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ORIGINAL ARTICLE

Clinical outcomes and predictive value of programmed cell death-ligand 1 expression in response to anti-programmed cell death 1/ligand 1 antibodies in non-small cell lung cancer patients with performance status 2 or greater

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Abstract

Background Anti-programmed cell death protein-1/ligand-1 (anti-PD-1/PD-L1) therapy is promising for patients with non-small-cell lung cancer (NSCLC); however, clinical trials have focused on patients with a performance status (PS) 0 or 1. This study aimed to evaluate the clinical outcomes and correlation between PD-L1 expression status and tumor response to anti-PD-1/PD-L1 therapy among NSCLC patients with poor PS (i.e., PS ≥ 2).

Methods In total, 130 patients with NSCLC and PS ≥ 2 treated with anti-PD-1/PD-L1 monotherapy at 12 institutions between January 2016 and August 2019 were retrospectively reviewed. PD-L1 expression status was divided into four groups: < 1%, 1–49%, ≥ 50%, and unknown.

Results The objective response rate and PS improvement rate were 23 and 21% and were higher in the PD-L1 ≥ 50% group than in other groups ($P < 0.01$). Median progression-free survival (PFS) was 62 days and was longer in the PD-L1 ≥ 50% group than in other groups ($P = 0.03$). Multivariate analyses revealed that PD-L1 expression is significantly associated with prolonged PFS (PD-L1 < 1%; reference; 1–49%, hazard ratio [HR] 0.19, 95% confidence interval [CI] 0.04–0.99, $P = 0.05$; ≥ 50%, HR 0.12, 95% CI 0.02–0.71, $P = 0.02$; unknown, HR 0.30, 95% CI 0.08–1.22, $P = 0.09$).

Conclusions NSCLC patients with poor PS and PD-L1 ≥ 50% are expected to benefit from anti-PD-1/PD-L1 therapy, despite a modest overall response among NSCLC patients with poor PS. Accordingly, PD-L1 expression provides useful information regarding decision-making for anti-PD-1/PD-L1 therapy even in these populations.

Keywords Non-small cell lung cancer · Performance status · Anti-programmed cell death protein-1/ligand-1 therapy · Programmed cell death-ligand 1 expression

Introduction

Immune checkpoint blockade targeting programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) has drastically altered the therapeutic landscape of advanced non-small-cell lung cancer (NSCLC) [1]. A phase III study of anti-PD-1 or PD-L1 antibody monotherapy, including nivolumab, pembrolizumab, or atezolizumab, among NSCLC patients reported a prolonged overall survival compared with that for docetaxel as second-line treatment [2–5]. In a randomized phase III clinical trial, survival was significantly longer for patients with PD-L1-positive NSCLC treated with first-line pembrolizumab monotherapy than with platinum-based chemotherapy [6, 7]. However, these clinical trials involved patients with NSCLC and a performance status (PS) of 0 or 1 and excluded those with a poor PS ≥ 2, as defined by the Eastern Cooperative Oncology Group (ECOG) scale. Therefore, the anti-tumor effectiveness and

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tolerability of anti-PD-1/PD-L1 antibodies among NSCLC patients with poor PS remain unclear.

Approximately 30–40% of advanced NSCLC patients have a poor PS ≥ 2 on the ECOG scale, based on disease burden, comorbidities, or both [8]. NSCLC patients with poor PS are generally intolerant to chemotherapy and are advised high-quality supportive care, except for some patients classified as PS 2, being potential candidates for chemotherapy [8]. Monotherapy with an anti-PD-1/PD-L1 antibody has a lower risk of treatment-related symptoms and hematologic toxicity and is better tolerated than cytotoxic chemotherapy despite a risk of immune-related adverse events [9]. Therefore, physicians occasionally administer anti-PD-1/PD-L1 therapy to NSCLC patients with a poor overall clinical condition.

