DISCUSSION ABTRACTS: 380 +1270

Fred R. Hirsch, MD,PhD
Professor of Medicine and Pathology,
Univ. of Colorado Cancer Center, Aurora, CO, USA
CEO, IASLC

ABSTRACT 38O: A.D'Incecco et al PD-L! and PD-1 Expression in molecular selected NSCLC patients

- N=123 speciemns
- PDL-1 expression (IHC): 54.4%
- PD-1 expression : 34.4%

- PDL-1 expression statistically correlated to Females, EGFR +, ALK+, never smokers, ADC.
- PD-1 expression statistically correlated to Males, ADC, smokers, KRAS+.

ABSTRACT 38O: A.D'Incecco et al PD-L! and PD-1 Expression in molecular selected NSCLC patients

- N=123 specimens
- PDL-1 expression (IHC): 54.4%
- EGFRTKI (95 pts): RSP: 61% vs 35%
  TTP: 12 mo vs 6 mo
  13 mo vs 8.5
  OS: 22 mo vs 12.5 mo
  29.5 mo vs 21 mo (NS)

- PD-1: No impact on outcome to EGFRTKI

ABSTRACT 1270: Mansfield et al: PDL-1 in Mesothelioma

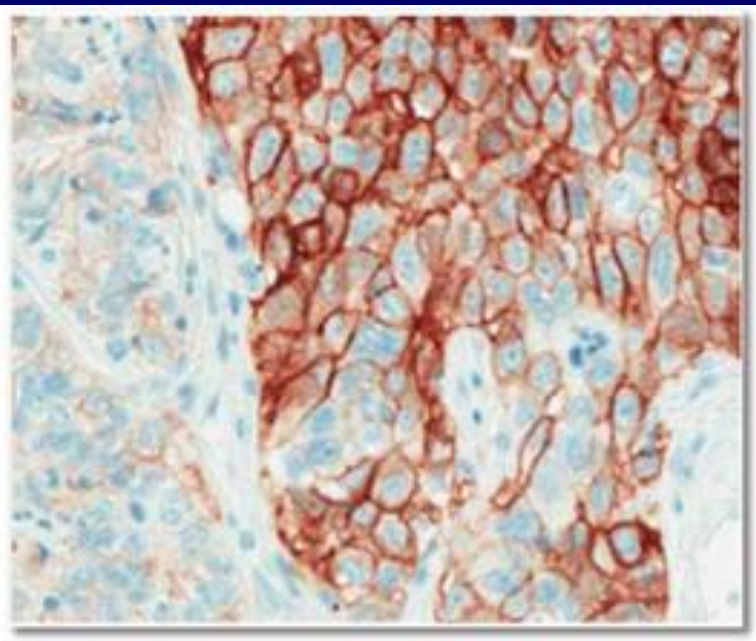
IS PDL-1 THERAPY A NEW OPPORTUNITY IN MESOTHELIOMA? NEW THERAPIES NEEDED!!

- PDL-1 expression in 30-40%
- Poor prognosis (median 6 mo vs 14 mo)

DISCUSSION 1:

IHC ASSESSMENT

PD-L1 testing



Positive PD-L1 staining in lung cancer
(GNE/Roche PD-L1 IHC)

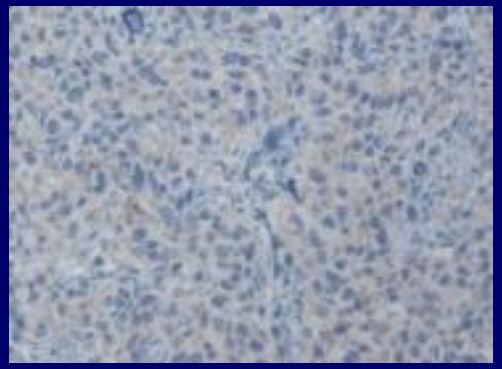
Tumor Type	Estimated PD-L1 Prevalence (≈ %)*
NSCLC (SCC)	50
NSCLC (adeno)	45

Expression of PD-L1: Required for Clinical Response to PD-1 Blockade

B7-H1 staining patterns (clone 5H1)

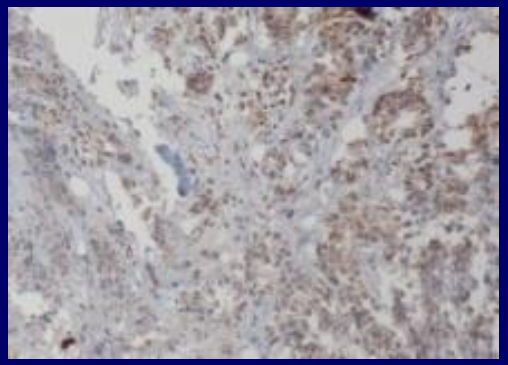
MDX-1106-01:
9 JHU pts
with
pre-Rx
biopsies

