SITC 2016

NATIONAL HARBOR, MD
NOVEMBER 9-13, 2016

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Society for Immunotherapy of Cancer

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PD-1 blockade in cancer treatment: immunotherapy meets precision medicine

Suzanne L. Topalian

November 12, 2016

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Society for Immunotherapy of Cancer

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Presenter Disclosure Information

Suzanne L. Topalian

The following relationships exist related to this presentation:

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

Grant/Research support from: Bristol-Myers Squibb; and (spouse) Aduro

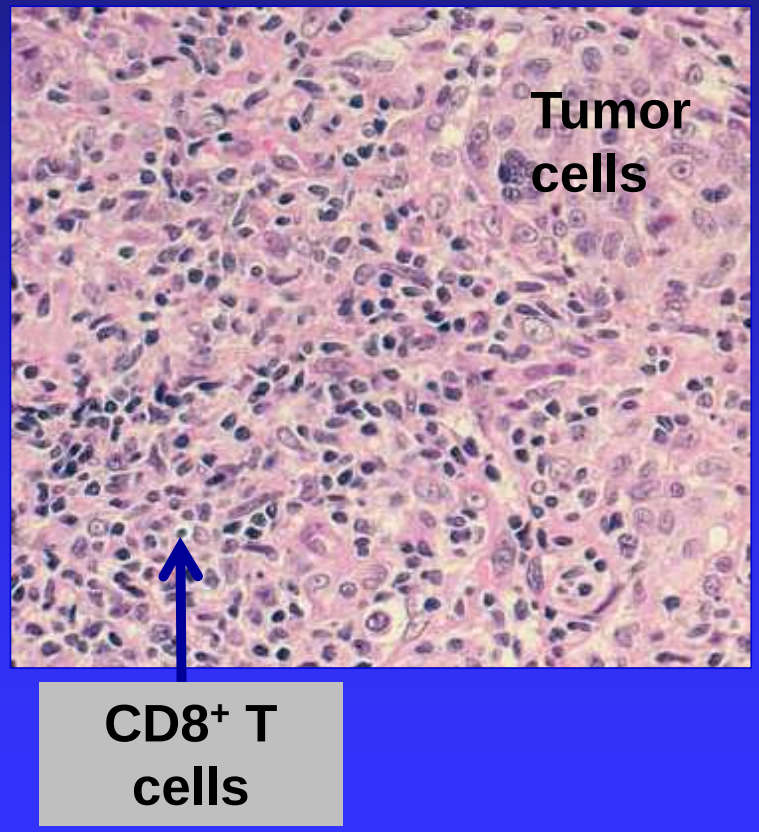
Stock/stock options: Five Prime Therapeutics; and (spouse) Aduro, Jounce Therapeutics, Potenza Therapeutics, Tizona

Royalties through institution (spouse): BMS, Potenza

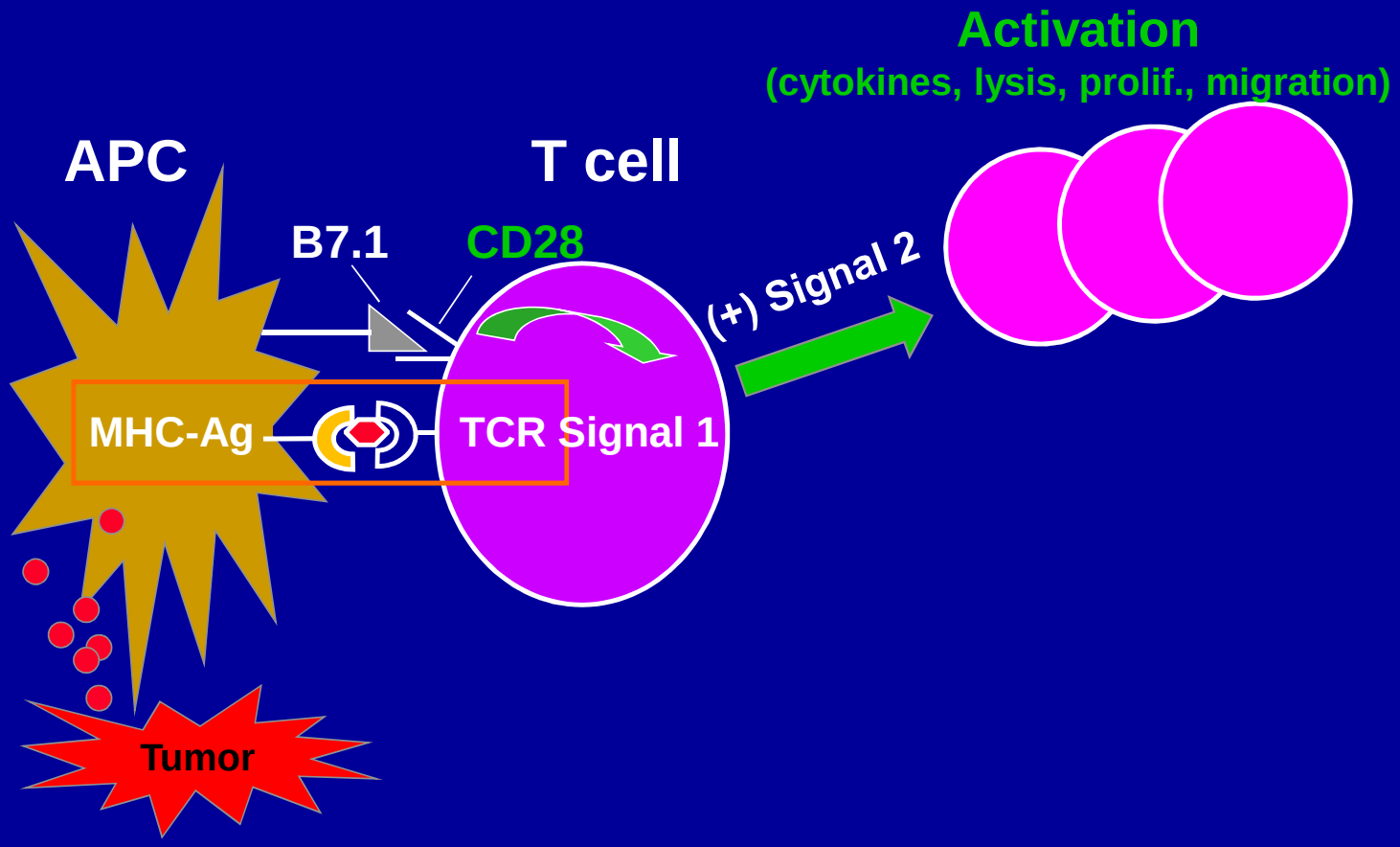
The war between the immune system and cancer

Melanoma as a case study: endogenous antitumor immunity exists but falls short

- Rare spontaneous regression of primary tumors
- Increased tumor incidence in immunosuppressed patients
- TILs and PBLs have anti-melanoma activity in vitro but are unable to halt tumor growth in the host



The PD-1/PD-L1 checkpoint: the tumor's first line of defense against immune attack



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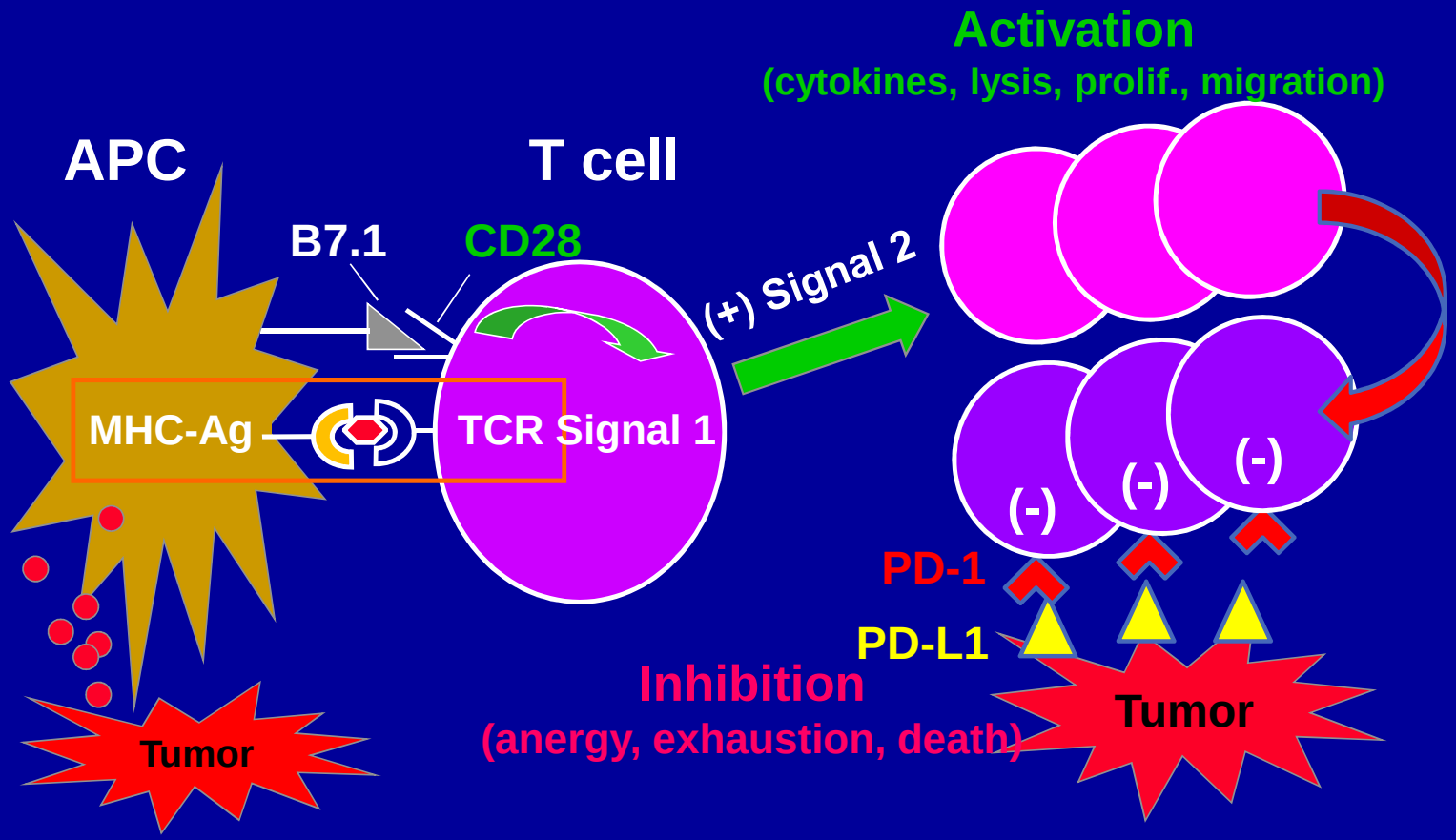
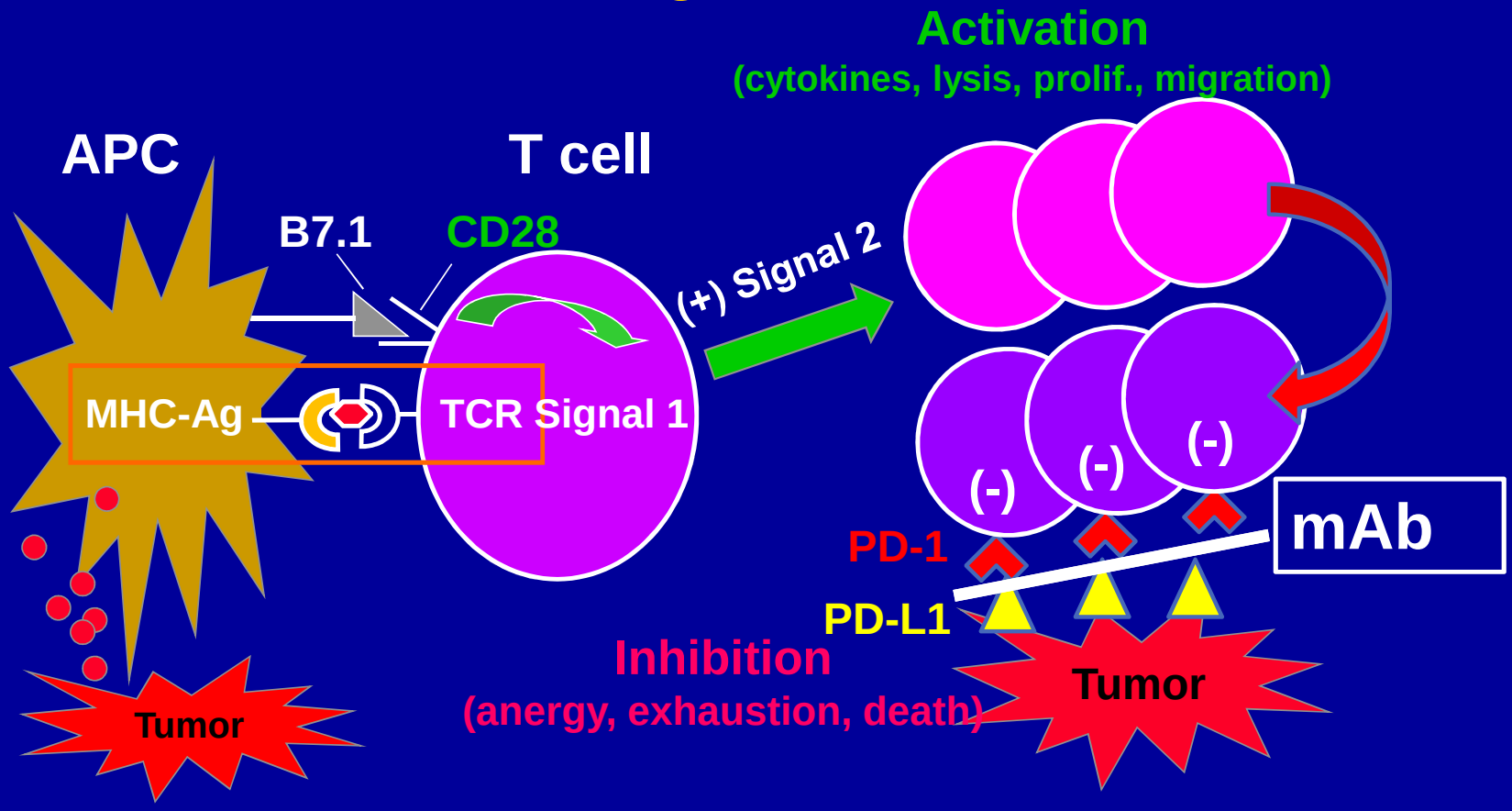


