

# Immune checkpoint Blockade

NCI CCR TRACO

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September 14, 2016

# 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



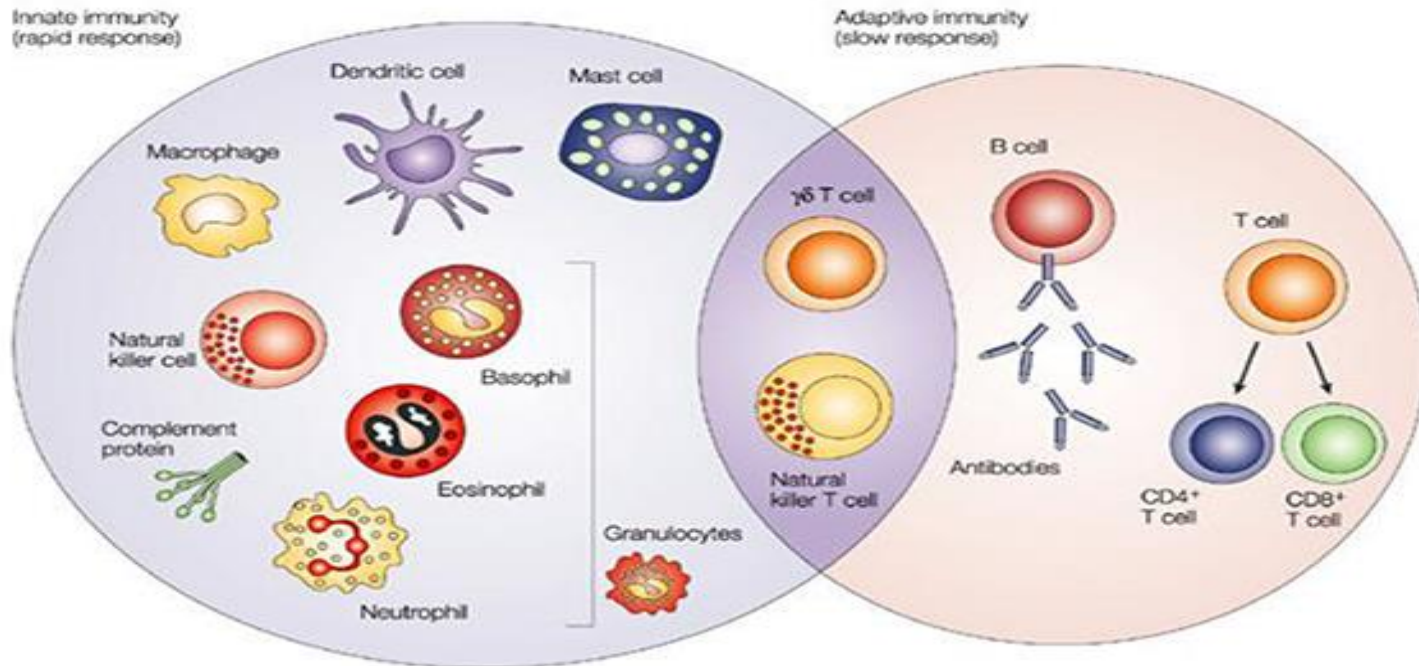
# Cancer Immunotherapy

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

## Cells of the Immune System



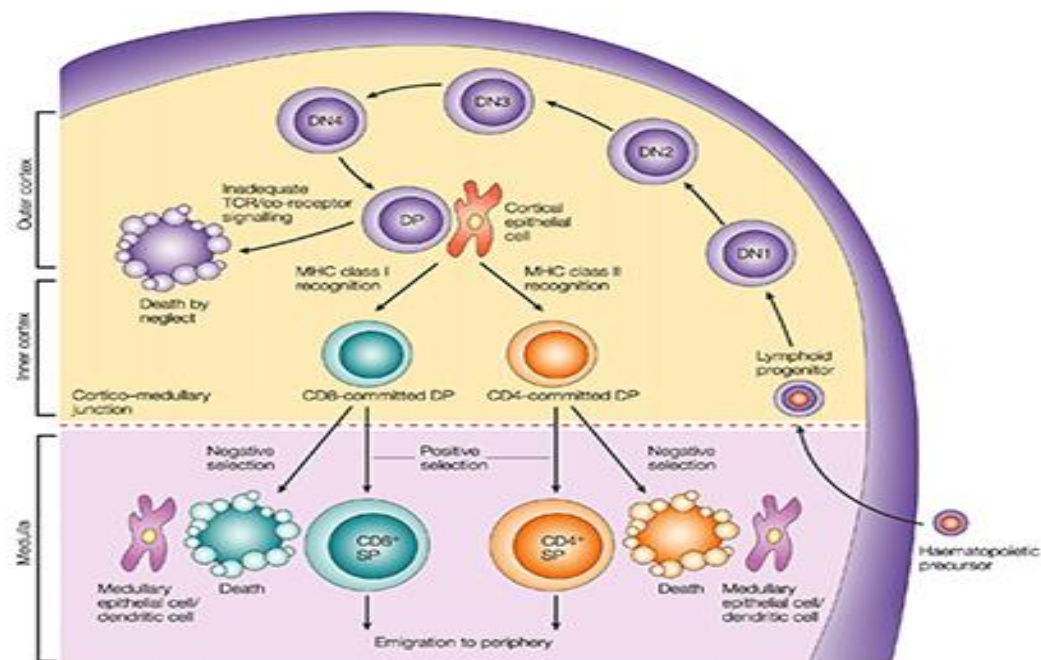
Nature Reviews | Cancer

Dranoff 2004

- Checkpoint blockade primarily affects T cells

# T cell birth

## T cell “birth”



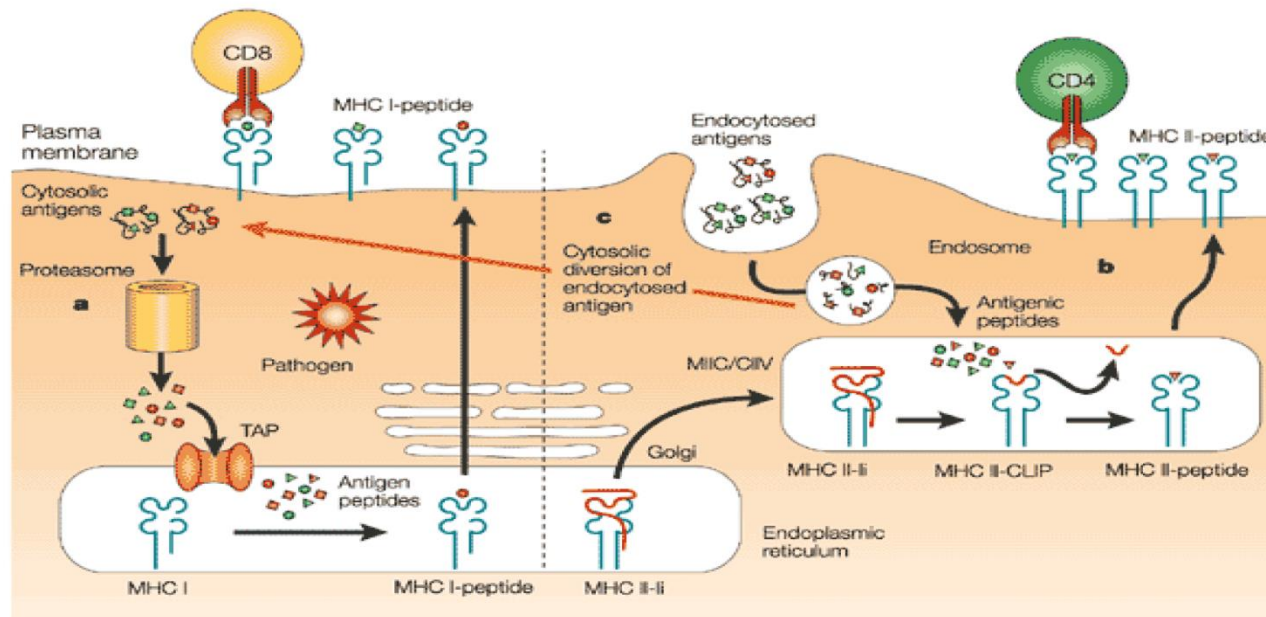
Nature Reviews | Immunology

Germain 2002

- Builds a repertoire of T cells

# T cell activation

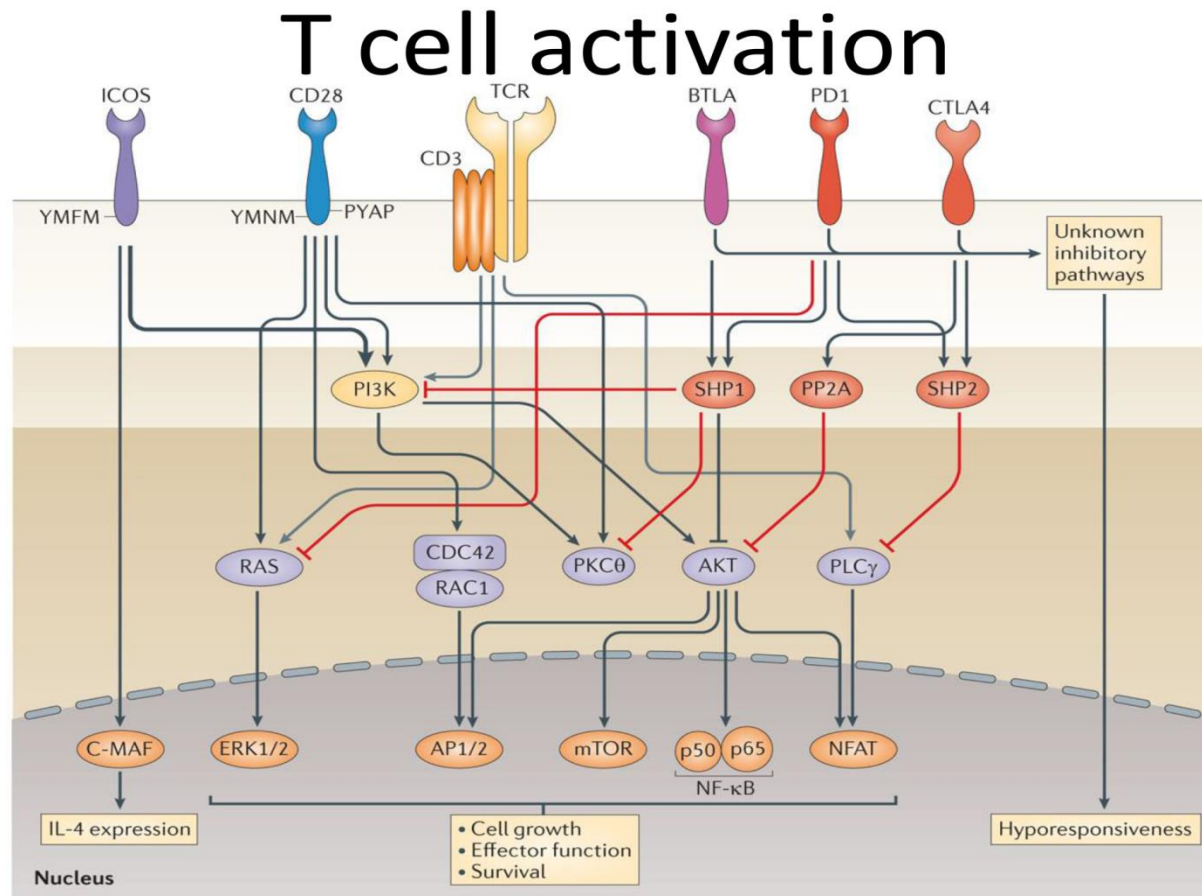
