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Efficacy and predictors of rechallenge with immune checkpoint inhibitors in non-small cell lung cancer

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Abstract

Background: The efficacy of rechallenge with immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC) patients has not yet been fully clarified. This study aimed to identify the clinical characteristics of patients with NSCLC who benefited from rechallenge with ICIs.

Methods: We retrospectively reviewed the clinical records of 24 patients who were diagnosed with NSCLC and rechallenged with ICIs between August 2016 and July 2021.

Results: Of the 24 patients included in the study, 11 were in the responder group (45.8%) and 13 in the nonresponder group (54.2%). The number of patients who used a different ICI from that used in the initial therapy was significantly higher in the responder group than in the nonresponder group ($p = 0.006$). Multivariate analysis identified lung metastasis and female sex as significant independent risk factors for nonresponse to rechallenge with ICIs. Compared to the nonresponder group, the duration of treatment after rechallenge with ICIs was significantly longer in the responder group ($p = 0.016$), and there was a trend toward longer overall survival ($p = 0.059$).

Conclusions: Patients with lung cancer who were rechallenged with ICIs and without progressive disease after initial ICI therapy were able to continue ICI therapy for a longer period of time. This may be associated with longer survival. Patients with lung metastases and female patients are more likely to be nonresponsive to rechallenge with ICIs. Administration of a different type of ICI from that used in the initial ICI therapy may result in disease control.

KEYWORDS
immune checkpoint inhibitors, lung neoplasm, non-small-cell lung carcinoma

INTRODUCTION

Immune checkpoint inhibitors (ICIs) for the treatment of patients with non-small cell lung cancer (NSCLC) have been found to significantly prolong survival compared to cytotoxic anticancer agents in multiple randomized controlled phase III trials and are now considered the standard of care.[1–4]

High programmed death-ligand 1 (PD-L1) expression,[3,5] low pretreatment neutrophil-to-lymphocyte ratio (NLR),[6–8] and pretreatment radiotherapy[9,10] have been reported as predictors of response to initial ICI therapy. In recent years, the development of biomarkers for therapeutic efficacy and prognosis, such as tumor mutation burden and tumor microenvironment, has been vigorously pursued.[11] Several

predictors of antitumor efficacy of ICIs have been reported; however, these reports are limited[12–17] because rechallenge with ICIs is not a standard treatment. Moreover, there are no reports focusing on patients who respond to rechallenge with ICIs, and the clinical characteristics and prognosis of patients who benefit from rechallenge with ICIs remain unclear. Therefore, in this study, we retrospectively examined patients with NSCLC who responded well to rechallenge with ICIs to identify clinical characteristics and risk factors that influence antitumor efficacy.

METHODS

From August 2016 to July 2021, we retrospectively examined patients with advanced (stage IIIB, IV) NSCLC who were eligible for medical therapy. This study was approved by the Institutional Review Board of Kanazawa Medical University (approval number: I683), and the need for written informed consent from the study subjects was waived. Data, such as age, sex, smoking history, performance status (PS), body mass index (BMI), histological type of lung cancer, metastatic site, tumor proportion score (TPS), NLR, and treatment details, were collected. Response to ICI therapy was evaluated based on the Response Evaluation Criteria in Solid Tumors version 1.1. Patients with complete response (CR), partial response (PR), or stable disease (SD) were classified into the responder group, while patients with progressive disease (PD) were classified into the nonresponder group. Patients who received radiation to the target lesion and those who received only one cycle of rechallenge with ICIs were excluded from the study because the response rate of these patients was difficult to assess accurately. The severity of immune-related adverse events (irAEs) was assessed using the Common Terminology Criteria for Adverse Events version 4.0. Immunohistochemistry was performed using the PD-L1 kit (PD-L1 IHC 22C3 pharmDX; Dako) according to the manufacturer's instructions. The TPS was used to classify the expression status as follows: <50% (Low) and >50% (High).

