# Immune Checkpoint Blockade

NCI CCR TRACO
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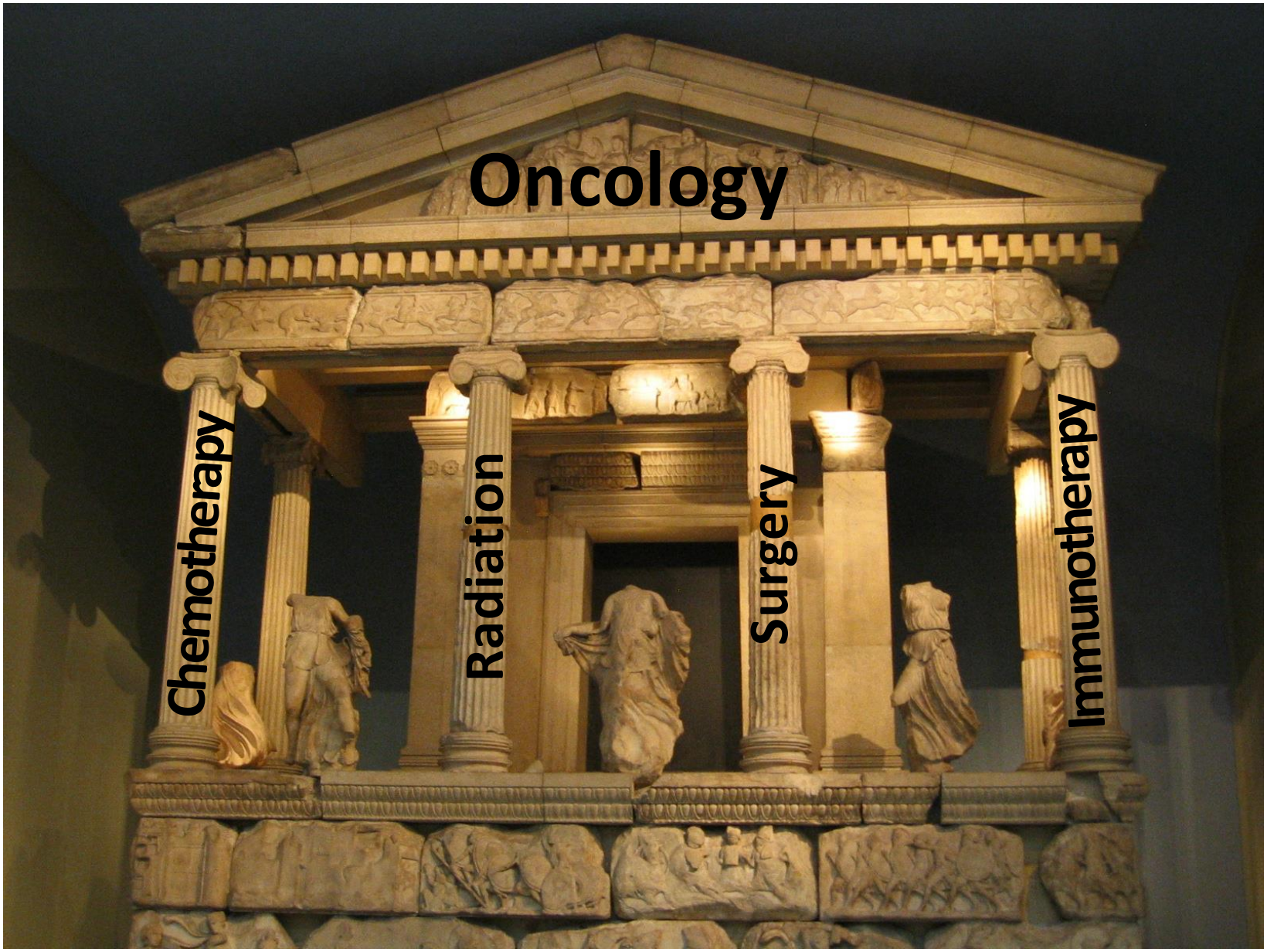
September 2, 2025

# Objectives

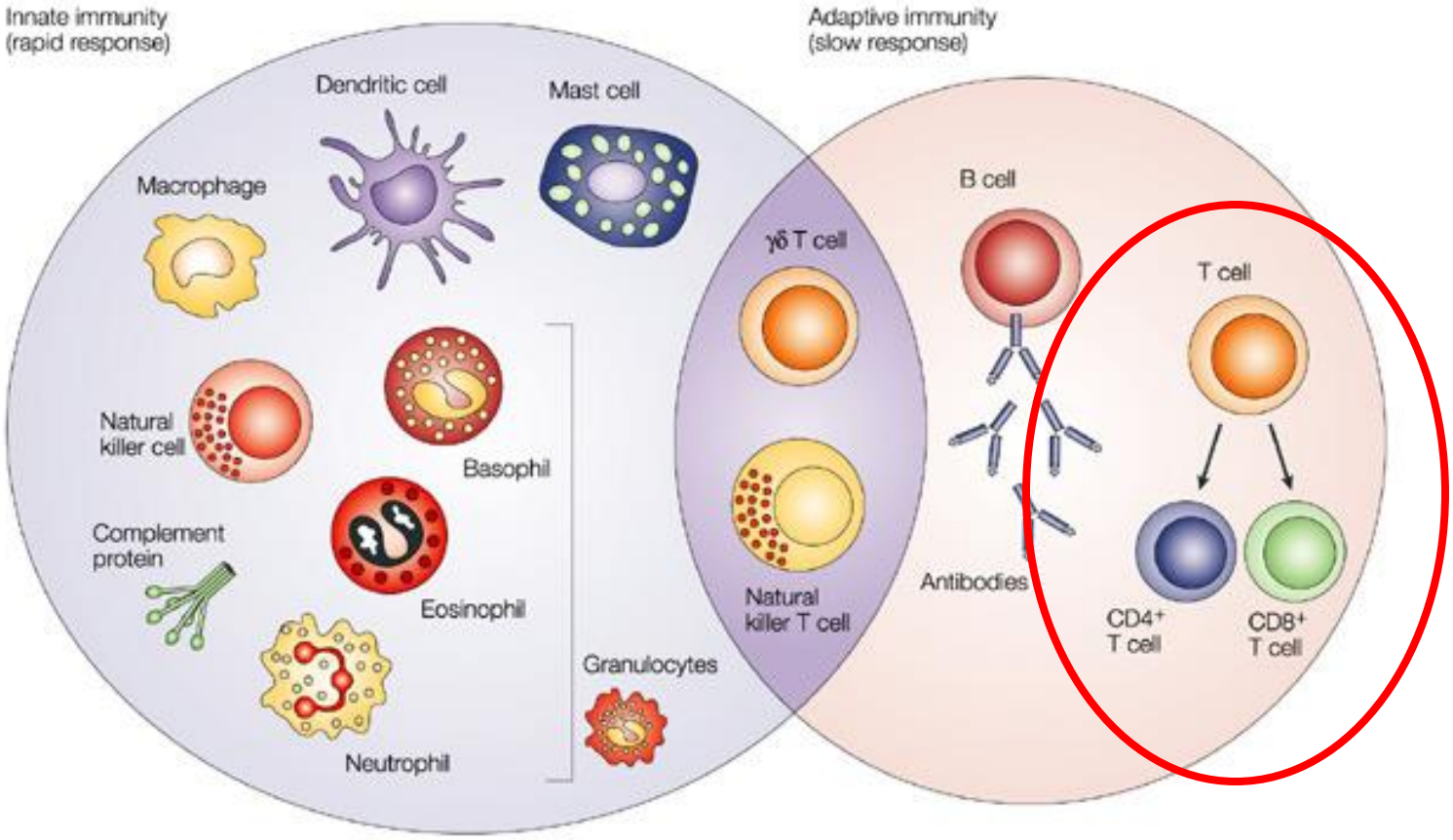
- The basics of cancer immunotherapy
- Mechanism of action of checkpoint blockade
- Early clinical experience and the discovery of immune related adverse events
- Milestones in development
- Experimental Questions


Oncology
Chemotherapy
Radiation
Surgery
Immunotherapy

# Cancer Immunotherapy

1. Nonspecific stimulation of immune reactions
    a) Stimulate effector cells
    b) Inhibit regulatory factors (checkpoint blockade)
2. Active immunization to enhance anti-tumor reactions (cancer vaccines)
3. Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)

