ORIGINAL ARTICLE

Brigatinib Versus Crizotinib in ALK Inhibitor–Naive Advanced ALK-Positive NSCLC: Final Results of Phase 3 ALTA-1L Trial

D. Ross Camidge, MD, PhD,[a,*] Hye Ryun Kim, MD, PhD,[b] Myung-Ju Ahn, MD, PhD,[c] James C. H. Yang, MD, PhD,[d] Ji-Youn Han, MD, PhD,[e] Maximilian J. Hochmair, MD,[f] Ki Hyeong Lee, MD, PhD,[g] Angelo Delmonte, MD, PhD,[h] Maria Rosario Garcia Campelo, MD,[i] Dong-Wan Kim, MD, PhD,[j] Frank Griesinger, MD, PhD,[k] Enriqueta Felip, MD, PhD,[l] Raffaele Califano, MD,[m,n] Alexander I. Spira, MD,[o] Scott N. Gettinger, MD,[p] Marcello Tiseo, MD,[q] Huamao M. Lin, PhD,[r] Yuyin Liu, PhD,[s] Florin Vranceanu, MD, PhD,[t] Huifeng Niu, PhD,[u] Pingkuan Zhang, MD,[v] Sanjay Popat, BSc, PhD, FRC[w]

[a]*Department of Medicine, University of Colorado Cancer Center, Aurora, Colorado*
[b]*Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*
[c]*Division of Hematology-Oncology, Samsung Medical Center, Seoul, South Korea*

*Corresponding author.

Disclosure: Dr. Camidge reports receiving honoraria from AstraZeneca, Takeda, Arrys/Kyn, Genoptix, G1 Therapeutics (Data Safety Monitoring Board), Mersana Therapeutics, Roche/Genentech, Ignyta, Daiichi Sankyo (Interstitial Lung Disease Adjudication Committee), Hansoh SRC, Bio-Thera Data Safety Monitoring Board, Lycera, Revolution Med, Orion, Clovis, Celgene, and Novartis; and research funding from ARIAD/Takeda. Dr. Kim reports receiving honoraria and having consulting or advisory roles for AstraZeneca, Roche, and Boehringer Ingelheim. Dr. Ahn reports receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, and Novartis; and having consulting or advisory roles for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, and Novartis. Dr. Yang reports receiving honoraria or serving an advisory role for Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, Merck Sharp & Dohme, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, Bristol-Myers Squibb, Ono Pharmaceutical, Daiichi Sankyo, Takeda, AstraZeneca, and Hansoh Pharmaceuticals. Dr. Han reports receiving honoraria from Roche, AstraZeneca, and Takeda; research grant from Roche, Pfizer, Ono, and Takeda; and serving an advisory role for AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer, MedPacto, and Novartis. Dr. Hochmair reports receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Roche, and Takeda; and having consulting or advisory roles for Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Roche, and Takeda. Dr. Lee reports receiving honoraria and serving an advisory role for AstraZeneca, Eli Lilly, and Boehringer Ingelheim. Dr. Delmonte reports having consulting/advisory roles for AstraZeneca and Boehringer Ingelheim. Dr. Campelo reports having consulting/advisory roles for Takeda, AstraZeneca, Roche, Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Janssen, and Eli Lilly. Dr. Kim reports receiving research funding from Alpha Biopharma, Amgen, AstraZeneca/Medimmune, Boehringer Ingelheim, Daiichi Sankyo, Hanmi, Janssen, Merus, Mirati Therapeutics, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, Yuhan, Chong Kun Dang, Bridge Biotherapeutics, and GSK (all to institution); and travel/accommodations support from Amgen and Daiichi Sankyo. Dr. Griesinger reports having consulting or advisory roles from ARIAD, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, Siemens, Amgen, GSK, and Janssen. Dr. Felip reports serving an advisory role and had been an invited speaker for Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Janssen, Merck Sharp & Dohme, Merck Serono, and Pfizer; serving in an advisory board for Bayer, BeiGene, Boehringer Ingelheim, GSK, Peptomyc, Puma, Regeneron, Sanofi, Syneos Health, and Takeda; and was an invited speaker for Medscape, PeerVoice, and Springer. Dr. Califano reports receiving honoraria and having consulting or advisory roles for AstraZeneca, Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Takeda, and Novartis. Dr. Spira reports having consulting/advisory roles for ARIAD, AstraZeneca, Clovis Oncology, Roche, Amgen, Mirati, Bristol-Myers Squibb, and Merck. Dr. Gettinger reports having consulting or advisory roles for ARIAD, Bristol-Myers Squibb, and Iovance; and receiving research funding from Takeda/ARIAD, Genentech/Roche, NextCure, Iovance (all to institution). Dr. Tiseo reports receiving speaker and consultant's fees from AstraZeneca, Pfizer, Eli Lilly, Bristol-Myers Squibb, Novartis, Roche, Merck Sharp & Dohme, Boehringer Ingelheim, Otsuka, Takeda, and Pierre Fabre; and institutional research grants from AstraZeneca and Boehringer Ingelheim. Drs. HM Lin, Y Liu, Vranceanu, Niu, and Zhang are currently employed by Takeda. Dr. Popat reports serving in an advisory board for Amgen, AstraZeneca, Bayer, BeiGene, Blueprint, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Guardant Health, Janssen, Eli Lilly, Merck KGaA, Novartis, Roche, and Takeda; serving as subinvestigator for institutional studies sponsored by Amgen and Merck Sharp & Dohme; serving as coordinating primary investigator for institutional studies sponsored by ARIAD, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Takeda, and Turning Point Therapeutics); serving as a local primary investigator for institutional studies sponsored by AstraZeneca, GSK, Roche, and Trizel); serving advisory roles for ALK Positive UK, International Association for the Study of Lung Cancer, Lung Cancer Europe, and Ruth Strauss Foundation; having leadership roles in British Thoracic Oncology Group and The European Thoracic Oncology Platform; is currently an officer in the European Society of Medical Oncology); and is a member of the Board of Directors for Mesothelioma Applied Research Foundation.

Address for correspondence: D. Ross Camidge, MD, PhD, Department of Medicine, University of Colorado Cancer Center, 1665 Aurora Court, Aurora, CO 80045. E-mail: ross.camidge@cuanschutz.edu

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2021.07.035

[d]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei, Taiwan
[e]Department of Precision Medicine, National Cancer Center, Gyeonggi, South Korea
[f]Department of Respiratory and Critical Care Medicine, Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Vienna, Austria
[g]Internal Medicine Department, Chungbuk National University Hospital, Chungbuk, South Korea
[h]Department of Medical Oncology, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST) Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Meldola, Italy
[i]Department of Medical Oncology, Complejo Hospitalario Universitario A Coruña (CHUAC), University Hospital A Coruña, A Coruña, Spain
[j]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea
[k]Department of Hematology and Oncology, Pius-Hospital Oldenburg, University of Oldenburg, Oldenburg, Germany
[l]Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain
[m]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom
[n]Department of Medical Oncology, Division of Cancer Sciences, The University of Manchester, Manchester, England, United Kingdom
[o]Department of Medical Oncology, Virginia Cancer Specialists, US Oncology Research, Fairfax, Virginia
[p]Department of Medical Oncology, Yale Cancer Center, New Haven, Connecticut
[q]Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy
[r]Global Evidence and Outcome, Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts
[s]Oncology Statistics, Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts
[t]Clinical Science, Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts
[u]Oncology Translational Sciences, Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts
[v]Oncology Clinical Research, Millennium Pharmaceuticals, Inc., a wholly-owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, Massachusetts
[w]Royal Marsden Hospital, London, United Kingdom

Received 28 July 2021; accepted 30 July 2021
Available online - XXX

ABSTRACT

Introduction: In the phase 3 study entitled ALK in Lung cancer Trial of brigAtinib in 1st Line (ALTA-1L), which is a study of brigatinib in ALK inhibitor–naive advanced ALK-positive NSCLC, brigatinib exhibited superior progression-free survival (PFS) versus crizotinib in the two planned interim analyses. Here, we report the final efficacy, safety, and exploratory results.

Methods: Patients were randomized to brigatinib 180 mg once daily (7-d lead-in at 90 mg once daily) or crizotinib 250 mg twice daily. The primary end point was a blinded independent review committee–assessed PFS. Genetic alterations in plasma cell-free DNA were assessed in relation to clinical efficacy.

Results: A total of 275 patients were enrolled (brigatinib, n = 137; crizotinib, n = 138). At study end, (brigatinib median follow-up = 40.4 mo), the 3-year PFS by blinded independent review committee was 43% (brigatinib) versus 19% (crizotinib; median = 24.0 versus 11.1 mo, hazard ratio [HR] = 0.48, 95% confidence interval [CI]: 0.35–0.66). The median overall survival was not reached in either group (HR = 0.81, 95% CI: 0.53–1.22). Posthoc analyses suggested an overall survival benefit for brigatinib in patients with baseline brain metastases (HR = 0.43, 95% CI: 0.21–0.89). Detectable baseline *EML4-ALK* fusion variant 3 and *TP53* mutation in plasma were associated with poor PFS. Brigatinib exhibited superior efficacy compared with crizotinib regardless of *EML4-ALK* variant and *TP53* mutation. Emerging secondary *ALK* mutations were rare in patients progressing on brigatinib. No new safety signals were observed.

Conclusions: In the ALTA-1L final analysis, with longer follow-up, brigatinib continued to exhibit superior efficacy and tolerability versus crizotinib in patients with or without poor prognostic biomarkers. The suggested survival benefit with brigatinib in patients with brain metastases warrants future study.

