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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

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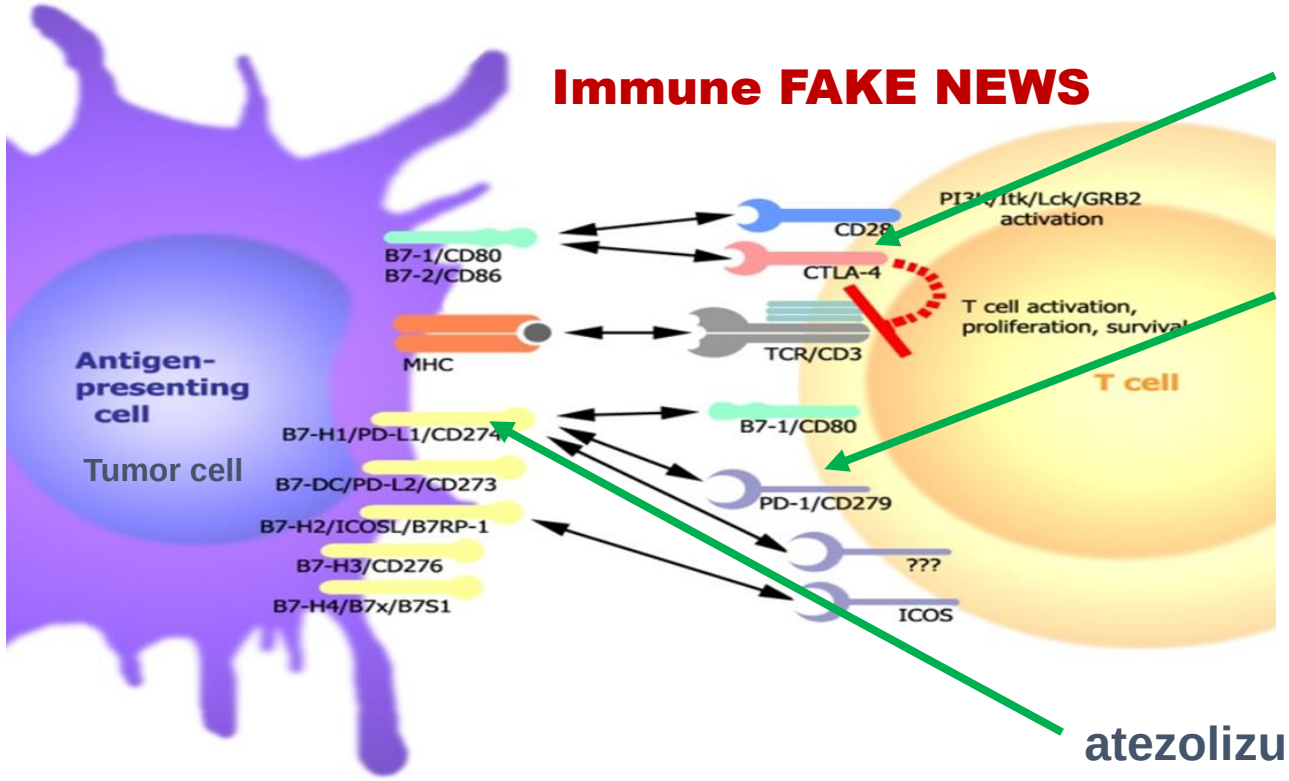
- **Disclosures:** Consultant for Agenus, Xencor, Dr. Reddy, Merck, Astra-Zeneca
- I will be discussing non-FDA approved indications during my presentation.

Learning Objectives

- Review the state-of-the-art in cancer immunotherapy
- Discuss the science behind new immunotherapy approaches
- Get updates on ongoing trials and selected promising new approaches

Immune checkpoints and their inhibition



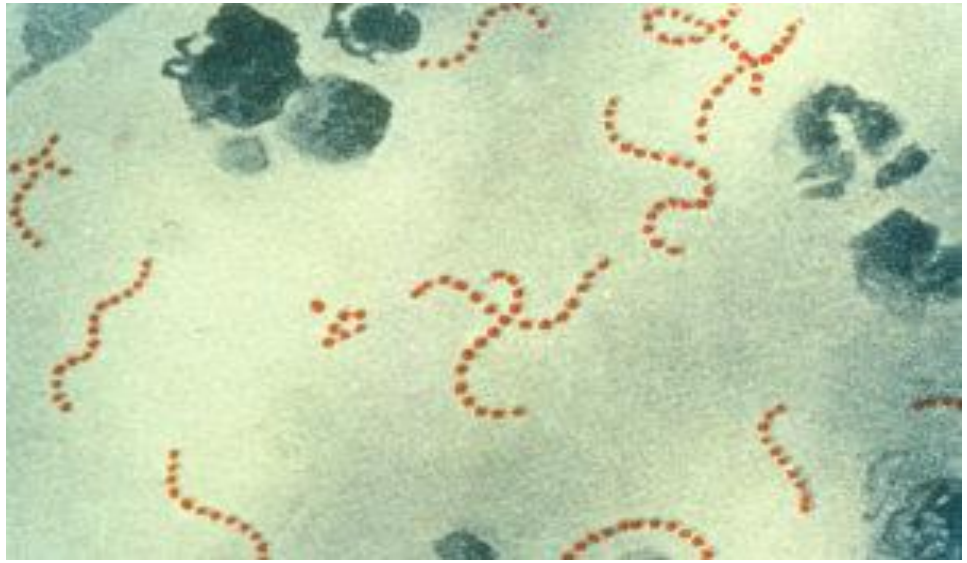
ipilimumab 2011
(anti-CTLA-4) melanoma, renal

pembrolizumab 2014
nivolumab 2014
cemiplimab 2018
(anti-PD-1)
melanoma, renal, lung
Hodgkin's disease,
head and neck, MSI+, DDR+
bladder, Merkel cell, pediatric,
colorectal, hepatocellular, skin

atezolizumab 2017 (anti-PD-L1)
avelumab 2017
durvalumab 2017
Merkel cell, bladder
breast, lung

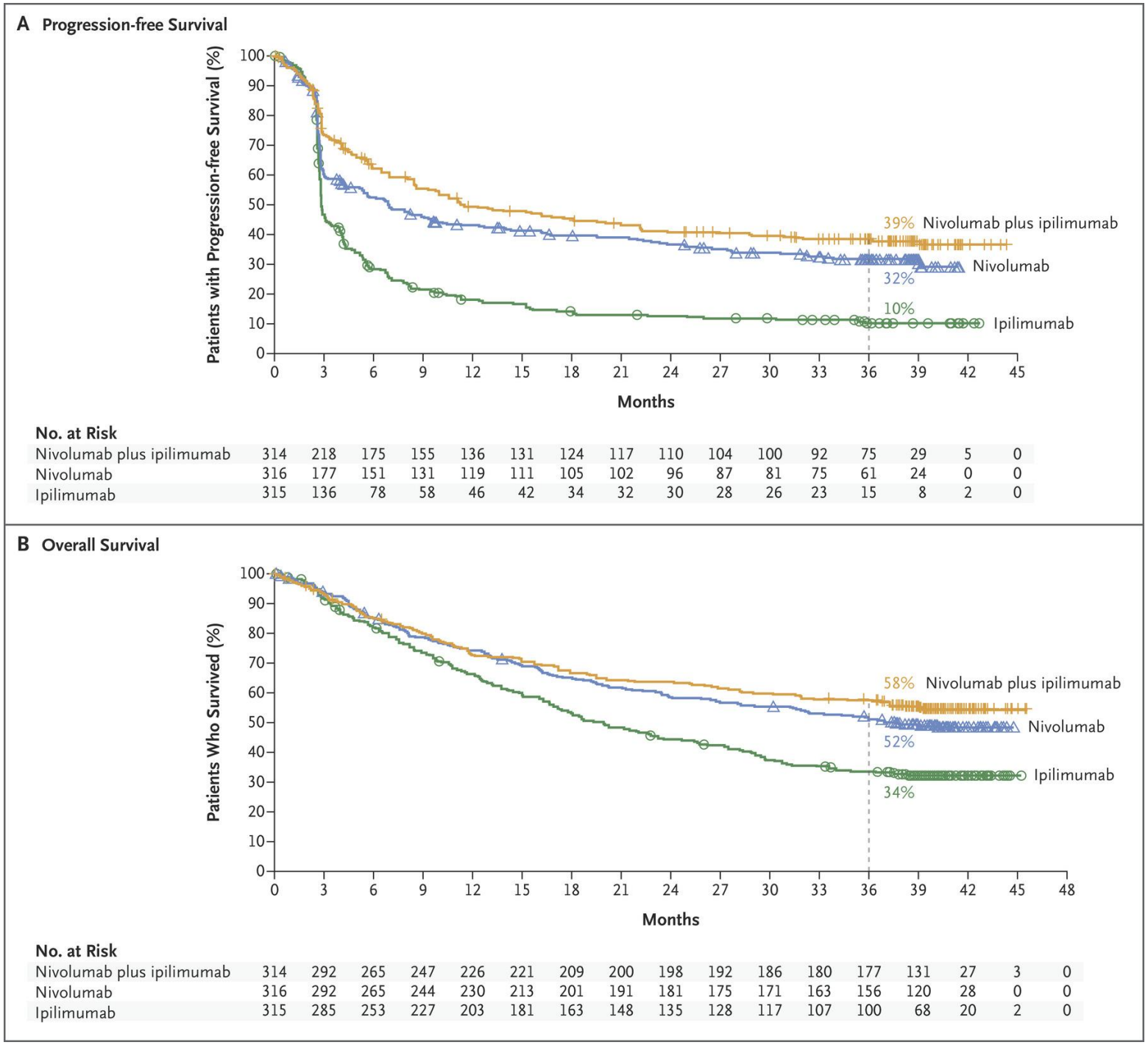
When was the first cancer immunotherapy FDA approved?

