Editorial

PD-L1 protein expression in non-small cell lung cancer based on different immunohistochemical antibodies

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Abnormal immune checkpoint activation leads to the immune escape of tumour cells, and one of the most important immune checkpoints is programmed cell death ligand 1 (PD-L1) (1). Our previous study showed that increased PD-L1 expression on tumour cells was significantly correlated with poor prognosis in breast cancer (2) gastric cancer (3), and non-small cell lung cancer (NSCLC) (unpublished results). However, the correlation between PD-L1 expression and prognosis remains controversial in NSCLC. Several studies demonstrated that high PD-L1 expression might be predictive of a poor prognosis. However, other studies could not confirm this finding (see *Table 1*). Whether the difference among these studies was the result of the use of different antibodies and cut-off values in each study is still unclear.

PD-L1 negatively regulates T-cell proliferation through the binding of programmed cell death protein 1 (PD-1) and induces activated T cell exhaustion and adaptive immune resistance (4). The blockade of the PD-1/PD-L1 pathway using monoclonal antibodies results in the restoration of activated T cells and is currently considered the most promising antitumour immunotherapy (5). A series of phase II-III studies have displayed the good clinical activity of PD-1/PD-L1 inhibitors in patients with NSCLC (6-9). However, an important issue is how to identify patients likely to benefit from PD-1/PD-L1 inhibitors. The findings of recent studies indicate that PD-L1 expression levels have emerged as a predictive biomarker useful for stratifying patients with NSCLC who are receiving PD-1/PD-L1 therapeutic agents (10). Each PD-1/PD-L1 inhibitor has been tested with a companion diagnostic assay or complementary diagnostic assay using different PD-L1 antibodies (clone 28-8, clone 22C3, clone SP142 and clone SP263), protocols, or cut-offs for PD-L1 positivity (see in *Table 2*). Therefore, it is imperative to compare the similarities and differences among 4 separate PD-L1 antibodies.

Recently, Hirsch *et al.* (11) reported the Blueprint PD-L1 Assay Comparison Project, which is collaboration between research organizations (the International Association for the Study of Lung Cancer and the American Association for Cancer Research), together with big pharma companies (Merck, Bristol-Myers Squibb, Genentech/Roche and AstraZeneca) and two diagnostic companies (Dako and Ventana). The Blueprint PD-L1 IHC Assay Comparison Project is planned in two phases. The aim of this project was to compare the performance of 4 PD-L1 IHC assays developed in combination with four PD-1/PD-L1 immune checkpoint inhibitors (Pembrolizumab, Nivolumab, Atezolizumab and Durvalumab) in NSCLC clinical trials. Four serial histologic sections from 38 NSCLC patients were stained with four PD-L1 IHC assays: 28-8 and 22C3 antibodies on the Dako Link 48 staining platform and SP142 and SP263 antibodies on the Ventana Benchmark platform. The slides were scanned and scored by three pathologists who estimated the percentages of tumour and immune cells that stained positive at any intensity. This study indicated that the percentage of PD-L1-stained tumour cells was comparable when the 22C3, 28-8, and SP263 assays were used, whereas the SP142 assay exhibited weak staining of tumour cell membranes. The concordance

Table 1 Previous studies examining the expression of PD-L1 in NSCLC

First author	Year	Country	Cancer type	Patients number	Stage	Detection method	PD-L1 positive	Company	Catalog	Prognostic value
Mu *et al.*	2011	China	NSCLC	109	I–III	IHC	53.2% (58/109)	NA	NA	Poor
Chen *et al.*	2012	China	NSCLC	120	I–III	IHC	57.5% (69/120)	NA	NA	Poor
Azuma *et al.*	2014	Japan	NSCLC	164	I–III	IHC	50% (82/164)	Lifespan Biosciences	NA	Poor
Mao *et al.*	2014	China	NSCLC	128	I–III	IHC	72.7% (96/128)	NA	Clone 2H11	Poor
Velcheti *et al.*	2014	Greek	NSCLC	303	I–IV	IHC	24.8% (75/303)	Yale University	Clone 5H1	Good
Velcheti *et al.*	2014	USA	NSCLC	155	I–IV	IHC	36.1% (56/155)	Yale University	Clone 5H1	Good
Cooper *et al.*	2015	Australia	NSCLC	678	I–III	IHC	7.4% (50/678)	Merck	Clone 22C3	Good
D'incecco *et al.*	2015	Italy	NSCLC	123	IV	IHC	55.3% (68/123)	Abcam	Ab58810	NS
Schmidt *et al.*	2015	Germany	NSCLC	321	I–III	IHC	24% (77/321)	CST	Clone E1L3N	Good
Tang *et al.*	2015	China	NSCLC	170	IIIB–IV	IHC	65.9% (112/170)	CST	Clone E1L3N	NS
Ameratunga *et al.*	2016	Australia	NSCLC	420	I–III	IHC	23.8% (100/420)	CST	Clone E1L3N	NS
Inoue *et al.*	2016	Japan	NSCLC	654	I–III	IHC	30.7% (201/654)	CST	Clone E1L3N	Poor
Ji *et al.*	2016	China	NSCLC	100	I–III	IHC	40% (40/100)	Abcam	Ab174838	Poor
Sorensen *et al.*	2016	USA	NSCLC	204	IV	IHC	75% (153/204)	Merck	Clone 22C3	NS
Sun *et al.*	2016	Korea	NSCLC	1070	I–IV	IHC	44.7% (478/1070)	Merck	Clone 22C3	Poor
Tokito *et al.*	2016	Japan	NSCLC	74	III	IHC	74.3% (55/74)	Abcam	EPR1161	NS
Yang *et al.*	2014	China	ADC	163	I	IHC	39.9% (65/163)	Proteintech Group	NA	NS
Zhang *et al.*	2014	China	ADC	143	I–III	IHC	49% (70/143)	NA	NA	Poor
Lin *et al.*	2015	China	ADC	56	IV	IHC	53.6% (30/56)	Abcam	Ab58810	Good
Cha *et al.*	2016	Korea	ADC	323	I–IV	IHC	18.6% (60/323)	Spring Bioscience	SP142	Poor
Song *et al.*	2016	China	ADC	385	I–III	IHC	48.3% (186/385)	Proteintech Group	66248-I-Ig	NS
Takada *et al.*	2016	Japan	ADC	417	I–III	IHC	20.4% (85/417)	Spring Bioscience	SP142	Poor
Huynh *et al.*	2016	USA	ADC	261	I–III	IHC	36.5% (95/261)	CST	CloneE1L3N	Poor
Wu *et al.*	2017	China	ADC	133	I–IV	IHC	13.5% (18/133)	Roche	SP263	Poor
Kim *et al.*	2015	Korea	SCC	331	I–III	IHC	26.9% (89/331)	CST	E1L3N	NS
Yang *et al.*	2016	China	SCC	105	I	IHC	56.2% (59/105)	Abcam	NA	Good
Takada *et al.*	2017	Japan	SCC	205	I–III	IHC	35.1% (72/205)	Spring Bioscience	SP142	Poor

