Published in final edited form as:
Lancet Oncol. 2012 October ; 13(10): 1011–1019. doi:10.1016/S1470-2045(12)70344-3.

Activity and safety of crizotinib in patients with *ALK*-positive non-small-cell lung cancer: updated results from a phase 1 study

D Ross Camidge, MD, **Prof Yung-Jue Bang, MD**, **Eunice L Kwak, MD**, **A John Iafrate, MD**, **Prof Marileila Varella-Garcia, PhD**, **Prof Stephen B Fox, PhD**, **Gregory J Riely, MD**, **Benjamin Solomon, MBBS**, **Sai-Hong I Ou, MD**, **Prof Dong-Wan Kim, MD**, **Ravi Salgia, MD**, **Panagiotis Fidias, MD**, **Jeffrey A Engelman, MD**, **Leena Gandhi, MD**, **Pasi A Jänne, MD**, **Daniel B Costa, MD**, **Geoffrey I Shapiro, MD**, **Patricia LoRusso, DO**, **Katherine Ruffner, MD**, **Patricia Stephenson, ScD**, **Yiyun Tang, PhD**, **Keith Wilner, PhD**, **Jeffrey W Clark, MD**, and **Alice T Shaw, MD**

University of Colorado Denver, Aurora, CO, USA (D R Camidge MD, Prof M Varella-Garcia PhD); Seoul National University College of Medicine, Seoul, South Korea (Prof Y-J Bang MD, Prof D-W Kim MD); Massachusetts General Hospital, Boston, MA, USA (E L Kwak MD, A J Iafrate MD, P Fidias MD, J A Engelman MD, J W Clark MD, A T Shaw MD); Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (Prof S B Fox PhD, B Solomon MBBS); Memorial Sloan-Kettering Cancer Center, New York, NY, USA (G J Riely MD); University of California at Irvine, Irvine, CA, USA (S-H I Ou MD); University of Chicago, Chicago, IL, USA (Prof R Salgia MD); Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA (L Gandhi MD, P A Jänne MD, G I Shapiro MD); Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA (D B Costa MD); Karmanos Cancer Institute, Detroit, MI, USA (P LoRusso DO); Pfizer Oncology, La Jolla, CA, USA (K Ruffner MD, Y Tang PhD, K Wilner PhD); Rho, Chapel Hill, NC, USA (P Stephenson ScD)

Summary

Background—*ALK* fusion genes occur in a subset of non-small-cell lung cancers (NSCLCs). We assessed the tolerability and activity of crizotinib in patients with NSCLC who were prospectively identified to have an *ALK* fusion within the first-in-man phase 1 crizotinib study.

Methods—In this phase 1 study, patients with *ALK*-positive stage III or IV NSCLC received oral crizotinib 250 mg twice daily in 28-day cycles. Endpoints included tumour responses, duration of response, time to tumour response, progression-free survival (PFS), overall survival at 6 and 12 months, and determination of the safety and tolerability and characterisation of the plasma

Correspondence to: Dr D Ross Camidge, Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Mailstop F704, Room ACP 1058, Aurora, CO 80045, USA, ross.camidge@ucdenver.edu.

Contributors

The phase 1 clinical trial was designed by Pfizer. DRC, PLR, KR, PS, YT, and KW analysed the data. Y-JB, ELK, AJI, MV-G, SBF, GJR, BS, S-HIO, D-WK, RS, PF, JAE, LG, PAJ, DBC, GIS, JWC, and ATS collected data. DRC wrote the report. All authors read and provided comments on the report.

Conflicts of interest

DRC, Y-JB, ELK, AJI, BS, S-HIO, D-WK, PAJ, DBC, PLR, and ATS received honoraria or consulting fees from Pfizer. ELK, GJR, BS, and JWC received research funding from Pfizer. AJI, MV-G, and GJR received honoraria or consulting fees from Abbott Molecular. GJR, LG, and ATS received honoraria or consulting fees from Chugai. GJR received research funding from Chugai, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Infinity Pharmaceuticals, and Merck; and honoraria or consulting fees from Daiichi and Tragara. GJR and ATS received honoraria or consulting fees from Novartis and Ariad and research funding from Novartis. PF received honoraria or consulting fees from Genentech. DBC received honoraria or consulting fees from AstraZeneca and Roche. KR, YT, and KW are employees and stockholders of Pfizer. ATS received research funding from AstraZeneca. SBF, RS, JAE, GIS, and PS declare that they have no conflicts of interest.

pharmacokinetic profile of crizotinib after oral administration. Responses were analysed in evaluable patients and PFS and safety were analysed in all patients. This study is registered with ClinicalTrials.gov, number NCT00585195.

Findings—Between Aug 27, 2008, and June 1, 2011, 149 *ALK*-positive patients were enrolled, 143 of whom were included in the response-evaluable population. 87 of 143 patients had an objective response (60·8%, 95% CI 52·3–68·9), including three complete responses and 84 partial responses. Median time to first documented objective response was 7·9 weeks (range 2·1–39·6) and median duration of response was 49·1 weeks (95% CI 39·3–75·4). The response rate seemed to be largely independent of age, sex, performance status, or line of treatment. Median PFS was 9·7 months (95% CI 7·7–12·8). Median overall survival data are not yet mature, but estimated overall survival at 6 and 12 months was 87·9% (95% CI 81·3–92·3) and 74·8% (66·4–81·5), respectively. 39 patients continued to receive crizotinib for more than 2 weeks after progression because of perceived ongoing clinical benefit from the drug (12 for at least 6 months from the time of their initial investigator-defined disease progression). Overall, 144 (97%) of 149 patients experienced treatment-related adverse events, which were mostly grade 1 or 2. The most common adverse events were visual effects, nausea, diarrhoea, constipation, vomiting, and peripheral oedema. The most common treatment-related grade 3 or 4 adverse events were neutropenia (n=9), raised alanine aminotransferase (n=6), hypophosphataemia (n=6), and lymphopenia (n=6).

Interpretation—Crizotinib is well tolerated with rapid, durable responses in patients with *ALK*-positive NSCLC. There seems to be potential for ongoing benefit after initial disease progression in this population, but a more formal definition of ongoing benefit in this context is needed.

Funding—Pfizer.

