ORIGINAL ARTICLE

Pembrolizumab and Pemetrexed for Older Patients With Nonsquamous NSCLC and Programmed Cell Death-Ligand 1 Tumor Proportion Scores of Less Than 50%

Yoshihito Kogure, MD, PhD,[a,*] Hiroya Hashimoto, PhD,[b] Haruko Daga, MD, PhD,[c] Yasushi Fukuda, MD,[d] Akihiro Bessho, MD, PhD,[e] Tadaaki Yamada, MD, PhD,[f] Yukihiro Toi, MD,[g] Tomoki Kimura, MD, PhD,[h] Hiroshige Yoshioka, MD, PhD,[i] Koichi Azuma, MD, PhD,[j] Naoki Furuya, MD, PhD,[k] Yasutaka Fukui, MD, PhD,[l] Akiko M. Saito, MD, PhD,[b] Nobuyuki Yamamoto, MD, PhD,[m] Hideo Saka, MD,[a,n] Masashi Kondo, MD, PhD[o]

[a]*Department of Respiratory Medicine, NHO Nagoya Medical Center, Nagoya, Japan*
[b]*Clinical Research Center, NHO Nagoya Medical Center, Nagoya, Japan*
[c]*Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan*
[d]*Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan*
[e]*Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital, Okayama, Japan*
[f]*Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan*
[g]*Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan*
[h]*Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, Japan*
[i]*Department of Thoracic Oncology, Kansai Medical University, Hirakata, Japan*
[j]*Department of Internal Medicine, Division of Respirology, Neurology, and Rheumatology, Kurume University School of Medicine, Kurume-Shi, Japan*
[k]*Division of Respiratory Medicine, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan*
[l]*Department of Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi, Japan*
[m]*Department of Pulmonary Medicine and Medical Oncology, Wakayama Medical University, Wakayama, Japan*
[n]*Department of Respiratory Medicine, Matsunami General Hospital, Kasamatsu, Japan*
[o]*Department of Respiratory Medicine, Fujita Health University School of Medicine, Toyoake, Japan*

Received 13 August 2024; revised 28 November 2024; accepted 14 December 2024
Available online - 24 December 2024

ABSTRACT

Introduction: Pembrolizumab with pemetrexed and cisplatin/carboplatin is an approved first-line treatment for metastatic nonsquamous NSCLC. Nevertheless, its efficacy and safety in patients aged 75 years and above remain unclear. We assessed the efficacy and safety of pembrolizumab with pemetrexed in patients with programmed cell death-ligand 1 expression tumor proportion scores of less than 50%.

Methods: This multicenter, open-label, phase 2 trial involved 42 institutions across Japan. Eligible participants had metastatic or recurrent nonsquamous NSCLC without sensitizing *EGFR* or *ALK* alterations, were aged 75 years or above, had a programmed cell death-ligand 1 tumor proportion score of less than 50%, had not undergone systemic chemotherapy, and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients received pemetrexed (500 mg/m^2) and pembrolizumab (200 mg) on day 1 of each 21-day cycle. The primary endpoint was the objective response rate. The secondary endpoints included progression-free survival, overall survival, and safety.

***Corresponding author.**

Address for correspondence: Yoshihito Kogure, MD, PhD, Department of Respiratory Medicine, NHO Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan. E-mail: yoshihito.kogure@nnh.go.jp

Cite this article as: Kogure Y, Hashimoto H, Daga H, et al. Pembrolizumab and pemetrexed for older patients with nonsquamous NSCLC and programmed cell death-ligand 1 tumor proportion scores of less than 50%. *JTO Clin Res Rep* 2025;6:100784

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100784

Results: Forty-nine patients were enrolled in this study between July 2020 and May 2022. The objective response rate was 36.7% (95% confidence interval [CI]: 23.4%–51.7%). The disease control rate was 65.3% (95% CI: 50.4–78.3%). The median progression-free survival was 7.6 months (95% CI: 4.8–16.2), and the median overall survival was 19.4 months (95% CI: 11.8 mo–unreached). The most common grade 3 or 4 adverse events were neutropenia (31.3%), leukopenia (20.8%), and anemia (12.5%). No treatment-related deaths occurred during this period.

Conclusions: Pembrolizumab with pemetrexed is a promising first-line treatment option for older patients with metastatic nonsquamous NSCLC. This trial was registered at ClinicalTrials.gov (NCT04396457) and the Japan Registry of Clinical Trials (jRCTs041200012).

Keywords: Pembrolizumab; Pemetrexed; Nonsquamous non-small cell lung cancer; Older patients; Programmed cell death 1

Introduction

Immune checkpoint inhibitors, either with or without platinum-containing chemotherapy, are the established standard of care for patients diagnosed with advanced NSCLC.[1–6] Specifically, pembrolizumab has been developed for patients exhibiting programmed cell death-ligand 1 (PD-L1) expression, as determined using tumor proportion scores (TPS). Notably, for patients with PD-L1 TPS of 50% or higher, pembrolizumab is the primary treatment option on the basis of the outcomes observed in the KEYNOTE-024 trial.[1]

Nevertheless, the objective response rate (ORR) of pembrolizumab for patients with 1% to 49% PD-L1 was 16.9% (95% confidence interval [CI]: 13.0–21.3), which was not superior to that of those receiving platinum-containing chemotherapy (ORR = 21.7%, 95% CI: 17.4–26.4).[7]

