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ORIGINAL ARTICLE

# Efficacy of cetuximab-containing regimens in the treatment of recurrent/metastatic head and neck cancer after progression to immune checkpoint inhibitors

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## Abstract

**Background:** The antiepidermal growth factor receptor (EGFR) monoclonal antibody cetuximab and immune checkpoint inhibitors (ICIs) are the current front-line treatment for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, understanding of the efficacy of cetuximab-containing regimens in patients who fail ICI treatments is limited. In this study, we present the efficacy of cetuximab-based regimens in heavily pretreated R/M HNSCC patients after progression to ICIs.

**Methods:** This was a retrospective study that analyzed patients diagnosed with R/M HNSCC who progressed after ICIs and then received their first-time cetuximab-based regimens at Taipei Veterans General Hospital from January 2017 to December 2020. The response rate, overall survival, and progression-free survival were measured.

**Results:** A total of 28 patients were included in this study. Most patients had received pembrolizumab as an ICI. The median duration of cetuximab-based regimens prescribed was 4.5 months. The objective response rate (ORR) was 32.1% (95% confidence interval [CI], 17.9%-50.6%), and the disease control rate (DCR) was 53.6% (95% CI, 42.4%-76.4%). The median overall survival and median progression-free survival were 9.1 months (95% CI, 1.3-16.8) and 2.9 months (95% CI, 2.2-3.5), respectively. The incidence of cetuximab-related adverse events was reported as 39.2%.

**Conclusion:** A cetuximab-based regimen is still an effective and tolerable treatment for R/M HNSCC after progression on ICIs. Future prospective studies are needed to identify better treatments for previously ICI-treated or heavily treated R/M HNSCC patients.

**Keywords:** Cetuximab; Head and neck cancer; Immune checkpoint inhibitors

## 1. INTRODUCTION

Head and neck cancer is the sixth most common type of cancer worldwide. More than 65% of these patients will eventually develop recurrent or metastatic disease associated with a dismal prognosis.[1] The EXTREME regimen, which includes cetuximab (a monoclonal anti-EGFR antibody) combined with platinum/5-fluorouracil chemotherapy, has been regarded as the front-line treatment for recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC) patients.[2] In recent years, immune checkpoint inhibitors (ICIs) have shown their efficacy in treating R/M HNSCC patients. The results of the KEYNOTE-048 study demonstrated that patients treated with pembrolizumab plus platinum and 5fluorouracil had better overall survival than those treated with the first-line, EXTREME regimen used for R/M HNSCC patients.[3] Patients with platinum-resistant HNSCC treated with pembrolizumab and nivolumab also showed better survival than those treated with traditional chemotherapy options in the KEYNOTE-040 and CheckMate 141 studies, respectively.[4,5] However, the treatment of patients with R/M HNSCC resistant to front-line regimens remains a major challenge. The salvage treatment for R/M HNSCC patients experiencing ICI failure is still not standardized, although ICI-induced chemosensitization effects have been implicated in patients with non–small-cell lung cancer.[6] A retrospective study conducted in Japan demonstrated better outcomes with salvage chemotherapy after nivolumab than those achieved using the best supportive care.[7] In another two retrospective studies, the rate responses to salvage chemotherapy after ICIs were 30% and 42%.[8,9] However, the efficacy of cetuximab-based regimens after ICI failure has seldom been reported. Hence, we presented

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a clinical perspective of cetuximab-based therapy in heavily pretreated R/M HNSCC patients after progression to ICIs.

## 2. METHODS

### 2.1. Study design and participants

We retrospectively reviewed the electronic medical records of all patients with R/M HNSCC who received at least one cycle of cetuximab-based therapy after at least one cycle of ICIs due to disease progression at Taipei Veterans General Hospital between January 2017 and December 2020. Those patients were ineligible for curative treatment, including surgical resection and definitive concurrent chemoradiation therapy (CCRT). Patients with a diagnosis of nasopharyngeal cancer, occult primary tumors, and salivary gland tumors were not included. We also excluded patients with previous cetuximab use for possible acquired resistance to cetuximab.[10] This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital (certificate No. 2021-12-004AC).

