Original Article

Prognostic significance of immunotherapy in postoperative recurrent non-small cell lung cancer without EGFR mutations or ALK rearrangements

Shunsuke Shigefuku^, Satoshi Takahashi, Masaru Hagiwara, Masatoshi Kakihana, Tatsuo Ohira, Norihiko Ikeda

Department of Surgery, Tokyo Medical University, Shinjuku, Tokyo, Japan

Contributions: (I) Conception and design: S Shigefuku, S Takahashi, M Hagiwara; (II) Administrative support: M Kakihana, T Ohira, N Ikeda; (III) Provision of study materials or patients: S Shigefuku; (IV) Collection and assembly of data: S Shigefuku; (V) Data analysis and interpretation: S Shigefuku, S Takahashi, N Ikeda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shunsuke Shigefuku, MD, PhD. Department of Surgery, Tokyo Medical University, 6–7–1 Nishishinjuku, Shinjuku, Tokyo, 160–0023, Japan. Email: ssshigefukuuu8888@gmail.com.

Background: Limited reports exist regarding postoperative recurrent non-small cell lung cancer (NSCLC) without major driver mutations [epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements] treated with immune checkpoint inhibitors (ICIs) when programmed cell death ligand 1 (PD-L1) is expressed in a real-world setting. The aim of this study was to evaluate the effect of ICIs for those NSCLC.

Methods: We enrolled 255 patients with postoperative recurrent NSCLC lacking EGFR mutations or ALK rearrangements who underwent lobectomy or more extensive resection between 2012 and 2021. Factors associated with post-recurrence survival (PRS) were determined using the Cox proportional hazards model. PRS was analyzed using Kaplan-Meier curves and compared using the log-rank test.

Results: Multivariable analysis demonstrated that squamous cell carcinoma, pathological stage III, and an Eastern Cooperative Oncology Group (ECOG) performance status ≥2 were significantly associated with worse PRS. Conversely, ICI use at first line was associated with improved PRS. Patients who used ICIs during the first line and subsequent therapies had better PRS than those who received chemotherapy alone. Among patients who used ICIs, there was no significant difference in response rate at the first line, nor in PRS among those with PD-L1 expression ≥50%, 1–49%, and <1% in surgically resected specimens.

Conclusions: ICI use at any treatment line improved the PRS of NSCLC patients without major driver mutations, irrespective of PD-L1 expression, in a real-world setting.

Keywords: Non-small cell lung cancer (NSCLC); postoperative recurrence; immunotherapy; immune checkpoint inhibitors (ICIs); programmed cell death ligand 1 expression (PD-L1 expression)

Submitted Feb 13, 2024. Accepted for publication Apr 26, 2024. Published online Jun 07, 2024.
doi: 10.21037/jtd-24-237
View this article at: https://dx.doi.org/10.21037/jtd-24-237

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers (1,2). Complete surgical resection remains the only potentially curative treatment for early-stage NSCLC. However, 30–55% of NSCLC patients who undergo complete resection experience recurrence and succumb to the disease (3-5). Most cases of

^ ORCID: 0000-0002-6116-6376.

postoperative recurrent NSCLC involve distant metastases, with or without locoregional recurrence. These patients often undergo systemic therapies. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) TKIs have improved the prognosis of postoperative recurrent NSCLC with EGFR mutations and ALK rearrangement (6-8). In contrast, patients with postoperative recurrent NSCLC without EGFR mutations or ALK rearrangements traditionally received chemotherapy until the emergence of immune checkpoint inhibitors (ICIs). Several clinical trials have shown favorable prognoses with ICIs in advanced NSCLC without major driver mutations (9-11). However, there is limited real-world data on postoperative recurrent NSCLC treated with ICIs (12). The role of programmed cell death ligand 1 (PD-L1) in postoperative recurrent NSCLC remains unclear.

Therefore, this study aimed to identify factors associated with post-recurrence survival (PRS), including ICI use, and to analyze the role of PD-L1 expression in postoperative recurrent NSCLC without EGFR mutations or ALK rearrangements. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-237/rc).

Highlight box

Key findings

- Immune checkpoint inhibitors (ICI) use at any treatment line improved the post-recurrence survival (PRS) of non-small cell lung cancer (NSCLC) patients without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

What is known and what is new?

