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Regulatory Issues: FDA

Benefit-Risk Summary of Crizotinib for the Treatment of Patients With ROS1 Alteration-Positive, Metastatic Non-Small Cell Lung Cancer

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Key Words. Crizotinib • Non-small cell lung cancer • ROS1 • Tyrosine kinase inhibitor

Abstract

On March 11, 2016, after an expedited 5-month review, the U.S. Food and Drug Administration expanded the crizotinib metastatic non-small cell lung cancer (mNSCLC) indication to include the treatment of patients whose tumors harbor a ROS1 rearrangement. The approval was based on a clinically meaningful, durable objective response rate (ORR) in a multicenter, single-arm clinical trial (ROS1 cohort of Trial PROFILE 1001) in patients with ROS1-positive mNSCLC. The trial enrolled 50 patients (age range: 25–77 years) whose tumors were prospectively determined to have a ROS1 gene rearrangement by break-apart fluorescence in situ hybridization (96%) or reverse transcriptase polymerase chain reaction (4%) clinical trial assays. Crizotinib demonstrated an ORR of 66% (95% confidence interval [CI]: 51%–79%) with a median duration of response of 18.3 months by independent radiology review and 72% (95% CI: 58%–84%) by investigator review. Patients received crizotinib 250 mg twice daily and had a median duration of exposure of 34.4 months. The toxicity profile in ROS1-positive patients was generally consistent with the randomized safety data in the U.S. Product Insert from two ALK-positive mNSCLC trials. The most common (≥25%) adverse reactions and laboratory test abnormalities included vision disorders, elevation of alanine transaminase and aspartate transaminase levels, nausea, hypophosphatemia, diarrhea, edema, vomiting, constipation, neutropenia, and fatigue. There were no treatment-related deaths. A favorable benefit-to-risk evaluation led to the traditional approval of crizotinib for this new supplemental indication. ***The Oncologist*** 2016;21:974–980

Implications for Practice: Given the results from the ROS1 cohort of the clinical trial PROFILE 1001, crizotinib represents a new treatment option and the first approved therapy for patients with metastatic non-small cell lung cancer whose tumors are ROS1 positive. Crizotinib demonstrated efficacy irrespective of prior treatment status.

Introduction

Lung cancer is the second most common cancer after prostate cancer in men and breast cancer in women. Estimates for lung cancer in the U.S. for 2016 are 224,390 new cases, with 158,080 deaths, and accounts for 27% of all cancer deaths [1]. Non-small cell lung cancer (NSCLC), consists of two major histologic subtypes: adenocarcinoma and squamous-cell carcinoma. First-line chemotherapy is the backbone of treatment for patients with newly diagnosed metastatic NSCLC (mNSCLC). Standard platinum doublets with or without bevacizumab result in a median survival time of approximately 10 to 12 months [2]. In the second-line setting, docetaxel with or without ramucirumab, pemetrexed, and erlotinib are regimens approved by the the U.S. Food and Drug Administration (FDA) [3–6]. However, response rates are generally low and effects on survival are modest in the unselected population. With the advent of targeted therapeutic approaches, a number of agents such as monoclonal antibodies, antibody-drug conjugates, and small molecule kinase inhibitors have been developed to target specific molecular aberrations [7]. Recently, programmed cell death-1 (PD-1) inhibitors have shown efficacy in the second-line setting, with both nivolumab and pembrolizumab approved [8–15].

In approximately half the cases of mNSCLC of adenocarcinoma histology, a genetic driver alteration (e.g., gene mutation, rearrangement, or amplification) has been identified [16]. These include alterations in the *KRAS*, *EGFR*, *ALK*, *PI3K*, *HER2*, *BRAF*, *RET*, *ROS1*, *MEK*, *MET*, and *NRAS* genes [17–21]. Furthermore, the Cancer Genome Atlas Research Network published comprehensive molecular profiling of lung adenocarcinoma and identified potentially new driver gene alterations [22]. The most-studied driver pathways have been the EGFR and ALK pathways. EGFR