Keir et al, Annu Rev Immunol 2008; Pardoll, Nat Rev Cancer 2012

The PD-1/PD-L1 checkpoint: the tumor's first line of defense against immune attack



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

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

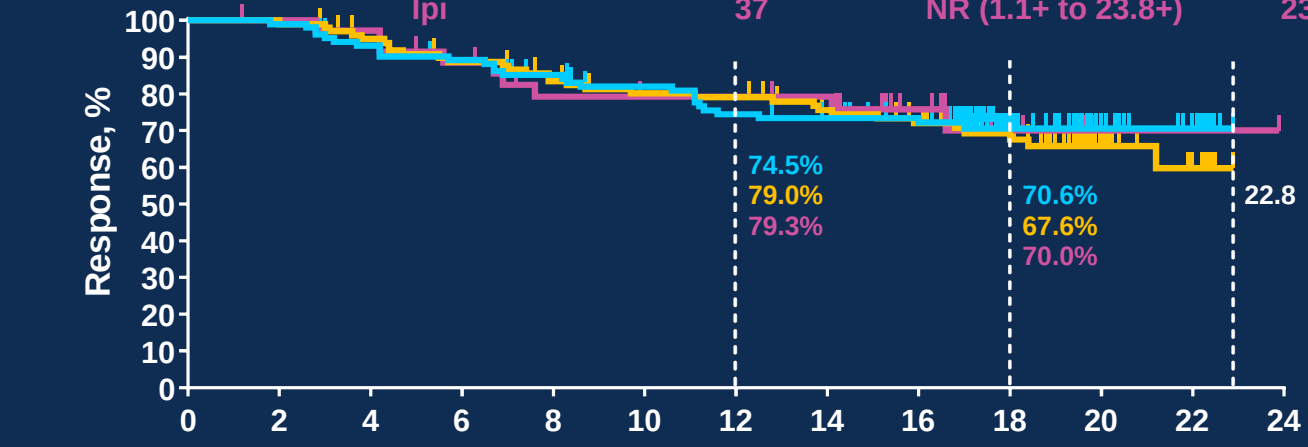
Objective tumor regressions in patients with:

- Melanoma (17-50% of patients responding)
- Lung cancer (10-30%)
- Kidney cancer (12-29%)
- Bladder cancer (15-30%)
- Head and neck cancer (20-25%)
- Hodgkin lymphoma (65-87%)
- Ovarian cancer (6-23%)
- Gastric cancer, TNBC, HCC, mesothelioma, ...

…… a "common denominator" for cancer therapy

Duration of Response: Keynote-006

Arm	Responders, n	Median (range), mo	Ongoing Response
Pembro Q2W	103	NR (1.8 to 22.8+)	69 (67%)
Pembro Q3W	100	NR (2.0 to 22.8+)	60 (60%)
Ipi	37	NR (1.1+ to 23.8+)	23 (62%)

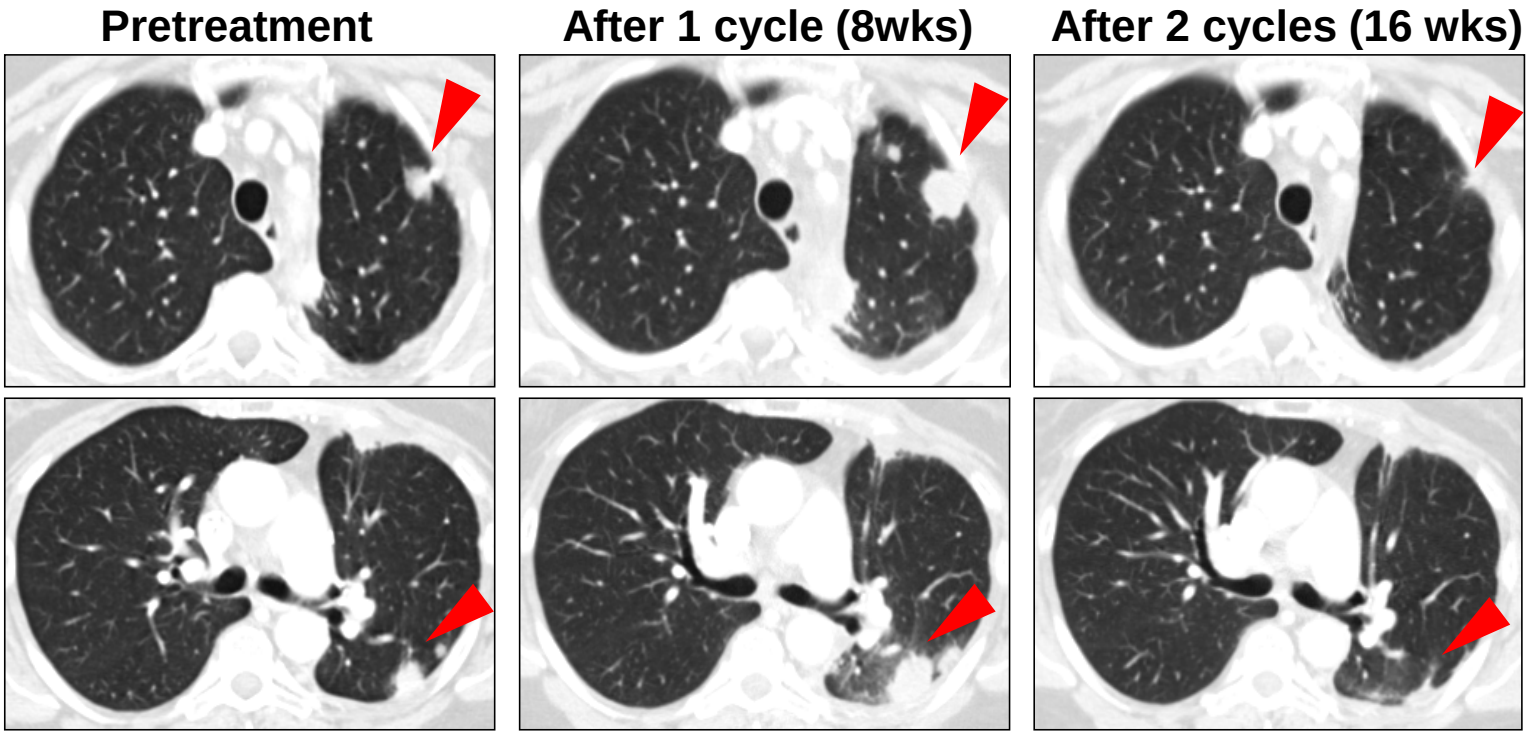


No. at risk

Pembro Q2W	103	102	94	89	82	76	69	66	62	32	17	9	0
Pembro Q3W	100	100	92	85	78	73	72	65	60	41	13	8	0
Ipi	37	36	34	30	25	24	24	23	16	9	4	3	0

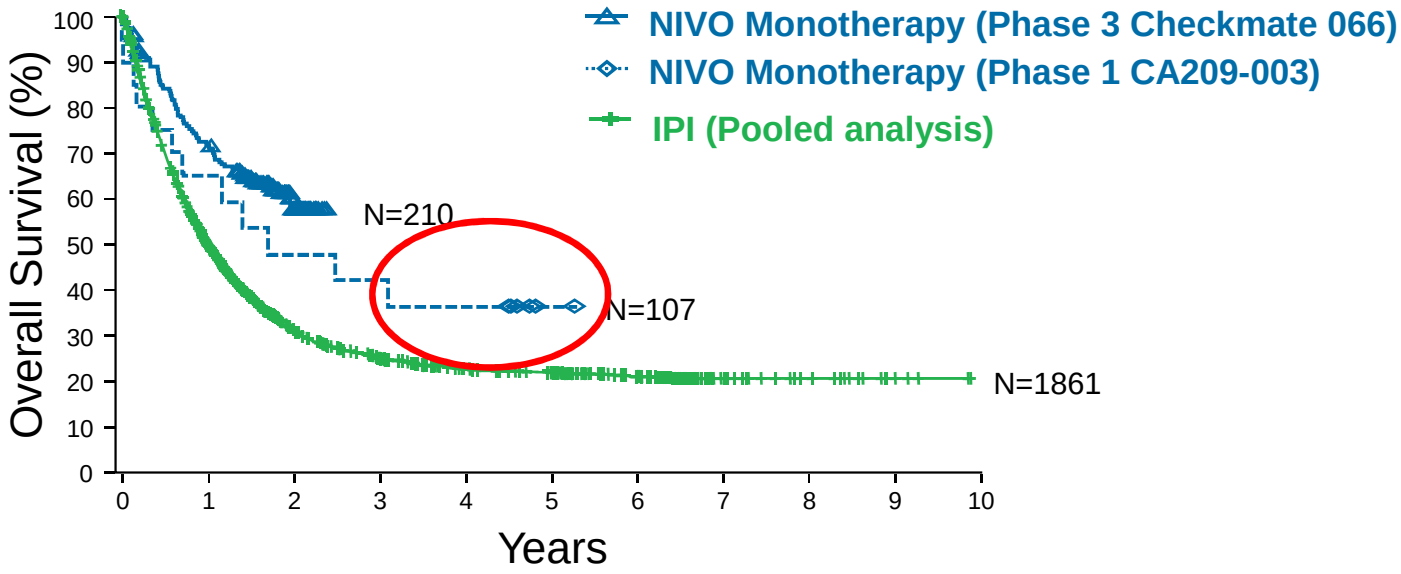
Adapted from Schachter et al., ASCO 2016

Unconventional response patterns: “immune-related” response of metastatic NSCLC to anti-PD-1



