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Cancer Immunotherapy at a glance

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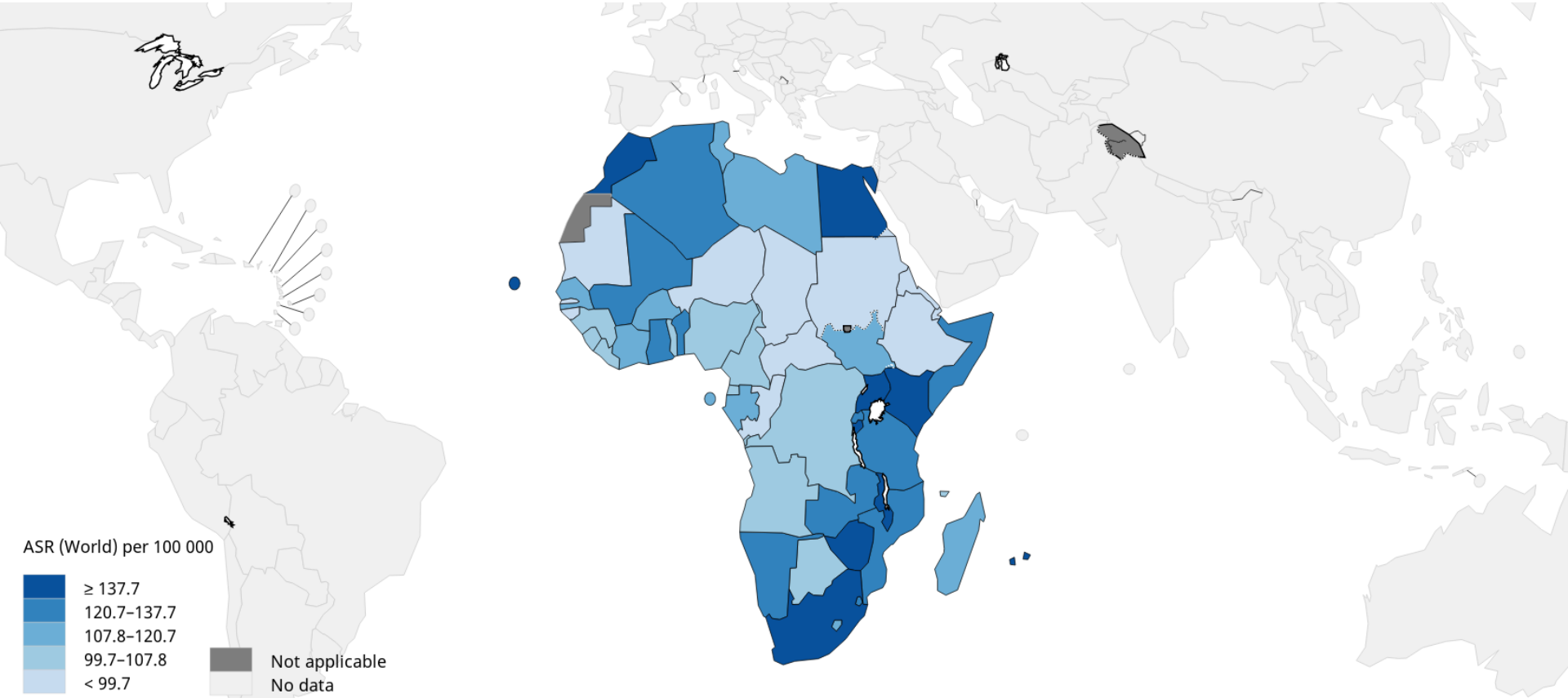
Estimated age-standardized incidence rates (World) in 2018, all cancers, both sexes, all ages



Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

December, 2013

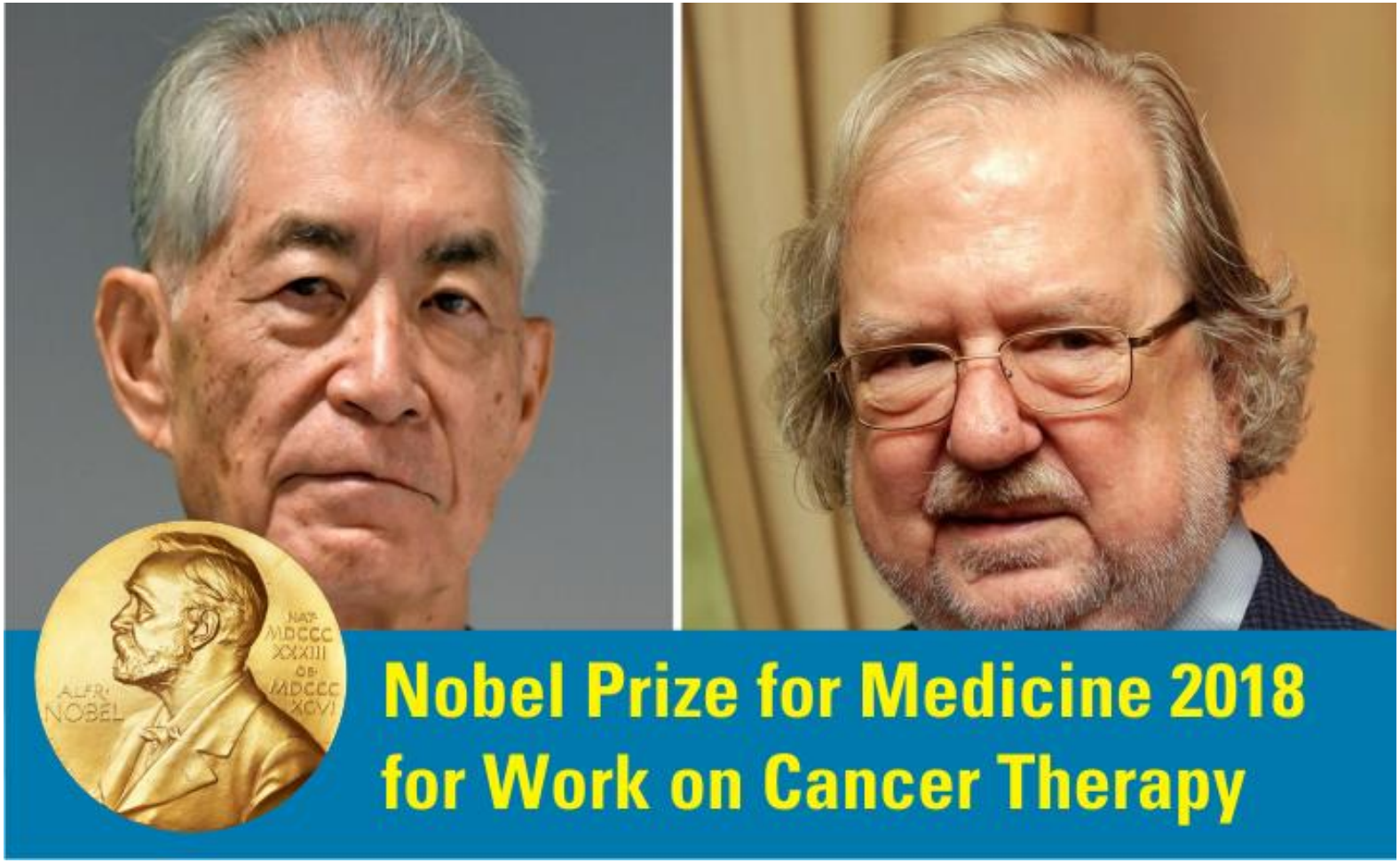
Science. 2013 Dec 20;342(6165):1432-3

Why “breakthrough of the year”?

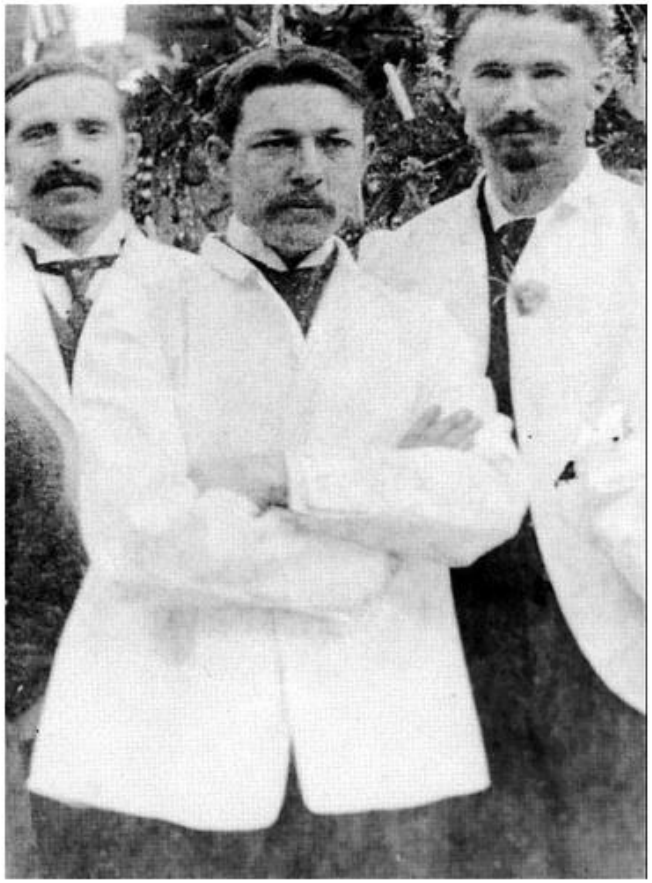
- **Remarkable results in cancer patients using multiple immunotherapies**

- CAR (Chimeric antigen receptor) therapy for B cell leukemia
- Anti-CTLA-4 & Anti-PD-1 therapies for advanced melanoma (checkpoint inhibitors)

James P. Allison & Tasuku Honjo



William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

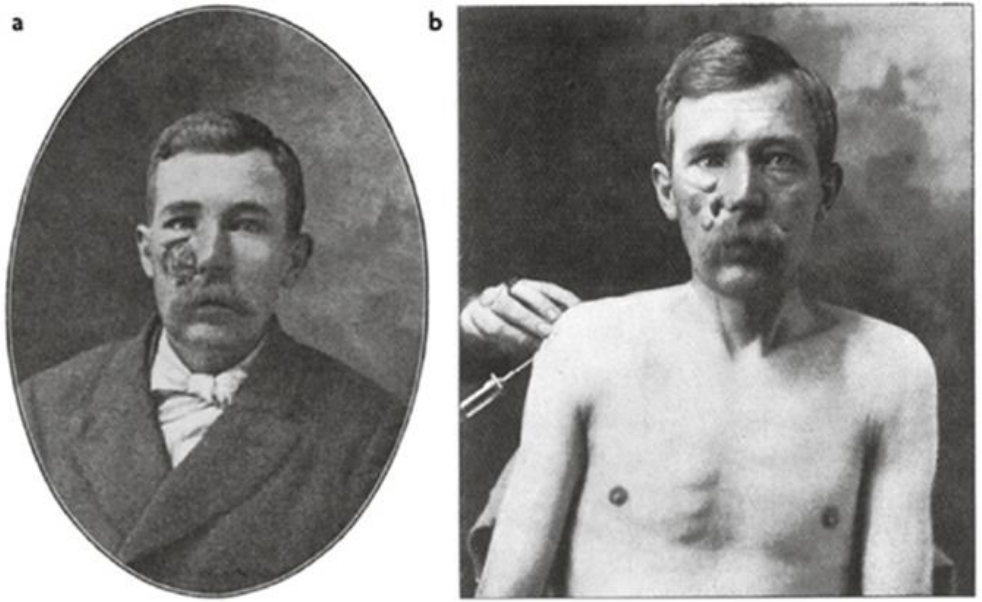
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later

Coley's Toxins (1891)

- Observation: Cancer patients with erysipelas had tumor regression
- Admixture of heat-killed *S. pyrogenes* and *S. marcescenes* injected into tumors daily (weeks to months)
- Side effects: fevers, chills



Coley's Toxins (1891)

- 104 inoperable soft-tissue sarcoma patients treated before 1940 (Compiled by Nauts, Flower, Starnes)
- 17 (16%) disease free but lost to FU 5-10 years
- 15 (14%) disease free but lost to FU 10-20 years
- 22 (21%) disease free up to 20 years

Evolution of cancer therapy

- Previously

—Anti-cancer drugs indiscriminately killed proliferating cells

- *Paradigm shift*

—New agents enhance anti-tumor immunity

Examples of Immunotherapy

- Monoclonal antibodies
- Vaccines directed against tumour-associated antigens (tumour peptides)
- Adoptive cell therapy (e.g. T effector cells transfusion)
- Cytokines (IL-7, IL-15, and IL-21), or inhibitors of cytokines (TGF-β) or their signaling pathways (CTLA-4).

