

## ORIGINAL ARTICLE

# Association between PD-L1 expression and initial brain metastasis in patients with non-small cell lung cancer and its clinical implications

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## Abstract

**Background:** Brain metastases frequently occur in patients with non-small cell lung cancer (NSCLC) resulting in a poor prognosis. Here, we investigated the association between PD-L1 expression and brain metastasis in patients with NSCLC and its clinical significance.

**Methods:** A total of 270 patients diagnosed with metastatic NSCLC who underwent PD-L1 testing on their tumor tissue between January 2017 and March 2019 were retrospectively reviewed. The VENTANA PD-L1 (SP263) assay was used, and positive PD-L1 expression was defined as staining in  $\geq 1\%$  of tumor cells.

**Results:** Positive PD-L1 expression was observed in 181 (67.0%) patients, and 74 (27.4%) patients had brain metastasis at diagnosis. Synchronous brain metastases were more frequently observed in PD-L1-positive compared with PD-L1-negative patients (31.5% vs. 19.1%,  $p = 0.045$ ). Multiple logistic regression analysis identified positive PD-L1 expression (odds ratio [OR]: 2.24,  $p = 0.012$ ) as an independent factor associated with synchronous brain metastasis, along with the histological subtype of nonsquamous cell carcinoma (OR: 2.84,  $p = 0.003$ ). However, the incidence of central nervous system (CNS) progression was not associated with PD-L1 positivity, with a two-year cumulative CNS progression rate of 26.3% and 28.4% in PD-L1-positive and PD-L1-negative patients, respectively (log rank  $p = 0.944$ ). Furthermore, positive PD-L1 expression did not affect CNS progression or overall survival in patients with synchronous brain metastasis (long rank  $p = 0.513$  and  $0.592$ , respectively).

**Conclusions:** Initial brain metastases are common in NSCLC patients with positive PD-L1 expression. Further studies are necessary to understand the relationship between early brain metastasis and cancer immunity.

## KEYWORDS

brain metastasis, non-small cell lung cancer, PD-L1, prognosis, screening

## INTRODUCTION

Lung cancer remains the most common cause of cancer-related deaths worldwide, but it is also a cancer that has experienced the greatest advances in treatment. Non-small cell lung cancer (NSCLC) has become a prominent example of the success of precision medicine among solid tumor

malignancies.<sup>1</sup> Treatment has been increasingly driven by molecular characteristics of the tumors,<sup>2</sup> and identifying a molecular profile from biopsied tissue for each patient during diagnosis is an essential step in establishing a treatment plan and for predicting patient outcome.

The success of programmed death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) targeted therapies has

led to interest in immune inhibitory factors as targets for NSCLC therapy.<sup>3</sup> The expression of PD-L1 in cancer cells has become an important marker to consider for treatment decisions despite its ambiguous validity. In addition to its predictive role, there have been several attempts to identify the clinical characteristics of tumors by PD-L1 expression, with a particular focus on its prognostic role. Despite controversial results with regard to histological subtype and pre-set cutoff values,<sup>4,5</sup> several studies have shown that positive PD-L1 expression is correlated with poor prognosis in patients with NSCLC.<sup>3,6</sup>

Typically, brain metastases result in a poor prognosis for most solid tumors, and the lung represents the most common primary tumor site for brain metastasis. Brain metastases occur in approximately 25% of patients at the diagnostic phase of NSCLC, and almost half of the patients will eventually develop brain metastasis during disease progression.<sup>7</sup> NSCLC patients with brain metastasis develop significant morbidity and mortality, although prognosis can vary depending on the molecular subtype of the patient, with median overall survival (OS) ranging from 3 to 15 months.<sup>7,8</sup> There have been many studies regarding the risk factors that predict the development of brain metastasis in patients with NSCLC<sup>9</sup>; however, little is known about the association between PD-L1 expression and brain metastasis. The purpose of this study is to investigate the correlation and clinical significance of PD-L1 expression and brain metastasis in NSCLC patients.