# Cells of the Immune System

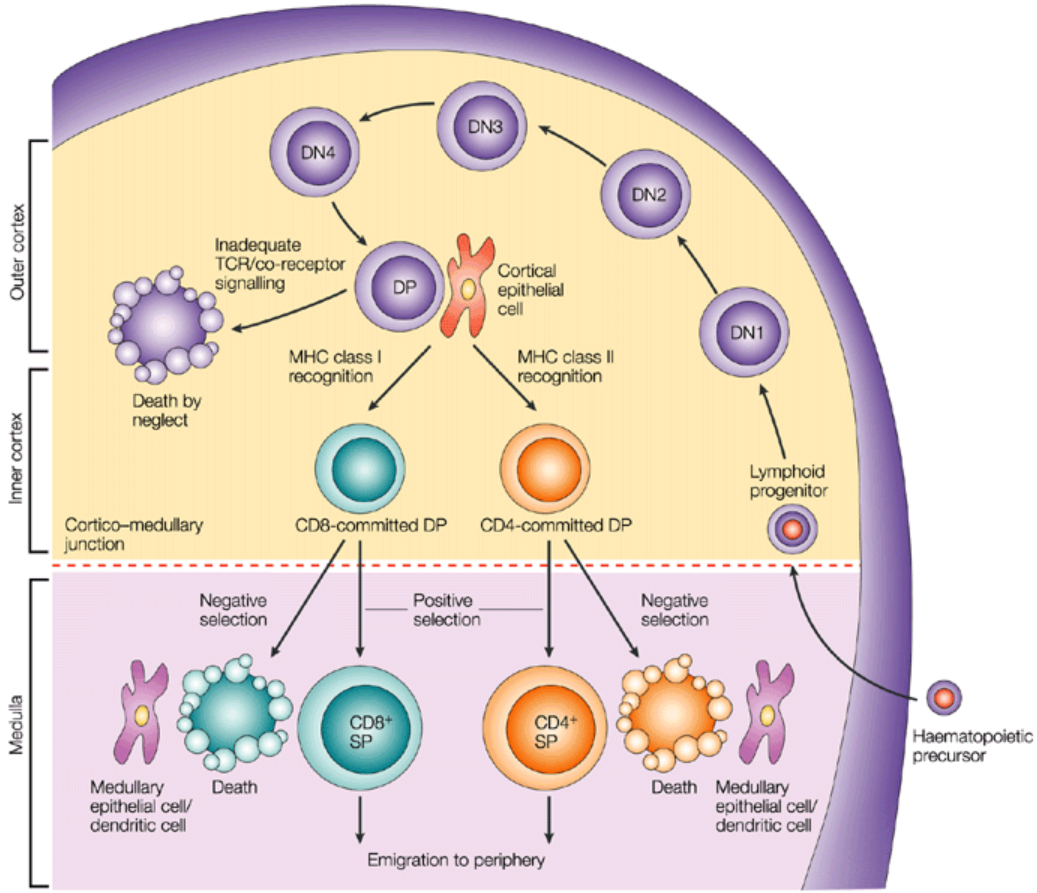



Nature Reviews | Cancer

Dranoff 2004

- Checkpoint blockade primarily affects T cells

# T cell “birth”

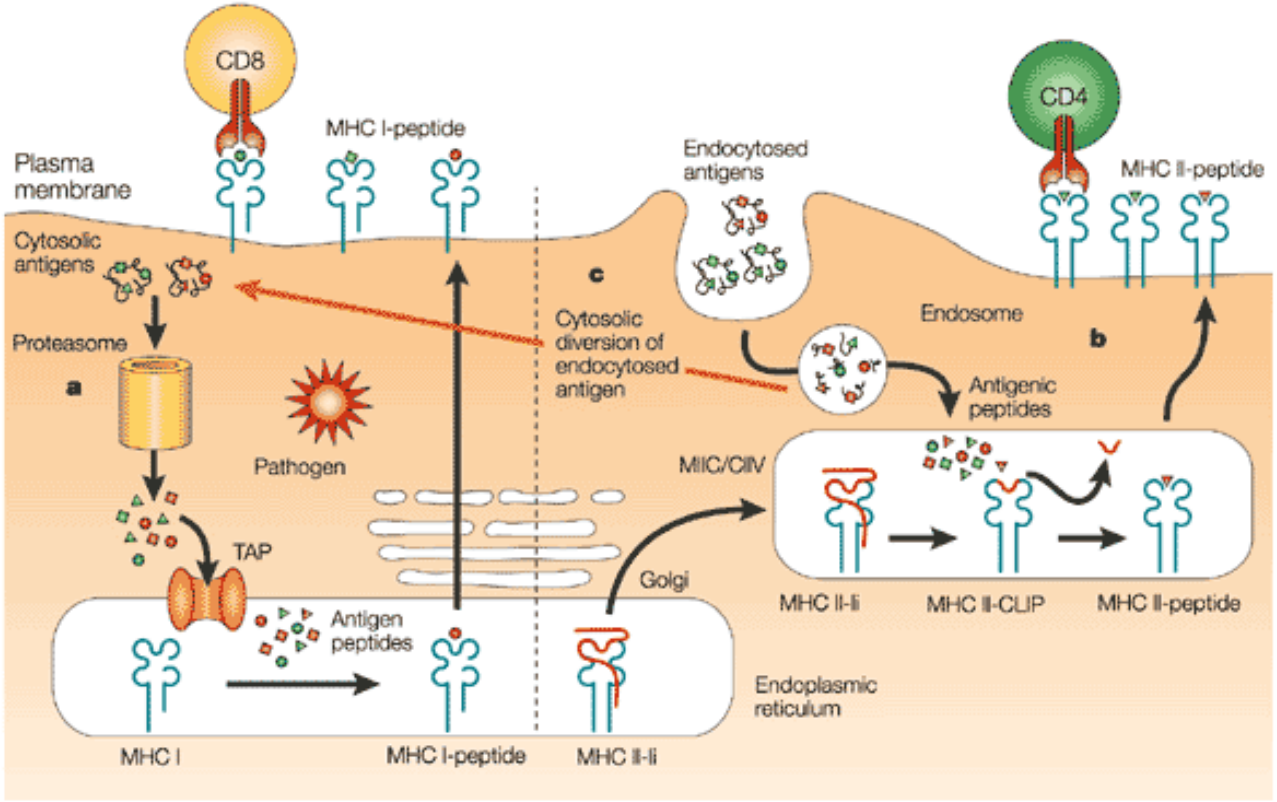



Nature Reviews | Immunology

Germain 2002

- Builds a repertoire of T cells
- ~$4x10^{11}$ circulating in an adult human

# T cell activation

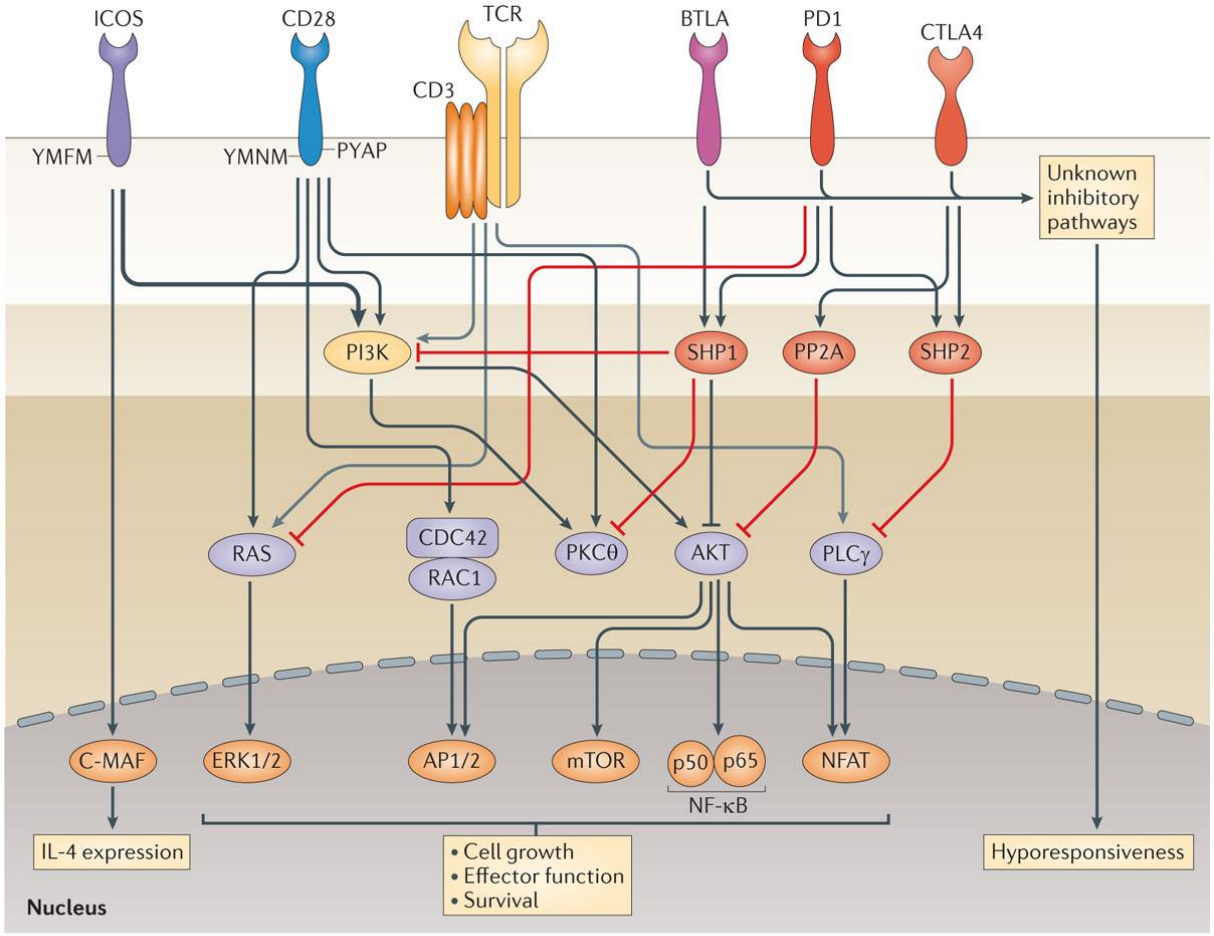



Nature Reviews | Immunology

Heath 2001

- Signal 1: Specificity
- TCR engages antigen in context of MHC

# T cell activation

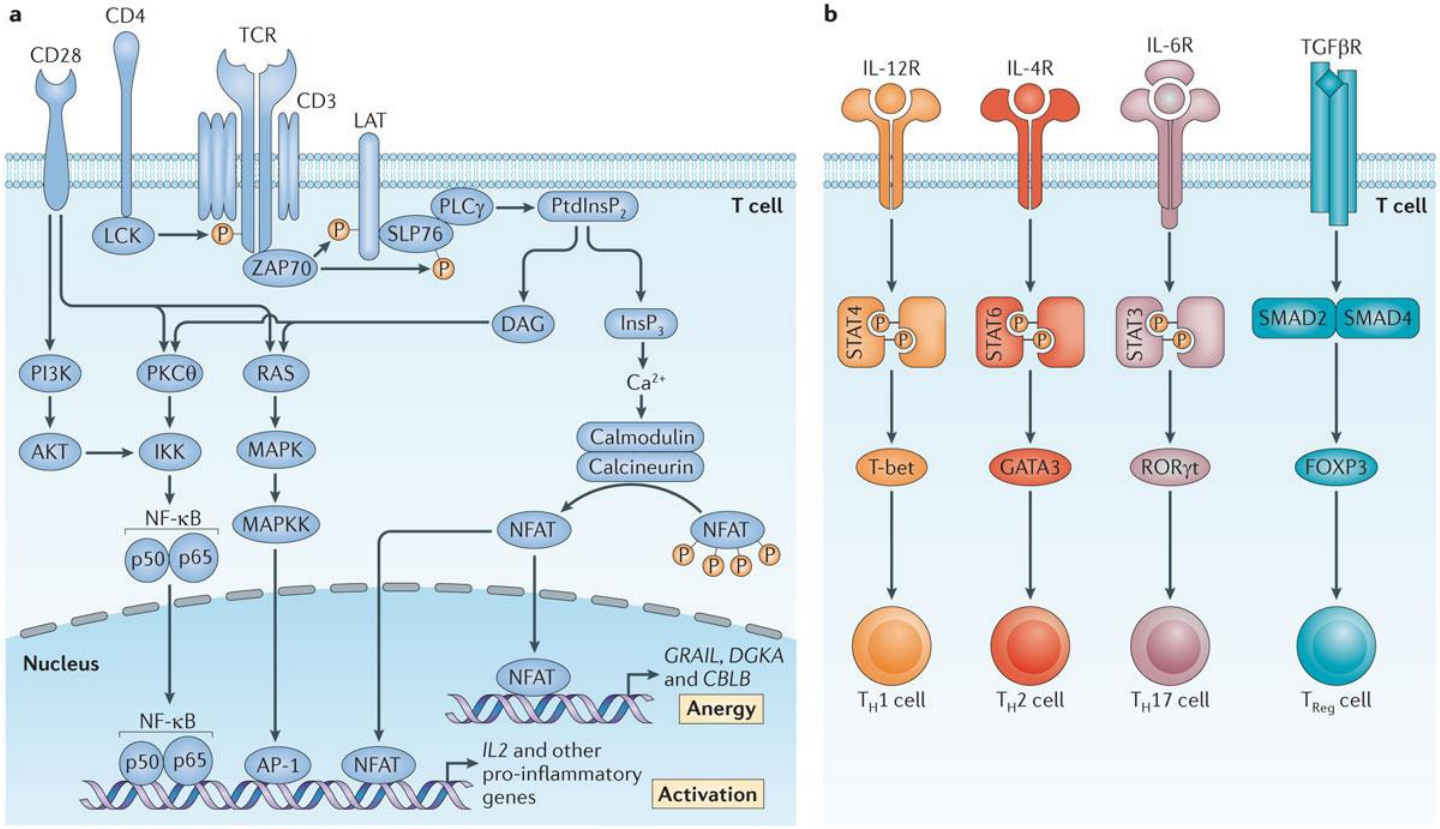



Chen 2013

Nature Reviews | Immunology

- Signal 2: Activation vs. Anergy
- Costimulatory molecules

# T cell activation




Pollizzi 2014

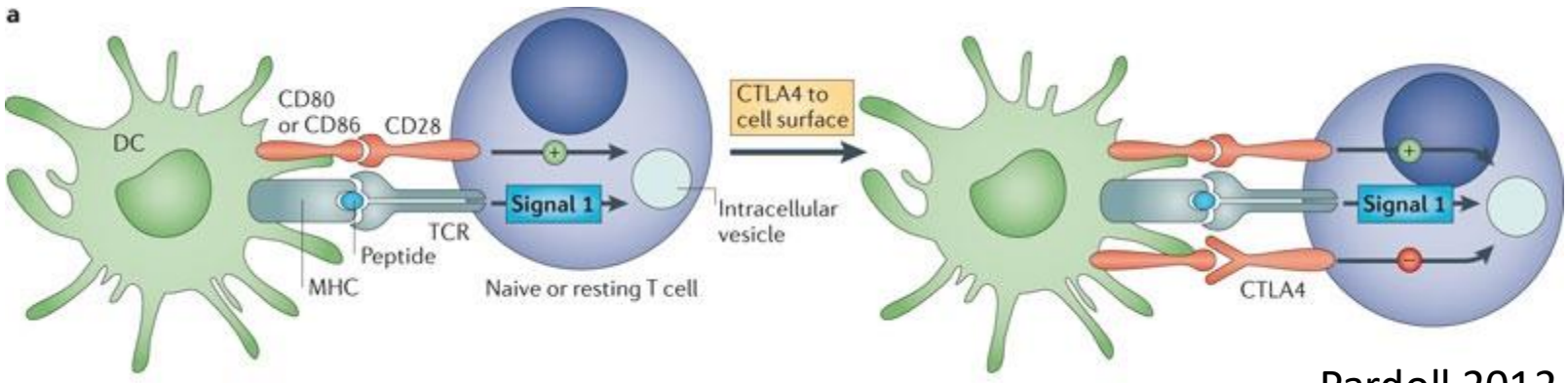
- Signal 3: Polarization
- Dependent on cytokine profile of the microenvironment

# The role of Signal 2 checkpoints

- Immune checkpoints promote self-tolerance
  - Initial response to antigen occurs primarily in secondary lymphoid organs (lymph nodes, tonsils, spleen, Peyer's patches, mucosa associated lymphoid tissue)
- Immune checkpoints limit "collateral damage"
  - Effector recognition in peripheral tissue/tumor

- For cancer immunotherapy, checkpoints create opportunities to break tolerance to self-antigen

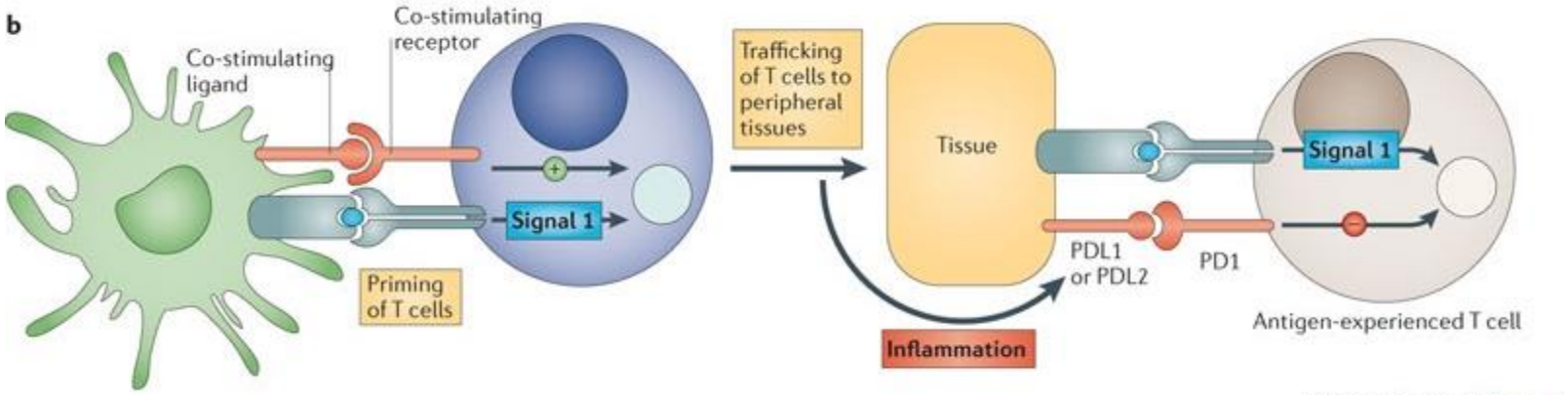
# CTLA-4




Pardoll 2012

- Naïve and memory T cells express surface CD28
- CTLA-4 is transported to the surface in correlation to the strength of CD28 stimulation
- CTLA-4 also competes with higher affinity for CD80/86
- A dampening effect on downstream processing
- Constitutively present on $T_{reg}$ cells

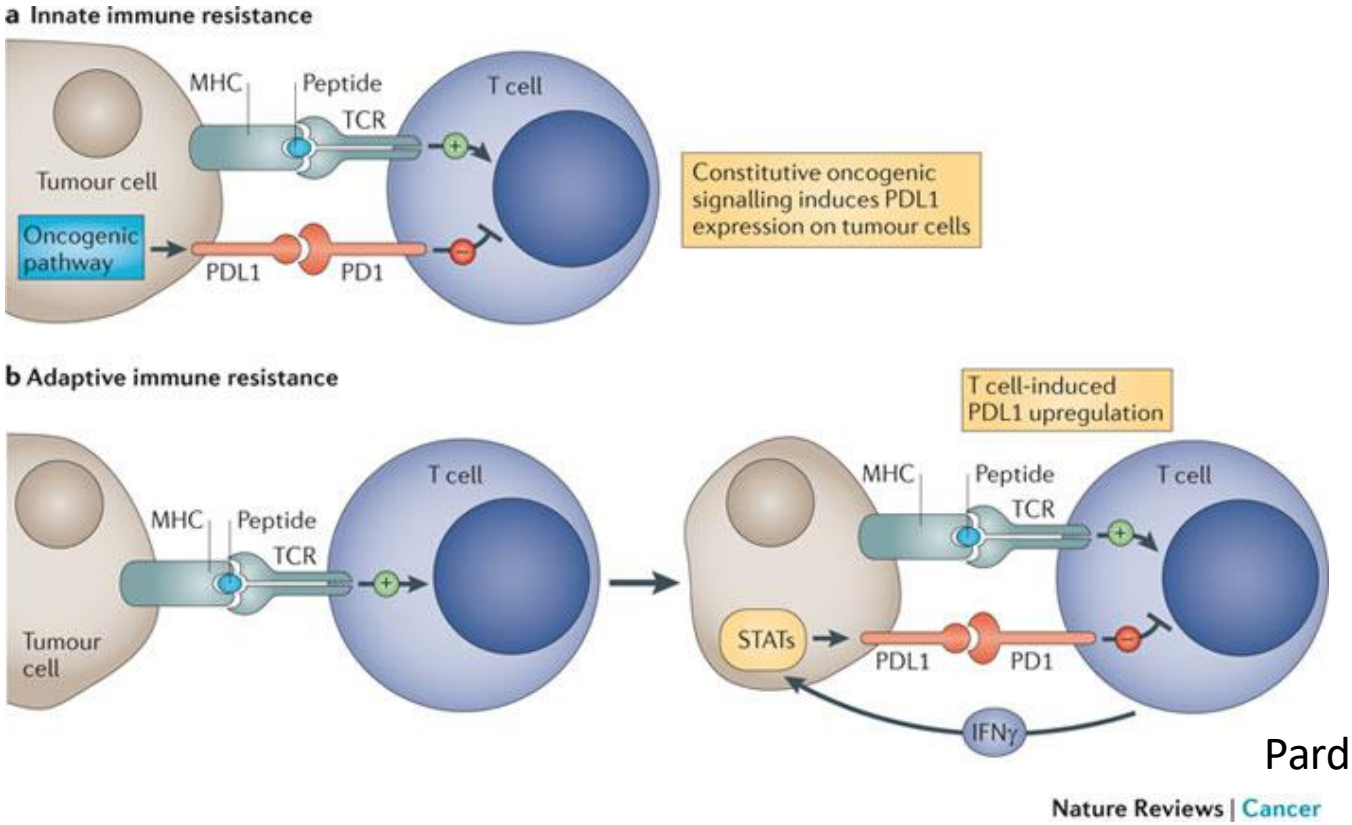
# PD-1




Pardoll 2012

- A primed T-cell is heading to peripheral tissue to engage a target, and once activated begin to express PD-1
- Inflammation present in the tissue can promote upregulation of the ligands of PD-1
- In general, this limits collateral damage during cell-mediated destruction of infection

