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Long-term survival comparison of first-line pembrolizumab versus pembrolizumab plus chemotherapy for patients with advanced non-small cell lung cancer: A multicenter propensity-matched cohort study

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ABSTRACT

Background: Pembrolizumab is currently used as a first-line therapy for EGFR- and ALK-negative advanced non-small cell lung cancer (NSCLC). However, whether pembrolizumab alone (P-mono) or combined with platinum chemotherapy (P-combo) provides superior long-term benefit remains unclear.
Methods: We retrospectively analyzed 392 patients with PD-L1 TPS ≥ 1 % treated first-line with P-mono (n = 194) or P-combo (n = 198) between 2019 and 2021. Propensity-score matching across 13 baseline variables yielded two well-balanced cohorts of 97 patients each, with a median follow-ups of 42.8 and 44.1 months, respectively.
Results: P-combo prolonged overall survival (OS) (median 31.8 vs 20.7 months; hazard ratio [HR] 0.67, 95 % confidence interval [CI] 0.46–0.96) and progression-free survival (12.5 vs 7.0 months; HR 0.59, 95 %CI 0.43–0.81). The 3- and 4-year OS rates were 49.8 % and 42.7 %, respectively, with P-combo, compared with 28.1 % and 22.3 % with P-mono. The 48-month restricted mean survival time also favored P-combo (p = 0.039). Additionally, greater benefits were observed among patients aged < 75 years, with ECOG performance status 0–1, PD-L1 TPS 1–49 %, and those using proton-pump inhibitors. Grade ≥ 3 treatment-related adverse events

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(TRAEs) were more frequent with P-combo (35 % vs 20 %, p = 0.024). However, treatment-related deaths (2 % each) and pneumonitis incidence and severity were comparable; cumulative toxicity curves plateaued after 3 years.

Conclusions: These findings suggest that P-combo showed a durable survival advantage over monotherapy and acceptable TRAEs in patients with PD-L1–positive NSCLC, identifying clinical subgroups most likely to benefit. Prospective randomized trials are warranted to validate these observations and guide optimal first-line treatment strategies.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide [1]. Immune checkpoint inhibitors (ICIs) have become the preferred first-line therapy for patients with advanced non-small cell lung cancer (NSCLC) lacking driver gene mutations. In the KEYNOTE (KN)-024 trial, pembrolizumab monotherapy (P-mono) replaced platinum-based chemotherapy as the standard first-line treatment for patients with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) of ≥ 50 % [2]. Furthermore, in the KN-042 trial, P-mono significantly prolonged overall survival (OS) compared to platinum-based chemotherapy in patients with PD-L1 TPS ≥ 1 % [3]. Combination therapy with pembrolizumab and platinum-based chemotherapy (P-combo), designed to address rapid disease progression, improved response rates and provided a survival benefit regardless of PD-L1 TPS [4,5]. Although both regimens are widely utilized in clinical practice, no randomized clinical trial has directly compared their efficacy.

We searched PubMed, Scopus, and Web of Science and identified four real-world studies in NSCLC that used propensity-score adjustment to indirectly compare P-mono with P-combo. A previous retrospective cohort study demonstrated superior progression-free survival (PFS) with P-combo compared with P-mono using a propensity score matching (PSM), although no significant difference in OS was observed [6]. Similarly, other real-world studies found no significant differences in PFS and OS between the two regimens while significantly more patients experienced treatment-related adverse events (TRAEs) with combination therapy as compared to monotherapy [7–9]. In a network *meta*-analysis, P-combo improved PFS and objective response rate compared to P-mono, although no significant OS benefit was observed. Furthermore, TRAEs occurred more frequently with P-combo than with P-mono, consistent with the previous real-world studies [10].

These results provide important guidance for selecting between P-mono and P-combo in patients with NSCLC and PD-L1 TPS ≥ 50 %; however, they have two major limitations. First, the analyses were based on short follow-up periods of only 12–22 months, preventing the assessment of the long-term survival advantages of ICIs. Second, PSM relies on only a few covariates, such as age, sex, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS), omitting many other factors that may influence ICI outcomes [11]. Moreover, real-world evidence directly comparing P-mono and P-combo in patients with PD-L1 TPS of 1–49 % remains limited [12].

Therefore, the present study aims to compare the clinical efficacy and safety of P-mono versus P-combo in patients with PD-L1 TPS of ≥ 1 % in a real-world setting, adjusting for 13 potentially relevant confounders and focusing on long-term follow-up periods exceeding 40 months. Our results provide additional real-world evidence that may help inform treatment selection for patients with advanced NSCLC and PD-L1 TPS ≥ 1 %.

2. Materials and methods

2.1. Study design and patient selection

This was a multicenter, retrospective cohort study. Consecutive patients with pathologically confirmed advanced or recurrent NSCLC were registered through 13 institutions in Japan. Patients with PD-L1 TPS ≥ 1 % who received P-mono or P-combo as first-line treatment between January 2019 and December 2021 were included. Those with positive or unknown major EGFR (exon 21 L858R or exon 19 deletion) mutations and ALK rearrangements were excluded, following the protocols of the KN-024, −042, and −189 trials. The study was conducted in accordance with the Declaration of Helsinki and the World Health Organization Good Clinical Practice guidelines and was approved by the central institutional review board of the University of Osaka (IRB #22349–5). Written informed consent was waived because of the retrospective design of the study. Participation was instead managed through an opt-out process posted on the institutional website, permitting patients and their families to refuse inclusion of their data.

