Original article

For which lung cancer patients is re-administration of immune checkpoint inhibitors effective?

Takanobu Sasaki[1, 3], Toshiharu Tabata[1], and Naruo Yoshimura[2]

[1]Department of Thoracic Surgery, Tohoku Medical and Pharmaceutical University, Japan
[2]Department of Respirology, Tohoku Medical and Pharmaceutical University, Japan
[3]Department of Public Health, Graduate School of Medicine, Tohoku University, Japan

Abstract

Objective: Currently, immune checkpoint inhibitors (ICIs) play a central role in the treatment of lung cancer. However, ICI re-administration is still uncommon, and its utility should be evaluated as early as possible.

Patients and Methods: Twenty-five patients who received ICIs twice or more in any of the drug treatment lines for advanced/relapsed non-small cell lung cancer were included. OS, PFS, ORR, and DCR were examined, and factors such as age, sex, histopathological type, PD-L1 expression, whether radical surgery was performed, driver gene mutations, and immune-related adverse events (irAEs), were evaluated for their relevance and as prognostic factors.

Results: Of the 25 patients, 17 were men and 8 were women, with an average age of 68 ± 8.4 (range, 48–85 years), and histology was non-squamous cell carcinoma/squamous cell carcinoma in 19/6 cases. One driver gene mutation positive case was included. PD-L1 TPS was $\geq50\%/1$–49%/0–1%/ unknown in 7/8/5/5 cases. The first ICI administered was pembrolizumab/nivolumab/atezolizumab in 5/13/7 cases. The median number of courses was 9 (range, 1–52) months, and the median PFS was 9 (95% CI, 6.0–12.0) months. Cytotoxic chemotherapy or radiation therapy was administered to 6 patients during the interval up to re-administration. The second ICI administered was pembrolizumab/nivolumab/atezolizumab in 5/8/12 cases, and all patients received antibody drugs different from those given as the first ICI. The median number of courses was 5 (range, 1–24), and the median PFS was 3 months (95% CI, 1.0–5.0) months. In 5 of the 6 patients (24%) who achieved PFS of 6 months or longer after re-administration, the order of administration was anti-PD-1 antibody to anti-PD-L1 antibody.

Conclusion: The effect of re-administration is limited, but it may be effective depending on the type of cases and the order of ICI administration. Further studies are required to verify its effectiveness.

Key words: lung cancer, immune checkpoint inhibitors, re-administration

Introduction

In the latest Japanese lung cancer clinical practice guidelines 2020 edition, monotherapy with an immune checkpoint inhibitor (ICI), or combination therapy with cytotoxic chemotherapy, is recommended as the first-line of treatment for advanced/recurrent non-small cell lung cancer (driver gene mutations negative), and is recommended as a standard treatment because of its effect. However, there are few reports on the efficacy and safety of ICI re-administration, especially re-administration after an immune-related adverse event (irAE), and re-administration itself is not common in clinical practice at present. Thus, re-administration should be evaluated as early as possible as a potential line of treatment.

Patients and Methods

Patients

Immune checkpoint inhibitors were administered twice or more (as a line of treatment) at Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan), for advanced/recurrent non-small cell lung cancer (NSCLC) be-

tween February 2016 and March 2020 in 25 cases.

Methods

The following data were retrospectively examined: patient background, including age, sex, histology, driver gene mutations, PD-L1 tumor proportion score (TPS), stage, whether radical surgery was performed, treatment before ICI administration (irradiation and cytotoxic chemotherapy), type of ICI administered, sequence of ICI administration, number of courses, interval treatment; and therapeutic effects, including overall response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and immune-related adverse events (irAEs).

The TNM staging system was used according to the 8th edition of the Lung Cancer Handling Regulations of the Japan Lung Cancer Society. PD-L1 TPS (22C3), a driver gene mutation test for lung cancer specimens, was performed by SRL. The response to treatment was evaluated using RE-CIST v1.1. Adverse events associated with drug treatment were evaluated using CTCAE v5.0.

Statistical analysis

The statistical software used was JMP v14.2. Statistical significance was set at $P<0.05$. PFS and OS were estimated using the Kaplan-Meier method, and differences between groups were tested using the log-rank test. A Cox proportional hazards model was used for multivariate analysis. OS started from the time when the initial ICI was administered. In this study, the first ICI was called the 1st ICI, and the re-administered ICI was called the 2nd ICI. PFS after the start of 1st ICI administration was defined as 1st PFS, and PFS after the start of 2nd ICI administration was defined as 2nd PFS.

