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Penpulimab and Anlotinib for R/M HNSCC Patients After Platinum-Based Therapy Failure: A Phase II Multicenter Study

Katarina Jelena Markovic[1]*, Milos Petar Jovanovic[1], Ana Sofija Popovic[1]

[1]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia.

***E-mail** ✉ k.markovic.uns@yahoo.com

Abstract

Patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) who no longer respond to platinum-based chemotherapy have few effective treatment options, and outcomes with current therapies are modest. This phase II, single-arm, multicenter study evaluated the combination of the PD-1 inhibitor penpulimab (200 mg) with the anti-angiogenic agent anlotinib (12 mg) in R/M HNSCC patients who progressed following at least one platinum-based chemotherapy regimen.Out of 38 enrolled participants, 13 (34.2%) achieved partial tumor shrinkage, while 16 (42.1%) maintained disease stability. Over a median follow-up of 7.06 months (range: 4.14–15.70), the objective response rate determined by independent review was 34.2%, and the overall disease control rate reached 76.3%. Median progression-free survival was 8.35 months (95% CI: 5.95–13.11). Twelve deaths occurred during follow-up, and median overall survival was not yet reached; the 12-month overall survival rate was 59.8%. Grade 3 or 4 treatment-related adverse events were observed in 47.4% of patients. Combining penpulimab with anlotinib demonstrated encouraging anti-tumor activity and an acceptable safety profile in R/M HNSCC patients after platinum therapy failure.

Keywords: Head and neck squamous cell carcinoma, Penpulimab, Anlotinib, PD-1, Anti-angiogenic therapy

Introduction

Head and neck cancers are among the most frequently diagnosed malignancies, typically occurring in the oral cavity, oropharynx, hypopharynx, or larynx. Approximately 90% of these tumors arise from the squamous cells of the mucosal epithelium and are classified as head and neck squamous cell carcinoma (HNSCC). In China, an estimated 74,500 new cases and 36,600 deaths from HNSCC were reported in 2015 [1]. Globally, HNSCC accounted for around 931,000 new cases and 467,000 deaths in 2020 [2]. Because early detection is challenging, many patients are diagnosed at a locally advanced stage, and even after surgical and radiotherapeutic interventions, over half experience local recurrence or distant metastases [3]. Only a minority of patients with recurrent or metastatic (R/M) HNSCC are eligible for radical surgery or definitive radiotherapy [4]. Platinum-based chemotherapy remains the standard first-line treatment for R/M HNSCC; however, its therapeutic effect is limited [5, 6]. This underscores the need to explore effective and safe second-line treatments for patients who progress after platinum-based therapy.

Immunotherapy has recently advanced in the management of various cancers, including HNSCC. As an immunosuppressive disease, HNSCC is associated with reduced lymphocyte counts, impaired natural killer cell activity, and decreased antigen-presenting capacity compared to healthy individuals [7, 8]. Key T-cell immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1), transmit inhibitory signals to cytotoxic T lymphocytes, enabling tumors to evade immune

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surveillance [9]. PD-1 inhibitors have received approval for first-line treatment of HNSCC [10]. Both earlier and updated studies indicate that immunotherapy, alone or combined with chemotherapy, represents a viable first-line treatment option in the definitive setting for HNSCC [11-13].

Tumor angiogenesis is essential for tumor progression and metastasis, as newly formed blood vessels provide oxygen and nutrients to the growing tumor mass [14]. Angiogenesis is regulated primarily via three pathways: vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), with interactions among them playing a central role in controlling vascular development in tumors [15, 16]. Among these, VEGFR-2 signaling is particularly critical and is considered the key driver of tumor angiogenesis, making it the main target of current anti-angiogenic therapies [17, 18].

For R/M HNSCC patients who have progressed after platinum-based chemotherapy, treatment options—such as single-agent cytotoxic drugs, targeted therapies, or immunotherapy—generally provide limited benefit. Tyrosine kinase inhibitors (TKIs) have been shown to modulate the tumor microenvironment, enhance CD8+ T-cell infiltration, and relieve tumor-induced immunosuppression, thereby improving the efficacy of immune checkpoint inhibitors [19]. Anlotinib, a novel multi-target TKI with anti-angiogenic properties, can produce synergistic effects when combined with immunotherapy. Studies indicate that anlotinib can reduce programmed death-ligand 1 (PD-L1) expression on endothelial cells and increase the local CD8+/FoxP3+ ratio, enhancing antitumor immunity [20]. Tumors often exist in a locally immunosuppressive state, characterized by high VEGF and PD-L1 expression, which impairs lymphocyte adhesion to endothelial cells, limits lymphocyte infiltration, and promotes immune escape [21, 22]. These findings suggest that combining immunotherapy with anti-angiogenic therapy may represent a promising approach for treating HNSCC.

