Pretreatment Glasgow prognostic score predicts survival among patients with high PD-L1 expression administered first-line pembrolizumab monotherapy for non-small cell lung cancer

Hisao Imai1,2 | Takayuki Kishikawa3 | Hiroyuki Minemura4 | Yutaka Yamada5 | Tatsuya Ibe6 | Ou Yamaguchi1 | Atsuto Mouri1 | Yoichiro Hamamoto6 | Kenya Kanazawa4 | Takashi Kasai3 | Kyoichi Kaira1 | Takayuki Kaburagi5 | Koichi Minato2 | Kunihiro Kobayashi1 | Hiroshi Kagam1

1Department of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan
2Division of Respiratory Medicine, Gunma Prefectural Cancer Center, Ota, Gunma, Japan
3Division of Thoracic Oncology, Tochigi Cancer Center, Utsunomiya, Tochigi, Japan
4Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan
5Division of Respiratory Medicine, Ibaraki Prefectural Central Hospital, Kasama, Ibaraki, Japan
6Department of Pulmonary Medicine, National Hospital Organization, Nishisaitama-Chuo National Hospital, Tokorozawa, Saitama, Japan

Correspondence
Hisao Imai, Department of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan.
Email: m06701014@gunma-u.ac.jp

Abstract

Background: There are no established biomarkers for predicting the efficacy of first-line pembrolizumab monotherapy in patients with high programmed death-ligand 1 (PD-L1) expression. In this study, we investigated whether the Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and body mass index (BMI) can be used to evaluate the effect of first-line pembrolizumab monotherapy in patients with advanced non-small cell lung cancer (NSCLC) who express high levels of PD-L1.

Methods: We reviewed data from 142 patients with high PD-L1 expression who underwent first-line pembrolizumab monotherapy for NSCLC at six Japanese institutions between February 2017 and June 2019 and assessed the prognostic value of the GPS, NLR, and BMI. The Kaplan–Meier method and Cox proportional hazard models were used to examine differences in progression-free survival (PFS) and overall survival (OS). The GPS, NLR, and BMI were calculated using C-reactive protein and albumin concentrations, neutrophil and lymphocyte counts, and body weight and height, respectively.

Results: The GPS independently predicted the first-line pembrolizumab monotherapy efficacy, as a good GPS (GPS 0–1) was associated with a significantly better PFS and OS compared to a poor GPS (GPS 2) (PFS: 11.8 vs. 2.9 months, p < 0.0001; OS: not reached vs. 8.3 months, p < 0.0001). Furthermore, BMI independently predicted efficacy, as patients with high BMI (BMI ≥21.4) exhibited significantly better OS compared to those with low BMI (BMI <21.4) (OS: not reached vs. 14.1 months, p = 0.006).
1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths globally, and non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. A previous open-label phase III trial revealed that pembrolizumab monotherapy is an effective first-line treatment for patients with NSCLC with high programmed death-ligand 1 (PD-L1) expression (≥50% of tumor cells). Thus, pembrolizumab monotherapy is now considered a standard first-line treatment for patients with high PD-L1 expression and with no contraindications to immune checkpoint inhibitors (ICIs).

Most patients with NSCLC are diagnosed at an advanced stage, and these patients frequently experience weight loss and a systemic inflammatory response (SIR), which influences cancer cachexia. Thus, cancer-related prognosis is examined using various SIR-based scoring systems, such as the Glasgow prognostic score (GPS) and neutrophil-to-lymphocyte ratio (NLR). The GPS is a SIR-based scoring system that comprises serum C-reactive protein (CRP) and albumin concentrations. The GPS is an independent prognostic marker for advanced NSCLC.

Although several studies have reported on the relationship between the GPS and ICI treatment efficacy in NSCLC for different lines of treatment, various ICIs, and various levels of PD-L1 expression, no studies have evaluated the relationship between the GPS and the efficacy of first-line pembrolizumab monotherapy for NSCLC in patients with high PD-L1 expression. SIR-based markers can predict the response to ICIs, with NLR predicting the response to ICIs in melanoma, renal cell carcinoma, and NSCLC. Additionally, body mass index (BMI) has been reported as a prognostic marker for various malignancies. The presence of sarcopenia was negatively associated with outcomes in patients with NSCLC receiving ICI. Additionally, BMI is associated with ICI treatment outcomes in solid tumors, including melanoma, renal cell cancer, and NSCLC. However, there is limited data regarding the relationship between the GPS, NLR, and BMI and response to first-line pembrolizumab monotherapy for NSCLC with high PD-L1 expression. A recent study reported a relationship between BMI and the effect of ICIs in NSCLC. When a BMI cutoff value of 22 kg/m² was used, no significant difference was observed in the progression-free survival (PFS) or overall survival (OS) between high- and low-BMI groups among patients with NSCLC with high PD-L1 expression (≥50%) who were treated with pembrolizumab as a first-line therapy. However, in patients with NSCLC treated with nivolumab/pembrolizumab/atezolizumab as a second- or later-line treatment, survival was significantly longer in patients with a high BMI versus those with a low BMI. Thus, the relationship between BMI and the efficacy of ICIs in NSCLC is unclear. Therefore, in the current study, we assessed whether the GPS, NLR, and BMI could predict the response to first-line pembrolizumab monotherapy in patients with NSCLC and high PD-L1 expression.

2 | METHODS

2.1 | Patients

This retrospective study assessed the clinical effects of first-line pembrolizumab monotherapy in 144 patients with NSCLC and high PD-L1 expression at six Japanese institutions between February 2017 and June 2019. Among them, pretreatment albumin and CRP values were missing in two patients. Thus, 142 patients were included in the analysis. The NSCLC was histologically classified using the 2015 World Health Organization system and staged using version 8 of the Tumor–Node–Metastasis staging system. The eligibility criteria were as follows: (1) histologically or cytologically confirmed NSCLC, (2) unresectable stage III/IV disease or postoperative recurrence, and (3) high PD-L1 expression (≥50% of tumor cells). The patients received first-line treatment with pembrolizumab
monotherapy (200 mg), and a confirmation of a censored event or death was made for each patient. Pretreatment Tumor–Node–Metastasis staging was based on physical examination, chest radiography, thoracic and abdominal computed tomography, brain computed tomography or magnetic resonance imaging, and bone scintigraphy or 18F-fluorodeoxyglucose positron emission tomography. We reviewed the patient charts to collect data regarding baseline characteristics and response to first-line pembrolizumab monotherapy. The study design was approved by the Institutional Review Board of each participating institution. The requirement for informed consent was waived owing to the retrospective nature of the study.

