Activity and safety of ceritinib in patients with *ALK*-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial

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Summary

Background *ALK*-rearranged non-small-cell lung cancer (NSCLC) is sensitive to ALK tyrosine kinase inhibitors (ALK inhibitors) such as crizotinib, but resistance invariably develops, often with progression in the brain. Ceritinib is a more potent ALK inhibitor than crizotinib in vitro, crosses the blood–brain barrier in vivo, and shows clinical responses in patients with crizotinib-resistant disease. We aimed to assess whole-body activity of ceritinib in both ALK inhibitor-pretreated and ALK inhibitor-naive patients with *ALK*-rearranged NSCLC.

Methods ASCEND-1 was an open-label, phase 1 trial that recruited patients from 20 academic hospitals or cancer centres in 11 countries in Europe, North America, and Asia-Pacific. Eligible patients were aged 18 years or older with *ALK*-rearranged locally advanced or metastatic cancer that had progressed despite standard therapy (or for which no effective standard therapy existed), who had at least one measurable lesion at baseline. The primary objective (to determine the maximum tolerated dose) has been reported previously. This updated analysis includes all patients with *ALK*-rearranged NSCLC given oral ceritinib at the recommended dose of 750 mg/day in the dose-escalation and expansion phases. Here we report the secondary outcomes of overall response, duration of response, and progression-free survival, analysed in all patients who received at least one 750 mg dose of ceritinib. Exploratory analyses included retrospective analysis of intracranial activity by independent neuroradiologists, in patients with untreated or locally treated neurologically stable brain metastases at baseline. Safety was assessed in all patients who received at least one dose of ceritinib. This study is no longer recruiting patients; however, treatment and follow-up are ongoing. This study is registered with ClinicalTrials.gov, number NCT01283516.

Findings Between Jan 24, 2011, and July 31, 2013, 255 patients were enrolled and received at least one dose of ceritinib 750 mg/day, of whom 246 had *ALK*-rearranged NSCLC. At data cutoff (April 14, 2014), median follow-up was 11·1 months (IQR 6·7–15·2) and 147 (60%) patients had discontinued treatment, 98 (40%) as a result of disease progression. An overall response was reported in 60 (72% [95% CI 61–82]) of 83 ALK inhibitor-naive patients and 92 (56% [49–64]) of 163 ALK inhibitor-pretreated patients. Median duration of response was 17·0 months (95% CI 11·3–non-estimable [NE]) in ALK inhibitor-naive patients and 8·3 months (6·8–9·7) in ALK inhibitor-pretreated patients. Median progression-free survival was 18·4 months (95% CI 11·1–NE) in ALK inhibitor-naive patients and 6·9 months (5·6–8·7) in ALK inhibitor-pretreated patients. Of 94 patients with retrospectively confirmed brain metastases and at least one post-baseline MRI or CT tumour assessment, intracranial disease control was reported in 15 (79% [95% CI 54–94]) of 19 ALK inhibitor-naive patients and in 49 (65% [54–76]) of 75 ALK inhibitor-pretreated patients. Of these 94 patients, 11 had measurable brain lesions and no previous radiotherapy to the brain, six of whom achieved a partial intracranial response. Serious adverse events were recorded in 117 (48%) of 246 patients. The most common grade 3–4 laboratory abnormalities were increased alanine aminotransferase (73 [30%] patients) and increased aspartate aminotransferase (25 [10%]). The most common grade 3–4 non-laboratory adverse events were diarrhoea and nausea, both of which occurred in 15 (6%) patients. Two on-treatment deaths during the study were deemed to be related to study drug by the investigators, one due to interstitial lung disease and one as a result of multiorgan failure that occurred in the context of infection and ischaemic hepatitis.

Interpretation The durable whole-body responses reported, together with the intracranial activity, support a clinical benefit for treatment with ceritinib in patients with *ALK*-rearranged NSCLC who have received crizotinib, or as an alternative to crizotinib. A confirmatory phase 2 clinical trial is ongoing to assess ceritinib activity in patients with *ALK*-rearranged NSCLC and brain or leptomeningeal metastases.

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Introduction

Anaplastic lymphoma kinase *(ALK)* rearrangement is a therapeutically tractable oncogenic driver that occurs in 2–7% of patients with non-small-cell lung cancer (NSCLC).[1] So far, three ALK-targeted small-molecule tyrosine kinase inhibitors have been approved by

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Research in context

Evidence before this study

We searched PubMed, ClinicalTrials.gov, and conference abstracts for reports published in English with terms related to ALK and NSCLC, with no data limits. These searches, which were one before finalisation of the protocol (August, 2010), indicated that the standard of care for most patients with advanced non-small-cell lung cancer (NSCLC) is cytotoxic chemotherapy. However, the identification of oncogenic drivers has led to the development of targeted therapeutics that have become the first-line treatment in suitable patients. The success of this targeted approach has highlighted the need to identify genotype-specific subsets of patients who might benefit from targeted therapies. *ALK* rearrangement occurs in 2–7% of patients with NSCLC, in which it acts as a potent oncogenic driver. ALK is one of the newer molecular targets, and at the time of study design (2010) no ALK-targeted therapeutic was available for patients with *ALK*-rearranged NSCLC. The first-in-class ALK-targeted therapeutic, crizotinib, which was originally synthesised as an inhibitor of cMET, was in the early stages of efficacy assessment in this patient population. More recent searches using terms related to crizotinib, resistance, and brain metastases , which were done throughout the study duration and, most recently, before submission of the manuscript (October, 2015), have indicated that crizotinib is more effective than chemotherapy in patients with *ALK*-rearranged NSCLC in both first-line and second-line settings. However, patients invariably develop resistance within a year, with frequent disease progression in the brain. Consequently, this population of patients is in need of effective alternative therapeutics.

Added value of this study

This updated analysis of the ASCEND-1 phase 1 study builds upon early reports of 130 patients who received the second-generation ALK inhibitor, ceritinib, at 50–750 mg/day. Here, notable antitumour activity and a high proportion of durable responses are reported in 246 patients with advanced metastatic *ALK*-rearranged NSCLC who received ceritinib at the recommended dose of 750 mg/day. Tumour responses were noted in patients who were ALK-inhibitor naive and in patients who had previously received ALK inhibitors. Moreover, durable whole-body responses were reported for patients with brain metastases at study entry. A retrospective analysis by independent neuroradiologists of intracranial responses in these patients with brain metastases at baseline and at least one post-baseline tumour assessment found a high proportion of patients with intracranial disease control.