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, Version 26.0 (IBM Corp.). Statistical significance was set at $p < 0.05$. All categorical variables were analyzed using the chi-square test, except for those with predictive frequencies <5. Variables with predictive frequencies <5 were analyzed using Fisher's exact test. An unpaired *t*-test was used to compare the means of continuous variables between the two groups.

Multivariate analysis was performed using logistic regression. Survival curves were generated using the Kaplan–Meier method using data collected from the initiation of lung cancer treatment to discontinuation of treatment or death. Survival analysis was performed in mid-September 2021.

The log-rank test was used to analyze whether there was a difference in survival rates due to differences in response to readministration of ICIs. A risk rate <5% was considered statistically significant.

RESULTS

Patient characteristics

Of the 26 patients, 24 were included in the final analysis. Further, 11 (45.8%) and 13 (54.2%) patients were included in the responder and nonresponder groups, respectively. In the responder group, there were two patients with PR (8.3%) and nine with SD (37.5%). There were no patients with CR. The response rate (RR) was 8.3%, and the disease control rate (DCR) was 45.8%. The imaging findings of the patients with PR in the responder group are shown in Figure 1.

Patient characteristics are shown in Table 1. Most of the patients had an Eastern Cooperative Oncology Group PS of 0 or 1, but three patients (23.1%) in the nonresponder group had a PS of 2. None of the patients had any genetic abnormalities. With regard to the reasons for discontinuation of the initial ICIs, in the responder group, treatment was discontinued in eight patients due to PD and in four due to irAE. In the nonresponder group, treatment was discontinued in nine patients due to PD, in three due to irAE, and one at the discretion of the attending physician due to cerebral hemorrhage unrelated to disease progression.

In the responder group, there were no patients with liver metastases or patients who were administered steroids. In the nonresponder group, one patient received dexamethasone at a dose of 2 mg/day for palliative purposes. There were no significant differences in age, sex, BMI, smoking history, PS, histological type of lung cancer, PD-L1 expression, NLR, reasons for discontinuation of initial ICI therapy, history of irAEs, steroid administration, radiotherapy, and time from discontinuation of initial ICI therapy to rechallenge with ICIs between the two groups. The responder group had a significantly longer duration of treatment after rechallenge with ICIs (21.6 vs. 10.9 weeks; $p = 0.016$). Switching administration (change from PD-1 inhibitors to PD-L1 inhibitors or from PD-L1 inhibitors to PD-1 inhibitors) was performed in all patients in the responder group, and there was a statistically significant difference between the two groups ($p = 0.003$).

Patients with irAEs

Table 2 shows the details of treatment and its side effects in patients who developed irAEs during the course of treatment. IrAEs were observed in nine of 24 (37.5%) patients. Further, five of 11 (45.5%) patients in the responder group and four of 13 (30.8%) in the non-responder group developed irAEs. Out of 24, four (16.7%) patients experienced irAEs after rechallenge with ICIs. Moreover, three of

