Observational Study

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Evaluation of clinicopathological features determining treatment response in patients with ALK mutant NSCLC

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Abstract

ALK (anaplastic lymphoma kinase) inhibitors may be used to treat patients with ALK mutant metastatic nonsmall cell cancer (NSCLC). This study aimed to investigate the factors affecting the patients response to treatment with ALK-positive metastatic NSCLC. Data of the patients were investigated retrospectively. Binary regression analysis was performed to evaluate response predictors of treatment. Furthermore, we determined the cut-off value of the ALK-positivity for objective response to the therapy using ROC analysis. A total of 68 patients were included in the research. The median overall survival was observed 39.2 months. The overall response rate was 66.2%. The ratio of ALK positivity (P = .02), gender (P = .04), and the total number of metastatic sites (P = .02) all were detected as predictors of the response to ALK inhibitor in binary regression analysis. ALK inhibitor type (P = .56), primary tumor location (P = .35), pathological subtype (P = .68), de-novo metastatic disease (P = .28), and age (P = .94) were not predictive indicators for response. The cut-off level of ALK positivity was found to be 33% in patients with an objective response. The real-life effectiveness of ALK inhibitors in NSCLC patients with ALK mutations was shown in this research. We determined that having less than 3 metastatic sites, having a high ALK positivity ratio, and being female were all good predictors of ALK inhibitor response.

Abbreviations: ALK = anaplastic lymphoma kinase, FISH = fluorescence in situ hybridization, IHK = Immunohistochemistry, NSCLC = non-small cell cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival

Keywords: alectinib, anaplastic lymphoma kinase, crizotinib, lung adenocarcinoma, prognosis

1. Introduction

Lung cancer is one of the most frequent and deadly malignancies in the world. Although surgery is the primary treatment in the early stage in lung cancer, radiotherapy and chemotherapy are used in the case of locally advanced and metastatic disease. The prognosis of lung cancer is generally poor. Smoking cessation programs and early diagnosis are critical for disease prognosis. Compared to a chest X-ray screening, lung cancer screening with low-dose CT in individuals over 55 years old with a 30 pack/year smoking history decreased to the rate of lung cancer-related death.[1] Tumor size, tumor differentiation, and lymphovascular invasion are posed a risk for recurrence in early-stage lung cancer patients. Also, age, performance status, smoking cessation, nodal involvement, and presence of distant metastases have been defined as clinical prognostic parameters in nonsmall cell cancer (NSCLC).[2]

In the treatment of metastatic NSCLC, individual treatment options can be determined according to the genetic profile. Many driver mutations (EGFR, ROS1, ALK, etc) exist in lung cancer development. The anaplastic lymphoma kinase (ALK) mutation is located on chromosome 2 and is detected at a rate of about 3–7% in NSCLC.[3] ALK mutation is frequently detected in nonsmokers, young individuals, and a solid tumor with signet-ring cells histology.[4] ALK positivity is detected by immunohistochemistry (IHK), fluorescence in situ hybridization (FISH) methods, and next-generation sequencing.[5] ALK inhibitors such as crizotinib, ceritinib, alectinib, and lorlatinib are used in the treatment of ALK-positive metastatic NSLC. The second and third-generation ALK inhibitors had shown superior efficacy to survival results and intracranial response against crizotinib, the first-generation ALK inhibitor.[6,7] In clinical practice, treatment-related resistance mutations such as G1202R may develop. Lorlatinib, a third-generation ALK inhibitor, has

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval: The Istanbul University Faculty of Medicine local ethics committee approved this study at the (Number:2021/266748).

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therapeutic efficacy in the presence of resistance mutations against other ALK inhibitors.[8]

In the treatment of NSCLC, studies on targeted therapies and checkpoint inhibitors have increased in recent years, and the use of these drugs in clinical practice is becoming increasingly common. In cancer treatment, it is important to determine the patient subgroups that will benefit most from the treatment in terms of appropriate treatment selection and cost-effectiveness evaluation. PD-L1 levels and different biomarkers are used to predict the response of immunotherapeutic drugs in the treatment of NSCLC.[9] Data on parameters predicting patients response to treatment and the development of treatment-related resistance in ALK mutant NSCLC are limited. The study's aim was to research the predictors of the overall response to treatment in patients with ALK-mutant metastatic NSCLC.

