

Discontinuation of Immune Checkpoint Inhibitor due to irAEs in NSCLC Patients With *EGFR* Mutation

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Abstract. *Background/Aim:* Immune checkpoint inhibitors (ICIs) have revolutionized advanced non-small cell lung cancer (NSCLC) treatment. Even patients with epidermal growth factor receptor (EGFR)-mutated NSCLC may choose an ICI after failure of EGFR-tyrosine kinase inhibitor treatment. ICI-mediated immune-related adverse events (irAEs) may prompt NSCLC patients to discontinue their treatment. This study evaluated the effect of ICI treatment discontinuation on the prognosis of patients with EGFR-mutated NSCLC. *Patients and Methods:* We performed a retrospective study that reviewed the clinical courses of patients with EGFR-mutated NSCLC treated with ICI therapy from February 2016 to February 2022. 'Discontinuation' was defined as failure to receive at least two treatment courses of ICI due to grade 2 irAEs (grade 1 in the lung) or higher in patients responding to ICI. *Results:* During the study period, 13 of 31 patients discontinued ICI therapy due to irAEs. Survival from the initiation of ICI therapy was significantly longer in patients who discontinued ICI therapy compared with those who did not discontinue. In uni- and multivariate analyses, 'discontinuation' was a favourable factor. There

was no significant difference in survival from ICI initiation between patients with grade 3 or higher irAEs and those with grade 2 or lower irAEs. *Conclusion:* In this patient cohort, discontinuation of ICI therapy due to irAEs did not adversely affect prognosis in patients with EGFR-mutant NSCLC. Our results suggest that when treating patients with EGFR-mutant NSCLC with ICIs, chest physicians should consider discontinuing ICI with close monitoring.

Immune checkpoint inhibitors (ICIs) have transformed treatment for many advanced carcinomas including non-small cell lung cancer (NSCLC) (1-4). The long-tailed plateau of survival curves in patients receiving ICI therapy is extremely positive, with a considerable cure rate in patients with advanced NSCLC (1-4). With conventional cytotoxic anti-tumour drugs, dosing and treatment intervals are determined by pharmacokinetics and pharmacodynamics, such as drug half-life and blood concentrations (5). The therapeutic effect might be expected to decline if the drug is discontinued for some reasons. However, some previous studies have shown that the prognosis of patients who discontinue ICI therapy due to immune-related adverse events (irAEs) does not necessarily worsen (6-19). To our knowledge however, there have been no prospective studies that clearly show discontinuation of ICIs due to irAEs does not impair prognosis.

ICI therapy for NSCLC patients has been primarily performed in those negative for driver mutations. In NSCLC patients with driver mutations, specific tyrosine kinase inhibitors (TKIs) are usually selected as first-line therapy, but these patients are commonly difficult to cure. ICI therapy is an attractive treatment due to its long-tailed survival curve plateau. As such, ICIs are likely to be the therapy of choice for the second and subsequent treatment lines in patients with driver gene-positive NSCLC. The impact of discontinuation of ICI therapy has not been established in patients with epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC, where previous studies were only in small numbers

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Key Words: Immune checkpoint inhibitor, discontinuation, non-small cell lung cancer, epidermal growth factor receptor, EGFR, driver mutation.

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Table I. Characteristics of patients with or without discontinuation of immune checkpoint inhibitor (ICI).

	Patients		<i>p</i> -Value*
	With discontinuation	Without discontinuation	
Number of patients	13	18	
Sex, M:F	6: 7	11:7	0.481
Age (years), >70<:≤70	8:5	12:6	0.999
PS, 0-1:2-3	13:0	17:1	0.999
Pathology, AD:others	12:1	17:1	0.999
Stage, IIIA-C:IVA-B	0:13	2:16	0.497
EGFR, Exon 19 del:others	5:8	13:5	0.079
PD-L1, 0%:≤1%	6:7	13: 5	0.232
ICI, mono:comb	9:4	15:3	0.413

PS: Performance status; AD: adenocarcinoma; EGFR: epidermal growth factor receptor; del: deletion; PD-L1: programmed death ligand 1; mono: monotherapy; comb: combination chemotherapy with ICI.

of patients (15, 16). As such, we conducted this study with the aim of clarifying the clinical significance of ICI discontinuation in patients with *EGFR* mutation-positive NSCLC.

