Targeting immune checkpoints in cancer: new insights and opportunities

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SITC 2015 Primer on Tumor Immunology and Cancer Immunotherapy

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Disclosure Information

SITC 2015

Suzanne L. Topalian

I have the following financial relationships to disclose:

***Consultant for*: Five Prime Therapeutics, GSK, Jounce Therapeutics; and (spouse) Amgen, MedImmune, Merck, Pfizer, Potenza, Sanofi**

***Grant/Research support from*: Bristol-Myers Squibb**

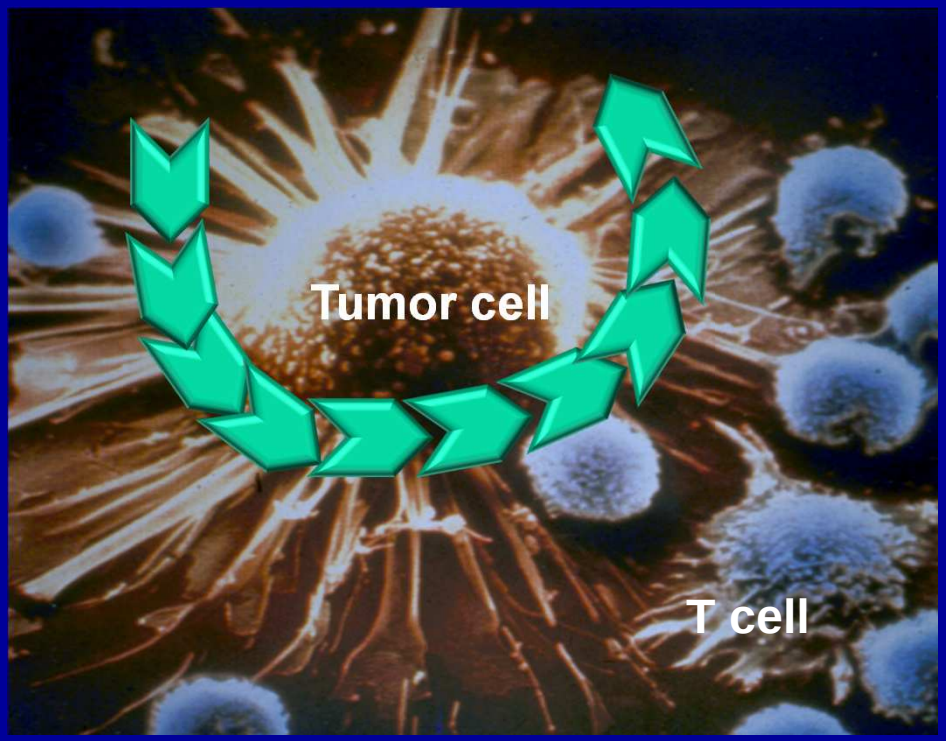
***Stock/stock options*: Five Prime Therapeutics; and (spouse) Jounce Therapeutics, Potenza Therapeutics**

***Royalties through institution (spouse*): BMS, Potenza**

- and –

I will discuss the following off label use and/or investigational use in my presentation: anti-PD-1, anti-PD-L1

The walls of cancer's defense against immune attack

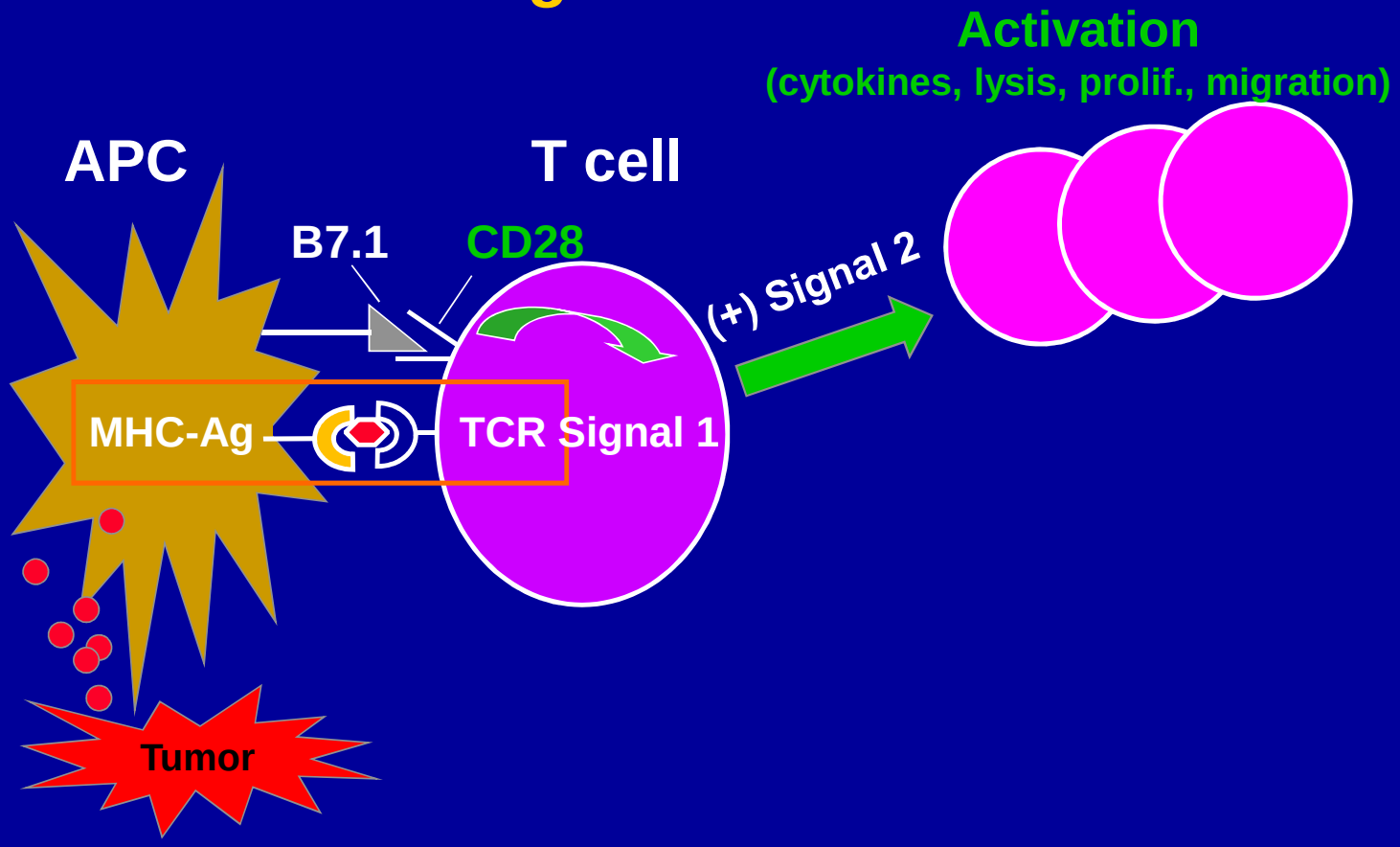


Regulatory immune cells

Suppressive cytokines

Immune "checkpoints"

The PD-L1 checkpoint: first line of defense against immune attack



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

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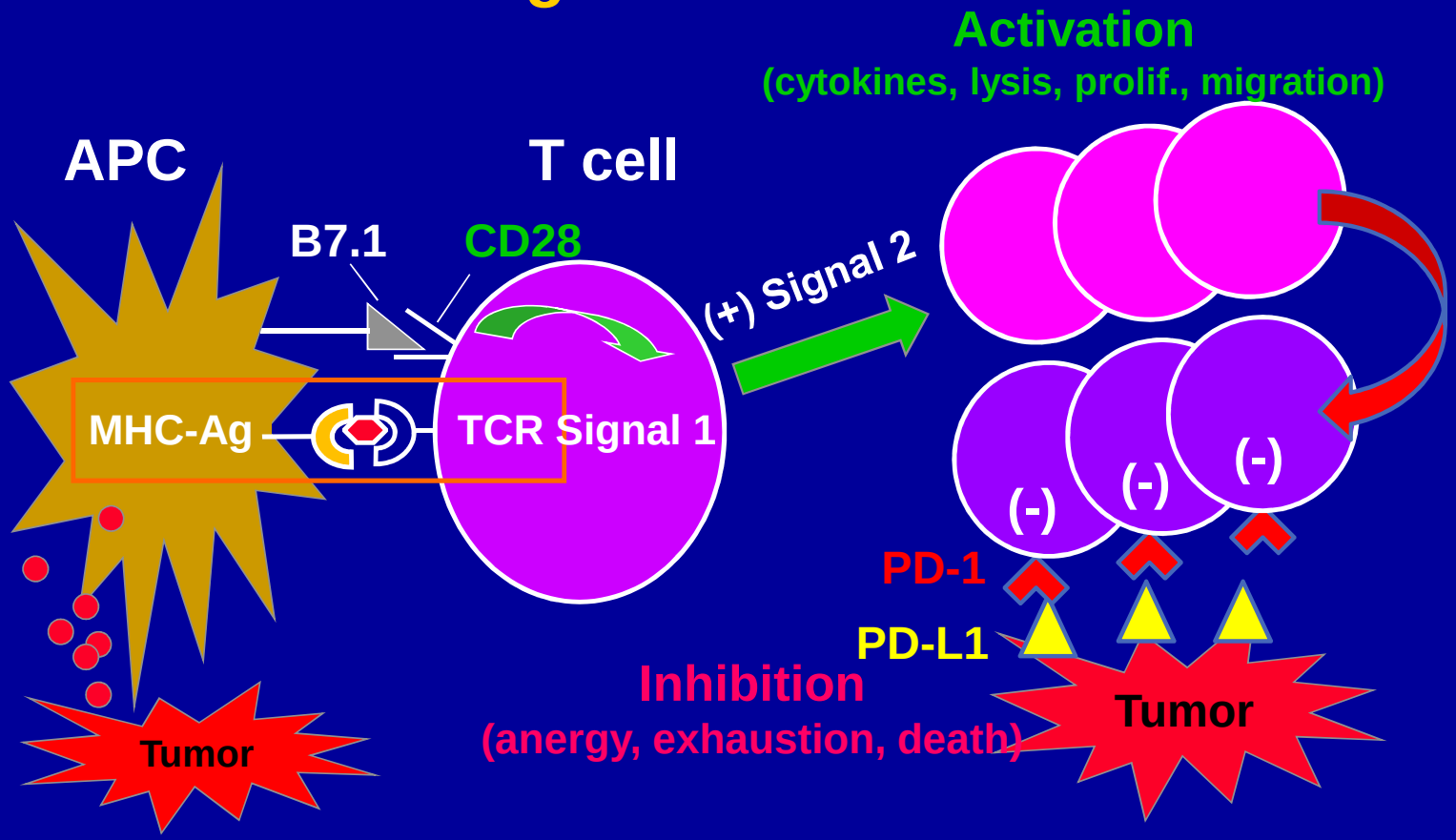

