Immune checkpoint blockade

Immune Checkpoint Blockade

NCI CCR TRACO

Stephanie L. Goff, MD, FACS

Objectives

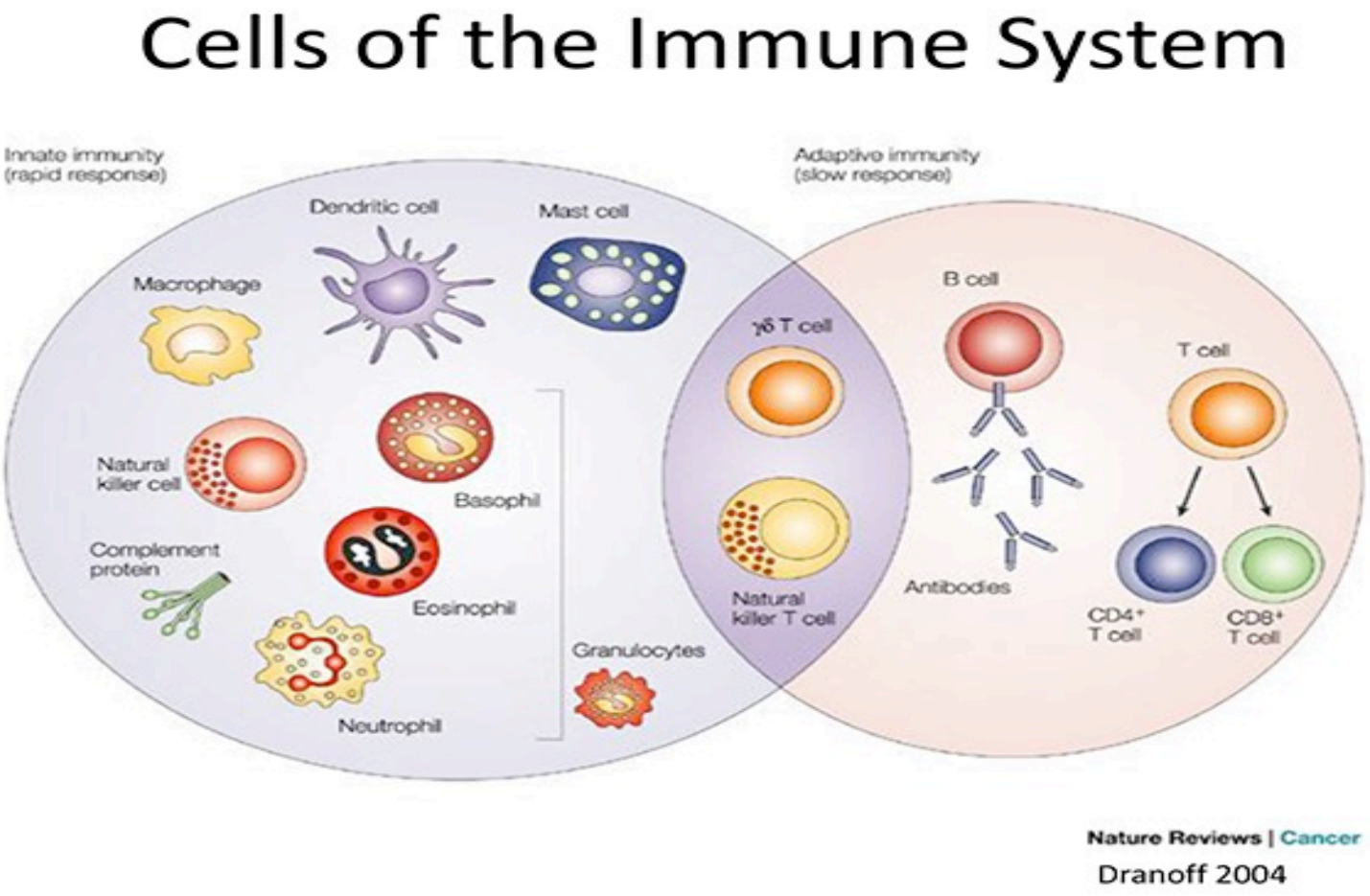
- The basics of immunotherapy
- Mechanism of action of checkpoint blockade
- Early clinical experience and the discovery of immune related adverse events
- Checkpoint blockade in melanoma
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
- Experimental Questions

Oncology

Cancer Immunotherapy

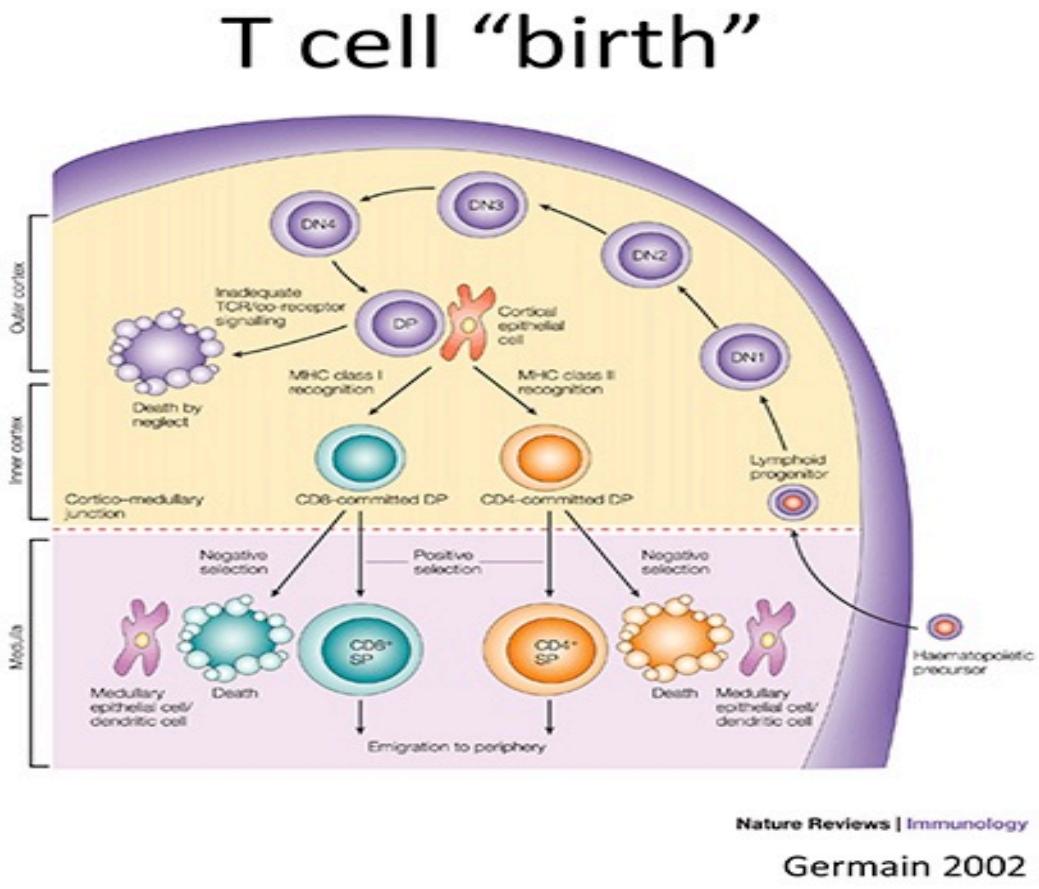
1. Nonspecific stimulation of immune reactions
    a) Stimulate effector cells
    b) Inhibit regulatory factors (checkpoint blockade)
2. Active immunization to enhance anti-tumor reactions (cancer vaccines)
3. Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)

Immune system



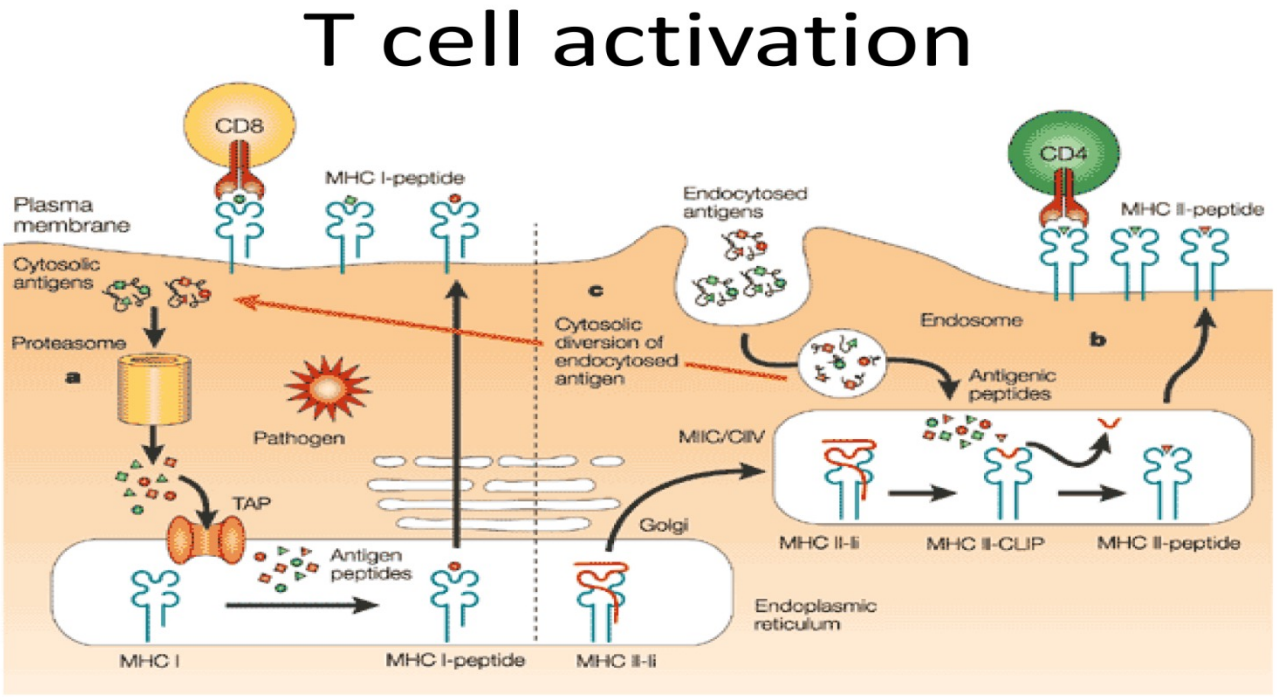
- Checkpoint blockade primarily affects T cells