Patients and Methods

Patients. The medical records of all consecutive patients diagnosed with NSCLC in our three tertiary hospitals between February 2016 and February 2022 were examined. All patients with NSCLC who received ICI therapy, whether as monotherapy or in combination with chemotherapy, were included in the study. NSCLC was diagnosed using the classification of the World Health Organization. The clinical stage was assessed according to the TNM classification (8th Edition) (20) using computed tomography scans or magnetic resonance imaging of the head, bone scans, and ultrasonography and/or computed tomography of the abdomen in all patients prior to ICI therapy initiation. In all the NSCLC patients, *EGFR* mutation was evaluated by cobas® *EGFR* Mutation Test v2 (Roche Diagnostics, Tokyo, Japan) or Oncomine Dx Target Test Multi-CDx system (Life Technologies, Tokyo, Japan) using bronchoscopic or surgically resected tissue specimens prior to initiation of systemic therapy including TKIs.

Background patient data, such as age, sex, Eastern Cooperative Oncology Group score for performance status, histopathology, disease stage and programmed death ligand 1 (PD-L1) expression were obtained from the patients' medical records. Objective tumour response was evaluated according to Response Evaluation Criteria in Solid Tumours guidelines (version 1.1) (21). All irAEs were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0) (22).

Discontinuation of ICI. The reason for ICI discontinuation was extracted from the patients' medical records. 'Discontinuation' was defined as failure to receive at least two treatment courses of ICI due to grade 2 irAEs (grade 1 in the lung) or higher in patients who

had 'partial response' or 'complete response' status ICI. In other words, patients that requested to discontinue ICI therapy while in a 'progressive disease' state of lung cancer were not included in the 'discontinuation' group.

Statistical analysis. For comparing nominal variables, we used the χ^2 test. To compare values with unknown variance, we used the nonparametric Mann-Whitney test. We used progression free survival (PFS) and overall survival (OS) to assess the duration of therapy. In addition, we evaluated survival from the initiation of the first ICI therapy until the last follow-up. Survival time was estimated by the Kaplan-Meier method and compared using the log rank test. We used the Cox proportional hazards model and the forward-backward stepwise method to determine the independent variables used in the final model. All statistical analyses were conducted using SPSS, version 23 (IBM Corporation, Armonk, NY, USA). A *p*-value of less than 0.05 was considered significant.

Ethics. This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labour, and Welfare of Japan. Written informed consent for a non-interventional retrospective study was obtained from each patient. Analysis of patient medical records was approved by the ethics committee of the Mito Medical Centre, University of Tsukuba (NO 20-57).

Results

Clinicopathological features of patients treated with ICI. During the study period, 31 *EGFR*-positive patients received ICIs as second or later-line therapy after *EGFR*-TKIs. Thirteen of the 31 patients (41.9%) discontinued ICI treatment due to irAEs (10 after ICI monotherapy, 3 after chemotherapy plus ICI). The median (range) length of discontinuation was 3.0 (2.0-27.0) months. The remaining 18 patients did not discontinue ICI treatment. No patient continued ICI treatment despite the appearance of a grade 2 or higher irAE (respiratory grade 1 or higher irAE). Table I compares patient backgrounds. There were no significant differences in patient characteristics between the groups with and without discontinuation of ICI therapy. At the end of the study period, 25 of the 31 patients had died, four were undergoing anti-cancer treatment, and two were transferred to a palliative care facility.

Comparison of patients with or without discontinuation of ICI. Figure 1 shows OS, treatment details and clinical course from the initiation of first-line therapy of the 31 patients who did or did not have ICI discontinuation. The median (range) OS from the initiation of *EGFR*-TKI until the last follow-up in patients with or without ICI discontinuation was 44.0 (11.0-79.0) and 27.0 (12.0-132.0) months, respectively. These values were not significantly different (*p*=0.459).

Details of treatment and survival from initiation of ICI therapy until last follow-up in the two groups of patients are shown in Figure 2. The median (range) length of survival from initiation of ICI until the last follow-up in patients with

