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ABSTRACT

Introduction: Brigatinib is a potent next-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) approved for treatment-naive and crizotinib-refractory advanced *ALK*+ non–small cell lung cancer (NSCLC). We evaluated brigatinib following other next-generation ALK TKIs.

Methods: In this single-arm, phase 2, ALTA-2 trial (NCT03535740), patients with advanced *ALK*+ NSCLC whose disease progressed on alectinib or ceritinib received brigatinib 180 mg once daily (QD; after 7-day 90-mg lead-in). Primary endpoint 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 months [0.5–17.7]), confirmed IRC-ORR was 26.2% (95% CI: 18.0–35.8), median duration of response, 6.3 months (95% CI: 5.6–not reached [NR]), 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% (26/78) of baseline ctDNA; 14/26 (54%) mutations were G1202R; 52% (33/64) 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 QD) was 85.9%.

Conclusion: In ALTA-2, brigatinib demonstrated limited activity in patients with *ALK*+ NSCLC post-ceritinib or post-alectinib therapy. Median PFS was longer with brigatinib in patients without baseline detectable plasma *ALK* fusion.

Trial registration: https://clinicaltrials.gov/ct2/show/NCT03535740

Key words: non–small cell lung cancer, anaplastic lymphoma kinase, tumor biomarker, circulating tumor DNA

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; *ALK*, anaplastic lymphoma kinase gene; *ALK*+, anaplastic lymphoma kinase positive; BIRC, blinded independent review committee; BL, baseline; CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EML4, echinoderm microtubule-associated protein-like 4; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; FDA, US Food and Drug Administration; HR, hazard ratio; HRQoL, health-related quality of life; iPFS, intracranial progression-free survival; IRC, independent review committee; ITT, intent-to-treat; LS, least squares; mPFS, median progression-free survival; n, no; NA, not available; ND, not determined; NE, not evaluable; NGS, next-generation sequencing; NR, not reached; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, every day; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-LC13, Quality of Life Questionnaire–Lung Cancer

module; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor; *TP53*, tumor protein p53 gene; TRAE, treatment-related adverse event; v, variant; WT, wild type; y, yes

INTRODUCTION

Brigatinib is a potent, oral second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI). Brigatinib demonstrated significant improvement in median progression-free survival (mPFS) over crizotinib as first-line ALK-TKI therapy for *ALK*+ non–small cell lung cancer (NSCLC) in the phase III ALTA-1L trial[1, 2] (hazard ratio: 0.48, 95% CI: 0.35–0.66; mPFS by blinded independent review committee (BIRC): 24.0 vs 11.1 months; *P*<.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 demonstrated 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 (QD).[6] We conducted a multinational phase II trial (ALTA-2) to investigate the clinical efficacy of brigatinib immediately post-ceritinib or post-alectinib in patients with advanced *ALK*+ NSCLC.

METHODS

Study Design and Patients

ALTA-2 is a prospective, multicenter, phase II trial (ClinicalTrials.gov identifier: NCT03535740) conducted at 54 centers in 15 countries/regions. Eligible patients (age ≥ 18 years) had advanced cytologically or histologically confirmed (stage IIIB/IV by

American Joint Committee on Cancer, 7th edition) *ALK*+ NSCLC. *ALK* rearrangement was determined by a US 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, USA; Zaventem, Belgium; Singapore; and Shanghai, China); central confirmation was not required before starting brigatinib treatment. Patients had to have progressive disease (PD) while on treatment (occurring within one month of last dose) per investigator assessment following prior 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 prior 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 0–1, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, adequate organ and hematologic function, and up to three different prior systemic anticancer regimens. Patients with uncontrolled, symptomatic central nervous system metastases were excluded; patients with asymptomatic brain metastasis 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 **Supplemental Data 1** for the study protocol.

Treatment

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

Assessments

Disease was assessed by computed tomography or magnetic resonance imaging (MRI; imaging of chest, abdomen, and brain) at screening and every eight weeks thereafter (Day 28 [±seven days] 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 four weeks after the initial response was observed. A central BIRC evaluated all images collected during the study. Contrast-enhanced MRI of the brain was required at screening and at post-baseline assessments for all patients (unless contraindicated).

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

Health-related quality-of-life (HRQoL) assessments (European Organization 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 anaplastic lymphoma kinase (*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, USA) 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, China), which only detects *ALK* and *EGFR* mutations.

Endpoints

The primary endpoint was confirmed ORR per RECIST v.1.1 per IRC. Secondary endpoints included safety, tolerability, duration of response (DOR) per IRC, 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 endpoints 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 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 endpoints (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, USA) v 9.4 or higher.

RESULTS

Patients

From February 2019 to December 2019, 123 patients were screened; 103 patients were enrolled and treated. Patient demographic and baseline characteristics are shown in **Table 1**. *ALK* rearrangement in tumors was determined using an FDA-approved test in 86 (83.5%) patients. Of the remaining 17 patients, 11 provided sufficient tumor samples tested in central laboratory, of whom 9 were confirmed *ALK* positive. Eighty-six patients (83.5%) received prior alectinib (median duration: 11.6 months [range 2.4–58.9]), including 42 (40.8%) patients treated with alectinib as their first TKI (median duration: 11.3 months [range: 2.8–58.7]). Thirty-six (35.0%) patients had received prior chemotherapy.