Introduction

Activation of the *ALK* gene has been described in several human cancers, including non-small-cell lung cancer (NSCLC), inflammatory myofibroblastic tumours, neuroblastomas, and diffuse large B-cell lymphomas, suggesting that ALK-mediated signalling might play a part in the development or progression of these tumours.[1–3] Activation of the *ALK* gene is usually through chromosomal rearrangement resulting in the placement of one of several different 5′ fusion partners and their associated promoter region upstream of the kinase domain of *ALK*.

ALK rearrangements in NSCLC were first described in 2007[4,5] and have an estimated prevalence of 3–5% in series mostly dominated by adenocarcinoma on histology.[6,7] *EML4–ALK* is the most common *ALK* fusion gene in NSCLC and occurs as several variants with different breakpoints in the *EML4* gene.[8,9] Other, more rare non-*EML4* fusions, including *KIF5B–ALK* and *TFG-ALK*, have also been described in lung cancer.[5,9] Their exact frequency and clinical significance remain under investigation but, by analogy with *EML4* and other oncogenic *ALK* fusions,[10] they also probably represent targets for therapeutic ALK inhibition in NSCLC. *ALK* fusions typically occur independently of *EGFR* and *KRAS* gene mutations,[11–15] although these aberrations are not mutually exclusive.[11,15,16] In the recent Lung Cancer Mutation Consortium series,[17] 8% of *ALK*-positive adenocarcinomas were also positive for either an *EGFR* or *KRAS* mutation.

Crizotinib (PF-02341066) is a potent, orally available, ATP-competitive, small-molecule inhibitor of ALK and c-Met receptor tyrosine kinase, with half maximum inhibitory concentration values of 5–25 nmol/L.[18,19] Preclinical testing against over 120 kinases showed crizotinib to be highly (>20 times) selective for these targets.[18]

The first-in-man crizotinib study began in 2006 with a dose-escalation phase undertaken in patients with solid tumours, which was followed by protocol-defined patient prescreening

for evidence of *ALK* or *MET* activation in specific tumour types. Patients with *ALK*-positive or *MET*-positive tumours were enrolled into a series of molecularly defined expansion cohorts at the proposed recommended phase 2 dose (250 mg twice daily in 28-day cycles).

After the discovery of *ALK* gene rearrangements in NSCLC and promising results in two patients with *ALK*-positive NSCLC enrolled during the dose-escalation phase of the study,[20,21] the protocol was amended and an additional *ALK*-positive NSCLC expanded cohort was instigated in 2008. Response data from the first 19 evaluable patients with *ALK*-positive NSCLC within the cohort revealed a high proportion of objective responses (53%).[20] Subsequent data from the first 82 patients confirmed these findings (57%).[21]

Here, we present an updated analysis of patients with *ALK*-positive NSCLC who were treated with crizotinib in the first-in-man single-arm crizotinib study before the data cutoff of June 1, 2011.

Methods

Patients

The design, methods, and objectives of this phase 1 single-arm study have been described previously[21] and are briefly summarised here. Patients aged 18 years or older with measurable *ALK*-positive stage III or IV NSCLC (defined by a break-apart fluorescence in-situ hybridisation assay), adequate organ function, and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1 were eligible for enrolment. Patients with an ECOG PS score of 2 were eligible on investigator and sponsor agreement. With the exception of alopecia, resolution of all previous acute treatment-related toxic effects to grade 1 or less was required and patients were excluded if they had received systemic anticancer treatment, radiation treatment, or major surgery within 2 weeks before starting study treatment. Additional key exclusion criteria included previous ALK-directed treatment; previous high-dose chemotherapy needing haemopoietic-stem-cell rescue; brain metastases, spinal cord compression, carcinomatous meningitis, or lepto-meningeal disease unless appropriately treated and neurologically stable for at least 2 weeks; myocardial infarction, severe or unstable angina, coronary or peripheral artery bypass graft, congestive heart failure, or cerebrovascular accident including transient ischaemic attack within 12 months or pulmonary embolus within 6 months before starting study treatment; ongoing cardiac dysrhythmias of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 grade 2 or higher, uncontrolled atrial fibrillation of any grade, or QT interval, corrected over 470 ms; uncontrolled hypertension; and use of drugs that are known potent cytochrome P450 3A4 inducers within 12 days before the first dose of crizotinib. Patients participating in the study were treated at sites in the USA, Australia, and South Korea. The protocol was approved by the investigational review board at each study site, and all patients provided written informed consent before enrolment.

Procedures

Patients received oral crizotinib 250 mg twice daily in 28-day cycles. Tumour response was assessed every 8 weeks (two cycles) using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0,[22] with confirmation of complete response or partial response a minimum of 4 weeks after initial response. The response-evaluable population was defined as patients who received at least one dose of crizotinib and had an adequate baseline disease assessment (ie, had a scan done no more than 35 days before the first dose of the study drug and had a scan showing disease that was evaluable per RECIST) plus had either at least one post-baseline disease assessment at least 6 weeks after the first dose or had withdrawn from the study, or those patients who had withdrawn from the study or progressed or died without

receiving a second scan at least 6 weeks after the first dose. Patients who had withdrawn, progressed, or died in these latter groups were classified as non-responders. Patients with investigator-defined tumour progression were allowed to continue study treatment if, in the opinion of the investigator, there was reasonable evidence of ongoing clinical benefit. In such patients, local ablative treatments such as surgery or radiation to sites of progression could be used, but the use of additional systemic anticancer drugs, other than the continued use of crizotinib after disease progression, was not allowed.

Safety was assessed at least every 2 weeks for the first 8 weeks of treatment and at least every 4 weeks thereafter until cycle 10, when visits every 8 weeks were permissible. Safety assessments included physical examination, documentation of adverse events, and routine laboratory tests including haematology (eg, haemoglobin, platelet, and white blood cell counts), chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and lactate dehydrogenase concentrations), coagulation (prothrombin time and activated partial thromboplastin time), and urinalysis. Adverse events were graded according to NCI CTCAE version 3.0. After initial reports of visual disturbances,[21] the clustered term visual effects—including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters—was introduced to record such reports effectively.

Endpoints included assessment of antitumour activity as measured by tumour response by RECIST, duration of response, time to tumour response, progression-free survival (PFS), overall survival at 6 and 12 months, and determination of the safety and tolerability and characterisation of the plasma pharmacokinetic profile of crizotinib after oral administration.

