Original Research Article

Cancer Control
Volume 27: 1-11

DOI: 10.1177/1073274820977200
journals.sagepub.com/home/ccx
SAGE

Factors Associated With Efficacy and Nivolumab-Related Interstitial Pneumonia in Non-Small Cell Lung Cancer: A Retrospective Survey

Hiroki Hata, MS[1,2], Tadashi Mio, PhD[3], Daisuke Yamashita, BS[1], Chikako Matsumura, PhD[2], Yugo Chisaki, PhD[2], Hideyuki Motohashi, PhD[2,4], and Yoshitaka Yano, PhD[2]

Abstract

Background and Objectives: Immune-checitors have been established as a novel standard treatment for non-small cell lung cancer (NSCLC). The aim of this study was to identify factors associated with efficacy and nivolumab-related interstitial pneumonia in NSCLC by evaluating clinical data at the initiation of and during treatment.

Methods: We retrospectively reviewed the medical records of patients who underwent treatment with nivolumab between October 2015 and December 2017. Using pretreatment patient data, we investigated factors associated with overall survival (OS) and the onset of nivolumab-related pneumonitis. We investigated serum biochemistry during treatment to identify the determinants associated with progressive disease (PD) and the onset of nivolumab-related pneumonitis.

Results: A total of 94 patients were included. Eleven patients continued treatment, and 54 patients were diagnosed with progressive disease. Nivolumab-related pneumonitis occurred in 15 patients. A pretreatment Eastern Cooperative Oncology Group Performance Status (ECOG PS) = 0 was linked to significantly longer OS than ECOG PS = 1 (median: 20.1 vs. 6.5 months, respectively; $p < 0.001$). There was a higher incidence of nivolumab-related pneumonitis in patients with a history of interstitial pneumonia than in those without it ($p = 0.008$). During treatment, the level of albumin gradually decreased prior to PD and onset of nivolumab-related pneumonitis.

Conclusion: These results suggest that the pretreatment ECOG PS is the determining factor that is associated with OS, whereas history of interstitial pneumonia is the factor associated with nivolumab-related pneumonitis. A decrease in albumin during treatment may be associated with both PD and nivolumab-related pneumonitis.

Keywords

NSCLC, Biomarker, nivolumab, nivolumab-related pneumonitis, albumin

Received February 09, 2020. Received revised September 17, 2020. Accepted for publication October 18, 2020.

[1] Department of Pharmacy, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
[2] Education and Research Center for Clinical Pharmacy, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto, Japan
[3] Division of Respiratory Medicine, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
[4] Department of Pharmaceutics, Osaka University of Pharmaceutical Sciences, Nasahara, Takatsuki, Osaka, Japan

Corresponding Author:
Yoshitaka Yano, Education and Research Center for Clinical Pharmacy, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607-8414, Japan.
Email: yano@mb.kyoto-phu.ac.jp

Key Point

This study was a retrospective survey to identify factors associated with efficacy and nivolumab-related interstitial pneumonia by evaluating clinical data at the initiation of and during treatment, and this study included good Eastern Cooperative Oncology Group Performance Status (ECOG PS) patients with advanced non-small cell lung cancer (NSCLC).

In conclusion, the pretreatment ECOG PS is associated with progression-free survival and overall survival in patients with advanced NSCLC who underwent treatment with nivolumab. The history of interstitial pneumonia prior to treatment with nivolumab may correlate with the onset of nivolumab-related pneumonitis. Furthermore, it has been suggested that a decrease in albumin during treatment may be a factor associated with disease progression and the onset of nivolumab-related pneumonitis.

Introduction

Immune-checkpoint inhibitors (ICIs) have been established as a novel standard treatment for various types of malignancies, including non-small cell lung cancer (NSCLC). Several anti-programmed cell death protein-1 agents (e.g., nivolumab and pembrolizumab) and anti-programmed death-ligand 1 agents (e.g., atezolizumab) have demonstrated promising systemic activity in patients with NSCLC.[1-4]

Clinical trials of ICIs indicate favorable safety profiles compared with those of conventional cytotoxic agents.[1-4] However, ICIs cause inflammatory side effects termed immune-related adverse events (irAEs),[1-4] which can be severe in some cases. Especially, nivolumab-related pneumonitis is prominent irAEs in clinical settings and is notable owing to its severe outcomes.[5,6] A previous study demonstrated that the rate of irAEs in clinical practice patients is higher than that reported in clinical trial participants.[7] Furthermore, recent studies found a positive association between the onset of irAEs and efficacy of ICIs.[8-11] However, thus far, risk factors for the development of irAEs have not been identified.[12,13] The action mechanism of nivolumab activates lymphocytes with blocking immune checkpoint molecules, and this activation of lymphocytes presumably causes nivolumab-related pneumonitis.[12] A retrospective cohort study involving melanoma patients who received treatment with nivolumab demonstrated that an increase in the white peripheral blood count (PBC) and a decrease in the relative lymphocyte count correlated with the onset of irAEs in the lungs.[14] In recent years, it has become increasingly apparent that cancer-associated inflammation is a key determinant of disease progression and survival in a multitude of solid tumors.[15] The pretreatment neutrophil-to-lymphocyte ratio (NLR), a marker of systemic inflammation, has previously been correlated with outcomes in a variety of cancers.[16-22] Previous studies indicated that the PBC and serum biochemistry may predict the efficacy of nivolumab and the onset of irAEs.[18,23-31] However, most of the cancer-related inflammation studies analyzed pretreatment data, while few studies observed the changes in PBC and serum biochemistry during treatment.

A retrospective study also reported that the incidence of nivolumab-related pneumonitis in patients with NSCLC was significantly higher in patients with a history of interstitial pneumonia than in those without it.[32] However, the risk factors for the incidence of nivolumab-related pneumonitis in the former group of patients have not been found.[32]

Therefore, accumulation of a large amount of efficacy and safety data from patients who received ICIs in clinical practice settings would be beneficial for the purpose of validating previous observations. The aim of this study was to identify the factors associated with efficacy and nivolumab-related interstitial pneumonia in NSCLC by evaluating clinical data at treatment initiation and during treatment.