At data cutoff (September 30, 2020), 26 (25.2%) patients 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 months (0.5–17.7).

Treatment Exposure

Median duration of brigatinib treatment was 4.6 months (range: 0.03–16.8). The mean (standard deviation) relative dose intensities were 85.9% (18.5) in patients receiving brigatinib 90–180 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% (27/103) (95% CI: 18.0–35.8). Eight patients were not evaluable for response (only one postbaseline scan assessment as CR or PR or stable disease [SD] within 6 weeks from first dose date). Decreases in the sum of target lesion measurements were observed in 65 patients (63%; **Figure 1A**). Median DOR was 6.3 months (95% CI: 5.6–not reached [NR]) (**Figure 1B**). Median time to response was 1.8 months (range: 1.5–5.4). Kaplan-Meier estimates for 6- and 12-month PFS rates were 39.4% (95% CI: 28.9–49.7) and 22.3% (13.3–32.7), respectively. IRC-assessed disease control rate (DCR, confirmed ORR + SD) was 54.4% (56/103; 95% CI: 44.3–64.2). Median IRC-assessed PFS was 3.8 months (95% CI: 3.5–5.8) in the overall ITT population (**Figure 1C**).

Among 86 patients previously treated with alectinib, IRC-assessed ORR was 29.1% (25/86; 95% CI: 19.8–39.9). Median IRC-assessed DOR was 5.9 months (95% CI: 3.8–NR). Median time to response was 1.8 months (range: 1.5–3.8). Decreases in the sum of target lesion measurements occurred in 55 patients (64%). DCR was 54.7% (47/86; 95% CI: 43.5–65.4). Median PFS 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 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 shown in **Figure 2**.

Intracranial efficacy

Among 55 patients with any baseline brain metastases, intracranial ORR was 15% (8/55; 95% CI: 6.5–26.7); 7/8 responses were CRs (**Table, Supplemental 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%. Nineteen 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 64/100 (64.0%) of these baseline samples, among which 26/64 (40.6%) harbored ALK secondary mutations.

Prior TKI treatment and availability of baseline and end-of-treatment samples from all 103 patients are included in **Figure, Supplemental Data 3**. At baseline, echinoderm microtubule-associated protein-like 4 *(EML4)-ALK* fusions represented the majority of *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%]). Distribution of *ALK* fusions is shown by prior alectinib or ceritinib therapy in **Figure 3**. G1202R mutations were detected at baseline in 14 patients, nine of whom had *ALK* fusion V3. In patients with prior alectinib treatment, baseline secondary *ALK* mutations were detected in 25 (29.8%) of 84 patients, of whom 12 (48.0%; 12/25) also had G1202R and eight (32.0%; 8/25) had V3.

Efficacy by baseline biomarker status is shown in **Table, Supplemental 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=64) compared with those without detectable ctDNA at baseline (n=36); IRC-assessed ORR was 20.5% vs 45.5%, mPFS 3.5 months vs 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 (**Figure, Supplemental Data 5**). In 64 patients with detectable baseline *ALK* fusions, IRC-assessed ORR was 20.3% (95% CI: 11.3–32.2) and mPFS was 1.9 months (95% CI: 1.8–3.7). In patients who received prior alectinib and in whom EML4-ALK fusion status was known at baseline, those with V3 (n=30) had higher ORR (23% vs 7%) but not longer mPFS (1.9 vs 3.5 months) than those with V1 (n=15; **Table, Supplemental Data 6** and **Figure, Supplemental 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 months (1.7–not available). Outcomes in patients with secondary *ALK* mutations at baseline are summarized in **Table, Supplemental 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 an end-of-treatment plasma sample analyzed, 22 (55%) had an emerging mutation, of whom *ALK* fusions remained in the majority (77.2%). 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 over half of patients (**Figure, Supplemental Data 9**), including 7 of the 13 patients who escalated to brigatinib 240 mg after PD. A full listing of patient-level mutation data is provided in **Table, Supplemental Data 10**.

Post-progression 240 mg daily cohort

Among 13 patients who escalated to 240 mg QD 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 QD.

Safety

Treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) observed in ≥10% of patients by system organ class are shown in **Table 2**. At the brigatinib 180-mg QD 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 TEAEs that led to discontinuation of brigatinib (pneumonia, cerebral hemorrhage, pneumonitis, dyspnea in two patients each; and cardiac arrest, abdominal sepsis, meningitis, malignant lung neoplasm, epilepsy, spinal cord compression, pulmonary edema, and hypertension in one patient

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

Health-Related Quality of Life

EORTC-QLQ 30 global health status/QoL was maintained from baseline throughout the treatment phase (**Figure, Supplemental Data 11**). Core symptoms of QLQ-LC13 lung cancer (cough, dyspnea, pain in chest) were maintained or improved compared with baseline throughout treatment (**Figure, Supplemental Data 12)**. Other functioning subscales, including physical, role, emotional cognitive, and social functioning scores, were generally maintained during treatment. In addition, 51 of 93 evaluable patients (54.8%) had clinically meaningful improvement (≥10-point increase) in global health/QoL for at least one cycle. A total of 60/93 patients (64.5%) had at least one cycle with improved (≥10-point decrease) lung cancer symptoms (cough, dyspnea, pain in chest).

