

# Implementation of programmed death-ligand 1 (PD-L1) expression as a prognostic biomarker for patients with lung cancer

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We thank Li *et al.* for showing interest in our article entitled "*The clinicopathological and prognostic significance of programmed death-ligand 1 (PD-L1) expression assessed by immunohistochemistry in lung cancer: a meta-analysis of 50 studies with 11,383 patients*" (1). We would like to respond to the concerns one by one raised by Li *et al.* (2).

Firstly, we felt sorry for the carelessness in extracting hazard ratios (HRs) and 95% confident intervals (95% CIs) from two studies on lymphoepithelioma-like carcinoma (LELC) (3,4). We thus performed additional analysis with upper limit of 9.863 and converted HR and 95% CI, and the results did not alter the overall findings. After reanalysis, the pooled HRs and 95% CIs suggested that PD-L1 immunohistochemistry (IHC) expression was related to poor OS in lung cancer (HR =1.42, 95% CI: 1.22-1.65) (Figure 1), consistent with results in the primary analysis. Subgroup analyses according to histology (Figure 2) revealed that high PD-L1 expression was significantly related to poor overall survival (OS) of non-small cell lung cancer (NSCLC) patients (HR =1.35, 95% CI: 1.13-1.61), adenocarcinoma (ADC) patients (HR =1.79, 95% CI: 1.22-2.64), squamous cell carcinoma (SCC) patients (HR =1.79, 95% CI: 1.39-2.32), but there was no association of PD-L1 expression with survival in small cell lung cancer (SCLC) patients (HR =1.05, 95% CI: 0.39-2.78) and LELC patients (HR =0.91, 95% CI: 0.10-8.16). In fact, the relationship between PD-

L1 expression and prognosis in LELC has long been debated and remains controversial. A recent study by Sha *et al.* (5) showed that participants with positive PD-L1 expression tended to have longer progression-free survival (PFS) and OS times than those with negative PD-L1 expression, while Yu *et al.* (6) revealed that positive expression of PD-L1 in tumor cells had no association with OS in LELC. Different testing platforms and thresholds for defining positive PD-L1 expression may partly explained this discrepancy. More studies are needed to explore the prognostic significance of PD-L1 expression in LELC patients.

Secondly, Fang and colleagues defined cases with more than 5% expression of PD-L1 as positive ones while PD-L1 H-score 30 was further determined as the best threshold to discriminate OS and analyzed in the Cox proportional hazard regression analysis. The authors did not clearly illustrate the definition of higher or positive PD-L1 expression as previous publications usually divided patients into high/low PD-L1 expression based on PD-L1 expression values (5%, etc.). We re-performed the subgroup analysis based on cutoff value (*Figure 3*), which was comparable with results in our previous analysis.

Thirdly, we would like to emphasize that P values in the Abstract indeed indicated values of heterogeneity. Although random-effect models were used to deal with significant heterogeneity in both primary and subgroup analyses in the

