

The efficacy of immune checkpoint inhibitors in advanced non-small cell lung cancer harboring driver mutations

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Abstract. The present retrospective study was conducted to evaluate the efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced non-small cell lung cancer (NSCLC) harboring driver mutations. Patients with NSCLC harboring driver mutations who received ICIs (nivolumab or pembrolizumab) were reviewed in Hirosaki University and Aomori Prefectural Central Hospital. There were 139 patients who received molecular targeted drugs, including 24 patients treated with ICIs. Patient characteristics were as follows: Male/female, 5/19; median age 68 (range 39-82); smoking/non-smoking, 6/18; PS 0-1/2, 20/4; driver mutation status, EGFR/ALK/RET/ROS1: 21/1/1/1. The overall response rate was 16.7% [95% confidence interval (CI), 7.0-37.1%] and the disease control rate was 33.4% (95% CI, 18.9-55.1%). The median progression-free survival (PFS) time was 62 days (95% CI 52-81 days). In the patients who had been treated by the preceding tyrosine kinase inhibitor (TKI) for >1 year, the PFS time was 110 days. On the other hand, in the patients who had received a TKI for less than a year, the PFS time was 56 days, which was significantly shorter (P=0.012). To conclude, some of the patients with NSCLC harboring driver mutation could benefit from ICIs, and the duration of previous TKI treatment may be associated with the efficacy.

Introduction

Lung cancer is the leading cause of cancer-related death in the world, with non-small cell lung cancer (NSCLC) accounting

for 85% (1,2). Management of advanced NSCLC has changed drastically over the past 15 years. Specific targeted therapies have been available for the treatment of advanced NSCLC. Tyrosine kinase inhibitors (TKIs) for driver mutations such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocations, and c-ros oncogene 1 (ROS-1) are superior to conventional platinum based cytotoxic agents in clinical trials (3-7). Moreover, immune checkpoint inhibitors (ICIs) which target programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) have been shown to contribute to overall survival (OS) as first or second line therapy in advanced NSCLC (8-11). However, subset analysis of phase III clinical trials indicated that ICIs might be less effective in advanced NSCLC harboring driver mutations (12). A retrospective study showed that ICIs had progression-free survival (PFS) as short as 1.2-2.1 months in those with EGFR mutations (13). It has been reported that the overall response rate (ORR) was 3.6% when ICIs were used for the patients with EGFR mutation (14). In addition, a basic research suggested that the expression of PD-L1 in patients with EGFR/ALK wild type is lower than that of patients with EGFR/ALK mutated patients (15). In this study, we analyzed a real world cohort of patients with NSCLC harboring driver mutations who were treated with ICIs.

Patients and methods

Study design. In this retrospective observational study, we aimed to evaluate the efficacy of ICIs in advanced NSCLC harboring driver mutations. The medical records were collected from two institutions, Hirosaki University (Hirosaki, Japan) and Aomori Prefectural Central Hospital (Aomori, Japan). This study was approved by the Hirosaki University institutional review board and Aomori Prefectural Central Hospital institutional review board.

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Target lesion assessment. The efficacy of ICIs was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The size of the target lesions were measured by imaging studies (i.e, chest radiography, computed tomography, magnetic resonance imaging).

Evaluation and statistical analysis. The PFS was estimated using the Kaplan-Meier method. The PFS has been defined as the time from the date of treatment initiation to the date of disease progression, death or the last contact. If neither event was observed, it was considered to be censored with the latest observation date. In case, post-treatment was started, it was considered to be censored with the date of initiation of next line chemotherapy. If the event was unknown in the case of transfer or non-arrival, it was censored with the final date when the patient survival was confirmed. Statistical analyses were performed using JMP 10 (SAS Institute, Cary, NC, USA). Intergroup comparisons of response rate and other parameters were made using the log-rank and chi-square tests. The significance level was set at $P < 0.05$.