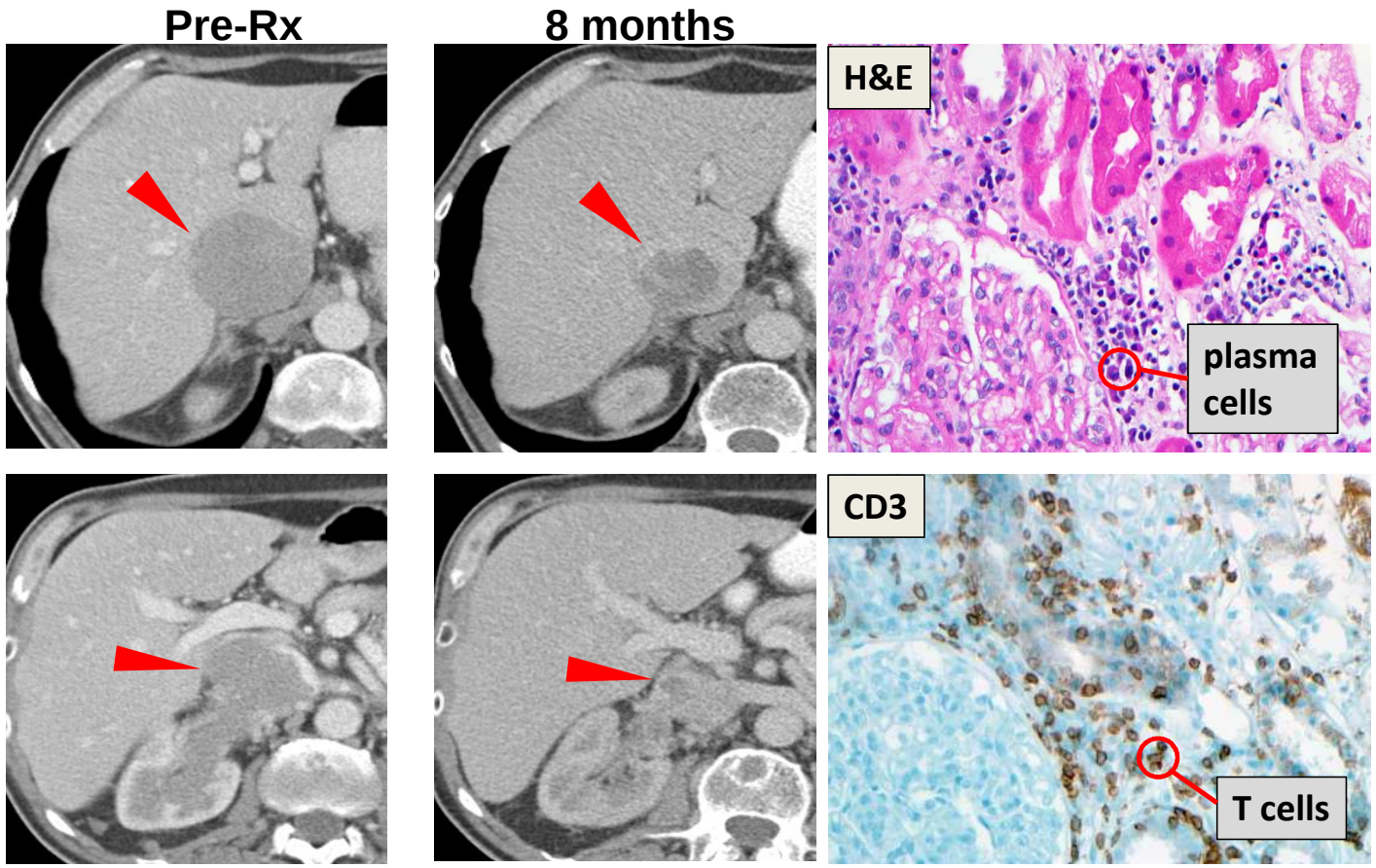
Topalian et al., NEJM 2012

Long-term survival: patients with melanoma receiving immune checkpoint blocking drugs



Hodi et al, AACR 2016, abstr. CT001

Immune-related toxicities consistent with MOA: nephritis (T and B cell infiltrates) in a patient with metastatic melanoma responding to anti-PD-1



Current challenges in I-O drug development

- Deeper mechanistic knowledge of underlying biology
- Synergistic combination regimens to enhance efficacy (*next session*….)
- Biomarkers to identify patients or tumor types most likely to respond to therapy

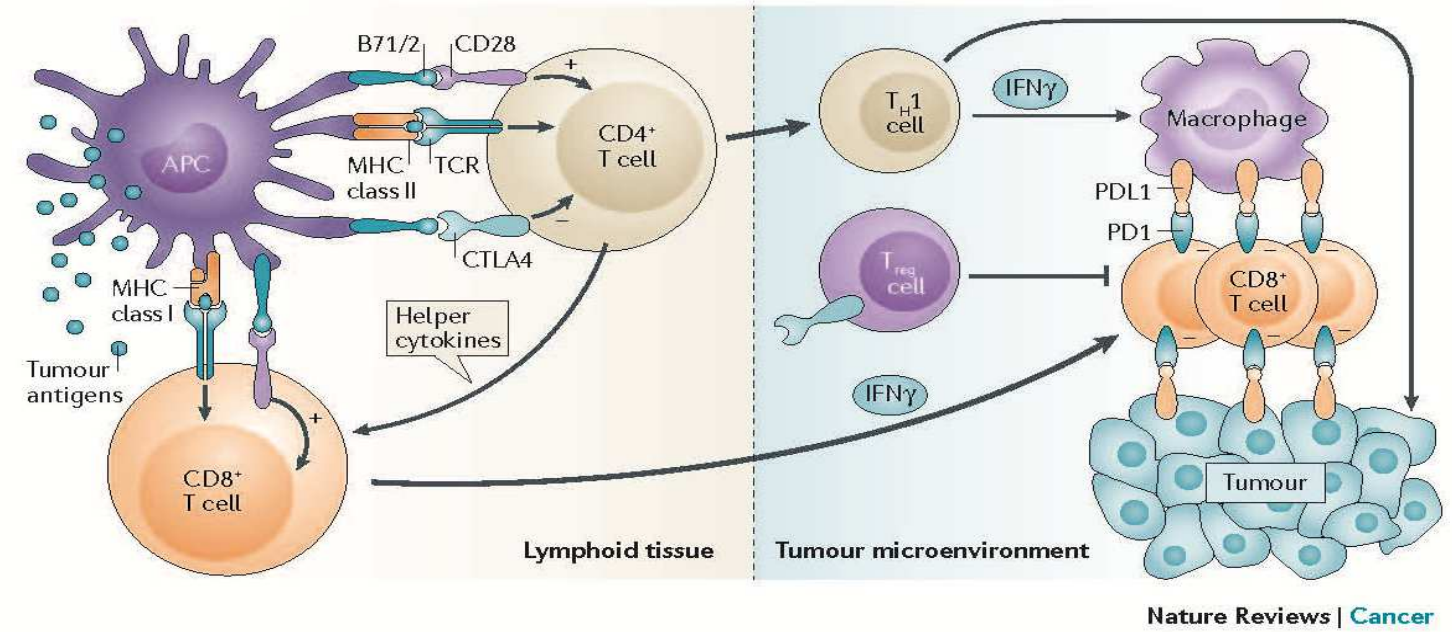
Can a “precision medicine” approach enhance the impact and applicability of anti-PD-1?

***Areas of unmet need*:**

- In generally unresponsive tumor types, identify patient subsets likely to benefit (e.g., colorectal, pancreatic, prostate Ca)
- Within responsive tumor types, identify patients unlikely to benefit
- Decisions for treatment sequencing: first-line vs. later line therapy

➢ ***Although anti-PD1/ PD-L1 drugs are broadly applicable, these considerations may be tumor type-specific***

Mechanism-driven biomarkers for immune checkpoint blockade



- **What are the recognized antigens?**
- **Does the tumor contain reactive T cells?**
- **Does the tumor express PD-1 ligands?**

Topalian et al., 2016

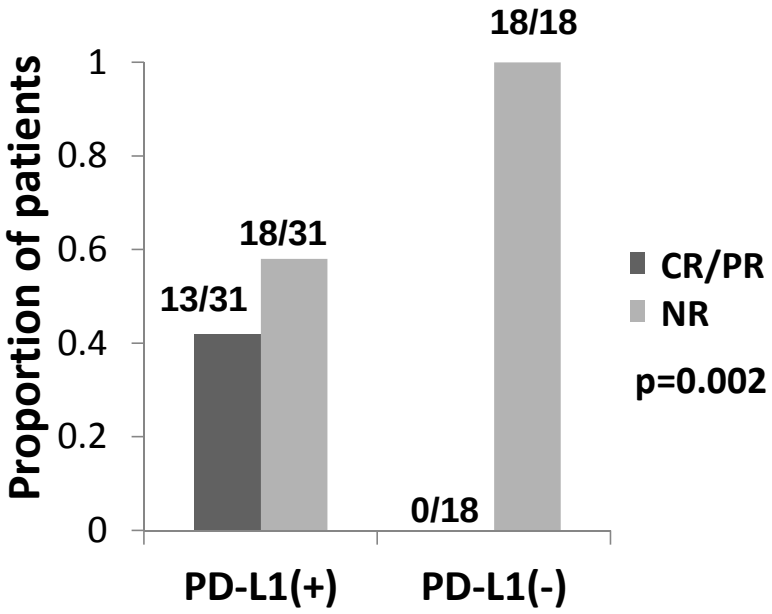
Areas of opportunity for mechanism-based biomarker development for anti-PD-1 therapies

- Immunologic
- Genetic
- Viral

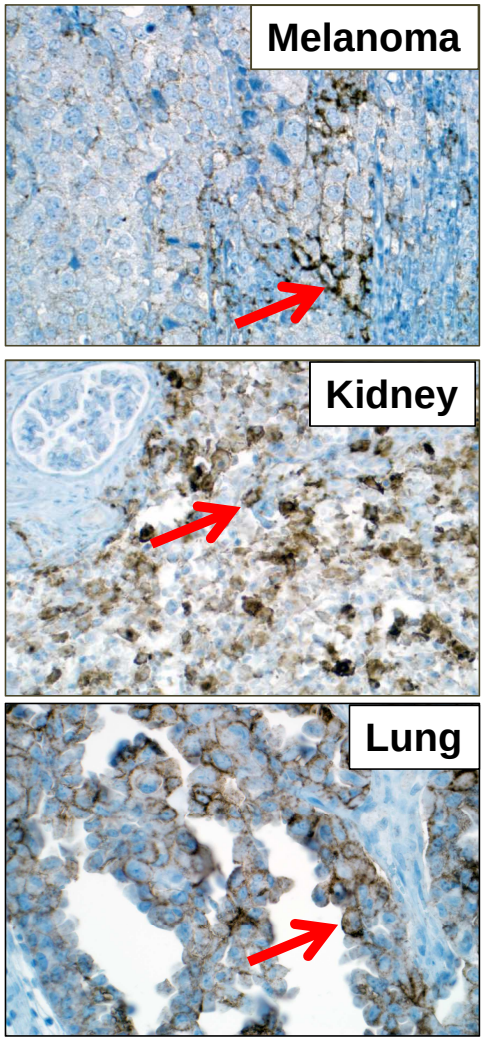
QUESTION:

Can immunological factors provide cross-cutting biomarkers for anti-PD-1 activity?

