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ORIGINAL RESEARCH

A phase II trial of paclitaxel plus biweekly cetuximab for patients with recurrent or metastatic head and neck cancer previously treated with both platinum-based chemotherapy and anti-PD-1 antibody

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Background: An important unmet need for new treatment options remains for patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) previously treated with both platinum-based chemotherapy and anti-programmed cell death protein 1 (PD-1) antibody. Retrospective studies suggest that previous treatment with immune checkpoint inhibitor might augment the efficacy of subsequent chemotherapy. Here, we conducted a phase II trial aimed to evaluate the efficacy and safety of paclitaxel plus biweekly cetuximab for patients in this setting.

Patients and methods: This was a single-arm, multicenter, phase II trial. Key eligibility criteria were R/M-HNSCC, and previous treatment with both platinum-based chemotherapy and PD-1 antibody. Paclitaxel plus biweekly cetuximab consisted of weekly paclitaxel 100 mg/m² (days 1, 8, 15) and biweekly cetuximab 500 mg/m² (days 1, 15) with a cycle of 28 days until progression or unacceptable toxicity. Primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and adverse events (AEs) (Common Terminology Criteria for Adverse Events version 5.0).

Results: Between August 2020 and August 2022, 35 patients were enrolled, of whom 33 were assessable for response. ORR was 69.6% (95% confidence interval 51.2% to 84.4%). With a median follow-up period for survivors of 16.6 months, median PFS and OS were 5.5 and 13.3 months, respectively. DCR was 93.7%. Twenty-three patients (65%) experienced grade 3 or 4 AEs, including neutropenia (34%), infection (14%), leukopenia (11%), mucositis (8%), and pneumonitis (8%). Eight patients discontinued study treatment due to treatment-related AEs, and no treatment-related death was observed.

Conclusions: Paclitaxel plus biweekly cetuximab showed highly encouraging efficacy and manageable toxicities in R/M-HNSCC patients previously treated with both platinum-based chemotherapy and PD-1 antibody. This combination therapy warrants further investigation in this setting.

Key words: head and neck cancer, PD-1 inhibitors, cisplatin, paclitaxel, cetuximab

INTRODUCTION

Patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M-HNSCC) have a poor prognosis of <1 year.¹ In recent years, immune checkpoint inhibitors have improved treatment outcomes for patients with R/M-HNSCC.

After the failure of platinum-based chemotherapy, nivolumab and pembrolizumab showed a survival benefit.^{2,3} In the KEYNOTE-048 trial, pembrolizumab alone improved overall survival (OS) in the programmed death-ligand 1 (PD-L1)-positive population and pembrolizumab combination chemotherapy improved OS in the total population as compared with the EXTREME regimen, namely combination chemotherapy with 5-fluorouracil, platinum, and cetuximab.⁴

However, for patients with R/M-HNSCC with failure of platinum-based chemotherapy and immune checkpoint inhibitors, prognosis is dismal. A retrospective study showed that median OS for these patients who could not receive subsequent chemotherapy was only 3.1 months.⁵ Furthermore, no standard treatment has been established.

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Nevertheless, recent retrospective studies have suggested that previous treatment with immune checkpoint inhibitor might augment the efficacy of subsequent chemotherapy.^{6–8}

Combination chemotherapy with paclitaxel and cetuximab has potential as an attractive subsequent chemotherapy option for R/M-HNSCC.^{5,9} In the majority of studies, cetuximab was administered under a weekly schedule with a loading dose of 400 mg/m² followed by a weekly dose of 250 mg/m². In Japan, a biweekly schedule of cetuximab was approved for colorectal cancer and head and neck cancer. In patients with colorectal cancer, the pharmacokinetics and pharmacodynamics of biweekly administration of cetuximab 500 mg/m² are equivalent to those of the weekly administration of 400 mg/m² followed by 250 mg/m².^{2,10} Biweekly dosing suggested no significant difference in efficacy and adverse events (AEs) from weekly dosing.^{11,12} Further, a retrospective study showed that biweekly dosing retained efficacy and improved treatment compliance in patients with head and neck cancer.¹³

Here, we conducted a phase II trial to evaluate the efficacy and safety of paclitaxel plus biweekly cetuximab for patients with R/M-HNSCC who were previously treated with both platinum-based chemotherapy and programmed cell death protein 1 (PD-1) antibody.

