Lung Cancer 174 (2022) 146–156

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Patient-reported outcomes from the randomized phase 3 CROWN study of first-line lorlatinib versus crizotinib in advanced *ALK*-positive non-small cell lung cancer

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ARTICLE INFO

Keywords:
Lorlatinib
Crizotinib
NSCLC
Patient-reported outcomes

ABSTRACT

Objectives: Quality of life (QoL) for patients with non-small cell lung cancer (NSCLC) is negatively impacted by their disease and treatment side effects. We present detailed patient-reported outcome (PRO) data from the phase 3 CROWN study, which compared lorlatinib with crizotinib in patients with previously untreated *ALK*-positive advanced NSCLC.

Materials and methods: PROs were assessed using the European Organisation for Research and Treatment of Cancer QoL Questionnaire with Lung Cancer module. A longitudinal, random-intercept, random-slope, mixed-effect model assessed score changes from baseline up to (not including) end of treatment. Mean changes of absolute scores from baseline at each cycle were calculated and presented up to cycle 18 ($\geq$ 10-point change considered clinically meaningful).

Results: In both lorlatinib (n = 148) and crizotinib (n = 140) arms, there were longitudinal improvements across multiple functioning and symptom scores during treatment compared with pre-treatment. Numerical improvements for most longitudinal functioning scores (physical, role, emotional, social) favored lorlatinib; cognitive functioning favored crizotinib. Numerical improvements favored lorlatinib for several symptoms (fatigue, nausea and vomiting, insomnia, appetite loss, constipation, diarrhea [clinically meaningful improvement], and cough); peripheral neuropathy favored crizotinib. Subgroup analyses showed PROs did not differ by presence/absence of baseline brain metastases.

Conclusions: Patients receiving first-line lorlatinib or crizotinib showed improvements and delayed deterioration in QoL, functioning, and several symptoms. Alongside the previously reported significantly longer progression-

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BL, baseline; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: lung cancer module; NSCLC, non-small cell lung cancer; OR, odds ratio; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; SE, standard error; SD, standard deviation; TTD, time to deterioration.

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https://doi.org/10.1016/j.lungcan.2022.11.004
Received 11 August 2022; Received in revised form 28 October 2022; Accepted 2 November 2022
Available online 7 November 2022

free survival and higher intracranial response rates for lorlatinib versus crizotinib, these data further support the use of lorlatinib over crizotinib in patients with advanced *ALK*-positive NSCLC with/without baseline brain metastases and provide evidence of several QoL improvements with lorlatinib when used in the first-line setting.

1. Introduction

The quality of life (QoL) of a patient with lung cancer is negatively impacted by factors such as the number of symptoms they experience (e.g., fatigue, loss of appetite, pain in chest, cough, dyspnea), side effects of treatment, and disease progression [1,2]. Brain metastases are common in patients with lung cancer, particularly in those with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) [3]. The presence of brain metastases can impact a patient's QoL further due to increased symptom burden, the development of neurological symptoms, a reduced capacity for daily functioning, and broader aspects such as financial issues [3–5]. Treatments that target brain metastases not only prolong progression-free survival (PFS) or overall survival [6–9] but may also reduce the associated QoL burden experienced by patients who develop brain metastases during the course of their disease [3].

Several second-generation ALK inhibitors have shown improved efficacy over crizotinib (a first-generation ALK inhibitor) in patients with *ALK*-positive NSCLC [8,10–13]. Lorlatinib is a potent, brain-penetrant, third-generation ALK inhibitor [14] indicated for the first-line treatment of adult patients with *ALK*-positive metastatic NSCLC [15]. In the phase 3 CROWN study (NCT03052608), lorlatinib significantly improved independently assessed PFS (primary endpoint by blinded independent central review assessment based on Response Evaluation Criteria In Solid Tumors [RECIST] v1.1), with a 72 % reduction in the risk of progression or death compared with crizotinib [16]. Overall response rates were 76 % (95 % confidence interval [CI]: 68–83) with lorlatinib versus 58 % (95 % CI: 49–66) with crizotinib (odds ratio [OR] 2.25 [95 % CI: 1.35–3.89]). Intracranial response rates in patients with measurable or non-measurable brain metastases at baseline were 66 % (95 % CI: 49–80; 61 % complete response rate) with lorlatinib versus 20 % (95 % CI: 9–36; 15 % complete response rate) with crizotinib (OR 8.41 [95 % CI: 2.59–27.23]). Respective intracranial response rates for patients with measurable brain metastases at baseline were 82 % (95 % CI: 57–96; 71 % complete response rate) with lorlatinib versus 23 % (95 % CI: 5–54; 8 % complete response rate) with crizotinib (OR 16.83 [95 % CI: 1.95–163.23]) [16].

Treatment side effects are a potential contributor to reduced QoL in patients with NSCLC [1]. The safety profile of lorlatinib was initially described following a phase 1/2 study (NCT01970865) [17,18], and safety data obtained from the CROWN study were consistent with this [16]. The most frequently occurring lorlatinib-associated adverse events (AEs) were hypercholesterolemia, hypertriglyceridemia, edema, increased weight, peripheral neuropathy, diarrhea, and neuropsychological effects [16,17]. In the CROWN study, 21 % of patients receiving lorlatinib experienced cognitive effects and 16 % experienced mood effects (mostly grade 1 or 2), compared with 6 % and 5 % for crizotinib, respectively [16]. The potential clinical impact of cognitive and mood effects following treatment with lorlatinib has been debated previously [19,20]. Most AEs associated with lorlatinib treatment can be managed effectively by dose modification and concomitant medication [16–18,21]. Permanent treatment discontinuations due to AEs associated with lorlatinib were uncommon in both the phase 2 part of the phase 1/2 study (3 %) and in CROWN (7 %) [16,17].

Patient-reported outcome (PRO) data for lorlatinib from the phase 2 part of the phase 1/2 study showed improvements from baseline in global QoL as well as several symptom and functioning scales [22]. Global QoL data from the CROWN study also supported the safety and favorable AE profile of lorlatinib relative to crizotinib [16]. Improvements in global QoL were seen from cycle 2 of treatment and were maintained over time in the lorlatinib arm [16]. Here, we build on the global QoL data reported previously and present a detailed analysis of PRO data from the CROWN study, focusing on cognitive and emotional functioning and subgroup analyses in patients in the lorlatinib arm with or without brain metastases at baseline.

2. Materials and methods

2.1. Study design and patients

Full details of the CROWN study have been reported previously [16] and are summarized in the Supplementary Methods. Patients with treated or untreated central nervous system metastases were eligible if asymptomatic.

Patients were randomized 1:1 to either oral lorlatinib 100 mg once daily or oral crizotinib 250 mg twice daily, stratified by the presence of brain metastases (yes or no) and ethnicity (Asian or non-Asian). Treatment continued until disease progression (RECIST defined, determined by blinded independent central review), death, withdrawal of consent, loss to follow-up, or unacceptable toxicity. Crossover between treatment arms was not permitted.

