ANTICANCER RESEARCH *42*: 4477-4484 (2022)
doi:10.21873/anticanres.15948

Real-world Therapeutic Outcomes of the Pembrolizumab Regimen as First-line Therapy for Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: A Single-center Retrospective Cohort Study in Japan

DAISUKE SANO[1], MOTOHIKO TOKUHISA[2], HIDEAKI TAKAHASHI[1], TAKASHI HATANO[1], GOSHI NISHIMURA[1], YASUSHI ICHIKAWA[2] and NOBUHIKO ORIDATE[1]

[1]*Department of Otorhinolaryngology-Head and Neck Surgery, School of Medicine, Yokohama City University, Yokohama, Japan;*
[2]*Department of Oncology, School of Medicine, Yokohama City University, Yokohama, Japan*

Abstract. *Background/Aim: This Japanese single-center retrospective cohort study aimed to evaluate the real-world therapeutic outcomes of pembrolizumab or pembrolizumab plus chemotherapy (pembrolizumab regimen) as first-line therapy for patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Patients and Methods: Thirty-two Japanese patients with R/M SCCHN treated with the pembrolizumab regimen between January 2020 and January 2022 were analyzed. The primary endpoint of the study was overall survival. Results: The median follow-up duration was 9.8 months (range=1.6-25.1 months). Fourteen patients received pembrolizumab alone, whereas the others received pembrolizumab with chemotherapy. The 1-year overall and progression-free survival rates were 64.5% (95% CI=38.9-81.6) and 54.9% (95% CI=33.9-71.8), respectively. The objective response rate was 56.2%. The Kaplan–Meier analysis showed that patients with favorable objective responses and an Eastern Cooperative Oncology Group performance status of 0 had longer survival. Immune-related adverse events (irAEs) occurred in 16 out of 32 patients (50.0%) during treatment; however, there were no irAEs greater than grade 4. Conclusion: The observed therapeutic efficacy and safety of pembrolizumab in real-world clinical practice was consistent with the data of the KEYNOTE-048 trial.*

Correspondence to: Daisuke Sano, MD, Ph.D., Department of Otorhinolaryngology-Head and Neck Surgery, Yokohama City University, School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Tel: +81 457872687, e-mail: dsano@yokohama-cu.ac.jp

Key Words: Recurrent/metastatic squamous cell carcinoma, head and neck, programmed cell death protein 1, pembrolizumab.

Squamous cell carcinoma of the head and neck (SCCHN) accounts for the majority of malignant tumors of the head and neck and is often observed as a locally advanced disease. More than half of the patients with advanced SCCHN develop locoregional or distant recurrence within 3 years; thus, their prognosis is poor (1, 2). Based on the results of the EXTREME trial reported by Vermorken *et al*. in 2008, the Extreme regimen was widely used until very recently as the standard first-line treatment for patients with recurrent/metastatic SCCHN (R/M SCCHN), which is a combination of cisplatin (CDDP)/carboplatin (CBDCA) plus 5-fluorouracil and cetuximab, showing better treatment outcomes than platinum-based chemotherapy plus 5-fluorouracil (3). However, the prognosis of R/M SCCHN did not improve dramatically until the advent of immunotherapy, with a median overall survival (OS) of less than 1 year.

Recently, immune checkpoint inhibitors (ICIs) have been developed and used to treat various types of malignancies, including R/M SCCHN, resulting in a paradigm shift in the management of patients with R/M SCCHN. ICIs have demonstrated durable improvements in patient outcomes by regulating immune escape through the blockade of programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), and programmed cell death ligand 1/2 (PD-L1/2), the ligands for PD-1 (4, 5). SCCHN is a malignancy in which the immune surveillance mechanism is suppressed due to the decreased function of tumor-infiltrating lymphocytes (TIL), increased function of regulatory T-cells (T-reg), and overexpression of cancer antigens (6). Furthermore, a high tumor mutation burden is frequently observed in SCCHN as in malignant melanoma (7) and lung cancer (8).

Virus-associated SCCHN such as nasopharyngeal and oropharyngeal SCC evade tumor T-cell immunity due to persistent viral infection; thus, ICIs are expected to be effective for patients with R/M SCCHN (6). In fact, the Checkmate141 trial showed that nivolumab, an anti-PD-1 monoclonal antibody, significantly prolonged OS compared to the investigator's choice monotherapy in platinum-refractory R/M SCCHN, a population with a poor prognosis for which no previous randomized controlled trial has previously reported any survival benefit (9). Furthermore, the KEYNOTE-048 trial showed that pembrolozumab, another anti-PD-1 monoclonal antibody, as monotherapy or in combination with chemotherapy (platinum plus 5-fluorouracil), improved OS compared to the EXTREME regimen, especially in R/M SCCHN patients with PD-L1 expressing tumors (10). Based on these results, the approval of these two anti-PD-1 monoclonal antibodies in Japan has led to the current use of nivolumab in patients with platinum-refractory R/M SCCHN and pembrolizumab (plus chemotherapy) as the standard first-line treatment for R/M SCCHN.