PATIENTS AND METHODS

Study design

The study was conducted under a single-arm, multicenter, phase II design in five institutions in Japan (Japan Registry of Clinical Trials: jRCTs051200040). Eligible patients were ≥ 18 years old and had an Eastern Cooperative Oncology Group performance status of 0 or 1, histologically confirmed squamous cell carcinoma of the head and neck with distant metastasis or recurrence which was not amenable to curative locoregional treatment, refractory or intolerant to both platinum-based chemotherapy and PD-1 antibody, and no previous taxane-based chemotherapy for R/M-HNSCC. Additional inclusion and exclusion criteria are listed in [Supplementary Appendix S1](https://doi.org/10.1016/j.esmoop.2024.103476), available at <https://doi.org/10.1016/j.esmoop.2024.103476>.

Procedures

Paclitaxel plus biweekly cetuximab consisted of weekly paclitaxel 100 mg/m² (days 1, 8, 15) and biweekly cetuximab 500 mg/m² (days 1, 15) with a cycle of 28 days and continued until progression or unacceptable toxicity. Weekly paclitaxel at a dose of 100 mg/m² was selected as this is the approved dose in Japan based on the results of a phase II trial.¹⁴ Cetuximab was administered in 2 h followed by paclitaxel in 1 h. Dose modifications of study drugs were allowed in accordance with the severity of AEs ([Supplementary Appendix S2](https://doi.org/10.1016/j.esmoop.2024.103476), available at <https://doi.org/10.1016/j.esmoop.2024.103476>).

Tumor response was assessed every 8 weeks after registration by computed tomography or magnetic resonance imaging. AEs were assessed throughout study

treatment, 7 days after last administration, and until improvement of treatment-related AEs. Severe AEs were also reported during study treatment.

Outcomes

Primary endpoint was objective response rate (ORR), defined as the best complete (CR) or partial response (PR) according to RECIST version 1.1.

Secondary endpoints were progression-free survival (PFS), OS, disease control rate (DCR), and AEs graded as per the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analyses

Previous studies have shown that around 10% of platinum-refractory R/M-HNSCC patients respond to chemotherapeutic agents^{2,4,15} and that 30% of platinum-refractory R/M-HNSCC patients respond to chemotherapy after progression with immune checkpoint inhibitors.⁶ The binomial analysis set for the null hypothesis had an ORR of 10% and alternative of 30% with a one-sided α of 0.05 and a power of 90%. Accordingly, the target accrual size was 33 patients. Allowing for a potential drop-out rate of 10%, we planned to enroll 35 patients in total. Binominal confidence intervals (CIs) for ORR and DCR were estimated by the exact method.

Time-to-event (PFS, OS) analyses were calculated by the Kaplan–Meier method with 95% CIs. All analyses were carried out using SPSS version 28.0.1.0 (IBM Corp., Armonk, NY).

The study protocol was approved by the Kobe University Clinical Research Ethical Committee and each participating hospital. This study was carried out in accordance with the international ethical recommendations stated in the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research. All patients who were enrolled in this study provided written informed consent to participate in the trial.

RESULTS

Patients

Between August 2020 and August 2022, 35 patients met the eligibility criteria and were enrolled, of whom 33 were assessable for response (date of data cut-off was 15 August 2023). Two patients were not assessable for response because one patient was lost to follow-up and the second experienced severe paclitaxel allergy before the first disease evaluation. [Table 1](#) shows patient characteristics at baseline. All patients had received treatment with both platinum-based chemotherapy and PD-1 antibody. Six patients had received previous treatment with cetuximab-containing chemotherapy for R/M-HNSCC. Among these six patients, five patients responded to the treatment and all six discontinued the treatment due to disease progression. At study entry, 12 patients had locoregional recurrence, 16 patients had distant metastases, and 7 patients had both locoregional recurrence and distant metastases.

