ORIGINAL ARTICLE

Natural History and Factors Associated with Overall Survival in Stage IV *ALK*-Rearranged Non–Small Cell Lung Cancer

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ABSTRACT

Introduction: Clinical variables describing the natural history and longitudinal therapy outcomes of stage IV anaplastic lymphoma kinase gene rearrangement positive (*ALK*-positive) NSCLC and their relationship with long-term overall survival (OS) have not previously been described in detail.

Methods: Patients with stage IV NSCLC treated with an ALK inhibitor at the University of Colorado Cancer Center from 2009 through November 2017 were identified retrospectively. OS curves were constructed by using Kaplan-Meier methods. Multivariate Cox proportional hazard analysis was used to determine the relationship of variables with OS.

Results: Of the 110 patients with *ALK*-positive NSCLC who were identified, 105 received crizotinib as their initial ALK inhibitor. With a median follow-up time of 47 months, the median OS time from diagnosis of stage IV disease was 81 months (6.8 years). Brain metastases at diagnosis of stage IV disease (hazard ratio = 1.01, $p = 0.971$) and year of stage IV presentation ($p = 0.887$) did not influence OS. More organs with tumor at diagnosis of stage IV disease was associated with worse OS (HR = 1.49 for each additional organ with disease, including the CNS [$p = 0.002$]). Each additional month of pemetrexed-based therapy was associated with a 7% relative decrease in risk of death.

Conclusion: Patients with stage IV *ALK*-positive NSCLC can have prolonged OS. Brain metastases at diagnosis of stage IV disease does not influence OS. Having more organs involved with tumor at stage IV presentation is associated with worse outcomes. Prolonged benefit from pemetrexed is associated with better outcomes.

Keywords: ALK; Anaplastic lymphoma kinase; Non–small cell lung cancer; Overall survival; Stage IV

Introduction

Targeted therapy has increased 5-year overall survival (OS) for select patients with NSCLC when compared with historical estimates.[1–6] Patients with NSCLC and anaplastic lymphoma kinase gene

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rearrangement positive (*ALK*-positive) disease comprise one population that has benefited from targeted therapy. The Food and Drug Administration (FDA) has licensed multiple anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib (first-line license granted in 2011), ceritinib (license for use after crizotinib granted in 2014 plus license for first-line use granted in 2017), alectinib (license for use after crizotinib granted in 2015 plus license for first-line use granted in 2017), brigatinib (license for use after crizotinib granted in 2017), and lorlatinib (license for use after a noncrizotinib ALK inhibitor [ALKI] granted in 2018).[7,8]

The historical 5-year OS rate for molecularly unselected stage IV NSCLC is approximately 2%.[9] However, a retrospective review of 26 patients with stage IV ALK-positive NSCLC treated with crizotinib as their first ALKI suggested a 5-year OS rate of 36%.[5] The 4-year OS rate in PROFILE-1014 for patients receiving crizotinib as initial systemic therapy was 57%.[6] Two retrospective studies have suggested median OS times ranging from 49 months (n = 71) to 89 months (n = 84) from time of diagnosis of metastatic disease in ALK-positive patients treated with crizotinib followed by a next-generation ALKI at any time point after progression.[1,2] However; detailed information on clinical factors associated with long-term survival has not been reported. We present data on 110 patients with stage IV ALK-positive NSCLC, providing detailed information on a multitude of clinical factors and their relationship with long-term OS.

Methods

Patients with stage IV NSCLC treated with an ALKI at University of Colorado Cancer Center (UCCC) from 2009 through November 2017 were identified retrospectively. Electronic records were searched using the terms *crizotinib*, *ceritinib*, *alectinib*, and *brigatinib*. Patients were excluded if they were not *ALK*-positive or had more than one active malignancy. Clinical data were obtained from review of patient records. In a separate analysis, patients with molecularly unselected stage IV NSCLC diagnosed at UCCC during the same time period were identified from our cancer center registry to compare their OS with that of patients with stage IV *ALK*-positive NSCLC. An institutional review board–approved protocol at UCCC permitted clinical correlates to be made for patients in whom molecular analyses had been conducted within the program.

Patients may have received an ALKI on or off trial. If the drug was subsequently FDA-approved, it is identified by name. Experimental agents that have not been FDA-approved are identified by class but not by name. Non-ALKI systemic therapy included chemotherapy, immunotherapy, or clinical trials of agents that were not ALKIs.

