의학박사 학위논문

면역관문억제제를 투여 받은 환자에서 soluble PD-L1의 치료 반응 또는 예후 예측인자로서의 역할

Role of soluble PD-L1 as a predictive or prognostic factor for patients receiving immune-checkpoint inhibitor treatment

2021년 8월

서울대학교 대학원

의학과 중개의학 전공

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Abstract

Circulating soluble programmed death-1 ligand (sPD-L1) is measurable in serum of patients with cancer. This study aimed to investigate the significance of sPD-L1 in patients receiving immune checkpoint inhibitor therapy. Blood samples were obtained before and after the therapy (January 2015 to January 2019). The study cohort consisted of 128 patients. Patients with high sPD-L1 levels (>11.0 pg/μL) were more likely to have progressive disease than those with low levels (41.8% versus 20.7%, respectively, p=0.013). High sPD-L1 levels were associated with a worse prognosis, the median progression-free survival (PFS) time was 2.9 (95% confidence interval [CI], 2.1-3.7) months versus 6.3 (95% CI, 3.0-9.6) months, respectively (p=0.023); the median overall survival (OS) times were 7.4 (95% CI, 6.3-8.5) months versus 13.3 (95% CI, 9.2-17.4) months, respectively (p=0.005). Multivariate analyses found that high sPD-L1 was a poor independent prognostic factor for PFS (HR, 1.928; p=0.038) and OS (HR, 1.788; p=0.004). sPD-L1 level did not correlate with tissue PD-L1 expression. But, sPD-L1 levels were positively correlated with neutrophil to lymphocyte

ratios and negatively correlated with lymphocyte proportions or counts. We found that high pre-treatment sPD-L1 levels were associated with progressive disease and were an independent prognostic factor predicting PFS and OS in these patients.

Keyword: soluble programmed death-1 ligand, programmed death-1 ligand, immune checkpoint inhibitor, cancer immunotherapy, cancer

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Chapter 1. Introduction

Since the first immune checkpoint inhibitor (ICI), ipilimumab, was approved in 2011, the treatment paradigm for solid tumors has changed greatly. ICIs have important roles in treatment of various types of solid tumors. However, most patients still do not benefit from ICIs. For example, pembrolizumab or nivolumab shows an objective response rate (ORR) of 20% as second-line treatment in non-small cell lung cancer (NSCLC)[1,2]. Whereas, 16% to 55% of patients suffer from severe toxicities with ICI treatment[3]. Therefore, it is important to find the predictors of the response. Some biomarkers that predict treatment response have been identified. The representative biomarker is programmed death ligand 1 (PD-L1)[4]. PD-L1 expression in tumor tissue is a predictive factor for a higher response rate to programmed death 1 (PD-1) or PD-L1 inhibitor therapy in patients with NSCLC[5-7]. It is also a poor prognostic marker in some solid tumors[8-10]. However, inter-assay discordance and tumor heterogeneity hinder standardization of PD-L1 testing and interpretation[11,12]. Researchers have tried to standardize the methods used to measure PD-L1 expression, but no clinically validated assays are available[13]. Microsatellite instability or deficient mismatch repair (dMMR) is one of the biomarkers studied as a predictor of ICI

response[4]. dMMR is associated with favorable clinical outcomes in patients with colorectal cancer[14,15]. PD-1 blockade results in a durable response in some subjects with dMMR-positive solid tumors[16]. Tumor mutational burden, tumor infiltrating lymphocytes, and genetic signatures are also predictive factors. However, these markers lack standardization and have large variability across tumor types and study settings[4].

Lack of sufficient tissue for examination is another common and important limitation of these markers. Shortage of tumor tissue is especially problematic in patients with NSCLC because the biopsies used to diagnose the tumors often yield only tiny pieces of tissues. However, approximately five molecular genetic tests are required to select the therapeutic agents used for patients with NSCLC[17,18]. Use of small biopsies can also result in misclassification of up to 35% of PD-L1 assessments in patients with advanced NSCLCs[19]. Therefore, circulating blood biomarkers are being investigated to predict response to PD-1/PD-L1 blockade. They include circulating immune cells, circulating PD-L1, and lots of other circulating markers[20-25]. In previous studies, CD8+ T-cells showed proliferative burst or functional reinvigoration after PD-1 blockade[26,27]. Other study showed that functionally active CD8+ T cells or NK cells are

associated with good prognosis after PD-1 blockade[28].

PD-L1 present as a membrane-bound form in tumor cells or immune cells. But it is also known that it may be secreted as truncated forms, which is also named as soluble PD-L1 (sPD-L1). It may mediate immunosuppression or resistance to PD-L1 blockade therapy[29-31]. Compared with healthy subjects, circulating sPD-L1 concentrations are elevated in the plasma of patients with cancer. In patients with lymphoma, these concentrations return to normal levels after a complete response[32]. High concentrations of sPD-L1 are associated with a poor prognosis in patients with hepatocellular carcinoma, gastric cancer, and NSCLC[33-36]. We examined circulating sPD-L1 and its roles as prognostic and predictive markers in patients with cancer who received ICI treatment. We hypothesized that 1) high pre-treatment sPD-L1 is associated with low response rate and poor prognosis, 2) change of sPD-L1 level after ICI treatment is associated with prognosis, and 3) sPD-L1 level reflects the level of PD-L1 expression of tumor tissue. Therefore, we analyzed pre-treatment and post-treatment levels of blood soluble PD-L1 and associated clinical outcomes in patients with advanced solid tumors.

Chapter 2. Materials & Methods

2.1. Patients

Blood samples were taken from each patient with cancer before they received ICI treatment. Some patients participated in other studies, and the results have been published[37-39]. Post-treatment samples were obtained at the next visit, or a later visit, in 67 patients. Patients were eligible for the study if they 1) were 18 years of age or older, 2) had a histologically confirmed malignancy, 3) received treatment with ICIs at Seoul National University Hospital, 4) had study samples taken before and/or after ICI treatment, and 5) completed a written consent form for research using human derivatives, which allowed secondary utilization of samples (IRB No. 1104-086-359). A patient was excluded from the study if they had a diagnosis of two or more types of malignancy within the previous 5 years, withdrew consent before or during the study, or not enough samples were stored for analysis. Retrospective clinical and follow-up information was obtained from the medical records. Pre- and post-treatment samples from patients who received molecularly targeted agents were also analyzed in the comparative analysis. Blood sampling and

analyses were performed after the protocol was approved by the Institutional Review Board. All patients provided written informed consent to participate in this study. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 2002-070-110). All study procedures were performed in accordance with the Helsinki Declaration and its later amendments, or comparable ethical standards.

