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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TITLE PAGE

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Study highlights

- Global retrospective chart review of crizotinib-treated *ALK*+ NSCLC patients
- 47% of patients received no antineoplastic therapy after crizotinib discontinuation
- Survival following crizotinib discontinuation was poor (8.2 months)
- Patients without 2nd-generation *ALK* inhibitors had particularly poor survival

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.

KEYWORDS

Lung Neoplasms; Carcinoma, Non-Small-Cell Lung; Anaplastic Lymphoma Kinase; Protein Kinase Inhibitor; Survival

1.0 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 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).

2.0 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).

3.0 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 21.4 months (interquartile range: 10.3-33.1 months) from locally advanced or metastatic NSCLC diagnosis.

3.2 Treatment patterns and survival

A majority (64%) of patients initiated chemotherapy as the first treatment following locally advanced or metastatic NSCLC diagnosis (Table 2). The remaining patients received either crizotinib (22%) or another targeted therapy (15%, specifically, bevacizumab and erlotinib-based regimens).

Among patients who discontinued first-line chemotherapy, 55% were treated with second-line crizotinib, 37% with a subsequent chemotherapy regimen, and 7% with other targeted therapies (with or without chemotherapy). Among first-line chemotherapy patients who received second-line crizotinib (n=56), median OS following crizotinib initiation was 22.6 months.

Overall, most (41%) patients received crizotinib in the second-line setting, though the line of crizotinib initiation varied across regions. Approximately half of the patients in the US (53%) and LATAM (50%) initiated crizotinib as first-line therapy, while in the EU and Korea, crizotinib was typically initiated in later lines. Median time to clinician-defined PFS since the start of crizotinib among all 158 crizotinib-treated patients was 6.9 months, ranging from 4.2 months in LATAM (n=12) to 8.7 months in the EU (n=99).

Most crizotinib-treated patients (88%) discontinued the initial crizotinib therapy (Figure 1). The remainder either died while still on crizotinib treatment (11%) or were still on that crizotinib line at last follow-up (1%). Median duration of initial crizotinib treatment was 5.6 months.

Approximately half (47%) of those who discontinued crizotinib were reported to have received no additional antineoplastic therapy. Of the 53% who received further systemic therapy after crizotinib discontinuation (n=73), most either switched to a second-generation *ALK* inhibitor (44%) or to chemotherapy (42%). The remaining patients either re-initiated or modified crizotinib (10%), switched to another targeted therapy (3%), or received an unknown systemic therapy (1%). Among the patients treated with a second-generation *ALK* inhibitor following crizotinib discontinuation (n=32), a majority (78%) received ceritinib; the remaining patients were treated with alectinib (19%) or brigatinib (3%).

Following crizotinib discontinuation, median OS (n=139) was 8.2 months, with 12- and 24-month survival rates of 39.7% and 32.1%, respectively. Among the subgroup of patients who did not initiate a second-generation *ALK* inhibitor at any time after discontinuing crizotinib (n=98), median OS was 4.9 months, with 12- and 24-month survival rates of 28.8% and 19.8% (Figure 2). Median OS in this group varied from 6.0 months in the EU (n=58) to 3.4 months in Korea (n=20). The patients in this group who switched to chemotherapy (n=27) had a median OS of 7.2 months and the patients reported to have received no additional antineoplastic therapy (n=66) had a median OS of 4.0 months. In the subgroup of patients who initiated a second-generation *ALK* inhibitor in the line following crizotinib discontinuation (n=32), median OS was not reached (Figure 3). Among these patients, the survival rate at 12 months was 59.9% and was 52.4% at 24 months.

Among the 31 patients who received chemotherapy immediately following crizotinib discontinuation, four later initiated a second-generation *ALK* inhibitor and were excluded from the analysis of PFS as progression information was not collected. Among the remaining 27 patients, time to clinician-defined PFS from post-crizotinib chemotherapy initiation was 3.6 months (Figure 4).

