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Crizotinib efficacy and safety in patients with advanced NSCLC harboring MET alterations

A real-life data of Turkish Oncology Group

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Abstract

Crizotinib is a multikinase inhibitor, effective in non-small cell lung cancer (NSCLC) harboring mesenchymal-epidermal transition (MET) alterations. Although small prospective studies showed efficacy and safety of crizotinib in NSCLC with MET alterations, there is limited real-life data. Aim of this study is to investigate real-life efficacy and safety of crizotinib in patients with advanced NSCLC harboring MET alterations. This was a retrospective, multicenter (17 centers) study of Turkish Oncology Group. Patients' demographic, histological data, treatment, response rates, survival outcomes, and toxicity data were collected. Outcomes were presented for the study population and compared between MET alteration types. Total of 62 patients were included with a median age of 58.5 (range, 26–78). Major histological type was adenocarcinoma, and 3 patients (4.8%) had sarcomatoid component. The most common MET analyzing method was next generation sequencing (90.3%). MET amplification and mutation frequencies were 53.2% (n = 33) and 46.8% (n = 29), respectively. Overall response rate and disease control rate were 56.5% and 74.2% in whole study population, respectively. Median progression free survival (PFS) was 7.2 months (95% confidence interval [CI]: 3.8–10.5), and median overall survival (OS) was 18.7 months (95% CI: 13.7–23.7), regardless of treatment line. Median PFS was 6.1 months (95% CI: 5.6–6.4) for patients with MET amplification, whereas 14.3 months (95% CI: 6.7–21.7) for patients with MET mutation ($P = .217$). Median PFS was significantly longer in patients who have never smoked ($P = .040$), have good performance score ($P < .001$), and responded to the treatment ($P < .001$). OS was significantly longer in patients with MET mutation (25.6 months, 95% CI: 15.9–35.3) compared to the patients with MET amplification (11.0 months; 95% CI: 5.2–16.8) ($P = .049$). In never-smokers, median OS was longer than smoker patients (25.6 months [95% CI: 11.8–39.3] vs 16.5 months [95% CI: 9.3–23.6]; $P = .049$). The most common adverse effects were fatigue (50%), peripheral edema (21%), nausea (29%) and diarrhea (19.4%). Grade 3 or 4 adverse effects were observed in 6.5% of the patients. This real-life data confirms efficacy and safety of crizotinib in the treatment of advanced NSCLC harboring MET alteration.

Abbreviations: ALK = anaplastic lymphoma kinase, CI = confidence interval, MET = mesenchymal-epidermal transition, NSCLC = non-small cell lung cancer, ORR = overall response rate, OS = overall survival, PFS = progression free survival.

Keywords: alteration, crizotinib, MET, non-small cell lung cancer (NSCLC)

The authors have no funding and conflicts of interest to disclose.

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

Approval of ethical committee was obtained from Ankara University Faculty of Medicine Ethics Committee in compliance with Helsinki Declaration (Decision number: İ9-598-20).

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1. Introduction

Molecular pathogenesis of the non-small cell lung cancer (NSCLC) has been improved by discovering gene mutations, gene copy number alterations and gene rearrangements in the last decade.[1] Detection of activating mutations of epidermal growth factor receptor, anaplastic lymphoma kinase (ALK) rearrangement, ROS-1 rearrangement, BRAF V600E mutation, mesenchymal-epidermal transition (MET) amplification and mutations have led to targeted therapy options with better survival outcomes in NSCLC patients carrying these alterations.[2]

MET gene is located on the long arm of human chromosome 7 (7q21-31). c-MET is a transmembrane receptor coded by MET gene. Physiological expression of c-MET pathway is required for tissue differentiation and repair, however its abnormal expression cause tumor proliferation and metastasis. The causes of pathological activation in c-MET pathway include MET mutation, MET amplification and MET protein overexpression.[3] MET gene amplification and MET exon 14 skipping mutation are detected 2 to 4% and 3 to 4% of the lung adenocarcinomas, respectively.[4,5]

Crizotinib is an oral selective adenosine triphosphate-competitive, small tyrosine kinase inhibitor targeting ALK, ROS-1 and c-MET/hepatocyte growth factor receptor tyrosine kinase and their oncogeneic variants.[6] Crizotinib was the first drug approved by the US Food and Drug Administration for the treatment of NSCLC with ALK or ROS-1 fusions.[7] The role of crizotinib efficacy in NSCLC with MET exon 14 alteration was investigated in the PROFILE 1001 trial.[8] Sixty-five patients were assessed in this trial and overall response rate (ORR) was 32%, complete response was achieved in 3 and partial response in 18 patients. Median durability of response was 9.1 months, and median progression free survival (PFS) was 7.3 months. Type of MET exon 14 alteration was not associated with objective response to crizotinib. However, there is very limited data in the literature about real-life efficacy and safety of crizotinib in the treatment of NSCLC with MET alterations, which was obtained from studies that have small number of patients.

