Checkpoint Modulation

NCI CCR TRACO
Stephanie L. Goff, MD
September 21, 2015

Objectives

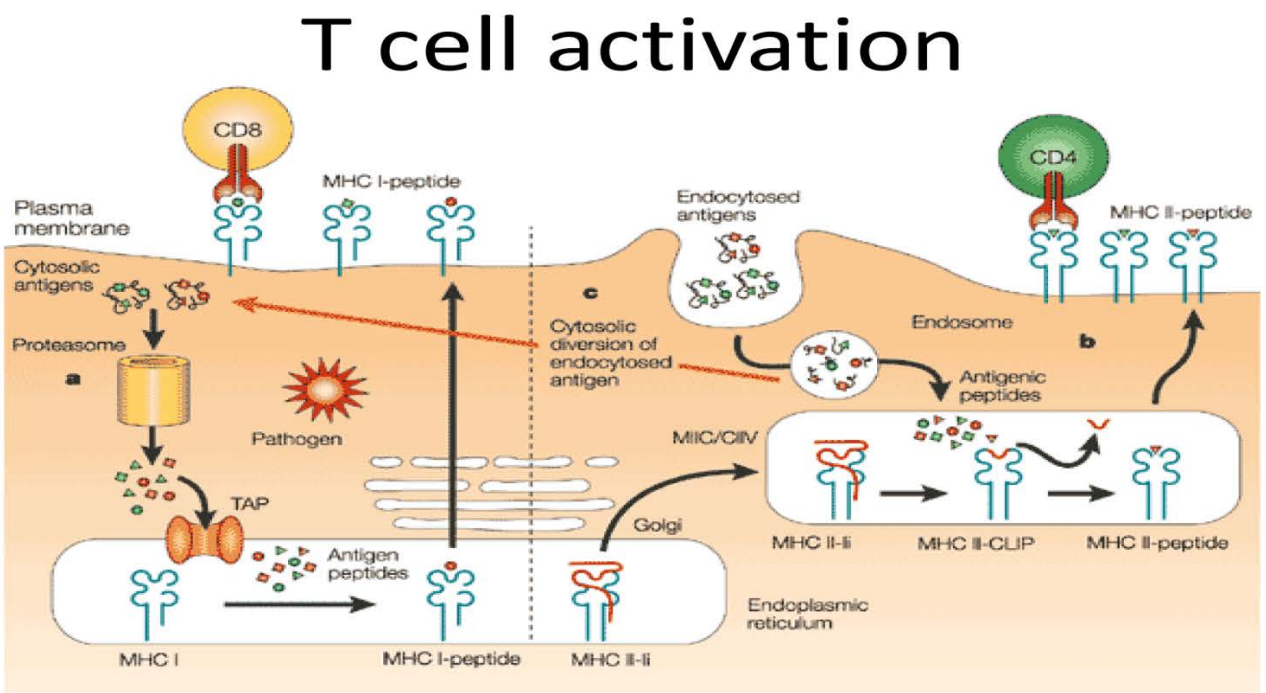
- Mechanism of action
- Early clinical experience and the discovery of immune related adverse events
- FDA-approved checkpoint modulators
  - Ipilimumab
  - Nivolumab
  - Pembrolizumab
- Experimental checkpoint modulators

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)