However, patient populations that are not included in clinical trials need to be treated in real-world settings; thus, there is a data gap between clinical trials and real-world settings. In addition, the results of the subgroup analysis of the Checkmate 141 trial for the Asian population also suggest that the effects of checkpoint inhibitors may differ substantially between races (11). Thus, the real-world benefits of pembrolizumab plus chemotherapy (pembrolizumab regimen) in Japanese patients with R/M SCCHN remain unclear. Herein, we conducted a single-center retrospective cohort study to investigate the real-world treatment outcomes of the pembrolizumab regimen as a first-line therapy for Japanese patients with R/M SCCHN.

Patients and Methods

Study design. This single-center retrospective cohort study was conducted between January 2020 and January 2022 at the Yokohama City University Hospital, Yokohama, Japan. The medical records of R/M HNSCC patients treated with pembrolizumab or pembrolizumab plus chemotherapy as first-line therapy were reviewed retrospectively. The primary endpoint of the study was the overall survival (OS) of the patients. The protocol was reviewed and approved by the institutional review board (approval ID: B210500037).

Patients. Patients were eligible if they were 20 years or older; had histologically confirmed recurrent or metastatic SCC of the nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, external auditory canal, or sinonasal cavity; received the pembrolizumab regimen as first-line therapy; were examined for treatment response by CT scans at least once; and had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Medical records were retrospectively reviewed for the following characteristics: age, sex, primary tumor location, status of human papillomavirus (HPV) with tumor p16 expression in patients with oropharyngeal SCC, ECOG PS prior to the use of the pembrolizumab regimen, date of diagnosis and treatment, last follow-up visit or death, histology, PD-L1 expression, and prior treatment. Patients who had previously received immunotherapy or every chemotherapeutic regimen as first-line therapy were excluded. A total of 32 patients with R/M SCCHN who received the pembrolizumab regimen as first-line therapy were enrolled in this study. All patients involved in this study were Japanese, and patients were classified by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells presented as percentages following a CPS of less than 1, CPS of 1 and above, less than 20, and CPS of 20 or more (10).

Treatment response was evaluated using CT scans in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The objective response rate (ORR) was defined as the percentage of patients with complete or partial responses (CR or PR, respectively). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

Treatment regimen. Patients were treated with either intravenous pembrolizumab alone (200 mg) every 3 weeks or intravenous pembrolizumab (200 mg) every 3 weeks plus either cisplatin (100 mg/m^2 body surface area as a 2-hour intravenous infusion on day 1) or carboplatin (with an area under the curve of 5 mg per milliliter per minute as a 1-hour intravenous infusion on day 1) and 5-fluorouracil (1,000 mg/m^2 per day for 4 days under continuous infusion) every 3 weeks for a maximum of six cycles. Pembrolizumab was administered until disease progression, intolerable toxicity, or patient decision was made. In the case of patients with stable disease, patients were able to receive pembrolizumab (400 mg) every 6 weeks.

Statistical analysis. The Chi-squared test was used to examine the correlations between categorical variables. The progression-free survival (PFS) was defined as the period from the first disease relapse after the patients received the pembrolizumab regimen until death due to any cause. OS and PFS were analyzed using the Kaplan–Meier method with the Wilcoxon log-rank test. Statistical analysis was performed using the JMP software (Version 12.2.0, SAS Institute Inc., Cary, NC, USA) and GraphPad Prism version 6.05 (GraphPad Software, San Diego, CA, USA). For all comparisons, a p-value <0.05 was considered significant.

Results

Patient characteristics. The clinical characteristics of the 32 R/M HNSCC patients are summarized in Table I. The median age at treatment was 70.5 years (range=54-88 years). Most patients were men (93.8%). Twenty patients had an ECOG PS score of 0 (62.5%), 10 patients had an ECOG PS score of 1 (31.3%), and two patients had an ECOG PS score of 2 (6.3%). The primary sites of disease were as follows: oropharynx (34.4%, including three p16-positive cases and eight p16-negative cases), hypopharynx (28.1%), oral cavity (12.5%), larynx (12.5%), sinonasal

Table I. *Patient characteristics*.