Table 1. Patient characteristics at baseline

Characteristic (N = 35)	
Age (years), median (range)	72 (45-81)
Sex, male, n (%)	28 (80)
Primary site, n (%)	
Hypopharynx	13 (37)
Oral cavity	11 (31)
Nasal/paranasal sinus	6 (17)
Oropharynx ^a	2 (6)
Larynx	2 (6)
External auditory canal	1 (3)
ECOG PS, n (%)	
0	9 (26)
1	26 (74)
Platinum refractory, n (%)	31 (89)
Platinum intolerable, n (%)	4 (11)
Previous PD-1 Ab, n (%)	
Nivolumab	19 (54)
Pembrolizumab	16 (46)
Previous cetuximab, n (%)	
For R/M-HNSCC	6 (17)
Site of disease, n (%)	
Locoregional only	12 (34)
Metastasis only	16 (46)
Locoregional and metastasis	7 (20)

Ab, antibody; ECOG PS, Eastern Cooperative Oncology Group score for performance status; PD-1, programmed cell death protein 1; R/M-HNSCC, recurrent and metastatic head and neck squamous cell carcinoma.

^aOne patient was p16 positive.

Major sites of metastasis were lung (31%) and lymph nodes (28%). At the time of analysis, 4 patients (11%) were still receiving study treatment, and 13 patients (37%) were receiving subsequent anticancer treatment (Supplementary Figures S1 and S2, available at <https://doi.org/10.1016/j.esmooop.2024.103476>).

Efficacy

Of the 33 patients assessable for response, response was observed in 23 patients. ORR was 69.6% (95% CI 51.2% to 84.4%), which met the prespecified criteria for the primary endpoint. DCR was 93.7% (95% CI 79.7% to 99.2%) (Table 2 and Figure 1A and B).

With a median follow-up period for survivors of 16.6 months, the median PFS and OS were 5.5 months (95% CI 4.3-6.6 months) and 13.3 months (95% CI 10.7-15.8

Table 2. Objective response in assessable patients

Response	N = 33 n (%)
CR	6 (18)
PR	17 (51)
SD	8 (24)
PD	2 (6)
In the efficacy analysis population	
ORR: 69.6% (95% CI 51.2% to 84.4%)	
DCR: 93.7% (95% CI 79.7% to 99.2%)	

Of 35 patients, 2 patients were not assessable.

CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

months), respectively (Figure 2A and B). One-year PFS and OS were 24.2% and 54.6%, respectively. Median time to response and duration of response were 1.7 months and 5.7 months (95% CI 0.9-10.5 months), respectively. Treatment response according to the time from last administration of PD-1 antibody was CR for 42 days (range 25-182 days), PR for 32 days (7-266 days), stable disease for 38.5 days (14-544 days), and progressive disease (PD) for 105 days (76-134 days), respectively (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2024.103476>). The ORR of patients who received study treatment within 60 days from the last administration of PD-1 antibody was 73% and that of the patients over 60 days was 57% (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2024.103476>).

Among the six patients resistant to previous cetuximab-containing chemotherapy, four patients (66.6%) responded to the protocol treatment.

Safety

Safety data were available for all 35 patients. The most common AEs of any grade were skin rash (65%), peripheral nerve neuropathy (45%), neutropenia (40%), fatigue (40%), and paronychia (37%). Twenty-three of 35 patients (65%) experienced grade 3 or 4 AEs, including neutropenia (34%), leukopenia (11%), infection (8%), mucositis (8%), and pneumonitis (8%). Any grade of pneumonitis (interstitial lung disease) occurred in four patients (11%) (Table 3, Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2024.103476>). Twenty-four patients (68%) required a reduction in paclitaxel or cetuximab dose due to AEs; of these, 22 patients required a reduction in paclitaxel and 11 patients required a reduction in cetuximab.