### 2.2 Assessment of PD-L1 expression

PD-L1 expression in formalin-fixed tumor specimens was evaluated using a commercially available immunohistochemistry kit for detecting PD-L1 (22C3 pharmDx assay; Dako North America). Biopsy specimens from the time of lung cancer diagnosis or from the time of initiation of pembrolizumab monotherapy were collected from the institutional archives. PD-L1 expression (membranous staining) was quantified as the proportion of positive cells among the tumor cells and tumor-infiltrating immune cells.

### 2.3 Treatment

The patients included in the study had not previously received ICI therapy; they received first-line treatment with pembrolizumab monotherapy (200 mg intravenously once every 3 weeks), which was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

### 2.4 Assessment of treatment efficacy

Serum CRP and albumin levels as well as neutrophil and lymphocyte counts were measured at treatment initiation. Blood samples were usually collected on the day before pembrolizumab administration or on the day of administration. The GPS values were defined as: a GPS of 0 (CRP <1.0 mg/dl and albumin >3.5 mg/dl), a GPS of 1 (CRP ≥1.0 mg/dl or albumin <3.5 mg/dl), or a GPS of 2 (CRP ≥1.0 mg/dl and albumin <3.5 mg/dl). NLR was defined as the ratio of absolute neutrophil and absolute lymphocyte counts; the NLR cut-off value was set at 5. BMI, which was determined at treatment initiation, was defined as the weight (kg) divided by the height (m) squared. The patients were stratified into BMI groups, as defined by the receiver operating characteristic (ROC) curve: low-weight group (BMI <21.4 kg/m²) and high-weight group (BMI ≥21.4 kg/m²). The optimal cut-off value that differentiated high BMI from low BMI, as determined by the ROC curve analysis for PFS, was 21.4 (AUC: 0.578; sensitivity: 68.2%; specificity: 48.5%).

Tumor response was quantified as the best overall response and maximum tumor shrinkage. Radiological tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1): disappearance of all target lesions (complete response [CR]); a ≥30% decrease in the sum of the target lesion diameters relative to the baseline (partial response [PR]), a ≥20% increase in the sum of the target lesion diameters relative to the smallest value during the study period (progressive disease [PD]), and insufficient shrinkage for being qualified as PR and insufficient growth for being qualified as PD (stable disease [SD]). The PFS interval was calculated from the start of pembrolizumab monotherapy until the first instance of PD or death from any cause. The OS interval was calculated from the start of pembrolizumab monotherapy until the first instance of death or censoring at the last follow-up.

### 2.5 Statistical analyses

Categorical and continuous variables were analyzed using Fisher’s exact test and Welch’s t-test, respectively. A Cox proportional hazards model with stepwise regression was used to identify factors that predicted PFS and OS, and the results were described as hazard ratios (HRs) and 95% confidence intervals (CIs). PFS and OS were compared using the log-rank test. Differences were considered statistically significant at a two-tailed \( p \leq 0.05 \). All analyses were conducted using the JMP software for Windows, version 11.0 (SAS Institute).

### 3 RESULTS

#### 3.1 Patient characteristics and treatment efficacy

Table 1 presents the characteristics of the 142 patients who received pembrolizumab monotherapy; they included 117 men (82.4%) and 25 women (17.6%), with a median age of 70 years (range, 47–86 years). The Eastern Cooperative Oncology Group (ECOG)-performance status (PS) scores were 0–1 for 110 patients (77.4%) and 2–3 for 32 patients (22.6%). Adenocarcinoma was observed in 75 of the 142 patients (52.8%). A total of 123 patients (86.6%) had stage III–IV disease. Nineteen patients (13.4%) experienced
postoperative recurrence. All patients presented high PD-L1 expression (≥50% of the tumor cells). The driver gene mutation/translocation status of the patients was wild type, negative, or unknown. The median number of pembrolizumab cycles was five (range, 1–55), and the responses to treatment among all patients were classified as CR (n = 1), PR (n = 60), SD (n = 44), and PD (n = 25). The overall response rate was 42.9% (95% CI: 34.8–51.0), and the disease control rate was 73.9% (95% CI: 66.7–81.1).

### 3.2 Comparison of the GPS, NLR, and BMI

Table 2 presents the patient characteristics according to the GPS, NLR, and BMI. The GPS values at the initiation of pembrolizumab monotherapy were 0–1 (85 patients) and 2 (57 patients). The ECOG-PS, clinical stage at diagnosis, liver metastases, bone metastases, and response rate showed statistically significant differences (p < 0.05) with the GPS values. The NLR values at the initiation of pembrolizumab monotherapy were low (86 patients) and high (56 patients). The ECOG-PS, liver metastases, bone metastases, prior radiotherapy, and disease control rate showed statistically significant differences (p < 0.05) with the NLR values. The BMI at the initiation of pembrolizumab monotherapy was low (90 patients) and high (52 patients). The administration cycles of pembrolizumab, response rate, and number of lymphocytes exhibited statistically significantly differences (p < 0.05) with the BMI.

### 3.3 Survival analysis

Over a median follow-up period of 15.7 (range, 0.1–39.6) months, the median PFS interval was 7.1 months (95% CI 5.6–10.6) (Figure 1A) and the median OS interval was 17.4 months (95% CI 12.4–31.3) (Figure 1B). Among the 142 patients, 78 died and 64 were alive at the data cut-off date of June 30, 2020. Table 3 shows the results of univariate and multivariate analyses of PFS and OS. Univariate analyses of PFS showed significant correlations with the ECOG-PS, prior radiotherapy, the GPS, and NLR. Multivariate analyses showed that PFS was correlated with prior radiotherapy (HR: 1.57, p = 0.03) and a GPS of 0–1 (HR: 0.40, p = 0.0002). Furthermore, univariate analyses of OS demonstrated significant correlations with the ECOG-PS, GPS, NLR, and BMI. Multivariate analyses revealed that OS was associated with a GPS of 0–1/2 (HR: 0.42, p = 0.001) and low BMI/high BMI (HR 1.99, p = 0.005). Figure 2 presents the Kaplan–Meier curves for PFS and OS, according to the GPS, NLR, and BMI; a GPS of 0–1 was correlated with significantly longer PFS and OS than a GPS of 2 (both, p < 0.05; Figure 2A,B). Low NLR was correlated with significantly longer PFS and OS than high NLR (both p < 0.05, Figure 2C,D). Although high

