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Regulatory Issues: FDA

FDA Approval Summary: Crizotinib for the Treatment of Metastatic Non-Small Cell Lung Cancer With Anaplastic Lymphoma Kinase Rearrangements

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. EML4-ALK fusion protein • Crizotinib • Non-small cell lung carcinoma • Molecular targeted therapy • Neoplasm metastasis

ABSTRACT

On August 26, 2011, crizotinib received accelerated approval for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is ALK-positive as detected by a test approved by the U.S. Food and Drug Administration (FDA). Approval was based on two single-arm trials demonstrating objective response rates (ORRs) of 50% and 61% and median response durations of 42 and 48 weeks. On November 20, 2013, crizotinib received regular approval based on confirmation of clinical benefit in study A8081007, a randomized trial in 347 patients with ALK-positive advanced NSCLC who had previously received one platinum-containing regimen. Patients were assigned (1:1) to receive crizotinib 250 mg orally twice daily or standard of care (docetaxel or pemetrexed). The primary endpoint was progression-free survival (PFS) determined by independent radiology review; secondary endpoints were ORR and overall survival (OS). PFS was significantly longer in the crizotinib arm, with median PFS of 7.7 and 3.0 months in the crizotinib and chemotherapy arms, respectively, and a 46% absolute increase in ORR but no difference in OS between treatment arms at the interim analysis. The most common adverse drug reactions (>25%) in crizotinib-treated patients were vision disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue. The most serious toxicities of crizotinib were hepatotoxicity, interstitial lung disease or pneumonitis, and QT-interval prolongation. Crizotinib's rapid clinical development program (6 years from identification of *ALK* rearrangements in a subset of NSCLC to full FDA approval) is a model of efficient drug development in this new era of molecularly targeted oncology therapy. ***The Oncologist*** 2014;19:e5–e11

Implications for Practice: Prior to identification of activating genetic alternations and their targeted therapies in non-small cell lung cancer (NSCLC), patients with metastatic disease were treated with platinum-doublet chemotherapy and cytotoxic monotherapy regimens in the first- and second-line settings, respectively. However, with the identification of *EGFR*-mutation-targeted therapies and now *ALK*-alteration-targeted therapies, standard treatment in patients with NSCLC containing specific genetic alterations is evolving toward more efficacious and less toxic therapies. As more molecular targets are identified and their respective drugs developed, the management of metastatic NSCLC will move away from traditional cytotoxic chemotherapy regimens.

INTRODUCTION

Lung cancer is the leading cause of cancer death in the U.S., with more people dying of lung cancer than of colon, breast, and prostate cancers combined [1]. Estimated new lung cancer cases for 2014 total 224,210, resulting in 159,260 deaths [2]. Non-small cell lung cancer (NSCLC) accounts for 85% of new lung cancer cases, with a 5-year survival rate of 1%–16% [3, 4]. Cytotoxic platinum doublet-based chemotherapy has been the standard first-line treatment for patients with metastatic NSCLC, with median survival of 8–10 months [5]. In the second-line treatment setting for advanced NSCLC, docetaxel, pemetrexed (nonsquamous NSCLC only), and erlotinib are regimens approved by the U.S. Food and Drug Administration (FDA); however, response rates are low, less than 10%, and effects on survival are modest [6].

Through the use of high-throughput screening techniques, a number of genetic "driver mutations" have been identified in NSCLC, particularly in patients with adenocarcinoma histology, most notably, mutations in the kinase domain of the *EGFR* gene [7]. Studies in patients whose tumors harbor *EGFR* mutations have demonstrated that treatment with EGFR tyrosine kinase inhibitors (TKIs) yields higher response rates and longer progression-free survival (PFS) compared with standard

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chemotherapy [8, 9]. With the success of EGFR TKIs, clinicians and biochemists sought to discover other genetic drivers of NSCLC [10].