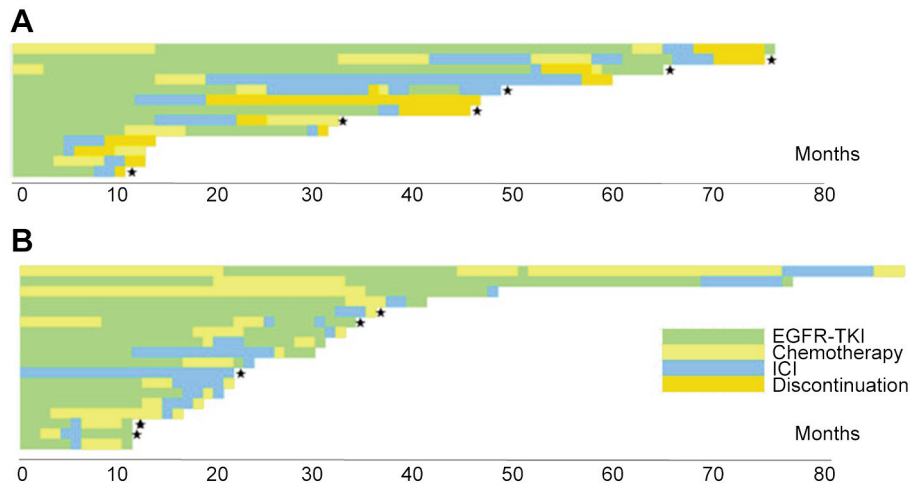


Figure 1. Treatment content and overall clinical course from the initial treatment for each patient treated with immune checkpoint inhibitor (ICI)-containing therapy. The upper rows (A) show treatment periods for patients with discontinuation of ICI therapy and the lower rows (B) show treatment periods for patients without discontinuation of ICI therapy. Star: patient alive at last follow-up.

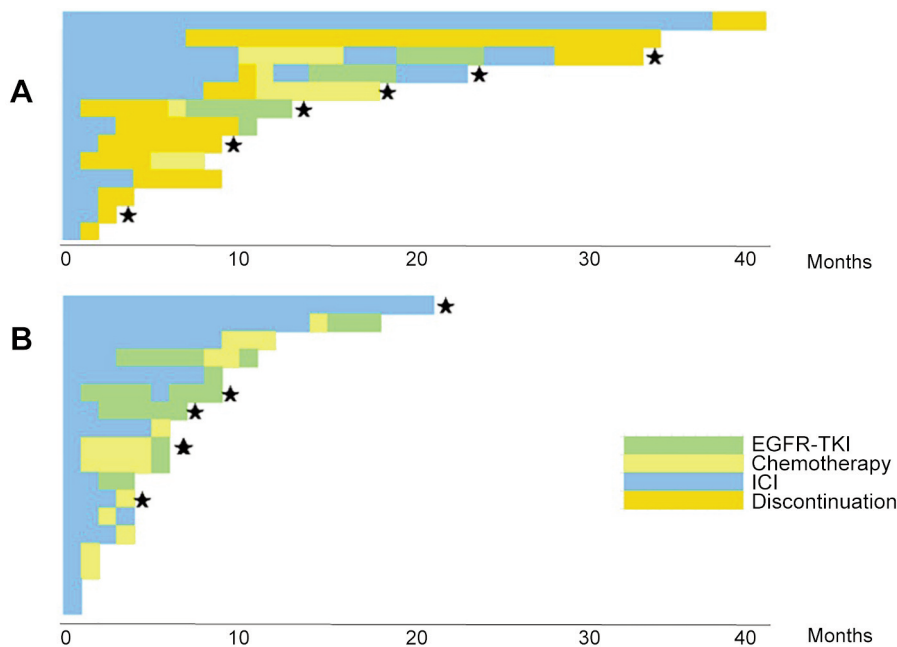


Figure 2. Treatment content and clinical course from the initiation of ICI therapy for each patient treated with immune checkpoint inhibitor (ICI)-containing therapy. The upper rows (A) show treatment periods for patients with discontinuation of ICI therapy and the lower rows (B) show treatment periods for patients without discontinuation of ICI therapy. Star: patient alive at last follow-up.

and without ICI discontinuation was 13.0 (2.0-56.0) and 8.0 (2.0-39.0) months, respectively; which were significantly different ($p=0.040$).

Contribution of ICI discontinuation to survival. Since there was no difference in background characteristics

between patients with or without ICI discontinuation, factor analysis for survival from ICI initiation until the last follow-up was performed. As shown in Table II, univariate analysis revealed that 'presence of PD-L1 expression' and 'discontinuation of ICI therapy' contributed to survival. Multivariate analysis confirmed

Table II. Uni- and multivariate analysis of survival from the initiation of immune checkpoint inhibitor (ICI) therapy in patients with or without discontinuation of ICI.

