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ORIGINAL ARTICLE

Clinical difference between discontinuation and retreatment with nivolumab after immune-related adverse events in patients with lung cancer

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Abstract

Background After the cessation of immune checkpoint inhibitor (ICI) therapy due to an immune-related adverse event (irAE), it remains unclear whether retreatment with ICI is more effective than its discontinuation. To explore the clinical significance of its retreatment, patients with non-small cell lung cancer (NSCLC) who had treatment interruption of nivolumab due to irAEs were identified and the clinical differences between discontinuation and retreatment with nivolumab were retrospectively reviewed.

Methods 49 (26%) of 187 patients treated with nivolumab experienced the cessation of treatment due to a serious irAE. Retreatment was chosen in 21 patients (retreatment cohort), while 28 patients discontinued treatment (discontinuation cohort).

Results The most common irAEs requiring treatment cessation in 49 patients included pneumonitis (59.2%), adrenal insufficiency (8.2%), liver dysfunction (8.2%) renal dysfunction (8.2%), colitis (6.1%), hypothyroidism (4.1%), and rash (2.0%). The frequency of grade 3 or 4 initial irAEs did not differ between the retreatment and discontinuation cohorts; however, the incidence of renal dysfunction and colitis was higher in the retreatment cohort than in the discontinuation cohort. Retreatment with nivolumab displayed an overall response rate of 15%, without a significant increase in irAEs. The median overall survival and progression-free survival did not differ significantly between the retreatment and discontinuation cohorts, irrespective of the efficacy of prior nivolumab.

Conclusions Retreatment exhibited a slightly higher efficacy without a significant increase in irAEs; however, the clinical significance of retreatment and discontinuation was similar in NSCLC patients that led to treatment interruption due to any irAE after initial nivolumab.

Keywords PD-1 inhibitor · Nivolumab · Discontinuation · Retreatment · NSCLC · irAE

Introduction

Nivolumab, an anti-programmed-death 1 (PD-1) antibody, is an immune checkpoint inhibitor (ICI) with significant efficacy in patients with several different tumor types. A recent study reported that approximately 16% of patients with advanced non-small-cell lung cancer (NSCLC) survived more than 5 years after the administration of nivolumab as salvage treatment and that patients who survived to 5 years received no subsequent therapy following the 2 years of nivolumab treatment [1]. Although it remains unclear how many years we should continue to administer nivolumab if there is no disease progression, there appeared to be a suppression of disease progression after discontinuation of nivolumab. Recently, Haratani et al. reported that the

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development of immune-related adverse events (irAEs) was closely related to favorable survival of nivolumab treatment in patients with advanced or recurrent NSCLC [2]. In daily practice, however, some patients must discontinue ICI treatment due to severe irAE, even if the treatment is effective. Thus, the clinical significance of retreatment with ICI after its discontinuation due to any irAE remains unclear.

Santini et al. reported the safety and efficacy of retreatment with ICI after irAE in patients with advanced NSCLC [3]. In their study, patients with advanced NSCLC who discontinued treatment due to irAE after ICI therapy were divided into two groups: those retreated with ICI (retreatment cohort) and those who had treatment discontinued (discontinuation cohort) [3]. They concluded that progression-free survival (PFS) and overall survival (OS) were more favorable in the retreatment cohort than those in the discontinuation cohort among patients without a partial response prior to the irAE, whereas the PFS and OS were similar in both cohorts for those with an objective response prior to the irAE [3]. The results of their study suggest that the prognostic significance of ICI retreatment differs according to the efficacy of ICI prior to the irAE onset. However, their study included an anti-PD-1 antibody, anti-programmed death ligand-1 (PD-L1) antibody, and the combination of anti-PD-1 and anti-CTLA-4 antibodies and lacked information on the retreatment of ICI with the same mechanism. Although the clinical significance of re-challenge of anti-PD-1 antibody is largely unknown, Fujita et al. described that retreatment with pembrolizumab yielded an objective response in selected NSCLC patients who were previously treated with nivolumab [4]. However, these studies were retrospective investigations and included small sample sizes, which may bias their results. It remains unknown whether nivolumab retreatment should be considered in patients who had treatment held due to irAE after prior nivolumab.

