Efficacy and safety of molecularly targeted agents and immune checkpoint inhibitors for unresectable or recurrent/metastatic oral cancer in Japan

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Abstract *Background/purpose:* For unresectable recurrent/metastatic head and neck cancer, pembrolizumab alone or pembrolizumab combined with cisplatin and 5-fluorouracil is the first-line therapy, depending on the PD-L1 combined positive score (CPS). However, this is based on clinical studies of head and neck cancer, and few similar studies have been

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conducted on oral cancer alone. This study aimed to investigate the current status of pharmacotherapy for unresectable, recurrent, or metastatic oral cancer.

Materials and methods: Patients with unresectable or recurrent/metastatic oral cancer who received cetuximab, nivolumab, or pembrolizumab as first-line treatment were reviewed. Overall survival (OS), progression-free survival (PFS), PFS 2 (PFS2), overall response rate (ORR), disease control rate (DCR), and immune-related adverse events were obtained from medical records.

Results: A total of 155 patients were enrolled from six hospitals. The ORR in the nivolumab, pembrolizumab, and cetuximab groups was 17.2 %, 4.2 %, and 21.6 %, respectively, and the DCR was 37.9 %, 41.7 %, and 58.8 %, respectively. Median OS in nivolumab, pembrolizumab, and cetuximab groups was 10.3, 9.5, and 11.1 months, respectively. No significant differences were observed in survival among the three groups. The small number of cases and the retrospective nature of the study precluded the determination of the more effective first-line treatment among the three drugs.

Conclusion: The current statuses of nivolumab, pembrolizumab, and cetuximab in unresectable recurrent metastatic oral cancer was reported.

Introduction

Only a limited number of drugs have shown efficacy against head and neck cancer. Recently, the effectiveness of molecularly targeted therapy with cetuximab and immune checkpoint inhibitors (ICIs) like nivolumab and pembrolizumab in treating head and neck cancer has been reported.[1,2] Therefore, drug therapy is currently the standard option for unresectable or recurrent metastases of head and neck cancer.[1—3] ICIs are reported to be more effective when administered after chemotherapy. Some studies have also reported that the effectiveness of ICIs is enhanced when administered after chemotherapy.[4—6]

In contrast, among head and neck cancers, pharyngeal and oral cancers differ greatly in their sensitivities to radiotherapy and drug therapy. Oral cancer accounts for 1/2 to 2/3 of head and neck cancer and is very frequent in some countries, such as South or Southeast Asian countries, because of its relationship to oral habits. In Japan, however, the frequency of oral cancer is as low as about 1 % of all cancers, and limited research has explored the effectiveness of molecularly targeted drugs and ICIs specifically for oral cancer. Therefore, the Joint Research Committee of the Japanese Society of Oral Tumors conducted a multicenter retrospective study on the efficacy and safety of drug therapy in patients with unresectable or recurrent metastatic oral cancer.

Materials and methods

Patients

Patients with unresectable or recurrent/metastatic oral cancer who received cetuximab, nivolumab, or pembrolizumab as a first-line treatment between January 1, 2013, and June 30, 2021, were included. Malignancies other than squamous cell carcinoma were excluded.

Regimens of immune checkpoint inhibitors/target therapy/chemotherapy

Pembrolizumab alone group received pembrolizumab (200 mg) once every 3 weeks until disease progression or intolerable toxicity. Pembrolizumab combined with chemotherapy group received pembrolizumab (200 mg), cisplatin (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2 per day for 4 consecutive days) every 3 weeks for six cycles or until intolerable toxicity. Nivolumab group received 3 mg per kilogram body weight every 2 weeks until disease progression or intolerable toxicity. Cetuximab with chemotherapy group received cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 per week), cisplatin (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2 per day for 4 consecutive days) every 3 weeks for six cycles or until intolerable toxicity. Cetuximab was then administrated until disease progression or intolerable toxicity (Fig. 1).