2.2. sPD-L1 ELISA

Serum was obtained by centrifugation (1300xg for 10 min), aliquoted, and stored at -80°C until analysis for the study. sPD-L1 was assayed using a commercially available ELISA Kit (BMS2212, Invitrogen, Vienna, Austria) following the manufacturer's instructions. Samples were analyzed in duplicate for each marker

2.3. Statistical analyses

Demographic and clinical parameters were analyzed using descriptive statistics. The differences in distributions and median values of sPD-L1 in healthy donors or patients with cancer were compared using

non-parametric Mann-Whitney U tests. The mean values were compared using Student's t-test. ROC curve analysis was used to determine optimal cut-off points of sPD-L1 for predicting treatment resistance. Treatment responses in relation to sPD-L1 or clinical variables were analyzed using χ^2-tests and Student's t-tests. Kaplan-Meier survival analysis and Cox proportional hazards models were used to analyze progression-free survival (PFS) and overall survival (OS) times. Correlation analyses of sPD-L1 and blood immune cells were performed by calculating Pearson correlation coefficients because the data met the assumptions of a normal distribution. Because the data for tissue PD-L1 expression did not follow a normal distribution, analysis of correlations with sPD-L1 were performed using the non-parametric Spearman's rho method. Statistical analyses and graphics were performed using IBM SPSS statistics v.21 (IBM, Armonk, NY, USA) and Excel 2019 (Microsoft, Redmond, WA, USA) software. A P value<0.05 was considered statistically significant.

Chapter 3. Results

3.1. Characteristics of patients and samples

A total of 128 patients with stage IV solid tumors were included in this study. Samples were obtained between January 2015 and January 2019. The results for characteristics of the study population are presented in Table 1. The sample interval range was 14 to 49 days in 66 of the 67 patients with available pre- and post-treatment samples; the sample interval was 576 days in the remaining patient (median, 21 days; range, 14–576 days; Table 2). The ORR was 18.8% (among 113 evaluable patients). The median PFS time and OS time were 4.2 months (95% CI, 2.3–6.1 months) and 10.8 months (95% CI, 7.9–13.8 months).

Table 1. Characteristics of patients

	N (%) or median(range)
Total	128 (100)
Age	62 (21-82) years
Sex	
Male	89 (69.5)
Female	39 (30.5)
State of cancer	
Recurrent/metastatic	128 (100)
Relapsed after curative treatment	47 (36.7)
Initially diagnosed with metastasis	81 (63.3)
ECOG PS	
0	27 (21.1)
1	98 (76.6)
2	1 (0.8)
unknown	2 (1.6)

Diagnosis	
NSCLC	50 (39.1)
Melanoma	31 (24.2)
SCLC	14 (10.9)
UCC	13 (10.2)
RCC	6 (4.7)
HNSCC	5 (3.9)
Salivary gland cancer	4 (5.8)
Others	5 (3.9)
Tissue PD-L1 expression	
Negative	22 (17.2)
0%< and < 5%	21 (16.4)
5%≤ and <10%	10 (7.8)
10%≤	15 (11.7)
Insufficient/inappropriate specimen	3 (2.3)
Result not available	57 (44.5)
History of radiotherapy*	
Never irradiated	50 (39.1)
Received radiotherapy	78 (60.9)
Before ICI treatment	57 (73.1)

Definitive/adjuvant	26 (45.6)
Palliative	31 (54.4)
After end of ICI treatment	21 (26.9)
Type of ICI treated †	
Monotherapy	
Nivolumab	41 (32.0)
Pembrolizumab	32 (25.0)
Durvalumab	15 (11.7))
Ipilimumab	5 (3.9)
Atezolizumab	4 (3.1)
Combination therapy	
Pembrolizumab/ other	13 (10.2)
Atezolizumab/ other	13 (10.2)
Nivolumab and ipilimumab	2 (1.6)
Others	3 (2.3)

ECOG PS eastern cooperative oncology group performance status, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *UCC* urothelial carcinoma, *RCC* renal cell carcinoma, *HNSCC* head and neck squamous cell carcinoma, *ICI* immune checkpoint inhibitor

* Encompasses all type of radiotherapy including stereotactic radiosurgery.

† Almost patients received ICI as a clinical trial.

Table 2. Sampling intervals according to major primary cancer types (Total N=67)

Diagnosis	N (%)	Mean ± SD	Median (min−max)	P value*	
NSCLC	17	18 ± 8	15 (14−49)	0.005	<0.001
Melanoma	17	25 ± 10	21 (14−49)		
SCLC	13	38 ± 9	42 (14−48)		
GU cancer	9	20 ± 2	21 (14−21)		
Others	11	−	−		

GU cancer genitourinary carcinoma, includes urothelial carcinoma and renal cell carcinoma

*Mann−Whitney U test, significance at p <0.05.

3.2. Pre-treatment sPD-L1 level and response

The mean level of pre-treatment sPD-L1 was 13.5±12.1 pg/μL; the median level was 11.0 pg/μL (range, 3.2–122.1 pg/μL). The mean sPD-L1 value in the patients with cancer was not significantly different compared with the mean level in healthy volunteers (13.5 pg/μL versus 10.6 pg/μL, respectively; p=0.312, t-test). Numerically, the mean concentration of sPD-L1 was high in cancer patients. However, we have to consider the possibility that there was no statistical significance because of the small number of healthy volunteers (Fig. 1). Then, we checked whether the baseline sPD-L1 level was different for each cancer types. Although the mean and median values appeared different for each cancer type, there was no statistically significant difference (Table 3). In ROC curve analysis, a cut-off value of 11.0 pg/μL distinguished best between patients whose response is progressive disease from responding patients (sensitivity, 65.7%; specificity, 60.3%)(Fig. 2). The area under the curve value was 0.668 (95% confidence interval (CI), 0.568–0.769; p=0.004). We used X^2 tests to compare treatment response according to sPD-L1 level (low versus high). The ORRs were not significantly different (19.0% versus 18.2% in low and high group,

respectively; p=0.573). However, the disease control rates were 79% versus 58% in patients with low and high levels, respectively, of sPD-L1 (p=0.013) (Table 4). A bar chart is presented in Fig. 3 to illustrate relationships between sPD-L1 levels and treatment response.

Figure 1. Comparison of mean value of sPD-L1 in healthy volunteers (n=20) and cancer patients (n=128).

