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Unique distribution of programmed death ligand 1 (PD-L1) expression in East Asian non-small cell lung cancer

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Background: To determine the proportion and clinical features of programmed death ligand 1 (PD-L1) expression in East Asian non-small cell lung cancer (NSCLC).

Methods: PD-L1 expression was assessed by immunohistochemistry (IHC) and tumor proportion score (TPS) with the use of PD-L1 IHC 22C3 antibody (Dako North America) in 108 surgically resected lung squamous cell carcinomas (SCC) and 221 lung adenocarcinomas (LUADs), and was correlated with clinical variables, histologic subtypes, and common driver mutations.

Results: Positive PD-L1 expression was found in 37 lung SCC (37/108, 34.3%), including 15 cases with TPS \geq 50% (15/108, 13.9%) and 22 cases with TPS $<$ 50% (22/108, 20.4%). In adenocarcinoma cohort, 9 cases were found PD-L1 expression positive (9/221, 4.1%), including 1 case with TPS \geq 50% (1/221, 0.5%) and 8 cases with TPS $<$ 50% (8/221, 3.9%). Totally, high PD-L1 expression (TPS \geq 50%) was significantly associated with male sex ($P=0.026$), current/ever smoking history ($P=0.008$) and SCC subtype ($P<0.001$). Positive PD-L1 expression (including TPS \geq 50% and TPS $<$ 50%) in LUAD cohort was significantly associated with male sex ($P=0.046$), current/ever smoking history ($P=0.002$), mutation pan-negative status ($P=0.038$), solid-predominant subtype ($P<0.001$), large tumor size ($P=0.027$) and lymph node metastasis ($P=0.019$). No significant difference was found between PD-L1 high expression group (TPS \geq 50%) and low/negative expression group in SCC cohort.

Conclusions: This study revealed the unique distribution of PD-L1 expression in East Asian NSCLCs, which is largely different from Western populations. Since the high response rate of pembrolizumab in the treatment of lung cancer patients with PD-L1 TPS \geq 50%, this result indicates that prospective PD-L1 expression testing in specific East Asian patients could facilitate decision making for immunotherapy.

Keywords: Programmed death ligand 1 expression (PD-L1 expression); non-small cell lung cancer (NSCLC); survival

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Introduction

With advances in the investigation of mechanisms on immune recognition and immune escape, and development of immune checkpoint blockage agents, the treatment of non-small cell lung cancer (NSCLC) has entered into a new era of immunotherapy. Recent years, multiple clinical trials were conducted to assess the efficacy of immunotherapy antibodies, as well as the predictive value of PD-L1 expression from different antibody manufacturers. However, controversy still remains that there is no specific relationship between positive PD-L1 expression and response rate in patients receiving immunotherapy (1-4). As patients who cannot benefit from immunotherapy may suffer quick progression after receiving immunotherapy (5), it is urgent to find a biomarker which could effectively predict the efficacy of anti-PD-1/PD-L1 treatment. The serial of KEYNOTE clinical trials showed high response rates of pembrolizumab ranged from 44.6% to 45.2% among patients with NSCLC (6-8). And the efficacy of this anti-PD-1 agent was closely related to the expression of PD-L1 with a tumor proportion score (TPS) at least 50% which was detected by PD-L1 IHC 22C3 pharmDx Assay. Based on this encouraging data, using antibody specific PD-L1 expression in tumors seems optimal approach to screen eligible patients for immunotherapy to date.

Although PD-L1 IHC 22C3 pharmDx Assay was quite effective and reliable (9), and was till now the only companion diagnostic approved by the FDA as an aid in identifying patients with NSCLC for treatment with KEYTRUDA® (pembrolizumab), cost of this test could not be ignored. In a cost-effectiveness perspective, it was unreasonable to perform PD-L1 expression testing for all NSCLC patients.

On the other hand, current data of PD-L1 expression on NSCLC was mainly based on Western populations, situation on Asian populations remained unclear. Spectrum of PD-L1 expression and association between PD-L1 expression and clinicopathological variables of Asian patients with NSCLC were to be revealed. Therefore, we hope to identify some clinical and pathological features which could help narrow down the qualified patients for immunotherapy and facilitate the choice of treatment and enrollment of clinical trials.

In this study, we carried out an immunohistochemistry (IHC) investigation of PD-L1 expression in surgically resected lung squamous cell carcinomas (SCC) and adenocarcinomas using PD-L1 IHC 22C3 antibody, and correlated PD-L1 expression level with clinicopathological

and molecular parameters, including pathological subtypes, age, gender, smoking history, tumor size and common driver mutations. Meanwhile, the prognostic value of PD-L1 expression was also assessed.