2.2. Data collection

Clinical data were extracted from the patients' electronic medical records, including age, sex, smoking status, ECOG-PS, histology, clinical stage, PD-L1 TPS, use of steroids, proton pump inhibitors (PPIs), antibiotics before treatment, brain and liver metastasis, body mass index (BMI), treatment outcomes, and TRAEs. Steroid use was defined as corticosteroid administration equivalent to ≥ 10 mg/day of prednisolone within 30 days before treatment initiation. PPI use was defined as administration at treatment initiation, while antibiotic use was defined as administration within 30 days before treatment initiation, excluding short-term use immediately after bronchoscopy [13–15]. A cutoff BMI value of 20 kg/m^2 was adopted according to an international consensus definition of cancer cachexia [16]. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. OS was defined as the time from first-line treatment initiation to death from any cause, whereas PFS was defined as the time from first-line treatment initiation to disease progression or death from any cause. Safety was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE, ver5), based on TRAE incidence, treatment discontinuation, and treatment-related deaths (TRDs) [18]. While pneumonitis was evaluated as any grade, the other TRAEs were classified as grade 3 or higher. The date of data cut-off was June 30, 2024.

2.3. Statistical analysis

The primary endpoints were OS, PFS, and TRAEs, while the secondary endpoint was OS in each subgroup. A 1:1 nearest-neighbor PSM method was applied with a caliper size of 0.2, adjusting for clinically relevant covariates, including age, sex, ECOG-PS, histology, clinical stage, PD-L1 TPS, use of steroids, PPIs, antibiotics before treatment, brain metastasis, liver metastasis, and BMI [11]. Covariate balances were assessed using standardized mean differences (SMDs) after PSM. OS and PFS were reanalyzed in the matched cohort and compared between the two groups.

Group comparisons were performed using the Mann–Whitney *U* test for continuous data, the chi-squared test for categorical data, and Wilcoxon rank-sum test for ordinal variables, before and after PSM. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Additionally, long-term survival was evaluated using the OS rate and restricted mean survival time (RMST). OS rates were estimated at 36 and 48 months from Kaplan–Meier curves.

Greenwood standard errors were used to calculate 95 % confidence intervals (CIs), and absolute differences between treatment arms were compared using a two-sided z-test. Calculation of RMST remains a robust method, even when the number of events is limited [19]. Hazard ratios (HRs) and 95 % CIs were calculated using the Cox proportional hazards model to determine the association between patient characteristics and survival outcomes. Gray's test was used to estimate and compare the cumulative incidence of grade 3 or higher adverse events, and Fine–Gray regression was applied to calculate subdistribution HRs for the risk comparison. Statistical significance was defined as a two-sided p-value < 0.05. Analyses were performed using JMP (version 17.0.0; SAS Institute Inc., Cary, NC, USA) and R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Of the 622 patients enrolled, 91 were excluded due to known or suspected EGFR mutations or ALK rearrangements, 133 due to PD-L1 TPS < 1 % or unknown status, and six due to missing baseline data. The remaining 392 patients (194 in the P-mono group and 198 in the P-combo group) were eligible for analysis. PSM produced 97 matched pairs (n = 194; Fig. 1).

