Immune checkpoint Blockade

NCI CCR TRACO
Stephanie L. Goff, MD

Objectives

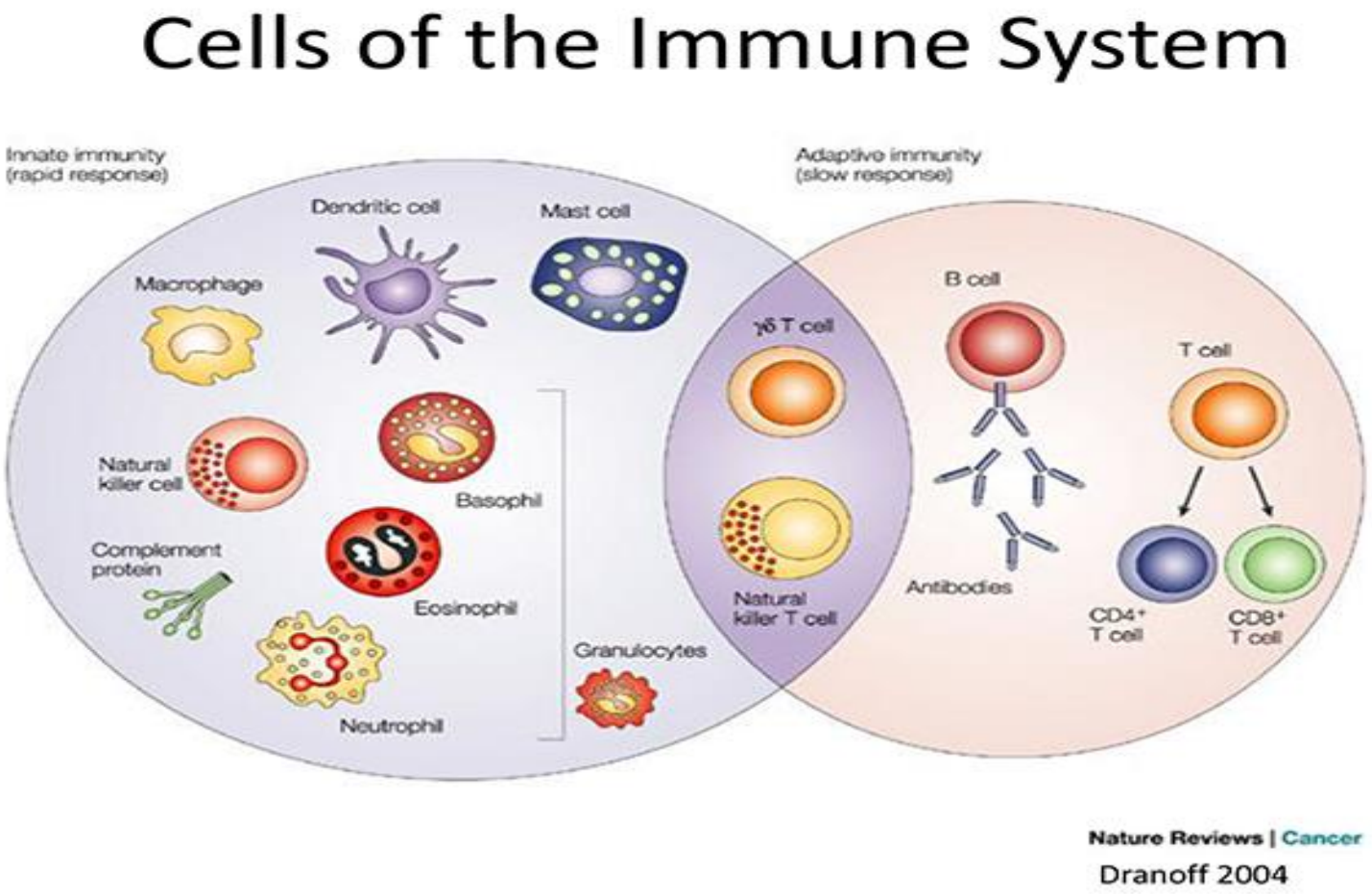
- The basics of immunotherapy
- Mechanism of action of checkpoint blockade
- Early clinical experience and the discovery of immune related adverse events
- Checkpoint blockade in melanoma
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
- Experimental Questions

Oncology

Cancer Immunotherapy

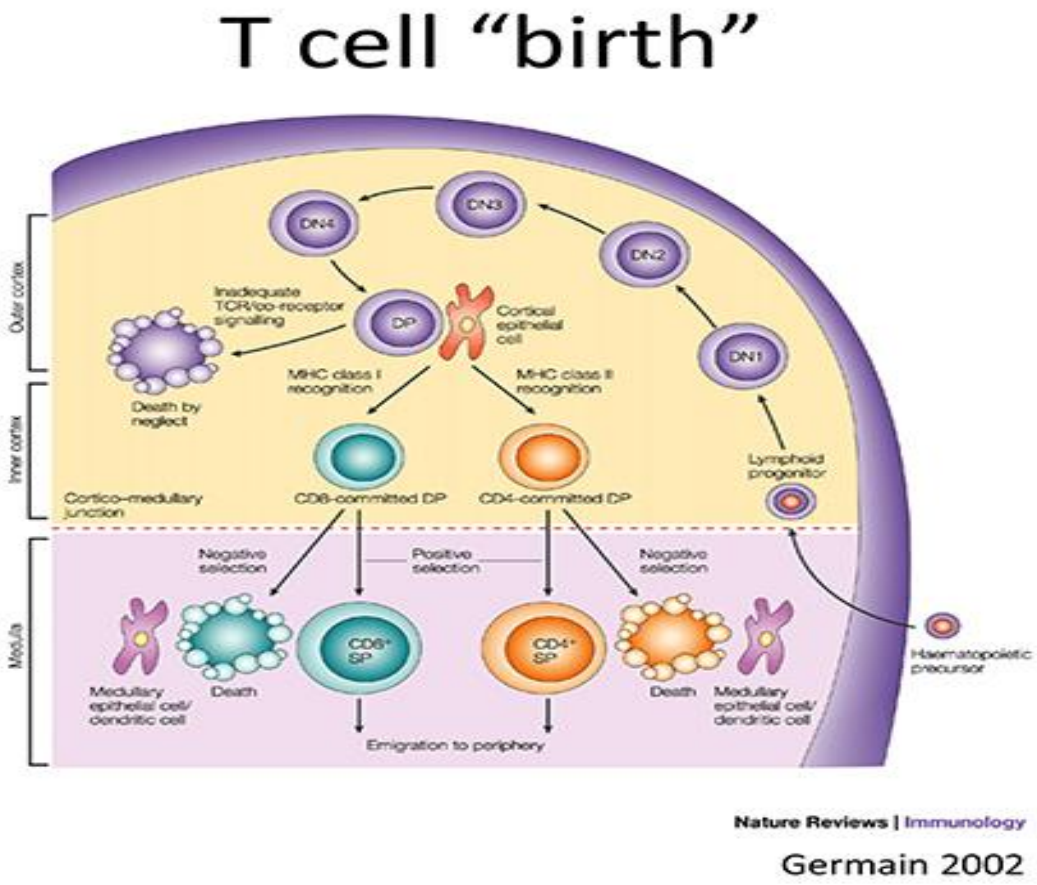
1. Nonspecific stimulation of immune reactions
    a) Stimulate effector cells
    b) Inhibit regulatory factors (checkpoint blockade)
2. Active immunization to enhance anti-tumor reactions (cancer vaccines)
3. Passively transfer activated immune cells with anti-tumor activity (adoptive immunotherapy)

Immune system



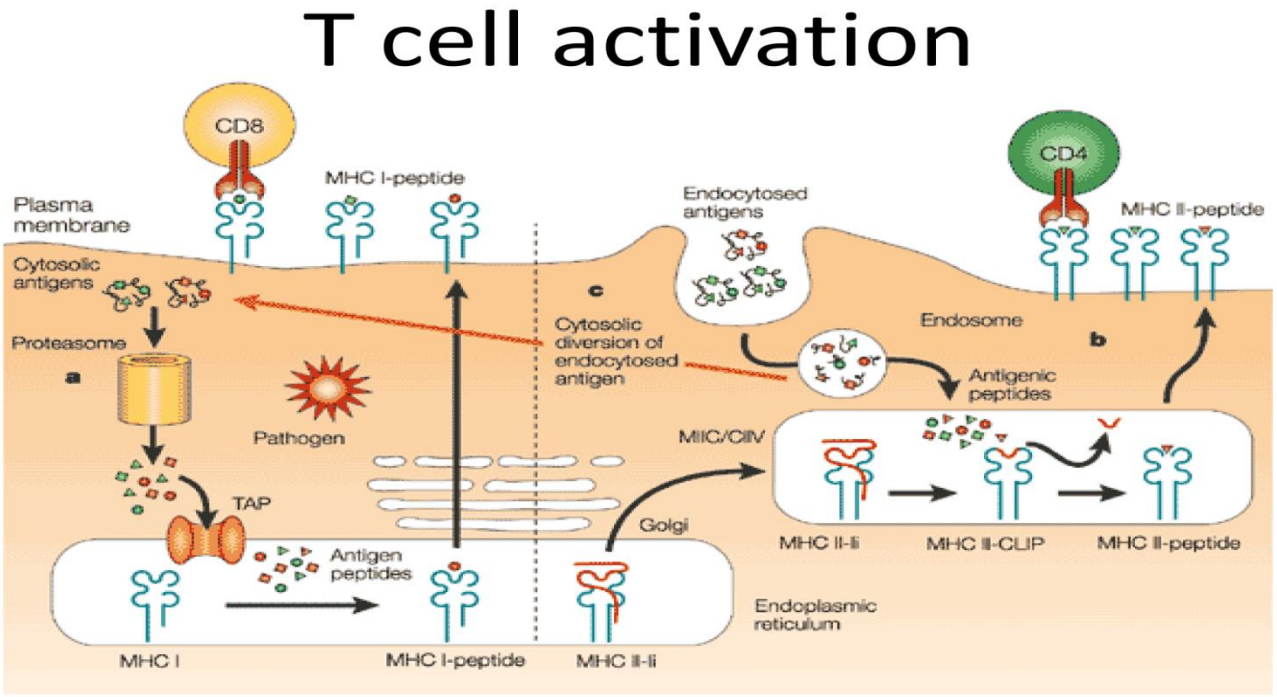
- Checkpoint blockade primarily affects T cells