Variable

Age, sex, performance status,[7] primary site, TMN classification,[8] previous treatment, histological findings of differentiation, vascular invasion, lymphatic invasion, mode of invasion, YK classification[9] at first treatment, next treatment, number of treatment lines, overall survival (OS), progression-free survival (PFS), PFS 2 (PFS2), overall response rate (ORR), disease control rate (DCR), and immune-related adverse events (irAEs) were extracted from the medical records.

Adverse events

Adverse events were determined by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAEs) version 4.03[10] and ORR was determined by the Response Evaluation Criteria in Solid Tumors (RECIST).[11]

	1	2	3	4	5	6	7	8	9	
Pembrolizumab	200mg			200mg			200mg			···· Until PD or intolerable toxicity
Pembrolizumab Cisplatin* 5-FU**	200 mg ↓ ↓↓↓↓			200 mg ↓ ↓↓↓↓			200 mg ↓ ↓↓↓↓			···· Up to 6 cycles
Nivolumab	3mg/kg		3mg/kg		3mg/kg		3mg/kg		3mg/kg	···· Until PD or intolerable toxicity
Cetuximab Cisplatin* 5-FU**	400 mg 250 mg 250 mg ↓ ↓↓↓↓			250 mg 250 mg 250 mg ↓ ↓↓↓↓			250 mg 250 mg 250 mg ↓ ↓↓↓↓			···· Up to 6 cycles

*Cisplatin: 100mg/m^2 day 1
**5-FU: 1000mg/m^2 day 1-4

Fig. 1 Regimens of immune checkpoint inhibitors/target therapy/chemotherapy.

Statistical analysis

The Kaplan-Meier method was used to estimate survival curves. The log-rank test was used to compare the survival curves between the two groups. Factors related to overall response rate and disease control rate were analyzed by Fisher's exact test or one way ANOVA. Multivariate analysis was not performed due to small number of cases. Two-sided $P < 0.05$ was considered statistically significant.

Ethics

This study conformed to the ethical guidelines of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan. Ethical approval was obtained from the Institutional Review Board (IRB) of Nagasaki University Hospital (#21081610). The research plan was published on the homepages of the participating hospitals' websites, with an opt-out option according to IRB instructions.

Results

Patient characteristics

A total of 155 patients were enrolled from six hospitals. Patient backgrounds are shown in Table 1. The first-line treatments were nivolumab in 29 patients (nivolumab group), pembrolizumab in 24 patients (pembrolizumab group, pembrolizumab alone in 17 patients, pembrolizumab + 5-fluorouracil, cisplatin (FP) in seven patients), and cetuximab in 102 patients (cetuximab group, cetuximab alone in 10 patients, cetuximab + FP in 48 patients, cetuximab + paclitaxel (PTX) in 34 patients, and cetuximab + other chemotherapy in 10 patients).

Response and survival

The ORRs in the nivolumab, pembrolizumab, and cetuximab groups were 5/29 (17.2 %), 1/24 (4.2 %), and 22/102 (21.6 %), respectively, and the DCR were 11/29 (37.9 %), 10/24 (41.7 %), and 60/102 (58.8 %), respectively. No significant differences were observed in responses among the three groups.

Second-line treatment was administered to 18 of 29 (62.1 %) patients in the nivolumab group, nine of 24 (37.5 %) in the pembrolizumab group, and 51 of 102 (50.0 %) in the cetuximab group (Table 2).

Median OS in the nivolumab, pembrolizumab, and cetuximab groups was 10.3, 9.5, and 11.1 months, respectively. The median PFS in the nivolumab, pembrolizumab, and cetuximab groups was 2.2, 3.1, and 3.5 months, respectively. Median PFS2 in nivolumab, pembrolizumab, and cetuximab groups was 5.6, 4.5, and 5.9 months, respectively (Fig. 2). No significant differences were observed in survival among the three groups.

Nivolumab was used in 29 patients as the first-line treatment, whereas 75 patients received nivolumab, including the second- and third-line treatments. The ORR and DCR for all 75 patients were 10/75 (13.3 %) and 22/75 (29.3 %), respectively. The PFS for all 75 patients was 3.4 months (Fig. 3).