# PD-1/PD-L1 in cancer




Pardoll 2012

- Cancer cells can increase the amount of PD-L1
- Successful T-cell tumor destruction can increase PD-L1 through upregulation in response to IFNγ

# Checkpoint Blockade

- Where to start?
- Tumors known to respond to other immunotherapy

- **Melanoma**
- Estimated 9,320 deaths/year in US
- Metastatic disease 20% 5 yr survival
- Interleukin-2 durable *cure* in 4%

Smith FO Clin Cancer Res 2008

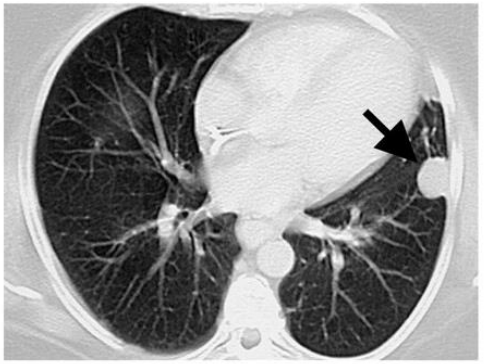
- **Renal Cell Cancer**
- Estimated 14,970 deaths/year in US
- Metastatic disease 12% 5 yr survival
- Interleukin-2 durable *cure* in 7%

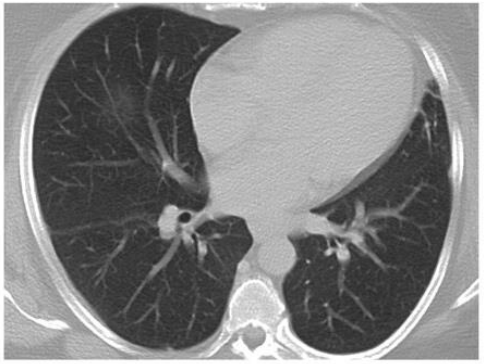
Klapper JA Cancer 2008

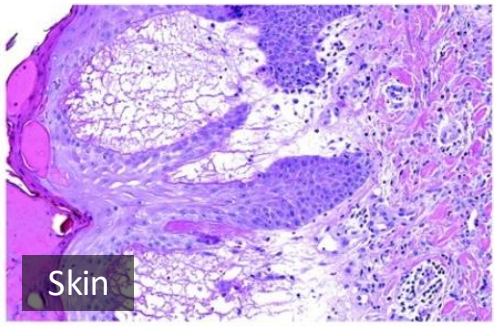
American Cancer Society Facts and Figures 2018

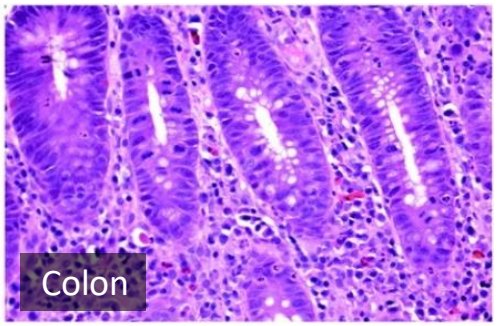
# Checkpoint Blockade @ NCI

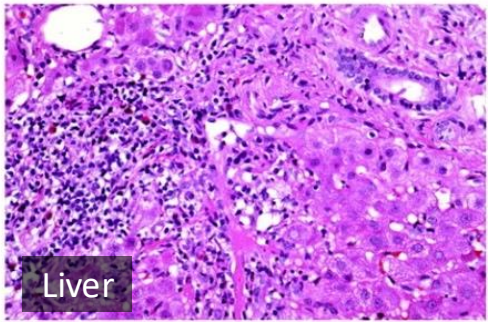
- αCTLA-4, ipilimumab
- Phase I trial
- mAb (3mg/kg) + peptide
- Enrolled 14 patients
- 2 complete responders
- 1 partial response
- Accrual stopped for toxicity
  - Dermatitis, colitis, hepatitis, hypophysitis (not pictured)

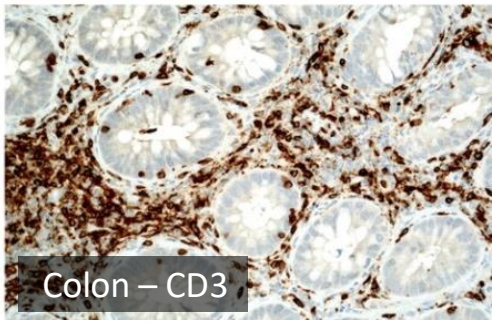







Phan GQ 2003 PNAS

# Checkpoint Blockade @ NCI

- Cautiously proceeded with Phase II trials in melanoma and RCC, initially with dose reduction (3 → 1 mg/kg)
- Objective response was associated with development of autoimmune events

**Melanoma**, p=0.008

| | > Gr 3 AE | < Gr 3 AE |
|---|---|---|
| Objective Response (CR = 2) | 5 (36%) | 2 (5%) |
| Non-responder | 9 | 40 |

Attia P 2005

**RCC**, p=0.009

| | > Gr 3 AE | < Gr 3 AE |
|---|---|---|
| Objective Response (CR = 0) | 5 (29%) | 0 (0%) |
| Non-responder | 12 | 23 |

Yang JC 2007

# Checkpoint Blockade @ NCI

- Formal Phase II intra-patient dose escalation demonstrated association of response with immune-related adverse events of any grade
- Enterocolitis was the most common grade 3/4 IRAE in patients with melanoma (18%) or RCC (28%)
- The administration of steroids to manage IRAE did not truncate responses

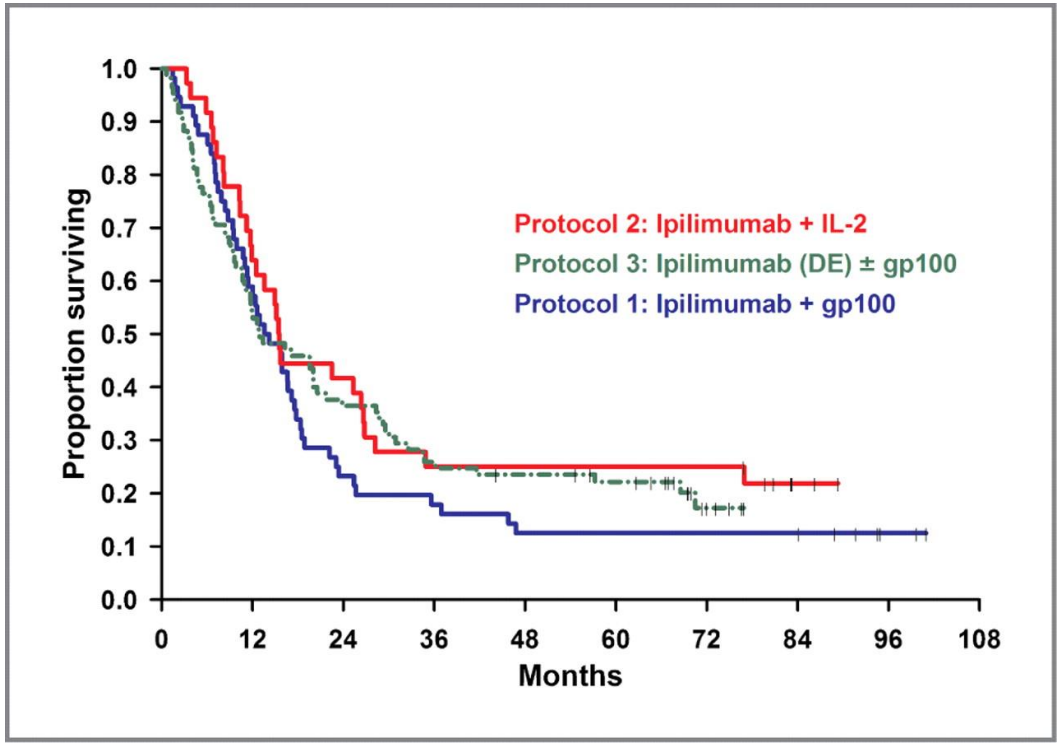
**Melanoma**, p=0.0004

| | Gr 3/4 IRAE | Gr 1/2 IRAE | No IRAE |
|---|---|---|---|
| Objective Response (CR = 3) | 14 (28%) | 8 (22%) | 1 (2%) |
| Non-responder | 36 | 28 | 52 |

Beck KE 2006
Downey SG 2007

# Checkpoint Blockade @ NCI

- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
  - OR 13-20%
  - 5 yr OS 13-23%

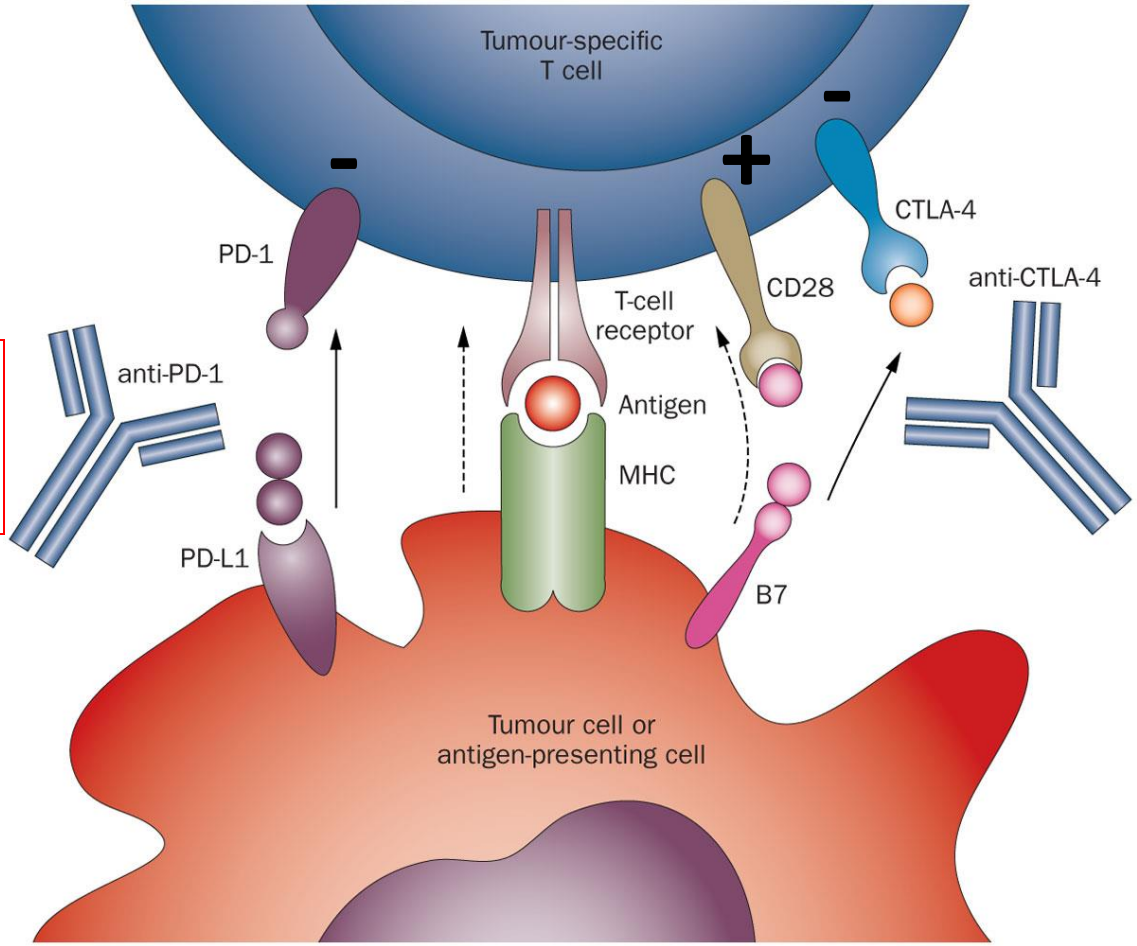



Prieto PA 2012

Clinical Cancer Research

# Initial FDA approvals

Nivolumab
Pembrolizumab
2014



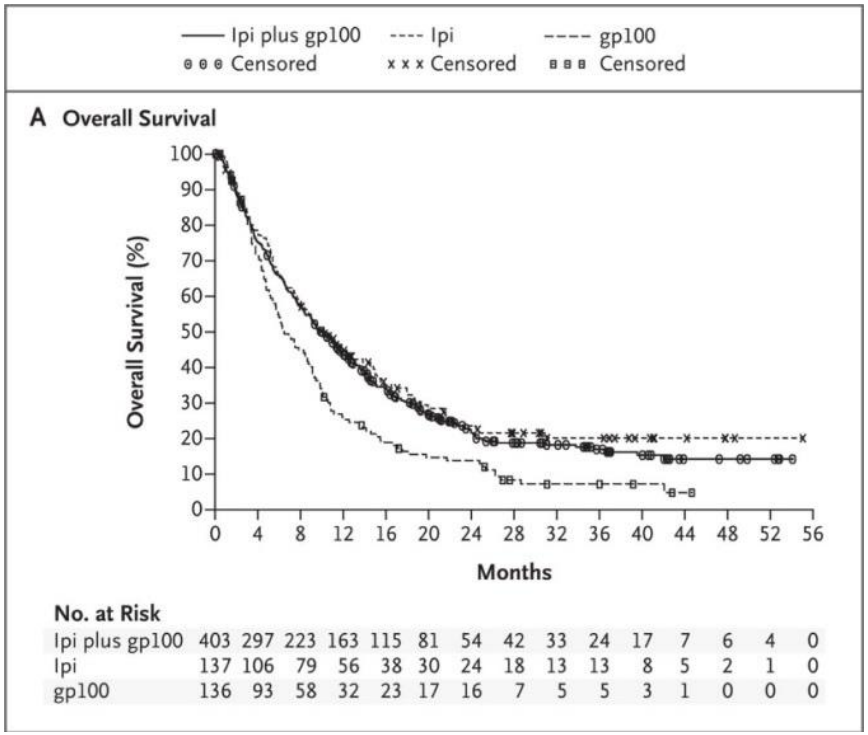

Ipilimumab
2011

Drake C 2013

nature REVIEWS CLINICAL ONCOLOGY

# Ipilimumab for melanoma

- 11% response rate in Phase II trials at highest doses (10 mg/kg)
- Randomized Phase III ipilimumab ± gp100 vaccine vs. gp100 vaccine
- Allowed re-induction
- OR: ipilimumab arms
  7% (38/540)
  CR in 3 patients
- Disease control rate 22%
- Gr 3/4 irAE 10-15%