The ALK fusion protein, with the fusion partner neucleophosmin, was identified as an oncogenic driver in 1994 in anaplastic large cell lymphoma resulting from a chromosomal translocation event, t(2;5) [11]. In 2007, it was reported that in NSCLC, a small inversion within chromosome 2p resulted in the expression of a fusion protein with the ability to transform mouse embryonic fibroblast cells in culture and to form dermal tumors in nude mice [12]. The authors determined that this chimeric tyrosine kinase fusion protein incorporated a 5′ region of the breakpoint partner *EML4* gene and the 3′ intracellular cellular kinase domain of the *ALK* gene and that 5 of 75 NSCLC archived patient tumor samples had this aberration.

Crizotinib is a small molecule TKI that inhibits the activity of the ALK fusion proteins, MET, ROS1, and MST1R (RON) [13]. In late 2007, the first patient with ALK-positive NSCLC was enrolled in the phase I crizotinib trial (Fig. 1). After the first two patients with ALK-positive NSCLC responded, Pfizer (New York, NY, http://www.pfizer.com) added an ALK-positive NSCLC cohort to the phase I study. In 2009, Pfizer initiated both a single-arm, activity-estimating trial (A8081005) and a randomized trial (A8081007) comparing progression-free survival with crizotinib and with docetaxel or pemetrexed. An investigational, analytically validated fluorescence in situ hybridization (FISH) assay that detects *ALK* inversion or translocation events was used for patient selection in both clinical trials. In 2011, crizotinib received accelerated approval for the treatment of ALK-positive NSCLC, as detected by an FDA-approved companion diagnostic. The approval was based on the results from a single-arm study that demonstrated an objective response rate (ORR) of 61% (95% confidence interval [CI], 52%–70%), with a median response duration of >11 months and an additional supportive single-arm study demonstrating an ORR of 50% [14]. As a condition of accelerated approval under 21 CFR 314 (Applications for FDA Approval to Market a New Drug), subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses), Pfizer was required to conduct two postmarketing studies to verify the clinical benefit of crizotinib. Study A8081007 was a randomized, open-label trial comparing crizotinib with either pemetrexed or docetaxel for second-line treatment of advanced ALK-positive NSCLC. Study A8081014 was a randomized, open-label trial comparing crizotinib with either pemetrexed/cisplatin or pemetrexed/carboplatin in patients with previously untreated, locally advanced, or metastatic; ALK-positive; nonsquamous NSCLC. This paper outlines the FDA review of A8081007, which was submitted to confirm the clinical benefit of crizotinib and to support conversion to regular approval.

Methods

Study A8081007 was an international, open-label, multicenter, randomized trial in patients with metastatic, ALK-positive NSCLC who were previously treated with platinum-doublet chemotherapy. Patients were randomly assigned (1:1) to receive crizotinib administered orally at a dose of 250 mg twice daily or chemotherapy. Per protocol, patients randomized to chemotherapy were to receive pemetrexed 500 mg/m^2 (if pemetrexed-naïve) or docetaxel 75 mg/m^2 (if previously treated with pemetrexed) intravenously every 21 days. Patients must have received one line of platinum-based doublet chemotherapy and have locally advanced or metastatic, ALK-positive NSCLC, as determined by the Vysis ALK Break Apart FISH Probe Kit (Vysis, Downers Grove, IL, http://www.vysis.com). Randomization was stratified by Eastern Cooperative Oncology Group performance status (0–1, 2), brain metastases (present, absent), and prior EGFR TKI treatment (yes, no).

Patients were treated until the investigator determined (Response Evaluation Criteria In Solid Tumors [RECIST]) progression, there was unacceptable toxicity, or the investigator determined that a patient was not experiencing clinical benefit. At the time of progression, chemotherapy-treated patients were given the option to enroll in a single-arm trial (A8081005) to receive crizotinib. The primary efficacy endpoint for study A8081007 was PFS defined as the time from randomization to the first documentation of objective tumor progression or death on study due to any cause, whichever occurred first. Progression was determined by independent radiology review (IRR) assessment and was based on RECIST

