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Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with *ALK*-positive non-small-cell lung cancer

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ABSTRACT

Objectives: Alectinib demonstrated superior efficacy and a safety profile that compared favorably with crizotinib in treatment-naïve *ALK*+ non-small-cell lung cancer (NSCLC) in the phase III ALEX study. We present patient-reported outcomes (PROs) from ALEX to assess disease burden, treatment-related symptom tolerability, and health-related quality of life (HRQoL) with alectinib versus crizotinib.

Materials and Methods: Patients were randomized to receive alectinib 600 mg or crizotinib 250 mg twice daily until disease progression, death, or withdrawal. Pre-specified PRO endpoints were: mean change from baseline in symptoms, HRQoL, and functioning; and time to deterioration (TTD) in cough, dyspnea, chest pain, arm/shoulder pain, fatigue, and a composite of three symptoms (cough, dyspnea, chest pain). PRO data were collected using EORTC QLQ-C30 and LC13 questionnaires. Raw scores were standardized to a 0–100-point range, with a ≥10-point score change defined as clinically meaningful. TTD was defined as the time from randomization until confirmed clinically meaningful deterioration (i.e., a ≥10-point score change from baseline).

Results: Baseline completion rates and characteristics were balanced in the PRO-evaluable population (alectinib n = 100, 66%; crizotinib n = 97, 64%). On average, alectinib-treated patients reported clinically meaningful improvements in lung cancer symptoms for longer than crizotinib-treated patients. Between-treatment differences in lung cancer symptoms tended to favor alectinib from 11.1 months (45 weeks) onwards, around the time of median PFS with crizotinib (11.1 months). TTD in lung cancer symptoms was similar between treatment arms, despite longer duration of symptom improvement with alectinib; composite symptom endpoint (hazard ratio 1.10 [95% confidence interval: 0.72–1.68]). Duration of clinically meaningful improvement in HRQoL was longer with alectinib versus crizotinib (Week 88 vs. Week 68, respectively). Better patient-reported tolerability was observed with alectinib versus crizotinib on common treatment-related symptoms.

Conclusion: PRO data support the superior efficacy and tolerability of alectinib relative to crizotinib demonstrated in the ALEX study.

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1. Introduction

Anaplastic lymphoma kinase fusion gene-positive (*ALK*+) disease occurs in approximately 5% of patients with advanced non-small-cell lung cancer (NSCLC) [1]. Current standard first-line therapy for patients with advanced stage *ALK*+ NSCLC is an ALK inhibitor, such as crizotinib, ceritinib, brigatinib, or alectinib [2].

Alectinib is a highly selective central nervous system (CNS) active ALK inhibitor that showed superior efficacy and a safety profile that compared favorably with crizotinib in patients with treatment-naïve *ALK*+ NSCLC in the global phase III ALEX study (NCT02075840) [3]. In the primary ALEX analysis, investigator-assessed progression-free survival (PFS; primary endpoint) was significantly improved with alectinib versus crizotinib (hazard ratio [HR] 0.47, 95% confidence interval [CI]: 0.34–0.65; $P < 0.001$); median PFS for alectinib not reached (NR) (95% CI: 17.7–not estimable [NE]) versus 11.1 months (95% CI: 9.1–13.1) for crizotinib [3]. In an updated analysis of ALEX data, with 10 months' longer follow-up, median PFS was 34.8 months (95% CI: 17.7–NE) with alectinib and 10.9 months (95% CI: 9.1–12.9) with crizotinib (HR 0.43, 95% CI: 0.32–0.58) [4]. Alectinib demonstrated superior CNS efficacy to crizotinib, irrespective of prior radiotherapy treatment [5]. Grade ≥3 adverse events (AEs) were less common with alectinib (41%) than with crizotinib (50%), despite a longer treatment duration [3].

In addition to increasing survival, a key objective of cancer treatment is preserving patients' health-related quality of life (HRQoL), which can be compromised by disease progression and treatment-related toxicities, especially in cases of prolonged daily oral treatment administration. Significant worsening of disease-related symptoms is often experienced by patients with NSCLC during progression of their disease; palliation of these symptoms and/or prolongation of the time until the patient deteriorates are important factors when considering the impact of therapy on HRQoL [6–8]. This is especially relevant for studies with PFS as a primary endpoint, where it is important to translate the delay in disease progression into an endpoint that is meaningful to patients.

Worsening of lung cancer symptoms has been correlated with a poorer treatment response as well as a reduced overall survival (OS) in patients with NSCLC [9]. Disease symptoms commonly associated with lung cancer include cough, dyspnea, chest pain, pain (particularly arm/shoulder pain), hemoptysis, anorexia, and fatigue [10,11]. Of these, loss of appetite, cough, pain, shortness of breath, and fatigue were identified as significant predictors of HRQoL in NSCLC studies in the USA, France, and Germany [12,13]. In addition, the toxicities associated with chemotherapy and other treatment can also severely impair HRQoL in patients with NSCLC [14], despite relieving some of the disease-related symptoms, highlighting the need to evaluate the overall risk/benefit of each treatment.