The PD-L1 expression status of tumor cells, as evaluated via immunohistochemistry, is a potential predictor of the response to anti-PD-1/PD-L1 antibody therapy and is frequently evaluated on the basis of a three cut-point system in routine clinical practice: PD-L1 expression status < 1, 1–49, and ≥ 50% [10]. Since patients with poor PS experience cancer-related symptoms and have a shorter survival, strict patient selection based on predictive biomarkers is essential among them [8, 11]. Clarification of clinical outcomes based on PD-L1 expression among NSCLC patients with poor PS, treated with anti-PD-1/PD-L1 therapy, could facilitate clinical decision-making by physicians.

In this study, we retrospectively investigated the antitumor effectiveness and tolerability of anti-PD-1/PD-L1 antibodies among patients with NSCLC and PS ≥ 2. Moreover, based on clinical outcomes, we evaluated the value of PD-L1 expression for identifying patients with poor PS potentially benefiting from this therapeutic approach.

Patients and methods

Patients

NSCLC patients with PS ≥ 2, receiving anti-PD-1/PD-L1 antibody monotherapy between January 2016 and August 2019 at the Kumamoto University Hospital and 11 general hospitals in Kumamoto or Miyazaki (Miyazaki Higashi Hospital, Kumamoto Regional Medical Center, Saiseikai Kumamoto Hospital, Japanese Red Cross Kumamoto Hospital, Kumamoto Chuo Hospital, Miyazaki Prefectural Nobeoka Hospital, Tamana Central Hospital, Omuta Tenryo Hospital, Kumamoto Rosai Hospital, Kumamoto Saishun Medical Center, and Minamata City General Hospital & Medical Center) were included herein. Nivolumab, pembrolizumab, or atezolizumab were administered as the anti-PD/PD-L1 antibody. We recorded the following data upon initiation of anti-PD-1/PD-L1 monotherapy: age, sex, ECOG PS, smoking, histology, epidermal growth factor receptor (*EGFR*) mutations/anaplastic lymphoma kinase (ALK) status, PD-L1 expression, stage at diagnosis, treatment, and adverse events. PD-L1 expression was evaluated via the PD-L1 Immunohistochemistry 22C3 pharmDx assay by SRL, Inc. (Tokyo, Japan), BML, Inc. (Tokyo, Japan), and LSI Medience Corporation (Tokyo, Japan). PD-L1 expression was assessed in tumor cells and divided into four groups: < 1%, 1–49%, ≥ 50%, and unknown. This study was approved and registered as IRB number 1750 by our institutional review board.

Clinical assessment and outcome parameter

The highest PS status during anti-PD-1/PD-L1 therapy was defined as the best PS. The time to PS improvement was defined as the time from initial administration of anti-PD-1/PD-L1 monotherapy to the date of the first documented improvement to the best PS. The best tumor response during treatment of anti-PD-1/PD-L1 antibody was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST ver1.1). The time to response (TTR) was defined as the time from initial administration of anti-PD-1/PD-L1 monotherapy to the confirmation of a response. Progression-free survival (PFS) was defined as the time from the initial administration of anti-PD-1/PD-L1 monotherapy to disease progression, based on assessments of RECIST ver. 1.1, death of any cause, or censoring date of last follow-up. Overall survival (OS) was defined as the time from the initial administration of anti-PD-1/PD-L1 monotherapy to death of any cause or censoring date of last follow-up. The worst adverse events during the treatment course were estimated using the Common Terminology Criteria for Adverse Events version 4.0.

Statistical analyses

The chi-squared test or Fisher's exact test was used to compare clinical factors between categorical variables. Estimated PFS or OS were analyzed using the Kaplan–Meier method and compared among groups, using the log-rank test. A cumulative incidence analysis (Gray's test) was performed to verify whether PD-L1 expression influences PS considering cancer-specific deaths as competing risks. Stratified Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for each PD-L1 expression category. Variables (age [< 70/ ≥ 70 years], sex, smoking history, histology [squamous/non-squamous], stage at diagnosis [advanced/postoperative recurrence], driver mutation status, treatment line [1st/2nd/3rd line or later], brain metastasis status, liver metastasis status, history of radiotherapy) that violated the proportional hazards assumption were used as stratification

factors. Statistical analyses were conducted using JMP (version 10; SAS, Cary, NC, USA), SPSS (version 23.0; IBM, Armonk, NY, USA), and R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered significant.

