original report abstract

Overall Survival of Patients With *ALK*-Positive Metastatic Non–Small-Cell Lung Cancer in the Russian Federation: Nationwide Cohort Study

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PURPOSE The overall survival (OS) results in patients with *ALK*-positive metastatic non–small-cell lung cancer (NSCLC) have rarely been reported. The aim of this prospective-retrospective cohort study was to obtain real-world data on the use of crizotinib or chemotherapy in patients with *ALK*-positive metastatic NSCLC in Russia.

PATIENTS AND METHODS Patients with epidermal growth factor receptor–negative metastatic NSCLC were screened in 23 cancer centers. To be eligible, patients were required to have confirmation of *ALK* rearrangement. Patients were treated with crizotinib (250 mg twice daily; n = 96) or the investigator's choice of platinum-based chemotherapy (n = 53). The primary end point was OS.

RESULTS A total of 149 *ALK*-positive patients were included. Mean age was 53 years in both groups. Patients were predominately women (59%) and never-smokers (74%), and most patients had adenocarcinoma histology (95%). At a median follow-up time of 15 months, 79 of the 149 patients included in the analysis had died. Median OS from the start of treatment was 31 months (95% CI, 28.5 to 33.5 months) in the crizotinib group and 15.0 months (95% CI, 9.0 to 21.0 months) in the chemotherapy group ($P < .001$). The objective response rate was 34% in the crizotinib group. Among patients with brain metastasis, one complete response (6%) and five partial responses (31%) were achieved. Grade 3 adverse events were observed in three patients (3%) in the crizotinib group.

CONCLUSION The improved OS observed in crizotinib clinical trials in *ALK*-positive NSCLC was also observed in the less selective patient populations treated in daily practice in Russia. The use of standard chemotherapy in these patients remains common but seems inappropriate as a result of the effectiveness of newer treatments, such as crizotinib.

INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the most frequent cause of cancer-related death in the Russian Federation.[1] In 2016, a total of 51,476 lung cancer deaths were recorded and the age-standardized mortality rate per 100,000 population was 19.94.[2] However, molecular-driven therapies have revolutionized the treatment of NSCLC.[3]

Genetic alteration of the anaplastic lymphoma kinase (*ALK*) gene is present in 7.8% of selected Russian patients with adenocarcinoma.[4] A few *ALK* inhibitors are now approved for *ALK*-positive metastatic NSCLC treatment. The first approved *ALK* inhibitor, crizotinib, has demonstrated significant benefit in progression-free survival, objective response rate, and patient-reported outcomes compared with standard platinum-based chemotherapy in European and Asian patients with metastatic NSCLC who had the *ALK* gene rearrangement.[5,6] Although crizotinib has shown significant improvement in progression-free survival in phase III studies,[5-7] there are fewer data on overall survival (OS) and patient outcomes when using crizotinib in real-world clinical practice. The aim of this study was to examine treatment patterns and outcomes of crizotinib compared with chemotherapy in patients with NSCLC from Russian community oncology practices.

PATIENTS AND METHODS

Study Design

The current observational study used a prospective-retrospective cohort design on the basis of a review of medical records or prospective recruitment of patients with *ALK*-positive metastatic NSCLC who received crizotinib (study group) or chemotherapy (control group) in nonclinical trial settings. Oncologists treating patients with NSCLC were recruited for study

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participation from 23 regions of the Russian Federation. Eligible patients were prospectively included, or their relevant medical record data were retrospectively analyzed by the participating physicians using a protected, online-based data collection form. Patient data were depersonalized and anonymous. The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the principal investigators and the Russian Society of Clinical Oncology (RUSSCO) Independent Ethics Committee. All patients provided their written informed consent.

Patient Selection

In this study, patients with epidermal growth factor receptor (*EGFR*)–negative metastatic NSCLC were screened. To be eligible, patients were required to have confirmation of *ALK* rearrangement via diagnostic procedures (fluorescence in situ hybridization, immunohistochemistry, or polymerase chain reaction) used in the molecular testing RUSSCO national program and to be age 18 years or older at the time of diagnosis. Patients were included if treatment with crizotinib or the investigator's choice of platinum-based chemotherapy had been initiated as first-line or later therapy for metastatic *ALK*-positive NSCLC between January 2016 and January 2017. All patients in the study group received 250 mg of oral crizotinib twice daily at initiation. Patients who were treated with crizotinib as part of a clinical trial were excluded from the study.

Outcome Variables

Various demographic and clinical characteristics were described for each patient. The primary end point was OS in the study and control groups. Secondary end points included objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (evaluated by investigators), disease control rate, and rate of grade 3 or 4 adverse events according to Common Terminology Criteria for Adverse Events version 4.3 in the study group.

