

Real-world outcomes of pembrolizumab monotherapy in non-small cell lung cancer in Japan: A post-marketing surveillance

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Abstract

This post-marketing surveillance (PMS) was initiated in Japan to identify factors affecting the safety and effectiveness of pembrolizumab monotherapy in patients with advanced non-small cell lung cancer (NSCLC) with programmed cell death ligand-1 (PD-L1) expression. This PMS was conducted from December 2016 to June 2019 at 717 centers across Japan. Patients with unresectable advanced/recurrent NSCLC who received pembrolizumab monotherapy as first-line (1L) treatment for PD-L1-expressing tumors (Tumor Proportion Score [TPS] \geq 50%) or second-line or later (2L+) treatment for tumors with PD-L1 TPS \geq 1% were enrolled and followed up for 1 year. Of 2805 registered patients, 2740 and 2400 comprised the safety and effectiveness analysis sets, respectively. The median age (range) was 69 (27–92) years; 55.7% and 29.2% of patients experienced treatment-related adverse events and adverse events of special interest (AEOSIs), respectively. More common AEOSIs included interstitial lung disease, endocrine disorders, liver dysfunction, colitis/severe diarrhea, infusion reactions, and severe skin disorders. The frequency of experiencing \geq 2 AEOSIs was low (1L, 6.5%; 2L+, 2.8%). Most AEOSIs occurred within 150 days after initiation of pembrolizumab monotherapy. At 1-year follow-up, the objective response rate was 39.2% (1L, 51.5%; 2L+, 30.0%). In conclusion, the 1-year safety and effectiveness of pembrolizumab monotherapy in patients with unresectable advanced/recurrent NSCLC as 1L treatment for tumors with PD-L1 TPS \geq 50% and 2L+ treatment for tumors with PD-L1 TPS \geq 1% were similar to those reported in phase 2/3 trials.

KEYWORDS

Japan, NSCLC, PD-L1, pembrolizumab, post-marketing surveillance

Abbreviations: 1L, first line; 2L+, second-line or later; AE, adverse event; AEOSI, adverse events of special interest; ALK, anaplastic lymphoma kinase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CTCAE, Common Terminology Criteria for Adverse Events; EDC, Electronic Data Capture; EGFR, epidermal growth factor receptor; GPSP, Good Post-marketing Study Practice; ILD, interstitial lung disease; irAE, immune-related AE; MedDRA, Medical Dictionary for Regulatory Activities; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PMS, post-marketing surveillance; PS, performance status; TKI, tyrosine kinase inhibitor; TPS, Tumor Proportion Score; TRAE, treatment-related AE.

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1 | INTRODUCTION

Globally, lung cancer is the most common form of cancer and cause of mortality.¹ The incidence rates among men are high in Japan (>40/100,000) and comparable with those in North America and Europe.^{1,2}

The majority of lung cancer is non-small cell lung cancer (NSCLC; 85%), with two predominant histological phenotypes, adenocarcinoma (approximately 50%) and squamous cell carcinoma (approximately 40%).^{3,4} NSCLC is often diagnosed at an advanced stage; unfortunately, the prognosis for stage IV NSCLC was poor, with a 5-year survival rate of 0%–10% in the past.³

Pembrolizumab is a programmed cell death receptor-1 (PD-1)-blocking humanized monoclonal immunoglobulin (Ig) G4κ⁵ that is globally approved for cancer immunotherapy. Pembrolizumab monotherapy is currently indicated as the first-line (1L) treatment for patients with locally advanced or metastatic NSCLC with programmed cell death ligand-1 (PD-L1) expression (tumor proportion score [TPS] ≥ 1%) and no alterations in the epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) genes. It is also indicated for patients with tumors expressing PD-L1 TPS ≥ 1% with disease progression during or after platinum-doublet chemotherapy.⁵ In addition to monotherapy, combination therapies of pembrolizumab with platinum doublet are indicated for PD-L1 all-comers without alterations in *EGFR* and *ALK* genes.

The approval of pembrolizumab monotherapy for NSCLC was based on the results of KEYNOTE-024,⁶ KEYNOTE-042,⁷ and KEYNOTE-010,⁸ whereas the approvals of combination therapies of pembrolizumab with platinum doublet were based on the results of KEYNOTE-189⁹ and KEYNOTE-407.¹⁰ In the phase 3 KEYNOTE-024 trial, 1L pembrolizumab monotherapy demonstrated significantly longer progression-free survival (PFS) and overall survival (OS) with less-frequent adverse events (AEs) compared with the investigator's choice of platinum-based chemotherapy in patients with advanced NSCLC and PD-L1 TPS ≥ 50%.⁶ Prolonged follow-up (median, 25.2 months) of 1L pembrolizumab monotherapy in KEYNOTE-024 also indicated an OS benefit over chemotherapy despite a crossover from the control arm (chemotherapy) to pembrolizumab monotherapy as subsequent therapy.¹¹ In the phase 3 KEYNOTE-042 trial, 1L pembrolizumab monotherapy demonstrated a significantly longer OS with less frequent AEs compared with the investigator's choice of carboplatin plus paclitaxel or pemetrexed in treatment-naïve patients with locally advanced or metastatic NSCLC and PD-L1 TPS ≥ 1%.⁷ In the phase 2/3 KEYNOTE-010 trial, pembrolizumab monotherapy prolonged OS with a favorable benefit-to-risk profile compared with docetaxel in patients with previously treated advanced NSCLC and PD-L1 TPS ≥ 1%.⁸ Importantly, a pooled analysis was performed in elderly patients in the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 trials.¹² Clinical outcomes with pembrolizumab in patients aged ≥75 years were comparable with those in the overall population in the trials.¹²