Ethical considerations

This study was approved by the institutional review board of Tohoku Medical and Pharmaceutical University Hospital (approval number: 2021-2-062).

Results

Table 1 shows the characteristics and background of the study population. The age was 68 ± 8.4 (range, 48–85 years), the male-female ratio was 17/8, the histological type was non-SQ/SQ in 19/6 cases, respectively, and stage III/IV/postoperative recurrence was seen in 5/6/14 cases, respectively. One case of driver gene mutation was included. PD-L1 TPS was ≥50%/1–49%/0–1%/unknown in 7/8/5/5 cases, respectively (median TPS 20%).

The treatment results are shown in Table 2 and Figures

Table 1 Patients characteristics and backgrounds

N	25
Age (mean ± SD, years)	68 ± 8.4 (48–85)
Gender (male/female), n (%)	17 (68)/8 (32)
Histology (NonSQ/SQ), n (%)	19 (76)/6 (24)
Stage, n (%)	III/IV/Postoperative recurrence = 5 (20)/6 (24)/14 (56)
Driver gene mutations, n (%)	1 (4)
PD-L1 TPS (22C3), n (%)	≥50%/1–49%/<1%/not evaluated = 7 (28)/8 (32)/5 (20)/5 (20)

Table 2 Treatment results

Prior chemotherapy or irradiation before ICIs, n (%) (Exclude adjuvant chemotherapy)	11 (44)
First ICIs	
Pmab/Nivo/Atezo, n (%)	5 (20)/13 (52)/7 (28)
Course	Median 9 (range: 1–52)
irAE, n (%)	6 (24)
ORR/DCR (%)	32/64
1st PFS (month)	Median 9 (95% CI: 3.0–15.0)
Interval treatment, n (%)	5 (20)
Second ICIs	
Pmab/Nivo/Atezo, n (%)	5 (20)/8 (32)/12 (48)
Course	Median 5 (range: 1–24)
irAE, n (%)	3 (12)
ORR/DCR (%)	8/36
2nd PFS (month)	Median 3 (95% CI: 1.0–5.0)

1–3. The three-year OS was 28%, and the MST was 27 months for the entire population (n=25) from the start of 1st ICI (Figure 1). The one-year OS was 36.9%, and the MST was 9 months from the time of 2nd ICI administration (Figure 2). Treatment before 1st ICI administration (cytotoxic chemotherapy or irradiation, except adjuvant chemotherapy) was administered to 11 patients. Administration up to 3rd ICI was performed in 2 patients. The median follow-up period was 18 months (range, 4.0–41 months).

The 1st ICI was Pmab/Nivo/Atezo in 5 (20%)/13 (52%)/7 (28%) cases, respectively, and the number of courses performed was 1–52 (median, 9). There were 6 cases of irAEs (24%). ORR/DCR was 32/64 (%), and the median PFS was 9 months (95% CI, 3–15 months) (Figure 3). The irAEs were renal disorder in 1 case, rash in 3 cases, hepatitis/sclerosing cholangitis in 1 case, and peripheral neuropathy in 1 case. Grade 1/2/3 irAEs were seen in 4/1/1 cases, respectively, and irAE interruption was seen in 1 case (renal disorder).
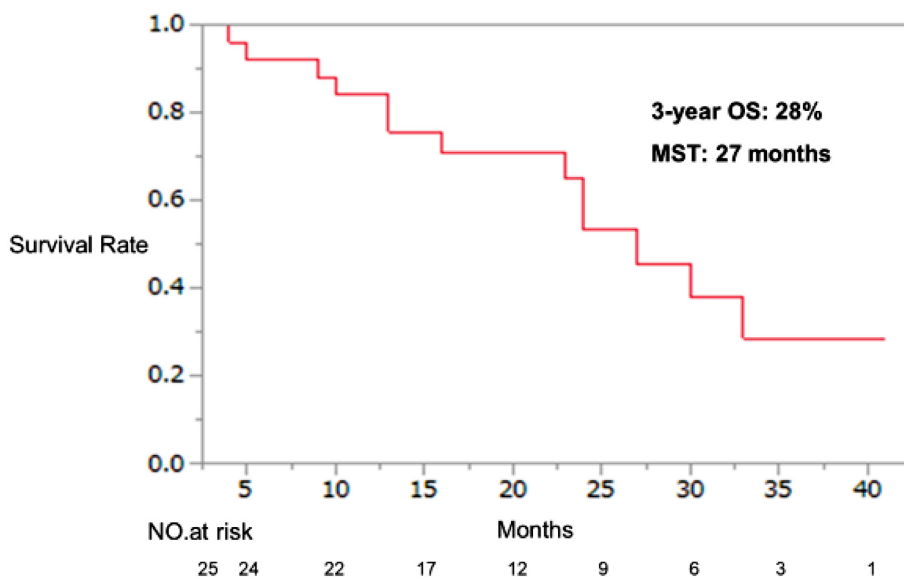