Adding to the complexity of treatment, CNS metastases are common in metastatic *ALK*+ NSCLC [15,16], occurring in up to 60% of patients during first-line therapy with crizotinib or chemotherapy [17,18]. Compared with other metastatic sites, CNS metastases are associated with significant morbidity, and a significant reduction in HRQoL, independence, and estimated life expectancy [19]. We present patient-reported outcomes (PROs) from the ALEX study to assess disease burden, treatment-related symptom tolerability, and HRQoL with alectinib versus crizotinib in patients with treatment-naïve, advanced *ALK*+ NSCLC, including a subgroup of patients with baseline CNS metastases.

2. Methods

2.1. Study design

ALEX was the first global phase III head-to-head comparison of two ALK inhibitors, unlike other studies that have compared ALK inhibitors with chemotherapy. The design of the ALEX study has been published previously [3]. In brief, patients aged ≥18 years with previously untreated, advanced *ALK*+ NSCLC were randomized 1:1 to receive alectinib (600 mg) or crizotinib (250 mg) twice daily until disease progression, death, or withdrawal. An open-label study design was considered more appropriate for patients enrolled in this particular trial, with the ultimate goal to ensure patient compliance as much as possible, notably due to the high pill count and complexity of dosing that would be required for a blinded study design. The study protocol was approved by the institutional review board or ethics committee at each participating center and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent before undertaking any study-related procedures.

2.2. Study endpoints

Pre-specified PRO endpoints of the ALEX study were: the mean change from baseline in symptoms, HRQoL, and functioning at each time point on treatment; and the time to deterioration (TTD) in patient-reported symptoms of cough, dyspnea (single and multi-item scales), chest pain, arm/shoulder pain, fatigue, and a composite of three symptoms (cough, dyspnea, chest pain). Changes in HRQoL and functioning was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the QLQ lung cancer module (LC13). A pre-specified subgroup analysis assessing the proportion of patients with clinically meaningful change in HRQoL was conducted in patients with CNS metastases at baseline, but was not included as an endpoint given its exploratory nature.

2.3. Study assessments

PRO data measuring HRQoL, day-to-day function, disease burden, and treatment burden were collected using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. The EORTC QLQ-C30 gathers data on generic aspects of HRQoL [20], while the LC13 captures information specifically related to lung cancer and its treatment [21]. The EORTC QLQ-C30 comprises 30 items encompassing five function scales (physical, role, social, emotional, cognitive), a global health status/HRQoL scale, three symptom scales (fatigue, pain, nausea/vomiting), and multiple single-item symptoms scales [20]. The QLQ-LC13 reports on lung cancer-related symptoms (e.g., cough, dyspnea, chest pain) and commonly reported treatment-related symptoms (e.g., peripheral neuropathy, sore mouth, alopecia) [21]. All function- and symptom-related items are measured over the previous week on a 4-point scale, ranging from 'not at all' to 'very much'. The global health status scale comprises two questions on a 7-point scale reflecting patients' HRQoL during the previous week. These questionnaires were completed using a self-administered electronic device at the patient's home, and were issued at baseline, every 4 weeks until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression. Data were also collected at the post-treatment visit (4 weeks after permanent treatment discontinuation) and at 8-weekly survival follow-up visits for a period of 6 months.

EORTC recommended scoring guidelines were used. A raw score was calculated as the average of items contributing to a scale. A linear transformation was used to standardize raw scores to a 0–100-point range. A ≥10-point score change within a patient/group in any scale was considered the threshold of clinically meaningful change [22]. An increase in score for the global health status and functioning scales indicated improvement, while a decrease in score for the symptom scales/items reflected a reduction in symptom severity.

2.4. Statistical analyses

With the exception of the TTD analyses, which were performed in the intent-to-treat (ITT) population, all analyses utilized the PRO-evaluable population, defined as all patients with a baseline assessment and at least one post-treatment assessment. All statistical analyses were pre-specified within the statistical analysis plan.

To understand the longitudinal course of a patient's experience on treatment, mean change from baseline analyses were used for disease symptoms, treatment-related symptoms, and HRQoL at each on-treatment time point for both treatment arms. Additionally, a pre-specified responder analysis was performed, which detailed the number and proportion of patients who improved, worsened, or remained stable compared with baseline for all disease symptoms, treatment-related symptoms, and HRQoL by treatment arm at each on-treatment time point. Clinically meaningful improvement was defined as ≥10-point decrease from baseline for any symptom or a ≥10-point increase from baseline for the global health status scale. Clinically meaningful worsening was defined as a ≥10-point increase from baseline for any symptom or a ≥10-point decrease from baseline for the global health status scale. The responder analysis was performed in the entire PRO-evaluable population as well as in PRO-evaluable subgroups with and without baseline CNS metastases.

TTD was defined as the time from randomization until confirmed clinically meaningful deterioration, defined as a ≥10-point change in score from baseline that was held for at least two consecutive assessments, or an initial ≥10-point change from baseline followed by death within 5 weeks from the last assessment [22,23]. TTD scores were summarized using Kaplan-Meier methods and a stratified log-rank test was used to compare TTD between arms. If a baseline or post-baseline PRO evaluation was not available, TTD was censored at the date of randomization. If they had not deteriorated, patients were censored at the time when they last completed a PRO assessment.