Therefore, we retrospectively reviewed the clinical data of patients with advanced NSCLC who received nivolumab treatment, with the aim to elucidate the clinical differences between nivolumab discontinuation and retreatment after irAE in patients with NSCLC.

Patients and methods

Patients

Patients with advanced NSCLC treated with nivolumab monotherapy at Saitama Medical University International Medical Center were retrospectively identified. Eligible patients were required to meet the following criteria: histologically or cytologically proven NSCLC; age older than 20 years; treatment delay of longer than 4 weeks due to an irAE; exhibiting complete response (CR), partial response (PR), or stable disease (SD) following nivolumab as initial treatment. Adverse events were defined as irAE at the discretion of the investigator based on the following events during nivolumab treatment: pneumonitis, hepatitis, nephritis, dermatitis, myositis, arthritis, colitis, endocrinopathies, or neurologic disorders. Patients who had treatment discontinued due to an irAE and later retreated were defined as the retreatment cohort, while those in which treatment was permanently interrupted due to an irAE were defined as the discontinuation cohort. Patients who were treated with additional chemotherapy or radiation therapy between treatment interruption due to an irAE and retreatment with nivolumab were excluded.

This study was approved by the institutional ethics committee of the Saitama Medical University International Medical Center, which waived the requirement for written informed consent because of the retrospective nature of the study. In the present study, mortality and recurrence were determined using medical records. The patient information used in the present study was collected as previously described [5, 6].

Evaluation of efficacy and adverse events

Prior to treatment, patients were evaluated with a complete blood cell count, a differential count, routine chemistry measurements, chest radiography, chest computed tomography (CT), abdominal CT, whole-brain magnetic resonance imaging or CT, and isotope bone scintigraphy. The weekly evaluations included complete blood cell counts, differential counts, routine chemistry measurements, physical examination, and toxicity assessment. Acute toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0. Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 [7]. Responses based on target and non-target lesions were defined as follows: CR, disappearance of all target and non-target lesions; PR, $\geq 30\%$ reduction in size or disappearance of one or more non-target lesions; SD, $< 30\%$ decrease and $< 20\%$ increase in size or the persistence of one or more non-target lesions; and progressive disease (PD), $> 20\%$ increase in size or the appearance of new non-target lesions and/or progression of existing non-target lesions. The overall response rate (ORR) was defined as the best response recorded from treatment initiation until disease progression or recurrence, as confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

Statistical analysis

Statistical significance was indicated by $p < 0.05$. Fisher's exact tests were used to examine the association between

two categorical variables. The Kaplan–Meier method was used to estimate survival as a function of time and survival differences were analyzed by log-rank tests. PFS was defined as the time from the cessation of initial nivolumab therapy to tumor recurrence or death from any cause, while OS was defined as the time from cessation of initial nivolumab therapy to death from any cause. Statistical analyses were performed using JMP 7.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient's demographics

From December 2015 to August 2018, 187 patients were treated with nivolumab at Saitama Medical University International Medical Center. Eighty-nine of these patients were excluded for PD after nivolumab administration. Of the remaining 98 patients, 49 were treated with nivolumab without cessation due to an irAE lasting more than 1 month. The other 49 patients (26%) experienced an irAE that led to treatment cessation lasting more than 1 month; of these, 21 (43%) and 28 (57%) were defined as the retreatment and discontinuation cohorts, respectively. No statistically significant differences in patient demographics were observed between the retreatment and discontinuation cohorts, except for the line of nivolumab therapy (Table 1).