The aim of this retrospective study of real-life data is to investigate efficacy and safety of crizotinib in the treatment of NSCLC harboring MET alterations.

2. Materials and Methods

2.1. Study design and patients

This study was a retrospective study of Turkish Oncology Group. Patients followed between 2018 and 2022 were included from 17 medical oncology centers. Inclusion criteria were; the histological diagnosis of NSCLC, radiologically proven advanced stage, harboring MET alterations (either MET amplification or MET mutation), being treated with crizotinib in any line of treatment, and being >18 years of age. Demographic, histological, and molecular data, treatment, response, survival outcomes, and toxicity data were all collected from centers' database.

MET alterations were analyzed in experienced local laboratories by immunohistochemistry, fluorescence in situ hybridization or next generation sequencing. Crizotinib is reimbursed by the Turkish Ministry of Health, if the patients have MET amplification, with MET/chromosome 7 centromere ratio of >5. The initial crizotonib dose was 250 mg twice a day, orally. Patients were treated until disease progression, patients' withdrawal, or for any other reason in the interest of the patient. Dose modifications, treatment interruptions and discontinuation were also assessed. Survival outcomes were presented as PFS and overall survival (OS). PFS was defined as the time between the first dose of crizotinib and first disease progression or death. OS was defined as the time between the first dose of crizotinib and death, or last hospital visit of the patient. Response to the treatment was evaluated by RECIST version 1.1 (Response Evaluation Criteria in Solid Tumours). Performance status was evaluated according to the Eastern Cooperative Oncology Group Performance Status Scale. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

The characteristics, response rates, and survival outcomes were presented for whole study population, and compared between MET alteration types.

Approval of Ankara University Faculty of Medicine Ethics Committee in compliance with Helsinki Declaration was obtained (Decision number: İ9-598-20).

2.2. Statistical analysis

Continuous variables were given as median (minimum [min]–maximum [max]) and categorical variables were given as percentage. Survivals were estimated by Kaplan–Meier method. Univariate and multivariate analyses were made by using Cox regression method. Only the variables which are statistically significant in univariate analysis were included to the multivariate analysis. All *P* values were based on a 2-tailed test of significance (*P* = .05). SPSS version 22 was used for the statistical analyses (SPSS Inc, Chicago, IL).

3. Results

3.1. Patients' characteristics and efficacy

The data of 62 patients was assessed. Median age was 58.5 (26–78), and 61.3% (n = 38) of the patients were male. Twenty-eight patients (45.1%) had comorbidities. Eastern Cooperative Oncology Group Performance Status Scale was "1" in 54.8% of patients and "0" in 29%. Thirty one percent of the patients were nonsmokers. Five patients had family history of lung cancer. The histological type of the cancer was adenocarcinoma in 90.3% (n = 56) of the patients, and 3 patients (4.8%) had sarcomatoid component. Pleural effusion was seen at the time of diagnosis in 32.3% (n = 20) of the patients. Patients having MET amplification and mutation were 53.2% (n = 33) and 46.8% (n = 29), respectively. Most common diagnostic method used to detect MET alterations was next generation sequencing (90.3%). Crizotinib was used as second line treatment in 58.1%, and third or further lines in 24.2% of patients. There was not any statistically significant difference in demographic parameters according to the type of MET alteration (Table 1).

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Table 1

Demographic characteristics and MET alterations.

		All patients N (%)	MET alterations		P
			Amplification N (%)	Mutation N (%)	
Age (median, min–max)		58.5 (26–78)	62 (34–78)	58 (26–77)	
Gender	Female	24 (38.7)	11 (33.3)	13 (44.8)	.354
	Male	38 (61.3)	22 (66.7)	16 (55.2)	
ECOG PS	0	18 (29.0)	7 (21.2)	11 (37.9)	.197
	1	34 (54.8)	18 (54.5)	16 (55.2)	
	2	10 (16.2)	8 (24.3)	2 (6.9)	
Smoking	Nonsmoker	19 (30.6)	9 (27.2)	10 (34.5)	.539
	Smoker	43 (69.4)	24 (72.8)	19 (65.5)	
Pleural effusion	Absent	42 (67.7)	24 (61.5)	18 (62.1)	.374
	Present	20 (32.3)	9 (38.5)	11 (37.9)	
Brain metastases	Absent	48 (77.4)	25 (75.8)	23 (79.3)	.476
	Present	14 (22.6)	8 (24.2)	6 (20.7)	
Crizotinib line	1	11 (17.7)	6 (18.2)	5 (17.2)	.044
	2	36 (58.1)	15 (45.4)	21 (72.4)	
	3+	15 (24.2)	12 (36.4)	3 (10.4)	

ECOG-PS = Eastern Cooperative Oncology Group Performance Status Scale, MET = mesenchymal-epidermal transition.