Penpulimab and anlotinib

Penpulimab is a humanized monoclonal antibody targeting PD-1, developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd., China. It received approval from the China National Medical Products Administration (NMPA) on August 3, 2021. The antibody is composed of two γ1 heavy chains and two κ light chains connected by disulfide bonds, with modifications in its Fc region to prevent Fc receptor binding and complement-mediated cytotoxicity [23].

Anlotinib, also developed by the same company, was approved by NMPA on May 8, 2018 [24]. This multi-target small-molecule tyrosine kinase inhibitor not only inhibits angiogenesis but also suppresses tumor proliferation and metastasis. It has shown clinical activity and an acceptable safety profile across various solid tumors, including as a third-line treatment in advanced non-small-cell lung cancer [25].

Immunotherapy has emerged as a promising approach for patients with recurrent or metastatic HNSCC (R/M HNSCC). Clinical evidence suggests that combining PD-1 inhibitors with chemotherapy can improve survival outcomes in these patients [10]. However, data on combining immunotherapy with targeted therapies—particularly VEGFR-targeting TKIs—remain limited. The current study was designed to explore the safety and anti-tumor efficacy of penpulimab in combination with anlotinib in R/M HNSCC patients who had previously failed at least one platinum-based chemotherapy regimen.

Materials and Methods

Study design and patient selection

This phase II, single-arm, open-label study was conducted at 11 hospitals in China. Eligible participants were adults (≥18 years) with histologically confirmed R/M HNSCC, measurable disease per RECIST 1.1, ECOG performance status of 0–1, and an expected survival exceeding 3 months. All patients must have experienced disease progression following at least one line of platinum-based chemotherapy. Lesions previously irradiated could be considered measurable if disease progression was documented post-treatment.

Exclusion criteria included prior treatment with PD-1/PD-L1 antibodies or anti-angiogenic agents, participation in other clinical trials or receipt of anticancer therapy within 4 weeks, presence of other malignancies within 5 years, pregnancy or lactation, and severe comorbid conditions.

The study adhered to the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and was approved by the ethics committees of all participating centers. Written informed consent was obtained from each patient before enrollment. The trial is registered at ClinicalTrials.gov (NCT04203719).

Procedures and assessments

In this study, patients received penpulimab at a fixed intravenous dose of 200 mg on day 1 of a 21-day treatment cycle. Anlotinib was administered orally at 12 mg daily for the first 14 days of each 21-day cycle.

While penpulimab dosing remained constant, anlotinib could be reduced in response to grade ≥3 treatment-related adverse events (TRAEs) at the investigator's discretion. Dose reductions were sequential from 12 mg to 10 mg and then to 8 mg, without the option to revert to a previous lower dose. If patients on reduced doses demonstrated stable safety profiles but were at risk of disease progression, the dose could be escalated back to the previous level. Patients unable to tolerate the 8 mg dose were required to discontinue anlotinib.

Endpoints

Efficacy analyses were performed on the full analysis set (FAS), defined as all patients who received at least one dose of the study drugs. The primary endpoint was the objective response rate (ORR) assessed by an independent review committee (IRC). Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety outcomes. Tumor responses were evaluated according to RECIST version 1.1 criteria. ORR was calculated as the proportion of patients achieving either complete response (CR) or partial response (PR). CR was defined as the complete disappearance of all target lesions, with any pathological lymph nodes reduced to a short axis <10 mm. PR required at least a 30% reduction in the sum of diameters of target lesions from baseline. DCR included CR, PR, and stable disease (SD). DoR was measured from the date of first confirmed CR or PR until disease progression or death. PFS was defined as the time from the first treatment dose to documented progression or death from any cause, and OS as the time from treatment initiation to death from any cause. In cases of progressive disease per RECIST 1.1, iRECIST criteria were applied to guide subsequent treatment decisions [26].