In this study, 12 patients (34%) discontinued study treatment with paclitaxel plus biweekly cetuximab due to AEs (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmooop.2024.103476>). Additionally, no patients discontinued paclitaxel only and five patients (14%) discontinued cetuximab only. Of these, discontinuation was due to treatment-related AEs in eight patients. Four patients (11%) had treatment-related pneumonitis, from which all recovered following discontinuation of the study treatment and treatment with steroids. Other treatment-related discontinuations were infection in two, pharyngeal fistula in one, and grade 3 allergy against paclitaxel in one. Four patients (11%) discontinued study treatment due to non-treatment-related AEs. These AEs were manageable and no treatment-related death was observed.

DISCUSSION

The results of this study showed that combination of paclitaxel plus biweekly cetuximab was highly effective for the treatment of R/M-HNSCC in patients who were previously treated with both platinum-based chemotherapy and PD-1 antibody. Although previous retrospective studies suggested that previous immunotherapy might augment the efficacy of salvage chemotherapy, this is the first

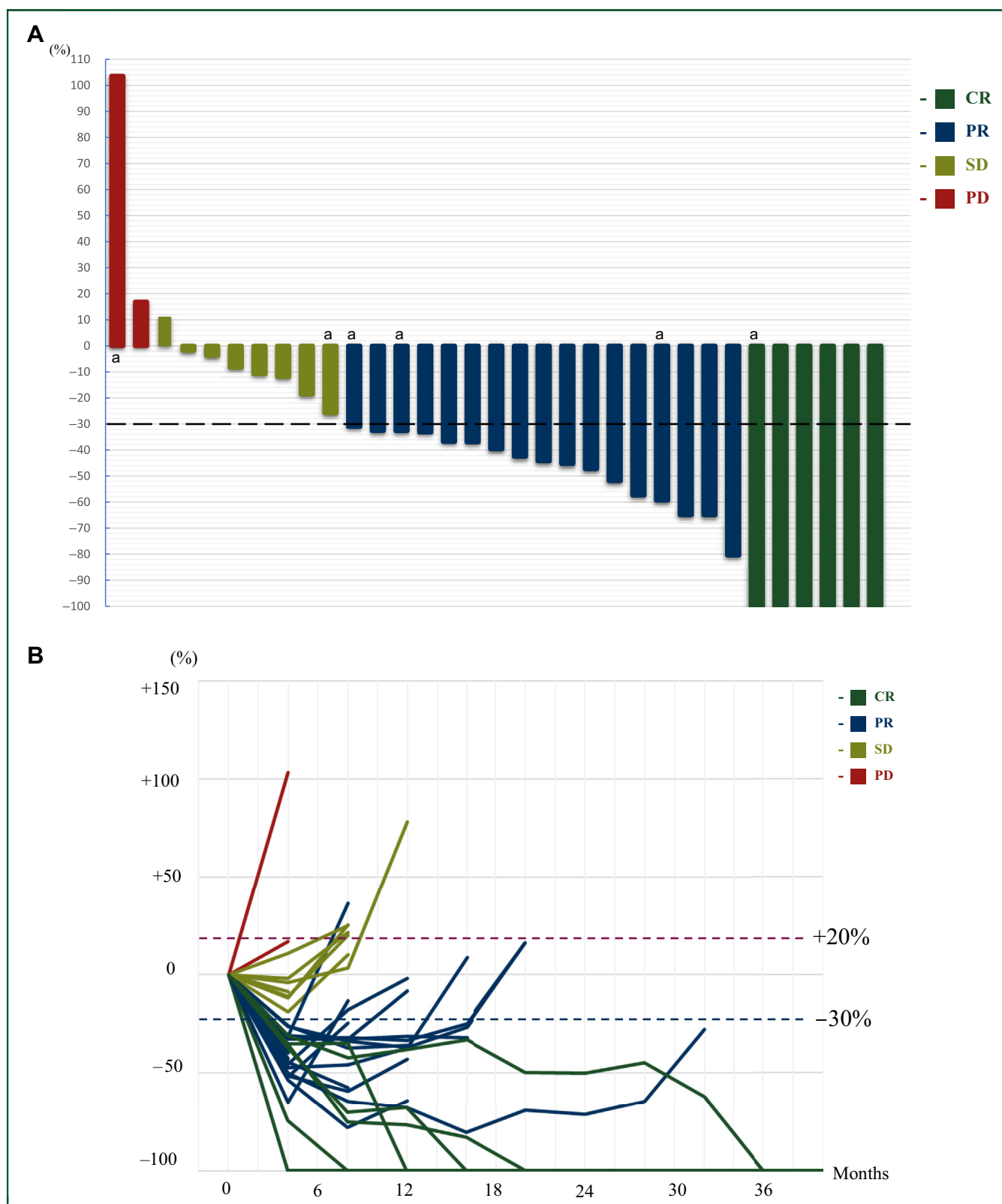


