Lung Cancer 155 (2021) 68–77

Contents lists available at ScienceDirect

Lung Cancer

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

Health-related quality of life in the randomized phase III trial of brigatinib vs crizotinib in advanced ALK inhibitor–naive ALK + non−small cell lung cancer (ALTA-1L)

Maria Rosario Garcia Campelo [a,*], Huamao M. Lin [b], Yanyan Zhu [b,1,2], Maurice Pérol [c], Mohammad Jahanzeb [d], Sanjay Popat [e,f], Pingkuan Zhang [g], D. Ross Camidge [h]

[a] Medical Oncology Service, University Hospital A Coruña (XXIAC-SERGAS), Xubias de Arriba, 84, 15006, A Coruña, Spain
[b] Millennium Pharmaceuticals, Inc, 35 Landsdowne Street, Cambridge, MA, 02139, USA[3]
[c] Department of Medical Oncology, Centre Léon Bérard, 28 Prom. Léa et Napoléon Bullukian, 69008, Lyon, France
[d] Florida Precision Oncology, a division of 21st Century Oncology, 3651 FAU Boulevard, Suite 100, Boca Raton, FL, 33431, USA
[e] The Royal Marsden Hospital, 203 Fulham Road, Chelsea, London, SW3 6JJ, United Kingdom
[f] The Institute of Cancer Research, 123 Old Brompton Road, London, SW7 3RP, United Kingdom
[g] Millennium Pharmaceuticals, Inc, 300 Massachusetts Avenue, Cambridge, MA, 02139, USA[3]
[h] University of Colorado Cancer Center, 1665 Aurora Court, Aurora, CO, 80045, USA

ARTICLE INFO

Keywords:
Brigatinib
Anaplastic lymphoma kinase
Carcinoma
Non-small-cell lung
Quality of life
First-line therapy

ABSTRACT

Objective: In ALTA-1 L, first-line brigatinib versus crizotinib significantly prolonged progression-free survival in advanced ALK-positive (ALK+) non–small cell lung cancer (NSCLC). We report health-related quality of life (HRQOL) outcomes from ALTA-1 L.

Materials and Methods: HRQOL was assessed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) and lung cancer–specific module (QLQ-LC13). HRQOL time to worsening, change from baseline, and duration of improvement were analyzed.

Results: EORTC QLQ-C30 and QLQ-LC13 compliance was >90 % for both groups (n = 131 each). Brigatinib versus crizotinib significantly delayed time to worsening in the EORTC QLQ-C30 global health status (GHS)/QOL (median: 26.74 vs 8.31 months; hazard ratio [HR]: 0.70; 95 % CI: 0.49, 1.00; log-rank $P = 0.0485$); emotional functioning, social functioning, fatigue, nausea and vomiting, appetite loss, and constipation scales (log-rank $P < 0.05$); delays in time to worsening for the physical, role, and cognitive functioning scales were not statistically significant. Mean change from baseline showed greater improvement in GHS/QOL and most EORTC QLQ-C30 functional and symptom scales with brigatinib versus crizotinib. Among patients with GHS/QOL improvement, brigatinib had longer duration of improvement versus crizotinib (median: not reached vs 11.99 months); similar results were seen in the physical, role, emotional, and social functioning; fatigue; nausea and vomiting; and appetite loss scales. Median time to worsening in dyspnea (QLQ-LC13) was 23.98 versus 8.25 months (brigatinib vs crizotinib; HR: 0.64; 95 % CI: 0.39, 1.05).

Abbreviations: ALK, anaplastic lymphoma kinase; *ALK*, anaplastic lymphoma kinase gene; ALK+, ALK gene rearrangement; ALTA-1 L, ALK in lung cancer trial of brigatinib in 1st line; CI, confidence interval; CNS, central nervous system; CONSORT, Consolidated Standards of Reporting Trials; ECOG PS, Eastern Cooperative Oncology Group performance status; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer–Specific Module; FDA, United States Food and Drug Administration; GHS, global health status; HR, hazard ratio; HRQOL, health-related quality of life; ITT, intention to treat; NE, not estimable; NSCLC, non–small cell lung cancer; PFS, progression-free survival; PRO, patient-reported outcome; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; v3, version 3.

* Corresponding author at: Medical Oncology Service, University Hospital A Coruña (XXIAC-SERGAS), As Xubias s/n, A Coruña, 15006, Spain.
E-mail addresses: MA.Rosario.Garcia.Campelo@sergas.es (M.R. Garcia Campelo), mark.lin@takeda.com (H.M. Lin), Yanyan.zhu@takeda.com (Y. Zhu), maurice.perol@lyon.unicancer.fr (M. Pérol), mj@fponcology.com (M. Jahanzeb), sanjay.popat@rmh.nhs.uk (S. Popat), Pingkuan.Zhang@takeda.com (P. Zhang), Ross.Camidge@CUAnschutz.edu (D.R. Camidge).

[1] Author was an employee of Millennium Pharmaceuticals, Inc.[3], at the time the study was conducted.
[2] Current address: AstraZeneca, 35 Gatehouse Drive, Waltham, MA, 02451, USA.
[3] Millennium Pharmaceuticals, Inc, is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

https://doi.org/10.1016/j.lungcan.2021.03.005
Received 11 September 2020; Received in revised form 29 January 2021; Accepted 8 March 2021
Available online 9 March 2021

Conclusion: Brigatinib significantly delayed time to worsening and prolonged duration of improvement in GHS/QOL versus crizotinib, supported by improvement in functional and symptom scores. These preliminary analyses suggest brigatinib is the first ALK inhibitor with better HRQOL versus another ALK inhibitor in ALK inhibitor–naive advanced ALK + NSCLC.

1. Introduction

Non–small cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancers [1]. In these patients, genetic testing is helping personalize treatment decisions [2]. Approximately 3%–13% of patients diagnosed with NSCLC test positive for anaplastic lymphoma kinase (ALK) gene rearrangement (ALK+), making them candidates for ALK inhibitor therapy [3]. In the United States, available ALK inhibitors include crizotinib, the first available ALK inhibitor therapy [4], and next-generation ALK inhibitor therapies (i.e., alectinib [5], brigatinib [6], ceritinib [7], and lorlatinib [8]). Crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib have US Food and Drug Administration (FDA) approval for first-line use [4].

When making treatment decisions, the effect of therapy on health-related quality of life (HRQOL) should be considered along with efficacy and safety data [9]. Both the FDA and the European Medicines Agency (EMA) encourage use of well-defined, reliable patient-reported outcome (PRO) instruments that capture the treatment benefits and risks in the targeted patients [9,10]. Data generated through PRO instruments are valued by regulators, clinicians, and patients and provide information on treatment effects from a patient perspective [11].

The median age of patients diagnosed with ALK + NSCLC is approximately 52 years and they are generally younger than patients diagnosed with other types of NSCLC [12]. Younger patients with ALK + NSCLC may receive prolonged therapy with a next-generation ALK inhibitor [12], so the effect of treatment on HRQOL may be of particular importance in these patients.

HRQOL outcomes are available for several studies evaluating ALK inhibitor therapy in ALK inhibitor–naive patients [13–15]. Results from the PROFILE 1014 and ASCEND-4 trials showed significant improvement in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) global health status (GHS)/quality of life (QOL) scale with ALK inhibitor therapy compared with platinum-based chemotherapy [14,15]. In contrast, results from the ALEX study, a head-to-head trial of ALK inhibitor therapies, showed no significant difference in HRQOL outcomes between alectinib and crizotinib [13].