Implications of all the available evidence

Clinical activity of ceritinib was noted in patients with *ALK*-rearranged NSCLC who had progressed on previous treatment with crizotinib, providing a therapeutic option for patients who might otherwise have limited choices. Moreover, in patients with brain metastases at study entry, both whole-body and intracranial responses were reported, suggesting the potential for ceritinib to effectively treat this patient population and the possibility that ceritinib could be an alternative therapeutic approach to local ablative therapy in patients with *ALK*-rearranged NSCLC and brain metastases. Our results raise the possibility that ceritinib might also have a role as an alternative to crizotinib in patients with *ALK*-rearranged NSCLC.

several health authorities.[2–5] The first ALK-targeted therapeutic was crizotinib, which targets cMET, ALK, and ROS1.[6,7] Results of two phase 3 studies comparing crizotinib with chemotherapy in patients with advanced *ALK*-rearranged NSCLC showed that progression-free survival and response were improved with crizotinib therapy in both second-line and first-line settings.[8,9] However, most responding patients acquire resistance within 1 year, with recurrence generally occurring in the brain or liver.[10–12] In a retrospective analysis[11] of patients with *ALK*-rearranged NSCLC given crizotinib, the site of disease progression was brain in 41% of patients, and liver in 25% of patients. The high incidence of recurrence in the brain might partly be a result of limited blood–brain barrier penetration of crizotinib, which has been described in the clinical setting.[13,14] Crizotinib resistance can result from both *ALK*-dependent and *ALK*-independent mechanisms.[10,15,16] Therefore, treatment options for patients who progress on crizotinib are needed.[17]

Ceritinib (LDK378) is a potent and selective oral tyrosine kinase inhibitor of ALK.[18] In vitro, ceritinib inhibits ALK with a potency that is 20 times greater than that of crizotinib, and has nanomolar potency against patient-derived crizotinib-resistant tumour cell lines.[19] In preclinical xenograft studies, immediate tumour regrowth was reported after completion of crizotinib treatment, whereas regrowth upon stopping ceritinib treatment was notably delayed.[19] Further, in a tissue distribution study using a rat model, ceritinib crossed the blood–brain barrier with a brain-to-blood exposure ratio of about 15%.[20] Consistent with these preclinical observations, ceritinib has shown activity against crizotinib-resistant tumours in patients with *ALK*-rearranged NSCLC, including brain metastases.[18]

Preliminary activity and safety data from the dose-escalation phase of the ASCEND-1 study have been reported previously.[18] The objective of the analyses reported here was to investigate the antitumour activity of ceritinib in a larger cohort of patients with *ALK*-rearranged NSCLC, including both ALK inhibitor-naive and ALK inhibitor-pretreated patients, given the recommended dose of 750 mg/day, with a longer median duration of follow-up than reported previously. Additionally, we report the results from a retrospective review of brain MRI and CT scans to assess intracranial activity of ceritinib in patients with treated and untreated neurologically stable brain metastases at study entry.

Methods

Study design and participants

The study methods for the multicentre, open-label, phase 1, ASCEND-1 study have been published previously.[18] Briefly, patients were recruited from 20 academic hospitals, or cancer centres associated with academic hospitals, in 11 countries across Europe, North America, and Asia-Pacific (appendix p 1). Patients were eligible if they had *ALK*-rearranged NSCLC, were aged 18 years or older, had locally advanced or metastatic NSCLC that had progressed (by physician assessment) despite standard therapy (including chemotherapy or ALK inhibitor) or for which no effective standard therapy existed, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate organ function and laboratory results (required laboratory tests: neutrophil count, haemoglobin, platelets, serum total bilirubin, aspartate aminotransferase, alanine aminotransferase, calculated creatinine clearance, serum amylase, serum lipase, and fasting plasma glucose), and a life expectancy of at least 12 weeks. Patients were required to have at least one measurable lesion at baseline according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Patients with untreated or locally treated asymptomatic and stable (>4 weeks) CNS disease were eligible. Patients with tumours other than NSCLC were permitted to be enrolled on the study; data from these patients were reported previously[18] and were not included in the analysis described here.

Patients were not permitted to have received any chemotherapy, biological therapy, or other investigational agent for 1–4 weeks (depending upon half-life) before starting ceritinib, or during the study. Patients with unresolved nausea, vomiting, or diarrhoea (Common Terminology Criteria for Adverse Events [CTCAE] grade 2 or worse), impairment of gastrointestinal function, a history of pancreatitis, liver disease, known HIV, clinically significant cardiac disease, previous or current second malignancy (other than adequately treated in-situ carcinoma of the cervix, non-melanoma carcinoma of the skin, or any other curatively treated malignancy that has not recurred in the previous 3 years), and patients with symptomatic, neurologically unstable CNS disease were not eligible for inclusion.

This trial was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was approved by the local human investigations committee at each study centre. All patients provided written informed consent before screening. The study protocol has been published online.[18]

Procedures

Patients were given ceritinib orally at the recommended dose of 750 mg/day, after fasting, in continuous 21-day treatment cycles. Patients who received 750 mg/day in the dose-escalation phase of the study were included in the analysis, as well as those who received 750 mg/day during the dose-expansion phase. Treatment was continued until objective evidence of disease progression (treatment beyond progression was permitted in patients who continued to have a clinical benefit; it was originally permitted only in patients whose sole site of progression was the CNS, but the protocol was amended on Jan 16, 2013, to take into account changing treatment practices), development of intolerable side-effects, or withdrawal of consent. Dose adjustments were permitted for patients who had a dose-limiting toxicity (DLT). A DLT was defined as any grade 3 or worse adverse event with the exception of controlled vomiting, nausea, or diarrhoea, increases in alkaline phosphatase, and less than 3 days of grade 3 fatigue. Increased total bilirubin of grade 2 or worse, concurrent with grade 2 or worse alanine aminotransferase, was regarded as a DLT, as was grade 2 or worse pancreatitis or phototoxicity. Any toxicity resulting in an inability to receive 75% or more of the planned doses in a treatment cycle was classified as a DLT. In patients with a dose delay of more than 21 days due to ceritinib-related toxicity, treatment was discontinued unless the patient showed evidence of a clinical benefit. Patients were permitted a maximum of three dose reductions (of 150 mg/day per reduction), after which they were required to discontinue treatment. Reescalation after dose reduction was not permitted.

See Online for appendix

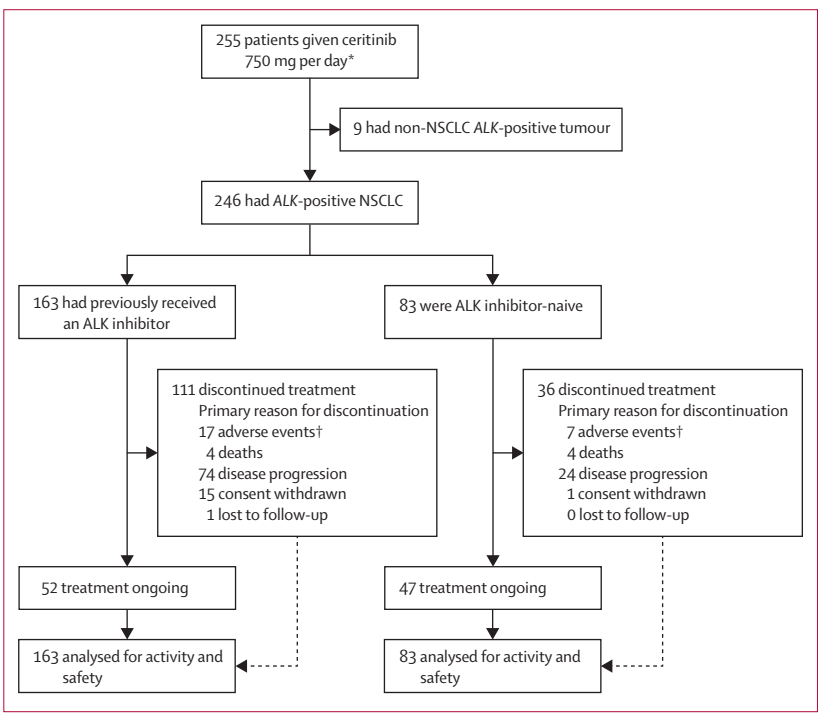

Figure 1: **Trial profile**
NSCLC=non-small cell lung cancer. *Included ten patients who received the recommended dose of 750 mg/day during the dose-escalation phase of the study. †The total number of ALK inhibitor-pretreated and ALK inhibitor-naive patients who discontinued treatment as a result of adverse events were 18 patients and eight patients, respectively; however, for one patient from each group, an adverse event was not considered the primary reason for discontinuation, and as such the number of patients listed in the patient disposition are 17 and seven, respectively.