Methods

Patients, Data Collection, and Study Design

This study was a retrospective observational study including patients with advanced NSCLC [IIIB or IV according to the 7th edition of Tumor-Node-Metastasis classification] who underwent treatment with nivolumab (3 mg/kg intravenously every 2 weeks) at the National Hospital Organization Kyoto Medical Center (Kyoto, Japan). Patients were enrolled from October 2015 to December 2017 and followed up until August 31, 2018. The exclusion criteria were patients with Eastern Cooperative Oncology Group Performance Status grade (ECOG PS) $\geq$2 at treatment and during initiation in accordance with previous phase III trials[1-4] and patients who used anticancer drugs or were had other cancer diagnoses.

The outline of the research is shown in the Figure 1. In Step 1, data from all patients (n = 94) for overall survival (OS), progression-free survival (PFS), and irAEs were investigated. In Step 2, the patients were divided into three groups to identify factors associated with progressive disease and to identify the onset of nivolumab-related pneumonitis according to laboratory data obtained during treatment. To identify factors associated with progressive disease and whether these factors affect the onset of nivolumab-related pneumonitis, patients who discontinued treatment for reasons other than progressive disease and the onset of nivolumab-related pneumonitis were excluded from our analysis in Step 2.

Patient data were collected from the medical records in the hospital. The data collected at the time of treatment initiation were age, sex, smoking history, histological type, ECOG PS, epidermal growth factor receptor (EGFR) mutation status, anaplastic lymphoma kinase (ALK) translocation, history of interstitial pneumonia, PBC (i.e., absolute neutrophil count [ANC], absolute lymphocyte count [ALC], absolute monocyte count, and platelet count) and serum biochemistry (i.e., levels of C-reactive protein, albumin [ALB], lactate dehydrogenase). The NLR was calculated as the ANC divided by the ALC, while the platelet-to-lymphocyte ratio (PLR) was calculated as the platelet count divided by the ALC. The data collected

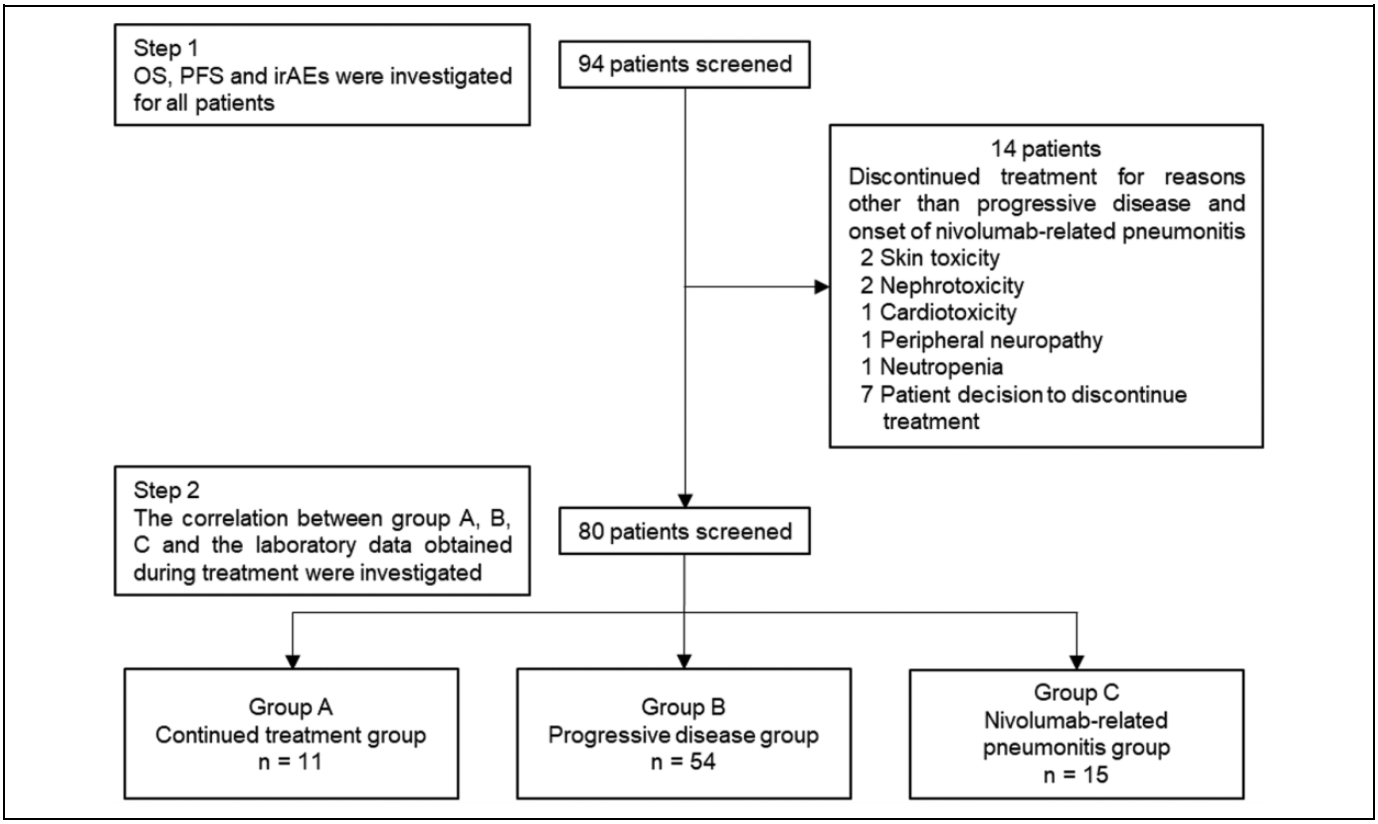

Figure 1. In Step 1, OS, PFS and irAEs were determined for all patients. In Step 2, the patients were divided into three groups to identify factors associated with progressive disease and onset of nivolumab-related pneumonitis according to the laboratory data obtained during treatment.

during treatment with nivolumab were onset date and severity of irAEs, PBC, serum biochemistry, date of disease progression, and date of death. Tumor assessment was performed according to the Response Evaluation Criteria in Solid Tumor (Version 1.1). IrAEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.0. Patients with nivolumab-related pneumonitis were defined as those who received treatment for interstitial pneumonia after the administration of nivolumab.