Pembrolizumab was administered to 38 patients (pembrolizumab alone in eight patients and pembrolizumab + FP in 30 patients), including second- and third-line treatments. The ORR and DCR of the 38 cases were 3/38 (7.9 %) and 16/38 (42.1 %), respectively. The PFS for all 38 patients was 3.4 months (Fig. 3).

Factors related to the response rate

Factors affecting overall response rate and disease control rate were examined. In the nivolumab group, patients with moderately or poorly differentiated carcinoma had a higher disease control rate than those with well differentiated type, and in the cetuximab group, patients with no prior surgery or those with distant metastasis alone had a higher disease control rate, but no factors significantly related to overall control rate. There were no significant factors in the pembrolizumab group (Table 3). However, the clinical significance of these findings is unclear because of the small number of patients and lack of multivariate analysis, and more studies with larger numbers of patients are needed.

Table 1 Clinicopathological data of the cancer patients.

Variable		Total	1st Line		
			Cetuximab group	Nivolumab group	Pembrolizumab group
Age: minimum - maximum (median)		15 - 90 (66)	15 - 88 (65)	33 - 77 (64)	47 - 90 (70)
Gender	Male	86	62	16	8
	Female	69	40	13	16
PS (time of diagnosis as unresectable)	0	50	28	15	7
	1	96	70	11	15
	2	8	3	3	2
	3	1	1	0	0
Primary Site	Tongue	63	39	17	7
	Gingiva	58	28	7	13
	Others	33	25	5	3
T stage (first visit)	T1-2	60	37	13	10
	T3-4	95	65	16	14
N Stage (first visit)	N0	52	34	9	9
	N1-3	103	68	20	15
History of surgery	—	26	19	3	4
	+	129	83	26	20
History of radiation therapy	—	44	32	2	10
	+	111	70	27	14
History of chemotherapy	—	71	53	4	14
	+	84	49	25	10
Histologic features					
Differentiation	Well	69	46	9	14
	Moderately or poorly	76	47	19	10
	Unknown	10	9	1	0
Mode of invasion	YK2-3	65	42	13	10
	YK4	64	41	12	11
	Unknown	26	19	4	3
Lymphatic invasion	—	98	70	13	15
	+	36	20	12	4
	Unknown	21	12	4	5
Vascular invasion	—	68	50	12	6
	+	66	40	13	13
	Unknown	21	12	4	5
Perineural invasion	—	78	56	13	9
	+	56	34	12	10
	Unknown	21	12	4	5
Unresectable site	Primary or cervical recurrence	85	58	12	15
	Distant metastasis	54	33	14	7
	Both	16	11	3	2
Total number of treatment lines	1	73	10	14	49
	2	44	9	7	28
	3	18	5	1	12
	4	16	4	2	10
	5	4	1	0	3
Cisplatin resistance	—			5	
	+			24	
CPS	−1				3
	1−20				3
	20-				17
	Unknown				1
Chemotherapy					
Pembrolizumab + FP					7
Pembrolizumab only					17
Cetuximab only				10	

(continued on next page)

Table 1 (*continued*)

Variable	Total	1st Line		
		Cetuximab group	Nivolumab group	Pembrolizumab group
Cetuximab + FP		48		
Cetuximab + paclitaxel		34		
Cetuximab + others		10		
Nivolumab			29	
Total	155	102	29	24

Abbreviation, PS: performance status, FP: 5-fluorouracil + cisplatin, CPS: combined positive score.

Table 2 Second line treatments for the cancer patients.

1st line	2nd line	Number of patients
Nivolumab (n = 29)	Cetuximab	2
	Cetuximab + Paclitaxel	10
	Paclitaxel	1
	Others	5
	None	11
Pembrolizumab + FP (n = 7)	Cetuximab + Paclitaxel	3
	Paclitaxel	2
	None	2
Pembrolizumab only (n = 17)	Cetuximab + Paclitaxel	4
	None	13
Cetuximab (n = 10)	Nivolumab	1
	Pembrolizumab	1
	Others	2
	None	6
Cetuximab + Cisplatin (n = 10)	Cetuximab + Paclitaxel	5
	Nivolumab	2
	None	3
Cetuximab + FP (n = 48)	Cetuximab + Paclitaxel	5
	Nivolumab	13
	Paclitaxel	3
	others	6
	None	21
Cetuximab + Paclitaxel (n = 30)	Nivolumab	5
	Pembrolizumab	1
	Paclitaxel	3
	Others	2
	None	19
Cetuximab + Paclitaxel + Carboplatin (n = 4)	Nivolumab	2
	Others	2

Abbreviation FP: 5-fluorouracil + cisplatin.