	ALK inhibitor-naive patients (n=83)	ALK inhibitor-pretreated patients (n=163)
Age (years)	55 (22–80)	52 (24–80)
Sex		
Female	44 (53%)	88 (54%)
Male	39 (47%)	75 (46%)
ECOG performance status		
0	25 (30%)	38 (23%)
1	51 (61%)	104 (64%)
2	7 (8%)	20 (12%)
≥3	0	1 (1%)
Smoking history		
Never or ex-smoker	82 (99%)	158 (97%)
Current smoker	1 (1%)	5 (3%)
Race		
White	48 (58%)	108 (66%)
Black	0	4 (2%)
Asian	35 (42%)	47 (29%)
Other	0	4 (2%)
Tumour histology or cytology		
Adenocarcinoma	76 (92%)	152 (93%)
Other	7 (8%)	11 (7%)
Site of metastasis		
Brain	26 (31%)	98 (60%)
Lung	62 (75%)	111 (68%)
Liver	30 (36%)	68 (42%)
Bone	26 (31%)	69 (42%)
Previous treatment regimens		
0	16 (19%)	0
1	38 (46%)	26 (16%)
2	16 (19%)	45 (28%)
3	7 (8%)	35 (21%)
≥4	6 (7%)	57 (35%)
Time from diagnosis to initiation of ceritinib (months), median (IQR)	8·1 (3·6–20·2)	21·2 (13·6–33·6)

Data are median (range) or number (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small cell lung cancer.

Table 1: **Baseline characteristics of all patients with *ALK*-rearranged NSCLC (n=246)**

	ALK inhibitor-naive patients (n=83)	ALK inhibitor-pretreated patients (n=163)
Complete response	1 (1%)	3 (2%)
Partial response	59 (71%)	89 (55%)
Stable disease	14 (17%)	29 (18%)
Progressive disease	0	16 (10%)
Unknown response	9 (11%)	26 (16%)
12-month duration of response	64% (49–76)	26% (16–36)
12-month progression-free survival	62% (50–72)	27% (20–35)
12-month overall survival	83% (72–90)	67% (59–74)

Data are number (%), or % (95% CI). NSCLC=non-small cell lung cancer. NE=non-estimable.

Table 2: **Investigator-assessed best whole-body responses for all patients with *ALK*-rearranged NSCLC receiving at least one dose of ceritinib (n=246)**

At baseline, MRI or CT scans of the brain, chest, and abdomen were done in all patients. During treatment, tumour response was assessed every 6 weeks by RECIST 1.0. CT or MRI scans were done every 6 weeks for the first 18 weeks (six cycles) and then every 12 weeks thereafter, until progression of disease. Responses were assessed by the investigator and by a blinded independent review committee (BIRC). Routine follow-up brain MRI or CT scans were done, every 6 weeks, only in patients with brain metastases at study entry. Intracranial (CNS) responses were retrospectively assessed according to RECIST 1.1. Brain lesions for which the longest diameter was 10 mm or greater were defined as measurable. Previous radiotherapy information, including time from the last dose of radiotherapy to start of ceritinib treatment, was collected. Assessments of laboratory parameters, ECOG performance status, and overall physical condition were done at baseline, days 1, 2, 8, and 15 of cycle 1, days 1, 2, and 15 of cycle 2, days 1 and 15 of cycles 3–6, and day 1 of each cycle thereafter, until end of treatment. Assessments were also done at the end of study or time of withdrawal. All adverse events reported during the study were recorded and graded according to the CTCAE 4.03.

Outcomes

Secondary endpoints of the ASCEND-1 trial reported here are overall response, duration of response, progression-free survival (assessed by investigators and by the BIRC), and safety. An overall response was defined as a complete response or partial response, as assessed by whole-body (all sites of disease, including brain) responses (RECIST 1.0 criteria). Responses had to be confirmed by repeat assessments 4 weeks or more after response criteria were first met. Duration of response was defined as the time from first documented partial or complete response to the date of first disease progression or death from any cause. Progression-free survival was defined as the time from start of treatment with ceritinib to the date of radiologically documented disease progression or death from any cause.

We assessed overall survival as a prespecified exploratory endpoint, defined as time from start of treatment to date of death from any cause. We also assessed time to response as a prespecified exploratory endpoint, defined as time from start of treatment with ceritinib to first overall tumour response that was subsequently confirmed.

A post-hoc retrospective central review of brain MRI and CT scans to assess intracranial activity of ceritinib in patients with untreated or locally treated neurologically stable brain metastases at baseline, was done by two independent neuroradiologists (masked to the investigator and BIRC assessments) according to RECIST 1.1. Endpoints included overall intracranial response (complete response or partial response), intracranial disease control (complete response, partial response, or stable disease), and time to intracranial response (time from start of treatment to first overall

intracranial response that was subsequently confirmed). In patients with non-measurable lesions, stable disease was defined as non-complete response or non-progressive disease. Intracranial duration of response was defined as time from first complete or partial intracranial response to intracranial disease progression (not considering extracranial disease progression) or death.

Statistical analysis

For determination of the maximum tolerated dose (MTD) and recommended dose (primary objective, dose-escalation phase, reported previously),[18] we did no formal statistical power calculations to determine sample size. For the dose-escalation phase of this study, we estimated that 40 patients would be enrolled, including at least six patients who would be treated at the MTD level. For the expansion phase of this study, we planned to enrol up to 310 patients (including all patients given the MTD [recommended dose] during the dose-escalation phase, who were eligible for the safety set) with at least 25 and up to 100 patients in each of the following patient groups: ALK inhibitor-naive patients, ALK inhibitor-pretreated patients who progressed during previous ALK inhibitor treatment, and ALK inhibitor-pretreated patients who did not progress during previous ALK inhibitor treatment. We planned to enrol about ten patients with tumours other than NSCLC. We deemed that preliminary evidence of antitumour activity of ceritinib would be shown if the lower bound of the 95% credible interval was greater than 10% at the MTD (recommended dose) within that patient group. Given a sample size of 25 patients per group, assuming that 28% achieve an overall response, the 95% credible interval would be 12·6–45·7. Based on a Bayesian approach, given a sample size of 100 patients per group, assuming that 25% achieve an overall response, the 95% credible interval would be 17·0–33·7.

Investigator-assessed activity and safety assessments included all patients with *ALK*-rearranged NSCLC enrolled on the study who received at least one 750 mg dose of ceritinib. Data were summarised using descriptive statistics (continuous data) or contingency tables (categorical data) for demographic and baseline characteristics, activity measurements, and safety measurements. We assessed time to response with summary statistics. We estimated all other time-to-event data, and their associated 95% CIs, using Kaplan-Meier methods. The data cutoff date was April 14, 2014. We used SAS version 9.3 for analyses.

This study is registered with ClinicalTrials.gov, number NCT01283516.