Methods

Specimen collection

Lung cancer samples were collected from patients who underwent surgical resection with curative intent in our institution from September 2009 to March 2013. To validate the IHC procedure, a cohort of newly resected lung cancer samples was also collected in 2017. Eligible patients were required to have sufficient tissue for immunohistochemical staining and comprehensive mutational analyses. Patients who received neoadjuvant chemotherapy, had a history of malignant tumors, as well as without integrated clinicopathological and survival data were excluded. All cases were rereviewed by two pathologists for confirmation of tumor histology and tumor content. This study was approved by the institutional review board of the Shanghai Cancer Center, Fudan University, Shanghai, China. All patients underwent surgery and provided written informed consent.

IHC and interpretation

Tissue specimen preparation and IHC

All specimens used in this IHC procedure were formalin fixed paraffin-embedded (FFPE). Sections were cut at 4 μm thickness, dried for 1 hour at 60 °C and stored in dark at 4°C. IHC staining procedure was performed using the Dako Autostainer Link 48 platform and an adjusted automated staining process from validated protocol for the PD-L1 IHC 22C3 (9). As only Monoclonal Mouse Anti-Human PD-L1 antibody (Clone 22C3, Dako) was purchased, other required agents were replaced by a validated kit from Dako company [EnVison™ FLEX +, Mouse, High pH, (Link), Code K8002]. Deparaffinization, rehydration, and target retrieval was performed in the PT Link (Dako PT100) using a 3-in-1 procedure. After incubation with the monoclonal mouse anti-human PD-L1 antibody, clone 22C3, specimens were incubated with anti-mouse linker antibody specific to the host species of the primary antibody, and then were incubated with a ready-to-use visualization reagent consisting of secondary antibody molecules and horseradish peroxidase molecules coupled to a dextran polymer backbone. The specimens were then counterstained with

hematoxylin and cover-slipped. Results were interpreted using a light microscope by two pathologists (Yuan Li and Xiaoyan Zhou).

TPS

For determination of PD-L1 protein expression, positivity was defined as complete circumferential or partial cell membrane staining of viable tumor cells with 1+ to 3+ intensity. Tumor associated immune cells were excluded from PD-L1 scoring. Cytoplasmic staining, was excluded from the scoring. Scoring was recorded as percentage of PD-L1-positive tumor cells over total tumor cells in the denominator (TPS). NSCLC specimens stained with the negative control reagent must have 0 specific membrane staining and $\leq 1+$ intensity nonspecific (nonmembrane) staining.

Mutational analysis

Apart from PPFE samples, surgical resected lung cancer specimens were routinely collected and stored in liquid nitrogen until use in our center, which has been well described in our previous studies. Genomic DNA and RNA were extracted as per standard protocols (RNeasy Mini Kit, and QiAamp DNA Mini Kit, Qiagen, Hilden, Germany). Total RNA samples were reverse transcribed into single-stranded cDNA using RevertAid First Strand cDNA Synthesis Kit (Fermentas, St Leon-Rot, Germany). Either genomic DNA or cDNA were used for polymerase chain reaction (PCR) amplification and sequencing. *EGFR* (exons 18-22), *HER2* (exons 18 to 21), *KRAS* (exons 2 to 3), and *BRAF* (exons 11 to 15) were PCR amplified using cDNA for further sequencing. FISH assay and real-time PCR were simultaneously used in detecting *ALK*, *ROS1* and *RET* translocations. Samples without *EGFR*, *KRAS*, *HER2*, *BRAF* mutations and *ALK/ROS1/RET* translocations were defined as “pan-negative”.

Statistical analysis

Pearson's chi-squared test or Fisher's exact test was used to assess correlations between different PD-L1 expression level and clinicopathologic variables as well as mutational status. Kaplan–Meier method was used to draw the survival curves. Relapse-free and overall survival of patients with TPS $\geq 50\%$ or $< 50\%$ immunostaining was compared using the log-rank test. The statistical analyses were done using

SPSS 16.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 6 (GraphPadCorp, San Diego, CA, USA). The two-sided significance level was set at $P < 0.05$.