T cell birth



- Builds a repertoire of T cells

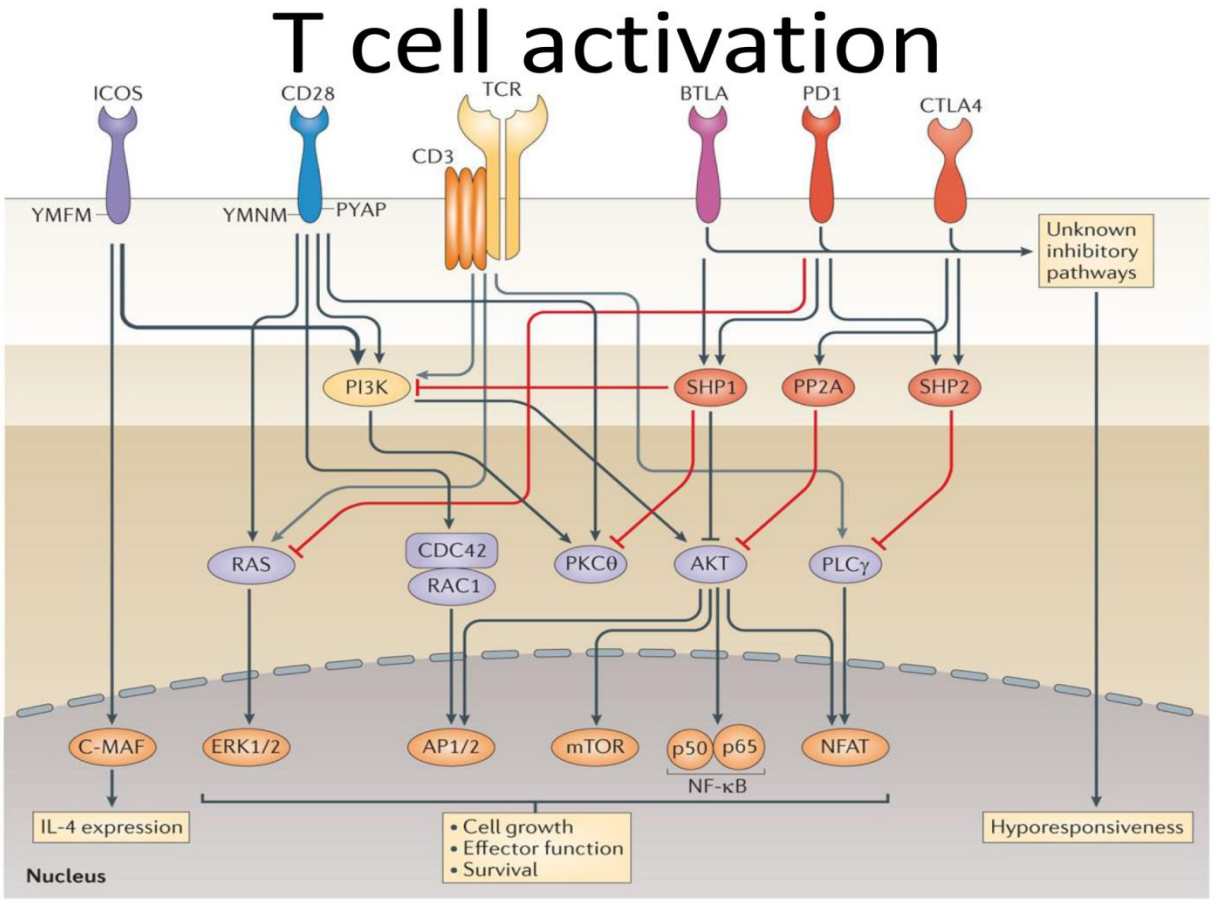
T cell activation



Nature Reviews | Immunology
Heath 2001

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

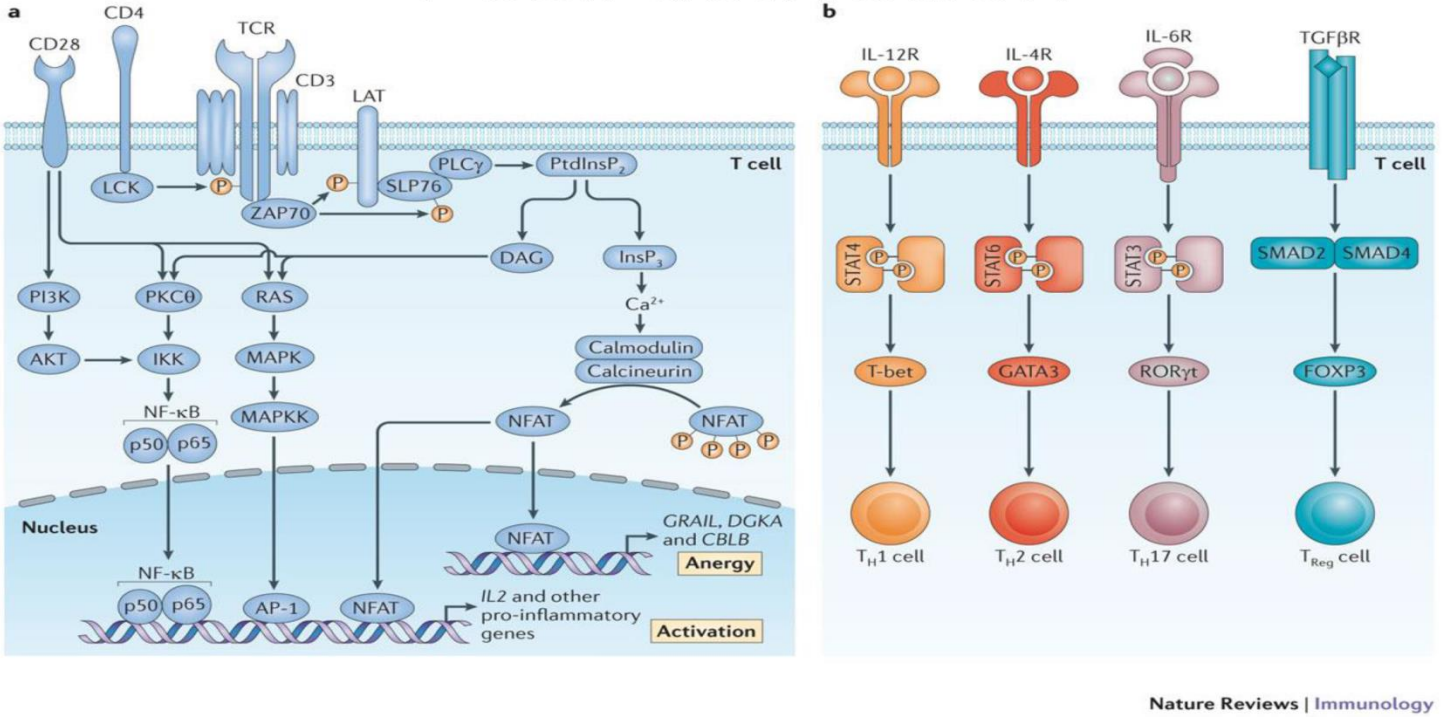
T cell activation



Chen 2013
Nature Reviews | Immunology

- Signal 2: Activation vs. Anergy

T cell activation



Pollizzi 2014

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

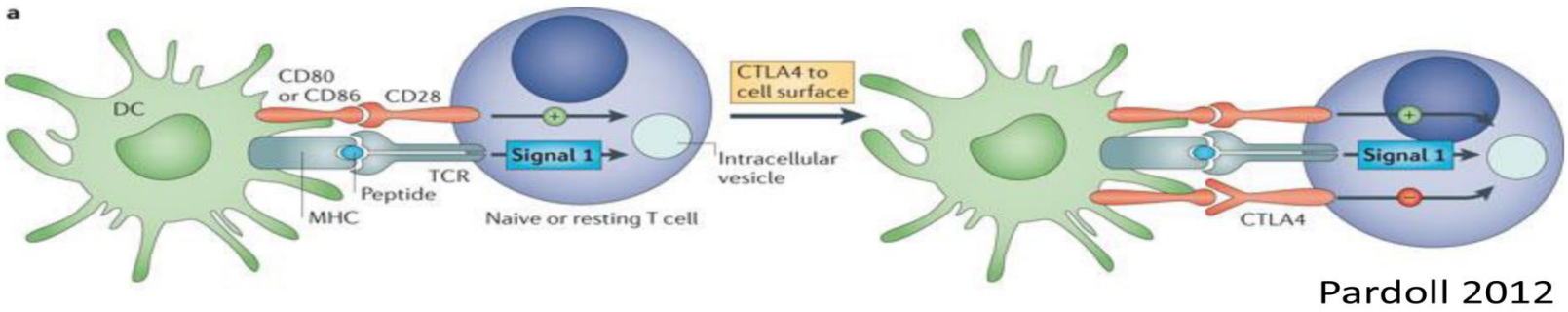
The role of Signal 2 checkpoints

- 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

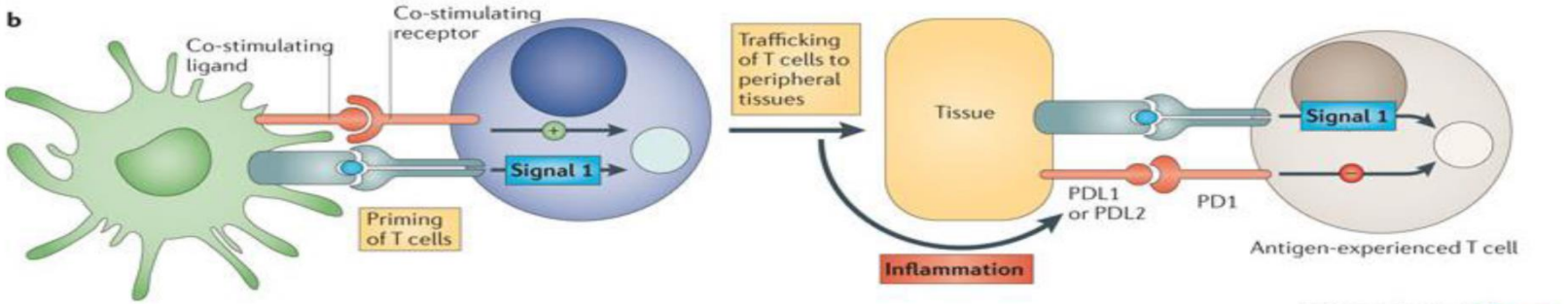


Pardoll 2012

- 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

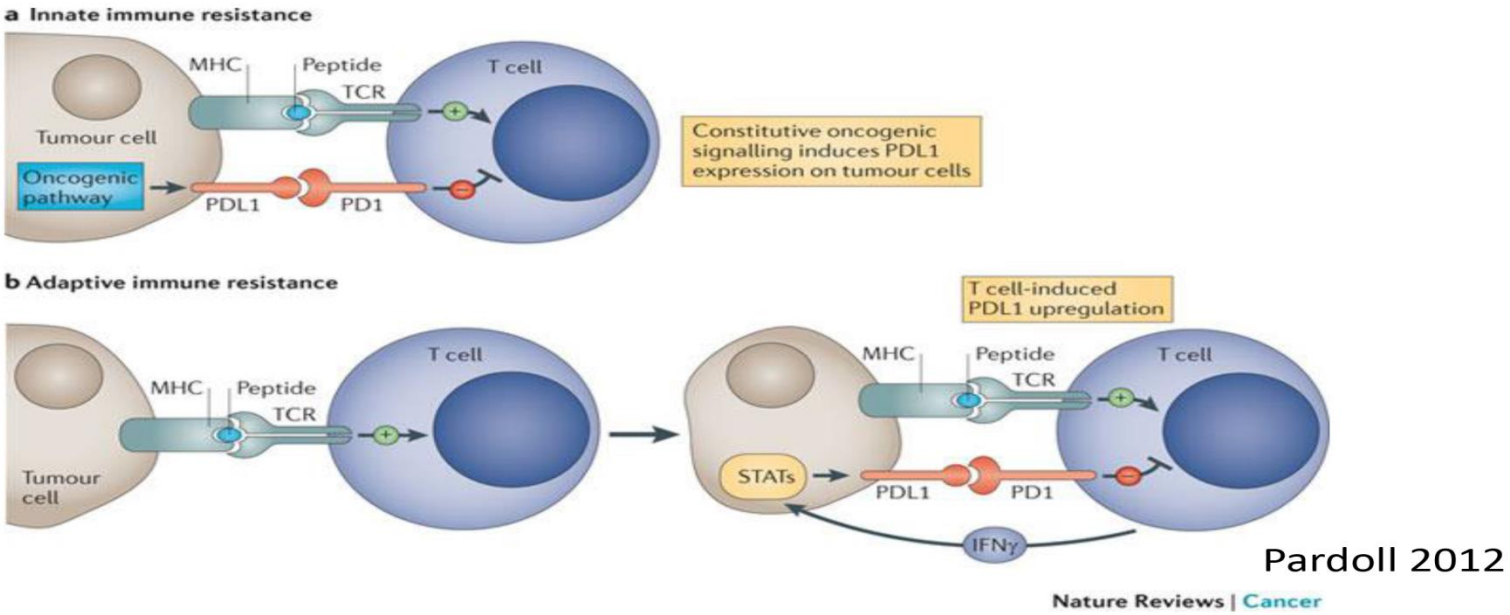
PD-1



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



- 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%

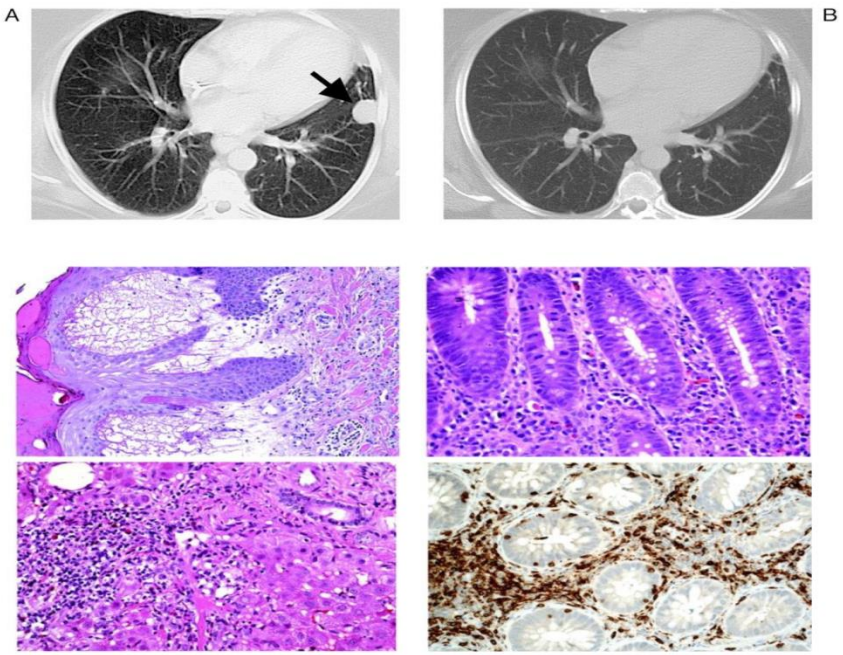
Smith FO Clin Cancer Res 2008

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

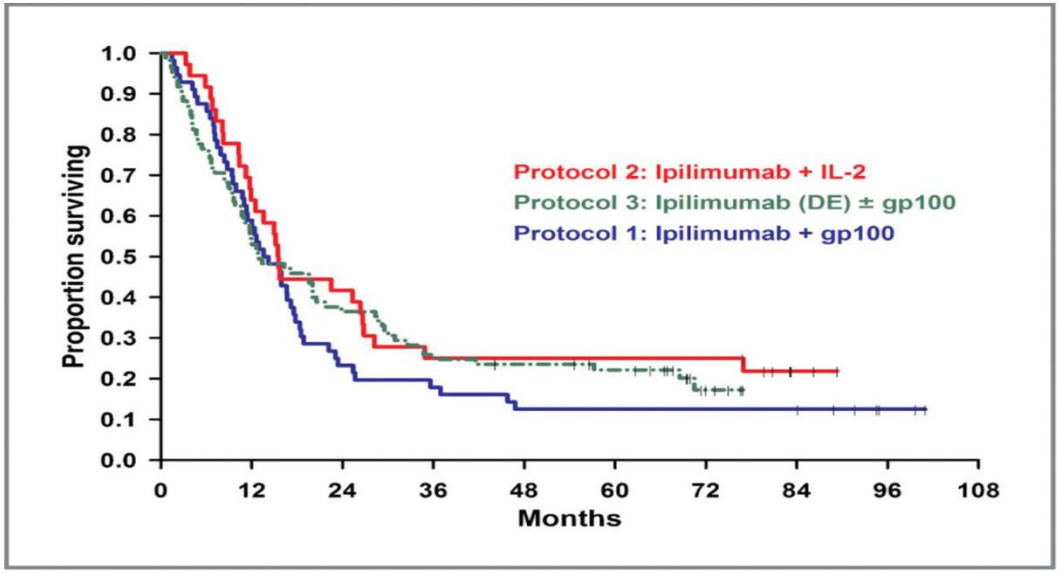
	Gr 3/4 IRAE	Gr 1/2 IRAE	No IRAE
Objective Response (CR = 3)	14 (28%)	8 (22%)	1 (2%)