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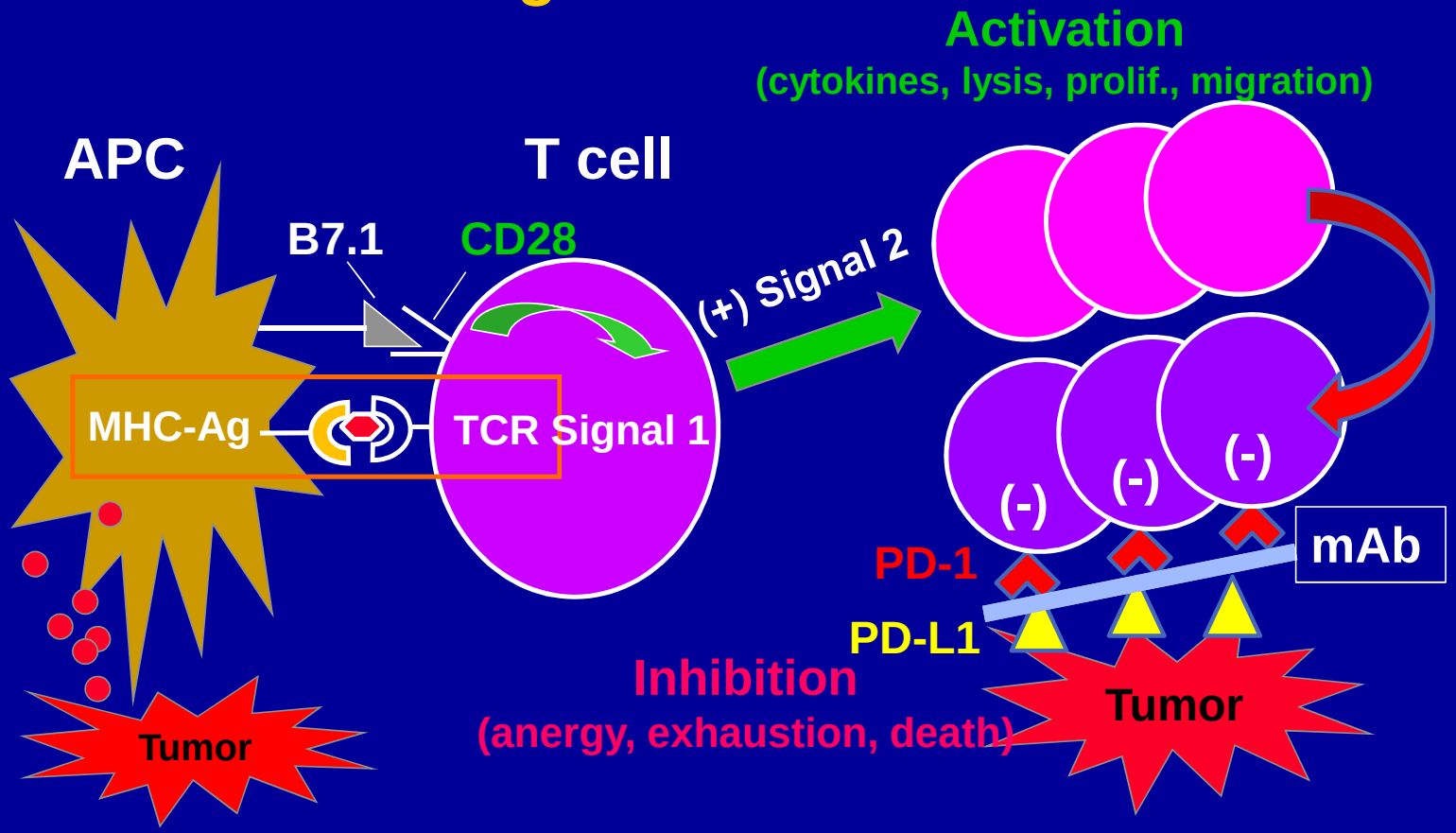
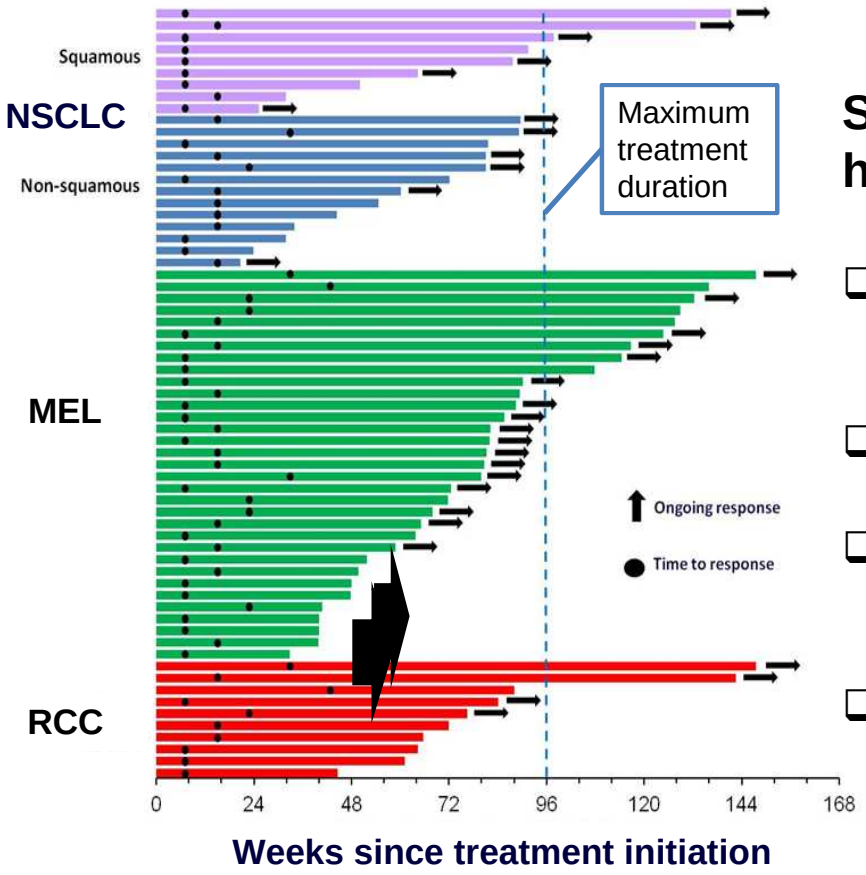
The PD-L1 checkpoint: first line of defense against immune attack



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Objective responses induced by anti-PD-1 (nivolumab) are rapid and durable



Sixty-five of 306 patients had ORs (CR+PR, 21%):

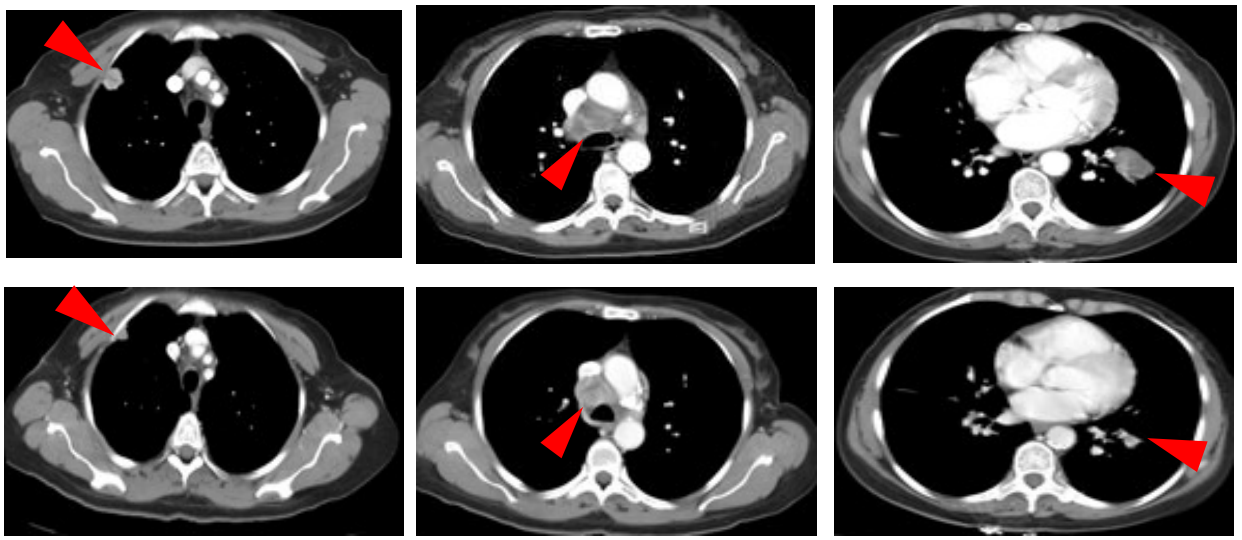
- ❑ 30 of 65 (**46%**) responses were evident at first tumor evaluation (8 weeks)
- ❑ 42 of 65 (**65%**) patients had responses lasting >1 year
- ❑ 35 of 65 (**54%**) responses were ongoing at time of data analysis (March 2013)
- ❑ Partial responses persisted *off-drug*

