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ORIGINAL ARTICLE

Neutrophil-to-lymphocyte ratio after four weeks of nivolumab administration as a predictive marker in patients with pretreated non-small-cell lung cancer

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Keywords
Immunological and nutritional status; neutrophil-to-lymphocyte ratio (NLR); nivolumab; non-small-cell lung cancer; predictive marker.

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Abstract

Background: Although phase III trials have shown improved overall and progression-free survival (PFS) using nivolumab compared to docetaxel in patients with non-small-cell lung cancer, the progressive disease ratio of nivolumab is higher than docetaxel. Furthermore, nonconventional response patterns of nivolumab make it difficult to determine the time point for nivolumab discontinuation. Therefore, a method to detect non-responders to nivolumab at an early time point is crucial. This retrospective study was conducted to identify immunological and nutritional markers, including neutrophil-to-lymphocyte ratios (NLR), which would predict the efficacy of nivolumab treatment. Because the expression of these markers fluctuates dramatically during treatment, repeat evaluation was performed.

Methods: We retrospectively investigated 30 patients with non-small-cell lung cancer who were treated with nivolumab. The stratified data of each marker obtained during four weeks after nivolumab treatment were evaluated by Cox proportional hazards regression to verify the differences in PFS.

Results: One and four patients experienced progressive disease within two and four weeks, respectively. Therefore, 29 and 26 patients were analyzed two and four weeks after nivolumab administration, respectively. The results showed that the NLR after four weeks could predict PFS. The median PFS in 21 patients with NLR < 5 after four weeks of nivolumab administration was 95 days (95% confidence interval [CI] 50–NA), while the mPFS in five patients with NLR ≥ 5 was 10 days (95% CI 6–NA). NLR ≥ 5 showed a hazard ratio of 5.995 (95% CI 1.225–29.35).

Conclusion: Clarifying NLR four weeks after nivolumab administration may be useful to predict outcomes in nivolumab-treated patients.

Introduction

Immune-checkpoint inhibitors (ICIs) have drastically altered the treatment framework of non-small-cell lung cancer (NSCLC), and nivolumab was the first ICI approved by the US Food and Drug Administration. Two phase III randomized controlled trials (CheckMate-017 and CheckMate-057 trials in squamous-cell NSCLC [SqCC] and non-squamous NSCLC [non-Sq NSCLC] patients, respectively) demonstrated improved overall survival (OS) and progression-free survival (PFS) using nivolumab compared to the former standard second-line treatment of docetaxel.[1,2] When comparing the survival advantage, the progressive disease (PD) ratios for nivolumab were higher than docetaxel in both SqCC (41% vs. 35%, respectively) and non-Sq NSCLC (44% vs. 29%, respectively). Furthermore, for non-Sq NSCLC, the Kaplan–Meier curve for nivolumab shows a temporal drop below docetaxel during the first six months, suggesting the existence of a subpopulation that does not benefit from nivolumab treatment.[2]

PD-1 is a co-inhibitory receptor that is expressed on the surface of inactivated T lymphocytes, activated cytotoxic T lymphocytes, and B lymphocytes. Although PD-L1 and

PD-L2 are ligands that are expressed on the surface of antigen-presenting cells, only PD-L1 is expressed on tumor cells.[3,4] In addition to its association with immune tolerance, PD-1 is able to escape from the immune surveillance system[5,6] and is mainly activated by co-stimulation through PD-L1 and PD-L2.[7,8] Upregulation of PD-L1 expression is considered to be a predictive marker for the administration of nivolumab for pretreated non-Sq NSCLC,[9] as well as pembrolizumab for both first and second-line treatment of NSCLC.[10,11] However, PD-L1 expression is not a definitive marker, and many studies have been conducted to assess other markers to predict outcomes for the administration of ICIs. Furthermore, nonconventional response patterns of ICIs,[1] including pseudoprogression, make it difficult to determine the PD and time point to discontinue ICIs. Considering the high PD ratio and nonconventional response patterns of ICIs, a method to detect non-responders to ICIs (e.g. nivolumab) at an early time point is crucial.

