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Research Paper

Comparison of long-term survival between nivolumab plus ipilimumab with chemotherapy and pembrolizumab with chemotherapy in advanced non-small cell lung cancer: A multicenter retrospective cohort study

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ABSTRACT

Background: Nivolumab plus ipilimumab with chemotherapy (NICT) and pembrolizumab with chemotherapy (PCT) are widely used first-line regimens for advanced non–small-cell lung cancer (NSCLC) lacking actionable driver mutations. However, real-world evidence comparing long-term survival outcomes between two regimens, particularly when stratified by PD-L1 tumor proportion score (TPS), remains limited.

Methods: We retrospectively analyzed 457 patients treated with NICT or PCT across 13 institutions in Japan between January 2019 and December 2022. Patients were classified into PD-L1 TPS $< 1\%$ and $\geq 1\%$ cohorts. Overall survival (OS) and treatment-related adverse events (TRAEs) were assessed using propensity score methods, including inverse probability treatment weighting (IPTW) and overlap weighting (OW), adjusting for 10 clinically relevant covariates.

Results: The duration of median follow-up exceeded 40 months. Among 161 patients with PD-L1 TPS $< 1\%$ (NICT n = 43; PCT n = 118), NICT achieved significantly longer OS than PCT (median 47.4 versus 16.6 months; IPTW-adjusted hazard ratio 0.50; p = 0.007), with superior 36-month OS rates (51.5% versus 28.2%; p = 0.016). These trends remained robust in the OW sensitivity analysis. In contrast, among 296 patients with PD-L1 TPS $\geq 1\%$ (NICT n = 45; PCT n = 251), no significant differences were observed in median OS or 36-month OS rates

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between regimens. Grade ≥ 3 TRAEs, treatment discontinuation, and treatment-related death rates were comparable (p = 0.37, 0.78, and 0.32, respectively).
Conclusions: NICT provides a sustained long-term survival advantage over PCT with comparable tolerability and may be a promising therapeutic option for the treatment of advanced NSCLC that are PD-L1 negative.

1. Introduction

Anti-programmed cell death-1 (PD-1), anti-programmed cell death ligand-1 (PD-L1), and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies combined with platinum-based chemotherapy are currently used as standard therapy for patients with advanced or recurrent non–small-cell lung cancer (NSCLC) that lack actionable driver mutations such as EGFR or ALK [1–6]. Nivolumab plus ipilimumab with chemotherapy (NICT) and pembrolizumab with chemotherapy (PCT) have been approved based on phase III randomized controlled trials, including CheckMate-9LA, KEYNOTE-189, and KEYNOTE-407. These regimens have demonstrated clinical efficacy irrespective of histological subtype or PD-L1 expression level, establishing them as among the most widely adopted first-line treatment options.

In KEYNOTE-189 and KEYNOTE-407, the 5-year overall survival (OS) rates with PCT were 19.4% and 18.4%, respectively. Similarly, in CheckMate-9LA, the 5-year OS rate with NICT was 18%, suggesting comparable long-term outcomes between the regimens. When stratified by PD-L1 tumor proportion score (TPS), the 5-year OS rate in patients with PD-L1 TPS ≥ 1% was 19.8–29.6% for PCT versus 18% for NICT. Conversely, among patients with PD-L1 TPS < 1%, the 5-year OS rate favored NICT (22%) over PCT (9.6–10.7%) [1–3]. To directly compare these regimens, the phase III NIPPON trial was conducted in Japan. However, the study was terminated early due to 11 treatment-related deaths (TRDs) in the NICT arm [7,8]. Among enrolled patients, the median OS did not significantly differ between groups (NICT 23.7 months versus PCT 20.5 months), and further no significant difference was observed when stratified by PD-L1 TPS ≥ 1% or < 1%. Because the median follow-up duration was only 15.3 months, longer-term results are awaited to clarify the relative benefits of these regimens.

Recently, several real-world reports have compared NICT and PCT. Verschueren et al. evaluated 58 patients receiving NICT and 60 receiving PCT for advanced NSCLC with PD-L1 TPS < 1% [9]. The median progression-free survival (PFS) did not differ significantly between groups, whereas OS was not reached due to the short follow-up period of 6–8 months. Notably, the NICT group included a significantly higher proportion of patients with favorable Eastern Cooperative Oncology Group performance status (ECOG-PS), resulting in imbalanced baseline characteristics. Kaneko et al. conducted a propensity score-matched analysis comparing the regimens. However, the study was limited by a small sample size (21 patients per arm) and a median follow-up of only approximately 12 months [10]. Similarly, Nagano et al. reported outcomes in 44 patients treated with NICT versus 61 with PCT, representing the longest follow-up available to date; however, follow-up remained limited to approximately 20 months [11].

Given that long-term survival outcomes are a key factor in treatment selection—as highlighted by the pivotal KEYNOTE-189, KEYNOTE-407, and CheckMate-9LA trials—real-world evidence is lacking on survival with NICT versus PCT assessed beyond 36 months. Furthermore, while several studies have focused specifically on NSCLC that is PD-L1 negative, no real-world study has comprehensively assessed outcomes in both PD-L1 TPS ≥ 1% and < 1% populations.