DISCUSSION

The primary endpoint of the ALTA-2 trial did not rule out the null hypothesis, given that the lower limit of the 95% CI of the IRC-ORR achieved with brigatinib was below 20% (18%); however, our results provided an important signal for further exploration. Brigatinib did demonstrate modest clinical activity in patients with *ALK*+ NSCLC following 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 median PFS was 6.9 months (95% CI: 5.4–8.2)[7]; ORR was 40% in patients whose last prior TKI was alectinib (n=62) or ceritinib (n=47).[8] However, 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 impacted by the baseline disease characteristics, baseline molecular features, or prior treatment history of the selected population. Clinical studies have shown that brigatinib has a different toxicity profile than lorlatinib.[9] In the safety population of that phase 2 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-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 US population.[11] It is also notable that the prior alectinib duration of treatment in ALTA-2 was substantially shorter than in J-ALTA study (11.3 months and 19.9 months, respectively; [data on file, Takeda]), which suggests the alectinib pre-treated patients enrolled in ALTA-2 study may be enriched to those with poor prognosis by uncontrollable factors. Limited data from the alectinib-refractory Japanese patients with *ALK*+ NSCLC also showed that G1202R was the most common secondary mutation, similar to the findings in other patient populations.[12]

Brigatinib demonstrated limited intracranial activity in this ALK TKI-refractory patient population. Among patients with any baseline brain metastases (n=55), intracranial ORR was 15%, with 7 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 prior non-crizotinib ALK TKI therapy without chemotherapy (n=28) and who had at least one measurable CNS lesion (n=9), confirmed intracranial response was observed in 56% (5/9) of patients, with 11% (1/9) achieving complete response.[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 demonstrated 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 EML4-ALK V3 patients 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 (9/14 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; median PFS of 8.2 months).[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 over half of patients at disease progression. Some of these patients with double ALK-related mutations may benefit from 4th-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 QD.

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 demonstrated 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 an option post-crizotinib, with a median PFS of 16.7 months based on ALTA.[4, 5] Given that brigatinib, like 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.

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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 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.

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Table 1. Demographic and Baseline Characteristics

	Brigatinib **N = 103**
Median age, years (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 to initial diagnosis to study entry, mo (range)	24.2 (4.2–95.3)
Highest prior anticancer therapy line, n (%)	
1	35 (34)
2	41 (40)
3	27 (26)
Prior alectinib, n (%)	86 (84)
First-line prior alectinib, n	35

Second-line prior alectinib, n	51
Median time on alectinib, mo (range)	11.6 (2.4–58.9)
Median time on alectinib as first-line prior TKI (range)	11.0 (2.8–58.7)
Median time on alectinib as second-line+ prior TKI (range)	11.6 (2.4–58.9)
Prior ceritinib, n (%)	17 (17)
First-line prior ceritinib, n	0
Second-line prior ceritinib, n	10
Third-line prior ceritinib, n	7
Median time on ceritinib, mo (range)	8.0 (1.6–78.2)
Prior crizotinib, n (%)	57 (55)
Median time on crizotinib, mo (range)	10.0 (0.3–86.9)
Prior chemotherapy and alectinib, n (%)	23 (22)
Prior chemotherapy and ceritinib, n (%)	13 (13)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Adverse Event Overview and Treatment-Emergent and Treatment-Related Adverse Events With Brigatinib 180 mg QD and 240 mg QD

	Brigatinib 180 mg QD (N=103)		**Brigatinib 240 mg QD (N=13)**	
Adverse Event	**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)	-	-	-

[a]By system organ class.

Abbreviation: AE, adverse event; QD, once daily.

FIGURE LEGENDS

Fig 1. Efficacy results in overall population (N=103) of *ALK*+ NSCLC patients enrolled in the ALTA-2 trial. (A) Waterfall plot of IRC-assessed best percentage change from baseline in target lesions by best overall confirmed response. (B) Duration of response in total population per IRC. (C) Progression-free survival in total population per IRC.
Abbreviations: *ALK*+, anaplastic lymphoma kinase positive; DOR, duration of response; IRC, independent review committee; ORR, objective response rate; NR, not reached; NSCLC, non–small cell lung cancer; PFS, progression-free survival.

Fig 2. Best confirmed objective response in prespecified subgroups (per independent review committee).
Dotted line indicates ORR observed in the overall population (N=103).
Abbreviations: ALK, anaplastic lymphoma kinase; CR, complete response; IRC, independent review committee; ORR, objective response rate; PR, partial response; TKI, tyrosine kinase inhibitor.

Fig 3. *ALK* fusion and *EML-4* fusion detected at baseline in patients receiving prior alectinib (n=84) or prior ceritinib (n=16) (A) and *EML-4* fusion variants in patients receiving prior alectinib (B) or ceritinib (C)
Abbreviations: ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4.

