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PHASE III STUDIES

Efficacy and safety of pembrolizumab as first-line therapy in advanced non-small cell lung cancer with at least 50% PD-L1 positivity: a multicenter retrospective cohort study (HOPE-001)

Motohiro Tamiya[1] · Akihiro Tamiya[2] · Kazutaka Hosoya[3] · Yoshihiko Taniguchi[2] · Toshihide Yokoyama[4] · Yasushi Fukuda[4] · Katsuya Hirano[5] · Hirotaka Matsumoto[5] · Ryota Kominami[6] · Hidekazu Suzuki[7] · Tomonori Hirashima[7] · Junji Uchida[8] · Mitsunori Morita[9] · Masaki Kanazu[10] · Nobuhiko Sawa[10] · Yoshinori Kinoshita[11] · Satoshi Hara[11] · Toru Kumagai[1] · Daichi Fujimoto[3]

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Summary

Objectives As first line therapy, pembrolizumab provides longer progression free survival (PFS) and overall survival (OS) than platinum doublets in programmed death ligand 1 (PD-L1)-positive non-small cell lung cancer (NSCLC) with tumor propensity scores (TPS) ≥50%. However, clinical trials do not represent real-world patients. *Materials and Methods* This multicenter retrospective study conducted across 11 medical centers in Japan analyzed clinical data from patients receiving first-line pembrolizumab for NSCLC between February 1, 2017 and April 30, 2018. The efficacy, safety, and suitability of pembrolizumab monotherapy were evaluated. *Results* The median age of the 213 enrolled patients was 71 (range: 39–91) years. Among them, 176 (82.6%) were male, 20 (9.4%) were never smokers (median Brinkman index: 900), 172 (80.8%) had an ECOG PS of 0–1, 55 (25.8%) had squamous-cell carcinoma (SQ). PD-L1 TPS were 50–74%, 75–89%, and 90–100% in 97 (45.5%), 47 (22.1%), and 69 (32.4%) patients, respectively. Adverse events (AEs) of grades ≥3 were observed in 39 (18.3%) patients. Pneumonitis was the most common severe AE, occurring in 10 patients (4.7%) including 1 with grade 4 toxicity; no severe AE-related deaths occurred. The overall response rate, median PFS, and median OS was 51.2%, 8.3 months, and 17.8 months, respectively. On multivariate analysis, ECOG PS (0–1 vs. ≥2: HR: 1.69, 95.0% CI: 1.05–2.72; $p = 0.03138$), CRP/Alb (<0.3 vs. ≥0.3: HR: 1.92, 95.0% CI: 1.28–2.87; $p = 0.00153$), steroid usage (not usage vs. usage: HR: 2.94, 95.0% CI: 1.45–5.95; $p = 0.00267$), and PD-L1 TPS (50–89% vs. 90–100%: HR: 0.65, 95.0% CI: 0.43–1.00; $p = 0.04984$) were significantly and independently correlated with PFS of pembrolizumab. *Conclusion* The results confirm the efficacy and safety of pembrolizumab in real-world patients. Poor PS and steroid usage at the time of commencing pembrolizumab treatment indicate poor outcomes. First-line pembrolizumab particularly benefits patients with PD-L1 TPS ≥90% or low inflammatory states (CRP/ALB<0.3).

✉ Motohiro Tamiya
moto19781205@yahoo.co.jp

[1] Department of Thoracic Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka City, Osaka 541-8567, Japan

[2] Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180, Nagasone-cho, Kita-ku, Sakai City, Osaka 591-8555, Japan

[3] Department of Respiratory Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojimaminamimachi, Chuo-ku, Kobe City, Hyogo 650-0047, Japan

[4] Department of Respiratory Medicine, Kurashiki Central Hospital, 1-1-1, Miwa, Kurashiki City, Okayama 710-8602, Japan

[5] Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, 2-17-77, Higashi-Naniwa-Cho, Amagasaki City, Hyogo 660-8550, Japan

[6] Department of Respiratory Medicine, National Hospital Organization Himeji Medical Center, 68, Honmachi, Himeji City, Hyogo 670-8520, Japan

[7] Department of Thoracic Malignancy, Osaka Habikino Medical Center, 3-7-1, Habikino, Habikino City, Osaka 583-8588, Japan