4.0 DISCUSSION

This retrospective chart review described real-world patient characteristics, treatment patterns, and outcomes of *ALK*+ NSCLC patients who were treated with crizotinib. Patient characteristics varied across the study countries with racial differences reflecting the sample's geographic diversity. Notably, the 47% proportion of smokers was higher than has historically been observed in clinical trial studies populations of *ALK*+ NSCLC patients.[20, 21, 28] Two recent studies, a US chart review study and a study of 28 French genetic centers, also observed high proportions of smokers among the included *ALK*+ NSCLC patients;[10, 12] the reasons for this difference in smoking history merits further investigation. Across the eight study countries, treatment options following discontinuation of crizotinib were limited, with nearly half of patients receiving no further antineoplastic therapy. Survival following crizotinib discontinuation was poor among patients who did not receive a second-generation *ALK* inhibitor.

Chemotherapy was the most common first-line treatment across regions, despite recent NCCN guidelines that recommend initiation of crizotinib in the first line for *ALK*+ disease.[15] Crizotinib is approved as a first-line therapy for *ALK*+ NSCLC patients in the US and, recently, in the EU, whereas in most other geographical regions, it has been approved as a second-line therapy. The

present study may underestimate the current rate of first-line crizotinib use in the US; crizotinib was recently approved at the time of data collection in the present study and some patients may have received first-line treatment prior to the approval of crizotinib. Likewise, the CHMP recommendation for first-line crizotinib use was granted after the conclusion of the data collection.

Post-crizotinib treatment options were limited, with roughly half of patients receiving no subsequent antineoplastic treatment. In recent Phase I-II trials, ceritinib has demonstrated a PFS of 5.7 to 11.1 months and an OS of 14.9 months among pretreated patients with locally advanced or metastatic *ALK*+ NSCLC.[32-34] With the its recent approval and the development of other second-generation *ALK* inhibitors such as alectinib and brigatinib, physicians now have more treatment options for patients who fail or become intolerant to crizotinib; these approvals overlapped with the data collection in the current study. Treatment patterns will likely continue to evolve in the near term as access to second-generation *ALK* inhibitors increases.

Following crizotinib discontinuation, survival and clinician-defined PFS were short, particularly among patients who did not receive a subsequent second-generation *ALK* inhibitor. Many patients initiated crizotinib in later lines during their course of therapy, which may have contributed to the short survival rates. However, as measured from crizotinib initiation, survival rates were consistent with previously reported clinical trial results. Among patients who received second-line crizotinib following first-line chemotherapy, the 12-month survival rate from crizotinib initiation was 65.5%; this finding is similar to a retrospective analysis which found a 70% 12-month survival rate among patients who initiated crizotinib in the second or third line.[35]

Likewise, the median clinician-defined PFS of 6.9 months among crizotinib patients in the current study was similar to crizotinib PFS rates found in a previous trial of chemotherapy-experienced patients using crizotinib (7.7 months).[20]

This study has several limitations. Because charts are reviewed retrospectively, it is possible that patient information is incomplete. Additionally, generalizability of the findings may be limited. Characteristics of patients in the study may differ from characteristics of *ALK*+ patients in the general population, and practices of the responding physicians may not be representative of overall physician practices. Generalizability within regions may also be limited due to small sample sizes.

A small group of patients was enrolled in clinical trials for some of the studied regimens; as such, their treatment may be dictated by the protocol of those trials rather than real-world practices. Because the addition of second-generation *ALK* inhibitors to the treatment landscape is relatively recent, further changes in treatment patterns can be expected and physician practices may have already changed since data collection. Additionally, when evaluating survival outcomes, it is important to note that patients who received a second-generation *ALK* inhibitor following crizotinib discontinuation should not be directly compared to those who did not receive that therapy. Many of the patients in the former group were enrolled in clinical trials and may have different demographic and clinical characteristics than the latter group of patients.

5.0 CONCLUSION

In this retrospective, global chart review study of *ALK*+ NSCLC patients, many crizotinib-treated patients received no further antineoplastic therapy following crizotinib discontinuation, suggesting that greater access to post-crizotinib treatment options was needed at the time of data collection in this study. Survival following crizotinib discontinuation was poor, particularly 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.

