ORIGINAL ARTICLE

Real-World Data Analysis of Pembrolizumab Monotherapy for NSCLC Using Japanese Postmarketing All-Case Surveillance Data

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ABSTRACT

Introduction: Pembrolizumab is a programmed death-ligand 1 inhibitor that was initially indicated for monotherapy in patients with advanced lung cancer. The Japanese Lung Cancer Society conducted an observational study on pembrolizumab using confirmative data obtained through postmarketing all-case surveillance (PMACS), which was performed by a pharmaceutical company under the Japanese law in 2017.

Methods: This multicenter observational study was conducted by the Japanese Lung Cancer Society using PMACS data with the newly created central registration system regarding patients with NSCLC who received pembrolizumab monotherapy between February 1, 2017 and June 30, 2017; a new database was created by adding the clinical information regarding prognosis for 3 years after therapy to the existing data collected by PMACS.

Results: A total of 300 patients from 43 facilities were enrolled in this study. The median overall survival and progression-free survival after pembrolizumab initiation were 558 and 188 days, respectively. Moreover, the 1- and 3-year survival rates were 58.9% and 33.7%, respectively. Results of multivariate analysis revealed performance status ($p < 0.0001$), histology ($p = 0.0118$), previous chemotherapy ($p = 0.0007$), programmed death-ligand 1 expression status ($p = 0.0195$), and previous steroid use ($p = 0.0460$) as significant factors that affected overall survival. The toxicity profile was similar to that previously reported.

Conclusions: In this first attempt to use PMACS data, we successfully collected clinical information and found the real-world efficacy and safety of pembrolizumab.

Keywords: Real-world data; Pembrolizumab; Immune checkpoint inhibitor; Immune-related adverse events

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] NSCLC accounts for approximately 80% of all lung cancers, and most cases are unresectable.[1]

As revealed in previous clinical trials, chemotherapy can improve the prognosis of patients with advanced NSCLC, and new and effective drugs are developed every year.[2–4] Immune checkpoint inhibitors (ICIs) were found to have outstanding efficacy and are recognized as an important treatment option for patients with NSCLC.

ICIs targeting programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and CTLA4 were found to have excellent effects in clinical trials for various types of cancer.[5] In 2016, pembrolizumab was approved as an anti–PD-1 antibody for NSCLC treatment by the Food and Drug Administration and Pharmaceuticals and Medical Devices Agency. Pembrolizumab (Keytruda, Merck, Kenilworth, NJ) is a humanized immunoglobulin 4 antibody that inhibits the interaction between PD-1 and PD-L1. PD-L1 is expressed in the tumor tissue and can be detected using the 22C3 antibody, a companion diagnostic test used to evaluate the tumor proportion score (TPS) of PD-L1 expression.

In the KEYNOTE-024 trial,[6,7] pembrolizumab was found to have a markedly better survival benefit than that of cisplatin combination chemotherapy in the first-line treatment of patients with NSCLC with PD-L1 expression in tumor cells equals to or greater than 50%. Long-term follow-up data revealed a median overall survival (OS) of 26.3 and 13.4 months in the pembrolizumab and chemotherapy arms, respectively.

Moreover, pembrolizumab has been approved as a second-line treatment for NSCLC in which PD-L1 is expressed in at least 1% of the tumor tissue. This approval was supported by results from the phase 2/3 KEYNOTE-010 study,[8,9] in which pembrolizumab was found to have improved OS compared with docetaxel in previously treated patients with NSCLC (11.8 versus 8.4 mo).

New ICIs are also being developed for monotherapy and combination therapy.[10] The development of cancer therapies using host immunity is desirable, although the efficacy and safety profiles in clinical practice with long-term follow-up data remain elusive.