Tumor assessments using CT or MRI were performed at baseline and repeated every 6 weeks until disease progression was confirmed. Treatment continued until progression or intolerable toxicity occurred. Safety was evaluated in the safety set (SS), which included all patients who received at least one dose of the study drugs and had post-treatment safety data, according to the NCI-CTCAE version 5.0.

Statistical analysis

Previous studies reported an ORR of 5.8% for chemotherapy alone [27]. The combination of penpulimab and anlotinib was hypothesized to achieve an ORR of 18%. With a one-sided significance level of 0.05 and 80% statistical power, 34 patients were required; to account for a potential 10% dropout rate, 38 patients were enrolled.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). The Clopper-Pearson method was used to calculate 95% confidence intervals (CI) for ORR. Kaplan-Meier methodology was applied to estimate median PFS and OS, with 95% CIs calculated using the Brookmeyer-Crowley approach.

Results and Discussion

Patient characteristics

Between June 1, 2020, and November 22, 2021, a total of 52 patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) were screened for eligibility, and 38 were enrolled across eight hospitals in China **(Figure 1).** The study population included 32 males (84.2%) and 6 females (15.8%), with a median age of 61.5 years (range: 34–79). Tumor sites were distributed as follows: oral cavity in 15 patients (39.5%), larynx in 10 (26.3%), oropharynx in 6 (15.8%), hypopharynx in 4 (10.5%), and other head and neck locations in 3 (7.9%).

All patients had an ECOG performance status of ≤2. Distant metastases were present in 29 patients (76.3%), with a median of 2 metastatic sites per patient (range: 1–7). Most patients (32, 84.2%) were classified as stage IVA–IVC according to the AJCC 8th edition. Prior treatments included chemotherapy in 37 patients (97.4%) and targeted therapy in 6 patients (15.8%), with an average of 1.6 prior therapy lines (range: 1–4). Regarding HPV-P16 status, 7 patients (18.4%) were positive, 29 (76.3%) were negative, and 2 (5.3%) had unknown status.

Baseline patient characteristics are summarized in **Table 1.**

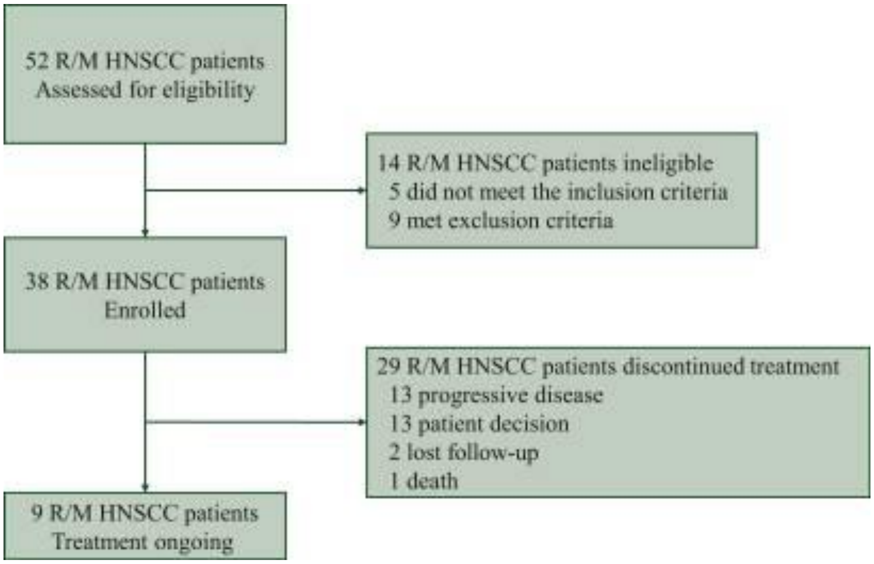


Figure 1. The flowchart of patient disposition. R/M, recurrent or metastatic; HNSCC, head and neck squamous cell carcinoma.

