Original Article

Baseline Neutrophil-to-Lymphocyte Ratio and Glasgow Prognostic Score are Associated with Clinical Outcome in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma Treated with Nivolumab

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Recurrent or metastatic head and neck squamous cell carcinoma (R/MHNSCC) has a poor prognosis. Although nivolumab is approved in Japan for treating R/MHNSCC, the response rate is low. Therefore, identifying pretreatment prognostic factors is necessary. This study assessed the utility of the neutrophil-to-lymphocyte ratio (NLR) and Glasgow Prognostic Score (GPS) as biomarkers of response to nivolumab. We retrospectively collected the data of 56 R/MHNSCC patients treated with nivolumab between May 2017 and December 2019. The Kaplan–Meier method and log-rank test were used to estimate overall survival (OS) and progression-free survival (PFS), and multivariate Cox hazard regression analysis was used to identify independent predictors of survival. Patients with a low pretreatment NLR had prolonged OS, and patients with a low pretreatment GPS had increased OS and PFS. A performance score (PS) of 0-1, development of immune-related adverse events, and GPS of 0-1 were significantly associated with OS in multivariate analysis. In summary, baseline pretreatment NLR and GPS are independently associated with OS in R/MHNSCC patients treated with nivolumab. Administration of nivolumab while maintaining the PS reflects a immune status of the host and leads to a good OS.

Key words: neutrophil-to-lymphocyte ratio, nivolumab, Glasgow Prognostic Score, recurrent or metastatic head and neck squamous cell carcinoma (R/MHNSCC)

H ead and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally, and the prognosis of HNSCC remains poor, since the disease is locally advanced at diagnosis in more than 60% of patients [1]. The prognosis is especially poor and the treatment choices are particularly limited for patients with recurrent disease or distant metastases [2]. Although cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), and platinum-based chemotherapy are the standard treatments for recurrent/metastatic (R/M) HNSCC [3], the treatment efficacy must be improved and the treatment-related toxicity decreased. Immunotherapeutic approaches are continually being developed and improved in the field of oncology. A prominent example is nivolumab, an anti-programmed cell death protein-1 (PD-1) monoclonal antibody, which achieved

an improvement in overall survival (OS) compared with standard therapy (cetuximab, methotrexate, or docetaxel) for patients with platinum-refractory R/M HNSCC in the CheckMate 141 trial [4]. Based on these results, the authors of the CheckMate 141 trial concluded that nivolumab should be considered the standard subsequent-line treatment for R/MHNSCC [5]. Unfortunately, despite the initial expectations, it has become increasingly clear that only a minority of R/MHNSCC patients derive benefit from nivolumab in clinical practice. There is thus a critical need to identify novel biomarkers to predict the nivolumab response.

For this reason, a significant amount of research in HNSCC has been devoted to clarifying the tumor PDL-1 expression, tumor mutational burden, interferon-γ signature, tumor microenvironment, *etc.* [6]. Although these researches are often helpful, such approaches are not feasible for some patients due to the limited availability, amount, and condition of preserved tumor tissues. To overcome the need for tissue samples, efforts have been directed toward readily accessible samples such as peripheral blood. In recent researches, peripheral blood-based parameters (PBBPs), such as C-reactive protein (CRP), albumin (Alb), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been reported as prognostic indicators for the efficacy of immunotherapy in various cancers [7-9]. Pretreatment NLR and PLR have shown particular promise as cheap and readily available biomarkers in melanoma, lung carcinoma and renal cell carcinoma [7,10-12]. However, the utility of PBBPs has not been studied in HNSCC.

This study aimed to evaluate whether PBBPs could have predictive value in R/MHNSCC patients treated with nivolumab.