[8] Department of Respiratory Medicine, Osaka General Medical Center, 3-1-56, Bandai-Higashi, Sumiyoshi-ku, Osaka City, Osaka 558-8558, Japan

[9] Department of Respiratory Medicine, Kobe City Medical Center West Hospital, 2-4, Ichiban-cho, Nagata-ku, Kobe City, Hyogo 653-0013, Japan

[10] Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, 5-1-1, Toneyama, Toyonaka City, Osaka 560-0045, Japan

[11] Department of Respiratory Medicine, Itami City Hospital, 1-100, Koyaike, Itami City, Hyogo 664-8540, Japan

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1, 2]. Prior to the introduction of immune checkpoint inhibitor (ICI) therapy, the scope of effective treatments for non-small cell lung cancer (NSCLC), particularly in patients not suitable for molecular targeting agents, was limited. However, the recognition of the key role of immune system evasion in cancer has contributed to the rapid evolution of ICIs for the treatment of various malignancies, including NSCLC [3, 4].

The programmed death (PD)-1 receptor is an IC expressed on activated B- and T-cells, which down-regulates overwhelming immune responses [3, 5]. The binding of PD-1 to its ligands PD-L1 and PD-L2 on tumor cells suppresses T-cells through a negative feedback loop, which allows evasion from the immune response [6–9]. Among the therapeutic agents for NSCLC, PD-1/PD-L1 inhibitors have become the most popular owing to superior survival benefits compared with standard therapy in multiple randomized trials [10–12]. The results of the Keynote-024 established pembrolizumab monotherapy as the treatment of choice in patients with NSCLC with PD-L1 tumor proportion scores (TPS) of ≥50%. In this trial, pembrolizumab demonstrated promising efficacy with a response rate of 44.8%, median progression free survival (PFS) of over 10 months, and median overall survival (OS) of 30.0 months [13, 14]. The Keynote-042 trial, which studied pembrolizumab in the first-line for NSCLC with a PD-L1 TPS ≥1%, demonstrated longer PFS and OS compared with platinum doublet therapy in the subgroup of patients with a PD-L1 TPS ≥50% [15]. In recent years, key trials on pembrolizumab-chemotherapy combinations have demonstrated impressive efficacy in advanced NSCLC in the first line, particularly in cases with PD-L1 TPS ≥50%. However, these combinations entail more toxicity than pembrolizumab monotherapy [16, 17].

The eligibility criteria of clinical trials have become increasingly detailed and stringent [18, 19]. Therefore, only selected patients in good general condition, and without organ failure are able to participate in most trials. In several previous studies, only 27–45% of patients with advanced NSCLC met the eligibility criteria for clinical trials [20–22]. Therefore, clinical trial outcomes may not be entirely representative of outcomes in real-world patients. It is important to identify patients with a PD-L1 TPS of ≥50% who may obtain clinical benefit from pembrolizumab in the first line.

At present, the choice between first line pembrolizumab monotherapy and chemotherapy with ICI is difficult in cases of NSCLC with PD-L1 TPS ≥50%. In this retrospective multicenter cohort study, we aimed to identify patients who are better suited for pembrolizumab monotherapy. The study also aimed to confirm the efficacy and safety of pembrolizumab in the clinic, which provides a wider variety of patient characteristics compared to the clinical trial setting.

Materials and methods

This multicenter retrospective study was conducted across 11 medical centers (Hanshin Oncology clinical Problem Evaluation group [HOPE]) in Japan. The study design and methodology were approved by the Institutional Review Board of each participating institution. Research was conducted in accordance with the principles of the Declaration of Helsinki, and the Guidelines for Good Clinical Practice of the World Health Organization. The study protocol is registered with the UMIN (University Hospital Medical Information Network in Japan, number: 000032470).

Patient selection

Data from patients who received pembrolizumab as first-line treatment between February 1, 2017 (the date that pembrolizumab was approved as first-line treatment in Japan) and April 30, 2018 in the 11 medical centers participating in HOPE, were retrospectively reviewed. Study participants were consecutively enrolled from patients in the clinic. Patients with advanced NSCLC (unresectable stage III or IV disease based on the 7th edition of the TNM classification, including postoperative recurrence), and PD-L1 TPS ≥50%, who received pembrolizumab (200 mg/kg body weight, intravenously, every 3 weeks) as first-line therapy were eligible. Patients were excluded from analysis if they had received pembrolizumab as part of a clinical trial, or if any additional anti-neoplastic therapies were administered concurrently.

