Combination of pembrolizumab and lenvatinib is a potential treatment option for heavily pretreated recurrent and metastatic head and neck cancer

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Abstract

Background: Immunotherapy has become the current standard of care for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC). One potential approach to improve immunotherapy efficacy is to combine pembrolizumab, an anti-PD-1 agent, with lenvatinib, a potent multikinase inhibitor. In this study, we presented our up-to-date experience with pembrolizumab/lenvatinib combination therapy in heavily pretreated R/M HNSCC.

Methods: Patients who had R/M HNSCC, were ineligible for curative treatment, progressed after at least two lines of systemic treatment and had received pembrolizumab/lenvatinib combination therapy were enrolled in this study. The primary endpoint was the objective response rate. The secondary endpoints included the disease control rate, overall survival, progression-free survival, and the duration of response.

Results: A total of 14 patients were enrolled in this study. All the patients had received at least two lines of systemic treatment and radiation therapy, and 71% of patients had failed previous anti-PD-1 treatment. The objective response rate of pembrolizumab/lenvatinib combination therapy was 28.6% (95% confidence interval [CI], 5.0%-52.2%). The disease control rate was 42.9% (95% CI, 17.0%-68.8%). The overall survival and progression-free survival were 6.2 months (95% CI, 2.9-9.6) and 4.6 months (95% CI, 0.05-0.9.2), respectively. Of those who had failed previous anti-PD-1 therapy, partial responses were observed in two patients. All the patients with partial responses were in the tumor proportion score <50 and combined positive score 1 to 19 groups.

Conclusion: Our study provided up-to-date evidence that pembrolizumab/lenvatinib combination therapy achieved objective responses in both heavily pretreated and anti-PD-1 refractory R/M HNSCC patients. This study supported the use of pembrolizumab/lenvatinib combination therapy in R/M HNSCC patients without standard of care.

Keywords: Head and neck cancer; Lenvatinib; Pembrolizumab; Programmed cell death 1

1. INTRODUCTION

The treatment of recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC) has long been composed of the EXTREME regimen as frontline therapy and taxane, methotrexate, or afatinib as subsequent treatments.[1–4] In recent years, the advent of immunotherapy has greatly changed the landscape of R/M HNSCC treatment. According to the KEYNOTE-048 study, the addition of pembrolizumab to the platinum/fluorouracil chemotherapy backbone decreased the risk of death by 23% in the total population compared to the EXTREME regimen as frontline treatment.[5] Compared to traditional chemotherapy options, pembrolizumab and nivolumab have also shown efficacy in prolonging survival in patients who progressed on platinum-based treatment.[6,7] With the incorporation of immunotherapy into current treatment protocols, the median overall survival (OS) of R/M HNSCC has reached 13 months in the total population and 15 months in those with a combined positive score (CPS) ≥20. Efforts to further improve immunotherapy efficacy are ongoing.

One potential approach to improve immunotherapy efficacy in R/M HNSCC is to combine pembrolizumab and lenvatinib. Lenvatinib is a potent tyrosine kinase inhibitor that selectively inhibits VEGFR, FGFR, PDGFRα, KIT, and RET.[8] Accordingly, lenvatinib exhibits both antiangiogenic and antiproliferative potency and has been approved by the US Food and Drug Administration for the treatment of radio-iodine refractory differentiated thyroid cancer, unresectable hepatocellular carcinoma, and renal cell carcinoma.[9–11] Preclinical studies have shown that adding anti-VEGF agents to immunotherapy may decrease VEGF-mediated immunosuppression. It has also been reported that lenvatinib may decrease tumor-associated macrophages and enhance the TH1-mediated immune response in the tumor microenvironment. These novel mechanisms make adding lenvatinib to pembrolizumab an attractive approach to increase immunotherapy efficacy.[12–14]

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The combination of pembrolizumab and lenvatinib has been evaluated in multiple clinical trials. This combination showed substantial clinical responses in immunotherapy-refractory melanoma and renal cell carcinoma in two separate phase II studies.[15,16] Clinical responses were also observed in heavily pretreated triple-negative breast cancer, ovarian cancer, colorectal cancer, gastric cancer, cholangiocarcinoma, and glioblastoma in a phase II basket trial.[17] This combination is currently undergoing study in LEAP-010, and a phase III study enrolling PD-L1-positive R/M HNSCC patients for their first-line treatment, with objective response rate (ORR), progression-free survival (PFS), and OS as the primary endpoints.[18] On the basis of these data, we presented our up-to-date experiences of pembrolizumab and lenvatinib combination therapy in heavily pretreated R/M HNSCC.