Figure 1. Tumor response by waterfall plot and spider plot. (A) Best percentage change from baseline in the target lesion in the efficacy analysis population ($N = 33$). (B) Longitudinal changes in target lesion size from baseline in the efficacy analysis population ($N = 33$). Responses were calculated using RECIST version 1.1. The black dashed line means 30% reduction and the red dashed line means 20% increase.

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

^aPatients who were resistant to a cetuximab-containing regimen.

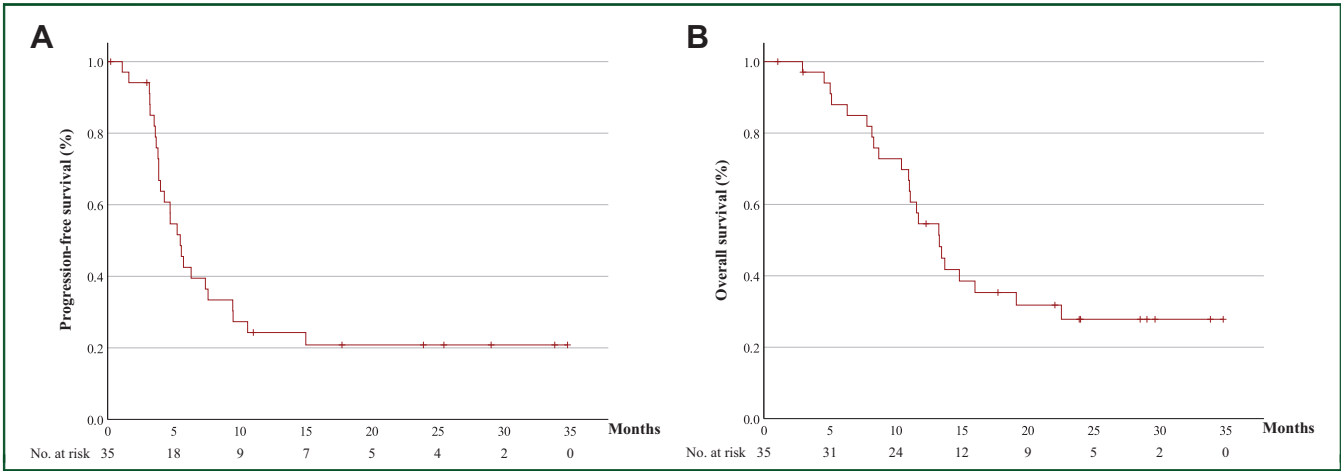


Figure 2. Survival outcomes for patients receiving study treatment. Kaplan–Meier curves for progression-free survival (A) and overall survival (B) in the total population ($N = 35$). The x-axis represents months.

prospective study to show promising efficacy for salvage chemotherapy after immunotherapy.

In first-line treatment of R/M-HNSCC with paclitaxel and anti-epidermal growth factor receptor (EGFR) antibody, median ORR, PFS, and OS have been reported as 37%-54%, 4.2-7.5 months, and 8.1-9.9 months, respectively.¹⁶⁻¹⁸ By contrast, in a retrospective study, the efficacy of paclitaxel with or without cetuximab for platinum-refractory R/M-HNSCC was modest as compared with the first-line setting, with an ORR of 6.2%-30%, a median PFS of 2.5-4.2 months,

