell adoptive transfer



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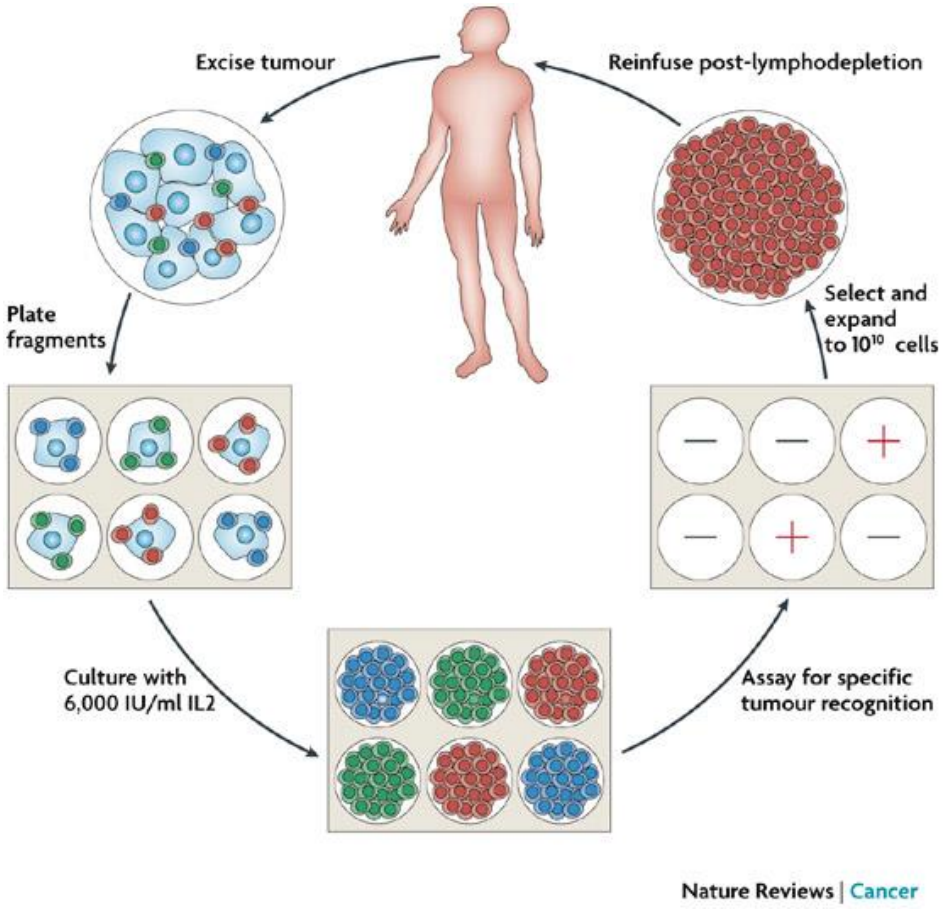
TIL based T cell adoptive transfer