Table 1 Patient's demographics

Different variables	Retreatment $N=21$	Discontinuation $N=28$	P value
Age			
Mean, years	69	70	0.50
(Range, years)	(43–84)	(57–80)	
Gender			
Male/female	19/2	25/3	0.86
Smoking			
Yes/no	20/1	27/1	0.83
Histology			
Ad/non-adeno	11/10	9/19	0.15
EGFR mutation			
Yes/no	0/21	2/26	0.21
PS (ECOG)			
0–1/2–3	19/2	23/5	0.41
Line of nivolumab therapy			
Second/third and beyond	15/6	5/23	<0.01*
Best overall response			
CR or PR/SD or PD	13/8	10/18	0.06
Staging			
III or IV/recurrence	18/3	20/8	0.23

Ad adenocarcinoma, *Non-ad* non-adenocarcinoma, *ECOG* Eastern Clinical Oncology Group, *PS* performance status, *EGFR* epidermal growth factor receptor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

*$p<0.05$ is considered statistically significant

Clinical feature of initial irAE

The initial irAEs in the 49 patients with treatment cessation included pneumonitis (59.2%), adrenal insufficiency (8.2%), liver dysfunction (8.2%) renal dysfunction (8.2%), colitis (6.1%), hypothyroidism (4.1%), and rash (2.0%). Between the retreatment and discontinuation cohorts, the frequency of grade 3 or 4 initial AEs did not differ significantly, although the incidence of all-grade irAE was higher in the discontinuation cohort than that in the retreatment cohort. However, the incidence of renal dysfunction and colitis was higher in the retreatment cohort than in the discontinuation cohort (Table 2). The administration interval and use of steroids, time interval to irAE, and hospitalization for management of irAE were similar in both cohorts (Table 2). Resolution of irAE or improvement of grade 1 irAE was observed in all patients with retreatment compared to 82.1% of patients with discontinuation ($p=0.04$) (Table 2).

Clinical characteristics and irAE of patients with retreatment after initial irAEs

Table 3 shows the clinical features of the 21 patients who received retreatment after initial irAEs. An ORR of nivolumab as initial treatment was observed in 13 of the 21 patients (61.9%). In 20 patients with evaluable lesions who received nivolumab retreatment, 3 (15%) achieved PR, 15 (75%) SD, and 2 (10%) PD. Two of three patients with PR in retreatment yielded a PR or CR as the efficacy of the initial treatment of nivolumab and these three patients had received only a few cycles of initial nivolumab. Assessment of PD-L1 expression by immunohistochemistry was performed in 4 of 21 patients (19%). Any treatment, including cytotoxic chemotherapy or radiation, was not performed between initial nivolumab and retreatment. Figure 1 shows the swimmer's plot of therapeutic course from the initiation of nivolumab.

The irAEs of the 21 patients who received retreatment are listed in Table 4. 15 of these 21 patients experienced an irAE. The steroid administration interval and use were had more much patients with initial nivolumab than those with retreatment (Table 4). There were no irAE-related deaths.

Survival analysis according to retreatment and discontinuation

The median OS and PFS of the 49 patients were not reached and 398 days, respectively. Figure 2 shows the Kaplan–Meier survival curve according to the comparison