Materials and Methods

Patients. This retrospective cohort study was conducted at the Hiroshima University Hospital in Japan between May 2017 and December 2019. Eligibility criteria for inclusion in this study were the presence of pathologically confirmed HNSCC, age of ≥18 years, and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-2 at the initiation of nivolumab treatment. Patients who had previously received immunotherapeutic agents were excluded from the analysis. Nivolumab was administered at a dose of 240 mg/kg body weight every 2 weeks.

The Institutional Review Board of Hiroshima University Hospital approved this study (Hiroshima University Hospital IRB E-1324).

Data collection. We retrospectively collected the following clinical data for all patients: age, sex, body mass index (BMI), smoking history, primary tumor location, tumor-node-metastasis (TNM) stage, previous treatments, immune-related adverse events (irAEs), CRP, Alb, ALC, NLR, PLR, tumor response, outcomes, and ECOG PS, of R/MHNSCC patients in electronic medical databases. BMI was categorized as either underweight (BMI < 18.5 kg/m²), normal weight (18.5 kg/m² < BMI < 25.0 kg/m²) or above (BMI ≥ 25.0 kg/m²) according to standard World Health Organization definitions. The NLR was calculated as the ratio of ANC to ALC, and the PLR was calculated as the ratio of PLT to ALC. The ALC, NLR, and PLR at immunotherapy initiation were considered as the baseline values. Baseline blood cell counts were categorized according to the upper (ANC) or lower (ALC) limits of normal. The Glasgow Prognostic Score (GPS) has been reported to reflect systemic inflammatory conditions and malnutrition due to cancer [13]. The GPS classification was calculated using CRP and Alb based on the cutoff values from previous reports [14]—namely, a CRP cutoff of 1.0 mg/dL and an Alb cutoff of 3.5 g/dL. TNM classification was determined using the 8th edition of the Union for International Cancer Control staging system. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The imaging interval for assessment was 8 to 12 weeks for most patients.

The primary outcome was OS, defined as the number of months between the first nivolumab treatment and death or the date of last patient contact. The secondary outcome was PFS, which was defined as the number of months between the first nivolumab treatment and death or progression.

Statistical analysis. Statistical analyses were performed using JMP pro version 14.0 (developed by the SAS Institute). Continuous variables are reported as the median (range) and categorical variables are reported as the proportion and/or percentage. The Kaplan–Meier method and log-rank test were used to estimate and compare OS and PFS rates. We obtained hazard ratios (HRs) using a Cox proportional hazards model. Factors

significantly associated with response to nivolumab were analyzed using a Cox regression analysis. We performed multivariate Cox hazard regression analysis on variables that showed significance in the univariate analysis. HRs and corresponding 95% confidence intervals (CIs) were reported.

To evaluate the ability of the ALC, NLR, and PLR to predict survival, receiver operating characteristic (ROC) curve analysis with the Delong method was used to determine the area under the curve (AUC).

Results

Patients characteristics. The number of recruited patients was 56 and their characteristics are listed in Table 1. The majority of patients were male, had a history of smoking, BMI ≥ 18.5, ECOG PS of 0-1, Stage IV, and pharynx cancer. More than half of patients had previously received lines of systemic cancer therapy for metastasis (60.7%) and had previously received cetuximab (58.9%). The median baseline ALC, NLR, and PLR were 1,025/μL, 5.16 and 275.2, respectively. GPS0/1 patients accounted for 67% of the total population (Table 1).

Survival outcomes. For the whole group analysis, the median observation period, median OS, and median PFS were 19.5 months, 9.0 months (95%CI 7-12), and 5.0 months (95%CI 2-9), respectively (Fig. 1). The overall response rate (ORR) was 32.1% (18 of 56 patients). The median time to response was 2.59 months.

Immuno-related adverse events. 15 (26.7%) patients experienced irAEs and the most common irAE was liver dysfunction. Only one patient developed severe diarrhea (Grade 3); this patient was treated with systemic corticosteroids (Table 2).