Why cancer Immunotherapy?

- Specificity
- Memory
- Adaptability

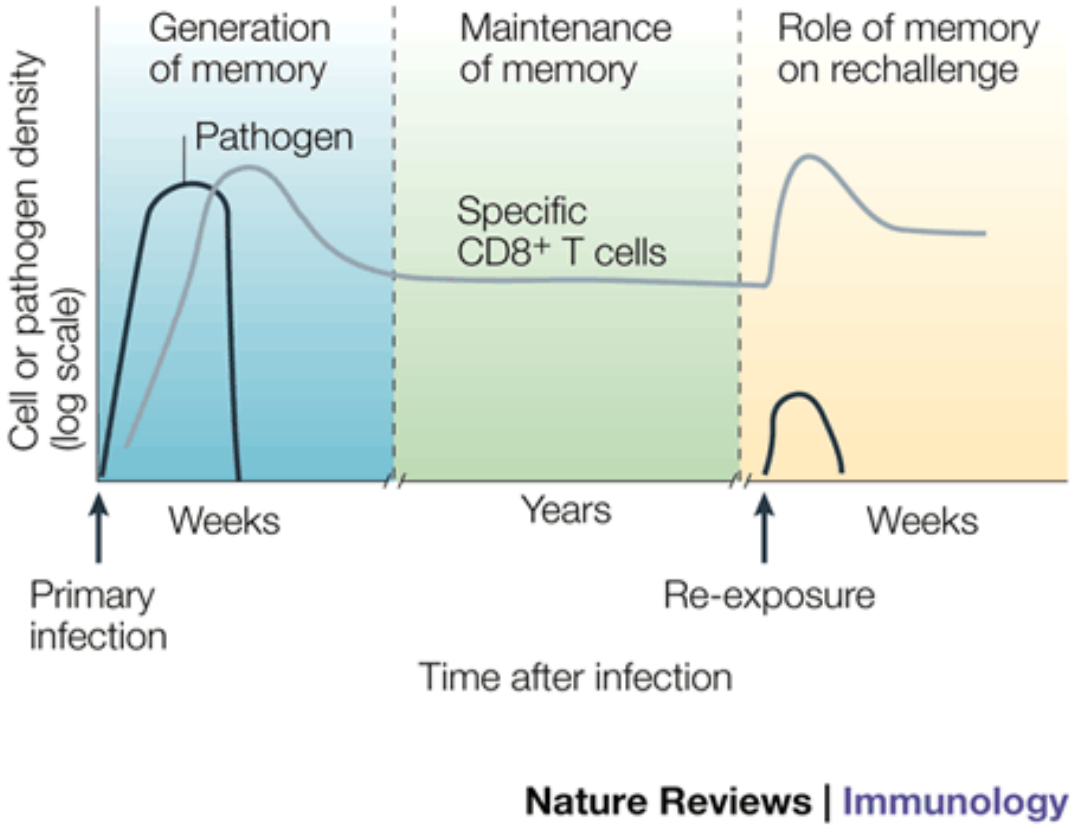
Goals of cancer immunotherapy

- To expand and/or activate the patients adaptive immune response to specifically target/kill cancer cells

Immune Responses

	Innate	Adaptive
Response rate	Minutes/Hours	Days
Specificity	Shared structures	Antigen-Specific
Diversity	Limited	Very Large (~10^{18})
Memory	(NK cells)	Yes
	-intracellular	-T lymphocytes
	Phagocytic cells	-B Lymphocytes
	-Macrophages	
	Dendritic Cells	
	NK Cells	

CD8+ T cell Response to infection



Effective & Durable T cell Response

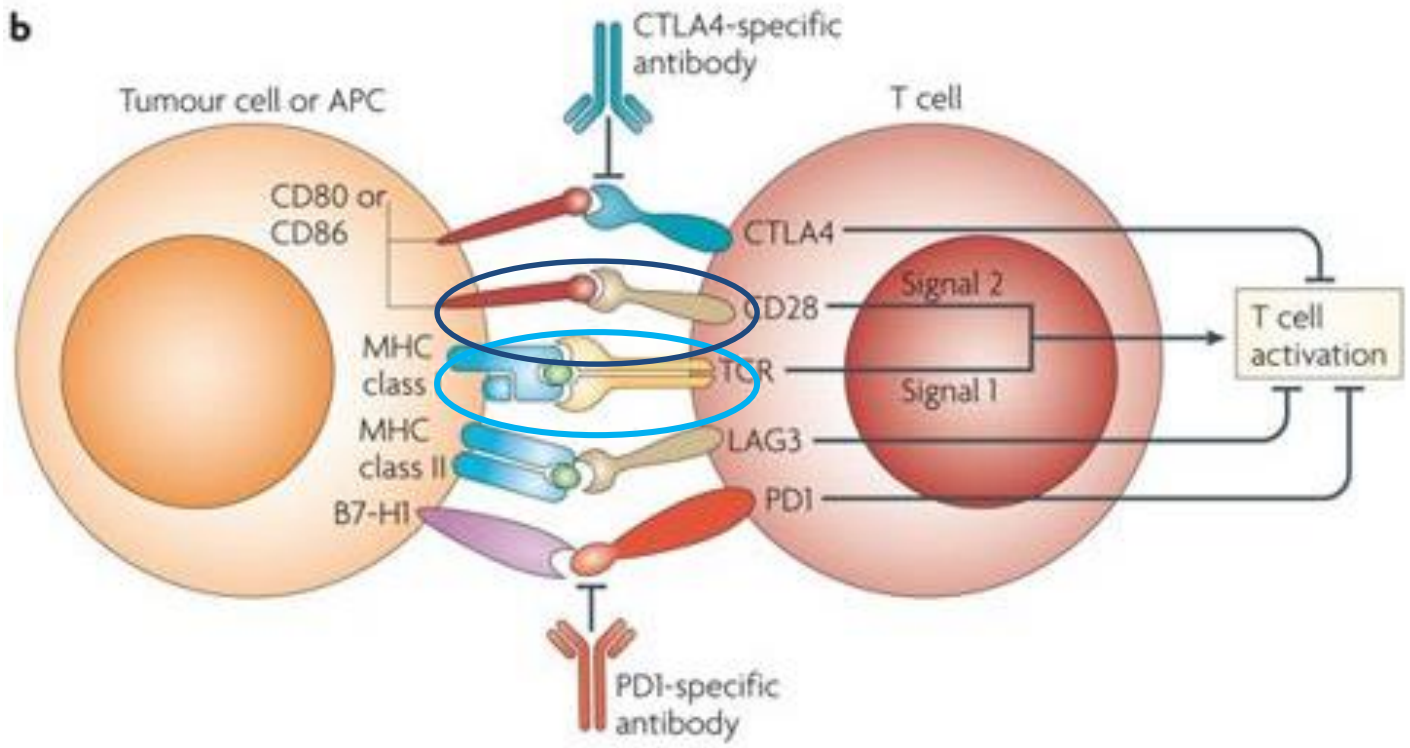
- Recognition
- Proliferation
- Effector function
  - Cytokine secretion (IFN-y, TNF-a, etc.)
  - Killing of infected cells
  - B cell help
- Memory formation