The phase III ALTA-1 L trial compared brigatinib versus crizotinib in ALK inhibitor–naive patients with ALK + NSCLC [16]. Results from a preplanned interim efficacy analysis (median follow-up: 24.9 months for brigatinib vs 15.2 months for crizotinib) showed that first-line brigatinib significantly reduced the risk of disease progression or death compared with crizotinib in ALK inhibitor–naive patients with advanced ALK + NSCLC [17]. A secondary objective of the ALTA-1 L study was to compare HRQOL, including GHS/QOL, functioning, and symptoms, in ALK + NSCLC patients treated with brigatinib or crizotinib. This report presents HRQOL results from the second interim analysis, including time to worsening, change from baseline, and duration of improvement in GHS/QOL and other EORTC QLQ-C30 functional and symptom scales; and time to worsening and duration of improvement in core symptoms of lung cancer as assessed using the 13-item EORTC lung cancer–specific module (QLQ-LC13).

2. Materials and methods

ALTA-1 L (NCT02737501) is an open-label, multicenter, international, phase III, randomized controlled trial that enrolled patients with ALK + NSCLC, as previously reported [16]. Patients were randomly assigned to brigatinib or crizotinib, with crossover to brigatinib permitted for the crizotinib group after disease progression (see Clinical Study Protocol, Supplementary Data 1).

2.1. Study population

2.1.1. Inclusion/exclusion criteria

Patients enrolled in ALTA-1 L were 18 years of age or older, diagnosed with locally advanced or metastatic NSCLC with 1 or more measurable lesions per Response Evaluation Criteria in Solid Tumors (RECIST) version 1 criteria, and were ALK inhibitor therapy–naive. Patients with untreated, asymptomatic central nervous system (CNS) metastases could enroll.

Patients were excluded if they received more than 1 systemic anticancer therapy for advanced NSCLC or radiation therapy (other than stereotactic radiosurgery or stereotactic body radiation therapy) within the 14 days prior to the first dose of study drug. Patients with prior chemotherapy for advanced NSCLC were allowed to be enrolled.

2.2. Treatments and randomization

Patients were randomized 1:1 to brigatinib 90 mg daily for 7 days then 180 mg daily, or to crizotinib 250 mg twice daily. Treatment cycles were 28 days and continued until the patient had disease progression (determined by blinded independent review), experienced unacceptable toxic effects, or met other discontinuation criteria [16]. There were no breaks or washout between cycles per the study design, but if a patient experienced toxicity and/or other issues, there might have been dose delay.

2.3. Patient-reported outcomes assessment

The PROs evaluated included the EORTC QLQ-C30 version 3 (v3) and the EORTC QLQ-LC13, added per protocol Amendment 1 in September 2016.

The EORTC QLQ-C30 is the most commonly and consistently used cancer-specific questionnaire in randomized, controlled trials for NSCLC [18–20]. The questionnaire is specifically validated to assess QOL in cancer patients participating in clinical trials [21], which was the rationale for its selection in this study. When tested among lung cancer patients, the measure is a reliable and valid measure of QOL for cancer patients in multicultural clinical research settings [21–23]. The EORTC QLQ-C30 is scored for GHS/QOL and 5 functional (physical, role, cognitive, emotional, and social) and 3 symptom (fatigue, pain, and nausea/vomiting) scales. Additionally, 6 single-item scales are included (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The EORTC QLQ-LC13 module was added to the study as part of Amendment 1 in September 2016. This tool was constructed to be used alongside the EORTC QLQ-C30. It comprises 13 questions assessing lung cancer–associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and use of pain medication [21,24]. The EORTC QLQ-LC13 module incorporates 1 multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. For both the EORTC QLQ-C30 and QLQ-LC13, raw scores are converted into scale scores ranging from 0 to 100. For the GHS/QOL and functional scales, higher scores represent better HRQOL; for the symptom scales, lower scores represent fewer symptoms.

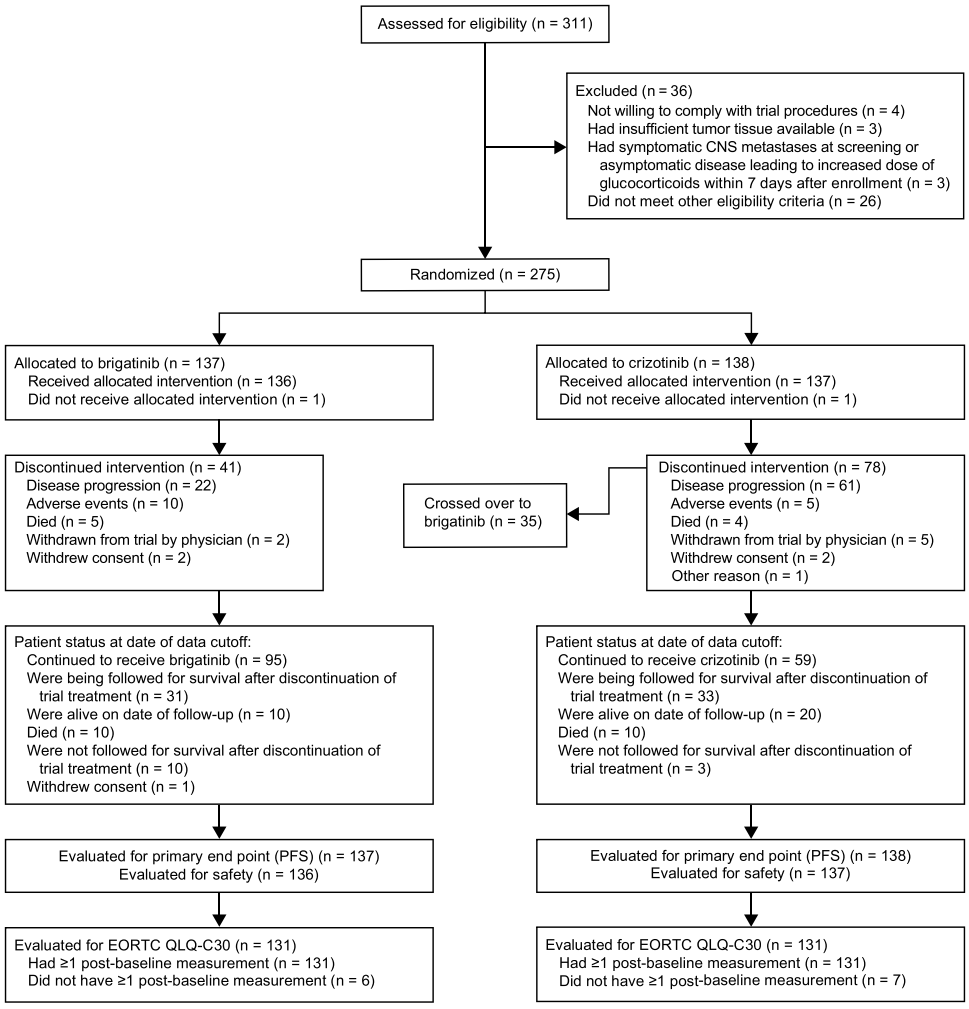


Fig. 1. CONSORT Flow Diagram.
Abbreviations: CNS, central nervous system; CONSORT, Consolidated Standards of Reporting Trials; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; PFS, progression-free survival.