## METHODS

### Study population

We retrospectively reviewed patient records of a consecutive cohort of patients who were diagnosed with metastatic NSCLC and underwent PD-L1 testing on their tumor tissue at the Korea University Guro Hospital, Seoul, Republic of Korea, between January 2017 and March 2019. Patients found to have recurrence or metastases after treatment for early stage NSCLC were not included in the study. All patients suspected of having lung cancer underwent brain magnetic resonance imaging (MRI) for staging work-up at the time of diagnosis. Information on initial brain metastasis could therefore be retrieved from all lung cancer patients. In the case of patients with initial brain metastasis, brain MRI was performed every 3 to 6 months after treatment for brain metastasis as determined by the physician. In patients without initial brain metastasis, brain MRI was performed when there was a suspicion of new onset of brain metastasis during systemic treatment.

Data collected from the electronic medical records included clinicopathological variables such as patient demographics, smoking status, site of metastatic lesions, histopathological characteristics, and molecular subtypes, including anaplastic lymphoma kinase (*ALK*) gene rearrangement and epidermal growth factor receptor (*EGFR*) gene

mutation status. Data for therapeutic regimen and treatment response were also collected, and tumor response was graded according to the Response Evaluation Criteria in Solid Tumors version 1.1.

This study was approved by the Institutional Review Board of the Korea University Guro Hospital (IRB number 2019GR0370) and conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

### PD-L1 immunohistochemistry

All patients diagnosed with metastatic NSCLC in Korea have been tested for PD-L1 since 2017, because positive PD-L1 expression was used as a criterion for medical reimbursement of anti-PD-1 or PD-L1 antibodies.

For PD-L1 testing, formalin-fixed, paraffin-embedded biopsy specimens of the primary tumors were subjected to immunohistochemical analysis. The entire tumor section was used to account for PD-L1 expression heterogeneity. The sections were stained with an anti-PD-L1 (SP263, Ventana Medical Systems) rabbit monoclonal primary antibody using the OptiView DAB immunohistochemistry (IHC) detection kit on a BenchMark XT automated staining platform, according to the manufacturer's instructions. The proportion of tumor cells with positive membranous staining (tumor proportion score, TPS) was assessed, and positive PD-L1 expression was defined as staining in  $\geq 1\%$  of the tumor cells. In our institution, the reproducibility of staining results was maintained through regular quality control processes, and the staining result of each patient was finally reported after being reviewed by two pathologists.

### Statistical analysis

Descriptive statistics were analyzed for the demographic and clinicopathological characteristics of patients. Univariate and multiple logistic regression analyses using the backward elimination method were performed to determine the independent effects of PD-L1 positivity on the presence of brain metastasis and to find the risk factors associated with brain metastasis at diagnosis of NSCLC. The results were reported as an odds ratio (OR) with a 95% confidence interval (CI).

Central nervous system (CNS) progression was defined as progression of existing brain metastases or newly developed CNS metastases in the brain, meninges, and cerebrospinal fluid during treatment. Time to CNS progression was calculated from the date of the initial diagnosis of metastatic NSCLC to the date of first CNS progression, whereas deaths were censored. OS was calculated from the first day of diagnosis to the day of death from any cause. Survival analysis was based on all data available until the cutoff date of February 28, 2021.

Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The follow-up duration was described as median values based on the reverse Kaplan–Meier estimator. All statistical analyses were

performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp.), and survival curves were generated using GraphPad Prism 5.0 (GraphPad Software). A *p*-value of <0.05 was considered statistically significant.

