First-line ceritinib versus platinum-based chemotherapy in advanced *ALK*-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study

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Summary

Background The efficacy of ceritinib in patients with untreated anaplastic lymphoma kinase (*ALK*)-rearranged non-small-cell lung cancer (NSCLC) is not known. We assessed the efficacy and safety of ceritinib versus platinum-based chemotherapy in these patients.

Methods This randomised, open-label, phase 3 study in untreated patients with stage IIIB/IV *ALK*-rearranged non-squamous NSCLC was done in 134 centres across 28 countries. Eligible patients were assigned via interactive response technology to oral ceritinib 750 mg/day or platinum-based chemotherapy ([cisplatin 75 mg/m² or carboplatin AUC 5–6 plus pemetrexed 500 mg/m²] every 3 weeks for four cycles followed by maintenance pemetrexed); randomisation was stratified by World Health Organization performance status (0 *vs* 1–2), previous neoadjuvant or adjuvant chemotherapy, and presence of brain metastases as per investigator's assessment at screening. Investigators and patients were not masked to treatment assignment. The primary endpoint was blinded independent review committee assessed progression-free survival, based on all randomly assigned patients (the full analysis set). Efficacy analyses were done based on the full analysis set. All safety analyses were done based on the safety set, which included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01828099.

Findings Between Aug 19, 2013, and May 11, 2015, 376 patients were randomly assigned to ceritinib (n=189) or chemotherapy (n=187). Median progression-free survival (as assessed by blinded independent review committee) was 16·6 months (95% CI 12·6–27·2) in the ceritinib group and 8·1 months (5·8–11·1) in the chemotherapy group (hazard ratio 0·55 [95% CI 0·42–0·73]; p<0·00001). The most common adverse events were diarrhoea (in 160 [85%] of 189 patients), nausea (130 [69%]), vomiting (125 [66%]), and an increase in alanine aminotransferase (114 [60%]) in the ceritinib group and nausea (in 97 [55%] of 175 patients), vomiting (63 [36%]), and anaemia (62 [35%]) in the chemotherapy group.

Interpretation First-line ceritinib showed a statistically significant and clinically meaningful improvement in progression-free survival versus chemotherapy in patients with advanced *ALK*-rearranged NSCLC.

Funding Novartis Pharmaceuticals Corporation.

Introduction

Anaplastic lymphoma kinase (*ALK*)-rearrangements are oncogenic drivers that occur in 3–7% of patients with non-small-cell lung cancer (NSCLC). Most patients with *ALK*-rearranged NSCLC are usually younger, are never smokers or have a light smoking history, and have adenocarcinoma histology.[1,2]

Crizotinib, an oral small-molecule tyrosine kinase inhibitor of ALK, MET, and ROS1 kinases, was superior to pemetrexed-platinum chemotherapy in patients with untreated advanced *ALK*-rearranged NSCLC (median progression-free survival was 10·9 months *vs* 7·0 months, respectively).[3] However, most patients treated with crizotinib ultimately progress,[4,5] with the CNS being the common site of progression.[6]

Ceritinib (LDK378; Novartis, East Hanover, NJ, USA) is a next-generation, selective oral ALK inhibitor with a 20 times greater potency than crizotinib in enzymatic assays.[7] It crosses the blood–brain barrier with a brain-to-blood exposure ratio of about 15% in a rat model.[8] Results from the phase 1 ASCEND-1 study[9,10] and phase 2 ASCEND-3 study[11] demonstrated consistent, high, and durable antitumour efficacy of ceritinib 750 mg/day in ALK inhibitor-naive patients with *ALK*-rearranged NSCLC who had progressed on multiple lines of chemotherapy (median progression-free survival of 18·4 months for both studies).[10,11]

ASCEND-4 is the first randomised, global, phase 3 study to evaluate the efficacy, safety, and patient-reported outcomes of ceritinib versus platinum-pemetrexed doublet followed by pemetrexed maintenance in untreated patients with advanced *ALK*-rearranged NSCLC. The comparator group, platinum-pemetrexed doublet, was the standard of care in patients with non-squamous NSCLC[12,13]

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Research in context

Evidence before this study

We searched PubMed on Dec 6, 2016, for reports on clinical trials in advanced untreated anaplastic lymphoma kinase (*ALK*)-rearranged non-small-cell lung cancer (NSCLC) using the following search string "(ALK AND NSCLC) AND (naïve OR naive OR untreated OR first-line)". We did not limit our search by date or language. These searches indicated that the only phase 3 trial published for first-line treatment of ALK-positive NSCLC was for crizotinib (PROFILE 1014) that compared efficacy and safety of crizotinib, an ALK inhibitor with platinum-pemetrexed combination without maintenance treatment. Ceritinib is a next-generation, selective oral ALK inhibitor with 20 times greater potency than crizotinib in enzymatic assays. Results from the phase 1 ASCEND-1 study and phase 2 ASCEND-3 study demonstrated consistent, high, and durable antitumour efficacy of ceritinib 750 mg/day in ALK inhibitor-naive patients with *ALK*-rearranged NSCLC who had progressed on multiple lines of chemotherapy.

Added value of this study

Ceritinib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival versus pemetrexed-platinum chemotherapy including maintenance pemetrexed in untreated patients with *ALK*-rearranged NSCLC. The study's primary objective, median progression-free survival as assessed by blinded independent review committee, was 16·6 months (95% CI 12·6–27·2) for ceritinib versus 8·1 months (5·8–11·1) for chemotherapy (with an estimated 45% risk reduction for progression-free survival [HR 0·55, 95% CI 0·42–0·73; p<0·00001]). Improvement in progression-free survival was observed both in patients with or without brain metastases at study entry. The overall response with ceritinib was high, rapid, and prolonged. Additionally, ceritinib had a higher overall intracranial response as compared with chemotherapy. Ceritinib significantly improved the general quality of life and significantly prolonged time to deterioration for lung cancer-specific symptoms compared with chemotherapy. The safety profile of ceritinib was consistent with previous reports.

Implications of all the available evidence

Patients with advanced *ALK*-rearranged NSCLC treated with first-line ceritinib had a statistically significant and clinically meaningful improvement in progression-free survival compared with chemotherapy. Overall, ceritinib should be considered as a new first-line therapeutic option in patients with *ALK*-rearranged NSCLC.

when ASCEND-4 was implemented and pemetrexed maintenance demonstrated additional improvement in progression-free survival and overall survival versus placebo.[14–16]

Methods

Study design and participants

This randomised, open-label, global, phase 3 study was done in 134 sites that randomly assigned at least one patient across 28 countries (Australia, New Zealand, Austria, Brazil, China, Colombia, Denmark, France, Germany, Greece, India, Ireland, Italy, Japan, South Korea, Lebanon, Mexico, Netherlands, Norway, Portugal, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, and UK). Adult patients (aged ≥18 years) were eligible if they had histologically or cytologically confirmed locally advanced or metastatic non-squamous *ALK*-rearranged NSCLC, untreated with any systemic anticancer therapy (except neoadjuvant or adjuvant systemic therapy [if relapse had occurred >12 months from the end of therapy]); measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, WHO performance status 0–2, and asymptomatic or neurologically stable brain metastases (for ≥2 weeks). *ALK*-rearrangement was determined centrally by the VENTANA anti-ALK (D5F3) immunohistochemistry assay. Previous radiotherapy to the brain must have been completed at least 2 weeks before the start of ceritinib treatment. Patients were excluded if they had known hypersensitivity to any of the excipients of ceritinib; history of severe hypersensitivity reaction to platinum-containing drugs, pemetrexed, or any known excipients of these drugs; history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis; history of carcinomatous meningitis; a concurrent malignancy or history of a malignant disease other than NSCLC that had been diagnosed or required therapy within the past 3 years (except completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type); clinically significant, uncontrolled heart disease, or recent cardiac event (within 6 months); and impairment of gastrointestinal function or gastrointestinal disease that could substantially alter the absorption of ceritinib. Patients who received thoracic radiotherapy to lung fields 4 weeks or less before starting the study treatment or patients who had not recovered from radiotherapy-related toxicities were excluded. Additionally, patients who underwent major surgery within 4 weeks before (2 weeks for resection of brain metastases) starting study treatment or had not recovered from side-effects of such procedure were also excluded. This study was done in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review