In the case of patients with nonsquamous (non-Sq) NSCLC, the combination of pembrolizumab and pemetrexed with platinum is the standard therapeutic approach, as corroborated by the findings of the KEYNOTE-189 trial.[3] Platinum doublet plus atezolizumab with or without bevacizumab and platinum doublet chemotherapy with or without anti–PD-(L)1 antibody plus anti cytotoxic T-lymphocyte antigen-4 antibody are also options for patients with non-Sq NSCLC.[5,8–10]

In a pooled analysis of pembrolizumab, the overall survival (OS) of patients aged 75 years and above receiving pembrolizumab treatment was comparable to that of the overall study population,[7] and pembrolizumab is the standard of care for patients with NSCLC aged 75 years and above with PD-L1 TPS of 50% or higher. Immune-related adverse events (AEs) of pembrolizumab were noted in a similar frequency regardless of age (24.8% in those aged ≥75 y and 25.0% in those aged <75 y).[11] A subgroup analysis focusing on 57 patients aged 75 years and above revealed a hazard ratio (HR) of 2.09 (95% CI: 0.84–5.23) for OS and an HR of 1.73 (95% CI: 0.77–3.90) for progression-free survival (PFS) after the administration of pembrolizumab to pemetrexed and platinum.[12] Serious AEs (SAEs) were more common in patients aged 75 years or above (64.7%) than in those aged below 65 years (43.7%).[12] These findings suggest that pembrolizumab plus carboplatin and pemetrexed might neither be effective nor safe for patients with non-Sq NSCLC aged 75 years or above.

In a preclinical model, pemetrexed has reported the ability to enhance T-cell activation in mouse tumors in vivo, induce immunogenic cell death in mouse tumor cells, and exert a T-cell-intrinsic effect characterized by increased mitochondrial function and augmented T-cell activation in vitro.[9] Furthermore, using an anti–PD-L1 antibody with pemetrexed enhanced the antitumor effect more effectively than pemetrexed or an anti–PD-L1 antibody alone.[13] These findings suggest that the pembrolizumab and pemetrexed combination demonstrates notable efficiency while reducing the severe AEs associated with carboplatin.

If these preliminary findings hold clinical significance, pembrolizumab plus pemetrexed might prove more effective than pembrolizumab plus pemetrexed with carboplatin. In addition, excluding carboplatin may benefit older patients in terms of reduced toxicity.

Therefore, in this study, we assessed the efficacy and safety of pembrolizumab and pemetrexed therapy in patients aged 75 years and above with non-Sq NSCLC and PD-L1 TPS of less than 50%.

Materials and Methods

Patients

The enrollment criteria included patients aged 75 years and above with pathologically confirmed metastatic non-Sq NSCLC with a PD-L1 TPS of less than 50% (22C3), absence of sensitizing *EGFR* or *ALK* alterations, serum creatinine level of 1.5 mg/dL or less and creatinine clearance level of 45 mL/min or above, no prior systemic therapy for metastatic disease, Eastern Clinical Oncology Group performance status of 0 or 1, and at least one measurable lesion. The exclusion criteria comprised symptomatic central nervous system metastases, a history of noninfectious pneumonitis requiring

glucocorticoid use, active autoimmune disease, or ongoing systemic immunosuppressive treatment.

Study Design and Treatment

This multicenter, open-label, single-arm phase 2 study evaluated the efficacy and safety of pemetrexed and pembrolizumab in older patients with metastatic/recurrent non-Sq NSCLC.

The study was approved by the National Hospital Organization Review Board for Clinical Trials (Nagoya, Japan; approval date March 25, 2020, approval number C2019-007) and registered at the Japan Registry of Clinical Trials (jRCTs041200012). This clinical trial was also registered in ClinicalTrials.gov (NCT04396457). Before participation, each patient provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki (2013) and the Clinical Trial Act. Patients were intravenously administered pemetrexed 500 mg/m^2 and pembrolizumab 200 mg on day 1 of each 21-day cycle. Administration of folic acid and vitamin B12 was initiated one week before pemetrexed treatment initiation. Dose reduction criteria for pemetrexed are provided in the protocol. Pembrolizumab administration was capped at 35 cycles, whereas pemetrexed administration persisted until treatment cessation criteria were met. Granulocyte colony stimulating factor formulations were administered according to insurance coverage.

Endpoints

The primary endpoint was the ORR assessed by investigators, whereas the secondary endpoints included the disease control rate (DCR), duration of response (DOR), PFS, OS, and safety. The ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR) on the basis of the best objective response, whereas the DCR was defined as the proportion of patients with CR, PR, or stable disease on the basis of the best objective response. Tumor response was assessed using the new response evaluation criteria in solid tumors (Revised Response Evaluation Criteria in Solid Tumors guidelines version 1.1). Determining the CR and PR of the best overall assessment required confirmation with an effect duration of at least four weeks. DOR was defined as the time from the first response (CR or PR) to PD. PFS was defined as the time from registration to disease relapse, disease progression, or death from any cause. Finally, OS was defined as the time from registration until death from any cause.

Statistical Analysis

Assumptions of threshold and expected response rates at 20% and 40%, respectively, were made on the basis of the KEYNOTE-189 trial.[3] A sample size of 47 patients was deemed necessary to achieve a one-sided type I error of 5% and 90% power on the basis of the exact binomial distribution. Allowing for expected patient dropouts, the target sample size was set at 50. A binomial test was performed on the null hypothesis that "the true ORR was 20%," with a significance level of 5% (one-sided). For ORR and DCR, 95% CI was calculated using the Clopper-Pearson method. The Kaplan-Meier method was used to estimate survival curves, whereas the Brookmeyer and Crowley method, with complementary logarithm transformation, was used to calculate the 95% CIs of median time. The 95% CI of probability at selected time points was determined using Greenwood's formula with complementary logarithm transformation. Statistical analyses were performed using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, United States).