2. METHODS

2.1. Study design and participants

We identified patients in Taipei Veterans General Hospital who had R/M HNSCC and were ineligible for curative treatment, including surgical resection and definitive concurrent chemoradiation therapy. Patients who had progressed after receiving at least two lines of systemic treatment were enrolled in this study. Patients who were under clinical trial protocols were excluded. Patient characteristics were recorded, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities (diabetes mellitus, impaired renal function, and liver cirrhosis), smoking history, human papillomavirus (HPV) status, primary site of HNSCC, initial T stage, nodal status, and metastasis status denoted by the American Joint Committee on Cancer staging system (seventh edition), site of first recurrence/relapse, previous curative surgery and radiation therapy history, previous systemic treatments (treatment numbers, platinum/taxane/cetuximab/anti-PD1 treatment), previous anti-PD-1 combinations, tumor proportion score (TPS, Dako 22C3), combined positive score (CPS, Dako 22C3), and tumor cells (TC, Dako 28-8). According to the current standard, HPV status was only tested in oropharyngeal cancer. The primary sites of HNSCC were recorded according to the following categorization: oral cavity, oropharynx, larynx, hypopharynx, and nasal cavity. Previous systemic therapies were documented as the number of systemic therapies received before starting combination therapy of pembrolizumab and lenvatinib. Concurrent chemoradiation therapy was counted as one line of systemic therapy. TPS and CPS were categorized according to the KEYNOTE-048 study: TPS was categorized as <50 and ≥50, and CPS was categorized as <1, 1 to 19, 20 to 49, and ≥50. This study was approved by the Institutional Review Board (IRB) and Ethics Committee of Taipei Veterans General Hospital (IRB number: 2020-11-001AC).

2.2. Outcomes

The primary endpoint was the ORR, defined as the percentage of patients who achieved a complete response or partial response (PR), which was assessed according to RECIST version 1.1 by the investigator's review. The secondary endpoints included the disease control rate (DCR), defined as the percentage of patients who achieved an objective response or stable disease (SD); PFS, defined as the duration from the start of pembrolizumab/lenvatinib combination therapy to first disease progression (PD), which was assessed according to RECIST version 1.1 by investigator's review; PFS2, defined as the duration from the start of pembrolizumab/lenvatinib combination therapy to second disease progression; OS, defined as the duration from the start of pembrolizumab/lenvatinib combination therapy to death from any cause; and duration of response (DoR), defined as the duration from the start of pembrolizumab/lenvatinib combination therapy to disease progression (PD) in patients with an objective response. All patients included in our study underwent radiological evaluation with a minimum frequency of once every 3 months. Clinical responses were further analyzed according to previously received immunotherapy combinations and PD-L1 status. Acute adverse effects were evaluated at each treatment visit and were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.

2.3. PD-L1 status

PD-L1 status was evaluated by at least one of the Dako antibodies (Dako 22C3 or Dako 28-8) before the start of pembrolizumab/lenvatinib combination therapy. The pathology slides were stained by the Dako Autostainer Link 48 platform and Dako pharmDx kits for clone 22C3 or clone 28-8. PD-L1 status was expressed as CPS and TPS for those stained with the Dako 22C3 antibody and was expressed as TC for those stained with the Dako 28-8 antibody.

2.4. Statistical analysis

SPSS version 18 (SPSS Inc., Chicago, IL) was used for statistical analysis. ORR and DCR are expressed as percentages with 95% confidence intervals (95% CIs). OS and PFS were estimated by the Kaplan-Meier method. The median OS and PFS and 95% CI are also presented. The data of patients who were still alive at the end of the study or lost to follow-up were censored at the time of the last medical visit for OS estimation. The data of patients who did not have disease progression at the end of study or were lost to follow-up were censored at the time of the last tumor imaging for PFS estimation. The data of patients who started next-line anticancer treatment without evidence of radiographic progression were censored at the time of the last tumor imaging before starting next-line treatment for PFS estimation. Clinicopathologic factors, including ECOG performance status, smoking history, primary tumor site, initial T stage, nodal status, previous curative surgery, number of previous systemic treatments, previous cetuximab or anti-PD1 treatment, site of first recurrence/relapse, CPS and TPS, were analyzed by a univariate Cox proportional hazards model to identify prognostic factors of OS. Factors with an extremely low number of cases in the arms to be compared were excluded from univariate analysis.