Although assessing the aggressiveness of cancer based on genetics is important, determination of local host–tumor interaction is also vital to cancer treatment because of its effects on the immunological and nutritional status of cancer patients. This interaction fluctuates greatly based on treatment status, including surgery, radiotherapy, and chemotherapy.[12] Candidate markers have been developed to predict disease progression and prognosis in patients with several kinds of cancers, such as the Glasgow prognostic score (GPS) or modified GPS (mGPS),[13–18] C-reactive protein (CRP)-albumin ratio (CAR),[19–22] pretreatment neutrophil-to-lymphocyte ratio (NLR),[23–28] platelet-lymphocyte ratio (PLR),[29–31] and prognostic nutrition index (PNI).[32,33] The pretreatment advanced lung cancer inflammation index (ALI) has also been postulated to predict treatment efficacy in patients with NSCLC.[34,35] Because these immunological and nutritional markers are known to change dynamically during treatment, they should be evaluated repeatedly. Furthermore, they may be important to predict treatment efficacy.

We retrospectively investigated the relationship between the observed outcomes of nivolumab treatment (PFS) and the immunological and nutritional markers during the time course of nivolumab treatment, which were assessed at first administration and two and four weeks after treatment commenced.

Methods

Patients

A retrospective study was conducted of patients with pretreated NSCLC administered nivolumab treatment (3 mg/kg every two weeks) at our hospital. Thirty consecutive patients were enrolled between January 2016 and October 2017. The data collected from electrical medical records included: patient demographics, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS) at the time of introduction, histology, previous treatment regimens, response to prior treatment, and sites of disease progression from prior treatment. Oncogenic driver mutation profiles including *EGFR* mutations, *ALK* rearrangements, and *ROS1* proto-oncogene receptor tyrosine kinase rearrangements, as well as PD-L1 expression status were collected when available. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Uji-Tokushukai Medical Center (approval date: 29 September 2017; approval number, TGE00856-007). Written informed consent was not required because of the retrospective nature of the study and assured anonymity.

Treatment assessment

Anti-tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. RECIST evaluation was conducted by chest X-ray and computed tomography (CT), and the treating physicians and radiologists assessed disease progression. The continuation of nivolumab was allowed at the time of RECIST-PD considering the nonconventional response of ICIs, and was reassessed by CT within one month.

Adverse events were evaluated by Common Terminology Criteria in Adverse Events (CTCAE) version 4.0.

Definitions of variables and subpopulations

The following markers reflecting the immunological and nutritional status of the host were investigated: mGPS, CAR, NLR, PLR, PNI, and ALI. The mGPS was constructed as a combination of CRP and albumin. Patients with CRP ≤ 1 mg/dL were allocated a score of 0, elevated CRP (>1 mg/dL) a score of 1, and those with both elevated CRP and hypoalbuminemia (<3.5 g/dL) were allocated a score of 2. The CAR was calculated as the ratio of CRP (mg/dL) to albumin (g/dL), and the cutoff value was set at <0.424 or ≥0.424. The NLR is the ratio of absolute neutrophil count/μl to absolute lymphocyte count/μl, and the cutoff value was set at < 5 or ≥5. The PLR was calculated as the ratio of the absolute platelet count/μL to absolute lymphocyte count/μL, and the cutoff values were set at <150, 150–300, and >300. The PNI was calculated using the formula 10 × albumin (g/dL) + 0.005 × absolute lymphocyte count/μL, and the cutoff value was set at < 40 or ≥40. The ALI was calculated using the formula of body mass index at each time point × albumin (g/dL) divided by the NLR,

and the cutoff value was set at <18 or ≥18. The cutoff values were set based on previous reports.