### 2.2. Data collection

Patient characteristics were obtained from medical records and included age; sex; history of betel quid chewing, cigarette smoking and alcohol drinking; comorbidities; primary tumor site; information on primary tumor differentiation; initial stage defined by the American Joint Committee on Cancer staging system (seventh edition); Eastern Cooperative Oncology Group performance status (ECOG PS) before the use of cetuximab-based treatment; history of initial curative therapies used (including induction chemotherapy, curative surgery, and concurrent chemoradiation); history of subsequent systemic treatment; and programmed death ligand 1 (PD-L1) expression information including combined positive score (CPS, Dako 22C3) and tumor cell expression (TC, Dako 28-8). PDL1 staining was considered positive when CPS ≥ 1 and TC ≥ 1%, according to guidelines of the KEYNOTE-048 and CheckMate 141 studies.

### 2.3. Outcome

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by the investigator's review. The objective response rate (ORR) was defined as the percentage of patients who achieved a complete response (CR) or partial response. The disease control rate (DCR) was defined as the percentage of patients who achieved an objective response or stable disease. The median progression-free survival (mPFS) was measured from the time of cetuximab-based treatment initiation to first disease progression (PD) or death from any cause. The median overall survival (mOS) was measured from the time of cetuximab-based treatment initiation to death from any cause. Adverse events were evaluated and graded according to the guidelines provided by the Common Terminology Criteria for Adverse Events, version 4.1 (CTCAE 4.1).

### 2.4. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY. The ORR and DCR are expressed as percentages with 95% confidence intervals (95% CIs). Survival curves of OS and PFS were estimated using the Kaplan–Meier method. The 95% CI of the mOS and mPFS are also presented. For patients who were still alive or who lacked follow-up, data collected at the time of the last follow-up were used. Clinicopathologic factors were analyzed by a univariate Cox proportional hazards model to identify prognostic factors of OS. Factors with an extremely low number of cases were excluded from univariate analysis.

**Table 1**

**Clinical characteristics of patients**

| | Total Population, n = 28 | % |
|---|---|---|
| Median age at cancer diagnosis (range), y | 55 (36-93) | |
| Median age at cetuximab initiation (range), y | 57 (39-93) | |
| Gender | | |
| Male | 27 | 96.5 |
| Female | 1 | 3.5 |
| Smoking | 16 | 57.1 |
| Alcohol | 19 | 67.8 |
| Betel nuts | 18 | 64.2 |
| Comorbidities | 11 | 39.3 |
| Diabetes | 3 | 10.7 |
| Stroke | 3 | 10.7 |
| Hepatitis B | 3 | 10.7 |
| Primary tumor site | | |
| Oral cavity | 21 | 75 |
| Oropharynx | 2 | 7.1 |
| Hypopharynx | 3 | 10.7 |
| Larynx | 2 | 7.1 |
| Differentiation | | |
| Well | 0 | 0 |
| Moderate | 19 | 67.8 |
| Poor | 3 | 10.7 |
| Unknown | 6 | 21.4 |
| Stage at initial diagnosis (AJCC 7thEd) | | |
| I | 1 | 3.5 |
| II | 3 | 10.7 |
| III | 4 | 14.2 |
| IVA | 10 | 35.7 |
| IVB | 6 | 21.4 |
| IVC | 3 | 10.7 |
| Unknown | 1 | 3.5 |
| Initial curative therapy | | |
| Induction chemotherapy | 6 | 21.4 |
| Curative surgery | 20 | 71.4 |
| Concurrent chemoradiation | 16 | 57.1 |
| PD-L1 status[a] | | |
| Positive | 7 | 25.0 |
| Negative | 2 | 7.1 |
| No data | 19 | 67.8 |
| ECOG PS (at the start of Cetuximab) | | |
| ≦2 | 20 | 71.4 |
| ≧3 | 8 | 28.5 |
| Type of relapse | | |
| Local regional disease only | 13 | 46.4 |
| Distant metastases | 15 | 53.6 |
| No. of previous systemic therapies | | |
| 1 | 10 | 35.7 |
| 2 | 14 | 50.0 |
| 3 | 4 | 14.2 |
| Prior ICIs | | |
| Pembrolizumab only | 17 | 60.7 |
| Nivolumab only | 3 | 10.7 |
| Two kinds of immunotherapy[b] | 3 | 10.7 |
| Nivolumab and Ipilimumab | 3 | 10.7 |
| Other Investigational drugs[c] | 2 | 7.1 |
| Prior systemic regimen | | |
| Platinum-based chemotherapy | 10 | 35.7 |
| Taxane-based chemotherapy | 10 | 21.4 |
| Afatinib | 5 | 17.8 |
| Lenvatinib | 4 | 14.2 |

AJCC = American Joint Committee on Cancer staging system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICIs = immune checkpoint inhibitors; PD-L1 = programmed death ligand 1.
[a]PD-L1 was considered positive when the combined positive score (CPS) ≥ 1 or tumor cells (TC) ≥ 1%.
[b]Nivolumab and pembrolizumab were alternately used in those three patients.
[c]One patient used durvalumab combined with tremelimumab, one patient used avelumab.

