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ORIGINAL ARTICLE

Switching administration of anti-PD-1 and anti-PD-L1 antibodies as immune checkpoint inhibitor rechallenge in individuals with advanced non-small cell lung cancer: Case series and literature review

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Keywords
Immune checkpoint inhibitor; non-small cell lung cancer; prognosis; rechallenge.

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Abstract

Background: Based on several phase III studies, immune checkpoint inhibitors (ICIs) are essential and promising drugs for the treatment of non-small cell lung cancer (NSCLC). However, in patients previously treated with ICI, the efficacy and safety of rechallenging the same or another type of ICI inhibitor remain unclear. Moreover, clinical data about the efficacy of switching the administration of anti-programmed death-1 (PD-1) antibodies (e.g. nivolumab, pembrolizumab) and anti-programmed death-ligand 1 (PD-L1) antibodies (e.g. atezolizumab) as ICI rechallenge are limited. Thus, the current study aimed to evaluate the efficacy and safety of such treatment strategy in NSCLC patients.

Methods: We retrospectively reviewed the medical records of 17 patients with advanced or recurrent NSCLC who received both anti-PD-1 and anti-PD-L1 antibodies during their clinical courses.

Results: Among the 17 patients, one (5.9%) and nine (52.9%) achieved partial response and stable disease, respectively, after ICI rechallenge. The median progression-free survival of ICI rechallenge in these patients was 4.0 (range: 0.4–8.0) months, and the median overall survival from the start of the initial ICI was 31.0 (range: 7.6–46.8) months. Of the 10 patients who developed immune-related adverse events (irAEs) during the first ICI treatment, five presented with these events after the readministration of ICI. Among them, four experienced relapsed irAEs and two patients had pneumonitis, which is a grade 3 or higher irAE. Almost all irAEs during the rechallenge treatment were manageable.

Conclusions: Switching the administration of anti-PD-1 and anti-PD-L1 antibodies as ICI rechallenge could be a treatment option for some NSCLC patients.

Key points

• **Significant findings of the study:** In this study, switching the administration of anti-PD-1 and anti-PD-L1 antibodies as ICI rechallenge could be an effective and safe treatment option for some patients with advanced or recurrent NSCLC.

• **What this study adds:** Switching the administration of ICI may increase the efficacy of readministration. However, the mechanism is unknown. Thus, further accumulation of cases is required, and extensive investigations must be conducted to elucidate the mechanism and benefits of such treatment.

Introduction

The use of immune checkpoint inhibitor (ICI), including anti-programmed death-1 (PD-1) antibody and anti-programmed death-ligand 1 (PD-L1) antibody, has been approved for the treatment of unresectable advanced or recurrent non-small cell lung cancer (NSCLC). Several phase III trials[1–4] have shown the clinical and long-term effects of these agents compared with docetaxel, which is the standard of care in second-line therapy. Furthermore, the KEYNOTE 024[5] and 042[6] trials revealed that patients who received pembrolizumab had a longer survival than those who received platinum doublet chemotherapy as first-line treatment. More recently, several phase III trials have shown that combined ICI and platinum doublet chemotherapy is superior to chemotherapy alone.[7–10]

Under such conditions, the proportion of patients with advanced NSCLC who receive ICI as the first- or early-line treatment is increasing. Although some patients who received ICI achieve a long-term response, disease progression cannot be avoided in most cases. Thus, later lines of treatment are required. Furthermore, immune-related adverse events (irAEs), which occur in approximately 20%–30% of patients, are the leading adverse events correlated to ICI. Approximately 10% of patients present with grade 3 or higher irAEs. Thus, clinicians require the discontinuation of ICI in these patients. Although the resolution of irAEs is achieved with corticosteroid treatment in most cases, the readministration of ICI is often challenging considering the risk of irAE relapse. At present, cytotoxic chemotherapy is the standard treatment for advanced NSCLC after treatment failure with ICI.

Nonetheless, the efficacy and safety of ICI rechallenge in such conditions remain unclear. Several case series and case reports about ICI rechallenge have been published.[11–17] However, in most cases, the ICI used for rechallenge was either the same ICI administered previously or another anti-PD-1 antibody (nivolumab to pembrolizumab or pembrolizumab to nivolumab). Clinical data about the efficacy of switching from anti-PD-1 antibody (nivolumab or pembrolizumab) to anti-PD-L1 antibody (atezolizumab) as ICI rechallenge are still limited. Thus, the current study aimed to evaluate the efficacy and safety of such treatment strategy in patients with advanced or recurrent NSCLC.