Adverse events

Adverse events are summarized in Table 4. Among the patients treated with nivolumab, six had hypothyroidism; three had enteritis; two had interstitial pneumonia, dry mouth, pruritus, and fatigue; and one had hemorrhage, hypophysitis, leukopenia, anemia, hepatitis, anorexia, and dry skin. No adverse events of grade 3 or higher were observed. Among patients treated with pembrolizumab, interstitial pneumonia was seen in two patients, and cerebral infarction, diarrhea, drug eruption, arthritis, and mucositis were seen in one patient. Diarrhea was defined as a grade 3 adverse event.

Discussion

The CheckMate 141 and KEYNOTE-048 studies demonstrated the efficacy of nivolumab and pembrolizumab in
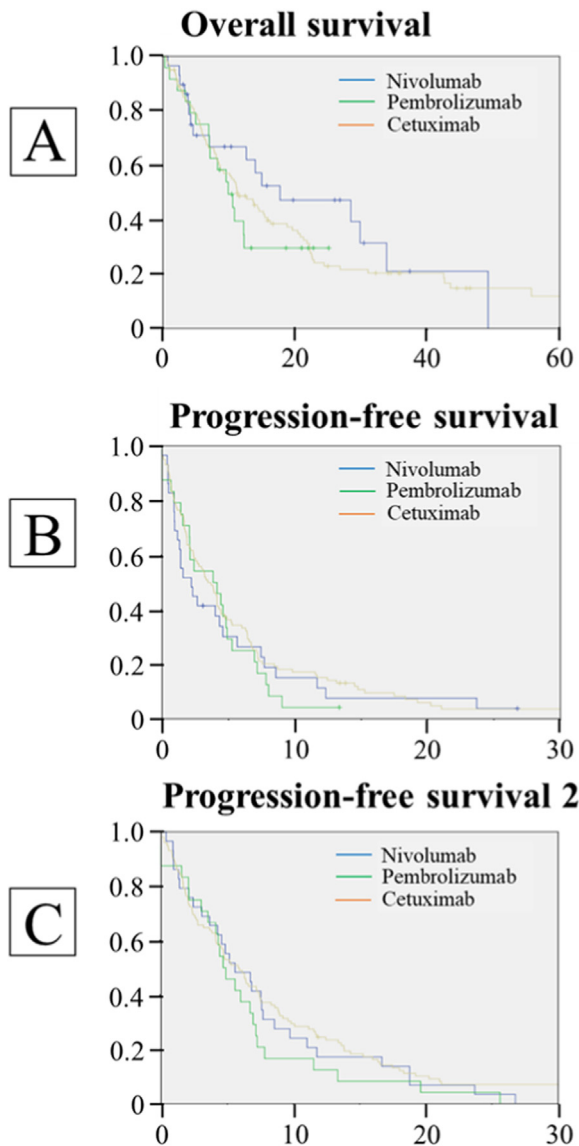
Fig. 2 First-line Kaplan-Meier survival curves. A: Overall survival; B: progression-free survival; C: progression-free survival 2. Blue line, nivolumab; green line, pembrolizumab; and yellow line, cetuximab. No significant differences were observed between the first- and second-line treatments.