Characteristics	Number of patients	%
Median age (range, in years)	70.5 (54-88)	
Age		
≥70	19	59.4
<70	13	40.6
Sex		
Male	30	93.8
Female	2	6.3
Primary site		
Oropharynx	11	34.4
p16 positive	3	9.4
p16 negative	8	25.0
Hypopharynx	9	28.1
Oral cavity	4	12.5
Larynx	4	12.5
Sinonasal	3	9.4
External auditory canal	1	3.1
Eastern Cooperative Oncology Group Performance status		
0	20	62.5
1	10	31.3
2	2	6.3
Combined positive score		
≥20	13	40.6
≥1, <20	11	34.4
<1	2	6.3
Unknown	6	18.8
Presence of locoregional disease		
Yes	13	40.6
No	19	59.4
Presence of distant metastasis		
Yes	16	50.0
No	16	50.0
Initial treatment		
Surgery	13	40.6
Radiation±Chemotherapy	6	18.8
Previously untreated	13	40.6

Table II. *Treatment characteristics*.

Characteristics	Number of patients	
Regimen		
Pembrolizumab only	16	50.0
Pembrolizumab+Chemotherapy	16	50.0
Reason for discontinuing treatment		
Disease progression	11	34.4
Adverse event	11	34.4
Treatment ongoing	10	31.3
Best overall response		
Complete response	5	15.6
Partial response	13	40.6
Stable disease	10	31.3
Progressive disease	4	12.5
Immune-related adverse event		
None	16	50.0
Grade 1	6	18.8
Grade 2	6	18.8
Grade 3	4	12.5

(9.4%), and external auditory canal (3.1%). Thirteen patients had a PD-L1 CPS of 20, 11 patients had a PD-L1 CPS of 1 and above, less than 20, two patients had a CPS of less than 1, and six patients had unknown CPS status in this data set. Thirteen patients had disease recurrence in the locoregional area, whereas 16 had distant metastases. Thirteen patients underwent surgery for the primary tumor, six patients underwent concurrent chemoradiotherapy or radiotherapy as an initial treatment, and 13 patients had unresectable disease.

Treatment characteristics. Treatment characteristics are shown in Table II. Sixteen patients received pembrolizumab alone, whereas the others received pembrolizumab with chemotherapy. A median of 2.5 (range=1-6) cycles of 5-fluorouracil and cisplatin or carboplatin were administered. Twelve patients received carboplatin-based chemotherapy; therefore, carboplatin was the preferred platinum-based therapy used in this study. After cycles of chemotherapy, patients with stable disease received pembrolizumab monotherapy until disease progression, unacceptable toxicity, or patient decision was made. The pembrolizumab regimen was discontinued in 11 and 11 patients owing to disease progression and the occurrence of adverse events, respectively. In contrast, the pembrolizumab regimen was continued beyond progression in 2 patients in this study. The median follow-up duration from the start date of treatment for all patients was 9.8 months (range=1.6-25.1 months) in this study.

Treatment outcomes. The 1-year OS and PFS rates in the present study were 64.5% (95% CI=38.9-81.6) and 54.9% (95% CI=33.9-71.8), respectively (Figure 1A and Figure 1B), which were comparable to the results of the previous Keynote-048 study. Five patients (15.6%) had a complete response, and 13 patients (40.6%) had a partial response, with an ORR of 56.2%. Ten patients (31.3%) showed stable disease as the best response, with a disease control rate of 87.5%. Lastly, four patients (12.5%) had disease progression as the best response in this study. The median time to best response for 28 responders (including those with CR, PR, and SD) was 1.8 months (range=1.1-13.1 months). In this dataset, 10 patients remained on treatment with the pembrolizumab regimen, including five patients with PR and one patient with CR (Figure 2). Univariate analysis of the correlation between clinical/treatment characteristics and survival revealed that patients with ECOG PS 1 and 2 had poorer OS than those with ECOG PS 0 (Table III, hazard

