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ORIGINAL ARTICLE

Brigatinib in Japanese Patients With ALK-Positive NSCLC Previously Treated With Alectinib and Other Tyrosine Kinase Inhibitors: Outcomes of the Phase 2 J-ALTA Trial

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ABSTRACT

Introduction: This phase 2 trial evaluated the efficacy and safety of brigatinib in patients with advanced ALK-positive NSCLC refractory to alectinib or other ALK tyrosine kinase inhibitors (TKIs).

Methods: This single-arm, multicenter, open-label study in Japanese patients consisted of a safety lead-in followed by an expansion stage in patients refractory to ALK TKI or those naive for ALK TKI. Patients received brigatinib 180 mg once daily with 7-day lead-in at 90 mg once daily. Primary end point was independent review committee (IRC)–assessed confirmed objective response rate per the Response Evaluation Criteria in Solid Tumors version 1.1.

Results: We report the results of the lead-in and expansion in the patients refractory to ALK TKI. Of 72 patients enrolled, 47 had alectinib as most recent ALK TKI (with or without previous crizotinib). At analysis cutoff, 14 of the 47 remained on brigatinib (median follow-up: 12.4 mo). In the alectinib-refractory population, IRC-assessed confirmed objective response rate was 34% (95% confidence interval [CI]: 21%–49%) with median duration of response of 11.8 months (95% CI: 5.5–16.4). Disease control rate was 79% (95% CI: 64%–89%). Median IRC-assessed progression-free survival was 7.3 months (95% CI: 3.7–9.3). Two of eight patients with measurable brain lesions at baseline had confirmed intracranial partial response. Brigatinib has been found to have antitumor activity in patients with G1202R, I1171N, V1180L, and L1196M secondary mutations. The safety profile in Japanese patients was consistent with that in previous reports in broader populations.

Conclusions: Brigatinib has been found to have clinically meaningful efficacy in Japanese patients with ALK+ NSCLC refractory to alectinib (with or without previous crizotinib).

Keywords: Anaplastic lymphoma kinase; Tyrosine kinase inhibitor; Brigatinib; Alectinib; Crizotinib; Non–small cell lung cancer

Introduction

Rearrangements in the ALK gene occur in an estimated 3% to 5% of patients with NSCLC.[1-3] Several ALK tyrosine kinase inhibitors (TKIs) have been developed for the treatment of ALK-rearranged (ALK+) NSCLC.[4] Although crizotinib was the first ALK TKI developed and approved in Japan, alectinib is currently the standard first-line therapy for TKI-naive ALK+ NSCLC.[5] Randomized trials consistently revealed first-line alectinib to have superior efficacy compared with crizotinib in Japanese[6,7] and broader populations of patients with ALK+ NSCLC.[8,9] However, as with crizotinib, most patients eventually progress on alectinib.[7]

Multiple molecular mechanisms cause resistance to ALK TKIs, including acquisition of secondary mutations in ALK that interfere with drug binding and amplification of the ALK fusion gene and up-regulation of secondary signaling pathways.[10,11] Secondary resistance mutations have been detected in approximately 20% of ALK+ patients who progressed on crizotinib[3,11] and more than 50% of patients who developed resistance to ceritinib or alectinib.[11] The most common secondary ALK mutations associated with clinical resistance include F1174L and F1174C for ceritinib, I1171N, I1171T, and I1171S for alectinib, and G1202R for both agents.[11]

Brigatinib is a next-generation ALK TKI designed to have potent and broad activity against clinically relevant ALK mutants.[12,13] The inhibitory profile of brigatinib was superior to that observed with crizotinib, ceritinib, and alectinib when the in vitro potencies were compared with steady-state plasma concentrations observed in patients for each drug at its approved dose.[12,14] Brigatinib has been found to have substantial activity against 17 different ALK variants with mutations associated with clinical resistance or identified in mutagenesis screen to have resistance to crizotinib, ceritinib, or alectinib.[12] Thus, brigatinib is predicted to have activity against a broad array of ALK mutants, including secondary mutants associated with resistance to alectinib or ceritinib, such as G1202R, I1171N, L1152R, L1198F, and V1180L.[12] Brigatinib has been found to have high clinical efficacy post-crizotinib[15-17] and as first-line ALK TKI treatment in patients with ALK+ NSCLC[18,19] and has similar efficacy and tolerability in Asian and non-Asian patients.[20]

Brigatinib has the potential to be efficacious in patients who have developed resistance to alectinib and other next-generation ALK TKIs. We conducted a phase 2 trial to evaluate the efficacy and safety of brigatinib in Japanese patients with advanced ALK+ NSCLC who had progressed on alectinib (with or without previous crizotinib).

Materials and Methods

This was a single-arm, multicenter, phase 2, open-label study in Japanese patients with advanced ALK+ NSCLC (ClinicalTrials.gov identifier: NCT03410108) consisting of a safety lead-in stage followed by an expansion stage with two cohorts of patients refractory to ALK TKI and one cohort of patients naive to the treatment (Fig. 1). We report the results of the safety lead-in and refractory cohorts in the expansion stage; results of the treatment-naive cohort will be reported separately. This trial was conducted in compliance with the ethical principles originating from the Declaration of Helsinki, the International Council for Harmonisation guideline for Good Clinical Practice, and all applicable local regulations. All patients provided written informed consent before any screening procedures. The informed consent and protocol documents were approved by the local institutional review board or ethics committee at each site.

