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ORIGINAL RESEARCH

Penpulimab combined with anlotinib in patients with R/M HNSCC after failure of platinum-based chemotherapy: a single-arm, multicenter, phase II study

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Background: Treatment regimens for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) after failure of platinum-based chemotherapy have been illustrated with limited efficacy.

Patients and methods: Here, we report a single-arm, multicenter, phase II study of R/M HNSCC patients treated with a programmed cell death-1 antibody penpulimab (200 mg) and anlotinib (12 mg) after failing at least one line of platinum-based chemotherapy.

Results: Of 38 patients in total, 13 (34.21%) patients achieved partial response and 16 (42.11%) patients achieved stable disease. After a median follow-up of 7.06 months (range: 4.14-15.70 months), the independent review committee-assessed objective response rate was 34.21%, the disease control rate was 76.32%. The median progression-free survival was 8.35 months (95% confidence interval 5.95-13.11 months). Twelve patients died and the median overall survival (OS) was not reached. The 12-month OS rate was 59.76%. Grade 3/4 treatment-related adverse events occurred in 47.37% of the patients.

Conclusion: Penpulimab combined with anlotinib demonstrated promising efficacy and manageable safety in R/M HNSCC patients after failure of platinum-based chemotherapy.

Key words: head and neck squamous cell carcinoma, penpulimab, anlotinib, programmed cell death-1, anti-angiogenesis

INTRODUCTION

Head and neck tumors are one of the most common malignancies, and their incidence sites are mainly in the mouth, oropharynx, hypopharynx, or larynx. About 90% of head and neck tumors originate from squamous cell of the mucosal epithelium and belong to the head and neck squamous cell carcinoma (HNSCC). In 2015, there were about 74 500 new HNSCC patients and 36 600 deaths in China.[1] According to global cancer statistics 2020, HNSCC caused about 931 000 new cases and 467 000 deaths in 2020.[2] Due to the difficulty of early detection at the site of the disease, patients often enter a locally advanced stage when they are diagnosed for the first time, and more than half of the patients will still have local recurrence or distant metastases even after surgery and radiotherapy.[3] Only a small proportion of patients with recurrent or metastatic (R/M) HNSCC are candidates for radical surgery or definitive radiotherapy.[4] Platinum-based chemotherapy is the standard first-line treatment regimen for patients with R/M HNSCC, but with limited efficacy.[5,6] Therefore, it is imperative to investigate effective and safe second-line treatment strategies for patients with R/M HNSCC who have failed at least one line of platinum-based chemotherapy.

In recent years, immunotherapy has made great progress in many types of cancer, including HNSCC. As an immunosuppressive disease, patients with HNSCC have a reduced absolute number of lymphocytes, impaired natural killer cell

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activity, and weakened antigen presentation ability compared with healthy people.[7,8] Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1) are main T-cell immune checkpoints transmit inhibitory signals through multiple links to tumor-killer T lymphocytes, mediating tumor immune escape.[9] PD-1 monoclonal antibodies have been approved for the first-line treatment of patients with HNSCC[10]. Earlier and updated findings of studies demonstrated that immunotherapy alone or in combination with chemotherapy are appropriate first-line therapies for the definitive setting for HNSCC.[11-13] Tumor angiogenesis plays a vital role in tumor growth and metastasis. The neovascularization in tumor provides oxygen and nutrients to the tumor tissue and promotes the continuous expansion of tumor cells.[14] The three signaling pathways are mediated by vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and fibroblast growth factor receptor, and the interaction between them are the main mechanisms for regulating tumor angiogenesis.[15,16] Among them, the signaling pathway mediated by VEGFR-2 is the most important and is considered to be most closely related to tumor angiogenesis, thus current anti-angiogenesis-targeted drugs mostly target VEGFR-2.[17,18]