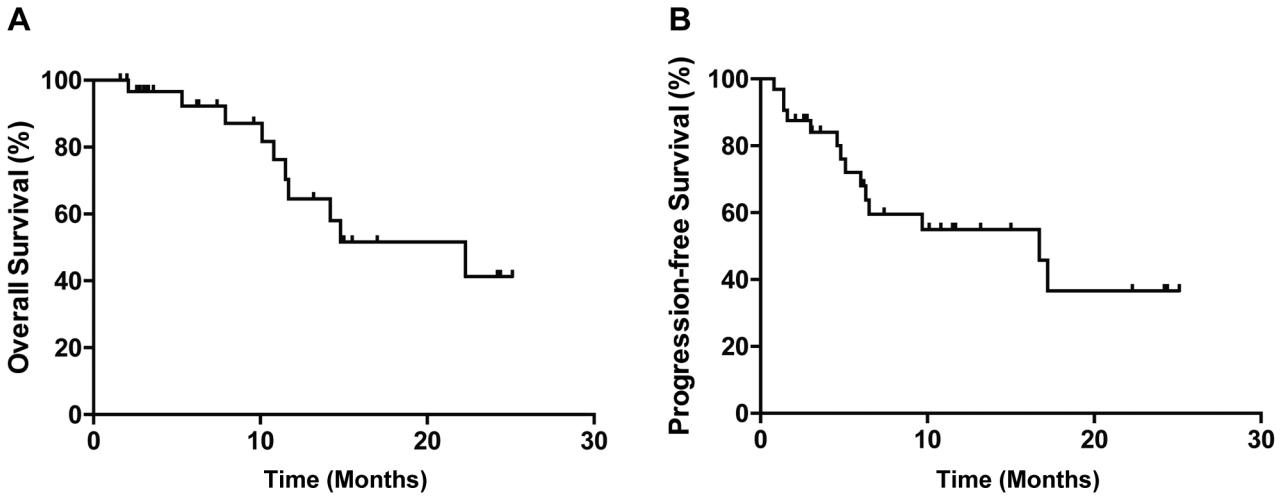

Figure 1. *(A) Kaplan–Meier curve for overall survival (OS). (B) Kaplan–Meier curve for progression-free survival (PFS).*

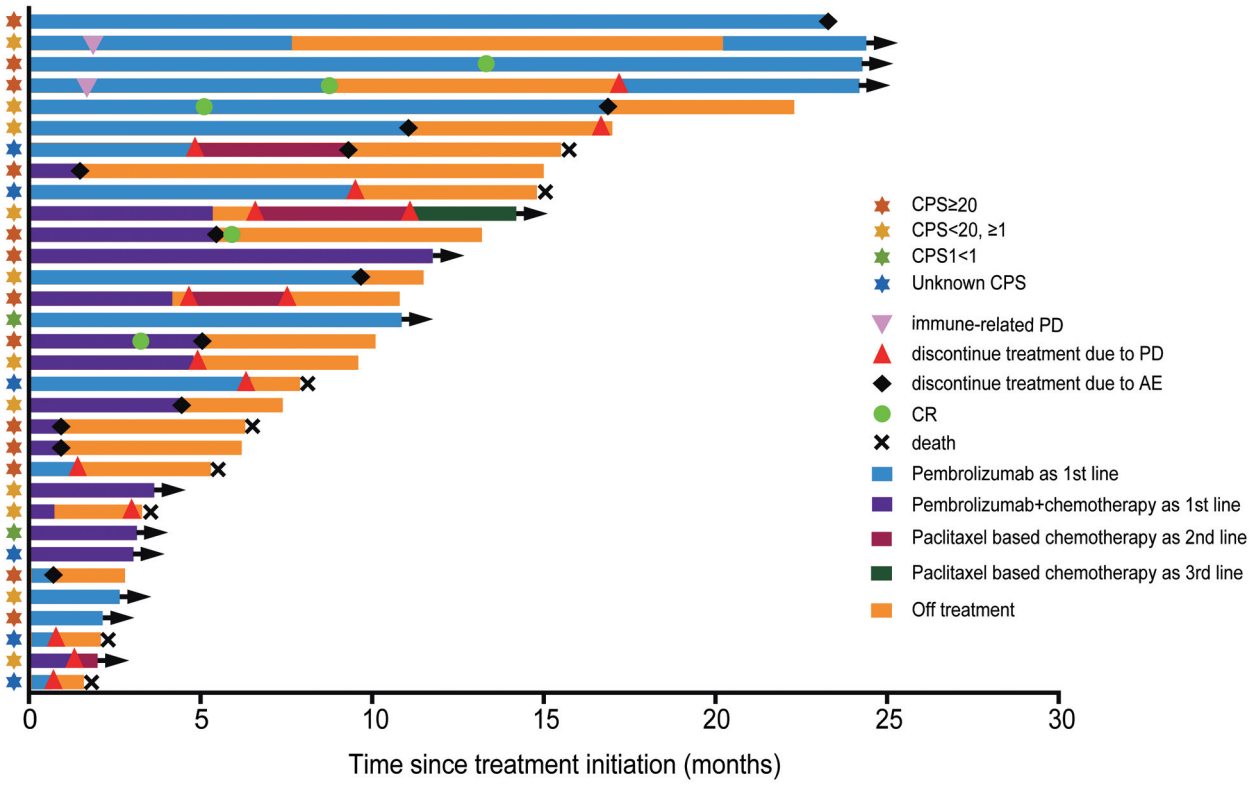

Figure 2. *Swimmer plots showing treatment exposure and response duration. CPS: Combined positive score; PD: progressive disease; AE: adverse event; CR: complete response.*

ratio for death, 9.00; 95% CI=1.42-57.1; p=0.030). Patients with PD or SD also had poorer OS than those with CR or PR as the best overall response (Table III; hazard ratio for death, not available; 95% CI=not available; p=0.0003).