Table 2

Crizotinib response and MET alterations.

		All patients N (%)	MET alterations		P
			Amplification N (%)	Mutation N (%)	
Response	Complete	4 (6.5)	2 (6.1)	2 (6.9)	.267
	Partial	31 (50.0)	13 (39.4)	18 (62.1)	
	Stable	11 (17.7)	7 (21.2)	4 (13.8)	
	Progression	16 (25.8)	11 (33.3)	5 (17.2)	
ORR		35 (56.5)	15 (45.5)	20 (69)	.054

MET = mesenchymal-epidermal transition, ORR = overall response rate.

ORR and disease control rate (DCR) were 56.5% and 74.2% in whole study population, respectively (Table 2). Nonsmoker patients had a higher ORR than smokers (78.9% vs 48.8% respectively, $P = .033$). ORR were 63.6%, 61.1% and 40% in first, second and third or further lines of treatment, respectively.

3.2. Survival outcomes

In the study population, median PFS and OS was 7.2 months (95% confidence interval [CI]: 3.8–10.5) and 18.7 months (95% CI: 13.7–23.7), regardless of treatment line. Median PFS was 6.1 months (95% CI: 5.6–6.4) for patients with MET amplification, whereas it was 14.3 months (95% CI: 6.7–21.7) for the group with MET mutation ($P = .217$) (Fig. 1).

In patients treated with crizotinib in the first, second, and third or further lines of treatment; median PFS was 20.4 months (95% CI: 3–37.7), 8.9 months (95% CI: 4.5–13.1) and 6.9 months (95% CI: 5–8.8) respectively, without statistical significance ($P = .84$). Median PFS was significantly longer in subgroups of patients who have never smoked ($P < .040$), have good performance score ($P < .001$), and responded to the treatment ($P < .001$).

Median OS was significantly longer in patients with MET mutation (25.6 months, 95% CI: 15.9–35.3) comparing to the patients with MET amplification (11.0 months; 95% CI: 5.2–16.8) ($P = .049$) (Fig. 2). Median OS was longer in nonsmokers compared to smoker patients (25.6 months [95% CI: 11.8–39.3] vs 16.5 months [95% CI: 9.3–23.6]; $P = .049$). In patients who responded to the treatment, median OS was also superior compared to non-responders (25.6 months [95% CI: 16.4–34.7] vs 11.0 months [95% CI: 4.4–17.7]; $P = .007$).

3.3. Toxicity

Adverse events occurred in 53.2% of the patients. The most common adverse events were fatigue (50%), peripheral edema (21%), nausea (29%) and diarrhea (19.4%), respectively. Grade 3 or 4 adverse events were observed in 6.5% of the patients. The most common grade 3 or 4 treatment-related adverse events were elevated transaminases (3.2%), and dyspnea (1.6%). Drug-related dose reduction was performed in 4.8% of the patients. The treatment was discontinued in only 1.6% patients because of the adverse effects. No treatment-related death was observed.

4. Discussion

This study is, as far as we know, the most comprehensive real-life experience evaluating efficacy and safety of crizotinib in patients with NSCLC harboring MET alterations. ORR and DCR were 56.5% and 74.2% in whole study population, respectively. Median PFS was 7.2 months and median OS was 18.7 months. Although there was no significant difference between groups, median PFS was numerically shorter in patients with MET amplification (6.1 months vs 14.3 months for patients with MET mutation). Nonsmokers, patients with good performance status and responders to crizotinib had significantly longer PFS. Median OS was significantly longer in patients with MET mutation compared to the group with MET amplification (25.6 months vs 11.0 months), and in nonsmokers than smokers.

