

Immune checkpoint blockade

Immune Checkpoint Blockade

NCI CCR TRACO

Stephanie L. Goff, MD, FACS

September 10, 2022

Objectives

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

Oncology

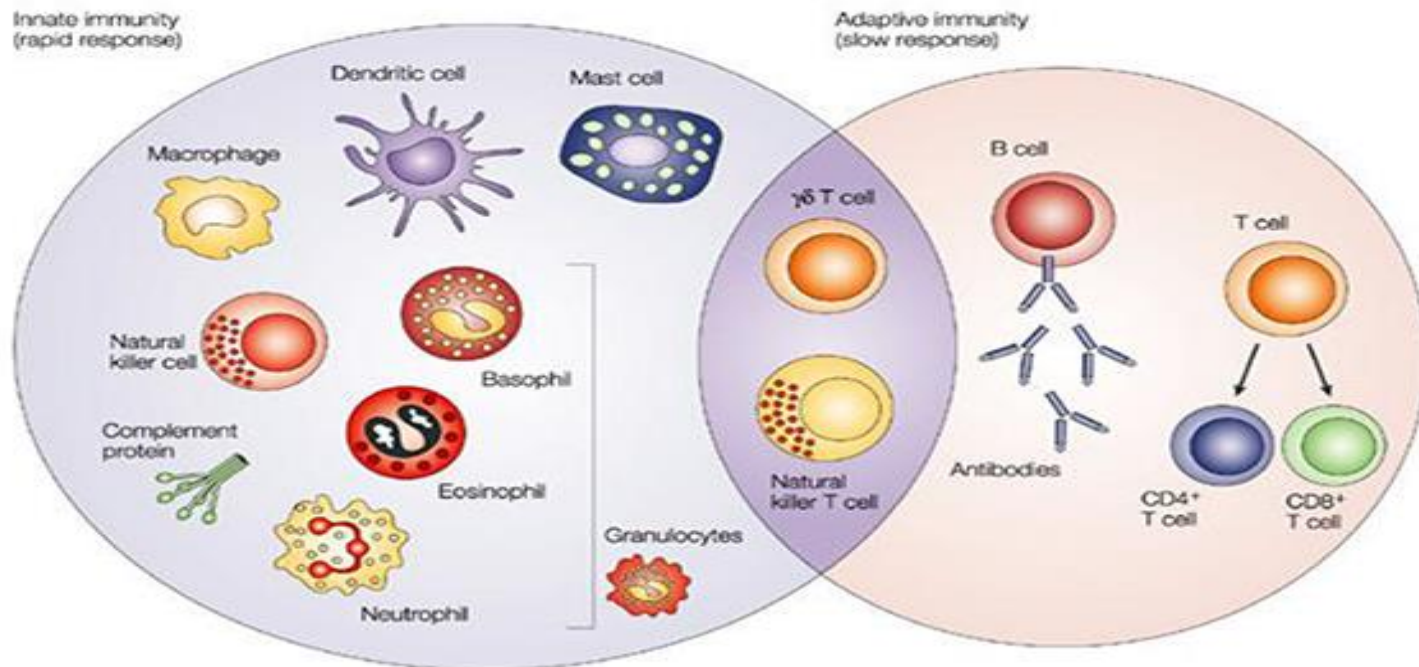


Cancer Immunotherapy

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

Cells of the Immune System



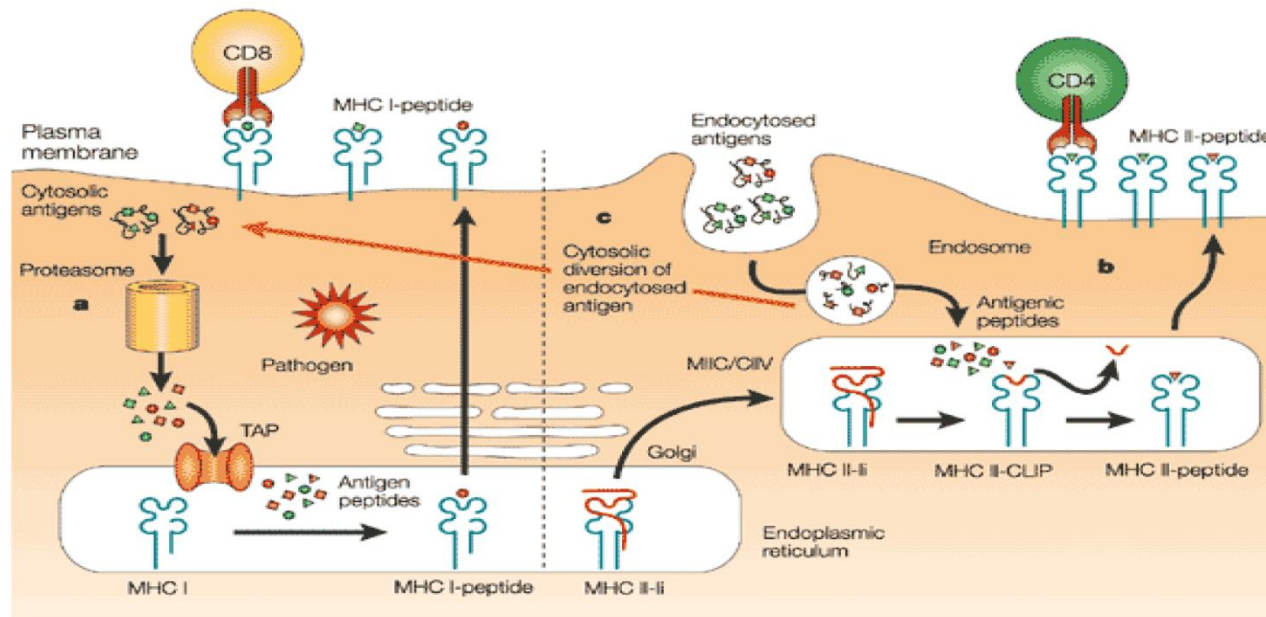
Nature Reviews | Cancer

Dranoff 2004

- Checkpoint blockade primarily affects T cells

T cell activation

T cell activation

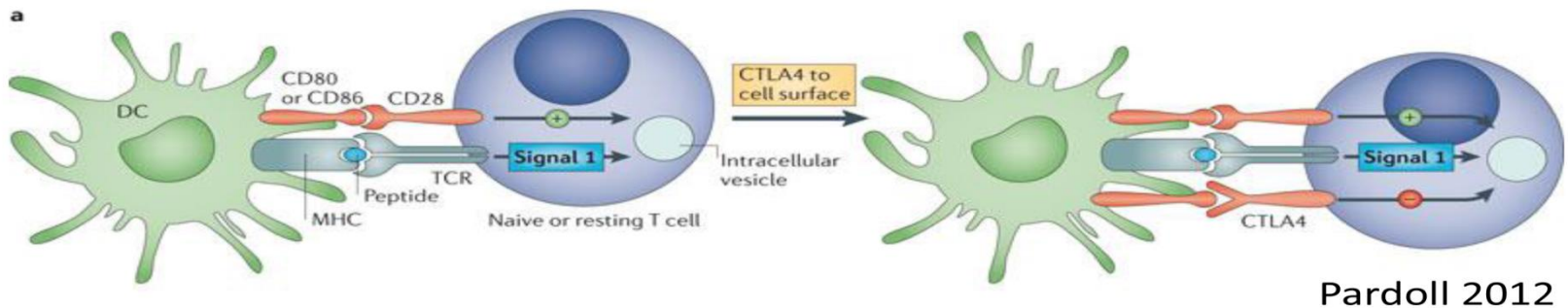


Nature Reviews | Immunology
Heath 2001

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

CTLA-4

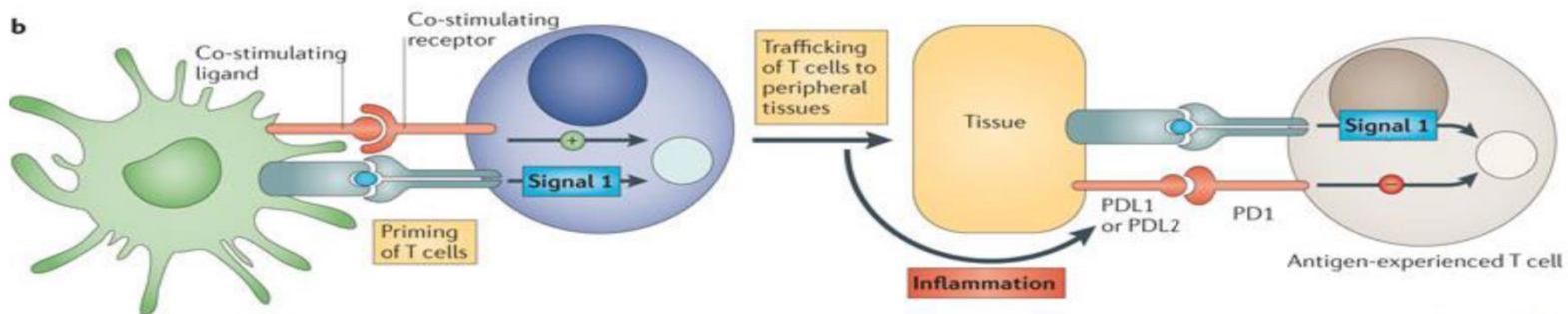
CTLA-4



- 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