Coley's Toxins: the first FDA-approved cancer immunotherapy 1923



- Heat killed *Streptococcus pyogenes* and *Serratia marcescens*
- CpG motifs in bacterial DNA probably induced endogenous TNF-α and other cytokines
- CpGs in human cancer trials to date have not been successful

Coley's Toxins marketed by Parke-Davis from 1923-1962 to treat sarcoma



Ipilimumab plus Nivolumab combo beats single agents (but not by much)

Response durability good

Wolchok, J. D., (2017) Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* **377**, 1345-1356

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Chemotherapy and anti-PD-1 a great new combination:

KEYNOTE-189 trial

1 year OS in metastatic non-squamous NSCLC

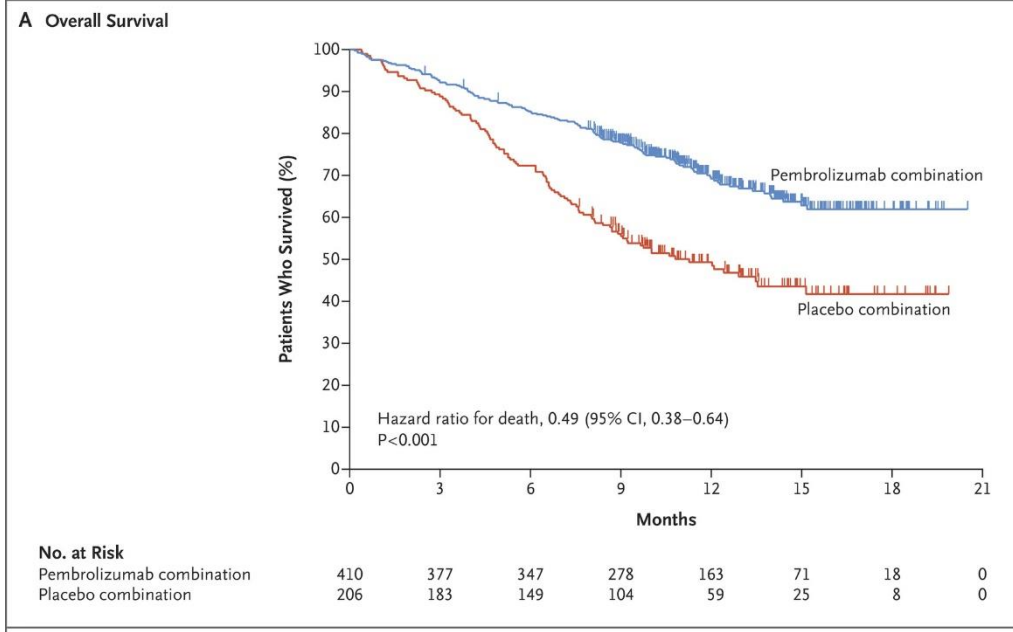
69.2% pembro vs. 49.4% placebo

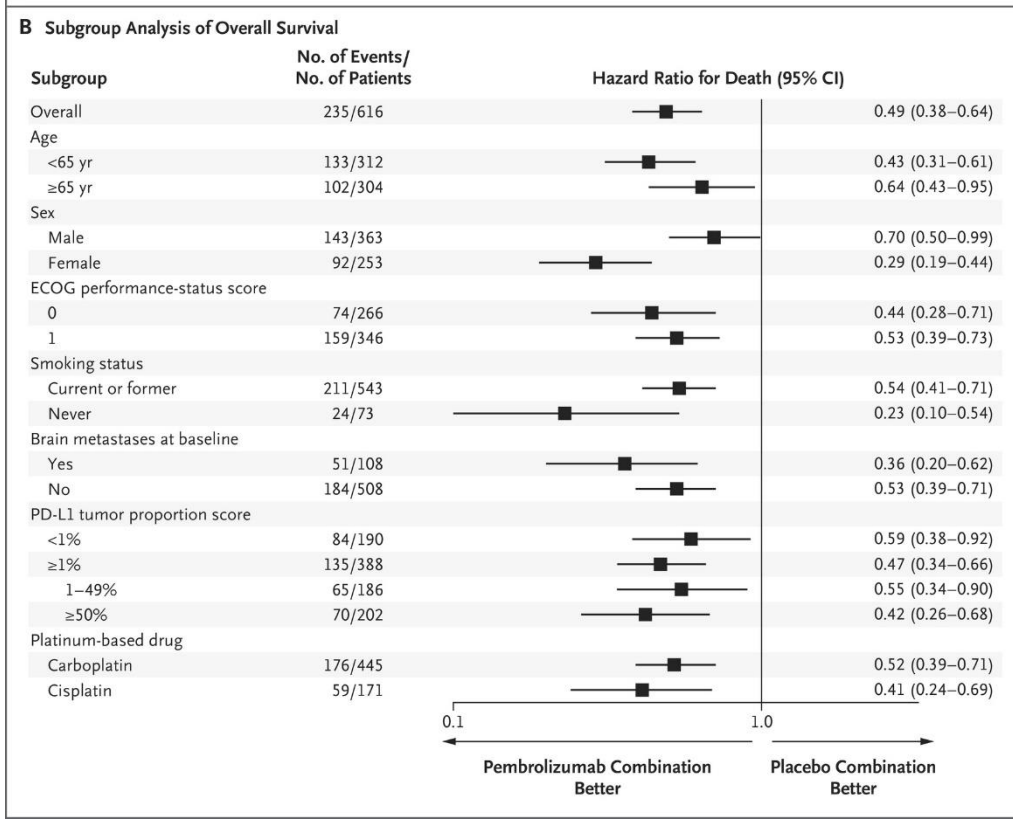
August 20, 2018 non-squamous 1L

October 30, 2018 squamous 1L

Gandhi, L., (2018) Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* **378**, 2078-2092

