ORIGINAL ARTICLE

Efficacy of Brigatinib in Patients With Advanced *ALK*-Positive NSCLC Who Progressed on Alectinib or Ceritinib: ALK in Lung Cancer Trial of brigAtinib-2 (ALTA-2)

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ABSTRACT

Introduction: Brigatinib is a potent next-generation ALK tyrosine kinase inhibitor approved for treatment-naive and crizotinib-refractory advanced *ALK*-positive (*ALK*+) NSCLC. We evaluated brigatinib after other next-generation ALK tyrosine kinase inhibitors.

Methods: In this single-arm, phase 2, ALK in Lung Cancer Trial of brigAtinib-2 (NCT03535740), patients with advanced *ALK*+ NSCLC whose disease progressed on alectinib or ceritinib received brigatinib 180 mg once daily (after 7-d 90-mg lead-in). Primary end point was independent review committee (IRC)-assessed overall response rate (ORR). Circulating tumor DNA (ctDNA) was analyzed.

Results: Among 103 patients (data cutoff: September 30, 2020; median follow-up [range]: 10.8 [0.5–17.7] mo), confirmed IRC-ORR was 26.2% (95% confidence interval [CI]: 18.0–35.8), median duration of response, 6.3 months (95% CI: 5.6–not reached), and median progression-free survival (mPFS), 3.8 months (95% CI: 3.5–5.8). mPFS was 1.9 months (95% CI: 1.8–3.7) in patients with ctDNA-detectable baseline *ALK* fusion (n = 64). Among 86 patients who progressed on alectinib, IRC-ORR was 29.1% (95% CI: 19.8–39.9); mPFS was 3.8 months (95% CI: 1.9–5.4). Resistance mutations were present in 33.3% (26 of 78) of baseline ctDNA; 54% (14 of 26) of mutations were G1202R; 52% (33 of 64) of patients with detectable *ALK* fusion had *EML4-ALK* variant 3. Most common all-grade treatment-related adverse events were increased creatine phosphokinase (32%) and diarrhea (27%). The mean dose intensity of brigatinib (180 mg once daily) was 85.9%.

Conclusions: In ALK in Lung Cancer Trial of brigAtinib-2, brigatinib was found to have a limited activity in patients with *ALK*+ NSCLC post-ceritinib or post-alectinib therapy. mPFS was longer with brigatinib in patients without baseline detectable plasma *ALK* fusion.

Keywords: Non–small cell lung cancer; Anaplastic lymphoma kinase; Tumor biomarker; Circulating tumor DNA

Introduction

Brigatinib is a potent, oral, second-generation ALK tyrosine kinase inhibitor (TKI). Brigatinib was found to have a significant improvement in median progression-free survival (mPFS) compared with crizotinib as a first-line ALK TKI therapy for *ALK*-positive (*ALK*+) NSCLC in the phase 3 **A**LK in **L**ung Cancer **T**rial of brig**A**tinib in **1**st **L**ine[1,2] (ALTA-1L; hazard ratio = 0.48, 95% confidence interval [CI]: 0.35–0.66, mPFS by blinded independent review committee [IRC]: 24.0 versus 11.1 mo, $p < 0.0001$).[3] Brigatinib is also active in crizotinib-refractory *ALK*+ NSCLC, with an overall response rate (ORR) of 56%, mPFS of 16.7 months, and overall survival (OS) of 40.6 months.[4,5] Brigatinib is approved in multiple countries and regions for these two indications.

Preclinically, brigatinib inhibits a wide spectrum of *ALK*-acquired resistance mutations that confer resistance to next-generation ALK TKIs such as ceritinib and alectinib. In vitro, brigatinib was found to have equal or better inhibition for 17 *ALK* mutations versus crizotinib (except L1198F), ceritinib, and alectinib at the average plasma concentrations achieved with brigatinib 180 mg once daily.[6] We conducted a multinational phase 2 trial (**A**LK in **L**ung Cancer **T**rial of brig**A**tinib-**2** [ALTA-2]) to investigate the clinical efficacy of brigatinib immediately post-ceritinib or post-alectinib in patients with advanced *ALK*+ NSCLC.

Materials and Methods

Study Design and Patients

ALTA-2 is a prospective, multicenter, phase 2 trial (ClinicalTrials.gov identifier: NCT03535740) conducted at 54 centers in 15 countries or regions. Eligible patients (age ≥18 y) had advanced cytologically or histologically confirmed (stage IIIB/IV by American Joint Committee on Cancer, seventh edition) *ALK*+ NSCLC. *ALK* rearrangement was determined by a U.S. Food and Drug Administration (FDA)-approved test (Vysis ALK Break-Apart FISH Probe Kit; Ventana ALK [D5F3] CDx Assay; or FoundationOne CDx). *ALK* rearrangement detected by any other test required central laboratory confirmation (next-generation sequencing; Resolution Bio, Highland Heights, KY; Zaventem, Belgium; Singapore; and Shanghai, People's Republic of China); central confirmation was not required before starting brigatinib treatment. Patients had to have progressive disease (PD) while on treatment (occurring within 1 mo of last dose) per investigator assessment after previous treatment with alectinib, ceritinib, or crizotinib for at least 12 weeks, with either alectinib or ceritinib as the most recent ALK TKI therapy. Patients were ineligible if they had previous treatment with ALK TKIs other than crizotinib, alectinib, or ceritinib. Patients could not have received both alectinib and ceritinib. Other eligibility criteria included Eastern Cooperative Oncology Group performance status score of 0 to 1, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1, adequate organ and hematologic function, and up to three different previous systemic anticancer regimens. Patients with uncontrolled, symptomatic central nervous system metastases were excluded; patients with asymptomatic brain metastases or who had stable symptoms that did not require an increased dose of corticosteroids could be enrolled. The study protocol and amendments were approved by appropriate institutional review boards or ethics committees. The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation E6 Guideline for Good Clinical Practice, and applicable local regulations. All patients provided written informed consent. See Supplementary Data 1 for the study protocol.

