Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib

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ABSTRACT

Purpose: Anaplastic lymphoma kinase (ALK) rearrangements are important therapeutic targets in non-small cell lung cancer (NSCLC) that confer sensitivity to the ALK inhibitors crizotinib and ceritinib. To determine the outcome of sequential treatment with crizotinib and ceritinib, we retrospectively evaluated a cohort of ALK-positive patients treated with both agents.

Design: We identified 73 ALK-positive NSCLC patients treated with crizotinib followed by ceritinib at four institutions. Medical records were reviewed to determine overall survival (OS) and progression-free survival (PFS) on crizotinib and ceritinib.

Results: Among 73 ALK-positive patients, the median PFS (mPFS) on crizotinib was 8.2 months [95% confidence interval (CI) 7.4-10.6]. The median interval from crizotinib discontinuation to initiation of ceritinib was 25 days (range 1-694). The mPFS on ceritinib was 7.8 months (6.5-9.1). Among 53 patients with no interval therapies between crizotinib and ceritinib, the mPFS on ceritinib was similar at 7.8 months (5.4-9.8). The median combined PFS for sequential treatment with crizotinib and ceritinib was 17.4 months (15.5-19.4). Among 23 patients who underwent post-crizotinib/pre-ceritinib biopsies, there was no difference in PFS on ceritinib between patients with or without ALK resistance mutations (mPFS 5.8 versus 6.5 months, respectively; P = 0.510). In the overall study population, median OS was 49.4 months (35.5-63.1).
Conclusions: Ceritinib has significant anti-tumor activity in ALK-positive NSCLC—even when crizotinib immediately precedes treatment with ceritinib (median combined PFS 17.0 months). Additional studies are necessary to further define the impact of specific ALK resistance mutations on duration of response to ceritinib.
Statement of Translational Relevance

Anaplastic lymphoma kinase (ALK) inhibitors are now considered standards of care in ALK-rearranged lung cancer; however, questions remain regarding the benefits of sequential therapy with multiple ALK inhibitors. To provide a context for ongoing trials of next-generation ALK inhibitors in the treatment-naive setting, we conducted a retrospective analysis of patients treated with sequential crizotinib and ceritinib. We find that ceritinib is highly active in ALK-positive patients previously treated with crizotinib and that sequential therapy produces a median combined PFS of 17.4 months. Post-crizotinib/pre-ceritinib biopsies were performed in a subset of patients to identify molecular mechanisms of resistance to crizotinib and to correlate these findings with treatment outcomes. Herein, we find that there was no difference in PFS on ceritinib for ALK-positive patients with or without acquired ALK secondary mutations. Future studies will be necessary to evaluate the clinical impact of treatment with ceritinib on patients with specific ALK resistance mutations.
INTRODUCTION

Anaplastic lymphoma kinase (ALK) gene rearrangements have emerged as well-established oncogenic drivers and therapeutic targets in non-small cell lung cancer (NSCLC) (1). Found in 3-5% of NSCLC patients, ALK rearrangements define a distinct molecular subset of the disease with characteristic clinicopathological features (2). Importantly, ALK-positive NSCLCs are oncogene-addicted due to aberrant, constitutively active ALK kinase activity, providing the basis for the efficacy of ALK targeted therapies (3).

Crizotinib was the first approved ALK tyrosine kinase inhibitor (TKI). Single-arm studies demonstrated high objective response rates (ORRs; 60%) and a median progression-free survival (PFS) of 8-10 months in ALK-positive NSCLC (4, 5). More recently, two randomized phase III trials have also shown that crizotinib produces significant improvements in ORR and PFS compared to first- and second-line cytotoxic chemotherapy (6, 7). Thus, crizotinib has become a standard of care for patients with ALK-positive NSCLC.

Despite the effectiveness of crizotinib, patients ultimately develop resistance to therapy (4-6). Molecular mechanisms of resistance to crizotinib include acquired resistance mutations within the ALK tyrosine kinase domain, ALK gene amplification, and up-regulation of bypass signaling pathways (8-10). To date, therapeutic strategies to overcome crizotinib resistance have centered on the use of structurally distinct and more
potent, second-generation ALK inhibitors, such as ceritinib (LDK378) and alectinib (RO5424802/CH5424802), among others.