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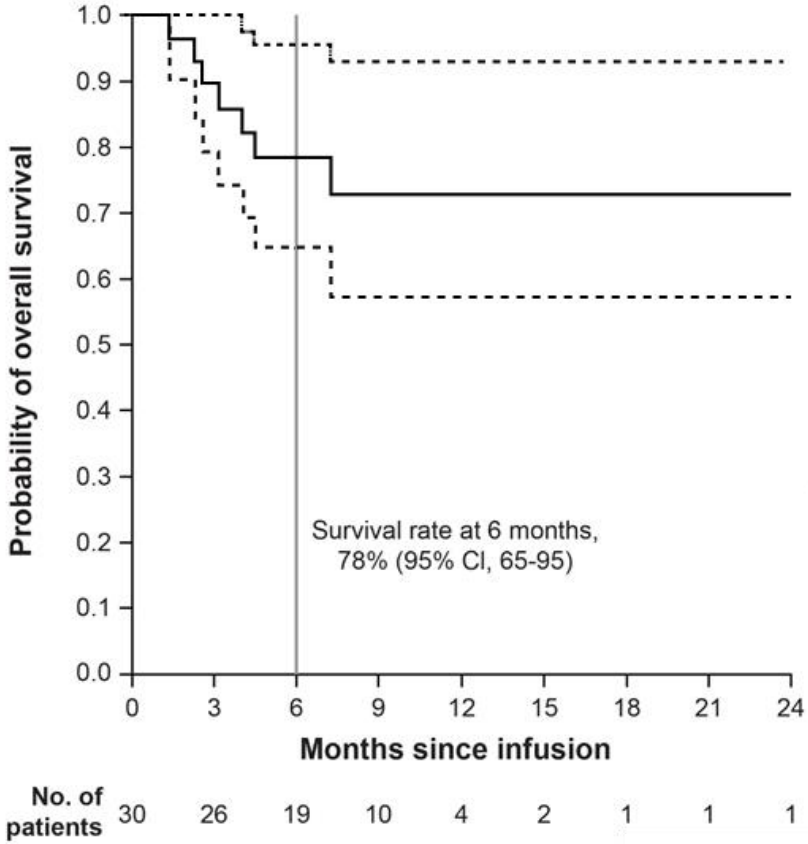
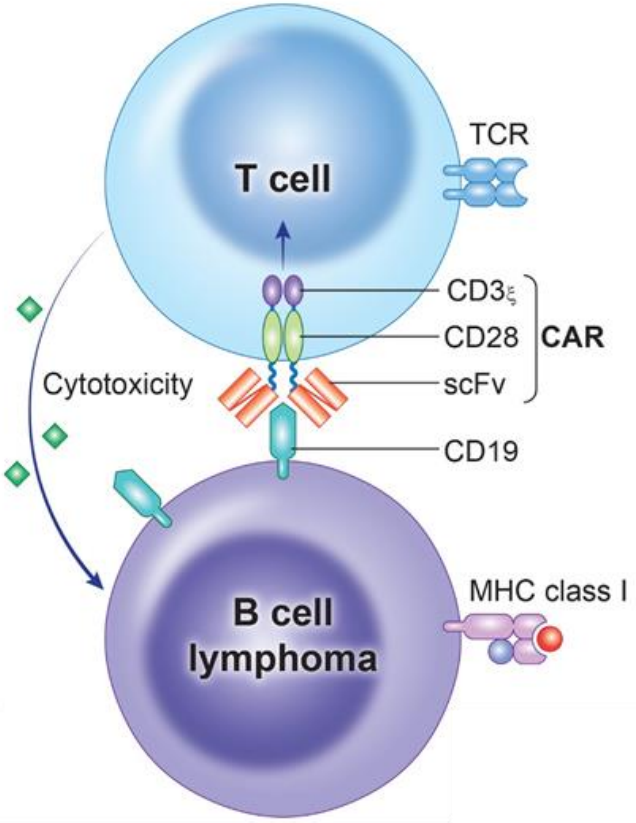
Effective treatment of relapsed B cell ALL with CD19 CAR T cell therapy





Maude S, Frey N, Shaw P, Aplenc R, Barrett D, Bunin N, Chew A, Gonzalez V, Zheng Z, Lacey S, et al. 2014. Chimeric antigen receptor T cells for sustained remissions in leukemia. The New England Journal of Medicine. 374(10): 998.

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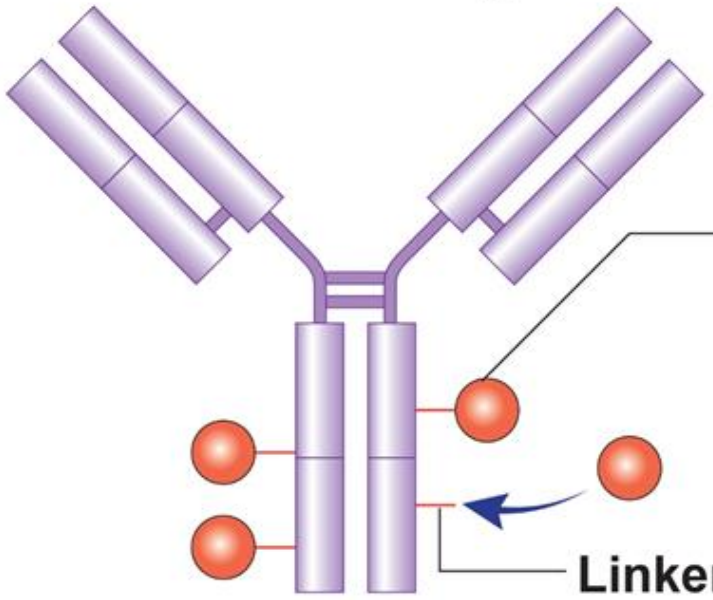
Effector antibodies and antibody-drug conjugates (ADCs)



