ORIGINAL ARTICLE

Brigatinib in Crizotinib-Refractory *ALK*+ NSCLC: 2-Year Follow-up on Systemic and Intracranial Outcomes in the Phase 2 ALTA Trial

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ABSTRACT

Introduction: We report updated data from a phase 2 randomized study evaluating brigatinib in crizotinib-refractory anaplastic lymphoma kinase–positive NSCLC.

Methods: Patients were randomized 1:1 to take either oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (arm B), stratified by central nervous system (CNS) metastases and best response to crizotinib. The primary end point was investigator-assessed confirmed objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included independent review committee (IRC)-assessed progression-free survival (PFS), intracranial PFS (iPFS), and overall survival (OS). Exploratory analyses included CNS versus ex-CNS target lesion response and correlation of depth of response with PFS and OS.

Results: Among 222 randomized patients (112 and 110 in arms A and B, respectively), 59 (27%) remained on brigatinib at analysis (median follow-up: 19.6 versus 24.3 months). At baseline, 71% and 67% had brain lesions among A and B arms, respectively. Investigator-assessed confirmed objective response rate was 46% versus 56%. Median IRC-assessed PFS was 9.2 months (95% confidence interval: 7.4–12.8) versus 16.7 months (11.6–21.4). Median OS was 29.5 months (18.2–not reached) versus 34.1 months (27.7–not reached). IRC-confirmed intracranial objective response rate in patients with measurable baseline brain lesions was 50% (13 of 26) versus 67% (12 of 18); median duration of intracranial response was 9.4 versus 16.6 months. IRC-assessed iPFS was 12.8 versus 18.4 months. Across arms, median IRC-assessed PFS was 1.9, 5.5, 11.1, 16.7, and 15.6 months for patients with no, 1%–25%, 26%–50%, 51%–75%, and 76%–100% target lesion shrinkage, respectively. No new safety findings were observed with longer follow-up.

Conclusions: Brigatinib (180 mg once daily with lead-in) continues to demonstrate robust PFS, long iPFS and duration of intracranial response, and high intracranial objective response rate in crizotinib-refractory patients. Depth of response may be an important end point to capture in future targeted therapy trials.

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

Introduction

Approximately 3%–5% of patients with NSCLC have oncogenic rearrangements in the anaplastic lymphoma kinase gene (*ALK*).[1,2] Crizotinib is effective in *ALK*-positive (*ALK*+) NSCLC,[3] but most patients experience disease progression on crizotinib caused by acquired *ALK* resistance mutations, secondary driver pathways, or poor central nervous system (CNS) drug penetration.[4-6] After crizotinib, next-line treatment with second-generation ALK inhibitors ceritinib and alectinib, and third-generation inhibitor lorlatinib, is associated with median progression-free survival (PFS) of less than 1 year.[7-14]

Brigatinib is a next-generation oral ALK inhibitor approved in the United States and European Union for the treatment of metastatic *ALK*+ NSCLC patients with progressive disease on or with intolerance to crizotinib.[15,16] In the primary analysis of the phase 2 ALTA trial with 8-month median follow-up, investigator-assessed median PFS was 9.2 months in patients treated with brigatinib 90 mg once daily and 12.9 months in patients treated with 180 mg once daily with 7-day lead-in at 90 mg.[17]

Here, we report updated data and new exploratory analyses on the two brigatinib dosing regimens evaluated in patients with crizotinib-refractory, advanced *ALK*+ NSCLC in the ALTA trial[17] with approximately 2 years of follow-up since the last patient enrolled.

Materials and Methods

The ALTA trial (ClinicalTrials.gov identifier: NCT02094573) is an ongoing phase 2, open-label, randomized, multicenter, international study. Methods and complete protocol for ALTA have been previously published.[17] In summary, eligible patients (≥18 years old) had locally advanced or metastatic *ALK*-positive NSCLC, with disease progression while receiving crizotinib, with no other previous ALK-directed therapy, with at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST version 1.1),[18] and Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to two. Patients should not have had any of the following: (1) received

crizotinib within 3 days of the first brigatinib dose; (2) cytotoxic chemotherapy or radiation therapy (except stereotactic [body] radiosurgery) within 14 days; or (3) monoclonal antibodies within 30 days. Patients were excluded if they had a history or presence of pulmonary interstitial disease or drug-related pneumonitis, or symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids. The protocol was approved by the institutional review board or ethics committee at each site. The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation guidelines for good clinical practice. All patients provided written informed consent.

Procedures

Patients were stratified by the presence or absence of baseline brain metastases and best response to crizotinib (investigator-assessed complete response [CR] or partial response [PR] versus other or unknown), and randomized 1:1 to either 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (arm B). Patients continued to receive brigatinib until any of the following ensues: (1) disease progression, requiring alternative systemic therapy; (2) intolerable toxicity; or (3) consent withdrawal. Treatment in either arm could be continued after progression at the investigator's discretion. Patients in arm A could transition to brigatinib 180 mg once daily after progression at 90 mg once daily. Dose interruptions or reductions were mandated to manage treatment-related adverse events (AEs). AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Disease was assessed per RECIST version 1.1 in chest and abdomen images obtained by means of contrast-enhanced computed tomography or magnetic resonance imaging at screening and every 8 weeks through cycle 15 (28 days per cycle) and then every 12 weeks until progression. Baseline CNS imaging was required in all patients; for patients with CNS metastases, contrast-enhanced magnetic resonance imaging of the brain was also required every 8 weeks thereafter. A central independent review committee (IRC) reviewed on-study images. Objective responses were confirmed at least 4 weeks after initial response. Follow-up for survival and subsequent therapy continued every 3 months after treatment discontinuation.