Role of the funding source

This study was funded by Novartis Pharmaceuticals Corporation. It was designed by the funder, study investigators, and an independent steering committee. Data were collected by investigators and analysed by the funder. All authors, including those employed by the funder (SSu, SL, TS, and AY), were involved in data interpretation. All authors had full access to the data, and contributed to the development of and approved the manuscript for submission. 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

We enrolled 255 patients between Jan 24, 2011, and July 31, 2013, who received at least one dose of ceritinib at the 750 mg/day recommended dose. Of these, 246 (96%) had *ALK*-rearranged NSCLC, of whom 83 (34%) patients were ALK inhibitor-naive and 163 (66%) were ALK inhibitor-pretreated (figure 1). Of the 163 ALK inhibitor-pretreated patients, 149 (91%) had progressive disease on (or within 2 weeks of the last dose of) the previous ALK inhibitor. All ALK inhibitor-pretreated patients had received crizotinib, and five patients had also received the investigational ALK inhibitor alectinib

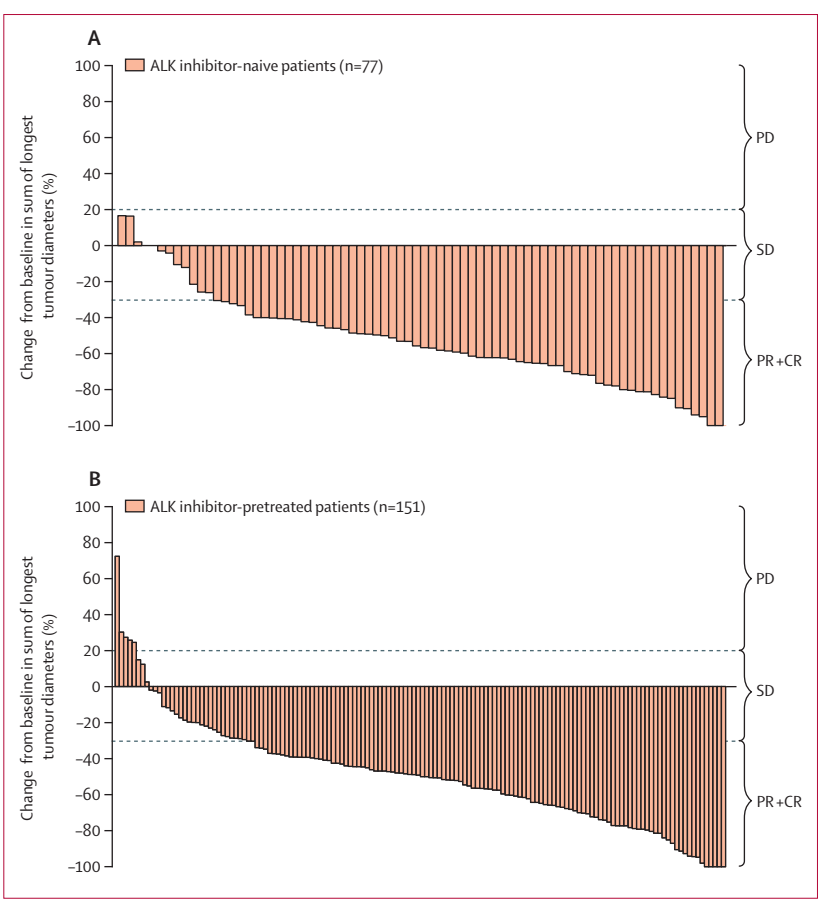

Figure 2: **Best percentage change from baseline in tumour volume in patients with at least one post-baseline measurement**

(A) ALK inhibitor-naive patients and (B) ALK inhibitor-pretreated patients. Dotted line at 20% is the threshold for progressive disease (PD), dotted line at –30% is the threshold below which a partial response (PR) or complete response (CR) is defined, and any changes that fall between the two dotted lines are defined as stable disease (SD). NSCLC=non-small cell lung cancer.

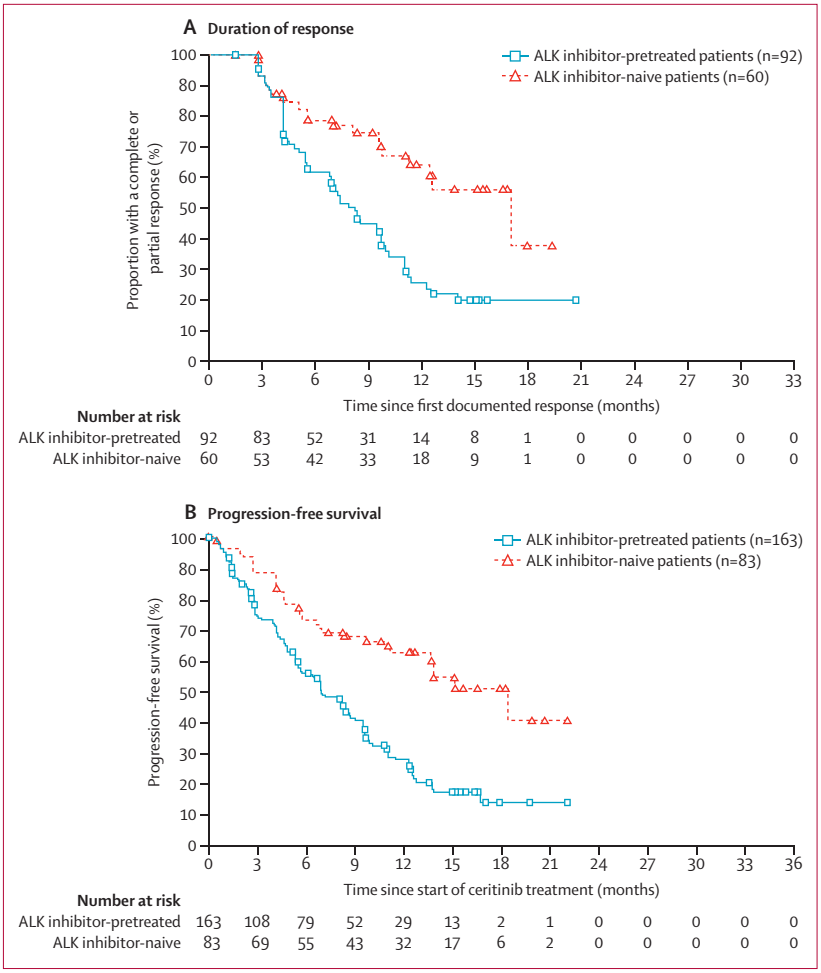

Figure 3: **Kaplan-Meier curves of duration of response and progression-free survival**
(A) Duration of response in all patients who responded to ceritinib treatment (n=152). (B) Progression-free survival (n=246). NSCLC=non-small cell lung cancer.

after crizotinib. Baseline demographics were consistent with those reported in other studies for patients with *ALK*-rearranged NSCLC,[6,21] and were similar between the patient groups (table 1). Overall, most patients were heavily pretreated, having received several antineoplastic therapies (chemotherapy or ALK inhibitor, or both; table 1). All 163 (100%) ALK inhibitor-pretreated patients had previously received crizotinib, of whom 137 (84%) had also received one or more lines of chemotherapy. Of the 83 ALK inhibitor-naive patients, 67 (81%) had received one or more lines of chemotherapy.

At study entry, 124 (50%) patients (26 [21%] ALK inhibitor-naive and 98 [79%] ALK inhibitor-pretreated patients) with *ALK*-rearranged NSCLC had asymptomatic or controlled brain metastases (appendix p 2), of whom 83 (67%) had received previous brain radiotherapy (15 [58%] of 26 ALK inhibitor-naive and 68 [69%] of 98 ALK inhibitor-pretreated patients). Baseline patient characteristics for patients with and without brain metastases were similar (appendix pp 3–4).