board at each centre. All patients provided written informed consent before screening. The study protocol, including the statistical analysis plan, is available in the appendix.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive either ceritinib 750 mg/day orally (given in a fasted state) daily or intravenous chemotherapy (cisplatin [75 mg/m²], or carboplatin [target area under the curve of 5–6] plus pemetrexed [500 mg/m²]) given every 21 days. Randomisation was done via interactive response technology (see study protocol in appendix for more details). Randomisation was stratified by WHO performance status (0 *vs* 1–2), previous neoadjuvant or adjuvant chemotherapy (yes *vs* no), and brain metastases as per investigator's assessment at screening (present *vs* absent). In this open-label study, investigators and patients were not masked to treatment assignment; most study sponsor personnel remained masked to treatment assignment until database lock for the primary analysis. An exception was made for some members of the clinical trial team who were allowed to view individual patient data reported on the following case report forms: pharmacokinetics-related data; study drug dose administration records; and previous and concomitant medications.

Procedures

Patients who completed four cycles of chemotherapy without progressive disease subsequently received pemetrexed maintenance (500 mg/m²) every 21 days. Treatment was continued until patients experienced progressive disease according to RECIST 1.1 criteria as confirmed by the blinded independent review committee, or development of unacceptable toxicity. Treatment beyond progression was permitted in patients who (according to investigators' judgment) continued to have a clinical benefit (patients receiving ceritinib post progression were not followed for efficacy or patient-reported outcomes). Patients randomly assigned to chemotherapy were allowed to crossover to ceritinib if they had blinded independent review committee confirmed RECIST-defined progressive disease. Patients treated with ceritinib were allowed a maximum of three dose reductions (150 mg per reduction, to a lowest dose of 300 mg/day). For patients treated with chemotherapy, dose reductions followed package insert or local guidelines.

Outcomes

The primary endpoint was progression-free survival, defined as the time from randomisation to the date of the first radiologically documented disease progression (assessed by the blinded independent review committee according to RECIST 1.1) or death due to any cause. The key secondary endpoint was overall survival. Other secondary endpoints included progression-free survival assessed by the investigator; overall response rate, duration of response, disease control rate, and time to response assessed by the blinded independent review committee and the investigator; overall intracranial response rate; intracranial disease control rate; duration of intracranial response; intracranial clinical benefit rate (this was added added post hoc); patient-reported outcomes and safety; and ceritinib pharmacokinetics. Ceritinib pharmacokinetics are not reported here but were similar to those previously reported.[17]

See Online for appendix

Tumour response was assessed by the investigator and blinded independent review committee based on RECIST 1.1 criteria. All patients who had progressive disease determined by the investigator required an expedited review by the blinded independent review committee. The intracranial response was assessed based on images collected for the blinded independent review committee, by an independent central neuroradiologist (from the blinded independent review committee) who was masked to treatment. RECIST 1.1 was modified to allow a more rigorous evaluation of intracranial response to the treatment; a maximum of five target lesions located in the brain could be selected (if the minimum size of the longest diameter was 10 mm) at baseline and evaluated at each subsequent timepoint.

Tumour assessments were done at baseline, every 6 weeks after cycle 1 day 1 through month 33, every 9 weeks, and at end of treatment for response determination. Patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, or progressive disease continued assessments as per schedule until progressive disease, consent withdrawal, or death. Patients who progressed as per progressive disease, assessed by the blinded independent review committee, or withdrew consent were subsequently followed for survival every 12 weeks until death, lost to follow-up, or consent withdrawal. All adverse events reported were recorded and graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Efficacy endpoints were analysed based on the full analysis set, which consisted of all randomly assigned patients. Safety analyses were done in patients who received at least one dose of study drug (safety set). Patient-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life core questionnaire (QLQ-C30), the corresponding lung cancer module (QLQ-LC13), Lung Cancer Symptom Scale (LCSS), and the EuroQol Group 5-Dimension (EQ-5D-5L) self-report questionnaire (appendix).

Statistical analysis

Assuming a median progression-free survival of 8 months in the chemotherapy group, it was expected that ceritinib would result in 38% risk reduction in the hazard rate. Assuming a true hazard ratio (HR) of 0·62,

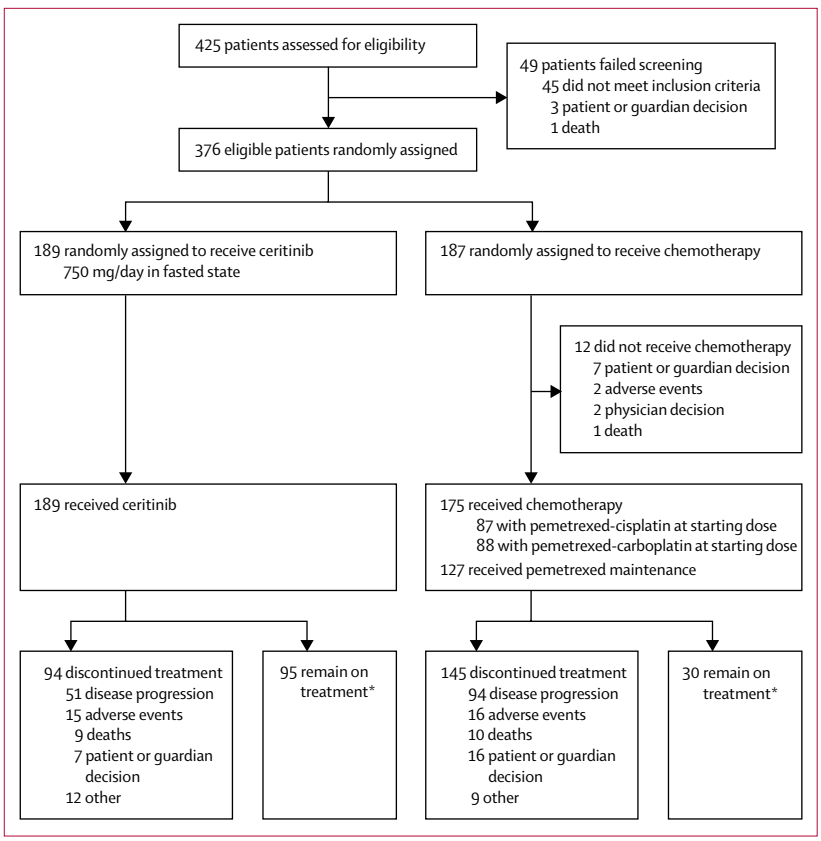

Figure 1: **Trial profile**
*At data cutoff (June 24, 2016).

under the alternative hypothesis, about 205 progression-free survival events were required to have 90% power at a one-sided 2·5% level of significance to reject the null hypothesis (HR=1) using a log-rank test and a two-look group sequential design. Approximately 348 patients were needed to be randomly assigned to the two treatment groups in a 1:1 ratio. One futility interim analysis was planned for the primary endpoint of progression-free survival as per the blinded independent review committee assessment when approximately 72 progression-free survival events of the targeted 205 progression-free survival events (35% of the required number of events) were documented. At the cutoff date of March 23, 2015, for interim analysis, 85 progression-free survival events (41·4% of the required number of events) were observed. Upon data monitoring committee recommendation, the study continued without modification. Overall survival analyses were to be done if the primary endpoint was statistically significant using a group sequential design with three interim analyses and final analysis at approximately 253 deaths (one-sided 2·5% significance level). The alpha-spending function prespecified in the protocol to calculate the stopping boundary was used to control the cumulative type I error rate.