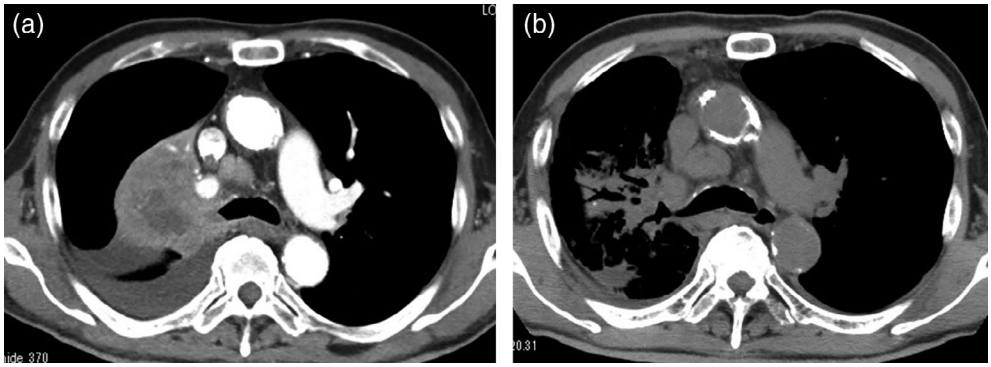

FIGURE 1 Computed tomography (CT) image of the chest. Chest CT image of a 68-year-old man with a high incidence of tumor proportion score (TPS) (95%) with lung adenocarcinoma complicated by carcinomatous pleurisy. Pembrolizumab therapy was administered as initial therapy, but was discontinued after two cycles due to progressive disease (PD). Atezolizumab therapy was started as fourth-line therapy, and the airway obstruction was resolved by tumor shrinkage. The patient's respiratory status improved, and he no longer required home oxygen. Atezolizumab therapy was continued for 19 cycles. (a) Pretreatment contrast chest CT showed a right hilar mass protruding into the airway. (b) Plain chest CT after rechallenge with ICIs showed a reduction in the size of the right hilar mass

TABLE 1 Patient characteristics

	Responder	Nonresponder	*p*-value (responder vs. nonresponder)
Total *n*	11 (45.8%)	13 (54.2%)	
Age, years	67 (56–78)	72 (50–82)	0.172
Sex (male/female)	(9/2)	(7/7)	0.105
Smoking history (never/prior・current)	(2/9)	(4/9)	0.649
ECOG PS (0–1/2–4)	(11/0)	(10/3)	0.223
Tumor type (Nonadeno/adeno)	(5/6)	(5/8)	1.000
BMI	22.7 (16.8–29.2)	22.5 (17.8–29.5)	0.890
Albumin	3.6 (2.1–4.5)	3.5 (2.8–4.6)	0.973
Antinuclear antibody (Positive/Negative)	(6/5)	(8/5)	0.729
NLR	4.17 (2.02–7.48)	7.22 (1.98–38.93)	0.319
Distant metastasis			
Brain	(4/7)	(5/8)	0.916
Lung	(1/10)	(5/8)	0.166
Pleura	**(2/9)**	**(2/12)**	**1.000**
Liver	(0/11)	(4/9)	0.223
Bone	**(3/8)**	**(5/9)**	**1.000**
PD-L1 expression (22C3) (low/high/untested)	(6/4/1)	(6/7/0)	0.435
Switching administration (Yes/No)	(11/0)	(6/7)	0.006[a]
Initial ICI therapy (week)	21.6 (2–51)	15.8 (2–54)	0.354
Rechallenge with ICIs (weeks)	21.6 (10–51)	10.9 (4–21)	0.016[b]
Withdrawal period (days)	453.1 (8–1163)	310.4 (26–1445)	0.354
Discontinuation reasons (PD/others)	**(8/3)**	**(9/4)**	**1.000**
History of irAE (Yes/No)	(5/6)	(4/9)	0.459
Corticosteroid administration (Yes/No)	(0/11)	(1/12)	1.000
Radiotherapy	(1/10)	(4/9)	0.327

Abbreviations: Adeno, adenocarcinoma; BMI, body mass index; Discontinuation reasons, reasons for discontinuation of initial ICI therapy; ECOG, Eastern Cooperative Oncology Group; ICIs, immune checkpoint inhibitors; irAE, immune-related adverse events; Initial ICI therapy, duration of initial ICI therapy; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; PS, performance status; Rechallenge with ICIs, duration of treatment after rechallenge with ICIs; Radiotherapy, radiotherapy between the initial ICI therapy and rechallenge with ICIs; Withdrawal period, time from discontinuation of initial ICI therapy to rechallenge with ICIs.

[a]Fisher's exact test.

[b]Unpaired *t*-test.