Biological Challenges

- Cancer cell-induced immune suppression
- Immune incompetence
- -Age

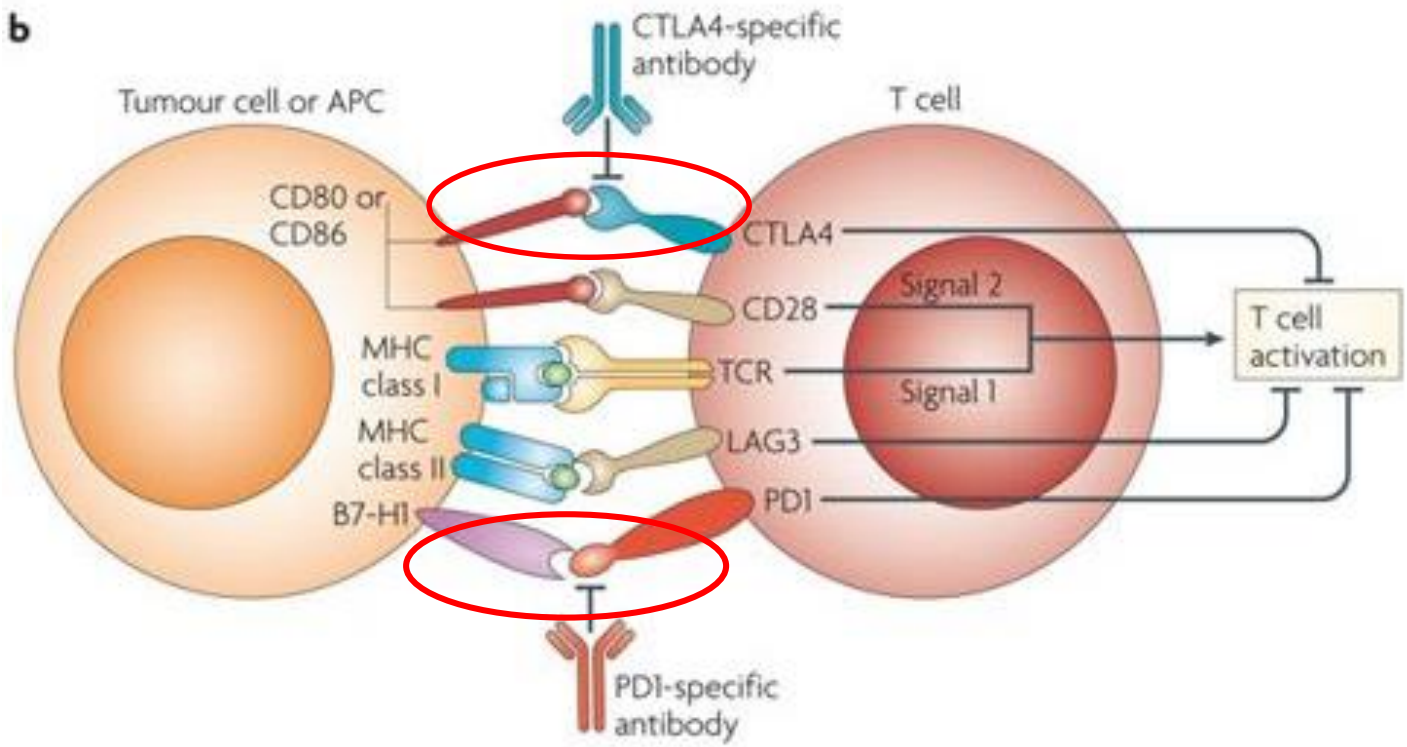
- Immune Tolerance (Peripheral and Central Tolerance)

