Immuno-Oncology

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Outline

- Background on Cancer Immunotherapy
  - History
  - Cancer-Immunity Cycle
- Immunotherapeutic approaches, mechanisms, challenges
  - Immune Checkpoints
  - T Cell Therapies
  - Vaccines

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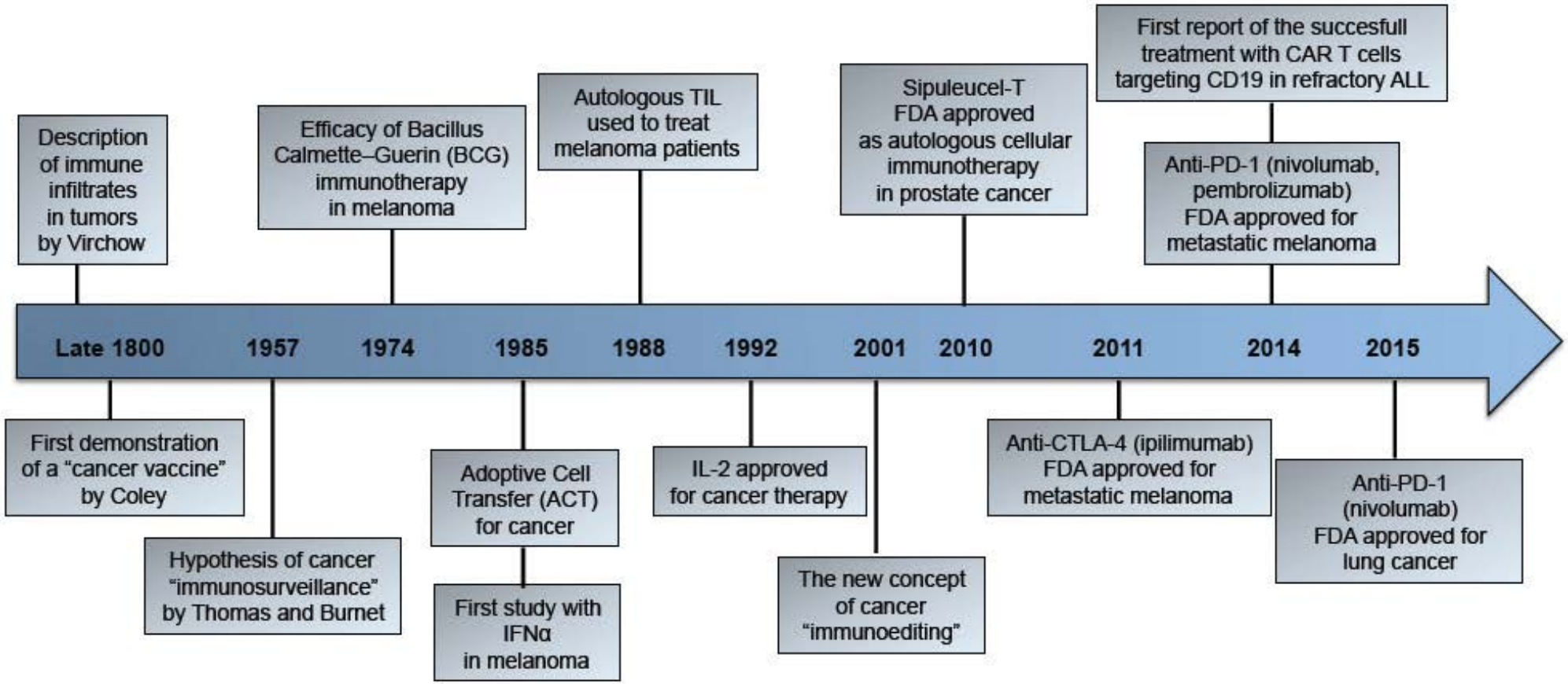
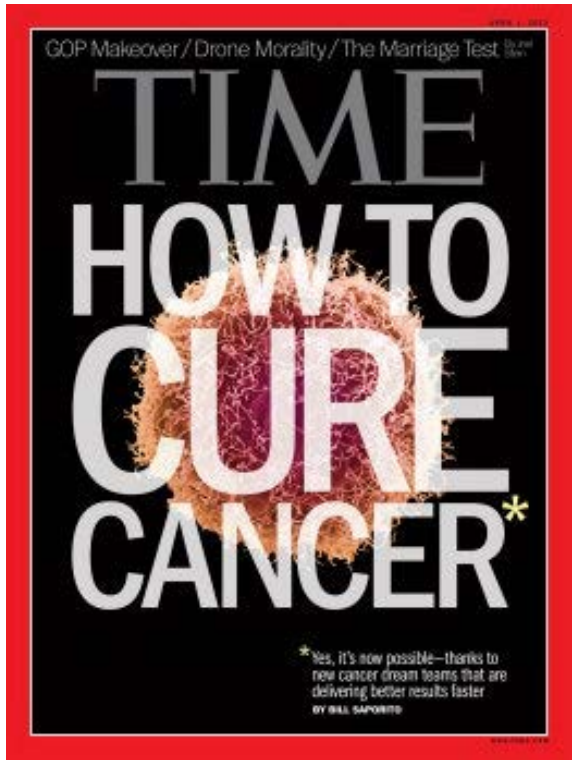
Timeline for Cancer Immunotherapy



(Discovery Medicine)



The New York Times | https://nyti.ms/2C8lipN

HEALTH

Doctors Said Immunotherapy Would Not Cure Her Cancer. They Were Wrong.

By GINA KOLATA FEB. 19, 2018

No one expected the four young women to live much longer. They had an extremely rare, aggressive and fatal form of ovarian cancer. There was no standard treatment.

The women, strangers to one another living in different countries, asked their doctors to try new immunotherapy drugs that had revolutionized treatment of cancer. At first, they were told the drugs were out of the question — they would not work against ovarian cancer.

Now it looks as if the doctors were wrong. The women managed to get immunotherapy, and their cancers went into remission. They returned to work; their lives returned to normalcy.

The tale has befuddled scientists, who are struggling to understand why the drugs worked when they should not have. If researchers can figure out what happened here, they may open the door to new treatments for a wide variety of other

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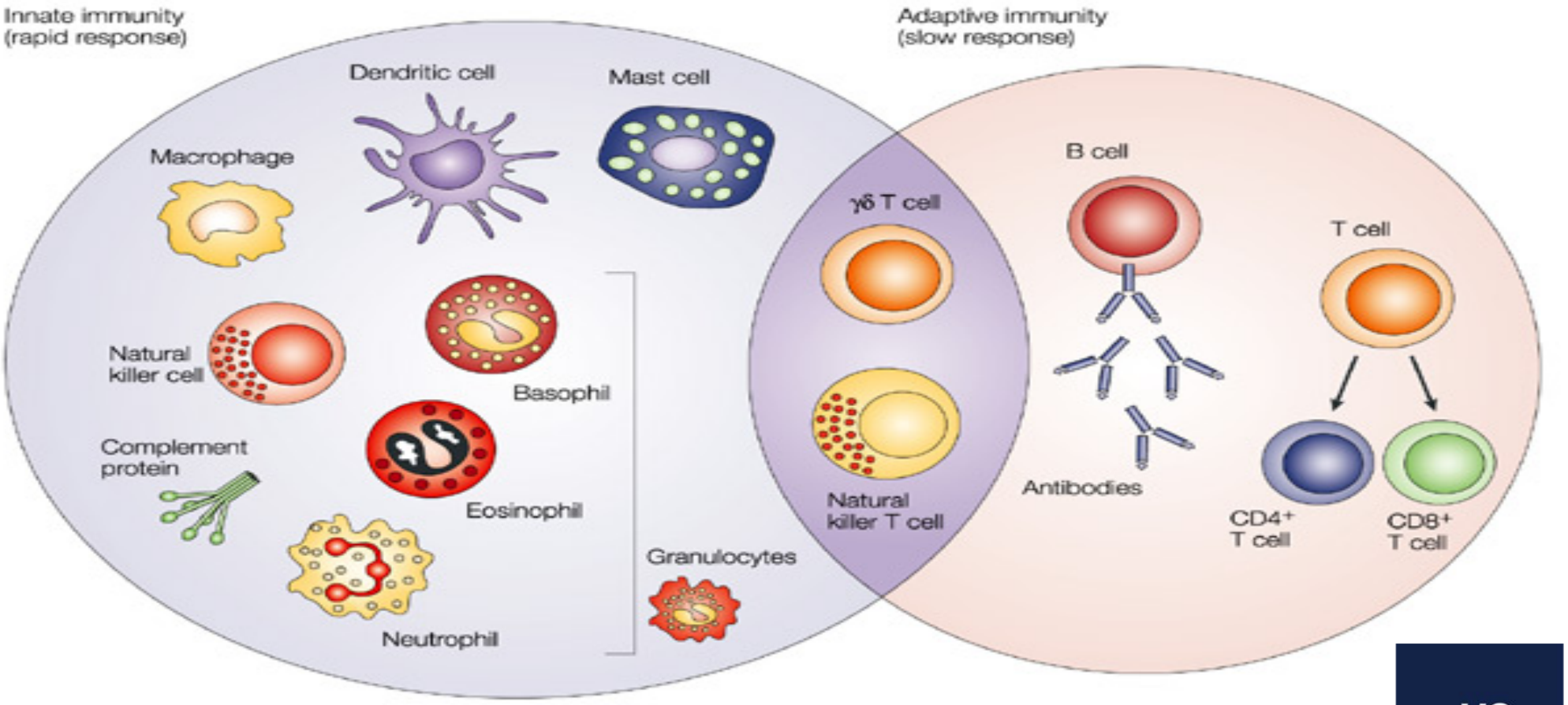
Metastatic cancers that respond to IO

2005	2019	
Melanoma	Melanoma (incl adjuvant)	Approved 2011, 2014, (2019)
Kidney cancer	Kidney cancer	Approved in 2015
	Prostate cancer	Approved 2010
	Lung cancer (NSCLC incl adjuvant, SCC, SCLC)	Approved 2015, 2019
	Bladder cancer	Approved in 2016
	Colorectal cancer	
	Gastric cancer	Approved in 2017
	Cholangiocarcinoma	
	Hepatocellular	Approved in 2017
	Ovarian cancer	
	Endometrial	
	Cervical SCC	Approved in 2018
	Breast cancer (TNBC)	Approved in 2019
	Lymphoma (NHL)	Approved in 2017
	Hodgkin's	Approved in 2016
	Mycosis Fungoides	
	Merkel Cell	Approved in 2017
	Cutaneous SCC	Approved in 2018
	Leukemia (ALL)	Approved in 2017
	Any MSI solid tumor	Approved in 2017

COMPONENTS OF THE IMMUNE SYSTEM



(Dranoff, G. Nat Rev Cancer 2004, 4:11-22.)