Figure 1 Kaplan-Meier curves of OS from the time of 1st ICI administration. 3-year OS: 28%, MST: 27 months. The median follow up period was 18 (4.0–41) months.
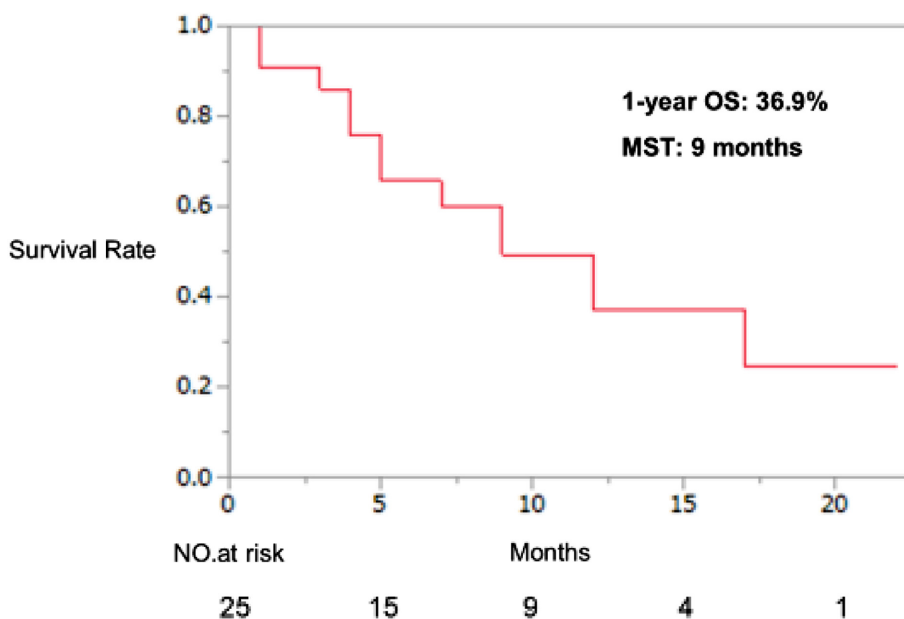

Figure 2 Kaplan-Meier curves of OS from the time of the 2nd ICI administration. 1-year OS: 36.9%, MST: 9 months. The median follow up period was 5 (0–22) months.
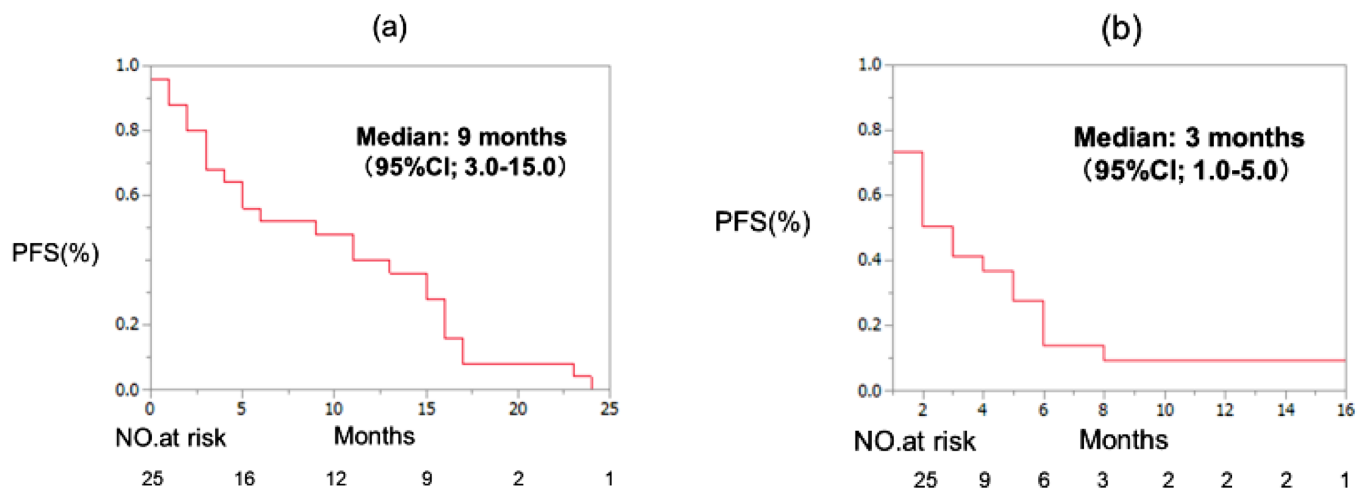
Figure 3 Kaplan-Meier curves of 1st PFS(a) and 2nd PFS(b).

