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ORIGINAL ARTICLE

# Updated overall survival and final progression-free survival data for patients with treatment-naive advanced *ALK*-positive non-small-cell lung cancer in the ALEX study

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**Background:** The ALEX study demonstrated significantly improved progression-free survival (PFS) with alectinib versus crizotinib in treatment-naive *ALK*-positive non-small-cell lung cancer (NSCLC) at the primary data cut-off (9 February 2017). We report mature PFS (cut-off: 30 November 2018) and overall survival (OS) data up to 5 years (cut-off: 29 November 2019).

**Patients and methods:** Patients with stage III/IV *ALK*-positive NSCLC were randomized to receive twice-daily alectinib 600 mg ($n = 152$) or crizotinib 250 mg ($n = 151$) until disease progression, toxicity, withdrawal or death. Primary end point: investigator-assessed PFS. Secondary end points included objective response rate, OS and safety.

**Results:** Mature PFS data showed significantly prolonged investigator-assessed PFS with alectinib [hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.32—0.58; median PFS 34.8 versus 10.9 months crizotinib]. Median duration of OS follow-up: 48.2 months alectinib, 23.3 months crizotinib. OS data remain immature (37% of events). Median OS was not reached with alectinib versus 57.4 months with crizotinib (stratified HR 0.67, 95% CI 0.46—0.98). The 5-year OS rate was 62.5% (95% CI 54.3—70.8) with alectinib and 45.5% (95% CI 33.6—57.4) with crizotinib, with 34.9% and 8.6% of patients still on study treatment, respectively. The OS benefit of alectinib was seen in patients with central nervous system metastases at baseline [HR 0.58 (95% CI 0.34—1.00)] and those without [HR 0.76 (95% CI 0.45—1.26)]. Median treatment duration was longer with alectinib (28.1 versus 10.8 months), and no new safety signals were observed.

**Conclusions:** Mature PFS data from ALEX confirmed significant improvement in PFS for alectinib over crizotinib in *ALK*-positive NSCLC. OS data remain immature, with a higher 5-year OS rate with alectinib versus crizotinib. This is the first global randomized study to show clinically meaningful improvement in OS for a next-generation tyrosine kinase inhibitor versus crizotinib in treatment-naive *ALK*-positive NSCLC.

**Clinical trials number:** NCT02075840.

**Key words:** alectinib, *ALK*-positive, crizotinib, non-small-cell lung cancer, overall survival, progression-free survival

## INTRODUCTION

Five-year relative survival rates for patients with metastatic non-small-cell lung cancer (NSCLC) remain extremely low, and were estimated to be just 6.1% for those diagnosed between 2009 and 2015.[1] However, recent advances in the development of targeted therapies have extended survival outcomes in NSCLC, especially in patients whose tumors harbor *EML4-ALK* translocations (*ALK*-positive).[2]

Next-generation *ALK* tyrosine kinase inhibitors (TKIs; alectinib, ceritinib and brigatinib) have generally replaced the first-generation TKI crizotinib as first-line treatments for patients with *ALK*-positive NSCLC. This has been possible due to the improved pharmacological properties of next-generation versus first-generation ALK TKIs, including greater potency/selectivity, central nervous system (CNS)

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penetration and targeting of resistant mutations.[3] Next-generation TKIs are listed as the recommended first-line therapy for advanced *ALK*-positive NSCLC in treatment guidelines, with alectinib listed as the preferred option.[4,5] This recommendation is supported by the superior efficacy reported from the phase III, global, randomized ALEX study (NCT02075840). At the primary data cut-off (9 February 2017), after approximately 18 months of follow-up in both arms, the study met its primary end point and demonstrated significantly improved progression-free survival (PFS) with alectinib versus crizotinib in patients with treatment-naive *ALK*-positive NSCLC.[6] Median investigator-assessed PFS was not reached (NR) with alectinib and was 11.1 months with crizotinib. By independent review committee (IRC) assessment, median PFS was 25.7 months with alectinib and 10.4 months with crizotinib.[6] In an exploratory analysis of ALEX, with an additional 10 months of follow-up (data cut-off: 1 December 2017), alectinib continued to demonstrate a similar degree of improvement in investigator-assessed PFS versus crizotinib [stratified hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.32—0.58].[7]