Non-responder	36	28	52

Beck KE 2006
Downey SG 2007

Checkpoint Blockade

Checkpoint Blockade @ NCI

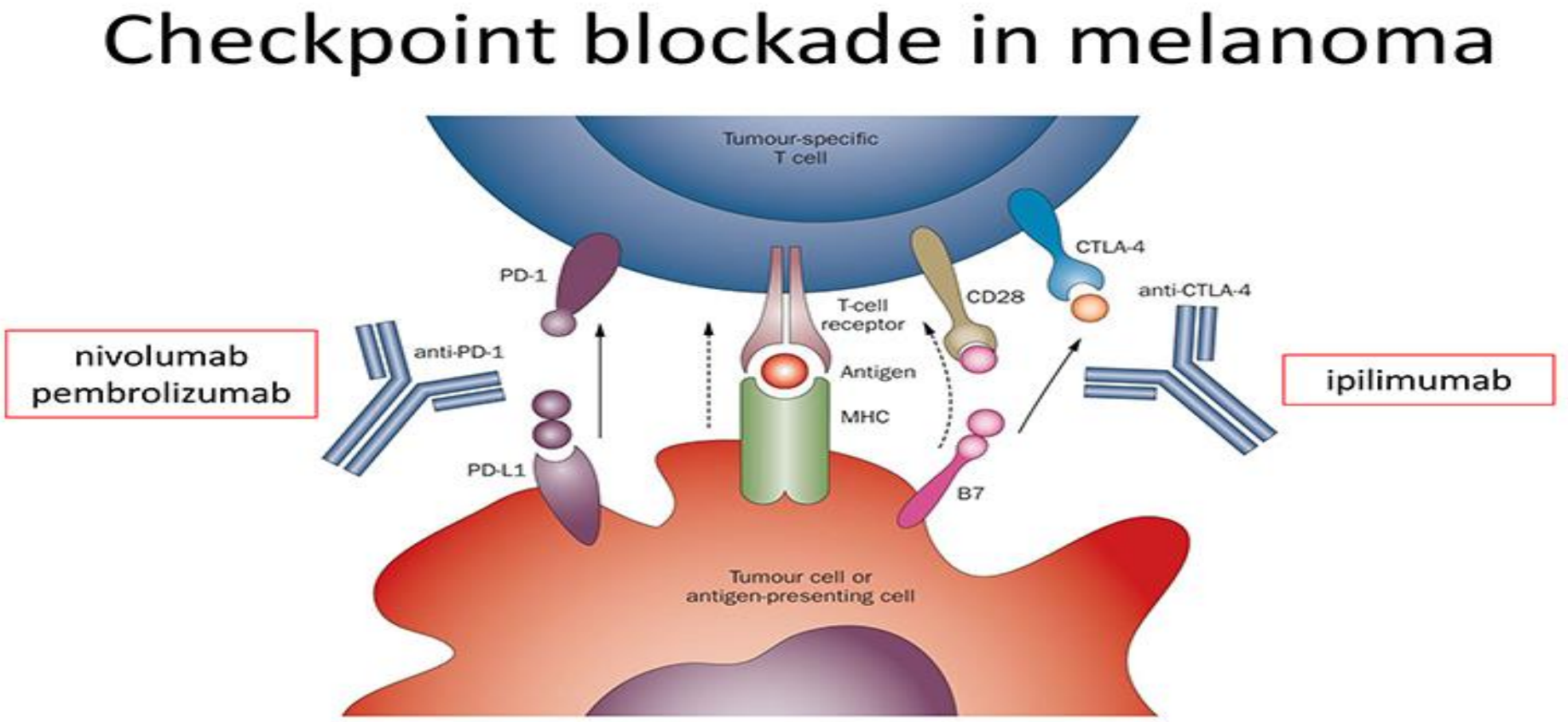
- Developed algorithms for management of IRAEs
- Demonstrated durability of responses
  - OR 13-20%
  - 5 yr OS 13-23%



Prieto PA 2012

Clinical Cancer Research
AACR American Association for Cancer Research

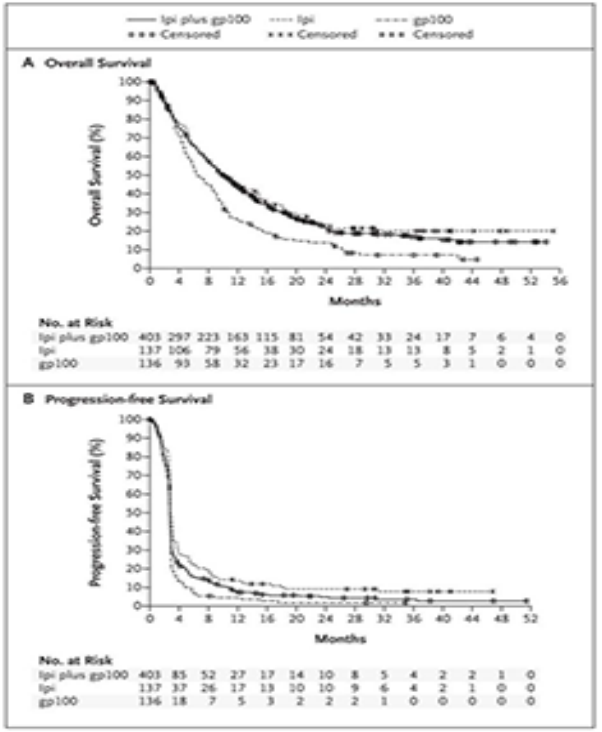
Checkpoint blockade



Ipilimumab

Ipilimumab for melanoma

- 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%
- **FDA approved for metastatic melanoma in March 2011**



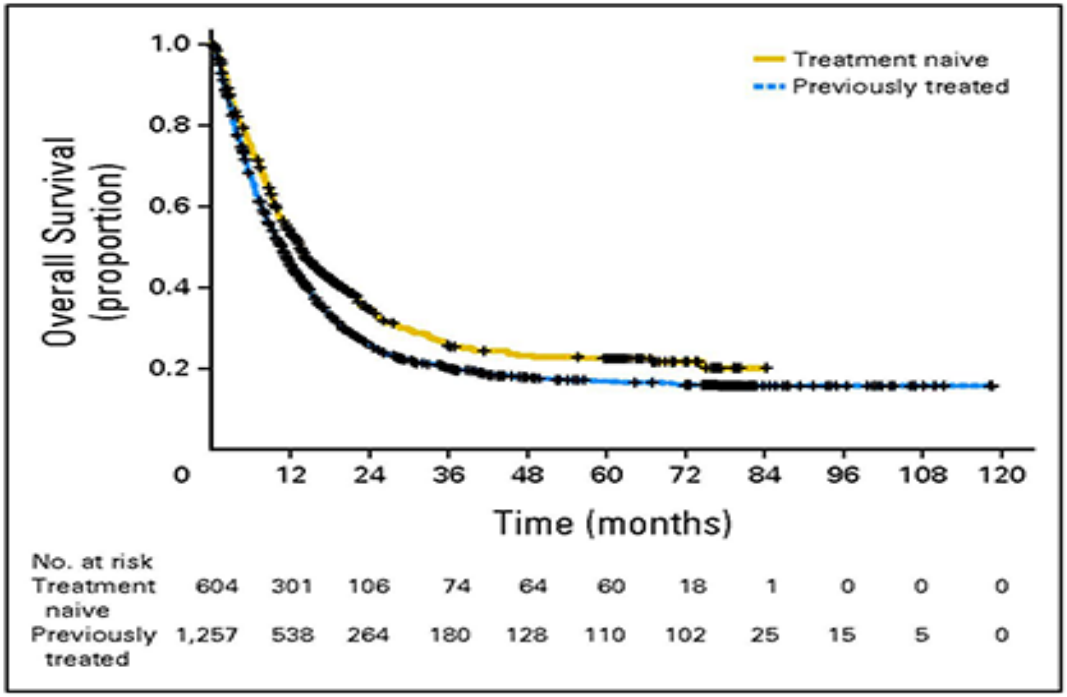
Hodi FS 2010

The NEW ENGLAND JOURNAL of MEDICINE

Ipilimumab

Ipilimumab for melanoma

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



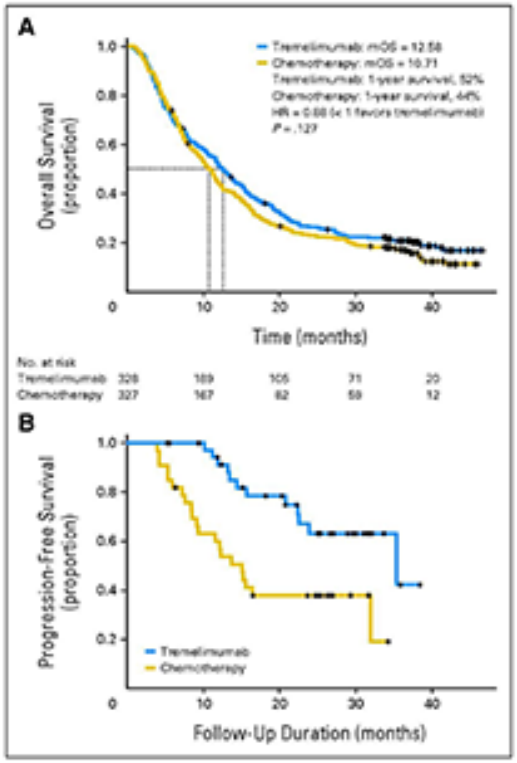
Schadendorf D 2015

JOURNAL of CLINICAL ONCOLOGY ASCO

Tremelimumab

Tremelimumab

- αCTLA-4
- 10% response rate in Phase II trials
- Randomized Phase III tremelimumab vs. dacarbazine/temozolomide
- No cross-over
- Failed to demonstrate survival advantage
- Currently being studied in combination trials