The study protocol and amendments were approved by the institutional review board or independent ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

2.2. PRO assessments

In the CROWN study, PROs were assessed as a secondary endpoint using the European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire (EORTC QLQ-C30) [23] and its corresponding module for lung cancer (QLQ-LC13) [24]. The EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire [25] was also completed by patients; these results will be presented separately. PROs were assessed at baseline and then on day 1 of each 28-day treatment cycle through to the end of treatment. Patients completed paper-based questionnaires in the clinic prior to their physician visit, per protocol. All questionnaires were translated into local languages as appropriate for each site. These translations underwent the EORTC's rigorous procedures for translation and cultural adaptation [26].

The EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires have been used in previous assessments of ALK inhibitor therapy in patients with NSCLC [27–29]; further details of these questionnaires can be found in the Supplementary Methods. Higher scores on the global health/QoL and functioning scales indicate higher health status/QoL and functioning, whereas higher scores on symptom scales/items and the financial impact item represent a greater presence of symptoms/financial impact.

2.3. Statistical analysis

The PRO analysis set comprised all treated patients who completed a baseline assessment and at least one post-baseline PRO assessment. Baseline data were summarized descriptively in tabulated form.

A longitudinal, random-intercept, random-slope, mixed-effect model was used to assess EORTC QLQ-C30 and EORTC QLQ-LC13 score changes from baseline up to, but not including, end of treatment. The model had an intercept term, treatment, time (as a continuous variable), treatment-by-time, baseline, and randomization stratification factors as covariates. Analysis was based on restricted maximum likelihood using

an unstructured covariance matrix. Longitudinal mean score changes from baseline were compared between treatment arms (≥ 10-point difference was considered clinically meaningful [27,30,31]). No adjustments were made for multiple comparisons. Mean changes in absolute scores from baseline and standard errors at each cycle were calculated and presented as line charts up to cycle 18 for all patients and those with and without brain metastases at baseline. Data are presented for the first 18 cycles, as later cycles had a smaller (approximately ≤ 20 %) number of participants in each arm, which limited the interpretation of the data.

The Kaplan–Meier method was used to estimate time to deterioration (TTD), defined as the time from randomization to the first time a patient's score showed a ≥ 10-point decrease for global QoL (EORTC QLQ-C30) or a ≥ 10-point increase for a composite lung cancer symptom endpoint of pain in chest, dyspnea, or cough. The TTD analysis of global QoL was performed post hoc.

3. Results

A total of 296 patients were randomized in the CROWN study: 149 to lorlatinib and 147 to crizotinib. The baseline demographics and clinical characteristics of the overall patient population have been reported previously [16]. Of the 296 patients, 288 patients (97 %) had evaluable PRO data, as they had PRO data at baseline and at least one post-baseline assessment (n = 148 in the lorlatinib arm and n = 140 in the crizotinib arm; Table 1). All PRO analyses are based on a data cutoff date of March 20, 2020, consistent with the primary analysis. PRO completion rates (defined as at least one question answered) remained ≥ 96 % through cycle 18 in both treatment arms (Supplementary Table 1). As randomization was stratified according to the presence of brain metastases (yes or no) and ethnic group (Asian or non-Asian), patients were well balanced between the treatment arms. In total, 77 patients in the PRO analysis population (38 patients in the lorlatinib arm and 39 patients in the crizotinib arm) had measurable or non-measurable brain metastases at baseline.

Table 1
Summary of patient demographics and baseline disease characteristics in the CROWN PRO analysis set.

Characteristic	Lorlatinib (n = 148)	Crizotinib (n = 140)
Age, median (interquartile range), years[a]	61 (51, 69)	56 (45, 66)
Sex, female, n (%)	84 (57)	86 (61)
Race, n (%)[b]		
White	71 (48)	67 (48)
Asian	65 (44)	63 (45)
Black or African American	0	1 (1)
Missing	12 (8)	9 (6)
ECOG PS, n (%)[c]		
0	67 (45)	52 (37)
1	78 (53)	79 (56)
2	3 (2)	9 (6)
Smoking status, n (%)[d]		
Never smoked	81 (55)	90 (64)
Previous smoker	54 (37)	40 (29)
Current smoker	13 (9)	9 (6)
Use of previous anti-cancer drug therapy, n (%)[e]	12 (8)	8 (6)
Time from end of prior brain radiotherapy to randomization		
Previous brain radiotherapy, n (%)	9 (6)	10 (7)
Mean (SD), days	94 (110)	71 (66)
Median (min., max.), days	63 (26, 374)	49 (16, 235)
Brain metastasis at baseline, n (%)[f]	38 (26)	39 (28)

ECOG PS, Eastern Cooperative Oncology Group performance status; PRO, patient-reported outcome; SD, standard deviation.

[a] Age at screening (years) = (date of given informed consent − date of birth + 1)/365.25.

[b] Race was reported by the investigator.

[c] ECOG PS ranged from 0 to 5, with higher scores indicating greater disability.

[d] Smoking status was not reported for one patient in the crizotinib arm.

[e] According to the protocol, previous adjuvant or neoadjuvant anti-cancer therapy was allowed if it had been completed > 12 months before randomization. One patient who had received previous chemotherapy for metastatic disease was reported as having a protocol violation.

[f] Per independent central neuroradiological review.

Baseline scores for EORTC QLQ-C30 and EORTC QLQ-LC13 for all patients and by subgroups of presence or absence of brain metastases are shown in Table 2. Patients with brain metastases at baseline had lower scores on all functioning domains and higher scores on most symptom domains, with the exceptions of diarrhea, peripheral neuropathy, pain in chest, and pain in other parts in the lorlatinib arm and dyspnea, cough, hemoptysis, sore mouth, and pain in the arm or shoulder in the crizotinib arm.

3.1. PRO changes from baseline according to EORTC QLQ-C30 and EORTC QLQ-LC13

As shown previously [16], overall improvement from baseline in global QoL (according to EORTC QLQ-C30) was significantly higher in patients in the lorlatinib arm compared with those in the crizotinib arm, but this difference was below the clinically meaningful difference threshold of ≥ 10 points (Fig. 1A). There was no difference in TTD for global QoL between treatment arms (Supplementary Fig. 1).

Numerical improvements in change from baseline favoring lorlatinib were seen in physical, role, emotional, and social functioning scales, although a numerical improvement favoring crizotinib was observed in the cognitive functioning scale (Fig. 1A). Patients in both treatment arms showed longitudinal improvement in most functioning scales during the entire treatment period, compared with their pre-treatment values (Supplementary Fig. 2). Cognitive functioning remained relatively stable over time for patients in both treatment arms, although the changes from baseline were generally numerically better with crizotinib than lorlatinib. Emotional functioning improved in both arms within the first four cycles, after which there was stability; patients in the lorlatinib arm generally had numerically better emotional score improvements than those in the crizotinib arm throughout the study.