**TABLE 1** Baseline characteristics of all patients

	Total ( <i>N</i> = 270)	Synchronous brain metastasis		<i>p</i> -value
		No ( <i>N</i> = 196)	Yes ( <i>N</i> = 74)	
Sex				0.416
Male	187 (69.3%)	139 (70.9%)	48 (64.9%)	
Female	83 (30.7%)	57 (29.1%)	26 (35.1%)	
Age at diagnosis	71.0 (63.0; 77.0)	72.0 (64.0; 77.0)	70.0 (62.0; 77.0)	0.476
Smoking history				0.050
Never smoker	131 (48.5%)	89 (45.4%)	42 (56.8%)	0.127
Smoker	139 (51.5%)	107 (54.6%)	32 (43.2%)	
Ex-smoker	81 (30.0%)	67 (34.2%)	14 (18.9%)	
Current-smoker	58 (21.5%)	40 (20.4%)	18 (24.3%)	
Histology				
ADC	173 (64.1%)	116 (59.2%)	57 (77.0%)	0.010
SqCC	76 (28.1%)	64 (32.7%)	12 (16.2%)	0.012
Large cell NEC	3 (1.1%)	3 (1.5%)	0 (0.0%)	0.564
Others	18 (6.7%)	13 (6.6%)	5 (6.8%)	1.000
EGFR mutation				
Mutation	64 (23.7%)	41 (20.9%)	23 (31.1%)	0.112
Exon 19 del	39 (14.4%)	27 (13.8%)	12 (16.2%)	
L858R	20 (7.4%)	12 (6.1%)	8 (10.8%)	
L858R + others	1 (0.4%)	0 (0.0%)	1 (1.4%)	
Other rare mutation	4 (1.5%)	2 (1.0%)	2 (2.7%)	
Wild-type	123 (45.6%)	87 (44.4%)	36 (48.6%)	0.624
Not available	83 (30.7%)	68 (34.7%)	15 (20.3%)	0.032
ALK rearrangement				
Rearrangement	6 (2.2%)	5 (2.6%)	1 (1.4%)	1.000
Wild-type	176 (65.2%)	117 (59.7%)	59 (79.7%)	0.003
Not available	88 (32.6%)	74 (37.8%)	14 (18.9%)	0.005
PD-L1 expression				0.175
Positive (>1%)	181 (67.0%)	124 (63.3%)	57 (77.0%)	0.045
1%–9%	57 (21.1%)	40 (20.4%)	17 (23.0%)	
10%–49%	47 (17.4%)	33 (16.8%)	14 (18.9%)	
≥50%	77 (28.5%)	51 (26.0%)	26 (35.1%)	
Negative (0%)	89 (33.0%)	72 (36.7%)	17 (23.0%)	

Abbreviations: ADC, adenocarcinoma; ALK, anaplastic lymphoma receptor tyrosine kinase; EGFR, epidermal growth factor receptor; N, number; NEC, neuroendocrine carcinoma; PD-L1, programmed death-ligand 1; SqCC, squamous cell carcinoma.

**TABLE 2** Incidence of initial brain metastasis according to histology and PD-L1 status

PD-L1 status	Total ( <i>N</i> = 270)			Non-SqCC ( <i>N</i> = 194)			SqCC ( <i>N</i> = 76)		
	<1% ( <i>N</i> = 89)	≥1% ( <i>N</i> = 181)	<i>p</i> -value	<1% ( <i>N</i> = 72)	≥1% ( <i>N</i> = 122)	<i>p</i> -value	<1% ( <i>N</i> = 17)	≥1% ( <i>N</i> = 59)	<i>p</i> -value
Brain metastasis at diagnosis	17 (19.1%)	57 (31.5%)	0.045	16 (22.2%)	46 (37.7%)	0.038	1 (5.9%)	11 (18.6%)	0.279

Abbreviations: N, number; PD-L1, programmed death-ligand 1; SqCC, squamous cell carcinoma.

## RESULTS

## Patient characteristics

A total of 270 patients who were diagnosed with metastatic lung cancer were included in this study. The median patient age was 71 years (interquartile range, 63–77) at the time of diagnosis, and 186 (68.9%) patients were male. There were 131 (48.5%) patients who had never smoked, and 139 (51.5%) patients, including 81 ex-smokers, had a history of smoking. The most frequent histological type was adenocarcinoma (ADC) ( $n = 173$ , 64.1%), followed by squamous cell carcinoma (SqCC) ( $n = 76$ , 28.1%) and large cell neuroendocrine carcinoma ( $n = 3$ , 1.1%). Furthermore, there were 18 (6.7%) patients whose histological type could not be classified, such as poorly differentiated carcinoma, adenosquamous carcinoma, pleomorphic carcinoma, and carcinoma not otherwise specified. Regarding molecular subtypes, 64 (23.7%) and six (2.2%) patients exhibited an *EGFR* mutation and *ALK* rearrangement, respectively.