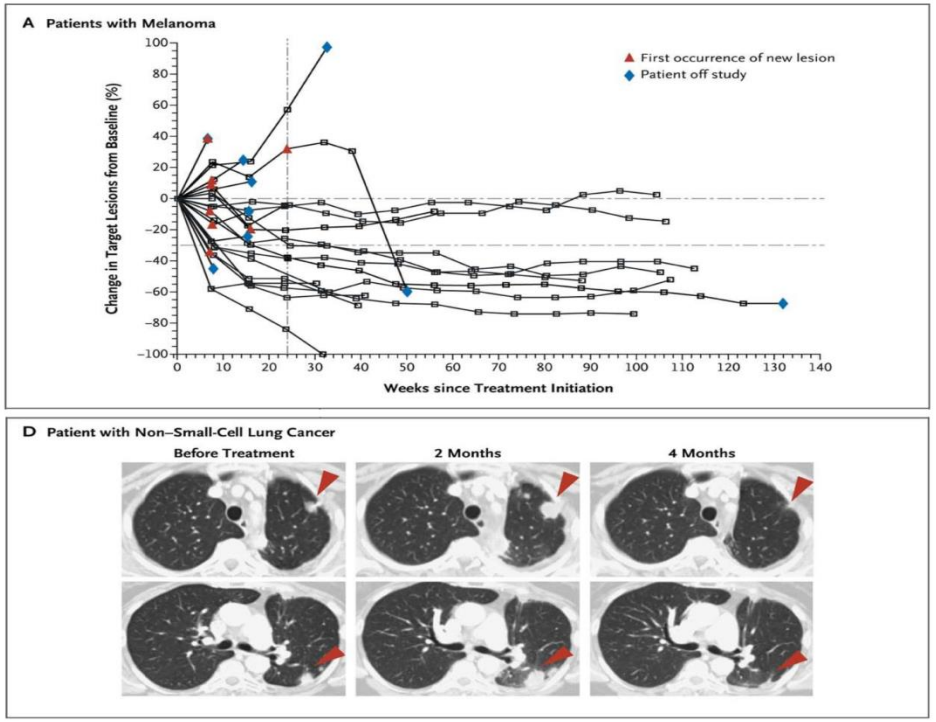
Ribas A 2013

JOURNAL of CLINICAL ONCOLOGY ASCO

Nivolumab

Nivolumab

- αPD-1
- Phase I dose escalation
- 0.1 mg/kg → 10 mg/kg
  - Melanoma (26/94, 28%)
  - NSCLC (14/76, 18%)
  - RCC (9/33, 27%)
  - CRPC (0/13)
  - CRC (0/19)
- Grade 3/4 toxicities in 6%



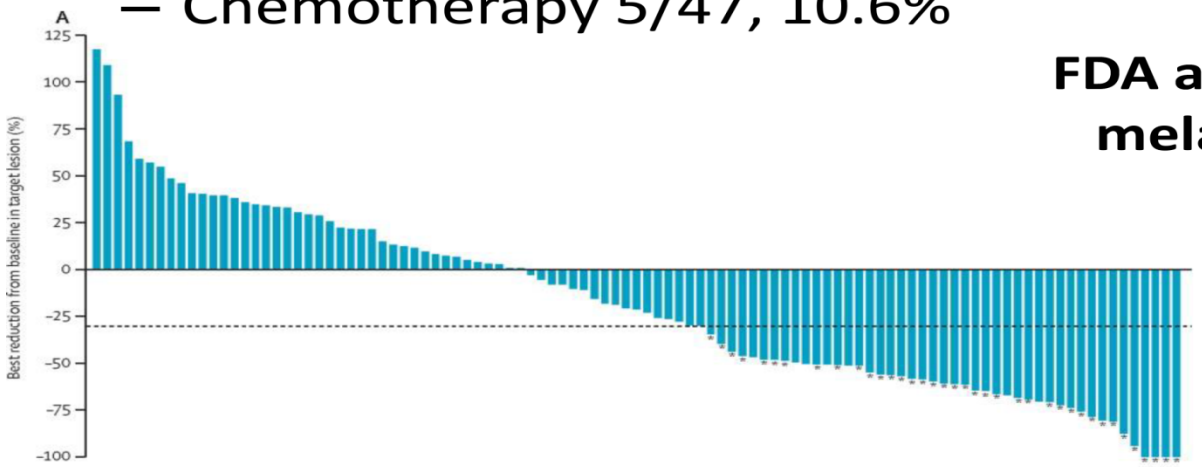
Topalian SL 2010

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

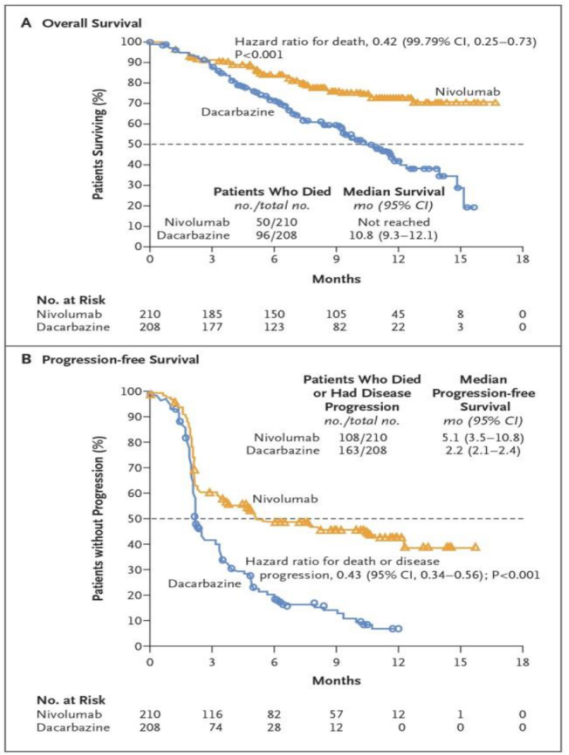
Weber JS 2015

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%)



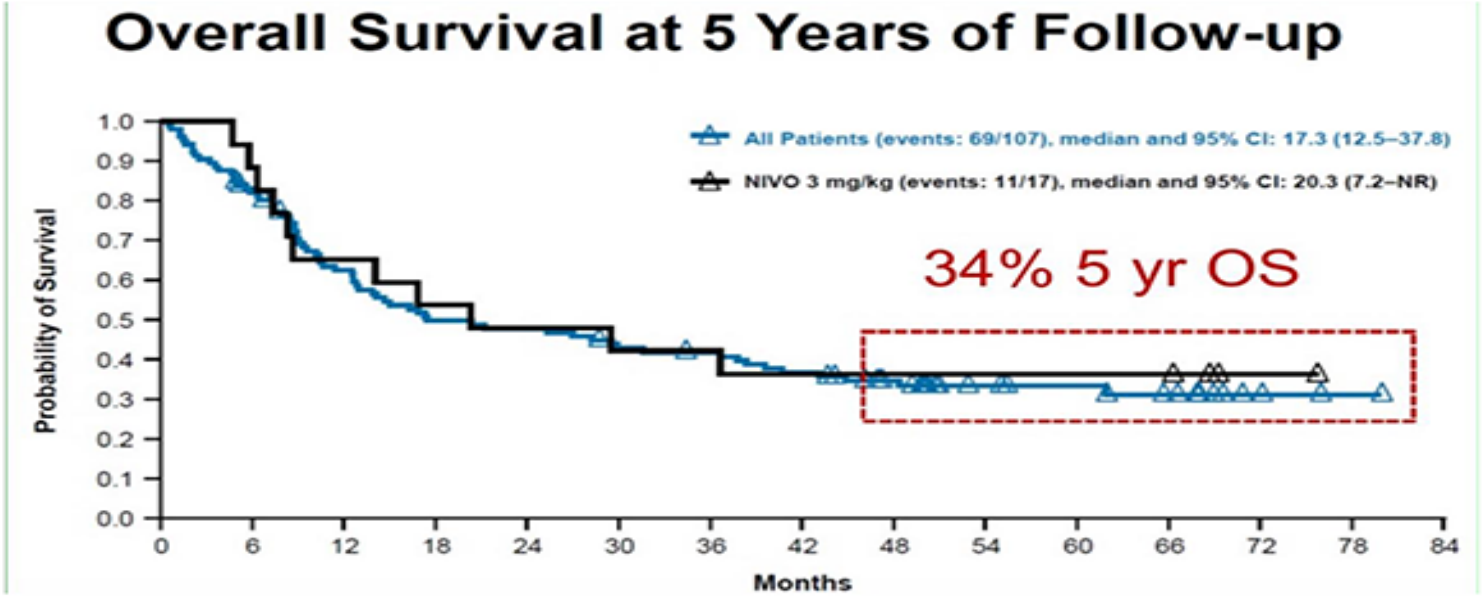
Robert C 2015

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab for melanoma

Nivolumab for melanoma

- Updated survival
- "Tail of the curve"



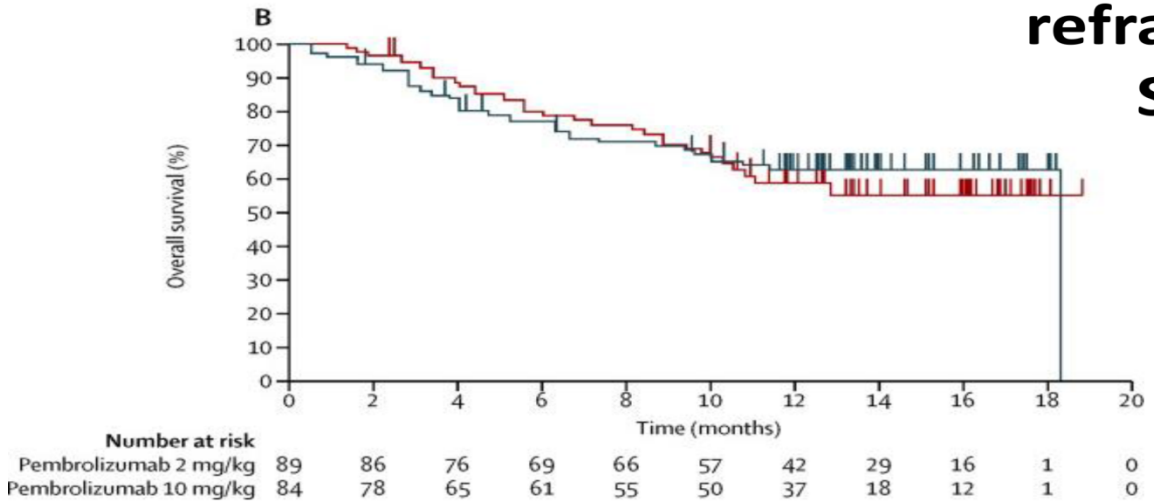
Hodi F
(presented at AACR 2016)

Pembrolizumab for melanoma

Pembrolizumab for melanoma

- Ipilimumab-refractory
- Phase I, dose comparison (2mg/kg vs 10 mg/kg)
- 157 evaluable patients with OR 41 (26%), CR in 2 pts
- Disease control rate 50%
- Grade 3/4 AE 12%