Antibody
Specific to tumor-associated antigen

Radiolabeled or Cytotoxic agent
Designed to kill target cells when internalized and released or activated

Linker
Attaches cytotoxic agent to the antibody

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Key ADC / antibody principles

- **Specificity:** The more tumor specific the target antigen is, the higher the agent can be dosed without limiting toxicity

- **Internalization:** The target tumor surface protein must internalize to deliver the toxin - it should do so frequently and to a suitable endosomal compartment.

- **Stability:** The toxin must remain inert and tethered to the antibody until it is delivered to its target cell.

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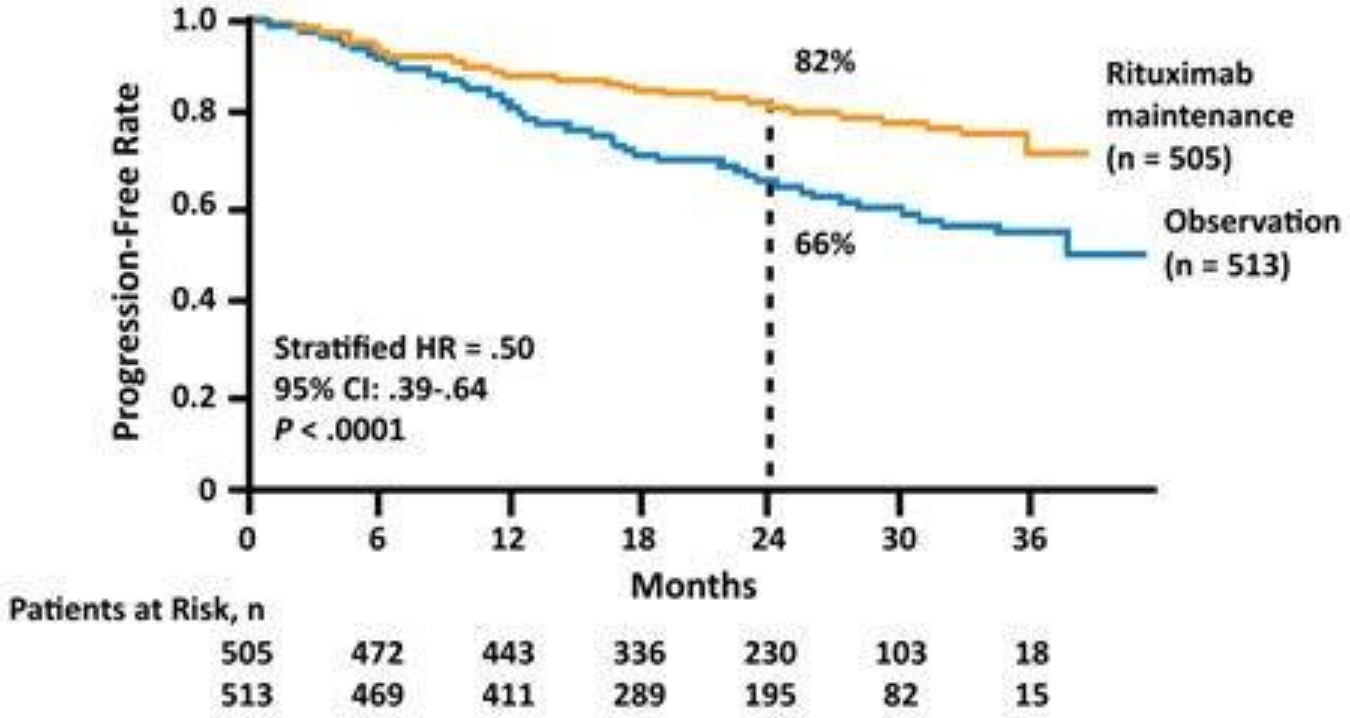
Rituximab maintenance improves survival of NHL following therapy