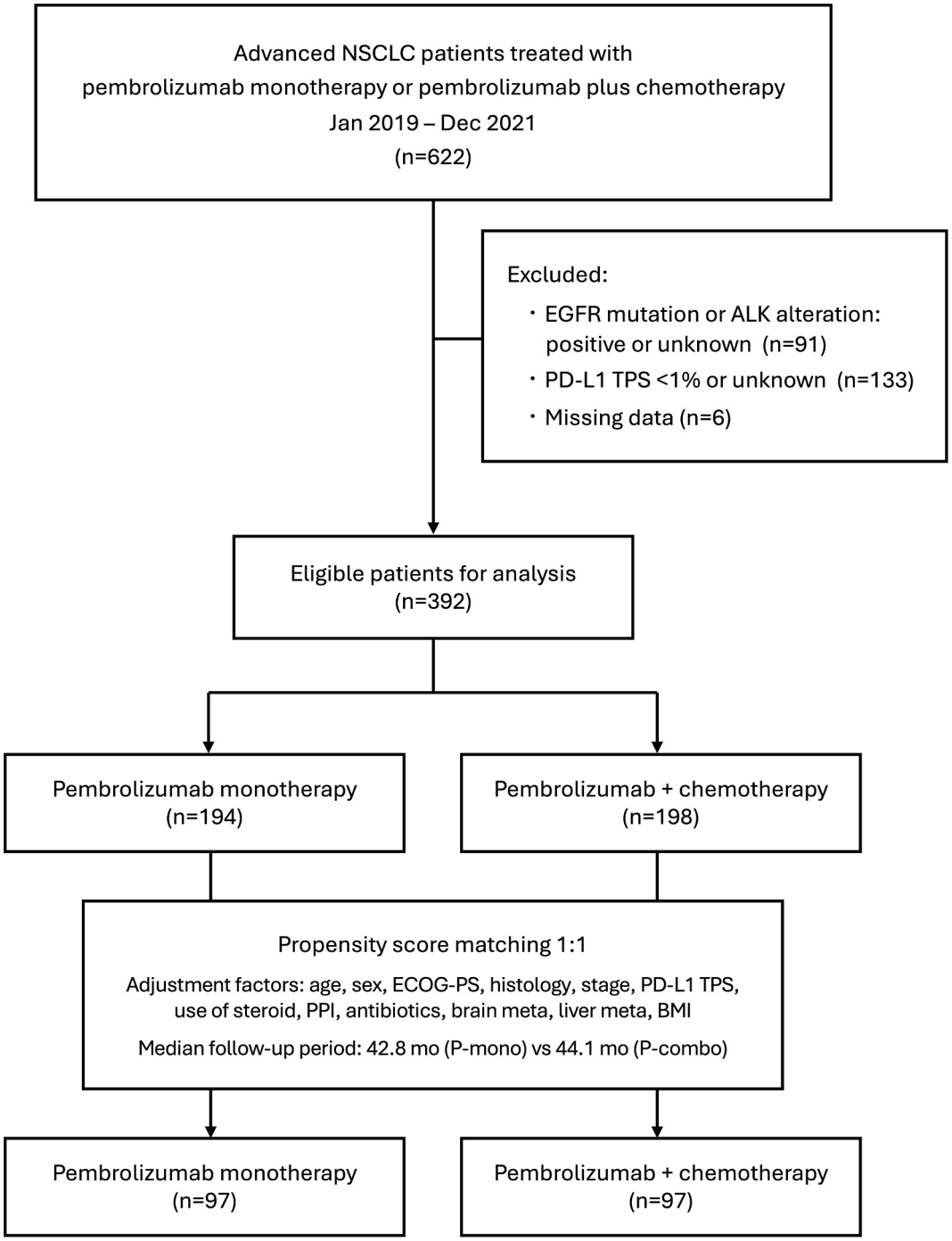

Fig. 1. CONSORT diagram of the study. BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small-cell lung cancer; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PPI, proton pump inhibitor.

The baseline characteristics before and after PSM are shown in Table 1. In the original cohort, patients in the P-mono group were older (median age: 77 vs. 70 years) and more likely to have ECOG PS ≥ 2 (26 % vs. 11 %) than those in the P-combo group. PD-L1 TPS ≥ 50 % (68 % vs. 52 %), baseline corticosteroid use (14 % vs. 5 %), and PPI use (38 % vs. 26 %) were also more frequent in the P-mono group. After matching, all covariates had SMDs < 0.2, indicating adequate balance. Before PSM, P-combo patients had slightly higher cumulative treatment line counts than P-mono patients (p = 0.011). The imbalance was resolved after matching (p = 0.95) (Supplementary Fig. S1). In the matched P-combo arm, 61 patients received carboplatin plus pemetrexed, 2 received cisplatin plus pemetrexed, 7 received carboplatin plus paclitaxel, and 27 received carboplatin plus nab-paclitaxel.

3.2. Comparison of clinical outcomes between treatment groups in the overall cohort

The median follow-up period was comparable between treatment arms (42.8 months for P-mono vs. 44.1 months for P-combo; p = 0.82). At the data cut-off, 64 deaths had occurred in the P-mono group and 52 in the P-combo group within the PSM cohort. OS and PFS consistently favored pembrolizumab plus chemotherapy. In the original cohort, the median OS was 27.5 months with P-combo and 21.0 months with P-mono. In the PSM cohort, OS was 31.8 months and 20.7 months, respectively (HR 0.67, 95 % CI 0.46–0.96; p = 0.029) (Figs. 2a,b). In the original cohort, the median PFS was 10.1 months with P-combo compared with 7.8 months with P-mono. In the PSM cohort, it was 12.5 months and 7.0 months, respectively (HR 0.59, 95 % CI 0.43–0.81; p = 0.001) (Figs. 2c,d). At the 36-month landmark, the OS rate was 28.1 % for P-mono and 49.8 % for P-combo (p = 0.003). At 48 months, the rates were 22.3 % and 42.7 %, respectively (p = 0.007). Concordantly, the 48-month RMST was significantly longer in the P-combo arm (p = 0.039) (Table 2). Moreover, in the original cohort, a multivariable Cox model incorporating 13 baseline covariates did not reach statistical significance; however, it showed the same favorable trend for P-combo consistent with the PSM analysis (HR 0.80, 95 % CI 0.58–1.10; p = 0.16) (Supplementary Table S1). P-combo achieved markedly higher antitumor efficacy than P-mono, yielding an objective response rate of 68.0 % vs. 41.2 % (p < 0.001) and a disease control rate of 88.7 % vs. 62.9 % (p = 0.016) (Supplementary Fig. S2).

3.3. Comparison of long-term survival across each subgroup

Subgroup analysis showed that four clinically meaningful factors displayed statistically significant differences in both the 48-month OS rate and RMST. In patients aged < 75 years, P-combo achieved a 48-month OS of 49.6 % vs. 26.8 % with P-mono (p = 0.025), with a concordant RMST advantage (p = 0.013). Similar patterns were observed in those with ECOG PS 0–1 (47.2 % vs. 24.5 %; p = 0.007), in tumors with PD-L1 expression of 1–49 % (38.5 % vs. 10.4 %; p = 0.012), and in patients receiving baseline PPIs (36.2 % vs. 8.7 %; p = 0.017), all accompanied by significant RMST improvements (p = 0.002, 0.031, and 0.007, respectively). In contrast, no statistically significant survival differences were observed in subgroup with age ≥ 75 years, ECOG-PS ≥ 2, PD-L1 ≥ 50 %, or no PPI use (Table 2 and Fig. 3). Additional factors such as female sex, current or past smoking, and no antibiotics use showed the same trend (Supplementary Table S2 and Supplementary Fig. S3).