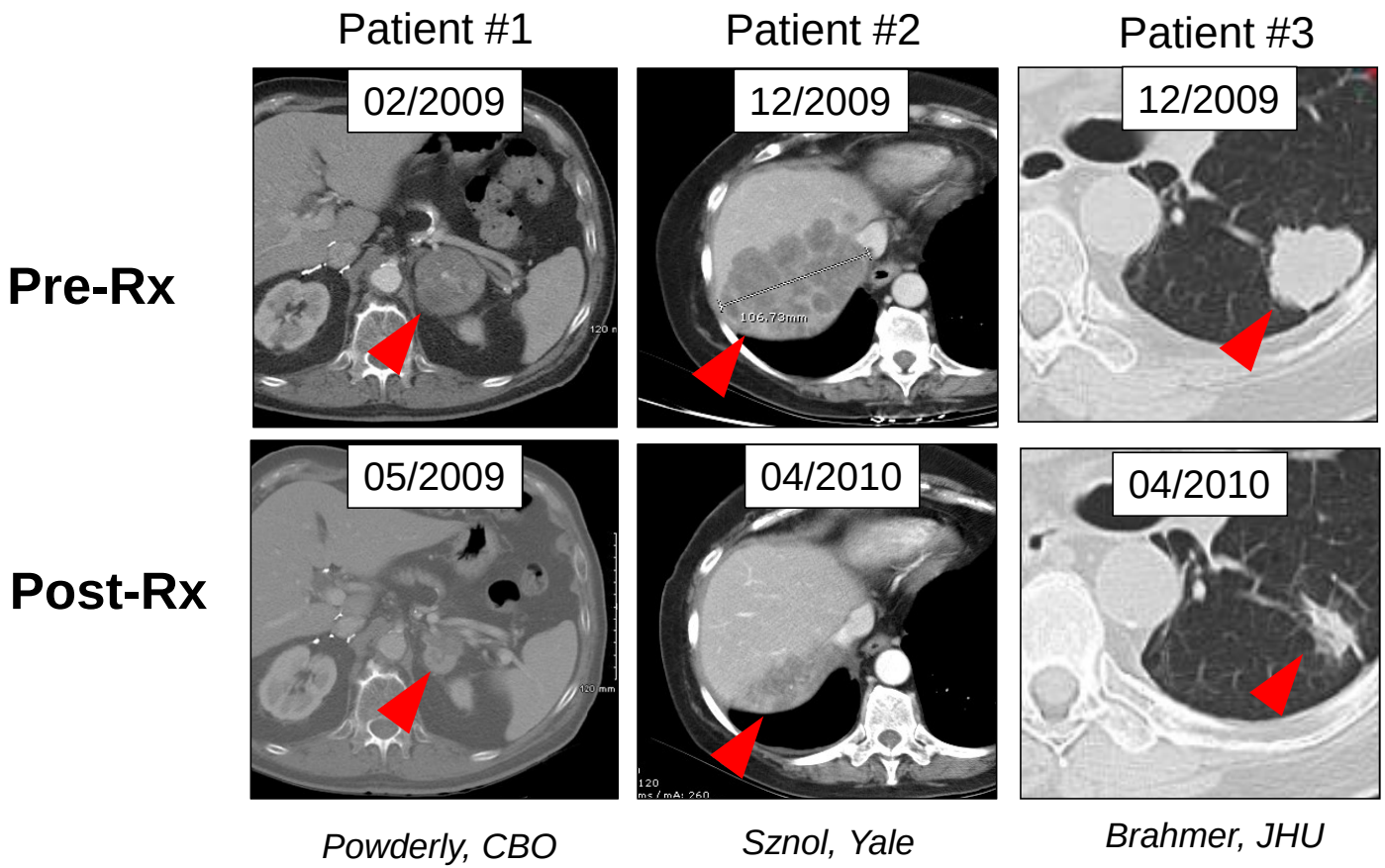
Topalian et al., NEJM 2012, ASCO 2013

First signal of activity from anti-PD-1 in NSCLC: first-in-human trial of nivolumab

Pre-Rx
05/2007

Post-Rx
07/2007




Patient #1
Patient #2
Patient #3
Pre-Rx
Post-Rx
02/2009
12/2009
12/2009
05/2009
04/2010
04/2010
Powderly, CBO
Sznol, Yale
Brahmer, JHU

Immunotherapy landmark: anti-PD-1 is approved for patients with advanced lung cancer

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA expands approved use of Opdivo to treat lung cancer

For Immediate Release March 4, 2015

Release

Español (/NewsEvents/Newsroom/ComunicadosdePrensa/ucm436728.htm)

The U.S. Food and Drug Administration today expanded the approved use of Opdivo (nivolumab) to treat patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy.

Lung cancer is the leading cause of cancer death in the United States, with an estimated 224,210 new diagnoses and 159,260 deaths in 2014. The most common type of lung cancer, NSCLC affects seven out of eight lung cancer patients, occurring when cancer forms in the cells of the lung.

Opdivo works by inhibiting the cellular pathway known as PD-1 protein on cells that blocks the body's immune system from attacking cancerous cells. Opdivo is intended for patients who have previously been treated with platinum-based chemotherapy.

.....

PD-1 pathway blocking mAbs in clinical testing

	Target Molecule	
Source	**PD-1**	**PD-L1**
BeiGene	BGB-A317 (humanized mAb)	N/A
Bristol-Myers Squibb	Nivolumab/BMS-936558/ MDX-1106/ ONO-4538 (human IgG4)	BMS-936559/MDX-1105 (human IgG4)
CureTech	Pidilizumab/CT-011 (humanized IgG1)	N/A
EMD Serono	N/A	Avelumab, MSB0010718C (human IgG1)
Genentech/ Roche	N/A	Atezolizumab, MPDL3280A (Fc-modified human IgG1)
MedImmune/ AstraZeneca	MEDI0680/AMP-514 (humanized IgG4)	Durvalumab, MEDI4736 (Fc-modified human IgG1)
Merck	Pembrolizumab/MK-3475 (humanized IgG4)	N/A
Novartis	PDR001 (humanized IgG4)	N/A
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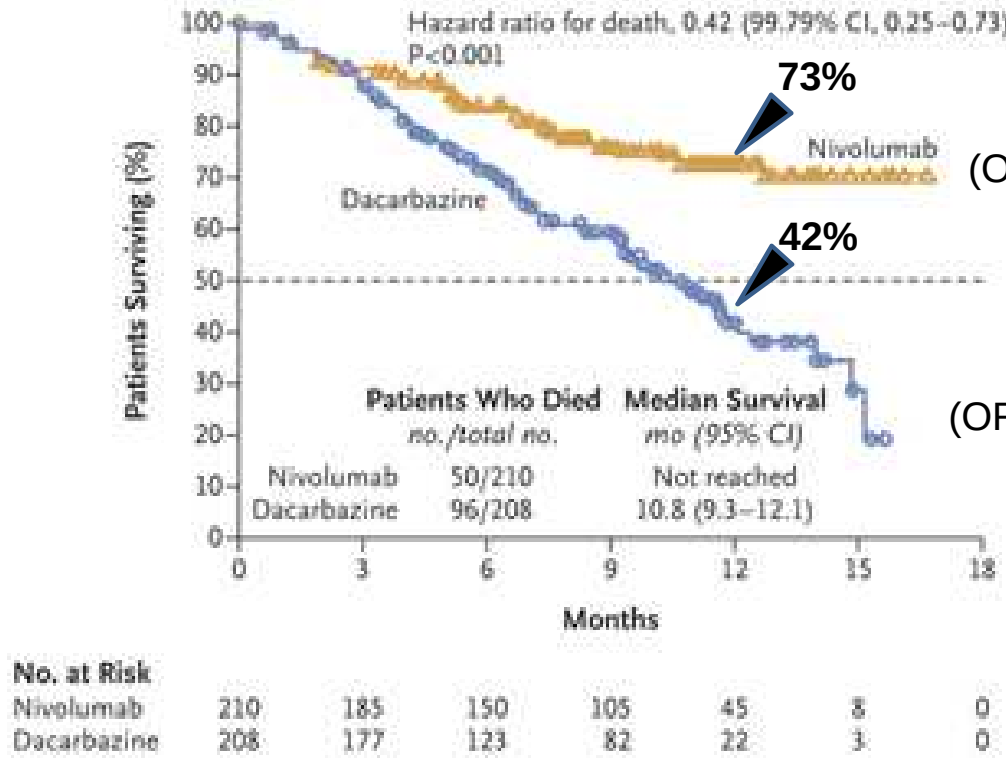
Phase 3 trial results: Improved overall survival in patients with metastatic melanoma receiving first-line anti-PD-1 (nivolumab) vs. chemotherapy



(ORR nivo = 40%)

(ORR chemo =14%)

Robert et al., NEJM 2014

Drugs blocking PD-1/PD-L1 are active against multiple cancer types

Durable objective tumor regressions in patients with:

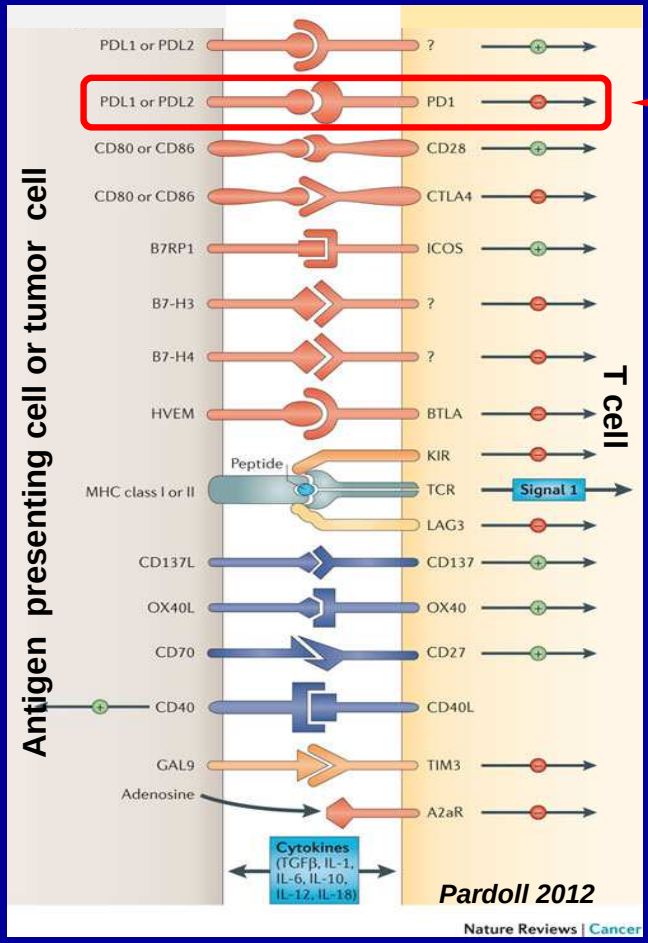
- Melanoma (17-50% of patients responding)
- Lung cancer (10-30%)
- Kidney cancer (12-29%)
- Bladder cancer (25%)
- Ovarian cancer (6-23%)
- Head and neck cancer (14-25%)
- Hodgkin's lymphoma (87%)
- Gastric cancer, TNBC, HCC, mesothelioma, ...

