

Nivolumab for Platinum-refractory and -sensitive Recurrent and Metastatic Head and Neck Squamous Cell Carcinoma

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Abstract. *Background/Aim:* Nivolumab has antitumor efficacy in patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) who relapse within 6 months after platinum-based therapy; however, the efficacy of nivolumab for platinum-sensitive R/M HNSCC has not been shown. Therefore, this study compared the efficacy and safety of nivolumab for platinum-refractory and platinum-sensitive R/M HNSCC. *Patients and Methods:* This was a retrospective study of patients who received nivolumab for R/M HNSCC who had been previously treated with platinum-based anticancer drugs. Patients were divided into a platinum-sensitive and a platinum-refractory group, and progression-free survival (PFS), overall survival (OS), the overall response rate (ORR) [complete response (CR) + partial response (PR)], the disease control rate (DCR) (CR + PR + stable disease), and the incidence of immune-related adverse events (irAEs) were compared between the two groups. *Results:* We included 88 patients with squamous cell carcinoma: 60 with platinum-refractory disease and 28 with platinum-sensitive disease. The median PFS in the platinum-

refractory and platinum-sensitive groups were 2.7 months and 5.3 months, respectively ($p=0.03$), and the median OS were 8.8 months and 17.1 months, respectively ($p=0.06$). There were no significant differences in the ORR, DCR, or incidence of irAEs between the two groups ($p>0.99$, $p=0.11$, and $p>0.99$, respectively). *Conclusion:* Nivolumab is a safe and effective treatment for platinum-sensitive R/M HNSCC.

Systemic platinum-based anticancer drugs are the mainstay of chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, some patients have acquired or innate resistance to platinum therapies, and the 1-year survival rate of these patients is only 3% (1). Therefore, the EXTREME regimen (cetuximab + cisplatin/carboplatin + 5-fluorouracil) is recognized as the standard treatment for initial chemotherapy for R/M HNSCC (2).

In a global phase III trial (CheckMate-141), the human anti-human programmed cell death 1 (PD-1) monoclonal antibody nivolumab has antitumor efficacy in patients who relapse within 6 months after platinum-based radiation therapy or platinum-based chemotherapy (3). Compared to the overall survival (OS) of 5.1 months in the standard single agent group (methotrexate, docetaxel, and cetuximab), the OS of the nivolumab group was 7.7 months, which represented a significantly extended survival. While in a global phase III trial (KEYNOTE-048), the PD-1 monoclonal antibody pembrolizumab was effective in patients who relapsed 6 months after combined platinum chemotherapy and in chemotherapy-naïve patients. The study compared the therapeutic effect based on the combined positive score (CPS), which grades the expression of PD-L1 in tumor cells and

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Table I. Patient characteristics.

	All patients		Platinum-refractory		Platinum-sensitive		p-Value
	n=88	(%)	n=60	(%)	n=28	(%)	
Age (years)							0.21
Median	66		69		61		
Range	30-81		23-81		41-81		
Sex							0.15
Male	71	(81)	51	(85)	20	(71)	
Female	17	(19)	9	(15)	8	(29)	
Performance status							0.17
0-1	83	(94)	55	(92)	28	(100)	
≥2	5	(6)	5	(8)	0	(0)	
Primary site							0.001
Oral cavity	17	(19)	13	(22)	4	(14)	
Nasopharynx	10	(11)	3	(5)	7	(25)	
Oropharynx	19	(22)	13	(22)	6	(21)	
Hypopharynx	21	(24)	19	(32)	2	(7)	
Larynx	10	(11)	9	(15)	1	(4)	
Paranasal sinus	6	(7)	1	(2)	5	(18)	
Salivary gland	2	(2)	1	(2)	1	(4)	
Other	3	(3)	1	(2)	2	(7)	
Administration line							0.048
1 st	31	(35)	16	(27)	15	(54)	
2 nd	46	(52)	36	(60)	10	(36)	
3 rd or later	11	(13)	8	(13)	3	(11)	
Prior cetuximab administration	58	(66)	43	(72)	15	(54)	0.058

surrounding immune cells, like lymphocytes and macrophages. In the pembrolizumab monotherapy group, patients with a CPS ≥20 had a median progression-free survival (PFS) of 3.4 months and a median OS of 14.9 months, whereas patients with a CPS ≥1 had a median OS of 12.3 months (4). Based on these results, nivolumab is administered for platinum-resistant R/M HNSCC, and pembrolizumab is administered for platinum-sensitive R/M HNSCC. However, there has not been a report comparing the usefulness and safety of nivolumab in platinum-resistant and platinum-sensitive R/M HNSCC. Therefore, we compared the therapeutic effect of nivolumab for platinum-resistant and platinum-sensitive R/M HNSCC and retrospectively examined its efficacy and safety.