Results

A total of 329 NSCLC cases including 108 SCCs and 221 lung adenocarcinomas (LUADs) were screened for PD-L1 expression, among which, 10 SCC samples were collected in 2017 which are lack of sufficient follow-up time were only used in PD-L1 expression analysis. Totally, 16 (4.9%) cases were found with PD-L1 high (TPS $\geq 50\%$) expression, 30 (9.1%) cases with PD-L1 low (TPS $< 50\%$) expression, and 283 (86%) cases with PD-L1 negative staining. In subgroup analysis, positive PD-L1 expression was found in 37 lung SCCs (37/108, 34.3%), including 15 cases with TPS $\geq 50\%$ (15/108, 13.9%) and 22 cases with TPS $< 50\%$ (22/108, 20.4%). In LUAD cohort, 9 cases were found PD-L1 expression positive (9/221, 4.1%), including 1 case with TPS $\geq 50\%$ (1/221, 0.5%) and 8 cases with TPS $< 50\%$ (8/221, 3.9%) (Figure 1). The representative photos of PD-L1 high expression in the SCCs (Figure 2A,B) and LUADs (Figure 2C,D) were shown in Figure 2.

Of those patients with PD-L1 TPS $\geq 50\%$, 15 (15/16, 93.8%) were male and 14 (14/16, 87.5%) were current or ever smokers. Of those samples with PD-L1 TPS $\geq 50\%$, 15 (15/16, 93.8%) were SCCs, 7 (7/16, 43.8%) were with tumor size less than or equal to 3 cm, 9 (9/16, 46.2%) were N0 status and 8 (8/16, 50%) were stage I (Figure 1, Table 1). Notably, in the LUAD subgroup, 1 sample with PD-L1 TPS $\geq 50\%$ and 7 samples with PD-L1 TPS $< 50\%$ were found in the pan-negative LUAD group, and only 1 sample with PD-L1 TPS $< 50\%$ was found in the LUADs with *EGFR* mutation (Figure 1).

Comparison of clinicopathologic characteristics was performed between PD-L1 high expression group (TPS $\geq 50\%$) and PD-L1 low/negative group. The results showed that high PD-L1 expression was significantly associated with male sex ($p=0.026$), current/ever smoking history ($P=0.008$) and SCC subtype ($P < 0.001$) (Table 1).

Furthermore, no significant difference was identified between PD-L1 high (TPS $\geq 50\%$) and low/negative expression groups in the SCCs subgroups (Table 2). As only 1 sample with PD-L1 high expression (TPS $\geq 50\%$) was found in LUAD group, comparison of clinicopathologic characteristics was performed between PD-L1 positive and negative groups. We found that positive PD-L1 expression (including TPS $\geq 50\%$ and TPS $< 50\%$) in LUAD cohort

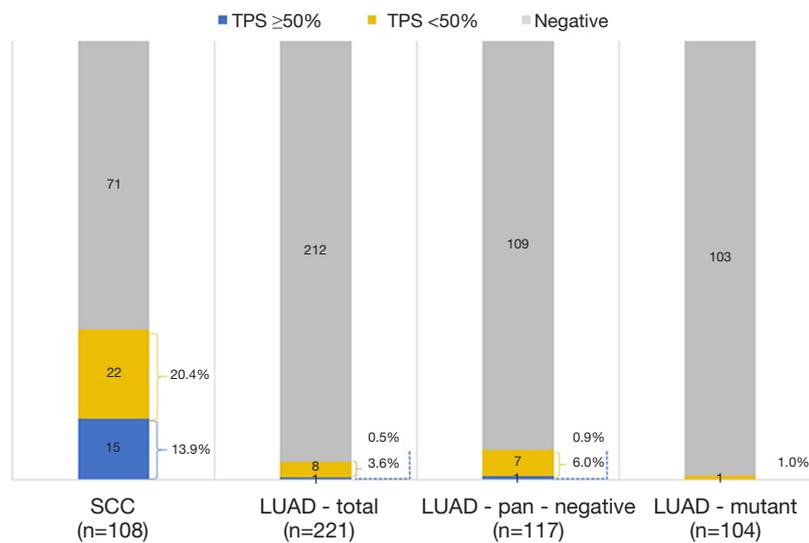


Figure 1 Comparison of PD-L1 expression in different subgroups. PD-L1, programmed death ligand 1 expression; TPS, tumor proportion score; SCC, squamous cell carcinomas; LUAD, lung adenocarcinoma.