3.4. Incidence of grade ≥ 3 TRAEs and any-grade pneumonitis

The cumulative incidence of grade ≥ 3 TRAEs was significantly higher in the P-combo group (HR 1.86, 95 % CI: 1.06–3.26, p = 0.029) (Fig. 4). Grade ≥ 3 TRAEs were observed in 34 patients (35 %) in the P-combo group and 19 patients (20 %) in the P-mono group (p = 0.024). Treatment discontinuation due to TRAEs occurred in 39 patients (40 %)

Table 1
Patient characteristics.

	Original cohort (n = 392)			PSM cohort (n = 194)		
Characteristic	P-mono (n = 194)	P-combo (n = 198)	SMD	P-mono (n = 97)	P-combo (n = 97)	SMD
Median age (range)	77 (38–91)	70 (39–82)	0.899	74 (38–90)	72 (42–82)	0.166
<75	74 (38)	159 (80)	0.950	56 (58)	59 (61)	0.063
≥75	120 (62)	39 (20)		41 (42)	38 (39)	
Sex, n (%)						
Male	149 (77)	164 (83)	0.151	75 (77)	78 (80)	0.076
Female	45 (23)	34 (17)		22 (23)	19 (20)	
Smoking history, n (%)						
Current/past smoker	181 (93)	181 (91)	0.071	87 (90)	89 (92)	0.071
Never smoker	13 (7)	17 (9)		10 (10)	8 (8)	
ECOG PS, n (%)						
0/1	144 (74)	177 (89)	0.401	83 (86)	82 (84)	0.029
2/3/4	50 (26)	21 (11)		14 (14)	15 (16)	
Histology n (%)						
Non-squamous	133 (69)	136 (69)	0.003	66 (68)	68 (70)	0.045
Squamous	61 (31)	62 (31)		31 (32)	29 (30)	
Disease stage, n (%)						
IV	111 (57)	151 (76)	0.413	62 (64)	65 (67)	0.065
Others	83 (43)	47 (24)		35 (36)	32 (33)	
PD-L1 TPS, n (%)						
≥50 %	131 (68)	103 (52)	0.320	55 (57)	62 (64)	0.148
1–49 %	63 (32)	95 (48)		42 (43)	35 (36)	
Steroid use, n (%)						
No	167 (86)	189 (95)	0.328	90 (93)	89 (92)	0.039
Yes	27 (14)	9 (5)		7 (7)	8 (8)	
PPI use, n (%)						
No	120 (62)	146 (74)	0.256	66 (68)	62 (64)	0.087
Yes	74 (38)	52 (26)		31 (32)	35 (36)	
Antibiotics use, n (%)						
No	167 (86)	167 (84)	0.049	86 (89)	85 (88)	0.032
Yes	27 (14)	31 (16)		11 (11)	12 (12)	
Brain metastases, n (%)						
No	160 (82)	160 (81)	0.043	78 (80)	77 (79)	0.026
Yes	34 (18)	38 (19)		19 (20)	20 (21)	
Liver metastases, n (%)						
No	184 (95)	181 (91)	0.136	90 (93)	91 (94)	0.041
Yes	10 (5)	17 (9)		7 (7)	6 (6)	
BMI, n (%)						
≥20	127 (65)	132 (67)	0.025	63 (65)	67 (69)	0.088
<20	67 (35)	66 (33)		34 (35)	30 (31)	

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; P-combo, pembrolizumab plus chemotherapy; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; P-mono, pembrolizumab monotherapy; PPI, proton pump inhibitor; PSM, propensity score matching; SMD, standard mean difference.

