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Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

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Abstract

BACKGROUND—Chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (*ROS1*) define a distinct molecular subgroup of non–small-cell lung cancers (NSCLCs) that may be susceptible to therapeutic ROS1 kinase inhibition. Crizotinib is a small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and another proto-oncogene receptor tyrosine kinase, MET.

METHODS—We enrolled 50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement in an expansion cohort of the phase 1 study of crizotinib. Patients were treated with crizotinib at the standard oral dose of 250 mg twice daily and assessed for safety, pharmacokinetics, and response to therapy. *ROS1* fusion partners were identified with the use of next-generation sequencing or reverse-transcriptase–polymerase-chain-reaction assays.

RESULTS—The objective response rate was 72% (95% confidence interval [CI], 58 to 84), with 3 complete responses and 33 partial responses. The median duration of response was 17.6 months (95% CI, 14.5 to not reached). Median progression-free survival was 19.2 months (95% CI, 14.4 to not reached), with 25 patients (50%) still in follow-up for progression. Among 30 tumors that were tested, we identified 7 *ROS1* fusion partners: 5 known and 2 novel partner genes. No correlation was observed between the type of *ROS1* rearrangement and the clinical response to

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crizotinib. The safety profile of crizotinib was similar to that seen in patients with *ALK*-rearranged NSCLC.

CONCLUSIONS—In this study, crizotinib showed marked antitumor activity in patients with advanced *ROS1*-rearranged NSCLC. *ROS1* rearrangement defines a second molecular subgroup of NSCLC for which crizotinib is highly active.

The *ROS1* oncogene encodes an orphan receptor tyrosine kinase related to anaplastic lymphoma kinase (ALK), along with members of the insulin-receptor family.[1] First discovered as the oncogene product of an avian sarcoma RNA tumor virus,[2–4] ROS1 (ROS1 proto-oncogene receptor tyrosine kinase) is activated by chromosomal rearrangement in a variety of human cancers, including non–small-cell lung cancer (NSCLC), cholangiocarcinoma, gastric cancer, ovarian cancer, and glioblastoma multiforme.[5–9] Rearrangement leads to fusion of a portion of ROS1 that includes the entire tyrosine kinase domain with 1 of 12 different partner proteins.[10] The resulting ROS1 fusion kinases are constitutively activated and drive cellular transformation. Whether the various ROS1 fusion kinases may have different oncogenic properties is unknown.

ROS1 rearrangements occur in approximately 1% of patients with NSCLC.[11] Of the estimated 1.5 million new cases of NSCLC worldwide each year, approximately 15,000 may be driven by oncogenic *ROS1* fusions. As with *ALK* rearrangements, *ROS1* rearrangements are more commonly found in patients who have never smoked or have a history of light smoking and who have histologic features of adenocarcinoma.[11,12] However, at the genetic level, *ALK* and *ROS1* rearrangements rarely occur in the same tumor, with each defining a unique molecular subgroup of NSCLC.[11]

Several lines of evidence suggest that ROS1 may represent another therapeutic target of the ALK inhibitor crizotinib (Xalkori, Pfizer). First, the kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites. Crizotinib binds with high affinity to both ALK and ROS1, which is consistent with this homology.[13] Second, in cell-based assays for inhibition of autophosphorylation of different kinase targets, both ALK and ROS1 are sensitive to crizotinib, with a half-maximal inhibitory concentration of 40 to 60 nM.[14] Third, in cell lines expressing *ROS1* fusions, crizotinib potently inhibits ROS1 signaling and cell viability.[12,15,16] Finally, case reports have described marked responses to crizotinib in patients with *ROS1*-rearranged NSCLC.[12,17] Here we report the efficacy and safety of crizotinib in patients with advanced, *ROS1*-rearranged NSCLC.

METHODS

PATIENTS

Eligible patients had histologically confirmed, advanced NSCLC with a *ROS1* rearrangement. In 49 of 50 patients (98%), we identified the *ROS1* rearrangement using break-apart fluorescence in situ hybridization (FISH).[12,17] In the remaining patient, we identified the *ROS1* rearrangement using a reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. We used FISH results that were obtained at most of the participating sites. All patients with positive results on FISH had more than 15% split signals. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group

performance status of 0 to 2 (on a scale of 0 to 5, with 0 indicating that the patient is fully active and able to carry on all predisease activities without restriction and 5 indicating that the patient has died),[18] adequate organ function, and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[19] (For details, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

The protocol, which is available at NEJM.org, was approved by the institutional review board or independent ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

STUDY DESIGN AND TREATMENT

This phase 1 study was originally designed to include an initial dose-escalation phase, followed by an expansion phase in which the maximum dose established in the initial phase would be evaluated in molecularly defined cohorts of patients.[20] Details on the dose-escalation phase have been reported previously,[21] as have efficacy and safety data from the ALK-positive expansion cohort.[20,22] In November 2009, the study was amended to include an expansion cohort of patients with advanced, *ROS1*-rearranged NSCLC. The primary end point of this expansion study was the response rate.