➢ ***Drugs targeting a single molecular pathway have an unprecedented activity spectrum and provide a "common denominator" for cancer therapy***

The immune synapse

On the horizon: multiple opportunities to enhance antitumor immunity

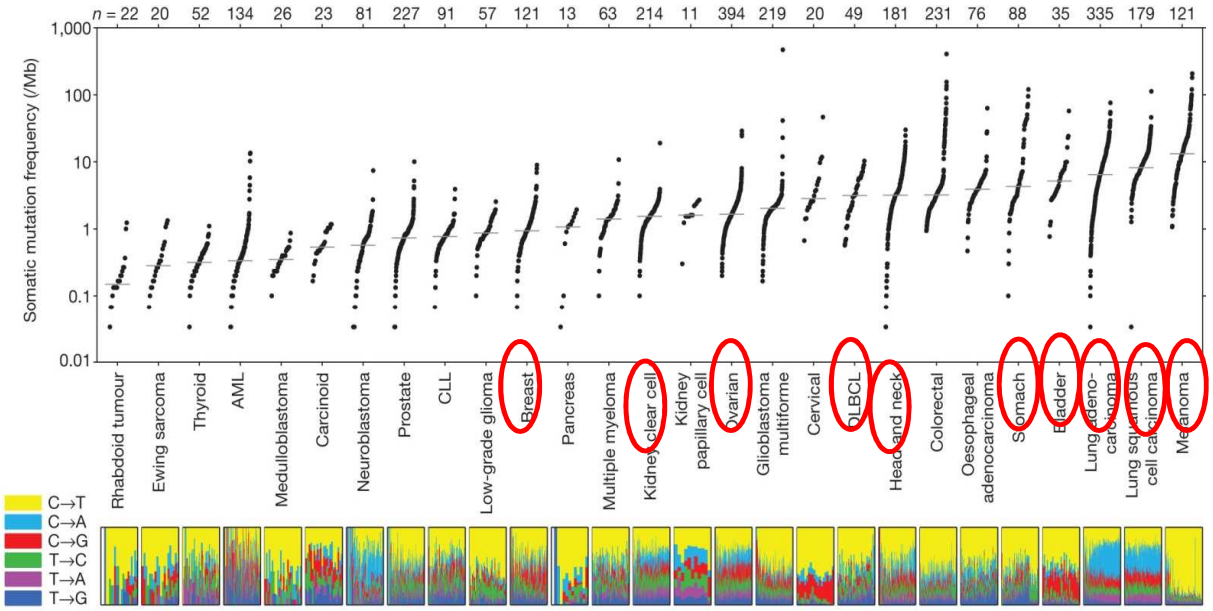
A complex series of receptor-ligand interactions modulating immune cell activity are druggable



QUESTION:

Can cancer genetics guide immunotherapy?

Does mutational load correlate with responsiveness to immune checkpoint blockade?

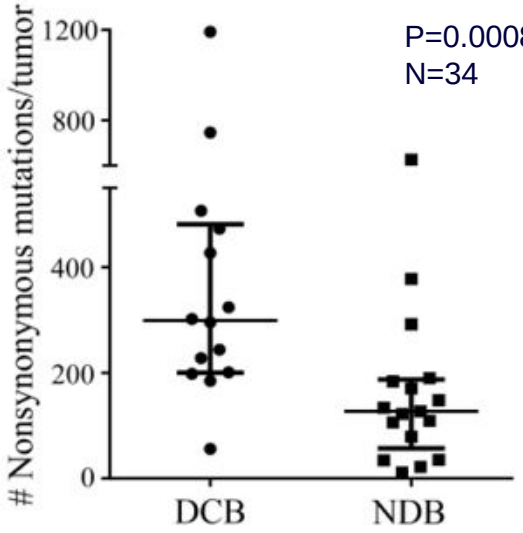


Lawrence et al., Nature 2013

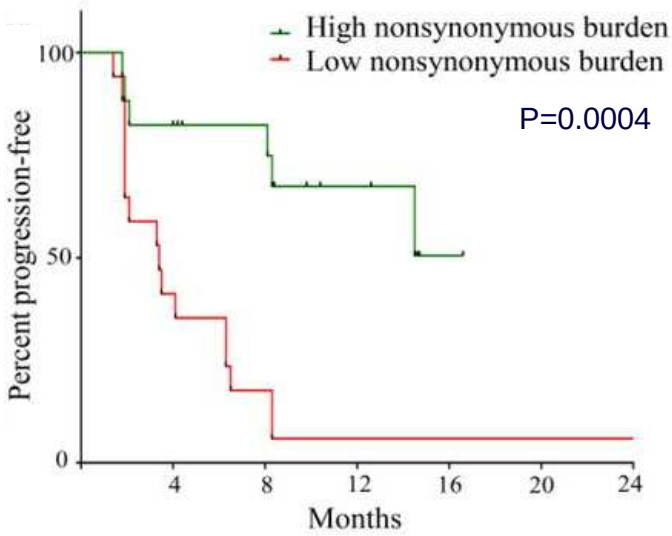
- ***Altered proteins contain neoepitopes for immune recognition***

Preliminary findings: Mutational load in NSCLC correlates with response to anti-PD-1 (pembrolizumab) therapy

Endpoint: "durable clinical benefit"



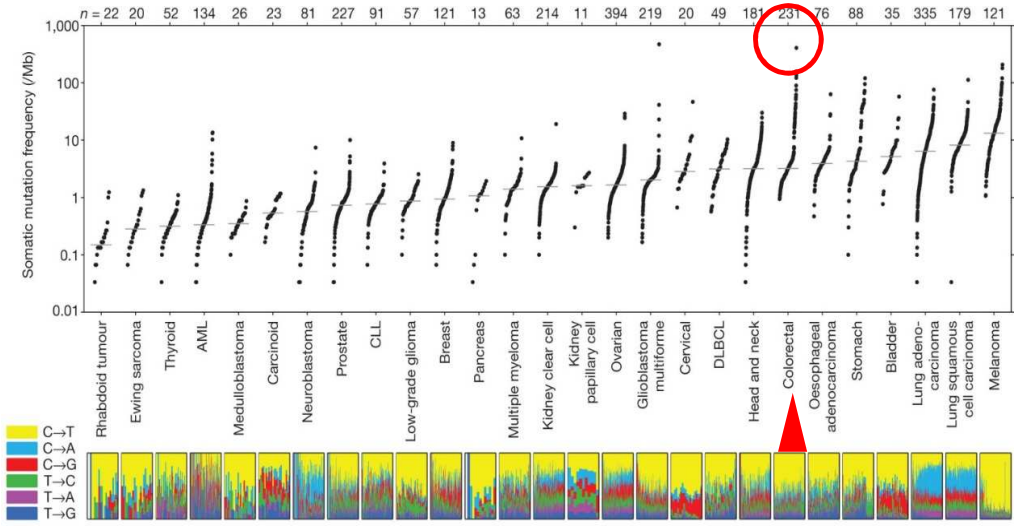
Endpoint: PFS



- Somatic exomic mutations create new proteins potentially recognized by the immune system

Rizvi, Chan et al., Science 2015

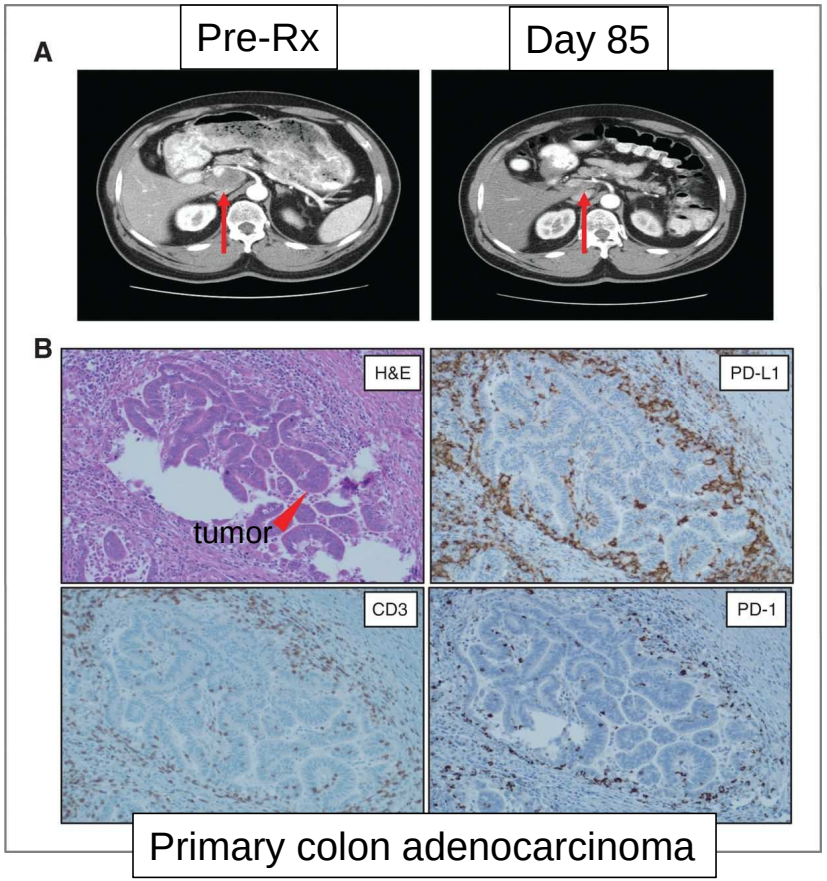
Colorectal cancers are generally unresponsive to PD-1 blockade, but the MSI-high subset has a high mutational burden



Lawrence et al., Nature 2013

- ***Microsatellite instability (MSI): genetic hypermutability resulting from deficient mismatch repair (dMMR), present in ~15% colon cancers and in some other tumor types***

“Exceptional responder”: Complete response of metastatic colorectal cancer to anti-PD-1 therapy



Lipson et al., Clin Cancer Res 2013

History: 71-yr-old male had disease progression following multiple chemotherapies, bevacizumab, cetuximab.