Kaplan–Meier analysis revealed that OS was significantly longer in patients with PR or CR than in those with PD or SD as the best overall response (hazard ratio for death, 0.04; 95% CI=0.01-0.20; p=0.0007, Figure 3A). OS was also significantly

Table III. *Univariate analysis of overall survival.*

	N	Odd ratio	95% CI	*p*-Value
Age				
<70	13	1	reference	
≥70	19	2.538	0.424-15.21	0.420
Sex				
Female	2	1	reference	
Male	30	NA	NA	1.000
Performance status				
ECOG 0	20	1	reference	
ECOG 1-2	12	9.000	1.418-57.11	0.030
Combined positive score				
<20 or unknown	19	1	reference	
≥20	13	0.394	0.066-2.361	0.420
Locoregional recurrence				
No	19	1	reference	
Yes	13	0.840	0.162-4.354	1.000
Initial treatment				
Ope or (Chemo-) radiotherapy	19	1	reference	
Previously untreated	13	0.840	0.162-4.354	1.000
Regimen				
Pembrolizumab only	16	1	reference	
Pembrolizumab+Chemo	16	0.238	0.040-1.432	0.220
Best overall response				
SD or PD	14	1	reference	
CR or PR	18	NA	NA	0.0003
Immune-related adverse event				
No	15	1	reference	
Yes	17	0.200	0.033-1.211	0.106

ECOG, Eastern Cooperative Oncology Group; SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response.

Table IV. *Immune-related adverse events.*

	Onset period after administration
Grade 3	
Adrenal insufficiency	4 months
Skin rash	5 months
Skin rash	3 weeks
Myositis	3 weeks
Grade 2	
Hypothyroidism	6 weeks
Cheilitis	1 week
Bronchospasm (Bronchial asthma)	8 months
Fatigue	8 weeks
Pneumonitis (Interstitial pneumonia)	11 months
Hypothyroidism	12 months
Grade 1	
Pruritus	9 weeks
Pruritus	4 weeks
Pruritus	3 weeks
Adrenal insufficiency	7 months
Fatigue	3 weeks
Fatigue, Hypothyroidism	3 weeks

longer in patients with an ECOG PS of 0 than in those with an ECOG PS of 1 or 2 (hazard ratio for death, 0.21; 95% CI=0.05-0.87; p=0.032, Figure 3B). Thus, these results suggested that ECOG PS and best overall response for treatment could be associated with the survival of patients with R/M SCCHN treated with the pembrolizumab regimen as first-line therapy.

The immune-related adverse events (irAEs) in the present study are summarized in Table IV. IrAEs occurred in 16 of the 32 patients (50.0%) during treatment. A wide variety of irAEs were observed; grade 3 adverse events of any cause occurred in four patients, while there were six patients with grade 2 adverse events and six patients with grade 1 adverse events in this study. The onset period of adverse events after pembrolizumab administration also varied widely, as shown in Table IV (range=1 week-12 months). Thus, the pembrolizumab regimen demonstrated a favorable safety profile, as described previously.

Discussion

We herein presented the results of a single-center retrospective cohort study to determine real-world treatment outcomes of the pembrolizumab regimen as a first-line therapy for Japanese patients with R/M SCCHN. We observed that the pembrolizumab regimen showed a high response rate with an ORR of 61.9% and a favorable survival benefit with a 1-year OS of 64.5% and 1-year PFS of 54.9%, which were comparable to those in the previous KEYNOTE-048 study (10). While half the patients presented with varied irAEs, there were no irAEs greater than grade 4. Thus, the safety profile of the pembrolizumab regimen was comparable to that reported in the KEYNOTE-048 study. Furthermore, we observed that patients with R/M SCCHN with an ECOG PS of 0 and PR or CR as best overall response showed good survival in this study, suggesting that these factors might contribute to a better survival of patients with R/M SCCHN receiving the pembrolizumab regimen as the first-line treatment. In addition, the current study addresses the data gap between clinical trials and real-world settings, as this study included R/M SCC patients with rare primary lesions in the nasal sinuses and external auditory canal, who were excluded from the previous KEYNOTE-048 study. In this study, the response to treatment in these diseases was comparable to that in the oropharynx, hypopharynx, oral cavity, and larynx.