Eligible patients ($\geq$20 y of age) had histologically or cytologically confirmed stage IIIB, stage IIIC (locally advanced or recurrent and not a candidate for definitive multimodality therapy), or stage IV NSCLC with documented ALK rearrangement. ALK rearrangement must have been documented by the Vysis ALK Break Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Laboratories, Des Plaines, IL), the Nichirei Histofine ALK intercalated antibody-enhanced polymer Kit (Nichirei Biosciences, Tokyo, Japan), or the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Tucson, AZ) at any time during the previous disease course. Patients diagnosed as being ALK positive by a different test could have been enrolled if adequate tissue was available for confirmation by Vysis ALK Break Apart FISH. Central confirmation of ALK rearrangement was not required before enrollment. Patients were also required to have the following: at least one measurable lesion by investigator assessment according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[21]; recovered from toxicities related to previous anticancer therapy; Eastern Cooperative Oncology Group performance status of 2 or lower; and had at least 7 days washout period between the previous TKI and the study drug brigatinib. Patients were excluded if they had previously received more than one regimen (more than three regimens for the safety lead-in) of systemic anticancer therapy (other than ALK TKIs) for locally advanced or metastatic disease; had a history or presence of interstitial lung disease (ILD); had current spinal cord compression; or had symptomatic central nervous system (CNS) metastases or asymptomatic CNS metastases requiring an increasing dose of corticosteroids. Patients with asymptomatic leptomeningeal disease without cord compression were allowed. The protocol (Supplementary Data 2) lists the complete inclusion and exclusion criteria.

Procedures

Safety Lead-In. Nine patients with any number of previous ALK TKI treatments (including alectinib, crizotinib, ceritinib, or lorlatinib followed by at least a 7-d washout) received brigatinib at 90 mg once daily for the first 7 days and then at 180 mg once daily (180 mg once daily with a 7-d lead-in at 90 mg once daily) for cycle 1 (28 d per cycle) (Fig. 1).

Tolerability of the 180 mg once daily (with a 7-d lead-in at 90 mg) regimen was determined on the basis of the dose-limiting toxicities (DLTs) observed in cycle 1 following the 3 plus 3 study design. Patients who have assessable DLT had to complete at least 75% of their planned cumulative doses, unless the missed doses were due to treatment-related adverse events (AEs). Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. The DLTs were defined to be any of the following events occurring within the first 28 days of treatment that were considered by the investigator to be at least possibly related to therapy with brigatinib: any grade 3 or worse nonhematologic toxicity (except for self-limiting or medically controllable toxicities lasting no $>$3 d and isolated asymptomatic laboratory abnormalities of grade $\geq$3 that resolved to grade $\leq$1, or to baseline, within 7 d), any specific hematologic toxicity (febrile neutropenia not related to underlying disease, prolonged [$>$7 d] grade 4 neutropenia, grade $\geq$3 neutropenic infection, grade $\geq$3 thrombocytopenia with bleeding or requiring platelet transfusion, extended [$>$7 d] grade 4 thrombocytopenia, or grade $\geq$3 anemia requiring blood transfusion), and missing more than 25% of planned doses within this period because of treatment-related AEs (except for grade 1 or 2 ILD or pneumonitis in the first 7 d).

Expansion Stage. The expansion part of the study began after the regimen was confirmed to be tolerable on the basis of the total safety data available at that time, available pharmacokinetic (PK) results, and recommendation from an independent data monitoring committee. The main cohort for the primary efficacy analysis included patients who had previously received alectinib

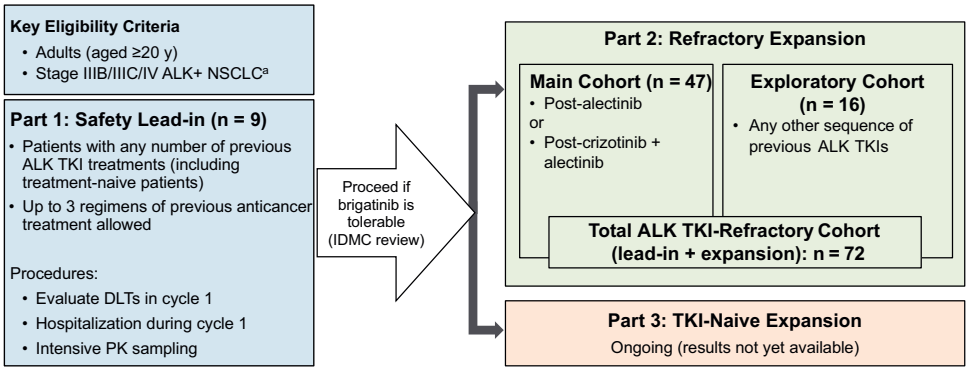

Figure 1. Study design. [a]Patients must have had documentation of the *ALK* gene rearrangement by Vysis ALK Break Apart FISH Probe Kit, Nichirei Histofine ALK iAEP Kit, or Ventana ALK (D5F3) CDx Assay or have had adequate tissue available for confirmation by Vysis ALK Break Apart FISH. Central confirmation of ALK rearrangement was not required before enrollment. DLT, dose-limiting toxicity; FISH, fluorescence in situ hybridization; iAEP, intercalated antibody-enhanced polymer; IDMC, independent data monitoring committee; PK, pharmacokinetics; TKI, tyrosine kinase inhibitor.