Negative



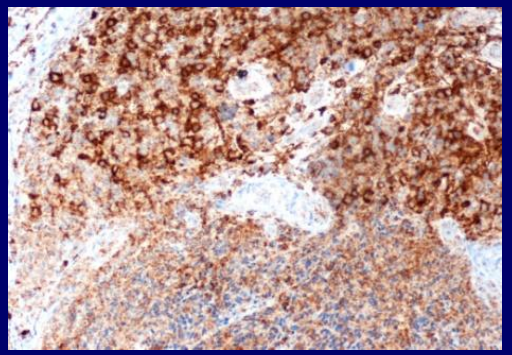
0/1 responders

Cytosolic



0/4 responders

Membranous



3/4 responders

J. Taube and S. Topalian, Brahmer J et al JCO 2010

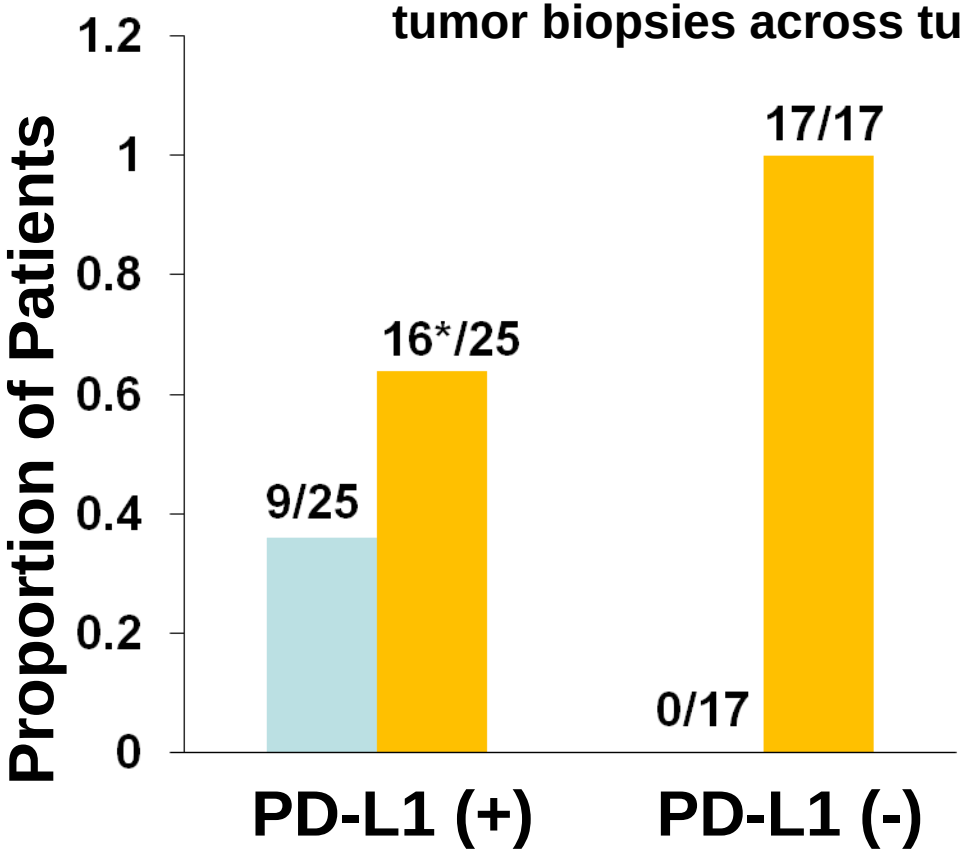
Objective Response Rates by PD-L1 Expression in Patients with Solid Tumors

Rx Antibody	Testing Method	N	PD-L1 Positive RR	PD-L1 Negative RR
Nivolumab Topalian 2013	Manual staining – 5H1 5% cutoff Tumor staining	49	13/31 42%	0/18 0%
Nivolumab Grosso 2013	Dako automated 5% cutoff Tumor staining	38	7/17 41%	3/21 14%
MPDL3280A Herbst 2013	Automated Genentech Roche Dx IHC 1% cutoff Tumor immune cell staining	103	13/36 36%	9/67 13%

Topalian S et al ASCO 2013, Grosso J et al ASCO 2013, Herbst R et al ASCO 2013

Correlation of PD-L1 Expression in Pretreatment Tumor Biopsies with Clinical Outcomes