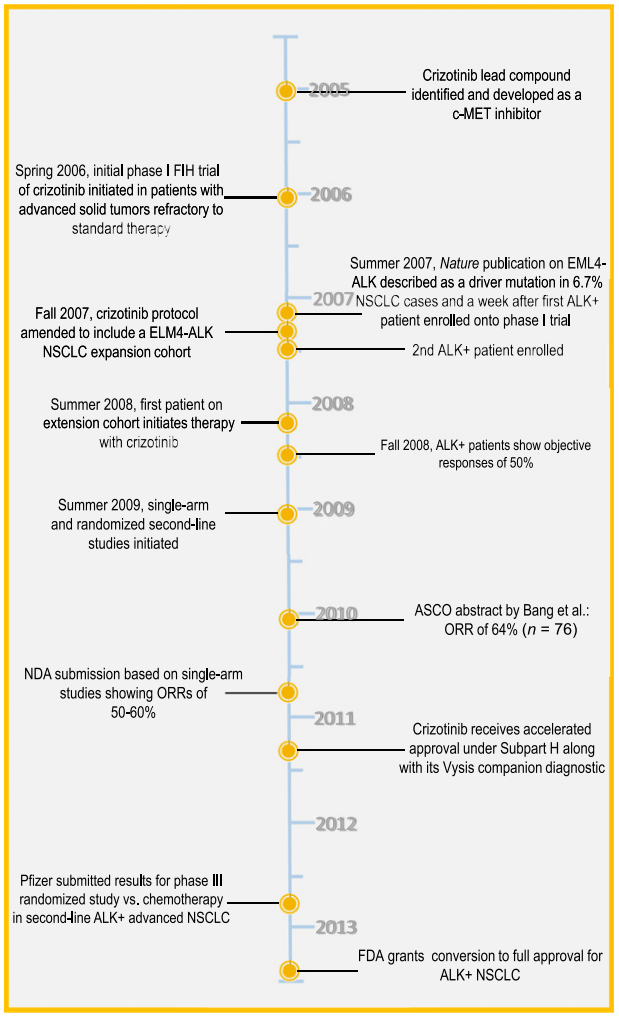

Figure 1. Timeline for crizotinib development.

Abbreviations: ALK+, ALK-positive; ASCO, American Society of Clinical Oncology; FIH, first in human; NDA, new drug application; NSCLC, non-small cell lung cancer; ORR, objective response rate.

version 1.1. Tumor assessments occurred every 6 weeks and when clinically indicated. All patients had baseline brain imaging and, if positive, were monitored every 6 weeks. Secondary efficacy endpoints for this study included overall survival (OS), objective response rate (ORR), duration of response (DR), disease control rate (DCR), and time to response (TTR). Other secondary endpoints included patient-reported lung cancer symptoms, quality of life, and general health status. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The visual symptoms were also evaluated using a patient-reported visual-symptom assessment questionnaire.

The trial was designed with a sample size of 288 patients, and the final analysis of PFS was to occur after 217 events to provide 90% probability of demonstrating that crizotinib is superior to chemotherapy, assuming a 1.56-fold improvement over chemotherapy (median PFS: 7 vs. 4.5 months; hazard ratio [HR]: 0.643) and using a 1-sided log-rank test at a 2.5% level of significance. Median OS for the chemotherapy arm was assumed to be 8 months. With an overall 1-sided α of 0.025 and one interim analysis (at the time of PFS analysis), the study would have 80% power to detect a 44% increase in OS when 241 deaths had occurred. To control the family-wise type I error for the comparison between crizotinib and chemotherapy, a step-down procedure was applied to the efficacy endpoints in the following order: PFS, ORR, OS, and DCR.

Results

A total of 347 patients (intention-to-treat [ITT] population) were randomly allocated to crizotinib ($n = 173$) or to chemotherapy ($n = 174$). The final analyses for all endpoints except OS were conducted following 227 PFS events. One patient on the crizotinib arm and three patients on the chemotherapy arm did not receive any therapy; therefore, the safety population consisted of 343 patients, 172 on the crizotinib arm and 171 on the chemotherapy arm. A total of 106 medical centers in 21 countries enrolled patients into this study. Table 1 summarizes the baseline patient demographics and disease characteristics, which were balanced across the two arms. The median duration of treatment with crizotinib was 7.1 months compared with 2.8 months for chemotherapy.