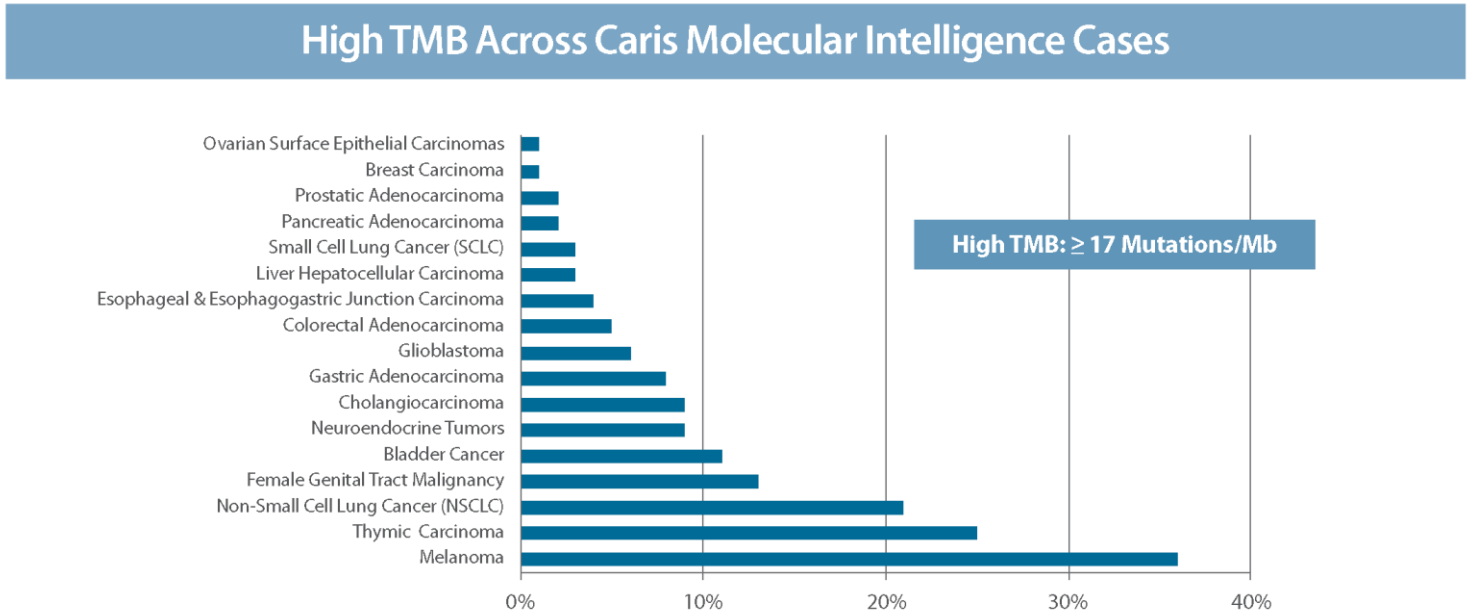
Similar improvements in breast cancer, bladder cancer, others





Nivolumab approved for 3L in metastatic small cell lung cancer

August 17, 2018



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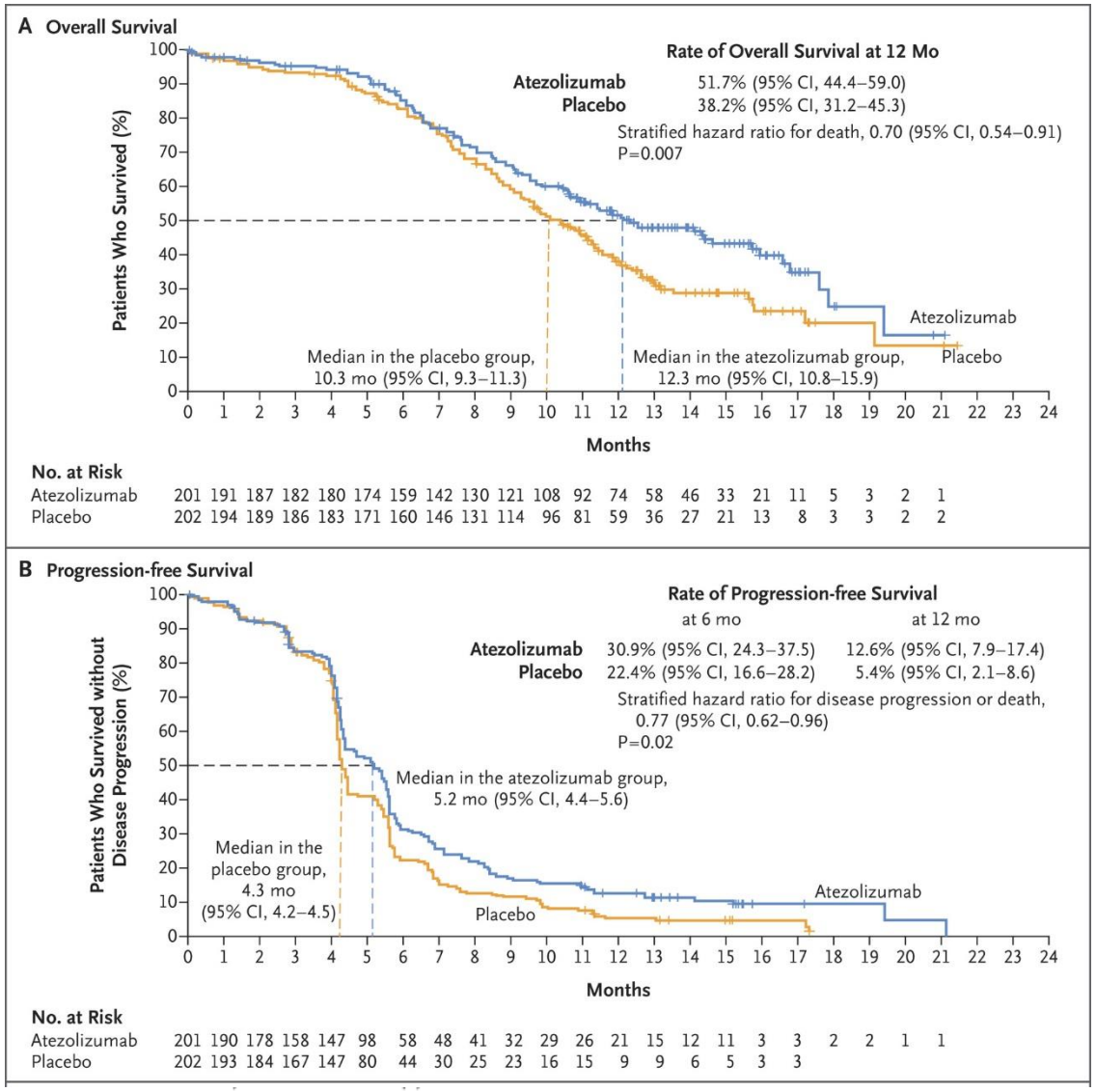
First-Line Atezolizumab (anti-PD-L1) plus Chemotherapy Effective in Extensive-Stage Small-Cell Lung Cancer

Horn, L., Mansfield, (2018) *N Engl J Med* 379, 2220-2229



1L + chemo in extended stage SCLC
March 19, 2019

1L + chemo + bevacizumab in metastatic non-squamous NSCLC
December 6, 2018

1L + chemo PD-L1⁺ in unresectable, metastatic or locally advanced triple-negative breast cancer
March 8, 2019

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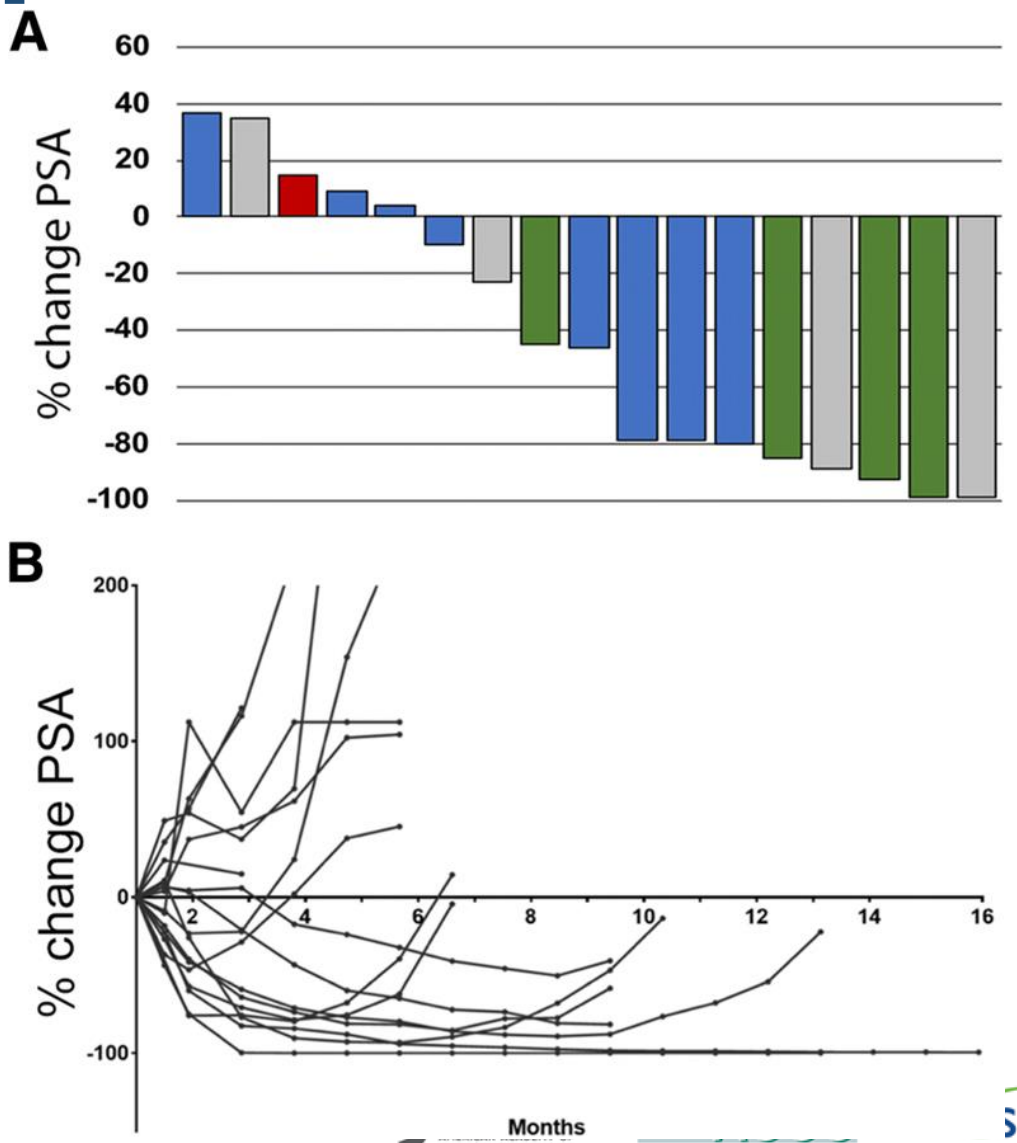
Anti-PD-L1 is active metastatic castration-resistant prostate cancer

Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations.

F. Karzai, *et al.*, *J Immunother Cancer* 6, 141 2018



DNA damage repair plus immune checkpoint inhibition

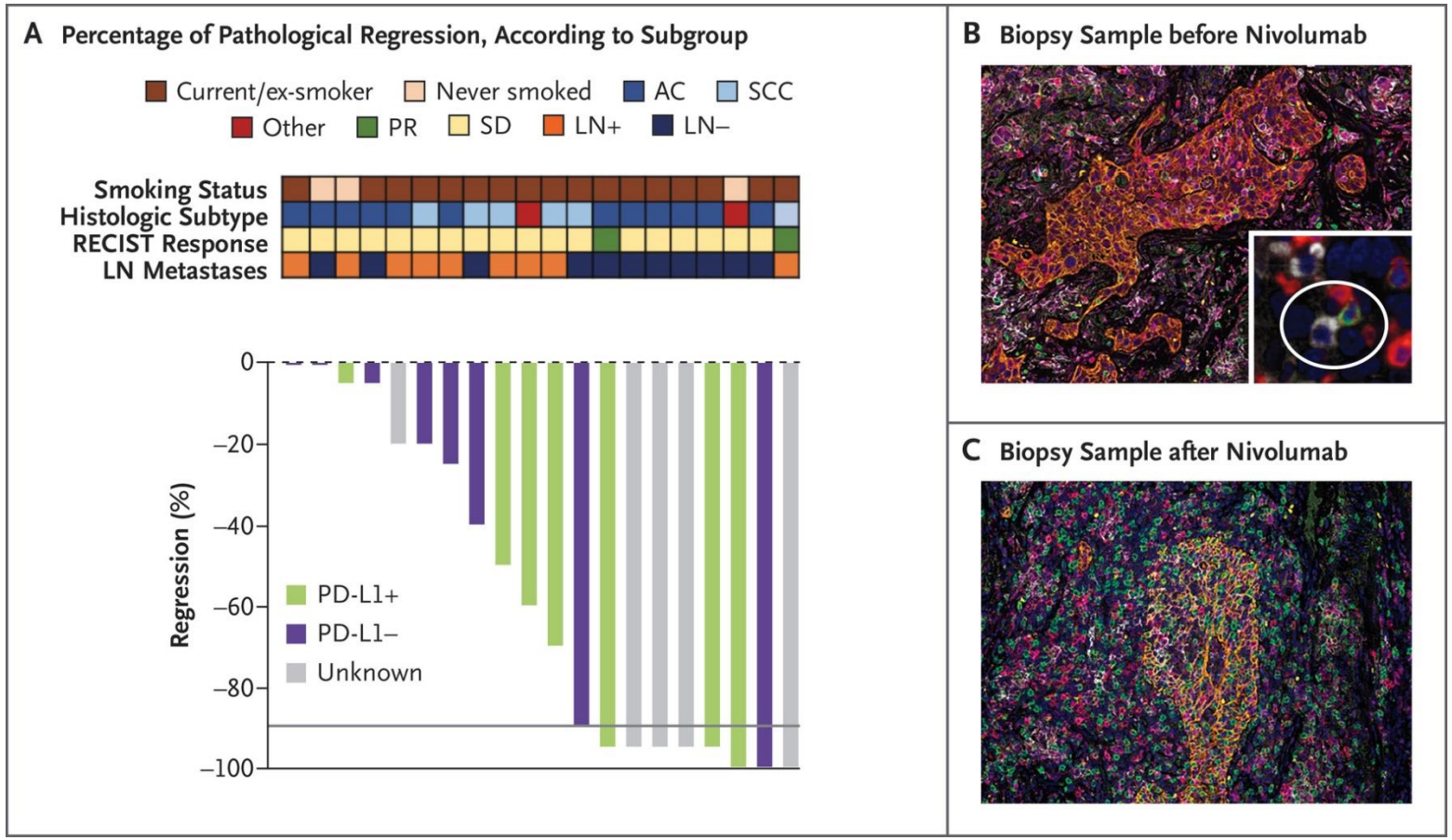
- **PARP inhibitors upregulate tumor PD-L1**
- **PARP inhibitors inhibit DNA damage repair, and thus can increase tumor mutational burden to make tumors more immunogenic**
  - **Breast cancer**
  - **Ovarian cancer**
  - **NSCLC**
  - **Anti-PD-1 and anti-PD-L1**

Neoadjuvant immunotherapy is effective

- Major pathological response in 9 of 20 resected tumors (45%)
- Responses in both PD-L1–positive and PD-L1–negative
- Significant correlation between path response and tumor mutational burden mutation-associated, neoantigen-specific T-cells from a primary tumor with CR on path rapidly expand in blood 2 to 4 weeks after treatment
- Some T cells not detected before nivolumab treatment