These markers were reassessed two and four weeks after the first cycle of nivolumab. After grouping the cohort by mGPS, CAR, NLR, PLR, and PNI using the abovementioned cutoff values, the PFS in each subgroup was analyzed during the time course of nivolumab treatment in order to clarify whether these markers were associated with PFS.

Evaluation of each marker during treatment

The abovementioned markers were retrospectively evaluated in each subpopulation at three time points: the initial administration of nivolumab, and two and four weeks later. When disease progression was observed within two or four weeks, subjects were excluded from further analysis.

Statistical analysis

All statistical analyses were performed using EZR, a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).[36] The median PFS (mPFS) with 95% confidence interval (CI) and the objective response rate (ORR) were calculated, and PFS curves were generated according to the Kaplan–Meier method. The stratified data of each marker related to mPFS were evaluated by Cox proportional hazards regression analysis. The Kaplan–Meier curves of PFS were assessed and compared between subpopulations.

Results

Baseline patient characteristics

The baseline characteristics of the patients are listed in Table 1. The median age was 71 years (range: 54–83); 11 patients were female and 19 were male; 24 patients had ECOG PS scores of 0–1 and 6 had scores of 2–3; 26 patients were current or former smokers, while 4 were never smokers; and 21 patients had adenocarcinoma (without any driver oncogenes, except for one *EGFR* mutant patient) and 9 patients had squamous cell carcinoma. Nivolumab was administered as second-line treatment in 8 patients, third-line in 9, fourth-line in 5, fifth-line in 6, sixth-line in 1, and ninth-line in 1. Only one patient had a preexisting autoimmune disease (rheumatoid arthritis). PD-L1 status was obtained in 17 out of 30 patients. PD-L1 expression was <1% in seven patients, 1–49% in 3, and ≥50% in 7.

Table 1 Baseline patient characteristics (n = 30)

Characteristics	N (%)
Age (years)	
Median	71
Range	54–83
Gender	
Female	11 (36.7)
Male	19 (63.3)
ECOG PS	
0	6 (20.0)
1	18 (60.0)
2	3 (10.0)
3	3 (10.0)
4	0 (0.0)
Smoking history	
Never smokers	4 (13.3)
Former smokers	17 (56.7)
Current smokers	9 (30.0)
PD-L1 expression (n = 17)	
<1%	7 (41.2)
1–49%	3 (17.6)
≥50%	7 (41.2)
Histology	
Adenocarcinoma	21 (70.0)
Squamous cell carcinoma	9 (30.0)
Number of prior therapies	
1	8 (26.7)
2	9 (30.0)
3	5 (16.7)
4	6 (20.0)
5	1 (3.3)
8	1 (3.3)
Modified GPS score	
0	15 (50.0)
1	5 (16.7)
2	10 (33.3)
CAR	
<0.424	18 (60.0)
≥0.424	12 (40.0)
NLR	
<5	21 (70.0)
≥5	9 (30.0)
PLR	
<150	9 (30.0)
150–300	13 (43.3)
>300	8 (26.7)
PNI	
≤40	12 (40.0)
>40	18 (60.0)
ALI	
<18	13 (43.3)
≥18	17 (56.7)

ALI, advanced lung cancer inflammation index; CAR, C-reactive protein-albumin ratio; ECOG, Eastern Cooperative Oncology Group; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutrition index; PS, performance status.

Table 2 PFS and objective response (overall, n = 30)

Median PFS (days, 95% CI) 81.0 days (41.0–151.0)	
Response	
Partial response (n, %)	9 (30.0%)
Stable disease (n, %)	11 (36.7%)
Progressive disease (n, %)	8 (26.7%)
Not evaluable (n, %)	2 (6.6%)

CI, confidence interval; PFS, progression-free survival.

Progression-free survival (PFS) in the overall population

Progression-free survival rates are shown in Table 2 and Fig 1. The mPFS of the 30 patients was 81 days (95% CI 41–151). Of these patients, a partial response (PR) was observed in 9 (30.0%), stable disease (SD) in 11 (36.7%), progressive disease (PD) in 8 (26.7%), and the results could not be evaluated (NE) in 2 patients (6.6%).