	Univariate analysis (p-Value)	Multivariate		
		Odds ratio	95%CI	p-Value
Age, less than 70 years	0.458			
Sex, female	0.920			
PS, 0-1	0.103			
Stage, IIIA-C	0.057			
Pathology, AD	0.843			
PD-L1, ≤1%	0.036	0.730	0.73-2.08	0.172
Discontinuation of ICI	0.004	1.03	1.03-3.67	0.049

PS: Performance status; AD: adenocarcinoma; CI: confidence interval; PD-L1: programmed cell death-ligand 1.

discontinuation of ICI due to irAEs as a favourable factor that contributed to patient survival.

Patients with discontinuation of ICI. The clinicopathological features of each of the 13 patients who discontinued ICI therapy are shown in Table III. Eight patients had irAEs of grade 2 or less and five had irAEs of grade 3-4. For survival from the initiation of ICI treatment to final follow-up, we examined age (70 years and older, under 70 years), sex, *EGFR* gene mutation type (Exon 19 deletion, others), PD-L1 expression (none, 1% or more), ICI (PD-L1 antibody, PD-1 antibody), ICI administration method (single agent, chemotherapy combination), and irAE (up to grade 2, grade 3 and higher). There were no significant differences between groups (*p*-values: 0.181, 0.772, 0.564, 0.107, 0.734, 0.962 and 0.271, respectively).

Treatment after ICI discontinuation was performed in nine patients (chemotherapy in 5, TKIs in 3, and ICI in 1 patient). No irAEs occurred in the patient re-challenged with ICI.

Discussion

In the present study, treatment courses for 31 patients who had ICI therapy at any stage were investigated in detail. Thirteen patients had discontinuation of ICI-containing therapy due to grade 2 or higher irAEs (or grade 1 or higher pulmonary irAEs). The median (range) length of discontinuation was 3.0 (2.0-27.0) months. There was no difference in the clinicopathological backgrounds of the 13 patients who discontinued ICI therapy and the 18 patients who did not, and there was no difference in OS between the two groups. However, survival from the initiation of ICI therapy was significantly longer in the 13 patients who discontinued ICI therapy compared with the 18 patients who did not. In uni- and multivariate analyses, “discontinuation of

ICI therapy due to irAEs” was a favourable factor. There was no significant difference in survival from initiation of ICI to final follow-up between patients with irAEs grade 3 or higher, and those with grade 2 or lower irAEs. These data indicate discontinuation of ICI due to irAEs occurring during treatment response period could be an acceptable treatment option. Of course, in such cases, continuous image evaluation for the presence or absence of recurrence would be essential.

In driver gene-negative NSCLC patients treated with ICIs, it is common to encounter patients who have had to discontinue treatment due to, for example, the occurrence of irAEs. In such cases, these patients may change to a treatment other than ICI or discontinue ICI therapy (23). Several studies have been conducted on ICI discontinuation in driver mutation-negative NSCLC (6-16). Many of these studies found discontinuation did not adversely affect prognosis, indicating discontinuation could be chosen without hesitation in situations where discontinuation is necessary (6-16). However, there are no universal guidelines regarding the rationale and conditions for discontinuation, meaning decisions would need to be made on a case-by-case basis. However, in patients with *EGFR* gene mutation NSCLC, treatment with *EGFR*-TKI has been established as the standard therapy (24) and usually selected as first-line treatment. However, cure with *EGFR*-TKIs is considered impossible. Therefore, incorporation of other treatments into the TKI treatment regimen needs further exploration. Some years ago, osimertinib after nivolumab treatment was associated with a high risk of developing drug-induced lung injury (25, 26). However, there have been no further reports of this association, perhaps due to an avoidance of these treatments in this order. Despite these circumstances, there is increasing evidence that ICI is a useful option for patients with *EGFR*-mutated NSCLC. While there have been some reports on ICI discontinuation in patients that included those with *EGFR*-mutated NSCLC (15, 16), these studies did not perform any specific prognostic sub-analysis in these patients. Therefore, our current study is the first to focus on ICI discontinuation in NSCLC patients with an *EGFR* driver mutation.

