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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Running Title: FDA Approval Summary: Crizotinib for ALK-positive NSCLC

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The authors have no conflicts of interest.

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Abstract

On August 26, 2011, the U.S. Food and Drug Administration 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% 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 (≥25%) were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. Accelerated approval was granted based on the high objective response rates 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.

Introduction

Until recently, first-line treatment for advanced 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, epidermal growth factor 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).

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).

The 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 mg 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 employing 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 four to six 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, 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 [^{14}C] 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 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.

Co-administration of ketoconazole BID, a strong CYP3A inhibitor, with a single 150 mg crizotinib dose increased the mean AUC by approximately 3.2-fold compared to 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 twice daily 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 1 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 2 regimen of 250 mg orally twice daily. Testing of tumor tissue for *ALK* gene rearrangement was performed by local laboratories.

Study 1005 was a multicenter, single-arm phase 2 trial of crizotinib 250 mg administered orally twice daily 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 non-smokers or ex-smokers, 95% had adenocarcinoma and the majority had an ECOG performance status of 0-1. Most patients had received two or more regimens and multiple approved agents.

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% CI: 52%, 70%) with 2 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 eight 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 eight 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 to 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 to 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 IHC, RT-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 a ~442 kb green probe on the 5' (centromeric) side and a ~300 kb orange probe on the 3' (telomeric) side (Figure 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 fluorescent signals are enumerated in 50 tumor nuclei (Figure 2). For cells without an *ALK* rearrangement, co-located 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 10-50% 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 (PPA) and negatives (NPA). Duplicate interpretations within readers also showed 100% PPA and NPA. High inter-laboratory reproducibility was suggested by pair-wise PPA, NPA, and overall percent agreement ranging from 94.9%-100%, 91.1%-100%, and 96.7%-100%, respectively.

Safety Results

A total of 397 patients were included in the analysis of deaths and serious adverse events (SAEs). 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 ARDS,

dyspnea, pneumonitis, empyema, pulmonary hemorrhage, septic shock, DIC, cardiovascular, and unknown in one patient each. SAEs 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 (ARs) occurring in at least 25% 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 ARs occurring in >5% of patients included elevated ALT/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 co-development of a drug and companion diagnostic. FDA approval was just five years after the first in human clinical trials were initiated. This was due in part to early and open communication among Pfizer, Abbott and two FDA centers (CDER and CDRH). The drug and the test were approved by 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 to 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 to chemotherapy (17). These results led to submission of a supplemental application and subsequent full approval of crizotinib.

Post-marketing 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. Post-marketing 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.

References

1. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.

2. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicenter, open-label, randomized, phase 3 study. Lancet Oncol 2011;12:735-42.

3. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.

4. Togashi Y, Soda M, Sakata S, Sugawara E, Hatano S, Asaka R, et al. KLC1-ALK: a novel fusion in lung cancer identified using a formalin-fixed paraffin-embedded tissue only. PLoS One 2012;7:e31323. Epub 2012 Feb 8.

5. Takeuchi K, Choi YL, Togashi Y, Soda M, Hatano S, Inamura K, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009;15:3143-9.

6. Wong DW, Leung EL, So KK, Tam IY, Sihoe AD, Cheng LC, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723–33.

7. Koivunen JP, Mermel C, Zejnullahu K, Murphy C, Lifshits E, Holmes AJ, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008;14:4275–83.

8. Takeuchi K, Choi YL, Soda M, Inamura K, Togashi Y, Hatano S, et al. Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts. Clin Cancer Res 2008;14:6618–24.

9. Perner S, Wagner PL, Demichelis F, Mehra R, Lafargue CJ, Moss BJ, et al. EML4-ALK fusion lung cancer: A rare acquired event. Neoplasia 2008;10:298–302.

10. Inamura K, Takeuchi K, Togashi Y, Nomura K, Ninomiya H, Okui M, et al. EML4-ALK fusion is linked to histological characteristics in a subset of lung cancers. J Thorac Oncol 2008;3:13–7.

11. Shinmura K, Kageyama S, Tao H, Bunai T, Suzuki M, Kamo T, et al. EML4-ALK fusion transcripts, but no NPM-, TPM3-, CLTC-, ATIC-, or TFG-ALK fusion transcripts, in non–small-cell lung carcinomas. Lung Cancer 2008;61:163–9.

12. Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53.

13. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-703.

14. Camidge DR, Bang YJ, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-9.

15. Kim D-W, Ahn M-J, Shi Y, De Pas TM, Yang P-C, Riely, GJ, et al. Results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). J Clin Oncol 2012;30, 2012 (suppl; abstr 7533).

16. Thunnissen E, Bubendorf L, Dietal M, Elmberger G, Kerr K, Lopez-Rios F, et al. EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations.Virchows Arch 2012;461:245-57.

17. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.