Keywords: Anaplastic lymphoma kinase; ALK tyrosine kinase inhibitor; Brigatinib; Crizotinib; Non–small cell lung cancer

Introduction

Brigatinib is an oral tyrosine kinase inhibitor (TKI) that has potent activity against the *EML4-ALK* fusion that drives 3% to 5% of NSCLC.[1–4] Furthermore, brigatinib has exhibited activity against a broad range of *ALK* resistance mutations.[1] The phase 3 study ALK in Lung cancer Trial of brigAtinib in 1st Line (ALTA-1L) reported

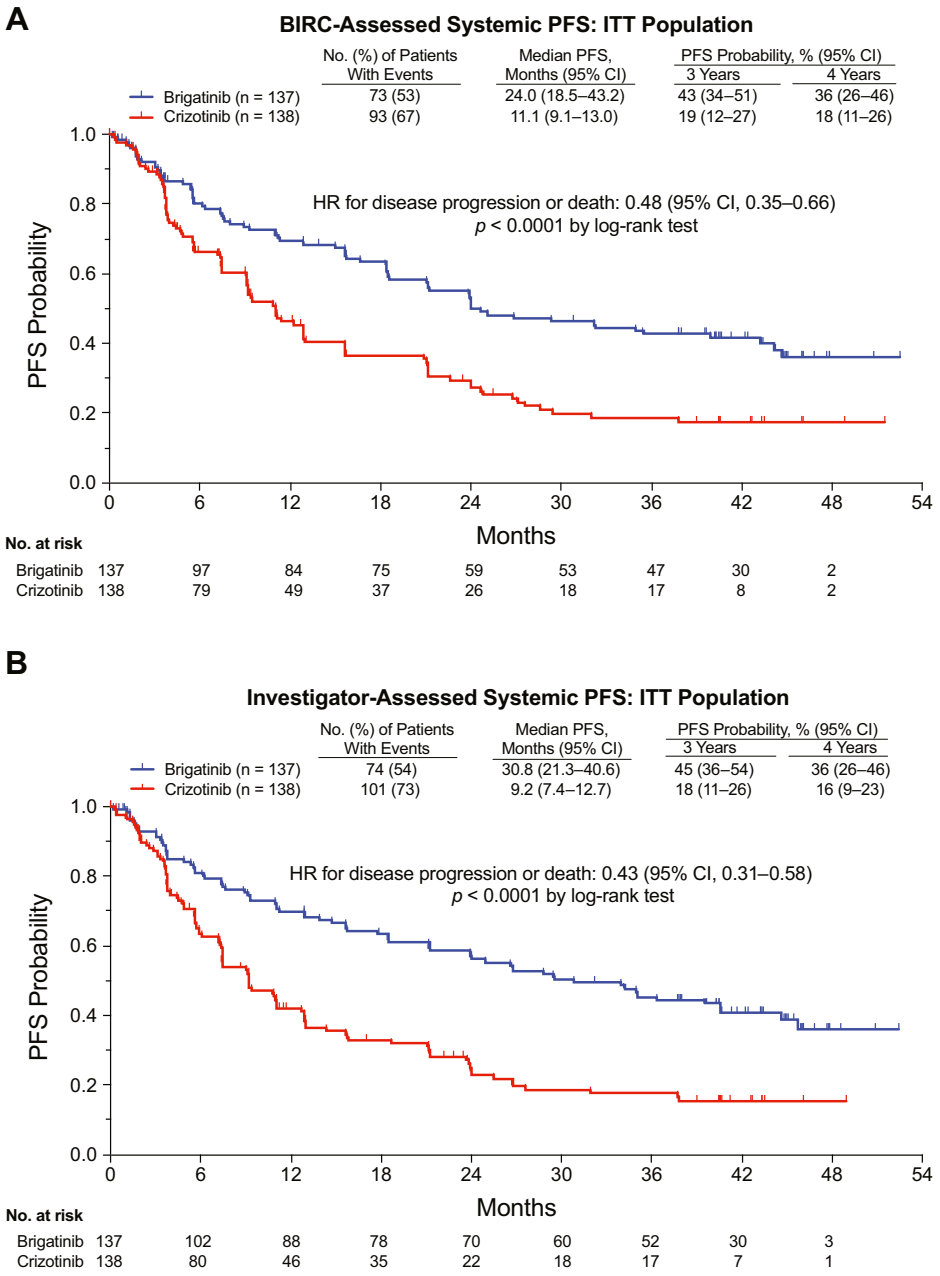

Figure 1. Efficacy of brigatinib and crizotinib in TKI-naive ALK+ NSCLC. (*A*) BIRC-assessed and (*B*) investigator-assessed PFS for the ITT population. (*C*) Forest plot of HRs for BIRC-assessed PFS across predefined patient subgroups. (*D*) Duration of response in confirmed responders. Intracranial PFS by BIRC in (*E*) patients with baseline brain metastases by BIRC assessment and (*F*) all patients (ITT population). Time-to-event plots illustrate Kaplan-Meier estimates. [a]HR was not calculated for current smokers because of insufficient patient numbers (brigatinib, n = 3; crizotinib, n = 7). [b]HR was not calculated for patients who had an ECOG performance status of 2 because of insufficient patient numbers (brigatinib, n = 7; crizotinib, n = 7). [c]Brain metastases at baseline as assessed by the investigator. [d]Previous chemotherapy in a locally advanced or metastatic setting. [e]Intracranial reviewers were independent from systemic reviewers. Only brain lesions were reviewed. Patients were counted as having an event if there was a radiologic progression, radiotherapy to the brain, or death. [f]Per BIRC assessment. [g]Includes one patient with radiotherapy to the brain. [h]Includes three patients with radiotherapy to the brain. [i]Includes one patient with radiotherapy to the brain. [j]Includes six patients with radiotherapy to the brain. BIRC, blinded independent review committee; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival.

the superior efficacy of brigatinib compared with crizotinib in patients with ALK TKI–naive advanced ALK-positive (ALK+) NSCLC.[5,6] After the median follow-up of 11 months in the brigatinib arm, ALTA-1L met its primary end point, exhibiting significantly improved blinded independent review committee (BIRC)–assessed progression-free survival (PFS) with brigatinib versus crizotinib (hazard ratio [HR] = 0.49, 95% confidence

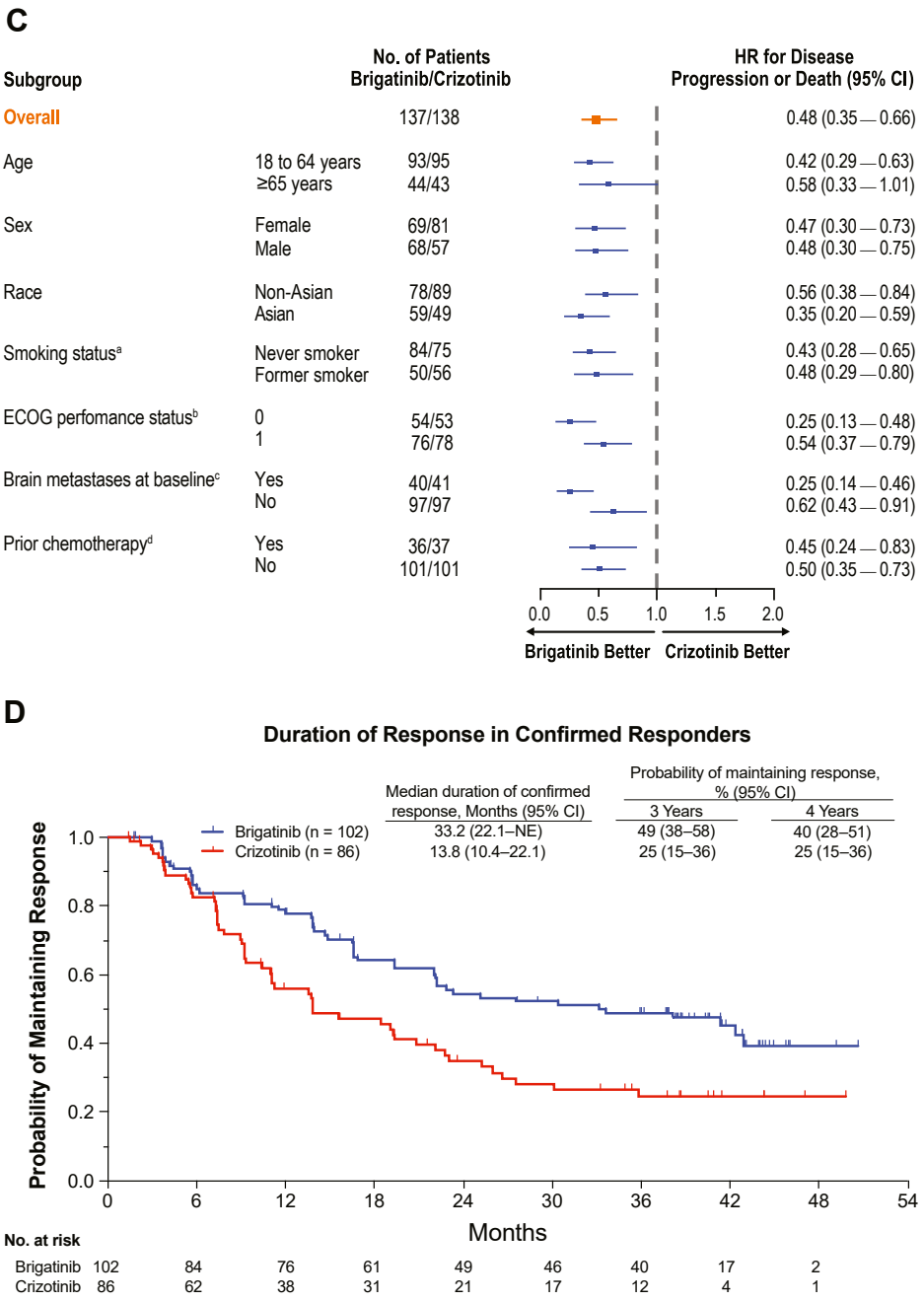

Figure 1. Continued.

interval [CI]: 0.33–0.74, $p < 0.001$).[5] At the second interim analysis with a median follow-up of 25 months for brigatinib, the PFS was consistent with the first analysis (HR = 0.49, 95% CI: 0.35–0.68, $p < 0.0001$), and data on overall survival (OS) was maturing (HR = 0.92, 95% CI: 0.57–1.47; brigatinib, 24% of events; crizotinib, 27% of events).[6]

More than 15 *EML4-ALK* fusion variants have been identified, most often variants 1 (V1), 2 (V2), and 3a/b (V3).[7] Emerging evidence suggests that *EML4-ALK* variant status may affect treatment outcomes and acquired resistance to ALK inhibitors.[7–9] In addition, concomitant *TP53* mutations may negatively affect treatment outcomes.[10–12] However, there are limited clinical trial data on the effect of *EML4-ALK* variant and *TP53* mutation status on the efficacy of ALK inhibitors including brigatinib, especially in the first-line setting.