**Table 2**

**Cetuximab-based therapy and further salvage therapy**

| | n | % |
|---|---|---|
| First Cetuximab-based therapy (n = 28) | | |
| Cetuximab alone | 8 | 28.5 |
| Platinum and Fluorouracil-based chemotherapy | 12 | 42.8 |
| ME-MOCLUB regimen | 6 | 21.4 |
| Others | 2 | 7.1 |
| Salvage therapy at progression after Cetuximab-based therapy (n = 17) | | |
| Cetuximab combined with different chemotherapy | 5 | 31.2 |
| Immunotherapy combined with chemotherapy | 6 | 37.5 |
| Chemotherapy alone | 2 | 18.7 |
| Others | 4 | 23.5 |

ME-MOCLUB: methotrexate, epirubicin, alternating with mitomycin-C, vincristine, cisplatin, leucovorin, 5-fluorouracil, and bleomycin.

## 3. RESULTS

### 3.1. Patient characteristics

A total of 28 patients with R/M HNSCC were included and followed until May 2021. The details of the patients' clinical characteristics are listed in Table 1. The median age was 55 years, and the patients were predominantly male (96.5%) and had histories of betel quid chewing, cigarette smoking, and alcohol drinking. Approximately, 85% of the patients had an ECOG PS less than or equal to two. A minority of patients had diabetes mellitus, hepatitis B carrier, and experienced stroke (10.7%). Eleven patients exhibited evaluated HPV status, with two of them reported as positive. The most common primary site of cancer was the oral cavity (75%). Most of the tumors were moderately differentiated (67.8%). The initial stage of the cancer in these patients was mainly stage IVA or IVB. Regarding the disease status, 13 patients had local regional disease (46.4%), and 15 patients had metastatic disease (53.6%). Most of the patients had received curative surgery (71.4%), pembrolizumab only for ICIs (60.7%), and platinum- or taxane-based chemotherapy (both 35.7%). Nine patients (32.1%) had platinum-refractory disease, which was defined as progression to a platinum-based regimen for advanced disease or relapse within 6 months for curative intent. Patients in our study received a median of five cycles of ICIs, and a major proportion of patients received over two lines of systemic therapy.

### 3.2. Cetuximab-based regimen

Most patients received a cetuximab-based regimen as salvage therapy with an initial loading dose of 400 mg/m², followed by a subsequent maintenance dose of 250 mg/m². The median duration from the last course of ICIs to the first course of cetuximab was 1.3 months. Cetuximab was prescribed with chemotherapy alone and with other medications in 64.2%, 28.5%, and 7.1% of the total population, respectively.

In the group of patients treated with cetuximab with chemotherapy, the most common chemotherapy regimen consisted of a combination of platinum and fluorouracil, followed by the ME-MOCLUB regimen (methotrexate 30 mg/m² and epirubicin 30 mg/m² on day 1, alternating with mitomycin-C 4 mg/m², vincristine 1 mg/m², cisplatin 25 mg/m², leucovorin 120 mg/m², 5-fluorouracil 1000 mg/m², and bleomycin 10 mg/m² on day 8).[11] Seventeen patients received another salvage therapy after cetuximab failure; five of them were treated with cetuximab combined with other chemotherapies, and six of them were retreated with ICI-related regimens. The details above are listed in Table 2.

### 3.3. Objective responses

Twenty-four patients from the total population were evaluated for the best tumor response, and the results are described in Table 3. Those patients who were not evaluated had early mortality after the cetuximab-based regimen (the median time period was 1.6 months). Across all evaluated patients, the ORR was 32.1% (95% CI, 17.9%-50.6%), and the DCR was 53.6% (95% CI, 42.4%-76.4%). CR was observed in one patient (3.5%). Partial response was observed in eight patients (28.5%), stable disease was observed in six patients (21.4%), and PD was observed in eight patients (57%). In the group of patients with local regional disease, the ORR and DCR were 30.7% and 53.8%, respectively. In the metastatic disease group, the ORR and DCR were 33.3% and 53.3%, respectively. In the group treated with cetuximab alone, the ORR and DCR were 25.0% and 37.5%, respectively. In the group treated with cetuximab and chemotherapy, the ORR and DCR were 35.0% and 37.5%, respectively.