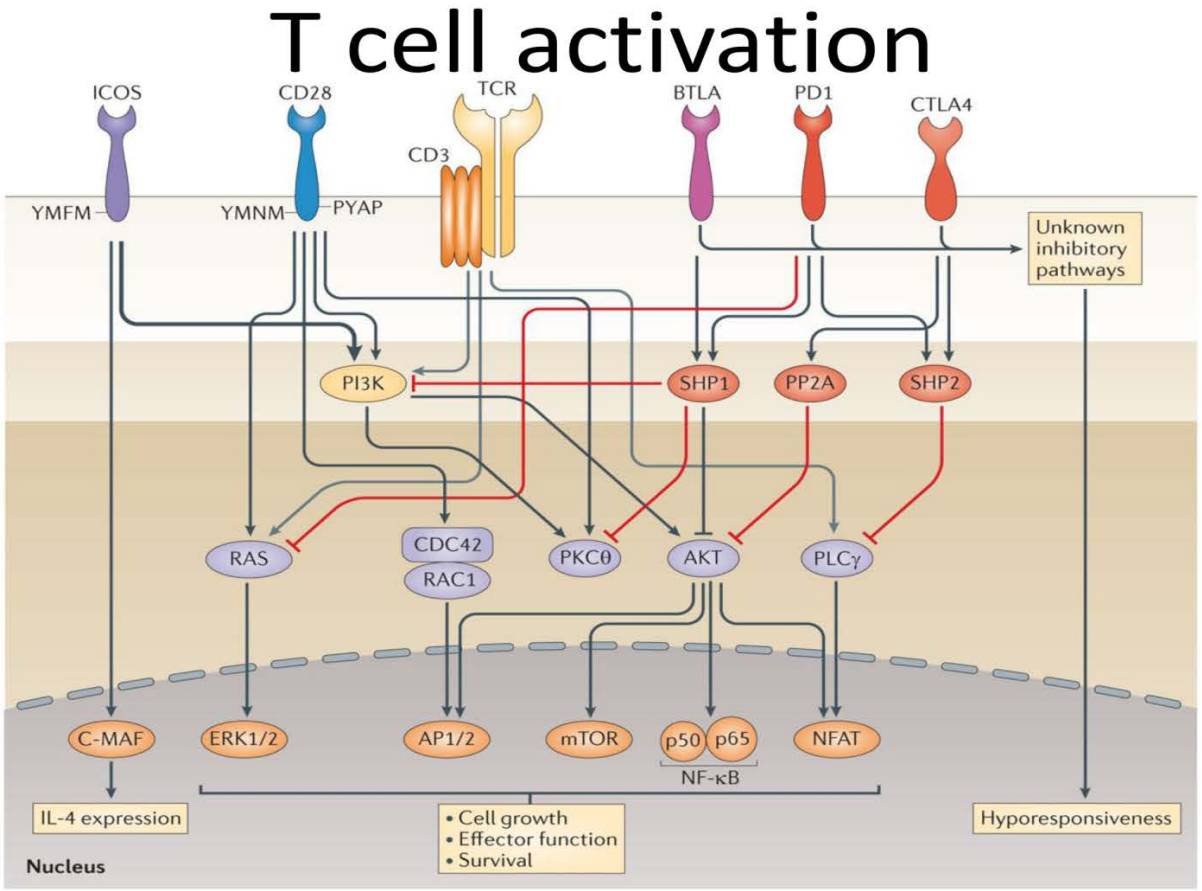
T cell activation



Nature Reviews | Immunology
Heath 2001

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

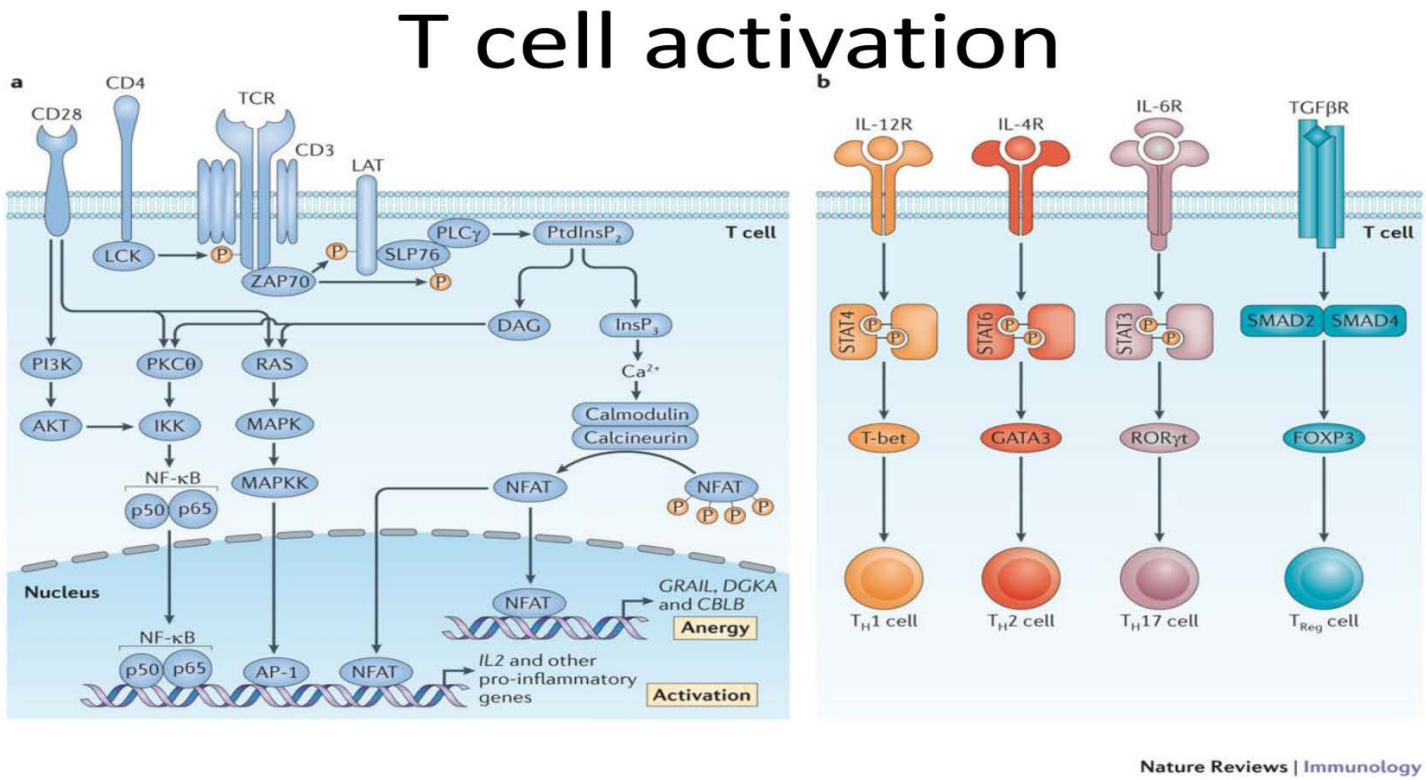
T cell activation



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

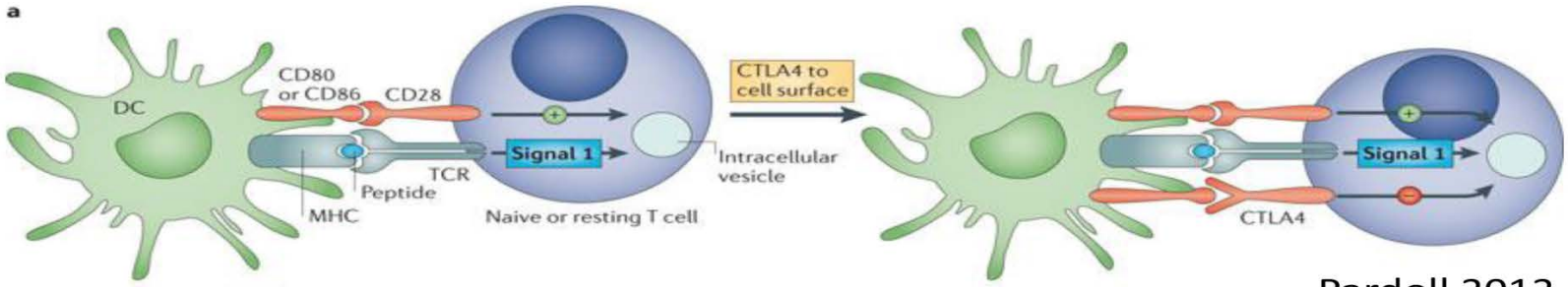
The role of Signal 2 checkpoints

- 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

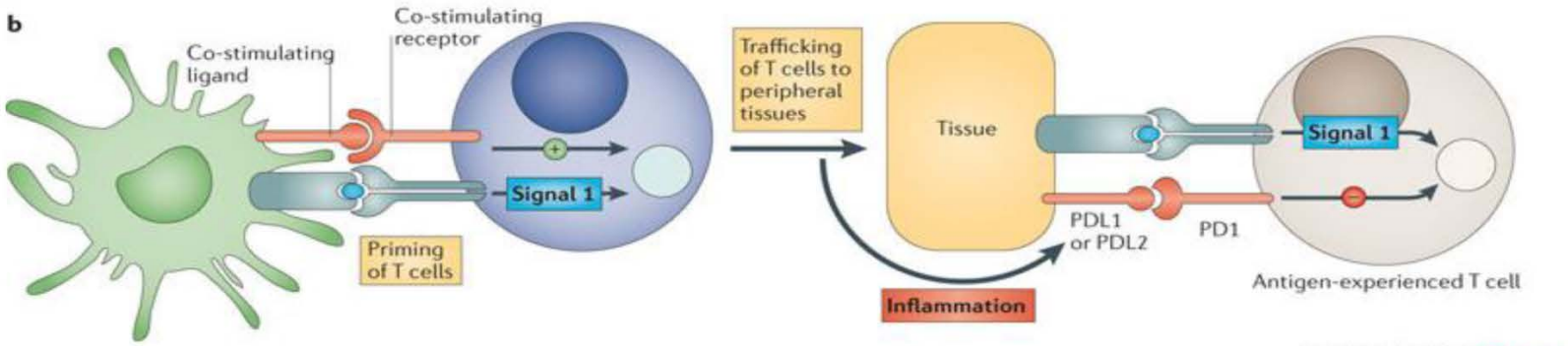


Pardoll 2012

- 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