### Table 1 Patient characteristics

| Variables                                      | All patients |
|------------------------------------------------|--------------|
| Patients (n)                                   | 142          |
| Characteristics                                |              |
| Gender                                         |              |
| Male/female                                    | 117/25       |
| Median age at treatment (years) [range]        | 70 (47–86)   |
| PS                                             |              |
| 0/1/2/3/4                                      | 48/62/23/9/0 |
| Smoking history                                |              |
| Yes/No                                         | 130/12       |
| Histology                                      |              |
| Adenocarcinoma/Squamous cell carcinoma/other   | 75/40/27     |
| Clinical stage at diagnosis                    |              |
| III/IV/postoperative recurrence                | 18/105/19    |
| PD-L1 TPS (%)                                  |              |
| 50–89/90–100                                   | 85/57        |
| Driver mutation/translocation                   |              |
| EGFR/ALK/WT, negative, unknown                 | 0/0/142      |
| Intracranial metastases at initial treatment   |              |
| Yes/No                                         | 34/108       |
| Liver metastases at initial treatment          |              |
| Yes/No                                         | 11/131       |
| Bone metastases at initial treatment           |              |
| Yes/No                                         | 44/98        |
| BMI (kg/m²)                                    |              |
| Median (range)                                 | 20.3 (14.1–31.7) |
| Prior radiotherapy                             |              |
| Yes/No                                         | 45/97        |
| Administration cycles of pembrolizumab         |              |
| Median (range)                                 | 5 (1–55)     |
| Tumor response                                 |              |
| Complete response                              | 1            |
| Partial response                               | 60           |
| Stable disease                                 | 44           |
| Progressive disease                            | 25           |
| Not evaluated                                  | 12           |
| Response rate (%) (95% CI)                     | 42.9 (34.8–51.0) |
| Disease control rate (%) (95% CI)              | 73.9 (66.7–81.1) |
| Laboratory data (median)                       |              |
| CRP (mg/dl)                                    | 1.23         |
| Albumin (g/dl)                                 | 3.5          |
| Neutrophil (cells/μl)                          | 5395         |
| Lymphocyte (cells/μl)                          | 1285         |

Abbreviations: ALK, anaplastic lymphoma kinase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; PS, performance status; TPS, tumor proportion score; WT, wild type.
| Variables                                | GPS | NLR | BMI |
|------------------------------------------|-----|-----|-----|
|                                          | 0–1 | 2   |     |
| Patients (n)                             | 85  | 57  |     |
| Characteristics                          |     |     |     |
| Gender                                   |     |     |     |
| Male/female                              | 68/17 | 49/8 | 0.50 |
| Median age at treatment (years) [range]  | 70 (48–85) | 70 (47–86) | 0.71^a |
| PS                                       |     |     |     |
| 0–1/≥2                                   | 78/7 | 32/25 | <0.0001 |
| Smoking history                          |     |     |     |
| Yes/No                                   | 76/9 | 54/3 | 0.36 |
| Histology                                |     |     |     |
| Adenocarcinoma/ non-adenocarcinoma       | 48/37 | 27/30 | 0.3 |
| Clinical stage at diagnosis              |     |     |     |
| III–IV/postoperative recurrence          | 69/16 | 54/3 | 0.02 |
| PD-L1 TPS (%)                            |     |     |     |
| 50–89/90–100                             | 50/35 | 35/22 | 0.86 |
| Driver mutation/translocation            |     |     |     |
| EGFR/ALK/WT, negative, unknown           | 0/0/85 | 0/0/57 | - |
| Intracranial metastases at initial treatment |     |     |     |
| Yes/No                                   | 21/64 | 13/44 | 0.84 |
| Liver metastases at initial treatment    |     |     |     |
| Yes/No                                   | 3/82 | 8/49 | 0.02 |
| Bone metastases at initial treatment     |     |     |     |
| Yes/No                                   | 17/68 | 27/30 | 0.0008 |
| BMI (kg/m^2)                             |     |     |     |
| Median (range)                           | 20.4 (14.1–28.4) | 20.0 (16.0–31.7) | 0.46^a |

(Continues)
| Variables                                | GPS   | NLR   | BMI   |
|------------------------------------------|-------|-------|-------|
|                                            | 0–1   | 2     | Low (<5) | High (≥5) | p-value | Low (<21.4) | High (≥21.4) | p-value |
| Prior radiotherapy                       |       |       |       |           |         |       |       |         |
| Yes/No                                   | 28/57 | 17/40 | 21/65 | 24/32 | 0.02    | 28/62 | 17/35 | 0.85    |
| Administration cycles of pembrolizumab   |       |       |       |           |         |       |       |         |
| Median (range)                           | 8 (1–55) | 2 (1–31) | 7.5 (1–55) | 3 (1–36) | 0.21a | 4 (1–34) | 8 (1–55) | 0.0082a |
| Tumor response                           |       |       |       |           |         |       |       |         |
| Complete response                        | 1     | 0     | 1     | 0     | 0     | 1     | 0     | 1     |
| Partial response                         | 43    | 17    | 40    | 20    | 0.02  | 29    | 31    |
| Stable disease                           | 24    | 20    | 29    | 15    | 0.85  | 36    | 8     |
| Progressive disease                      | 11    | 14    | 13    | 12    | 0.71  | 18    | 7     |
| Not evaluated                            | 6     | 6     | 3     | 9     | 0.46a | 7     | 5     |
| Response rate (%) (95% CI)               | 51.7  | 29.8  | 47.6  | 35.7  | 0.17  | 32.2  | 61.5  | 0.0008  |
| Disease control rate (%) (95% CI)        | 80.0  | 64.9  | 81.3  | 62.5  | 0.01  | 72.2  | 76.9  | 0.69    |
| Laboratory data                          |       |       |       |           |         |       |       |         |
| CRP (mg/dl)                              | 0.38  | 5     | 0.71  | 2.86  | <0.0001a | 1.2  | 1.7  | 0.23a   |
| Albumin (g/dl)                           | 3.8   | 3     | 3.6   | 3     | <0.0001a | 3.5  | 3.6  | 0.43a   |
| Neutrophil (cells/µl)                    | 4840  | 7187  | 4808  | 6879  | <0.0001a | 5330 | 5469 | 0.45a   |
| Lymphocyte (cells/µl)                    | 1410  | 1073  | 1615  | 863.5 | <0.0001a | 1238 | 1395 | 0.04a   |

*p-values in bold are statistically significant (p < 0.05).

Abbreviations: ALK, anaplastic lymphoma kinase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; EGFR, epidermal growth factor receptor; GPS, Glasgow prognostic score; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death ligand 1; PS, performance status; TPS, tumor proportion score; WT, wild type.

*Welsh’s t-test.
BMI was not associated with longer PFS than low BMI ($p = 0.06$, Figure 2E), high BMI was associated with significantly longer OS than low BMI ($p < 0.05$, Figure 2F).