INNATE VS. ADAPTIVE IMMUNITY

Innate Immunity

- First line of defense
- Immediate reactivity
- Not antigen-specific
- No memory

Adaptive Immunity

- Antigen-specific
- First encounter may taken time to build up efficacy
- Life-long immunity possibly
- Preemptive immunization (vaccination) possible

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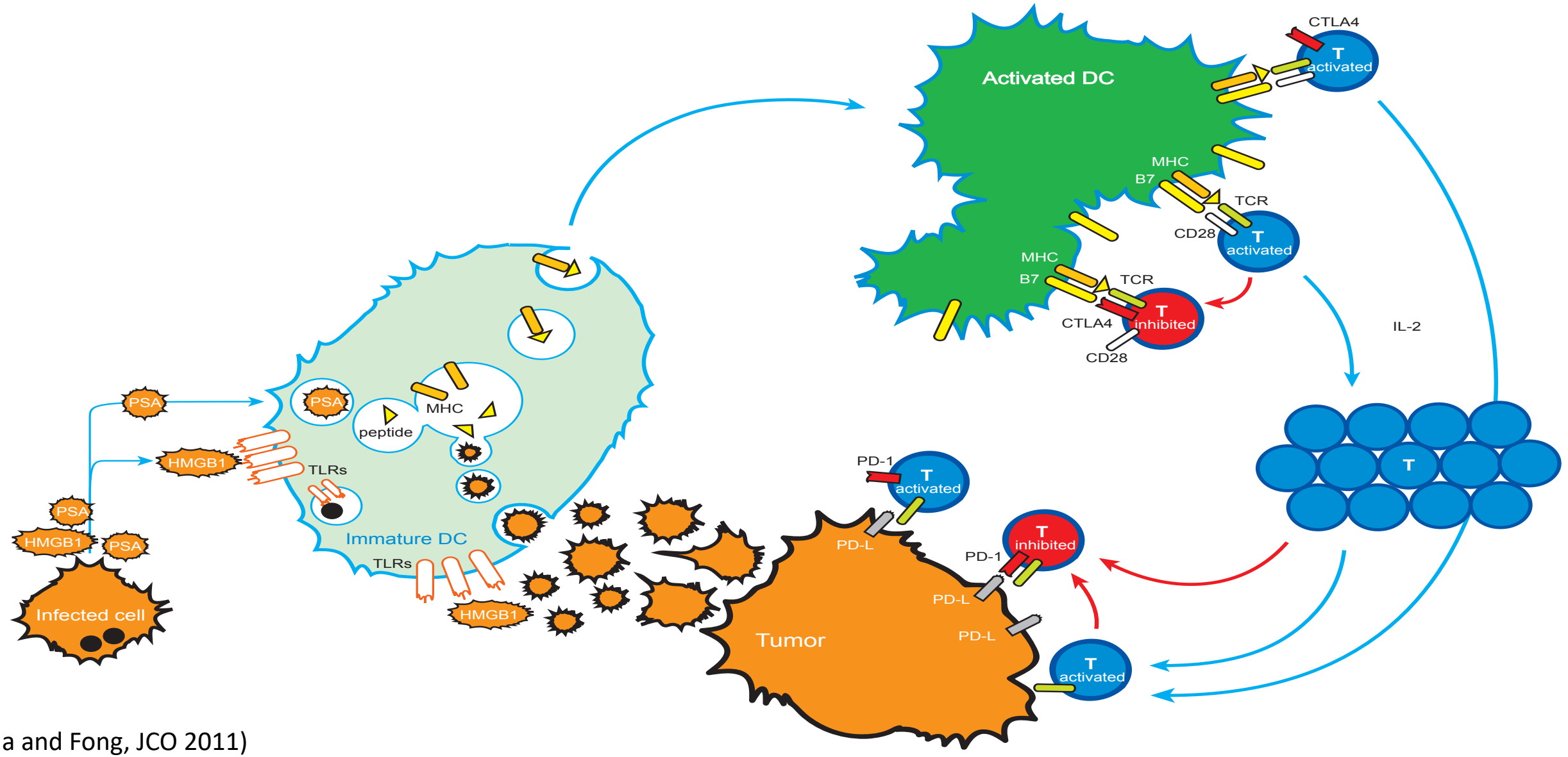
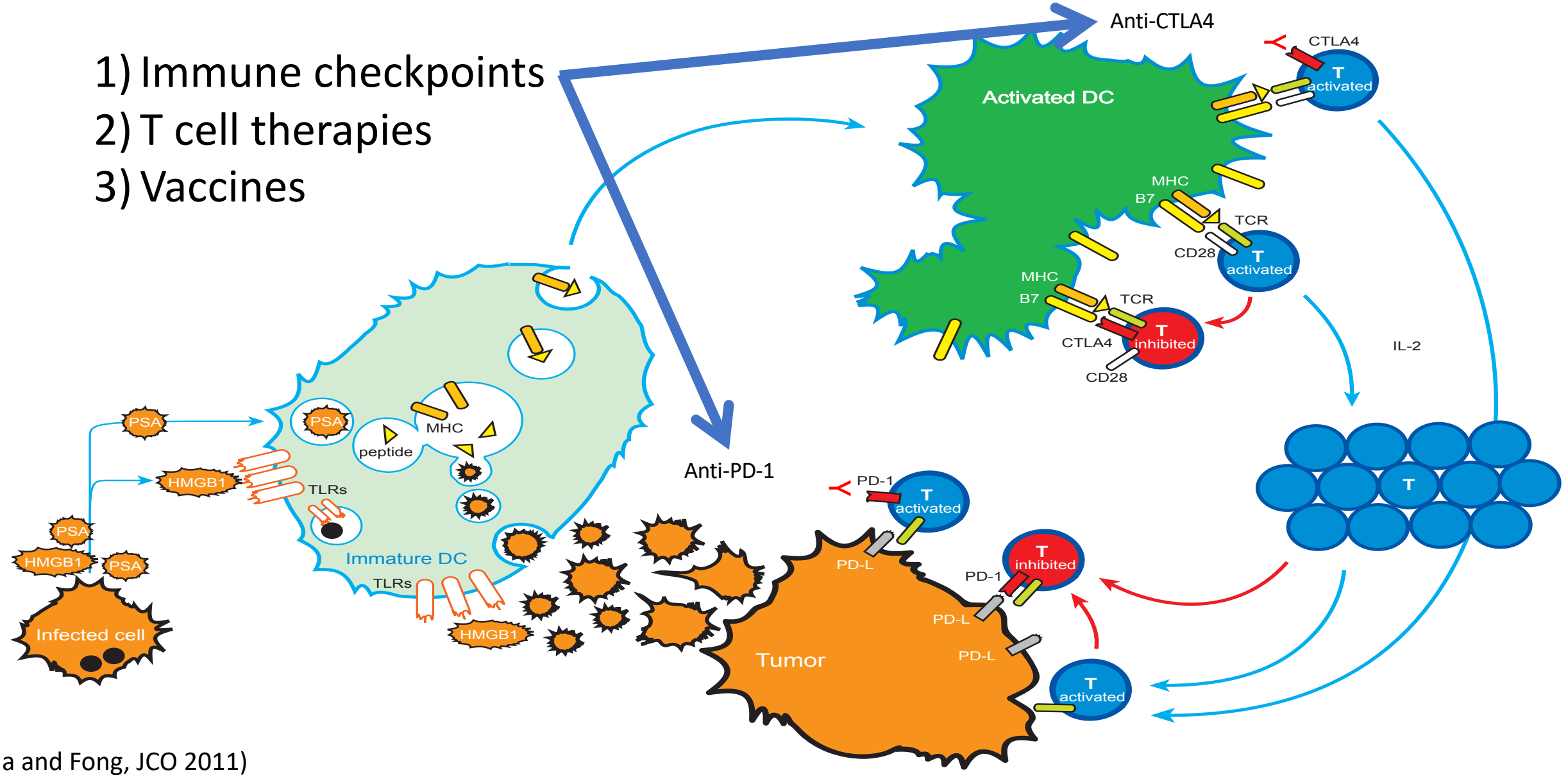
“Cancer-Immunity Cycle”



(Cha and Fong, JCO 2011)