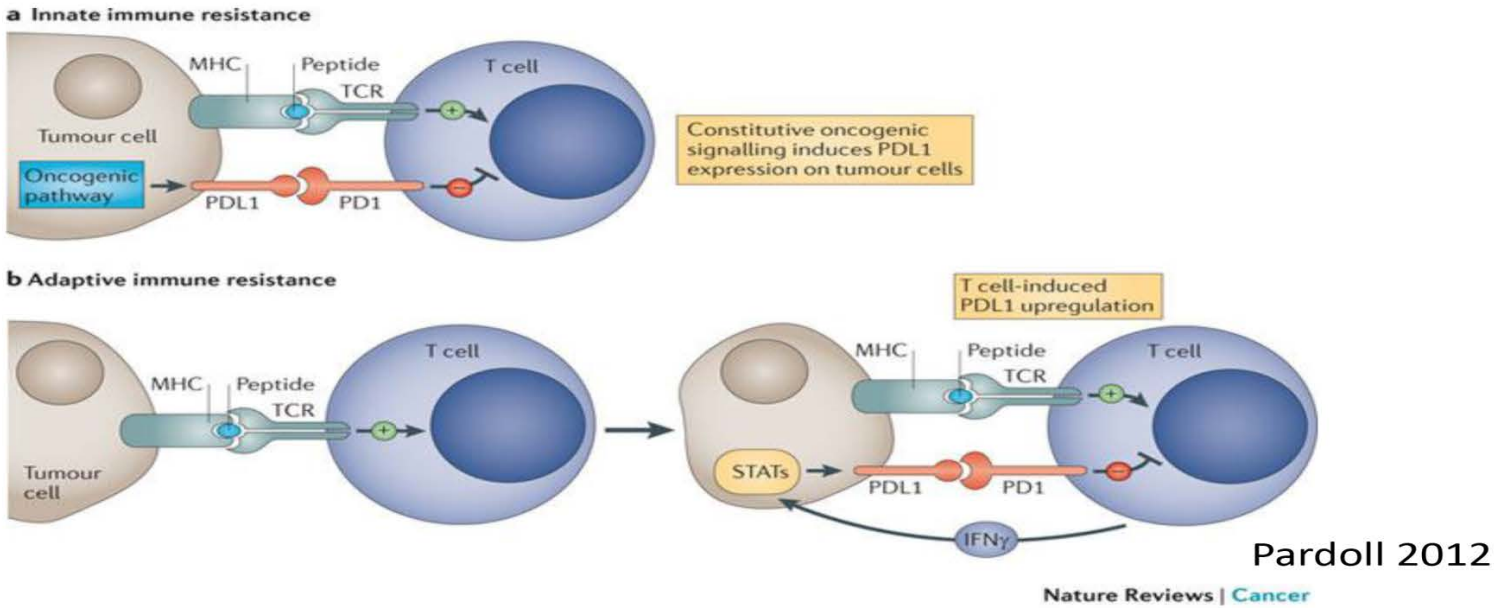


Pardoll 2012

- 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

PD-1/PD-L1 in cancer



Pardoll 2012

- 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%

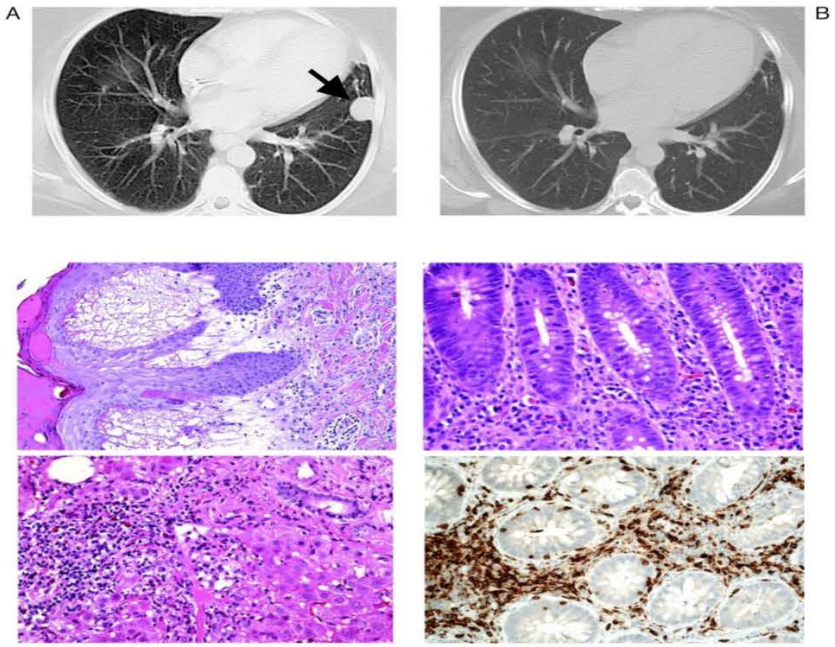
Smith FO Clin Cancer Res 2008

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

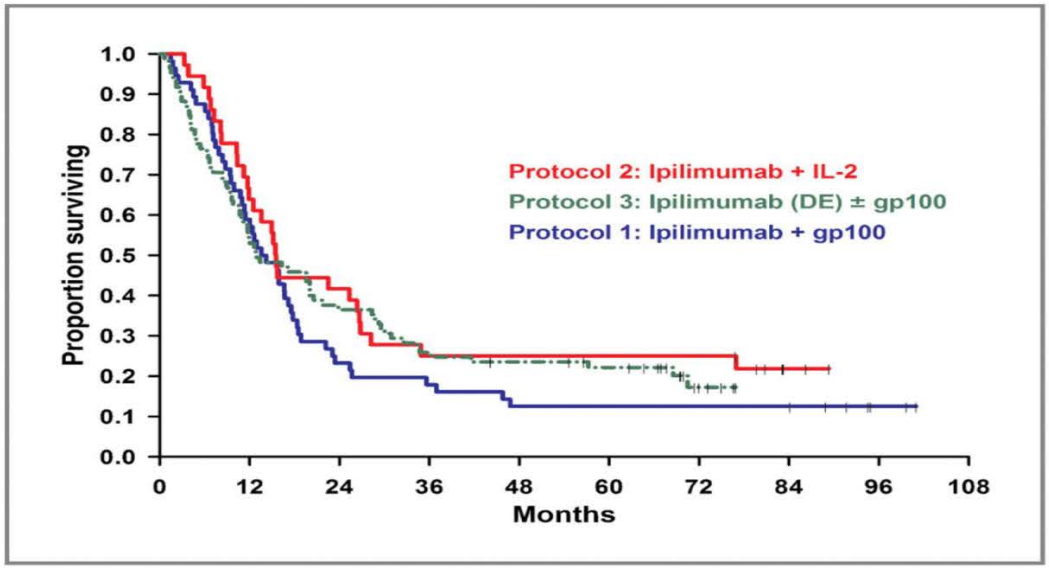
	Gr 3/4 IRAE	Gr 1/2 IRAE	No IRAE
Objective Response (CR = 3)	14 (28%)	8 (22%)	1 (2%)
Non-responder	36	28	52