To further explore factors affecting PFS and OS between patients with a GPS of 0–1 and those with a GPS of 2, we performed a subgroup analysis of the ECOG-PS by the groups 0–1 and 2–3; histology by adenocarcinoma and non-adenocarcinoma; PD-L1 expression by the groups with 50%–89% and 90%–100% expression; NLR by the high- ($\geq 5$) and low- ($< 5$) value groups, BMI by the high- ($\geq 21.4$) and low- ($< 21.4$) BMI groups, and tumor response by PR (CR + PR) and non-PR (SD + PD) (Table S1). The subgroup analysis showed statistically significant differences in both PFS and OS between a GPS of 0–1 and a GPS of 2 in all groups, except in the ECOG-PS 2–3 cohort, high NLR cohort, low BMI cohort, and tumor response PR cohort.

4 | DISCUSSION

The current study evaluated the relationship of the GPS, NLR, and BMI with treatment efficacy among patients with high PD-L1 expression undergoing first-line pembrolizumab monotherapy for NSCLC. Multivariate analyses revealed that the GPS and BMI were independently associated with OS, suggesting that the GPS and BMI may be used to predict the OS among patients with high PD-L1 expression undergoing first-line pembrolizumab monotherapy for NSCLC. To the best of our knowledge, this is the first study to assess the relationship among the GPS, NLR, and BMI and survival among patients with high PD-L1 expression undergoing first-line pembrolizumab monotherapy for NSCLC.

Although ICIs are key drugs for patients with NSCLC with high PD-L1 expression, a subset of patients does not respond to ICIs. In the present study, the group with a GPS of 0–1 presented a significantly higher response rate and disease control rate than the group with a GPS of 2. In addition, the GPS was significantly predictive of both PFS and OS. The GPS has prognostic importance in lung cancer independent of disease stage and conventionally used prognostic markers$^{5-14}$; additionally, it has been reported to correlate with elevated cytokine levels, adipokine levels, drug metabolism, weight and muscle loss, and poor PS$^{4,29-35}$ These factors may be related to the immune status of the host, and they may affect the efficacy of anti-programmed cell death protein 1 (PD-1) therapy. In our analysis, the relationship between patient background and the GPS was significantly related to the ECOG-PS (0–1/$\geq 2$), clinical stage (III–IV/postoperative recurrence), and the presence of metastases such as liver and bone metastases, suggesting that the GPS is affected by these clinical factors. Table 4 summarizes the studies till date that have evaluated the GPS in patients administered anticancer drug therapy for advanced NSCLC. All reports on studies using cytotoxic anticancer drugs, molecularly targeted drugs, and ICIs have indicated the usefulness of the GPS$^{5,6,13,14,36-40}$ However, although certain reports have incorporated first-line pembrolizumab monotherapy, no reports have focused on first-line pembrolizumab monotherapy in patients with high PD-L1 expression. Furthermore, the GPS is calculated from serum CRP and albumin levels, which indicates that these tests are easily used in clinical practice in most institutions. Multivariate analysis revealed that the GPS, but not the ECOG-PS, was independently correlated with PFS and OS (Table 3). There are opinions in favor of the GPS being superior to the ECOG-PS in predicting the prognosis of patients with NSCLC and high PD-L1 expression who receive first-line pembrolizumab monotherapy; however, the GPS and ECOG-PS
### TABLE 3 Univariate and multivariate analyses of PFS and OS

| Variables                                      | Median PFS (months) | Univariate analysis | Multivariate analysis | Median OS (months) | Univariate analysis | Multivariate analysis |
|------------------------------------------------|--------------------|---------------------|-----------------------|--------------------|---------------------|-----------------------|
|                                                 |                    | HR                  | 95% CI                | p-value            | HR                  | 95% CI                | p-value |
| Gender                                          |                    |                     |                       |                    |                     |                       |         |
| Male/female                                     | 7.1/6.9            | 0.86                | 0.54–1.44             | 0.57               |                     |                       |         |
| Age                                             |                    |                     |                       |                    |                     |                       |         |
| <75/≥75                                         | 6.5/7.7            | 1.21                | 0.80–1.89             | 0.36               |                     |                       |         |
| PS                                              |                    |                     |                       |                    |                     |                       |         |
| 0–1/2/3                                         | 9.7/2.9            | 0.56                | 0.36–0.88             | **0.01**           | 0.92                | 0.56–1.56             | 0.77     |
| Smoking history                                 |                    |                     |                       |                    |                     |                       |         |
| Yes/No                                          | 7.0/12.9           | 1.17                | 0.62–2.50             | 0.63               |                     |                       |         |
| Histology                                       |                    |                     |                       |                    |                     |                       |         |
| Adenocarcinoma/non-adenocarcinoma                | 8.5/6.2            | 0.87                | 0.59–1.27             | 0.47               |                     |                       |         |
| Clinical stage at diagnosis                     |                    |                     |                       |                    |                     |                       |         |
| III–IV/postoperative recurrence                 | 7.1/7.1            | 1.4                 | 0.78–2.77             | 0.26               |                     |                       |         |
| PD-L1 TPS (%)                                   |                    |                     |                       |                    |                     |                       |         |
| 50–89/90–100                                    | 7.1/7.5            | 1.01                | 0.68–1.49             | 0.95               |                     |                       |         |
| Intracranial metastases at initial treatment    |                    |                     |                       |                    |                     |                       |         |
| Yes/No                                          | 8.5/7.1            | 0.96                | 0.60–1.48             | 0.86               |                     |                       |         |
| Liver metastases at initial treatment           |                    |                     |                       |                    |                     |                       |         |
| Yes/No                                          | 2.3/7.9            | 1.79                | 0.87–3.28             | 0.1                |                     |                       |         |
| Bone metastases at initial treatment            |                    |                     |                       |                    |                     |                       |         |
| Yes/No                                          | 5.5/9.7            | 1.49                | 0.98–2.20             | 0.05               |                     |                       |         |
| Prior radiotherapy                              |                    |                     |                       |                    |                     |                       |         |
| Yes/No                                          | 5.5/8.5            | 1.6                 | 1.06–2.36             | **0.02**           | 1.57                | 1.02–2.36             | **0.03** |
| GPS                                             |                    |                     |                       |                    |                     |                       |         |
| 0, 1/2                                          | 11.8/2.9           | 0.4                 | 0.27–0.59             | <**0.0001**        | 0.4                 | 0.24–0.64             | **0.0002** |
| NLR                                             |                    |                     |                       |                    |                     |                       |         |
| Low(<5)/high(≥5)                                | 8.6/5.3            | 0.66                | 0.45–0.97             | **0.03**           | 1.13                | 0.71–1.83             | 0.59     |
| BMI (kg/m²)                                     |                    |                     |                       |                    |                     |                       |         |
| Low(<21.4)/high(≥21.4)                          | 6.2/11.5           | 1.45                | 0.97–2.21             | 0.06               |                     |                       |         |

The reference arms are the variables shown in the right-sided arms. *p*-values in bold are statistically significant (*p* < 0.05).