- Several clinical trials have shown progression-free and overall survival benefits of ICIs in advanced NSCLC without major driver mutations.
- This study revealed use of ICIs at any treatment line improved PRS of postoperative recurrent NSCLC patients without major driver mutations. Furthermore, despite subgroup analysis involving patients who received ICIs during their clinical course, the response rate to first-line treatment and PRS in patients with programmed death ligand 1 (PD-L1) positive expression were not superior to those in patients with PD-L1-negative expression.

What is the implication, and what should change now?

- ICI use in clinical course is recommended even in postoperative recurrent NSCLC patients without EGFR mutations or ALK rearrangements. This might be valid regardless of PD-L1 expression.

Methods

Study population

We used a retrospective cohort study design. This study considered 2,159 consecutive patients with NSCLC who underwent complete anatomical resection of primary lung cancer at the Tokyo Medical University Hospital between January 2012 and December 2021. Complete anatomical resection was defined as a lobectomy or greater resection with hilar and mediastinal lymphadenectomy, leading to gross and histological cancer-free surgical margins. Among them, 418 experienced postoperative recurrence during the follow-up period. Patients with EGFR mutations (n=125) and ALK rearrangements (n=21) were excluded from the study. Patients whose clinical course after postoperative recurrence was unknown were also excluded (n=17). The remaining 255 patients with postoperative recurrent NSCLC were included in this study. We reviewed the medical records to collect clinicopathological information including the following factors: age at recurrence, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, pathological stage, tissue type with or without adjuvant chemotherapy, recurrence type, and treatment at recurrence and determine the factors associated with PRS. Survival information was collected from the medical records at our hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Tokyo Medical University Review Board approved the protocols for data collection and analyses (T2023-0047), and individual consent for this retrospective analysis was waived.

Patient follow-up

The patients were postoperatively followed up at every 3–6-months for the first 2 years, 6–12-month intervals for the next 3 years, and 1-year intervals thereafter with evaluations, including a physical examination, chest radiography, blood examination, and computed tomography (CT) scans of the chest and abdomen. Further evaluations were performed whenever any symptoms or signs of recurrence were detected, including brain magnetic resonance imaging and bone scintigraphy. Positron emission tomography/CT was implemented when considered appropriate. Recurrence was diagnosed according to the physical examination and radiological imaging results. Recurrence was confirmed through histological and cytological means, including transbronchial lung biopsy of

a new lung lesion or endobronchial ultrasonography-guided transbronchial needle aspiration of enlarged mediastinal lymph nodes. The date of recurrence was defined as when histologically confirmed or identified according to clinicoradiological findings by a physician.

Pathological examinations

After fixing the specimens with formalin and embedding them in paraffin, serial 4-µm sections were stained with hematoxylin and eosin. Histological identification of tissues were determined based on the World Health Organization classification (13). TNM classification was referred to the Union for International Cancer Control and American Joint Committee on Cancer staging system (8th edition) (14). DNA was extracted from the specimens formalin-fixed and paraffin-embedded. EGFR gene mutations were evaluated using the Cobas® EGFR mutation test v2, cycleave/fragment method, or loop-hybrid mobility shift assay (15). ALK rearrangement was evaluated using a highly sensitive immunohistochemical (IHC) method or fluorescent *in situ* hybridization. IHC for PD-L1 was performed using a Dako PharmDx 22C3 IHC assay (Dako North America Inc., Carpinteria, CA, USA) or a VENTANA SP142 PD-L1 IHC assay (Ventana Medical Systems Inc., Oro Valley, USA) (22C3, n=116; SP142, n=1).

Statistical analysis

Categorical variables were compared using the chi-square test. PRS was measured from the date of recurrence to the one of death from any cause or the last follow-up visit. PRS curves were plotted using the Kaplan-Meier method, and differences in PRS rates were determined using the log-rank test. Patients were terminated at the date of last follow-up visit if they were alive or untraceable. A Cox proportional hazards regression model calculated hazard ratio (HR) and 95% confidence interval (CI), and was used for univariable and multivariable analyses, including the following factors: age at recurrence, sex, smoking history, ECOG performance status, pathological stage, tissue type with or without adjuvant chemotherapy, recurrence type, and treatment at recurrence. The study size except for 15 patients who underwent local treatment (n=240) was 10 times larger than the independent variables for multivariable analyses. All tests were two-sided, and P values <0.05 were considered to indicate a statistically significant difference. SPSS statistical software (version 28.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

