Invited Discussant Abstract 26O

Prof Keith M Kerr
Aberdeen University Medical School
Aberdeen Royal Infirmay
Foresterhill, Aberdeen, UK

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Molecular Epidemiology Study of PD-L1 Expression in Patients With *EGFR*-Mutant NSCLC - Abstract 26O

Jong Ho Cho[1], Wei Zhou[2], Yoon-La Choi[1], Jong-Mu Sun[1], Hyejoo Choi[1], Tae-Eun Kim[1], Marisa Dolled-Filhart[2], Kenneth Emancipator[2], Mary Anne Rutkowski[2], Jhingook Kim[1]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Merck & Co., Inc., Kenilworth, NJ USA

Disclosures: Keith Kerr

- I have acted as consultant/advisor for Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Clovis, Bristol Myers Squibb, Merck Sharp Dohme

- I have received honoraria for speaker bureau from Roche Genentech, Astra Zeneca, Pfizer, Eli Lilly, Novartis, Boehringer Ingelheim, Bristol Myers Squibb

PD-L1 expression……

- Ligand for PD1, in combination, an immune inhibitory checkpoint
- Adopted by tumours to inhibit an effective immune response
- PD1 or PD-L1 as a therapeutic target
- PD-L1 as a biomarker
- EFGR mutation: a biomarker for EGFR TKI therapy
- Role for immunotherapy in this tumour subset?

PD-L1 IHC in resected EGFR-mutant lung cancer

- Retrospective analysis (2006-2014)
- PD-L1 assay 22C3 PharmDx kit (Dako)
  - High expression ≥50% cells
  - Low expression 1-49% cells
- Correlate expression with RFS, OS, EGFR mutation type, Stage, smoking status

Patient Characteristics

EGFR mutant, resected adenocarcinomas

	N = 319*
Age, median (range), y	62.0 (35-84)
Sex, n (%)	
Male	125 (39%)
Female	194 (61%)
Never Smokers	64%
Stage IA Disease	48%
Median Follow-up, y	7
Resection with Curative Intent	94%
Post-surgery Chemotherapy	43%
EGFR-TKI	30%
Radiation	18%

*** 97% of patients had adenocarcinoma.**

Mutation findings in an EGFR-mutated cohort

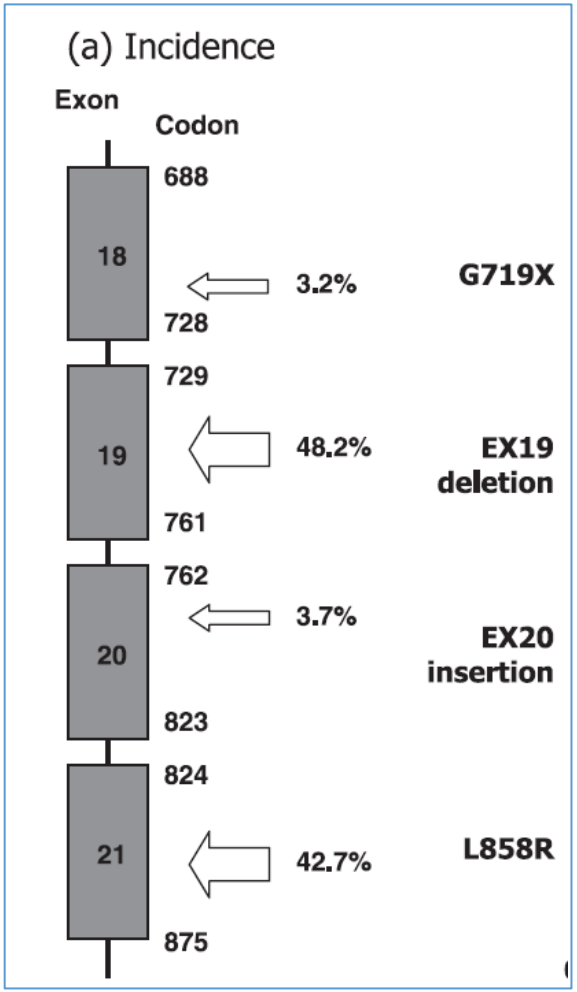
- N=319
- 54% exon 19 (most exon19del)
- 39% exon 21 (most L858R)
- 4% exon 18
- 3% exon 20