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8.0 FIGURE LEGEND

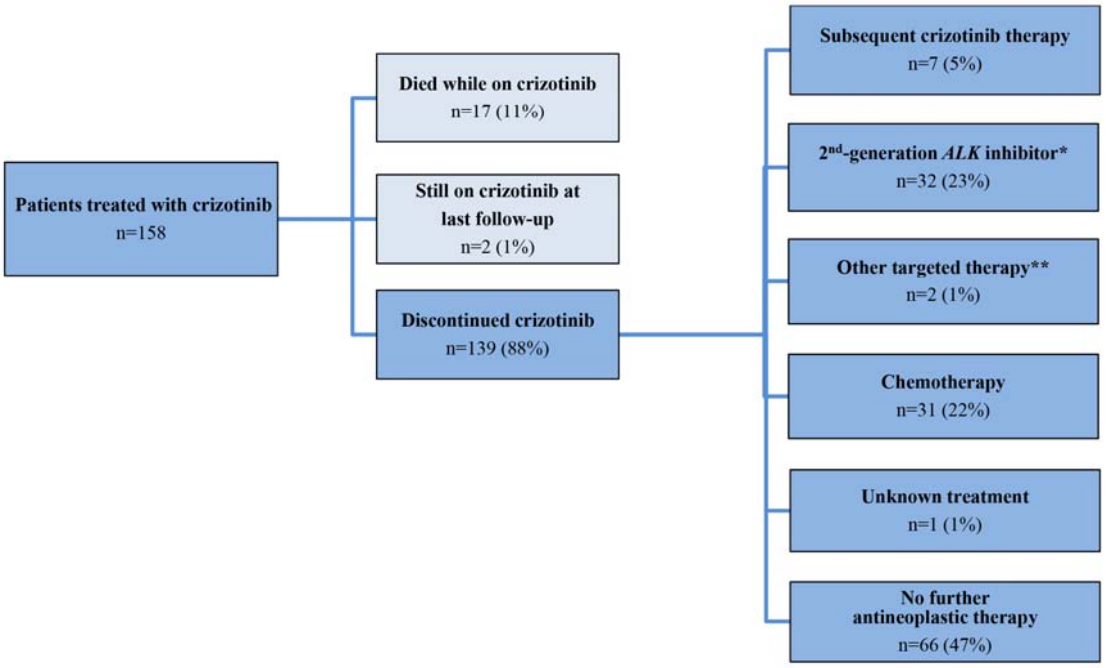
Figure 1
Title: Treatment patterns following crizotinib
Notes:
* 2nd-generation ALK inhibitors included ceritinib (78%), alectinib (19%), and brigatinib (3%).
** One patient received afatinib; the other patient received bevacizumab, cetuximab, and pemetrexed (combination therapy).

Figure 2
Title: Post-crizotinib overall survival among patients who did not receive a second-generation *ALK* inhibitor in any line of therapy
Note:
* US (n=12) and LATAM (n=8) are not displayed due to small sample sizes.

Figure 3
Title: Post-crizotinib overall survival among patients who received a second-generation *ALK* inhibitor in the line following crizotinib
Note:
* Korea (n=4), US (n=3), and LATAM (n=0) are not displayed due to small sample sizes.

Figure 4
Title: Clinician-defined progression among patients who initiated chemotherapy in the line following crizotinib