only or alectinib after crizotinib only (Fig. 1). Patients who had previously received treatment with other combinations of up to two previous ALK TKIs (alectinib, ceritinib, crizotinib, or lorlatinib) were enrolled in the exploratory cohort but were not included in the primary efficacy analysis. All refractory patients were required to have had documented disease progression during the treatment or within 30 days after discontinuation of the previous ALK TKI.

Patients received brigatinib 180 mg once daily (with a 7-d lead-in at 90 mg) during the expansion stage and continued brigatinib until they experienced objective progressive disease (PD) or intolerable toxicity, withdrew consent, or discontinued for any other reason. Patients who progressed only in the brain were permitted to receive additional treatment of radiation, continuous brigatinib monotherapy, or both beyond PD.

Disease was assessed at enrollment and every two cycles (8 wk) from day 1 of cycle 3 (±7 d) to day 1 of cycle 15, every three cycles (12 wk) thereafter until end of treatment and at the end of treatment if more than 4 weeks had passed since the last scan. All patients had magnetic resonance imaging scans of the brain at enrollment and at subsequent disease assessments. All radiographic images were assessed by an IRC according to the RECIST version 1.1. Complete responses or partial responses (PRs) were confirmed at least 4 weeks after the initial response. The AEs were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

End points

The primary end point for the main refractory expansion cohort was confirmed objective response rate (ORR) as assessed by the IRC, per RECIST version 1.1, at the primary analysis cutoff. Secondary efficacy end points included the ORR, duration of response, progression-free survival (PFS), disease control rate, and time to response by investigator and IRC; overall survival (OS); IRC-assessed intracranial ORR (iORR) and intracranial duration of response in patients with measurable CNS metastases at baseline; and intracranial PFS in all patients (regardless of the presence of CNS metastases).

Statistical Analysis

Nine patients with assessable DLT were enrolled for intensive safety and PK monitoring. This number was derived from the following considerations: (1) meaningful intensive PK characterization needs to be conducted with more than six patients, and nine patients may be reasonable to secure the number of patients needed, even with potential dropouts, and to evaluate study drug tolerability and (2) nine patients are enough to evaluate tolerability before expanding the dose cohort to a larger population using a conventional 3 plus 3 design.

The sample size of the main refractory cohort was $n = 47$. The null hypothesis was to reject an uninteresting ORR of 15% in this population. An interim analysis was conducted after the first 29 patients in the main cohort had completed disease assessments on day 1 of cycle 7. At interim analysis, statistical significance was not met. The study continued to enroll the full sample size of 47 patients. The point estimate of confirmed ORR at primary analysis was calculated by the method suggested by Kunzmann and Kieser[22] with weight function of uniform distribution of (0, 1). Statistical inference was performed at a one-sided 0.025 level of significance or a two-sided 0.05 level of significance, as appropriate, to preserve a one-sided overall type I error rate at or below 0.025 or two-sided overall type I error rate at or

below 0.05. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

The number of patients in the exploratory refractory cohort was limited to 20. These patients were included in overall population evaluations.

An updated analysis was performed 4 months after the primary analysis to evaluate durability of efficacy. For the primary analysis, the primary end point is provided in this report. Full efficacy and safety results are provided for the updated analysis only.

Results

Patients

Between January 29, 2018, and April 12, 2019, a total of 72 Japanese patients with ALK TKI-refractory ALK+ NSCLC were enrolled in the safety lead-in stage (n = 9; last patient enrolled March 2018) and in the expansion stage (main cohort, n = 47; exploratory cohort, n = 16). Demographic and clinical characteristics at baseline are summarized in Table 1. Among all 72 patients, the median age was 53.0 years; 18% of patients were at least 65 years of age. Of the 47 patients in the main cohort, 35 (74%) had previously received one line of alectinib and 12 (26%) had received both alectinib and crizotinib. At the updated analysis (cutoff date: January 22, 2020), a total of 22 of the 72 patients (31%) continued to receive brigatinib (Fig. 2), with median duration of follow-up of 13.7 months (range = 1.5–23.5 mo) and median duration of treatment of 8.2 months (range = 0.2–22.4 mo). For the 47 patients in the main cohort, median follow-up duration was 12.4 months (range = 1.5–20.0 mo) and median treatment duration was 7.5 months (range = 0.2–20.0 mo). Swimmer plots revealing time on treatment in all patients are found in Supplementary Data 1—Supplementary Figure 1.

