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Activity of Nivolumab and Utility of Neutrophil-to-Lymphocyte Ratio as a Predictive Biomarker for Advanced Non–Small-Cell Lung Cancer: A Prospective Observational Study

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Abstract

Immune checkpoint inhibitor has greatly altered the standard of care for patients with advanced non–small-cell lung cancer (NSCLC). This prospective study reported the benefits of nivolumab in a routine clinical practice. Furthermore, neutrophil-to-lymphocyte ratio was identified as a candidate of predictive markers in nivolumab-treated NSCLC patients.

Background: The immune checkpoint inhibitor nivolumab is entering routine oncologic practice. We investigated the safety and efficacy of nivolumab in the real world and alternative predictive factors for survival in patients with advanced non–small-cell lung cancer (NSCLC). **Patients and Methods:** We performed a prospective observational study to evaluate the activity of nivolumab treatment for chemotherapy-refractory NSCLC. Patients were treated with nivolumab once every 2 weeks, and the efficacy was assessed every 8 ± 2 weeks. **Results:** Fifty-two patients were enrolled after nivolumab approval in Japan. These patients received a median of 4 (range, 1-43) cycles of nivolumab. Overall objective response was observed in 12 patients (23.1%). Median progression-free survival was 2.1 (95% confidence interval, 1.0-3.2) months, and 1-year overall survival rate was 59.9%. A total of 23 immune-related adverse events occurred in 20 patients, as follows: 7 cases of pneumonitis, 6 of oral mucositis, 5 of hypothyroidism, 2 of colitis, 2 of liver dysfunction, and 1 of arthritis. All patients recovered after appropriate management. A pretreatment neutrophil-to-lymphocyte ratio (NLR) of ≥ 5 was significantly associated with poor prognosis compared to NLR < 5 (hazard ratio, 4.52; 95% confidence interval, 1.84-11.14; $P = .013$), independently. **Conclusion:** Nivolumab showed promising activity with a manageable safety profile in clinical practice, consistent with effects of previous clinical trials. This drug could affect a specific population of patients with advanced NSCLC, and pretreatment NLR was a candidate for surrogate markers for survival benefit of patients with NSCLC treated with nivolumab.

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Introduction

Checkpoint immunotherapy, which targets regulatory pathways in T cells to enhance antitumor responses,[1,2] has demonstrated high activity in many types of cancer.[3,4] In advanced non–small-cell lung cancer (NSCLC), immune checkpoint blockades targeting programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1)

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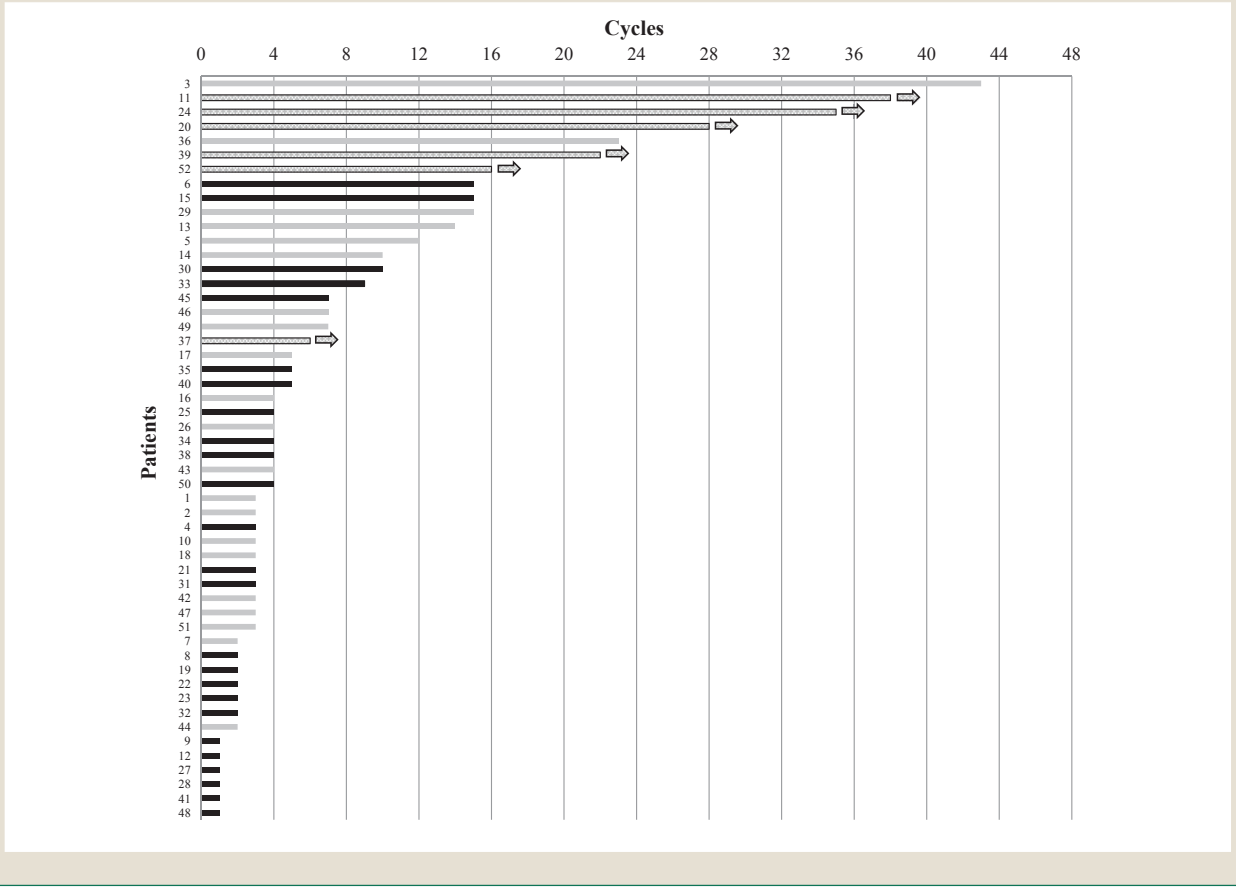
Figure 1 Cycles of Nivolumab Treatment in 52 Patients With Previously Treated NSCLC. Each Bar Represents Individual Patient With NSCLC Treated With Nivolumab. Black Bar, Deceased Patients; Gray Bar, Patients With Disease Progression After Nivolumab Treatment; Gray Dotted Bar With Arrow, Patients Who Continued to Nivolumab Treatment. Median of 4 (Range, 1-43) Cycles of Therapy Was Provided. Median Follow-up Was 10.9 (Interquartile Range, 5.6-16.4) Months