Therefore, the aim of present study was to compare the clinical efficacy and safety of NICT and PCT in patients with NSCLC stratified by PD-L1 TPS ≥ 1% versus < 1%, adjusting for 10 clinically relevant confounding variables and leveraging a follow-up duration exceeding 40 months. These findings are expected to provide additional real-world evidence to guide treatment selection in advanced NSCLC.

2. Material and methods

2.1. Study design and patient selection

This multicenter, retrospective cohort study enrolled consecutive patients with pathologically confirmed advanced or recurrent NSCLC across 13 medical institutions in Japan. Eligible participants received either NICT or PCT as first-line therapy between January 2019 and December 2022. In accordance with the inclusion criteria of the KEYNOTE-189, KEYNOTE-407, and CheckMate-9LA trials, patients harboring major EGFR gene mutations (exon 21 L858R or exon 19 deletion) or ALK rearrangements, as well as those with unknown status, were excluded from the analysis. The study followed the ethical principles of the Declaration of Helsinki and the World Health Organization's Good Clinical Practice guidelines. Ethical approval was obtained from the central institutional review board at Osaka University (approval number 22349–5). Owing to the retrospective nature of the research, the need for written informed consent was waived. Instead, an opt-out procedure was implemented via institutional websites, allowing patients and their families the opportunity to decline participation.

2.2. Data collection and outcome assessment

Clinical data collected from medical records included age, sex, smoking history, ECOG-PS, clinical stage (cStage), driver gene mutation, histology, PD-L1 expression, liver and brain metastasis, use of steroids, body mass index (BMI), treatment regimens, number of treatment lines, treatment outcomes, and treatment-related adverse events (TRAEs). Steroid use was defined as corticosteroid administration equivalent to ≥ 10 mg/day of prednisolone within 30 days before treatment initiation [12]. BMI of 20 kg/m^2 was adopted as cutoff according to an international consensus definition of cancer cachexia [13]. Clinical response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [14]. OS was determined from the first-line treatment start date to the date of death or last follow-up, and PFS was defined as the period from the first-line treatment start date to the date of disease progression or death from any cause. The safety level was evaluated using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE, ver5), based on TRAE incidence, treatment discontinuation, and TRDs [15]. While pneumonitis was evaluated as any grade, the other TRAEs were classified as grade 3 or higher. Severe adverse events (SAEs) were defined as TRAEs ≥ grade 3 in this study. The date of data cut-off was June 30, 2025.

2.3. Statistical analyses

The primary endpoints were median OS and 36-month OS rate in patients receiving NICT and PCT in both PD-L1 TPS ≥ 1% and < 1% cohorts. Secondary endpoints were TRAEs with long-term follow-up periods. Patients characteristics were compared using standardized mean differences (SMD). Propensity score (PS) analyses were performed adjusting for clinically relevant covariates, including age, sex, smoking history, ECOG-PS, cStage, histology, liver and brain metastasis, use of steroid, and BMI, with PD-L1 TPS additionally included in PD-L1 TPS ≥ 1% cohort [16]. Stabilized inverse probability of treatment weighting (IPTW) with 1–99% winsorization was performed, assigning weights of p/PS for the NICT group and (1 − p)(1 − PS) for the PCT group [17,18]. As sensitivity analyses, we applied 1:1 nearest-neighbor matching with a caliper size of 0.2 and overlap weighting (OW) assigned weights of 1 −

PS for the NICT group and PS for the PCT group [19,20]. Adjusted survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Additionally, OS rates were estimated at 36 and 42 months from Kaplan–Meier curves and compared using point-estimate survival tests based on standard-error-derived Z statistics. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the adjusted cox proportional hazards model. Group comparisons were performed using the Mann–Whitney *U* test for continuous data and the chi-squared or Fisher's exact test for categorical data. Cumulative incidences of SAEs, treatment discontinuation, and TRDs were compared using Gray's test, and hazard ratios were derived through Fine–Gray regression for risk assessment. Statistical significance was defined as a two-sided P-value < 0.05. Analyses were performed using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Of the 584 registered patients, 457 were eligible for analysis after excluding 127 patients with positive or suspected EGFR mutations or ALK rearrangements, unavailable PD-L1 TPS data, and missing baseline information. Among the 161 patients with PD-L1 TPS $< 1\%$, 43 received