Statistical analyses

Primary tumour response analyses were based on investigator assessment of tumour data, as per RECIST version 1.0.[22] Time-to-event data were estimated using the Kaplan–Meier method to generate median event times with two-sided 95% CIs (by the Brookmeyer–Crowley method) and 6-month and 12-month overall survival probabilities. Median duration of follow-up for PFS and overall survival including quartiles were estimated using the reverse Kaplan–Meier method. All analyses were done with SAS statistical software, version 9.2.

This study is registered with ClinicalTrials.gov, number NCT00585195.

Role of the funding source

The sponsor of the study participated in the study design, data collection, data analysis, and data interpretation. The report was written by the corresponding author with contributions and review by all coauthors, including those employed by the sponsor. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first patient in the *ALK*-positive NSCLC cohort was enrolled on Aug 27, 2008, and received their first dose on Aug 28, 2008, and the last patient was enrolled on May 29, 2011, and received their first dose on June 1, 2011. The data cutoff for this study was June 1, 2011. Table 1 lists the baseline clinicopathological characteristics for the 149 patients enrolled before the data cutoff. At the data cutoff, the median duration of treatment was 43·1 weeks (range 0·1–138·6) and treatment was ongoing in 82 patients (55%), 52 of whom had yet to experience disease progression per RECIST.

The overall response-evaluable population consisted of 143 patients. The remaining six patients did not have adequate baseline scans. Within this population, 87 achieved an objective response (60·8%, 95% CI 52·3–68·9): three patients had a complete response and 84 had a partial response. Disease control (ie, complete response, partial response, or stable disease) was achieved by 118 patients (82·5%, 95% CI 75·3–88·4) at week 8 and 101 patients (70·6%, 62·4–77·9) at week 16. Figure 1 shows the best percent change from baseline in size of target lesions for patients with measurable disease (n=133), excluding those with early death before repeat imaging, those without an interpretable response assessment scan, or those who had only non-target lesions. 125 patients (94%) experienced some degree of tumour shrinkage during the study (figure 1).

The median time to first documented objective response was 7·9 weeks (range 2·1–39·6)—ie, at the first protocol-specified assessment. However, some patients had responded within days of treatment with crizotinib, as shown on non-protocol-mandated scans done at individual investigators' discretion.[23,24] Responses seemed durable, with an estimated median response duration of 49·1 weeks (95% CI 39·3–75·4; based on Kaplan–Meier estimates). At the time of this analysis (June 1, 2011) 46 (53%) of 87 responders had disease progression or had died.

In an analysis of response according to patient characteristics, the proportion of patients with an objective response was similar regardless of age (<65 years, ≥65 years) or sex (table 2). The proportion of patients with an objective response was high in patients with a poor ECOG PS score and among those who had received multiple lines of previous treatment for advanced or metastatic disease. The proportion of patients who had an objective response seemed to be higher in Asian than in non-Asian patients (table 2).

Median follow-up for PFS was 16·3 months (95% CI 13·8–18·4; quartiles: 25% 10·4, 75% 20·9), and the estimated median PFS was 9·7 months (95% CI 7·7–12·8) for all patients who received at least one dose of crizotinib (figure 2). In patients receiving first-line crizotinib (n=24), median PFS was 18·3 months (95% CI 8·3 to not reached; appendix), and in patients receiving crizotinib as second-line or later treatment (n=125), median PFS was 9·2 months (95% CI 7·3–12·7). At the time of data cutoff, there had been 85 PFS events (69 disease progressions and 16 deaths without documented disease progression) and 64 patients were censored. 52 (81%) of the 64 censored patients remained in follow-up for PFS, with the others censored because of absence of adequate baseline assessments (n=2), no on-study disease assessments (n=4), starting of a new anticancer treatment before tumour progression (n=2), and unacceptably long gap between disease progression or death and the most recent disease assessment (n=4). Among the 67 patients who had stopped treatment, the reasons for doing so were RECIST-defined progressive disease (n=41), death (n=15), adverse events (n=6; three were crizotinib-related: two pneumonitis and one increased ALT), and clinical or non-RECIST-defined disease progression (n=5). Dosing was interrupted in 63 patients, although in 21 of these patients the dose interruption lasted less than 1 week.

At the time of data cutoff, median overall survival had not been reached; 101 (68%) of 149 of the patients were still in follow-up for survival, 46 (31%) had experienced events, and the remaining two (1%) were censored and no longer assessed for survival. The median duration of follow-up for overall survival was 16·6 months (95% CI 15·0–18·6; quartiles: 25% 11·6, 75% 21·5). Preliminary estimates of the 6-month and 12-month overall survival were 87·9% (95% CI 81·3–92·3) and 74·8% (66·4–81·5), respectively.

Of the 69 patients with investigator-documented disease progression, 39 continued to receive crizotinib for more than 2 weeks after disease progression because, in the opinion of the investigators, they were deriving ongoing clinical benefit from the drug (table 3; figure

3). 12 of these patients received crizotinib for at least 6 months from the time of their initial investigator-defined disease progression. Excluding predefined target lesions, the most common sites of investigator-defined disease progression in these 39 patients were brain (n=10), lung (n=5), and liver (n=3).

144 (97%) of 149 patients experienced treatment-related adverse events (table 4), 108 of whom reported adverse events of grade 1 or 2 severity. The most frequently occurring treatment-related adverse events were visual effects, gastrointestinal events (nausea, diarrhoea, vomiting, and constipation), and peripheral oedema. Nausea, vomiting, and diarrhoea occurred early in treatment (range of median times to first onset 2–5 days; range 1–518), with visual effects occurring slightly later (median time to onset 14·5 days; range 1–173). By contrast, the median time to onset of oedema was 85 days (range 1–617). During treatment, the prevalence of common treatment-related grade 1 gastrointestinal adverse events and visual effects decreased over time, whereas that of oedema increased with continuing treatment (figure 4). The prevalence of treatment-related grade 2 events remained stable throughout treatment cycles.

Visual effects were of grade 1 severity and were described as light trails, flashes, or brief image persistence (post-flashbulb effect). The flipped dark-light registration of high-contrast images, such as stripes, was also reported. Investigators reported that these visual effects usually occurred at the edges of the visual field and were most pronounced on changing from low to bright light conditions. No patient needed dosing interruption, dose reduction, or permanent discontinuation of crizotinib treatment because of visual effects.