Prognostic factors. The details of the analysis of factors prognostic for survival are shown in Tables 3 and 4. The CDDP-resistant group had significantly worse prognosis compared with the other groups (Fig. 2). CDDP intolerance group was defined as an inability to receive adequate administration of CDDP for any of several reasons: a performance status of ECOG 3 or higher, organ dysfunction of grade 2 or higher based on the NCI CTCAE (National Cancer Institute Common Toxicity Criteria for Adverse Events), such as hearing loss, tinnitus, neurologic disorders, prolonged bone-marrow suppression, hypersensitivity to platinum, and renal dysfunction (creatinine clearance of < 50 ml/min).

Cutoff values of NLR, PLR, and MLR as analyzed by the receiver operating characteristic (ROC) curve were 5.2 (AUC: 0.6834), 0.46 (AUC: 0.6377) and 238 (AUC: 0.6531), respectively (Fig. 3).

In the univariate analysis for OS, NLR ($p = 0.039$), PLR ($p = 0.011$), PS $p = 0.0002$), developing irAEs ($p = 0.03$), and GPS ($p = 0.005$) showed statistical significance. PS ($p = 0.011$) and developing irAEs ($p = 0.061$) also showed significance in the multivariate analysis (Fig. 4).

Finally, the univariate analyses also indicated that PS ($p = 0.011$), BMI ($p = 0.036$), PLR ($p = 0.047$), and GPS ($p = 0.015$) were significantly associated with PFS, while none of these factors was found to be significant in the multivariate analysis.

Discussion

Over the past several years, immune checkpoint inhibitors (ICIs), which target inhibitory receptors on T cells and reinvigorate immune responses, have begun to transform clinical cancer treatment strategies, and the recent approval of several blockers of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the PD-1/PD-L1/PD-L2 pathway have ushered in an era of ICI therapy. Checkpoint blockers can induce good antitumor response and survival advantage in patients with advanced melanoma, NSCLC, renal cancer, gastric cancer, and head and neck cancer, among others. However, most patients show only a limited or transient response. Therefore, intense research is underway to identify and develop biomarkers predictive of ICI response.

Biomarkers are indicators of a particular disease state or some other physiological state of an organism, and they are classified in accordance with their purpose, which could be early diagnosis, prospective prognosis, or prediction of treatment response. Regarding predictive biomarkers for ICIs, numerous studies have focused on the status of the tumor microenvironment, such as PD-L1 expression, tumor-infiltrating lymphocytes, T-cell receptor clonality, mutational or neoantigen burden, immune gene signatures, and multiplex immuno-histochemistry as potentially beneficial predictors [15]. However, the evaluation of these aspects of the tumor microenvironments has some limitations. Sometimes,

Table 1   Patient characteristics

Patient Characteristic	
Number (n)	56
Age Median (range)—years	66 (31–90)
≧75 years—no. (%)	11 (19.6)
≥65 years—no. (%)	29 (51.7)
<65—no. (%)	27 (48.2)
Male　—no. (%)	40 (71.4)
Smoking—no. (%)	40 (71.4)
BMI (kg/m²)—no. (%)	
<18.5	23 (41.1)
18.5≦	33 (58.9)
ECOG　PS—no. (%)	
0–1	47 (83.9)
≧2	9 (16.1)
GPS　—no.(%)	
0–1	38 (69)
2	18 (31)
Clinical　Stage—no. (%) (UICC TNM Classification 8th)	
Ⅰ	5 (8.9)
Ⅱ	6 (10.7)
Ⅲ	5 (8.9)
Ⅳ	40 (71.4)
Site of primary tumor—no. (%)	
Larynx	3 (5.4)
Oral cavity	17 (30.4)
Pharynx	34 (60.6)
Others	2 (3.6)
No. of previous lines of systemic cancer therapy for metastasis—no. (%)	
0	22 (39.3)
1	24 (42.9)
2	5 (8.9)
≧3	5 (8.9)
Recurrent site—no. (%)	
Primary site	20 (35.7)
Neck	14 (25.0)
Distant	22 (39.2)
Previous receipt of cetuximab—no. (%)	33 (58.9)
CDDP intolerance/resistance—no. (%)	
Intolerance	8 (14.2)
resistance	12 (21.4)
N/A	36 (64.2)
Hematologic parameters, median [range]	
ALC	1,025 [360–2,420]
ANC	400 [0–1,932]
NLR	4.81 [1.12–23.78]
MLR	0.425 [0–1.67]
PLR	257.2 [76.44–803.7]
CRP	0.93 [0.02–18.2]
Alb	3.6 [1.9–5.0]