SUPPLEMENTAL DATA.

Supplemental Data 1. Study Protocol

Supplemental Data 2. IRC-assessed ORR in Patients with Brain Metastases

Supplemental Data 3. Plasma sample availability for ctDNA analysis

Supplemental Data 4. Efficacy by Baseline Biomarkers

Supplemental Data 5. Association of baseline ctDNA shedding with sum of target lesion diameters

Supplemental Data 6. Impact of *EML4-ALK* Fusions on Clinical Outcomes Post Alectinib Treatment

Supplemental Data 7. Progression-free survival by prior treatment in patients with V1 and V3 *ALK* fusions versus those with no *ALK* fusion

Supplemental Data 8. Outcomes in Patients With Secondary *ALK* Mutations at Baseline

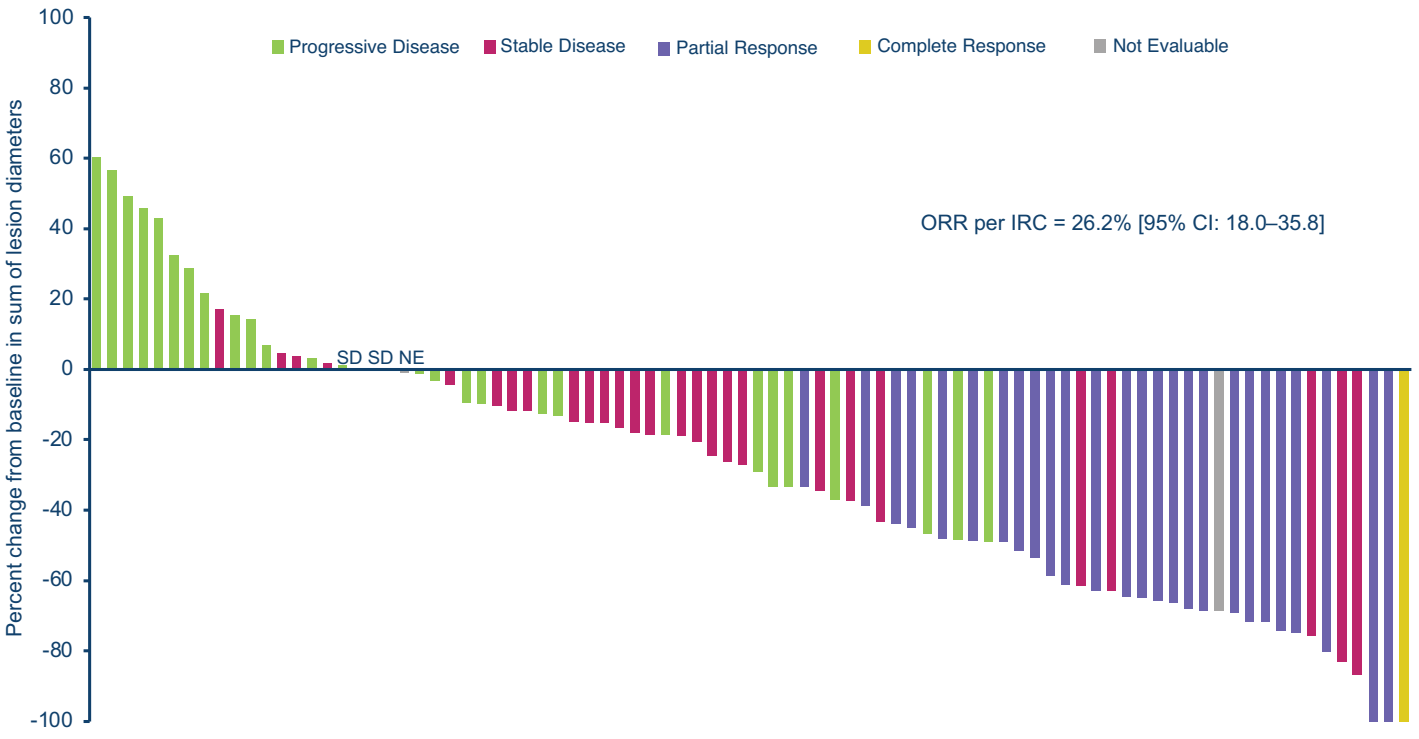
Supplemental Data 9. Emerging mutations and response among patients (excluding patients enrolled in China) with prior alectinib therapy (A) and prior ceritinib therapy (B)