Crizotinib was administered orally at the standard dose of 250 mg twice daily in continuous 28-day cycles. Treatment continued until the occurrence of RECIST-defined disease progression or clinical deterioration, unacceptable toxic effects, withdrawal from the study, or death. In patients with RECIST-defined progression, the study treatment could be continued at the investigator's discretion and with approval from the sponsor.

STUDY ASSESSMENTS

Patients underwent baseline tumor imaging, with computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis. Brain and bone scans were obtained at baseline if disease at these sites was suspected. Tumor assessments were performed by the investigators every 8 weeks until RECIST-defined disease progression; starting with cycle 15, tumor assessments could be performed every 16 weeks, as determined by the investigator. All tumor responses were confirmed at least 4 weeks after the initial response. Adverse events were assessed from the time informed consent was obtained until at least 28 days after the last dose of crizotinib was administered. All adverse events were classified and graded with the use of the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). The data-cutoff date was April 11, 2014, for safety and pharmacokinetics data and May 16, 2014, for efficacy data.

MOLECULAR ANALYSES

In patients with sufficient tumor tissue available, we performed additional molecular analyses. Formalin-fixed, paraffin-embedded tumors were screened for *ALK* rearrangement with the use of a break-apart FISH assay.[20] Tumors were also screened for amplification of

MET, a gene encoding another proto-oncogene receptor tyrosine kinase, with the use of a dual-color FISH probe (Repeat-Free Poseidon *C-MET* [7q31] probe, Kreatech) and a copy-number control probe (centromere chromosome 7 gene [*CEP7*], Abbott-Vysis). In 30 patients, tumor tissue or nucleic acid was available for molecular characterization of the *ROS1* rearrangement. For 27 of these patients, we performed targeted next-generation sequencing with the use of anchored multiplex PCR, as described previously.[23] This assay detects fusion transcripts involving *ALK* (exons 19 through 22), *ROS1* (exons 31 through 37), and rearranged during transfection proto-oncogene (*RET*) (exons 8 through 13). For the remaining 3 patients, we used RT-PCR to detect specific *ROS1* fusion transcripts.[17]

STUDY OVERSIGHT

The study was designed jointly by the investigators and representatives of the sponsor, Pfizer. The sponsor collected and analyzed the data. The first author wrote the first draft of the manuscript. All the authors were involved in the data analysis and manuscript preparation and vouch for the completeness and accuracy of the data and analyses and for the adherence of the study to the protocol. No one who is not listed as an author contributed to the writing of the manuscript.

STATISTICAL ANALYSIS

We initially determined that we would need to enroll 30 patients in order to achieve a power of at least 85% to test the null hypothesis that the rate of response to crizotinib would be 10% or less, versus the alternative hypothesis that the response rate would be more than 10%, at a one-sided alpha level of 0.05 and with the use of a single-stage design. For the alternative hypothesis, the response rate was assumed to be 30%. As of April 2012, there were eight responses (among 14 patients who could be evaluated), which exceeded the six responses required to reject the null hypothesis.[14] To permit a more accurate assessment of the efficacy and safety of crizotinib in this population, we expanded the sample size to a maximum of 50 patients. The overall response rate was similar for the first 30 patients who were enrolled (67%) and the additional 20 patients who were enrolled (80%).

We used a Kaplan–Meier analysis of time-to-event data to estimate median event times and the Brookmeyer–Crowley method to calculate two-sided 95% confidence intervals. All analyses were performed with the use of SAS statistical software, version 9.2 (SAS Institute).

RESULTS

PATIENTS

From October 2010 through August 2013, we enrolled 50 patients with advanced NSCLC in the ROS1 expansion cohort of the phase 1 study of crizotinib. Table 1 summarizes the clinicopathological characteristics of all 50 patients. The majority of patients had never smoked and had histologic features of adenocarcinoma. Most patients (86%) had received at least one previous line of standard therapy for advanced NSCLC (Table S1 in the Supplementary Appendix).

