

Efficacy of Nivolumab and Pembrolizumab in Platinum-sensitive Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

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Abstract. *Background/Aim:* This study evaluated the efficacy of nivolumab and pembrolizumab in treating platinum-sensitive recurrent or metastatic head and neck squamous cell carcinomas (R/M-HNSCC). *Patients and Methods:* Platinum-sensitive patients with R/M-HNSCC were selected at Tokyo Medical University Hospital from May 1, 2017, to June 30, 2022. Patients with a history of treatment with nivolumab or pembrolizumab were included. Nivolumab was used in 21 cases and pembrolizumab in 15 cases. *Results:* The median overall survival (OS) was 16.9 months in the nivolumab group and 19.2 months in the pembrolizumab group and no significant differences were observed between the two groups. The median progression-free survival (PFS) was 4.8 months in the nivolumab group and 9.3 months in the pembrolizumab group. No significant differences were observed between the two groups. The objective response rates (ORR) were 38% and 47% in the nivolumab and pembrolizumab groups, respectively. *Conclusion:* Nivolumab as well as pembrolizumab were found to be effective in platinum-sensitive patients with R/M-HNSCC. Nivolumab can be considered a potential treatment option for platinum-sensitive R/M-HNSCC in the future.

The outcomes of recurrent or metastatic head and neck squamous cell carcinomas are poor. Previous studies have reported a median overall survival of approximately 6 months (1, 2). Within 1 year of diagnosis, 90% of patients die (3).

Currently, the National Comprehensive Cancer Network (NCCN) guidelines recommend two anti-PD-1 antibodies,

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nivolumab and pembrolizumab, as category 1 agents for recurrent metastatic squamous cell carcinoma (4).

In 2016, nivolumab clinical trials revealed that the international phase III Checkmate 141 trial prolonged overall survival (OS) in patients with platinum-resistant recurrent or metastatic head and neck squamous cell carcinomas (R/M-HNSCC) compared to standard therapy. The median OS was 7.5 months, median progression-free survival (PFS) was 2.0 months, and overall response rate (ORR) was 13.3% (5).

In ovarian cancer, the response rate to subsequent treatment increases with time after prior treatment with platinum-based drugs (6). For ovarian cancer, platinum resistance was defined as "recurrence or metastasis within 6 months" and the same criteria were introduced for R/M-HNSCC (7). In contrast, recurrence or metastasis more than 6 months after platinum-based chemotherapy or chemoradiation is considered platinum-sensitive.

In the international phase III KEYNOTE-048 trial, pembrolizumab was compared with cetuximab + platinum + 5-FU (standard treatment group) and pembrolizumab alone. The results showed the non-inferiority of the monotherapy for OS. In the pembrolizumab monotherapy group, the median OS was 11.6 months, median PFS was 2.3 months, and ORR was 16.6% (8). These results indicated that pembrolizumab is effective in treating platinum-sensitive R/M-HNSCC.

Similar to pembrolizumab, nivolumab is an anti-PD-1 antibody. Okamoto et al. reported the efficacy of nivolumab in platinum-sensitive R/M-HNSCC (9). However, no study has examined the efficacy of nivolumab and pembrolizumab in patients with platinum-sensitive R/M-HNSCC. Therefore, this retrospective study aimed to compare the efficacies of nivolumab and pembrolizumab in platinum-sensitive R/M-HNSCC.

Patients and Methods

Patients. Patients with R/M HNSCC who had prior platinum treatment at Tokyo Medical University Hospital (Tokyo, Japan) from May 1, 2017, to June 30, 2022, were selected for the study.

Patients who had received prior treatment with Nivolumab or Pembrolizumab were included in the study. Patients with recurrent or metastatic head and neck cancer with no prior treatment with platinum, those who received pembrolizumab in combination with chemotherapy, those who refused to participate in the study, and those considered inappropriate as study patients by the principal investigator were excluded.