Types of progression were identified by review of patient records and radiographic images. Patients with all progressing lesions treated with local ablative therapy (LAT) while continuing to take the same ALKI with which they were previously being treated were described as having oligoprogressive disease (OPD) treated with LAT. For the definition of OPD, the brain was considered a single site of OPD regardless of the number of lesions progressing in the brain at the time. Each progressing lesion outside of the brain that was treated with LAT was considered a separate site of OPD.

ALK mutations were evaluated as mechanisms of resistance to crizotinib by next-generation sequencing or direct sequencing. Mutations in bypass track mechanisms were evaluated for by next-generation sequencing or SNAPshot assay.

OS curves were constructed by using Kaplan Meier-methods. Multivariate Cox proportional hazard analysis was used to determine the relationship of variables with OS. The data cutoff for OS was November 24, 2017. Very long-term (VLT) survivors, defined as patients alive 8 or more years from diagnosis of stage IV disease, were also identified as a relevant subgroup of interest. The characteristics and treatment course of VLT survivors were described with descriptive statistics and illustrated graphically with a swimmer's plot.

Results

Patient Characteristics at Diagnosis of Stage IV ALK-Positive Disease

A total of 110 *ALK*-positive patients were identified. Details of these patients are shown in Table 1. Of the 110 patients, 88 (80%) presented with stage IV disease and 22 (20%) developed stage IV disease after presenting at an earlier stage. Their median age was 53 years. Sex distribution was equal. Most patients were never-smokers and non-Hispanic whites. In all, 33 patients (30%) had brain metastases at diagnosis of stage IV disease, and in five patients (4.5%) the brain was their only site of metastatic disease. The median number of organs with metastases at diagnosis of stage IV disease, including the central nervous system (CNS), was 3 (range 1–6). Most patients (86%) were identified as *ALK*-positive by fluorescence in situ hybridization (Supplementary Table 1). In all, 105 patients (95%) received crizotinib as their initial ALKI. The median time to initiation of first systemic therapy for stage IV disease was 20 days from the time when stage IV disease was diagnosed (range 1-2499).

OS from Diagnosis of Stage IV Disease

The median follow-up time for OS was 47 months. A total of 49 patients (45%) were known to be alive at data

Table 1. Patient Characteristics at Diagnosis of Stage IV Disease (N = 110)

Characteristic	n, %
ALK variant status	
Variant 1	9 (8.2%)
Variant 3	9 (8.2%)
Other variant	5 (4.5%)
Not available	87 (79.1%)
Brain metastasis at diagnosis of stage IV disease	
Yes	33 (30.0%)
No	75 (68.2%)
Not available	2 (1.8%)
Ethnicity	
Non-Hispanic	96 (87.3%)
Hispanic	6 (5.4%)
Not available	8 (7.3%)
Race	
White	88 (80.0%)
Others	14 (12.7%)
Not available	8 (7.3%)
Sex	
Male	55 (50.0%)
Female	55 (50.0%)
Smoking status	
Current/former[a]	17 (15.5%)
Never	91 (82.7%)
Not available	2 (1.8%)
Median age, y	53 (range 21-85)
Median number organs with metastases[b]	3 (range 1-6)

[a]The median number of pack-years for the current or former smokers was 7.
[b]Two patients had missing data.
ALK, anaplastic lymphoma kinase gene rearrangement.

cutoff. The median OS time from diagnosis of stage IV disease was 81 months (6.8 years), range: 3 to 125+ (Fig. 1).

There was no significant difference in OS time between patients who received crizotinib first (median 86 months [n = 40]) and those who received a non-ALKI systemic therapy before crizotinib (median 79 months [n = 65]) ($p = 0.653$) (Supplementary Fig. 1). There was a numerical difference in OS time that was not statistically significant when patients with and without crizotinib dose reductions were compared: the median OS time was 79 months without dose reduction (n = 86) versus 50 months with dose reduction (n = 19) ($p = 0.281$). Five patients were treated with a next-generation ALKI as initial therapy; as a result, there were insufficient data to compare OS in these patients with that of patients receiving crizotinib as their initial ALKI.

In a multivariate analysis looking at features identifiable in 102 patients at baseline, brain metastases at diagnosis of stage IV disease did not influence OS (HR = 1.01, $p = 0.971$). However, a greater number of organs with tumor at diagnosis of stage IV disease (HR = 1.49 for each additional organ with disease including the CNS, $p = 0.002$) and male sex (HR = 2.38, $p = 0.021$) were associated with worse OS. Additionally, Hispanic ethnicity was associated with worse OS than non-Hispanic ethnicity (Table 2).