Li et al. PD-L1	expression	and proc	anosis in	lung cancer

studyid	HR (95% CI)	% Weight
Ameratunga 2016	1.05 (0.62, 1.78)	2.25
Azuma 2014	1.60 (1.08, 2.38)	2.55
Cha 2016	2.70 (1.78, 4.10)	2.50
Chang 2016	1.54 (0.94, 2.54)	2.32
Chang 2017	2.90 (1.44, 5.86)	1.86
Chen 2012	<ul> <li>2.90 (1.44, 5.86)</li> <li>2.95 (1.63, 4.38)</li> </ul>	2.32
Chen 2016	1.25 (0.75, 2.08)	2.32
Cooper 2015		2.29
	0.65 (0.45, 0.85)	2.71
D'incecco 2015	0.70 (0.44, 1.11)	
Fang 2015	2.73 (0.76, 9.86)	0.97
Guo 2017	2.29 (1.47, 3.57)	2.44
Hirai 2017	2.81 (1.06, 8.23)	1.28
Huynh 2016	1.65 (0.79, 3.45)	1.79
Igawa 2017	0.90 (0.60, 1.35)	2.52
Ilie 2016	1.79 (0.28, 11.44)	0.55
Inamura 2016	1.88 (1.25, 2.74)	2.55
Inamura 2017 - I	0.29 (0.11, 0.61)	1.56
Inoue 2016	1.23 (0.86, 1.76)	2.63
Ishii 2015	0.44 (0.24, 0.80)	2.08
Ji 2017	<ul> <li>2.21 (1.10, 4.42)</li> </ul>	1.87
Jiang 2015	0.29 (0.07, 1.16)	0.87
Kim 2015	1.24 (0.76, 2.02)	2.33
Lin 2015	0.26 (0.11, 0.62)	1.54
Mao 2014	1.90 (1.09, 3.30)	2.18
Miao 2017	0.94 (0.57, 1.56)	2.30
Mori 2017	2.59 (1.25, 5.39)	1.80
Mu 2011	1.78 (1.12, 2.83)	2.39
Okita 2017	3.32 (1.10, 9.97)	1.18
Pan 2017	3.23 (0.80, 13.12)	0.85
Schmidt 2015	0.95 (0.68, 1.33)	2.68
Shimoji 2016	2.42 (1.25, 4.68)	1.95
Song 2016	1.79 (1.30, 2.46)	2.71
Sorensen 2016	1.17 (0.83, 1.65)	2.66
Sun 2016	1.23 (1.00, 1.51)	2.91
Takada 2017	2.08 (1.42, 3.09)	2.56
Takada 2017a	1.65 (1.08, 2.54)	2.47
Tang 2015	1.90 (0.95, 3.79)	1.88
Teng 2016	1.00 (0.47, 2.14)	1.74
Tokito 2016		
	0.47 (0.37, 1.53)	1.84
Toyokawa 2017	5.86 (2.66, 12.91)	1.68
Tsao 2017	1.01 (0.76, 1.35)	2.77
Uruga 2017	0.68 (0.40, 1.16)	2.23
Vieira 2016	1.07 (0.60, 2.00)	2.08
Wu 2017	3.39 (1.25, 9.19)	1.32
Yang 2014	0.85 (0.21, 3.44)	0.86
Yang 2017	1.68 (0.83, 3.40)	1.85
Yvorel 2017	• 1.30 (0.40, 4.27)	1.07
Zhang 2014	2.72 (1.29, 5.73)	1.77
Zhang 2017	2.49 (1.27, 4.88)	1.92
Zhou 2017	2.57 (1.46, 4.52)	2.16
Overall, DL ( $l^2$ = 75.0%, p = 0.000)	1.42 (1.22, 1.65)	100.00
0.05 0.5 1	10 20	

Figure 1 Forest plot describing the association between PD-L1 expression and OS of patients with lung cancer. PD-L1, programmed death-ligand 1; OS, overall survival.

meta-analysis, enough attention should be paid to and the findings need be cautiously interpreted (7).

Moreover, we agreed with Li *et al.* that the above two studies (3,4) may be overlapped. However, the two studies were conducted separately by two research teams. Jiang *et al.* enrolled 79 pulmonary LELC cases from January 2001 to December 2013 while Fang *et al.* enrolled 113 surgically resected pulmonary LELC cases from January 2008 to December 2012. In fact, it is hard to conclude