Patients and Methods

This was a retrospective study of patients who received nivolumab for R/M HNSCC who had been previously treated with platinum-based anticancer drugs. Patients who had no history of platinum-based anticancer drugs and those who were not treated under medical insurance were excluded. Patients were recruited between May 2017 and August 2018 at four institutions (Tokyo Medical University Hospital, Tokyo Medical University Hachioji Medical Center, International University of Health and Welfare Mita Hospital, and Kitasato University Hospital). There were 102 patients treated with nivolumab during the study period, of whom 100 had a history of platinum-based anticancer drug administration. Of these 100 patients,

88 patients with squamous cell carcinoma were included. There were 71 men and 17 women with a median age of 66 years (range=30-81 years). Performance status (PS) was 0-1 in 83 patients, and 2 in five patients. The primary tumor site was the oral cavity in 17 patients, the nasopharynx in 10 patients, the oropharynx in 19 patients, the hypopharynx in 21 patients, the larynx in 10 patients, the paranasal sinus in six patients, the salivary gland in two patients and others in three patients. Regarding administration, 31 patients were in first line, 46 were in second line, and 11 were in third line and later. Patients were divided into platinum-sensitive and platinum-refractory groups. Patients were classified as having platinum-refractory disease if the period between administration of platinum-based anticancer drugs and recurrence was less than 6 months and as having platinum-sensitive disease if recurrence occurred more than 6 months after administration of platinum-based anticancer drugs. Sixty patients had platinum-refractory disease and 28 had platinum-sensitive disease.

Written informed consent for the publication of this work was obtained from all patients. This study was approved by the institutional review board of each institution and conducted in accordance with the Declaration of Helsinki (approval no. T2018-0021, 5-18-71, B18-256).

Nivolumab was administered at a dose of 3 mg/kg every 2 weeks. Target lesions were evaluated every 2-3 months using computed tomography or magnetic resonance imaging. Treatment was continued until the lesions increased, unacceptable adverse events occurred, or the attending physician discontinued treatment for other reasons. No dose reduction criteria were set.

The endpoints were PFS, OS, the overall response rate (ORR) [complete response (CR) + partial response (PR)], the disease

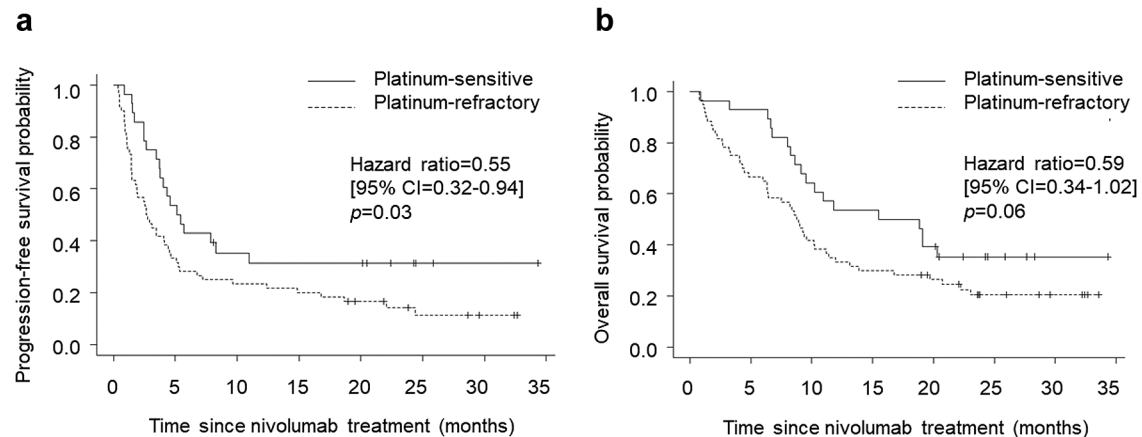


Figure 1. Kaplan-Meier survival curves of progression-free survival (a) and overall survival (b) in patients with platinum-refractory and platinum-sensitive recurrent/metastatic head and neck squamous cell carcinoma receiving nivolumab.

control rate (DCR) (CR + PR + stable disease), and the incidence of immune-related adverse events (irAEs). We compared all outcomes between the platinum-refractory and platinum-sensitive groups. PFS was defined as the period from the start of nivolumab administration to disease progression or death, and OS was defined as the period from the start of nivolumab administration to death or the date of the final follow-up. The therapeutic effect on target lesions was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (5). irAEs were evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (6). ORR and DCR analyses were limited to patients who could be evaluated by imaging. Patients with clinically apparent disease progression were designated as having progressive disease. The Eastern Cooperative Oncology Group PS was evaluated prior to nivolumab administration.