In preclinical studies, ceritinib demonstrates significant anti-tumor activity in ALK-positive model systems, including various crizotinib-resistant models (11). In a recently reported phase I trial, ceritinib was also highly active in patients with advanced, ALK-positive NSCLC (12). Among 114 patients receiving ceritinib at doses of 400 mg or greater daily, the ORR was 58% with a median PFS of 7.0 months. Importantly, among patients previously treated with crizotinib (n=80), the ORR was similar at 56% with a median PFS of 6.9 months.

The U.S. Food and Drug Administration recently granted accelerated approval of ceritinib for the treatment of ALK-positive NSCLC patients who experience disease progression or intolerance to crizotinib. Moving forward, however, a pressing question will be regarding the proper sequencing of ALK inhibitors. Specifically, will treatment with first-line crizotinib followed by ceritinib at the time of relapse produce additive benefits? And will first-line treatment with more potent next-generation ALK inhibitors (e.g., ceritinib) produce a comparable duration of response, or possibly one that surpasses the sequential approach? Clinical trials evaluating ceritinib in the ALK TKI-naive setting are ongoing (NCT01685138, NCT01828099), but data from these trials are currently not available. To provide a context and benchmarks for these ongoing trials, however, we have performed a multicenter retrospective analysis of the efficacy of sequential crizotinib and ceritinib in a series of 73 ALK-positive patients treated with both agents.
PATIENTS AND METHODS:

Study Population

ALK-positive patients (n=73) were identified at four institutions: Massachusetts General Hospital (MGH; n=40), National Cancer Center Singapore (n=14), Istituto Europeo di Oncologia (n=12) and Peter MacCallum Cancer Center (n=7). All patients had biopsy-proven NSCLC harboring an ALK rearrangement. All patients were treated with sequential crizotinib and ceritinib between 2008-2014. Patients received ceritinib either as part of a clinical trial (N=71; NCT01283516) or on a compassionate use basis (N=2). This study was approved by the Institutional Review Board (IRB) at each participating institution.

Data Collection

Medical records were reviewed and data extracted on clinical and pathologic features and treatment histories. Data were updated as of June 2014. PFS was measured from the time of crizotinib/ceritinib treatment initiation to clinical/radiographic progression or death. Patients without documented clinical or radiographic disease progression were censored on the date of last follow-up. In patients who discontinued crizotinib or ceritinib for reasons other than disease progression (e.g., toxicity), data were censored on the date that these agents were discontinued. Of note, the crizotinib-ceritinib interval was defined as the time from discontinuation of single-agent crizotinib to initiation of ceritinib. Combined PFS for sequential treatment with crizotinib and ceritinib did not include post-progression crizotinib use or the crizotinib-ceritinib interval. Lastly, overall survival (OS)
was measured from the date of metastatic NSCLC diagnosis unless otherwise specified. Patients without a known date of death were censored at the time of last follow-up.

**Tumor Pathology and Genetic Analysis**

Tumor histology was defined according to World Health Organization criteria. ALK rearrangements were identified using ALK fluorescence in situ hybridization (FISH) using dual-color, break-apart assays and standardized criteria.

A subset of ALK-positive patients underwent repeat biopsies of progressing lesions following treatment with crizotinib at two centers (MGH and National Cancer Center Singapore). Samples underwent repeat ALK FISH and testing for ALK resistance mutations as previously described (8). One sample underwent targeted next-generation sequencing (Foundation One, Foundation Medicine Inc, Cambridge, MA). These analyses were performed under IRB-approved protocols.

**Statistical Analysis**

The Kaplan-Meier method was used to estimate all PFS and overall survival endpoints, and the log-rank test was used to compare differences between groups. Data analysis was performed using MedCalc version 12.5 (MedCalc Software, Ostend, Belgium).

**RESULTS:**

**Patient Characteristics and Outcomes to Treatment with Crizotinib**
We identified 73 ALK-positive patients who were treated with both crizotinib and ceritinib. The baseline clinical and pathologic characteristics of these patients are summarized in Table 1. Median age at diagnosis was 50 (range 22-72). A majority of patients were never-smokers (78%) with adenocarcinoma histology (95%). Of note, all patients received crizotinib prior to treatment with ceritinib. Among 73 ALK-positive patients, crizotinib was administered in the first-line setting in 10 (13.7%), whereas the remainder received crizotinib as second-line therapy or beyond. The median number of prior lines of therapy was 1 (range 0-8).