During Step 1, OS and PFS were determined for all patients who had been dichotomized according to the cutoff value of baseline NLR $\geq$5 vs. 5 and ECOG PS = 0 vs. 1, as identified in previous studies on nivolumab.[25] In addition, the risk of occurrence of nivolumab-related pneumonitis was investigated using pretreatment patient data. Patients with unavailable data regarding their smoking history and histological type were excluded from this particular analysis.

During Step 2, the patients were divided into three groups to identify the patient characteristics associated with progressive disease and onset of nivolumab-related pneumonitis according to the laboratory data obtained during treatment. Group A included patients who continued to receive nivolumab throughout the course of treatment; group B included patients who discontinued nivolumab because of a progressive disease; and group C included patients who discontinued nivolumab because of nivolumab-related pneumonitis. Changes in PBC and serum biochemistry in each group during the course of treatment were evaluated. We compared PBC values and serum biochemistry results among groups A, B, and C at four time points. The first time point was determined as immediately prior to treatment ("Pre"), the second time point was during treatment period ("Average"), the third time point was the nearest time before the date of onset of progressive disease or the date of onset of nivolumab-related pneumonitis ("Last-1"), and the fourth time point was the date of onset of progressive disease or the and the date of onset of nivolumab-related pneumonitis ("Last").

Cutoff values were determined for PBC and serum biochemistry during treatment; these values were useful for determining the threshold values associated with the onset of progressive disease and nivolumab-related pneumonitis.

Statistical Analysis

The PFS and OS were compared between subgroups based on NLR and ECOG PS using a log-rank test. The chi-squared test was used to determine whether the patient baseline characteristics were associated with the onset of nivolumab-related pneumonitis. Two-way analysis of variance was applied to assess the comparison between the three groups and four time points. In case of a significant interaction, Tukey's test was used for subsequent comparisons between multiple groups. For cutoff values that were significant in Tukey's test, we

Table 1. Patient Characteristics.

	Total n = 94	Group A Continued treatment group n = 11	Group B Progressive disease group n = 54	Group C Nivolumab-related pneumonitis group n = 15
Age (years)				
Mean ± SD	69.5 ± 7.9	68 ± 10.9	71 ± 7.3	70 ± 9.5
Sex				
Male	69	7	36	12
Female	25	4	18	3
Smoking status				
Yes	78	11	40	14
No	12	0	12	0
Unknown	4	0	2	1
Histology				
Adenocarcinoma	57	6	38	9
Squamous	33	5	15	6
Other	4	0	1	0
ECOG PS				
0	58	9	31	9
1	36	2	23	6
EGFR status				
Mutated	13	0	9	3
Wild-type	41	6	27	6
Not investigated	40	5	18	6
ALK rearrangement				
Positive	0	0	0	0
Negative	54	6	36	9
Not investigated	40	5	18	6
History: interstitial pneumonia				
Yes	18	3	5	8
No	76	8	49	7
Baseline NLR				
<5	61	7	33	11
≥5	33	4	21	4
Baseline PLR				
<180	32	2	22	4
≥180	62	9	32	11
Baseline ALB				
<3.5	44	3	30	5
≥3.5	50	8	24	10

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor gene; ALK, anaplastic lymphoma kinase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALB, albumin; SD, standard deviation. Fourteen patients who discontinued treatment for reasons other than progressive disease and onset of nivolumab-related pneumonitis were excluded from total.

performed receiver operating characteristic (ROC) curve analysis to identify the cutoff values associated with the onset of progressive disease and nivolumab-related pneumonitis. The area under the curve (AUC) was determined to estimate the diagnostic accuracy. Statistical significance was defined as $p < 0.05$, and 95% confidence intervals (CI) were calculated. All statistical analyses were performed using BellCurve® for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan.).

Results

Patient Characteristics

The patient characteristics are summarized in Table 1. A total of 94 patients were included in the study; all of these patients were previously treated for advanced NSCLC. The EGFR status and ALK rearrangement are shown only for 57 patients with adenocarcinoma. The median baseline NLR was 5.2 (range: 1.2–19.3).

Univariate Analysis of OS and PFS

The median OS for all patients was 15.9 months (95% CI: 9.9–20.1) (Figure 2A). ECOG PS = 1 was associated with shorter OS compared with ECOG PS = 0 (median: 6.5 vs. 20.1 months, respectively; $p < 0.001$) (Figure 2B). Baseline NLR was not significantly associated with OS; however, the NLR ≥5 group tended to be associated with shorter OS compared with the NLR < 5 group (median: 7.8 vs. 17.2 months, respectively; $p = 0.112$) (Figure 2C).