Medscape

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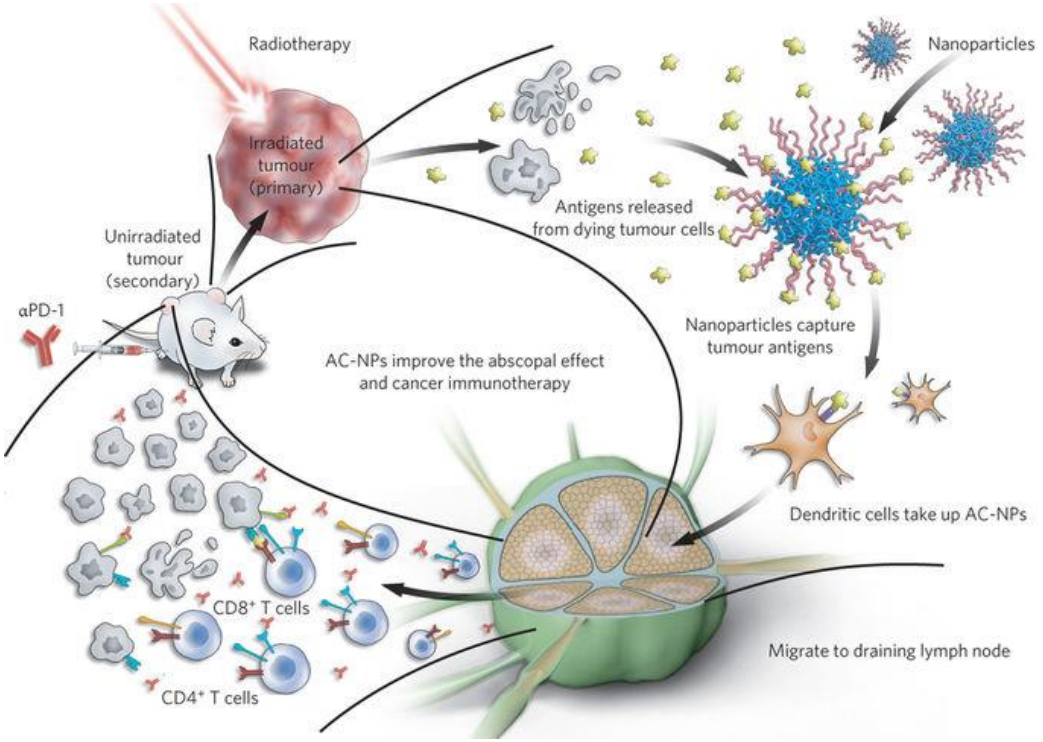
The Abscopal effect (Hidden Immunotherapy)

- Localized treatment of a tumor causes/evokes reduction of distant ones
- Caused by tumor cells killed by initial treatment priming secondary anti-tumor responses
- Effectively acting as positive immunotherapy