Disease progression was assessed using radiology and clinical investigation. Markers of progression were therapy change and death. Switch to subsequent treatment was defined as a switch as a result of disease progression or toxicity. Some patient records did not include all the parameters; available data from these patients were used when applicable.

Statistical Analysis

Descriptive statistics (mean, median, and proportion) were used to summarize baseline patient characteristics and treatment patterns. OS time was calculated from the date of therapy initiation to the date of death. Survival was analyzed using the Kaplan-Meier method, with statistical significance of survival differences assessed using a nonparametric log-rank test. The statistical significance of descriptive differences in study variables and clinical outcomes between the two groups was assessed using *t* tests and χ^2 tests, as appropriate, with corresponding *P* values reported. All statistical analyses were performed using IBM SPSS Statistics Base v22.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

We screened 1,817 patients with *EGFR*-negative metastatic NSCLC. In total, 149 *ALK*-positive patients (8.2%) were included in the study for analysis. No *ALK*-positive patients were excluded from the overall cohort. Fluorescence in situ hybridization was the most common diagnostic procedure used to confirm *ALK* rearrangement (Table 1). Ninety-six patients (64%) were included in the study group and received crizotinib according to protocol. Fifty-three patients (36%) were included in the control group and received chemotherapy. Chemotherapy included combination regimens with either cisplatin or carboplatin plus paclitaxel, pemetrexed, etoposide, or gemcitabine. The most common reason for not assigning crizotinib was lack of access to the drug.

Mean number of enrolled patients in one region was 6.5 patients (range, one to 13 patients). A majority of patients (greater than 60%) were recorded as having never smoked. Mean age at diagnosis of *ALK*-positive metastatic NSCLC was 53 years in both groups, which did not vary by line of therapy (first or second line) initiation. No significant differences in age (younger *v* older than age 55 years), sex (male *v* female), or histology (adenocarcinoma *v* other subtypes) between the study and control groups were found (all $P > .1$). Among the 96 patients for whom crizotinib initiation was documented, 16 patients (17%) had brain metastases. No patients in the chemotherapy group had brain metastasis at or before treatment initiation.

More than half of patients received no prior adjuvant therapy (69%) or radiation (89%), and chemotherapy was the most common cancer-directed treatment modality used before crizotinib initiation. Sixty-eight patients (71%) were treated with crizotinib as first-line therapy, and 28 patients (29%) were treated with crizotinib as second-line therapy. In the control group, all patients received chemotherapy as first-line treatment.

Disease progression after initial clinical response was the most common reason (71% of patients) for crizotinib discontinuation. Treatment-related toxicities or adverse effects were cited as the reason for final crizotinib discontinuation in 3% of patients.

Clinical Outcomes

Median follow-up was 15.0 months (range, 11 to 24 months). At the time of the last follow-up, 79 of 149 patients included in the analysis had died, whereas 70 patients were still alive. Median OS time from the start of treatment was 31 months (95% CI, 28.5 to 33.5 months) in the crizotinib group and 15.0 months (95% CI, 9.0 to 21.0 months) in

TABLE 1. Patient and Treatment Characteristics

Characteristic	No. of Patients (%)*	
	Crizotinib (n = 96)	Chemotherapy (n = 53)
Mean age, years (SD)	53 (14)	53 (10)
Sex		
Male	40 (42)	21 (40)
Female	56 (58)	32 (60)
Smoking status		
Former smoker	9 (10)	8 (15)
Current smoker	7 (7)	11 (21)
Never smoked	76 (79)	34 (64)
Missing/unknown	4 (4)	0
Stage at initial NSCLC diagnosis		
IIIB	12 (12.5)	2 (4)
IV	84 (87.5)	51 (96)
Brain metastases present at or before crizotinib initiation	16 (17)	0
Histology		
Adenocarcinoma	91 (95)	51 (96)
Squamous	2 (2)	1 (2)
Large-cell carcinoma	1 (1)	1 (2)
Missing/unknown	2 (2)	0
Tumor grade		
1	3 (3)	4 (8)
2	14 (15)	10 (19)
3	24 (25)	5 (9)
Missing/unknown	55 (57)	34 (64)
Diagnostic test used to determine ALK status		
FISH	35 (36)	19 (36)
IHC	25 (26)	19 (36)
PCR	15 (16)	13 (24)
Missing/unknown	21 (22)	2 (4)
Histologic material used to determine ALK status		
Primary tumor	55 (57)	36 (68)
Metastasis	41 (43)	17 (32)
Previous cancer treatment		
Surgery	27 (28)	12 (23)
Radiotherapy	16 (17)	5 (9)
Mean radiation dose, Gy (SD)	34 (12)	41 (2)
Adjuvant therapy	30 (31)	2 (4)
First-line chemotherapy (before crizotinib)		—
Carboplatin or cisplatin plus pemetrexed	7 (7)	
Carboplatin plus paclitaxel	4 (4)	
Pemetrexed	4 (4)	
Cisplatin plus etoposide	3 (3)	
Carboplatin plus gemcitabine	2 (2)	
Carboplatin plus docetaxel	1 (1)	