Results

Patient characteristics

Between January 2016 and August 2019, 130 NSCLC patients with PS ≥ 2, receiving nivolumab, pembrolizumab, or atezolizumab, were recruited from 12 institutions. The patient characteristics at the start of anti-PD-1/ PD-L1 monotherapy are summarized in Table 1. The median age at the initial anti-PD-1/PD-L1 monotherapy was 68 years. Among 130 patients, 93 (72%) were male, 104 (77%) were smokers, 90 (69%) had non-squamous type, 105 (81%) were at an advanced stage at diagnosis, 17 (13%) had liver metastasis, 25 (19%) had brain metastasis, 56 (43%) had history of radiotherapy, and 94 (72%) were classified as PS 2. *EGFR* mutations and *ALK* fusions were detected in 17 (13%) and two patients (2%), respectively. Among 91 patients (70%) examined through immunohistochemical analysis for PD-L1, 17 (13%), 20 (15%), and 54 patients (42%) were classified as PD-L1 < 1, 1–49, and ≥ 50%, respectively. Nivolumab, pembrolizumab, and atezolizumab were administered to 59 (45%), 60 (46%), and 11 patients (8%), respectively. Anti-PD-1/PD-L1 therapy was administered as first-line treatment to 34 patients (26%), as second-line treatment to 45 patients (35%), and as third-line treatment to 51 patients (39%).

Treatment responses

The objective response rate (ORR) and median TTR were 23% (95% CI 17–31%) and 50 days (95% CI 43–73 days), respectively, for all patients (Table 2). The ORR for the PD-L1 ≥ 50% group was higher than those of the PD-L1 < 1%, 1–49%, and unknown groups (37, 18, 0, 18%, respectively, $P < 0.01$). The median TTRs for the PD-L1 < 1%, 1–49%, ≥ 50%, and unknown groups were 49 days, not available (owing to a lack of responders), 51, and 50 days, respectively ($P = 0.84$).

Improvement of PS

PS improved in 27 patients (21%). The rate of PS improvement in the PD-L1 ≥ 50% group was higher than that in the PD-L1 < 1%, 1–49%, and unknown groups (37, 12, 0, 13%, respectively, $P < 0.01$, Fig. 1a, supplementary Table 1). The time to PS improvement was 44 days (95% CI 42–78 days). The times to the improvement of the

Table 1 Patient characteristics

	N = 130	%
Age, years		
Median (range)	68 (41–91)	
Sex		
Male	93	72
Female	37	28
PS		
2	94	72
3	31	24
4	5	4
Smoking		
Yes	104	77
No	26	21
Histology		
Sq	40	31
Non-sq	90	69
EGFR		
Wild type	82	63
Mutant	17	13
Unknown	31	24
ALK		
Positive	2	2
Negative	81	62
Unknown	46	36
Stage at diagnosis		
Advanced	105	81
Postoperative recurrence	25	19
Liver metastasis		
Present	17	13
Absent	113	87
Brain metastasis		
Present	25	19
Absent	105	81
History of radiotherapy		
Yes	56	43
No	74	57
PD-L1 expression		
< 1%	17	13
1–49%	20	15
≥ 50%	54	42
Unknown	39	30
Treatment line		
1st line	34	26
2nd line	45	35
3rd line or later	51	39
Pre-treatment regimen		
Platinum chemotherapy	77	59
Other cytotoxic chemotherapy	39	30
EGFR–TKI	17	13
ALK–TKI	2	2

Table 1 (continued)

	N = 130	%
Anti-PD1/PD-L1 antibody		
Nivolumab	59	45
Pembrolizumab	60	46
Atezolizumab	11	8

PS Eastern Cooperative Oncology Group Performance Status, *Sq* squamous cell carcinoma, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *TKI* tyrosine kinase inhibitor, *PD-L1* programmed death ligand 1, *PD-1*pProgrammed death 1

best PS in the PD-L1 < 1%, 1–49%, ≥ 50%, and unknown groups were 68 days (95% CI 58–77 days), not available (owing to a lack of improvement), 39 days (95% CI 24–57 days), and 93 days (95% CI 36–191 days), respectively ($P < 0.01$, Fig. 1b).