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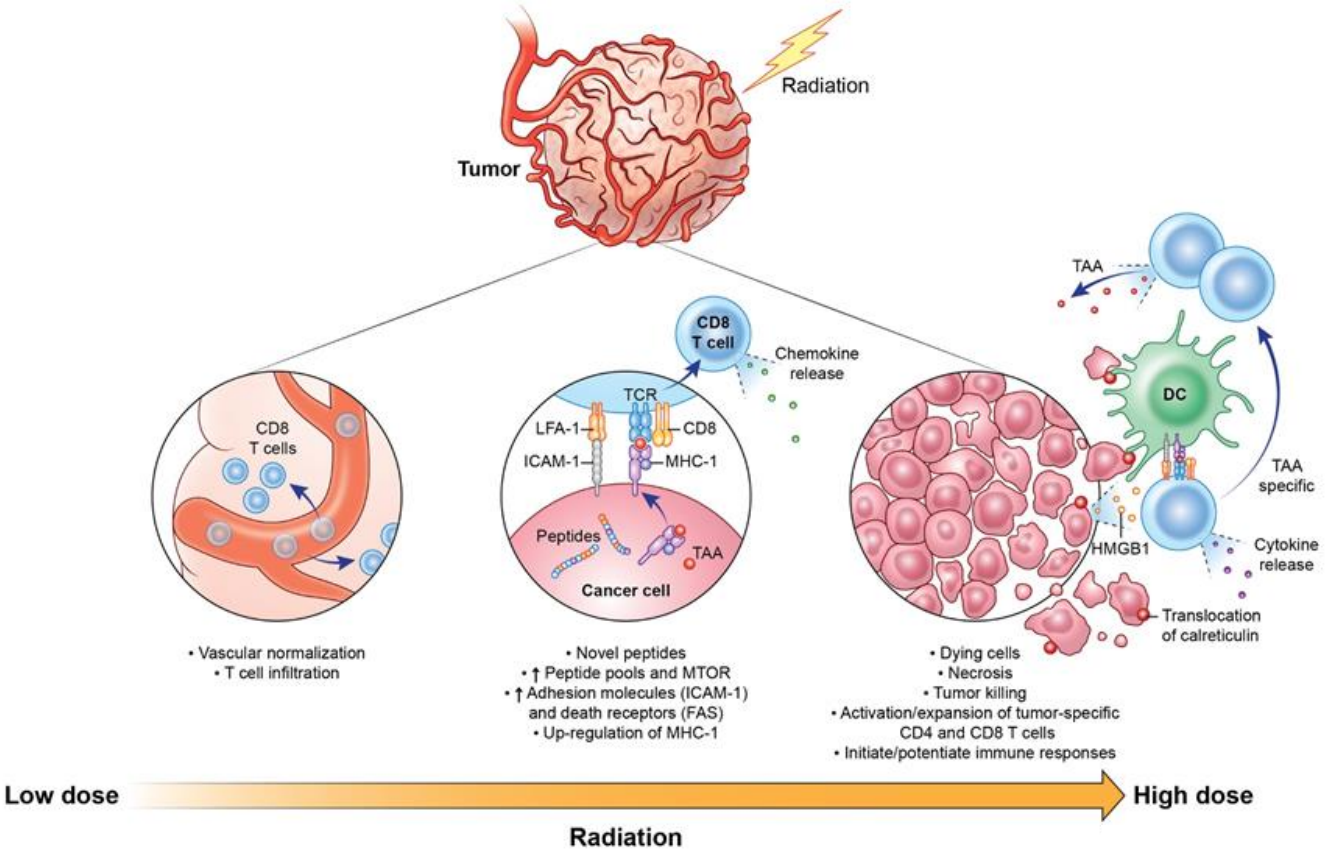
Radiation Therapy:

A potent adjuvant for tumor immunity



Exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer

http://www.ncbi.nlm.nih.gov/pubmed/18777956

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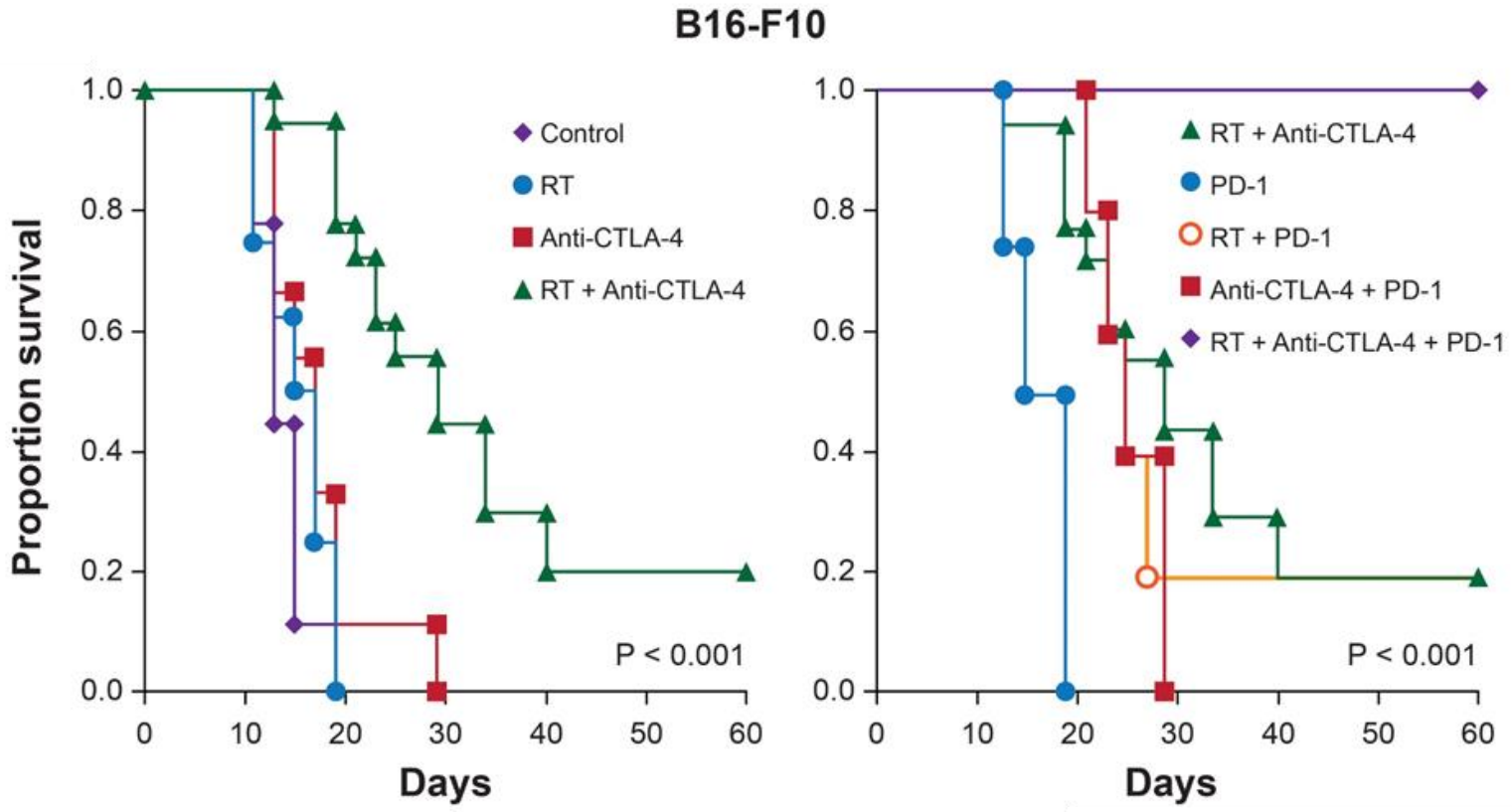
Radiotherapy synergizes with blockade of CTLA-4 and PD-1 to cure melanoma lung metastases



Victor CT, Rech A, Maity A, Rengan R, Pauken K, Stelekati E, Benci J, Xu B, Dada H, Odorizzi P, et al. 2015. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 520: 373-377.