## T cell activation



Nature Reviews | Immunology  
Heath 2001

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

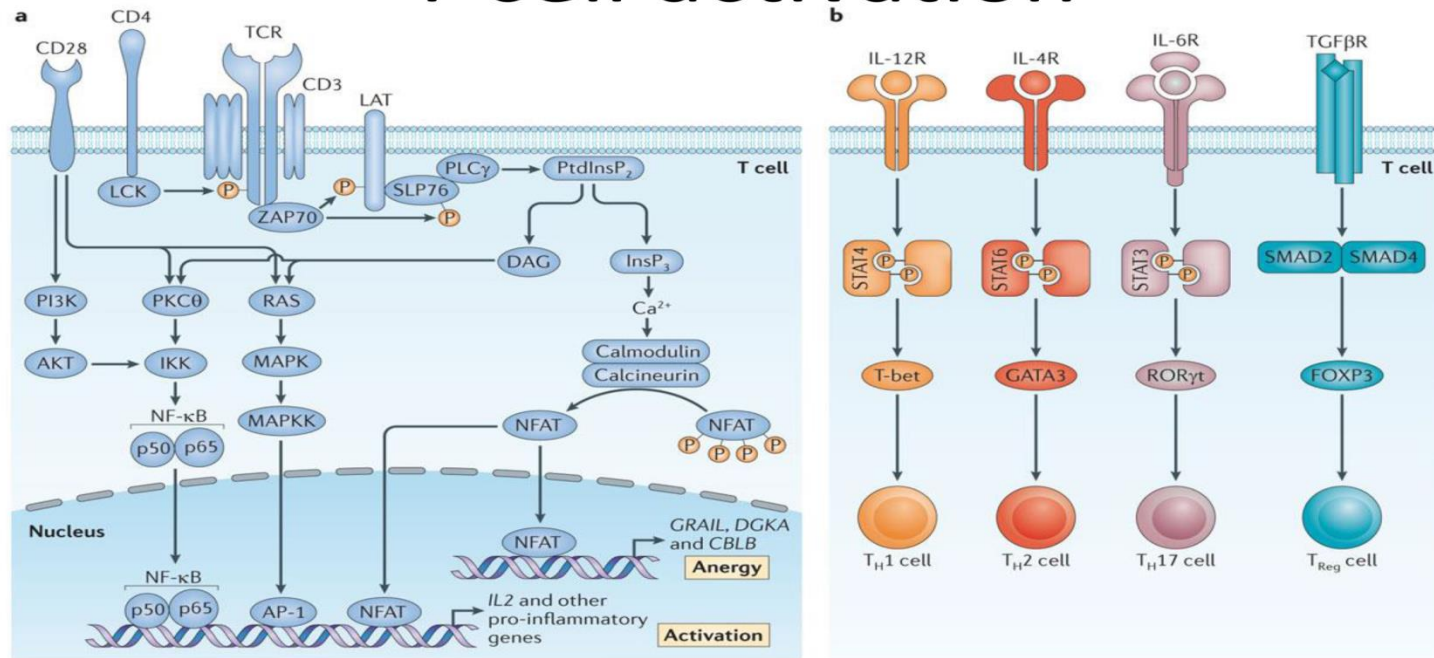
# T cell activation



- Signal 2: Activation vs. Anergy

# T cell activation

## T cell activation



Nature Reviews | Immunology

Pollizzi 2014

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

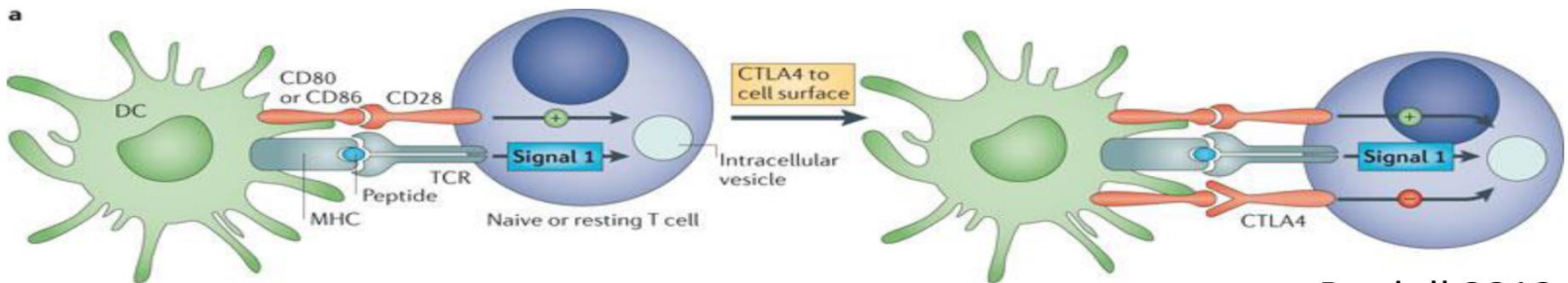
# The role of Signal 2 checkpoints

- 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

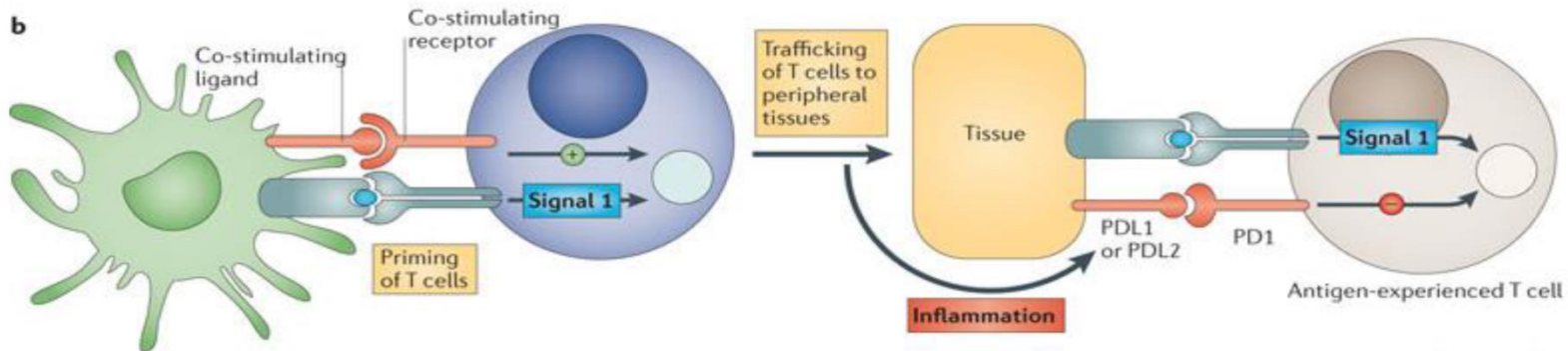


Pardoll 2012

- 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



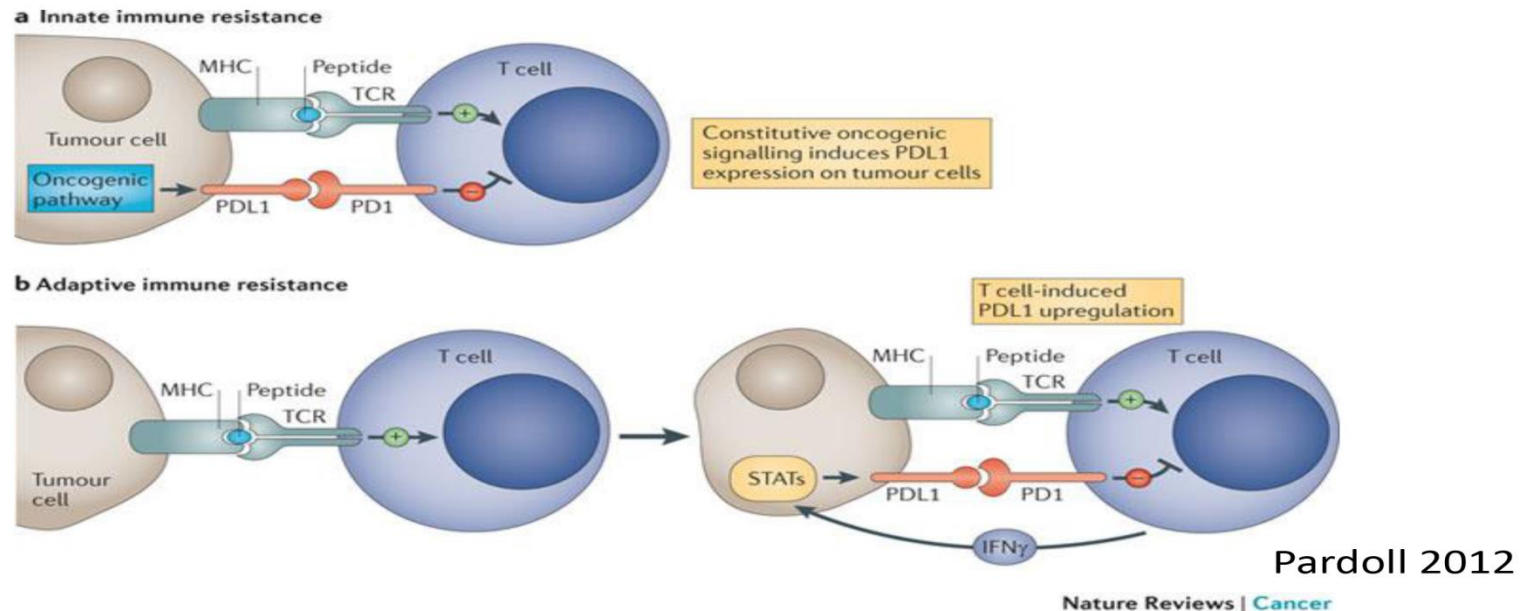
Nature Reviews | **Cancer**  
Pardoll 2012