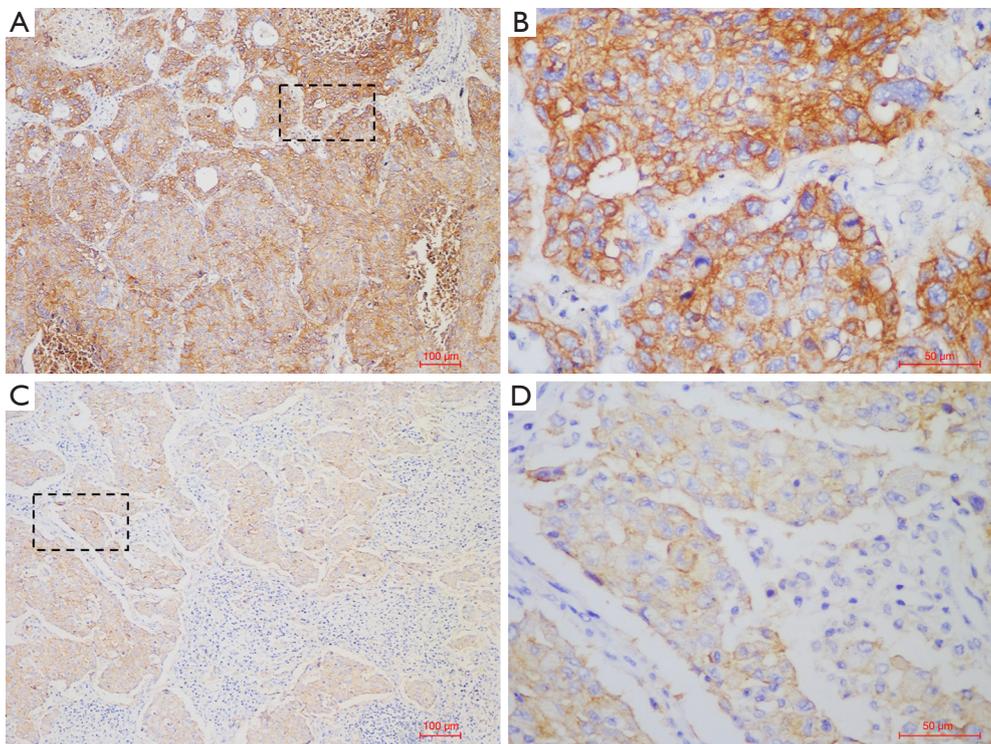


Figure 2 Representative images of positive PD-L1 expression in lung squamous cell carcinoma and adenocarcinoma. (A) Shows an image of squamous cell carcinoma with PD-L1 expression and amplified image is shown in (B). (C) Shows an image of adenocarcinoma with PD-L1 expression and amplified image is shown in (D). PD-L1, programmed death ligand 1 expression.

Table 1 Clinicopathologic characteristics of 329 patients with non-small cell lung cancers

Characteristic	PD-L1 high group [†] (n=16)	PD-L1 low/negative group [‡] (n=313)	P value
Age-year			0.752
Median	61	60.5	
Range	39–79	27–83	
Gender			0.026
Male	15	210	
Female	1	103	
Smoking status			0.008
Never*	2	148	
Current/former	14	165	
Histology			<0.001
Squamous	15	93	
Adenocarcinoma	1	220	
Tumor size			0.104
T1	7	200	
T2–3	9	113	
LN status			0.123
N0	9	231	
N1–2	7	82	
TNM stage			0.176
I	8	208	
II–III	8	105	

[†], including PD-L1 TPS \geq 50%; [‡], including PD-L1 TPS <50% and negative staining; *, never smokers are patients who smoked less than 100 cigarettes in their lifetime. PD-L1, programmed death ligand 1 expression.

was significantly associated with male sex ($P=0.046$), current/ever smoking history ($P=0.002$), mutation pan-negative status ($P=0.038$), solid-predominant subtype ($P<0.001$), large tumor size ($P=0.027$) and lymph node metastasis ($P=0.019$) (Table 3).