TABLE 2 Patients with irAE

Group	Age/sex	First ICI regimen	irAE of first ICIs (grade)	Re-ICI regimen	irAE of re-ICIs (grade)
r	65/M	Durvalumab	GGT increased (3)	Nivolumab	Hypothyroidism (3)
r	67/M	Pembrolizumab	Pneumonitis (3)	Atezolizumab	Pneumonitis (3)
r	67/M	Pembrolizumab	Pneumonitis (1)	Atezolizumab	None
r	78/F	Pembrolizumab	AST increased (3)	Atezolizumab	None
r	59/M	Nivolumab	Hypothyroidism (2)	Atezolizumab	Pneumonitis (3)
non-r	71/F	CBDCA+nab-PTX + pembrolizumab	Neutropenia (4)	Atezolizumab	None
non-r	82/F	Pembrolizumab	Myasthenia gravis (2)	Pembrolizumab	None
non-r	75/M	CBDCA + PTX + pembrolizumab	Neutropenia (2)	Nivolumab	None
non-r	76/M	Pembrolizumab	None	Atezolizumab	Pneumonitis (2)

Abbreviations: AST, aspartate aminotransferase; CBDCA, carboplatin; F, female; GGT, gamma-glutamyl transferase; ICIs, immune checkpoint inhibitors; irAE, immune-related adverse events; M, male; non-r, nonresponder group; PTX, paclitaxel; r, responder group; Re-ICIs, rechallenged ICIs.

TABLE 3 Univariable and multivariable analysis of risk factors of nonresponse to rechallenged ICIs

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*-value	OR	*p*-value
NLR (<5 vs. ≥5)	0.600 (0.106–3.400)	0.564	0.194 (0.011–3.499)	0.266
BMI (<20 vs. ≥20)	10.550 (0.043–7.034)	0.646	0.112 (0.003–3.728)	0.221
Lung metastasis (Yes or No)	6.250 (0.602–64.862)	0.125	57.520 (1.347–245.650)	0.034
Age (≥75 years vs. <75 years)	0.259 (0.040–1.700)	0.159	1.091 (0.092–12.994)	0.945
Sex (Female vs. Male)	**5.250 (0.801–34.426)**	**0.084**	**26.709 (1.187–601.176)**	**0.039**
TPS (<50% vs. ≥50%)	0.511 (0.108–3.036)	0.571	1.104 (0.099–12.323)	0.936

Abbreviations: BMI, body mass index; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; TPS, tumor proportion score.

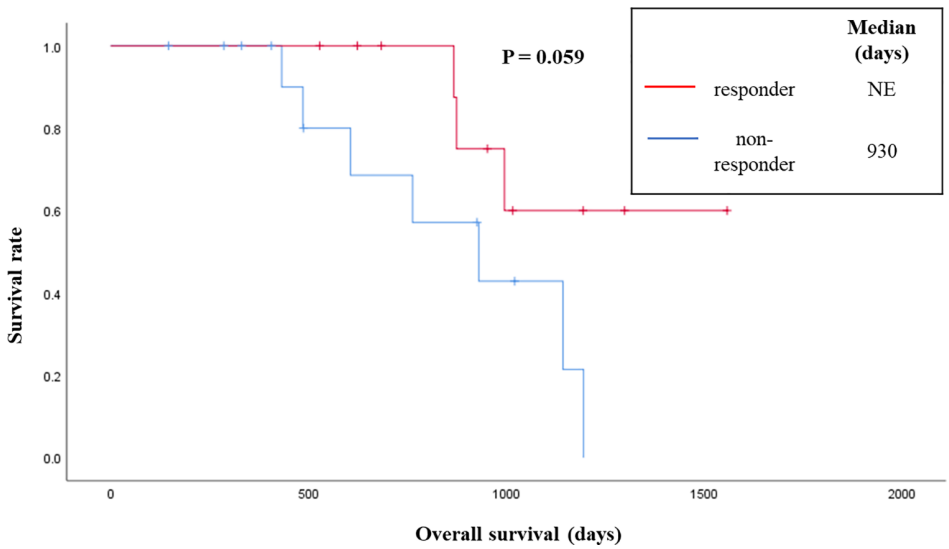

FIGURE 2 Overall survival of patients in the responder and nonresponder groups. The median survival time of patients in the responder group was not evaluated (NE), and that of patients in the nonresponder group was 930 days. There was no significant difference between the two groups ($p = 0.059$, log-rank test)

11 (27.3%) patients in the responder group and one of 13 (7.7%) in the nonresponder group had irAEs after rechallenge with ICIs.