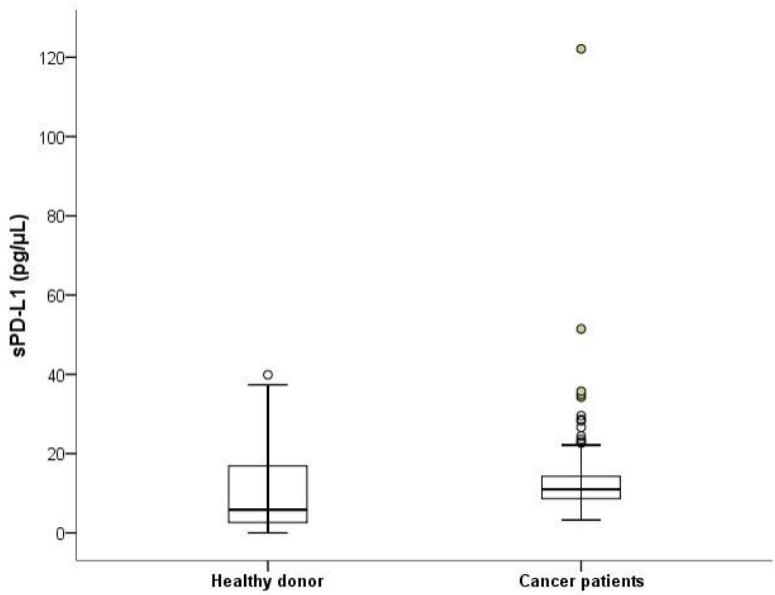


Table 3. The pre-treatment sPD-L1 level according to cancer types.

Diagnosis	N	Mean	P value*		Median	P value†	
NSCLC	50	13.5±8.6	0.155	0.084	11.7(3.6-51.5)		
Melanoma	31	11.1±5.1			9.9(3.2-24.4)	0.102	
SCLC	14	10.2±2.7	0.162		10.4(5.8-16.4)		
UCC	13	22.1±30.6			14.4(6.0-122.1)		
RCC	6	13.6±7.9			10.9(8.4-29.6)		
Others	14	-			-		

* Student's t-test, significance at p <0.05.

† Mann-Whitney U test, significance at p <0.05.

Figure 2. Receiver operating characteristic (ROC) curve to determine optimal cut-off level of sPD-L1 in prediction of progressive disease after immune checkpoint inhibitor treatment.

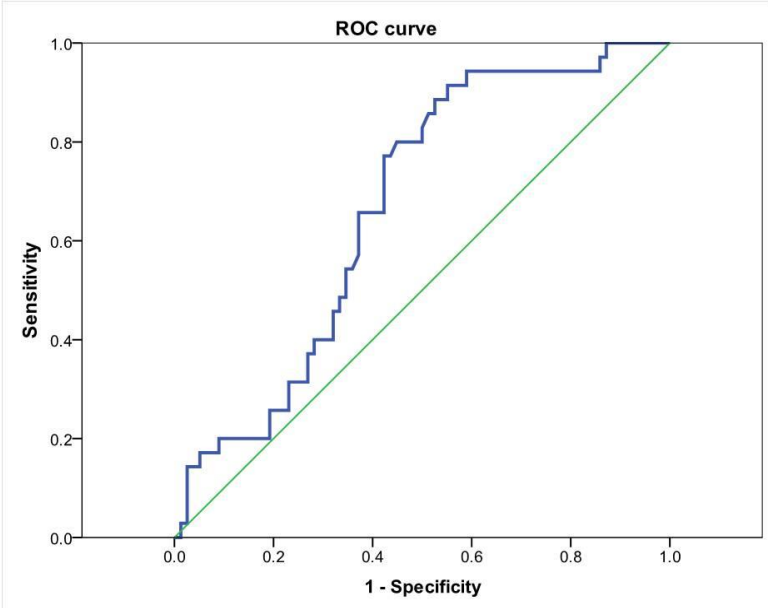


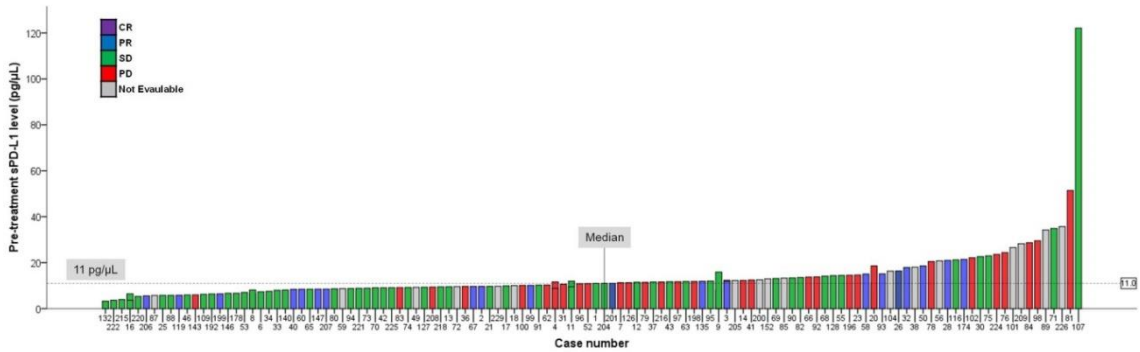
Table 4. Response according to level of pre-treatment sPD-L1. Response was evaluated in 113 patients. Results are presented as numbers (%).

	ICI response			
	CR, PR, SD	PD	Total	P value*
Low sPD-L1	46 (79)	12 (21)	58 (100)	
High sPD-L1	32 (58)	23 (42)	55 (100)	0.013
Total	78	35	113	

sPD-L1 soluble programmed death ligand-1, *ICI* immune checkpoint inhibitor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* Significance at $p < 0.05$, by X^2 test.

Figure 3. In this figure, the red bars (mean PD) are more frequently seen in the right side of the chart where cases with higher sPD-L1 level was depicted than the left side.



3.3. Pre-treatment sPD-L1 level and prognosis

PFS time was different between patients with low versus high levels of sPD-L1. The median PFS time was 6.3 months (95% CI, 3.0–9.6 months) versus 2.9 months (95% CI, 2.1–3.7 months), and the difference was statistically significant (p=0.023, log-rank test; Fig. 4a). The OS times were also significantly different according to sPD-L1 level. The median OS times were 13.3 months (95% CI, 9.2–17.4 months) versus 7.4 months (95% CI, 6.3–8.5 months) (p=0.005, log-rank test; Fig. 4b). Univariate and multivariate analyses were performed to investigate associations of sPD-L1 levels and clinical factors with PFS and OS (Table 5). The results of the univariate analysis indicated that performance status, tissue PD-L1 expression, neutrophil to lymphocyte ratio (NLR), serum albumin level, and sPD-L1 level were significant variables predicting PFS. Performance status, NLR, platelet count, serum albumin level, serum total protein level, and sPD-L1 level were significant variables predicting OS. The PFS and OS of patients who received radiation before ICI were not statistically significant with those not received radiation before ICI. Factors with p-values<0.05 were included in the multivariate analysis. The multivariate analysis found that tissue PD-L1

expression, and sPD-L1 level were significant factors for PFS. NLR, serum total protein level, and sPD-L1 level were significant factors for OS (Table 5).