36 patients experienced treatment-related grade 3 or 4 events (grade 3 unless otherwise stated) comprising neutropenia (n=9, including one grade 4), raised ALT (n=6, including one grade 4), hypophosphataemia (n=6), lymphopenia (n=6), raised AST (n=5), pneumonitis (n=3, including one grade 4), fatigue (n=2), and nausea, vomiting, constipation, dysphagia, anaemia, peripheral neuropathy, dyspnoea, hyponatraemia, subcutaneous emphysema, increased aminotransferases, urinary tract infection, spontaneous abortion (experienced by the patient's partner), increased blood glucose, increased blood triglycerides, leucocytosis, abnormal liver function test, pneumomediastinum, pneumonia, respiratory distress, respiratory failure, and traumatic lung injury (all n=1). Ten patients (7%) needed a dose reduction because of treatment-related adverse events (increased ALT or AST, or both [n=6]; neutropenia [n=2]; nausea [n=1]; and fatigue [n=1]).

Three patients permanently discontinued as a result of treatment-related adverse events (one with grade 4 and one grade 2 pneumonitis, and one patient with grade 3 raised ALT). 46 deaths had occurred at the time of data cutoff, none of which was judged to be treatment related.

Discussion

In this updated analysis, crizotinib was well tolerated and resulted in rapid and durable responses in patients with *ALK*-positive advanced NSCLC (panel), with more than 60% of patients having an objective response and median PFS of almost 10 months.

Clinical and demographic details from the 149 patients revealed many of the features now thought to be characteristic of patients with *ALK*-positive lung cancer.[11,12] The median age was young (52 years), although the age range was wide. Although some patterns of metastatic spread at diagnosis, notably pleural, pericardial, and liver disease, have been associated with *ALK*-positivity,[27] we were unable to expand on this issue from the baseline scans used within this study because the time since diagnosis was not standardised in the

patients and there was no relevant comparator group. There was a preponderance of never smokers and tumours with adenocarcinoma on histology. Histology was not centrally reviewed, and patients were not randomly screened. Potential bias in the screened population because of increasing knowledge of clinical and pathological features associated with *ALK*-positivity in lung cancer therefore cannot be excluded.[11] Because of limitations of available tissue, extension of reverse transcriptase PCR analysis to either confirm *EML4* as the 5′ fusion partner or to identify the exact *EML4-ALK* breakpoints in patients beyond that already reported was not possible.[21]

In the *ALK*-positive lung cancer population within this study, crizotinib showed marked efficacy, with tumour shrinkage in over 90% of patients and with 61% achieving an objective response. The efficacy results within this study have remained consistent as the number of patients assessed has increased over time, showing the potential of robust efficacy data to be generated from even small numbers of patients when the population is molecularly predefined.[20,21] Responses seemed to be rapid and durable. The proportion of patients with an objective response seemed to be largely independent of age, sex, performance status, or line of therapy, which is consistent with the presence of the *ALK* rearrangement being the primary driver of benefit from crizotinib. The greatest proportions of objective responses were noted in treatment-naive patients, those with the lowest performance status score, and Asian patients. However, because of the small numbers of patients involved, no univariate or multivariate statistical comparisons were undertaken to formally compare the response rate of different categories within or between subgroups. Differences in crizotinib pharmacokinetics between Asian and non-Asian patients have been reported[28] and suggest that Asian patients might be subject to greater crizotinib exposure than non-Asians. Further analysis with a more robust sample size from multiple trial centres is needed to confirm these data.

Median PFS in the overall population was almost 10 months. The median PFS was longer in the treatment-naive subgroup than in the group in which crizotinib was a second-line or later treatment, which seems out of context with the minor differences in objective responses noted by line of treatment and at odds with what has been reported for EGFR tyrosine kinase inhibitors in *EGFR* mutant disease,[29] suggesting this finding might simply show the high variability associated with data derived from small subgroups. Median overall survival data are not yet mature, but the estimated overall survival at 6 and 12 months from the first dose of crizotinib were 88% and 75%, respectively. When interpreting these single-arm survival data, whether historical NSCLC datasets represent the best comparator group is hard to know. Within this study, many patients had survived to receive several lines of previous treatment, which might preselect for those with a good prognosis. Additionally, because of other inclusion and exclusion criteria, study populations are always likely to include patients who are healthier than those in an otherwise unselected population. Within this study, we did not capture subsequent treatments and patients might have gone on to receive any of several other standard and experimental drugs being explored for their activity in *ALK*-positive NSCLC, which might or might not have influenced overall survival in this cohort.[30–33] Finally, given its recent discovery, the true natural history of advanced *ALK*-positive NSCLC compared with NSCLC (not otherwise specified) is still being assessed.[12,34,35] A series of randomised registration studies are ongoing after the activity of crizotinib was shown within this first-in-man study. Because all of these studies comparing crizotinib in advanced *ALK*-positive NSCLC with defined chemotherapy standards in the first-line or second-line setting allow patients in the chemotherapy group to cross over to crizotinib after RECIST-defined disease progression, per independent assessment, none of them include an effect on overall survival as their primary endpoint. However, in a separate retrospective study comparing overall survival in *ALK*-positive patients who received crizotinib with those who had died before crizotinib was available to them, crizotinib use

was associated with significantly longer overall survival.[36] Within the present study, because less than a third of patients had an overall survival event and because of the small numbers involved, we did not undertake further analyses of overall survival by line of treatment or other subgroups.

Crizotinib seemed to be well tolerated. Most treatment-related adverse events in the *ALK*-positive lung cancer population were grade 1 or 2. The normal function of ALK in adult human beings is unknown, but it is involved in the development of the gut and visual system in other organisms.[2] Therefore, the predominance of gastrointestinal (notably diarrhoea, constipation, nausea, and vomiting) and visual side-effects could represent on-target anti-ALK effects within host tissues. However, crizotinib is also a MET inhibitor, and whether anti-MET effects, other off-target effects, or factors specific to the structure of crizotinib separate from its direct pharmacological targets could also be contributing to these side-effects is unclear. Peripheral oedema has recently been reported as a side-effect from MET-Mab, a monoclonal antibody directed against the extracellular MET domain.[37] Almost all of the common adverse events in the present study occurred early and seemed to improve over time, with the exception of the treatment-emergent oedema that seemed to be a late-onset cumulative adverse event. With protracted follow-up, shown by the proportion of total patients at risk who had specific adverse events for cycle 7 and beyond, no other changes in tolerability or prominent new adverse events relating to prolonged exposure were noted. In the initial study design, crizotinib was taken on an empty stomach in the first 1–2 cycles when blood samples were taken to assess pharmacokinetic exposures. Later, after a food-effect study was completed, the protocol was amended to allow dosing with food. Anecdotally, when the tablets were taken with food many patients reported less nausea and vomiting.