Overall survival (OS) data from ALEX were immature (the target maturity for survival is 50% per protocol) at both the primary analysis (stratified HR 0.76, 95% CI 0.48—1.20; 23% of events with alectinib versus 26% with crizotinib) and at the 1 December 2017 exploratory analysis (stratified HR 0.76, 95% CI 0.50—1.15; 28% of events with alectinib versus 32% with crizotinib).[6,7] In the phase III PROFILE 1014 study comparing crizotinib with chemotherapy in previously untreated *ALK*-positive NSCLC, final OS data were reported after approximately 46 months of median follow-up in both arms.[8] The difference in OS between crizotinib and chemotherapy was not statistically significant (HR 0.76, 95% CI 0.55—1.05; $P = 0.0978$).[8] This was attributed to a crossover rate of more than 80% to the crizotinib arm at the point of disease progression (PD). Median OS was NR (95% CI 45.8—NR) with crizotinib and was 47.5 months (95% CI 32.2—NR) with chemotherapy. The 4-year OS rate was 56.6% (95% CI 48.3—64.1) and 49.1% (95% CI 40.5—57.1) with crizotinib and chemotherapy, respectively.[8]

Here, we report final, mature PFS data from ALEX (data cut-off: 30 November 2018), together with OS and safety data up to 5 years after a further 12 months of follow-up (data cut-off: 29 November 2019).

## METHODS

### Study design

The ALEX study design has been published previously.[6] Briefly, patients aged ≥18 years with previously untreated stage III/IV *ALK*-positive NSCLC were randomized 1 : 1 to receive twice-daily alectinib 600 mg or crizotinib 250 mg until PD, toxicity, withdrawal or death. Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0/1 versus 2), race (Asian versus non-Asian) and the presence or absence of CNS metastases at baseline. Crossover between treatment arms was not permitted before PD. Further lines of therapy after PD were at the physician's discretion and based on treatment availability. Patients with asymptomatic brain or leptomeningeal metastases were eligible for enrolment.

The protocol was approved by the institutional review board or ethics committee at each participating center and the study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice Guidelines and local laws. Written informed consent was obtained from all patients before any study-related procedures.

### End points

The primary end point was investigator-assessed PFS. Secondary end points included IRC-assessed PFS, objective response rate, OS and safety. End points that were assessed by the IRC were only undertaken for the primary analysis and were not repeated at later data cuts.

### Assessments

Imaging, including systematic brain imaging even in patients without brain metastases, was carried out in all patients at baseline and every 8 weeks until PD or death. PFS was defined as the time from randomization to the date of confirmed PD or death, whichever occurred first. OS was defined as the time from randomization to the date of death from any cause. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and classified according to the Medical Dictionary for Regulatory Activities.

### Statistical analysis

In total, 170 PD or death events were required to achieve 80% power of the log-rank test to detect a target HR of 0.65 (corresponding to an increase in median PFS from 10.9 months with crizotinib to 16.8 months with alectinib) at a two-sided alpha level of 5%. Comparison between the treatment groups with respect to PFS was based on a stratified log-rank test at a 5% level of significance (two-sided). PFS and OS were pre-planned analyses, while assessment of OS data up to 5 years was an exploratory analysis. The Kaplan—Meier method was used to estimate median PFS and OS for each treatment arm with 95% CIs. A stratified Cox proportional-hazards regression model was used to estimate the treatment effect, expressed as an HR (alectinib versus crizotinib) with a 95% CI. The median duration of survival follow-up was calculated as the time from randomization until last follow-up for all patients.

Secondary end points were analyzed using a hierarchical testing strategy to account for multiplicity. If the difference between the treatment groups with respect to the primary end point of investigator-assessed PFS was significant, secondary end points were each tested (at a two-sided 5% significance level) in the following sequence: IRC-assessed PFS, time to IRC-assessed CNS progression according to RECIST criteria, investigator-assessed response rate and OS.

## RESULTS

### Patients

The ALEX patient population has been described previously.[6] A total of 303 patients were randomized to receive treatment [$n = 152$, alectinib; $n = 151$, crizotinib; intent-to-treat (ITT) population]. Of these, 122 patients (40.3%) had CNS metastases at baseline as assessed by the IRC ($n = 64$, alectinib; $n = 58$, crizotinib). Baseline patient characteristics were generally balanced between treatment arms in the ITT population (supplementary Table S1, available at *Annals of Oncology* online).[6]