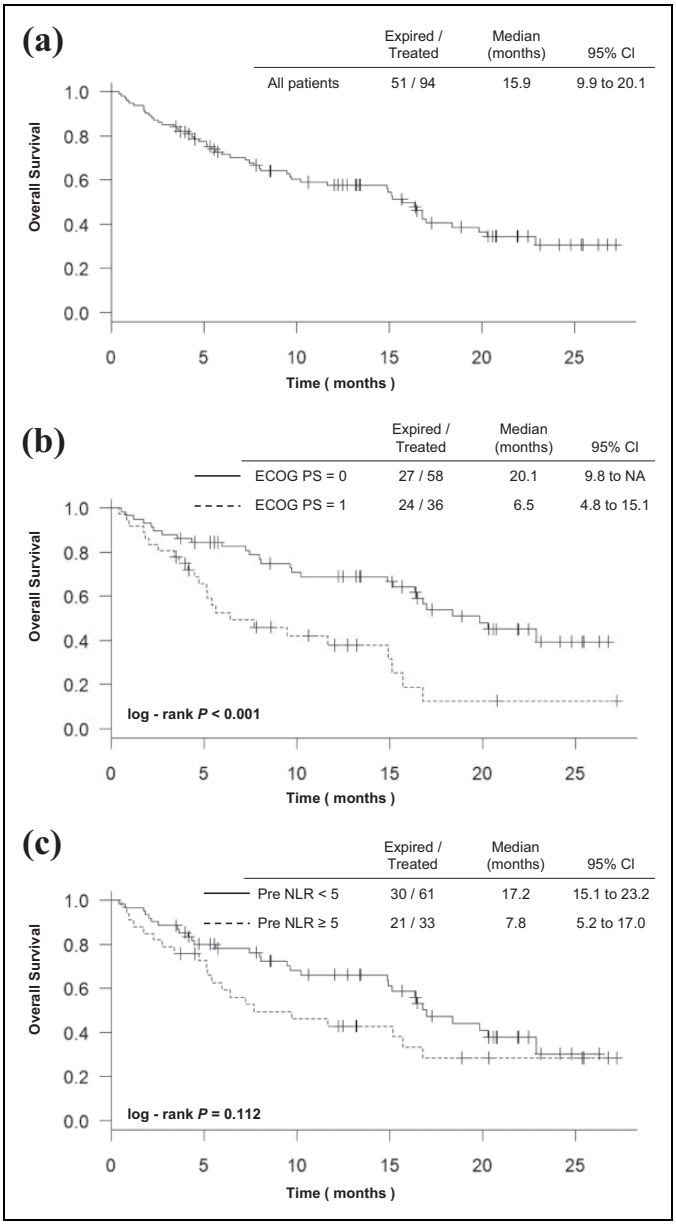

Figure 2. Kaplan–Meier curves for OS according to each prognostic factor: (a) all patients, (b) baseline ECOG PS = 0 (solid line) vs. ECOG PS = 1 (dotted line), and (c) baseline NLR < 5 (solid line) vs. NLR ≥5 (dotted line).

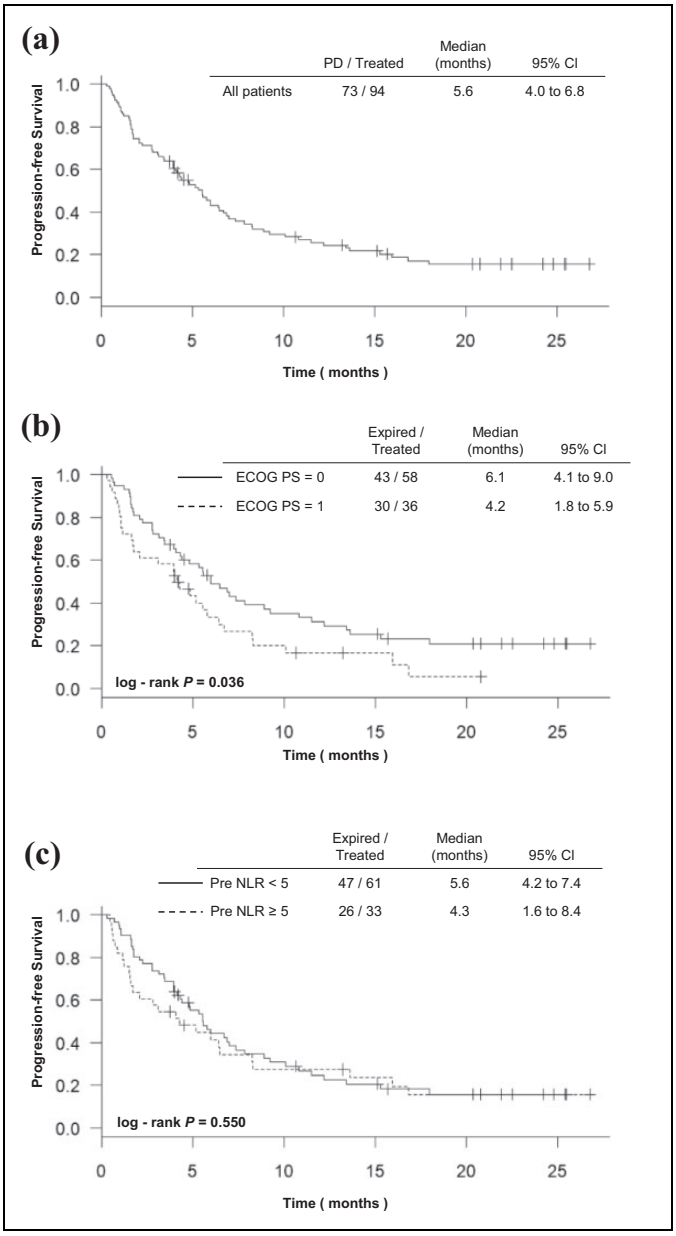

Figure 3. Kaplan–Meier curves for PFS according to each prognostic factor: (a) all patients, (b) baseline ECOG PS = 0 (solid line) vs. ECOG PS = 1 (dotted line), and (c) baseline NLR < 5 (solid line) vs. NLR ≥5 (dotted line).

The median PFS for all patients was 5.6 months (95% Cl: 4.0–6.8) (Figure 3A). ECOG PS = 1 was associated with shorter OS versus ECOG PS = 0 (median: 4.2 vs. 6.1 months, respectively; $p = 0.036$) (Figure 3B). There was no significant difference in PFS between patients in the NLR ≥5 group and those in the NLR < 5 group (median: 4.3 vs. 5.6 months respectively; $p = 0.550$) (Figure 3C).

IrAEs and Onset of Nivolumab-Related Pneumonitis

IrAEs which occurred after the administration of nivolumab are shown in Table 2. Forty-one, eight, and one patient experienced one, two, and three irAEs, respectively. Twenty-two patients had grade III/IV irAEs. The most frequent and serious irAE was nivolumab-related pneumonitis.

The results of the chi-squared test for correlation between the pretreatment patient characteristics and onset of nivolumab-related pneumonitis are presented in Table 3. Four patients who had unknown smoking history and four patients who had other histological types were excluded from this analysis. The median time to onset of nivolumab-related pneumonitis was 4.1 months. Among all examined factors, only the history of interstitial pneumonia

Table 2. Treatment-Related Immune-Related Adverse Events.

Immune-related adverse events	All grades	Grades 1–2	Grade 3–4
Overall	60	38	22
Interstitial pneumonia	19	8	11
Skin toxicity	12	10	2
Thyroid dysfunction	11	11	0
Fatigue	4	4	0
Nephrotoxicity	3	0	3
Cardiotoxicity	3	1	2
Peripheral neuropathy	2	1	1
Stomatitis	1	0	1
Type I diabetes mellitus	1	0	1
Neutropenia	1	0	1
Hypoadrenalism	1	1	0
Hypopituitarism	1	1	0
Infusion reaction	1	1	0

exhibited a significant difference in the onset of nivolumab-related pneumonitis.