- Screening all 4 exons

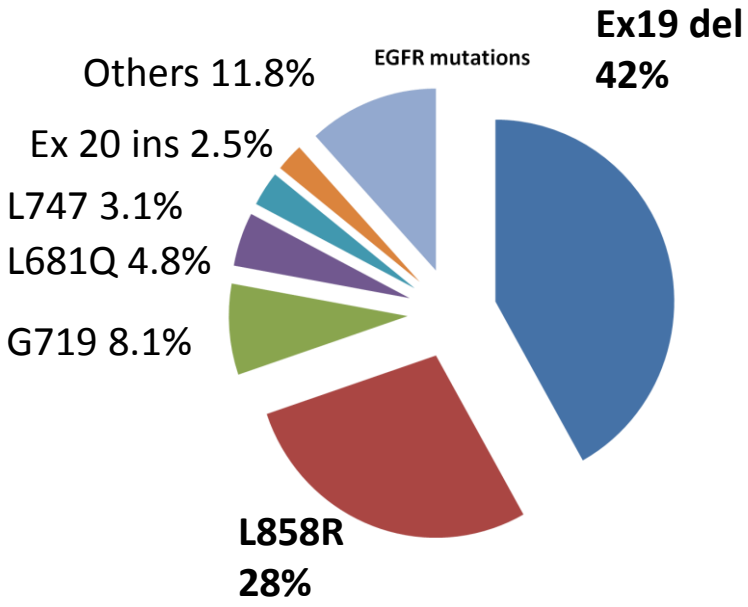
Comparative EGFR mutation epidemiology

Ex18: nil
Ex19: 19.4%
Ex20: 8.3%
Ex21 L858R: 72%

Lee at al. JTO 2010



Mitsudomi and Yatabe. Can Sci 2007



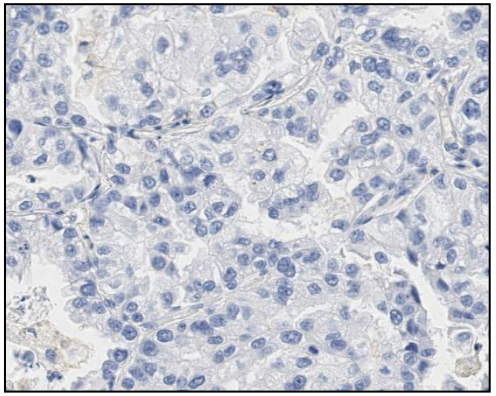
Kret et al.
Lung Cancer 2015

Comparison confounded
By methodology

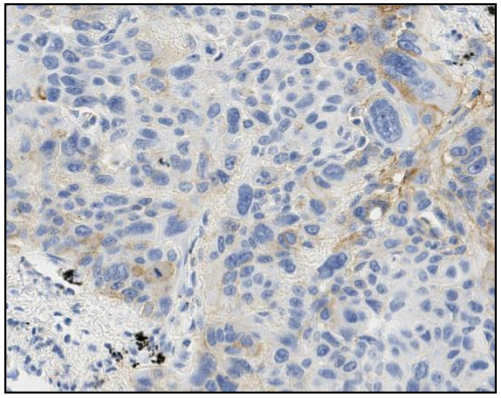
PD-L1 status: 22C3 PharmDx kit

- 54% 'positive'
  - 8% 'strong': High ≥50%
  - 44% 'weak': Low 1-49%
  - 46%: negative