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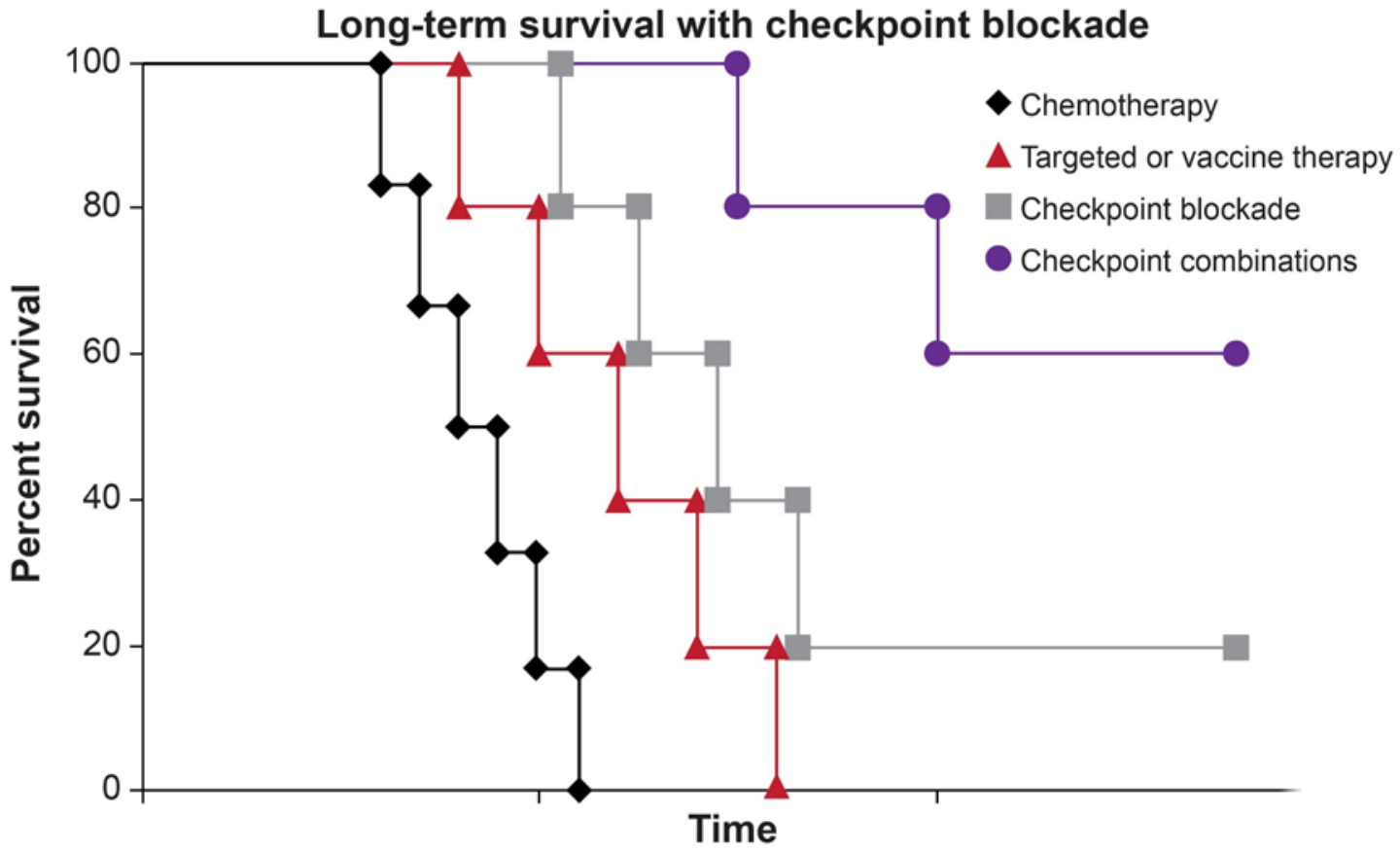
Combination Immunotherapy:

Conceptually, if you penetrate more 'onion layers', these therapies work better!



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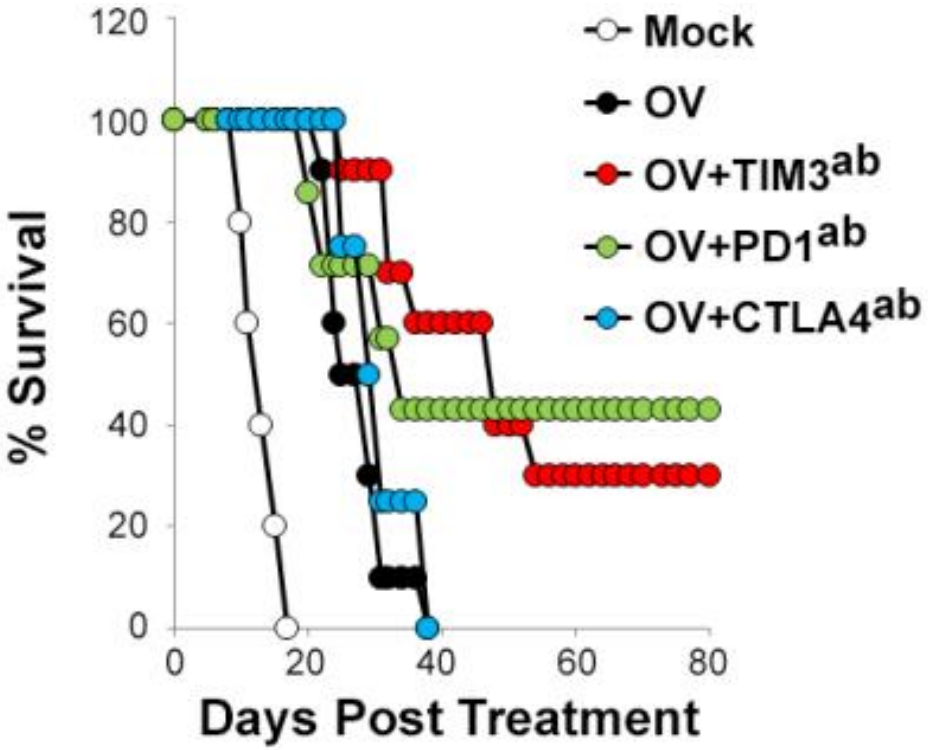
Not all combinations work