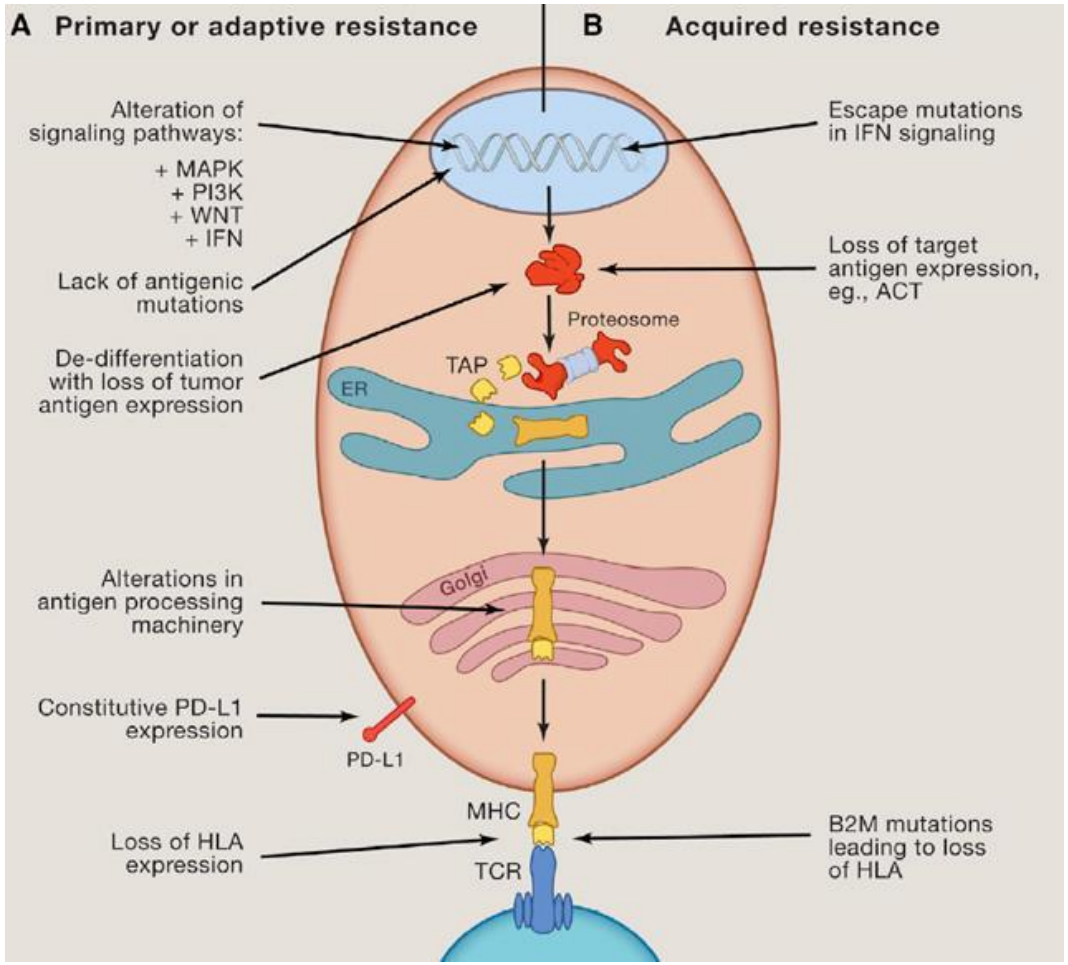
Neoadjuvant chemo + checkpoint block

- Invasive bladder cancer



Forde, P. M., *et al.* (2018) Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. *N Engl J Med* 378, 1976-1986

Checkpoint blockade resistance

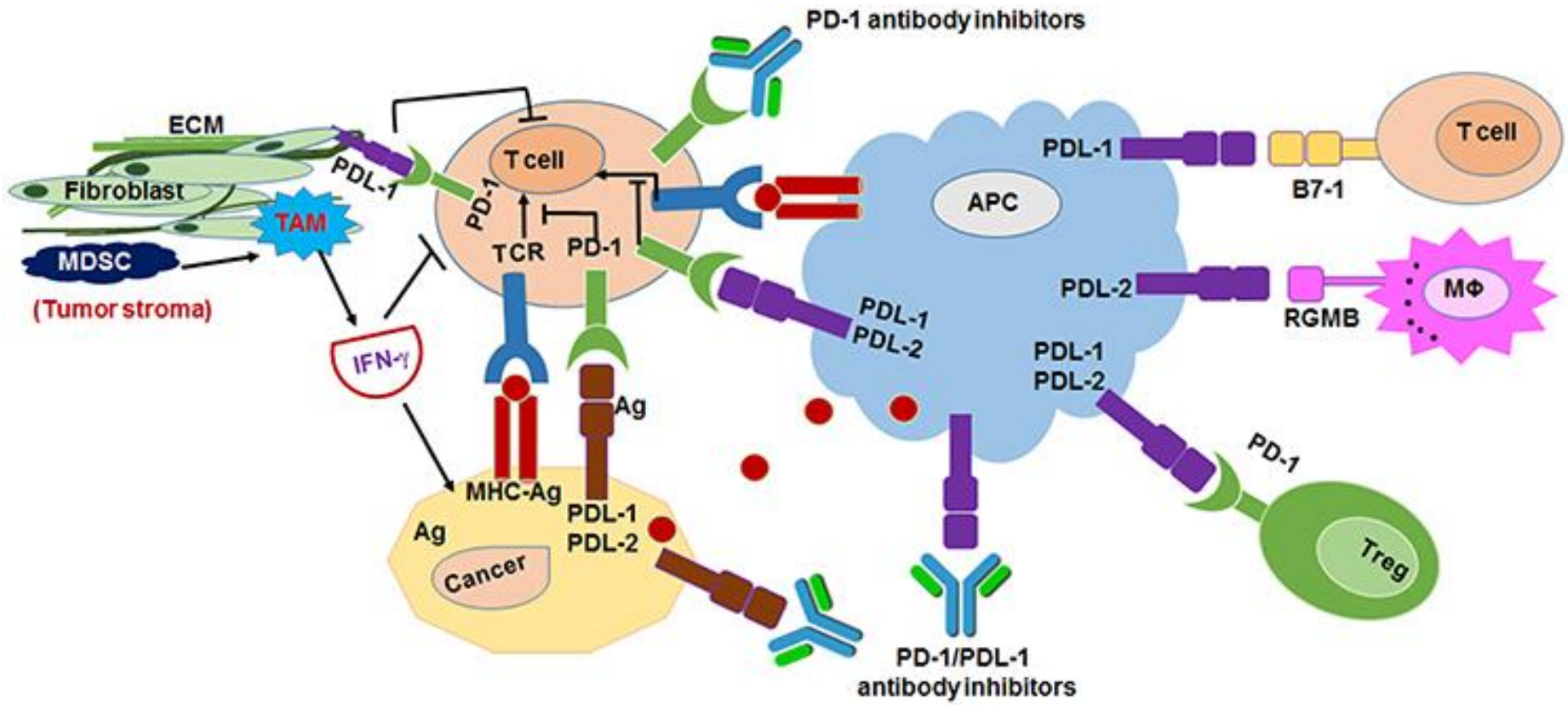


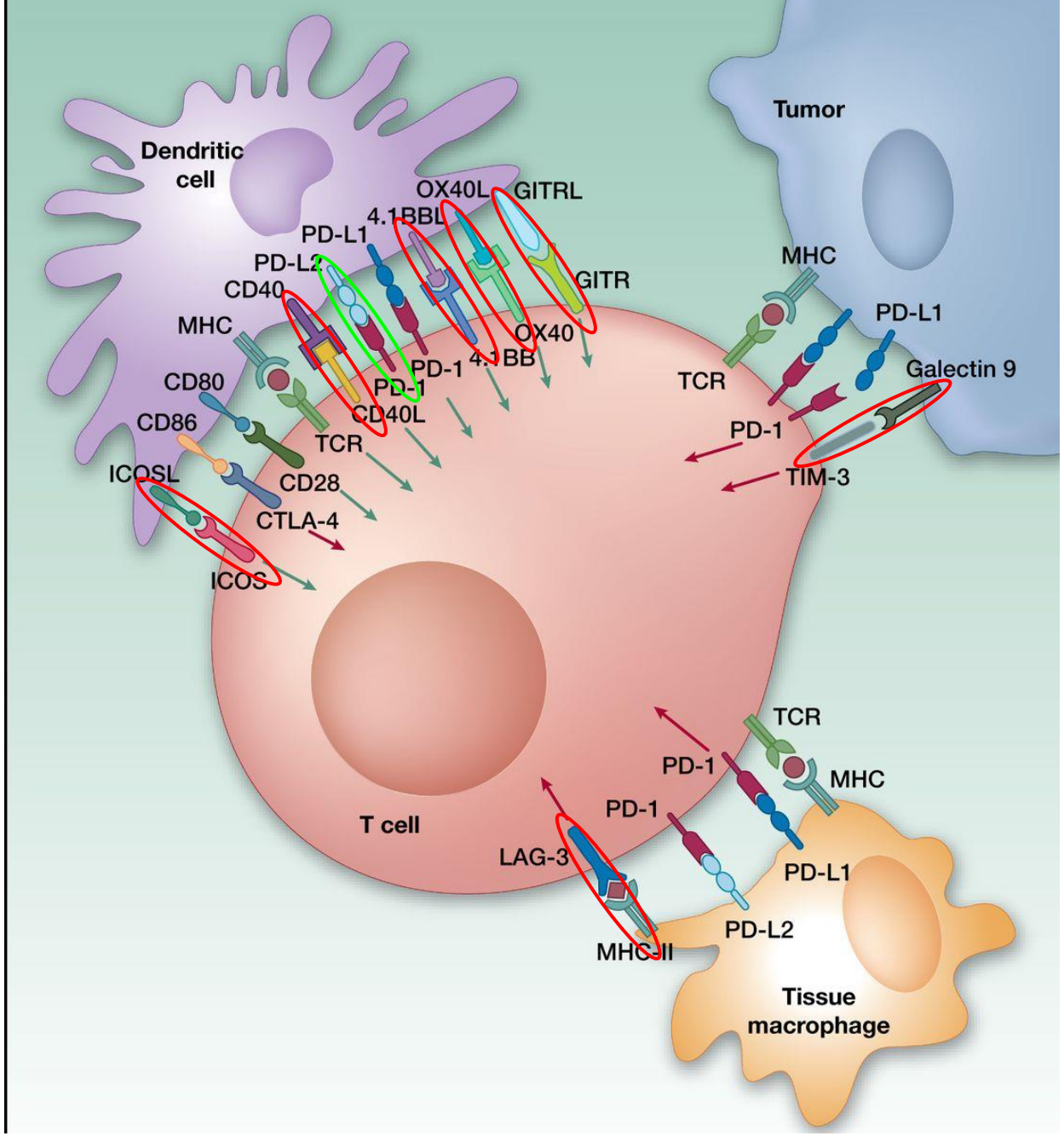
Sharma, P., *et al.*
***Cell* 168, 707-723**