We first evaluated the efficacy of crizotinib within the overall study population. Among 73 ALK-positive patients, the median PFS on crizotinib was 8.2 months (95% CI 7.4-10.6 months; Figure 1A). Two patients permanently discontinued crizotinib due to toxicity (transaminase elevation and development of renal cysts). The remainder discontinued due to disease progression. Of note, crizotinib was commonly continued beyond radiographic evidence of disease progression in this study population. The median duration of post-progression crizotinib use was 25 days (range 0-318). When patients transitioned to new systemic therapies, the majority (72.6%) received ceritinib as the next line of therapy. The median number of intervening lines of therapy between crizotinib and ceritinib was 0 (range 0-3). Post-crizotinib/pre-ceritinib therapies are listed in Supplementary Table 1.

Outcomes to Treatment with Ceritinib
We next examined the efficacy of ceritinib in ALK-positive patients previously treated with crizotinib. A majority of patients (n=56, 76.7%) received a starting dose of 750 mg once daily. In the overall study population (n=73), the median PFS was 7.8 months (95% CI 6.5-9.1 months; Figure 1B). In these patients, the median interval from the last dose of crizotinib to initiation of ceritinib was 25 days (range 1-694 days). In 53 (72.6%) patients, single-agent crizotinib was the last line of systemic therapy received prior to treatment with ceritinib (median interval 20 days, range 1-84 days). Among this subset (n=53), the median PFS on ceritinib was 7.8 months (95% CI 5.4-9.8 months; Figure 1C), which was similar to that observed in the overall study population.

We next evaluated the combined PFS for sequential treatment with crizotinib and ceritinib within the overall study population. Here, the median combined PFS was 17.4 months (95% CI 15.5-19.4 months). Importantly, among 53 patients treated with sequential crizotinib and ceritinib without intervening therapies, the median combined PFS was similar at 17.0 months (95% CI 15.6-19.8 months). For each patient, PFS on crizotinib, duration of post-progression crizotinib treatment, duration of intervening therapy, and PFS on ceritinib are depicted in Figure 2.

**Molecular Characteristics of Post-Crizotinib/Pre-Ceritinib Biopsy Specimens**

A subset of ALK-positive patients (n=23) underwent repeat biopsies following disease progression on crizotinib (Table 2). Biopsies were evaluated for molecular mechanisms of resistance to crizotinib. Repeat ALK FISH was performed in 19 patients, confirming the continued presence of the original ALK rearrangement in all 19 patients. In addition,
two of these specimens (10.5%) demonstrated amplification of the ALK fusion gene as assessed by FISH. ALK resistance mutations were identified in 7/23 (30.4%) patients. Resistance mutations included 1151Tins, C1156Y, L1196M, S1206Y, and G1269A. For each patient who underwent a post-crizotinib/pre-ceritinib biopsy, individual responses to crizotinib and ceritinib are listed in Table 2 and Supplemental Figure 1.

We first compared treatment outcomes to crizotinib among patients with and without ALK resistance mutations identified in post-crizotinib/pre-ceritinib biopsies. The median PFS on crizotinib for patients who were ultimately found to have an ALK resistance mutation in a post-crizotinib/pre-ceritinib biopsy was 11.5 months (95% CI 8.1-18.2). The median PFS on crizotinib for patients without an ALK resistance mutations was 7.1 months (95% CI 5.6-11.2), but this difference was not statistically significant ($P=0.171$).

We next compared the PFS on ceritinib among patients with and without ALK resistance mutations in post-crizotinib/pre-ceritinib biopsies (Figure 1D). Among patients with ALK resistance mutations (n=7), the median PFS on ceritinib was 5.4 months (95% CI 2.7-10.8), while the median PFS on ceritinib for patients without ALK resistance mutations (n=16) was 6.5 months (95% CI 4.0-9.7). This difference was not statistically significant ($P=0.510$). Individual PFS data based upon ALK resistance mutation are provided in Figure 3.