Among the patients, 74 (27.4%) had synchronous brain metastasis at diagnosis. No difference was observed regarding sex, age, and smoking status between the patients with or without synchronous brain metastasis, but there was a significant difference in terms of histologic subtype. The rate of ADC was higher in patients with brain metastasis, whereas the rate of SqCC was higher in patients without brain metastasis. The detailed information about the baseline characteristics of all patients are summarized in Table 1.

## PD-L1 expression and synchronous brain metastasis

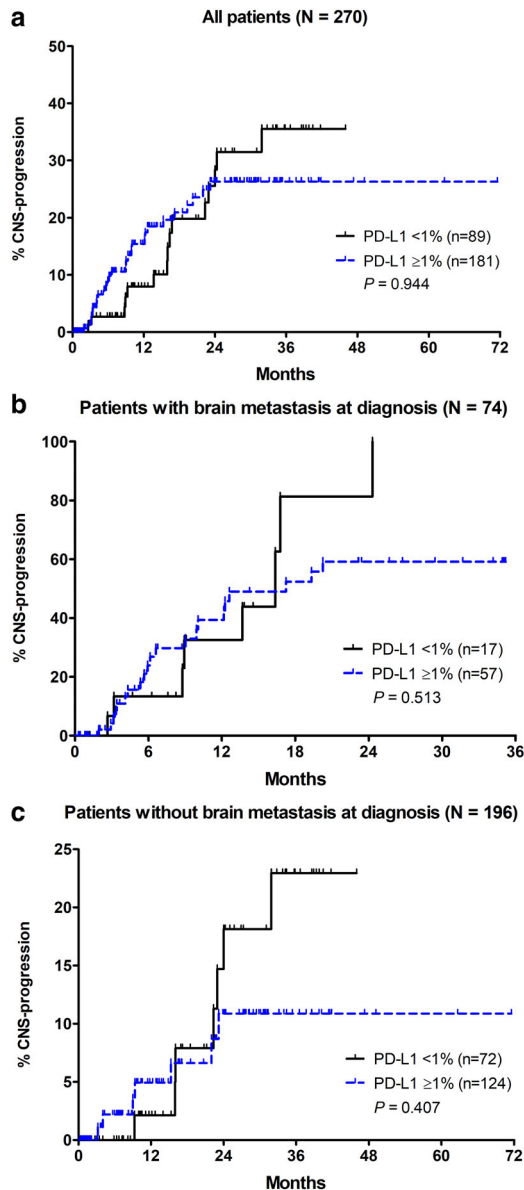
Of the total study population, positive PD-L1 expression was observed in 181 (67.0%) patients, whereas the remaining 89 patients exhibited negative PD-L1 staining. The prevalence of various PD-L1 TPS ranges was as follows: 0%: 89/270 (33.0%); 1%–9%: 57/270 (21.1%); 10%–49%: 47/270 (17.4%); and  $\geq 50\%$ : 77/270 (28.5%) (Table 1). Compared with PD-L1-negative patients, the proportion of patients with synchronous brain metastasis was significantly higher in PD-L1-positive patients (31.5% vs. 19.1%,  $p = 0.045$ ). The higher incidence of synchronous brain metastasis in PD-L1-positive patients was also observed when analyzed in two different histological subgroups, non-SqCC ( $n = 194$ ) and SqCC ( $n = 76$ ). No statistical significance was observed in the SqCC group, with 18.6% and 5.9% incidence of synchronous brain metastasis in PD-L1-positive and PD-L1-negative patients, respectively ( $p = 0.279$ ). For non-SqCC patients, 37.7% of PD-L1-positive patients and 22.2% of PD-L1-negative patients were found to have synchronic brain metastasis, thus confirming a significant difference ( $p = 0.038$ ) (Table 2).