Five patients (20%) underwent some kind of treatment (cytotoxic chemotherapy or irradiation) in the interval between administration and re-administration, with EGFR-TKI in 1 case, cytotoxic chemotherapy in 4 cases, and irradiation in 4 cases.

The 2nd ICI was Pmab/Nivo/Atezo in 5 (20%)/8 (32%)/12 (48%) cases, respectively, and the number of courses performed was 1–24 (median, 5). An irAE was observed in 3 cases (12%). One of these three patients experienced irAEs even after the first dose. ORR/DCR was 8%/36%, and median PFS was 3 months (95% CI 1.0–5.0 months) (Figure 3). The breakdown of irAEs was pancreatitis/retroperitoneal fibrosis in 1 case, rash in 1 case, and anemia in 1 case. Grade 1/2/3 irAEs were seen in 1/1/1 cases, respectively, and irAE interruption occurred in 1 case (pancreatitis).

In the present study, 2nd PFS after ICI re-administration was 6 months or more in 6 patients. The characteristics of the participants are presented in Table 3. Adenocarcinoma was the most common (83%) type of histology, and driver gene mutations were not observed in any cases. The median PD-L1 TPS was relatively high (55%), and all patients received cytotoxic chemotherapy before 1st ICI administration. ICIs were administered in the order of anti-PD-1 antibody to anti-PD-L1 antibody in 5 cases (83%), and irAEs were observed in 2 cases (33%); interval treatment was not performed in any cases.

Table 4 shows the results of multivariate analysis (Cox proportional hazards). Stage III–IV was identified as a significant factor associated with poor prognosis affecting OS. No significant prognostic factors affecting 1st/2nd PFS were identified.

Table 5 shows a comparison of the treatment results by the order of ICI administration. The distribution in the order of administration was anti PD-1 Ab to anti PD-1 Ab/anti PD-1 Ab to anti PD-L1 Ab/anti PD-L1 Ab to anti PD-1 Ab

Table 3 Characteristics of 6 cases with PFS ≥ 6 months after 2nd ICI administration

1	5 cases of adenocarcinoma, 1 case of squamous cell carcinoma
2	No driver gene mutations in all cases
3	Median PD-L1 TPS was 55%
4	All cases received Chemotherapy before ICI administration
5	Anti PD-1 Ab to Anti PD-L1 Ab of 5 cases
6	irAE: 2 cases
7	No interval treatment in all cases

in 6/12/7 cases, respectively. Although there was no statistically significant difference in the order of administration in OS and 1st/2nd PFS, the order of administration of PD-1 to PD-L1 Ab showed the best results.

Discussion

A combination of immune checkpoint inhibitors (ICIs) with monotherapy or cytotoxic chemotherapy is recommended as the first choice for the treatment of driver gene mutations/translocation-negative cases in the Japanese lung cancer clinical guidelines. Its effectiveness has often been reported in clinical practice, and numerous clinical trials are underway to further expand its indications, such as induction chemotherapy or adjuvant chemotherapy. However, there is no information on the effectiveness of ICI re-administration, which is an issue at present, and it is not recommended in the guidelines. The results of the present study were compared with those in the published literature on the efficacy and safety of re-administration.