### Final PFS data

These final PFS results are based on a data cut-off of 30 November 2018. The median duration of survival follow-up (i.e. time from randomization until last follow-up) for investigator-assessed PFS was 37.8 months (range 0.5—50.7) with alectinib and 23.0 months (range 0.3—49.8) with crizotinib. Overall, 203 patients experienced PD or death [81/152 (53.3%) with alectinib versus 122/151 (80.8%) with crizotinib]. Investigator-assessed PFS was significantly prolonged with alectinib compared with crizotinib (stratified HR 0.43, 95% CI 0.32—0.58; Figure 1A). Median PFS was 34.8 months [95% CI 17.7—not evaluable (NE)] in the alectinib arm and 10.9 months (95% CI 9.1—12.9) in the crizotinib arm. IRC assessments of PFS were not repeated beyond the primary analysis.[6]

The PFS benefit of alectinib was maintained irrespective of the absence or presence of CNS metastases at baseline. In patients with baseline CNS metastases, median PFS was 25.4 months (95% CI 9.2—NE) with alectinib ($n = 64$) and 7.4 months (95% CI 6.6—9.6) with crizotinib ($n = 58$) (HR 0.37, 95% CI 0.23—0.58). In patients without baseline CNS metastases, median PFS was 38.6 months (95% CI 22.4—NE) with alectinib ($n = 88$) and 14.8 months (95% CI 10.8—20.3) with crizotinib ($n = 93$) (HR 0.46, 95% CI 0.31—0.68).

In the ITT population, PFS rates were higher with alectinib than with crizotinib at 1, 2, 3 and 4 years, with 43.7% of alectinib-treated patients event-free at 4 years (supplementary Figure S1, available at *Annals of Oncology* online). The PFS rate was higher with alectinib than with crizotinib regardless of the absence or presence of baseline CNS metastases (Figure 1B and C).

### Updated OS data

Updated OS results are based on a data cut-off of 29 November 2019, providing an additional 12 months of follow-up from the final PFS data cut-off. The median duration of survival follow-up for OS was 48.2 months (range 0.5—62.7) with alectinib and 23.3 months (range 0.3—60.6) with crizotinib. Overall, 113 patients had died [51/152 (33.6%) with alectinib versus 62/151 (41.1%) with crizotinib]. OS data remain immature with 37% of events recorded (stratified HR 0.67, 95% CI 0.46—0.98). Median OS was NR with alectinib and was 57.4 months with crizotinib (95% CI 34.6—NR) (Figure 2A). The 5-year OS rate was 62.5% (95% CI 54.3—70.8) with alectinib and 45.5% (95% CI 33.6—57.4) with crizotinib (Table 1). At present, 53 patients (34.9%) in the alectinib arm and 13 patients (8.6%) in the crizotinib arm remain on their original study treatment. The OS benefit of alectinib was evident across a number of patient subgroups, including those with CNS metastases at baseline [HR 0.58 (95% CI 0.34—1.00); 50.0% of events] and those without [HR 0.76 (95% CI 0.45—1.26); 35.5% of events] (Figure 2B).

### Follow-up anticancer therapy

Overall, 21 patients died without PD and without receiving any follow-up therapy. At the data cut-off of 29 November 2019, among 84 patients in the alectinib arm and 114 patients in the crizotinib arm who experienced PD (including symptomatic deterioration), subsequent therapy was given in 51/84 (60.7%) and 72/114 (63.2%) patients, respectively (Table 2). Access to other next-generation ALK TKIs occurred in 32/84 patients (38.1%) who progressed in the alectinib arm and in 61/114 patients (53.5%) who progressed in the crizotinib arm. The most frequently received ALK TKIs were crizotinib (13.1%), lorlatinib (13.1%), brigatinib (9.5%) and ceritinib (8.3%) in patients in the alectinib arm; in the crizotinib arm, patients mainly received ceritinib (21.1%), alectinib (21.1%), brigatinib (9.6%) and lorlatinib (8.8%). Post-progression access to pemetrexed occurred in 22/84 (26.2%) and 13/114 (11.4%) patients, respectively—details on whether this was given as part of a platinum-doublet, with or without maintenance therapy, with or without TKI continuance were not captured. Of the 51 patients in the alectinib arm and 72 patients in the crizotinib arm with PD, who received follow-up anti-cancer therapy, 15.7% and 11.1%, respectively, had more than one additional line of therapy.

Among 51 patients in the alectinib arm and 62 patients in the crizotinib arm who died, subsequent therapy was given in 31/51 (60.8%) and 31/62 (50.0%) patients, respectively (Table 2). Access to a next-generation ALK TKI occurred in 18/51 patients (35.3%) who died in the alectinib arm and in 23/62 (37.1%) patients who died in the crizotinib arm. The most frequently received ALK TKIs in patients who died in the alectinib arm were crizotinib (15.7%), lorlatinib (13.7%), ceritinib (11.8%) and brigatinib (5.9%); in the crizotinib arm, patients mainly received ceritinib (22.6%), alectinib (9.7%), brigatinib (9.7%) and lorlatinib (8.1%). Access to pemetrexed as a follow-up therapy occurred in 19/51 (37.3%) and 8/62 (12.9%) patients who died, respectively.