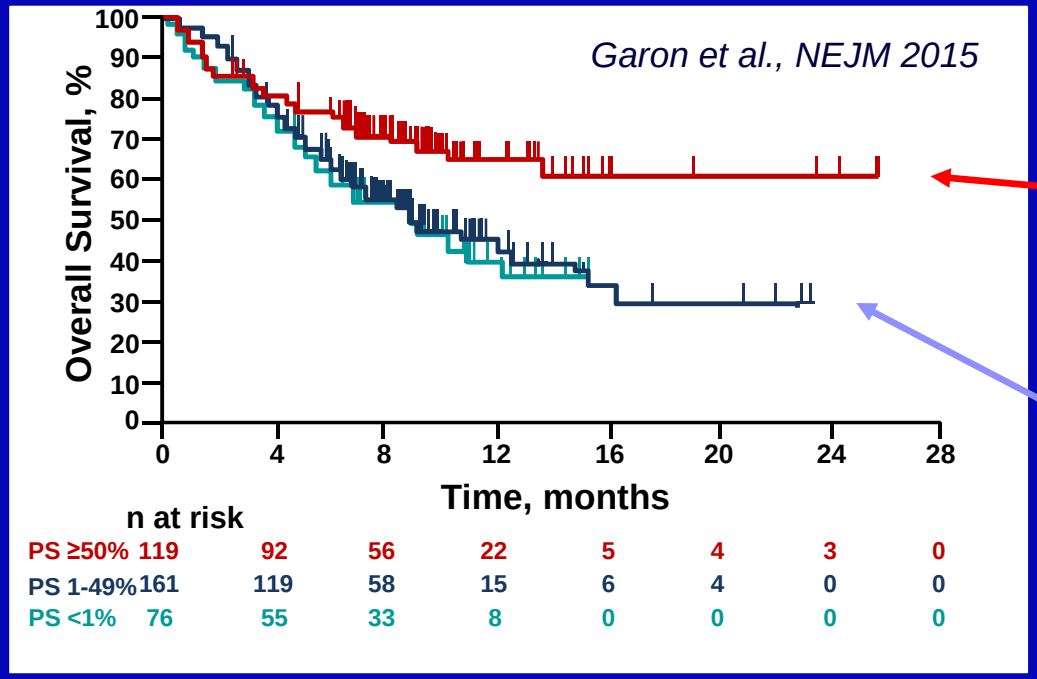
Preliminary correlation of PD-L1 expression in pre-treatment tumor biopsies, with response to anti-PD-1 therapy



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 efficacy of anti-PD-1 (pembrolizumab) in NSCLC: individualizing treatment strategy



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

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

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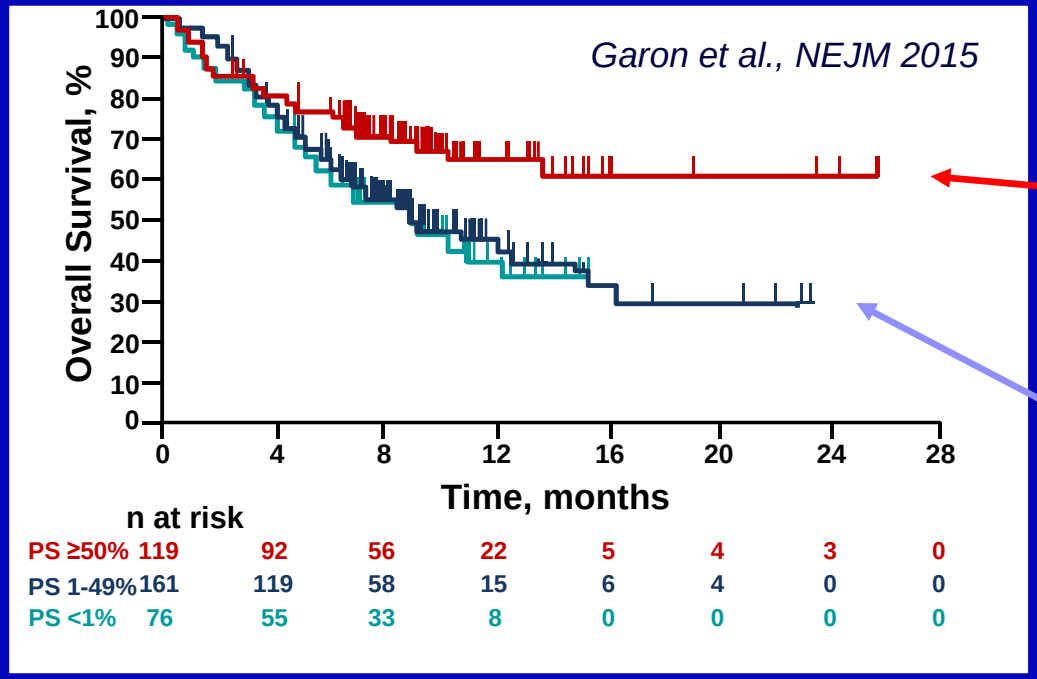

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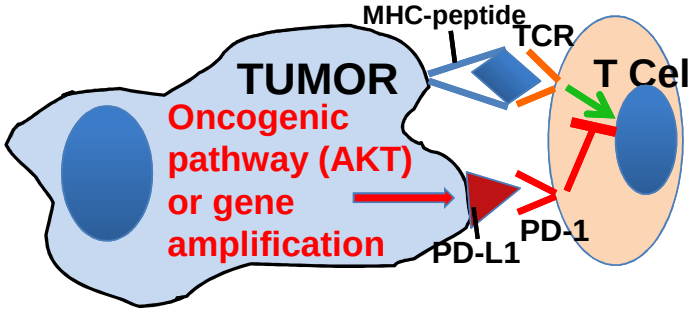
- **Response rate 45%**
- **Median OS not reached**

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

➢ ***Oct. 2016: FDA approves pembro as 1st line therapy for patients with tumors ≥50% PD-L1+, 2nd line for tumors ≥1% PD-L1+***

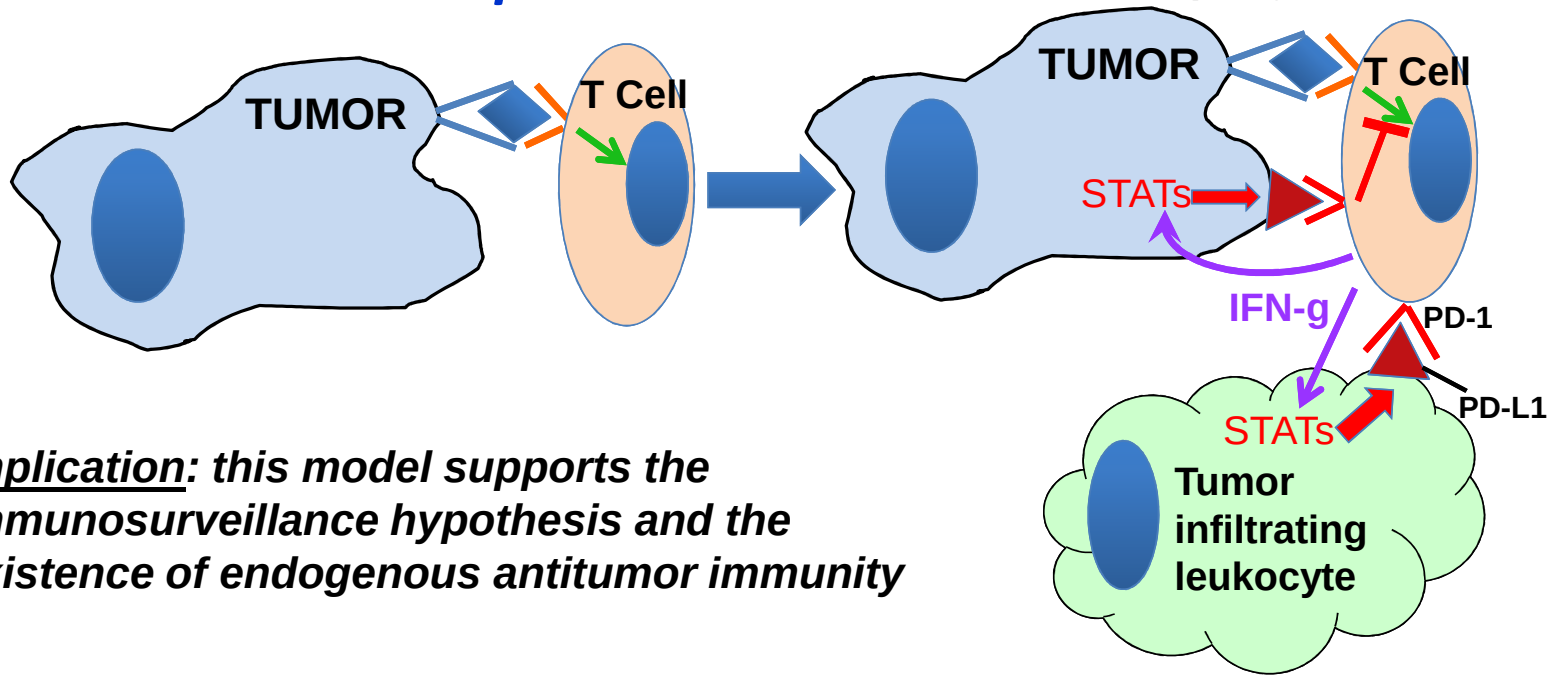
Innate (tumor cell intrinsic) Resistance



Constitutive tumor signaling induces PD-L1 on tumor cells

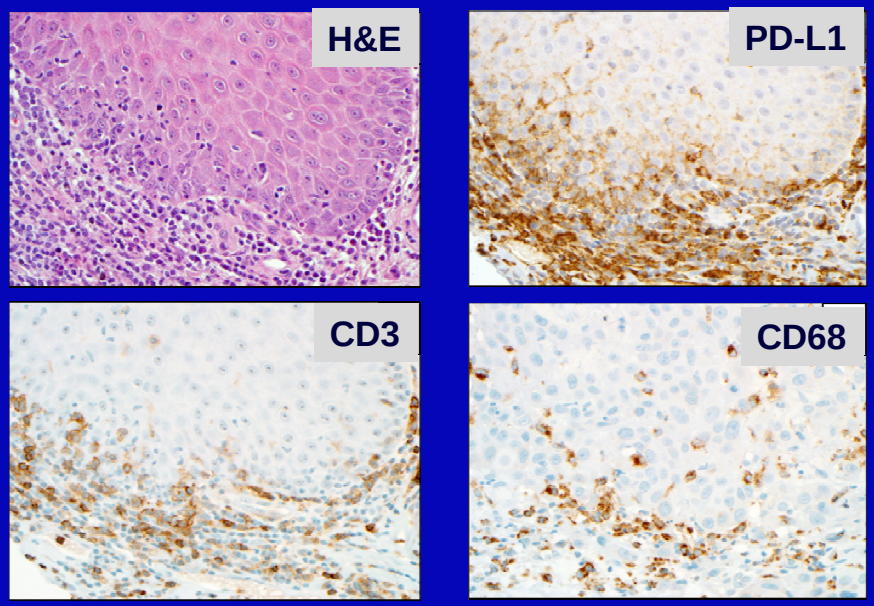
Adaptive Resistance

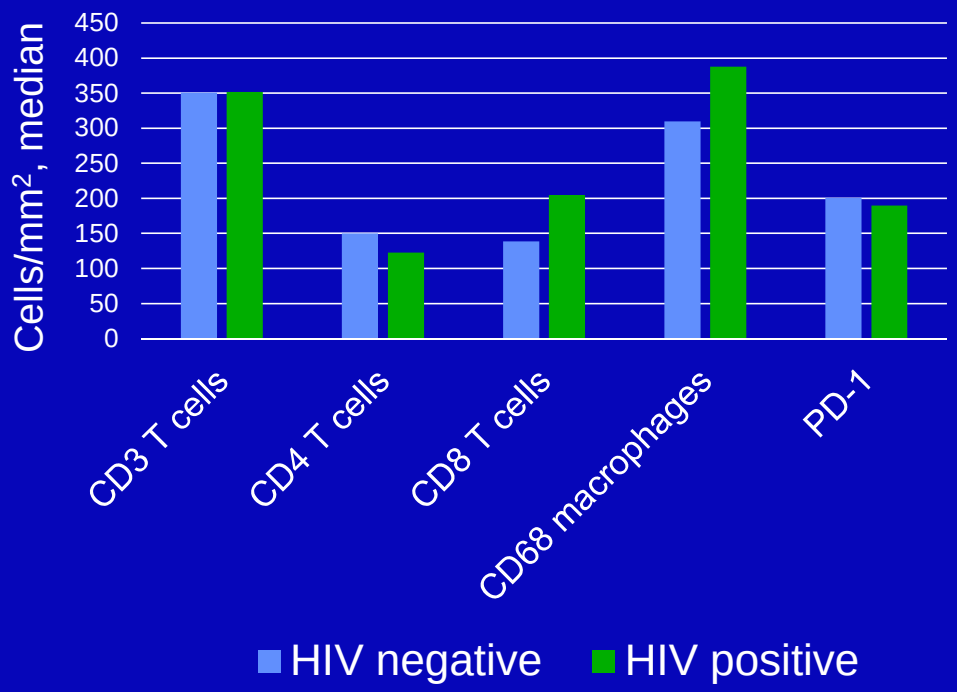
T cell-induced PD-L1 up-regulation



- ***<u>Implication</u>: this model supports the immunosurveillance hypothesis and the existence of endogenous antitumor immunity***

Re-examining underserved populations: tumor immune microenvironment in anal SCCs from HIV(+) vs. (-) patients