The treatment of R/M HNSCC after platinum-based chemotherapy mainly included a single-agent cytotoxic agent, targeted therapy or immunotherapy, which demonstrated limited clinical benefit. Studies have shown that tyrosine kinase inhibitors (TKIs) can improve the tumor microenvironment, promote the infiltration of $CD8^+$ T cells in tumor tissues, and relieve the immunosuppressive state of malignant tumors, thereby enhancing the efficacy of immune checkpoint inhibitors.[19] Anlotinib is a new class of multi-target TKI with an antiangiogenic effect. Anlotinib combined with immunotherapy can generate a synergistic effect. Studies have shown that anlotinib can inhibit the expression of programmed death-ligand 1 (PD-L1) on the surface of endothelial cells and increase the local CD8/forkhead box P3 (FoxP3) ratio to enhance the immune response.[20] Meanwhile, malignant tumor is locally in an immune-tolerant state, in which VEGF as well as PD-L1 are highly expressed, and it can further reduce the infiltration of lymphocytes in the tumor microenvironment by inhibiting the adhesion of lymphocytes on the surface of endothelial cells, reducing the body's immune response, and thereby inducing immune escape.[21,22] Therefore, immunotherapy combined with anti-angiogenesis therapy might be a potential therapeutic strategy for HNSCC.

Penpulimab is a humanized monoclonal antibody that specifically binds to PD-1 developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd, China, which was approved by the China National Medical Products Administration (NMPA) on 3 August 2021. Penpulimab has a typical antibody structure, consisting of two γ1 subclass heavy chains and two κ type light chains covalently linked by disulfide bonds. The fragment crystallizable (Fc) of penpulimab is modified to eliminate the Fc receptor and complement-mediated cytotoxic effects.[23] Anlotinib is developed by Chia Tai Tianqing Pharmaceutical Group Co., Ltd, China, and it was approved by NMPA on 8 May 2018.[24] As a novel multi-target small-molecule TKI, anlotinib has shown promising efficacy in inhibition of tumor cell proliferation, metastasis, and so on apart from anti-angiogenesis. It has demonstrated its safety and efficacy in a variety of solid tumors, especially as a third-line treatment for advanced non-small-cell lung cancer.[25] On the other hand, immunotherapy, as a new treatment, brings new hope for patients with R/M HNSCC. Previous clinical study has shown that PD-1 monoclonal antibody combined with chemotherapy can improve survival in patients with R/M HNSCC.[10] However, there are fewer studies of immunotherapy combined with targeted therapy, especially VEGFR TKIs, in patients with R/M HNSCC. This study aimed to evaluate the efficacy and safety of penpulimab combined with anlotinib in patients with R/M HNSCC after the failure of at least one line of platinum-based chemotherapy.

PATIENTS AND METHODS

Study design and patients

This was a single-arm, open-label, multicenter phase II study conducted in 11 hospitals across the People's Republic of China. Inclusion criteria included the following: (i) age $\geq$18 years; (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score: 0-1; (iii) expected survival of $>$3 months; (iv) histopathologically confirmed R/M HNSCC and had failed at least one line of platinum-based chemotherapy; (v) with measurable lesions according toResponse Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Previous irradiation lesions can be considered measurable if there is progression after radiotherapy. Exclusion criteria included the following: (i) patients who have previously used antiangiogenic agents or PD-1/PD-L1 monoclonal antibodies; (ii) patients who have participated in clinical trials of other agents or have received chemotherapy, radiotherapy, or other anticancer therapies within 4 weeks; (iii) patients who have other malignant tumors within 5 years; (iv) pregnant or lactating women; (v) patients with severe concomitant diseases.

All procedures carried out in this study were in accordance with the 1964 Helsinki Declaration and its later amendments and the International Council for Harmonisation guidelines for Good Clinical Practice. This study was approved by the review committees of each participating hospital. All patients signed informed consent forms before enrollment. This study was registered with ClinicalTrials.gov (NCT04203719).

Procedures and assessments

Penpulimab was infused intravenously at a dose of 200 mg on day 1 at every 21-day cycle. Anlotinib 12 mg was taken orally once per day from day 1 to day 14 at every 21-day cycle.

During the study, penpulimab was given at a fixed dose, while dose reduction of anlotinib was permitted according

to the discretion of the investigator when ≥grade 3 treatment-related adverse events (TRAEs) occurred (12 mg—10 mg—8 mg in turn and cross-dose adjustment was not allowed). For patients with anlotinib downgraded to 10 mg or 8 mg, the dose can be increased again if the investigator determined that there was a possibility of disease progression and the patient's safety was stable after taking the dose for a period of time. For patients who were intolerable to anlotinib 8 mg, treatment should be discontinued.