3. Results

3.1. Patients

The data cutoff for the analyses presented here was February 9, 2017. Between August 2014 and January 2016, 303 patients were enrolled in ALEX and randomized to receive treatment with alectinib (n = 152) or crizotinib (n = 151); all randomized patients received at least one dose of study drug [3]. The PRO-evaluable population comprised 197 patients (65%): alectinib n = 100, 66%; crizotinib n = 97, 64% (Fig. 1). Baseline demographic and clinical characteristics were generally balanced between treatment arms in the PRO-evaluable population and similar to the ITT population of ALEX (Table 1) [3]. Patients reported minimal-to-moderate lung cancer symptom burden at baseline, and moderate-to-high functioning and HRQoL, suggesting minimal impairment at baseline, with comparable scores between arms (Table 2).

3.2. Questionnaire completion rates

In the ITT population, 70% of alectinib-treated patients and 64% of crizotinib-treated patients completed the EORTC QLQ-C30 and QLQ-LC13 HRQoL questionnaires as planned at baseline (Supplementary Tables 1A and 1B). Among these patients, moderate-to-high compliance rates (≥60%) were observed in the alectinib arm for the majority of subsequent PRO assessments. However, compliance rates throughout the study were lower in the crizotinib arm, dropping to ≤60% for the majority of time points from Week 68 onwards. The reasons for non-compliance were not recorded, but may relate to the use of the self-administered test on the electronic device, poorer QoL, higher symptom

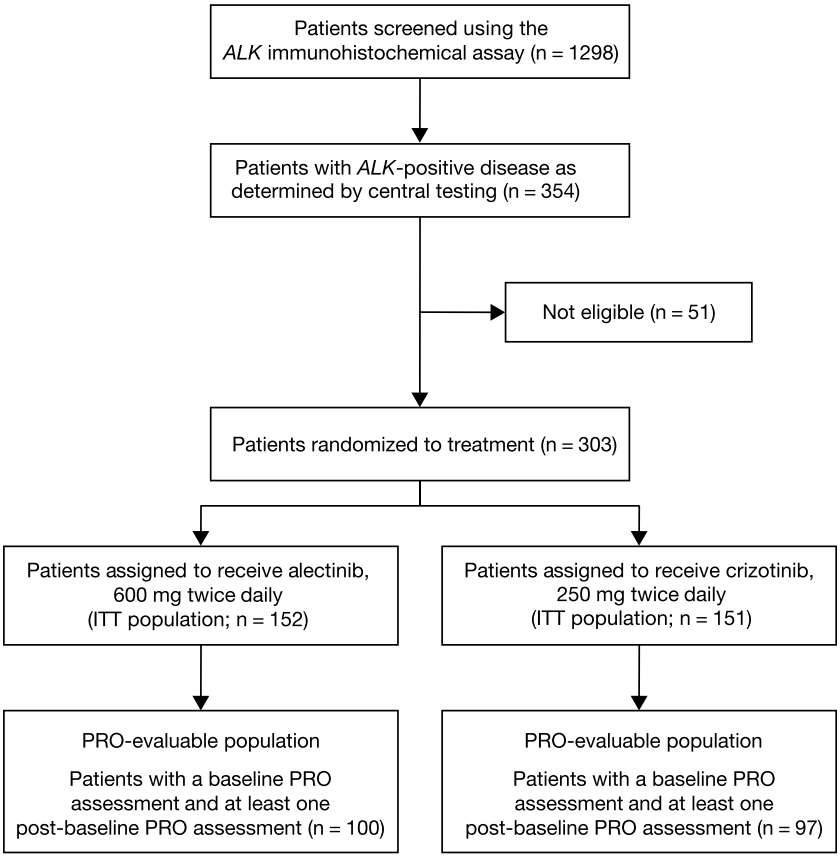

Fig. 1. Patient disposition.

Table 1
Baseline demographic and clinical characteristics of the PRO-evaluable population and the ITT population of ALEX.

	PRO-evaluable population		ITT population	
	Alectinib (n = 100)	Crizotinib (n = 97)	Alectinib (n = 152)	Crizotinib (n = 151)
Mean age, years	56.2	53.1	56.3	53.8
Age ≥65 years, n (%)	27 (27.0)	20 (20.6)	37 (24.3)	33 (21.9)
Female, n (%)	59 (59.0)	55 (56.7)	84 (55.3)	87 (57.6)
Race, n (%)				
Asian	56 (56.0)	52 (53.6)	69 (45.4)	69 (45.7)
White	41 (41.0)	40 (41.2)	76 (50.0)	75 (49.7)
Smoking status, n (%)				
Current smoker	8 (8.0)	5 (5.2)	12 (7.9)	5 (3.3)
Past smoker	31 (31.0)	29 (29.9)	48 (31.6)	48 (31.8)
Non smoker	61 (61.0)	63 (64.9)	92 (60.5)	98 (64.9)
ECOG PS 0–1, n (%)	99 (99.0)	91 (93.8)	142 (93.4)	141 (93.4)
CNS lesions at baseline, n (%)	38 (38.0)	39 (40.2)	64 (42.1)	58 (38.4)

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent to treat; PRO = patient-reported outcome.

Table 2
Baseline lung cancer symptom burden and functioning scores.

