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Prognostic Value of the Pretreatment Lung Immune Prognostic Index in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma Treated with Nivolumab

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Abstract

Background

Reliable biomarkers are needed to improve risk stratification for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) receiving nivolumab. The Lung Immune Prognostic Index (LIPI), calculated from the derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH), is prognostic in several malignancies treated with immune checkpoint inhibitors, but its value in R/M-HNSCC remains unclear. We evaluated associations between pretreatment LIPI and treatment response, progression-free survival (PFS), and overall survival (OS).

Methods

We retrospectively analyzed 73 patients with R/M-HNSCC who received nivolumab between March 2017 and April 2024. Patients were classified into LIPI 0 (n = 29), 1 (n = 39), and 2 (n = 5) groups by pretreatment dNLR and LDH. Primary endpoints were PFS and OS; secondary endpoints were objective response rate (ORR) and disease control rate (DCR). Survival was analyzed using Kaplan–Meier and Cox regression methods.

Results

The ORR was 27.6%, 7.7%, and 0% in the LIPI 0, 1, and 2 groups, respectively (P = 0.065), whereas the DCR differed significantly (72.4%, 33.3%, and 20.0%; P = 0.001). Median PFS was 10.5, 2.8, and 0.7 months, and median OS was 50.8, 10.9, and 2.9 months (both log-rank P < 0.001). Higher LIPI scores were independently associated with shorter PFS and OS in multivariable analyses.

Conclusions

Pretreatment LIPI was significantly associated with disease control and survival in nivolumab-treated R/M-HNSCC. As a simple, inexpensive, and readily available blood-based biomarker, LIPI may aid risk stratification. Prospective multicenter validation is warranted.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide, accounting for approximately 890,000 new cases and 450,000 deaths annually (1). Although multimodal treatment has improved outcomes for patients with locally advanced disease, recurrent or metastatic HNSCC (R/M-HNSCC) remains associated with a poor prognosis, with a median overall survival (OS) of less than one year following platinum failure (2–3).

Immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1) pathway have become a standard treatment option for patients with platinum-refractory R/M-HNSCC. The phase III CheckMate 141 trial demonstrated that nivolumab significantly improved OS compared with the investigator's choice of chemotherapy, leading to its approval for this indication (3). However, only a limited proportion of patients derive durable clinical benefit from nivolumab, highlighting the need for reliable biomarkers to improve pretreatment risk stratification and better characterize the prognosis of individual patients.

Programmed death-ligand 1 (PD-L1) expression is the most widely used biomarker for immune checkpoint inhibitors in HNSCC. However, the clinical utility of PD-L1 expression is limited by several factors, including intratumoral heterogeneity, differences between specimen types, temporal changes in expression, and variability among assessment methods (4–7). Therefore, there remains an unmet need for simple, objective, and readily available biomarkers that can complement existing tissue-based biomarkers in routine clinical practice.

The Lung Immune Prognostic Index (LIPI) is a blood-based biomarker initially established in patients with advanced non-small cell lung cancer receiving immune checkpoint inhibitors (8). LIPI is calculated using two routinely available laboratory parameters: the derived neutrophil-to-lymphocyte ratio (dNLR) and serum lactate dehydrogenase (LDH). Because dNLR reflects systemic inflammatory status and LDH is associated with tumor-related metabolic activity, LIPI has been proposed as a surrogate marker integrating host inflammatory status and tumor biology (8–10). Subsequent studies and a recent meta-analysis have demonstrated that pretreatment LIPI is associated with prognosis and survival outcomes across multiple malignancies treated with immune checkpoint inhibitors (11–12).

Although the prognostic value of LIPI has recently been reported in patients with recurrent or metastatic nasopharyngeal carcinoma receiving immune checkpoint inhibitors (13), evidence regarding its prognostic value in the broader population of patients with non-nasopharyngeal R/M-HNSCC remains limited. Moreover, the relationship between pretreatment LIPI and treatment response to nivolumab has not been fully investigated in this patient population.

Therefore, this study aimed to evaluate the prognostic value of pretreatment LIPI in patients with R/M-HNSCC treated with nivolumab. Specifically, we investigated the associations of pretreatment LIPI with treatment response, progression-free survival (PFS), and overall survival (OS) to determine whether this readily available blood-based biomarker could provide useful pretreatment prognostic stratification in routine clinical practice.

Patients and Methods

Patients

We conducted a retrospective single-center cohort study of consecutive patients with R/M-HNSCC who received nivolumab at Yokohama City University Hospital between March 2017 and April 2024.

Eligible patients were aged ≥ 20 years, had histologically confirmed squamous cell carcinoma arising from the head and neck, had recurrent or metastatic disease and had previously received platinum-based chemotherapy, and received at least one cycle of nivolumab. Patients with non-squamous histology, active autoimmune disease requiring systemic immunosuppressive therapy, or insufficient clinical or laboratory data for calculation of the LIPI were excluded.

Clinical data were retrospectively collected from electronic medical records, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumor site, smoking history, alcohol consumption, body mass index (BMI), previous treatments, disease status, and laboratory parameters obtained immediately before the first nivolumab administration. These baseline laboratory values were used to calculate the pretreatment LIPI.

This study was approved by the Institutional Review Board of Yokohama City University (approval number: F260900007) and was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, the requirement for written informed consent was waived by the Institutional Review Board.

Lung Immune Prognostic Index

Pretreatment LIPI was calculated using two routinely available laboratory parameters, the dNLR and LDH, as originally described by Mezquita et al. (8).

The dNLR was calculated as follows:

dNLR = absolute neutrophil count / (white blood cell count − absolute neutrophil count)

One point was assigned for each of the following adverse factors:

- dNLR > 3
- Serum LDH above the institutional upper limit of normal (ULN)

Patients were subsequently classified into three groups according to the LIPI score:

- Low LIPI (score = 0)
- Intermediate LIPI (score = 1)
- High LIPI (score = 2)

Treatment and response evaluation

All patients received nivolumab according to the approved Japanese prescribing information during the study period. Nivolumab was administered intravenously according to the standard schedule of every two weeks. Dose intervals were occasionally extended to four weeks or temporarily prolonged based on

clinical circumstances. Treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision.

Tumor response was assessed by computed tomography and/or magnetic resonance imaging according to routine clinical practice and evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (14). Objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) or partial response (PR), whereas disease control rate (DCR) was defined as the proportion achieving CR, PR, or stable disease (SD).

Study endpoints

The primary endpoints were PFS and OS.