Results

Patients

Between July 2020 and May 2022, 49 patients were enrolled from 42 sites across Japan. Of these, one patient did not receive any treatment (Fig. 1).

The median age was 79 years (range: 75–91), 38 patients (77.6%) were male individuals, and 28 (57.1%) had a PD-L1 TPS of 1% to 49%. Thirty-three patients (67.3%) had an Eastern Clinical Oncology Group Performance Status 1, and 35 patients (71.4%) had a smoking history. Regarding comorbidities, 23 patients (46.9%) had hypertension, 21 patients (42.9%) had dyslipidemia, 10 patients (20.4%) had diabetes mellitus, 15 patients (30.6%) had chronic obstructive pulmonary disease, and six patients (12.2%) had cardiovascular disease (Table 1).

Efficacy Outcomes

As of the data collection deadline, 18 patients (36.7%) discontinued treatment owing to disease progression, 10 patients (20.4%) owing to AEs, and four patients (8.2%) at the patient's request (Fig. 1). With a median follow-up time of 15.4 months (range: 0.3–34.5), the median treatment cycle for both pembrolizumab and pemetrexed was five (range: 1–28). One patient achieved CR, and 17 patients had PR for ORR of 36.7% (95% CI: 23.4–51.7%, $p = 0.005$). Fourteen patients exhibited stable disease, and 10 patients had progressive disease (Table 2, Supplementary Fig. 1). The DCR was 65.3% (95% CI: 50.4%–78.3%)

Of the 18 patients with an objective response, the DOR was 13.3 months (95% CI: 6.1–22.8 mo), and 61.1% maintained their response for at least 12 months (Fig. 2*A*). The median time to response was 1.5 months

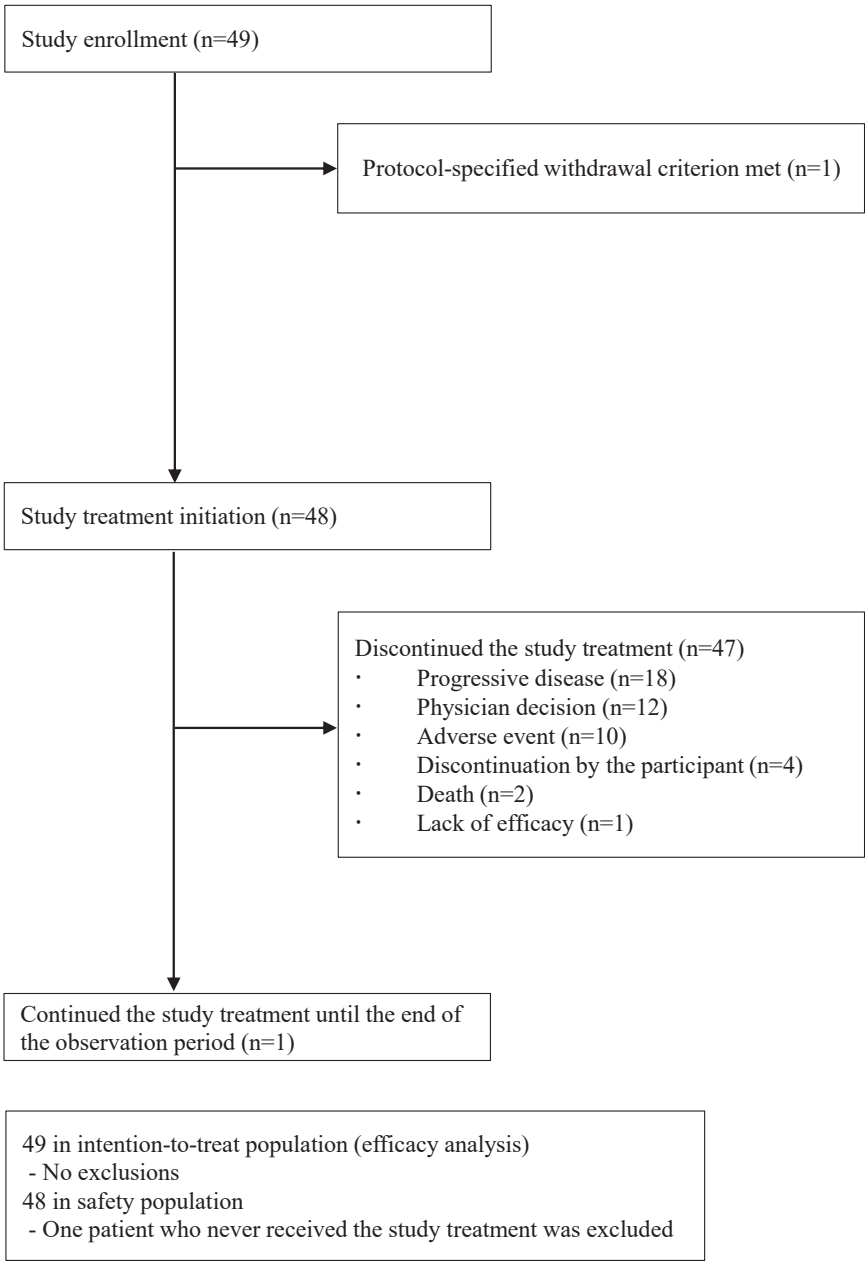

Figure 1. Patient disposition.