FDA approval for refractory melanoma in September 2014

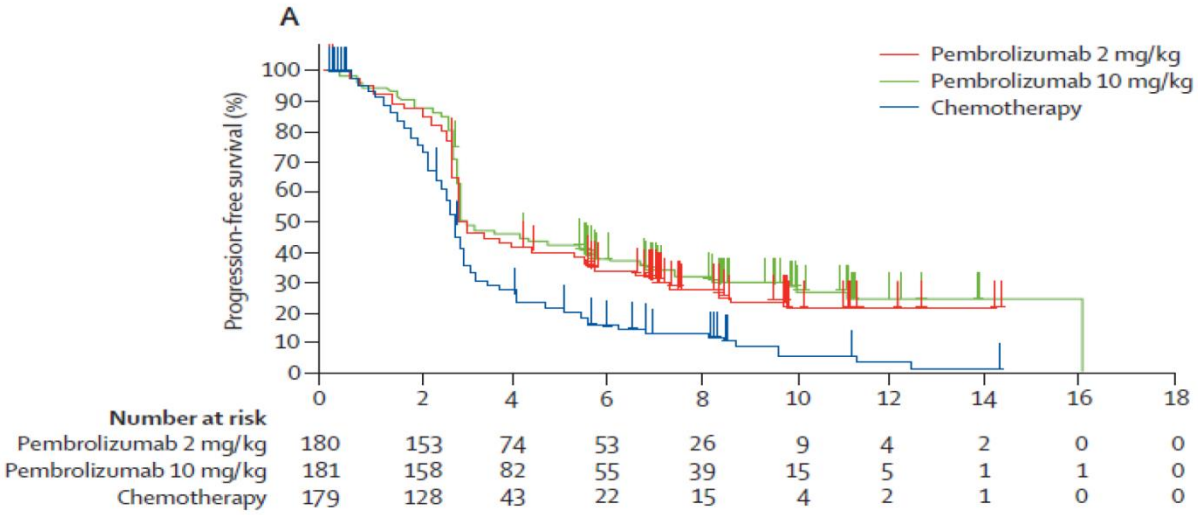


Robert C 2014
THE LANCET

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

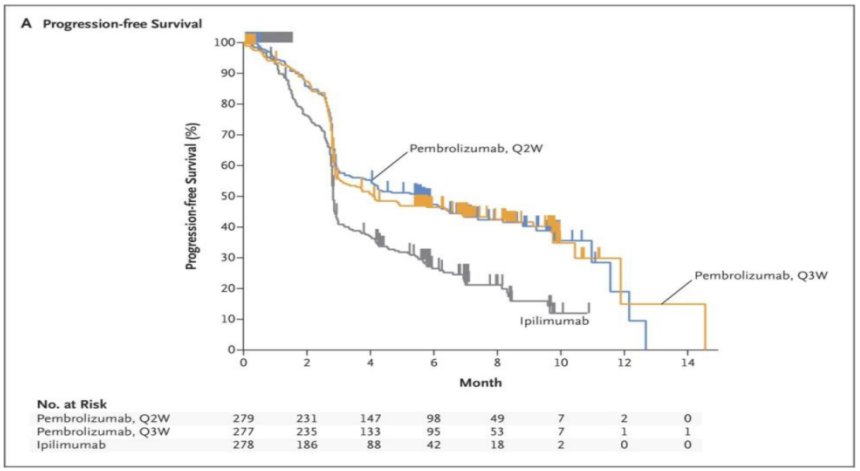
- RCT, KEYNOTE-006, first-line therapy
- Pembrolizumab (q2w, q3w) vs ipilimumab
- 1:1:1
- 834 patients
- Objective Response
  - Pembrolizumab q2w 94/279 (33.7%), CR 14
  - Pembrolizumab q3w 91/277 (32.9%), CR 17
  - Ipilimumab 33/278 (11.9%), CR 4

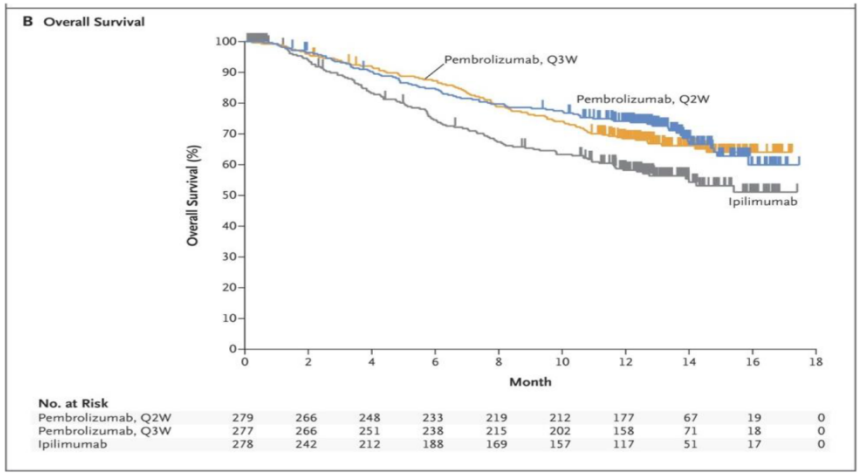
Robert C 2015

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)

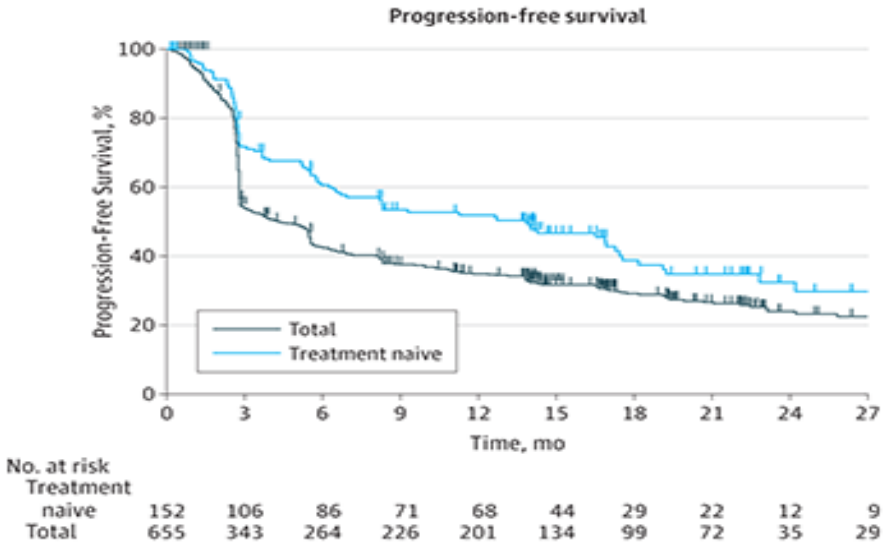
Robert C 2015

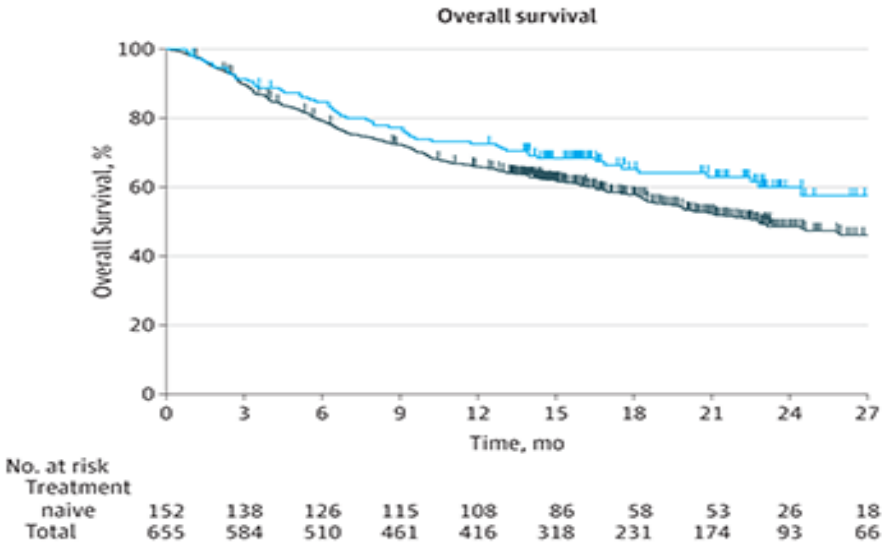
The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for melanoma

Pembrolizumab for melanoma

- Updated survival
- "Tail of the curve"



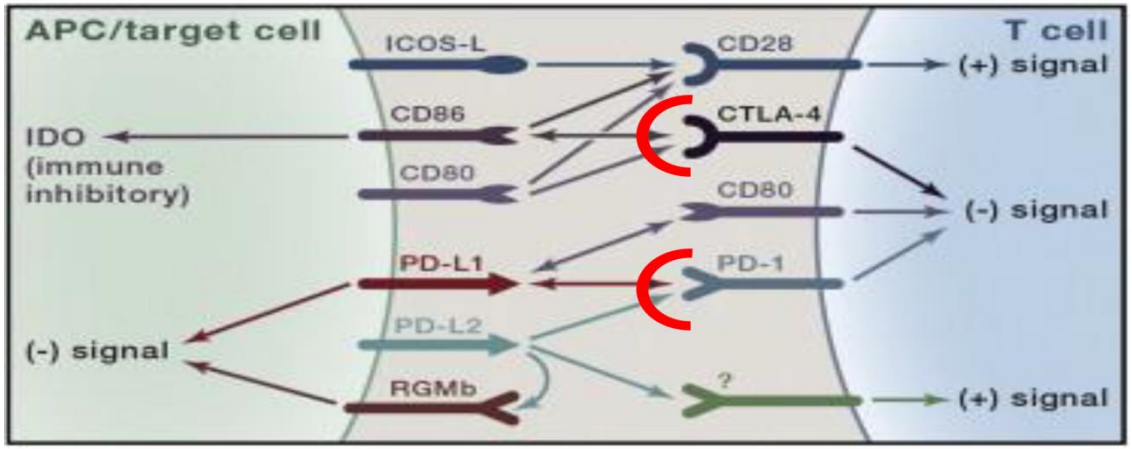


Ribas A 2016

JAMA

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 (+) ≥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/Ipilimumab

Nivolumab/Ipilimumab for melanoma

	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	Total
Overall ORR	43.7%	57.6%	19.0%	40.1%
PD-L1 (+)	46/80 57.5%	49/68 72.1%	16/75 21.3%	111/223 49.8%
PD-L1 (-)	86/208 41.3%	115/210 54.8%	36/202 17.8%	237/620 38.2%
PD-L1 unknown	6/28 21.4%	17/36 47.2%	8/38 21.1%	31/102 30.3%

Larkin J 2015

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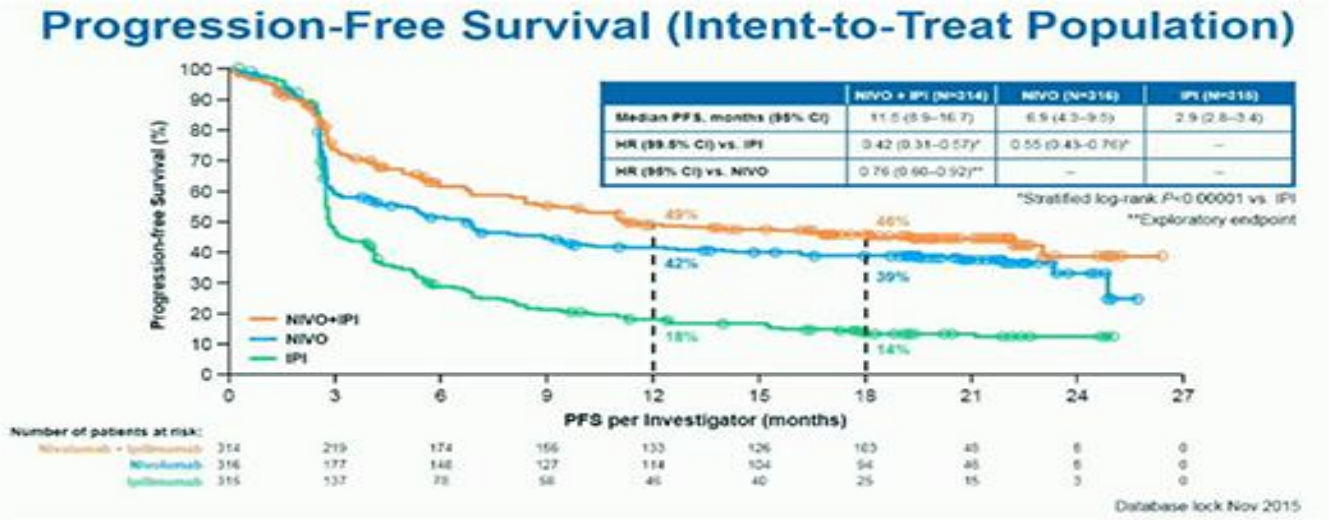
Nivolumab/ipilimumab

