

U.S. Food and Drug Administration Approval: Crizotinib for Treatment of Advanced or Metastatic Non–Small Cell Lung Cancer That Is Anaplastic Lymphoma Kinase Positive

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Abstract

On August 26, 2011, the U.S. Food and Drug Administration (FDA) approved crizotinib (XALKORI Capsules, Pfizer Inc.) for treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive as detected by an FDA-approved test. The Vysis ALK Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) was approved concurrently. In two multicenter, single-arm trials, patients with locally advanced or metastatic ALK-positive NSCLC previously treated with one or more systemic therapies received crizotinib orally at a dose of 250 mg twice daily. In 119 patients with ALK-positive NSCLC by local trial assay, the objective response rate (ORR) was 61% [95% confidence intervals (CI), 52%–70%] with a median response duration of 48 weeks. In 136 patients with ALK-positive NSCLC by the to-be-marketed test, the ORR was 50% (95% CI, 42%–59%) with a median response duration of 42 weeks. The most common adverse reactions ($\geq 25\%$) were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Accelerated approval was granted on the basis of the high ORRs and durable responses. On November 20, 2013, crizotinib received full approval based on an improvement in progression-free survival in patients with metastatic ALK-positive NSCLC previously treated with one platinum-based chemotherapy regimen. *Clin Cancer Res*; 20(8); 2029–34. ©2014 AACR.

Introduction

Until recently, first-line treatment for advanced non–small cell lung cancer (NSCLC) was platinum-based doublet chemotherapy. The discovery of molecular targets has enabled the development of new and potentially more effective treatments for this disease. Although previously approved targeted agents bevacizumab and erlotinib did not require demonstration of specific molecular abnormalities in tumor tissue of patients with NSCLC, EGF receptor (EGFR) tyrosine kinase inhibitors were reported to have

high response rates and improved progression-free survival in patients with specific *EGFR* mutations (1, 2).

Anaplastic lymphoma kinase (ALK), also known as ALK tyrosine kinase receptor or CD246 (cluster of differentiation 246), is an enzyme that in humans is encoded by the *ALK* gene and that plays an important role in brain development. The oncogenic potential of the *ALK* gene can be generated by chromosomal rearrangement resulting in the formation of fusion products with any of several other genes and by DNA mutations within the gene itself. An inversion within chromosome 2p resulting in the formation of a fusion gene product consisting of parts of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the *ALK* gene was discovered in NSCLC cell lines and archived clinical specimens (3). This *EML4*–*ALK* fusion gene results in the expression of a cytoplasmic chimeric protein with constitutive kinase activity and is a key driver of oncogenesis in a subset of patients with NSCLC. A number of variants of the *EML4*–*ALK* fusion gene have also been reported along with rarer fusion partners for *ALK* (4, 5).

In unselected populations of patients with NSCLC, the frequency of *EML4*–*ALK* ranges from 1.5% to 6.7% (6–10); however, in a small series of never/light smokers, the frequency was significantly higher (6). The majority of *ALK* gene rearrangements occur in younger patients with adenocarcinoma histology and with a never or light smoking history (7–12).

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The U.S. Food and Drug Administration (FDA) summary of the marketing applications for crizotinib and a companion diagnostic is provided below.

Chemistry

Crizotinib is described chemically as (*R*)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1*H*-pyrazol-4-yl]pyridin-2-amine. The commercial crizotinib drug product is a hard gelatin capsule formulation in two strengths (200 and 250 mg).

Nonclinical pharmacology and toxicology

Crizotinib is an inhibitor of receptor tyrosine kinases, including ALK and hepatocyte growth factor receptor (HGFR; c-Met), and their oncogenic variants (i.e., ALK fusion proteins or c-Met/HGFR-mutant variants). Crizotinib also inhibits Recepteur d'Origine Nantais (RON) and ROS1. Crizotinib demonstrated concentration-dependent inhibition of ALK and c-Met phosphorylation in cell-based assays using tumor cell lines. In various xenograft models using human-derived tumors or tumor cell lines, crizotinib inhibited tumor growth, decreased proliferation, increased apoptosis, and caused dose-dependent inhibition of c-Met/HGFR, NPM-ALK, and EML4-ALK phosphorylation.

Repeat-dose toxicology studies in both rats and dogs demonstrated toxicity to the liver, gastrointestinal tract, mesenteric lymph nodes, bone marrow, and heart. Cardiotoxicity observed in dogs included decreases in heart rate and contractility, increases in left ventricular end diastolic pressure, and increases in the PR, QRS, and QT/QTc intervals. Decreased bone formation in growing long bones was observed in immature rats administered crizotinib daily for 28 days.