Figure 4. Kaplan–Meier curves for progression–free survival (a) and overall survival (b) stratified by soluble programmed death ligand 1 level. *PFS* progression–free survival, *OS* overall survival.

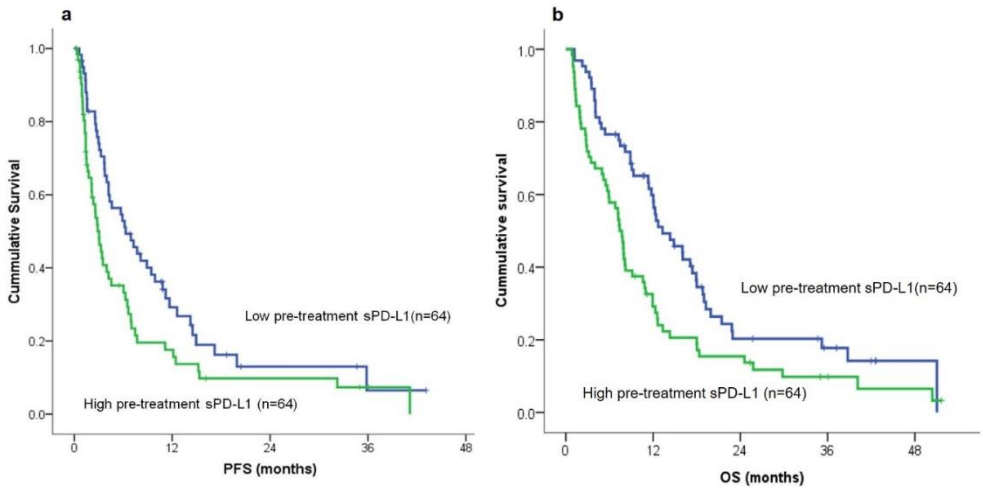


Table 5. Univariate and multivariate analysis of PFS and OS, by prognostic variable*

		PFS				OS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	N=128	Median (95% CI) (months)	*P* value	Exp(B) (95% CI)	*P* value	Median (95% CI) (months)	*P* value	Exp(B) (95% CI)	*P* value
Age (years)						8.2 (5.4−11.0)			
< 65	78	3.4 (2.4−4.4)	0.191			14.9 (10.5−	0.387		
≥ 65	50	7.3 (5.8−8.7)				19.2)			
Sex									
M	89	3.7 (2.4−5.0)	0.163			9.1 (6.0−12.3)	0.122		
F	39	6.3 (2.4−10.2)				12.1 (9.1−15.1)			
ECOG PS				1.223				1.402	
0	28	7.7 (0.8−14.6)	0.012	(0.560−	0.614	12.7 (0−27.3)	0.036	(0.852−	0.184

1	100	4.0 (3.1−4.8)		2.671)		10.6 (7.2−14.0)		2.308)	
Radiation therapy									
Prior to ICI	57	3.7 (2.2−5.2)	0.056			8.1 (3.4−12.9)	0.058		
After ICI or never irradiated	71	6.2 (3.3−9.0)				12.3 (8.1−15.9)			
Tissue PD−L1 IHC									
Negative, weak	43	3.0 (2.4−3.7)	0.021	2.232 (1.119−4.453)	0.023	8.2 (3.4−13.0)	0.841		
Moderate/strong	25	6.9 (5.8−8.1)				12.6 (6.0−19.1)			
Unknown	60	−				−			
NLR				1.055				1.913	
< 2.8	62	5.7 (3.8−7.6)	0.042	(0.531−	0.878	14.3 (9.5−19.2)	<0.001	(1.242−	0.003
≥ 2.8	66	3.3 (1.8−4.7)		2.099)		7.2 (4.2−10.1)		2.946)	
Platelet count								1.474	
< 250k	67	6.3 (3.4−9.2)	0.065			12.4 (10.4−	0.016	(0.990−	0.056

≥ 250k	61	3.3 (2.0−4.6)				14.4)		2.195)	
						7.7 (6.7−8.7)			
Serum albumin (g/dL)				1.788				1.083	
< 4.0	70	2.8 (2.1−3.5)	0.047	(0.908−	0.093	6.8 (4.3−9.3)	0.006	(0.690−	0.729
≥ 4.0	58	6.9 (5.5−8.4)		3.521)		14.3 (9.9−18.8)		1.700)	
Serum total protein (g/dL)								1.766	
< 7.2	65	3.4 (2.5−4.3)	0.078			8.0 (6.5−9.4)	0.009	(1.148−	0.010
≥ 7.2	63	6.2 (2.7−9.7)				12.7 (9.6−15.8)		2.719)	
Glucose (mg/dL)									
< 126	85	3.7 (2.5−4.8)				11.0 (7.2−14.8)			
≥ 126	41	6.5 (3.3−9.7)	0.124			12.3 (8.1−16.5)	0.808		
Unknown	2	−				−			

sPD-L1 level (pg/μL)				1.928				1.788	
< 11	64	6.3 (3.0-9.6)	0.023	(1.038-3.581)	0.038	13.3 (9.2-17.4)	0.005	(1.207-2.650)	0.004
≥ 11	64	2.9 (2.1-3.7)				7.4 (6.3-8.5)			

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *ECOG PS* eastern cooperative oncology group performance status, *PD-L1* programmed death ligand-1, *IHC* immunohistochemical stain, *NLR* neutrophil to lymphocyte ratio, *sPD-L1* soluble programmed death ligand-1

* Significant when p value is less than 0.05. Variable with p <0.05 were examined in the multivariate analyses.