2. Methods

2.1. Patients and data collection

Our study was designed retrospectively. Ethics approval was obtained from the local ethics committee. The research was conducted in conformity with the Helsinki Declaration and good clinical practice recommendations. The data of the patients followed in the outpatient clinics of 2 oncology centers were included in the study. Patients with ALK mutant metastatic NSCLC followed between 2015 and 2020 and who received ALK inhibitor therapy were evaluated. Patients were identified from the hospital database. Patients who did not have sufficient data for analysis were excluded from the study. The clinical characteristics of the patients (age, gender, tumor stage, metastasis sites, etc) and pathological data of the patients (tumor type, ratio of ALK positivity, and other driver mutations) were recorded. The surgical history of the patients, radiotherapy, and previously used chemotherapy regimens were determined from the hospital registry system. ALK positivity rate in the tumor was determined by the FISH method. The FISH method detects ALK positivity with a break-apart/split-signal method, and the rate of positive cells is determined. This positive cell ratio was stated as the ALK positivity rate. ALK was considered positive in the presence of more than 15% signal in the FISH method.

Patients had received alectinib 400 mg twice daily, crizotinib 250 mg/day, and ceritinib 450 mg/day as tyrosine kinase inhibitors. Treatment response assessment with imaging was performed every 2 or 3 months. Treatment responses were assessed with response evaluation criteria in solid tumors (RECIST). Treatment-related toxicities were recorded and were assessed with The Common Terminology Criteria for Adverse Events (CTCAE v5) grading system. The existence of a complete or partial reaction was described as the overall response rate (ORR). Also, factors of predicting the ORR were investigated.

The death status of the patients was checked from the death notification system of the Ministry of Health. The time from starting ALK inhibitors to death from any cause was determined as overall survival (OS). The time from initiation of treatment to disease progression was determined as progression-free survival (PFS). In addition, follow-up of patients after progression was continued, and their subsequent treatments were recorded.

2.2. Statistical analysis

SPSS version 25 was used for statistical analysis. Categorical variables were defined by number and percentage. The median value, as well as the lowest and maximum values, were shown for continuous variables. For the survival analysis and curve, Kaplan Meier analysis was employed. Binary logistic regression analysis was applied for parameters that predict treatment response. In addition, ROC analysis was applied to determine the cutoff value of the ALK positivity ratio for the ORR.

Table 1

Clinical, pathological and treatment features of the patients.

Characteristics	Number of patients (total number: 68)	%
Gender		
Male	36	52.9
Female	32	47.1
Smoking History		
Yes	32	47.1
No	27	39.7
Unknown	9	13.2
Primary tumor locations		
Left	21	30.9
Right	44	64.7
Unknown	3	4.4
De-novo metastatic disease		
Yes	56	82.4
No	12	17.6
Primary surgery		
Yes	7	10.3
No	61	89.7
Pathological subtype		
Adenocarcinoma	61	89.7
SCC	7	10.3
Metastatic locations		
Liver	15	22.7
Brain	14	20.9
Bone	21	31.8
Lung	47	71.2
Adrenal gland	7	10.6
Number of metastatic sites		
1–2	46	67.7
>2	20	29.4
Unknown	2	2.9
Type of ALK inhibitor		
Alectinib	36	52.9
Crizotinib	30	44.1
Ceritinib	2	2.9

3. Results

3.1. Patients characteristics

The study comprised a total of 68 patients. The patients' median age was 55 (range: 30–81), with 36 (52.9%) of them being male. The histology of adenocarcinoma was identified in 61 (89.7%) patients. The rate of de-novo metastatic disease was 82.4 %. Thirty-five patients (51.5%) were given chemotherapy before receiving the ALK inhibitor. Patients were given ALK inhibitors such as crizotinib (44.1%), alectinib (53%), and ceritinib (2.9%). Table 1 presents to clinicopathological features of the patients.

3.2. Outcomes of the treatments

The ORR was 66.2% (Table 2). The ratio of ALK positivity (P = .025), gender (P = .045), and the number of metastatic

Table 2

Responses of the treatment in the patients.