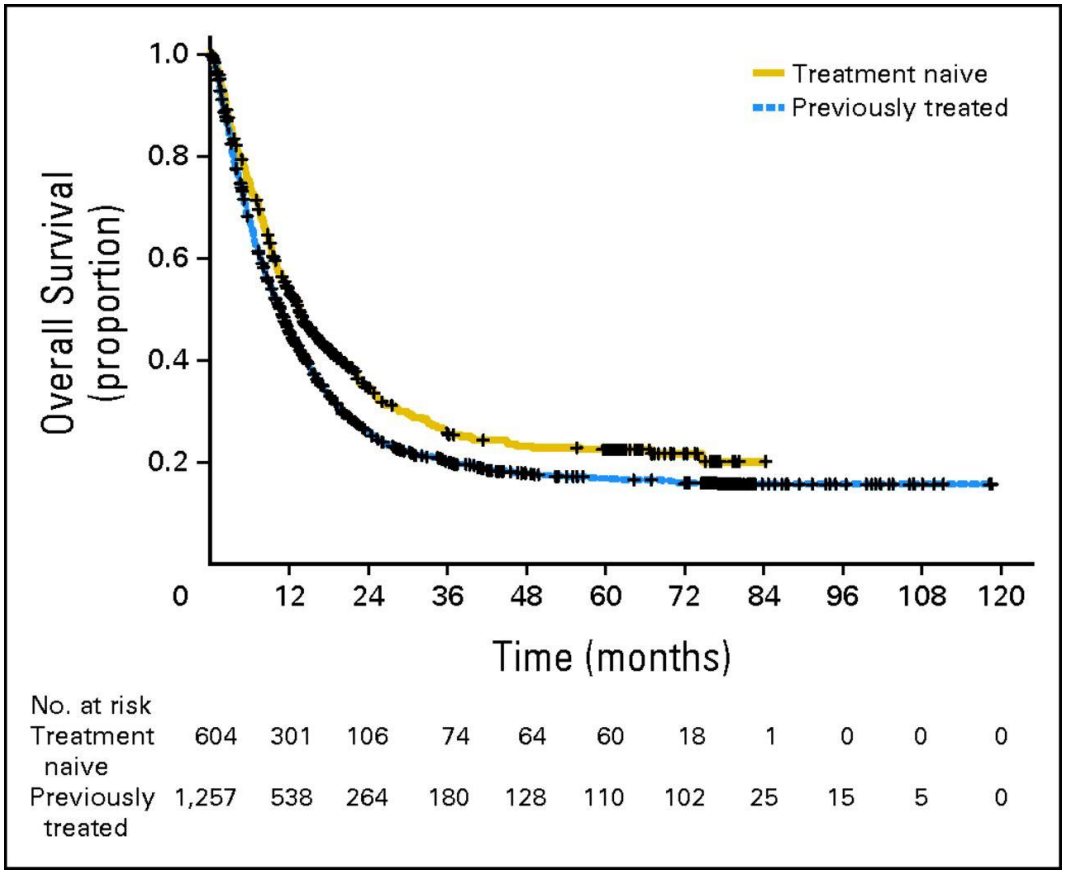

**FDA approval for metastatic melanoma in March 2011**

Hodi FS 2010

The NEW ENGLAND JOURNAL of MEDICINE

# Ipilimumab for melanoma

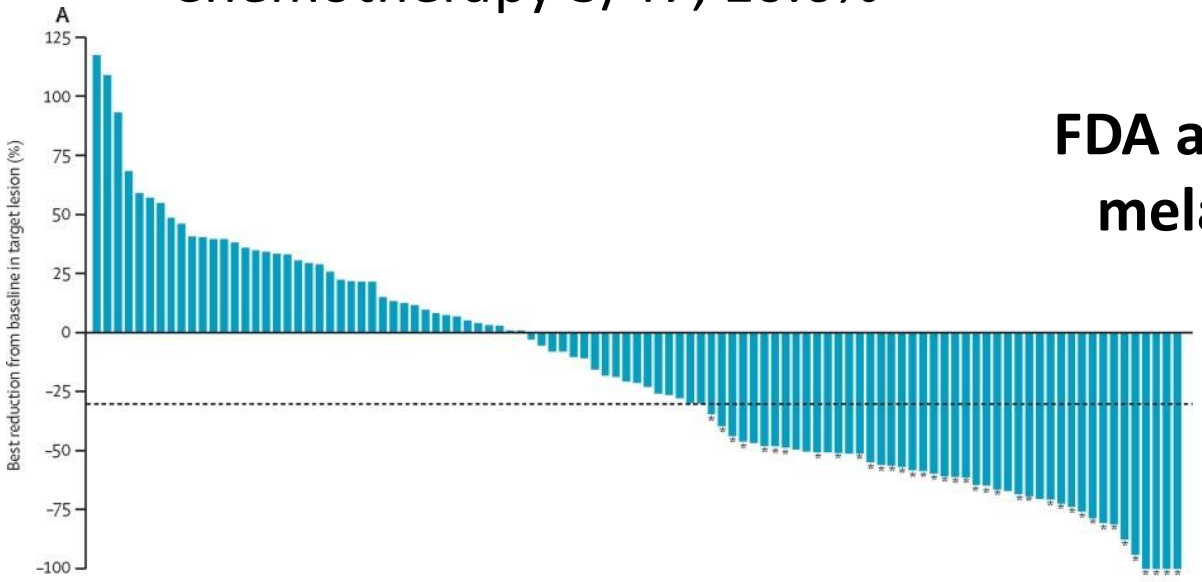
- Updated survival
- 3 year OS, 20-26%
- “Tail of the curve”
  - Durable for a small # of patients




Schadendorf D 2015
Journal of Clinical Oncology®

# Nivolumab for melanoma

- Ipilimumab-refractory
- RCT: nivolumab vs chemotherapy of choice (CheckMate 037)
- Objective Response
  - Nivolumab 38/120, 31.7% with 4 CR
  - Chemotherapy 5/47, 10.6%



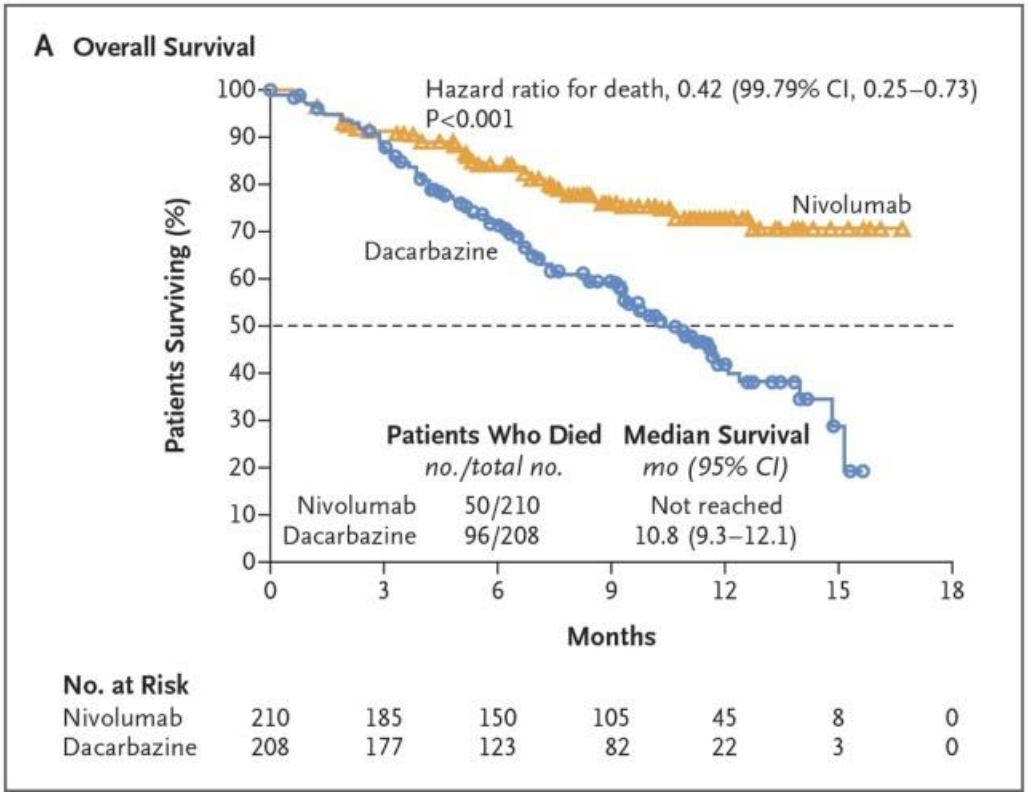

**FDA approval for refractory melanoma in December 2014**

Weber JS 2015

THE LANCET Oncology

# Nivolumab for melanoma

- Untreated metastatic disease
- Wildtype *BRAF*
- RCT: nivolumab vs dacarbazine (CheckMate 066)
- Objective response
  - Nivolumab 84/210 (40%)
    CR in 16 pts (7.6%)
  - Dacarbazine 29/208 (14%)
    CR in 2 pts (1%)




**Approved for initial treatment (*BRAF*-wt) in November 2015**

Robert C 2015

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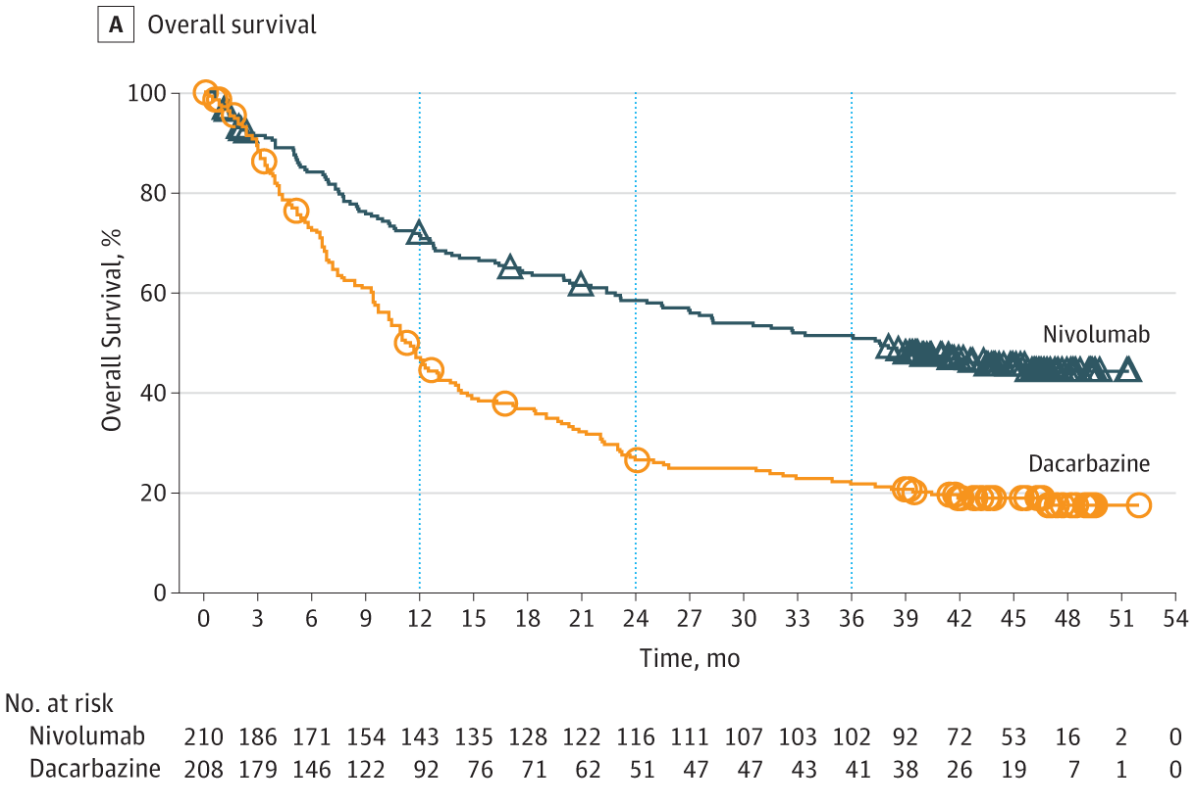
# Nivolumab for melanoma

- Overall Survival update for Checkmate 066
- Three-year OS:
  - Nivolumab 51%
  - Dacarbazine 22%