histology and studyid	HR (95% CI)	% Weight
NSCLC		
Ameratunga 2016	1.05 (0.62, 1.78)	2.42
Azuma 2014	1.60 (1.08, 2.38)	2.75
Chen 2012	2.95 (1.63, 4.38)	2.50
Chen 2016	1.25 (0.75, 2.08)	2.46
Cooper 2015	0.65 (0.45, 0.85)	2.93
D'incecco 2015	0.70 (0.44, 1.11)	2.58
loawa 2017	0.90 (0.60, 1.35)	2.72
Inoue 2016	1.23 (0.86, 1.76)	2.83
Ji 2017	2.21 (1.10, 4.42)	2.01
Mao 2014	1.90 (1.09, 3.30)	2.35
Mu 2011	1.78 (1.12, 2.83)	2.58
Okita 2017	3.32 (1.10, 9.97)	1.26
Pan 2017	3.23 (0.80, 13.12)	0.91
Schmidt 2015		2.89
	0.95 (0.68, 1.33)	
Shimoji 2016		2.09
Sorensen 2016	1.17 (0.83, 1.65)	2.87
Sun 2016	1.23 (1.00, 1.51)	3.15
Takada 2017	2.08 (1.42, 3.09)	2.76
Tang 2015	1.90 (0.95, 3.79)	2.02
Teng 2016	1.00 (0.47, 2.14)	1.87
Tokito 2016	0.47 (0.37, 1.53)	1.98
Tsao 2017	1.01 (0.76, 1.35)	2.99
Yang 2017	1.68 (0.83, 3.40)	1.99
Zhou 2017	2.57 (1.46, 4.52)	2.32
Subgroup, DL (l <sup>2</sup> = 71.7%, p = 0.000)	<b>Q</b> 1.35 (1.13, 1.61)	57.22
ADC		
Cha 2016	2.70 (1.78, 4.10)	2.69
Hirai 2017	2.81 (1.06, 8.23)	1.37
Huynh 2016	1.65 (0.79, 3.45)	1.92
Inamura 2016	1.88 (1.25, 2.74)	2.75
Lin 2015	0.26 (0.11, 0.62)	1.65
Mori 2017	2.59 (1.25, 5.39)	1.93
Song 2016	1.79 (1.30, 2.46)	2.92
Toyokawa 2017	5.86 (2.66, 12.91)	1.80
Uruga 2017	0.68 (0.40, 1.16)	2.40
Wu 2017	3.39 (1.25, 9.19)	1.42
Yang 2014	0.85 (0.21, 3.44)	0.91
Zhang 2014	2.72 (1.29, 5.73)	1.90
Subgroup, DL (l <sup>2</sup> = 78.0%, p = 0.000)	1.79 (1.22, 2.64)	23.68
SCLC		
Chang 2017	2.90 (1.44, 5.86)	2.00
Ishii 2015	0.44 (0.24, 0.80)	2.23
Miao 2017	0.94 (0.57, 1.56)	2.48
Subgroup, DL (l <sup>2</sup> = 87.5%, p = 0.000)	1.05 (0.39, 2.78)	6.70
LELC		
Fang 2015	2.73 (0.76, 9.86)	1.03
Jiang 2015	0.29 (0.07, 1.16)	0.91
Subgroup, DL (l <sup>2</sup> = 81.3%, p = 0.021)	0.91 (0.10, 8.16)	1.94
SCC	li	
Guo 2017	2.29 (1.47, 3.57)	2.63
llie 2016	1.79 (0.28, 11.44)	0.59
Kim 2015	1.24 (0.76, 2.02)	2.51
Takada 2017a	1.65 (1.08, 2.54)	2.67
Zhang 2017	2.49 (1.27, 4.88)	2.06
Subgroup, DL (l <sup>2</sup> = 9.4%, p = 0.353)	<b>b</b> 1.79 (1.39, 2.32)	10.46
Heterogeneity between groups: p = 0.317		
Overall, DL (l <sup>2</sup> = 75.3%, p = 0.000)	1.46 (1.25, 1.71)	100.00

NOTE: weights and between-subgroup heterogeneity test are from random-effects model

**Figure 2** Forest plot describing subgroup analysis of the association between PD-L1 expression and OS according to histology. PD-L1, programmed death-ligand 1; OS, overall survival; NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCLC, small cell lung cancer; LELC, lymphoepithelioma-like carcinoma; SCC, squamous cell carcinoma.

whether patients in the two studies were overlapped. We further conducted sensitivity analysis by omitting one study each time and the results remain robust (*Figures 4*,5).