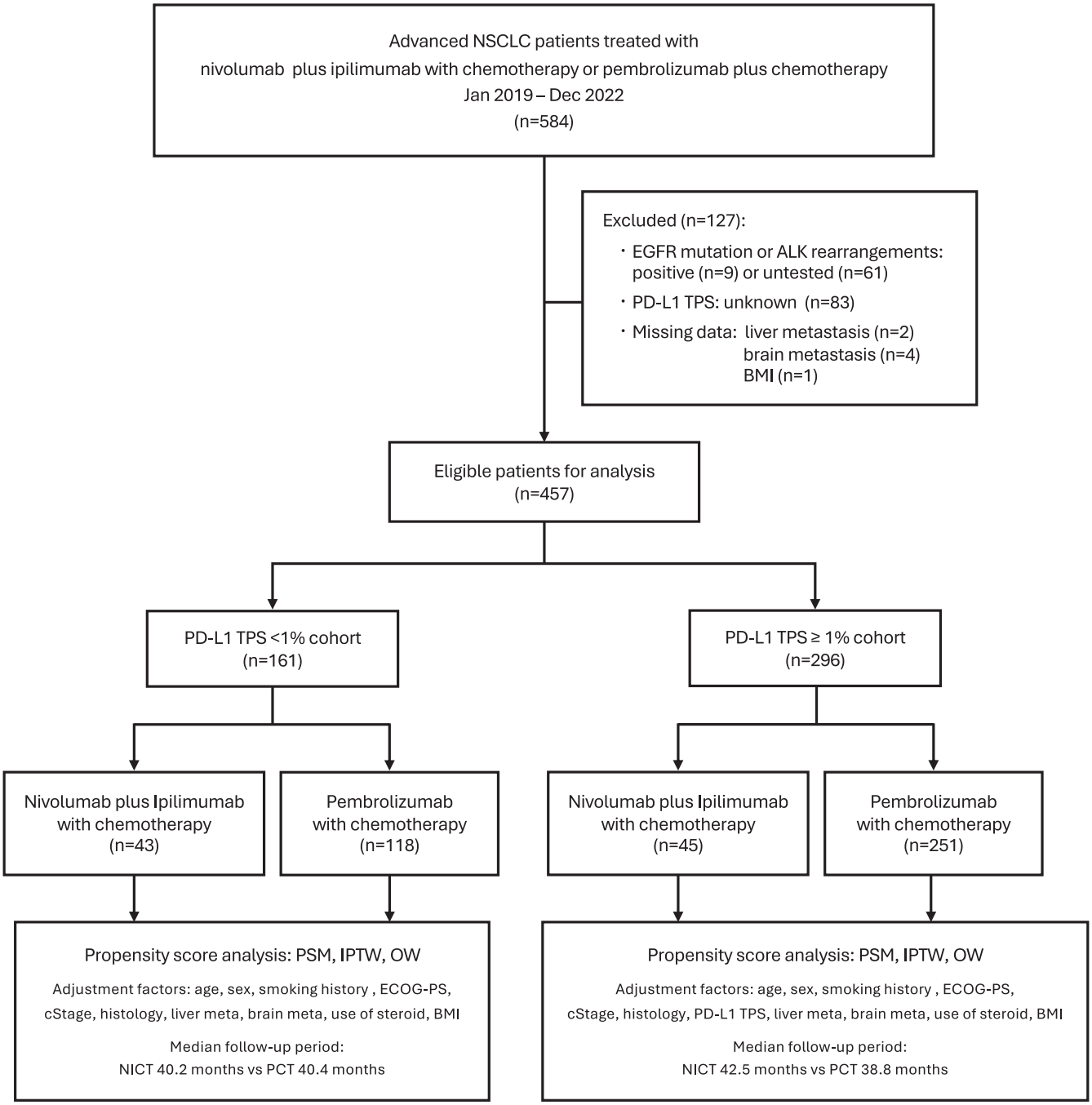

Fig. 1. CONSORT diagram of the study. BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; IPTW, inverse probability of treatment weighting; NICT, nivolumab plus ipilimumab with chemotherapy; NSCLC, non-small cell lung cancer; OW, overlap weighting; PCT, pembrolizumab with chemotherapy; PD-L1 TPS, programmed death-ligand 1 tumor proportion score; PSM, propensity score matching.

NICT and 118 received PCT, while among the 296 with PD-L1 TPS ≥ 1%, 45 received NICT and 251 received PCT. Clinical outcomes were compared between NICT and PCT within each cohort using propensity score–based adjustment (Fig. 1). Baseline characteristics of the study patients are presented in Tables 1, S1, and S2. Most baseline variables demonstrated SMDs below 0.1, indicating adequate balance; however, brain metastasis and PD-L1 TPS in the PD-L1 TPS ≥ 1% cohort and BMI in both cohorts exceeded this threshold. After applying propensity score adjustment, both IPTW and OW achieved substantially improved covariate balance with stable SMD distributions across groups (Fig. S1).

3.2. Comparison of outcomes between treatment groups in the PD-L1 TPS < 1% cohort

The median follow-up period was 40.2 months (interquartile range [IQR], 38.9–49.3) for patients receiving NICT and 40.4 months (IQR, 34.0–53.7) for those receiving PCT, with no significant difference (P = 0.45). In the IPTW-adjusted analysis, median OS was significantly longer with NICT (47.4 versus 16.6 months; HR 0.50; 95% CI 0.31–0.83; p = 0.007), and median PFS showed a favorable trend with NICT without statistical significance (10.8 versus 6.7 months; HR 0.71; 95% CI 0.48–1.06; p = 0.10). These findings remained robust in the OW sensitivity analysis. (Fig. 2).

The 36-month OS rate was 51.5% with NICT and 28.2% with PCT (p = 0.016), while the 42-month OS rates were 51.5% and 24.8%, respectively (p = 0.006). Similar patterns were observed in the PS–adjusted sensitivity analyses for both 36-month and 42-month OS (Table S3).