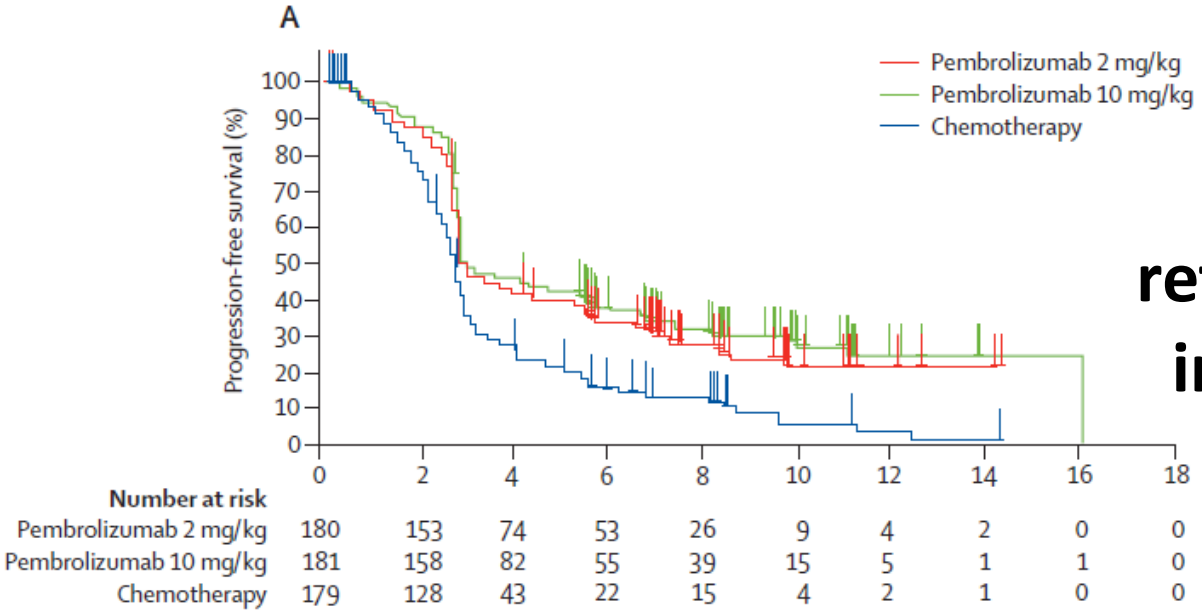



Ascierto P 2018

JAMA Oncology

# Pembrolizumab for melanoma

- Ipilimumab-refractory
- Phase II, dose comparison (2mg/kg vs 10 mg/kg) vs chemo
- 540 patients
  - 2mg/kg ORR 38 (21%), 10 mg/kg ORR 46 (25%), chemo 8 (4%)
- Grade 3/4 AE 12%




**FDA approval for refractory melanoma in September 2014**

Ribas A 2015

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# Pembrolizumab for melanoma

- RCT, KEYNOTE-006, first-line therapy
- Pembrolizumab (q2w, q3w) vs ipilimumab
- 1:1:1
- 834 patients
- Objective Response
  - Pembrolizumab q2w 94/279 (33.7%), CR 14
  - Pembrolizumab q3w 91/277 (32.9%), CR 17
  - Ipilimumab 33/278 (11.9%), CR 4

Robert C 2015

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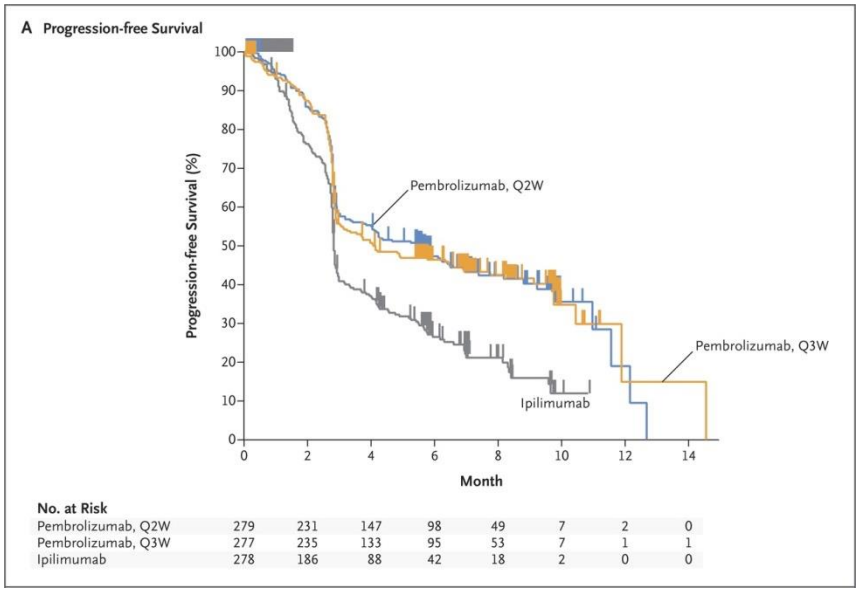
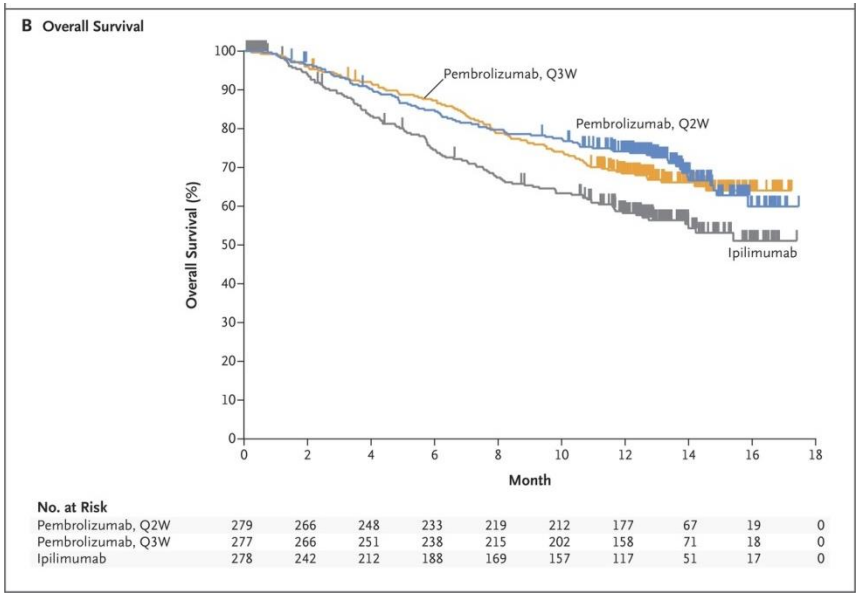
# Pembrolizumab for melanoma




- Grade ≥3 AE
  - Pembrolizumab q2w 13.3% (1.4% Colitis)
  - Pembrolizumab q3w 10.1% (2.5% Colitis)
  - Ipilimumab 19.9% (7% Colitis)

**Front-line FDA approval for melanoma in December 2015**

Robert C 2015

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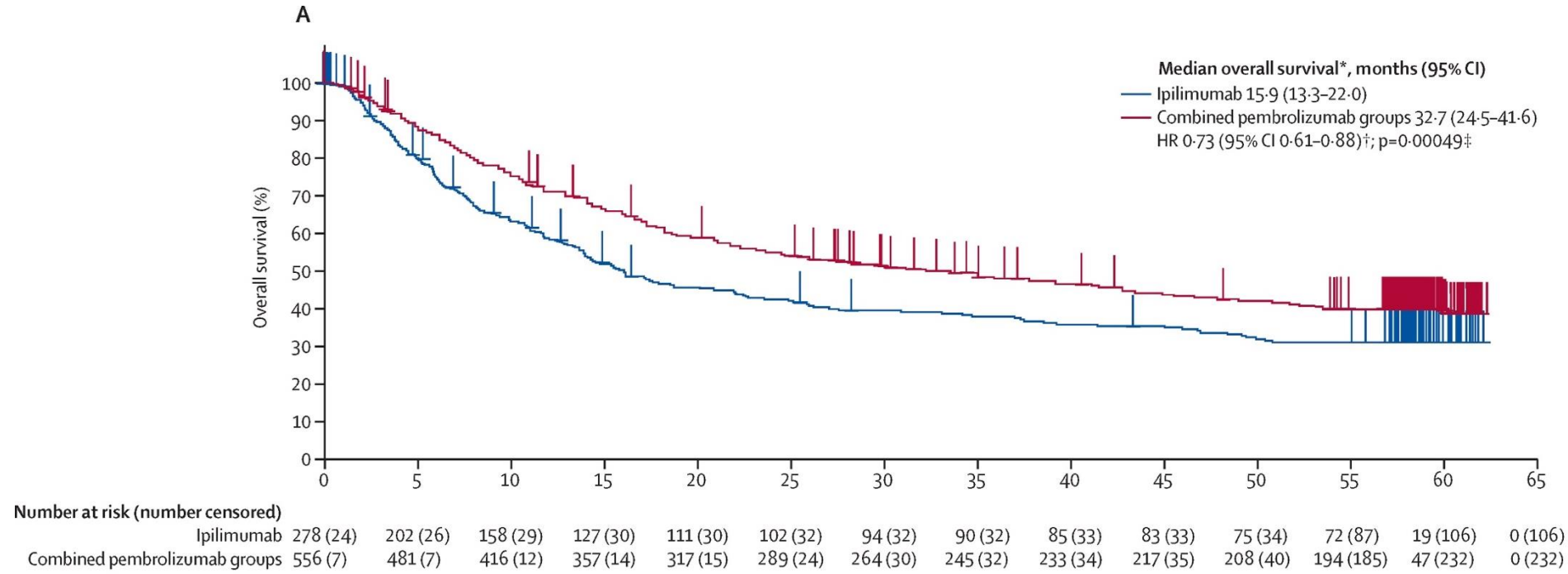
# Pembrolizumab for melanoma

- Three year OS of 48.1% vs 37.8%




Robert C 2019

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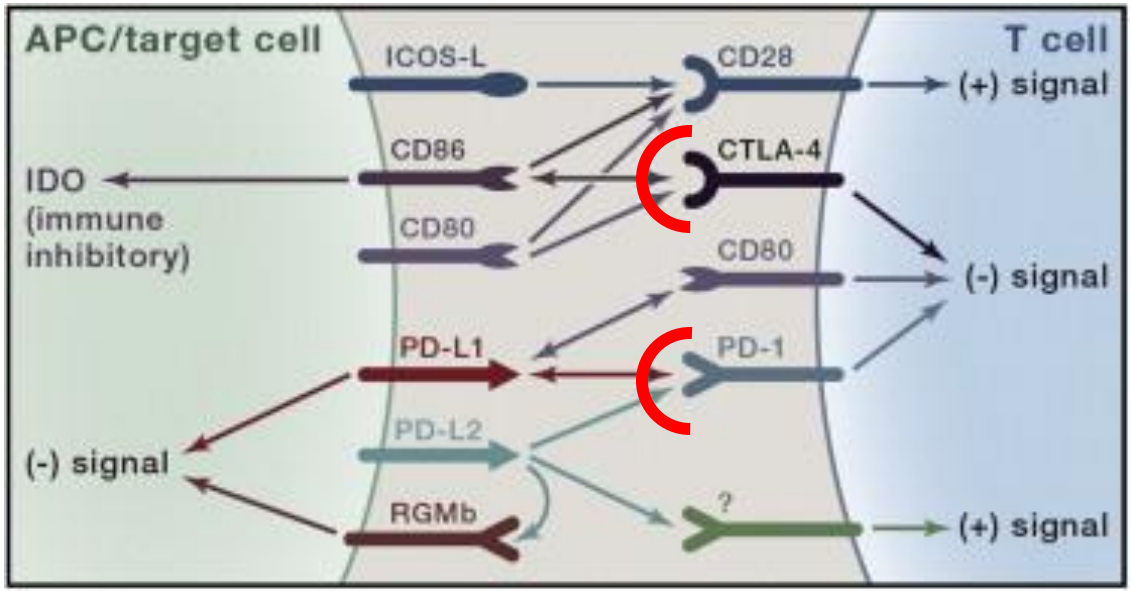
# Checkpoint Modulation




Topalian, Cancer Cell 2015

- In melanoma, the first two approved antibodies interfere with separate receptor/ligand complexes
- Could combination therapy improve response or survival?

# Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1
- PD-L1 (+)  ≥5%

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Nivolumab (N=316) | Nivolumab plus Ipilimumab (N=314) | Ipilimumab (N=315) | Total (N=945) |
|---|---|---|---|---|
| PD-L1 status — no. (%) | | | | |
| Positive | 80 (25.3) | 68 (21.7) | 75 (23.8) | 223 (23.6) |
| Negative | 208 (65.8) | 210 (66.9) | 202 (64.1) | 620 (65.6) |
| Could not be determined or evaluated | 28 (8.9) | 36 (11.5) | 38 (12.1) | 102 (10.8) |
| *BRAF* status — no. (%) | | | | |
| Mutation | 100 (31.6) | 101 (32.2) | 97 (30.8) | 298 (31.5) |
| No mutation | 216 (68.4) | 213 (67.8) | 218 (69.2) | 647 (68.5) |

Larkin J 2015

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# Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1

- Grade 3/4 AE
  - Nivolumab 16.3%
  - Ipilimumab 27.3%
  - Combo 55.0%

**Table 2. Response to Treatment.**

| Variable | Nivolumab (N=316) | Nivolumab plus Ipilimumab (N=314) | Ipilimumab (N=315) |
|---|---|---|---|
| Best overall response — no. (%)* | | | |
| Complete response | 28 (8.9) | 36 (11.5) | 7 (2.2) |
| Partial response | 110 (34.8) | 145 (46.2) | 53 (16.8) |
| Stable disease | 34 (10.8) | 41 (13.1) | 69 (21.9) |
| Progressive disease | 119 (37.7) | 71 (22.6) | 154 (48.9) |
| Could not be determined | 25 (7.9) | 21 (6.7) | 32 (10.2) |
| Objective response† | | | |
| No. of patients with response | 138 | 181 | 60 |
| % of patients (95% CI) | 43.7 (38.1–49.3) | 57.6 (52.0–63.2) | 19.0 (14.9–23.8) |
| Estimated odds ratio (95% CI)‡ | 3.40 (2.02–5.72) | 6.11 (3.59–10.38) | — |
| Two-sided P value | <0.001 | <0.001 | — |
| Time to objective response — mo | | | |
| Median | 2.78 | 2.76 | 2.79 |
| Range | 2.3–12.5 | 1.1–11.6 | 2.5–12.4 |

* The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
† Data included patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. These analyses were conducted with the use of a two-sided Cochran–Mantel–Haenszel test stratified according to PD-L1 status, *BRAF* mutation status, and metastasis stage.
‡ The comparison is with the ipilimumab group.