Results

Patient characteristics. Among 139 patients who were treated previously with molecular targeted therapy at Hirosaki University and Aomori Prefectural Central Hospital from September 2014 to January 2017, 24 received ICI. The characteristics of the 24 eligible patients were listed in Table I. Five male (20.8%) patients and 19 female (79.2%) patients, with a median age of 68 years (range, 39-82 years), were included. Twenty (83.3%) patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1, and 23 (95.8%) had adenocarcinoma histology. Only one patient had squamous cell carcinoma histology. Two patients had stage IIIB, 12 had stage IV, and 10 had recurrent disease. The driver mutation status was as follows: Exon 19 del/exon 21 L858R/ALK/ROS-1/Rearranged during transfection (RET) in 14/7/1/1/1, respectively. The reason for discontinuation of prior TKI treatment for all patients was caused by progressive disease (PD). All patients except one patient who had ROS-1 positive patients received prior molecular target therapy. There were 7 patients (29.2%) who had resistant mutation. Twenty two (91.7%) patients were treated with nivolumab, 2 (8.3%) patients were treated with pembrolizumab.

Efficacy. The response to ICIs was shown in Table II. Four patients attained a partial response (PR) but no patients attained a complete response (CR). The ORR was 16.7%, and 4 patients (16.7%) had stable disease (SD). Fifteen patients (62.5%) had PD. Subset analysis for the ORR by baseline characteristics of patient was shown in Table III. There were no significant relationships between patient characteristics and response to ICIs. No patients (0%) with T90M achieved PR. On the other hand, 4 patients (23.5%) with negative or unknown of resistance gene achieved PR, although the difference did not reach statistical significance ($P = 0.10$).

The median PFS was 62 days (95% CI, 52- 81) (Fig. 1). A significant difference was observed in the PFS between the patients with longer treatment with TKI and those with shorter treatment (110 vs. 56 days; $P = 0.012$; Fig. 2). Of the 23 patients who received prior TKI treatment, 9 patients had TKI treatment period of 1 year or more, and the remaining 14 patients had TKI administration period of less than 1 year. One patient who had ROS-1 mutation was not treated with any TKI. There were no significant correlations between other clinical characteristics and PFS. In our study, there

Table I. Patient characteristics (n=24).

Variable	Number
Sex, n (%)	
Male	5 (20.8)
Female	19 (79.2)
Age, years (range)	68 (39-82)
ECOG PS, n (%)	
0-1	20 (83.3)
2	4 (16.7)
Clinical stage, n (%)	
IIIB	2 (8.3)
IV	12 (50.0)
Recurrence	10 (41.7)
Histological type, n (%)	
Adenocarcinoma	23 (95.8)
Squamous cell carcinoma	1 (4.2)
Smoking history, n (%)	
Smoker	6 (25.0)
Non smoker	18 (75.0)
Driver mutation, n (%)	
Exon 19 del	14 (58.3)
Exon 21 L858R	7 (29.1)
ALK	1 (4.2)
ROS-1	1 (4.2)
RET	1 (4.2)
Resistance gene, n (%)	
T790M positive	7 (29.2)
Negative or unknown	17 (70.8)
Treatment, n (%)	
Nivolumab	22 (91.7)
Pembrolizumab	2 (8.8)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS-1, c-ros oncogene 1; RET, Rearranged during transfection; T790M, EGFR-T790M mutation.

were 2 patients with rare mutation. One patient had ROS-1 and another patients had RET.

A 71-year old woman was diagnosed with stage IV lung adenocarcinoma with ROS-1 in November 2015. After her four cycles of carboplatin plus pemetrexed followed 4 cycles of maintenance therapy, she had PD. Increased primary tumor and multiple liver metastases appeared. She was treated with nivolumab and on 9 cycles of treatment, a PR was confirmed (Fig. 3).

Discussion

In this retrospective study, we evaluated that the efficacy of ICIs in patients with advanced NSCLC harboring driver mutations and relationship between the efficacy and the patient characteristics. We found that ORR was 16.7%, which

Table II. Response to immune checkpoint inhibitors.

Response	Number of patients	Percentage, %
Complete response	0	0
Partial response	4	16.7
Stable disease	4	16.7
Progressive disease	15	62.5
Not evaluable	1	4.2
Response rate		16.7

Table III. Univariate analysis of clinical factors for ORR of immune checkpoint inhibitors.