Table 1. Baseline characteristics of patients in the FAS

	Patients (*N* = 38)
Age, year, median (range)	61.5 (34.0-79.0)
Sex	
Male	32 (84.21%)
Female	6 (15.79%)
ECOG PS	
0	3 (7.89%)
1	35 (92.11%)
Primary tumor site	
Hypopharyngeal cancer	4 (10.53%)
Laryngeal cancer	10 (26.32%)
Oral cancer	15 (39.47%)
Oropharyngeal cancer	6 (15.79%)
Other cancer	3 (7.89%)
Clinical stage (AJCC 8th edition)	
IA	1 (2.63%)
IIA	2 (5.26%)
IIIA	1 (2.63%)
IIIB	2 (5.26%)
IVA	14 (36.84%)
IVB	15 (39.47%)
IVC	3 (7.89%)
Metastasis	29 (76.32%)
Number of metastatic sites (median)	2 (1-7)
Bone metastases	5 (13.16%)
Brain metastases	0 (0.00%)
Liver metastases	2 (5.26%)
Lung metastases	11 (28.9%)
Lymphatic metastases	19 (50.0%)
Previous surgery	27 (71.05%)
Previous conservative surgery	4 (10.53%)

Previous targeted therapy	6 (15.79%)
Previous radiotherapy	28 (73.68%)
Previous radio/chemoradiotherapy	27 (71.05%)
Previous treatment lines on average	1.6 (range: 1-4)
Adjuvant radio/chemoradiotherapy	24 (63.16%)
Smoking history	15 (39.47%)
Alcohol history	12 (31.58%)
HPV-P16 status	
Positive	7 (18.42%)
Negative	29 (76.32%)
Unknown	2 (5.26%)

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; PS, performance status; HPV, human papillomavirus.

Efficacy

At the data cut-off on January 6, 2022, the median follow-up duration was 7.06 months (95% CI: 4.14–15.70 months), and the study successfully met its primary endpoint. The objective response rate (ORR), as assessed by the independent review committee (IRC), was 34.2% (13/38; 95% CI: 19.6–51.4%), with all responses being partial responses (PR). Additionally, 16 patients (42.1%) achieved stable disease (SD). Tumor shrinkage was observed in 23 patients (60.5%) **(Figures 2a and 2b).** Three patients (7.9%) experienced immune unconfirmed progressive disease (iUPD), while 6 patients (15.8%) were not evaluable. The disease control rate (DCR) was 76.3% (29/38; 95% CI: 59.8–88.6%) **(Table 2).**

Median treatment exposure was 5.26 months for penpulimab (range: 0.03–19.42 months) and 4.22 months for anlotinib (range: 0.23–19.15 months). The median time to response was 2.66 months (95% CI: 1.38–2.76 months) **(Figure 2c).** Among the 13 patients achieving PR, tumor locations included oral cavity (n=5), oropharynx (n=3), larynx (n=2), hypopharynx (n=2), and neck squamous carcinoma (n=1). Notably, patients with oropharyngeal and hypopharyngeal cancers demonstrated higher ORRs, each reaching 50% (3/6; 95% CI: 11.8–88.2% and 2/4; 95% CI: 6.8–93.2%, respectively) **(Table 2).** Regarding HPV-P16 status, 28.6% (2/7) of HPV-P16-positive patients and 34.5% (10/29) of HPV-P16-negative patients achieved a partial response.