The median duration of follow-up at the data cutoff (April 14, 2014) was 11·1 months (IQR 6·7–15·2). On the basis of investigator assessment of whole-body activity (all sites of disease, including brain), the proportion of ALK inhibitor-naive patients who had achieved an overall response was 72% (95% CI 61–82; 60 of 83 patients), and the proportion of ALK inhibitor-pretreated patients was 56% (49–64; 92 of 163 patients; table 2). In a post-hoc analysis, the proportion of ALK inhibitor-naive patients with no previous systemic anti-neoplastic therapy who achieved an overall response was 69% (95% CI 41–89; 11 of 16 patients). Median time to response was 6·1 weeks for both ALK inhibitor-naive (IQR 6·1–7·6) and ALK inhibitor-pretreated (5·9–7·6) patients. A decrease in tumour burden from baseline was observed in most of the 77 ALK inhibitor-naive patients and 151 ALK inhibitor-pretreated patients with measurable disease at baseline and at least one post-baseline assessment (figure 2). For ALK inhibitor-naive patients, median duration of response was 17·0 months (95% CI 11·3–non-estimable [NE]) and median progression-free survival was 18·4 months (95% CI 11·1–NE; figure 3; table 2); at data cutoff, 27 (33%) had progressed. ALK inhibitor-pretreated patients had a median duration of response of 8·3 months (95% CI 6·8–9·7) and median progression-free survival of 6·9 months (5·6–8·7; figure 3; table 2); at data cutoff 96 (59%) had progressed.

In a prespecified exploratory analysis of overall survival, the median had not yet been reached (95% CI 19·6–NE) in the ALK inhibitor-naive patients and was 16·7 months (95% CI 14·8–NE) in the ALK inhibitor-pretreated patients (table 2). At the time of this analysis of overall survival, 16 (19%) ALK inhibitor-naive and 63 (39%) ALK inhibitor-pretreated patients had died. The results of the BIRC assessment for activity were consistent with the results of the investigator-assessed activity analyses (appendix p 6).

Treatment was continued beyond disease progression (defined as ceritinib treatment for more than 3 weeks after documentation of progressive disease) in 12 (14%) of 83 ALK inhibitor-naive patients and in 48 (29%) of 163 ALK inhibitor-pretreated patients. At the time of data cutoff, treatment was ongoing in five (42%) of the 12 ALK inhibitor-naive patients treated beyond progression, with the remaining seven (58%) having discontinued as a result of progressive disease. Of the 48 ALK inhibitor-pretreated patients treated beyond progression, treatment was ongoing in 18 (38%) patients, with the remaining 30 patients having discontinued, either as a result of progressive disease (n=25; 52%), adverse events (n=1; 2%), loss to follow-up (n=1; 2%), or withdrawal of consent (n=3; 6%). At the time of data cutoff, death was reported in two (29%) of seven ALK inhibitor-naive patients and 14 (47%) of 30 ALK inhibitor-pretreated patients who had discontinued after treatment beyond disease progression.

Whole-body responses for the 124 ALK inhibitor-naive and ALK inhibitor-pretreated patients with brain metastases at study entry were similar to those of the

	ALK inhibitor-naive patients			ALK inhibitor-pretreated patients		
	All NSCLC	No previous radiotherapy	Previous radiotherapy	All NSCLC	No previous radiotherapy	Previous radiotherapy
Intracranial response in all patients with measurable and non-measurable baseline brain metastases (n=94)						
Number of patients	19	8	11	75	23	52
Complete response	3 (16%)	1 (13%)	2 (18%)	4 (5%)	2 (9%)	2 (4%)
Partial response	5 (26%)	3 (38%)	2 (18%)	10 (13%)	3 (13%)	7 (13%)
Stable disease*	7 (37%)	3 (38%)	4 (36%)	35 (47%)	10 (43%)	25 (48%)
Progressive disease	0	0	0	12 (16%)	5 (22%)	7 (13%)
Unknown response†	4 (21%)	1 (13%)	3 (27%)	14 (19%)	3 (13%)	11 (21%)
Intracranial duration of response, months	NE (5·6–NE)	NA	NA	6·9 (2·9–NE)	NA	NA
Intracranial response in patients with measurable baseline brain metastases (n=36)						
Number of patients	8	4	4	28	7	21
Complete response	0	0	0	0	0	0
Partial response	5 (63%)	3 (75%)	2 (50%)	10 (36%)	3 (43%)	7 (33%)
Stable disease	0	0	0	7 (25%)	1 (14%)	6 (29%)
Progressive disease	0	0	0	6 (21%)	2 (29%)	4 (19%)
Unknown response‡	3 (38%)	1 (25%)	2 (50%)	5 (18%)	1 (14%)	4 (19%)
Overall intracranial response	5 (63; 25–92)	NA	NA	10 (36; 19–56)	NA	NA
Intracranial duration of response, months	8·2 (5·6–NE)	NA	NA	11·1 (2·8–NE)	NA	NA

Data are number (%), number (%; 95% CI), or median (95% CI). NA=non-applicable because the sample size was too small. NE=non-estimable. NSCLC=non-small-cell lung cancer. *Referred to as non-complete response or non-progressive disease in patients with non-measurable brain lesions at baseline. †A response was regarded as unknown if all post-baseline assessments had overall response as unknown (n=5), there was no valid post-baseline assessment (n=1), assessment of progressive disease was done too late (eg, no valid assessment before week 12; n=3), or assessment of stable disease was done too early (eg, assessed before day 42 with no further valid assessment; n=9). ‡A response was listed as unknown if all post-baseline assessments had overall response as unknown (n=2), there was no valid post-baseline assessment (n=1), assessment of progressive disease was done too late (n=0), or assessment of stable disease was done too early (n=5).

Table 3: **Retrospective analyses of intracranial responses in patients with *ALK*-rearranged NSCLC with baseline brain metastases and evaluable MRI or CT scans**

overall patient population, with the same pattern of progression-free survival and duration of response times (appendix p 5); results were also consistent between investigator and BIRC assessment (appendix p 6). On this basis, we did retrospective analyses to specifically assess intracranial responses in this subgroup. Of the 124 patients with baseline brain metastases by investigator assessment, brain metastases were retrospectively confirmed by independent neuroradiologists for 94 patients (19 ALK inhibitor-naive patients and 75 ALK inhibitor-pretreated patients) with baseline and at least one post-baseline MRI or CT tumour assessment (20 by CT and 74 by MRI). Based on RECIST 1.1, 36 (38%) of 94 patients had measurable intracranial lesions at baseline (eight were ALK inhibitor naive and 28 were ALK inhibitor pretreated). 30 patients with brain metastases at baseline, as assessed by the investigator, were excluded from the retrospective analysis as a result of no available baseline (n=8) or post-baseline (n=7) image for review, no consent for central review (n=2), no post-baseline assessment (either in brain or elsewhere; n=6), or because the image was deemed non-assessable by the neuroradiologists (n=7). 31 (33%) of 94 patients in the retrospective analysis had not previously received radiotherapy to the brain (appendix p 8). Most patients with measurable brain lesions at baseline had received previous radiotherapy to the brain (25 [69%] of 36; appendix p 9). Overall response and duration of response in these patients is shown in table 3.