Anti-PD-1 (nivolumab) therapy started in 2007, 5 doses over 9 months. Patient disease-free and off therapy since 2008.

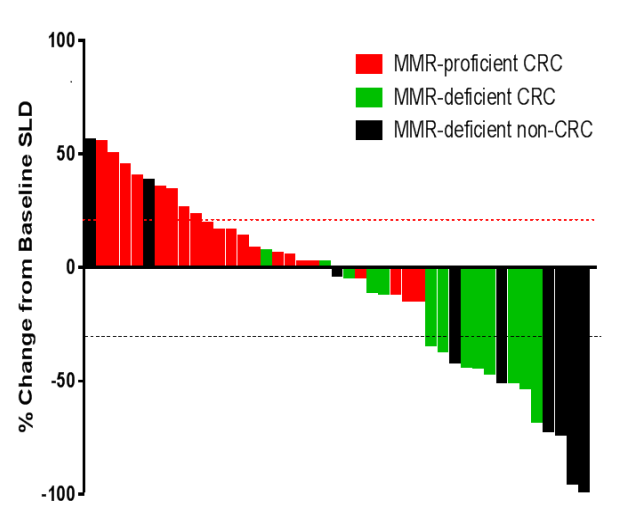
- **Tumor genotype MSI-high**

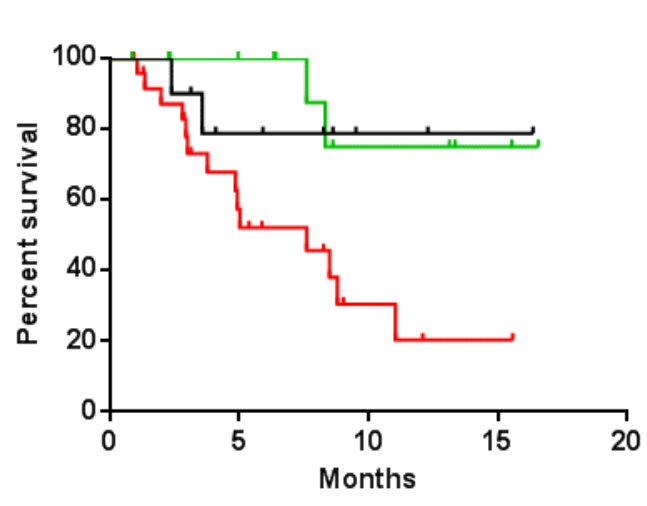
Genetic subsetting predicts response to anti-PD-1 therapy

(Le, Diaz, et al., ASCO 2015 and NEJM 2015)

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC
Objective Response Rate	62%	0%	60%
Disease Control Rate	92%	16%	70%

GI, GYN, prostate Ca

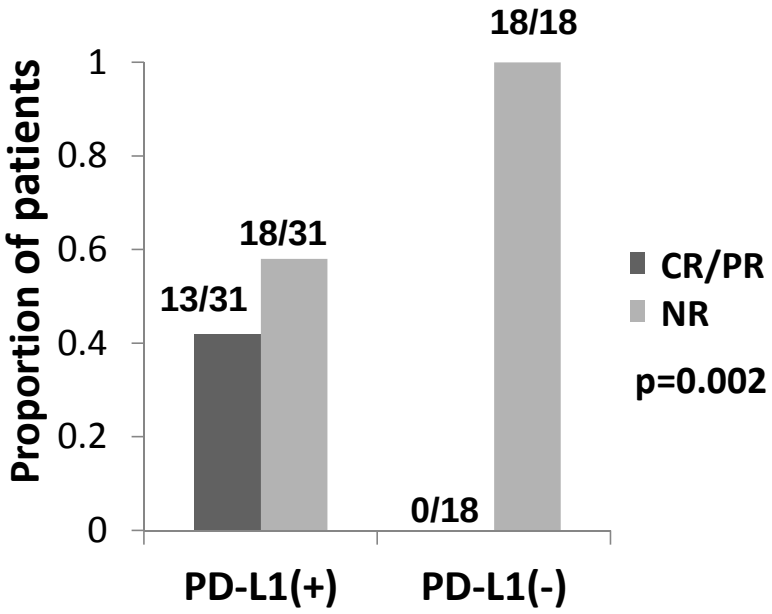




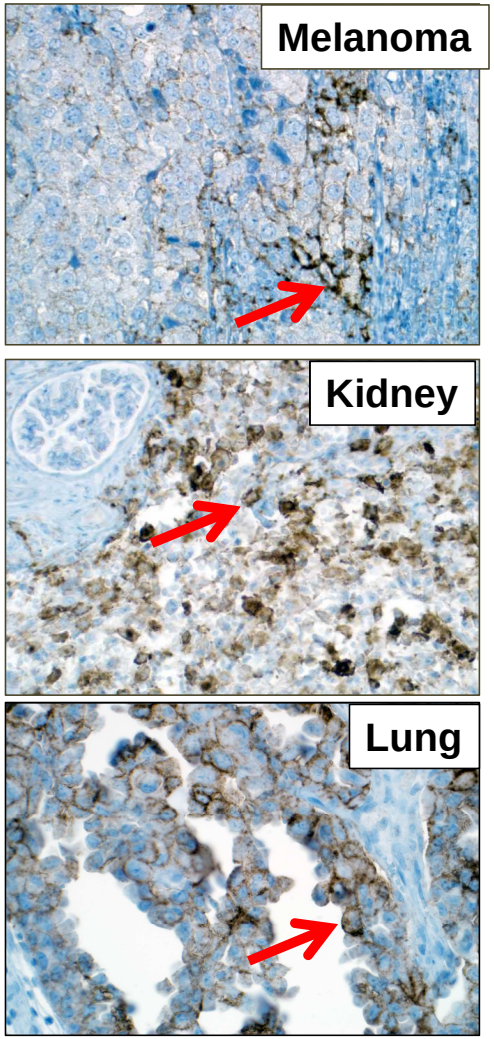
QUESTION:

Can immunological factors provide cross-cutting biomarkers for clinical response to checkpoint blockade?

Preliminary correlation of PD-L1 expression in pre-treatment tumor biopsies, with clinical response to anti-PD-1 therapy

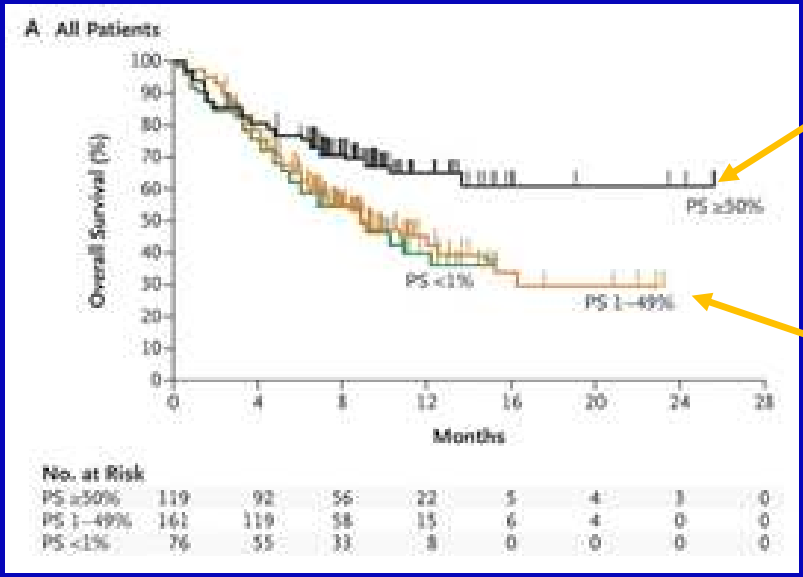


49 patients include 20 with melanoma,13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer (updated from Topalian et al., NEJM 2012)



Pre-treatment tumor PD-L1 expression correlates with response to anti-PD-1 (pembrolizumab) in NSCLC: individualizing treatment strategy