Fig. 3 Progression-free survival curve for total nivolumab and pembrolizumab.

patients with unresectable recurrent or metastatic head and neck cancer.[1,2] However, the percentages of oral cancer cases in these clinical studies are not high, being 29.2 % and 48.5 % in the KEYNOTE-048 and CheckMate 141 studies, respectively.[1,2] Few studies exist on the benefits of ICI for oral cancer alone, with none originating from Asia.[4,5] Additionally, patient background factors may differ significantly between randomized controlled trials and real-world data. Therefore, the Japanese Society of Oral Tumors decided to collect oral cancer data re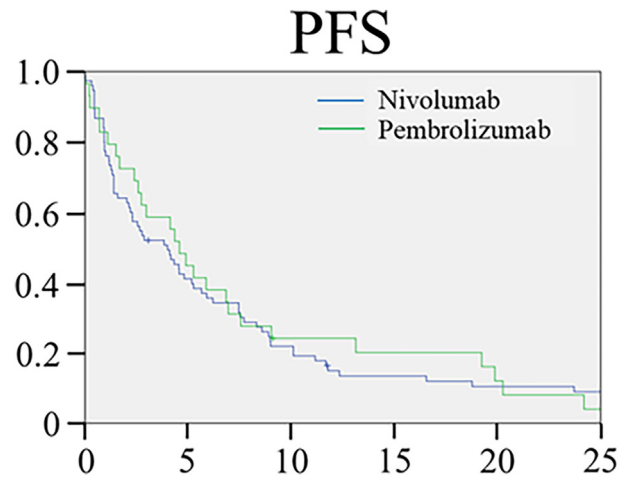trospectively to investigate the current status of drug therapy for unresectable, recurrent, and metastatic oral cancers.

In the CheckMate 141 study, the median OS (months) and PFS (months) for nivolumab were 12.1 and 2.0, respectively, with an ORR of 13.3 %.[12] Although we cannot simply compare the results due to the different backgrounds of the patients, our results showed OS and PFS of 10.3 and 2.2, respectively, and the ORR was 5/29 (17.2 %), which was comparable to the checkmate141 study.

The KEYNOTE-048 study showed that the median OS (months) for pembrolizumab alone and pembrolizumab + FP was 11.6 and 11.6, respectively, and the median PFS for pembrolizumab alone and pembrolizumab + FP was 2.3 and 4.9, respectively. The ORR for pembrolizumab alone and pembrolizumab + FP was 51/301 (17 %) and 100/281 (35.6 %), respectively.[13] In contrast, the OS and PFS of patients treated with pembrolizumab in our study were 9.5 and 3.1, respectively, which were slightly inferior to those of KEYNOTE-048, and the ORR was only 4.2 %, significantly lower than that of KEYNOTE-048. Determining the cause of the suboptimal outcomes for pembrolizumab in this study proved challenging, given the study's retrospective nature and uncertainties regarding pembrolizumab's efficacy in oral cancer.

The EXTREME study showed that in cetuximab + FP therapy, the median OS (months), median PFS (months), and ORR were 10.1, 5.6, and 36 %, respectively.[14] The results for cetuximab in this study (OS, PFS, ORR of 11.1, 3.5, and 21.6 %, respectively) were slightly lower than that of the EXTREME study, potentially influenced by the retrospective nature of this study.

Recently, PFS2, the duration of response to second-line therapy, has attracted attention as a measure of ICI efficacy.[4–6,15] This is thought to restore chemosensitivity owing to changes in the tumor microenvironment induced by ICI use. Wada et al. reported OFS, PFS2, PFS3, and OS

Table 3 Clinicopathological factors related to response rate.