This study included 255 patients with postoperative recurrent NSCLC without EGFR mutations or ALK rearrangements. *Table 1* shows patient clinicopathological characteristics. The median time to recurrence after surgery was 11.9 months. There were 196 male and 59 female patients with a median age at recurrence of 71 years. The pathological stages (number of patients) at the initial surgery were as follows: stage IA (n=29), stage IB (n=41), stage IIA (n=9), stage IIB (n=70), stage IIIA (n=82), and stage IIIB (n=24). Histologically, adenocarcinoma (54.1%) was more prevalent than squamous cell carcinoma (25.5%). The initial treatment for postoperative recurrence involved local treatment, systemic therapy, and best supportive care for 15, 170, and 70 patients, respectively. Seventy-nine patients received ICIs during their clinical course. Multivariable analysis revealed that squamous cell carcinoma (HR, 2.165; 95% CI, 1.494–3.138; P<0.001), pathological stage III (HR, 1.697; 95% CI, 1.209–2.381; P=0.002), and ECOG performance status ≥2 (HR, 3.925; 95% CI, 2.523–6.107; P<0.001) were significantly associated with worse PRS. Conversely, ICI use at first line (HR, 0.586; 95% CI, 0.371–0.924; P=0.02) was associated with improved PRS (*Table 2*).

Table 3 presents a comparison between systemic therapy with and without ICIs during the clinical course based on clinicopathological features. No significant differences were observed in age at recurrence, sex, smoking history, use of adjuvant chemotherapy, tissue type, or pathological stage at the initial surgery. Among patients receiving systemic therapy with ICIs, 54 and 25 underwent ICIs during the first line and subsequent treatments, respectively, and 86% (n=68) of those examined had PD-L1 expression at the initial surgery. Specifically, 52 patients had positive PD-L1 expression, and 16 had negative PD-L1 expression. Details of the ICI regimens are shown in Table S1.

Figure 1 illustrates PRS curves using the Kaplan-Meier method stratified by ICI use for systemic therapy. The 3-year PRS rate of patients who received systemic therapy with ICIs during the first-line therapy was 43.5%. The log-rank test demonstrated a significant difference in PRS between patients with and without ICIs during the first-line treatment (P=0.027, *Figure 1A*). The 3-year survival rate after the second-line treatment was 29.8% among those who received subsequent systemic therapy with ICIs. The log-rank test showed a significant difference in survival after

Table 1 Patients characteristics

Variable	Values (N=255)
Age at recurrence (years old)	71 [40–88]
Male	196 (76.9)
Smoking history	224 (87.8)
Neoadjuvant chemotherapy	15 (5.9)
Initial surgical procedure	
Lobectomy	243 (95.3)
Bilobectomy	6 (2.4)
Pneumonectomy	6 (2.4)
Histological type	
Adenocarcinoma	138 (54.1)
Squamous cell carcinoma	65 (25.5)
Others	52 (20.4)
Pathological stage at initial surgery	
Stage I–II	151 (59.2)
Stage III	104 (40.8)
Adjuvant chemotherapy	155 (60.8)
Type of recurrence	
Locoregional recurrence only	89 (34.9)
Distant recurrence only	117 (45.9)
Locoregional and distant recurrence	49 (19.2)
ECOG performance status at recurrence	
0–1	216 (84.7)
2–4	49 (15.3)
Initial treatment at recurrence	
Local treatment	15 (5.9)
Surgery	3 (1.2)
Radiotherapy	5 (2.0)
Chemoradiotherapy	7 (2.7)
Systemic therapy	170 (66.7)
Chemotherapy	116 (45.5)
Immunochemotherapy	30 (11.8)
Immunotherapy	24 (9.4)
Best supportive care	70 (27.5)
Use of immunotherapy in clinical course	79 (31.0)

Data are presented as median [range] or number (%). ECOG, Eastern Cooperative Oncology Group.

the second-line therapy between patients with and without ICIs (P=0.006, *Figure 1B*). *Figure 2* presents the PRS curves according to histological type (squamous and non-squamous cell carcinoma). There was a significant difference in PRS between patients with squamous cell carcinoma treated with ICIs and those treated with chemotherapy alone (P=0.04, *Figure 2A*). Similarly, a significant difference was found in PRS between patients with non-squamous cell carcinoma treated with ICIs and those treated with chemotherapy alone (P=0.008, *Figure 2B*).