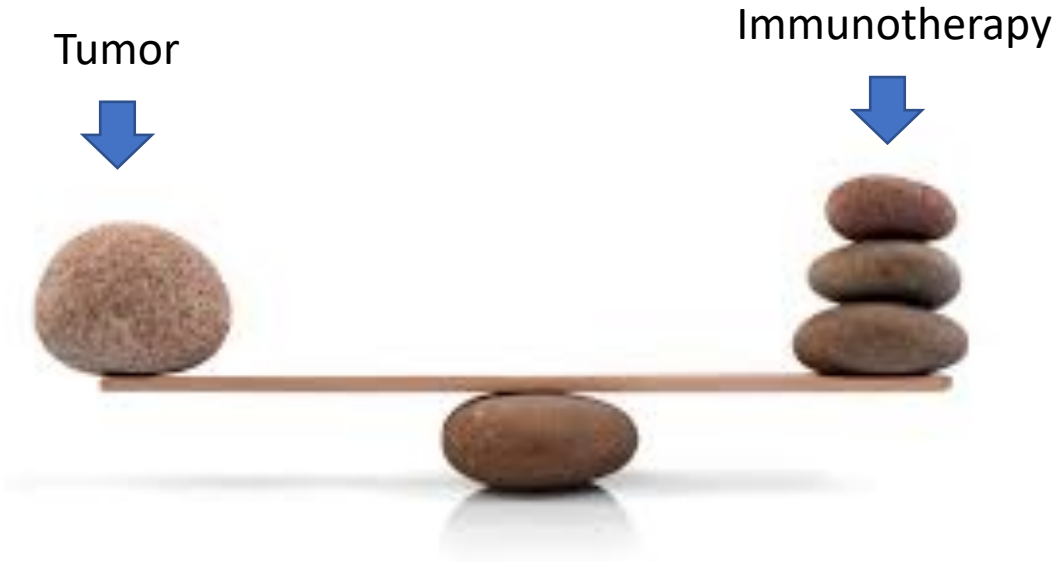
Cancer Immunotherapy

1) Immune checkpoints
2) T cell therapies
3) Vaccines



(Cha and Fong, JCO 2011)

IMMUNE CHECKPOINTS: A BALANCE THAT CONTROLS THE IMMUNE SYSTEM

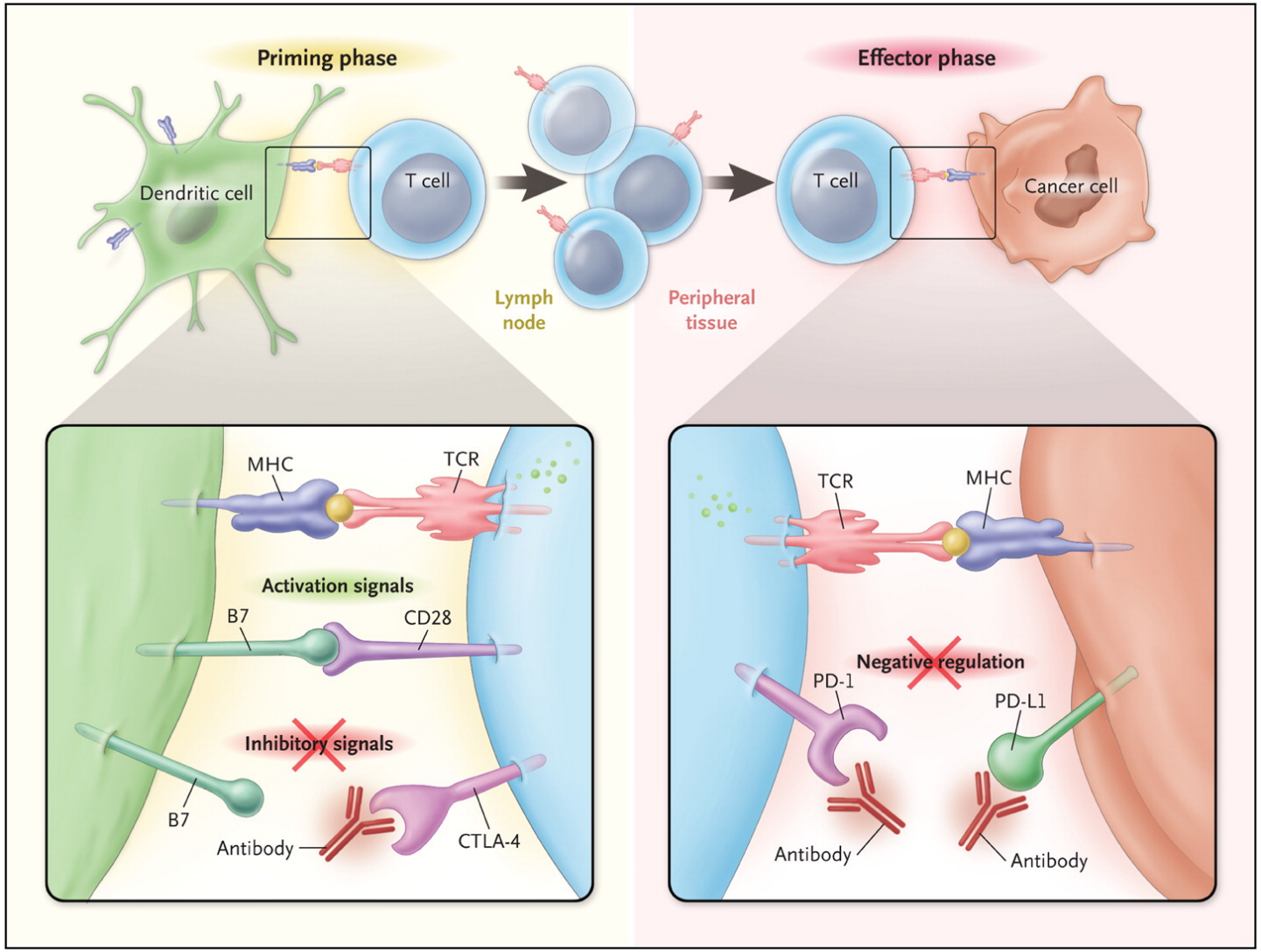


Immune checkpoint blockade

- "Removing the brakes" on T cells

Agent	Target
*Ipilimumab	CTLA-4
Tremelimumab	CTLA-4
*Nivolumab	PD-1
*Pembrolizumab	PD-1
*Atezolizumab	PD-L1
*Avelumab	PD-L1
*Durvalumab	PD-L1

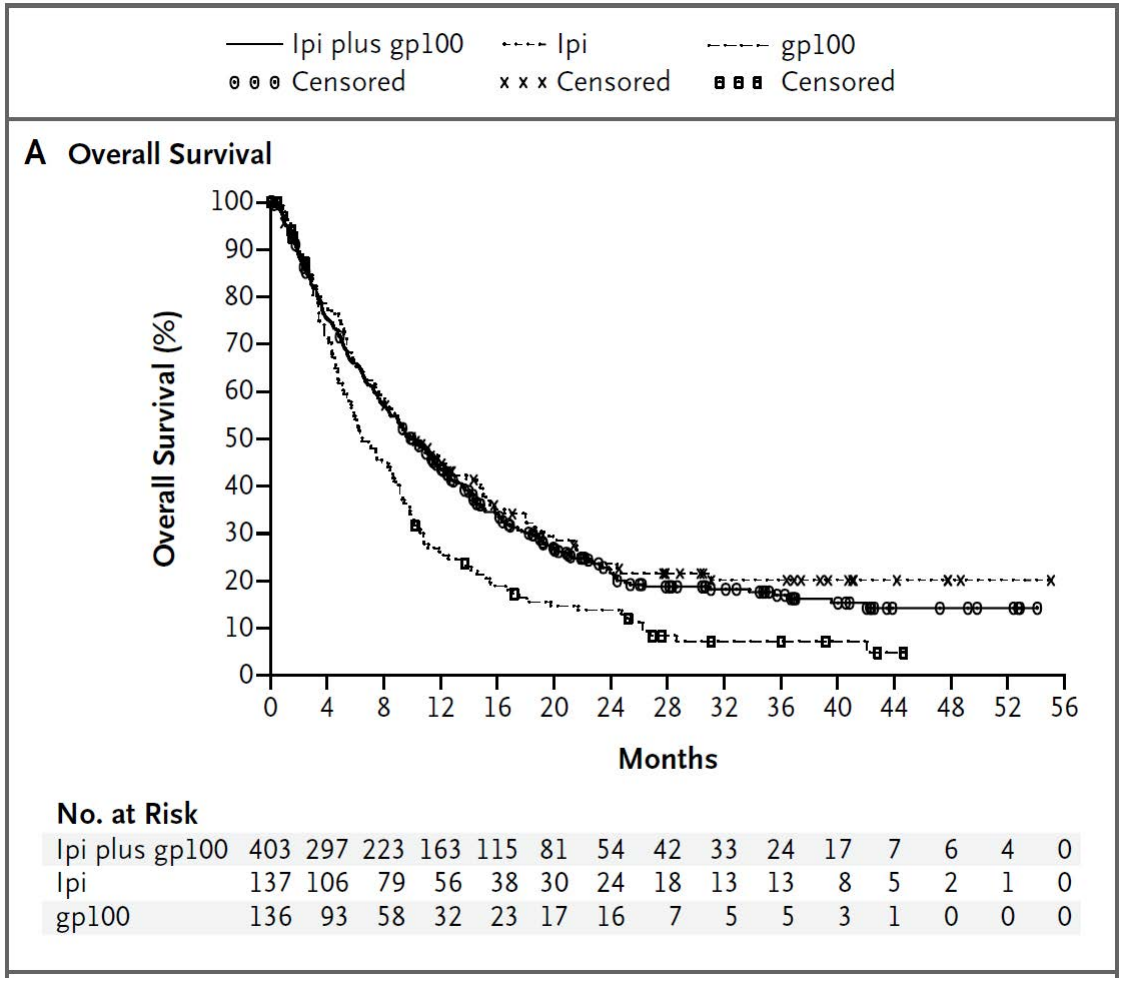
*FDA approved



(Ribas A. N Engl J Med 2012;366:2517-19)