Crizotinib was genotoxic in both *in vitro* and *in vivo* assays. The genotoxic activity was clastogenic rather than mutagenic. Carcinogenicity studies were neither conducted nor required for approval in this patient population. Results of embryo-fetal development studies in the rat showed that crizotinib was embryotoxic and fetotoxic at exposures similar to and above those observed in humans at the recommended clinical dose.

Clinical pharmacology

Following single-dose oral administration, crizotinib was absorbed with median time to peak concentration of 4 to 6 hours and a mean apparent plasma terminal half-life of 42 hours. The mean absolute bioavailability was 43%. Following administration of crizotinib 250 mg twice daily (b.i.d), steady state was reached within 15 days, with an accumulation ratio of 4.8.

Crizotinib can be administered with or without food, as a high-fat meal reduced crizotinib AUC_{inf} and C_{max} by only 14%. A mass balance trial with a single 250 mg dose of [¹⁴C] crizotinib suggested that the mean recovery of administered dose was 85%, with 63% (53% unchanged) in feces and 22% (1.3% unchanged) in urine. Crizotinib is predominantly metabolized by CYP3A4/5, and hepatic impairment might increase the area under the curve (AUC). However, no

patients with hepatic impairment or severe renal impairment were studied. Mild and moderate renal impairment had no clinically relevant effect on crizotinib exposure.

Coadministration of ketoconazole b.i.d, a strong CYP3A inhibitor, with a single 150 mg crizotinib dose, increased the mean AUC by approximately 3.2-fold compared with crizotinib alone. Rifampin, a strong CYP3A inducer, decreased the AUC of a single dose of crizotinib by 82%. Because crizotinib also caused time-dependent inhibition of CYP3A4, the magnitude of the interaction by CYP3A inhibitors or inducers on steady-state crizotinib exposure is unknown.

Crizotinib inhibits CYP3A reversibly and in a time-dependent manner. Administration of 250 mg crizotinib b.i.d for 28 days increased the oral midazolam AUC by 3.7-fold, suggesting that crizotinib is a moderate inhibitor of CYP3A.

Because increasing pH reduces crizotinib solubility, absorption could potentially be reduced by drugs that elevate gastric pH (e.g., proton pump inhibitors, H2 blockers, or antacids).

QT interval prolongation was observed in some patients treated with crizotinib. A pharmacokinetic-pharmacodynamic analysis indicated that the increases in QT may be concentration dependent.

Clinical trials

Study 1001 was a multicenter, single-arm phase I trial of crizotinib in any tumor type except leukemia (13, 14). Stable disease noted in two patients with ALK-positive NSCLC during the dose-escalation phase led to an amendment providing an expansion cohort of patients with ALK-positive NSCLC who received the recommended phase II regimen of 250 mg orally b.i.d. Testing of tumor tissue for ALK gene rearrangement was performed by local laboratories.

Study 1005 was a multicenter, single-arm phase II trial of crizotinib 250 mg administered orally b.i.d in patients with advanced NSCLC after tumor progression on at least one line of chemotherapy (15). The diagnostic test used to detect ALK fusion events was performed by central laboratories using the to-be-marketed Vysis ALK Break-Apart FISH assay.

In both trials, the primary efficacy endpoint was objective response rate (ORR) based on investigator assessment (INV) with imaging assessments at baseline and every other cycle. Responses were also evaluated by an Independent Radiologic Committee (IRC). Safety evaluations included periodic physical examinations, laboratory evaluations, and electrocardiograms.

Efficacy results

Demographic and disease characteristics were similar in the two studies. The proportion of males and females was equal and the median age was 51 years. Sixty-three percent were White, 30% were Asian, 98% were nonsmokers or ex-smokers, 95% had adenocarcinoma, and the majority had an Eastern Cooperative Oncology Group performance status of 0 to 1. Most patients had received two or more regimens and multiple approved agents.

Table 1. Efficacy data

Primary endpoint	Study 1001		Study 1005	
	INV N = 116	IRC N = 105	INV N = 135	IRC N = 105
Response rate ^a (95% CI)	71 (61.2%; 52%–70%)	55 (52.4%; 42%–62%)	68 (50.0%; 42%–59%)	44 (41.9%; 32%–52%)
Complete response	2	0	1	1
Partial response	69	55	67	43
Duration of response (partial response) Median (range) ^b	48.1 wks (4.1+ to 76.6+)	58.1 wks (7.3+ to 76.6+)	41.9 wks (6.1+ to 42.1+)	33.1 wks (6.1+ to 42.1+)

^aRECIST v1.0 in Study 1001 and v1.1 in Study 1005.