In 49 of the 50 patients (98%), we used a break-apart FISH assay to identify the presence of a *ROS1* rearrangement. In 1 of these 49 patients, an atypical *ROS1* FISH pattern was noted (isolated 5′ green signal), and next-generation sequencing subsequently revealed normal, nonrearranged *ROS1*. In another patient, the tumor was positive for both *ROS1* and *ALK* rearrangement on the basis of FISH, but next-generation sequencing revealed only an *EML4-ALK* fusion and no *ROS1* rearrangement. Among an additional 32 *ROS1*-positive tumors tested for *ALK* rearrangement, none were positive. Among 15 *ROS1* FISH-positive tumors tested for *MET* amplification with the use of FISH, 1 was positive, with a *MET*-to-*CEP7* ratio of 5.34, whereas the remaining 14 were negative. (A ratio of *MET* to the control of more than 2.0 is an indicator of copy-number gain.)

EFFICACY

Among the 50 study patients, 3 patients (6%) had a complete response, 33 patients (66%) had a partial response, and 9 patients (18%) had stable disease as their best response (Fig. 1A, and Table S2 in the Supplementary Appendix). The overall response rate was 72% (95% confidence interval [CI], 58 to 84). The median time to the first response was 7.9 weeks (range, 4.3 to 32.0) (Fig. 1B, and Table S2 in the Supplementary Appendix). At the time of data cutoff, 23 of the 36 responses (64%) were ongoing (Fig. 1C). The estimated median duration of response was 17.6 months (95% CI, 14.5 to not reached [NR]) (Table S2 in the Supplementary Appendix).

Three of the 50 patients (6%) had evidence of progressive disease on the first restaging scans. For 1 of the 3 patients, results on FISH were atypical, and next-generation sequencing was negative for *ROS1* rearrangement, as noted above. A second patient, whose tumor was positive for *ROS1* rearrangement, had discontinued crizotinib for 6 weeks before the first restaging scans because of bowel perforation that was thought to be related to glucocorticoid use and preexisting diverticular disease. This patient was later able to resume treatment with crizotinib and subsequently had a 62% reduction in the tumor burden. For the third patient, FISH results were positive for *ROS1* rearrangement, but the first restaging scans showed an increase in the tumor burden of 26%.

Among the 50 patients, the median duration of treatment was 64.5 weeks (range, 2.3 to 182.0), and 30 patients (60%) continued to receive crizotinib after the data cutoff date. Median progression-free survival was 19.2 months (95% CI, 14.4 to NR) (Fig. 2). Data for 27 patients (54%) were censored, including data for 25 patients (50%) undergoing follow-up for progression. Median follow-up for overall survival was 16.4 months (95% CI, 13.8 to 19.8). Nine of the 50 patients (18%) had died by the time of data cutoff. The overall survival rate at 12 months was 85% (95% CI, 72 to 93); the median had not been reached.

ADVERSE EVENTS

The safety profile of crizotinib in this study was similar to that reported previously.[22,24] Treatment-related adverse events (as determined by the investigators) that were seen in at least 10% of the patients are listed in Table 2; the most common events were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (40%), constipation (34%), vomiting (34%), an elevated aspartate aminotransferase level (22%), fatigue (20%),

dysgeusia (18%), and dizziness (16%). Of the 388 treatment-related adverse events that were reported, 365 (94%) were grade 1 or 2. Of the 42 visual-impairment events that were reported, all were grade 1; they were often described as brief image persistence triggered by dark-to-light adaptation, as reported previously.[22] One patient (2%) discontinued crizotinib because of treatment-related nausea.

The most common treatment-related grade 3 adverse events, reported in at least 4% of the patients, were hypophosphatemia (10%), neutropenia (10%), and an elevated alanine aminotransferase level (4%). There were no treatment-related grade 4 or five adverse events. Grade 4 adverse events that were not deemed to have been related to treatment were reported in 4 patients: pulmonary embolism, hypoxemia, hypotension, and pericardial effusion. There were five deaths, all of which were due to disease progression and were considered to be unrelated to treatment. There were no serious adverse events or deaths in the 5-week period between the cutoff date for safety data and the cutoff date for efficacy data.

