EJMO

DOI: 10.14744/ejmo.2024.67906
EJMO 2024;8(1):24–31

Research Article

Baseline Pan-Immune-Inflammation Value is Associated with Clinical Outcome in Patients with Recurrent or Metastatic Head and Neck Cancer Treated with Immune Checkpoint Inhibitors

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Abstract

Objectives: Immune checkpoint inhibitors (ICIs) have played an important role in the treatment of patients with recurrent or metastatic head and neck cancer (R/M HNC). However, we lack prognostic and predictive markers of ICIs in R/M HNC. In this study, we aimed to evaluate the prognostic and predictive markers of the anticancer effect of ICIs.

Methods: Fifty-seven patients with R/M HNC treated with ICIs were included in this retrospective study. The baseline pan-immune-inflammation value (PIV) was calculated as follows: (neutrophil count × platelet count × monocyte count)/lymphocyte count, with a cut off value of 940.27.

Results: With a median follow-up of 12 months, the 1-year overall survival (OS) rates were significantly lower in the high PIV group compared with those in the low PIV group (OS: 40.0% vs. 73.1%, p=0.03). In the multivariate analyses, we observed that a high PIV was a significantly unfavorable predictor of OS (hazard ratio (HR) 2.52, 95% confidence interval (CI) 1.09–5.81, p=0.003).

Conclusion: For R/M HNC, PIV is an independent survival predictor for the efficacy of ICIs. Novel intensified treatments are needed for the subgroup of patients with R/M HNC and a high PIV.

Keywords: Immune checkpoint inhibitors, recurrent or metastatic head and neck cancer, pan-immune-inflammation value

Cite This Article: *Su Z, Tang J, Zeng WH, He Y, Yin C, Zou GR. Baseline Pan-Immune-Inflammation Value is Associated with Clinical Outcome in Patients with Recurrent or Metastatic Head and Neck Cancer Treated with Immune Checkpoint Inhibitors. EJMO 2024;8(1):24–31.*

Head and neck cancer, arising from the mucosal tissue of the oral cavity, nasal cavity, larynx, pharynx, paranasal sinuses, and salivary glands, is a heterogeneous disease, accounting for more than 650,000 new cancer diagnoses and 330,000 deaths globally per year, and representing the seventh most frequent cancer worldwide.[1, 2] Chemotherapy, primarily using platinum based regimens, combined with surgery or radiation, is the standard treatment for local advanced head and neck cancer. However, approximately 50% of patients with locally advanced head and neck cancer develop recurrence or metastasis.[3] Furthermore, treatment options are limited and the median overall survival (OS) is no more than 1 year.[4] The EXTREME phase 3 study demonstrated that a combination of platinum-based chemotherapy and Cetuximab, a monoclonal antibody targeting the epidermal growth factor re-

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Submitted Date: September 19, 2023 **Revision Date:** December 20, 2023 **Accepted Date:** January 21, 2024 **Available Online Date:** March 06, 2024

ceptor, achieved improved disease control and prolonged the OS of patients with recurrent or metastatic head and neck cancer (R/M HNC), compared with chemotherapy alone.[5] The recently published KEYNOTE-048 trial provided strong evidence for new treatment programs, with the application of immune checkpoint inhibitors (ICIs), either alone or in combination.[6, 7] However, response rates of only 13–18% to programmed death-1 (PD-1) inhibition were observed and higher early mortality for ICIs was reported compared with the active control arms in patients with platinum-resistant disease.[8-10] In the KEYNOTE-048 study, the progression free-survival (PFS) rate at 12 months was 17% in the overall population of patients who were treated with Pembrolizumab alone or in combination with chemotherapy, suggesting that only a small proportion of patients would benefit from ICIs.[6, 7] The objective response rates (ORRs) in studies carried out in China were 40%[11] and 15%.[12] Considering the low survival rate of patients with late-stage HNCs, the decision for salvage therapy must be individualized, with management that involves well-informed patients resulting in the best outcomes, and reduced cost burden and mortality. In addition to investigating new drugs and treatment combinations, there is an urgent need to identify simple, convenient, and feasible factors to improve prognostication and treatment selection.