Methods

We retrospectively reviewed the medical records of 17 patients with advanced or recurrent NSCLC whose treatment was switched from anti-PD-1 to anti-PD-L1 antibodies as ICI rechallenge between April 2018 and September 2019 at our institution. The inclusion criteria were as follows: (i) patients with histologically or cytologically confirmed unresectable advanced (stage III or IV) or recurrent NSCLC; and (ii) those who received both anti-PD-1 antibody (nivolumab or pembrolizumab) and anti-PD-L1 antibody (atezolizumab) in their clinical courses, irrespective of the lines or sequence of treatment. In addition, the baseline characteristics of the patients, such as sex, age,

Table 1 Characteristics of the patients (n = 17)

Characteristics	
Age, years	
Median (range)	69 (55–79)
Age group, n (%)	
<75	13 (76.4)
≥75	4 (23.6)
Sex, n (%)	
Female	6 (35.3)
Smoking status, n (%)	
Brinkman index score < 400	4 (23.6)
Brinkman index score ≥ 400	13 (76.4)
ECOG-PS score, n (%)	
0–1	14 (82.4)
2	3 (17.6)
≥3	0 (0.0)
Histological subtypes, n (%)	
Adenocarcinoma	13 (76.4)
Squamous cell carcinoma	2 (11.8)
NSCLC, NOS	2 (11.8)
Others	0 (0.0)
Staging, n (%)	
III	1 (5.9)
IV	12 (70.5)
Recurrence	4 (23.6)
PD-L1 expression, n (%)	
<1%	5 (29.4)
1%–49%	4 (23.5)
≥50%	3 (17.7)
Unknown	5 (29.4)
EGFR mutation status, n (%)	
Positive	1 (5.9)
Negative/unknown	16 (94.1)
Alb level, g/dL	
Median (IQR)	3.6 (3.1, 3.9)
LDH level, U/L	
Median (IQR)	209 (180, 250)
CRP level, mg/dL	
Median (IQR)	0.68 (0.275, 2.06)
NLR	
Median (IQR)	3.68 (2.46, 6.37)
Use of anti-PD-1 antibody, n (%)	
Prior to anti-PD-L1 antibody	15 (88.2)
After anti-PD-L1 antibody	5 (29.4)

Alb, albumin; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; EGFR, epidermal growth factor receptor; IQR, interquartile range; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Table 2 Clinical course of the patients treated with both anti-PD-1 and anti-PD-L1 antibodies (n = 17)

		First ICI				Second ICI				Third ICI			
Cases	OS (months)	Type of antibody	Lines of therapy	Best response	PFS (months)	Type of antibody	Lines of therapy	Best response	PFS (months)	Type of antibody	Lines of therapy	Best response	PFS (months)
1	7.6	Anti-PD-L1	2	PD	0.7	Anti-PD-1	6	PD	1.8				
2	11.5	Anti-PD-L1	2	PD	2.1	Anti-PD-1	4	SD	4.8				
3	16.3	Anti-PD-1	2	SD	5.5	Anti-PD-L1	3	SD	7.8				
4	25.4	Anti-PD-1	1	SD	6.8	Anti-PD-L1	3	SD	3.7	Anti-PD-1	6	PD	1.8
5	16.1	Anti-PD-1	2	SD	7.5	Anti-PD-L1	4	SD	6.3				
6	31.2	Anti-PD-1	4	SD	7.8	Anti-PD-L1	7	PD	1.7				
7	21.8	Anti-PD-1	2	PR	9.1	Anti-PD-L1	5	SD	4.9				
8	31.4	Anti-PD-1	2	SD	9.7	Anti-PD-L1	4	SD	8.0				
9	31.6	Anti-PD-1	2	PR	9.7	Anti-PD-L1	9	PD	1.7				
10	16.2	Anti-PD-1	1	PR	10.8	Anti-PD-L1	3	PD	0.4				
11	15.1	Anti-PD-1	1	SD	12.7	Anti-PD-L1	2	PD	1.3				
12	31.0	Anti-PD-1	3	PR	14.9	Anti-PD-L1	4	PD	1.4	Anti-PD-1	6	PD	3.7
13	34.1	Anti-PD-1	2	SD	16.1	Anti-PD-1	5	SD	6.7	Anti-PD-L1	6	PD	1.3
14	37.5	Anti-PD-1	4	PR	19.5	Anti-PD-L1	6	PD	2.0	Anti-PD-1	7	PD	1.8
15	35.4	Anti-PD-1	2	SD	25.1	Anti-PD-L1	3	PR	4.0				
16	39.6	Anti-PD-1	2	SD	31.3	Anti-PD-L1	3	SD	7.1				
17	46.8	Anti-PD-1	2	PR	34.9	Anti-PD-L1	3	SD	4.7				

ICI, immune checkpoint inhibitor; OS, overall survival; PD-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; programmed death-1; PS, progressive disease; SD, stable disease.

histological subtype, epidermal growth factor receptor mutation status, PD-L1 expression and staging (Union for International Cancer Control classification, eighth edition), Eastern Cooperative Oncology Group (ECOG)-Performance Status, serum albumin and lactate dehydrogenase levels, neutrophil-to-lymphocyte ratio, and history of preceding chemotherapy or radiotherapy were examined.