MOLECULAR CHARACTERIZATION OF *ROS1* REARRANGEMENTS

We used a targeted next-generation sequencing assay or an RT-PCR assay to identify *ROS1* fusion partners in available tumor specimens. A total of 30 samples were tested, 27 with the use of next-generation sequencing and 3 with the use of RT-PCR. Of the 27 samples tested by means of next-generation sequencing, 22 had a specific *ROS1* rearrangement. Among the remaining 5 samples, the assay failed in 1 and was negative for *ROS1* rearrangement in 4. In 1 of the 4 negative samples, a different oncogenic fusion gene, *EML4-ALK*, was identified, and FISH results were positive for *ALK*, suggesting that results on FISH were falsely positive for *ROS1*. In a second negative sample, FISH results were atypical and were probably not indicative of a *ROS1* rearrangement. In the remaining two samples, the failure to detect *ROS1* fusions may have been due to the limited quantity of tumor material.

The most common *ROS1* fusion partner that we identified was the gene encoding CD74, which was present in 11 of 25 samples (44%); other partner genes included *SDC4* (in 4 tumors), *EZR* (in 4 tumors), *SLC34A2* (in 3 tumors), and *TPM3* (in 1 tumor), all of which have previously been identified as *ROS1* fusion partners. Using next-generation sequencing, we also discovered 2 novel partners, *LIMA1* (LIM domain and actin binding 1) and *MSN* (moesin).[23,25,26] The predicted structures of both novel ROS1 fusion proteins are shown in Figure S1 in the Supplementary Appendix. Tumor responses were observed regardless of the *ROS1* fusion partner (Fig. S2 in the Supplementary Appendix). There was also no apparent correlation between the specific *ROS1* rearrangement and the duration of crizotinib treatment (Fig. 3). However, given the number of different *ROS1* fusions, the relationship between *ROS1* fusion and the response to crizotinib is difficult to assess on the basis of this small study.

DISCUSSION

We found that crizotinib had potent antitumor activity in patients who had advanced NSCLC with a *ROS1* rearrangement. These results validate ROS1 as a therapeutic target in *ROS1*-rearranged lung cancers.

In preclinical studies, cell lines expressing oncogenic fusions of either ALK or ROS1 were highly sensitive to crizotinib.[12,14,16] The dual inhibition of ALK and ROS1 by the same small molecule is probably due to structural similarities between these two closely related tyrosine kinases. The three-dimensional structures of the sites of crizotinib binding with ALK and ROS1 are similar (Fig. S3 in the Supplementary Appendix).[27,28] Most of the amino acid differences between ALK and ROS1 are conservative or do not contact crizotinib. Only one difference, a valine-to-leucine difference at codon 1180 of ALK and codon 2010 of ROS1, is predicted to have an effect on binding, since the larger leucine in ROS1 extends closer to and makes more direct contact with crizotinib. The functional significance of this and other amino acid differences has not yet been studied.

Clinically, although *ALK* and *ROS1* rearrangements define different subgroups of NSCLC, there are several important similarities between the two disease subtypes. Patients with *ALK*-rearranged NSCLC and those with *ROS1*-rearranged NSCLC have similar clinicopathological features. In addition, the *ALK*-rearranged and *ROS1*-rearranged disease subtypes were both highly responsive to crizotinib, with similar times to the first response (median, 7.9 weeks for both) and similar response rates (61% and 72%, respectively).[22] For both *ALK*-rearranged NSCLC and *ROS1*-rearranged NSCLC, responses were observed independently of the specific type of rearrangement.[20]

One apparent difference between *ALK* rearrangement and *ROS1* rearrangement in patients with NSCLC may lie in the durability of the response to crizotinib. In the ALK expansion cohort of 143 patients, the median duration of response was 49.1 weeks, and the median progression-free survival was 9.7 months.[22] In contrast, the estimated median duration of response in the ROS1 cohort was longer, at 17.6 months (75.9 weeks), and the median progression-free survival was 19.2 months. This estimate is still preliminary, since half the patients remain in follow-up for progression. The apparent difference in efficacy is not attributable to differences in drug exposure, since the mean trough plasma levels of crizotinib were similar in patients with *ALK* rearrangements and in those with *ROS1* rearrangements (Fig. S4 in the Supplementary Appendix).