Statistically significant improvements in change from baseline favoring lorlatinib over crizotinib were also seen in the symptom scores for fatigue, nausea and vomiting, insomnia, appetite loss, constipation, diarrhea, and coughing, although diarrhea was the only symptom with a clinically meaningful difference of ≥ 10 points (Fig. 1B). Peripheral neuropathy was the only symptom score with a statistically significant improvement favoring crizotinib over lorlatinib; however, this difference was below the threshold of ≥ 10 points.

Changes from baseline in the composite endpoint score and its components (pain in chest, dyspnea, and cough) up to cycle 18 (week 68) are presented in Fig. 2. Composite symptom scores improved from baseline in both treatment arms; mean score improvements from baseline were generally ≥ 10 points from cycle 2 in the lorlatinib arm and from cycle 3 in the crizotinib arm; although changes from baseline in composite symptom scores were comparable between the treatment arms (Fig. 2A), there was some variability in the scores observed at each cycle. There was also no difference between treatment arms in TTD for the composite symptom endpoint (Supplementary Fig. 3); however, a greater proportion of patients remained on-treatment and available for analysis with lorlatinib versus crizotinib (Fig. 2A), indicative of a lower rate of progression with lorlatinib. Changes over time in the individual symptoms from which the composite scores were generated are presented in Fig. 2B (pain in chest), Fig. 2C (dyspnea), and Fig. 2D (cough), where there were improvements in both treatment arms from baseline

Table 2
Baseline scores for EORTC QLQ-C30 and EORTC QLQ-LC13 in the lorlatinib and crizotinib treatment arms in all patients and according to the presence or absence of brain metastases at baseline (PRO analysis set).

Characteristic	Lorlatinib									Crizotinib								
	All patients (n = 148)			Patients with brain metastases at baseline (n = 38)			Patients without brain metastases at baseline (n = 110)			All patients (n = 140)			Patients with brain metastases at baseline (n = 39)			Patients without brain metastases at baseline (n = 101)		
	n	Mean	95 % CI	n	Mean	95 % CI	n	Mean	95 % CI	n	Mean	95 % CI	n	Mean	95 % CI	n	Mean	95 % CI
EORTC QLQ-C30 global QoL/functioning scales																		
Global QoL	148	64.6	60.99, 68.18	38	55.7	47.64, 63.76	110	67.7	63.78, 71.52	139	59.8	56.02, 63.52	39	51.7	43.72, 59.70	100	62.9	58.81, 67.02
Physical functioning	148	81.2	77.86, 84.61	38	70.1	61.64, 78.54	110	85.1	81.82, 88.36	140	78.8	75.07, 82.55	39	74.5	65.89, 83.17	101	80.5	76.44, 84.49
Role functioning	148	79.2	74.22, 84.11	38	65.8	53.25, 78.33	110	83.8	78.90, 88.68	140	72.5	67.21, 77.79	39	66.7	54.97, 78.36	101	74.8	68.89, 80.61
Emotional functioning	148	81.8	79.22, 84.41	38	76.8	70.74, 82.77	110	83.6	80.77, 86.35	140	80.0	76.87, 83.17	39	77.8	71.82, 83.73	101	80.9	77.12, 84.65
Cognitive functioning	148	87.7	84.84, 90.61	38	82.5	75.84, 89.07	110	89.5	86.41, 92.68	140	88.5	85.70, 91.21	39	83.3	76.54, 90.12	101	90.4	87.66, 93.20
Social functioning	148	83.9	79.88, 87.91	38	75.4	66.92, 83.96	110	86.8	82.34, 91.29	140	73.9	69.11, 78.75	39	64.1	53.77, 74.44	101	77.7	72.43, 83.01
EORTC QLQ-C30 symptoms and financial difficulties																		
Fatigue	148	28.3	24.31, 32.29	38	38.3	28.94, 47.67	110	24.8	20.66, 29.04	140	33.4	29.14, 37.68	39	36.5	26.98, 45.96	101	32.2	27.49, 36.97
Nausea and vomiting	148	6.1	3.65, 8.51	38	9.2	2.75, 15.67	110	5.0	2.57, 7.43	140	7.0	4.83, 9.22	39	7.7	3.25, 12.13	101	6.8	4.21, 9.32
Pain	148	19.6	15.60, 23.59	38	21.5	12.40, 30.58	110	18.9	14.50, 23.38	140	22.9	18.69, 27.02	39	23.1	15.28, 30.88	101	22.8	17.77, 27.78
Dyspnea	148	24.3	20.06, 28.59	38	28.1	17.71, 38.43	110	23.0	18.46, 27.61	140	28.1	23.13, 33.06	39	26.5	16.22, 36.77	101	28.7	22.97, 34.45
Insomnia	148	24.8	19.84, 29.71	38	29.8	18.21, 41.44	110	23.0	17.65, 28.41	140	28.8	24.12, 33.50	39	31.6	21.42, 41.83	101	27.7	22.45, 32.99
Appetite loss	148	16.9	12.40, 21.38	38	26.3	15.46, 37.17	110	13.6	8.94, 18.33	140	18.6	14.03, 23.12	39	23.1	12.81, 33.34	101	16.8	11.85, 21.81
Constipation	148	14.4	10.03, 18.80	38	18.4	7.12, 29.73	110	13.0	8.51, 17.55	140	13.8	9.53, 18.09	39	22.2	10.77, 33.67	101	10.6	6.62, 14.50
Diarrhea	147	6.3	4.21, 8.49	37	5.4	1.25, 9.56	110	6.7	4.14, 9.20	140	7.1	4.10, 10.19	39	8.5	1.23, 15.87	101	6.6	3.37, 9.83
Financial difficulties	147	16.8	12.36, 21.20	37	22.5	11.39, 33.65	110	14.8	10.21, 19.49	140	21.4	16.94, 25.91	39	26.5	16.52, 36.47	101	19.5	14.52, 24.42
EORTC QLQ-LC13 symptoms																		
Dyspnea	144	20.1	16.87, 23.25	36	26.9	19.15, 34.55	108	17.8	14.43, 21.16	138	24.3	20.59, 28.04	38	23.1	15.44, 30.76	100	24.8	20.46, 29.10
Coughing	146	37.0	32.45, 41.52	38	39.5	29.02, 49.93	108	36.1	31.11, 41.11	139	33.3	28.67, 38.00	39	31.6	22.04, 41.21	100	34.0	28.60, 39.40
Hemoptysis	146	4.1	2.00, 6.22	38	5.3	–0.16, 10.68	108	3.7	1.52, 5.89	138	3.4	1.68, 5.08	39	2.6	–0.35, 5.48	99	3.7	1.60, 5.80
Sore mouth	146	3.9	2.01, 5.75	38	6.1	1.84, 10.44	108	3.1	1.04, 5.13	138	5.3	3.14, 7.48	39	3.4	0.10, 6.74	99	6.1	3.31, 8.81
Dysphagia	146	3.9	2.01, 5.75	38	4.4	0.63, 8.14	108	3.7	1.52, 5.89	138	5.8	2.93, 8.67	39	9.4	2.41, 16.39	99	4.4	1.43, 7.33
Peripheral neuropathy	146	9.4	6.11, 12.61	38	8.8	2.70, 14.85	108	9.6	5.68, 13.46	139	6.7	4.09, 9.34	39	8.5	3.16, 13.93	100	6.0	2.97, 9.03
Alopecia	145	7.4	3.92, 10.80	37	17.1	6.44, 27.80	108	4.0	1.30, 6.72	139	5.3	2.73, 7.82	39	12.0	4.74, 19.19	100	2.7	0.63, 4.70
Pain in chest	143	14.7	10.95, 18.42	37	13.5	4.27, 22.76	106	15.1	11.12, 19.07	139	18.9	14.74, 23.15	39	18.8	9.94, 27.67	100	19.0	14.18, 23.82
Pain in arm or shoulder	146	16.2	12.15, 20.27	38	18.4	8.01, 28.83	108	15.4	11.22, 19.64	139	18.7	14.72, 22.69	39	12.0	5.65, 18.28	100	21.3	16.40, 26.26
Pain in other parts	143	21.0	16.23, 25.73	36	17.6	7.69, 27.49	107	22.1	16.64, 27.59	139	18.9	14.38, 23.51	39	20.5	10.72, 30.31	100	18.3	13.15, 23.51

