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

BRIGATINIB IN CRIZOTINIB-REFRACTORY ALK+ NON–SMALL CELL LUNG CANCER: 2-YEAR FOLLOW-UP ON SYSTEMIC AND INTRACRANIAL OUTCOMES IN THE PHASE 2 ALTA TRIAL

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Brigatinib in Crizotinib-Refractory ALK+ Non–Small Cell Lung Cancer: 2-Year Follow-up on Systemic and Intracranial Outcomes in the Phase 2 ALTA Trial

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Abbreviations: AEs, adverse events; ALK , anaplastic lymphoma kinase; *ALK,* anaplastic lymphoma kinase gene; CIs, confidence intervals; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; ECOG, Eastern Cooperative Oncology Group; *EGFR,* epidermal growth factor receptor*;* HR, hazard ratio; iDOR, duration of intracranial response; iORR, intracranial ORR; iPFS, intracranial PFS; IRC, independent review committee; NR, not reached; NSCLC , non–small cell lung cancer; PFS, progression-free survival; PR, partial response; ORR, objective response rate; OS, overall survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKIs, tyrosine kinase inhibitors; TRAEs, AEs judged as related to treatment by the investigator

Text word count: 3313 (limit: 4000); Abstract: 263 (limit: 250); Figures: 3; Tables: 2; References: 34; Supplemental Tables: 3

ABSTRACT

Introduction: We report updated data from a phase 2 randomized study evaluating brigatinib in crizotinib-refractory anaplastic lymphoma kinase (ALK)-positive non–small cell lung cancer (NSCLC).

Methods: Patients were stratified by brain metastases and best response to crizotinib, and randomized 1:1 to oral brigatinib 90 mg qd (arm A) or 180 mg qd with 7-day lead-in at 90 mg (B). Primary endpoint was investigator-assessed confirmed objective response rate (cORR). Secondary endpoints included independent review committee (IRC)-assessed progression-free survival (PFS), intracranial PFS (iPFS) and overall survival (OS). Exploratory analyses included central nervous system (CNS) vs ex-CNS target lesion response and correlation of depth of response with PFS and OS.

Results: Among 222 randomized patients (A/B: n=112/110), 59 (27%) continued brigatinib at analysis (median follow-up: 19.6/24.3 months in A/B). At baseline, 71%/67% had brain lesions. Investigator-assessed cORR was 46%/56%. Median IRC-assessed PFS was 9.2 months (95% CI, 7.4–12.8)/16.7 months (11.6–21.4). Median OS was 29.5 months (18.2–not reached [NR])/34.1 months (27.7–NR). IRC-confirmed intracranial ORR (iORR) in patients with measurable baseline brain lesions was 50% (13/26)/67% (12/18); median duration of intracranial response (iDOR) was 9.4/16.6 months. IRC-assessed iPFS was 12.8/18.4 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.

Conclusions: Brigatinib (at 180 mg qd with lead-in) continues to demonstrate the longest recorded post-crizotinib PFS of any next-generation ALK inhibitor, long iPFS

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and iDOR, and high iORR. Depth of response may be an important endpoint to capture in future targeted therapy trials.

Keywords: anaplastic lymphoma kinase, ALK tyrosine kinase receptor, brigatinib, non–small cell lung cancer

INTRODUCTION

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Approximately 3%−5% of patients with non–small cell lung cancer (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 progress on crizotinib due to acquired ALK resistance mutations, secondary driver pathways, and/or poor central nervous system (CNS) drug penetration.[4-6] Post-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) <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 who had progressive disease on or 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 daily with 7-day lead-in at 90 mg.[17]

Herein, we report updated data and new exploratory analyses on the 2 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 are published.[17] Briefly, eligible patients (≥18 years) had locally advanced or metastatic ALK-positive NSCLC, disease progression while receiving crizotinib, no other prior ALK-directed therapy, ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1),[18] and Eastern Cooperative Oncology Group (ECOG) performance status ≤2. Patients could not have received crizotinib within 3 days of the first brigatinib dose; cytotoxic chemotherapy or radiation therapy (except stereotactic [body] radiosurgery) within 14 days; or 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/absence of baseline brain metastases and best response to crizotinib (investigator-assessed complete response [CR] or partial response [PR] vs other or unknown) and randomized 1:1 to either 90 mg qd (arm A) or 180 mg qd with a 7-day lead-in at 90 mg (180 mg qd [with lead-in]; arm B). Patients

