A Study of Patients with Recurrent or Metastatic Head and Neck Cancer Treated with Pembrolizumab

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Background/Aim: In December 2019, pembrolizumab was approved in Japan for the treatment of head and neck cancer with recurrence or distant metastasis, making it a new option for first-line treatment. However, there are still many unanswered questions about Overall survival (OS), Progression free survival (PFS), adverse events including immune-related adverse events (irAEs), and biomarkers.
Aims/Objectives: The aim of this study was to retrospectively review first-line treatment of head and neck cancer with recurrence or distant metastasis treated with pembrolizumab and to determine whether Combined positive score (CPS) is still useful as a biomarker in the clinical practice.
Material and Methods: We retrospectively reviewed clinical records of 20 patients who received pembrolizumab as first-line treatment for head and neck cancer with recurrence or distant metastasis between December 2019 and March 2021.
Results: Age ranged from 45 to 83 years (median 66 years), 17 male patients and 3 female patients. The response rate was 40%, and the disease control rate was 60%. OS and PFS in patients with CPS < 1 were significantly worse than those with CPS ≤ 1 (CPS-positive patients). The OS and PFS of patients with CPS < 1 were significantly worse than those of patients with 1 < = CPS (CPS-positive patients), and there was no significant difference between the group with CPS between 1 and 20 and the group with CPS over 20. And we experiences several CR cases with high CPS.
Conclusion: CPS is a useful biomarker for pembrolizumab.
Significance: There are no reported cases of CR after two courses of pembrolizumab in head and neck cancer. There are no reports of pembrolizumab in patients with head and neck cancer in Japan.

Key words: Combined positive score, immune checkpoint inhibitors, immune-related adverse events, Keynote048 study

INTRODUCTION

In Japan, nivolumab, an immune checkpoint inhibitor (ICI) approved in 2017 for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) [1], is steadily increasing the number of patients at each institution and is accumulating knowledge on OS, PFS, adverse events including immune-related Adverse Events (IRAEs), and biomarkers. On the other hand, pembrolizumab has been in use for a short period of time and there are still many unanswered questions. As in Keynote 048 [2], Pembrolizumab was indicated for treating patients with recurrent or distantly metastatic squamous cell carcinoma of the head and neck who had not received prior chemotherapy.

This study aims to evaluate the efficacy and safety of pembrolizumab for the patients with recurrent or distantly metastatic squamous cell carcinoma and to demonstrate the usefulness of CPS as a biomarker for pembrolizumab in real clinical practice. In this study, we reviewed the cases of pembrolizumab therapy performed in our department. We retrospectively evaluated the age, performance status (PS), clinical background, treatment outcome (Combined Positive Score [CPS] and response rate, overall survival, and progression-free survival), and AEs, including IRAEs, of 20 patients who received Pembrolizumab as the first-line treatment for head and neck cancer with recurrence or distant metastasis between December 2019 and March 2021.

MATERIALS AND METHODS

Pembrolizumab monotherapy was used for CPS-positive patients (1 ≤ CPS), and Pembrolizumab + 5-FU + CDDP/CBDCA (Pembrolizumab + FP) was used for CPS-negative patients (CPS < 1). Pembrolizumab alone was administered at a dose of 200 mg every three weeks, while Pembrolizumab + FP, comprising Pembrolizumab (200 mg), CDDP (100 mg/m^2), or CBDCA (AUC5), was administered on day 1 every three weeks, followed by 5-FU (1000 mg/m^2/day) for four days. The regimen was decided in a multidisciplinary conference, considering the patient's general condition and preference for outpatient treatment.