T cell birth



- Builds a repertoire of T cells

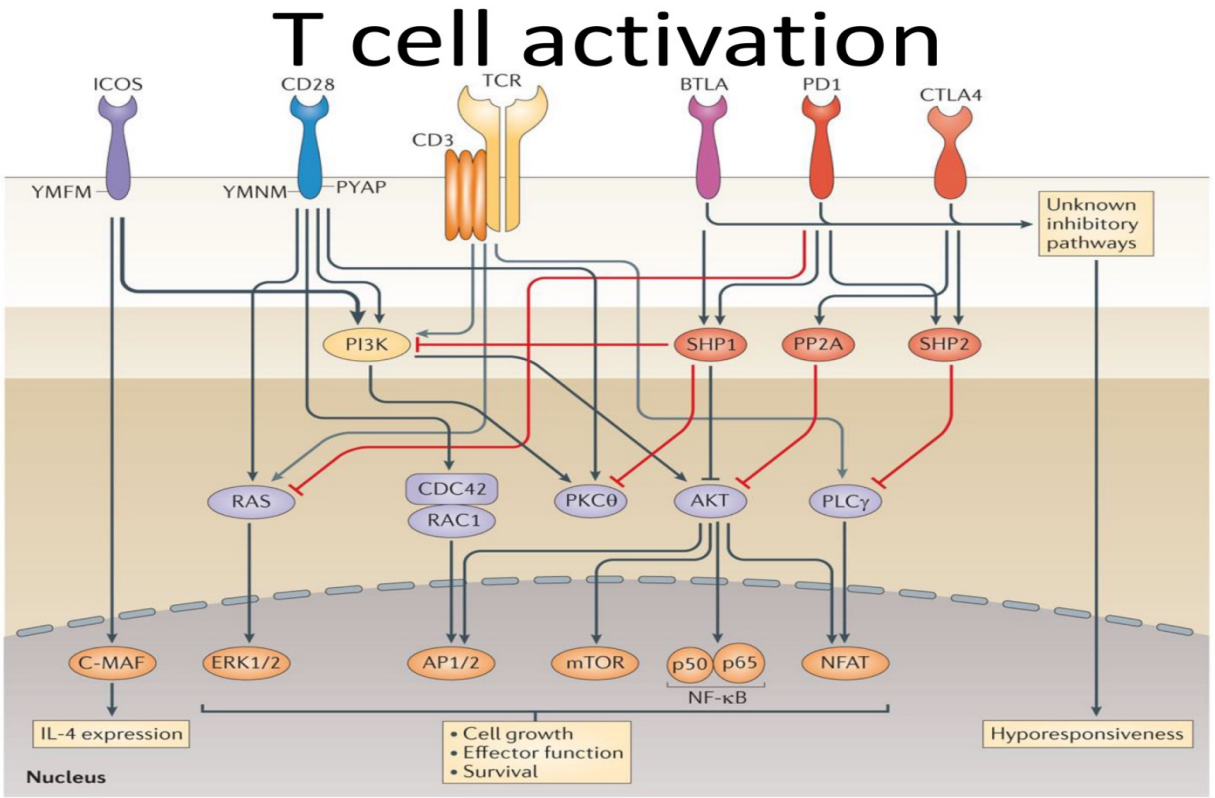
T cell activation



Nature Reviews | Immunology
Heath 2001

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

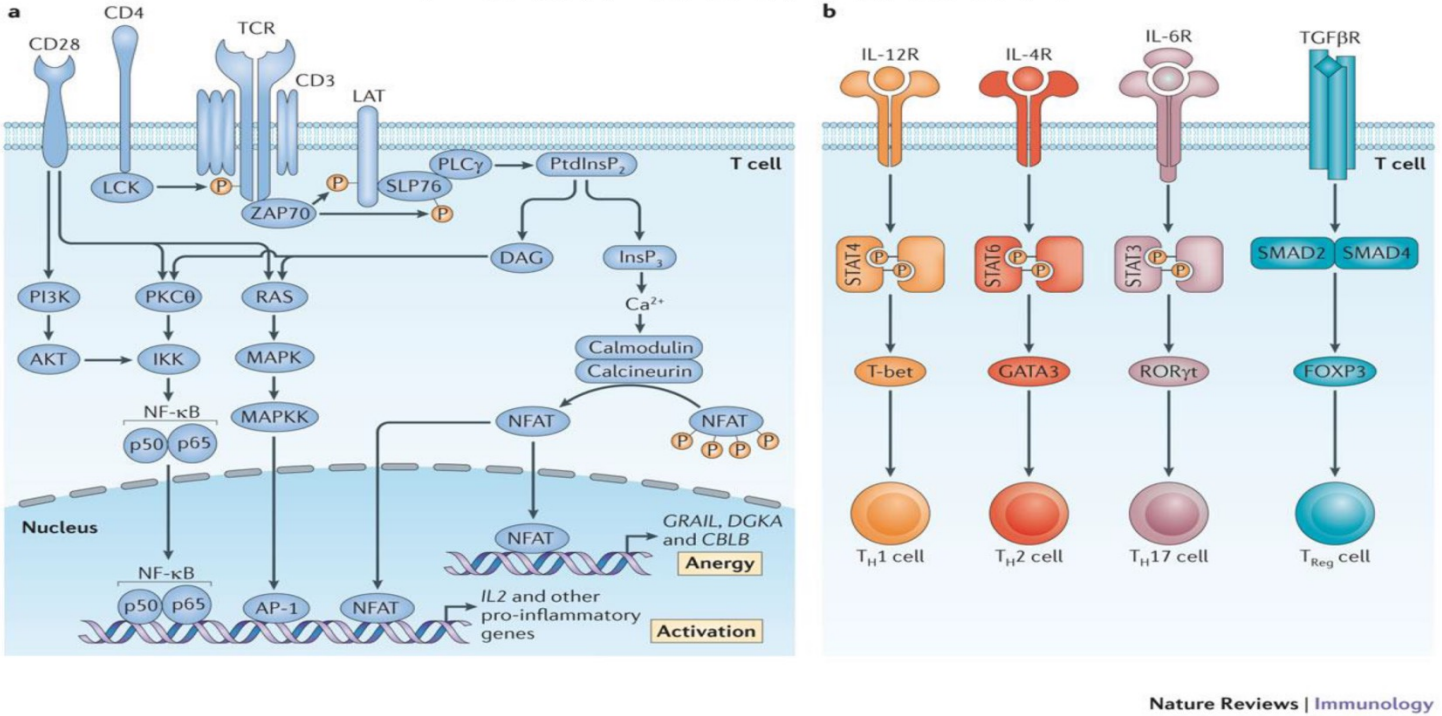
T cell activation



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

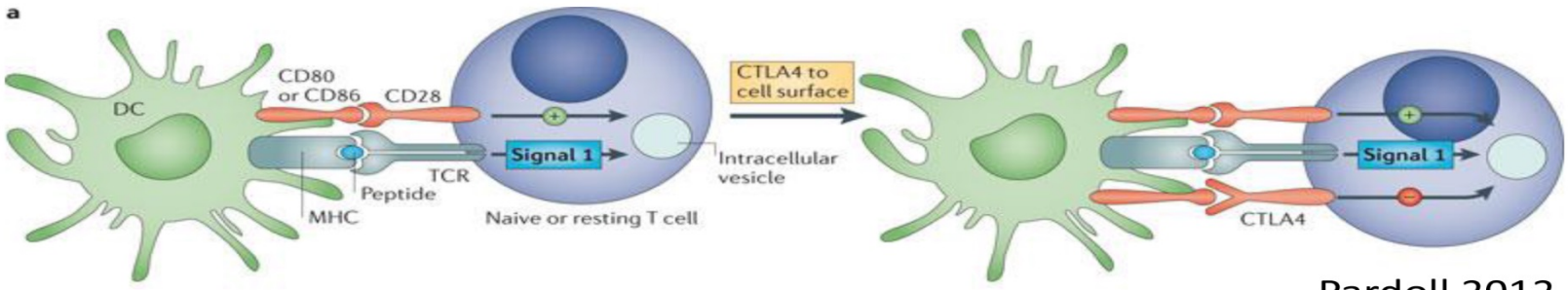
The role of Signal 2 checkpoints

- 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, two opportunities to break tolerance to self-antigen

CTLA-4

CTLA-4

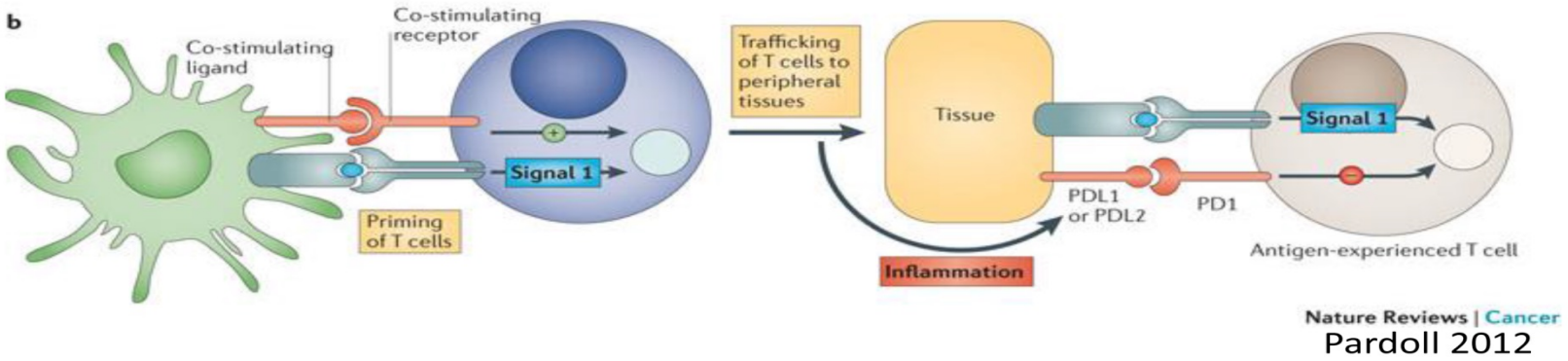


Pardoll 2012

- 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 Treg cells

PD-1

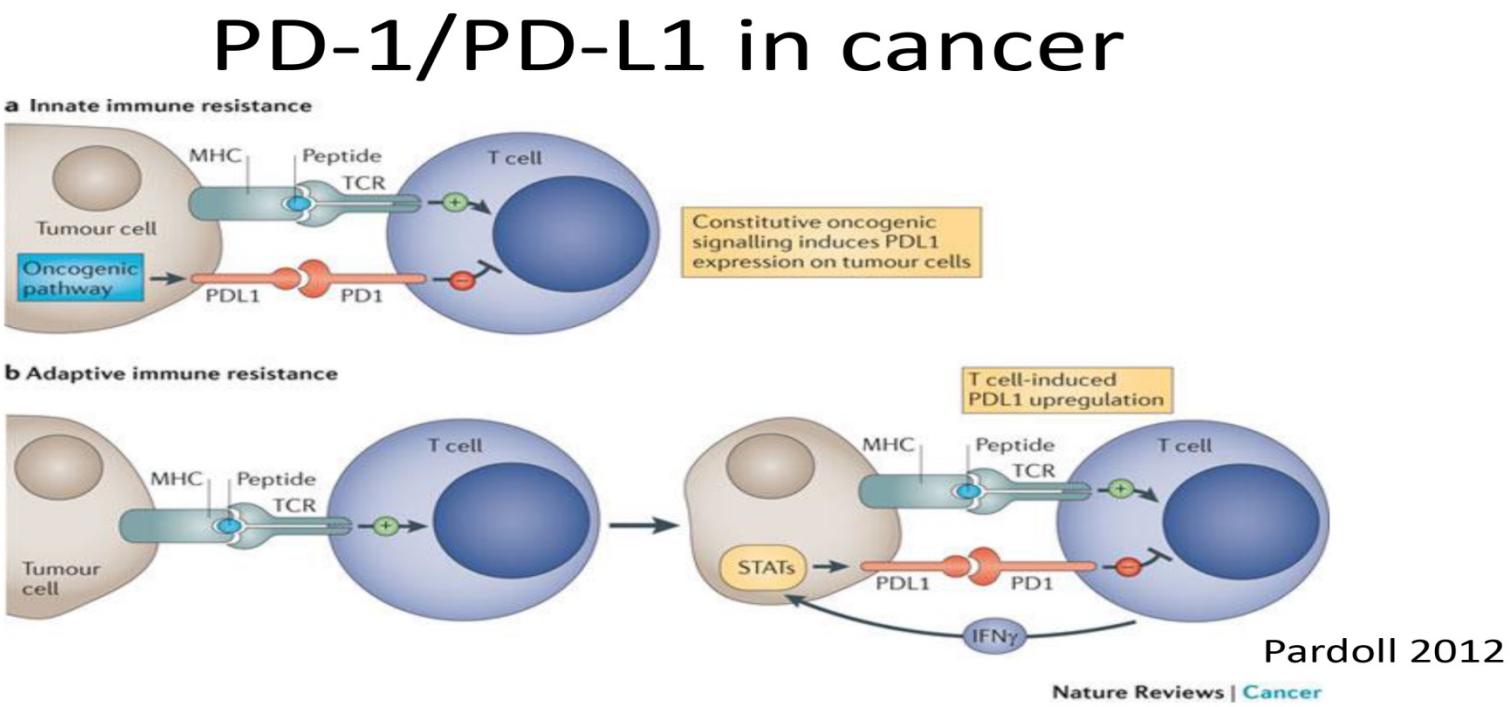
PD-1



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



- Cancer cells can increase the amount of PDL1
- Successful T-cell tumor destruction can increase PDL1 through upregulation in response to IFNγ