Endpoints

The efficacy analysis was conducted in the full analysis set (FAS) which was defined as efficacy analysis of all patients enrolled and used the study drugs at least once. The primary endpoint of this study was the independent review committee (IRC)-assessed objective response rate (ORR) in the FAS. Secondary endpoints were disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. The efficacy evaluation criteria were based on the RECIST version 1.1. ORR refers to the proportion of patients who achieved complete response (CR) or partial response (PR). Based on RECIST version 1.1, CR refers to disappearance of all target lesions, and any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm. PR refers to at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. DCR refers to the proportion of patients with CR or PR or stable disease (SD). DoR refers to the time from first confirmed CR or PR to disease progression or death. PFS was defined as the time from the first dose of study drugs treatment to the first documented disease progression or death from any reason, whichever occurred first. OS was defined as the time from the first dose of study drug treatment to death from any reason. Patients with progressive disease (PD) according to RECIST version 1.1 will be further confirmed according to immune RECIST (iRECIST) to decide further treatment.[26]

Efficacy evaluation was carried out using computed tomography or magnetic resonance imaging at baseline and was repeated every 6 weeks until the patients develop confirmed PD. The treatment was continued until PD or intolerable toxicity. Survival follow-up was carried out to the patient's death or loss to follow-up. The safety evaluation was conducted in accordance with the National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.0 in the safety set (SS), which was defined as all patients who had used the study drugs at least once and had a post-medication safety record.

Statistical analysis

According to the previous study, the ORR for chemotherapy was 5.8%.[27] It was assumed that penpulimab combined with anlotinib regimen can give an ORR of 18%. Based on 80% power and a one-sided test at a significance level of 0.05, 34 patients were required and 38 patients were planned for enrollment based on a drop-out rate of 10%.

All statistical analyses were programmed using SAS Software version 9.4 (SAS Institute, Cary, NC). The 95% CI for the ORR were calculated using the Clopper-Pearson method. The median PFS and median OS were estimated using Kaplan-Meier method and 95% CI for the median PFS and median OS were calculated using the Brookmeyer-Crowley method.

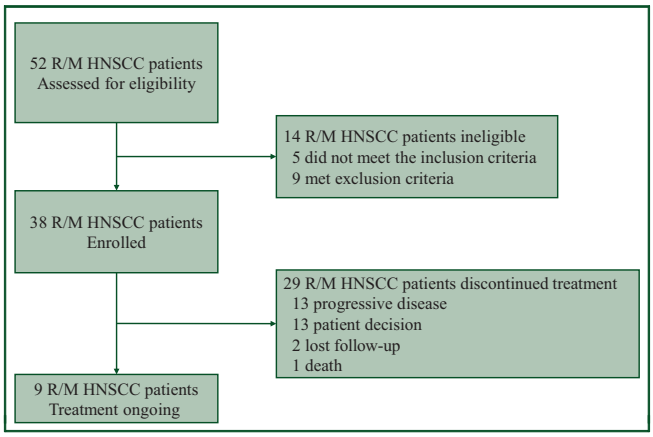

Figure 1. The flowchart of patient disposition.
R/M, recurrent or metastatic; HNSCC, head and neck squamous cell carcinoma.

RESULTS

Patients

From 1 June 2020 to 22 November 2021, 52 R/M HNSCC patients were assessed for eligibility and 38 patients were enrolled in eight hospitals across the People's Republic of China (Figure 1), of which 32 (84.21%) were males and 6 (15.79%) were females. The median age was 61.5 years (range: 34.0-79.0 years). Among them, 15 (39.47%) patients had oral cancer, 10 (26.32%) patients had laryngeal cancer, 6 (15.79%) patients had oropharyngeal cancer, 4 (10.53%) patients had hypopharyngeal cancer, and 3 (7.89%) patients had other HNSCC types. All patients had an ECOG PS ≤2. Twenty-nine (76.31%) patients were with at least one distant metastasis. The median number of metastatic sites was 2 (range: 1-7); 32 (84.21%) patients were in stage IVA-IVC (American Joint Committee on Cancer Staging Manual, 8th Edition). Thirty-seven (97.37%) patients had prior chemotherapy and six (15.79%) patients had prior targeted therapy. The previous treatment lines on average were 1.6 (range: 1-4). There were 7 (18.42%) patients with a positive human papillomavirus (HPV)-P16, 29 (76.32%) patients with a negative HPV-P16, and the HPV-P16 status of the rest 2 (5.26%) patients were unknown. The detailed patients' baseline characteristics were summarized in Table 1.