In all, 23 patients had information on *ALK* variant status: nine patients (39%) had variant 1, nine patients (39%) had variant 3, and five patients (22%) had other variants. OS was not significantly different when *ALK* variant 3 or other variants were compared with variant 1 (for variant 3, HR = 1.61 [p = 0.44]; for other variants, HR = 1.11 [p = 0.90]).

Year of diagnosis of stage IV disease (2004–2010, 2011–2014, and 2015–2017) was not associated with OS ($p = 0.887$) (Fig. 2). These diagnostic periods were chosen to represent a time before there were any approved ALKIs, a time with limited approved ALKIs, and a time with multiple approved ALKIs, respectively.

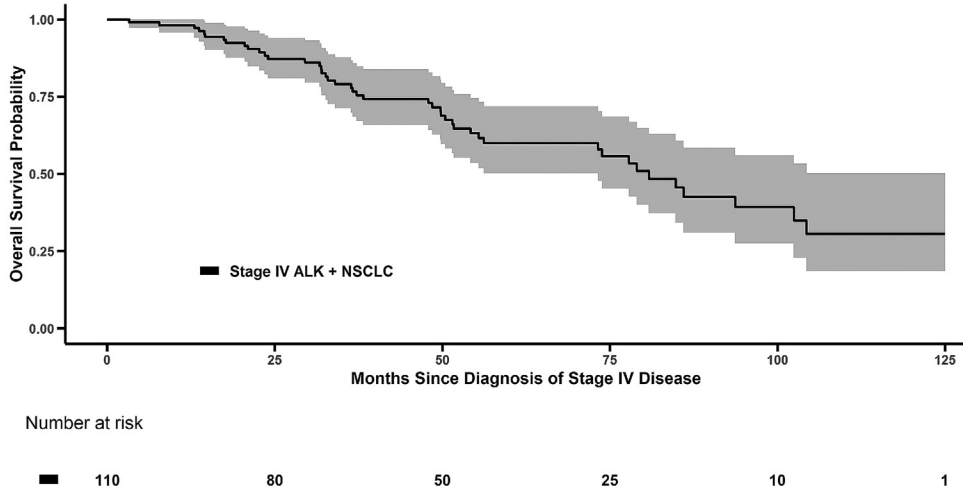

Figure 1. Overall survival from diagnosis of stage IV anaplastic lymphoma kinase gene rearrangement positive (*ALK*-positive) NSCLC. The 95% confidence interval is indicated by the shaded area.

Table 2. Multivariate Analysis of Variables Present at Diagnosis of Stage IV Disease and Relationship with Overall Survival

Variable	HR (95% CI)	*p* Value
Brain metastases present	1.01 (0.49-2.12)	0.971
Each additional organ with tumor (including the CNS as an organ)	1.49 (1.16-1.91)	**0.002**
Male sex	2.38 (1.14-4.96)	**0.021**
Non-Hispanic ethnicity	0.25 (0.08-0.75)	**0.014**
Smoking status (never smoker)	1.25 (0.53-2.94)	0.605

A total of 102 patients were included in this multivariate analysis; eight patients were not included owing to incomplete data.
HR, hazard ratio; CI, confidence interval; CNS, central nervous system.

The median follow-up times for patients who experienced development of stage IV disease during 2004–2010 (n = 48), 2011–2014 (n = 45), and 2015–2017 (n = 17) were 67 months, 45 months, and 21 months, respectively.

In all, 46 patients had information on duration of pemetrexed-based therapy (PBT). Details on PBT regimens and whether maintenance pemetrexed was administered are provided in Supplementary Table 2. The median number of cycles of PBT was 6 (range 1–45); this number did not differ according to whether it was given before crizotinib (median 6, range 1–45) or after crizotinib (median 6, range 2–30). The median line of administration of PBT was second line (range 1–5). Reasons for stopping PBT are listed in Supplementary Table 3. Each additional month of PBT (given before or after crizotinib) was associated with a 7% relative decrease in risk of death (HR = 0.93 and $p = 0.03$).

Details of Patients with Brain Metastases at Diagnosis of Stage IV Disease

There were no significant differences in demographics between patients with (n = 33) and without (n = 75) brain metastases at diagnosis of stage IV disease (Supplementary Table 4). At diagnosis of stage IV disease, the median size of the brain metastases were 0.6 cm (range 0.2–2.8) and the median number of brain metastases was 4 (range 1–50). In all, 49% of patients with baseline brain metastases had evaluable CNS disease per the Response Evaluation Criteria in Solid Tumors version 1.1 (size ≥1 cm).