Figure 1. Treatment patterns following crizotinib



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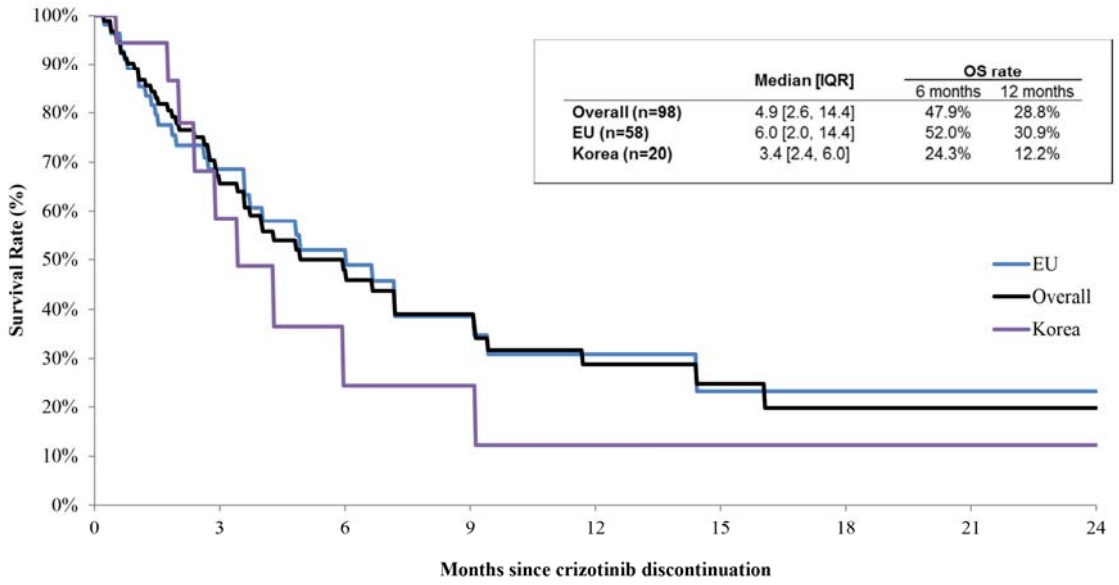
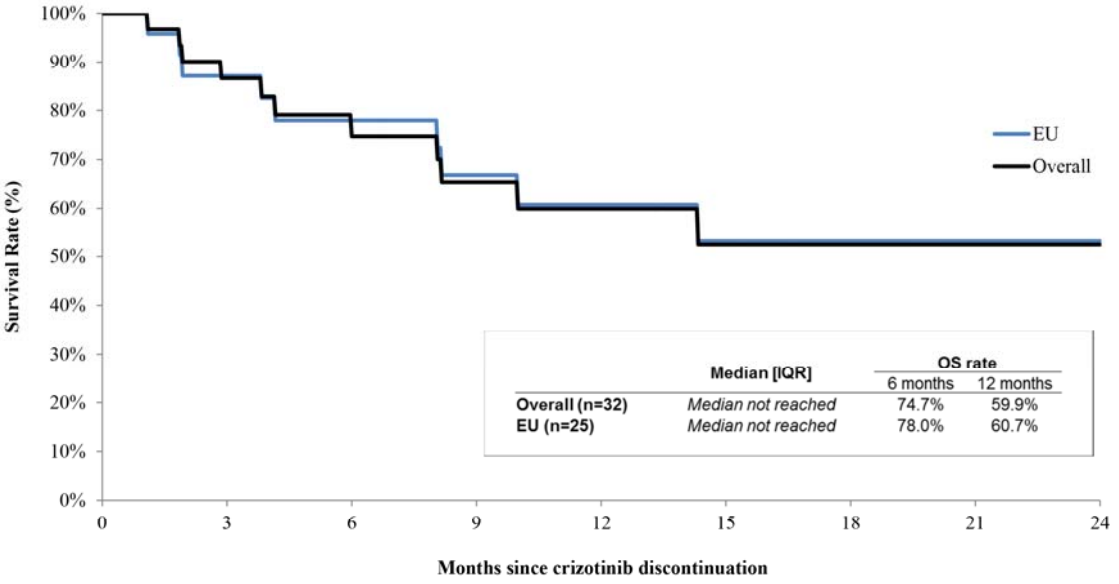


	Median [IQR]	OS rate	
		6 months	12 months
Overall (n=98)	4.9 [2.6, 14.4]	47.9%	28.8%
EU (n=58)	6.0 [2.0, 14.4]	52.0%	30.9%
Korea (n=20)	3.4 [2.4, 6.0]	24.3%	12.2%

Note:

* US (n=12) and LATAM (n=8) are not displayed due to small sample sizes.

Figure 3. Post-crizotinib overall survival among patients who received a second-generation *ALK* inhibitor in the line following crizotinib



	Median [IQR]	OS rate	
		6 months	12 months
Overall (n=32)	*Median not reached*	74.7%	59.9%
EU (n=25)	*Median not reached*	78.0%	60.7%

Note:

* Korea (n=4), US (n=3), and LATAM (n=0) are not displayed due to small sample sizes.