Larkin J 2015

# Nivolumab/Ipilimumab for melanoma

- Previously untreated
- Phase III, RCT
- 945 patients
- 1:1:1

- Grade 3/4 AE
  - Nivolumab 21%
  - Ipilimumab 28%
  - Combo 59%

**Table 1. Response to Treatment.***

| Variable | Nivolumab plus Ipilimumab (N=314) | Nivolumab (N=316) | Ipilimumab (N=315) |
|---|---|---|---|
| Best overall response — no. (%)† | | | |
| Complete response | 61 (19) | 52 (16) | 16 (5) |
| Partial response | 122 (39) | 88 (28) | 43 (14) |
| Stable disease | 38 (12) | 31 (10) | 69 (22) |
| Progressive disease | 74 (24) | 121 (38) | 159 (50) |
| Unable to determine | 19 (6) | 24 (8) | 28 (9) |
| Objective response‡ | | | |
| No. of patients with response | 183 | 140 | 59 |
| % of patients (95% CI) | 58 (53–64) | 44 (39–50) | 19 (15–24) |
| Estimated odds ratio (95% CI)§ | 6.46 (4.45–9.38) | 3.57 (2.48–5.15) | — |
| P value | <0.001 | <0.001 | — |
| Median duration of response (95% CI) — mo | NR | NR (36.3–NR) | 19.3 (8.3–NR) |

**FDA approval of combination for melanoma in January 2016**

Wolchok J 2017

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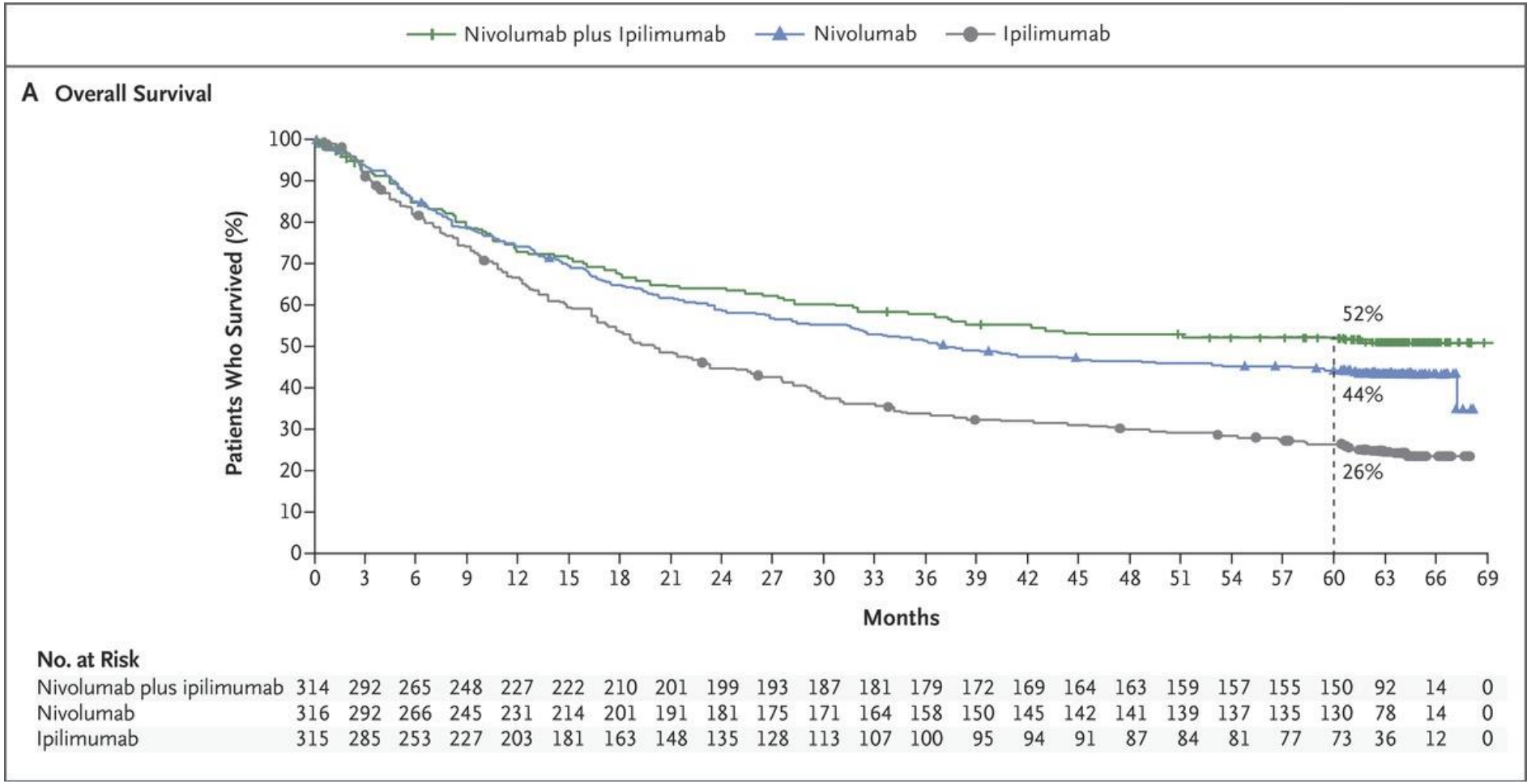
# Nivolumab/Ipilimumab for melanoma




Larkin J 2019

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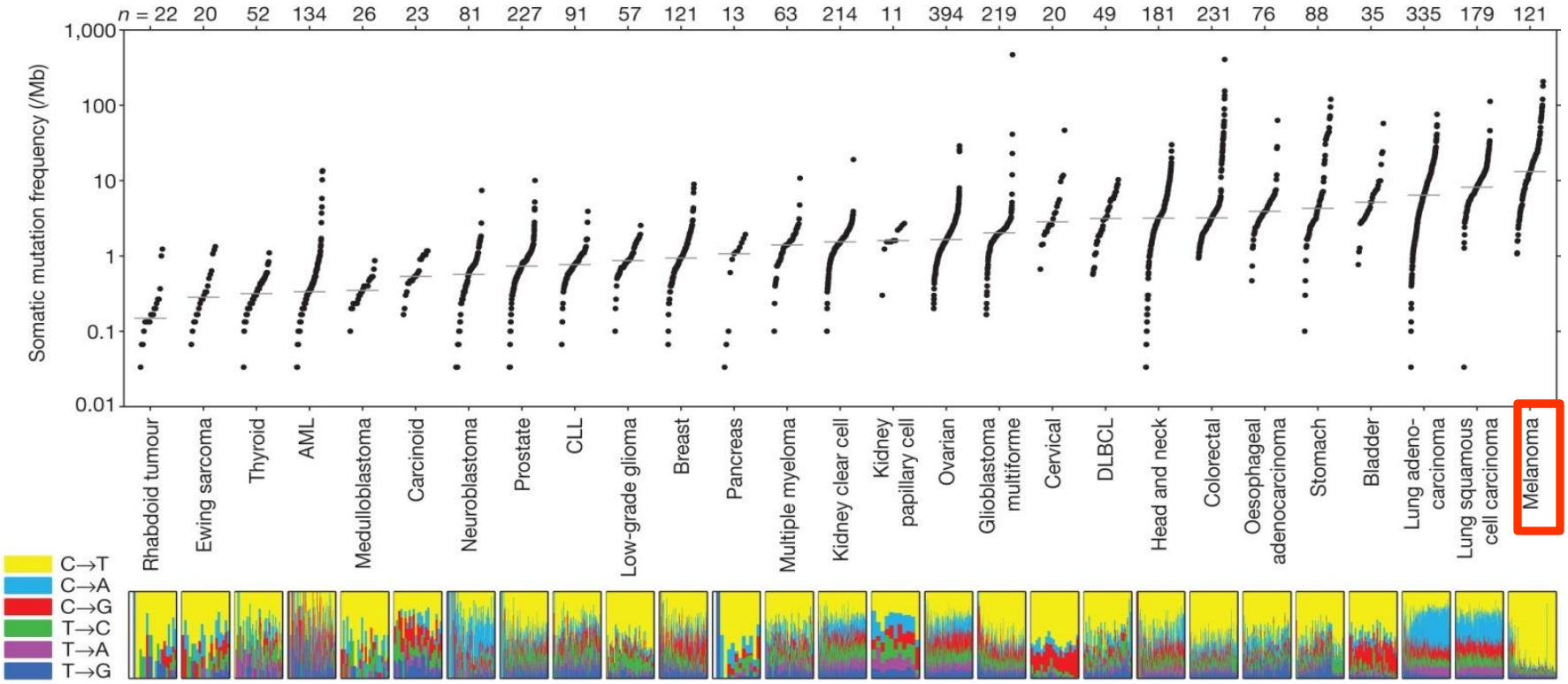
# Why melanoma?




Lawrence MS 2013

nature
International weekly journal of science

# Highly mutated tumors

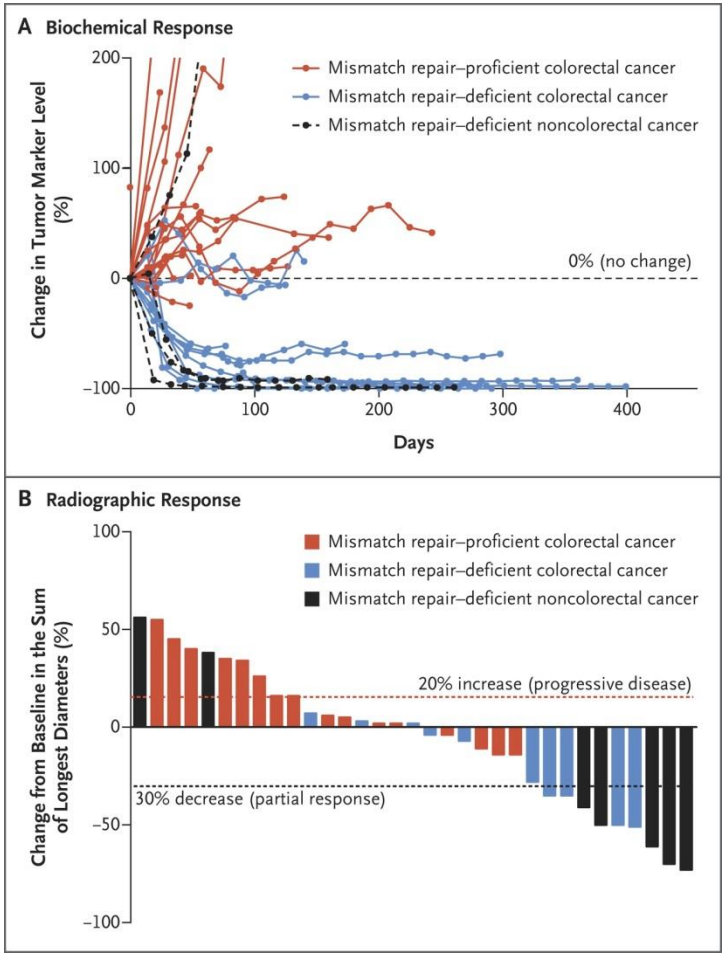
- Non-small cell lung cancer (NSCLC)
  - ~154,050 deaths/year in US
  - Regional disease 29% 5 yr survival
  - Metastatic disease 5% 5 yr survival
  - Correlation between smoking and # mutations
- Bladder cancer
  - 17,240 deaths/year in US
  - Highly lethal once metastatic
- Tumors with mismatch repair (MMR) deficiency
  - Lynch syndrome (germline mutation)
  - Sporadic mutation
  - MSH2, MLH1, MSH6, PMS2

American Cancer Society Facts and Figures 2018

https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape

# Pembrolizumab for mismatch repair deficient (dMMR) cancer

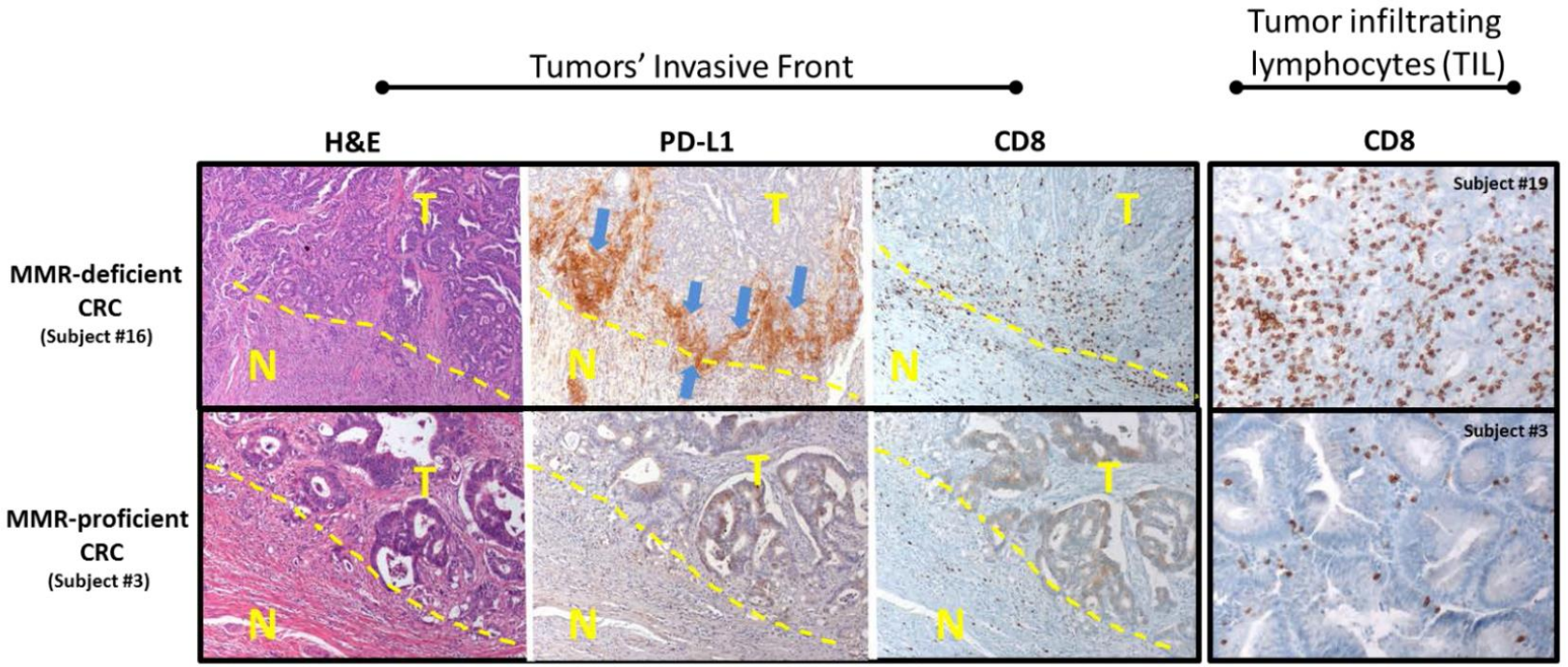
- Builds on hypothesis of neoantigens from somatic mutations
- Phase 2 study
- Three parallel cohorts
  - MMR-proficient CRC
  - MMR-deficient CRC
  - MMR-deficient other




Le DT 2015

The NEW ENGLAND JOURNAL of MEDICINE

# Pembrolizumab at the tumor-stroma interface




**FDA approval for dMMR tumors in May 2017**

Le DT 2015

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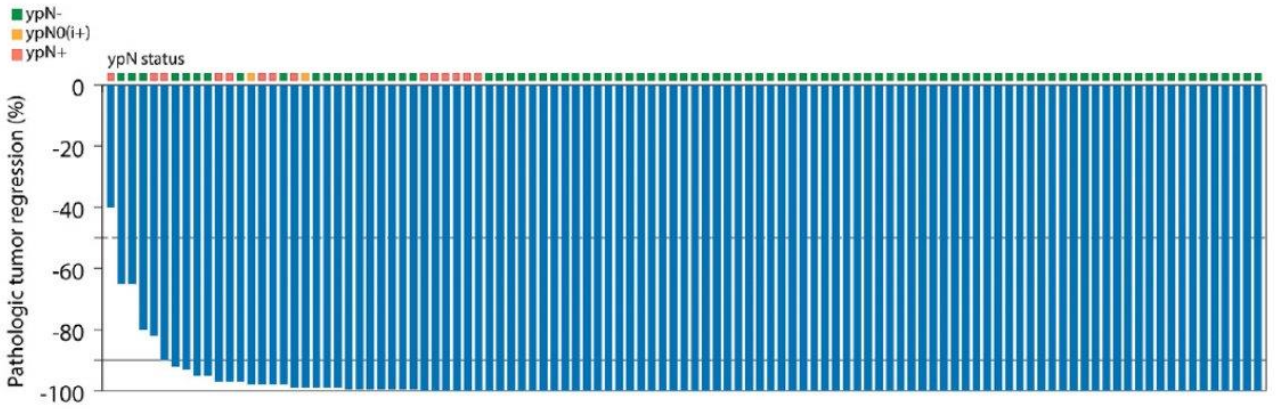
# Pre-op combination checkpoint

PARIS 2022 ESMO congress
#ESMO22




ypN- = post-treatment pathologic lymph nodes tumor-free; ypN+ = post-treatment pathologic lymph nodes with tumor; ypN(i) = post-treatment pathologic lymph nodes with isolated tumor cells. Patients with pathologic complete responses in the primary tumor and viable tumor rest (N+ or N(i+)) in the lymph nodes are considered major pathologic responders.

