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Characteristics, treatment patterns, and survival among *ALK*+ non-small cell lung cancer (NSCLC) patients treated with crizotinib: A chart review study

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ABSTRACT

Objectives: Second-generation *ALK* inhibitors are recently available for *ALK*+ non-small cell lung cancer (NSCLC) patients previously treated with crizotinib. This study described characteristics, treatment sequencing, and outcomes among locally advanced/metastatic crizotinib-experienced *ALK*+ NSCLC patients.
Materials and methods: From July 2014 to June 2015, a retrospective patient chart review was conducted among physicians from the US, EU, Korea, and Latin America. Participating clinicians identified their *ALK*+ NSCLC patients who received crizotinib and reported on their clinical characteristics, treatments, and survival using a pre-defined case report form. Kaplan-Meier analyses were used to describe overall survival (OS) and clinician-defined progression-free survival (PFS).
Results: Participating clinicians reviewed charts of 158 *ALK*+ NSCLC patients treated with crizotinib during the study period. Crizotinib was most commonly received in the second-line setting (41% of patients), though this varied across geographical regions. Roughly half (53%) of the patients who discontinued crizotinib received further antineoplastic therapy; second-generation *ALK* inhibitors (44%) and chemotherapy (42%) regimens were used most frequently. Following crizotinib discontinuation, median OS was 8.2 months. Among patients who did not initiate a second-generation *ALK* inhibitor following crizotinib, median OS was 4.9 months; among those who did, median OS was not reached. Among patients who received chemotherapy immediately following crizotinib discontinuation, time to clinician-defined PFS from post-crizotinib chemotherapy initiation was 3.6 months.
Conclusion: Following crizotinib discontinuation, many patients received no further antineoplastic therapy, and OS was poor among patients who did not receive a second-generation *ALK* inhibitor. Recently available second-generation *ALK* inhibitors may provide important treatment options for *ALK*+ NSCLC patients.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases (85–90%) [1]. Among them, roughly 2–7% of NSCLC patients have tumors with detectable anaplastic lymphoma

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kinase (*ALK*) rearrangements, [2–10] wherein portions of the *ALK* gene and the echinoderm microtubule-associated protein-like 4 (*EML4*) gene fuse to form *EML4-ALK*, an oncogene implicated in the pathogenesis of lung cancer. Patients with *ALK*+ NSCLC are often light or never smokers with adenocarcinoma histology and are younger than other NSCLC patients, though in recent studies, *ALK*+ patients had more diverse characteristics [10–14].

Recently developed therapies targeting the *EML4-ALK* oncogene, offer new treatment options for *ALK*+ NSCLC patients. Crizotinib was granted accelerated approval in August 2011 by the US Food and Drug Administration (FDA) to treat locally advanced or metastatic *ALK*+ NSCLC, [13,15] and in October 2015 was indicated as first-line treatment by the European Committee for Medicinal Products for Human Use (CHMP) [16]. In most other regions, crizotinib has been approved as a second-line therapy [17,18]. Crizotinib demonstrated an objective response rate (ORR) of 53–65%, and is associated with significantly longer progression-free survival (PFS) than chemotherapy [19–21]. However, the majority of patients develop resistance to crizotinib within one year of treatment initiation [22,23].

Several second-generation *ALK* inhibitors were recently approved and provide additional treatment options for patients who have been treated with crizotinib. Ceritinib was recently granted approval in a number of regions following a pivotal Phase I clinical trial of crizotinib-experienced, metastatic *ALK*+ NSCLC patients, in which the median PFS was 7.0 months and the ORR was 56% [24–28]. Alectinib was first approved in Japan and was later granted approval in the US in December 2015 [29]. In Phase II trials, the ORR on alectinib ranged from 48% to 50% among crizotinib-pretreated *ALK*+ NSCLC patients [30,31].

Information pertaining to clinical characteristics, treatment patterns, and outcomes of *ALK*+ NSCLC patients is limited. The objective of this study was to describe the real-world characteristics, treatment sequencing, and outcomes of crizotinib-treated *ALK*+ NSCLC patients across the US, EU, Korea, and Latin America (LATAM).