Abbreviations: BMI, body mass index; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death-1; PFS, progression-free survival; PS, performance status; TPS, tumor proportion score.
TABLE 3
Univariate and multivariate analyses of PFS and OS

| Variables                        | Median PFS (months) | HR   | 95% CI        | p-value | Median OS (months) | HR   | 95% CI        | p-value |
|----------------------------------|--------------------|------|---------------|---------|--------------------|------|---------------|---------|
| Gender                           |                    |      |               |         |                    |      |               |         |
| Age ≥ 75                         | 6.5/7.7            | 1.21 | 0.80–1.89    | 0.36    | 20.0/10.8          | 0.82 | 0.51–1.34    | 0.42    |
| Age < 75                         |                    |      |               |         |                    |      |               |         |
| Performance status (PS)          |                    |      |               |         |                    |      |               |         |
| PS 0                             | 0.92               | 0.56–1.56 | 0.77 | 20.9/6.7          | 0.48 | 0.30–0.81    | 0.007   |
| PS 1                             |                    |      |               |         |                    |      |               |         |
| Smoking history                  |                    |      |               |         |                    |      |               |         |
| Yes                              | 7.0/12.9           | 1.17 | 0.62–2.50    | 0.63    | 17.5/18.5          | 1.02 | 0.50–2.45    | 0.94    |
| No                               |                    |      |               |         |                    |      |               |         |
| Histology                        |                    |      |               |         |                    |      |               |         |
| Adenocarcinoma                   | 8.5/6.2            | 0.87 | 0.59–1.27    | 0.47    | 21.1/14.4          | 0.72 | 0.46–1.13    | 0.15    |
| Non-adenocarcinoma               |                    |      |               |         |                    |      |               |         |
| Clinical stage at diagnosis      |                    |      |               |         |                    |      |               |         |
| III–IV                          | 7.1/7.1            | 1.4  | 0.78–2.77    | 0.26    | 17.5/31.3          | 1.09 | 0.59–2.27    | 0.77    |
| Postoperative recurrence         |                    |      |               |         |                    |      |               |         |
| PD-L1 expression                 |                    |      |               |         |                    |      |               |         |
| 50–89                           | 7.1/7.5            | 1.01 | 0.68–1.49    | 0.95    | 17.1/20.0          | 1.1  | 0.70–1.75    | 0.67    |
| 90–100                          |                    |      |               |         |                    |      |               |         |
| NLR                              |                    |      |               |         |                    |      |               |         |
| ≥ 5                              | 8.6/5.3            | 0.66 | 0.45–0.97    | 0.03    | 12.7/21.1          | 1.46 | 0.91–2.30    | 0.05    |
| Low (<5)                         |                    |      |               |         |                    |      |               |         |
| BMI                              |                    |      |               |         |                    |      |               |         |
| <21.4                           | 11.8/2.9           | 0.4  | 0.27–0.59    | <0.0001 | 8.3/8.3            | 0.38 | 0.24–0.60    | <0.0001 |
| ≥21.4                           |                    |      |               |         |                    |      |               |         |
| Intracranial metastases at initial treatment | |      |               |         |                    |      |               |         |
| Yes                              | 8.5/7.1            | 0.96 | 0.60–1.48    | 0.86    | 20.9/17.1          | 0.82 | 0.46–1.40    | 0.49    |
| No                               |                    |      |               |         |                    |      |               |         |
| Liver metastases at initial treatment | |      |               |         |                    |      |               |         |
| Yes                              | 2.3/7.9            | 1.79 | 0.87–3.28    | 0.10    | 9.3/18.7           | 1.86 | 0.82–3.64    | 0.12    |
| No                               |                    |      |               |         |                    |      |               |         |
| Bone metastases at initial treatment | |      |               |         |                    |      |               |         |
| Yes                              | 5.5/9.7            | 1.49 | 0.98–2.20    | 0.05    | 14.4/18.7          | 1.16 | 0.71–1.85    | 0.53    |
| No                               |                    |      |               |         |                    |      |               |         |
| Prior radiotherapy               |                    |      |               |         |                    |      |               |         |
| Yes                              | 5.5/8.5            | 1.6  | 1.06–2.36    | 0.08    | 12.7/21.1          | 1.46 | 0.91–2.30    | 0.11    |
| No                               |                    |      |               |         |                    |      |               |         |
| NLR                              |                    |      |               |         |                    |      |               |         |
| ≥ 5                              | 8.6/5.3            | 0.66 | 0.45–0.97    | 0.03    | 12.7/21.1          | 1.46 | 0.91–2.30    | 0.05    |
| Low (<5)                         |                    |      |               |         |                    |      |               |         |
| Abbreviations: BMI, body mass index; CI, confidence interval; GPS, Glasgow prognostic score; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-L1, programmed death-1; PFS, progression-free survival; PS, performance status; TPS, tumor proportion score.

The reference arms are the variables shown in the right-sided arms. -values in bold are statistically significant (p < 0.05).

should complement each other. Besides, GPS consisting of a combination of albumin and CRP should be used in a complementary manner by combining the two factors rather than by using them alone. In addition, the assessment of the GPS is more objective than the conventional prognostic factor of the ECOG-PS.\textsuperscript{41} In this study, we analyzed various patient subgroups according to the ECOG-PS, histology, PD-L1 expression, NLR, BMI, and tumor response. We found significant prognostic differences among patients with a GPS of 0–1 and those with a GPS of 2 in most patient subgroups. Therefore, it is reasonable to consider the use of the GPS in clinical practice.