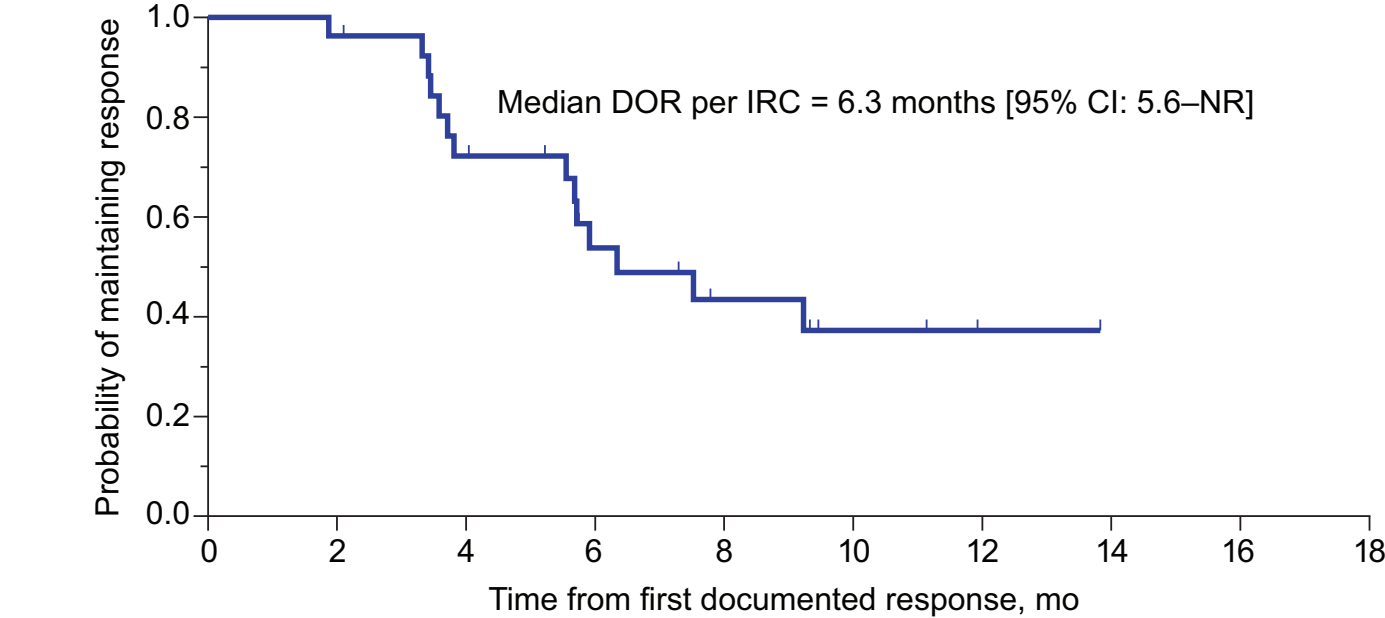
Supplemental Data 10. Patient-Level Mutation Data

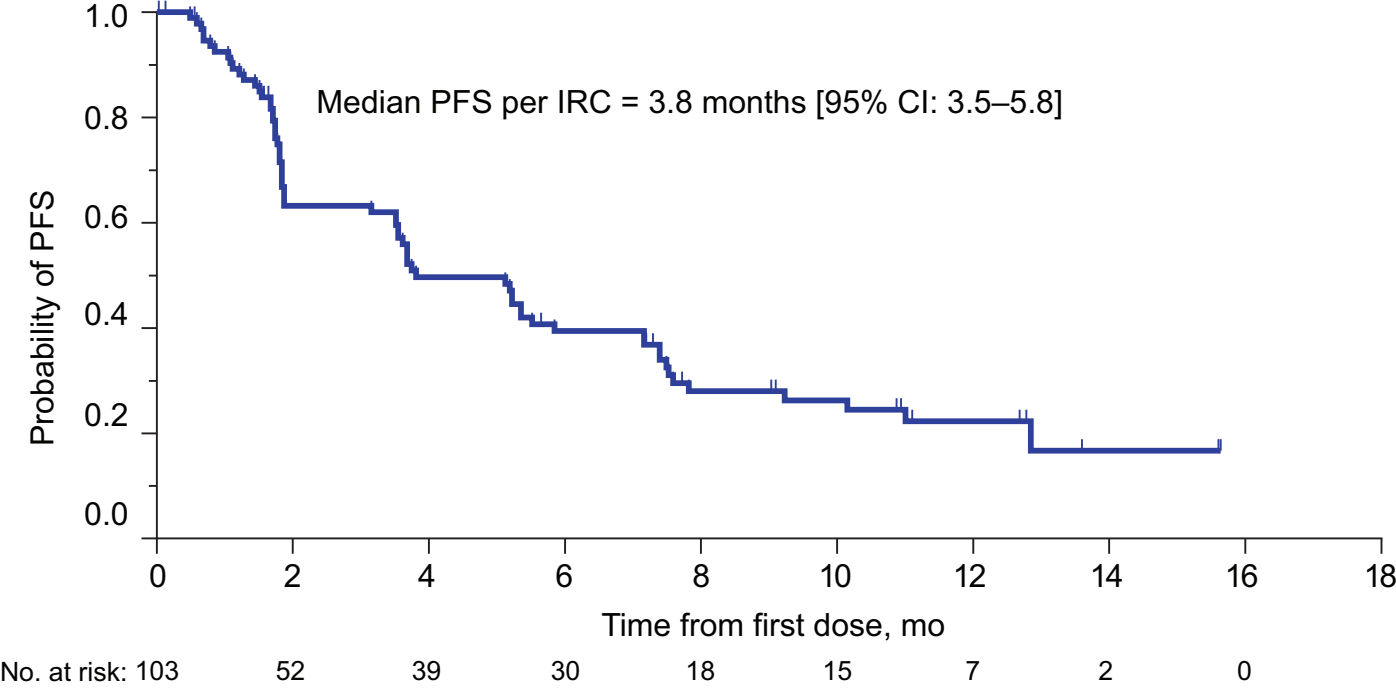
Supplemental Data 11. Least squared mean (95% confidence interval) change from baseline in EORTC-QLQ C30 global health status/QoL over time

