L'IMMUNOTERAPIA, PRIMO APPUNTAMENTO PER IL FARMACISTA OSPEDALIERO, IL POLMONE: INNOVAZIONE, EFFICACIA E SOSTENIBILITÀ

Torino, 29 marzo 2017

Il ruolo del'anatomo patologo: immunoterapia e biomarcatori

Mauro Papotti

Università di Torino

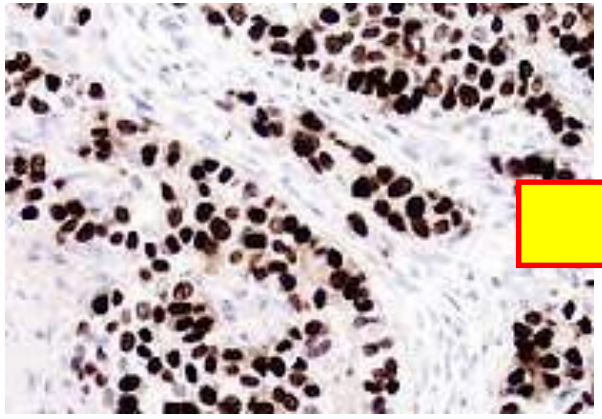
THE FIRST PREDICTIVE MARKER

ER positive breast cancer → tamoxifen

- **Jensen:** Estrogen Receptor mediates estrogen action.
- **Jordan:** reinvented contraceptive ICI46,474 as the first targeted therapy (tamoxifen).

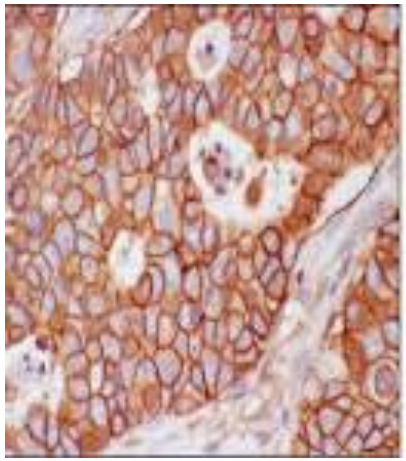
V. Craig Jordan: Tamoxifen: catalyst for the change to targeted therapy. Eur J Cancer 2008;44:30-38 (Fig. 1)

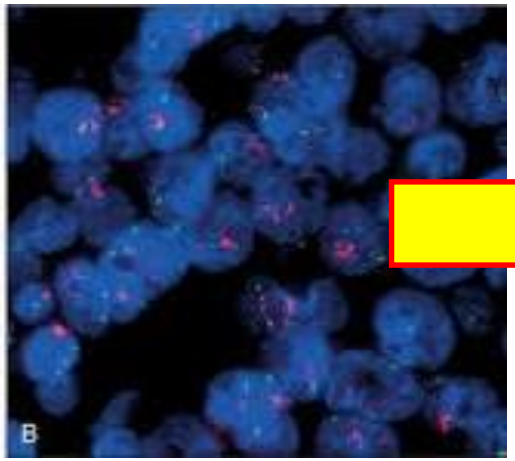
ER



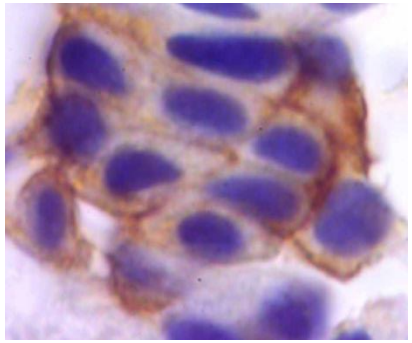
OTHER PREDICTIVE BIOMARKERS

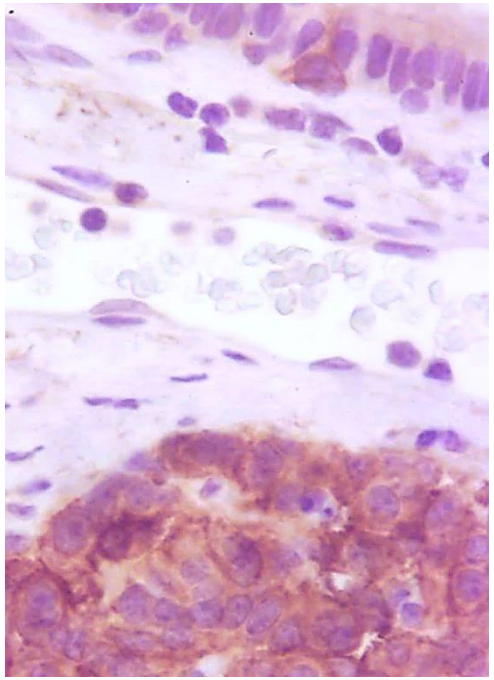
Her 2

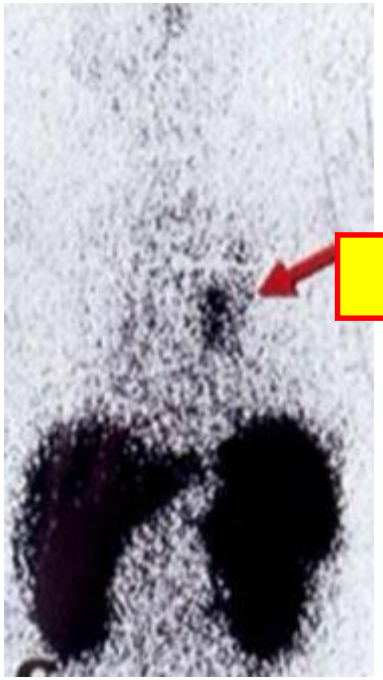




SSTR2





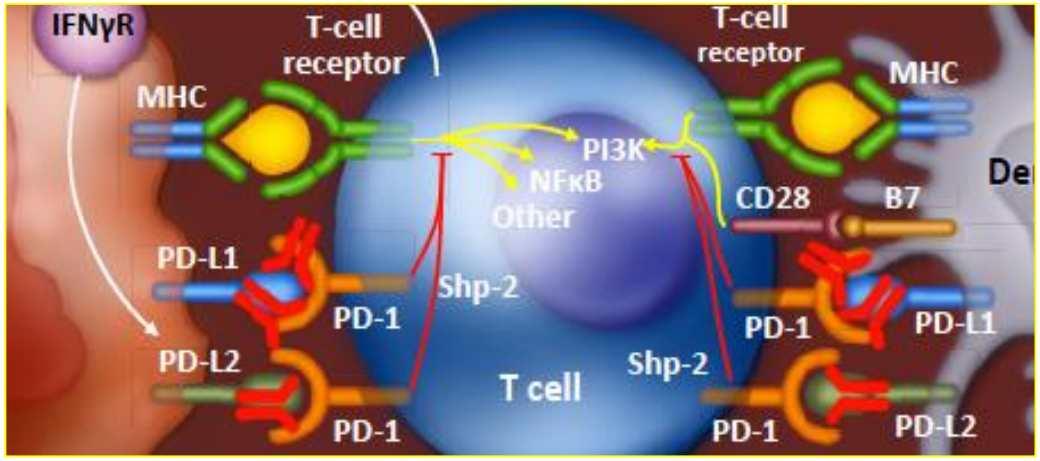


EGFR

VEGFR

FAQ

What is the best predictor?

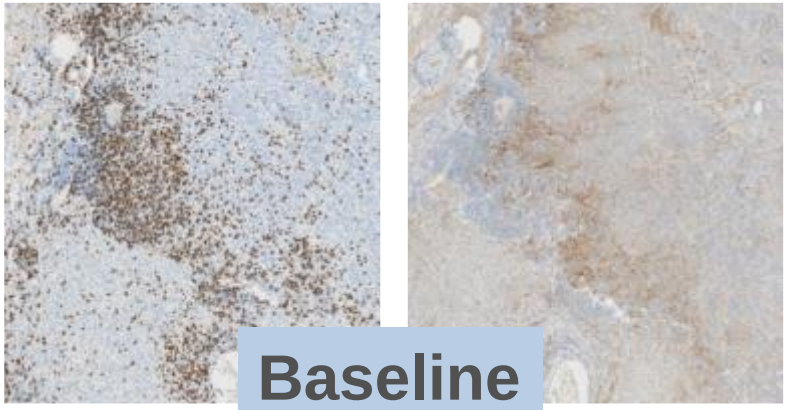


PD-L1 expression?
PD-1 expression?
Cytokines?
Lymphocytes?

PD-L1 expression is dynamic and may change after exposure to treatment

CD8 T cells

PD-L1

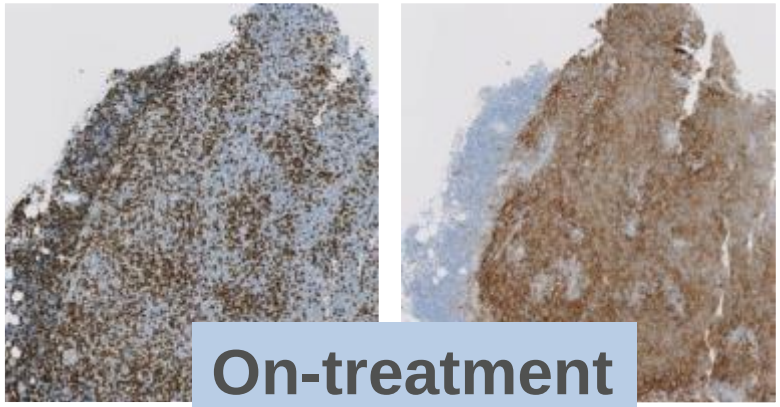


Baseline

MPDL3280A (PD-L1 inhibitor)

CD8 T cells

PD-L1

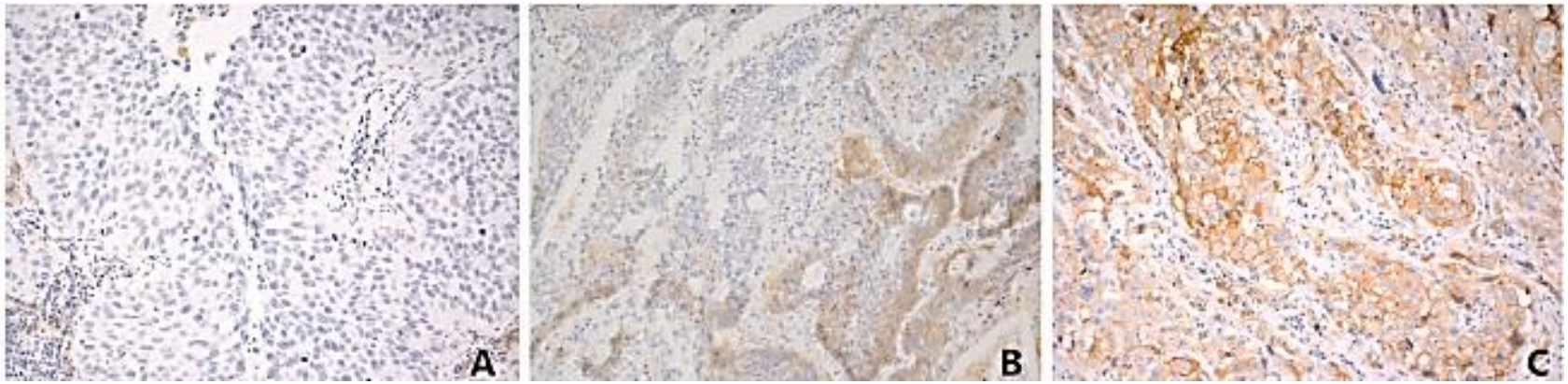


On-treatment

Mechanisms & heterogeneity

Table 1 Mechanisms of PD-L1 expression on tumor cells

Innate immune resistance	Adaptive immune resistance	Other
Constitutive oncogenic signaling*	Active tumor immunity leading to the production of interferon γ (and other interferons and cytokines)	Simultaneous amplification of *PD-L1* and *JAK2* (chromosome 9p21)
Loss of PTEN expression (PI3K pathway activation)		MicroRNA
ALK rearrangements		Upregulation of miR-20b, -21, -130b
EGFR mutations		Downregulation of miR-200, miR-197
		Hypoxia (through the production of HIF1α)
		Epithelial-mesenchymal transformation (up-regulation of ZEB1)



Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer?

Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0009

Mari Mino-Kenudson

PD-L1 expression is associated to a better response

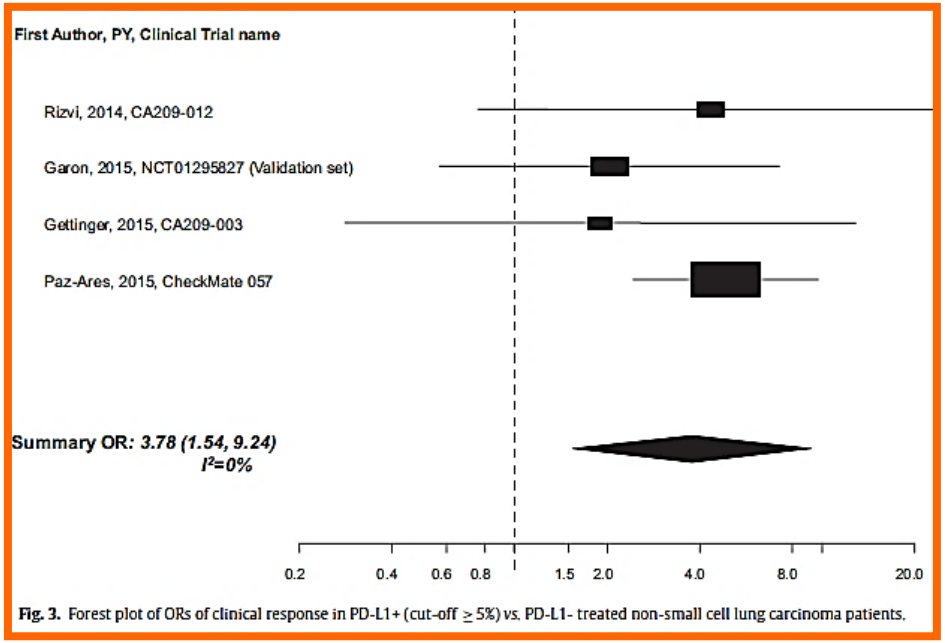


Fig. 3. Forest plot of ORs of clinical response in PD-L1+ (cut-off ≥ 5%) vs. PD-L1- treated non-small cell lung carcinoma patients.

PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis

Sara Gandini[a], Daniela Massi[b], Mario Mandalà[c,*]

Critical Reviews in Oncology/Hematology 100 (2016) 88–98

Table 1
Summary estimates according to PD-L1 status for clinical objective response and deaths.