continued to receive brigatinib until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Treatment in either arm could be continued after progression at investigator's discretion. Patients in arm A could transition to brigatinib 180 mg qd after progression at 90 mg qd. 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 v1.1 in chest and abdomen images obtained by contrast enhanced computed tomography or magnetic resonance imaging (MRI) at screening and every 8 weeks through cycle 15 (28 days/cycle) and then every 12 weeks until progression. Baseline CNS imaging was required in all patients; for patients with CNS metastases, contrast-enhanced MRI of the brain was also required every 8 weeks thereafter. A central independent review committee (IRC) reviewed on-study images. Objective responses were confirmed ≥4 weeks after initial response. Follow-up for survival and subsequent therapy continued every 3 months after treatment discontinuation.

Outcomes

The primary endpoint was investigator-assessed confirmed objective response rate (cORR) per RECIST v1.1. Secondary endpoints 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 ≥30% decrease in measurable 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 vs 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 ≥1 evaluable response assessment from arms A and B were pooled and those with any target lesion shrinkage were sorted into 4 categories (1%–25%; 26%–50%; 51%–75%; and 76%–100% shrinkage) based on greatest decrease from baseline using RECIST v1.1.[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 vs 2), and smoking status (never/unknown vs current/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.[17] 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 endpoint), and 95% CIs were used for other endpoints.[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 whole-body and intracranial efficacy data had a last scan date of 18-Sep-2017. Statistical analyses were performed using SAS software (version 9.4).[17]

RESULTS

Patients

Among 222 randomized patients (arm A: n=112; arm B: n=110), 59 (27%) remained in the study (arm A: 27 [24%]; arm B: 32 [29%]) as of 29-Sep-2017 (**Figure 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 (**Table S1**) are published.[17] At baseline, the majority of patients had brain lesions (arm A: 80/112 [71%]; arm B: 74/110 [67%]) and approximately half had active brain lesions (arm A: 54/112 [48%]; arm B: 55/110 [50%]). Approximately 16% (70/451) of all target lesions were located in the CNS (arm A: 15% [38/247]; arm B: 16% [32/204]). A total of 51 (23%) patients had ≥1 target lesion in the CNS (arm A: 28 [25%]; arm B: 23 [21%]). Of 44 patients with measurable brain lesions identified by IRC at baseline, 34 had at least 1 active brain lesion identified by the investigator.

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

Efficacy

Whole-body 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 (**Figure 2A**). 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 (**Figure 2B**). Probability of OS 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 ORR (iORR) in patients with measurable baseline CNS lesions was 50% (13/26) in arm A and 67% (12/18) in arm B, with median duration of confirmed intracranial 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 vs extracranial and overall) in patients with or without target baseline brain lesions is shown in **Figure 3A**. In patients with ≥1 intracranial target lesion at baseline, 68% (17/25) in arm A and 82% (18/22) in arm B had ≥30% shrinkage of intracranial target lesions and 59% (10/17) in arm A and 67% (6/9) in arm B had ≥30% shrinkage of extracranial target lesions. In patients without intracranial target lesions at baseline, 64% (49/76) and 68% (53/78), respectively, had ≥30% shrinkage of extracranial target lesions.

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

Investigator-assessed depth of target lesion response and survival outcomes

Investigator-assessed depth of target lesion response was evaluated in 201 patients who had ≥1 evaluable response assessment (arm A, n=101; arm B, n=100). Across treatment arms, 17 patients had no target lesion shrinkage, while 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, 7 had a confirmed CR, 34 had a confirmed PR, and 2 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]), 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 19.5 (12.9–NR) for 76%–100% shrinkage (HR: 0.26 [0.13–0.51]) (**Figure 3C**). 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]), 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 ≥1 evaluable response assessment (arm A, n=97; arm B, n=94). Across treatment arms, 4 patients had no target lesion shrinkage, while 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 PR, and 6 had stable disease; 2 had progressive

disease despite substantial target lesion shrinkage based on 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 (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]) (**Figure 3D**).

Multivariate analyses based on both investigator-assessed and IRC-assessed outcomes showed that 26–50%, 51–75%, and 76%–100% target lesion shrinkage versus no shrinkage was independently associated with longer PFS and OS (**Table S2**).