A Cox regression model stratified by randomisation stratification factors was used to estimate the HR, together with 95% CIs based on the Wald test. A stratified log-rank test (randomisation stratification factors) was used for treatment comparisons of progression-free survival and overall survival. The statistical basis for a claim of efficacy was the statistical significance (at the 2·5% one-sided level of significance) for progression-free survival in favour of ceritinib. Kaplan-Meier methodology was used to analyse the time-to-event endpoints (appendix). This trial is registered with ClinicalTrials.gov, number NCT01828099.

Role of the funding source

The study was designed by academic investigators and representatives of the funder (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA). All authors contributed to the interpretation of data and the subsequent writing, reviewing, and amending of the report; the first draft of the report was prepared by the first author (J-CS) and a medical writer employed by the funder. All authors vouch for the accuracy and completeness of the data and attest that the study conformed to the protocol and statistical analysis plan.

Results

Between Aug 19, 2013, and May 11, 2015, 376 patients were randomly assigned to ceritinib (n=189) or chemotherapy (n=187; the full analysis set). All patients assigned to ceritinib were treated. In the chemotherapy group, 175 patients were treated, 87 patients received pemetrexed-cisplatin, and 88 patients received pemetrexed-carboplatin at starting dose (figure 1). None of the patients in the ceritinib group and two patients in the chemotherapy group had protocol deviations that led to exclusion from the per-protocol set. Furthermore, 127 (73%) of 175 patients in the chemotherapy group received pemetrexed maintenance. Among the patients who discontinued chemotherapy (n=145), 105 (72%) received an ALK inhibitor as a first treatment after discontinuation of chemotherapy, including 80 patients who received ceritinib after crossing over to ceritinib in the study (extension phase). Baseline and disease characteristics were well balanced between the groups (table 1). 50 patients had previous radiotherapy to the brain; 45 of 50 within 3 months from randomisation (table 1). Among patients with brain metastases, 19 (31%) of 61 patients in the ceritinib group and 15 (25%) of 60 patients in the chemotherapy group had at least five documented brain lesions as per the blinded independent review committee neuroradiologist. Among the 59 patients with baseline brain metastases treated with ceritinib, 31 had documented progressive disease at the data cutoff date (15 [48%] of 31 patients had intracranial progression only, 13 [42%] patients had extracranial progression only, and three [10%] patients had intracranial and extracranial progression). Among the

130 patients without baseline brain metastases and treated with ceritinib, 81 had documented progressive disease at the data cutoff date (24 [30%] of 81 patients had intracranial progression only, 56 [69%] patients extracranial progression only, and one [1%] patient had intracranial and extracranial progression). Of the 121 patients who had brain metastases (measurable or non-measurable) at baseline, 55 patients had measurable disease in the brain at baseline; of these, 44 patients (22 patients in each group) had active brain metastases and at least one post-baseline assessment.

At data cutoff (June 24, 2016), the median duration between randomisation and progression-free survival analysis for all patients was 19·7 months; 202 progression-free survival events had been documented by the blinded independent review committee and 218 by investigator assessment.

The study met its primary objective. Median progression-free survival as assessed by the blinded independent review committee was 16·6 months (95% CI 12·6–27·2) in the ceritinib group versus 8·1 months (5·8–11·1) in the chemotherapy group, with an estimated risk reduction of 45% in progression-free survival (HR 0·55 [95% CI 0·42–0·73]; p<0·00001; figure 2A). The robustness of the progression-free survival results by the blinded independent review committee was supported by the results of the investigator assessments. The median progression-free survival assessed by the investigators was 16·8 months (95% CI 13·5–25·2) for ceritinib versus 7·2 months (95% CI 5·8–9·7) for chemotherapy (HR 0·49 [95% CI 0·37–0·64]; p<0·00001; figure 2B). The progression-free survival benefit in favour of ceritinib was observed across most predefined subgroups, except in subgroups where there was large variability due to a small sample size (figure 3).

The progression-free survival benefit of ceritinib over chemotherapy was recorded in patients with or without baseline brain metastases (figure 2C). The median progression-free survival assessed by the blinded independent review committee in patients without brain metastases (n=126, 34%) was 26·3 months (95% CI 15·4–27·7) in the ceritinib group versus 8·3 months (6·0–13·7) in the chemotherapy group (HR 0·48 [95% CI 0·33–0·69]). The median progression-free survival assessed by blinded independent review committee in patients with brain metastases (n=121, 32%) was 10·7 months (95% CI 8·1–16·4) in the ceritinib group versus 6·7 months (4·1–10·6) in the chemotherapy group (HR 0·70 [95% CI 0·44–1·12]). The results of the progression-free survival analysis assessed by blinded independent review committee using the per-protocol set (appendix) were consistent with that of the primary analysis based on the full analysis set. Investigator-reported progression-free survival in patients with or without baseline brain metastases were consistent with those reported by the blinded independent review committee. The median progression-free survival assessed by investigator in patients without brain metastases was 25·2 months (95% CI 13·9 to not estimable) in the ceritinib group versus 8·3 months (5·8–11·1) in the chemotherapy group (HR 0·44 [95% CI

	Ceritinib (n=189)	Chemotherapy (n=187)
Median age (years)	55·0 (22–81)	54·0 (22–80)
Sex		
Female	102 (54%)	114 (61%)
Male	87 (46%)	73 (39%)
Race		
Asian	76 (40%)	82 (44%)
Caucasian	104 (55%)	98 (52%)
Other	9 (5%)	7 (4%)
WHO performance status		
0	69 (37%)	70 (37%)
1	107 (57%)	105 (56%)
2	13 (7%)	11 (6%)
Missing	0	1 (1%)
Smoking history		
Current smoker	15 (8%)	15 (8%)
Ex-smoker	66 (35%)	50 (27%)
Never smoked	108 (57%)	122 (65%)
Histology or cytology		
Adenocarcinoma	180 (95%)	183 (98%)
Stage at time of study entry		
Locally advanced (stage IIIb)	9 (5%)	5 (3%)
Metastatic (stage IV)	180 (95%)	182 (97%)
Metastatic site of cancer		
Bone	77 (41%)	80 (43%)
Brain	59 (31%)	62 (33%)
Liver	34 (18%)	39 (21%)
Previous antineoplastic therapy		
Surgery		
No	145 (77%)	144 (77%)
Yes	44 (23%)	43 (23%)
Radiotherapy		
No	152 (80%)	147 (79%)
Yes	37 (20%)	40 (21%)
Previous radiotherapy to the brain		
No	165 (87%)	161 (86%)
Yes	24 (13%)	26 (14%)
Time from radiotherapy to the brain to randomisation*		
≤3 months	22/24 (92%)	23/26 (89%)
Medication: chemotherapy setting		
Adjuvant	10 (5%)	7 (4%)
Neoadjuvant	0	2 (1%)
Number of previous regimens of neoadjuvant or adjuvant chemotherapy		
1	10 (5%)	9 (5%)

Data are mean (SD), n (%), or n/N (%). *Denominator is the number of patients with previous radiotherapy to the brain.