- 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

## 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 $\gamma$

# Checkpoint blockade

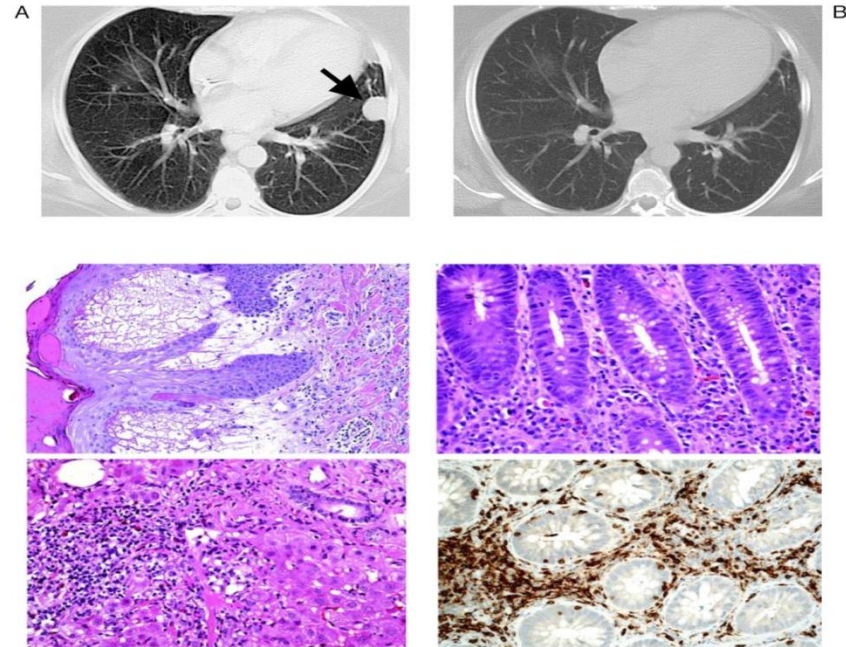
## Checkpoint Blockade

- 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%

# Checkpoint Blockade

## Checkpoint Blockade @ NCI

- $\alpha$ 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

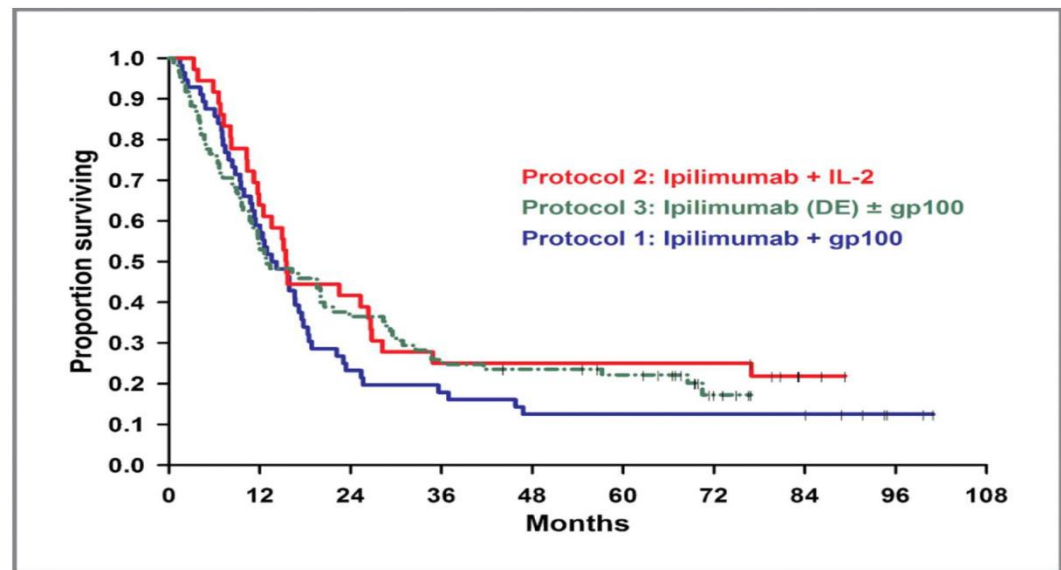
### Melanoma, $p=0.0004$

	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%

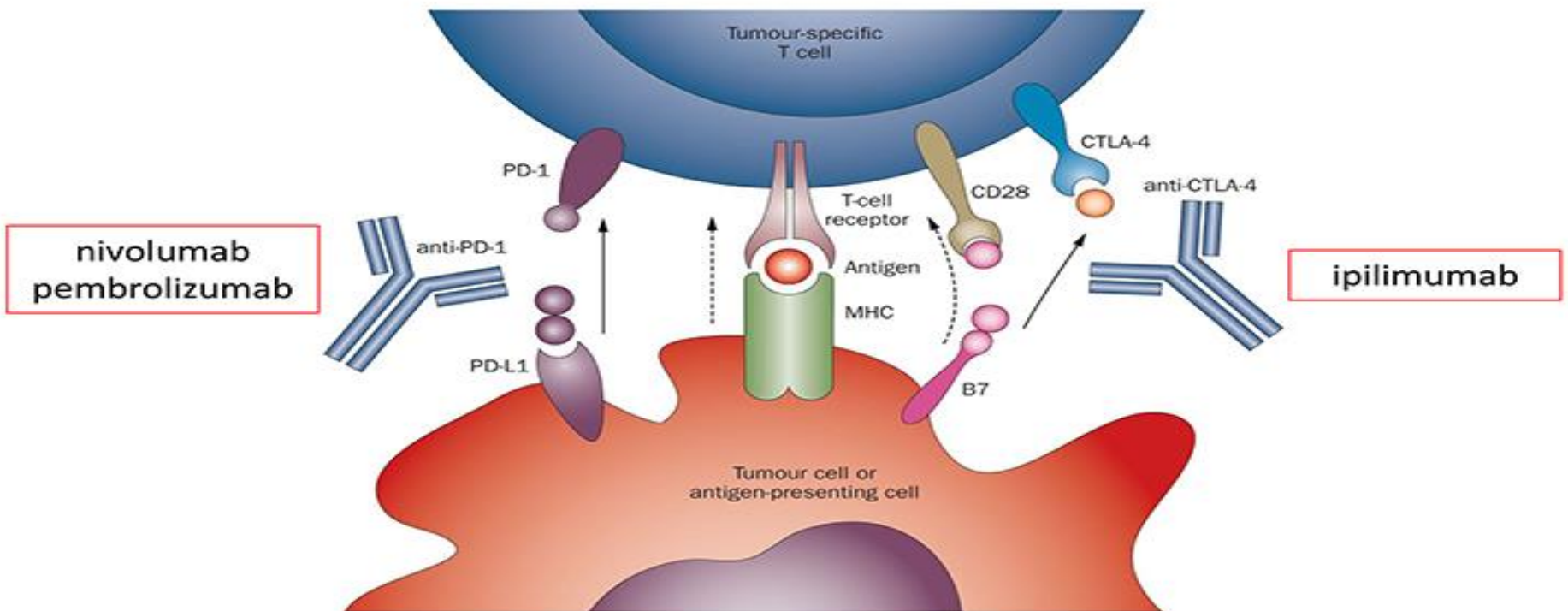


Prieto PA 2012



# Checkpoint blockade

## Checkpoint blockade in melanoma

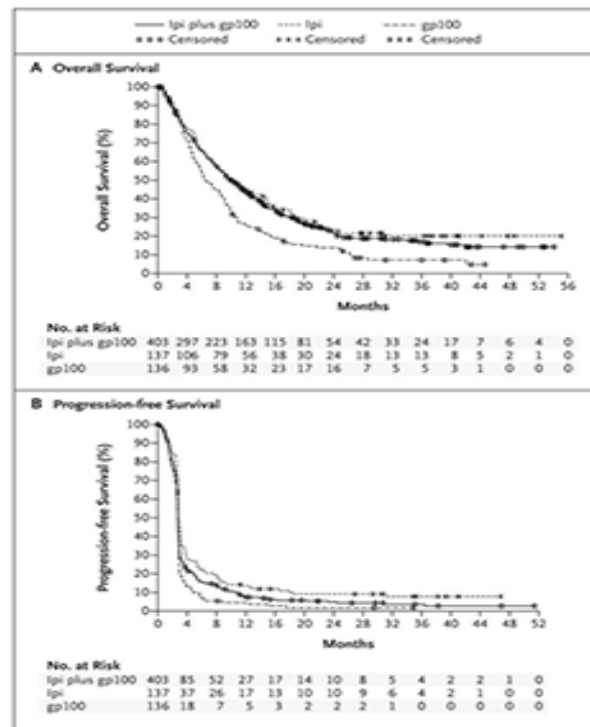


Drake C 2013

# Ipilimumab

## Ipilimumab for melanoma

- 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



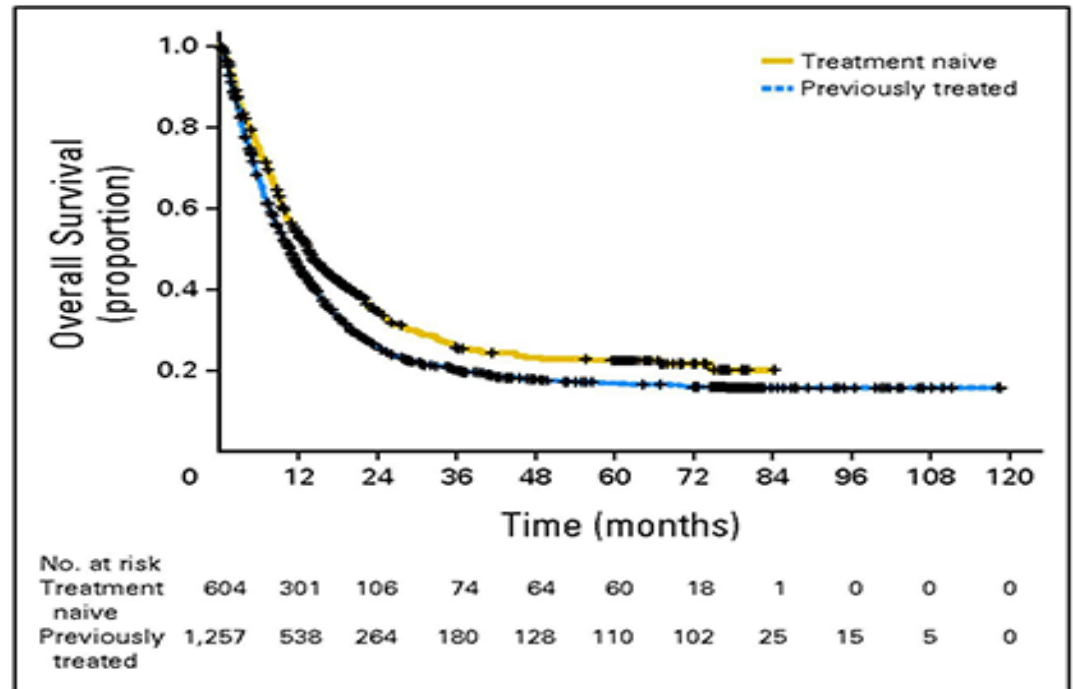
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JOURNAL of MEDICINE