Table 2 Clinical features of initial irAE

Different variables	All patients $n=49$	Retreatment $n=21$	Discontinuation $n=28$	p value
Grade of the initial irAE, *n* (%)				
Grade 1 and 2/grade 3 and 4	34 (69.4)/15 (30.6)	14 (66.6)/7 (33.3)	19 (67.6)/9 (32.1)	0.92
Type of irAE, *n* (%)				
All grades, *n* (%) [grade 3/4, *n* (%)]				
Pneumonitis	29 (59.2)	7 (33.3)/[1 (4.7)]	22 (78.6)/[3 (10.7)]	< 0.01*/ [0.45]
Adrenal insufficiency	4 (8.2)	2 (9.5)/[2 (9.5)]	2 (7.1)/[1 (3.6)]	0.76/[0.39]
Liver dysfunction	4 (8.2)	1 (4.7)/[1 (4.7)]	3 (10.7)/[2 (7.1)]	0.45/[0.73]
Renal dysfunction	4 (8.2)	4 (19.0)/[0 (0.0)]	0 (0.0)/[0 (0.0)]	< 0.01*/[0.99]
Colitis	3 (6.1)	3 (14.3)/[1 (4.7)]	0 (0.0)/[0 (0.0)]	0.03*/[0.24]
Hypothyroidism	2 (4.1)	0 (0.0)/[0 (0.0)]	2 (7.1)/[1 (3.6)]	0.21/[0.38]
Rash/pruritus	1 (2.0)	1 (4.7)/[1 (4.7)]	0 (0.0)/[0 (0.0)]	0.24/[0.24]
Other	10 (20.4)	6 (28.6)/[1 (4.7)]	4 (14.3)/[2 (7.1)]	0.21/[0.73]
Corticosteroid used, *n* (%)				
Yes/no	32 (65.3)/17 (34.7)	15 (71.4)/6 (28.6)	17 (60.7)/11 (39.3)	0.43
Intravenous	12	4	8	
Oral	20	11	9	
Steroids ≧ 4 weeks, *n* (%)				
Yes/no	31 (63.3)/18 (36.7)	14 (66.7)/7 (33.3)	17 (60.7)/11 (39.3)	0.66
irAE resolved to, *n* (%)				
Grades 0 and 1/grade ≧ 2	44 (89.8)/5(10.2)	21 (100)/0 (0.0)	23 (82.1)/5 (17.9)	0.04*
Time interval to irAE days				
Median (range)	76 (15-476)	119 (15-437)	71 (15-476)	0.46
Hospitalization, *n* (%)	20 (40.8)	8 (38.1)	12 (42.8)	0.73
Death related to irAE, n (%)	0	0	0	0.99

irAE immune-related adverse event

*$p < 0.05$ is considered statistically significant

of the retreatment and discontinuation cohorts. The median OS and PFS did not differ significantly between the retreatment and discontinuation cohorts (Fig. 2a, b). The survival analysis of the 23 patients with CR or PR (Fig. 2c, d) and the 26 patients with SD (Fig. 2e, f) following an initial treatment with nivolumab revealed no statistically significant differences in OS and PFS.

In 15 patients with irAEs after retreatment, the survival and response of 9 patients with the same irAEs as those for initial nivolumab did not differ from those of the 6 patients with different irAEs (Table A1 and Figure A1, online only).

Discussion

This retrospective study examined the clinical significance of retreatment and discontinuation after the cessation of initial nivolumab due to irAEs. Approximately half of the patients who exhibited non-PD after initial nivolumab experienced treatment interruption due to irAEs. The most common irAE requiring the cessation of nivolumab was interstitial lung disease and there was a low incidence of grade 3 or 4 irAEs. Some patients who experienced grade 1 or 2 irAEs require cessation of nivolumab treatment. Our results indicated that the prognostic impact of discontinuation cohort was similar to that of the retreatment cohort. We found that nivolumab retreatment was feasible and slightly effective after the cessation of initial treatment, without a significant increase in irAEs. Although it remains unclear whether retreatment should be performed after the cessation of nivolumab due to any irAEs that led to treatment interruption, discontinuation may be clinically recommended according to the severity of the irAE.

In a retrospective study at Memorial Sloan Kettering-Cancer Center (MSKCC), the clinical significance of retreatment and discontinuation of ICI did not differ among the patients with PR prior to the irAE, concordant with the results of our study [3]. However, patients without objective response prior to the irAE displayed a favorable survival benefit after retreatment compared to those with treatment