Postmarketing all-case surveillance (PMACS) is a unique pharmacovigilance program conducted by a pharmaceutical company under the Japanese law when a drug is newly approved and released for use in clinical practice. In PMACS, a pharmaceutical company works with individual medical institutes to collect clinical data, mainly concerning safety, about all patients who receive a specific drug. PMACS plays a key role in postmarketing activities in Japan and has been implemented for more than 20 years.[11,12] Despite tremendous effort and costs incurred for PMACS, the use of these data has been limited. The Japanese Lung Cancer Society planned this observational study on pembrolizumab as a case model for the effective use of PMACS data.

Materials and Methods

Data Collection and Patient Enrollment

This multicenter observational study was conducted by the Japanese Lung Cancer Society using a central

Table 1. Patient Background Characteristics

Characteristics	Patients (N = 300)
Age (y)	
Mean (range)	67.1 (28-91)
Sex	
Male/female	228/72
Smoking history	
Never/former/current/other	39/199/53/9
Smoking index (N = 253)	
Mean (range)	965.7 (9-3300)
Performance status	
0/1/2/3/4	88/161/38/11/2
Histology	
Squamous/nonsquamous	79/221
EGFR mutation	
Positive/negative/unknown	22/250/28
ALK fusion	
Positive/negative/unknown	2/257/41
PD-L1 TPS	
1%-49%/≤50%/unknown	57/242/1
Stage	
II-III/IV/recurrence	44/191/65
Previous chemotherapy	
≤1 line/≤2 lines/unknown	244/53/3
Liver metastasis	
None/metastasis	277/23
Brain metastasis	
None/metastasis	248/52
Bone metastasis	
None/metastasis	226/74
Malignant pleural effusion	
None/metastasis	286/14
Steroid usage	
None/use/unknown	286/11/3
Radiation (before ICI)	
No/yes	209/91
Surgery (before ICI)	
No/yes	243/57
Body mass index (kg/m^2)	
Mean (range)	21.7 (14.3-40.0)

ICI, immune checkpoint inhibitor; PD-L1 TPS, programmed cell death-ligand 1 tumor proportion score.

registry and electronic data capture system developed by the Japan National Clinical Database.

The study design and methodology were approved by the institutional review boards of each participating institution. The requirement for written informed consent was waived by the institutional review boards owing to the retrospective nature of the study and use of anonymized data. Researchers obtained verbal consent from the patients and recorded it in a medical chart. This research was conducted in accordance with the principles of the Declaration of Helsinki and the WHO Guidelines for Good Clinical Practice. The study protocol was registered with the University Hospital Medical Information Network(UMIN) in Japan (number: 000045538).

We enrolled patients with NSCLC who (1) initiated pembrolizumab treatment between February 1, 2017, and June 30, 2017; (2) were treated at a facility that participated in PMACS and belonged to the Japan Lung Cancer Society; and (3) agreed to participate in this study.

Clinical information regarding background characteristics, pretreatment information, pembrolizumab-related adverse events (AEs), post-treatment information, and prognosis at 1 year and 3 years after pembrolizumab treatment was collected. Anonymized registry data regarding basic patient clinical information, AEs, treatment course, and treatment results were automatically collected by uploading the PMACS data. PMACS data were returned to each institution by Merck Sharp & Dohme pharmaceutical company (Merck & Co., Inc., Rahway, NJ) after they were organized. Survival information at 1 year and 3 years after treatment was input directly into the central system by the researchers at each institution. The institutions that participated in this study are listed in Supplementary Table 1.

Statistical Analysis

The Kaplan-Meier method was used to perform time-to-event analyses, including OS and progression-free survival (PFS), from the initiation of pembrolizumab treatment. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. Factors with p less than 0.10 in the univariate analysis were included in the multivariate analyses. All statistical analyses were conducted using SAS software (version 9.4, SAS Institute Inc., Cary, NC). Statistical significance was set at p value less than 0.05.

Results

Baseline Characteristics

A total of 300 patients were enrolled, and their baseline characteristics are summarized in Table 1. Overall, 76.0% were men, 84.0% were smokers, 26.6% were older than 75 years, and 17.0% had a poor performance status (PS ≥2) score.