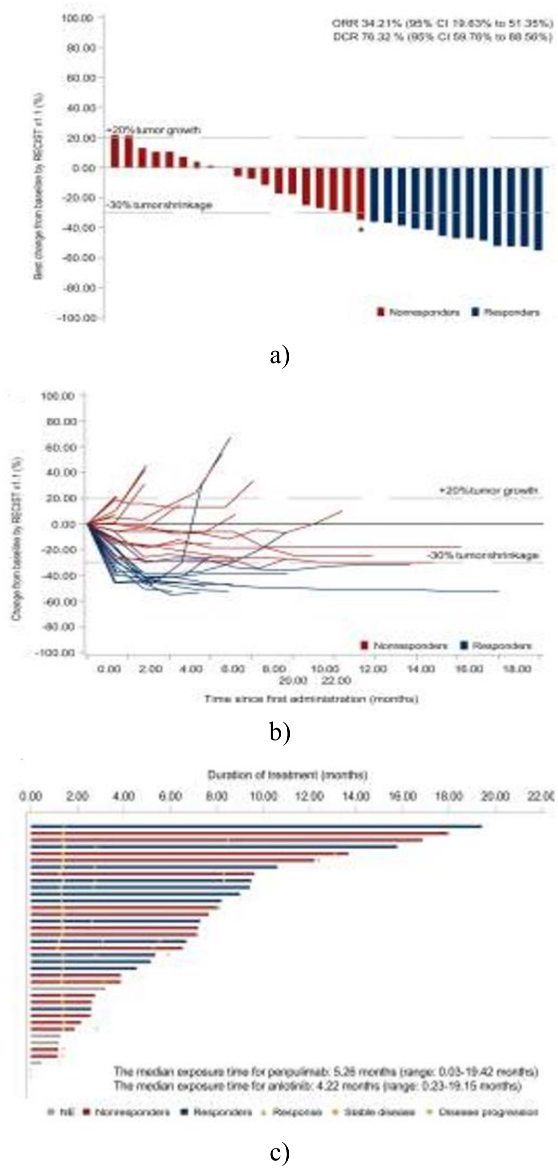


Figure 2. (a) Maximum change in target lesion size for patients in the full analysis set (FAS) is shown in

a waterfall plot (n = 32). ∗One patient's tumor showed a peak reduction of 34.84% compared with baseline, though the confirmed measurement was 27.05%.
(b) Longitudinal tumor response in the FAS (n = 32) is displayed in a spider plot. Horizontal dashed lines indicate key RECIST thresholds: +20% represents tumor growth exceeding 20% from the smallest recorded sum of target lesions, while −30% denotes tumor shrinkage of at least 30% from baseline measurements.
(c) Individual patient treatment timelines and outcomes are illustrated in a swimmer plot (all enrolled patients, N = 38).

Table 2. Summary of clinical efficacy for patients with recurrent or metastatic HNSCC receiving penpulimab in combination with anlotinib, including ORR, DCR, and response rates stratified by tumor site and HPV-P16 status.

Efficacy	Hypopharyngeal cancer *n* (%)	Laryngeal cancer *n* (%)	Oral cancer *n* (%)	Oropharyngeal cancer *n* (%)	Other cancer[a] *n* (%)	Total patients *N* (%)
PR	2 (50.00)	2 (20.00)	5 (33.33)	3 (50.00)	1 (33.33)	13 (34.21)
SD	1 (25.00)	5 (50.00)	7 (46.67)	1 (16.67)	2 (66.67)	16 (42.11)
iUPD		1 (10.00)	2 (13.33)			3 (7.89)
NE	1 (25.00)	2 (20.00)	1 (6.67)	2 (33.33)		6 (15.79)
ORR, % (95% CI)	50.00 (6.76-93.24)	20.00 (2.52-55.61)	33.33 (11.82-61.62)	50.00 (6.76-93.24)	33.33 (0.84-90.57)	34.21 (19.63-51.35)
DCR, % (95% CI)	75.00 (19.41-99.37)	70.00 (34.75-93.33)	80.00 (51.91-95.67)	66.67 (22.28-95.67)	100.00 (29.24-100.00)	76.32 (59.76-88.56)

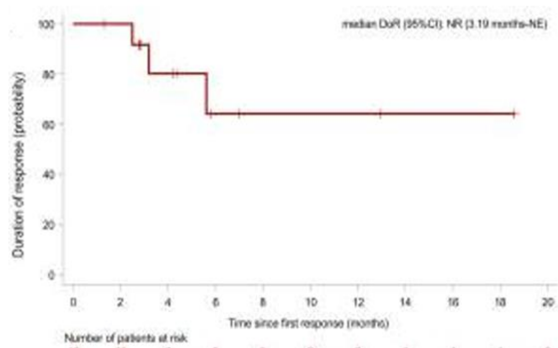
CI, confidence interval; DCR, disease control rate; HNSCC, head and neck squamous cell carcinoma; iUPD, unconfirmed immune progressive disease; NE, not estimated; ORR, objective response rate; PR, partial response; R/M, recurrent or metastatic; SD, stable disease.

[a]Including two neck squamous carcinoma and one temporal squamous carcinoma.