Several factors may account for the longer responses observed in *ROS1*-rearranged NSCLC. First, crizotinib may be a more potent inhibitor of ROS1 than of ALK, leading to more effective target inhibition and more durable responses. In support of this hypothesis, in vitro measurements of the equilibrium dissociation constant (K_d) with the use of isothermal titration calorimetry indicated that crizotinib binds significantly more tightly to ROS1 than to ALK, with values of 0.4 nM and 4.4 nM, respectively.[13] This finding is consistent with cell-viability assays showing that crizotinib is approximately five times as potent against ROS1 as against ALK in Ba/F3 cells engineered to express either *CD74-ROS1* or *EML4-ALK*.[14] Second, *ROS1* rearrangement could in theory confer a more favorable prognosis regardless of treatment, perhaps because of the intrinsic biology of ROS1-positive NSCLC. However, in several small series, overall survival among patients with *ROS1* rearrangement was similar to that among patients without *ROS1* rearrangement.[12,29]

As in patients with *ALK*-rearranged NSCLC, resistance to crizotinib eventually develops in patients with *ROS1*-rearranged NSCLC. As of the data cutoff date, disease progression or

death had occurred in 23 of 50 patients (46%). Two distinct mechanisms of resistance to crizotinib in *ROS1*-rearranged NSCLC have been described: a secondary mutation that hinders drug binding[27] and activation of epidermal growth factor receptor, which enables cancer cells to bypass crizotinib-mediated inhibition of ROS1 signaling.[30] Recently, more potent, structurally distinct, next-generation ALK inhibitors have been shown to effectively overcome crizotinib resistance in *ALK*-rearranged NSCLC.[31–33] Some, but not all, of these new ALK inhibitors also target ROS1.[33,34] Whether *ROS1*-rearranged NSCLC will also be susceptible to sequential therapy with increasingly potent inhibitors remains to be determined.

In conclusion, *ROS1* rearrangement defines a second molecular subgroup of NSCLC for which crizotinib is highly active. In the majority of patients, crizotinib induced durable clinical responses and was associated with grade 2 or lower toxic effects. These results highlight the importance of screening for this genetic alteration in patients with advanced NSCLC. Although FISH was used in this study, other diagnostic methods have been proposed, and further work is required to establish the most effective screening strategy for *ROS1* rearrangement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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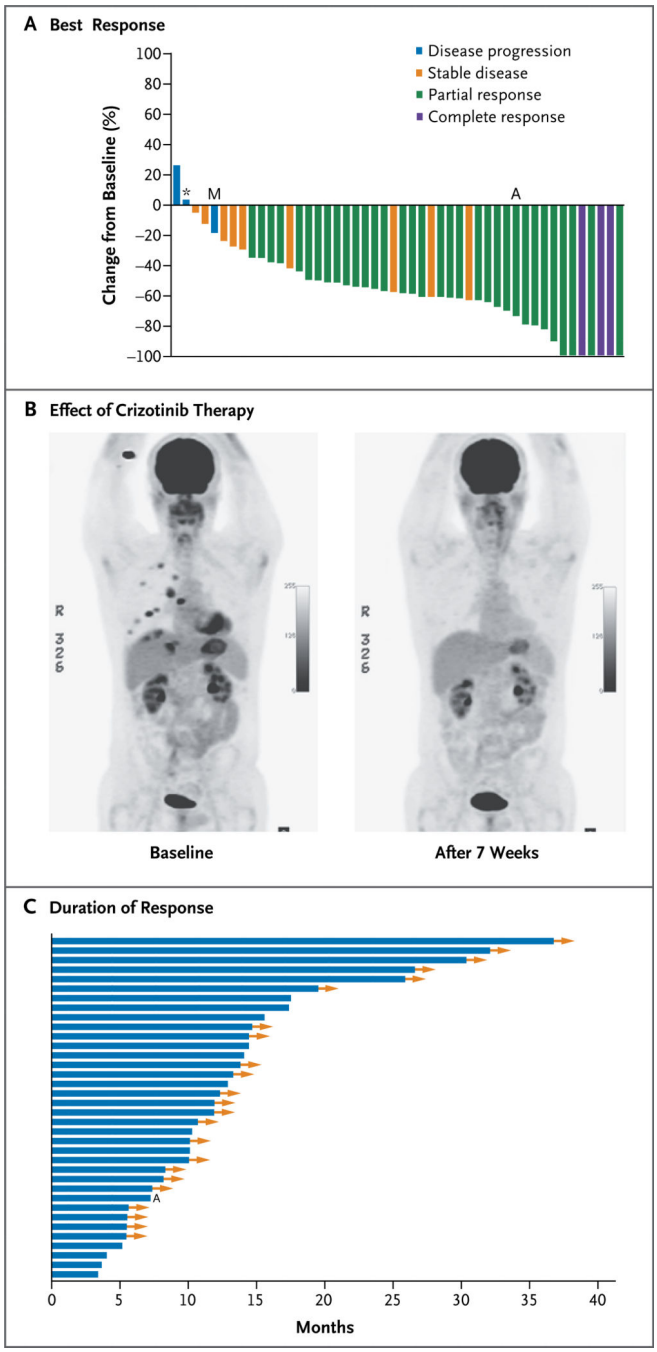