Table 1. Study demographics and disease characteristics

Demographic ($n = 347$)	Crizotinib ($n = 173$)	Chemotherapy ($n = 174$)
Safety population	172	171
Age (years)		
Mean	50.3	49.8
Median	51	49
Range	22–81	24–85
Age, years (%)		
<65	84	87
≥65	16	13
Male sex	43.4	44.8
Race (%)		
White	52	52.3
Black	1.2	1.7
Asian	45.7	44.8
Smoking (%)		
Never	62.4	63.8
Ex-smoker	34.1	31.0
Smoker	2.9	5.2
Adenocarcinoma histology (%)	94.2	92
Extent of disease (%)[a]		
Metastatic	95.4	90.8
Locally advanced	4.6	9.2
ECOG PS (%)		
0	41.6	37.4
1	48.6	54.6
Brain metastasis (%)	34.7	34.5
EGFR TKI prior use (%)	11.6	12.1

[a]On further investigation with the sponsor, it was determined that at least half of the locally advanced patients in the crizotinib arm, according to current American Joint Committee on Cancer version 7 staging criteria, would have stage IV disease. Consequently, almost all crizotinib-treated patients had metastatic disease.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

Efficacy

As shown in Figure 2, in the ITT analysis, there was a statistically significant improvement in IRR-assessed PFS, with a median PFS of 7.7 months (95% CI: 6.0–8.8) for patients randomized to the crizotinib arm and 3.0 months (95% CI: 2.6–4.3) for patients randomized to the chemotherapy arm (HR: 0.49; 95% CI: 0.37–0.64; $p < .0001$). These results were confirmed by the FDA. In subgroup analyses based on stratification factors, PFS was longer with crizotinib in all subgroups. In addition, a subgroup analysis conducted by the FDA using patient data from the highest enrolling sites showed no difference in efficacy results across centers. The improvement in PFS was also observed using investigator-based assessments.

With regard to key secondary endpoints, in the ITT population, the ORR was 65% for crizotinib and 20% for chemotherapy, an improvement of 46% (95% CI: 37%–55%; $p < .0001$). In the crizotinib arm, 1 patient achieved a complete response (CR) and 112 patients achieved partial responses (PRs) compared with no CRs and 34 PRs in the chemotherapy arm. The median DR was 7.4 months (95% CI: 6.1–9.7) in the crizotinib arm and 5.6 months (95% CI: 3.4–8.3) in the chemotherapy arm.

In the chemotherapy arm, patients received pemetrexed ($n = 99$) unless they had previously received it, in which case they received docetaxel ($n = 72$). An exploratory analysis based on the chemotherapy regimen administered showed that the median PFS for pemetrexed- and docetaxel-treated patients was 4.2 and 2.6 months, respectively. In addition, the ORRs for pemetrexed- and docetaxel-treated patients were 29% and 7%, respectively.

There was no difference in OS in the protocol-specified interim analysis of OS between the crizotinib and chemotherapy arms (HR: 1.02; 95% CI: 0.68–1.54; $p = .54$). Median OS was 20.3 months (95% CI; 18.1 to not reached [NR]) and 22.8 months (95% CI: 18.6 to NR) in the crizotinib and chemotherapy arms, respectively; however, approximately 64% of