Despite the small population size and short observation period of the study, we found that the pembrolizumab regimen showed a high response rate with an ORR of 61.9% and favorable survival benefit with a 1-year OS of 64.5% and 1-year PFS of 54.9%, whereas the KEYNOTE-048 study in the overall population had an ORR of 17% and a 1-year OS of 49% for pembrolizumab alone and an ORR of 36%

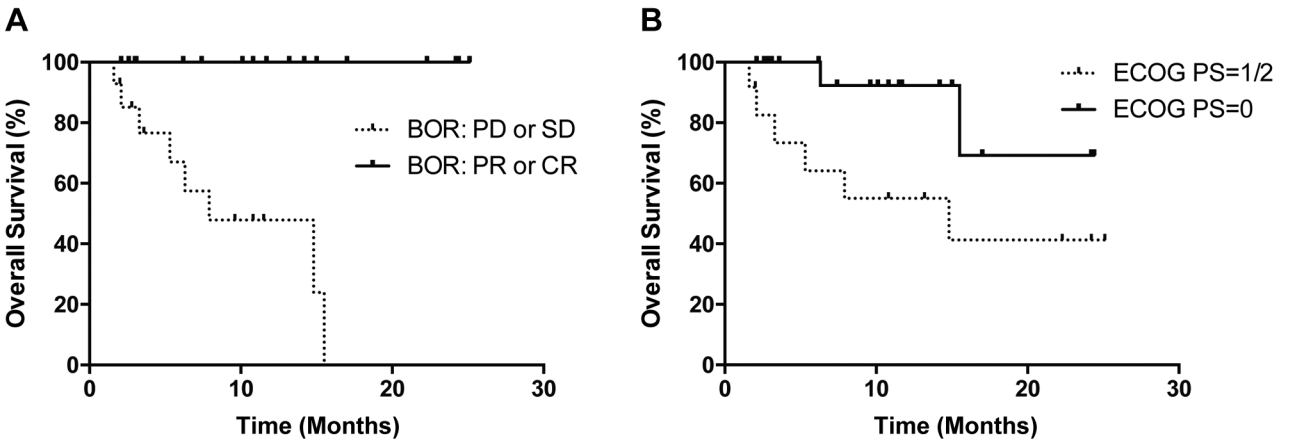

Figure 3. *(A) Kaplan–Meier curve for OS according to the best overall response (BOR). (B) Kaplan–Meier curve for OS according to an Eastern Cooperative Oncology Group performance status (ECOG PS).*

and a 1-year OS of 53% for pembrolizumab plus chemotherapy (10). In particular, the present study showed a high 1-year PFS and OS rate, suggesting that the pembrolizumab regimen itself may have been highly effective for the treatment of patients with R/M SCCHN. The large proportion of patients with CPS ≥20 may have contributed to this favorable result, as both pembrolizumab and pembrolizumab plus chemotherapy groups showed the highest treatment response with CPS≥20 in the KEYNOTE-048 study (10). The large proportion of untreated patients, high occurrence of irAEs, and the Japanese population might also have affected our results. To date, the fact that only 4 patients received second-line therapy in this study may also suggest that the pembrolizumab regimen was highly effective as a first-line therapy. In fact, patients who received first-line treatment for a prolonged period seemed to have a longer survival in this study. As several reports have demonstrated that administration of systemic therapy after progression on ICI was highly effective in patients with R/M SCCHN (12, 13), a similar phenomenon may be observed in future longer observation periods. In contrast, the difference in treatment outcomes between pembrolizumab alone and pembrolizumab plus chemotherapy was unclear in this study. However, this is a single-center retrospective study involving a small number of patients with multiple biases, suggesting that several covariates such as tumor volume of recurrent disease, reported to be associated with treatment outcomes previously (14, 15), may have affected the results.

In this study, we observed that R/M SCCHN patients with an ECOG PS of 0 showed higher treatment efficacy of the pembrolizumab regimen than those with an ECOG PS of 1 or 2, which is consistent with a previous report demonstrating the treatment outcomes of nivolumab in patients with R/M head and neck cancer in Japanese real-world clinical practice (16). It is generally believed that ICIs are less effective in patients with poor ECOG PS, since ECOG PS could be related to immunocompetence in cancer patients, as previously reported that the T-lymphocyte subpopulation (CD8+/CD4+ T cells) could reflect the ECOG PS in patients with gastric cancer (17). In addition, as several studies have reported that palliative chemotherapy generally does not prolong survival in patients with a poor ECOG PS (18, 19), R/M SCCHN patients with poor PS are unlikely to be eligible for chemotherapy. Thus, pembrolizumab regimens are likely to be unsuitable as first-line treatment for R/M SCCHN patients with poor PS. In addition, patients with R/M SCCHN with PR or CR as best overall response showed good survival in this study, consistent with a meta-analysis reporting that objective responders had significantly better survival than non-responders across tumor types (20). In fact, patients with PR or CR as best overall response might also be considered cases in which the therapeutic efficacy of the pembrolizumab regimen was retained for a long duration, resulting in favorable survival in the current study.