Table 3 Clinical course of 21 patients with retreatment

Patient's number	Initial nivolumab			Any treatment before retreatment	PD-L1	Nivolumab retreatment		
	Cycles	PFS (days)	Response		22C3	Cycles	PFS (days)	Response
1	5	432	CR	–	Unknown	6	110	PR
2	1	268	PR	–	Unknown	1	244	PR
3	28	926	PR	–	Unknown	1	245	SD
4	5	263	PR	–	Unknown	3	234	SD
5	29	973	PR	–	Unknown	19	373	SD
6	1	470	SD	–	Unknown	25	357	PR
7	3	191	PR	–	Unknown	4	88	PD
8	20	574	SD	–	Unknown	2	151	SD
9	2	398	PR	–	Unknown	1	305	SD
10	4	249	SD	–	Unknown	3	227	SD
11	7	553	PR	–	Unknown	8	374	SD
12	8	409	SD	–	Unknown	18	232	NE
13	9	319	PR	–	Unknown	17	117	SD
14	5	277	SD	–	0	7	154	SD
15	8	195	SD	–	Unknown	8	129	SD
16	11	207	SD	–	5	8	117	SD
17	17	864	PR	–	Unknown	35	573	SD
18	7	280	PR	–	Unknown	1	157	SD
19	19	548	PR	–	Unknown	13	221	SD
20	4	122	SD	–	30	3	45	PD
21	18	446	PR	–	0	7	172	SD

PFS Progression-free survival, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progression disease, *NE* not evaluable, *PD-L1* programmed death ligand-1

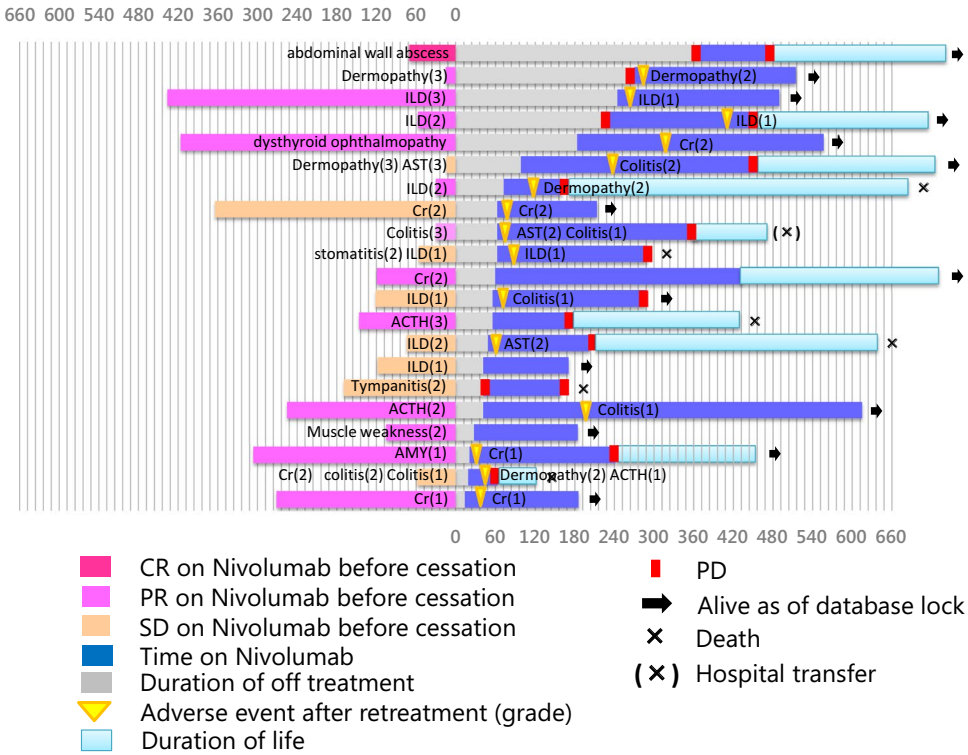


Fig. 1 Treatment duration of retreatment with nivolumab in 21 patients. In 20 patients with evaluable lesions who received nivolumab retreatment, 3 patients (15%) achieved PR, 15 (75%) SD and 2 (10%) PD. Two of three patients with PR as retreatment yielded a PR or CR after initial treatment of nivolumab. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ILD* interstitial lung disease, *Cr* creatinine, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ACTH* adrenocorticotropic hormone