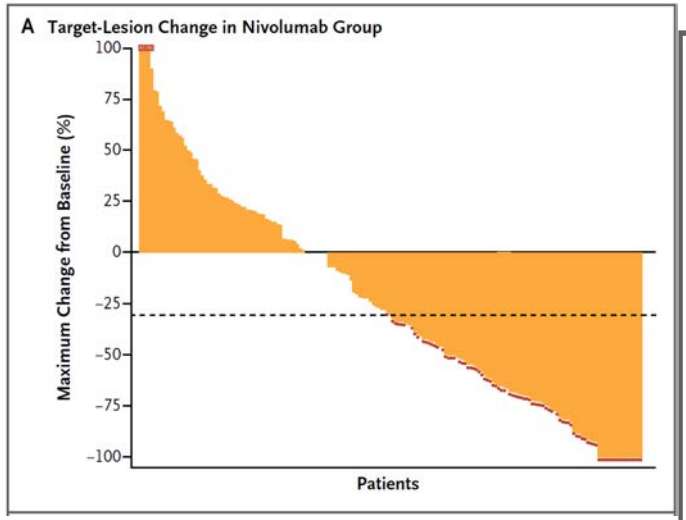
Anti-CTLA-4 in metastatic melanoma

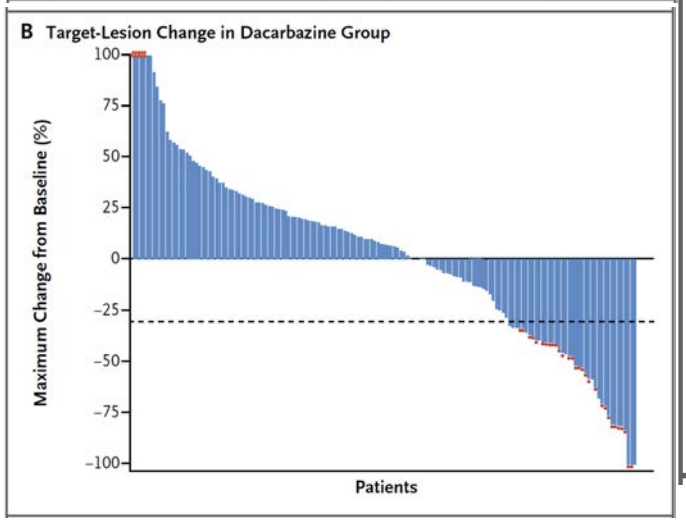
- Patients with metastatic melanoma (previously treated)
- Ipilimumab vs. vaccine/ipilimumab vs. vaccine
- OS (median):
  - 10 vs. 10.1 vs. 6.4 months
- FDA approved 3/2011

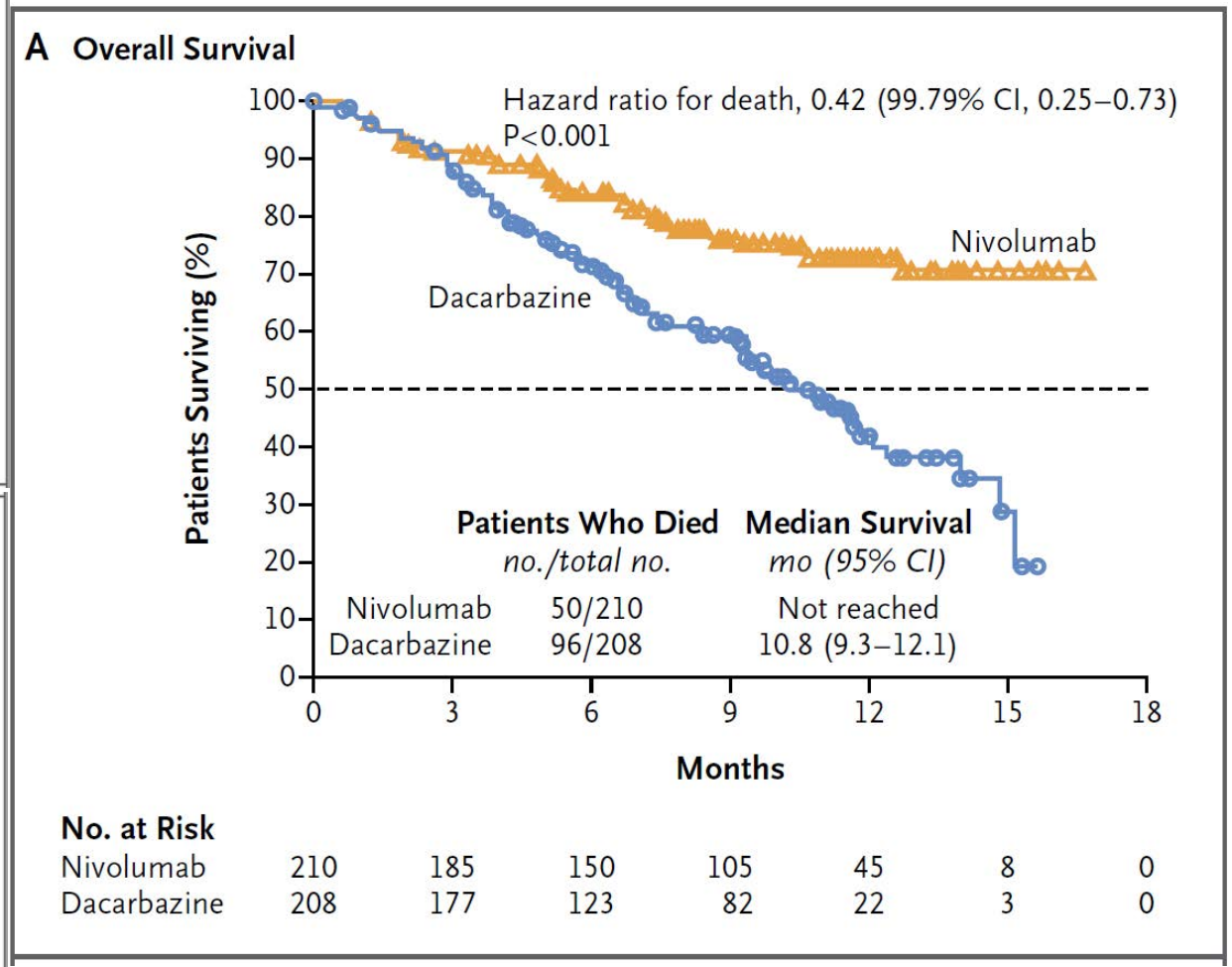


(Hodi et al, NEJM 2010, Wolchok et al Ann Oncol 2013)

Anti-PD-1 in metastatic melanoma







Previously treated

(Robert et al. NEJM 2015)