Panel: Research in context

Systematic review

No systematic review was done before the start of this study. This was a phase 1 first-in-man study that included plans to assess crizotinib at the recommended dose in a series of molecularly defined cohorts in different tumours. The *ALK*-positive non-small-cell lung cancer (NSCLC) cohort of this study was started on the basis of expert opinion and a solid preclinical rationale for crizotinib as an ALK inhibitor after the discovery of ALK as an oncogenic driver in NSCLC (after the start of the main study), and promising responses during the dose-escalation phase.[4]

Interpretation

Although the natural history of untreated advanced *ALK*-positive NSCLC is uncertain, in general, 1-year survival for advanced NSCLC, even within first-line clinical trials, is usually lower than 50%.[25,26] Here, we have shown that crizotinib use in a heavily pretreated *ALK*-positive NSCLC population was associated with a 1-year survival rate of 75%. In conjunction with a high proportion of patients having an objective response, these data support the potential of crizotinib to have a major effect on the lives of patients with *ALK*-positive NSCLC. Given its potential for protracted use, good tolerability of crizotinib over many cycles is important.

Information available on the efficacy and safety of crizotinib within the first-in-man study has increased over time.[20,21] As with any anticancer treatment, new clinical challenges emerge when patients start to progress on treatment. In our study, patients experiencing investigator-defined disease progression were allowed to continue on crizotinib if the investigator felt that the patient had ongoing clinical benefit from the drug. This assessment was subjective, and surveillance and decision making after initial disease progression were

not standardised. Undoubtedly, guidelines are needed to formalise the definition of ongoing benefit. Nonetheless, several patients received crizotinib treatment for months and in five cases over 1 year after their initial investigator-defined disease progression, suggesting that, at least in the opinion of the investigators, ongoing clinical benefit could be prolonged. In ten of the 39 patients with extended crizotinib treatment, the sole site of initial disease progression was the brain, raising the possibility of primary pharmacokinetic failure within the CNS as a sanctuary site rather than overall biological failure.[38] However, CNS imaging was not mandated within this study either at baseline or on study, and so whether this figure represents an accurate estimate of the true CNS failure rate with crizotinib remains uncertain. In contrast to CNS failure, in patients with systemic disease progression, failure is more likely secondary to more classical mechanisms of resistance to targeted treatments.[39] Anecdotally, some patients had progression in one lesion only, which might be consistent with clonal evolution at that site. As an example of a possible clonal resistance mechanism, several different *ALK* mutations, associated with ALK inhibitor resistance in vitro, have been isolated from patients with *ALK*-positive NSCLC who developed acquired resistance to crizotinib.[40–43] By analogy with the acquired resistance to EGFR inhibitors that emerges in *EGFR*-mutant NSCLC, although resistance develops, sensitive subclones of the disease that are still being suppressed by the inhibitor might continue to exist.[42,44] Therefore, if ALK-inhibitor resistance emerges, particularly in isolated sites potentially amenable to local treatment such as radiation therapy, the true potential for deriving ongoing clinical benefit through continuing crizotinib exposure after disease progression deserves further investigation.

On the basis of data from this study and preliminary data from a single-arm phase 2 study,[45] accelerated approval for crizotinib in *ALK*-positive locally advanced or metastatic NSCLC has been granted by the US Food and Drug Administration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all the participating patients, their families, and the network of investigators, research nurses, study coordinators, and operations staff. The phase 1 clinical trial was sponsored by Pfizer. Investigators were supported in part by the National Cancer Institute P50-CA090578 (PAJ, DBC), the American Society of Clinical Oncology Conquer Cancer Foundation (DBC), and by internal funds from the Massachusetts General Hospital Cancer Center and Pathology Department (ATS, AJI). Editorial assistance was provided by Martin Quinn at Acumed (Tytherington, UK) and was funded by Pfizer.

References

1. Mano H. Non-solid oncogenes in solid tumors: *EML4-ALK* fusion genes in lung cancer. Cancer Sci. 2008; 99:2349–55. [PubMed: 19032370]
2. Palmer RH, Vernersson E, Grabbe C, et al. Anaplastic lymphoma kinase: signalling in development and disease. Biochem J. 2009; 420:345–61. [PubMed: 19459784]
3. Pulford K, Morris SW, Turturro F. Anaplastic lymphoma kinase proteins in growth control and cancer. J Cell Physiol. 2004; 199:330–58. [PubMed: 15095281]
4. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. Nature. 2007; 448:561–66. [PubMed: 17625570]
5. Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell. 2007; 131:1190–1203. [PubMed: 18083107]