Table 4 Immune-related adverse events of nivolumab retreatment

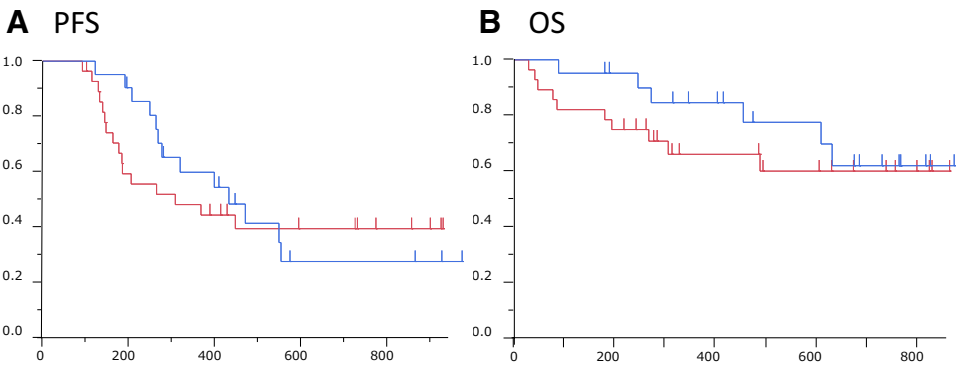
Adverse events	Initial treatment *n* (%)		Retreatment *n* (%)	
	Any grade	Grade ≧3	Any grade	Grade ≧3
Type of irAE, n (%)	21 (100)	7 (33.3)	15 (71.4)	1 (4.7)
Pneumonitis	7 (33.3)	1 (4.7)	3 (14.3)	0 (0.0)
Adrenal insufficiency	2 (9.5)	2 (9.5)	1 (4.7)	0 (0.0)
Hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver dysfunction	1 (4.7)	1 (4.7)	2 (9.5)	0 (0.0)
Renal dysfunction	4 (19.0)	0 (0.0)	4 (19.0)	0 (0.0)
Colitis	3 (14.3)	1 (4.7)	4 (19.0)	1 (4.7)
Rash/pruritus	1 (4.7)	1 (4.7)	3 (14.3)	0 (0.0)
Other	6 (28.6)	1 (4.7)	0 (0.0)	0 (0.0)
Corticosteroid used, *n* (%)				
Yes/no	15 (71.4)/6 (28.6)		5 (33.3)/10 (66.7)	
Intravenous	4 (26.7)		1 (20)	
Oral	11 (73.3)		4 (80)	
Steroids ≧4 weeks, *n* (%)				
Yes/no	14 (66.7)/7 (33.3)		5 (33.3)/10 (66.7)	