Among the ICI group (n=79) during the clinical course, the response rates during the first-line therapy among patients with PD-L1 expression ≥50%, 1–49% and <1% were 41.7%, 38.8% and 33.3%, respectively. The 3-year PRS rates for those with PD-L1 expression ≥50%, 1–49% and <1% were 48.7%, 47.9% and 42.1%, respectively (*Table 4*). There was no statistically significant difference in the response rates at first-line treatment and PRS between patients with any PD-L1 expressions.

Discussion

This study revealed the clinical significance of ICI use in patients with postoperative recurrent NSCLC without major driver mutations in a real-world setting. ICIs at any line of systemic therapy were independently associated with favorable PRS, whereas PD-L1 expression at the initial surgery did not affect the PRS or the response rate at the first-line therapy in those with postoperative recurrent NSCLC who received ICIs in the present study.

Most cases involving postoperative recurrent NSCLC manifest as distant metastases, often accompanied by locoregional recurrence. Chemotherapy regimens, such as platinum doublets, were practically administered as the first-line therapy for diseases without EGFR mutations or ALK rearrangements based on evidence for unresectable advanced NSCLC. However, the median PRS was poor and ranged from 8.1–17.7 months (3,16) until the emergence of ICIs. In the last decade, ICIs, including PD-1 and PD-L1 inhibitors, have revolutionized the NSCLC treatment landscape (17). Several clinical trials have shown progression-free and overall survival benefits of ICIs in advanced NSCLC without major driver mutations (18,19). In Japan, nivolumab first received approval for advanced NSCLC as an ICI for treatment beyond the second line in 2015 based on the results of the Checkmate 017 and 057 trials (20,21). Pembrolizumab was first approved in 2016 as monotherapy in the first-line treatment setting for

Table 2 Univariable and multivariable analysis of post-recurrence survival for patients with non-small cell lung cancer without EGFR mutations or ALK rearrangements except for patients receiving local treatment (N=240)

Variable	Univariable			Multivariable		
	Hazard ratio	95% confidence interval	P value	Hazard ratio	95% confidence interval	P value
Age at recurrence (≥75 years old)	1.583	1.110–2.258	0.01	1.317	0.908–1.911	0.15
Sex (male)	1.185	0.798–1.760	0.40			
Smoking history (ever)	1.551	0.922–2.610	0.10			
Neoadjuvant chemotherapy (yes)	0.861	0.434–1.710	0.67			
Initial surgical procedure (bilobectomy or pneumonectomy)	1.195	0.584–2.447	0.63			
Adjuvant chemotherapy (yes)	0.639	0.451–0.906	0.01	0.781	0.536–1.136	0.20
Histological type (squamous)	2.092	1.460–2.997	<0.001	2.165	1.494–3.138	<0.001
Pathological stage at initial surgery (stage IIII)	1.660	1.201–2.295	0.002	1.697	1.209–2.381	0.002
Distant recurrence (yes)	1.281	0.907–1.810	0.16			
ECOG performance status (≥2)	5.216	3.444–7.900	<0.001	3.925	2.523–6.107	<0.001
ICI use at first line (yes)	0.527	0.340–0.816	0.004	0.586	0.371–0.924	0.02

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor.

advanced NSCLC with high PD-L1 positive expression (≥50%) using 22C3 assays based on the results of the KEYNOTE-024 trial (9). According to the results of the OAK trial, atezolizumab, the third ICI to be approved in Japan, received its approval in 2017 for advanced NSCLC, regardless of PD-L1 expression, following second-line treatment (22). Combination immunotherapy in the first-line setting also received approval in 2018 based on the results of randomized clinical trials (18,23,24). Our hospital first used ICIs with nivolumab for postoperative recurrent NSCLC in May 2016. One hundred fourteen patients of those who underwent systemic therapy has started after ICIs became an additional indication, and there was no significant difference in PRS of the periods between before and after ICIs became available (P=0.30; data not shown). Patients except for 79 patients who received ICIs in clinical course were unable to receive ICIs after ICIs approval, mainly due to interstitial pneumonia or decreased PS.