Outcomes

The primary end point was investigator-assessed confirmed objective response rate (cORR) per RECIST version 1.1. Secondary end points included duration of response, overall survival (OS), IRC-assessed cORR, PFS, CNS response and intracranial PFS (iPFS), safety, and tolerability. Active brain metastases were defined as lesions that had not been previously treated with radiotherapy or had investigator-assessed progression after radiotherapy. Intracranial response was defined as greater than or equal to 30% decrease in measurable ($\geq$10 mm) lesions or in patients with no measurable lesions, as complete disappearance of lesions.[17] Exploratory analyses evaluated investigator-assessed target lesion response by location (CNS versus ex-CNS), and correlation of investigator-assessed depth of target lesion shrinkage with investigator-assessed PFS and OS and IRC-assessed depth of target lesion shrinkage with IRC-assessed PFS. For the exploratory analysis of depth of target lesion shrinkage and survival outcomes, patients with at least one evaluable response assessment from arms A and B were pooled and sorted into five categories (no shrinkage, 1%–25%, 26%–50%, 51%–75%, and 76%–100% shrinkage) on the basis of greatest decrease from baseline using RECIST version 1.1.[18] Multivariate analyses were conducted using a Cox proportional hazards regression model that included variables of best target lesion shrinkage category, treatment arm, baseline ECOG performance status (0–1 versus 2), and smoking status (never or unknown versus current or former).

Statistical Analysis

The intention-to-treat population (all randomized patients) was used for efficacy analyses. Only patients with IRC-assessed brain metastases at baseline were included in IRC intracranial efficacy analyses. The safety population comprised all patients who received at least one dose of brigatinib. Exact binomial method was used to calculate confidence intervals (CIs); 97.5% CIs were estimated for cORR (primary end point), and 95% CIs were used for other end points.[17] Median values and two-sided 95% CIs for time-to-event (duration of response, PFS, and OS) analyses were calculated using Kaplan-Meier methods. IRC-assessed systemic and intracranial efficacy data had a last scan date of September 18, 2017. Clinical data are reported as of September 29, 2017. Statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, NC, USA; version 9.4).[17]

Results

Patients

Among 222 randomized patients (112 and 110 in arms A and B, respectively), 59 (27%) remained in the study (27 [24%] in arm A and 32 [29%] in arm B) as of

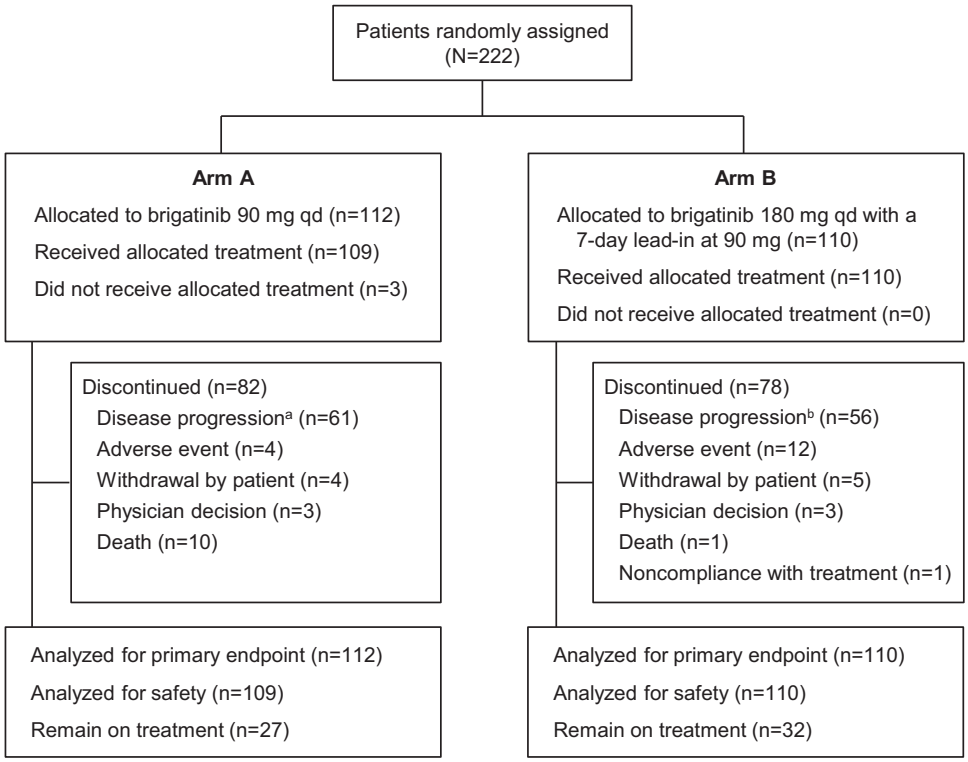


Figure 1. CONSORT diagram for the ALTA trial. [a]54 patients had documented disease progression per RECIST version 1.1; seven had clinical disease progression. [b]45 patients had documented disease progression per RECIST version 1.1; 11 had clinical disease progression. RECIST, Response Evaluation Criteria in Solid Tumors.

September 29, 2017 (Fig. 1). Median follow-up was 19.6 months (range: 0.1–35.2) in arm A and 24.3 months (0.1–39.2) in arm B. Median duration of treatment was 13.2 months (range: 0.03–35.0) and 17.1 months (0.07–39.2), respectively.