Safety Lead-In

All nine patients enrolled in the safety lead-in were assessable for DLTs. One patient had one DLT event of asymptomatic grade 3 lipase increase on day 23 of cycle 1. The patient had a concurrent non-DLT event of grade 2 amylase increase. Brigatinib was interrupted for 15 days owing to the DLT and subsequently resumed without dose reduction or recurrence of lipase increase. This patient was not clinically diagnosed with having pancreatitis. The standard dose of brigatinib 180 mg once daily (with a 7-d lead-in at 90 mg) was recommended in the expansion cohort.

Primary End Point in Main Cohort (Post-Alectinib ± Previous Crizotinib) at Primary Analysis

At the primary analysis cutoff (September 26, 2019), the point estimate of IRC-assessed confirmed ORR in the main cohort was 31% (95% CI: 17%–44%) adjusted for the two-stage study design (Supplementary Data 1—Supplementary Table 1).

Efficacy in the Main Cohort (Post-Alectinib ± Previous Crizotinib) at Updated Analysis

At the updated analysis cutoff (January 22, 2020), 16 of the 47 patients in the main cohort (post-alectinib ± previous crizotinib) had achieved confirmed IRC-assessed objective response (confirmed ORR = 34%, 95% CI: 21%–49%; Table 2). The investigator-assessed confirmed ORR (38%, 95% CI: 25%–54%) was consistent with that of the IRC. The IRC-assessed disease control rate was 79% (95% CI: 64%–89%). Best changes from baseline in the sums of target lesions are revealed in Figure 3*A*. Supplementary Data 1—Supplementary Figure 2 reveals best changes in the sums of target lesions by method of ALK assessment. Median time to response was 1.9 months (range = 1.3–9.2). At analysis cutoff, eight of the 16 confirmed responders (50%) had had an event of PD or death. Median duration of response was 11.8 months (95% CI: 5.5–16.4) (Fig. 3*B*).

At the updated analysis cutoff, 27 of the 47 patients (57%) in the main cohort had had an event of objective PD or death. Median IRC-assessed PFS was 7.3 months (95% CI: 3.7–9.3 mo; Fig. 3*C*). The 1-year probability of PFS was 33% (95% CI: 19%–48%). A total of 12 patients in the main cohort had died. The 1-year OS rate was 79% (95% CI: 63%–89%). Median OS was not reached (NR) (95% CI: 14.8 mo–NR).

Intracranial Efficacy. Among eight patients in the main cohort with measurable CNS lesions at baseline, two patients had IRC-assessed confirmed intracranial PR (Table 2). The confirmed iORR was 25% (95% CI: 3%–65%). Among all patients in the main cohort (regardless of the presence of CNS metastases at baseline), median intracranial PFS was NR (95% CI: 9.2 mo–NR; Fig. 3*D*).

Response by Mutation Status

Among all 72 patients refractory to ALK TKI, three had the G1202R mutation centrally or locally detected at baseline. One of the three patients (33%) with the G1202R mutation at baseline had an IRC-assessed confirmed objective response (PR). A total of 11 patients had secondary mutations other than G1202R, of whom six had IRC-assessed confirmed objective response (confirmed ORR = 55%; 95% CI: 23%–83%). The secondary mutations and responses in these patients are listed in Supplementary Data 1—Supplementary Table 2.

Table 1. Baseline Patient Characteristics

Characteristic	Main Cohort (Post-Alectinib ± Crizotinib)[a] n = 47	All ALK TKI-Refractory Patients n = 72
Age, median (range), y	53 (23–82)	53 (23–82)
Sex, no. (%)		
Male	22 (47)	32 (44)
Female	25 (53)	40 (56)
ECOG performance status score, no. (%)		
0	29 (62)	41 (57)
1	18 (38)	31 (43)
Smoking history, no. (%)		
Never smoked	22 (47)	37 (51)
Former smoker	21 (45)	31 (43)
Current smoker	4 (9)	4 (6)
Stage of disease, no. (%)		
IIIB	1 (2)	2 (3)
IV	46 (98)	70 (97)
Histologic type of NSCLC, no. (%)		
Adenocarcinoma	46 (98)	70 (97)
Adenosquamous carcinoma	1 (2)	1 (1)
Other	0	1 (1)
Brain metastases at baseline, no. (%)	19 (40)	32 (44)
Time from initial diagnosis to brigatinib treatment, mo, median (range)	26 (9–96)	29 (5–112)
Previous exposure to ALK TKIs, no. (%)		
Alectinib only	35 (74)	39 (54)
Crizotinib and alectinib	12 (26)	12 (17)
Alectinib and ceritinib	0	9 (13)
Crizotinib only	0	8 (11)
Lorlatinib only	0	2 (3)
Crizotinib and ceritinib	0	1 (1)
Other[b]	0	1 (1)
Previous radiotherapy to the brain, no. (%)	14 (30)	21 (29)
Previous chemotherapy,[c] no. (%)	19 (40)	33 (46)
Methods used for mutation assessment, no. (%)[d]		
Vysis ALK Break Apart FISH Probe Kit	38 (81)	57 (79)
Nichirei Histofine ALK iAEP Kit	24 (51)	36 (50)
RT-PCR	6 (13)	11 (15)
Ventana ALK (D5F3) CDx Assay	2 (4)	9 (13)
Sequencing	3 (6)	5 (7)
Other	5 (11)[e]	8 (11)[f]
Detected fusion partner on *ALK*, no. (%)		
EML4	10 (21)	16 (22)
Unknown	37 (79)	56 (78)
Detected secondary mutations on *ALK*, no. (%)		
G1202R	2 (4)	3 (4)
L1196M	2 (4)	2 (3)
I1171N	1 (2)	2 (3)
I1171S	1 (2)	1 (1)
E1210K	1 (2)	1 (1)
L1196M and G1202del	0	1 (1)
V1180L	0	1 (1)