PFS was defined as the interval from nivolumab initiation to the first documented disease progression or death from any cause, whichever occurred first. OS was defined as the interval from nivolumab initiation to death from any cause. The secondary endpoints were ORR and DCR.

Statistical analysis

Continuous variables are presented as the median (range), whereas categorical variables are presented as numbers and percentages. Baseline clinical characteristics and laboratory parameters among the three LIPI groups were compared using the Kruskal–Wallis test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate. When the Kruskal–Wallis test showed statistical significance, pairwise comparisons were performed using Dunn's multiple comparison test with Bonferroni correction.

Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to identify prognostic factors associated with PFS and OS. Variables with a P value < 0.05 in the univariable analysis were entered into the multivariable analysis. The proportional hazards assumption was assessed using Schoenfeld residuals. Because only five patients were classified as LIPI 2, a sensitivity analysis was performed by combining LIPI 1 and LIPI 2 into a single category. Additional sensitivity analyses were performed by excluding female patients and by modeling LIPI as an ordinal variable (0, 1, and 2). These sensitivity analyses were prespecified to assess whether the observed association between LIPI and survival was robust to alternative handling of the small LIPI 2 subgroup and the marked imbalance in sex distribution.

All statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

All statistical analyses were performed using EZR (version 1.54; Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (15). Figures were generated using GraphPad Prism version 6 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

A total of 73 consecutive patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) who received nivolumab between March 2017 and April 2024 were included in this study. Patient disposition is illustrated in Fig. 1. During follow-up, 68 patients experienced disease progression (PD), whereas five remained free from PD. Among patients with PD, 36 received salvage chemotherapy, 11 underwent local treatment, and 21 received best supportive care. Of the five patients without PD, nivolumab was continued in two patients, whereas the remaining three were managed with observation after treatment discontinuation.

Among the 36 patients who received subsequent chemotherapy, the most frequently administered regimen was cetuximab plus paclitaxel (n = 16, 44.4%), followed by paclitaxel monotherapy (n = 10, 27.8%) and S-1 monotherapy (n = 5, 13.9%). The details of subsequent chemotherapy regimens are provided in Supplementary Table 1.

The median follow-up duration was 10.8 months (range, 0.6–76.8 months). Baseline patient characteristics are summarized in Table 1. According to pretreatment LIPI, 29 patients (39.7%) were classified into the low-LIPI group, 39 (53.4%) into the intermediate-LIPI group, and five (6.8%) into the high-LIPI group. No major differences in baseline demographic and clinical characteristics were observed among the three groups, although the number of patients in the high-LIPI group was limited. As expected, patients with higher LIPI scores had significantly higher neutrophil counts, dNLR, LDH, and CRP levels, whereas lymphocyte counts and serum albumin levels were significantly lower (Fig. 2).

Treatment response

Treatment responses according to pretreatment LIPI are summarized in Table 2 and illustrated in Fig. 3. The overall ORR was 15.1% (11/73). ORR was 27.6% (8/29) in the low-LIPI group, 7.7% (3/39) in the intermediate-LIPI group, and 0% (0/5) in the high-LIPI group, demonstrating a trend toward improved response with lower pretreatment LIPI, although the difference did not reach statistical significance (P = 0.065). The overall DCR was 47.9% (35/73). DCR differed significantly among the three LIPI groups, with rates of 72.4% (21/29), 33.3% (13/39), and 20.0% (1/5) in the low-, intermediate-, and high-LIPI groups, respectively (P = 0.001).

Progression-free survival

Kaplan–Meier curves for PFS are shown in Fig. 4A. The median PFS for the overall cohort was 1.9 months. Median PFS according to pretreatment LIPI was 10.5 months in the low-LIPI group, 2.8 months in the intermediate-LIPI group, and 0.7 months in the high-LIPI group. Patients with lower pretreatment LIPI experienced significantly longer PFS than those with intermediate or high LIPI (log-rank P < 0.001).

The results of the Cox proportional hazards analyses for PFS are presented in Table 3. In univariable analysis, sex, ECOG PS, serum albumin level, and pretreatment LIPI were significantly associated with PFS. In the multivariable model, male sex remained an independent favorable prognostic factor (HR, 0.374; 95% CI, 0.166–0.841; $P = 0.017$), whereas ECOG PS ≥ 1 (HR, 2.277; 95% CI, 1.208–4.291; $P = 0.011$), intermediate LIPI (HR, 3.886; 95% CI, 2.011–7.510; $P < 0.001$), and high LIPI (HR, 18.80; 95% CI, 5.377–65.75; $P < 0.001$) were independently associated with shorter PFS. However, because only five patients were classified as LIPI 2, the large HR estimate for this subgroup should be interpreted cautiously, as reflected by the wide confidence interval.

Overall survival

Kaplan–Meier curves for OS are shown in Fig. 4B. The median OS for the overall cohort was 14.0 months. Median OS according to pretreatment LIPI was 50.8 months in the low-LIPI group, 10.9 months in the intermediate-LIPI group, and 2.9 months in the high-LIPI group. Patients with lower pretreatment LIPI experienced significantly longer OS than those with intermediate or high LIPI (log-rank $P < 0.001$).

The results of the Cox proportional hazards analyses for OS are presented in Table 4. In univariable analysis, sex, ECOG PS, serum albumin level, and pretreatment LIPI were significantly associated with OS. Multivariable analysis identified male sex as an independent favorable prognostic factor (HR, 0.344; 95% CI, 0.139–0.847; $P = 0.020$), whereas ECOG PS ≥ 1 (HR, 2.589; 95% CI, 1.271–5.273; $P = 0.009$), intermediate LIPI, and high LIPI remained independently associated with poorer OS. As with PFS, the estimate for LIPI 2 should be interpreted cautiously because of the small subgroup size and the resulting uncertainty in the estimated magnitude of association.

No evidence of violation of the proportional hazards assumption was observed in the multivariable Cox regression models for PFS and OS. Sensitivity analyses excluding female patients, treating LIPI as an ordinal variable, and dichotomizing LIPI into LIPI 0 versus LIPI 1–2 yielded consistent results, with LIPI remaining significantly associated with both PFS and OS (Supplementary Tables 2A–4B). These analyses supported the robustness of the overall association between increasing LIPI and poorer survival, although they did not eliminate the statistical uncertainty inherent in the small LIPI 2 subgroup.