NICT was associated with a higher objective response rates compared with PCT (65.1% versus 49.2%; p = 0.072), whereas disease control rates were similar between the groups (86.0% versus 76.3%; p = 0.18) (Table S2).

3.3. Comparison of outcomes between treatment groups in the PD-L1 TPS ≥ 1% cohort

The median follow-up duration was 42.5 months (IQR, 39.4–44.6) among patients receiving NICT and 38.8 months (IQR, 35.7–44.7) among those receiving PCT (p = 0.25). In the IPTW-adjusted analysis, no significant differences were observed in either median PFS (10.9 versus 10.1 months; HR 0.93; 95% CI 0.60–1.42; p = 0.76) or median OS (28.0 versus 28.4 months; HR 0.89; 95% CI 0.56–1.42; p = 0.63). These results were consistent in the OW sensitivity analysis (Fig. 3).

The 36-month OS rates for NICT and PCT were 41.1% and 45.5%, respectively (p = 0.68), and the 42-month OS rates were 41.1% and 42.4%, respectively (p = 0.89). Comparable trends were observed in the PS–adjusted sensitivity analyses for both 36-month and 42-month OS (Table S3).

Objective response rates did not differ significantly between the two groups (66.7% versus 68.1%; p = 0.85), and disease control rates were also similar (84.4% versus 90.4%; p = 0.23) (Table S2).

3.4. Association between clinical factors and survival outcomes in all patients

To identify clinical factors associated with favorable outcomes following ICI–based therapy, we evaluated the relationships between baseline characteristics and survival. In the multivariable analysis for PFS, poor ECOG-PS, PD-L1 TPS < 1%, and the presence of liver metastasis were independently associated with significantly shorter PFS.

Table 1
Patient characteristics.

	PD-L1 TPS < 1% cohort (n = 161)			PD-L1 TPS ≥ 1% cohort (n = 296)		
	NICT (n = 43)	PCT (n = 118)	SMD	NICT (n = 45)	PCT (n = 251)	SMD
Median age (IQR)	69 (54.5–74)	70.5 (64.2–75)		65 (57–71)	69 (63.5–73)	
<75	33 (76.7)	86 (72.9)	0.039	40 (88.9)	204 (81.3)	0.076
≥75	10 (23.3)	32 (27.1)		5 (11.1)	47 (18.7)	
Sex, n (%)			0.020			0.022
Female	9 (20.9)	27 (22.9)		6 (13.3)	39 (15.5)	
Male	34 (79.1)	91 (77.1)		39 (86.7)	212 (84.5)	
Smoking, n (%)			0.083			0.009
Never	3 (7.0)	18 (15.3)		3 (6.7)	19 (7.6)	
Former/current	40 (93.0)	100 (84.7)		42 (93.3)	232 (92.4)	
ECOG-PS, n (%)			0.012			0.020
0/1	38 (88.4)	103 (87.3)		40 (87.7)	218 (86.9)	
2/3	5 (11.6)	15 (12.7)		5 (12.3)	33 (13.1)	
cStage, n (%)			0.034			0.015
IV	35 (81.4)	92 (78.0)		34 (75.6)	186 (74.1)	
Others	8 (18.6)	26 (22.0)		11 (24.4)	65 (25.9)	
Histology, n (%)			0.084			0.025
Non-Sq	31 (72.1)	95 (80.5)		29 (64.4)	168 (66.9)	
Sq	12 (27.9)	23 (19.5)		16 (35.6)	83 (33.1)	
PD-L1 TPS, n (%)			–			0.296
≥50	–	–		10 (22.2)	130 (51.8)	
1–49	–	–		35 (77.8)	121 (48.2)	
Liver metastasis, n (%)			0.021			0.029
No	37 (86.0)	99 (83.9)		42 (93.3)	227 (90.4)	
Yes	6 (14.0)	19 (16.1)		3 (6.7)	24 (9.6)	
Brain metastasis, n (%)			0.017			0.122
No	35 (81.4)	98 (83.1)		32 (71.1)	209 (83.3)	
Yes	8 (18.6)	20 (16.9)		13 (28.9)	42 (16.7)	
Use of steroid, n (%)			0.093			0.003
No	43 (100)	107 (90.7)		43 (95.6)	239 (95.2)	
Yes	0 (0)	11 (9.3)		2 (4.4)	12 (4.8)	
BMI, n (%)			0.155			0.171
≥20	5 (11.6)	32 (27.1)		7 (15.6)	82 (32.7)	
<20	38 (88.4)	86 (72.9)		38 (84.4)	169 (67.3)	

Abbreviations: NICT, nivolumab plus ipilimumab with chemotherapy; PCT, pembrolizumab with chemotherapy; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; PD-L1 TPS, programmed cell death ligand-1 tumor proportion score.