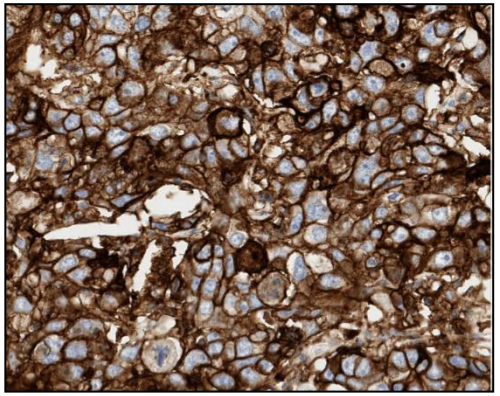
Language is quite important when referring to staining



PD-L1 Negative
(TPS = 0)

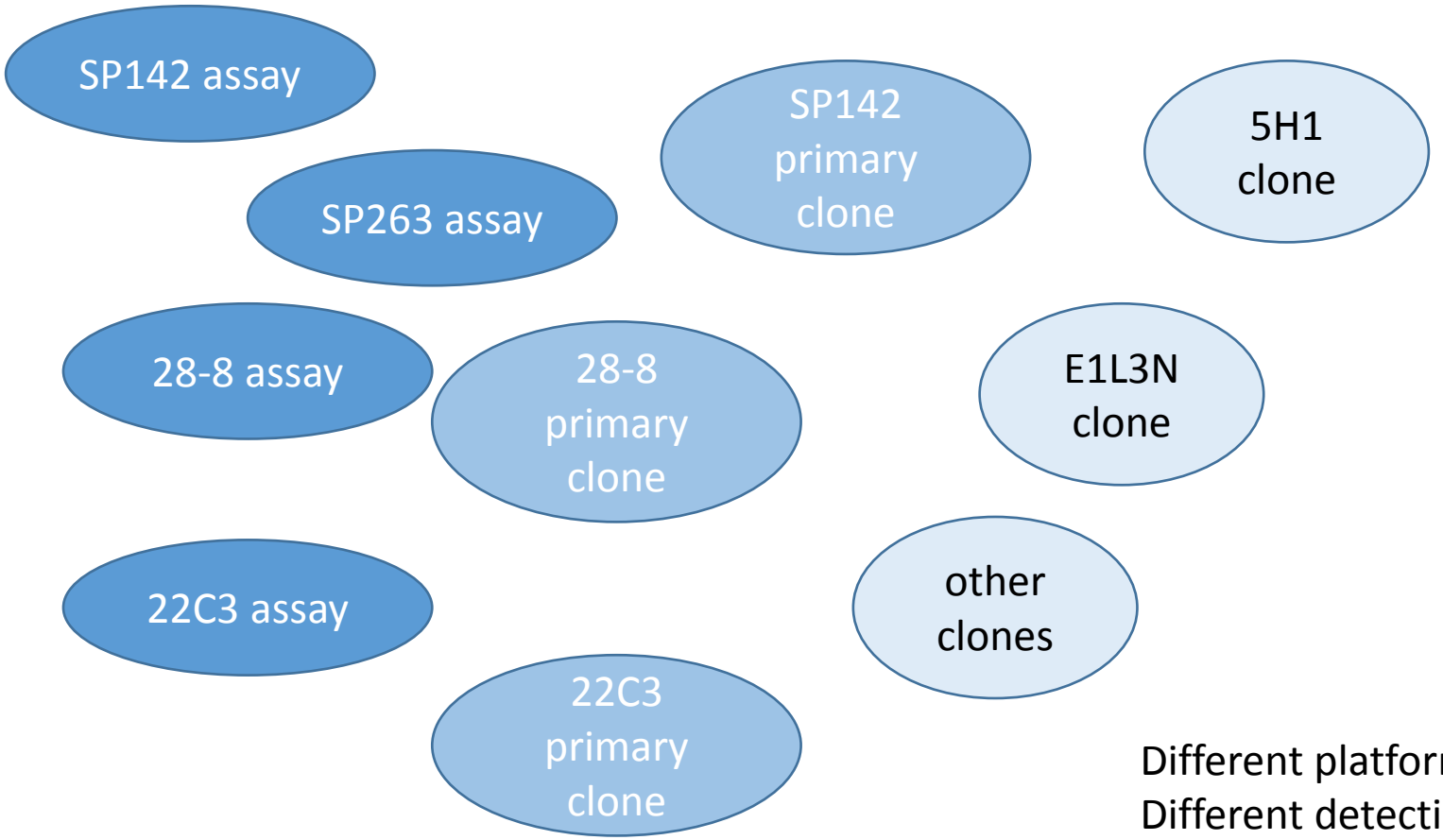


PD-L1 Weak Positive
(TPS = 15%)



PD-L1 Strong Positive
(TPS = 100%)

Widely different PD-L1 IHC assays are used in trials or as RUO agents



Different platforms
Different detection chemistry
Primary clones have different Epitope specificity

Programmed Death Receptor 1 and Its Ligand Immunohistochemistry in Lung Cancer

In what state is this art?

TABLE 1. Summary of Published Findings for PD-L1 Immunohistochemistry in Therapeutic Trials

Drug	Biomarker Antibody	Rx Line	Definition of "Positive"[a] (%)	N Positive (%)	Positive Predictive Outcome	ORR % IHC pos. Cases	ORR % IHC neg. Cases
Nivolumab	Dako 28-8	1st	≥5 in >100 cells	59	Yes	31[b]	10
Nivolumab	Dako 28-8	≥2nd	≥5, ≥1	49, 56	No	15, 13	14, 17
Nivolumab + Ipilimumab	Dako 28-8	1st	≥5 in >100 cells	42	No	19	14
Nivolumab	Dako 28-8	≥2nd	≥5	33[c]	Yes	24	14
Nivolumab	5H1[d]	≥2nd	≥5, also studied TIICs	67	Yes	No data for lung	No data for lung
Pembrolizumab	Dako 22C3	Any	"Strong" ≥50, "Weak" 1–49	25, 70	Yes, Yes	37, 17	9
Pembrolizumab	Dako 22C3	1st	≥50, ≥1	?	Yes	47, 26	?
MPDL3280A	Roche Ventana, SP142	≥2nd	≥10,[e] ≥5, ≥1 TIICs	13, 28, 56	Yes	83, 46, 31	18, 18, 20
MEDI-4736	Roche Ventana, SP263	≥2nd	Data not available	41	Yes	25	3

Frequency of PD-L1 'positivity' is variable,
as are definitions of positivity and assays used