Changes in Laboratory Data

The characteristics of patients in groups A, B, and C are presented in Table 1. Fourteen patients who discontinued treatment for reasons other than progressive disease and onset of nivolumab-related pneumonitis were excluded. Four out of 19 patients were diagnosed with progressive disease before they developed immune-related pneumonitis, and these were included in Group B. The interactions of ALB, PLR, and NLR were statistically significant. By contrast, the interactions of ANC, ALC, absolute monocyte count, lactate dehydrogenase, and C-reactive protein did not demonstrate statistical significance. We analyzed ALB, PLR, and NLR by performing multiple comparisons using Tukey's test; the results are illustrated in Figure 4. ALB was significantly different between group A and group B at all measurement time points (group A vs. B, respectively, median at "Pre": 3.6 vs. 3.4, $p = 0.031$; median at "Average" 3.8 vs. 3.4, $p < 0.001$; median at "Last-1" 3.8 vs. 3.4, $p < 0.001$; median at "Last" 4.0 vs. 3.0, $p < 0.001$). ALB was significantly different between group A and group C at all measurement time points, except "Pre" (group A vs. C, respectively, median at "Pre": 3.6 vs. 3.5; $p = 0.998$, median at "Average": 3.8 vs. 3.6, $p = 0.006$; median at "Last-1": 3.8 vs. 3.4, $p = 0.002$; median at "Last": 4.0 vs. 3.0, $p < 0.001$). PLR was not significantly different between group A and groups B and C at all measurement time points. NLR was significantly different between group A and group C only at the "Last" time point (group A vs. C, respectively, median at "Last": 2.7 vs. 11.5, $p < 0.001$). However, NLR was not significantly different between group A and group B at all measurement time points.

Determination of the Appropriate Cutoff Values for Progressive Disease and Nivolumab-Related Pneumonitis

For cutoff values of ALB that were significant in Tukey's test (group A vs. B; "Pre", "Average", and "Last-1", group A vs. C; "Average" and "Last-1"), we performed a ROC curve analysis to identify cutoff values for the progressive disease and the onset of nivolumab-related pneumonitis. The results are illustrated in Figure 5.

The results of the ROC curve analysis for groups A and B indicated that ALB at the "Average" and "Last-1" time points exhibited moderate ability to diagnose progressive disease. However, ALB at the "Pre" time point exhibited low diagnostic accuracy (i.e., cutoff value, AUC, sensitivity, and specificity at "Pre": 3.5, 0.62, 54%, 73%, respectively; at "Average": 3.7, 0.80, 70%, 91%, respectively; and at "Last-1": 3.6, 0.78, 72%, 82%, respectively).

The results of the ROC curve analysis for groups A and C indicated that ALB at the "Average" and "Last-1" time points exhibited moderate ability to diagnose the onset of nivolumab-related pneumonitis (i.e., AUC, cutoff value, sensitivity, and specificity at "Average": 3.8, 0.78, 79%, 64%, respectively; and at "Last-1", 3.7, 0.81, 86%, 64%, respectively).

Discussion

This retrospective single-institution survey was conducted to identify factors associated with the efficacy of nivolumab and its association with interstitial pneumonia prior to and during treatment with nivolumab. The study patients had been previously treated with nivolumab for NSCLC in a real-world setting.

In this study only patients with ECOG PS = 0–1 were included, the OS and PFS of patients with ECOG PS = 1 were significantly shorter than those of patients with ECOG PS = 0. However, there was no significant difference in OS and PFS between patients with NLR $\geq$ 5 and those with NLR < 5 prior to treatment with nivolumab. In a previous retrospective single-facility analysis, it was demonstrated that the OS and PFS of patients with ECOG PS > 2 were significantly lower than in those with ECOG PS < 1.[25] However, ECOG PS is a subjective assessment, and differences between the patients' conditions among ECOG PS = 0 and PS = 1 were reported.[33] Thus, our results should be carefully considered. Previous studies reported that NLR $\geq$5 prior to treatment with nivolumab is related to decreased efficacy.[23-25] Nevertheless, this relationship was not observed in the present study. In a previous report, 58% and 25% of patients had NLR $\geq$5 and ECOG PS $\geq$2, respectively.[25] However, in this study, these proportions were 34% and 0%, respectively. In patients with good ECOG PS (as in the present study), NLR before treatment with nivolumab may be not be correlated with the treatment effect.

The results of this study indicate that the efficacy of treatment with nivolumab did not correlate with variations in NLR during treatment. It has been reported that, after 6 weeks of treatment with nivolumab, patients with NLR $\geq$5 exhibited

Table 3. Correlation Between Each Factor and Onset of Nivolumab-Related Pneumonitis.

		All patients (n = 94)		Univariate analysis		
Risk factor		**IP**	**No-IP**	**Odds ratio**	**95% CI**	***p***
Age	≥70 years	12	35	1.945	0.624–6.523	0.304
	<70 years	7	40			
Gender	Male	14	55	1.018	0.296–4.084	1.000
	Female	5	20			
ECOG PS	1	9	27	1.592	0.504–4.982	0.432
	0	10	48			
Smoking history (n = 90)*1	Yes	14	64	0.660	0.139–4.267	0.691
	No	3	9			
History of interstitial pneumonia	Yes	8	10	4.626	1.289–16.686	0.008
	No	11	65			
Histological type (n = 90)*2	Adenocarcinoma	12	45	1.010	0.297–3.206	1.000
	Squamous	7	26			

ECOG PS, Eastern Cooperative Oncology Group performance status; IP, interstitial pneumonia
*1 4 patients who had unknown smoking history were excluded from this particular analysis.
*2 4 patients who had other histological type were excluded from this particular analysis.

worse PFS than those with NLR < 5.[34] In this study, the PBC and serum biochemistry after the initiation of treatment with nivolumab were obtained as an average value, irrespective of the treatment period. Hence, it may be difficult to observe changes in clinical laboratory test values immediately after the initiation of treatment with nivolumab. It has been suggested that the correlation between nivolumab efficacy with NLR should be limited prior to or immediately after the initiation of treatment.