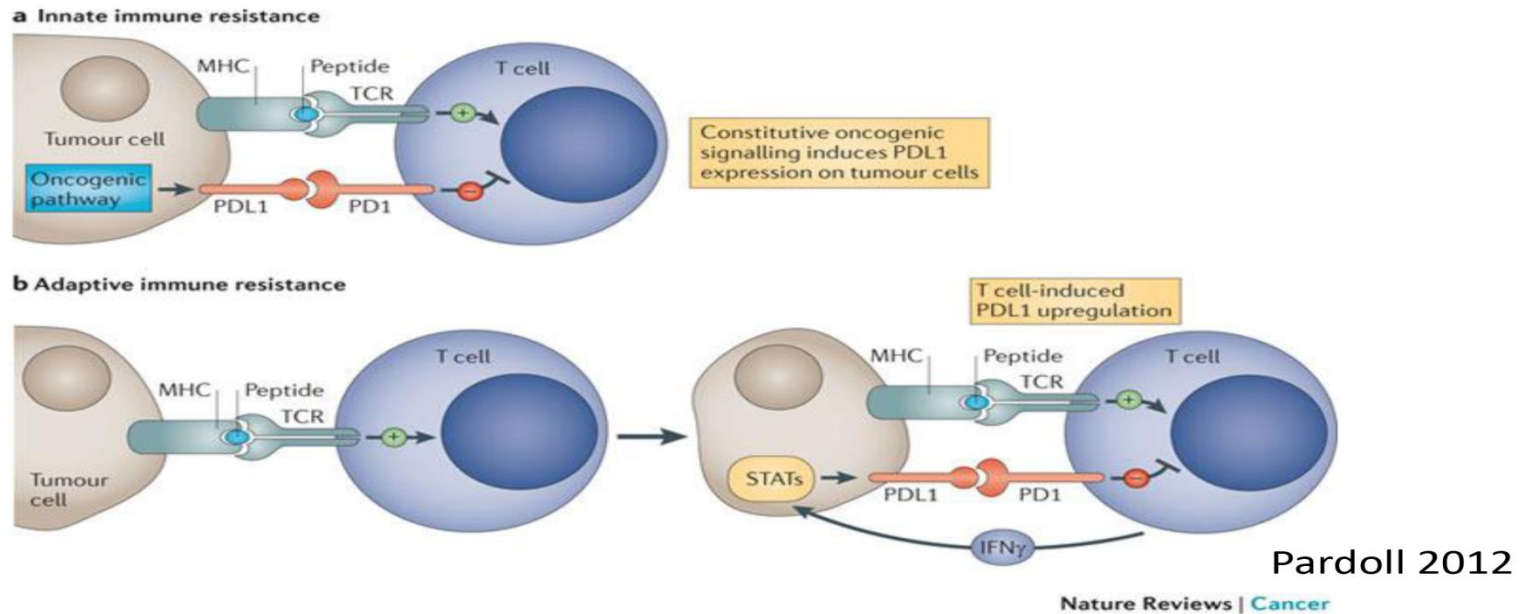


Nature Reviews | Cancer
Pardoll 2012

- 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

PD-1/PD-L1 in cancer

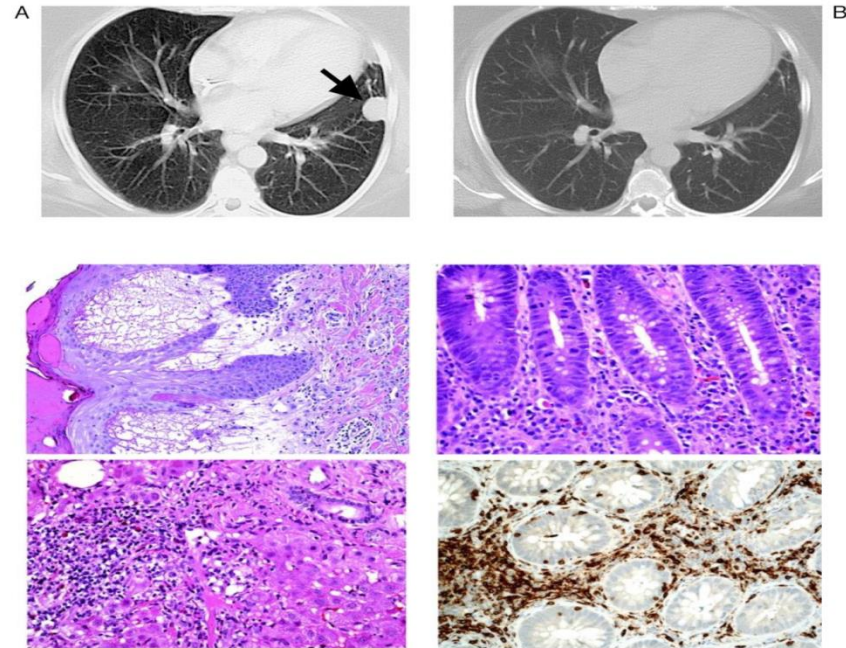


- Cancer cells can increase the amount of PDL1
- Successful T-cell tumor destruction can increase PDL1 through upregulation in response to IFN γ

Checkpoint Blockade

Checkpoint Blockade @ NCI

- α CTLA-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

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

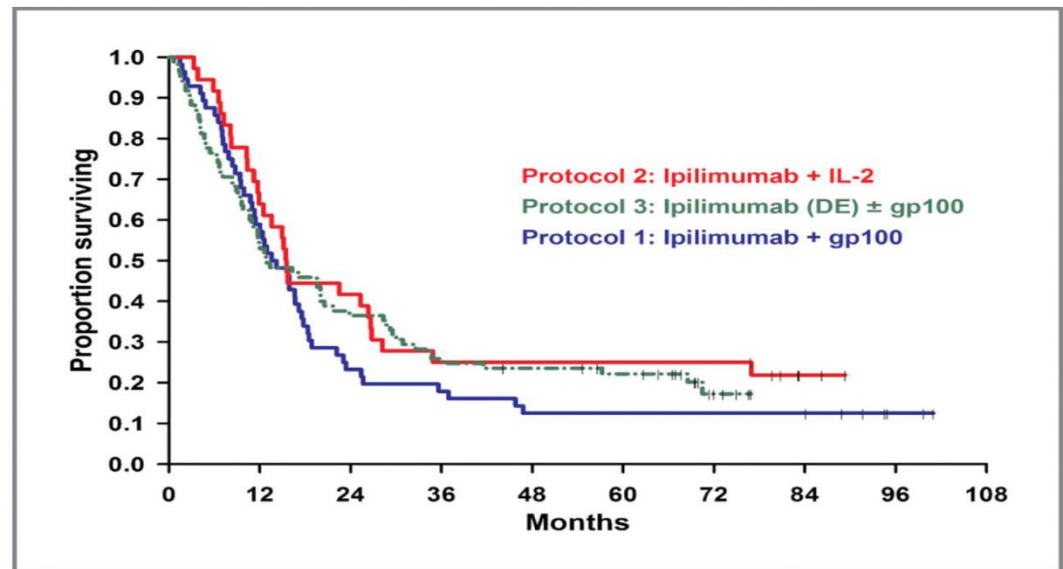
Melanoma, $p=0.0004$

	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

Checkpoint Blockade

Checkpoint Blockade @ NCI

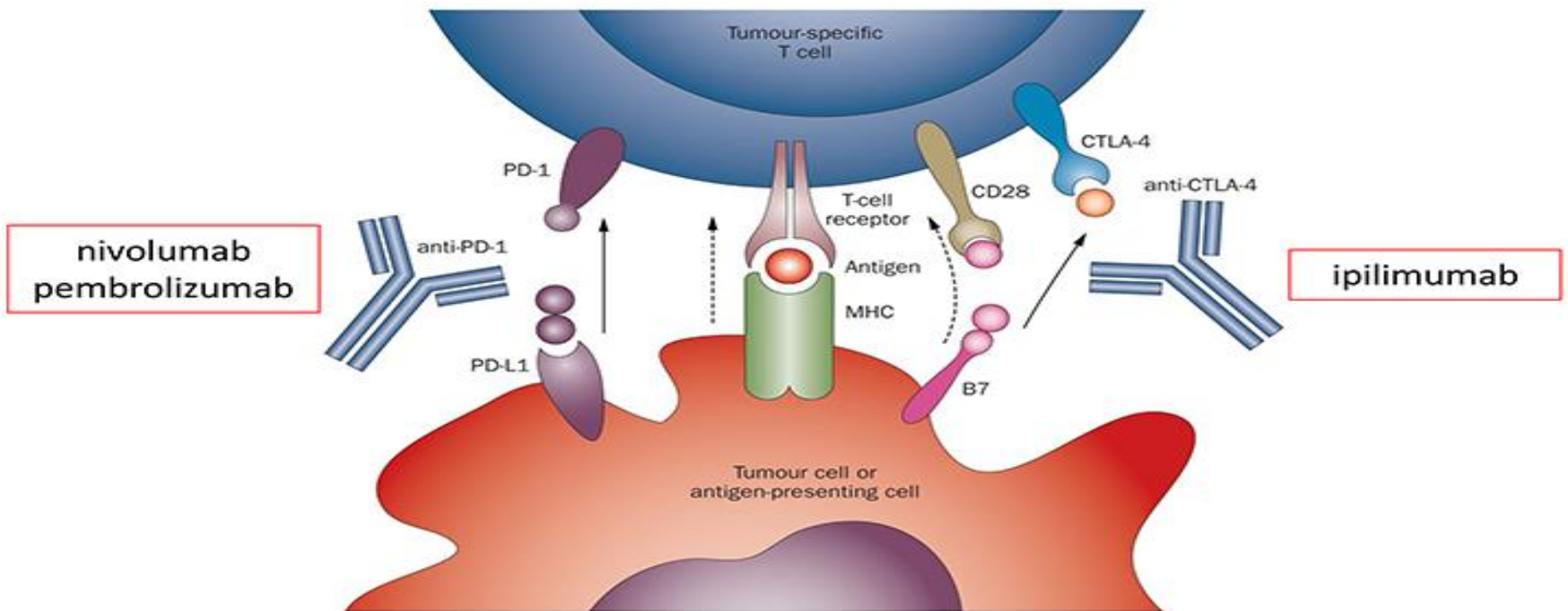
- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
 - OR 13-20%
 - 5 yr OS 13-23%