This study was approved by the Ethics Committee of Tokyo Medical University (T2022-0116) and conducted in accordance with the Declaration of Helsinki.

Treatment and follow-up. Nivolumab was administered at 240 mg every 2 weeks for 1 h. Pembrolizumab was administered at a dose of 200 mg per session for 30 min. The dosing interval was 3 weeks. Target lesions were evaluated using computed tomography (CT) and magnetic resonance imaging (MRI) every 2-3 months. Treatment was continued until disease progression, unacceptable side effects occurrence, or until the attending physician determined that discontinuation was necessary for other reasons. Weight loss criteria were not applied.

Endpoint. The primary endpoint was overall survival (OS), and the secondary endpoints were the overall response rate (ORR) and progression-free survival (PFS). OS was defined as the period from the start of treatment to the date of death or last follow-up. PFS was defined as the time from treatment initiation to disease progression or death. ORR was evaluated using RECIST version 1.1 (10).

Statistical analysis. PFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. Survival was analyzed according to the Cox proportional hazards model, with $p < 0.05$ being statistically significant.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface in R (R Statistical Computing Foundation, Vienna, Austria) (11).

Results

Clinical characteristics. During the study period, there were 164 patients with recurrent metastatic head and neck carcinomas. A total of 117 platinum-resistant patients were excluded. Of the 47 platinum-sensitive cases, 11 non-SCC cases were excluded. Finally, 36 patients were diagnosed with platinum-sensitive R/M-HNSCC. Among these, 21 patients were treated with nivolumab and 15 with pembrolizumab (Figure 1).

The clinical characteristics of the patients are summarized in Table I. There were no significant differences in performance status, sex, or age between the treatment groups. Regarding the primary tumor site, there were more cases of hypopharyngeal carcinoma in the pembrolizumab group. All the patients in the nivolumab group had Stage IV disease, while the pembrolizumab group included patients who were not Stage IV. The tumor proportion score (TPS) ≥ 1 was observed in 71.4% of the nivolumab group (Table II). All patients in the pembrolizumab group had a combined positive score (CPS) > 1 (Table III).

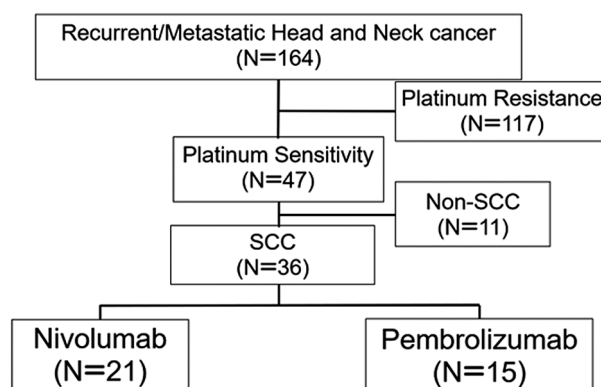


Figure 1. Study schema.

Efficacy. In the nivolumab group, the median length of follow-up for censored cases was 47.6 months (range=16.3-51.6 months). In the pembrolizumab group, the median length of follow-up for censored cases was 15.2 months (range=4.1-28.3 months).

The median OS was 16.9 months (range=3.1-51.6 months) [95% confidence interval (CI)=9.1-20.3 months] for the nivolumab group and 19.2 months (range=1.0-28.3 months) [95%CI=6.6 months to not calculable (N/C)] in the pembrolizumab group. No significant differences were observed ($p=0.561$) (Figure 2). The median PFS was 4.8 months (range=1.6-51.6 months) [95%CI= 2.8 months to (N/C)] in the nivolumab group and 9.3 months (range=1.0-28.3 months) (95%CI=2.2 months to N/C) in the pembrolizumab group. No significant differences were observed ($p=0.573$) (Figure 3). The ORR was 38% (one CR and seven PR) in the nivolumab group and 47% (four CR and three PR) in the pembrolizumab group (Table II).