Patients with NSCLC harboring *EGFR* (n = 22) or *ALK* (n = 2) driver mutations were also included. Most patients received pembrolizumab as an early line treatment (first line, n= 164; second line, n = 82), although 17.7% of the patients were treated with pembrolizumab as a third-line treatment or more.

Efficacy

During a median follow-up period of 505 days, 243 (81.0%) and 211 (70.3%) PFS and OS events were observed, respectively (Fig. 1). The median PFS and OS were 188 (95% confidence interval [CI]: 165–226) and

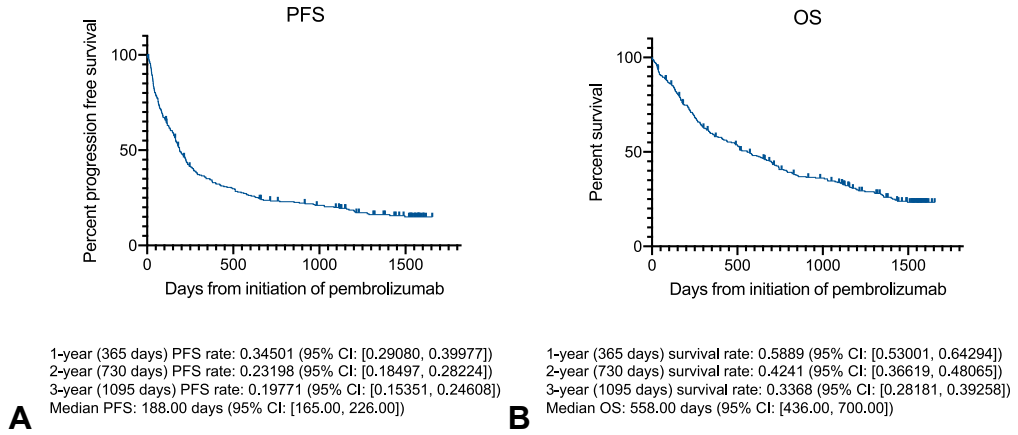

Figure 1. Kaplan-Meier curves of OS and PFS of the patients with prognosis data. Survival curves of (*A*) OS and (*B*) PFS, with detailed data at the indicated time points (1 y, 2 y, and 3 y after pembrolizumab initiation). CI, confidence interval; OS, overall survival; PFS, progression-free survival.

558 (95% CI: 436–700) days, respectively. The median OS in patients who received first-line treatment was 700 (95% CI: 557–843) days and 488 (95% CI: 266–822) days in patients who received second-line treatment. Overall, the efficacy of pembrolizumab was similar to that reported in previous clinical trials (6-996-996-996-9).

In a univariate analysis using a Cox proportional hazards model excluding patients with missing values, the factors related to longer PFS were "good PS (0, 1)," "nonsquamous cell carcinoma," "Brinkman Index [BI] $>$ 400," "PD-L1 TPS $\geq$ 50%," "number of previous chemotherapies $=$ 0 or 1," "none or small amount of steroid use (less than or equivalent to 10 mg of prednisolone) before pembrolizumab," "treatment-related AE (grade $\geq$3)," and "no previous medical history." In a multivariate analysis, a PS of 0 or 1 (hazard ratio [HR] $=$ 0.49, 95% CI: 0.33–0.71, $p = 0.0002$), nonsquamous cell carcinoma (HR $=$ 0.72, 95% CI: 0.53–0.98, $p = 0.0349$), number of previous chemotherapies more than or equal to two (HR $=$ 1.72, 95% CI: 1.15–2.58, $p = 0.0083$), BI more than 400 (HR $=$ 0.64, 95% CI: 0.42–0.97, $p =$ 0.0355), and treatment-related AE (grade $\geq$3) (HR $=$ 0.60, 95% CI: 0.41–0.88, $p = 0.0095$) were significant independent predictors of PFS (Supplementary Table 2, Supplementary Data 1, Supplementary Fig. 1, and Supplementary Data 2 illustrate the Kaplan-Meier curves for PFS stratified by each predictor).