Prieto PA 2012

Checkpoint blockade

Checkpoint blockade in melanoma

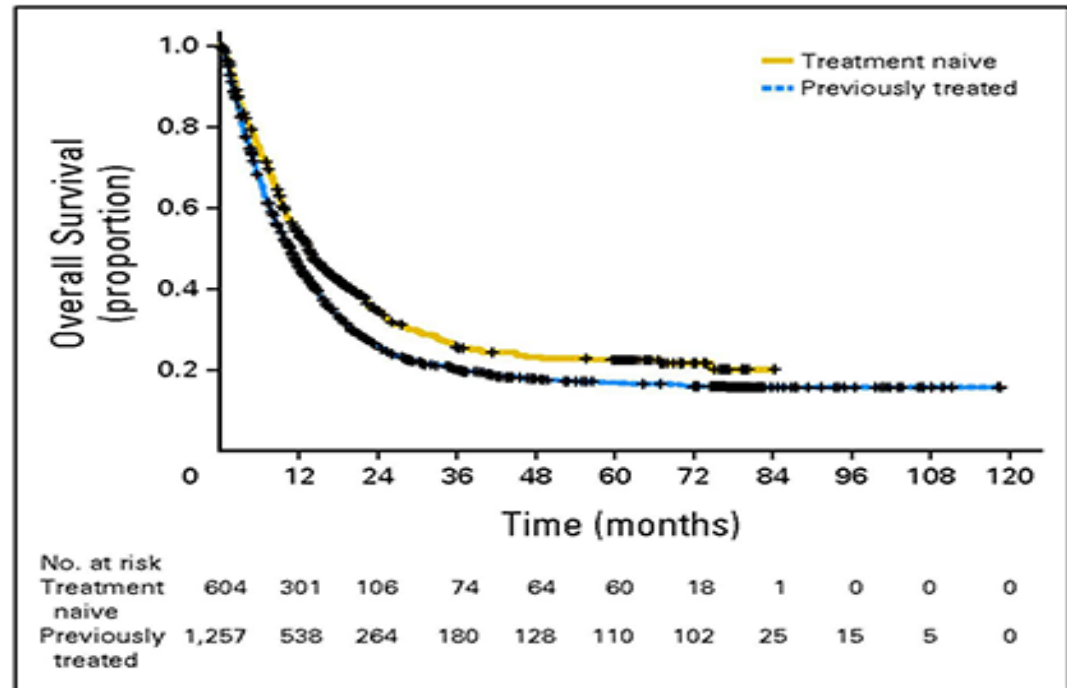


Drake C 2013

Ipilimumab

Ipilimumab for melanoma

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

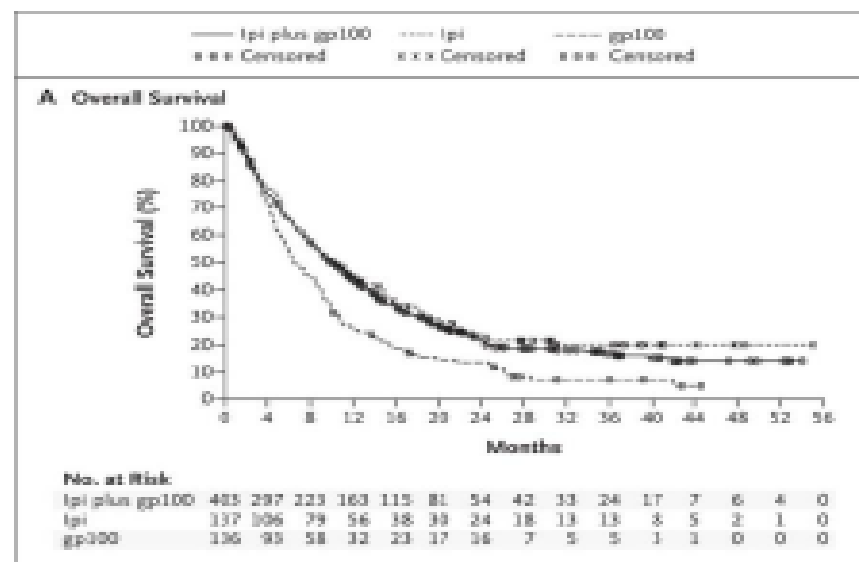


Schadendorf D 2015

Ipilimumab

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

Hadi B 2010

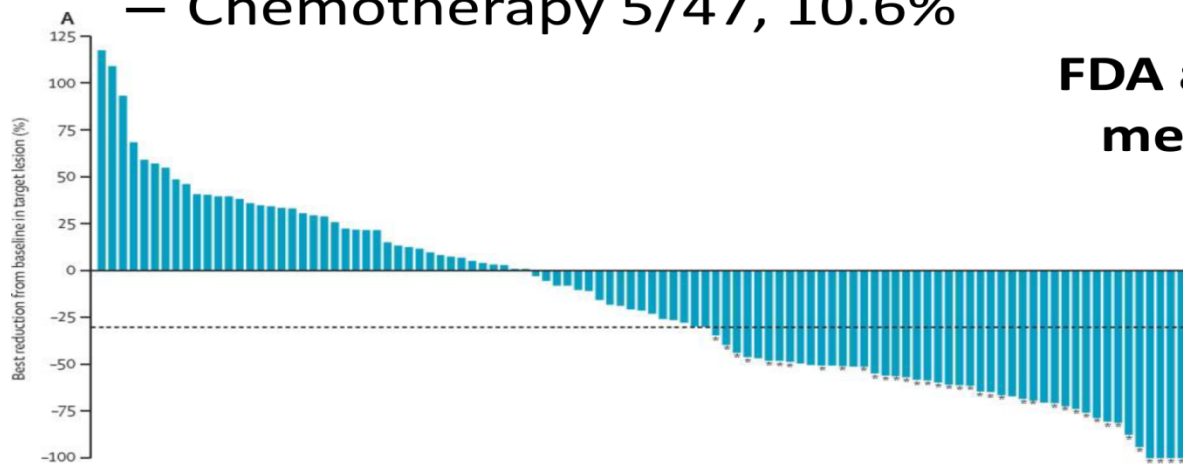


THE NEW ENGLAND
JOURNAL of MEDICINE

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%

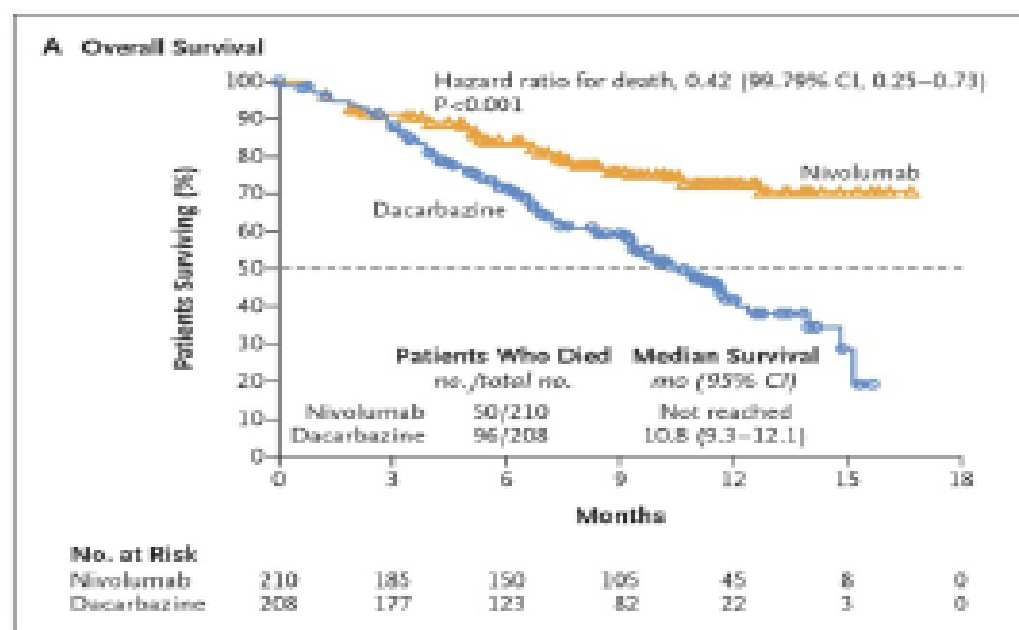


**FDA approval for refractory
melanoma in December
2014**

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

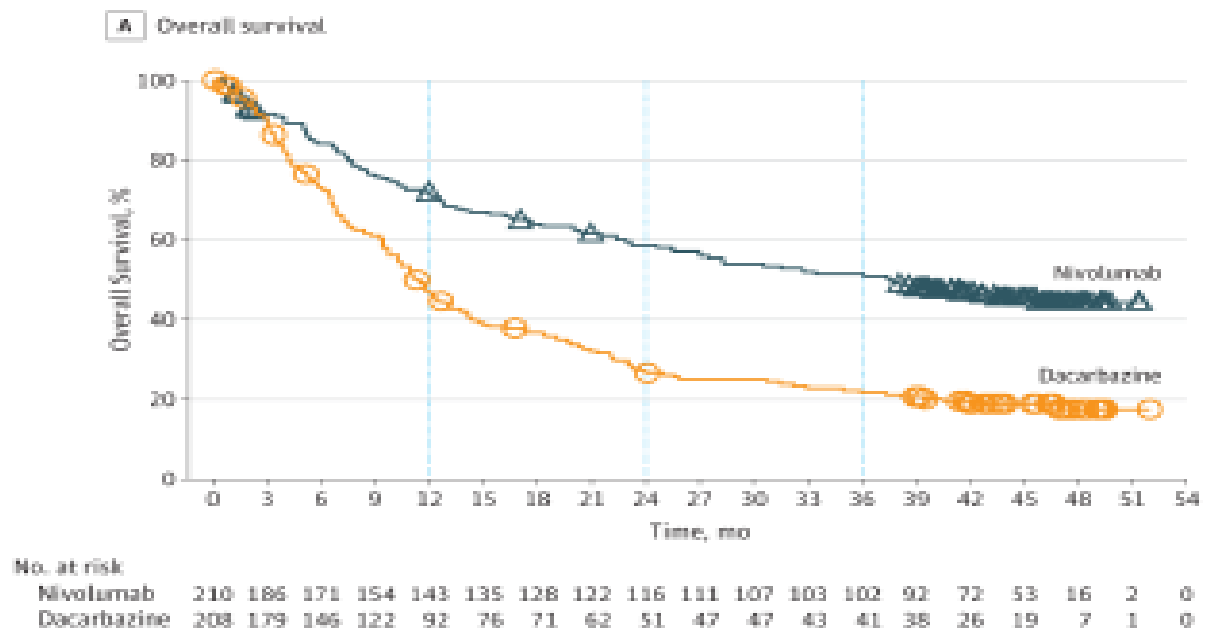