Combining anti-CTLA-4 and anti-PD-1

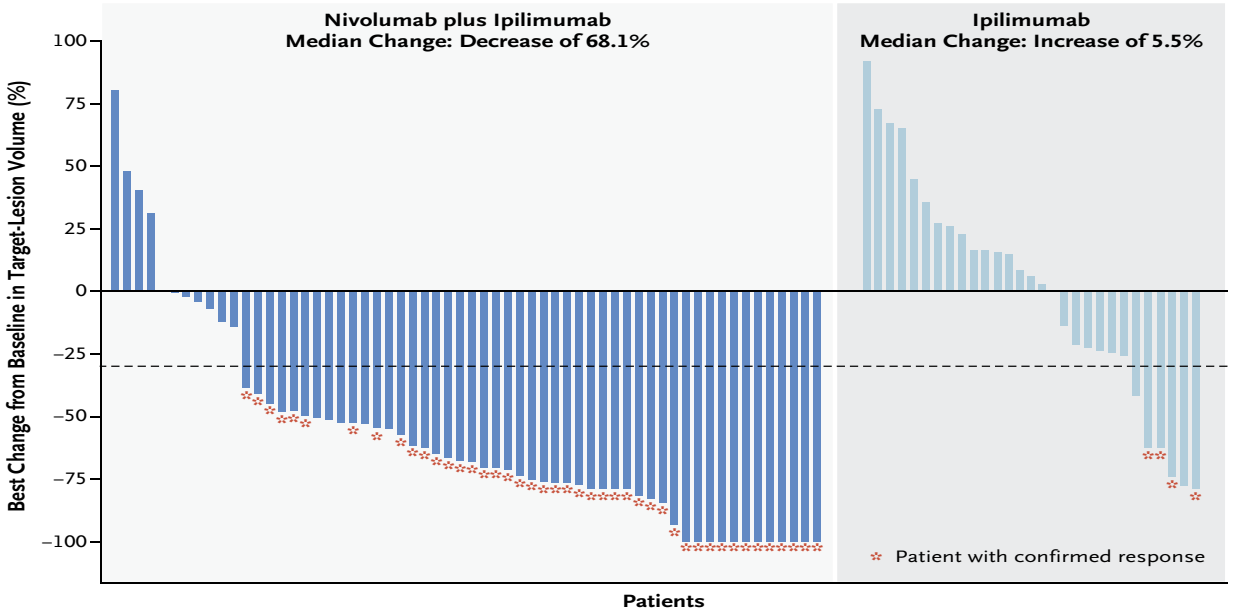


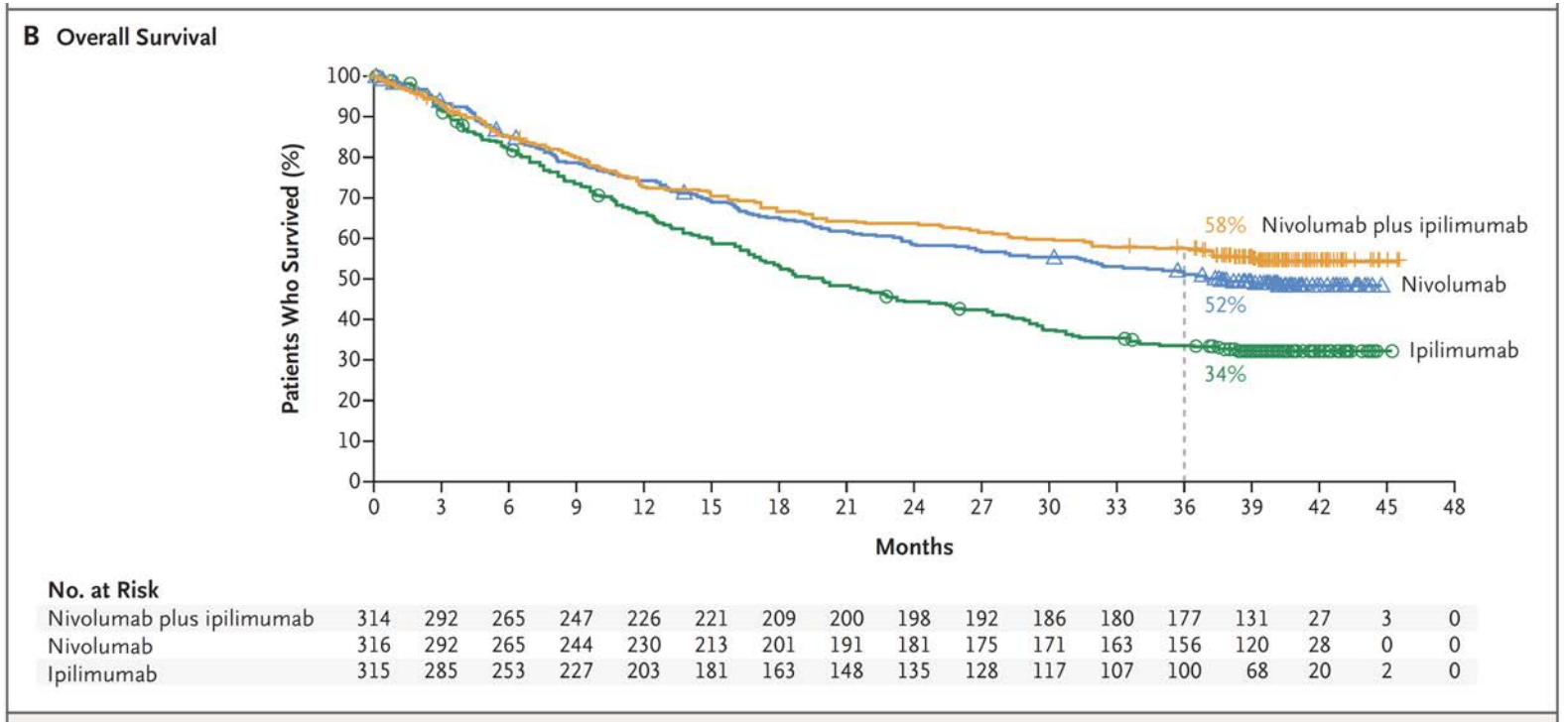
Table 2. Response to Treatment.

Variable	Patients with *BRAF* Wild-Type Tumors		Patients with *BRAF* V600 Mutation–Positive Tumors	
	Nivolumab plus Ipilimumab (N = 72)	Ipilimumab (N = 37)	Nivolumab plus Ipilimumab (N = 23)	Ipilimumab (N = 10)
Best overall response — no. (%)*				
Complete response	16 (22)	0	5 (22)	0
Partial response	28 (39)	4 (11)	7 (30)	1 (10)
Stable disease	9 (12)	13 (35)	3 (13)	1 (10)
Progressive disease	10 (14)	15 (41)	5 (22)	7 (70)
Could not be determined	9 (12)	5 (14)	3 (13)	1 (10)
Patients with objective response — no. (% [95% CI])†	44 (61 [49–72])	4 (11 [3–25])	12 (52 [31–73])	1 (10 [0–45])

(Postow et al. NEJM 2015)

Previously untreated

COMBINING ANTI-CTLA-4 AND ANTI-PD-1

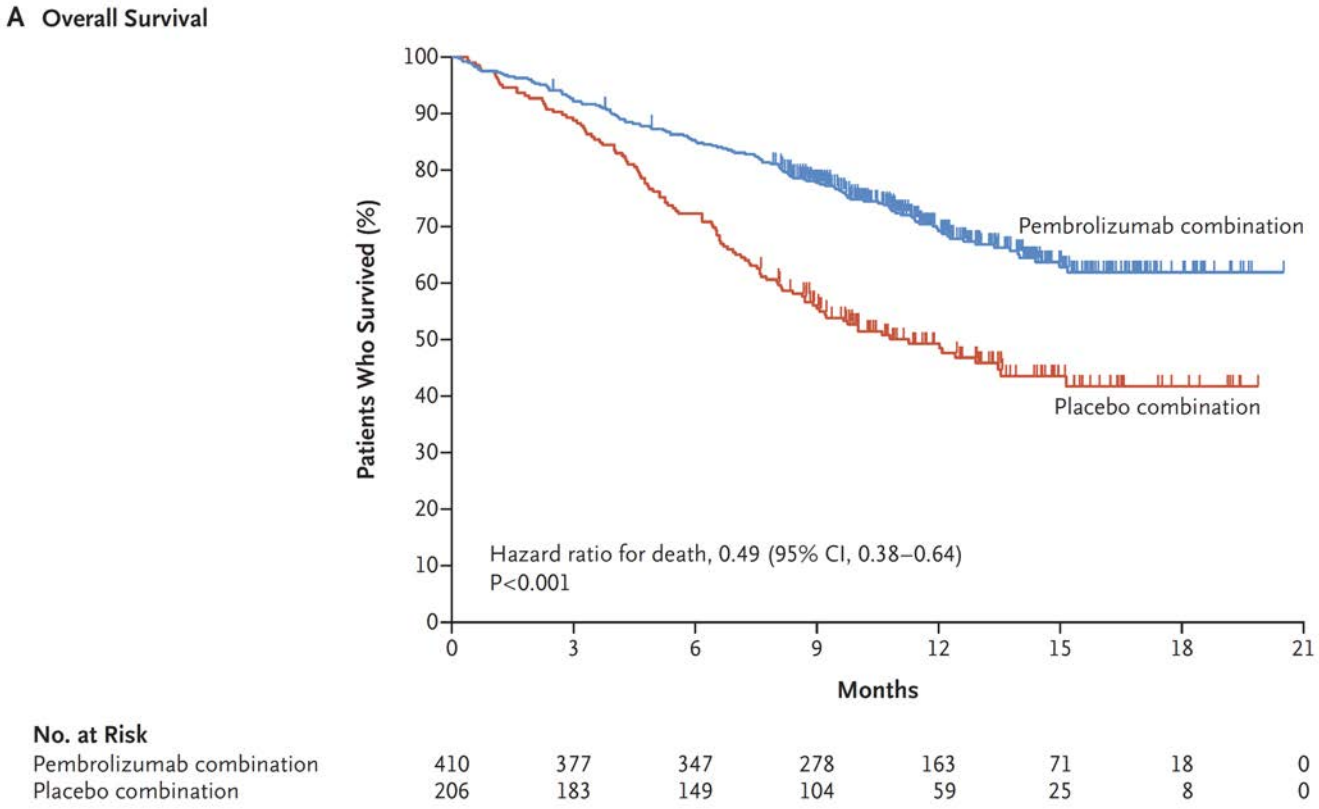


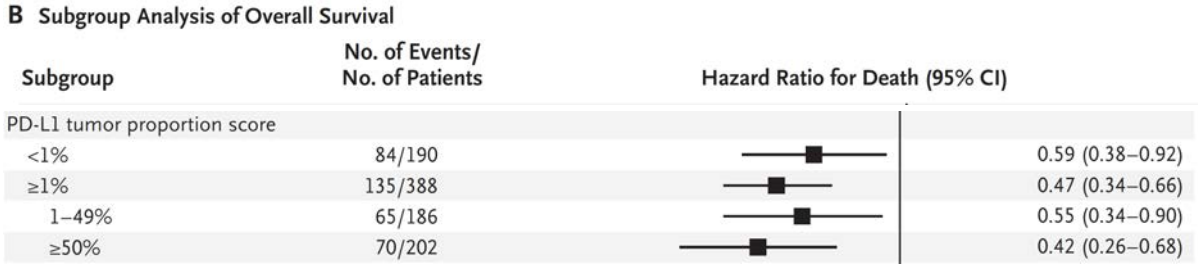
Previously untreated

- This combination also approved for second-line metastatic renal cell carcinoma (4/2018)

(Wolchok et al. NEJM 2017)

