PD-L1 IHC in clinical decision-making for immune checkpoint blockade

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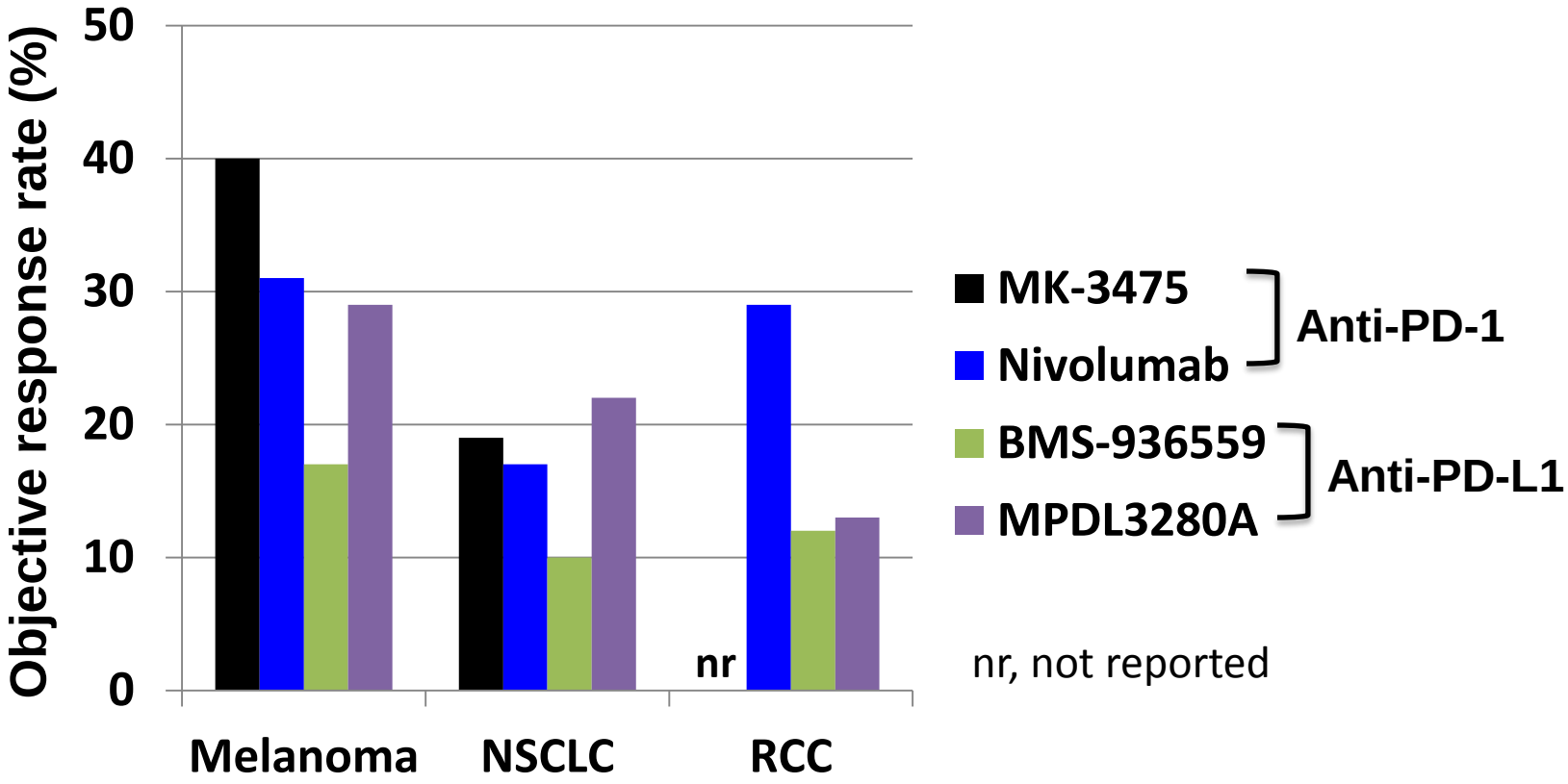
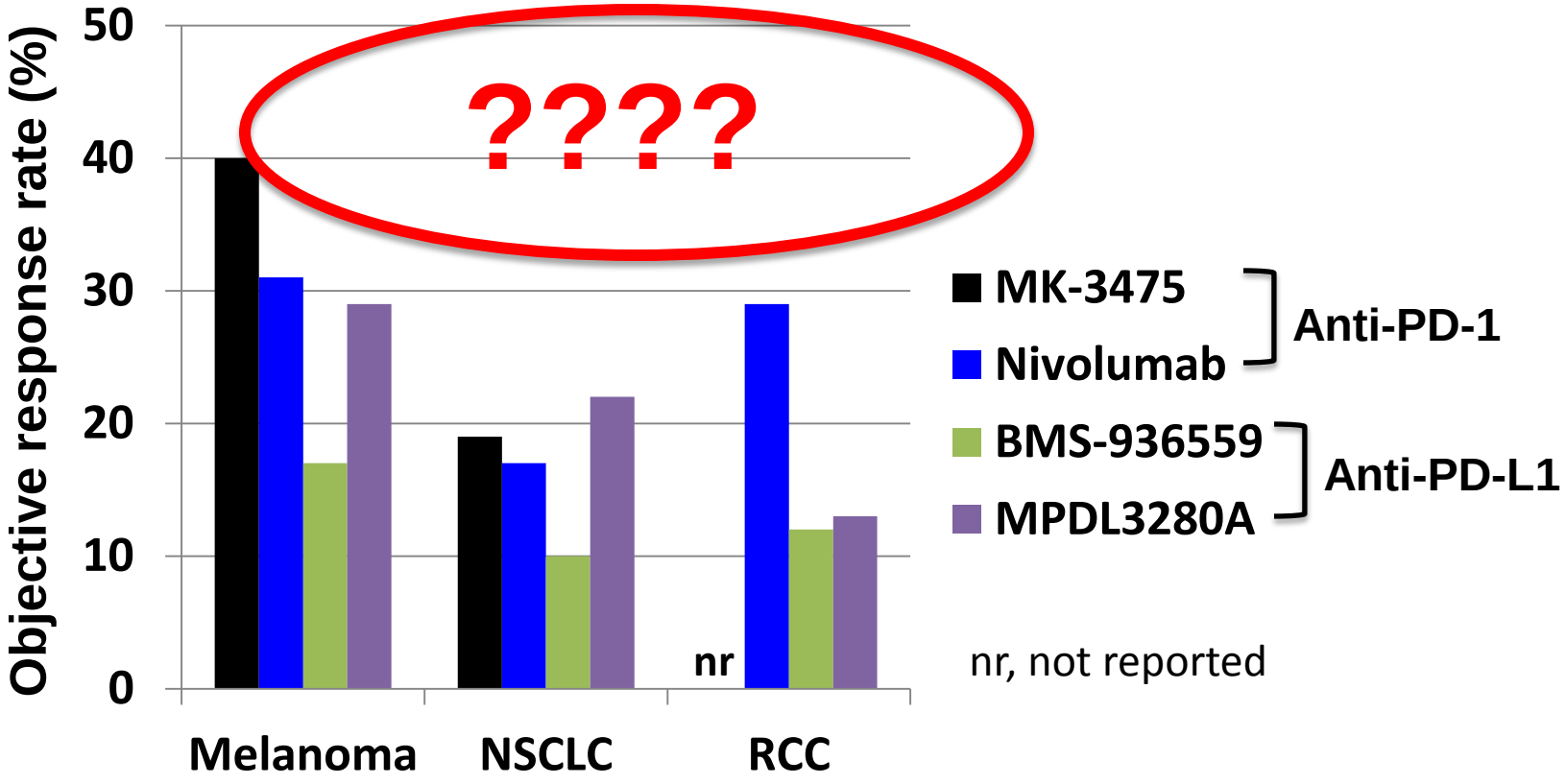
Clinical activity of PD-1 and PD-L1 blocking antibodies validates this pathway as a target for cancer therapy