The pan-immune-inflammation value (PIV), a recently developed biomarker, integrates different peripheral blood immune cell sub-populations (neutrophils, platelets, monocytes, and lymphocytes), and has a great potential to comprehensively represent patient immunity and systemic inflammation. It has been proven that the PIV is a strong predictor of outcomes in advanced cancer patients receiving surgery, traditional chemotherapy, ICIs, and targeted therapy for breast cancer, colorectal cancer, metastatic melanoma, and other advanced cancers.[13-19] However, no study on the role of the PIV in R/M HNC has been performed.

The present study aimed to evaluate the prognostic power of the PIV, including all the immune inflammatory populations from peripheral blood with a proven prognostic relevance in patients with R/M HNC treated with ICIs.

Methods

Our retrospective database was built to include all patients with R/M HNC treated with ICIs in Panyu central hospital between July, 2018 and April, 2022. Demographic features, Eastern Cooperative Oncology Group performance status (ECOG PS), anthropometric measures (weight, height, and body mass index (BMI)), the sites of the primary tumor, baseline lactate dehydrogenase (LDH) levels, and the baseline PIV were recorded or calculated together with the best response to ICIs and survival data. The patients' clinical features (such as fever, rash, and arthritis), past medical history (including concomitant hematological malignancies and current use of corticosteroids), and the results of blood tests, stool tests, urinalysis, chest x-rays, or computed tomography, were thoroughly evaluated. Patients with such causes of abnormal blood tests were excluded.[20] The PIV was calculated using the following equation [neutrophil count (10^3/mL) × platelet count (10^3/mL) × monocyte count (10^3/mL)]/lymphocyte count (10^3/mL).[13-19] This study was approved by the Ethics Committee of Panyu Central Hospital, Guangzhou, China, in accordance with the Declaration of Helsinki and our editorial ethics policy. The written forms of informed consent for individual patients were not required since the study was retrospective, and the data was anonymized or maintained with confidentiality.

Statistical Analysis

Descriptive statistics were presented as the median, interquartile range (IQR; 25th–75th percentile) and standard errors for continuous variables, and frequency and percentages for categorical variables. Fisher's exact test and the Mann–Whitney U test were performed to compare baseline characteristics as appropriate. The 75% PIV quartile value was used as the cut-off for PIV, based on PIV quartiles (Fig. 1). The 75% PIV value was 940.27. The patients were classified into a high PIV or low PIV group according to the 75% PIV value. OS was defined as the period from treatment initiation to the last follow-up and/or death, and PFS was defined as the period between treatment initiation to disease progression and/or death. Survival analyses were conducted using Kaplan–Meier analyses, and comparisons of survival times between prognostic subgroups were carried out using the log-rank test. Multivariate analyses were conducted using Cox-regression analyses and the hazard ratio (HR) was calculated together with the 95% confidence interval (CI). All statistical tests were 2-sided and P values lower than 0.05 were considered statisti-

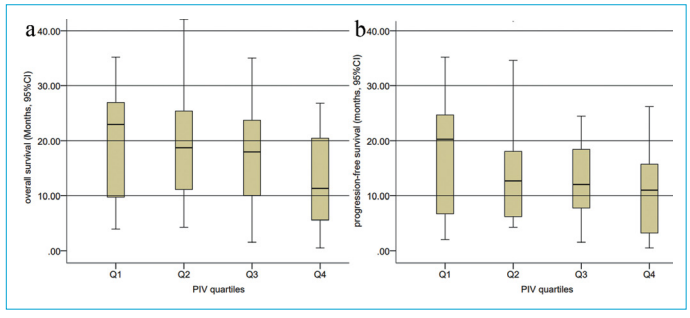

Figure 1. Overall survival **(a)** and progression-free **(b)** according to PIV quartiles.

cally significant. The statistical analyses were performed using SPSS, version 26.0 (IBM Corp., Armonk, NMY, USA).