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance score; UICC, union for international cancer control; TNM, tumor-node-metastasis; CDDP, cisplatin; ALC, absolute lymphocyte count; AMC, absolute monocyte count; NLR, neutrophil to lymphocyte ration; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein; Alb, Albumin.
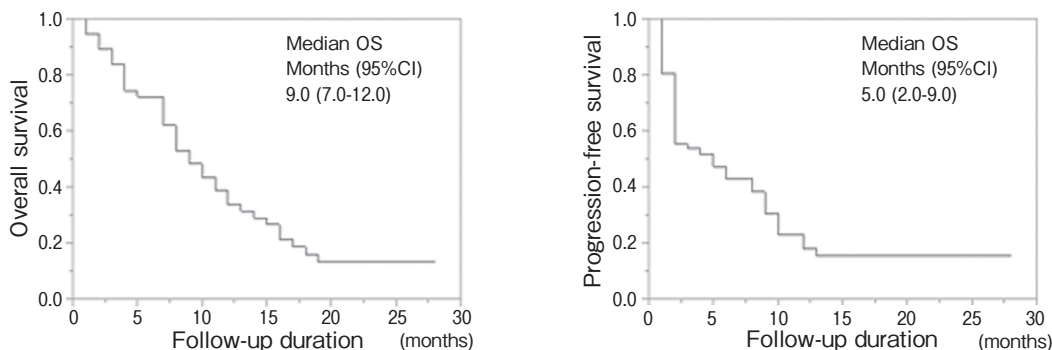
Fig. 1   Median overall survival (OS) with and Median progression free survival (PFS) of whole group analysis. CI, confidence interval.

Table 2   Response to nivolumab and immune-related adverse events

Best response of nivolumab	
CR/PR	18 (32.1)
SD	11 (19.6)
PD	27 (48.2)
Time to response (TTR), months	2.59
Immune-related adverse Events—no. (%)	15 (26.7)
Diarrhea	2
Liver dysfunction	4
Hypothyroidism	2
Skin pruritus	3
Malaise	1
Nausea	1
Muscle pain	1
Peripheral neuropathy	1

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Fig. 2   Comparison of overall survival (OS) between CDDP resistance group and CDDP intolerance group.

invasive procedures are required to obtain fresh tumor cells, such as open biopsy, core-needle biopsy, or lung tissue biopsy with computed tomographic guidance. Additionally, individual biomarkers can vary in appearance depending on the state of tissue preservation, the part of the tumor tissue, the selection of immunohistochemical antibody agents, and time-dependent changes. For all these reasons, immunohistochemical biomarkers have low reliability and are not considered conclusive.