In the clinical trials mentioned above, limited data are available on Japanese patients. Recently, however, a prespecified subanalysis was conducted on Japanese patients in the KEYNOTE-024 trial. The results demonstrated that pembrolizumab monotherapy improved PFS and OS versus chemotherapy, with a manageable safety profile in Japanese patients with advanced NSCLC. The results were consistent with those of the overall population in KEYNOTE-024.¹³

This post-marketing surveillance (PMS) was initiated to investigate the safety and effectiveness of pembrolizumab monotherapy in Japanese clinical practice for patients with unresectable advanced/recurrent NSCLC with PD-L1 expression in accordance with Good Post-marketing Study Practice (GPSP) and Japanese regulations for PMS.

2 | MATERIALS AND METHODS

2.1 | Study design

Patients ($n = 2832$) treated with pembrolizumab monotherapy were enrolled at 726 medical oncology centers between December 19, 2016 and June 23, 2017 and observed for 1 year. Subsequently, 717 medical oncology centers (with 2805 registrations) agreed to use data for publication purposes. However, case report forms could not be collected from seven patients (out of 2805). Thus, the findings reported here comprise data from 2798 patients. This PMS was initiated after approval based on KEYNOTE-024 (1L, TPS ≥ 50%) and KEYNOTE-010 (second-line or later [2L+], TPS ≥ 1%).^{6,8} The 1-year follow-up was also based on the observation that most AEs, including interstitial lung disease (ILD), occurred within 1 year in KEYNOTE-024 and KEYNOTE-010. Eligible patients were followed up at 1, 3, 6, and 12 months after treatment initiation with pembrolizumab monotherapy. The survey was conducted using an all-case surveillance approach mainly with an electronic data capture (EDC) system. The EDC system utilizes the InForm of Japanese Oracle K.K. and provides data from forms collected from the relevant study sites.

Approval from the institutional review board and ethics committee and written informed consent from patients, although not mandatory, was obtained on the basis of the requirements of each study site.

2.2 | Patients

This PMS enrolled patients with unresectable advanced/recurrent NSCLC who received pembrolizumab monotherapy as 1L treatment for tumors with PD-L1 TPS ≥ 50% or as 2L+ treatment for tumors with PD-L1 TPS ≥ 1%. Notably, this PMS was conducted before the approval of KEYNOTE-042 (1L, TPS ≥ 1%).⁷ Therefore, 1L treatment with pembrolizumab was based on KEYNOTE-024 (TPS ≥ 50%)⁶ and not on KEYNOTE-042 (TPS ≥ 1%).⁷

2.3 | Treatment

Pembrolizumab monotherapy was initiated at a fixed dose of 200 mg pembrolizumab every 3 weeks.

2.4 | Assessment of safety and effectiveness

Data regarding the safety and effectiveness of pembrolizumab monotherapy included patient characteristics, information on pembrolizumab administration (date of completion/discontinuation, reasons for discontinuation/dropout, and each date of pembrolizumab administration), AEs and adverse drug reactions, and objective response rate (ORR) as effectiveness. AEs were assessed by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and were coded by preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1. Priority items of AEs were defined as AEs of special interests (AEOSIs) (Table S1). Tumor responses were assessed by investigators by reference to RECIST, version 1.1. ORRs were then calculated based on the assessment.

2.5 | Statistical analysis

The planned sample size was 1000 patients positive for PD-L1: 500 per treatment line (1L [TPS \geq 50%] versus 2L+ [TPS \geq 1%]).

Among the safety survey items for pembrolizumab, the incidence rate of the following AEOSIs was \geq 0.5% in KEYNOTE-010⁸ or KEYNOTE-024⁶: ILD, colitis/severe diarrhea, thyroid dysfunction, infusion reactions, and type 1 diabetes mellitus. Assuming an incidence rate in the PMS at the same level as that in clinical trials, a target sample size of 1000 cases was required to capture the incidence of events for one or more cases with a reliability of 99%. The safety analysis set was defined as patients who received at least one dose of pembrolizumab. Patients were excluded if their safety data were

absent or uncollectible. The effectiveness analysis set was defined as patients with available effectiveness evaluations with no treatment/administration/protocol deviations. Data were summarized descriptively; continuous values were summarized as the mean, median, and range and 95% confidence intervals (CIs), whereas discrete values were summarized as the number and percentage of patients. A univariate analysis of ILD onset due to patient background factors such as sex, age, ECOG performance status (PS), predose inpatient/outpatient status, smoking history, NSCLC status (e.g. metastasis to other sites), pre-existing conditions or complications, and prior treatment history for NSCLC was performed because ILD was the AE of most concern in Japan (see Discussion). A multivariate analysis was performed on all patients, 1L patients, and 2L+ patients, with the lower limit of the 95% CI of the odds ratio exceeding 1 in univariate analysis and considering the factors thought to be related to ILD as explanatory factors. The incidence of ILD and associated mortality per 100 person-weeks were evaluated during the 1-year observation period.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