**Neoadjuvant immunotherapy in dMMR colon cancer - a paradigm shift?**

ESMO daily REPORTER

Chalabi et al ESMO Presidential Session September 2022

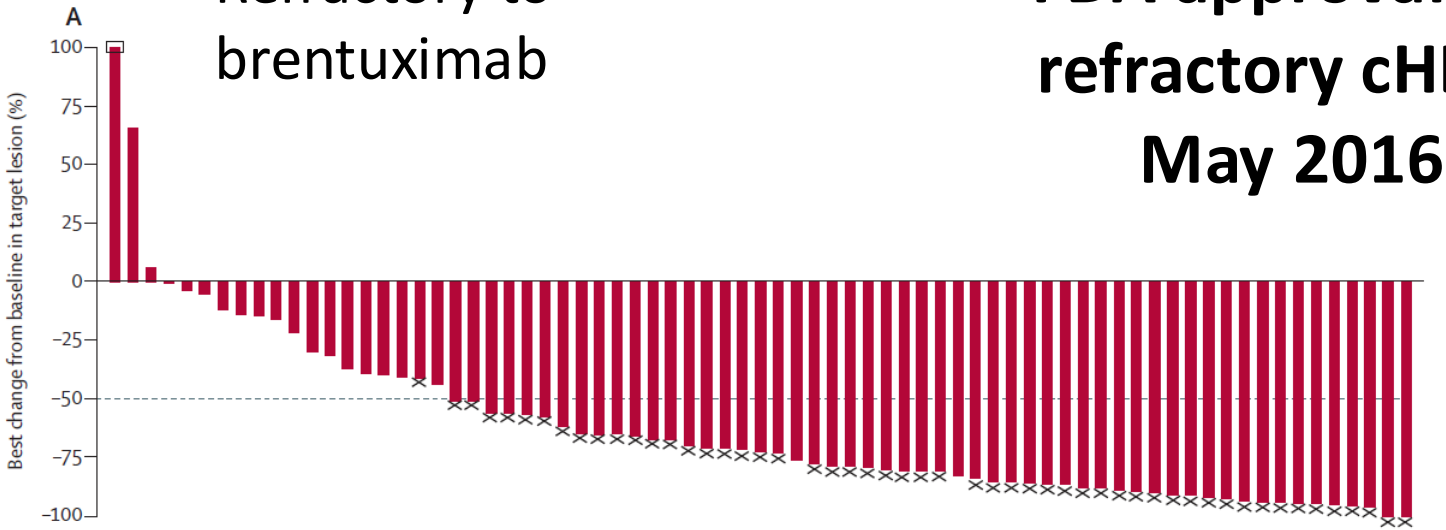
# Checkpoint Blockade

- Highly mutated tumors
  - Melanoma
  - Non-small cell lung cancer
  - Bladder cancer
  - Tumors with mismatch repair deficiency
- Use in other tumors?
  - Renal cell
    - Responds to other immunotherapy
  - Hodgkin's lymphoma
    - Reed-Sternberg cells have elevated amounts of PD-L1
  - Head and neck SCC
    - HPV and mutations

# Nivolumab for Hodgkin's Lymphoma

- 80 patients
  - Classical (cHL)
  - Refractory to stem cell transplant
  - Refractory to brentuximab
- Objective Response
  - 53/80 (66%)
  - 7 complete remission

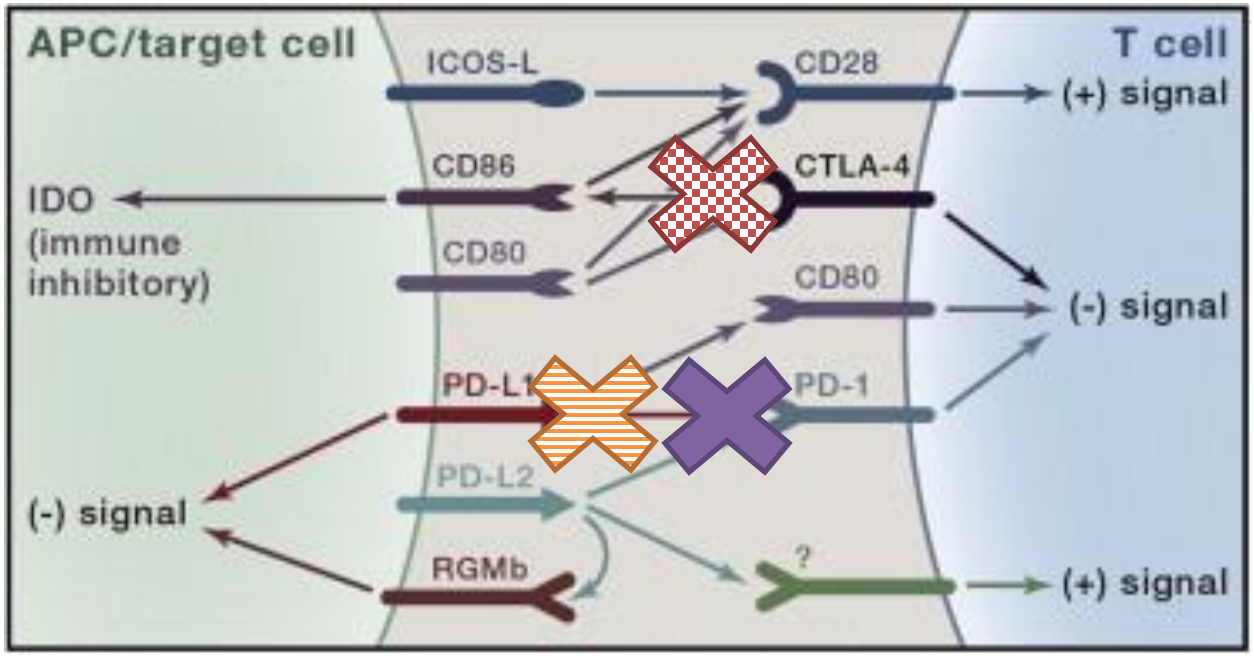
**FDA approval for refractory cHL in May 2016**




Younes A 2016

THE LANCET Oncology

# Checkpoint Modulation

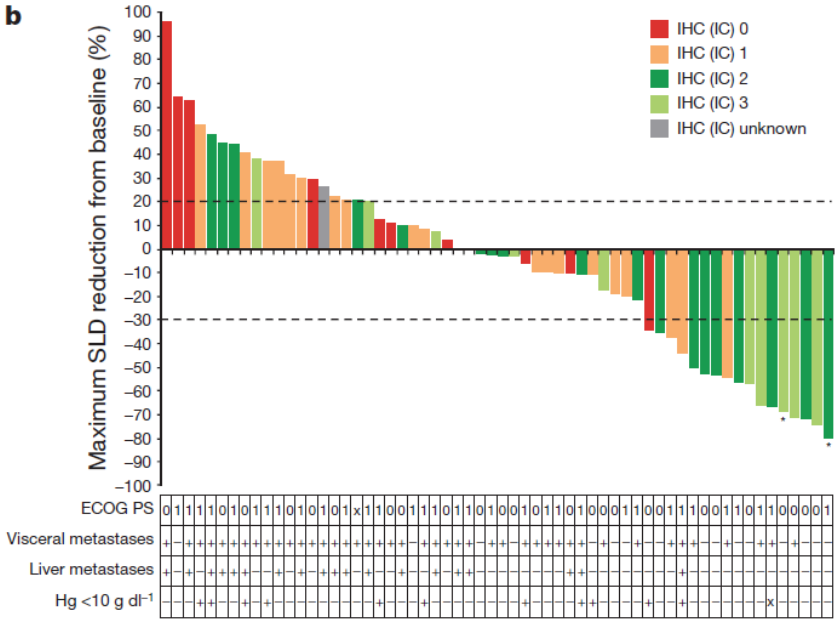



Topalian, Cancer Cell 2015

- Initial focus on blocking Signal 2 on the T cell side
  - Anti-CTLA-4: ipilimumab (Yervoy), tremelimumab (Imjudo)
  - Anti-PD-1: nivolumab (Opdivo), pembrolizumab (Keytruda), cemiplimab (Libtayo), dostarlimab (Jemperli)
- Newer development on blocking Signal 2 on the target
  - Anti-PD-L1: atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi)

# αPD-L1 in Urothelial bladder cancer

- MPDL3280A
- Atezolizumab
- 15 mg/kg q3w
- 27% tumors with >5% PD-L1 by IHC
- 65 patients with pre-treatment biopsy
- Objective Response
  - ≥ 5% PD-L1 13/30 (43.3%)
  - < 5% PD-L1 4/35 (11.4%)
- Grade 3/4 AE 4%

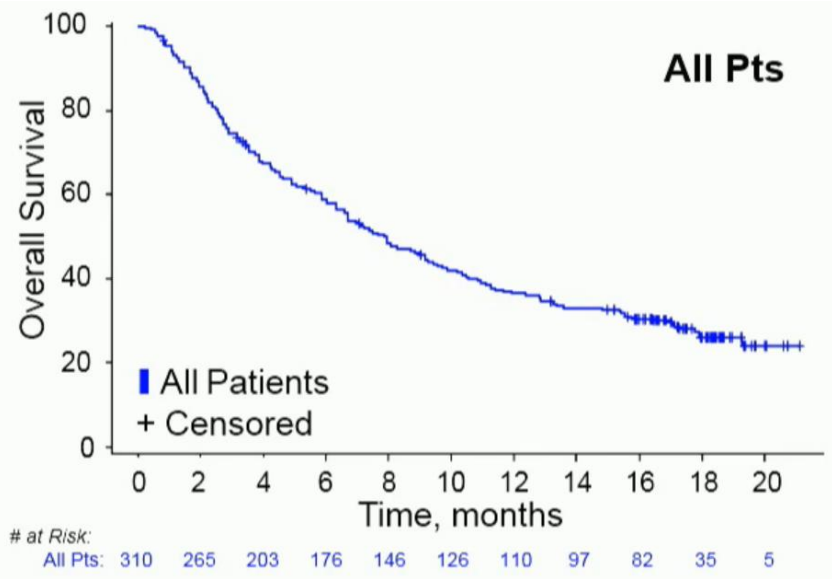



Powles T 2014

nature
International weekly journal of science

# αPD-L1 in Urothelial bladder cancer

- 310 patients
- Objective Response
  - 45 (15%)
  - With 15 complete responses
- Overall Survival
  - 7.9 months
- 1 yr Survival
  - 37%




**FDA approval for urothelial cancer in May 2016**

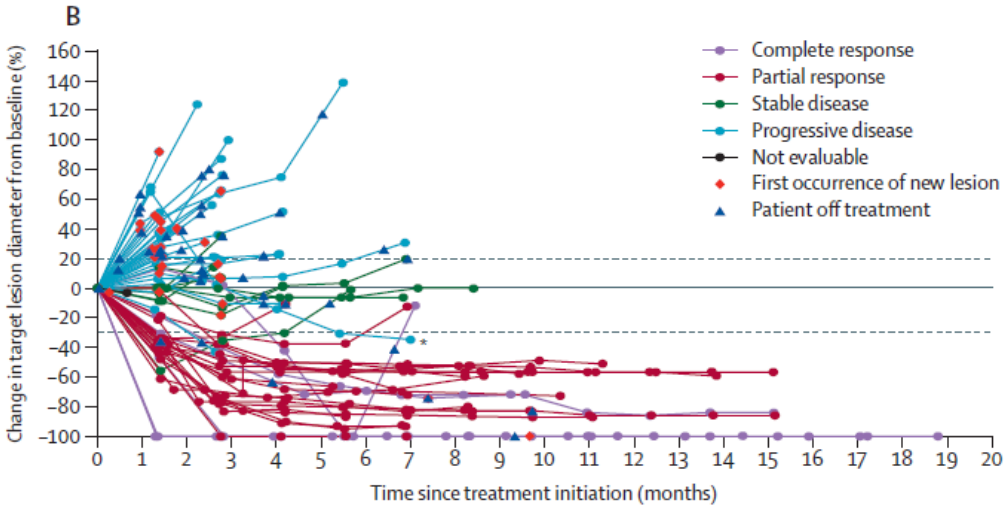
Rosenberg JE 2016 THE LANCET

Updated Dreicer R, 2016 ASCO

# Avelumab in Merkel cell carcinoma

- Polyoma virus & UV damage
- 88 patients
  - Confirmed metastatic disease

- Objective Response
  - 28/88 (32%)
  - 8 complete remission




**FDA approval for Merkel cell carcinoma in March 2017**

Kaufman HL 2016

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# Blocking the PD-1/PD-L1 pathway

| | Drug | Melanoma | NSCLC | RCC | Bladder |
|---|---|---|---|---|---|
| Anti-PD-1 | Nivolumab | 32% (n=107) | 17% (n=129)<br>30% (n=20) | 29% (n=34)<br>21% (n=168) | 20% (n=270)*[1] |
| | Pembrolizumab | 38% (n=135)<br>26% (n=157) | 26% (n=42)<br>20% (n=194) | - | 24% (n=29) |
| Anti-PD-L1 | Durvalumab | - | 16% (n=58) | - | 18% (n=191)*[2] |
| | Atezolizumab | 30% (n=43) | 23% (n=53) | 14% (n=56) | 26% (n=65) |
| | Avelumab* | - | - | - | 18% (n=44)*[3] |