Figure 1. Tumor Responses to Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Panel A shows the best response of patients treated with crizotinib in the ROS1 expansion cohort. The bars indicate best percent change in the target tumor burden from baseline. Two patients died within 6 weeks after receiving the first dose of crizotinib, so the tumor response was unknown. The asterisk indicates the tumor burden in a patient who had an atypical result on fluorescence in situ hybridization (FISH) for *ROS1* (an isolated 5′ green signal). Since this tumor was subsequently shown to be negative for *ROS1* rearrangement on next-generation sequencing, an isolated green signal is probably not indicative of a *ROS1*

rearrangement. The letter A denotes a FISH-positive tumor that was negative for *ROS1* rearrangement on next-generation sequencing but positive for *ALK* rearrangement on FISH and next-generation sequencing. The letter M denotes a FISH-positive tumor that was also positive for *MET* amplification on FISH (*MET*-to-*CEP7* ratio, 5.34). Panel B shows positron-emission tomographic scans obtained at baseline (left panel) and after 7 weeks of crizotinib treatment (right panel) in a representative patient. On the basis of Response Evaluation Criteria in Solid Tumors, this patient had a partial response (a decrease in tumor burden of 46%), which was ongoing at the time of data cutoff. Panel C shows the duration of response among the 36 patients with a partial or complete response. Arrows indicate patients who had an ongoing response at the time of data cutoff. The letter A indicates that the patient's tumor was positive for *ALK* rearrangement.