### Safety

As of 29 November 2019, the median treatment duration was 28.1 months with alectinib and 10.8 months with crizotinib. Similar proportions of patients in each treatment arm experienced grade 3—5 AEs (52.0% alectinib, 56.3% crizotinib), AEs leading to dose reduction (20.4% alectinib, 19.9% crizotinib), dose interruption (26.3% alectinib, 26.5% crizotinib) or treatment discontinuation (14.5% alectinib,

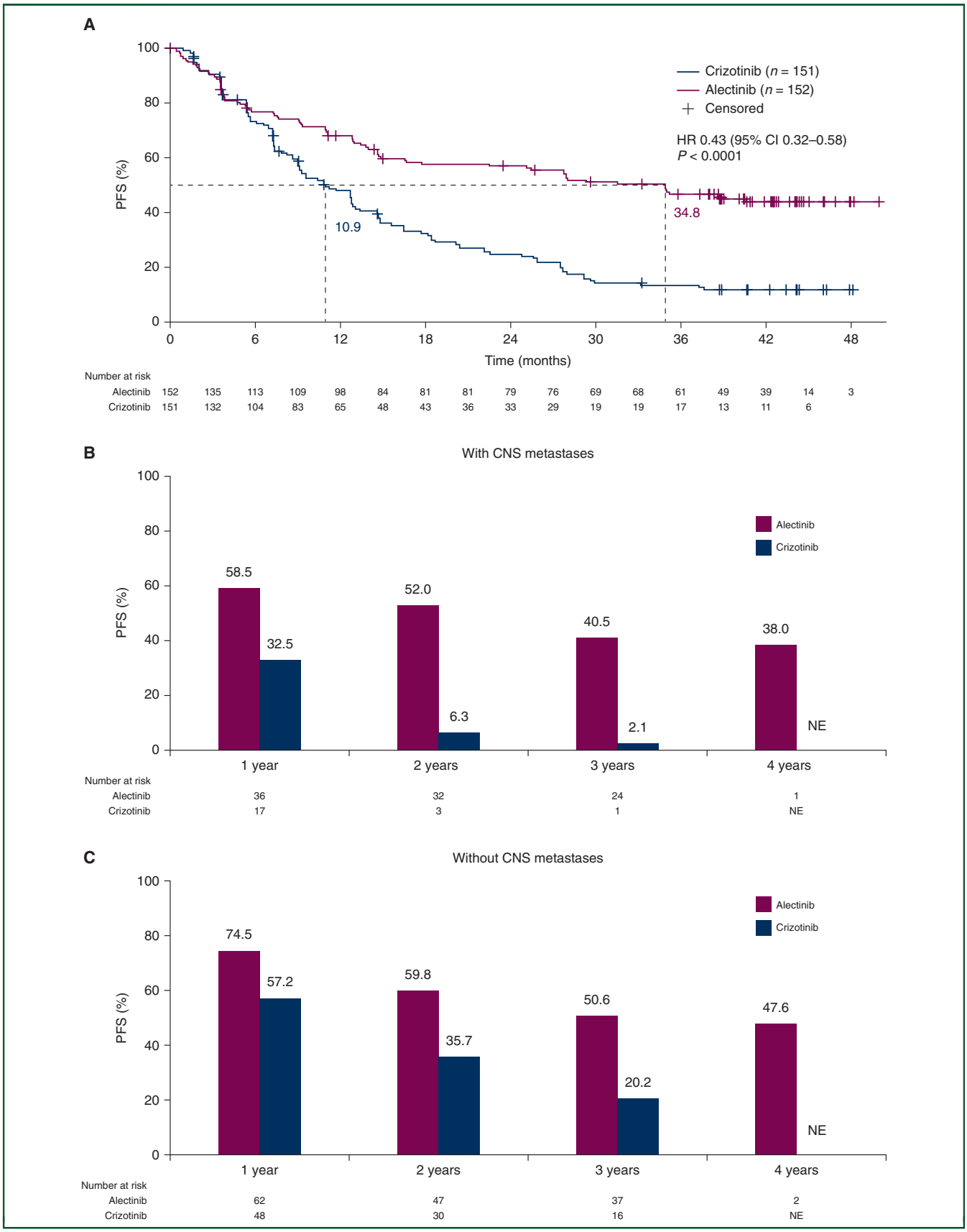


**Figure 1. (A) Kaplan–Meier plot of investigator-assessed progression-free survival (PFS) in the intent-to-treat population, and PFS rates (B) in patients with baseline central nervous system (CNS) metastases, and (C) in patients without baseline CNS metastases.**
CI, confidence interval; HR, hazard ratio; NE, not evaluable.