Garon et al., NEJM 2015



≥ 50% tumor cells PD-L1+
- Response rate 45%
- Median survival not reached

< 50% tumor cells PD-L1+
- Response rate 11-17%
- Median survival 8.8 months

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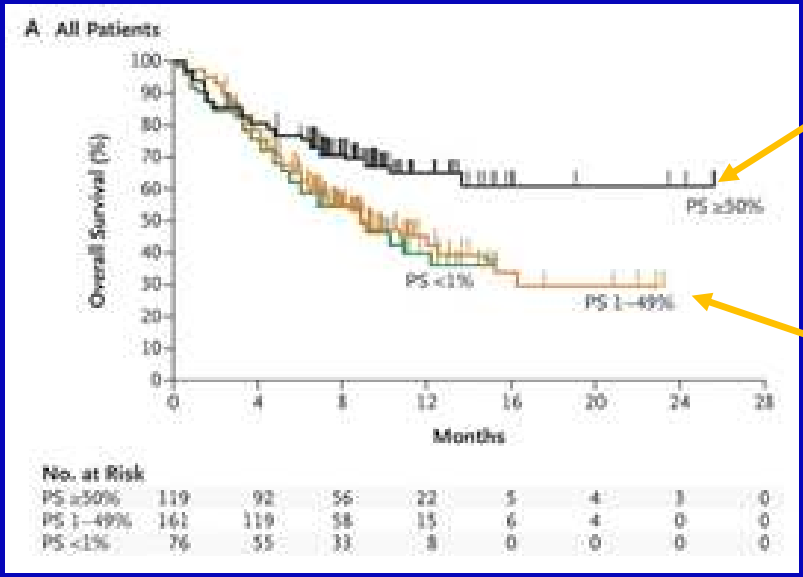

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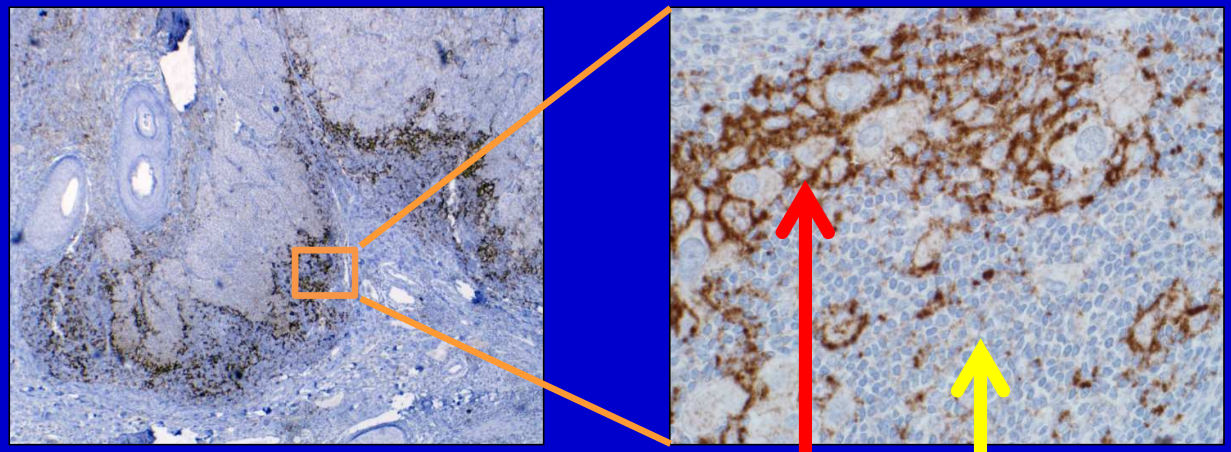
➢ ***Oct. 2015: two PD-L1 IHC assays approved by FDA as diagnostics for anti-PD-1 therapy in lung cancer***

Tumor infiltrating lymphocytes at the interface with PD-L1+ tumor cells secrete cytokines that drive PD-L1 expression

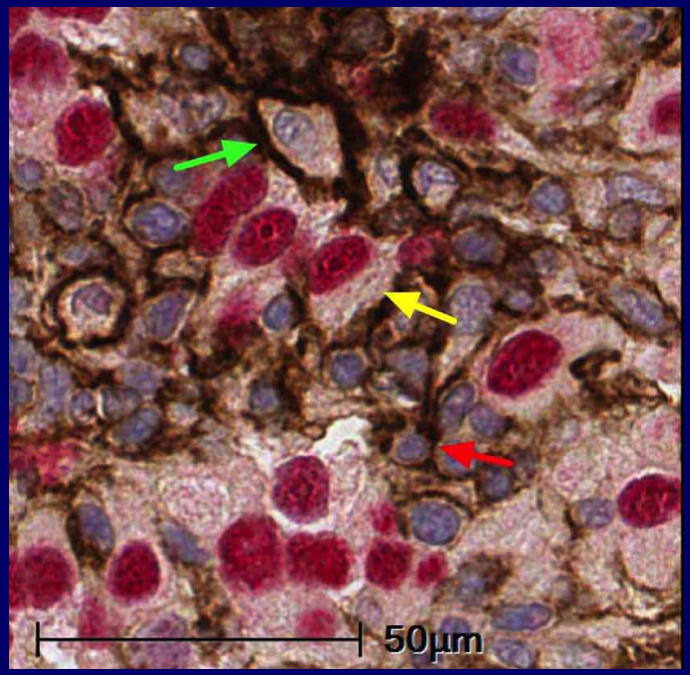


Tumor

Lymphocytes secreting IFN-g and other factors

Taube et al., Science Transl Med 2012 and Clin Cancer Res 2015

Multiple cell types in the tumor microenvironment can express PD-L1



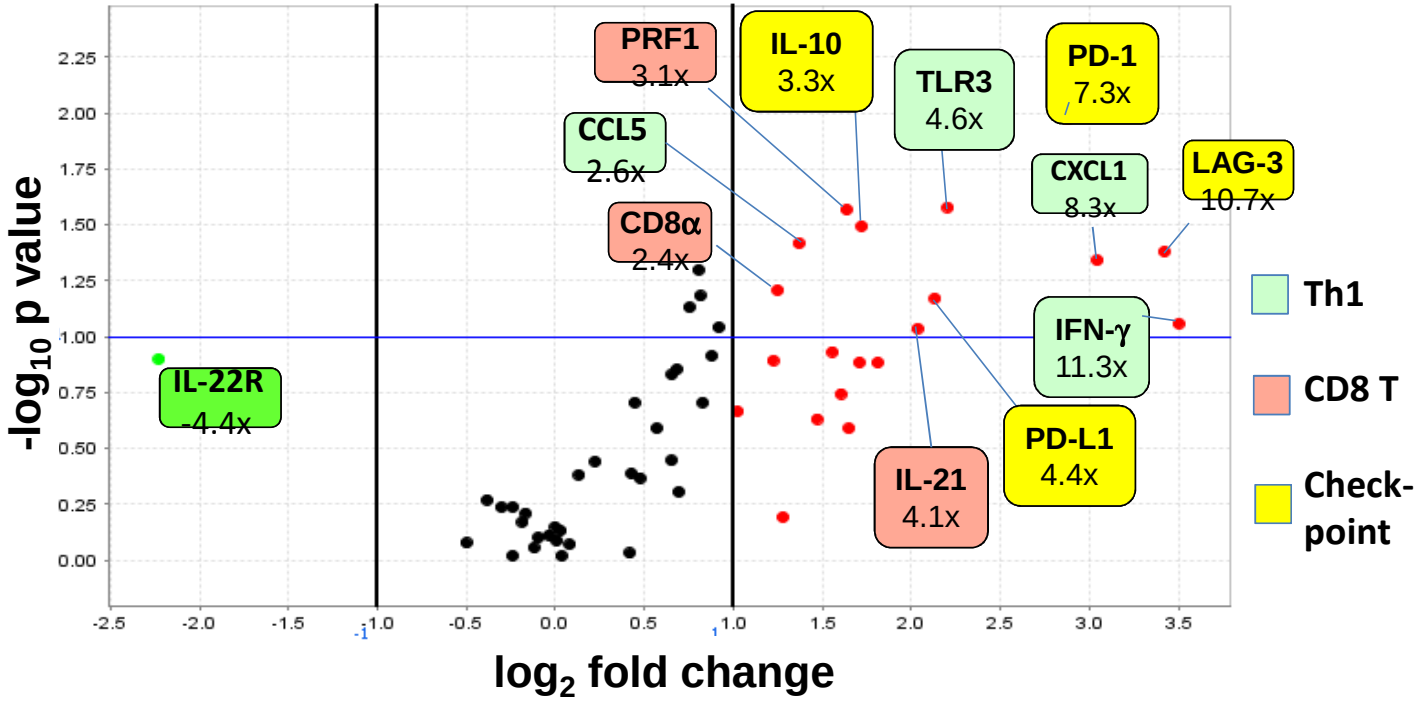
Melanoma cells

Macrophages

Lymphocytes

Tumeh, Ribas, et al., Nature 2014

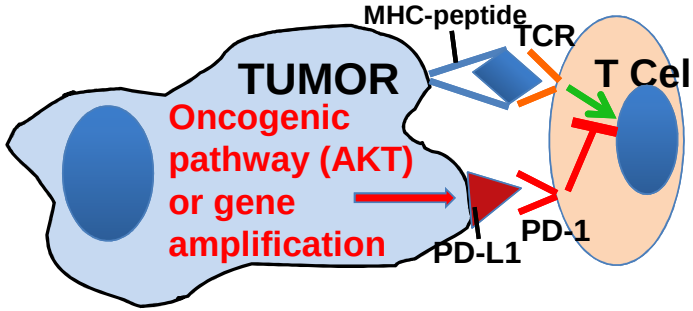
TILs from PD-L1(+) vs. (-) melanomas: functional groups of differentially expressed genes and potential treatment resistance pathways



multiplex qRT-PCR, CD45 normalization

(Taube, Topalian et al., Clin Cancer Res 2015)