	Alectinib (n = 100)	Crizotinib (n = 97)
Mean lung cancer symptom score (SD)		
Dyspnea (single item)	29.3 (27.7)	27.5 (27.6)
Dyspnea (multi-item)	28.1 (23.3)	26.0 (23.7)
Coughing	43.3 (29.8)	36.1 (30.8)
Chest pain	20.0 (22.2)	18.4 (24.6)
Arm/shoulder pain	18.3 (24.8)	19.8 (24.0)
Fatigue	34.8 (21.8)	31.9 (24.1)
Pain	24.3 (23.7)	22.2 (23.8)
Pain in other parts	24.7 (24.9)	21.9 (25.1)
Hemoptysis	3.0 (10.7)	3.8 (12.7)
Mean functioning score (SD)		
Global health status/QoL	60.1 (21.7)	62.1 (24.1)
Physical functioning	77.3 (19.8)	78.9 (20.5)
Cognitive functioning	86.8 (17.5)	88.0 (17.0)

SD = standard deviation; QoL = quality of life.
All scales and single-item measures were linearly transformed so that each score ranges from 0 to 100. A high functioning or global health status score represents a high level of functioning/QoL; a low symptom scale/item score represents a low level of symptoms.
Baseline PRO assessment was completed within 7 days of randomization.

burden, disease progression, or death. Towards the later study time points, the number of evaluable patients who were still required to complete the questionnaires was low, especially in the crizotinib arm.

With the exception of the pre-specified TTD analyses, PRO data were only interpreted up to Week 84 for crizotinib and Week 96 for alectinib, at which point approximately 20% of the PRO-evaluable population remained (Supplementary Tables 1A and 1B), thus limiting interpretation and comparisons between arms.

3.3. Improvement in lung cancer symptoms from baseline (EORTC QLQ-C30 and QLQ-LC13 questionnaires)

Patients in both treatment arms reported clinically meaningful improvement for multiple lung cancer symptom scores while on treatment. However, patients treated in the alectinib arm tended to report benefit for a longer duration of time while on treatment; the magnitude

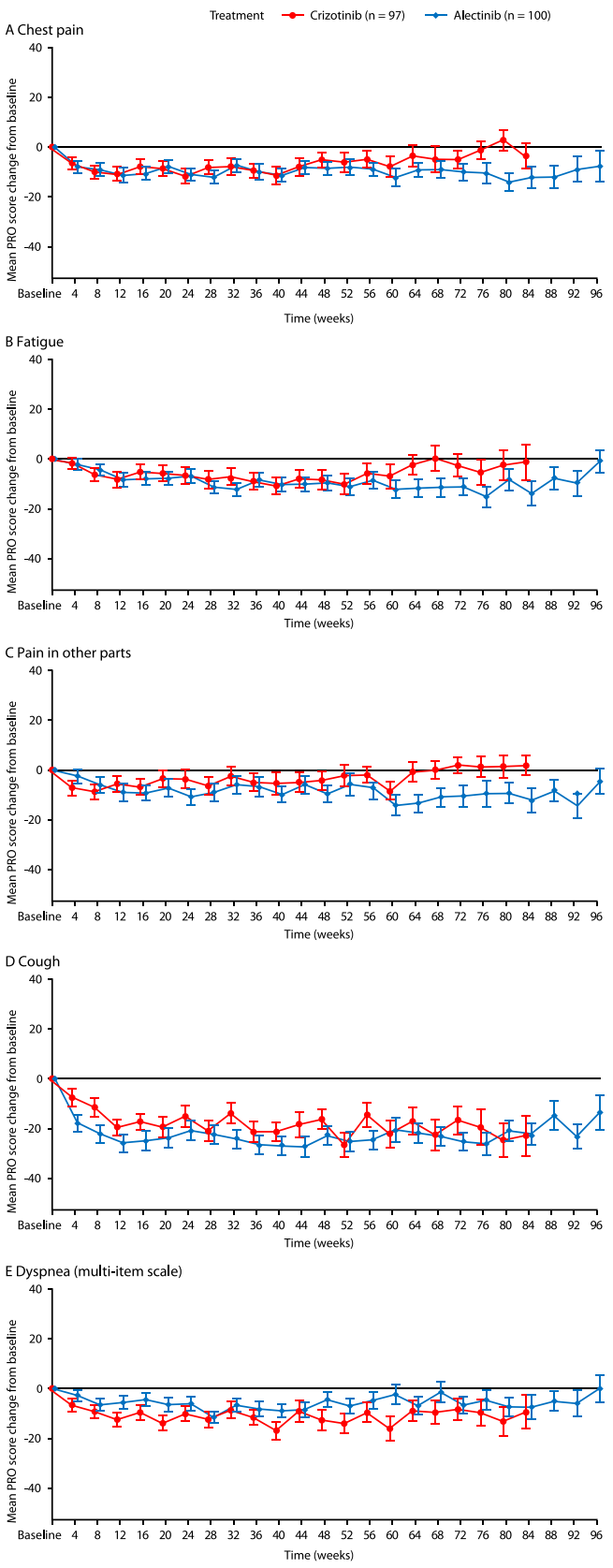

Fig. 2. Mean (± standard error) change in lung cancer symptoms from baseline: A) chest pain (EORTC QLQ-LC13), B) fatigue (EORTC QLQ-C30), C) pain in other parts (EORTC QLQ-LC13), D) cough (EORTC QLQ-LC13), and E) dyspnea (multi-item scale, EORTC QLQ-LC13). Analyses are based on the PRO-evaluable population.