In the present study, the 3-year OS was 28%, and the MST was 27 months starting from the time of 1st ICI administration (Figure 1, Table 2). In case of re-administration in Japan, Kitagawa *et al.*[1] reported that the median OS was

Table 4 Univariate analysis and cox proportional hazards for OS and 1st/2nd PFS

	Variable	Univariate analysis	Multivariate analysis	
		P value	*P* value	HR (95% CI)
OS	Squamous histology	0.77	0.19	0.23 (0.03–2.06)
	Driver mutations negative	0.87	0.8	0.75 (0.08–7.22)
	After surgery recurrence	0.07	0.34	0.49 (0.11–2.1)
	irAE positive	0.8	0.27	0.35 (0.06–2.24)
	anti PD-1 Ab→anti PD-L1 Ab	0.07	0.03	0.68 (0.008–0.76)
1st PFS	Non-squamous histology	0.37	0.93	0.94 (0.28-3.15)
	Driver mutations negative	0.61	0.3	0.31 (0.04-2.74)
	After surgery recurrence	0.13	0.37	0.61 (0.21-1.79)
	irAE positive	0.34	0.94	0.96 (0.34-2.77)
	anti PD-1 Ab (1st ICI)	0.01	0.04	0.3 (0.1-0.95)
2nd PFS	Squamous histology	0.1	0.27	0.44 (0.1-1.91)
	Driver mutations negative	0.53	0.27	0.28 (0.03-2.72)
	After surgery recurrence	0.06	0.3	0.55 (0.17-1.71)
	irAE positive	0.1	0.12	0.2 (0.03-1.48)
	anti PD-1 Ab→anti PD-L1 Ab	0.36	0.06	0.17 (0.03-1.1)

Table 5 Treatment results regarding the order of administration of antibody drugs

Order of administration	n	%	OS (median, months)	1st PFS (median, months)	2nd PFS (median, months)
anti PD-1 Ab→anti PD-1 Ab	6	24	24	4.5	4
anti PD-1 Ab→anti PD-L1 Ab	12	48	30	15.5	10
anti PD-L1 Ab→anti PD-1 Ab	7	28	13	3	6
P value			0.07	0.01	0.36

31 months from the initial ICI administration, which is similar to the present results. When OS was compared, it was better than the results of the existing chemotherapy phase III study[2] and not significantly inferior to the results of the ICI monotherapy clinical trial[3, 4].

Important issues for re-administration are response and PFS after 2nd ICI administration. In the present study, ORR/DCR was 8%/36%, 1-year-OS was 36.9%, MST was 9 months, and median PFS was 3.0 months after 2nd ICI administration. In a study involving rechallenge by Matteo *et al.*[5], MST was 14.8/–18.1 months after ICI resumption/rechallenge, which exceeds 12 months, and is better than the present results. The results after administration of the 2nd ICI in the report in Japan are different, from ORR/DCR = 0% ~27.2%/21.4% ~58.8%[1, 6–11], but the present results are also within this range. As for median PFS, domestic reports indicate about 1.6–4.0 months[1, 6–11], and although there are differences in the populations, the results are almost the same as in the present study; overall, PFS after re-administration is poor. Predictors that contribute to the outcomes of re-administration include continuous administration of initial nivolumab for 3 months or longer[5], interval treatment (cytotoxic chemotherapy or irradiation) between adminis-

tration and re-administration[11, 12], high PD-L1 expression (TPS ≥−80%)[6], development of irAEs during initial treatment[9], and short time to re-administration[9]. Poor PS and low BMI have been reported as negative predictors of re-administration[10]. In the present study, multivariate analysis for OS showed that Stage III–IV was a significant factor associated with a poor prognosis. This is thought to be because the tumor volume in postoperative recurrent lung cancer is smaller than that in advanced lung cancer. However, the number of cases was small, and the results lacked reliability.

PD-L1 TPS, microsatellite instability (MSI), and tumor mutation burden (TMB) are typical biomarkers for predicting the effect of immunotherapy in lung cancer, and tumor-infiltrating immune cells, which were used as a predictor of the effect of atezolizumab in the IM power/OAK study, are also known to be ICs. Based on KEYNOTE-158 data[14], the FDA approved Pmab monotherapy for a subgroup of patients with solid tumors with TMB ≥10 mut/Mb that were refractory, and had no alternative treatment options (not approved in Japan). High TMB and a T-cell-inflamed gene expression profile in the KEYNOTE-028 population is expected to be successful[15]. Interestingly, the response rate to atezolizumab, which is an anti-PD-L1 antibody, was high-

er due to the expression of PD-L2 at the same time as the expression of PD-L1 in the tumor in solid cancers, including NSCLC[16]. Gene mutations such as STK11 and KEAP1 have been reported as prognostic biomarkers for anti-PD-1/anti-PD-L1 therapy[17], and DDR gene mutations have been administered with PD-1/PD-L1 blockade in urothelial cancers[18]. It is expected that new biomarkers that can be applied in clinical practice will be identified in the future.