Furthermore, the GPS is associated with survival in patients receiving not only ICIs, but also in those receiving cytotoxic agents. Thus, GPS has an aspect of prognostic factor similar to PS. If GPS is solely a prognostic factor and does not affect the survival as a predictive factor, it

FIGURE 2 Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) according to Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and body mass index (BMI). (A) PFS according to GPS at the start of pembrolizumab monotherapy (GPS 0–1, median PFS = 11.8 months; GPS 2, median PFS = 2.9 months). (B) OS according to GPS at the start of pembrolizumab monotherapy (GPS 0–1, median OS = not reached; GPS 2, median OS = 8.3 months). (C) PFS according to NLR at the start of pembrolizumab monotherapy (NLR high, median PFS = 5.3 months; NLR low, median PFS = 8.6 months). (D) OS according to NLR at the start of pembrolizumab monotherapy (NLR high, median OS = 10.5 months; NLR low, median OS = 28.0 months). (E) PFS according to BMI at the start of pembrolizumab monotherapy (BMI high, median PFS = 11.5 months; BMI low, median PFS = 6.2 months). (F) OS according to BMI at the start of pembrolizumab monotherapy (BMI high, median OS = not reached; BMI low, median OS = 14.1 months)
| Report                     | Year | Region  | Ethnicity          | Study type | Sample size | Stage | Treatment                                      | Use of ICIs | Treatment line | Outcomes | Significance of GPS | HR (95% CI)                  |
|----------------------------|------|---------|------------------|------------|-------------|-------|-----------------------------------------------|-------------|----------------|----------|-------------------|----------------------------|
| Forrest et al.⁵            | 2004 | UK      | European         | Prospective | 109         | III–IV| Chemotherapy (platinum-based)                | No          | Untreated      | OS       | GPS 2/0–1: OS;    | 1.88 (95% CI 1.25–2.84)    |
| Gioulbasanis et al.⁶       | 2012 | Greece  | European         | Retrospective | 96          | IV    | Chemotherapy (platinum-based)                | No          | Untreated      | PFS and OS; | GPS 2/0: PFS;      | 3.78 (95% CI 1.78–8.03), OS; 2.63 (95% CI 1.29–5.34) |
| Rinehart et al.³⁶          | 2013 | USA     | Caucasian and African | Prospective | 51          | IV    | Chemotherapy (carboplatin plus gemcitabine)  | No          | Untreated      | OS       | NR                |                            |
| Jiang and Lu³⁷             | 2014 | China   | Chinese          | Prospective | 138         | III–IV| Chemotherapy (cisplatin-based)              | No          | Untreated      | PFS and OS; | GPS 2/0: PFS;      | 0.5 (95% CI 0.3–0.8), OS; 0.5 (95% CI 0.2–0.8) |
| Fan et al.³⁸               | 2016 | China   | Chinese          | Retrospective | 1745        | I–IV  | Radiotherapy and/or Chemotherapy (any cytotoxic drugs) | No          | Untreated      | OS       | GPS 2/0–1: OS;    | 1.872 (95% CI 1.504–2.330)  |
| Kasahara et al.¹³          | 2019 | Japan   | Japanese         | Retrospective | 47          | I–IV  | Chemotherapy (pembrolizumab, or nivolumab monotherapy) | Yes (ICIs only) | Untreated and treated | PFS and OS; | GPS 0–1/2: PFS;    | 0.45 (95% CI 0.21–0.99), OS; 0.18 (95% CI 0.06–0.48) |
| Kasahara et al.⁴⁰          | 2020 | Japan   | Japanese         | Retrospective | 214         | I–IV  | Chemotherapy (gefitinib, erlotinib, or afatinib) | No (EGFR-TKIs only) | Untreated and treated | PFS and OS; | GPS 2/0–1: PFS;    | 1.66 (95% CI 1.03–2.61), OS; 1.77 (95% CI 1.03–2.97) |

(Continues)
may not contribute to the selection of treatment options. For example, if a prognosis would be poor in patients with poor GPS for any treatment, such as ICI monotherapy, combination therapy with ICIs plus cytotoxic agents, or cytotoxic agents, GPS itself may not be useful for the selection of treatment options. In the present study, we cannot draw a conclusion whether GPS is a predictive or prognostic factor because we did not include patients who received other treatments, including cytotoxic agent or combination therapy with ICIs and cytotoxic agents. However, we cannot exclude the possibility that GPS might be a predictive factor for survival of patients receiving pembrolizumab monotherapy. Furthermore, even if GPS is a prognostic factor rather than a predictive factor, it can contribute to the selection of treatment in clinical practice settings.

Several studies have demonstrated the relationship of NLR with clinical response and outcomes in patients with NSCLC treated with anti-PD-1 inhibitors.\textsuperscript{42,43} For example, NLR may be able to predict the prognosis of patients with NSCLC treated with nivolumab.\textsuperscript{20} In our analysis, the relationship between patient background and NLR was significantly related to the ECOG-PS (0–1/≥2), the presence of metastases such as liver and bone metastases, and prior radiotherapy, suggesting that NLR is affected by these clinical factors. Although there was no significant difference in the response rate between the low-NLR and high-NLR groups, the disease control rate was significantly higher in the low-NLR group. Furthermore, although log-rank tests showed that low NLR was associated with significantly longer PFS and OS than high NLR, according to the multivariate analysis, the NLR did not correlate with either PFS or OS in patients with high PD-L1 expression treated with first-line pembrolizumab monotherapy. These results indicate that NLR did not significantly affect PFS and OS in our patient cohort.

Regarding BMI, a large cohort retrospective study demonstrated that a high BMI is correlated with longer PFS and OS beyond ICI administration in patients with metastatic melanoma.\textsuperscript{44} Another retrospective study demonstrated that BMI is correlated with ICI efficacy in solid malignant tumors, including melanoma, renal cell carcinoma, and NSCLC.\textsuperscript{24} In addition, a study has shown a relationship between BMI and ICI outcomes in patients with NSCLC.\textsuperscript{25} The study demonstrated that BMI was significantly associated with the efficacy of ICIs in patients with NSCLC treated with second- or later-line PD-1/PD-L1 inhibitors. However, according to that report, PFS and OS were not significantly different between high- and low-BMI groups of patients with NSCLC and high PD-L1 expression (≥50%) who were treated with pembrolizumab as first-line therapy. The reason for this result may be that their study consisted of 84 patients with high PD-L1 expression.
(≥50%), which may have been an insufficient number for detecting a statistically significant difference. In the current analysis, the patient background was not significantly different between the high- and low-BMI groups, except for administration cycles of pembrolizumab and lymphocyte count. Although there was no significant difference in the disease control rate between the low-BMI and high-BMI groups, the response rate was significantly higher in the high-BMI group. Furthermore, the BMI was significantly predictive of OS but not of PFS. This may indicate that a higher BMI not only increases the efficacy of pembrolizumab monotherapy in these patients, but it may also provide an opportunity for patients to receive additional treatment cycles of pembrolizumab.

The current study has several limitations. First, the retrospective study design relied on subjective physician evaluations of treatment response, which may have introduced variability in the data regarding response and PFS. Second, the sample size was relatively small; however, this would be an inherent limitation at most centers that generally do not have many patients with high PD-L1 expression who are undergoing first-line pembrolizumab monotherapy for NSCLC. Thus, it is important to consider the potential significance of these sources of bias when interpreting our data. Third, the cut-off values for laboratory data or BMI have not been established, as there were various cut-off values in previous studies. In our analysis, for the GPS and NLR, we used the cut-off values reported previously; for BMI, we determined the cut-off values using ROC curves. Therefore, it is necessary to examine whether these values are clinically valid for a larger population in the future.