A total 319 patients from September 2009 to March 2013 were included for survival analysis. The median follow-up duration of these patients was 23.6 months (range, 0.8–80.0 months). The results showed that patients with PD-L1 high expression (TPS \geq 50%) had a significant shorter RFS than patients with PD-L1

Table 2 Clinicopathologic characteristics of 108 patients with squamous cell carcinoma

Characteristic	PD-L1 high group [†] (n=15)	PD-L1 low/negative group [‡] (n=93)	P value
Age-year			0.529
Median	62.9	61.3	
Range	50–79	37–81	
Gender			1.000
Male	14	88	
Female	1	5	
Smoking status			0.672
Never*	2	10	
Current/former	13	83	
Tumor size			0.204
T1	7	28	
T2–3	8	65	
LN status			0.950
N0	9	55	
N1–2	6	38	
TNM stage			0.722
I	8	45	
II–III	7	48	

[†], including PD-L1 TPS \geq 50%; [‡] including PD-L1 TPS <50% and negative staining; *, never smokers are patients who smoked less than 100 cigarettes in their lifetime. PD-L1, programmed death ligand 1 expression; TPS, tumor proportion score.

low/negative expression (median RFS: 47 vs. 62 months, log-rank $P=0.023$, Figure 3A). Whereas, there was no significant difference in OS ($P=0.679$, Figure 3B) between patients with PD-L1 high and low/negative expression. Multivariate analysis showed that PD-L1 status was not an independent risk factor for RFS in the all samples. Therefore, survival analysis was performed in the SCC cohort. Whereas, there were no significant differences in RFS ($P=0.393$, Figure 3C) and OS ($P=0.554$, Figure 3D) between patients with PD-L1 high expression and patients with PD-L1 low/negative expression.

Discussion

Over the last decade, with the discovery of various oncogenic

Table 3 Clinicopathologic characteristics of 221 patients with adenocarcinoma

Characteristic	PD-L1 high/low group [†] (n=9)	PD-L1 negative group [‡] (n=212)	P value
Age-year			0.649
Median	58.6	60.2	
Range	39–74	27–83	
Gender			0.046
Male	8	115	
Female	1	97	
Smoking status			0.002
Never*	1	137	
Current/former	8	75	
Driver mutation			0.038
with	1	103	
without	8	109	
Subtype predominant			<0.001
Solid	7	37	
Non-solid	2	175	
Tumor size			0.027
T1	4	168	
T2–3	5	44	
LN status			0.019
N0	4	172	
N1–2	5	40	
TNM stage			0.055
I	4	159	
II–III	5	53	

[†], including PD-L1 TPS $\geq 50\%$ and TPS $< 50\%$; [‡], including PD-L1 negative staining; *, Never smokers are patients who smoked less than 100 cigarettes in their lifetime. PD-L1, programmed death ligand 1 expression; TPS, tumor proportion score.

driver mutations and development of corresponding molecular agents, the treatment of NSCLC has entered into the era of targeted therapy. Genomic sequencing has revealed different mutation landscapes between Western and East Asian populations. Compared with the highest rate of *KRAS* mutation in Western population, *EGFR* mutation in East Asian population ranked the most frequent genetic

aberration, which could be effectively inhibited by EGFR-TKIs (10–13).

Although the relationship between oncogenic mutations and immunotherapy efficacy remains unclear, there is a trend that patients suitable for immunotherapy are often lack of known driver mutations (14). In our study, we enrolled 117 LUAD patients who were diagnosed as “pan-negative” by excluding common mutations and translocations, and 104 LUAD patients who harbored one of the six gene aberrations mentioned above. It was interesting that both pan-negative and mutant patients presented low PD-L1 expression, which was significantly different from the high PD-L1 expression rate reported in previous studies (6–8,15). This result indicates that LUAD patients in East Asian population may not benefit from immunotherapy. And this condition is independent of mutation status. However, patients with PD-L1 expression (regardless of TPS) shared some common clinical features, including male, with current/ever smoking history, lack of mutation, solid-predominant subtype, big tumor size and lymph node metastasis, which will be helpful in clinical PD-L1 expression testing. Several studies also reported that smoking history was associated with better immunotherapy response (6,16,17). In our study, we showed smokers are more likely to present high PD-L1 expression. Low proportion of smokers in East Asian LUAD patients may explain the discrepancy of PD-L1 expression between Western and East Asian LUAD populations.

In KEYNOTE-024 study, 500 out of 1,653 patients (30.2%) were diagnosed PD-L1 positive with TPS $\geq 50\%$ and non-squamous carcinoma is the predominant pathological type (7). This result is totally opposite with our current study. In our study, 34.3% of SCC patients present positive PD-L1 expression, however, only 13.9% of SCC patients could meet the criteria of immunotherapy (with TPS $\geq 50\%$). Compared with LUAD, patients with SCC in East Asian are the most suitable population for immunotherapy. Our previous study has shown that SCC in China are characterized by high proportion of never smoker, compared with the reported data of TCGA project from West SCC patients (18–20). This difference may add to the explanation of relatively low PD-L1 expression in East Asian SCC patients. If lung cancer with smoking is defined as a separate disease regardless of pathological type, a significantly different proportion of PD-L1 expression was observed between smoker and never smokers (22.3% vs. 4%, $P < 0.001$).