Discussion

In the present study, pretreatment LIPI was significantly associated with disease control and survival outcomes in patients with R/M-HNSCC treated with nivolumab. Patients with low pretreatment LIPI demonstrated significantly prolonged PFS and OS, as well as superior disease control, compared with those with intermediate or high LIPI. Although the prognostic value of LIPI has recently been reported in patients with recurrent or metastatic nasopharyngeal carcinoma receiving immune checkpoint inhibitors (13), its prognostic relevance in non-nasopharyngeal R/M-HNSCC remains unclear. To our knowledge, this is the first study to demonstrate the prognostic value of pretreatment LIPI in a non-nasopharyngeal R/M-HNSCC cohort treated with nivolumab monotherapy. These findings extend the potential prognostic applicability of LIPI to non-nasopharyngeal R/M-HNSCC in routine clinical practice.

Our findings were obtained in a Japanese real-world setting, where nivolumab has been used for R/M-HNSCC since its approval in 2017. Previous Japanese real-world studies have demonstrated effectiveness and safety broadly consistent with those reported in CheckMate 141 (16–17). Our findings complement these studies by suggesting that pretreatment LIPI may provide prognostic stratification in routine clinical practice.Although the single-center design limits generalizability, the consistent association of pretreatment LIPI with both PFS and OS supports further multicenter validation.

Our findings are consistent with previous studies in advanced non-small cell lung cancer, where LIPI was initially established and subsequently shown to be associated with outcomes in patients treated with immune checkpoint inhibitors (8, 11). Moreover, a recent systematic review and meta-analysis demonstrated that pretreatment LIPI is associated with survival outcomes across multiple solid tumors receiving immune checkpoint inhibitors (12). The consistent prognostic association across tumor types suggests that LIPI may capture common biological features related to systemic inflammation, host immune status, and tumor biology.

Although ORR showed only a trend toward significance, DCR differed significantly among the three LIPI groups. DCR decreased progressively from 72.4% in LIPI 0 to 33.3% in LIPI 1 and 20.0% in LIPI 2, suggesting that the prognostic association of LIPI may extend beyond objective tumor shrinkage to broader disease control. However, this interpretation should be considered exploratory because the present study was retrospective and the LIPI 2 subgroup was very small.

The biological mechanisms underlying these findings may be related to the two components of LIPI, dNLR and LDH. dNLR reflects systemic inflammatory and immune status, whereas LDH may reflect tumor metabolic activity and an adverse tumor microenvironment. In HNSCC, systemic inflammation, malnutrition, cachexia, and tumor-associated metabolic alterations may contribute to an immunosuppressive state (23–27). Thus, LIPI may capture complementary aspects of host inflammation and tumor biology. Nevertheless, the present study cannot establish the biological mechanisms underlying this association.

Interestingly, male sex was independently associated with favorable PFS and OS in the present study. However, the prognostic impact of sex has remained unclear in patients with HNSCC treated with immune checkpoint inhibitors, with previous studies not consistently identifying sex as an independent prognostic factor (3, 28).

Because female patients accounted for only 8 of 73 patients (11.0%) in our cohort, the observed association may have been influenced by the marked imbalance in sex distribution. Importantly, the association between LIPI and survival remained significant after excluding female patients, supporting the robustness of the primary findings. Nevertheless, the favorable prognostic association of male sex should be interpreted cautiously and should not be considered a definitive biological finding. Larger studies with a more balanced sex distribution are needed to clarify the prognostic relevance of sex in this setting.

Several sensitivity analyses further supported the robustness of the association between LIPI and survival. The association remained significant when LIPI 1 and LIPI 2 were combined and when LIPI was modeled as an ordinal variable, suggesting that the overall association was not solely driven by the five patients classified as LIPI 2. Nevertheless, subgroup-specific estimates for LIPI 2 remain uncertain because of the small sample size and wide confidence intervals.

Subsequent treatment after nivolumab should also be considered when interpreting the observed survival differences. Among patients with disease progression, salvage chemotherapy, local treatment, and best supportive care were used across the LIPI groups. Although best supportive care was numerically more frequent in the high-LIPI group (80.0%) than in the low- and intermediate-LIPI groups (6/29, 20.7% and 11/39, 28.2%, respectively), the distribution of subsequent treatment did not differ significantly among the LIPI groups ($P = 0.256$). Subsequent treatment was not assigned according to LIPI and was likely influenced by clinical factors such as disease status, performance status, comorbidities, organ function, treatment tolerance, and patient preferences. The heterogeneity of post-progression treatment is particularly important when interpreting OS, because salvage chemotherapy, local treatment, and best supportive care may have substantially different effects on post-progression survival. Therefore, residual confounding by subsequent treatment cannot be excluded, and the association between pretreatment LIPI and OS should be interpreted as prognostic rather than causal. In contrast, PFS is less likely to be affected by subsequent treatment because these treatments occur after progression.

Our findings also have important clinical implications. Compared with tissue-based biomarkers such as PD-L1 expression, pretreatment LIPI can be calculated from routinely available peripheral blood parameters, making it inexpensive, objective, minimally invasive, and readily applicable in routine clinical practice (8, 11–12). Although PD-L1 expression provides clinically relevant information for treatment selection, its assessment may be limited by tissue availability, assay variability, and spatial or temporal heterogeneity (4–5, 29). Importantly, LIPI should not be considered a replacement for established tissue-based biomarkers such as PD-L1 CPS. Rather, it may provide complementary information regarding systemic inflammatory and host-related factors that are not captured by tumor PD-L1 expression. Because PD-L1 CPS data were unavailable for most patients in the present cohort, we could not determine whether LIPI provides prognostic information independently of PD-L1 status. Prospective studies should therefore evaluate the complementary value of LIPI and PD-L1 CPS and determine whether their combination improves pretreatment risk stratification. This study has several limitations. First, this was a retrospective single-center study with a relatively small sample size, which may have introduced selection bias and limited the generalizability of our findings. Second, PD-L1 expression (e.g., combined positive score [CPS]), an established biomarker for immune checkpoint inhibitors in HNSCC, was unavailable for the majority of patients, precluding evaluation of the complementary value of LIPI when combined with PD-L1 expression. In Japan, nivolumab received regulatory approval for R/M-HNSCC in 2017 regardless of PD-L1 expression status, which explains why PD-L1 CPS was not routinely tested in clinical practice during the earlier study period. Hence, whether LIPI provides prognostic information independently of PD-L1 status could not be determined. Third, LIPI was assessed only