Efficacy by prior response to crizotinib

Investigator-assessed cORR was higher among patients who had CR or PR as best response to prior crizotinib (arm A: 51% [36/71]; B: 67% [49/73]) compared with patients with other or unknown response to prior crizotinib (A: 37% [15/41]; B:35% [13/37]). Median investigator-assessed PFS (95% CI) was longer in patients with PR/CR to prior 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 prior 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 (TRAEs) were diarrhea (16%/35% in arms A/B, respectively), nausea (26%/33%), and increased blood creatine phosphokinase (14%/32%; **Table 2**). Most common grade ≥3 TRAEs were increased blood creatine phosphokinase (4%/13%), hypertension (5%/5%), and increased lipase (4%/5%). Dose reduction due to any AE occurred in 7% (8/109) and 29% (32/110) of treated patients in arms A and B, respectively. The most common AE leading to dose reduction was increased blood creatinine phosphokinase (2%/6%; **Table S3** in the Supplemental Data). Dose interruption due to any AE occurred in 41% (45/109) and 62% (68/110) of treated patients in arms A and B, respectively. Discontinuation due to any AE occurred in 4% (4/109) and 10.9% (12/110) 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 (7 [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 empiric treatment (eg, steroids and antibiotics).

DISCUSSION

With a median follow-up of 24 months, the approved brigatinib dosing regimen of 180 mg qd (with 7-day lead-in at 90 mg) given post-crizotinib was associated with a high cORR (56%), comparable to the ORR reported for US Food and Drug Administration–approved ALK inhibitors ceritinib (33%–58%)[7-10] and alectinib (46%–50%),[11,12] and lower than reported for lorlatinib (73%; approved following crizotinib and ≥1 other ALK inhibitor, or following 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) appears numerically prolonged relative to these 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, consistent with the high reproducibility of median PFS values post-crizotinib for the same drug seen with all next-generation ALK inhibitors, the median PFS for brigatinib, representing the longest reported PFS value in this setting for any next-generation ALK inhibitor to date, 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 which arise post-crizotinib than 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 present for brigatinib but not 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 appear numerically superior to post-crizotinib data for ceritinib (median iDOR, 7 months[10]) and alectinib (median iDOR, 11 months).[23-25] Lorlatinib appears 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% (20/23 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 manifesting ≥30% shrinkage of target lesions inside vs outside of the CNS was high in both body compartments. However, although the dataset is too small to impute statistical significance, the numerical difference (82% vs 67% in favor of the CNS) continues to support the importance of assessing CNS and extra-CNS data

separately, as well as in the usual combined overall ORR and PFS datasets.[26,27] Specifically, due to the poor CNS penetration of crizotinib, CNS penetrant drugs given post-crizotinib have been predicted to have higher efficacy in the CNS than extra-CNS, as the CNS lesions will behave as if they are more treatment naive.[28] This effect is also apparent from the available lorlatinib data, where the CNS versus extra-CNS ORR difference post-crizotinib is 88% vs 63%, remarkably similar to the brigatinib data shown here, but becomes 64% vs 37% post–2 prior 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.

Prior response to crizotinib was associated with greater efficacy from 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 prior 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 epidermal growth factor receptor (*EGFR*)-mutant NSCLC.[29-31] A multivariate analysis of the 2 crizotinib trials (n=305) showed that OS increased as the quartile for depth of target lesion response increased (adjusted OS HR vs 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 significant predictor of OS or PFS in advanced *EGFR*-mutant lung cancer in a landmark multivariate analysis of data from 5 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 qd with 7-day lead-in at 90 mg) is associated with significant intracranial, extracranial, and whole body activity and the longest reported median PFS post-crizotinib of any second- or third-generation ALK TKI to date. 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 per arm B of this study.[34] Intracranial versus extracranial efficacy and depth of response may be important endpoints to capture in

future targeted therapy trials, and response to prior crizotinib may be important to consider when comparing data between trials.

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TABLES

Table 1. Whole-Body and Intracranial Objective Response and Disease Control Rates by Arm

	Investigator Assessed		**IRC Assessed**	
	Arm A 90 mg qd n=112	**Arm B 90 mg → 180 mg qd[a] n=110**	**Arm A 90 mg qd n=112**	**Arm B 90 mg → 180 mg qd[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]

Abbreviations: CR, complete response; DCR, disease control rate; IRC, independent review committee; NR, not reached; ORR, objective response rate; PR, partial response.
[a]180 mg qd with 7-day lead-in at 90 mg.
[b]Primary endpoint tested at 0.025 alpha level for each dose.