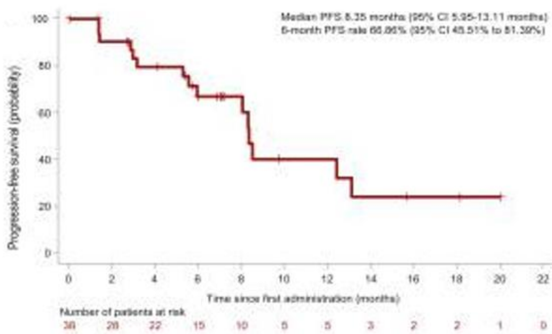
Survival outcomes

Among the 13 patients who experienced a measurable tumor response, the median duration of response (DoR) could not yet be determined, with the lower confidence limit at 3.19 months (95% CI: 3.19 months–not estimable) **(Figure 3a).** Across the full cohort, the median progression-free survival (PFS) was 8.35 months (95% CI: 5.95–13.11 months), and the proportion of patients free from disease progression at 6 months was 66.9% (95% CI: 45.5–81.4%) **(Figure 3b).** In patients with HPV-P16-positive tumors (n = 7), median PFS reached 13.11 months (95% CI: NE–NE), compared with 8.31 months (95% CI: 5.29–12.42 months) in the HPV-P16-negative subgroup (n = 29)

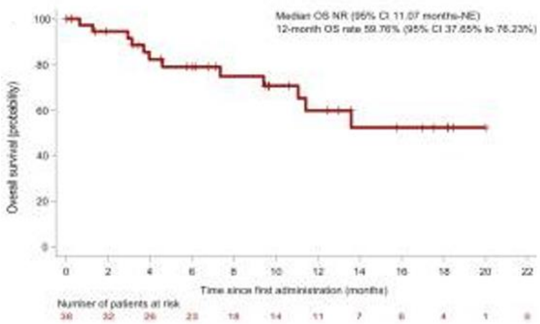
The median follow-up for overall survival (OS) was 10.61 months (95% CI: 6.77–15.77 months). At the time of analysis, 12 patients had died. Median OS had not been reached (95% CI: 11.07 months–NE), while the estimated OS rate at 12 months was 59.8% (95% CI: 37.7–76.2%) **(Figure 3c).**



a)



b)



c)

Figure 3. Treatment outcomes for patients receiving the combination of penpulimab and anlotinib (full analysis set, FAS).

(a) Duration of response (DoR) among responders; (b) progression-free survival (PFS) across all patients; (c) overall survival (OS) for the cohort.

Abbreviations: CI, confidence interval; DoR, duration of response; NE, not estimable; NR, not reached; PFS, progression-free survival; OS, overall survival; FAS, full analysis set.

Safety profile

All 38 treated patients were included in the safety analysis. Overall, 89.5% experienced at least one adverse event related to study treatment. The most frequently reported events were hypothyroidism (34.2%) and hypertension (31.6%). Severe (grade 3 or 4) treatment-related adverse events occurred in 18 patients (47.4%), with the most common being hypertension (7.9%), hypothyroidism (5.3%), palmar-plantar erythrodysesthesia (5.3%), decreased white blood cell count (5.3%), and oral mucositis (5.3%). No fatal (grade 5) events were observed.

Immune-related adverse events (irAEs) were reported in six patients (15.8%), but only one patient (2.6%) experienced a severe grade 3/4 irAE (elevated troponin T). No serious immune-related events occurred. Discontinuation of penpulimab due to adverse events was required in three patients (7.9%). For anlotinib, six patients (15.8%) stopped treatment and nine (23.7%) had their doses reduced because of adverse events; however, no patient permanently discontinued anlotinib solely due to treatment toxicity.

Table 3. TRAEs (≥5%) and grade 3-4 TRAE (≥1%) of penpulimab combined with anlotinib treatment

TRAEs	All grade, *n* (%)	Grade 3-4, *n* (%)
Any event	34 (89.47)	18 (47.37)
Hypothyroidism	13 (34.21)	2 (5.26)
Hypertension	12 (31.58)	3 (7.89)
Palmar-plantar redness and swelling syndrome	6 (15.79)	2 (5.26)
Hypoleukocytosis	5 (13.16)	2 (5.26)
High alanine aminotransferase	4 (10.53)	
Proteinuria	4 (10.53)	1 (2.63)
Hyperlipidemia	4 (10.53)	1 (2.63)
Oral mucositis	4 (10.53)	2 (5.26)
Fatigue	4 (10.53)	
Anemia	4 (10.53)	
High aspartate aminotransferase	4 (10.53)	
Elevated thyroid-stimulating hormone	4 (10.53)	
Thrombocytopenia	4 (10.53)	1 (2.63)
Elevated γ-glutamyltransferase	3 (7.89)	1 (2.63)
Hypertriglyceridemia	3 (7.89)	
Rash	3 (7.89)	1 (2.63)