3.4. Change in sPD-L1 level after treatment

We analyzed the patterns of change in sPD-L1 concentrations in 67 patients with pre- and post-treatment samples. The sPD-L1 level generally increased following ICI administration during the 2- to 7-week period from the start of treatment. However, the changes in sPD-L1 concentration (ΔsPD-L1) varied (Fig. 5a), and the patterns of change were somewhat different for each cancer type (Fig. 5b-5e). A sharp increase was apparent in some patients with NSCLC or genitourinary cancer (Fig. 5b, 5e). However, with one exception, the amplitude of change was negligible in most patients with SCLC and melanoma (Fig. 5c, 5d). For comparison, we analyzed ΔsPD-L1 between pre- and post-treatment samples of patients with NSCLC who were treated with tyrosine kinase inhibitors. The results indicated that the pattern of change of patients with NSCLC who were treated with tyrosine kinase inhibitors was very similar to that of the patients with SCLC (Fig. 5f). Interestingly, the pattern of change was quite different among the 'immunogenic' tumor types like melanoma, NSCLC, and genitourinary tumors. Possible explanations for these different patterns include different sources of sPD-L1 or differences in biology associated with each carcinoma. Differences in sampling intervals might also have affected these patterns; the median

sampling interval for the patients with NSCLC was significantly shorter than the intervals used for the patients with melanoma or SCLC (Table 2). Therefore, we examined the effect of the sampling interval on post-treatment sPD-L1 level (Fig. 6). In this analysis, the linear regression model was statistically significant (p=0.018) but the explanatory power of this regression model was found to be only about 8.5% (R^2=0.085, Fig.6). This result suggested that the sampling interval and the post-treatment sPD-L1 level are inversely related in some cases, but not in most cases.

Figure 5. Change in sPD-L1 level before and after treatment, according to cancer type and treatment type in all patients (a), NSCLC (b), SCLC (c), melanoma (d), GU cancer (e), and NSCLC treated with TKIs (f). Median time points for post-ICI sampling are 15 days for NSCLC, 21 days for melanoma and GU cancer, and 42 days for SCLC. *Pre-ICI* before administration of immune checkpoint inhibitor, *Post-ICI* after administration of immune checkpoint inhibitor, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *GU* genitourinary, *TKI* tyrosine kinase inhibitor.

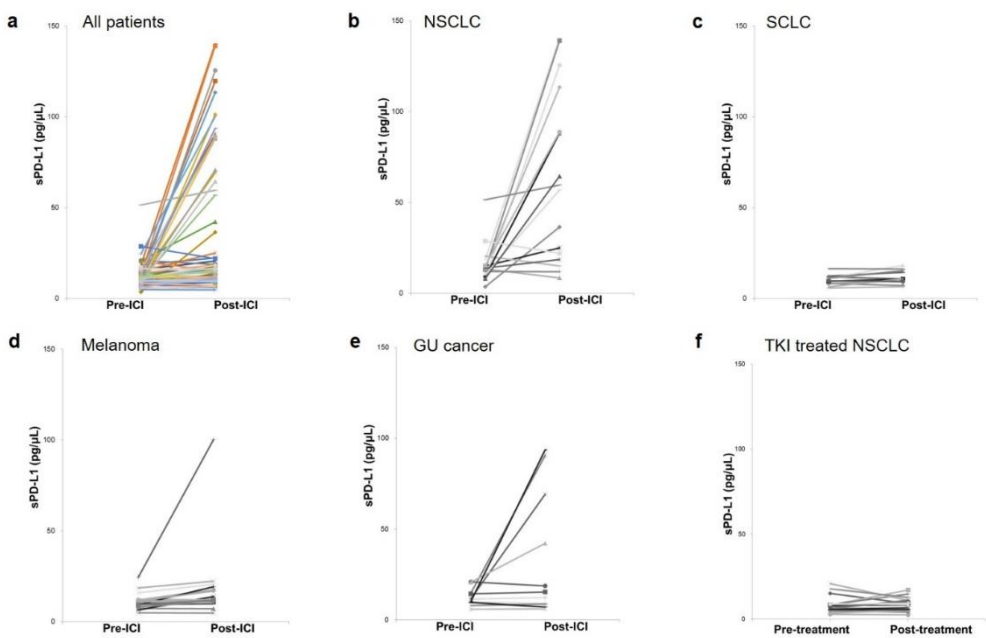
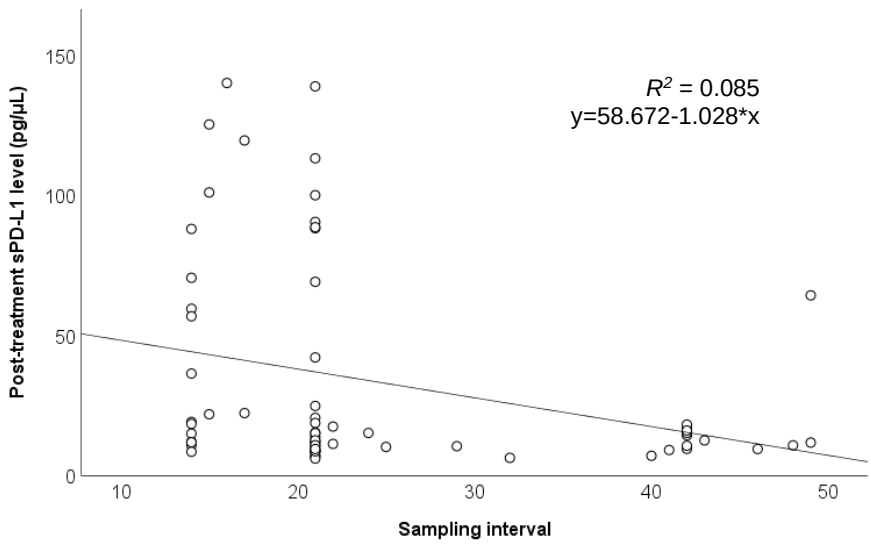


Figure 6. Simple linear regression model to test the effect of the sampling interval on post-treatment sPD-L1 level. This regression model was statistically significant (p=0.018) with low explanatory power (R^2=0.085). One outlier was excluded in this model.



3.5. Change in sPD-L1 levels and response, or prognosis

The analyses to examine relationships between ΔsPD-L1 and treatment response did not reveal correlation (Fig. 7 and Table 6). Again, there were no significant differences in PFS according to ΔsPD-L1. However, in the patients with NSCLC, those with sPD-L1 levels that increased by more than 100% after ICI treatment had longer PFS times than those without this increase (Fig. 8a); the median PFS times were 6.3 months (95% CI, 0.0–19.4 months) versus 1.2 months (95% CI, 0.6–1.8 months), respectively ($p=0.029$, log-rank test). The opposite occurred in patients with melanoma. The median PFS times were 0.9 months (95% CI not available) versus 5.7 months (95% CI, 3.8–7.6 months) in patients with a ΔsPD-L1 of 100% or more versus those with ΔsPD-L1 less than 100% after ICI treatment ($p<0.001$, log-rank test; Fig. 8b). The OS response was in the same direction as PFS. But it was not statistically significant in patients with melanoma. In patients with NSCLC, the median OS was 14.3 months (95% CI, 0.0–30.8 months) versus 5.7 months (95% CI, 0.0–11.4 months) in those with sPD-L1 levels that increased by 100% or more after ICI treatment versus those without that change, respectively ($p=0.022$, log-rank test; Fig. 8c). The

median OS times were 3.9 months (95% CI, 2.1–5.7 months) versus 11.4 months (95% CI, 10.6–12.2 months), respectively (p=0.827, log−rank test), in patients with melanoma (Fig. 8d).