PFS and objective response rate in subpopulations assessed at initial nivolumab administration

There were no significant differences in PFS in the subpopulations at the time of initial nivolumab administration. The mPFS in 15 patients with an mGPS score of 0 was 81.0 days (95% CI 36.0–125.0), in 5 patients with a score of 1 was 126.0 days (95% CI 25.0–NA [not applicable]), and in 10 patients with a score of 2 was 109.5 days (95% CI 13.0–NA). The mPFS in 18 patients with CAR < 0.424 was 82.0 days (95% CI 42.0–151.0) and in 12 patients with CAR ≥ 0.424 was 47.0 days (95% CI 25.0–NA). The mPFS in 21 patients with NLR < 5 was 82.0 days (95% CI 42.0–166.0) and in 9 patients with NLR ≥ 5 was 40.0 days (95% CI 13.0–208.0). The mPFS in 9 patients with PLR < 150, 13 with PLR 150–300, and 8 with PLR > 300 was 95.0 (95% CI 26.0–NA), 54.0 (95% CI 36.0–151.0), and 89.0 (95% CI 19.0–NA) days, respectively. The mPFS in 18 patients with PNI > 40 was 81.0 days (95% CI 41.0–126.0) and in 12 patients with PNI ≤ 40 was 89.0 days (95% CI 26.0–NA). The mPFS in 13 patients with ALI < 18 was 41.0 days (95% CI 25.0–166.0) and 17 patients with ALI ≥ 18 was 82.0 days (95% CI 42.0–151.0).

The hazard ratios (HR) and P values of each parameter assessed by Cox proportional hazards regression analysis were not statistically significant. The HRs and P values were: 0.5175 (95% CI 0.2024–1.323) and 0.1689 for mGPS; 1.0750 (95% CI 0.1892–6.112) and 0.9346 for CAR; 1.226 (95% CI 0.3090–4.867) and 0.7717 for NLR; 0.8617 (95% CI 0.3892–1.908) and 0.7136 for PLR; 1.563 (95% CI 0.4677–5.222) and 0.4683 for PNI; and 0.2393 (95% CI 0.03107–1.843) and 0.1698 for ALI.

PFS in subpopulations assessed two weeks after nivolumab administration

As disease progression was observed in 1 patient within 2 weeks, 29 patients were analyzed.

There were no significant differences in PFS in any subpopulations assessed two weeks after nivolumab administration. The mPFS in 12 patients with an mGPS score of 0 was 66.0 days (95% CI 21.0–136.0), in 5 with a score of 1 was 111.0 days (95% CI 24.0–NA), and in 12 patients with a score of 2 was 74.0 days (95% CI 10.0–193.0). The mPFS in 13 patients with CAR < 0.424 was 67.0 days (95% CI 25.0–NA) and in 16 with CAR ≥ 0.424 was 74.5 days (95% CI 24.0–193.0). The mPFS in 21 patients with NLR < 5 was 67.0 days (95% CI 27.0–111.0) and in 8 with NLR ≥ 5 was 109.0 days (95% CI 4.0–NA). The mPFS in 13 patients with PLR < 150, 11 with PLR 150–300, and 5 with PLR > 300 was 66.0 (95% CI 24.0–111.0), 39.0 (95% CI 24.0–NA), and 110.0 (95% CI 4.0–NA) days, respectively. The mPFS in 16 patients with PNI > 40 was 80.0 days (95% CI 27.0–151.0) and in 13 with PNI ≤ 40 was 38.0 days (95% CI 11.0–193.0). The mPFS in 14 patients with ALI < 18 was 88.0 days (95% CI 24.0–193.0) and in 15 with ALI ≥ 18 was 67.0 days (95% CI 24.0–136.0).