To our knowledge, this study represents the first

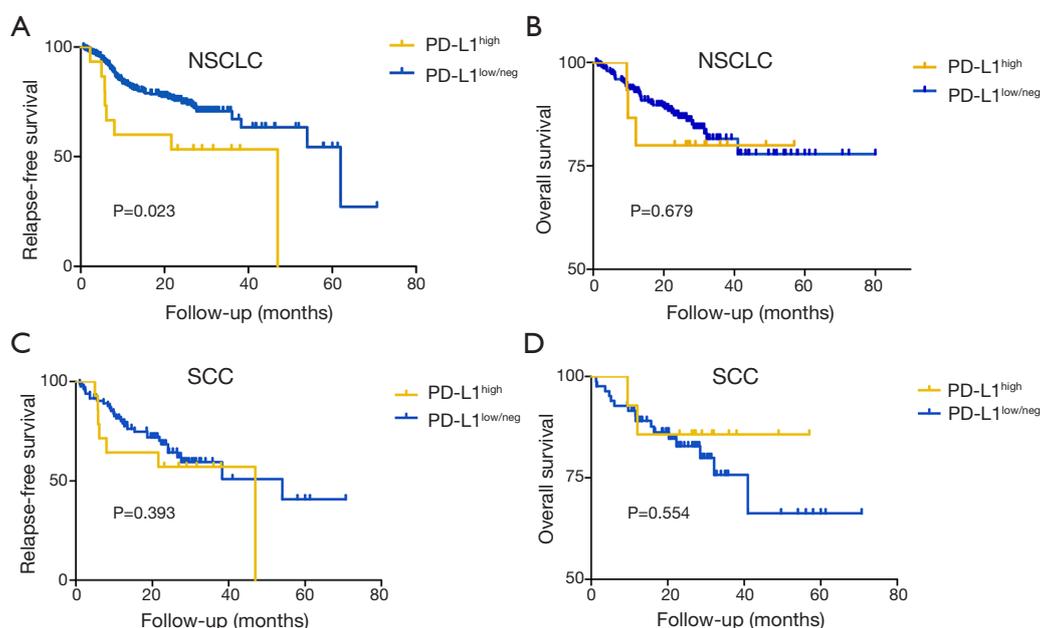


Figure 3 Kaplan-Meier survival curves for relapse-free survival and overall survival. (A) Relapse-free survival of 319 NSCLC patients; (B) overall survival of 319 NSCLC patients; (C) relapse-free survival of 98 SCC patients; (D) overall survival of 98 SCC patients. NSCLC, non-small cell lung cancer; SCC, squamous cell carcinomas.

comprehensive analysis of PD-L1 expression status with clinical and mutational features by using 22C3 antibody. Previous studies have analyzed the relationship between PD-L1 expression level and clinical parameters, but not with this efficient antibody clone. In addition, we selected surgically resected lung cancer specimens to comprehensively assess the proportion of PD-L1 expression tumor cells, which is superior to biopsy samples often used in the diagnosis of advanced NSCLC. In our study, enrolled patients are almost at early stage. So far, there is no evidence to prove that tumor stage is associated with PD-L1 expression, whether tumor stage is one of the underlying reasons for low PD-L1 expression in East Asian still needed to be explored.

PD-L1 expression was reported to be associated with poor prognosis in NSCLC. In the current study, patients with high PD-L1 expression have an inferior relapse-free survival comparing with low/negative PD-L1 expression group. However, there is no difference between two groups in overall survival. In order to enroll sufficient “pan-negative” LUAD patients into this study, the time span of enrollment varied significantly among three subgroups. The inevitable selection bias may affect the survival analysis.

In conclusion, our study represents a comprehensive PD-L1 expression study with clinicopathological features in East

Asian populations, which has a great significance in guiding the clinical screening before immunotherapy. Although the underlying molecular mechanism between PD-L1 expression and clinical parameters are still unknown, further next-generation sequencing and mechanism investigation may help to illustrate this issue.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the institutional review board of the Shanghai Cancer Center, Fudan University, Shanghai, China (No. IRB# 090977-1). All patients underwent surgery and provided written informed consent.

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