In all, 85% of patients (28 of 33) with baseline brain metastases received documented local therapy for these metastases either before or concurrently with their initial systemic therapy. Of the 28 patients who underwent local therapy for brain metastases, 89.3% were treated with radiation (n = 25), 7.1% had an operation plus radiation (n = 2), and 3.6% underwent an operation (n = 1). Of the 27 patients with radiation for baseline brain metastases, 59.3% received whole brain radiation therapy (n = 16) and 40.7% received stereotactic radiosurgery (SRS) (n = 11). Two of the 11 patients who received SRS did not receive SRS to all brain metastases: one patient received SRS to 10 of 13 lesions and the other patient had SRS to two of 50 lesions.

The initial systemic therapy for patients with brain metastases at diagnosis of stage IV disease was as follows: chemotherapy for 48.5% (n = 16), crizotinib for 45.5% (n = 15), and brigatinib for 6% (n = 2). Two patients with baseline brain metastases who were treated with crizotinib as initial systemic therapy have

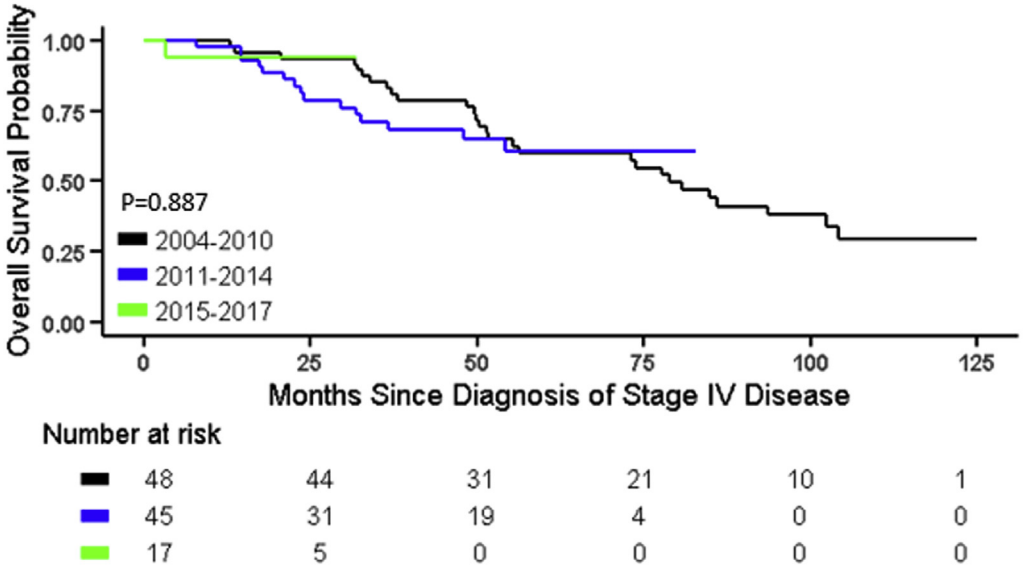

Figure 2. Overall survival by period during which stage IV disease was diagnosed.

yet to develop progressive disease (median follow-up times 5 months and 39 months); one had an operation and the other was treated with surgery plus radiation to the brain. In all, 94% of patients with baseline brain metastases (31 of 33) received crizotinib as their initial ALKI. Of the 29 patients with baseline brain metastases who developed progressive disease while taking crizotinib, 70% received a next-generation ALKI at some time after crizotinib; two patients were lost to follow-up and did not have this information available.

Patients with Progressive Disease while Taking Crizotinib

Of the 105 patients treated with crizotinib, 102 (97%) had documented progression while taking crizotinib. The median time to first progression during crizotinib therapy was 11 months, and the median duration of crizotinib therapy was 14 months. Of the three patients without documented progression while taking crizotinib, one was lost to follow-up at 29 months and the other two were still receiving crizotinib at data cutoff after 5 and 39 months.

A total of 100 patients who developed progressive disease while taking crizotinib had information available on whether they had experienced development of OPD treated with LAT. Of these 100 patients, 49 received LAT for OPD while taking crizotinib and 51 did not receive LAT. Those who received LAT for OPD continued taking crizotinib beyond progression. Of the 51 patients who did not receive LAT for progression, 50 had available data on subsequent therapy and 46 of the 50 (92%) received another systemic therapy after crizotinib. Of the 49 patients who received LAT for OPD while taking crizotinib, 47 had information on subsequent therapy and 37 of the 47 (79%) received another systemic therapy at some time after having taken crizotinib.