of benefit was similar between arms. Differences in the duration of symptomatic benefit typically began after the time of median PFS in the crizotinib arm (11.1 months; 45 weeks). For example, patients in the alectinib arm maintained their improvement in chest pain (QLQ-LC13), fatigue (QLQ-C30), and pain in other parts (QLQ-LC13) relative to crizotinib starting at Week 60 and persisting through Week 84 (Fig. 2A-C). Patients in both arms demonstrated a deep and durable clinically meaningful improvement (≥10-point change) in cough (QLQ-LC13) as

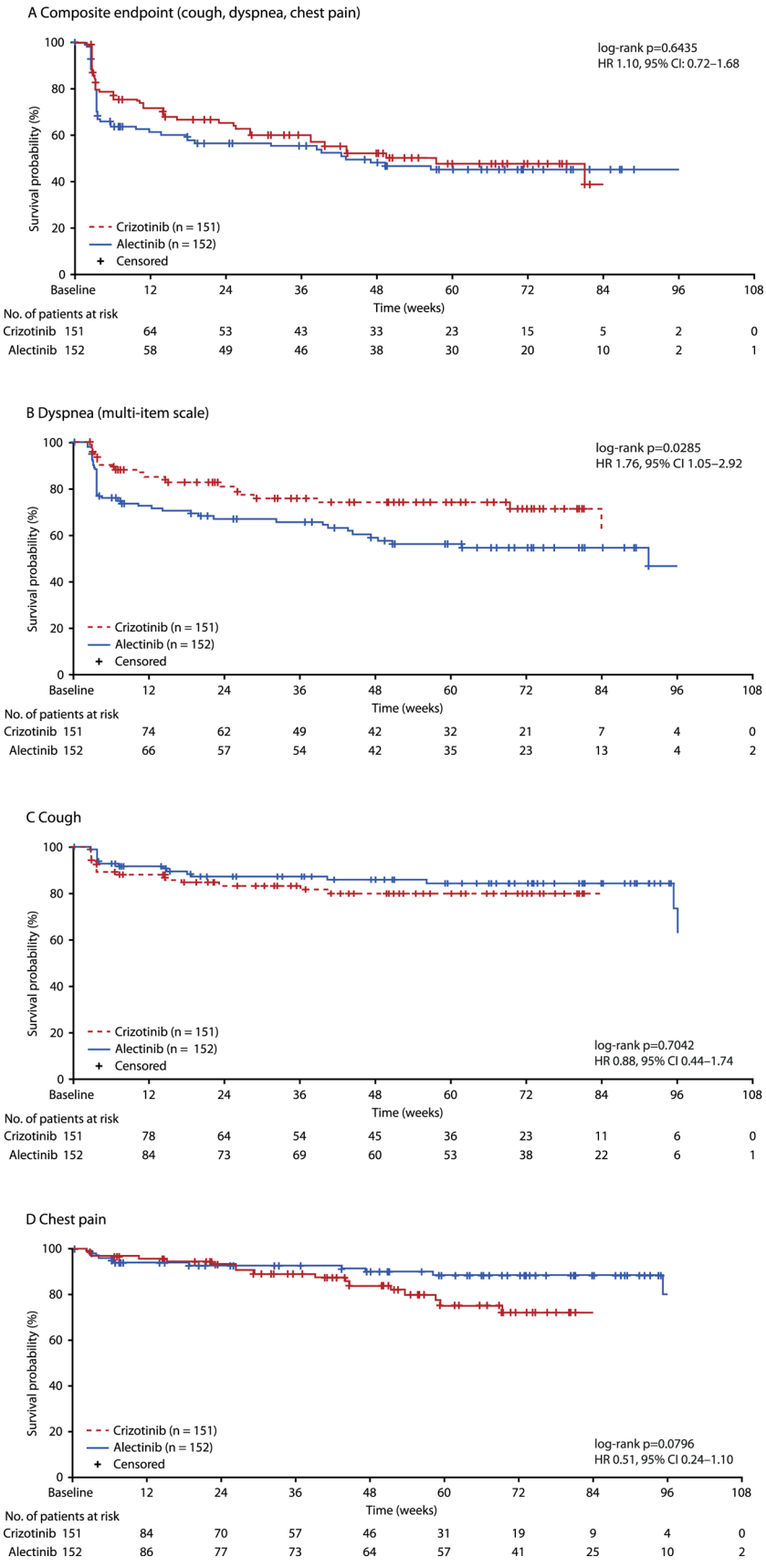

Fig. 3. Time to deterioration in lung cancer symptoms: A) composite endpoint (cough, dyspnea, chest pain), B) dyspnea (multi-item scale), C) cough, and D) chest pain (ITT population). A confirmed clinically meaningful deterioration in any of the lung cancer symptoms was defined as a ≥10-point increase from baseline on any of the linearly transformed individual scores ranging from 0 (lowest level of symptoms) to 100 (highest level of symptoms) held for at least two consecutive assessments or an initial ≥10-point increase from baseline followed by death within 5 weeks from the last assessment [20]. Patients without confirmed deterioration at the time of analysis were censored at the last time they were known to have not deteriorated.