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%



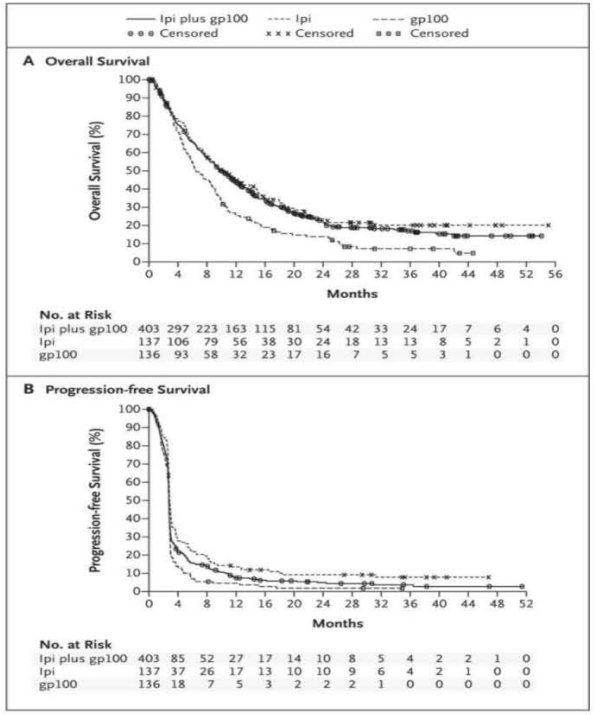
Prieto PA 2012

Clinical Cancer Research

Ipilimumab

Ipilimumab

- 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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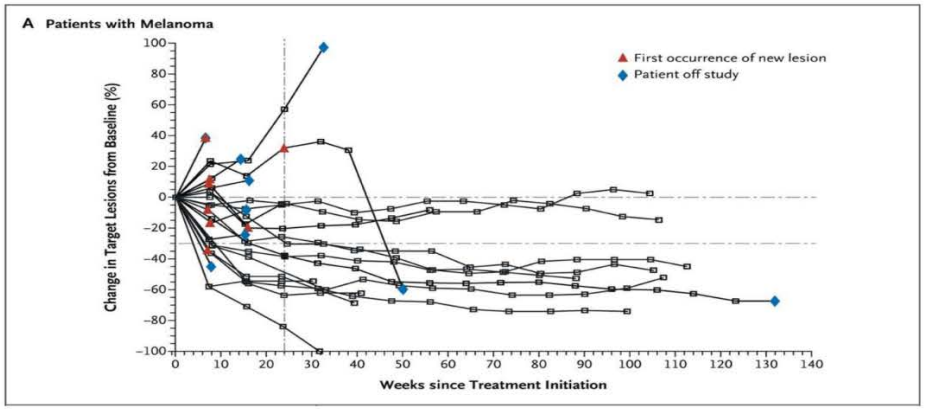
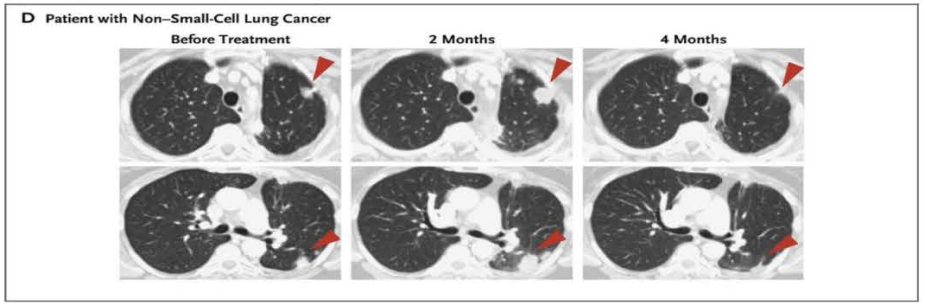
Nivolumab

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

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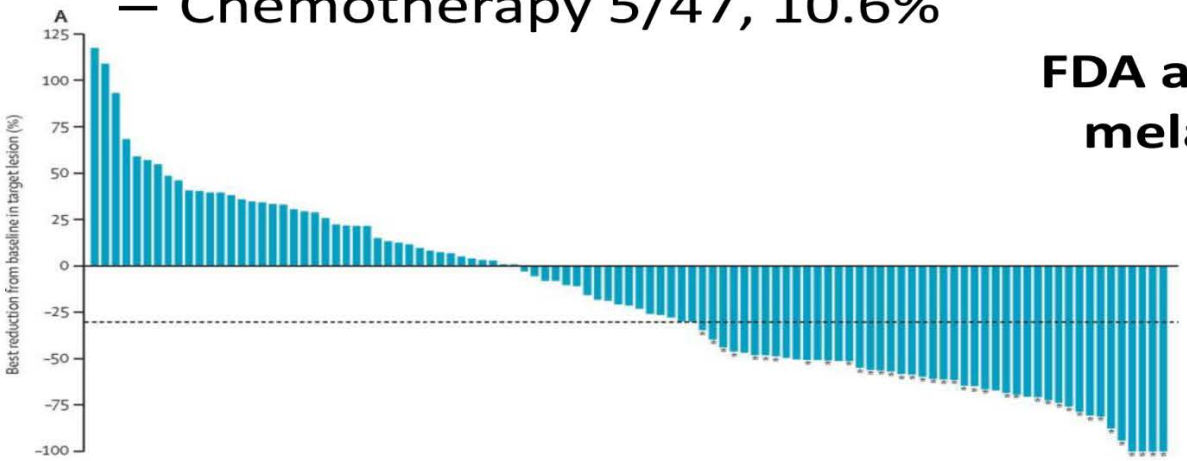
Nivolumab for melanoma

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

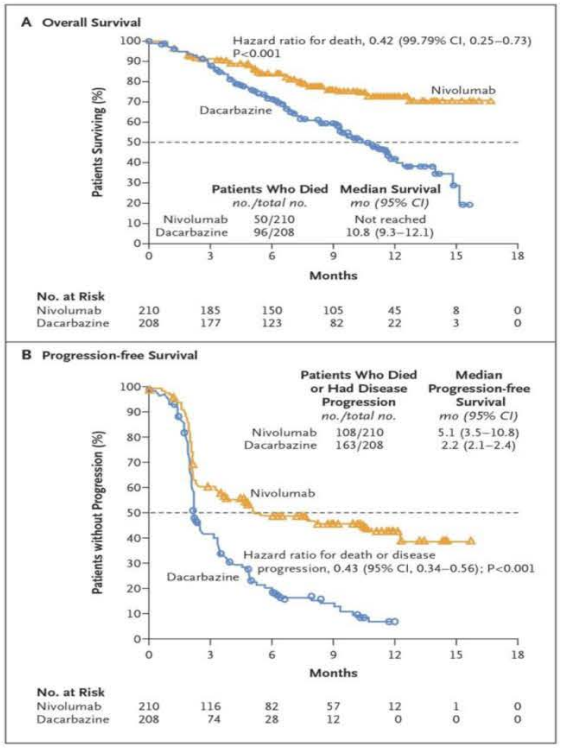
Weber JS 2015

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%)