THE NEW ENGLAND
JOURNAL of MEDICINE

Nivolumab

Nivolumab for melanoma

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



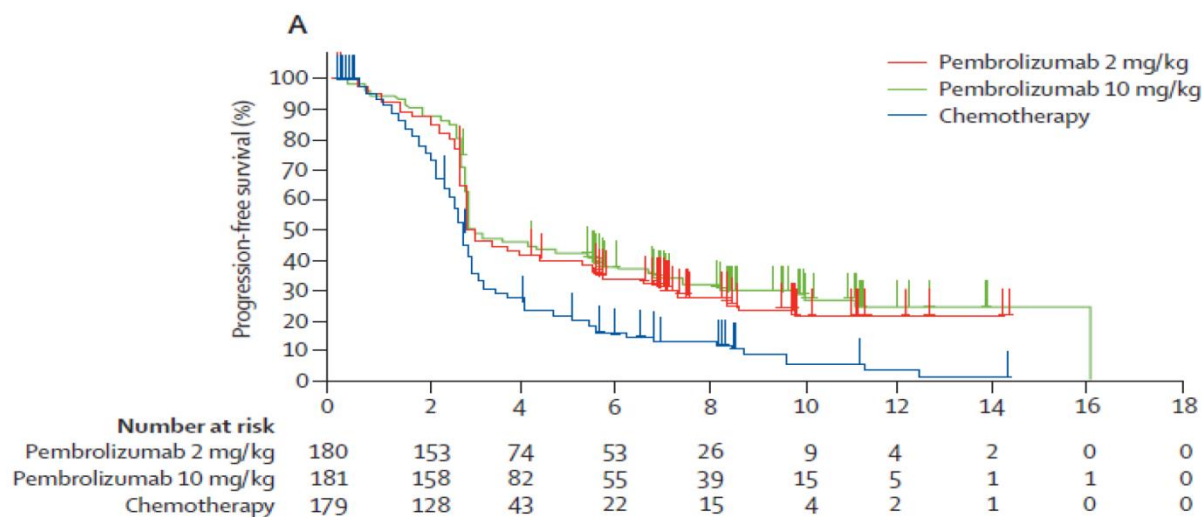
Ascierto P 2018

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

THE LANCET **Oncology**

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

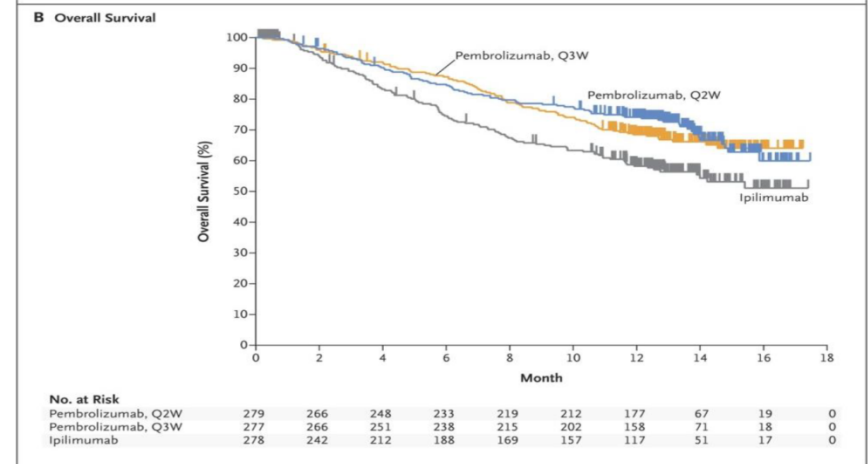
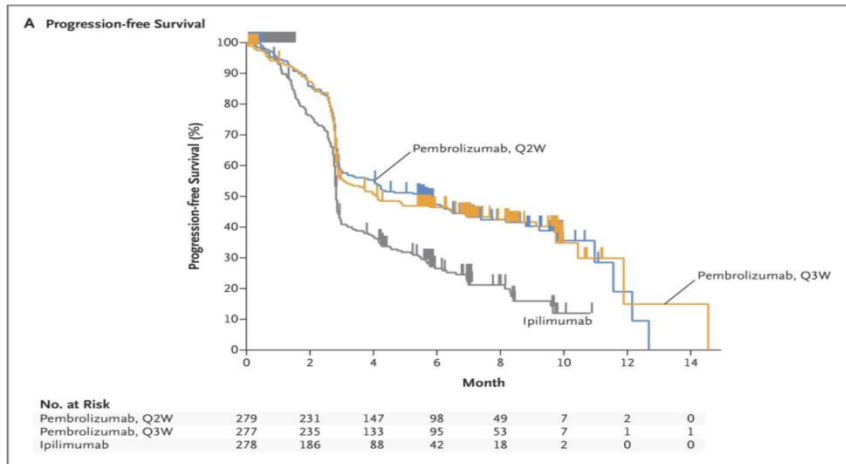
Robert C 2015



The NEW ENGLAND
JOURNAL of MEDICINE

Pembrolizumab for melanoma

Pembrolizumab for melanoma



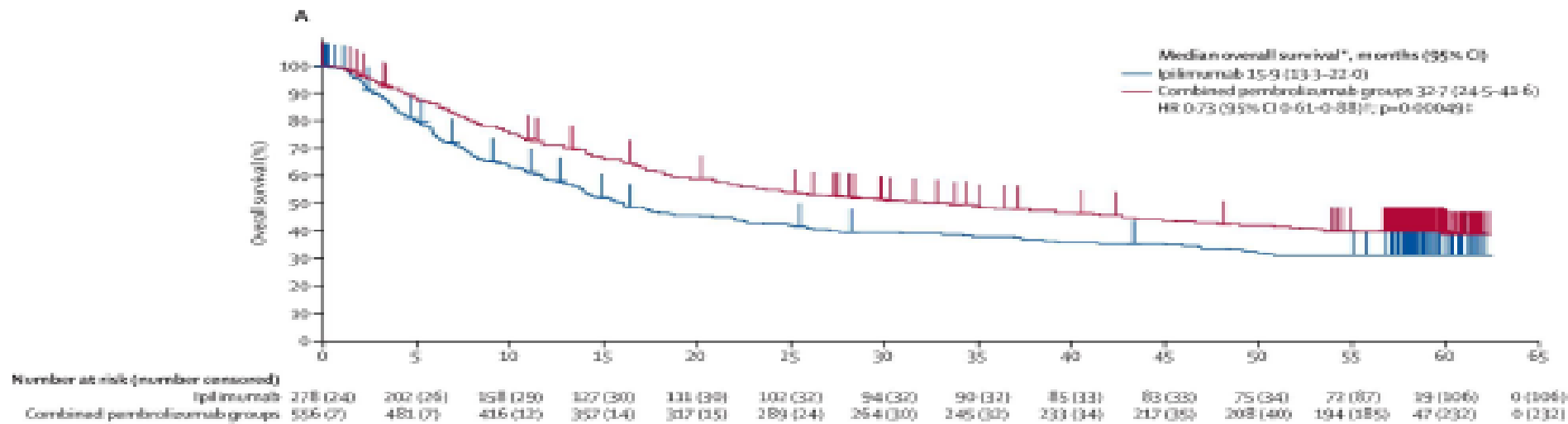
- Grade ≥ 3 AE
 - Pembrolizumab q2w 13.3% (1.4% Colitis)
 - Pembrolizumab q3w 10.1% (2.5% Colitis)
 - Ipilimumab 19.9% (7% Colitis)