T cell activation- Start the car



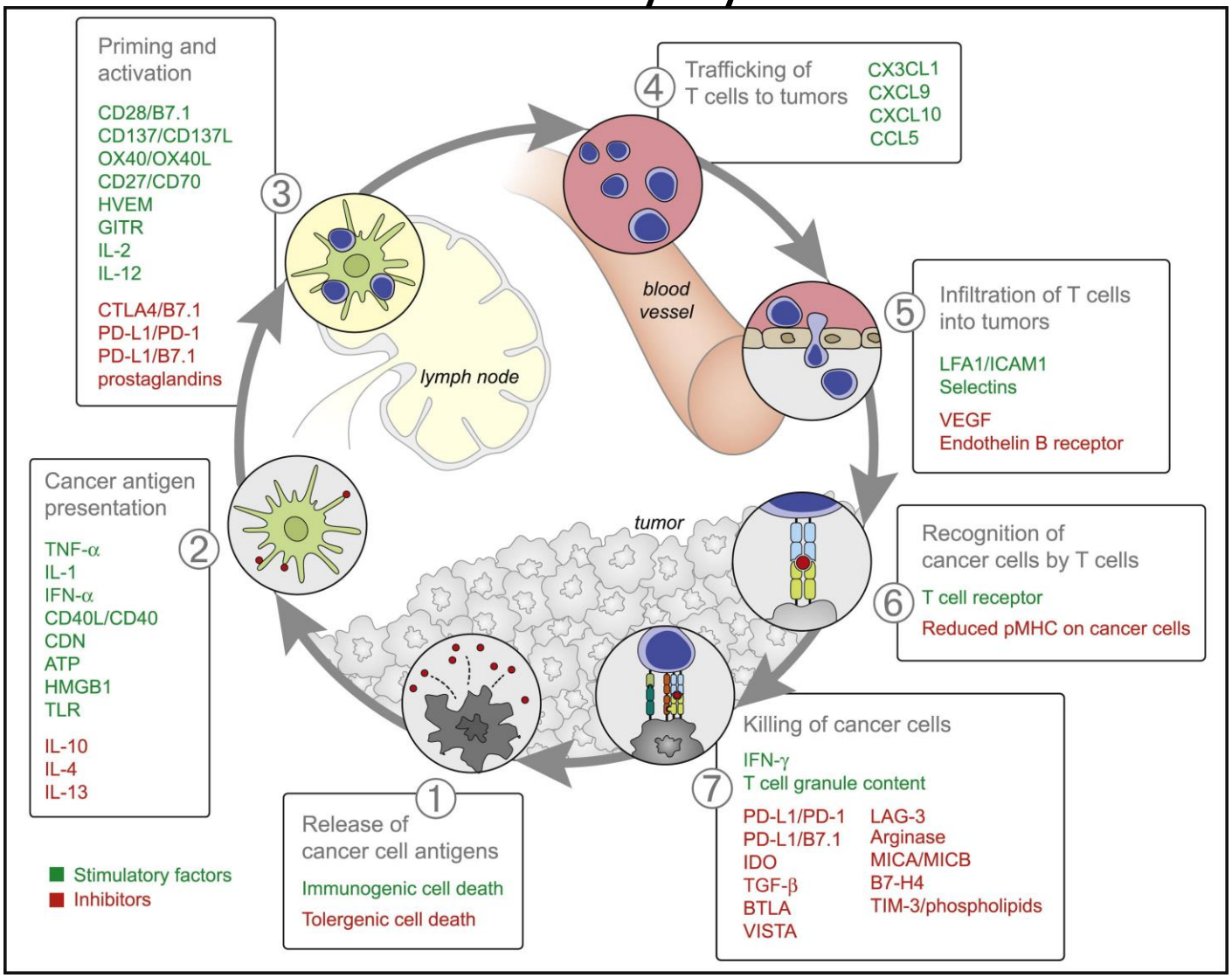
Drake CG. Nat Rev Immunol 2010;10:580–593

Putting on the brakes



Drake CG. Nat Rev Immunol 2010;10:580–593

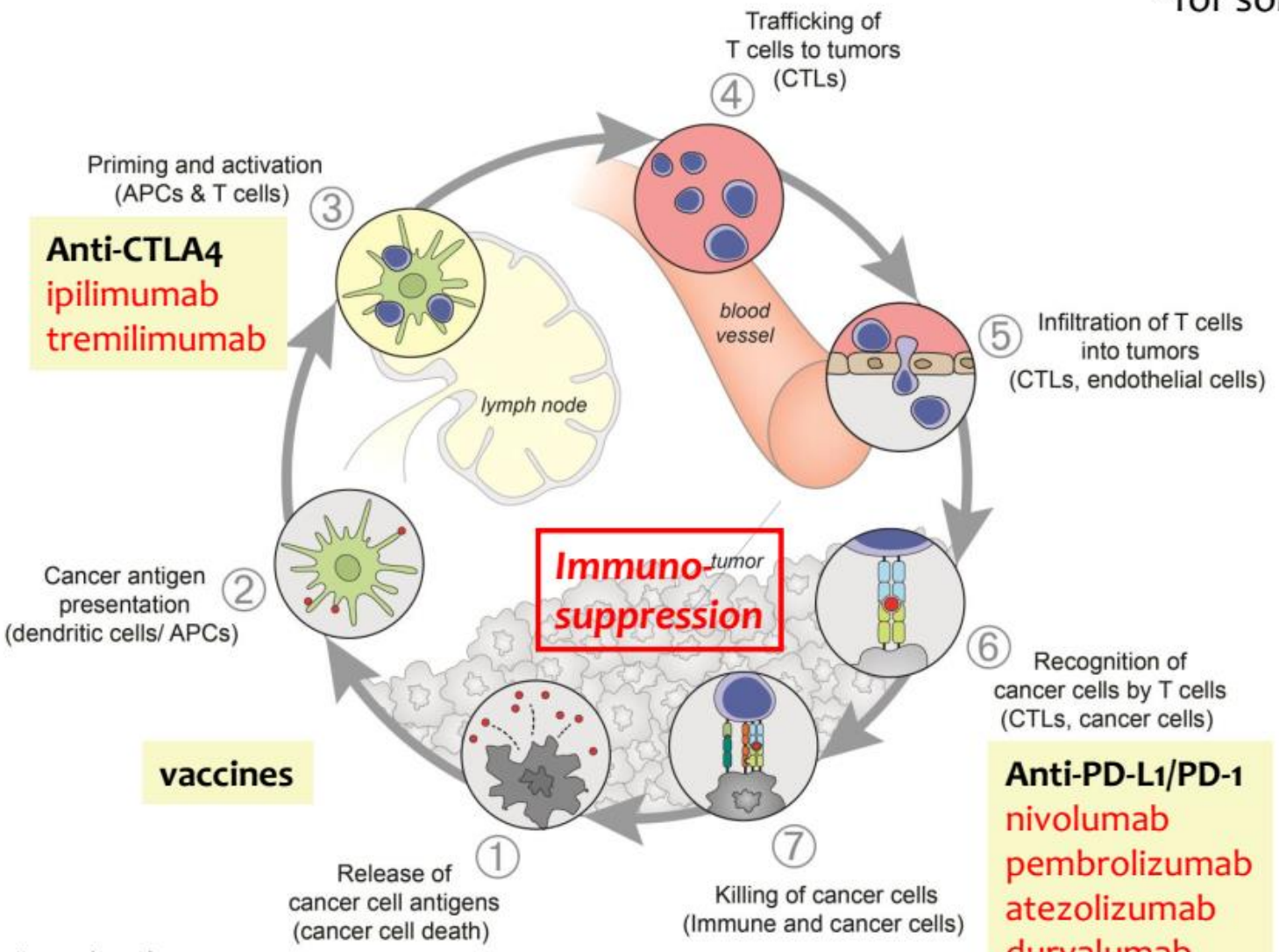
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle



Immunity Volume 39, Issue 1, 25 July 2013, Pages 1-10

What we have learned: immunosuppression is a rate limiting step to effective anti-tumor immunity*

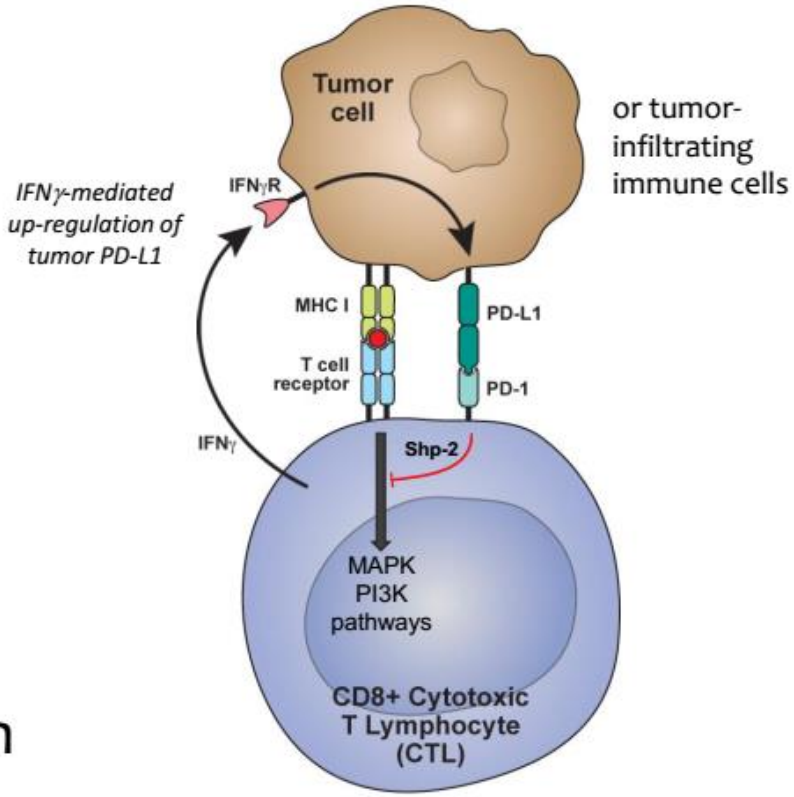
*for some patients



Chen & Mellman (2013) Immunity

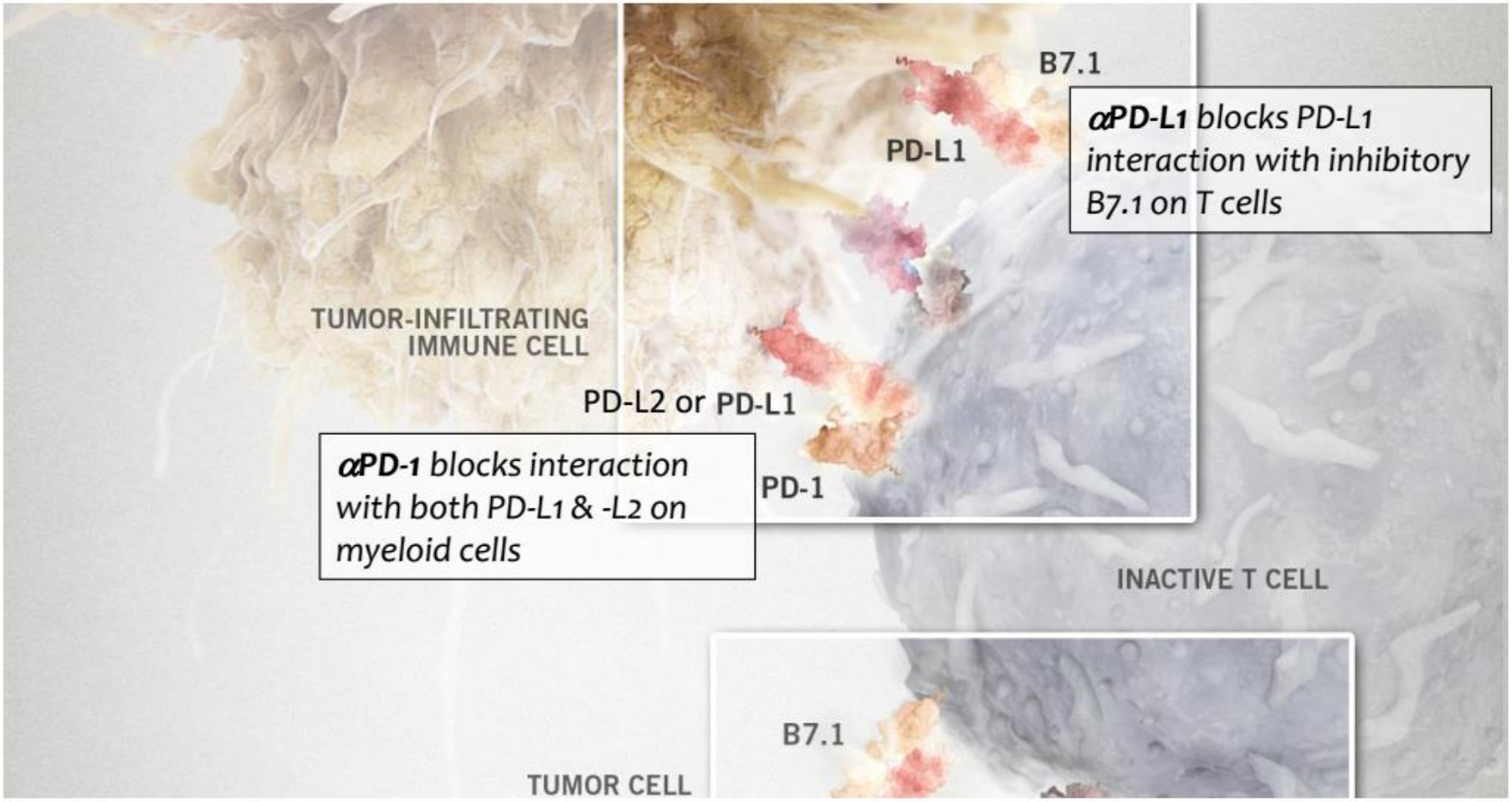
Blocking the PD-L1/PD-1 axis restores, or prevents loss of, T cell activity