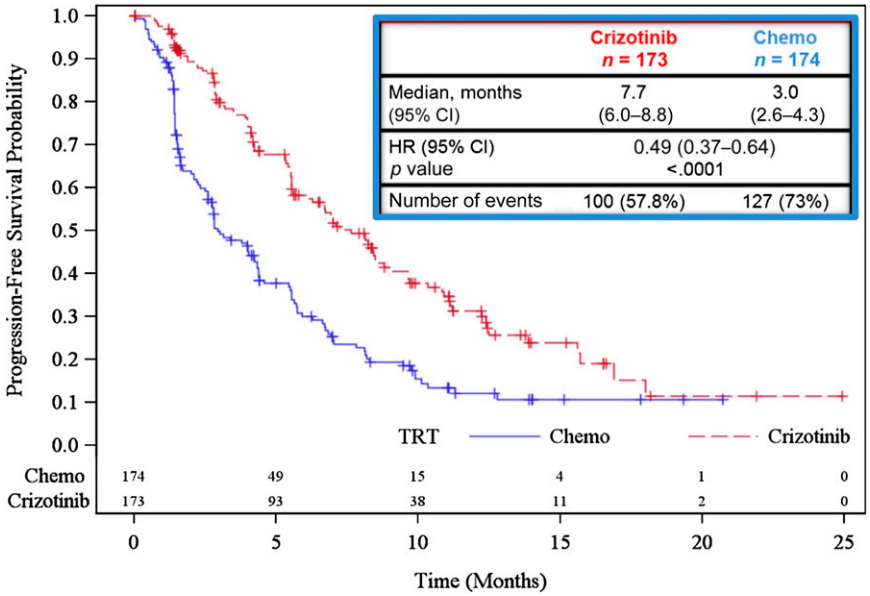

Figure 2. Progression-free survival based on independent radiology review.
Abbreviations: Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TRT, treatment arm.

patients on the chemotherapy arm subsequently received treatment with crizotinib, most in the single-arm study A8081005. Patient-reported lung cancer symptoms and global quality-of-life data were collected in this trial [15]. However, the FDA did not consider the measurement tools to be sufficiently robust, and results were not included in the prescribing information.

Toxicity

Patients receiving crizotinib remained on therapy two to three times as long as those receiving chemotherapy. Overall, 100% of crizotinib-treated patients experienced adverse reactions, 17% discontinued crizotinib due to an adverse reaction, 16% required dose reductions, and 39% required temporary discontinuation of crizotinib. In the chemotherapy arm, 98% of patients experienced adverse reactions, 14% discontinued chemotherapy due to adverse reactions, 15% required dose reductions, and 16% required temporary discontinuation of chemotherapy. Table 2 summarizes the incidence of adverse drug reactions and dose modifications by treatment arm. The most common adverse drug reactions (>25%) for crizotinib were vision disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue. Vision disorders included diplopia, photophobia, photopsia, vision blurred, visual acuity reduced, visual impairment, and vitreous floaters. All reported cases of vision disorders were grade 1 or 2 in severity, and no patient had to alter therapy due to visual changes. Based on patient-administered questionnaires, the onset of vision disorders usually began in the first week of starting crizotinib. The visual disorders that occurred in this study were reported to occur 4–7 days each week, lasted up to 1 minute, and had mild or no impact on daily activities, as captured on the patient survey. Table 3 lists common adverse events, regardless of attribution, occurring with ≥5% incidence in crizotinib-treated patients and with grade 3–4 adverse events occurring more frequently (≥2-fold higher) in crizotinib-treated patients compared with chemotherapy. Alanine transaminase elevation (17%) based on laboratory evaluation in the crizotinib-treated patients was the most common grade 3–4 adverse event. The most common serious adverse reaction on crizotinib was pneumonia (4%). The most clinically significant toxicities of crizotinib were hepatotoxicity, bradycardia, interstitial lung disease (ILD) or pneumonitis, and QT-interval prolongation. Fatal adverse reactions of crizotinib included acute respiratory distress syndrome, arrhythmia, venous thromboembolism, sudden death, respiratory not otherwise specified, ILD or pneumonitis, and pneumonia. Following the safety database closure (March 2012), one case of drug-induced fatal hepatotoxicity occurred in a crizotinib-treated patient.

Discussion

The FDA granted regular approval to crizotinib based on a favorable benefit-risk assessment for the indication of treatment of patients with NSCLC whose tumors are ALK positive, as detected by an FDA-approved test. Crizotinib met its primary objective of a clinically important and statistically significant improvement in PFS. Crizotinib-treated patients had a longer duration of treatment, with a tolerable safety profile that included a low frequency of clinically significant adverse reactions such as ILD and hepatotoxicity and common mild or moderate adverse reactions of diarrhea, nausea, visual disorders, and vomiting.

Lung cancer is the leading cause of cancer-related death, and approximately 5% of NSCLC cases involve the *ALK* inversion event leading to expression of an oncogenic chimeric protein [16]. Based on clinically significant results in ORR and DR, crizotinib received accelerated approval in 2011 under 21 CFR 314, subpart H [14]. Study A8081007, a randomized, international, active-controlled trial, confirmed the efficacy of crizotinib through demonstration of a statistically significant and clinically meaningful improvement in IRR-assessed PFS, with an improvement in median PFS of 4.7 months compared with chemotherapy (HR: 0.49; 95% CI: 0.37–0.64; $p < .0001$).