Checkpoint blockade

Checkpoint Blockade

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

- **Melanoma**
- Estimated 9,940 deaths/year in US
- Metastatic disease 16% 5 yr survival
- Interleukin-2 durable *cure* in 4%

- **Renal Cell Cancer**
- Estimated 14,080 deaths/year in US
- Metastatic disease 12% 5 yr survival
- Interleukin-2 durable *cure* in 7%

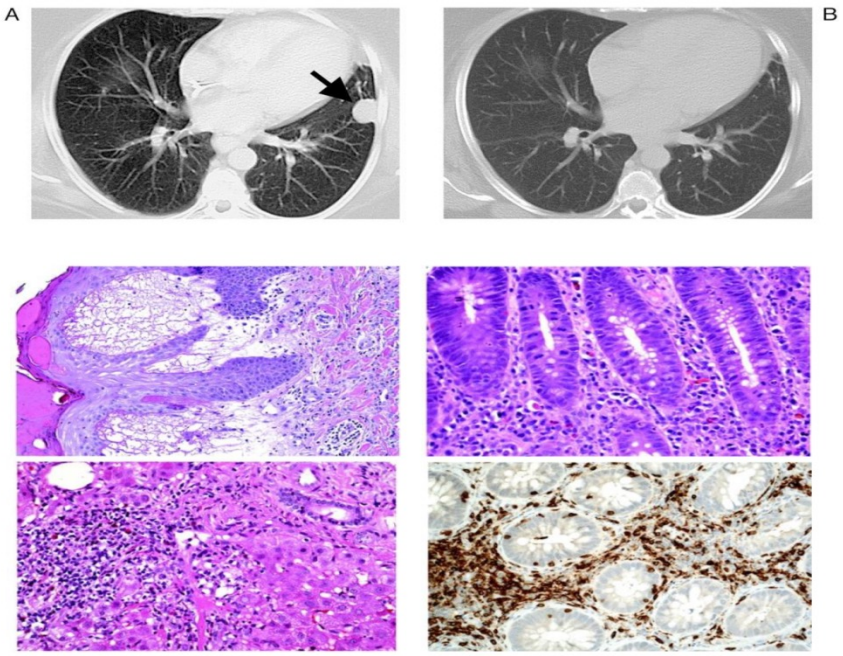
Smith FO Clin Cancer Res 2008

Klapper JA Cancer 2008
American Cancer Society Facts and Figures 2015

Checkpoint Blockade

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



Phan GQ 2003

PNAS

Checkpoint Blockade

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

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

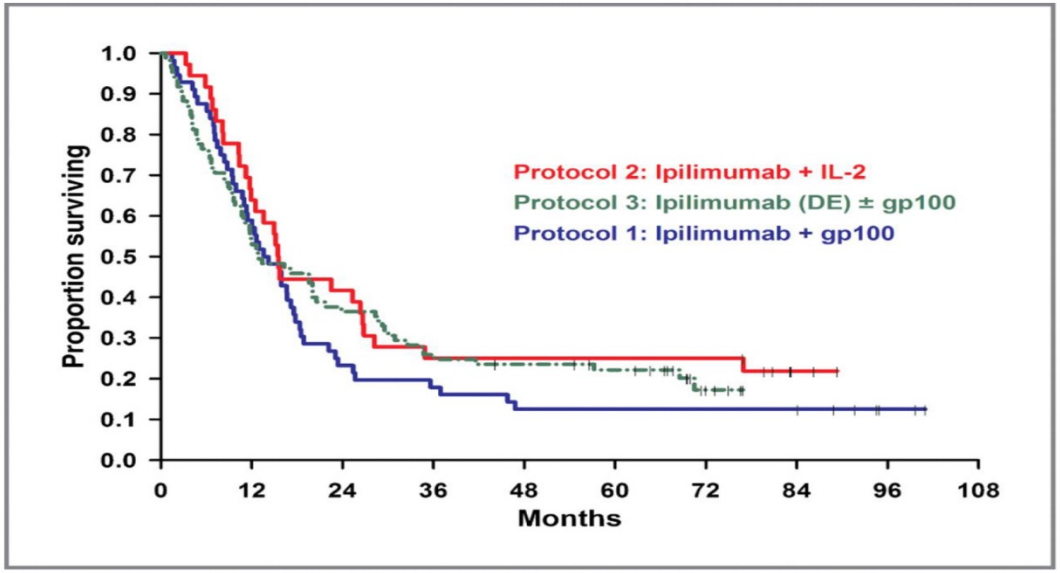
	Gr 3/4 IRAE	Gr 1/2 IRAE	No IRAE
Objective Response (CR = 3)	14 (28%)	8 (22%)	1 (2%)
Non-responder	36	28	52

Beck KE 2006
Downey SG 2007

Checkpoint Blockade

Checkpoint Blockade @ NCI

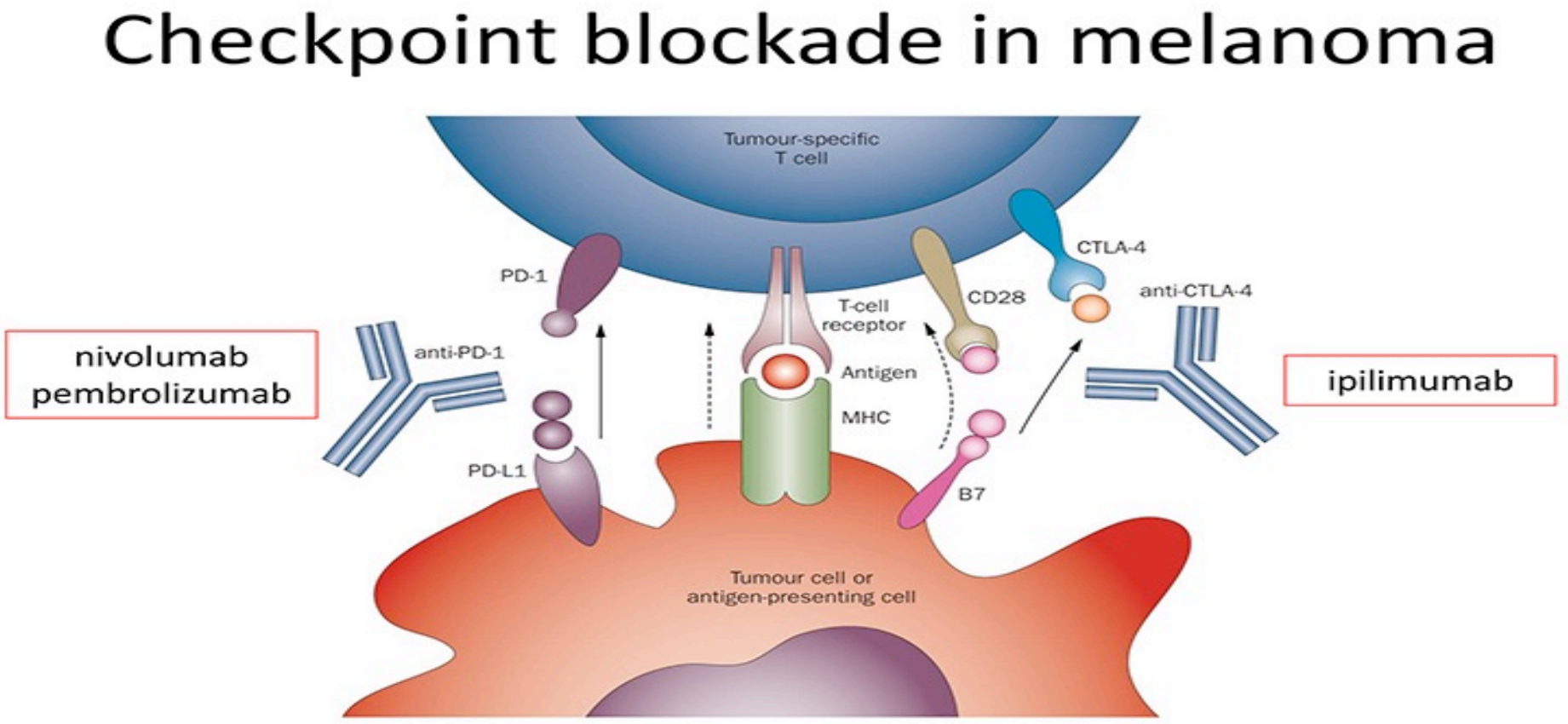
- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
  - OR 13-20%
  - 5 yr OS 13-23%