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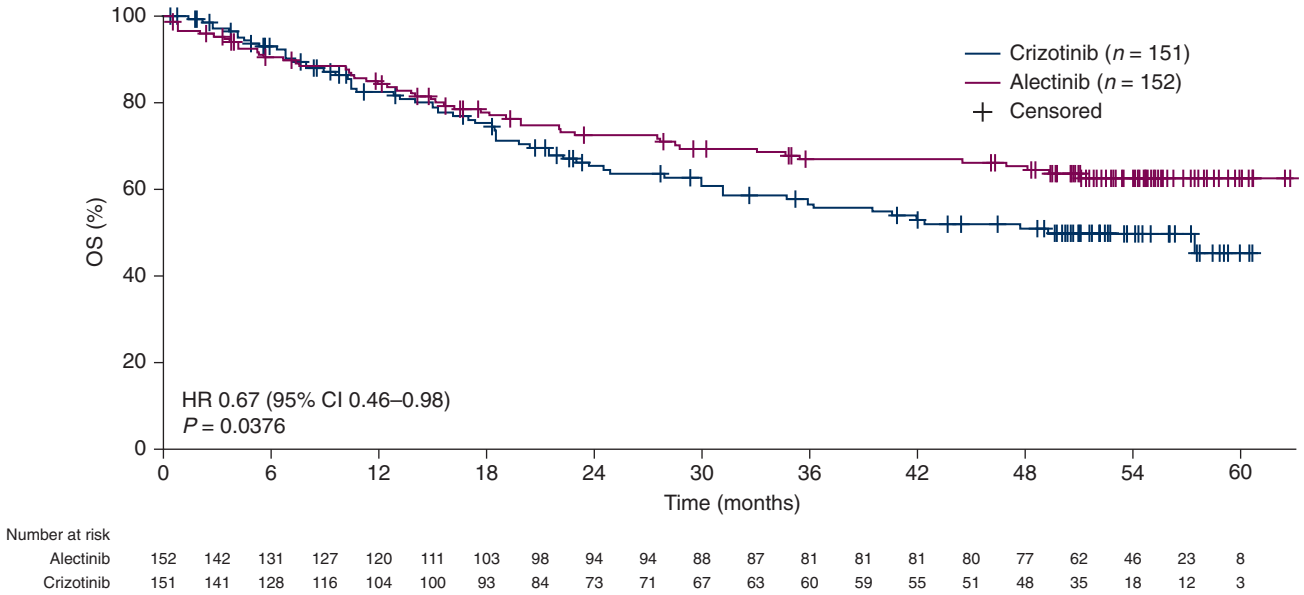
A




B

| Name | | Level | Log-rank *P* value | Hazard ratio Hazard ratio | Hazard ratio 95% CI | Interaction test *P* value (likelihood ratio) |
|---|---|---|---|---|---|---|
| All | | n/a | 0.0609 | 0.70 | (0.48–1.02) | |
| Age group (years) | | < 65 | 0.1481 | 0.73 | (0.48–1.12) | 0.6768 |
| | | ≥ 65 | 0.2189 | 0.63 | (0.30–1.33) | |
| Sex | | Female | 0.3020 | 0.76 | (0.45–1.28) | 0.6923 |
| | | Male | 0.1155 | 0.66 | (0.39–1.11) | |
| Race | | Asian | 0.3298 | 0.74 | (0.40–1.36) | 0.8575 |
| | | Non-Asian | 0.1161 | 0.69 | (0.43–1.10) | |
| Smoking status | *n* = 17 | Active smoker | 0.4126 | 1.97 | (0.38–10.20) | 0.5471 |
| | | Non-smoker | 0.1181 | 0.68 | (0.42–1.11) | |
| | | Past smoker | 0.1339 | 0.62 | (0.33–1.17) | |
| ECOG PS | | 0 | 0.1266 | 0.52 | (0.22–1.22) | 0.4636 |
| | | 1 | 0.0960 | 0.68 | (0.44–1.07) | |
| | *n* = 20 | 2 | 0.6440 | 1.30 | (0.43–3.90) | |
| CNS mets at baseline (IRC) | | Yes | 0.0477 | 0.58 | (0.34–1.00) | 0.4677 |
| | | No | 0.2851 | 0.76 | (0.45–1.26) | |
| Prior brain radiation | | Yes | 0.0889 | 0.39 | (0.13–1.19) | 0.2064 |
| | | No | 0.1956 | 0.77 | (0.52–1.14) | |