The HRs and P values of each parameter assessed by Cox proportional hazards regression analysis were not statistically significant. The HRs and P values were: 0.7473 (95% CI 0.1265–4.413) and 0.7478 for mGPS; 2.487 (95% CI 0.2094–29.53) and 0.4705 for CAR; 0.6647 (95% CI 0.1837–2.406) and 0.5537 for NLR; 0.5337 (95% CI

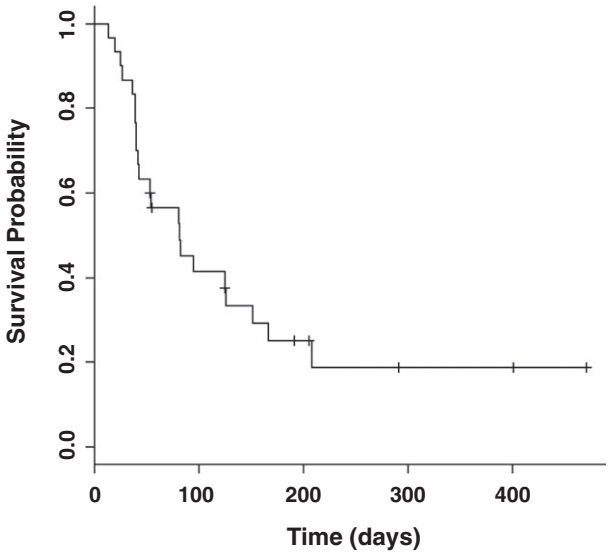

Figure 1 Kaplan–Meier plot of progression-free survival (PFS).The median PFS was 81 days (95% confidence interval 41–151), and durable responses longer than nine months were observed in 20%.

Table 3 Median PFS in each subpopulation assessed four weeks after nivolumab administration (n = 26)

Subpopulation	N	mPFS (days, 95% CI)
Modified GPS score		
0	10	65.0 (6.0–136.0)
1	7	96.0 (9.0–NA)
2	9	23.0 (9.0–NA)
CAR		
<0.424	13	65.0 (12.0–136.0)
≥0.424	13	52.0 (10.0–NA)
NLR		
<5	21	95.0 (50.0–NA)
≥5	5	10.0 (6.0–NA)
PLR		
<150	13	65.0 (24.0–NA)
150–300	9	12.0 (6.0–136.0)
>300	4	100.5 (10.0–NA)
PNI		
≤40	8	65.0 (24.0–121.0)
>40	18	100.5 (9.0–NA)
ALI		
<18	11	23.0 (9.0–178.0)
≥18	15	95.0 (24.0–NA)

ALI, advanced lung cancer inflammation index; CAR, C-reactive protein-albumin ratio; CI, confidence interval; GPS, Glasgow prognostic score; NA, not applicable; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutrition index; mPFS, median progression-free survival.

0.2015–1.414) and 0.2065 for PLR; 0.1988 (95% CI 0.03654–1.081) and 0.06154 for PNI; and 2.012 (95% CI 0.3831–10.57) and 0.4087 for ALI.

PFS in subpopulations assessed four weeks after nivolumab administration

As disease progression was observed in 4 patients within four weeks, 26 patients were analyzed. Table 3 shows the mPFS results after four weeks.

There were significant differences between the subpopulation when predicting longer PFS in NLR < 5 at four weeks after nivolumab administration (P = 0.00683). The mPFS in 21 patients with NLR < 5 after four weeks was 95.0 days (95% CI 50.0–NA) and in 5 patients with NLR ≥ 5 was 10.0 days (95% CI 6.0–NA). NLR ≥ 5 showed a HR of 4.02 (95% CI 1.345–12.02).