In a univariate analysis using a Cox proportional hazards model excluding patients with missing values, the factors related to longer OS were "good PS (0, 1)," "nonsquamous cell carcinoma," "BI $>$ 400," "PD-L1 expression $\geq$ 50%," "number of previous chemotherapies $=$ 0 or 1," "none or small amount of steroid use (less than or equivalent to 10 mg of prednisolone) before pembrolizumab," and "no previous medical history." In a multivariate analysis, a PS of 0 or 1 (HR $=$ 0.41, 95% CI: 0.28–0.61, $p <$ 0.0001), nonsquamous cell carcinoma (HR $=$ 0.66, 95% CI: 0.47–0.91, $p = 0.0118$), number of previous chemotherapies more than or equal to two (HR $=$ 2.01, 95% CI: 1.34–3.01, $p =$ 0.007), PD-L1 TPS more than or equal to 50% (HR $=$ 0.64, 95% CI: 0.43–0.93, $p = 0.0195$), and steroid use (HR $=$ 2.20, 95% CI: 1.01–4.77, $p = 0.0460$) were significant independent predictors of OS (Table 2 and Fig. 2 illustrate the Kaplan-Meier curves for OS stratified by each predictor).

Toxicity

Overall, 55 patients (18%) had more than or equal to grade 3 AEs (Table 3, Supplementary Table 3, and Supplementary Data 1 illustrate the treatment-related AEs). Five patients (1.7%) died of treatment-related AEs attributed to pembrolizumab, including pneumonitis (n $=$ 3) and pneumonia (n $=$ 2). Among the patients who developed grade 3 or higher nonhematologic AEs, the most frequent AE was pneumonitis (n $=$ 17, 5.7% of all patients) (Table 3).

Pseudoprogression

Pseudoprogression is an uncommon phenomenon observed in patients treated with ICIs. The actual frequency of this phenomenon and its effect on patients' prognoses are not well understood. We have collected data on pseudoprogression in this study and found seven patients who experienced pseudoprogression (Supplementary Fig. 2). Pseudoprogression did not reveal great effect on patients' prognoses in this study; however, a larger sample size is necessary to clarify the clinical effect of pseudoprogression.

Table 2. Univariate and Multivariate Analyses of OS

			Univariate Analysis			Multivariate Analysis		
	N	Median OS (d)	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age								
≤75	78	440	1.255	0.928-1.698	0.1397			
≤74	220	614						
Gender								
Male	226	513	1.171	0.852-1.608	0.3303			
Female	72	626						
Smoking history								
Former or current	250	526	1.217	0.805-1.838	0.3517			
Never	39	626						
Smoking index								
<400	217	636	0.556	0.373-0.830	0.0041	0.684	0.449-1.043	0.0777
≤400	33	283						
Performance status								
0, 1	248	700	0.337	0.239-0.475	<0.0001	0.409	0.276-0.607	<0.0001
2, 3, 4	50	133						
Histology								
Nonsq	220	645	0.667	0.495-0.899	0.0079	0.656	0.473-0.911	0.0118
Squamous	78	366						
PD-L1 TPS								
≤50%	240	654	0.571	0.415-0.787	0.0006	0.635	0.433-0.929	0.0195
1%-49%	57	288						
Previous chemotherapy								
≤2 lines	53	246	1.748	1.249-2.446	0.0011	2.009	1.342-3.007	0.0007
≤1 line	244	662						
Liver metastasis								
Metastasis	23	420	1.401	0.852-2.302	0.1839			
None	275	574						
Brain metastasis								
Metastasis	52	585	0.894	0.616-1.296	0.5533			
None	246	515						
Bone metastasis								
Metastasis	73	420	1.214	0.891-1.654	0.2195			
None	225	589						
Malignant pleural effusion								
Metastasis	14	294	1.411	0.769-2.591	0.2665			
None	284	574						
Steroid use								
Use	11	62	3.515	1.907-6.478	<0.0001	2.200	1.014-4.773	0.0460
None	284	585						
Radiation (before ICI)								
Yes	92	557	0.950	0.706-1.277	0.7321			
No	206	558						
Surgery (before ICI)								
Yes	57	717	0.930	0.661-1.308	0.6747			
No	241	513						
Treatment-related AE (≥grade 3)								
Yes	60	557	0.805	0.567-1.145	0.2276			
No	238	572						
Previous medical history								
Yes	194	440	1.569	1.169-2.105	0.0027	1.395	0.996-1.955	0.0529
No	104	716						