**Figure 2. (A) Kaplan–Meier plot of investigator-assessed overall survival (OS) in the intent-to-treat population (stratified analysis) and (B) OS subgroup analysis (unstratified analysis).**

CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative oncology group performance status; HR, hazard ratio; IRC, independent review committee; mets, metastases.

14.6% crizotinib; Table 3). AEs occurring at a frequency of ≥10% in either treatment arm are listed in supplementary Table S2, available at *Annals of Oncology*, online. The most common grade ≥3 AEs with alectinib were anemia (5.9%), increased aspartate transaminase (5.3%), increased alanine aminotransferase (4.6%) and pneumonia (4.6%), and with crizotinib were increased alanine aminotransferase (15.9%), increased aspartate aminotransferase (10.6%), neutropenia (5.3%) and blood creatine phosphokinase increased (4.0%) (Table 4).

**Table 1. Overall survival (OS) rates in the intent-to-treat population**

| OS rate, % (95% CI) [patients at risk, *n*] | Alectinib (*N* = 152) | Crizotinib (*N* = 151) | Difference, % (95% CI) |
|---|---|---|---|
| Year 1 | 84.3 (78.4–90.2) [120] | 82.5 (76.2–88.9) [104] | −1.8 (−10.4–6.9) |
| Year 2 | 72.5 (65.1–79.9) [94] | 65.3 (57.0–73.6) [73] | −7.2 (−18.3–3.9) |
| Year 3 | 67.0 (59.1–74.8) [81] | 57.0 (42.1–65.9) [60] | −9.9 (−21.8–1.9) |
| Year 4 | 65.3 (55.3–73.3) [77] | 51.2 (42.1–60.3) [48] | −14.1 (−26.2 to −2.0) |
| Year 5 | 62.5 (54.3–70.8) [8] | 45.5 (33.6–57.4) [3] | −17.0 (−33.5 to −2.5) |

CI, confidence interval.

## DISCUSSION

This is the first and largest global randomized study in the first-line setting comparing a next-generation ALK TKI with crizotinib to have demonstrated improvement in both PFS and OS. The investigator-assessed PFS data have reached maturity with 53% of events recorded in the alectinib arm. Alectinib continued to show significantly prolonged PFS compared with crizotinib in patients with treatment-naive *ALK*-positive NSCLC (HR 0.43, 95% CI 0.32–0.58; median 34.8 versus 10.9 months, respectively), supporting the current recommendation by multiple national treatment guidelines of using a next-generation ALK TKI as first-line therapy in this patient population, with alectinib indicated as the preferred option.[4,5] The median PFS of 10.9 months with first-line crizotinib in the ALEX study is consistent with data from other randomized phase III trials of crizotinib. Median PFS with crizotinib was 10.9 months in the phase III PROFILE 1014 study of first-line crizotinib versus chemotherapy,[8] and was 9.2 months in the second interim analysis of the phase III ALTA-1L trial of first-line crizotinib versus brigatinib.[9]

Other next-generation TKIs in the first-line setting have also shown improved PFS versus chemotherapy or crizotinib for patients with *ALK*-positive NSCLC. In the randomized phase III ASCEND-4 study comparing first-line ceritinib with platinum-based chemotherapy, median PFS was 16.6 months (95% CI 12.6–27.2) versus 8.1 months (95% CI 5.8–11.1), respectively.[10] At the second interim analysis of ALTA-1L, comparing brigatinib with crizotinib, median investigator-assessed PFS in the brigatinib arm was 29.4 months (95% CI 21.2–NR).[9]

After a median survival follow-up of 48.2 months, only 37% of OS events have occurred in the ALEX study, while the target maturity for survival is 50% per protocol. At this