First line treatment		Nivolumab						Pembrolizumab						Cetuximab					
Response rate		Overall response			Disease control			Overall response			Disease control			Overall response			Disease control		
		CD/PR	SD/PD	P-value	CR/PR/SD	PD	P-value	CR/PR	SD/PD	P-value	CR/PR/SD	PD	P-value	CR/PR	SD/PD	P-value	CR/PR/SD	PD	P-value
Gender	Male	2	11	0.811	5	8	0.958	0	8	0.470	4	4	0.558	14	48	0.757	39	23	0.297
	Female	3	13		6	10		1	15		6	10		8	32		21	19	
Age		63.8 ± 17.7	61.8 ± 9.5	0.715	62.1 ± 14.7	62.1 ± 8.2	0.987	54	69.3 ± 10.7	0.179	67.5 ± 9.5	69.5 ± 12.2	0.671	66.5 ± 14.8	63.3 ± 11.6	0.288	65.4 ± 12.5	61.8 ± 11.9	0.149
Performance Status	0	4	11	0.152	7	8	0.593	1	6	0.282	3	4	0.452	6	22	0.760	17	11	0.510
	1	0	11		3	8		0	15		7	8		16	54		42	28	
	2	1	2		1	2		0	2		0	2		0	3		1	2	
	3													0	1		0	1	
Primary Site	Tongue	2	15	0.622	5	12	0.438	0	7	1.000	3	4	1.000	11	28	0.223	22	17	0.836
	Others	3	9		6	6		1	14		7	10		11	52		38	25	
T stage	T1-2	4	9	0.082	7	6	0.111	0	10	0.388	4	6	0.889	5	32	0.136	18	19	0.115
	T3-4	1	15		4	12		1	13		6	8		17	48		42	23	
N stage	+	3	17	0.634	8	12	0.732	0	15	0.187	5	10	0.285	15	53	0.865	39	29	0.670
	−	2	7		3	6		1	8		5	4		7	27		21	13	
History of surgery	+	5	21	0.404	9	17	0.279	1	19	0.648	8	12	0.711	15	68	0.073	45	38	0.048
	−	0	3		2	1		0	4		2	2		7	12		15	4	
History of radiation therapy	+	5	22	0.504	10	17	0.715	1	13	0.388	7	7	0.327	17	53	0.324	43	27	0.429
	−	0	2		1	1		0	10		3	7		5	27		17	15	
History of chemotherapy	+	1	3	0.658	2	2	0.592	1	9	0.227	5	5	0.484	14	35	0.098	32	17	0.201
	−	4	21		9	16		0	14		5	9		8	45		28	25	
Unresectable site	Primary or cervical recurrence	2	10	0.670	5	7	0.359	1	14	0.731	8	7	0.251	13	39	0.091	30	22	0.028
	Distant metastases	3	11		6	8		0	7		2	5		6	27		21	12	
	Both	0	3		0	3		0	2		0	2		0	11		3	8	
	Refusal of surgery	0	0		0	0		0	0		0	0		3	3		6	0	
Histological differentiation	Well	0	8	0.289	0	8	0.012	1	13	1.000	8	6	0.104	14	32	0.087	34	12	0.001
	Moderately or poorly	4	15		10	9		0	10		2	8		7	40		18	29	
Mode of invasion	YK 1-3	1	12	1.000	5	8	0.673	1	9	0.478	4	6	0.659	9	33	0.782	27	15	0.080
	YK 4	1	11		3	9		0	11		3	8		7	34		18	23	
Lymphatic invasion	+	3	9	0.645	4	8	1.000	0	4	1.000	1	3	1.000	5	15	0.764	11	9	1.000
	−	2	11		5	8		1	14		6	9		15	55		40	30	
Vascular invasion	+	1	12	0.160	2	11	0.041	1	12	1.000	6	7	0.333	8	32	0.800	23	17	1.000
	−	4	8		7	5		0	6		1	5		12	38		28	22	
Perineural invasion	+	1	11	0.322	3	9	0.411	1	9	1.000	4	6	1.000	8	26	0.801	19	15	0.826
	−	4	9		6	7		0	9		3	6		12	44		32	24	
irAE	+	0	6	0.553	0	6	0.058	1	5	0.250	3	3	0.665						
	−	5	18		11	12		0	18		7	11							
Cisplatin resistance	+	4	20	1.000	10	14	0.622												
	−	1	4		1	4													
CPS	−1							0	3		0	3	0.229						
	1−20							0	3		2	1							
	20-							0	17		7	10							