Results

Participants' Characteristics

The patients' demographic, clinical, and behavioral characteristics are shown in Table 1. A total of 57 patients suffering from R/M HNC were included in this retrospective, anonymized study, with a higher prevalence of males (87.7%) and a median age of 56 years old. Cancer entities were heterogeneous, comprising oral cancer (n=5), oropharyngeal carcinoma (n=9), hypopharyngeal carcinoma (n=14), and nasopharyngeal carcinoma (n=29), with a higher occurrence rate of 50.9%. Twenty-four patients (42.1%) received at least second line treatment. The choice of ICIs was based on the patient's own financial situation. Finally, Triprimab was most frequently prescribed (n=27, 47.4%) and only six patents chose Pembrolizumab because of its expense.

Relationships between Patient Clinical Characteristics and Pretreatment PIV

Table 2 presents the demographic and treatment characteristics of the 57 included patients, of whom 42 (73.7%) and 15 (26.3%) were stratified into the low and high PIV groups, respectively. Patients with a high PIV tended to have an elevated LDH (> upper limit of normal (ULN)) (p=0.011) and a significantly lower BMI (< 18.5) (p=0.002) compared with those in the low PIV group. The groups did not differ significantly in terms of treatment lines and primary cancer sites.

Table 1. Baseline patient characteristics of the study population

Clinical feature	n (%)
Age (median, range)	56 (23.82)
Sex	
Male	50 (87.7)
Female	7 (12.3)
ECOG PS	
0-1	14 (24.6)
2	43 (75.4)
Immunotherapy agent	
Carelizumab	6 (10.5)
Triprimab	27 (47.4)
Tislelizumab	7 (12.3)
Sindillimab	11 (19.3)
Pembrolizumab	6 (10.5)
Primary tumor	
Oral	5 (8.8)
Oropharynx	9 (15.8)
Nasopharynx	29 (50.9)
Hypopharyngeal	14 (24.6)
Line of treatment	
1	33 (57.9)
2 or later	24 (42.1)

Survival Analysis

The patients were followed up for a median of 12 months (range, 1.5 to 50). During the follow up period, 27 patients died and 35 patients experienced disease progression. The 1-year PFS and OS rates for all patients were 55.3% and 64.1%, respectively, and the OS rate was significantly lower in the high PIV group than in the low PIV group (OS: 40.0% vs. 73.1%, p=0.03), whereas the PFS did not differ significantly (PFS: 40.0% vs. 61.1%, p=0.151) (Fig. 2).

Table 2. Comparison of baseline characteristics in the PIV low and high groups

	Low PIV group	High PIV group	p
Age			0.131
<56	17	10	
>56	25	5	
Sex			0.07
Male	39	11	
Female	3	4	
ECOG PS			0.825
0-1	10	4	
2	32	11	
Immunotherapy agent			0.797
Carelizumab	4	2	
Triprimab	21	6	
Tislelizumab	4	3	
Sindillimab	8	3	
Pembrolizumab	5	1	
Primary tumor			0.525
Oral	5	0	
Oropharynx	7	2	
Nasopharynx	20	9	
Hypopharyngeal	10	4	
Lines of treatment			0.677
1	25	8	
2 or later	17	7	
LDH levels			
Normal	31	5	0.011
>ULN	11	10	
Smoking			0.713
Yes	7	3	
No	35	12	
BMI			0.002
<18.5	3	7	
>18.5	39	8	

Analysis of Prognostic Factors

The results of univariate and multivariate analyses performed to identify prognostic factors for PFS and OS are shown in Table 3 and Table 4, respectively.

The univariate analysis (Table 3) revealed significant associations between a high PIV and poor OS (HR 2.33, 95% CI 1.06–5.13, p=0.035). ECOG PS (HR 3.74, 95% CI 1.12–12.51, p=0.032), LDH levels (HR 2.30, 95% CI 1.08–4.90, p=0.031), primary tumor site (HR 1.94, 95% CI 1.13–3.15, p=0.016) and lines of treatment (HR 2.45, 95% CI 1.13–5.28, p=0.023), all of which were associated with a significantly decreased OS. Significant associations of LDH levels (HR 2.44, 95% CI 1.25–4.78, p=0.009), primary tumor site (HR 1.79, 95% CI 1.13–2.84, p=0.013) and lines of treatment (HR 2.58, 95% CI 1.32–5.07, p=0.006) with PFS were observed, too.