Although there have been several large-scale randomized clinical trials on ICIs for unresectable advanced NSCLC, there is a paucity of reports concerning postoperative recurrent NSCLC treated with ICIs in real-world settings. Yuasa *et al.* reported that the median OS of postoperative NSCLC patients receiving ICIs as first line treatment was 25.0 months, compared with 22.8 months in this study, and these results were similar (25). Hashimoto *et al.* reported that, in their hospital, survival after postoperative recurrent NSCLC has significantly improved since 2010. Their multivariable analysis indicated that increased ICI use in patients without driver mutations may have contributed to this improvement (12). In the present study, patients with recurrent NSCLC treated with ICIs during the clinical course had better PRS than those treated with chemotherapy alone, regardless of ICI use as first-line or subsequent treatments. However, no significant difference was observed in the clinicopathological features between patients treated with ICIs and those treated with chemotherapy alone. Furthermore, these trends were also observed in patients with squamous and non-squamous cell carcinoma (*Figure 2*). Consequently, we recommend that patients with NSCLC experiencing postoperative recurrence without major driver mutations, as well as those with unresectable advanced NSCLC, be considered for ICI treatment at any stage of their therapy.

PD-L1 expression serves as a crucial predictor of the efficacy of anti-PD-L1 therapy in patients with NSCLC. Reck *et al.* reported that pembrolizumab was associated with significantly longer progression-free and overall

Table 3 Comparison of clinicopathological features between patients with ICIs and without ICIs in postoperative recurrent non-small cell lung cancer without EGFR mutations or ALK rearrangements

Variable	Systemic therapy in clinical course		P value
	Without ICIs (N=93)	With ICIs (N=79)	
Age at recurrence (years old)	70 [40–84]	70 [47–83]	0.74
Male	77 (82.8)	59 (74.7)	0.19
Smoking history	83 (89.2)	65 (82.3)	0.19
Neoadjuvant chemotherapy	7 (7.5)	4 (5.1)	0.51
Lobectomy	86 (92.5)	74 (93.7)	0.76
Squamous cell carcinoma	21 (22.6)	17 (21.5)	0.87
Pathological stage at initial surgery			0.98
Stage I–II	54 (58.1)	46 (58.2)	
Stage III	39 (41.9)	33 (41.8)	
Adjuvant chemotherapy	63 (67.7)	47 (59.5)	0.26
Type of recurrence			
Locoregional recurrence only	27 (29.0)	31 (39.2)	0.16
Distant recurrence only	46 (49.5)	30 (38.0)	0.13
Locoregional and distant recurrence	20 (21.5)	18 (22.8)	0.84
ECOG performance status at recurrence			0.87
0–1	89 (95.7)	76 (96.2)	
≥2	4 (4.3)	3 (3.8)	
PD-L1 expression			<0.001
Positive	10 (10.8)	52 (65.8)	
Negative	15 (16.1)	16 (20.3)	
Unknown	68 (73.1)	11 (13.9)	
Use of ICI			–
First line	–	54 (68.4)	
≥ second line	–	25 (31.6)	

Data are presented as median [range] or number (%). EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoid kinase; ICI, immune checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.

survivals than platinum-based chemotherapy in patients with advanced NSCLC whose tumor cells exhibited PD-L1 expression in at least 50% of cases (9). Conversely, Xu *et al.* reported that combining chemotherapy and immunotherapy significantly improved survival, regardless of PD-L1 expression levels, when used as the first-line treatment for NSCLC (26). PD-L1 expression in surgically resected samples has recently been reported as a biomarker in patients with NSCLC. Sun *et al.* reported that the overall survival was significantly shorter in the PD-L1-positive group than in the PD-L1-negative group in 1,070 patients with NSCLC post-surgery, using PD-L1 expression in surgically resected specimens (27). Kojima reported that the recurrence-free survival was significantly shorter in the PD-L1-positive group than in the PD-L1-negative group in 280 patients with NSCLC post-surgery (28). Conversely, Sun *et al.* reported that the association between PD-L1 expression and overall survival or progression-free survival was not statistically