PFS and OS were evaluated using the Kaplan-Meier method and analyzed by the log-rank test. Survival was analyzed using the Cox proportional hazards model. The patient background characteristics, ORR, DCR, and incidence of irAEs were analyzed using Fisher's exact test. In all analyses, $p < 0.05$ was considered to be a statistically significant difference. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (7).

Results

The patient background characteristics are shown in Table I. There were no significant differences in age, sex, PS, or premedication with cetuximab between the two groups.

The median PFS in the platinum-refractory and platinum-sensitive groups were 2.7 months [95% confidence interval (CI)=1.5-4.4] and 5.3 months (95% CI=3.7-10.9), respectively, with significantly better survival in the platinum-sensitive group [hazard ratio (HR)=0.55; 95% CI=0.33-0.94; $p=0.03$; Figure 1a]. The median OS in the platinum-refractory and platinum-sensitive groups were 8.8 months (95% CI=6.3-11.2)

and 17.1 months (95% CI=9.1-not reached), respectively, and the survival rate of the platinum-sensitive group had a trend towards significance (HR=0.59; 95% CI=0.34-1.02; $p=0.06$; Figure 1b).

The ORRs in the platinum-refractory and platinum-sensitive groups were 17% and 18%, respectively ($p > 0.99$), and the respective DCRs were 41% and 61% ($p=0.11$). The incidence of irAEs in the platinum-refractory and platinum-sensitive groups were 32% and 33%, respectively ($p > 0.99$, Table II).

Discussion

We compared the outcomes of 88 patients who received nivolumab for R/M HNSCC who had been treated with platinum-based anticancer drugs based on whether they had platinum-refractory or platinum-sensitive disease. The PFS was significantly better in the platinum-sensitive group, and the incidence of irAEs in the platinum-refractory and platinum-sensitive groups were not significantly different. These data suggest that nivolumab has a good clinical effect on platinum-sensitive R/M HNSCC and that safety could be maintained.

The concept of platinum refractivity/sensitivity has since long been used in ovarian cancer (8). A longer period from pre-treatment, including platinum preparation, to platinum re-administration [platinum-free interval (PFI)] is associated with a higher response rate during platinum re-administration. The PFI is a well-known prognostic factor, and in recent years, it has been used as a prognosticator for head and neck cancer. It has been reported that platinum re-administration is more effective for platinum-sensitive R/M HNSCC than for platinum-resistant R/M HNSCC (9, 10). Based on the results of the CheckMate-141 and KEYNOTE-048 trials, nivolumab has been used for platinum-resistant R/M HNSCC, and the EXTREME regimen and pembrolizumab have been used for

Table II. Efficacy and safety of nivolumab treatment.

	All patients		Platinum-refractory		Platinum-sensitive		p-Value
	n=88	(%)	n=60	(%)	n=28	(%)	
Best overall response							
Complete response (CR)	5	(6)	5	(8)	0	(0)	
Partial response (PR)	11	(13)	6	(10)	5	(18)	
Stable disease (SD)	26	(30)	14	(23)	12	(43)	
Progressive disease	46	(52)	35	(58)	11	(39)	
Overall response (CR+PR)	16	(18)	11	(18)	5	(18)	>0.99
Disease control (CR+PR+SD)	42	(48)	25	(42)	17	(61)	0.11
Immune-related adverse events							>0.99
Yes	29	(33)	20	(33)	9	(32)	
No	59	(67)	40	(67)	19	(68)	

platinum-sensitive R/M HNSCC (3, 4, 11-14). Thus far, there has not been a large-scale clinical trial investigating the usefulness of nivolumab for platinum-sensitive R/M HNSCC. Although it was a small-scale study, Okamoto et al. reported on a single-site, single-arm prospective study of nivolumab for platinum-sensitive R/M HNSCC, wherein the median PFS was 9.6 months, and the median OS was 17.4 months (15). In the present study, nivolumab produced favorable results, with a median PFS of 5.3 months and a median OS of 17.1 months in patients with platinum-sensitive R/M HNSCC, and this PFS was significantly better than that in patients with platinum-resistant disease. This suggests that nivolumab may be useful for patients with platinum-sensitive R/M HNSCC.