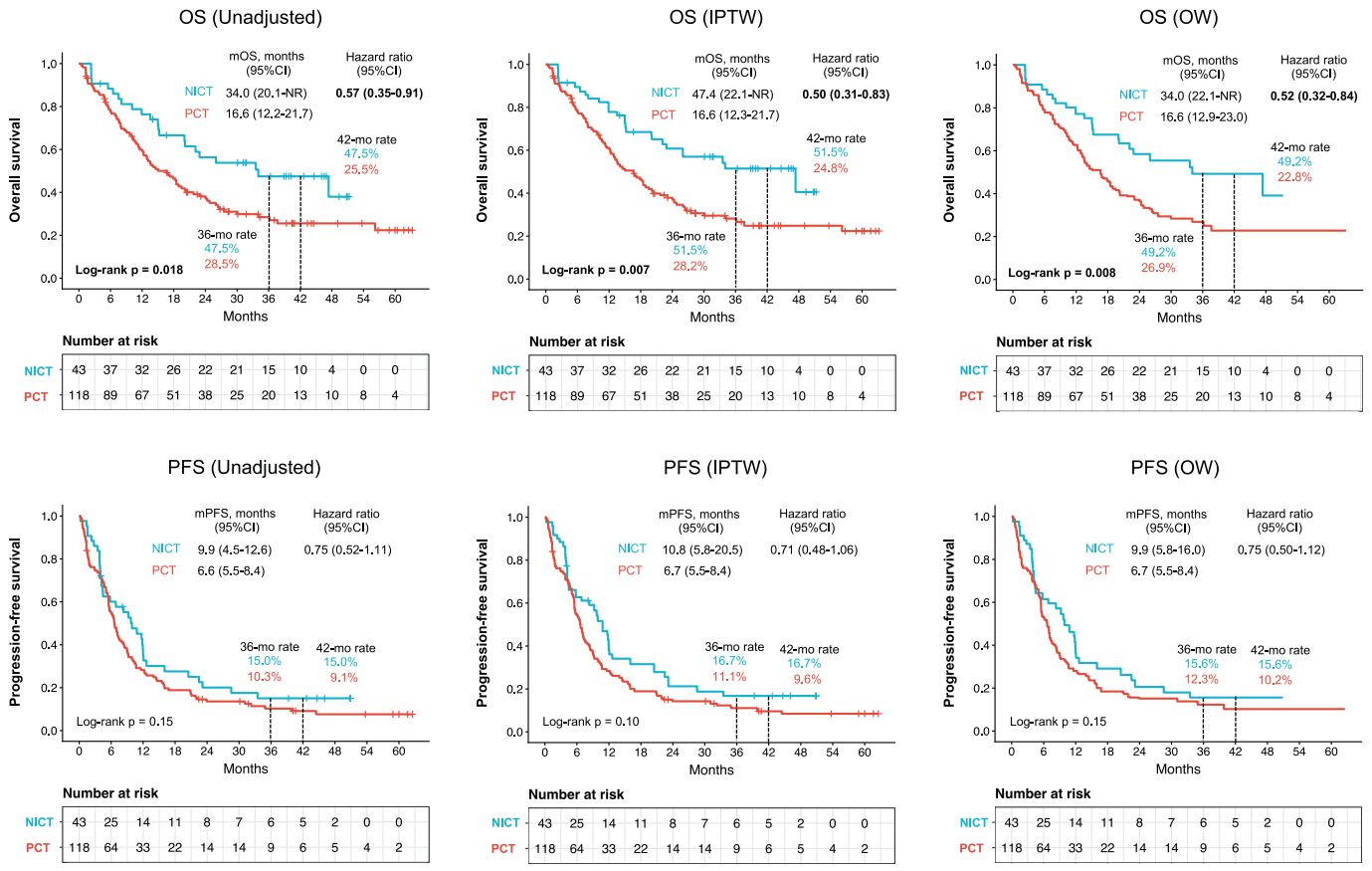

Fig. 2. Overall survival (OS) and progression-free survival (PFS) for NICT versus PCT in PD-L1 TPS < 1% cohort. Kaplan–Meier curves demonstrate OS (top panels) and PFS (bottom panels) for NICT versus PCT, shown using unadjusted, IPTW-adjusted, and OW-adjusted analyses (from left to right). CI, confidence interval; IPTW, inverse probability of treatment weighting; NICT, nivolumab plus ipilimumab with chemotherapy; OW, overlap weighting; PCT, pembrolizumab with chemotherapy; PD-L1 TPS, programmed death-ligand 1 tumor proportion score.

However, no significant difference was observed between NICT and PCT (HR 0.92; 95% CI 0.70–1.20; p = 0.52) (Fig. S2). In the multivariable analysis for OS, poor ECOG-PS, PD-L1 TPS < 1%, liver metastasis, older age, male sex, and squamous histology were significantly associated with shorter OS. By contrast, NICT was associated with a significant improvement in OS compared with PCT (HR 0.70; 95% CI 0.50–0.97; p = 0.031) (Fig. S3).

3.5. *Treatment-related adverse events stratified by onset time*

Table 2 summarizes TRAEs from treatment initiation. The incidence of SAEs and TRDs were 39.8% and 2.3% in the NICT group, compared with 34.7% and 4.6% in the PCT group (p = 0.37 and 0.32, respectively). Regarding toxicity profiles, skin toxicity and adrenal–pituitary disorder were significantly more frequent in the NICT group (p = 0.005 and 0.038, respectively). No significant differences were observed in the incidence of pneumonitis across severity grades. Cytokine release syndrome (CRS) was observed in one patient in each group. The 36-month cumulative incidences of SAEs, treatment discontinuation, and TRDs did not differ significantly between the two groups (p = 0.39, 0.42, and 0.23, respectively) (Fig. 4).