The EORTC measures were administered using pen-and-paper approaches only; measures were completed independently at study sites prior to any medical testing or discussions with the treating physicians. The measures were administered at screening, day 1 of each 4-week cycle, end of treatment, and 30 days after the last dose of study drug.

The prespecified study objectives in the study protocol were to examine time to worsening, change from baseline, and duration of improvement in GHS/QOL and other functional and symptom scales assessed with the EORTC QLQ-C30, and time to worsening and duration of improvement in core symptoms of lung cancer (dyspnea, cough, and chest pain), assessed with the EORTC QLQ-LC13.

2.4. Statistical analysis

The PRO intention-to-treat (ITT) population included all randomized patients with a PRO assessment at baseline and at least 1 postbaseline measurement during the randomized phase of the study.

The EORTC QLQ-C30 and QLQ LC-13 were scored according to the EORTC QLQ-C30 (v3) Scoring Manual [25]. Descriptive statistics were used to summarize all scale scores and change from baseline; linear mixed models including treatment group, visit, the interaction between treatment group and visit, baseline score, and stratification factors (i.e., presence of CNS metastases at study entry, prior chemotherapy at baseline) as covariates were used to analyze change from baseline over time.

A change of ≥10 points was used to determine the minimal clinically meaningful worsening or improvement [26–28]. Time to worsening was defined as time from the date of randomization to the earliest date at which the patient's score had a ≥10-point deterioration from baseline. Duration of improvement was defined as time from date of first improvement to date of first deterioration after the improvement. The first improvement was defined as a ≥10-point improvement from baseline. For time to worsening, a 2-sided stratified log-rank test was used to compare treatment groups and an unadjusted stratified Cox model was used to estimate the hazard ratios (HRs) and 95 % confidence intervals (CIs). Kaplan-Meier survival curves were generated for time to worsening and duration of improvement. Subgroup analyses by baseline brain metastases were also conducted.

To assess any effect of study attrition on the estimate of treatment differences, a sensitivity analysis was performed on change from baseline in GHS/QOL score using a pattern mixture model to incorporate information on patterns of missing data. Assuming intermittent missing data occurred at random, patients were classified into 2 pattern groups: early dropout (i.e., dropout before 12 cycles) versus late dropout (i.e., dropout after ≥12 cycles).

P values reported were not adjusted for multiple comparisons due to the exploratory nature of the analysis.

This publication was written according to the Consolidated Standards of Reporting Trials (CONSORT) PRO extension guidelines [29].

Table 1
Baseline Patient Characteristics, PRO-ITT Population.

Characteristic	Brigatinib (N = 131)	Crizotinib (N = 131)	Total (N = 262)
Age, years			
Median	57	60	58
Range	27–85	29–83	27–85
Female sex, no. (%)	65 (49.6)	76 (58.0)	141 (53.8)
Race, no. (%)*			
Non-Asian	72 (55.0)	86 (65.6)	158 (60.3)
Asian	59 (45.0)	45 (34.4)	104 (39.7)
ECOG PS score, no. (%)†			
0 or 1	127 (96.9)	128 (97.7)	255 (97.3)
2	4 (3.1)	3 (2.3)	7 (2.7)
History of tobacco use, no. (%)			
Never smoked	78 (59.5)	73 (55.7)	151 (57.6)
Former smoker	49 (37.4)	51 (38.9)	100 (38.2)
Current smoker	4 (3.1)	7 (5.3)	11 (4.2)
Stage of disease at trial entry, no. (%)			
IIIB	7 (5.3)	12 (9.2)	19 (7.3)
IV	124 (94.7)	119 (90.8)	243 (92.7)
Histologic type, no. (%)			
Adenocarcinoma	120 (91.6)	130 (99.2)	250 (95.4)
Adenosquamous carcinoma	3 (2.3)	1 (0.8)	4 (1.5)
Squamous-cell carcinoma	4 (3.1)	0	4 (1.5)
Large-cell carcinoma	2 (1.5)	0	2 (0.8)
Other	2 (1.5)	0	2 (0.8)
ALK status assessed locally with the use of FDA-approved test, no. (%)‡	117 (89.3)	105 (80.2)	222 (84.7)
CNS metastases at baseline, no. (%)	39 (29.8)	37 (28.2)	76 (29.0)
Previous radiotherapy to brain, no. (%)§	17 (13.0)	18 (13.7)	35 (13.4)
Previous chemotherapy in patients with locally advanced or metastatic disease, no. (%)	38 (29.0)	41 (31.3)	79 (30.2)

Abbreviations: *ALK*, anaplastic lymphoma kinase gene; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, United States Food and Drug Administration; ITT, intention to treat; PRO, patient-reported outcome.

* Race was reported by the investigator.

† ECOG PS scores range from 0 to 5, with higher numbers indicating increasing impairment in activities of daily living.

‡ *ALK*-positive status was confirmed locally by fluorescence in situ hybridization (Vysis) or immunohistochemical assay (Ventana).

§ The presence of brain metastases was assessed by the investigator.

2.5. Ethics

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization and Good Clinical Practice guidelines, the EMA guidance on ethical considerations for clinical trials on medicinal products, and other applicable regulatory requirements. The protocol and the informed consent document were approved by an institutional review board/independent ethics committee initially and then at least annually or biannually. Patients were allowed to participate in the trial once they had provided written informed consent.

3. Results

3.1. Patient/study selection

Patients were enrolled between April 2016 and August 2017 and were randomized to brigatinib (n = 137) or crizotinib (n = 138) (Fig. 1). Results are at a median follow-up (range) of 24.9 (0.0–34.1) months for brigatinib and 15.2 (0.1–36.0) months for crizotinib.

In the PRO-ITT population (n = 131 for each group), EORTC QLQ-C30 and QLQ-LC13 compliance among all eligible patients (i.e., patients who reached the visits and expected to complete these PRO questionnaires) was greater than 90 % for brigatinib and crizotinib from baseline to end of treatment (see Table, Supplementary Data 2, which enumerates compliance with EORTC QLQ-C30 assessments over time). However, the number of patients remaining in the study decreased over time; by cycle 12 (i.e., dropout cutoff for pattern mixture model groups), there were 154 (58.8 %) patients total remaining in the study. By cycle 20, EORTC QLQ-C30 assessments were provided by 63.4 % (83/131) of patients in the brigatinib PRO-ITT group and 26.0 % (34/131) of patients in the crizotinib PRO-ITT group. Baseline characteristics (Table 1) for the PRO-ITT population were similar to those for the ITT population in the primary study [9].

3.2. Outcomes

3.2.1. Time to worsening in GHS/QOL and functional and symptom scores, EORTC QLQ-C30

GHS/QOL worsened in 43.5 % (57/131) of patients receiving brigatinib and 53.4 % (70/131) of patients receiving crizotinib as reflected by a 10-point or greater reduction in score from baseline at any time of follow-up before crossover. The median time to worsening in GHS/QOL for brigatinib was 26.74 months and for crizotinib was 8.31 months (HR: 0.70; 95 % CI: 0.49, 1.00; log-rank $P = 0.0485$; Fig. 2). Time to worsening of GHS/QOL was also delayed among patients with baseline brain metastases (n = 38 for each group); median time to worsening in GHS/QOL was 16.6 months for brigatinib and 4.7 months for crizotinib (HR: 0.54; 95 % CI: 0.29, 1.00; log-rank $P = 0.04$). Brigatinib also significantly delayed time to worsening versus crizotinib for the emotional and social functioning scores and the fatigue, nausea and vomiting, appetite loss, and constipation symptom scores (Fig. 2, Table 2). Results for additional symptom scale scores are presented in Figure, Supplementary Data 3. Differences between brigatinib and crizotinib in time to worsening were not statistically significant for the physical, role, or cognitive functioning scales or the pain, dyspnea, insomnia, or diarrhea symptom scales.