Robert C 2015

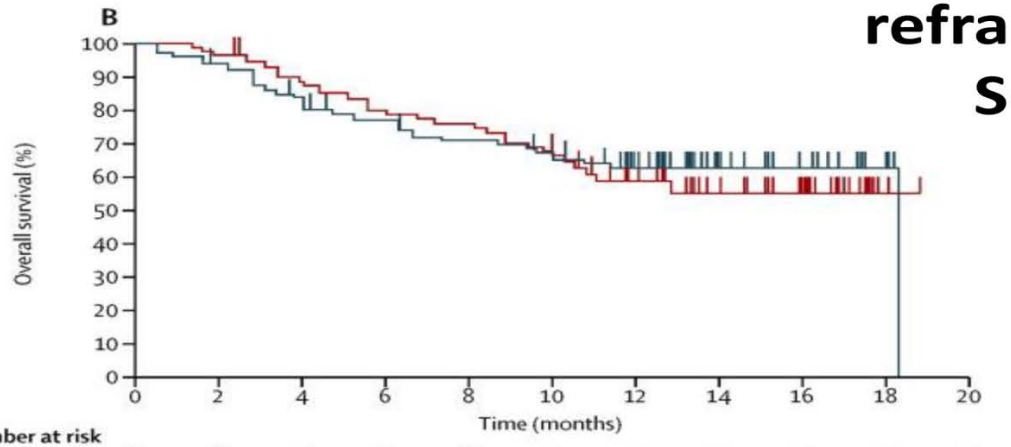
The NEW ENGLAND JOURNAL of MEDICINE

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



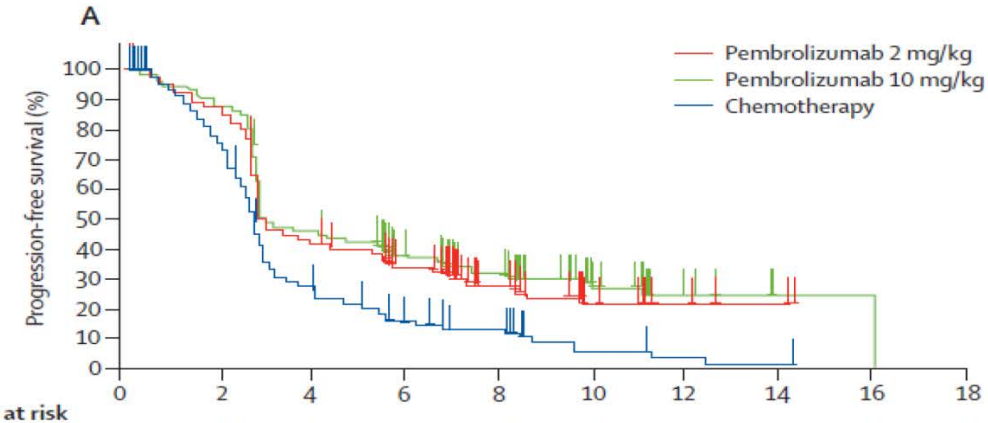
Number at risk											
Pembrolizumab 2 mg/kg	89	86	76	69	66	57	42	29	16	1	0
Pembrolizumab 10 mg/kg	84	78	65	61	55	50	37	18	12	1	0

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%



Number at risk										
Pembrolizumab 2 mg/kg	180	153	74	53	26	9	4	2	0	0
Pembrolizumab 10 mg/kg	181	158	82	55	39	15	5	1	1	0
Chemotherapy	179	128	43	22	15	4	2	1	0	0

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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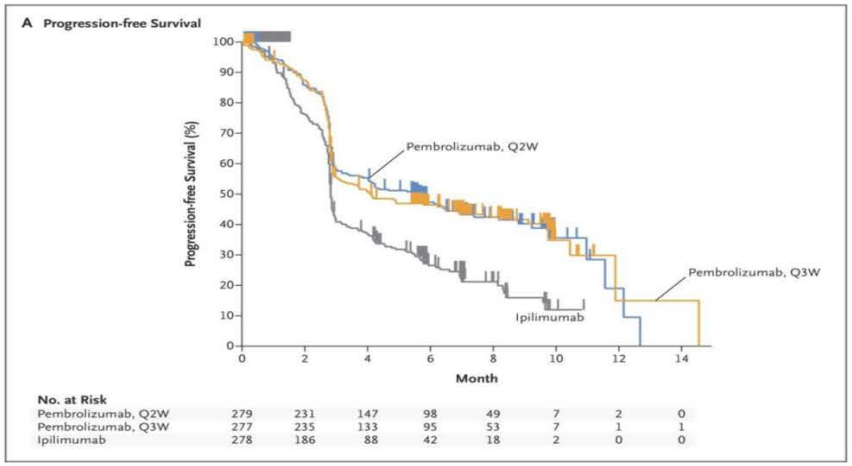
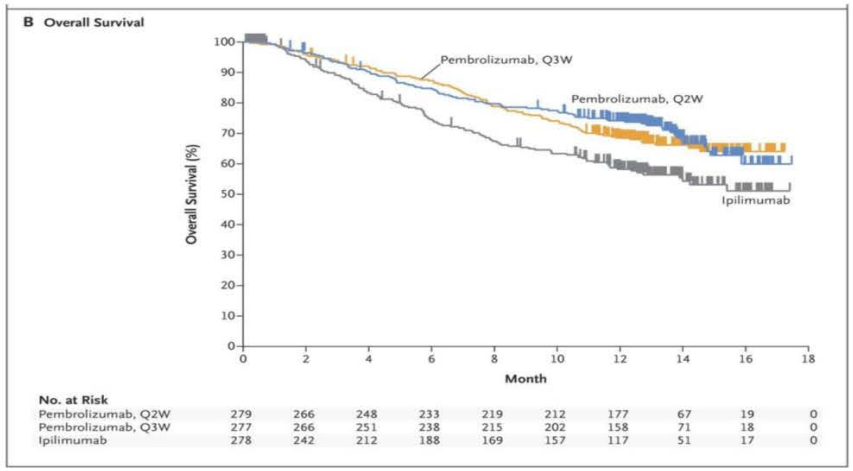
Pembrolizumab for melanoma

Pembrolizumab for melanoma





- Grade ≥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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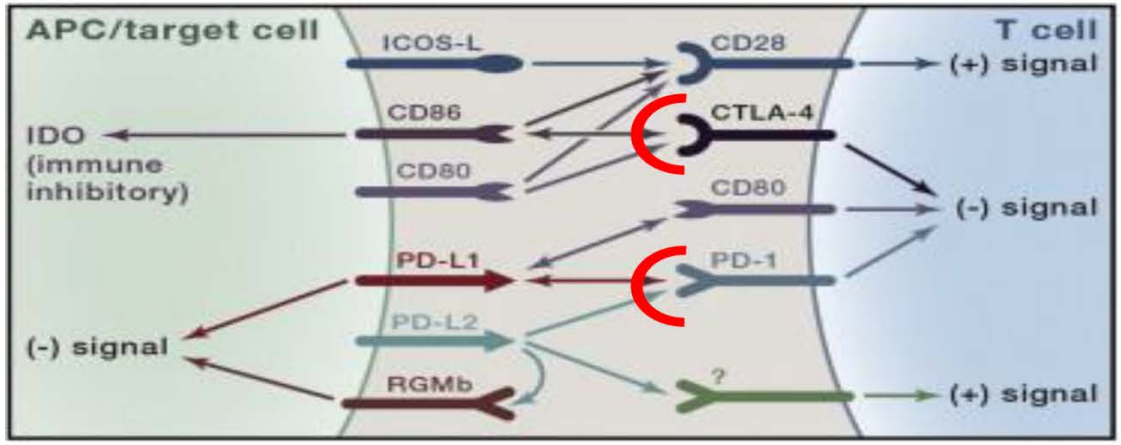
Checkpoint modulation

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.

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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%

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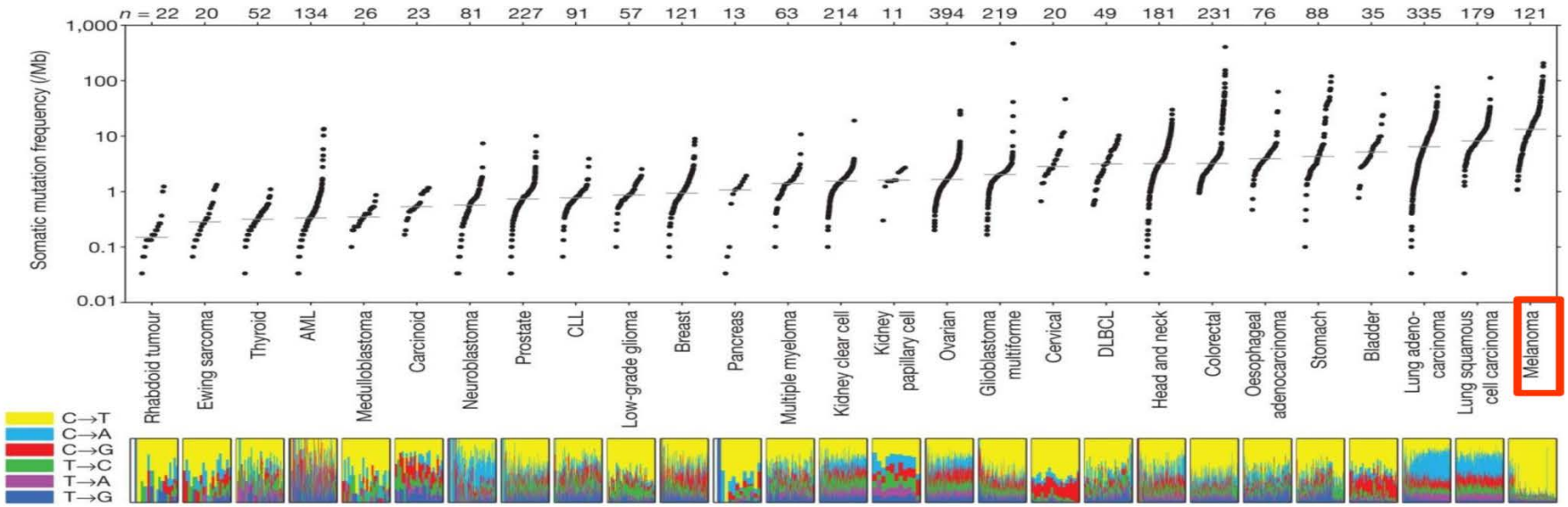
Melanoma

Why melanoma?