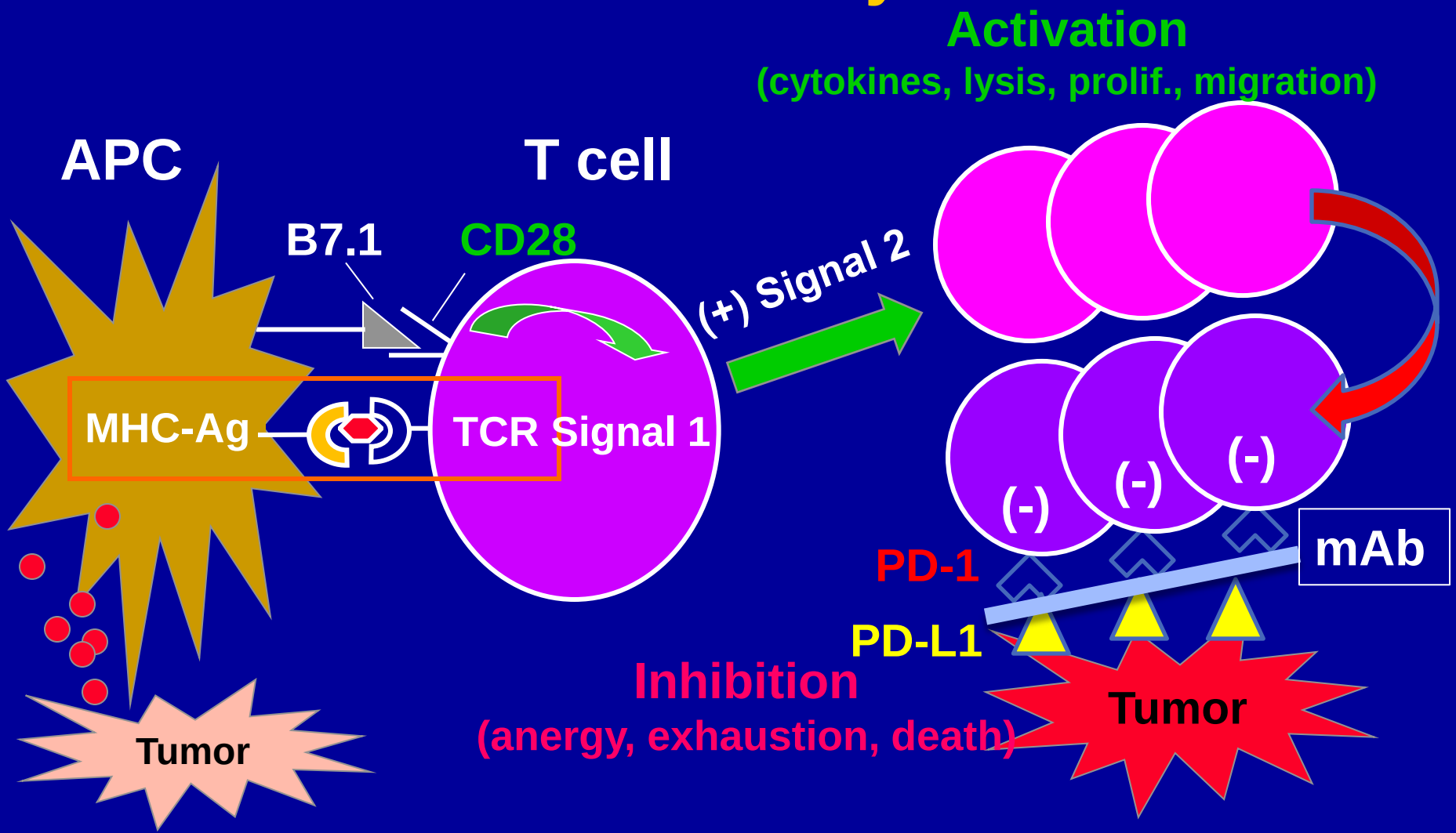
ASCO 2014: *New evidence for activity in advanced* ***bladder cancer*** *(ORR 25%, MPDL),* ***SCCHN*** *(20%, MK-3475; 14%, MEDI4736);* ***ovarian cancer*** *(17%, nivo)*

Clinical activity of PD-1 and PD-L1 blocking antibodies validates this pathway as a target for cancer therapy



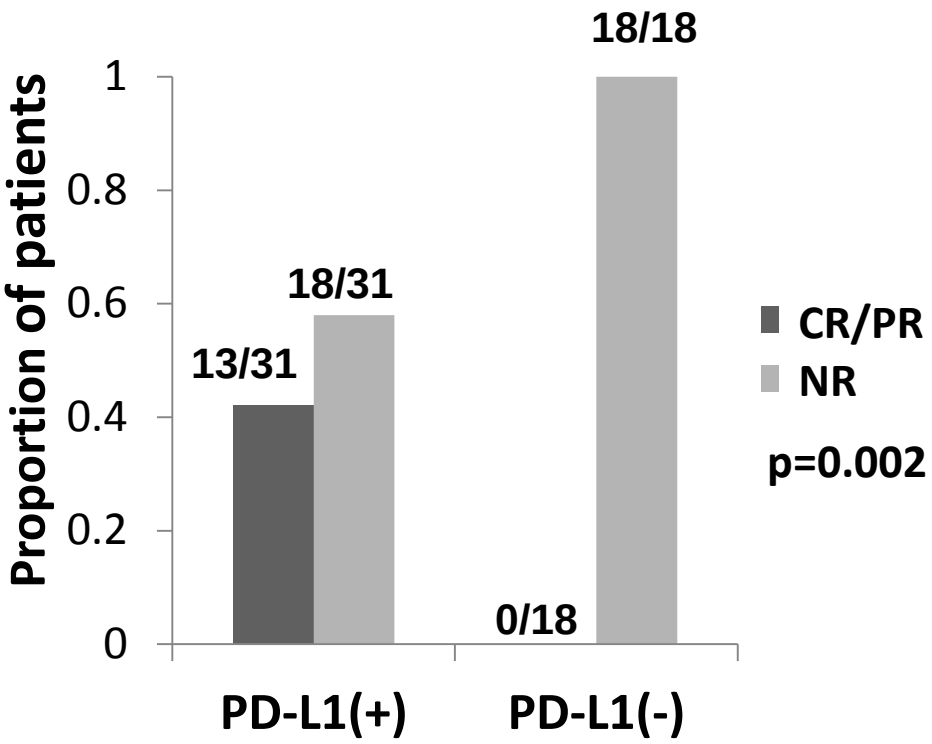
?? How to identify additional potentially responsive cancer types for clinical testing??