All scores are linearly transformed to a 0–100 scale. Baseline was defined as the last assessment performed on or prior to the date of the first dose of study treatment. Higher scores on the global health/QoL and functioning scales indicate higher health status/QoL and functioning. Higher scores on symptom scales/items or with the 'financial difficulties' item represent a greater presence of symptoms/financial difficulties.
CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: lung cancer module; PRO, patient-reported outcome; QoL, quality of life.

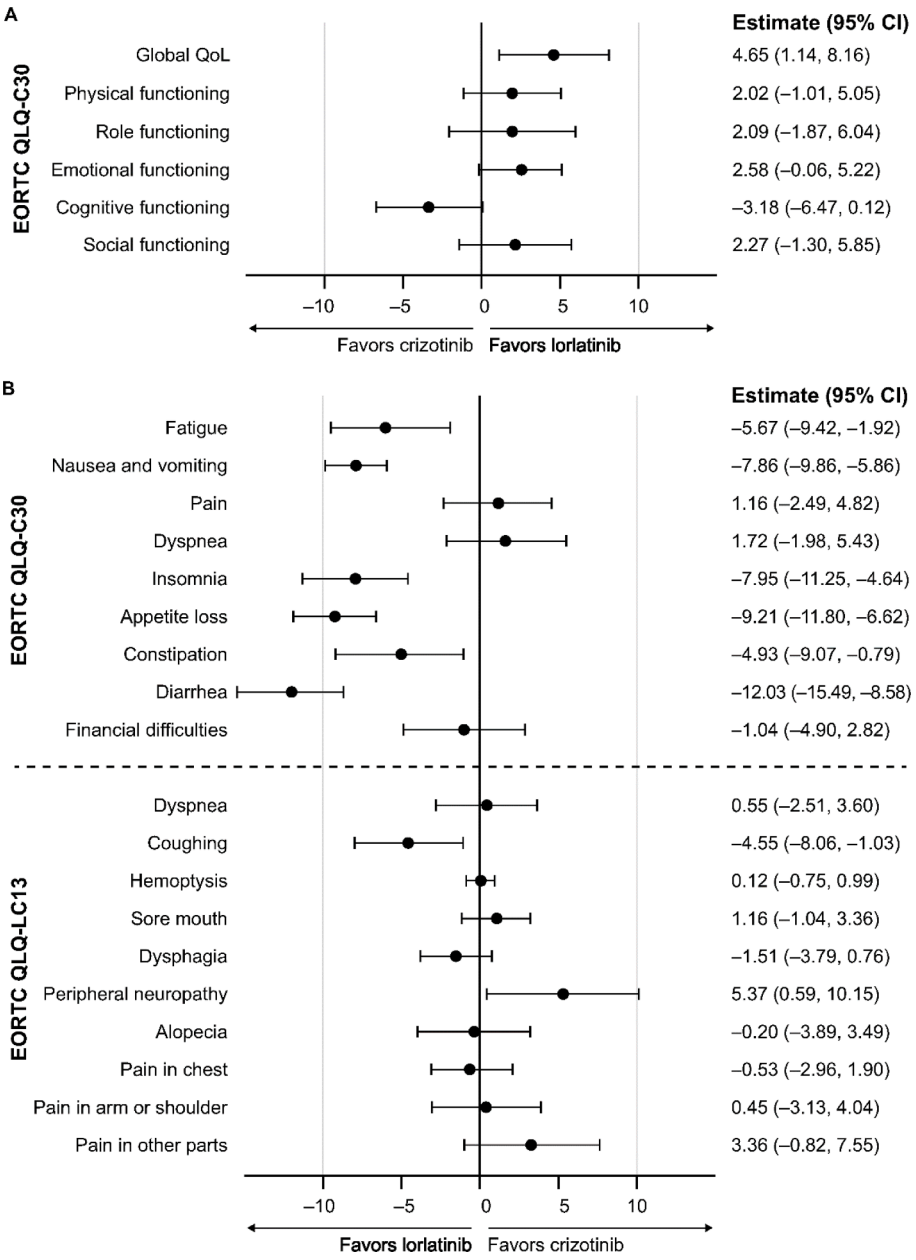

Fig. 1. Forest plot for difference in change from baseline in (*A*) EORTC QLQ-C30 global QoL and individual functioning scales and (*B*) EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales (based on the PRO analysis set). Included were patients with a score at baseline and at least one post-baseline assessment. Analyses are based on random-intercept, random-slope, mixed-effect model with an intercept term, treatment, time (as a continuous variable), treatment-by-time, baseline, and randomization stratification factors as covariates. Analysis based on restricted maximum likelihood using unstructured covariance matrix. Analysis model included post-baseline assessments up to (but not including) end of treatment. Higher scores on functional domains represent greater functioning, whereas higher scores on symptoms scales/items represent a greater presence of symptoms. Score changes of ≥ 10 points were considered clinically meaningful [31]. CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: lung cancer module; PRO, patient-reported outcome; QoL, quality of life.

for all three symptoms. Of note, cough symptom scores were markedly improved in the lorlatinib arm, with a clinically meaningful score change of > 20 points.

Changes over time in EORTC QLQ-C30 symptom and financial difficulty scores and other EORTC QLQ-LC13 individual symptom scores are presented in Supplementary Fig. 4 Most symptom scores showed improvement from baseline, with subsequent stability over time, in both treatment arms, although worsening from baseline was observed in the crizotinib arm for the gastrointestinal symptoms of nausea and vomiting (up to cycle 13), constipation (all time points), and diarrhea (all time points). Peripheral neuropathy symptom scores worsened (increased) from baseline (but by ≤ 10 points) to cycle 2 for both treatment arms. These remained relatively stable for the crizotinib arm after cycle 2 but worsened to > 10 points in the lorlatinib arm from cycles 4 and 5 up to cycle 12, before generally stabilizing at around 10 points.