Table 1: **Patient characteristics at baseline (the full analysis set)**

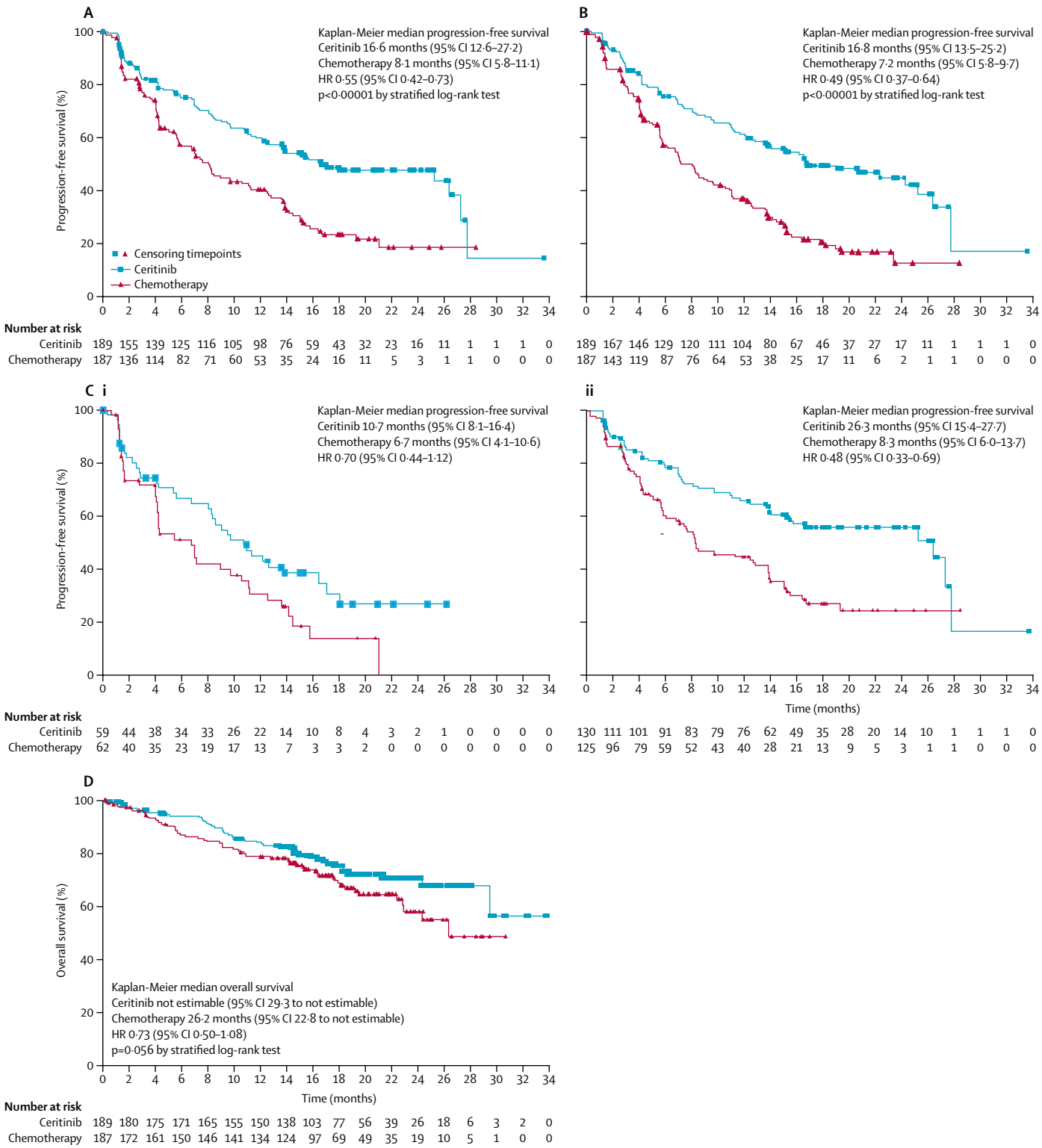

Figure 2: **Progression-free survival and overall survival**

(A) Kaplan-Meier plot of progression-free survival by blinded independent review committee. (B) Kaplan-Meier plot of progression-free survival by investigator assessment. (C) Kaplan-Meier plot of progression-free survival by brain metastases at baseline as per blinded independent review committee assessment: (i) brain metastases at baseline; (ii) no brain metastases at baseline. (D) Overall survival in the full analysis set.