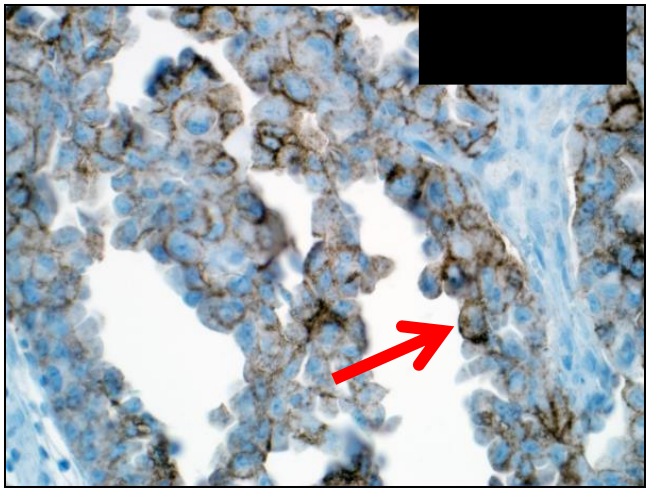
PD-L1 expression by IHC in 61 pretreatment tumor biopsies across tumor types from 42 pts



P=0.006

*** 2 pts still under evaluation**

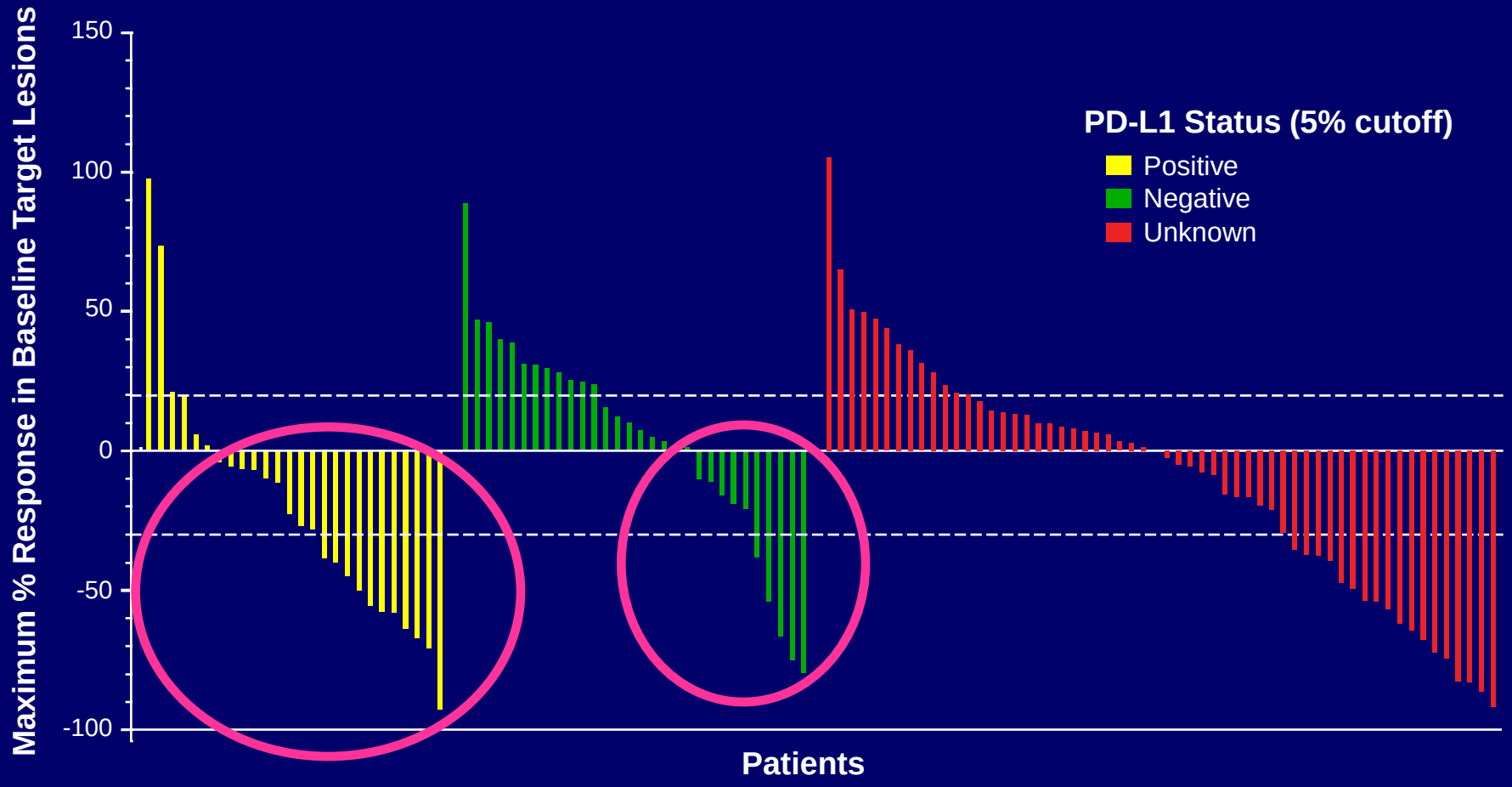
CR/PR
Non-responders



- **1 PR out 5 pts with PD-L1+ NSCLC**
- **No responses for 5 pts with PD-L1- NSCLC**