Abbreviation: NSCLC = non–small-cell lung cancer.

showed durable clinical benefit and long-term remissions in some patients; they also have been shown to have fewer toxicities compared to cytotoxic chemotherapy.[5-9] The use of immune checkpoint inhibitors has greatly altered the standard of care for patients with advanced NSCLC and an adequate performance status.

After randomized phase 3 trials were performed in patients with advanced NSCLC,[5,6] nivolumab was approved as second or subsequent line of therapy in Japan in December 2015 and became a powerful treatment option in clinical practice. The PD-1 inhibitor produced durable response in the disease of approximately 20% of patients, although the disease of 30% to 40% had no response.[5,6,10] Therefore, patient selection may be needed to improve survival considering the limited response, immune-related adverse events (irAEs), and cost.[11,12] PD-L1 expression in tumor has been associated with higher response to and longer survival rates with PD-1/PD-L1 blockades, although high efficacy also has been observed in PD-L1–negative patients.[5-8,13] Despite the activity of checkpoint immunotherapy in patients with NSCLC, it is needed urgently to find an effective prediction model for survival benefits.

We performed a prospective observational study to evaluate the activity of nivolumab in a routine oncologic practice. We also investigated alternative predictive factors for survival in patients with chemotherapy-refractory NSCLC.

Patients and Methods

Study Patients

A prospective observational study was performed to evaluate the activity of nivolumab treatment at Kitasato University Hospital after nivolumab approval in Japan. Eligible patients had NSCLC refractory to prior systemic chemotherapy and planned to undergo nivolumab administration in clinical practice. After obtaining written consent, the patients were treated with 3 mg/kg nivolumab administrated intravenously once every 2 weeks until disease progression or unacceptable adverse events (AEs).

Clinical Data Collection

Lung cancer clinical stages were determined according to the 7th edition of the tumor, node, metastasis classification system of malignant tumors.[14] Patients' physical conditions, symptoms based on

Table 1 Characteristics of 52 Patients

Characteristic	n (%)
Age	
<75	41 (79)
≥75	11 (21)
Sex	
Male	37 (71)
Female	15 (29)
ECOG Performance Status	
0	19 (37)
1	30 (58)
2	2 (4)
3	1 (2)
Smoking History	
Never	10 (19)
Former	32 (62)
Current	10 (19)
Clinical Stage	
IIIa	5 (10)
IIIb	8 (15)
IVa	12 (23)
IVb	17 (33)
Rec	10 (19)
Histology	
Ad	33 (63)
Sq	16 (31)
NOS	3 (6)
Targetable Driver Mutations	
EGFR	6 (12)
ALK	1 (2)
No. of Prior Systemic Therapy	
1	22 (42)
2	15 (29)
3	10 (19)
4	5 (10)
Site of Metastatic Disease	
Brain	8 (15)
Lung	22 (42)
Liver	10 (19)
Bone	16 (31)