Treatment

Enrolled patients received the approved brigatinib dose of 180 mg once daily after an initial 7-day lead-in period at 90 mg once daily. On radiological progression, at investigator discretion, patients receiving brigatinib 180 mg once daily who had not experienced any grade greater than 2 toxicities during treatment were allowed to escalate to 240 mg once daily or continue treatment at current dose if still benefiting from brigatinib.

Assessments

Disease was assessed by computed tomography or magnetic resonance imaging (imaging of chest, abdomen, and brain) at screening and every 8 weeks thereafter (day 28 [±7 d] of every even-numbered cycle) through 14 cycles after the initial dose of brigatinib and every 12 weeks (three cycles) thereafter until radiological disease progression. Complete responses (CRs) and partial responses (PRs) had to be confirmed at least 4 weeks after the initial response was observed. A central blinded IRC evaluated all images collected during the study. Contrast-enhanced magnetic resonance imaging of the brain was required at screening and at post-baseline assessments for all patients (unless contraindicated).

Patients who continued brigatinib at 240 mg once daily beyond documented PD continued disease assessments on the same schedule. The disease assessment at the time of documented progression served as the new baseline for dose escalation of brigatinib to 240 mg once daily.

Health-related quality-of-life (HRQoL) assessments (European Organisation for Research and Treatment of Cancer [EORTC] Quality-of-Life Questionnaire Core 30 [QLQ-C30], Lung Cancer module [QLQ-LC13]) were performed at screening, on day 1 of every treatment cycle, at end of treatment, and 30 days after the last brigatinib dose.

Next-generation DNA sequencing of circulating tumor DNA in plasma. Plasma was collected for centralized characterization of circulating tumor DNA (ctDNA) by next-generation sequencing (NGS) and to determine mutation status of *ALK* and other frequently altered oncogenic driver genes in NSCLC at baseline and end of treatment. The mutation status of *ALK* and other relevant genes was determined by sequencing- or polymerase chain reaction-based analyses of tumor tissue collected at screening and at development of progressive disease and of blood samples collected at screening, on cycle 3 day 1, cycle 5 day 1, and at development of progressive disease.

NGS was performed at Resolution Bioscience (Kirkland, WA) using its proprietary Resolution Bio Liquid ctDx Lung NGS Panel. Per Chinese regulations, samples collected from mainland China were analyzed locally using the AmoyDx Essential NGS Panel (Amoy DX, Xiamen, People's Republic of China), which only detects *ALK* and *EGFR* mutations.

End Points

The primary end point was confirmed ORR per Response Evaluation Criteria in Solid Tumors version 1.1 per IRC. Secondary end points included safety, tolerability, duration of response (DOR) per IRC, progression-free survival (PFS) per IRC, and OS with brigatinib treatment overall and in the subgroup of patients with brain metastases. Additional secondary objectives were to assess patient-reported symptoms and HRQoL using the EORTC QLQ-C30 and QLQ-LC13. Confirmed ORR was determined in prespecified subgroups. Exploratory end points included characterization of molecular determinants of clinical outcomes.

Statistical Analysis

Approximately 103 patients were to be enrolled to test whether the true ORR (expected response rate) differed from a 20% response rate (null hypothesis) for patients previously treated with alectinib or ceritinib. This sample size provided at least 90% power to rule out the null hypothesis, assuming the true ORR was 35%. The calculation was based on an exact binomial test with a total one-sided alpha level of 0.025 at primary analysis, allowing for dropout. Detailed statistical methods are in the study protocol in the Supplementary Appendix (online only).

All patients who received at least one brigatinib dose were included in the full analysis set. Exact two-sided 95% binomial CIs were calculated for IRC-confirmed ORR. For time-to-event end points (DOR, PFS, OS), median values and associated two-sided 95% CIs were estimated using the Kaplan-Meier method. All statistical analyses were performed using SAS Statistical Software (Cary, NC) version 9.4 or higher.

Results

Patients

From February 2019 to December 2019, a total of 123 patients were screened; 103 patients were enrolled and treated. Patient demographic and baseline characteristics are found in Table 1. *ALK* rearrangement in tumors was determined using an FDA-approved test in