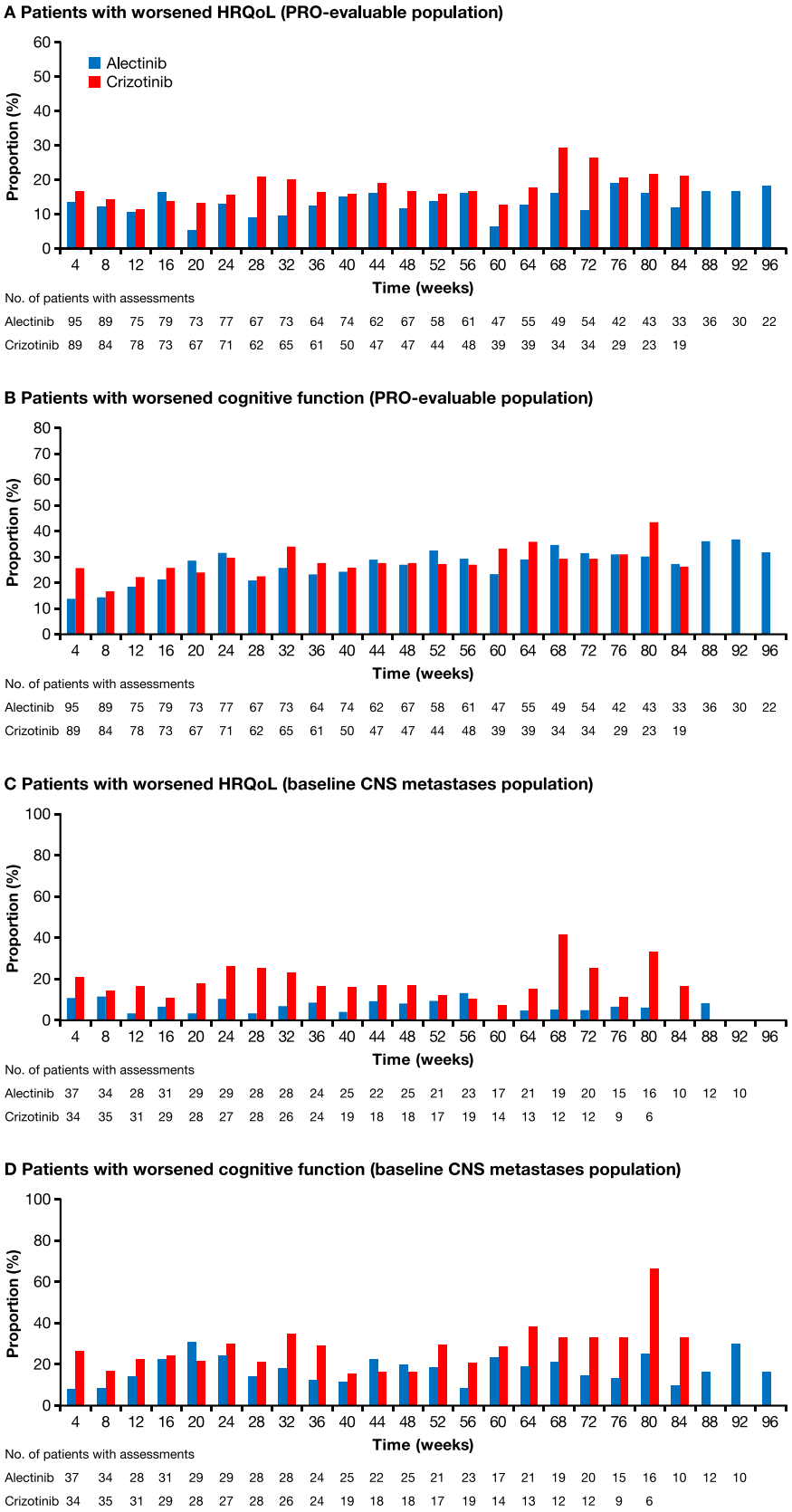

Fig. 4. Proportion of patients with worsened HRQoL and cognitive function from baseline. Analyses are based on the PRO-evaluable population (A and B) or the subset of PRO-evaluable patients with CNS metastases at baseline (C and D). HRQoL and cognitive function were assessed using the EORTC QLQ-C30.

early as Week 4, which was maintained at all PRO assessments through Week 84 in the crizotinib arm and Week 96 in the alectinib arm (Fig. 2D). An improvement from baseline in multi-item dyspnea (QLQ-LC13) was also seen in both treatment arms (Fig. 2E).

The proportion of patients reporting clinically meaningful improvement or worsening, for each of the lung cancer symptoms in the PRO-evaluable population showed similar findings to the mean change from baseline analyses. A greater proportion (≥10% difference) of patients in the alectinib arm versus the crizotinib arm reported clinically meaningful improvement for multiple symptoms from Week 60 through to Week 84 (Supplementary Fig. 1).