Clinical factor	ORR (%)	P-value
Age, years		0.95
<75	16.7	
≥75	17.7	
Smoking status		0.10
Smoker	0	
Never	23.5	
PS		0.67
0-1	15.8	
2	25.0	
Resistance gene		0.10
T790M positive	0	
Negative or unknown	23.5	

ORR, overall response rate; ICI, immune checkpoint inhibitor; PS, performance status; T790M, EGFR-T790M mutation.

was higher than the numbers reported previously (14,16). Moreover, a subset analysis revealed that patients who had received TKIs for longer term had better PFS than those treated with shorter terms of TKIs (110 vs. 56 days; $P=0.012$). Today, it is a serious clinical problem that there are few treatment choices after standard molecular target therapy. A previous subset analysis of phase III trials of ICIs did not show the OS benefit compared with docetaxel in patients with EGFR mutation (8,9,11). However, because the number of patients included in these studies was small, it has been unclear whether ICIs are effective or not.

Tumor mutation burden (TMB) and PD-L1 are key biomarkers predictive of the effectiveness of ICIs treatment (17). **TMB does not correlate with PD-L1 expression** and both markers have similar predictive capacity (18). In NSCLC with either EGFR mutation, or ROS-1 or ALK oncogene, TMB is lower than wild type (19-21). This is one of the main reasons why ICIs are less effective for mutant NSCLC. Recently, 80 patients with NSCLC harboring EGFR/ALK mutation were analyzed. The population with PD-L1 tumor proportion score of 50% or higher was reported to be 11.3% (22). **Several studies showed that PD-L1 expression** is also regulated by oncogenic drivers in NSCLC. EGFR

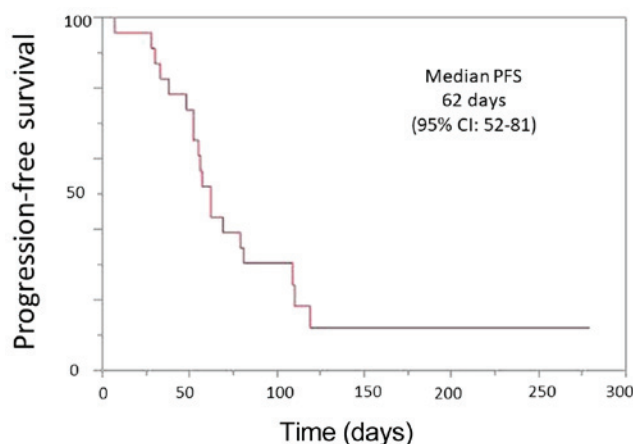


Figure 1. Kaplan-Meier analysis of progression-free survival for all 24 treated patients. The median progression-free survival was 62 days (95% CI, 52-81). CI, confidence interval.

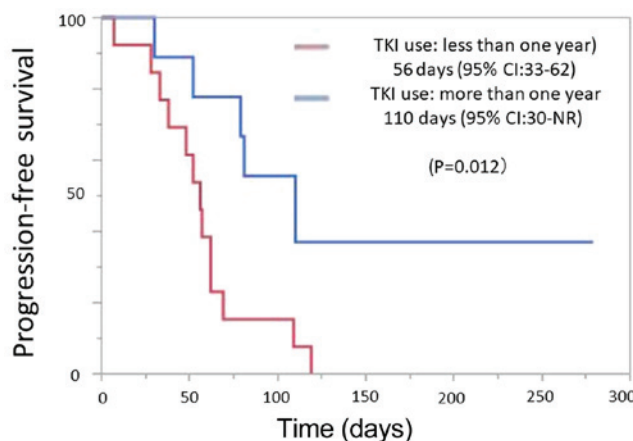


Figure 2. Kaplan-Meier analysis of progression-free survival of patient treated with TKI for >1 vs. <1 year. A significant difference was observed in the progression-free survival between the patients with longer treatment with TKI and those with shorter treatment (110 vs. 56 days; $P=0.012$). TKI, tyrosine kinase inhibitor.