Demographics and baseline characteristics (Supplementary Table 1) have been published.[17] At baseline, most patients had brain lesions (80 of 112 [71%] in arm A, 74 of 110 [67%] in arm B) and approximately half had active (i.e. lesions without previous radiotherapy or with investigator-assessed progression after previous radiotherapy) brain lesions (54 of 112 [48%] in arm A, 55 of 110 [50%] in arm B). Approximately 16% (70 of 451) of all target lesions were located in the CNS (38 of 247 [15%] in arm A, 32 of 204 [16%] in arm B). A total of 51 (23%) patients had at least one target lesion in the CNS (28 [25%] in arm A, 23 [21%] in arm B). Of 44 patients with measurable brain lesions identified by IRC at baseline, 34 had at least one active brain lesion identified by the investigator.

Overall, 96 (43%) patients had received previous radiation therapy in the brain (50 [45%] in arm A, 46 [42%] in arm B). Slightly more than half (54 of 96 [56%]) had last received brain radiotherapy more than 6 months before their first dose of brigatinib (23 of 50 [46%] in arm A, 31 of 46 [67%] in arm B). Among patients with baseline brain lesions, 94 (61%) had received previous radiation therapy in the brain (49 [61%] in arm A, 45 [61%] in arm B).

Efficacy

Systemic Efficacy. The cORR (97.5% CI) per investigator assessment was 46% (35%–57%) in arm A and 56% (45%–67%) in arm B (Table 1), with median duration of response of 12.0 months (95% CI: 9.2–17.7) and 13.8 months (95% CI: 10.2–19.3), respectively. The IRC-assessed cORRs were 51% (95% CI: 41%–61%) and 56% (95% CI: 47%–66%) in arms A and B, respectively.

Median IRC-assessed PFS was 9.2 months (95% CI: 7.4–12.8) in arm A and 16.7 months (95% CI: 11.6–21.4) in arm B (Fig. 2*A*). Median investigator-assessed PFS was 9.2 months (95% CI: 7.4–11.1) in arm A and 15.6 months (11.1–21.0) in arm B. Median OS was 29.5 months (95% CI: 18.2–not reached [NR]) in arm A and 34.1 months (27.7–NR) in arm B (Fig. 2*B*). Probability of survival at 1 year and 2 years was 70% and 55% in arm A and 80% and 66% in arm B, respectively.

Intracranial Versus Extracranial Efficacy. IRC-assessed confirmed intracranial objective response rate (iORR) in patients with measurable baseline CNS lesions was 50% (13 of 26) in arm A and 67% (12 of 18) in arm B, with median duration of confirmed intracranial

Table 1. Systemic and Intracranial Objective Response and Disease Control Rates by Arm

	Investigator-Assessed		IRC-Assessed	
	Arm A 90 mg Once Daily n = 112	Arm B 90 mg → 180 mg Once Daily[a] n = 110	Arm A 90 mg Once Daily n = 112	Arm B 90 mg → 180 mg Once Daily[a] n = 110
All patients				
Confirmed ORR, n (%)	51 (46)	62 (56)	57 (51)	62 (56)
[97.5% CI][b] or [95% CI]	[35-57][b]	[45-67][b]	[41-61]	[47-66]
Confirmed CR, n (%)	2 (2)	5 (5)	6 (5)	6 (5)
Confirmed PR, n (%)	49 (44)	57 (52)	51 (46)	56 (51)
DCR, n (%)	91 (81)	95 (86)	87 (78)	92 (84)
[95% CI]	[73-88]	[79-92]	[69-85]	[75-90]
Patients with ≥1 baseline investigator-assessed CNS target lesion				
≥1 baseline CNS target lesion	n = 28	n = 23		
Confirmed ORR, n (%)	12 (43)	14 (61)	-	-
[95% CI]	[25-63]	[39-80]		
No baseline CNS target lesion	n = 84	n = 87		
Confirmed ORR, n (%)	39 (46)	48 (55)	-	-
[95% CI]	[36-58]	[44-66]		
Intracranial response rates in patients with measurable brain metastases at baseline per IRC				
			n = 26	n = 18
Confirmed intracranial ORR, n (%)	-	-	13 (50)	12 (67)
[95% CI]			[30-70]	[41-87]
Confirmed intracranial CR, n (%)	-	-	2 (8)	0
Confirmed intracranial PR, n (%)	-	-	11 (42)	12 (67)
Intracranial DCR, n (%)	-	-	22 (85)	15 (83)
[95% CI]			[65-96]	[59-96]
			n = 13	n = 12
Median duration of intracranial response in responders, months	-	-	9.4	16.6
[95% CI]			[3.7-24.9]	[3.7-NR]

[a]180 mg once daily with 7-day lead-in at 90 mg.
[b]Primary end point tested at 0.025 alpha level for each dose.
CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; IRC, independent review committee; NR, not reached; ORR, objective response rate; PR, partial response.

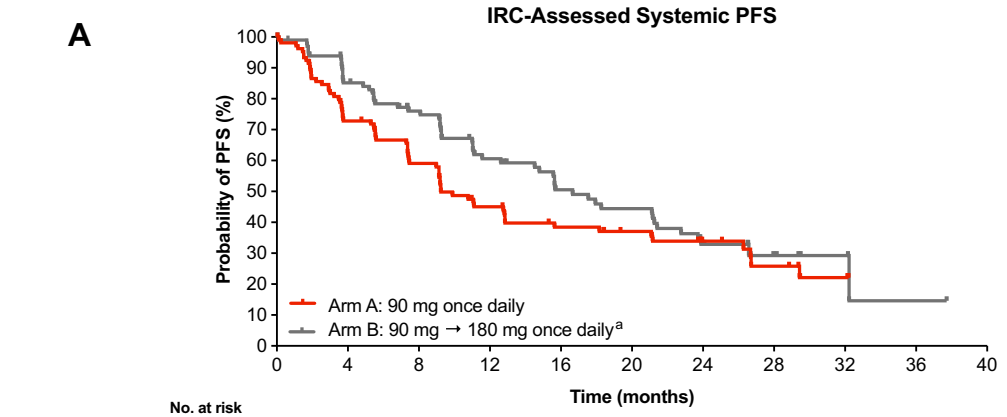
response of 9.4 months (95% CI: 3.7–24.9) and 16.6 months (3.7–NR), respectively (Table 1).