6. Solomon B, Varella-Garcia M, Camidge DR. *ALK* gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol. 2009; 4:1450–54. [PubMed: 20009909]
7. Weickhardt AJ, Camidge DR. The therapeutic potential of anaplastic lymphoma kinase inhibitors in lung cancer: rationale and clinical evidence. Clin Invest. 2011; 1:1119–26.
8. Choi YL, Takeuchi K, Soda M, et al. Identification of novel isoforms of the *EML4-ALK* transforming gene in non-small cell lung cancer. Cancer Res. 2008; 68:4971–76. [PubMed: 18593892]
9. Takeuchi K, Choi YL, Togashi Y, et al. *KIF5B-ALK*, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for *ALK*-positive lung cancer. Clin Cancer Res. 2009; 15:3143–49. [PubMed: 19383809]
10. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. N Engl J Med. 2010; 363:1727–33. [PubMed: 20979472]
11. Camidge DR, Kono SA, Flacco A, et al. Optimizing the detection of lung cancer patients harboring anaplastic lymphoma kinase (*ALK*) gene rearrangements potentially suitable for ALK inhibitor treatment. Clin Cancer Res. 2010; 16:5581–90. [PubMed: 21062932]
12. Shaw AT, Yeap BY, Mino-Kenudson M, 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. [PubMed: 19667264]
13. Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with *EML4-ALK* fusion gene. Ann Surg Oncol. 2010; 17:889–97. [PubMed: 20183914]
14. Wong DW, Leung EL, So KK, 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. [PubMed: 19170230]
15. Zhang X, Zhang S, Yang X, et al. Fusion of EML4 and ALK is associated with development of lung adenocarcinomas lacking *EGFR* and *KRAS* mutations and is correlated with *ALK* expression. Mol Cancer. 2010; 9:188. [PubMed: 20624322]
16. Varella-Garcia M, Cho Y, Lu X, et al. ALK gene rearrangement in unselected Caucasians with non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol. 2010; 28(suppl):abstract 10533.
17. Kris MG, Johnson BE, Kwiatkowski DJ, et al. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: the NCI's Lung Cancer Mutation Consortium (LCMC). Proc Am Soc Clin Oncol. 2011; 29(suppl):abstract CRA7506.
18. Christensen JG, Zou HY, Arango ME, et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther. 2007; 6:3314–22. [PubMed: 18089725]
19. Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res. 2007; 67:4408–17. [PubMed: 17483355]
20. Kwak EL, Camidge DR, Clark J, et al. Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066. Proc Am Soc Clin Oncol. 2009; 7(suppl):abstract 3509.
21. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; 363:1693–1703. [PubMed: 20979469]
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000; 92:205–16. [PubMed: 10655437]
23. Camidge DR, Bang Y, Iafrate AJ, et al. Clinical activity of crizotinib (PF-02341066), in *ALK*-positive patients with non-small cell lung cancer (NSCLC). Ann Oncol. 2010; 21(suppl 8):abstract 366PD.
24. Ou SH, Bazhenova L, Camidge DR, et al. Rapid and dramatic radiographic and clinical response to an ALK inhibitor (crizotinib, PF02341066) in an ALK translocation-positive patient with non-small cell lung cancer. J Thorac Oncol. 2010; 5:2044–46. [PubMed: 21102269]

25. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist. 2009; 14:253–63. [PubMed: 19221167]
26. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002; 346:92–98. [PubMed: 11784875]
27. Doebele RC, Lu X, Sumey C, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. Cancer. 2012 published online Jan 26. 10.1002/cncr.27409
28. Ou, SI.; Salgia, R.; Clark, J., et al. Comparison of crizotinib (PF-02341066) pharmacokinetics between Asian and non-Asian patients with advanced malignancies. 4th Asia Pacific Lung Cancer Conference (APLCC); Seoul, South Korea. Dec 2–4, 2010; Oral presentation O35
29. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009; 361:958–67. [PubMed: 19692684]
30. Camidge DR, Kono SA, Lu X, et al. Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed. J Thorac Oncol. 2011; 6:774–80. [PubMed: 21336183]
31. Lee JO, Kim TM, Lee SH, et al. Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. J Thorac Oncol. 2011; 6:1474–80. [PubMed: 21642865]
32. Mehra R, Camidge DR, Sharma S, et al. First-in-human phase I study of the ALK inhibitor LDK378 in advanced solid tumors. Proc Am Soc Clin Oncol. 2012; 30(suppl):abstract 3007.
33. Sequist LV, Gettinger S, Senzer NN, et al. Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. J Clin Oncol. 2010; 28:4953–60. [PubMed: 20940188]
34. Lee JK, Park HS, Kim DW, et al. Comparative analyses of overall survival in patients with anaplastic lymphoma kinase-positive and matched wild-type advanced nonsmall cell lung cancer. Cancer. 2012; 118:3579–86. [PubMed: 22086654]
35. Kim HR, Shim HS, Chung JH, et al. Distinct clinical features and outcomes in never-smokers with nonsmall cell lung cancer who harbor *EGFR* or *KRAS* mutations or *ALK* rearrangement. Cancer. 2012; 118:729–39. [PubMed: 21720997]
36. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in advanced NSCLC harboring anaplastic lymphoma kinase gene rearrangement: a retrospective analysis. Lancet Oncol. 2011; 11:1004–12. [PubMed: 21933749]
37. Spigel DR, Ervin TJ, Ramlau R, et al. Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC. Proc Am Soc Clin Oncol. 2011; 29(suppl):abstract 7505.
38. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol. 2011; 29:e443–45. [PubMed: 21422405]
39. Engelman JA, Janne PA. Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small cell lung cancer. Clin Cancer Res. 2008; 14:2895–99. [PubMed: 18483355]
40. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med. 2010; 363:1734–39. [PubMed: 20979473]
41. Sasaki T, Koivunen J, Ogino A, et al. A novel ALK secondary mutation and EGFR signaling cause resistance to ALK kinase inhibitors. Cancer Res. 2011; 71:6051–60. [PubMed: 21791641]
42. Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res. 2012; 18:1472–82. [PubMed: 22235099]
43. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. Sci Transl Med. 2012; 4:120ra17.
44. Chaft JE, Oxnard GR, Sima CS, et al. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res. 2011; 17:6298–6303. [PubMed: 21856766]

45. Crinò L, Kim D-W, Riely G, et al. Initial phase 2 results with crizotinib in advanced *ALK*-positive non-small cell lung cancer (NSCLC): PROFILE 1005. Proc Am Soc Clin Oncol. 2011; 29(suppl):abstract 7514.