This study presented some interesting findings, but also had some limitations. First, this study was retrospective in nature with a small number of patients. As such the analysis grouped several different ICIs together. Using data from a larger number of patients would allow analysis of ICI discontinuation across discrete ICIs. Similarly, patients treated with ICI monotherapy and those treated with chemotherapy and ICI should ideally have been analysed separately. Second, in this study, discontinuation was defined as failure to receive at least two treatment courses due to irAEs of grade 2 (grade 1 in the lung) or higher but it was unclear whether the period of discontinuation was appropriate. Therefore, a clear and universally acceptable

Table III. Clinicopathological features of patients who discontinued immune checkpoint inhibitor (ICI) therapy.

Patient	Age (years)	Sex	PS	Histology	Stage	EGFR	PD-L1 (%)	TKI	ICI	ICI therapy	irAE	Discontinuation	Post-discontinuation therapy
1	53	F	0	AD	4A	Ex19 deletion	0	O	Ipilimumab+Nivolumab	Combination	Diabetes (G3)	7 months	None
2	56	F	0	AD	4B	Ex19 deletion	70	E	Atezolizumab	Mono	Thyroid (G2)	2 months	Chemotherapy
3	57	F	1	AD	4B	Ex21 L858R	0	A	Nivolumab	Mono	Heart (G3)	2 months	None
4	57	M	1	AD	4B	Ex19 deletion	40	G	Pembrolizumab	Mono	Skin (G2)	3 months	None
5	59	M	1	AD	4B	Ex18 G719X	90	O	Atezolizumab	Mono	Skin (G2)	5 months	TKI
6	65	M	1	AD	4B	Ex19 deletion	30	E	Atezolizumab	Mono	Liver (G3)	5 months	Chemotherapy
7	67	F	1	AD	4B	Ex21 L858R	0	O	Pembrolizumab	Combination	Lung (G4)	5 months	None
8	68	M	1	AD	4A	Ex18G719X, Ex21L861Q	0	A	Pembrolizumab	Mono	Skin (G2)	2 months	Chemotherapy
9	71	F	0	AD	4B	Ex21 L858R	70	O	Pembrolizumab	Combination	Lung (G1)	3 months	Chemotherapy
10	74	M	1	AD	4A	Ex21 L868R	0	G	Nivolumab	Mono	Pituitary (G2)	27 months	TKI
11	75	M	1	ADSQ	4B	Ex19 deletion	0	G	Nivolumab	Mono	Skin (G2)	2 months	TKI
12	75	M	1	AD	4B	Ex21 L858R	70	O	Atezolizumab	Combination	Colon (G3)	7 months	Chemotherapy
13	76	F	1	AD	4B	Ex21 L858R	5	A	Pembrolizumab	Mono	Skin (G2)	2 months	ICI

PS: Performance status; EGFR: epidermal growth factor inhibitor; PD-L1: programmed death-ligand 1; TKI: tyrosine kinase inhibitor; irAE: immune-related adverse event; AD: adenocarcinoma; ADSQ: adenosquamous carcinoma; Ex: Exon; O: osimertinib; E: erlotinib; A: afatinib; G: gefitinib.

definition of ‘discontinuation of ICI therapy’ is required. Third, there is the possibility that the evaluation of ICI discontinuation was simply that of irAEs. In other words, the patients who underwent ICI discontinuation were exactly the same patients who developed irAEs, thus the results obtained could be interpreted as the result of irAEs development. Continuing ICI in patients with severe irAEs is ethically inappropriate. Therefore, since it is difficult to analyse these two separately, it was a limitation that could not be analysed separately in this study. Despite these limitations, this study, which more reflects actual clinical practice, provided preliminary indications that warrant further study. It might be informative to divide patients into two groups, one with ICI discontinuation and the other without discontinuation at the time of appearance of irAEs and compare the prognosis between these two groups. However, it might be difficult to design an optimal prospective comparative study when it remains debatable what treatment the control group should receive. As such, an alternative could be to collect and analyse the results of as many patients as possible in a retrospective manner.

Conclusion

It would not be appropriate to recommend discontinuation of ICI based on the results of this study alone. However, discontinuation of ICI might be an option if severe irAEs develop that require ICI discontinuation, or the patient chooses discontinuation even though responding to ICI treatment. A prospective clinical trial with discontinuation of ICI as a study arm should be considered in the future. In all cases, however, regardless of whether discontinuation of ICI occurs, close attention should be paid to monitoring for recurrence.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors’ Contributions

SO, SH, TS, KM and HS designed the study. SO, SH, TS, KM and HS collected the data. SO, SH and HS analysed the data. SO, SH, HS and NH prepared the manuscript. HY, HS, and NH supervised the study. All Authors approved the final version for submission.

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