(range: 1.2–8.9) and 14 patients were alive at the data cutoff (Fig. 2*B*).

The median PFS was 7.6 months (95% CI: 4.8–16.2 mo), whereas the PFS at 12 months was 41.8% (95% CI: 27.6%–55.4%) (Fig. 3*A*). The median OS was 19.4 months (95% CI: 11.8–not reached), with OS at 12 months being 65.2% (95% CI: 49.6%–77.1%) (Fig. 3*B*).

Objective response occurred irrespective of PD-L1 TPS; nevertheless, response rates were numerically higher in patients with PD-L1 values of 1% to 49% (23.8% in those with PD-L1 <1%, 46.4% in those with PD-L1 at 1%–49%) (Supplementary Fig. 2).

The most prevalent cause of treatment discontinuation was disease progression (18 patients [38.3%]), followed by physician decisions (11 patients [23.4%]) and AEs (10 patients [21.3%]). Nab-paclitaxel, docetaxel, or S1 is typically administered as a subsequent systemic therapy.

Safety

All patients experienced AEs (Table 3). The most common AEs included anemia (41 patients [85.4%]), lymphocytopenia (30 patients [62.5%]), elevated aspartate transaminase levels (30 patients [62.5%]), leukopenia (27 patients [56.3%]), neutropenia (26 patients

Table 1. Patient Characteristics

Characteristic	N = 49
Median age, y (range)	79.0 (75-91)
Sex	
Male	38 (77.6%)
Female	11 (22.4%)
ECOG PS	
0	16 (32.7%)
1	33 (67.3%)
Histology	
Adenocarcinoma	48 (98.0%)
Others	1 (2.0%)
Stage	
IV	37 (75.5%)
Recurrence	12 (24.5%)
Smoking history	
Never	14 (28.6%)
Former	31 (63.3%)
Current	4 (8.2%)
PD-L1 TPS	
<1%	21 (42.9%)
1%-49%	28 (57.1%)
Comorbidity	
Hypertension	23 (46.9%)
Dyslipidemia	21 (42.9%)
Diabetes mellitus	10 (20.4%)
COPD	15 (30.6%)
Cardiovascular disease	6 (12.2%)

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Clinical Oncology Group; PD-L1, programmed cell death-ligand1; PS, performance status; TPS, tumor proportion score.

[54.2%]), thrombocytopenia (23 patients [47.9%]), and hyperglycemia (22 patients [45.8%]). Grade 3 to 5 AEs occurred in 30 of 48 patients (62.5%), with the most common events being neutropenia (15 patients [31.3%]), leukopenia (10 patients [20.8%]), and anemia (six patients [12.5%]). Treatment-related SAEs were observed in 12 patients (25.0%) (four patients [8.3%] with pneumonitis, two patients [4.2%] with decreased appetite, and two patients [4.2%] with febrile neutropenia) (Supplementary Table 1). Hypothyroidism, hypophysitis, and hyperthyroidism, which are grade 1 to 2 AEs, were observed in nine patients (18%), three patients (6.3%), and two patients (4.2%), respectively. Grade 5 SAEs were observed in two patients (delirium and cardiac arrest, one each); nevertheless, these SAEs were unrelated to treatment. No treatment-related deaths occurred during this period.

Table 2. Tumor Response

Response	ITT (n = 49)
CR, n (%)	1 (2.0%)
PR, n (%)	17 (34.7%)
SD, n (%)	14 (28.6%)
PD, n (%)	10 (20.4%)
NE, n (%)	7 (14.3%)
ORR (%) (95% CI)	36.7 (23.4-51.7)
DCR, % (95% CI)	65.3 (50.4-78.3)

CI, confidence interval; CR, complete response; DCR, disease control rate; ITT, intention-to-treat; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Discussion

To the best of our knowledge, this is the first study to investigate the efficacy and safety of pembrolizumab and pemetrexed, a cytotoxic monotherapy, in older patients with advanced non-Sq NSCLC. The achieved ORR of 36.7% (95% CI: 23.4%–51.7%) met the primary endpoint. The median PFS and OS were 7.6 months (95% CI: 4.8–16.2) and 19.4 months (95% CI: 11.8–not reached), respectively.

The ORR was 47.6% (95% CI: 42.6–52.5) for pembrolizumab and pemetrexed plus platinum and 18.9% (95% CI: 13.8–25.0) for platinum plus pemetrexed in the KEYNOTE-189 trial, and the difference in ORR was 28.7%.[3] HRs for pembrolizumab and pemetrexed plus platinum versus platinum plus pemetrexed were 0.60 (95% CI: 0.50–0.72) for OS and 0.50 (95% CI: 0.42–0.60) for PFS.[14] Subgroup analysis from the KEYNOTE-189 trial, specifically including patients aged 75 years and above, found a difference in ORR of 14.4% (pembrolizumab and pemetrexed plus platinum versus platinum plus pemetrexed), suggesting that the addition of pembrolizumab to pemetrexed with platinum was less effective than pemetrexed with platinum (HR = 2.09 in OS and HR = 1.73 in PFS).[12] Moreover, Morimoto et al.[15] reported significantly shorter PFS and OS with pembrolizumab, pemetrexed, and carboplatin in older patients than younger patients. Collectively, the efficacy of pembrolizumab and pemetrexed may surpass that of pembrolizumab combined with pemetrexed and platinum.