The median number of sites of progressive disease at development of OPD treated with LAT was 1 (range 1–5), two patients had four or more progressing sites (four and five sites, respectively). The brain was the only site of progression in 51% of those who received LAT for OPD (n = 25). When also including those who developed extra-CNS sites of OPD, the brain was a site of OPD in 28 patients (57%). Other locations of progression in those treated with LAT for OPD were bone (18%), lung (16%), lymph node (8%), adrenal gland (6%), liver (4%), pleura (4%), and chest wall (2%). LAT for OPD consisted of radiation in all but one instance (in which an adrenal gland metastasis was excised). When cranial radiation was used as LAT for initial CNS OPD, there were 21 patients (75%) treated with SRS, six patients (21.4%) treated with whole brain radiation therapy, and one patient (3.6%) in whom the modality of radiation therapy was not identifiable.

We performed a multivariate analysis of 95 patients with available data at the time of progression during crizotinib therapy (including sex, ethnicity, number of organs involved with tumor at progression [both progressing and nonprogressing sites], and LAT for OPD while continuing to receive crizotinib). Non-Hispanic ethnicity was associated with improved OS (HR = 0.25, $p = 0.001$), as was having fewer organs with tumor at time of progression (for each additional organ with tumor the HR was 1.55 ($p < 0.001$) (Table 3). LAT for OPD was not associated with improved OS, although there was a trend toward benefit (HR = 0.58, $p = 0.14$).

In patients with CNS-only OPD there was an improvement in OS when compared to patients with extra-CNS OPD; however, this difference was not significant (the median OS time from diagnosis of stage IV disease was 94 months for patients with CNS-only OPD and 74 months for patients with extra-CNS OPD [$p = 0.271$], similarly, median OS from time of starting crizotinib was 85 months for patients with CNS-only OPD and 68 months for patients with extra-CNS OPD [$p = 0.311$]). The median time to first progression during crizotinib therapy did not differ significantly when patients with CNS-only OPD were compared with patients with extra-CNS OPD ($p = 0.158$); however, the total time taking crizotinib was significantly greater for patients with CNS-only OPD (median 29 months versus 16 months [$p = 0.018$]) (Supplementary Tables 5 and 6 and see also Supplementary Fig. 2).

At time of progression during crizotinib therapy, there were 23 patients who had testing for both *ALK* mutations and bypass track mechanisms of resistance. The OS from time of diagnosis of stage IV disease ($p = 0.924$) and the OS from time of starting treatment with crizotinib ($p = 0.423$) did not differ according to presence or absence of detectable *ALK* mutations (Supplementary Table 7).

Table 3. Multivariate Analysis of Variables at Time of Progression during Crizotinib Therapy and Their Association with Overall Survival

Variable	HR (95% CI)	*p* Value
Local ablative therapy for oligoprogressive disease while continuing crizotinib	HR 0.58 (0.28-1.20)	0.143
Male sex	HR 1.91 (0.87-4.18)	0.105
Non-Hispanic ethnicity	HR 0.25 (0.09-0.71)	**0.001**
Each additional organ with tumor at progression (Including the CNS as an organ)	HR 1.55 (1.21-1.98)	**<0.001**

In all, 95 patients were included in this multivariate analysis; seven patients were not included owing to incomplete data.
HR, hazard ratio; CI, confidence interval; CNS, central nervous system.

Outcomes for Patients Receiving Further Systemic Therapy after Crizotinib

Of 102 patients who experienced progression during crizotinib therapy, 83.3% received a different systemic therapy, 78.4% received another ALKI at some point after progression, 2.0% had missing data, and 14.7% did not receive any further systemic therapy beyond crizotinib (11.8% died and 2.9% were alive at data cutoff after LAT with continuation of crizotinib therapy). Among these 102 patients, use of another ALKI at any time point after crizotinib varied by year of diagnosis of stage IV disease, 63% for diagnosis in 2004–2010, 93% for diagnosis in 2011–2014, and 83% for diagnosis in 2015–2017 ($p = 0.002$). The median OS time was 86 months from diagnosis of stage IV disease for patients who received a next-generation ALKI at some point after crizotinib and 52 months for patients who did not ($p = 0.085$). Details of progression-free survival (PFS) and duration of treatment with an FDA-approved next-generation ALKI received as immediate next systemic therapy after crizotinib are provided in Supplementary Table 8 and are generally consistent with the published trial results. Nine patients (9%) were retreated with crizotinib after initial progression during crizotinib therapy (excluding OPD treated with LAT). For these nine patients, intervening lines of therapy, time since receipt of last ALKI, PFS while undergoing retreatment, and duration of response while undergoing retreatment are provided in Supplementary Table 9.