Kerr et al, JTO 2015

PD-L1 Expression In Patients With EGFR Mutations

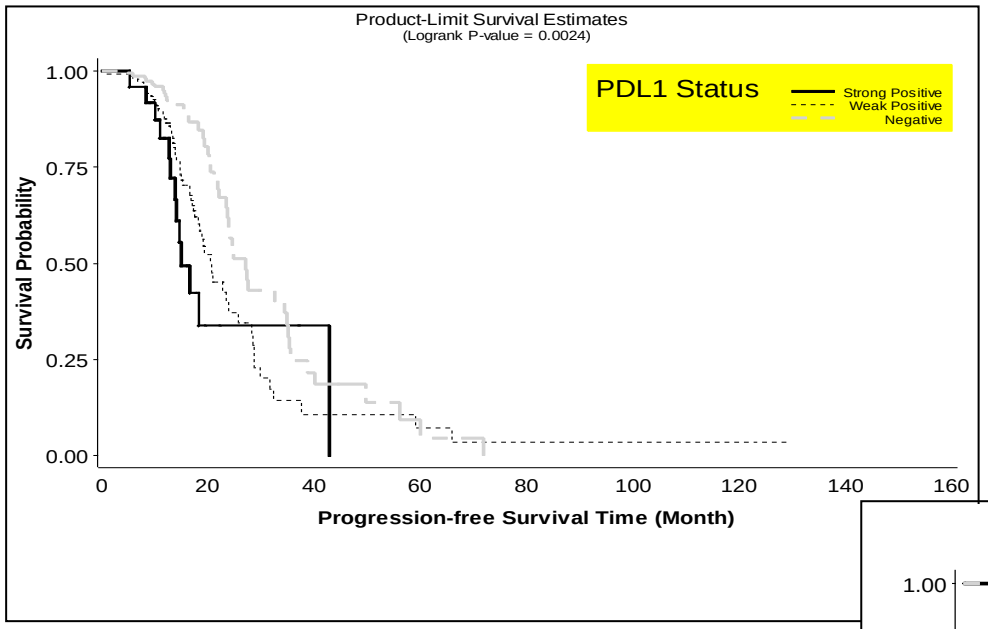
Subgroup	Sample Size	PD-L1 Expression Status			Chi-square
		Strongly Positive	Weakly Positive	Negative	
	N	n (%)	n (%)	n (%)	P-value
Overall	319	24 (7.5)	139 (43.6)	156 (48.9)	
Gender					
Male	125	13 (10.4)	64 (51.2)	48 (38.4)	0.008
Female	194	11 (5.7)	75 (38.7)	108 (55.7)	
Smoking Status					
Never	205	11 (5.4)	82 (40.0)	112 (54.6)	0.011
Smokers	114	13 (11.4)	57 (50.0)	44 (38.6)	
ECOG					
0	202	12 (5.9)	88 (43.6)	102 (50.5)	0.345
1/2/3/4	116	12 (10.3)	50 (43.1)	54 (46.6)	
Stage					
IA	154	6 (3.9)	61 (39.6)	87 (56.5)	0.004
IB	47	1 (2.1)	20 (42.6)	26 (55.3)	
II	40	7 (17.5)	20 (50.0)	13 (32.5)	
III	59	9 (15.3)	28 (47.5)	22 (37.3)	
IV	16	1 (6.3)	9 (56.3)	6 (37.5)	