Abbreviations: Ad = adenocarcinoma; ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NOS = not otherwise specified; Rec = recurrence after surgical resection or thoracic radiotherapy; Sq = squamous-cell carcinoma.

our interview sheet, blood and urine tests, and chest X-rays were evaluated every 2 weeks throughout nivolumab treatment. Drug efficacy was assessed every 8 ± 2 weeks after initiation of nivolumab. AEs also were monitored and graded on the basis of chart review according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Survival was defined as the time from the start of nivolumab treatment until each event.

Statistical Analyses

All survival analyses were performed by the Kaplan-Meier method. Survival between the subgroups based on predictive factors was compared by a log-rank test. To identify predictive factors, a Cox proportional hazards model was used for univariate and multivariate analyses. All analyses were performed by SPSS software, version 11.0.1, (IBM SPSS, Chicago, IL).

This study was approved by the Kitasato University Medical Ethics Organization (B15-173) and was registered with University Hospital Medical Information Network Clinical Trials Registry (UMIN000021600).

Results

Efficacy of Nivolumab Treatment in Clinical Practice

Between March 2016 and April 2017, we recruited consecutive 55 patients with advanced and refractory NSCLC and received consent from 52 patients prospectively. These patients received a median of 4 (range, 1-43) cycles of nivolumab, and 6 patients continued nivolumab treatment. A total of 23 patients had disease progression, and 20 had died at the cutoff date, December 2017 (Figure 1). Patient characteristics are listed in Table 1. Median age was 69 (range, 46-83) years. Objective response was observed in 10 (19%) of the 52 patients at first evaluation using computed tomography (CT) scan, which was performed at a median of 7.5 (range, 2.7-16.9) weeks. Disease control at first CT evaluation and 12-week progression-free survival (PFS) were associated with better OS after nivolumab initiation (data not shown), although median follow-up was 10.9 (interquartile range, 5.6-16.4) months. Overall objective response was observed in 12 patients (23.1%; 95% confidence interval [CI], 17.2-28.9), and 23 (44.2%; 95% CI, 37.3-51.1) experienced disease control (Table 2). Disease progressed in 23 patients (44%), and 6 (12%) were not evaluated at first CT evaluation. Median PFS was 2.1 (95% CI, 1.0-3.2) months, and the 1-year overall survival (OS) rate was 59.9% (95% CI, 52.2-67.6).

Adverse Events

AEs in 52 nivolumab-treated patients are shown in Supplemental Tables 1 and 2 in the online version, including 13 patients (25%) who had grade 3/4 AEs. irAEs were observed in 20 patients with 23 irAEs of any grade (and 5 irAEs of grade 3/4) based on CTCAE version 4.0: 7 (1 irAE of grade 3/4) cases of pneumonitis, 6 (2) of mucositis oral, 5 (0) of hypothyroidism, 2 (1) of colitis, 2 (1) of liver dysfunction, and 1 (0) of arthritis in the 20 patients (Table 3). All patients recovered after appropriate management. Of the 14 patients who had grade 2 or higher irAEs, 11 discontinued nivolumab treatment, and in 3, nivolumab was readministered after recovery from toxicities.

Predictive Biomarker Analyses

PD-L1 (22C3) expression was analyzed in 46 of 52 patients, although 6 patients were excluded (2 had cytology only and 4 had insufficient samples). PD-L1 expression was not associated with OS in patients with NSCLC treated with nivolumab (Table 3). Next, we calculated pretreatment neutrophil-to-lymphocyte ratio (NLR) as a candidate predictive biomarker for survival benefit of nivolumab treatments (Supplemental Figure 1 in the online version). A total of 18

Table 2 Efficacy and Immune-Related Adverse Events of Nivolumab Treatment in 52 Subjects

Characteristic	n	%
Response, Overall (at First Evaluation)		
Complete response	0 (0)	0 (0)
Partial response	12 (10)	23 (19)
Stable disease	11 (13)	21 (25)
Progressive disease	23 (23)	44 (44)
Not evaluated	6 (6)	12 (6)
irAEs, Any Grade (Grade 3/4)	23 (5)	44 (10)
Pneumonitis	7 (1)	13 (2)
Mucositis oral	6 (2)	12 (4)
Hypothyroidisms	5 (0)	10
Colitis	2 (1)	4 (2)
Liver dysfunctions	2 (1)	4 (2)
Arthritis	1 (0)	2 (0)

Abbreviations: irAE = immune-related adverse event; CI = confidence interval; OS = overall survival; PFS = progression-free survival.

