Treatment of ALK-Positive Non–Small Cell Lung Cancer

Yung-Jue Bang, MD

- Crizotinib (Xalkori), the first inhibitor of both anaplastic lymphoma kinase (ALK) and c-Met receptor kinases, has been approved in the United States, Korea, and other countries for the treatment of ALK-positive non–small cell lung cancer (NSCLC). This approval came within just 4 years of the discovery of rearrangements in the ALK gene in a subset of patients with NSCLC. Oral crizotinib 250 mg twice daily showed excellent efficacy in patients with advanced ALK-positive NSCLC, with objective response rates of 61% and 51% in ongoing phase I and II studies, respectively. Objective response rates of current standard, single-agent, second-line therapies are less than 10%. Median progression-free survival was 10 months (95% confidence interval, 8.2–14.7) in the phase I study; progression-free survival with current therapies is less than 3 months. Crizotinib was well tolerated; grade II treatment of advanced

- Several methods are available to detect ALK rearrangements, including break-apart fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription-polymerase chain reaction (RT-PCR). Break-apart FISH involves labeling the areas that flank the ALK gene with red and green fluorescent probes. Under normal circumstances the probes are close together, sometimes emitting a yellow signal. In the presence of an ALK rearrangement, where the gene is split, the red and green signals “break apart” (ie, are separated). The assay is considered positive for ALK rearrangement if greater than 15% of tumor cells have split green and red signals. Break-apart FISH detects ALK rearrangement irrespective of the ALK fusion partner and is currently the gold standard approved by the US Food and Drug Administration (FDA); however, this assay may not be widely available in clinics.

- Clinical diagnosis of ALK-rearranged NSCLC

Several methods are available to detect ALK rearrangements, including break-apart fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription-polymerase chain reaction (RT-PCR).

Break-apart FISH involves labeling the areas that flank the ALK gene with red and green fluorescent probes. Under normal circumstances the probes are close together, sometimes emitting a yellow signal. In the presence of an ALK rearrangement, where the gene is split, the red and green signals “break apart” (ie, are separated). The assay is considered positive for ALK rearrangement if greater than 15% of tumor cells have split green and red signals. Break-apart FISH detects ALK rearrangement irrespective of the ALK fusion partner and is currently accepted by the US Food and Drug Administration (FDA); however, this assay may not be widely available in clinics.

Immunohistochemistry is a cost-effective and efficient technique that is readily available in clinical pathology laboratories. Antibodies labeled with markers are used to localize specific antigens in tissue samples. However, owing to low levels of ALK protein expression, greater than 30% of ALK-rearranged NSCLCs are not identified by currently commercially available IHC assays. Recently, a novel molecularly targeted agents for specific cancer subtypes in patients, such as non–small cell lung cancer (NSCLC). Non–small cell lung cancer accounts for approximately 80% of lung cancer cases and is often diagnosed at advanced stages. Numerous oncogenes have now been identified in NSCLC, including mutations in the genes coding for epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), phosphoinositide-3–kinase catalytic, α polypeptide (PIK3CA), and human epidermal growth factor receptor 2 (HER2/neu). More recently, in 2007 a translocation in the gene encoding the receptor tyrosine kinase anaplastic lymphoma kinase (ALK), leading to the expression of ALK fusion proteins, was identified as an oncogenic driver in a subset of patients with NSCLC. ALK rearrangements are found in approximately 3% of unselected patients with NSCLC. ALK-positive NSCLC has been associated with a younger patient population than that associated with EGFR mutations and that associated with wild-type ALK and EGFR. ALK-positive patients are also generally never-smokers or are light smokers, and predominantly have adenocarcinoma. Data indicating the prognosis of patients with ALK-positive NSCLC compared to ALK-negative NSCLC are inconclusive. As ALK tyrosine kinase is required for oncogenesis, inhibition by a tyrosine kinase inhibitor should provide therapeutic efficacy.

The treatment of cancer is becoming more personalized, moving away from histology-driven empirical treatments toward targeting specific oncogenic drivers. This approach has led to the emergence of a number of new

Accepted for publication May 14, 2012.

From the Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.

Dr Bang is a consultant/advisor to Pfizer and has received honoraria and research funding from Pfizer. Medical writing assistance was provided by Martin Quinn at ACUMED (Tytherington, United Kingdom) with funding from Pfizer.

Presented at the Houston Lung Symposium; April 28–29, 2012; Houston, Texas.