Cancer Type	n. of estimates (n. of trials)	Subgroups	PD-L1 status	Summary Objective Response Rate (95% CI)	Odd Ratio	I^2%
MM	12 (10)		Positive Negative	45% (35, 55) 27% (17, 39)	2.14 (1.65, 2.77)	40
	5 (6)	In anti-PD-1 treatment arms	Positive Negative	46% (27, 65) 35% (19, 53)	1.89 (1.35, 2.64)	0
	5 (6)	In anti-PD-1 other treatment arms	Positive Negative	16% (11, 2) 12% (5, 23)	0.96 (0.5, 1.87)	5
NSCLC	9 (8)		Positive Negative	25% (20, 31) 14% (10, 18)	2.12 (1.23, 3.66)	26
	5 (5)	Squamous	Positive Negative	26% (16, 38) 15% (8, 24)	1.49 (0.48, 4.64)	0
	4 (4)	Non-squamous	Positive Negative	29% (19, 4) 11% (5, 19)	3.78 (1.54, 9.24)	0
RCC	4 (3)		Positive Negative	29% (8, 57) 25% (0, 76)	1.70 (0.32, 9.02)	33
MM	6 (4)	Deaths			0.47 (0.30, 0.75)	0

PD-1 / PDL-1

What to investigate?

PDL1 rather than PD1

Which method?

IHC vs mRNA expression

Best reagents?

depending on treatment

Preanalytical issues (tissue fixation and processing)

Journal of Thoracic Oncology® • Volume 10, Number 7, July 2015

How to interpret?

Generally expression in tumor cells

Role of expression by immune cells

Cutoffs and scoring systems

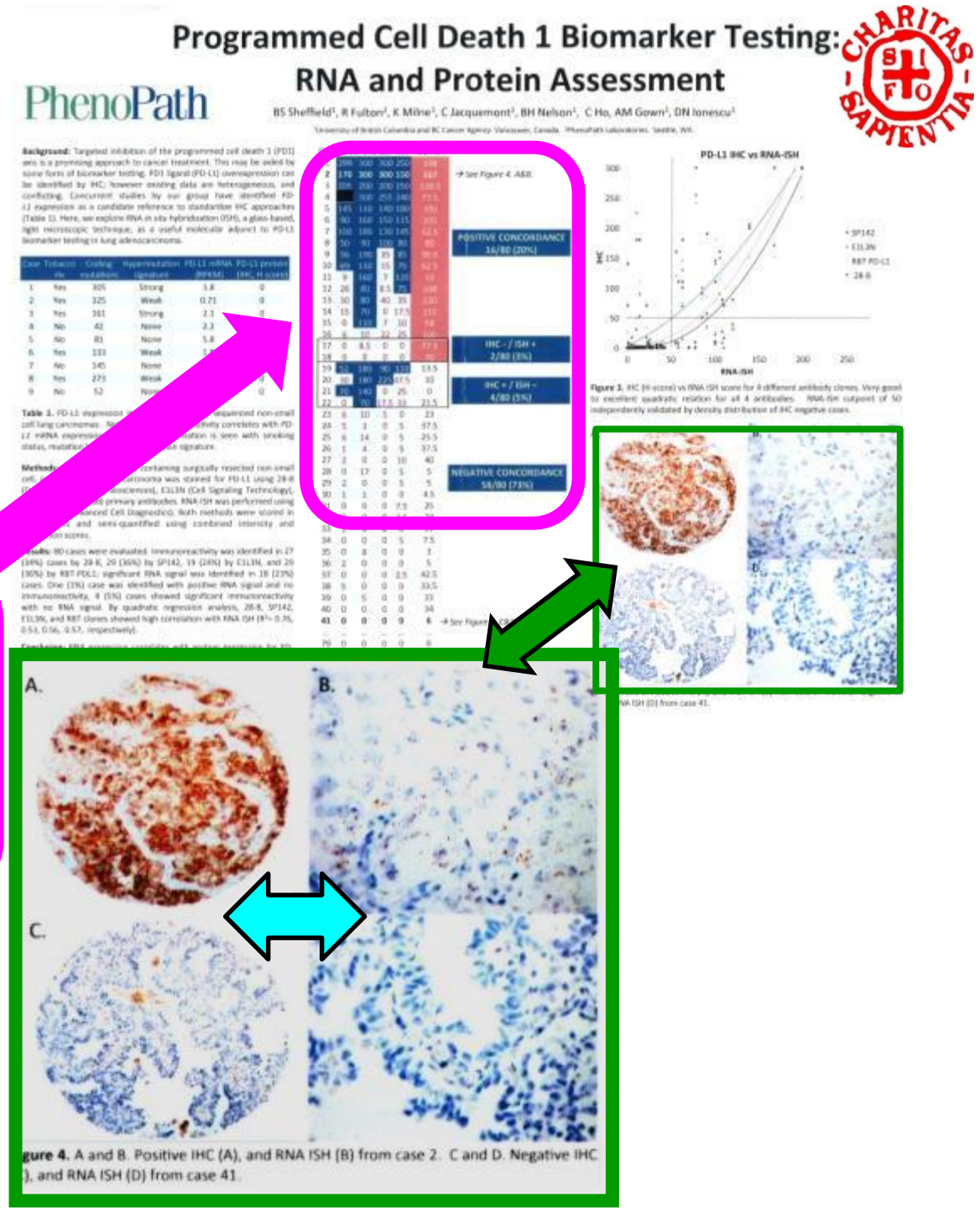
-membrane reactivity in neopl cells
-variable cutoffs (1-10-50%)

PDL-1 protein vs gene

SP142

83% concordance IHC - ISH

Mod Pathol 2016; 2S2:483A



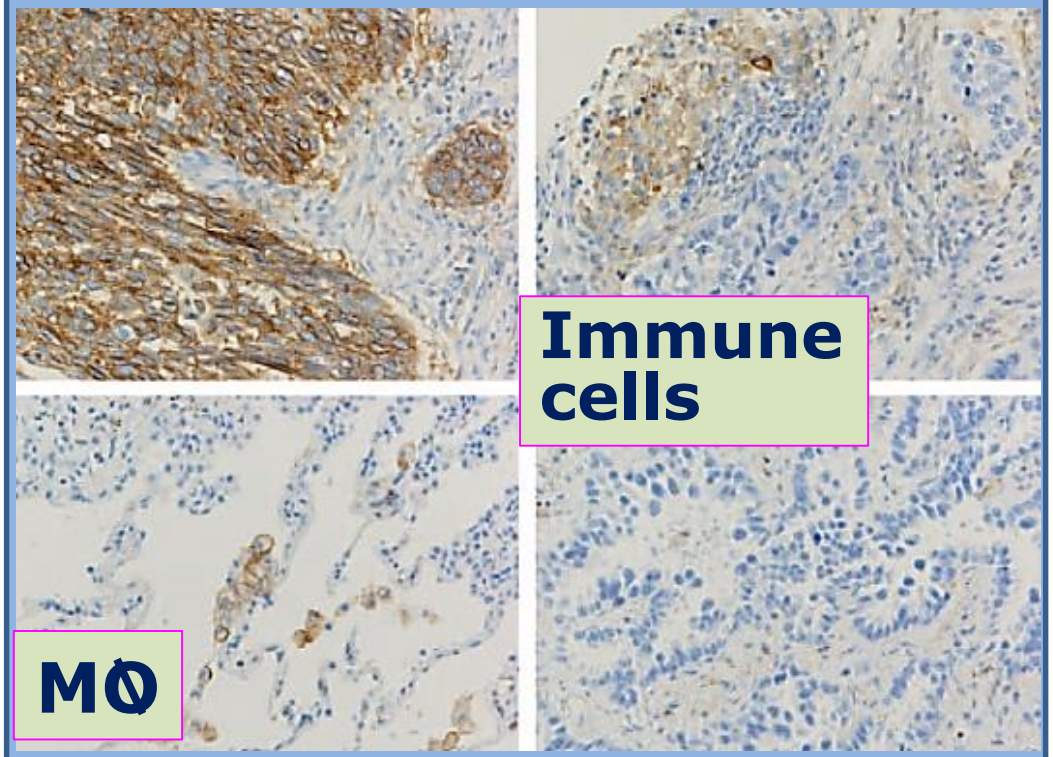
PDL1 antibodies

#13684 Store at -20°C

PD-L1 (E1L3N®) XP® Rabbit mAb

- Small 100 µl (10 western blots)
- Petite 40 µl (4 western blots)

Cell Signaling TECHNOLOGY®



Journal of Thoracic Oncology® • Volume 10, Number 7, July 2015

Keith M. Kerr, MBChB, FRCPath, Ming-Sound Tsao, MD, PhD,† Andrew G. Nicholson, DM, FRCPath, Yasushi Yatabe, MD, PhD,§ Ignacio I. Wistuba, MD, PhD,‖ and Fred R. Hirsch, MD, PhD,¶*
On behalf of the IASLC Pathology Committee

Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer

In what state is this art?

Pdl1 Antibodies & Related Drugs

Programmed Death Ligand-1 Immunohistochemistry—A New Challenge for Pathologists

Arch Pathol Lab Med. 2016;140:341–344;

A Perspective From Members of the Pulmonary Pathology Society

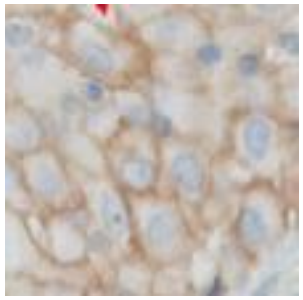
Lynette M. Sholl, MD; Dara L. Aisner, MD; Timothy Craig Allen, MD, JD; Mary Beth Beasley, MD; Alain C. Borczuk, MD; Philip T. Cagle, MD; Vera Capelozzi, MD, PhD; Sanja Dacic, MD, PhD; Lida Hariri, MD, PhD; Keith M. Kerr, BSc, MB, ChB, FRCPath, FRCPE; Sylvie Lantuejoul, MD, PhD; Mari Mino-Kenudson, MD; Kirtee Raparia, MD; Natasha Rekhtman, MD, PhD; Sinchita Roy-Chowdhuri, MD, PhD; Eric Thunnissen, MD, PhD; Ming Sound Tsao, MD; Yasushi Yatabe, MD, PhD; for the members of the Pulmonary Pathology Society

Programmed Death Ligand-1 Inhibitors

Drug	Company	FDA Approval	mAb/Platform	Scoring Criteria	Comment
Pembrolizumab (Keytruda)	Merck (Kenilworth, New Jersey)	FDA approved for NSCLC	22C3 (DAKO pharmDx/ Link 48 Autostainer (Dako, Carpenteria, California)	≥50% tumor cells	Companion diagnostic[a] (as of October 2015)
Nivolumab (Opdivo)	Bristol-Myers Squibb (New York, New York)	FDA approved for squamous and nonsquamous NSCLC	28-8 (DAKO pharmDx)/ Link 48 Autostainer	≥1% tumor cells	Complementary diagnostic[b] (as of October 2015); predictive only in nonsquamous carcinomas
Atezolizumab (MPDL3280)	Roche (Basel, Switzerland)	Expected in 2016	SP142 (Ventana, Tucson, Arizona)	Tumor cells and/or tumor-infiltrating immune cells	In development
Durvalumab (MEDI4736)	Astra-Zeneca (London, United Kingdom)	Expected in 2016	SP263 (Ventana)	≥25% tumor cells	In development

Ab 28-8

Dako
An Agilent Technologies



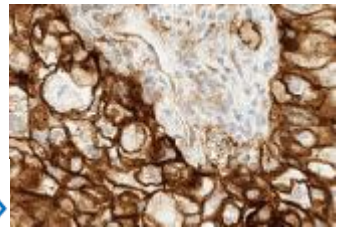
Appl Immunohistochem Mol Morphol • Volume 23, Number 8, September 2015

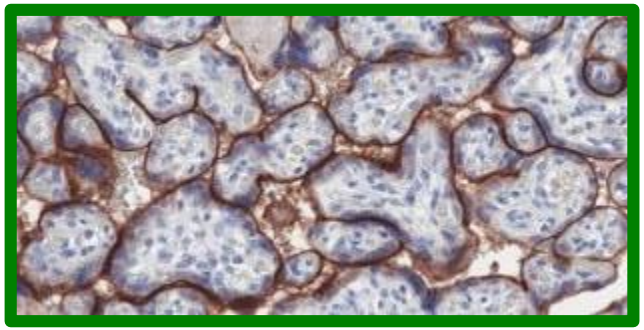
Development of an Automated PD-L1 Immunohistochemistry (IHC) Assay for Non–Small Lung Cancer

Therese Phillips, MA, Pauline Simmons, BS,* Hector D. Inzunza, MD, PhD,† John Cogswell, PhD,† James Novotny, Jr, PhD,† Clive Taylor, MD, PhD,‡ and Xiaoling Zhang, PhD**

Ab SP263

VENTANA Roche





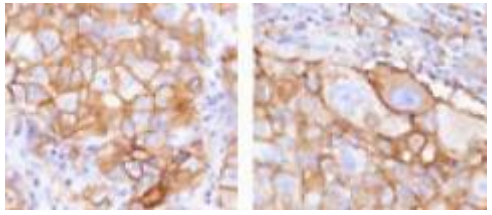
VENTANA PD-L1 (SP263)

Rabbit Monoclonal Primary Antibody

The VENTANA PD-L1 (SP263) Rabbit Monoclonal Primary Antibody is the first ready-to-use IVD IHC antibody that empowers you to evaluate the expression of PD-L1 protein using the OptiView DAB IHC Detection Kit.

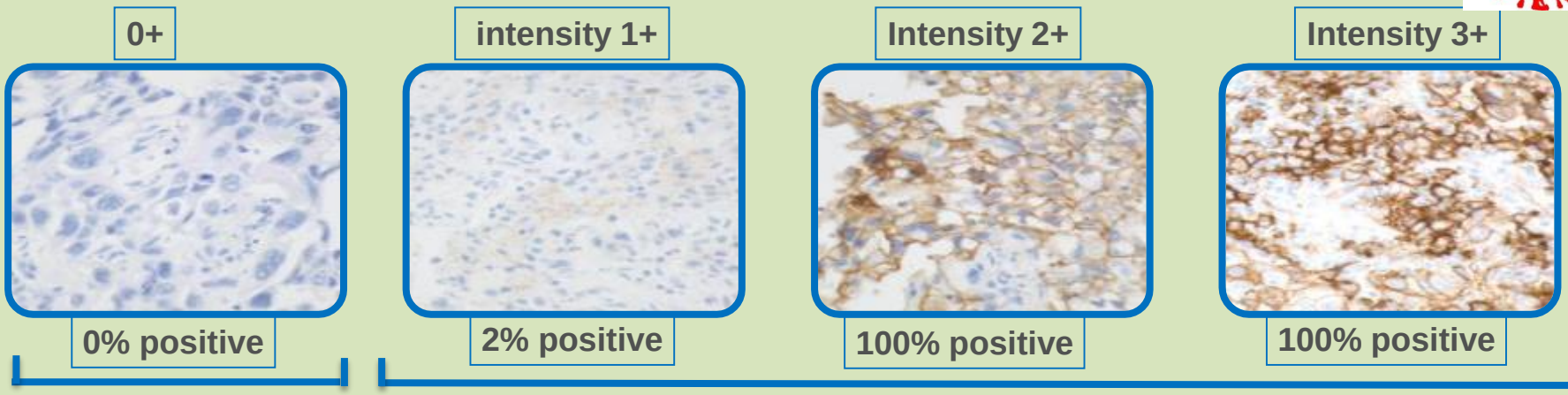
Ab SP142

VENTANA Roche



SP142 was developed for Roche/Genentech anti-PD-L1 (MPDL3280A) immunotherapy

Ab22C3



PD-L1 PROBLEMATIC ISSUES

Low thresholds (eg 1% or 5% of TC) → risk of scoring inconsistencies (due to heterogeneity).