The response of the patients was assessed after three

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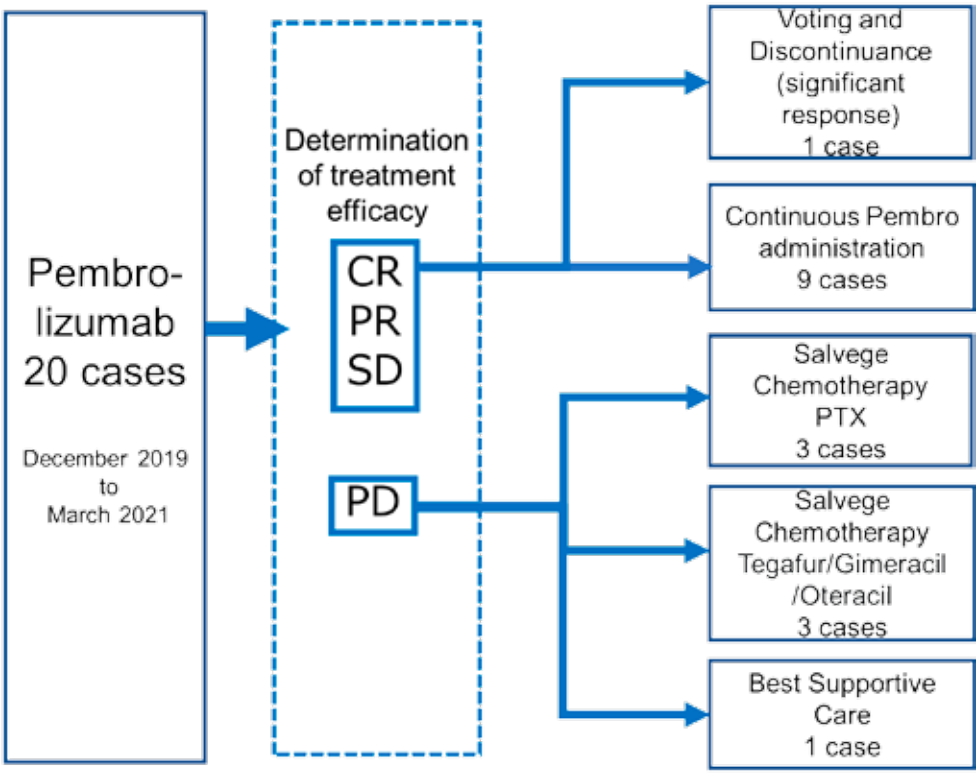

Fig. 1 The outcome of the cases. Of the 20 patients treated with pembrolizumab, the treatment in one patient with a significant response was discontinued at the patient's request, while nine patients with a successful response continued the treatment. Six patients developed poor responses during the pembrolizumab treatment and were converted to salvage chemotherapy.

months of pembrolizumab administration (usually after 4 cycles of treatment), and if a treatment response was observed, the treatment was continued as long as the response was sustained. If the patients were diagnosed with progressive disease (PD), pembrolizumab was discontinued, and the patient was switched to a subsequent therapy. However, if there was no apparent decline in performance status, the treatment was continued at the patient's request.

Salvage chemotherapy after pembrolizumab included paclitaxel (PTX) plus cetuximab (Cmab) or PTX alone and TS-1. The PTX dose was 100 mg/m^2 for seven weeks (administered on days 1, 8, 15, 22, 29, and 36), and the dose was reduced if grade 3 or higher AEs occurred.

The efficacy of treatment with pembrolizumab, overall survival (OS) and progression-free survival (PFS) by CPS, and AEs were evaluated. The efficacy of treatment includes complete response (CR), partial response (PR), stable disease (SD), and PD. PFS and OS were calculated using the response evaluation criteria in solid tumors (RECIST) guideline revision version 1.1, with the date of initial pembrolizumab treatment as the starting point. Kaplan–Meier method was used to analyze the survival curves. Chi-square test was used for statistical analysis and a P-value < 0.05 was defined as significant.

PD-L1 staining with PD-L1 IHC 22C3 pharmDx 'Dako' was used to measure CPS.

This study was conducted under the approval of the Clinical Research Review Committee of Tokai University School of Medicine (No. 20R-276). Patients have given their written consent for material about them to be published in this study. The material has been completely anonymised to ensure that no individual can be identified by the paper.