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were 3.2, 8.1, 14.0, and 17.2 months, respectively, in Japanese head and neck cancer patients receiving Nivolumab.[16] PFS2 for pembrolizumab + FP and cetuximab + FP in the KEYNOTE-048 study was 11.7 vs. 9.4 and 9.4 vs. 8.9 for CPS≥20 and CPS≥1, respectively. PFS2 for pembrolizumab alone and cetuximab + FP was 11.3 vs. 9.8 and 10.3 vs. 9.0 for CPS ≥20 and CPS ≥1, respectively. In both cases, pembrolizumab demonstrated significantly longer PFS2 compared to cetuximab.[17] In this study, PFS2 was 5.6 for nivolumab and 4.5 for pembrolizumab. The PFS2 of the ICI group in this study was shorter, although this cannot be compared to previous studies. Moreover, reports indicate effectiveness in recurrent and metastatic head and neck cancer with the combination of cetuximab and paclitaxel, serving as both first-line and second-line treatments following ICI therapy.[18,19] In this study, cetuximab + PTX after ICI was often used; however, the PFS2 results were not effective.

Several factors could contribute to the poor prognosis observed with ICIs (nivolumab and pembrolizumab) in this study. Firstly, the retrospective nature of the study might have led to the inclusion of a patient group with poor backgrounds. Secondly, the relatively recent regulatory approval in Japan introduces the possibility of a discrepancy in the efficacy evaluation. The consistency in judging pseudo-progression may vary, prompting patients to transition to the next treatment in case of early-stage disease progression. Thirdly, poor OS may be associated with a short PFS2. Short PFS2 may be caused by ICI, which improves the tumor microenvironment and is inhibited by other factors. Finally, ICI may be less effective against oral cancer than against head and neck cancer. This study, being retrospective with a limited number of patients, requires careful evaluation. Further accumulation of cases is required in the future. Yamakawa et al.[2] reported that nivolumab is more effective in patients with oral cancer who develop irAEs. However, this was not the case in this study, and future studies are required.

In this study, the irAEs of ICI were deemed safe, with no severe cases. However, some irAEs, such as hypophysitis, hypothyroidism, pruritus, fatigue, and interstitial pneumonia, did not appear until six months or more later. Using ICI requires careful monitoring due to the potential occurrence of irAEs.

This study had some limitations. First, this was a retrospective study with a small number of patients. Determining distinctions in the efficacy of nivolumab, pembrolizumab, and cetuximab was not possible. Due to the multicenter nature of the study, variability in the assessment of efficacy could have existed. However, few studies have focused exclusively on oral cancer among head and neck cancers. We would like to increase the number of cases in the future and clarify the selection criteria for pharmacological therapy for unresectable recurrent or metastatic oral cancer.

Herein, we report the current status of nivolumab, pembrolizumab, and cetuximab in patients with unresectable recurrent or metastatic oral cancer. Determining the comparative effectiveness of these drugs as a first-line therapy was not possible in this study. In the future, we would like to further investigate this issue by increasing the number of patients.

Table (rotated on page):

FP	+												
	−				0.324								
NLR	Neutrophil/ lymphocytes	5.22 ± 2.41	7.52 ± 5.29	0.356		8.07 ± 6.69	6.48 ± 3.51	0.418	0 / 1	10.89	8.58 ± 6.83	0.512	4 / 6	7.67 ± 5.88	3 / 11	9.41 ± 7.35	0.324	13.7 ± 5.65	13.6 ± 17.1	0.912	13.4 ± 13.9	13.8 ± 20.3	0.725
PLR	Platelet/ lymphocytes	265 ± 129	399 ± 223	0.212		425 ± 296	342 ± 140	0.327	7 / 16	486.78	435 ± 263	0.540	477 ± 328	409 ± 203	0.540	679 ± 495	696 ± 265	0.931	681 ± 279	717 ± 191	0.804
FP	Unknown								1 / 0			0.512	1 / 4									
	+								0 / 7													
	−				0.324				1 / 16				6 / 11									
NLR	Neutrophil/ lymphocytes	5.22 ± 2.41	7.52 ± 5.29	0.356		8.07 ± 6.69	6.48 ± 3.51	0.418		10.89	8.58 ± 6.83	0.744	7.67 ± 5.88	9.41 ± 7.35	0.535	13.7 ± 5.65	13.6 ± 17.1	0.912	13.4 ± 13.9	13.8 ± 20.3	0.725
PLR	Platelet/ lymphocytes	265 ± 129	399 ± 223	0.212		425 ± 296	342 ± 140	0.327		486.78	435 ± 263	0.850	477 ± 328	409 ± 203	0.540	679 ± 495	696 ± 265	0.931	681 ± 279	717 ± 191	0.804

irAE: immune-related adverse events, CPS: combined positive score, NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, FP: 5-FU + cisplatin.