An exploratory analysis of the investigator-assessed best change from baseline in target lesions by lesion location (intracranial versus extracranial and overall) in patients with or without target baseline brain lesions is shown in Figure 3*A*. In patients with at least one intracranial target lesion at baseline, 68% (17 of 25) in arm A and 82% (18 of 22) in arm B had greater than or equal to 30% shrinkage of intracranial target lesions and 59% (10 of 17) in arm A and 67% (6 of 9) in arm B had greater than or equal to 30% shrinkage of extracranial target lesions. In patients without intracranial target lesions at baseline, 64% (49 of 76) and 68% (53 of 78), respectively, had greater than or equal to 30% shrinkage of extracranial target lesions.

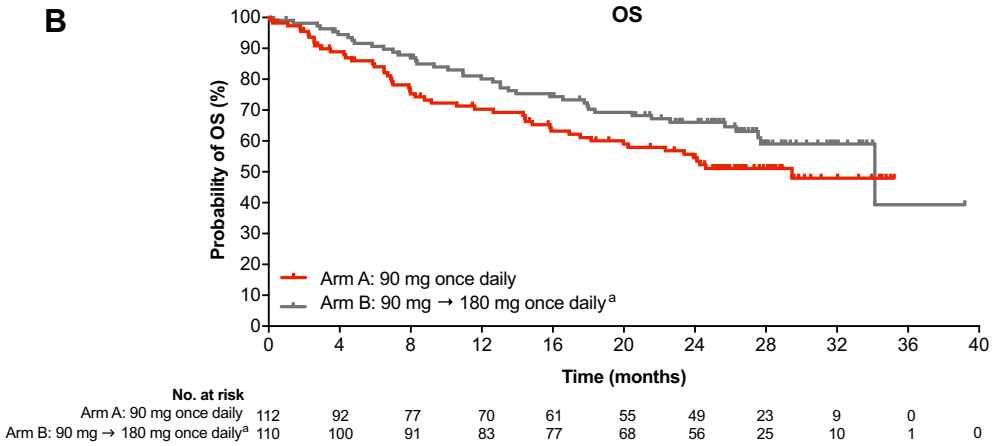
For patients with any baseline brain lesions (81 and 74 patients in arms A and B, respectively), the median IRC-assessed iPFS was 12.8 months (95% CI: 9.2–18.3; events: 49%) in arm A and 18.4 months (95% CI: 12.6–23.9; events: 41%) in arm B (Fig. 3*B*).

Investigator-Assessed Depth of Target Lesion Response and Survival Outcomes. Investigator-assessed depth of target lesion response was evaluated in 201 patients who had at least one evaluable response assessment (101 and 100 patients in arms A and B, respectively). Across treatment arms, 17 patients had no target lesion shrinkage, whereas 39, 57, 45, and 43 patients had best target lesion shrinkage of 1%–25%, 26%–50%, 51%–75%, and 76%–100%, respectively. Among the 43 patients with 76%–100% shrinkage, seven had a confirmed CR, 34 had a confirmed PR, and two had stable disease.

Median investigator-assessed PFS was 3.6 months (95% CI: 1.9–11.0) for patients with no investigator-assessed shrinkage, 9.3 (3.7–15.7) for those with 1%–25% shrinkage (hazard ratio [HR] [95% CI]: 0.48 [0.25–0.95] in comparison with no shrinkage), 11.1 months (8.3–15.6) for 26%–50% shrinkage (HR: 0.42 [0.22–0.78]), 11.3 months (8.8–18.5) for 51%–75% shrinkage (HR: 0.37 [0.19–0.70]), and



	Investigator-Assessed		IRC-Assessed	
	Arm A: 90 mg once daily n=112	Arm B: 90 mg→ 180 mg once daily[a] n=110	Arm A: 90 mg once daily n=112	Arm B: 90 mg→ 180 mg once daily[a] n=110
Median PFS, months (95% CI)	9.2 (7.4–11.1)	15.6 (11.1–21.0)	9.2 (7.4–12.8)	16.7 (11.6–21.4)
1-year PFS probability, % (95% CI)	37 (27–46)	58 (47–67)	45 (35–55)	61 (49–70)



	Arm A: 90 mg once daily n=112	Arm B: 90 mg → 180 mg once daily[a] n=110
Median OS, months (95% CI)	29.5 (18.2–NR)	34.1 (27.7–NR)
1-year OS probability, % (95% CI)	70 (61–78)	80 (71–87)
2-year OS probability, % (95% CI)	55 (44–64)	66 (56–74)

Figure 2. Brigatinib systemic efficacy in crizotinib-refractory *ALK*+ NSCLC by arm. (*A*) IRC-assessed PFS is shown for the ITT population. Of the 112 patients in arm A, 65 (58%) had an event; of the 110 patients in arm B, 54 (49%) had an event. (*B*) OS is shown for the ITT population. Of the 112 patients in arm A, 50 (45%) had an event; of the 110 patients in arm B, 40 (36%) had an event. [a]180 mg once daily with 7-day lead-in at 90 mg. *ALK*, anaplastic lymphoma kinase gene; IRC, independent review committee; ITT, intention-to-treat; NR, not reached; OS, overall survival; PFS, progression-free survival.