Efficacy

At the data cut-off date of 6 January 2022, the median follow-up was 7.06 months (95% CI 4.14-15.70 months), the study reached its primary endpoint. IRC-assessed ORR was

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.

34.21% (13/38, 95% CI 19.63% to 51.35%). 34.21% (13/38) of patients achieved PR, and 42.11% (16/38) of patients achieved SD. The best percentage change in target lesions in the FAS are shown in Figure 2A. Tumor shrinkage was seen in 60.53% (23/38) of patients (Figure 2A and B); 7.89% (3/38) of patients had immunity unconfirmed progressive disease (iUPD) and 15.79% (6/38) of patients were not evaluable. The DCR was 76.32% (29/38, 95% CI 59.76% to 88.56%) (Table 2). The median exposure time for penpulimab was 5.26 months (range: 0.03-19.42 months) and that of anlotinib was 4.22 months (range: 0.23-19.15 months). The median time to response was 2.66 months (95% CI 1.38-2.76 months) (Figure 2C). Of the 13 patients who achieved PR, five patients had oral cancer, three patients had oropharyngeal cancer, two patients had laryngeal cancer, two patients had hypopharyngeal cancer, and one patient had neck squamous carcinoma. Oropharyngeal carcinoma and hypopharyngeal carcinoma have higher ORR, which were 50.00% (3/6, 95% CI 11.81% to 88.19%) and 50.00% (2/4, 95% CI 6.76% to 93.24%), respectively (Table 2). Twenty-eight point five seven percent (2/7) of the HPV-P16-positive patients achieved PR and 34.48% (10/29) of the HPV-P16-negative patients achieved PR.

Thirteen patients had observed tumor response, and the median DoR was not reached [95% CI 3.19 months-not estimated (NE)] (Figure 3A). The median PFS was 8.35 months (95% CI 5.95-13.11 months). The 6-month PFS rate was 66.86% (95% CI 45.51% to 81.39%) (Figure 3B). For seven HPV-P16-positive patients, the median PFS was 13.11 months (95% CI NE-NE), which was longer than the 8.31 months (95% CI 5.29-12.42 months) in 29 negative patients (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.102194). The median follow-up for OS was 10.61 months (95% CI 6.77-15.77 months); 12 patients died and the median OS was not reached (95% CI 11.07 months-NE), and the 12-month OS rate was 59.76% (95% CI 37.65% to 76.23%) (Figure 3C).

Safety

All 38 patients were included in the SS. TRAEs occurred in 89.47% of patients (Table 3). The most common TRAEs were hypothyroidism (34.21%, 13/38) and hypertension (31.58%, 12/38). Grade 3/4 TRAEs occurred in 47.37% (18/38) of the patients. The most common grade 3/4 TRAEs were hypertension (7.89%, n = 3), hypothyroidism (5.26%, n = 2), palmar-plantar redness and swelling syndrome (5.26%, n = 2), reduced leucocyte count (5.26%, n = 2), and oral mucositis (5.26%, n = 2). No grade 5 TRAEs occurred. Six (15.79%) patients had experienced at least one immune-related adverse event (irAE) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.102194). Grade 3/4 irAEs only occurred in one (2.63%) patient (elevated troponin T). No patients developed immune-related serious adverse events (irSAEs). Three (7.89%) patients discontinued penpulimab treatment due to TRAE. Six (15.79%) patients discontinued anlotinib treatment and nine (23.68%) patients reduced the dose due to TRAE; no patient had treatment termination of anlotinib due to TRAE.