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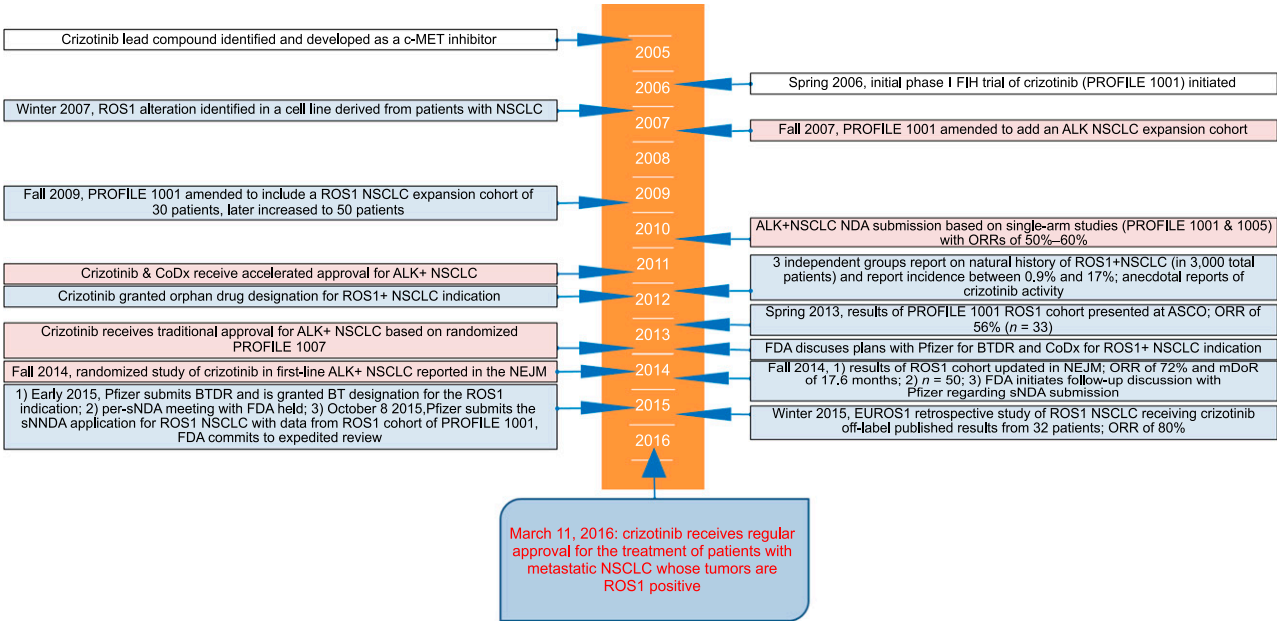

Figure 1. Time line of crizotinib development in ROS1- and ALK-positive NSCLC.

Abbreviations: ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology annual meeting; BT, breakthrough therapy; BTDR, breakthrough therapy designation request; CoDx, companion diagnostic; FDA, U.S. Food and Drug Administration; FIH, first in human; mDoR, median duration of response; NDA, new drug application; NEJM, *New England Journal of Medicine*; NSCLC, non-small cell lung cancer; ORR, objective response rate; sNDA, presupplemental new drug application.

tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and osimertinib have been shown to benefit patients with drug-sensitive EGFR mutations (present in approximately 10%–15% of patients with lung adenocarcinoma). Crizotinib, ceritinib, and alectinib are FDA approved for patients with NSCLC whose tumors harbor ALK rearrangements (present in approximately 5% of adenocarcinoma NSCLC) [16].

ROS1 represents a receptor tyrosine kinase related to ALK, which is not usually highly expressed in normal lung tissue. The wild-type function of ROS1 is unknown and a natural ligand has not been identified [23]. *ROS1* gene rearrangements were first associated with human cancer in 1987, when they were discovered in a human glioblastoma cell line, and subsequently in 2007 in a cell line derived from a patient with NSCLC [24–26]. The mechanism by which the ROS1 fusion protein is activated remains unclear. This is in contrast to ALK, which, as a fusion protein, becomes activated by dimerization mediated through a domain of the partner protein. However, dimerization of the fusion partner is unlikely to play a major role in activation of the kinase domain, because the majority of fusion partners lack a dimerization domain [27]. Also, unlike ALK-positive NSCLC, where the partner fusion gene is mostly EML4, many partners have been identified for ROS1, including FIG, SLC34A2, CD74, TPM3, SDC4, EZR, LRIG3, KDELR2, CLTC, LIMA1, MSN, TMEM106B, and CCDC6 [21, 28–31]. Most of the rearrangements identified are interchromosomal translocations, except FIG, which is created by a small intrachromosomal deletion rather than a translocation or inversion [32, 33]. ROS1 fusions have also been identified in cholangiocarcinoma, as well as ovarian, gastric, and colorectal cancers [34].