Mariathasan, S. *et al.* TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells.
***Nature* 554, 544-548**

Small molecule TGF-β inhibitor or anti-TGF- β antibody improves anti-PD-L1 in mouse bladder cancer model

Blocking PD-L1 versus PD-1 is not symmetrical





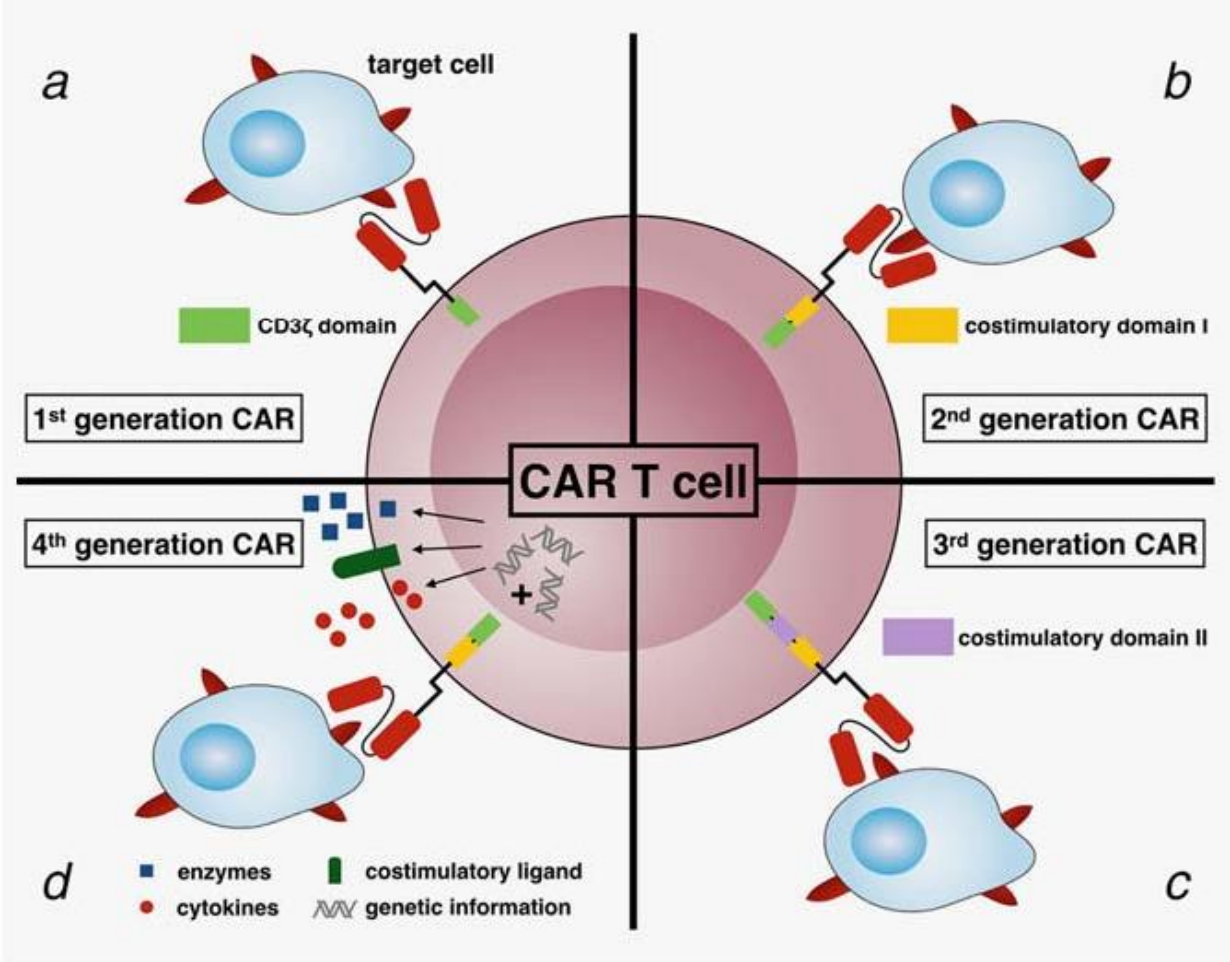
Newer checkpoint blockade antibodies in the clinic now

Representative new immune checkpoint/related antibodies in trials

- **Anti-CD40 APX005M(agonist)**
  - **In a pivotal Phase III trial with chemo ± anti-PD-1 in 1L metastatic pancreatic cancer**
- **Anti-Tim-3 (plus anti-PD-1)**
  - **Salvaged an anti-PD-1 failure**
- **Anti-KIR lirilumab (promotes NK cell functions)**
- **Anti-PD-1 could degrade anti-OX40 effects**
  - **Shrimali, R. K. *et al. Cancer Immunol Res* 5, 755-766 (2017).**
  - **Messenheimer, D. J. *et al.. Clin Cancer Res* 23, 6165-6177 (2017).**
- **Anti-ICOS**
  - **Unimpressive in Phase I**
- **Anti-CD137 (4-1BB)**
  - **Early molecules failed from liver toxicity**

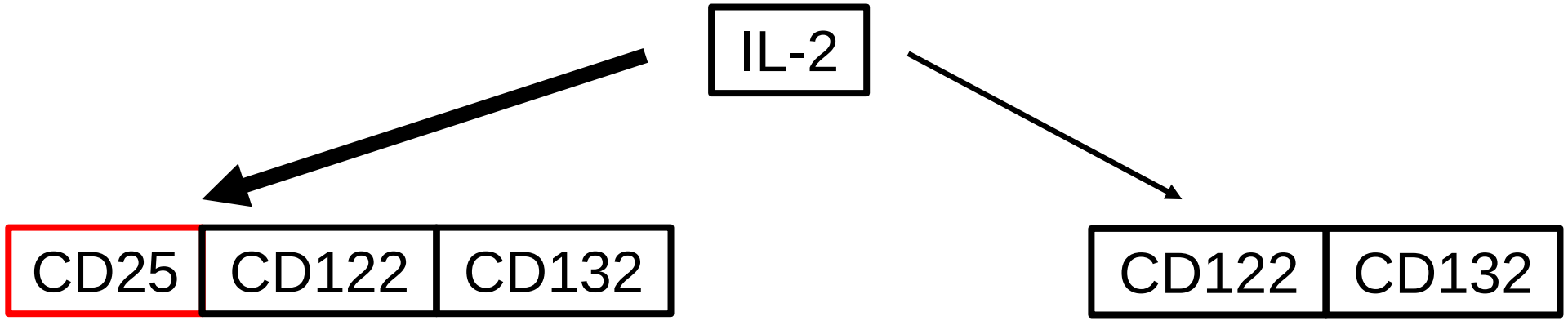
Fourth generation CAR immune cells: T cells, NK cells, NK T cells and γδ T cells

- Some responses in carcinomas
  - Mesothelin CAR T inducing remission in metastatic pancreatic cancer
- CD19 CAR NK cells inducing remission in refractory lymphoma
- Next generation CARs with better safety, harder to suppress, off-the-shelf engineering, armored CAR, new targets



Engineered cytokines

IL-2 promotes immunity and tolerance



High-affinity IL-2 receptor

- Highly expressed on Tregs and essential for suppressive function

  Chinen et al., *Nat Immunol* (2016)

- Transiently expressed on CD8$^+$ T cells after activation and sustains antitumor activity

  Su et al., *Sci Transl Med* (2015)