3. RESULTS

3.1. Patient characteristics

In total, 14 patients with R/M HNSCC who were ineligible for definitive treatment were enrolled in this study. The details of the patient characteristics are listed in Table 1. The median age was 55 years, and the patients were predominantly male (86%) and had a smoking history (64%). Approximately 60% of the patients had an ECOG performance status ≤2. Only a minority of patients had diabetes mellitus (21%), impaired renal function (14%), and liver cirrhosis (7%). According to the current diagnostic consensus, HPV status evaluation is recommended only in oropharyngeal cancer patients. Five patients were evaluated for HPV status, with only one reported as positive. The primary sites of cancer were mainly the oral cavity (50%), followed by the oropharynx (29%), hypopharynx (14%), and nasal sinus (7%). Most patients had an initial diagnosis of T1-3 (50%), T4a (43%), and N1-2 (100%). None of the patients had distant metastasis at initial diagnosis. The initial stage of HNSCC was mainly stage IVA (57%), followed by stage I-II (21%), stage III (14%), and stage IVB (7%). The sites of first recurrence/relapse were the head and neck (79%) and lung (21%). All of the patients had received previous radiation therapy and at least two

Table 1

Patient characteristics

Patient characteristics	Total population (n = 14)	%
Age, y/o (95% CI)	55.0 (48.7-61.3)	
Sex		
Male	12	85.7
Female	2	14.3
ECOG PS		
0	4	28.6
1	2	14.3
2	2	14.3
3	4	28.6
4	2	14.3
Diabetes mellitus		
Yes	3	21.4
No	11	78.6
CCR < 60 mL per minute		
Yes	2	14.3
No	12	85.7
Liver cirrhosis		
Yes	1	7.1
No	13	92.9
Smoking		
Yes	9	64.3
No	5	35.7
HPV-associated		
Yes	1	7.1
No	4	28.6
Unknown	9	64.3
Primary site		
Oral cavity	7	50.0
Oropharynx	4	28.6
Hypopharynx	2	14.3
Nasal sinus	1	7.1
T		
T1-T3	7	50.0
T4a	6	42.9
T4b	1	7.1
N		
N0	5	35.7
N1	5	35.7
N2	4	28.6
N3	0	0.0
M		
M0	14	100.0
M1	0	0
Stage		
I/II	3	21.4
III	2	14.3
IVA	8	57.2
IVB	1	7.1
Previous curative surgery		
Yes	8	57.2
No	6	42.8
Previous RT		
Yes	14	100.0
No	0	0.0
Previous systemic treatment		
2	3	21.4
3	5	35.7
≧4	6	42.9
Previous platinum treatment		
Yes	13	92.9
No	1	7.1
Previous taxane treatment		
Yes	11	78.6
No	3	21.4
Previous cetuximab treatment		
Yes	7	50.0
No	7	50.0
Previous anti-PD1 treatment		
Yes	10	71.4
No	4	28.6
Site of first recurrence/relapse		
Head and neck	11	78.6
Lung	3	21.4
TPS (Dako 22C3)		
<50	10	71.5
≧50	3	21.4
Unknown	1	7.1
CPS (Dako 22C3)		
<1	0	0.0
1-19	5	35.7
20-49	5	35.7
≧50	3	21.5
Unknown	1	7.1
TC (Dako 28-8)		
1-9	4	28.6
Unknown	10	71.4

CCR = creatinine clearance rate; CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HPV = human papillomavirus; RT = radiation therapy; TC = tumor cells; TPS = tumor proportion score.

prior lines of systemic treatment. A major proportion of patients received ≥4 lines of systemic therapy (43%), followed by 36% of patients who received three lines and 21% of patients who received two lines before starting pembrolizumab/lenvatinib combination treatment. Most of the patients had received previous platinum (93%), taxane (79%), and anti-PD1 (71%) treatment, while half of the patients had received previous cetuximab treatment. In total, 13 patients had their pathology specimens evaluated by the Dako 22C3 antibody, and four patients had their specimens evaluated by the Dako 28-8 antibody. In total, 72% of cases had TPS <50, and 28% of cases had TPS ≥50. In total, 0% of cases had CPS <1, 36% of cases had CPS 1-19, 36% of cases had CPS 20-50, and 22% of cases had CPS ≥50. All four cases evaluated by Dako 28-8 had TC 1-9.