Table 1. Demographic and Baseline Characteristics

Characteristic	Brigatinib N = 103
Median age, y (range)	56.0 (22-80)
Female, n (%)	52 (51)
Race, n (%)	
Asian	49 (48)
Non-Asian	54 (52)
ECOG performance status, n (%)	
0	43 (42)
1	60 (58)
2	0
Disease stage at study entry	
IIIB	1 (1)
IV	102 (99)
Median time from initial diagnosis to study entry, mo (range)	24.2 (4.2-95.3)
Highest previous anticancer therapy line, n (%)	
1	35 (34)
2	41 (40)
3	27 (26)
Previous alectinib, n (%)	86 (84)
First-line previous alectinib, n	35
Second-line previous alectinib, n	51
Median time on alectinib, mo (range)	11.6 (2.4-58.9)
Median time on alectinib as first-line previous TKI (range)	11.0 (2.8-58.7)
Median time on alectinib as second-line + previous TKI (range)	11.6 (2.4-58.9)
Previous ceritinib, n (%)	17 (17)
First-line previous ceritinib, n	0
Second-line previous ceritinib, n	10
Third-line previous ceritinib, n	7
Median time on ceritinib, mo (range)	8.0 (1.6-78.2)
Previous crizotinib, n (%)	57 (55)
Median time on crizotinib, mo (range)	10.0 (0.3-86.9)
Previous chemotherapy and alectinib, n (%)	23 (22)
Previous chemotherapy and ceritinib, n (%)	13 (13)

ECOG, Eastern Cooperative Oncology Group.

86 patients (83.5%). Of the remaining 17 patients, 11 provided sufficient tumor samples tested in central laboratory, of whom nine were confirmed *ALK*+. There were 86 patients (83.5%) who received alectinib previously (median duration: 11.6 [range: 2.4–58.9] mo), including 42 patients (40.8%) treated with alectinib as their only previous TKI (median duration: 11.3 [range: 2.8–58.7] mo). Furthermore, 36 patients (35.0%) had received chemotherapy previously.

At data cutoff (September 30, 2020), 26 patients (25.2%) continued to receive brigatinib treatment, including 16 patients receiving study treatment at regular dosing beyond progression and four patients receiving the 240-mg dose. The median time from initial diagnosis of locally advanced or metastatic disease to study entry was 24.5 months. Median (range) follow-up for all 103 patients was 10.8 (0.5–17.7) months.

Treatment Exposure

Median duration of brigatinib treatment was 4.6 (range: 0.03–16.8) months. The mean (SD) relative dose intensities were 85.9% (18.5) in patients receiving brigatinib 90 to 180 mg once daily (n = 103) and 96.4% (9.9) in patients (n = 13) dose escalated to 240 mg once daily.

Efficacy

IRC-assessed confirmed ORR for the intent-to-treat population was 26.2% (27 of 103) (95% CI: 18.0–35.8). Eight patients were not assessable for response (only one postbaseline scan assessment as CR or PR or stable disease within 6 wk from first dose date). Decreases in the sum of target lesion measurements were observed in 65 patients (63%; Fig. 1*A*). Median DOR was 6.3 months (95% CI: 5.6–not reached) (Fig. 1*B*). Median time to response was 1.8 (range: 1.5–5.4) months. Kaplan-Meier estimates for 6- and 12-month PFS rates were 39.4% (95% CI: 28.9–49.7) and 22.3% (95% CI: 13.3–32.7), respectively. IRC-assessed disease control rate (DCR, confirmed response + stable disease) was 54.4% (56 of 103; 95% CI: 44.3–64.2). Median IRC-assessed PFS was 3.8 months (95% CI: 3.5–5.8) in the overall intent-to-treat population (Fig. 1*C*).

Among 86 patients previously treated with alectinib, IRC-assessed ORR was 29.1% (25 of 86; 95% CI: 19.8–39.9). Median IRC-assessed DOR was 5.9 months (95% CI: 3.8–not reached). Median time to response was 1.8 (range: 1.5–3.8) months. Decreases in the sum of target lesion measurements occurred in 55 patients (64%). DCR was 54.7% (47 of 86; 95% CI: 43.5–65.4). mPFS for patients previously treated with alectinib (n = 86) was 3.8 months (95% CI: 1.9–5.4). In patients previously treated with ceritinib (n = 17), confirmed IRC-assessed ORR was 11.8% (95% CI: 1.5–36.4). Among patients who had *ALK* rearrangement detected by an FDA-approved test (n = 86; not the same 86 patients treated with alectinib), the confirmed IRC-assessed ORR was 30.2% (95% CI: 20.8–41.1). Confirmed responses by various subgroups are found in Figure 2.

Intracranial efficacy. Among 55 patients with any baseline brain metastases, intracranial ORR was 15% (eight of 55; 95% CI: 6.5–26.7); seven of eight responses were CRs (Supplementary Data 2). Median IRC-assessed intracranial PFS (iPFS) was 5.2 months (95% CI: 3.5–7.4) at an event rate of 56.4%. Furthermore, 19 patients had measurable brain metastases, of whom one had PR, and the median iPFS was 3.8 months (95% CI: 1.8–10.9).

Efficacy in patients with and without detectable ALK alterations in plasma ctDNA at baseline. Among 100 patients with baseline plasma samples, ctDNA was detected at baseline in 78 patients (78.0%). *ALK* fusions were detected in 64 of 100 (64.0%) of these baseline samples, among which 26 of 64 (40.6%) harbored *ALK* secondary mutations.

Previous TKI treatment and availability of baseline and end-of-treatment samples from all 103 patients are included in Supplementary Data 3. At baseline, *EML4-ALK* fusions represented most of the *ALK* fusions, which included variant 1 (V1; n = 18 [30.0%]), V2 (n = 3 [5.0%]), V3 (n = 33 [55.0%]), V5 (n = 3 [5.0%]), V5' (n = 2 [3.3%]), and undetermined (n = 1 [1.7%]). Proportions of patients with *ALK* fusion and *EML4-ALK* fusion at baseline are shown in Figure 3A. Distribution of *EML4-ALK* fusions is shown by previous alectinib or ceritinib therapy in Figures 3B and 3C, respectively. G1202R mutations were detected at baseline in 14 patients, nine of whom had *ALK* fusion V3. In patients with previous alectinib treatment, baseline secondary *ALK* mutations were detected in 25 (29.8%) of 84 patients, of whom 12 (48.0%; 12 of 25) also had G1202R and eight (32.0%; eight of 25) had V3.