Patient samples: 18 MEL,10 NSCLC, 7 CRC, 5 RCC, 2 CRPC

Figure 5. Maximum response in target lesion tumor burden according to PD-L1 status



PD-L1 Status and Predictive Biomarkers in NSCLC Patients Treated With MPDL3280A: Efficacy

Elevated baseline PD-L1 expression is associated with response to MPDL3280A

PD-L1 Status	N = 53	
	ORR[a]	PD Rate[b]
IHC 3 (n = 6)	83% (5/6)	17% (1/6)
IHC 2 and 3 (n = 13)	46% (6/13)	23% (3/13)
IHC 1/2/3 (n = 26)	31% (8/26)	38% (10/26)
All patients [c] (N = 53)	23% (12/53)	40% (21/53)

[a] ORR includes investigator-assessed unconfirmed and confirmed PR by RECIST v1.1.
[b] PD rate indicates patient with best response with progressive disease.
[c] Includes patients with IHC 0/1/2/3 and 7 patients with unknown diagnosis.

Gettinger et al. IASLC WLCL 2013. Abstract 1653, Presentation MO19.09.

Response According to PD-L1 Expression

- There is no apparent association between PD-L1 expression and NSCLC histology
- There was no clear association of ORR in patients with PD-L1+ tumors and tumor histology or nivolumab dose
- Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation-positive tumors appear to have higher PD-L1 expression at both the 1% and 5% cutoff

PD-L1 as a Predictive Immune Biomarker: Assays and Sample Collection

- **PD-1 ligand expression on tumor cells can prevent antitumor immune responses; blockade of the PD-1 pathway may enhance antitumor immunity[1]**
  - **Expression patterns of PD-1 ligands may be important for determining the suitability of the role of PD-1 pathway blockade in an antitumor immune response[1]**
  - **The ability of PD-L1 to act as a predictive biomarker is being actively investigated:**

PD-L1 Assay	**Immunohistochemistry (IHC), but antibody used varies[2-4]**
Sample Source and Collection	**Varies: tumor cells, tumor and immune cells or tumor-infiltrating lymphocytes (TILs)[3-5]**
	Varies: archival or fresh tissue[3,5]
Definition of Positivity	**Varies: strong vs weak expression; percentage cut offs[2-4]**

NSCLC, non-small cell lung cancer; OR, overall response; ORR, objective response rate; PD-1, programmed death-1; PD-L1, PD ligand-1.

1. Ceeraz S et al. *Trends Immunol.* 2013;34(11):556-563.
2. Garon EB et al. Oral presentation at WCLC 2013. 2416.
3. Soria JC et al. Oral presentation at ECCO 2013. 3408.
4. Sosman JA et al. Oral presentation at SMR 2013.
5. Clinicaltrials.gov. NCT01704287.

Table 1. PD-L1 expression in melanoma and NSCLC tissue samples

PD-L1 Expression	Melanoma n/N = 38/107 n (%)	NSCLC n/N = 63/129 n (%)
1% -tumor only	25 (66)	35 (56)
5% -tumor only	17 (45)	31 (49)
5% -tumor + immune cells[a]	35 (92)	56 (89)

[a]Includes 5% PD-L1 expression on tumor cells and any PD-L1 expression on immune cells

PDL-1/ PD-1 IHC Needs Validation

NO ASSAY IS FULLY VALIDATED YET!

- Diff
- Different antibodies
- Different cut –off values
- Diff
  ass

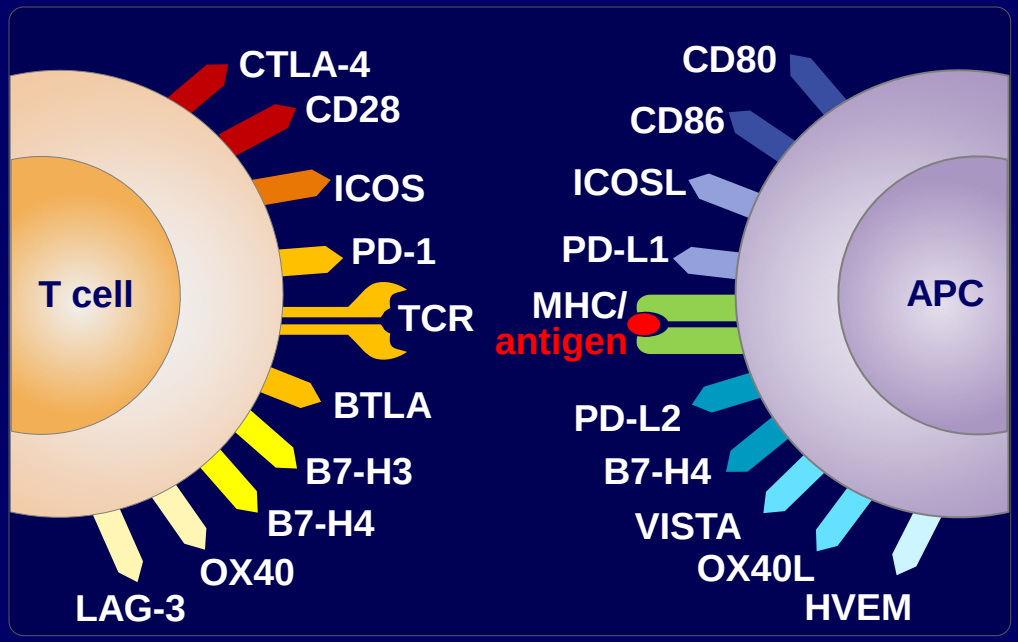
WHAT ABOUT DIFFERENT ASSAY FOR EACH DRUG IN THE PDL-1/PD-1 FAMILY ?