irAE immune-related adverse event

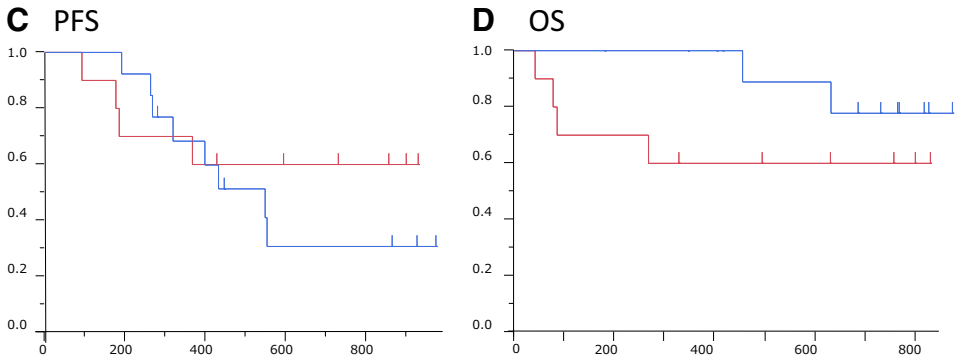
discontinuation [3]. Although it remains unclear why the effect of retreatment differed according to the efficacy of prior ICI, we believe that discontinuation is one therapeutic strategy after treatment interruption, irrespective of the objective response prior to the irAE. In our study, the irAE rate after retreatment was 71.5% (15/21) and the same irAE as had occurred during the initial nivolumab did not necessarily occur in retreatment. More than half of our patients experienced several kinds of irAEs. In the MSKCC study, 38 of 72 patients (54%) received ICI retreatment and irAEs occurred in 50% of the retreatment patients. The same and different irAEs were observed in 48% and 52% of these 38 patients, respectively [3]. The MSKCC study included patients treated with anti-PD-1/PD-L1 antibodies (nivolumab, pembrolizumab, atezolizumab, or durvalumab), either as monotherapy or in combination with anti-CTLA4 antibodies (ipilimumab or tremelimumab), whereas our study focused only patients who received nivolumab monotherapy. We believe that the population receiving the same ICI is superior to that with different ICIs for the elucidation of the clinical differences between ICI discontinuation and retreatment after irAE in patients with NSCLC. Further study is warranted to compare the prognostic significance of retreatment and discontinuation in larger sample sizes.

Survival analysis of 4-year follow-up data in patients with melanoma indicated that the proportions of patients who continued treatment discontinuation after any response in ICI treatment were 71% (113/159) for ipilimumab plus nivolumab, 50% (69/138) for nivolumab, and 39% (32/82) for ipilimumab [8]. These long-term follow-up data suggest that the cessation of ICI treatment after any response contribute to sustained survival benefit. Although there are several discussions about the relationship between the occurrence of irAEs and the efficacy of PD-1 inhibitors, the survival time after ICI treatment seemed to be longer in patients who developed grade 3 or 4 irAEs compared to those who did not [2, 9].

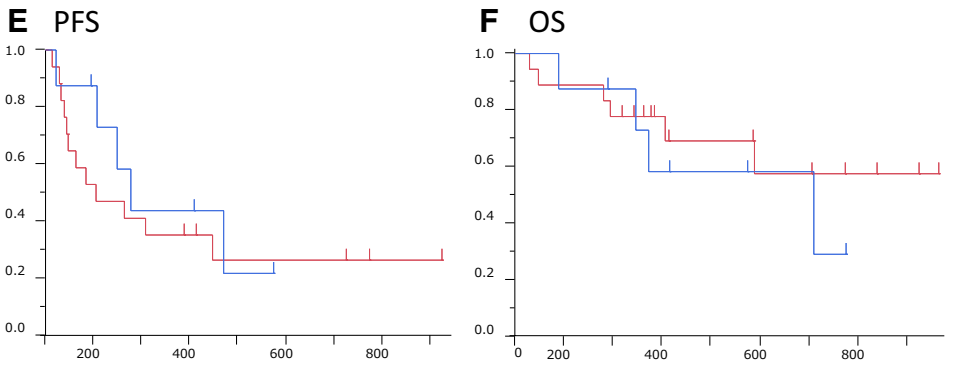
In the present study, nivolumab re-challenge had an ORR of 15%. The MSKCC report also observed an ORR of 13% in patients with ICI retreatment after treatment interruption due to irAE [6], concordant with our results. Niki et al. reported that 3 (27%) of 11 patients achieved PR after re-challenge with nivolumab or pembrolizumab, with a median PFS of 2.7 months [10]. They concluded that re-challenge with PD-1 inhibitors might be a therapeutic option for advanced NSCLC. Moreover, Fujita et al. also retrospectively reviewed NSCLC patients retreated with pembrolizumab who had previously received nivolumab [4]. In their study, 1 (8.3%) of 12 patients achieved PR and 4 (33.3%) patients achieved SD, suggesting that retreatment with PD-1 inhibitors could provide a clinical benefit in selected patients with high PD-L1 expression. Previous studies of melanoma patients reported that the response to the initial PD-1 inhibitor was a possible marker linked to the efficacy of retreatment [10] and that the PFS after the initial PD-1 inhibitor was a parameter for predicting the efficacy of retreatment with a PD-1 inhibitor [11]. Although it remains unclear whether the response or PFS after administration of an initial PD-1 inhibitor could predict the efficacy of retreatment with a PD-1 inhibitor in patients with advanced



