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

Justin F. Gainor1, Daniel S.W.Tan2, Tomasso De Pas3, Benjamin J. Solomon4, Aziah Ahmad2, Chiara Lazzarri3, Filippo de Marinis3, Gianluca Spitaleri3, Katherine Schultz1, Luc Friboulet1, Beow Y. Yeap1, Jeffrey A. Engelman1, and Alice T. Shaw1

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.

Experimental 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 vs. 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 antitumor 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.

Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements have emerged as well-established oncogenic drivers and therapeutic targets in non–small cell lung cancer (NSCLC; ref. 1). Found in 3% to 5% of NSCLC patients, ALK rearrangements define a distinct molecular subset of the disease with characteristic clinicopathologic features (2). Importantly, ALK-positive NSCLCs are oncogene-addicted because of 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 (ORR; 60%) and a median progression-free survival (PFS) of 8 to 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 with 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 upregulation 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 antitumor 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 (mPFS) of 7.0 months. Importantly, among patients previously treated with crizotinib (n = 80), the ORR was similar at 56% with an mPFS of 6.9 months.

The FDA recently granted accelerated approval of ceritinib for the treatment of ALK-positive NSCLC patients who experience
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.

### 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.

### 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 and 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 ceritinib–ceritinib interval. Finally, 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 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.). These analyses were performed under IRB-approved protocols.

### Statistical analysis

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

### 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 before 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 mPFS on crizotinib was 8.2 months [95% confidence interval (CI), 7.4–10.6 months; Fig. 1A]. Two patients permanently discontinued crizotinib due to toxicity (transaminase elevation and development of renal cysts). The remainder discontinued because of 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 S1.
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 mPFS was 7.8 months (95% CI, 6.5–9.1 months; Fig. 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 before treatment with ceritinib (median interval 20 days, range 1–84 days). Among this subset (n = 53), the mPFS on ceritinib was 7.8 months (95% CI, 5.4–9.8 months; Fig. 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 Fig. 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 mutations.
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 of 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 Supplementary Fig. S1.

We first compared treatment outcomes with crizotinib among patients with and without ALK resistance mutations identified in post-crizotinib/pre-ceritinib biopsies. The mPFS 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 mPFS 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 =

![Figure 2.](image)

Individual swimmer plots for each patient in the overall study population, depicting 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 cutoff. Patients who discontinued crizotinib due to toxicity are depicted with a #, whereas patients who discontinued ceritinib due to toxicity are depicted with a †.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Crizotinib PFS (mo)</th>
<th>Crizotinib beyond progression (mo)</th>
<th>ALK resistance mutations or amplification in crizotinib-resistant biopsy</th>
<th>Interval lines of therapy</th>
<th>Crizotinib-ceritinib interval (mo)</th>
<th>Ceritinib PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.2</td>
<td>0.4</td>
<td>C1156Y</td>
<td>0</td>
<td>0.3</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>4.6</td>
<td>1.6</td>
<td>ALK amplification</td>
<td>0</td>
<td>0.8</td>
<td>4.3</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>3.4</td>
<td>L1196M</td>
<td>0</td>
<td>0.7</td>
<td>3.9</td>
</tr>
<tr>
<td>4</td>
<td>11.2</td>
<td>0.8</td>
<td>NM</td>
<td>2</td>
<td>4.4</td>
<td>8.2</td>
</tr>
<tr>
<td>5</td>
<td>32.0</td>
<td>3.3</td>
<td>S1206Y</td>
<td>0</td>
<td>0.8</td>
<td>14.8</td>
</tr>
<tr>
<td>6</td>
<td>6.1</td>
<td>5.4</td>
<td>NM</td>
<td>0</td>
<td>0.5</td>
<td>9.7</td>
</tr>
<tr>
<td>7</td>
<td>18.5</td>
<td>9.2</td>
<td>L1196M</td>
<td>0</td>
<td>0.3</td>
<td>16.2†</td>
</tr>
<tr>
<td>8</td>
<td>8.1</td>
<td>5.2</td>
<td>NM</td>
<td>1</td>
<td>11.0</td>
<td>10.8</td>
</tr>
<tr>
<td>9</td>
<td>6.9</td>
<td>2.1</td>
<td>NM</td>
<td>2</td>
<td>10.2</td>
<td>11.3</td>
</tr>
<tr>
<td>10</td>
<td>9.8</td>
<td>0.0</td>
<td>NM</td>
<td>0</td>
<td>2.0</td>
<td>18.0</td>
</tr>
<tr>
<td>11</td>
<td>14.5</td>
<td>0.0</td>
<td>L1196M</td>
<td>0</td>
<td>0.6</td>
<td>5.4</td>
</tr>
<tr>
<td>12</td>
<td>7.4</td>
<td>1.0</td>
<td>ALK amplification</td>
<td>0</td>
<td>0.9</td>
<td>9.5</td>
</tr>
<tr>
<td>13</td>
<td>13.5</td>
<td>0.1</td>
<td>NM</td>
<td>0</td>
<td>1.6</td>
<td>5.2</td>
</tr>
<tr>
<td>14</td>
<td>3.1</td>
<td>2.5</td>
<td>NM</td>
<td>0</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>2.6</td>
<td>0.2</td>
<td>NM</td>
<td>0</td>
<td>0.5</td>
<td>6.5</td>
</tr>
<tr>
<td>16</td>
<td>8.1</td>
<td>0.0</td>
<td>NM</td>
<td>1</td>
<td>15.7</td>
<td>2.7</td>
</tr>
<tr>
<td>17</td>
<td>10.8</td>
<td>2.0</td>
<td>G1269A, 1151Tins</td>
<td>1</td>
<td>3.6</td>
<td>2.7</td>
</tr>
<tr>
<td>18</td>
<td>7.1</td>
<td>1.5</td>
<td>NM</td>
<td>0</td>
<td>0.3</td>
<td>2.9</td>
</tr>
<tr>
<td>19</td>
<td>2.8</td>
<td>1.4</td>
<td>NM</td>
<td>1</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>20</td>
<td>5.6</td>
<td>1.5</td>
<td>NM</td>
<td>0</td>
<td>0.3</td>
<td>4.0</td>
</tr>
<tr>
<td>21</td>
<td>20.6</td>
<td>0.0</td>
<td>NM</td>
<td>3</td>
<td>23.1</td>
<td>8.2</td>
</tr>
<tr>
<td>22</td>
<td>20.4</td>
<td>7.4</td>
<td>NM</td>
<td>0</td>
<td>0.5</td>
<td>16.8</td>
</tr>
<tr>
<td>23</td>
<td>11.5</td>
<td>1.0</td>
<td>L1196M</td>
<td>0</td>
<td>0.8</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Table 2. Molecular characteristics of post-crizotinib biopsies and individual responses to crizotinib and ceritinib