Higher In Males

Smokers

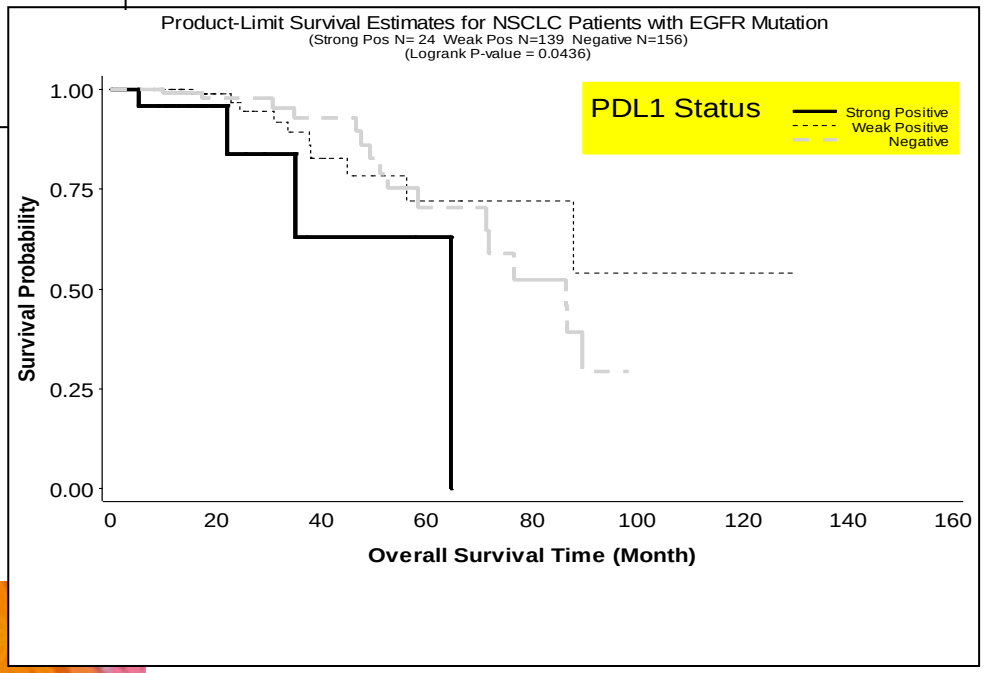
Higher Stage disease

PD-L1 high expression: poorer prognosis



PFS

OS



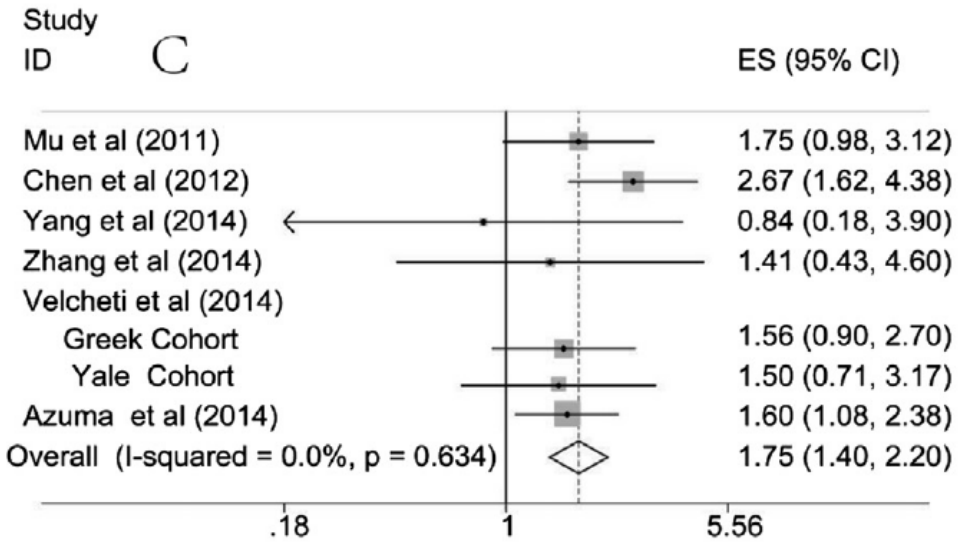
PD-L1 'over-expression' is associated with poorer post-operative prognosis

Table 1
Clinical characteristics of qualified records in meta-analysis.

Author	Year	Region	Cancer type	Stage	Method	Cut-off	Number of patients		Outcome
							Positive-PD-L1	Negative-PD-L1	
Mu et al.[22]	2011	China	NSCLC	I–III	IHC	Media H-scores	58	51	OS
Chen et al.[23]	2012	China	NSCLC	I–III	IHC	IRS >3 points	69	51	OS
Yang et al.[6]	2014	Taiwan	AD	I	IHC	≥5%	65	98	OS
Zhang et al.[24]	2014	China	AD	I–III	IHC	NM	70	73	OS
Velcheti et al.[a,25]	2014	USA (Greek Chorot)	NSCLC	I–IV	AQUA	AQUA scores	75	228	OS
	2014	USA (Yale Chorot)	NSCLC	I–IV	AQUA	AQUA scores	56	99	OS
Azuma et al.[26]	2014	Japan	NSCLC	I–III	IHC	NM	82	82	OS

IHC – variable techniques
IHC positive – variably defined
IHC – variably interpreted

Conclusion reasonably consistent



Wang A et al. Eu J Surg Oncol 2015

PD-L1 status using the 22C3 PharmDx assay: are there comparable data?