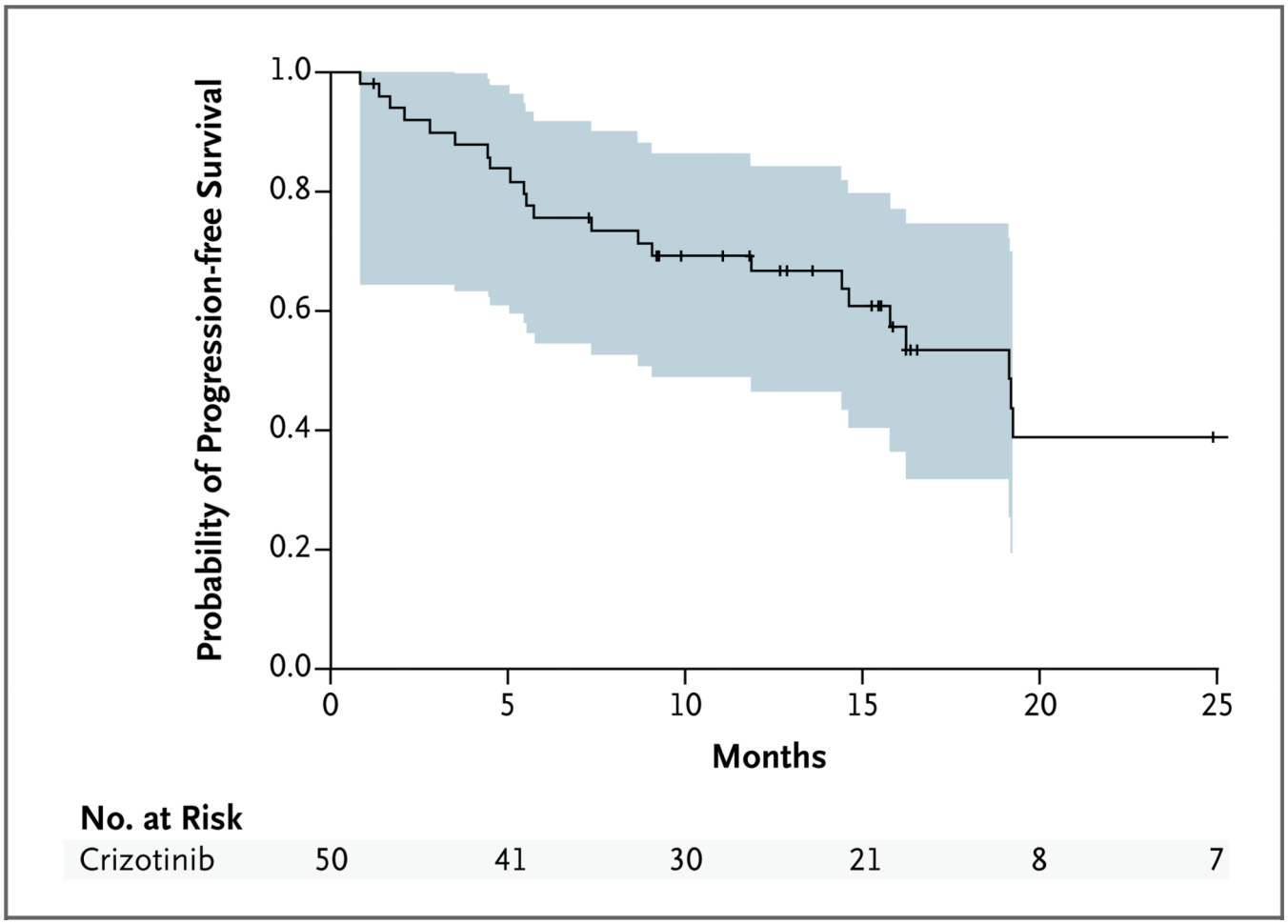

Figure 2. Progression-free Survival

Shown is the Kaplan–Meier curve for estimated progression-free survival in the ROS1 cohort of patients treated with crizotinib. Progression-free survival was defined as the time from the administration of the first dose of crizotinib to objective disease progression or death from any cause. Data from 27 patients were censored; of these patients, 25 remained in follow-up for progression-free survival at the time of data cutoff. The shaded area represents the 95% Hall–Wellner confidence limits. Vertical lines on the survival curve indicate censoring of data.