Of the 60 patients who started taking crizotinib at UCCC (30% as first-line therapy and 70% as second- or greater-line therapy), 57 had documented progression during crizotinib therapy. Among these 57 patients, five had no systemic therapy after first progression (all five died), 33 patients had LAT and continued to take crizotinib, 91% had any subsequent systemic therapy (two of whom [3.8%] were still taking crizotinib at data cutoff), and 67% received another ALKI at some point after progression.

Characteristics of VLT Survivors

A separate analysis limited to patients diagnosed with stage IV disease in 2010 or earlier was conducted to identify characteristics of VLT survivors. Of the 48 patients whose disease was diagnosed during this time, 12 (25%) were alive 8 or more years after development of stage IV disease and 10 of the 12 (83%) were alive at data cutoff. These patients were characterized as follows: 83% started taking an ALKI at UCCC, the median age at diagnosis of stage IV disease was 41 years (range 27–68), race and ethnicity distributions did not differ from those of the whole study population, sex distribution did not differ from that of the whole study population (42% male and 58% female), 83% were never-smokers, the median number of organs with tumor at stage IV presentation was 2 (range 1–6), 17% had brain metastasis at diagnosis of stage IV disease, and 92% had received chemotherapy before crizotinib (64% of whom had PBT). In all, 75% received LAT for OPD while continuing crizotinib therapy, 75% received a next-generation ALKI at some point after progression while taking crizotinib, and 67% received PBT during their disease course. Of the patients receiving PBT, 75% received pemetrexed as monotherapy and 25% received it with a platinum. Reasons for discontinuation of PBT are listed in Supplementary Table 3. The median line of therapy during which PBT was administered was second (range first to third). The median number of cycles of PBT was 15 (range 4–45). Four patients recieved LAT for three distinct episodes of OPD while taking crizotinib. When LAT for OPD during treatment with a next-generation ALKI was accounted for, 11 of 12 VLT survivors (92%) received LAT for OPD while continuing to take an ALKI during their disease course. Supplementary Figure 3 illustrates the treatment course of these patients.

Discussion

Patients with stage IV *ALK*-positive NSCLC may have prolonged OS. Prior studies have suggested a 5-year OS rate of 36% (n = 26) and 4-year OS rate of 57% (n = 172).[5,6] Within our study the 4- and 5-year OS rates were 73% and 60%, with a median OS time of 81 months (range 3 to 125+). With longer follow-up, the median OS in our cohort may increase further as 45% of patients in our study were still alive at data cutoff.

For 57 patients in PROFILE-1014 who recieved a next-generation ALKI after progression during crizotinib therapy, the 5-year OS rate was an estimated 75%; in constrast, for 37 patients receiving any systemic therapy that did not include a next-generation ALKI after crizotinib, the 5-year OS was an estimated 28%.[6] The percentage of patients receiving a next-generation ALKI after crizotinib was 38% in the study by Rangachari et al.[5] In studies by Duruisseaux et al. and Gainor. et al, median OS times were 89 months and 49 months, respectively, for subsets of patients who all received crizotinib followed by a next-generation ALKI.[1,2]

In our study, patients receiving crizotinib followed by a next-generation ALKI at some time after progression had a median OS time of 86 months, whereas patients who experienced progression while taking crizotinib who did not receive a next-generation ALK had a median OS time of 52 months. These data suggest that OS is improved if patients are administered a next-generation

ALKI after development of progressive disease during crizotinib therapy. In part, our cohort may have had such a long OS because of the high percentage of patients receiving a next-generation ALKI after progression during crizotinib therapy (59% as next systemic therapy and 78.4% at any time after progression). Although use of next-generation ALKIs did vary by year of diagnosis in our data set ($p = 0.002$), year of diagnosis of stage IV disease (in 2004–2010, 2011–2014, or 2015–2017) was not associated with OS ($p = 0.887$); however, this conclusion may have been biased owing to differences in follow-up for patients with stage IV disease diagnosed in each time period.

The patient characteristics in our cohort are similar to those in the literature for *ALK*-positive patients with newly diagnosed stage IV disease (see Table 1). Of the patients in our series, 41% initiated an ALKI at another facility and were later referred to UCCC; however, the median OS time of these patients was no different from that of those who commenced initial therapy at UCCC (not reached versus 79 months [$p = 0.39$]), suggesting that referral bias of more fit patients from the community into UCCC was not a major factor in the outcomes. It is important to note that at some point in their disease course, all patients in our series received care at a large academic medical center, with the care provided within a tumor type–focused thoracic oncology team with considerable access to novel agents through clinical trials before FDA approval dates. However, because most of the next-generation ALKIs that our patients received are now FDA-approved and widely available, patients with stage IV *ALK*-positive NSCLC treated in the community setting should now have comparable access to many of the drugs used in our series.