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 qd n=109		Arm B 90 mg → 180 mg qd[b] n=110	
	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)

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

FIGURE LEGENDS

Figure 1. CONSORT diagram for the ALTA trial. CONSORT, Consolidated Standards of Reporting Trials.

[a]54 patients had documented disease progression per RECIST v1.1; seven had clinical disease progression.

[b]45 patients had documented disease progression per RECIST v1.1; eleven had clinical disease progression.

Figure 2. Brigatinib whole body 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.

IRC, independent review committee; ITT, intention-to-treat; NR, not reached; PFS, progression-free survival.

[a]180 mg qd with 7-day lead-in at 90 mg.

(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. ITT, intention-to-treat; OS, overall survival.

[a]180 mg qd with 7-day lead-in at 90 mg.

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 v1.1.

[a]180 mg qd with 7-day lead-in at 90 mg.

(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.

[a]180 mg qd with 7-day lead-in at 90 mg.

(C) Investigator-assessed PFS by best target lesion shrinkage and (D) IRC-assessed PFS by best target lesion shrinkage in patients with ≥1 evaluable response assessment.

IRC, independent review committee; NE, not estimable; NR, not reached; PFS, progression-free survival.

[a]Evaluable patients (n=201); [b]Kaplan-Meier estimate; [c]Per investigator assessments; [d]Evaluable patients (n=194).

FIGURES

Figure 1.

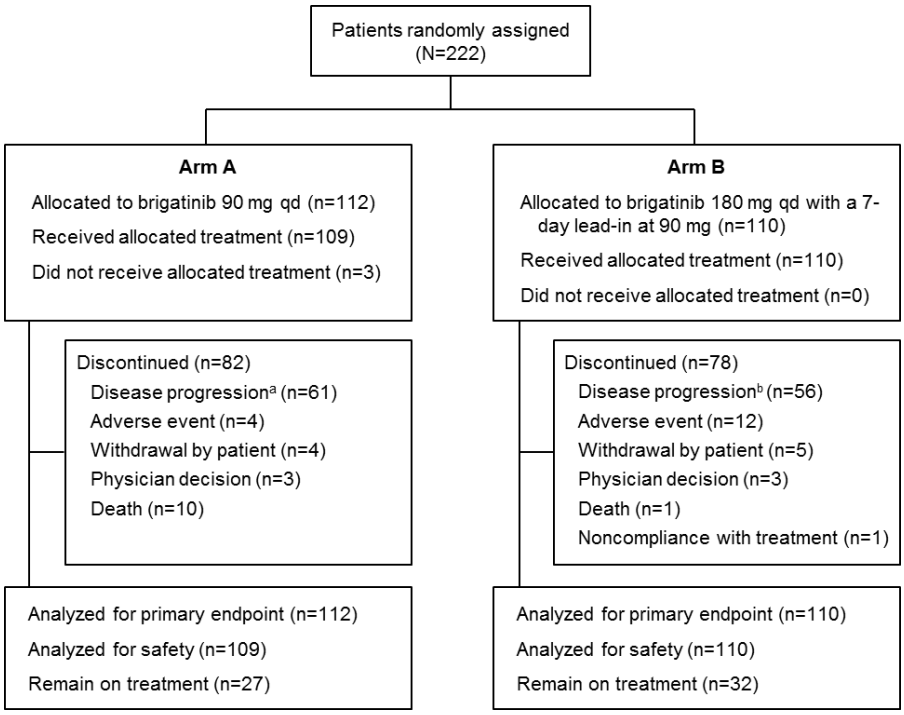
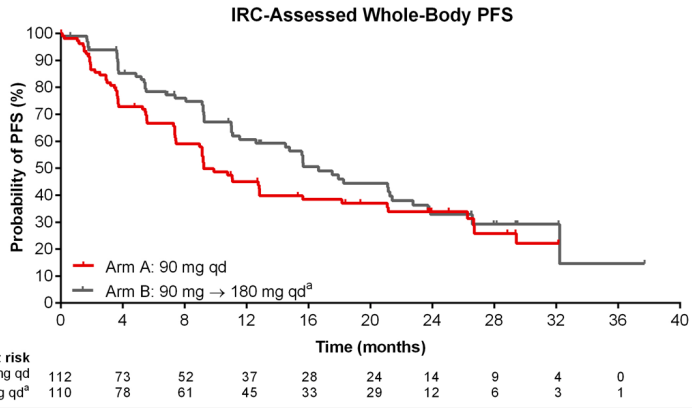