Role of PD-1 in suppressing anti-tumor immunity

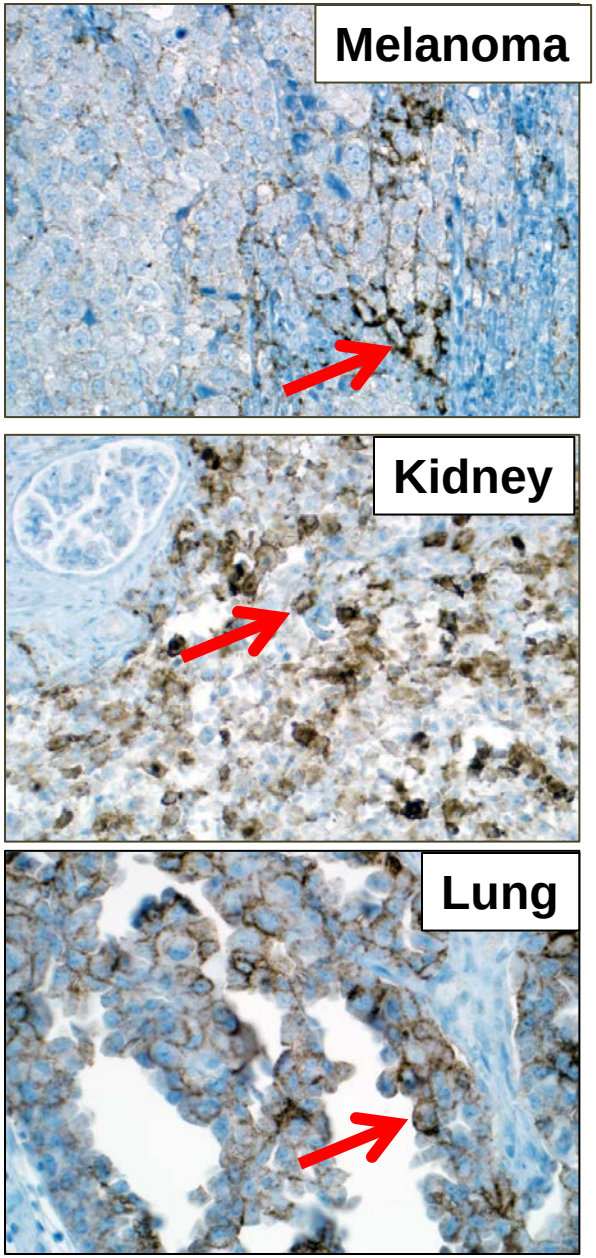


Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

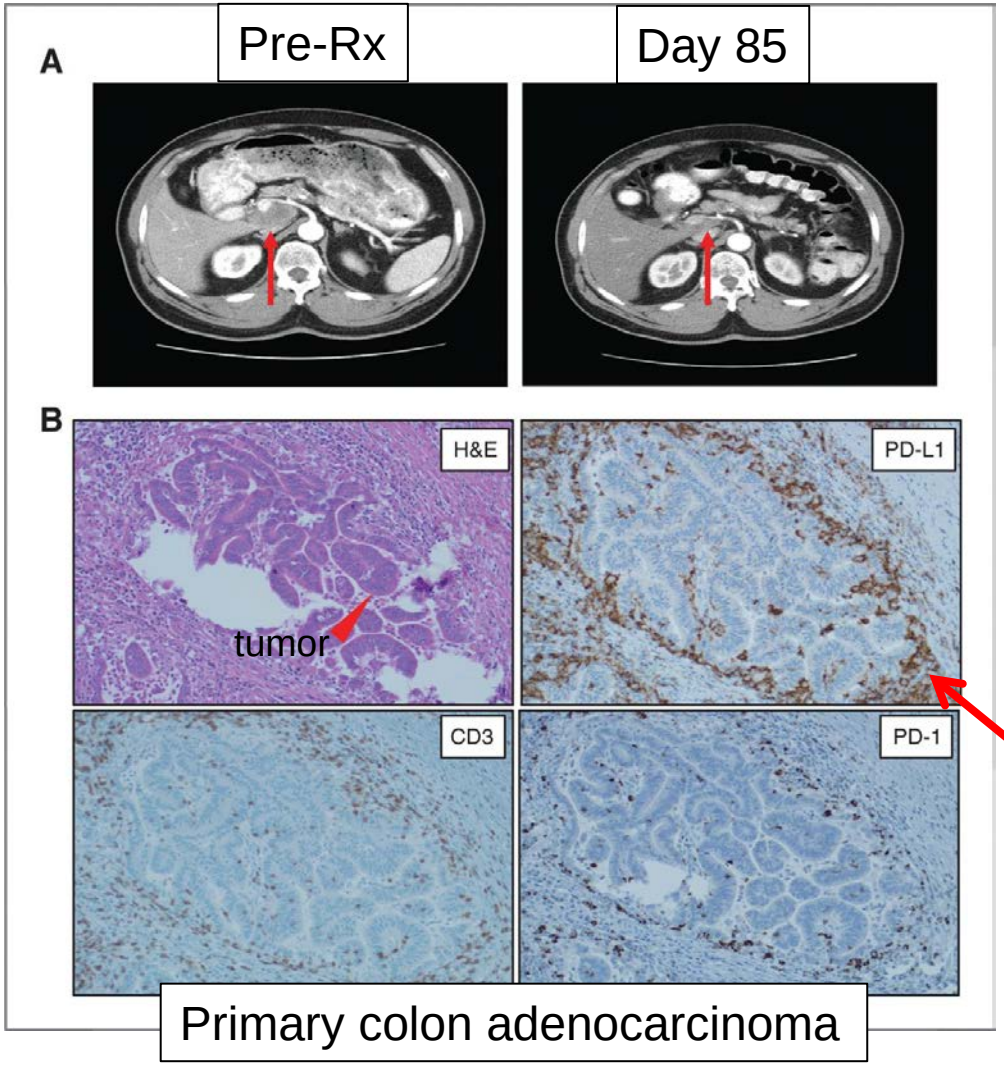
Preliminary correlation of PD-L1 expression in pre-treatment tumor biopsies, with clinical response to anti-PD-1 therapy