19.5 (12.9–NR) for 76%–100% shrinkage (HR: 0.26 [0.13–0.51]) (Fig. 3*C*). Median OS was 8.3 months (95% CI: 4.7–NR) for patients with no shrinkage, NR (14.5–NR) for those with 1%–25% shrinkage (HR [95% CI]: 0.47 [0.21–1.02] in comparison with no shrinkage), NR (24.6–NR) for 26%–50% shrinkage (HR: 0.33 [0.15–0.72]), 34.1 months (26.3–NR) for 51%–75% shrinkage (HR: 0.37 [0.17–0.80]), and NR (22.6–NR) for 76%–100% shrinkage (HR: 0.27 [0.12–0.60]).

IRC-Assessed Depth of Target Lesion Response and Survival Outcomes. Depth of target lesion response per IRC assessments was evaluated in 194 patients who had at least one evaluable response assessment (97 and 94 in arms A and B, respectively). Across treatment arms, four patients had no target lesion shrinkage, whereas 30, 41, 59, and 60 patients had best target lesion shrinkage of 1%–25%, 26%–50%, 51%–75%, and 76%–100%, respectively. Among the 60 patients with 76%–100% shrinkage, 12 had a confirmed CR, 40 had a confirmed

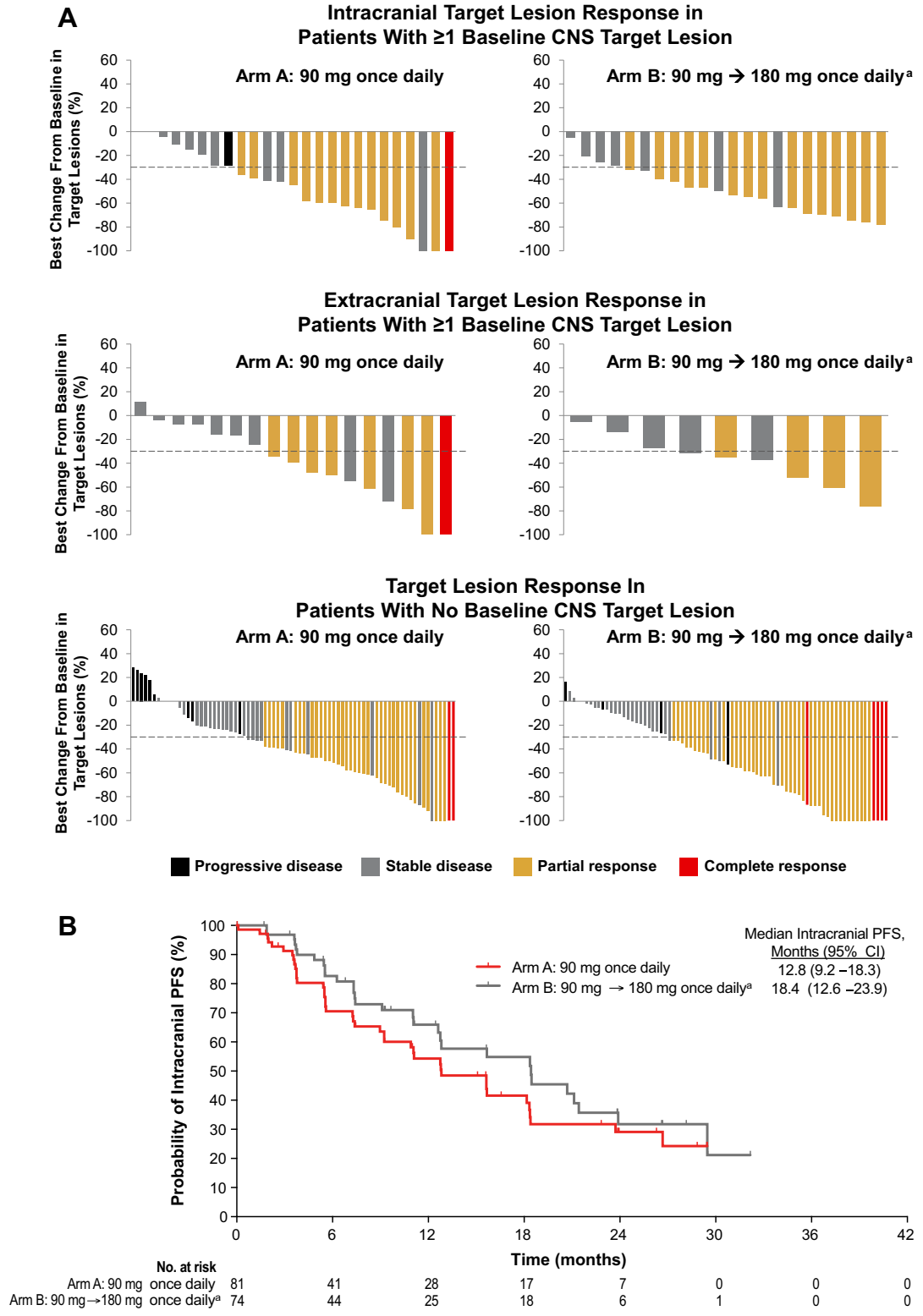
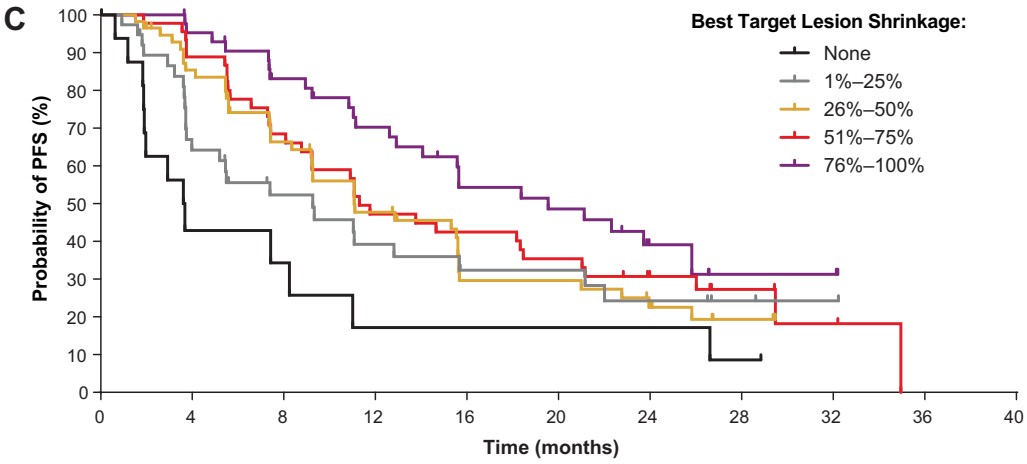
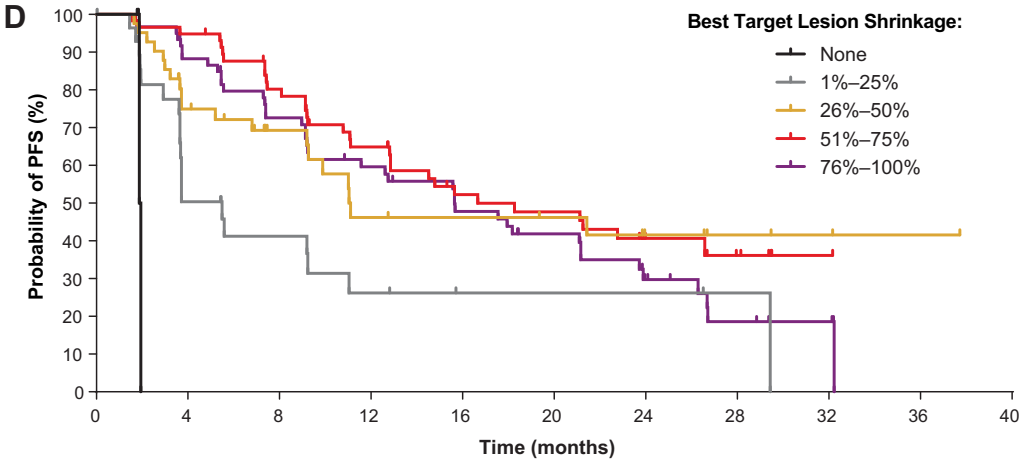