AE, adverse event; CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1 TPS, programmed cell death death-ligand 1 tumor proportion score.

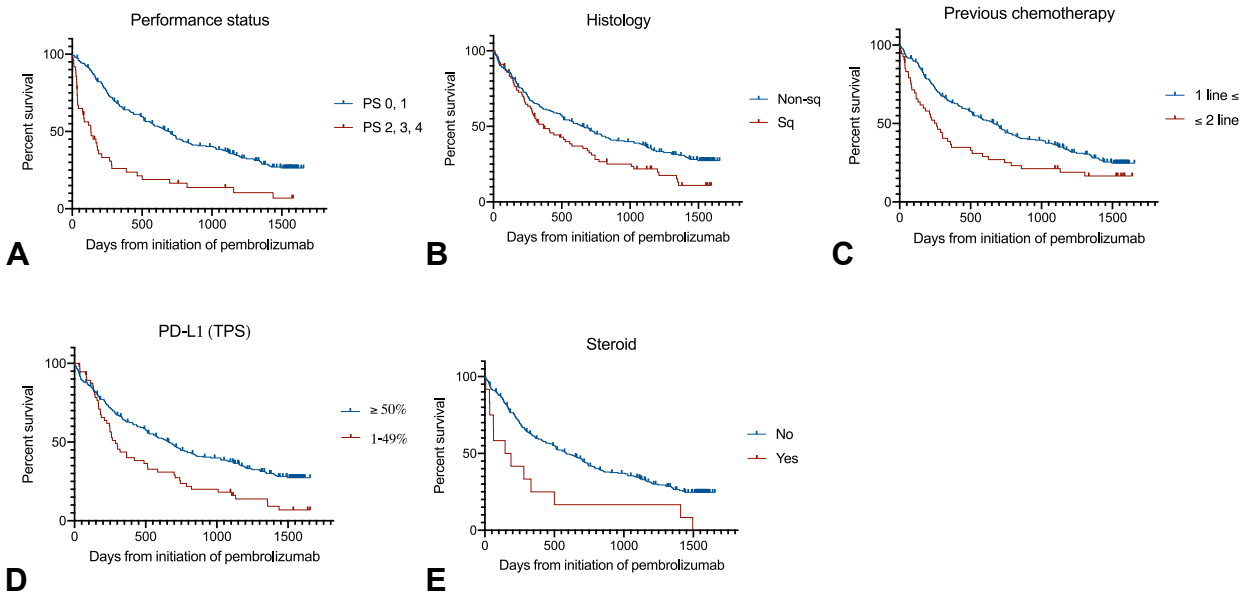

Figure 2. Kaplan-Meier curves of survival stratified by prognostic factors identified by multivariate analysis. Survival data were stratified by (*A*) performance status, (*B*) histology, (*C*) number of previous chemotherapies, (*D*) TPS of PD-L1, and (*E*) steroid use before treatment. PD-L1, programmed death-ligand 1; PS, performance status; Sq, squamous; TPS, tumor proportion score.