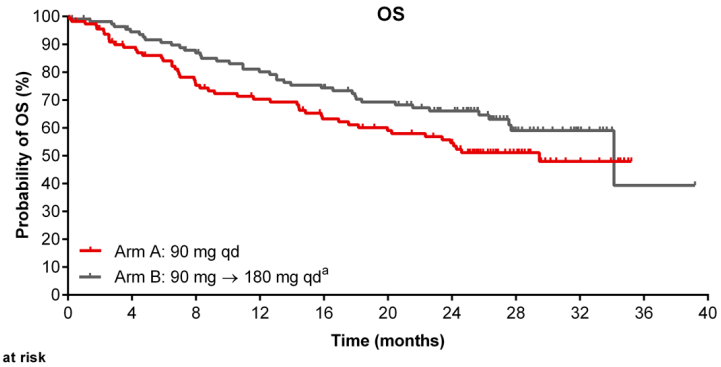
Figure 2.

(A)



	Investigator-Assessed		IRC-Assessed	
	Arm A: 90 mg qd n=112	**Arm B: 90 mg → 180 mg qd[a] n=110**	**Arm A: 90 mg qd n=112**	**Arm B: 90 mg → 180 mg qd[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)

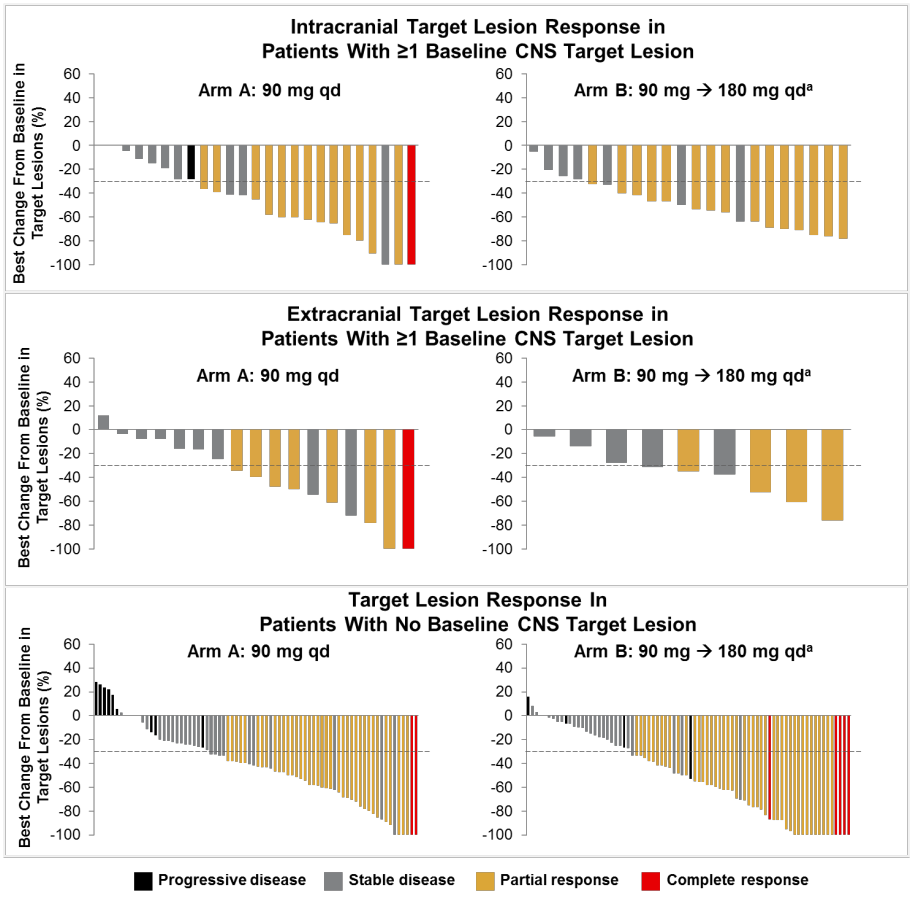
(B)