Efficacy by baseline biomarker status is found in Supplementary Data 4. Among 100 patients with baseline plasma samples, the confirmed ORR was 26.0% (95% CI: 17.7–35.7), with mPFS of 5.1 months (95% CI: 3.5–7.2). ORR was lower and mPFS shorter in patients with ctDNA present at baseline (n = 78) compared with those without detectable ctDNA at baseline (n = 22); IRC-assessed ORR was 20.5% versus 45.5% and mPFS was 3.5 months versus 11.0 months. Patients with detectable ctDNA at baseline tended to have a larger sum of target lesion diameters compared with patients without detectable ctDNA (Supplementary Data 5). In 64 patients with detectable baseline *ALK* fusions, IRC-assessed ORR was

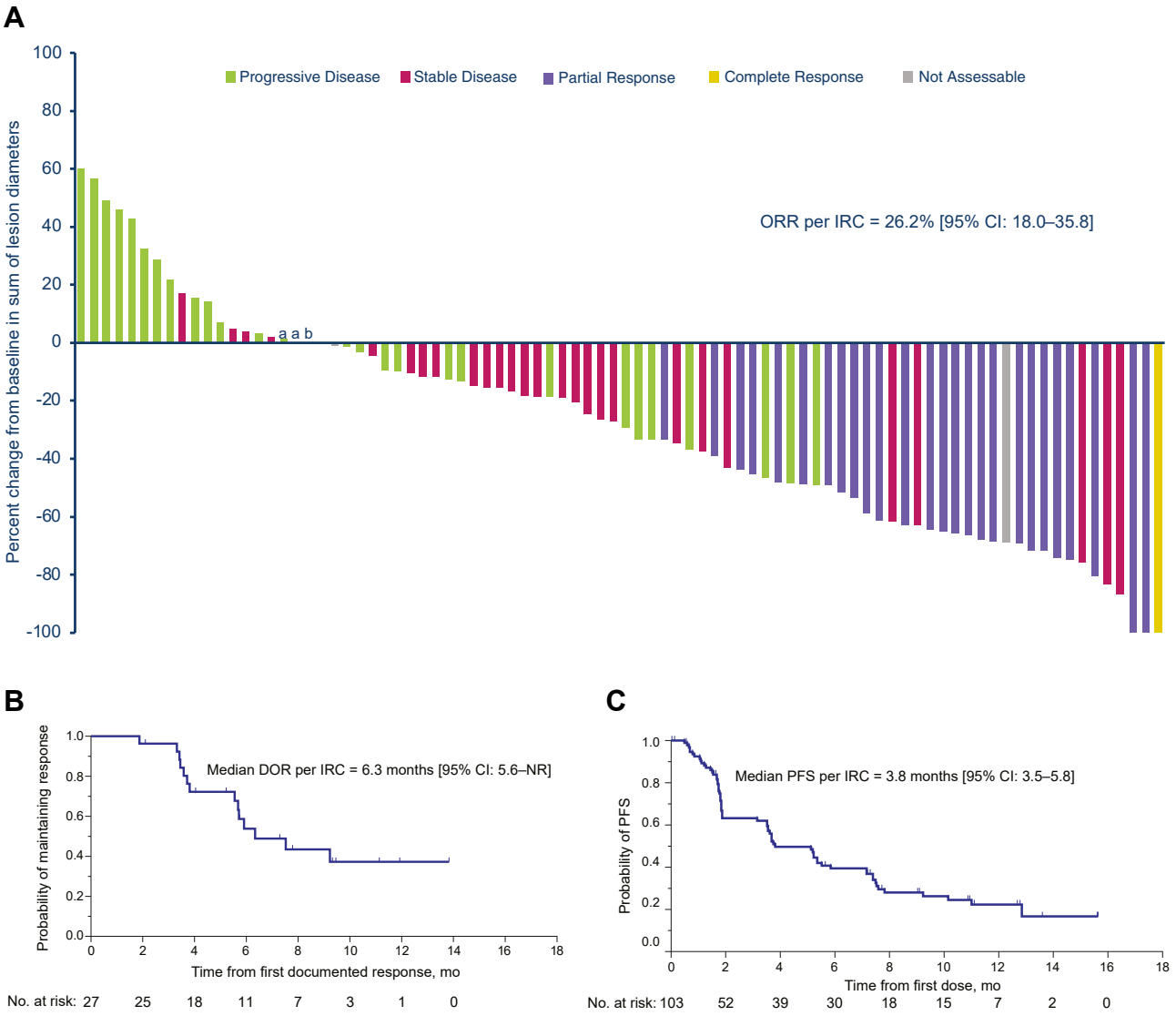

Figure 1. Efficacy results in overall population (N = 103) of patients with *ALK*+ NSCLC enrolled in ALTA-2. (*A*) Waterfall plot of IRC-assessed best percentage change from baseline in target lesions by best overall confirmed response. (*B*) DOR in total population per IRC. (*C*) PFS in total population per IRC. [a]Stable disease. [b]Not assessable. *ALK*+, *ALK*-positive; CI, confidence interval; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