before nivolumab initiation, and dynamic changes during treatment were not evaluated. Fourth, the number of patients in the high-LIPI group was small (n = 5), which may have resulted in imprecise estimates and limited the statistical power of analyses involving this subgroup. The large hazard ratio observed for LIPI 2 in the PFS analysis should therefore be interpreted cautiously. The sensitivity analyses described above provide additional support for the overall prognostic association of LIPI but do not eliminate the uncertainty surrounding the LIPI 2 subgroup. Fifth, subsequent treatments after disease progression were heterogeneous and were selected according to individual clinical circumstances. Although their distribution did not differ significantly among the LIPI groups, the small number of patients, particularly in the high-LIPI group, limited the ability to fully assess their potential influence on survival outcomes. Because subsequent treatment was not randomly assigned and may have been influenced by clinical factors associated with both baseline prognosis and post-progression survival, residual confounding cannot be excluded. Therefore, the observed association between pretreatment LIPI and OS should not be interpreted as a causal effect of LIPI on survival. Sixth, only eight patients (11.0%) were female, resulting in substantial sex imbalance and limiting the reliability of the observed association between male sex and favorable survival. Although exclusion of female patients yielded consistent associations between LIPI and survival, the sex-specific finding itself requires validation in larger and more balanced cohorts. Finally, our findings have not been externally validated.

Prospective multicenter studies are warranted to validate these findings, clarify the complementary role of LIPI alongside established biomarkers, including PD-L1 CPS, and further define the prognostic utility of LIPI in patients receiving immunotherapy.

In conclusion, pretreatment LIPI was significantly associated with disease control and survival outcomes in patients with R/M-HNSCC treated with nivolumab. As a simple and readily available blood-based biomarker, LIPI may provide useful pretreatment prognostic stratification in this setting. Given the small number of patients with LIPI 2, these findings should be interpreted cautiously and validated in prospective multicenter studies.

Declarations

Authorship contribution statement

Kaname Sato: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, and writing – review and editing. Daisuke Sano: Conceptualization, methodology, validation, supervision, and writing – review and editing. Nobuhiko Oridate: Conceptualization, supervision, and writing – review and editing. All authors read and approved the final manuscript.

Conflicts of Interest:

The authors declare that they have no competing interests.

Ethical approval:

This study was approved by the Institutional Review Board of Yokohama City University (F260900007).

Informed consent:

The requirement for obtaining informed consent was waived by the ethics committee because this retrospective observational study used anonymized secondary data.

Data availability statement:

The datasets used in the present study are available from the corresponding author upon reasonable request.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A (2024) Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74(3):229–263
2. Cohen EEW, Bell RB, Bifulco CB, Burtness B, Gillison ML, Harrington KJ, Le QT, Lee NY, Leidner R, Lewis RL, Licitra L, Mehanna H, Mell LK, Raben A, Sikora AG, Uppaluri R, Whitworth F, Zandberg DP, Ferris RL (2019) The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC). J Immunother Cancer 7(1):184
3. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW, Gillison ML (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 375(19):1856–1867
4. National Comprehensive Cancer Network NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 1.2026
5. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, González Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F, Rischin D (2019) KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 394(10212):1915–1928
6. Paolino G, Pantanowitz L, Barresi V, Pagni F, Munari E, Moretta L, Brunelli M, Bariani E, Vigliar E, Pisapia P, Malapelle U, Troncone G, Girolami I, Eccher A (2021) PD-L1 evaluation in head and neck squamous cell carcinoma: Insights regarding specimens, heterogeneity and therapy. Pathol Res Pract 226:153605
7. Rasmussen JH, Lelkaitis G, Håkansson K, Vogelius IR, Johannesen HH, Fischer BM, Bentzen SM, Specht L, Kristensen CA, von Buchwald C, Wessel I, Friborg J (2019) Intratumor heterogeneity of PD-

L1 expression in head and neck squamous cell carcinoma. Br J Cancer 120(10):1003–1006

8. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, Ponce S, Ares LP, Leroy L, Audigier-Valette C, Felip E, Zerón-Medina J, Garrido P, Brosseau S, Zalcman G, Mazieres J, Caramela C, Lahmar J, Adam J, Chaput N, Soria JC, Besse B (2018) Association of the Lung Immune Prognostic Index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMA Oncol 4(3):351–357
9. Kumar D (2017) Regulation of glycolysis in head and neck squamous cell carcinoma. Postdoc J 5(1):14–28
10. Walenta S, Mueller-Klieser WF (2004) Lactate: mirror and motor of tumor malignancy. Semin Radiat Oncol 14(3):267–274
11. Meyers DE, Stukalin I, Vallerand IA, Lewinson RT, Suo A, Dean M, North S, Pabani A, Cheng T, Heng DYC, Bebb DG, Morris DG (2019) The Lung Immune Prognostic Index discriminates survival outcomes in patients with solid tumors treated with immune checkpoint inhibitors. Cancers (Basel) 11(11):1713
12. Guo Y, Pan Y, Wan J, Gong B, Li Y, Kan X, Zheng C (2024) Prognosis stratification of cancer patients treated with immune checkpoint inhibitors through Lung Immune Prognostic Index: a meta-analysis and systematic review. BMC Cancer 24(1):523
13. Min Y, Liu X, Wei Z, Song G, Li Y, Gao K, Liu Z, Pei Y, Li H, Ge J, Qing Y, Wei Y, Peng X (2024) Lung immune prognostic index is associated with clinical outcomes in recurrent or metastatic nasopharyngeal carcinoma receiving immunotherapy: results from the multicenter, single-arm, phase 2 study. Oral Oncol 159:107028
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247
15. Kanda Y (2013) Investigation of the freely available easy-to-use software EZR for medical statistics. Bone Marrow Transpl 48(3):452–458
16. Hanai N, Shimizu Y, Kariya S et al (2021) Effectiveness and safety of nivolumab in patients with head and neck cancer in Japanese real-world clinical practice: a multicenter retrospective clinical study. Int J Clin Oncol 26(3):494–506
17. Tahara M, Kiyota N, Nibu KI et al (2021) Real-world safety and effectiveness of nivolumab for recurrent or metastatic head and neck cancer in Japan: a post-marketing surveillance. Int J Clin Oncol 26(9):1619–1627
18. Kelleher T, Cai J, Botwood NA, Labriola DF (2021) Characterizing tumor shrinkage as a measure of clinical benefit for immune checkpoint inhibitors. J Immunother Cancer 9(2):e001177
19. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15(23):7412–7420