activated by EGF stimulation, exon 19 deletion and L858R mutation induced **PD-L1 expression, suggesting that constitutive oncogene pathway activation can up-regulate PD-L1**. Chen and colleagues reported that inhibiting EGFR activation could reduce PD-L1 expression (23). Omori and colleagues showed that **treatments with EGFR-TKIs may increase PD-L1 expression** in NSCLC harboring EGFR mutations. In that report, 38% of the patients who were treated with EGFR-TKI increased PD-L1 expression (24). Other research group also suggested PD-L1 expression in tumor cells markedly increased in a subset of patients after gefitinib treatment (25). On the other hand, Lin and colleagues reported that PD-L1 expression did not correlate with treatment response and PFS in EGFR mutant patients, suggesting that PD-L1 status may not be associated with the efficacy of ICIs in patients with driver mutation (26). In our study, PD-L1 expression was not determined in most patients, which is one of the major limitations of our study. In our study, there were no patients who achieved tumor PR in the patients with T790M. Haratani *et al* reported that T790M-negative patients had longer PFS than T790M-positive

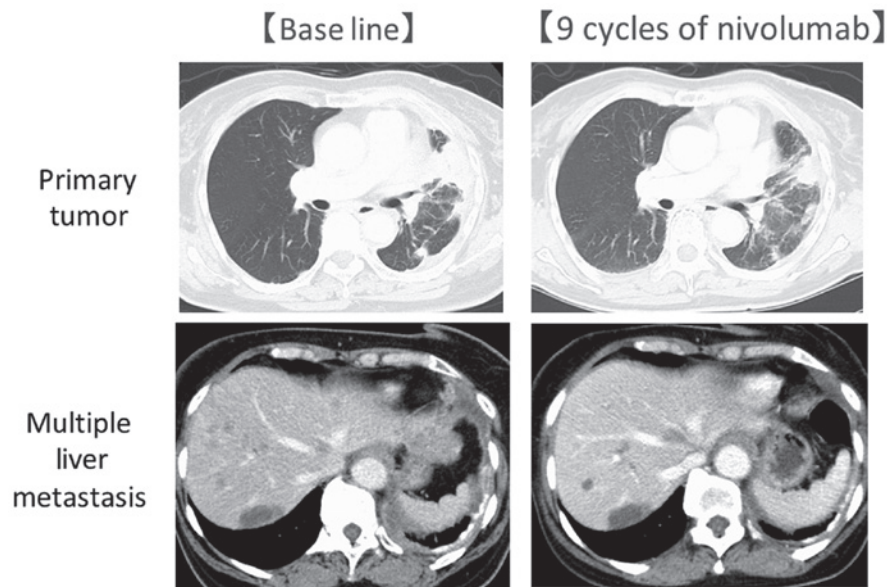


Figure 3. A 71-year old woman was diagnosed with stage IV lung adenocarcinoma with ROS-1 in November 2015. She was treated with nivolumab as second line therapy. After 9 cycles of nivolumab, a computed tomography scan revealed a reduction in size of primary tumor of the left lung and multiple liver metastatic lesions.

patients (2.1 vs. 1.3 months) after EGFR-TKI treatment (27). They suggested that prospective clinical trials are required to confirm the efficacy of PD-1 inhibitors in T790M-negative patients with EGFR mutation-positive NSCLC. Clinical trial is in progress (UMIN000021133). In our study, one patient with ROS-1 was included. The patient had achieved PR. Treatments of ICIs for the patients with rare mutations such as ROS-1, RET has been unclear yet.

Our study had some limitations. First, this study was retrospective study. Second, PD-L1 expression and T790M were not evaluated in every patient. Finally, sample size was small. Further analyses are warranted to determine the efficacy of ICIs in patients with driver mutations after TKI treatment. In conclusion, Even in NSCLC harboring driver mutation, there were some patient who could receive benefit of ICI and the treatment duration of TKI might be related to the efficacy.

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Availability of data and materials

The datasets used in this current study are available from the corresponding author on reasonable request.

Authors' contributions

HS prepared the manuscript and made contributions to acquisition of data. HT was involved in the conception of this study. HT and KT conducted statistical analysis. TS, KB, YI and

MI treated and observed patients in Hirosaki University. YH treated and observed patients in Aomori Prefectural Central Hospital. ShT advised and revised the statistical analysis. SaT contributed in evaluating the tumor efficacy on the CT scan and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review boards of all participating institutions.

Patient consent for publication

The present study was performed on a retrospective observational cohort. Therefore, informed consent was not obtained. The opt out approach was used.

Competing interests

The authors declare that they have no competing interests.

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