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



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



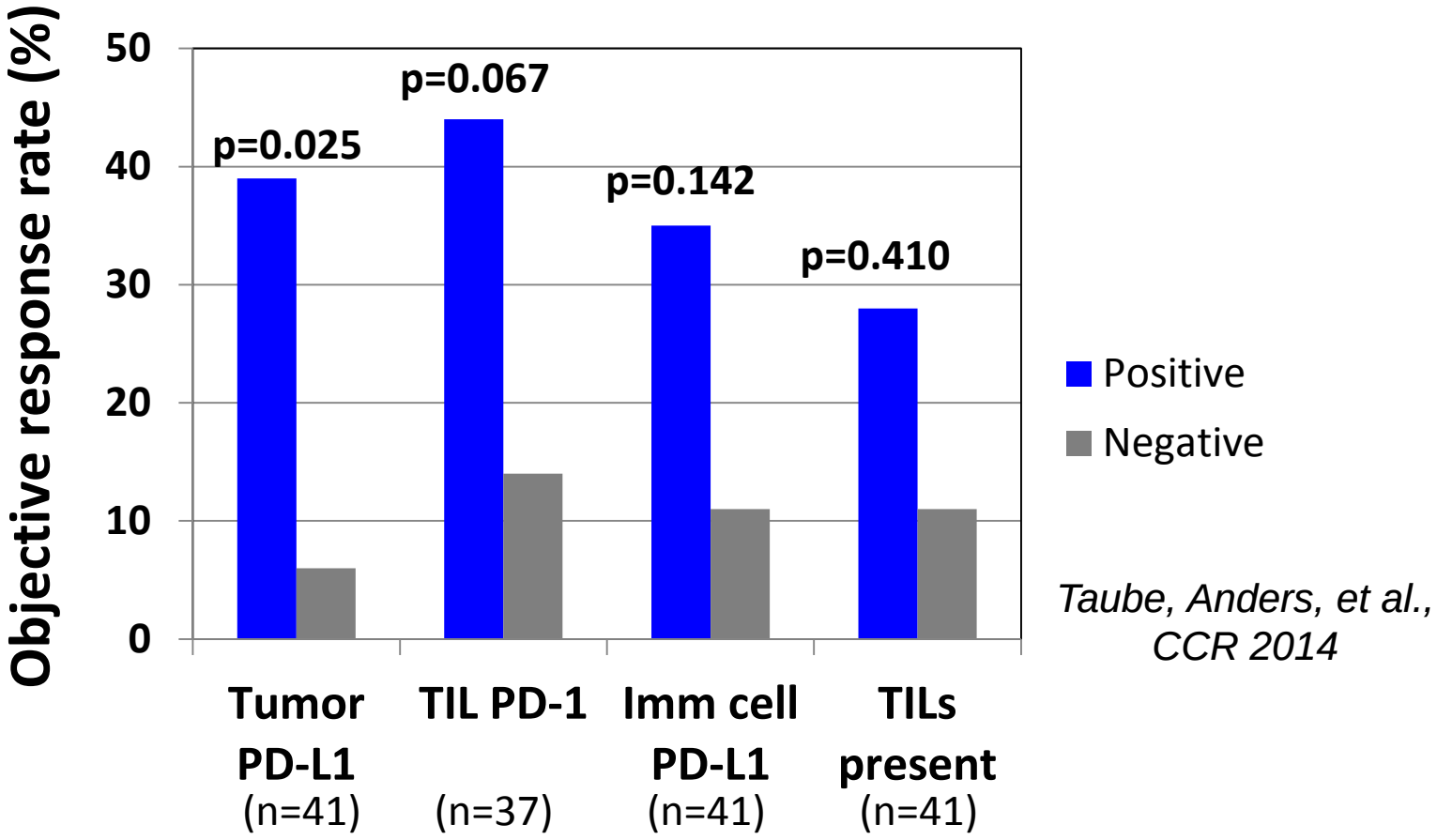
Lipson et al., Clin Cancer Res 2013

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.

PD-L1 expression in macrophages but not tumor cells

PD-L1 expression by tumor cells is the strongest single predictor of response to anti-PD-1 therapy



Taube, Anders, et al., CCR 2014

A multifactorial biomarker may have greater predictive value

PD-L1 IHC methods currently in testing

	Hopkins	BMS	Merck	Roche
mAb clone	5H1	28-8	22C3	SP142
Automated	No	Yes	Yes	Yes
Staining location scored	Membrane	Membrane	Membrane	Membrane
Cell type(s) scored	Tumor cells	Tumor cells	Tumor and/or infiltrating immune cells	Infiltrating immune cells
Positive cutoff	≥ 5%	≥ 5%	≥ 1%	≥1% to ≥10% (“IHC 1-2-3”)