4. Discussion

In a real-world setting with a follow-up duration exceeding 40 months, we compared the clinical efficacy and safety of NICT and PCT within the PD-L1 TPS ≥ 1% and < 1% cohorts. Multiple propensity score–based adjustments incorporating 10 clinically relevant confounding variables were applied to confirm the robustness of the findings. As a result, NICT achieved a more than 20% higher 36-month OS rate compared with PCT among patients with PD-L1 TPS < 1%, whereas survival outcomes were comparable between the two regimens in patients with PD-L1 TPS ≥ 1%. Moreover, the 36-month incidences of SAEs and TRDs were acceptable in both groups. To our knowledge, this study represents the first long-term comparative investigation of NICT relative to PCT, and these findings provide supportive evidence to guide treatment selection between the two regimens.

Di Federico et al. recently conducted a *meta*-analysis incorporating CheckMate-9LA, KEYNOTE-189, KEYNOTE-407, CheckMate-227, POSEIDON, and IMpower150, reporting 5-year survival outcomes achieved with dual ICI therapy targeting CTLA-4 and PD-1/PD-L1 [21]. In subgroup analyses, dual ICI therapy significantly improved OS compared with ICI monotherapy exclusively in patients with PD-L1 TPS < 1%. Although the improvement in median OS was modest (approximately 1 month), the 5-year OS rate nearly doubled. Similarly, O'Byrne et al. demonstrated that the annual HR for survival with nivolumab plus ipilimumab surpassed that of PCT after 12 months and remained consistently favorable thereafter [22]. Although the difference in long-term OS did not reach statistical significance, nivolumab plus ipilimumab was associated with a 12–27% reduction in mortality risk at 60 months. Collectively, these findings suggest that the benefit of dual ICI therapy may strengthen over longer follow-up periods. Only these two studies have specifically investigated long-term survival, although several network *meta*-analyses have indirectly compared first-line ICI regimens. In these analyses, NICT appears to be consistently superior to PCT in patients with PD-L1 TPS < 1%, whereas the opposite trend is