TABLE 1. Summary of Published Findings for PD-L1 Immun

Drug	Biomarker Antibody	Rx Line	Definition of "Positive"[a] (%)
Nivolumab	Dako 28-8	1st	≥5 in >100 cells
Nivolumab	Dako 28-8	≥2nd	≥5, ≥1
Nivolumab + Ipilimumab	Dako 28-8	1st	≥5 in >100 cells
Nivolumab	Dako 28-8	≥2nd	≥5
Nivolumab	5H1[d]	≥2nd	≥5, also studied TIICs

Journal of Thoracic Oncology® • Volume 10, Number 7, July 2015

PDL-1

22C3 >50% of TC

Two years ago:

N ENGL J MED 372;21 NEJM.ORG MAY 21, 2015

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M. Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.I Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.I Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

Today:

NOVEMBER 10, 2016

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Pl Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D for the KEYNOTE-024 Investigators*

PFS 10.3 mos vs 6.0 mos (platinum) [p<.001]

One year ago:

Are we ready for immune checkpoint inhibitors for advanced non-small-cell lung cancer?

*Tony S K Mok, Herbert H Loong

http://dx.doi.org/10.1016/S0140-6736(15)01308-2

See Articles page 1540 Lancet 2016 Apr 9

At present, there appear to be no solid data to support the routine application of PD-L1 expression as a predictive biomarker before the use of immune checkpoint inhibitors. Because patients with a tumour proportion score of less than 1% were excluded from this study, it is unclear whether such patients would have a different response to pembrolizumab compared with the 1–49% subgroup. On the basis of previous findings

?

Clinical trials & PDL1 & outcome

What matters

Table 2. The Association between PD-L1 Protein Expression and Clinical Outcome in Patients with Lung Cancer

Reference	Tumor Type	Sample Size	Method	Antibody/ Platform (Anti-PD-L1)	Cell Location	Cutoff	Prevalence	Outcome Associated with PD-L1 Positivity	Treatment
Kim et al.[15]	Squamous carcinoma	331	IHC analysis	E1L3N (Cell Signaling Technologies)/ Ventana Benchmark XT automated staining system	Tumor cell membrane	≥2+ (weak to moderate or strong staining in ≥10% tumor cells)	26.9%	No significant association with prognosis	
Schmidt et al.[16]	Squamous carcinoma	149	IHC analysis	E1L3N (Cell Signaling Technologies), #13684 clone, rabbit IgG1	Tumor cell membrane	5% of the tumor cells displayed at least moderate staining	28%	Improved OS	Adjuvant therapy
Zhang et al.[34]	NSCLC	109	ELISA	Beijing Keyingmei Science and Technology Ltd	Peripheral blood	0.636 ng/mL	56% above the threshold	Worse prognosis	NR
Tang et al.[17]	*EGFR* wild-type advanced NSCLC	56	IHC analysis	E1L3N (Cell Signaling Technologies), 1:200	Tumor cell membrane	H-score ≥5	57.1%	Worse prognosis	
Lin et al.[35]	*EGFR* mutated adenocarcinoma	56	IHC analysis	#ab58810 (Abcam)	Tumor cell membrane and cytoplasm	≥Mean H-score	53.6%	Improved OS	EGFR-targeted TKI therapy
Zhang et al.[36]	Adenocarcinoma	143	IHC analysis	#SAB2900365 (Sigma-Aldrich)	Tumor cell membrane and cytoplasm	Semiquantitative quick score ≥8 (median quick score)	50%	Worse OS	Surgical resection
Schmidt et al.[16]	NSCLC	321	IHC analysis	E1L3N (Cell Signaling Technologies)	Tumor cell cytoplasm	≥5% with at least moderate staining	24%	Improved prognosis in squamous cell carcinoma subset	Curative resection
Azuma et al.[37]	NSCLC	164	IHC analysis	Lifespan Biosciences/ Ventana BenchMark XT platform	Tumor cell membrane and/or cytoplasm	>Median value of H-score (30)	50%	Worse OS	Surgical resected
Yang et al.[38]	Stage I lung adenocarcinoma	163	IHC analysis	Proteintech Group	Tumor cell membrane staining	≥5% with at least moderate staining	39.9%	Improved relapse-free survival	Surgical resection
Velcheti et al.[39]	NSCLC (Yale) NSCLC (Greece)	204 340	QIF	5H1 (Dr. Lieping Chen's laboratory)		AQUA quantitative score higher than signal intensity from normal lung and negative controls	25% 36%	Improved OS	
Chen et al.[40]	NSCLC	120	IHC analysis		Tumor cell membrane and cytoplasm		57.5%	Worse OS	

PD-L1 Expression in Lung Cancer

Hui Yu, MD, PhD,[a] Theresa A. Boyle, MD, PhD,[a,b,c,d] Caicun Zhou, David L. Rimm, MD, PhD,[f] Fred R. Hirsch, MD, PhD[a,b,*]

Journal of Thoracic Oncology Vol. 11 No. 7: 964-975 July 2016

Predictive or prognostic in NSCLC?

PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis

Oncotarget, Vol. 7, No. 15 2016

Francesco Passiglia[1,*], Giuseppe Bronte[1,*], Viviana Bazan[1,*], Clara Natoli[2], Sergio Rizzo[1], Antonio Galvano[1], Angela Listì[1], Giuseppe Cicero[1], Christian Rolfo[3], Daniele Santini[4], Antonio Russo[1]

Study or Subgroup	PD-L1+ Events	PD-L1+ Total	PD-L1- Events	PD-L1- Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Borghaei et al. 2015	38	123	10	108	22.8%	4.38 [2.06, 9.32]
Brahmer et al., 2015	11	63	9	54	24.8%	1.06 [0.40, 2.78]
Garon et al., 2015	37	134	2	22	7.7%	3.81 [0.85, 17.13]
Gulley et al. 2015	17	118	2	20	9.1%	1.51 [0.32, 7.13]
Rizvi et al. 2014	8	26	5	26	10.7%	1.87 [0.52, 6.73]
Rizvi et al., 2015	9	45	4	31	11.8%	1.69 [0.47, 6.06]
Spira et al. 2015	17	93	4	51	13.1%	2.63 [0.83, 8.29]
Total (95% CI)		**602**		**312**	**100.0%**	**2.44 [1.61, 3.68]**
Total events	137		36			

Heterogeneity: $Chi^2 = 6.39$, $df = 6$ ($P = 0.38$); $I^2 = 6\%$

Test for overall effect: $Z = 4.24$ ($P < 0.0001$)

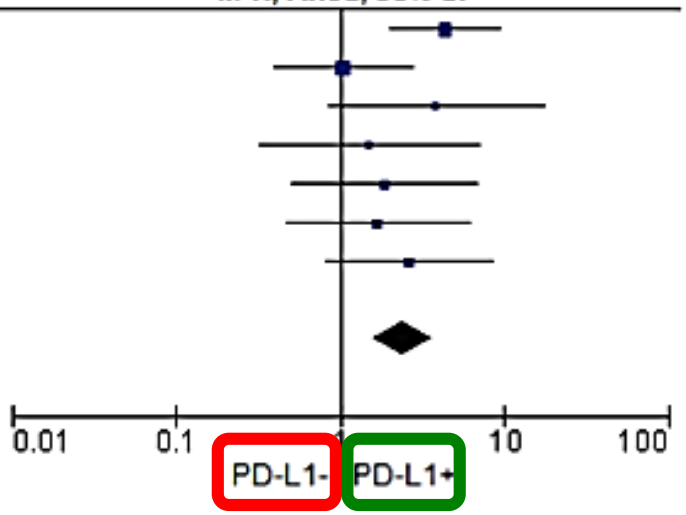
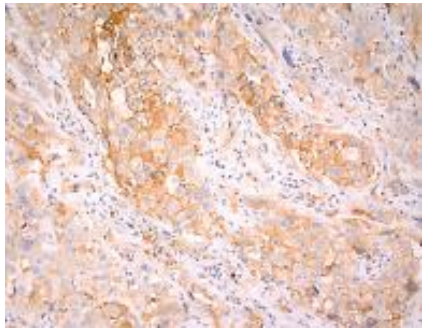


Figure 2: Forest plot showing odds ratio for overall response rate to anti-PD-1/PD-L1 monoclonal antibodies according to the tumor PD-L1 expression status, in pre-treated NSCLC patients.

Predictive or prognostic in NSCLC?

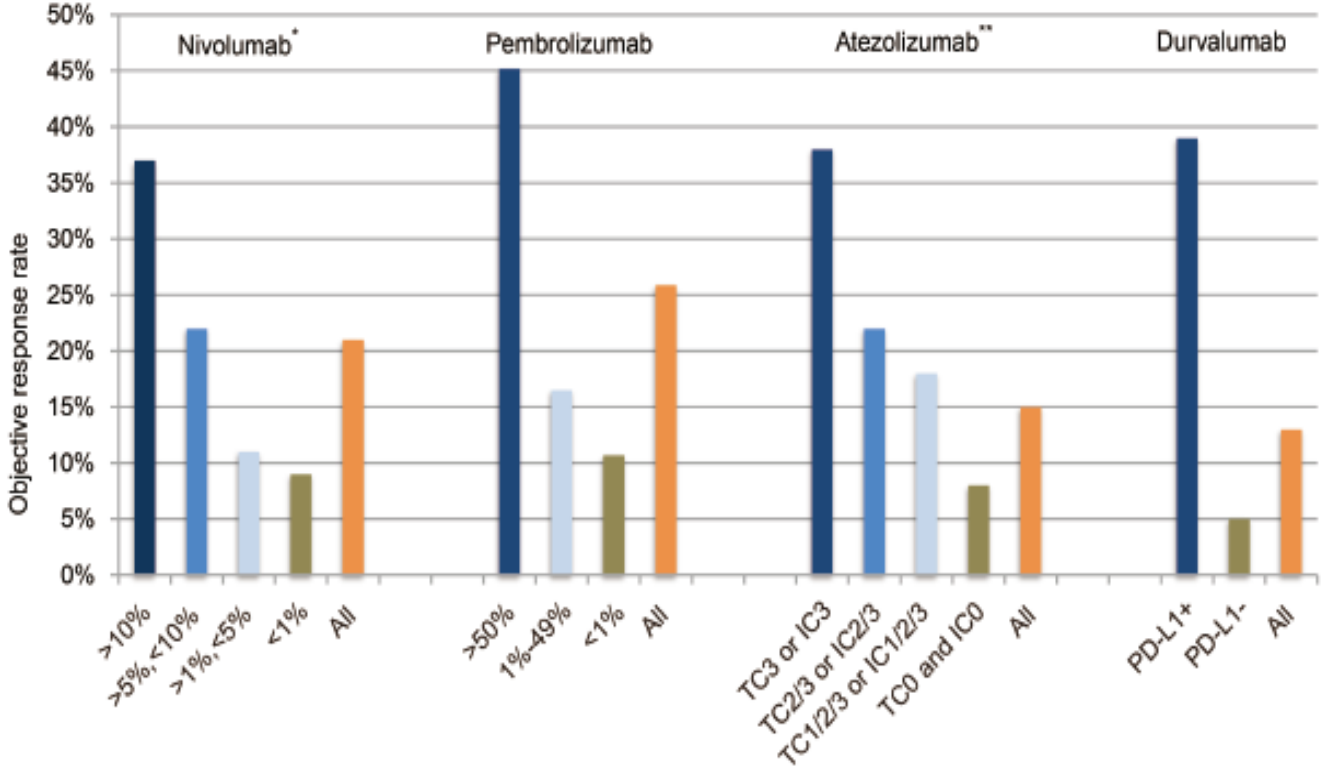
Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer?



Mari Mino-Kenudson

Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0009

PD-L1 expression and response to PD-1/PD-L1 inhibitors in NSCLC.