NSCLC patients (35%) had pretreatment NLR $\geq$ 5. PFS was significantly shorter in NSCLC patients with NLR $\geq$ 5 compared to those with NLR < 5 (3.3 [95% CI, 0.9-5.7] months for NLR < 5 vs. 1.7 [95% CI, 1.3-2.1] months for NLR $\geq$ 5; P = .014; Figure 2A). OS also was significantly worse in NSCLC patients with NLR $\geq$ 5 (median not reached for NLR < 5 vs. 4.2 [95% CI, 3.4-5.0] months for NLR $\geq$ 5, P = .0003; Figure 2B). Furthermore, the interaction of pretreatment NLR for OS was significant after adjustments for performance status, presence of bone metastases, and PD-L1 expression $\geq$ 50% using the multiple Cox proportional hazard model analysis (hazard ratio, 4.17; 95% CI, 1.35-12.92; P = .013; Table 3). Interestingly, patients with high expression of PD-L1 who experienced disease progression earlier had NLR $\geq$ 5 before nivolumab treatment (Figure 3 and Supplemental Figure 2 in the online version).

Discussion

Immune checkpoint blockade has become a pillar of cancer treatment and has greatly changed clinical practice because of its high therapeutic effects, especially data on long-term survival in some patients,[10] and tolerable AEs. In clinical trials,[5-7,9] the response rate of immune checkpoint blocking antibodies in second-line treatment for NSCLC patients was 18% to 20%, and median PFS was 2 to 4 months. In our study, overall response rate, disease control rate, and median PFS were 23%, 44%, and 2.1 months, respectively. It is of note that disease control at first CT evaluation, which was performed at approximately 2 months after nivolumab initiation, and 12-week PFS were associated with better OS (Supplemental Figure 1 in the online version). Against the equivalent therapeutic effects between clinical trials and clinical practice, there is concern that frequency of AEs is increased because of the widening of patient choice. In this study, 13 patients (25%) had grade 3/4 AEs Supplemental Tables 1 and 2 in the online version, which were reported as 6% to 10% in previous randomized phase 3 trials of nivolumab.[5,6] Although there are more frequent AEs in clinical practice than reported in clinical trials, the AEs were tolerable and manageable with careful observation and prompt attention during the course of treatment. In the future, patient selection will be demanded, including selection of patients who would benefit, patients who are likely at high risk of severe AEs, and patients whose disease cannot expect to respond to therapy.

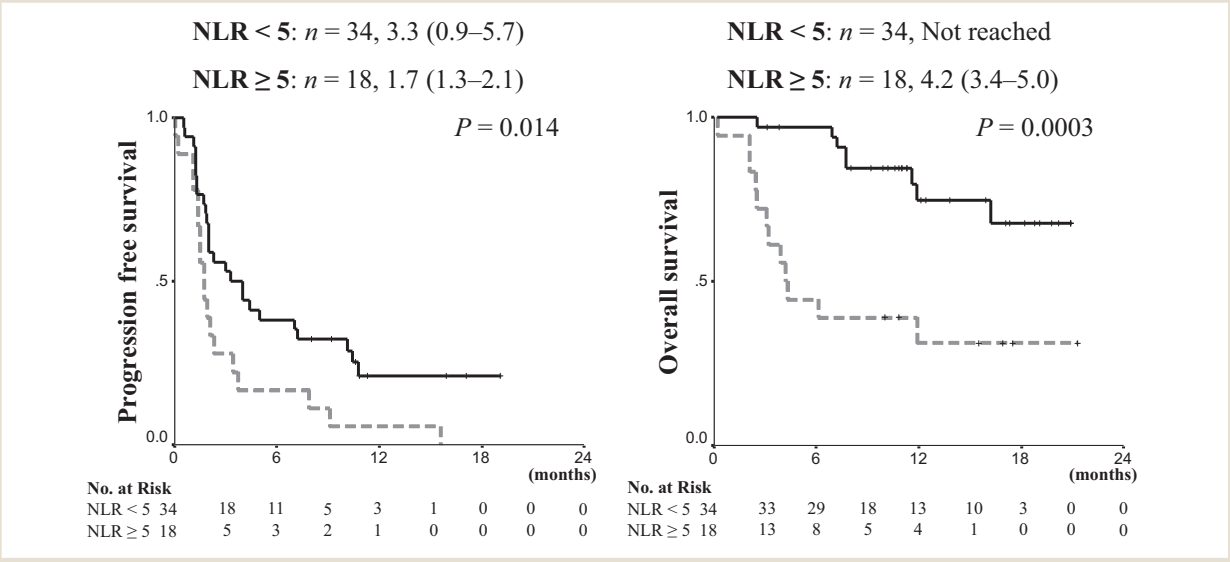
Recently, 2 PD-1 antibodies, nivolumab and pembrolizumab, were approved for patients with NSCLC in Japan. Nivolumab is indicated for all patients with NSCLC disease progression after initial chemotherapy, but pembrolizumab was used for selected patients on the basis of levels of PD-L1 (22C3) immunostaining. However, it was considered that the 2 drugs did not differ greatly even in preclinical data[15] and clinical trial results.[5-7] In routine clinical practice, selection of treatment is confirmed by PD-L1 expression rate because first-line chemotherapy showed high efficacy with pembrolizumab for patients with advanced NSCLC and PD-L1 $\geq$ 50% in the tumor,[8] but with nivolumab.[16] Even