Progression and OS

The median follow-up time from the initial administration of anti-PD-1/PD-L1 antibodies was 141 days. In all patient populations, median PFS and OS were 62 days (95% CI 43–78 days) and 168 days (95% CI 95–231 days), respectively (Fig. 2a, b). The median PFS was longer in the PD-L1 ≥ 50% group than in the PD-L1 < 1%, 1–49%, and unknown groups (89 days [95% CI 55–189 days], 45 days [95% CI 29–129 days], 41 days [95% CI 26–68 days], and 58 days [95% CI 34–67 days], respectively, $P = 0.03$, Fig. 2c). The median OS did not differ among PD-L1 groups (Fig. 2d).

Efficacy according to PS

ORR, PFS, and OS according to PS are shown in supplementary Table 2 and supplementary Fig. 1. There was no significant difference in ORR, PFS, and OS between PS2 and PS 3 or 4 patients (ORR 23% [95% CI 16–33%] vs. 22% [95% CI 12–38%], $P = 1.00$, median PFS 63 days [95% CI 50–75 days] vs. 45 days [95% CI 29–85 days], $P = 0.61$, median OS 176 days [95% CI 102–249 days] vs. 81 days [95% CI 22–139 days], $P = 0.35$). With respect to the PD-L1 ≥ 50% group, ORR, PFS, and OS did not differ between patients with PS 2 and PS 3 or 4 (ORR 44% [95% CI 28–60%] vs. 27% [95% CI 13–48%], $P = 0.29$, median PFS 90 days [95% CI 13–168 days] vs. 81 days [95% CI 0–163 days], $P = 0.92$, median OS 231 days [95% CI 5–457 days]vs. 81 days [95% CI 0–221 days], $P = 0.58$, supplementary Table 3).

Multivariate analysis of PFS and OS in different PD-L1 expression groups

We performed multivariate analyses of PFS and OS stratified based on PD-L1 expression (Table 3). PD-L1 expression was significantly associated with an improved PFS (PD-L1 < 1%; reference; PD-L1 1–49%, HR = 0.19 [95% CI 0.04–0.99], $P = 0.05$; PD-L1 ≥ 50%, HR = 0.12, [95% CI 0.02–0.71], $P = 0.02$; unknown, HR = 0.30, 95% CI [0.08–1.22], $P = 0.09$). Multivariate analysis of OS displayed no significant differences among PD-L1 groups.

Safety

Adverse events of any grade and grade ≥ 3 were observed in 69 patients (53%) and 20 patients (15%), respectively.

Table 2 Response to anti-PD1/PD-L1 antibody

	All patients		PD-L1 expression								
	N = 130		< 1% *N* = 17		1–49% *N* = 20		≥ 50% *N* = 54		Unknown *N* = 39		*P*
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	
CR	1	1	0	0	0	0	1	2	0	0	
PR	29	22	3	18	0	0	19	35	7	18	
SD	20	15	3	18	2	10	8	15	7	18	
PD	64	49	10	59	15	75	19	35	20	51	
NE	16	12	1	6	3	15	7	13	5	13	
ORR, % (95% CI)	23 (17–31)		18 (6–41)		0 (NA)		37 (25–50)		18 (9–33)		< 0.01
Time to response, days, (95% CI)	50 (43–73)		49 (23–105)		NA NA		51 (40–74)		50 (43–73)		0.84

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* objective response rate, *95% CI* 95% confidence interval, *NA* not available