DISCUSSION 2:

OTHER BIOMARKERS?

Regulation of T-cell Function by Cell Surface Markers

- The immune response is regulated by an array of molecules[1]
  - This is achieved in part by the regulation of T-cell activation, which requires two signals[1]:
    - Activation through the T-cell receptor (TCR) by recognition of antigen presented by MHC on antigen-presenting cells (APCs)[1]
    - Then, the ligation of costimulatory and coinhibitory molecules expressed on T cells and APCs[1]



Adapted from Ceeraz et al 2013, Sugamura et al 2004[1,2].

APC, antigen-presenting cell; BTLA, B and T lymphocyte attenuator; CTLA-4, cytotoxic T-lymphocyte antigen-4; HVEM, herpesvirus entry mediator; ICOS, inducible costimulator; ICOSL, ICOS ligand; LAG-3, lymphocyte-activation gene 3; OX40L, OX40 ligand; PD-1, programmed death-1; PD-L1, PD ligand-1; PD-L2, PD ligand-2; VISTA, V-domain immunoglobulin suppressor of T cell activation.

1. Ceeraz S et al. *Trends Immunol*. 2013;34(11):556-563.
2. Sugamura K et al. *Nat Rev Immunol*. 2004;4(6):420-431.

The Immune Contexture

- The immune contexture is a representation of the complex immune parameters within the tumor microenvironment; it has prognostic value and may additionally be predictive of response to immunotherapies[1,2]
- The "immune contexture" is defined as the type, density, location, and functional orientation of immune cells within distinct tumor regions[1]

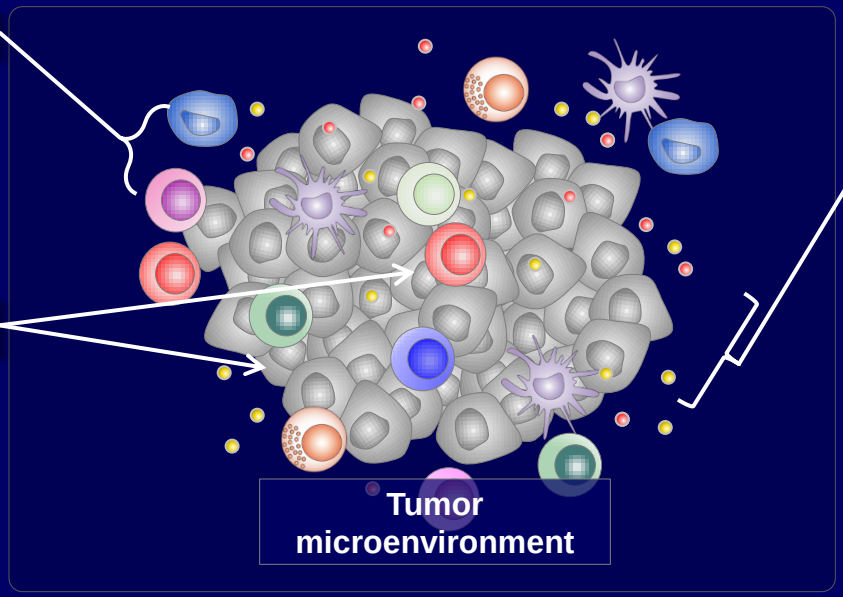
Immune Contexture[1]

Type | **Density**

- Quantification of immune cells
- CD3+ T cells
- CD8+ T cells
- CD45RO+ T cells

Location

- Tumor
  - Center
  - Invasive margin
- Tertiary lymphoid structures



Functional Orientation represents the cell's potential for immune activity and reflects expression patterns associated with observed immune-mediated tissue destruction*

- IFN-γ and other cytokines
- Granzymes, perforin, granulysin
- CXCL9, CXCL10, and other chemokines
- Adhesion molecules