In the 94 patients included in the retrospective analysis, the median time to intracranial response was 6·1 weeks (IQR 6·1–12·3; appendix p 7), consistent with that reported for whole-body responses in the full patient population (n=246). On the basis of central review by two independent neuroradiologists, intracranial disease control was achieved in 79% (95% CI 54–94; 15 of 19) of ALK inhibitor-naive patients and 65% (54–76; 49 of 75) of ALK inhibitor-pretreated patients with baseline brain metastases. 63 (67%) of 94 patients had previously received radiotherapy to the brain (appendix p 8). Intracranial responses in patients who had not received previous radiotherapy to the brain were similar to those in patients who had previously received radiotherapy, irrespective of timing of radiotherapy (≥3 months *vs* <3 months before starting ceritinib; figure 4, table 3; appendix p 9). For the 36 patients with measurable brain metastases at baseline, the proportion of ALK inhibitor-naive patients with intracranial disease control was 63% (95% CI 25–92; five of eight) and the proportion of ALK inhibitor-pretreated patients was 61% (95% CI 41–79; 17 of 28; table 3). Best overall intracranial response and exposure to ceritinib is shown in figure 4.

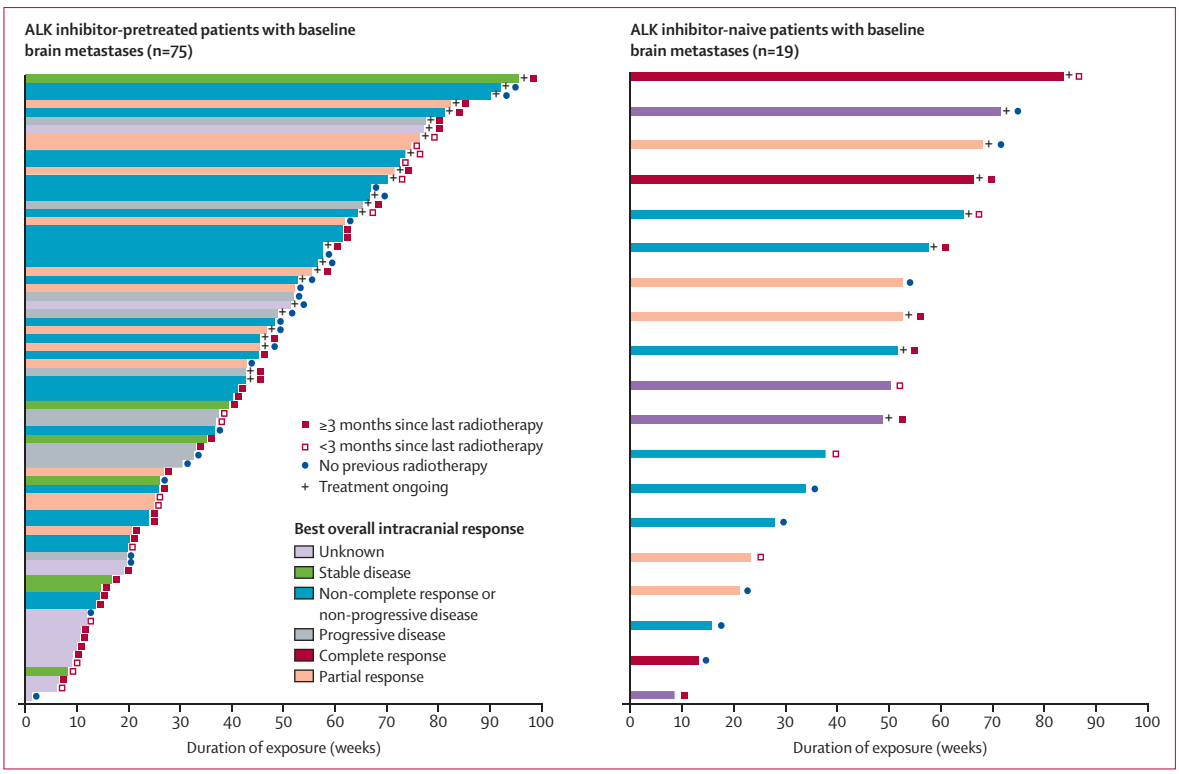

Figure 4: **Duration of exposure and best overall intracranial response in patients with baseline brain metastases and evaluable MRI or CT scans**
For patients who received previous radiotherapy, the duration between last radiotherapy treatment and start of ceritinib treatment (≥3 months or <3 months) is shown. NSCLC=non-small cell lung cancer.

Median duration of exposure to ceritinib 750 mg/day for all 246 patients was 38·6 weeks (IQR 18·3–59·4; appendix p 12), with a median average daily dose of 664·2 mg (607·8–750·0) and median relative dose intensity of 82·8% (70·6–97·5). Overall, 181 (74%) of 246 patients had at least one dose interruption, and 152 (62%) of 246 patients had at least one dose reduction. Dose reductions occurred throughout the dosing period (appendix p 10): 88 (36%) of 246 patients had one dose reduction, 48 (20%) had two dose reductions, and 16 (7%) had three or more dose reductions. In patients who discontinued ceritinib treatment, irrespective of the primary reason, 19 (23%) of 83 ALK inhibitor-naive and 43 (26%) of 163 ALK inhibitor-pretreated patients received further antineoplastic therapy after discontinuation (appendix p 11). However, data on antineoplastic therapy after discontinuation were collected for only 28 days after discontinuation, limiting the clinical interpretation of these data. In the 60 patients who continued ceritinib 750 mg/day beyond disease progression, the median duration of post-progression exposure was 10·1 weeks (IQR 6·6–26·1).

All 246 patients with *ALK*-rearranged NSCLC given ceritinib 750 mg/day had at least one adverse event (irrespective of study drug association; table 4), and 238 (97%) had an adverse event suspected to be related to treatment. At least one grade 3–4 adverse event was reported in 200 (81%) of 246 patients and at least one serious adverse event was reported in 117 (48%) of 246 patients (table 4; appendix pp 13–15, 17). Treatment-related grade 3–4 adverse events were reported in 125 (51%) of 246 patients and serious adverse events (of any grade) suspected to be drug-related were reported in 29 (12%) patients.

The most common grade 3–4 non-laboratory adverse events (irrespective of study drug association) were diarrhoea and nausea, both of which occurred in 15 (6%) patients. Gastrointestinal disorders occurred in 243 (99%) of patients, at mostly grade 1–2 and generally occurred early in treatment (median time to onset 4 days [IQR 1–13] for diarrhoea, 8 days [1–22] for nausea, and 8 days [2–32] vomiting). Gastrointestinal toxic effects were manageable through administration of concomitant medication and, when required, dose modification. The most common grade 3–4 laboratory adverse events (irrespective of study drug association) were increased alanine aminotransferase (73 [30%] patients) and increased aspartate aminotransferase (25 [10%] patients). These were manageable through dose interruption until resolution; no cases of Hy's law (ie, symptoms indicative of fatal liver injury) were recorded.