# Ipilimumab

## Ipilimumab for melanoma

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

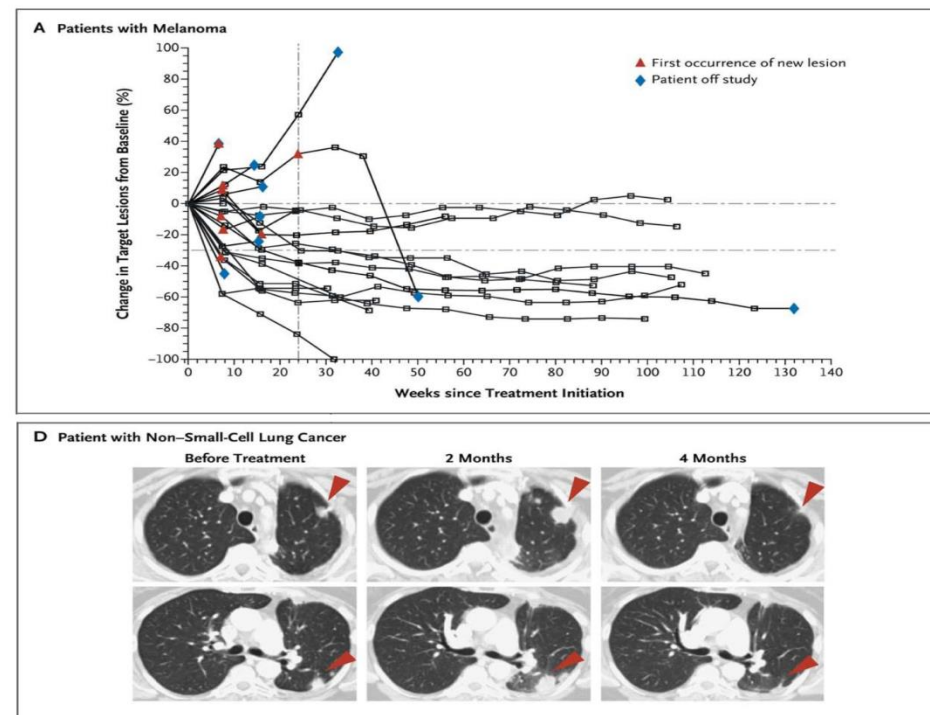


Schadendorf D 2015

# Nivolumab

## Nivolumab

- $\alpha$ PD-1
- Phase I dose escalation
- 0.1 mg/kg  $\rightarrow$  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%

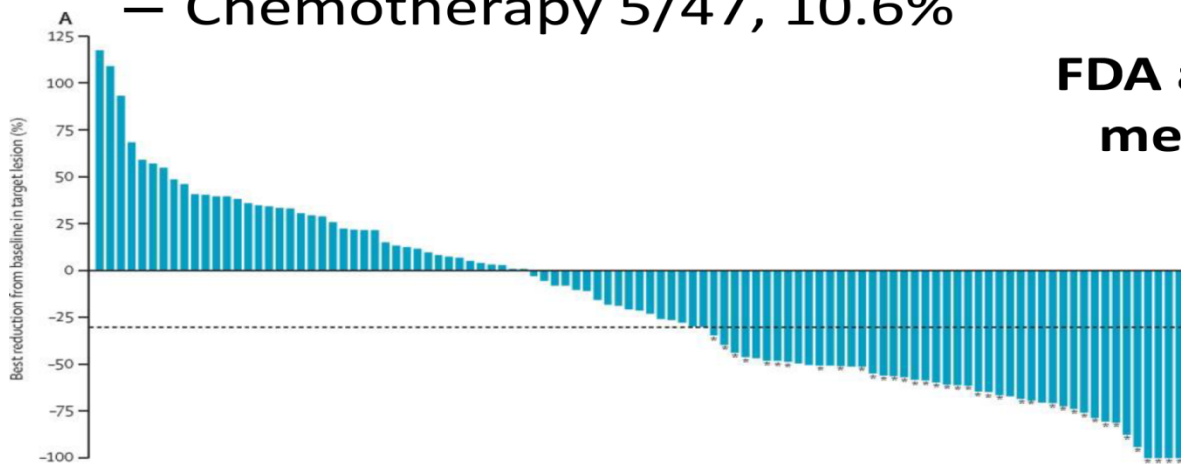


Topalian SL 2010

# 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%

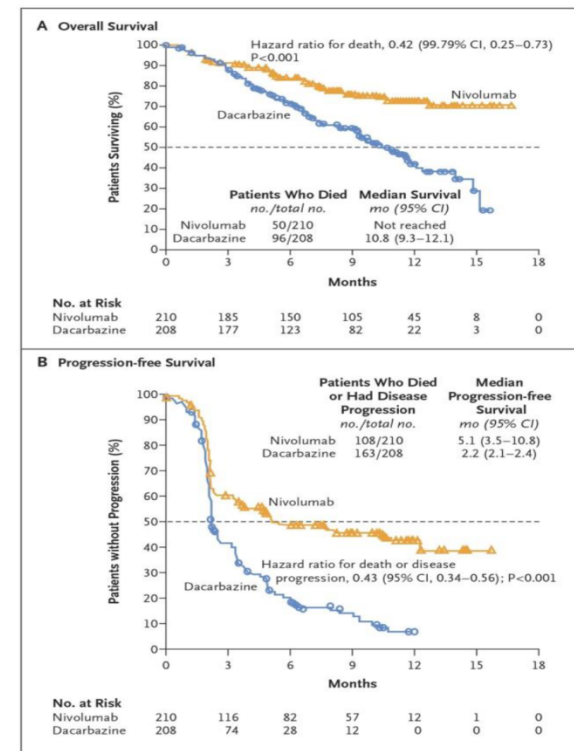


**FDA approval for refractory  
melanoma in December  
2014**

# 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%)



Robert C 2015

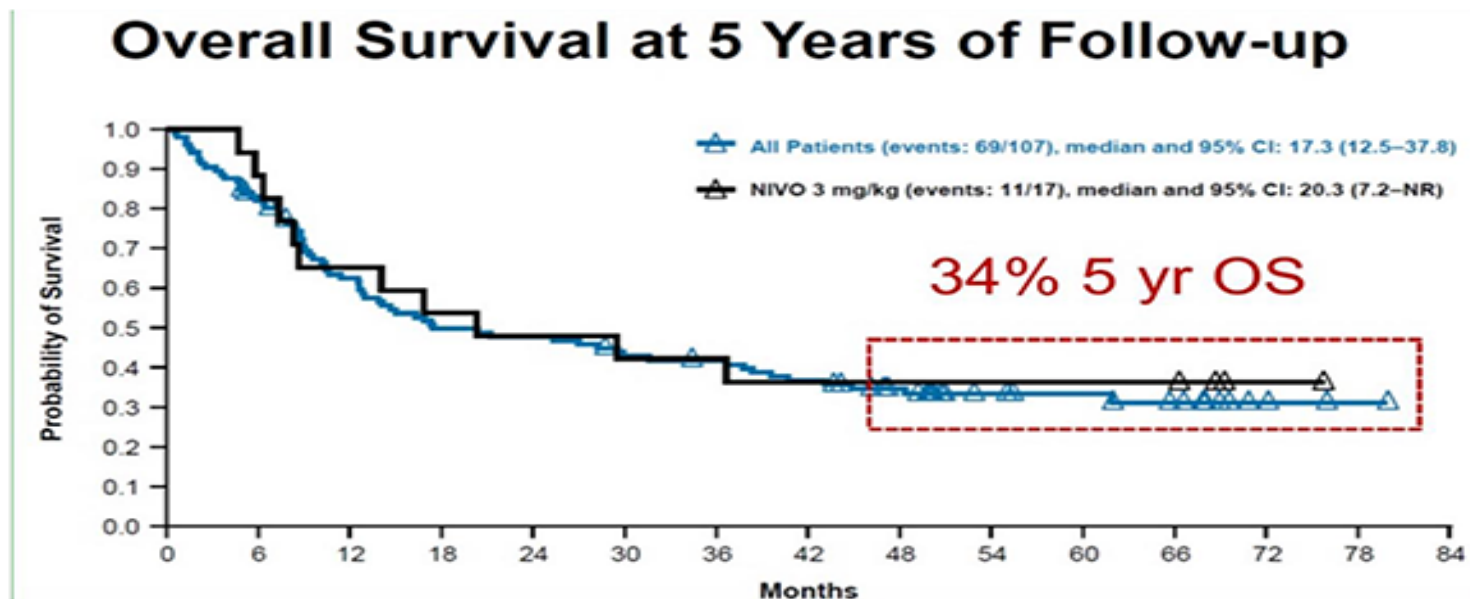


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# Nivolumab for melanoma

## Nivolumab for melanoma

- Updated survival
- “Tail of the curve”



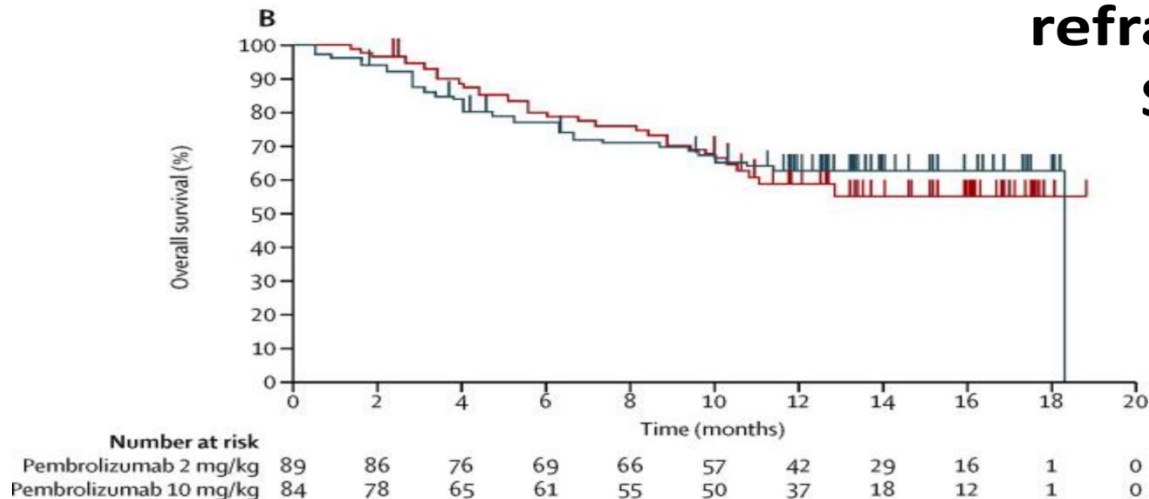
Hodi F  
(presented at AACR 2016)