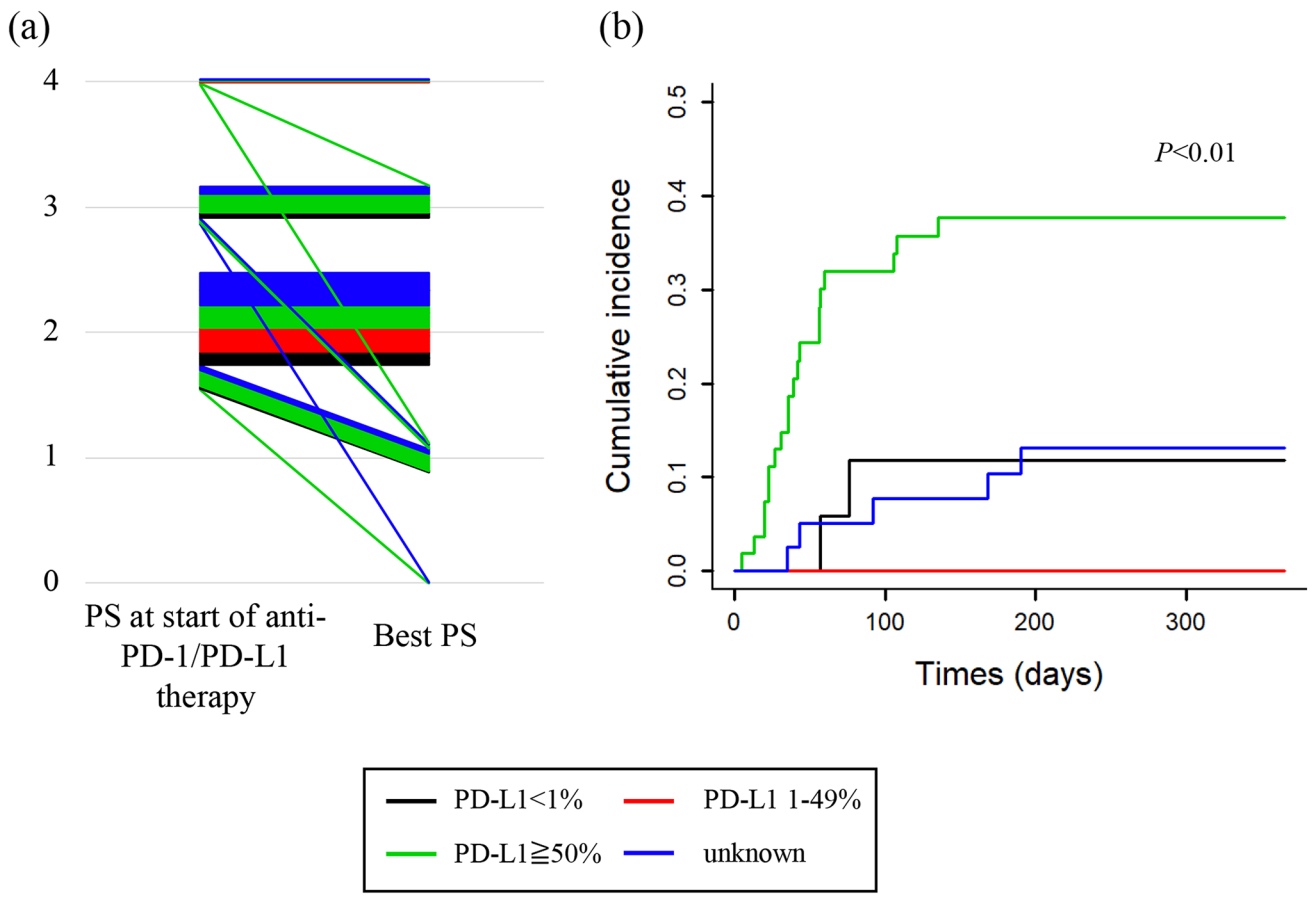

Fig. 1 Change in performance status (PS) (**a**) for each patient from baseline to best PS during treatment and the time to the improvement of best PS (**b**)

Treatment-related adverse events commonly include fever (23%), liver dysfunction (18%), pneumonitis (14%), skin toxicity (10%), and diarrhea (10%). Grade ≥ 3 adverse events, including fever, pneumonitis, skin toxicity, liver dysfunction, and diarrhea, occurred in 2 (2%), 5 (4%), 1 (1%), 4 (3%), and 3 (2%) patients, respectively. Moreover, adverse events of any grade and grade ≥ 3 showed no significant difference between PS2 and PS 3 or 4 patients (any grade; 53% vs. 52%, $P = 1.00$, grade ≥ 3; 13% vs. 22%, $P = 0.19$, supplementary Table 4). Treatment-related death occurred in three patients. Two patients with PS 2 and one patient with PS 4 died due to pneumonitis and septic shock, respectively (Table 4).