^bThe Kaplan–Meier method with censored values (+).

Efficacy results at the time of data cutoff are shown in Table 1. One hundred sixteen of 119 patients with ALK-positive advanced NSCLC from Study 1001 were evaluable. The median duration of treatment was 32 weeks. The ORR by INV was 61% [95% confidence intervals (CI), 52%–70%] with two complete and 69 partial responses. The ORR by IRC was 52% (95% CI, 42%–62%). Fifty-five percent of objective responses were achieved during the first 8 weeks of treatment. The median response duration was 48.1 weeks.

One hundred thirty-five of 136 patients with ALK-positive advanced NSCLC from Study 1005 were evaluable. The median duration of treatment was 22 weeks. The ORR by INV was 50% (95% CI, 42%–59%) with 1 complete and 67 partial responses. The ORR by IRC was 42% (95% CI, 32%–52%). Seventy-nine percent of objective tumor responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks.

In subgroup analyses, there were no clear differences in ORR by performance status, sex, age, or number of prior chemotherapeutic regimens. There was, however, a difference in response by race, with Asian patients having a higher ORR.

Exposure–response relationship

An exploratory exposure–response analysis was conducted in both trials, and ORR was found to increase with increasing exposure. In Study 1001, an ORR of 24% was observed in patients in the lowest steady state trough concentration quartile compared with an ORR >70% in patients in the higher quartiles. In trial 1005, there was a less steep exposure–response relationship and even patients in the lowest quartile had an ORR of 47%. Asians had higher systemic exposures compared with non-Asians which may be explained, in part, by their lower body weight.

In vitro diagnostic

EML4–ALK testing in NSCLC was recently reviewed (16). Although ALK can be detected in tumor tissue by immunohistochemistry, reverse transcriptase PCR, and FISH, only the Vysis ALK Break-Apart FISH Probe Kit is approved by FDA as a companion diagnostic to detect the presence of an

ALK gene rearrangement. The test uses formalin-fixed, paraffin-embedded NSCLC tissue. Deparaffinized tissue sections are heated to denature DNA and then exposed to two fluorescently labeled probes. The hybridized probes flank the breakpoint of the ALK gene, with an approximately 442 kb green probe on the 5' (centromeric) side and an approximately 300 kb orange probe on the 3' (telomeric) side (Fig. 1). The catalytic domain of ALK that is the target of crizotinib is encoded by a region encompassed by the 3' orange probe. Specimens are then washed and exposed to a blue fluorescing DNA counterstain. Using an appropriately configured fluorescence microscope, orange and green fluorescence signals are enumerated in 50 tumor nuclei (Fig. 2). For cells without an ALK rearrangement, colocalized orange and green signals show as a single yellow signal. When the ALK gene is rearranged, there are either split green and orange signals separated by at least two signal diameters or a single orange signal. A sample is considered positive if >50% of cells are positive, equivocal if 10% to 50% of cells are positive, and negative if <10% of cells are positive. If the sample is equivocal, a second reader evaluates the slide and counts an additional 50 cells for a total of 100 cells. The specimen is then considered positive if ≥15% of cells are positive. Studies of inter-reader reproducibility of specimen interpretation showed 100% agreement both for positives [positive percent agreement (PPA) and negatives [negative percent agreement (NPA)]. Duplicate interpretations within readers also showed 100% PPA and NPA. High inter-laboratory reproducibility was suggested by pairwise PPA, NPA, and overall percent agreement ranging from 94.9% to 100%, 91.1% to 100%, and 96.7% to 100%, respectively.

Safety results

A total of 397 patients were included in the analysis of deaths and serious adverse events (SAE). Forty-five patients died within 28 days of their last dose of study drug. Causes of death included disease progression (32), pneumonia (2), hypoxia (2), and acute respiratory distress syndrome, dyspnea, pneumonitis, empyema, pulmonary hemorrhage, septic shock, disseminated intravascular coagulation, cardiovascular, and unknown in one patient each. SAEs