Table 1 Comparison with Keynote048

	This study N = 20	Keynote048 Pembro alone N = 301
OS median (M)	Not reached	11.6
12-month survival rate(%)	78.0	49.2
response rate(%)	40.0	16.9

RESULTS

The clinical course of 20 patients treated with pembrolizumab is shown in Fig.1. A comparison between this study and the Keynote048 study is shown in Tables 1 and 2.

The observation period and duration of the pembrolizumab treatment ranged from 4 to 16 months (median 5.5 months) and from 1 to 13 months (median 4.0 months), respectively. The age of the patients ranged from 45 to 83 years (median 66 years). Seventeen were men, and three were women. There were 8 cases of recurrence and 12 cases of distant metastases. All patients had a PS of 0. The primary sites were the oral cavity in two cases, middle pharynx

Table 2 Comparison with Keynote048 by CPS

	CPS < 1		1 ≦ CPS < 20		20 ≦ CPS	
	This study N = 4	Keynote048 Pembro alone N = 44	This study N = 5	Keynote048 Pembro alone N = 124	This study N = 11	Keynote048 Pembro alone N = 133
OS median (M)	4.0	7.9	Not reached	10.8	Not reached	14.9
12-month survival rate (%)	0	N/A	100	51.0	100	56.9

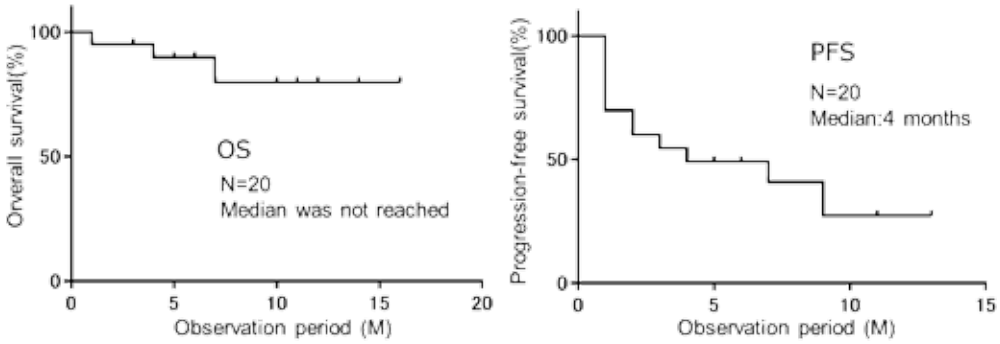

Fig. 2 OS and PFS. The median OS was not reached, and the median PFS was four months.