### 3.4. Survival

The median follow-up time was 8.4 months (interquartile range [IQR] 0.8-47.7). The median duration of receiving the cetuximab-based regimen was 4.5 months (IQR 2.1-7.8). Across all patients, the mOS was 9.1 months (95% CI, 1.3-16.8), and the mPFS was 2.9 months (95% CI, 2.2-3.5). The details above are listed in Table 3. The Kaplan–Meier plots of OS and PFS are shown in the Fig. 1. The patients with metastatic disease had a nonsignificantly shorter OS and PFS than those of the patients with local regional disease (mOS= 13.6 vs 5.7 months; $p = 0.44$,

**Table 3**

**The best response and survival**

| | Total | Loco regional | Metastases |
|---|---|---|---|
| Number of patients (n, %) | 28 | 13 | 15 |
| Median follow-up times, mo (range) | 8.4 (0.8-47.7) | 10.3 (1.9-39.6) | 5.4 (0.8-47.7) |
| Types of best responses (n, %) | | | |
| CR | 1, 3.5% | 1, 7.7% | 0, 0% |
| PR | 8, 28.5% | 3, 23.0% | 5, 33.3% |
| SD | 6, 21.4% | 3, 23.0% | 3, 20.0% |
| PD | 9, 32.1% | 4, 30.7% | 5, 33.3% |
| No evaluation | 4, 14.3% | 2, 15.4% | 2, 13.3% |
| Overall response rate | 32.1% (17.9%-50.6%) | 30.7% (12.6%-57.6%) | 33.3% (15.1%-58.2%) |
| Disease control rate | 53.6% (42.4%-76.4%) | 53.8% (29.1%-76.7%) | 53.3% (30.1%-75.1%) |
| Median progression-free survival (mo, 95% CI) | 2.9 (2.2-3.5) | 3.2 (2.6-3.7) | 2.9 (0.2-5.5) |
| Median overall survival (mo, 95% CI) | 8.4 (7.3-16.5) | 13.6 (6.6-20.5) | 5.7 (4.9-6.4) |