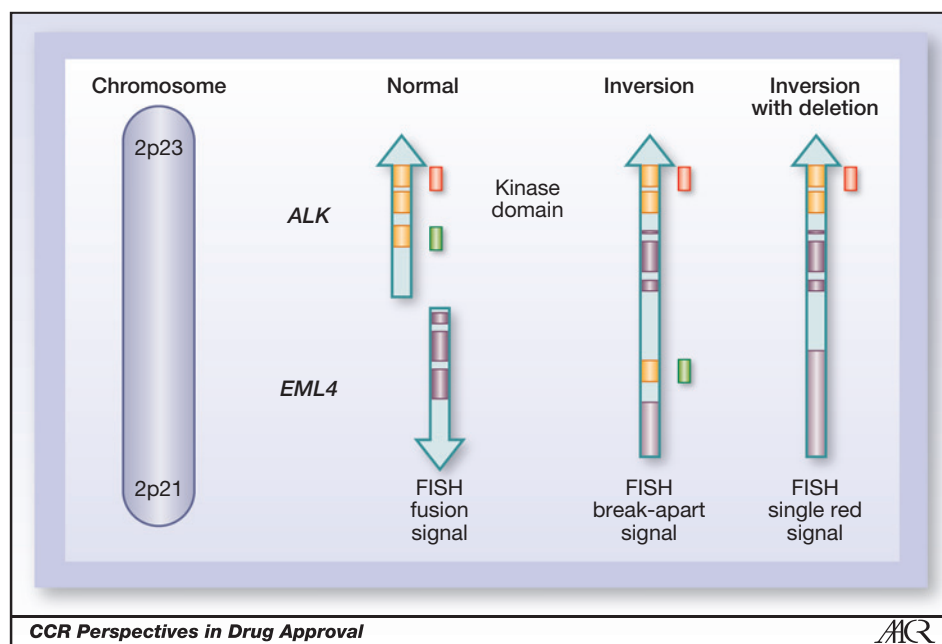


Figure 1. Signal pattern of Vysis Break-Apart FISH Kit. *ALK* and *EML4* are located on chromosome 2p21–2p23. *EML4* is normally on the opposite strand to *ALK* and both probes on the *ALK* gene (red orange and green) are close together, explaining the FISH fusion signal. The *EML4*–*ALK* fusion gene is the result of an inversion of the N-terminal portion of *EML4* with the kinase domain of *ALK* which leads to an increased distance between the red orange and green probes. A deletion of the proximal part combined with the inversion explains the single red orange signal. The *EML4*–*ALK* fusion protein has a fully functional *ALK* kinase domain and has gain-of-function properties. Adapted from Thunnissen et al (16). The article in which this image originally appeared is published with open access at Springerlink.com.

occurring in at least 2% of patients, included pneumonia, dyspnea, and pulmonary embolism.

The primary analysis of safety was based on 255 patients from Studies 1001 and 1005 who received at least one dose. The most common grade 1–4 adverse reactions occurring in at least 25% of patients included vision disorder, nausea, diarrhea, vomiting, edema, and constipation (Table 2). The vision disorders were mostly grade 1 and included visual impairment, photopsia, blurred vision, vitreous floaters, diplopia, photophobia, and visual field defects. Grade 3–4 adverse reactions occurring in >5% of patients included elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), dyspnea, pneumonia and neutropenia. Grade 3–4 laboratory abnormalities included neutropenia,

thrombocytopenia, lymphopenia, and ALT elevations. No patient experienced liver failure, but there was one potential Hy's law case and four patients required permanent discontinuation of treatment due to liver enzyme elevations.

Discussion

Crizotinib is the first personalized therapy for NSCLC in which patients are selected using an analytically and clinically validated test for *ALK* translocations. Crizotinib is also an example of rapid codevelopment of a drug and companion diagnostic. FDA approval was just 5 years after the first-in-human clinical trials were initiated. This was, in part, due to early and open communication among Pfizer,