Table 3 Overall Survival Analyses for NSCLC Patients Treated With Nivolumab

	Univariate Analysis			Multivariate Analysis		
Characteristic	HR	95% CI	*P*	HR	95% CI	*P*
Age, <75 vs. ≥75 y	0.34	0.08-1.45	.15			
Sex, male vs. female	1.37	0.54-3.43	.51			
Smoking status, never vs. former/current	0.62	0.24-1.61	.32			
ECOG performance status, 0 vs. 1-3	2.83	0.94-8.50	.064	1.64	0.43-6.25	.47
Histology, non-Sq vs. Sq	0.77	0.28-2.12	.61			
Driver mutations, no vs. yes	0.83	0.24-2.84	.76			
Brain metastases, no vs. yes	1.07	0.31-3.66	.92			
Liver metastases, no vs. yes	2.18	0.84-5.70	.11			
Bone metastases, no vs. yes	3.68	1.52-8.93	.004	2.35	0.79-7.03	.13
Treatment line, 2 vs. ≥3	1.21	0.78-1.90	.40			
PD-L1 expression, ≥1% vs. 0	1.57	0.51-4.88	.43			
PD-L1 expression, ≥50% vs. 0-49%	4.10	1.47-11.42	.007	3.66	1.22-10.98	.021
NLR, <5 vs. ≥5	4.52	1.84-11.14	.001	4.17	1.35-12.92	.013

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; NSCLC = non–small-cell lung cancer; PD-L1 = programmed death ligand 1; Sq = squamous-cell carcinoma.

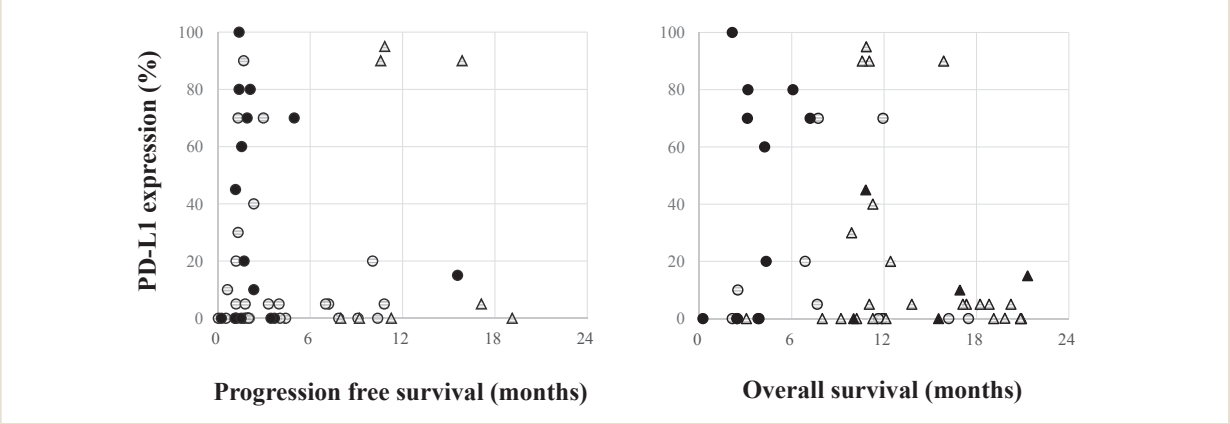
Figure 2 Survival Analyses Based on Pretreatment NLR. Progression-free Survival (A) and Overall Survival (B) Between Patients With NLR < 5 (Black Solid Line) and NLR ≥ 5 (Gray Dotted Line) (n = 52). *P* Values Were Determined by Log-rank Test; Number of Individuals and Survival Times (Median [95% Confidence Interval] Months) in Each Group Are Indicated