COMBINING ANTI-PD-1 AND CONVENTIONAL THERAPY



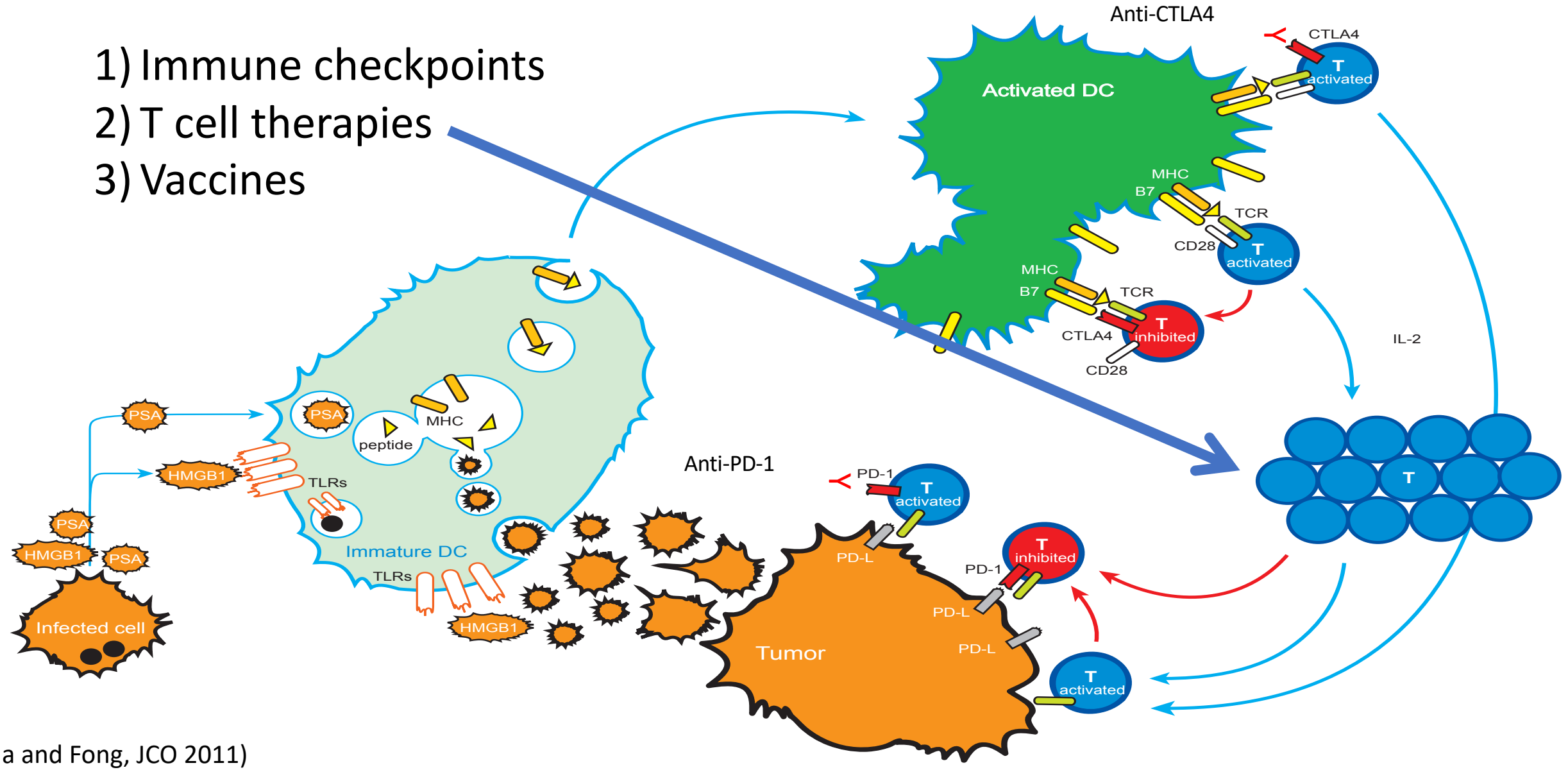


- Metastatic non-small cell lung cancer (not squamous cell)
- No mutations that would respond to targeted therapy (EGFR, ALK)
- PD-1 plus chemo superior regardless of PD-L1 staining level
- Chemo/PD-1 now approved for:
  - NSCLC (non-squam, squamous)
  - SCLC

(Gandhi et al. NEJM 2018)

Cancer Immunotherapy

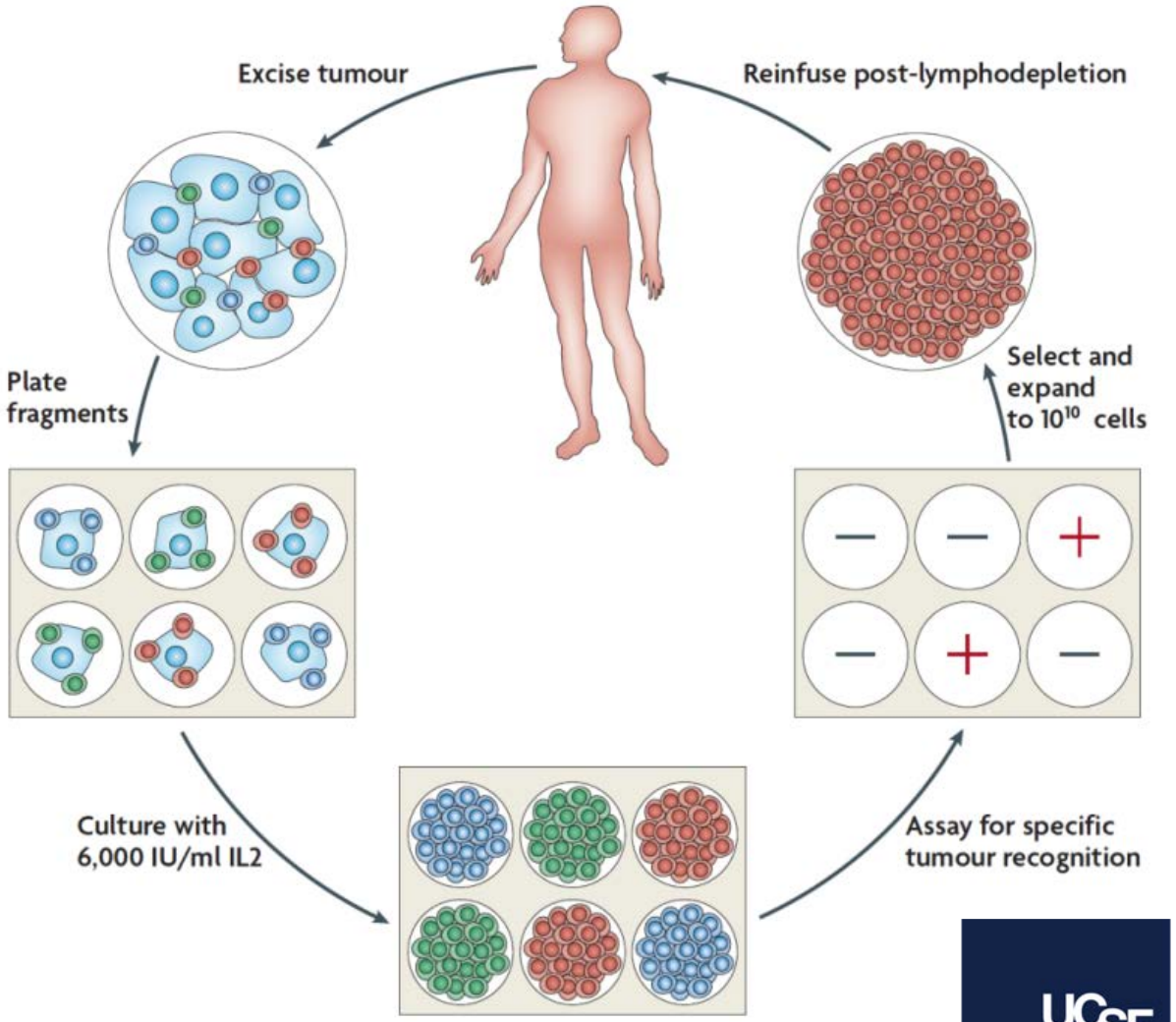
1) Immune checkpoints
2) T cell therapies
3) Vaccines



(Cha and Fong, JCO 2011)

Adoptive CELL THERAPY (ACT)

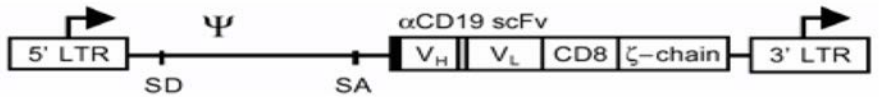
- Tumor cut into small fragments
- Tumor fragments grown in cultures with high-dose IL-2
- Tumor infiltrating lymphocytes (TILs) expanded for ~3 weeks
- Expanded TILs are assayed and pooled for reinfusion after conditioning lymphodepleting chemotherapy



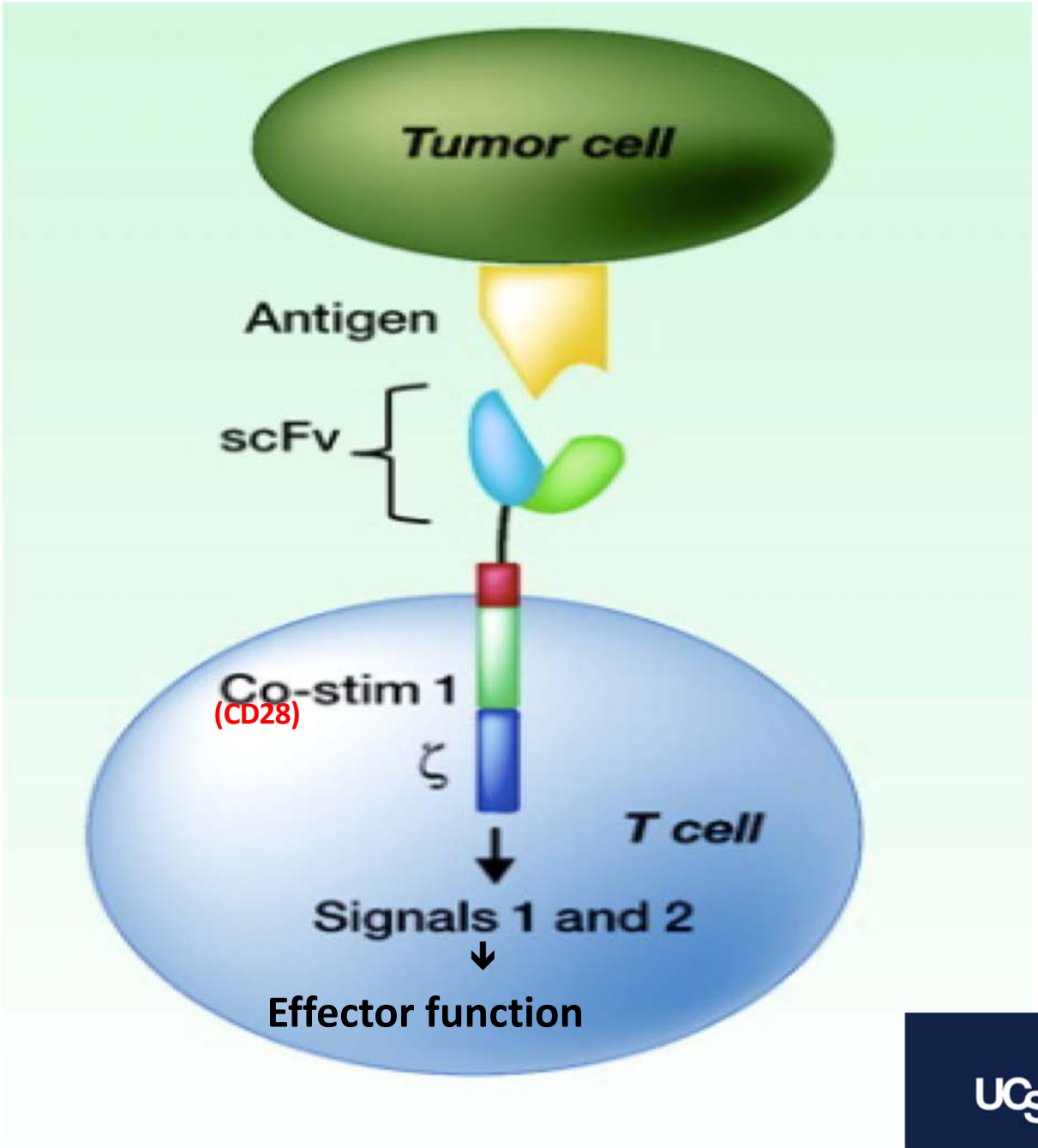
(Rosenberg SA, et al. Nature Reviews Cancer 2008;8:299-308)