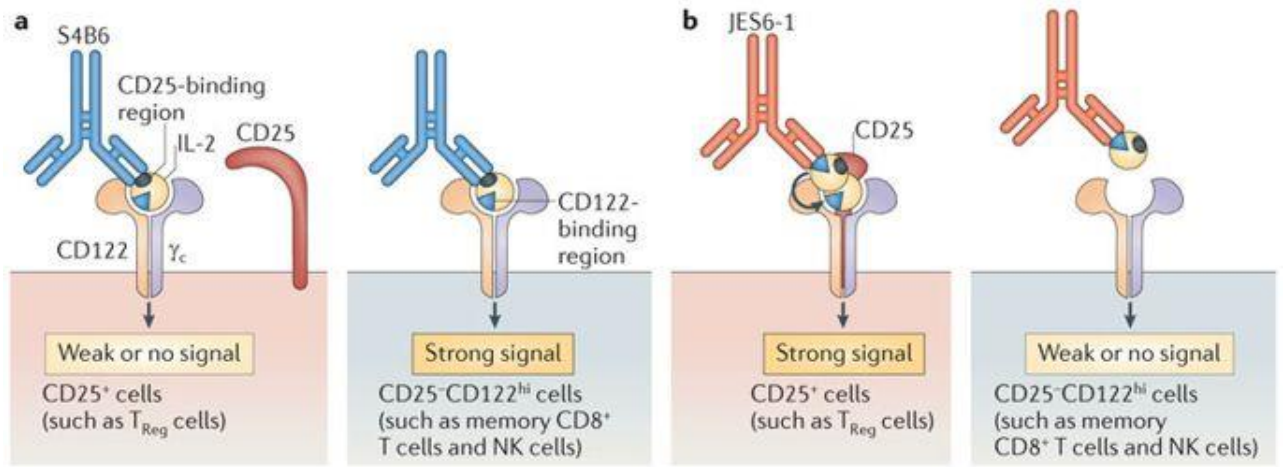
Medium-affinity IL-2 receptor

- Highly expressed on memory-phenotype antitumor CD8$^+$ T cells and NK cells

  Malek, *Annu Rev Immunol* (2008)

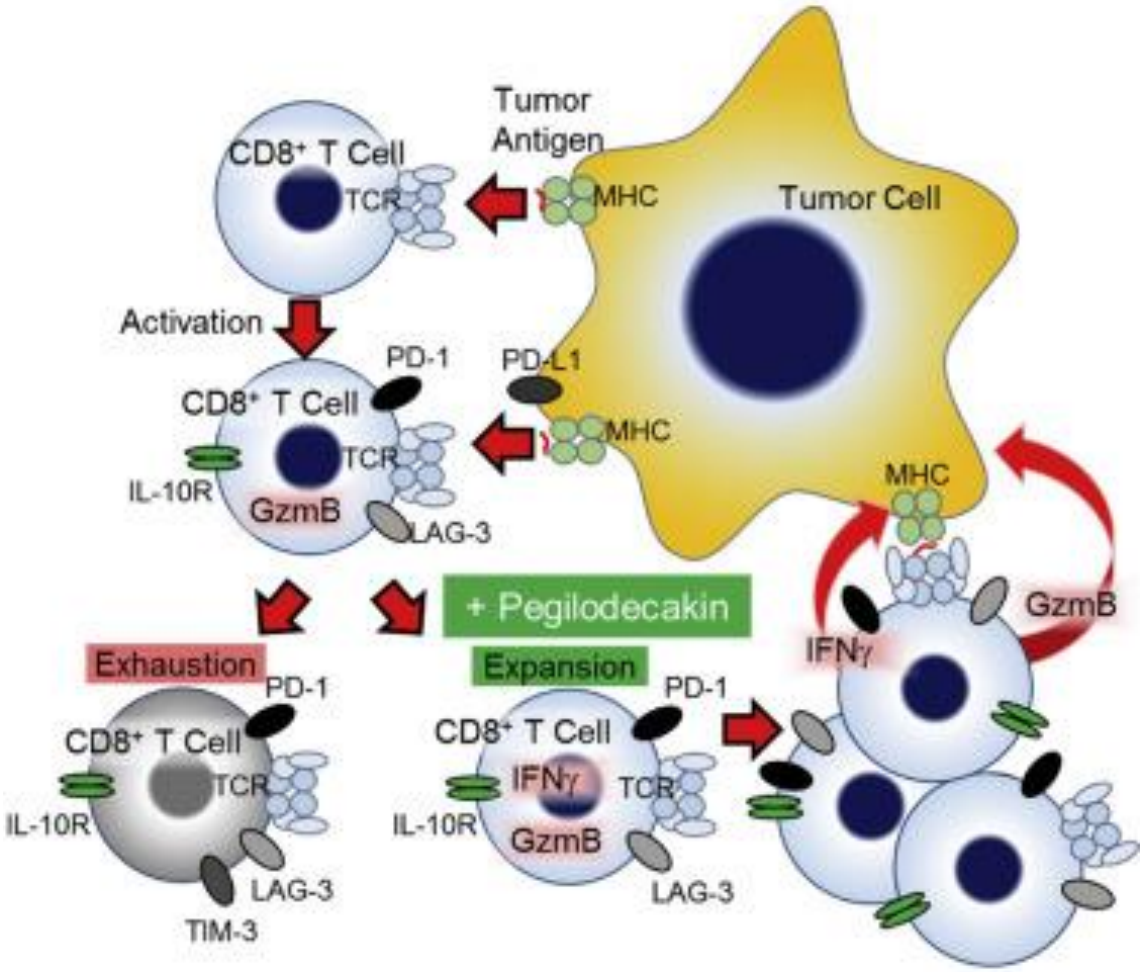
Pegylated IL-2 (NKTR0214)

- At least 4 strategies to direct IL-2 to CD122 and/or away from CD25
  - Pegylated IL-2
  - Engineer CD25 binding out of IL-2
  - Bind CD25 to IL-2
  - Use antibody to block IL-2 CD25 binding site
- Phase I/II PIVOT trial of pegylated IL-2 (NKTR0214) met the criteria needed to advance anti-PD-1 inhibitor (nivolumab)
- and CD122-biased agonist NKTR0214
- into pivotal trials in melanoma, renal
- cell carcinoma and urothelial cancer.
- Some say the response rates are not impressive.



Pegylated IL-10 (AM0010, pegilodecakin)

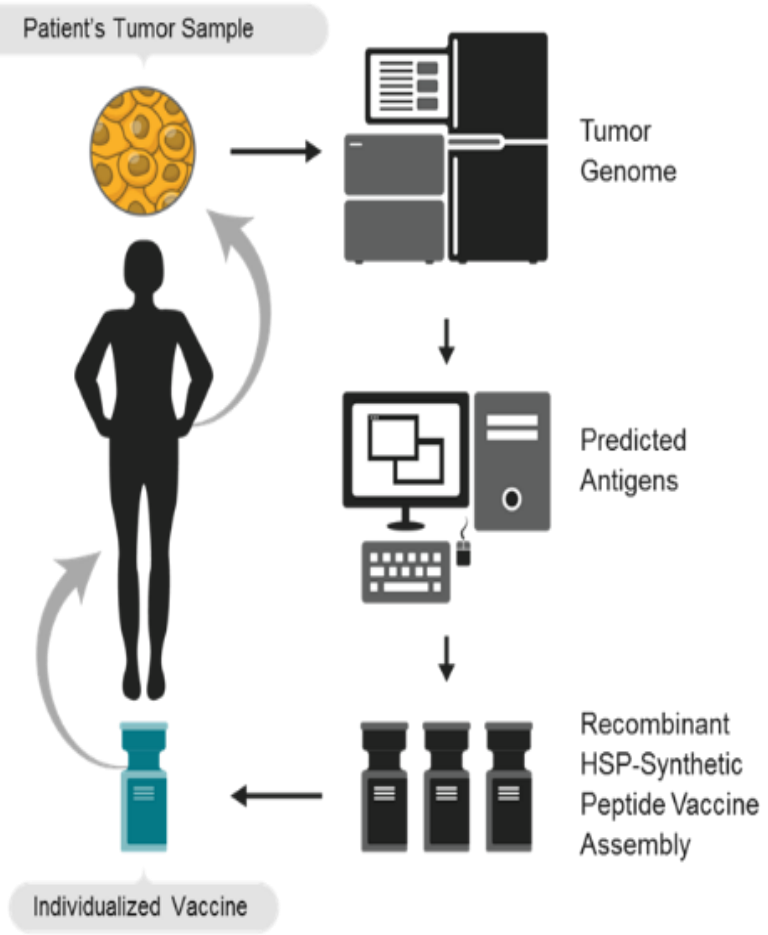
- **IL-10 receptors are expressed on activated and exhausted CD8⁺ T cells.**
- **IL-10 stimulates the cytotoxicity and proliferation of CD8⁺ T cells.**
- **Activity in metastatic renal cell carcinoma and lung cancer**
- **Now in a pivotal Phase III trial in pancreatic cancer**