The PFS and OS rates for pembrolizumab and pemetrexed at 24 months, with a follow-up time of 15.4 months, were 16.6% and 44.3%, respectively. In contrast, the PFS and OS rates for pembrolizumab and pemetrexed carboplatin in patients with PD-L1 TPS of 1% to 49% were 22.3% and 44.3% at 24 months, respectively; nevertheless, for patients with a PD-L1 TPS of than 1%, the corresponding rates were 13.3% and 39.3%, respectively.[16] The long-term efficacy of pembrolizumab and pemetrexed was also similar to that of pembrolizumab and pemetrexed with carboplatin.

Regarding toxicities, all patients experienced AEs; nevertheless, grade 3 to 4 AEs occurred in 58.3% of patients, and no treatment-related deaths were observed in our study. In the KEYNOTE-189 trial, grade 3 to 5 AEs

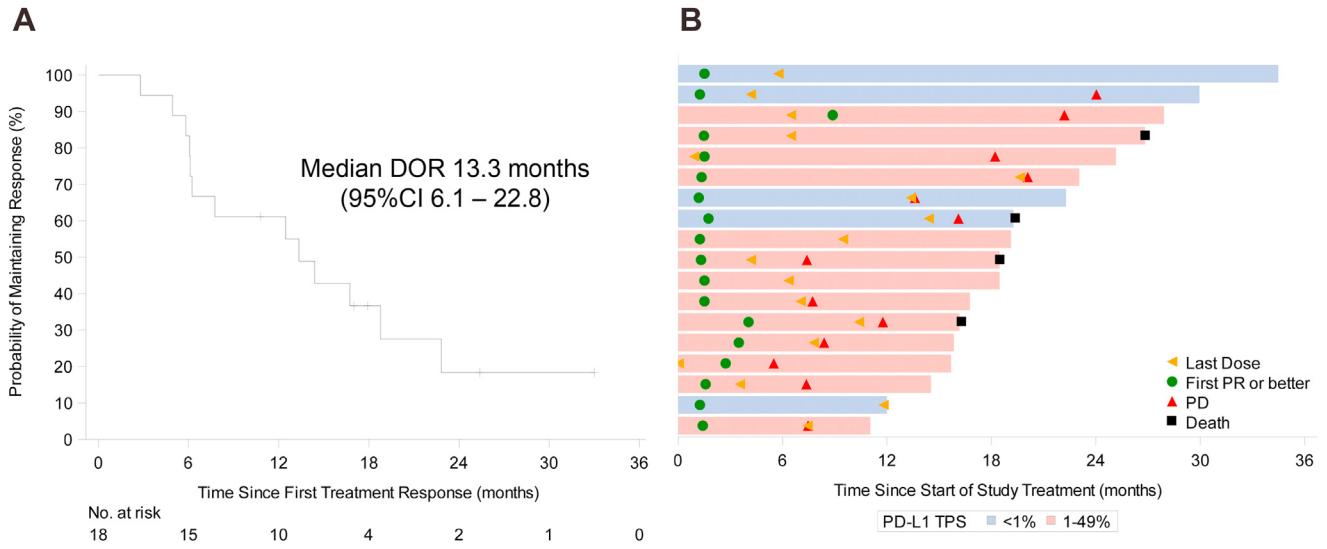

Figure 2. Kaplan-Meier plots of duration of response *(A)* and treatment duration with time to response *(B)*. DOR, duration of response; No, number; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PR, partial response; TPS, tumor proportion score.

occurred in 67.2% of patients, and treatment-related deaths were observed in 7.2% of patients.[3]

Grade 3 to 5 hematological toxicities, specifically neutropenia (31.3%), anemia (12.5%), and thrombocytopenia (0%), were observed in this study. In JCOG1210/WJOG7813L, a randomized phase 3 study to evaluate the efficacy and safety of carboplatin plus pemetrexed among patients with non-Sq NSCLC aged 75 years or above, grade 3 to 5 neutropenia, anemia, and thrombocytopenia were observed in 46.2%, 29.5%, and 25.6% of patients, respectively. Grade 3 to 5 fatigue and anorexia were observed in one (2.1%) and zero (0%) patients in this study, respectively.[17] In JCOG1210/WJOG7813L, it was observed in 6.1% and 5.1% of patients, respectively. Hematological and symptomatic AEs were numerically reduced by omitting carboplatin, and pembrolizumab and pemetrexed were considered more tolerable than pemetrexed and carboplatin for patients aged 75 years or above.

Nevertheless, pneumonitis was frequently observed in this study. Pneumonitis was documented in 18.8% of patients, with grade 3 pneumonitis in 8.3%. Fujimoto et al.[18] reported pneumonitis in 12.4% of patients, with grade 3 or higher pneumonitis occurring in 3.3% when pembrolizumab was administered with pemetrexed and carboplatin. In the KEYNOTE-189 trial, all grades of