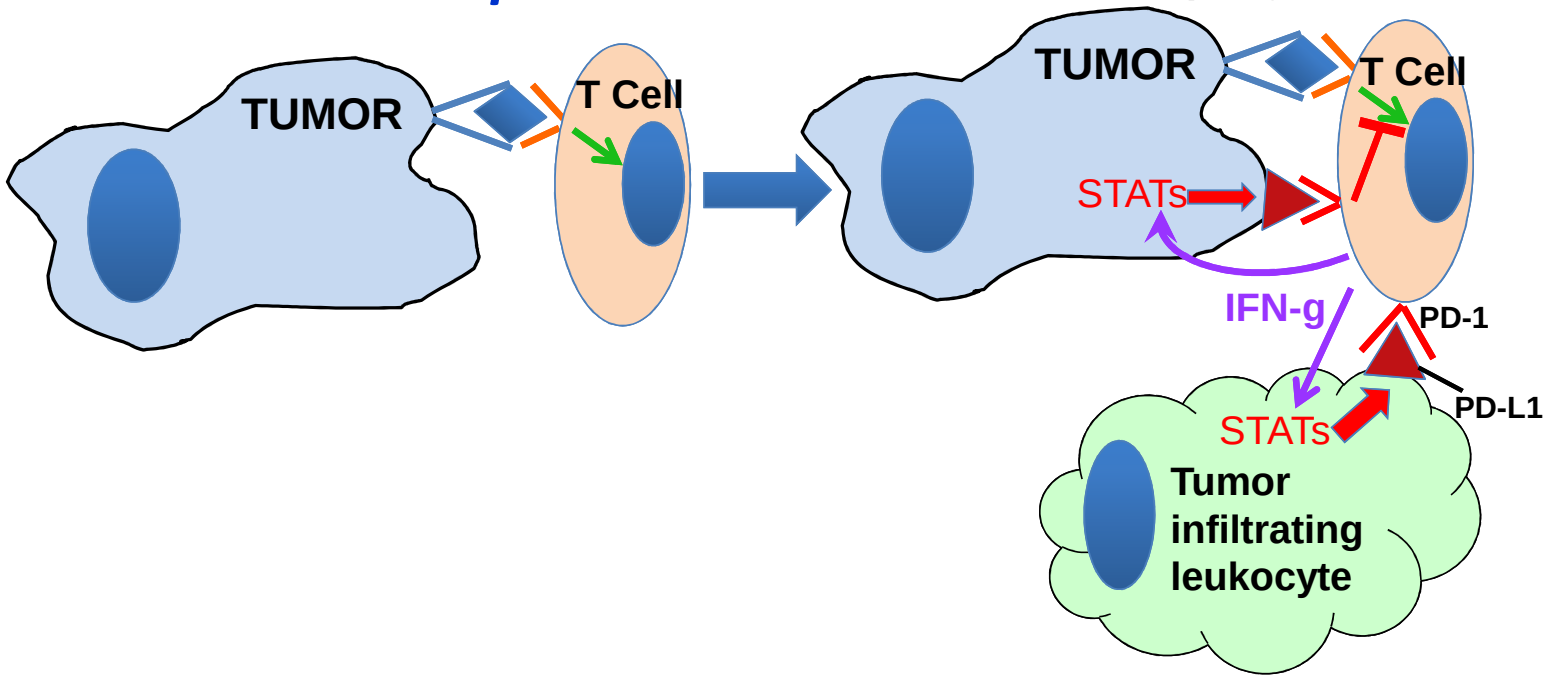
Innate (tumor cell intrinsic) Resistance



Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive Resistance

T cell-induced PD-L1 up-regulation

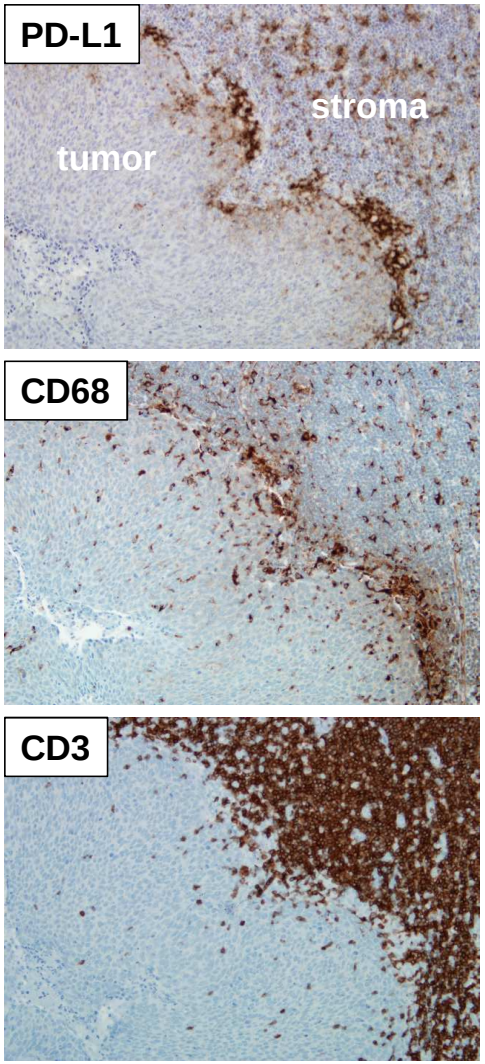


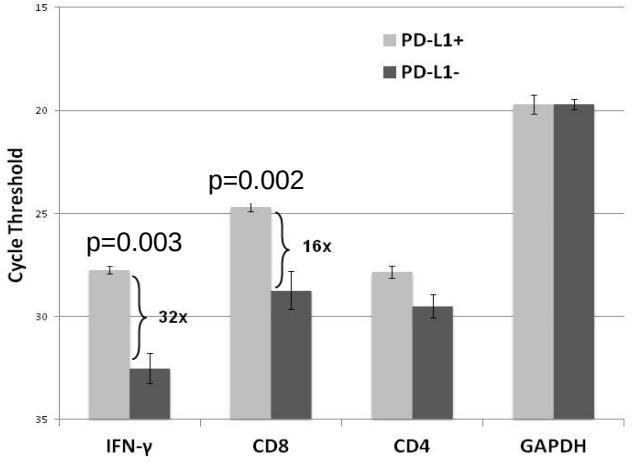
Viral antigens are foreign to the immune system and should be strong immune stimulants in virus-associated cancers

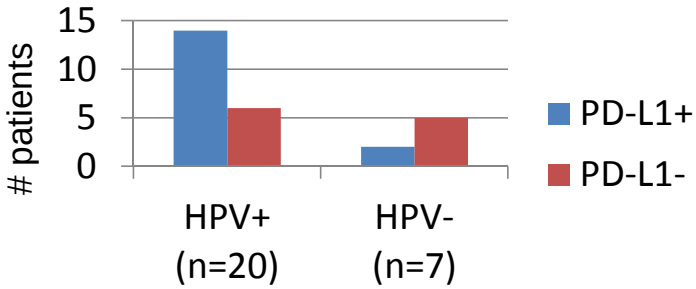
QUESTIONS:

- Do virus-associated cancers over-express PD-L1, PD-1, and other immunosuppressive ligands/receptors?
- Are virus-associated cancers responsive to anti-PD-1 therapy?
- Do viral antigens provide biomarkers for clinical response?

“Interface” PD-L1 expression in oropharyngeal SCCHN: association with HPV, TILs, and IFN-g







Lyford-Pike, Pai et al., Cancer Res 2013

Response in patient with head and neck cancer receiving anti-PD-L1 (MEDI4736) therapy

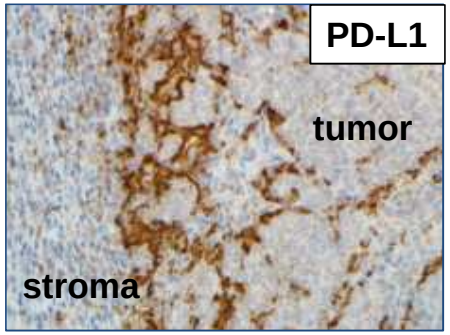
Baseline

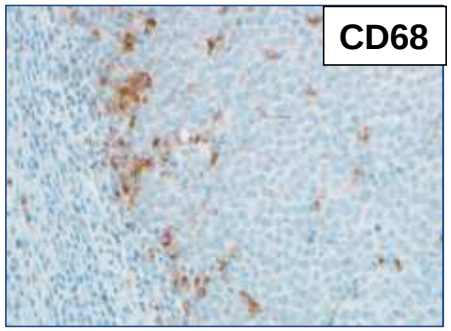
Day 28

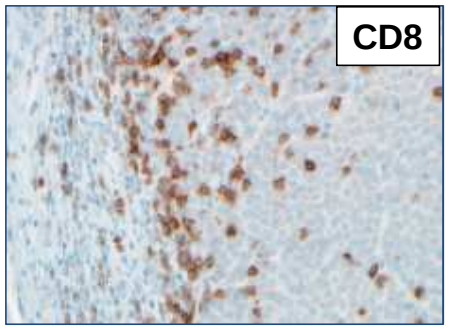
- 96 y.o. female
  - Progressed on previous cetuximab
  - HPV negative, PD-L1 positive
  - Treatment ongoing at 8 weeks

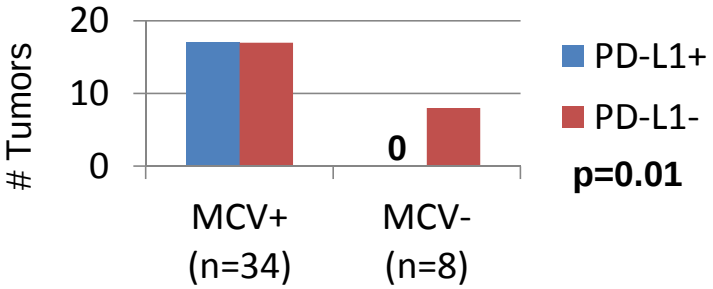
Preliminary response rate 14% in patients with advanced SCCHN.