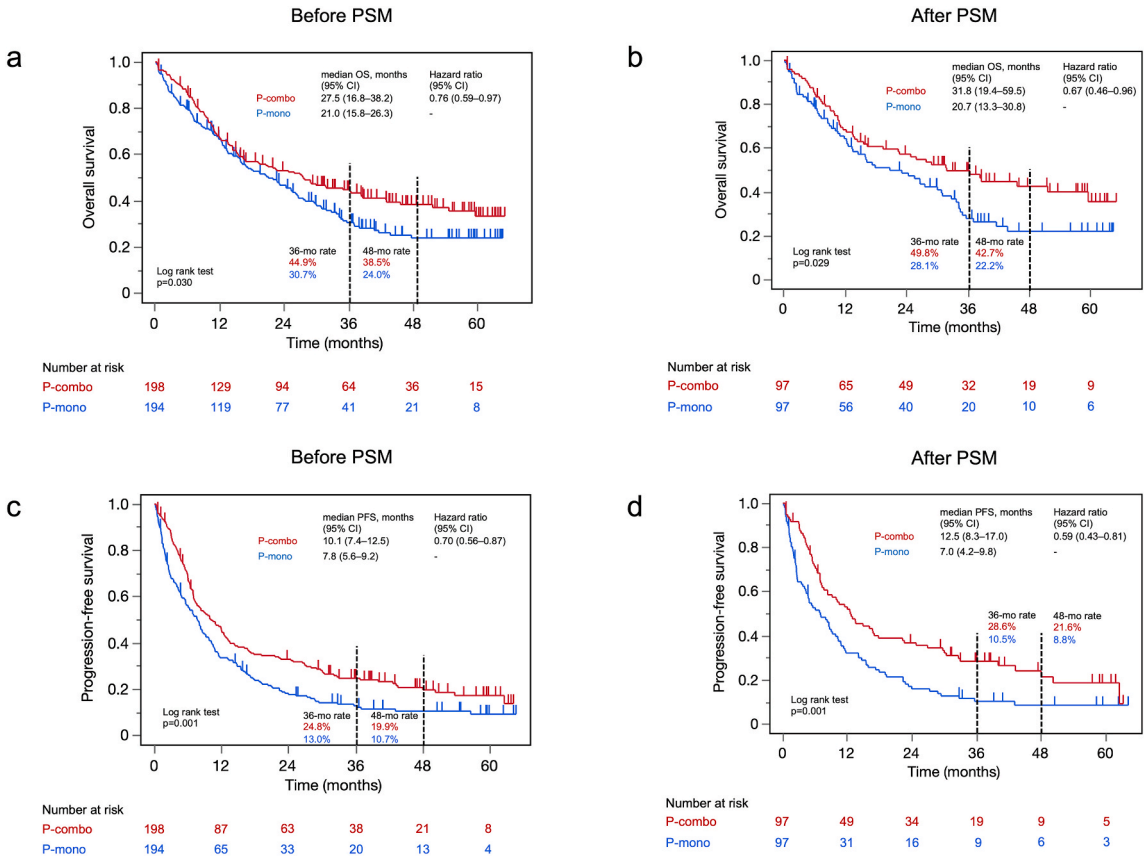

Fig. 2. Kaplan–Meier curves for overall survival (OS) in (a) the original cohort and (b) the matched cohort, followed by progression-free survival (PFS) in (c) the original cohort and (d) the matched cohort of patients with advanced NSCLC, according to first-line treatment with pembrolizumab monotherapy (P-mono) or pembrolizumab plus chemotherapy (P-combo). CI, confidence interval; NSCLC, non-small-cell lung cancer; PSM, propensity score matching.

Table 2
OS rate at 36 and 48 month and RMST at 48 month by subgroup in the matched cohort.

Characteristics	OS rate (%) at 36 month (95 % CI)			OS rate (%) at 48 month (95 % CI)			RMST (months) at 48 month (95 % CI)		
	P-mono	P-combo	P value	P-mono	P-combo	P value	P-mono	P-combo	P value
PSM cohort	28.1 (19.7 – 40.2)	49.8 (40.4 – 61.3)	0.003	22.2 (14.2 – 34.8)	42.7 (33.0 – 55.3)	0.007	23.7 (20.1 – 27.4)	29.3 (25.5 – 33.1)	0.039
Age									
<75	33.5 (22.1 – 50.7)	60.2 (48.5 – 74.8)	0.006	26.8 (15.9 – 45.0)	49.6 (37.1 – 66.3)	0.025	24.7 (19.7 – 29.8)	33.3 (28.8 – 37.9)	0.013
≥75	21.3 (11.1 – 40.8)	33.4 (20.8 – 53.5)	0.26	17.8 (8.5 – 37.3)	33.4 (20.8 – 53.5)	0.14	22.5 (17.3 – 27.8)	23.0 (16.8 – 29.3)	0.90
ECOG-PS									
0–1	30.9 (21.7 – 43.9)	53.9 (43.6 – 66.6)	0.004	24.5 (15.7 – 38.1)	47.2 (36.4 – 61.3)	0.007	25.3 (21.4 – 29.1)	31.8 (27.8 – 35.7)	0.022
2–4	NA	NA		NA	NA		9.6 (3.9–15.4)	16.1 (6.8–25.4)	0.25
PD-L1 TPS									
≥50 %	34.2 (22.8 – 51.4)	48.5 (37.1 – 63.6)	0.14	30.8 (19.5 – 48.6)	45.8 (34.2 – 61.4)	0.13	26.1 (21.1 – 31.1)	29.3 (24.5 – 34.1)	0.37
1–49 %	19.6 (9.7 – 39.4)	52.0 (37.4 – 72.3)	0.004	10.4 (3.3 – 33.0)	38.5 (23.9 – 61.9)	0.012	20.4 (15.4 – 25.5)	29.4 (23.5 – 35.7)	0.031
PPI use									
No	37.8(26.8 – 53.3)	50.7(39.3 – 65.4)	0.17	28.7(17.9 – 45.9)	45.2(33.4 – 61.1)	0.09	27.2 (22.8 – 31.6)	29.8 (25.0 – 34.6)	0.45
Yes	8.7(2.4 – 32.2)	48.2(33.5 – 69.3)	<0.001	8.7(2.4 – 32.2)	36.2(21.1 – 62.1)	0.017	16.6 (11.0 – 22.3)	28.3 (22.0 – 34.5)	0.007

CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NA, not applicable; OS, overall survival; P-combo, pembrolizumab plus chemotherapy; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; P-mono, pembrolizumab monotherapy; PPI, proton pump inhibitor; PSM, propensity score matching; RMST, restricted mean survival time.