**Table 2. Follow-up anticancer therapies**

| | Patients with progressive disease (including symptomatic deterioration), *n* (%) | | Patients who died, *n* (%) | |
|---|---|---|---|---|
| | Alectinib (*N* = 84) | Crizotinib (*N* = 114) | Alectinib (*N* = 51) | Crizotinib (*N* = 62) |
| Patients with at least one treatment | 51 (60.7) | 72 (63.2) | 31 (60.8) | 31 (50.0) |
| Pemetrexed | 22 (26.2) | 13 (11.4) | 19 (37.3) | 8 (12.9) |
| Ceritinib | 7 (8.3) | 24 (21.1) | 6 (11.8) | 14 (22.6) |
| Alectinib | 2 (2.4) | 24 (21.1) | 0 | 6 (9.7) |
| Carboplatin | 16 (19.0) | 7 (6.1) | 12 (23.5) | 5 (8.1) |
| Lorlatinib | 11 (13.1) | 10 (8.8) | 7 (13.7) | 5 (8.1) |
| Cisplatin | 13 (15.5) | 7 (6.1) | 10 (19.6) | 3 (4.8) |
| Crizotinib | 11 (13.1) | 9 (7.9) | 8 (15.7) | 2 (3.2) |
| Brigatinib | 8 (9.5) | 11 (9.6) | 3 (5.9) | 6 (9.7) |
| Paclitaxel | 5 (6.0) | 4 (3.5) | 2 (3.9) | 2 (3.2) |
| Bevacizumab | 2 (2.4) | 2 (1.8) | 2 (3.9) | 1 (1.6) |
| Docetaxel | 0 | 3 (2.6) | 0 | 3 (4.8) |
| Gemcitabine | 3 (3.6) | 0 | 2 (3.9) | 0 |
| Atezolizumab | 0 | 1 (0.9) | 0 | 0 |
| Cyclophosphamide | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Cytarabine | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Doxorubicin | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Ensartinib | 1 (1.2) | 0 | 0 | 0 |
| Entrectinib | 0 | 1 (0.9) | 0 | 1 (1.6) |
| Erlotinib | 0 | 1 (0.9) | 0 | 0 |
| Gefitinib | 0 | 1 (0.9) | 0 | 2 (3.2) |
| Methotrexate | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Monoclonal antibodies | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Nivolumab | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Other | 0 | 1 (0.9) | 0 | 0 |
| Ribociclib | 1 (1.2) | 0 | 0 | 0 |
| Tyrosine kinase inhibitors | 0 | 1 (0.9) | 0 | 0 |
| Vincristine | 1 (1.2) | 0 | 1 (2.0) | 0 |
| Osimertinib mesilate | 0 | 0 | 0 | 1 (1.6) |

**Table 3. Safety summary**

| | Alectinib ($N = 152$) | Crizotinib ($N = 151$) |
|---|---|---|
| Median treatment duration, months | 28.1 | 10.8 |
| Patients with at least one, *n* (%) | | |
| All-grade AE | 147 (96.7) | 147 (97.4) |
| Serious AE | 59 (38.8) | 48 (31.8) |
| Grade 3–5 AE | 79 (52.0) | 85 (56.3) |
| Treatment-related AE | 123 (80.9) | 134 (88.7) |
| Fatal AE | 7 (4.6) | 7 (4.6) |
| AE leading to treatment discontinuation | 22 (14.5) | 22 (14.6) |
| AE leading to dose reduction | 31 (20.4) | 30 (19.9) |
| AE leading to dose interruption | 40 (26.3) | 40 (26.5) |

Data cut-off: 29 November 2019.
AE, adverse event.

data cut-off point, median OS was NR with alectinib and was 57.4 months with crizotinib (stratified HR 0.67, 95% CI 0.46–0.98). No formal statistical testing was planned for OS at this stage, but the trend of improvement will likely persist. The difference of 17% (62.5% for alectinib versus 45.5% for crizotinib) in 5-year OS rate is clinically meaningful. The 5-year OS rate for crizotinib was not available in the final analysis of the PROFILE 1014 study. Their 4-year OS rate of 56.6%[8] is slightly higher than the 51.2% reported in the crizotinib arm of ALEX. This slight difference can be explained by the much higher incidence of CNS metastases at baseline in the ALEX study, possibly related to the requirement in PROFILE 1014 that only patients with treated brain metastases were eligible for the study.