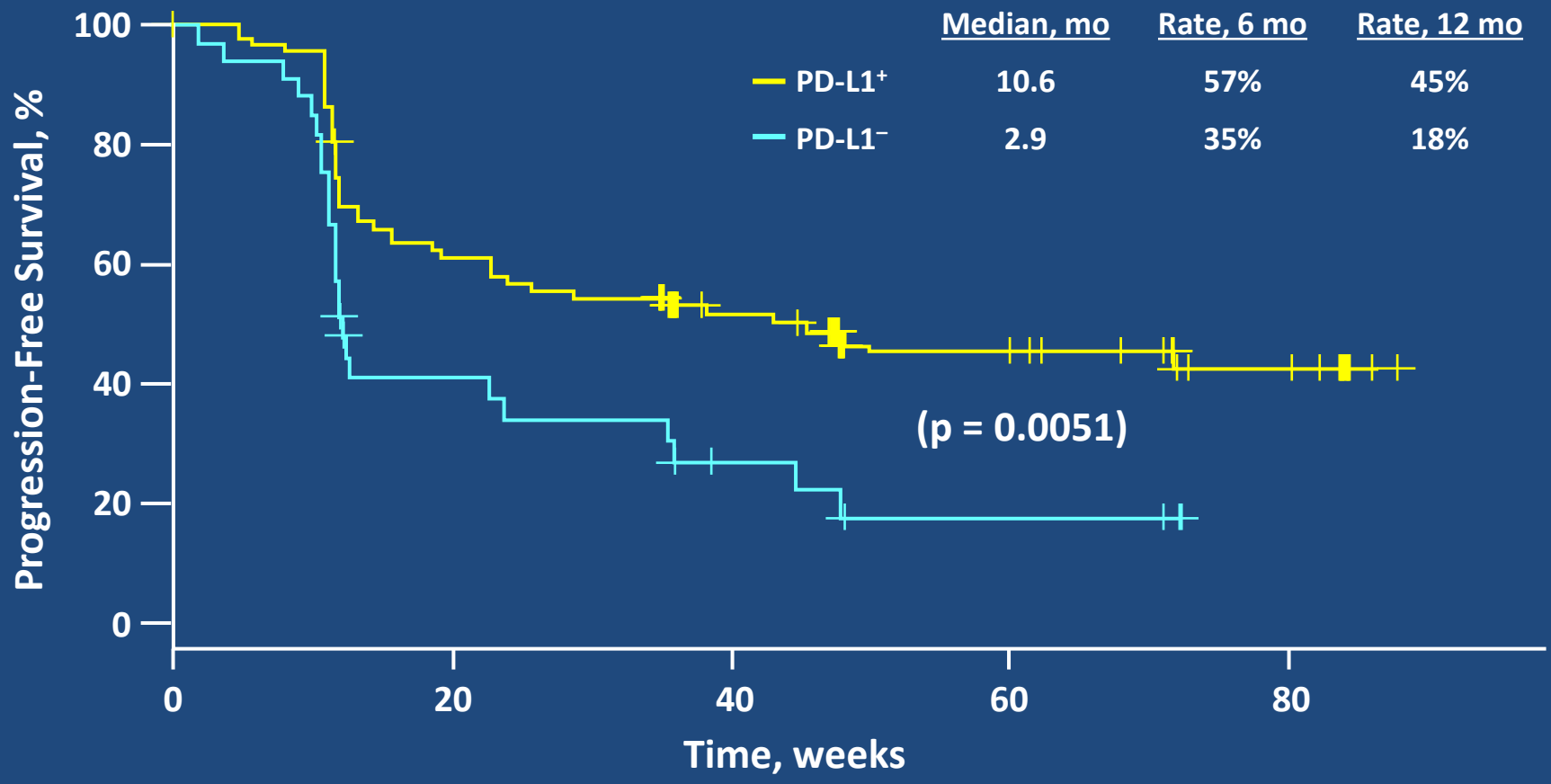
- *Note: these assays are still under development pending additional clinical correlative data*

Intra-tumoral PD-L1 expression and response to PD-1/PD-L1 blockade

	Nivolumab Solid Tumors (Topalian et al. NEJM 2012)	**Nivolumab Melanoma** (Weber ASCO 2013)	**Nivolumab Melanoma** (Grosso et al. ASCO 2013)	**MPDL3280a Solid Tumors** (Herbst et al ASCO 2013)	**MPDL3280a Melanoma** (Hamid et al ASCO 2013)	**MPDL3280a NSCLC** (Sorial et al ECC 2013)	**Pembrolizumab Melanoma** (Daud et al AACR 2014)	**Pembrolizumab NSCLC** (Gandhi et al AACR 2014)	**MPDL3280a Bladder** (Powels et al ASCO 2014)	**Pembrolizumab Head & Neck** (Selwert et al ASCO 2014)	**Pembrolizumab Melanoma** (Ribas et al ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 –	0%	19%	17%	13%	20%	15%*	13%	11%	11%	11%	13%

PFS in melanoma patients receiving pembrolizumab

PD-L1 Evaluable Patients (n = 113), Independent Central Review



- 71% of melanomas were PD-L1+ using a 1% cutoff
- PFS was significantly longer in patients with PD-L1+ tumors
- OS was not significantly prolonged

Analysis October 18, 2013

Adapted from Daud et al., AACR 2014

Pitfalls for PD-L1 “biomarker”: Immunologic heterogeneity of anatomically and chronologically distinct tumors

Patient no.	Clinical Resp.	Biopsy site	PD-L1 IHC (%pos. tumor cells)
1	NR	SQ met #1	5-10
		SQ met #2	0
2	NR	Skin primary	20
		LN met	0
3	CR	Skin primary	5
		SQ met	0
		LN met	0
4	NR	Skin primary	5
		LN met #1	0
		LN met #2	5
5	PR	Lung met #1	5
		Lung met #2	50

Variable expression of PD-L1 among melanoma lesions from individual patients receiving anti-PD-1 therapy.

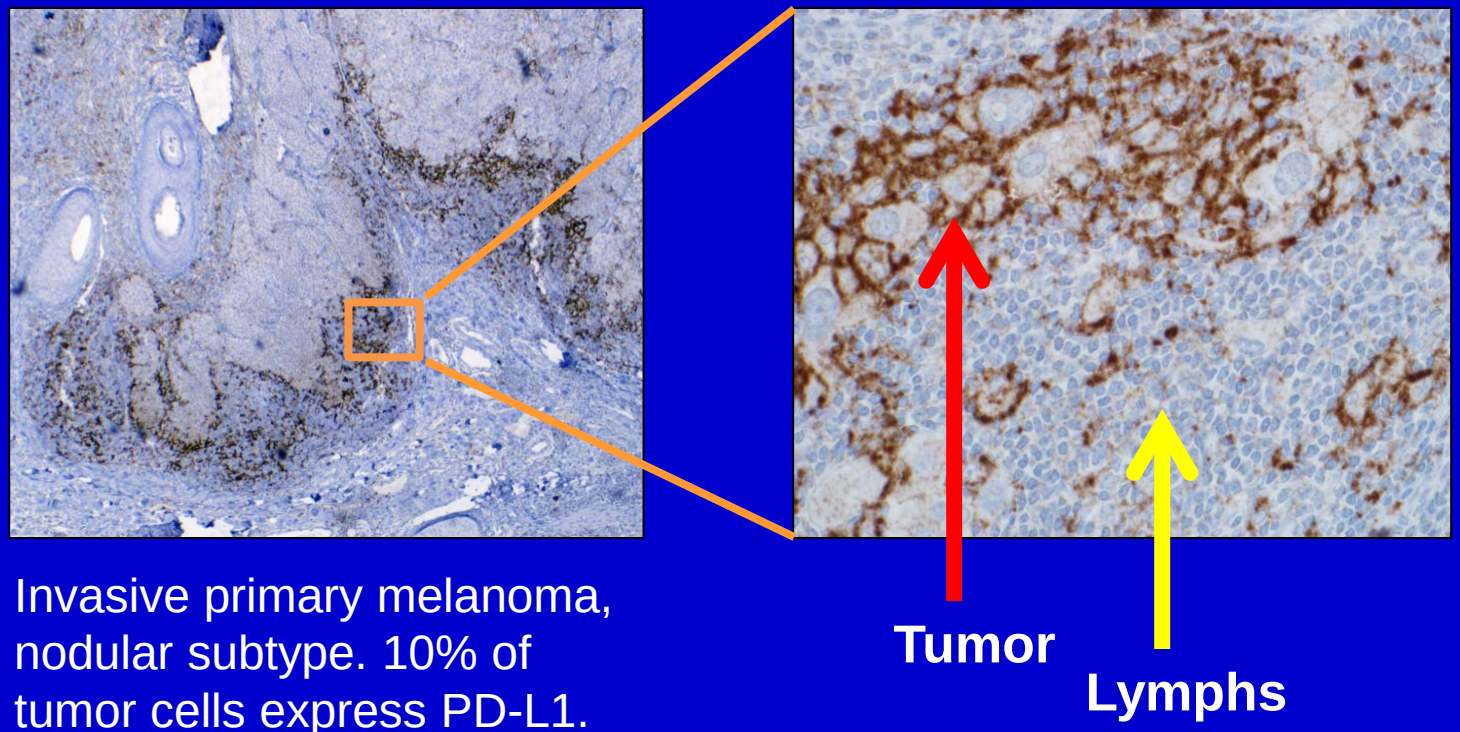
“PD-L1+ tumor”: ≥5 % tumor cells with cell surface PD-L1 expression