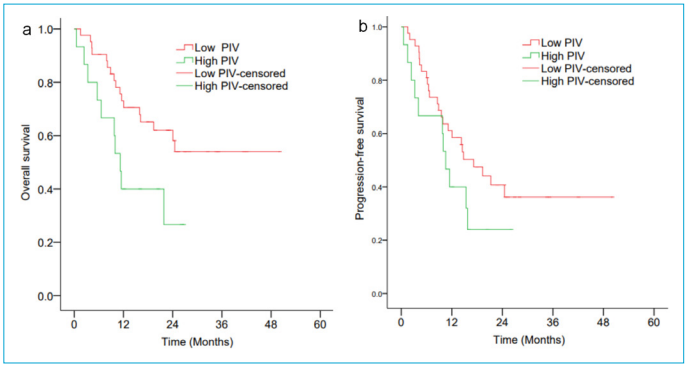

Figure 2. The association between the PIV and overall survival **(a)** and progression-free survival **(b)** assessed using the Kaplan–Meier method and a log-rank test.

In the Cox multivariate analysis (Table 4), high PIV was associated with worse OS (adjusted HR 2.52, 95% CI 1.09–5.81; p=0.003). In addition, ECOG PS (adjusted HR 6.89, 95% CI 1.95–24.33, p=0.003), LDH levels (adjusted HR 2.18, 95% CI 0.99–4.80, p=0.053), primary tumor site (adjusted HR 3.27, 95% CI 1.51–7.08, p = 0.003), and lines of treatment (adjusted HR 3.43, 95% CI 1.51–7.78, p=0.003) were associated with survival outcomes. ECOG PS (adjusted HR 3.01, 95% CI 1.20–7.52, p=0.019), LDH levels (adjusted HR 2.49, 95% CI 1.23–5.04, p=0.011), primary tumor site (adjusted HR 2.65, 95% CI 1.45–4.83, p = 0.001) and lines of treatment (adjusted HR 4.05, 95% CI 1.89–8.68, p<0.001) were identified as prognostic factors for PFS.

Discussion

ICIs have played an important role in the treatment of patients with R/M HNC. However, the curative effect of this treatment in different patients remains to be clarified. Prognostic factors for ICIs have yet to be defined. Therefore, we focused on patients with R/M HNC who received

Table 3. Univariate analyses for overall survival and progression free survival

Variables	OS		PFS	
	HR (95%CI)	p	HR (95%CI)	p
Age	1.06(0.49-2.29)	0.88	0.99(0.50-1.94)	0.970
Gender	0.86(0.26-2.87)	0.81	0.81(0.28-2.31)	0.691
Smoking	1.04(0.39-2.75)	0.93	1.16(0.50-2.65)	0.734
BMI	0.61(0.25-1.52	0.29	0.98(0.40-2.36)	0.956
ECOG	3.74(1.12-12.51)	0.032	2.18(0.90-5.28)	0.084
Primary tumor	1.94(1.13-3.15)	0.016	1.79(1.13-2.84)	0.013
Lines of treatment	2.45(1.13-5.28)	0.023	2.58(1.32-5.07)	0.006
LDH	2.30(1.08-4.90)	0.031	2.44(1.25-4.78)	0.009
PIV	2.33(1.06-5.13)	0.035	1.68(0.82-3.46)	0.156

Table 4. Multivariate analyses for overall survival and progression free survival

Variables	OS		PFS	
	HR (95%CI)	p	HR (95%CI)	p
ECOG	6.89 (1.95-24.33)	0.003	3.01 (1.20-7.52)	0.019
Primary tumor	3.27 (1.51-7.08)	0.003	2.65 (1.45-4.83)	0.001
Lines of treatment	3.43 (1.51-7.78)	0.003	4.05 (1.89-8.68)	<0.001
LDH	2.18 (0.99-4.80)	0.053	2.49 (1.23-5.04)	0.011
PIV	2.52 (1.09-5.81)	0.003	/	/

ICIs and analyzed the associations between outcomes and clinical parameters obtained in routine clinical practice. In the present study, we found that a high PIV was associated with poor clinical outcomes in patients with R/M HNC. We propose that the baseline PIV, derived from simple routine blood tests, should be used as a predictive or prognostic marker for the efficacy of ICIs in these patients.