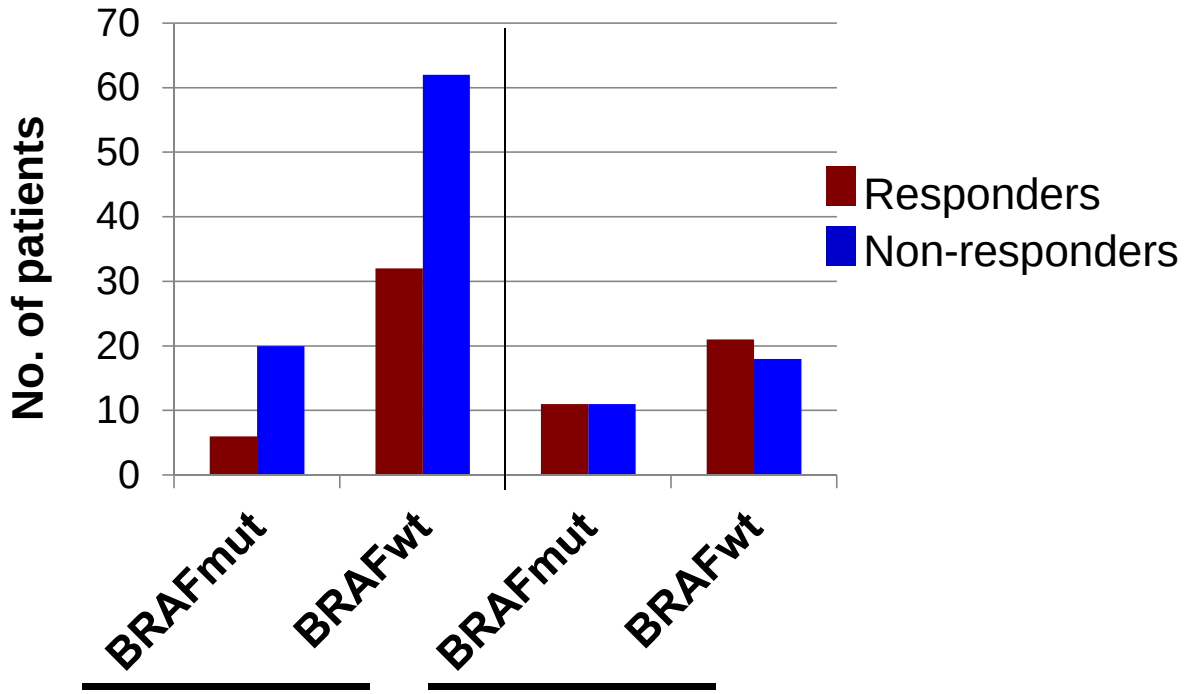


Kaunitz et al., Soc Invest Derm 2016, abstr. #241

QUESTION:

Can cancer genetics guide immunotherapy?

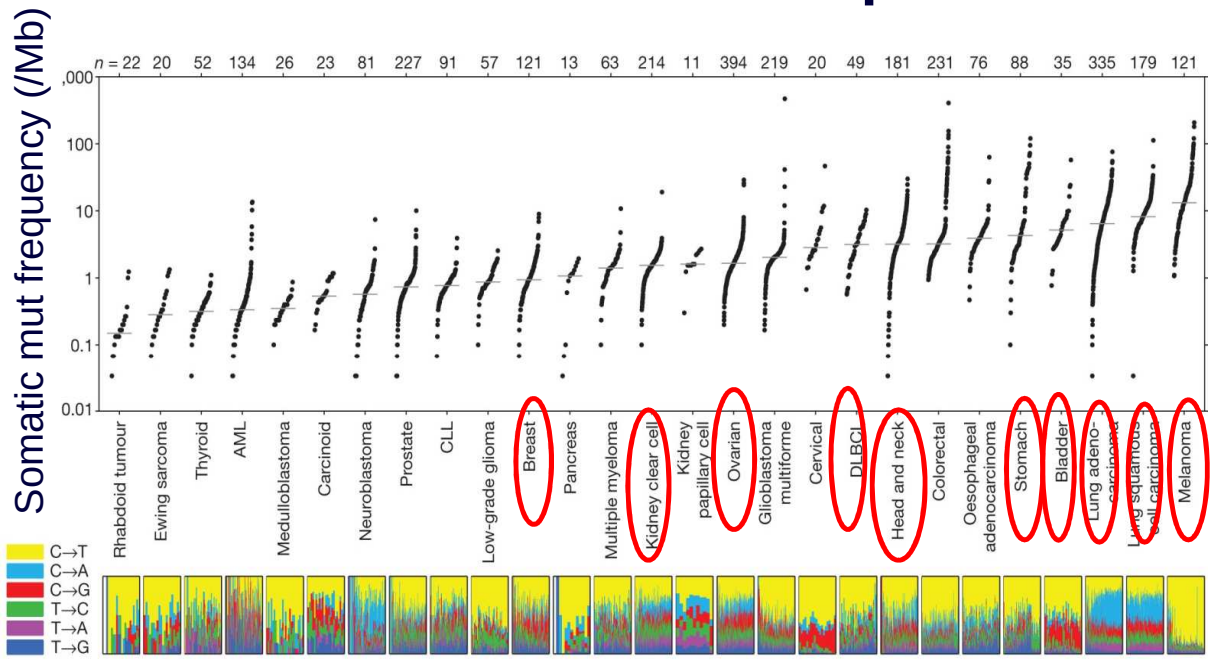
Response of melanoma to anti-PD-1 does *not* depend on BRAF mutational status



Weber et al., Lancet Oncol 2015 (nivolumab)

Tumeh et al., Nature 2014 (pembrolizumab)

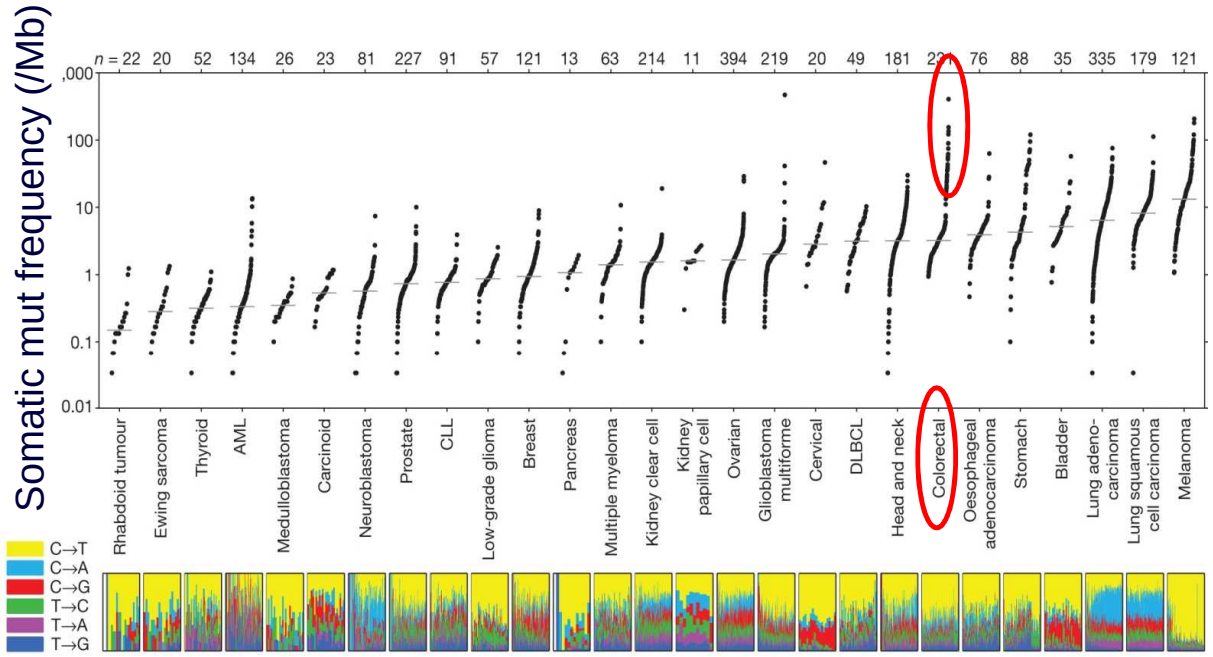
Does mutational load correlate with responsiveness to immune checkpoint blockade?



Lawrence et al., Nature 2013

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

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



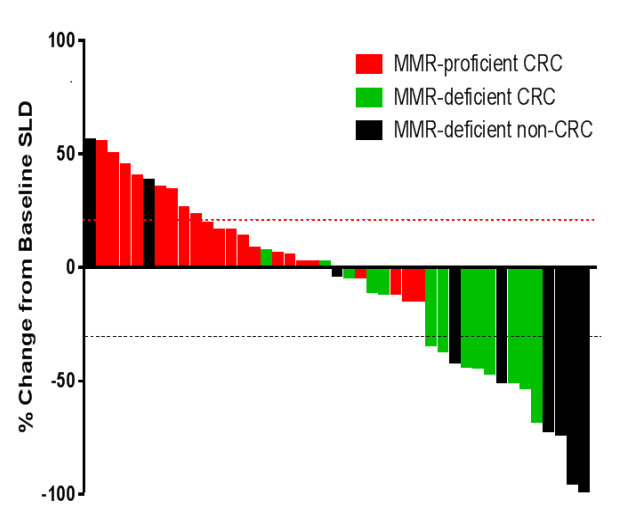
Lawrence et al., Nature 2013

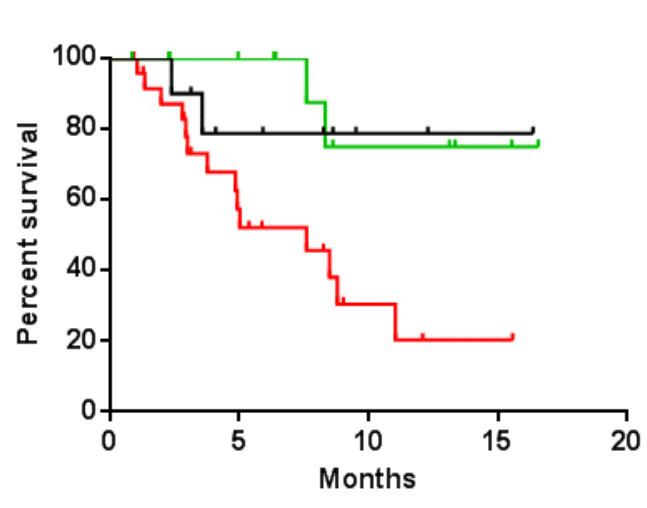
- ***Microsatellite instability (MSI): genetic hypermutability resulting from deficient mismatch repair (dMMR), present in ~15% colon cancers and in some other tumor types***

MSI-high genotype identifies patients likely to respond to anti-PD-1 therapy

	MMR-proficient colon cancer	MMR-*deficient* colon cancer	MMR-*deficient* non-colon Ca
Objective Response Rate	0%	62%	60%
Disease Control Rate	16%	92%	70%

GI, GYN, prostate Ca

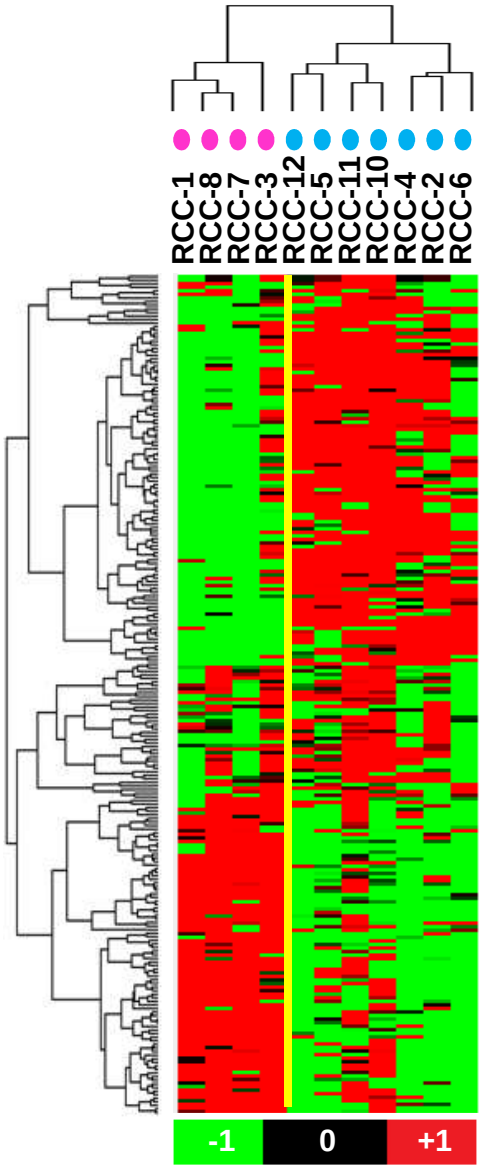




(Le, Diaz, et al., NEJM 2015)