Discussion

This is the first observational study to use Japanese PMACS data. Although collected and validated by pharmaceutical companies, the data are mainly used to report unexpected AEs observed in clinics and are not used to evaluate the efficacy of the drug. In this study, we established a new system for collecting and analyzing the clinical information of patients who were administered newly approved drugs and enrolled in PMACS in Japan. We recycled the collected data from each hospital and collected and incorporated additional original follow-up data to evaluate the efficacy and safety of the study drug during a long-term follow-up period. A strength of this study is that we were able to conduct the analysis independently from the pharmaceutical companies, as they only provided PMACS data. Notably, with the exception of requesting the addition of simple prognostic information, this study reduced the burden of case report forms usually placed on researchers.

PMACS is a unique surveillance system in Japan and is often required by the Pharmaceutical and Medical Devices Agency when a new drug is approved, especially an anticancer drug.

Recently, multiple reports on real-world data analysis have been published,[13–16] among which ICIs were often analyzed.[17–19] Regarding pembrolizumab monotherapy, Cramer-van der Welle et al.[18] compared efficacy data from electronic health records and clinical trials. In first-line treatment settings, the OS was significantly lower in real-world compared with that in clinical trial settings (HR = 1.55, 95% CI: 1.07–2.25, $p = 0.018$).[18] The authors analyzed the data and suggested that the reason for the difference in efficacy was that fewer subsequent treatments were administered in real-world settings than in clinical trials.

As mentioned in a recent report, Japanese patients were only assessed as a small subpopulation in global, large-scale, phase 3 trials, and the evaluation of efficacy and safety specific to the Japanese population may be insufficient.[14] Because it is extremely difficult to conduct another phase 3 trial in a Japanese subpopulation after approval of innovative new treatments, assessments using postmarketing data become important.

This study had some limitations. Although more than 3000 patients were originally included in PMACS for pembrolizumab, only 300 ultimately participated in this study, thus failing to reveal a sufficient number for real-data analysis. Furthermore, as the PMACS system was created by a pharmaceutical company to collect data of unexpected AEs in clinics, it did not contain enough information to assess the real-world effectiveness of drugs.

Theoretically, our system may be applied to other newly approved drugs, and our experience may be useful for the establishment of a more efficient and informative system for using PMACS data. Indeed, several ongoing studies intend to use PMACS data in Japan (UMIN000044375, UMIN000033133, UMIN000041263, and UMIN000037090), although most of these projects

Table 3. List of Adverse Events (Grade ≥3) Observed in This Study

Drug-Related Adverse Events	Grades 3-5
Overall	74
Pneumonitis	17
Hepatotoxicity	8
Skin toxicity	5
Pneumonia	5
Colitis	3
Diabetes mellitus	3
Hypopituitarism	3
Hyperglycemia	2
Herpes zoster	2
Encephalitis	2
Respiratory failure	2
Dyspnea	2
Arthritis	2
Hyponatremia	1
Decreased appetite	1
Pleural effusion	1
Empyema	1
Uveitis	1
Myasthenia gravis	1
Optic neuritis	1
Cerebeller ataxia	1
Cerebral infarction	1
Bronchial fistula	1
Oral mucositis	1
Pericardial effusion	1
Pericarditis	1
AV block	1
Cardiac tamponade	1
Myocardial infarction	1
Intestinal obstruction	1
Digestive tract perforation	1

AV, atrioventricular.

are funded by pharmaceutical companies. Collaboration among academic societies, pharmaceutical companies, and clinicians is required in modern health care to build a system that effectively uses valuable patient medical information, as new drugs are being developed every day.

Japanese PMACS is useful for assessing real-world data, as revealed with our new system. In the first trial of this system, we successfully collected and used a combination of PMACS and direct input information for real-world data analysis of pembrolizumab in Japan. In the future, a more sophisticated system should be established to collect more valuable data from PMACS efficiently.

CRediT Authorship Contribution Statement

Hideki Terai: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing—original draft, Writing—review and editing.

Kenzo Soejima: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing—original draft, Writing—review and editing.

Asanao Shimokawa: Formal analysis, Methodology, Writing—original draft, Writing—review and editing.

Hidehito Horinouchi: Conceptualization, Data curation, Investigation, Methodology, Writing—review and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100404.

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