There have been 3 major studies that describe the incidence and natural history of ROS1 rearrangements in patients with NSCLC (across 3,000 patients) and have determined the incidence to be between 0.9% and 1.7% [35–37]. Similar to patients with ALK-positive NSCLC, patients with ROS1-positive mNSCLC tend to be younger, never-smokers, and to have tumors of adenocarcinoma histology with mutually exclusive driver alterations. The median survival in 1 cohort ($n = 18$) of patients with ROS1-positive mNSCLC was 21.8 months versus 20 months for those with ROS1-negative disease [35]. In another cohort ($n = 13$), no difference in overall survival (OS) was observed between the ALK, RET, or ROS1 fusion group compared with the EGFR-mutant group [36].

Crizotinib was first developed as a c-MET inhibitor and later found to have activity against ALK and ROS1. In early clinical development, there were case reports showing that crizotinib demonstrated antitumor activity in patients with ROS1-positive NSCLC [37]. Following these reports, the crizotinib single-arm, dose-finding trial (PROFILE 1001) was expanded to include a ROS1 cohort; it is the largest trial of crizotinib-treated patients with ROS1-positive NSCLC to date. In May 2013, results of crizotinib treatment in 33 patients enrolled in PROFILE 1001 were presented at the American Society of Clinical Oncology (ASCO) annual meeting [38]. Ou et al. reported an objective response rate (ORR) of 56% (95% confidence interval [CI]: 24–65) including 2 complete responses (CRs). Subsequently, Shaw et al. published the updated results of the trial, which included 50 patients [30].

In addition, Mazières et al. reported results of a separate European ROS1 cohort of 32 patients who were treated with crizotinib [39]. The authors conducted a retrospective trial in patients who tested positive for ROS1 rearrangement by fluorescent in situ hybridization (FISH) and had received off-label crizotinib. The ORR was reported to be 80%. Last, Moro-Sibilot et al. reported on the preliminary results of AcSé (the Phase II Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET, or ROS1) in ROS1-positive NSCLC [40]. Of the 29 patients who had clinical

information, 24 were evaluable for response and had an ORR of 63% (95% CI: 41–81). This article summarizes the FDA's approval of crizotinib in ROS1-positive mNSCLC.

Regulatory History

Crizotinib first received accelerated approval in 2011 for the ALK-positive NSCLC indication based on the single-arm trial results of PROFILE 1001 and PROFILE 1005 [41–43]. Subsequently, in 2013, results of the randomized second-line trial, PROFILE 1007, were published [44] and led to the traditional approval of crizotinib for the ALK-positive NSCLC indication [45]. In 2014, the results of PROFILE 1014, a randomized first-line trial in ALK-positive NSCLC were reported and were subsequently added to the U.S. Product Insert (USPI) in 2015 [46].

With respect to the crizotinib ROS1 indication, the FDA first engaged the applicant for discussion regarding a breakthrough therapy designation request (BTDR) and a potential presupplemental new drug application (sNDA) meeting, after learning about the preliminary results presented at the annual ASCO meeting in May 2012, and again with updated results in 2013 [38, 47]. In August 2013, the FDA asked the applicant for an update on the ORR and duration of response (DoR) of the ROS1-positive NSCLC cohort, and recognized the difficulty of conducting a randomized controlled trial (RCT) given the low incidence of ROS1-positive mNSCLC and potential lack of clinical equipoise to randomize patients to a chemotherapy control. During an FDA-initiated meeting with the applicant in October 2013, the FDA recommended that the applicant submit a BTDR, given the unmet medical need in this population, and that the in vitro companion diagnostic assay to detect ROS1 be submitted to the FDA expeditiously. After the publication by Shaw et al. [30], the FDA initiated a second meeting in November 2014, during which the FDA requested an independent radiology review (IRR) of ORR and reconfirmed that the data would be acceptable for sNDA submission and FDA review. Figure 1 illustrates other key regulatory and clinical milestones in the development of crizotinib for mNSCLC.