3.4. Time to deterioration in patient-reported lung cancer symptoms

Despite a longer duration of symptom improvement with alectinib, median TTD in the composite symptom endpoint (cough, dyspnea, chest pain) was not significantly different between the treatment arms (HR 1.10, 95% CI: 0.72–1.68; Fig. 3A). The HR for TTD in multi-item dyspnea (QLQ-LC13) was 1.76 (95% CI: 1.05–2.92; Fig. 3B). No significant differences were observed between the treatment arms in TTD in individual lung cancer symptoms (QLQ-LC13: cough HR 0.88, 95% CI: 0.44–1.74 [Fig. 3C]; QLQ-LC13: chest pain HR 0.51, 95% CI: 0.24–1.10 [Fig. 3D]; QLQ-C30: fatigue HR 0.74, 95% CI: 0.46–1.19 [Supplementary Fig. 2A]; QLQ-LC13: pain in arm/shoulder HR 1.43, 95% CI: 0.79–2.61 [Supplementary Fig. 2B]). Fewer than 32% of patients in each arm reported a confirmed deterioration event in the composite symptom endpoint, with fewer than 18% of patients reporting confirmed deterioration in any of the individual symptoms, with the exception of the dyspnea multi-item scale in the alectinib arm (28%).

3.5. Mean change from baseline in HRQoL and cognitive functioning (EORTC QLQ-C30 questionnaire)

Within the PRO-evaluable population, mean change from baseline analyses suggested a trend towards benefit with alectinib relative to crizotinib in HRQoL. Patients in both treatment arms reported a clinically meaningful improvement (≥10 point increase) from baseline as early as Week 8. However, the duration of clinically meaningful improvement was longer in the alectinib arm versus the crizotinib arm (Week 88 vs. Week 68, respectively). Similarly, a greater proportion (≥10% difference) of patients in the crizotinib arm reported clinically meaningful worsening in HRQoL from baseline compared with alectinib at many timepoints through Week 56 (Fig. 4A). A similar proportion of patients in both arms reported clinically meaningful worsening in cognitive function through Week 56 (Fig. 4B). No differences between treatment arms were observed within the TTD analyses in the ITT population (Supplementary Fig. 3); median TTD in global health status (HR 0.72, 95% CI: 0.38–1.39) and cognitive function (HR 0.85, 95% CI: 0.55–1.33).

In the pre-specified exploratory analysis assessing patients with baseline CNS metastases, fewer patients (≥10% difference) in the alectinib arm than in the crizotinib arm reported clinically meaningful worsening in HRQoL (Fig. 4C) starting at Week 12 (4% vs. 16%, respectively) and persisting for most assessments through Week 84 (0% vs. 17%, respectively). Similarly, within the same CNS-metastases baseline population, fewer alectinib-treated patients reported clinically meaningful worsening in cognitive function as compared with crizotinib starting at Week 4 (8% vs. 27%, respectively) and continuing for many assessments through Week 84 (10% vs. 33%, respectively) (Fig. 4D). The proportion of patients without baseline CNS metastases with worsened HRQoL and cognitive function from baseline is shown in Supplementary Fig. 4.

3.6. Worsening in lung cancer symptoms from baseline (EORTC QLQ-C30 and QLQ-LC13 questionnaires)

Both the comparison of mean changes from baseline and of the proportion of patients with clinically meaningful change analyses suggested greater tolerability with alectinib for commonly reported treatment-related symptoms, including nausea/vomiting, diarrhea, peripheral neuropathy, constipation, appetite loss, dysphagia, and sore mouth, as compared with crizotinib.

Fewer alectinib-treated patients (≥10% difference) experienced a clinically meaningful worsening in nausea/vomiting (QLQ-C30) versus crizotinib, at most time points through Week 84 (Supplementary Fig. 5A). Mean change from baseline analyses indicated that patients in the crizotinib arm, on average, reported clinically meaningful worsening (≥10 point increase) in both diarrhea (QLQ-C30, from Week 4 through Week 84; Supplementary Fig. 5B) and peripheral neuropathy (QLQ-LC13, Week 4 and multiple time points thereafter; Supplementary Fig. 5C), which were not reported by patients receiving alectinib (Supplementary Fig. 5C). In addition, an initial clinically meaningful worsening in constipation (QLQ-C30) was seen in both the alectinib and crizotinib arms at Week 4 through Week 12, but this attenuated over time in the alectinib arm relative to the crizotinib arm (Supplementary Fig. 5D). The proportion of patients with worsened tolerability outcomes for appetite loss (QLQ-C30), dysphagia (QLQ-LC13), and sore mouth (QLQ-LC13) are shown in Supplementary Figures 5E to 5G.

4. Discussion

Alectinib demonstrated superior systemic and CNS efficacy, with improved tolerability, relative to crizotinib in the phase III ALEX study in *ALK*+ NSCLC [3]. In this analysis of PRO data from ALEX, a consistent pattern emerged showing that patients treated with alectinib reported clinically meaningful improvement in HRQoL and multiple lung cancer symptoms for a longer duration than those treated with crizotinib. Differences between treatment arms tended to favor alectinib following the time of median PFS with crizotinib (11.1 months [45 weeks]) and were maintained until Week 84. In addition, the PRO analyses overall confirmed the better tolerability seen with alectinib versus crizotinib.