By contrast, the cutoff value of ALB was within the normal range. However, this study indicated a reduction in ALB in parallel with disease progression. A prospective cohort study revealed that malnutrition was a factor associated with OS in patients with advanced cancer.[35] Cancer cells are characterized by high demands for energy and nutrients to support their rapid proliferation, with glucose and amino acids (e.g., glutamine) representing important fuels for tumor cell growth.[36] Currently, the mechanism through which cancer cells acquire sufficient amino acids to support their high proliferative rate has not been well understood. It has been reported that downregulation of the neonatal Fc receptor (FcRn) promotes tumor cell growth and proliferation through accumulation of ALB within the tumor cells.[37] Furthermore, it has been demonstrated that downregulation of the FcRn in NSCLC tissue was associated with poor prognosis.[38] The hypoalbuminemia observed in group B may indicate downregulation of FcRn in tumor cells. Therefore, the mechanism of disease progression during treatment with nivolumab in NSCLC patients may include loss of FcRn in tumor cells. Few longitudinal studies have examined the relationship between disease progression and PBC and serum biochemistry.[18,23-31] It was suggested that monitoring of ALB over time is useful for detecting disease progression.

This study has demonstrated that the onset of nivolumab-related pneumonitis correlated with the history of interstitial pneumonia and reduction in ALB prior to and during treatment with nivolumab, respectively. The present study included only patients with good performance status, unlike a previous report that included patients with ECOG PS > 2 (26%).[32] The onset of nivolumab-related pneumonitis may correlate with the history of interstitial pneumonia prior to treatment, irrespective of the ECOG PS prior to treatment. In a previous study, it was hypothesized that there are two etiologies of nivolumab-related pneumonitis: (i) the exacerbation type, exhibiting exacerbation of a preexisting interstitial pneumonia, and (ii) the *de novo* type, newly induced by nivolumab and independent of preexisting interstitial pneumonia.[32] The history of interstitial pneumonia may be a risk factor for the former type, whereas reduction in ALB during treatment with nivolumab may be a risk factor for the latter type. Group C included eight patients (53.3%, 8/15) with a history of interstitial pneumonia. These eight patients may have had exacerbations, but we cannot differentiate patients who have had an exacerbation and patients with de novo disease. Patients with fibrosis had lower levels of FcRn mRNA versus those without this complication.[39] The hypoalbuminemia observed in group C may include downregulation of FcRn in normal tissue of the lung. We could not investigate the association between reduced levels of ALB and the severity of nivolumab-related pneumonitis because this study had a limited number of patients with nivolumab-related pneumonitis. This study indicated that NLR increases at the onset of nivolumab-related pneumonitis. These results suggest that the onset of nivolumab-related pneumonitis rapidly progressed. Presumably, it is difficult to determine the development of nivolumab-related pneumonitis based on PBC obtained every 2 weeks. A retrospective cohort study involving melanoma

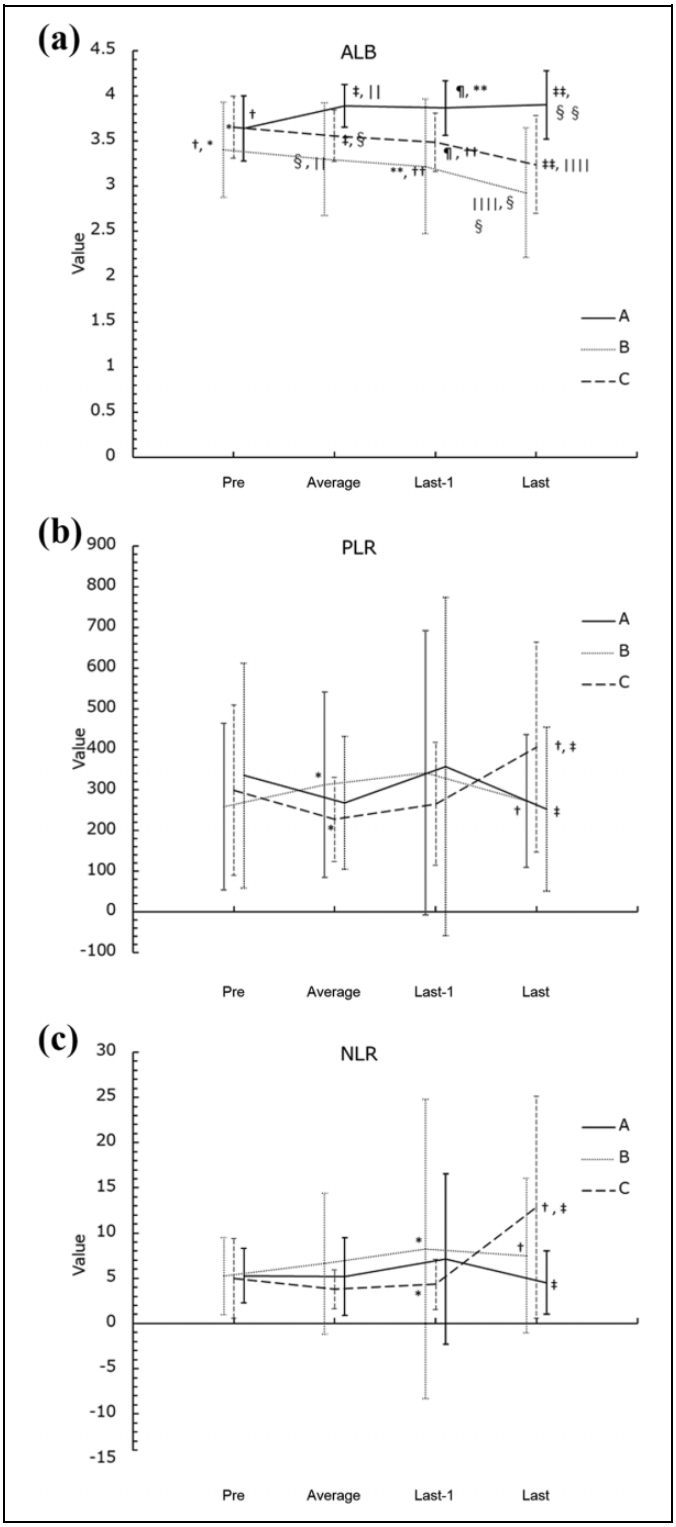

Figure 4. 4-Point blood tested at "Pre", "Average", "Last-1", and "Last". A $p < 0.05$ indicated statistical significance. Results are presented as mean $\pm$ SD. (a) ALB, (b) PLR, and (c) NLR.