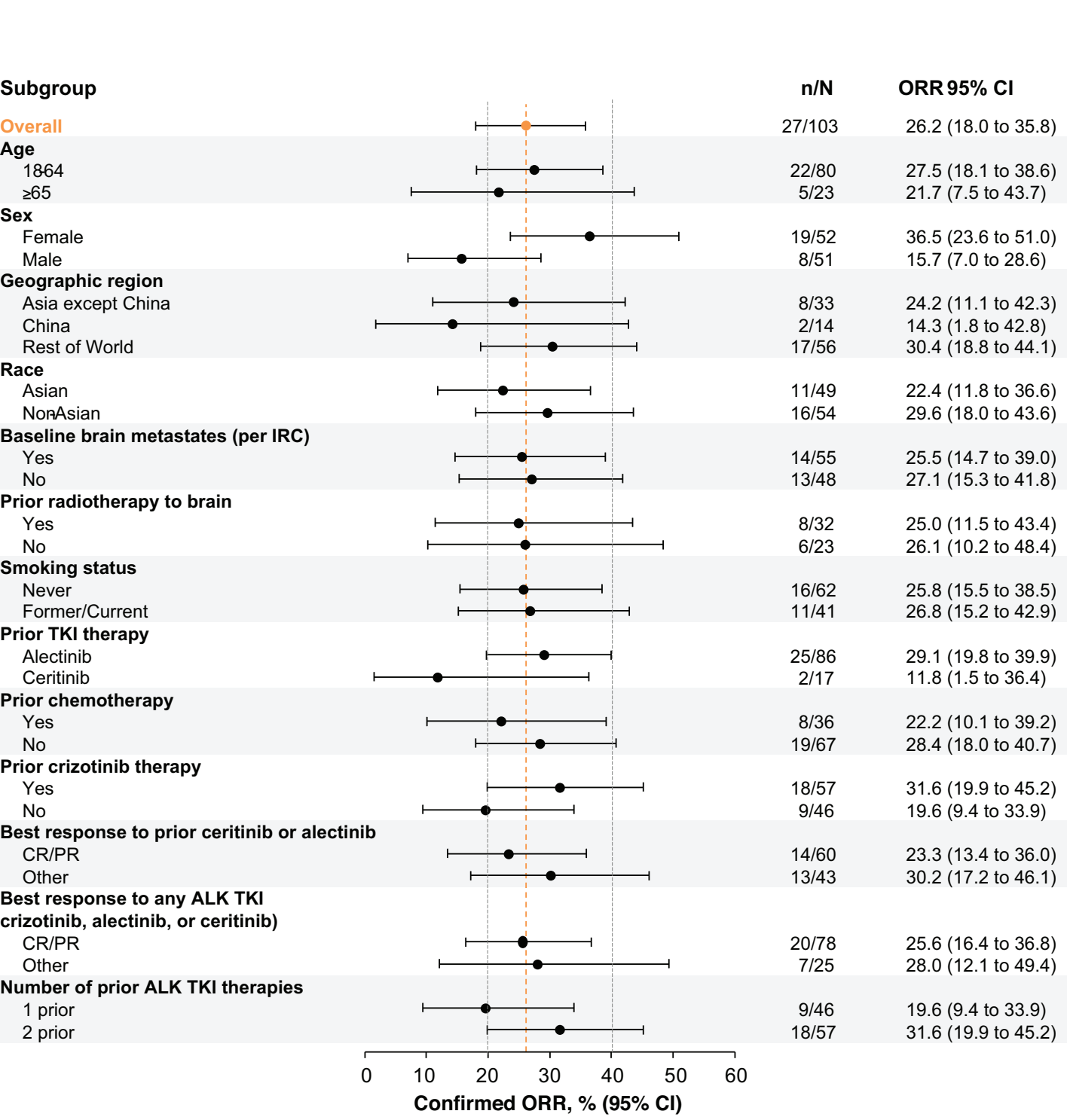
Supplemental Data 12. Least squared mean (95% confidence interval) change from baseline in QLQ-LC13 scores for dyspnea (A), cough (B), and chest pain (C)