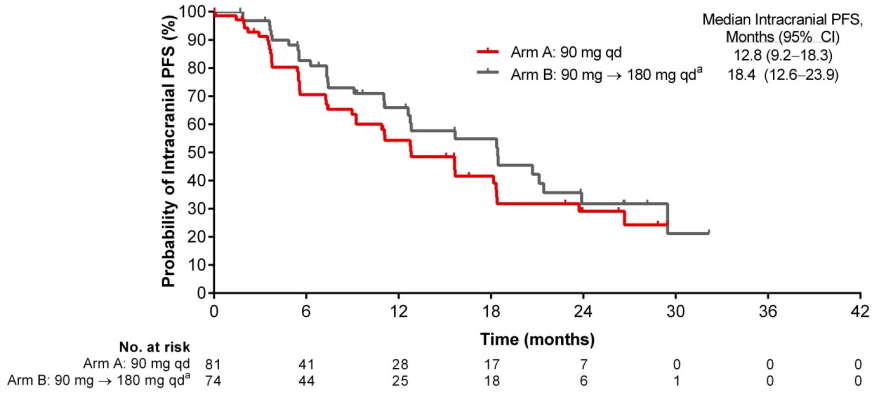
	Arm A: 90 mg qd n=112	Arm B: 90 mg → 180 mg qd[a] n=110
Median OS, months (95% CI)	29.5 (18.2–NR)	34.1 (27.7–NR)
1-year OS probability, % (95% CI)	70 (61–78)	80 (71–87)
2-year OS probability, % (95% CI)	55 (44–64)	66 (56–74)

Figure 3.

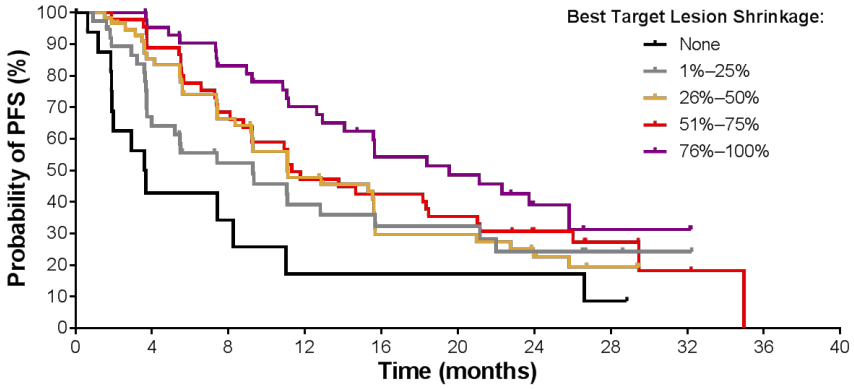
(A)


Intracranial Target Lesion Response in Patients With ≥1 Baseline CNS Target Lesion
Arm A: 90 mg qd
Arm B: 90 mg → 180 mg qd[a]
Best Change From Baseline in Target Lesions (%)
Extracranial Target Lesion Response in Patients With ≥1 Baseline CNS Target Lesion
Arm A: 90 mg qd
Arm B: 90 mg → 180 mg qd[a]
Best Change From Baseline in Target Lesions (%)
Target Lesion Response In Patients With No Baseline CNS Target Lesion
Arm A: 90 mg qd
Arm B: 90 mg → 180 mg qd[a]
Best Change From Baseline in Target Lesions (%)
60
40
20
0
-20
-40
-60
-80
-100
Progressive disease
Stable disease
Partial response
Complete response

(B)