Responses to each ICI treatment were evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) was defined as the time from the start of each ICI therapy to the first documented disease progression or the date of death. Overall survival (OS) was defined as from the date of starting the first ICI therapy to the date of death, irrespective of the cause of death. Of note, patients who did not present with disease progression or who did not die at the time of the analysis were censored at the date of the last contact. Adverse drug reactions caused by each ICI therapy were monitored until the first documented disease progression or the date of death according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The highest-grade toxicities during each therapy were recorded.

The ethics committee of Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital approved the study protocol (approval number: 2480), and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

Results

Patient characteristics

A total of 17 patients (six women and 11 men) received both anti-PD-1 and anti-PD-L1 antibodies as rechallenge ICI during their clinical courses. The median age of the patients was 69 (range: 55–79) years. Based on the 8th edition of the TNM classification for lung cancer, one (5.9%), 12 (70.5%), and four (23.6%) patients presented with stage III, stage IV, and recurrent disease, respectively. Overall, 13 (76.4%) patients presented with adenocarcinoma, and two (11.8%) had squamous cell carcinoma. Regarding treatment sequence, 15 (88.2%) patients received anti-PD-1 antibody treatment prior to anti-PD-L1 antibody treatment, and five (29.4%) had the treatment after anti-PD-L1 antibody treatment. Four (23.5%) patients received both nivolumab and pembrolizumab. Among these patients, three received anti-PD-1 antibody treatment before and after anti-PD-L1 antibody treatment. Table 1 depicts the characteristics of the patients.

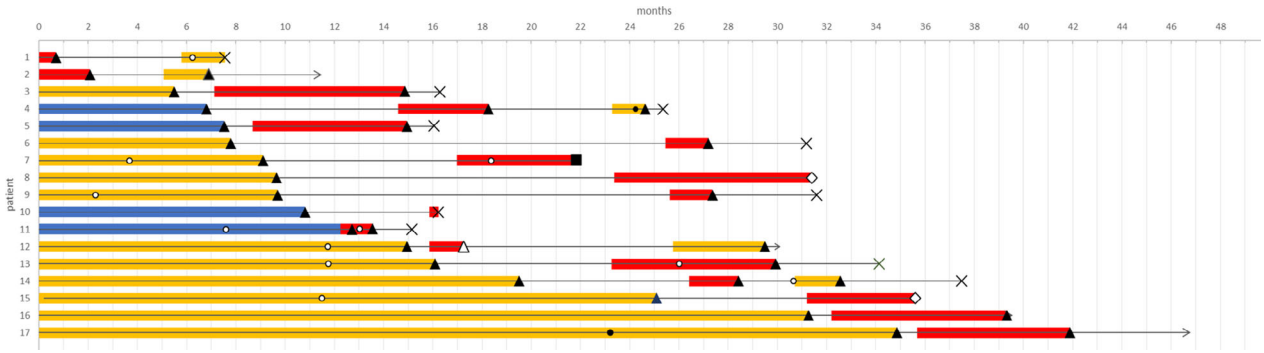

Figure 1 Swimmers plot showing the overall clinical course from the start of the initial ICI. Atezolizumab, Nivolumab, Pembrolizumab, ▲ PD, ✕ Death, → Alive, ◇ Ongoing ICI treatment, ○ ICI discontinuation due to irAE, and ● ICI discontinuation due to patient's choice.

Efficacy

Upon the initial ICI treatment, six (35.3%) patients achieved partial response (PR) and nine (52.9%) stable disease (SD) (Table 2). The median PFS was 9.7 (range: 0.7–34.9) years. The reasons for discontinuing treatment were progressive disease (PD) in 10 (58.9%) and irAEs in seven (41.1%) patients (Fig 1). During the second ICI treatment, one (5.9%) patient achieved PR and nine (52.9%) SD. The median PFS was 4.0 (range: 0.4–8.0) months. The reasons for discontinuing treatment were PD in 12 (70.6%) and irAEs in three (17.6%) patients. Two patients continually received the treatment until the end of the observation period. Of the 15 patients whose treatment was discontinued, four received a third ICI treatment. However, the best response was PD. The median OS of 17 patients who were rechallenged with ICI was 31.0 (range: 7.6–46.8) months.