Discussion

This study compared the efficacies of nivolumab and pembrolizumab in platinum-sensitive R/M-HNSCC. The median OS was 16.9 months in the nivolumab group and 19.2 months in the pembrolizumab group, with no significant differences. The median PFS was 4.8 months in the nivolumab group and 9.3 months in the pembrolizumab group, with no significant difference. ORRs were 38% and 47% in the nivolumab and pembrolizumab groups, respectively.

Prior studies have reported on the efficacy of nivolumab in platinum-sensitive R/M-HNSCC (9, 12). However, to our knowledge, no study has directly compared the efficacy of nivolumab and pembrolizumab in platinum-sensitive R/M-HNSCC, and this is the first such report in the world. In the KEYNOTE048 study, the OS of the single-agent pembrolizumab group in the CPS > 1 arm was 11.6 months

Table I. Patient characteristics.

Factor	Group	Treatment Nivolumab	Treatment Pembrolizumab	p-Value
n		21	15	
ECOG performance status (%)	0	17 (81.0)	11 (73.3)	0.694
	1	4 (19.0)	4 (26.7)	
Sex (%)	Female	1 (4.8)	1 (6.7)	1
	Male	20 (95.2)	14 (93.3)	
Primary site (%)	Hypopharynx	6 (28.6)	10 (66.7)	0.035
	Larynx	1 (4.8)	0 (0.0)	
	Nasopharynx	5 (23.8)	1 (6.7)	
	Oropharynx	5 (23.8)	2 (13.3)	
	Paranasal sinus	4 (19.0)	0 (0.0)	
	Unknown	0 (0.0)	2 (13.3)	
Reason for unresectable (%)	Locally advanced	3 (14.3)	2 (13.3)	0.179
	Metastatic	11 (52.4)	12 (80.0)	
	Recurrent	7 (33.3)	1 (6.7)	
UICC Stage (%)	Stage I/II/III	0 (0.0)	4 (26.7)	0.023
	Stage IV	21 (100.0)	11 (73.3)	
Age		61.14 (9.79)	67.13 (8.98)	0.07

ECOG: Eastern Cooperative Oncology Group; UICC: Union for International Cancer Control.

(8). In this study, the OS in the Nivolumab group was 16.9 months, indicating that nivolumab is also effective in treating platinum-sensitive R/MHNSCC.

No studies have compared the efficacies of nivolumab and pembrolizumab in recurrent or metastatic platinum-sensitive carcinomas. Previous studies have compared the efficacies of nivolumab and pembrolizumab for the treatment of advanced-stage small cell lung cancer (13). In that study, there were no significant differences in OS or PFS between the nivolumab and pembrolizumab groups, as observed in this study.

At our institution, we use the 28-8 antibody for PD-L1 evaluation in all patients prior to nivolumab treatment. TPS, the result of staining with the 28-8 antibody, is used to measure PD-L1 expression in tumor cells. In contrast, the CPS was evaluated before pembrolizumab treatment. CPS measures PD-L1 expression in tumor cells as well as PD-L1 expressed on macrophages and lymphocytes (14). The CPS and TPS could not be directly compared because the pembrolizumab group in this study had a CPS >1, whereas the nivolumab group had a measured TPS.

The study also included patients with platinum-sensitive R/M-HNSCC treated with Nivolumab and Pembrolizumab from May 2017 to June 2022. Pembrolizumab was approved in Japan in December 2019 for the treatment of recurrent metastatic head and neck carcinomas. Therefore, the observation period in the pembrolizumab group was shorter than that in the nivolumab group, and a longer observation period is desirable.

The present study was conducted at a single institution; therefore, the number of cases was limited. It would be desirable to validate the results in a multi-case, multicenter

Table II. PD-L1 expression [tumor proportion score (TPS)].