Here, we report the final efficacy and safety data from ALTA-1L, with a median follow-up of 40 months in the brigatinib arm and exploratory analyses of the impact of

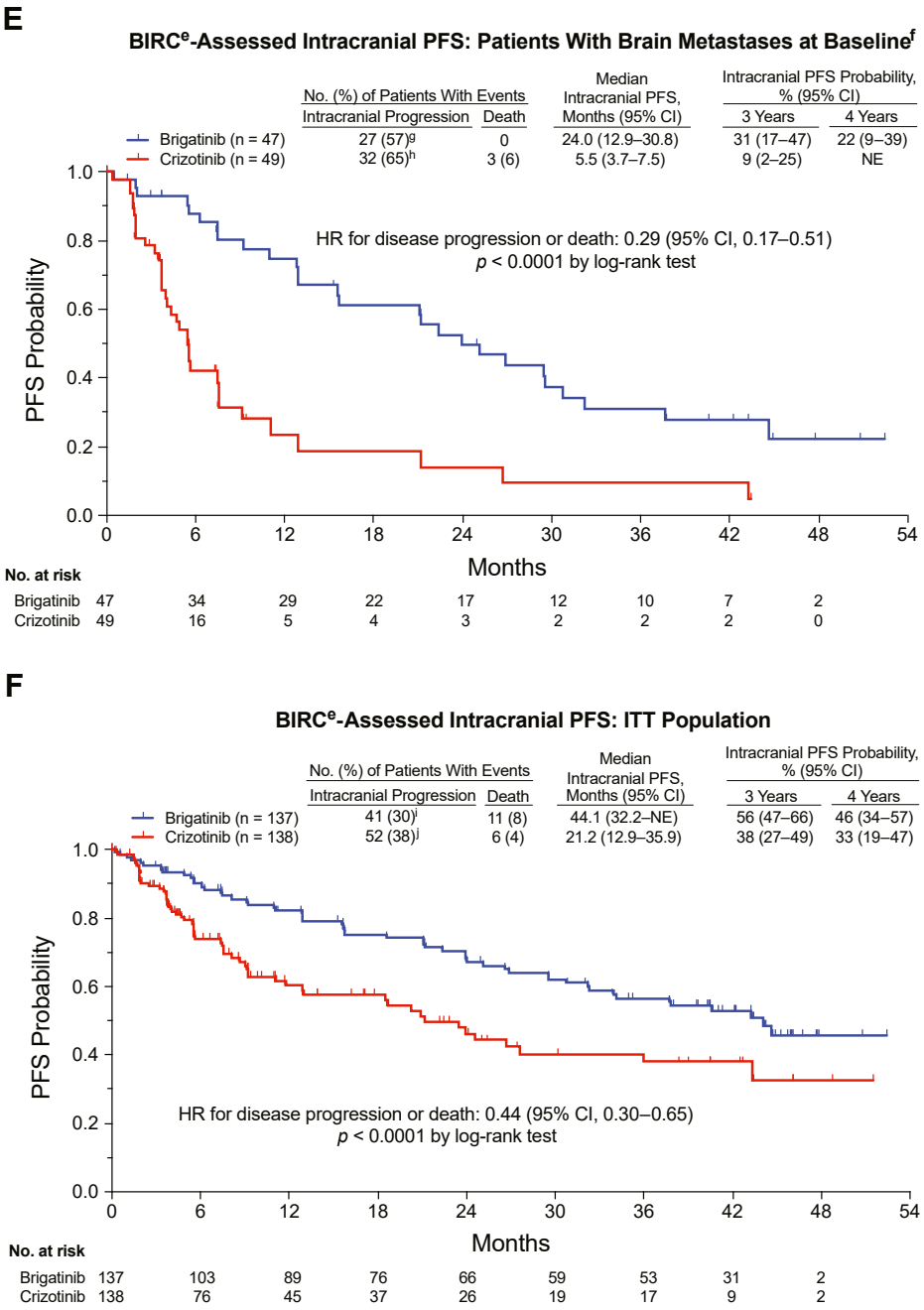

Figure 1. Continued.

EML4-ALK fusion variants and other molecular oncogenic mutations, including *TP53* status, on clinical efficacy.

Materials and Methods

Study Design and Patients

ALTA-1L was a randomized, open-label, phase 3, multicenter, international study (ClinicalTrials.gov identifier: NCT02737501). Detailed methods have been published.[5,6] Patients aged 18 years or older with locally advanced or metastatic NSCLC who had not received ALK-targeted therapy were randomized (1:1) to receive oral brigatinib 180 mg once daily (with 7-d lead-in at 90 mg once daily) or oral crizotinib 250 mg twice daily until the achievement of progressive disease (PD), intolerable toxicity, or another discontinuation criterion. Randomization was stratified by the presence or absence of baseline brain metastases and completion of at least one full cycle of chemotherapy for locally advanced or metastatic disease (yes or no). Patients with asymptomatic or stable central

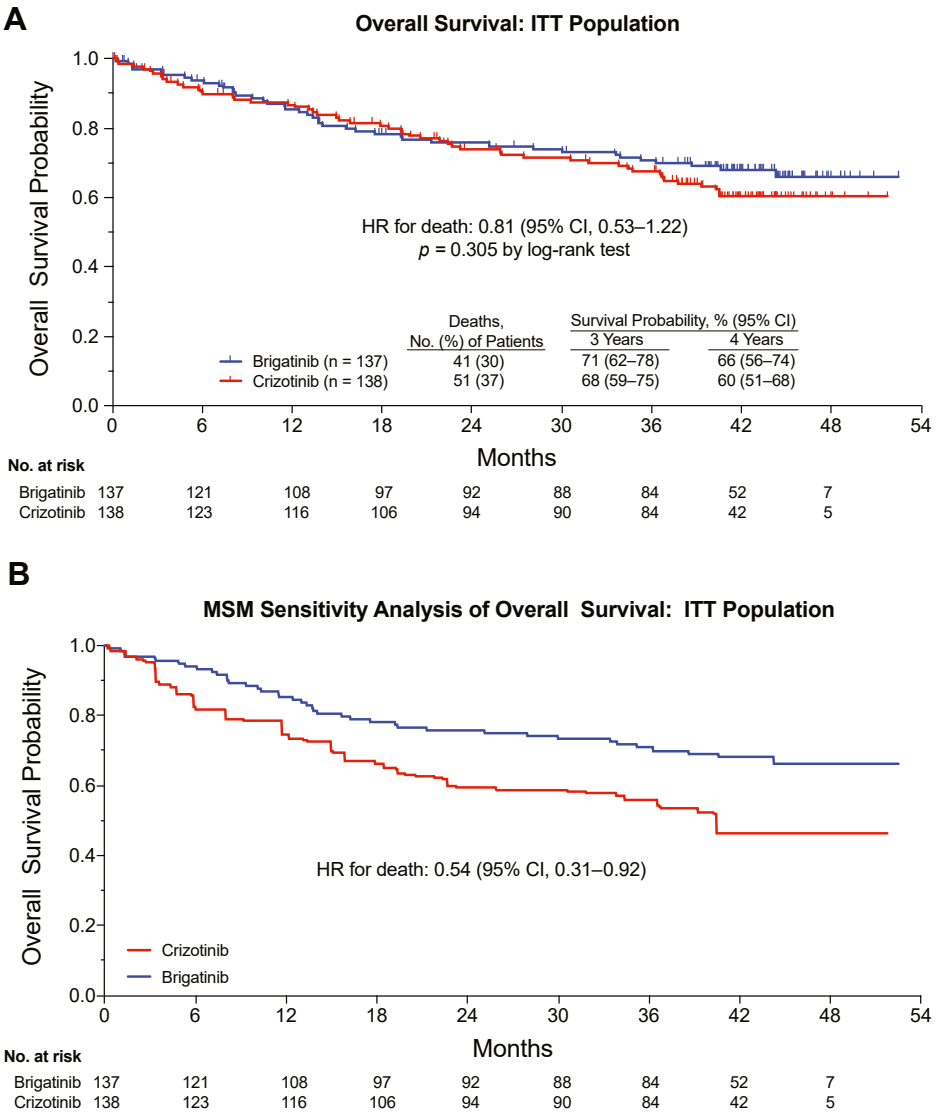

Figure 2. Overall survival (*A*) in the ITT population without adjustment for crossover, (*B*, *C*) in sensitivity analyses that adjusted for crossover using (*B*) the MSM and (*C*) IPCW Cox models, and in patients (*D*) with and (*E*) without brain metastases at baseline. [a]Brain metastasis present at baseline on the basis of investigator assessment. CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; IPCW, inverse probability of censoring weight; MSM, marginal structural model.

nervous system (CNS) metastases were permitted. Patients in the crizotinib arm could cross over to brigatinib after BIRC-assessed progression (after 10-d washout from crizotinib). Subsequent anticancer therapies after discontinuation of the study drug were selected by the physician in agreement with the patient.

The protocol was approved by local institutional review boards or ethics committees at each site. The trial was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonization guidelines for good clinical practice. All patients provided written informed consent.

Outcomes

The primary end point was BIRC-assessed PFS per Response Evaluation Criteria in Solid Tumors, version 1.1.[13] Secondary end points included BIRC-assessed confirmed objective response rate (ORR), confirmed intracranial ORR, intracranial PFS, OS, duration of response (DoR), safety, and change from baseline in global health status (GHS)/quality of life (QoL) (per European Organization for Research and Treatment of Cancer [EORTC] QoL Questionnaire [QLQ]–C30 version 3.0). Exploratory end points included BIRC-assessed PFS and confirmed ORR on brigatinib in patients who crossed over to brigatinib after progression on crizotinib. Investigator-assessed PFS and intracranial DoR were also analyzed. Exploratory analyses assessed molecular