Safety

During the first ICI treatment, the common grade 2 or higher irAEs were rash and hypothyroidism. IrAEs of grade 3 or higher were pneumonitis, cholangitis, and hypokalemia. In the second and subsequent ICI treatments, two patients had pneumonitis. Of the 10 patients who developed irAEs during the first ICI treatment, four experienced relapses of irAEs during the second ICI. One patient developed hypothyroidism during the first ICI treatment. Colitis was observed during the second ICI treatment, and it recurred during the third ICI treatment. One patient experienced relapse of diarrhea during the second and third ICI treatments. The relapsed irAEs included rash, hypothyroidism, pneumonitis, diarrhea, and infusion reaction. Pneumonitis was a grade 3 relapse. However, it improved with steroid treatment. Moreover, one patient with newly developed pneumonitis during the second ICI treatment died. Table 3 shows the summary of irAEs.

Table 3 Immune-related adverse events

	First ICI		Second ICI		Third ICI	
Grade	1/2	≥3	1/2	≥3	1/2	≥3
Rash	5	0	2	0	0	0
Hypothyroidism	3	0	1	0	0	0
Pneumonitis	1	1	0	2	0	0
Diarrhea/colitis	1	0	3	0	2	0
Infusion reaction	1	0	1	0	0	0
Cholangitis	0	1	0	0	0	0
Hypokalemia	0	1	0	0	0	0
Increased AST/ALT levels	1	0	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate transaminase; ICI, immune checkpoint inhibitor.

Discussion

In this study, 17 patients with unresectable advanced or recurrent NSCLC received sequential anti-PD-1 and anti-PD-L1 antibody treatments in their clinical courses. Several retrospective studies on ICI rechallenge have shown that may have some clinical benefits for some patients with advanced NSCLC (Table 4). However, only a small number of patients who have treated with both anti-PD-1 and anti-PD-L1 antibody were included in previous studies. Under such circumstances, data from our cohort in which all patients were switched between anti-PD-1/PD-L1 antibody treatment as ICI rechallenge ICI may have some implications for future treatment strategy for advanced NSCLC.

In terms of efficacy, 10 (58.8%) of 17 patients achieved PR or SD after the administration of different types of ICI ("switching administration"). In our cohort, ICI rechallenge was based on the discretion of the physician, who were more likely to select patients with long-term disease control by initial ICI treatment. The PFS of 15 (88.2%) patients was >six months for the initial ICI

Table 4 Prior reports about immune checkpoint inhibitor rechallenge in advanced non-small cell lung cancer

		First ICI				Second ICI			
Authors	N	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)	Type of antibody	ORR (%)	DCR (%)	Median PFS (months)
Fujita *et al.*[11]	12	Anti-PD-1	58.3	75	6.2	Anti-PD-1	8.3	41.7	3.1
Niki *et al.*[12]	11	Anti-PD-1	45.5	63.6	4.9	Anti-PD-1	27.2	45.5	2.7
Watanabe *et al.*[13]	14	Anti-PD-1/ PD-L1	21.4	57.1	3.7	Anti-PD-1	7.1	21.4	1.6
Fujita *et al.*[14]	18	Anti-PD-1	NA	NA	NA	Anti-PD-L1	0	38.9	1.7
Fujita *et al.*[15]	15	Anti-PD-L1	0.0	33.3	2.8, 6.0	Anti-PD-1	0	26.7	1.9, 2.8
Katayama *et al.*[16]	35	Anti-PD-1/ PD-L1	34.3	68.6	3.9	Anti-PD-1/ PD-L1	2.9	45.7	2.7
Current cases	17	Anti-PD-1/ PD-L1	35.0	88.2	9.7	Anti-PD-1/ PD-L1	5.9	58.8	4.0

DCR, disease control rate; ICI, immune checkpoint inhibitor; ORR, overall response rate; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