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

Highly mutated tumors

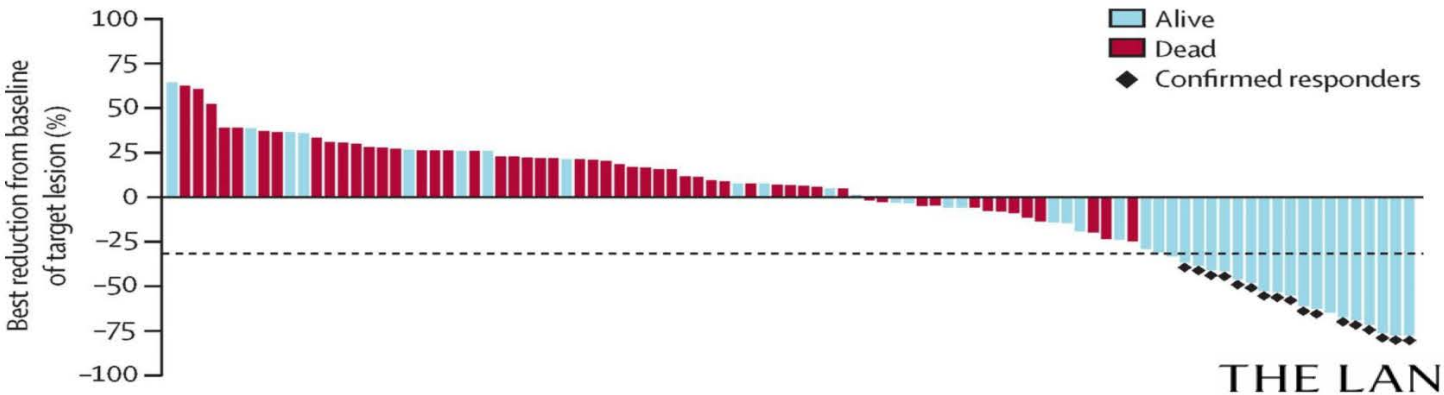
- Non-small cell lung cancer
- ~158,040 deaths/year in US
- Regional disease
  16% 5 yr survival
- Metastatic disease
  2% 5 yr survival
- Correlation between smoking and # mutations

- 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

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



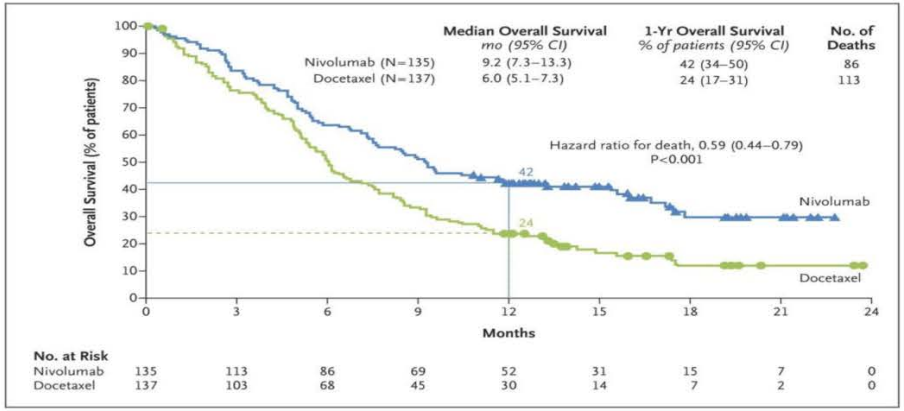
Rizvi NA 2015

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

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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 ≥3 AE
  - Dyspnea 3.8%
  - Pneumonitis 1.8% including a fatality

FDA decision to be made October 2, 2015

Garon EB 2015

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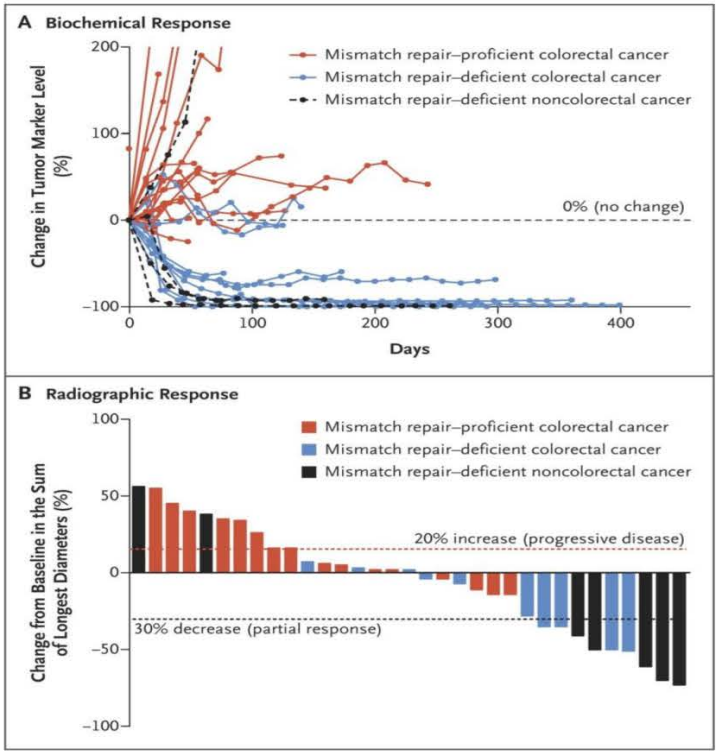
MMR-deficient cancer