Personalized cancer vaccines

ASV™ Concept

- Synthetic individualized cancer vaccine designed to impart an immune response against tumor-specific mutations
- Exploits cutting-edge NGS and bioinformatics technologies, rapid peptide synthesis and rh-Hsc70/QS21 vaccine platform



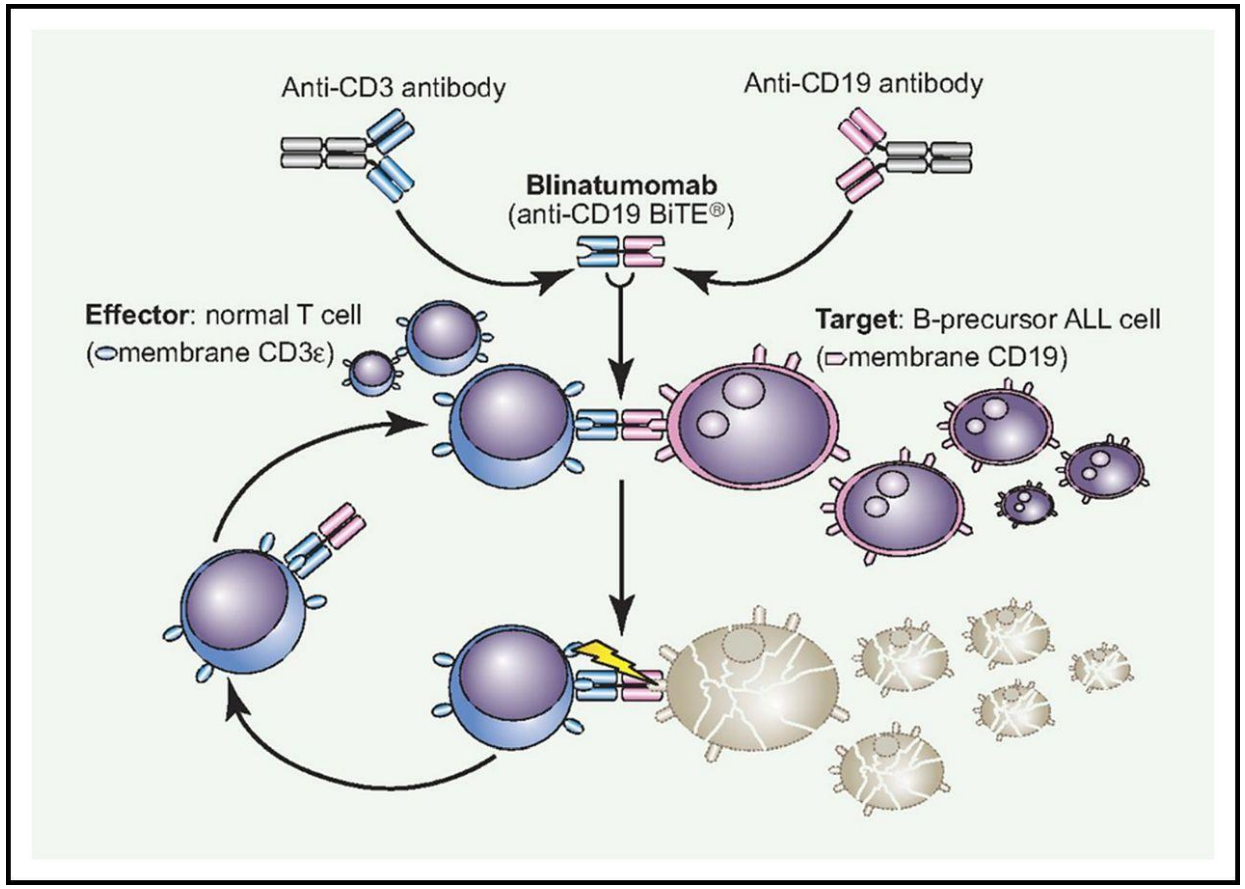
Three companies have personalized cancer vaccines in trials

Regulatory T cell depletion strategies

- **Anti-CD25**
- **Anti-CCR4**
- **Fc-competent anti-CTLA-4**
- **Denileukin diftitox**
- **Cyclophosphamide?**
- **Novel classes entering trials**

Dual targeting agents

- **Blincyto approved July 12, 2017 some patients with ALL and March 29, 2018 for adults and children with B-cell precursor ALL First FDA-approved treatment for MRD-positive ALL**
- **Anti-PD-L1/TGF-β trap in phase I**
- **A multitude of agents entering trials in 2019/2010**



Many other concepts are in trials

- Dual targeting agents
- Gut microbiome manipulations
- Radiation and immunotherapy
- Metabolic inhibitors to alter immunity or tumor susceptibility to immune attack
- Novel immune modulating agents
- New viral vectors
- New vaccine adjuvants
- Epigenetic modifiers to improve immunotherapy
- Response biomarkers

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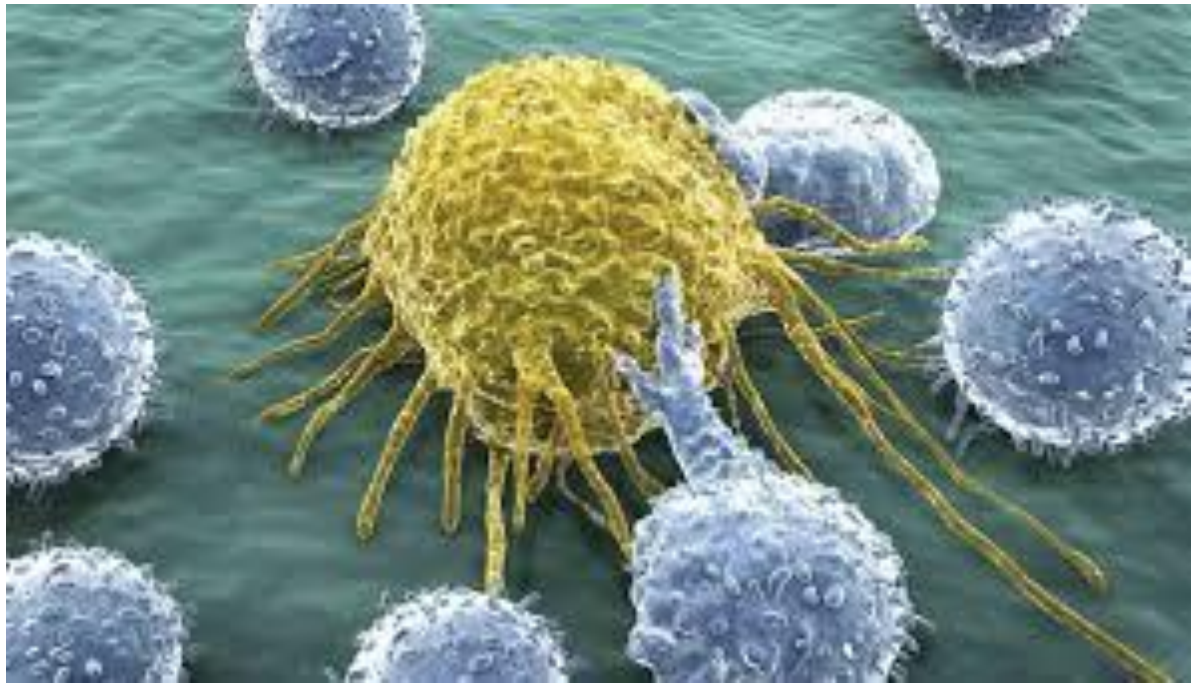
Summary of Cancer Immunotherapy in 2019

- Immune checkpoint antibodies are the most successful class of cancer drugs ever developed
- Use with chemotherapy and in neoadjuvant setting established
- Moving to the front line in many cancers
- However, most patients still do not respond well enough
- Treatment response biomarkers a challenge
- Consider clinical trials



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