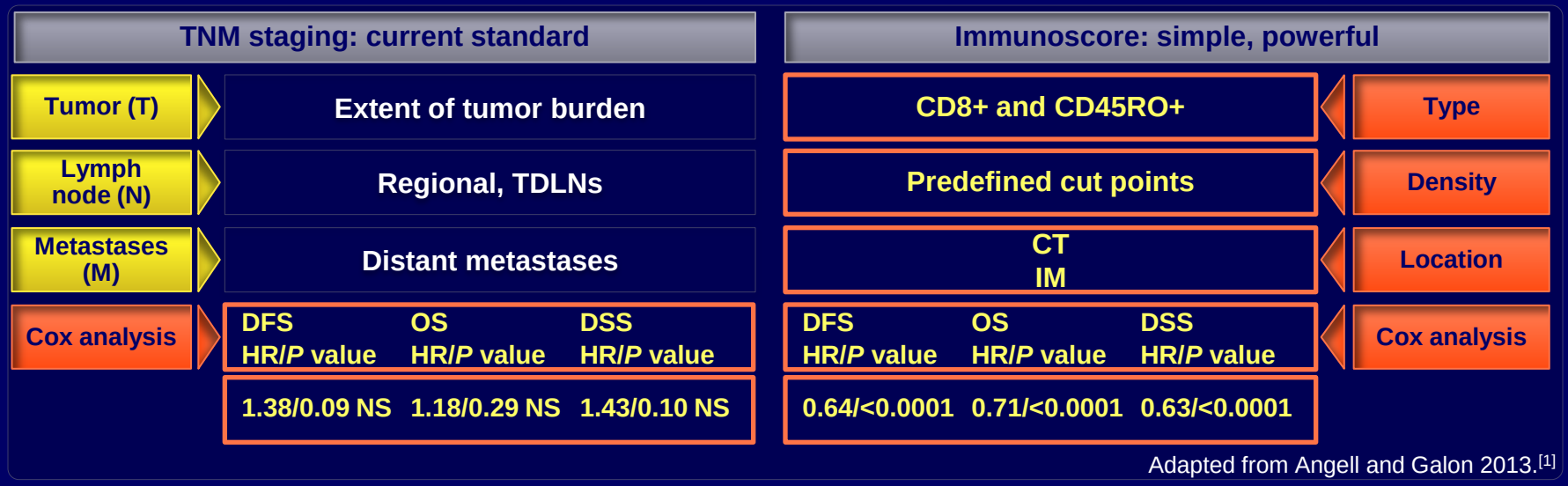
* Allograft rejection, graft versus host disease, autoimmune flares, destruction of virally infected cells, cancer regression following immunotherapy.[1]

CXCL, chemokine (C-X-C motif) ligand; IFN-γ, interferon-gamma.

1. Galon J et al. *Immunity*. 2013;39(1):11-26.
2. Fridman WH et al. *Cancer Microenviron*. 2013;6(2):117-122.

Immune-Based System: The Immunoscore in CRC (cont'd)

- Validation efforts of the Immunoscore are underway, and may result in its implementation as a new component of the traditional cancer classification system, TMN-Immune (TMN-I)[1,3]



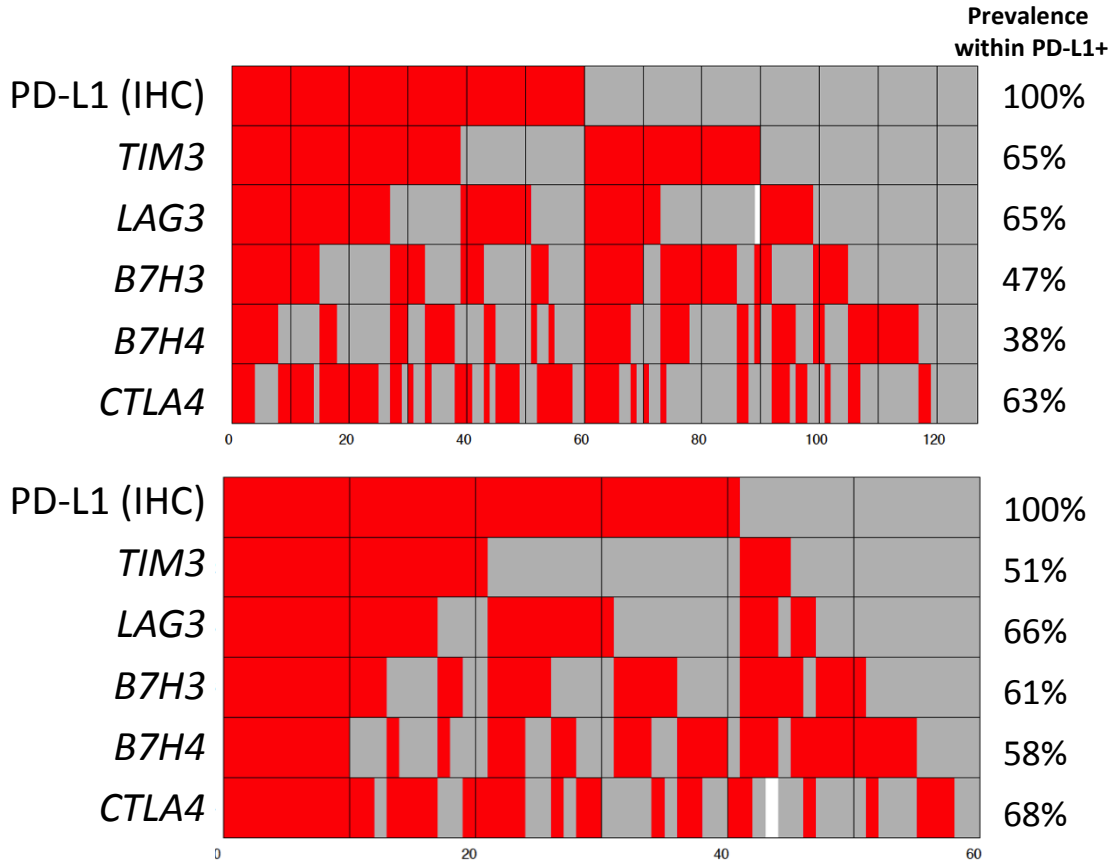
Adapted from Angell and Galon 2013.[1]