The mPFS in 10 patients with a mGPS score of 0 was 65.0 days (95% CI 6.0–136.0), in 7 with a score of 1 was 96.0 days (95% CI 9.0–NA), and in 9 patients with a score of 2 was 23.0 days (95% CI 9.0–NA). The mPFS in 13 patients with CAR < 0.424 was 65.0 days (95% CI 12.0–136.0) and in 13 patients with CAR ≥ 0.424 was 52.0 days (95% CI 10.0–NA). The mPFS in 13 patients with PLR < 150, 9 with PLR 150–300, and 4 with PLR > 300 were 65.0 (95% CI 24.0–NA), 12.0 (95% CI 6.0–136.0), and 100.5 (95% CI 10.0–NA) days, respectively. The mPFS in 18 patients with PNI > 40 was 65.0 days (95% CI 24.0–121.0) and in 8 patients with PNI ≤ 40 was 100.5 days (95% CI 9.0–NA). The mPFS in 11 patients with ALI < 18 was 23.0 days (95% CI 9.0–178.0), and in 15 with ALI ≥ 18 was 95.0 days (95% CI 24.0–NA).

The HRs and P values of each parameter assessed by Cox proportional hazards regression analysis were: 1.675 (95% CI 0.3106–9.030) and 0.5487 for mGPS; 0.2584 (95% CI 0.02608–2.561) and 0.2475 for CAR; 5.995 (95% CI 1.225–29.35) and 0.0271 for NLR; 1.277 (95% CI 0.5135–3.173) and 0.5992 for PLR; 1.835 (95% CI 0.2016–16.70) and 0.5901 for PNI; and 1.103 (95% CI 0.3097–3.931) and 0.8794 for ALI. Thus, the NLR assessed four weeks after nivolumab administration was statistically significant in predicting the treatment effect.

Kaplan–Meier plots of PFS in subpopulations with NLR < 5 compared to NLR ≥ 5 assessed at initial nivolumab introduction and four weeks later are shown in Fig 2. There were no significant differences in PFS between pretreatment NLR < 5 compared to NLR ≥ 5 (Fig 2a). On the other hand, mPFS in a subpopulation with NLR < 5 after four weeks of nivolumab administration was statistically longer than in patients with NLR ≥ 5 (Fig 2b).

Immune-related adverse events

In this study, ir-AEs of any grade were observed in seven patients: hypothyroidism in two patients; and diabetes, adrenal insufficiency, interstitial lung disease, rash acneiform, and allergic reaction in one patient each. All patients with ir-AEs were diagnosed at grade 1 and managed appropriately.

Discussion

The introduction of ICIs has expanded the treatment options for patients with NSCLC. The pronounced efficacy of ICIs in the treatment of NSCLC has been demonstrated in several phase III clinical trials.[1,2,10,11]

However, the PD rate of patients administered nivolumab is relatively high and the Kaplan–Meier curve of nivolumab for non-Sq NSCLC patients temporarily drops below docetaxel during the first six months. Therefore, detailed evaluations at appropriate time points are critical.

PD-L1 expression is reported to correlate with PFS and OS in ICI treatment, as ICIs inhibit the PD-1/PD-L1 pathway.[2,10,11] However, PD-L1 expression is considered to have special and temporal heterogeneity, which is one of the main reasons that PD-L1 expression is not a definitive biomarker for predicting outcomes of ICIs.[37,38] Furthermore, tumor microenvironments are classified into four types based on tumor infiltrating lymphocytes and PD-L1