20.3% (95% CI: 11.3–32.2) and mPFS was 1.9 months (95% CI: 1.8–3.7). In patients who received alectinib previously and in whom *EML4-ALK* fusion status was known at baseline, those with V3 (n = 30) had higher ORR (23% versus 7%) but not longer mPFS (1.9 versus 3.5 mo) than those with V1 (n = 15; Supplementary Data 6 and Supplementary Data 7). Among 14 patients with the G1202R mutation detected by plasma genotyping, the IRC-assessed ORR was 14.3% (95% CI: 1.8–42.8) and mPFS was 1.8 months (95% CI: 1.1–not available); among patients with only non-G1202R mutations (n = 14), the ORR was 35.7% (95% CI: 12.8–64.9) and mPFS was 3.7 (1.7–not available) months. Outcomes in patients with secondary *ALK* mutations at baseline are summarized in Supplementary Data 8. Among 25 post-alectinib patients with secondary *ALK* mutations at baseline, seven (28%) had PR with brigatinib.

Of 40 patients who had PD and both a screening and an end-of-treatment plasma sample analyzed, 22 (55.0%) had an emerging mutation, 19 of whom (86.4%) also had ALK fusions. No pattern of common emerging mutations could be identified. Non-*ALK* mutations, such as *KRAS*, *TP53*, *MET* amplification, *ERBB2* amplification, and *KEAP1*, were observed. Acquired compound mutations were identified in more than half of the patients (Supplementary Data 9A and 9B), including seven of the 13 patients who escalated to brigatinib 240 mg after PD. A full listing of patient-level mutation data is provided in Supplementary Data 10.

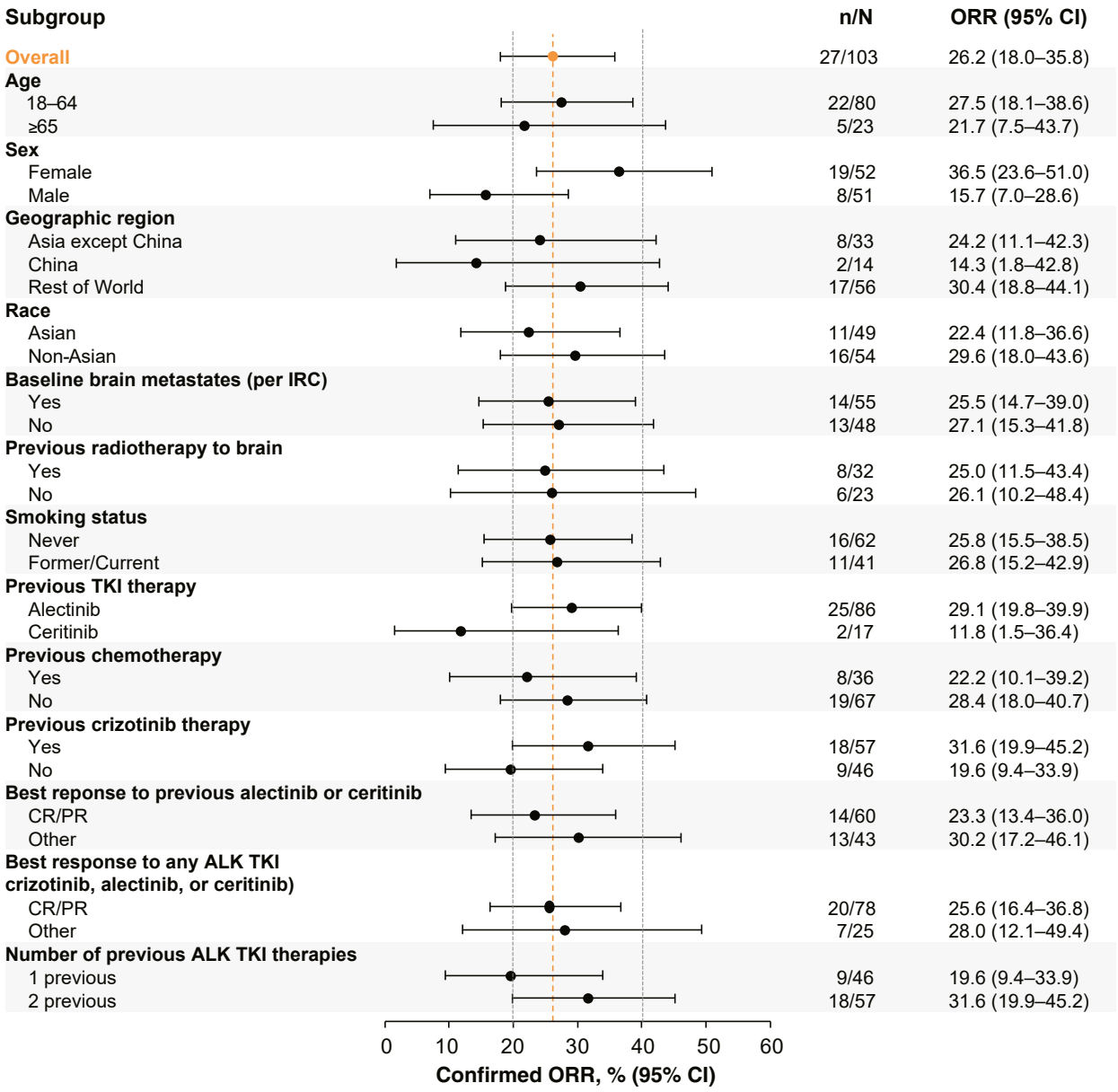

Figure 2. Best confirmed objective response in prespecified subgroups (per IRC). Dotted line indicates ORR observed in the overall population (N = 103). CI, confidence interval; CR, complete response; IRC, independent review committee; ORR, objective response rate; PR, partial response; TKI, tyrosine kinase inhibitor.