A total of 2805 patients were registered, of whom 2740 and 2400 comprised the safety and effectiveness analysis sets, respectively (Figure 1). As shown in Table 1, the median age (range) of the patient population was 69 (27–92) years (\geq 75 years, 27.6%), and 76.1% of patients were male. Overall, among patients who received 1L therapy, 97.5% had tumors with PD-L1 TPS \geq 50%. The proportion of current smokers was higher in the 1L versus 2L+ treatment group (15.4% vs 7.4%). The remaining patient characteristics were similar between patients who received pembrolizumab as 1L or 2L+ therapy. Notably, 17.0% and 15.2% of patients showed a baseline ECOG PS of \geq 2 in the 1L and 2L+ setting,

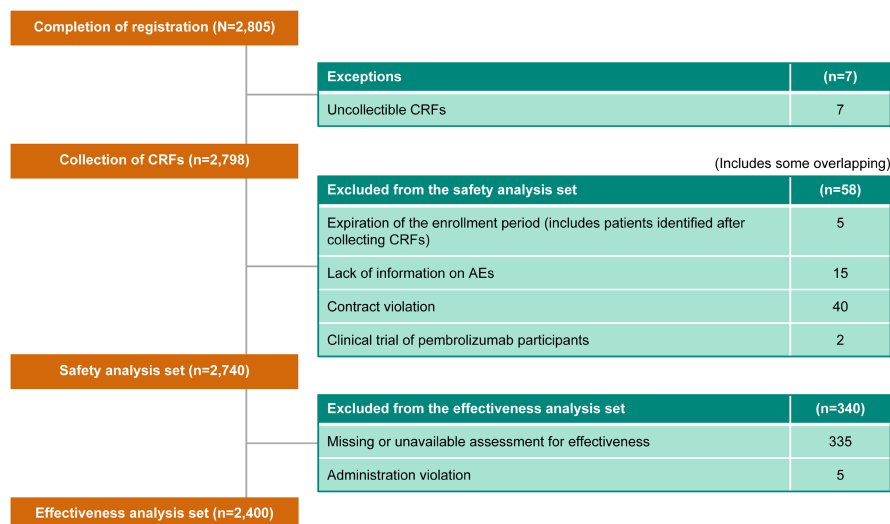


FIGURE 1 Patient disposition. AE, adverse event; CRF, case report form

TABLE 1 Patient demographics and baseline characteristics in the safety analysis set

Characteristic, n (%)	1L N = 1179	2L+ N = 1561	Total N = 2740
Age, years			
Median (range)	70 (28–91)	69 (27–92)	69 (27–92)
Age, n (%)			
≥75 years	382 (32.4)	374 (24.0)	756 (27.6)
Male	914 (77.5)	1172 (75.1)	2086 (76.1)
ECOG PS			
0 or 1	977 (82.9)	1319 (84.5)	2296 (83.8)
≥2	200 (17.0)	238 (15.2)	438 (16.0)
Unknown	2 (0.2)	4 (0.3)	6 (0.2)
Histology (multiple counts included)			
Adenocarcinoma	692 (58.7)	1020 (65.3)	1712 (62.5)
Squamous cell carcinoma	347 (29.4)	419 (26.8)	766 (28.0)
Large cell carcinoma	15 (1.3)	20 (1.3)	35 (1.3)
Others	127 (10.8)	108 (6.9)	235 (8.6)
Unknown	3 (0.3)	4 (0.3)	7 (0.3)
Smoking status			
Never	161 (13.7)	292 (18.7)	453 (16.5)
Current	182 (15.4)	115 (7.4)	297 (10.8)
Former	778 (66.0)	1058 (67.8)	1836 (67.0)
PD-L1 TPS			
≥50%	1149 (97.5)	966 (61.9)	2115 (77.2)
1%–49%	29 (2.5)	594 (38.1)	623 (22.7)
<1%	1 (0.1)	0 (0.0)	1 (0.0)
Unknown	0 (0.0)	1 (0.1)	1 (0.0)
EGFR mutant	37 (3.1)	201 (12.9)	238 (8.7)
ALK fusion gene	27 (2.3)	56 (3.6)	83 (3.0)
Brain metastasis	206 (17.5)	266 (17.0)	472 (17.2)
Liver metastasis	88 (7.5)	114 (7.3)	202 (7.4)
Prior thoracic radiation	48 (4.1)	267 (17.1)	315 (11.5)
Prior or pre-existing interstitial lung disease	34 (2.9)	66 (4.2)	100 (3.6)
Current autoimmune disease	11 (0.9)	13 (0.8)	24 (0.9)

Abbreviations: 1L, first-line; 2L+, second-line or later; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed cell death ligand-1; PS, performance status; TPS, Tumor Proportion Score.

respectively. The treatment profile is shown in Table 2. The median time on treatment was longer among patients who received pembrolizumab as 1L vs those who received pembrolizumab as 2L+ therapy (15.6 weeks vs 11.2 weeks). Pembrolizumab was discontinued in 68.2% vs 76.0% of patients in the 1L vs 2L+ treatment group over the 1-year follow-up period. The most common reason

for treatment discontinuation was disease progression, followed by AEs, death, and transfer or loss of follow-up, in both the 1L and 2L+ treatment groups.