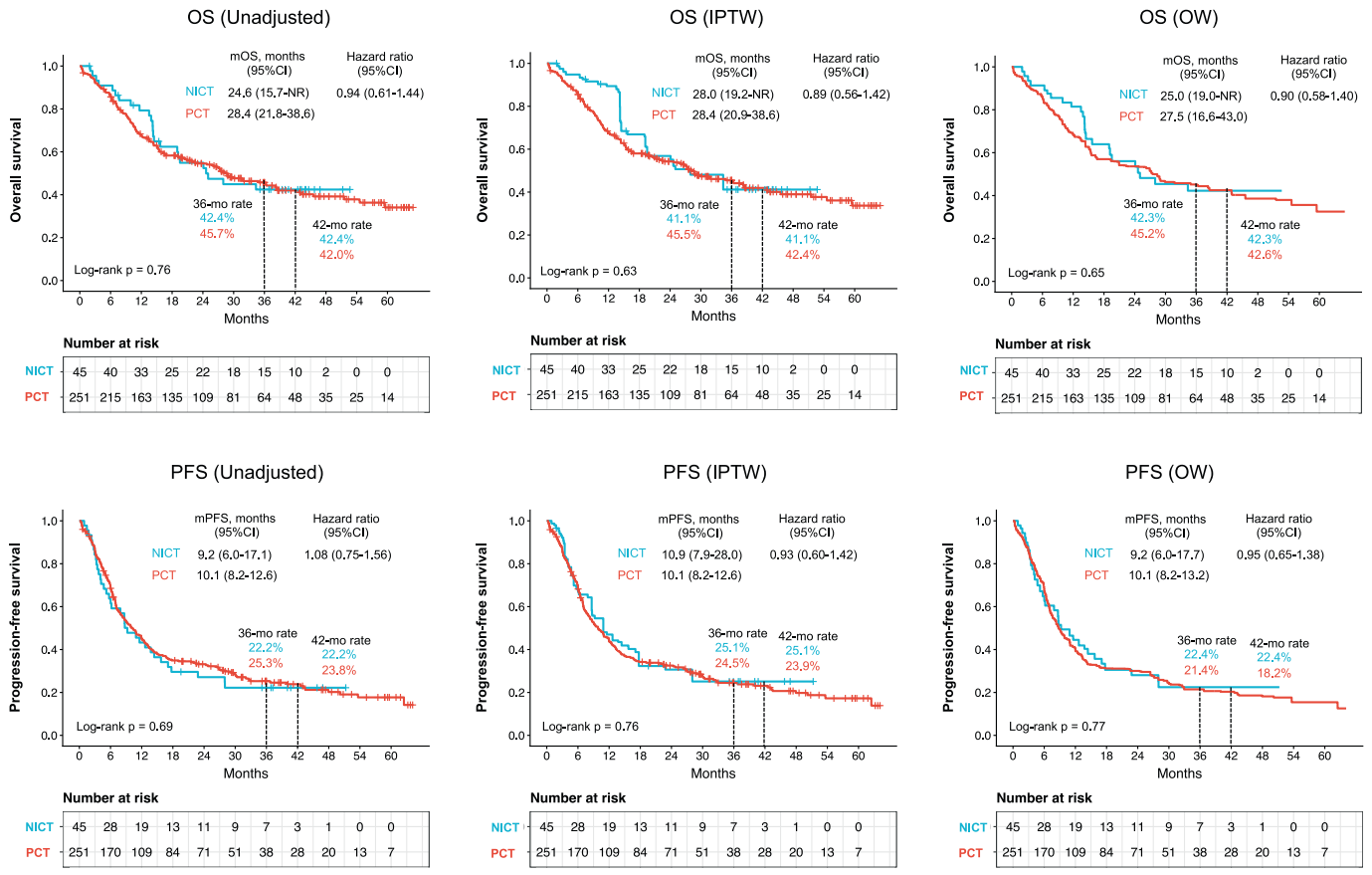

Fig. 3. Overall survival (OS) and progression-free survival (PFS) for NICT versus PCT in PD-L1 TPS ≥ 1% cohort. Kaplan–Meier curves demonstrate OS (top panels) and PFS (bottom panels) for NICT versus PCT, shown using unadjusted, IPTW-adjusted, and OW-adjusted analyses (from left to right). CI, confidence interval; IPTW, inverse probability of treatment weighting; NICT, nivolumab plus ipilimumab with chemotherapy; OW, overlap weighting; PCT, pembrolizumab with chemotherapy; PD-L1 TPS, programmed death-ligand 1 tumor proportion score.

Table 2
Treatment-related adverse events.

	NICT (n = 88)	PCT (n = 369)	P value
Number of patients with SAEs*, (%)	35 (39.8)	128 (34.7)	0.37
SAEs leading to discontinuation, n (%)	20 (22.7)	89 (24.1)	0.78
Treatment related death, n (%)	2 (2.3)	17 (4.6)	0.32
SAEs occurring in ≥ 3 patients, n (%)			
Skin toxicity	9 (10.2)	12 (3.3)	**0.005**
Colitis	5 (5.7)	9 (2.4)	0.11
Hepatobiliary toxicity	5 (5.7)	15 (4.1)	0.51
Renal toxicity	3 (3.4)	7 (1.9)	0.42
Adrenal-pituitary disorder	6 (6.8)	9 (2.4)	**0.038**
Neuromuscular toxicity	2 (2.3)	6 (1.6)	0.66
Febrile neutropenia	2 (2.3)	15 (4.1)	0.75
Other SAEs	4 (4.5)	28 (7.6)	0.48
Pneumonitis, n (%)			
Grade 1–2	9 (10.2)	48 (13.0)	0.48
Grade 3–5	7 (8.0)	49 (13.3)	0.17
Cytokine release syndrome, n(%)	1 (1.1)	1 (0.3)	0.35

Abbreviations: NICT, nivolumab plus ipilimumab with chemotherapy; PCT, pembrolizumab with chemotherapy.
* Severe AEs (SAEs) were defined as TRAEs ≥ grade 3.

observed in patients with PD-L1 TPS ≥ 1% [23,24]. The question of whether such a crossover pattern will emerge in long-term follow-up from the NIPPON trial remains clinically important in guiding regimen selection in the future.

Previously, we had conducted a comparative analysis of NICT versus PCT using propensity score matching to investigate the superiority of one regimen over the other [25]. However, that study was limited by several major constraints: (1) the number of covariates included in the adjustment model was insufficient, and only matching was applied among the propensity score adjustments; (2) survival outcomes stratified by PD-L1 TPS were compared without covariate balance assessment using SMD; and (3) the median follow-up duration was relatively short, at approximately 20 months. These limitations likely restricted the strength of the evidence produced. In the present study, after addressing these limitations, no significant differences in PFS or OS were observed between NICT and PCT in the PD-L1 TPS ≥ 1% cohort. In contrast, among patients with PD-L1 TPS < 1%, we observed a trend toward improved PFS and significantly longer OS with NICT.

Mechanistically, adding ipilimumab to anti–PD-1/PD-L1 therapy can attenuate regulatory T-cell activity through Fc-mediated cytotoxic mechanisms and enhance memory $CD8^+$ T-cell responses [26,27]. Cytotoxic chemotherapy further potentiates antitumor immunity by inducing immunogenic cell death and increasing antigen availability within the tumor microenvironment [28]. Thus, combining chemotherapy with dual PD-1/CTLA-4 blockade may enhance antitumor immune activation, particularly in PD-L1 TPS < 1% tumors in which dependence on CTLA-4–mediated immune modulation may be greater. Consistent with this, NICT achieved a higher tumor response rate than PCT in PD-L1–negative tumors in our cohort. Although differences in PFS between the two regimens were modest, OS diverged substantially. This dissociation may be explained by durable immune reprogramming driven by ipilimumab-mediated Treg modulation and expansion of tumor-specific T-cell responses, potentially sustaining tumor control