However, this study has several limitations. First, it had a retrospective design as a single-center cohort study with a small number of patients and a short follow-up period. The heterogeneity of patient backgrounds, including the primary site of disease, site of RM disease, ECOG PS, approach for initial treatment, treatment regimen, and comorbidity, may have also affected the results. In addition, as there were six cases with unknown CPS status, the impact of CPS on patient survival and disease progression has not been accurately analyzed, while the significance of PD-L1 expression as a prognostic biomarker for patients with R/M SCCHN treated with ICI has been reported previously (21). Further multi-institutional studies with longer observational periods and larger patient populations are warranted to

evaluate the real-world treatment outcomes of the pembrolizumab regimen as first-line therapy for patients with R/M SCCHN in the future.

In conclusion, this single-center retrospective cohort study in a real-world clinical setting showed favorable treatment efficacy of the pembrolizumab regimen as the first-line treatment for Japanese patients with R/M SCCHN, accompanied by a safety profile comparable to that of the previous KEYNOTE-048 study. In our dataset, patients with a good PS and response were associated with favorable survival. Further evaluation by a multi-institutional study is warranted to determine the real-world treatment outcomes of the pembrolizumab regimen as first-line therapy for patients with R/M SCCHN.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Conceptualization, D.S. and N.O.; Methodology, D.S.; Validation, H.T. and N.O.; Formal Analysis, D.S.; Investigation, D.S., M.T., H.T., T.H., G.N., and Y.I.; Resources, D.S., M.T., H.T., T.H., G.N., and Y.I.; Data Curation, H.T.; Writing – Original Draft Preparation, D.S.; Writing – Review and Editing, N.O.; Visualization, D.S.; Supervision, N.O.

Acknowledgements

The Authors thank Yasuhiro Arai, MD, Yosuke Kitani, MD, Takashi Wada, MD, Yohei Hiiragi, MD, and Ayana Odaira, MD, who contributed to the study.

References

1 Argiris A, Karamouzis MV, Raben D and Ferris RL: Head and neck cancer. Lancet *371(9625)*: 1695-1709, 2008. PMID: 18486742. DOI: 10.1016/S0140-6736(08)60728-X

2 Specenier PM and Vermorken JB: Recurrent head and neck cancer: current treatment and future prospects. Expert Rev Anticancer Ther *8(3)*: 375-391, 2008. PMID: 18366286. DOI: 10.1586/14737140.8.3.375

3 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer HR, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N and Hitt R: Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med *359(11)*: 1116-1127, 2008. PMID: 18784101. DOI: 10.1056/NEJMoa0802656

4 Ribas A: Tumor immunotherapy directed at PD-1. N Engl J Med *366(26)*: 2517-2519, 2012. PMID: 22658126. DOI: 10.1056/NEJMe1205943

5 Pardoll DM: The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer *12(4)*: 252-264, 2012. PMID: 22437870. DOI: 10.1038/nrc3239

6 Ferris RL: Immunology and immunotherapy of head and neck cancer. J Clin Oncol *33(29)*: 3293-3304, 2015. PMID: 26351330. DOI: 10.1200/JCO.2015.61.1509

7 Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS, Hollmann TJ, Bruggeman C, Kannan K, Li Y, Elipenahli C, Liu C, Harbison CT, Wang L, Ribas A, Wolchok JD and Chan TA: Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med *371(23)*: 2189-2199, 2014. PMID: 25409260. DOI: 10.1056/NEJMoa1406498

8 Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN and Chan TA: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science *348(6230)*: 124-128, 2015. PMID: 25765070. DOI: 10.1126/science.aaa1348

9 Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW and Gillison ML: Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med *375(19)*: 1856-1867, 2016. PMID: 27718784. DOI: 10.1056/NEJMoa1602252

10 Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, González Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F, Rischin D and KEYNOTE-048 Investigators: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet *394(10212)*: 1915-1928, 2019. PMID: 31679945. DOI: 10.1016/S0140-6736(19)32591-7