In conclusion, the results of this investigation suggest that the GPS is independently associated with PFS and OS. In addition, BMI was independently associated with OS. Therefore, our results should be evaluated in larger studies to determine whether they are generalizable to other patient populations. Although further studies are warranted to validate these findings, our results suggest that determination of the GPS and BMI may aid in predicting treatment outcome for patients with NSCLC and high PD-L1 expression who are administered first-line treatment with pembrolizumab monotherapy.

ACKNOWLEDGMENTS
The authors thank Ms. Kyoko Nakagawa for her assistance in preparing the manuscript and Editage (www.editage.jp) for English language editing.

CONFLICT OF INTEREST
Kyoichi Kaira has received research grants and a speaker honorarium from Ono Pharmaceutical Company, Boehringer Ingelheim, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly Japan, and AstraZeneca. Atsuto Mouri has received a speaker honorarium from Eli Lilly, Taiho Pharmaceutical, Pfizer, Chugai Pharmaceutical, and AstraZeneca. Hiroshi Kagamu has received research grants and a speaker honorarium from Ono Pharmaceutical Company, Bristol-Myers Company, Boehringer Ingelheim, MSD, Daiichi Sankyo Company, Chugai Pharmaceutical, Taiho Pharmaceutical, Merck Biopharma Company, Eli Lilly Japan, and AstraZeneca. Kunihiko Kobayashi has received research grants and a speaker honorarium from Boehringer Ingelheim, AstraZeneca, and Bristol-Myers Company.

ETHICAL APPROVAL STATEMENT
All procedures complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of Saitama Medical University International Medical Center (No. 20–222). The requirement for informed consent was waived owing to the retrospective nature of the study.

CLINICAL TRIAL REGISTRATION NUMBER
Not applicable.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID
Hisao Imai https://orcid.org/0000-0003-3097-4255
Takayuki Kishikawa https://orcid.org/0000-0002-8957-4814
Hiroyuki Minemura https://orcid.org/0000-0001-8710-1960
Yutaka Yamada https://orcid.org/0000-0001-6823-4231
Ou Yamaguchi https://orcid.org/0000-0001-7194-6459
Takashi Kasai https://orcid.org/0000-0002-3112-4001
Kyoichi Kaira https://orcid.org/0000-0001-5548-7686

REFERENCES
1. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics. CA Cancer J Clin. 2019;69(5):363-385. https://doi.org/10.3322/caac.21565
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823-1833. https://doi.org/10.1056/NEJMoaa1606774
3. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. *Proc Nutr Soc.* 2008;67(3):257-262. https://doi.org/10.1017/S0029665108007131

4. Proctor MJ, Talwar D, Balmar SM, et al. The relationship between the presence and site of cancer, an inflammation-based prognostic score and biochemical parameters. Initial results of the Glasgow Inflammation Outcome Study. *Br J Cancer.* 2010;103(6):870-876. https://doi.org/10.1038/sj.bjc.6605855

5. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. *Br J Cancer.* 2004;90(9):1704-1706. https://doi.org/10.1038/sj.bjc.6601789

6. Gioulbasanis I, Pallis A, Vlahostergios PJ, et al. The Glasgow prognostic score (GPS) predicts toxicity and efficacy in platinum-based treated patients with metastatic lung cancer. *Lung Cancer.* 2012;77(2):383-388. https://doi.org/10.1016/j.lungcan.2012.04.008

7. Leung EY, Scott HR, McMillan DC. Clinical utility of the pretreatment Glasgow prognostic score in patients with advanced inoperable non-small cell lung cancer. *J Thorac Oncol.* 2012;7(4):655-662. https://doi.org/10.1097/JTO.0b013e318244fe1

8. Umihanic S, Umihanic S, Jamakosmanovic S, et al. Glasgow prognostic score in patients receiving chemotherapy for non-small-cell lung cancer in stages IIIb and IV. *Med Arch.* 2014;68(2):83-85. https://doi.org/10.5455/medarch.2014.68.83-85

9. Jiang AG, Chen HL, Lu HY. Comparison of Glasgow prognostic score and prognostic index in patients with advanced non-small cell lung cancer. *J Cancer Res Clin Oncol.* 2015;141(3):563-568. https://doi.org/10.1007/s00039-014-1839-4

10. Simmons CP, Koinis F, Fallon MT, et al. Prognosis in advanced lung cancer—a prospective study examining key clinicopathological factors. *Lung Cancer.* 2015;88(3):304-309. https://doi.org/10.1016/j.lungcan.2015.03.020

11. Zhu L, Li X, Shen Y, et al. A new prognostic score based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Oncotargets Ther.* 2016;9:4879-4886. https://doi.org/10.2147/OTT.S107279

12. Minami S, Ibara S, Kim SH, Yamamoto S, Komuta K. Lymphocyte to monocyte ratio and modified Glasgow prognostic score predict prognosis of lung adenocarcinoma without driver mutation. *World J Oncol.* 2018;9(1):13-20. https://doi.org/10.14740/wjoe1048w

13. Kasahara N, Sunaga N, Tsukagoshi Y, et al. Post-treatment Glasgow prognostic score predicts efficacy in advanced non-small-cell lung cancer treated with anti-PD1. *Anticancer Res.* 2019;39(3):1455-1461. https://doi.org/10.21873/anticancer.13262

14. Takamori S, Takada K, Shimokawa M, et al. Clinical utility of pretreatment Glasgow prognostic score in non-small-cell lung cancer patients treated with immune checkpoint inhibitors. *Lung Cancer.* 2021;152:27-33. https://doi.org/10.1016/j.lungcan.2020.11.026

15. Araki T, Tateishi K, Sonehara K, et al. Clinical utility of the C-reactive protein:albumin ratio in non-small cell lung cancer patients treated with nivolumab. *Thorac Cancer.* 2021;12(5):603-612. https://doi.org/10.1111/1759-7714.13788

16. Ferrucci PF, Gandini S, Battaglia A, et al. Baseline neutrophil-to-lymphocyte ratio is associated with outcome of ipilimumab-treated metastatic melanoma patients. *Br J Cancer.* 2015;112(12):1904-1910. https://doi.org/10.1038/bjc.2015.180

17. Ferrucci PF, Asciero PA, Pigozzo J, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. *Ann Oncol.* 2016;27(4):732-738. https://doi.org/10.1093/annonc/mdw016