Trial Design

PROFILE 1001 was a single-arm, multicohort, multicenter, international trial [42, 48]. The trial was initially a dose-finding study, with the protocol later being amended to include specific molecularly defined cohorts. In addition to the ROS1 NSCLC cohort that was initiated in November 2009, the trial included an ALK-positive NSCLC cohort (results of which supported the initial accelerated approval crizotinib), an ALK-negative NSCLC cohort, a *c-MET*-amplified NSCLC cohort, and an enriched other-cancer ALK-, ROS1-, c-MET-positive cohort. A total of 30 patients were initially planned to be enrolled into the ROS1-positive NSCLC cohort, which was later increased to a total of 50 patients to provide a more accurate estimation of efficacy in this patient population. The ROS1-positive cohort consisted of patients with mNSCLC whose tumors were prospectively determined to have *ROS1* genetic rearrangements. Patients with mNSCLC were eligible irrespective of receipt of prior lines of therapy. Other key criteria included having an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, measurable disease, adequate organ function, and no prior treatment with an ALK or c-MET inhibitor. Patients received crizotinib 250 mg by mouth twice daily until disease progression or intolerable drug toxicity.

Table 1. Study demographics and disease characteristics

Characteristics ($N = 50$ patients)	%
Age, years	
Median	53
Range	25–77
Sex	
Female	56
Race	
White	54
Asian	42
Black	4
Smoking	
Never	78
Clinical trial center location	
U.S.	75
South Korea	12.5
Australia	12.5
Histology	
Adenocarcinoma	96
Extent	
Advanced	6
Metastatic	92
ECOG-PS	
0–1	98
Prior treatment for metastatic disease	
Naïve	14
Platinum doublet	80
Assay[a]	
MGH FISH[b]	52
Other FISH[c]	44
RT-PCR	4

Data given as % unless otherwise indicated.
[a]Assays used on tumor specimens to detect ROS1 rearrangements.
[b]Includes two patients who were classified as "non-MGH" but were identified as ROS1 positive via a MGH research ROS1 FISH assay rather than the clinically validated MGH laboratory-developed test at MGH.
[c]Other laboratories included Abbott, Kreatech, Cytocell, and Metasystems.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance scale; FISH, fluorescence in situ hybridization; MGH, Massachusetts General Hospital; RT-PCR, reverse transcriptase-polymerase chain reaction.

ROS1 rearrangement testing was performed primarily by Massachusetts General Hospital (MGH), using a laboratory-developed ROS1 FISH assay, although other local laboratory-developed tests were used that incorporated either ROS1 FISH or a reverse transcriptase polymerase chain reaction assay. The FISH test required at least 15% of a minimum of 50 evaluated nuclei containing a ROS1 gene rearrangement to be classified as ROS1 positive. The major efficacy outcome measure was ORR with an additional DoR outcome measure, according to Response Evaluation Criteria in Solid Tumors version 1.0, as evaluated by an independent radiologic review (IRR) and by the investigator. Patients underwent tumor assessments with computed tomography or magnetic resonance imaging scans of the chest, abdomen, and pelvis every 8 weeks for the first 60 weeks.

Table 2. Key efficacy results for the ROS1 cohort of PROFILE 1001

Efficacy outcome	IRR ($N = 50$)	Investigator assessed ($N = 50$)
Objective response rate, % (95% CI)	66 (51–79)	72 (58–84)
Complete response, no.	1	5
Partial response, no.	32	31
Duration of response, months, median (95% CI)	18.3 (12.7, NR)	NR (14.5, NR)
Treatment-naïve patient responses ($n = 7$)		
Complete response, no.	0	1
Partial response, no.	6	5
Stable disease, no.	1	1

Abbreviations: CI, confidence interval; IRR, independent radiology review; NR, not reached.

Results

A total of 50 patients were enrolled from 8 clinical sites in 3 countries, all of whom received at least 1 dose of crizotinib. Table 1 summarizes the baseline patient demographics and disease characteristics. Further details of the patient population can be found in the Shaw et al. report [30]. At the time of the data cutoff (November 30, 2014), the median duration of crizotinib exposure was 34.4 months. Overall, 30% of patients had died, and 70% of patients were censored. Of the latter, 89% were still in follow-up by the time of the data cutoff.

Efficacy

As shown in Table 2, the ORR by IRR was 66% (95% CI: 51%–79%) with a median DoR of 18.3 months. The ORR according to investigators was 72% (95% CI: 58%–84%). Furthermore, six of the seven patients who were treatment naïve had an objective tumor response. At the time of this analysis, at least 85% of patients had responses of 6 months or longer and at least 18% had responses lasting 2 years or longer.