Figure 3. Brigatinib intracranial efficacy and best target lesion response in crizotinib-refractory *ALK*-positive NSCLC. (*A*) The best percentage change from baseline in the sum of the longest diameters of intracranial and extracranial target lesions is reported in patients who had at least one target brain lesion at baseline, as assessed by investigators. The dotted line at −30% indicates the threshold for partial response per RECIST version 1.1. (*B*) Intracranial PFS is shown for patients with any brain metastases at baseline, as assessed by an IRC (n = 81, arm A; n = 74, arm B). Of the 81 evaluable patients in arm A, 40 (49%) had an event; of the 74 evaluable patients in arm B, 30 (41%) had an event. (*C*) Investigator-assessed PFS by best target lesion shrinkage and (*D*) IRC-assessed PFS by best target lesion shrinkage in patients with one or more evaluable response



Best Target Lesion Shrinkage	n (%)[b]	Median PFS[c,d] Months (95% CI)	1-Year PFS[c,d] % (95% CI)	Hazard Ratio (95% CI)
None	17 (8)	3.6 (1.9–11.0)	17 (3–41)	Reference
1%–25%	39 (19)	9.3 (3.7–15.7)	39 (23–55)	0.48 (0.25–0.95)
26%–50%	57 (28)	11.1 (8.3–15.6)	48 (34–61)	0.42 (0.22–0.78)
51%–75%	45 (22)	11.3 (8.8–18.5)	47 (32–61)	0.37 (0.19–0.70)
76%–100%	43 (21)	19.5 (12.9–NR)	70 (54–82)	0.26 (0.13–0.51)



Best Target Lesion Shrinkage	n (%)[e]	Median PFS[c,d] Months (95% CI)	1-Year PFS[c,d] % (95% CI)	Hazard Ratio (95% CI)
None	4 (1)	1.9 (1.9–1.9)	NE	Reference
1%–25%	30 (15)	5.5 (3.6–11.0)	26 (10–45)	0.17 (0.04–0.82)
26%–50%	41 (21)	11.1 (9.2–NR)	46 (28–63)	0.07 (0.01–0.35)
51%–75%	59 (30)	16.7 (12.8–NR)	65 (51–76)	0.06 (0.01–0.29)
76%–100%	60 (31)	15.6 (9.2–21.2)	60 (46–71)	0.08 (0.02–0.39)

Figure 3. (*continued*).

PR, and six had stable disease; two had progressive disease despite substantial target lesion shrinkage on the basis of progression in non–target lesions.