	Number of patients (total number: 68)	%
Response ratios		
Complete response	9	13.2
Partial response	36	52.9
Stable disease	6	8.8
Progression	17	25
Overall response rate	45	66.1
Disease control rate	51	75

Table 3

Multivariate logistic regression analysis for treatment responses.

	P-value	Odds ratio %95 CI
Age	0.948	
Gender (male vs female)	**0.045**	5.5 (1.0–29.8)
Primary tumor location (right vs left)	0.359	
Pathological subtype (adenocarcinoma vs SCC)	0.686	
ALK positivity ratio	**0.025**	1.063 (1.008–1.121)
De-novo metastatic disease: yes vs no	0.281	
Number of metastatic sites (>2 vs 1–2)	**0.026**	5.79 (1.22–27.35)
ALK inhibitor type	0.561	

Bold values denote statistically significant.

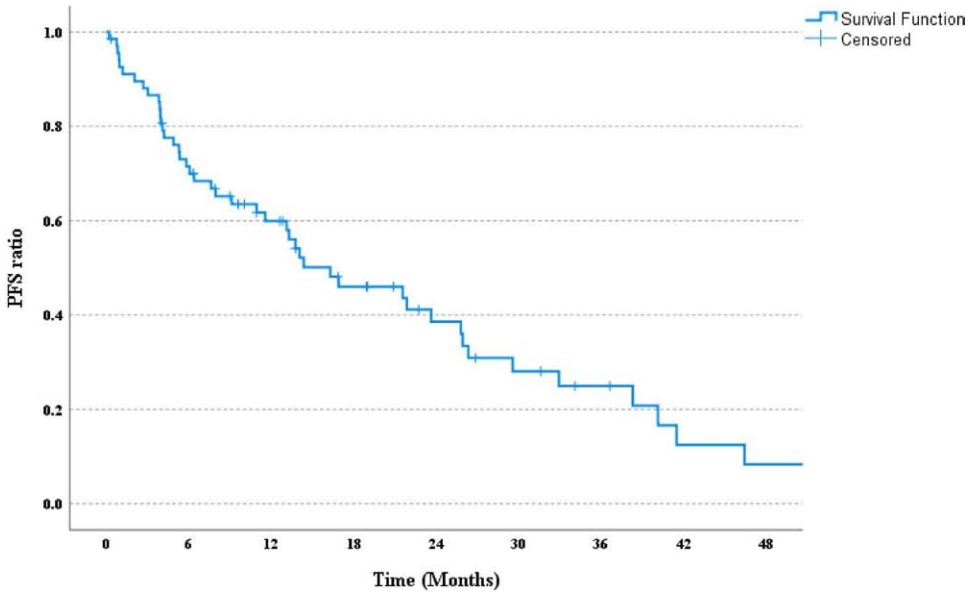

Figure 1. Kaplan Meier curves for PFS in the patients.

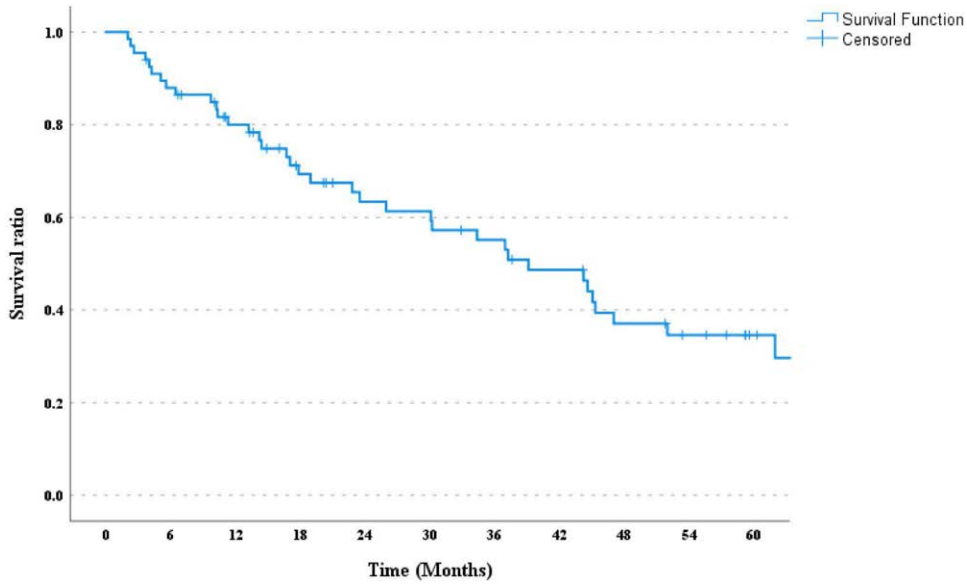

Figure 2. Kaplan Meier curve for OS in the patients.

sites (P = .026) were statistically significant predictors for the response to ALK inhibitor in binary regression analysis. However, type of ALK inhibitor (P = .561), the primary localization of the tumor (right or left) (P = .359), histopathological type of tumor (P = .686), de-novo metastatic disease (P = .281), and age (P = .948) were not (Table 3). The cut-off level of ALK positivity was found to be 33% in patients with an objective response (AUC:0.740, P = .002, sensitivity 57.5%, specificity 78.3%) (Fig. 3). Thirty-eight (56.7%) patients died during the study period. The median time of follow-up was 21 months. We determined that the median PFS was 16.3 months (95% CI, 7.7–24.8) (Fig. 1), and OS was 39.2 months (95% CI: 26.6–51.6) (Fig. 2). We performed a survival analysis according to the ALK positivity rate. We found statistically significant better results in patients with an ALK positivity rate of 33% and above in terms of PFS and OS. The median PFS was 25.8 to 7.6 months (P = .04) at the 95% confidence interval (Fig. 4). Median OS was 45.3 vs 23.5 months (P = .004) at 95% confidence interval (Fig. 5). Treatment-related grade 1–2 toxicity was observed in 35 (51.5%) patients. Also, grade 3–4 toxicity was observed in 4 (5.9%) patients. The frequency of nonhematologic toxicity was 45.6%, while the frequency of hematologic toxicity was 25%.

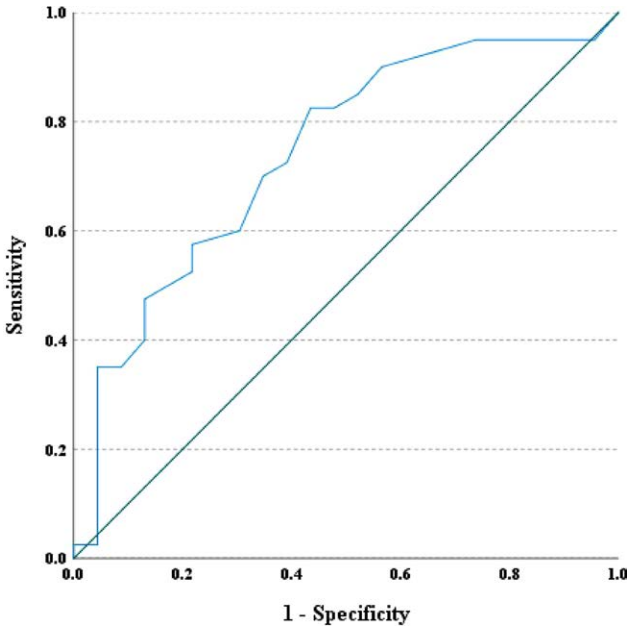

Figure 3. ROC curve by ALK positivity ratio for treatment response.(P = .002, AUC:0.740, sensitivity 57.5%, specificity 78.3%)

4. Discussion

In this study, we investigated clinicopathological factors that predict treatment-related response in ALK mutant NSCLC. We observed that ALK inhibitors are effective and safe in terms of PFS and OS in ALK mutant NSCLC in real-life outcomes. Randomized controlled studies have shown that second and third-generation ALK inhibitors are superior to the first-generation crizotinib. In the ALEX study, which included 303 patients and compared alectinib and crizotinib, the median PFS was found to be 35 months in the patients who received alectinib and 11 months in the patients who received crizotinib.[10] Also, the median OS with alectinib was not reached compared to 57 months for crizotinib, although the data were still preliminary. In the ALTA trial, which included 275 patients, the second-generation ALK inhibitor brigatinib and crizotinib were compared. The median PFS of patients with NSLSC was found to be better in the brigatinib arm, with a median PFS of 24 months versus 11 months.[11] Also, in the phase 3 CROWN study, lorlatinib, a third-generation ALK inhibitor, increased PFS over crizotinib in patients with ALK mutant NSCLC.[7] Our results show real-life data of ALK inhibitors. The survival data in our study is seen to be lower than the primary studies in the literature. This can be explained by the fact that some of the patients included in our study received a series of chemotherapy before and that patients with poor performance status were included in the study.

Numerous studies have been conducted to determine factors to predict treatment response and prognosis in lung cancer. Also, the effects of various biomarkers and clinicopathological features in predicting treatment response were evaluated. PD-L1 level predicts the treatment response in patients with NSCLC using immunotherapy. In a study that included patients with NSCLC who have good performance and using nivolumab

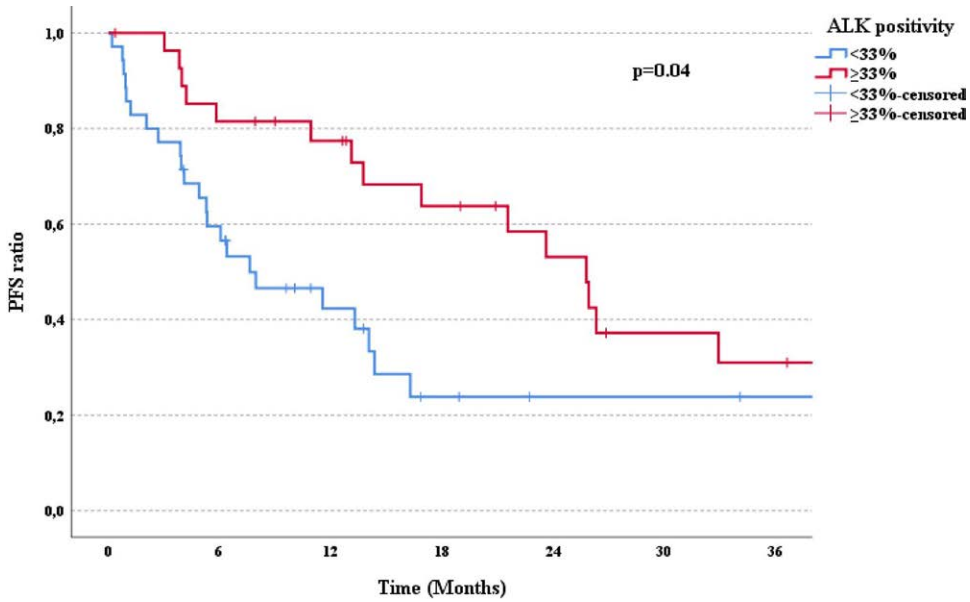

Figure 4. Kaplan-Meier curves for PFS by ALK positivity rate.

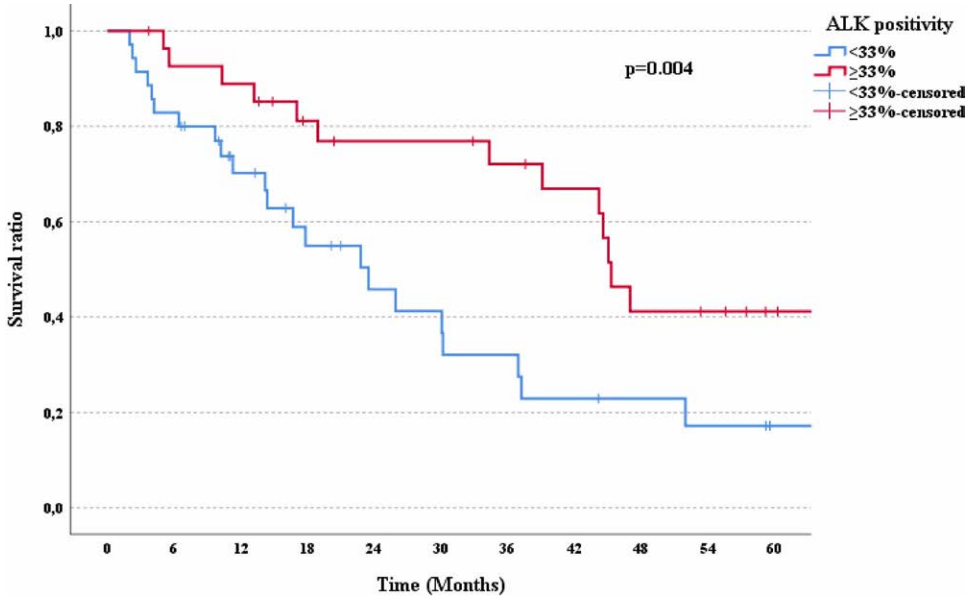

Figure 5. Kaplan-Meier curves for OS by ALK positivity rate.

showed that no smoking history, high CRP, presence of liver metastases, presence of pleural effusion, and steroid use are predictive factors that worsen PFS.[12] Also, in some studies, immunotherapy has been found to be ineffective in patients with ALK-positive NSCLC.[13]

Our study showed that the ALK positivity ratio is an important parameter for treatment response. Our results were showed that a statistically significant objective response could be seen in patients with an ALK positivity rate above 33%. Zhang et al found that nonreciprocal/ reciprocal ALK translocations were related to poor clinical outcomes with first-line crizotinib, compared to 3'-ALK fusion alone.[14] Patients with nonreciprocal/reciprocal ALK translocation were also more likely to develop brain metastases, according to this research. The method of determining ALK positivity can be an important predictor in predicting treatment. In a study that included a small number of patients, detection of ALK expression status by IHK with dichotomous scoring was found to be superior for predicting treatment response compared to the FISH method.[15] There are also different case reports related to the treatment response to ALK inhibitors in the literature. In a patient with NSCLC using alectinib, alkaline phosphatase (ALP) levels increased up to 6 times after the start of treatment, and the alkaline phosphatase level returned to normal after a rapid and complete response was detected in the patient.[16] In the case report, it was stated that rapid ALP elevation after alectinib could predict treatment response. A similar result was also found in a presentation of 2 different cases. The researchers reported a transient elevation in creatine phosphokinase and liver function tests after alectinib initiation in ALK-mutant NSCLC patients, which was associated with tumor destruction and treatment response.[17] Platelets can hold the RNA released by tumor cells, and the level of ALK positivity in platelets can be checked noninvasively.[18] In a study published by Nilsson et al, the median PFS was found as 3.7 months in the presence of ALK-positive platelets in NSCLC patients receiving crizotinib, while 16 months in the presence of ALK-negative platelets.[19] Researchers have stated that the presence of ALK-positive platelets could be used as a marker to predict the response to crizotinib. In a study created the Deep Learning Model using CT findings and clinicopathological parameters, the presence of ALK mutations could be detected in patients with NSCLC, and it has been shown that the crizotinib response can be predicted.[20]

Our study had some limitations. It was a retrospective study, and some data used for analysis were missing. Because it is a rare mutation, the number of patients was relatively low. In addition, the heterogeneity of the patient group and the use of different drugs in the treatment can be considered a limitation.

In conclusion, the effectiveness of ALK inhibitors in ALK mutant NSCLC patients was investigated in this research. We discovered that having less than 3 metastatic sites, having a high ALK positivity ratio, and being female were all good predictors of ALK inhibitor response. Our study is one of the few studies in the literature showing that the rate of ALK positivity affects treatment-related response. A cut-off value of ALK positivity to predict objective response was determined in our study. Studies involving a large number of patients are needed to determine the parameters to be used to predict treatment response in ALK-positive NSLC patients.

Author contributions

Study concept and design: ID, MG, AD, AA
Acquisition of data: ID, MG, NP, FF, SV, PS
Analysis and interpretation of data: ID, MG, NP, FF
Drafting of the manuscript: ID, MG, NP, FF, SV
Critical revision of the manuscript for important intellectual content: SV, PS, AD, AA

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