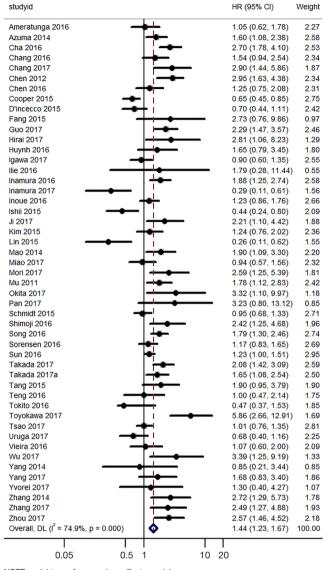
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%

studyid	HR (95% CI)	% Weight
Ameratunga 2016	1.05 (0.62, 1.78)	2.27
Azuma 2014	1.60 (1.08, 2.38)	2.57
Cha 2016	2.70 (1.78, 4.10)	2.52
Chang 2016	1.54 (0.94, 2.54)	2.34
Chang 2017	2.90 (1.44, 5.86)	1.88
Chen 2012	2.95 (1.63, 4.38)	2.34
Chen 2016	1.25 (0.75, 2.08)	2.31
Cooper 2015	0.65 (0.45, 0.85)	2.74
D'incecco 2015	0.70 (0.44, 1.11)	2.42
Guo 2017	2.29 (1.47, 3.57)	2.46
Hirai 2017	2.81 (1.06, 8.23)	1.30
Huynh 2016	■ 1.65 (0.79, 3.45)	1.80
Igawa 2017	0.90 (0.60, 1.35)	2.55
llie 2016	1.79 (0.28, 11.44)	0.56
Inamura 2016	1.88 (1.25, 2.74)	2.58
Inamura 2017	0.29 (0.11, 0.61)	1.57
Inoue 2016	- 1.23 (0.86, 1.76)	2.65
Ishii 2015	0.44 (0.24, 0.80)	2.10
Ji 2017	2.21 (1.10, 4.42)	1.89
Jiang 2015	0.29 (0.07, 1.16)	0.88
Kim 2015	1.24 (0.76, 2.02)	2.36
Lin 2015	0.26 (0.11, 0.62)	1.56
Mao 2014	1.90 (1.09, 3.30)	2.21
Miao 2017	• 0.94 (0.57, 1.56)	2.32
Mori 2017	2.59 (1.25, 5.39)	1.82
Mu 2011	1.78 (1.12, 2.83)	2.42
Okita 2017	3.32 (1.10, 9.97)	1.19
Pan 2017	3.23 (0.80, 13.12)	0.86
Schmidt 2015	0.95 (0.68, 1.33)	2.70
Shimoji 2016	2.42 (1.25, 4.68)	1.97
Song 2016	1.79 (1.30, 2.46)	2.74
Sorensen 2016	1.17 (0.83, 1.65)	2.68
Sun 2016	1.23 (1.00, 1.51)	2.94
Takada 2017	2.08 (1.42, 3.09)	2.59
Takada 2017a	<b>1</b> .65 (1.08, 2.54)	2.50
Tang 2015	1.90 (0.95, 3.79)	1.90
Teng 2016	1.00 (0.47, 2.14)	1.76
Tokito 2016	• 0.47 (0.37, 1.53)	1.86
Toyokawa 2017	<b>5.86 (2.66, 12.91)</b>	1.70
Tsao 2017	1.01 (0.76, 1.35)	2.80
Uruga 2017	0.68 (0.40, 1.16)	2.26
Vieira 2016	- 1.07 (0.60, 2.00)	2.10
Wu 2017	3.39 (1.25, 9.19)	1.34
Yang 2014	0.85 (0.21, 3.44)	0.86
Yang 2017	■ 1.68 (0.83, 3.40)	1.87
Yvorel 2017	1.30 (0.40, 4.27)	1.09
Zhang 2014	2.72 (1.29, 5.73)	1.79
Zhang 2014	2.49 (1.27, 4.88)	1.94
Zhou 2017	2.57 (1.46, 4.52)	2.18
Overall, DL ( $l^2 = 75.4\%$ , p = 0.000)		100.00
0.05 0.5 1	10 20	