**Overall Survival Analysis**

Lastly, we examined OS among ALK-positive patients treated with sequential crizotinib and ceritinib. With a median follow-up of 53.2 months, the median OS from the date of
metastatic NSCLC diagnosis was 49.4 months (95% CI 35.5-63.1 months; Figure 4A). Among 25 ALK-positive patients with brain metastases identified prior to initiation of crizotinib, the median OS was 42.2 months (95% CI 26.4-51.2; Supplementary Figure 2). Thirty-two (44%) patients received crizotinib in the second-line setting – a population similar to that in the PROFILE 1007 trial. The median OS from the time of crizotinib initiation in this subset of patients was 30.3 months (95% CI 18.0-43.8 months; Figure 4B).

**DISCUSSION**

Targeted therapies have reshaped the management of various oncogene-driven malignancies, such as chronic myeloid leukemia (CML), gastrointestinal stromal tumors and BRAF-mutant melanoma (13-15). With a deeper understanding of acquired resistance and as the number of available kinase inhibitors have grown, a recurring question across these fields has been whether next-generation inhibitors used sequentially will produce additive effects. One approach has been to use more potent, next-generation inhibitors as initial therapy, which may in theory, afford more durable responses. An alternative strategy has been to use first-generation inhibitors upfront followed by more potent agents at the time of relapse. In CML, for example, both strategies have been explored. The more potent second-generation inhibitors nilotinib and dasatinib have been found to produce faster and deeper responses compared to imatinib; however, these agents have yet to demonstrate improvements in long-term outcomes, such as overall survival (16, 17).
In lung cancer, similar questions have emerged. In patients with epidermal growth factor receptors (EGFR) mutations, several third-generation, T790M mutant-specific EGFR inhibitors have been developed and have recently demonstrated promising anti-tumor activity (18, 19). This has prompted questions of whether these agents may ultimately delay the emergence of resistance if used earlier in the disease course. In ALK-positive NSCLC, the therapeutic landscape has also rapidly evolved. Crizotinib and ceritinib are now approved in the U.S., while a third ALK inhibitor, alectinib, has received breakthrough therapy designation status by the FDA. At least 7 other ALK inhibitors are also currently in clinical development (20); thus, the proper sequencing of these agents will be important to establish.

In this retrospective analysis, we evaluated a large cohort of ALK-positive NSCLC patients treated with crizotinib and ceritinib. We find that ceritinib is highly active in patients who have previously received crizotinib. Our analysis also demonstrates that sequential treatment with crizotinib followed by ceritinib results in a median combined PFS of 17.4 months, suggesting an incremental benefit with the addition of ceritinib. Furthermore, this effect was maintained among patients who directly transitioned from crizotinib to ceritinib (median combined PFS 17.0 months), suggesting that these results are unlikely to be due to a “re-challenge” effect (21). Importantly, this retrospective analysis expands upon prior reports of the clinical activity of ceritinib in ALK-positive NSCLC (12) by providing detailed information on prior treatment outcomes with crizotinib, duration of post-progression crizotinib use, and specifics on intervening therapies received by patients between crizotinib discontinuation and initiation of
ceritinib—information that has not been captured to date in prospective trials of next-generation ALK inhibitors, including ceritinib.

This analysis is meant to inform and provide context for ongoing prospective trials of second-generation ALK inhibitors in the crizotinib-naive setting. Outside of isolated reports (22), crizotinib is generally thought to be ineffective in patients previously treated with second-generation ALK inhibitors. Thus, if a second-generation ALK TKI is used in the first-line setting, a reasonable benchmark for efficacy would be for it to surpass the combined PFS of crizotinib followed by ceritinib. Based upon this retrospective analysis, that benchmark would be approximately 17.4 months.

Thus far, data on ceritinib in the ALK TKI-naive setting has been limited. Data from 34 ALK-positive, crizotinib-naive patients were recently reported as part of the phase I study (12). The ORR to ceritinib was 62% with a median PFS of 10.4 months; however, the median duration of follow-up was only 9.5 months. In a recently presented update, the median PFS was 18.4 months among a larger cohort of crizotinib-naive patients (n=83) (23), which appears comparable to the combined PFS of crizotinib followed by ceritinib in this retrospective analysis. A phase II trial of ceritinib in crizotinib-naive, ALK-positive patients (NCT01685138) is currently ongoing, along with a phase III trial of ceritinib versus chemotherapy in untreated, ALK-positive NSCLC (NCT01828099).