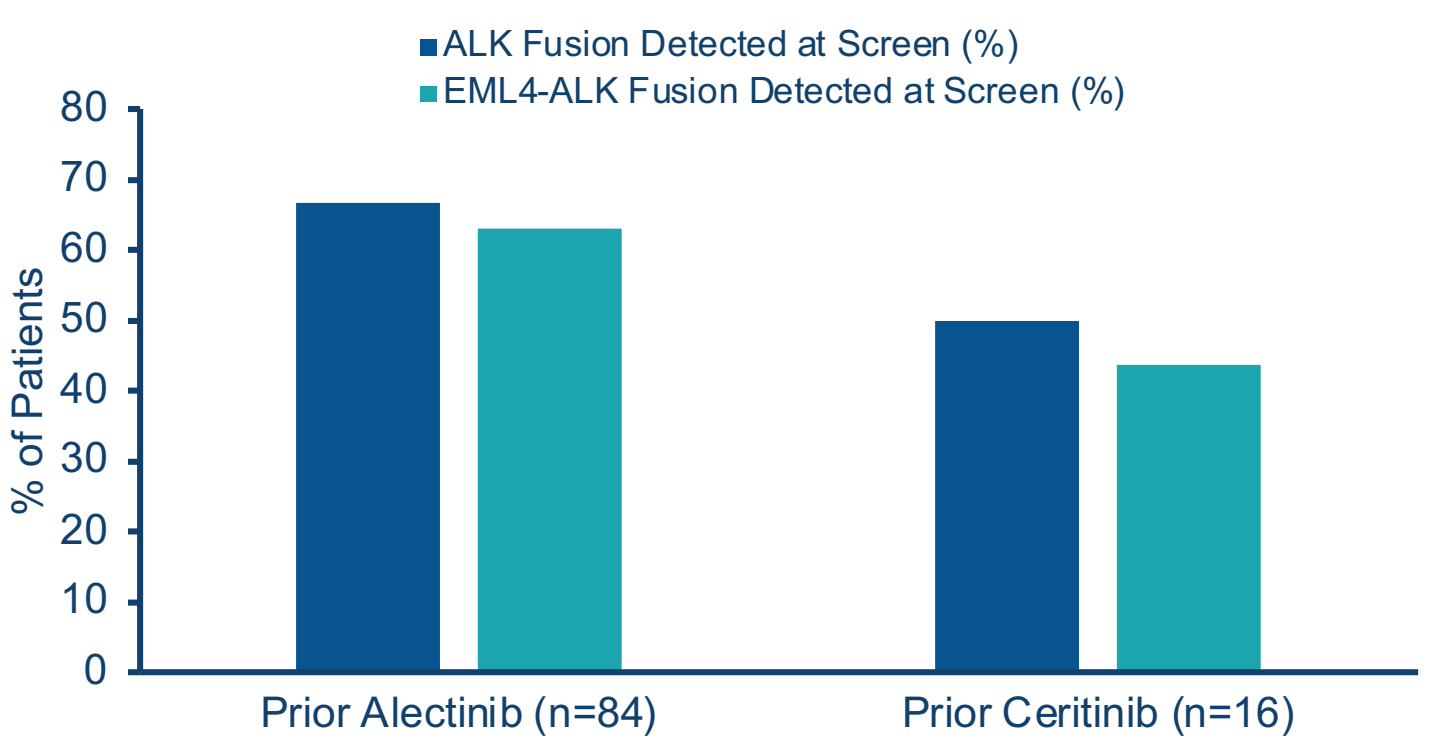
rate; *TP53*, tumor protein p53 gene; WT, wild type


Progressive Disease
Stable Disease
Partial Response
Complete Response
Not Evaluable
Percent change from baseline in sum of lesion diameters
100
80
60
40
20
0
-20
-40
-60
-80
-100
SD SD NE
ORR per IRC = 26.2% [95% CI: 18.0–35.8]