NSCLC, non-small cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; IHC, immunohistochemistry; OS, overall survival; NA, not available; CST, Cell Signaling Technology.

Table 2 PD-L1 IHC assay system in NSCLC

Agent	Company	FDA approval	Monoclonal antibodies	Staining platform	Diagnostic	Scoring criteria
Nivolumab	Merck	Yes	Clone 28-8	Dako Link 48	Complementary diagnostic	≥1% tumor cells
Pembrolizumab	Bristol-Myers Squibb	Yes	Colon 22c3	Dako Link 48	Companion diagnostic	≥50% tumor cells
Atezolizumab	Genentech/Roche	Yes	Clone SP142	Ventana Benchmark	Complementary diagnostic	Tumor cells and/or tumor infiltrating immune cells
Durvalumab	AstraZeneca	Expected in 2017	Clone SP263	Ventana Benchmark	Unknow	≥25% tumor cells

IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

between four assays for immune cell staining appears to be lower than for tumour cell staining. It is recommended that the different trial-validated PD-L1 IHC assays should not be considered interchangeable. This is the first step in the harmonization of PD-L1 IHC assays and helps us to establish standardized and validated companion diagnostic tests. This study had several limitations. First, the number of patients enrolled in the study is relatively small. Second, PD-L1 expression was evaluated from NSCLC samples obtained by surgical resection in most cases. The consistency of surgically resected specimens and biopsy specimens remains unclear. An ongoing phase 2 of this study in a larger cohort of patients will assess agreements and discrepancies between surgically resected specimens and biopsy specimens. Third, it only compares the performance of four PD-L1 platforms; there are no therapeutic outcome data to evaluate the clinical predictive power of alternative PD-L1 IHC testing strategies.

Recent United States-based study concurs with the Blueprint study (12). This study was funded by pharmaceutical companies (Bristol-Myers Squibb) and the NCCN oncology research programme. It is a prospective, multi-centre, pathologist-based study. A total of 90 surgically resected samples of NSCLC were submitted to 4 PD-L1 IHC assays (clone 28-8, clone 22c3, clone SP142, and clone E1L3N). Compared with the Blueprint PD-L1 Assay Comparison Project, this study has more pathologists than any single assay. This study showed concordance between 3 of the 4 assays, and the SP142 assay was lower in staining intensity than the other 3 assays for both tumour proportion scores and immune cell proportion scores. This study also showed that high concordance among 4 separate PD-L1 antibodies for tumour cell staining and poor concordance for immune cell staining. This finding suggested that IHC may be a good way to detect PD-L1 expression in tumour cells but not in immune cells. Unfortunately, this study did not provide patients' outcome data, and it could only evaluate diagnostic concordance and not clinical concordance. In 2017, Ratcliffe *et al.* (13) also analysed the concordance between three PD-L1 IHC diagnostic assays in patients with NSCLC (clone SP263, clone 22C3 and clone 28-8). This study included more samples than any other study. Four hundred and ninety-three patients with NSCLC were examined. The data showed that three PD-L1 IHC diagnostic assays had similar patterns of tumour membrane staining, with a high concordance rate among percentages PD-L1 staining. As a result of these studies with only diagnostic assays, the clinical utility of this assay needs to be verified in clinical studies.

In conclusion, this Blueprint study provided vital information regarding four diagnostic PD-L1 assays. Considering the limited number of patients in this study, the Blueprint results need to be validated in a larger, more comprehensive phase 2 study.

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Footnote

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

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