# 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%

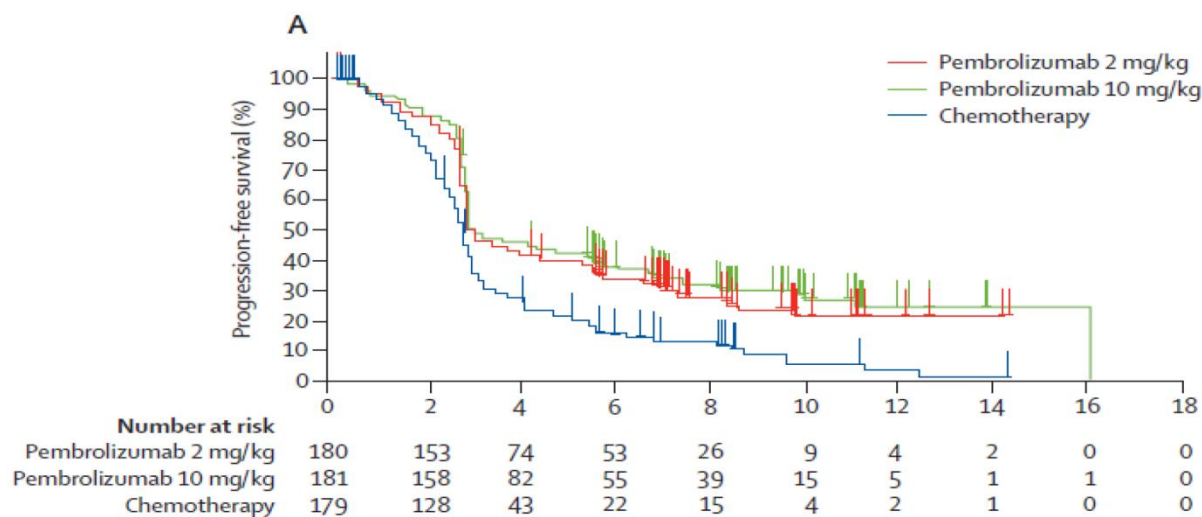
**FDA approval for  
refractory melanoma in  
September 2014**



# 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

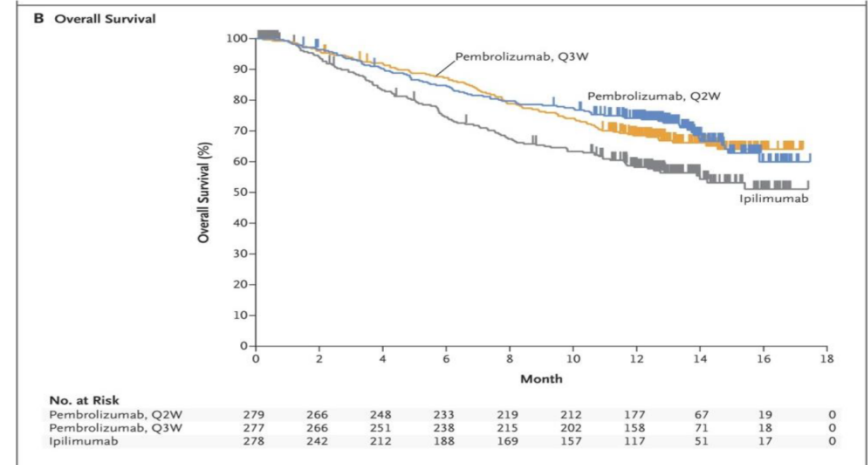
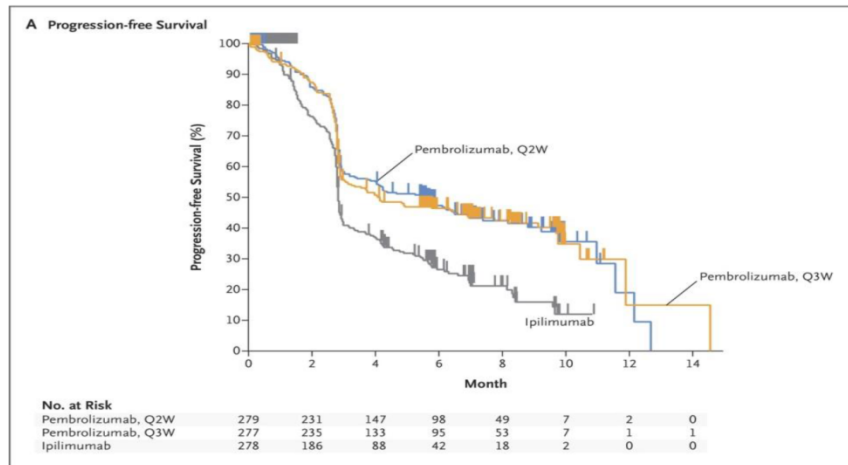


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# Pembrolizumab for melanoma

# Pembrolizumab for melanoma



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

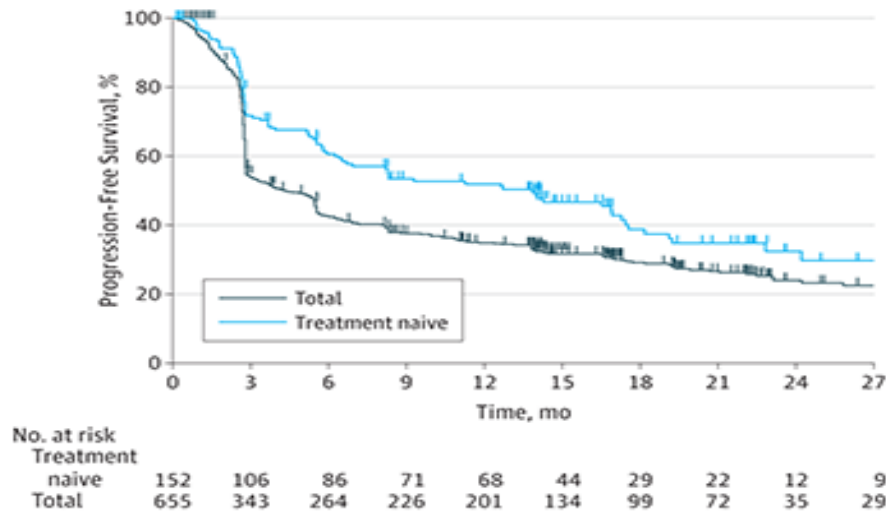
Robert C 2015

# Pembrolizumab for melanoma

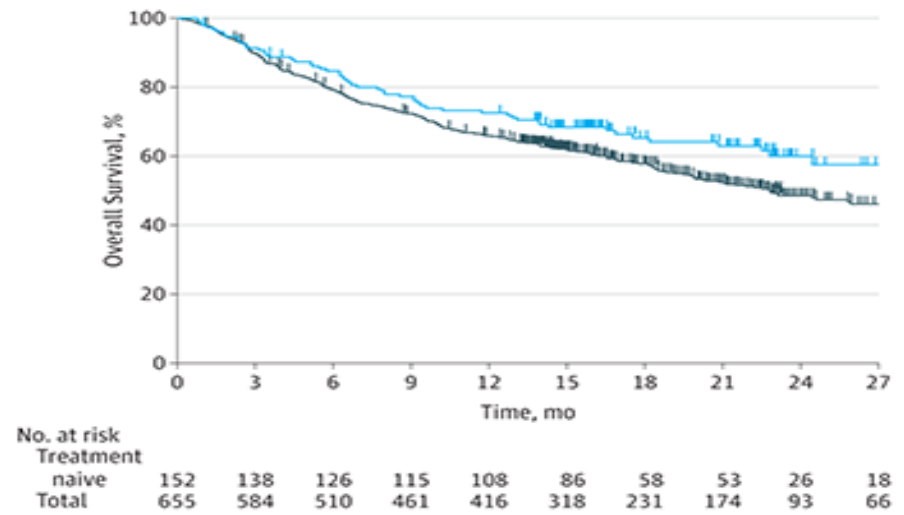
## Pembrolizumab for melanoma

- Updated survival
- “Tail of the curve”

Progression-free survival



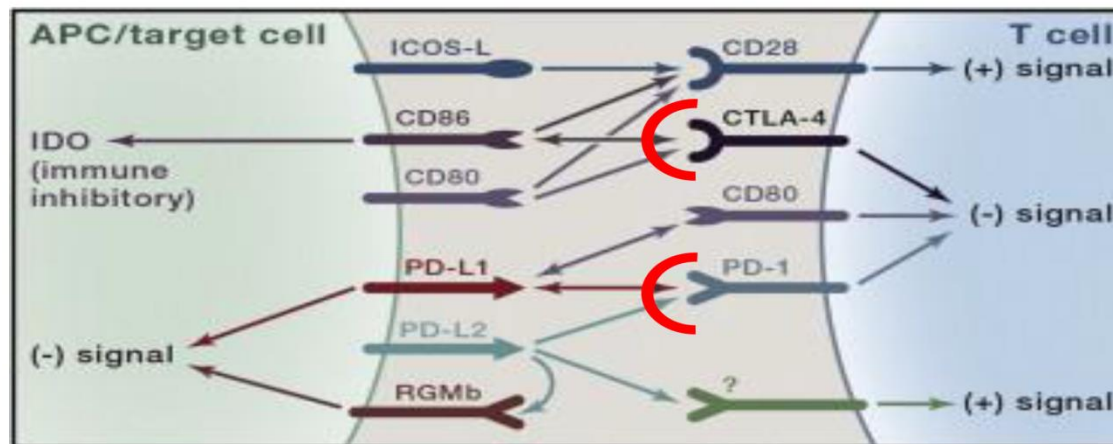
Overall survival



Ribas A 2016

# 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)	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

## 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. (%) <sup>*</sup>			
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 <sup>†</sup>			
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) <sup>‡</sup>	5.40 (2.02–5.72)	6.11 (5.59–10.58)	—
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

<sup>\*</sup> The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

<sup>†</sup> 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.

<sup>‡</sup> The comparison is with the ipilimumab group.