Antibody	28-8 (Dako)	22c3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Scoring	Tumor cells	Tumor cells	Tumor and immune cells	Tumor cells

PDL-1 IHC (22C3 Ab) in lung cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

METHODS

In this open-label, phase 3 trial, we randomly assigned 305 patients who had previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene or translocation of the anaplastic lymphoma kinase gene to receive either pembrolizumab

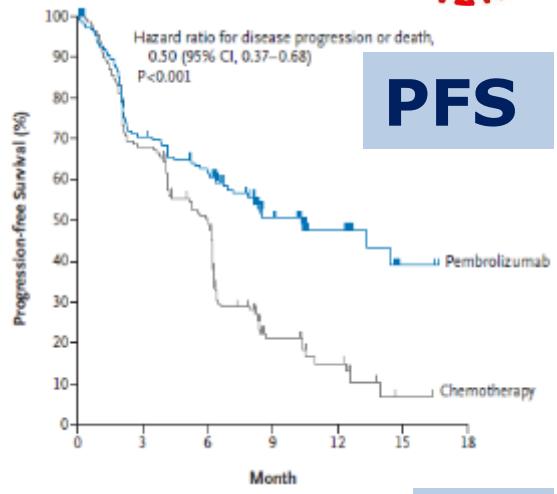
RESULTS

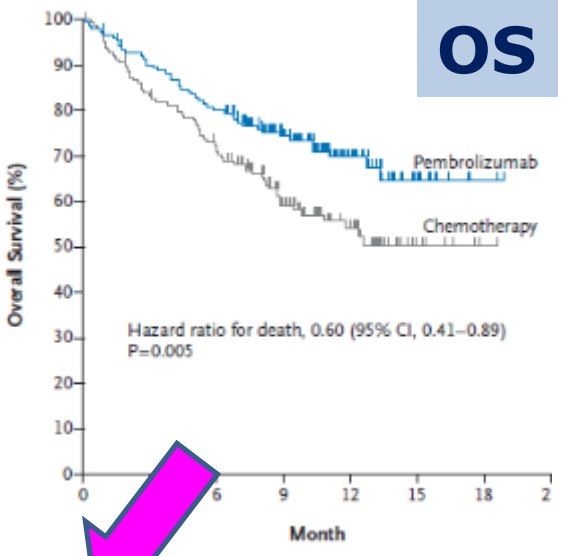
Median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the

The response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), the median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+]), and treatment-related adverse events of any grade were less frequent

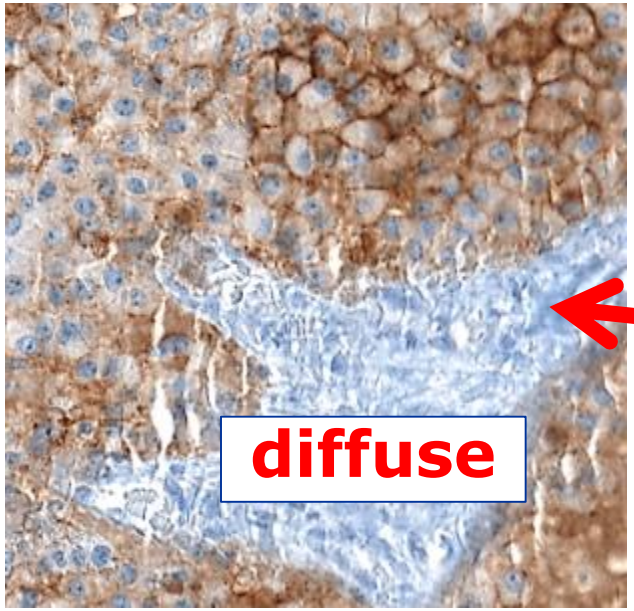
CONCLUSIONS

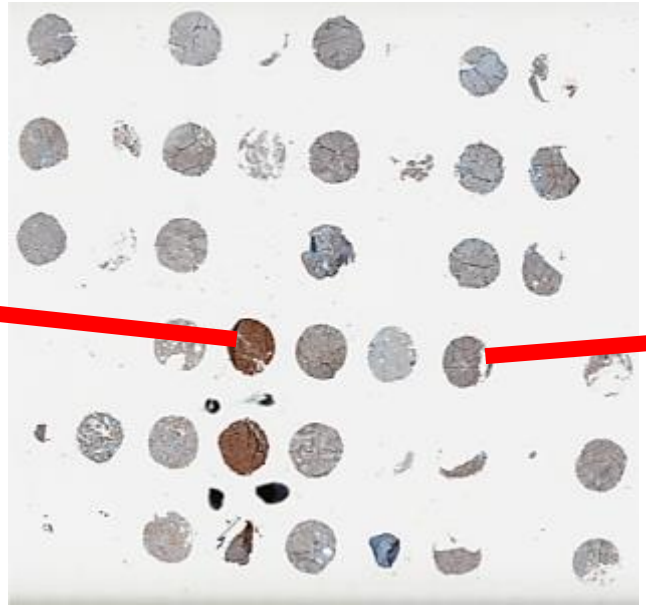
In patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.

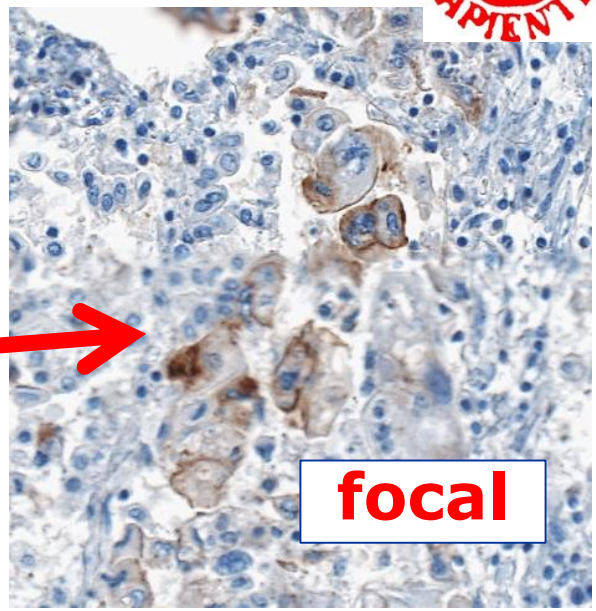




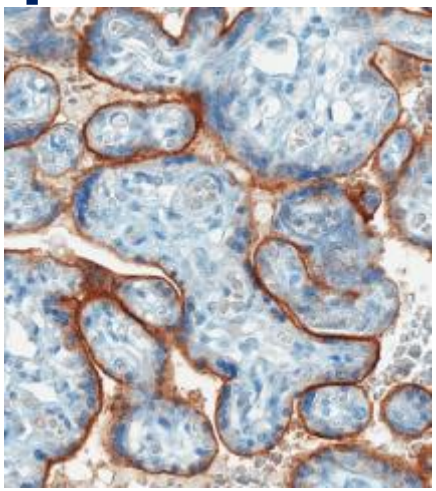
PDL-1 IHC (Ab SP142)

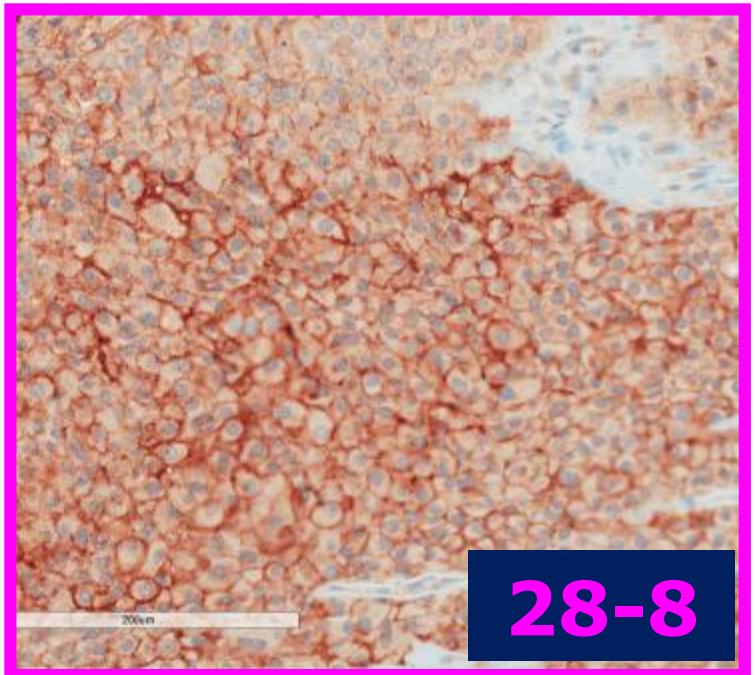


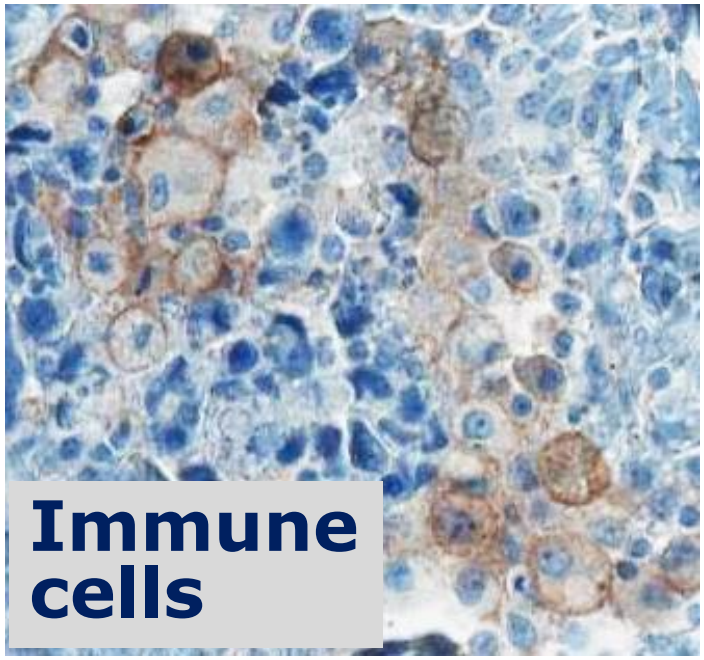




Control placenta





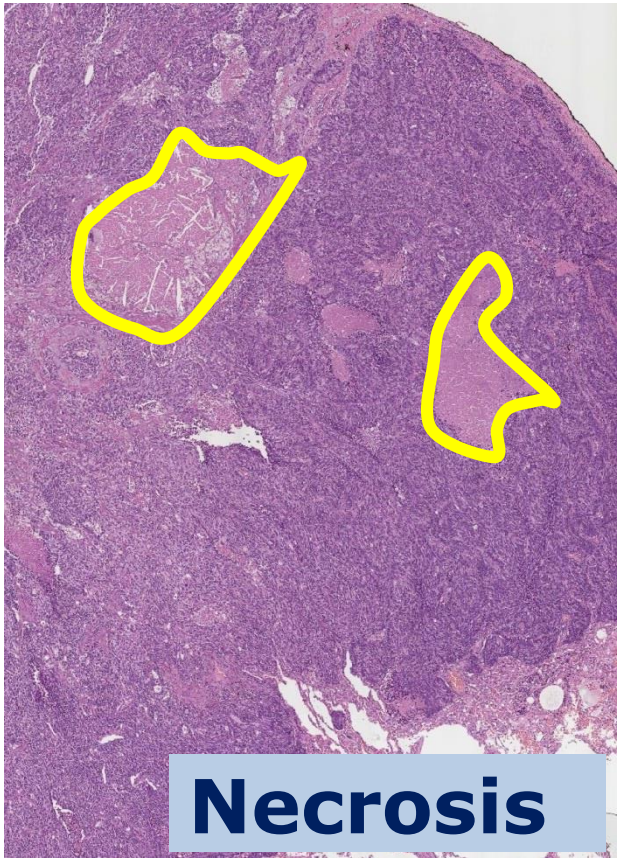


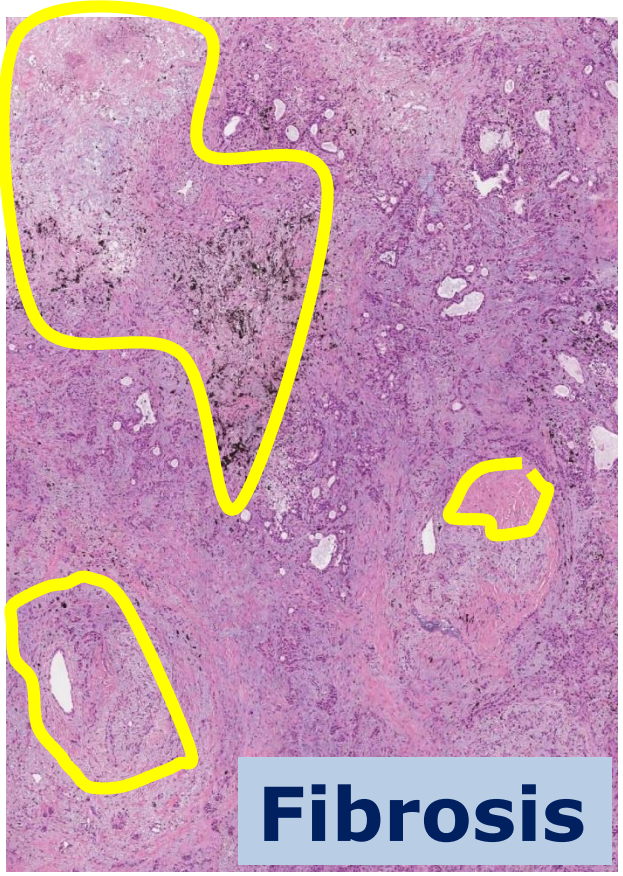
PDL-1 interpretation - SP142 Ab

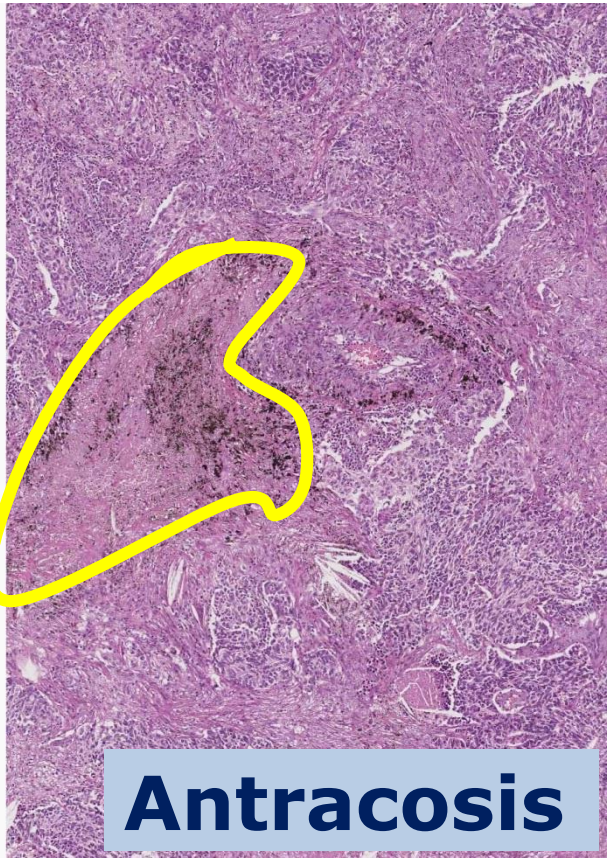
TC0: neg TC1: <5%
TC2: 5-50% TC3: >50%

To define the % of positivity the denominator is crucial

Exclude areas of:





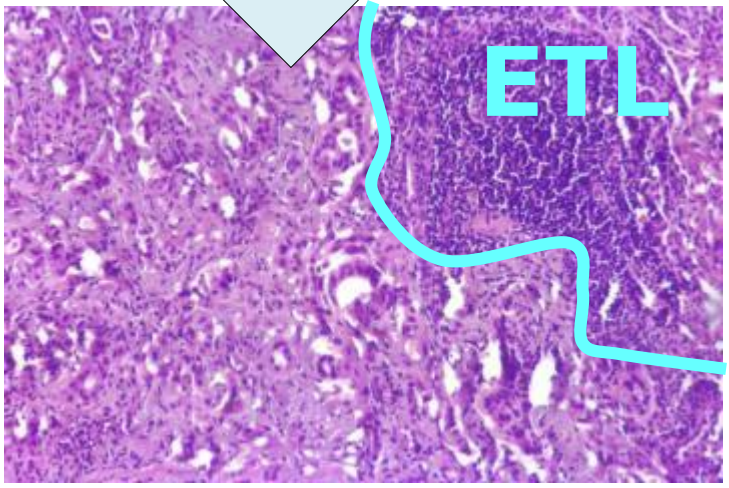


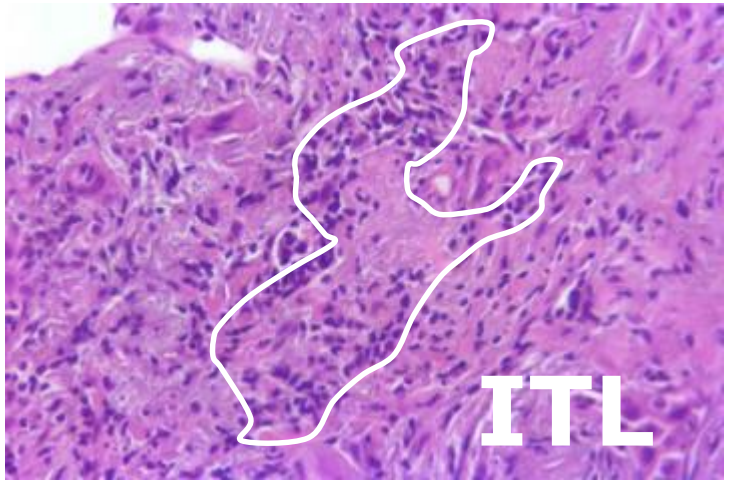
PDL-1 interpretation - SP142 Ab

TC0: neg TC1: <5%
TC2: 5-50% TC3: >50%

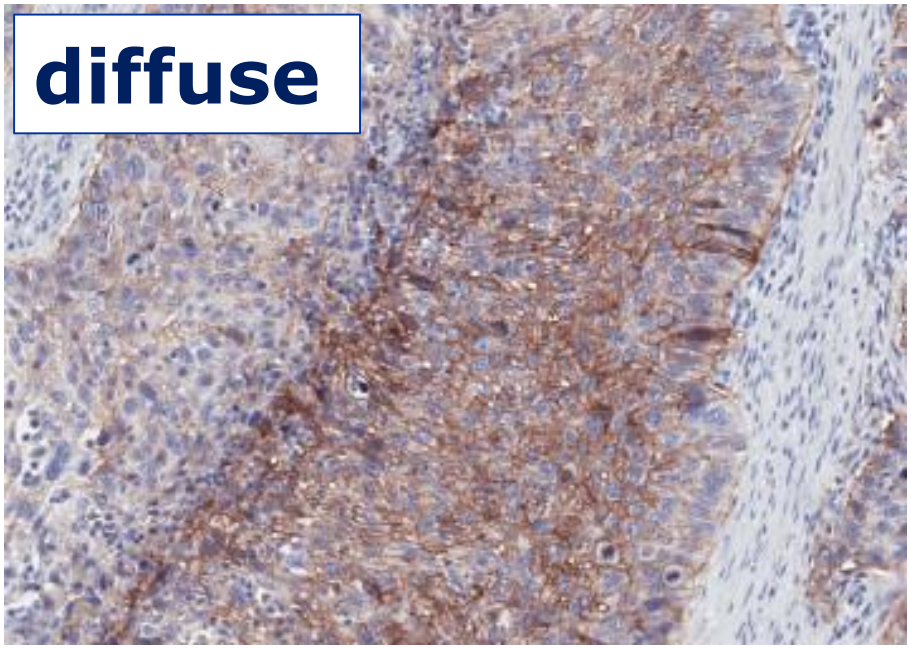
IC0: neg IC1: 1-5%
IC2: 5-9% IC3: >10%

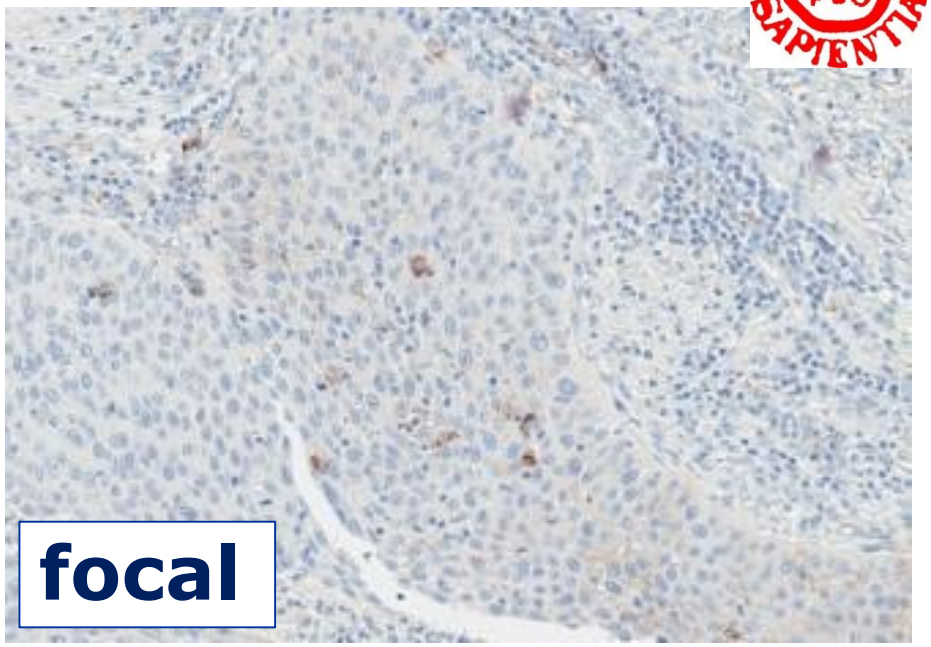
To define the % of positivity the denominator is crucial