3.2.2. Change from baseline in GHS/QOL and functional and symptom scores, EORTC QLQ-C30

Based on the overall least squares mean difference in change from baseline across different time points using linear mixed models, brigatinib showed numerically greater improvements compared with crizotinib in scores for GHS/QOL and most functional and symptom scales (Fig. 3), with between-arm differences of ≥5 points in favor of the brigatinib arm for appetite loss and constipation. In the pattern mixture models, conducted as a sensitivity analysis for missing data, the treatment differences across the treatment groups were not statistically significant or clinically meaningful.

3.2.3. Duration of improvement in GHS/QOL and functional and symptom scores, EORTC QLQ-C30

Among patients with improved GHS/QOL, the median duration of improvement was significantly longer with brigatinib than crizotinib (not reached for brigatinib vs 11.99 months for crizotinib; log-rank $P < 0.001$; Fig. 4). The median duration of improvement was also significantly longer with brigatinib than crizotinib for several functional and symptom scale scores, including the physical, role, emotional, and social functioning scales, and the fatigue, nausea and vomiting, and appetite loss symptom scales (log-rank $P \leq 0.05$; Fig. 4). Results for additional symptom scale scores are presented in Figure, Supplementary Data 4. Differences in duration of improvement were not statistically significant for the cognitive functioning, constipation, dyspnea, insomnia, or diarrhea scales.

3.2.4. Core symptoms of lung cancer (dyspnea, cough, chest pain) from EORTC QLQ-LC13

The EORTC QLQ-LC13 instrument was completed by 141/262 (54 %) patients. Dyspnea worsened during treatment in 42.9 % (27/63) of

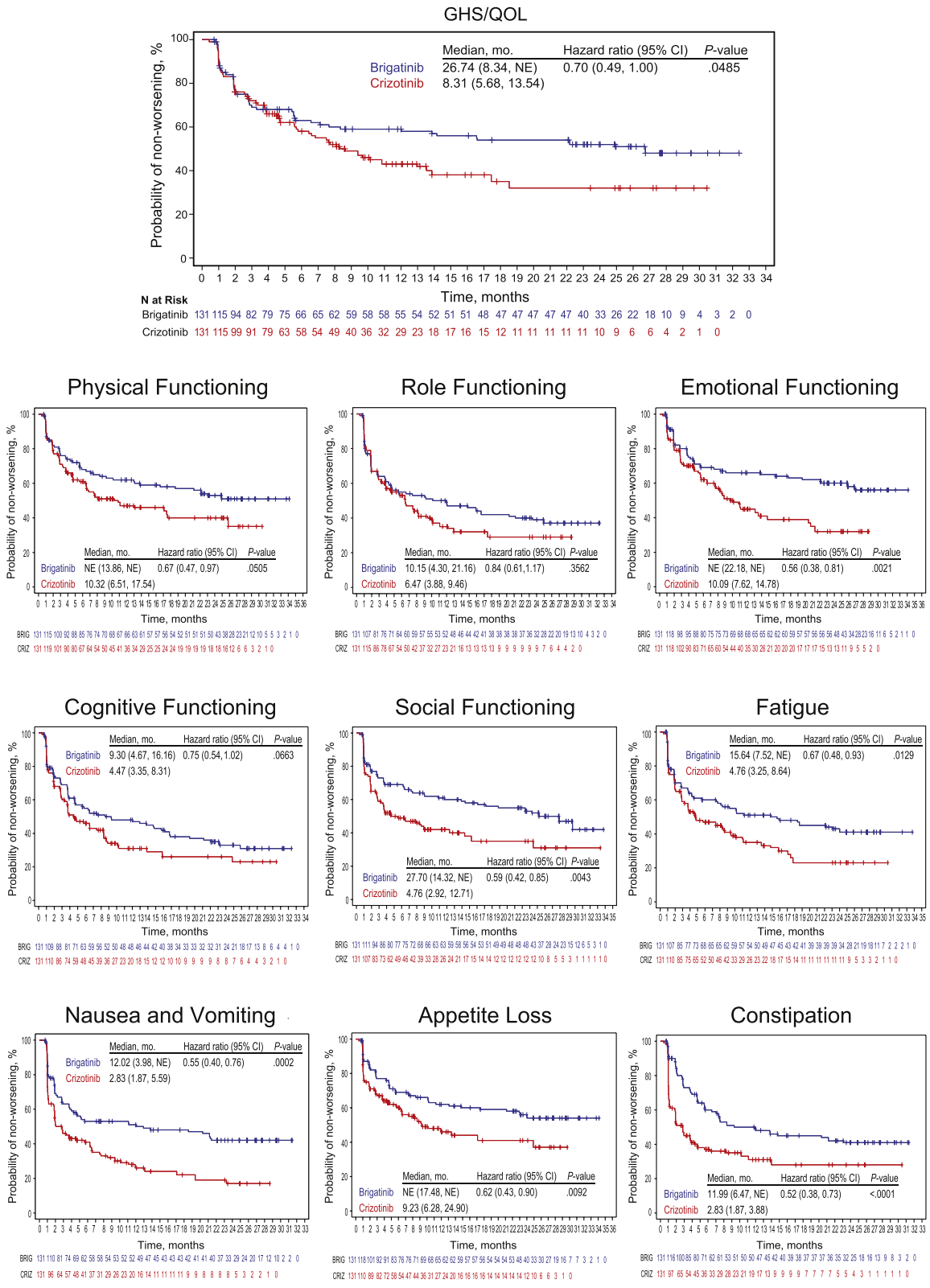


Fig. 2. Time to Worsening in EORTC QLQ-C30 Scores Among PRO-ITT Population [17]*.

Abbreviations: BRIG, brigatinib; CI, confidence interval; CRIZ, crizotinib; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS, global health status; ITT, intention to treat; NE, not estimable; PRO, patient-reported outcome; QOL, quality of life.

* Selected functional and symptom subscales only, including all functional subscales, fatigue, and gastrointestinal-related symptoms, which showed significantly longer time to worsening and better mean change from baseline for brigatinib vs crizotinib.

Adapted with permission.

Table 2
Time to Worsening in EORTC QLQ-C30 Scores Among PRO-ITT Population.