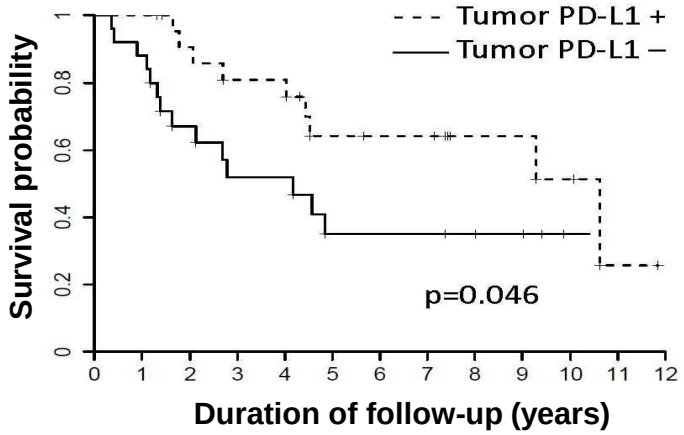
PD-L1 expression in Merkel cell Ca: association with MCPyV, CD8+ TILs, and overall survival









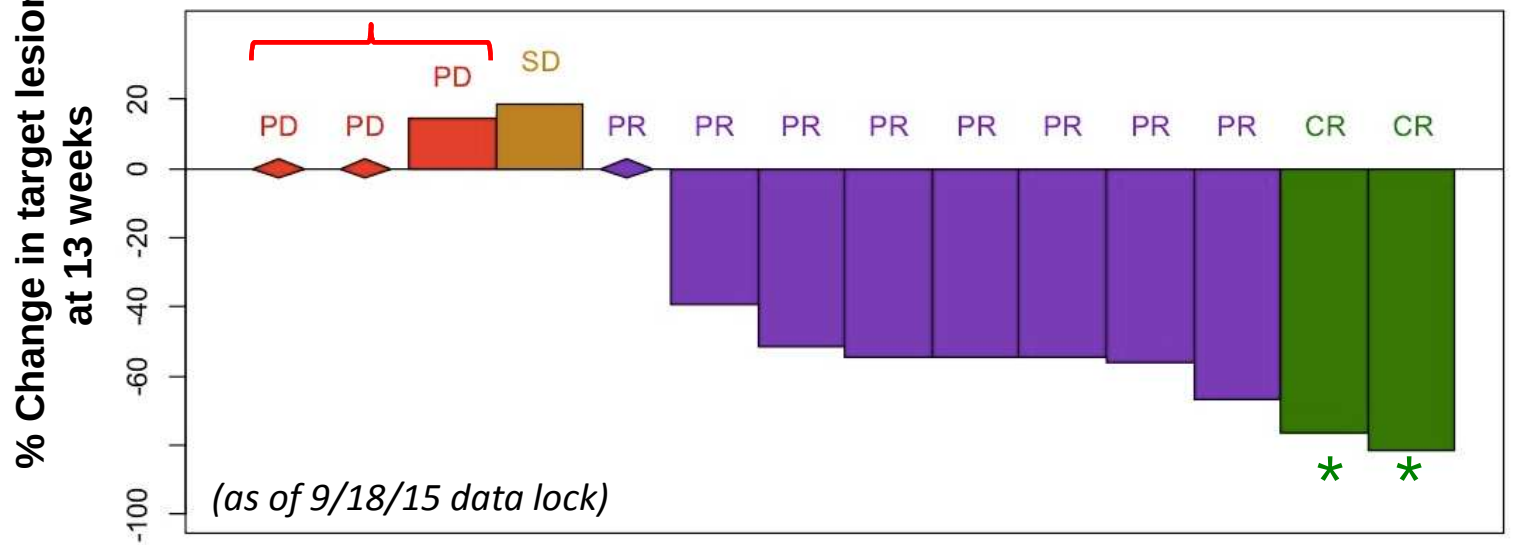


Lipson et al., Cancer Immunol Res 2013

Interim data: response of MCC to anti-PD-1 (pembrolizumab)

Progression based on new lesions

10/14 patients = 71% ORR



Progressive disease: target lesion f/u data initially not available =

Partial Response: 1st scan data initially not available, at 2nd scan was -70% =

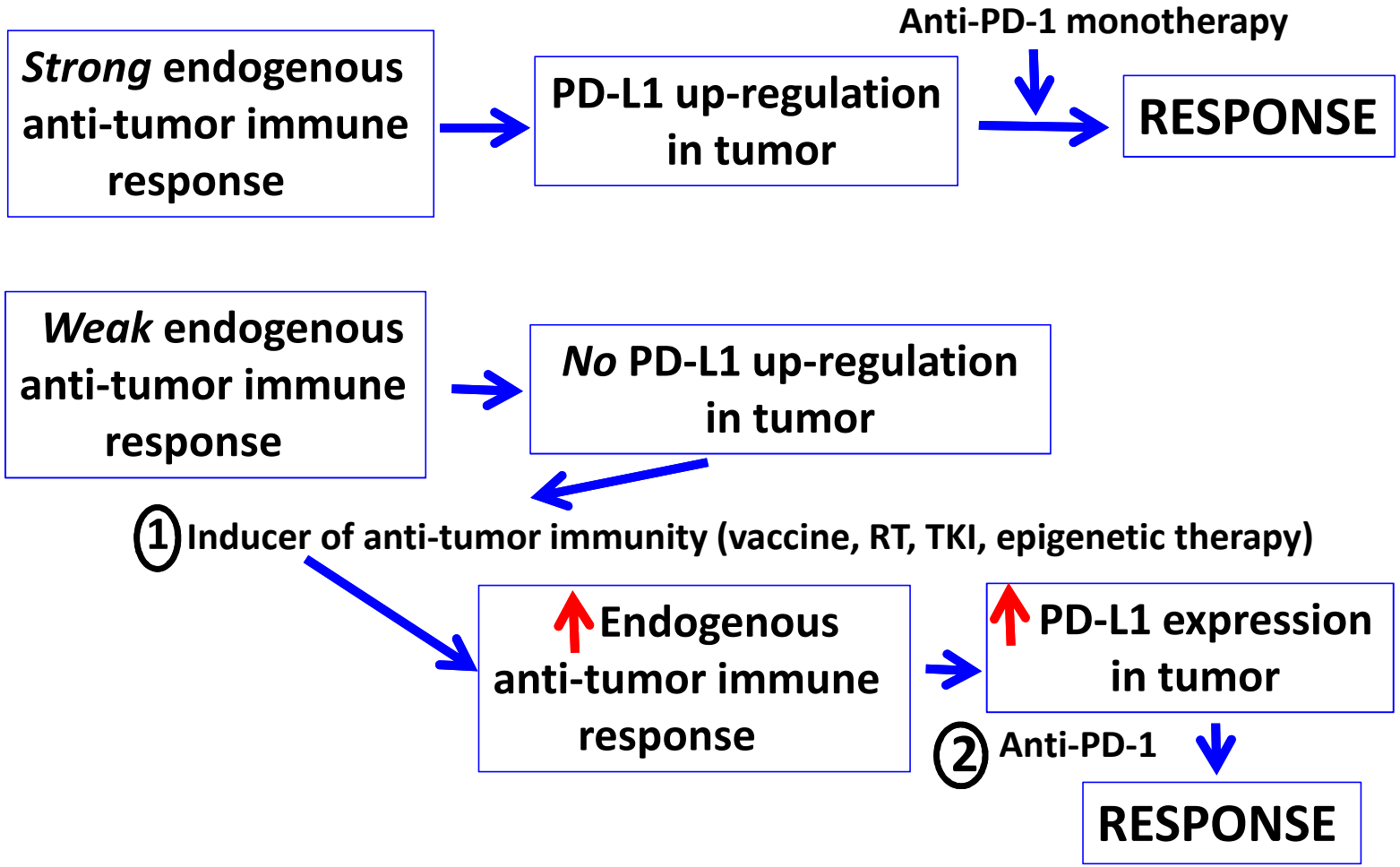
Nghiem et al., ESMO 2015

*Complete responses (RECIST 1.1) occurred in lymph nodes that regressed to < 10 mm.

Finding synergistic treatment combinations: PD-L1 expression as a guide to prioritizing clinical testing

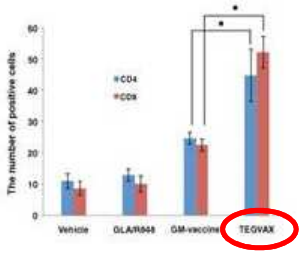
- Can *post-treatment enhancement* of tumor PD-L1 expression identify immunogenic cancer therapies that could be combined effectively with anti-PD-1/PD-L1?

Therapeutic implications for PD-1 pathway blockade in adaptive resistance model

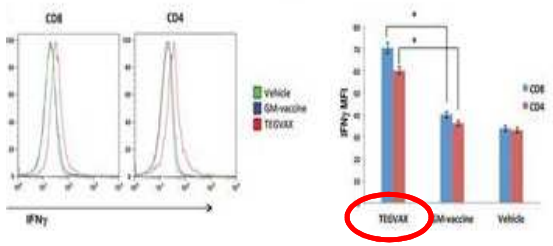


Synergy of a melanoma vaccine with anti-PD-1 in a murine model

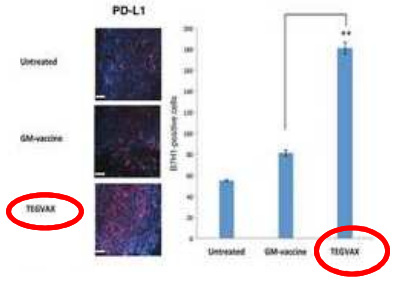
Vaccine increases TILs



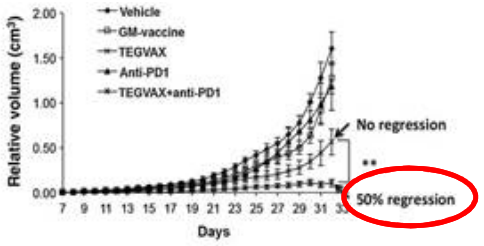
TILs produce IFN-gamma



Tumor expresses PD-L1



Tumor responds to vaccine + anti-PD-1



Fu, Kim, et al., Cancer Res 2014

Conclusions

- Monotherapy with anti-PD-1/PD-L1 is a “common denominator” for treating diverse cancer types
- Immunologic, genetic and viral biomarkers can guide the “personalized” application of these drugs
- Tumor markers can guide combination therapies to enhance the impact of anti-PD-1/PD-L1 and render “resistant” tumors sensitive to treatment
- Preclinical research can provide the evidence needed to prioritize treatment combinations for clinical testing

Cancer Immunology Program at Johns Hopkins 2015

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