Reprints: Yung-Jue Bang, MD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110–744, Republic of Korea (e-mail: bangyj@snu.ac.kr).
CRIZOTINIB, AN ORAL ALK RECEPTOR KINASE INHIBITOR

Crizotinib (PF-2341066; Xalkori, Pfizer, New York, NY) is an oral, small-molecule inhibitor of ALK and c-Met receptor kinases.11 It is highly selective for ALK and c-Met kinases at nanomolar concentrations, exhibiting selectivity at least 20-fold higher than other kinases.11,12 Crizotinib has been shown to potently inhibit cell proliferation and induce apoptosis in ALK-positive cells in vitro, and has demonstrated dose-dependent antitumor efficacy in tumor xenografts, with complete tumor regression at 100 mg/kg/d given orally.11

The first in-man study of crizotinib began in 2006 in patients with measurable advanced solid tumors whose disease was refractory to standard therapy (A8081005; Clinicaltrials.gov identifier NCT00585195). This dose-escalation study identified crizotinib 250 mg twice daily given on a continuous schedule (28-day cycle) as the maximum tolerated dose, owing to dose-limiting fatigue in the 300-mg bid cohort.5

Table 1. Patient Baseline Characteristics in Phase I (Expanded Cohort) and Phase II Studies of Crizotinib in Non–Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase I* (N = 119)</th>
<th>Phase II† (N = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>51 (21–79)</td>
<td>52 (29–82)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59 (50)</td>
<td>64 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>60 (50)</td>
<td>72 (53)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>74 (62)</td>
<td>86 (53)</td>
</tr>
<tr>
<td>Asian</td>
<td>34 (29)</td>
<td>43 (32)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (9)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker</td>
<td>86 (72)</td>
<td>92 (68)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>32 (27)</td>
<td>39 (29)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (1)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (13)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>36 (30)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>2</td>
<td>24 (20)</td>
<td>39 (29)</td>
</tr>
<tr>
<td>3</td>
<td>17 (14)</td>
<td>42 (31)</td>
</tr>
<tr>
<td>≥4</td>
<td>26 (22)</td>
<td>25 (18)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

monoclonal antibody with increased sensitivity for ALK was used to develop an IHC assay that accurately identifies ALK-rearranged lung adenocarcinoma with high reproducibility, sensitivity, and specificity.8 A 2-step algorithm was proposed: screening by IHC followed by confirmation by FISH.9

RT-PCR is well suited for clinical high-throughput assessments and uses reverse transcriptase to convert an RNA sequence to complementary DNA, which is amplified using PCR. However, as this technique requires predefined primers against known fusion genes, previously unrecognized ALK fusion partners may not be detected.10 RT-PCR is optimally executed with fresh frozen tumor specimens, which are not always available in routine practice.

CLINICAL EFFICACY OF CRIZOTINIB IN NSCLC

Preliminary data indicate that similar tumor responses were achieved with crizotinib in both the expanded cohort in the phase I study and the phase II study.14,15 Tumor shrinkage was observed in most patients, with an objective response rate (ORR) of 61% (71 of 116) and 51% (68 of 133) in the phase I and II studies, respectively (Table 2).14–16 Responses were rapid (median, 8 weeks to response) and prolonged (median response duration estimate was 48 weeks in phase I). Median progression-free survival (PFS) was 10.0 months (95% confidence interval [CI], 8.2–14.7) in the phase I expanded cohort14 and has yet to be reached in the phase II study. Standard, second-line, single-agent treatments for unselected patients with advanced NSCLC are associated with an ORR of less than 10% and PFS of less than 3 months.17,18