Toxicity

The most common adverse events occurring in at least 10% of patients treated with crizotinib were vision disorders nausea, edema, vomiting, diarrhea, constipation, dizziness, fatigue, bradycardia, rash, dysgeusia, decreased appetite, and dyspepsia. No grade 3 adverse events occurred at an incidence of greater than 2% and there were no grade 4 adverse events. One serious treatment-related serious adverse reaction of bradycardia occurred, and there were no treatment-related deaths.

Treatment-emergent laboratory abnormalities occurring at an incidence of greater than 10% were aspartate aminotransferase and alanine amino transferase elevations, hypophosphatemia, lymphopenia, neutropenia, and hypokalemia. Table 3 describes the incidence of adverse reactions of the ROS1 cohort and, in comparison, shows the incidence from the ALK-positive crizotinib arm of PROFILE 1007 found in the USPI [49].

Table 3. Common adverse reactions and laboratory abnormalities with ≥10% incidence in the ROS1 cohort and proportion reported for the crizotinib arm of PROFILE 1007 [49]

Adverse reaction or laboratory abnormality	ROS1 cohort of PROFILE 1001, %	Crizotinib arm of ALK PROFILE 1007 trial, % [49]
Vision disorder[a]	92	60
AST elevation	74	61
ALT elevation	66	76
Nausea	58	55
Edema[a]	56	31
Vomiting	52	47
Constipation	46	42
Diarrhea	46	60
Lymphopenia	46	51
Hypophosphatemia	44	28
Dizziness[a]	42	22
Neutropenia	38	49
Fatigue	32	—
Bradycardia[a]	28	5
Rash	28	—
Decreased appetite	24	—
Dysgeusia	24	26
Hypokalemia	14	18
Dyspepsia	12	8

[a]Applicant-derived cluster terms used.
Abbreviations: —, <10% incidence; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Discussion

On March 11, 2016, the FDA granted traditional approval to crizotinib based on a favorable benefit-risk assessment for the treatment of patients with mNSCLC whose tumors are ROS1 positive. Table 4 summarizes the FDA benefit-risk analysis.

In the ROS1 cohort ($n = 50$) of PROFILE 1001, crizotinib demonstrated a clinically meaningful ORR of 66% by IRR and 72% by the investigators. The median duration of response was 18.3 months by IRR. Responses in the ROS1-positive metastatic NSCLC were maintained irrespective of line of therapy. Table 5 shows the ORR, DoR, and other major efficacy outcomes from the randomized ALK-positive crizotinib trials PROFILE 1014 (first line) and PROFILE 1007 (after platinum doublet) in comparison with the ROS1-cohort results [44, 46, 49].

There is limited information available regarding the natural history of ROS1 mNSCLC treated with traditional chemotherapeutic agents. A case series by Bergethon et al. showed that of 1,073 tumors screened, 18 (1.7%) were ROS1 positive; these patients were on average younger and more likely to be nonsmokers [35]. The ROS1-positive tumors were all adenocarcinomas and more likely to be of higher pathologic grade. Importantly, the ROS1-positive group showed no difference in overall survival compared with the ROS1-negative group, suggesting that the natural history of ROS1-positive NSCLC is similar to the unselected population and is likely to have similar ORRs with nontargeted chemotherapeutics, ranging from 10% to 35% depending on line of therapy. Therefore, the ORR of 66% demonstrated the efficacy of crizotinib in ROS1-positive mNSCLC. This ORR observed in this patient population was supported by the long durability of response. Furthermore, the ORR was similar to the ORR in patients with ALK-positive

Table 4. Benefit-risk analysis for crizotinib in the treatment of patients with ROS1-positive mNSCLC