Prior treatment effects on tumor cells mean that recurrent cancer has a higher likelihood of tumor cells infiltrating the tissue, and is multifocal.[21] The choice of salvage treatment is often limited because of such prior therapy and the increasing morbidity of re-treatment. The costs of treatment must be measured against the anticipated quality and quantity of life recovered, even in cases of resectable disease. A systematic review revealed that Nivolumab was not cost-effective compared with chemotherapy for R/M HNC, in which Nivolumab was compared with "standard" therapy, based on three Markov modeling studies evaluating the cost effectiveness of Nivolumab for R/M HNCs.[22-25] From the perspective of American patients, as payers, first-line Pembrolizumab monotherapy in patients with combined positive scores (CPS) ≥ 1, and Pembrolizumab combination therapy in the overall R/M HNC population are cost-effective.[26] However, Pembrolizumab is not likely to be a cost-effective strategy in China.[27] At present, domestic immunotherapy drugs have been reduced in price; however, their status in recurrent metastatic head and neck tumors is unclear, with only phase I/II studies being carried out involving a very small number of enrolled patients.[11, 12] Based on cost effectiveness research, it is important and necessary to select patients who would benefit from ICIs.

A number of prognostic and predictive factors for ICI efficacy have been studied. Human Papillomavirus (HPV) positivity is proposed to be predictive of a better response to ICIs in head and neck squamous cell carcinoma (HNSCC) because of the less immunosuppressive environment in HPV positive tumors.[28, 29] Indeed, some trials reported higher response rates in patients with p16 and/or HPV positive tumors when treated with Pembrolizumab, Durvalumab, and Nivolumab.[10, 30, 31] However, in the KEYNOTE-040 and KEYNOTE 055 studies, these differences in response were not observed, and in the clinically most relevant KEYNOTE 048 study, the benefit from Pembrolizumab was observed independently of p16 status.[7, 32, 33] The prognosis of HPV infection and p16 positivity are still unclear in non oropharyngeal HNC and at present, routine testing is not recommended.[34] Based on the results of the KEYNOTE-048 study, Pembrolizumab is recommended in R/M HNC with combined positive scores (CPS) > 1, leading to compulsory and mandatory CPS testing in patients with recurrent or metastatic disease.[7] In the KEYNOTE-040 study, programmed death ligand 1 (PD-L1) expression was only evaluated in tumor cells and the thresholds of ≥ 1%, ≥ 5%, and ≥ 10% showed no clear correlation with improved survival outcomes.[10] An increased benefit of Nivolumab compared with that of standard of care in patients with programmed cell death 1 ligand 1 (PD-L1)-negative disease was observed during longer follow-up.[35] In the EAGLE-trial, PD-L1 status was determined on tumor cells only and cut-offs of ≥ 25% and ≥ 1% were used, showing no benefit of Durvalumab alone or in combination with Tremilimumab in PD-L1 positive patients.[9] The inconsistent results of trials investigating ICIs in HNC indicate that it remains unclear which PD-L1 cut-off and detection method best serve as a biomarker in HNC. A high tumor mutational burden (TMB), which is estimated from whole exome sequencing or comprehensive gene panels, is thought to provide a high number of neoantigens and thus enhances the immunogenicity of the tumor, thereby improving the response to ICIs. The TMB correlates significantly with the objective response rate to anti-PD-1 or anti-PD-L1 therapy based on a landmark analysis of 27 tumor types.[36] However, the results of research on the TMB in R/M HNC are conflicting. The cut-off points were different and one was evaluated in plasma samples.[37, 38] Moreover, studies have shown that tumor infiltrating lymphocytes and circulating immune cells have the potential to serve as prognostic and predictive biomarkers in HNC.[39, 40] Increasing numbers of predictive biomarkers for ICIs in HNC are being investigated.[41] However, in our opinion, these biomarkers are obscure, complicated, and difficult to apply. There is still a long way to go from research to mature clinical practice. The routine determination of these biomarkers remains challenging and they also require validation in prospective trials. Taken together, the role of these indicators is not clear and the detection technology is not mature. Furthermore, such unconventional examinations are expensive, increasing the financial burden of patients.