Data collection

We collected clinical data including age, sex, smoking history, PS score, body surface area, histological type, PD-L1 TPS values, epidermal growth factor receptor (EGFR) mutation status, laboratory data including neutrophil count, lymphocyte count, albumin (Alb), lactate dehydrogenase (LDH), and C-reactive protein (CRP), and drug use (including steroids, opioids, statins, biguanides, and fibrates) at the time of initiation of pembrolizumab. Clinical responses were defined according to the Response Evaluation Criteria in Solid Tumors 1.1. PFS was estimated as the duration between pembrolizumab initiation and documented disease progression or death from any

cause. Patients were followed-up for disease status until August 31, 2018.

Statistical analysis

Continuous and categorical data were summarized as medians (range) and numbers (percentage), respectively. Kaplan-Meier curves were used to evaluate PFS and OS, which were compared using the log-rank test. Median values and 95.0% confidence intervals (CI) were also reported. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. The factors with $p < 0.10$ on univariate analysis, sex, and age, were included in the multivariate analysis. All statistical analyses were conducted using the R, version 2.8.1 (http://R-project.org) software package. Statistically, p values of <0.05 and < 0.10 were considered significant and moderately significant, respectively.

Results

A total of 213 patients treated with pembrolizumab were enrolled in this study. The median duration of follow-up was 11.0 months. At the time of initiation of pembrolizumab, the median age was 71 (range: 39–91) years; 176 patients were male, only 20 patients were never smokers (median Brinkman index: 900 [range, 0–4800]), 172 patients had an ECOG PS of 0–1, 55 patients had squamous carcinoma (SQ), and only 6 patients had EGFR mutations (mainly uncommon EGFR mutations). PD-L1 TPS values were 50–74%, 75–89%, and 90–100% in 97 (45.5%), 47 (22.1%), and 69 (32.4%) patients, respectively; the median PD-L1 TPS value was 75 (range: 50–100%) (Table 1).

The incidences of drug-related adverse events (AEs) of grade ≥ 3 are summarized in Table 2; 39 patients (18.3%) had AEs of grades ≥3. The most common severe (grades ≥3) AE was pneumonitis, noted in 10 patients (4.7%), among whom 1 had grade 4 severity. The second most common severe AE was hepatotoxicity, noted in 5 patients (2.3%). Only 1 fatality was related to an AE (pneumonitis); no patients died of severe AEs.

The rates of overall response, disease control, and progressive disease were 51.2%, 71.9%, and 24.9%, respectively. The median PFS of the cohort was 8.3 (95.0% CI: 6.0–10.7) months (Fig. 1a), and the median OS was 17.8 (95% CI: 17.8-NA) months (Fig. 1b). The PFS was determined using the univariate Cox proportional hazards regression model (Table 3). Sex, age, histological subtype, smoking status, PD-L1 TPS (50–74% vs. 75–100%), body surface area, LDH levels, liver metastasis status, opioid usage, biguanide usage, statin usage, and fibrate usage did not correlate with a shorter PFS with pembrolizumab. However,

Table 1 Patients' characteristics

Characteristics	$N = 213$
Age	
Median (range)	71 (39–91)
Gender	
Male / Female	176 / 37
Smoking history	
Never / Ever	20 / 193
Performance Status	
0 / 1 / 2 / 3 / 4	50 / 122 / 32/ 9 / 1
Histology	
SQ / Adenocarcinoma / Others	55 / 129 / 29
Sensitive *EGFR* mutation	
Positive / Negative	6 / 207
Stage	
III / VI / Recurrence	38 / 144 / 31
Liver metastasis	
None / Meta +	185 / 28
PD-L1 TPS	
50–74% / 75–89% / 90–100%	97 / 47 / 69
Steroid usage	
None / Usage	199 / 14
Opioid usage	
None / Usage	38 / 38
Statin usage	
None / Usage	191 / 22
Biguanide usage	
None / Usage	207 / 6
Fibrate usage	
None / Usage	211 / 2