Robert C 2015

Pembrolizumab

Pembrolizumab for melanoma

- Three year OS of 48.1% vs 37.8%

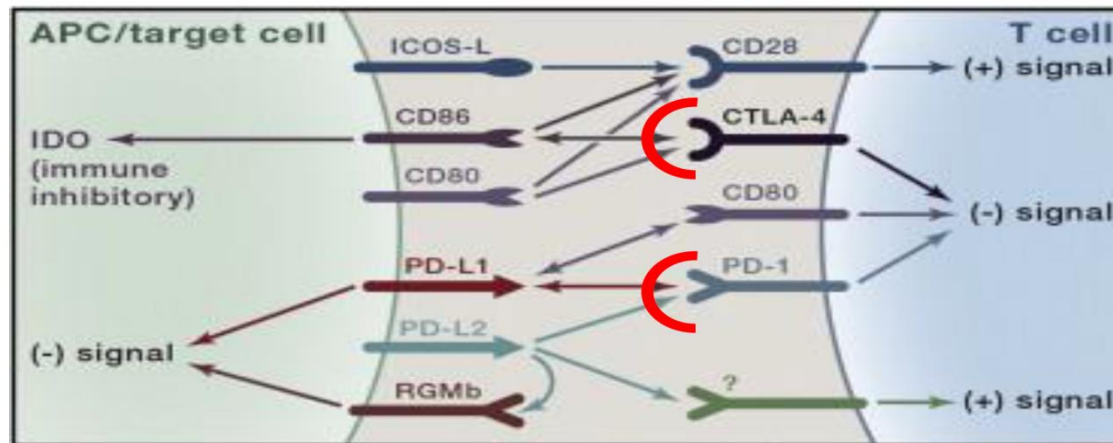


Robert C 2019

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/Ipilimumab

Nivolumab/Ipilimumab for melanoma

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

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)	230 (66.9)	200 (64.1)	638 (65.6)
Could not be determined or evaluated	28 (8.9)	16 (5.1)	18 (5.7)	62 (6.5)
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)

Nivolumab/Ipilimumab

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) [‡]	5.40 (2.02–13.72)	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

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.^a

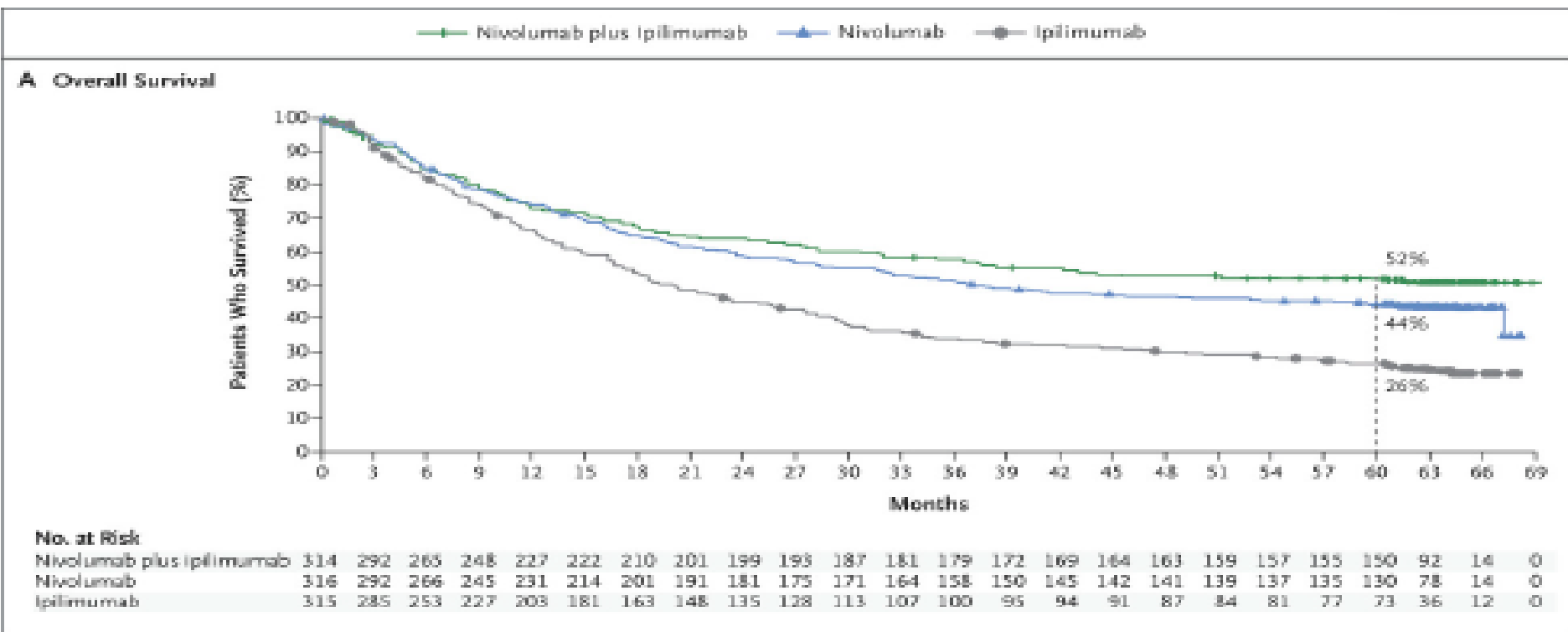
Variable	Nivolumab plus ipilimumab (N = 314)	Nivolumab (N = 314)	Ipilimumab (N = 315)
Best overall response — no. (%)†			
Complete response	81 (26)	52 (16)	16 (5)
Partial response	122 (39)	88 (28)	43 (14)
Stable disease	38 (12)	31 (10)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	28 (9)
Objective response‡			
No. of patients with response	181	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

Nivolumab/Ipilimumab for melanoma

Nivolumab/Ipilimumab for melanoma



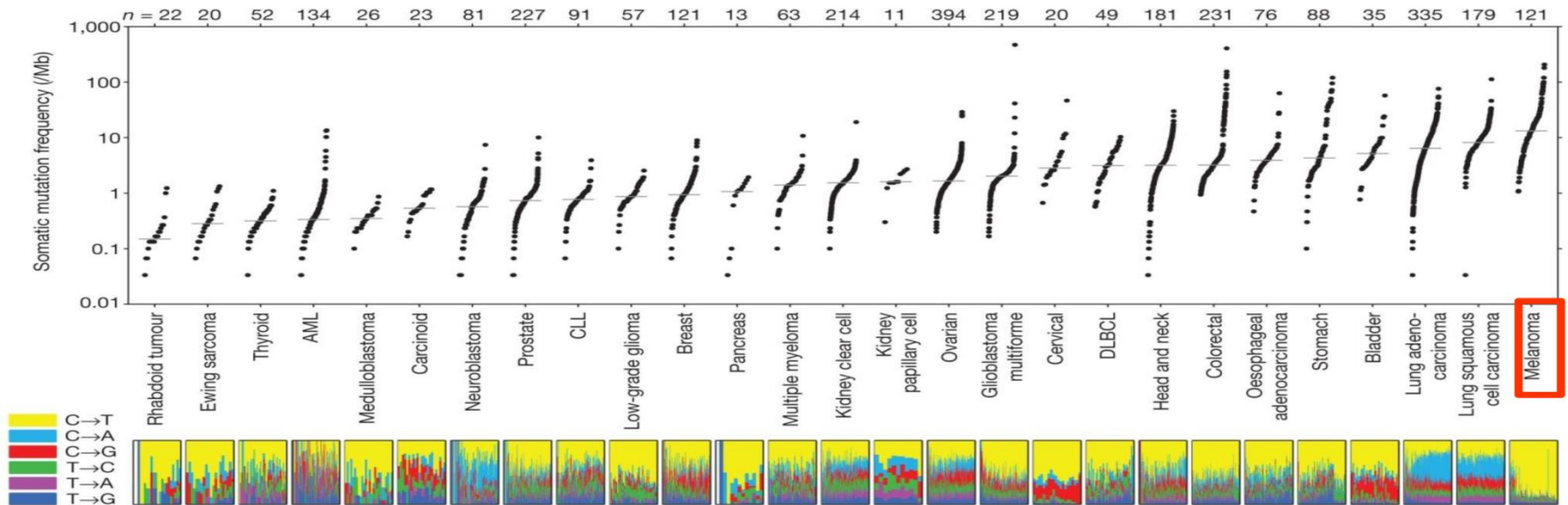
Larkin J 2019



THE NEW ENGLAND
JOURNAL of MEDICINE

Melanoma

Why melanoma?