DISCUSSION

In recent years, immunotherapy has developed rapidly with the deepening of the complex correlation between the immune system and tumors. In the process of oncogenesis and development, tumor cells evade immune surveillance, promoting tumor growth, invasion, and metastasis. Therefore, a variety of agents have been approved for different solid and hematological malignancies. Immunotherapy effectively and persistently controls tumor growth by normalizing the host's own immune function.[28] New treatment strategies are clinically needed to improve efficacy of patients with R/M HNSCC. PD-1 monoclonal antibodies have shown efficacy in improving survival outcomes in patients with R/M HNSCC.[10,27] In the phase III CheckMate-141 study, patients with R/M HNSCC who developed PD within 6 months of platinum-based chemotherapy had a better

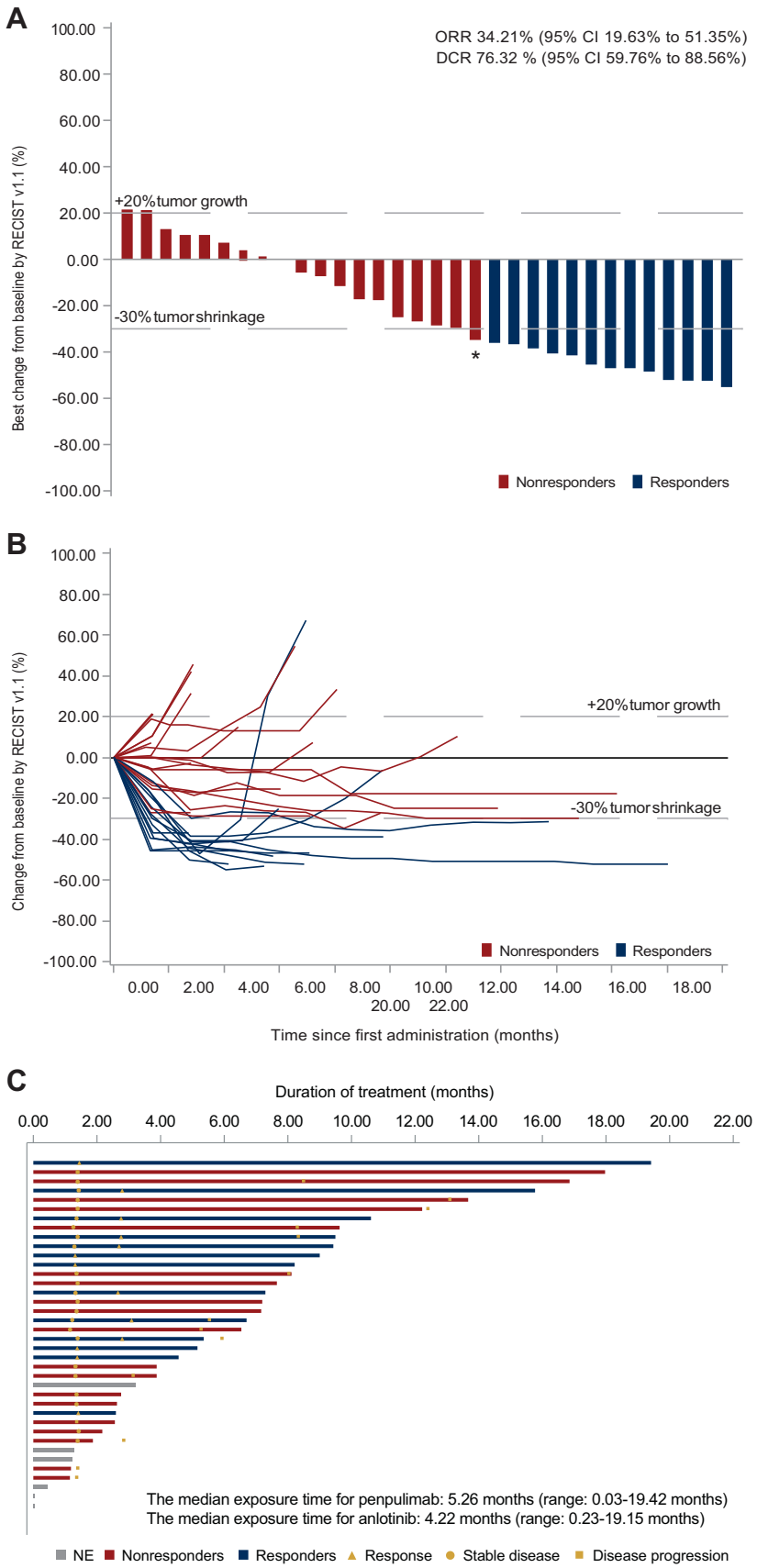

Figure 2. (A) Waterfall plot for best percentage change in target lesion size in the the FAS. A total of 32 patients are included. *This patient demonstrated a best change of 34.84% tumor shrinkage from baseline, but the confirmed evaluation was 27.05% tumor reduction. (B) Spider plot for best percentage change in target lesion size in the FAS. A total of 32 patients are included. Dashed lines at '+20% tumor growth': a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Dashed lines at '−30% tumor shrinkage': a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. (C) Swimmer plot of patient outcomes. All patients ($N = 38$) are included.
CI, confidence interval; DCR, disease control rate; FAS, full analysis set; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours.