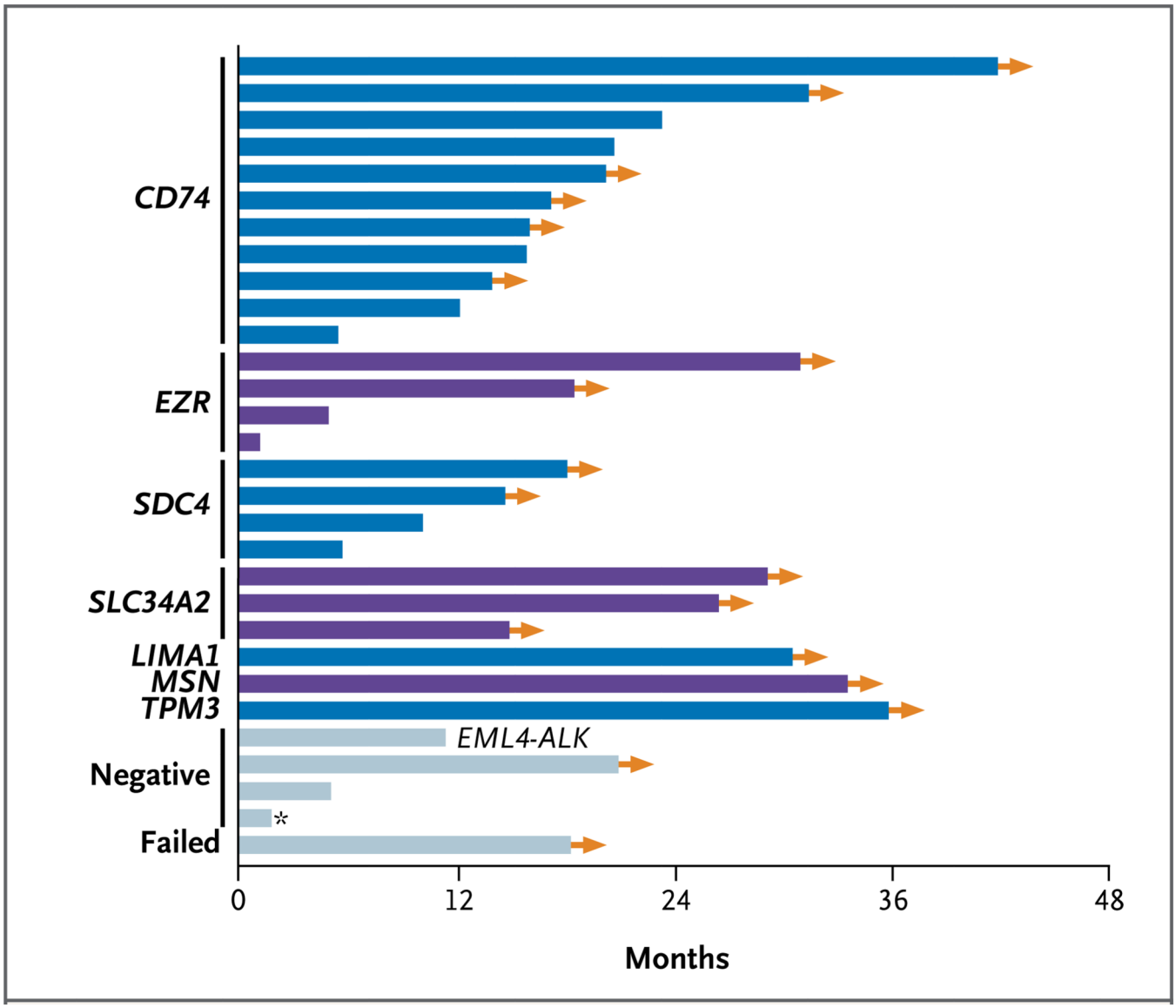

Figure 3. Duration of Treatment and *ROS1* Fusion Partners

The duration of crizotinib treatment is shown for the 25 patients in whom the *ROS1* fusion partner was identified with the use of either a next-generation sequencing assay or a reverse-transcriptase–polymerase-chain-reaction assay. Patients are grouped according to the *ROS1* fusion partner, as indicated on the left. The four patients with negative results on next-generation sequencing and the one patient in whom next-generation sequencing failed are indicated by gray bars. One of the four patients with negative results was positive for *EML4-ALK* rearrangement, as indicated. One patient had negative results on next-generation sequencing and had an atypical FISH pattern (as indicated by an asterisk). The arrows indicate patients who were continuing to receive crizotinib at the time of data cutoff.

Table 1

Characteristics of the Patients at Baseline.

Characteristic	ROS1 Cohort (N = 50)
Age — yr	
Median	53
Range	25–77
Sex — no. (%)	
Male	22 (44)
Female	28 (56)
Race — no. (%)*	
White	27 (54)
Asian	21 (42)
Other	2 (4)
Smoking status — no. (%)	
Never smoked	39 (78)
Former smoker	11 (22)
Histologic type — no. (%)	
Adenocarcinoma	49 (98)
Squamous-cell carcinoma	1 (2)
ECOG performance status — no. (%)†	
0	22 (44)
1	27 (54)
2	1 (2)
Previous regimens for advanced disease — no. (%)	
0	7 (14)
1	21 (42)
>1	22 (44)

*Race was determined by the investigators.

†Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher numbers indicating increasing impairment in activities of daily living.

Table 2

Adverse Events.*

Adverse Event	Grade 1	Grade 2	Grade 3	All Grades
	number of patients (percent)			
Visual impairment	41 (82)	0	0	41 (82)
Diarrhea	21 (42)	1 (2)	0	22 (44)
Nausea	18 (36)	2 (4)	0	20 (40)
Peripheral edema	15 (30)	5 (10)	0	20 (40)
Constipation	16 (32)	1 (2)	0	17 (34)
Vomiting	15 (30)	1 (2)	1 (2)	17 (34)
Elevated aspartate aminotransferase	9 (18)	1 (2)	1 (2)	11 (22)
Fatigue	9 (18)	1 (2)	0	10 (20)
Dysgeusia	9 (18)	0	0	9 (18)
Dizziness	8 (16)	0	0	8 (16)
Elevated alanine aminotransferase	3 (6)	2 (4)	2 (4)	7 (14)
Hypophosphatemia	0	2 (4)	5 (10)	7 (14)
Decreased testosterone†	2 (9)	1 (5)	0	3 (14)
Neutropenia	1 (2)	0	5 (10)	6 (12)
Dyspepsia	5 (10)	0	0	5 (10)
Sinus bradycardia	5 (10)	0	0	5 (10)

*Listed are adverse events that were reported in at least 10% of the 50 study patients and that were deemed by the investigators to be related to treatment. No grade 4 or grade 5 treatment-related adverse events were reported.

†The frequency of a decreased testosterone level was calculated in 22 men only. The protocol did not require the testing of testosterone, so not all men were evaluated.