In addition to ceritinib, there are also preliminary data on the ALK inhibitor alectinib in the crizotinib-naive setting (24). In a phase I/II trial of alectinib conducted in Japan, the
ORR was 93.5% among 46 ALK-positive, TKI-naive patients receiving the recommended phase II dose (300 mg twice daily). At the time of initial reporting, the median treatment duration was 7.1 months with a median follow-up of 7.6 months. In a subsequent report, the median PFS had still not been reached, but the one-year PFS rate was 83% (25). In contrast to the phase I trial of ceritinib, however, this study involved an entirely non-Western patient population with either stage IIIB/IV NSCLC or recurrent disease, and all patients were required to have ALK rearrangements confirmed by both immunohistochemistry and FISH.

In a subset of patients in this analysis, post-crizotinib/pre-ceritinib biopsies were available for molecular profiling. ALK resistance mutations were identified in 30.4% of patients. Of note, Shaw et al. recently reported no correlation between response to ceritinib and the presence of acquired ALK gene alterations (ALK secondary mutations or ALK amplification) in patients with crizotinib resistance (12); however, no data was provided in this report on the durability of responses to ceritinib in these patients. Here, we expand on these findings and demonstrate that the median PFS on ceritinib for patients with ALK resistance mutations was 5.4 months versus 6.5 months for patients without ALK resistance mutations, but this difference was not statistically significant. It should be noted, however, that all ALK resistance mutations were grouped together in this analysis owing to the low frequency of events and the small sample size of our cohort. This is particularly relevant as preclinical model systems have demonstrated that different ALK secondary mutations have varying degrees of sensitivity to next-generation ALK inhibitors. For example, ceritinib is able to effectively overcome L1196M, G1269A,
I1171T and S1206Y in vitro (11). By contrast, the ALK secondary mutations C1156Y, 1151Tins, G1202R and F1174C all confer resistance to ceritinib in similar in vitro models. One intriguing observation is that our preliminary clinical data, though limited in size, is consistent with these findings. The two patients in our cohort with C1156Y and 1151Tins in post-crizotinib biopsies had relatively short PFS on ceritinib (2.4 and 2.7 months, respectively). Conversely, the one patient in our cohort with an ALK S1206Y mutation, which is highly sensitive to treatment with ceritinib in vitro, experienced a prolonged PFS of 14.8 months on ceritinib. Nonetheless, further studies with larger cohorts of patients examining treatment responses among patients with specific ALK resistance mutations are clearly needed.

Lastly and perhaps most impressive, we find that the median OS for patients with metastatic, ALK-positive lung cancer in this cohort exceeded 4 years from the time of metastatic diagnosis. Of note, OS analyses from ongoing prospective trials of ALK inhibitors are immature. In the phase III PROFILE 1007 trial, however, the median OS of ALK-positive patients was 20.3 months among patients randomized to crizotinib and 22.8 months among patients treated with chemotherapy, but both were measured from the time of initiation of second-line therapy (6). In order to compare these results with our study population, we evaluated the subset of 32 patients who received crizotinib in the second-line setting, observing a median OS of 30.3 months from the time of crizotinib initiation.
It should be noted that our study has several important limitations. First, this was a retrospective analysis without a comparator population. As a result, ALK-positive patients received crizotinib and ceritinib at different time-points throughout their disease course. A subset of patients also received additional therapies between discontinuation of crizotinib and initiation of ceritinib. In order to account for these potential limitations, we focused our analysis on PFS and performed separate analyses on the overall study population and the subset of patients without interval therapies. Another major limitation of this analysis is the possibility of sampling bias. Indeed, a majority of ALK-positive patients in this series were clinical trial participants and/or were referred to specialized centers. Thus, these patients may not be representative of a typical ALK-positive patient population. Lastly and perhaps most importantly, our OS analysis may be biased because our study population included only ALK-positive patients who were able to receive at least two ALK inhibitors. Patients with rapid progression, poor performance status and/or medical co-morbidities precluding additional therapies/clinical trial participation may not have been captured in this analysis. Therefore, additional prospective analyses of ALK-positive patients will be needed to confirm these findings.