Using univariate logistic regression analysis, non-SqCC histological type and positive PD-L1 expression were identified as factors associated with synchronous brain metastasis in NSCLC patients. Multivariate analysis with other covariates including gender, age, smoking status, and molecular subtypes also showed that two factors, non-SqCC

**TABLE 3** Univariate and multivariable logistic regression analysis for risk factors associated with synchronous brain metastasis in patients with non-small cell lung cancer (NSCLC)

Covariates	Univariable			Multivariable (full)			Multivariable (backward elimination)		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Gender									
Female	Ref			Ref			–	–	–
Male	0.76	0.43–1.35	0.337	1.30	0.62–2.75	0.485	–	–	–
Age at diagnosis	0.99	0.96–1.02	0.564	0.98	0.95–1.01	0.256	–	–	–
Smoking									
Never smoker	Ref			Ref			–	–	–
Smoker (ex- or current-)	0.63	0.37–1.08	0.097	0.57	0.28–1.16	0.118	–	–	–
Histology									
SqCC	Ref			Ref			Ref		
Non-SqCC	2.51	1.30–5.18	0.009	2.63	1.29–5.69	0.010	2.84	1.46–5.95	0.003
<i>EGFR</i> mutation									
WT or NA	Ref			Ref			–	–	–
<i>EGFR</i> -mutated	1.70	0.93–3.09	0.082	1.19	0.58–2.41	0.625	–	–	–
<i>ALK</i> rearrangement									
WT or NA	Ref			Ref			–	–	–
<i>ALK</i> -rearranged	0.52	0.03–3.32	0.557	0.31	0.02–2.15	0.305	–	–	–
PD-L1 expression									
PD-L1 negative	Ref			Ref			Ref		
PD-L1 positive	1.95	1.07–3.68	0.034	2.42	1.30–4.69	0.007	2.24	1.22–4.30	0.012

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; NA, not available; OR, odds ratio; PD-L1, programmed death-ligand 1; Ref, reference; SqCC, squamous cell carcinoma; WT, wild-type.

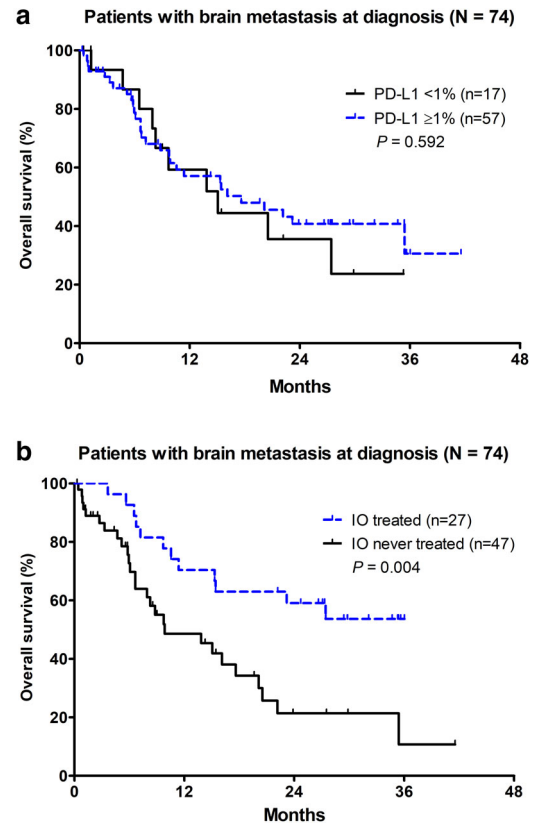


**FIGURE 1** Kaplan–Meier curves for time to central nervous system (CNS) progression by PD-L1 positivity in (a) all patients and patients (b) with or (c) without synchronous brain metastasis

subtype (OR: 2.84, 95% CI: 1.41–5.72,  $p = 0.003$ ) and positive PD-L1 expression (OR: 2.24, 95% CI: 1.20–4.21,  $p = 0.012$ ), were independent risk factors with a high probability of brain metastasis at the time of NSCLC diagnosis (Table 3).