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Table 2. Efficacy of penpulimab combined with anlotinib treatment for R/M HNSCC patients

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 outcome than standard single-agent chemotherapy after receiving nivolumab.[27] But the median OS was only 7.5 months, and the ORR was 13.3%.[27] In the KEYNOTE-048 study, pembrolizumab alone improved OS versus cetuximab with chemotherapy in the combined positive score (CPS) $\geq$20 populations [median 14.9 months versus 10.7 months, hazard ratio (HR) 0.61 (95% CI 0.45-0.83), $P = 0.0007$] and CPS $\geq$1 population [12.3 months versus 10.3 months, HR 0.78 (0.64-0.96), $P = 0.0086$].[10] Pembrolizumab with chemotherapy improved OS versus cetuximab with chemotherapy in the total population [13.0 months versus 10.7 months, HR 0.77 (95% CI 0.63-0.93), $P = 0.0034$] at the second interim analysis and in the CPS $\geq$20 population [14.7 months versus 11.0 months, HR 0.60 (0.45-0.82), $P = 0.0004$] and CPS $\geq$1 population [13.6 months versus 10.4 months, HR 0.65 (0.53-0.80), $P < 0.0001$] at final analysis.[10] Based on the observed efficacy and safety in the KEYNOTE-048 study, pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for R/M HNSCC, and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive R/M HNSCC.[10] In the KEYNOTE-040 study, patients with R/M HNSCC who developed PD after platinum-based chemotherapy received pembrolizumab and did not meet the primary efficacy endpoints with a median OS of 8.4 months.[29] Although these studies demonstrated beneficial effects, the median OS was still shorter than 1 year and only modest effects were found on ORR and median PFS. Since immunotherapy had not been approved as first-line treatment in China at the beginning of this study, we made it a second-line choice for patients who had failed platinum-based chemotherapy.

Anlotinib can inhibit the downstream phosphatidylinositol 3 kinase/threonine kinase (PI3K/AKT) pathway by acting on VEGFR-2, thereby suppressing the proliferation and invasion of tumor cells while promoting tumor cell apoptosis.[30] Anlotinib can not only inhibit the generation of blood vessels but also improve the tumor immune microenvironment. Penpulimab is the only new PD-1 monoclonal antibody in the world that adopts the γ1 subclass heavy chains and modifies the Fc segment, and its advantages are obvious. The special γ1 subclass heavy chains are relatively stable and won't form dimers easily, which can avoid the self-aggregation observed in the IgG4 subclass PD-1 monoclonal antibody and the aggregation of antitumor IgG1 *in vivo*, thereby enhancing the efficacy of immunotherapy and reducing the possibility of hyperprogression of immunotherapy. In addition, the IgG1 subclass monoclonal antibodies are easier to be purified during production, which can further reduce host protein carryover, thus decreasing the risk of fever and other adverse effects during infusion. Studies have shown that the combination of penpulimab and anlotinib can actively modulate the therapeutic effect by simultaneously acting on the tumor microenvironment, promoting vascular normalization, and the regimen have also shown promising antitumor activity and favorable safety profile.[31,32]