Median IRC-assessed PFS was 1.9 months (95% CI: 1.9–1.9) for patients with no IRC-assessed shrinkage, 5.5 months (3.6–11.0) for those with 1%–25% shrinkage

assessment. [a]180 mg once daily with 7-day lead-in at 90 mg; [b]Evaluable patients (n = 201); [c]Kaplan-Meier estimate; [d]Per investigator assessments; [e]Evaluable patients (n = 194). *ALK*, anaplastic lymphoma kinase gene; IRC, independent review committee; NE, not estimable; NR, not reached; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2. Treatment-Related[a] Adverse Events of Any Grade Reported in ≥10% of Patients or Grade ≥3 in ≥3% of Patients

	No. of Patients (%)			
	Arm A 90 mg Once Daily n = 109		Arm B 90 mg → 180 mg Once Daily[b] n = 110	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	17 (16)	0	38 (35)	0
Nausea	28 (26)	0	36 (33)	1 (1)
Increased blood creatine phosphokinase	15 (14)	4 (4)	35 (32)	14 (13)
Vomiting	16 (15)	0	21 (19)	0
Fatigue	11 (10)	1 (1)	20 (18)	0
Hypertension	8 (7)	5 (5)	19 (17)	5 (5)
Increased lipase	8 (7)	4 (4)	19 (17)	5 (5)
Muscle spasms	9 (8)	0	19 (17)	0
Rash	6 (6)	1 (1)	19 (17)	4 (4)
Increased aspartate aminotransferase	12 (11)	0	18 (16)	3 (3)
Increased amylase	11 (10)	1 (1)	17 (15)	2 (2)
Increased alanine aminotransferase	12 (11)	0	13 (12)	4 (4)
Pneumonitis	3 (3)	2 (2)	10 (9)	4 (4)

[a]Relationship to study treatment was as per investigator assessment.
[b]180 mg once daily with 7-day lead-in at 90 mg.
Note: Median time on treatment was 13.2 months in arm A and 17.1 months in arm B.

(HR [95% CI]: 0.17 [0.04–0.82]), 11.1 months (9.2–NR) for 26%–50% shrinkage (HR: 0.07 [0.01–0.35]), 16.7 months (12.8–NR) for 51%–75% shrinkage (HR: 0.06 [0.01–0.29]), and 15.6 (9.2–21.2) for 76%–100% shrinkage (HR: 0.08 [0.02–0.39]) (Fig. 3*D*).

Multivariate analyses on the basis of both investigator-assessed and IRC-assessed outcomes reported that 26%–50%, 51%–75%, and 76%–100% target lesion shrinkage versus no shrinkage was independently associated with longer PFS and OS (Supplementary Table 2).

Efficacy by Previous Response to Crizotinib. Investigator-assessed cORR was higher among patients who had CR or PR as best response to previous crizotinib (51% [36 of 71] in arm A; 67% [49 of 73] in arm B) compared with patients with other or unknown response to previous crizotinib (37% [15 of 41] in arm A; 35% [13/37] in arm B). Median investigator-assessed PFS (95% CI) was longer in patients with PR or CR to previous crizotinib (11.0 months [7.4–15.6] in A; 15.6 months [11.1–21.1] in B) compared with those with other or unknown response to previous crizotinib (7.4 months [3.7–9.3] in A; 12.9 months [5.2–22.8] in B).

Safety

Most common any-grade AEs judged as related to treatment by the investigator were diarrhea (16% and 35% in arms A and B, respectively), nausea (26% and 33%), and increased blood creatine phosphokinase (14% and 32%; Table 2). Most common grade 3 or higher AEs judged as related to treatment by the investigator were increased blood creatine phosphokinase (4% and 13%); hypertension (5% and 5%); and increased lipase (4% and 5%). Dose reduction because of any AE occurred in 7% (8 of 109) and 29% (32 of 110) of treated patients in arms A and B, respectively. The most common AE leading to dose reduction was increased blood creatine phosphokinase (2% and 6%; Supplementary Table 3). Dose interruption because of any AE occurred in 41% (45 of 109) and 62% (68 of 110) of treated patients in arms A and B, respectively. Discontinuation because of any AE occurred in 4% (4 of 109) and 11% (12 of 110) of treated patients in arms A and B, respectively. The median dose intensity was 90 mg per day in arm A and 169 mg per day in arm B.

As reported previously,[17] a subset of pulmonary AEs with early onset (median: Day 2; range: Days 1–9) including dyspnea, hypoxia, cough, pneumonia, and pneumonitis occurred in 14 (6%) of 219 treated patients (seven [3%] had grade ≥3 events). All events occurred at 90 mg in both arms; no such events occurred after escalation to 180 mg. Management of these events included dose interruption or discontinuation and empirical treatment (e.g., steroids and antibiotics).

Discussion

At a median follow-up of 24 months, the approved brigatinib dosing regimen of 180 mg once daily (with 7-day lead-in at 90 mg) given post-crizotinib was

associated with a high cORR (56%), comparable to the objective response rate (ORR) reported for the United States Food and Drug Administration–approved ALK inhibitors ceritinib (33%–58%)[7-10] and alectinib (46%–50%).[11,12] It was lower than that reported for lorlatinib (73%; approved after crizotinib use plus at least one other ALK inhibitor, or after alectinib or ceritinib as the first ALK inhibitor) in this setting.[19] These similar response rates may well reflect shared activity against comparable percentages of the most common post-crizotinib resistance mechanisms in either the body (extra-CNS) or CNS. However, the median IRC-assessed PFS with this brigatinib regimen (16.7 months) seems numerically prolonged relative to other drugs in the same clinical setting (ceritinib median PFS: 5−7 months,[7-10] alectinib median PFS: 8−9 months,[11,12] lorlatinib median PFS: 11.1 months).[14,19] In addition, the median PFS for brigatinib was remarkably similar for the same dose in the same setting explored in the phase 1 study of brigatinib (16.3 months).[20]

Why brigatinib is associated with the longest recorded median PFS to date of any second- or third-generation ALK inhibitor in the post-crizotinib setting is only partially understood. Preclinically, it has a broader spectrum of activity against the *ALK* resistance mutations that arise after crizotinib use than that of either ceritinib or alectinib, but not that of lorlatinib.[21,22] Whether this reflects either some aspect of clinical anti-*ALK* activity missed by preclinical modeling or some clinically relevant non–*ALK*-related activity inherent in brigatinib but not in the other drugs has to be considered.