In the phase I study, best tumor response did not correlate with the percentage of ALK-positive tumor cells identified...
by FISH ($P = .31$) in patients receiving crizotinib. Camidge et al.\textsuperscript{19} concluded that ALK positivity was not correlated to response. Analysis of early data from the phase I study ($N = 82$) by baseline characteristic revealed that the ORR to crizotinib differed between Asian and non-Asian patients, with Asian patients achieving a higher ORR (22 of 29; 76%; 95% CI, 57–90) than their non-Asian counterparts (25 of 53; 47%; 95% CI, 33–61).\textsuperscript{20} Higher ORR was also observed among Asian patients in the phase I and II studies than among non-Asian patients.\textsuperscript{14,21} Reasons underlying the difference in ORR between Asian and non-Asian patients are currently under investigation and may be related to different pharmacokinetic profiles of crizotinib in these patients.\textsuperscript{20} Median predose concentrations of crizotinib measured at a single point during each of 5 cycles of treatment were higher in a subgroup of Asian patients (Japanese and Korean; $n = 29$) in the phase I study than in a subgroup of non-Asian patients ($n = 63$) with ALK-positive NSCLC.\textsuperscript{20} Steady-state area under the plasma concentration–time curve ($AUC_{\text{ss}}$) for crizotinib was 65% higher in Asian than non-Asian patients.\textsuperscript{20} Body weight and body surface area can at least partially explain the differences in the pharmacokinetics of crizotinib, as Asian patients tended to have a lower body weight and body surface area than non-Asian patients. When adjusted for body weight, $AUC_{\text{ss}}$ for crizotinib for Asian patients was reduced from 65% higher to 26% higher than in non-Asian patients, and was 46% higher when adjusted for body surface area.\textsuperscript{20}

In the absence of data from a randomized controlled trial, Shaw et al.\textsuperscript{22} retrospectively compared the survival outcomes of crizotinib-treated patients and crizotinib-naïve controls screened during the same time period to determine whether crizotinib impacts the overall survival (OS) of patients with ALK-positive NSCLC. Patients with advanced NSCLC from 3 patient cohorts were included: 82 ALK-positive patients treated with crizotinib from the expansion cohort of a phase I trial of crizotinib, 36 ALK-positive controls who did not receive crizotinib, and 253 ALK-negative/EGFR-negative patients.\textsuperscript{22} Among the ALK-positive patients treated with crizotinib, median OS from initiation of crizotinib had not been reached, and OS did not differ with age, sex, smoking history, or ethnic origin.\textsuperscript{22} Overall survival in the ALK-positive crizotinib-naïve controls was similar to the entire cohort; however, OS was significantly improved in patients receiving crizotinib as second- or third-line therapy, compared with crizotinib-naïve patients receiving any second-line therapy.

**CLINICAL SAFETY AND PATIENT-REPORTED OUTCOMES FOR CRIZOTINIB IN NSCLC**

Preliminary data indicate that most treatment-related adverse events (AEs) in the phase I expanded cohort ($N = 119$) and the phase II study ($N = 136$) were mild (grade 1/2).\textsuperscript{14,15} The most common treatment-related AEs in phase I and II trials were gastrointestinal toxicities including nausea (49% and 57%, respectively), diarrhea (43% and 43%, respectively), and vomiting (35% and 43%, respectively), as well as visual disturbances (62% and 59%, respectively), all grade 1/2.\textsuperscript{14,15} Visual disturbances characteristic of crizotinib have been described as “trails” of light in the peripheral vision when adapting from dark to light.\textsuperscript{14} In the phase II PROFILE 1005 study, these visual events were common, generally transient, lasting up to 60 seconds, were not bothersome to the patient, having minimal or no effect on their activities of daily living, and did not require crizotinib dose adjustment.\textsuperscript{23}

As would be expected, owing to data suggesting increased crizotinib exposure in Asian patients, an analysis of the first 82 patients enrolled in the phase I expanded cohort demonstrated a higher frequency of AEs in Asian than non-Asian patients, particularly the most common AEs (gastrointestinal and visual disturbances).\textsuperscript{20} Interestingly, the incidence of grade 3/4 AEs was higher in non-Asian patients, and no cases of elevated liver enzyme levels (any grade) were reported in Asian patients.

Patient-reported outcomes of disease- and treatment-related symptoms, quality of life (QoL), and health status are being assessed in the phase II PROFILE 1005 study.\textsuperscript{24} Preliminary data for symptom scores and QoL from the first 136 patients for whom efficacy and safety data are available have been presented.\textsuperscript{24} Data were collected on days 1 and 21 of each cycle with 2 validated European Organisation for Research and Treatment of Cancer questionnaires, C30 and LC13. Patients receiving crizotinib showed clinically meaningful (≥10-point change) and statistical ($P < .05$) improvements in some symptoms from baseline. There were clinically meaningful improvements in pain, dyspnea, and cough from as early as cycle 2, and for fatigue from cycle 5, and these improvements were maintained throughout subsequent cycles.\textsuperscript{25} Furthermore, global QoL was maintained throughout treatment with crizotinib, with clinically meaningful improvement at cycle 7.\textsuperscript{25} Clinically significant reductions in pain (pain, pain in arm or shoulder, pain in other parts, and pain in chest),\textsuperscript{24} cough fatigue, insomnia, and alopecia symptom scales were maintained with therapy.\textsuperscript{25} Improvement in mean QoL was also reported but changes were not clinically significant, indicating that QoL was maintained with treatment.\textsuperscript{24}