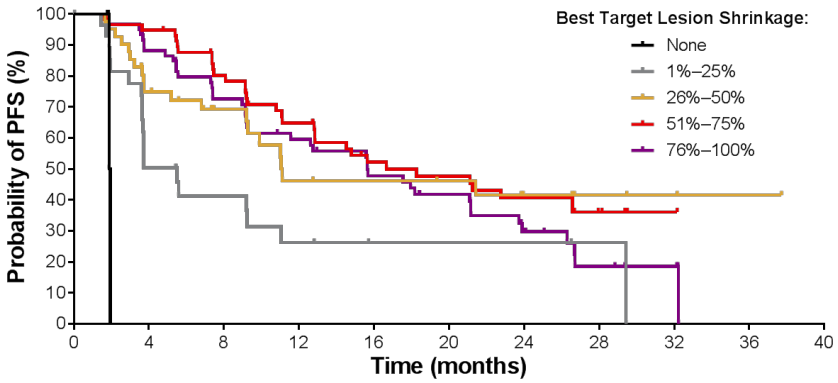

Probability of Intracranial PFS (%)
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
Time (months)
Arm A: 90 mg qd
Arm B: 90 mg → 180 mg qd[a]
Median Intracranial PFS, Months (95% CI)
12.8 (9.2–18.3)
18.4 (12.6–23.9)
No. at risk
Arm A: 90 mg qd 81 41 28 17 7 0 0 0
Arm B: 90 mg → 180 mg qd[a] 74 44 25 18 6 1 0 0

(C) Investigator-Assessed PFS by Best Target Lesion Shrinkage



Best Target Lesion Shrinkage	n (%)[a]	Median PFS[b, c] Months (95% CI)	1-Year PFS[b, c] % (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)

(D) IRC-Assessed PFS by Best Target Lesion Shrinkage



Best Target Lesion Shrinkage	n (%)[d]	Median PFS[b, c] Months (95% CI)	1-Year PFS[b, c] % (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)

SUPPLEMENTAL DATA

Supplemental Data 1.doc

Table S1. Demographics and Baseline Characteristics[17]

	Arm A 90 mg qd n=112	**Arm B 90 mg → 180 mg qd[a] n=110**	**Total N=222**
Median age, years (range)	50.5 (18–82)	56.5 (20–81)	54 (18–82)
Gender, female, n (%)	62 (55)	64 (58)	126 (57)
Race, n (%)			
White	72 (64)	76 (69)	148 (67)
Asian	39 (35)	30 (27)	69 (31)
Other	1 (1)	4 (4)	5 (2)
ECOG performance status, n (%)			
0	34 (30)	45 (41)	79 (36)
1	71 (63)	56 (51)	127 (57)
2	7 (6)	9 (8)	16 (7)
Smoking history, n (%)			
Never	71 (63)	63 (57)	134 (60)
Former	34 (30)	43 (39)	77 (35)
Current	6 (5)	4 (4)	10 (5)
Unknown	1 (1)	0	1 (<1)
Histology, n (%)			
Adenocarcinoma	107 (96)	108 (98)	215 (97)
Adenosquamous	1 (1)	0	1 (<1)

carcinoma			
Squamous	2 (2)	1 (1)	3 (1)
Large cell	1 (1)	1 (1)	2 (1)
Mucoepidermoid carcinoma	1 (1)	0	1 (<1)
Baseline brain metastases,[b] n (%)	80 (71)	74 (67)	154 (69)
Prior chemotherapy, n (%)	83 (74)	81 (74)	164 (74)
Best response to prior crizotinib,[b] n (%)			
CR or PR	71 (63)	73 (66)	144 (65)
SD	28 (25)	21 (19)	49 (22)
PD	8 (7)	6 (5)	14 (6)
Unknown	5 (4)	10 (9)	15 (7)
Median cumulative duration of prior crizotinib regimens, months (range)	11.3 (1–59)	13.2 (1–72)	12.6 (1–72)
Location of target lesions, n (%) of lesions			
Total	n=247	n=204	n=451
Extracranial	209 (85)	172 (84)	381 (84)
Intracranial	38 (15)	32 (16)	70 (16)
≥1 baseline CNS target lesion, n (%) of patients			
No	84 (75)	87 (79)	171 (77)
Yes	28 (25)	23 (21)	51 (23)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease.

[a]180 mg qd with 7-day lead-in at 90 mg.
[b]As assessed by the investigator.

Table S2. Multivariable Analyses[a] of PFS and OS in Patients With ≥1 Evaluable Response Assessment.