### PD-L1 expression and CNS progression

The median follow-up time for all patients in this study was 27.35 (95% CI: 24.99–29.71) months. A total of 43 patients experienced CNS progression during the study period, including two cases of leptomeningeal seeding. The time to CNS progression was not different based on PD-L1



**FIGURE 2** Overall survival (OS) in patients with synchronous brain metastasis according to (a) PD-L1 positivity and (b) immuno-oncology (IO) treatment

positivity. The two-year cumulative CNS progression incidence rates were 26.3% and 28.4% in PD-L1-positive and PD-L1-negative patients, respectively (log rank  $p = 0.944$ ) (Figure 1a). Differences in CNS progression were not evident even when the patients were analyzed in two different subgroups depending on the presence or absence of synchronous brain metastasis at diagnosis (Figure 1b,c). Of note, there was also no difference in CNS progression according to the histologic subtypes SqCC and non-SqCC (Figure S1).

### Survival outcomes in patients with synchronous brain metastasis

Of the 74 patients with synchronous brain metastasis, 57 (77.0%) received local treatment for their brain lesions in addition to systemic therapy for NSCLC. The most frequently applied treatment was gamma knife radiosurgery (GKRS) ( $n = 38$ ), followed by whole-brain radiotherapy (WBRT) ( $n = 18$ ) and surgical resection ( $n = 4$ ). Of these, two patients received WBRT following GKRS, and one patient received GKRS following resection. The application rate of local treatment for brain metastasis did not differ between PD-L1-positive and PD-L1-negative patients (78.9% vs. 70.6%,  $p = 0.518$ ). The median OS of the

patients with synchronous brain metastasis was 16.11 (95% CI: 9.46–22.76) months, and no significant difference was observed between PD-L1-positive and PD-L1-negative patients (17.62 vs. 15.06 months,  $p = 0.592$ ) (Figure 2a). Meanwhile, about a third of patients ( $n = 27$ , 36.5%) received immuno-oncology (IO) therapies during their treatment course; patients who received IO therapy showed significantly longer OS than who did not (not reached vs. 9.86 months,  $p = 0.004$ ) (Figure 2b).

## DISCUSSION

In the present study, we evaluated the significance of PD-L1 expression including its association with early brain metastasis and its clinical impact on CNS progression and survival in patients with NSCLC. Patients with tumors exhibiting positive PD-L1 expression (TPS  $\geq 1\%$ ) were found to have a higher frequency and risk of synchronous brain metastasis when diagnosed with advanced NSCLC. However, no prognostic impact of positive PD-L1 expression was observed on either CNS progression in the entire cohort of patients or OS in patients presenting with synchronous brain metastasis. It is already known that nonsquamous histology is one risk factor for the development of brain metastasis in NSCLC,<sup>10,11</sup> and EGFR/ALK-mutated NSCLC exhibits a significantly higher incidence of brain metastasis.<sup>12–16</sup> On the basis of these results, we performed a multivariate analysis including histology and molecular tumor type, and positive PD-L1 expression was analyzed as an independent factor in the occurrence of brain metastasis at initial presentation for patients with NSCLC.

The basic principle for the relationship between PD-L1 expression and synchronous brain metastasis has not been elucidated. To metastasize to other organs, tumor cells must avoid recognition and destruction by the host immune system during their journey through the hematological and lymphatic circulation and adapt to the new environment of the distant site.<sup>17</sup> The long-held CNS immune privilege paradigm, consisting of the presence of the blood–brain barrier (BBB) and the absence of a classic lymphatic drainage system, has become obsolete following the discovery of a lymphatic system in the CNS and the ability of T cells to cross the BBB.<sup>18</sup> Studies have revealed that the brain has an idiosyncratic immune environment that maintains homeostasis and curbs inflammatory responses that may otherwise be harmful. Current data suggest that various immunosuppressive factors contribute toward this unique environment in the brain including regulatory T (Treg) cells and suppressor T cell activity.<sup>19,20</sup>