	Variables	N	Median PFS (days)		Median OS (days)	
—	Discontinuation	28	308	*p*=0.69	NR	*p*=0.39
—	Retreatment	21	432		NR	



	Variables	N	Median PFS (days)		Median OS (days)	
—	Discontinuation	10	NR	*p*=0.50	NR	*p*=0.13
—	Retreatment	13	548		NR	



	Variables	N	Median PFS (days)		Median OS (days)	
—	Discontinuation	18	205	*p*=0.58	NR	*p*=0.53
—	Retreatment	8	277		709	

Fig. 2 Kaplan–Meier survival curves according to the comparison of retreatment and discontinuation cohorts. Survival analysis of 49 patients with treatment cessation: no statistically significant difference in the PFS (**a**) and OS (**b**) was observed between the patients with retreatment and discontinuation cohorts. Survival analysis of 23 patients with CR or PR by prior nivolumab: no statistically significant difference in the PFS (**c**) and OS (**d**) was observed between the patients with retreatment and discontinuation cohorts. Survival analysis of 26 patients with SD by prior nivolumab: no statistically significant difference in the PFS (**e**) and OS (**f**) was observed between the patients with retreatment and discontinuation cohorts. *CR* complete response, *PR* partial response, *SD* stable disease, *PFS* progression-free survival, *OS*, overall survival

NSCLC, a large-scale study is warranted to confirm whether retreatment with a PD-1 inhibitor should be considered as a sequential therapeutic strategy of patients with previously treated NSCLC. However, it remains controversial whether retreatment with PD-1 inhibitor is better as a therapeutic option after the cessation of prior PD-1 inhibitor due to serious irAE.

The present study has several limitations. First, our study had a small sample size and a retrospective design, which may bias our results. Similar to the previous study, it may be impossible to prospectively conduct a clinical study such as our study. The accumulation of experience in daily practice is required to elucidate the validity of our approach. Second, the optimal judgment for retreatment or discontinuation is obscure. Considering the severity of irAE, clinical physicians must carefully judge the timing of treatment interruption and select between nivolumab retreatment or discontinuation.

In conclusion, retreatment exhibited a slightly higher efficacy without a significant increase in irAE; however, the clinical impact of retreatment and discontinuation was similar in patients with previously treated NSCLC with treatment interruption due to irAE after initial nivolumab. Considering the incidence of irAE in retreatment, discontinuation may be suitable for patients who require the cessation of nivolumab for any irAEs.

Clinical Practice Points

- The efficacy of ICI is expected for the patients with irAE such as interstitial lung disease, even if retreatment with ICI is not considered.
- After the cessation of ICI therapy due to an irAE, it remains unclear whether retreatment with ICI is more effective than its discontinuation.
- The clinical impact of retreatment and discontinuation was similar in patients with previously treated NSCLC with treatment interruption due to irAE after initial ICI.
- Retreatment displayed a slightly higher efficacy without a significant increase in irAE.
- Our study suggests that future discontinuation should be considered for patients who require the cessation of ICI because of any irAEs.

Author contributors AS, KK and HK: conception and preparation of the manuscript. AM, AS, OY, KH, TU, YM, FM and YM: management of the patients. OY: statistical analysis and patients' data collection. AS, AM, OY, KK and HK: revising the manuscript. All authors contributed and agreed with the content of the manuscript.

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Compliance with ethical standards

Conflict of interest OY, AM, KK, and HK have received research grants and a speaker honorarium from Ono Pharmaceutical Company and Bristol-Myers Company. All remaining authors have declared they have no conflicts of interest.

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