treatment. The initial effect of the ICI treatment tended to be better in patients with long-term PFS. Interestingly, of the nine patients who had SD during the initial ICI treatment, seven achieved PR or SD during ICI rechallenge. This may implicate that the favorable outcomes, including sustained SD, in the initial ICI treatment can be one of clinical features which predicts efficacy of subsequent ICI rechallenge. Studies about ICI rechallenge for malignant melanoma revealed that the response to the initial treatment might have been good.[18, 19] By contrast, of the six patients who had PR during the initial ICI treatment, only two achieved SD during ICI rechallenge. These conflicting results may also suggest that the favorable outcomes in initial ICI treatment are not definite predictive marker for the subsequent ICI rechallenge. For the better prediction for outcomes of ICI rechallenge, the associations of other clinical factors might also need to be explored Previous studies have reported following factors as potential candidates for such predictive factors: High PD-L1 expression, radiotherapy prior to ICI rechallenge,[15] occurrence of irAEs in the initial ICI, and duration from the initial ICI to ICI rechallenge.[12] Several reports have shown that the time between the initial ICI treatment and ICI rechallenge may be correlated to the efficacy of rechallenge.[12] In our cohort, three of seven patients who received a second ICI within six months after completing the first ICI achieved SD. In addition, of the four patients who rechallenged ICI after more than one year, two had SD. In our study, 10 patients who achieved PR or SD during ICI rechallenge had a median treatment line of four (range: 3–5). Seven patients with PD had a median retreatment line of six (range: 2–9). Four patients received a third ICI, all of whom had PD, and the median treatment line was six (range: 6–7). It has also been suggested that preceding chemotherapy may affect the efficacy of ICI rechallenge.[17] Eleven patients were treated with cytotoxic anticancer drugs such as platinum containing between the two immunotherapies, and the median treatment line was one (range: 1–6). Five of the 11 patients had PD. Patients who were rechallenged with ICI at an earlier treatment line may have better outcomes with or without chemotherapy between the two immunotherapies. As previously mentioned, ICI rechallenge may be beneficial for a portion of advanced cancer patients. Thus, this study also implicated the efficacy of switching the administration of anti-PD-1 and anti-PD-L1 antibodies. Anti-PD-1 antibody inhibits PD-1 and prevents its binding to the ligand, thereby maintaining T cell activation, eliciting tumor immunity, and exerting antitumor effects. Moreover, anti-PD-L1 antibody has a similar effect as it inhibits ligand PD-L1.[20] As speculated, anti-PD-1 and anti-PD-L1 antibodies can shrink tumors that can no longer be suppressed due to their structural differences. Furthermore, there is an important clinical question regarding the duration of ICI treatment in NSCLC. The CheckMate 153 study has shown that continuous treatment with nivolumab for more than one year significantly maintains response. In addition, ICI rechallenge was found to have therapeutic benefits in some patients whose condition worsened after treatment discontinuation.[21] These data suggest that extending the duration of ICI treatment may be clinically important. The treatment period of ICI rechallenge can be substantially extended in some patients, thereby increasing therapeutic efficacy.

Regarding safety, the administration of different types of ICI certainly caused the recurrence of irAEs which developed during the initial ICI treatment. Of the 10 patients who developed irAEs during the first ICI treatment, four experienced relapses of irAEs during the second ICI. However, most relapsed irAEs were grade 2 or lower, which were manageable. In previous report,[22] of the 38 patients

who were retreated with anti-PD-L1 following an initial irAEs, 10 (26%) had recurrence of the initial irAEs. The majority of recurrent irAEs were mild, and were manageable. The safety of switching the administration of ICI was similar to that of a previous report. In our cohort, 10 (58.8%) patients had irAEs of grade 2 or higher during the initial ICI treatment. Moreover, seven patients discontinued the treatment, and three patients continually received the initial ICI treatment until PD. Of the 10 patients, five achieved PR or SD during the ICI rechallenge. Of the five patients who did not respond to the rechallenge, four achieved PR before the occurrence of irAEs in the initial ICI treatment. Preceding reports suggest that ICI rechallenge might not improve survival in patients who develop irAEs requiring immunotherapy after achieving PR in the first ICI.[20] By contrast, the other prior reports showed that the occurrence of irAEs during ICI treatment might improve its effect.[23, 24] The occurrence of irAEs in the first ICI may be a factor we need to take into account to predict the efficacy of ICI rechallenge.

The current study had several limitations. This was a retrospective, nonrandomized analysis that was conducted at a single institution with a small number of patients. Also, a possible selection bias might have existed because ICI rechallenge was based on the discretion of the physician. Three patients had a high PD-L1 expression, and one patient received radiation therapy before readministration. However, due to the small sample size, the complete evaluation of the efficacy and safety of ICI readministration was challenging to perform considering the different background characteristics of the participants.

In conclusion, ICI rechallenge may be beneficial for some groups of patients. Moreover, a successful response period must be maintained by selecting a patient group that can benefit from ICI rechallenge and by extending the treatment period of ICI. In addition, switching the administration of ICI may increase the efficacy of ICI rechallenge. Thus, further accumulation of cases is required, and extensive research must be conducted. Switching the administration of anti-PD-1 and anti-PD-L1 antibodies as ICI rechallenge can be a treatment option for some NSCLC patients.

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