NOTE: weights are from random-effects model

**Figure 3** Forest plot describing subgroup analysis of the association between PD-L1 expression and OS according to cutoff value. PD-L1, programmed death-ligand 1; OS, overall survival.



NOTE: weights are from random-effects model

**Figure 4** Forest plot describing the association between PD-L1 expression and OS of patients with lung cancer. PD-L1, programmed death-ligand 1; OS, overall survival.

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cutoff and studyid				HR (95% CI)	% Weight
cutoff value 50%					
Ameratunga 2016	-	<u> </u>		1.05 (0.62, 1.78)	4.46
Cooper 2015		1		0.65 (0.45, 0.85)	5.30
Subgroup, DL (l <sup>2</sup> = 57.1%, p = 0.127)	9	*		0.79 (0.50, 1.25)	9.76
cutoff value 5%		1			
Cha 2016				2.70 (1.78, 4.10)	4.92
Chang 2017		i —		2.90 (1.44, 5.86)	3.74
Hirai 2017	ŀ	+	-	2.81 (1.06, 8.23)	2.63
Huynh 2016	-	֥		1.65 (0.79, 3.45)	3.60
Inamura 2016		<b></b>		1.88 (1.25, 2.74)	5.02
Inamura 2017	<u> </u>	i i		0.29 (0.11, 0.61)	3.16
Ishii 2015 -	<b></b>	1		0.44 (0.24, 0.80)	4.15
Jiang 2015		i i		0.29 (0.07, 1.16)	1.81
Miao 2017		+-		0.94 (0.57, 1.56)	4.56
Song 2016		-		1.79 (1.30, 2.46)	5.30
Teng 2016		-		1.00 (0.47, 2.14)	3.52
Tokito 2016		+		0.47 (0.37, 1.53)	3.71
Toyokawa 2017		i 🗕	_	5.86 (2.66, 12.91)	3.40
Vieira 2016	-	<b>-</b>		1.07 (0.60, 2.00)	4.15
Yang 2017	-	<b>∔</b> •		1.68 (0.83, 3.40)	3.73
Yvorel 2017		┝──		1.30 (0.40, 4.27)	2.22
Subgroup, DL (l <sup>2</sup> = 80.7%, p = 0.000)	4	$\diamond$		1.28 (0.90, 1.84)	59.60
cutoff value 1%		1			
Sorensen 2016	+	←		1.17 (0.83, 1.65)	5.21
Sun 2016	ŀ	÷-		1.23 (1.00, 1.51)	5.66
Takada 2017				2.08 (1.42, 3.09)	5.03
Takada 2017a	ŀ	╈╾		1.65 (1.08, 2.54)	4.88
Tsao 2017	-+	+		1.01 (0.76, 1.35)	5.41
Uruga 2017	-+	-		0.68 (0.40, 1.16)	4.44
Subgroup, DL (l <sup>2</sup> = 67.7%, p = 0.009)	4	�		1.24 (0.97, 1.59)	30.63
Heterogeneity between groups: p = 0.1 Overall, DL (l <sup>2</sup> = 79.9%, p = 0.000)	89	<b>◇</b>		1.22 (0.98, 1.53)	100.00
0.01	0.5 1		1 1 10 2	0	

NOTE: weights and between-subgroup heterogeneity test are from random-effects model

**Figure 5** Forest plot describing the association between PD-L1 expression and OS of patients with lung cancer. PD-L1, programmed death-ligand 1; OS, overall survival.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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