“PD-L1+ patient”: patient in whom *any* tumor is/was PD-L1+

(Topalian et al., NEJM 2012)

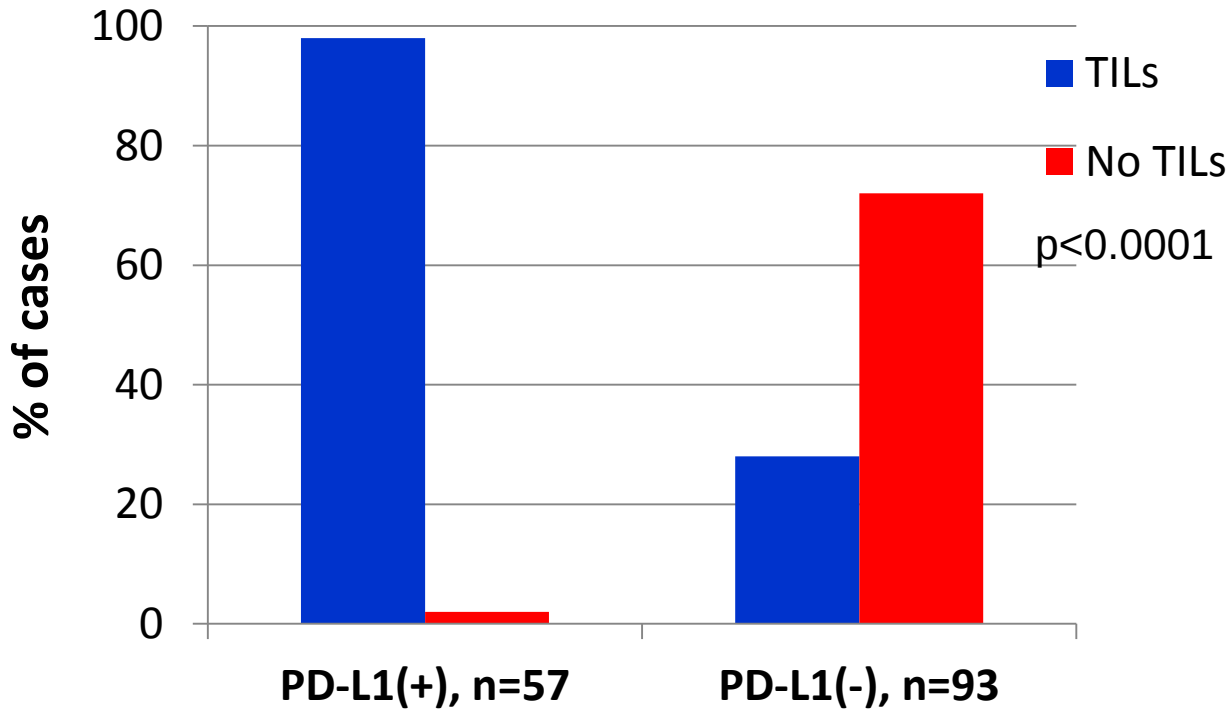
Pitfalls for PD-L1 biomarker: focal expression in some tumors

"Marker negative" specimen or sampling error???



Invasive primary melanoma, nodular subtype. 10% of tumor cells express PD-L1.

TILs are necessary but *not* sufficient for PD-L1 expression in melanomas

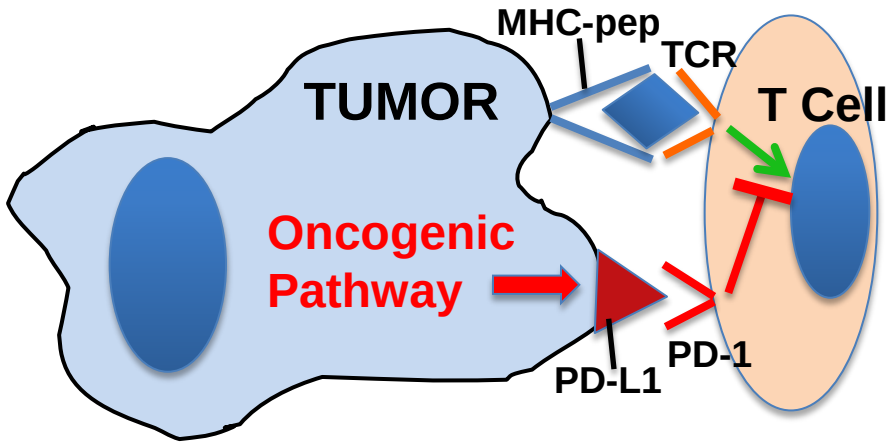


Finding: functional differences in TILs (IFN-g up-regulation) are associated with differential PD-L1 expression by tumor cells