After rechallenge with ICIs, two patients in the responder group developed grade 3 pneumonitis; therefore, ICI therapy was discontinued. In the non-responder group, grade 2 pneumonitis occurred in one patient, but ICI therapy was continued.

Univariate and multivariate analysis

The dependent variable was the presence or absence of PD, and the independent variables were NLR, BMI, age, sex, TPS, and lung metastasis. Binomial logistic regression analysis revealed that lung metastasis ($p = 0.034$, odds ratio = 75.520, and 95% confidence interval = 1.347–245.650) and being female ($p = 0.039$, odds ratio = 26.709,

and 95% confidence interval = 1.187–601.176) were independent risk factors for nonresponse to rechallenge with ICIs (Table 3).

The survival curves of the responder and nonresponder groups are shown in Figure 2. There was no significant difference between the two groups ($p = 0.059$ by log-rank test), but there was a trend toward prolonged survival in the responder group.

DISCUSSION

In this study, we performed an analysis to determine the clinical characteristics and predictors of patients with NSCLC who responded well to rechallenge with ICIs.

The results of this study showed that TPS, NLR, and history of radiotherapy, which are considered predictors of response to initial ICI therapy, were not significantly different between the two groups and could not be used as predictors of response to rechallenge with ICIs. In addition, the occurrence of irAEs has been reported to correlate with prognosis,[18,19] but there was no significant difference in the occurrence of irAEs between the responder and nonresponder groups.

Although there are very few reports on rechallenge with ICIs, it has been reported that poor PS and low BMI are predictors of a negative impact on progression-free survival,[12,13] and that patients who discontinue their initial ICI therapy due to toxicity or clinical judgment are associated with a favorable prognosis.[14]

In this study, there were no significant differences in PS, BMI, or reasons for discontinuation of initial ICI therapy between the responder and nonresponder groups. However, in the responder group, initial ICI therapy was discontinued in eight of 11 (72.7%) patients due to PD. For some patients, even though the response to initial ICI therapy was judged to be PD, airway obstruction was reduced by tumor shrinkage after rechallenge with ICIs, and home oxygen therapy was terminated (Figure 1). It was suggested that some patients can benefit from rechallenge with ICIs, even those with PD after initial ICI therapy.

This study suggested that rechallenge with ICIs can provide long-term disease control and prolonged prognosis with continued treatment, even if tumor growth within the SD range is observed in the initial response assessment. Additionally, rechallenge with ICIs should be a treatment option, even in patients with characteristics that might cause nonresponse to ICIs, such as low TPS, NLR, PS, and BMI.

A review of rechallenge with ICIs reported that the RR and DCR of rechallenge with ICIs were 43.1 and 73.6%,[20] respectively, which suggest a similar efficacy with initial ICI therapy. In the present study, the RR and DCR of rechallenge with ICIs were 8.3 and 45.8%, respectively. This difference may be partly due to the fact that the review article was an analysis of a variety of primary tumors with different responses to ICIs. Moreover, three of the five studies included patients with NSCLC who discontinued initial ICI therapy due to irAEs. The RR of nivolumab in previously treated NSCLC has been reported to be 19%, and the antitumor effect is sustained for a very long time, especially in cases of response.[1] Based on the results of this study, rechallenge with ICIs is less likely to result in a better response than initial ICI therapy. However, even if the initial response is judged to be SD, a treatment strategy of continuing treatment with the hope of long-term disease control may be considered.

In the current study, switching administration was performed in all patients in the responder group, and there was a statistically significant difference between the two groups ($p = 0.006$). In one case series, it was reported that switching between PD-1 and PD-L1 inhibitors could be a treatment option for some patients with NSCLC,[15] and it has been speculated that tumor heterogeneity may contribute to the difference in response to switching administration. The results of our study suggest that switching administration may be involved in the response to rechallenge with ICIs.