3.2. Objective responses

All patients had received a pembrolizumab and lenvatinib combination regimen (pembrolizumab 100 mg every 3 weeks, lenvatinib 10 mg/d) as salvage therapy. All 14 patients were eligible for the best overall response evaluation and are described in Table 2. The ORR was 28.6% (95% CI, 5.0%-52.2%), and the DCR was 42.9% (95% CI, 17.0%-68.8%). PR was observed in four patients (29%), SD was observed in two patients (14%), and PD was observed in eight patients (57%). The patients were also grouped according to the previously received anti-PD-1 combination for objective response evaluation. PR was observed in two patients who had never received immunotherapy (50%) and in two patients who had progressed under the anti-PD-1/afatinib regimen (67%). No objective responses were noted in groups who progressed under anti-PD-1 and chemotherapy combination regimens (platinum-based or taxane-based regimens). Objective responses were also evaluated in different TPS/

Table 2

Treatment response

	Total population (n = 14)	% (95% CI)
ORR	4	28.6 (5.0-52.2)
DCR	6	42.9 (17.0-68.8)
Best overall response		
CR	0	0.0
PR	4	28.6
SD	2	14.3
PD	8	57.1

Previous anti-PD-1 agent combination	Best overall response
No prior anti-PD-1	PR:2, PD:2
Anti-PD-1 alone	-
Anti-PD-1/afatinib	PR:2, PD:1
Anti-PD-1/paclitaxel	SD:1, PD:2
Anti-PD-1/cisplatin/paclitaxel	SD:1
Anti-PD-1/cisplatin/fluorouracil	PD:3

CR = complete response; DCR = disease control rate; ORR = objective response rate; PD = progressive disease; PD-1 = programmed cell death protein 1; PR = partial response; SD = stable disease.

CPS groups, and the details are described in Table 3. For the 10 patients with TPS <50, PR was observed in four patients, and SD was noted in one patient. The pre- and posttreatment images of two of the responders are shown in Fig. 1. No PR was noted in the three patients with TPS ≥50. For the 5 patients with CPS 1-19, PR was observed in 4 patients. No PR was noted in the CPS 20-49 and CPS 50 groups. Of the 13 patients with known CPS/TPS, nine patients had received immunotherapy treatment after the date of biopsy and before the start of pembrolizumab/lenvatinib combination therapy. For the four patients who did not receive immunotherapy between the date of biopsy and the start of pembrolizumab/lenvatinib combination therapy, PR was noted in two patients in the TPS <50 and CPS 1-19 groups.

3.3. Survival

The median follow-up time was 2.8 months (interquartile range [IQR] 2.2-6.8). The median duration of receiving pembrolizumab/lenvatinib combination therapy was 2.3 months (IQR 1.4-5.5). At the end of this study, five patients (36%) died, two patients (14%) were lost to follow-up, seven patients (50%) remained on treatment, and one patient was still receiving pembrolizumab/lenvatinib combination therapy. The median OS was 6.2 months (95% CI, 2.9-9.6). The median PFS was 4.6 months (95% CI, 0.05-9.2). The median PFS2 was 6.2 months (95% CI, 2.9-9.6). The Kaplan-Meier plots of OS, PFS, and PFS2 are shown in Fig. 2. The median DoR was 7.3 months (range 5.0-9.1). All patients stopped investigational medication due to disease progression or death, and none of the participants stopped medication due to intolerance. None of the clinicopathologic factors were significant in univariate analysis for OS (Table 4).