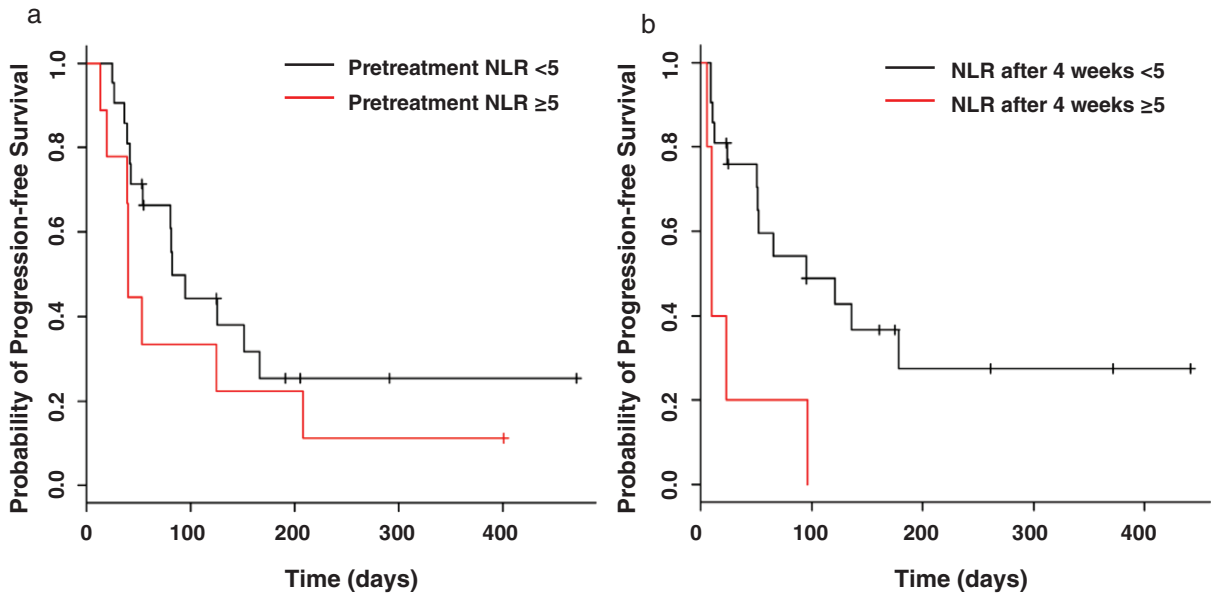

Figure 2 Kaplan–Meier plots of progression-free survival (PFS) in subpopulations with neutrophil-to-lymphocyte ratio (NLR) < 5 compared to NLR ≥ 5 assessed at (**a**) initial administration and (**b**) four weeks later. (**a**) There were no significant differences in PFS between pretreatment NLR < 5 compared to NLR ≥ 5. (**b**) The median PFS (mPFS) in a subpopulation with NLR < 5 after four weeks was statistically longer than NLR ≥ 5 ($P = 0.00683$). The mPFS with NLR < 5 was 95 days (95% confidence interval [CI] 50–not applicable [NA]), while mPFS with NLR ≥ 5 was 10 days (95% CI 6–NA). NLR ≥ 5 showed a hazard ratio of 4.02 (95% CI 1.345–12.02).

expression in which the resistance mechanism to ICIs is partly explained by cancer-associated inflammation.[39] Therefore, the development of other predictive biomarkers associated with inflammation is promising and necessary.

Because cancer-associated inflammation plays an important role in tumor progression, the immunological and nutritional status of the host are crucial.[40,41] They are closely related to each other, reflect host immunity, and affect the tumor microenvironment. Therefore, immunological and nutritional markers may predict outcomes of ICIs that exert actions against inhibitory signals to CD8-positive T lymphocytes in the effector phase.

In cancer immunity, several steps are required to effectively kill cancer cells.[3] Cancer-specific antigens, or neoantigens, are viewed as foreign and result in the priming and activation of effector T lymphocytes. Activated effector T lymphocytes then enter the blood stream and migrate to the tumor bed. Therefore, peripheral blood samples may reflect the immune reaction at the tumor site. Moreover, neoantigen-specific lymphocytes have been detected in peripheral blood samples of melanoma patients whose T-cell receptor repertoires are similar to those found in the tumor.[42] Therefore, we attempted to identify noninvasive predictive markers of ICIs that can be assessed from blood examinations.