Table 2. Incidence of adverse events and dose modifications

AEs	Crizotinib[a]	Chemotherapy[a]
Number of AE events	2,085	1,358
Patients with AEs	172 (100.0)	168 (98.2)
Patients with SAEs	64 (37.2)	40 (23.4)
Grade 3 or 4 AEs[b]	76 (44.2)	72 (42.1)
Grade 5 AEs[b]	25 (14.5)	7 (4.1)
Patients discontinued due to AEs	30 (17.4)	23 (13.5)
Patients dose reduced due to AEs	28 (16.3)	25 (14.6)
Patients temporarily discontinued due to AEs	67 (39.0)	27 (15.8)

[a]Data are presented as *n* (%) except for the number of AE events.
[b]Grading by National Cancer Institute common terminology criteria for adverse events version 4.
Abbreviations: AE, adverse event; SAE, serious adverse event.

Crizotinib treatment also resulted in a threefold increase in ORR compared with chemotherapy. Although the planned interim analysis of OS did not demonstrate a statistically significant difference, treatment effects on survival may have been confounded because 64% of patients in the chemotherapy arm received crizotinib on disease progression. The median survivals in this trial were 20.3 and 22.8 months for the crizotinib and chemotherapy arms, respectively. These results are much longer than those observed in historical trials of single-agent docetaxel or pemetrexed as second-line therapy. It appears that survival may be prolonged by crizotinib therapy and that receiving crizotinib at any time (second or third line) is beneficial (i.e., patients who crossed over to receive crizotinib). Alternatively, the natural history of ALK-positive NSCLC may be more indolent than unselected NSCLC.

Severe or life-threatening adverse drug reactions of crizotinib included ILD or pneumonitis, drug-induced liver injury, and QT-interval prolongation. Fatal adverse reactions occurred in nine patients (5%) and consisted of acute respiratory distress syndrome, arrhythmia, dyspnea, pneumonia, pneumonitis, pulmonary embolism, ILD, respiratory failure, and sepsis. Common low-grade toxicities such as diarrhea were usually easily managed with temporary dose interruption or dose reduction. Compared with chemotherapy, although it appears that the incidence of adverse reactions was higher for crizotinib, it should be noted that patients receiving crizotinib were on therapy three times longer than patients receiving chemotherapy, and this may introduce a bias favoring chemotherapy. In addition, patients in the chemotherapy arm had a 16-fold higher rate of neutropenic fever. The benefit-risk analysis was considered sufficiently favorable to allow conversion to regular approval.

Review of data in this application raised a number of important questions. This study suggested that ALK-positive NSCLC either has a less aggressive natural history than unselected NSCLC or that crizotinib changes the natural history of ALK-positive NSCLC. Conducting a trial to directly assess which is true, by withholding crizotinib treatment in patients with ALK-positive NSCLC, would be considered unethical; therefore, available tumor tissue banks and registries should be interrogated to address this question.

Until additional agents are available for this population, chemotherapy will continue to be used for treatment. Consequently, the FDA assessed outcomes in chemotherapy subgroups in an exploratory manner. The outcomes suggest that patients with ALK-positive NSCLC derive greater benefit from pemetrexed than from docetaxel, with a higher ORR (29% for pemetrexed compared with 7% for docetaxel) and longer PFS (median 4.2 months for pemetrexed compared with 2.6 months for docetaxel). The greater efficacy of pemetrexed in ALK-positive NSCLC is also suggested by retrospective analyses of other studies. In a multivariate analysis of a retrospective exploratory study consisting of 117 patients treated with pemetrexed and tested for EGFR, RAS, and ALK alterations (including 19 patients with ALK-positive NSCLC) that adjusted for important variables, the only variable associated with prolonged PFS on pemetrexed was ALK positivity (HR: 0.36; 95% CI: 0.17–0.73) [17]. In a retrospective study of Korean patients with NSCLC treated with second-line pemetrexed and screened for ALK and EGFR alterations, the subgroup of patients with ALK-positive cancer had a longer time to progression than patients with EGFR mutant or wild type cancer (medians of 9.2, 1.4, and 2.9 months, respectively); ALK positivity alone was a significant predictor of a favorable ORR in multivariate analyses (HR: 0.07; 95% CI: 0.01–0.32) [18]. However, a third study with retrospective assessment of ALK status suggested that PFS was similar with pemetrexed treatment among patients with ALK-positive or ALK-negative cancer.