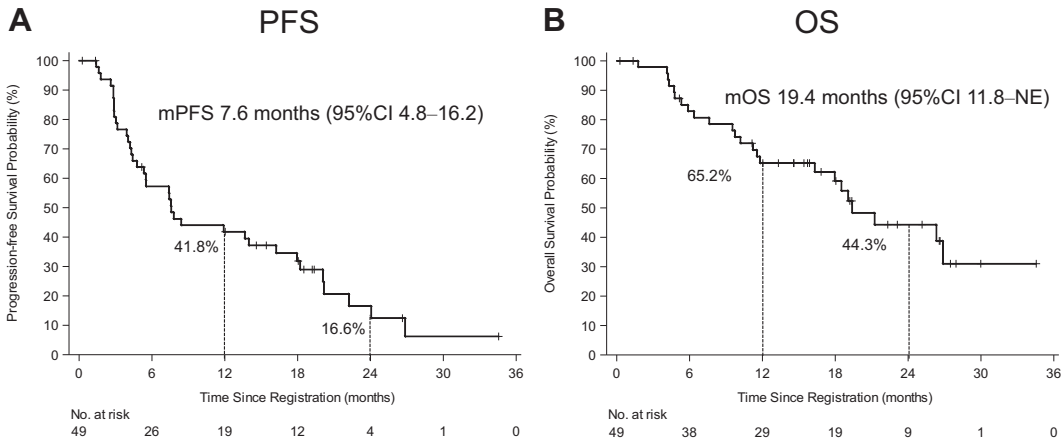

Figure 3. Kaplan-Meier plots of progression-free survival *(A)* and overall survival *(B)*. CI, confidence interval; m, median; No, number; NE, not estimated; OS, overall survival; PFS, progression-free survival.

Table 3. Adverse Events

Adverse event	Grade 1–2	Grade 3	Grade 4	Grade 5	Any Grade
Any adverse event	18 (37.5%)	24 (50.0%)	4 (8.3%)	2 (4.2%)	48 (100%)
Anemia	35 (72.9%)	6 (12.5%)	0 (0%)	0 (0%)	41 (85.4%)
Lymphocytopenia	21 (43.8%)	9 (18.8%)	0 (0%)	0 (0%)	30 (62.5%)
AST increased	27 (56.3%)	3 (6.3%)	0 (0%)	0 (0%)	30 (62.5%)
Leukopenia	17 (35.4%)	10 (20.8%)	0 (0%)	0 (0%)	27 (56.3%)
Neutropenia	11 (22.9%)	12 (25.0%)	3 (6.3%)	0 (0%)	26 (54.2%)
Thrombocytopenia	23 (47.9%)	0 (0%)	0 (0%)	0 (0%)	23 (47.9%)
Hyperglycemia	21 (43.8%)	1 (2.1%)	0 (0%)	0 (0%)	22 (45.8%)
Fatigue	17 (35.4%)	1 (2.1%)	0 (0%)	0 (0%)	18 (37.5%)
Pruritis	16 (33.3%)	2 (4.2%)	0 (0%)	0 (0%)	18 (37.5%)
ALT increased	14 (29.2%)	3 (6.3%)	0 (0%)	0 (0%)	17 (35.4%)
Creatinine increased	17 (35.4%)	0 (0%)	0 (0%)	0 (0%)	17 (35.4%)
Nausea	15 (31.3%)	0 (0%)	0 (0%)	0 (0%)	15 (31.3%)
ALP increased	14 (29.2%)	1 (2.1%)	0 (0%)	0 (0%)	15 (31.3%)
AMY increased	14 (29.2%)	1 (2.1%)	0 (0%)	0 (0%)	15 (31.3%)
Dyspnea	9 (18.8%)	2 (4.2%)	0 (0%)	0 (0%)	11 (22.9%)
Diarrhea	8 (16.7%)	2 (4.2%)	0 (0%)	0 (0%)	10 (20.8%)
Pneumonitis	5 (10.4%)	4 (8.3%)	0 (0%)	0 (0%)	9 (18.8%)
Hypothyroidism	9 (18.8%)	0 (0%)	0 (0%)	0 (0%)	9 (18.8%)
Facial edema	8 (16.7%)	0 (0%)	0 (0%)	0 (0%)	8 (16.7%)
Edema limbs	6 (12.5%)	2 (4.2%)	0 (0%)	0 (0%)	8 (16.7%)
Dry skin	8 (16.7%)	0 (0%)	0 (0%)	0 (0%)	8 (16.7%)
Maculopapular rash	7 (14.6%)	1 (2.1%)	0 (0%)	0 (0%)	8 (16.7%)
T-Bil increased	7 (14.6%)	1 (2.1%)	0 (0%)	0 (0%)	8 (16.7%)
Lung infection	5 (10.4%)	2 (4.2%)	0 (0%)	0 (0%)	7 (14.6%)
Fever	6 (12.5%)	0 (0%)	0 (0%)	0 (0%)	6 (12.5%)
Vomiting	5 (10.4%)	0 (0%)	0 (0%)	0 (0%)	5 (10.4%)
CK increased	4 (8.3%)	1 (2.1%)	0 (0%)	0 (0%)	5 (10.4%)
Sensory neuropathy	5 (10.4%)	0 (0%)	0 (0%)	0 (0%)	5 (10.4%)
Erythema multiforme	4 (8.3%)	1 (2.1%)	0 (0%)	0 (0%)	5 (10.4%)
Rash acneiform	5 (10.4%)	0 (0%)	0 (0%)	0 (0%)	5 (10.4%)
Adrenal deficiency	4 (8.3%)	0 (0%)	0 (0%)	0 (0%)	4 (8.3%)
Hypokalemia	4 (8.3%)	0 (0%)	0 (0%)	0 (0%)	4 (8.3%)
Hyperuricemia	4 (8.3%)	0 (0%)	0 (0%)	0 (0%)	4 (8.3%)
Febrile neutropenia	0 (0%)	3 (6.3%)	0 (0%)	0 (0%)	3 (6.3%)
Watering eyes	3 (6.3%)	0 (0%)	0 (0%)	0 (0%)	3 (6.3%)
Hypophysitis	3 (6.3%)	0 (0%)	0 (0%)	0 (0%)	3 (6.3%)
Lipase increased	3 (6.3%)	0 (0%)	0 (0%)	0 (0%)	3 (6.3%)
Hyperthyroidism	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	2 (4.2%)
Colitis	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	2 (4.2%)
Dehydrated	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	2 (4.2%)
Arthralgia	2 (4.2%)	0 (0%)	0 (0%)	0 (0%)	2 (4.2%)
Anorexia	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	2 (4.2%)
Dry mouth	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)
Allergic rhinitis	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)
Papulopustular rash	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)
Delirium	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	1 (2.1%)
Cardiac arrest	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	1 (2.1%)
Hip fracture	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Hyponatremia	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Myocardial infarction	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	1 (2.1%)
Pleural effusion	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)
Lung tuberculosis	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)
Lower gastrointestinal hemorrhage	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)