Postprogression 240 mg daily cohort. Among 13 patients who escalated to 240 mg once daily after PD, there was no IRC-assessed confirmed response; the DCR was 30.8% (95% CI: 9.1–61.4). Median IRC-assessed PFS was 1.9 months (95% CI: 0.9–3.6) in the study population who escalated to 240 mg once daily.

Safety

Treatment-emergent adverse events and treatment-related adverse events (TRAEs) observed in more than or equal to 10% of patients by system organ class are found in Table 2. At the brigatinib 180-mg once daily dose, the most common TRAEs were increased creatine phosphokinase (32.0%), diarrhea (27.2%), and nausea (19.4%). The most common TRAEs leading to dose modifications (treatment interruption or dose reductions) were increased creatine phosphokinase (13%), amylase increased (11%), and hypertension (11%). Fourteen (14%) patients experienced treatment-emergent adverse events that led to discontinuation of brigatinib (pneumonia, cerebral hemorrhage, pneumonitis, and dyspnea in two patients each; and cardiac arrest, abdominal sepsis, meningitis, malignant lung neoplasm, epilepsy, spinal cord compression, pulmonary

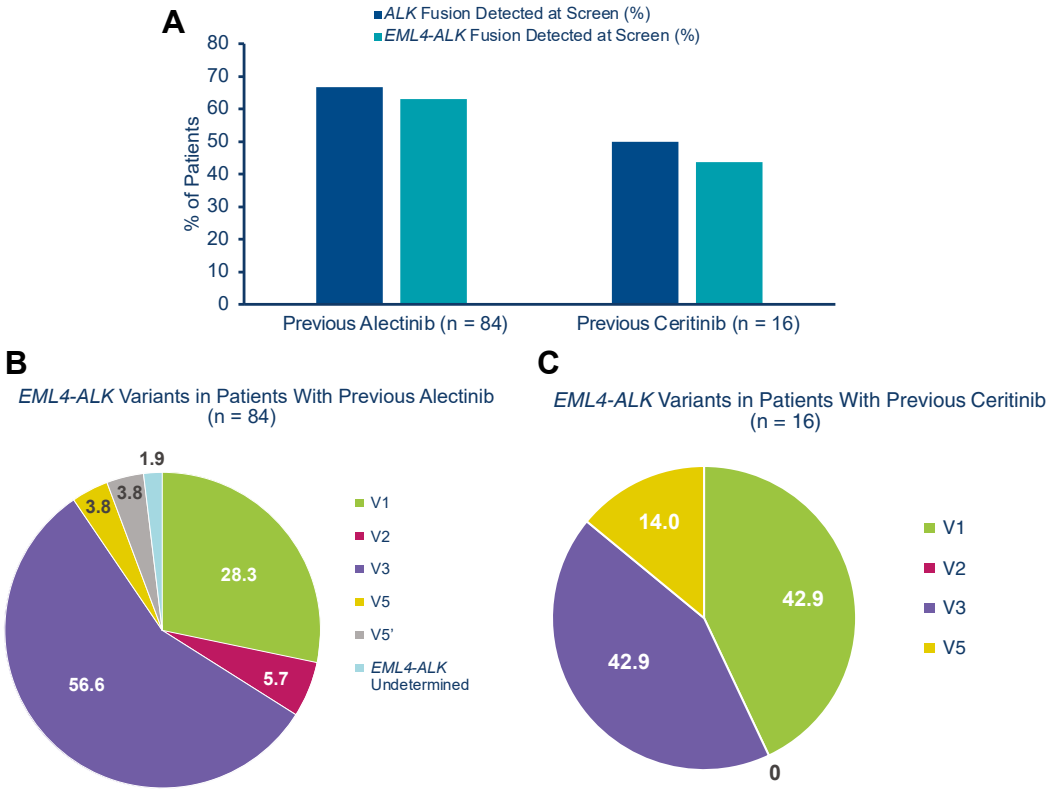

Figure 3. (*A*) *ALK* fusion and *EML4* fusion detected at baseline in patients receiving previous alectinib (n = 84) or previous ceritinib (n = 16) and *EML4* fusion variants in patients receiving previous (*B*) alectinib or (*C*) ceritinib. V1, variant 1; V2, variant 2; V3, variant 3; V5, variant 5.

edema, and hypertension in one patient each). Three patients discontinued brigatinib owing to TRAEs, one with pneumonitis, one with pulmonary edema, and one with pneumonitis and pneumonia. Among the 13 patients who received brigatinib 240 mg once daily, the most common TRAEs were diarrhea (39%), increased creatine phosphokinase (31%), and asthenia (15%).