18. Capone M, Giannarelli D, Mallardo D, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. *J Immunother Cancer.* 2018;6(1):74. https://doi.org/10.1186/s40425-018-0383-1

19. Jeyakumar G, Kim S, Bumma N, et al. Neutrophil lymphocyte ratio and duration of prior anti-angiogenic therapy as biomarkers in metastatic RCC receiving immune checkpoint inhibitor therapy. *J Immunother Cancer.* 2017;5(1):82. https://doi.org/10.1186/s40425-017-0287-5

20. 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. https://doi.org/10.1016/j.lungcan.2017.01.013

21. Mezquita L, Aulin C, 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. https://doi.org/10.1001/jamaoncol.2017.4771

22. 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. https://doi.org/10.1007/s00262-017-2092-x

23. Shiroyama T, Nagatomo I, Koyama S, et al. Impact of sarcopenia in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors: a preliminary retrospective study. *Sci Rep.* 2019;9(1):2447. https://doi.org/10.1038/s41598-019-39120-6

24. Cortellini A, Bersanelli M, Buti S, et al. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. *J Immunother Cancer.* 2019;7(1):57. https://doi.org/10.1186/s40425-019-0527-y

25. Ichihara E, Harada D, Inoue K, et al. The impact of body mass index on the efficacy of anti-PD-1/PD-L1 antibodies in patients with non-small cell lung cancer. *Lung Cancer.* 2020;139:140-145. https://doi.org/10.1016/j.lungcan.2019.11.011

26. Roach C, Zhang N, Corigliano E, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. *Appl Immunohistochem Mol Morphol.* 2016;24(6):392-397. https://doi.org/10.1016/j.aim.2015.12.004

27. 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. https://doi.org/10.1016/j.critrevonc.2013.03.010

28. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline
29. Brown DJ, Milroy R, Preston T, McMillan DC. The relationship between an inflammation-based prognostic score (Glasgow Prognostic Score) and changes in serum biochemical variables in patients with advanced lung and gastrointestinal cancer. *J Clin Pathol.* 2007;60(6):705-708. https://doi.org/10.1136/jcp.2005.033217

30. Kerem M, Ferahkose Z, Yilmaz UT, et al. Adipokines and ghrelin in gastric cancer cachexia. *World J Gastroenterol.* 2008;14(23):3633-3641. https://doi.org/10.3748/wjg.v14.i23

31. Giannousi Z, Gioulbasanis I, Pallis AG, et al. Nutritional status, acute phase response and depression in metastatic lung cancer patients: correlations and association prognosis. *Support Care Cancer.* 2012;20(8):1823-1829. https://doi.org/10.1007/s00520-011-1282-x

32. Naito T, Tashiro M, Yamamoto K, Ohnishi K, Kagawa Y, Kawakami J. Impact of cachexia on pharmacokinetic disposition of and clinical responses to oxycodone in cancer patients. *Eur J Clin Pharmacol.* 2012;68(10):1411-1418. https://doi.org/10.1007/s00228-012-1266-x

33. Naito T, Tashiro M, Ishida T, Ohnishi K, Kawakami J. Cancer cachexia raises the plasma concentration of oxymorphone through the reduction of CYP3A but not CYP2D6 in oxycodone-treated patients. *J Clin Pharmacol.* 2013;53(8):812-818. https://doi.org/10.1002/jcph.112

34. McMillan DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. *Cancer Treat Rev.* 2013;39(5):491-501. https://doi.org/10.1016/j.ctrv.2012.08.003

35. Kim SJ, Ryu KJ, Hong M, Ko YH, Kim WS. The serum CXCL13 level is associated with the Glasgow prognostic score in extranodal NK/T-cell lymphoma patients. *J Hematol Oncol.* 2015;8:49. https://doi.org/10.1186/s13045-015-0142-4

36. Rinehart J, Arnold S, Kloecker G, et al. Phase II randomized trial of carboplatin and gemcitabine with or without dexamethasone pre-treatment in patients with Stage IV non-small cell lung cancer. *Cancer Chemother Pharmacol.* 2013;71(5):1375-1383. https://doi.org/10.1007/s00280-013-2111-3

37. Jiang AG, Lu HY. The Glasgow prognostic score as a prognostic factor in patients with advanced non-small cell lung cancer treated with cisplatin-based first-line chemotherapy. *J Chemother.* 2015;27(1):35-39. https://doi.org/10.1119/1973947814Y.000000188

38. Fan H, Shao ZY, Xiao YY, et al. Comparison of the Glasgow prognostic score (GPS) and the modified Glasgow prognostic score (mGPS) in evaluating the prognosis of patients with operable and inoperable non-small cell lung cancer. *J Cancer Res Clin Oncol.* 2016;142(6):1285-1297. https://doi.org/10.1007/s00432-015-2113-0

39. Pan M, Zhao Y, He J, et al. Prognostic value of the Glasgow prognostic score on overall survival in patients with advanced non-small cell lung cancer. *J Cancer.* 2021;12(8):2395-2402. https://doi.org/10.7150/jca.52215

40. Kasahara N, Imai H, Naruse I, et al. Glasgow prognostic score predicts efficacy and prognosis in patients with advanced non-small cell lung cancer receiving EGFR-TKI treatment. *Thorac Cancer.* 2020;11(8):2188-2195. https://doi.org/10.1111/1759-7714.13526

41. Dajczman E, Kasymjanova G, Kreisman H, Swinton N, Pepe C, Small D. Should patient-rated performance status affect treatment decisions in advanced lung cancer? *J Thorac Oncol.* 2008;3(10):1133-1136. https://doi.org/10.1097/JTO.0b013e318186a272

42. Park W, Lopes G. Perspectives: neutrophil-to-lymphocyte ratio as a potential biomarker in immune checkpoint inhibitor for non-small-cell lung cancer. *Clin Lung Cancer.* 2019;20(3):143-147. https://doi.org/10.1016/j.clcc.2018.12.003

43. Jiang T, Bai Y, Zhou F, et al. Clinical value of neutrophil-to-lymphocyte ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors. *Lung Cancer.* 2019;130:76-83. https://doi.org/10.1016/j.lungcan.2019.02.009

44. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol.* 2018;19(3):310-322. https://doi.org/10.1016/S1470-2045(18)30078-0

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

**How to cite this article:** Imai H, Kishikawa T, Minemura H, et al. Pretreatment Glasgow prognostic score predicts survival among patients with high PD-L1 expression administered first-line pembrolizumab monotherapy for non-small cell lung cancer. *Cancer Med.* 2021;10:6971–6984. https://doi.org/10.1002/cam4.4220