3.2. PROs according to the presence or absence of brain metastases at baseline by treatment arm

As brain metastases are common in patients with *ALK*-positive NSCLC and can reduce patients' QoL [32], further analyses were performed according to the presence or absence of brain metastases at baseline. In the lorlatinib arm, global QoL generally improved from cycle 2 regardless of whether patients had brain metastases at baseline, although there was a tendency for higher QoL improvement in those with brain metastases versus those without; patients with brain metastases had clinically meaningful improvements from baseline (≥10 points) from cycle 2 (Fig. 3A). Patients with brain metastases at baseline in the crizotinib arm also tended to experience higher QoL improvements from baseline compared with those without brain metastases (Supplementary Fig. 5).

Improvements from baseline in the composite lung cancer symptom endpoint in the lorlatinib arm were observed regardless of whether patients had brain metastases at baseline; improvements were ≥ 10

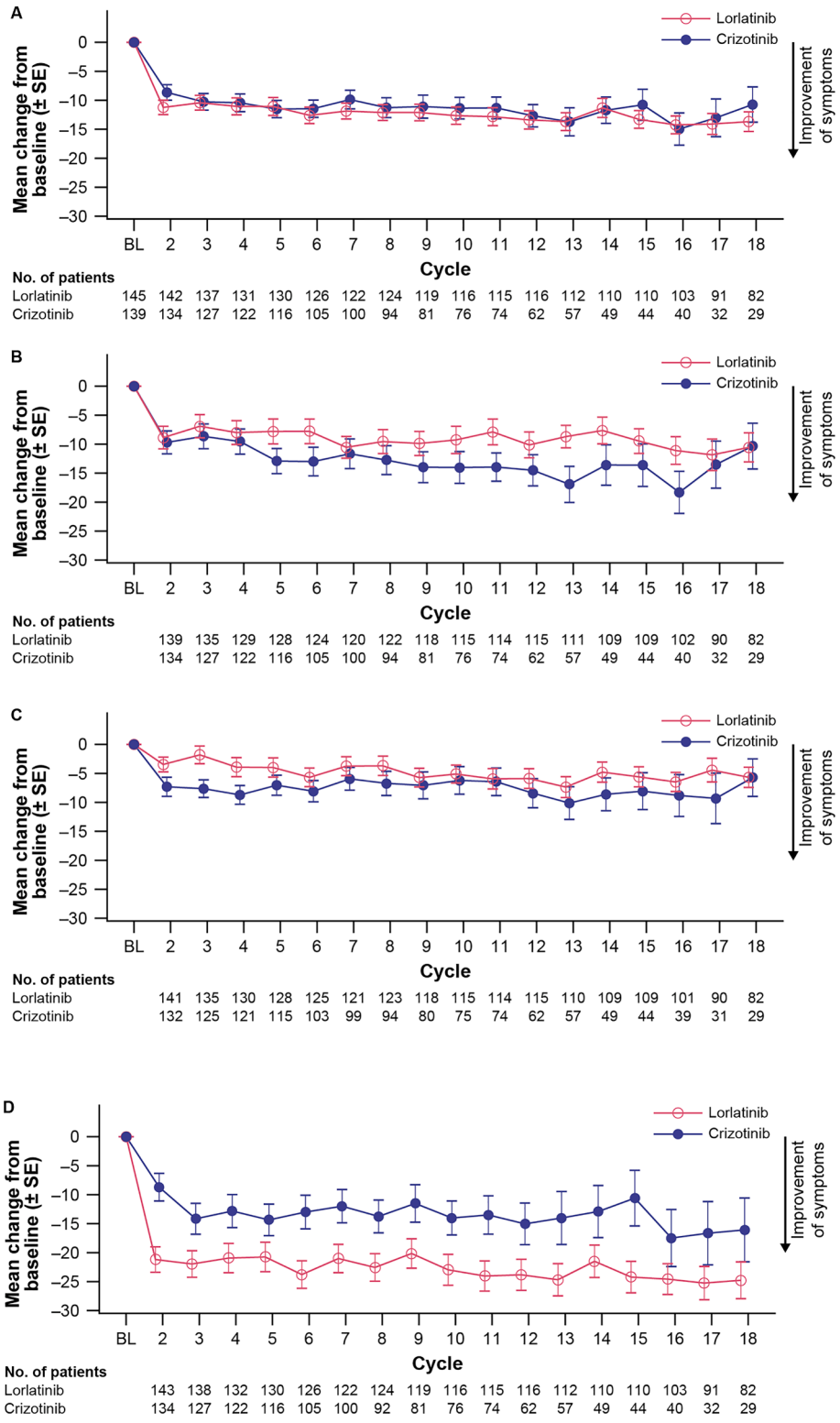

Fig. 2. Mean change from baseline in EORTC QLQ-LC13 for (*A*) the composite symptom endpoint consisting of pain in chest, dyspnea, and cough, (*B*) pain in chest, (*C*) dyspnea, and (*D*) cough (based on the PRO analysis set). Baseline was defined as the last assessment performed on or prior to the date of the first dose of study treatment. PROs were assessed at baseline and then on day 1 of each 28-day treatment cycle through to the end of treatment. The composite score was generated as the arithmetic mean of the scores for pain in chest, dyspnea, and cough for each patient at each cycle. Score changes of $\geq$ 10 points were considered clinically meaningful [31]. Higher scores on symptom scales/items represent a greater presence of symptoms. BL, baseline; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: lung cancer module; PRO, patient-reported outcome; SE, standard error.

points from baseline at most timepoints (Fig. 3B). There was a tendency toward greater composite symptom improvement in patients with brain metastases versus those without at baseline, although there was greater variability in the data for this subgroup. Changes over time in the individual symptoms from which the composite scores were generated are presented in Supplementary Fig. 6.

Cognitive and emotional functioning scores remained generally stable over time regardless of whether patients had brain metastases at baseline (Fig. 4A and B). However, for cognitive functioning, patients with brain metastases had small improvements whereas patients without brain metastases appeared to have small deteriorations (all changes from baseline were $<$ 10 points). Accordingly, mean emotional functioning score improvements from baseline of $\geq$ 10 points were more frequently observed for those with baseline brain metastases.