and a median OS of 4.2-6.9 months.^{2,19,20} Recently, retrospective studies have suggested that chemotherapy after immune checkpoint inhibitors showed better efficacy than a historical control of chemotherapy in the platinum-refractory setting. The ORR, median PFS, and median OS in such conditions were 30%-54%, 2.1-4.2 months, and 6.9-9.8 months, respectively.^{6,21-23} In addition to these reports, recent findings from a randomized phase II trial of ficlatuzumab, a humanized anti-hepatocellular growth factor monoclonal antibody, with or without cetuximab indicated that ficlatuzumab plus cetuximab demonstrated a better ORR of 19%, compared to the 4% ORR observed with ficlatuzumab alone, in patients with HNSCC treated with both platinum-based chemotherapy and immunotherapy.²⁴ In the INTERLINK-1 trial, the addition of the anti-natural killer group 2A antibody monalizumab to cetuximab failed to show a survival improvement. However, cetuximab monotherapy in that trial showed an ORR of 19.1% for the patients with R/M-HNSCC who progressed after platinum and PD-1 antibody, which was numerically higher than the ORR with cetuximab alone in previous reports.²⁵ Accordingly, the combination of chemotherapy with cetuximab appears to offer better efficacy than other chemotherapeutic options. In our current phase II study, paclitaxel plus biweekly cetuximab showed an ORR of 69.6%, a median PFS of 5.5 months, and a median OS of 13.3 months. To our knowledge, this is the first prospective demonstration of this highly encouraging efficacy for these populations.

The mechanism underlying how this combination chemotherapy worked well for patients treated with both platinum-based chemotherapy and PD-1 antibody remains unclear. The mechanisms of resistance to immune checkpoint inhibitors are associated with various factors, including tumor microenvironment and immune antigen presentation.²⁶ Moreover, cetuximab increases not only PD-1-positive tumor-infiltrating lymphocytes but also causes the infiltration of suppressive regulatory T cells and myeloid-derived suppressor cells with increased expression of PD-1 and PD-L1, which could be inhibited by PD-1 antibody.^{27,28}

Table 3. All AEs ≥10% and all grade 3/4 AEs			
AEs ($N = 35$)	Grade 1/2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	35 (100)	19 (54)	4 (11)
Non-hematologic AEs			
Skin rash	22 (62)	1 (2)	0
Dry skin	21 (60)	0	0
Peripheral nerve neuropathy	15 (42)	1 (2)	0
Fatigue	12 (34)	2 (2)	0
Mucositis	11 (31)	3 (8)	0
Paronychia	12 (24)	1 (2)	0
Loss of appetite	9 (25)	1 (2)	0
Alopecia	9 (25)	0	0
Dysgeusia	9 (25)	0	0
Hypomagnesemia	8 (22)	0	0
Infection	3 (8)	3 (8)	1 (2)
Dysphagia	5 (14)	1 (2)	0
Diarrhea	5 (14)	1 (2)	0
Pneumonitis	1 (2)	3 (8)	0
Hand–foot skin reaction	4 (11)	0	0
Infusion reaction/allergy	3 (8)	1 (2)	0
Myalgia	4 (11)	0	0
Hypokalemia	0	1 (2)	0
Pharyngeal fistula	0	1 (2)	0
Cerebral infarction	0	0	1 (2)
Hematologic AEs			
Leukopenia	4 (11)	4 (11)	0
Neutropenia	2 (5)	8 (22)	4 (11)
Anemia	4 (11)	3 (8)	0
Febrile neutropenia	—	1 (2)	0

AEs, adverse events.

Therefore, we focused on the PD-1 occupancy of peripheral T cells after administration of PD-1 antibody. The elimination half-life of PD-1 antibody is 12-20 days, whereas PD-1 occupancy of peripheral T cells with PD-1 antibody is sustained at 57%-70% for ~60 days and PD-1 occupancy declines gradually over time.^{29,30} In the KEYNOTE-048 trial, PFS until progression under subsequent chemotherapy was longer for patients receiving pembrolizumab-containing treatment.³¹ Furthermore, combination of PD-1 antibody and cetuximab showed promising activity for platinum-refractory R/M-HNSCC.³² Indeed, in the present study, median duration from the last administration of PD-1 antibody was 35 days and no patient who received study treatment within 60 days after the last administration of PD-1 antibody experienced PD. Further, ORR was 73%, which was numerically higher than the ORR of 57% for patients over 60 days. On this basis, residual activity of PD-1 antibody might produce a synergistic effect with chemotherapy, resulting in enhancement of the immune microenvironment.³³⁻³⁵