3.2 | Safety

Overall, 55.7% and 29.2% of patients experienced treatment-related AEs (TRAEs) and AEOs designated in the Japanese risk management plan (see Table S1 for the AEOs list), respectively (Table 3). Grade ≥3 TRAEs and AEOs were reported in 21.1% and 11.2% of patients, respectively. The most common TRAE (≥3%), excluding AEOs, was pyrexia (9.7%), followed by rash (6.9%), diarrhea (4.2%), malaise (3.5%), and decreased appetite (3.0%).

3.2.1 | AEOs

The most common AEO was ILD (interstitial lung disease, pneumonitis, and organizing pneumonia), followed by endocrine disorders, liver dysfunction, colitis/severe diarrhea, infusion reactions, and severe skin disorders (Figure 2). The incidence of AEOs, such as ILD, liver dysfunction, infusion reactions, and severe skin disorders, was approximately 1.5–2 times higher among 1L patients compared with 2L+ patients. The incidence of AEOs was similar between patients aged <75 years and those ≥75 years (Table 4). However, liver dysfunction and infusion reactions tended to occur in younger patients (aged <75 years) in the 1L setting compared with the 2L+ setting (Table 4 and Table S2). The frequency of experiencing more than one AEO was low (one event, 24.8%; two events, 4.0%; three events, 0.4%; four events, 0%) and similar between the 1L (one event, 29.2%; two events, 6.0%; three events, 0.5%; four events, 0%) and 2L+ (one event, 21.5%; two events, 2.5%; three events, 0.3%; four events, 0.1%) treatment groups (Table S3). Notably, however, 15.1% (121/680+121) of patients in whom AEOs were observed experienced ≥2 events of AEOs (Table S3), suggesting that monitoring of various organs is important during pembrolizumab monotherapy.

When individual AEOs were categorized by the occurrence of ≥2 events of AEOs, patients in whom ILD was observed ($n = 333$; one event, 80.8% [$n = 269$]) also experienced endocrine disorders (6.9%, $n = 23$), followed by liver dysfunction (5.4%, $n = 18$), colitis/severe diarrhea (2.7%, $n = 9$), infusion reactions (2.4%, $n = 8$), severe skin disorders (1.5%, $n = 5$), myocarditis (0.9%, $n = 3$), myositis/rhabdomyolysis and nervous system disorders (0.6%, $n = 2$ patients each), and type 1 diabetes mellitus, uveitis, and myasthenia gravis (0.3%, $n = 1$ patient each) (Table S4).

Most AEOs occurred within 150 days after initiation of pembrolizumab as 1L or 2L+ treatment (Figure 3). Notably, more than a few patients experienced type 1 diabetes mellitus or renal dysfunction after day 150. AEOs related to death included ILD (1.3%, $n = 35$), colitis/severe diarrhea (0.1%, $n = 2$), liver dysfunction (0.1%, $n = 2$), myocarditis (0.1%, $n = 2$), and nervous system disorders (0.04%, $n = 1$) (Table S5).

	1L	2L+	Total
	N = 1179	N = 1561	N = 2740
Mean (range) time on treatment, weeks	22.5 (0.1–52.3) ^a	19.0 (0.1–52.3) ^b	20.5 (0.1–52.3) ^c
Median time on treatment, weeks	15.6 ^a	11.2 ^b	12.6 ^c
Treatment status, n (%)			
Continuation	375 (31.8)	375 (24.0)	750 (27.4)
Discontinuation	804 (68.2)	1186 (76.0)	1990 (72.6)
Reason for discontinuation, n (%)			
Disease progression	357 (44.4)	670 (56.5)	1027 (51.6)
Adverse event	255 (31.7)	261 (22.0)	516 (25.9)
Death	127 (15.8)	188 (15.9)	315 (15.8)
Transfer or loss of follow-up	24 (3.0)	32 (2.7)	56 (2.8)
Others/unknown	41 (5.1)	35 (3.0)	76 (3.8)

Abbreviations: 1L, first-line; 2L+, second-line or later.

^aTreatment period of 20 patients was unknown. These 1L patients were excluded for this analysis (N = 1159).

^bTreatment period of 15 patients was unknown. These 2L+ patients were excluded for this analysis (N = 1546).

^cTreatment period of 35 patients was unknown. These patients were excluded for this analysis (N = 2705).

Using multivariate analysis, the main factors associated with ILD onset or deterioration were then investigated (Table 5). Among patients receiving 1L treatment, the main factors were current/former smoking status, a history of or pre-existing ILD, and a history of or pre-existing neoplasms except lung cancer. Among patients receiving 2L+ treatment, the main factors were a history of or pre-existing chronic obstructive pulmonary disease (COPD) and a history of or pre-existing respiratory/thoracic/mediastinal disorders. Over 52 weeks, the incidence of ILD and associated mortality per 100 person-weeks tended to be higher in the early phase (week 1 to week 25) of treatment for both 1L and 2L+ treatment groups (Figure 4).

3.3 | Effectiveness

At the 1-year follow-up, the investigator-assessed ORR was 39.2% (Figure 5). ORR was 51.5% in the 1L treatment group and 30.0% in the 2L+ treatment group. In addition, in the 2L+ treatment group, ORR was 37.6% among patients with PD-L1 TPS \geq 50% and 17.8% among patients with PD-L1 TPS 1%–49%.