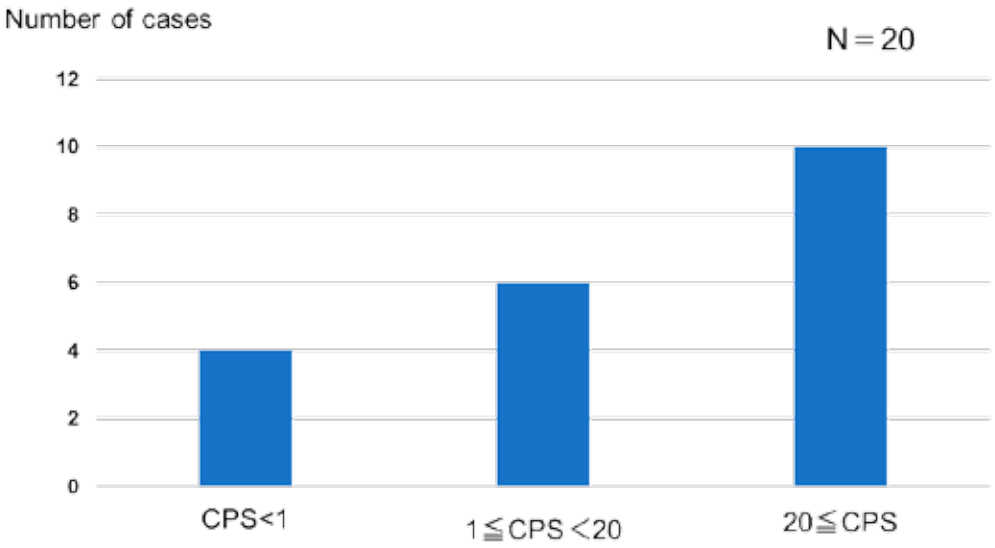

Fig. 3 Distribution of cases by CPS. There were three cases with CPS < 1 and two cases with CPS > 100.

in four cases, hypopharynx in six cases, larynx in two cases, salivary glands in three cases (parotid gland in two cases and submandibular gland in one case), and other glands in three cases (nasal cavity in one case, lip in one case, and ear canal in one case). None of the patients had received prior chemotherapy.

The best assessments were CR in 5 cases, PR in 3 cases, SD in 4 cases, and PD in 8 cases. The survival rate at 12 months after starting pembrolizumab was 78%. (Fig. 2).

CPS was assessable in all 20 patients treated with pembrolizumab (Fig. 3). CPS was determined using biopsy specimens from the first visit or the first treatment, and there was no clear difference between the two groups of recurrent and distant metastatic cases. The median CPS was 25; patients with higher CPS tended to have the significantly better OS and PFS ($p = 0.045$) (Fig. 4 and 5).

Three IRAEs were observed in three patients: one grade 2 hypothyroidism, one adrenal insufficiency, and one grade 3 autoimmune hepatitis. All IRAEs occurred in patients with high CPS (20 ≤ CPS), and all patients with IRAEs had high CPS (20 ≤ CPS). Two cases are presented below.

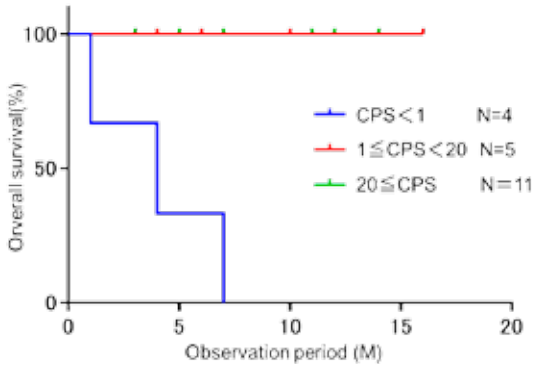

Fig. 4 OS by CPS. All patients with CPS ≥ 1 were alive.

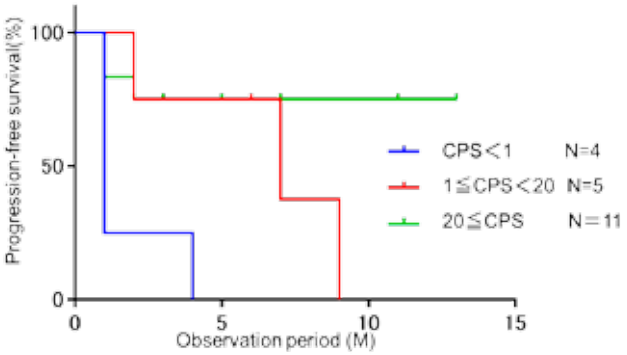

Fig. 5 PFS by CPS. The higher the CPS, the better the PFS tended to be.