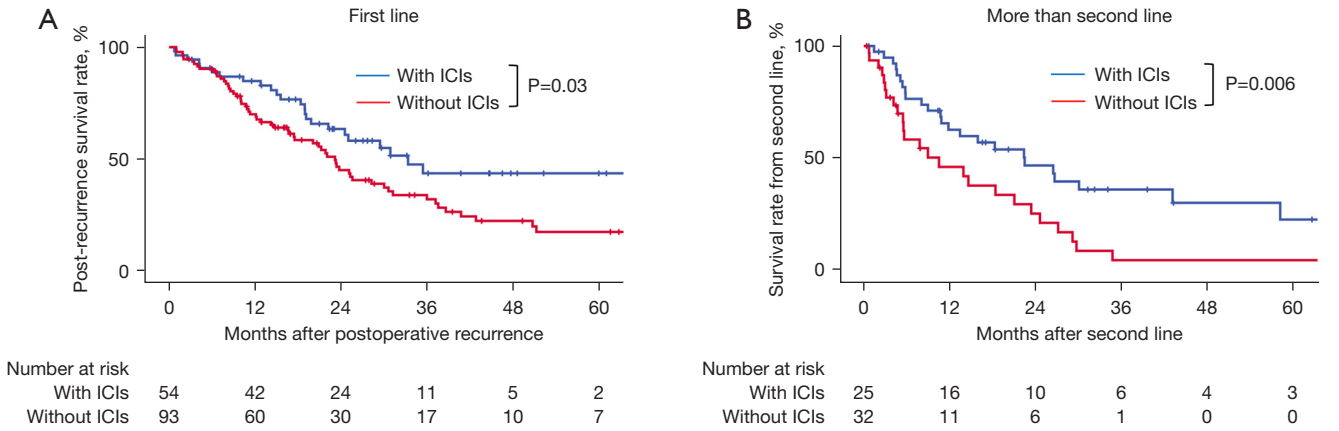

Figure 1 PRS and survival from second line curves of patients with non-small cell lung cancer without epidermal growth factor receptor mutations or anaplastic lymphoid kinase rearrangements according to systemic therapy with or without ICIs. (A) There was a significant difference PRS between systemic therapy with ICIs and chemotherapy alone at first line (P=0.027). (B) There was a significant difference survival from second line between systemic therapy with ICIs and chemotherapy alone at more than second line (P=0.006). PRS, post-recurrence survival; ICIs, immune checkpoint inhibitors.

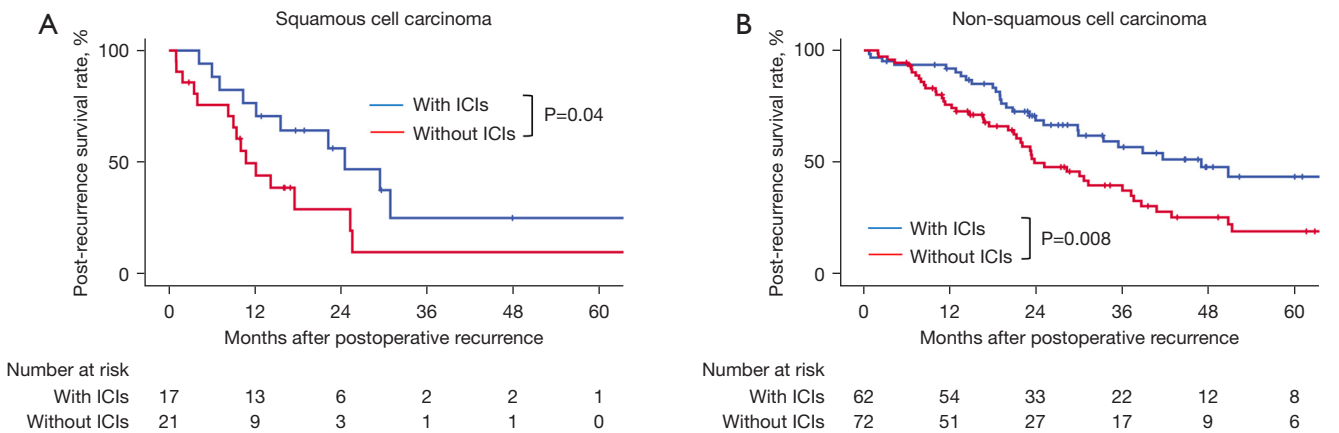

Figure 2 PRS curves of patients with non-small cell lung cancer without epidermal growth factor receptor mutations or anaplastic lymphoid kinase rearrangements according to histological types. (A) There was a significant difference PRS between systemic therapy with ICIs and chemotherapy alone in squamous cell carcinoma (P=0.039). (B) There was a significant difference PRS between systemic therapy with ICIs and chemotherapy alone in non-squamous cell carcinoma (P=0.008). PRS, post-recurrence survival; ICIs, immune checkpoint inhibitors.