SQ, Squamous cell carcinoma, TPS, tumor propensity score

the median PFS for ECOG PS (0–1 vs. ≥2: 9.0 [95.0% CI: 7.2-NA] vs. 4.0 [95.0% CI: 2.2–8.6] months; HR: 2.11, 95.0% CI: 1.37–3.27; $p = 0.000598$) (Fig. 2a), CRP/Alb (<0.3 vs. ≥0.3: NA [95.0% CI: 8.7-NA] vs. 5.9 [95.0% CI: 4.5–8.6] months; HR: 1.88, 95.0% CI: 1.27–2.79; $p = 0.001467$) (Fig. 2b), and steroid usage (no usage vs. usage: 8.7 [95.0% CI: 6.7-NA] vs. 2.0 [95.0% CI: 1.3-NA] months; HR: 3.17, 95.0% CI: 1.63–6.15; $p = 0.000326$) (Fig. 2c) were significantly different. PD-L1 TPS (50–89% vs. 90–100%: 6.6 [95.0% CI: 4.9–9.0] vs. 10.0 [95.0% CI: 8.7-NA] months; HR: 0.68, 95.0% CI: 0.45–1.04; $p = 0.07265$) (Fig. 2d) were associated with the trends of PFS.

On the multivariate Cox proportional hazards regression model, ECOG PS (0–1 vs. ≥2: HR: 1.69, 95.0% CI: 1.05–2.72; $p = 0.03138$), CRP/Alb (<0.3 vs. ≥0.3: HR: 1.92, 95.0% CI: 1.28–2.87; $p = 0.00153$), steroid usage (not usage vs. usage: HR: 2.94, 95.0% CI: 1.45–5.95; $p = 0.00267$), and PD-L1 TPS (50–89% vs. 90–100%: HR: 0.65, 95.0% CI:

Table 2 The incidences of drug-related adverse events (AEs) of grade ≥ 3

Drug-related AEs	Grade 3–5
Over all	39 (18.3%)
Pneumonitis	10 (4.7%)
Hepatotoxicity	5 (2.3%)
Skin toxicity	3 (1.4%)
Fatigue	3 (1.4%)
Colitis	2 (0.9%)
Type I diabetes mellitus	2 (0.9%)
Thrombosis	2 (0.9%)
Pneumonia	2 (0.9%)
Adenal insufficiency	1 (0.5%)
Hypopituitarism	1 (0.5%)
Anemia	1 (0.5%)
Nephrotoxicity	1 (0.5%)
Infusion reaction	1 (0.5%)
Decreased appetite	1 (0.5%)
Hyponatremia	1 (0.5%)
Creatine kinase increased	1 (0.5%)
Urinary tract infection	1 (0.5%)
Herpes zoster	1 (0.5%)
Tumor lysis syndrom	1 (0.5%)

0.43–1.00; $p = 0.04984$) were significantly and independently correlated with PFS in pembrolizumab-treated patients with advanced NSCLC (Table 3).

Discussion

This study demonstrated the efficacy and safety of pembrolizumab monotherapy in a real-world setting. To our knowledge, this is the first study providing substantial data on the efficacy of first-line pembrolizumab in subgroups that are relatively understudied in clinical trials on NSCLC. In the present study, the overall response rate was 51.2% and the median PFS was 8.3 months. These results are consistent with the efficacy data reported from previous key clinical trials. Although this study had included patients from various backgrounds in the real-world setting, the safety profile (no new safety signals identified) of pembrolizumab was generally consistent with that of reports from the Keynote-024 and -042 trials [13–15]. This study provided certain clinically useful observations.