- PD-L1/PD-1 interaction inhibits T cell activation, attenuates effector function, maintains immune homeostasis
- Tumors & surrounding cells up-regulate PD-L1 in response to T cell activity
- Blocking PD-L1/PD-1 restores or prevents loss of T effector function

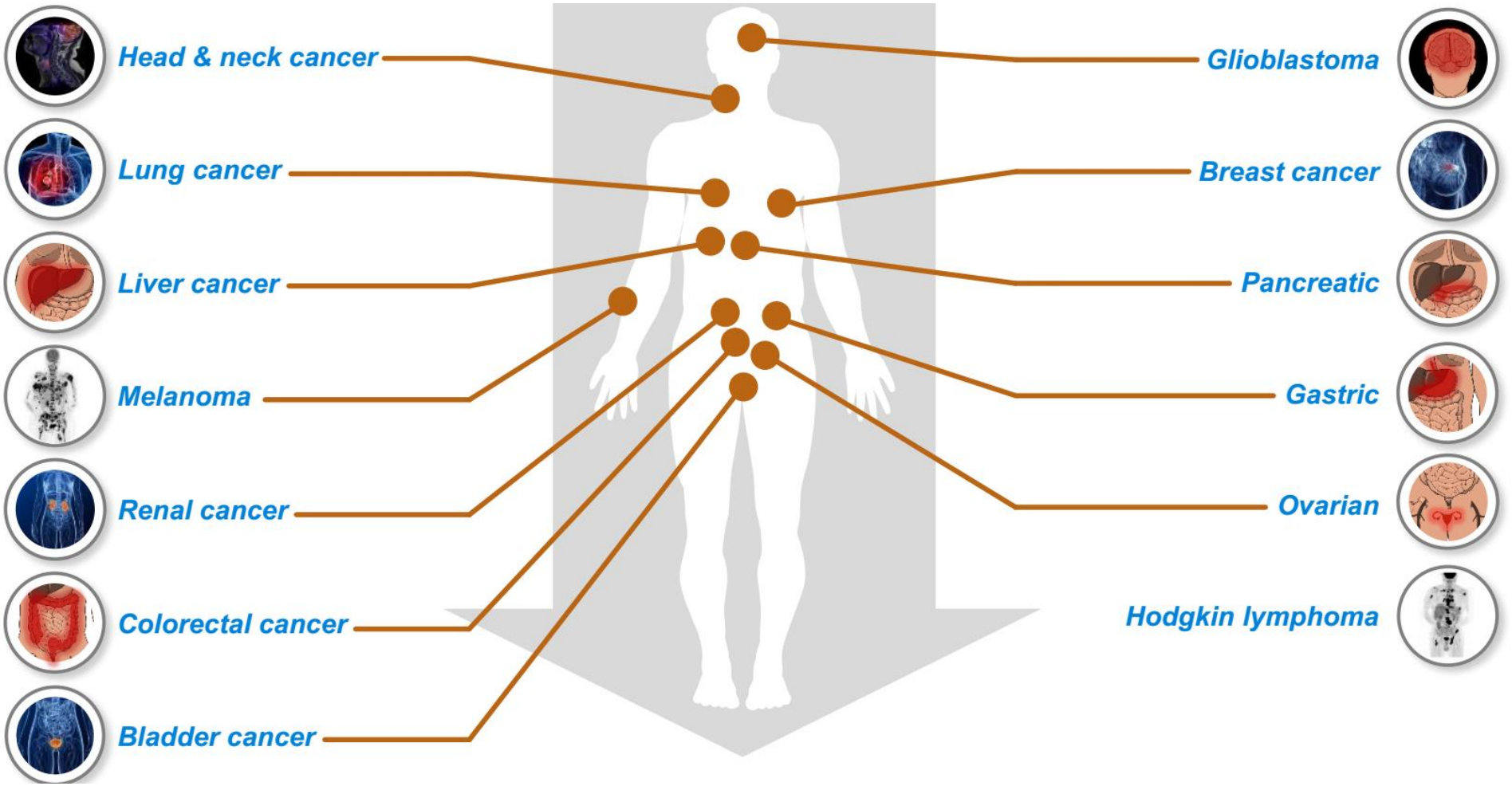


CancerImmunology
Genentech

αPD-L1 and αPD-1 exhibit similar early activities despite blocking different secondary interactions



Broad activity for anti-PD-L1/PD-1 in human cancer



- Broad activity, but only subset of patients benefit: ~10-30%

Immune Checkpoint Blockade

- Paradigm shift in cancer therapy
- Do not target tumor cells
- Do not involve vaccines or cytokines to turn “on” immune response
- Works by blocking inhibitory pathways to unleash anti-tumor immune responses