Preclinical studies revealed efficacy of crizotinib on c-MET positive tumors. PROFILE 1001 trial was the first prospective study that reported the efficacy of MET inhibition in patients with NSCLC harboring MET exon 14 alteration.[9] Total of 65

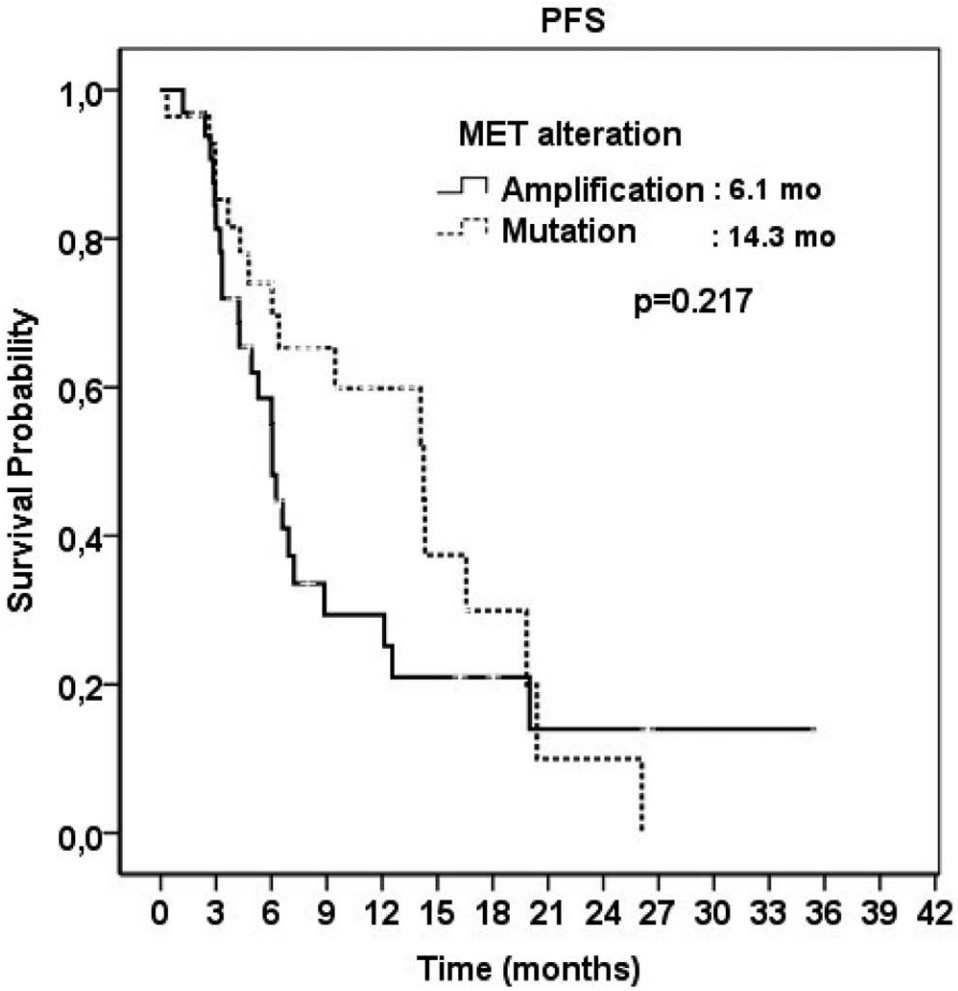

Figure 1. MET alterations and PFS. MET = mesenchymal-epidermal transition, PFS = progression free survival.

patients were assessed in the expansion cohort, 61% of whom were former smokers, and 84% had adenocarcinoma. ORR was 32% (95% CI, 21–45), complete response was observed in 3 patients and partial response in 18. DCR was 78%. Median PFS was 7.3 months (95% CI, 5.4–9.1), and OS was 20.5 months (95% CI, 14.3–21.8).[8] Our study population had similar median PFS and OS times with this trial. The objective response to crizotinib was independent from MET alteration type in PROFILE 1001.

In a prospective phase 2, METROS trial which included patients for second and further line crizotinib; ORR, median PFS and OS were 27%, 4.4 months (95% CI 3.0–5.8), and 5.4 months (95% CI, 4.2–6.5), respectively.[10] No difference in any clinical end-point was observed between MET-amplified and exon 14–mutated patients. However, patients with MET mutation had better median PFS and OS comparing to patients with MET amplification; although it was not statistically significant for PFS, which is similar to our study. In another retrospective study, MET mutation group also had a better PFS than MET amplified patient group (11.0 months vs 7.0 months).[11]

Among patients with NSCLC harboring MET exon 14 alteration, the patients treated with MET inhibitor had better survival comparing to the patients not treated with targeted therapy, in a retrospective study.[12] In this study, 22 patients had crizotinib in any line. Median PFS was 7.4 months and 59% of the patients had smoking history. The majority of c-MET positive patients in phase 2 METROS and AcSé trials were male and had smoking history.[10,13] In another study with MET positive patients, 60% of the patients were male and 55% had smoking history.[14] The majority of the patients in our study were male and had smoking history similarly with the literature. This male predominancy and the relationship with smoking habit makes MET alterations different from the other targets such as epidermal growth factor receptor, ALK and ROS-1.