Abbreviation: NLR = neutrophil-to-lymphocyte ratio.

after second-line treatment, pembrolizumab was targeted to PD-L1 ≥ 1%,[7] and there was a slight difference in patient adaptation between nivolumab and pembrolizumab. Our study also confirmed the activities of nivolumab for previously treated NSCLC patients with low (≥ 1%) PD-L1 expression, although high expression (≥ 50%) of PD-L1 was associated with good survival. Considering the intratumoral heterogeneity,[17,18] genetic process for PD-L1 expression,[19] and temporal change of PD-L1 expression in tumor,[20] prediction of effects of immune checkpoint inhibitors as a single biomarker, such as PD-L1, might not identify specific patients for treatment. Research development regarding predictive factors or ineffective predictors based on the mechanism of drug action is expected. Considering the diversity of the immune system,[21-23] not only a single marker but also some characteristics of a combined model[24] may be needed.

Figure 3 Association Between PD-L1 Expression, PFS (A), and OS (B) in 46 Subjects. Circles Represent Individual Patients Who Experienced Disease Progression or Patients Who Died After Nivolumab Treatment; Triangle Represents Individual Patients Who Continued Nivolumab Treatment or Surviving Patients. Horizontal Axis Corresponds to PFS or OS; Vertical Axis Shows Percentage of PD-L1 (22C3) Expression. Gray, Patients With NLR < 5; Black, Patients With NLR ≥ 5 Before Nivolumab Treatment



Abbreviations: NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival.

The pretreatment NLR, a marker of systemic inflammation, has previously been associated with outcomes in a variety of cancers.[25-32] When considering the antitumor effect due to inhibition of the immune checkpoints, PD-L1 expression in the tumorigenic process is considered a tumor-side escape molecule when T lymphocytes attack the tumor cells. Activation and intratumoral invasion of lymphocytes are thought to be necessary for this immune response to occur.[2] Neutrophils suppress the immune activity of lymphocytes by producing some chemokines and cytokines.[33] NLR functions as an indicator of inflammation and tumor immune response,[32] and NLR reflects the extent of local neutrophil inflammatory cell infiltration.[34] To our knowledge, there is increased evidence[29,30,35,36] that the high NLR value also correlates with poor prognosis in lung cancer. In our study, pretreatment NLR was significantly associated with survival in nivolumab-treated patients with NSCLC. Interestingly, even if the expression of PD-L1 was high, the effects of nivolumab for patients with pretreatment NLR $\geq$ 5 were limited. Pretreatment NLR level may become a candidate factor as a convenient surrogate marker of host-side general immune status. Enrichment strategies, such as PD-L1 staining, tumor mutation burden, immunoscore, and immune gene signature, to select patients with disease more likely to respond to immune checkpoint inhibitors have been discussed.[11,12] Pretreatment NLR, a simple liquid marker, is a good candidate for this predictive model in additional prospective studies.

There are several limitations to our study. First, because this is an observational study performed at a single institution and in a relatively small cohort of patients, the results cannot be regarded as definitive. However, clinical and laboratory data were prospectively collected, and the response to nivolumab treatment was evaluated at regular intervals throughout the treatment course. Second, nivolumab was administrated to patients with previously treated NSCLC as a routine clinical practice; thus, a potential selection bias may exist. Survival was analyzed since the initiation of nivolumab treatment using a multivariate model to adjust for confounding factors, although the follow-up period was not long enough, with a wide range of the hazard ratio. We found that the correlation between high NLR and poor prognosis was statistically significant and clinically meaningful. Finally, in this study, PD-L1 testing was performed using 22C3 antibody, although PD-L1 expression has been evaluated using 28-8 immunostaining assay in previous clinical trials of nivolumab.[5,6] However, PD-L1 testing is mainly performed using the 22C3 assay in clinical practice, and a PD-L1 immunohistochemistry assays comparison project revealed that PD-L1–stained tumor cells are comparable when the 22C3 and 28-8 assays are used.[37]

Conclusion

Our prospective observational study confirmed the activities of nivolumab treatment for previously treated patients with NSCLC in clinical practice. As in previous clinical trial results, the number of patients treated effectively with nivolumab is small. In the clinical setting, reliable predictive markers are lacking, so it was considered feasible to find appropriate patients by judging the first CT evaluation as early as 2 months from initiation of nivolumab treatment. In the future, it will be necessary to construct a predictive model for patient selection considering the characteristics of immunity, and pretreatment NLR is suggested as a candidate for a convenient marker obtained from simple blood tests.