[a]Patients with previous alectinib only or previous alectinib and crizotinib.
[b]One patient enrolled only in the safety lead-in stage had received crizotinib, alectinib, and ceritinib.
[c]Chemotherapy includes immune checkpoint inhibitor monotherapy.
[d]Patients could have more than one documentation of ALK rearrangements detected by different methods.
[e]Other methods of mutation assessment in the main cohort were immunohistochemistry in four patients and the Oncomine cancer panel (Thermo Fisher Scientific) in one patient.
[f]Other methods of mutation assessment in all patients refractory to ALK TKI were immunohistochemistry in six patients, Oncomine Comprehensive Assay v3 (Thermo Fisher Scientific) in one patient, and Oncomine cancer panel (unspecified) in one patient.
ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; iAEP, intercalated antibody-enhanced polymer; RT-PCR, reverse transcriptase polymerase chain reaction; TKI, tyrosine kinase inhibitor.

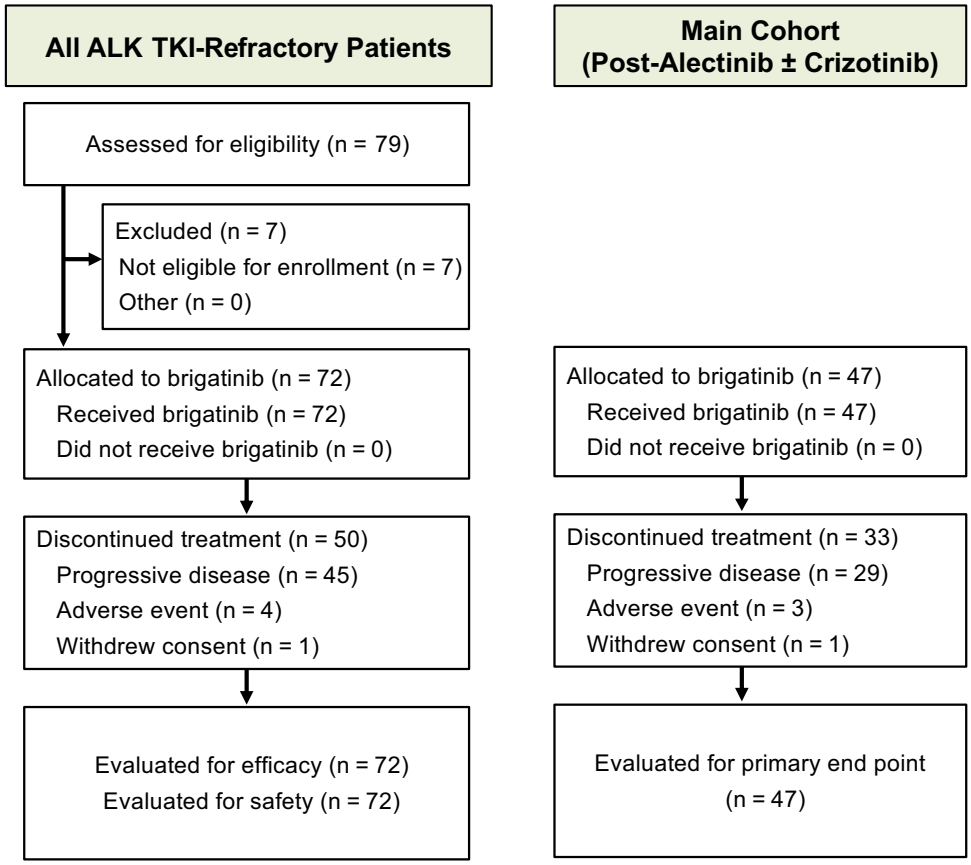

Figure 2. Disposition of patients at updated analysis. TKI, tyrosine kinase inhibitor.