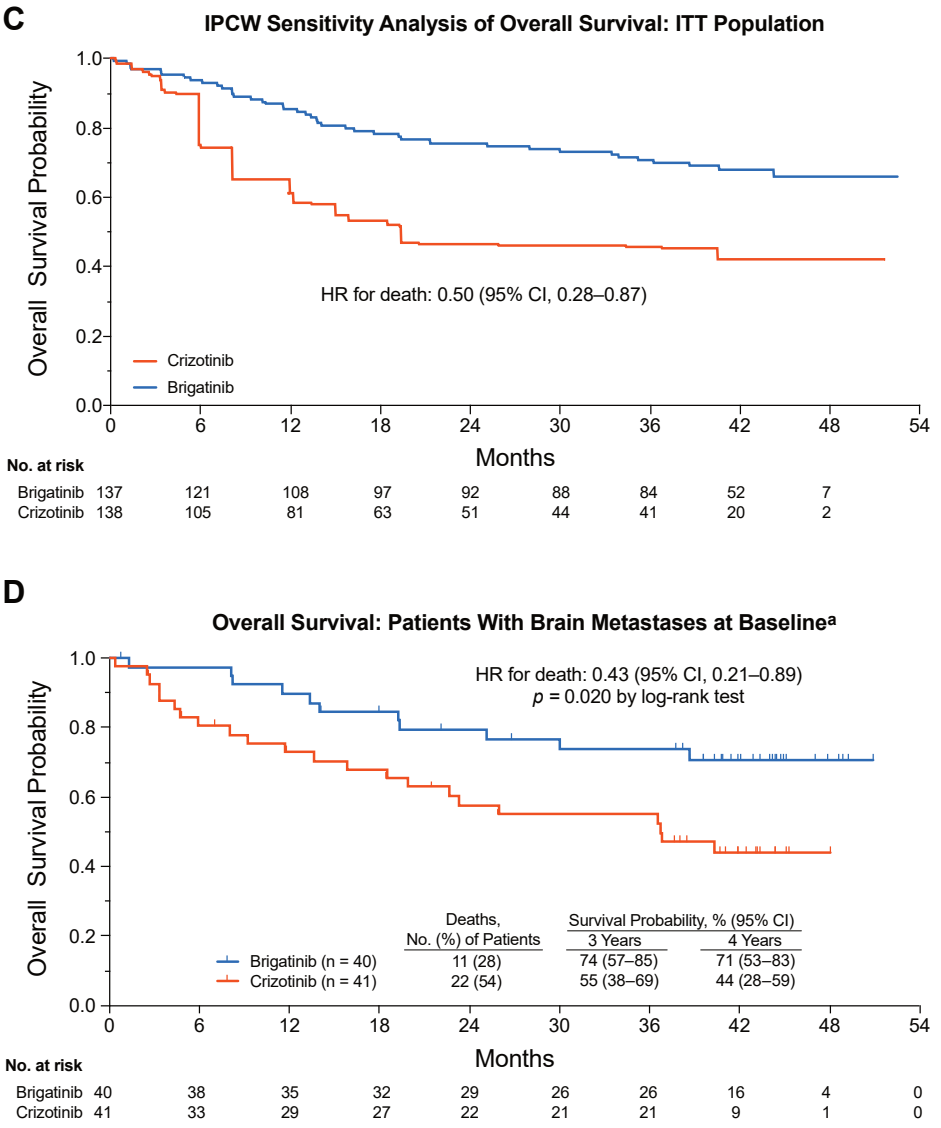

Figure 2. Continued.

determinants (e.g., *ALK-EML4* fusion variant and *TP53* mutation status) of efficacy (PFS, OS, and confirmed ORR assessed by BIRC) and emerging mutations over time.

Assessments

The disease was assessed by imaging at screening, every 8 weeks through cycle 14 (28 d/cycle), and then every 12 weeks through treatment discontinuation. There were two BIRCs: one evaluated all diseases; the other evaluated only intracranial CNS disease. Objective responses were confirmed at least 4 weeks after the initial observation.

Blood samples for biomarker studies were collected at screening, cycle 3, day 2, and end of treatment (EOT). The mutation status of *ALK* and other oncogenes was determined through next-generation sequencing (NGS) of cell-free DNA in plasma (ctDx Lung NGS panel, Resolution Bioscience, Kirkland, WA).

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for AEs, version 4.03.

The EORTC QLQ-C30 (version 3.0)[14] and its lung cancer-specific module (QLQ-LC13 version 3.0)[15] were administered at baseline, day 1 of every 4-week cycle, EOT, and 30 days after the last dose.

Statistical Analysis

The study was closed approximately 3 years after the last patient was enrolled because the primary end point (BIRC-assessed PFS) met the prespecified critical value at the first interim analysis and was confirmed at the second interim analysis. Efficacy was evaluated in the intention-to-treat population. The primary end point was

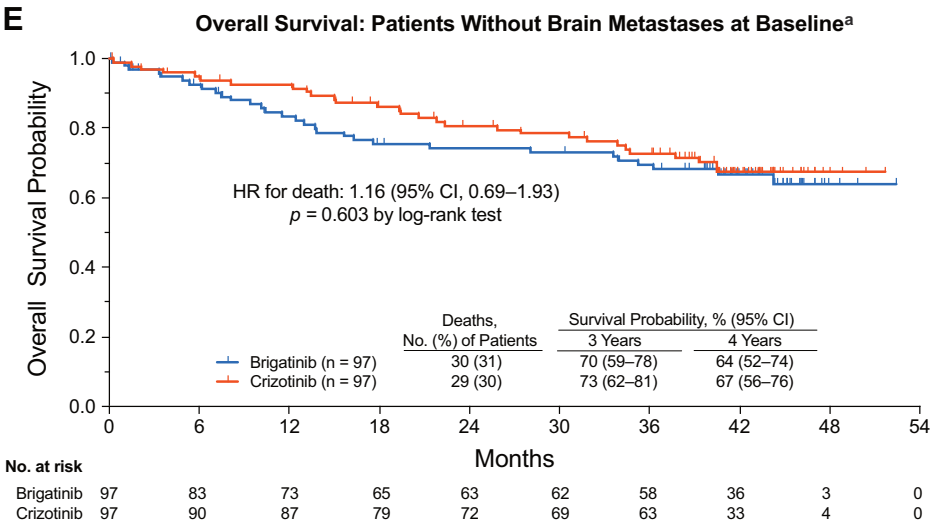

Figure 2. Continued.

compared between treatment arms using a two-sided log-rank test stratified by baseline brain metastases (yes or no) and previous chemotherapy (yes or no). The preplanned analyses of OS were performed at the final analysis, as the primary end point was met at the first interim analysis. The analysis of OS was performed using a two-sided stratified log-rank test. Time-to-event analyses estimated median values and two-sided 95% CIs using Kaplan-Meier (KM) methods. Analyses of OS by baseline brain metastases status were posthoc.

To adjust for potential time-dependent confounding effects of crossover after patients discontinued crizotinib,

Table 1. Baseline *ALK* Fusion Variant and *TP53* Mutation Status: Prevalence and Effect on Efficacy

Baseline Mutation Status	Brigatinib	Crizotinib
Patients with plasma samples, n	123	127
ALK fusion detected, n/N (%)	67/123 (54)	69/127 (54)
EML4-ALK fusion detected	57/123 (46)	64/127 (50)
V1, n/N (%)	25/57 (44)	30/64 (47)
ORR, n/N (%) [95% CI]	21/25 (84) [64-96]	22/30 (73) [54-88]
Median PFS, mo (95% CI)	29.0 (18.0-NE)	13.0 (7.4-24.0)
V2, n/N (%)	6/57 (11)	5/64 (8)
ORR, n/N (%) [95% CI]	5/6 (83) [36-100]	3/5 (60) [15-95]
Median PFS, mo (95% CI)	16.0 (6.3-NE)	11.0 (7.4-NE)
V3, n/N (%)	23/57 (40)	21/64 (33)
ORR, n/N (%) [95% CI]	19/23 (83) [61-95]	14/21 (67) [43-85]
Median PFS, mo (95% CI)	16.0 (7.6-NE)	7.4 (3.7-13.0)
V5, n/N (%)	1/57 (2)	0
ORR, n/N (%) [95% CI]	1/1 (100) [3-100]	—
Median PFS, mo (95% CI)	5.5 (NE-NE)	—
V5', n/N (%)	2/57 (4)	7/64 (11)
ORR, n/N (%) [95% CI]	2/2 (100) [16-100]	3/7 (43) [10-82]
Median PFS, mo (95% CI)	16.0 (16.0-NE)	9.9 (3.7-NE)
Undetermined, n/N (%)	0	1/64 (2)
TP53 status in patients with *EML4-ALK* fusion detected		
TP53 mutant, n/N (%)	22/57 (39)	23/64 (36)
ORR, n/N (%) [95% CI]	17/22 (77) [55-92]	14/23 (61) [39-80]
Median PFS, mo (95% CI)	18.0 (5.6-NE)	7.4 (5.6-13.0)
TP53 WT, n/N (%)	35/57 (61)	41/64 (64)
ORR, n/N (%) [95% CI]	31/35 (89) [73-97]	29/41 (71) [55-84]
Median PFS, mo (95% CI)	24.0 (18.0-NE)	13.0 (9.2-21.0)

Note: N = 250 treated patients who had plasma samples at screening.
CI, confidence interval; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; V, variant; WT, wild type.