First, in this cohort, the PFS of patients with PS 2 or poorer was 4.0 months; this was significantly shorter than that of patients with PS 0–1 (9.0 months). To the best of our knowledge, no outcome data are currently available for patients with a PD-L1 TPS ≥50% and PS 2 or poorer, receiving first-line pembrolizumab. Therefore, the data from this study in a real-world setting is particularly significant. In 2 previous key studies, the PFS with pemetrexed and carboplatin with pemetrexed for non-squamous NSCLC with only PS 2 was 2.8 and 5.8 months, respectively, and that of carboplatin with paclitaxel or cisplatin with gemcitabine was 3.5 and 3.0 months, respectively [23, 24]. In our study, the PFS of those with PS 2 or poorer was shorter compared to that of patients with good PS. However, compared with the PFS of historical controls with PS 2 or poorer treated with cytotoxic chemotherapy, the PFS in this study was not considerably inferior. In previous retrospective observational studies, the PFS in patients receiving nivolumab in second or later lines was considerably short (less than 2.0 months and 1.5 months, respectively) [25, 26]. This study shows that pembrolizumab is a valid therapeutic option in the first line for patients with NSCLC with PS 2 or poorer, with priority over cytotoxic chemotherapy.

Second, in this cohort, the PFS increased in direct proportion with the PD-L1 TPS values; this was particularly

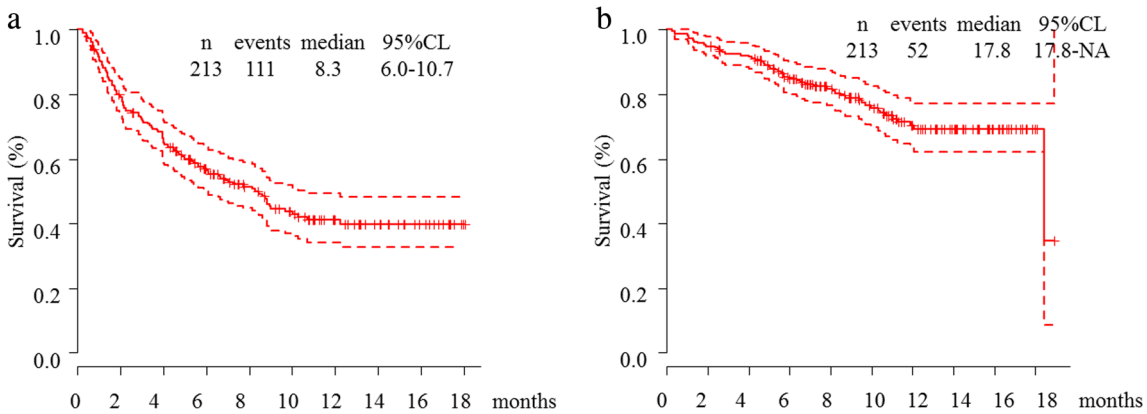

Fig. 1 Kaplan-Meier curve of (**a**) progression free survival, **b** overall survival of all patients

Table 3 The univariate and multivariate Cox proportional hazards regression model

				Univariate analysis			Multivariate analysis		
		N	Median PFS (M)	HR	95% CI	p value	HR	95% CI	p value
Gender	Male	176	8.5	1.04	0.64–1.71	0.8674	1.10	0.66–1.83	0.71859
	Female	37	8.2						
Age	75>	135	9.0	1.34	0.91–1.95	0.1337	1.15	0.76–1.72	0.50685
	75≤	78	6.1						
PS	0.1	172	9.0	2.11	1.37–3.27	0.000598	1.69	1.05–2.72	0.03138
	2≤	41	4.0						
Histology	Non-SQ	158	8.7	1.18	0.79–1.78	0.4221			
	SQ	55	7.0						
BI	400≤	176	8.5	0.99	0.60–1.64	0.9722			
	400>	37	8.2						
TPS	50–74	97	6.7	0.91	0.62–1.31	0.6049			
	75–100	116	8.8						
TPS	50–89	144	6.6	0.68	0.45–1.04	0.07265	0.65	0.43–1.00	0.04984
	90–100	69	10.0						
CRP/Alb	0.3>	94	NA	1.88	1.27–2.79	0.001467	1.92	1.28–2.87	0.00153
	0.3≤	119	5.9						
BSA	1.48≤	163	8.6	1.12	0.73–1.73	0.6059			
	1.48>	50	6.6						
LDH	222>	133	8.8	1.22	0.83–1.78	0.3114			
	222≤	80	6.9						
Liver meta	(−)	185	8.5	1.12	0.64–1.97	0.6898			
	(+)	28	5.9						
Steroid	(−)	199	8.7	3.17	1.63–6.15	0.000326	2.94	1.45–5.95	0.00267
	(+)	14	2.0						
Opioid	(−)	195	8.5	1.37	0.75–2.50	0.3017			
	(+)	18	5.9						
Statin	(−)	191	8.3	1.12	0.60–2.08	0.7281			
	(+)	22	10.3						
Biguanide	(−)	207	8.5	2.24	0.82–6.10	0.1051			
	(+)	6	2.1						
Fibrate	(−)	211	8.3	0.72	0.10–5.16	0.7422			
	(+)	2	4.5						