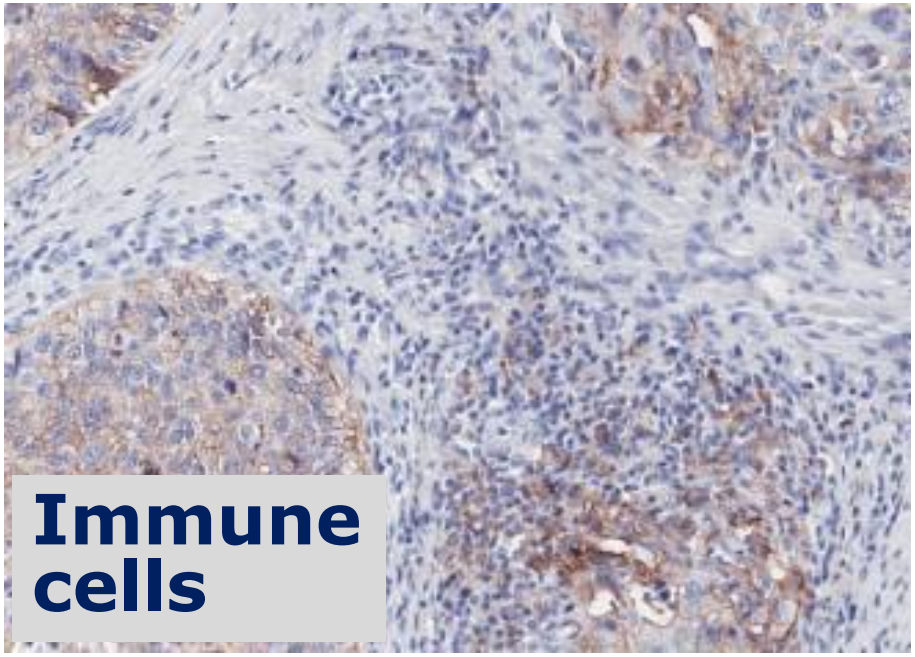




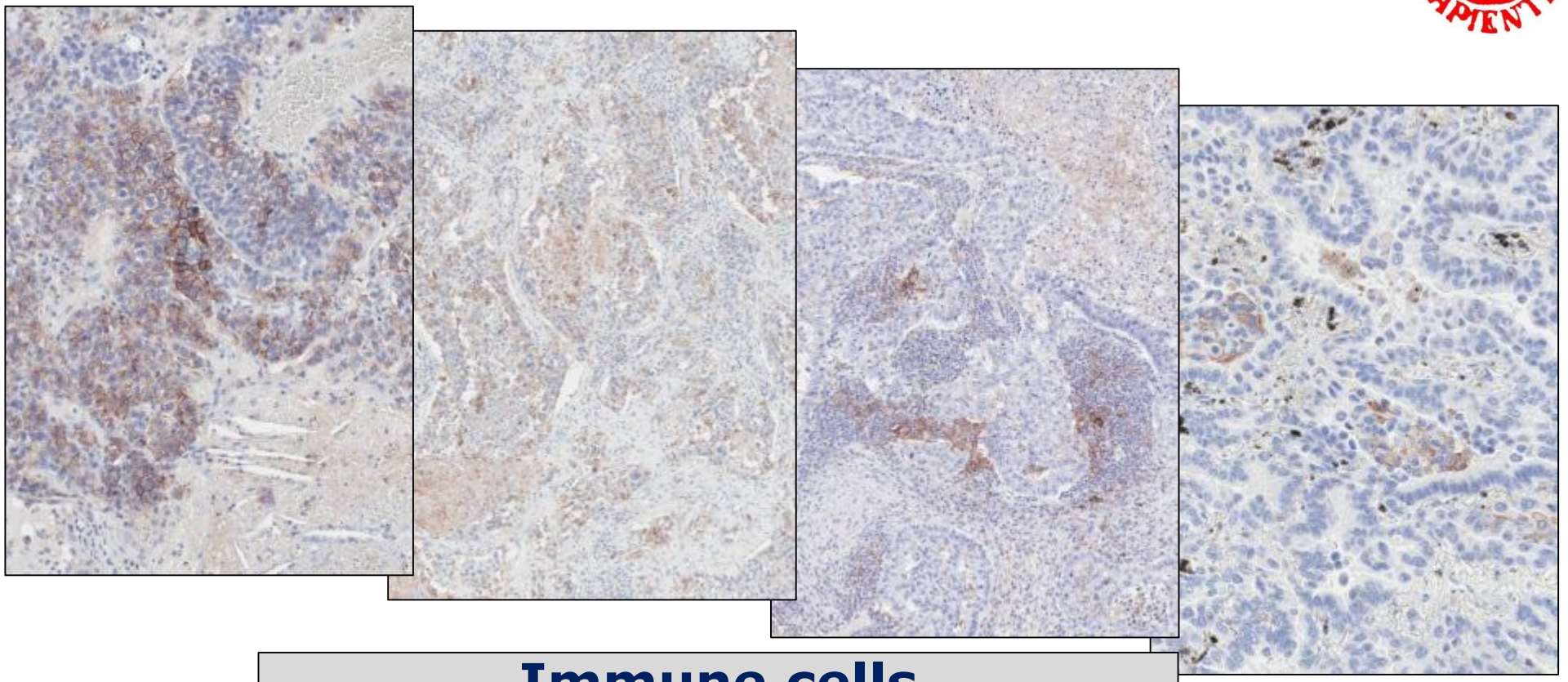
PDL-1 IHC (22C3 Ab) in lung SqC



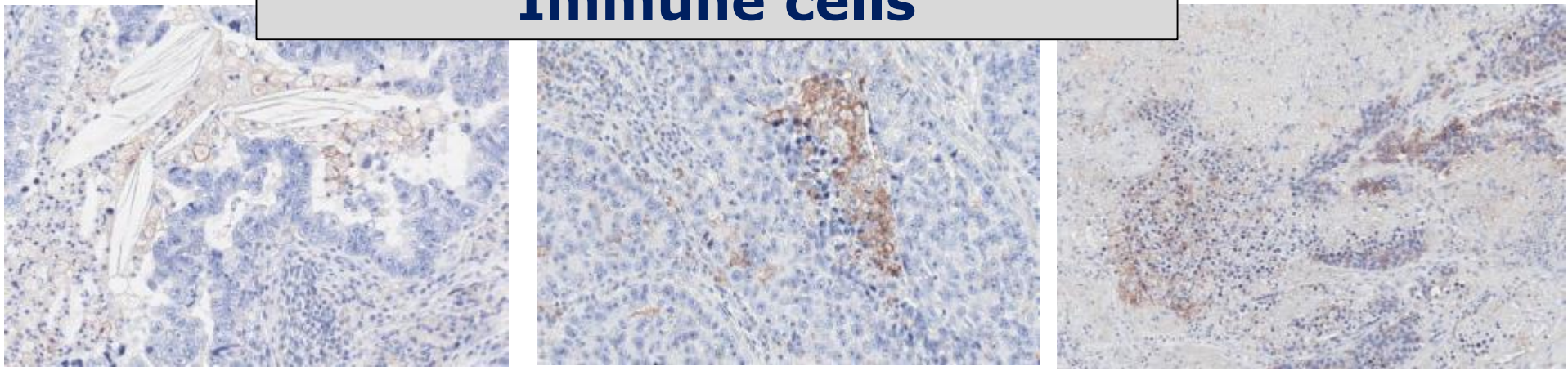




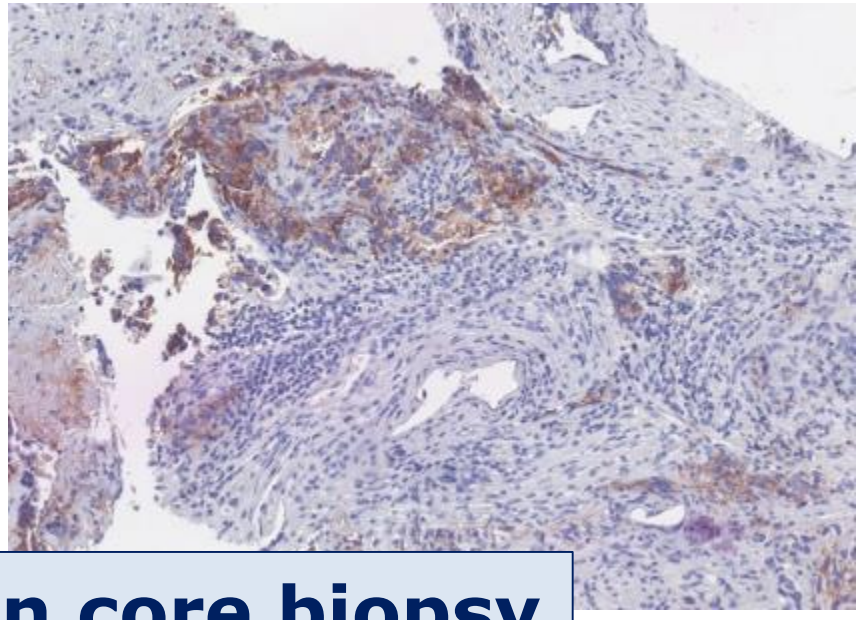
PDL-1 IHC (22C3 Ab) in lung ADC



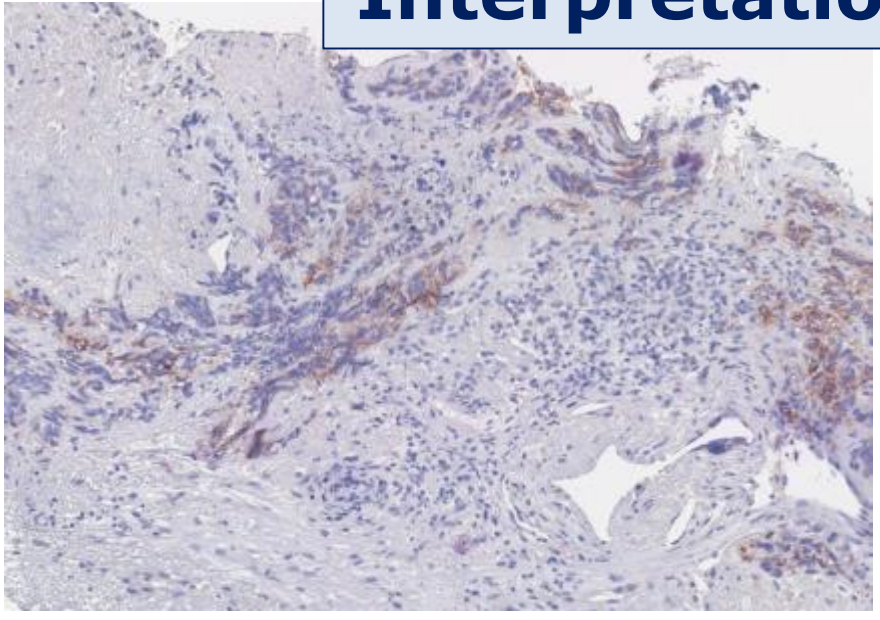
Immune cells

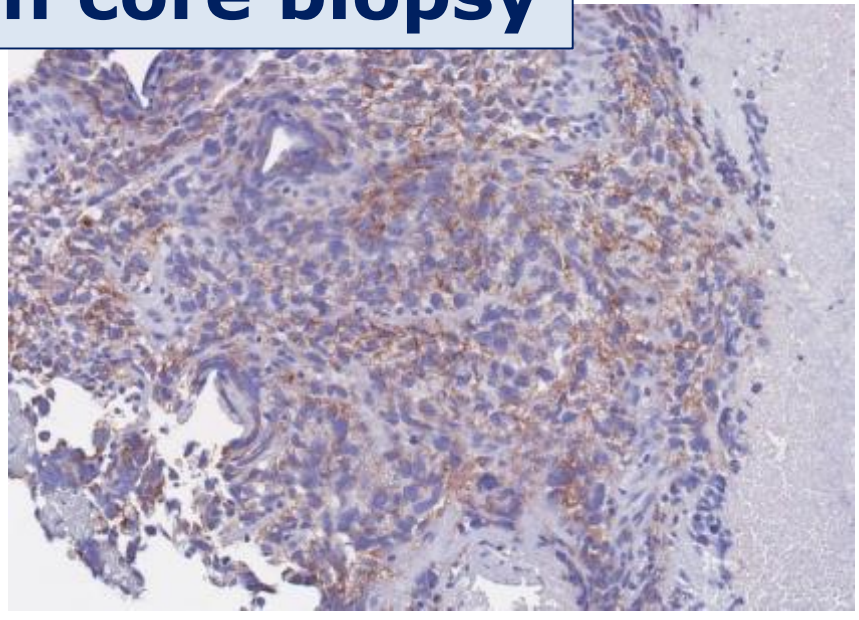


PDL-1 IHC (22C3 Ab) in lung ca



Interpretation in core biopsy



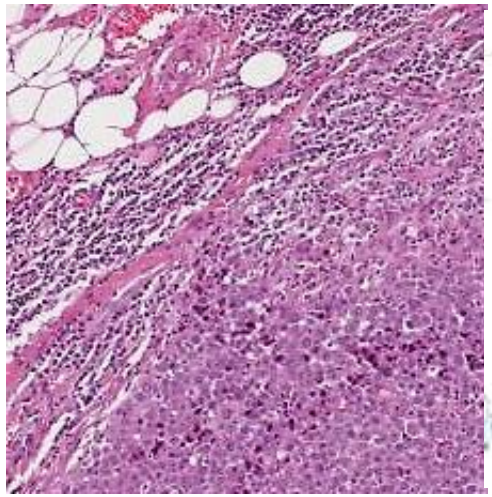


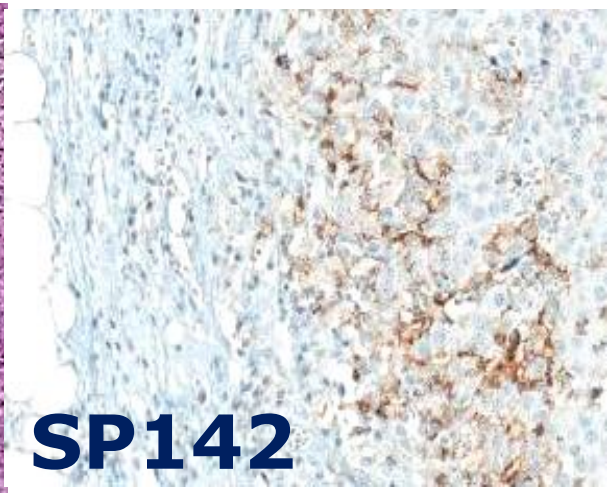
PDL-1 22C3 IHC on Ventana platform

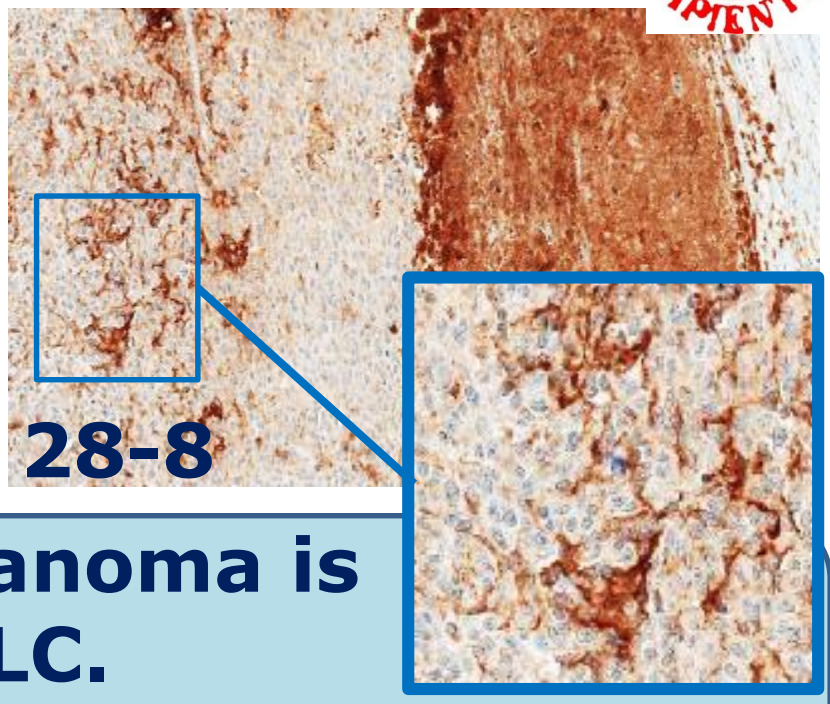
-Anti-PD1 pembrolizumab is approved for NSCLC with companion diagnostic [Dako 22C3 PDL1 Ab].
-Ventana's BenchMark is a common IHC platform.
-Dako 22C3 Ab calibrated on the Ventana platform (2 detection systems) in 41 NSCLC and scored.
-Dako platform: 8 strongly +ve, 7 weakly +ve, 26-
-Ventana's UltraView: 36/41 cases (87.8%) same results as Dako platform; Ventana's OptiView: 35/41 cases (85.3%) same results as Dako platform (Pearson 0.91 & 0.89; $p < 10^{-4}$).
-Ventana detected all strongly +ve cases with high inter- & intraobserver agreement.
-The same PD-L1 IHC algorithm can be reliably applied to Ventana platforms to stratify patients for pembrolizumab tx.

Neuman et al. A Harmonization Study for the Use of 22C3 PD-L1 IHC Staining on Ventana's Platform. JTO 2016; 11, 1863–8

PDL-1 IHC MELANOMA (LN mets)







PDL-1 expression in melanoma is lower than RCC and NSCLC.
PDL1 in IC (not TC) → longer PFS/OS

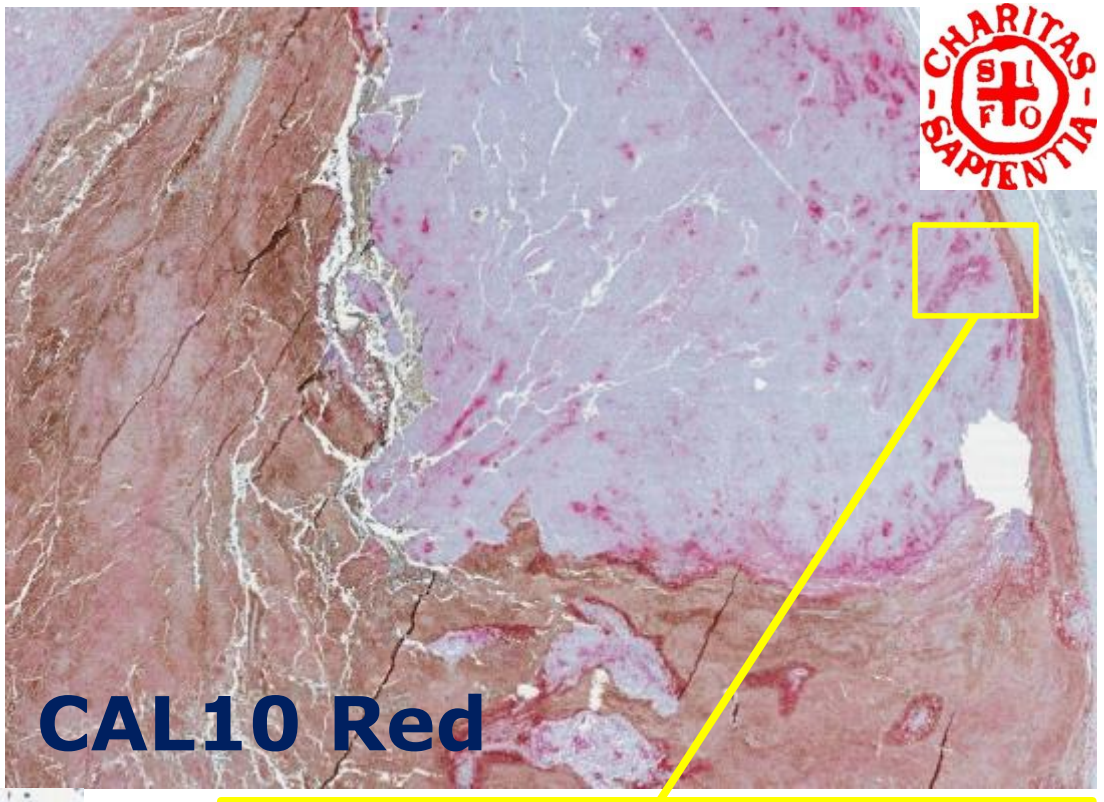
Kluger et al. Clin Cancer Res 2017. pii: clincanres.3146.2016.

BRAF mutation, high PDL-1, no TIL → worse prognosis (mediated by miR17-5p)

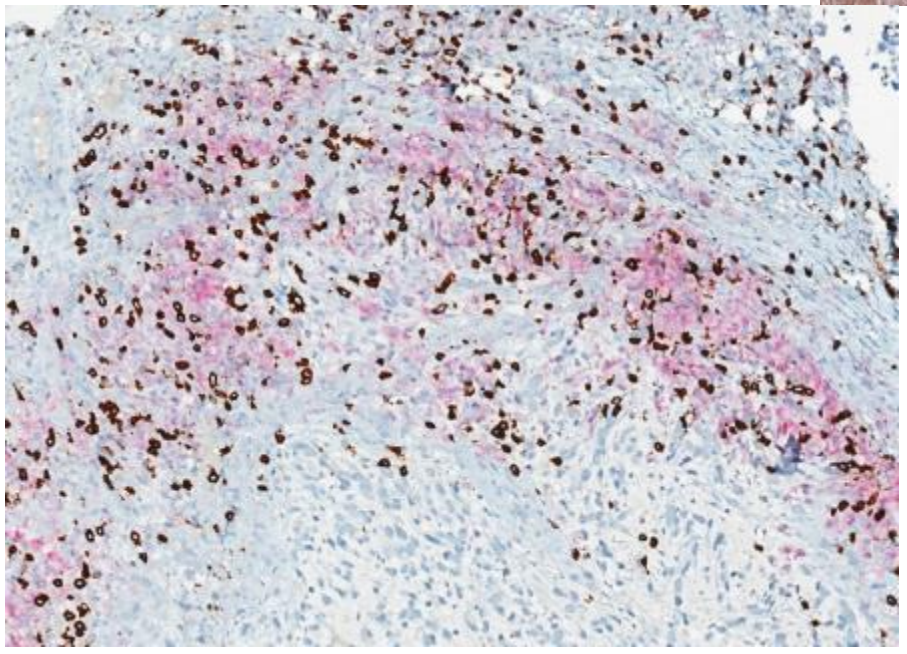
Audrito et al. Oncotarget. 2017 Feb 9. doi: 10.18632/15213

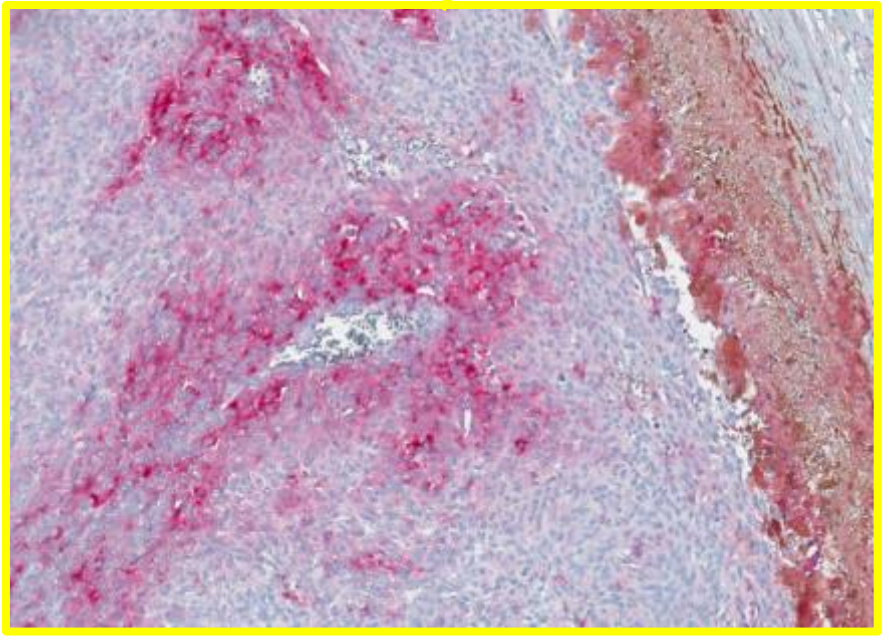
PDL-1 IHC

MELANOMA (LN mets)