PIV is a recently developed biomarker that is based on peripheral blood cell counts, and integrates different subsets of peripheral blood immune cells, i.e., neutrophils, platelets, monocytes, and lymphocytes. Considering that it might combine immunity and systemic inflammation, PIV was deemed to be a powerful and robust predictor of outcomes in cancer patients receiving surgery, conventional chemotherapy, targeted therapy and especially ICIs.[13-19] PIV plays a very important role in predicting the efficacy of ICIs in advanced cancer.[17] In this study, most patients had renal cell carcinoma (n=39, 32.5%), non-small cell lung cancer (n=32, 26.7%), or melanoma (n=22, 18.7%); however, only five patients had HNC. Patients with a higher PIV had significantly decreased OS (7.75±1.64 vs. 18.63±4.26 months, p=0.037) compared with those with a low PIV.

Combined with LDH (normal vs. higher than normal) and ECOG PS, PIV can distinguish patients who would gain a survival benefit from ICIs.[17] Moreover, in a study of the PIV in patients with metastatic melanoma, a high PIV was also associated with primary resistance to both immunotherapy (odds ratio [OR]: 3.98; 95% CI 1.45–12.32; p=0.005) and targeted therapy (OR: 8.42; 95% CI 2.50–34.5; p<0.001); thus, the PIV might guide the treatment decision process and the development of novel first-line treatment strategies.[18] More interestingly, in patients with breast cancer treated with neoadjuvant chemotherapy, the low PIV group had significantly better disease-free survival and OS than those in the high PIV group (p=0.034, p=0.028, respectively).[15] In line with the above mentioned studies, we showed that patients with R/M HNC with a high PIV had a poor survival outcome. Furthermore, to the best of our knowledge, this is the first study to report the PIV as a reliable predictor of OS in patients with R/M HNC. In contrast to the above mentioned markers, the PIV is a simple, readily available, and inexpensive marker. The tests to detect peripheral blood immune cells are mature and robust. More importantly, they are routine tests carried out at no extra cost to the patient, which are cheap, convenient, and stable, and thus have a great clinical prospects.

Several limitations of this study should be discussed. First, the study's retrospective nature and the small patient numbers made it difficult to draw definitive conclusions. Second, we were unable to adjust for tissue PD-L1 levels because of insufficient data in most cases. Our cohort included a heterogeneous group of patients and most of our patients were treated with ICIs in the later stages because of reimbursement and financial issues. However, despite these limitations, we demonstrated the potential of a simple biomarker derived from the complete blood count data and basic clinical variables in patients with R/M HNC treated with ICIs. Subject to validation in prospective studies, we believe that the PIV is a promising biomarker for the efficacy of ICIs.

Conclusion

In conclusion, this study demonstrated that a high baseline PIV was associated with poor survival after ICI treatment in patients with R/M HNC. We propose that the baseline PIV could be used as a predictive or prognostic marker for the efficacy of ICIs in these patients. Further studies are needed to determine the value of the PIV in the context of other biomarkers of checkpoint therapy.

Disclosures

Ethics Committee Approval: This study was approved by the Ethics Committee of Panyu Central Hospital, Guangzhou, China, in accordance with the Declaration of Helsinki and our editorial ethics policy.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

Funding: This work was supported by the Panyu Science and Technology Medical Project, Guangzhou, China (Grant number 2019-Z04-29) and the Guangzhou Municipal Health Commission (grant number 20211A011115).