- The relevance of Immunoscore-like markers in diverse tumor types such as melanoma, breast, ovarian, lung, prostate, pancreatic, and head and neck has yet to be defined[2]

CRC, colorectal cancer; CT, tumor center; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; IM, invasive margin; NS, not significant; OS, overall survival; TDLN, tumor-draining lymph node.

1. Angell H, Galon J. *Curr Opin Immunol*. 2013;25(2):261-267.
2. Ascierto PA et al. *J Transl Med.* 2013;11:54. doi: 10.1186/1479-5876-11-54.
3. Galon J, Mlecnik B, Bindea G, et al. *J Pathol.* 2014;232(2):199-209.

PD-L1 expression in the context of other immune regulators



- **PD-L1 expression partially overlaps with other immune checkpoints in AdenoCa and SCC**

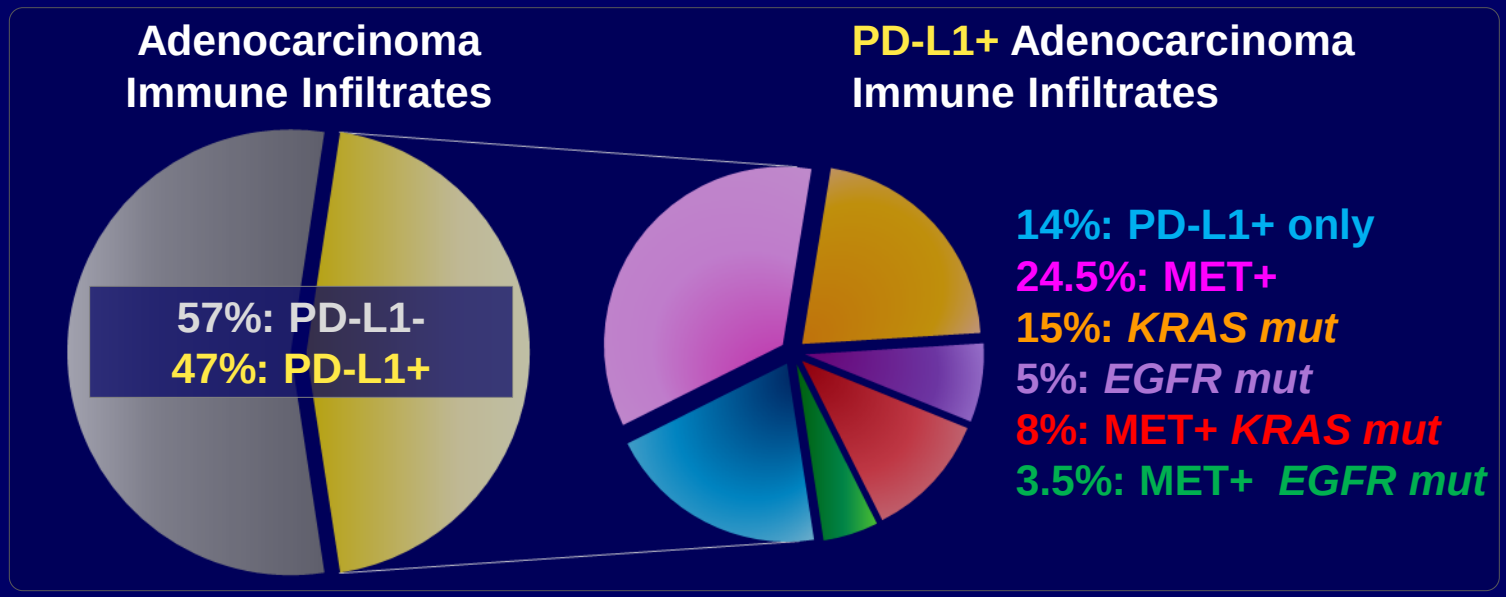
Samples from NSCLC stage I-IV
PD-L1 assessed by IHC
Other Immune checkpoints assessed by qPCR (Genentech's ImmunoChip), High>Median, Low<Median