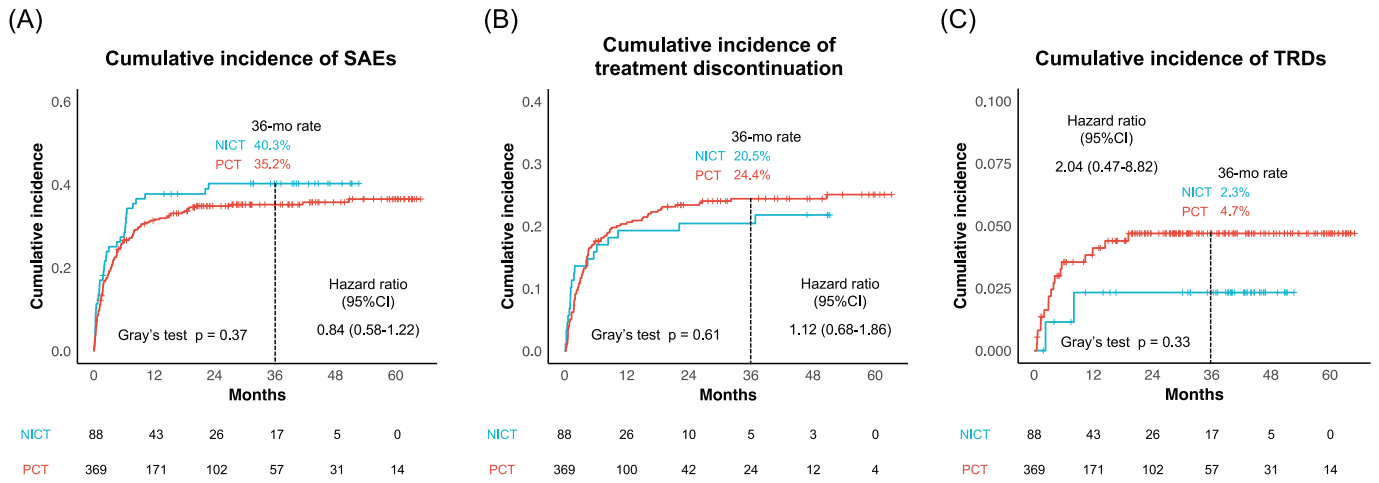

Fig. 4. Cumulative incidence curves associated with treatment-related adverse events. (A) Cumulative incidence of severe adverse events (SAEs), (B) treatment discontinuation due to toxicity, and (C) treatment-related deaths (TRDs) were compared between patients with NICT and PCT. CI, confidence interval; NICT, nivolumab plus ipilimumab with chemotherapy; PCT, pembrolizumab with chemotherapy.

beyond radiographic progression or treatment discontinuation [29].

In the NIPPON trial, TRDs included four cases of pneumonitis, three cases of CRS, and two cases of myocarditis, among others [8]. In our study, two TRDs occurred in the NICT group: one due to pneumonitis and the other due to severe sepsis secondary to steroid-induced immunosuppression administered for pneumonitis management. Real-world studies have reported heterogeneous TRD rates associated with NICT range from approximately 2.8% to 9.1%, reflecting variation in patient backgrounds [10,11,30,31]. In the present analysis, with more than 40 months of follow-up, no additional TRD events were observed when updating grade $\geq$ 3 TRAEs. This aligns with findings from CheckMate-9LA where the number of TRDs did not increase between the 2- and 5-year follow-up analyses. These data suggest that prolonged ipilimumab exposure may not be associated with an increased risk of treatment-related mortality [32]. However, since the incidence of severe skin toxicity and adrenal–pituitary dysfunction was significantly higher with NICT than with PCT, careful monitoring for these toxicities remains essential when administering NICT [33,34].

A major strength of this study is the comparison of long-term survival outcomes between NICT and PCT stratified by PD-L1 expression. However, several limitations should be acknowledged. First, the sample size of the NICT group was relatively small, and the retrospective nature of the study introduces the potential for selection bias. Second, because nearly all enrolled patients were of a single ethnicity (Japanese), the generalizability of these findings to other populations may be limited. Finally, although the analytic approach was designed to minimize confounding, unmeasured variables not included as covariates in the propensity score model may still have influenced the results. Nonetheless, the model incorporated most clinically recognized prognostic factors for ICI treatment.

In conclusion, with more than 40 months of follow-up, our data demonstrate that NICT achieved significantly longer survival compared with PCT among patients with PD-L1 TPS $<$ 1%, whereas no survival advantage was observed in patients with PD-L1 TPS $\geq$ 1%. Although the incidence of grade $\geq$ 3 skin toxicity and adrenal–pituitary disorder was higher with NICT, the TRD rate was comparable between the two regimens, indicating similar overall tolerability. Taken together, NICT may represent a promising option capable of providing sustained survival benefit for patients with advanced NSCLC and PD-L1 TPS $<$ 1%. However, given the relatively small number of NICT-treated patients, further validation in larger prospective cohorts is warranted.

Statement of Ethics

The study followed the ethical principles of the Declaration of Helsinki and the World Health Organization's Good Clinical Practice guidelines. Ethical approval was obtained from the central institutional review board at Osaka University (approval number 22349-5). Owing to the retrospective nature of the research, the need for written informed consent was waived. Instead, an opt-out procedure was implemented via institutional websites, allowing patients and their families the opportunity to decline participation.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2026.109336.

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