- 52% 'positive'
  - 8% 'strong': High ≥50%
  - 44% 'weak': Low 1-49%
  - 46%: negative

Keynote 001 trial *(Garon E et al, NEJM 2015)*

- *60.8% 'positive'*
  - *23.2% high expression*
  - *37.6% low expression*

But

All NSCLC, although 81% adenoca

15.5% EGFR mutated

Advanced disease

PD-L1 status using the 22C3 PharmDx assay: are there comparable data?

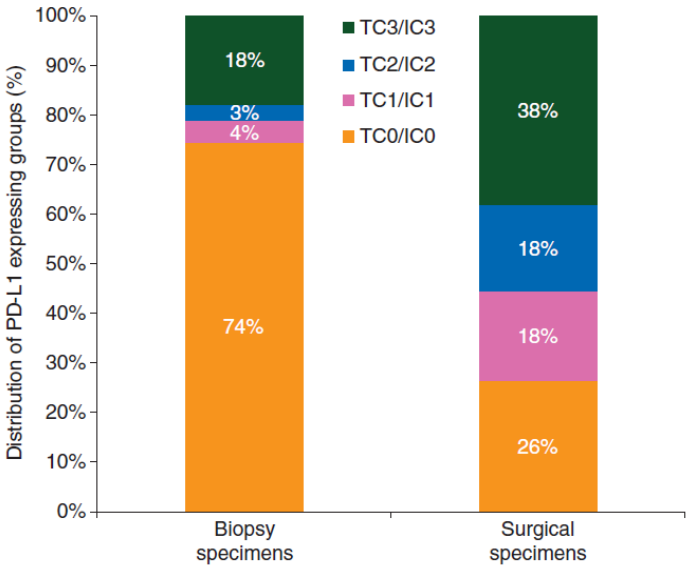
Keynote 001 trial *(Garon E et al, NEJM 2015)*

PD-L1 status	Garon et al Non-Squamous	Cho et al All mutant adenos	Garon et al Never smokers	Cho et al Never smokers	Garon et al Current/ Former smokers	Cho et al Smokers
High (≥50%)	35.8%	8%	32.5%	5.4%	36.2%	11.4%
Low (1-49%)	51.2%	44%	55.8%	40%	49.7%	50%
Absent	13.0%	46%	11.7%	54.6%	14.1%	14.1%

Discordant PD-L1 expression between biopsy and surgical resection? Could the sample type influence findings?

- Ventana SP142 IHC
- LDT, not the CDx assay
- Most of discordance due to lack of Immune cell staining in biopsy

- Yet these findings still opposite those for 22C3



Ilie et al, Ann Oncol 2015

PD-L1 expression is a favorable prognostic factor in early stage non-small cell carcinoma