DISCUSSION III

RELATION TO OTHER TARGETED THERAPIES AND POTENTIAL COMBINATIONS

PD-L1 Expression and Driver Mutation 'Map' in NSCLC

- In lung adenocarcinoma, approximately 47% of the immune infiltrate is PD-L1+[1]
  - Approximately 70% of these PD-L1+ tumors are also MET+, *KRAS* mutant or *EGFR* mutant[1]



Modified from Kowanetz et al 2013[1].

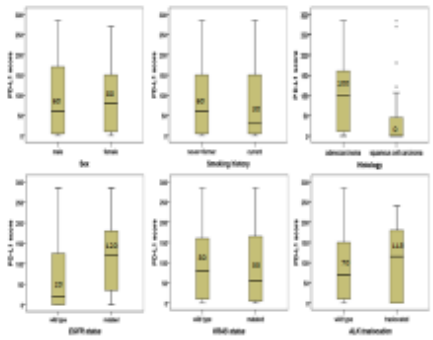
- Further, PD-L1+ NSCLC also expresses other immune checkpoints such as TIM3, LAG-3, B7-H3, B7-H4, and CTLA-4[1]

1. Kowanetz M et al. Oral presentation at WCLC 2013. MO19.10.

elcc European Lung Cancer Conference

PD-L1 results

	PD-L1 (N/%)
	123/100
Positive	68/55.3
Negative	55/44.7



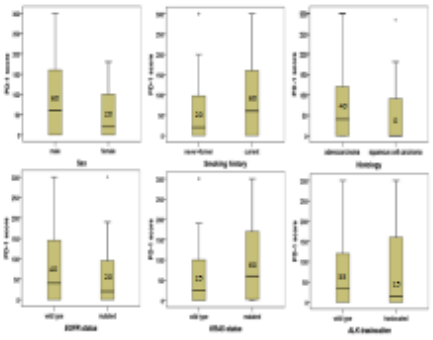
Characteristic	PD-L1+ (N/%)	PD-L1 – (N/%)	p-value
Male	36/52.9	30/54.5	0.86
Female	32/47.1	25/45.5	
Never/Former smokers	53/86.9	41/82.0	0.48
Current smokers	8/13.1	9/18.0	
Adenocarcinoma	52/88.1	30/65.2	0.005
Squamous cell carcinoma	7/11.9	16/34.8	
EGFR mutated	40/58.8	16/29.1	0.001
EGFR wild type	28/41.2	39/70.9	
KRAS mutated	15/22.1	13/23.6	0.84
KRAS wild type	53/77.9	42/76.4	
ALK translocated	6/8.8	4/7.3	1.00
ALK wild type	62/91.2	51/92.7	

26-29 March 2014, Geneva, Switzerland

Organisers IASLC ESMO

IS PDL-1 AND PD-1 EXPRESSING TUMORS TWO DIFFERENT DISEASES?

	PD-1 (N/%)
	122/100
Positive	43/35.2
Negative	79/64.8



Characteristic	PD-1+ (N/%)	PD-1 – (N/%)	p-value
Male	24/55.8	41/51.9	0.68
Female	19/44.2	38/48.1	
Never/Former smokers	27/73.0	65/90.3	0.02
Current smokers	10/27.0	7/9.7	
Adenocarcinoma	29/85.3	52/75.4	0.25
Squamous cell carcinoma	5/14.7	17/24.6	
EGFR mutated	17/39.5	38/48.1	0.56
EGFR wild type	26/60.5	41/51.9	
KRAS mutated	16/37.2	12/15.2	0.006
KRAS wild type	27/62.8	67/84.8	
ALK translocated	3/7.0	7/9.0	1.00
ALK wild type	40/93.0	72/91.1	

26-29 March 2014, Geneva, Switzerland

Organisers IASLC ESMO

16TH WORLD CONFERENCE ON LUNG CANCER

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

WWW.IASLC.ORG

Abstract Submission Open	January 2015
Registration Open	January 2015
Abstract Submission Deadline	April 24, 2015
Abstract Notifications	June 22, 2015
Early Registration Deadline	June 26, 2015
Late Breaking Abstract Submission Deadline	July 10, 2015
Regular Registration Deadline	July 24, 2015

SEPTEMBER 6–10, 2015

→ DENVER, COLORADO, USA

CURE FOR LUNG CANCER