In summary, in this large retrospective analysis of ALK-positive NSCLC, we find that ceritinib is associated with significant anti-tumor activity in a crizotinib-resistant patient population. This was observed regardless of whether patients received interval therapies between crizotinib and ceritinib. We anticipate that this study will provide a historical context and benchmark for clinical trials evaluating ceritinib and other next generation ALK inhibitors in the crizotinib-naïve setting. Finally, these insights into the proper
sequencing of targeted therapies in ALK-positive NSCLC may also inform approaches to other subtypes of oncogene-driven lung cancers (e.g., EGFR).

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References
Legends:

**Figure 1.** Progression-free survival (PFS) of anaplastic lymphoma kinase (ALK)-positive patients treated with ALK inhibitors. (A) PFS on crizotinib. The median number of lines of therapy prior to treatment with crizotinib was 1 (range 0-8). (B) PFS on ceritinib. All patients received crizotinib prior to treatment with ceritinib. (C) PFS on ceritinib among patients who had no intervening therapies between discontinuation of crizotinib and initiation of treatment with ceritinib. (D) PFS on ceritinib among patients with or without ALK resistance mutations identified in post-crizotinib/pre-ceritinib biopsies.

**Figure 2.** Individual swimmer plots for each patient in the overall study population, depicting progression-free survival (PFS) on crizotinib (blue), duration of crizotinib use post-progression (red), interval between crizotinib discontinuation and initiation of ceritinib (green), and PFS on ceritinib (purple). Arrows indicate patients who remain on ceritinib at the time of data cut-off. Patients who discontinued crizotinib due to toxicity are depicted with a (#), while patients who discontinued ceritinib due to toxicity are depicted with a (*).

**Figure 3.** Individual ceritinib progression-free survival (PFS) data in patients with post-crizotinib/pre-ceritinib biopsies. ALK-positive patients with ALK resistance mutations are represented in gray, while those without ALK resistance mutations are presented in black. All samples analyzed by ALK FISH (n=19) were positive for the original ALK rearrangement. ALK amp refers to patients with amplification of the ALK fusion gene identified via ALK FISH. NM refers to patients without ALK resistance mutations or ALK...
gene amplification. Arrows indicate patients who remain on ceritinib at the time of data cut-off.

**Figure 4.** Overall survival (OS) for anaplastic lymphoma kinase (ALK)-positive patients. (A) OS from the time of metastatic diagnosis for overall study population. (B) OS of ALK-positive patients treated with second-line crizotinib. OS is measured from the start of crizotinib.
Figure 1

A) Progression-Free Survival Probability (%)

Time (Months)

Progression-Free Survival Probability (%)

Number at risk

B) Progression-Free Survival Probability (%)

Time (Months)

Progression-Free Survival Probability (%)

Number at risk

C) Progression-Free Survival Probability (%)

Progression-Free Survival Probability (%)

Number at risk

D) Progression-Free Survival Probability (%)

Progression-Free Survival Probability (%)

Number at risk
Figure 3
Figure 4

A) Overall Survival

B) ALK (2nd-Line Crizotinib)

Overall Survival

Number at risk

0 20 40 60 80 100 120 140

Survival probability (%)

Time (Months)

Number at risk

0 20 40 60 80 100 120 140

Survival probability (%)

Time (Months)

Overall Survival

Number at risk

32 19 4 1 0

73 59 28 14 3 1 1 0
Table 1. Clinical and Pathologic Features of ALK-Positive Patients at Baseline

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<th>Characteristic</th>
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ALK, anaplastic lymphoma kinase
<sup>a</sup>All patients received crizotinib prior to eventual treatment with ceritinib.
<sup>b</sup>Neuro-imaging was not available in one patient.
Table 2. Molecular Characteristics of Post-Crizotinib Biopsies and Individual Responses to Crizotinib and Ceritinib

<table>
<thead>
<tr>
<th>Patient</th>
<th>Crizotinib PFS (m)</th>
<th>Crizotinib Beyond Progression (m)</th>
<th>ALK Resistance Mutations or Amplification in Crizotinib-Resistant Biopsy</th>
<th>Interval Lines of Therapy</th>
<th>Crizotinib-Ceritinib Interval (m)</th>
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Abbreviations: M, months; NM, no ALK resistance mutation; * Censored
Progression-Free and Overall Survival in ALK-Positive NSCLC Patients Treated with Sequential Crizotinib and Ceritinib

Justin F. Gainor, Daniel S.W. Tan, Tommaso De Pas, et al.

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