Table 3

PD-L1 status and treatment response

	PR	SD	PD
Known PD-L1 status (n = 13), TPS (Dako22C3)			
<50	4	1	5
≧50	0	1	2
Known PD-L1 status (n = 13), CPS (Dako22C3)			
<1	0	0	0
1-19	4	0	1
20-49	0	1	4
≧50	0	1	2
No prior anti-PD-1 exposure (n = 4), TPS (Dako22C3)			
<50	2	0	1
≧50	0	0	1
No prior anti-PD-1 exposure (n = 4), CPS (Dako22C3)			
<1	0	0	0
1-19	2	0	1
20~49	0	0	0
≧50	0	0	1

CPS = combined positive score; PD = progressive disease; PR = partial response; SD = stable disease; TPS = tumor proportion score.

3.4. Safety

The treatment-related adverse events are listed in Table 5. In total, adverse events of all grades were noted in 77% of patients, and grade 3 or 4 adverse events were noted in 29% of patients. The most frequent adverse events of any grade included anemia (79%), hypertension (57%), and elevated alanine transaminase (36%). Severe adverse events included hypertension in two cases (14%), infection in one case (7%), and thrombocytopenia in one case (7%). No treatment-related deaths were noted in our cohort.

4. DISCUSSION

Further improving the efficacy of immunotherapy is a major issue in current treatment strategies for R/M HNSCC. In this study, we provided strong evidence confirming the objective responses of pembrolizumab/lenvatinib combination therapy in heavily pretreated R/M HNSCC. More importantly, this study also provided evidence that an objective response can be achieved by pembrolizumab/lenvatinib combination therapy even after progression under previous anti-PD-1 therapy. These data suggested the potential feasibility of the pembrolizumab/lenvatinib combination in the management of heavily pretreated R/M HNSCC and HNSCC patients who had failed anti-PD-1 therapy.

In this study, the treatment efficacy was reported with an ORR of 29% and a DCR of 43%. The median OS and median PFS were 6.2 and 4.6 months, respectively. All the patients had received radiation therapy and at least two lines of systemic treatment, 79% of patients had received at least three lines of systemic treatment, and 71% of patients had failed previous anti-PD-1 therapy. There are currently two large, randomized phase III studies, KEYNOTE-040 and CHECKMATE-141, applying anti-PD-1 agents in the management of platinum-refractory HNSCC.[6,7] In KEYNOTE-040, almost all the patients had received ≤2 lines of systemic therapy, and in CHECKMATE-141, 80% of participants had received ≤2 lines of systemic therapy. The ORR was 15% in the pembrolizumab arm in KEYNOTE-040, 13% in the nivolumab arm in CHECKMATE-141, and between 6% and 10% in the standard-of-care arms (methotrexate, docetaxel, and cetuximab). The median OS was 8.4 months in the pembrolizumab arm in KEYNOTE-040, 7.5 months in the nivolumab arm in CHECKMATE-141, and between 5.1 and 6.9 months in the standard-of-care arms. The median PFS was 2.1 months in the pembrolizumab arm in KEYNOTE-040, 2.0 months in the nivolumab arm in CHECKMATE-141, and 2.3 months in the standard-of-care arms. In our study, the enrolled patients were more heavily pretreated than in the abovementioned two clinical trials, while an impressive ORR of nearly 30% was still noted. The median OS and median PFS were similar to those of the two clinical trials.