The corresponding longitudinal cognitive and emotional functioning scores by presence or absence of brain metastases in the crizotinib arm

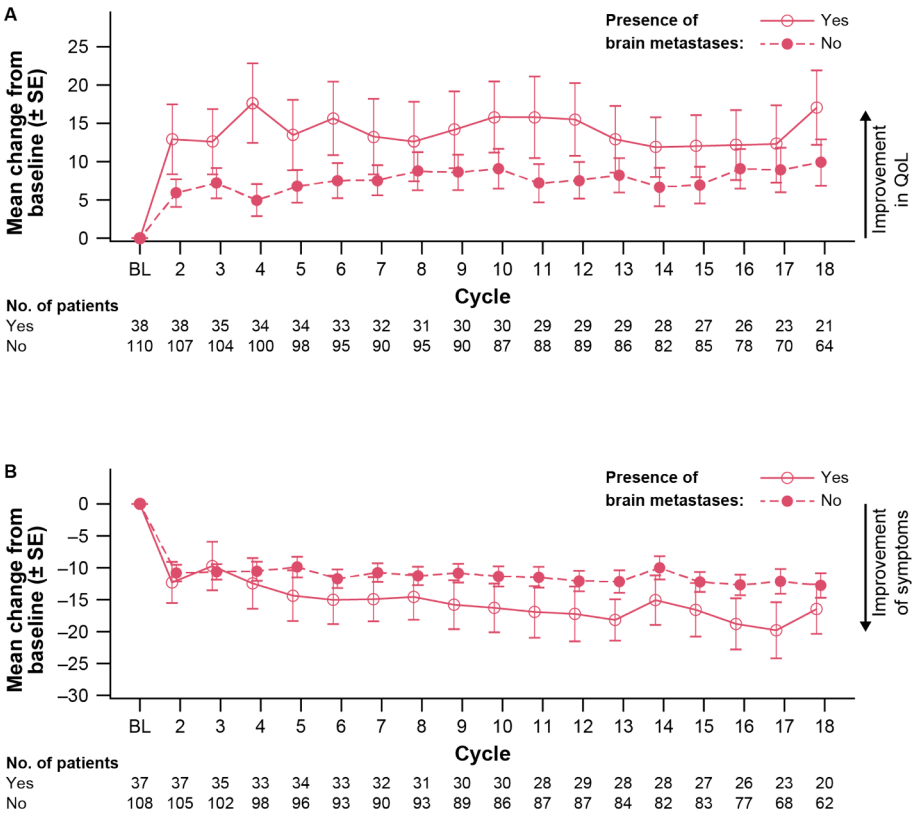

Fig. 3. Mean change from baseline according to the presence or absence of brain metastases at baseline in the lorlatinib arm in (*A*) EORTC QLQ-C30 global QoL and (*B*) EORTC QLQ-LC13 for the composite symptom endpoint consisting of pain in chest, dyspnea, and cough (based on the PRO analysis set). Baseline was defined as the last assessment performed on or prior to the date of the first dose of study treatment. PROs were assessed at baseline and then on day 1 of each 28-day treatment cycle through to the end of treatment. Score changes of ≥ 10 points were considered clinically meaningful [31]. Higher scores on the global health/QoL scale indicate higher health status/QoL; higher scores on symptom scales/items represent a greater presence of symptoms. BL, baseline; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; EORTC QLQ-LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: lung cancer module; PRO, patient-reported outcome; QoL, quality of life; SE, standard error.

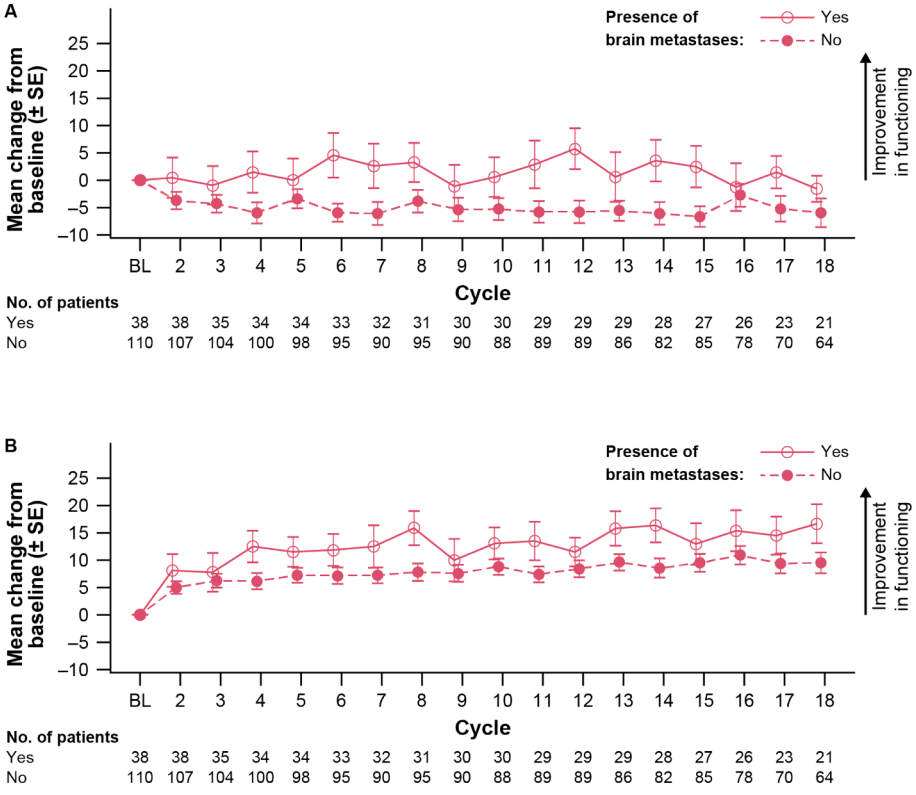

Fig. 4. Mean change from baseline according to the presence or absence of brain metastases at baseline in the lorlatinib arm in EORTC QLQ-C30 (*A*) cognitive functioning scores and (*B*) emotional functioning scores (based on the PRO analysis set). Baseline was defined as the last assessment performed on or prior to the date of the first dose of study treatment. PROs were assessed at baseline and then on day 1 of each 28-day treatment cycle through to the end of treatment. Score changes of ≥ 10 points were considered clinically meaningful [31]. Higher scores on functioning scales indicate higher functioning. BL, baseline; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; PRO, patient-reported outcome; SE, standard error.

are presented in Supplementary Fig. 7.

4. Discussion

These in-depth PRO analyses build on previously published global QoL improvements from the CROWN study [16], showing early and sustained improvements following treatment with lorlatinib in patients with previously untreated advanced *ALK*-positive NSCLC [16]. These additional analyses are important for addressing questions related to the management of cognitive- and mood-related side effects in patients receiving lorlatinib [19,20], as well as the more general detrimental effects on QoL associated with lung cancer disease and treatment [1,2].

Overall, patients receiving first-line lorlatinib or crizotinib showed improvements, and delays in deterioration, of QoL and functioning. There were no statistically significant differences in TTD between the two treatment arms, despite the greater efficacy with lorlatinib versus crizotinib [16]. However, the study was not powered to detect such differences with the planned population size. As such, the differences were too small to allow statistical significance to be demonstrated. Numerical improvements favored lorlatinib in physical, role, emotional, and social functioning scales, while cognitive functioning favored crizotinib. None were clinically meaningful, as expected given the good levels of functioning prior to treatment (evidenced by high baseline functioning scores). A numerical improvement was seen in the cognitive functioning scale with crizotinib versus lorlatinib, although this was also not clinically meaningful. This is consistent with the high brain penetrance of lorlatinib [14], which may result in an increased incidence of cognitive side effects versus crizotinib; however, these are mostly low grade and manageable [16]. Nonetheless, the robust intracranial efficacy of lorlatinib is not associated with a significant deterioration in a patient's global QoL, and results here show that overall QoL is preserved with lorlatinib versus crizotinib, if not improved.