Safety

As of the updated analysis cutoff date (January 22, 2020), all patients who received brigatinib treatment (n = 72) had one or more treatment-related treatment-emergent AEs (TEAEs). The most common (>25% of patients) any-grade TEAEs were increased blood creatine phosphokinase, diarrhea, hypertension, nausea, increased lipase, increased amylase, increased aspartate aminotransferase, and stomatitis (Table 3). Grade 3 to 5 TEAEs occurred in 64% of the patients, and these events were treatment related in 56% of the patients. The most common (>5% of patients) grade ≥3 TEAEs were increased blood creatine phosphokinase, increased lipase, and hypertension (Table 3). There was one death owing to TEAEs that was attributed to respiratory failure because of disease progression and deemed not drug related by the investigator. Five of 72 patients (7%) discontinued brigatinib because of TEAEs (pneumonitis, n = 2; adenosquamous cell carcinoma, n = 1; cerebral infarction, n = 1; cognitive disorder, n = 1). Median dose intensity was 170 mg per day (range = 62–179 mg/d).

ILD or Pneumonitis. One of the 72 patients (1%) had ILD or pneumonitis with early onset (defined as occurring within 14 d after the initiation of treatment). This patient had grade 2 pneumonitis on day 12. Brigatinib was continued without dose reduction, but the pneumonitis worsened to grade 3 on day 15 and brigatinib was discontinued. The event resolved on day 73.

Six patients had at least one investigator-reported event of ILD or pneumonitis at any time (worst severity: grade 1, n = 1; grade 2, n = 4; grade 3, n = 1), and one additional patient had an event of lung disorder (grade 3), considered to be an ILD event by the independent data monitoring committee. Most events of ILD or pneumonitis improved after brigatinib discontinuation with or without steroid treatment.

Discussion

There is an unmet need for effective treatments for ALK+ NSCLC after disease progression on alectinib. Platinum-based chemotherapy has been found to have modest efficacy in ALK+ NSCLC after failure of alectinib, with an ORR (30%) similar to that observed in the

Table 2. Rates of Systemic and Intracranial Objective Response by IRC Assessment at Updated Analysis

Variable	Main Cohort (Post-Alectinib ± Crizotinib) n = 47	All ALK TKI-Refractory Patients n = 72
Confirmed ORR, no. (%)	16 (34)	23 (32)
[95% CI]	[21-49]	[21-44]
Best overall response, no. (%)		
Confirmed complete response	0	0
Confirmed partial response	16 (34)	23 (32)
Stable disease	21 (45)	30 (42)
Not assessable	2 (4)	2 (3)
Disease control rate, no. (%)	37 (79)	53 (74)
[95% CI]	[64-89]	[62-83]
Time to response, mo, median (range)	n = 16 1.9 (1.3-9.2)	n = 23 1.9 (1.3-9.2)
Duration of response, mo, median (95% CI)	n = 16 11.8 (5.5-16.4)	n = 23 16.4 (5.6-NR)
Patients with measurable CNS metastases at baseline	n = 8	n = 14
Confirmed intracranial ORR, no. (%)	2 (25)	3 (21)
[95% CI]	[3-65]	[5-51]
Best overall intracranial response, no. (%)		
Confirmed complete response	0	0
Partial response	2 (25)	3 (21)
Stable disease	5 (63)	10 (71)
Not assessable	1 (13)	1 (7)

Note: Data cutoff date: January 22, 2020.
CI, confidence interval; CNS, central nervous system; IRC, independent review committee; NR, not reached; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

first-line setting (27%) but with shorter PFS (median = 4.3 mo versus 7.0–8.1 mo).[23-25] Ceritinib had low ORR (25%) and short duration of response (median = 6.3 mo) in a small Japanese study (n = 20).[26] So far, lorlatinib is the only ALK TKI to have received regulatory approval to be used in the treatment of patients who progressed from alectinib. Lorlatinib had relatively high ORR (40%) with median duration of response of 7.1 months in an analysis of 139 patients previously treated with at least one previous second-generation ALK TKI.[27] In the 13 patients previously treated with alectinib only, the estimate of the ORR (31%) had a large 95% CI (9%–61%) and median PFS was not reported.[28,29] The most concerning AEs associated with lorlatinib treatment are CNS toxicities, which have been reported in 54% of the treated patients.[28] These events include hallucinations, seizures, and changes in cognitive function, mood (including suicidal ideation), speech, and sleep. Severe CNS events (grades 3–4) were reported in 0.3% to 2.0% of the patients.[28]

The results of three previous studies in small numbers of patients support the efficacy of brigatinib in patients refractory to alectinib.[30-32] A case series from a single hospital in Austria reported that four of six patients (67%) had PR during brigatinib treatment after receiving alectinib as either first-, second-, or third-line therapy.[30] A single-arm, phase 2 U.S. trial of brigatinib in 20 patients who progressed on treatment with another next-generation ALK TKI (16 of 20 [80%] had progressed on alectinib) revealed a promising response rate (ORR = 40%).[31] A retrospective review of medical records from 22 patients with alectinib-refractory ALK+ NSCLC treated with brigatinib at three centers reported a confirmed ORR of 17% (three of 18 patients with measurable disease) and median PFS of 4.4 months (95% CI: 1.8–5.6).[32] These ORR and PFS values were smaller than those observed in our study, possibly owing to the high rate of baseline brain metastases in the chart review (82% versus 40% in our study) and the inclusion of patients with three previous ALK TKIs (18% versus none in our study).