Several factors affecting survival in patients with R/M HNSCC receiving nivolumab have been reported. A sub-analysis of the Checkmate 141 trial reported that OS was better in patients without a history of cetuximab treatment (16). Another report indicated that patients who develop irAEs have a better OS than those who do not (14). In this study, there were no significant differences in the administration history of cetuximab or the incidence of irAEs between the two groups. However, it is possible that the survival rate was worse in the platinum-refractory group because more patients were receiving nivolumab as a second-line or later treatment. The rate of PD-L1 expression in tumor cells has been suggested to be a predictor of the effectiveness of nivolumab. In a sub-analysis of the Checkmate 141 trial, tumor proportion score (TPS) is used as measurement PD-L1 expression in tumor cells. The response rates were 17% in patients with TPS ≥1% and 12% in patients with TPS <1%. Therefore, patients with higher PD-L1 expression had a better response to nivolumab; however, long-term follow-up data suggested a certain level of effect even for patients with low or no PD-L1 expression (3, 17). Therefore, nivolumab is expected to demonstrate some effect regardless of the tumor PD-L1 expression, and

it may not be necessary to assess PD-L1 expression when administering nivolumab in clinical practice. However, the KEYNOTE-048 trial showed that pembrolizumab was not effective for patients with a CPS <1, and the EXTREME regimen was recommended for such patients. However, the EXTREME regimen may not be suitable for patients that have received a high total dose of platinum anticancer agents, patients with kidney damage, and elderly patients. Therefore, nivolumab was considered a possible treatment option in patients with unknown CPS due to inability to measure PD-L1 and those who cannot be treated with the EXTREME regimen.

TPS measures PD-L1 expression on tumor cells, while CPS measures PD-L1 in both tumor cells and surrounding immune cells. Therefore, TPS-based nivolumab administration and CPS-based pembrolizumab administration cannot be simply compared. However, there is also a positive correlation between TPS and CPS, with TPS ≥40 having significantly better OS and PFS compared to TPS <40 ($p=0.016$, $p=0.007$, respectively) (18). It may be possible to decide whether or not to administer nivolumab according to TPS, but in Japan, it is not possible to measure both CPS and TPS due to insurance reasons.

This study had several limitations. This was a retrospective study and had selection bias. It included the nasopharynx, paranasal sinus, and salivary gland, which were not included in the CheckMate-141. However, because it was a multicenter study, the sample size was larger, and a multifaceted analysis was possible. The results were useful as real-world data. Additionally, the status of platinum-based anticancer drug administration before administration of nivolumab was not constant, and there were significantly more patients receiving second-line or later therapy in the platinum-refractory group than in the platinum-sensitive group, which may have affected the survival rate. In addition, the PD-L1 expression in tumor cells was not

assessed, and its link to efficacy was not examined. Further, including patients with homogeneous backgrounds for examination would have been preferable.

In conclusion, the results of this study suggest that nivolumab is a clinically acceptable regimen for patients with platinum-sensitive HNSCC. It was considered to be useful for platinum-sensitive patients whom CPS cannot be measured from past biopsy or surgical specimens and cannot collect new tissue due to distant metastasis, and patients with CPS <1 who cannot use EXTREME regimen due to old age or poor general condition. Further prospective studies are needed to examine the efficacy of pembrolizumab in these patients.

Conflicts of Interest

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

Authors' Contributions

TO, TM, HT, CF, IO, and HS contributed to the conception and design of this study. TK, KT, TI, TM, and KH were responsible for the data collection. HT, GO, and NO contributed to data analysis. TO, TM, CF, IO, HS, TK, and KT were in charge of drafting the manuscript. TM, YT, KM, TY, and KT revised the manuscript critically for important intellectual content. The final version was read and approved by all the Authors.