11 Yen CJ, Kiyota N, Hanai N, Takahashi S, Yokota T, Iwae S, Shimizu Y, Hong RL, Goto M, Kang JH, Li WSK, Ferris RL, Gillison M, Endo T, Jayaprakash V and Tahara M: Two-year follow-up of a randomized phase III clinical trial of nivolumab vs. the investigator's choice of therapy in the Asian population for recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141). Head Neck *42(10)*: 2852-2862, 2020. PMID: 32583557. DOI: 10.1002/hed.26331

12 Saleh K, Daste A, Martin N, Pons-Tostivint E, Auperin A, Herrera-Gomez RG, Baste-Rotllan N, Bidault F, Guigay J, Le Tourneau C, Saada-Bouzid E and Even C: Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Eur J Cancer *121*: 123-129, 2019. PMID: 31574417. DOI: 10.1016/j.ejca.2019.08.026

13 Pestana RC, Becnel M, Rubin ML, Torman DK, Crespo J, Phan J, Hanna E, Bell D, Glisson BS, Johnson JM, Lee JJ and Ferrarotto R: Response rates and survival to systemic therapy after immune checkpoint inhibitor failure in recurrent/metastatic head and neck squamous cell carcinoma. Oral Oncol *101*: 104523, 2020. PMID: 31864957. DOI: 10.1016/j.oraloncology.2019.104523

14 Inoue H, Yokota T, Hamauchi S, Onozawa Y, Kawakami T, Shirasu H, Notsu A, Yasui H and Onitsuka T: Pre-treatment tumor size impacts on response to nivolumab in head and neck squamous cell carcinoma. Auris Nasus Larynx *47(4)*: 650-657, 2020. PMID: 32035695. DOI: 10.1016/j.anl.2020.01.003

15 Suzuki C, Kiyota N, Imamura Y, Rikitake J, Sai S, Koyama T, Hyogo Y, Nagatani Y, Funakoshi Y, Toyoda M, Otsuki N, Nibu KI and Minami H: Effect of tumor burden and growth rate on treatment outcomes of nivolumab in head and neck cancer. Int J Clin Oncol *25(7)*: 1270-1277, 2020. PMID: 32277393. DOI: 10.1007/s10147-020-01669-y

16 Hanai N, Shimizu Y, Kariya S, Yasumatsu R, Yokota T, Fujii T, Tsukahara K, Yoshida M, Hanyu K, Ueda T, Hirakawa H, Takahashi S, Ono T, Sano D, Yamauchi M, Watanabe A, Omori K, Yamazaki T, Monden N, Kudo N, Arai M, Sakurai D, Asakage T, Doi I, Yamada T and Homma A: Effectiveness and safety of nivolumab in patients with head and neck cancer in Japanese real-world clinical practice: a multicenter retrospective clinical study. Int J Clin Oncol *26(3)*: 494-506, 2021. PMID: 33219460. DOI: 10.1007/s10147-020-01829-0

17 Wang L and Shen Y: Imbalance of circulating T-lymphocyte subpopulation in gastric cancer patients correlated with performance status. Clin Lab *59(3-4)*: 429-433, 2013. PMID: 23724636.

18 Wheatley-Price P, Ali M, Balchin K, Spencer J, Fitzgibbon E and Cripps C: The role of palliative chemotherapy in hospitalized patients. Curr Oncol *21(4)*: 187-192, 2014. PMID: 25089101. DOI: 10.3747/co.21.1989

19 Crosara Teixeira M, Marques DF, Ferrari AC, Alves MF, Alex AK, Sabbaga J, Hoff PM and Riechelmann RP: The effects of palliative chemotherapy in metastatic colorectal cancer patients with an ECOG performance status of 3 and 4. Clin Colorectal Cancer *14(1)*: 52-57, 2015. PMID: 25442812. DOI: 10.1016/j.clcc.2014.09.010

20 Ye J, Ji X, Dennis PA, Abdullah H and Mukhopadhyay P: Relationship between progression-free survival, objective response rate, and overall survival in clinical trials of PD-1/PD-L1 immune checkpoint blockade: a meta-analysis. Clin Pharmacol Ther *108(6)*: 1274-1288, 2020. PMID: 32564368. DOI: 10.1002/cpt.1956

21 Ito T, Okamoto I, Tokashiki K, Sato H, Okada T, Yamashita G, Nagao T, Hirai H, Saigusa N and Tsukahara K: PD-L1 expression and survival rates using TPS and CPS for nivolumab-treated head-and-neck cancer. Anticancer Res *42(3)*: 1547-1554, 2022. PMID: 35220251. DOI: 10.21873/anticanres.15628

Received May 31, 2022
Revised June 24, 2022
Accepted July 6, 2022