Taube et al., Science Transl Med 2012

2 Mechanisms for PD-L1 up-regulation in tumors

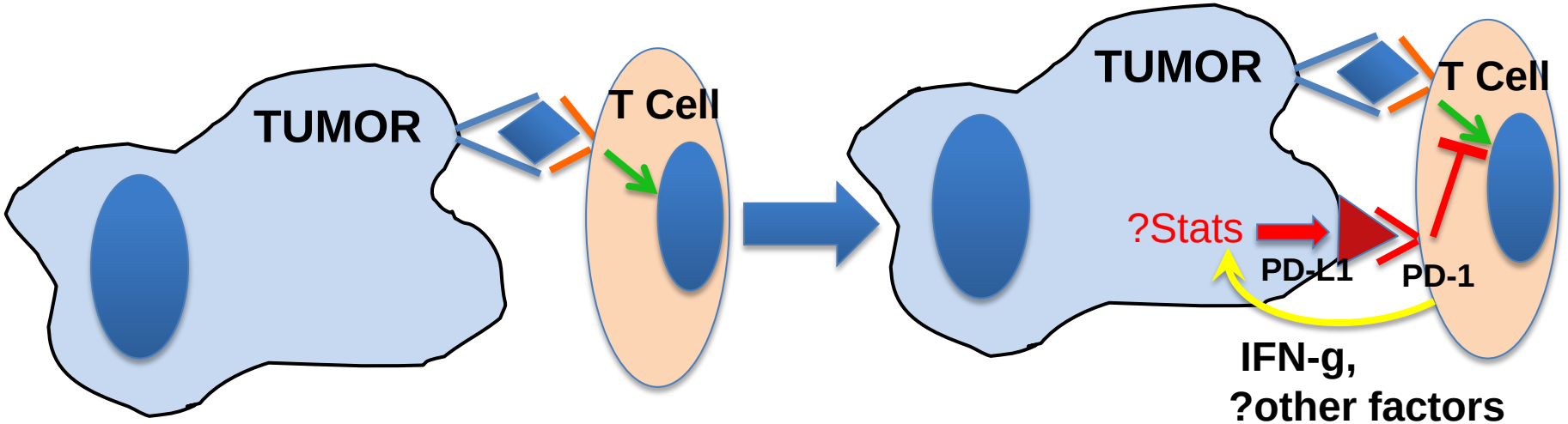
Innate Resistance



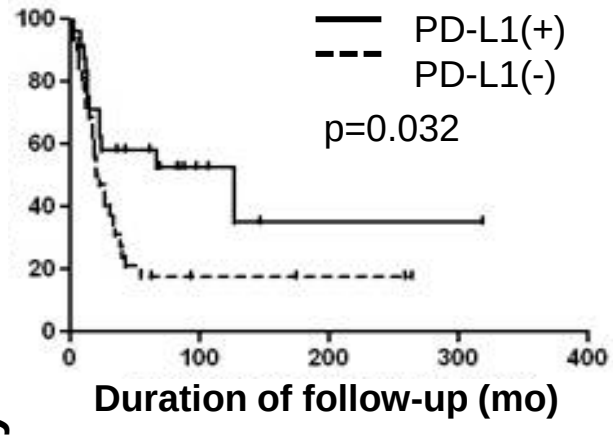
Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive Resistance

PD-L1 expression reflects immune reaction

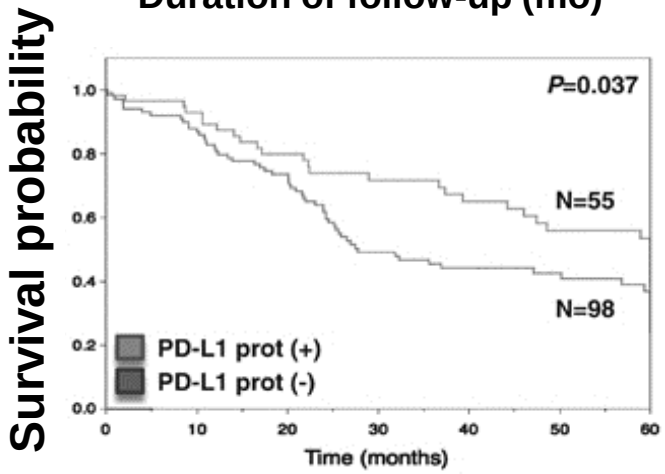


PD-L1 expression as a prognostic marker: prolonged OS in select cancer types associated with TILs



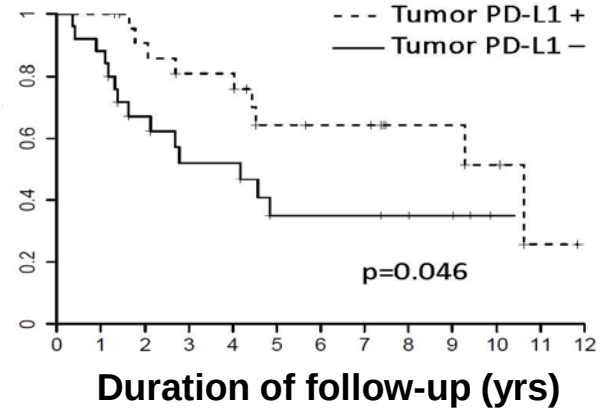
Metastatic melanoma (n=56)

(Taube et al., Science Transl Med 2012)



Primary NSCLC (n=153)

(Velcheti et al., Lab Invest 2013)