Transcriptomics: a new dimension for I-O biomarker development

- Kidney cancers *resistant* to anti-PD-1 therapy express a metabolic gene signature
- Up-regulation of immunologic pathways is associated with *response*



- **Responders (R)**
- **Non-Responders (NR)**

Whole genome expression profiling

M. Ascierto et al., Cancer Immunol Res 2016

Virus-associated cancers

Observations:

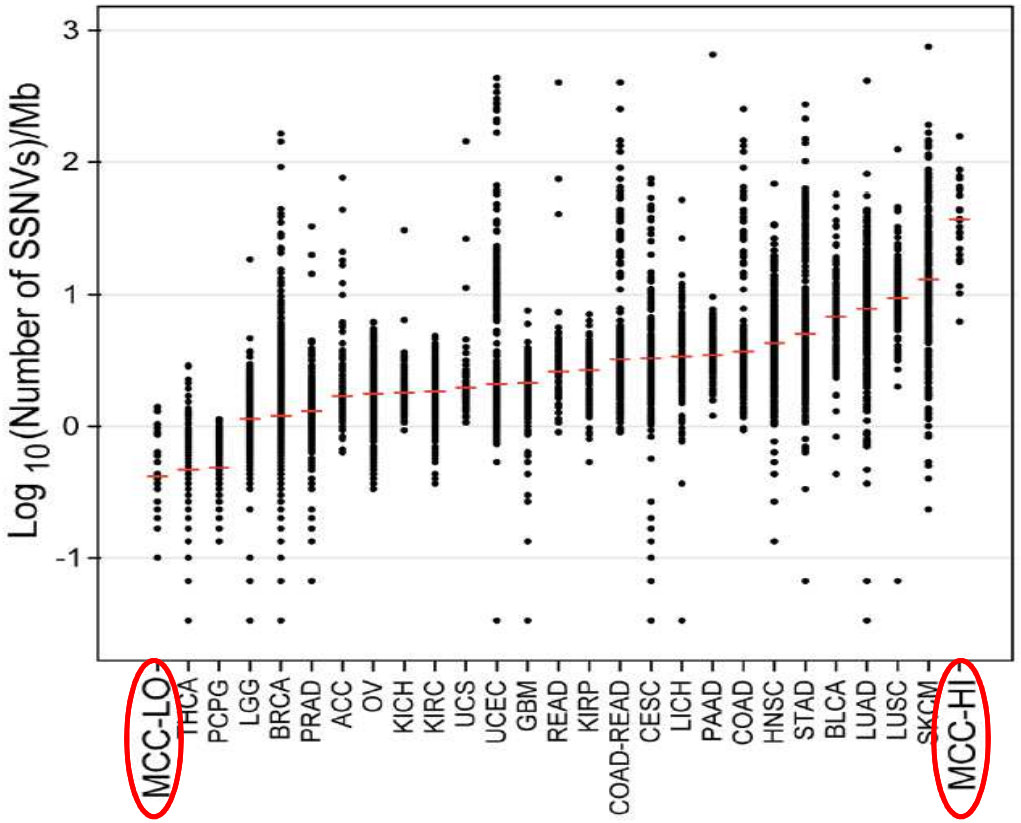
- Viral antigens are foreign to the immune system and are strong immune stimulants
- PD-1 and PD-L1 are expressed in virus+ tumors

Question:

- Do oncogenic viruses provide biomarkers for response to anti-PD-1 therapies?

Quality vs. quantity of tumor antigens: Merkel cell Ca

Virus(+) vs. (-) Merkel cell Ca: at the extremes of mutational frequency compared to TCGA data from other cancers



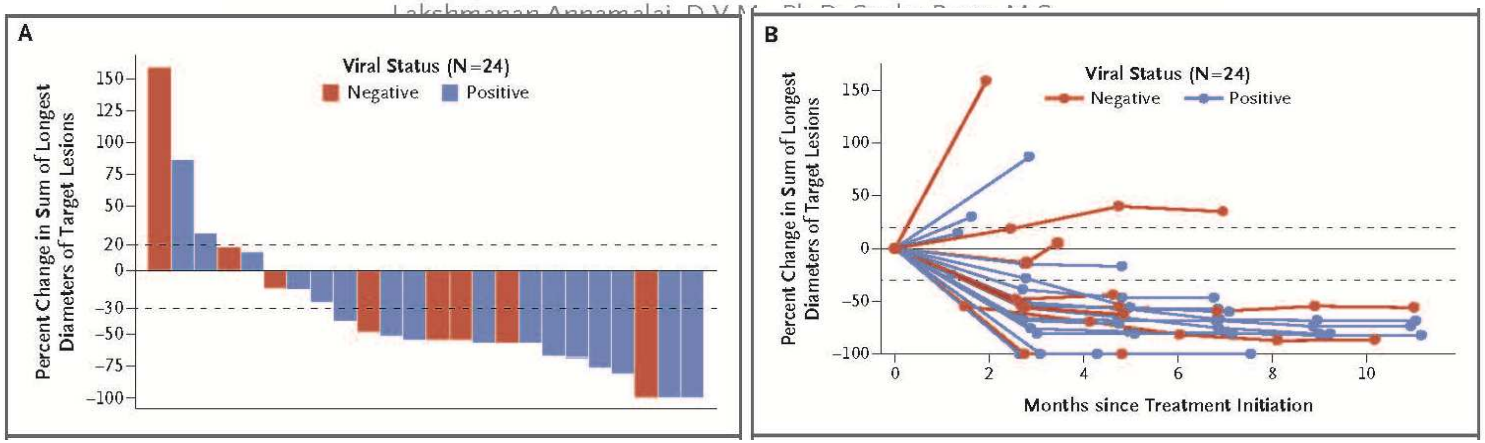
Goh et al., Oncotarget 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma

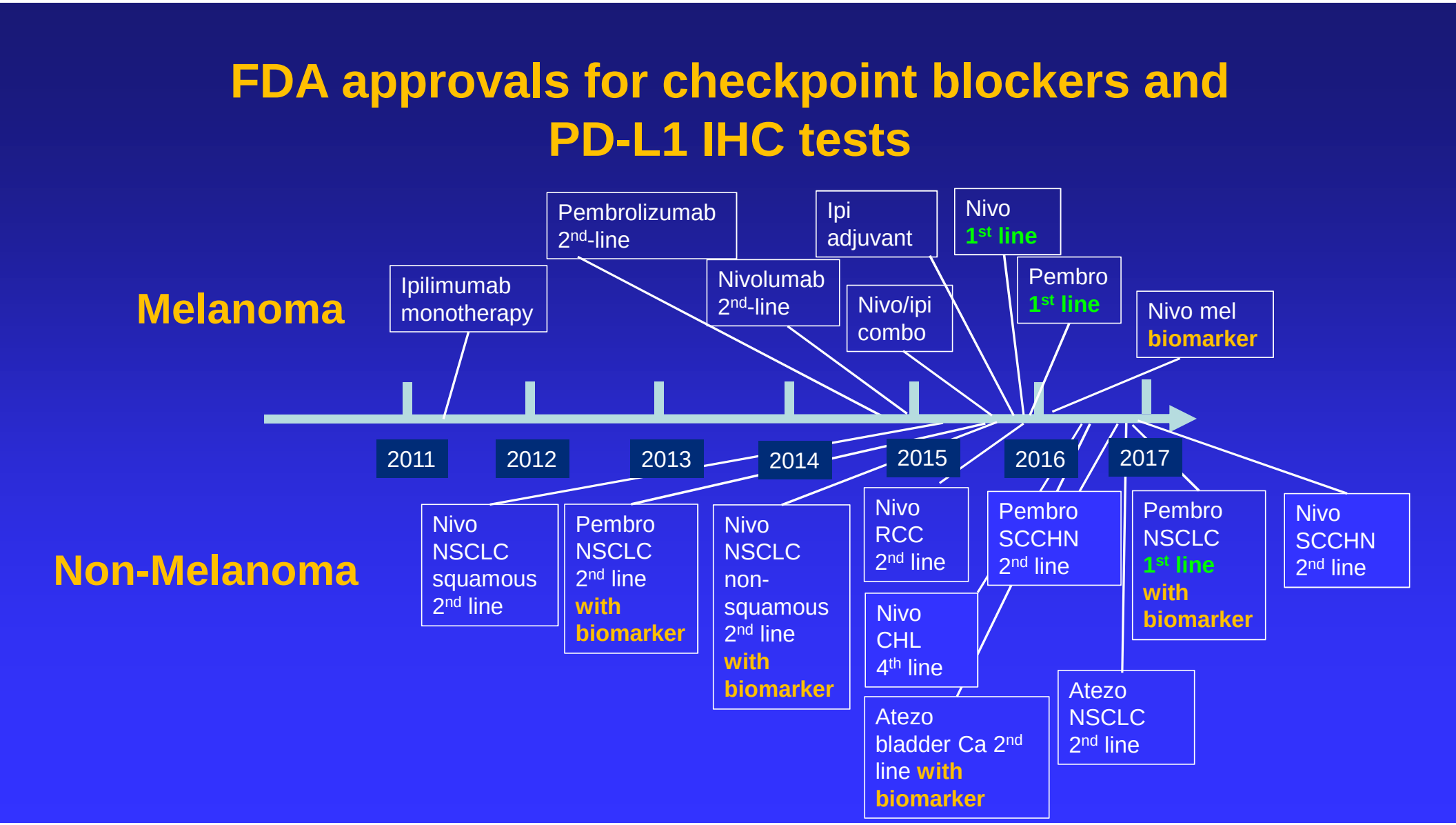
Paul T. Nghiem, M.D., Ph.D., Shailender Bhatia, M.D., Evan J. Lipson, M.D.,
Ragini R. Kudchadkar, M.D., Natalie J. Miller, B.A.,



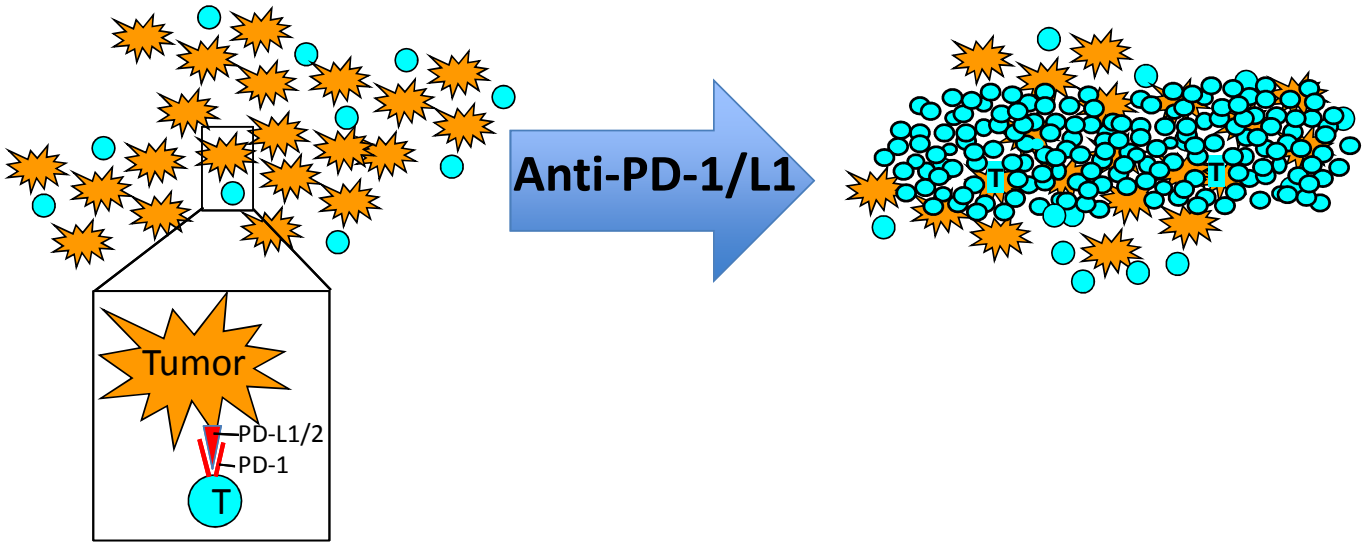
MCC antigens:

- Virus(+) tumors have a very low mutational burden but express shared viral oncoproteins that are strong immune stimulants (*ORR = 62%*)
- Virus(-) tumors have a very high carcinogen (UV light)-induced mutational burden (*ORR = 44%)*

FDA approvals for checkpoint blockers and PD-L1 IHC tests



Neoadjuvant checkpoint blockade as a primer for systemic antitumor T cell responses



Pardoll 2016

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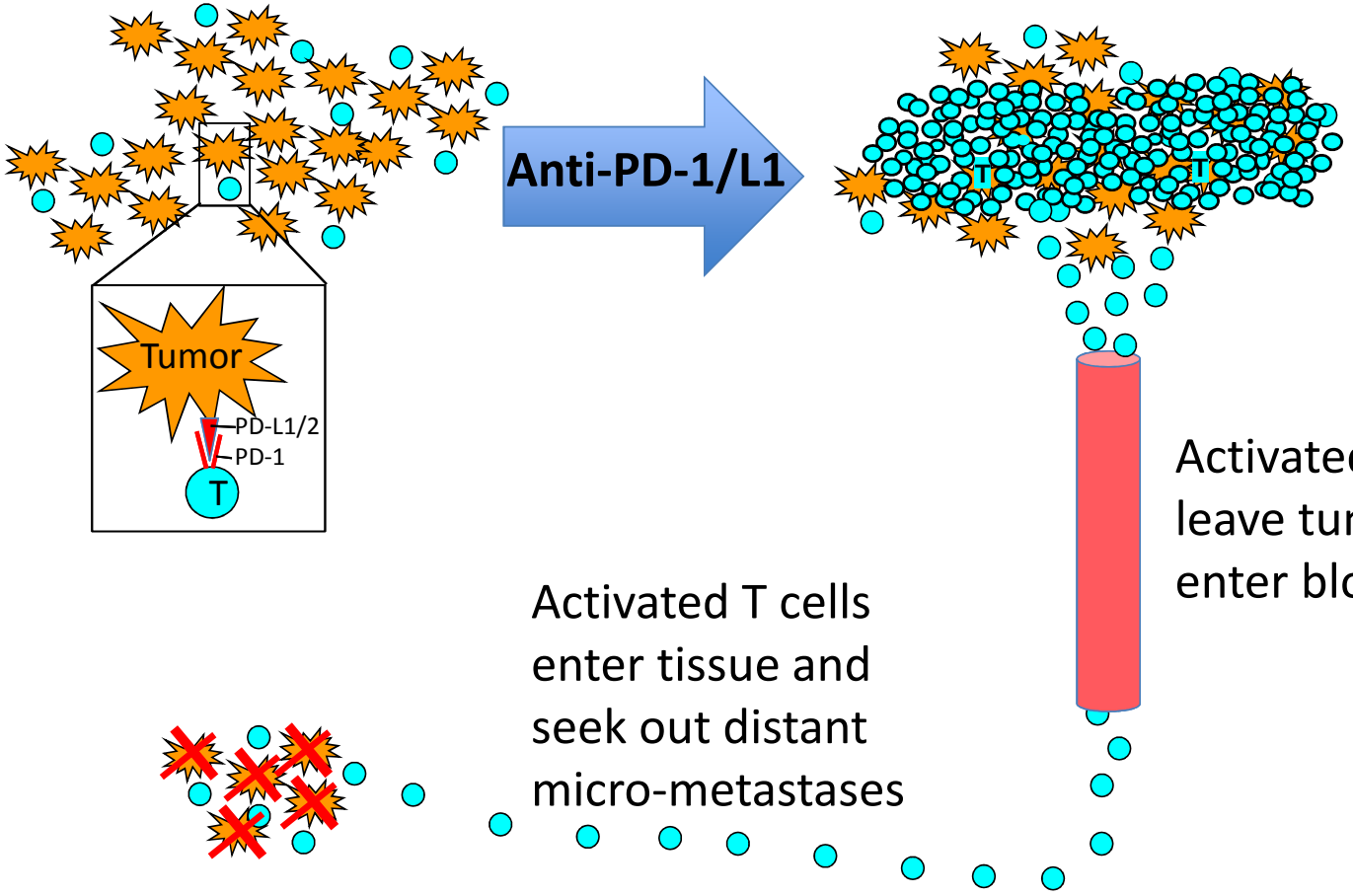
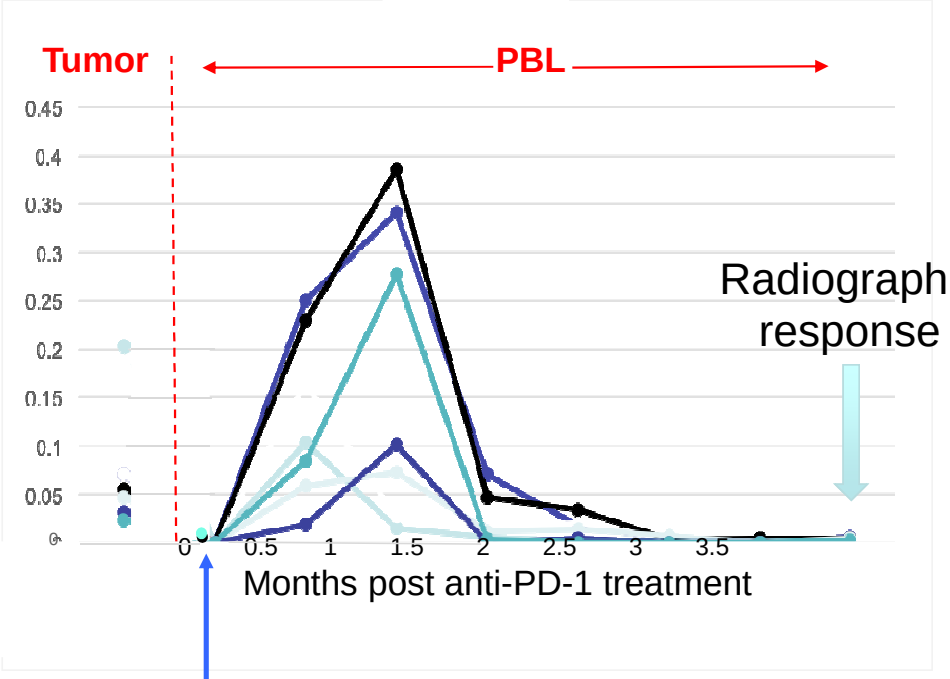


Pardoll 2016

Appearance of tumor-resident T cell clones (TCRseq) in peripheral blood following anti-PD-1 therapy (colon Ca)