Larkin J 2015



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# Nivolumab/Ipilimumab

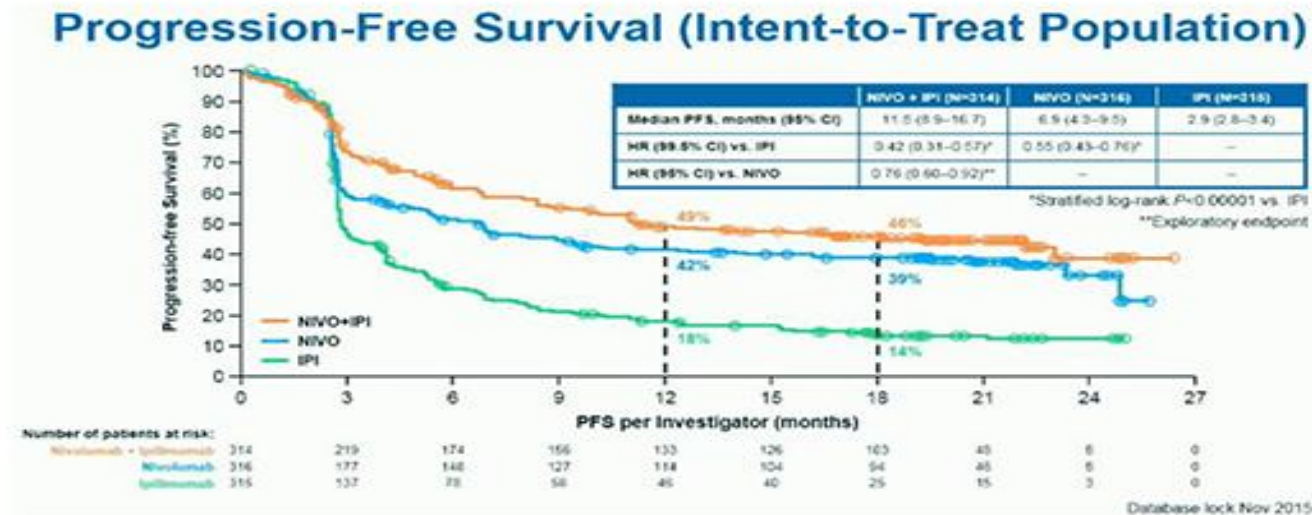
## Nivolumab/Ipilimumab for melanoma

	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

# Nivolumab/ipilimumab

## Nivolumab/Ipilimumab for melanoma -updated results-



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

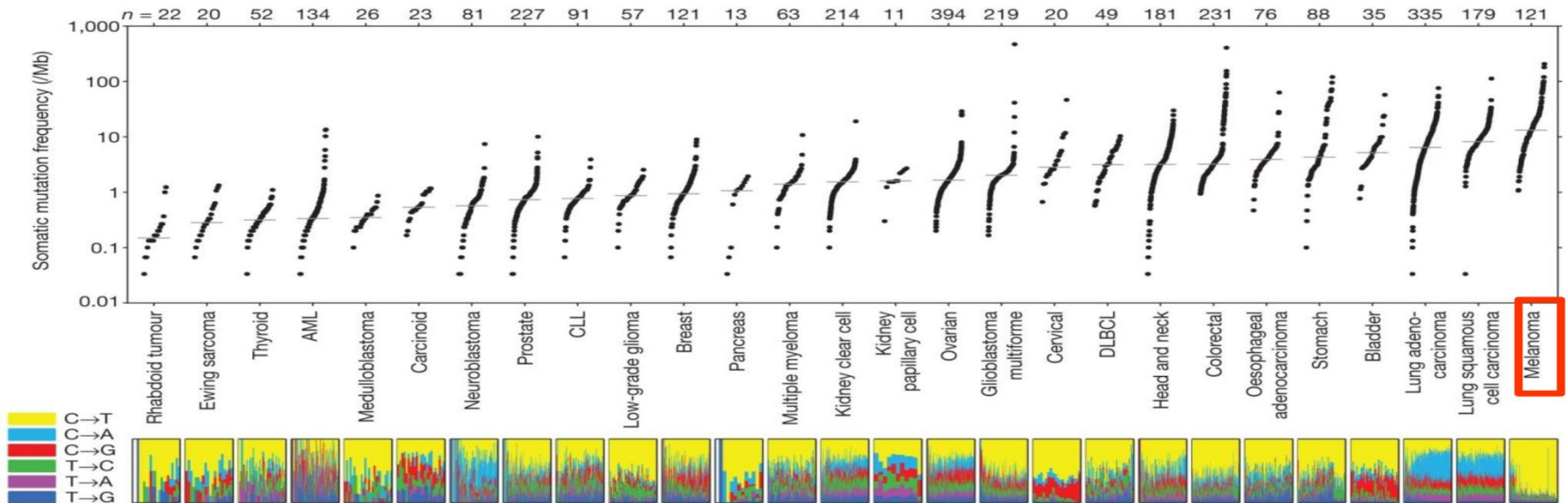
**FDA approval of  
combination for melanoma  
in January 2016**

Wolchok  
(presented at ASCO 2016)



# Melanoma

## Why melanoma?



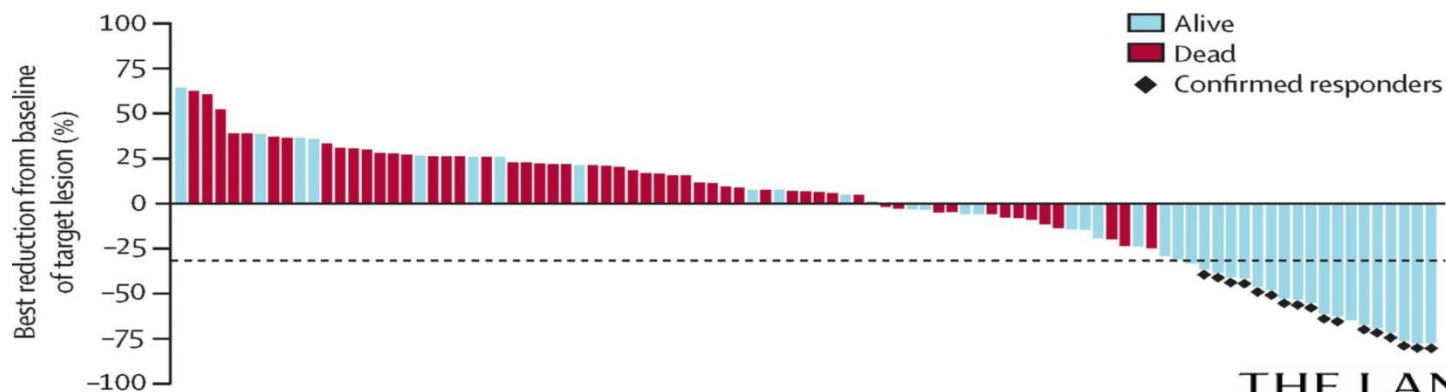
# Highly mutated tumors

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



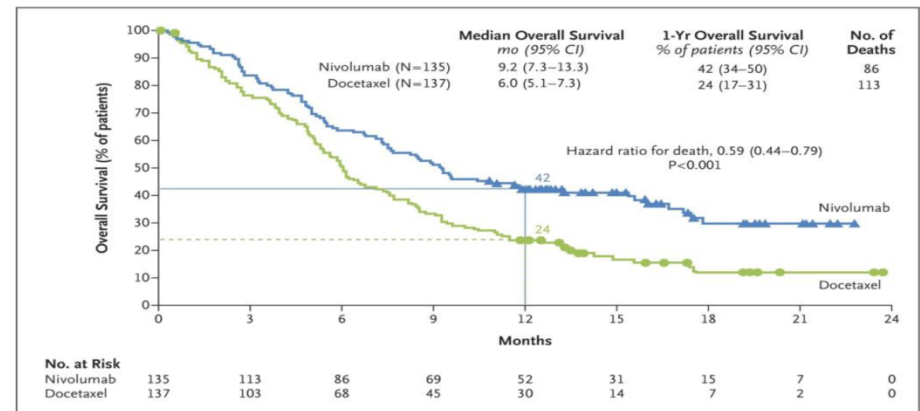
Rizvi NA 2015

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%)



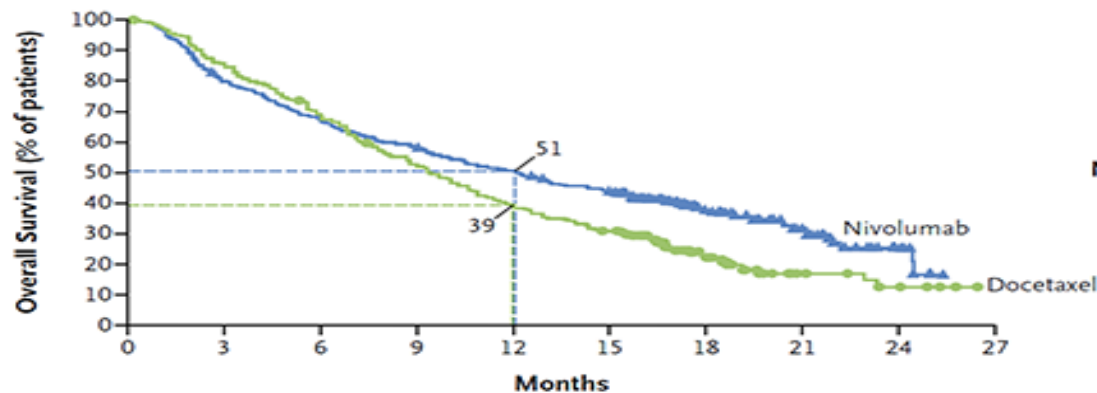
**FDA approval for  
refractory NSCLC in  
March 2015**

Brahmer 2015

# Nivolumab for NSCLC

## Nivolumab for NSCLC

A Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI) mo	1-Yr Overall Survival Rate (95% CI) %
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

No. at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

- 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



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# 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  $\geq 3$  AE
  - Dyspnea 3.8%
  - Pneumonitis 1.8% including a fatality

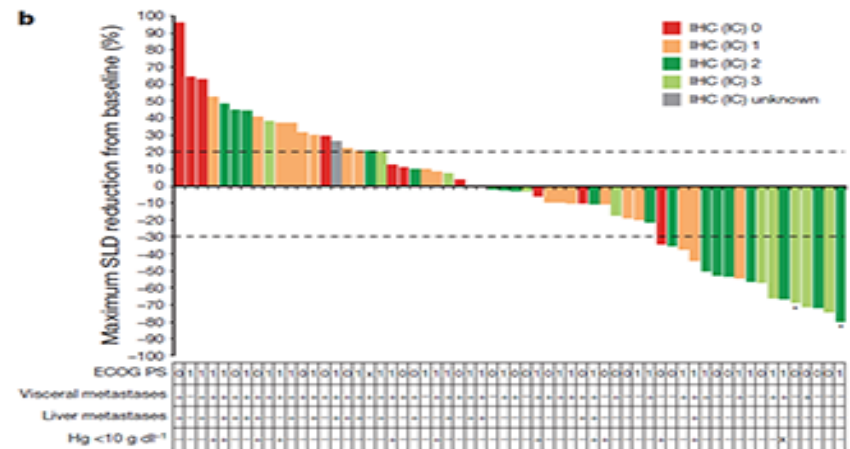
**FDA decision to  
be made  
October 2, 2015**