Health-related Quality-of-Life

EORTC QLQ-C30 global health status/quality-of-life (QoL) was maintained from baseline throughout the treatment phase (Supplementary Data 11). Core symptoms of QLQ-LC13 lung cancer (cough, dyspnea, pain in chest) were maintained or improved compared with baseline throughout the treatment (Supplementary Data 12A [dyspnea], 12B [cough], and 12C [chest pain]). Other functioning subscales, including physical, role, emotional cognitive, and social functioning scores, were generally maintained during the treatment. In addition, 51 of 93 assessable patients (54.8%) had clinically meaningful improvement (≥10-point increase) in global health/QoL for at least one cycle. A total of 60 of 93 patients (64.5%) had at least one cycle with improved (≥10-point decrease) lung cancer symptoms (cough, dyspnea, pain in chest).

Discussion

The primary end point of ALTA-2 did not rule out the null hypothesis, given that the lower limit of the 95% CI of the IRC-assessed ORR achieved with brigatinib was below 20% (18%); however, our results provided an important signal for further exploration. Brigatinib did have modest clinical activity in patients with *ALK*+ NSCLC after immediate disease progression on ceritinib or alectinib, with an IRC-assessed ORR of 26.2%, median DOR of 6.3 months, and mPFS of 3.8 months. Among patients from a phase 2 study of lorlatinib who had received treatment with at least one second-generation TKI (n = 139), the ORR was 40% (95% CI: 32–49), median DOR was 7.1 months (95% CI: 5.6–24.4), and mPFS was 6.9 months (95% CI: 5.4–8.2)[7]; ORR was 40% in patients whose last previous TKI was alectinib (n = 62) or ceritinib (n = 47).[8] Nevertheless, comparing the efficacy between brigatinib and lorlatinib in patients whose disease progressed on alectinib or ceritinib is challenging without a direct randomized study. The observed differences in ORR and PFS may be affected by the baseline disease characteristics, baseline molecular features, or previous treatment history of the selected population. Clinical studies have revealed that brigatinib has a different toxicity profile than lorlatinib.[9] In the safety population of that phase 2

Table 2. AE Overview and Treatment-emergent and Treatment-related AEs With Brigatinib 180 mg Once Daily and 240 mg Once Daily

	Brigatinib 180 mg Once Daily (N = 103)		Brigatinib 240 mg Once Daily (n = 13)	
AE	Treatment-emergent	Treatment-related	Treatment-emergent	Treatment-related
Any grade	103 (100)	84 (82)	10 (77)	10 (77)
Grade 3 or 4	71 (69)	36 (35)	4 (31)	1 (8)
Serious adverse events	47 (46)	7 (7)	2 (15)	0
Adverse events leading to treatment interruption	44 (43)	28 (27)	1 (8)	1 (8)
Adverse events leading to treatment reduction	13 (13)	13 (13)	0	0
Adverse events leading to discontinuation	14 (14)	3 (3)	0	0
Serious adverse events leading to death	15 (15)	1 (1)	0	0
	Treatment-emergent AEs in ≥ 10% of Patients[a] (N = 103)	Treatment-related AEs in ≥ 10% of Patients[a] (N = 103)	Treatment-emergent AEs in ≥ 10% of Patients[a] (n = 13)	Treatment-related AEs in ≥ 10% of Patients[a] (n = 13)
Diarrhea	40 (39)	28 (27)	6 (46)	5 (39)
Blood creatine phosphokinase increased	35 (34)	33 (32)	4 (31)	4 (31)
Nausea	29 (28)	20 (19)	-	-
Cough	24 (23)	-	3 (23)	-
Aspartate aminotransferase increased	21 (20)	17 (17)	-	-
Hypertension	20 (19)	11 (11)	2 (15)	-
Alanine aminotransferase increased	18 (18)	14 (14)	-	-
Lipase increased	18 (18)	18 (18)	-	-
Vomiting	18 (18)	9 (9)	-	-
Amylase increased	15 (15)	13 (13)	-	-
Dyspnea	15 (15)	-	-	-
Pain in extremity	13 (13)	-	-	-
Pneumonia	11 (11)	-	-	-
Pyrexia	13 (13)	-	-	-
Weight decreased	13 (13)	-	-	-
Asthenia	12 (12)	7 (7)	3 (23)	2 (15)
Back pain	12 (12)	-	-	-
Decreased appetite	12 (12)	-	-	-

AE, adverse event.
[a]By system organ class.

study (N = 275), TRAEs observed with lorlatinib included hypercholesterolemia (81%), hypertriglyceridemia (60%), edema (43%), and peripheral neuropathy (30%).[9] In the current study, the most common TRAEs observed with brigatinib were increased creatine phosphokinase (32%), diarrhea (27%), and nausea (19%).

A similar study (**J**apan-**A**LK in **L**ung Cancer **T**rial of brig**A**tinib [J-ALTA]) was conducted in Japanese patients with advanced *ALK*+ NSCLC.[10] Among the alectinib-refractory population in J-ALTA (n = 47), IRC-assessed confirmed ORR with brigatinib was 34% (95% CI: 21%–49%), with median DOR of 11.8 months (95% CI: 5.5–16.4). DCR was 79% (95% CI: 64%–89%). Median IRC-assessed PFS was 7.3 months (95% CI: 3.7–9.3). The numerically better DOR and PFS results achieved in J-ALTA may reflect the alectinib dose, which is 300 mg twice daily in Japan, half the dose of alectinib globally approved ex-Japan and used in the current study. The exposure to alectinib in the Japanese population is similar at 300 mg twice daily to higher doses in a U.S. population.[11] It is also notable that the previous alectinib duration of treatment in ALTA-2 was substantially shorter than that in J-ALTA (11.3 mo and 19.9 mo, respectively; [data on file, Takeda]), which suggests that the alectinib pretreated patients enrolled in ALTA-2 may be enriched in those with poor prognosis by uncontrollable factors. Limited data from the alectinib-refractory Japanese patients with *ALK*+ NSCLC also revealed that G1202R was

the most common secondary mutation, similar to the findings in other patient populations.[12]