Parameter	Summary
Disease	Patients with mNSCLC whose tumors are positive for ROS1 alterations may have median survival rates of approximately 1 year with no approved targeted therapies.
Unmet medical need	Before crizotinib, patients with ROS1-positive mNSCLC were treated similarly to patients without an identified actionable genomic alteration. Patients who progress after first-line, platinum-doublet-based therapy have few options and are usually treated with standard cytotoxic monotherapy. Given the lack of available targeted therapies for these patients, available therapies in the second-line setting include pemetrexed, docetaxel with or without ramucirumab, and erlotinib, which are associated with relatively low response rates (ORR: 5%–22%) with substantial toxicity. More recently, the PD-1 inhibitors nivolumab and pembrolizumab have demonstrated OS advantages over docetaxel, but may be less effective in patients with oncogene-addicted disease such as EGFR or ALK-positive mNSCLC. The benefit of the PD-1 inhibitors in patients with mNSCLC with driver alterations including ROS1 is unknown.
Clinical benefit	In a prospectively selected ROS1-positive mNSCLC cohort of a single-arm study, crizotinib was associated with an ORR determined by the IRR of 66%, which was durable with a median DoR of 18.3 months; ≥85% of patients had durations of at least 6 months long and ≥64% of patients had responses of 1 year or longer.
Risk	The most common adverse reactions and laboratory abnormalities in patients receiving crizotinib included vision disorder, elevation of AST and ALT leves, nausea, edema, vomiting, constipation, diarrhea, lymphopenia, hypophosphatemia, dizziness, neutropenia, fatigue, bradycardia, and rash. The overall safety profile of crizotinib from the ROS1 cohort was similar to the randomized first- and second-line ALK-positive mNSCLC studies reported in the USPI [49]. There were a total of 4 treatment-related, grade 3, adverse reactions of decreased appetite, QT prolongation, sixth nerve palsy, and vomiting. There was a high incidence (higher than recorded from the ALK-positive trials) of vision disorders; however, they were all grade 1–2.
Uncertainties	The primary uncertainty is the lack of an approved companion diagnostic to reliably select patients with tumors that contain the ROS1 alterations. In the trial, testing was performed primarily by MGH using a laboratory-developed ROS1 FISH assay, and other local laboratory-developed tests were used incorporated either ROS1 FISH or an RT-PCR assay. This uncertainty will be mitigated by a postmarketing commitment by Pfizer to support the availability of an in vitro diagnostic device for the detection of ROS1-positive mNSCLC. Once a companion diagnostic is developed and approved, the drug label will be revised to reflect the new information. Per the guidance for industry [53] , FDA may decide to approve a drug, even if a companion diagnostic device is not yet approved, when the drug is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the drug are so pronounced as to outweigh the risks from the lack of an approved device [54]. The indication statement is another area of uncertainty. Most patients had received previous doublet therapy. However, the radiographic responses in the few ($n = 7$) of the treatment-naïve patients were exceptional, with all but one patient achieving a partial response as best response and the one patient achieving stable disease. The final uncertainties are that the data presented are from a small ($N = 50$) single-arm study and there is the lack of a randomized study demonstrating improvement in PFS or OS. However, the magnitude of the ORR benefit was sufficiently high to limit this uncertainty. Furthermore, the large safety database, including two randomized controlled trials in the ALK-positive mNSCLC, limits the uncertainty about safety.
Conclusions	Crizotinib meets the criteria for traditional approval based on a favorable benefit-risk profile for the treatment of patients with mNSCLC whose tumors are ROS1 positive. Crizotinib demonstrated clinical benefit with an acceptable risk profile and is the first targeted agent for ROS1-positive tumors.

Abbreviations: ALK, anaplastic lymphoma kinase; ALT, alanine amino transferase; AST, aspartate amino transferase; DoR, duration of response; EGFR, epidermal growth factor receptor; FISH, fluorescent in situ hybridization; IRR, independent radiology review; MGH, Massachusetts General Hospital; mNSCLC, metastatic non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; FS, progression-free survival; RT-PCR, reverse transcriptase-polymerase chain reaction; USPI, U.S. Product Insert.

NSCLC. In ALK-positive NSCLC, this large effect on ORR translated into a progression-free survival (PFS) benefit when crizotinib was compared with standard chemotherapy in either the first or second line of treatment.

The adverse reaction profile reported from the single-arm trial was similar to that reported in the USPI for the ALK-positive randomized studies [49]. Of note, the median duration of study treatment with crizotinib in the 50 patients from the ROS1 cohort was more than three times longer that in patients with the ALK-positive subtype [49]. The most notable difference between indications was the frequency of vision disorders in the ROS1 group, which may have been related to the longer exposure to crizotinib; however, the vision disorders were all grade 1 or 2.