Garon EB 2015

# antiPD-L1

## $\alpha$ 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%



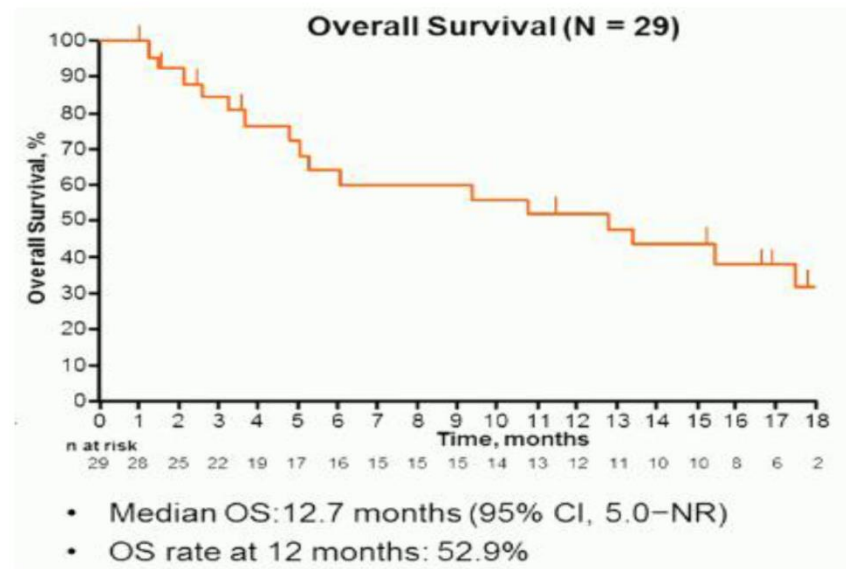
**FDA approval for  
urothelial cancer in  
May 2016**



# Urothelial Cancer

## Pembrolizumab in Urothelial Cancer

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

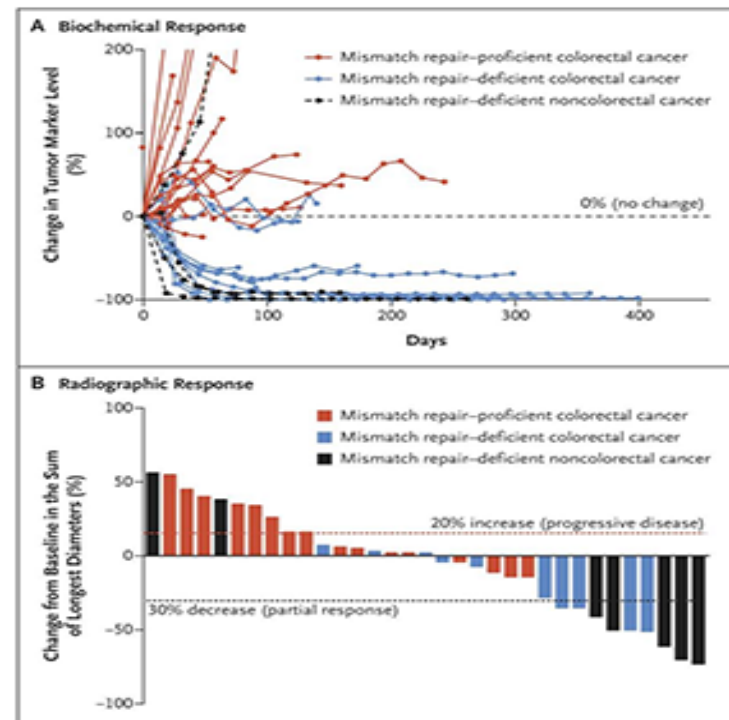


Abstract: Plimack E 2015

# MMR-deficient cancer

## Pembrolizumab for MMR-deficient cancer

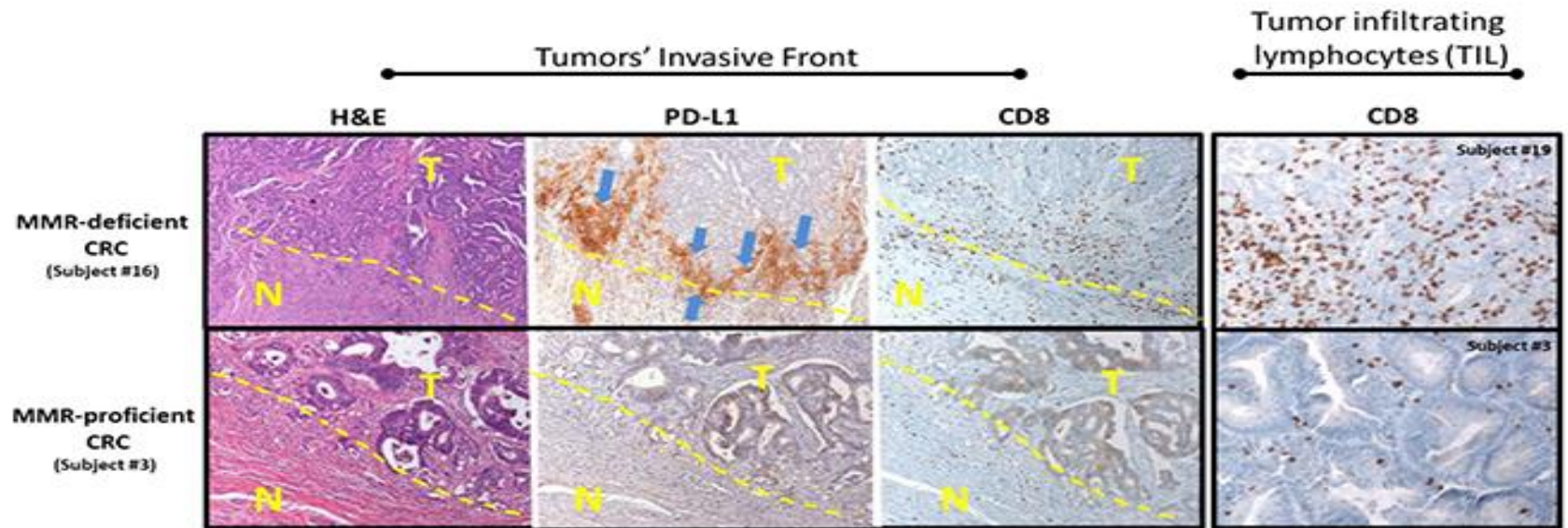
- Builds on hypothesis of neoantigens from somatic mutations
- Phase 2 study
- Three parallel cohorts
  - MMR-proficient CRC
  - MMR-deficient CRC
  - MMR-deficient other



Le DT 2015

# Tumor-stromal interface

## Pembrolizumab at the tumor-stroma interface



Le DT 2015



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# Checkpoint blockade

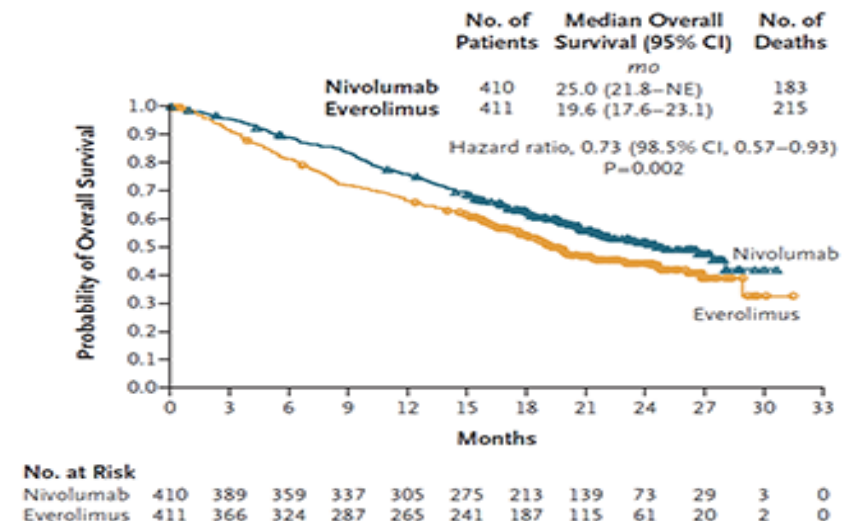
## Checkpoint Blockade

- 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



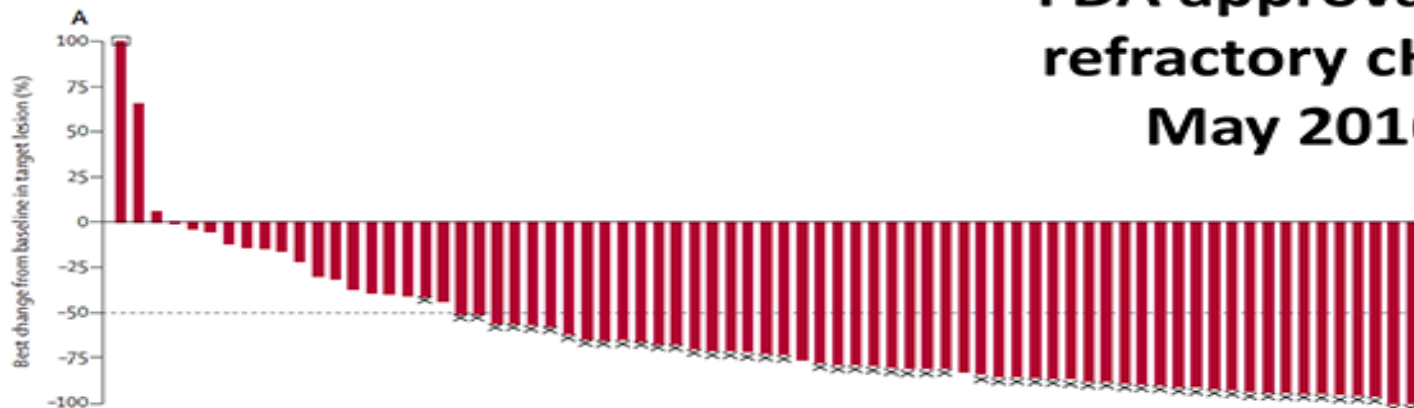
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# Hodgkin's lymphoma

## 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

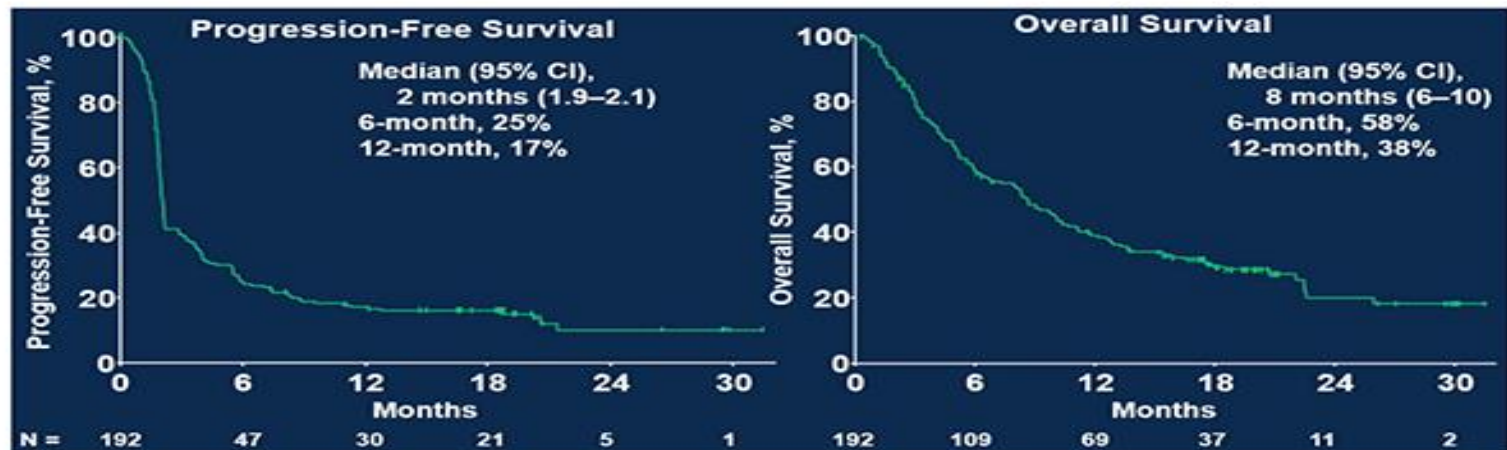
- Part of KEYNOTE-012
- No requirement for PD-L1 expression
- 200mg q3w
- 192 patients, HPV+ 45/192 (23%)