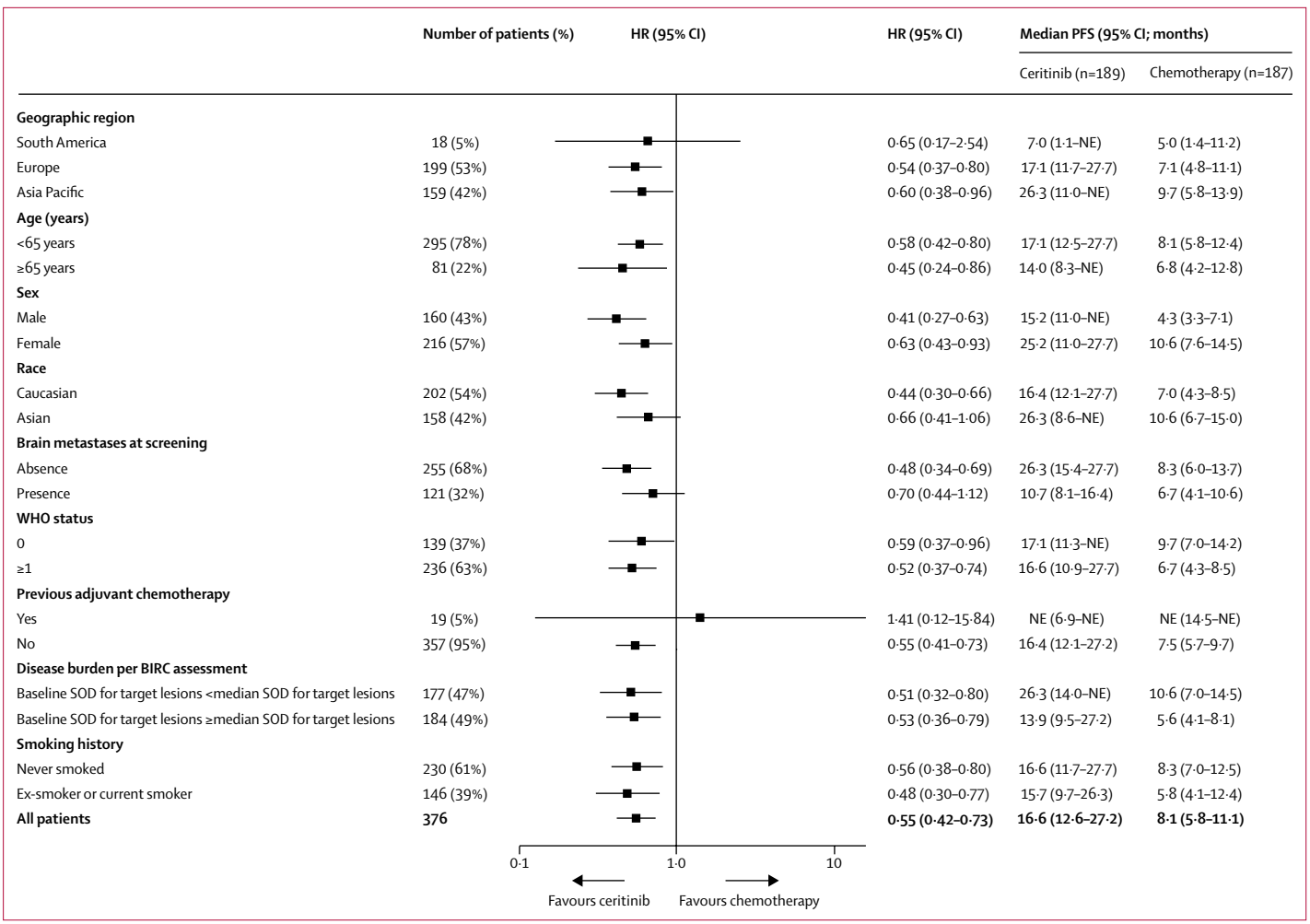

Figure 3: **Progression-free survival according to subgroups as per blinded independent review committee assessment**
All subgroup analyses yielded hazard ratios (HRs) favouring treatment with ceritinib except for the subgroup of patients who had previous adjuvant therapy and the subgroup of patients from South America where there was large variability due to a small sample size of only 19 patients (HR 1·41 [95% CI 0·12–15·84]) and 18 patients (HR 0·65 [95% CI 0·17–2·54]), respectively. In Asians, the upper bound CI of median progression-free survival is not estimable with a high censoring rate of 57·9% (44 patients), of which 34 patients were ongoing treatment; the 18-month progression-free survival by blinded independent review committee assessment was 53·7% (95% CI 40·8–65·0). Patients with missing subgroup information were not included. Among races, black and other races were not included since the number of patients were not more than ten. In the disease burden subgroup, only patients with target lesions were included. BIRC=blinded independent review committee. PFS=progression-free survival. SOD=sum of diameters. NE=not estimable.

0·31–0·63]). The median progression-free survival by investigator assessment in patients with brain metastases was 13·5 months (95% CI 9·0–16·7) in the ceritinib group versus 6·7 months (4·2–10·6) in the chemotherapy group (HR 0·58 [95% CI 0·36–0·92]).

Because the progression-free survival assessed by the blinded independent review committee was statistically significant favouring ceritinib, statistical testing was done for overall survival based on a predefined hierarchical testing procedure as per the study protocol. At the time of analysis (June 24, 2016), the overall survival data were not mature with 107 overall survival events (48 events in the ceritinib group and 59 events in the chemotherapy group) representing 42% of the required events for final overall survival analysis. The median overall survival was not reached in the ceritinib group (95% CI 29·3 to not estimable) and was 26·2 months (22·8 to not estimable) in the chemotherapy group (HR 0·73 [95% CI 0·50–1·08]; p=0·056; figure 2D). The estimated overall survival rates at 24 months were 70·6% (95% CI 62·2–77·5) in the ceritinib group and 58·2% (47·6–67·5) in the chemotherapy group. The study did not cross the efficacy stopping boundary for overall survival (–3·2546 [Z-scale] corresponding to p=0·0006 on the p-value scale) at this analysis. 105 (72%) of 145 patients received an ALK inhibitor after discontinuation of chemotherapy.

An overall response as assessed by the blinded independent review committee was recorded in 137 (72·5% [95% CI 65·5–78·7]) of 189 patients in the ceritinib group and 50 (26·7% [20·5–33·7]) of 187 patients in the chemotherapy group (appendix). The best percentage change from baseline in the sum of tumour diameters in

	All patients		Patients with no previous radiotherapy	
	Ceritinib	Chemotherapy	Ceritinib	Chemotherapy
Intracranial response in all patients with baseline brain metastases and at least one post-baseline assessment (BIRC neuroradiologist)				
Number	54	52	32	31
Overall intracranial response rate	25 (46·3%, 32·6–60·4)	11 (21·2%, 11·1–34·7)	15 (46·9%, 29·1–65·3)	9 (29·0%, 14·2–48·0)
Complete response	11 (20·4%)	7 (13·5%)	8 (25·0%)	6 (19·4%)
Partial response	14 (25·9%)	4 (7·7%)	7 (21·9%)	3 (9·7%)
Stable disease	23 (42·6%)*	37 (71·1%)†	14 (43·8%)‡	21 (67·7%)§
Progressive disease	3 (5·6%)	3 (5·8%)	3 (9·4%)	0
Unknown	3 (5·6%)	1 (1·9%)	0	1 (3·2%)
Intracranial clinical benefit rate at ≥12 weeks	43 (79·6%, 66·5–89·4)	39 (75·0%, 61·1–86·0)	..	..
Intracranial clinical benefit rate at ≥24 weeks	38 (70·4%, 56·4–82·0)	29 (55·8%, 41·3–69·5)	..	..
Intracranial response in patients with measurable baseline brain metastases and at least one post-baseline assessment (BIRC neuroradiologist)				
Number	22	22	13	18
Overall intracranial response rate	16 (72·7%, 49·8–89·3)	6 (27·3%, 10·7–50·2)	9 (69·2%, 38·6–90·9)	5 (27·8%, 9·7–53·5)
Complete response	2 (9·1%)	2 (9·1%)	2 (15·4%)	2 (11·1%)
Partial response	14 (63·6%)	4 (18·2%)	7 (53·8%)	3 (16·7%)
Stable disease	3 (13·6%)	14 (63·6%)	3 (23·1%)	12 (66·7%)
Progressive disease	1 (4·5%)	1 (4·5%)	1 (7·7%)	0
Unknown	2 (9·1%)	1 (4·5%)	0	1 (5·6%)
Intracranial clinical benefit rate at ≥12 weeks	19 (86·4%, 65·1–97·1)	15 (68·2%, 45·1–86·1)	..	..
Intracranial clinical benefit rate at ≥24 weeks	19 (86·4%, 65·1–97·1)	11 (50·0%, 28·2–71·8)	..	..

Data are n (%) or n (%, 95% CI). Intracranial clinical benefit rate is the proportion of patients with a best overall response of complete response or partial response, or an overall lesion response of stable disease or non-complete response and non-progressive disease or better at ≥12 weeks or ≥24 weeks. BIRC=blinded independent review committee. *20 cases with no complete response or progressive disease are based on patients with non-measurable disease. †23 cases with no complete response or progressive disease are based on patients with non-measurable disease. ‡11 cases with no complete response or progressive disease are based on patients with non-measurable disease. §Nine cases with no complete response or progressive disease are based on patients with non-measurable disease.

Table 2: **Overview of intracranial responses (by blinded independent review committee using mRECIST 1.1) in patients with brain metastases at baseline and at least one post-baseline assessment in the full analysis set**

individual patients is shown in the appendix. Responses with ceritinib were deep, rapid, and prolonged. The median time to response assessed by the blinded independent review committee was 6·1 weeks (IQR 5·9–6·7, n=137) for ceritinib and 13·4 weeks (11·1–29·7, n=50) for chemotherapy. The median duration of response was 23·9 months (95% CI 16·6 to not estimable) in the ceritinib group and 11·1 months (7·8–16·4) with chemotherapy; in the responders, estimated event-free rates at 21 months were 59·0% (49·3–67·4) with ceritinib and not estimable with chemotherapy (appendix). Investigator-reported overall response and duration of response were consistent and similar to those reported by the blinded independent review committee (appendix).

An overall intracranial response in patients with measurable brain metastases at baseline (all of whom had active brain metastases and who had at least one post-baseline assessment) was recorded in 16 (72·7%) of 22 patients (two complete responses and 14 partial responses) in the ceritinib group and six (27·3%) of 22 patients (two complete responses and four partial responses) in the chemotherapy group (table 2). Median duration of intracranial response was 16·6 months (95% CI 8·1 to not estimable) in the ceritinib group, and it was not estimable in the chemotherapy group because four of six patients had not progressed at the time of analysis. The best percentage change from baseline in sum of tumour diameters as per neuroradiologist review in patients with measurable brain metastases at baseline and at least one post-baseline assessment is shown in the appendix. The intracranial clinical benefit rate at 24 weeks or longer was recorded in 19 (86·4%) of 22 patients (95% CI 65·1–97·1) with ceritinib and 11 (50·0%) of 22 patients (28·2–71·8) with chemotherapy (table 2).