Clinical Practice Points

- Immune checkpoint inhibitors have greatly altered the standard care of patients with advanced NSCLC.
- In this prospective observational study, nivolumab showed promising activity, with equivalent therapeutic effects between clinical trials and clinical practice.
- A manageable safety profile for nivolumab-treated NSCLC patients was confirmed in routine clinical practice, although frequency of AEs was higher than in clinical trials.
- A reliable predictive model associated with the benefits of nivolumab treatment is necessary to guide treatment options.
- Pretreatment NLR may be a candidate for a convenient biomarker regardless of PD-L1 expression.

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Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2018.04.021.

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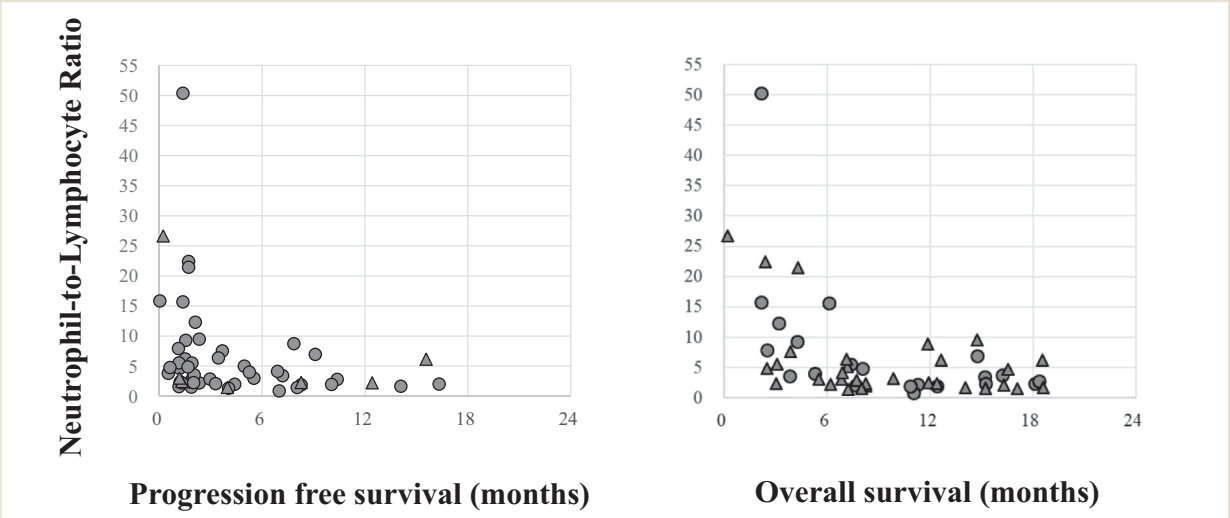
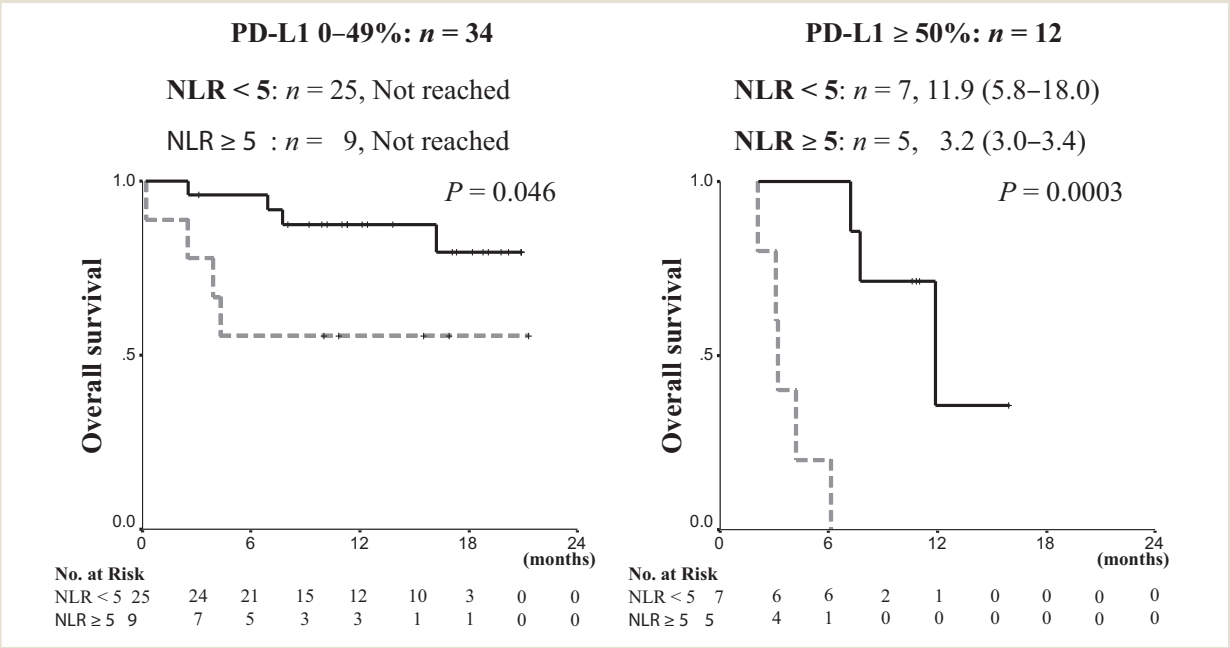
Supplemental Figure 1 Association Between NLR, PFS, and OS in 52 Subjects. Circles Represent Individual Patients Who Had Disease Progression or Who Died After Nivolumab Treatment; Triangle Represents Individual Patients Who Continued Nivolumab Treatment or Surviving Patients. Horizontal Axis Corresponds to PFS or OS; Vertical Axis Shows NLR Value Before Nivolumab Treatment