Chimeric antigen receptor (CAR) T cells

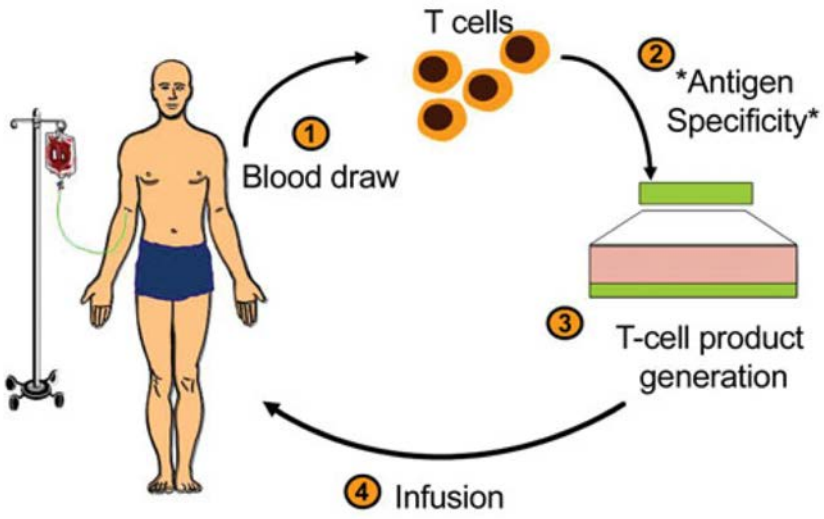
- Specificity of a monoclonal antibody
- Not dependent on MHC
- Activates T cells with signals 1 & 2



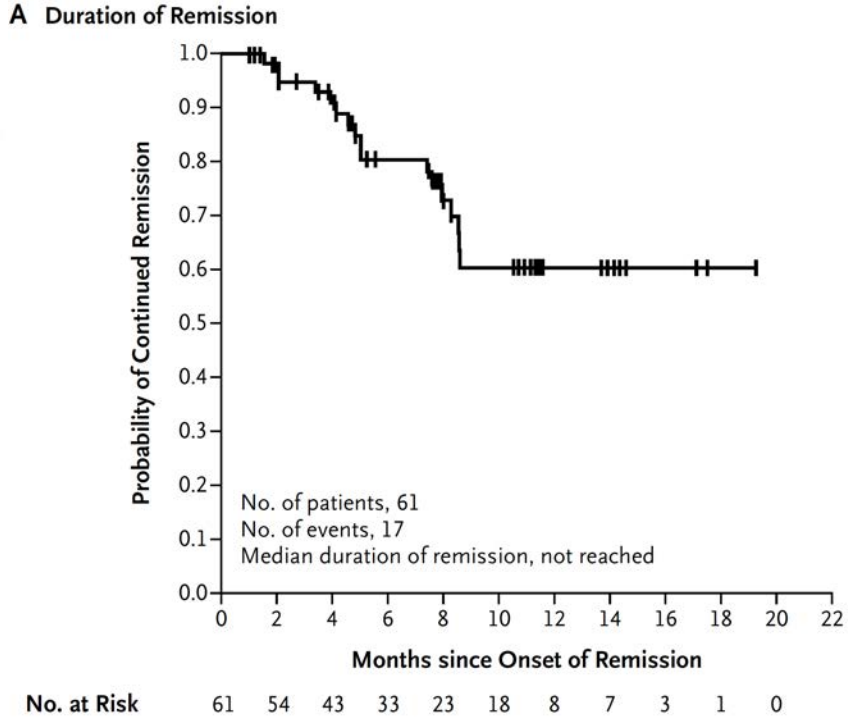
Sample CAR gene construct

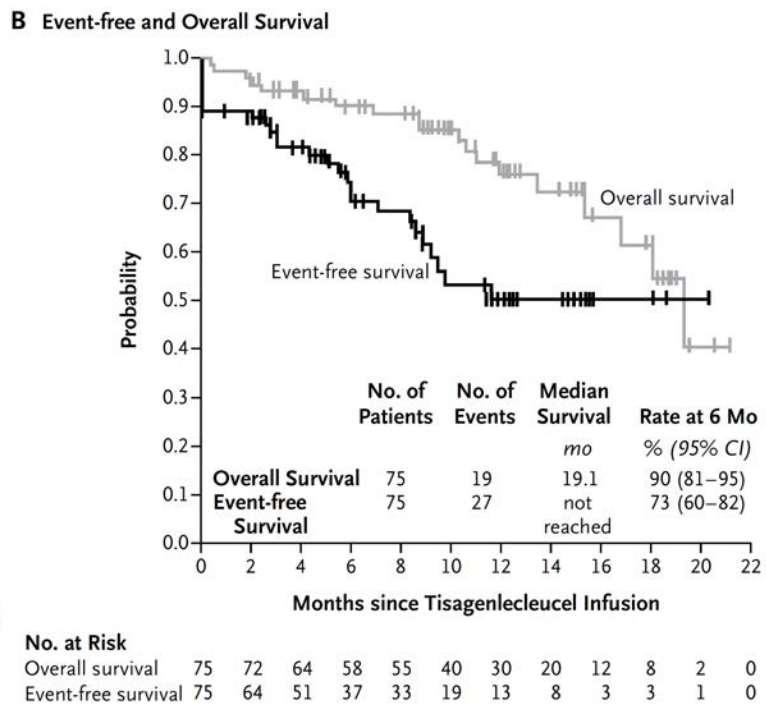


CAR19-T CELL THERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA



- 81% of patients with remission at 3 months





*** FDA approved for pediatric and young adult B cell ALL (8/2017)**
*** FDA approved for adult non-Hodgkin lymphoma (10/2017)**

(Maude et al. NEJM 2018)

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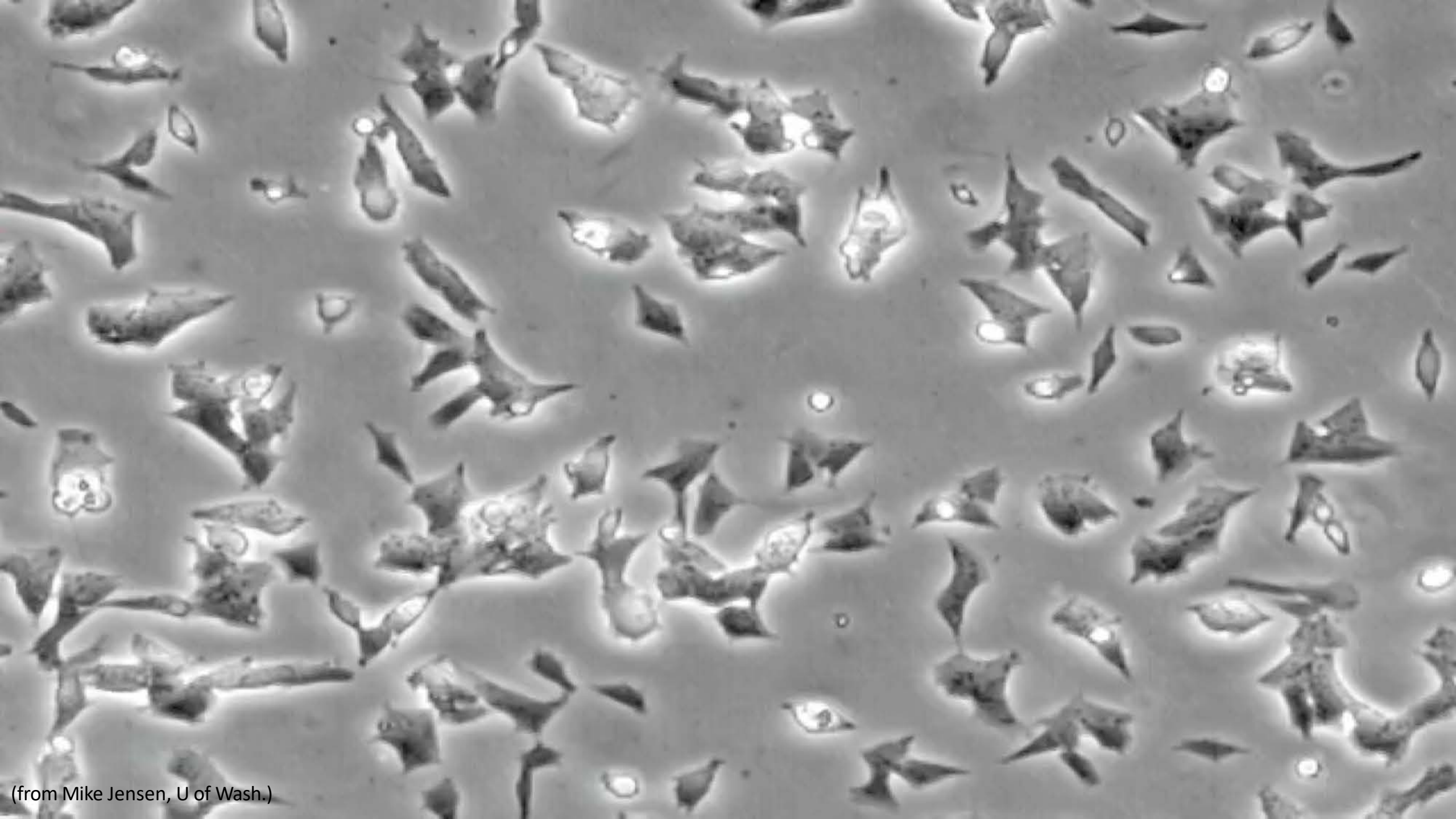

(from Mike Jensen, U of Wash.)