Scores	Median Time to Worsening, Months		Hazard Ratio (95 % CI)	Log-rank *P*-value
	Brigatinib	Crizotinib		
GHS/QOL	26.74 (8.34, NE)	8.31 (5.68, 13.54)	0.70 (0.49, 1.00)	0.0485
Functioning				
Physical functioning	NE (13.86, NE)	10.32 (6.51, 17.54)	0.67 (0.47, 0.97)	0.0505
Role functioning	10.15 (4.30, 21.16)	6.47 (3.88, 9.46)	0.84 (0.61, 1.17)	0.3562
Emotional functioning	NE (22.18, NE)	10.09 (7.62, 14.78)	0.56 (0.38, 0.81)	0.0021
Cognitive functioning	9.30 (4.67, 16.16)	4.47 (3.35, 8.31)	0.75 (0.54, 1.02)	0.0663
Social functioning	27.70 (14.32, NE)	4.76 (2.92, 12.71)	0.59 (0.42, 0.85)	0.0043
Symptoms				
Fatigue	15.64 (7.52, NE)	4.76 (3.25, 8.64)	0.67 (0.48, 0.93)	0.0129
Nausea and vomiting	12.02 (3.98, NE)	2.83 (1.87, 5.59)	0.55 (0.40, 0.76)	0.0002
Pain	12.06 (6.37, 23.20)	8.08 (5.65, 11.63)	0.82 (0.59, 1.15)	0.3008
Dyspnea	28.58 (10.18, NE)	16.76 (10.15, NE)	0.98 (0.67, 1.43)	0.8391
Insomnia	NE (18.63, NE)	22.11 (12.68, NE)	0.91 (0.61, 1.35)	0.7362
Appetite loss	NE (17.48, NE)	9.23 (6.28, 24.90)	0.62 (0.43, 0.90)	0.0092
Constipation	11.99 (6.47, NE)	2.83 (1.87, 3.88)	0.52 (0.38, 0.73)	<0.0001
Diarrhea	2.07 (1.87, 3.75)	2.79 (1.91, 3.75)	1.00 (0.75, 1.34)	0.9682
Financial difficulties	NE (24.94, NE)	NE (19.35, NE)	1.04 (0.67, 1.62)	0.8333

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS, global health status; ITT, intention to treat; NE, not estimable; PRO, patient-reported outcome; QOL, quality of life.

patients receiving brigatinib and 53.8 % (42/78) of patients receiving crizotinib. The median time to worsening in dyspnea was 23.98 months for brigatinib versus 8.25 months for crizotinib; the corresponding HR was 0.64 in favor of brigatinib (95 % CI: 0.39, 1.05; log-rank $P = 0.0758$; Figure, Supplementary Data 5, which shows time to worsening in core symptoms of lung cancer from EORTC QLQ-LC13). The results for time to worsening in cough, chest pain, and the composite score of dyspnea, cough, and chest pain are also summarized in Figure, Supplementary Data 5. Median duration of improvement in dyspnea was also longer with brigatinib (not reached) compared with crizotinib (16.56 months; Figure, Supplementary Data 6, showing time to worsening in core symptoms of lung cancer from EORTC QLQ-LC13).

4. Discussion

Results from the ALTA-1 L study show not only a significant reduction in risk of disease progression or death [16] but also a significant improvement in HRQOL with brigatinib compared with crizotinib in patients with advanced ALK + NSCLC who were ALK inhibitor naive. The HRQOL improvement with brigatinib compared with crizotinib seen in this analysis was consistently shown in multiple functional and symptom domains.

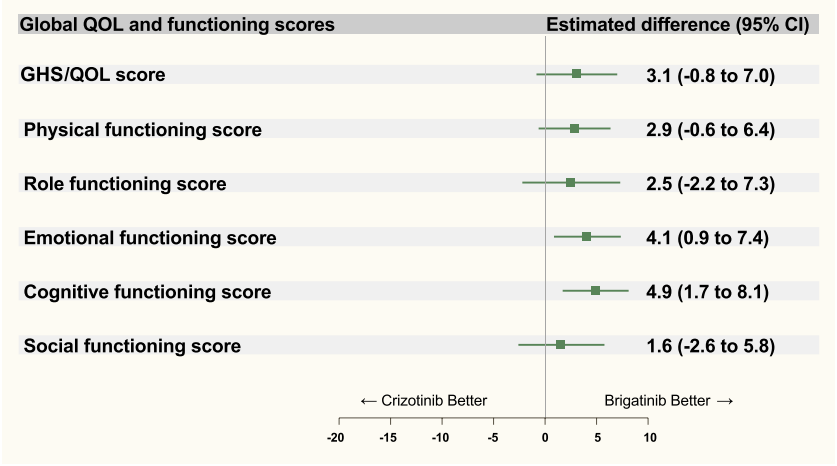
Time to worsening of GHS/QOL was significantly prolonged with brigatinib compared with crizotinib (median: 26.7 vs 8.3 months), consistent with the clinical benefit noted for brigatinib in delaying disease progression [17]. Time to worsening, assessed for all patients included in the PRO-ITT population in this analysis, is commonly used to study the longitudinal data collected over time, especially given that the number of patients remaining in the study decreased at later cycles. Time to worsening of GHS/QOL was also delayed among patients with baseline brain metastases, suggesting that brigatinib prolonged time to worsening in a range of patients with advanced ALK + NSCLC who were ALK inhibitor naive. Our results are consistent with results of the PROFILE 1014 and ASCEND-4 trials, which noted significant improvement in GHS/QOL with ALK inhibitor therapy compared with platinum-based chemotherapy in ALK inhibitor–naive patients [14,15]. In contrast, results from the ALEX trial, which compared alectinib and crizotinib in patients previously untreated for advanced NSCLC, showed no significant difference between arms on the time to deterioration in GHS/QOL [13].

In addition to GHS/QOL, our results showed brigatinib also significantly delayed time to worsening versus crizotinib on the EORTC QLQ-C30 emotional and social functioning scales and fatigue, nausea and vomiting, appetite loss, and constipation symptom scales. The delays in time to worsening with brigatinib were not significant for the physical, role, or cognitive functioning scales or the pain, dyspnea, insomnia, or diarrhea symptom scales. The improvement seen with brigatinib compared with crizotinib on the nausea and vomiting, appetite loss, and constipation symptom scales was consistent with the differences in adverse event rates previously reported for brigatinib and crizotinib. In the ALTA-1 L trial [17], rates of nausea (30 % vs 58 %), vomiting (21 % vs 44 %), decreased appetite (9% vs 19 %), and constipation (18 % vs 42 %) were all lower with brigatinib than crizotinib. These patient-reported results provide additional and consistent evidence on the HRQOL benefit of brigatinib over crizotinib. In comparison, the ALEX trial results showed no significant difference between alectinib and crizotinib in time to deterioration in cough, chest pain, or fatigue, and time to deterioration for dyspnea was worse with alectinib compared with crizotinib [13].

The improvement in HRQOL with brigatinib versus crizotinib was also shown in our analysis of mean change from baseline in EORTC QLQ-C30 scores. Brigatinib showed numerically greater improvements compared with crizotinib in scores for GHS/QOL and most functional and symptom scales. However, it is worth noting that mean change from baseline included all cycles, with decreasing numbers of patients over time. Thus, the magnitude of difference between the treatment arms should be interpreted with caution.

Similar to our results, improvement in GHS/QOL was also seen with brigatinib in the ALTA study, an open-label, phase II, randomized dose-comparison study that evaluated brigatinib in ALK + NSCLC patients with disease progression on crizotinib [30]. Improvements were noted in GHS/QOL scores from cycle 2 onward, with most mean symptom scale scores improving or remaining stable with time. Most patients (88 %) enrolled in ALTA who received brigatinib 180 mg once daily noted improvement or stabilization in GHS/QOL from baseline to treatment cycle 5, with few patients (7%) reporting GHS/QOL worsening; more than two-thirds of patients noted improvement or stabilization in all functioning and symptom scale scores [31]. In the ALEX study, results showed improved EORTC QLQ-C30 HRQOL scores from baseline in both arms, but there was no significant difference in the overall improvement between alectinib and crizotinib [13].