The median duration of treatment exposure was 66·4 weeks (IQR 30·0–83·7) for ceritinib and 26·9 weeks (13·0–62·3) for chemotherapy. The median relative dose intensity was 78·4% (IQR 63·2–97·5) for patients receiving ceritinib and varied from 93·8% to 99·2% for each individual component in patients treated with chemotherapy. Among the 73 patients who had progressive disease with ceritinib confirmed by the blinded independent review committee, 61 (84%) patients

continued on ceritinib and 36 (49%) patients continued on ceritinib for at least two cycles after progression for continued clinical benefit, with a median additional exposure of 9·6 weeks (IQR 2·9–23·7).

Most adverse events in the two treatment groups were grade 1 or 2 in severity. Adverse events with a higher incidence in ceritinib than for chemotherapy were diarrhoea (160 [85%] of 189 patients), nausea (130 [69%]), vomiting (125 [66%]); all were predominantly grade 1–2 with grade 1 events of diarrhoea, nausea, and vomiting reported in 113 (60%) of 189 patients, 87 (46%), and 91 (48%) patients, respectively. Other common adverse events with ceritinib were an increase in alanine aminotransferase (ALT; 114 [60%] of 189 patients) and aspartate aminotransferase (AST; 100 [53%]; table 3). Anaemia was more frequently seen in the chemotherapy group (62 [35%] of 175 patients) than in the ceritinib group. Adverse events requiring dose adjustment or interruption were reported in 152 (80%) of 189 patients in the ceritinib group and 78 (45%) of 175 patients in the chemotherapy group. Dose adjustment or interruption were primarily due to gastrointestinal toxicity and liver function abnormalities. Gastrointestinal toxicity adverse events requiring dose adjustment or interruption accounted for 52 (28%) of 189 patients in the ceritinib group, including vomiting (29 [15%]), diarrhoea (24 [13%]), nausea (22 [12%]), and led to treatment discontinuation in three (2%) patients. Most of the diarrhoea events were managed by dose interruption and use of supportive medication. One patient discontinued ceritinib due to grade 2 diarrhoea.

Adverse events suspected to be related to study drug were reported in 184 (97%) of 189 patients in the ceritinib group and 156 (89%) of 175 patients in the chemotherapy group. Overall, 123 (65%) of 189 patients in the ceritinib group and 70 (40%) of 175 patients in the chemotherapy group had grade 3 or 4 adverse events suspected to be related to study drug. Of these, the most common grade 3 or 4 adverse events (>15%) related to study drug in the ceritinib group were an increase in ALT (56 [30%] of 189 patients; all grade 3), AST (30 [16%]; two patients had grade 4) and gamma-glutamyltransferase (50 [26%]; nine patients had grade 4). No Hy's law case was observed in either treatment group. Additionally, a low number of patients discontinued treatment due to adverse events suspected to be related to study drug in both groups (10 [5%] of 189 patients in the ceritinib group *vs* 20 [11%] of 175 patients in the chemotherapy group), with no one adverse event predominant in either treatment group.

Serious adverse events suspected to be study drug related were similar in both the treatment groups and no adverse event was predominant. No grade 4 QT prolongation or torsade de pointes, no Hy's law cases, and no pancreatitis cases were reported. Interstitial lung disease or pneumonitis was reported in four (2%) of 189 patients in the ceritinib group and one (1%) of 175 patients in the chemotherapy group.

	Ceritinib (n=189)		Chemotherapy (n=175)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Any adverse event	189 (100%)	148 (78%)	170 (97%)	108 (62%)
Diarrhoea	160 (85%)	10 (5%)	19 (11%)	2 (1%)
Nausea	130 (69%)	5 (3%)	97 (55%)	9 (5%)
Vomiting	125 (66%)	10 (5%)	63 (36%)	10 (6%)
Alanine aminotransferase increased	114 (60%)	58 (31%)	38 (22%)	5 (3%)
Aspartate aminotransferase increased	100 (53%)	32 (17%)	34 (19%)	3 (2%)
Gamma-glutamyltransferase increased	70 (37%)	54 (29%)	18 (10%)	3 (2%)
Decreased appetite	64 (34%)	2 (1%)	55 (31%)	2 (1%)
Blood alkaline phosphatase increased	55 (29%)	14 (7%)	8 (5%)	1 (1%)
Fatigue	55 (29%)	8 (4%)	52 (30%)	5 (3%)
Abdominal pain	47 (25%)	4 (2%)	13 (7%)	0
Cough	46 (24%)	0	28 (16%)	0
Weight decreased	45 (24%)	7 (4%)	26 (15%)	1 (1%)
Blood creatinine increased	42 (22%)	4 (2%)	17 (10%)	0
Upper abdominal pain	39 (21%)	3 (2%)	10 (6%)	0
Non-cardiac chest pain	38 (20%)	2 (1%)	17 (10%)	1 (1%)
Back pain	36 (19%)	3 (2%)	32 (18%)	4 (2%)
Constipation	36 (19%)	0	38 (22%)	0
Pyrexia	34 (18%)	0	24 (14%)	2 (1%)
Asthenia	33 (17·5)	5 (3%)	36 (21%)	6 (3%)
Headache	31 (16%)	0	21 (12%)	2 (1%)
Dyspnoea	29 (15%)	4 (2%)	35 (20%)	11 (6%)
Anaemia	28 (15%)	4 (2%)	62 (35%)	13 (7%)
Neutropenia	9 (5%)	1 (1%)	38 (22%)	19 (11%)
White blood cell count decreased	7 (4%)	0	31 (18%)	7 (4%)

Data are n (%).

Table 3: **Adverse events regardless of study drug relationship in the safety set (>15% of patients in either group)**

In total, 11 (6%) of 189 patients in the ceritinib group and six (3%) of 175 patients in the chemotherapy group died during the on-treatment period (first dose date to last dose date plus 30 days); none of these were suspected to be related to study drug. 11 patients (seven patients in the ceritinib group and five patients in the chemotherapy group) died due to disease progression. The remaining four patients in the ceritinib group died due to myocardial infarction (n=1), respiratory tract infection (n=1), pneumonitis (n=1), and unknown causes (n=1), whereas the remaining one patient in the chemotherapy group died due to lung infection.