CHALLENGES: CAR-T

- Can responses be enhanced for liquid tumors?
  - Which cell populations are responsible for benefit?
  - Are there specific microenvironments in the body where they act?
  - Can we avoid resistance?
    - Dual specificity CAR
  - Can we fine tune activity?

- Can we predict or minimize toxicity?
  - Cytokine release syndrome
  - Neurotoxicity

- Can CAR-T work for solid tumors?
  - What factors hinder CAR-T activity in the solid tumor environment?

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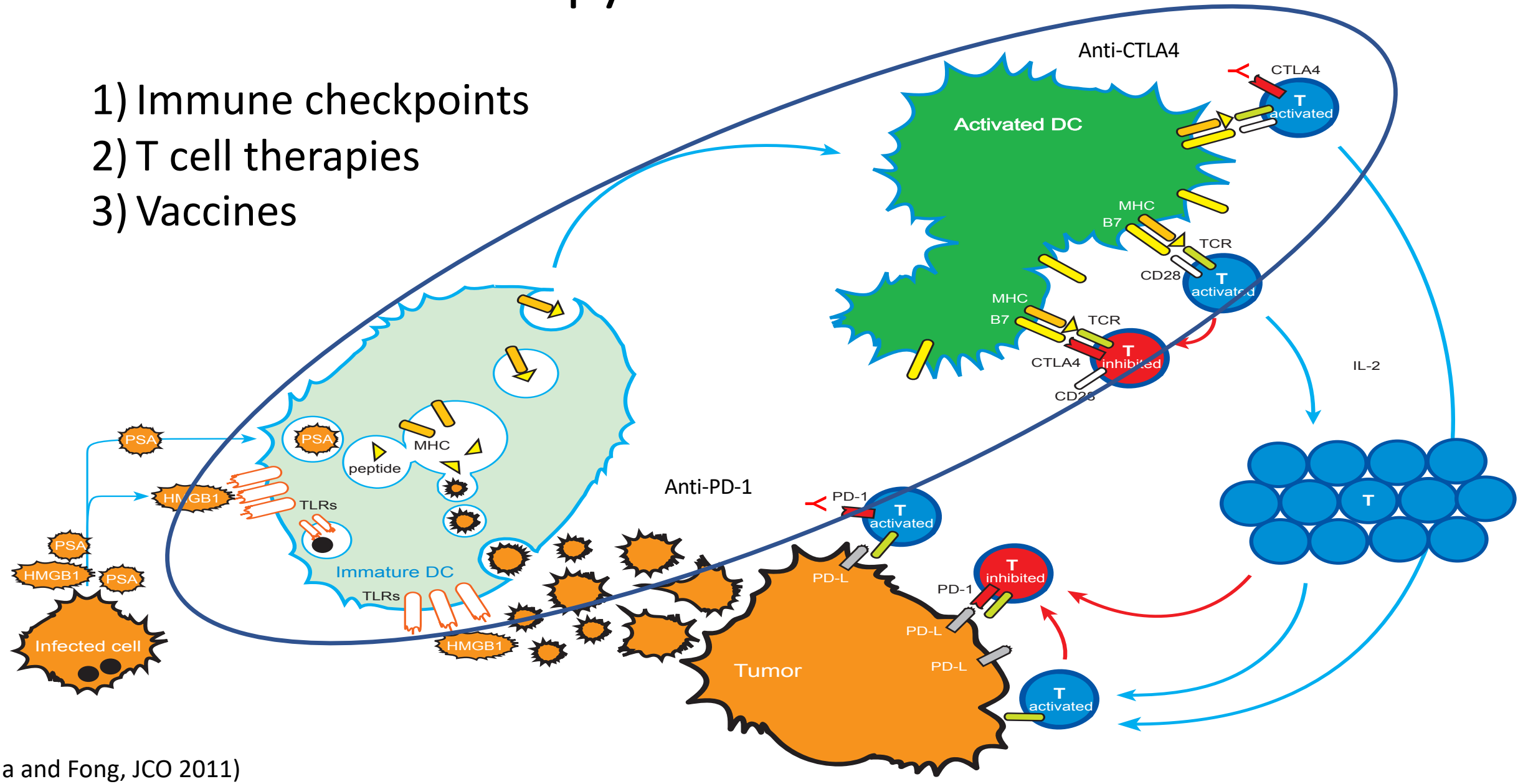
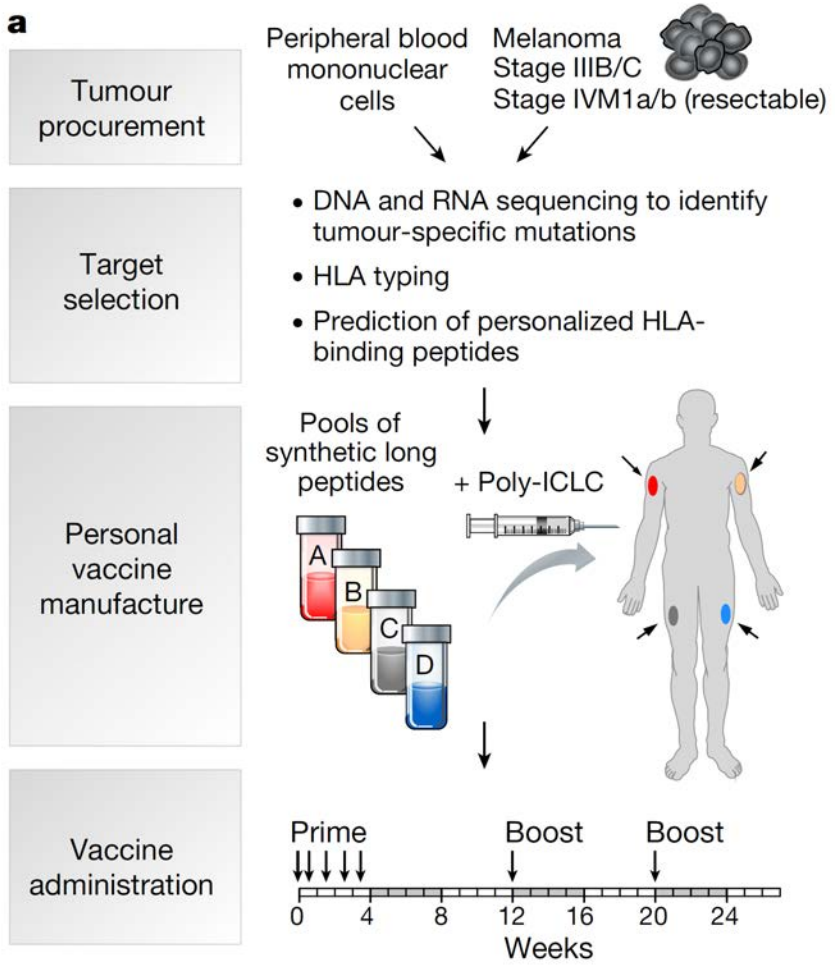
Cancer Immunotherapy

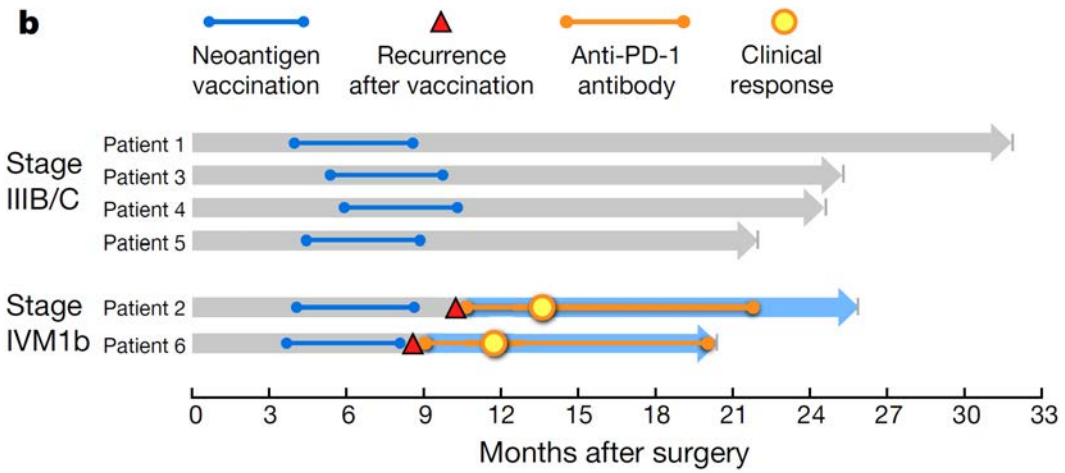
1) Immune checkpoints
2) T cell therapies
3) Vaccines



(Cha and Fong, JCO 2011)

PERSONALIZED CANCER VACCINES





- CD4+ (helper) and CD8+ (cytotoxic) immune responses to mutated peptide (neoantigen) but not the unmutated version
- Immune responses to the patient's own tumor cells (in some cases)
- Clinical activity of vaccine + PD-1, versus PD-1 alone, TBD

(Ott et al. Nature 2017)

Conclusions

- Cancer Immunotherapy has made significant progress over the last few years.
- Immunotherapy “treats the patient, not the tumor.”
- The same immunotherapy can work in a variety of cancers with very different origins and drivers.
- Immunotherapy is demonstrating therapeutic potential in difficult-to-treat cancers.
- If a patient responds, these responses can be durable.
- Immunotherapy has become the backbone therapy for many cancers.

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Challenges

- Immunotherapy currently does not work in all cancers.
- Even in cancers where it works, immunotherapy currently works in a minority of patients.
- We need biomarkers to help us select who can respond to these treatments.
- We need to find the best ways to combine these immunotherapies with each other and with conventional cancer treatments.

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