Symptom scores generally showed improvement or stability over time in both treatment arms, although worsening from baseline was observed in symptoms associated with treatment-related AEs: nausea and vomiting, constipation, and diarrhea (crizotinib arm) and peripheral neuropathy (lorlatinib arm). Scores for several symptoms were significantly improved from baseline with lorlatinib versus crizotinib, but only diarrhea showed a clinically meaningful improvement. Baseline scores for diarrhea (and nausea and vomiting) were < 10 points in both arms, indicating few problems prior to treatment. Thus, the ≥ 10-point difference between arms during treatment is likely due to an increased incidence of diarrhea (along with other gastrointestinal events) in the crizotinib arm [16], rather than a treatment effect of lorlatinib, especially given the stability of symptom scores around the level of baseline in the lorlatinib arm. Although not clinically meaningful, significant improvements were also seen with lorlatinib versus crizotinib (cycles 2 to 18) in other symptom scores that were > 10 points at baseline. Together, these results indicate that lorlatinib treatment results in at least similar or numerically improved QoL versus crizotinib for the majority of symptoms, with several being significantly improved, including symptoms particularly burdensome to patients. The exception was peripheral neuropathy, which showed worsening of symptom scores with lorlatinib versus crizotinib, likely due to the increased incidence of peripheral neuropathy in the lorlatinib arm in the CROWN study [16].

Change from baseline across cycles for the composite lung cancer symptom endpoint showed mean score improvements of ≥ 10 points in both treatment arms. Although the score changes showed variability at individual cycles, overall, there was no difference between treatment arms. This reflects the differences between treatment arms in the individual components of this endpoint. For example, pain in chest tended to show greater improvements in the crizotinib arm, whereas improvements in coughing were greater in the lorlatinib arm.

Greater improvements in global QoL scores were seen in patients with brain metastases versus those without in both the lorlatinib and crizotinib arms; however, in patients with brain metastases, a greater proportion were still on treatment at cycle 18 in the lorlatinib arm (21/38; 55 %) compared with crizotinib (4/39; 10 %), consistent with the brain penetrance and intracranial activity of lorlatinib [14,16]. There was also no significant reduction in global QoL for patients without brain metastases at baseline, suggesting that any side effects from lorlatinib treatment may be offset by the prevention of side effects from brain metastases. Additionally, patients in the lorlatinib arm with brain metastases had poorer baseline scores (i.e., lower baseline scores on functioning domains and, in general, higher baseline scores on symptom domains) compared with their counterparts without brain metastases at baseline. Therefore, patients with brain metastases had greater room for improvement in scores and, consequently, appeared to have greater improvements in functioning and symptom scores. However, the smaller number of patients with brain metastases (versus those without) at baseline limits the ability to directly compare data between these patient subgroups. It should also be considered that patients in poorer health may place more value on small incremental improvements in their QoL compared with healthier patient populations [33].

PRO data have been reported previously for the second-generation ALK inhibitors alectinib [29] and brigatinib [13,34]. In the CROWN study, a higher proportion of patients (97 %) provided evaluable PRO data, compared with the phase 3 ALEX trial (66 % and 64 % in the alectinib and crizotinib arms, respectively) [29]; having near-complete data collection reduces the chances of selection bias. In the phase 3 ALTA-1L trial, PRO questionnaire completion rates were > 90 % for the brigatinib and crizotinib arms; however, EORTC QLQ-LC13 was added as a protocol amendment, and only 54 % of patients completed the EORTC QLQ-LC13 questionnaire [34]. These differences in completion rates, particularly between the CROWN and ALEX trials, may complicate indirect cross-trial comparisons of PROs. Nonetheless, symptom improvements generally favored alectinib (ALEX) [29], brigatinib (ALTA-1L) [13,34], and lorlatinib (CROWN) over crizotinib. As with CROWN, the TTD in lung cancer symptoms between treatment arms in ALEX was not significantly different [29]. In ALTA-1L, TTD for global QoL was significantly longer with brigatinib, although statistical significance was only just reached (HR 0.70; 95 % CI: 0.49–1.00; $p = 0.049$) [13,34], and p values were not adjusted for multiplicity [34].

In conclusion, overall, patients receiving first-line lorlatinib or crizotinib showed improvements in, and delay in deterioration of, QoL, functioning, and several symptoms, with no clear difference in PRO outcomes of patients in the lorlatinib cohort based on the presence or absence of brain metastases at baseline. These data, along with the significantly longer PFS and higher intracranial response for lorlatinib versus crizotinib reported previously [16], support the use of lorlatinib over crizotinib in patients with advanced *ALK*-positive NSCLC with or without brain metastases at baseline. Lorlatinib is a recommended first-line option for *ALK*-positive NSCLC [35–37], alongside other options such as alectinib, brigatinib, crizotinib, and ceritinib [35–38]. The results of this study provide evidence for several QoL improvements with lorlatinib over crizotinib in the first-line setting, an important factor to consider during treatment selection. As long as patients are benefiting clinically from lorlatinib treatment, their QoL is not negatively affected by treatment and AEs are generally manageable [16]. Patients with (versus without) brain metastases at baseline had overall worse QoL before treatment and showed greater improvement in QoL that was maintained over time with tyrosine kinase inhibitor treatment. Patients treated with lorlatinib in the CROWN study showed greater clinical benefit and were on-treatment longer than those treated with crizotinib [16], which was reflected in improved PRO scores.

Funding

This study was sponsored by Pfizer. The study was designed by the sponsor, study investigators, and members of the steering committee. Data were collected by investigators and analyzed by the sponsor. All authors, including those employed by the sponsor of the study,

contributed to the interpretation of the data and the development, writing, and approval of the manuscript. Medical writing support was funded by the sponsor. All authors had full access to the raw data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Data Sharing

Upon request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

CRediT authorship contribution statement

Julien Mazieres: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. **Laura Iadeluca:** Conceptualization, Methodology, Formal analysis, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Alice T. Shaw:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Benjamin J. Solomon:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Todd M. Bauer:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Filippo de Marinis:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Enriqueta Felip:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Yasushi Goto:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Dong-Wan Kim:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Tony Mok:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Arlene Reisman:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Holger Thurm:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Anna M. Polli:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Geoffrey Liu:** Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

ICMJE form COIs

Dr Mazieres reports receiving personal consulting fees or honorarium from Pfizer, and personal consultancy fees from F. Hoffman La-Roche Ltd, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Hengrui Therapeutics, and Amgen.

Dr Iadeluca, Ms Reisman, Dr Thurm, Ms Polli are employees of Pfizer and hold Pfizer stock/stock options.

Dr Shaw reports receiving personal honoraria, advisory board or consultancy fees, and institutional research support from Pfizer, and is currently an employee of Novartis and holds Novartis stock/stock options.

Dr Solomon reports receiving personal honoraria or advisory board fees from Pfizer, Novartis, F. Hoffman La-Roche Ltd, Amgen, AstraZeneca, Merck Sharp & Dohme, Bristol Myers Squibb, BeiGene, Takeda, Janssen, and Lilly.