Table 4 Comparison of response ratio and postoperative recurrence between patients examined PD-L1 expression in postoperative recurrent non-small cell lung cancer using ICIs

PD-L1	Use of ICIs in clinical course (N=79)			P value		
	≥50% (N=26)	1–49% (N=26)	<1% (N=16)	≥50% *vs.* <1%	≥50% *vs.* 1–49%	1–49% *vs.* <1%
1st line RR	41.7%	38.8%	33.3%	0.663	0.856	0.778
3-year PRS	48.7%	47.9%	42.1%	0.885	0.834	0.971

PD-L1, programmed cell death ligand 1; ICI, immune checkpoint inhibitor; RR, response rate; PRS, post-recurrence survival.

significant after adjusting for postoperative chemotherapy and radiotherapy. They suggested that the therapeutic impact of such interventions may outweigh the prognostic effect of PD-L1 expression (27). This study found that despite subgroup analysis involving patients who received ICIs during their clinical course, the response rate to first-line treatment and PRS in patients with PD-L1-positive expression were not superior to those in patients with PD-L1-negative expression. This outcome may have been affected by adjuvant therapy, as 59.5% of patients in the ICI group received such therapy. Shima *et al.* reported that PD-L1 expression was significantly increased in rebiopsy specimens compared with archived surgical specimens in postoperative recurrent NSCLC (29). They concluded that the archived surgical specimens were inadequate for assessing the predictive ability of PD-L1 for nivolumab response, whereas PD-L1 expression in recurrent sites could be an accurate indicator of nivolumab response. In our study, out of the 68 cases with known PD-L1 expression in patients who received ICIs during their clinical course, 64 were based on surgically resected specimens, with only four originating from rebiopsies. This discrepancy could be a contributing factor explaining the lack of significant differences in the response rate and PRS between those with PD-L1-positive and negative expressions in the ICI group. As previously discussed, evaluating the efficacy of ICIs in postoperative recurrent NSCLC may require a focus on PD-L1 expression in rebiopsy specimens, rather than surgical specimens, for more accurate results.

This study had some limitations. First, this was a single-institution, retrospective study, which may have had a patient selection bias. In addition, all patients in this study were Japanese. Therefore, multi-institutional and multinational studies are warranted. Second, this study included patients with other driver mutations, such as ROS-1 or BRAF gene translocations, for which targeted therapy is effective, although patients with EGFR mutations or ALK rearrangements were excluded. Third, we evaluated the role of PD-L1 expression alone in the ICI group because of the large amount of missing data on PD-L1 expression in the chemotherapy-alone group. Therefore, this was supposed to be a statistical analysis of the role of PD-L1 expression in a small number of patients.

Conclusions

In conclusion, this study demonstrated that using ICIs at any stage of the clinical course was independently associated with a favorable PRS in patients experiencing postoperative recurrent NSCLC without major driver mutations in a real-world setting. Using ICIs in clinical course is recommended even in these postoperative recurrent NSCLC patients.