TTD in lung cancer symptoms was comparable between the treatment arms, at the composite or individual symptom level, with the exception of the multi-item dyspnea symptom scale. Further examination of the data indicated that early confirmed worsening of dyspnea often returned to baseline or attenuated over time, a finding for which currently there is no clear explanation. Dyspnea deterioration did not appear to affect HRQoL, as improvements in HRQoL were reported early in the alectinib arm (from Week 4) and were maintained at most subsequent time points. There also appeared to be no relationship between early dyspnea deterioration and disease progression, as the dyspnea deterioration events were not progressive disease events in the alectinib arm. Despite the early worsening of dyspnea with alectinib compared with crizotinib, there has been no significant reported lung toxicity with alectinib (compared with brigatinib [24]) but a higher proportion of patients with anemia (vs. crizotinib) [3].

Patients in both treatment arms experienced clinically meaningful improvements in multiple lung cancer symptoms, including cough, chest pain, and pain in other parts, which is consistent with a similar response rate in the two arms. These data are also consistent with previous findings from the phase III ALUR alectinib study [25], and the phase III PROFILE 1014 crizotinib study [26]. In addition, the ALUR study reported improvements from baseline in dyspnea (single and multi-item scales) with alectinib [25].

Median TTD in HRQoL was similar between treatment arms in the ALEX PRO-evaluable population. However, a greater proportion of patients reported clinically meaningful improvements in HRQoL with alectinib versus crizotinib and, on average, improvements in HRQoL

were maintained for a longer duration of time with alectinib. These data are consistent with previous studies that reported clinically meaningful improvements in global health status from baseline with alectinib [27] and crizotinib [26]. Among patients with baseline CNS metastases, fewer alectinib-treated patients reported clinically meaningful worsening in HRQoL or cognitive function, highlighting the patient-relevant benefit of the CNS activity observed with alectinib relative to crizotinib. However, the QoL questionnaires used in the study did not include any specific CNS-related symptoms, apart from cognitive function, which could have impacted the results obtained in these patients.

Our data also showed that, based on common treatment-related symptoms, better patient-reported tolerability was observed with alectinib relative to crizotinib, consistent with alectinib's safety profile [3]. Tolerability is a critical component of determining the overall risk/benefit profile of each treatment, especially given the longer duration of treatment exposure for alectinib.

There were limitations to this study that should be considered. Full compliance with HRQoL assessments was not reached, which is common in cancer studies. In addition, there was low baseline completion rate due to initial technical issues with the electronic capture devices, meaning that some baseline data were not captured accurately. However, the baseline demographics of the PRO-evaluable population are balanced and similar to the overall ITT study population. Overall, approximately one-third of randomized patients did not participate in the PRO assessments, which is a higher proportion than previously reported [26,28]. This may be due to the use of electronic devices in ALEX, on which questionnaires were required to be completed at home every 4 weeks, as opposed to every 8 weeks with site-based assessments. However, although these factors are likely independent of treatment and unrelated to outcome, we cannot exclude the introduction of selection bias. Thus, these results should be interpreted with caution, given that only a selection of the ITT population provided data for analysis. The lower compliance rate observed in the crizotinib arm may be a result of the earlier onset of disease progression compared with the alectinib arm. Notably, as with many questionnaire-based studies, it remains challenging to show a clinically meaningful improvement in HRQoL in patients who were generally asymptomatic at baseline.

5. Conclusions

Overall, patients treated with alectinib reported clinically meaningful improvement in HRQoL and multiple lung cancer symptoms for a longer duration than those treated with crizotinib, consistent with the improved PFS observed versus crizotinib. The totality of evidence seen in patients with baseline CNS metastases suggests a patient-relevant benefit of the CNS activity observed with alectinib. Additionally, better patient-reported tolerability was observed with alectinib relative to crizotinib on common treatment-related symptoms, consistent with alectinib's known safety profile. In conclusion, these PRO findings support the superior efficacy and tolerability of alectinib relative to crizotinib previously reported in the ALEX study.

6. Data sharing

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 here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Declaration of Competing Interest

Maurice Pérol has received advisory board honoraria from Roche, Pfizer, and Novartis; Nick Pavlakis has received advisory board honoraria from Roche, Pfizer, Novartis, and Takeda, and travel assistance from Roche; Evgeny Levchenko has no conflicts of interest to disclose; Marco Platania has no conflicts of interest to disclose; Julio Oliveira has no conflicts of interest to disclose; Silvia Novello has participated in speaker bureaus for AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck Sharp and Dohme, Roche, and Takeda; Rita Chiari has no conflicts of interest to disclose; Teresa Moran has no conflicts of interest to disclose; Emmanuel Mitry was a Roche employee at the time of these analyses and holds stocks in Roche; Eveline Nüesch is a Roche employee and holds stocks in Roche; Ting Liu is a Roche employee and holds stocks in Roche; Bogdana Balas is a Roche employee and holds stocks in Roche; Krzysztof Konopa has no conflicts of interest to disclose; Solange Peters has received education grants, provided consultation, attended advisory boards, and/or provided lectures for the following organizations: Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, F. Hoffmann-La Roche, Janssen, Merck Sharp and Dohme, Merck Serono, Pfizer, Regeneron, and Takeda. This work was funded by F. Hoffmann-La Roche Ltd.

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Appendix A. Supplementary data

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