Prieto PA 2012

Clinical Cancer Research
AACR American Association for Cancer Research

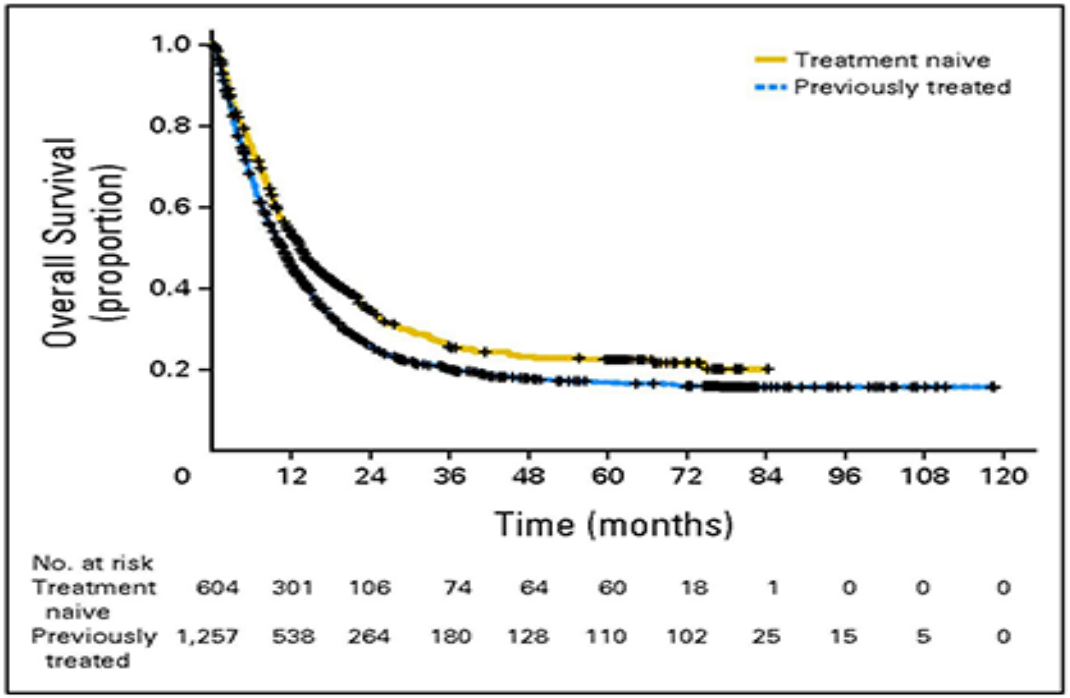
Checkpoint blockade



Ipilimumab

Ipilimumab for melanoma

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



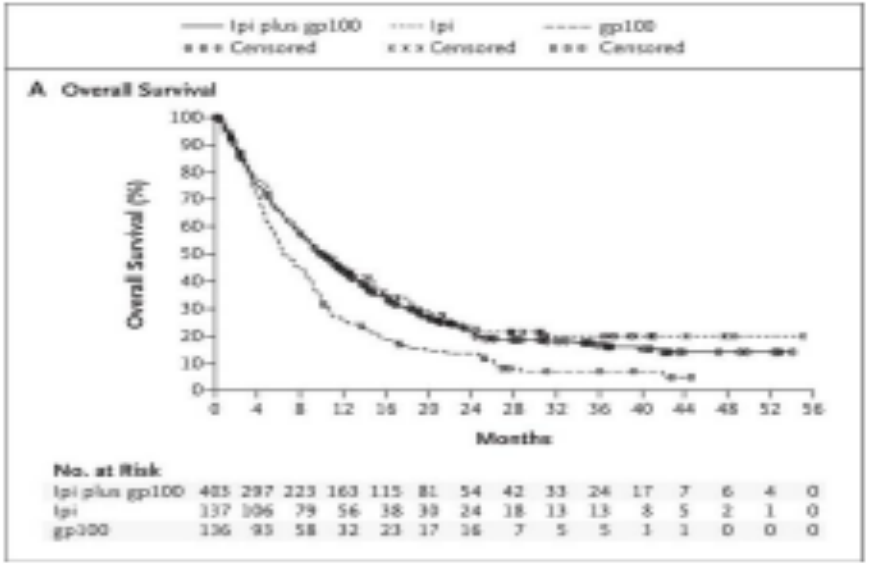
Schadendorf D 2015

JOURNAL OF CLINICAL ONCOLOGY ASCO

Ipilmumab

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

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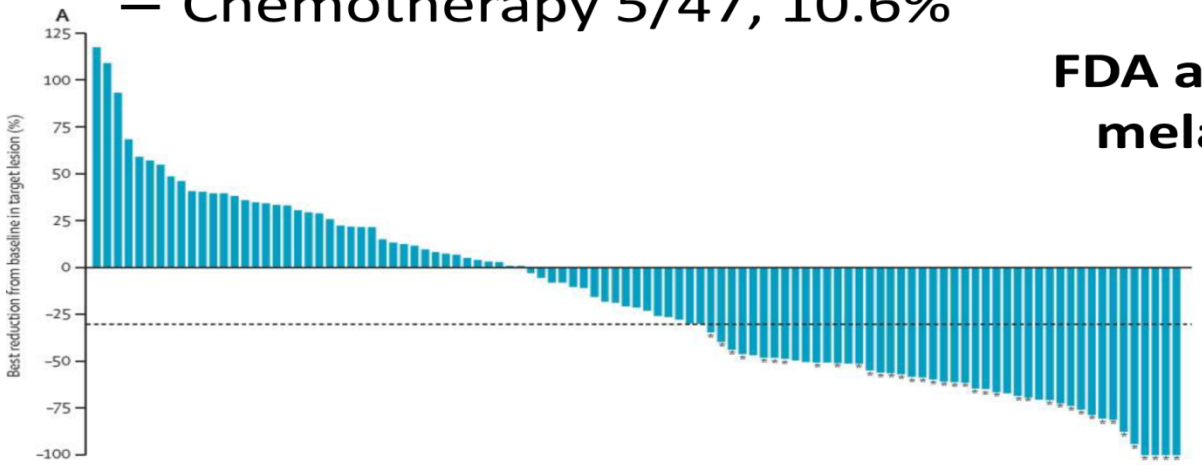
Nivolumab for melanoma

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

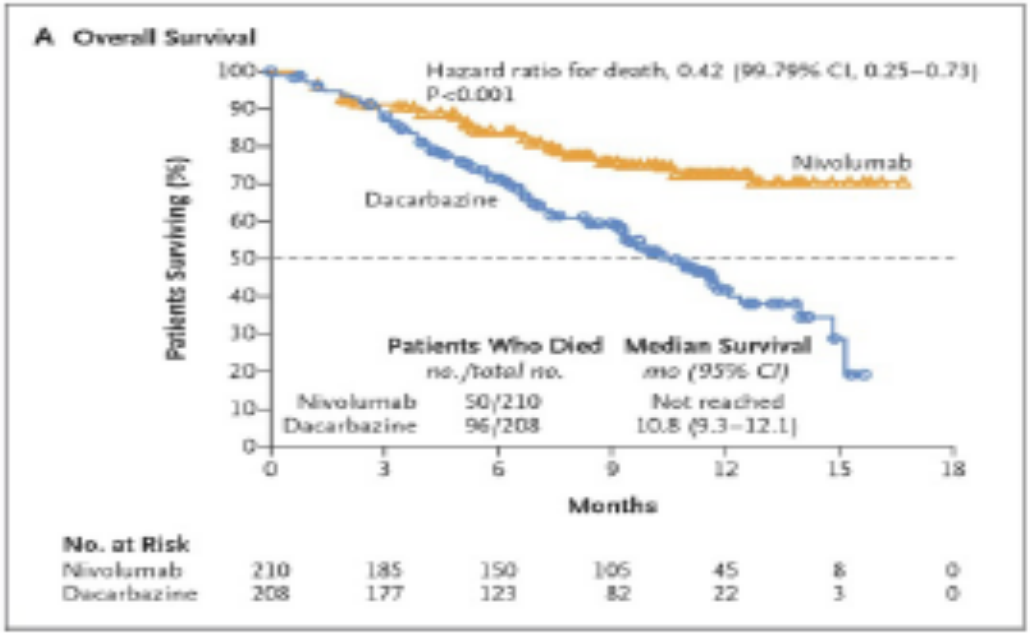
Weber JS 2015

THE LANCET Oncology

Nivolumab for melanoma

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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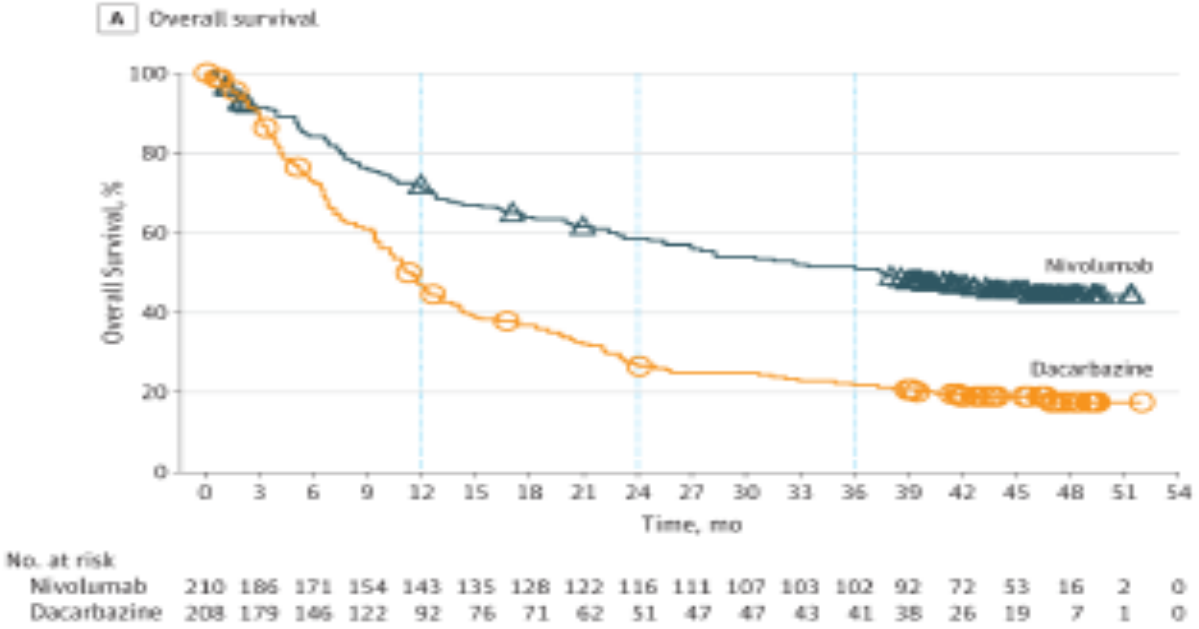
Nivolumab