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

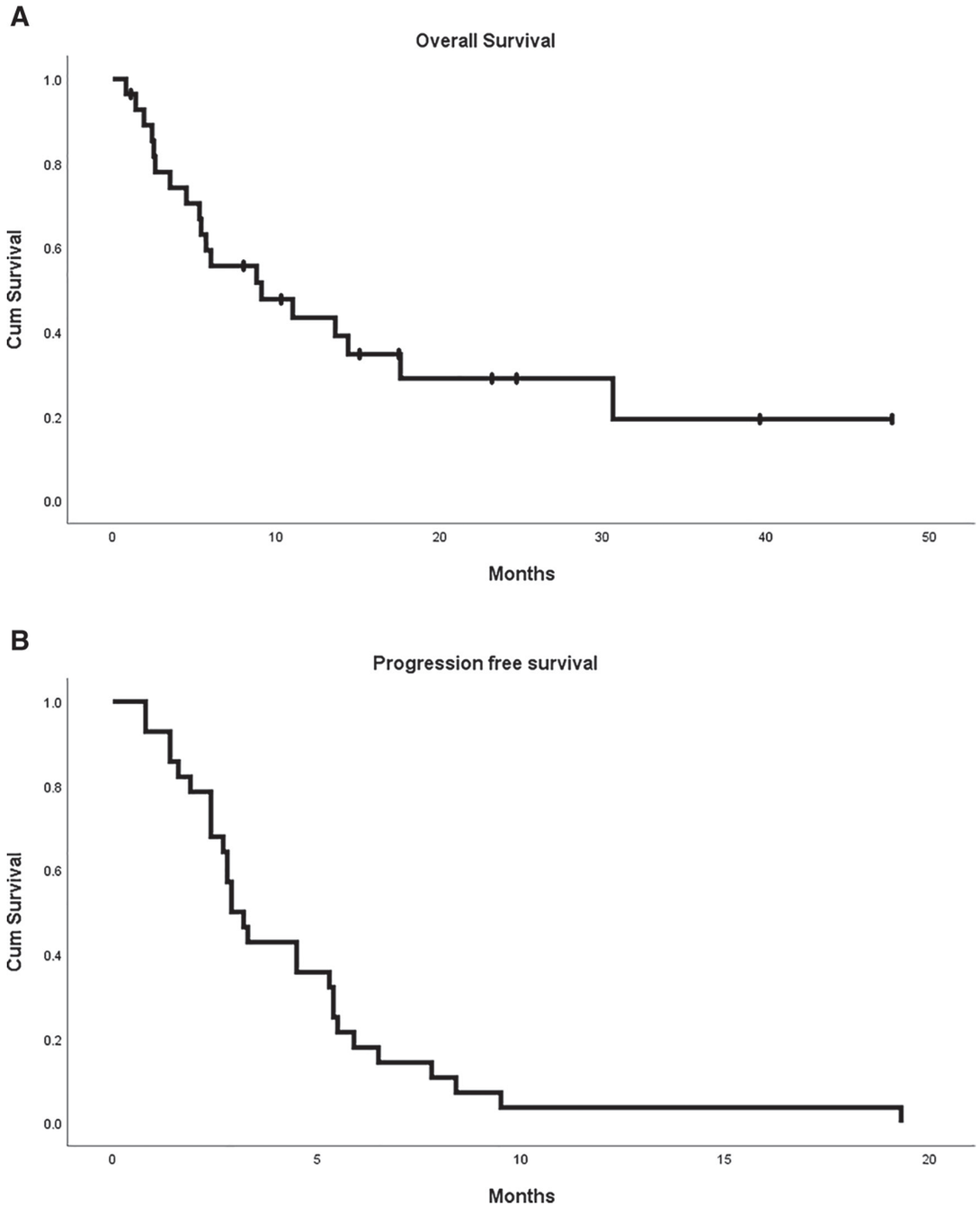


**Fig. 1** Kaplan–Meier curves for (A) OS and (B) PFS of patients in the study. OS = overall survival; PFS = progression-free survival.

mPFS= 3.2 vs. 2.9 months; $p = 0.64$). The patients who received cetuximab with chemotherapy had a longer OS and PFS than the patients who received cetuximab alone (mOS= 10.9 vs. 4.5 months; $p = 0.28$, mPFS= 4.5 vs. 2.4 months; $p = 0.003$). None of the clinicopathologic factors were significantly different in univariate analysis for OS (Table 4).

### 3.5. Safety

The incidence of cetuximab-related adverse events was reported as 39.2%, and the most common side effects were skin reaction and stomatitis. Severe adverse events (defined as grade 3 or above) not related to cetuximab use were mostly hematologic toxicity and were mainly neutropenia (25%) followed by anemia (21.4%). Grade 3 hepatitis was reported in two patients.

## 4. DISCUSSION

In R/M HNSCC patients, ICIs harbored survival benefits over conventional therapies in the first-line setting or platinum-refractory cases.[12] However, salvage therapies for R/M HNSCC patients after ICI failure have seldom been reported. Regarding non–small-cell lung cancers, studies have suggested

**Table 4**

**Univariate analysis for overall survival**

| Clinicopathologic features | Hazard ratio | 95% CI | *p* |
|---|---|---|---|
| Age, y | | | |
| ≥50 | 1.34 | 0.48-3.75 | 0.57 |
| < 50 | Ref | | |
| ECOG PS | | | |
| ≥3 | 1.29 | 0.48-3.49 | 0.60 |
| ≤2 | Ref | | |
| Smoking | | | |
| Yes | 1.01 | 0.39-2.61 | 0.98 |
| No | Ref | | |
| Alcohol | | | |
| Yes | 0.50 | 0.18-1.34 | 0.16 |
| No | Ref | | |
| Betel nuts | | | |
| Yes | 0.59 | 0.23-1.51 | 0.27 |
| No | Ref | | |
| Primary site | | | |
| Oral cavity | 0.56 | 0.21-1.49 | 0.24 |
| Nonoral cavity | Ref | | |
| Initial stage (AJCC 7th ED) | | | |
| IV | 0.76 | 0.29-1.98 | 0.57 |
| I-III | Ref | | |
| Previous curative surgery | | | |
| Yes | 0.74 | 0.26-2.08 | 0.56 |
| No | Ref | | |
| Previous CCRT | | | |
| Yes | 0.52 | 0.19-1.37 | 0.18 |
| No | Ref | | |
| Disease status | | | |
| Metastatic disease | 1.43 | 0.57-3.58 | 0.44 |
| Local regional disease | Ref | | |
| Previous platinum-based therapy | | | |
| Yes | 0.49 | 0.18-1.30 | 0.15 |
| No | Ref | | |
| Previous taxane-based therapy | | | |
| Yes | 0.92 | 0.36-2.38 | 0.87 |
| No | Ref | | |
| Previous ICIs | | | |
| Pembrolizumab alone | 1.37 | 0.53-3.49 | 0.50 |
| Others | Ref | | |
| Previous systemic therapy | | | |
| ≥2 | 0.47 | 0.18-1.25 | 0.13 |
| ≤1 | Ref | | |
| Cetuximab-adverse events | | | |
| Yes | 0.63 | 0.23-1.71 | 0.37 |
| No | Ref | | |