Figure 4. Clinician-defined progression among patients who initiated chemotherapy in the line following crizotinib

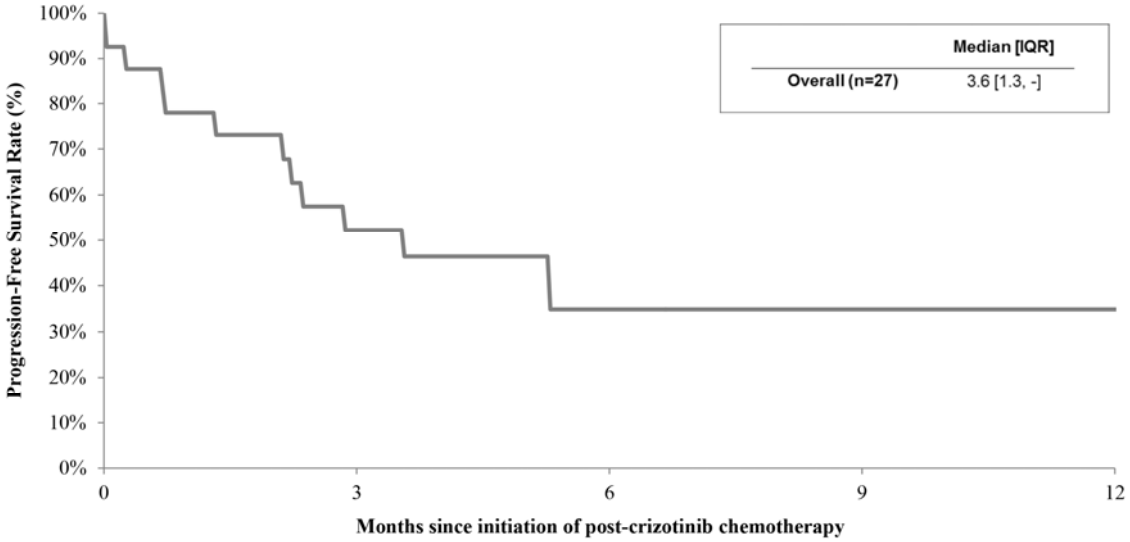


Table 1. Patient characteristics

Characteristic	Overall (n=158)	EU (n=99)	Korea (n=30)	US (n=17)	LATAM (n=12)
Age at locally advanced/metastatic NSCLC diagnosis (years), mean ± SD	56 ± 13	55 ± 13	57 ± 10	59 ± 13	59 ± 12
Male, %	47%	51%	50%	24%	42%
Race, %					
Caucasian	38%	40%	-	71%	67%
Asian	20%	-	100%	12%	-
Black	1%	-	-	6%	-
Other / unknown*	41%	60%	-	12%	33%
Smoking history, %					
Never smoker	53%	57%	60%	35%	25%
Light smoker (≤10 pack-year** history)	11%	10%	13%	6%	17%
Moderate smoker (11-19 pack-year history)	11%	13%	7%	-	17%
Heavy smoker (>20 pack-year history)	17%	14%	10%	41%	25%
Former smoker	6%	3%	3%	18%	17%
Metastatic disease at primary NSCLC diagnosis, %	82%	82%	87%	71%	83%
Adenocarcinoma histology at primary NSCLC diagnosis, %	97%	97%	97%	94%	100%
Brain metastases diagnosed by the end of follow-up, %	47%	54%	37%	29%	42%

Notes:
* Other/unknown race comprises the following patients: in the EU, patients whose race is unreported due to French privacy laws; in LATAM, Hispanic patients; and in the US, American Indian or Alaskan (n=1) and unknown (n=1).
** A pack-year is defined as smoking a pack (containing 20 cigarettes) per day for a year.

Table 2. Treatment patterns by line

Therapy, n (%)	First line (n=158)	Second line (n=140)	Third line (n=93)	Fourth and later lines* (n=52)
Crizotinib	34 (22%)	66 (47%)	37 (40%)	30

EU (n=99)	12	43	28	24
Korea (n=30)	7	12	6	6
US (n=17)	9	5	3	0
LATAM (n=12)	6	6	0	0
Second-generation *ALK* inhibitor**	0 (0%)	6 (4%)	13 (14%)	23
Other targeted therapy***	23 (15%)	15 (11%)	6 (6%)	15
Chemotherapy	101 (64%)	53 (38%)	37 (40%)	41

Note:

* Includes counts of all therapies patients received in the fourth or later lines. The same patient could contribute more than one line of the same therapy.

** Includes: alectinib (n=8), brigatinib (n=1), and ceritinib (n=33) regimens.

*** Includes: afatinib, bevacizumab, erlotinib, gefitinib, and nintedanib regimens.