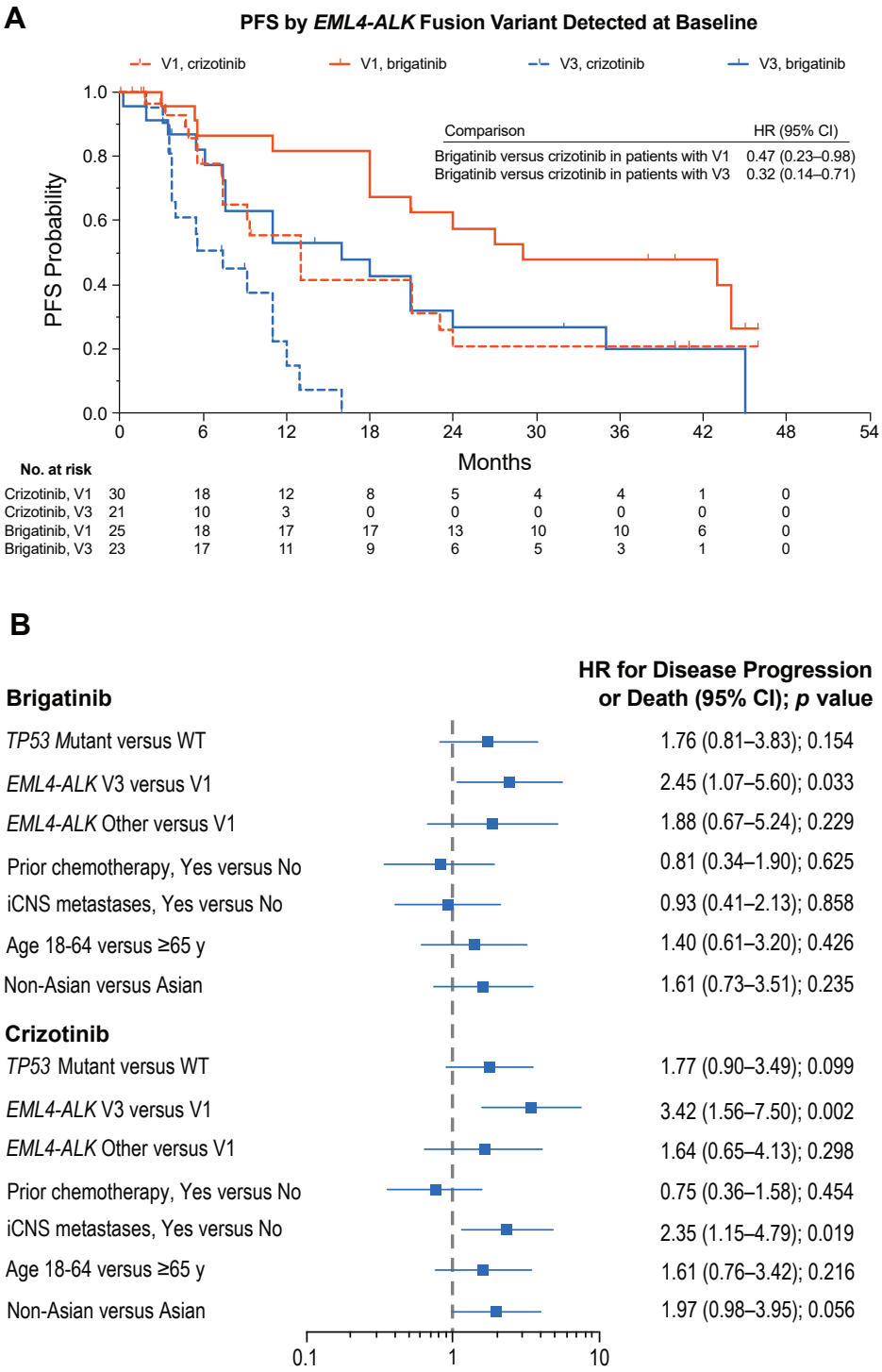

Figure 3. Efficacy by baseline molecular variables. (*A*) Kaplan-Meier plot of BIRC-assessed PFS by the presence of *EML4-ALK* fusion variant. (*B*) Multivariate analysis of PFS by baseline molecular and clinical covariates. (*C*) Overall survival by the presence of *EML4-ALK* fusion variant. (*D*) BIRC-assessed PFS and (*E*) overall survival by *TP53* mutation status in patients with *EML4-ALK* fusion detected in plasma at baseline. BIRC, blinded independent review committee; CI, confidence interval; HR, hazard ratio; iCNS, intracranial central nervous system; OS, overall survival; PFS, progression-free survival; V, variant; WT, wild type.

a marginal structural model (MSM) and an inverse probability of censoring weight Cox model were constructed.[16,17] The final model included baseline covariates of age, initial diagnosis stage, Eastern Cooperative Oncology Group score, tumor histopathologic class, measurable intracranial CNS disease (yes or no), race (Asian versus non-Asian), sex, smoking history, and strata at randomization and time-dependent covariates of

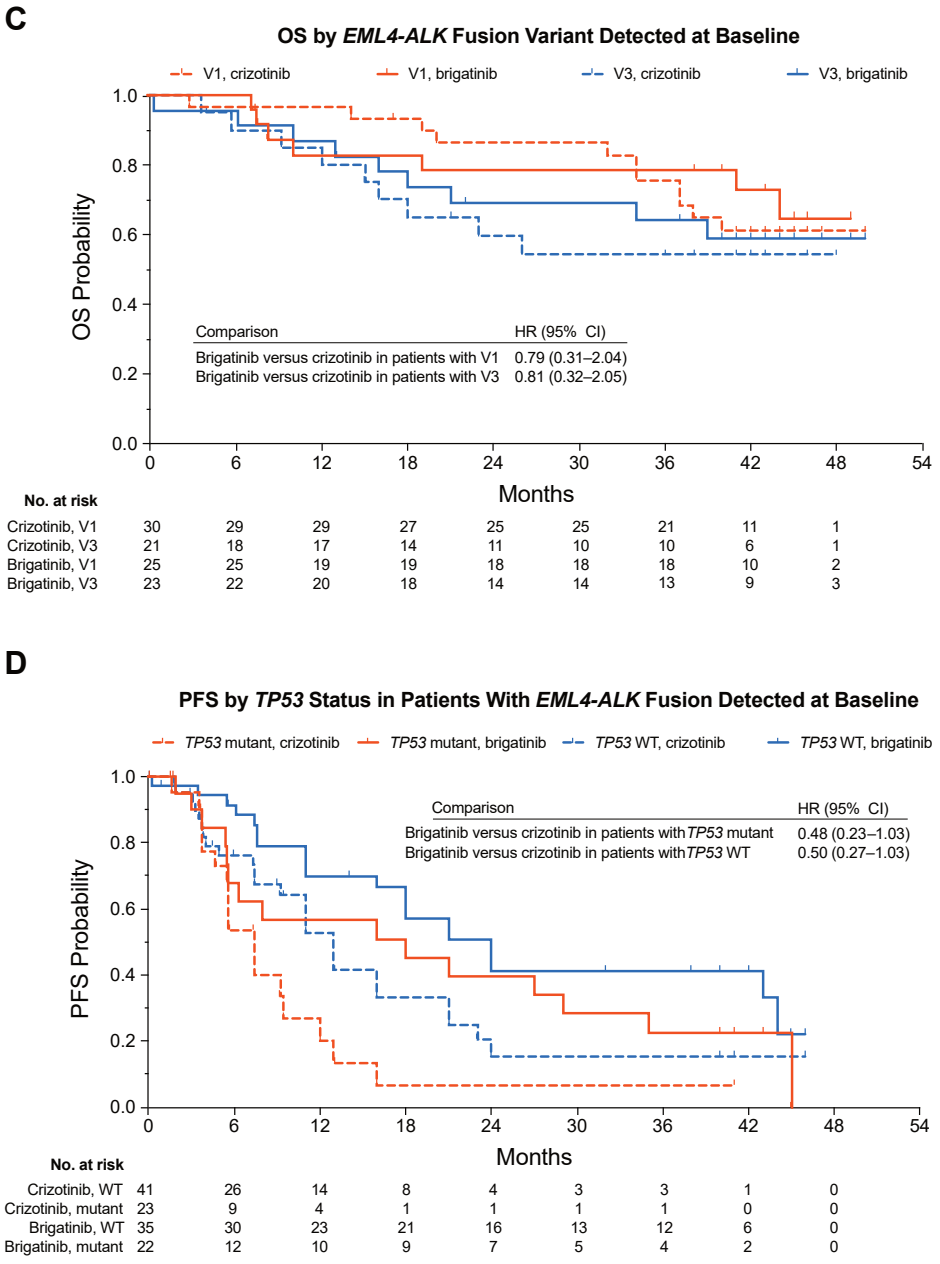

Figure 3. Continued.

intracranial disease progression, target-lesion size, and Eastern Cooperative Oncology Group score.

Baseline *ALK* fusion variants and other oncogenic mutations, including *TP53* gene status, were characterized in patients with assessable plasma samples, and correlations with ORR, PFS, and OS were evaluated.

The time to worsening in EORTC QLQ-C30 GHS/QoL and other functioning and symptom scores (defined as a $\geq$10-point decrease from baseline) in patients with baseline and any postbaseline EORTC assessment were compared between treatment arms using a two-sided stratified log-rank test. A Cox proportional hazard model with baseline brain metastases and previous chemotherapy as covariates was used to estimate HRs and 95% CIs.

The safety population included patients who received at least one dose of the study drug. Statistical analyses were performed using Base 9.4 SAS/STAT 15.1 software (SAS Institute, Cary, NC) and R (version 4.0.2, R Core Team, Vienna, Austria). Data were reported as of January 29, 2021 (last patient, last contact).

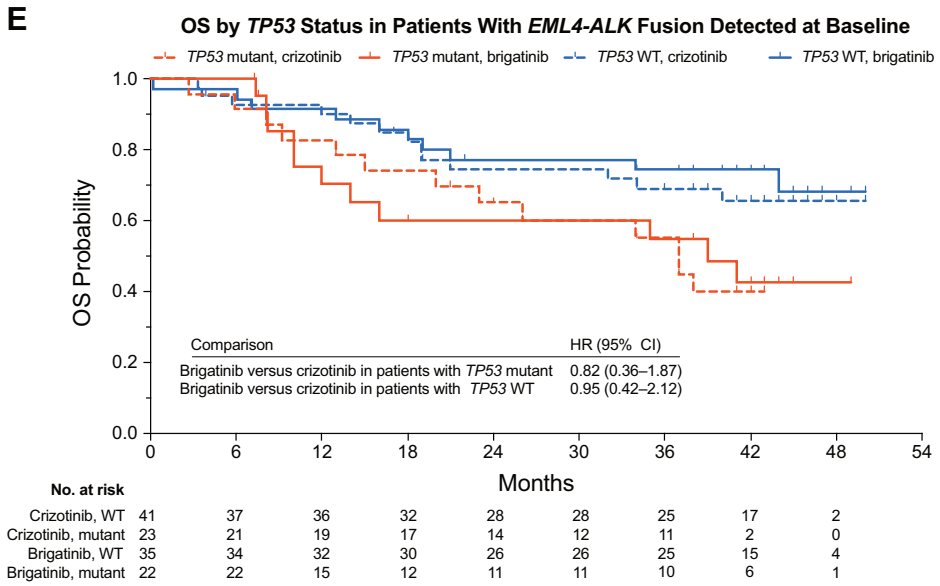

Figure 3. Continued.

Results

Patients

The ALTA-1L patient population has been previously described.[5] A total of 275 patients were randomly assigned to brigatinib (n = 137) or crizotinib (n = 138). Of these, 96 patients (38%) had baseline intracranial CNS metastases by BIRC assessment (brigatinib, n = 47; crizotinib, n = 49) and 81 (32%) had baseline CNS metastases by investigator assessment (brigatinib, n = 40; crizotinib, n = 41). Baseline demographic and clinical characteristics were balanced across treatment arms (Supplementary Table 1).

At study end (last patient last contact: January 2021), approximately 3.5 years after the last patient enrolled (August 2017), the median (range) follow-up was 40.4 (0–52.4) months in the brigatinib arm and 15.2 (0.1–51.7) months in the crizotinib arm. A total of 58 patients (42%) in the brigatinib arm and 16 patients (12%) in the crizotinib arm were still on the study drug before the end of the study (Supplementary Fig. 1). The median (range) duration of assigned treatment was 34.9 (0.1–52.4) months in the brigatinib arm and 9.3 (0.1–51.5) months in the crizotinib arm.

A total of 65 patients from the crizotinib arm crossed over to brigatinib after PD on crizotinib; of these, 23 patients (35%) remained on brigatinib up to study end. Crossover occurred in 46% of patients (19 of 41) who had brain metastases at baseline per investigators. The median duration of brigatinib treatment in the 65 patients who crossed over from crizotinib was 17.3 (range: 0.1–37.5) months.