AJCC = American Joint Committee on Cancer staging system; CCRT = concurrent chemotherapy; ICIs = immune checkpoint inhibitors; ECOG PS = Eastern Cooperative Oncology Group Performance Status.

that chemotherapy after ICIs is more effective than chemotherapy without previous ICIs.[13] Here, we retrospectively analyzed the treatment efficacy of a cetuximab-based regimen in R/M HNSCC patients after progression to ICIs. The result is promising, with patients exhibiting an ORR of 32.1% and a DCR of 53.6%. The mOS and mPFS were 9.1 and 2.9 months, respectively. The adverse events during the treatment were all manageable. These results suggest that cetuximab-containing treatment is effective and well tolerated even in patients with advanced age and who experienced poor performance of other drugs.

Regarding previous studies evaluating the responses to systemic salvage therapy in patients with R/M HNSCC after ICIs, the ORRs were 30% and 42%; the mPFS was 3.6 and 4.2 months; and the mOS was 7.8 and 8.4 months, respectively.[8,9] In those studies, cetuximab was prescribed in approximately half of the patients, and the survival benefit of the cetuximab-related regimen relative that achieved with another therapy was not evaluated. In another study executed before ICIs were available, heavily pretreated R/M HNSCC patients treated with cetuximab-combined salvage chemotherapy regimens of MEMOCLUB or GV (gemcitabine 1000 mg/m$^2$ on day 1 and vinorelbine 25 mg/m$^2$ on day 8) showed an ORR of 66.7% and a 1-year OS rate of 49%.[11] Those regimens were also widely used in our study, but patients on these regimens showed relatively poor responses, probably due to the poor performance of these approaches in our patients.

The combination of cetuximab with nivolumab was also reported recently, and approximately half of the patients in this study were ICI-pretreated. The mOS and mPFS were 3.4 and 11.5 months, respectively. However, the outcome of survival was more unfavorable in patients pretreated with ICI than in those not pretreated with ICI.[14] Therefore, in R/M HNSCC patients who progress after ICI treatment, the benefits of adding cetuximab need to be further evaluated. In another recent study investigating the treatment sequence of cetuximab and ICIs in R/M HNSCC patients, the results showed that patients with cetuximab exposure before ICI administration had worse survival than that of those without prior cetuximab exposure. Regarding the use of subsequent therapy after ICIs, there was a trend that the survival period of the patients receiving cetuximab-containing therapy was longer than that of the patients not receiving cetuximab therapy, but the difference was not statistically significant. Based on the results of this study, cetuximab administered after ICIs may be beneficial to those patients.[15] In the KEYNOTE-048 study, half of the patients had received subsequent therapy after first progression. A better time to second objective disease progression (PFS2) was observed in the CPS ≥20 and ≥1 populations for those treated with pembrolizumab than for those treated with the EXTREME regimen. A similar finding was also noted in the total population when comparing the pembrolizumab group to the EXTREME regimen group. These data also indicate the potential benefit of front-line ICI treatment followed by cetuximab-based salvage therapy in patients with R/M HNSCC.[16]

Several limitations of our analysis exist. First, the sample size was small, and this was a retrospective study conducted in a single medical center. Second, the PD-L1 status of the patients in our study was not examined in all cases. Third, the study lacks a control group to investigate the benefit of adding cetuximab. In our cohort, patients who failed ICI treatment were mostly heavily treated with multiple lines of chemotherapy. A better control group for cetuximab-containing regimens is unknown. To appropriately compare the benefits of different treatments, a further prospective study is needed. In conclusion, our study indicates that a cetuximab-based regimen is still an effective and tolerable treatment for R/M HNSCC patients after progression on ICIs. The best treatment sequence of cetuximab-based regimens and ICIs remains to be determined by large-scale prospective clinical trials.

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