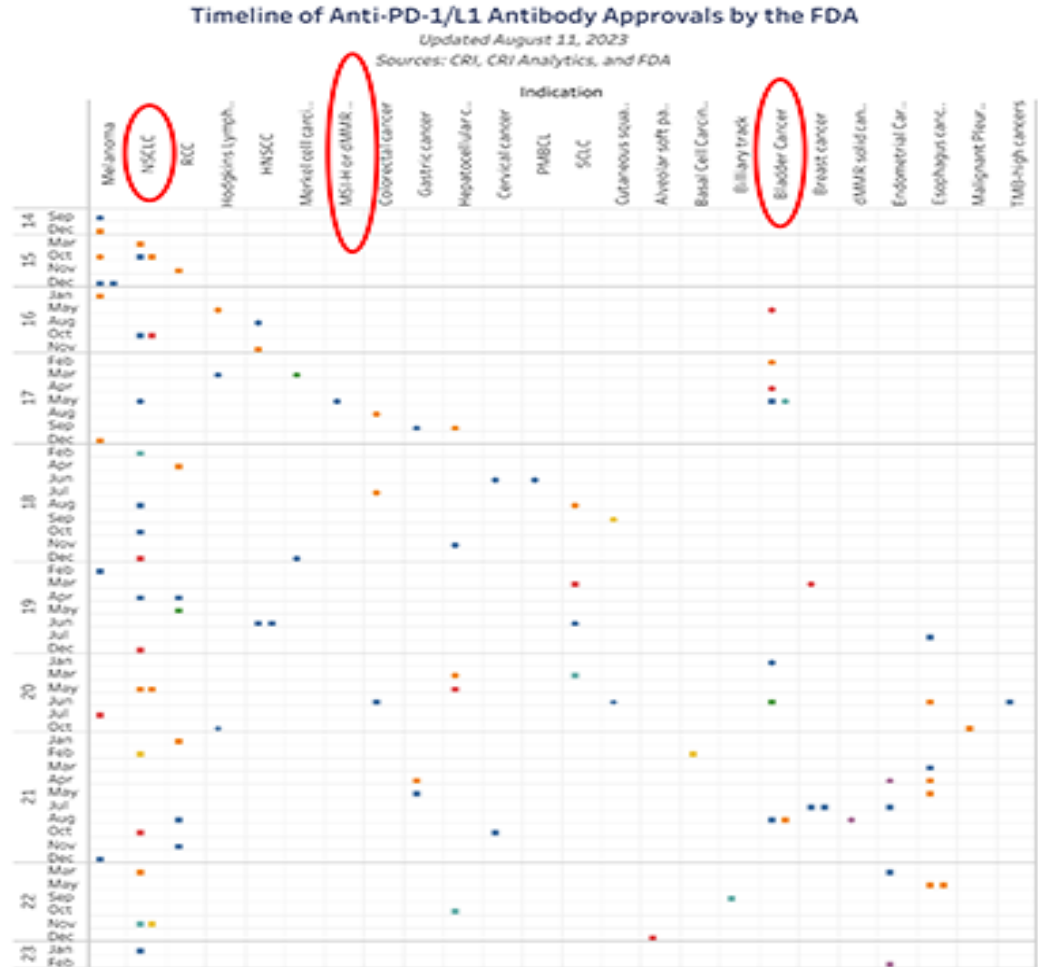


Highly mutated tumors

- 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

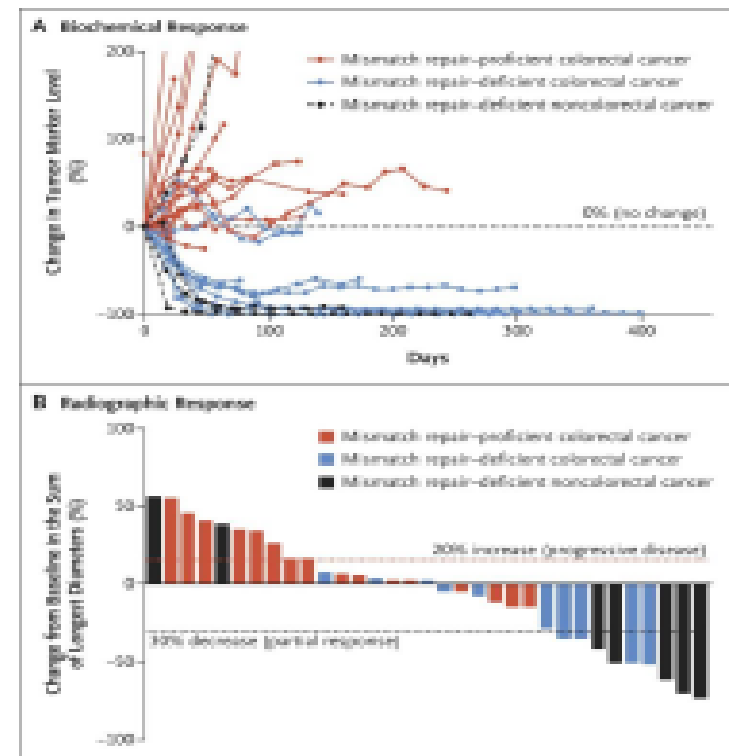
<https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape>



Mismatch/repair deficiency

Pembrolizumab for mismatch repair deficient (dMMR) cancer

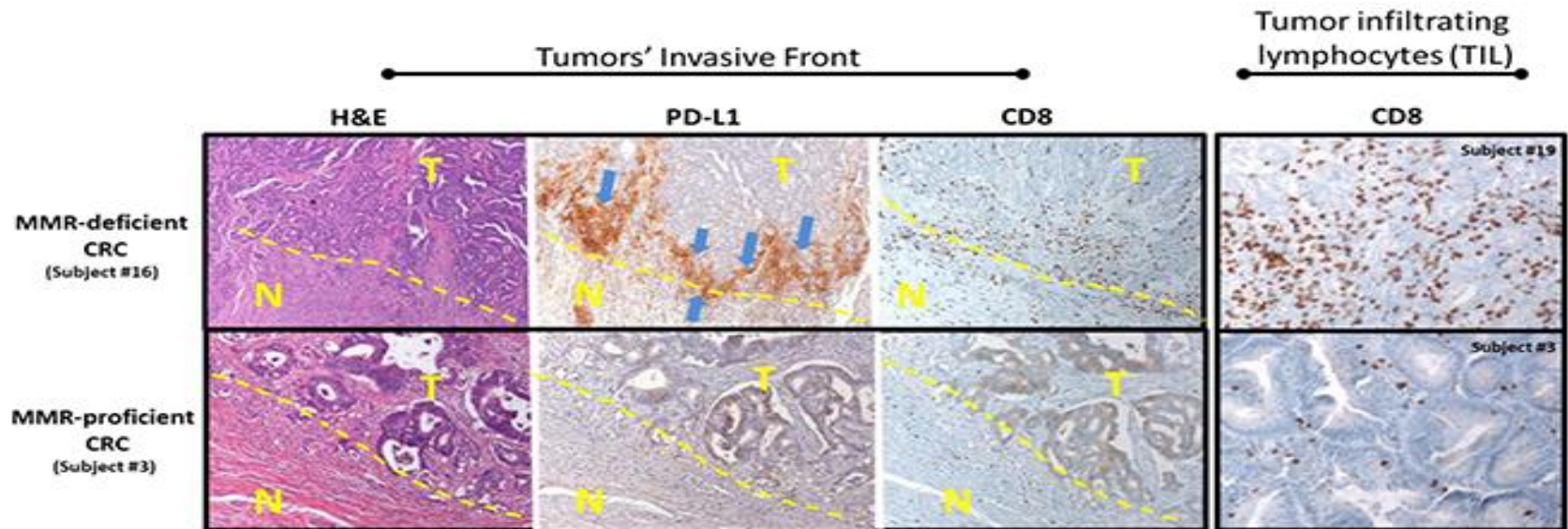
- Builds on hypothesis of neoantigens from somatic mutations
- Phase 2 study
- Three parallel cohorts
 - MMR-proficient CRC
 - MMR-deficient CRC
 - MMR-deficient other



Le DT 2015

Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface



Le DT 2015

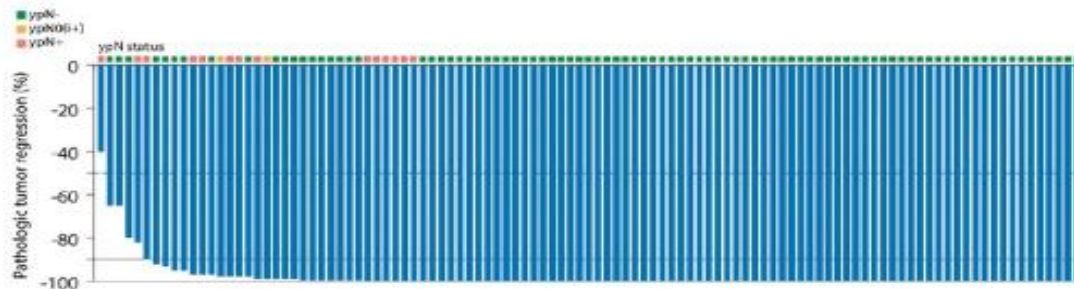


The NEW ENGLAND
JOURNAL of MEDICINE

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; ypN0(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 N0(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

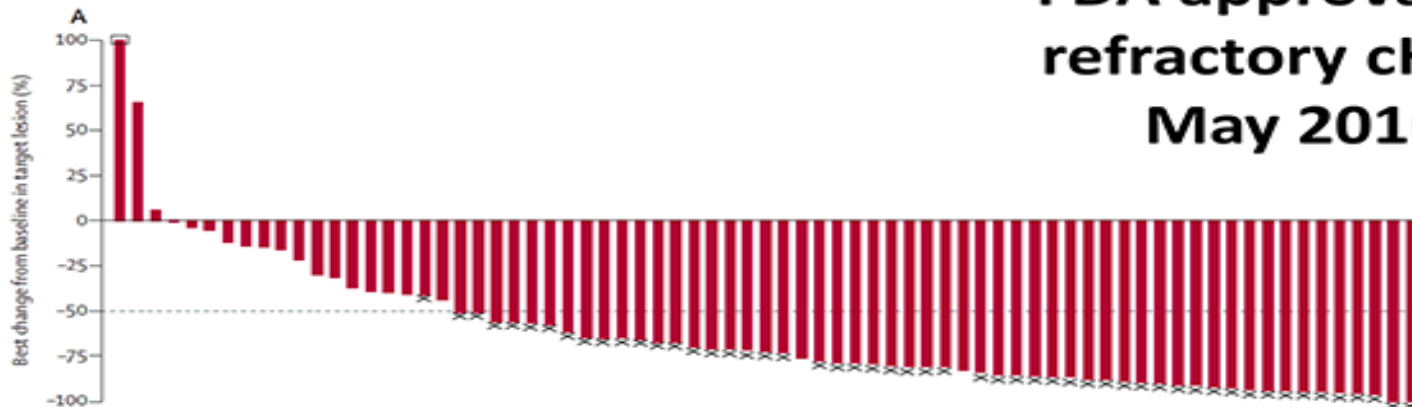
- **Highly mutated tumors**
 - Melanoma
 - Non-small cell lung cancer
 - Bladder cancer
 - Tumors with mismatch repair deficiency
- **Use in other tumors?**
 - Renal cell
 - Responds to other immunotherapy
 - Hodgkin's lymphoma
 - Reed-Sternberg cells have elevated amounts of PD-L1
 - Head and neck SCC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