ALP, alkaline phosphatase; ALT, alanine transaminase; AMY, amylase; CK, creatine kinase.

pneumonitis were observed in 8% of patients, and grade 3 to 5 pneumonitis occurred in 4% of patients.[19] Although the frequency of pneumonitis in this study surpassed that reported in previous Japanese studies, the incidence of pemetrexed-related pneumonitis was significantly high in older patients.[20] Thus, the increased incidence of pneumonitis in this study could be linked to the advanced age of the patients, and cases of pneumonitis resulting from pembrolizumab and pemetrexed administration seem manageable, as all affected patients with pneumonitis recovered.

The study has several limitations. First, this was a single-arm phase 2 trial, precluding a direct comparison of its efficacy with other regimens. Second, the attending physician, rather than a blinded, independent central reviewer, evaluated the ORR, potentially introducing bias into the assessment of treatment efficacy. Third, we did not assess quality of life. Fourth, the median exposure to treatment differed notably between the KEYNOTE-189 trial and the present study. In the KEYNOTE-189 trial, patients in the experimental arm had a median treatment duration of 7.2 months. In contrast, in the present study, the median number of cycles was five, equivalent to approximately 3.5 months. This suggests that the cumulative risk of AEs might be lower in the present study. Finally, the median follow-up period was 15.4 months, which might not be sufficient to assess long-term outcomes. To validate the efficacy and safety of pembrolizumab and pemetrexed for older patients with advanced non-Sq NSCLC, randomized phase 3 studies comparing this treatment with pembrolizumab with pemetrexed and carboplatin are warranted.

In conclusion, our findings suggest that pembrolizumab and pemetrexed are promising and novel treatment strategies for older patients with non-Sq NSCLC, indicating significant therapeutic advancement.

Data Availability Statement

The trial data will be made available at a reasonable request to the corresponding author. A proposal is required to assess the requests, and the information will be provided after review by the committee. The data will be shared with researchers once the independent review board grants approval.

CRediT Authorship Contribution Statement

Yoshihito Kogure: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing.

Hiroya Hashimoto: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing.

Haruko Daga: Investigation, Writing - original draft.

Yasushi Fukuda: Investigation, Writing - original draft.

Akihiro Bessho: Investigation, Writing - original draft.

Tadaaki Yamada: Investigation, Writing - original draft.

Yukihiro Toi: Investigation, Writing - original draft.

Tomoki Kimura: Investigation, Writing - original draft.

Hiroshige Yoshioka: Investigation, Writing - original draft.

Koichi Azuma: Investigation, Writing - original draft.

Naoki Furuya: Investigation, Writing - original draft.

Yasutaka Fukui: Investigation, Writing - original draft.

Akiko M. Saito: Data curation, Formal analysis, Project administration, Validation, Writing - original draft.

Nobuyuki Yamamoto: Conceptualization, Project administration, Supervision, Writing - review & editing.

Hideo Saka: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - review & editing.

Masashi Kondo: Conceptualization, Methodology, Project administration, Supervision, Writing - review & editing.

Disclosure

Dr. Kogure reports receiving grants from Merck Sharp & Dohme during the study's conduct and personal fees from Merck Sharp & Dohme, AstraZeneca, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Boehringer Ingelheim, Ono Pharmaceutical, Takeda Pharmaceutical, Kyowa Kirin, Nippon Kayaku, and GlaxoSmithKline outside the submitted work. Dr. Hashimoto reports personal fees from Chugai Pharmaceutical outside the submitted work. Dr. Daga reports personal fees from AstraZeneca and Chugai Pharmaceutical outside the submitted work. Dr. Fukuda reports personal fees from Merck Sharp & Dohme, AstraZeneca, Chugai Pharmaceutical, Merck Biopharma, Ono Pharmaceutical, Bristol-Myers Squibb, Eli Lilly, Boehringer Ingelheim, Novartis Pharma, and Takeda Pharmaceutical outside the submitted work. Dr. Bessho reports receiving grants from Merck Sharp & Dohme, AstraZeneca, and Chugai Pharmaceutical and personal fees from AstraZeneca, Chugai Pharmaceutical, Bristol-Myers Squibb, Merck Sharp & Dohme, Ono Pharmaceutical, Eli Lilly, Daiichi Sankyo, and Taiho Pharmaceutical outside the submitted work. Dr. Yamada reports personal fees from Ono Pharmaceutical,