Peripheral blood markers are a noninvasive source of potential biomarkers in patients receiving ICI therapies. Because both CTLA-4 and PD-1 are expressed mainly on lymphocytes, several reports have pointed t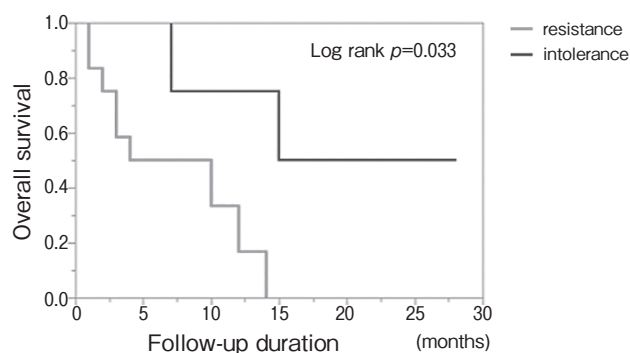o the association between the blood lymphocyte count and tumor response to ICI [16-18]. Martens et al. showed that high levels of relative lymphocyte counts at baseline were significantly associated with longer OS in patients with melanoma. In another study, Nakamura et al. showed that absolute lymphocyte counts of 3 and 6 ($\times 10^3$/μL) after the initial administration of nivolumab were significantly correlated with better OS in patients with melanoma. These results suggest that lymphocyte counts, both at baseline and after treatment with ICI, may be useful for predicting better outcomes.

Neutrophils have been shown to play a critical role in the production of cytokines that drive neoangiogenesis and of chemical ligands that induce an increase of tumor cells. Therefore, an increase of neutrophils can be viewed as a promotion of tumor increase and metastasis. However, a decrease of lymphocytes can represent an insult to the host immune mechanism, leading to a dismal prognosis. The utility of NLR lies in its reflection of the balance between a tumor promotion and an antitumor immune state. In other words, the

Table 3　Univariate and multivariate analyses for factors associated with overall survival

Characteristic		Reference	Univariate analysis		Multivariate analysis	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age	≧65 years	<65 years	0.894 (0.480–1.665)	0.724		
Sex	Male	Female	1.738 (0.884–3.419)	0.109		
Smoking	Smoker	non-smoker	0.988 (0.501–1.948)	0.972		
PS	0–1	≧2	0.197 (0.082–0.468)	0.0002	0.279 (0.104–0.748)	0.011
Stage	I–II	III–IV	1.270 (0.602–2.679)	0.529		
Number of prior therapies	≧2	<2	0.773 (0.339–1.761)	0.541		
Cetuximab	Yes	No	1.00 (0.523–1.919)	0.995		
IrAE	Yes	No	0.445 (0.214–0.926)	0.03	0.469 (0.213–1.035)	0.061
BMI	<18.5	≧18.5	1.704 (0.913–3.178)	0.094		
ALC	≧900	<900	1.127 (0.599–2.119)	0.709		
NLR	<5.2	≧5.2	0.515 (0.274–0.968)	0.039	0.731 (0.298–1.794)	0.495
MLR	<0.46	≧0.46	0.823 (0.439–1.544)	0.544		
PLR	<238	>238	0.449 (0.225–0.878)	0.019	0.918 (0.341–2.470)	0.866
GPS	0–1	2	0.382 (0.195–0.748)	0.005	0.491 (0.204–1.182)	0.112

HR, hazard ratio; CI, confidence interval; irAE, immune-related adverse event; BMI, body mass index; ALC, absolute lymphocyte count; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; GPS, Glasgow Prognostic Score.

Table 4　Univariate and multivariate analyses for factors associated with progression-free survival

Characteristic		Reference	Univariate analysis		Multivariate analysis	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age	≧65 years	<65 years	0.785 (0.428–1.441)	0.435		
Sex	Male	Female	0.62 (0.318–1.210)	0.161		
Smoking	Smoker	non-smoker	1.028 (0.525–2.010)	0.937		
PS	0–1	≧2	0.346 (0.153–0.785)	0.011	0.452 (0.191–1.07)	0.072
Stage	I–II	III–IV	1.165 (0.556–2.443)	0.685		
Number of prior therapies	≧2	<2	0.708 (0.312–1.603)	0.407		
Cetuximab	Yes	No	1.006 (0.538–1.881)	0.984		
IrAE	Yes	No	0.534 (0.260–1.094)	0.087		
BMI	<18.5	≧18.5	1.924 (1.043–3.549)	0.036	1.602 (0.850–3.020)	0.145
ALC	≧900	<900	1.287 (0.692–2.392)	0.425		
NLR	<5.2	≧5.2	0.686 (0.372–1.264)	0.227		
MLR	<0.46	≧0.46	1.023 (0.551–1.898)	0.942		
PLR	<238	>238	0.561 (0.292–1.077)	0.082		
GPS	0–1	2	0.438 (0.227–0.846)	0.014	0.591 (0.293–1.192)	0.142