Nivolumab/Ipilimumab for melanoma
-updated results-



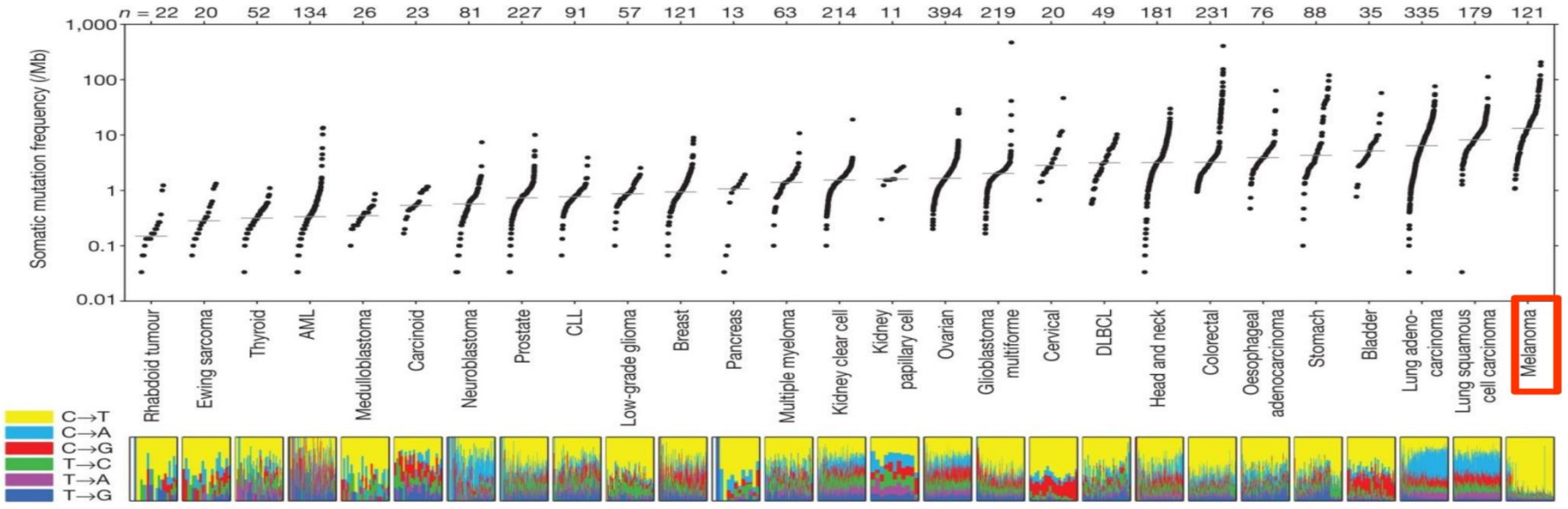
- Minimum follow-up of 18 months
- Overall survival not updated, still immature

FDA approval of combination for melanoma in January 2016

Wolchok
(presented at ASCO 2016)

Melanoma

Why melanoma?



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

Highly mutated tumors

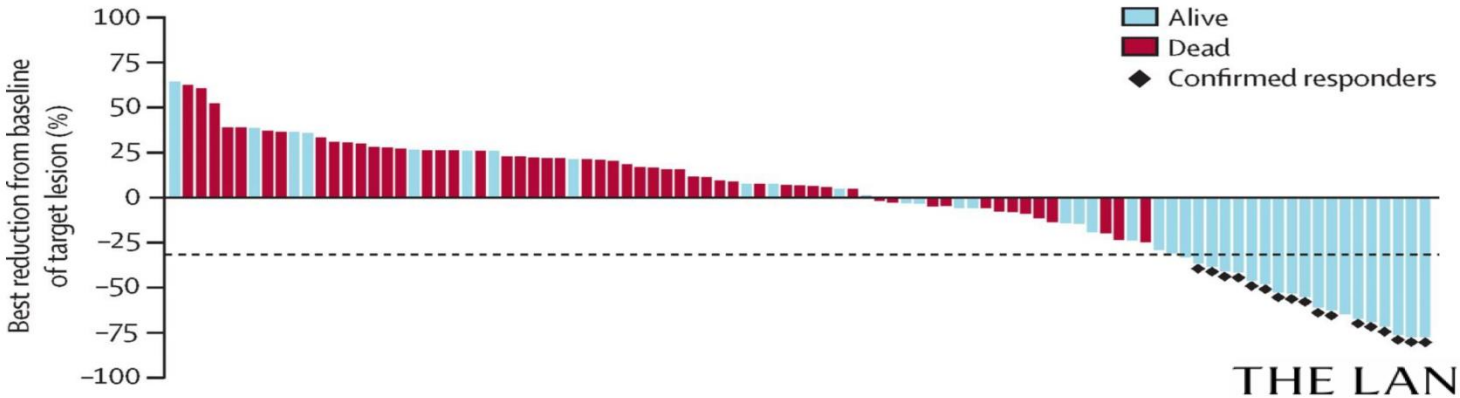
- Non-small cell lung cancer
- ~158,040 deaths/year in US
- Regional disease
  16% 5 yr survival
- Metastatic disease
  2% 5 yr survival
- Correlation between smoking and # mutations

- 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

Nivolumab for NSCLC

Nivolumab for NSCLC

- NSCLC refractory to ≥ 2 treatments
- Phase II (CheckMate 063)
- 3 mg/kg q2w until progression or toxicity
- 117 patients treated
- Objective Response 17 (14.5%), no CR



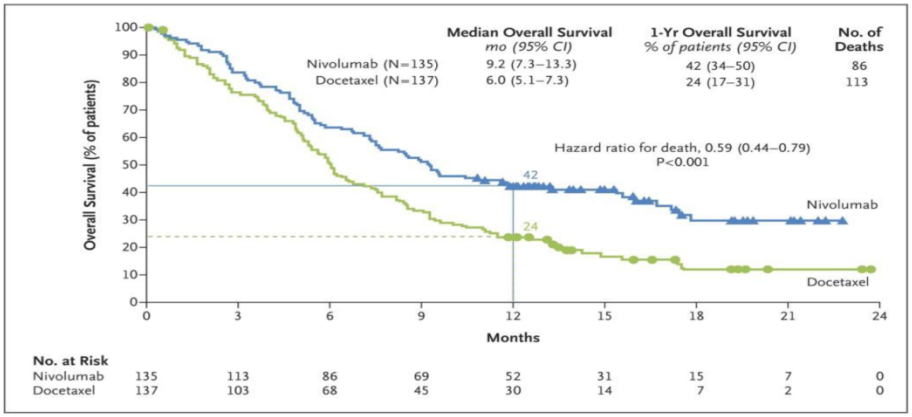
Rizvi NA 2015

THE LANCET Oncology

Nivolumab for NSCLC

Nivolumab for NSCLC

- RCT
- Nivolumab vs docetaxel
- Refractory to one platinum-based regimen
- Objective Response
  - Nivolumab 27/135 (20%)
  - Docetaxel 12/137 (9%)



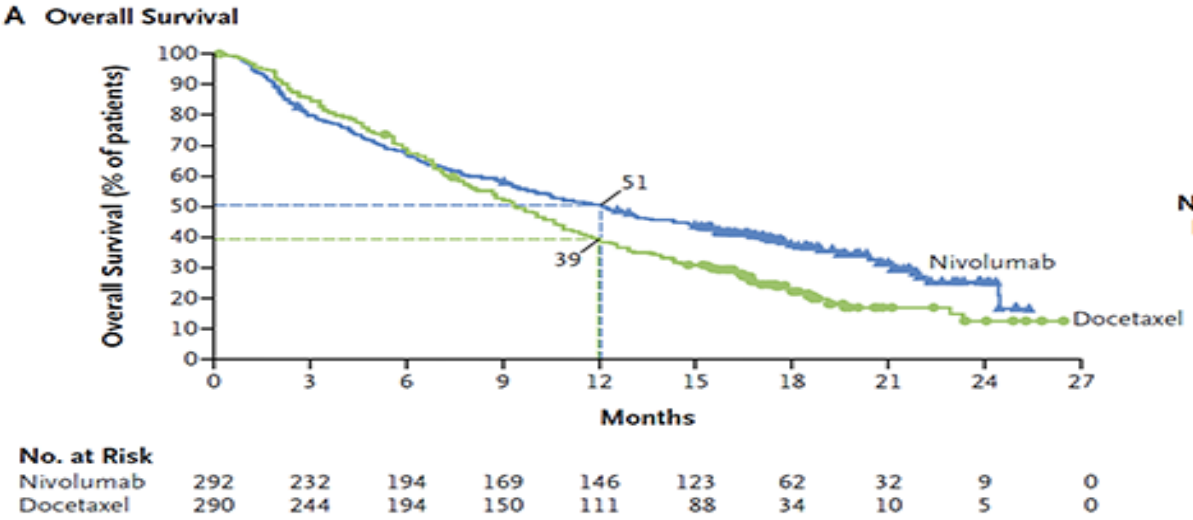
FDA approval for refractory NSCLC in March 2015

Brahmer 2015

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab for NSCLC

Nivolumab for NSCLC



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

- Nivolumab vs docetaxel
- Objective Response
  - Nivolumab 56/292 (19%)
  - Docetaxel 36/290 (12%)

FDA approval for refractory non-squamous NSCLC in October 2015

Borghaei 2015

The NEW ENGLAND JOURNAL of MEDICINE

Pembrolizumab for NSCLC

Pembrolizumab for NSCLC

- 495 patients, subset of KEYNOTE 001
- Wide range of inclusion criteria
  - 94 treatment naïve patients
  - 126 never smokers
  - 401 nonsquamous
- Majority at 10 mg/kg either q2w or q3w
- Objective response 96/495 (19.4%)
  - Never smokers 13/126 (10.3%)
  - Former/current 83/369 (22.5%)
- Grade ≥3 AE
  - Dyspnea 3.8%
  - Pneumonitis 1.8% including a fatality