OR % (size of trial)
*Added to original chart

FDA Approved

Adapted from Lipson 2015

Seminars in Oncology

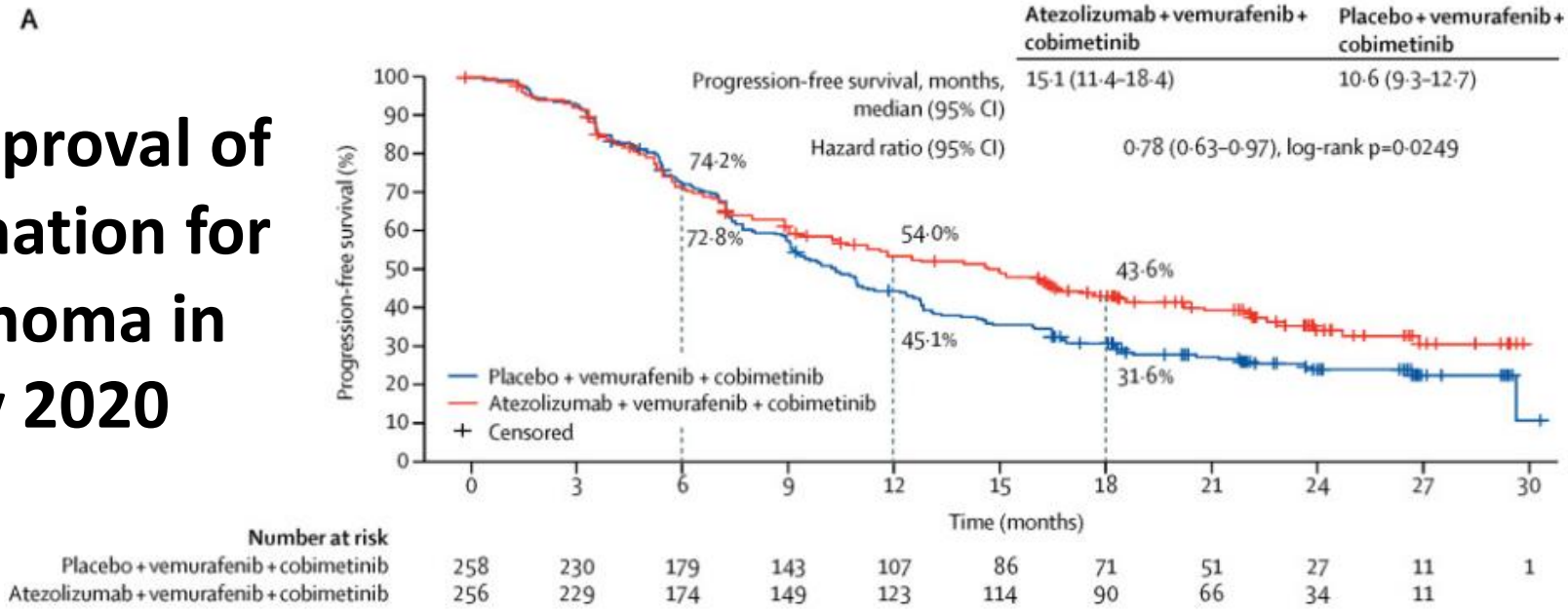
**What about combinations?**

[1] Sharma P Lancet Oncol 2017
[2] Powles T JAMA Oncol 2017
[3] Apolo A J Clin Oncol 2017

# Atezolizumab (αPD-L1) for melanoma

- BRAF V600E/K mutation
- Phase III RCT, with BRAK/MEK inhibitors
- 514 patients, randomized 1:1

**FDA approval of combination for melanoma in July 2020**

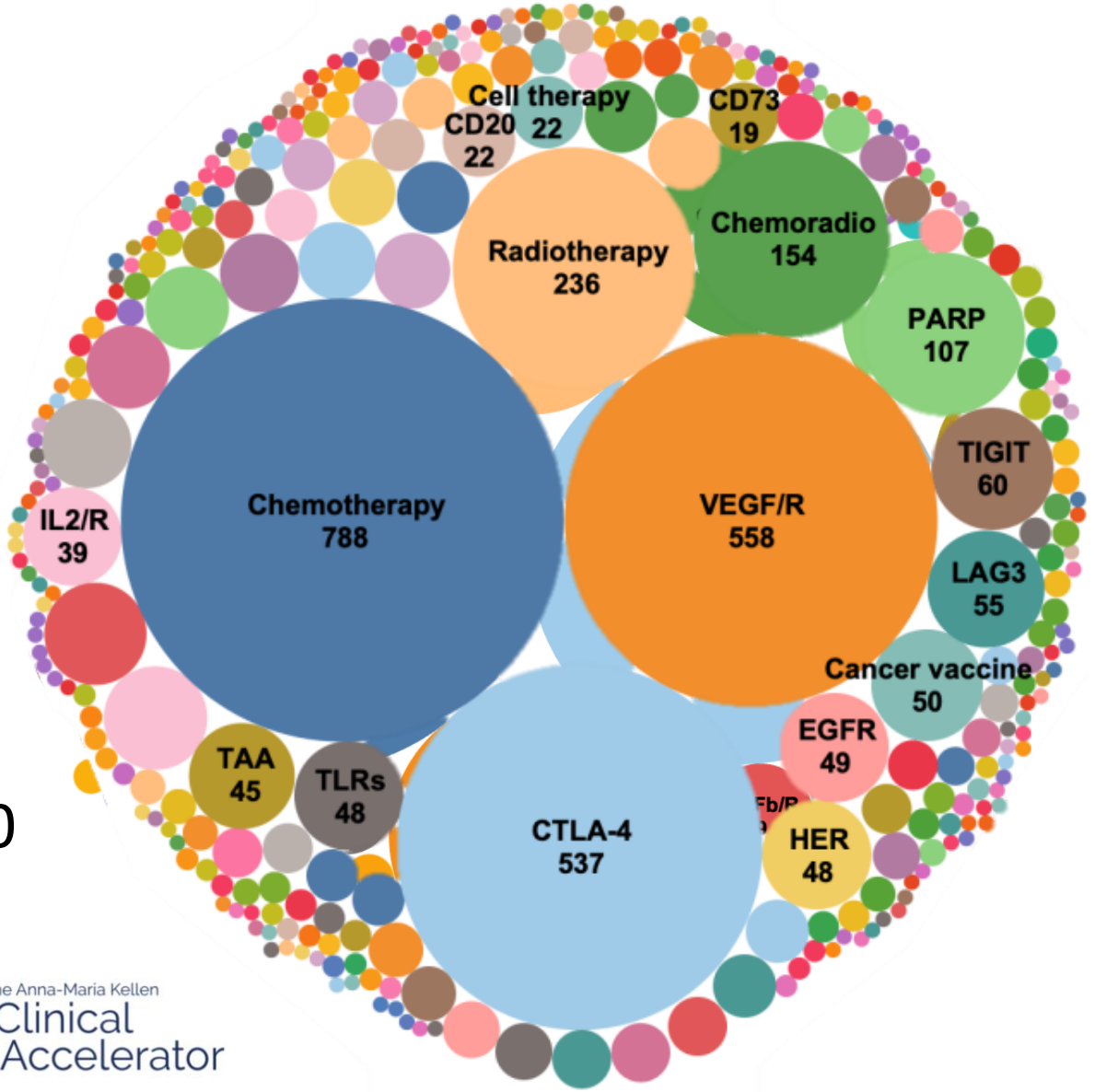



Gutzmer R 2020 THE LANCET

# Combination Clinical Trials

- Over 700 new trials started in 2020

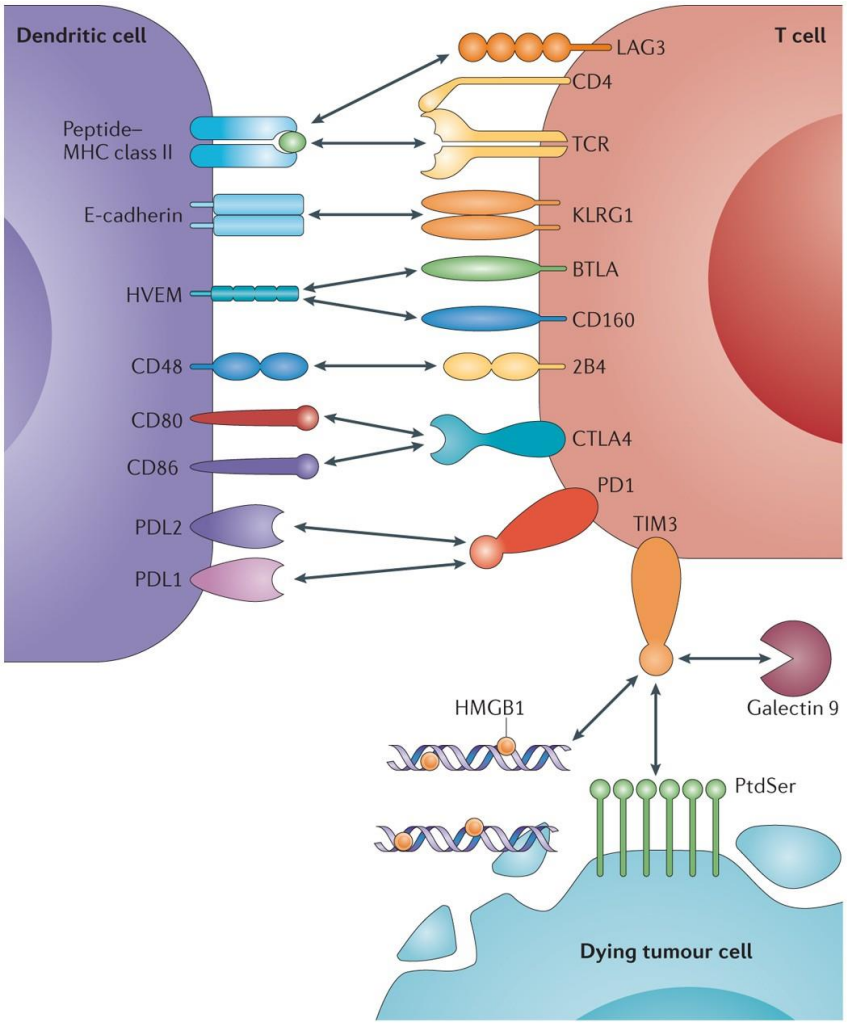
- **<u>2021</u>:** Over 4,600 different trials of combination therapy with ~300 different agents




CANCER RESEARCH INSTITUTE

The Anna-Maria Kellen Clinical Accelerator

# New checkpoint inhibitors

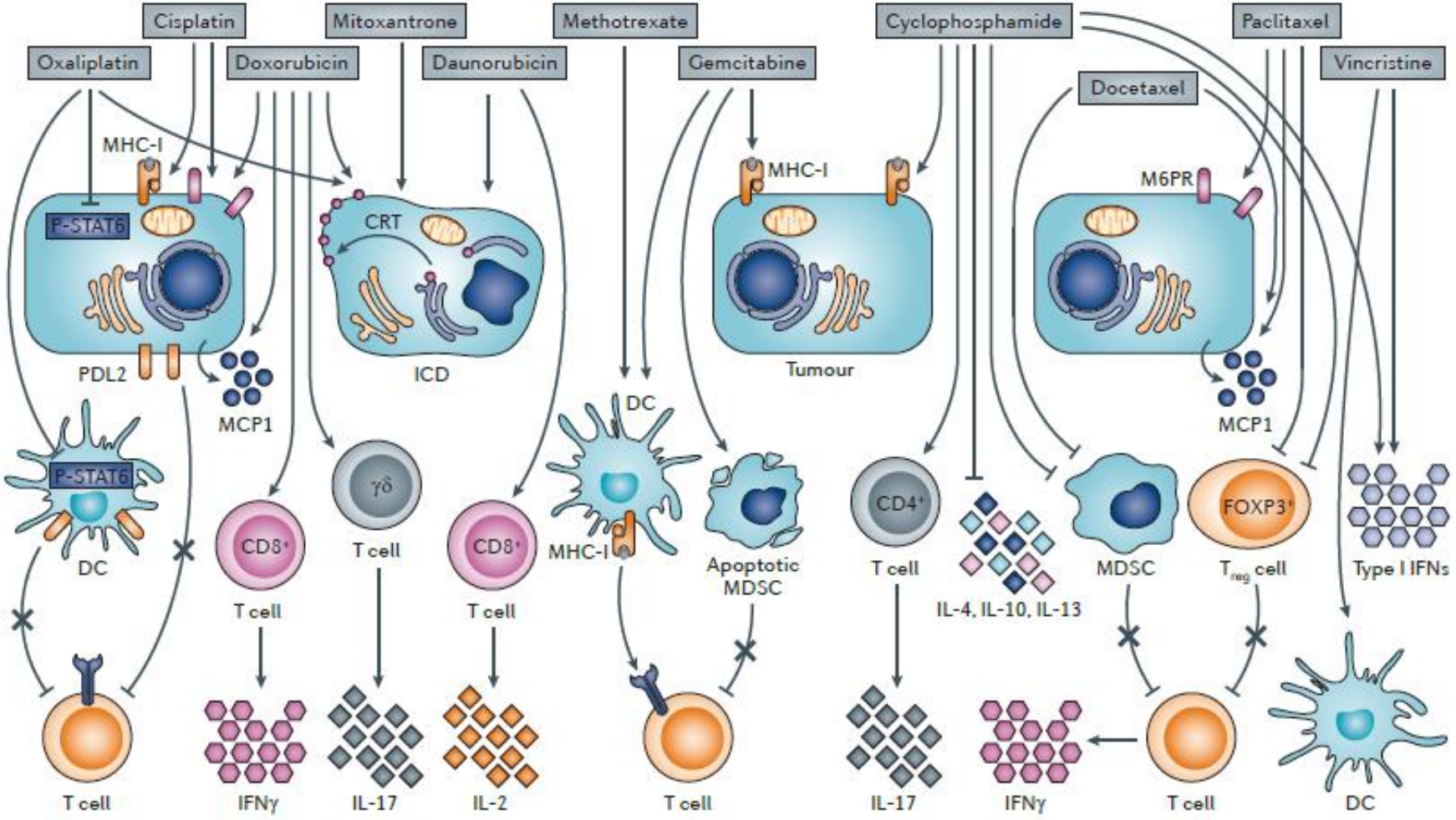



Nature Reviews | Immunology

Nguyen & Ohashi 2015

- LAG-3
- Combination formula
  - Anti PD-1
  - Anti LAG-3
- 16% complete response
- 27% partial response
- Approved for 1st line metastatic melanoma in March 2022

# Rationale for Chemotherapy Combinations




Galluzzi Nature Reviews Drug Discovery (2012)

# Checkpoint Modulators

- Every expanding list of indications
- Any questions?