Due to the limited efficacy of immune monotherapy in patients with R/M HNSCC who developed PD following platinum-based chemotherapy, some studies have further investigated the combination with immunotherapy. In this study, penpulimab combined with anlotinib in the treatment of patients with R/M HNSCC after the failure of at least one line of platinum-based chemotherapy had shown promising efficacy with an IRC-assessed ORR of 34.21% (95% CI 19.63% to 51.35%), a DCR of 76.32% (95% CI 59.76% to 88.56%), a median PFS of 8.35 months (95% CI 5.95-13.11 months), a 6-month PFS rate of 66.86% (95% CI 45.51% to 81.39%), a 12-month OS rate of 59.76% (95% CI 37.65% to 76.23%), and the median OS was not reached (95% CI 11.07 months-NE). These results showed that penpulimab combined with anlotinib has great potential for survival benefits in the treatment of patients with R/M HNSCC after the failure of at least one line of platinum-based chemotherapy. In addition, this study is currently the largest enrollment and the only backline study of immunotherapy combined with antiangiogenic therapy for R/M HNSCC patients in Asian population. Meanwhile, the evaluation of non-Asiatic patients would also be a good research direction in the future.

In this study, the incidence of grade 3/4 TRAEs was 47.37%, including hypothyroidism, hypertension, palmar-plantar redness and swelling syndrome, oral mucositis, etc. Among them, hypothyroidism, palmar-plantar redness and swelling syndrome, and oral mucositis may be associated with both penpulimab and anlotinib. But palmar-