Among patients who demonstrated improvement in QOL in our analysis, patients receiving brigatinib versus crizotinib demonstrated a significantly longer duration of improvement in GHS/QOL and in several functional and symptom domains, although no significant difference was found for the cognitive functioning, constipation, dyspnea, insomnia, or diarrhea scale scores. It is notable that improvement in the nausea and vomiting, appetite loss, and constipation domains was greater with brigatinib than crizotinib, as gastrointestinal adverse events (i.e., nausea, diarrhea, vomiting, constipation) were some of the most common adverse reactions (≥40 % of patients) reported in crizotinib clinical trials [4]. In the ALEX trial, the mean duration of HRQOL improvement was numerically longer with alectinib compared with crizotinib, and better patient-reported tolerability was observed with



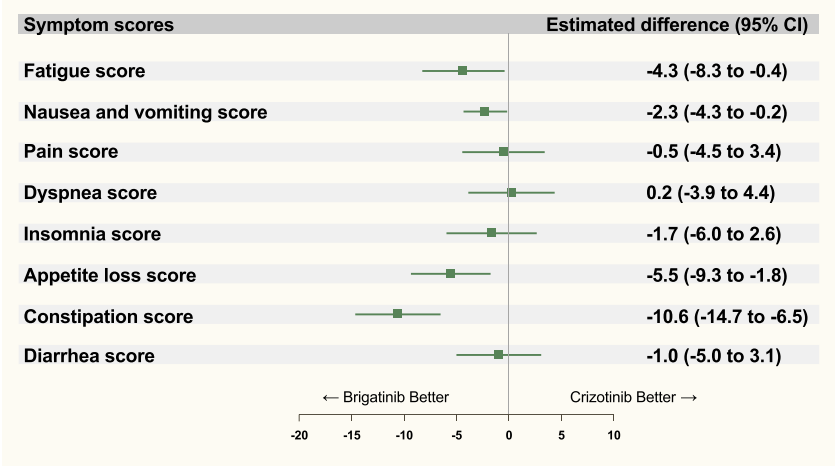


Fig. 3. EORTC QLQ-C30 Scores, Change From Baseline*.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS, global health status; QOL, quality of life.
* Estimated least squares mean difference on change from baseline across different time points. A positive change from baseline in the GHS/QOL and functional scales indicates that a patient's QOL and/or function have improved. A negative change from baseline in symptom scales indicates that a patient's symptoms have decreased (i.e., improved). Thus, higher scores in the GHSQOL and functional scales and lower scores in the symptom scales indicate better health-related QOL.

alectinib versus crizotinib on common treatment-related gastrointestinal symptoms [13].

The statistically significant GHS/QOL and functioning improvement seen in this study with brigatinib compared with crizotinib may reflect not only greater efficacy of brigatinib on disease-related symptom improvement and duration of improvement, but also a lower extent of clinically relevant side effects associated with the treatment. In comparison, while there is evidence of the superior clinical efficacy of alectinib over crizotinib in the first-line setting [13,32,33], there is no clear evidence to demonstrate a significant HRQOL benefit for alectinib. These results suggest that improvement in progression-free survival in oncology trials does not automatically translate into improvement in PROs that measure the effects of disease symptoms, treatment side effects, and functional and general HRQOL impacts.

PRO compliance in the ALTA-1 L study was greater than 90 % at baseline; in comparison, the questionnaire completion rate in the ALEX study was approximately 60 % [13]. However, owing to the small patient numbers in both treatment arms during later assessments, the HRQOL improvement seen in our results in later months may be attributable to patients with the worst disease dropping out of the study. Nevertheless, the sensitivity analysis we conducted to evaluate the effect of study attrition on the estimate of treatment differences did not show any significant difference in the treatment effect between patients who dropped out earlier versus later.

Treatment with next-generation ALK inhibitors is often prolonged for younger patients with ALK + NSCLC, so the effects of treatment on HRQOL may be particularly important to these patients. Incorporation of PRO tools that can be used to assess changes in HRQOL into real-world treatment settings allows physicians to not only assess the effects of treatment on delaying disease progression but also on patients' daily lives.

Our study has some limitations. The EORTC QLQ-LC13 was added in a protocol amendment several months into patient enrollment, and therefore only 54 % of patients completed the EORTC QLQ-LC13. Although the dyspnea and composite scores (i.e., dyspnea, cough, and chest pain) from the QLQ-LC13 assessments favored brigatinib compared with crizotinib, the HRs did not reach statistical significance, perhaps because of the small number of patients completing the QLQ-LC13 assessment. Therefore, it is possible that our analysis did not identify lung cancer–specific problems among all patients assessed. There was potential for type I errors in our results due to the multiple endpoints and comparisons in this analysis. Like many other oncology trials, patient numbers in ALTA-1 L decreased over time. Particularly in later cycles, the number of patients remaining in each treatment arm decreased significantly, which may impact the interpretability of between-arm comparisons on mean change from baseline scores. Since the study was not powered for secondary endpoints, all results should be interpreted with caution, especially for later cycles. Lastly, there is a potential risk of open-label bias for PROs in open-label oncology trials, although recent evidence has suggested this bias is likely limited [34].

5. Conclusion

Brigatinib is the first ALK inhibitor to demonstrate not only significantly improved efficacy but also significantly improved HRQOL compared with crizotinib in ALK inhibitor–naive patients with advanced ALK + NSCLC. Similar to the HRQOL benefits demonstrated with brigatinib during the ALTA study, which evaluated brigatinib as second-line