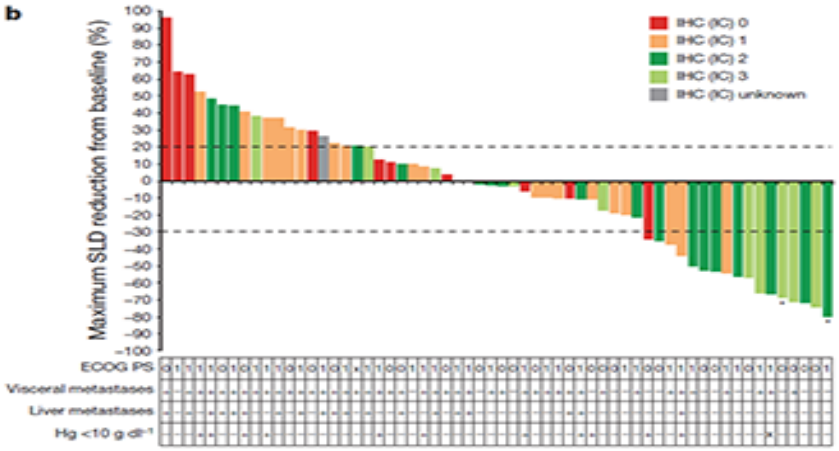
FDA decision to be made October 2, 2015

Garon EB 2015

antiPD-L1

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%

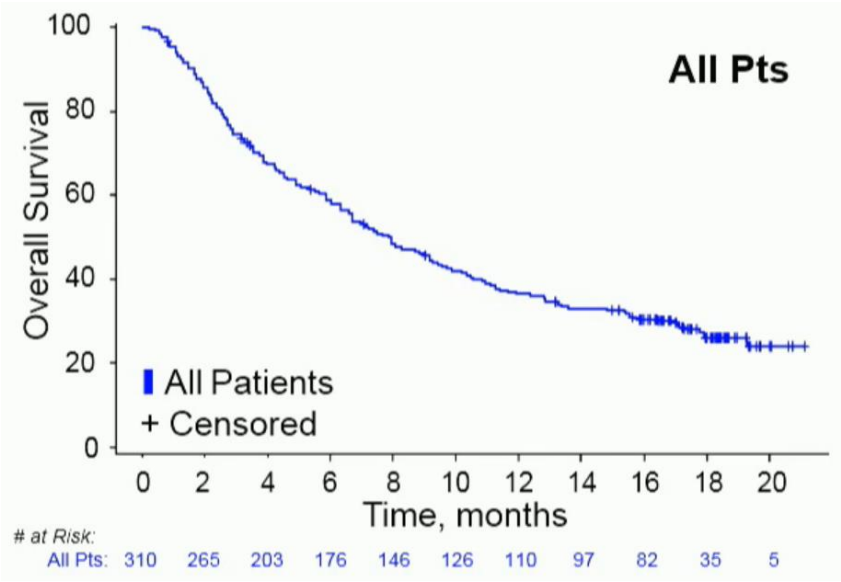


FDA approval for urothelial cancer in May 2016

Powles T 2014
nature

αPD-L1 in Urothelial bladder cancer

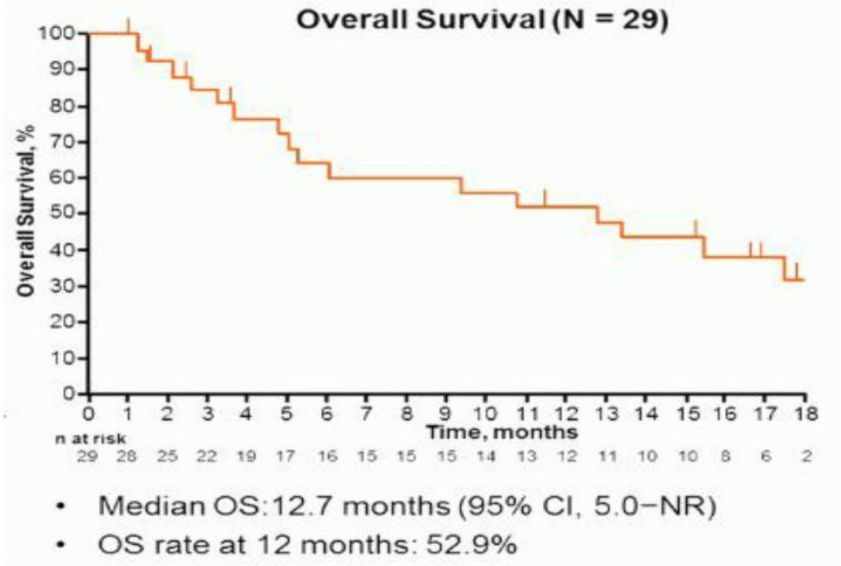
- 310 patients
- Objective Response
  - 45 (15%)
  - With 15 complete responses
- Overall Survival
  - 7.9 months
- 1 yr Survival
  - 37%



Urothelial Cancer

Pembrolizumab in Urothelial Cancer

- Part of KEYNOTE-012
- Required ≥ 1% PD-L1 staining (61/95, 64.2%)
- 10 mg/kg q2w
- 33 patients (29 eval)
- OR 27.6%,
  CR 10.3% (3 pts)
- Grade ≥ 3 AE 15%



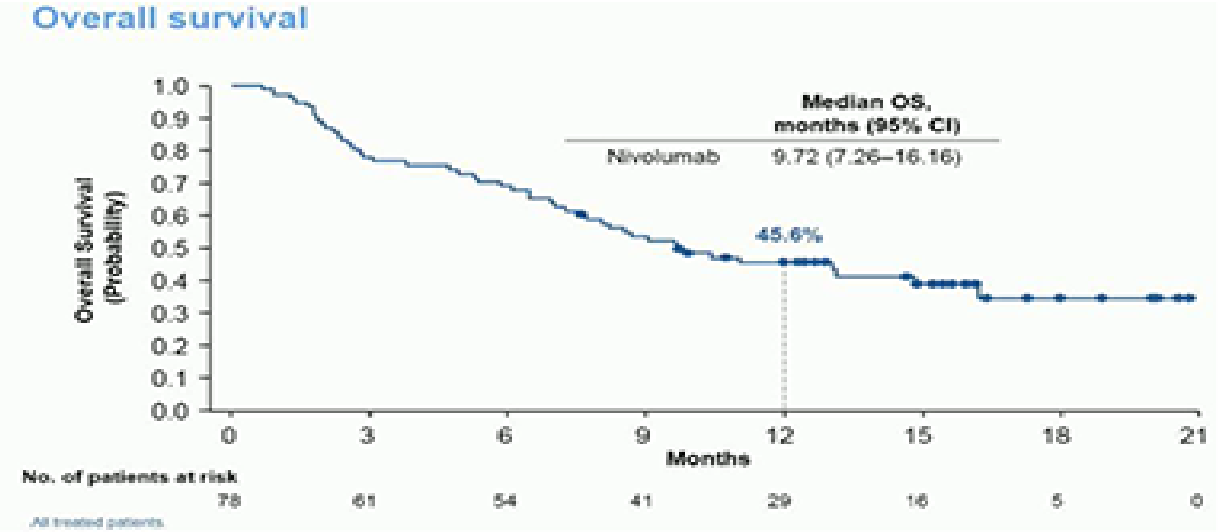
Abstract: Plimack E 2015

ASCO

Nivolumab in Urothelial Cancer

Nivolumab in Urothelial Cancer

- One cohort of a larger study, 3 mg/kg q2w
- Did not require ≥ 1% PD-L1 staining (25/67, 37%)
- 78 patients (29 eval)
- OR 24.4%, CR 6.4% (5 pts), Grade ≥ 3 AE 22%

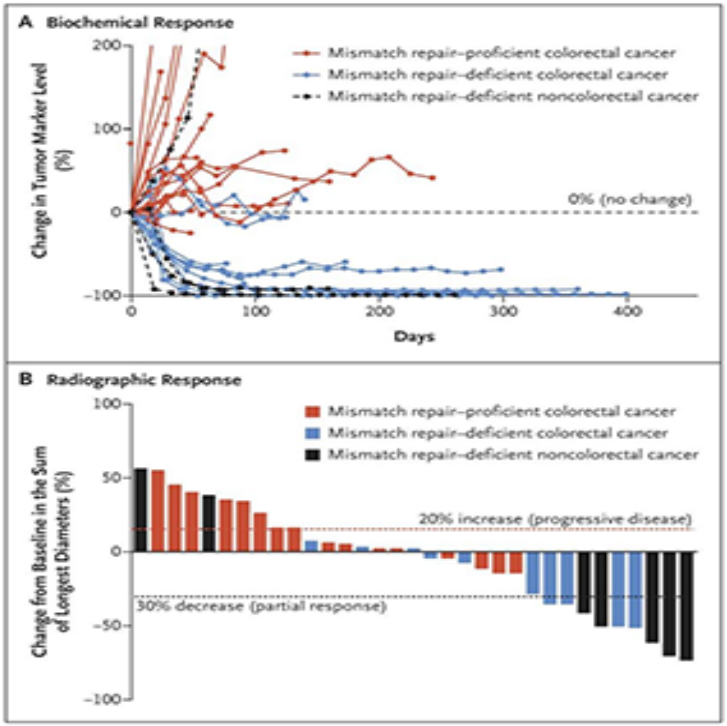


Sharma P, presented 2016

MMR-deficient cancer

Pembrolizumab for MMR-deficient cancer

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

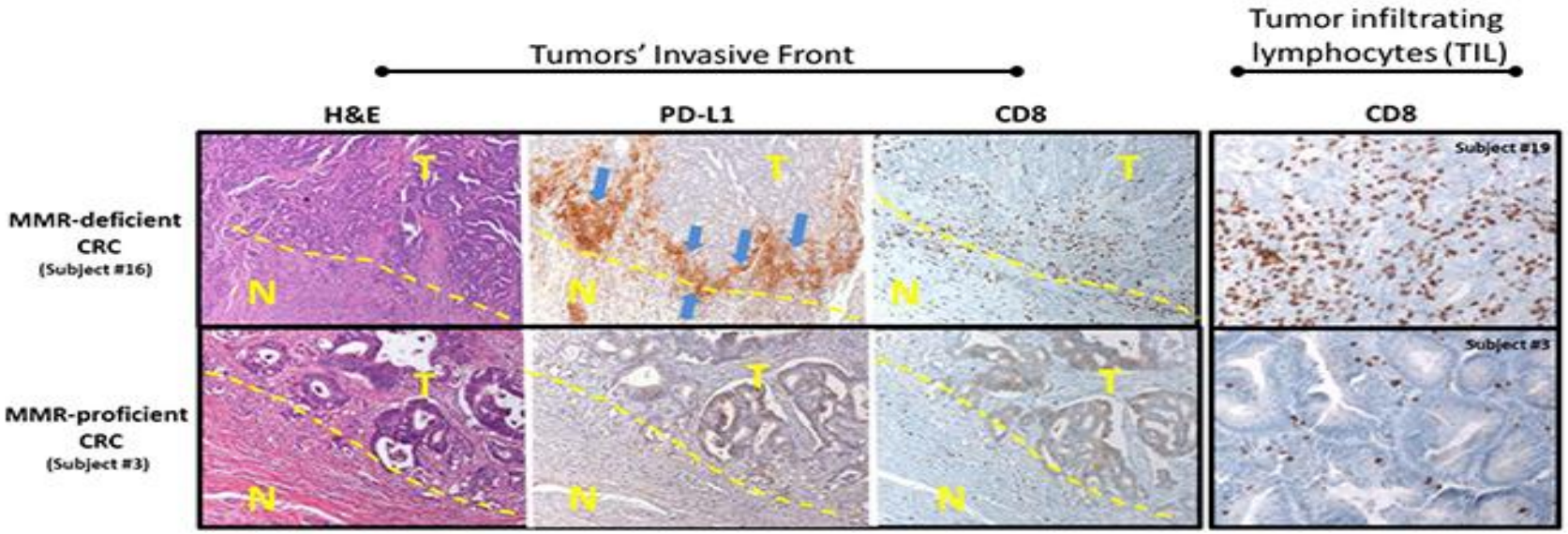


Le DT 2015

The NEW ENGLAND JOURNAL of MEDICINE

Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface



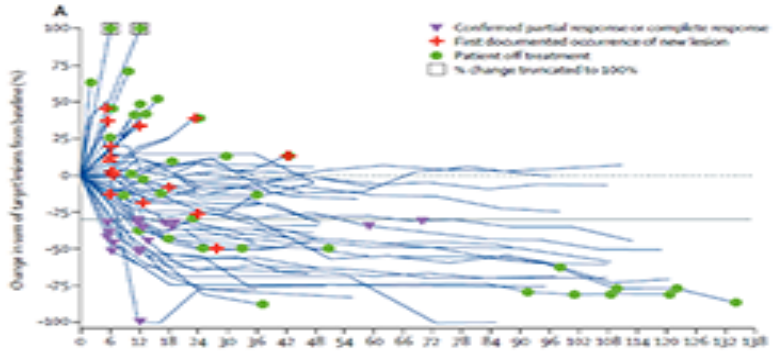
Le DT 2015

The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab for highly mutated colorectal cancer

Nivolumab for highly mutated colorectal cancer

- CheckMate 142
- dMMR or microsatellite instability-high (MSI-H)
- 53 patients verified dMMR/MSI-H
- OR 36% (19/53)
- CR 2% (1/53)



FDA approval for dMMR/MSI-H tumors in July 2017

Overman MJ 2017
THE LANCET Oncology

Checkpoint blockade

Checkpoint Blockade

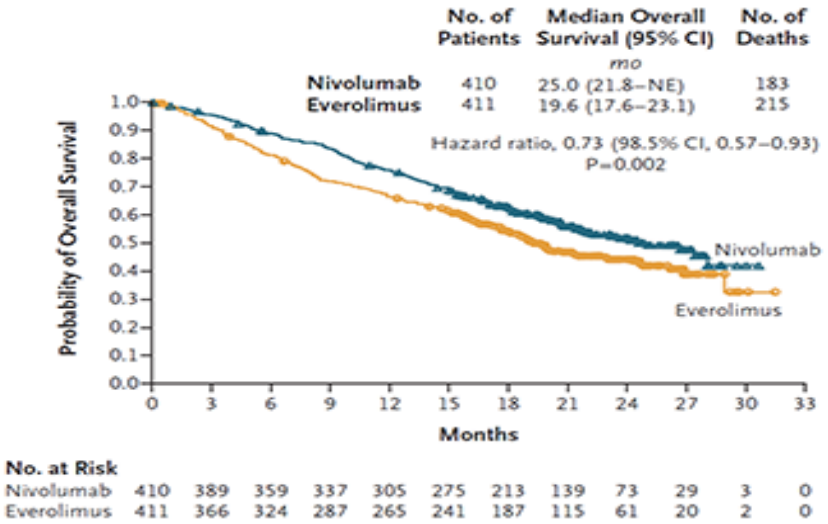
- Highly mutated tumors
  - Melanoma
  - Non-small cell lung cancer
  - Bladder cancer
  - Tumors with mismatch repair deficiency
- Use in other tumors?
  - Renal cell
    - Responds to other immunotherapy
  - Hodgkin's lymphoma
    - Reed-Sternberg cells have elevated amounts of PD-L1
  - Head and neck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