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

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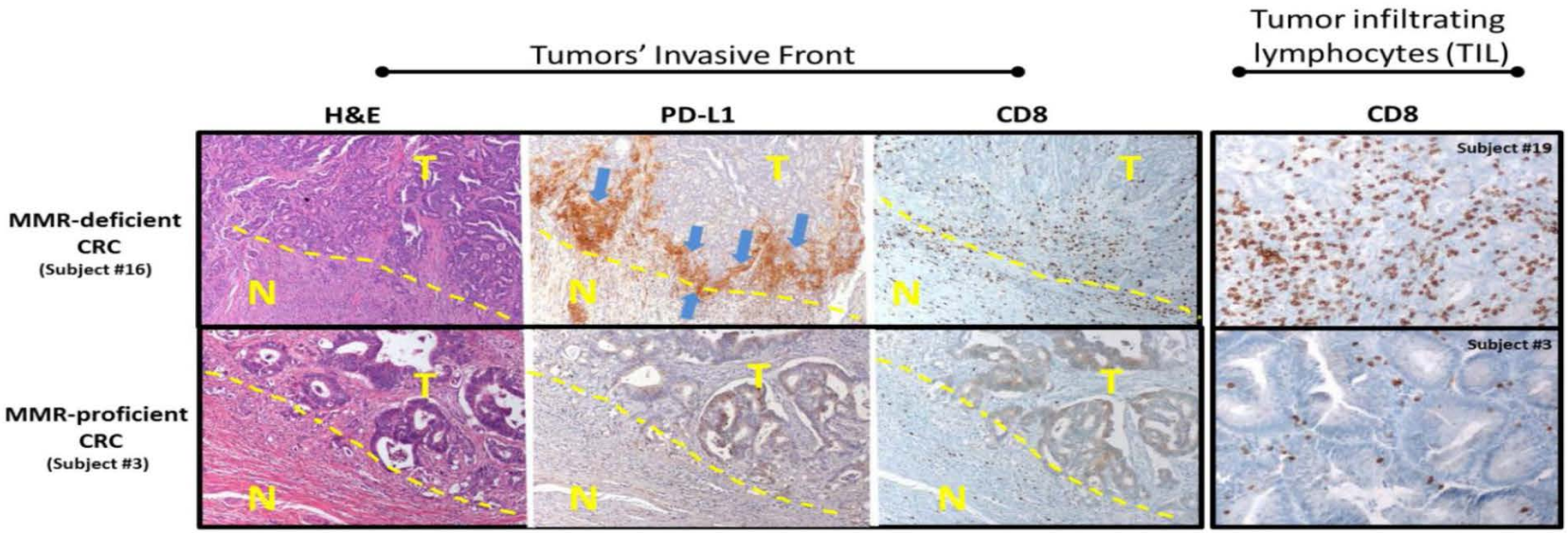
Tumor-stromal interface

Pembrolizumab at the tumor-stroma interface



Le DT 2015

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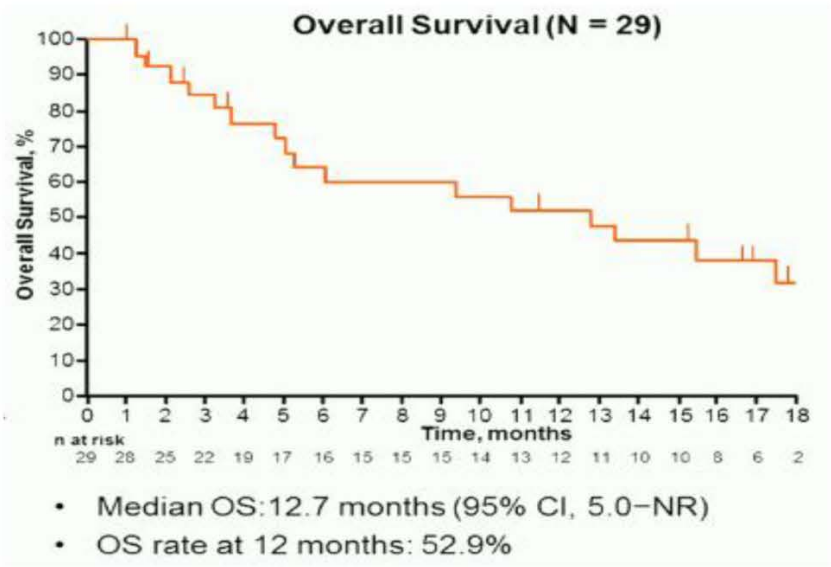
Utothelial Cancer

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%



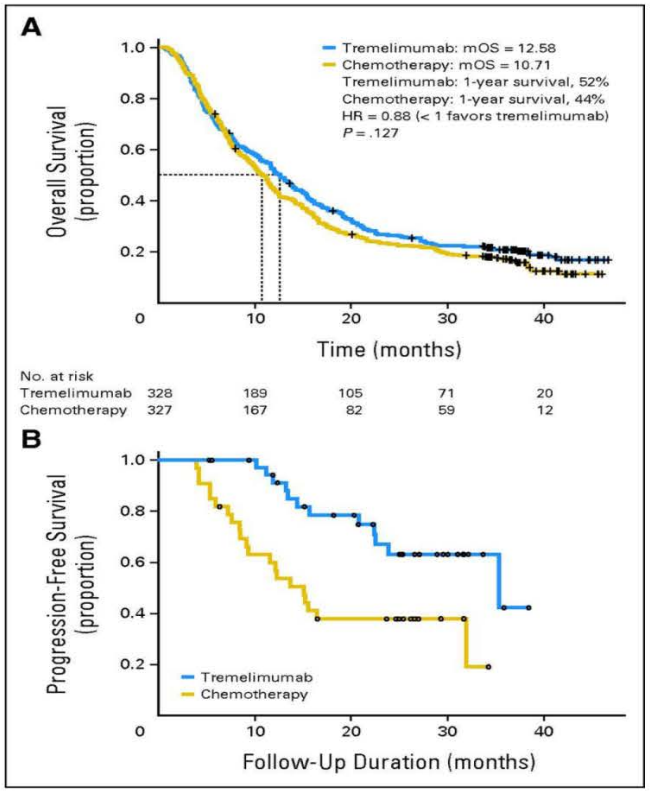
Abstract: Plimack E 2015

ASCO

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

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 ≥ 3 AE 9.4%

- TNBC
- PD-L1 (+) on IHC (20/105, 19%)

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%

Head and neck SCC

Pembrolizumab in Head and Neck SCC

- Part of KEYNOTE-012
- No requirement for PD-L1 expression
- 200mg q3w
- Grade ≥ 3 AE 7.6%

Overall Response Rate [Site Radiology Review]*

Best overall response	Total N = 117†		HPV+ n = 34		HPV– n = 81	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR	**29 (24.8)**	17.3-33.6	7 (20.6)	8.7-37.9	22 (27.2)	17.9-38.2
Complete Response	1 (0.9)	0.0-4.7	1 (2.9)	0.1-15.3	0 (0)	0-4.5
Partial Response	28 (23.9)	16.5-32.7	6 (17.6)	6.8-34.5	22 (27.2)	17.9-38.2
Stable Disease	29 (24.8)	17.3-33.6	9 (26.5)	12.9-44.4	19 (23.5)	14.8-34.2
Progressive Disease	48 (41.0)	32.0-50.5	13 (38.2)	22.2-56.4	34 (42.0)	31.1-53.5
No Assessment#	9 (7.7)	3.6-14.1	4 (11.8)	3.3-27.5	5 (6.2)	2.0-13.8
Non-evaluable±	2 (1.7)	0.2-6.0	1 (2.9)	0.1-15.3	1 (1.2)	0.0-6.7