BI, brinkman Index; BSA, body surface area; TPS, tumor propensity score; Liver meta, liver metastasis; NA, not achieved

notable in the PD-L1 TPS 0% vs. 1–49% vs. ≥50% groups [10–12]. Additionally, this increasing trend continued in patients with PD-L1 TPS values of 50% or higher. Currently, there are no reports on the extension of PFS in groups with higher PD-L1 TPS on multivariate analysis (50–89% vs. 90–100%: HR: 0.65, $p = 0.04984$). The standard of treatment in advanced NSCLC with a PD-L1 TPS ≥50% is either pembrolizumab [13–15] or platinum-doublet chemotherapy with ICIs [16, 17]. The toxicity of pembrolizumab monotherapy is milder than that of chemotherapy with ICIs. However, the response rate is lower and disease progression is higher by approximately 30% (8.8% and 6.1% in non-squamous and squamous NSCLC, respectively, including patients with PD-L1 TPS of 0% and 1–49%). Therefore, in cases resistant to platinum-doublet chemotherapy, chemotherapy with ICIs offers lower disease progression than pembrolizumab monotherapy. As evident from our results, the PD-L1 TPS ≥90% sub-group demonstrated longer PFS. Pembrolizumab monotherapy may therefore be recommended in these patients if treatment with chemotherapy-ICI combinations is not feasible.

Third, the study demonstrated that the effect of pembrolizumab depends on the inflammatory state (CRP/Alb) of the individual. This finding is consistent with that of a previous analysis in patients treated with nivolumab in second or subsequent lines for NSCLC {Inoue, 2018 #468}. CRP/Alb has been recognized as an inflammation-based prognostic factor [27–29], and it influences the