Brigatinib was found to have limited intracranial activity in this ALK TKI-refractory patient population. Among patients with any baseline brain metastases (n = 55), intracranial ORR was 15%, with seven CRs and iPFS of 5.2 months. Among 19 patients with measurable brain metastases, one patient had a PR and the median iPFS was 3.8 months. In the pivotal lorlatinib phase 2 study among patients who received previous non-crizotinib ALK TKI therapy without chemotherapy (n = 28) and who had at least one measurable central nervous system lesion (n = 9), confirmed intracranial response was observed in 56% of patients (five of nine), with 11% (one of nine) achieving CR.[9] Mean dose intensity of brigatinib in the present study was 85.9%, suggesting good tolerability and patient compliance with therapy. Furthermore, patients maintained HRQoL on global health status/QoL assessments and other functional and symptom domains.

The current study also revealed that detectable *ALK* fusions at baseline were associated with lower response rate and shorter mPFS with brigatinib treatment. Detectability of *ALK* fusions in ctDNA likely was associated with higher tumor burden. Not surprisingly, our study population is enriched with patients with *EML4-ALK* V3 as V3 is more resistant to all ALK TKIs,[13–15] and these patients likely harbor the solvent-front mutation G1202R.[14,15] Indeed in this study, the *ALK* G1202R mutation was enriched in patients with *EML4-ALK* fusion V3 (nine of 14 patients). Clinical activity was reported for brigatinib in patients with baseline G1202R mutation (n = 14) with an ORR of 14.3% and mPFS of 1.8 months; the activity was lower than that reported for lorlatinib (ORR 57% in 28 patients; mPFS of 8.2 mo).[7] Emerging compound mutations, such as the emergence of G1202R and *TP53* or STK11 V390M, or *ALK-QPCT* and *KRAS* G12V, or non-*ALK* aberrations, were identified in more than half of the patients at disease progression. Some of these patients with double *ALK*-related mutations may benefit from fourth-generation "double mutant active" ALK TKIs.[16] There was little clinical activity in patients who progressed on the regular dose of brigatinib and were escalated to 240 mg once daily.

Study limitations include a lack of centrally confirmed results of *ALK* testing and co-molecular alternation status before study enrollment. Baseline plasma samples were not available from all patients, and end-of-treatment plasma samples at disease progression were available from a small number of patients.

In conclusion, ALTA-2 found limited clinical activity in patients with advanced *ALK*+ NSCLC who have progressed on alectinib or ceritinib. Brigatinib is a first-line treatment option for patients with advanced *ALK*+ NSCLC based on ALTA-1L[1,2] and is an option post-crizotinib, with a mPFS of 16.7 months on the basis of ALTA.[4,5] Given that brigatinib, similar to other second- or third-generation ALK TKIs, has the best efficacy when used as first-line therapy, the question of sequential use of ALK TKIs to maximize patient survival remains to be addressed with more robust clinical and translational evidence.

CRediT Authorship Contribution Statement

Sai-Hong I. Ou: Conceptualization; Data curation; Formal analysis; Investigation; Validation; Visualization; Roles/Writing—original draft; Writing—review and editing.

Makoto Nishio: Conceptualization; Data curation; Formal analysis; Investigation; Writing—review and editing.

Myung-Ju Ahn: Supervision; Data curation; Formal analysis; Investigation; Writing—review and editing.

Tony Mok: Conceptualization; Data curation; Formal analysis; Investigation; Writing—review and editing.

Fabrice Barlesi: Investigation; Validation; Writing—review and editing.

Caicun Zhou: Data curation; Investigation; Project administration; Supervision; Writing—review and editing.

Enriqueta Felip: Investigation; Writing—review and editing.

Filippo de Marinis: Investigation; Writing—review and editing.

Sang-We Kim: Investigation; Writing—review and editing.

Maurice Pérol: Data curation; Investigation; Validation; Writing—review and editing.

Geoffrey Liu: Investigation; Resources; Writing—review and editing.

Maria Rita Migliorino: Investigation; Validation; Visualization; Writing—review and editing.

Dong-Wan Kim: Investigation; Resources; Writing—review and editing.

Silvia Novello: Investigation; Supervision; Validation; Writing—review and editing.

Alessandra Bearz: Investigation; Writing—review and editing.

Pilar Garrido: Investigation; Project administration; Writing—review and editing.

Julien Mazieres: Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing—review and editing.

Alessandro Morabito: Investigation; Project administration; Writing—review and editing.

Huamao M. Lin: Conceptualization; Formal analysis; Roles/Writing—original draft; Writing—review and editing.

Hui Yang: Data curation; Formal analysis; Writing—review and editing.

Huifeng Niu: Data curation; Formal analysis; Methodology; Writing—review and editing.

Pingkuan Zhang: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing—review and editing.

Edward S. Kim: Conceptualization; Data curation; Formal analysis; Investigation; Writing—review and editing.

Data Sharing Statement

The data sets, redacted statistical analysis plan, and individual participant data supporting the results reported in this article will be made available within 3 months from 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.

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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.2022.08.018.

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