To date, the well-studied PD-L1/PD-1 axis determines physiological immune homeostasis and suppresses the T cell activity in various ways including inhibiting T cell survival, proliferation, cytokine production, and other effector functions.<sup>21</sup> Intratumoral PD-L1 expression has been considered to be an indirect measure of locally suppressed antitumor immunity. Jacobs et al. demonstrated the important role of

the PD-L1/PD-1 pathway in malignant, but not benign, human brain tumors.<sup>22</sup> In response to this localized effect, the tumor may further affect the brain environment by inhibiting the overall immune response. Li et al. demonstrated a systemic immunosuppressive state in patients with brain metastatic NSCLC, showing increased peripheral myeloid cell PD-L1 expression correlating with decreased T cell activity.<sup>23</sup> Thus, decreased T cell function, which could be inferred from PD-L1 expression, may render the brain more vulnerable to metastatic disease. Therefore, previous reports that PD-L1 overexpression is associated with poor survival for NSCLC patients<sup>6</sup> may result from the high incidence of synchronous brain metastasis, which is a poor prognostic factor<sup>24</sup> and is consistent with the results of our study. Hence, a more careful examination may be required to monitor brain metastasis during staging workups when patients are diagnosed with PD-L1-positive NSCLC.

The prognostic impact of PD-L1 expression in NSCLC for CNS progression was not observed in this study. However, since the course of disease varied depending on response to treatment and brain lesions were particularly affected by local therapies, it would be difficult to prove the relationship between the PD-L1 expression and CNS-related survival from our results. Of note, previous studies reported significant intracranial activity of IO agents in various trials,<sup>25</sup> and recently published phase II data indicated that pembrolizumab was effective against brain metastases from NSCLC patients with PD-L1 expression of at least 1%.<sup>26</sup> This desired effect of IO treatment on survival improvement for NSCLC patients with brain metastasis was observed in our study as well, but it should be taken into account that patients received IO treatment during different courses of chemotherapy and CNS response data were lacking. Future well-organized studies are necessary to establish the clinical significance of PD-L1 expression on CNS-related survival and OS in patients with NSCLC.

To our knowledge, this is the first study to suggest that PD-L1 expression in NSCLC may be associated with early brain metastasis. The majority of early IO clinical trials included fewer patients with brain metastasis, and sufficient data were not available for these patients.<sup>27</sup> Our finding lays the groundwork for future research into the link between early brain metastasis and the PD-1/PD-L1 axis.

This study has several limitations that should be considered. The single-center retrospective design is a well-known weakness associated with various types of bias. Another limitation is that the results from only one antibody were used for evaluating PD-L1 expression. There are four standardized PD-L1 IHC assays using different antibodies: 22C3 and 28–8 pharmDx assays on Dako platforms<sup>28,29</sup> and SP142/SP263 on Ventana platforms.<sup>30,31</sup> Many concerns have been raised about the compatibility of the results from these different methods.<sup>32</sup> However, high concordance between the results from Dako 28–8, Dako 22C3, and Ventana SP263 assays was demonstrated,<sup>33–35</sup> and Adam et al. showed that clone SP263 had a unique ability in yielding concordant

results across all centers and platforms.<sup>36</sup> Therefore, our results obtained using SP263 are likely representative, widely applicable, and reliable.

In conclusion, a significant association between PD-L1 expression and synchronous brain metastasis in NSCLC, especially for non-SqCC, was found in this study. Although spatial tumor heterogeneity should always be considered in metastatic disease, this finding denotes that patients diagnosed with PD-L1-positive NSCLC may need a closer examination for the likelihood of accompanying brain metastasis. Future prospective, controlled studies with a large patient population are needed to validate this finding. The precise mechanism underlying the relationship between PD-L1 expression and brain metastasis remains to be elucidated.

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## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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