Local host–tumor interaction changes dramatically throughout treatment and affects both nutritional and immunological conditions.[12] GPS, CAR, NLR, PLR, PNI, and ALI, which can be obtained from complete blood counts and serum biochemistry profiles, are widely used as nutritional assessment methods. The GPS categorizes patients into three groups using serum CRP and serum albumin and is reported to predict treatment outcomes for several kinds of cancer.[13–18] The CAR, a simpler method than GPS in which serum CRP is categorized by serum albumin, is also reported to be a predictive biomarker.[19–22]

Lymphocytes are closely associated with nutritional status and immunity and possess suppressive effects against tumors.[43,44] However, neutrophils induce pro-inflammatory cytokines and chemokines that lead to tumor proliferation, invasion, and angiogenesis.[45,46] Pretreatment NLR is a nutritional assessment method that uses blood cells that can be complementary to methods employing serum markers, such as GPS and CAR.[23–28]

Platelet levels are also affected in patients with inflammation and poor prognosis; therefore, the PLR may also be a predictive marker in several kinds of cancers.[29–31] From a surgical point of view, nutritional status is important because of its correlation with postoperative complications. The PNI was developed to predict postoperative complications and prognosis.[32,33]

Among these markers, the pretreatment NLR has important associations not only with postoperative outcomes for a variety of cancers, but also with post-treatment outcomes

with ICIs in melanoma and NSCLC.[23–28,47] The NLR is a marker of systemic inflammatory response that reflects the balance between neutrophils the accelerators of tumor progression, and lymphocytes, the crucial players in tumor immunity.[13] The NLR is not static but is a dynamic marker reflecting the host–tumor interaction that comprises the nutritional and metabolic condition of the patient. Therefore, assessment of the NLR is not only important at the beginning of treatment, but repeat assessment during treatment is also necessary.

In contrast to our results, a study with a larger sample size showed that the pretreatment NLR in patients with NSCLC was significantly correlated with the outcome of nivolumab treatment.[28] This discrepancy may be a result of the small sample size used in our study. However, evaluating the NLR multiple times during the time course was reasonable, and the NLR after four weeks provided predictive value in this study.

The post-treatment NLR at week 6 was recently reported to be a prognostic marker in NSCLC treated with anti-PD-1 antibodies.[48] Our results are consistent with this report in that the post-treatment NLR could be a predictive marker. There was no significant difference between the pretreatment NLR and at two weeks in our investigation, but the NLR after four weeks showed a significant correlation. This could mean that post-treatment NLR evaluation should be conducted at four weeks or later. Because our study investigated NSCLC patients treated with nivolumab, it would be interesting to determine whether the NLR at four weeks after ICI treatment is useful in other ICIs. A study with a relatively smaller sample size focusing on the time-series behavior of the NLR during nivolumab treatment showed that an increase in the post-treatment NLR was associated with shorter time to treatment failure.[49] An increased post-treatment NLR was associated with poor outcome, while a stable or decreased NLR predicted a better outcome. Our findings are consistent with this report in that the post-treatment NLR has a stronger relationship with mPFS than the pretreatment NLR. Because we investigated the prognostic biomarkers of nivolumab treatment that reflect immunological and nutritional status during each time point, the time-series behavior of the NLR was not evaluated. Further prospective studies with a larger sample size are needed to elucidate the appropriate prognostic marker of nivolumab: single point evaluation of the NLR or time-series behavior of the NLR.

This study has several limitations. First, this study was retrospective. Second, because of the small sample size, the bias observed in the study population may be different from those of larger populations. Furthermore, the cutoff value for each immunological and nutritional marker was determined according to previous reports that included both early-stage and metastatic cancer. Because immunological and nutritional status changes dynamically during disease progression, reevaluation of the optimal cutoff values for each marker and their adoption would have enriched our results. However, reevaluation of the optimal cutoff value was not conducted because of the small sample size. The optimal cutoff values for each marker and the usefulness of relevant markers should be elucidated through prospective studies with larger sample sizes.

The NLR after four weeks of nivolumab administration may be useful in predicting the outcome of nivolumab in patients with pretreated NSCLC. Considering the high PD ratio and nonconventional response patterns of nivolumab, this may be a promising marker to predict efficacy at an early time point.

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Disclosure

No authors report any conflict of interest.

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