Cancer immunotherapy in 2018

- FDA-approved Immune Checkpoint Inhibitors
- 1 Anti-CTLA-4 antibody
- Ipilimumab (Yervoy)

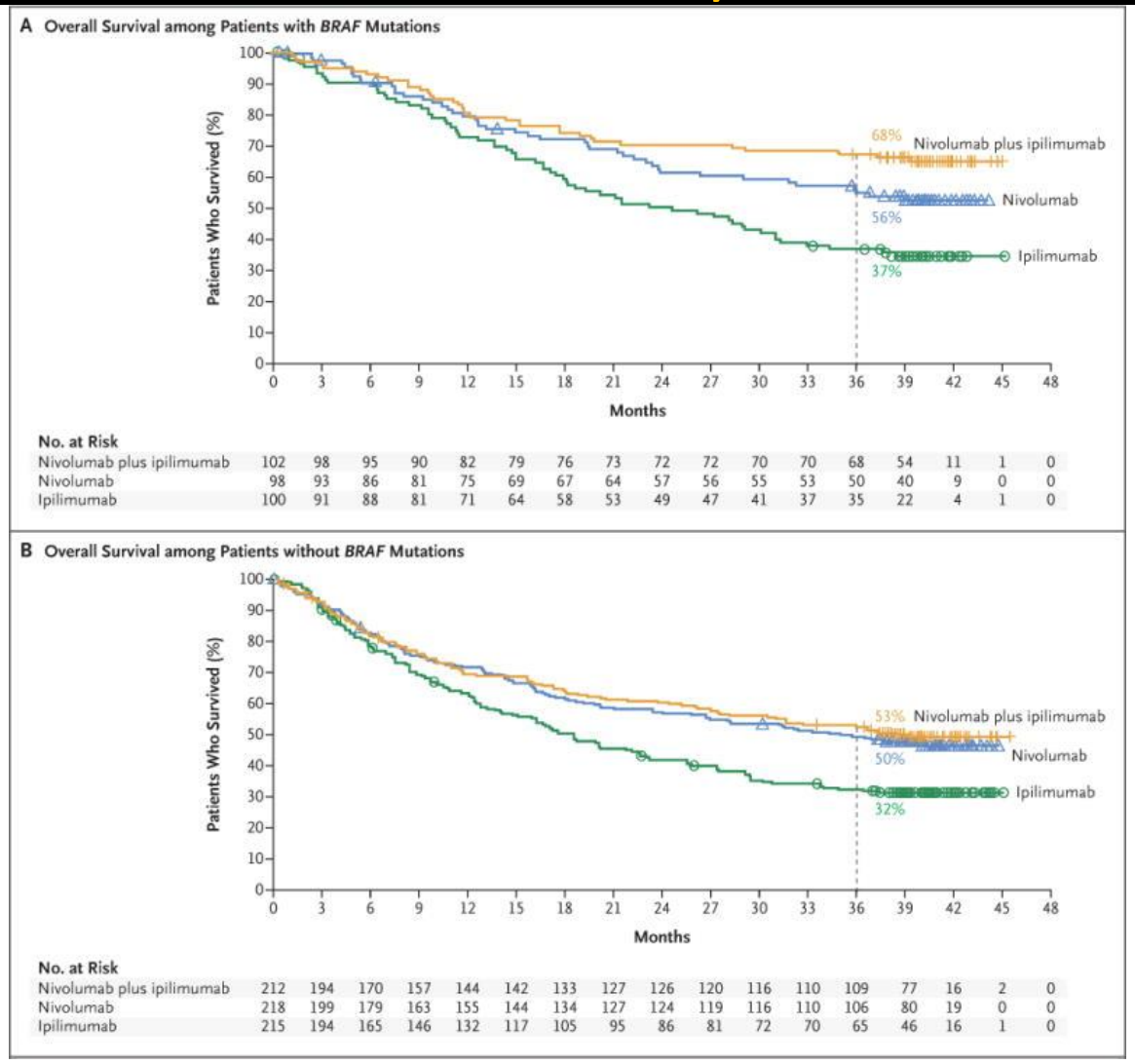
- 2 Anti-PD-1 antibodies
- Pembrolizumab (Keytruda)
- Nivolumab (Optivo)

- 3 Anti-PDL-1 antibodies
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)

Checkpoint Inhibitors

Cancer Type	Anti-CTLA4	Anti-PD1	Anti-PDL1
Metastatic Melanoma	x	x	
Metastatic non-small cell lung cancer (NSCLC) (Lung)		x	x
Metastatic squamous cell carcinoma of the head and neck		x	
Recurrent Hodgkin's Lymphoma		X	
Advanced Urothelial Cancer		x	x
Advanced Renal Cancer	x	x	
Advanced/Mets Gastric or GE Adenocarcinoma		x	
Progressive HCC (Liver)		X	
Metastatic Merkel Cell Carcinoma			x
Metastatic Solid Tumor with MMR or MSI		x	

Combination therapy is more effective (Advanced Melanoma)



N Engl J Med. 2017 Oct 5; 377(14): 1345–1356.

Immunotherapy in Ghana?

-Surgery
- Radiotherapy
- Chemotherapy
- Hormone therapy
- ~~Biologic therapy (Immunotherapy) ??~~

Presently there are only two centers (KBTH in Accra and KATH in Kumasi) that offer the full treatment for Breast cancer.

Source: National Strategy for Cancer Control In Ghana (2012 - 2016)

Summary

The past:

- Hampered by a poor understanding of human immunology

The present:

- Realization that normal immune homeostatic mechanisms restrict anti-cancer immunity
- Predominant focus on targets relevant to patients with pre-existing immunity

The frontier:

- Need to expand focus to include targeting stroma and to understand host genetics, the microbiome, and the environment
- Return to our origins to induce immunity in patients who have none

Acknowledgement

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Beyond Checkpoint Blockade for Cancer Immunotherapy

Prof. James P. Allison
Professor and chair of immunology and executive director of immunotherapy platform at the MD Anderson Cancer Center at the University of Texas.

Immune Checkpoint Blockade in Cancer Therapy

Ira Mellman
Genentech
South San Francisco, California
The immunotherapy of cancer: past, present & the next frontier