20. Yang K, Lu R, Mei J, Cao K, Zeng T, Hua Y, Huang X, Li W, Yin Y (2024) The war between the immune system and the tumor: using immune biomarkers as tracers. Biomark Res 12(1):51
21. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ (2013) The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol 88(1):218–230
22. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454(7203):436–444
23. Ferris RL (2015) Immunology and immunotherapy of head and neck cancer. J Clin Oncol 33(29):3293–3304
24. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12(5):489–495
25. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ (2014) Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 14(11):754–762
26. Kumagai S, Koyama S, Itahashi K, Tanegashima T, Lin YT, Togashi Y, Kamada T, Irie T, Okumura G, Kono H, Ito D, Fujii R, Watanabe S, Sai A, Fukuoka S, Sugiyama E, Watanabe G, Owari T, Nishinakamura H, Sugiyama D, Maeda Y, Kawazoe A, Yukami H, Chida K, Ohara Y, Yoshida T, Shinno Y, Takeyasu Y, Shirasawa M, Nakama K, Aokage K, Suzuki J, Ishii G, Kuwata T, Sakamoto N, Kawazu M, Ueno T, Mori T, Yamazaki N, Tsuboi M, Yatabe Y, Kinoshita T, Doi T, Shitara K, Mano H, Nishikawa H (2022) Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. Cancer Cell 40(2):201–218e9
27. Brand A, Singer K, Koehl GE, Kolitzus M, Schoenhammer G, Thiel A, Matos C, Bruss C, Klobuch S, Peter K, Kastenberger M, Bogdan C, Schleicher U, Mackensen A, Ullrich E, Fichtner-Feigl S, Kesselring R, Mack M, Ritter U, Schmid M, Blank C, Dettmer K, Oefner PJ, Hoffmann P, Walenta S, Geissler EK, Pouyssegur J, Villunger A, Steven A, Seliger B, Schreml S, Haferkamp S, Kohl E, Karrer S, Berneburg M, Herr W, Mueller-Klieser W, Renner K, Kreutz M (2016) LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab 24(5):657–671
28. Wang Q, Yin X, Wang S, Lu H (2024) Inflammatory markers as prognostic markers in patients with head and neck squamous cell carcinoma treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Front Oncol 14:1429559
29. Cristescu R, Mogg R, Ayers M, Albright A, Murphy E, Yearley J, Sher X, Liu XQ, Lu H, Nebozhyn M, Zhang C, Lunceford JK, Joe A, Cheng J, Webber AL, Ibrahim N, Plimack ER, Ott PA, Seiwert TY, Ribas A, McClanahan TK, Tomassini JE, Loboda A, Kaufman D (2018) Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science 362:6411

Tables

Table 1. Baseline clinicopathological characteristics according to LIPI

Characteristics	All (n = 73)	LIPI 0 (n = 29)	LIPI 1 (n = 39)	LIPI 2 (n = 5)	P value
Age, years					
Median (range)	65 (29–89)	64 (40–89)	68 (29–83)	71 (63–79)	
≤ 65	37 (50.7)	17 (58.6)	18 (46.2)	2 (40.0)	0.571
> 65	36 (49.3)	12 (41.4)	21 (53.8)	3 (60.0)	
Sex					0.608
Male	65 (89.0)	27 (93.1)	36 (92.3)	4 (80.0)	
Female	8 (11.0)	2 (6.9)	3 (7.7)	1 (20.0)	
Primary tumor site					0.111
Oral cavity	13 (17.8)	5 (17.2)	8 (20.5)	0	
Nasopharynx	5 (6.8)	1 (3.4)	3 (7.7)	1 (20.0)	
Oropharynx	14 (19.2)	9 (31.0)	4 (10.3)	0	
Hypopharynx	27 (37.0)	9 (31.0)	17 (43.6)	1 (20.0)	
Larynx	3 (4.1)	1 (3.4)	1 (2.6)	1 (20.0)	
Sinonasal tract	9 (12.3)	3 (10.3)	5 (12.8)	1 (20.0)	
Unknown primary	1 (1.4)	1 (3.4)	0	0	
External auditory canal	1 (1.4)	0	1 (2.6)	0	
Nivolumab treatment line					0.245
First-line	40 (54.8)	19 (65.5)	20 (51.3)	1 (20.0)	
Second-line	32 (43.8)	10 (34.5)	18 (46.2)	4 (80.0)	
Third-line	1 (1.4)	0	1 (2.6)	0	
ECOG PS					0.094
0	52 (71.2)	23 (79.3)	27 (69.2)	2 (40.0)	
1	16 (21.9)	5 (17.2)	10 (25.6)	1 (20.0)	
2	4 (5.5)	1 (3.4)	2 (5.1)	1 (20.0)	
3	1 (1.4)	0	0	1 (20.0)	

Table 1. Baseline clinicopathological characteristics according to LIPI					
Platinum-refractory disease					0.608
Yes	67 (91.8)	27 (93.1)	36 (92.3)	4 (80.0)	
No	6 (8.2)	2 (6.9)	3 (7.7)	1 (20.0)	
Previous cetuximab treatment					0.072
Yes	28 (38.4)	8 (27.6)	16 (41.0)	4 (80.0)	
No	45 (61.6)	21 (72.4)	23 (59.0)	1 (20.0)	
Previous radiotherapy					0.804
Yes	60 (82.2)	25 (86.2)	31 (79.5)	4 (80.0)	
No	13 (17.8)	4 (13.8)	8 (20.5)	1 (20.0)	
Distant metastasis					0.327
Yes	45 (61.6)	15 (51.7)	27 (69.2)	3 (60.0)	
No	28 (38.4)	14 (48.3)	12 (30.8)	2 (40.0)	
Recurrence pattern					0.702
Primary	13 (17.8)	6 (20.7)	5 (12.8)	2 (40.0)	
Neck	9 (12.3)	5 (17.2)	4 (10.3)	0	
Distant	21 (28.8)	6 (20.7)	13 (33.3)	2 (40.0)	
Primary + Neck	6 (8.2)	3 (10.3)	3 (7.7)	0	
Primary + Distant	7 (9.6)	2 (6.9)	5 (12.8)	0	
Neck + Distant	10 (13.7)	3 (10.3)	7 (17.9)	0	
Primary + Neck + Distant	7 (9.6)	4 (13.8)	2 (5.1)	1 (20.0)	
Footnote: Data are presented as number (%) unless otherwise indicated. Age is presented as median (range).					