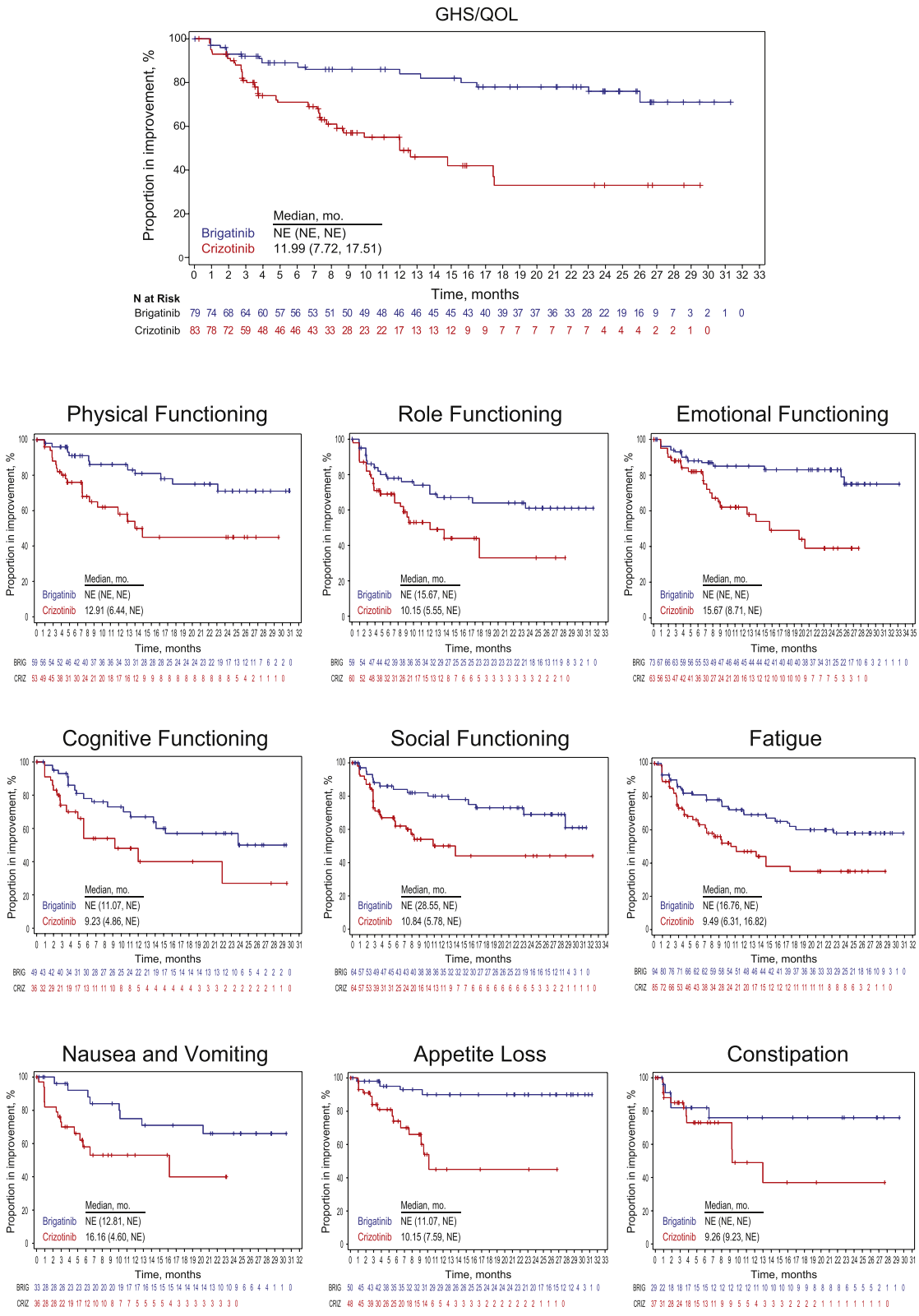


Fig. 4. Duration of Improvement in EORTC QLQ-C30 Functional and Key Symptom Scores Among PRO-ITT Population [17]*.
Abbreviations: BRIG, brigatinib; CRIZ, crizotinib; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; GHS, global health status; ITT, intention to treat; NE, not estimable; PRO, patient-reported outcome; QOL, quality of life.
* Selected functional and symptom subscales only, including all functional subscales, fatigue, and gastrointestinal-related symptoms, which showed significantly longer time to worsening and better mean change from baseline for brigatinib vs crizotinib.
Adapted with permission.

ALK inhibitor treatment in patients with advanced ALK + NSCLC [30], our results showed HRQOL improvement in the ALTA-1 L trial across multiple functional and symptom scales, particularly on delaying the worsening of GHS/QOL. These results, consistent with the reduced risk of disease progression or death previously reported for brigatinib in first-line ALK + NSCLC treatment [16], may reflect the magnitude of benefit seen with brigatinib over crizotinib and suggest that brigatinib is a better choice than crizotinib as the first ALK inhibitor for ALK + NSCLC patients. Because duration of therapy with brigatinib is likely to be prolonged in the first-line setting, the ALTA-1 L PRO data are key in determining the best initial ALK inhibitor to use in ALK + NSCLC patients. The efficacy, safety, and now HRQOL data obtained from the ALTA-1 L study support brigatinib as first-line ALK inhibitor therapy in patients with advanced ALK + NSCLC.

Data sharing statement

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Funding source

This study was sponsored by ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The trial was designed by the sponsor, ARIAD Pharmaceuticals, Inc., in collaboration with the senior author. Data were collected and trial procedures were overseen by the trial investigators. The sponsor analyzed the data and funded medical writing assistance and publication charges.

CRediT authorship contribution statement

Maria Rosario Garcia Campelo: Data curation, Investigation, Writing - review & editing. **Huamao M. Lin:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing - review & editing. **Yanyan Zhu:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing - review & editing. **Maurice Pérol:** Investigation, Writing - review & editing. **Mohammad Jahanzeb:** Investigation, Writing - review & editing. **Sanjay Popat:** Investigation, Writing - review & editing. **Pingkuan Zhang:** Conceptualization, Data curation, Investigation, Writing - review & editing. **D. Ross Camidge:** Data curation, Investigation, Writing - review & editing.

Declaration of Competing Interest

Maria Rosario Garcia Campelo: Honoraria (ARIAD, AstraZeneca, Roche, Pfizer, BMS, Boehringer Ingelheim), speakers bureau and/or advisory role (ARIAD, AstraZeneca, Roche, Pfizer, BMS, Boehringer Ingelheim)

Huamao M. Lin: Employment (Takeda)

Yanyan Zhu: Employment (Takeda)

Maurice Pérol: Research funding (AstraZeneca, Roche, Takeda, Boehringer Ingelheim, Chugai), consulting or advisory role (AstraZeneca, Roche, Novartis, Pfizer, BMS, Merck Sharp & Dohme, Takeda), honoraria for lectures (Eli Lilly, Roche, AstraZeneca, Pfizer, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Takeda, Novartis, Illumina, Chugai), travel, accommodations, expenses (AstraZeneca, Roche, Takeda, Boehringer Ingelheim, Pfizer)

Mohammad Jahanzeb: Consultant fees, speaking honoraria (Takeda, Novartis, Pfizer, Genentech, BMS, Merck)

Sanjay Popat: Research funding (Boehringer Ingelheim, Epizyme, BMS, Clovis Oncology, Roche, Lilly, Takeda [all to institution]), honoraria (Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Chugai Pharma), consulting or advisory role (Boehringer Ingelheim, Roche, Novartis, Pfizer, AstraZeneca, BMS, MSD, Guardant Health, AbbVie), travel, accommodations, expenses (Boehringer Ingelheim, BMS, Merck Sharp & Dohme)

Pingkuan Zhang: Employment (Takeda)

D. Ross Camidge: Honoraria (AstraZeneca, Takeda, Arrys/Kyn, Genoptix, G1 Therapeutics (DSMB), Mersana Therapeutics, Roche/Genentech, Ignyta, Daiichi Sankyo (ILD adjudication committee), Hansoh SRC, Bio-Thera DSMB, Lycera, Revolution Med, Orion, Clovis, Celgene, Novartis); research funding (ARIAD/Takeda)

Acknowledgments

We thank the patients, their families, and their caregivers, as well as the investigators and their team members, for participation in the ALTA-1 L trial. Professional medical writing support was provided by Beth Lesher, PharmD, BCPS, and Catherine Mirvis of Pharmerit International LP, and was funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. SP acknowledges NHS funding to the joint Royal Marsden Hospital-Institute of Cancer Research NIHR Biomedical Research Centre.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.03.005.