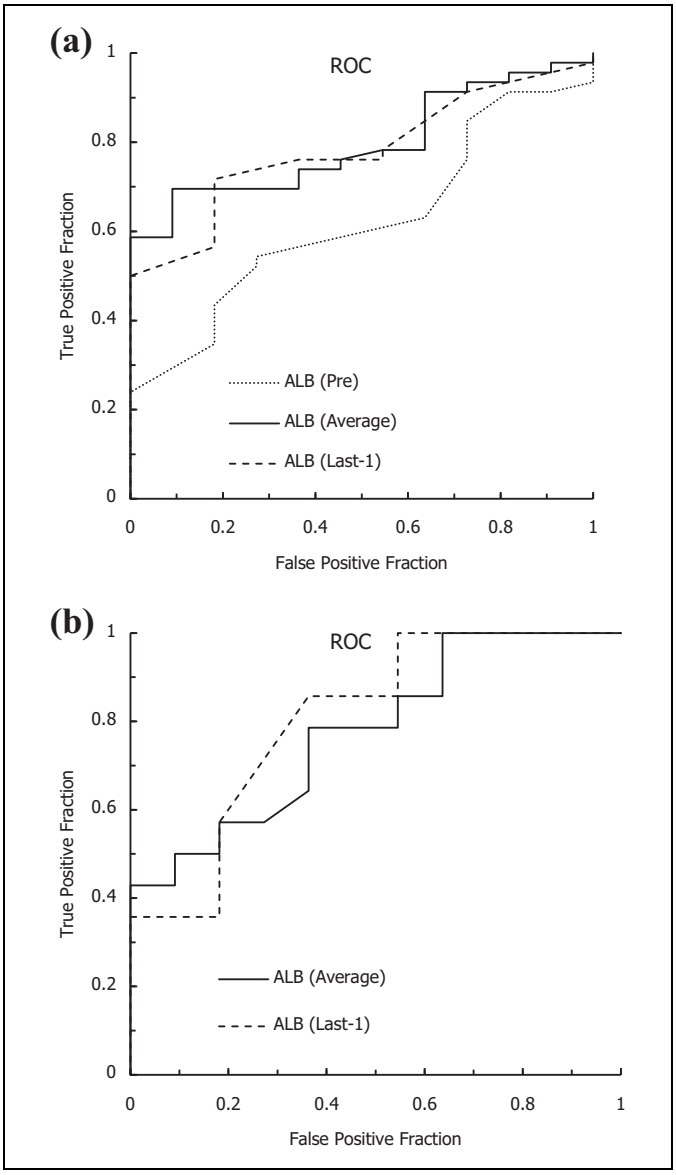

Figure 5. Receiver operating characteristic curve analyses for the cutoff values: (a) Group A vs. B, cutoff value of ALB at the "Pre", "Average", and "Last-1" time points; (b) Group A vs. C, cutoff value of ALB at the "Average" and "Last-1" time points.

patients who received treatment with nivolumab indicated that an increase in white PBC and a decrease in relative lymphocyte count correlated with the onset of irAEs in the lungs.[14] This discrepancy with our study may be explained by differences in tumors.[40] Interstitial pneumonia induced by the administration of ICIs has exhibited diverse radiologic and pathologic features.[41] The various characteristics of interstitial pneumonia caused by treatment with nivolumab may complicate the risk factors prior to treatment.

We acknowledge six limitations of this study. First, this study was retrospective in nature. Second, diagnoses of preexisting interstitial pneumonia and nivolumab-related interstitial pneumonitis were largely dependent on computed tomography findings. Thus, histological and physiological diagnoses of nivolumab-related pneumonitis are lacking. Third, patients in this study underwent treatment with nivolumab at 3 mg/kg

intravenously every 2 weeks; notably, the currently used dose in Japan and worldwide is 240 mg/body intravenously every 2 weeks. However, it has been demonstrated that the dose of nivolumab was not clinically difference at the efficacy and safety. Therefore, the results of this study may be applicable to the current clinical practice.[42] Fourth, as shown in previous studies,[16-22] NLR, ECOG PS, and ALB levels are known prognostic factors in patients with cancer and are likely to be associated with poor outcomes regardless of the treatment used. Fifth, our conclusions cannot be made about the predictive value of the clinical and biological data examined since there was no comparative group in this study. Finally, this study's cohort only consisted of Japanese patients. The results of this study may not be generalizable to different ethnic groups.

In conclusion, the pretreatment ECOG PS may be contributing factors that are associated with PFS and OS in patients with advanced NSCLC who underwent treatment with nivolumab. The history of interstitial pneumonia prior to treatment with nivolumab may correlate with the onset of nivolumab-related pneumonitis. Furthermore, it has been suggested that monitoring ALB over time may be useful in determining disease progression and the onset of nivolumab-related pneumonitis. This is the first study to examine Japanese patients with good PS in this setting. A prospective study is required to address the limitations of this retrospective study.

Acknowledgments

We have greatly benefited from Yoshihisa Honda and Katsuaki Kobayashi.

We have had the support and encouragement of Asami Hata, Shigeki Takematsu and Kohzoh Tatsumi. We would like to thank MARUZEN-YUSHODO Co., Ltd. (https://kw.maruzen.co.jp/kousei-honyaku/) for the English language editing.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Hiroki Hata, Chikako Matsumura, Yugo Chisaki, Hideyuki Motohashi and Yoshitaka Yano. The first draft of the manuscript was written by Hiroki Hata and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and analyses during the current study are available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical standards of the ethics committee of National Hospital Organization Kyoto Medical Center (reference number: 17-090), Kyoto Pharmaceutical University (reference number: 19-18-01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Hiroki Hata https://orcid.org/0000-0002-6798-816X
Hideyuki Motohashi, PhD https://orcid.org/0000-0002-4752-240X

Informed consent

We had not obtained Informed consent from individual participants included in the study, because this study was a retrospective observational study. However, we published information on the implementation of research on the Kyoto Medical Center website, and we guarantee the opportunity of patient rejection. It was based on the Ethical Guidelines for Medical Research on Humans established by Japan Ministry of Health, Labour, and Welfare.