Compliance was high for completion of the LCSS, QLQ–C30, QLQ–LC13, and EQ-5D questionnaires in both treatment groups, with at least 80% of patients completing the questionnaires at most timepoints. Ceritinib significantly prolonged time to definitive deterioration versus chemotherapy for the composite endpoint of lung cancer-specific symptoms (pain, cough, and shortness of breath; LCSS, HR 0·61 [95% CI 0·41–0·90]; p=0·0055 [appendix], and QLQ-LC13, HR 0·48 [0·34–0·69]; p<0·0001 [figure 4]). As measured by LCSS and QLQ-LC13, patient-reported outcomes in

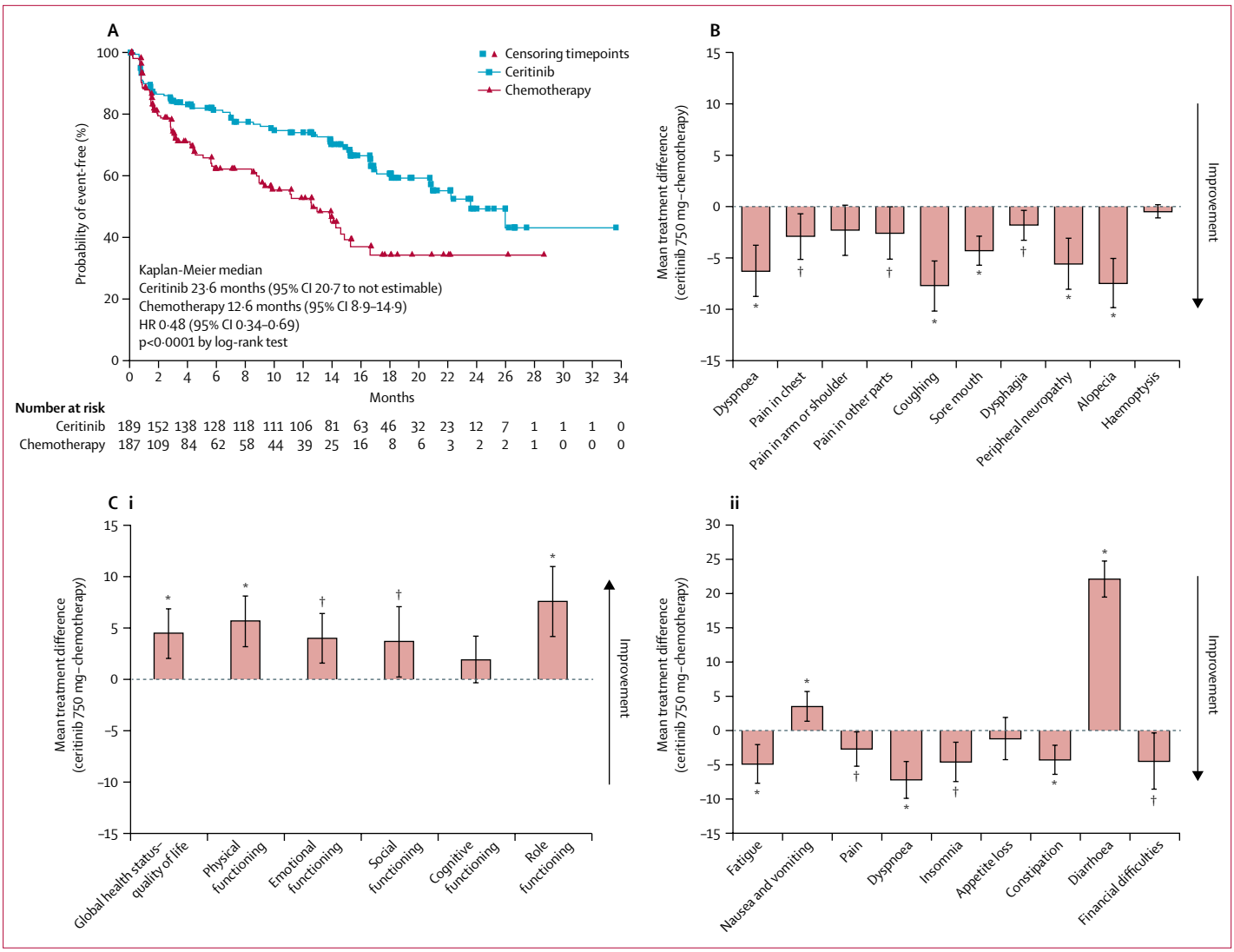

***Figure 4*: Patient-reported outcomes in the full analysis set**

(A) Time to definitive deterioration in the QLQ-LC13 as defined by the composite endpoint of lung cancer-specific symptoms (pain, cough, and shortness of breath). (B) Overall treatment difference (ceritinib 750 mg–chemotherapy) in lung cancer specific scores using QLQ-LC13. Data presented are mean (95% CI). *p<0·001, †p<0·05. Negative mean treatment difference measured using the QLQ-LC13 indicates an improvement following ceritinib treatment compared with chemotherapy. (C) Overall treatment difference (ceritinib 750 mg–chemotherapy). (i) Multi-item functional scales. Data presented are mean (95% CI). *p<0·001, †p<0·05. Positive mean treatment difference measured using the QLQ-C30 indicates an improvement following ceritinib treatment *vs* chemotherapy for multi-item functional scores. (ii) Symptom scores. Data presented are mean (95% CI). *p<0·001, †p<0·05. Negative mean treatment difference measured using the QLQ-C30 indicates an improvement following ceritinib treatment versus chemotherapy for symptom scores of fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, and financial difficulties.

lung cancer-specific symptoms were significantly improved for ceritinib versus chemotherapy (figure 4); LCSS data are reported in the appendix. All QLQ-LC-13 symptom scores improved with eight of ten improving significantly versus chemotherapy (figure 4B). In the QLQ-C30 instrument, four of five functional domains and six of nine symptom scales improved significantly with ceritinib versus chemotherapy; two scales related to diarrhoea as well as nausea and vomiting showed less favourable outcomes for ceritinib. However, general quality of life was in favour of ceritinib (figure 4). Patients receiving ceritinib also reported improvements in the EQ-5D-5L index value (p=0·0006) and a non-significant improvement in the EQ-5D-5L visual analogue scale (p=0·053) versus those treated with chemotherapy (appendix).

Discussion

In this study, treatment-naive patients with *ALK*-rearranged NSCLC in the ceritinib group had a statistically significant and clinically meaningful improvement in progression-free survival compared with those in the chemotherapy group that included pemetrexed maintenance. The unprecedented median

progression-free survival of 16·6 months in the overall population, 26·3 months in patients without brain metastases and 10·7 months in patients with baseline brain metastases (60% were active brain metastases) shows ceritinib to be an effective treatment for untreated *ALK*-rearranged NSCLC and has not been reported previously in this homogenous patient population.

Between the implementation and availability of data from the ASCEND-4 study, crizotinib has been approved as a first-line treatment in patients with *ALK*-rearranged NSCLC based on the results from the PROFILE 1014 study.[3] At the time of study inception, crizotinib was not globally approved as a first-line therapy except for accelerated approval in the USA. Platinum-based doublet with pemetrexed was a broadly used global standard of care for non-squamous NSCLC. Furthermore, pemetrexed maintenance therapy has given an additional improvement in progression-free survival and overall survival versus placebo in these patients.[12,13] Pemetrexed had a higher efficacy in *ALK*-rearranged NSCLC.[18,19] Thus, platinum-based doublet with pemetrexed followed by maintenance pemetrexed was considered as a valid comparator in this patient population. Both ASCEND-4 and PROFILE 1014 studies had a comparator group based on platinum and pemetrexed, with the main difference of pemetrexed maintenance introduced only in ASCEND-4. In the PROFILE 1014 study, a median progression-free survival of 7·0 months and 18-month progression-free survival rate of 5% was observed in the chemotherapy group.[3] In the chemotherapy group of the ASCEND-4 study, a median progression-free survival of 8·1 months and an 18-month progression-free survival rate of 23% were reported. These results are consistent with previous studies assessing maintenance in NSCLC and confirm the robustness of the comparator in the current study.

Median overall survival was not reached in either treatment group in the PROFILE 1014 study (HR 0·82 [95% CI 0·54–1·26]; p=0·36). The lack of a survival benefit in the PROFILE 1014 study might be due to the high crossover at the time of progression in the chemotherapy group in 70% of the patients.[3] In ASCEND-4, overall survival data are not mature and the study did not cross the efficacy stopping boundary at this interim analysis (HR 0·73 [95% CI 0·50–1·08]). The event-free probability estimates remained higher for the ceritinib group. Also in ASCEND-4, 72% of patients in the chemotherapy group received ceritinib or another ALK inhibitor as first treatment after chemotherapy. Furthermore, 16% of patients in the chemotherapy group are still receiving treatment.