Dr Bauer reports receiving personal consultancy and speakers' bureau fees from AstraZeneca, Lilly, Bayer; personal consultancy fees from Bristol Myers Squibb, Foundation Medicine, Pfizer, Loxo Oncology, Guardant Health, Exelixis, Blueprint Medicines; payment/reimbursement of exact expenses from Lilly, Bristol Myers Squibb, Foundation Medicine, Ignyta, Moderna Therapeutics, Loxo Oncology, Bayer, Guardant Health; institutional consultancy fees from Leap Therapeutics, Ignyta, Moderna Therapeutics, Pfizer; and institutional grant support from Pfizer, Daiichi Sankyo, Medpacto, Incyte, Mirati Therapeutics, MedImmune, AbbVie, AstraZeneca, MabVax, Stemline Therapeutics, Merck, Lilly, GlaxoSmithKline, Novartis, Genentech, Deciphera, Merrimack, Immunogen, Millennium, Phosplatin Therapeutics, Calithera Biosciences, Kolltan Pharmaceuticals, Principia Biopharma, Peleton, Immunocore, F. Hoffman La-Roche Ltd, Aileron Therapeutics, Bristol Myers Squibb, Amgen, Onyx, Sanofi, Boehringer Ingelheim, Astellas Pharma, Five Prime Therapeutics, Jacobio, Top Alliance BioScience, Janssen, Clovis Oncology, Takeda, Karyopharm Therapeutics, Foundation Medicine, ARMO BioSciences, Leap Therapeutics, Ignyta, Moderna Therapeutics, Pfizer, Loxo Oncology, and Bayer.

Dr de Marinis reports receiving personal advisory fees from AstraZeneca, Bristol Myers Squibb, Novartis, F. Hoffman La-Roche Ltd, and Merck Sharp & Dohme.

Dr Felip reports receiving personal speakers' bureau fees from Medscape, Peervoice, Springer, Touch Independent Medical Education, prIME Oncology, CME Outfitters; personal advisory board fees from AbbVie, Amgen, Bayer, Blueprint Medicines, Lilly, GlaxoSmithKline, Janssen, Merck, Puma Biotechnology, F. Hoffman La-Roche Ltd, Sanofi Genzyme, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, Daichii Sankyo; personal advisory or board member fees from Grifols; grant support from Fundación Merck Salud.

Dr Goto reports receiving grant support or contracts from Pfizer, AZK; institutional grant support or contracts from AbbVie, Lilly, Pfizer, Bristol Myers Squibb, ONO Pharmaceutical, Novartis, Kyorin Pharmaceutical, Daiichi Sankyo, Preferred Networks Inc.; personal honoraria for lectures, presentations, speakers' bureau, manuscript writing or educational events from Lilly, Chugai Pharmaceutical, Taiho Pharmaceutical, Boehringer Ingelheim, ONO Pharmaceutical, Bristol Myers Squibb, Pfizer, Merck Sharp & Dohme, Novartis, Merck, and Thermo Fisher; personal advisory board or data safety monitoring board fees from AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Lilly, Taiho Pharmaceutical, Pfizer, Novartis, Guardant Health, Illumina, Daiichi Sankyo, ONO Pharmaceutical, Bristol Myers Squibb, and Merck Sharp & Dohme; and reports a leadership, fiduciary or board role with Cancer Net Japan, and JAMT.

Dr Kim reports receiving medical writing support from Pfizer; institutional grant support from Pfizer, Alpha Biopharma, Amgen, AstraZeneca, Boehringer Ingelheim, Bridge BioTherapeutics, Chong Keun Dang, Daiichi Sankyo, GlaxoSmithKline, Hanmi, Janssen, Merck, Merus, Mirati Therapeutics, Merck Sharp & Dohme, Novartis, ONO Pharmaceutical, F. Hoffman La-Roche Ltd, Takeda, TP Therapeutics, Xcovery, and Yuhan; and travel support from Amgen, and Daiichi Sankyo.

Dr Mok reports receiving grant support from AstraZeneca, Bristol-Myers Squibb, Merck Serono, Merck Sharpe & Dohme, Novartis, Pfizer, Roche, Takeda, Clovis Oncology, SFJ Pharmaceuticals, XCovery, G1 Therapeutics Inc.; personal consultancy, advisory or lecture fees from Abbvie, ACEA Pharmaceuticals, Alpha Biopharma, Amgen, Amoy Diagnostics, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Blueprint Medicines Corporation, CStone Pharmaceuticals, Daiichi Sankyo, Eisai, Fishawack Facilitate Ltd., geneDecode (uncompensated), Gritstone Oncology Inc., Guardant Health, Hengrui Therapeutics, Ignyta Inc., IQVIA, Incyte Corporation, InMed Medical Communication, Janssen, Lilly, Loxo-Oncology, Lunit USA, Inc., MD Health (Brazil), Medscape/WebMD, Merck Serono, Merck Sharp & Dohme, Mirati Therapeutics Inc., MoreHealth, Novartis, OrigiMed, PeerVoice, Physicians' Education Resource, P. Permanyer SL, Pfizer, Inc, PrIME Oncology, Puma Biotechnology Inc, Research to Practice, Roche, Sanofi-Aventis R&D, Takeda, Touch Medical Media, Virtus Medical Group (stock option), Yuhan Corporation, HutchMed (shareholder), SFJ Pharmaceuticals, Curio Science, Inivata, Berry Oncology, G1 Therapeutics Inc., Aurora (shareholder), Qiming Development (HK) Ltd., Daz Group, Lucence Health Inc., Merck Pharmaceuticals HK Ltd, Shanghai BeBirds Translation & Consulting Co., Ltd, Liangyihui Network Technology Co., Ltd, Taiho, Gilead Sciences, Inc, Vertex Pharmaceuticals, Covidien LP, Elevation Oncology, C4 Therapeutics, Inc, D3 Bio Ltd.; shareholder or stock options from Loxo-Oncology, Lunit USA, Inc., Act

Genomics-Sanomics Group; Board of Director at AstraZeneca PLC (Jan 2019 onwards), HutchMed (Oct 2018 onwards), Act Genomics-Sanomics Group (Board Chairman 2015 onwards), Lunit USA, Inc. (Mar 2021 onwards), Aurora (Sep 2020 onwards).

Dr Liu reports receiving grants or contracts from institutions - NCI (US), CIHR (Canada), CCSRI (Canada), AstraZeneca, Takeda, Boehringer Ingelheim; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (personal) from AstraZeneca, Pfizer, EMD Serono, Takeda, Jazz; Participation on a Data Safety Monitoring Board or Advisory Board (personal) from AstraZeneca, Pfizer, EMD Serono, Merck, Abbvie, Jazz, Takeda, Roche, BMS, Novartis.

Acknowledgments

The authors would like to thank the study participants and study site personnel. Medical writing support was provided by Paul O'Neill, PhD, and Claire Lavin, PhD, of CMC AFFINITY, McCann Health Medical Communications, and Brian Law, PhD, of Health Interactions, and was funded by Pfizer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.11.004.

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