This study in Japanese patients is the first statistically powered prospective clinical trial to evaluate the efficacy of brigatinib in alectinib-refractory advanced ALK+ NSCLC. Brigatinib has been found to have clinically meaningful efficacy at the primary and the updated analyses, with IRC-assessed confirmed ORR of 34% and median duration of response of 11.8 months at the updated analysis. Furthermore, brigatinib has been found to have activity against alectinib-resistant brain metastases, with an iORR of 25% in patients with brain

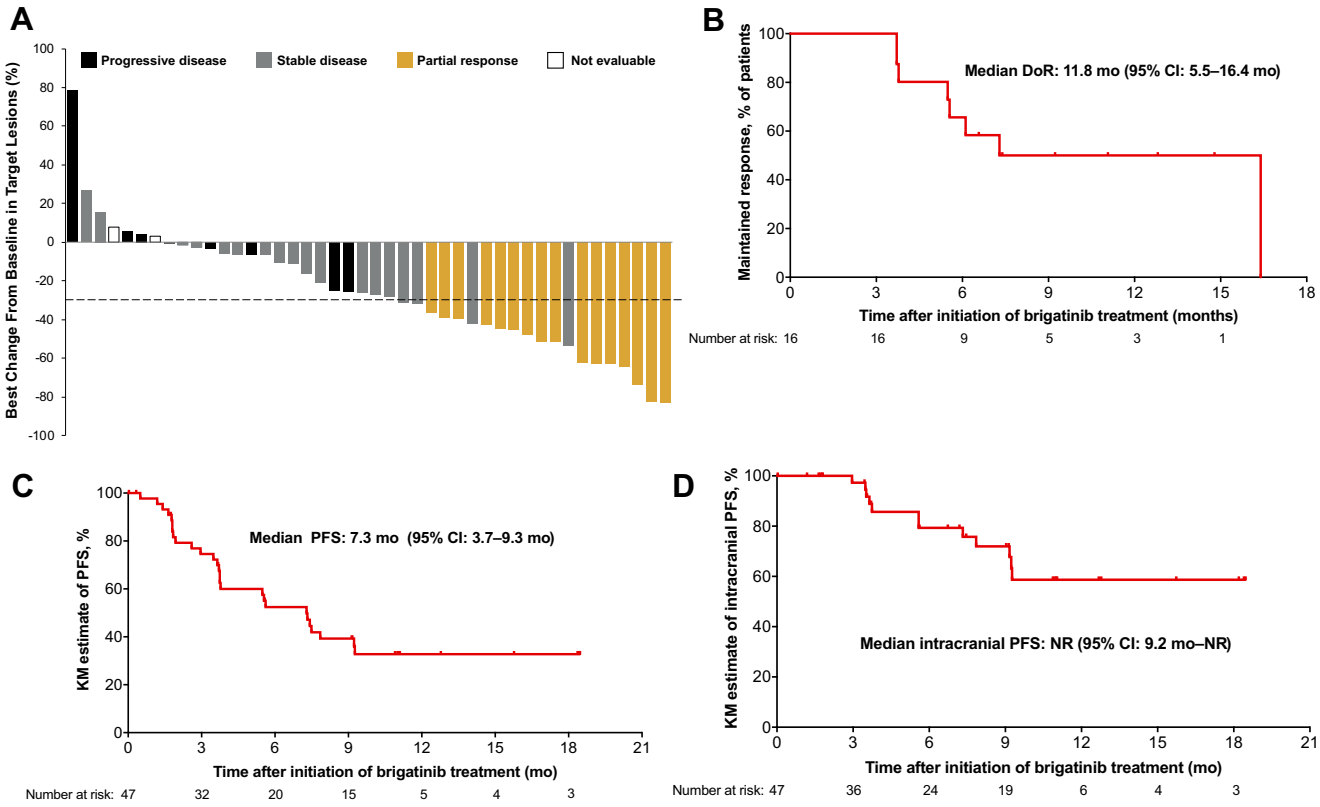

Figure 3. Updated analysis of efficacy of brigatinib in Japanese patients with ALK-positive NSCLC refractory to alectinib with or without previous crizotinib (main cohort). (*A*) Best percentage change from baseline in the sum of the longest diameters of target lesions per IRC assessment in patients who had a measurable lesion at baseline and at least one post-baseline assessment (n = 44). The line at −30% indicates the threshold for partial response according to the RECIST version 1.1. (*B*) DoR in patients with confirmed objective response per IRC assessment. (*C*) KM estimates of IRC-assessed PFS. Of the 47 patients in the main cohort, 27 (57%) had an event. (*D*) Intracranial PFS in all patients (regardless of presence of CNS metastases at baseline). Of the 47 patients, 12 had events of intracranial progression or death. In this analysis, a patient who had systemic PD followed by intracranial PD was handled as a patient with an intracranial event, whereas a patient who had systemic PD and withdrew from the study without an intracranial PD was handled as censored. Tick marks in KM plots indicate censored data. Data cutoff date: January 22, 2020. CI, confidence interval; CNS, central nervous system; DoR, duration of response; IRC, independent review committee; KM, Kaplan-Meier; NR, not reached; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

metastases at baseline and who were refractory to alectinib. In addition, brigatinib has antitumor activity in patients with various refractory secondary ALK mutations, including L1196M, G1202R, I1171N, and V1180L, consistent with its broad-spectrum preclinical activity against ALK mutants.[12] A multinational phase 2 trial (ALK in Lung Cancer Trial of AP26113 [ALTA]-2, NCT03535740) with 104 patients has fully enrolled and will be reporting further data of brigatinib in the post-alectinib or -ceritinib setting.[33]