The incidence of vision disorders (including diplopia, photopsia, photophobia, blurred vision, visual field defect, visual impairment, vitreous floaters, visual brightness, and reduced visual acuity) was high (60%) with crizotinib treatment. As of yet, the mechanism through which crizotinib causes these events has not been determined. With additional research, it may be possible to determine whether the mechanism for this toxicity is on target (i.e., mediated through ALK inhibition) or off target (mediated through one of the other pathways inhibited by crizotinib).

Crizotinib is an example of efficient drug development with a highly active drug, for which Pfizer worked closely and collaboratively with the clinical investigators and FDA. The development of crizotinib highlights the potential efficiency of drug development when there is a true understanding of the molecular underpinnings of a disease. The molecular pathway for this subset of NSCLC was first described in 2007 (Fig. 1). A few months later, crizotinib—a multikinase inhibitor initially identified in 2005 and developed to target cancers with c-MET alterations—was used to target ALK-positive cancers in the clinic. In the early clinical study, objective responses were observed in ALK-positive NSCLC, as presented at the American Society of Clinical Oncology plenary session and published in 2010 [19, 20]. In 2011, the FDA granted crizotinib accelerated approval under 21 CFR 314, subpart H, concurrently with the Vysis ALK Break Apart FISH Probe Kit companion diagnostic assay, and crizotinib became available to the U.S. population. Confirmatory studies were ongoing at the time of approval. Two years later, crizotinib was granted regular approval based on the results of one of these confirmatory trials.

Table 3. Common (≥5%) or ≥2% grades 3/4 adverse reactions

	Crizotinib (%)		Chemotherapy (pemetrexed or docetaxel) (%)	
Adverse reaction	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
ALT elevation (laboratory)	76	17	38	4
AST elevation (laboratory)	61	9	33	0
Vision disorder	60	0	9	0
Diarrhea	60	0	19	1
Nausea	55	1	37	1
Lymphopenia (laboratory)	51	9	60	25
Neutropenia (laboratory)	49	12	28	12
Vomiting	47	1	18	0
Constipation	42	2	23	0
Edema	31	0	16	0
Hypophosphatemia (laboratory)	28	5	25	6
Dysgeusia	26	0	9	0
Upper respiratory infection	26	0	13	1
Dizziness	22	1	8	0
Hypokalemia (laboratory)	18	4	10	1
Weight decreased	10	1	4	0
Dyspepsia	8	0	3	0
Pulmonary embolism	6	5	2	2
QT prolongation	5	3	0	0
Bradycardia	5	0	0	0
Syncope	3	3	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

The approval also highlights the rapid review of agents that demonstrate a large treatment effect in a disease with high unmet medical need. Specifically, the original crizotinib new drug application (NDA) was submitted on March 30, 2011, and 5 months later, crizotinib received accelerated approval. This supplemental NDA for the current study was submitted February 28, 2013, and 9 months later, regular approval was received. In an independent study, 35 new oncology drugs were approved either by the European Medicines Agency or the FDA between 2003 and 2010 [21]. The median time for approval by the FDA was 6 months, and in general, drugs became available in the U.S. more quickly than in Europe. Oncology drug development continues to accelerate in the U.S. With the passage of the Food and Drug Administration Safety and Innovation Act of 2012, which amended the Food, Drug, and Cosmetic Act to include provisions for breakthrough therapy designation, 43% (13) of the drugs designated are under development for the treatment of cancer [22].

Conclusion

Crizotinib serves as a model for expedited development and approval of highly efficacious and clinically meaningful new drugs for patients with unmet needs, including those now designated as breakthrough therapies.

Author Contributions

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Disclosures

The authors indicated no financial relationships.

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