HR, hazard ratio; CI, confidence interval; irAE, immune-related adverse event; BMI, body mass index; ALC, absolute lymphocyte count; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; GPS, Glasgow Prognostic Score.
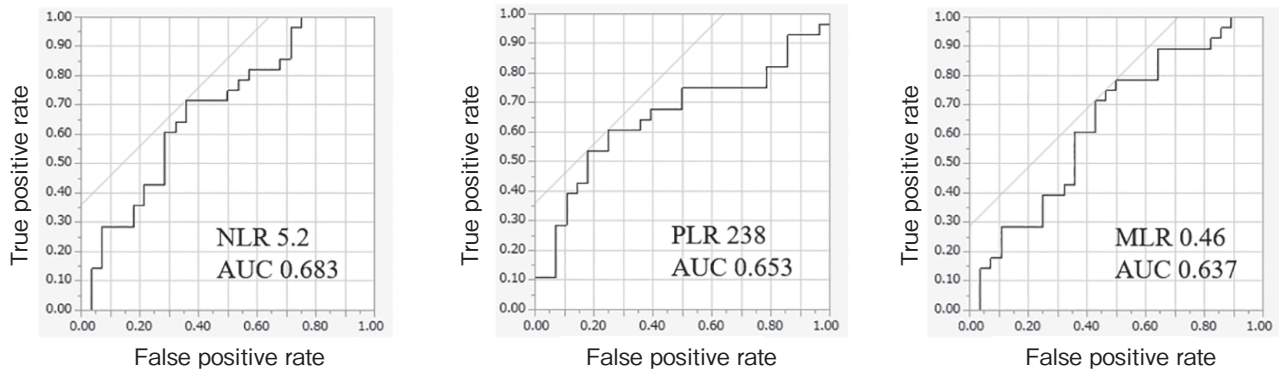
Fig. 3   Cutoff value of NLR/PLR/MLR analyzed with receiver operating characteristic (ROC) curve.
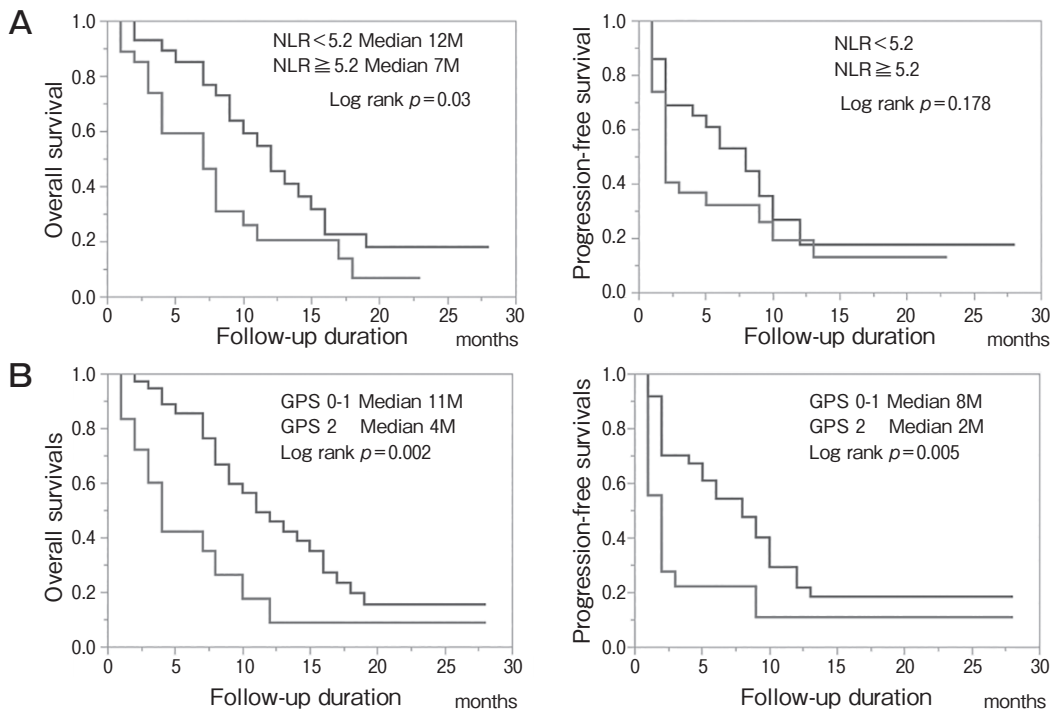