CAL10 Red + CD8 brown



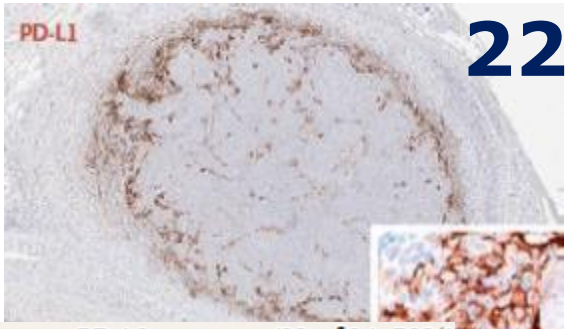


PDL-1 IHC Merkel cell carcinoma

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., Lakshmanan Annamalai, D.V.M., Ph.D, Sneha Berry, M.S., Elliot K. Chartash, M.D., Adil Daud, M.B., B.S., Steven P. Fling, Ph.D., Philip A. Friedlander, M.D., Harriet M. Kluger, M.D., Holbrook E. Kohrt, M.D., Ph.D.,* Lisa Lundgren, M.S., Kim Margolin, M.D., Alan Mitchell, M.Sc., Thomas Olencki, D.O., Drew M. Pardoll, M.D., Ph.D., Sunil A. Reddy, M.D., Erica M. Shantha, M.D., William H. Sharfman, M.D., Elad Sharon, M.D., M.P.H., Lynn R. Shemanski, Ph.D., Michi M. Shinohara, M.D., Joel C. Sunshine, M.D., Ph.D., Janis M. Taube, M.D., John A. Thompson, M.D., Steven M. Townson, Ph.D., Jennifer H. Yearley, D.V.M., Ph.D., Suzanne L. Topalian, M.D., and Martin A. Cheever, M.D.

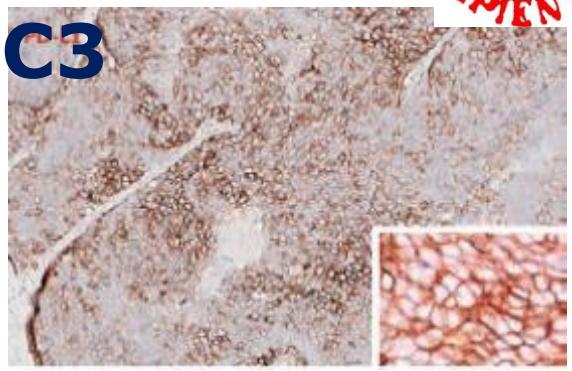
This article was published on April 19, 2016, at NEJM.org.



most PD-L1+ tumors (11 of 14; 79%)

"adaptive immune resistance" pattern

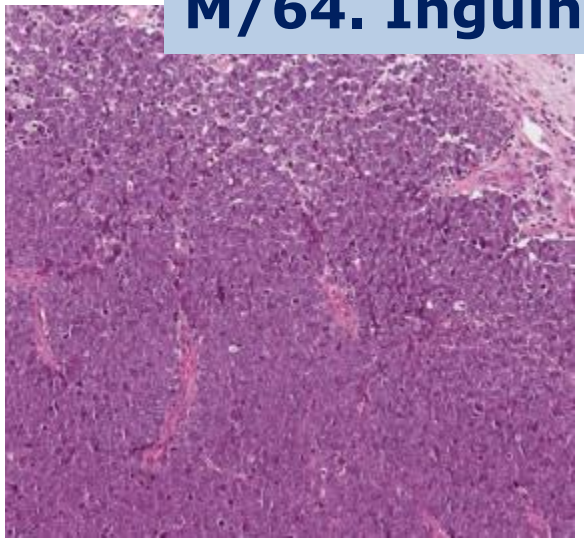
22C3

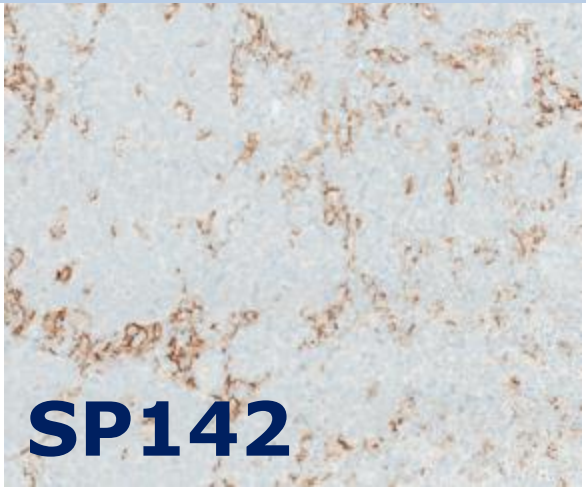


CONCLUSIONS

In this study, first-line therapy with pembrolizumab in patients with advanced Merkel-cell carcinoma was associated with an objective response rate of 56%. Responses were observed in patients with virus-positive tumors and those with virus-negative tumors.

M/64. Inguinal lymph node. No primary known





SP142

28-8

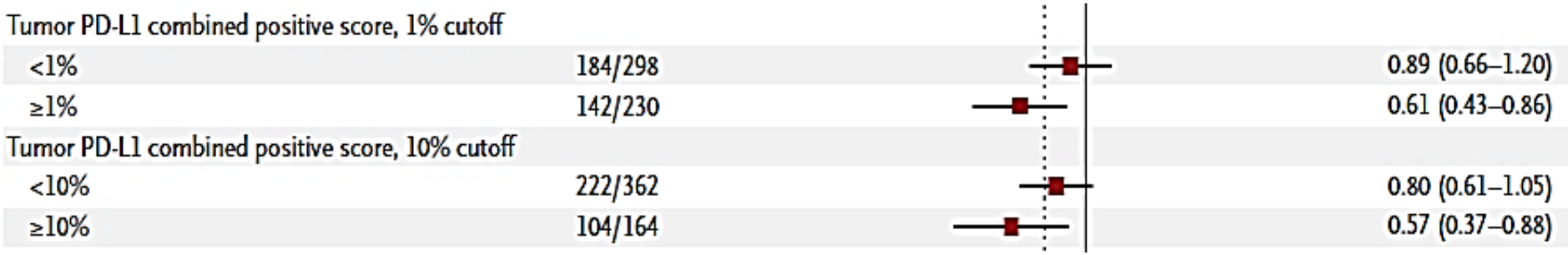
PDL-1 in bladder carcinoma

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

This article was published on February 17, 2017, at NEJM.org. DOI: 10.1056/NEJMoa1613683

The benefit of pembrolizumab over chemotherapy was seen in the total population, as well as in the coprimary population of patients who had a tumor PD-L1 combined positive score of 10% or more.



Tumor PD-L1 combined positive score, 1% cutoff		
<1%	184/298	0.89 (0.66–1.20)
≥1%	142/230	0.61 (0.43–0.86)
Tumor PD-L1 combined positive score, 10% cutoff		
<10%	222/362	0.80 (0.61–1.05)
≥10%	104/164	0.57 (0.37–0.88)

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

PD-1 and PD-L1 Inhibitors as Salvage Therapy for Urothelial Carcinoma

Guru Sonpavde, M.D.

This article was published on February 17, 2017, at NEJM.org.

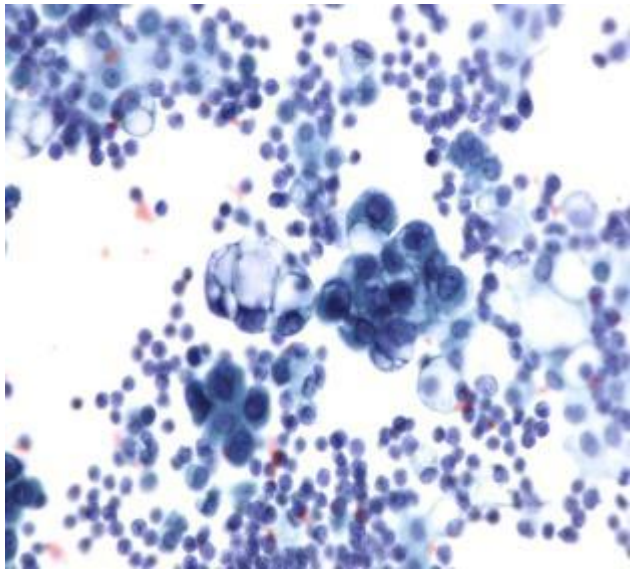
None of the above trials selected patients on the basis of a biomarker (e.g., PD-L1 expression in the tumor). The KEYNOTE-045 trial identified a survival benefit regardless of tumor PD-L1 expression.

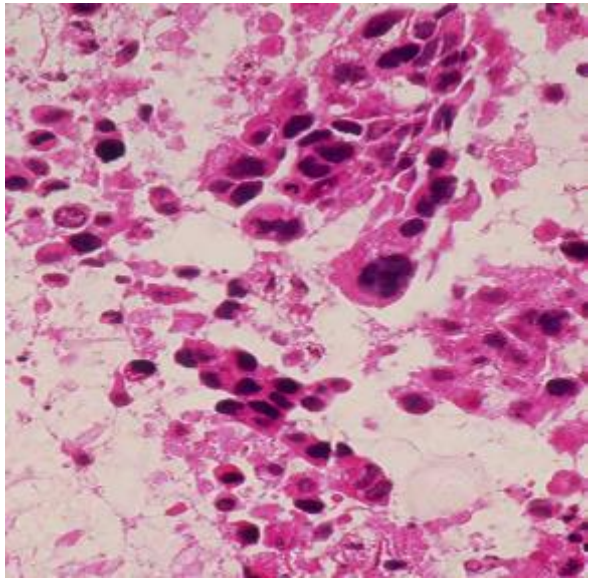
Benefit regardless PDL-1

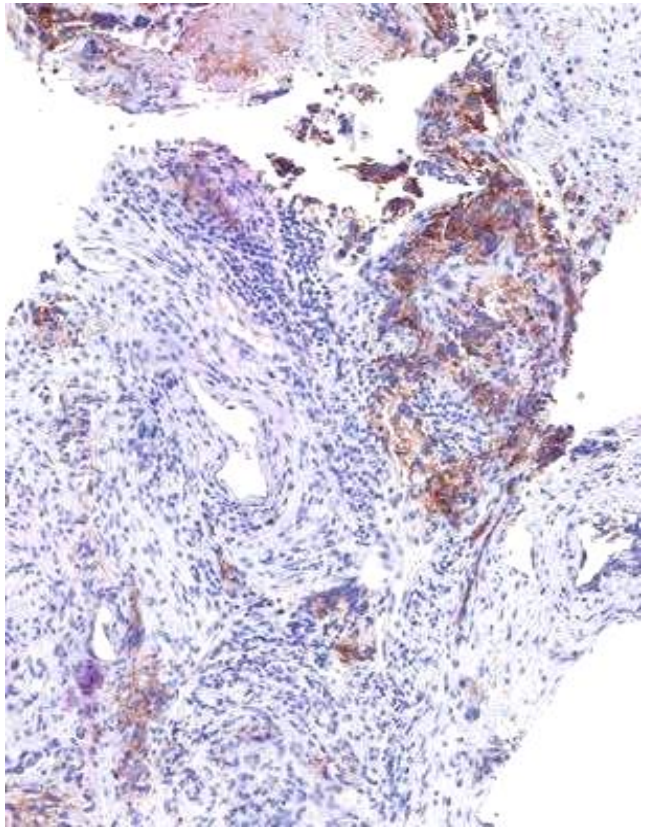
PDL1 in BIOPSY/CYTOLOGY?

-Heterogeneous expression or sampling error and/or old slides → wrong PD-L1 status of TC

-Some PD-L1 "negative" patients respond to therapy → how much reliable??







Cytology & small biopsies

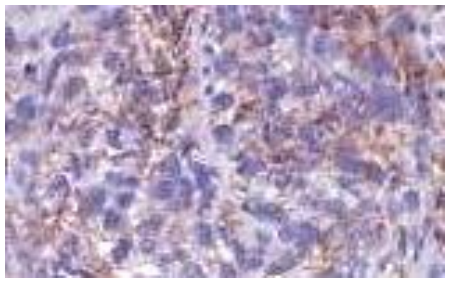
Journal of Thoracic Oncology® • Volume 10, Number 7, July 2015

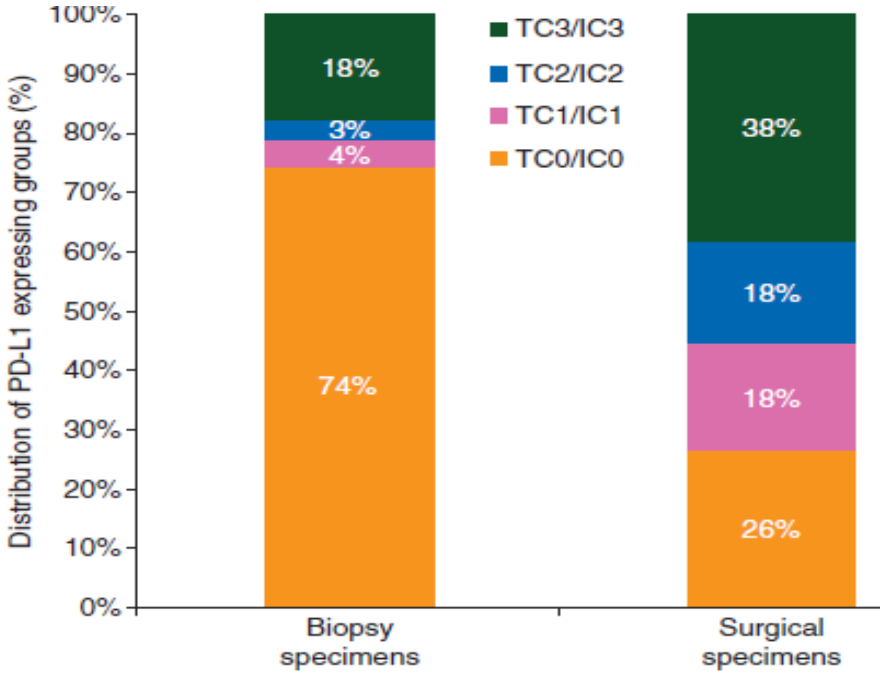
ACCURACY ON BIOPSY VS SURGERY

Annals of Oncology 27: 147–153, 2016

Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies

M. Ilie[1,2], E. Long-Mira[1,2], C. Bence[1], C. Butori[1], S. Lassalle[1,2], L. Bouhlel[2,3], L. Fazzalari[2], K. Zahaf[1] S. Lalvée[1], K. Washetine[4], J. Mouroux[2,5], N. Vénissac[5], M. Poudenx[3], J. Otto[6], J. C. Sabourin[7], C. H. Marquette[2,3], V. Hofman[1,2,4] & P. Hofman[1,2,4*]





PD-L1 in TMA of 79 SqC & 71 lung ADC → Substantial inconsistencies for the % of positive cells in both high and low PD-L1 expressors.