**FURTHER CLINICAL DEVELOPMENT OF CRIZOTINIB**

In addition to the ongoing phase I and II studies, 2 phase III studies investigating crizotinib for the treatment of ALK-positive NSCLC are ongoing. PROFILE 1007 (Clinicaltrials.gov identifier NCT00932893), a randomized, open-label study comparing second-line crizotinib with standard-of-care chemotherapy (pemetrexed or docetaxel), began in 2009. This study plans to enroll 318 patients for whom 1 prior platinum-based chemotherapy regimen has failed and, with enrollment completed, data for the primary endpoint (PFS) are expected in 2012. PROFILE 1014 (Clinicaltrials.gov identifier NCT01154140) is a randomized, open-label study investigating crizotinib for the first-line treatment of ALK-positive nonsquamous NSCLC compared with standard-care chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin). The study began in early 2011, plans to enroll 334 patients, and data for the primary endpoint (PFS) are expected at the end of 2013.

Tumors become resistant when they reactivate downstream signaling despite the presence of an inhibitor. As with other targeted agents such as EGFR kinase inhibitors, acquired resistance to crizotinib is expected, as point mutations in the kinase domain in response to ALK inhibition can confer resistance.\textsuperscript{26} Acquired resistant mutations have been identified in vitro\textsuperscript{26,27} and in patients.\textsuperscript{27,28} One mechanism of resistance is mutation in the ALK gatekeeper region (L1196M), in a similar way to that seen
with EGFR resistance mutations, possibly by interfering allosterically with the binding of tyrosine kinase inhibitors. Coactivation of EGFR signaling has also been shown to contribute to ALK inhibitor resistance, and concurrent inhibition of both ALK and EGFR was effective in this model. Katayama and colleagues reported findings from a series of patients with lung cancer (n = 18) with acquired resistance to crizotinib. They found resistance to be attributed to the secondary point mutations in the ALK tyrosine kinase inhibitor domain, ALK gene amplification, and aberrant activation of other kinases including amplification of KIT and increased autophosphorylation of EGFR. There was also evidence of multiple resistance mechanisms developing simultaneously in patients.

Research into the mechanisms underlying resistance to crizotinib continues, as this knowledge may help in overcoming crizotinib resistance by informing the development of rational treatment combination strategies, and informing the development of effective subsequent clinical therapies.

CONCLUSIONS

Crizotinib (Xalkori) has been approved by the FDA for the treatment of advanced ALK-positive NSCLC, because of the response rates achieved in patients in the phase I expanded cohort and the preliminary data from the phase II PROFILE 1005 study. Crizotinib has also been approved for the treatment of advanced ALK-positive NSCLC in Korea, Switzerland, and Japan, and applications have been filed with the European Medicines Agency. Further data from the ongoing phase II and III PROFILE studies are eagerly awaited.

As the first new drug in 6 years licensed in the United States for treatment of lung cancer, crizotinib represents a new standard of care for patients with ALK-positive NSCLC. Indeed, the National Comprehensive Cancer Network (NCCN) guidelines have already been updated to recommend crizotinib as first-line therapy for patients with advanced ALK-positive NSCLC. Crizotinib also provides an excellent example of what can be achieved through collaboration among academic research, pharmaceutical, and regulatory organizations, with only 4 years elapsing between the discovery of ALK rearrangement and the initial approval of crizotinib.

The approval of crizotinib for the treatment of a subset of patients with ALK-positive NSCLC underscores the important role of molecular biomarkers in the treatment of cancer, emphasizing the vital role of the pathologist. As a result of the approval of crizotinib, testing for EGFR mutations and ALK rearrangements should become a routine part of initial workup for newly diagnosed patients with advanced NSCLC to ensure they achieve the optimal benefit from treatment via a personalized approach. Indeed, the NCCN recommends EGFR and ALK testing in patients with NSCLC (except those with squamous histology) so that they can receive effective targeted treatment. Research into oncogenic drivers in NSCLC continues.

References