Figure 7. Change of sPD-L1 level before treatment to after treatment according to treatment response. *CR/PR* complete response and partial response, *SD* stable disease, *PD* progressive disease.

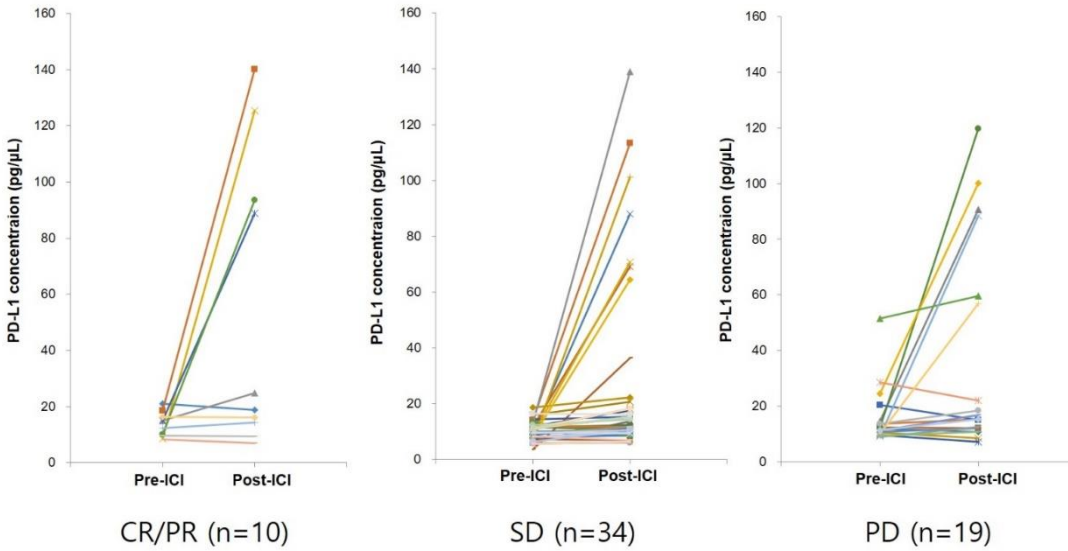
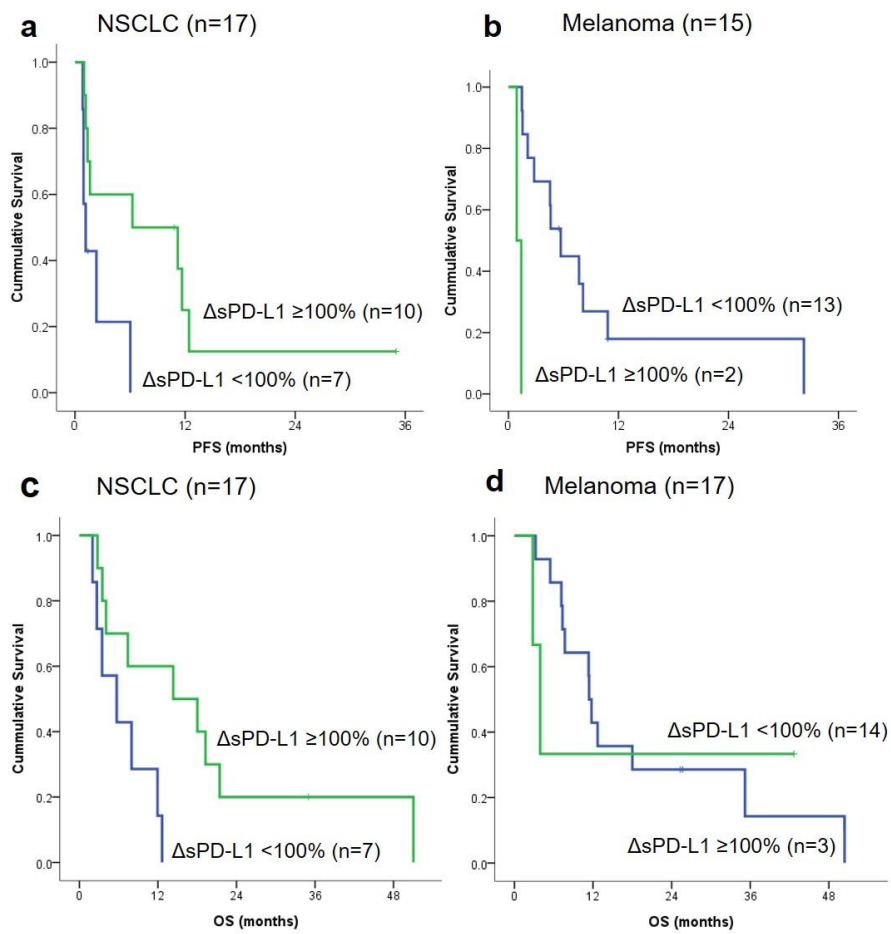


Table 6. The change in the concentration of sPD-L1 (⊿sPD-L1) and ICI response

	ICI response		Total	*P* value*
	CR, PR, SD	PD		
⊿sPD-L1< 0	11 (65)	6 (35)	17 (100)	0.758
⊿sPD-L1≥ 0	33 (72)	13 (28)	46 (100)	
Total	44	19	63*	

*Four patients' response was not available. Significance at $p < 0.05$.

Figure 8. Kaplan–Meier curves for progression–free survival and overall survival in patients with NSCLC (a, c) and patients with melanoma (b, d) stratified by soluble programmed death ligand 1 level. *NSCLC* non–small cell lung cancer, *⊿sPD–L1* change in the concentration of sPD–L1 from pre–treatment to post–treatment sample, *PFS* progression–free survival, *OS* overall survival.