Abbreviation: NM, no ALK resistance mutation.

*Censored.
0.171). We next compared the PFS on ceritinib among patients with and without ALK resistance mutations in post-crizotinib/pre-ceritinib biopsies (Fig. 1D). Among patients with ALK resistance mutations (n = 7), the mPFS on ceritinib was 5.4 months (95% CI, 2.7–10.8), whereas the mPFS 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 Fig. 3.

Overall survival analysis
Finally, we examined OS among ALK-positive patients treated with sequential crizotinib and ceritinib. With a median follow-up of 33.2 months, the median OS from the date of metastatic NSCLC diagnosis was 49.4 months (95% CI, 35.5–63.1 months; Fig. 4A). Among 25 ALK-positive patients with brain metastases identified before initiation of crizotinib, the median OS was 42.2 months (95% CI, 26.4–51.2; Supplementary Fig. S2).

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; Fig. 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 with imatinib; however, these agents have yet to demonstrate improvements in long-term outcomes, such as OS (16, 17).

In lung cancer, similar questions have emerged. In patients with EGFR mutations, several third-generation, T790M mutant–specific EGFR inhibitors have been developed and have recently demonstrated promising antitumor 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 United States, whereas a third ALK inhibitor, alectinib, has received breakthrough therapy designation status by the FDA. At least seven 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 “rechallenge” 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 ceritinib 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), ceritinib 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 have 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 an mPFS of 10.4 months; however, the median duration of follow-up was only 9.5 months. In a recently presented update, the mPFS was 18.4 months among a larger cohort of crizotinib-naive patients (n = 83; ref. 23), which appears comparable with 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 mPFS had still not been reached, but the 1-year PFS rate was 83% (25). In contrast with 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 and colleagues (12) 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; however, no data were provided in this report on the durability of responses to ceritinib in these patients. Here, we expand on these findings and demonstrate that the mPFS on ceritinib for patients with ALK resistance mutations was 5.4 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,
In summary, in this large retrospective analysis of ALK-positive NSCLC, we find that ceritinib is associated with significant anti-tumor activity in a ceritinib-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 ceritinib-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).

Disclosure of Potential Conflicts of Interest
J.F. Gainor is a consultant/advisory board member for Boehringer Ingelheim, Jounce Therapeutics, and Kyowa Hakko Kirin. D.S.W. Tan is a consultant/advisory board member for Novartis and Pfizer. B.J. Solomon is a consultant/advisory board member for Novartis, Pfizer, and Roche-Genentech. J.A. Engelman is a consultant/advisory board member for Genentech, Novartis, and Roche, and reports receiving commercial research support from AstraZeneca and Novartis. A.T. Shaw is a consultant/advisory board member for Ariad, Chugai, Daiichi-sankyo, Genentech, Ipsiva, Novartis, Pfizer, and Roche. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Conception and design: J.F. Gainor, T. De Pas, G. Spitaleri, J.A. Engelman, A.T. Shaw
Development of methodology: J.F. Gainor, A.T. Shaw
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.F. Gainor, D.S.W. Tan, T. De Pas, B.J. Solomon, A. Ahmad, C. Lazzari, F. de Marinis, L. Friboulet, B.Y. Yeap, A.T. Shaw
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.F. Gainor, T. De Pas, B.J. Solomon, L. Friboulet, B.Y. Yeap, A.T. Shaw
Writing, review, and/or revision of the manuscript: J.F. Gainor, D.S.W. Tan, T. De Pas, B.J. Solomon, C. Lazzari, F. de Marinis, G. Spitaleri, K. Schultz, B.Y. Yeap, J.A. Engelman, A.T. Shaw
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.F. Gainor, D.S.W. Tan, K. Schultz, B.Y. Yeap
Study supervision: G. Spitaleri, J.A. Engelman, A.T. Shaw

Acknowledgments
The authors thank “Be a Piece of the Solution” for support of lung cancer research.

Grant Support
This work was supported by grants from the U.S. National Institutes of Health SR01CA164273, S5POCA09578-10, and C06CA059267.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 19, 2014; revised January 6, 2015; accepted February 8, 2015; published OnlineFirst February 27, 2015.
Gainor et al.

III study (PROFILE 1014). J Clin Oncol 32:5s, 2014 (suppl; abstr 8002).


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

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


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-14-3009

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2015/02/28/1078-0432.CCR-14-3009.DC1

Cited articles
This article cites 24 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/21/12/2745.full.html#ref-list-1

Citing articles
This article has been cited by 10 HighWire-hosted articles. Access the articles at:
/content/21/12/2745.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.