The safety profile of brigatinib in Japanese patients was consistent with the known profile of this drug,[15,18] and no new safety concerns were identified. As in previous studies, reported AEs included elevated amylase, elevated lipase, hypertension, elevated creatine phosphokinase, hepatic enzyme abnormalities, and gastrointestinal AEs. Most events were manageable by dose modification and supportive care. Elevations in creatine phosphokinase levels were not associated with rhabdomyolysis or other clinically meaningful muscle-associated AEs, and there were no cases of clinical pancreatitis. Myalgia or musculoskeletal pain was reported in six patients, all of whom developed increased creatine phosphokinase. However, those events were manageable with temporary interruption, dose reduction, or both, of brigatinib. The rate of early-onset pulmonary AEs in the current study was 1%. This rate is lower than that previously reported in patients refractory to crizotinib in the ALTA study (6%)[15] and in patients naive to ALK TKI in ALK in Lung Cancer Trial of brigAtinib in 1st Line (ALTA-1L) (3%).[18] In ALTA, a shorter interval (<7 d) between the last crizotinib dose and the first brigatinib dose was significantly (p=0.035) associated with increased risk of early-onset pulmonary AEs.[15] The mandated minimum of 7-day washout between the last dose of the previous ALK TKI and the start

Table 3. TEAEs of Any Grade Reported in > 10% of Patients or Grade ≥ 3 Reported in ≥ Two Patients

	No. of Patients (%)	
	Brigatinib 90 mg → 180 mg Once Daily[a], n = 72	
AE	Any Grade	Grade ≥3
Increased blood creatine phosphokinase[b]	55 (76)	14 (19)
Diarrhea	31 (43)	0
Hypertension	29 (40)	8 (11)
Nausea	27 (38)	0
Increased lipase[c]	24 (33)	10 (14)
Increased amylase[c]	22 (31)	3 (4)
Increased aspartate aminotransferase	21 (29)	1 (1)
Stomatitis	20 (28)	1 (1)
Headache	13 (18)	1 (1)
Increased alanine aminotransferase	13 (18)	0
Rash	13 (18)	1 (1)
Vomiting	12 (17)	1 (1)
Back pain	11 (15)	0
Pyrexia	11 (15)	0
Increased blood alkaline phosphatase	10 (14)	1 (1)
Upper respiratory tract infection	9 (13)	0
Constipation	8 (11)	0
Hypophosphatemia	8 (11)	1 (1)
Photosensitivity reaction	8 (11)	0
Nasopharyngitis	8 (11)	0
Lung infection	6 (8)	3 (4)
Dyspnea	4 (6)	3 (4)
Hyponatremia	3 (4)	2 (3)
Malignant pericarditis	2 (3)	2 (3)

Note: Data cutoff date: January 22, 2020.
[a]180 mg once daily with 7-day lead-in at 90 mg.
[b]Myalgia or musculoskeletal pain was reported in six patients. All six of these patients also experienced increased blood creatine phosphokinase.
[c]No clinical cases of pancreatitis were reported.
AE, adverse event; TEAE, treatment-emergent AE.

of brigatinib in this study may have mitigated the risk of pulmonary AEs. Strategies for the management of these early onset pulmonary events include dose reduction or interruption and supportive care (including supplemental oxygen), which may allow for continued dosing through these transient events.[34,35]

There were limitations in this study. This was a single-arm trial in fewer than 100 patients. In addition, among patients enrolled at this time, ALK+ status was confirmed predominantly by means of FISH-based testing. Currently, immunohistochemistry is the main method used clinically in the detection of the ALK rearrangement. However, in the near future, next-generation sequencing will become the mainstream for detection of ALK mutations, allowing for the detection of a broader range of genetic abnormalities. As we learn more about prognostic variables (e.g., EML4-ALK variant and TP53 mutation status),[36] optimal drug selection may require consideration of gene abnormalities other than the ALK fusion mutation. Lastly, as treatment paradigms evolve in response to emerging data on other ALK TKIs in the first-line setting (e.g., lorlatinib),[37] the alectinib-refractory setting may become less clinically relevant over time.

In conclusion, brigatinib has been found to have clinically meaningful efficacy in Japanese patients with ALK+ NSCLC refractory to alectinib (first-line or post-crizotinib) in this single-arm trial. The safety profile of brigatinib in Japanese patients was consistent with that of previous studies in other populations. The results of this study reveal that brigatinib is a promising treatment in patients with ALK+ NSCLC who are refractory to alectinib with or without previous crizotinib, although additional studies in larger patient populations are needed.

Data Availability

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 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.2020.11.004.

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