Nivolumab	Number of patients (N)	Percentage (%)
PD-L1 expression (TPS)		
<1%	5	23.8
≥1%	15	71.4
≥20%	11	52.3
≥40%	7	33.3
Unknown	1	4.8

PD-L1: Programmed cell death 1-ligand 1; TPS: tumor proportion score.

Table III. PD-L1 expression [combined positive score (CPS)].

Pembrolizumab	Number of patients (N)	Percentage (%)
PD-L1 expression (CPS)		
<1	0	0
1≤CPS<20	4	26.7
≥20	11	73.3

PD-L1: Programmed cell death 1-ligand 1; CPS: combined positive score.

study in the future. In this study, nivolumab was also found to be effective against platinum-sensitive R/M-HNSCC, without significant differences from pembrolizumab. The results of this study suggest the possibility of nivolumab treatment for platinum-sensitive R/MHNSCC.

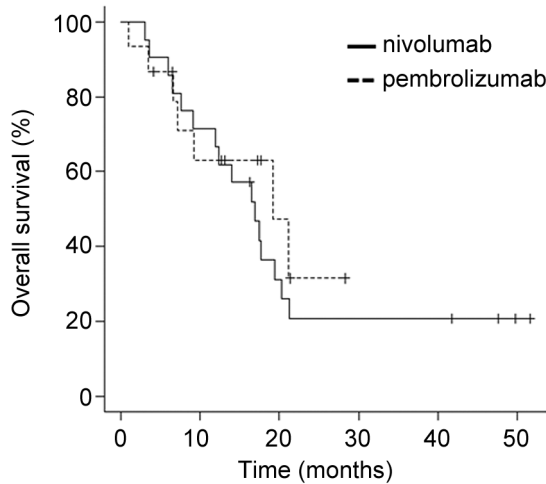


Figure 2. Overall-survival (OS) for the whole patient cohort. Median OS is 16.9 months (range=3.1-51.6 months) [95%CI=9.1 months to 20.3 months] in the nivolumab group, and the median OS is 19.2 months (range=1.0-28.3 months) [95% confidence interval (95%CI)=−6.6 months to not calculable (N/C)] in the pembrolizumab group.

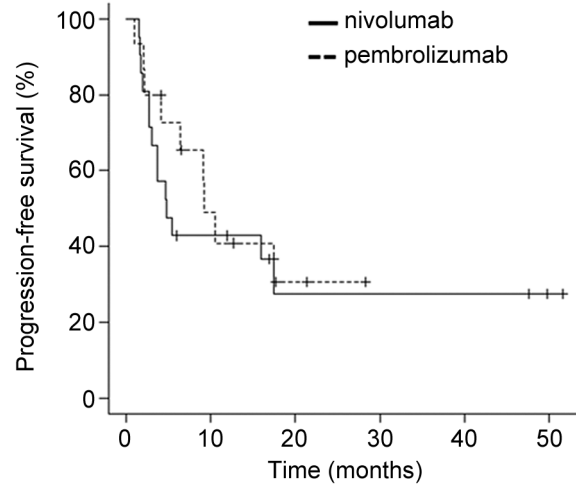


Figure 3. Progression-free survival (PFS) for the whole patient cohort. Median PFS is 4.8 months (range=1.6-51.6 months) [95% confidence interval (95%CI)=2.8 months to not calculable (N/C)] in the nivolumab group. Median OS is 9.3 months (range=1.0-28.3 months) (95%CI=2.2 months to N/C) in the pembrolizumab group.

Conflicts of Interest

The Authors report no conflicts of interest in relation to this study.

Authors' Contributions

Isaku Okamoto, Gai Yamashita and Kiyooki Tsukahara designed the study. Gai Yamashita wrote the main text and prepared the figures. Gai Yamashita, Isaku Okamoto, Tatsuya Ito, Kunihiko Tokashiki, Takuro Okada, and Kiyooki Tsukahara were involved in data collection. Isaku Okamoto and Gai Yamashita performed analyses. All Authors discussed the results of the study, made comments on the article, and approved the final version to be published.

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