Table 2. Subsequent treatment after nivolumab according to LIPI group

Subsequent treatment after nivolumab	All (n = 73)	LIPI 0 (n = 29)	LIPI 1 (n = 39)	LIPI 2 (n = 5)	P value
Patients with disease progression					0.256
SC	36 (49.3)	15 (51.7)	20 (51.3)	1 (20.0)	
LT	11 (15.1)	4 (13.8)	7 (17.9)	0	
BSC	21 (28.8)	6 (20.7)	11 (28.2)	4 (80.0)	
Patients without disease progression					0.400
Under observation	3 (4.1)	3 (10.3)	0	0	
Ongoing nivolumab	2 (2.7)	1 (3.4)	1 (2.6)	0	

Footnote: Data are presented as number (%). P values were calculated using the chi-square test or Fisher's exact test, as appropriate. SC, salvage chemotherapy; LT, local therapy; BSC, best supportive care.

Table 3. Cox proportional hazards regression analysis for progression-free survival

Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Male sex	0.276	0.124–0.613	0.001	0.374	0.166–0.841	0.017
Age > 65 years	1.114	0.671–1.849	0.675	—	—	—
ECOG PS ≥ 1	2.106	1.180–3.757	0.012	2.277	1.208–4.291	0.011
First-line nivolumab treatment	0.724	0.436–1.200	0.210	—	—	—
Platinum-refractory disease	1.327	0.526–3.343	0.549	—	—	—
Previous cetuximab treatment	1.295	0.776–2.162	0.322	—	—	—
Previous radiotherapy	0.859	0.455–1.619	0.637	—	—	—
Distant metastasis	1.125	0.666–1.900	0.659	—	—	—
LIPI = 1	3.834	2.062–7.132	< 0.001	3.886	2.011–7.510	< 0.001
LIPI = 2	17.90	5.878–54.49	< 0.001	18.80	5.377–65.75	< 0.001
Serum albumin ≤ 3.5 g/dL	1.769	1.027–3.045	0.040	0.885	0.466–1.681	0.709

Footnote: Multivariate analysis was performed using the Cox proportional hazards model. Reference categories were LIPI 0, female sex, age ≤ 65 years, ECOG PS 0, non-first-line nivolumab treatment, platinum-sensitive disease, no previous cetuximab treatment, no previous radiotherapy, no distant metastasis, and serum albumin > 3.5 g/dL.

Table 4. Cox proportional hazards regression analysis for overall survival

Factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Male sex	0.244	0.102–0.577	0.001	0.344	0.139–0.847	0.020
Age > 65 years	1.476	0.830–2.623	0.185	—	—	—
ECOG PS ≥ 1	2.84	1.479–5.454	0.002	2.589	1.271–5.273	0.009
First-line nivolumab treatment	0.606	0.341–1.079	0.089	—	—	—
Platinum-refractory disease	1.098	0.433–2.783	0.843	—	—	—
Previous cetuximab treatment	1.533	0.864–2.720	0.144	—	—	—
Previous radiotherapy	0.957	0.462–1.982	0.907	—	—	—
Distant metastasis	0.968	0.527–1.778	0.917	—	—	—
LIPI = 1	2.457	1.274–4.737	0.007	2.217	1.119–4.391	0.022
LIPI = 2	12.55	4.180–37.70	< 0.001	5.952	1.784–19.86	0.004
Serum albumin ≤ 3.5 g/dL	2.849	1.573–5.160	< 0.001	2.057	1.052–4.019	0.035

Footnote: Multivariate analysis was performed using the Cox proportional hazards model. Reference categories were LIPI 0, female sex, age ≤ 65 years, ECOG PS 0, non-first-line nivolumab treatment, platinum-sensitive disease, no previous cetuximab treatment, no previous radiotherapy, no distant metastasis, and serum albumin > 3.5 g/dL.

Figures

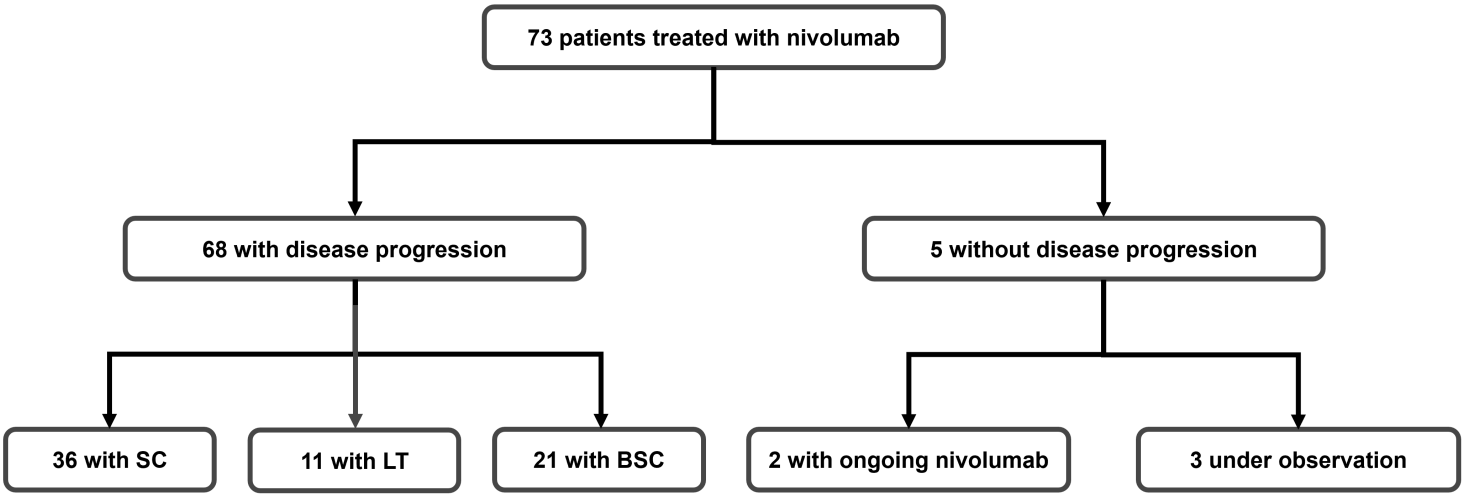


Figure 1

Patient flow after nivolumab treatment.

Flow diagram showing the clinical course of the 73 patients after nivolumab treatment. SC, salvage chemotherapy; LT, local treatment; BSC, best supportive care.