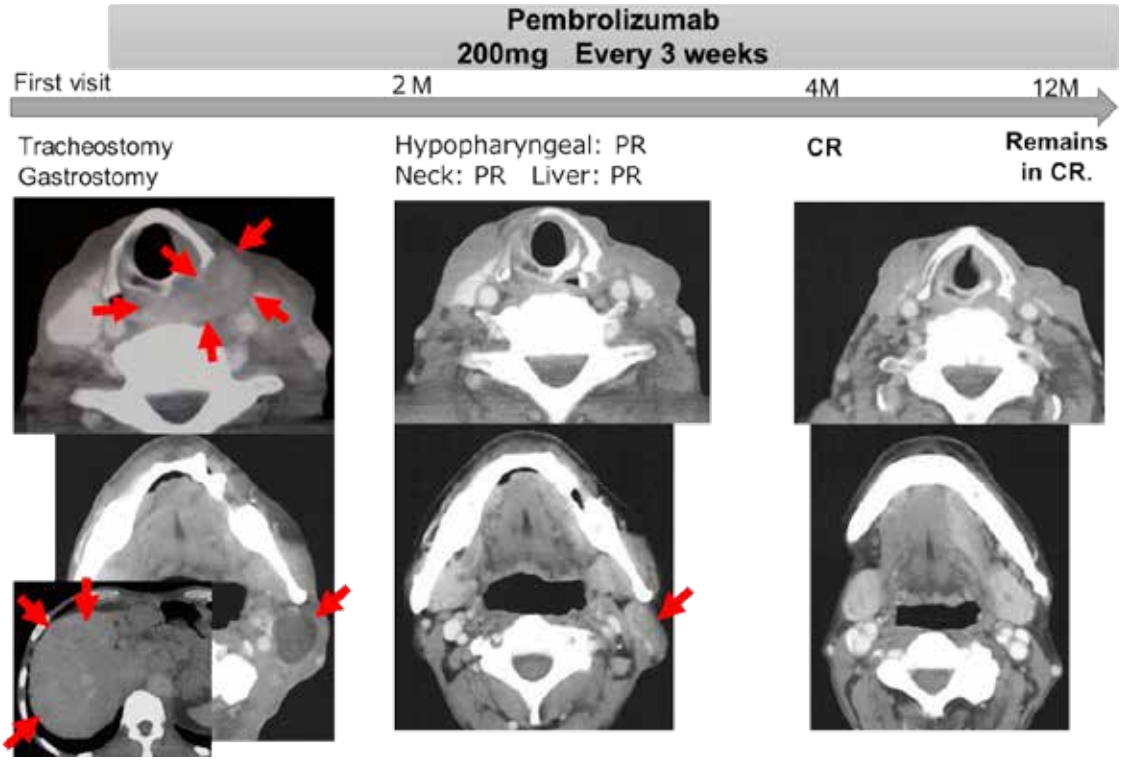

Fig. 6 A 76-year-old man with hypopharyngeal carcinoma (cT4aN2bM1: liver) CPS = 70. Four months after the pembrolizumab administration, the patient was still in CR.

Case presentation

Case 1: 76-year-old man with the hypopharyngeal cancer (cT4aN2bM1: liver) CPS = 70 (Fig. 6)

After performing tracheostomy and gastrostomy for hypopharyngeal cancer (cT4aN2bM1: liver), pembrolizumab was introduced. A computed tomography (CT) scan at two months after the introduction of pembrolizumab showed a PR of the primary tumor, cervical lymph node metastasis, and liver metastasis.

Pembrolizumab was continued, and after four months, a CT scan showed a CR of the primary tumor, cervical lymph nodes, and liver metastases. The patient remained in CR at 12 months of treatment and was still receiving pembrolizumab. The CPS of primary tumor biopsied before treatment was 70.

Case 2: 77-year-old man with laryngeal cancer (cT1bN0M0, rT0N3bM0) CPS ≥ 100

The patient had undergone radiation therapy alone for laryngeal cancer (glottis cT1bN0M0) and CR was achieved. Eleven years later he developed cervical lymph node metastasis and underwent neck dissection and pectoralis major flap reconstruction (rT0N3bM0). However, regional relapse occurred four months postoperatively. We indicated pembrolizumab as first line therapy. The patient had a fever of 39°C immediately after the first dose of pembrolizumab, and blood examination showed high levels of leukocytes (40,500/ μL) and CRP 9. He recovered with an antipyretic agent. The pembrolizumab treatment was repeated. However the patient requested to discontinue the treatment after two courses, so it was terminated. A CT scan after six months of pembrolizumab treatment showed CR. The patient remained in CR and was