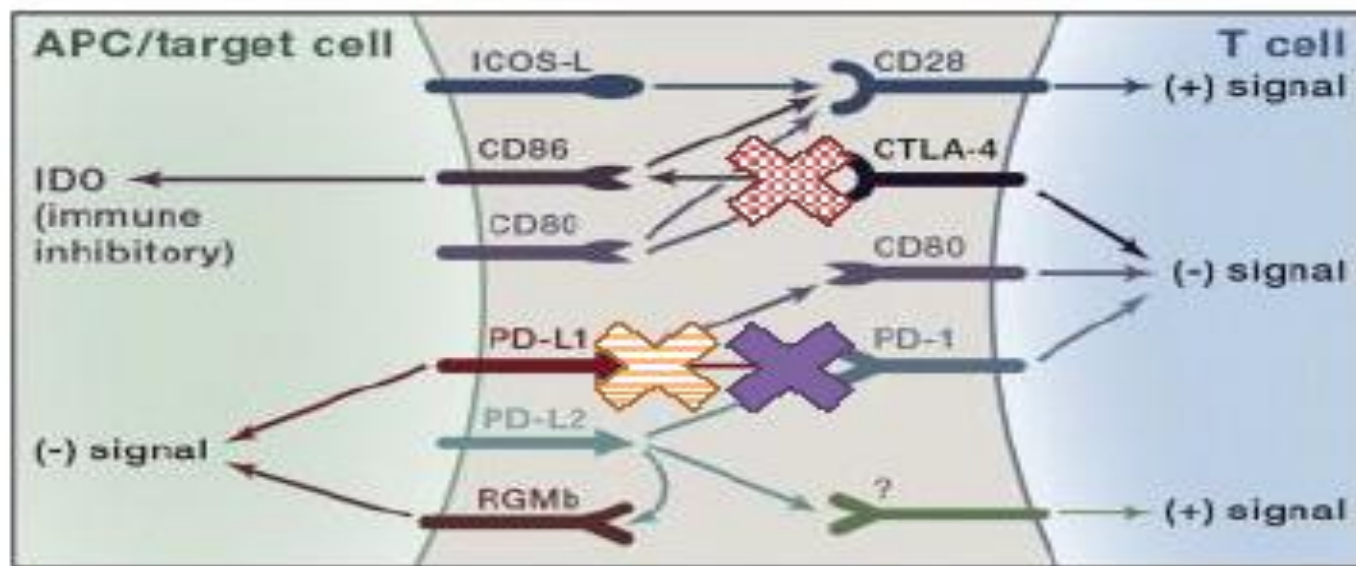


Younes A 2016

THE LANCET **Oncology**

Checkpoint modulation

Checkpoint Modulation



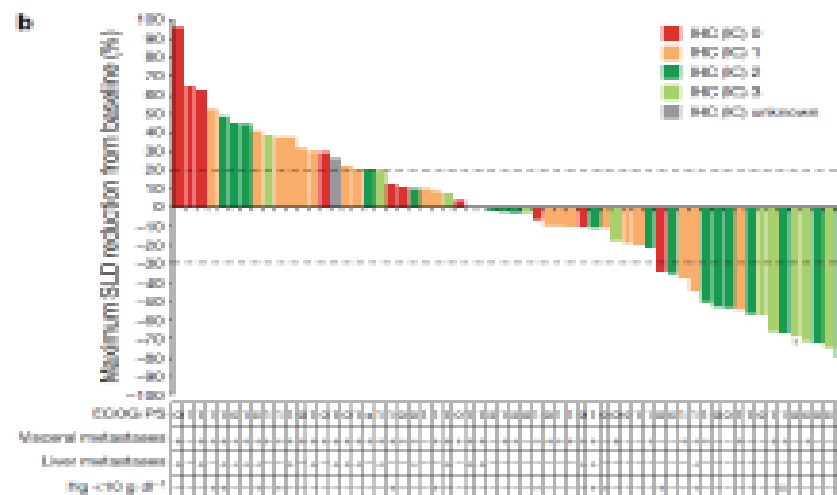
Topalian, Cancer Cell 2015

- 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

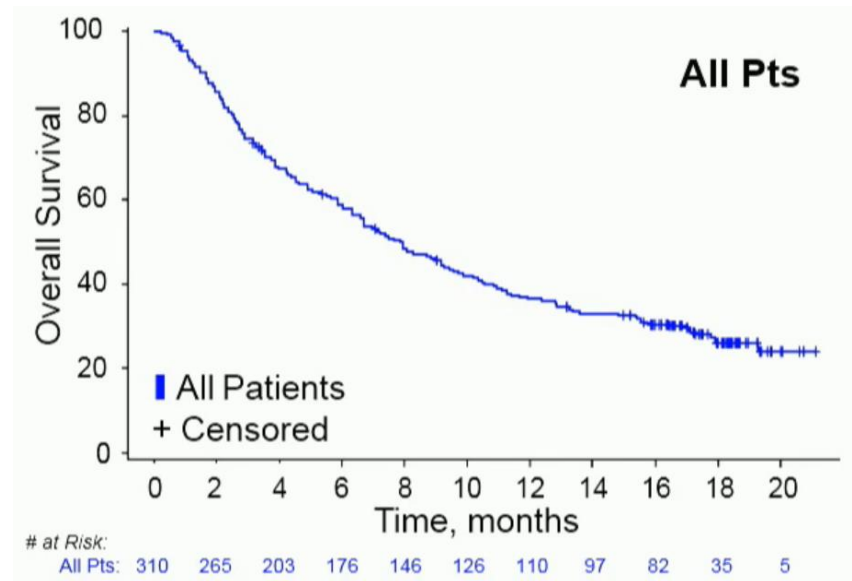
α PD-L1 in Urothelial bladder cancer

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



α PD-L1 in Urothelial bladder cancer

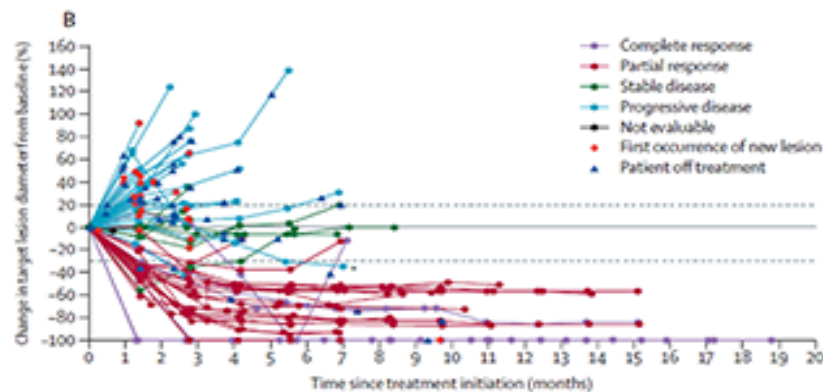
- 310 patients
- Objective Response
 - 45 (15%)
 - With 15 complete responses
- Overall Survival
 - 7.9 months
- 1 yr Survival
 - 37%



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**

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)