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	–



# Pembrolizumab

## Pembrolizumab in Head and Neck SCC



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

# 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

# Pembrolizumab in Breast Cancer

- Part of KEYNOTE 012
  - Triple Negative BC
  - PD-L1 (+) on IHC (65/111, 59%)
  - 10mg/kg q2w
  - 32 patients (27 evaluable)
  - OR 18.5%, CR 3.7% (1 pt)
  - Grade  $\geq 3$  AE 9.4%
- TNBC
  - PD-L1 (+) on IHC (20/105, 19%)

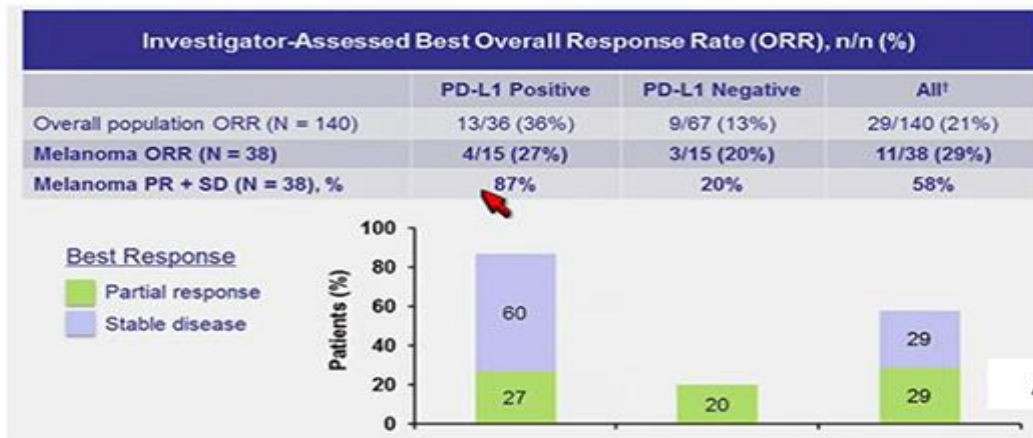
# Pembrolizumab in Gastric Cancer

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

# Anti-PD-L1in

## $\alpha$ PD-L1 in melanoma

- MPDL3280A
- Estimated prevalence of PD-L1 staining 40%
- Immune-related Grade 3/4 AE in 2 patients (5%)

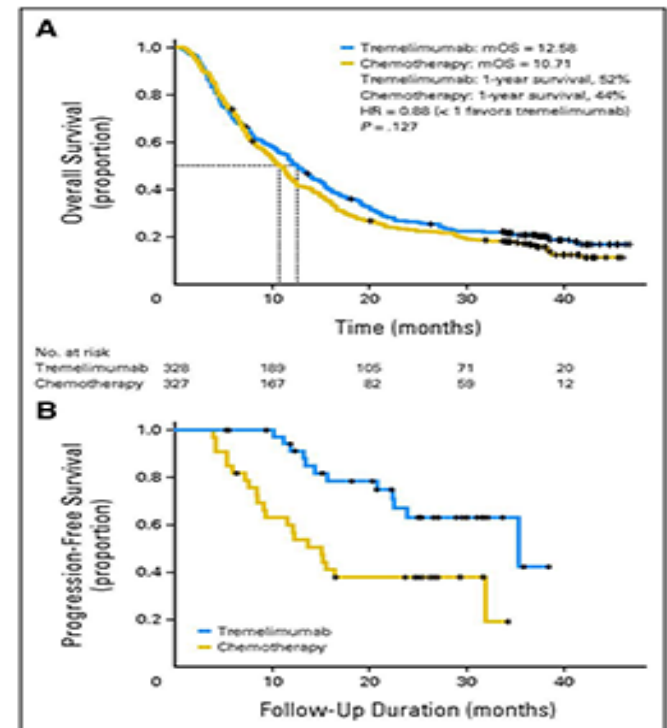


Abstract: Hamid O 2013

# Trimelimumab

## Tremelimumab

- $\alpha$ CTLA-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



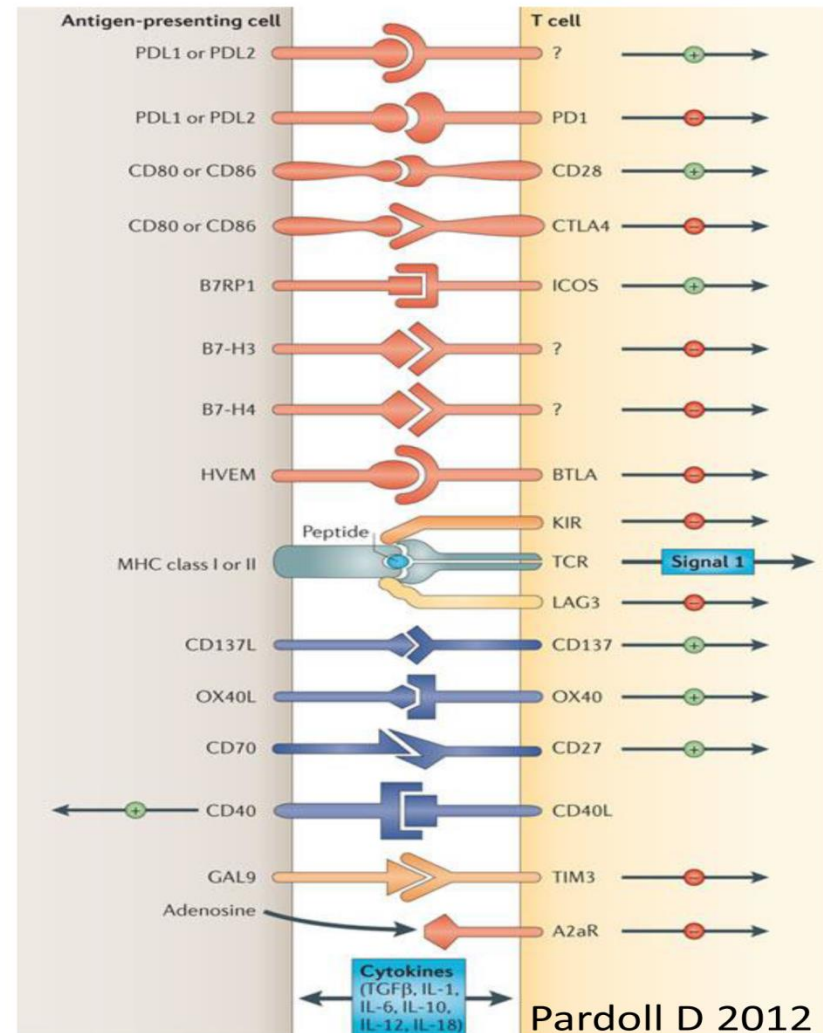
Ribas A 2013

# Checkpoint pipeline

## Checkpoint Pipeline

Target	Biological function	Antibody or Ig fusion protein	State of clinical development*
CTLA4	Inhibitory receptor	Ipilimumab	FDA approved for melanoma, Phase II and Phase III trials ongoing for multiple cancers
		Tremelimumab	Previously tested in a Phase III trial of patients with melanoma; not currently active
PD1	Inhibitory receptor	MDX-1106 (also known as BMS-936558)	Phase I/II trials in patients with melanoma and renal and lung cancers
		MK3475	Phase I trial in multiple cancers
		CT-011 <sup>†</sup>	Phase I trial in multiple cancers
		AMP-224 <sup>§</sup>	Phase I trial in multiple cancers
		Multiple mAbs	Phase I trials planned for 2012
PDL1	Ligand for PD1	MDX-1105	Phase I trial in multiple cancers
LAG3	Inhibitory receptor	IMP321 <sup>  </sup>	Phase III trial in breast cancer
		Multiple mAbs	Preclinical development
B7-H3	Inhibitory ligand	MGA271	Phase I trial in multiple cancers
B7-H4	Inhibitory ligand		Preclinical development
TIM3	Inhibitory receptor		Preclinical development

CTLA4, cytotoxic T-lymphocyte-associated antigen 4; FDA, US Food and Drug Administration; Ig, immunoglobulin; LAG3, lymphocyte activation gene 3; mAbs, monoclonal antibodies; PD1, programmed cell death protein 1; PDL, PD1 ligand; TIM3, T cell membrane protein 3. \*As of January 2012. <sup>†</sup>PD1 specificity not validated in any published material. <sup>§</sup>PDL2-Ig fusion protein. <sup>||</sup>LAG3-Ig fusion protein.

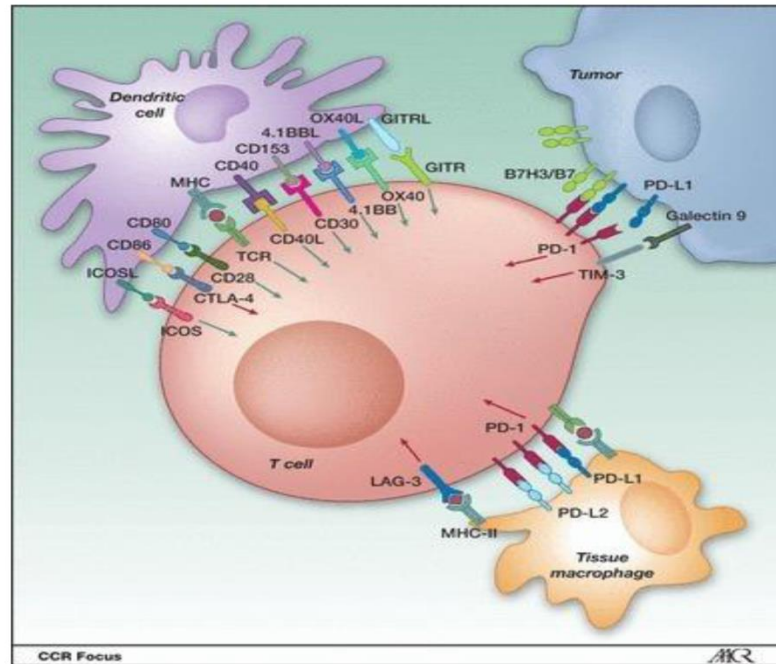


Pardoll D 2012



# Checkpoint modulation

## Checkpoint Modulation



Questions?