When considering re-administration, the following issues must be factored in.

Order of ICI administration

In the present study, the best results were obtained with the order of administration of anti PD-1 Ab to anti PD-L1 Ab (Table 5), and the same was true for the 6 patients who obtained 2nd PFS of 6 months or longer (Table 3). Kitagawa *et al.*[1] also reported that switching between ICIs on re-administration is more effective. It seems that factors such as the mechanism of action of antibody drugs, change (decrease) in PD-L1 TPS, and upregulation of suppressive immune checkpoint molecules, are intricately intertwined. To the best of our knowledge, the optimal dosing order is not specified in the literature, and it is difficult to recommend the optimal dosing order of antibodies in all cases.

Is it better to do interval treatment before 2nd ICI?

Multiple studies have stated that re-administration results are better if cytotoxic chemotherapy or irradiation is inserted in the interval between administration and re-administration[11, 12]. Possible reasons include increased antigen presentation due to the destruction of tumor cells, and increased therapeutic sensitivity for ICIs due to radiation therapy. The abscopal effect[19] due to irradiation may also be expected. In this regard, the present study yielded the opposite result. The reason is that cytotoxic chemotherapy was not administered in the interval, ICI was re-administered at a relatively early stage, and PS was maintained, which contributed to better outcomes. Based on the above findings, although the interval treatment can be expected to improve treatment sensitivity during re-administration, it cannot be unconditionally recommended due to negative aspects, such as decreased PS, bone marrow exhaustion, and drug resistance.

If an irAE appears during the 1st ICI administration, is re-administration acceptable?

There is a concern that irAEs could reappear during re-administration. It is known that the complication of irAEs and the response to ICIs are correlated. As mentioned above, the results of re-administration are better when an irAE occurs at the time of initial ICI administration[9]. Re-administration can be especially considered for cases where the ini-

tial ICI was successful, but was interrupted due to an irAE. Whether re-administration is possible depends on the grade and type of irAE, and if serious complications such as ILD occur, it is difficult to continue even if the initial ICI was successful. In contrast, ICI administration can be continued with symptomatic treatment for grade 1–2 rash and endocrine dysfunction. IrAEs such as pituitary dysfunction and adrenal insufficiency may be difficult to notice, and appropriate irAE management is required to improve tolerability. In the report by Charles *et al.*[13], the irAE recurrence rate after re-administration following an initial irAE was 28.8%, and ICI re-administration should be considered carefully, considering the risks and benefits. Based on the above observations, re-administration may be considered depending on the degree and type of irAE. The mechanism by which resistance to ICIs develops is complex. There could be a deficiency or decrease in the ability to present tumor antigens, with many T cells accumulated around the tumor expressing excessive immune checkpoint molecules, such as PD-1 and TIM3, and not getting reactivated even if an ICI is administered. Consequently, the effect of immunotherapy could be significantly impaired. The detailed mechanism is described by Adam *et al*[20]. With each addition of treatment lines, PS decreases, nutritional status deteriorates, effector T cells decrease, function declines, and drug resistance increases. The poor results of re-administration, including in the present study, are due to the difficulty of overcoming resistance by re-administration with anti-PD-1/PD-L1 Ab.

At the time of this study, ICI re-administration was not universally recommended. As in the previous report (in Japan), since the number of cases was small, it was not possible to discuss the advantages and disadvantages of general re-administration. Until consensus is reached, there is no choice but to judge the indication by considering the performance status and age of each patient, the degree of lung cancer progression, PD-L1 TPS, etc., on a case-by-case basis. In future, it will be necessary to determine for which type of patients re-administration is effective through clinical trials. Multiple re-administration clinical trials (WJOG 9616L, NJLCG 1901) are underway in Japan, and the results are awaited.

Study limitations

1. This was a retrospective, and not a prospective study, conducted at just one facility.
2. Conditions such as the presence or absence of treatment before ICI administration and PD-L1 TPS in the patient population were uneven, as were the orders of ICI administration (types).
3. Since the total number of cases was small (n=25), and the number of those for whom ICI re-administration was effective was also small (n=6), reliability cannot be guaranteed even if the conditions for success are specified.

Conclusion

The effect of ICI re-administration on lung cancer is limited, but it may be effective in certain cases. When considering re-administration, it appears to be better to conduct it at the earliest possible treatment line when performance status has not deteriorated.

Conflict of interest: The authors declare no conflict of interest.

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