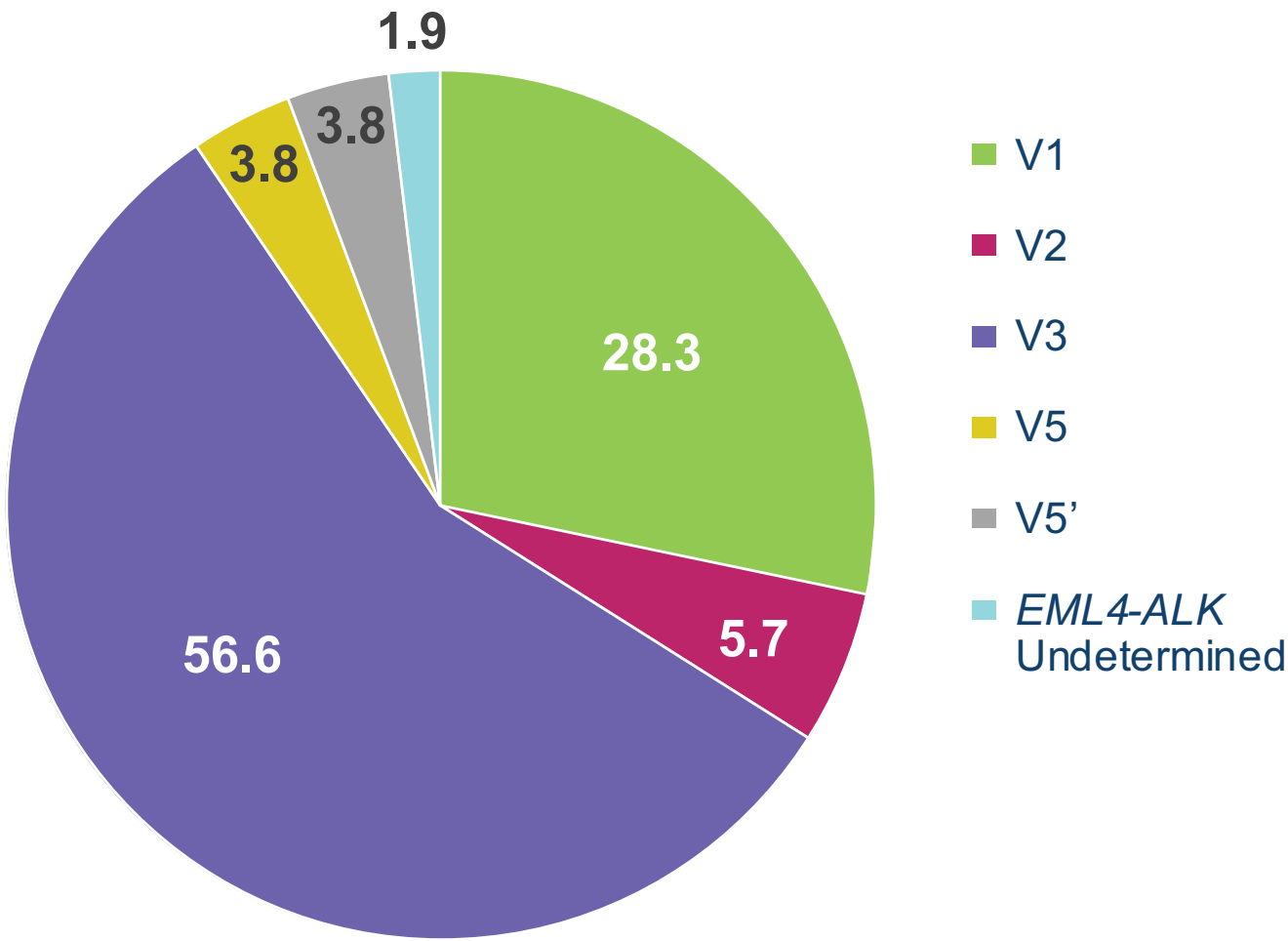

Probability of maintaining response
1.0
0.8
0.6
0.4
0.2
0.0
Median DOR per IRC = 6.3 months [95% CI: 5.6–NR]
0
2
4
6
8
10
12
14
16
18
Time from first documented response, mo
No. at risk: 27 25 18 11 7 3 1 0


Median PFS per IRC = 3.8 months [95% CI: 3.5–5.8]
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
Time from first dose, mo
No. at risk: 103
52
39
30
18
15
7
2
0


Subgroup
n/N
ORR 95% CI
Overall
27/103
26.2 (18.0 to 35.8)
Age
18-64
22/80
27.5 (18.1 to 38.6)
≥65
5/23
21.7 (7.5 to 43.7)
Sex
Female
19/52
36.5 (23.6 to 51.0)
Male
8/51
15.7 (7.0 to 28.6)
Geographic region
Asia except China
8/33
24.2 (11.1 to 42.3)
China
2/14
14.3 (1.8 to 42.8)
Rest of World
17/56
30.4 (18.8 to 44.1)
Race
Asian
11/49
22.4 (11.8 to 36.6)
Non-Asian
16/54
29.6 (18.0 to 43.6)
Baseline brain metastates (per IRC)
Yes
14/55
25.5 (14.7 to 39.0)
No
13/48
27.1 (15.3 to 41.8)
Prior radiotherapy to brain
Yes
8/32
25.0 (11.5 to 43.4)
No
6/23
26.1 (10.2 to 48.4)
Smoking status
Never
16/62
25.8 (15.5 to 38.5)
Former/Current
11/41
26.8 (15.2 to 42.9)
Prior TKI therapy
Alectinib
25/86
29.1 (19.8 to 39.9)
Ceritinib
2/17
11.8 (1.5 to 36.4)
Prior chemotherapy
Yes
8/36
22.2 (10.1 to 39.2)
No
19/67
28.4 (18.0 to 40.7)
Prior crizotinib therapy
Yes
18/57
31.6 (19.9 to 45.2)
No
9/46
19.6 (9.4 to 33.9)
Best response to prior ceritinib or alectinib
CR/PR
14/60
23.3 (13.4 to 36.0)
Other
13/43
30.2 (17.2 to 46.1)
Best response to any ALK TKI crizotinib, alectinib, or ceritinib)
CR/PR
20/78
25.6 (16.4 to 36.8)
Other
7/25
28.0 (12.1 to 49.4)
Number of prior ALK TKI therapies
1 prior
9/46
19.6 (9.4 to 33.9)
2 prior
18/57
31.6 (19.9 to 45.2)
0
10
20
30
40
50
60
Confirmed ORR, % (95% CI)


ALK Fusion Detected at Screen (%)
EML4-ALK Fusion Detected at Screen (%)
% of Patients
80
70
60
50
40
30
20
10
0
Prior Alectinib (n=84)
Prior Ceritinib (n=16)

EML4-ALK Variants in Patients with Prior Alectinib (n=84)



EML4-ALK Variants in Patients with Prior Ceritinib (n=16)