References

1. 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(2):123-135.
2. 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(17):1627-1639.
3. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *The Lancet*. 2016;387(10027):1540-1550.
4. 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(10066):255-265.
5. Gettinger SN, Horn L, Gandhi L, et al. Overall survival and long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol*. 2015; 33(18):2004-2012.
6. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21): 2018-2028.
7. Suresh K, Naidoo J, Lin CT, et al. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest*. 2018;154(6):1416-1423.
8. Sato K, Akamatsu H, Murakami E, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. *Lung Cancer*. 2018;115: 71-74.
9. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. 2018;4(3):374-378.

10. Osorio JC, Ni A, Chaft JE, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol*. 2017;28(3):583-589.
11. Teraoka S, Fujimoto D, Morimoto T, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J Thorac Oncol*. 2017;12(12):1798-1805.
12. Kato T, Masuda N, Nakanishi Y, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. *Lung Cancer*. 2017;104:111-118.
13. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Ther Adv Respir Dis*. 2016;10(3):183-193.
14. Fujisawa Y, Yoshino K, Otsuka A, et al. Fluctuations in routine blood count might signal severe immune-related adverse events in melanoma patients treated with nivolumab. *J Dermatol Sci*. 2017; 88(2):225-231.
15. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014; 15(11):e493-e503.
16. Mei Z, Shi L, Wang B, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: a systematic review and meta-analysis of 66 cohort studies. *Cancer Treat Rev*. 2017;58:1-13.
17. Kang MH, Go SI, Song HN, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. *Br J Cancer*. 2014;111(3):452-460.
18. Diem S, Schmid S, Krapf M, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer*. 2017;111:176-181.
19. van Soest RJ, Templeton AJ, Vera-Badillo FE, et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. *Ann Oncol*. 2015;26(4):743-749.
20. Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. *J Thorac Oncol*. 2015;10(2):280-285.
21. Templeton AJ, McNamara MG, Seruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106(6): dju124.
22. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88(1):218-230.
23. Fukui T, Okuma Y, Nakahara Y, et al. 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. *Clin Lung Cancer*. 2018;20(3):208-214.
24. Tanizaki J, Haratani K, Hayashi H, et al. Peripheral blood biomarkers associated with clinical outcome in non-small cell lung cancer patients treated with nivolumab. *J Thorac Oncol*. 2018; 13(1):97-105.
25. Bagley SJ, Kothari S, Aggarwal C, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2017;106:1-7.
26. Mezquita L, Auclin E, Ferrara R, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. *JAMA Oncol*. 2018;4(3):351-357.
27. Taniguchi Y, Tamiya A, Isa SI, et al. Predictive factors for poor progression-free survival in patients with non-small cell lung cancer treated with nivolumab. *Anticancer Res*. 2017;37(10): 5857-5862.
28. Zhang Z, Li Y, Yan X, et al. Pretreatment lactate dehydrogenase may predict outcome of advanced non small-cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Cancer Med*. 2019;8:1467-1473.
29. Pavan A, Calvetti L, Dal Maso A, et al. Peripheral blood markers identify risk of immune-related toxicity in advanced non-small cell lung cancer treated with immune-checkpoint inhibitors. *Oncologist*. 2019;24(8):1128-1136.
30. Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships between lymphocyte counts and treatment-related toxicities and clinical responses in patients with solid tumors treated with PD-1 checkpoint inhibitors. *Oncotarget*. 2017;8(69): 114268-114280.
31. Lang M, Yu J, Wang X, et al. Immunochemotherapeutic increase of peripheral absolute monocyte count predicts interstitial pneumonia in lymphoma patients. *Hematol Oncol*. 2018;36(5): 779-785.
32. Kanai O, Kim YH, Demura Y, et al. Efficacy and safety of nivolumab in non-small cell lung cancer with preexisting interstitial lung disease. *Thorac Cancer*. 2018;9(7):847-855.
33. Marianna C, Paula M, Nicola S, et al. Investigation of a patient reported outcome tool to assess radiotherapy-related toxicity prospectively in patients with lung cancer. *Radiother Oncol*. 2014; 112(2):244-249.
34. Suh KJ, Kim SH, Kim YJ, et al. Post-treatment neutrophil-to-lymphocyte ratio at week 6 is prognostic in patients with advanced non-small cell lung cancers treated with anti-PD-1 antibody. *Cancer Immunol Immunother*. 2018;67(3):459-470.
35. Tan CS, Read JA, Phan VH, Beale PJ, Peat JK, Clarke SJ. The relationship between nutritional status, inflammatory markers and survival in patients with advanced cancer: a prospective cohort study. *Support Care Cancer*. 2015;23(2):385-391.
36. Cantor JR, Sabatini DM. Cancer cell metabolism: one hallmark, many faces. *Cancer Discov*. 2012;2(10):881-898.
37. Swiercz R, Mo M, Khare P, Schneider Z, Ober RJ, Ward ES. Loss of expression of the recycling receptor, FcRn, promotes tumor cell growth by increasing albumin consumption. *Oncotarget*. 2017;8(2):3528-3541.
38. Dalloneau E, Baroukh N, Mavridis K, et al. Downregulation of the neonatal Fc receptor expression in non-small cell lung cancer tissue is associated with a poor prognosis. *Oncotarget*. 2016; 7(34):54415-54429.

39. Freiberger T, Grodecka L, Ravcukova B, et al. Association of FcRn expression with lung abnormalities and IVIG catabolism in patients with common variable immunodeficiency. *Clin Immunol*. 2010;136(3):419-425.
40. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. *JAMA Oncol*. 2016;2(12):1607-1616.
41. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35(7):709-717.
42. Zhang J, Cai J, Bello A, Roy A, Sheng J. Model-based population pharmacokinetic analysis of nivolumab in Chinese patients with previously treated advanced solid tumors, including non-small cell lung cancer. *J Clin Pharmacol*. 2019;59(10): 1415-1424.