Presence of baseline brain metastases is a known adverse prognostic factor in this population.[20] In the ASCEND-4 study, patients with brain metastases were eligible if neurologically stable, symptomatic or non-symptomatic, and without or with previous brain radiation. The incidence of patients with brain metastases in the ASCEND-4 study (32%) is slightly higher, well balanced between groups, and most patients with baseline brain metastases did not receive previous brain radiotherapy (59%) compared with other reported phase 3 studies[6,21] in a similar setting. The incidence of patients with brain metastases was 23% in each group in the PROFILE 1014 study[6] and 20·8% (13·6% in the alectinib group and 27·9% in the crizotinib group) in the J-ALEX trial.[21] The difference in incidence of brain metastases might reflect different eligibility criteria for patients with baseline brain metastases: all had to be treated with brain radiotherapy and be neurologically stable in PROFILE 1014 and treated and asymptomatic in the J-ALEX study. In ASCEND-4, the intracranial activity observed in ceritinib patients with measurable brain metastases at baseline and at least one post-baseline assessment (as assessed by the blinded independent review board neurologist) showed a high overall intracranial response rate of 72·7%, an intracranial clinical benefit rate of 86·4% at 24 weeks, and median duration of intracranial response of 16·6 months (95% CI 8·1 to not estimable).

The overall safety profile of ceritinib in this study is consistent with the established safety profile of ceritinib in the ASCEND-1 and ASCEND-3 studies.[9–11] Although gastrointestinal adverse events were most frequently reported with ceritinib, most were grade 1 or 2, manageable with supportive concomitant medication, dose interruption or adjustments allowing patients to remain on drug for a long period (66·4 weeks of exposure) and to maintain a median relative dose intensity of 78·4% (IQR 63·2–97·5), with ceritinib. Most adverse events were grade 1 and only three patients discontinued ceritinib for this event. Furthermore, only 5% of patients treated with ceritinib discontinued treatment due to an adverse event suspected to be related to study drug. No new safety signal with ceritinib was identified in this study. Other second generation ALK inhibitors have reported a very distinct safety profile compared with ceritinib.[22,23] We acknowledge that the starting dose of 750 mg/day fasted might be associated with a high frequency of gastrointestinal toxicity and raised liver enzymes. Even if manageable, as a mitigation strategy, administration of lower dose ceritinib with food might reduce the incidence of gastrointestinal toxicity. Encouraging data have been presented that suggested that ceritinib 450 mg/day with food has similar exposure and significantly reduces gastrointestinal toxicity.[24] Patients treated with ceritinib had improved overall quality of life versus chemotherapy consistently across the different instruments used in the study (QLQ-C30, LCSS, and EQ-5D-5L). Ceritinib also showed better outcomes versus chemotherapy for most individual symptom scores over time using LCSS, QLQ-LC13, QLQ-C30, and EQ-5D-5L. These results suggest that the observed improvements in patient-reported outcomes for ceritinib versus chemotherapy likely outweigh the impact of adverse events leading to an overall health status

improvement. Despite less favourable findings in two scales related to gastrointestinal symptoms, all other quality-of-life assessments indicate advantages for patients treated with ceritinib at the level of individual symptom burden and overall quality of life. Moreover, ceritinib significantly prolonged time to definitive deterioration (for lung cancer specific symptoms as a composite endpoint as shown by LCSS and QLQ-LC-13) versus chemotherapy.

Additional next-generation ALK inhibitors are also under development for use in ALK inhibitor-naive or first-line settings. A phase 3 study (J-ALEX)[21] comparing alectinib with crizotinib has been done in 207 Japanese ALK inhibitor-naive patients with advanced *ALK*-rearranged NSCLC. However, in the J-ALEX study, at least one previous therapy was allowed, more than 90% of patients were positive by immunohistochemistry and fluorescence in situ hybridisation or reverse transcription-polymerase chain reaction, and only 20·8% patients had brain metastases at baseline; there was no stratification by brain metastases leading to an imbalance favouring alectinib. The J-ALEX study reported a 76% progression-free survival risk reduction (HR 0·34 [99·7% CI 0·17–0·71]) versus crizotinib (median progression-free survival: not reached in the alectinib group *vs* 10·2 months [8·2–12·0] in the crizotinib group).[21] In an exploratory subgroup analysis of the J-ALEX study,[25] the median progression-free survival in the alectinib group for the subgroup of patients without brain metastases was 20·3 months (95% CI 17·5 to not estimable) versus 10·0 months (8·2–13·9) for crizotinib. Another phase 3 trial of alectinib (ALEX study, NCT02075840) is ongoing globally.[26] Brigatinib (NCT02737501) and ensartinib (NCT02767804) are another two next-generation ALK inhibitors being investigated in first-line settings versus crizotinib.

In conclusion, based on the findings of the current study, ceritinib could be considered a new first-line therapeutic option in patients with *ALK*-rearranged NSCLC.

Contributors

J-CS, DSWT, Y-LW, LP-A, JW, TM, PS, MD, SP, and FB contributed to study design. DSWT, RC, Y-LW, LP-A, JW, SLG, SO, DC, C-JY, MH, ABC, C-MT, DM-S, RGC, and GdC recruited patients. CM, TM, PS, and FB contributed to trial management, data collection, and data analysis. J-CS wrote the first draft of the manuscript with the help of a medical writer. All authors provided input for data interpretation, critically revised the content, and approved the final draft of the manuscript for publication.

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Declaration of interests

J-CS reports grants from Novartis (clinical research), and personal fees from Pfizer and Roche (advisory board) during the conduct of the study. DSWT reports grants and personal fees (research funding) from Novartis, during the conduct of the study; grants from GlaxoSmithKline and AstraZeneca (research funding); and personal fees from Pfizer, Merck, and Boehringer Ingelheim, outside the submitted work. Y-LW reports personal fees (speaker fees) from AstraZeneca, Roche, Eli Lilly, Pfizer, and Sanofi, outside the submitted work. LP-A reports an advisory or a consultant role for Novartis, Roche, Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Celgene, Boehringer Ingelheim, Pfizer, and Clovis, outside the submitted work. JW reports personal fees (advisory boards [compensated] and lecture fees) from AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Clovis; grants and personal fees (advisory boards [compensated] and lecture fees) from Bristol-Myers Squibb, Novartis, Pfizer, Roche, and grants and personal fees (research support) from Novartis, Pfizer, Bristol-Myers Squibb, and Merck Sharp & Dohme, during the conduct of the study. SLG reports grants and personal fees from AstraZeneca and Roche; grants and personal fees (advisory role) from Boehringer Ingelheim, Novartis, and Roche; non-financial support from Sanofi Aventis; and grants from Eisai and Teva, outside the submitted work. ABC reports personal fees from Novartis, Roche Hoffmann, Pfizer, Boehringer-Ingelheim, Lilly Oncology, AstraZeneca, Merck Sharp & Dohme, and Bristol-Myers Squibb, and grants from Boehringer-Ingelheim, outside the submitted work. DM-S reports personal fees from Novartis, during the conduct of the study; personal fees from Pfizer, Roche, Ariad, and Eli Lilly, outside the submitted work. TM, PS, FB, CM are employees of Novartis. MD is an employee and owns stock in Novartis. SP is an employee and owns stock in Novartis, and has a patent WO/2016/059600 pending. GdC reports advisory role for Novartis, Pfizer, outside the submitted work. RC, SO, DC, C-JY, MH, C-MT, and RGC declare no competing interests.

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