Efficacy

Updated PFS. At final analysis, 166 patients had experienced PFS events (PD or death; brigatinib, 73 of 137 [53%]; crizotinib, 93 of 138 [67%]). Brigatinib continued to exhibit superior BIRC-assessed PFS versus crizotinib; the KM-estimated 3-year PFS rate (95% CI) was 43% (34%–51%) in the brigatinib arm and 19% (12%–27%) in the crizotinib arm (median [95% CI] = 24.0 mo [18.4–43.2] versus 11.1 mo [9.1–13.0]; HR = 0.48, 95% CI: 0.35–0.66, log-rank $p < 0.0001$) (Fig. 1*A*). At 4 years, the BIRC-assessed PFS rate was 36% (26%–46%) in the brigatinib arm and 18% (11%–26%) in the crizotinib arm, although the 4-year data were limited by a high rate of censoring and small sample size (two patients at risk in each group) (Fig. 1*A*). The investigator assessments were consistent with BIRC assessments. The investigator-assessed 3-year PFS rate (95% CI) was 45% (36%–54%) with brigatinib and 18% (11%–26%) with crizotinib (median [95% CI] = 30.8 mo [21.3–40.6] versus 9.2 mo [7.4–12.7]; HR = 0.43, 95% CI: 0.31–0.58, log-rank $p < 0.0001$) (Fig. 1*B*). Improvements in BIRC-assessed PFS were consistent across all subgroups (Fig. 1*C*).

Updated Response Rate and Durability of Response. The BIRC-assessed confirmed ORR was consistent with previous reports (Supplementary Table 2).[5,6] The median DoR in confirmed responders (95% CI) was 33.2 months (22.1 mo–not reached) with brigatinib and 13.8 months (10.4–22.1 mo) with crizotinib (Fig. 1*D*).

Updated Intracranial Efficacy. The confirmed intracranial ORR in patients with measurable brain metastases at

Table 2. Safety Overview and Treatment-Emergent Adverse Events of Grade 3 or Higher Reported in at Least 2% of Patients in Either Treatment Arm

Patients with ≥1 event, n (%)	Brigatinib (n = 136)	Crizotinib (n = 137)
Overview of adverse events		
Any-grade adverse event	136 (100)	137 (100)
Grade 3-4 adverse event	95 (70)	77 (56)
Adverse events leading to death (grade 5)	11 (8)	11 (8)
Treatment-related	0	0
Adverse event leading to treatment discontinuation	18 (13)	12 (9)
Adverse event leading to dose reduction	60 (44)	34 (25)
Adverse event leading to dose interruption	98 (72)	65 (47)
Grade ≥3 adverse events reported in ≥2% of patients in either treatment arm		
Blood creatine phosphokinase increased[a]	36 (26)	2 (1)
Lipase increased[b]	21 (15)	11 (8)
Hypertension	19 (14)	6 (4)
Amylase increased[b]	8 (6)	2 (1)
Pneumonia	7 (5)	5 (4)
Alanine aminotransferase increased	6 (4)	14 (10)
Aspartate aminotransferase increased	6 (4)	9 (7)
Neoplasm progression	4 (3)	4 (3)
Anemia	4 (3)	1 (1)
Blood alkaline phosphatase increased	4 (3)	1 (1)
Dyspnea	3 (2)	6 (4)
Pulmonary embolism	3 (2)	5 (4)
Diarrhea	3 (2)	4 (3)
Nausea	3 (2)	4 (3)
Hypophosphatemia	3 (2)	3 (2)
Gamma-glutamyl transferase increased	3 (2)	3 (2)
Headache	3 (2)	0
Neutropenia	2 (1)	4 (3)
Pleural effusion	2 (1)	3 (2)
Vomiting	2 (1)	3 (2)
Neutrophil count decreased	1 (1)	7 (5)
Decreased appetite	1 (1)	4 (3)
Urinary tract infection	1 (1)	3 (2)
Upper abdominal pain	1 (1)	3 (2)
Noncardiac chest pain	0	3 (2)

[a]Myalgia was reported in 14 (10%) and 11 patients (8%) in the brigatinib and crizotinib arms, respectively. Musculoskeletal pain was reported in 15 (11%) and 11 patients (8%), respectively. No grade 3 or higher myalgia or musculoskeletal pain was reported in either arm.
[b]No clinical cases of pancreatitis were reported in either arm.

baseline was consistent with previous reports (Supplementary Table 2).[5,6] The median (95% CI) intracranial DoR in patients with measurable brain metastases at baseline by BIRC assessment was 27.9 months (5.7 mo–not estimable [NE]) in the brigatinib arm and 9.2 months (3.9 mo–NE) in the crizotinib arm. In patients with any brain metastases at baseline by BIRC assessment, the 3-year intracranial PFS rate (95% CI) was 31% (17%–47%) with brigatinib and 9% (95% CI: 2%–25%) with crizotinib (HR = 0.29, 95% CI: 0.17–0.51, log-rank $p < 0.0001$), and the 4-year rate was 22% (9%–39%; two patients at risk) with brigatinib and NE (zero patients at risk) with crizotinib (Fig. 1*E*). In all patients (intention-to-treat population), the 3-year intracranial PFS was 57% (47%–66%) with brigatinib and 38% (27%–49%) with crizotinib (HR = 0.44, 95% CI: 0.30–0.65), and the 4-year rate was 46% (34%–57%; two patients at risk) and 33% (19%–47%; two patients at risk), respectively (Fig. 1*F*).

Updated Efficacy of Crossover Brigatinib Treatment. Among 65 patients who crossed over to brigatinib (47% of total crizotinib arm, 65% of patients with PD on crizotinib), the median BIRC-assessed PFS was 16.8 months (95% CI: 10.1–23.9 mo) with a median follow-up of 22.7 months (range: 0.2–37.6 mo). The BIRC-assessed confirmed ORR was 57% (95% CI: 44%–69%), with median DoR in confirmed responders (95% CI) of 19.1 months (10.9–23.5 mo).

Subsequent Anticancer Therapy. Greater proportions of patients in the crizotinib arm received subsequent anticancer treatment after discontinuation of the study drug compared with the brigatinib arm (Supplementary

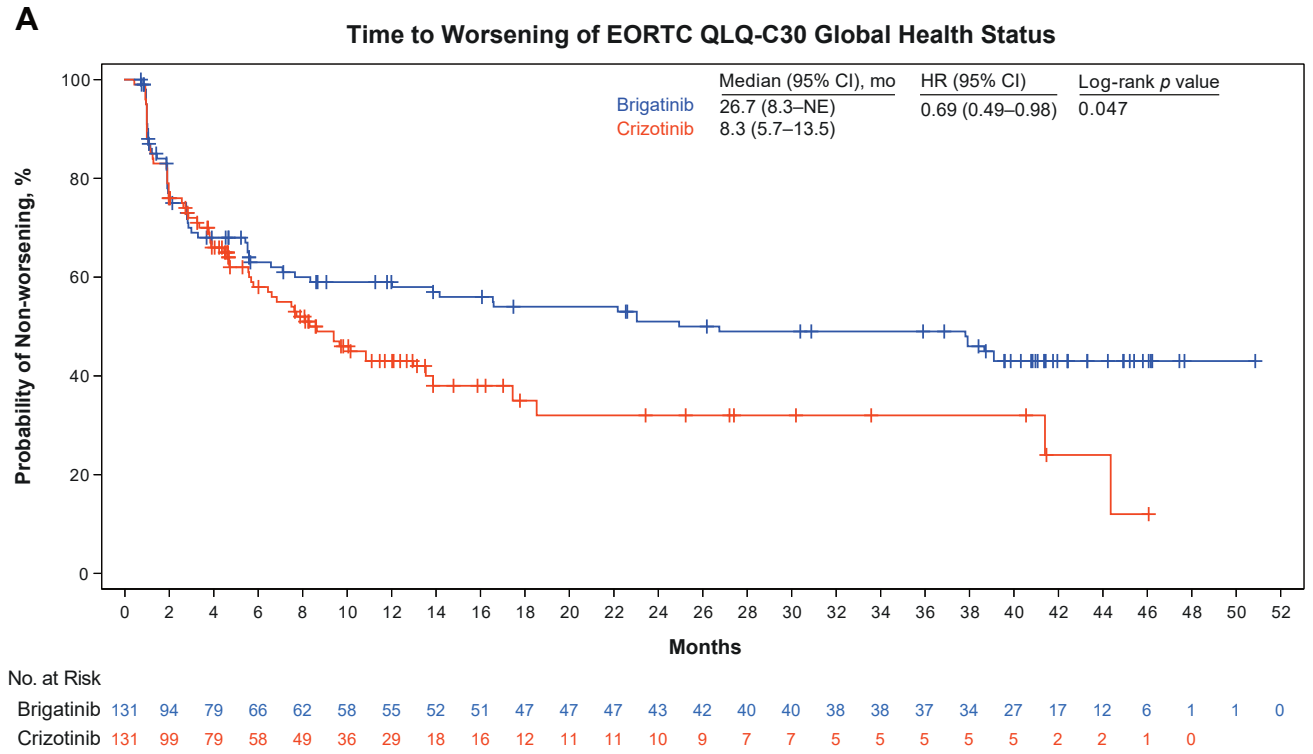

Figure 4. Time to worsening in EORTC QLQ-C30 scores among PRO-ITT population. (*A*) Kaplan-Meier plot of time to worsening (≥10-point deterioration from baseline) in EORTC QLQ-C30 GHS score. (*B*) Forest plot of HRs for time to worsening in global QoL and functioning and symptom scores in the brigatinib arm versus the crizotinib arm. CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; PRO, patient-reported outcome; QoL, quality of life.

Table 3). Among 121 patients who discontinued crizotinib before study end, 103 (85%) received subsequent anticancer treatment; 99 (82%) received subsequent ALK TKI treatment, most often brigatinib (80 [66%]) and alectinib (28 [23%]). Among 78 patients who discontinued brigatinib, 46 (59%) received subsequent systemic anticancer treatment and 42 (54%) received a subsequent ALK TKI, most often lorlatinib (22 [28%]) and alectinib (16 [21%]). For the 27 patients who discontinued brigatinib and had brain metastases at baseline, 19 (70%) received subsequent systemic treatment, most often lorlatinib (10 [37%]) and alectinib (10 [37%]). Among 39 patients who discontinued crizotinib and had brain metastases at baseline, 32 (82%) received subsequent systemic treatment, most often brigatinib (24 [62%]), alectinib (nine [23%]), and lorlatinib (nine [23%]).