- More isn't always better
- Combination of checkpoint therapies is often associated with increased auto-immune like toxicities



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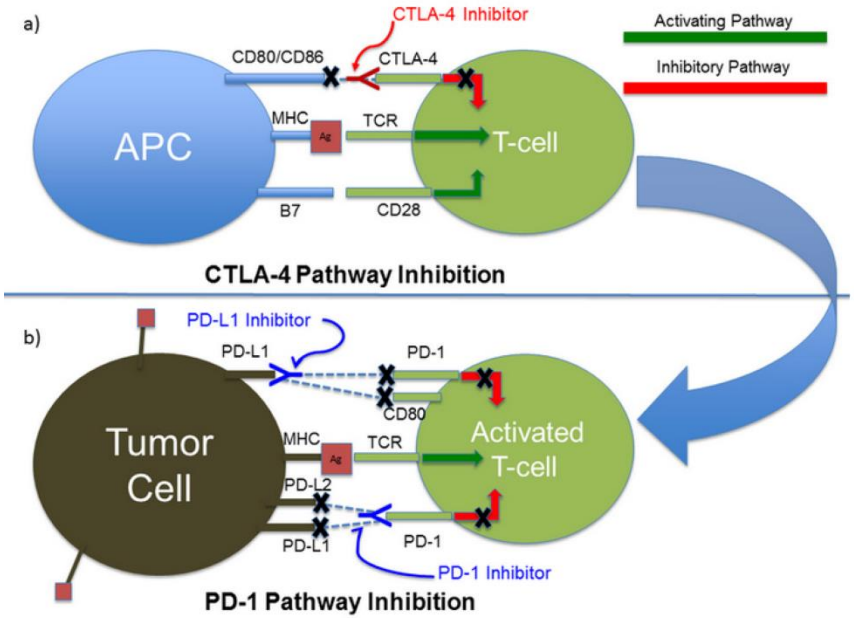
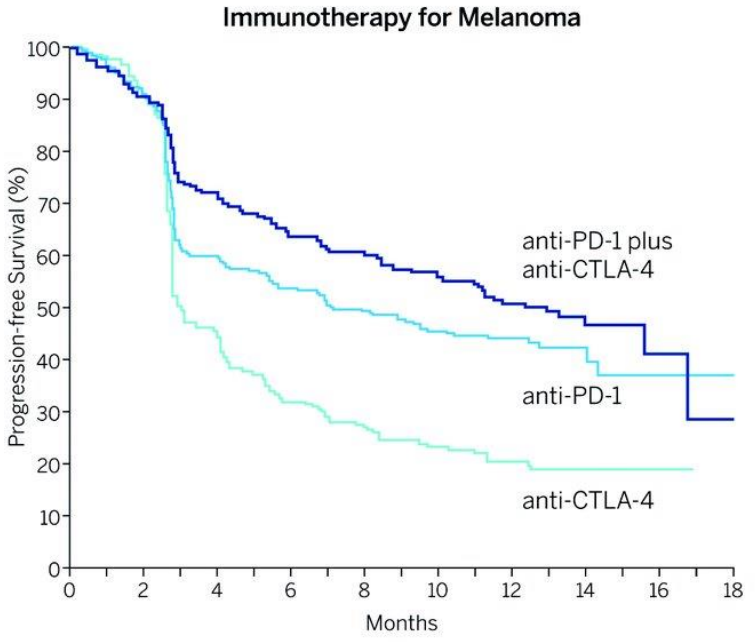
If you get the right combination, however, the results can be powerful





J. Larkin et al., *N Eng J Med* 373:23-34, 2015

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