With regard to CNS activity (which is not assessed in the preclinical comparison data), the 180-mg (with 7-day lead-in at 90 mg) brigatinib dosing regimen demonstrated sustained intracranial activity in patients with baseline brain metastases, with an IRC-assessed confirmed iORR of 67% in patients with measurable CNS lesions, a median duration of intracranial response (iDOR) of 16.6 months, and a median iPFS of 18.4 months. Although comparisons to CNS outcomes with other ALK inhibitors are limited by small sample sizes and differing patient characteristics and assessment methods, intracranial outcomes with brigatinib seem numerically superior to post-crizotinib data for ceritinib (median iDOR, 7 months[10]) and alectinib (median iDOR, 11 months).[23-25] Lorlatinib seems to have at least comparable CNS activity.[13] Among 59 patients who received lorlatinib in the post-crizotinib setting in a phase 2 study, the confirmed iORR in patients with measurable baseline CNS lesions was 87% (20 of 23 patients).[13]

In the exploratory analysis presented here using investigator-assessed data, the percentage of patients receiving the 180-mg (with 7-day lead-in at 90 mg) brigatinib dosing regimen who manifested at least 30% shrinkage of target lesions inside versus outside of the CNS was high in both body compartments. Although the data set is too small to impute statistical significance, the numerical difference (82% versus 67% in favor of the CNS) continues to support the importance of assessing CNS and extra-CNS data separately, and also in the usual combined overall ORR and PFS data sets.[26,27] Specifically, owing to the poor CNS penetration of crizotinib, CNS penetrant drugs given after crizotinib have been predicted to have higher efficacy in the CNS than extra-CNS, as the CNS lesions may behave as if they are more treatment naive.[28] This effect is also apparent from the available lorlatinib data in which the CNS versus extra-CNS ORR difference after crizotinib use is 88% versus 63%, remarkably similar to the brigatinib data shown here; the ORR rates for lorlatinib drop to 64% versus 37% after two previous ALK tyrosine kinase inhibitors (TKIs).[13] Notably, the target lesion response rates do not include any contribution from non–target lesions, which may explain the numerically higher values than those reported in the formal RECIST ORR in this study.

Previous response to crizotinib was associated with greater efficacy for brigatinib, potentially explicable by either baseline co-driver activity being present in those without a response to crizotinib, or the presence of false-positive *ALK* testing in these cases. These observations suggest the percentage of patients without a previous response to crizotinib should be considered when comparing between studies in the post-crizotinib setting.

Results of the exploratory analyses of survival outcomes in relation to the depth of target lesion shrinkage showed that patients who had target lesion shrinkage by IRC or investigator assessment, including patients who had not achieved confirmed PR, had numerically longer PFS and OS than patients without tumor shrinkage. The value of tumor shrinkage as an appropriate indicator of outcome in NSCLC has been evaluated in other retrospective analyses in patients with advanced *ALK*+ or *EGFR*–mutant NSCLC.[29-31] A multivariate analysis of the two crizotinib trials (n=305) found that OS increased as the quartile for depth of target lesion response increased (adjusted OS HR versus no tumor shrinkage [95% CI]: 1%–25% shrinkage, 0.94 [0.34–2.61]; 26%–50% shrinkage, 0.56 [0.21–1.51]; 51%–75% shrinkage, 0.28 [0.11–0.73]; 76%–100% shrinkage, 0.05 [0.01–0.28]). However, depth of response was not shown to be a substantial predictor of OS or PFS in advanced *EGFR*–mutant lung cancer in a landmark multivariate analysis of data from five randomized trials (n=1081) of front-line *EGFR*-TKI versus chemotherapy.[32]

The safety profile of brigatinib was consistent with previous reports, with no new safety concerns noted.[17,33] Clinically apparent pulmonary AEs occurring

within days of initiating brigatinib were observed in 6% of treated patients in ALTA. Management strategies of these transient events include dose interruption and clinical evaluation, with the potential for tolerization through supportive care and continued dosing.[34]

In conclusion, the recommended dosing regimen of brigatinib (180 mg once daily with 7-day lead-in at 90 mg) is associated with significant intracranial, extracranial, and systemic activity and the longest reported median PFS after crizotinib use to date of any second- or third-generation ALK TKI. The continued suggestion of a difference in efficacy between the 90- and 180-mg dose cohorts supports the goal to maximize the proportion of patients escalating to 180 mg (arm B of this study).[34] Intracranial versus extracranial efficacy and depth of response may be important end points to capture in future targeted therapy trials, and response to previous crizotinib may be important to consider when comparing data between trials.

Data Availability

Takeda makes patient-level, deidentified data sets and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research has been allowed, and other criteria have been met as set forth in Takeda's Data Sharing Policy (see https://www.takedaclinicaltrials.com/ for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict of interest that can result in potential bias. Once approved, qualified researchers who sign a data sharing agreement are provided access to these data in a secure research environment.

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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.2019.11.004.

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