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References

- 1 León X, Hitt R, Constenla M, Rocca A, Stupp R, Kovács AF, Amellal N, Bessa EH and Bourhis J: A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy. *Clin Oncol (R Coll Radiol)* 17(6): 418-424, 2005. PMID: 16149284. DOI: 10.1016/j.clon.2005.02.014
- 2 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotny 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
- 3 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
- 4 Burtneß B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrrí A, Basté N, Neupane P, Bratland Å, Fuehrer 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
- 5 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45(2): 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026
- 6 Common terminology criteria for adverse events (ctcae) v3.0 and v4.0. Bethesda, Maryland, National Institutes of Health, 2010. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm [Last accessed on July 4, 2022]
- 7 Kanda Y: Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 48(3): 452-458, 2013. PMID: 23208313. DOI: 10.1038/bmt.2012.244
- 8 Markman M, Rothman R, Hakes T, Reichman B, Hoskins W, Rubin S, Jones W, Almadrones L and Lewis JL Jr: Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 9(3): 389-393, 1991. PMID: 1999708. DOI: 10.1200/JCO.1991.9.3.389
- 9 Sano D, Fujisawa T, Tokuhisa M, Shimizu M, Sakagami T, Hatano T, Nishimura G, Ichikawa Y, Iwai H and Oridate N: Real-world treatment outcomes of the EXTREME regimen as first-line therapy for recurrent/metastatic squamous cell carcinoma of the head and neck: a multi-center retrospective cohort study in Japan. *Anticancer Res* 39(12): 6819-6827, 2019. PMID: 31810948. DOI: 10.21873/anticancer.13898
- 10 Sato H, Tsukahara K, Okamoto I, Katsube Y, Shimizu A, Kondo T, Hanyu K, Fushimi C, Okada T and Miura K: Clinical outcomes of platinum-based chemotherapy plus cetuximab for recurrent or metastatic squamous cell carcinoma of the head and neck: comparison between platinum-sensitive and platinum-resistant patients. *Acta Otolaryngol* 139(2): 201-205, 2019. PMID: 30794080. DOI: 10.1080/00016489.2018.1551623
- 11 Hori R, Shinohara S, Kojima T, Kagoshima H, Kitamura M, Tateya I, Tamaki H, Kumabe Y, Asato R, Harada H, Kitani Y, Tsujimura T, Honda K, Ichimaru K and Omori K: Real-world outcomes and prognostic factors in patients receiving nivolumab therapy for recurrent or metastatic head and neck carcinoma. *Cancers (Basel)* 11(9): 1317, 2019. PMID: 31500103. DOI: 10.3390/cancers11091317
- 12 Kiyota N, Hasegawa Y, Takahashi S, Yokota T, Yen CJ, Iwae S, Shimizu Y, Hong RL, Goto M, Kang JH, Sum Kenneth Li W, Ferris RL, Gillison M, Namba Y, Monga M, Lynch M and Tahara M: A randomized, open-label, Phase III clinical trial of nivolumab vs. therapy of investigator's choice in recurrent squamous cell carcinoma of the head and neck: A subanalysis of Asian patients versus the global population in checkmate 141. *Oral Oncol* 73: 138-146, 2017. PMID: 28939066. DOI: 10.1016/j.oraloncology.2017.07.023
- 13 Matsuo M, Yasumatsu R, Masuda M, Toh S, Wakasaki T, Hashimoto K, Taura M, Uchi R and Nakagawa T: Relationship between immune-related adverse events and the long-term outcomes in recurrent/metastatic head and neck squamous cell

- carcinoma treated with nivolumab. *Oral Oncol* 101: 104525, 2020. PMID: 31863963. DOI: 10.1016/j.oraloncology.2019.104525
- 14 Okamoto I, Sato H, Kondo T, Koyama N, Fushimi C, Okada T, Miura K, Matsuki T, Yamashita T, Omura G and Tsukahara K: Efficacy and safety of nivolumab in 100 patients with recurrent or metastatic head and neck cancer - a retrospective multicentre study. *Acta Otolaryngol* 139(10): 918-925, 2019. PMID: 31460818. DOI: 10.1080/00016489.2019.1648867
- 15 Okamoto I, Tsukahara K and Sato H: Single-center prospective study on the efficacy of nivolumab against platinum-sensitive recurrent or metastatic head and neck squamous cell carcinoma. *Sci Rep* 12(1): 2025, 2022. PMID: 35132165. DOI: 10.1038/s41598-022-06084-z
- 16 Ferris RL, Licitra L, Fayette J, Even C, Blumenschein G Jr, Harrington KJ, Guigay J, Vokes EE, Saba NF, Haddad R, Ramkumar S, Russell J, Brossart P, Tahara M, Colevas AD, Concha-Benavente F, Lynch M, Li L and Gillison ML: Nivolumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety in CheckMate 141 by prior cetuximab use. *Clin Cancer Res* 25(17): 5221-5230, 2019. PMID: 31239321. DOI: 10.1158/1078-0432.CCR-18-3944
- 17 Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, Harrington KJ, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Docampo LCI, Haddad R, Rordorf T, Kiyota N, Tahara M, Lynch M, Jayaprakash V, Li L and Gillison ML: Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncol* 81: 45-51, 2018. PMID: 29884413. DOI: 10.1016/j.oraloncology.2018.04.008
- 18 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/anticancer.15628

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