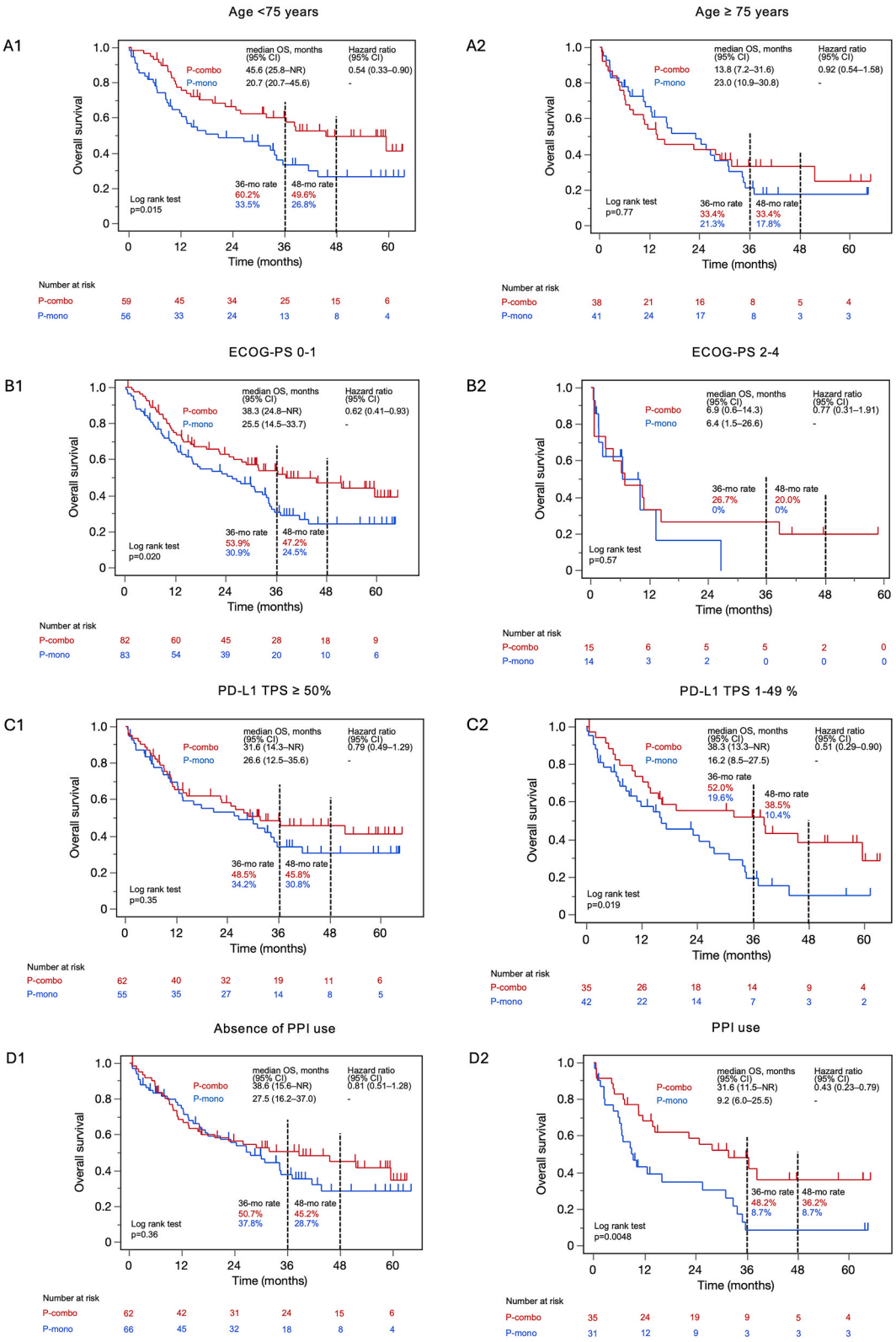

Fig. 3. Kaplan–Meier curves for overall survival (OS) by selected subgroup in the matched cohort of patients receiving first-line treatment with pembrolizumab monotherapy (P-mono) or pembrolizumab plus chemotherapy (P-combo), according to age (A1: <75 years; A2: ≥75 years), ECOG-PS (B1: 0–1; B2: 2–4), PD-L1 TPS (C1: ≥50 %; C2: 1–49 %), and PPI use (D1: no; D2: yes). CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PPI, proton pump inhibitor.

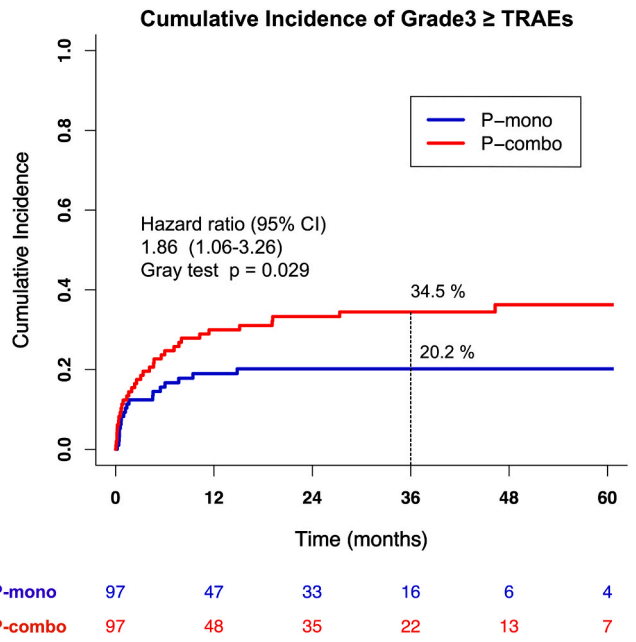

Fig. 4. Cumulative incidence curves for grade ≥ 3 treatment-related adverse events in the matched cohort, according to first-line treatment with pembrolizumab monotherapy (P-mono) or pembrolizumab plus chemotherapy (P-combo). CI, confidence interval.

in the P-combo group and 26 patients (27 %) in the P-mono group (p = 0.068). TRDs occurred in two patients (2 %) in each group. All-grade pneumonitis was analyzed separately. As shown in Supplementary Fig. S4, P-mono and P-combo showed comparable incidence patterns. Detailed profiles of grade ≥ 3 TRAEs are summarized in Table 3, and none of the toxicities showed a significant between-group difference.