4 | DISCUSSION

This large PMS was conducted to confirm the real-world safety and effectiveness of pembrolizumab monotherapy as 1L and 2L+ treatment in Japanese clinical practice in patients with unresectable advanced/recurrent PD-L1-positive NSCLC (TPS \geq 50% and TPS \geq 1%,

respectively). The 52-week safety analysis dataset (n = 2740) and effectiveness analysis dataset (n = 2400) were analyzed in this PMS.

The incidence rate of TRAEs was 63.4% in the 1L setting and 50.0% in the 2L+ setting. The incidence rate of pembrolizumab-induced AEOSIs was 35.7% in the 1L setting and 24.3% in the 2L+ setting. Thus, AE incidences in the 2L+ setting were lower than those in the 1L setting. Important differences were noted between the 1L and 2L+ settings for ILD (1L, 15.9%; 2L+, 9.4%) and liver dysfunction (1L, 7.7%; 2L+, 3.3%). There might be several reasons for these differences. First, patient characteristics were different between the 1L and 2L+ settings. For example, PD-L1 expression levels were different (1L, TPS \geq 50%; 2L+, TPS \geq 1%). In fact, a recent study suggests that high PD-L1 expression at the time of pre-treatment is a predictor of immune-related AE (irAE) development in Japanese patients treated with pembrolizumab monotherapy.¹⁴ Second, the drug exposure time of pembrolizumab was different. Specifically, the median time on treatment was 15.6 weeks in the 1L setting, whereas it was 11.2 weeks in the 2L+ setting. Thus, the drug exposure time was shorter in the 2L+ setting, which likely contributed to lower pembrolizumab toxicity. Third, 2L+ patients were already treated with chemotherapy agent(s) in prior treatment line(s), which might have induced immunosuppression through bone marrow suppression, as described previously.^{15–18} This immunosuppression might have reduced pembrolizumab-induced toxicity. Taken together, although a direct comparison cannot be made between the 1L and 2L+ settings, lower AE incidences were observed in the 2L+ setting in the real world.

In this PMS, the most common AEOSI was ILD (12.2%). Notably, its incidence was higher than that observed in the clinical trials

TABLE 2 Treatment profile in the safety analysis set

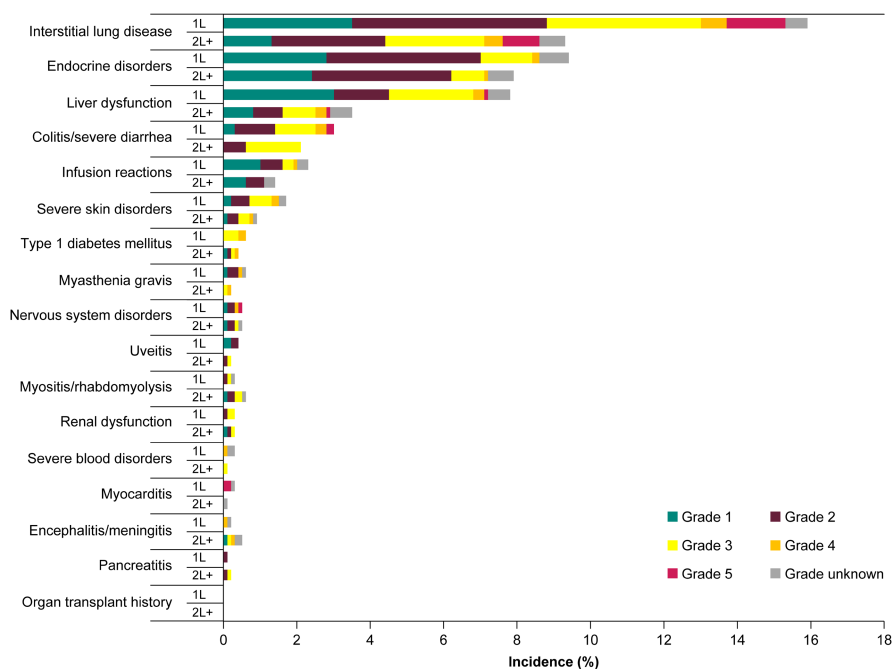
TABLE 3 Pembrolizumab-induced TRAEs, including AEOSIs, in the safety analysis set

	1L N = 1179	2L+ N = 1561	Total N = 2740			
TRAEs, n (%)						
Any	747 (63.4)	780 (50.0)	1527 (55.7)			
Grade ≥ 3	291 (24.7)	286 (18.3)	577 (21.1)			
Grade 5	70 (5.9)	63 (4.0)	133 (4.9)			
Pembrolizumab-induced AEOSIs, n (%) ^a						
Any	421 (35.7)	380 (24.3)	801 (29.2)			
Grade ≥ 3	161 (13.7)	145 (9.3)	306 (11.2)			
Grade 5	23 (2.0)	17 (1.1)	40 (1.5)			
Events in $\geq 3\%$ of patients (TRAEs, excluding AEOSIs), n (%)						
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Decreased appetite	43 (3.6)	7 (0.6)	38 (2.4)	11 (0.7)	81 (3.0)	18 (0.7)
Diarrhea	50 (4.2)	10 (0.8)	64 (4.1)	10 (0.6)	114 (4.2)	20 (0.7)
Rash	93 (7.9)	4 (0.3)	95 (6.1)	10 (0.6)	188 (6.9)	14 (0.5)
Malaise	40 (3.4)	2 (0.2)	56 (3.6)	3 (0.2)	96 (3.5)	5 (0.2)
Pyrexia	132 (11.2)	4 (0.3)	133 (8.5)	6 (0.4)	265 (9.7)	10 (0.4)

Abbreviations: 1L, first-line; 2L+, second-line or later; AEOSIs, adverse events of special interest designated in the Japanese risk management plan; TRAE, treatment-related adverse event.