AstraZeneca, Takeda Pharmaceutical, and Janssen Pharmaceutical outside the submitted work. Dr. Toi reports personal fees outside the submitted work from Ono Pharmaceutical, AstraZeneca, Merck Sharp & Dohme, Bristol-Myers Squibb, Chugai Pharmaceutical, and Taiho Pharmaceutical. Dr. Kimura reports personal fees from GlaxoSmithKline, Sanofi, Merck Sharp & Dohme, AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Novartis Pharma, Bristol-Myers Squibb, Meiji Seika Pharma, and Daiichi Sankyo outside the submitted work. Dr. Yoshioka reports grants from Daiichi Sankyo, Merck Sharp & Dohme, AstraZeneca, Janssen Pharmaceutical, Novartis Pharma, Boehringer Ingelheim, and Delta Fly Pharma; consulting fees from Delta Fly Pharma; and personal fees from Eli Lilly, Chugai Pharmaceutical, Merck Sharp & Dohme, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Novartis Pharma, Kyowa Kirin, Nippon Kayaku, Otsuka Pharmaceutical, Amgen, Pfizer, Nipro Pharma, Daiichi Sankyo, and Merck Biopharma outside the submitted work. Dr. Azuma reports personal fees from Merck Sharp & Dohme, AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, and Bristol-Myers Squibb outside the submitted work. Dr. Furuya reports personal fees from Merck Sharp & Dohme, AstraZeneca, Chugai Pharmaceutical, Bristol-Myers Squibb, and Eli Lilly, outside the submitted work. Dr. Yamamoto reports receiving grants from Merck Sharp & Dohme, Chugai Pharmaceutical, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Boehringer Ingelheim, Novartis, AbbVie, Amgen, Asahi Kasei, Janssen, Bristol-Myers Squibb, IQVIA, EPS Corporation, A2 Healthcare, Mebix, and AstraZeneca; consulting fees from AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Eli Lilly, Amgen, Novartis, and Ono Pharmaceutical; personal fees from Chugai Pharmaceutical, MSD, Takeda Pharmaceutical, Accuray, AbbVie, Amgen, Ono Pharmaceutical, Guardant Health, Kyorin, Daiichi Sankyo, Taiho Pharmaceutical, Tsumura, TERUMO, Eli Lilly, Boehringer Ingelheim, Novartis, Pfizer, Miyarisan Pharmaceutical, Merck Biopharma, and Janssen; and advisory board fees from AstraZeneca, all outside the submitted work. Dr. Kondo reports receiving grants from Chugai Pharmaceutical, Ono Pharmaceutical, MSD, Takeda Pharmaceutical, Daiichi Sankyo, and AstraZeneca; and personal fees from Chugai Pharmaceutical, Eli Lilly, Pfizer, AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb, MSD, Takeda Pharmaceutical, and Daiichi Sankyo, all outside the submitted work. The remaining authors declare no conflict of interest.

Acknowledgments

This study was partially supported by the National Cancer Center Research and Development Fund (2020-A-13, 2023-A-13). This study was conducted by the National Hospital Organization Nagoya Medical Center under a funding contract with MSD., Tokyo, Japan. We thank the patients, their families, and all the investigators who participated in this study.

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.2024.100784.

References

1. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-Positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
2. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830.
3. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
4. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040–2051.
5. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
6. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
7. Cho BC, Wu YL, Lopes G, et al. FP13.04 KEYNOTE-042 3-year survival update: 1L pembrolizumab vs platinum-based chemotherapy for PD-L1+ locally advanced/metastatic NSCLC. *J Thorac Oncol*. 2021;16:S225–S226.
8. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
9. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198–211.
10. Johnson ML, Cho BC, Luft A, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non-small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol*. 2023;41:1213–1227.
11. Nosaki K, Saka H, Hosomi Y, et al. Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small-cell lung cancer: pooled analysis from the KEYNOTE-010, KEYNOTE-024,

and KEYNOTE-042 studies. *Lung Cancer*. 2019;135:188–195.
12. Committee for Medicinal Products for Human Use (CHMP). European public assessment report. *Keytruda*. EMA Procedure *No*. *EMA/H/C/003820/II/0043*. https://ec.europa.eu › health › anx_151110_en. Accessed June 13, 2019.
13. Schaer DA, Geeganage S, Amaladas N, et al. The folate pathway inhibitor pemetrexed pleiotropically enhances effects of cancer immunotherapy. *Clin Cancer Res*. 2019;25:7175–7188.
14. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the Phase 3 KEYNOTE-189 Study. *J Clin Oncol*. 2023;41:1992–1998.
15. Morimoto K, Yamada T, Yokoi T, et al. Clinical impact of pembrolizumab combined with chemotherapy in elderly patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2021;161:26–33.
16. Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32:881–895.
17. Okamoto I, Nokihara H, Nomura S, et al. Comparison of carboplatin plus pemetrexed followed by maintenance pemetrexed with docetaxel monotherapy in elderly patients with advanced nonsquamous non-small cell lung cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6:e196828.
18. Fujimoto D, Miura S, Yoshimura K, et al. Pembrolizumab plus chemotherapy-induced pneumonitis in chemo-naïve patients with non-squamous non-small cell lung cancer: a multicentre, retrospective cohort study. *Eur J Cancer*. 2021;150:63–72.
19. Horinouchi H, Nogami N, Saka H, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. *Cancer Sci*. 2021;112:3255–3265.
20. Tomii K, Kato T, Takahashi M, et al. Pemetrexed-related interstitial lung disease reported from post marketing surveillance (malignant pleural mesothelioma/non-small cell lung cancer). *Jpn J Clin Oncol*. 2017;47:350–356.