Supraventricular extrasystrophic contraction	3 (7.89)	
Hypercrine creatine phosphokinase	3 (7.89)	
Sinus bradycardia	3 (7.89)	
Hypoalbuminemia	2 (5.26)	
Fever	2 (5.26)	
Hyperglycemia	2 (5.26)	
Hyperthyroidism	2 (5.26)	
Urinary tract infection	2 (5.26)	
Positive occult blood	2 (5.26)	
Elevated fibrin D-dimer	2 (5.26)	
Limb pain	2 (5.26)	
Tumor ulcers	2 (5.26)	2 (5.26)
Elevated troponin T	1 (2.63)	1 (2.63)
Oral mucosa shedding	1 (2.63)	1 (2.63)
Hematemesis	1 (2.63)	1 (2.63)
Pharyngeal bleeding	1 (2.63)	1 (2.63)
Elevated lipase	1 (2.63)	1 (2.63)
Tumor ruptures	1 (2.63)	1 (2.63)

TRAE, treatment-related adverse event.

Recent advances in immunotherapy have significantly expanded our understanding of the complex interactions between the immune system and tumor biology. During tumorigenesis and progression, cancer cells often evade immune surveillance, facilitating uncontrolled growth, invasion, and metastasis. As a result, numerous immunotherapeutic agents have been approved for both solid and hematological malignancies, harnessing the host's immune system to control tumor progression effectively and sustainably [28].

For patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), there remains a critical need for novel strategies to enhance clinical outcomes. Programmed cell death-1 (PD-1) inhibitors have demonstrated improvements in survival among this patient population [10, 27]. In the phase III CheckMate-141 trial, patients with R/M HNSCC whose disease progressed within six months of platinum-based chemotherapy experienced better outcomes with nivolumab compared to standard single-agent chemotherapy; however, median overall survival (OS) was only 7.5 months, and the objective response rate (ORR) was 13.3% [27].

Similarly, the KEYNOTE-048 study showed that pembrolizumab monotherapy improved OS compared with cetuximab plus chemotherapy in PD-L1-positive populations (CPS ≥20: 14.9 vs. 10.7 months, HR 0.61; CPS ≥1: 12.3 vs. 10.3 months, HR 0.78) [10]. The combination of pembrolizumab with chemotherapy further enhanced survival in both the overall population (13.0 vs. 10.7 months, HR 0.77) and PD-L1-selected subgroups (CPS ≥20: 14.7 vs. 11.0 months, HR 0.60; CPS ≥1: 13.6 vs. 10.4 months, HR 0.65) [10]. These findings supported pembrolizumab plus platinum and 5-fluorouracil as a first-line regimen for R/M HNSCC, while pembrolizumab monotherapy was considered appropriate for PD-L1-positive patients [10]. In the KEYNOTE-040 trial, pembrolizumab administered after platinum failure did not meet its primary efficacy endpoints, with a median OS of 8.4 months [29]. Collectively, these studies indicate that although immunotherapy offers clinical benefits, median OS generally remains below one year, with only modest improvements in ORR and progression-free survival (PFS). Given that immunotherapy had not yet been approved as a first-line option in China at the start of our study, it was implemented as a second-line strategy for patients following platinum-based chemotherapy failure.

Anlotinib exerts antitumor activity by targeting VEGFR-2, thereby inhibiting the PI3K/AKT signaling pathway, reducing tumor cell proliferation and invasion, and promoting apoptosis [30]. Beyond its antiangiogenic effect, anlotinib also modulates the tumor immune microenvironment, potentially enhancing responses to immunotherapy. Penpulimab, a novel PD-1 monoclonal antibody, utilizes γ1 subclass heavy chains with Fc segment modifications, offering several advantages. Its γ1 heavy chains are structurally stable, minimizing self-aggregation seen in IgG4 PD-1 antibodies and reducing the risk of hyperprogression associated with antitumor

IgG1 aggregation in vivo. Additionally, IgG1 subclass antibodies allow more efficient purification during production, lowering host protein contamination and thereby decreasing infusion-related adverse events.