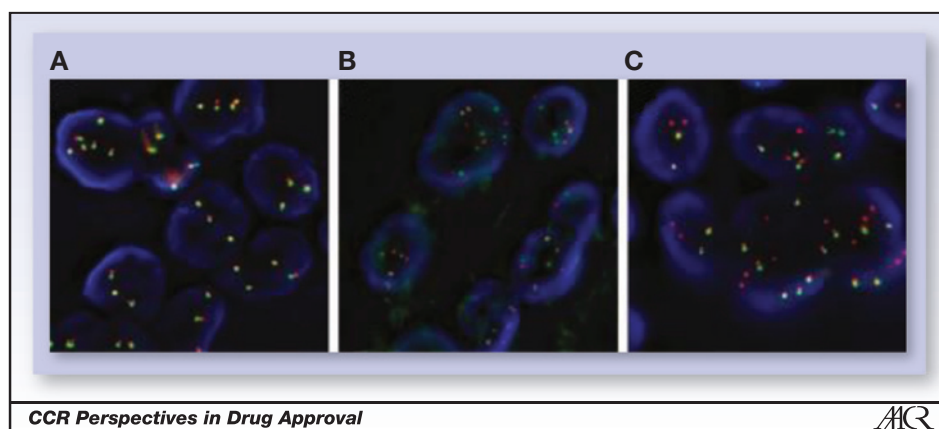


Figure 2. Representative examples of *ALK* FISH findings in three pulmonary adenocarcinomas (Vysis *ALK* Break-Apart FISH probe). All three carcinomas show increased *ALK* copy number. A, normal signals, no rearrangement. Note that some of the signals are fused and produce a yellow signal, whereas others have green and red signals in close proximity. B, one or two break-apart signals per nucleus, indicative of inversion. C, single red signals, indicative of inversion and deletion. Note that the cancer cells in B and C contain both rearranged and normal *ALK* signals. Adapted from Thunnissen et al. (16). The article in which this image originally appeared is published with open access at Springerlink.com.

Table 2. Grade 1–4 adverse reactions in >25% of patients

	Study 1001 ^a		Study 1005 ^a	
	Treatment emergent	Treatment related	Treatment emergent	Treatment related
	N = 119	N = 119	N = 136	N = 136
All	117 (98.3%)	114 (95.8%)	136 (100%)	131 (96.3%)
Eye disorders				
Visual disorder ^b	76 (63.9%)	75 (63.0%)	83 (61.0%)	80 (58.8%)
Gastrointestinal disorders				
Nausea	59 (49.6%)	58 (48.7%)	86 (63.2%)	78 (57.4%)
Vomiting	48 (40.3%)	42 (35.3%)	68 (50.0%)	59 (43.4%)
Diarrhea	57 (47.9%)	51 (42.9%)	67 (49.3%)	58 (42.6%)
Constipation	45 (37.8%)	32 (26.9%)	53 (39.0%)	37 (27.2%)
Esophageal disorder ^c	30 (25.2%)	20 (16.8%)	21 (15.4%)	9 (6.6%)
General disorders				
Edema/peripheral edema	43 (36.1%)	33 (27.7%)	54 (39.7%)	39 (28.7%)
Fatigue	30 (25.2%)	17 (14.3%)	50 (36.8%)	34 (25.0%)
Metabolism and nutrition				
Decreased appetite	29 (24.4%)	20 (16.8%)	42 (30.9%)	30 (22.1%)
Nervous system disorder				
Dizziness ^d	35 (29.4%)	25 (21.0%)	26 (19.1%)	19 (14.0%)
Respiratory disorders				
Cough/productive cough	16 (13.4%)	2 (1.7%)	38 (27.9%)	7 (5.1%)
Dyspnea/exertional dyspnea	22 (18.5%)	0	35 (25.7%)	5 (3.7%)

^aAdverse reactions were graded using NCI CTCAE v3.0 in Study 1001 and v4.0 in Study 1005.

^bIncludes diplopia, photopsia, blurred vision, visual field defect, visual impairment, vitreous floaters, and visual brightness.

^cIncludes dyspepsia, dysphagia, epigastric discomfort/burning, esophagitis, esophageal obstruction, pain, spasm, and ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.

^dIncludes balance disorder, postural dizziness, and presyncope.

Abbott, and two FDA centers (CDER and CDRH). The drug and the test were approved by the FDA 4.9 months after the submission of the applications.

Crizotinib received accelerated approval based on the surrogate endpoint of ORR. Although ORR data in patients with ALK-positive NSCLC were limited, the response rates were clearly higher than with therapies approved for unselected patients with advanced-stage NSCLC. The IRC response rates were lower in both studies but supported the investigator assessments. Two randomized trials, one in the first-line and another in the second-line setting, comparing crizotinib with chemotherapy in ALK-positive NSCLC were ongoing at the time of approval. The second-line trial was recently published and reported an improvement in progression-free survival and ORR compared with chemotherapy (17). These results led to submission of a supplemental application and subsequent full approval of crizotinib.

Postmarketing requirements included an *in vitro* study to evaluate the induction potential of crizotinib on CYP2B and CYP2C enzymes and clinical trials to further assess visual disorders, the risk of QT prolongation, multiple dose drug–drug interactions with strong CYP3A inhibitors and inducers and gastric pH elevating drugs, and the appropriate doses in patients with severe renal impairment and various

degrees of hepatic impairment. Postmarketing commitments included a trial to further explore response to crizotinib and to assess additional biomarkers (e.g., MET and ROS1) in patients with ALK-negative NSCLC.

Crizotinib is the first drug approved for NSCLC that targets a specific molecular abnormality and was the forerunner of recent approvals of erlotinib and afatinib for the first-line treatment of patients with metastatic NSCLC whose tumors have specific EGFR deletions or mutations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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