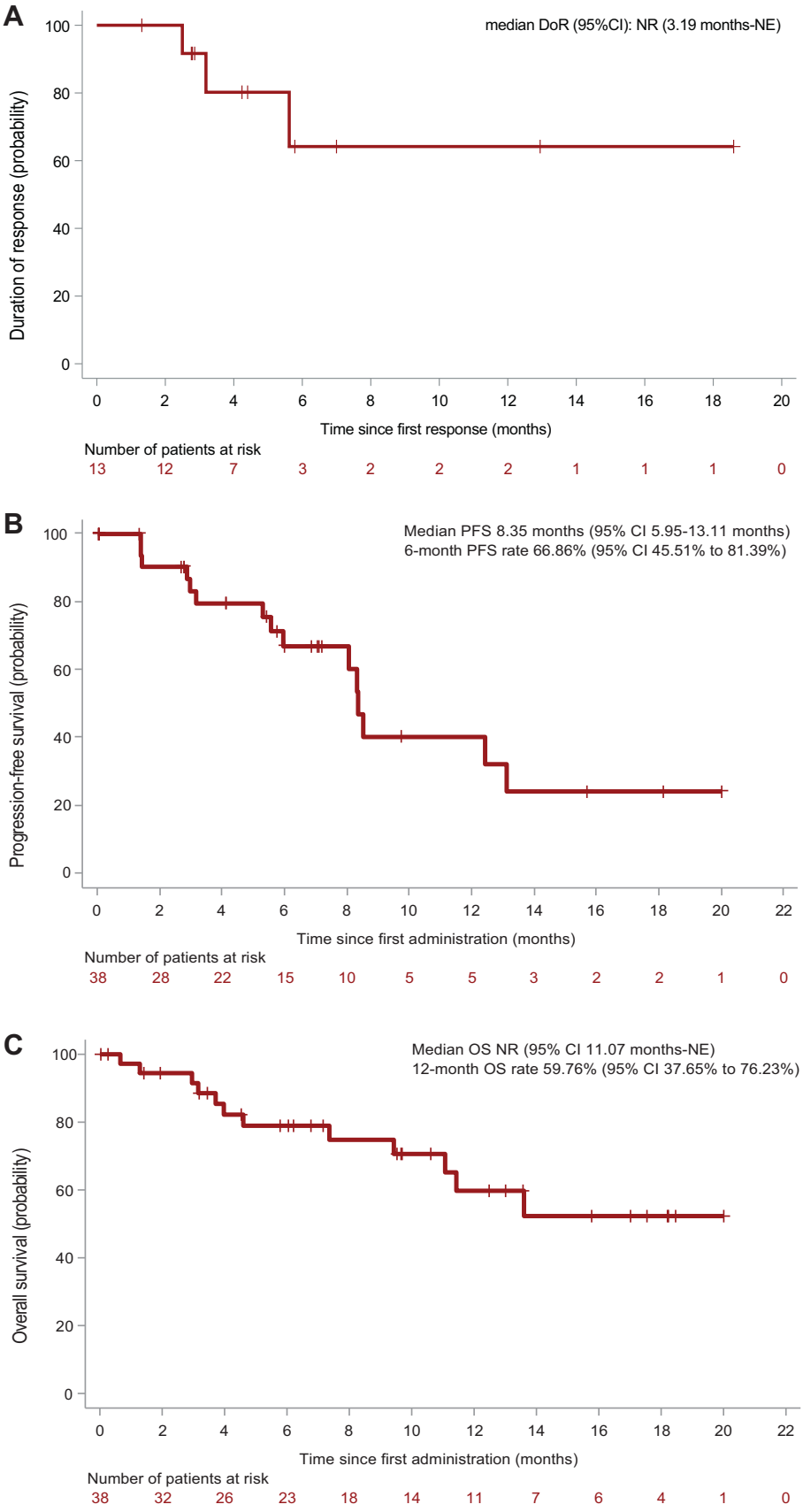

Figure 3. DoR, PFS, and OS of penpulimab combined with anlotinib treatment in the FAS. (A) DoR; (B) PFS; (C) OS.
CI, confidence interval; DoR, duration of response; NE, not estimated; NR, not reached; PFS, progression-free survival; OS, overall survival; FAS, full analysis set.

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.

plantar redness and swelling syndrome and oral mucositis are more likely to be related to anlotinib. In a nasopharyngeal cancer (NPC) post-line monotherapy study, hypothyroidism developed in 27.7% of patients treated with penpulimab.[33] In the phase II study of anlotinib monotherapy for NPC, the occurrence of grade 3 TRAEs ($n = 39$) mainly included hand-foot syndrome (HFS) ($n = 9$), mucositis ($n = 7$), hypertension ($n = 21$), liver dysfunction ($n = 2$), and pneumonia ($n = 1$). Only one grade 4 TRAE (mucositis) was reported and no treatment-related death was observed.[34] Overall, no new TRAE occurred. However, attention needed to be paid to the superimposed toxicity in terms of hypothyroidism. In contrast, pembrolizumab combined with lenvatinib had a ≥ grade 3 TRAE of 28.6% (hypertension, infection, thrombocytopenia).[35] In the study of pembrolizumab combined with lenvatinib, dose adjustment/suspension occurred in 85% of patients, of which 45% dose interruption occurred due to pembrolizumab, of which 15% discontinued, and 13% discontinued treatment was associated with lenvatinib.[36] In this study, no patients had treatment termination due to TRAEs, only three (7.89%) patients discontinued penpulimab, and six (15.79%) patients discontinued anlotinib due to TRAEs. One risk of HNSCC using antivascular drugs was bleeding.[35] Grade 5 bleeding has been reported in the sunitinib study of HNSCC patients.[37] In this study, bleeding was grade 1 or 2, which might be due to a lower risk of bleeding of anlotinib in addition to patients at high risk of bleeding being excluded. Even in patients with NPC, who were more prone to bleeding, anlotinib did not cause bleeding above grade 3.[35] Overall, as in NPCs, penpulimab combined with anlotinib combination showed manageable safety profile.

The complex mechanisms of tumor immunomodulation lead to limited effects in a single immunosuppressive modulatory therapy. Researchers have tried combination treatment options in recent years to explore whether they play a synergistic antitumor role. Immunotherapy represented by PD-1 and PD-L1 monoclonal antibodies has brought a new dawn to cancer treatment, among which the success of nivolumab and pembrolizumab in the clinical studies of R/M HNSCC also provides more confidence for the clinical application of immune checkpoint inhibitors (ICIs). However, the ORR of single-agent ICI therapy is not high. Therefore, ICI combined with targeted therapy provides a new idea for clinical investigation. At present, various combinations of ICI with targeted therapy regimens are also being carried out in R/M HNSCC, such as the combination of pembrolizumab and lenvatinib (NCT04199104, NCT05433116, NCT05523323), the combination of pembrolizumab and ramucirumab (NCT03650764), and the combination of monalizumab and cetuximab (NCT05414032).

There were some limitations in this study. Firstly, this was only a single-arm phase II study. The patients enrolled were only Chinese; caution should be taken in the application to other ethnicities. Secondly, this study did not test the PD-L1 expression.

Conclusion

In this study, penpulimab combined with anlotinib demonstrated promising efficacy and manageable safety profile in R/M HNSCC patients who failed at least one line of platinum-based chemotherapy.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

All data generated or analyzed during this study are included in this published article.

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