Renal cell cancer

Nivolumab for renal cell cancer

- Nivolumab vs everolimus
- Objective Response
  - Nivolumab 103/410 (25%)
  - Everolimus 22/411 (5%)
- Median Survival
  - Nivolumab 25.0 months
  - Everolimus 19.6 months

FDA approval for renal cell carcinoma in November 2015



Motzer 2015

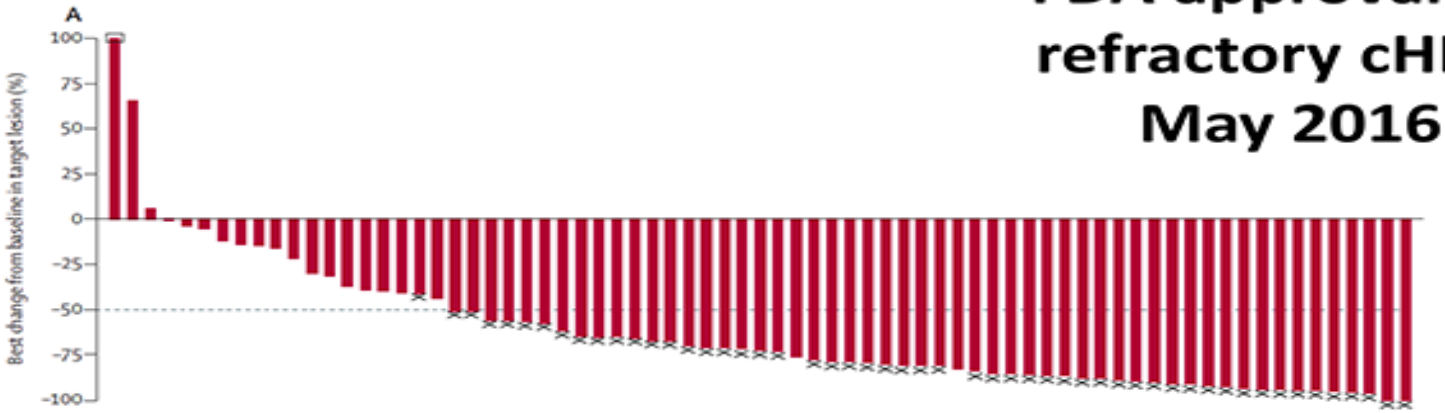
The NEW ENGLAND JOURNAL of MEDICINE

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

Head and Neck SCC

Pembrolizumab in Head and Neck SCC

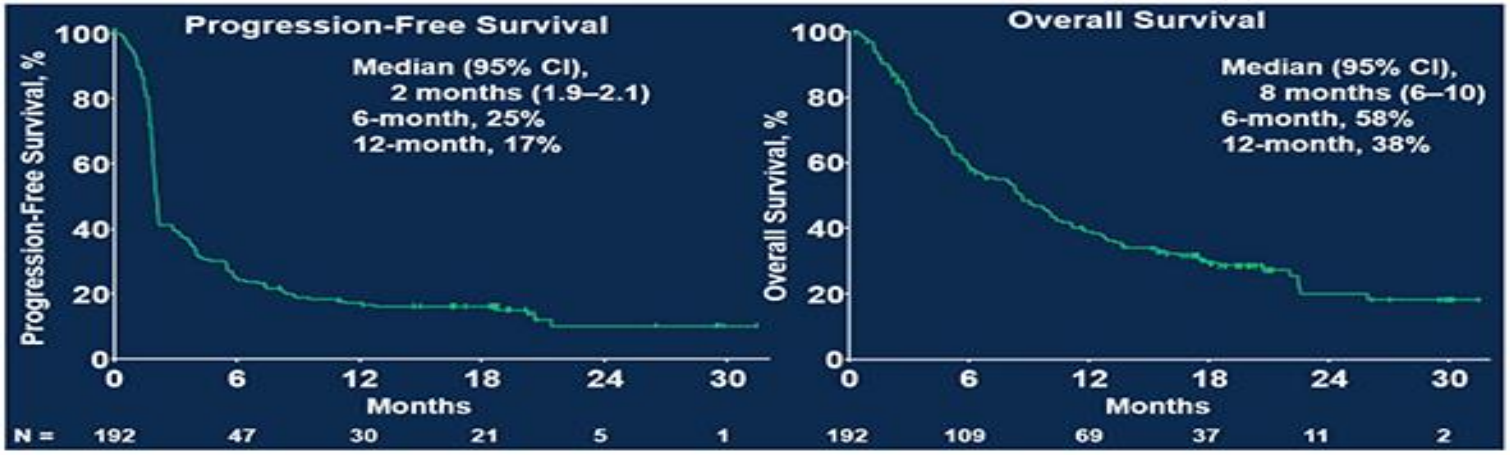
- Part of KEYNOTE-012
- No requirement for PD-L1 expression
- 200mg q3w
- 192 patients, HPV+ 45/192 (23%)

Best Overall Response	Total N = 192†			HPV+ n = 45‡			HPV– n = 147‡		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ORR	34	18	13–24	11	24	13–40	23	16	10–23
CR	8	4	–	4	9	–	4	3	–
PR	26	14	–	7	16	–	19	13	–
SD	33	17	–	7	16	–	26	18	–
PD	93	48	–	19	42	–	74	50	–
NA§	32	17	–	8	18	–	24	16	–

Mehra R, presented 2016

Pembrolizumab

Pembrolizumab in Head and Neck SCC



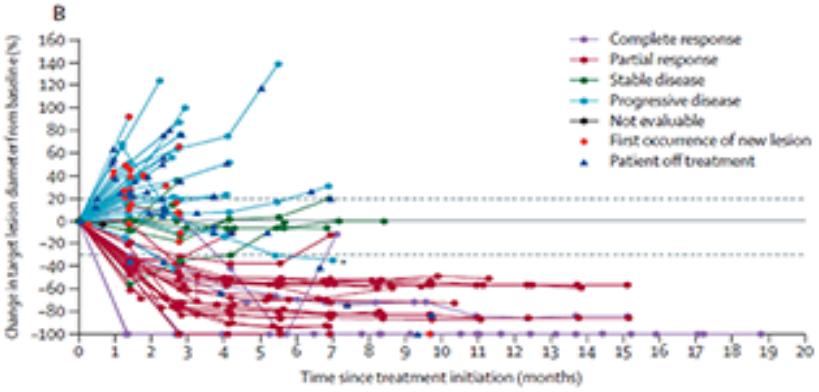
FDA approval for recurrent or metastatic head and neck squamous carcinoma in August 2016

Mehra R, presented 2016 ASCO

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

THE LANCET Oncology

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

PD-1/PD-L1 blockade

PD-1/PD-L1 blockade in mBrCa

Trial Characteristics	PD-L1 Status	Drug	Author	Ref.	n	OR	CR
KEYNOTE-12 **mTNBC**	PD-L1+ (≥1%)	pembrolizumab	Nanda	JCO 2016	27	5 (18.5%)	1
KEYNOTE-28 **ER+/Her2-**	PD-L1+ (≥1%)	pembrolizumab	Rugo	SABCS 2015	25	3 (12%)	0
KEYNOTE-86 Cohort A **mTNBC** (refractory)	N/A	pembrolizumab	Adams	ASCO 2017	170	8 (4.7%)	1
KEYNOTE-86 Cohort B **mTNBC** (1st line)	PD-L1+ (≥1%)	pembrolizumab	Adams	ASCO 2017	52	12 (23%)	2
JAVELIN Phase Ib Subgroup: **mTNBC** Sub-subgroup: PD-L1+	N/A (≥10%)	avelumab	Dirix	SABCS 2016*	168 58 9	8 (4.8%) 5 (8.6%) 4 (44%)	1 0 0
mTNBC Subgroup: 1st line Subgroup: PD-L1+	N/A (≥5%)	atezolizumab	Schmid	AACR 2017	112 19 71	11 (10%) 5 (26%) 9 (13%)	3 2 3

N/A: accepted patients regardless of PD-L1 status
* Initial data presented by Dirix, updated in material requested from EMD/Serrano

Pembrolizumab in Gastric Cancer

- Part of KEYNOTE-012
- Required ≥ 1% PD-L1 staining (65/162, 40%)
- 10 mg/kg q2w
- 39 patients
- OR 22%
- Grade ≥ 3 AE 10%

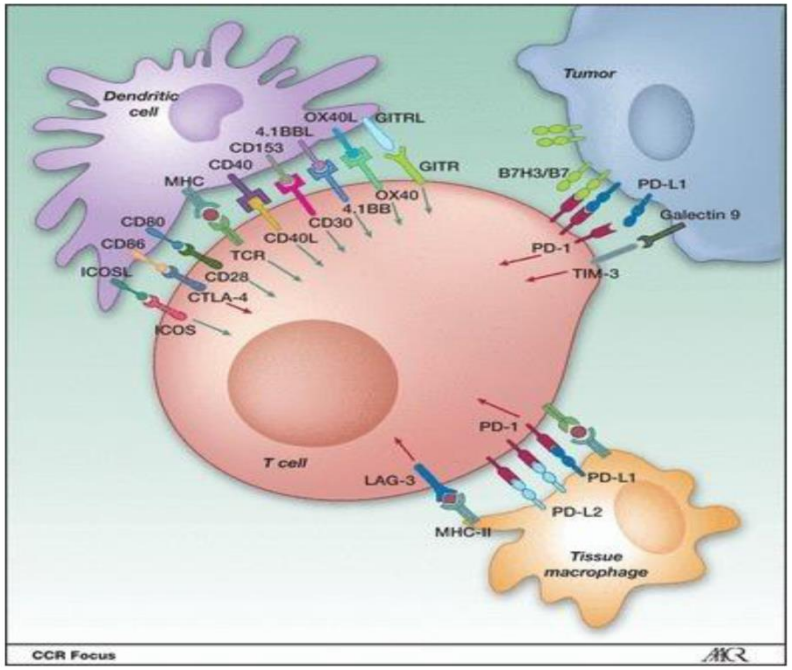
PD-1/PD-L1 blockade

PD-1/PD-L1 blockade at ASCO 2016/7

Disease	Drug	Author	n	OR	CR
Sarcoma	nivolumab	Paoluzzi	14	3 (21%)	0
Uterine leiomyosarcoma	nivolumab	George	12	0	0
Small cell lung cancer	nivo3 nivo1+ipi3 nivo3+ipi1	Antonia	98 61 54	10 (10%) 14 (23%) 10 (19%)	0 2 0
Salivary gland cancer	pembrolizumab	Cohen	26	3 (11.5%)	0
Cervical cancer	pembrolizumab	Frenel	24	4 (17%)	0
Endometrial cancer	pembrolizumab	Ott	24	3 (13%)	0
Esophageal cancer	pembrolizumab	Doi	23	7 (30%)	0
Thyroid cancer	pembrolizumab	Mehnert	22	2 (9%)	0
Gastric/GEJ	avelumab	Chung	151	14 (9%)	2
Adrenocortical cancer	avelumab	Le Tourneau	37	2/19 (10%)	0
Ovarian cancer	avelumab	Disis	124	12 (9.7%)	0
Mesothelioma	avelumab	Hassan	53	5 (9.4%)	0
Hepatocellular (liver) cancer	durvalumab	Wainberg	39	4 (10%)	0
Glioblastoma	durvalumab	Reardon	30	4 (13%)	0

Checkpoint modulation

Checkpoint Modulation



Questions?