Lung Cancer 89 (2015) 181–188

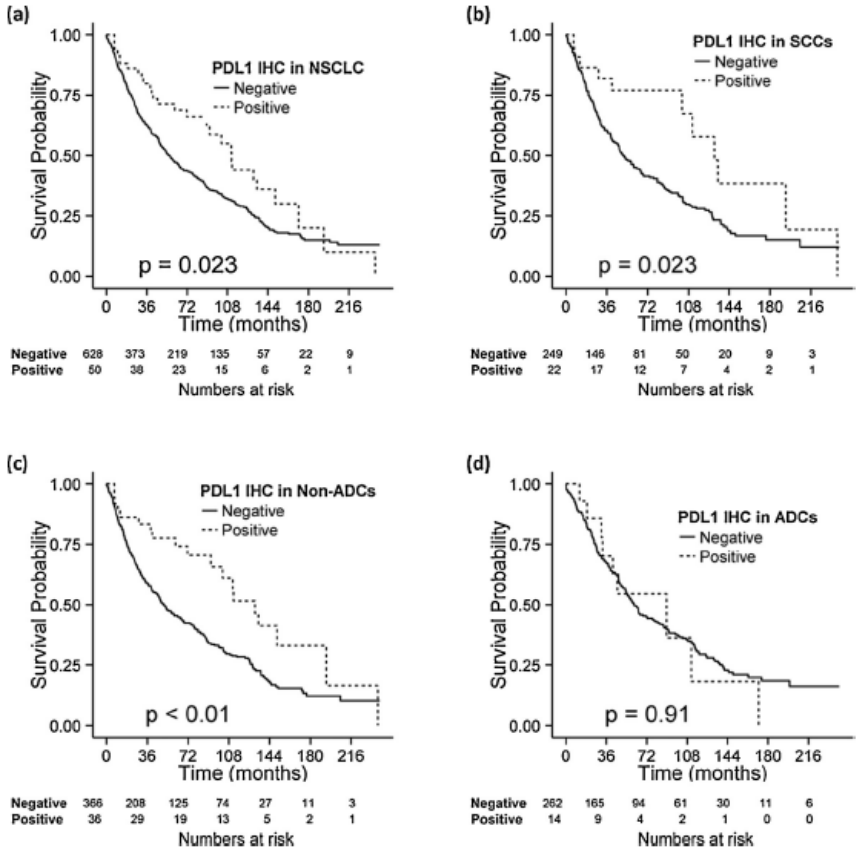
Wendy A. Cooper[a,b,c,*], Thang Tran[a], Ricardo E. Vilain[a,b,d], Jason Madore[d], Christina I. Selinger[a], Maija Kohonen-Corish[c,f,g], PoYee Yip[b,e,f,h], Bing Yu[b,i], Sandra A. O'Toole[a,b,f], Brian C. McCaughan[j], Jennifer H. Yearley[k], Lisa G. Horvath[b,e], Steven Kao[b,e], Michael Boyer[b,e], Richard A. Scolyer[a,b,d]

22C3 primary Ab
LDT assay
≥50% tumour cells staining= 'positive'

5.1% Adenocarcinomas 'positive'

Stage group, *n* (%)	PD-L1 negative	positive
I	316 (93.2%)	23 (6.8%)
II–III	312 (92%)	27 (8%)

No association with
Gender
EGFR mutation



PD-L1 Positivity is Lower in Patients With Exon 19 Deletion and Exon 21 L858R Mutation Compared with Other Mutations*

	PD-L1 Expression Status, n (%)			
EGFR Mutation Types	Strong Positive	Weak Positive	Negative	Total
Exon 19 Deletion	7 (5.4)	60 (46.2)	63 (48.4)	130
Exon 21 L858R	8 (7.0)	37 (32.2)	70 (60.9)	115
Other	9 (12.2)	42 (56.8)	23 (31.1)	74

*P = 0.001 by chi-square test.

PD-L1 IHC expression by mutation status

Population	No.[a]	PS ≥50% no. (%)	PS 1-49% no. (%)	PS <1% no. (%)
EGFR mutation				
Yes	54	18 (33.3)	21 (38.9)	15 (27.8)
No	288	95 (33.0)	135 (46.9)	58 (20.1)

Garon et al, NEJM 2015

22C3 CDx assay

≥5%

Parameter	PD-L1 positive				PD-L1 negative				
	total	PR	SD	PD	total	PR	SD	PD	P-value
EGFR status									
wild type	42	5	21	16	29	3	16	10	0.330
exon 19 del	26	6	19	1	14	7	6	1	
exon 21 L858R	35	11	23	1	12	4	7	1	
unknown classical	9	3	5	1	3	1	2	0	

E1L3N-based LDT

71.9% PD=L1 positive

57.1% PD=L1 positive

Tang et al. Oncotarget 2015

Can any conclusions be drawn?

- PD-L1 over expression is a poor prognostic factor in surgically resected lung cancer – probably

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- PD-L1 over expression is a poor prognostic factor in surgically resected lung cancer – probably
- Is disease stage relevant when considering PD-L1 expression data - maybe
- PD-L1 expression is less (or different) in EGFR mutated lung cancer – the jury is still out!
- **Technical variation in studies makes valid comparison difficult**