Table 3
Grade3 or higher treatment-related adverse events (TRAEs) in the matched cohort.

	All	P-mono	P-combo	p value
Number of patients, n (%)	194	97	97	
Number of patients with Grade ≥ 3 TRAEs, n (%)	53 (27)	19 (20)	34 (35)	0.024
Discontinuation due to TRAEs, n (%)	65 (34)	26 (27)	39 (40)	0.068
Treatment-related death, n (%)	4 (2)	2 (2)	2 (2)	1.0
Details of grade ≥ 3 TRAEs				
Neutropenia	2	–	2	
Anemia	1	–	1	
Pancytopenia	1	–	1	
Febrile neutropenia	4	–	4	
Fatigue	1	–	1	
Fever	1	–	1	
Gastrointestinal toxicity	4	3	1	
Hepatic toxicity	7	2	5	
Skin toxicity	3	–	3	
Type 1 diabetes mellitus	3	1	2	
Thyroid dysfunction	1	1	–	
Adrenal insufficiency / Hypophysitis	3	1	2	
Pneumonitis	16	9	7	
Lung infection	2	1	1	
Renal toxicity	3	2	1	
Neuromuscular toxicity	2	–	2	
Cardiac toxicity	2	–	2	
Cystitis	1	–	1	

P-combo, pembrolizumab plus chemotherapy; P-mono, pembrolizumab monotherapy.

4. Discussion

This study represents the largest multicenter real-world retrospective cohort to compare P-mono and P-combo using PSM with the most covariates. Among patients with advanced or recurrent NSCLC and PD-L1 TPS ≥ 1 %, P-combo was associated with significantly longer median OS (31.8 vs. 20.7 months) and PFS (12.5 vs. 7.0 months) compared with P-mono after rigorous 1:1 PSM. Crucially, the survival curves remained clearly separated beyond 3 years, and the OS rates at 36 and 48 months, as well as the 48-month RMST, favored P-combo, suggesting durable survival benefits in addition to early disease control. Subgroup analysis revealed no significant long-term survival difference between the regimens in patients aged ≥ 75 years, with ECOG-PS ≥ 2, or with PD-L1 ≥ 50 %. In contrast, P-combo conferred a significant survival advantage in those aged < 75 years, with ECOG-PS 0–1, or PD-L1 1–49 %. These results offer important guidance for selecting between the two regimens for patient subsets defined by these characteristics.

Notably, among patients with PD-L1 TPS ≥ 1 %, the 3- and 4-year OS rates reported for P-combo in the KN-189 trial were 36.1 % and 28.3 %, respectively, and those in the KN-407 trial were 33.5 % and 24.3 %, respectively [3,4]. In our real-world cohort, the corresponding OS rates were markedly higher. This observed superiority may be attributed to differences in case-composition; approximately 70 % of our patients had non-squamous histology, and approximately 60 % had high PD-L1 expression features that are associated with long-term benefit. In contrast, the 3- and 4-year OS rates in the KN-042 trial were 25.3 % and 20.2 %, respectively, closely aligning with those observed for P-mono in our study. Given that the KN-042 trial excluded patients with PD-L1 TPS < 1 % and included a patient composition similar to ours in terms of non-squamous histology and high PD-L1 expression, this alignment in outcomes is consistent and expected.

Real-world studies on long-term outcomes of chemoimmunotherapy remain limited; however, Tambo et al. recently published 5-year data on P-mono. Among patients with high PD-L1 expression, the 3- and 5-year OS rates were 33.9 % and 24.8 %, respectively, closely matching our results [20]. These convergent findings reinforce the consistency of real-world survival outcomes with single-agent pembrolizumab as first-line treatment.

In our dataset, a significant difference in OS between the treatment groups emerged only after 3 years. At 1 year, the OS rates were 64.4 % for P-mono and 68.4 % for P-combo, respectively (p = 0.56). At 2 years, the OS rates were 48.7 % and 57.3 %, respectively (p = 0.25). The early overlap in the Kaplan–Meier curves is consistent with previous real-world studies with follow-up duration of 20 months or less [6–9]. With a median follow-up exceeding 42 months in both treatment groups, our study demonstrated a clear survival advantage of P-combo beyond the third year.

Subgroup analyses in our study showed that the long-term benefit of P-combo was most prominent in patients aged < 75 years, those with ECOG-PS 0–1, and PD-L1 TPS 1–49 %. The difference was particularly striking in this TPS subgroup, where the 3-year OS rates were 19.6 % for P-mono and 52 % for P-combo, and the 4-year OS rates were 10.4 % and 38.5 %, respectively. These findings align with the reported 3- and 4-year OS rates for the same TPS subgroup in previous clinical trials: 28.5 % and 22.1 % in the KN-189 trial, 31.1 % and 24.1 % in the KN-407 trial, and only 19.9 % and 15.8 % in the KN-042 trial. Furthermore, in patients with a history of PPI use, the survival benefit of P-mono was significantly lower than that of P-combo, consistent with findings reported by Kawachi et al. [21]. Moreover, P-combo showed greater survival benefit in patients with stage IV disease than in those with postoperative or chemoradiotherapy relapse, suggesting that higher response rates associated with chemoimmunotherapy may benefit patients with rapidly progressing tumors [22]. BMI may also modulate treatment outcomes, with ICI monotherapy being less effective in underweight patients. Indeed, cachexia and inflammation have been linked to ICI resistance, with poor outcomes even in PD-L1–high tumors