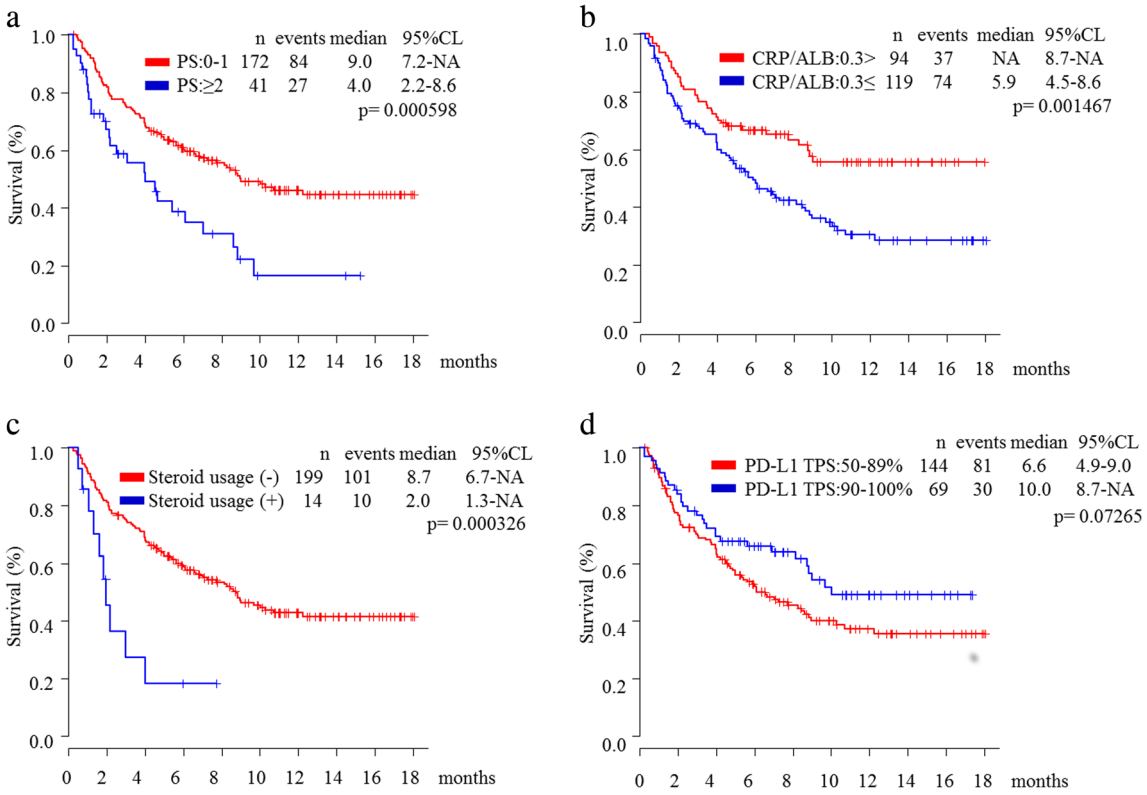

Fig. 2 Kaplan-Meier curves of progression-free survival according to (**a**) Eastern Cooperative Oncology Group performance status (PS), **b** CRP/Alb, **c** steroid usage, and (**d**) PD-L1 tumor propensity score (TPS)

efficacy of ICIs. It is also associated with early death in patients treated with nivolumab in the second line for NSCLC. Since CRP/Alb influenced the efficacy of pembrolizumab even in patients with PD-L1 TPS ≥50% in this cohort, it implies that similar to the case with ICIs, the inflammatory state governs the prognosis. However, since CRP/Alb is measurable and easy to use clinically, it may help in making the choice between pembrolizumab monotherapy and chemotherapy with ICIs.

Fourth, baseline corticosteroid use with doses of 10 mg prednisone equivalents or higher, was associated with poorer outcome in patients with NSCLC who were treated with first-line pembrolizumab. These results agree with that of patients previously treated for NSCLC with single agent PD-(L)1 inhibitors [30]. Prudent use of corticosteroids at the time of initiating PD-(L)1 blockade is recommended, irrespective of the duration of use.

Notably, multivariate analysis revealed that selected patients with NSCLC with a PD-L1 TPS ≥90% or a low inflammatory state (CRP/Alb<0.3) may obtain considerable benefit from first-line pembrolizumab despite other adverse prognostic factors. Ultimately, the choice of treatment will need to be individualized after discussion between the physician and patient, after weighing the risks and benefits of each option and patient-specific factors. Although a definitive conclusion cannot be made without a prospective and direct comparison between chemotherapy with ICIs and pembrolizumab alone, these findings may be helpful in the choice of first line treatment for patients with advanced NSCLC with a PD-L1 TPS ≥50%.

This study has some limitations. First, it had a retrospective design, with potential for bias. However, confounding effects were addressed by employing multivariate models to adjust for confounding factors. Second, almost all patients in our cohort were of single Japanese ethnicity. However, irrespective of ethnicity, the efficacy of pembrolizumab in NSCLC with a PD-L1 TPS ≥50% has been demonstrated previously [13–15]. Despite these limitations, this study probably included the largest multicenter cohort till date and demonstrated some novel findings.

Conclusion

In a real-world setting, this study demonstrated the efficacy and safety of pembrolizumab monotherapy with an overall response and PFS consistent with that of previous key clinical trials. Poor PS and steroid usage at initiation of pembrolizumab shorten PFS in patients with NSCLC with a PD-L1 TPS ≥50%. Selected patients with PD-L1 TPS ≥90% or low inflammatory states (CRP/Alb<0.3) may obtain benefit despite other adverse factors. Further studies in the real-world setting are warranted to validate our findings.

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Compliance with ethical standings

Disclosure of potential conflicts of interest Drs. M. Tamiya, A. Tamiya, Fujimoto, Hirano, and Kumagai have received lecture fees from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) and Merck Sharp & Dohme, Corp. (Tokyo, Japan). Drs. Yokoyama and Hirashima have received lecture fees from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). Drs. Taniguchi, Ishida and Kanazu have received lecture fees from Merck Sharp & Dohme, Corp. (Tokyo, Japan). The remaining authors have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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