Authorship Contributions: Zhen Su, Jie Tang, Wei hua Zeng, Yan He, Chen Yin, and Guo rong Zou contributed to the study conception and design. Jie Tang and Guo rong Zou contributed to supervision. Zhen Su, Jie Tang, Yan He, Wei Hua, Zeng and Chen Yin performed material preparation, data collection and analysis. Zhen Su done the literature search and wrote the first draft. Zhen Su, Jie Tang and Guo rong Zou contributed to critical review. All authors read and approved the final manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
3. Leeman JE, Li JG, Pei X, Venigalla P, Zumsteg ZS, Katsoulakis E, et al. Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques. JAMA Oncol 2017;3:1487–94.
4. Argiris A, Harrington KJ, Tahara M, Schulten J, Chomette P, Ferreira Castro A, et al. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. Front Oncol 2017;7:72.
5. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
6. Harrington KJ, Burtness B, Greil R, Soulieres D, Tahara M, de Castro G, Jr., et al. Pembrolizumab with or without chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma: Updated results of the Phase III KEYNOTE-048 Study. J Clin Oncol 2023;41:790–802.
7. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, Jr., et al. 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 2019;394:1915–28.
8. Larkins E, Blumenthal GM, Yuan W, He K, Sridhara R, Subrama-

niam S, et al. FDA approval summary: Pembrolizumab for the treatment of recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy. Oncologist 2017;22:873–8.
9. Ferris RL, Haddad R, Even C, Tahara M, Dvorkin M, Ciuleanu TE, et al. Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study. Ann Oncol 2020;31:942–50.
10. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.
11. Ju H, Wei D, Wu Y, Liu Y, Ding Q, Rui M, et al. A pilot study of camrelizumab with docetaxel and cisplatin for the first line treatment in recurrent/metastatic oral squamous cell carcinoma. MedComm 2020 2023;4:e312.
12. Desai J, Deva S, Lee JS, Lin CC, Yen CJ, Chao Y, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J ImmunoTher Cancer 2020;8:e000453.
13. Sato S, Shimizu T, Ishizuka M, Suda K, Shibuya N, Hachiya H, et al. The preoperative pan-immune-inflammation value is a novel prognostic predictor for with stage I-III colorectal cancer patients undergoing surgery. Surg Today 2022;52:1160–9.
14. Lin F, Zhang LP, Xie SY, Huang HY, Chen XY, Jiang TC, et al. Pan-immune-inflammation value: A new prognostic index in operative breast cancer. Front Oncol 2022;12:830138.
15. Sahin AB, Cubukcu E, Ocak B, Deligonul A, Oyucu OS, Tolunay S, et al. Low pan-immune-inflammation-value predicts better chemotherapy response and survival in breast cancer patients treated with neoadjuvant chemotherapy. Sci Rep 2021;11:14662.
16. Ligorio F, Fuca G, Zattarin E, Lobefaro R, Zambelli L, Leporati R, et al. The pan-immune-inflammation-value predicts the survival of patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer treated with first-line taxane-trastuzumab-pertuzumab. Cancers Basel 2021;13:1964.
17. Guven DC, Yildirim HC, Bilgin E, Aktepe OH, Taban H, Sahin TK, et al. PILE: A candidate prognostic score in cancer patients treated with immunotherapy. Clin Transl Oncol 2021;23:1630–6.
18. Fuca G, Beninato T, Bini M, Mazzeo L, Di Guardo L, Cimminiello C, et al. The pan-immune-inflammation value in patients with metastatic melanoma receiving first-line therapy. Target Oncol 2021;16:529–36.
19. Fuca G, Guarini V, Antoniotti C, Morano F, Moretto R, Corallo S, et al. The pan-immune-inflammation value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the valentino and TRIBE first-line trials. Br J Cancer 2020;123:403–9.
20. Su Z, Mao YP, OuYang PY, Tang J, Xie FY. Initial hyperleukocytosis and neutrophilia in nasopharyngeal carcinoma: Incidence and prognostic impact. PLoS One 2015;10:e0136752.
21. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck 2014;36:144–51.
22. Ward MC, Shah C, Adelstein DJ, Geiger JL, Miller JA, Koyfman SA, et al. Cost-effectiveness of nivolumab for recurrent or metastatic head and neck cancer. Oral Oncol 2017;74:49–55.
23. Tringale KR, Carroll KT, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness analysis of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. J Natl Cancer Inst 2018;110:479–85.
24. Verma V, Sprave T, Haque W, Simone CB, 2nd, Chang JY, Welsh JW, et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. J Immunother Cancer 2018;6:128.
25. Zargar M, McFarlane T, Chan KKW, Wong WWL. Cost-effectiveness of nivolumab in recurrent metastatic head and neck squamous cell carcinoma. Oncologist 2018;23:225–33.
26. Borse RH, Ramakrishnan K, Gandhi J, Dhankhar P, Chirovsky D. Cost-effectiveness of pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma in the United States. J Med Econ 2022;25:954–65.
27. Xin W, Ding H, Fang Q, Zheng X, Tong Y, Xu G, et al. Cost-effectiveness of pembrolizumab for treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma in China: An economic analysis based on a randomised, open-label, phase III trial. BMJ Open 2020;10:e038867.
28. Partlova S, Boucek J, Kloudova K, Lukesova E, Zabrodsky M, Grega M, et al. Distinct patterns of intratumoral immune cell infiltrates in patients with HPV-associated compared to non-virally induced head and neck squamous cell carcinoma. Oncoimmunology 2015;4:e965570.
29. Lechner A, Schlosser HA, Thelen M, Wennhold K, Rothschild SI, Gilles R, et al. Tumor-associated B cells and humoral immune response in head and neck squamous cell carcinoma. Oncoimmunology 2019;8:e1535293.
30. Mehra R, Seiwert TY, Gupta S, Weiss J, Gluck I, Eder JP, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: Pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer 2018;119:153–9.
31. Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: Results from a single-arm, phase II study in patients with >/=25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. Eur J Cancer 2019;107:142–52.
32. Cohen EEW, Soulieres D, Le Tourneau C, Dinis J, Licitra L, Ahn

MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): A randomised, open-label, phase 3 study. Lancet 2019;393:156–67.
33. Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: Results from a single-arm, phase II study. J Clin Oncol 2017;35:1542–9.
34. Fakhry C, Lacchetti C, Rooper LM, Jordan RC, Rischin D, Sturgis EM, et al. Human papillomavirus testing in head and neck carcinomas: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists Guideline. J Clin Oncol 2018;36:3152–61.
35. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-Year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol 2018;81:45–51.
36. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. N Engl J Med 2017;377:2500–1.
37. Hanna GJ, Lizotte P, Cavanaugh M, Kuo FC, Shivdasani P, Frieden A, et al. Frameshift events predict anti-PD-1/L1 response in head and neck cancer. JCI Insight 2018;3:e98811.
38. Li W, Ye J, Si H, Shetty J, He P, Raja R, et al. Plasma-based tumor mutational burden (bTMB) as Predictor for Survival in Phase III EAGLE Study: Durvalumab (D) ± Tremelimumab (T) versus Chemotherapy (CT) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) after platinum failure. J Clin Oncol 2020;38(suppl15):6511.
39. de Ruiter EJ, Ooft ML, Devriese LA, Willems SM. The prognostic role of tumor infiltrating T-lymphocytes in squamous cell carcinoma of the head and neck: A systematic review and meta-analysis. Oncoimmunology 2017;6:e1356148.
40. Zhang XM, Song LJ, Shen J, Yue H, Han YQ, Yang CL, et al. Prognostic and predictive values of immune infiltrate in patients with head and neck squamous cell carcinoma. Hum Pathol 2018;82:104–12.
41. Pfister DG, Haddad RI, Worden FP, Weiss J, Mehra R, Chow LQM, et al. Biomarkers predictive of response to pembrolizumab in head and neck cancer. Cancer Med 2023;12:6603–14.