	Hazard Ratio (95% CI)		
	PFS		
	Investigator Assessed	IRC Assessed	OS[b]
Best target lesion shrinkage			
None	Reference	Reference	Reference
1–25%	0.53 (0.27–1.04)	0.19 (0.04–0.93)	0.55 (0.25–1.22)
26–50%	0.47 (0.25–0.89)	0.08 (0.02–0.39)	0.38 (0.17–0.84)
51–75%	0.43 (0.22–0.83)	0.07 (0.01–0.33)	0.42 (0.19–0.95)
76–100%	0.31 (0.16–0.62)	0.09 (0.02–0.43)	0.33 (0.14–0.77)
Treatment arm			
Arm A (90 mg qd)	Reference	Reference	Reference
Arm B (90 mg → 180 mg qd)[c]	0.76 (0.54–1.07)	0.81 (0.55–1.18)	0.73 (0.46–1.15)

Baseline ECOG performance status			
0–1	Reference	Reference	Reference
2	1.81	1.54	2.01
	(0.94–3.48)	(0.71–3.35)	(0.93–4.33)
Smoking status			
Never/unknown	Reference	Reference	Reference
Current/former	1.46	0.97	1.02
	(1.02–2.08)	(0.64–1.46)	(0.63–1.65)

Abbreviations: OS, overall survival; PFS, progression-free survival.

[a]Cox proportional hazards regression model.

[b]Shrinkage categories based on investigator-assessed shrinkage.

[c]180 mg qd with 7-day lead-in at 90 mg.

Table S3. Adverse Events Leading to Dose Reduction in ≥2 Patients Overall

	Arm A[a] **90 mg qd** **n=109**	**Arm B** **90 mg →** **180 mg qd[b]** **n=110**
Patients with ≥1 AE leading to dose reduction, n (%)	8 (7.3)	32 (29.1)
Blood creatine phosphokinase increased	2 (1.8)	7 (6.4)
Rash	1 (0.9)	3 (2.7)
Lipase increased	1 (0.9)	2 (1.8)
Decreased appetite	0	2 (1.8)
Electrocardiogram Qt prolonged	0	2 (1.8)
Hyponatremia	0	2 (1.8)
Nausea	0	2 (1.8)
Pneumonitis	0	2 (1.8)
Amylase increased	1 (0.9)	1 (0.9)
Cough	1 (0.9)	1 (0.9)
Hypertension	1 (0.9)	1 (0.9)

[a]For arm A, dose modification was required for any grade 3 or 4 nonhematologic toxicity, including laboratory abnormalities.

- Grade 3: For 90 mg once daily (qd) dose, hold until event is grade 1 or lower, or has returned to baseline. Resume at 90 mg qd or 60 mg qd (at investigator's discretion). For recurrence at 90 mg qd, hold until event is grade 1 or lower, or has returned to baseline, and resume treatment at 60 mg qd. When the current dose is 60 mg qd, consider discontinuing treatment.

- Grade 4: For 90 mg qd dose, hold until event is grade 1 or lower, or has returned to baseline. Resume treatment at 60 mg qd or discontinue (at investigator's discretion). When the current dose is 60 mg qd, consider discontinuing treatment.

[b]For arm B, dose modification was required for grade 2 events lasting longer than 3 days or any grades 3 or 4 nonhematologic toxicity, including laboratory abnormalities.

- For 90 mg once daily (qd) dose (prior to dose escalation):
  - Grade 2 (>3 days) and grade 3: Hold until event is grade 1 or lower, or has returned to baseline. Resume at 90 mg qd (at investigator's discretion).
  - Grade 4: Hold until event is grade 1 or lower, or has returned to baseline. Resume treatment at 60 mg qd or discontinue (at investigator's discretion).
- After dose escalation:
  - Grade 3: When the dose is 180 mg qd, hold until event is ≤grade 1, or has returned to baseline and then resume at 180 mg qd or 120 mg qd at the discretion of the investigator. When the current dose is 120 mg qd, hold until event is ≤grade 1, or has returned to baseline and resume at 90 mg qd after recovery. When the current dose is 90 mg qd, hold until event is ≤grade 1, or has returned to baseline and resume at 60 mg qd after recovery, or discontinue at the discretion of the investigator. When the current dose is 60 mg qd, consider discontinuing treatment.
  - Grade 4: When the current dose is 180 mg qd, hold until event is ≤grade 1, or has returned to baseline; resume at 120 mg qd, or discontinue, at the discretion of the investigator. When the current dose is 120 mg qd, hold until event is ≤grade 1, or has returned to baseline. Resume at 90 mg qd, or discontinue, at the discretion of the investigator. When the current dose is 90 mg qd, hold until event is ≤grade 1, or has returned to baseline and resume at 60 mg qd after recovery, or discontinue at the discretion of the investigator. When the current dose is 60 mg qd, consider discontinuing treatment.