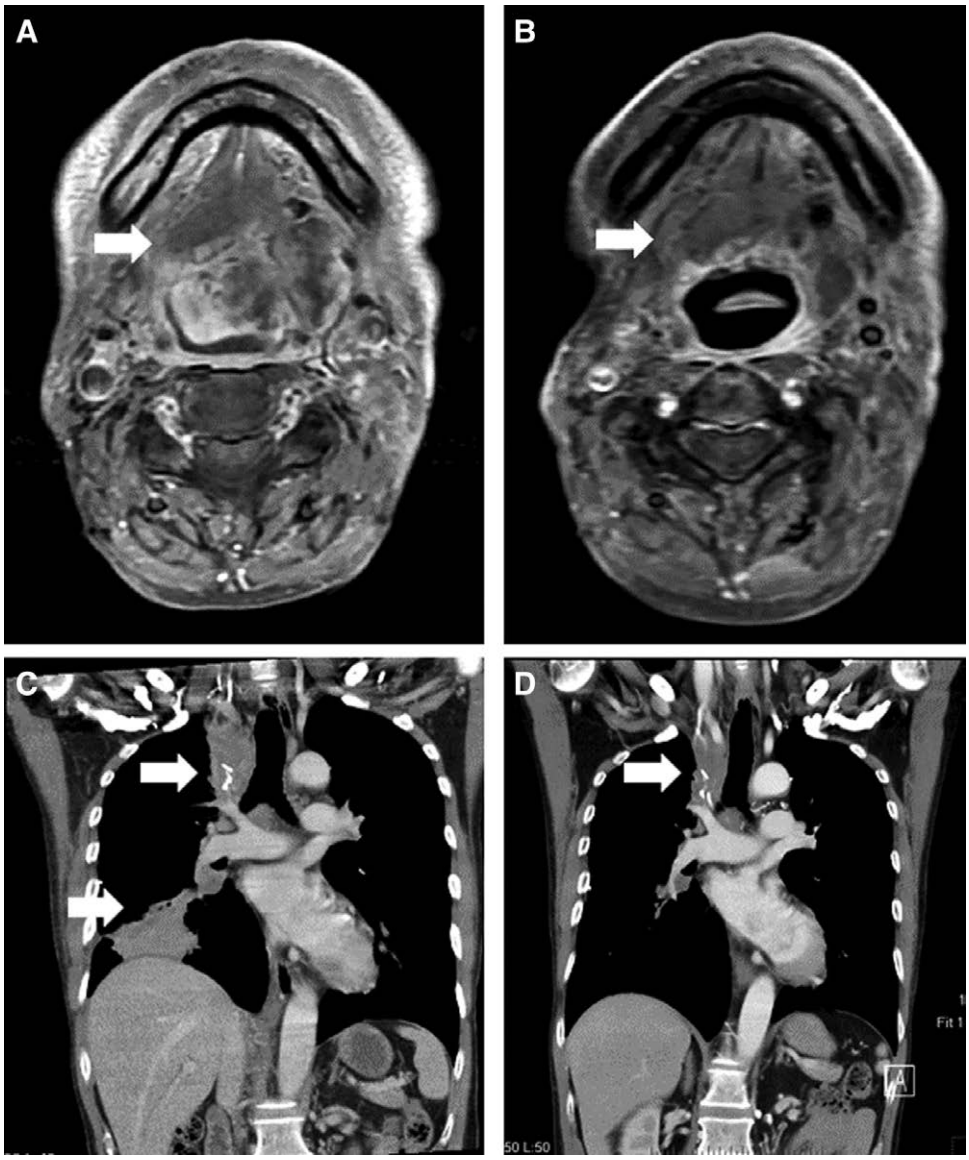
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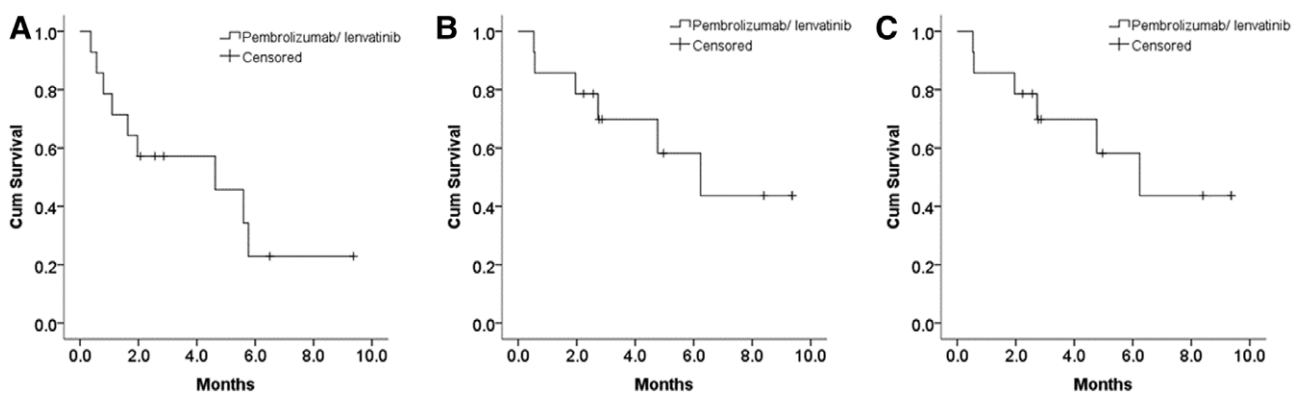
Fig. 1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4.0
6.0
8.0
10.0

Fig. 2

Table 4

Univariate analysis

Clinicopathologic features	Hazard ratio	95% CI	*p*
ECOG PS			
0-2	0.97	0.19-4.80	0.97
3-4	REF		
Smoking			
Yes	3.35	0.65-17.41	0.15
No	REF		
Primary site			
Oral cavity	0.47	0.09-2.56	0.38
Non-oral cavity	REF		
T			
T4	1.43	0.28-7.31	0.67
T1-3	REF		
N			
N2-3	4.23	0.70-25.56	0.12
N0-1	REF		
Previous curative surgery			
Yes	0.60	0.12-3.01	0.53
No	REF		
Previous systemic treatment			
≧4	0.22	0.03-1.91	0.17
≦3	REF		
Previous cetuximab treatment			
Yes	1.12	0.22-5.73	0.90
No	REF		
Previous anti-PD1 treatment			
Yes	34.97	0.02->100	0.35
No	REF		
Site of first recurrence/relapse			
Lung	0.78	0.09-6.76	0.82
Head and neck	REF		
TPS (Dako 22C3)			
<50	1.39	0.15-12.52	0.77
≧50	REF		
CPS (Dako 22C3)			
<20	0.19	0.02-1.84	0.15
≧20	REF		

CI = confidence interval; CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group Performance Status; REF = reference; TPS = tumor proportion score.

Table 5

Treatment-related adverse events

Event	All grade	%	Grade 3 or 4	%
Any event	11	78.6	4	28.6
Hypertension	8	57.1	2	14.3
Infection	2	14.3	1	7.1
Nausea	0	0.0	0	0.0
Poor appetite	0	0.0	0	0.0
Diarrhea	0	0.0	0	0.0
Hypothyroidism	4	28.6	0	0.0
Pneumonitis	0	0.0	0	0.0
Proteinuria	4	28.6	0	0.0
Neutropenia	3	21.4	0	0.0
Anemia	11	78.6	0	0.0
Thrombocytopenia	3	21.4	1	7.1
Elevated ALT	5	35.7	0	0.0
Jaundice	2	14.3	0	0.0

ALT = alanine transaminase.

In the KEYNOTE-048 study, a positive correlation between PD-L1 expression and the treatment efficacy of pembrolizumab was noted. Superior ORR and OS were both noted in groups with high CPS or TPS compared with groups with low CPS or TPS. However, in our study, all cases of PR were noted in the CPS 1-19 group and in the TPS <50 group. No PR cases were noted in the CPS ≥20 group or in the TPS ≥50 group. A possible explanation is that in patients with very high CPS or TPS (eg, CPS >20 or TPS ≥50) and unresponsiveness to previous anti-PD-1 agents, a dominant immunosuppressive mechanism other than PD-1/PD-L1 may exist. Hence, adding lenvatinib to pembrolizumab, which mainly acts by enhancing anti-PD-1 activity, in this case may not overcome immunosuppression in the tumor microenvironment. Further interpretation is limited by two reasons. First, the sample size was too small to reach a final conclusion. Second, most of the patients had received anti-PD-1 agents after biopsy and before the start of pembrolizumab/lenvatinib combination therapy, which may potentially change the tumor microenvironment and sensitivity to further anti-PD-1 therapy. Another study design may be needed to address this question.

Several limitations of this study existed. First, the sample size was too small to reach the final conclusion of treatment efficacy and limited the power of univariate analysis of clinicopathologic factors. Second, heterogeneity in previously received treatments may hinder interpretation. Last, a randomized phase III study design is more appropriate to compare the investigational treatment and current standard of care. In conclusion, our study provided up-to-date evidence that pembrolizumab/lenvatinib combination therapy achieved objective responses in both heavily pretreated and anti-PD-1-treated R/M HNSCC patients. This study supported the use of the pembrolizumab/lenvatinib combination in R/M HNSCC patients without standard of care. Further efficacy evaluation of the frontline use of pembrolizumab/lenvatinib in R/M HNSCC will be studied in the LEAP-010 study.

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