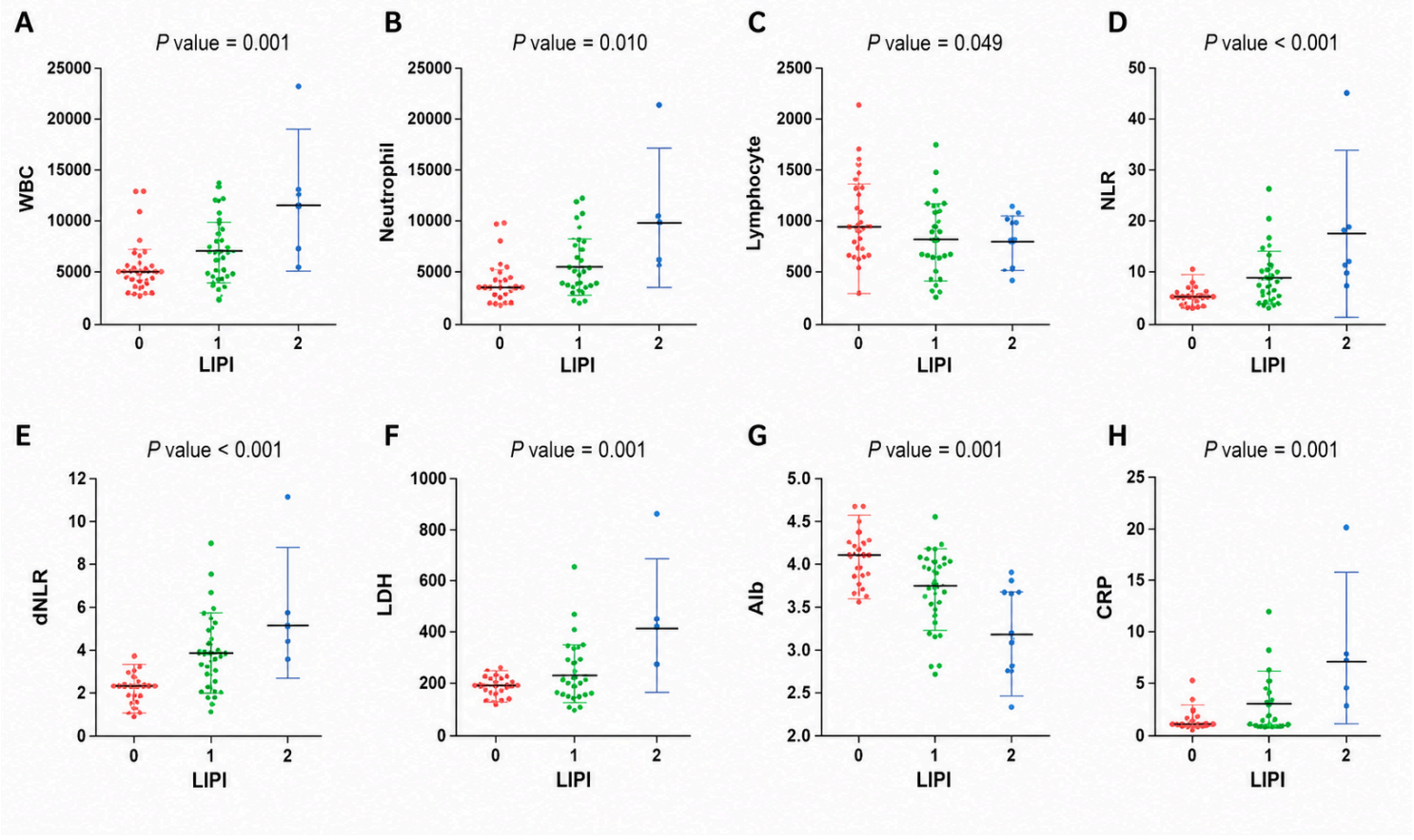
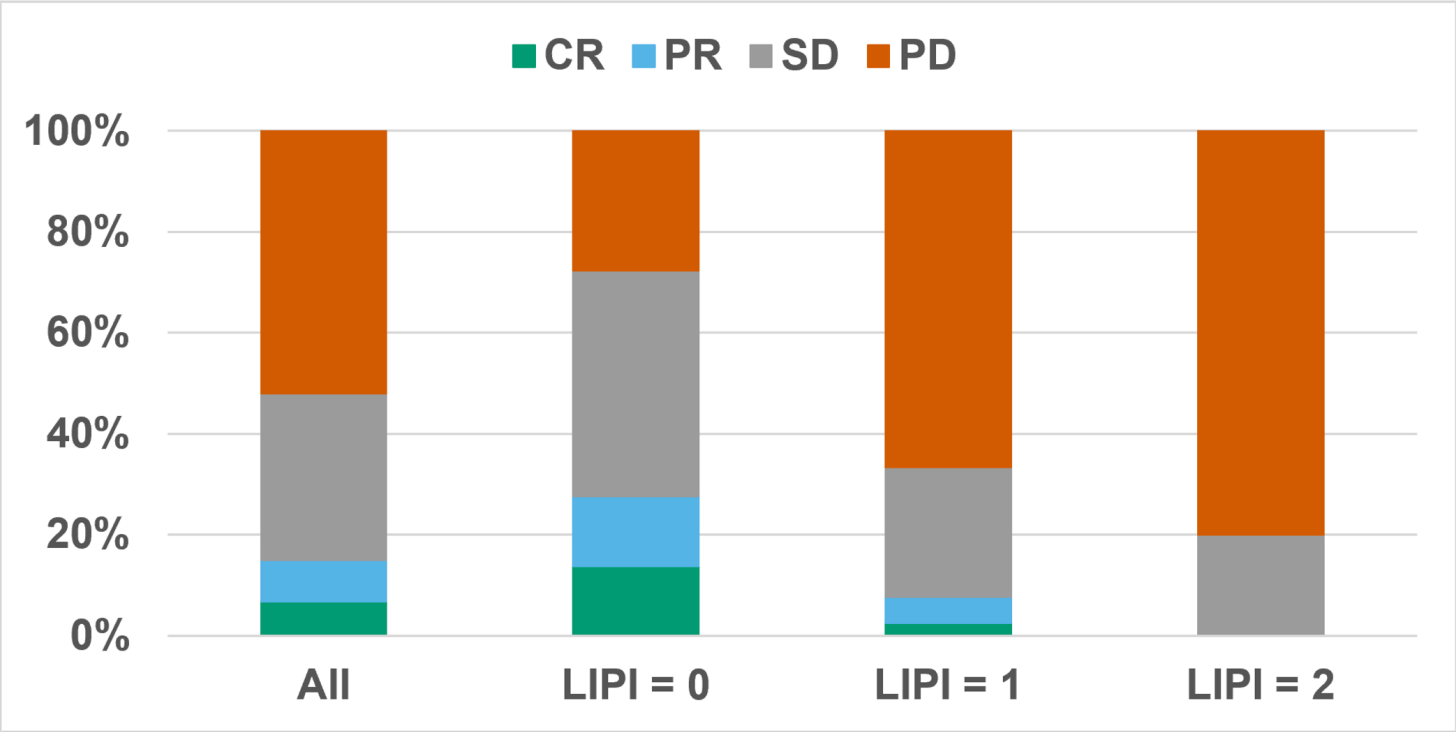


Figure 2

Comparison of pretreatment laboratory parameters according to Lung Immune Prognostic Index (LIPI).