Long-term survival in advanced *ALK*-positive NSCLC has been associated with access to next-generation ALK inhibitors, prolonged disease control with pemetrexed-based chemotherapy and use of local ablative therapies for oligoprogressive states.[11] While the details of oligoprogression versus polyprogression, local ablative therapy use and duration of benefit on subsequent therapies were not captured, use of next-generation ALK TKIs and of pemetrexed was assessed within our study. Among patients with PD or symptomatic deterioration, subsequent ALK TKIs were given in a greater proportion of patients in the crizotinib arm (53.5%) than in the alectinib arm (38.1%); conversely, use of pemetrexed-based chemotherapy was more common in the alectinib arm (26.2%) than in the crizotinib arm (11.4%). This is likely a reflection of the higher access to approved and experimental ALK TKIs in the post-crizotinib versus post-alectinib setting, especially at the time of conducting the ALEX trial. Also, information on further lines of therapy may have been underestimated in the study due to patients being lost to follow-up.

**Table 4. Grade ≥3 adverse events (AEs) reported in ≥2% of patients in either treatment arm**

| Patients with AEs, *n* (%) | Alectinib ($N = 152$) | Crizotinib ($N = 151$) |
|---|---|---|
| Total number of patients with grade ≥3 AEs | 79 (52.0) | 85 (56.3) |
| Alanine aminotransferase increased | 7 (4.6) | 24 (15.9) |
| Aspartate aminotransferase increased | 8 (5.3) | 16 (10.6) |
| Blood creatine phosphokinase increased | 5 (3.3) | 6 (4.0) |
| Anemia | 9 (5.9) | 1 (0.7) |
| Pneumonia | 7 (4.6) | 3 (2.0) |
| Neutropenia | 0 | 8 (5.3) |
| Pulmonary embolism | 2 (1.3) | 5 (3.3) |
| Urinary tract infection | 6 (3.9) | 1 (0.7) |
| Hyponatremia | 3 (2.0) | 4 (2.6) |
| Electrocardiogram QT prolonged | 1 (0.7) | 5 (3.3) |
| Nausea | 1 (0.7) | 5 (3.3) |
| Hypokalemia | 4 (2.6) | 1 (0.7) |
| Vomiting | 0 | 5 (3.3) |
| Blood bilirubin increased | 4 (2.6) | 0 |
| Neutrophil count decreased | 0 | 4 (2.6) |
| Diarrhea | 1 (0.7) | 3 (2.0) |
| Acute kidney injury | 4 (2.6) | 0 |
| Pneumonitis | 0 | 3 (2.0) |
| Rash | 3 (2.0) | 0 |
| Deep vein thrombosis | 0 | 3 (2.0) |
| Back pain | 3 (2.0) | 0 |

While we observed greater use of pemetrexed-based chemotherapy as subsequent therapy in patients who died in the alectinib arm versus the crizotinib arm (37.3% versus 12.9%, respectively), subsequent ALK TKIs were given in the same proportion in both treatment arms (35.3% and 37.1% in the alectinib and crizotinib arms, respectively). A similar proportion of patients who experienced PD or symptomatic deterioration received more than one subsequent line of therapy (15.7% in the alectinib arm and 11.1% in the crizotinib arm).

Use of next-generation ALK TKIs as salvage therapy is feasible, but their impact on OS is uncertain. In the phase II registration trial of lorlatinib, median PFS was NR in patients who failed prior crizotinib, and was 6.9 months among patients who had failed two or more ALK TKIs.[12] An ongoing phase II trial evaluating the efficacy of brigatinib given after progression on any non-crizotinib ALK TKI in 20 patients with *ALK*-positive NSCLC reported a median PFS of 6.4 months (95% CI 4.6–NR).[13] In addition, preliminary results from the J-ALTA phase II, single-arm, multicenter trial of brigatinib in Japanese patients with *ALK*-positive NSCLC showed a confirmed partial response in five out of nine (56%) patients who had progressed on alectinib.[14] Further results from these trials are awaited.

No new safety signals were observed in this updated analysis of the ALEX data with almost three times longer median treatment duration with alectinib versus crizotinib. After a median follow-up of 48.2 months, the safety profile of alectinib remains consistent with previous data cuts.[6,7] A 20.4% incidence of dose reductions due to AEs was reported with alectinib, compared with 38% with brigatinib in the ALTA-1L trial following just 24.9 months of follow-up.[9]

In conclusion, final mature PFS data from the ALEX study confirm the superior systemic and CNS efficacy of alectinib compared with crizotinib in patients with previously untreated *ALK*-positive NSCLC. A clinically meaningful difference in OS was seen between the treatment arms at 5 years in favor of alectinib, although the final OS data remain immature. No new safety signals for alectinib were observed. The experimental arm of the ALEX study shows unprecedented improvement in OS for the next-generation ALK TKI alectinib in patients with treatment-naive *ALK*-positive NSCLC.

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## DATA SHARING STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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