Acknowledgments

The authors are indebted to the medical editors from Editage for editing of the English manuscript. We also thank Mami Murakami for assistance with the statistical analyses in this study.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-237/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-237/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-237/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-237/coif). N.I. reports the relationship with AstraZeneca, Chugai pharma, Pfeizer, Taiho pharma, MSD, Boehringer Ingelheim, Eli Lilly, Ono pharma, Teiji n, Nihon Mediphysics, Fuji film, Johnson & Johnson, Bristol-Meyers, Olympus, Medtronics that includes: speaking and lecture fees. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Tokyo Medical University Review Board (T2023-0047), and individual consent for this retrospective analysis was waived.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Houston KA, Mitchell KA, King J, et al. Histologic Lung Cancer Incidence Rates and Trends Vary by Race/Ethnicity and Residential County. J Thorac Oncol 2018;13:497-509.
3. Sugimura H, Nichols FC, Yang P, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg 2007;83:409-17; discussioin 417-8.
4. Hoffman PC, Mauer AM, Vokes EE. Lung cancer. Lancet 2000;355:479-85.
5. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242-9.
6. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
7. Isaka T, Ito H, Yokose T, et al. Prognostic factors for relapse-free survival in stage IB-IIIA primary lung adenocarcinoma by epidermal growth factor receptor mutation status. BMC Cancer 2022;22:966.
8. Matsuura Y, Ninomiya H, Ichinose J, et al. Prognostic impact and distinctive characteristics of surgically resected anaplastic lymphoma kinase-rearranged lung adenocarcinoma. J Thorac Cardiovasc Surg 2022;163:441-451.e1.
9. 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;375:1823-33.
10. 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;383:1328-39.
11. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.
12. Hashimoto K, Ariyasu R, Ichinose J, et al. Advances in the treatment of postoperative recurrence of non-small cell lung cancer and their impact on survival in Asian patients. J Thorac Cardiovasc Surg 2023;165:1565-1574.e1.
13. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
14. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
15. Matsukuma S, Yoshihara M, Kasai F, et al. Rapid and simple detection of hot spot point mutations of epidermal growth factor receptor, BRAF, and NRAS in cancers using the loop-hybrid mobility shift assay. J Mol Diagn 2006;8:504-12.
16. Ichinose Y, Yano T, Yokoyama H, et al. Postrecurrent survival of patients with non-small-cell lung cancer undergoing a complete resection. J Thorac Cardiovasc Surg 1994;108:158-61.
17. Arbour KC, Riely GJ. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA 2019;322:764-74.
18. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
19. Socinski MA, Nishio M, Jotte RM, et al. IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC. J Thorac Oncol 2021;16:1909-24.
20. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
21. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
22. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
23. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
24. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
25. Yuasa I, Hamaji M, Ozasa H, et al. Outcomes of immune checkpoint inhibitors for postoperative recurrence of

non-small cell lung cancer. Gen Thorac Cardiovasc Surg 2023;71:534-41.
26. Xu Y, Wan B, Chen X, et al. The association of PD-L1 expression with the efficacy of anti-PD-1/PD-L1 immunotherapy and survival of non-small cell lung cancer patients: a meta-analysis of randomized controlled trials. Transl Lung Cancer Res 2019;8:413-28.
27. Sun JM, Zhou W, Choi YL, et al. Prognostic Significance of PD-L1 in Patients with Non-Small Cell Lung Cancer: A Large Cohort Study of Surgically Resected Cases. J Thorac Oncol 2016;11:1003-11.
28. Kojima K, Sakamoto T, Kasai T, et al. PD-L1 expression as a predictor of postoperative recurrence and the association between the PD-L1 expression and EGFR mutations in NSCLC. Sci Rep 2021;11:17522.
29. Shima Y, Sato Y, Morimoto T, et al. Predictive performance of PD-L1 tumor proportion score for nivolumab response evaluated using archived specimens in patients with non-small cell lung cancer experiencing a postoperative recurrence. Invest New Drugs 2023;41:35-43.

Cite this article as: Shigefuku S, Takahashi S, Hagiwara M, Kakihana M, Ohira T, Ikeda N. Prognostic significance of immunotherapy in postoperative recurrent non-small cell lung cancer without EGFR mutations or ALK rearrangements. J Thorac Dis 2024;16(6):3583-3592. doi: 10.21037/jtd-24-237

Supplementary

Table S1 ICIs regimen of postoperative recurrent non-small cell lung cancer without EGFR mutations or ALK rearrangements

Variable	ICI use in clinical course (N=79), n [%]	
	1st line (N=54)	2nd line or later (N=25)
Combination with cytotoxic chemotherapy		
Yes	29 [54]	0
No	25 [46]	25 [100]
ICIs regimen		
Pembrolizumab	45 [83]	7 [28]
Atezolizumab	7 [13]	7 [28]
Nivolumab	1 [2]	11 [44]
Ipilimumab	1 [2]	0

ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoid kinase.

https://dx.doi.org/10.21037/jtd-24-237