Discussion

To our knowledge, this is the largest retrospective study on the effectiveness and tolerability of anti-PD-1/PD-L1 therapy among NSCLC patients with PS ≥ 2.

Clinical studies on anti-PD-1/PD-L1 therapy among previously treated NSCLC patients with PS of 0 or 1 have reported median PFS and OS values of 2.3–4.0 months and 9.2–13.8 months, respectively [2–5]. Several retrospective studies analyzing actual clinical data have reported that a poor PS (≥ 2) is a negative predictive factor for PFS and a prognostic factor among NSCLC patients treated with anti-PD-1 antibodies [12–17]. Moreover, these studies have reported median PFS and OS values of 1.2–1.7 and 2.7–7.5 months among NSCLC patients with poor PS treated with anti-PD-1 antibodies [12–17]. Herein, the median PFS and OS were 62 and 168 days, being shorter than those of previous clinical trials and similar to estimates based on clinical data obtained from NSCLC patients with poor PS treated with anti-PD-1 antibodies. Hence, the efficacy of anti-PD-1/PD-L1 antibody therapy among NSCLC patients with poor PS might be relatively modest compared with that for patients with a good PS.

Among NSCLC patients with poor PS, several clinical guidelines have recommended carboplatin-based or single-agent chemotherapy for PS 2 and palliative care for PS 3–4 [18, 19]. A subgroup analysis of several randomized trials indicated that median PFS and OS are 1.6–5.8 and 3.0–11.5 months among NSCLC patients with PS of 2 treated with single-agent or combination chemotherapy,