^aObserved AEOSIs: interstitial lung disease, colitis/severe diarrhea, liver dysfunction, renal dysfunction, endocrine disorders, type 1 diabetes mellitus, uveitis, myositis/rhabdomyolysis, pancreatitis, nervous system disorders, severe skin disorders, encephalitis/meningitis, myasthenia gravis, myocarditis, severe blood disorders, infusion reactions, and pembrolizumab administration in patients with organ transplant history, including a medical history of hematopoietic stem cell transplant.

FIGURE 2 Pembrolizumab-induced AEOSIs^a by grade. ^aAEOSIs listed in the figure were evaluated by investigators as TRAEs. 1L, first-line; 2L+, second-line or later; AEOSIs, adverse events of special interest designated in the Japanese risk management plan; TRAE, treatment-related adverse event



KEYNOTE-024 (5.8%)⁶ and KEYNOTE-010 (4%–5%).⁸ However, since the incidences in clinical trials were derived from the overall population and not only from the Japanese subpopulation, the incidence of ILD in the Japanese PMS cannot be compared

directly with that observed in global clinical trials. Fortunately, the incidence of ILD in a Japanese subpopulation was recently reported in KEYNOTE-024.¹³ Although the number of Japanese patients treated with pembrolizumab was limited in KEYNOTE-024

TABLE 4 Pembrolizumab-induced major AEOSIs by age in the safety analysis set^a

	1L	2L+	Total
	N = 1179	N = 1561	N = 2740
Number of patients <75 years	797	1187	1984
Number of patients ≥75 years	382	374	756
Event (including related terms), n (%)	Any grade	Any grade	Any grade
Any AEOSIs			
<75 years	295 (37.0)	282 (23.8)	577 (29.1)
≥75 years	126 (33.0)	98 (26.2)	224 (29.6)
ILD			
<75 years	121 (15.2)	106 (8.9)	227 (11.4)
≥75 years	66 (17.3)	40 (10.7)	106 (14.0)
Colitis/severe diarrhea			
<75 years	24 (3.0)	23 (1.9)	47 (2.4)
≥75 years	10 (2.6)	9 (2.4)	19 (2.5)
Liver dysfunction			
<75 years	76 (9.5)	39 (3.3)	115 (5.8)
≥75 years	15 (3.9)	13 (3.5)	28 (3.7)
Endocrine disorders			
<75 years	80 (10.0)	89 (7.5)	169 (8.5)
≥75 years	29 (7.6)	34 (9.1)	63 (8.3)
Severe skin disorders			
<75 years	14 (1.8)	13 (1.1)	27 (1.4)
≥75 years	5 (1.3)	1 (0.3)	6 (0.8)
Infusion reactions			
<75 years	24 (3.0)	16 (1.3)	40 (2.0)
≥75 years	3 (0.8)	6 (1.6)	9 (1.2)

Abbreviations: 1L, first line; 2L+, second-line or later; AEOSIs, adverse events of special interest designated in the Japanese risk management plan; ILD, interstitial lung disease.

^aThis table is continued in Table S2.

($n = 21$), the ILD incidence rate was 14%. Thus, the ILD incidence observed in the Japanese PMS was similar to that reported in the KEYNOTE-024 Japanese subpopulation.¹³ The incidence rate of deaths due to ILD was 1.3% (35/2740) in the Japanese PMS, while that reported in previous clinical trials was 0.6% (1/154) in KEYNOTE-024¹¹ and 0.44% (3/682) in KEYNOTE-010.⁸ As described above, according to KEYNOTE-024 results, the incidence of ILD in the Japanese subpopulation was higher than that in the intent-to-treat population (14% vs 5.8%),^{6,13} which may also explain the higher fatality rate of ILD in the Japanese PMS. Interestingly, it is also recognized that ILD is more common in Japan than elsewhere during therapy with an EGFR-tyrosine kinase inhibitor (TKI) or ALK-TKI for patients with NSCLC.¹⁹⁻²³ However, the reason for this discrepancy between Japan and elsewhere is unclear. This may result from differences in genetic background, environment, or clinical practice in Japan.

Next, we tried to identify risk factors for ILD by using multivariate analysis. Although the risk factors for ILD onset or deterioration varied in each treatment setting, pembrolizumab monotherapy tended to be associated with the onset or deterioration of ILD in patients with a history of smoking or respiratory disease (pre-existing complications such as ILD and COPD) compared with those without. Similarly, the incidence of immune checkpoint inhibitor-related ILD has been reported to be higher in patients with pre-existing interstitial lung abnormalities, including pulmonary fibrosis, versus those without such abnormalities.²⁴⁻²⁶ Thus, based on the PMS and these reports, treatment with an immune checkpoint inhibitor for such patients should be done very carefully or avoided. Regarding the incidence of ILD and its mortality, the onset of ILD seemed to occur not only during the early phase but also in the middle and later phases of pembrolizumab treatment. Therefore, constant monitoring is required throughout the treatment period.