Gniadek et al. Heterogeneous expression of PD-L1 in pulmonary SqC and ADC: implications for assessment by small biopsy. Mod Pathol. 2017 Jan 6.

PD-L1 is not prognostic in NSCLC

PD-L1 IHC expression has been correlated with response and survival benefit from immune checkpoint inhibitor tx in advanced NSCLC. It remains controversial its prognostic role in NSCLC.

PD-L1 IHC (E1L3N Ab) assessed in TC & IC of 982 NSCLC from 3 trials (adjuvant CT after resection).

PD-L1 was positive in 32% (cutoff >1%) and 21% (cutoff 25%) of TC, and 39% and 15% (same cutoffs) of IC.

PD-L1 was correlated with SqC histology, intense TIL, KRAS mutation. PD-L1 IHC is not prognostic in early stage NSCLC, nor is predictive of CT benefit.

M.-S. Tsao

PD-L1 protein expression assessed by immunohistochemistry is neither prognostic nor predictive of benefit from adjuvant chemotherapy in resected non-small cell lung cancer

Annals of Oncology 0: 1–8, 2017
doi:10.1093/annonc/mdx003
Published online 30 January 2017

Any better predictor?

PD-L1 regulation

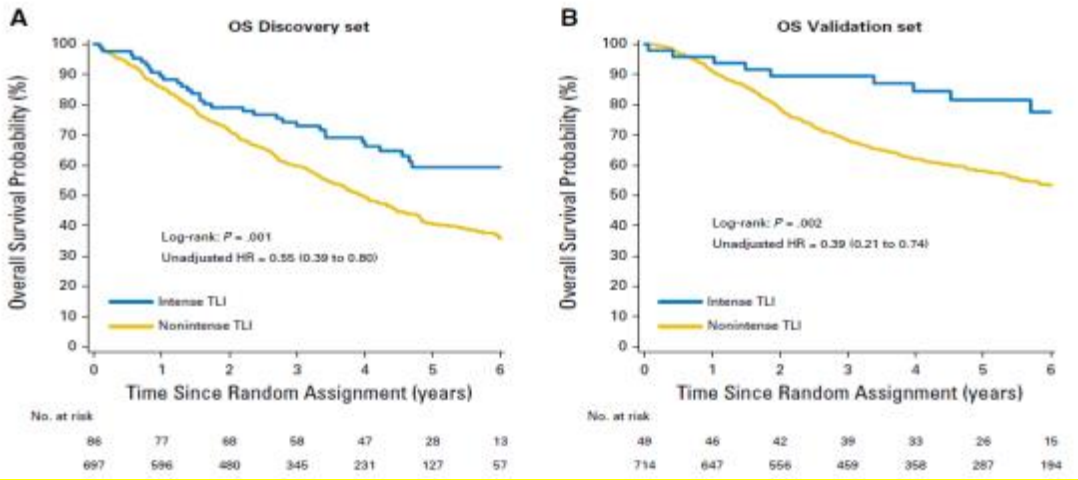
TIL

p53/miRNA

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

Prognostic Effect of Tumor Lymphocytic Infiltration in Resectable Non–Small-Cell Lung Cancer

Elisabeth Brambilla, Gwénaël Le Teuff, Sophie Marguet, Sylvie Lantuejoul, Ariane Dunant, Stephen Graziano, Robert Pirker, Jean-Yves Douillard, Thierry Le Chevalier, Martin Filipits, Rafael Rosell, Robert Kratzke, Helmut Popper, Jean-Charles Soria, Frances A. Shepherd, Lesley Seymour, and Ming Sound Tsao



PDL1 Regulation by p53 via miR-34

JNCI J Natl Cancer Inst (2016) 108(1): djv303

Maria Angelica Cortez, Cristina Ivan, David Valdecanas, Xiaohong Wang, Heidi J. Peltier, Yuping Ye, Luiz Araujo, David P. Carbone, Konstantin Shilo, Dipak K Giri, Kevin Kelnar, Desiree Martin, Ritsuko Komaki, Daniel R. Gomez, Sunil Krishnan, George A. Calin, Andreas G. Bader, James W. Welsh

p53 regulates PD-L1 via miR-34, that binds directly to *PDL1* 3' region in NSCLC models

Novel mechanism of tumor immune evasion. Delivery of miR34a combined with XRT ?

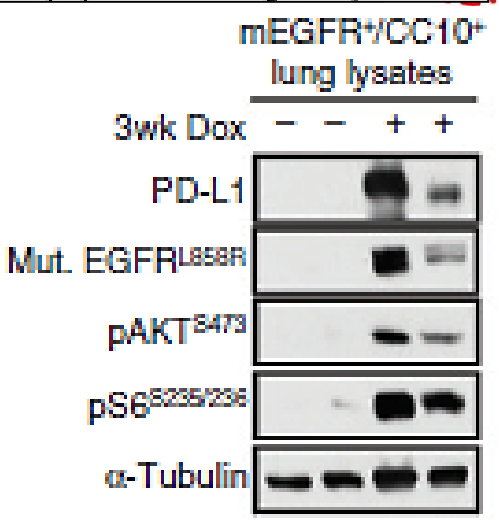
PDL1 and MUTATIONAL BURDEN

Control of PD-L1 Expression by Oncogenic Activation of the AKT–mTOR Pathway in Non-Small Cell Lung Cancer

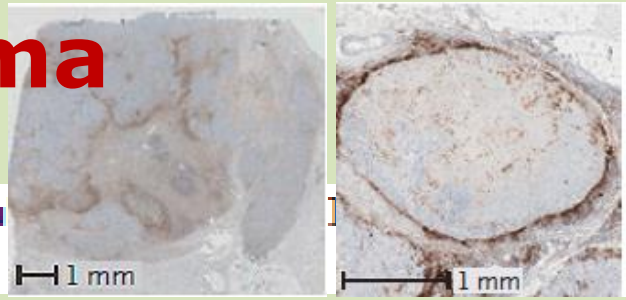
Cancer Res; 76(2) January 15, 2016

Kristin J. Lastwika[1,2], Willie Wilson III[3], Qing Kay Li[4], Jeffrey Norris[1], Haiying Xu[1], Sharon R. Ghazarian[6], Hiroshi Kitagawa[1], Shigeru Kawabata[1], Janis M. Taube[5], Sheng Yao[7], Linda N. Liu[7], Joell J. Gills[1], and Phillip A. Dennis[1]

squamous cell carcinomas, membranous expression of PD-L1 was significantly associated with mTOR activation. These data suggest that oncogenic activation of the AKT–mTOR pathway promotes immune escape by driving expression of PD-L1, which was confirmed in syngeneic and genetically engineered mouse models of lung cancer where an mTOR inhibitor combined with a PD-1 antibody decreased tumor growth, increased tumor-infiltrating T cells, and decreased regulatory T cells. *Cancer Res; 76(2);*



Melanoma



This article was pu
2016, at NEJM.org.

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., g, M.Sc., Jia Pang, B.S duix, Ph.D., M. Schumacher, Ph.D. M.D., Ph.D.

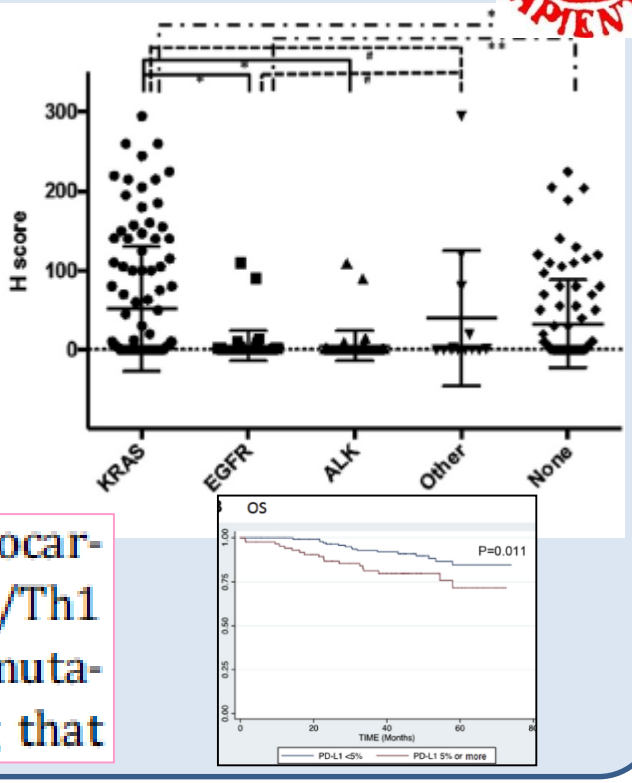
of-function mutations in the genes encoding interferon-receptor–associated Janus kinase 1 (*JAK1*) or Janus kinase 2 (*JAK2*), concurrent with deletion of the wild-type allele. A truncating mutation in the gene encoding the antigen-presenting protein beta-2-microglobulin (*B2M*) was identified in a third patient. *JAK1* and *JAK2* truncating mutations resulted in a lack of response to interferon gamma, including in-

MUTATIONAL BURDEN

Journal of Thoracic Oncology Vol. 11 No. 11: 1869-1878 © 2016

Programmed Cell Death Ligand 1 Expression in Resected Lung Adenocarcinomas: Association with Immune Microenvironment

Tiffany G. Huynh, BA,[a] Vicente Morales-Oyarvide, MD, MPH,[b] Meghan J. Campo, MD,[c] Justin F. Gainor, MD,[c,d] Emine Bozkurtlar, [illegible] Hironori Uruga, MD, PhD,[a] Ling Zhao, MD,[a] Maria Gomez-Caraballo, Aaron N. Hata, MD, PhD,[c,d] Eugene J. Mark, MD,[a,e] Michael Lanuti, Jeffrey A. Engelman, MD, PhD,[c,d] Mari Mino-Kenudson, MD[a,e,*]



Conclusion: PD-L1 expression in resected lung adenocarcinomas is frequently observed in the presence of CTL/Th1 microenvironment, in particular in those with *KRAS* mutations or no common molecular alterations, suggesting that

Li, Zhu, Wang, Li. Association between PD-L1 expression and driven gene status in NSCLC: A meta-analysis. Eur J Surg Oncol 2017. pii: S0748-7983(17)30354-2.

PD-L1 higher in KRAS-mutant > KRAS-wt NSCLC (51% vs 36%; p=0.045). No PD-L1 differences by EGFR or ALK status.

Open issues

-Better fresh cut sections?

-Date of tissue collection, tumor location, interim therapy

-Only partial concordance among different antibodies

-No uniform scoring systems (TC only vs IC)

-Tumor heterogeneity & small biopsies / cytology

-3 to 20% PD-L1 negative patients are responsive across trials.

AIOM/SIAPEC project of PDL1 interlaboratory concordance in lung ADC, with different abs & IHC platforms, and strict interpretation criteria

CONCLUSIONS

PDL1 testing or not???

YES, but probably it is not the only one!

Future (current) challenge: identify predictors of response to PD1/PDL1 targeted treatments, in relationship with the mutational burden & immune status in individual tumors.

Review 2016

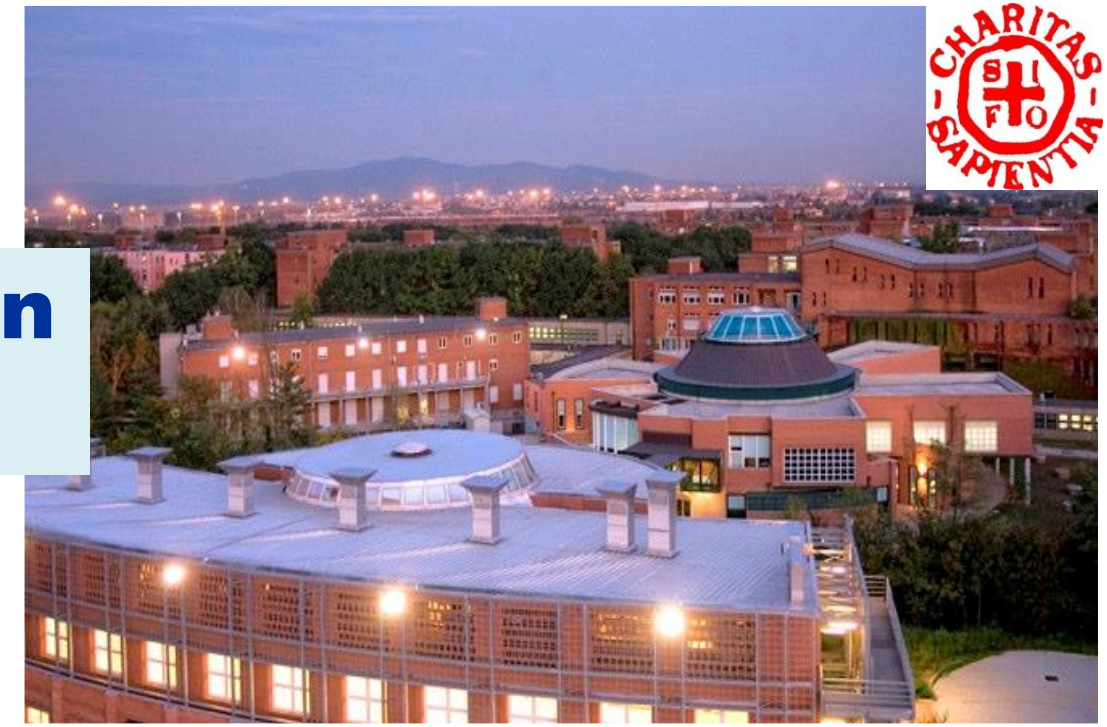
Journal of Thoracic Oncology Vol. 11 No. 7: 964-975

PD-L1 Expression in Lung Cancer

Hui Yu, MD, PhD,[a] Theresa A. Boyle, MD, PhD,[a,b,c,d] Caicun Zhou, MD, PhD, David L. Rimm, MD, PhD,[f] Fred R. Hirsch, MD, PhD[a,b,*]

Thank you!!

University of Turin Medical School



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