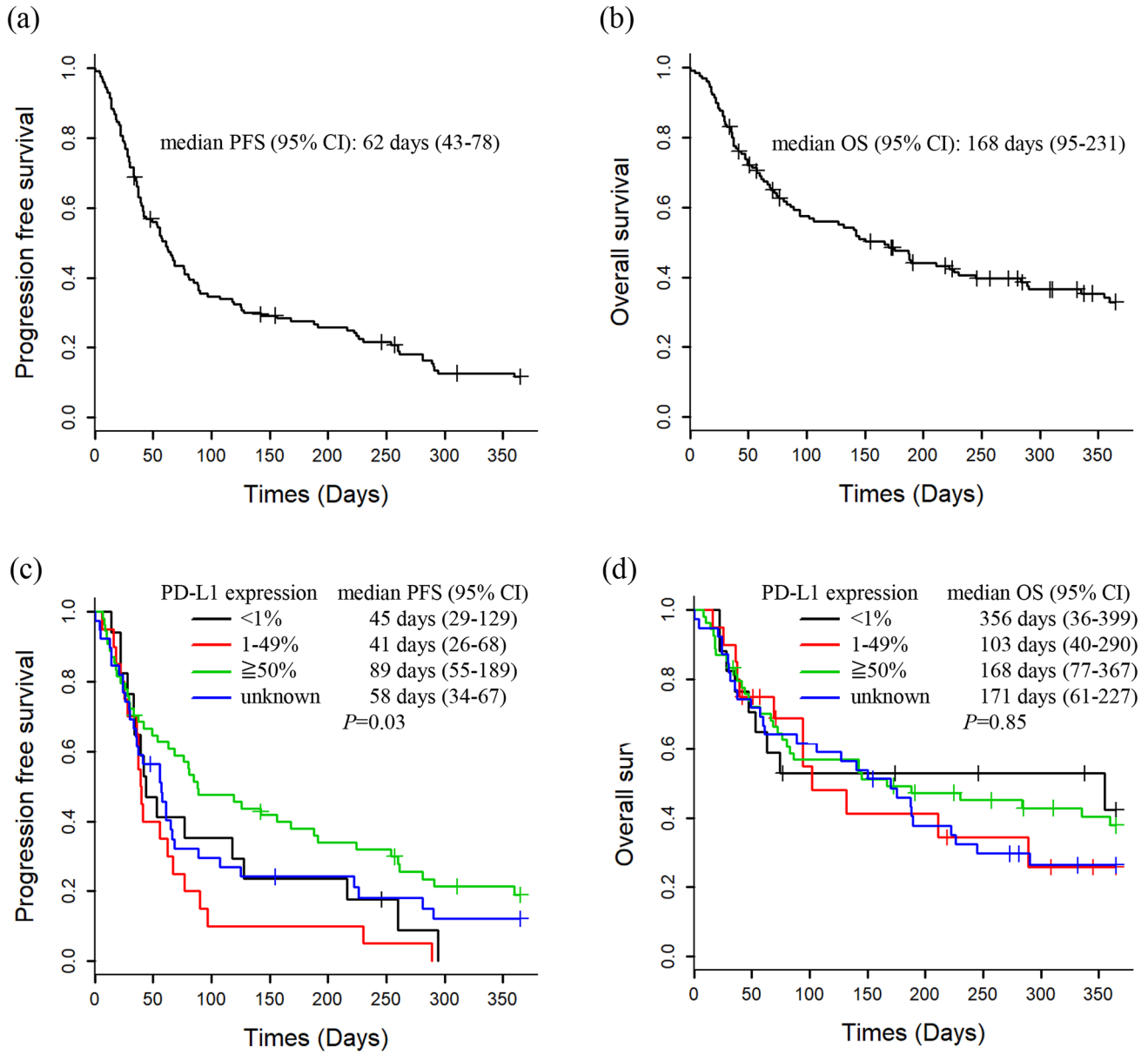

Fig. 2 Kaplan–Meier survival curves of progression-free survival (PFS) (**a**) and overall survival (OS) (**b**) among all patients. Curves of PFS (**c**) and OS (**d**) of each PD-L1 expression group

Table 3 Multivariate analysis for PFS and OS

PD-L1 expression	PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
< 1%	Ref	Ref	Ref	Ref	Ref	Ref
1–49%	0.19	0.04–0.99	0.05	0.74	0.13–4.1	0.73
≥ 50%	0.12	0.02–0.71	0.02	0.35	0.07–1.84	0.22
Unknown	0.30	0.08–1.22	0.09	0.41	0.09–1.84	0.25

Ref reference, *HR* hazard ratio, *95% CI* 95% confidence interval

Table 4 Adverse events

	All grade		Grade ≥ 3	
	N	(%)	*N*	(%)
Any	69	(53)	20	(15)
Fever	30	(23)	2	(2)
Pneumonitis	18	(14)	5	(4)
Skin toxicity	13	(10)	1	(1)
Liver dysfunction	24	(18)	4	(3)
Thyroid disorder	3	(2)	0	(0)
Diarrhea	13	(10)	3	(2)
Adrenal insufficiency	2	(2)	0	(0)

consistent with our results among patients with poor conditions, even though approximately 30% of patients were classified as PS 3 or 4 [20, 21]. A meta-analysis of randomized clinical trials including patients with advanced cancer reported that anti-PD-1/PD-L1 antibodies are better tolerated than chemotherapy, as evident from the lower incidence of any all-grade (67.6% versus 82.9%) or high-grade adverse events (11.4% versus 35.7%) [9]. Accordingly, anti-PD-1/PD-L1 monotherapy might be carefully considered a treatment alternative for patients with poor PS.