Overall Survival. At study end, 92 patients had died (brigatinib, 41 [30%]; crizotinib, 51 [37%]). The KM-estimated 3-year OS rate (95% CI) was 71% (62%–78%) in the brigatinib arm and 68% (59%–75%) in the crizotinib arm without adjustment for patients who crossed over from crizotinib to brigatinib (HR = 0.81, 95% CI: 0.53–1.22, log-rank $p = 0.331$) (Fig. 2*A*). At 4 years, the KM-estimated OS (95% CI) was 66% (56%–74%; seven patients at risk) in the brigatinib arm and 60% (51%–68%; five patients at risk) in the crizotinib arm. In sensitivity analyses adjusting for treatment crossover in the crizotinib arm, the OS HR was 0.54 (95% CI: 0.31–0.92, $p = 0.023$) by the MSM method (Fig. 2*B*) and 0.50 (95% CI: 0.28–0.87, $p = 0.014$) by the inverse probability of censoring weight approach (Fig. 2*C*).

Among patients with brain metastases at baseline per investigator, 33 patients had died (brigatinib, 11 of 40 [28%]; crizotinib, 22 of 41 [54%]). The HR for death was 0.43 (95% CI: 0.21–0.89, log-rank $p = 0.020$) (Fig. 2*D*), with a 3-year KM-estimated OS rate (95% CI) of 74% (57%–85%) with brigatinib and 55% (38%–69%) with crizotinib and a 4-year rate of 71% (53%–83%; four patients at risk) and 44% (28%–59%; zero patients at risk), respectively. The survival benefit of brigatinib versus crizotinib in this subset of patients was greater in patients without previous radiotherapy to the brain (HR = 0.25, 95% CI: 0.08–0.75, log-rank $p = 0.008$) than in patients with previous radiotherapy to the brain (HR = 0.76, 95% CI: 0.27–2.12, log-rank $p = 0.637$).

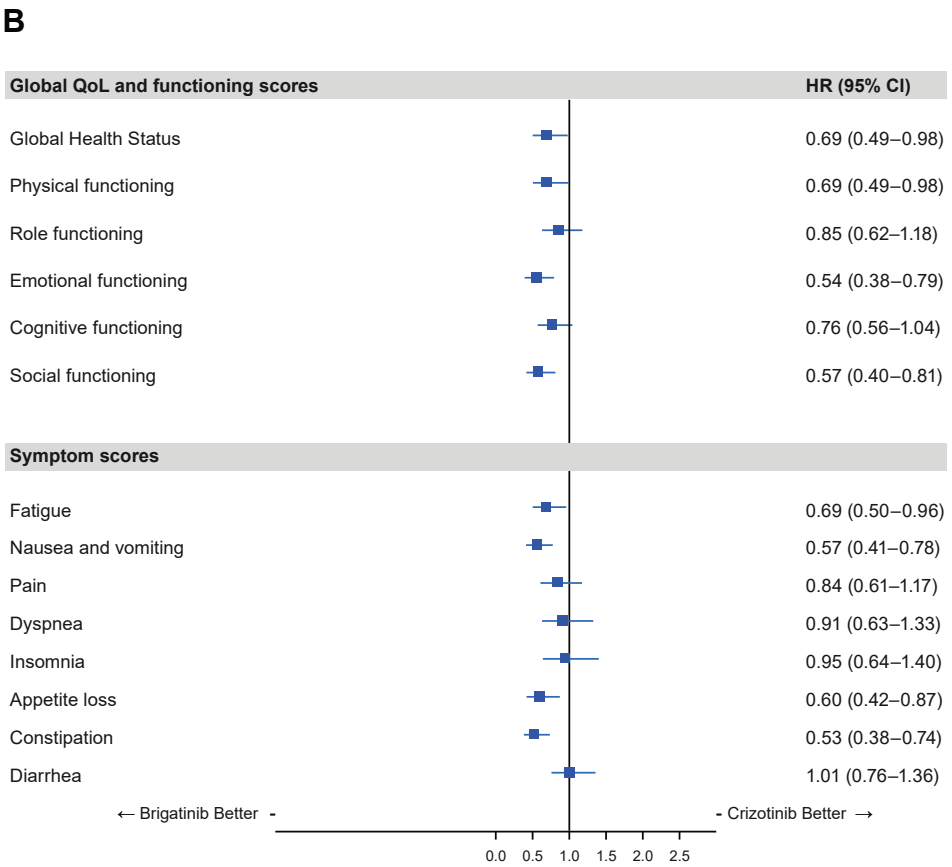

Figure 4. Continued.

Among patients without baseline brain metastases by investigator assessment (brigatinib, n = 97; crizotinib, n = 97), 59 patients had died (brigatinib, 30 [31%]; crizotinib, 29 [30%]; HR = 1.16, 95% CI: 0.69–1.93, log-rank $p = 0.603$; Fig. 2*E*), with the 3-year OS (95% CI) estimated at 70% (59%–78%) for brigatinib and 73% (62%–81%) for crizotinib and the 4-year OS estimated at 64% (52%–74%; three patients at risk) and 67% (56%–76%; four patients at risk), respectively.

Biomarker Analyses

Correlations Between Baseline ALK Fusion Variants and TP53 Mutation Status and Clinical Efficacy. Among 250 patients with baseline plasma samples for NGS analysis of circulating tumor DNA (brigatinib, n = 123; crizotinib, n = 127; Supplementary Fig. 1), *ALK* fusions were detected in 54% of patients in the brigatinib (67 of 123) and crizotinib (69 of 127) arms; *EML4-ALK* fusions were detected in 57 of 123 patients (46%) in the brigatinib arm and 64 of 127 patients (50%) in the crizotinib arm. The most common *EML4-ALK* fusions were V1 (brigatinib, 25 of 57 [44%]; crizotinib 30 of 64 [47%]) and V3 (brigatinib, 23 of 57 [40%]; crizotinib, 21 of 64 [33%]) (Table 1). Patients with *EML-ALK* fusion V3 exhibited worse PFS compared with patients with V1 or V2, regardless of the treatment group (Table 1 and Fig. 3*A*). Multivariate analysis adjusting for potential confounding effects of molecular and clinical covariates confirmed a significant independent effect of V3 versus V1 on PFS (HR [95% CI] for PD, V3 versus V1: 2.45 [1.07–5.60], brigatinib; 3.42 [1.56–7.50], crizotinib) (Fig. 3*B*). Although the OS data were immature, there was the suggestion of a trend for worse OS in patients with V3 compared with V1 (HR [95% CI] for death, V3 versus V1: 1.45 [0.54–3.91], brigatinib; 1.58 [0.65, 3.83], crizotinib) (Fig. 3*C*). Brigatinib exhibited a higher ORR and longer median PFS compared with crizotinib in all variant subgroups (Table 1).

Among patients with *EML4-ALK* fusions detected at screening, the *TP53* mutation was detected in 22 of 57 patients (39%) in the brigatinib arm and 23 of 64 patients (36%) in the crizotinib arm (Table 1). Patients with the *TP53* mutation exhibited a trend toward lower ORR and worse PFS compared with patients with wild type (WT) in both treatment arms (Table 1 and Fig. 3*D*). The *TP53* mutation maintained a strong prognostic trend toward worse PFS in the multivariate analysis (HR [95%

CI] for PD, *TP53* mutation versus WT = 1.76 [0.81–3.83], brigatinib; 1.77 [0.90–3.49], crizotinib) (Fig. 3*B*). There was also a trend for poorer OS (HR [95% CI] for death, *TP53* mutation versus WT = 2.36 [1.00–5.58], brigatinib; 1.98 [0.91–4.27], crizotinib) (Fig. 3*E*). Brigatinib exhibited superior ORR and PFS compared with crizotinib in patients with and without the *TP53* mutation (Table 1).

Emerging Mutations. Mutations detected in plasma at baseline, cycle 3, and EOT are listed in Supplementary Table 4. No clear pattern of emerging mutations was identified in patients who progressed on brigatinib. Among patients with assessable plasma samples who discontinued owing to PD, emerging non-ALK mutation types detected in at least one patient at cycle 3 or EOT were *EGFR, FGFR2, FGFR3, KEAP1, KRAS*, *MET, MYC, RICTOR*, *ROS1*, and *TP53* in the brigatinib arm and *EGFR, ERBB2, FGFR2, FGFR3, JAK2*, *KEAP1*, *MET*, *MYC*, *PIK3CA, STK11*, and *TP53* in the crizotinib arm (Supplementary Table 5). Emerging *ALK* mutations were detected at EOT in two patients in the brigatinib arm and 10 patients in the crizotinib arm (Supplementary Table 5).

Safety

The most common (>25% of patients overall) any-grade treatment-emergent AEs (TEAEs) were gastrointestinal events, increased blood creatine phosphokinase, cough, and increased aminotransferases. TEAEs reported in at least 5% of patients are listed in Supplementary Table 6. Grade 3 to 5 TEAEs were reported for 78% of patients in the brigatinib arm and 64% in the crizotinib arm (Table 2). Dose reduction owing to AEs occurred in 44% and 25% of patients in the brigatinib and crizotinib arms, respectively. AEs leading to dose reduction in at least one patient are listed in Supplementary Table 7. Treatment was interrupted owing to AEs in 72% versus 47% and discontinued owing to AEs in 13% versus 9% of treated patients in the brigatinib and crizotinib arms, respectively.

Interstitial lung disease (ILD) or pneumonitis at any time occurred in 8 of 136 patients (6%) in the brigatinib arm and 3 of 137 patients (2%) in the crizotinib arm; grade 3 or higher ILD or pneumonitis occurred in 4 of 136 (3%) and 1 of 137 (<1%) patients, respectively. Among patients who crossed over to brigatinib from crizotinib, 4 of 65 (6%) had ILD or pneumonitis (1 [2%] grade ≥3) after crossover.

Updated Health-Related QoL

The median time to worsening in GHS/QoL for brigatinib was 26.7 months, and for crizotinib was 8.3 months (HR = 0.69, 95% CI: 0.49–0.98, log-rank $p = 0.047$) (Fig. 4*A*). Compared with crizotinib, brigatinib significantly delayed the time to worsening of emotional and social functioning and symptoms of fatigue, nausea and vomiting, appetite loss, and constipation (log-rank $p < 0.05$) (Fig. 4*B*). No domain significantly favored crizotinib.

Discussion

Results of the final analysis of the ALTA-1L trial of brigatinib versus crizotinib in patients with ALK TKI–naive ALK+ NSCLC were consistent with those of the first two interim analyses,[5,6] with approximately 15 months' additional follow-up (median = 40 mo for brigatinib) since the second interim analysis. Brigatinib continued to exhibit superior BIRC-assessed PFS compared with crizotinib, with a 52% reduction in the risk of progression or death (HR = 0.48). DoR data have matured since the previous analysis, demonstrating more durable responses with brigatinib (median = 33.2 mo) than crizotinib (13.8 mo). OS data were still maturing at final analysis (30% event rate) and indicated similar OS in the two arms (HR = 0.81), although OS may be affected by the imbalance of subsequent anticancer therapies, including a high rate of crossover to brigatinib and a higher rate of receiving any subsequent anticancer therapy after discontinuing study treatment in the crizotinib arm. Sensitivity analyses of OS that adjusted for possible confounding from crossover suggested that brigatinib treatment would have been associated with improved OS (HR = 0.54 by MSM method) if treatment crossover had not been allowed in the crizotinib arm.