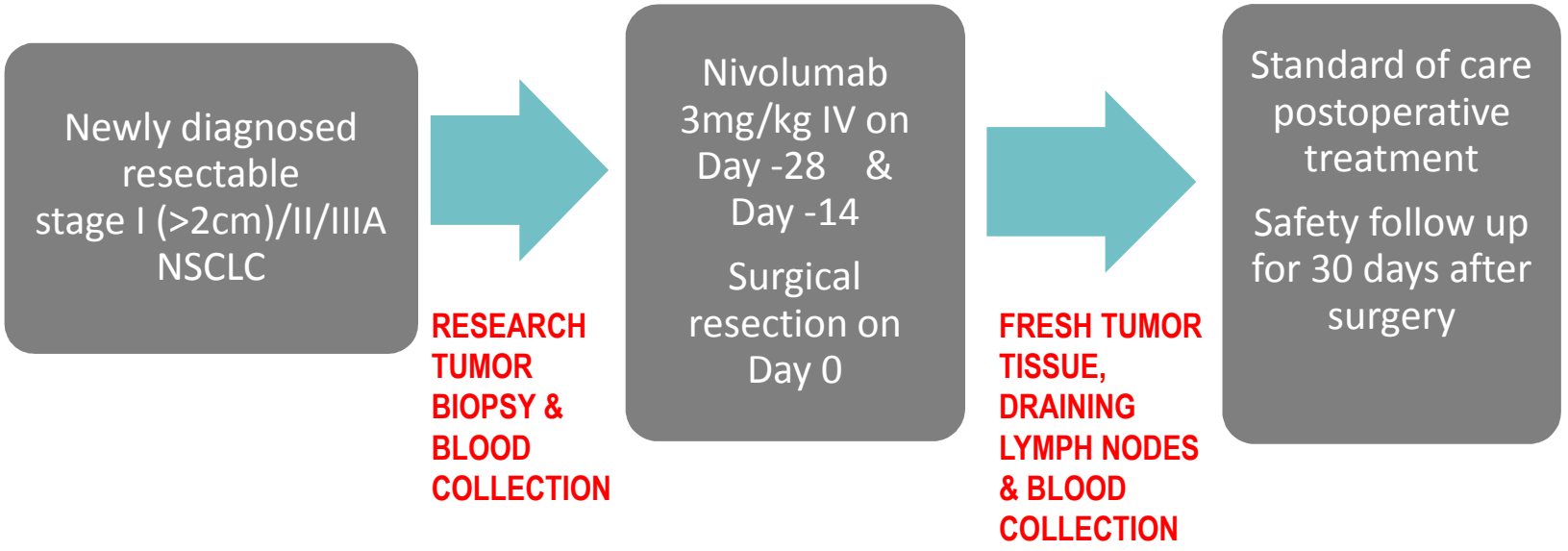
% T cells with individual clonotypes



K. Smith, D. Pardoll, et al.

NEOADJUVANT ANTI-PD-1 (NIVOLUMAB) IN NSCLC

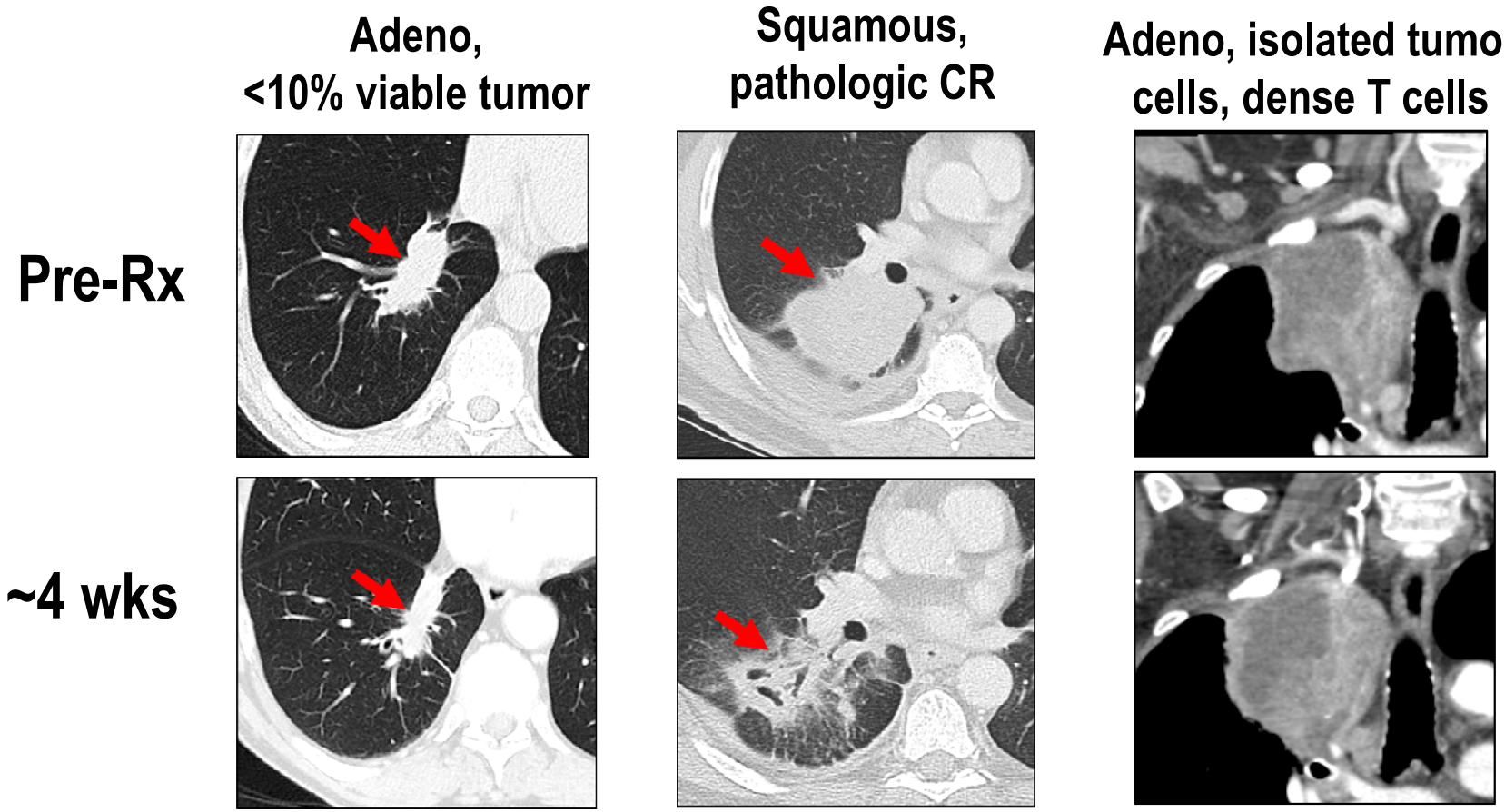
STUDY DESIGN & ENDPOINTS



Forde et al., ESMO 2016

PATTERNS OF RADIOGRAPHIC RESPONSE TO NEOADJUVANT ANTI-PD-1 IN EARLY STAGE NSCLC

Forde et al., ESMO 2016



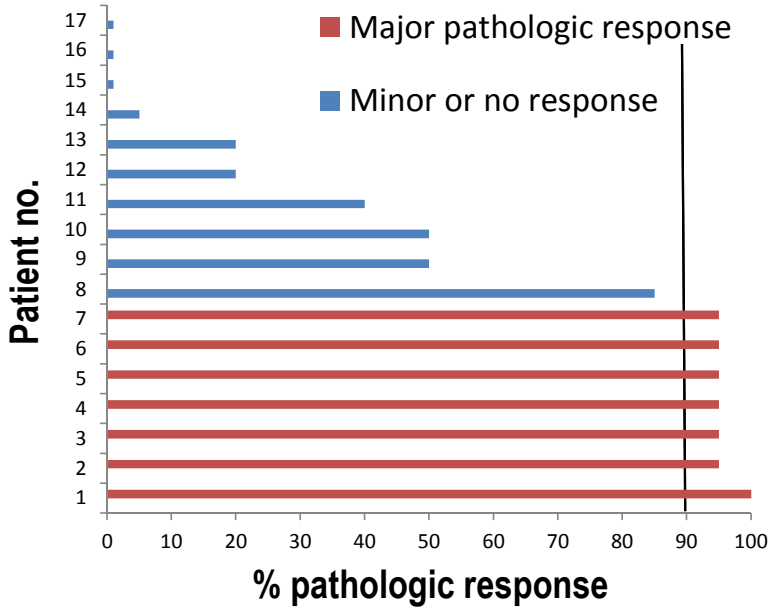
These tumors were PD-L1+ with IHC 28-8 assay, defined as ≥1% positive tumor cells

EXPLORATORY ANALYSES OF RESPONSE TO NEOADJUVANT ANTI-PD-1 (NIVOLUMAB) IN NSCLC

Radiographic response (n=18) RECIST 1.1	N (%)
Partial Response	4 (22)
Stable Disease	13 (72)
Progressive Disease	1 (6)

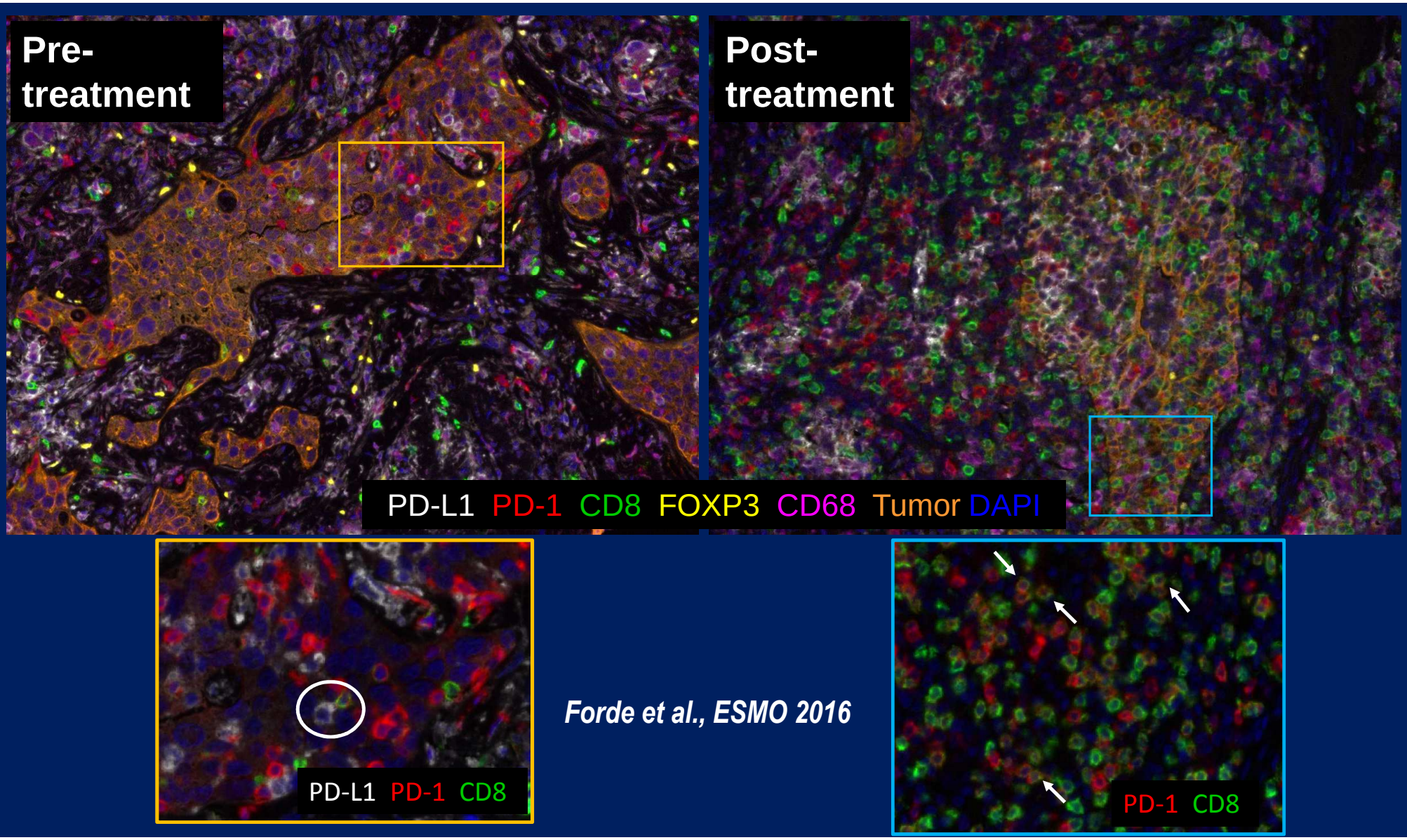
Forde et al., ESMO 2016

Pathologic response (n=17)

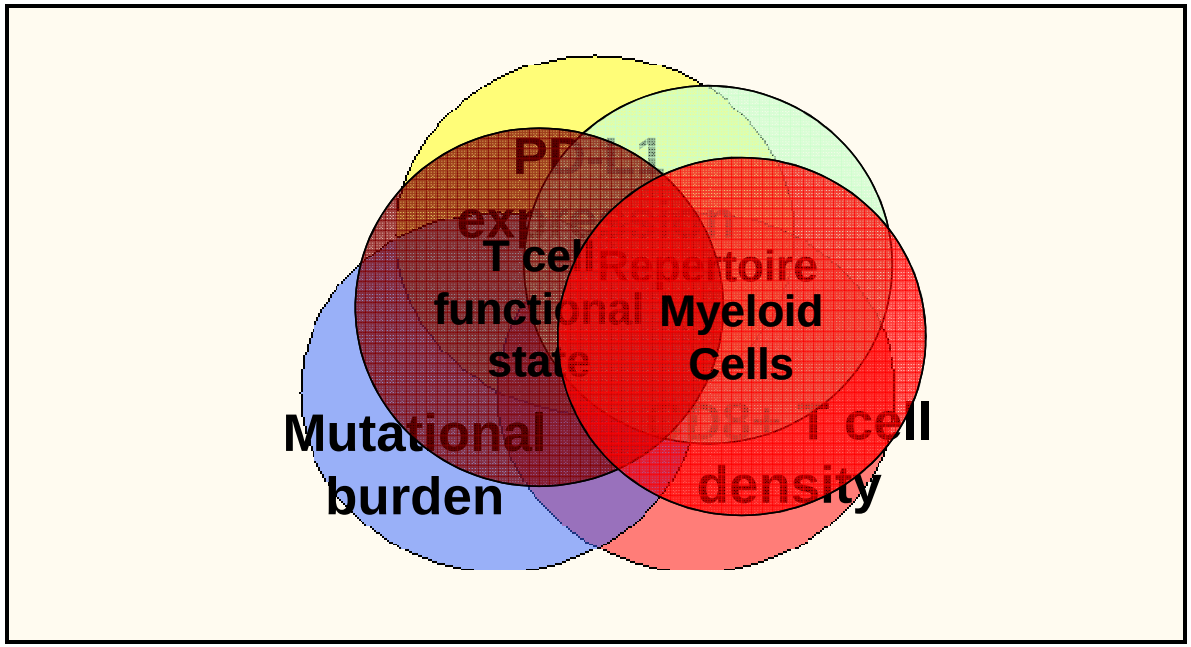


<10% residual viable tumor cells defines major pathologic response (Pataer et al., JTO 2012)

- 7/17 (**41%**) patients had <10% residual viable tumor at resection
- 1 patient had a pathologic complete response


Pre-treatment
Post-treatment
PD-L1 PD-1 CD8 FOXP3 CD68 Tumor DAPI
PD-L1 PD-1 CD8
Forde et al., ESMO 2016
PD-1 CD8

Complex biomarkers may be more highly predictive of response to anti-PD-1/PD-L1



- Multifactorial markers may be needed to guide combination therapy

1971: The National Cancer Act launches the "War on Cancer"

Nixon Signs $1.6 Billion Cancer Bill, Names Man to Head Fight

WASHINGTON (UPI)—President Nixon today signed into law a $1.6 billion program to find a cure for

the act was "a milestone in the long and difficult effort

and cures of can

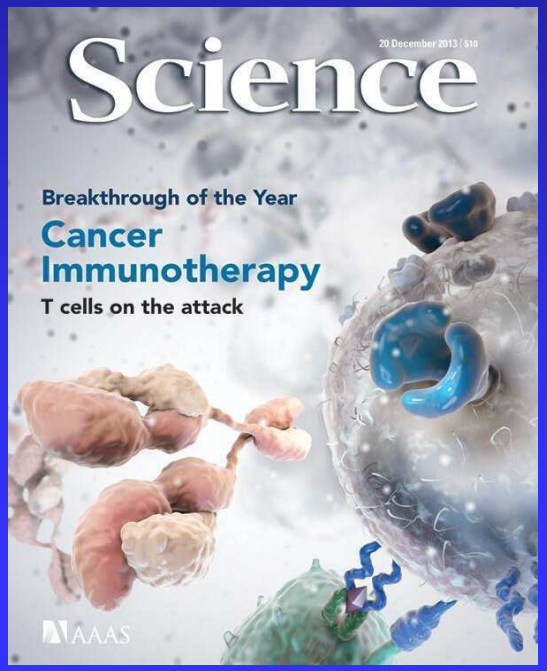
"This law is

2016: Winning key battles on our way to winning the war

The New York Times

Breaking Through Cancer's Shield

October 15, 2013



Science

20 December 2013 | $10

Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack

AAAS

Bloomberg~Kimmel Institute for Cancer Immunotherapy at Johns Hopkins 2016

Thanks to collaborating clinical trial centers.
Supported by BMS, NCI, SU2C-AACR-CRI, Melanoma Research Alliance, L. Hahn Trust, Moving for Melanoma, Barney Foundation, and others