In this PMS, the elderly subgroup (≥75 years of age) was investigated. The elderly population in Japan has been increasing at a faster rate; consequently, the number of elderly patients with lung cancer is increasing in Japan.^{27,28} However, elderly patients have been under-represented in clinical trials for several reasons, including poor ECOG PS, lack of adequate social support, and presence of multiple comorbid conditions.^{12,29} Therefore, in Japan, it is critical to evaluate

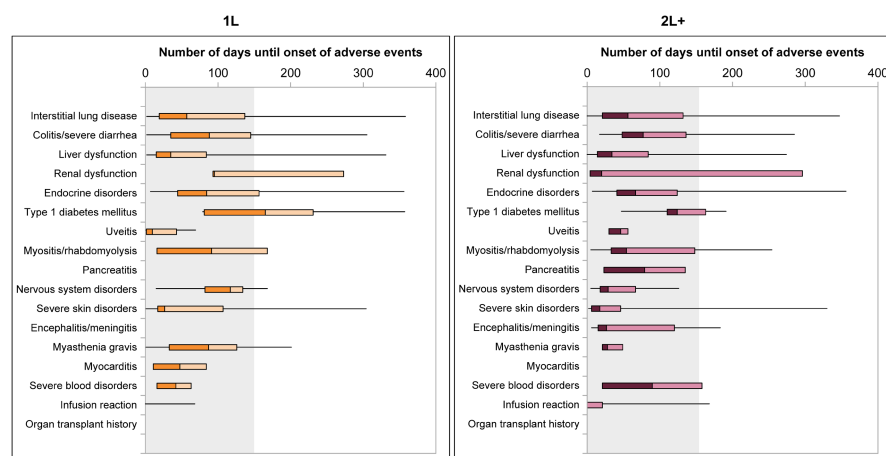


FIGURE 3 Time to onset of pembrolizumab-induced AEOSIs in the 1L and 2L+ treatment groups. Most AEOSIs occurred within 150 days in both treatment groups. Gray area indicates the observation period between days 0 and 150. 1L, first-line; 2L+, second-line or later; AEOSIs, adverse events of special interest designated in the Japanese risk management plan

TABLE 5 Multivariate analysis of ILD onset or deterioration

		Percentage of ILD, n (%)		Odds ratio (95% CI)
1L, N = 1100^a				
Smoking status (current/former vs never)	N = 942 vs N = 158	162 (17.2)	12 (7.6)	2.37 (1.28–4.39)
Prior or pre-existing ILD (yes vs no)	N = 33 vs N = 1067	12 (36.4)	162 (15.2)	3.03 (1.44–6.38)
Prior or concurrent neoplasms: benign, malignant, and unspecified (incl. Cysts and polyps, except lung cancer; SOC) (yes vs no)	N = 211 vs N = 889	47 (22.3)	127 (14.3)	1.63 (1.10–2.42)
Prior or concurrent respiratory, thoracic, and mediastinal disorders (SOC) ^b (yes vs no)	N = 106 vs N = 994	27 (25.5)	147 (14.8)	1.63 (0.99–2.67)
Concurrent disease; others ^c (yes vs no)	N = 635 vs N = 465	116 (18.3)	58 (12.5)	1.29 (0.89–1.86)
2L+, N = 1532^a				
Prior or concurrent COPD (yes vs no)	N = 104 vs N = 1428	20 (19.2)	122 (8.5)	2.52 (1.49–4.26)
Prior or concurrent respiratory, thoracic, and mediastinal disorders (SOC) ^b (yes vs no)	N = 153 vs N = 1379	24 (15.7)	118 (8.6)	2.00 (1.24–3.22)
Prior or pre-existing ILD (yes vs no)	N = 64 vs N = 1468	9 (14.1)	133 (9.1)	1.44 (0.69–3.02)

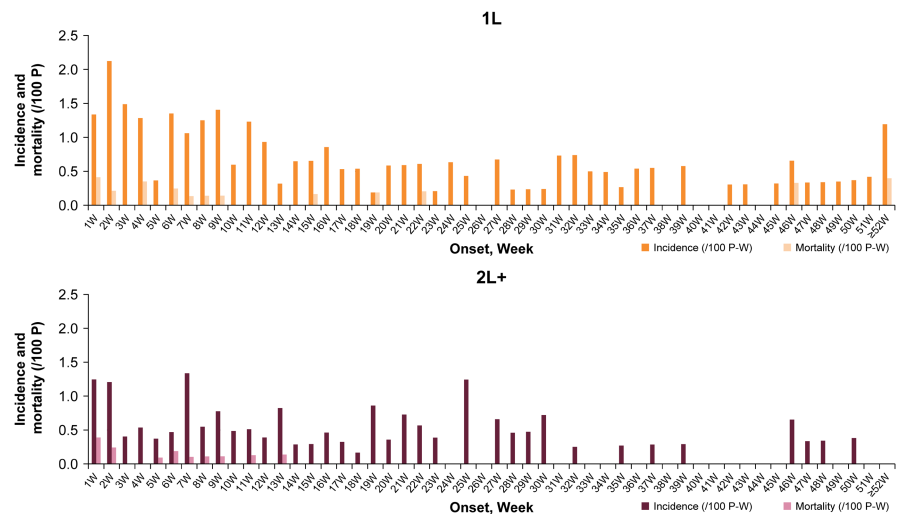
Abbreviations: 1L, first-line; 2L+, second-line or later; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; SOC, System Organ Class.