Fig. 4   **A**, Comparison of overall survival and progression free survival with cutoff value of NLR; **B**, Comparison of overall survival and progression free survival with cutoff value of GPS.
NLR, neutrophil to lymphocyte ration; GPS, Glasgow prognostic Score.

NLR can represent immunocompetence. Our previous study found that a baseline NLR < 5 and PS of 0 were associated with increased OS and clinical benefit in patients with R/MHNSCC treated with nivolumab [19]. In this study, we revealed the significant associations between the prognosis of patients treated with nivolumab and each of NLR, PLR, PS, and GPS and the development of irAEs. The patients with a good

prognosis had a tendency to exhibit decreased NLR and a slight change of the value.

As is true of neutrophils, blood platelets are one of the typical blood cell components driving the inflammatory response, and thrombocytosis often appears in solid tumors with chronic inflammation. Because blood platelets are deeply involved in tumor cell progression, it seems reasonable to infer that PLR may be an effective

prognosis prediction marker.

Previous studies have demonstrated that the host inflammatory response is a vital determinant of disease progression [20-22]. To evaluate the systemic inflammatory response, Forrest *et al*. introduced the Glasgow Prognostic Score (GPS), which combines the pretreatment albumin and C-reaction protein (CRP) levels, and showed that it was an independent predictor of OS in patients with NSCLC [23]. In 2007, McMillan *et al*. [24] suggested a modified GPS (mGPS) to evaluate the prognostic effect on patients with rectal and colon cancers, which could provide additional prognostic information for clinical practice. Recently, the prognostic role of GPS/mGPS was proved in various cancer types, and GPS/mGPS was introduced as a potential prognostic test for the response to immunotherapy [25-27]. In other words, a low GPS score represents good nutritional status and sufficient tumor immunity.

It has been reported that the incidence of irAEs correlates with the efficacy of nivolumab in patients with NSCLC or advanced melanoma [28, 29]. In this study, the rate of irAEs of any grade was similar to that reported in the CheckMate 141 trial. Although the exact mechanisms causing these adverse events are unknown, it is likely that inhibiting immune checkpoints affects the maintenance of immune homeostasis, allowing T cells to react with self-antigens, and that different checkpoint inhibitors will have distinct immune toxicity profiles [30].

Our results indicate that nivolumab treatment is more effective when the patient is in a good general condition and that PBBPs are convenient markers for patient outcome. Although a comparison between CDDP responses showed that the CDDP-resistant group had a significantly worse prognosis, treatment history with cetuximab showed no remarkable association. However, the results of this study should be interpreted with care. Several limitations must be considered, including the small sample size, retrospective nature, and single-center design of this study. Larger cohorts and longer follow-up periods will be needed to validate these findings.

In conclusion, This study demonstrates that baseline pretreatment NLR and GPS are independently associated with OS in patients with R/MHNSCC treated with nivolumab. Administration of nivolumab while maintaining PS reflects a immune status of the host and leads to a good OS. Further studies are needed to determine the value of NLR in the context of other biomarkers for ICI therapy.

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