Table 4 Immune-related adverse events for cancer patients treated with immune checkpoint inhibitors.

Drug	Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Unknown	Days to Onset
Nivolumab (n = 75)	Hemorrhage						1	5
	Hypophysitis		1					245
	Interstitial pneumonia	1	1					28, 54
	Hypothyroidism	3	3		1			32, 77, 97, 106, 125, 976
	Hepatitis	1						125
	Dry mouth	1	1					14, 35
	Anorexia		1					28
	Pruritus	2						126, 217
	Enteritis	1	2					−, −, 31
	Fatigue	1	1					28,280
	Dry skin	1						−
Pembrolizumab + FP (n = 8)	Cerebral infarction						1	98
	Interstitial pneumonia	1						772
Pembrolizumab only (n = 30)	Interstitial pneumonia		1					245
	Diarrhea			1				33
	Drug eruption						1	33
	Arthritis						1	−
	Mucositis						1	−

Abbreviation, FP: 5-fluorouracil + cisplatin.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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References

1. National Comprehensive Cancer Network (NCCN). *Head and neck cancers version 1*. 2022.
2. Yamakawa N, Umeda M, Yoshii Y, et al. Multicenter retrospective study of nivolumab for recurrent/metastatic oral squamous cell carcinoma. *Oral Dis* 2022 (in press).
3. Li J, He Z, Tao Y, et al. Efficacy and safety of pembrolizumab monotherapy for recurrent/unresectable/metastatic oral squamous cell carcinoma: a single-center study in China. *J Oncol* 2022:7283946.
4. Kacew AJ, Harris EJ, Lorch JH, et al. Chemotherapy after immune checkpoint blockade in patients with recurrent, metastatic squamous cell carcinoma of the head and neck. *Oral Oncol* 2020;105:104676.
5. Pestana RC, Becnel M, Rubin ML, et al. Response rates and survival to systemic therapy after immune checkpoint inhibitor failure in recurrent/metastatic head and neck squamous cell carcinoma. *Oral Oncol* 2020;101:104523.
6. Saleh K, Daste A, Martin N, et al. 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* 2019;121:123–9.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol* 1982;5:649–55.
8. *TNM classification of malignant tumours*, eighth ed. New York: Splinger-Verlag., 2017.
9. Yamamoto E, Kohama G. Mode of invasion, bleomycin sensitivity and clinical course in squamous cell carcinoma of the oral cavity. *Cancer* 1983;51:2175–80.
10. National Cancer Institute. Division of cancer treatment and diagnosis. *Common Terminology Criteria for Adverse Events (CTCAE)* 2017., version 5.0.
11. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer Institute of the United States, national cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
12. Ferris RL, Blumenschein Jr G, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856–67.
13. Burtness B, Harrington KJ, Greil R, et al. 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* 2019;394:1915–28.
14. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–27.
15. Dwary AD, Master S, Patel A, et al. Excellent response to chemotherapy post immunotherapy. *Oncotarget* 2017;8:91795–802.
16. Wada A, Enokida T, Okano S, et al. Proton pump inhibitors and antibiotics adversely effect the efficacy of nivolumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *Eur J Cancer* 2023;184:30–8.
17. Harrington KJ, Burtness B, Greil R, et al. Pembrolizumab with or without chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma: updated results of the phase III KEYNOTE-048 Study. *J Clin Oncol* 2023;41:790–802.

18. Hitt R, Irigoyen A, Cortes-Funes H, et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. *Ann Oncol* 2012;23: 1016—22.

19. Kurosaki T, Mitani S, Tanaka K, et al. Safety and efficacy of cetuximab-containing chemotherapy after immune checkpoint inhibitors for patients with squamous cell carcinoma of the head and neck: a single-center retrospective study. *Anti Cancer Drugs* 2021;32:95—101.