In multivariate analysis, the baseline features that were associated with worse OS in our data set included a greater number of organs with tumor at diagnosis of stage IV disease (HR = 1.49 for each additional organ involved with disease including the CNS, $p = 0.002$); and male sex (HR = 2.38, $p = 0.021$). Non-Hispanic ethnicity was associated with better OS (HR = 0.25, $p = 0.014$), but the number of Hispanic patients in our cohort was small (n = 6). In univariate analyses conducted among smaller subgroups with available data at baseline, the presence of *ALK* variant 3 or other variants did not influence OS when compared to patients with variant 1. However, most patients in our cohort (79%) did not have *ALK* variant testing.

Brain metastases at diagnosis of stage IV disease have been associated with worse OS in molecularly unselected patients and in patients with activating mutations in EGFR.[3,10,11] Johung et al. previously suggested that brain metastases diagnosed at any time during the course of stage IV disease may not be associated with worse outcomes in *ALK*-positive NSCLC.[12] PROFILE-1014 suggested that patients with brain metastases present when they start taking crizotinib do not have an OS benefit when compared with patients who undergo chemotherapy, whereas patients without brain metastases had improved OS with crizotinib. However, the confidence intervals for relative OS benefit of crizotinib compared to chemotherapy in patients with and without brain metastases overlapped, suggesting no significant difference in OS between the groups.[6]

Consistent with these data, in our multivariate analysis the presence of brain metastases at diagnosis of stage IV *ALK*-positive NSCLC did not significantly influence OS (HR = 1.01, $p = 0.971$). The characteristics of patients with brain metastases at diagnosis of stage IV disease did not significantly differ from those of patients without brain metastases (see Supplementary Table 4). This suggests that more favorable patient demographics did not account for the lack of influence of brain metastases on OS. However, the median follow-up time was shorter for patients with brain metastases present at diagnosis of stage IV disease (34 months) than for patients without brain metastases (49 months) ($p = 0.049$). Patients with baseline brain metastases had a median of four organs with tumor at diagnosis of stage IV disease (range 1–6), which is greater than the median number of organs with tumor at diagnosis in patients without baseline brain metastases (median 3, range 1–6), which should, if anything, bias toward worse OS in this group.

Our analysis suggests that males may have worse OS from diagnosis of stage IV disease when compared with females (HR = 2.38, $p = 0.021$). Prior work suggested that males and females have similar PFS benefit from ALKIs, whereas the data on differences in OS by sex have been conflicting.[1,6,13–19] Crizotinib is known to decrease free testosterone in males; however, although our site was active in discovering this, only 60% of males began taking crizotinib at UCCC.[20] Consequently, whether all male patients were screened and/or treated for low testosterone and the consequences of such treatment remain unknown.

For the 46 patients in our study with documented PBT, each additional month of PBT was associated with a 7% relative decrease in risk of death. This result is biased in that patients deriving a longer benefit from any therapy would be expected to do better; however, it is consistent with prior observations that patients with *ALK*-positive NSCLC may derive more benefit from PBT than other patients with stage IV NSCLC.[21]

Multivariate analysis suggested that at the time of progression during crizotinib therapy, having a greater number of organs with tumor (including both

progressing and nonprogressing sites) was associated with worse OS (HR = 1.55 for each additional organ involved with disease, including the CNS [$p < 0.001$]). Numerically, an association with male sex and worse OS was again noted; but unlike in the baseline analysis, the association was not statistically significant (HR = 1.91, $p = 0.105$). Although LAT for OPD that developed during crizotinib therapy was not significantly associated with improved OS, there was a strong trend toward benefit (HR = 0.58, $p = 0.14$).

In univariate analysis, presence of *ALK* mutations at time of progression during crizotinib therapy did not significantly influence OS. However, only 23 of the 102 patients who experienced progression during crizotinib therapy had testing for both *ALK* mutations and bypass track resistance mechanisms. Whether *ALK* mutations that develop during treatment with first-line next-generation ALKIs (e.g., alectinib or brigatinib) will influence OS differently from those developing during crizotinib therapy requires further study.