Brigatinib continued to exhibit compelling intracranial efficacy. The risk of intracranial progression was reduced by 56% in all patients (HR = 0.44) and by 71% in patients with any brain metastases at baseline (HR = 0.29) with brigatinib compared with crizotinib. Intracranial responses were durable, with median intracranial DoR of 27.9 months in the brigatinib arm and 9.2 months in the crizotinib arm in patients with measurable brain metastases at baseline. The HR for OS with brigatinib versus crizotinib in patients with baseline brain metastases was 0.43 (log-rank $p = 0.020$) despite the high rate of crossover in the crizotinib arm, suggesting a survival benefit in patients with brain metastases receiving brigatinib as the first ALK TKI treatment. The applicability of this finding, although limited by the small number of patients in the posthoc OS analysis, is supported by the strong intracranial response and intracranial DoR, and as such, generates interesting hypotheses for optimal drug sequencing in ALK+ NSCLC for evaluation in future studies.

Our analyses of *ALK* fusion variants in plasma revealed a predominance of *EML4-ALK* fusions V1 and V3 in the ALTA-1L population, consistent with previous

reports in ALK+ NSCLC.[9,18] The efficacy benefit (both PFS and ORR) of brigatinib versus crizotinib was consistent across patients with *EML4-ALK* fusion variants V1, V2, and V3, although the PFS was shorter in patients with V3 compared with other variants. Detection of the *EML4-ALK* fusion V3 in plasma was associated with significantly shorter PFS than V1 in multivariate analyses of the brigatinib ($p = 0.033$) and crizotinib arms ($p = 0.002$). Previous studies reported no significant difference in PFS with first-line crizotinib or alectinib in patients with V1 versus V3 detected in plasma or tumor specimens,[9,18] although one study revealed a shorter PFS in patients with V3 versus V1 (in tumor specimens) treated with lorlatinib after crizotinib.[9] That study also revealed that tumors with *EML4-ALK* V3 were more likely to develop resistance mutations, especially *ALK* G1202R.[9]

In ALTA-1L, the *TP53* mutation was detected in 37% of patients with the *EML4-ALK* fusion detected in plasma at screening. The presence of *TP53* mutations in tumor specimens has been correlated with lower response rates and shorter PFS and OS in patients with ALK+ NSCLC treated with crizotinib.[10–12] Our results revealed a trend for plasma detection of the *TP53* mutation as a prognostic biomarker of poor ORR and PFS. This trend persisted in multivariate analyses adjusting for confounding covariates, indicating that the effect of *TP53* mutations warrants further investigation in a larger population.

Resistance to ALK TKIs may develop through ALK-dependent and ALK-independent mechanisms.[19,20] Secondary acquired *ALK* resistance mutations, the primary mechanism of resistance, generate conformational changes in the ALK protein, interfering with the binding of ALK inhibitors. *ALK* resistance mutations develop more frequently with second- or next-generation ALK inhibitors compared with crizotinib.[20] Gainor et al.[20] reported *ALK* mutations in 20% of the 55 patients who progressed on crizotinib versus 54% with second-generation ALK inhibitors (n = 41) and 71% with brigatinib (n = 7). The most common mutations after progression on crizotinib and second-generation inhibitors were the *ALK* L119M gatekeeper mutation and *ALK* G1202R, respectively.[20] We detected only two emerging *ALK* mutations in plasma postprogression on brigatinib among 64 patients with EOT samples. No patient in either treatment arm developed the resistant G1202R mutation. Consistent with results from the ALTA study in patients with crizotinib-resistant NSCLC,[21] non-*ALK* emerging mutations were detected after progression on brigatinib in ALTA-1L, although with relatively less complexity and at a lower rate than observed with crizotinib. No clear patterns in ALK-dependent mechanisms of resistance to brigatinib were apparent in the first-line setting. An independent study with a larger sample size is needed.

The safety profile of brigatinib in the first-line setting was consistent with its known safety profile, with no new safety signals observed. Increases in blood creatine phosphokinase occurred frequently in patients treated with brigatinib (50%), but no cases of clinically diagnosed rhabdomyolysis were reported. Consistent with the primary clinical outcomes, brigatinib also continued to exhibit health-related QoL (HRQoL) benefits such as delaying the time to worsening in GHS/QoL and multiple other HRQoL domain scores compared with crizotinib.

In conclusion, the final results of ALTA-1L revealed efficacy and safety consistent with the two interim analyses, with longer follow-up. Brigatinib continued to exhibit superior efficacy and tolerability and better HRQoL than crizotinib. The superior efficacy of brigatinib compared with crizotinib was consistent across *EML4-ALK* fusion variants and in patients with and without the *TP53* mutation. Whereas OS data remained immature, the suggestion of a survival advantage in patients with brain metastases starting with brigatinib as the first ALK TKI generates interesting hypotheses for future study of optimal drug sequencing and supports brigatinib as a standard treatment option for treatment-naive ALK+ NSCLC.

CRediT Authorship Contribution Statement

D. Ross Camidge: Conceptualization, Investigation, Methodology, Project administration, Resources.

Hye Ryun Kim, Myung-Ju Ahn, James C. H. Yang, Ji-Youn Han, Ki Hyeong Lee, Angelo Delmonte, Dong-Wan Kim: Investigation.

Maximilian J. Hochmair: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Supervision, Visualization, Writing - original draft.

Maria Rosario Garcia Campelo: Investigation, Validation, Visualization.

Frank Griesinger: Data curation, Formal analysis, Investigation, Supervision, Validation.

Enriqueta Felip: Investigation, Validation.

Raffaele Califano: Investigation, Project administration, Validation.

Alexander I. Spira: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization.

Scott N. Gettinger: Conceptualization, Data curation, Formal analysis, Investigation.

Marcello Tiseo: Investigation, Supervision, Validation.

Huamao M. Lin: Formal analysis, Methodology.

Yuyin Liu: Data analysis.

Florin Vranceanu: Data curation, Formal analysis.

Huifeng Niu: Formal analysis, Investigation, Methodology.

Pingkuan Zhang: Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation.

Sanjay Popat: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization.

D. Ross Camidge, Hye Ryun Kim, Myung-Ju Ahn, James C. H. Yang, Ji-Youn Han, Maximilian J. Hochmair, Ki Hyeong Lee, Angelo Delmonte, Maria Rosario Garcia Campelo, Dong-Wan Kim, Frank Griesinger, Enriqueta Felip, Raffaele Califano, Alexander I. Spira, Scott N. Gettinger, Marcello Tiseo, Huamao M. Lin, Yuyin Liu, Florin Vranceanu, Huifeng Niu, Pingkuan Zhang, Sanjay Popat: Writing - review & editing.

Acknowledgments

This study was sponsored by ARIAD Pharmaceuticals, Inc., Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The authors thank the patients, their families, and their caregivers; the ALTA-1L (ALK in Lung cancer Trial of brigAtinib in the 1st Line) investigators and their team members at each study site; and colleagues from ARIAD Pharmaceuticals, Inc., a whollyowned subsidiary of Takeda Pharmaceutical Company Limited. Professional medical writing assistance was provided by Lauren Gallagher, RPh, PhD, and Lela Creutz, PhD, of Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, and funded by Millennium Pharmaceuticals, Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. The authors also thank Teodor G. Paunescu, PhD, (Millennium Pharmaceuticals) for editorial assistance.

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 the initial request to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2021.07.035.

References

1. Huang WS, Liu S, Zou D, et al. Discovery of brigatinib (AP26113), a phosphine oxide-containing, potent, orally active inhibitor of anaplastic lymphoma kinase. *J Med Chem*. 2016;59:4948–4964.
2. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res*. 2013;19:4273–4281.
3. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer*. 2009;115:1723–1733.
4. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res*. 2008;14:4275–4283.
5. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379:2027–2039.
6. Camidge R, Kim HR, Ahn M, 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*. 2020;38:3592–3603.
7. Sabir SR, Yeoh S, Jackson G, Bayliss R. EML4-ALK variants: biological and molecular properties, and the implications for patients. *Cancers (Basel)*. 2017;9:118.
8. Yoshida T, Oya Y, Tanaka K, et al. Differential crizotinib response duration among ALK fusion variants in ALK-positive non-small-cell lung cancer. *J Clin Oncol*. 2016;34:3383–3389.
9. Lin JJ, Zhu VW, Yoda S, et al. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. *J Clin Oncol*. 2018;36:1199–1206.
10. Song P, Zhang F, Li Y, et al. Concomitant TP53 mutations with response to crizotinib treatment in patients with ALK-rearranged non-small-cell lung cancer. *Cancer Med*. 2019;8:1551–1557.
11. Kron A, Alidousty C, Scheffler M, et al. Impact of TP53 mutation status on systemic treatment outcome in ALK-rearranged non-small-cell lung cancer. *Ann Oncol*. 2018;29:2068–2075.
12. Wang WX, Xu CW, Chen YP, et al. TP53 mutations predict for poor survival in ALK rearrangement lung adenocarcinoma patients treated with crizotinib. *J Thorac Dis*. 2018;10:2991–2998.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria In Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
14. Aaronson NK, Ahmedzai S, Bergman B, 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*. 1993;85:365–376.
15. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. 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 Quality of Life. *Eur J Cancer*. 1994;30A:635–642.

16. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168:656–664.
17. Fewell Z, Hernan MA, Wolfe F, Tilling K, Choi H, Sterne JAC. Controlling for time-dependent confounding using marginal structural models. *Stata J*. 2004;4:402–420.
18. Camidge DR, Dziadziuszko R, Peters S, et al. Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX study. *J Thorac Oncol*. 2019;14:1233–1243.
19. McCoach CE, Le AT, Gowan K, et al. Resistance mechanisms to targeted therapies in ROS1^{+} and ALK^{+} non-small cell lung cancer. *Clin Cancer Res*. 2018;24:3334–3347.
20. Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov*. 2016;6:1118–1133.
21. Bazhenova L, Hodgson JG, Langer CJ, et al. Activity of brigatinib (BRG) in crizotinib (CRZ)-resistant ALK+ NSCLC patients (pts) according to ALK plasma mutation status. *J Clin Oncol*. 2017;35(suppl 15): 9065–9065.