References

[1] American Cancer Society, What Is Non-small Cell Lung Cancer?, 2021. Accessed March 18, https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html.
[2] W. Jiang, G. Cai, P.C. Hu, Y. Wang, Personalized medicine in non-small cell lung cancer: a review from a pharmacogenomics perspective, Acta Pharm. Sin. B 8 (4) (2018) 530–538, https://doi.org/10.1016/j.apsb.2018.04.005.
[3] J. Wu, J. Savooji, D. Liu, Second- and third-generation ALK inhibitors for non-small cell lung cancer, J. Hematol. Oncol. 9 (2016) 19, https://doi.org/10.1186/s13045-016-0251-8.
[4] XALKORI [prescribing information], Pfizer Labs, New York, NY, 2021. Accessed March 11 http://labeling.pfizer.com/showlabeling.aspx?id=676.
[5] ALCENSA [prescribing information], Genentech, Inc., South San Francisco, CA, 2021. Accessed November 9, https://www.gene.com/download/pdf/alecensa_prescribing.pdf.
[6] ALUNBRIG [prescribing information], Takeda Pharmaceutical Company Limited, Cambridge, MA, 2021. Accessed November 9, https://www.alunbrig.com/assets/pi.pdf.
[7] ZYKADIA [prescribing information], Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2021. Accessed November 9, https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zykadia.pdf.
[8] LORBRENA [prescribing information], Pfizer Labs, New York, NY, 2021.
[9] U.S. Department of Health and Human Services Food and Drug Administration, Patient-Focused Drug Development, 2021. Accessed March 18, https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544143.htm.
[10] European Medicines Agency Committee for Medicinal Products for Human Use, Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man: The Use of Patient-Reported Outcome (PRO) Measures in Oncology Studies EMA/CHMP/292464/2014, European Medicines Agency, London, England, 2016.
[11] R. Mercieca-Bebber, M.T. King, M.J. Calvert, M.R. Stockler, M. Friedlander, The importance of patient-reported outcomes in clinical trials and strategies for future optimization, Patient Relat. Outcome Meas. 9 (2018) 353–367, https://doi.org/10.2147/PROM.S156279.
[12] P.L. Chia, P. Mitchell, A. Dobrovic, T. John, Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors, Clin. Epidemiol. 6 (2014) 423–432, https://doi.org/10.2147/CLEP.S69718.
[13] M. Pérol, N. Pavlakis, E. Levchenko, et al., Patient-reported outcomes from the randomized phase III ALEX study of alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer, Lung Cancer 138 (2019) 79–87, https://doi.org/10.1016/j.lungcan.2019.10.002.
[14] B.J. Solomon, T. Mok, D.W. Kim, et al., First-line crizotinib versus chemotherapy in ALK-positive lung cancer, N. Engl. J. Med. 371 (23) (2014) 2167–2177, https://doi.org/10.1056/NEJMoa1408440.

[15] D.S.W. Tan, J. Soria, G. de Castro Jr, et al., PROs with ceritinib versus chemotherapy in patients with previously untreated ALK-rearranged nonsquamous NSCLC (ASCEND-4), in: World Conference on Lung Cancer, Vienna, Austria, 2016.
[16] D.R. Camidge, H.R. Kim, M.J. Ahn, et al., Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer, N. Engl. J. Med. 379 (21) (2018) 2027–2039, https://doi.org/10.1056/NEJMoa1810171.
[17] R. Camidge, H.R. Kim, M. Ahn, et al., Brigatinib versus crizotinib in advanced ALK inhibitor–naive ALK-positive non–small cell lung cancer: second interim analysis of the phase III ALTA-1L trial, J. Clin. Oncol. 38 (31) (2020) 3592–3603, https://doi.org/10.1200/JCO.20.00505.
[18] A. Bottomley, F. Efficace, R. Thomas, V. Vanvoorden, S.H. Ahmedzai, Health-related quality of life in non-small-cell lung cancer: methodologic issues in randomized controlled trials, J. Clin. Oncol. 21 (15) (2003) 2982–2992, https://doi.org/10.1200/jco.2003.01.203.
[19] L. Claassens, J. van Meerbeeck, C. Coens, et al., Health-related quality of life in non-small-cell lung cancer: an update of a systematic review on methodologic issues in randomized controlled trials, J. Clin. Oncol. 29 (15) (2011) 2104–2120, https://doi.org/10.1200/jco.2010.32.3683.
[20] M. Koller, S. Warncke, M.J. Hjermstad, et al., Use of the lung cancer-specific Quality of Life Questionnaire EORTC QLQ-LC13 in clinical trials: a systematic review of the literature 20 years after its development, Cancer 121 (24) (2015) 4300–4323, https://doi.org/10.1002/cncr.29682.
[21] N.K. Aaronson, S. Ahmedzai, B. Bergman, et al., The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology, J. Natl. Cancer Inst. 85 (5) (1993) 365–376.
[22] M.J. Hjermstad, S.D. Fossa, K. Bjordal, S. Kaasa, Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire, J. Clin. Oncol. 13 (5) (1995) 1249–1254, https://doi.org/10.1200/jco.1995.13.5.1249.
[23] D. Osoba, N. Aaronson, B. Zee, M. Sprangers, A. te Velde, Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer, The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group, Qual. Life Res. 6 (2) (1997) 103–108.
[24] B. Bergman, N.K. Aaronson, S. Ahmedzai, S. Kaasa, M. Sullivan, The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials, EORTC Study Group on Qualityof Life, Eur. J. Cancer 30a (5) (1994) 635–642.
[25] P.M. Fayers, N.K. Aaronson, K. Bjordal, D. Curran, M. Groenvold, EORTC QLQ-C30 Scoring Manual, third edition, EORTC Quality of Life Group, Brussels, 2001.
[26] K. Cocks, M.T. King, G. Velikova, P.M. Fayers, J.M. Brown, Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 data in randomised controlled trials, Eur. J. Cancer 44 (13) (2008) 1793–1798, https://doi.org/10.1016/j.ejca.2008.05.008.
[27] M.T. King, The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30, Qual. Life Res. 5 (6) (1996) 555–567.
[28] D. Osoba, G. Rodrigues, J. Myles, B. Zee, J. Pater, Interpreting the significance of changes in health-related quality-of-life scores, J. Clin. Oncol. 16 (1) (1998) 139–144, https://doi.org/10.1200/jco.1998.16.1.139.
[29] M. Calvert, J. Blazeby, D.G. Altman, D.A. Revicki, D. Moher, M.D. Brundage, Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension, JAMA 309 (8) (2013) 814–822, https://doi.org/10.1001/jama.2013.879.
[30] D.W. Kim, M. Tiseo, M.J. Ahn, et al., Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial, J. Clin. Oncol. 35 (22) (2017) 2490–2498, https://doi.org/10.1200/JCO.2016.71.5904.
[31] W.R. Lenderking, H. Lin, R.M. Speck, et al., Patient-reported outcomes and quality of life in advanced ALK+ non-small-cell lung cancer trial of brigatinib (ALTA), Future Oncol. 15 (24) (2019) 2841–2855, https://doi.org/10.2217/fon-2019-0185.
[32] T. Seto, M. Nishio, T. Hida, et al., Final PFS analysis and safety data from the phase III J-ALEX study of alectinib (ALC) vs. Crizotinib (CRZ) in ALK-inhibitor naïve ALK-positive non-small cell lung cancer (ALK+ NSCLC), J. Clin. Oncol. 37 (15_suppl) (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.9092, 9092-9092.
[33] C. Zhou, S.-W. Kim, T. Reungwetwattana, et al., Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA): a randomised phase 3 study, Lancet Respir. Med. 7 (5) (2019) 437–446, https://doi.org/10.1016/S2213-2600(19)30053-0.
[34] J.K. Roydhouse, M.H. Fiero, P.G. Kluetz, Investigating potential bias in patient-reported outcomes in open-label cancer trials, JAMA Oncol. 5 (4) (2019) 457–458, https://doi.org/10.1001/jamaoncol.2018.6205.