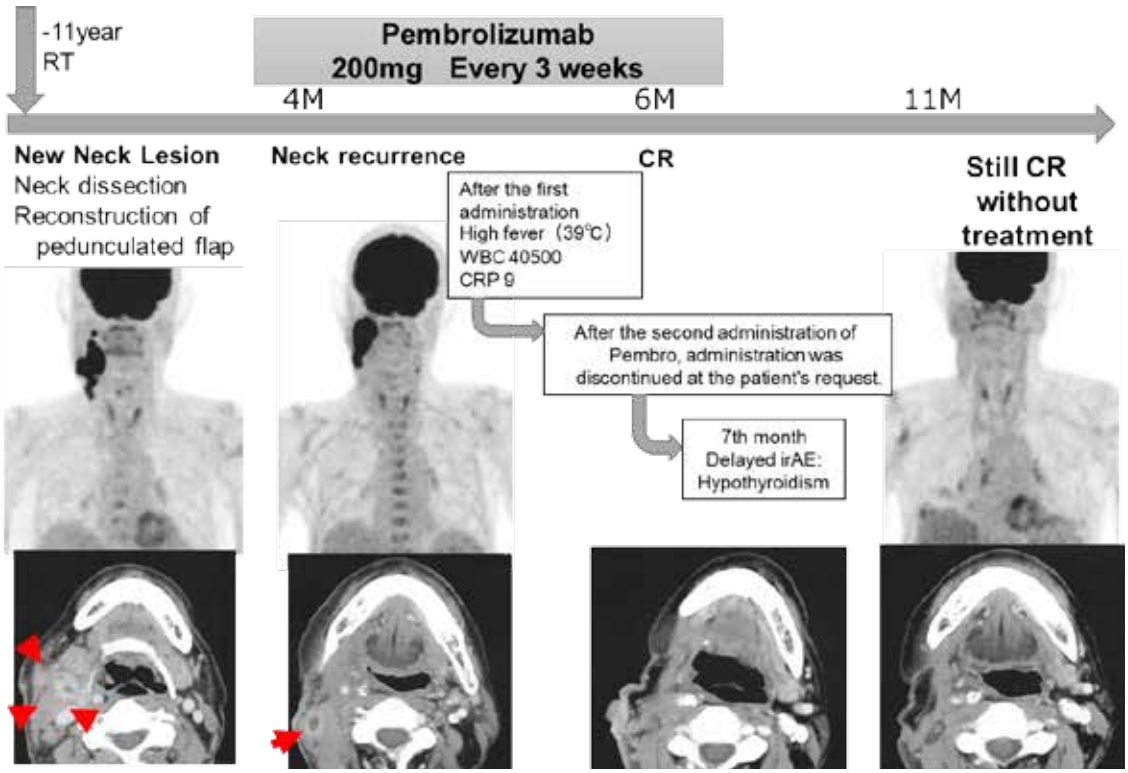

Fig. 7 A 77-year-old man with laryngeal cancer (cT1bN0M0, rT0N3bM0) CPS ≥ 100. The patient had a high fever and high white blood cell count after the first dose of pembrolizumab, and pembrolizumab was discontinued after two doses. The patient remained in CR.

currently on treatment-free follow-up 1year after the end of the treatment. The CPS of the neck dissection specimen was over 100.

DISCUSSION

In head and neck squamous cell carcinoma, the response rate of ICIs that target programmed cell death-1 (PD-1), including nivolumab, was about 15%–20% [3–5]. From the perspective of healthcare costs and side effects, predicting the response is important to determine their efficacy. Predictors of response to ICI have been reported to include PD-L1 expression rate (TPS; Tumor Proportion Score, CPS; Combined Positive Score) and the amount of regulatory T cells (Treg) present in the tumor [6]. Recently, the usefulness of peripheral blood neutrophil-to-lymphocyte ratio (NLR) as a prognostic factor in carcinomas, such as lung cancer and gastric cancer, has also been reported [7–9].