[23]. By contrast, recent studies suggest that survival outcomes with chemoimmunotherapy appeared to be consistent regardless of BMI, implying that chemotherapy could partially offset the disadvantage of low BMI [24]. These findings may explain why, in our study, OS was comparatively favorable with ICI plus chemotherapy rather than with ICI monotherapy in patients with BMI < 20 kg/m^2, although this observation should be cautiously interpreted.

In our study, the incidence of grade ≥ 3 TRAEs was significantly higher with P-combo than with P-mono (35 % vs. 20 %). In contrast, treatment-related mortality was identical in the two arms (2 % each). No statistically significant differences were observed between groups. The incidence and severity profile of pneumonitis were also virtually identical. As expected in a retrospective series, the absolute number of events was lower than that reported in randomized trials. The 20 % rate of grade ≥ 3 TRAEs in our P-mono arm closely aligned with the 21 % reported in the real-world analysis by Tambo et al. [20]. Meanwhile, the 35 % rate in our P-combo arm was within the 23.7–59.4 % range observed across previous retrospective studies [25–27]. Time-to-event analysis, which accounted for censoring and competing risks, confirmed a higher cumulative incidence of grade ≥ 3 TRAEs with P-combo. However, the curves plateaued after approximately 3 years in both arms, suggesting minimal late toxicity accrual. Although previous *meta*-analyses and a report by Ikezawa et al. suggested a higher risk of pneumonitis with P-combo compared with P-mono [9,10], our data showed equivalent frequencies between the two regimens. Taken together with the superior long-term OS achieved by P-combo, these findings suggest that concerns about grade ≥ 3 TRAEs or pneumonitis should not deter its selection when clinically appropriate.

A major strength of our study is the application of PSM to 13 baseline variables, which generated two well-balanced cohorts of approximately 100 patients each with extended follow-up. We further confirmed the robustness of our findings through multivariable analysis in the full cohort. However, this study has some limitations that must be acknowledged. First, as a retrospective study, it remains subject to selection bias, despite PSM. Although unmeasured confounding factors cannot be fully eliminated, we included most of the prognostic variables previously identified in the literature [11]. We excluded patients with NSCLC harboring EGFR or ALK alterations; however, comprehensive genomic profiling was not routinely available at the initiation of first-line treatments. Consequently, the status of other oncogenic drivers remains unknown and may have influenced treatment selection (Supplementary Table S3). In addition, all patients were Japanese, which may limit the generalizability of our findings to other ethnicities. Finally, some predefined subgroups contained few participants; therefore, OS estimates should be considered exploratory in the subgroup analyses. We mitigated this issue by evaluating the RMST and identifying the factors that showed consistent results across both analytic approaches.

In conclusion, our data showed that with more than 42 months of follow-up, P-combo achieved significantly longer survival. We identified patient subgroups that could derive the greatest long-term benefits from P-combo, including those who were younger, had ECOG-PS 0–1, exhibited PD-L1 1–49 % expression, or had a history of PPI use. Although P-combo was associated with a higher incidence of grade ≥ 3 TRAEs, the incidences of TRDs and pneumonitis were similar between the two regimens, indicating comparable overall tolerability. Collectively, these findings suggest that in patients with advanced NSCLC, P-combo may be a more promising option than P-mono for achieving durable survival. Further confirmation is warranted, particularly from ongoing phase III trials such as the PERSEE study in France (NCT04547504), which is directly comparing P-mono with P-combo [28].

CRediT authorship contribution statement

Nao Shoshihara: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kinnosuke Matsumoto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Takayuki Shiroyama:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kiyohide Komuta:** Writing – review & editing, Resources. **Akito Miyazaki:** Writing – review & editing, Resources. **Motohiro Tamiya:** Writing – review & editing, Supervision, Project administration. **Akihiro Tsukaguchi:** Writing – review & editing, Resources. **Akihiro Tamiya:** Writing – review & editing, Supervision, Project administration. **Tomoki Kuge:** Writing – review & editing, Resources. **Yasuhiro Mihashi:** Writing – review & editing, Resources. **Masahide Mori:** Writing – review & editing, Supervision, Project administration. **Keijiro Yamauchi:** Writing – review & editing, Resources. **Hidekazu Suzuki:** Writing – review & editing, Supervision, Project administration. **Yuhei Kinehara:** Writing – review & editing, Resources. **Hirotomo Machiyama:** Writing – review & editing, Resources. **Satoshi Tanaka:** Writing – review & editing, Resources. **Toshie Niki:** Writing – review & editing, Resources. **Soichiro Kato:** Writing – review & editing, Resources. **Yuki Nishikawa:** Writing – review & editing, Resources. **Akio Osa:** Writing – review & editing, Resources. **Kouji Azuma:** Writing – review & editing, Resources. **Yoshito Takeda:** Writing – review & editing, Supervision, Project administration. **Atsushi Kumanogoh:** Writing – review & editing, Supervision, Project administration.

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Declaration of competing interest

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Appendix A. Supplementary data

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