Scatter plots show pretreatment laboratory parameters according to LIPI group (LIPI 0, LIPI 1, and LIPI 2). Horizontal lines indicate the median, and error bars represent the interquartile range. Overall differences among the three groups were assessed using the Kruskal–Wallis test. P values shown in each panel represent the overall comparison. (A) White blood cell count (WBC), (B) neutrophil count, (C) lymphocyte count, (D) neutrophil-to-lymphocyte ratio (NLR), (E) derived neutrophil-to-lymphocyte ratio (dNLR), (F) lactate dehydrogenase (LDH), (G) serum albumin (Alb), and (H) C-reactive protein (CRP).

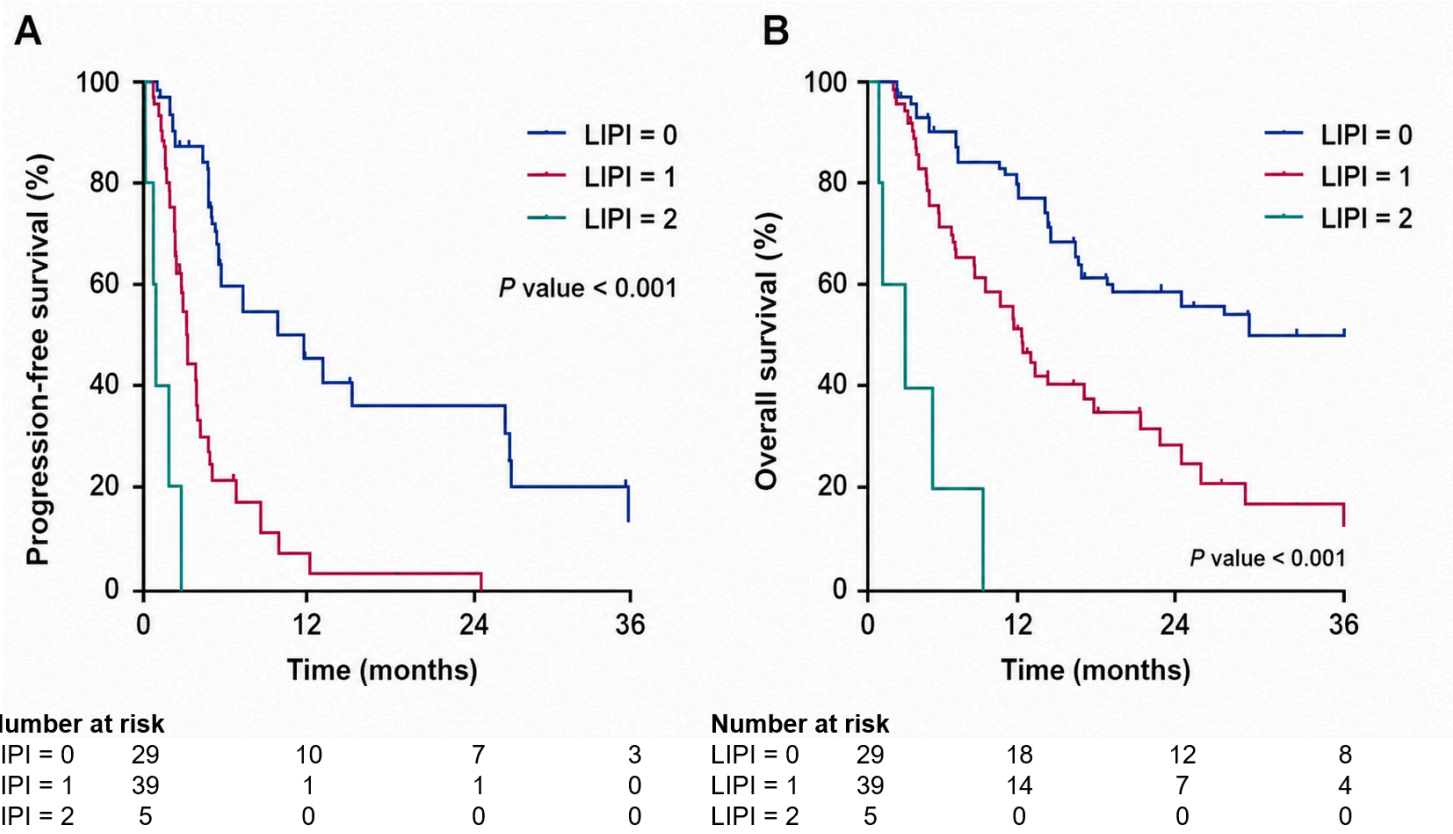


Response	All	LIPI = 0	LIPI = 1	LIPI = 2	*P* value
ORR	11 (15.1)	8 (27.6)	3 (7.7)	0 (0)	0.065
DCR	35 (47.9)	21 (72.4)	13 (33.3)	1 (20.0)	0.002

Figure 3

Best overall response according to the Lung Immune Prognostic Index (LIPI).

Tumor response was assessed according to iRECIST. Data are presented as n (%). ORR, objective response rate; DCR, disease control rate. *P* values were calculated using Fisher's exact test.



Number at risk				
LIPI = 0	29	10	7	3
LIPI = 1	39	1	1	0
LIPI = 2	5	0	0	0

Number at risk				
LIPI = 0	29	18	12	8
LIPI = 1	39	14	7	4
LIPI = 2	5	0	0	0

Figure 4

Kaplan–Meier survival curves according to pretreatment Lung Immune Prognostic Index (LIPI).

(A) Progression-free survival (PFS).

(B) Overall survival (OS).

Survival was compared using the log-rank test. P values are shown in each panel.

Supplementary Files

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