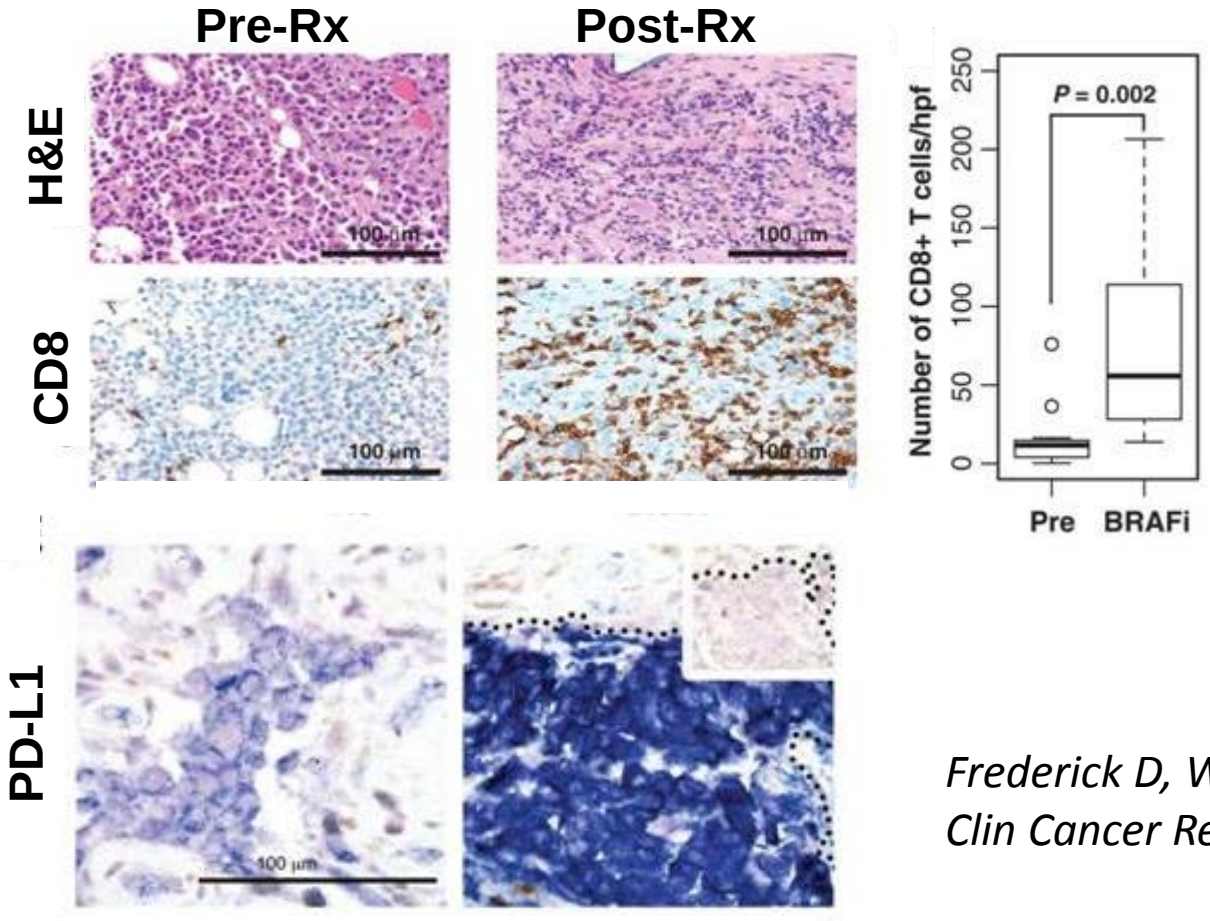


Merkel cell carcinoma (n=49)

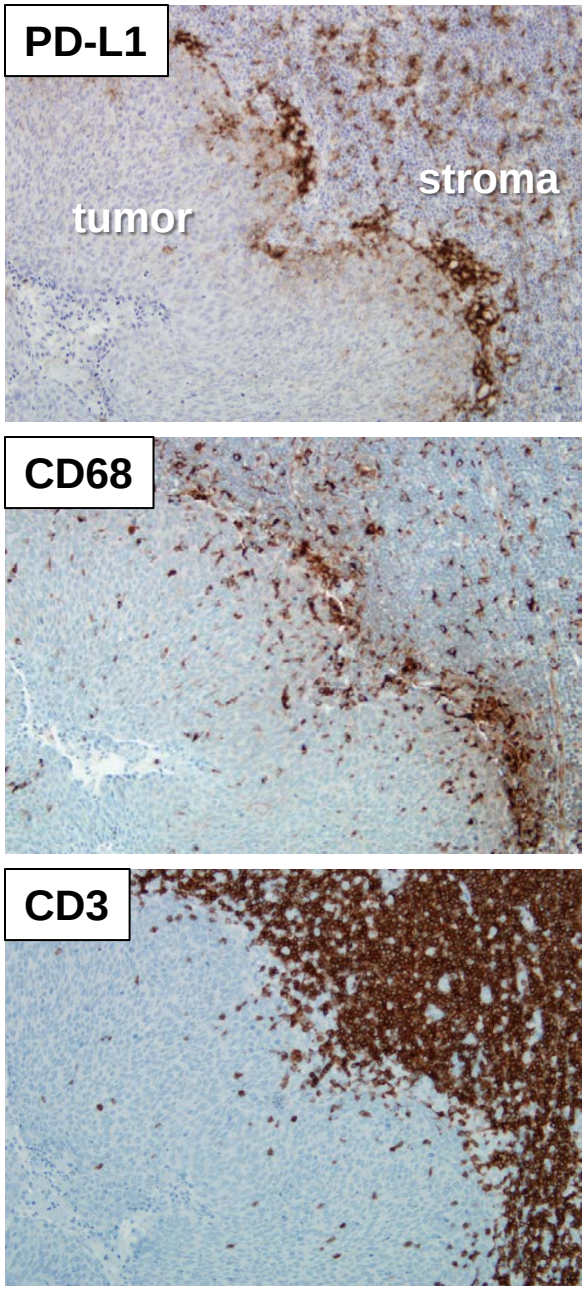
(Lipson et al., Cancer Immunol Res 2013)

PD-L1 expression as a guide to developing combination treatment regimens

Selective BRAF inhibition in melanoma associated with increased CD8+ TILs and tumor PD-L1 expression

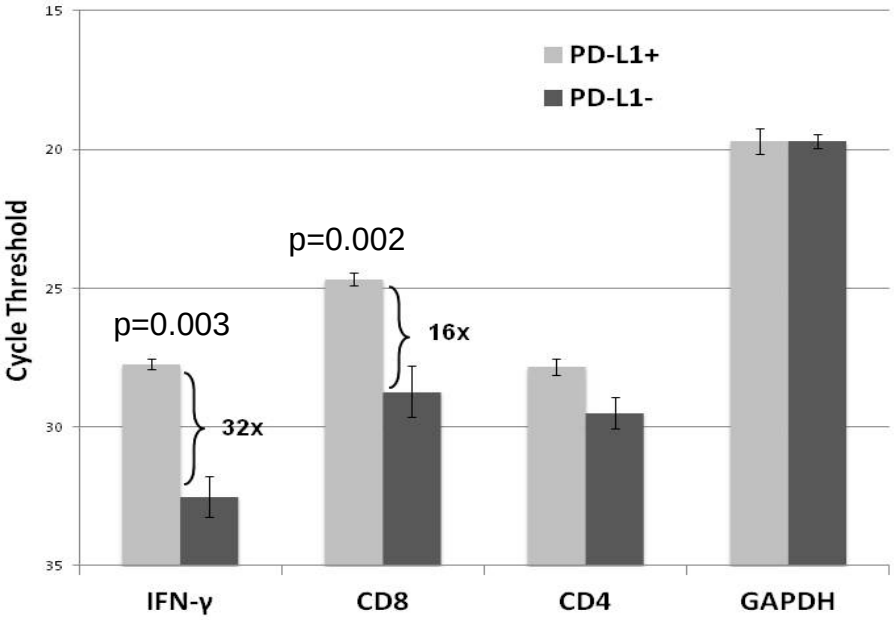


Frederick D, Wargo J, et al., Clin Cancer Res 2013



PD-L1 expression as a guide to identifying *tumor types* most likely to respond to PD-1/PD-L1 blockade

Oropharyngeal SCCHN: PD-L1 associated with CD8+ 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.

Conclusions: potential clinical applications for PD-L1 IHC

- Staging/prognosis: tumor PD-L1 *associated with TILs* may identify patients with improved prognosis
- Therapy
  - Design combination therapies of PD-1 blockade with treatments enhancing TILs and tumor PD-L1 expression
  - Identify new cancer types potentially responsive to PD-1 pathway blockade
  - Patient selection for PD-1 pathway blockade: responders among “PD-L1 negative” patients pose challenges

A deeper understanding of factors driving PD-L1 expression is needed to optimize the clinical application of this marker.

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