Table 1: Efficacy Data

Primary Endpoint	**Study 1001**		**Study 1005**	
	INV N = 116	IRC N = 105	INV N = 135	IRC N = 105
Response Rate[1] [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 Median (range)[2]	48.1 weeks (4.1+, 76.6+)	58.1 weeks (7.3+, 76.1+)	41.9 weeks (6.1+, 42.1+)	33.1 weeks (6.1+, 42.1+)

[1] RECIST v1.0 in study 1001 and v1.1 in study 1005
[2] Kaplan-Meier method with censored values (+)

Table 2: Grade 1-4 Adverse Reactions in > 25% of Patients

	Study 1001[1]		Study 1005[1]	
	Treatment Emergent N = 119	**Treatment Related N = 119**	**Treatment Emergent N = 136**	**Treatment Related N = 136**
All	117 (98.3%)	114 (95.8%)	136 (100%)	131 (96.3%)
Eye Disorders				
Visual Disorder[2]	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[3]	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[4]	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%)

[1]Adverse reactions were graded using NCI CTCAE v3.0 in Study 1001 and v4.0 in Study 1005.
[2]Includes diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, and visual brightness.
[3]Includes dyspepsia, dysphagia, epigastric discomfort/burning, esophagitis, esophageal obstruction, pain, spasm, and ulcer, gastroesophageal reflux, odynophagia, and reflux esophagitis.
[4]Includes balance disorder, dizziness postural, and presyncope

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.

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Figure 2: Representative Examples of ALK FISH Results

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, while 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.

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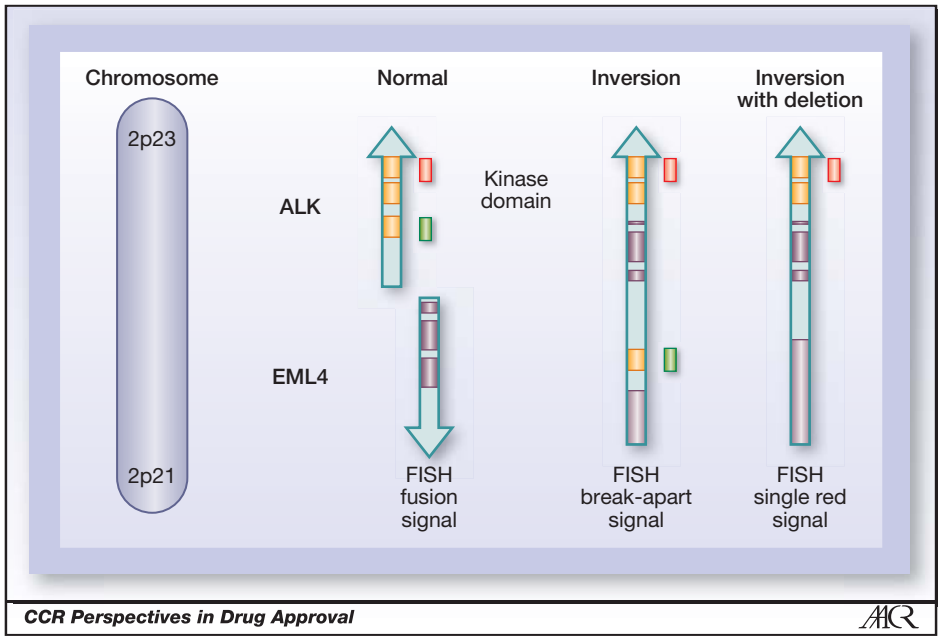
Figure 1:



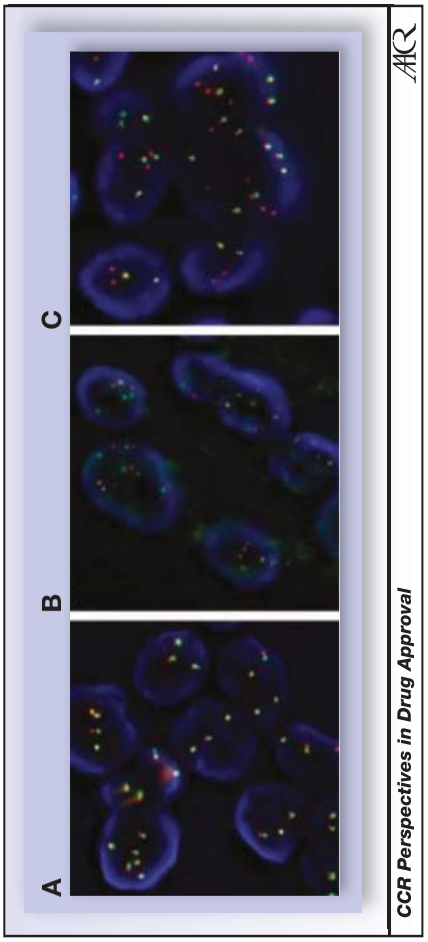


Figure 2:

AACR American Association for Cancer Research

Clinical Cancer Research

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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