However, some existing case series have controversial findings. Fujita et al. reported that the efficacy of rechallenge with anti-PD-L1 antibody after anti-PD-1 antibody therapy in patients with advanced NSCLC was limited due to a low DCR of 38.9%.[21]

The results of our study suggest that switching administration may influence the response to rechallenge with ICIs. However, switching ICI administration was performed for all patients in the responder group, and there was a bias between the two groups. Therefore, it was not possible to analyze switching administration in the multivariate analysis. Further investigation is required with studies of greater sample size in order to determine whether the use of ICI therapy with the same type of ICI has a negative effect on patient response to rechallenge with ICIs.

In this study, multivariate analysis identified lung metastasis and female sex as independent risk factors for nonresponse to rechallenge with ICIs.

It has previously been reported that the antitumor effect of the first dose of PD-1 inhibitors is attenuated by lung metastases,[22,23] suggesting that the microenvironment of the lung altered by lung metastases might have affected the response of the primary tumor to PD-1 inhibitors. The results of this study suggest that lung metastases are likely to be nonresponsive, not only in patients who receive an initial administration of PD-1 inhibitors but also in patients who are rechallenged with ICIs. In addition, it has been reported that the efficacy of ICIs is reduced in patients with brain, liver, bone, and pleural metastases.[21,24] However, in the present study, there was no significant difference in brain, liver, bone, and pleural metastases between the responder and nonresponder groups. Further accumulation of cases will be necessary to clarify whether metastatic lesions attenuate the effect of rechallenge with ICIs.

It has been reported that there is a sex difference in the efficacy of ICIs.[25] Conforti et al. conducted a systematic review and meta-analysis to evaluate the association between patient sex and risk of death in randomized clinical trials of

PD-1 and CTLA-4 inhibitors. A review meta-analysis showed that the hazard ratio of overall survival was 0.72 for male patients and 0.86 for female patients, indicating that there is a sex difference in the efficacy of ICIs. Although Conforti et al. did not mention the association between sex and RR, the results of this study suggest that the RR to rechallenge with ICIs may be lower in females.

Currently, there is no standard of care for patients with NSCLC beyond third-line treatment. The results of this study indicate that rechallenge with ICIs is a treatment that can be expected to provide long-term disease control in some cases and will have important implications for the treatment of patients with NSCLC after third-line treatment, for which there is poor evidence.

However, it has been shown that 50%–55% of patients with solid cancers experience any grade of irAE upon resumption of PD-1 inhibitors.[16,26] In our study, four of 24 (16.7%) patients experienced irAEs after rechallenging with ICIs. Although none of the tumors were of grade 3 or higher and could be managed, two patients in the responder group developed grade 3 pneumonitis and discontinued ICI therapy.

Checkpoint inhibitor pneumonitis (CIP) has a high recurrence rate in patients rechallenged with ICIs[17] and can be fatal in severe cases.[27] Furthermore, patients with deteriorating or persistent CIP have a worse prognosis than those with improving CIP.[28] When considering rechallenge with ICIs in patients who developed CIP after initial ICI therapy, the risks and benefits to patients should be more accurately assessed.

This study has some limitations. First, it was a retrospective study that did not have a randomized sample. There is a large potential for bias in patient selection and information collection. Furthermore, the sample size was small and may not have sufficient statistical power to detect differences between the responder and nonresponder groups. In the future, analyses with a larger number of patients in multiple facilities are needed. However, we believe that it is also important to accumulate evidence for rechallenge with ICIs in patients with NSCLC by accumulating evidence from small-scale clinical studies.

In conclusion, the findings of this study suggest that ICI rechallenge of the same type in patients with lung metastases and female patients may reduce the antitumor effect in the treatment of NSCLC. In addition, in the group of patients who achieved SD or better in the initial efficacy assessment after rechallenge with ICIs, ICI therapy can be continued for a longer period of time. This may be associated with prolonged survival.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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