3.6. Correlations between sPD-L1 level and tissue PD-L1 expression or blood immune cells

Because we hypothesized that sPD-L1 level reflects the level of PD-L1 expression of tumor tissue, we examined the correlation between tissue PD-L1 expression and sPD-L1 levels. The correlation analysis Spearman's rho value of 0.069 (p=0.575) suggested that these two factors were not correlated. The mean values for sPD-L1 level in the group with negative or low PD-L1 expression versus moderate or high expression were also not significantly different (12.0±1.0 pg/μL versus 12.9±1.2 pg/μL, respectively; p=0.649, t-test). We also examined the correlation between sPD-L1 levels and PD-L1 expression of stromal cell in the tumor tissue. The result of stromal PD-L1 immunostaining was available in 22 patients. In the correlation analysis, Spearman's rho value of -0.081 (p=0.720) suggested that sPD-L1 and stromal PD-L1 immunoreactivity have no correlation. Similarly, the mean values for sPD-L1 level in the group with less than 5% of stromal PD-L1 immunostaining (n=8) versus 5% or more stromal immunostaining (n=14) were also not significantly different (9.3±3.6 pg/μL versus 12.1±7.3 pg/μL, respectively; p=0.157, t-test). Because there was no correlation between sPD-L1 level and tissue PD-L1 expression,

we examined the correlations between sPD-L1 level and NLR or circulating blood immune cell counts (Table 7 and Fig. 9). NLR and white blood cell count, and absolute neutrophil count (ANC), were positively correlated with sPD-L1 level (Fig. 9a-c). Lymphocyte proportion and absolute lymphocyte count was negatively correlated with sPD-L1 level (Fig. 9e, f). These findings suggested that sPD-L1 have association with neutrophils rather than tumor cells or lymphocytes.

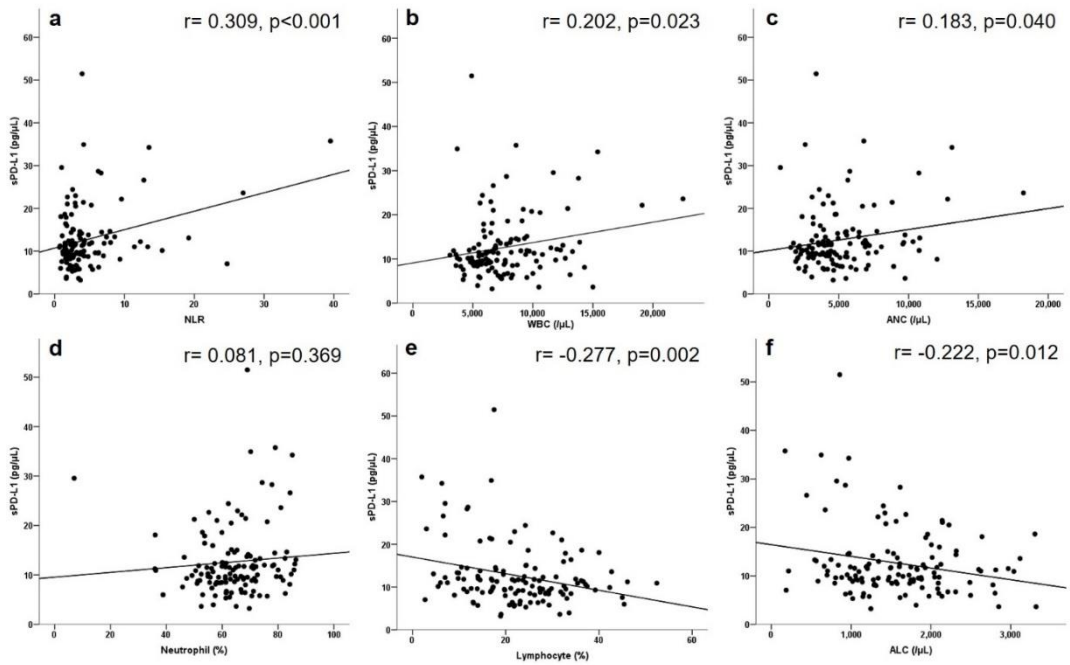
Table 7. Analysis of correlations between sPD-L1 and blood immune cells (n=126). Two outliers with extremely high sPD-L1 levels or absolute neutrophil counts were excluded from these analyses.

	Pearson's correlation coefficient	*P* value*
NLR	0.309	<0.001
WBC	0.202	0.023
ANC	0.183	0.040
Neutrophil	0.081	0.369
Lymphocyte	−0.277	0.002
ALC	−0.222	0.012

sPD-L1 soluble programmed death ligand-1, *NLR* neutrophil to lymphocyte ratio, *WBC* white blood cell count, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count

*Significance at $p < 0.05$.

Figure 9. Correlation analyses between sPD-L1 level and blood immune cells, such as NLR (a), WBCs (b), ANCs (c), neutrophils (d), lymphocytes (e), ALCs (f). Pearson's correlation coefficients are denoted as r. *NLR* neutrophil to lymphocyte ratio, *WBC* white blood cell, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count.



Chapter 4. Discussion

The results of this study suggested that pre-treatment serum sPD-L1 concentrations can be used to predict treatment response, PFS, and OS in patients receiving ICI treatment for advanced solid tumors. We found that a high baseline sPD-L1 level predicted a low disease control rate. Pre-treatment sPD-L1 level was an independent prognostic factor predicting PFS and OS, even after controlling for known prognostic variables. Many studies of sPD-L1 have been published in recent years. Most found that high levels of pre-treatment sPD-L1 are associated with shorter survival times in patients with advanced solid tumors (e.g., lung cancer, gastric cancer, renal cell carcinoma, melanoma, hepatocellular carcinoma, pancreatic cancer, and soft tissue sarcoma)[33,40-48]. High pre-treatment sPD-L1 levels are also associated with a poor response in patients with melanoma or lung cancer who receive ICI treatment [48,49].

Therefore, it has been generally accepted that high levels of pre-treatment sPD-L1 seem to be associated with a poor treatment response and a worse prognosis. The results of this study are consistent with those of previous studies in that pre-treatment sPD-L1 levels had predictive and prognostic value for patients with advanced cancer.

We also investigated whether change of sPD-L1 level after ICI treatment is associated with response or prognosis. We were not able to acquire the sample sizes required to find correlations between extent of sPD-L1 change and tumor response or PFS, before and after treatment. Because each tumor type had very different patterns of change in sPD-L1 levels, the effects of changes in sPD-L1 on PFS likely were diluted. This possibility was supported by finding the opposite pattern when each cancer type (melanoma and NSCLC) was analyzed separately. Few studies have examined relationships between sPD-L1 dynamics and prognosis in patients receiving radiation or chemoradiation, and results have been inconsistent. Increased sPD-L1 levels after chemoradiation are associated with a poor prognosis in patients with rectal cancer[50]. In contrast, preliminary results indicate that in patients with biliary tract cancer, increased sPD-L1 levels after chemotherapy are associated with longer PFS times[51]. In patients with advanced pancreatic cancer receiving cytotoxic chemotherapy, sPD-L1 dynamics correlate with disease course[43]. Several studies of patients receiving ICI treatment and the dynamics of sPD-L1 changes over time have been performed. One study of patients receiving ipilimumab-based treatment for advanced melanoma found that many who had a ≥1.5-fold increase in sPD-L1 within 4.5 months after treatment experienced

progressive disease[49]. A study analyzed PD-L1 mRNA expression in plasma-derived exosomes in melanoma and NSCLC patients at the baseline and 2 months later after PD-1 inhibitor. They showed that exosomal mRNA copies of PD-L1 were correlated with tumor response in melanoma (n=18) and NSCLC (n=8) patients[52]. Another study of 21 patients with lung, gastric, or bladder cancer who underwent anti-PD-1 therapy found that a reduction in plasma sPD-L1 level is significantly correlated with tumor size reduction[53]. Significance of sPD-L1 of in our NSCLC population was inconsistent with other studies. It seems too early to draw conclusions, as the sample size of all previously published studies were very small.