^aThe number is smaller than that shown in other Tables, because patients who had missing data were excluded in the multivariate analysis.

^bExcept ILD, COPD, asthma, and lung infection.

^cExcept ILD, COPD, asthma, lung infection, and respiratory, thoracic, and mediastinal disorders (SOC); neoplasms: benign, malignant, and unspecified (including cysts and polyps, except lung cancer) (SOC); nervous system disorders; vascular disorders; cardiopathy; endocrine disorders; liver function disorders; renal function disorders; and autoimmune disease.

FIGURE 4 Incidence^a and associated mortality of ILD per 100 person-weeks over 52 weeks by time of onset. ^aIncidence was calculated for patients with ILD onset or deterioration of pre-existing ILD. 1L, first-line; 2L+, second-line or later; ILD, interstitial lung disease; P-W, person-week; W, week



the safety of pembrolizumab in elderly patients with NSCLC. Here, we showed that the incidence of AEOSIs was not different between Japanese patients aged <75 years and ≥75 years. Importantly, this observation was confirmed by a recent pooled analysis of three clinical trials (KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042), in which outcomes with pembrolizumab in patients aged ≥75 years were comparable with those in the overall population in individual trials.¹² These results suggested that pembrolizumab monotherapy

can be safely administered to elderly patients in the real world as well as in clinical trials.

Regarding the real-world effectiveness of pembrolizumab monotherapy, the observation period was too short to properly evaluate OS and PFS in this PMS. Therefore, we only focused on ORR, which was 39.2% in the overall population treated with pembrolizumab monotherapy. Interestingly, ORR was higher in the 1L setting (51.5%) than in the 2L+ setting (30.0%) at the 1-year follow up. This

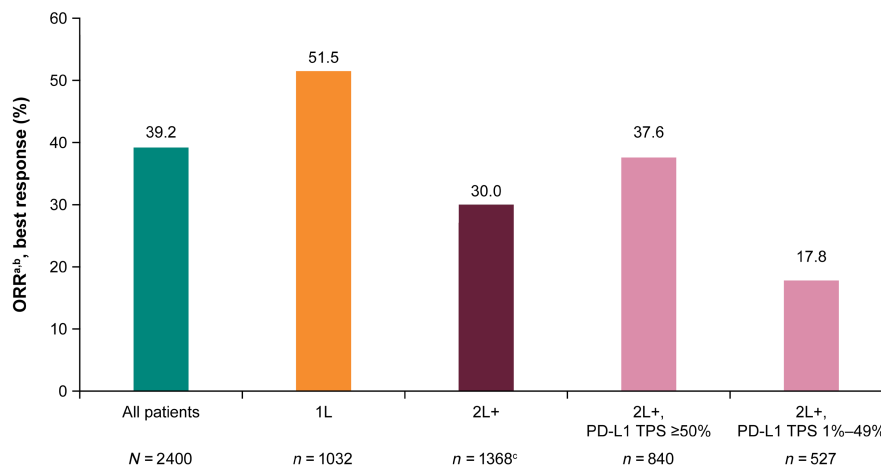


FIGURE 5 ORR in the effectiveness analysis set. ORR was higher among patients receiving 1L treatment compared with those receiving 2L+ treatment with TPS $\geq 50\%$ (51.5% vs 37.6%). ^aTumor responses were assessed by investigators (not by independent central review). ^bIncludes data for patients in whom compliance with RECIST guidelines was not confirmed. ^cIncludes patients with PD-L1 status unknown ($n = 1$). 1L, first-line; 2L+, second-line or later; ORR, objective response rate; PD-L1, programmed cell death ligand-1; TPS, tumor proportion score

tendency was consistent with the ORR results of KEYNOTE-024 versus KEYNOTE-010 (44.8% vs 18%, respectively). However, tumor responses were assessed by investigators in this PMS, whereas they were assessed by a blinded independent central radiologic review in clinical trials. This point needs to be paid special attention for comparison between the PMS and clinical trials.

In conclusion, our PMS results demonstrated the 1-year safety and effectiveness of pembrolizumab monotherapy in patients with unresectable advanced/recurrent NSCLC as 1L treatment for PD-L1 TPS $\geq 50\%$ tumors or 2L+ treatment for PD-L1 TPS $\geq 1\%$ tumors. No new AEs were observed over the 1-year follow-up period. The results were consistent with those observed in previous phase 3 trials. However, our PMS had some limitations. First, effectiveness evaluations were based on investigators' discretion. Therefore, inter-physician differences cannot be ruled out, in contrast to a centralized evaluation process. In addition, the observation period was too short to evaluate OS and PFS. Nevertheless, the PMS is an all-patient survey and the results represent the real-world observations of pembrolizumab monotherapy in Japan.

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CLINICAL TRIALS REGISTRATION

Not applicable.

DATA AVAILABILITY STATEMENT

The datasets analyzed during this PMS study are not available because data sharing with third parties was not included in the contract with all study sites or patients.

ETHICAL APPROVAL

The protocol for the research project has been approved by a suitably constituted ethics committee of the institution or has been approved according to the rules of the institution within which the work was undertaken. The study conforms with the provisions of the Declaration of Helsinki. Written informed consent from patients, although not mandatory, was obtained on the basis of requirements of each at the individual study site.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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