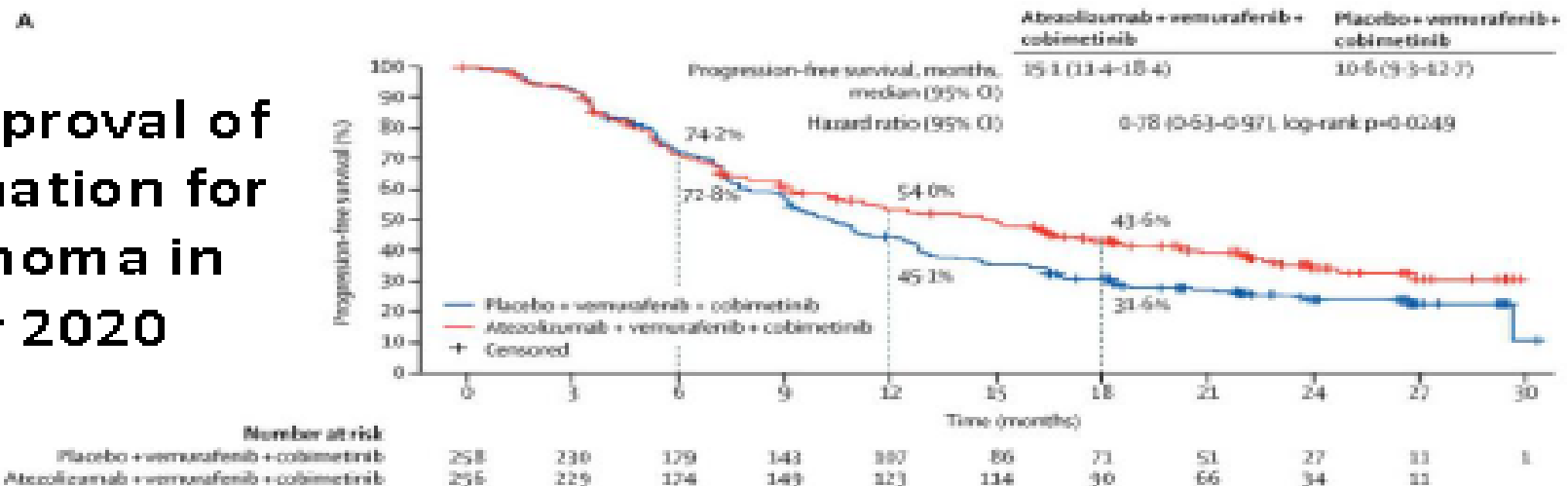
Adapted from Lipson 2015

Altezolizumab

Atezolizumab (α PD-L1) for melanoma

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

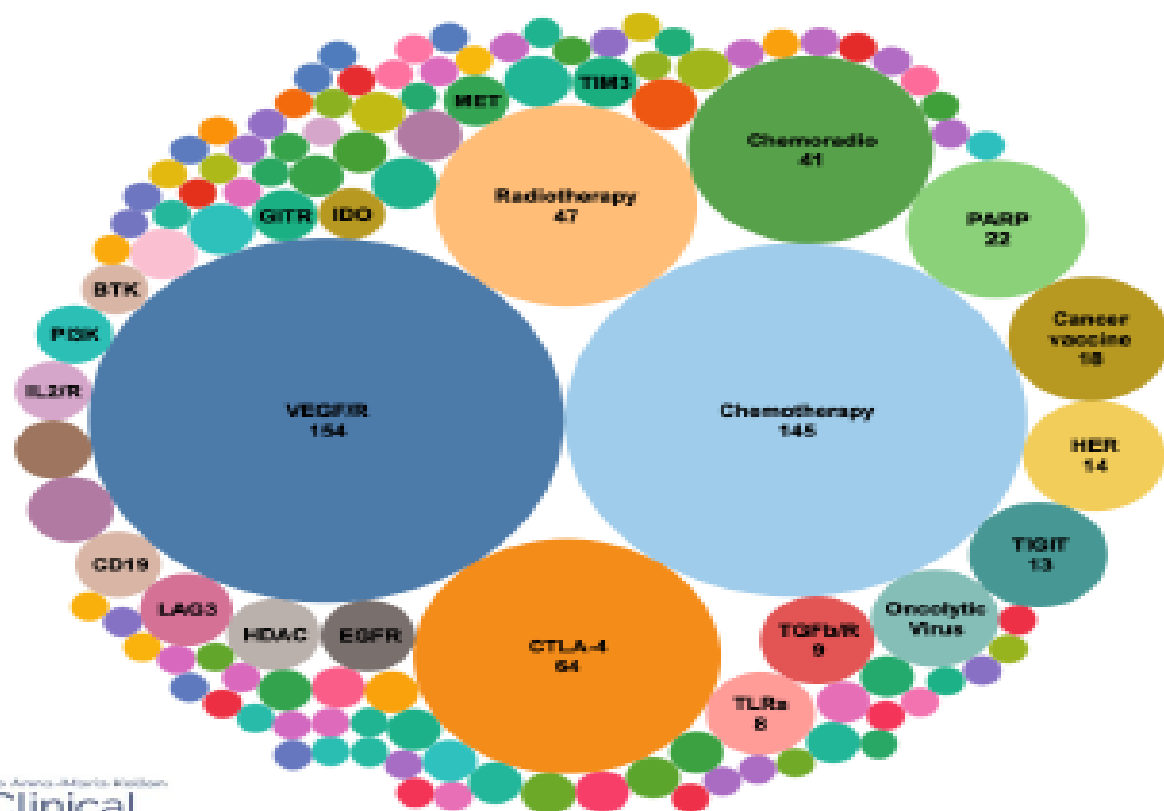
**FDA approval of
combination for
melanoma in
July 2020**



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



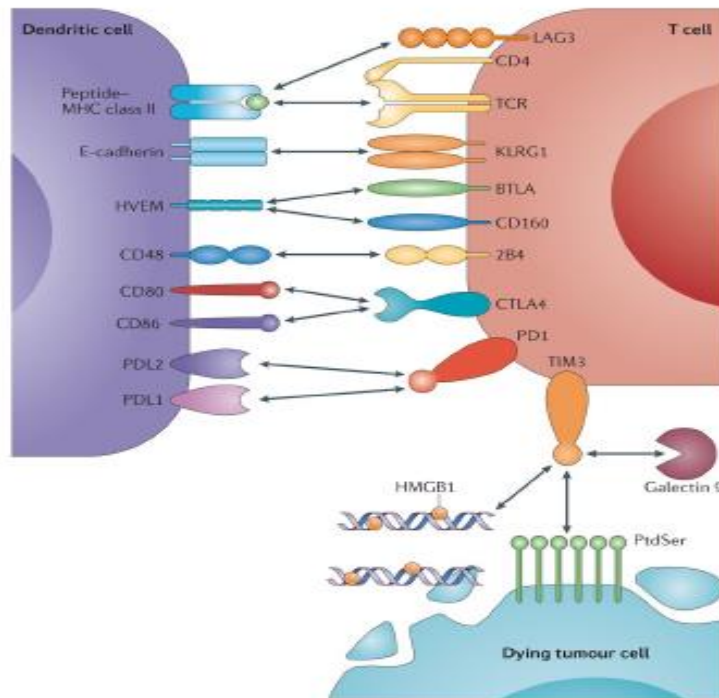
CANCER
RESEARCH
INSTITUTE

The Anna-Maria Weston

Clinical
Accelerator

New checkpoint inhibitors

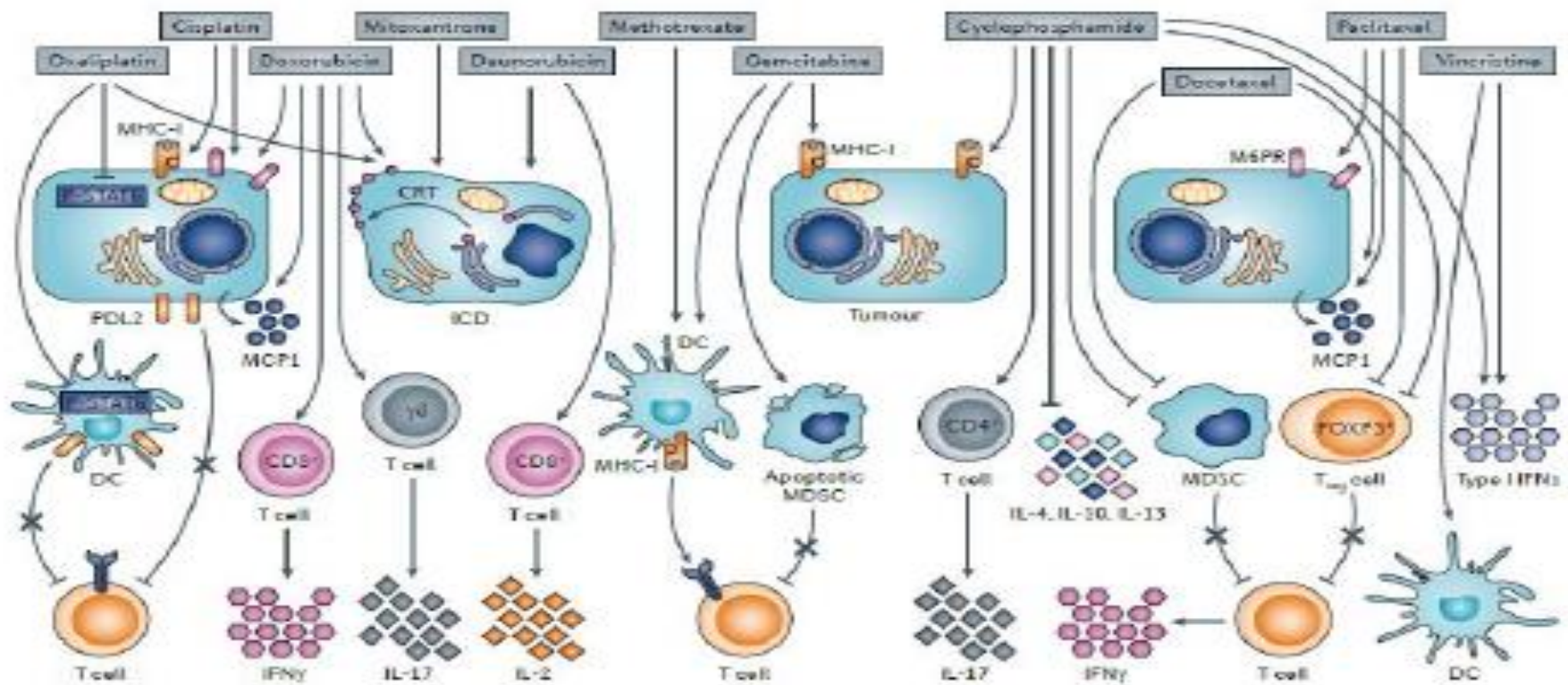
New checkpoint inhibitors



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

Chemotherapy combinations

Rationale for Chemotherapy Combinations



Checkpoint modulators

Checkpoint Modulators

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