Most patients in this study were treated with crizotinib as their initial ALKI. However, crizotinib is no longer the preferred ALKI in patients with newly diagnosed advanced *ALK*-positive NSCLC.[7] Two randomized phase III trials suggested a significantly improved PFS compared with that in patients receiving crizotinib with first-line use of the highly CNS-penetrant next-generation ALKIs alectinib or brigatinib.[16,22,23] In the ALEX study, which evaluated use of first-line alectinib versus crizotinib, the median investigator-assessed PFS time was significantly improved (34.8 months with alectinib versus 10.9 months with crizotinib).[22] The PFS with first-line alectinib appears to be greater than the theoretical PFS with first-line crizotinib followed by second-line alectinib.[22,24] This suggests that starting with a next-generation ALKI as the initial ALKI may lead to improved outcomes over starting with crizotinib and utilizing a next-generation ALKI at development of progressive disease. Thus, the OS of stage IV *ALK*-positive NSCLC may increase even further compared with that reported in our cohort with more patients being treated with next-generation ALKIs as the initial systemic therapy for stage IV disease.

Of the patients diagnosed with stage IV disease between 2004 and 2010, 25% were alive 8 or more years after diagnosis. These VLT survivors were younger (median age 41 years, range 37–68) than other patients whose disease was diagnosed during the same period (median age 53 years, range 21–78) and than others whose disease was diagnosed during any time period (median age 53 years, range 21–85). VLT survivors also had fewer organs involved with tumor at diagnosis of stage IV disease (median 2, range 1–6) when compared with others whose disease was diagnosed during the same time period (median 3, range 1–3) or with others whose disease was diagnosed during any time period (median 3, range 1–6). In all, 67% of VLT survivors received PBT in comparison with 39% of others in our cohort. Additionally, the median number of cycles of PBT was 15 in VLT survivors versus 6 in others. Although the numbers are small, LAT for OPD that developed during crizotinib therapy was more common in VLT survivors (75%) when compared with the incidence in others

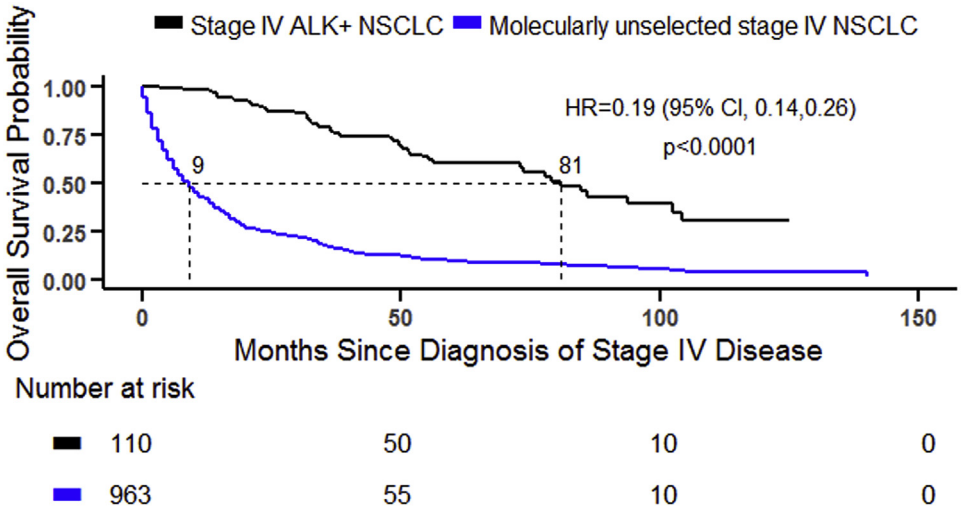

Figure 3. Overall survival from time of diagnosis of stage IV disease for patients with anaplastic lymphoma kinase gene rearrangement positive (*ALK*-positive) NSCLC compared with all patients with NSCLC diagnosed at University of Colorado Cancer Center between 2004 and November 2017. HR, hazard ratio; CI, confidence interval.

(44%). Additionally, when accounting for OPD that developed during treatment with next-generation ALKIs, there were 92% of VLT survivors who received LAT for OPD. Evaluation of molecular markers that are associated with VLT survivors will be important going forward.

Patients with stage IV *ALK*-positive NSCLC can have prolonged OS, with the median OS approaching 7 years, which is much longer than the median OS time of 0.75 years in patients with molecularly unselected stage IV NSCLC who are included in our cancer center tumor registry (n = 963) (Fig. 3). VLT survivors (≥8 years from stage IV diagnosis) now routinely exist among those affected by *ALK*-positive NSCLC. The proportion of VLT survivors will likely increase with greater incorporation of next-generation ALKIs as initial systemic therapy for patients with stage IV disease, emphasizing the importance of long-term tolerability of any therapeutic approaches. As the landscape of *ALK*-positive NSCLC is rapidly evolving, increasing our understanding of the biological basis for survival variation is essential to enhance our optimal management of this disease.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.12.014.

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