Abstract: Seiwert TY 2015

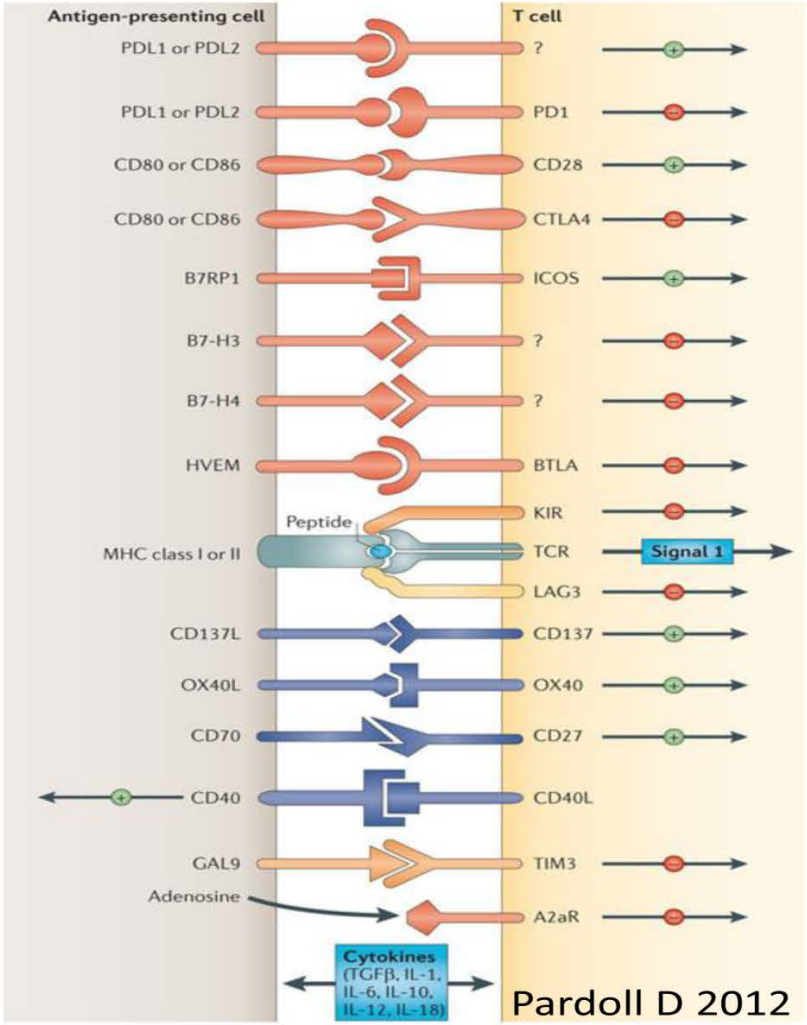
ASCO

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‡	Phase I trial in multiple cancers
		AMP-224§	Phase I trial in multiple cancers
PDL1	Ligand for PD1	MDX-1105	Phase I trial in multiple cancers
		Multiple mAbs	Phase I trials planned for 2012
LAG3	Inhibitory receptor	IMP321‖	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. ‡PD1 specificity not validated in any published material. §PDL2–Ig fusion protein. ‖LAG3–Ig fusion protein.



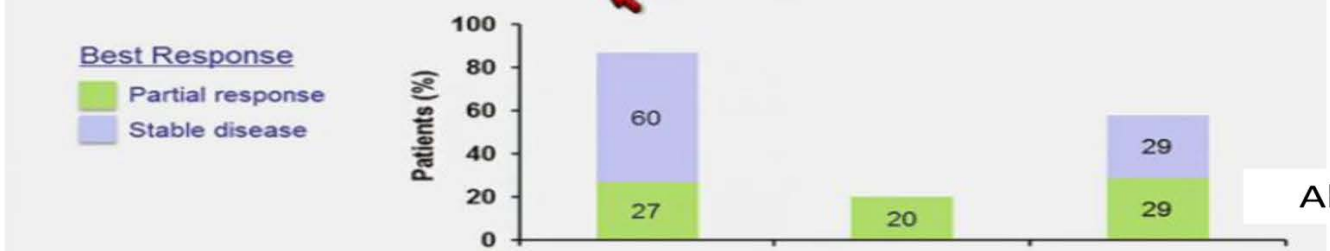
Nature Reviews | Cancer

Melanoma

αPD-L1 in melanoma

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

Investigator-Assessed Best Overall Response Rate (ORR), n/n (%)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population ORR (N = 140)	13/36 (36%)	9/67 (13%)	29/140 (21%)
Melanoma ORR (N = 38)	4/15 (27%)	3/15 (20%)	11/38 (29%)
Melanoma PR + SD (N = 38), %	87%	20%	58%



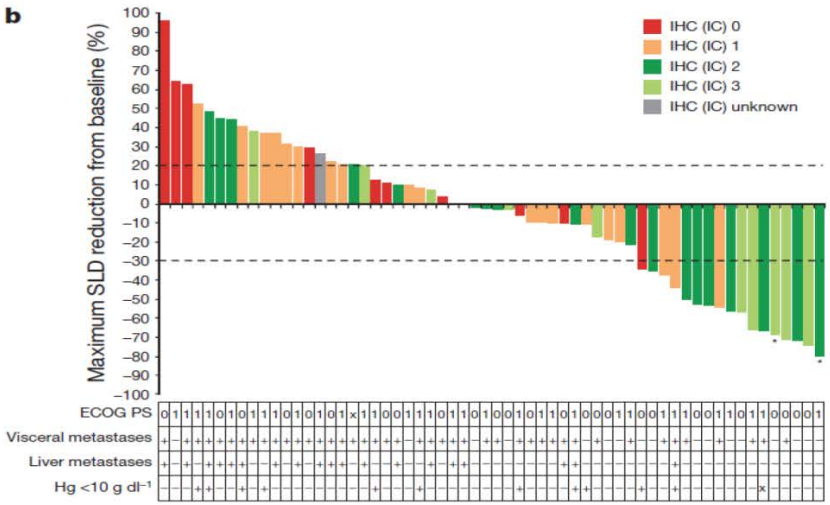
Abstract: Hamid O 2013

ASCO

Urothelial bladder cancer

αPD-L1 in Urothelial bladder cancer

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



Powles T 2014

nature
International weekly journal of science

Blocking the PD=1 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
	MPDL3280A	30% (n=43)	23% (n=53)	14% (n=56)	26% (n=65)

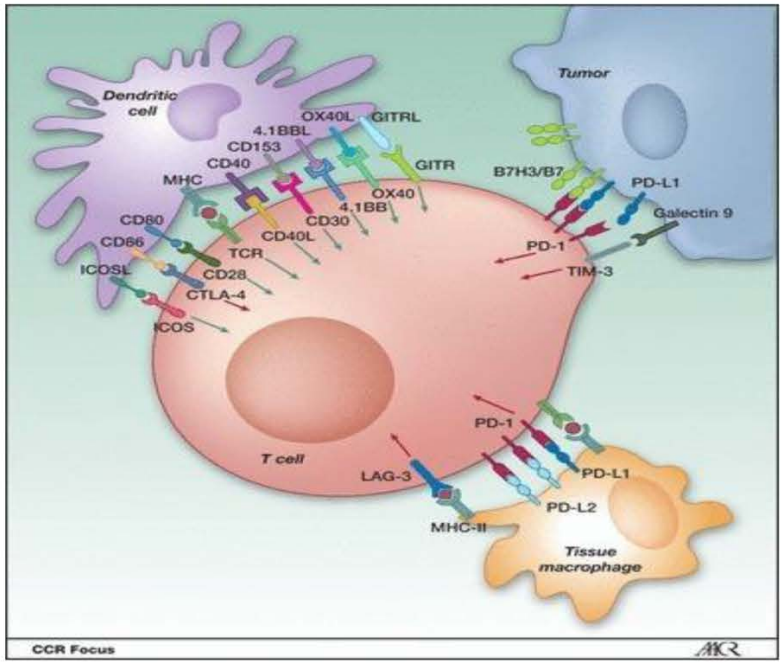
FDA Approved

Adapted from Lipson 2015

Seminars in Oncology

Checkpoint modulation

Checkpoint Modulation



Questions?