The association of the level of PD-L1 expression of tumor tissue and circulating sPD-L1 level was also examined. PD-L1 expression of tumor tissue did not correlate with sPD-L1 level. This was an unexpected finding, as we expected the levels of sPD-L1 to reflect the expression of tissue PD-L1. Therefore, we explored the correlation of sPD-L1 and blood immune cells, as a possible source of sPD-L1. The sPD-L1 level was positively correlated with NLR and negatively correlated with lymphocyte count. The results of previous studies suggest that sPD-L1 originates mainly from a membrane-bound form of PD-L1 present in cancer cells or immune cells[41,47,54]. The results of our study suggested that sPD-L1 was

correlated to cells identified as neutrophils in routine complete blood count tests. Additionally, in previous study which analyzed peripheral immune cells of 28 cancer patients, 5 to 35% of peripheral blood myeloid derived suppressor cells (MDSC) express PD-L1. Expression of PD-L1 is highest in granulocytic MDSC (35.8%), whereas T cells and majority of NK cells express PD-L1 in less than 1% and B cells express in 11%[55]. Therefore, we can carefully assume the relationship of sPD-L1 with granulocytic MDSC. One recent study added same finding with ours; the plasma sPD-L1 level was associated with inflammatory cells such as absolute monocyte count, and absolute neutrophil count in recurrent/metastatic breast cancer patients[56]. However, another study showed that sPD-L1 are cleaved from tumor cell membrane and shed to culture supernatant[57]. Thus, information is limited so far. The main source of sPD-L1 should be explained in the further study.

The biological function of sPD-L1 is known as to cause immune suppression by regulating T cell function, similar to the membrane-bound form[56,57]. In vitro renal cell carcinoma model, sPD-L1 which was shed from tumor cells induces CD8+ T cell death and inhibits anti-tumor immunity[57]. Tumor-derived sPD-L1 competes with PD-(L)1 inhibitors for effect on CD8+ T cells. Moreover, they also reported that reduced tumor site PD-L1 protein-to-mRNA ratios

predict poor outcomes in multiple cancers. This may explain the discordance between PD-L1 immunohistochemistry and PD-(L)1 inhibitor response.

This study had some limitations. The study population was heterogeneous in cancer type, blood sampling times, the timing of ICI administration, and in subsequent treatment after use of ICIs. This heterogeneity might have reduced the power to detect effects of various characteristics for individual types of cancer. There were also no reference levels for sPD-L1, and the results between assays kits seemed to be quite different. There are also no cut-off levels available that predict response or prognosis. To overcome this problem, some researchers are investigating reproducible, standardizable methods that can be used instead of ELISA[54].

In summary, high pre-treatment sPD-L1 levels were associated with low disease control rates. sPD-L1 level was an independent prognostic factor predicting PFS and OS in patients receiving ICI treatment for advanced cancer. sPD-L1 was likely derived from neutrophils in peripheral blood, and levels generally increased following ICI administration. The amplitude of sPD-L1 change after ICI treatment was associated with PFS in patients with NSCLC and melanoma, but in the opposite direction for the two cancer types. The significance of changes in sPD-L1 levels for each carcinoma should

be revealed in a larger, future study.

Chapter 5. Conclusions

In advanced cancer patients, high pre-treatment sPD-L1 levels were associated with low disease control rates. sPD-L1 level was an independent prognostic factor predicting PFS and OS in patients receiving ICI treatment. The sPD-L1 correlated with neutrophil to lymphocyte ratio, and levels generally increased following ICI administration. The amplitude of sPD-L1 change after ICI treatment was associated with PFS in patients with NSCLC and melanoma, but in the opposite direction for the two cancer types. The significance of changes in sPD-L1 levels for each carcinoma should be revealed in a larger, future study.

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Abstract

국문 초록

암 환자의 혈청에서 programmed death-1 ligand (sPD-L1)이 발견되며, 측정 가능하다는 사실이 알려졌다. 이 연구는 면역관문억제제 치료를 받는 진행성 암환자에서 sPD-L1의 의미와 중요성에 대해 알아보기 위해 계획되었다. 연구 대상 환자는 2015년 1월부터 2019년 1월까지 치료 전 후 연구용 채혈에 동의한 128명이다. 치료 전 sPD-L1이 높은 경우(> 11.0pg/μL)에 낮은 경우보다 면역관문억제제 치료 후 질병이 진행할 가능성이 더 높았다(41.8 % 대 20.7 %, p = 0.013). 치료 전 sPD-L1이 높은 경우 예후도 더 불량하여, 중앙 무진행생존기간(PFS)은 2.9 (95 % [CI], 2.1-3.7)개월 대 6.3 (95 % CI, 3.0-9.6)개월(p = 0.023); 전체생존기간(OS) 중앙값은 7.4 (95 % CI, 6.3-8.5)개월 대 13.3 (95 % CI, 9.2-17.4)개월(p = 0.005)이었다. 다변량 분석에서, 높은 sPD-L1 농도는 PFS (HR, 1.928; p = 0.038) 및 OS (HR, 1.788; p = 0.004)에 대해 불량한 독립적 예후 인자였다. sPD-L1 농도는 조직의 PD-L1 발현과 관련은 없었다. 그러나 sPD-L1 농도는 호중구 대 림프구 비율과 양의 상관 관계가 있었고 림프구 분율 또는 절대림프구수와 음의 상관 관계가 있었다. 이 연구에서, 높은 치료 전 sPD-L1 수치가 질병 진행과 관련이 있으며 PFS 및 OS를 예측하는 독립적인 예후 인자였다.

주요어: soluble programmed death−1 ligand, programmed death−1 ligand, 면역관문억제제, 면역항암제, 암

학번: 2008−30569