The study investigating crizotinib in patients with met amplified NSCLC have grouped the amplification level as low (met to cep7 ratio 1.8–2.2), medium (2.2–4) and (>4). However, as mentioned in the method section, only patients with met cep7 ratio >5 can reach the crizotinib treatment in Turkey, according to the health insurance regulations. Thus, our study includes only this group of patients.[15]

The treatment choices of advanced NSCLC with MET alterations have improved in the last decade. Capmatinib in GEOMETRY Mono-1 trial and tepotinib in VISION trial have been found to be effective in patients with NSCLC harboring MET alterations.[16,17] GEOMETRY Mono-1 trial investigated MET receptor selective inhibitor capmatinib. A total of 364 patients with MET exon 14 skipping mutation and MET amplification positive were included in this study. Similar to our study, this trial found better response rates in patients with MET exon 14 skipping mutation than with MET amplification. ORR was 68% versus 40% in previously untreated patients, while it was 41% versus 29% in previously treated patients.

The major limitation of our study is its retrospective design. The study has a heterogeneous patient group and crizotinib was used in different treatment lines. MET detection was performed in each local center, and this may cause variation.

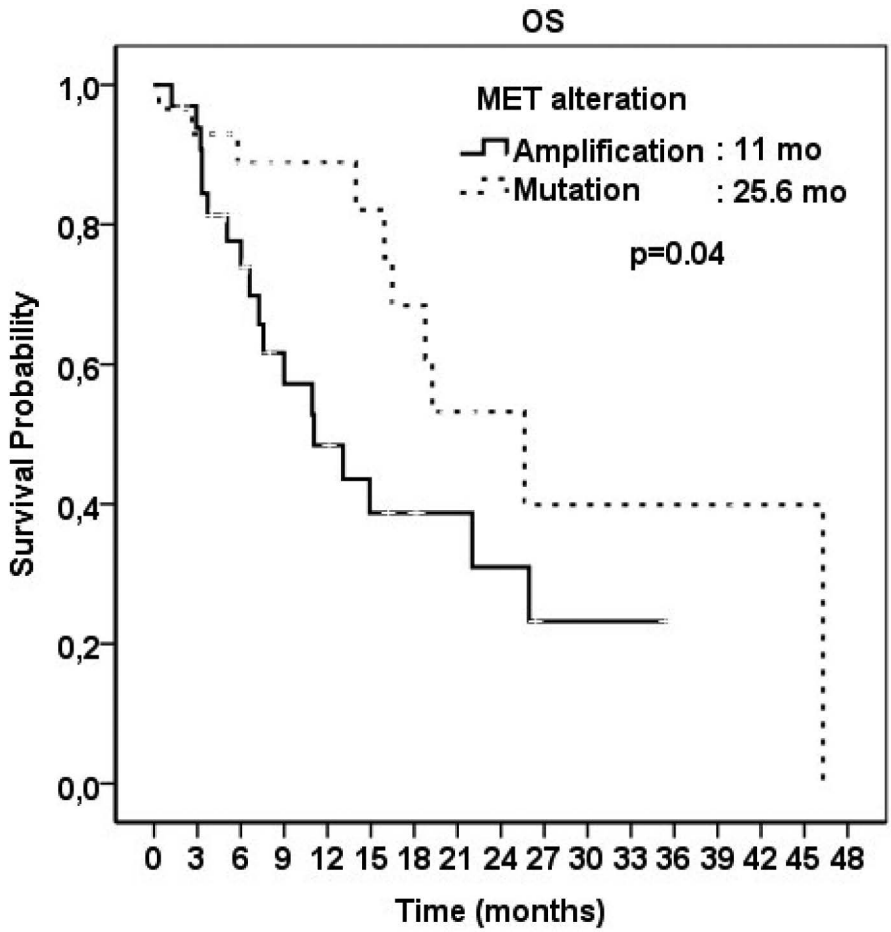

Figure 2. MET alterations and OS. MET = mesenchymal-epidermal transition, OS = overall survival.

In conclusion, this real-life data confirms efficacy and safety of crizotinib in the treatment of advanced NSCLC harboring MET alterations. The mutation is related with better survival than amplification. Crizotinib may be related to better survival in never smoked, good performanced and responder MET positive patients.

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