In the Keynote 048 study [8], CPS was useful as a complementary diagnosis in pembrolizumab: in patients with CPS < 1, pembrolizumab alone was inferior to Cmab + 5-FU + CDDP/CBDCA (EXTREME regimen [10]) in terms of OS and PFS. In these patients, pembrolizumab + 5-FU + CDDP/CBDCA pembrolizumab + FP) is recommended. In patients with 1 ≤ CPS < 20, pembrolizumab alone is recommended over pembrolizumab + FP for safety reasons, including AEs. In this study, there were four patients with CPS < 1, who were all considered for pembrolizumab + FP but were treated with pembrolizumab alone. Pembrolizumab + FP was not indicated because of the patients' request for outpatient treatment, inadequate renal function, or complications from other organ diseases. Their OS and PFS tended to be significantly lower than in patients with 1 ≤ CPS (Fig. 4, 5). These patients should be considered for pembrolizumab + FP or other chemotherapeutic options, such as the EXTREME [10] or paclitaxel, carboplatin, and cetuximab (PCE) regimens [11–12], including Cmab. In patients with 1 ≤ CPS < 20, all five patients received pembrolizumab alone, with OS and PFS comparable to those in the 20 ≤ CPS group. This may suggest that CPS-positive patients (1 ≤ CPS) respond to pembrolizumab regardless of its value.

It has been suggested that there is a correlation between PS and the efficacy of ICI at the start of the treatment [13]. In this study, the OS was better than that in the Keynote 048 study (Table 1, 2). The fact that all patients in this study had a good PS (PS0) may have contributed to better outcomes.

Additionally, this study showed a trend toward better OS and PFS than nivolumab-treated patients in our department [13]. Most patients treated with nivolumab for head and neck cancer were platinum-resistant and received (radiotherapy) within six months. Conversely, only patients without prior chemotherapy were treated with pembrolizumab in this study, which might have some influence on the results. Although a simple comparison cannot be made because of different patient backgrounds, the use of ICI as the first-line treatment may lead to a higher response, and further studies are needed.

The incidence of irAEs regardless of carcinoma was reported to be about 40%, of which Grade 3 and Grade 4 IRAEs were 9%–14%. OS and PFS were favorable in groups wherein irAEs occurred [14–17]. Although irAEs of pembrolizumab were more

common in the pembrolizumab + chemo group, in this study, the incidence of irAEs in all grades and Grade 3/Grade 4 was 15% (three cases) and 5% (one case), respectively, which were less than what was previously reported. The fact that all patients in this study were treated with pembrolizumab alone may have influenced the results. Further investigations on the relationship between CPS and irAEs are warranted.

In case 2, the initial reaction (fever, elevated white blood cell count, and high inflammatory response) could have been an irAE, tumor lysis syndrome, or cytokine storm, but the pathological background was unclear because of subjective symptoms and blood data improved and normalized with supplementation alone.

In this study, the effect of pembrolizumab on the response of patients with ICI to chemotherapy was investigated. OS and PFS of CPS-positive patients (CPS ≥ 1) were significantly better than those of CPS-negative patients (CPS < 1). Future studies are needed to investigate the use of pembrolizumab followed by salvage chemotherapy.

METHODOLOGICAL CONSIDERATIONS / LIMITATIONS

Limitations of this study include the small number of cases studied and the short follow-up period. Further study with increased case numbers is needed to elucidate the prognostic factor of the ICI treatment. Although the efficacy of salvage chemotherapy after pembrolizumab could not be well discussed in this study, the efficacy of PTX or PTX + Cmab as salvage chemotherapy for nivolumab has been reported [12, 16]. The indication of salvage chemotherapy after ICI will be also investigated in the future.

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Declaration of interest

No potential competing interest was reported by the authors.

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