Abbreviations: NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PFS = progression-free survival.

Supplemental Figure 2 OS Based on NLR and PD-L1 Expression in 46 Subjects. In NSCLC Patients With PD-L1 0, PD-L1 1% to 49%, and PD-L1 ≥ 50%, OS Was Shown Between Patients With NLR < 5 (Black) and NLR ≥ 5 (Gray Dot). *P* Values Were Determined by Log-rank Test; Number of Individuals and Survival Times (Median [95% Confidence Interval] Months) in Each Group Are Indicated



Abbreviations: NLR = neutrophil-to-lymphocyte ratio; NSCLC = non–small-cell lung cancer; OS = overall survival; PD-L1 = programmed death ligand 1.

Supplemental Table 1 AEs Based on Interview Sheet

AE	Any Grade, N (%)	Grade 1 (N)	Grade 2 (N)	Grade 3 (N)	Grade 4 (N)
Any event	46 (88)	10	23	12	1
Anxiety	26 (50)	23	3	0	0
Malaise	20 (38)	15	5	0	0
Arthralgia	19 (37)	16	3	0	0
Pruritus	19 (37)	16	3	0	0
Peripheral neuropathy	19 (37)	16	3	0	0
Dyspnea	18 (35)	7	10	1	0
Rash	17 (33)	14	1	2	0
Constipation	17 (33)	10	7	0	0
Pain	17 (33)	9	8	0	0
Anorexia	13 (25)	6	3	4	0
Edema	9 (17)	8	1	0	0
Nausea	8 (15)	7	1	0	0
Diarrhea	7 (13)	3	3	1	0
Vertigo	7 (13)	7	0	0	0
Loss of vision	7 (13)	7	0	0	0
Mucositis oral	6 (12)	4	0	2	0
Fever	3 (6)	3	0	0	0
Vomiting	2 (4)	2	0	0	0
Alopecia	2 (4)	2	0	0	0
Dysgeusia	1 (2)	1	0	0	0
Health care cost	26 (50)	14	12	0	0

Abbreviation: AE = adverse event.

Supplemental Table 2 AEs Based on Laboratory Data

AE	Any Grade, N (%)	Grade 1 (N)	Grade 2 (N)	Grade 3 (N)	Grade 4 (N)
Liver dysfunction	12 (23)	9	1	1	1
Pneumonitis	6 (12)	0	5	1	0
Hypothyroidism	5 (10)	3	2	0	0
Colitis	3 (6)	0	2	1	0
Hyperthyroidism	2 (4)	0	2	0	0
Anemia	1 (2)	0	0	1	0
Platelet count decreased	1 (2)	0	0	1	0
Hyponatremia	1 (2)	0	0	1	0
Hypophosphatemia	1 (2)	0	0	1	0
Hypertriglyceridemia	1 (2)	0	0	0	1
Hypokalemia	1 (2)	0	1	0	0

Abbreviation: AE = adverse event.