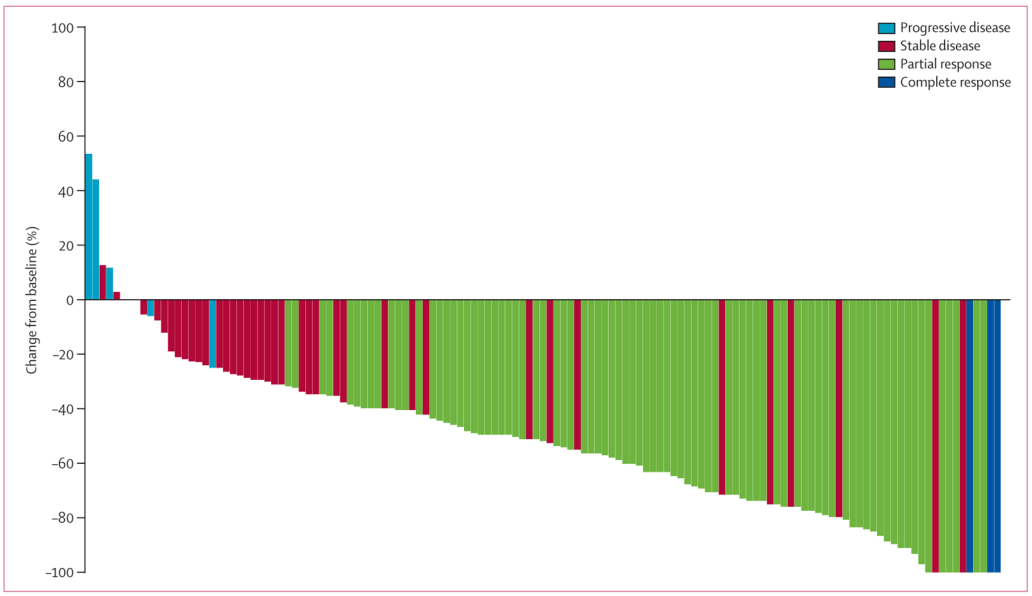

Figure 1. Waterfall plot of best percent change in target lesions from baseline for 133* patients on the basis of investigator assessment

*Excludes patients with early death before re-imaging, non-measurable non-target disease, or indeterminate responses: five patients with a best overall response of indeterminate either had available on-study scans that could not be assessed or discontinued the study before to obtaining adequate scans to assess response; three patients died within 42 days from first dose; and two patients had non-target lesions only.

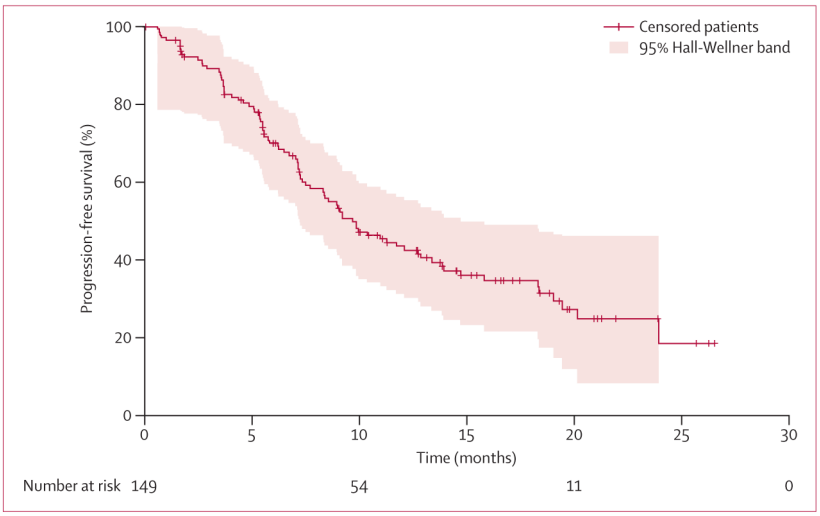

Figure 2. Kaplan–Meier plot of progression-free survival

64 patients were censored, of whom 52 remained in follow-up for progression-free survival.

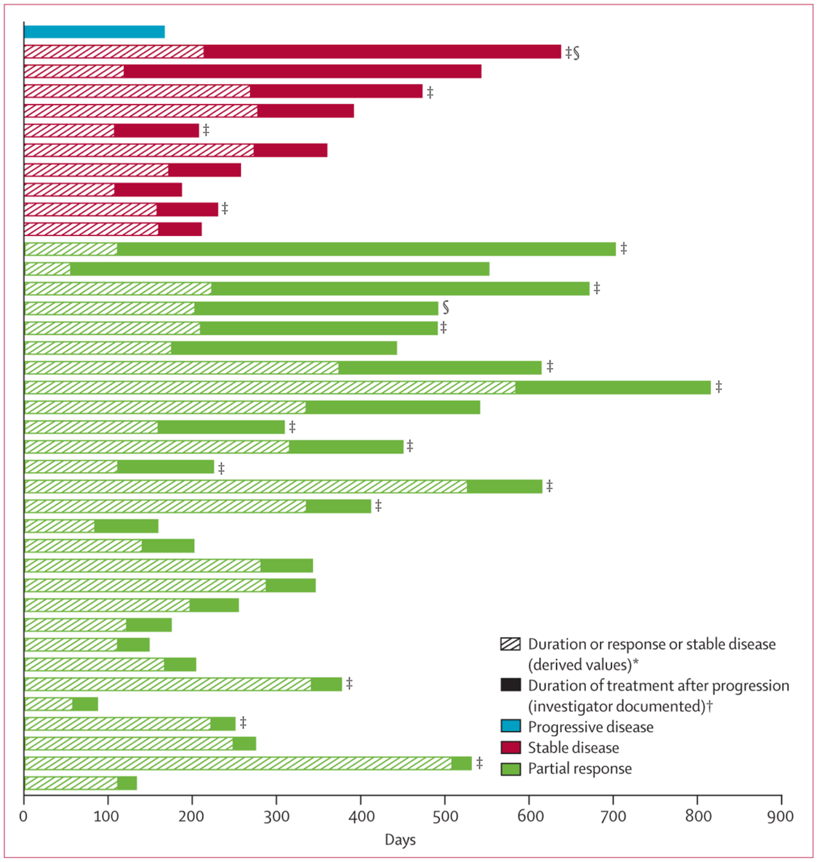

Figure 3. Duration of initial response or stable disease and of ongoing crizotinib treatment in patients who continued to receive crizotinib after progression

Patients are ordered by initial best response before progression and duration of crizotinib treatment after progression (n=39). *Defined as the time (in weeks) from the first documentation of objective tumour response (complete response or partial response) that was subsequently confirmed, to the first documentation of progressive disease or death. Stable disease duration was calculated from the date of the first dose to the date of first documented disease progression. †Defined as time from investigator-documented progressive disease to the last date of crizotinib dose or censor at the time of analysis. Disease progression and best objective response were derived according to Response Evaluation Criteria in Solid Tumors. ‡Treatment ongoing at the time of analysis. §Received crizotinib as first-line treatment.