Preclinical and clinical evidence suggests that combining penpulimab with anlotinib can synergistically enhance antitumor activity by concurrently targeting the tumor microenvironment and promoting vascular normalization, while maintaining a favorable safety profile [31, 32]. This dual-targeted approach provides a compelling rationale for further exploration in R/M HNSCC.

Given the limited benefits of immune monotherapy in patients with R/M HNSCC after progression on platinum-based chemotherapy, combination strategies have attracted increasing attention. In the present study, treatment with penpulimab plus anlotinib in patients who had failed at least one line of platinum-based therapy demonstrated encouraging efficacy. The independent review committee (IRC) reported an ORR of 34.2% (95% CI: 19.6–51.4%), a disease control rate (DCR) of 76.3% (95% CI: 59.8–88.6%), median progression-free survival (PFS) of 8.35 months (95% CI: 5.95–13.11 months), a 6-month PFS rate of 66.9% (95% CI: 45.5–81.4%), a 12-month overall survival (OS) rate of 59.8% (95% CI: 37.7–76.2%), and median OS not yet reached (95% CI: 11.07 months–NE). These findings suggest that this combination regimen has substantial potential to improve survival outcomes in this heavily pretreated population. Notably, this study represents the largest cohort and the first second-line trial of immunotherapy combined with antiangiogenic therapy for R/M HNSCC in an Asian population. Future studies evaluating this approach in non-Asian populations may be informative.

The safety profile of the combination was manageable. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 47.4% of patients, with hypothyroidism, hypertension, palmar-plantar erythrodysesthesia, oral mucositis, and other events reported. Some adverse events, such as hypothyroidism, palmar-plantar erythrodysesthesia, and mucositis, may be attributable to both agents, though the latter two are more likely associated with anlotinib. Previous monotherapy studies in nasopharyngeal carcinoma reported hypothyroidism in 27.7% of patients treated with penpulimab [33] and grade 3 TRAEs with anlotinib mainly included hand-foot syndrome, mucositis, hypertension, liver dysfunction, and pneumonia, with no treatment-related deaths [34]. Importantly, no novel TRAEs emerged in the combination study, although overlapping toxicities, particularly hypothyroidism, warrant monitoring. Compared with pembrolizumab plus lenvatinib, which exhibited ≥grade 3 TRAEs in 28.6% of patients and required frequent dose modifications or discontinuations [35, 36], our study showed lower rates of treatment interruption: three patients (7.9%) discontinued penpulimab, and six patients (15.8%) discontinued anlotinib due to adverse events, with no permanent termination of therapy due to toxicity. Bleeding, a concern with anti-angiogenic therapy, was mild (grade 1–2), likely reflecting both the lower bleeding risk of anlotinib and exclusion of high-risk patients. Overall, similar to findings in nasopharyngeal carcinoma, the combination demonstrated a manageable safety profile.

Tumor immune evasion and complex immunomodulatory mechanisms limit the efficacy of monotherapy with immune checkpoint inhibitors (ICIs). Combining ICIs with targeted therapies is a promising strategy to enhance antitumor activity. PD-1/PD-L1 antibodies have already demonstrated clinical benefit in R/M HNSCC, as evidenced by the success of nivolumab and pembrolizumab, but single-agent ORRs remain modest. Consequently, multiple clinical trials are investigating ICI-targeted therapy combinations in R/M HNSCC, including pembrolizumab with lenvatinib (NCT04199104, NCT05433116, NCT05523323), pembrolizumab with ramucirumab (NCT03650764), and monalizumab with cetuximab (NCT05414032).

This study has several limitations. First, it was a single-arm, phase II trial, and the results are limited to a Chinese population, so generalizability to other ethnic groups should be approached cautiously. Second, PD-L1 expression was not assessed, which could influence response to immunotherapy.

Conclusion

The combination of penpulimab and anlotinib demonstrated promising antitumor activity with a manageable safety profile in patients with R/M HNSCC who had failed at least one line of platinum-based chemotherapy, supporting further investigation of this regimen in this population.

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