When interpreting these data, several uncertainties remain. First, the ROS1-patient experience is limited to 50 patients. Furthermore, the results are from a single-arm trial and no randomized trial has been conducted; thus, no information is available for comparison of PFS or OS. Nevertheless, given the rarity of ROS1-positive metastatic NSCLC and the magnitude of effect of crizotinib on durable ORR in this patient population, RCTs would likely be infeasible and lack clinical equipoise. The magnitude of benefit in terms of durable ORR observed in PROFILE 1001 was sufficiently high to limit this uncertainty. Furthermore, a high ORR has translated into improved PFS in patients with ALK-positive NSCLC. As reported by Blumenthal et al., a meta-analysis conducted by the FDA suggested that in advanced NSCLC, a drug with a large magnitude of effect on ORR may likely result in a large improvement in PFS [50]. There may be scenarios in which conducting RCTs is not possible and nonrandomized trials may be more appropriate. The development of novel therapeutics with well-understood mechanisms of action, well-defined patient populations, and high magnitudes

Table 5. Summary of key evidence for the use of crizotinib in patients with metastatic NSCLC with whose tumors are either ALK or ROS1 positive

	ORR and DoR crizotinib vs. chemotherapy		PFS crizotinib vs. chemotherapy	
Study	**IRR ORR, % (95% CI)**	**DoR. months (95% CI)**	**HR (95% CI)**	**Median no. of months**
ROS1+ Cohort PROFILE 1001, $N = 50$	66 (51–79) vs. N/A	18.3 (12.7–NR) vs. N/A	N/A	N/A
$IC_{50} = 11$ nM for crizotinib in ROS1+ [55]				
First-line ALK+ PROFILE 1014, $N = 343$	74 (67–81) vs. 45 (37–53)	11.3 (8.1–13.8) vs. 5.3 (4.1–5.8)	0.45 (0.35–0.60) $p < .001$	10.9 vs. 7.0
>Second-line ALK+ PROFILE 1007, $N = 347$	65 (58–72) vs. 20 (14–26)	7.4 (6.1–9.7) vs. 5.6 (3.4–8.3)	0.49 (0.37–0.64) $p < .001$	7.7 vs. 3.0
$IC_{50} = 24$ nM for crizotinib in ALK+ [55]				

Abbreviations: ALK, anaplastic lymphoma kinase; DoR, duration of response; HR, hazard ratio; IC_{50}, median inhibitory concentration; IRR, independent radiology review; N/A, not applicable; NSCLC, non-small cell lung cancer; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

of durable responses have led to ORR as a potential endpoint for regulatory approval [51, 52]. In addition, the established efficacy and safety profile of crizotinib in two RCTs in ALK-positive mNSCLC further mitigated the uncertainty surrounding this approval.

The second important consideration during the review was the line of therapy to include as an indication for crizotinib in ROS1 mNSCLC. Most patients in the cohort had received previous treatment for their mNSCLC (mostly platinum-doublet therapy). However, best overall responses in the seven patients who were treatment naïve were high (six PRs and one stable disease). These responses were reassuring that the benefit of crizotinib for patients with ROS1 rearrangements appeared to be independent of line of therapy.

A final review issue was the lack of a concomitant approval of an in vitro companion diagnostic able to detect ROS1 rearrangements in tissue specimens. In the current trial, different assays were used to evaluate ROS1 gene rearrangement, most consisting of a FISH assay. As outlined in the FDA's final guidance [53], the FDA may approve a drug before approval of a companion diagnostic device when the drug is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the drug outweigh the risks from the lack of a contemporaneously approved device. This approval presented a unique circumstance in which a high response was observed in a rare patient population with a uniformly fatal disease. Therefore, the FDA believed it was appropriate to approve crizotinib for ROS1-positive NSCLC while a device was under development. Until a companion diagnostic is approved, clinicians should use an analytically validated test with acceptable performance characteristics to reliably detect ROS1 rearrangements in mNSCLC tumor specimens. Coincident with the approval, the applicant agreed to a postmarketing commitment to support the availability of an in vitro companion diagnostic device for the detection of ROS1 rearrangements in tumors from patients with mNSCLC. Once a companion diagnostic test to detect ROS1 rearrangements in NSCLC tissue specimens and identify patients eligible for treatment with crizotinib is developed and approved by the FDA, then the drug label will be revised to reflect the new information.

Conclusion

The approval of crizotinib for patients with ROS1-positive metastatic NSCLC is the first for this indication. This new era of targeted treatment for ROS1-positive NSCLC is similar to when crizotinib was first approved for ALK-positive NSCLC. The FDA granted traditional approval for crizotinib to treat this very rare and fatal disease, given the large magnitude of durable responses, leveraging the safety and efficacy data from the ALK-positive RCTs. This approval highlights an example where a nonrandomized trial was appropriate for traditional approval.

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Disclosures

The authors indicated no financial relationships.

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