A clinical trial reported that PD-L1 expression ≥ 50% on tumor cells is associated with better tumor shrinkage of pembrolizumab in NSCLC patients, consistent with the results of our study limited to NSCLC patients with poor PS [10, 22]. Furthermore, NSCLC patients with poor PS and PD-L1 ≥ 50% had higher PS improvement rates and earlier time to PS improvement than patients in the other PD-L1 groups. For patients with poor PS, tumor response and improvement of PS are essential for symptom relief because PS is associated with cancer-related symptoms. Thus, NSCLC patients with PD-L1 ≥ 50% could benefit from anti-PD-1/PD-L1 therapy in terms of anti-tumor response and early cancer-related symptom relief.

We further evaluated the clinical significance of PD-L1 expression in NSCLC patients with poor PS to predict the efficacy of anti-PD-1/PD-L1 therapy. Multivariate analyses herein revealed that PD-L1 expression is significantly correlated with better PFS. This finding is consistent with those of previous reports. A phase I study on pembrolizumab therapy for advanced NSCLC patients reported that PD-L1 expression ≥ 50% on tumor cells is associated with longer PFS in both previously treated and untreated patients than that for a value of < 50% [10, 23]. Moreover, a clinical study on advanced NSCLC patients treated with anti-PD-1 antibodies reported that PD-L1 upregulation is associated with longer PFS [15, 24]. Thus, our findings indicate that even in NSCLC patients with poor PS, PD-L1 expression is positively correlated with the anti-tumor activity of anti-PD-1/PD-L1 antibodies and can be a clinically useful biomarker.

Multivariate analysis of OS did not display a significant correlation with PD-L1 expression among patients with poor PS. However, a long-term follow-up clinical trial for nivolumab or pembrolizumab among advanced NSCLC patients with good PS revealed that PD-L1 expression ≥ 50% was associated with longer OS [25, 26]. The lack of a correlation between PD-L1 expression and OS herein might be attributed to variations in demographic factors among groups, a relatively small sample size, and short follow-up periods. Thus, prospective studies on larger cohorts and longer follow-up periods are required to confirm the correlation between PD-L1 expression and survival benefit among NSCLC patients with poor PS.

With respect to adverse events, clinical trials of anti-PD1/PD-L1 monotherapy for NSCLC patients have reported rates of any-grade treatment-related adverse events of 58–70.9% for PS 0 or 1 and 7–37% for grade ≥ 3 [2–7]. Our results for any-grade and grade ≥ 3 adverse events were consistent with the results of these clinical trials, suggesting that the administration of anti-PD-1/PD-L1 therapy to NSCLC patients with poor PS is feasible and does not have a higher rate of treatment-related adverse events than that for patients with good PS. However, further investigation is warranted for the safety of anti-PD-1/PD-L1 therapy because of the heterogeneity of populations, with various factors affecting immune-related adverse events, and lack of clinical information for patients with poor PS [27].

This study has several limitations. First, this was a retrospective review including a heterogeneous population, and a selection bias could not be avoided. Second, our study primarily included patients with pretreated NSCLC and poor PS, and data on anti-PD-1/PD-L1 therapy in first-line settings were insufficient. Third, only PD-L1 expression was assessed as a predictive marker for the response to anti-PD-1/PD-L1 therapy. Various candidate predictive biomarkers for anti-PD-1/PD-L1 therapy have been identified, such as the tumor mutation burden, microsatellite instability, and tumor-infiltrating CD8 + T cells; therefore, further studies are required to identify alternative biomarkers [28]. Finally, this study analyzed NSCLC patients with poor PS, including both PS2 and PS3 or 4 patients. Since clinical guidelines for NSCLC patients with PS3 or 4 recommend palliative care, clinicians should carefully consider the administration of anti-PD-1/ PD-L1 antibody for these populations.

In conclusion, anti-PD-1/PD-L1 therapy among NSCLC patients and patients with PS ≥ 2 had modest efficacy with acceptable toxicity. PD-L1 expression was correlated with prolonged PFS after anti-PD-1/PD-L1 therapy even in these populations, providing important information for clinical physicians. Anti-PD-1/PD-L1 therapy can even be beneficial in cases of poor PS and PD-L1 ≥ 50%, providing a potential therapeutic strategy for this critical patient subset.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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