With regard to adverse events and laboratory abnormalities known to have been previously associated with ceritinib, grade 3–4 lipase increases (irrespective of

	Grade 1–2	Grade 3	Grade 4
Adverse events			
Diarrhoea	198 (80%)	15 (6%)	0
Nausea	190 (77%)	15 (6%)	0
Vomiting	139 (57%)	11 (4%)	0
Fatigue	94 (38%)	12 (5%)	0
Abdominal pain	91 (37%)	3 (1%)	0
Decreased appetite	89 (36%)	4 (2%)	0
Constipation	75 (30%)	0	0
Cough	71 (29%)	0	0
Abdominal pain, upper	57 (23%)	2 (1%)	0
Dyspnoea	52 (21%)	9 (4%)	1 (<1%)
Back pain	49 (20%)	1 (<1%)	0
Headache	47 (19%)	4 (2%)	0
Asthenia	45 (18%)	2 (1%)	0
Weight decreased	41 (17%)	4 (2%)	0
Insomnia	37 (15%)	0	0
Pyrexia	37 (15%)	0	0
Musculoskeletal pain	36 (15%)	0	0
Rash	33 (13%)	0	0
Dizziness	31 (13%)	0	0
Dyspepsia	30 (12%)	1 (<1%)	0
Arthralgia	26 (11%)	0	0
Musculoskeletal chest pain	26 (11%)	0	0
Anaemia	18 (7%)	12 (5%)	0
Pneumonia	13 (5%)	12 (5%)	0
Convulsion	7 (3%)	7 (3%)	1 (<1%)
Pneumonitis	1 (<1%)	6 (2%)	1 (<1%)
Respiratory failure	0	1 (<1%)	5 (2%)
Laboratory abnormalities			
Aspartate aminotransferase increased	56 (23%)	20 (8%)	5 (2%)
Blood creatinine increased	42 (17%)	0	0
Alanine aminotransferase increased	36 (15%)	66 (27%)	7 (3%)
Blood alkaline phosphatase increased	31 (13%)	13 (5%)	0
Hypokalaemia	17 (7%)	10 (4%)	1 (<1%)
Amylase increased	10 (4%)	7 (3%)	1 (<1%)
Hyponatraemia	8 (3%)	11 (4%)	0
Hypophosphataemia	8 (3%)	8 (3%)	0
Lipase increased	8 (3%)	13 (5%)	3 (1%)
γ-glutamyl transferase increased	7 (3%)	6 (2%)	1 (<1%)
Hyperglycaemia	6 (2%)	12 (5%)	3 (1%)

Data are number of patients with at least one adverse event, irrespective of study drug association (% of patients). NSCLC=non-small cell lung cancer. *Grade 5 adverse events were not specifically recorded, per the protocol; however, there were two deaths during the study that were regarded as related to study drug: one from interstitial lung disease (ALK inhibitor-pretreated patient) and the other from multiorgan failure (ALK inhibitor-naive patient).

Table 4: **Adverse events occurring at grades 1–2 in ≥10% or at grade 3 or grade 4* in ≥2% of patients with *ALK*-rearranged NSCLC (n=246)**

study drug association) were reported in 16 (7%) patients; however, no cases of increased lipase were classified as a serious adverse event, and no patients discontinued treatment as a result of this adverse event.

Grade 3–4 hyperglycaemia (irrespective of study drug association) was reported in 15 (6%) patients, and as a serious adverse event in six (2%) patients; no patients discontinued treatment due to adverse events or serious adverse events associated with hyperglycaemia (irrespective of study drug association). Grade 3 diabetic ketoacidosis (not suspected to be study drug related) was reported in one patient; no action was taken with the study drug and the adverse event resolved, without recurrence of hyperglycaemia. Interstitial lung disease or pneumonitis (grade 1–2 in one patient and grade 3–4 in eight patients) was reported in nine (4%) patients. No cases of grade 3–4 bradycardia were reported. There were no cases of corrected QT interval of greater than 500 ms; changes from baseline of the corrected QT interval of greater than 60 ms occurred in eight (3%) patients.

26 (11%) of 246 patients discontinued treatment due to adverse events, of which nine (35%) were suspected to be related to study drug. Adverse events leading to treatment discontinuation that were related to treatment were increased blood alkaline phosphatase (n=1), decreased appetite (n=1), pneumonitis (n=2), increased alanine transaminase (n=1), increased aspartate transaminase (n=1), corneal infiltrates (n=1), hepatitis cholestatic (n=1), interstitial lung disease (n=1), nausea (n=1), pain in extremity (n=1), pleural effusion (n=1), pleuritic pain (n=1), and acute renal failure (n=1).

Two on-treatment deaths were deemed to be related to study drug, one due to interstitial lung disease and the other due to multiorgan failure that occurred in the context of infection and ischaemic hepatitis. Adverse events in the 124 patients with brain metastases at baseline were consistent with those reported for the full study population (appendix p 16).

Discussion

In the updated analysis of this phase 1 study, ceritinib treatment resulted in clinically meaningful, rapid, and durable antitumour responses in both ALK inhibitor-naive and ALK inhibitor-pretreated patients with *ALK*-rearranged NSCLC, most of whom had received several previous lines of antineoplastic therapy. Additionally, ceritinib antitumour activity was shown in patients who had asymptomatic or controlled brain metastases at baseline, with both extracranial and intracranial responses noted.

Despite the initial efficacy of crizotinib, development of resistance to crizotinib (and other targeted therapeutics) remains an ongoing challenge that has limited its benefit in patients with NSCLC.[10,15,22,23] The first-in-human phase 1 study of crizotinib[7] assessed 143 patients with advanced stage *ALK*-rearranged NSCLC who had not previously received treatment with an ALK inhibitor. In these ALK inhibitor-naive patients, who had baseline characteristics consistent with those reported for other trials in patients with *ALK*-rearranged NSCLC,[8,21] 60·8% of patients

achieved an overall response and median progression-free survival was 9·7 months, both of which are lower than that noted in ALK inhibitor-naive patients in our updated analysis. Moreover, the median progression-free survival in ALK inhibitor-naive patients in our study was longer than that reported for patients who had received crizotinib after chemotherapy in another study (7·7 months),[8] and for patients who received crizotinib as first-line therapy (10·9 months) in the phase 3 PROFILE 1014 trial.[9] Of note, patients in the PROFILE 1014 study were systemic-treatment naive; in our study, 81% of ALK inhibitor-naive patients had received at least one line of previous antineoplastic therapy.

Patients who were ALK inhibitor-pretreated also achieved responses after previous treatment with crizotinib. In this subgroup, more than half of the patients had received at least three previous lines of therapy. The observed response is consistent with that reported for another phase 1 study[21] (done in the USA) investigating the second-generation ALK inhibitor alectinib in patients who had previously received crizotinib; in this study 55% of patients achieved an overall response.

The high proportion of patients who achieved an overall response and the high median duration of response reported with ceritinib in our study, particularly in ALK inhibitor-naive patients, are indicative of durable responses. Overall, outcomes in patients with advanced NSCLC are poor, with 28–45% achieving an overall response with first-line chemotherapy and a duration of response ranging from 4·5 to 5·3 months.[9,24] Responses with targeted therapies are consistently higher than with non-targeted therapies in patients with NSCLC with oncogenic driver mutations.[25] Nonetheless, in the first-in-human phase 1 study of crizotinib,[7] 60·8% achieved an overall response, with a corresponding duration of response of 49·1 weeks.