In our present trial, previous treatment with cetuximab for R/M-HNSCC was allowed. Six patients had received previous cetuximab-containing chemotherapy for R/M-HNSCC. Although all six of these patients had discontinued cetuximab-containing chemotherapy due to disease progression, four patients (66.6%) responded to study treatment. Rechallenge of anti-EGFR antibody treatment has been investigated for patients with metastatic colorectal cancer, in whom it showed promising efficacy in late-line settings.^{36,37} In addition, rechallenge of cetuximab with chemotherapy for patients with R/M-HNSCC showed better ORR than those who received chemotherapy without cetuximab (16.4%-33.3% versus 6.2%, respectively).^{19,38} Consistent with these previous reports, rechallenge with cetuximab after PD-1 inhibitor appeared to yield a meaningful response in our study.

With regard to the safety profile of paclitaxel plus biweekly cetuximab, this was generally manageable. However, ~60% of patients required a reduction in study drug dosage. The main reason for dose reduction was peripheral neuropathy for paclitaxel and skin toxicity for cetuximab. These AEs could potentially affect the quality of life of patients. This regimen should be carefully managed accordingly, and dose adjustment in future clinical trials is considered. Moreover, attention should be given to the reasons for treatment discontinuation. Of 35 patients, 31 patients have discontinued study treatment and 4 patients are still on study treatment at the time of data cut-off. Eighteen patients (51%) discontinued because of PD. Eight patients (22%) discontinued due to treatment-related AEs, of whom four (11%) discontinued due to treatment-related pneumonitis, albeit that all four recovered with steroid treatment. After discontinuation, median time to progression was 177 days (range 50-665 days), while one patient showed a persistent response at the cut-off date. In a retrospective study of R/M-HNSCC, cetuximab-based chemotherapy showed a higher incidence of pneumonitis in

the setting of chemotherapy after progression on immune checkpoint inhibitor than no prior immune checkpoint inhibitor, at 21.1%-25.0% versus 0%-7%, respectively.^{3,8,19,39-41} Similarly, in non-small-cell lung cancer, EGFR-tyrosine kinase inhibitor after progression of immune checkpoint inhibitor might have increased the incidence of pneumonitis as compared with EGFR-tyrosine kinase inhibitor without prior immune checkpoint inhibitor (25.7% versus 4.59%, odds ratio 4.31).⁴² Although the incidence of pneumonitis in this study appeared to be lower than in reports in R/M-HNSCC patients with prior immune checkpoint inhibitors and all patients recovered from pneumonitis, close monitoring of patients during treatment with paclitaxel plus biweekly cetuximab after immune checkpoint inhibitors is warranted.

This study has some limitations. Firstly, it was conducted under a non-randomized, single-arm design. Secondly, although paclitaxel plus biweekly cetuximab demonstrated a high ORR of 69.6%, evaluation of response was assessed by the investigators and almost all patients had human papillomavirus (HPV)-unrelated cancer. The EXTREME regimen showed no difference by HPV status,⁴³ while the phase II trial of ficlatuzumab and trials of PD-1 antibody with cetuximab showed better efficacy for patients with HPV-unrelated cancer.^{24,44} Therefore, the difference in efficacy of paclitaxel plus biweekly cetuximab between HPV-related and HPV-unrelated cancer should be assessed in future trials. Thirdly, 11% of patients discontinued study treatment due to treatment-related pneumonitis. Hence, confirming the efficacy and safety of this combination would require a randomized comparison between paclitaxel plus biweekly cetuximab and paclitaxel alone in this setting.

In conclusion, paclitaxel plus biweekly cetuximab showed highly encouraging efficacy and a manageable toxicity profile in R/M-HNSCC patients who were previously treated with both platinum-based chemotherapy and PD-1 antibody. Paclitaxel plus biweekly cetuximab could be a potential treatment option and warrants further investigation in this setting.

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