Nivolumab for melanoma

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



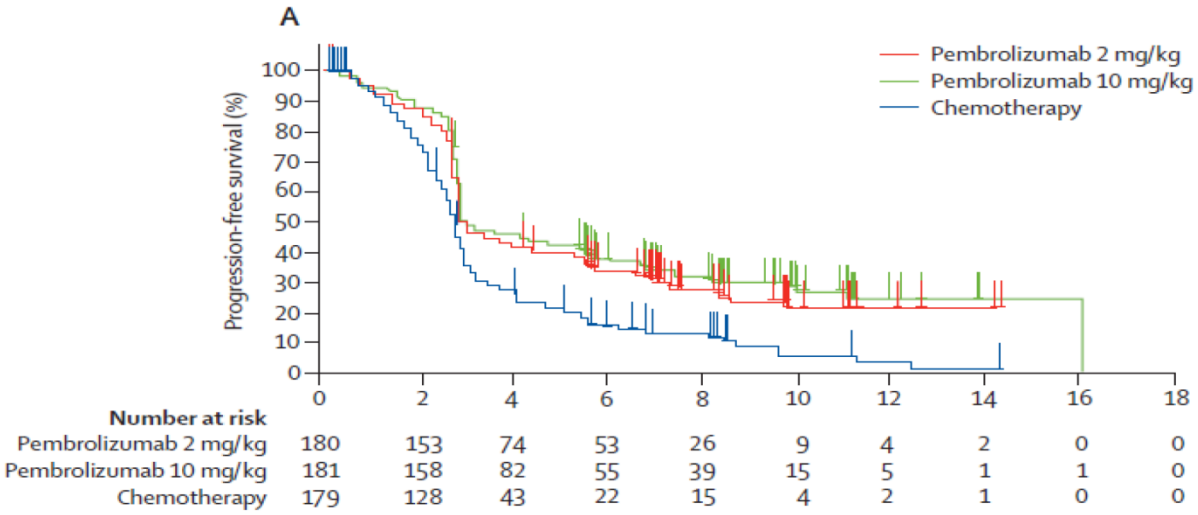
Ascierto P 2018

JAMA Oncology

Pembrolizumab for melanoma

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%



Weber JS 2015

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Pembrolizumab for melanoma

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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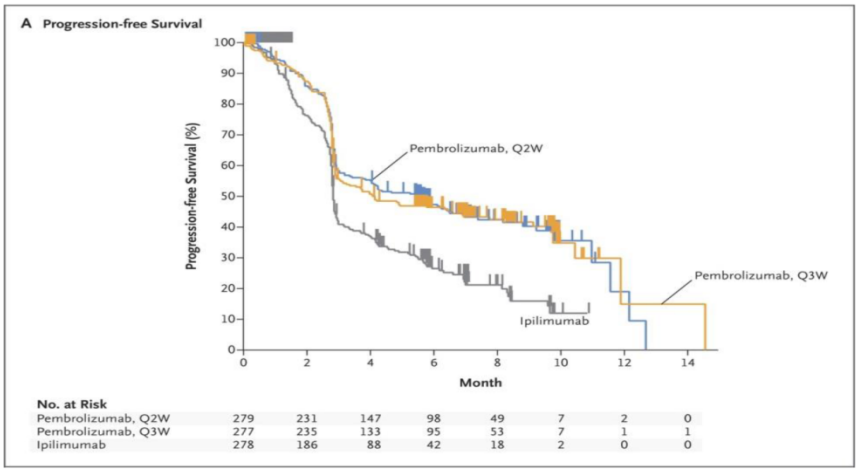
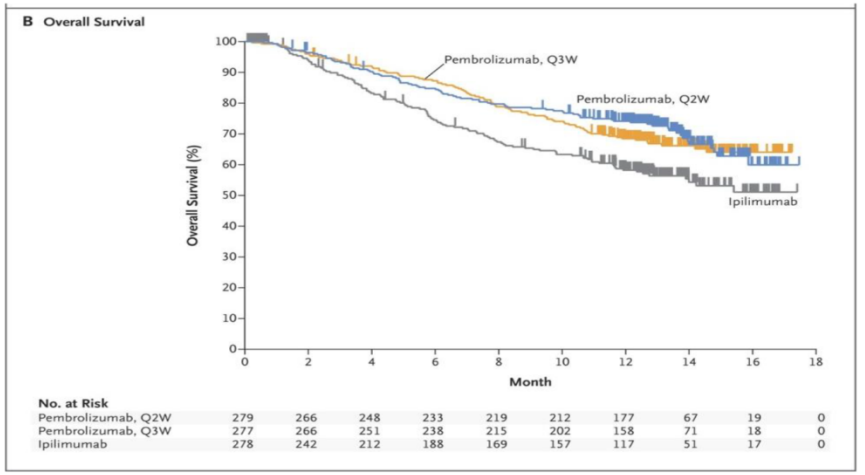
Pembrolizumab for melanoma

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)

Robert C 2015

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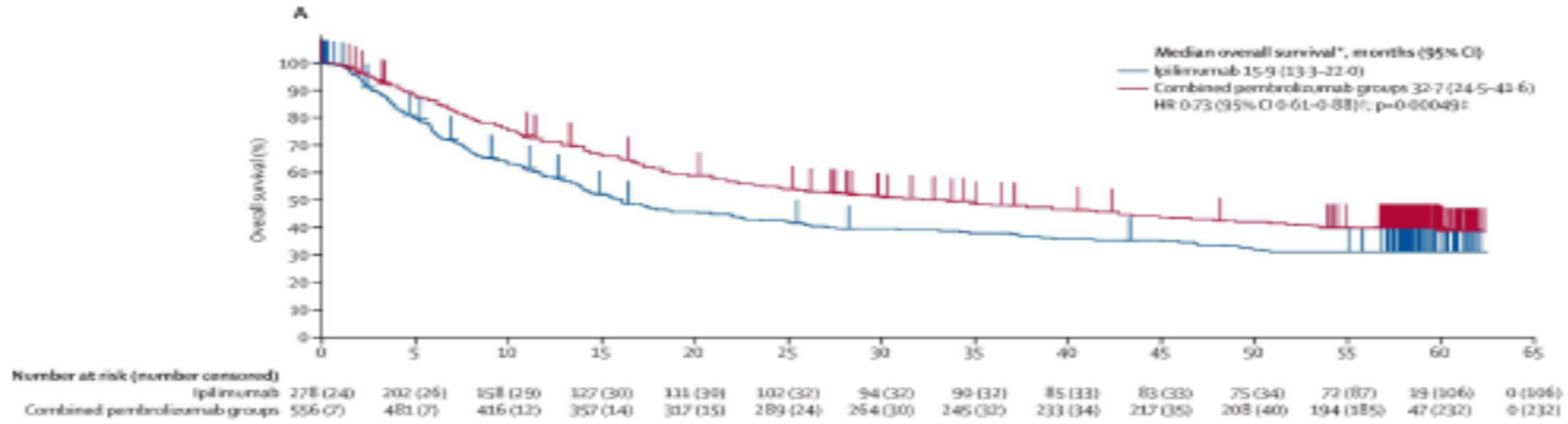
Pembrolizumab

Pembrolizumab for melanoma

- Three year OS of 48.1% vs 37.8%

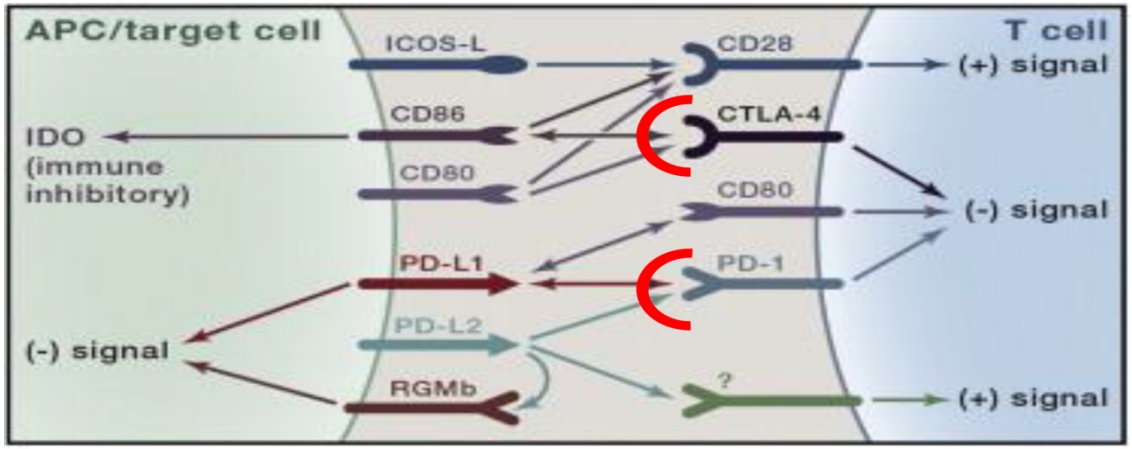


Robert C 2019

THE LANCET Oncology

Checkpoint modulation

Checkpoint Modulation



Topalian, Cancer Cell 2015

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

Nivolumab/Ipilmumab

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/Ipilmumab

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

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Nivolumab/Ipilmumab

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)	51 (16)	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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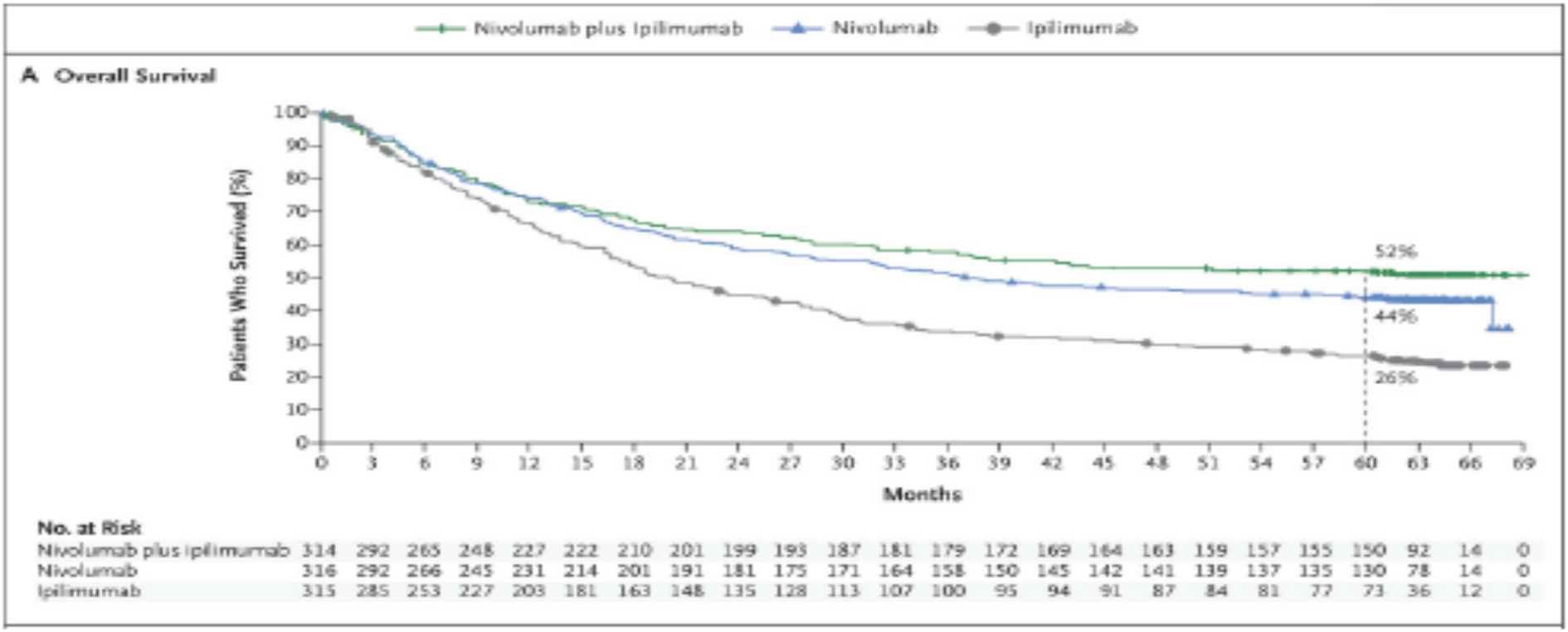
Nivolumab/Ipilmumab for melanoma

Nivolumab/Ipilimumab for melanoma



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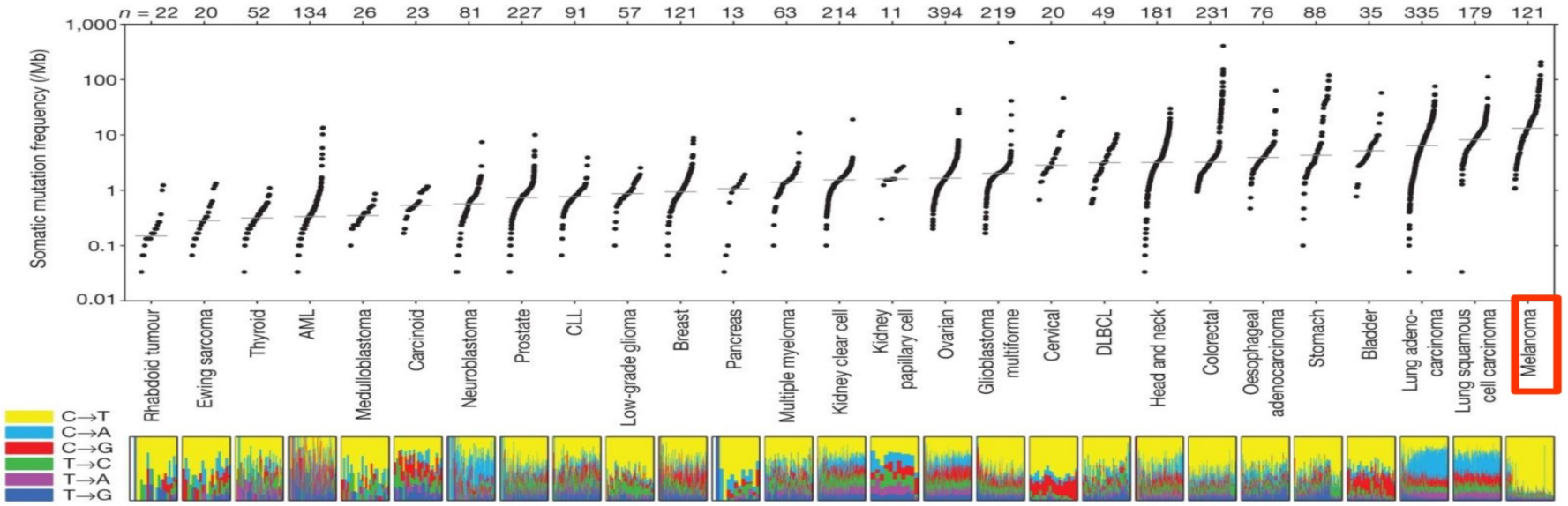
Melanoma

Why melanoma?



MS Lawrence *et al. Nature* 1-5 (2013) doi:10.1038/nature12213

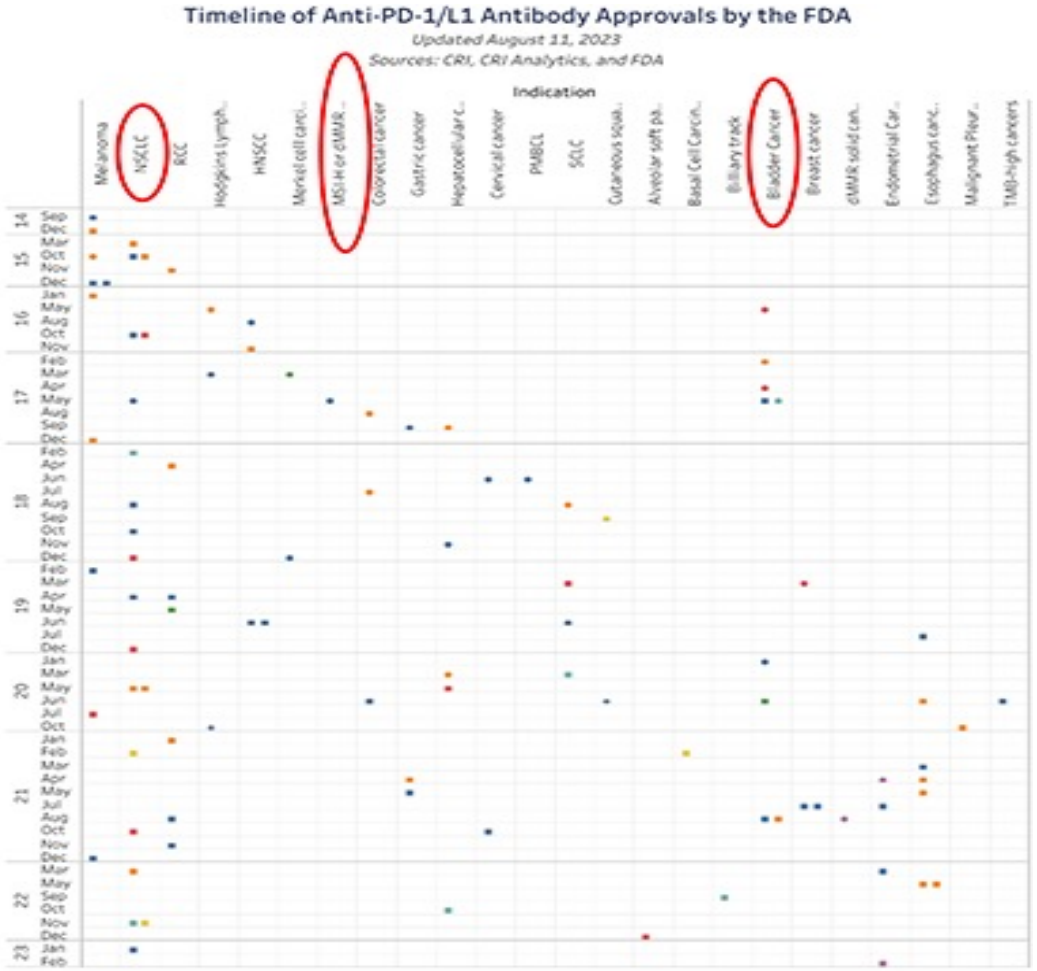
Highly mutated tumors

- Non-small cell lung cancer
- ~158,040 deaths/year in US
- Regional disease
  16% 5 yr survival
- Metastatic disease
  2% 5 yr survival
- Correlation between smoking and # mutations

- Tumors with mismatch repair (MMR) deficiency
  - Lynch syndrome (germline mutation)
  - Sporadic mutation
  - MSH2, MLH1, MSH6, PMS2
- Bladder cancer
  - 16,000 deaths/year in US
  - Highly lethal once metastatic

FDA approval time

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



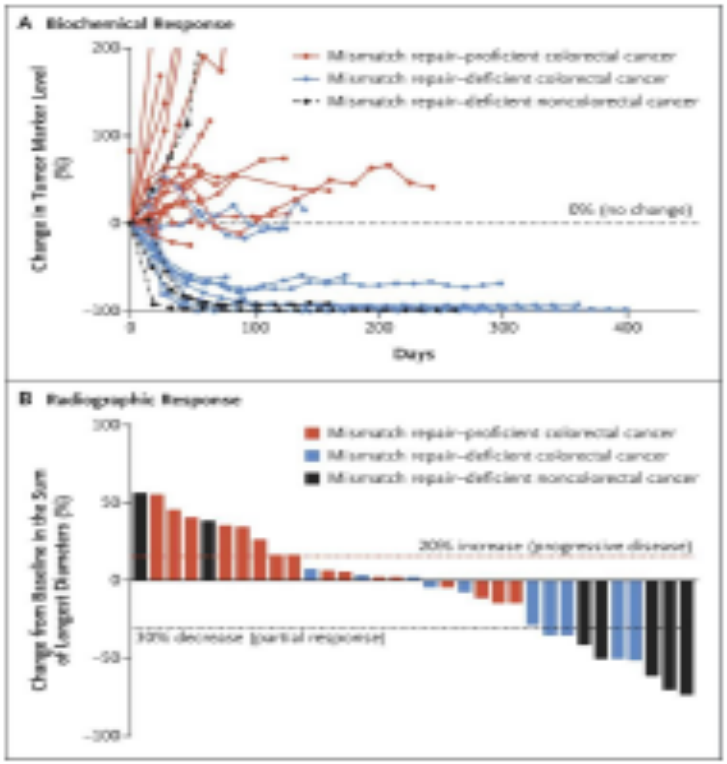
CRI

Drug & Company
Pembrolizumab, Merck & Co
Nivolumab, Bristol Myers Squibb
Atezolizumab, Roche
Durvalumab, AstraZeneca
Avelumab, EMD Serono
Cemiplimab, Regeneron
Dostarlimab, GlaxoSmithKline

Mismatch/repair deficiency

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

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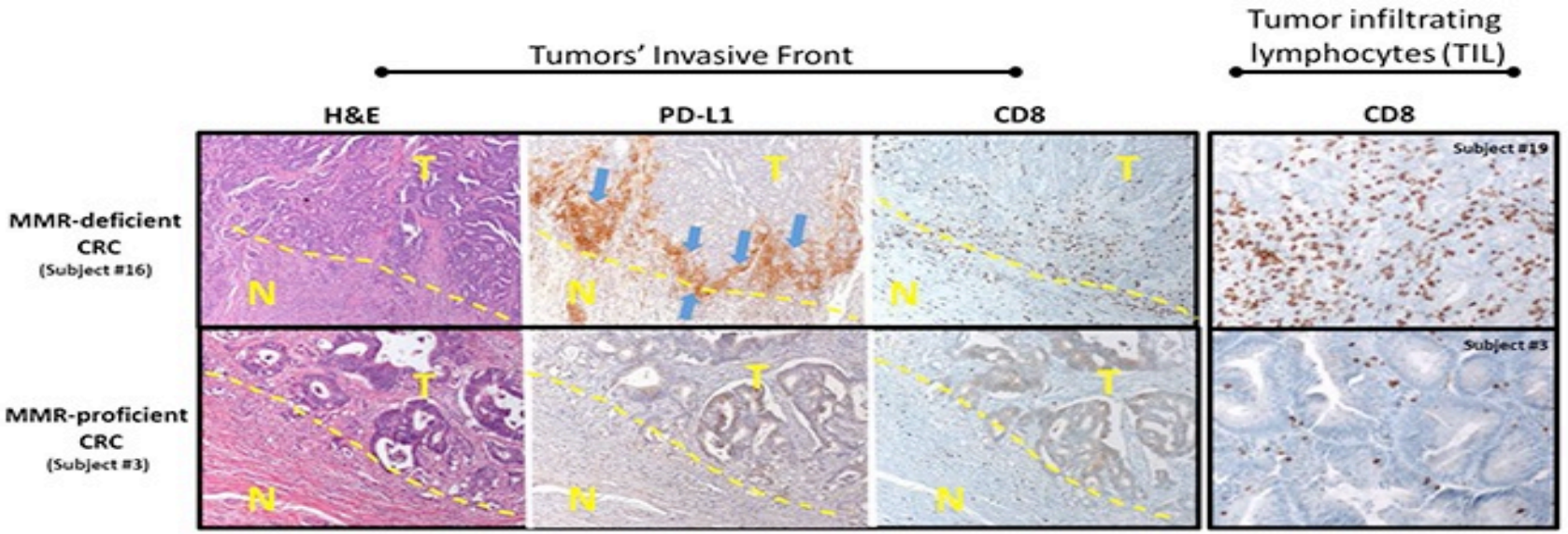
Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface



Le DT 2015

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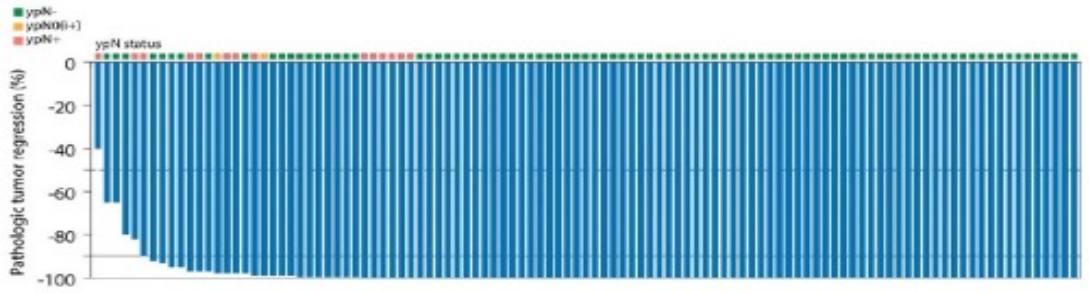
Pre-op combinations checkpoint

Pre-op combination checkpoint

PARIS 2022 ESMO congress
#ESM022



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

Checkpoint Blockade

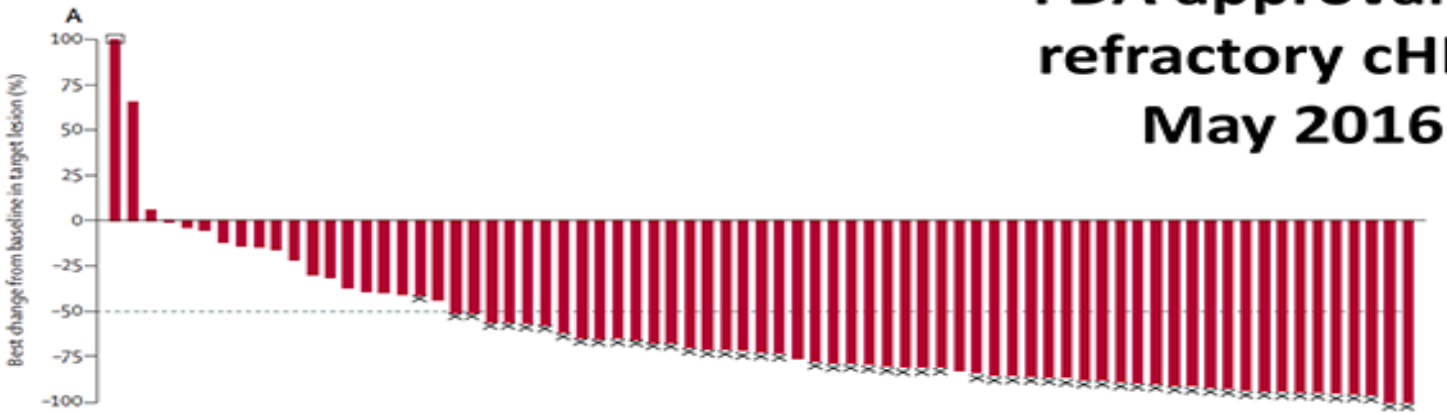
- **Highly mutated tumors**
  - Melanoma
  - Non-small cell lung cancer
  - Bladder cancer
  - Tumors with mismatch repair deficiency
- **Use in other tumors?**
  - Renal cell
    - Responds to other immunotherapy
  - Hodgkin's lymphoma
    - Reed-Sternberg cells have elevated amounts of PD-L1
  - Head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

Hodgkin's lymphoma

Nivolumab for Hodgkin's Lymphoma

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

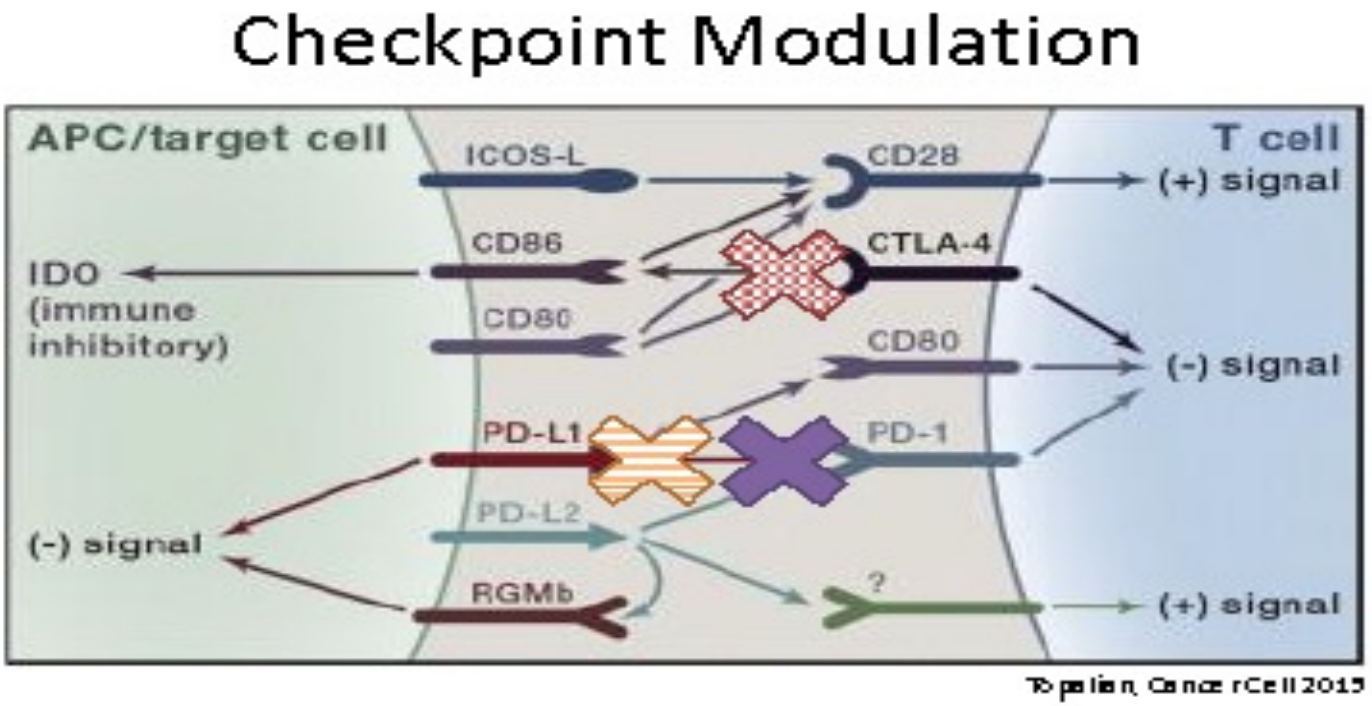
FDA approval for refractory cHL in May 2016



Younes A 2016

THE LANCET Oncology

Checkpoint modulation



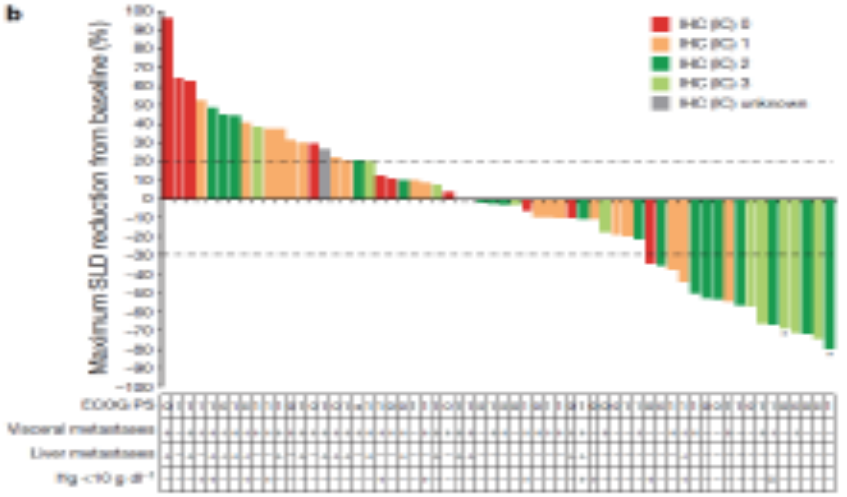
Topalian, Cancer Cell 2015

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

Bladder cancer

αPD-L1 in Urothelial bladder cancer

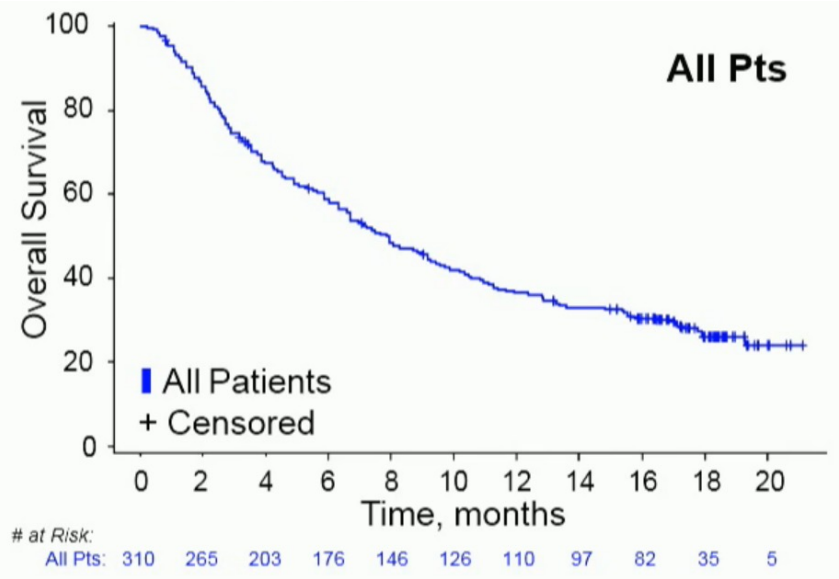
- MPDL3280A
- Atezolizumab
- 15 mg/kg q3w
- 27% tumors with >5% PD-L1 by IHC
- 65 patients with pre-treatment biopsy
- Objective Response
  - ≥ 5% PD-L1 13/30 (43.3%)
  - < 5% PD-L1 4/35 (11.4%)
- Grade 3/4 AE 4%



Powles T 2014
nature

αPD-L1 in Urothelial bladder cancer

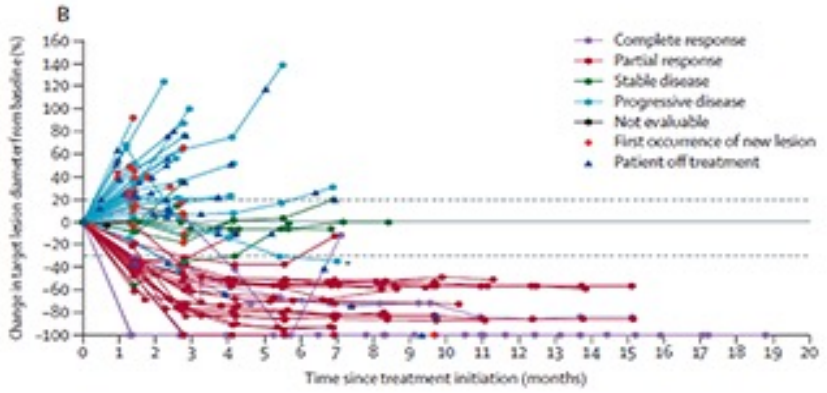
- 310 patients
- Objective Response
  - 45 (15%)
  - With 15 complete responses
- Overall Survival
  - 7.9 months
- 1 yr Survival
  - 37%



Avelumab

Avelumab in Merkel cell carcinoma

- 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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PD-1/PD-L1 pathway

Blocking the PD-1/PD-L1 pathway

	Drug	Melanoma	NSCLC	RCC	Bladder
Anti-PD-1	Nivolumab	32% (n=107)	17% (n=129) 30% (n=20)	29% (n=34) 21% (n=168)	NR
	Pembrolizumab	38% (n=135) 26% (n=157)	26% (n=42) 20% (n=194)	NR	24% (n=29)
Anti-PD-L1	BMS-936559	17% (n=52)	10% (n=49)	12% (n=17)	NR
	MEDI4736	NR	16% (n=58)	NR	NR
	Atezolizumab	30% (n=43)	23% (n=53)	14% (n=56)	26% (n=65)

FDA Approved
(As of 9/2016)

Adapted from Lipson 2015

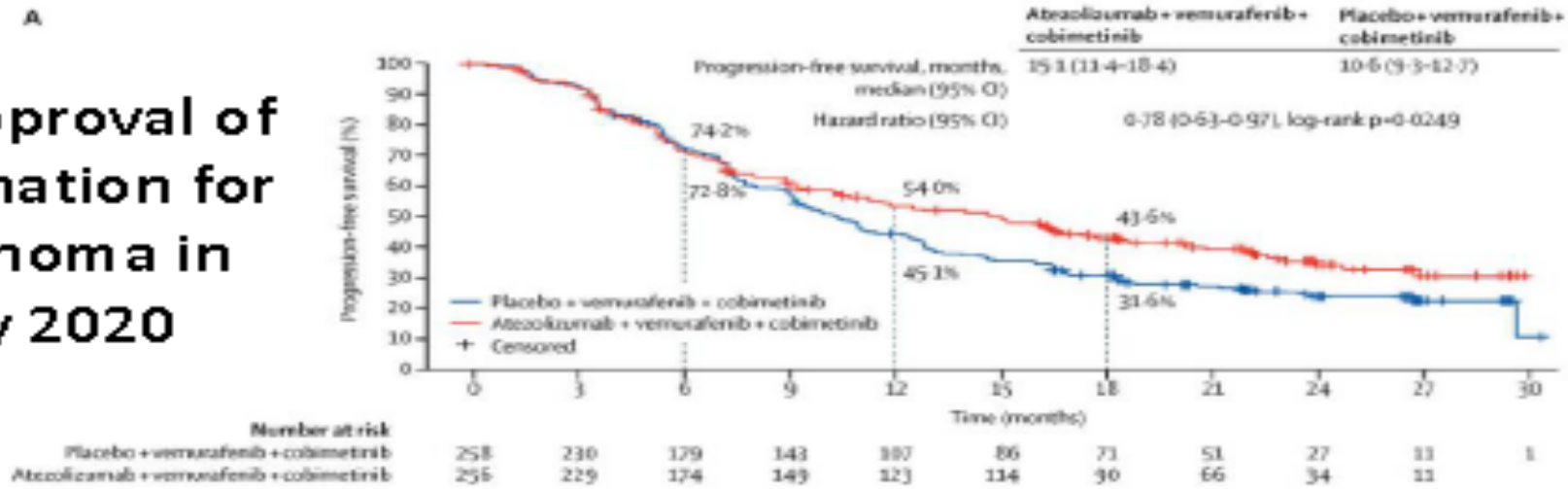
Seminars in Oncology

Altezolizumab

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

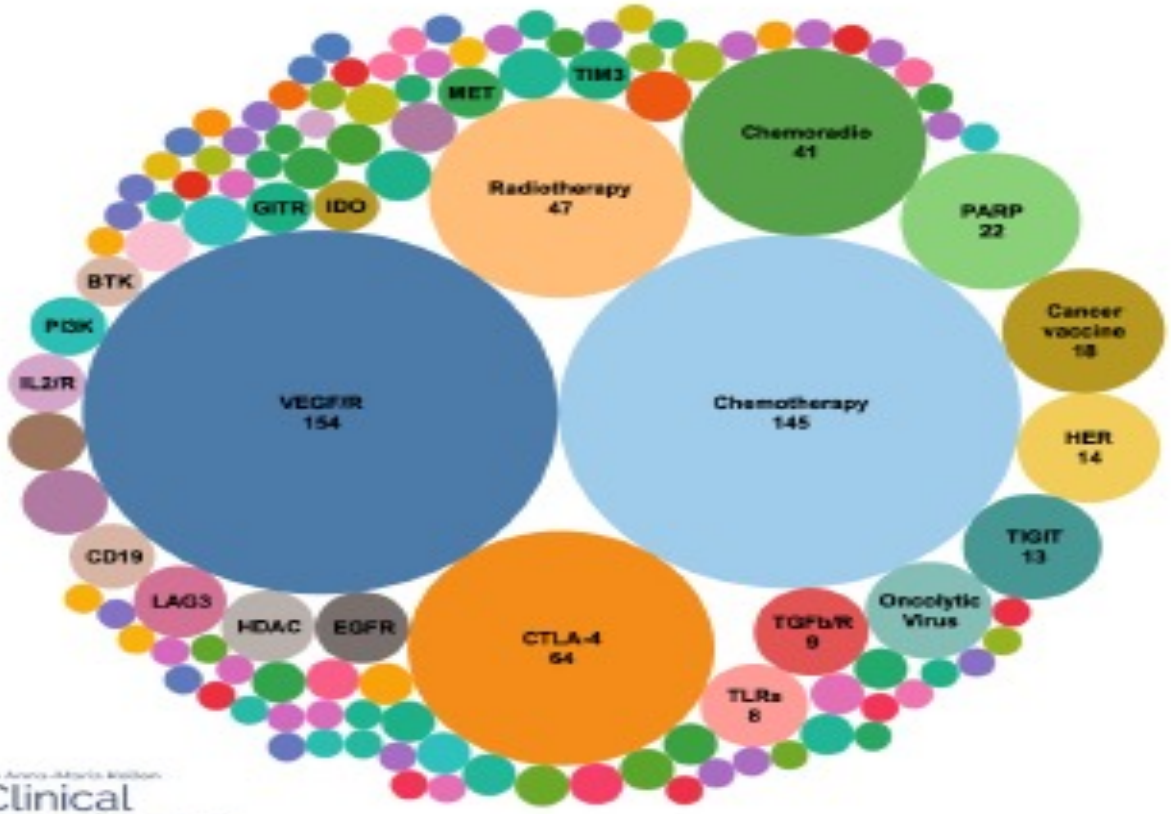


Gutzmer R 2020 THE LANCET

Combination clinical trials

Combination Clinical Trials

- Over 2900 different trials of combination therapy with 253 different agents
- 724 new trials in first 9 months of 2020

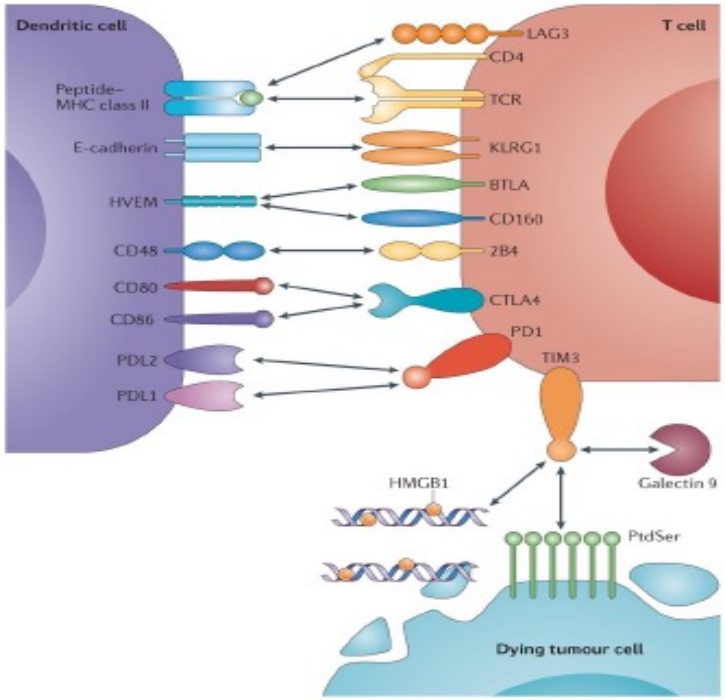


CANCER RESEARCH INSTITUTE

The Anne-Marie Anton Clinical Accelerator

New checkpoint inhibitors

New checkpoint inhibitors

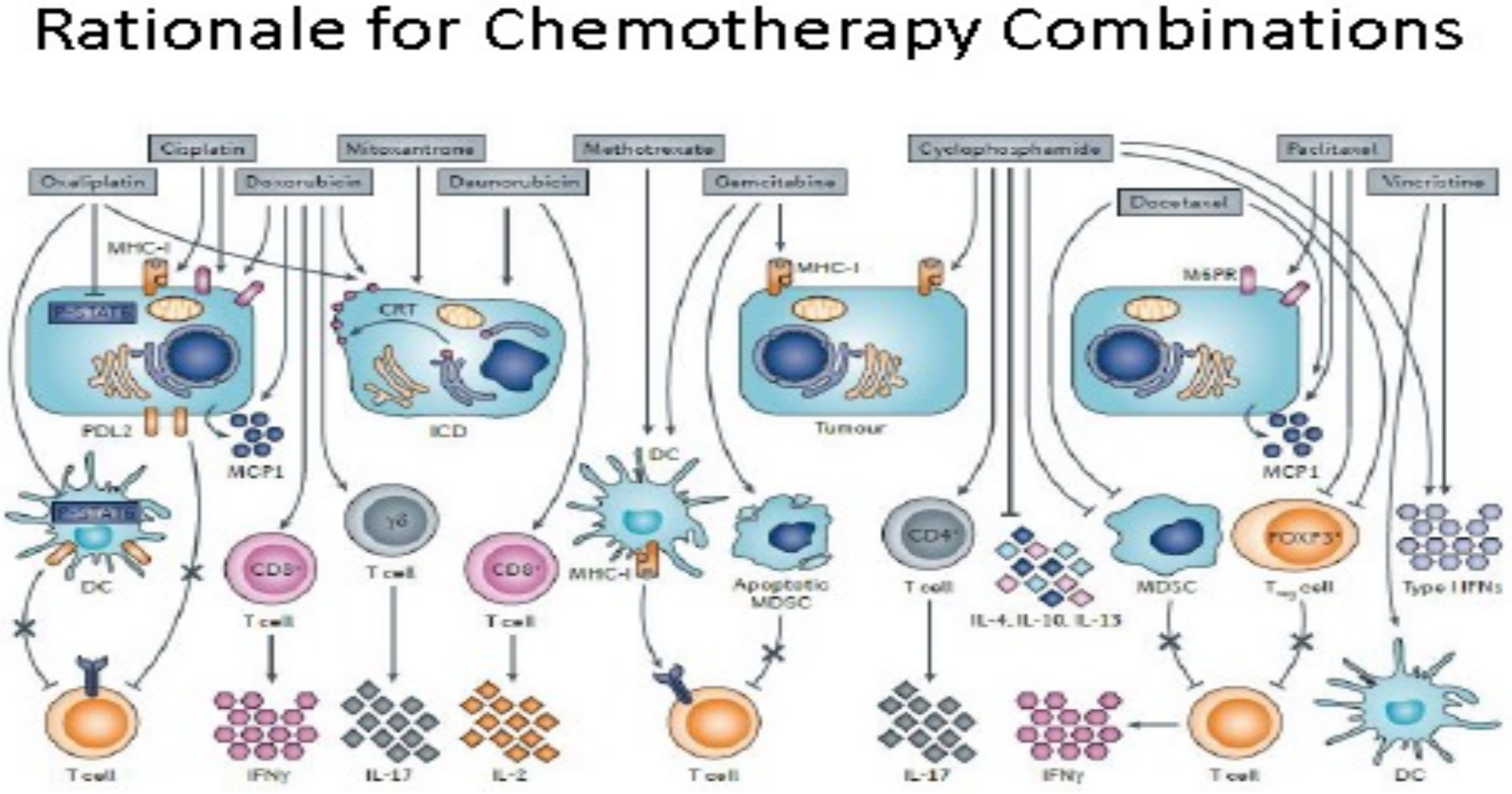


Nature Reviews | Immunology

Nguyen & Ohashi 2015

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

Chemotherapy combinations



Galluzzi Nature Reviews Drug Discovery (2012)

Checkpoint modulators

Checkpoint Modulators

- Every expanding list of indications
- Over 2200 different trials of combination therapy

- Any questions?