Brain metastases have been reported on diagnosis in around 24% of patients with advanced *ALK*-rearranged NSCLC, making activity in the brain an important feature of ALK-targeted therapies.[26] Despite evidence for potential clinical benefit of crizotinib in patients with baseline brain metastases,[27] the brain is the most common site of disease progression after resistance to crizotinib has been acquired.[11,12] Further, in a retrospective pooled analysis[28] of two crizotinib trials (PROFILE 1005 and 1007), 18% of patients achieved an overall intracranial response with crizotinib, which was substantially lower than the proportion who achieved an extracranial response (53%). The limited activity reported for crizotinib in the brain might be related to lower concentrations of the drug in cerebrospinal fluid compared with the plasma concentration (0·616 ng/mL *vs* 237 ng/mL, respectively, 5 h after administration of a 250 mg dose).[13]

Brain metastases are associated with a poor prognosis. In the general NSCLC population, survival is rarely extended beyond 12 months, and median progression-free survival times are in the range of 3–6 months.[29–31] Local ablative therapy is an option for patients with *ALK*-rearranged NSCLC receiving crizotinib who have progression in the brain.[12] However, recent data suggest that second-generation ALK inhibitors show both extracranial and intracranial antitumour activity,[21,32] representing an alternative to local ablative therapy. Nonetheless, these data should be interpreted with caution, because the contribution of previous radiotherapy to efficacy outcomes in this population of patients is unknown.

The retrospective central analysis of intracranial responses was done in patients with baseline brain metastases who were asymptomatic or had stable CNS disease. Because it was done retrospectively, this analysis has some limitations, including that the predefined study assessments, data collection schedule, and sample size were not specifically designed to assess this endpoint. Nevertheless, we found promising evidence of intracranial activity, with a high proportion of patients achieving intracranial disease control, in both ALK inhibitor-naive and ALK inhibitor-pretreated patients. Moreover, the median time to intracranial response was similar to that reported for whole-body responses. Because radiotherapy is often used to treat brain lesions,[31] 67% of patients included in the central analysis had previously received radiotherapy to the brain (although, because this was a retrospective analysis, whether radiotherapy was whole-brain or stereotactic had not been recorded). Nonetheless, six of 11 patients with measurable brain disease were radiotherapy-naive and achieved a partial response, indicative of blood–brain barrier penetration of this highly potent ALK inhibitor.[20] A confirmatory phase 2 clinical trial, which is expected to enrol about 125 patients, is ongoing to assess ceritinib activity in patients with *ALK*-rearranged NSCLC and metastases to the brain or leptomeninges (NCT02336451). Patients will be stratified according to previous ALK inhibitor treatment (pretreated or naive), whether they have received previous whole-brain radiotherapy, and presence of leptomeningeal disease.

Our analysis shows that the safety profile for ceritinib is similar to that reported previously after a shorter duration of follow-up,[18] and is broadly consistent in patients with or without brain metastases. Gastrointestinal adverse events, mostly grade 1–2, were the most frequent adverse events in patients who received ceritinib. These adverse events were manageable (only one patient discontinued ceritinib due to a gastrointestinal adverse event) and highlight the potential need for early, proactive management and patient education.[33] Direct comparison of adverse event frequency between different studies is not possible, limiting the direct comparison of adverse events between ceritinib and crizotinib. Common side-effects listed for crizotinib include diarrhoea and nausea,

reported in about 50–60% of patients, and visual disorders in about 60% of patients.[7,8] Raised liver aminotransferases have also been reported as a common side-effect with crizotinib; however, this finding seems to be more variable across studies than for nausea or diarrhoea.[7,8] In our study, grade 3–4 increases in liver enzymes were common, but manageable through dose interruption or reduction (after which patients could resume ceritinib treatment). Interstitial lung disease and pneumonitis, also known complications of crizotinib treatment,[8] were reported for a small proportion of patients in this study. Overall, discontinuation due to adverse events with ceritinib was low. Additionally, data for patient-reported outcomes from ongoing phase 2 studies of ceritinib (including patients who had previously received crizotinib as well as ALK inhibitor-naive patients) have shown that quality of life is maintained, with reductions in lung symptoms during the course of treatment.[34,35]

In this updated analysis of the ASCEND-1 study, ALK inhibitor-naive and ALK inhibitor-pretreated patients given 750 mg/day had durable responses and prolonged progression-free survival, along with a manageable safety profile and low frequency of study discontinuation. A high number of responses were observed in patients with and without baseline brain metastases. Furthermore, a high proportion of patients achieved intracranial responses, including patients with measurable brain lesions who were radiotherapy naive. Taken together, these data expand our understanding of the efficacy and safety of ceritinib and its role in the management of patients with *ALK*-rearranged NSCLC.

Contributors

RM, LQMC, AS, AY, and ATS were responsible for the study design. EF, SSh, and JW contributed to the protocol assessment. D-WK, RM, DSWT, LQMC, JV, TDP, GJR, BJS, GL, ATS, and MS contributed to data collection. D-WK, RM, DSWT, EF, DRC, JV, SSh, TDP, GJR, BJS, JW, MT, MS, GL, SSu, SL, TS, AY, and ATS contributed to data analysis. D-WK, RM, DSWT, EF, DRC, JV, SSh, TDP, GJR, BJS, JW, MT, MS, GL, AS, SSu, SL, TS, AY, and ATS contributed to data interpretation. AY was responsible for data cleaning. All authors were responsible for the preparation and review of the manuscript.

Declaration of interests

D-WK reports personal fees from Novartis and Pfizer, outside the submitted work. RM reports personal fees from Bristol-Myers Squibb and Novartis, and non-financial support from Bristol Myers Squibb, Novartis, and Pfizer, outside the submitted work. DSWT reports research grants from Novartis, and advisory roles for Novartis, Boehringer Ingelheim, and Pfizer. EF reports personal fees from Lily, Roche, Boehringer Ingelheim, Bristol-Myers Squibb, and Novartis, outside the submitted work. LQMC reports non-financial support from Novartis, during the conduct of the study, and grants, non-financial support, and personal fees from Novartis, outside the submitted work. DRC reports personal fees from Servier, Lilly, Roche, Astex, Ariad, ImmunoGen, Clarient, Excelixis, IndiPharm, Astellas, Boehringer Ingelheim, Chugai, Clovis, Array Biopharma, AstraZeneca, Novartis, and Synta, honoraria from Ariad, Boehringer Ingelheim, Synta, Array Biopharma, and Pfizer, and grants from Ariad, outside the submitted work. JV reports personal fees from Novartis, during the conduct of the study. SSh reports grants and personal fees from Novartis, stock from Salarius Pharmaceuticals, Beta Cat Pharmaceuticals, and ConverGene, and personal fees from VBL Therapeutics (for serving on an independent data monitoring committee) and Arrien Pharma, outside the submitted work. GJR reports grants from Novartis, during the conduct of the study, and personal fees from Novartis, outside the submitted work. BJS reports personal fees from Novartis, Pfizer, Clovis, Clovis Oncology, AstraZeneca, and Roche, outside the submitted work. JW reports grants and personal fees from AstraZeneca, Novartis, Roche, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, and Clovis, and non-financial support from Novartis, Roche, and Boehringer Ingelheim, outside of the submitted work. MT reports personal fees from Lilly, Bristol-Myers Squibb, Roche, Boehringer Boehringer Ingelheim, Novartis, Pfizer, MSD, and Celgene, outside the submitted work. MS reports personal fees from AstraZeneca, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Lilly, Novartis, and Pfizer, and grants from Boehringer Ingelheim and Novartis, outside the submitted work. GL reports personal fees from AstraZeneca, Pfizer, and Novartis, outside the submitted work. SSu, SL, and TS are employees of Novartis. AY is an employee and owns stock in Novartis. ATS reports grants and personal fees from Novartis, during the conduct of the study, and personal fees from Ignyta, Blueprint, Pfizer, Ariad, Chugai, Genentech, and Roche, outside the submitted work. TDP and AS declare no competing interests.

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