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TABLE 1. Patient and Treatment Characteristics (Continued)

Characteristic	No. of Patients (%)*	
	Crizotinib (n = 96)	Chemotherapy (n = 53)
Carboplatin	1 (1)	
Paclitaxel	1 (1)	
Missing/unknown	5 (5)	
Line of present therapy		
First line	68 (71)	53 (100)
Second line	28 (29)	0

Abbreviations: FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NSCLC, non–small-cell lung cancer; PCR, polymerase chain reaction; SD, standard deviation.

*Values are numbers and percentages, unless otherwise indicated.

the chemotherapy group ($P < .001$). Survival curves are shown in Figure 1. OS time was similar in patients initiating crizotinib as first- and second-line therapy ($P = .381$; Fig 2). The 1-year OS rates were 85.4% and 64% in the study and control groups, respectively.

Disease progression on crizotinib was documented in 13 patients (15%). The objective response rate was 34% (30 of 88 patients). Partial responses were observed in 27 patients, whereas complete responses were observed in three patients (3.4%). The median time to response was 4.1 months (range, 2 to 18 months). In the overall study sample, the disease control rate was 85%. Eight patients were not eligible for evaluation of response. Among patients with brain metastasis, one complete response (6%) and five partial responses (31%) were achieved. Nine patients (56%) had stable disease.

Grade 3 adverse events were observed in three patients (3%). No treatment-related grade 4 toxicities or deaths occurred. One or more dose interruptions as a result of the adverse effects of crizotinib were observed in six patients (6.25%). At least one dose reduction was reported in three patients (3%). The most common adverse events associated with crizotinib were elevation of AST or ALT (5.5%), vomiting (3%), dyspnea (3%), and edema (1%).

DISCUSSION

Real-world data describing outcomes of treatment in patients with *ALK*-positive metastatic NSCLC are limited and heterogeneous. This prospective-retrospective observational cohort study examined OS and treatment patterns of patients treated with crizotinib or chemotherapy in a Russian real clinical practice setting.

A total of 149 *ALK*-positive patients were included. The estimated prevalence of *ALK*-positive NSCLC was approximately 8% in the study. Higher rates of *ALK* positivity are consistent with results from other registries in Russia[4,8] and could be explained by the fact that testing is performed in *EGFR*-negative patients with predominant adenocarcinoma. To place the study population analyzed here into context with the populations analyzed in a French nationwide cohort retrospective study (IFCT-1302 CLINALK)[9]

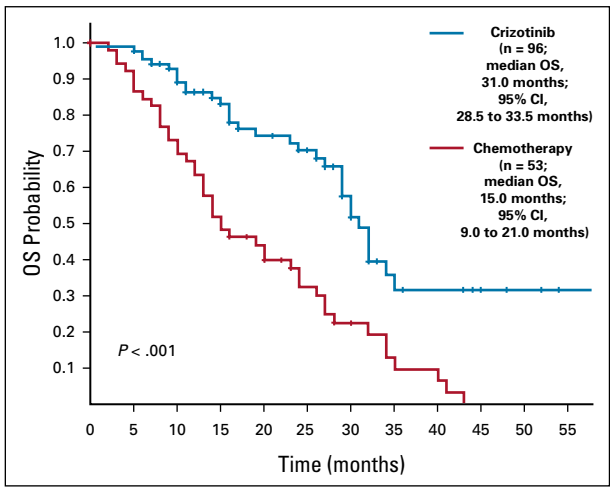

FIG 1. Kaplan-Meier curves for overall survival (OS).

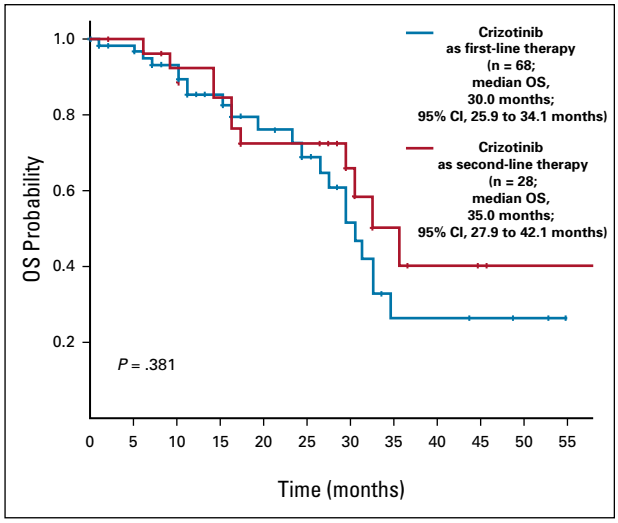

FIG 2. Kaplan-Meier curves for overall survival (OS) from crizotinib as first- and second-line therapy.

TABLE 2. Real-World Outcomes in Patients With *ALK*-Positive NSCLC Treated With Crizotinib in Different Countries

Study	No. of Patients	Treatment Line and % of Patients	Median OS (months)	1-Year OS Rate (%)
Russian observational study	96	First line, 71; second line, 29	31.0	85.4
US retrospective observational study[10]	199	First line, 62; second line and later, 38	33.8	79.0
Retrospective medical record review in North America[11]	212	First line, 65; second line and later, 35	23.4	81.9
French nationwide cohort retrospective study[9]	318	First line, 5; second line and later, 95	16.6	56.2
Retrospective medical record review in EU countries[12]	303	First line, 34; second line and later, 66	20.4	NA

Abbreviations: EU, European Union; NA, not available; NSCLC, non–small-cell lung cancer; OS, overall survival.

and a US retrospective observational study,[10] patients were, on average, younger in our study than what has been reported by these other studies (53 years *v* 58.2 and 60 years in the French and US studies, respectively). Moreover, our population included predominately women (59%) and never-smokers (74%) or former smokers (11%) and had a greater prevalence of adenocarcinoma histology (95%). Finally, 71% of patients were treated with crizotinib as first-line therapy in the study group, and all patients received first-line chemotherapy in the control group. Sixty-two percent of patients received crizotinib as first-line therapy in the US study, and only 5% of patients were treated with crizotinib in the first-line setting in the French study. No patients with *ALK*-positive NSCLC received chemotherapy in these trials. Treatment with crizotinib seemed to be well tolerated in our study; only 3% of patients experienced grade 3 treatment-related toxicity.

We report a median OS of 31.0 months after initiation of crizotinib, which is comparable with the previous estimation of 33.8 months reported by the US retrospective observational study evaluating crizotinib in the first- and second-line settings.[10] However, the median OS time in these two studies was longer than the median OS time of 23.4 months in the retrospective medical record review conducted in the United States and Canada by Davis et al.[11] Two hundred twelve patients were included in this review, and 65% of patients initiated crizotinib as first-line therapy. A majority of patients were men (69%), were current or former smokers (66.5%), and had not previously received other cancer-directed treatment (52.8%).

In prior studies in which more than half of the patients received crizotinib as second-line or later therapy, the median survival time ranges from 16.6 to 20.4 months.[9,12] In the US retrospective observational study, the median OS time was 26.8 months in patients initiating crizotinib as second-line treatment.[10] In the current study, 29% of patients received crizotinib in the second-line setting. No patients initiated crizotinib as third-line or later therapy, and this could increase the median OS to 35 months. All studies showed no statistically significant differences in OS between first and later lines of therapy. Our results support these findings. The efficacy data from different studies are listed in Table 2.

In patients with advanced, *ALK*-positive NSCLC, crizotinib therapy is associated with a two-fold increased survival rate compared with chemotherapy. Median OS has been significantly improved from 15 to 31 months.

The question of access to innovative drugs in oncology is extremely important and complicated by financial burden of the medical social problem. In a number of countries, access to drugs is regulated by separate reimbursement rules and restrictive lists. In this regard, there are often issues with fast and full access to drugs already approved by regulatory national authorities, including delay and other gaps. However, the contribution of innovative drug therapy in metastatic NSCLC could be considered as comparable to modern surgical intervention in operable NSCLC. Thus, despite the limited budget of health care systems in developing countries, therapy with *ALK* inhibitors should be considered as lifesaving and a priority first-line therapy in metastatic NSCLC. RUSSCO strongly recommends using crizotinib as first-line therapy in patients with *ALK*-positive metastatic NSCLC in the Russian Federation.[1]

A Russian study has several important limitations. First, this trial was not randomized and had a prospective-retrospective cohort design. Second, the study and control groups were not well balanced. Finally, our patients composed a heterogeneous population; for example, patients with brain metastases were included.

The improved OS observed in crizotinib clinical trials in *ALK*-positive metastatic NSCLC has been observed in less selective patient populations treated in daily practice. The use of chemotherapy in these patients seems inappropriate now that a more effective treatment is available.

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