2. Materials and methods

2.1. Data source

From July 2014 to June 2015, physicians at medical centers in Argentina, France, Italy, Korea, Mexico, the Netherlands, Switzerland, and the US took part in this retrospective chart review study. Physicians were asked to provide de-identified data from the medical records of eligible patients in response to survey questions. The study was granted IRB approval by the partnering institutions and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice Guidelines, the Declaration of Helsinki, and local laws.

2.2. Patient selection criteria

Physicians were instructed to select patients who met the following criteria: 1) at least 18 years of age at the time of diagnosis with locally advanced or metastatic *ALK*+ NSCLC; 2) not previously diagnosed with metastatic cancer or any other solid malignant tumor prior to the first diagnosis of NSCLC; 3) had received crizotinib and either had discontinued crizotinib, added another therapy or radiation therapy to the crizotinib regimen, or died on crizotinib treatment. Additionally, for patients who were alive at last follow-up (i.e., end of data availability or last medical visit prior to data collection), at least 28 days of follow-up time was required after discontinuation or modification of crizotinib. No follow-up was required for patients who died within the 28-day window.

2.3. Outcomes

Patient demographics and clinical characteristics at primary NSCLC diagnosis, including age, sex, race/ethnicity (not collected in France), smoking history (never smoked, current smoker, former smoker [i.e., had smoked for at least a year and quit at any time before primary NSCLC diagnosis]), cancer histology, and presence of metastatic disease were collected from patient charts. The location of specific metastases was assessed as of last follow-up.

Patient treatment information was collected from the diagnosis of locally advanced or metastatic NSCLC, including treatment sequencing, type of therapy, and dates of treatment initiation and discontinuation. Clinical outcomes were also collected, including date of death (if applicable) and dates of any clinician-defined progression based on an increase in lesion size, appearance of new lesions, symptomatic evidence, or a recorded progression of another or unknown type.

Overall survival (OS) was measured from crizotinib discontinuation to death and was stratified by the use of a second-generation *ALK* inhibitor immediately following crizotinib discontinuation. Clinician-defined PFS was measured from initiation of post-crizotinib chemotherapy in the line immediately following crizotinib discontinuation until progression or death. Patients who subsequently initiated a second-generation *ALK* inhibitor were excluded from the analysis of PFS on post-crizotinib chemotherapy, as progression information was not collected for patients who used a second-generation *ALK* inhibitor. As a secondary analysis to compare OS and PFS from the present study with findings from previous clinical trials, OS was also assessed from second-line crizotinib initiation to death and clinician-defined PFS was assessed from initiation of crizotinib until progression or death.

Where sample size permitted, analyses were stratified by region: US, EU (France, Italy, the Netherlands, and Switzerland), Korea, and LATAM (including Mexico and Argentina).

2.4. Statistical analyses

Patient characteristics and treatment information was analyzed descriptively. Kaplan-Meier (KM) estimation was used to assess median treatment duration, OS, and clinician-defined PFS. For the assessment of OS, patients were censored at last follow-up. In the analysis of PFS, patients who died on the studied treatment were considered to have progressed; patients who modified or discontinued the studied treatment or were still on the treatment at last follow-up were censored. All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Physicians from 25 medical centers extracted information on 158 patients from four regions: the EU (n = 99), Korea (n = 30), the US (n = 17), and LATAM (n = 12; Table 1). The mean age of patients at locally advanced or metastatic diagnosis was 56 years; 47% of the patients were male. Approximately half (53%) of patients were never smokers. Smoking history varied by region: most patients in the EU (57%) and Korea (60%) were never smokers, whereas 35% of US and 25% of LATAM patients were never smokers. The sample was racially diverse, reflecting the geographic diversity of the sample. Almost all patients (97%) had adenocarcinoma histology. At primary NSCLC diagnosis, a majority of patients were diagnosed with metastatic disease (82%). Overall, nearly half (47%) of patients were diagnosed with brain metastases by the end of follow-up; ranging from 29% in the US to 54% in the EU. Median follow-up time was