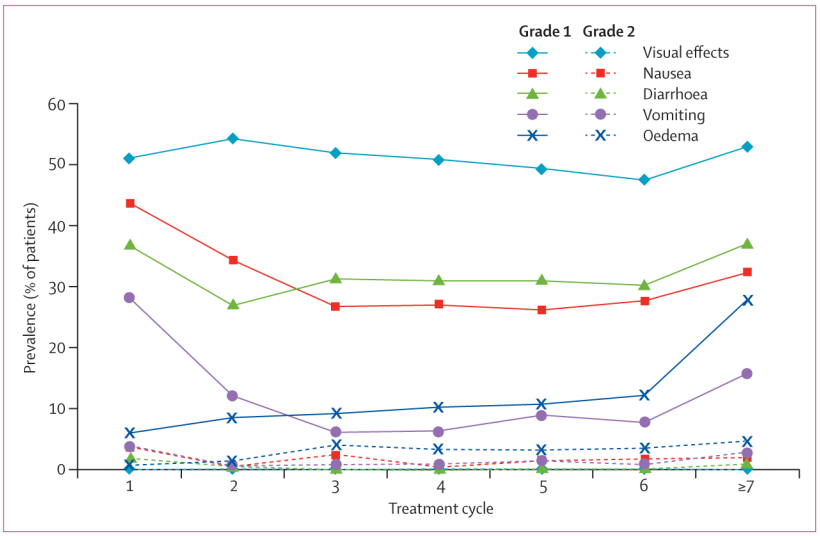

Figure 4. Prevalence of common treatment-related grade 1 or 2 adverse events during crizotinib treatment

Prevalence of adverse events for cycle 7 and beyond is presented as the proportion of patients at risk who experienced a particular event.

Table 1

Patient demographics and baseline disease characteristics

	Patients (n=149)
Age (years)	52 (21–86)
Men	73 (49%)
Women	76 (51%)
Ethnic origin	
White	95 (64%)
Asian	41 (28%)
Other	13 (9%)
Smoking status	
Never	106 (71%)
Former	42 (28%)
Present	1 (<1%)
Histological findings	
Adenocarcinoma	144 (97%)
Large-cell carcinoma	1 (<1%)
Squamous-cell carcinoma	2 (1%)
Other	2 (1%)
ECOG PS score	
0	56 (38%)
1	75 (50%)
≥2	18 (12%)
Number of previous advanced or metastatic treatment regimens	
0	24 (16%)
1	47 (32%)
2	31 (21%)
3	19 (13%)
≥4	28 (19%)

Data are median (range) or number (%). Some % do not sum to 100 because of rounding. ECOG PS=Eastern Cooperative Oncology Group performance status.

Table 2

Objective response rate according to patient characteristics

	n/N	Proportion with objective response (95% CI)*
Age		
<65 years	74/123	60·2% (50·9–68·9)
≥65 years	13/20	65·0% (40·8–84·6)
Sex		
Men	46/71	64·8% (52·5–75·8)
Women	41/72	56·9% (44·7–68·6)
ECOG PS score		
0	29/53	54·7% (40·4–68·4)
1	46/72	63·9% (51·7–74·9)
2	12/17	66·7% (44·0–89·7)
3	0/1	0·0% (0·0–97·5)
Number of previous advanced or metastatic systemic treatments		
0	14/22	63·6% (40·7–82·8)
1	26/44	59·1% (43·2–73·7)
2	20/31	64·5% (45·4–80·8)
≥3	27/46	58·7% (43·2–73·0)
Ethnic origin		
Asian	30/39	76·9% (60·7–88·9)
Non-Asian	57/104	54·8% (44·7–64·6)

143 patients were evaluable for response. ECOG PS=Eastern Cooperative Oncology Group performance status.

* Using the exact method based on the F distribution.

Table 3

Patients who received crizotinib for more than 2 weeks after progression

	Best objective response	Site of initial progression	Duration of treatment after progression (days)*
1	Progressive disease	Brain	169
2	Stable disease	Target lesions	49
3	Stable disease	Target lesions	>70
4	Stable disease	Diaphragm	79
5	Stable disease	Brain	82
6	Stable disease	Target lesions	85
7	Stable disease	Lung, pleural effusion	>98
8	Stable disease	Target lesions	114
9	Stable disease	Brain	>203
10	Stable disease	Target lesions	>422
11	Stable disease	Brain	422
12	Partial response	Target lesions	>22
13	Partial response	Target lesions, lung, liver	22
14	Partial response	Target lesions, pleural effusion	26
15	Partial response	Clinical progression	>28
16	Partial response	Liver	29
17	Partial response	Target lesions	>34
18	Partial response	Target lesions	35
19	Partial response	Target lesions	38
20	Partial response	Target lesions, lymph nodes	53
21	Partial response	Target lesions, gluteal soft tissue	57
22	Partial response	Target lesions	57
23	Partial response	Target lesions	60
24	Partial response	Liver	62
25	Partial response	Target lesions	75
26	Partial response	Target lesions, lung nodules	>77
27	Partial response	Brain	>88
28	Partial response	Brain	>114
29	Partial response	Brain	>134
30	Partial response	Target lesions	>150
31	Partial response	Lung nodules	205
32	Partial response	Clinical progression	>233
33	Partial response	Brain	>241
34	Partial response	Target lesions	266
35	Partial response	Brain	>282
36	Partial response	Adrenal glands	288
37	Partial response	Target lesions	>447

	Best objective response	Site of initial progression	Duration of treatment after progression (days)*
38	Partial response	Target lesions	496
39	Partial response	Brain	>591

CNS imaging before progression and body or CNS surveillance, decision-making, and capture of additional progression events after initial progression were not standardised within this study.

*Based on investigator-determined ongoing benefit.

Table 4

Treatment-related adverse events reported in at least 10% of patients in the safety population (N=149), by descending frequency (all grades)

	All grades	Grade 3 or 4
Any adverse event	144 (97%)	36 (24%)
Visual effects*	96 (64%)	0 (0%)
Nausea	84 (56%)	1 (<1%)
Diarrhoea	74 (50%)	0 (0%)
Vomiting	58 (39%)	1 (<1%)
Peripheral oedema	44 (30%)	0 (0%)
Constipation	41 (28%)	1 (<1%)
Dizziness	31 (21%)	0 (0%)
Decreased appetite	24 (16%)	0 (0%)
Fatigue	24 (16%)	2 (1%)
Increased alanine aminotransferase	18 (12%)	6 (4%)
Rash	17 (11%)	0 (0%)
Dysgeusia	16 (11%)	0 (0%)
Increased aspartate aminotransferase	15 (10%)	5 (3%)

Data are number (%). See text for further details of grade 3 or 4 adverse events.

*Includes diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters.