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ORIGINAL REPORT

Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial

Dong-Wan Kim, Marcello Tiseo, Myung-Ju Ahn, Karen L. Reckamp, Karin Holmskov Hansen, Sang-We Kim, Rudolf M. Huber, Howard L. West, Harry J.M. Groen, Maximilian J. Hochmair, Natasha B. Leighl, Scott N. Gettinger, Corey J. Langer, Luis G. Paz-Ares Rodríguez, Egbert F. Smit, Edward S. Kim, William Reichmann, Frank G. Haluska, David Kerstein, and D. Ross Camidge

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ABSTRACT

Purpose

Most crizotinib-treated patients with anaplastic lymphoma kinase gene (*ALK*)–rearranged non–small-cell lung cancer (ALK-positive NSCLC) eventually experience disease progression. We evaluated two regimens of brigatinib, an investigational next-generation ALK inhibitor, in crizotinib-refractory ALK-positive NSCLC.

Patients and Methods

Patients were stratified by brain metastases and best response to crizotinib. They were randomly assigned (1:1) to oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]; arm B). Investigator-assessed confirmed objective response rate (ORR) was the primary end point.

Results

Of 222 patients enrolled (arm A: n = 112, 109 treated; arm B: n = 110, 110 treated), 154 (69%) had baseline brain metastases and 164 of 222 (74%) had received prior chemotherapy. With 8.0-month median follow-up, investigator-assessed confirmed ORR was 45% (97.5% CI, 34% to 56%) in arm A and 54% (97.5% CI, 43% to 65%) in arm B. Investigator-assessed median progression-free survival was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months (95% CI, 11.1 to not reached) in arms A and B, respectively. Independent review committee–assessed intracranial ORR in patients with measurable brain metastases at baseline was 42% (11 of 26 patients) in arm A and 67% (12 of 18 patients) in arm B. Common treatment-emergent adverse events were nausea (arm A/B, 33%/40%), diarrhea (arm A/B, 19%/38%), headache (arm A/B, 28%/27%), and cough (arm A/B, 18%/34%), and were mainly grades 1 to 2. A subset of pulmonary adverse events with early onset (median onset: day 2) occurred in 14 of 219 treated patients (all grades, 6%; grade ≥ 3, 3%); none occurred after escalation to 180 mg in arm B. Seven of 14 patients were successfully retreated with brigatinib.

Conclusion

Brigatinib yielded substantial whole-body and intracranial responses as well as robust progression-free survival; 180 mg (with lead-in) showed consistently better efficacy than 90 mg, with acceptable safety.

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INTRODUCTION

In approximately 5% of patients with non–small-cell lung cancer (NSCLC), anaplastic lymphoma kinase gene (*ALK*) rearrangements encode an oncogenic fusion protein.[1,2] Treatment with crizotinib, the first ALK inhibitor approved for use in metastatic *ALK*-rearranged (ALK-positive) NSCLC, has yielded objective response rates (ORRs) of 61% to 74% and median progression-free survival (PFS) of approximately 8 to 11 months in patients with advanced ALK-positive NSCLC.[3-5] Most crizotinib-treated patients with ALK-positive NSCLC eventually experience progression, because of acquired changes in the dominant biology of the cancer, poor CNS drug penetration resulting in CNS progression, or both.[6-8]

ASSOCIATED CONTENT

See accompanying Editorial on page 2463

Data Supplements

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Mechanisms of acquired resistance to crizotinib typically involve changes in the *ALK* gene or activation of signaling pathways that bypass ALK.[9-11] Second-generation ALK inhibitors currently approved in the postcrizotinib setting, ceritinib and alectinib, have been associated with a median PFS of 5.7 to 6.9 months[12-14] and 8.1 to 8.9 months,[15,16] respectively. However, secondary ALK kinase domain mutations, including the recalcitrant G1202R mutation, have been identified in patients whose disease progressed with ceritinib or alectinib after crizotinib therapy.[17-19] Therefore, additional ALK inhibitors that are effective against (and can suppress the development of) a broader array of ALK mutations are needed.

Brigatinib (AP26113; ARIAD Pharmaceuticals, Cambridge, MA), an investigational next-generation ALK tyrosine kinase inhibitor, was designed for potent activity against a broad range of ALK resistance mutations.[20] In preclinical models, brigatinib potently inhibited all ALK resistance mutations tested, including G1202R, and overcame mechanisms of resistance to other ALK inhibitors at clinically achievable brigatinib levels.[21] In an ongoing phase I/II clinical trial (NCT01449461), brigatinib yielded promising antitumor activity (confirmed ORR, 62%; median PFS, 12.9 months) in patients with advanced ALK-positive NSCLC previously treated with crizotinib.[22] However, during dose escalation and an initial phase II expansion at 180 mg once daily, a small proportion of patients had moderate or severe pulmonary adverse events (AEs) with early onset (usually within 24 to 48 hours) that were observed more frequently at higher starting doses. The phase II expansion therefore explored two additional regimens, 90 mg once daily and 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]). These regimens had similar preliminary activity and acceptable overall safety; 180 mg once daily (with lead-in) seemed to reduce early pulmonary AE frequency while providing greater treatment exposure.[22,23]

On the basis of phase I/II trial results, we conducted a randomized phase II trial to prospectively assess brigatinib efficacy and safety at 90 mg once daily and 180 mg once daily (with lead-in) in patients with crizotinib-refractory advanced ALK-positive NSCLC.

PATIENTS AND METHODS

Study Design and Patients

The ALK in Lung Cancer Trial of AP26113 (ALTA trial; ClinicalTrials.gov identifier: NCT02094573) is an ongoing open-label, randomized, multicenter, international phase II study. Eligible patients (≥ 18 years of age) had locally advanced or metastatic ALK-positive NSCLC, investigator-determined disease progression while receiving crizotinib, at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1),[24] adequate organ and hematologic function, and Eastern Cooperative Oncology Group performance status ≤ 2. Patients must not have received any prior ALK inhibitor other than crizotinib; crizotinib within 3 days of the first brigatinib dose; cytotoxic chemotherapy, investigational agents, or radiation therapy (except stereotactic [body] radiosurgery) within 14 days; or monoclonal antibodies within 30 days. Patients were excluded on the basis of 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. Any number of prior chemotherapy regimens was allowed. The protocol (Data Supplement) lists complete inclusion/exclusion criteria and was approved by the local institutional review board or ethics committee at each site. This 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 baseline brain metastases (present *v* absent) and best investigator-assessed response to crizotinib (complete response [CR] or partial response [PR] *v* other or unknown) and were randomly assigned (1:1) to 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]; arm B). Treatment continued until disease progression requiring alternative systemic therapy, intolerable toxicity, or consent withdrawal. Treatment in either arm could be continued at the investigator's discretion after progression. Patients in arm A could receive brigatinib 180 mg once daily after objective progression at 90 mg once daily. Dose interruptions or reductions were allowed to manage treatment-related AEs, on the basis of the investigator's judgment. AEs were graded with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

At screening, disease assessment (per RECIST v1.1) included chest and abdomen imaging by computed tomography or magnetic resonance imaging (MRI) with contrast. Contrast-enhanced brain MRI was required at screening and was repeated postbaseline for patients with CNS metastases. A central independent review committee (IRC) reviewed on-study images. Disease was assessed every 8 weeks through cycle 15 (28 days per cycle), and then every 12 weeks until progression. Objective responses were confirmed ≥ 4 weeks after initial response.

Visits were scheduled to occur on days 1, 8, and 15 of the first 28-day cycle and then every 4 weeks (starting on day 1 of cycle 2), at treatment discontinuation, and at 30 days post-treatment. On days 8 and 15, patients were assessed for early pulmonary symptoms. Follow-up for survival and subsequent therapy continued every 3 months after treatment discontinuation. The protocol includes the assessment schedule.

Outcomes

The primary end point was confirmed ORR per RECIST v1.1 (per investigator). Secondary end points included confirmed ORR (per central IRC), CNS response (IRC-assessed intracranial confirmed ORR and PFS in patients with active brain metastases), duration of response, PFS, overall survival (OS), safety, tolerability, and patient-reported symptoms of lung cancer and health-related quality-of-life (QoL) scores assessed with the European Organisation for Research and Treatment of Cancer QoL questionnaire (EORTC QLQ-C30, version 3.0), including mean transformed global health status/QoL score (on the basis of questions 29 and 30). Active brain metastases were defined as lesions without prior radiotherapy or with investigator-assessed progression after prior radiotherapy. Intracranial response was defined as a ≥ 30% decrease in measurable lesions or complete disappearance of lesions in patients with only nonmeasurable lesions.

Statistical Analysis

A sample size of ≥ 109 patients in each arm provides approximately 90% power to rule out an ORR of 20% when the true ORR is ≥ 35% with a two-sided alpha level of 0.025. Efficacy was evaluated in the intention-to-treat population. Patients with baseline brain metastases (by IRC assessment) were included in IRC analyses of intracranial efficacy. Patients who received any brigatinib were included in the safety population. CIs were calculated using the exact binomial method; 97.5% CIs were estimated for confirmed ORR (primary end point), and 95% CIs were used for other end points. For time-to-event efficacy analyses (duration of response, PFS, and OS), median values and two-sided 95% CIs were estimated using Kaplan-Meier methods. Investigator-assessed efficacy data and all safety data are reported as of February 29, 2016. IRC-assessed whole-body and

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intracranial efficacy data had last scan dates of May 16, 2016, and April 14, 2016, respectively. The trial was not designed for statistical comparisons between arms; however, post hoc hazard ratios were estimated for PFS to support dose selection. Statistical analyses were performed using SAS software (version 9.4).

RESULTS

Patients

Between June 4, 2014, and September 21, 2015, 222 patients were enrolled at 71 centers in 18 countries. Patients were randomly assigned to brigatinib in arm A (90 mg once daily; n = 112) or arm B (180 mg with a 7-day lead-in at 90 mg [180 mg once daily (with lead-in)]; n = 110; Fig 1). Three patients in arm A were never treated and are included in intention-to-treat analyses. Overall, arms were balanced for baseline factors, including sex, Eastern Cooperative Oncology Group performance status, brain metastases, prior chemotherapy, and best response to prior crizotinib (Table 1). Of 222 patients, 154 (69%) had brain metastases at baseline per investigators, 164 (74%) had prior chemotherapy, 144 (65%) had a best response of CR or PR to prior crizotinib, and 69 (31%) were Asian. As of February 29, 2016, 64 patients (57%) in arm A and 76 patients (69%) in arm B remained on study treatment, with median (range) follow-ups of 7.8 (0.1 to 16.7) months and 8.3 (0.1 to 20.2) months, respectively.

Efficacy

Investigator-assessed efficacy. Response rates are shown in Table 2. Investigator-assessed confirmed ORR was 45% (97.5% CI, 34% to 56%) in arm A, including one CR, and 54% (97.5% CI, 43% to 65%) in arm B, including four CRs. Confirmed ORR in patients with prior chemotherapy was 42% (35 of 83 patients) in arm A and 54% (44 of 81 patients) in arm B; in patients without prior chemotherapy, confirmed ORRs were 52% (15 of 29 patients) in each arm. One patient in arm B with a G1202R mutation detected from tumor tissue at baseline had a confirmed PR. The median time to response was rapid: 1.8 months (range, 1.7 to 9.1 months) and 1.9 months (1.0 to 11.0 months) in arms A and B, respectively. As of data cutoff, the median duration of response was 13.8 months (95% CI, 5.6 to 13.8) in arm A (with 14 [28%] events in 50 responders) and 11.1 months (95% CI, 9.2 to 13.8) in arm B (with 12 [20%] events in 59 responders). The change from baseline in target lesions is shown in Fig 2A. Investigator-assessed median PFS was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months (11.1 to not reached) in arms A and B, respectively (Fig 2B). The PFS hazard ratio was 0.55 (95% CI, 0.35 to 0.86; arm B *v* A). Preliminary OS estimates are shown in Fig 2C. The 1-year OS probability was 71% (95% CI, 60% to 79%) and 80% (67% to 88%) in arms A and B, respectively.

IRC-assessed whole-body efficacy. IRC-assessed confirmed ORR was 48% (95% CI, 39% to 58%) and 53% (95% CI, 43% to 62%), with four and five CRs, in arms A and B, respectively. The median duration of response was 13.8 months (95% CI, 7.4 to not reached) in arm A and 13.8 months (95% CI, 9.3 to not reached) in arm B. The IRC-assessed median PFS was 9.2 months (95% CI, 7.4 to not reached) and 15.6 months (11.0 to not reached) in arms A and B, respectively (Data Supplement).

IRC-assessed intracranial efficacy. Of 222 patients, 217 had an IRC-evaluated baseline brain MR image; 153 had baseline brain metastases and 44 had measurable lesions. Table 3 shows intracranial response rates. The IRC-assessed intracranial ORR in patients with measurable baseline brain metastases was 42% (11 of 26 patients; 95% CI, 23% to 63%) in arm A and 67% (12 of 18 patients; 95% CI, 41% to 87%) in arm B. Within each arm, response rates were similar among all patients with measurable baseline brain metastases and those with active brain metastases (lesions without prior radiotherapy or with investigator-assessed progression after prior radiotherapy). In patients with only nonmeasurable baseline brain metastases, 7% (four of 54 patients;

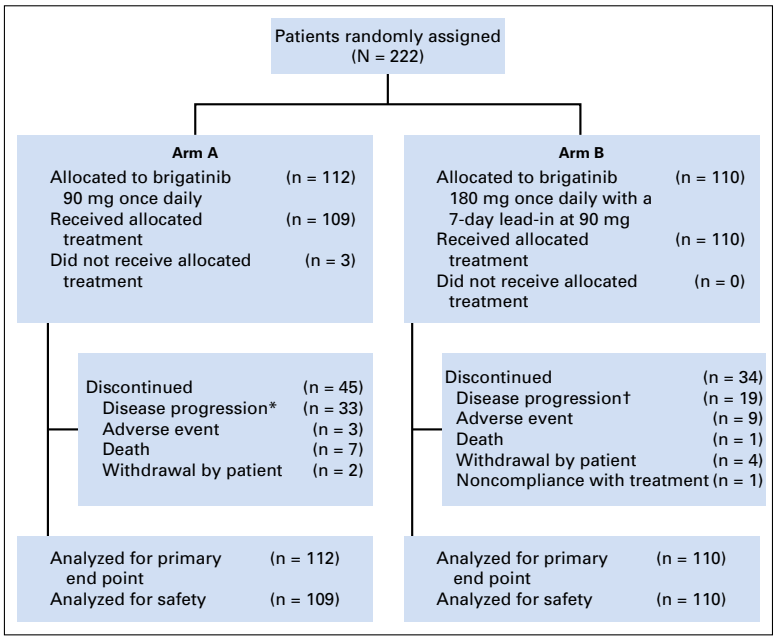

Fig 1. CONSORT diagram for the ALTA trial. ALTA, ALK in Lung Cancer Trial of AP26113; (*) Twenty-nine patients had documented disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; four had clinical disease progression. (†) Sixteen patients had documented disease progression per RECIST version 1.1; three had clinical disease progression.

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Table 1. Patient Demographic Data and Baseline Characteristics

Characteristic	Arm A, 90 mg Once Daily	Arm B, 180 mg Once Daily (with lead-in)*	Total
No. of patients	112	110	222
Median age, years (range)	50.5 (18-82)	56.5 (20-81)	54 (18-82)
Sex, female, No. (%)	62 (55)	64 (58)	126 (57)
Race, No. (%)			
White	72 (64)	76 (69)	148 (67)
Asian	39 (35)	30 (27)	69 (31)
Other	1 (1)	4 (4)	5 (2)
ECOG performance status, No. (%)			
0	34 (30)	45 (41)	79 (36)
1	71 (63)	56 (51)	127 (57)
2	7 (6)	9 (8)	16 (7)
Smoking history, No. (%)			
Yes	40 (36)	47 (43)	87 (39)
No	71 (63)	63 (57)	134 (60)
Unknown	1 (1)	0	1 (< 1)
Histology, No. (%)			
Adenocarcinoma	107 (96)	108 (98)	215 (97)
Adenosquamous carcinoma	1 (1)	0	1 (< 1)
Squamous	2 (2)	1 (1)	3 (1)
Large cell	1 (1)	1 (1)	2 (1)
Mucoepidermoid carcinoma	1 (1)	0	1 (< 1)
Brain metastases at baseline,† No. (%)	80 (71)	74 (67)	154 (69)
Prior chemotherapy, No. (%)	83 (74)	81 (74)	164 (74)
Best response to prior crizotinib,† No. (%)			
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)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PR, partial response; SD, stable disease.
*180 mg once daily with 7-day lead-in at 90 mg.
†As assessed by the investigator.

95% CI, 2% to 18%) in arm A and 18% (10 of 55 patients; 95% CI, 9% to 31%) in arm B had complete resolution of intracranial lesions. The change from baseline in measurable brain lesions is shown in Fig 3A. In patients with intracranial response, the median duration of intracranial response was not reached (95% CIs: 3.7 months to not reached, arm A; 5.6 months to not reached, arm B). The median intracranial PFS was 15.6 months (95% CI, 7.3 to 15.7) and 12.8 months (11.0 to not reached) in arms A and B, respectively (Fig 3B).

Safety

AEs. The most common any-grade treatment-emergent AEs (TEAEs) included GI symptoms (nausea, 33%/40% and diarrhea, 19%/38%, in arms A/B, respectively), headache (28%/27%, arms A/B), and cough (18%/34%, arms A/B; Table 4). Some TEAEs seemed to be dose related, although differences were mainly in grade 1 to 2 events. The most common grade ≥ 3 TEAEs (excluding neoplasm progression) were hypertension (6%/6%, arms A/B), increased blood creatine phosphokinase (3%/9%, arms A/B),

Table 2. Objective Response and Disease Control Rates by Arm

Variable	Investigator-Assessed		IRC-Assessed	
	Arm A, 90 mg Once Daily	Arm B, 180 mg Once Daily (with lead-in)*	Arm A, 90 mg Once Daily	Arm B, 180 mg Once Daily (with lead-in)*
No. of patients	112	110	112	110
Confirmed ORR, No. (%)	50 (45)	59 (54)	54 (48)	58 (53)
97.5% CI† or 95% CI	34 to 56†	43 to 65†	39 to 58	43 to 62
Confirmed CR, No. (%)	1 (1)	4 (4)	4 (4)	5 (5)
Confirmed PR, No. (%)	49 (44)	55 (50)	50 (45)	53 (48)
Disease control rate, No. (%)	92 (82)	95 (86)	87 (78)	92 (84)
95% CI	74 to 89	79 to 92	69 to 85	75 to 90

Abbreviations: CR, complete response; IRC, independent review committee; ORR, objective response rate; PR, partial response.
*180 mg once daily with 7-day lead-in at 90 mg.
†Primary end point tested at 0.025 alpha level for each dose.

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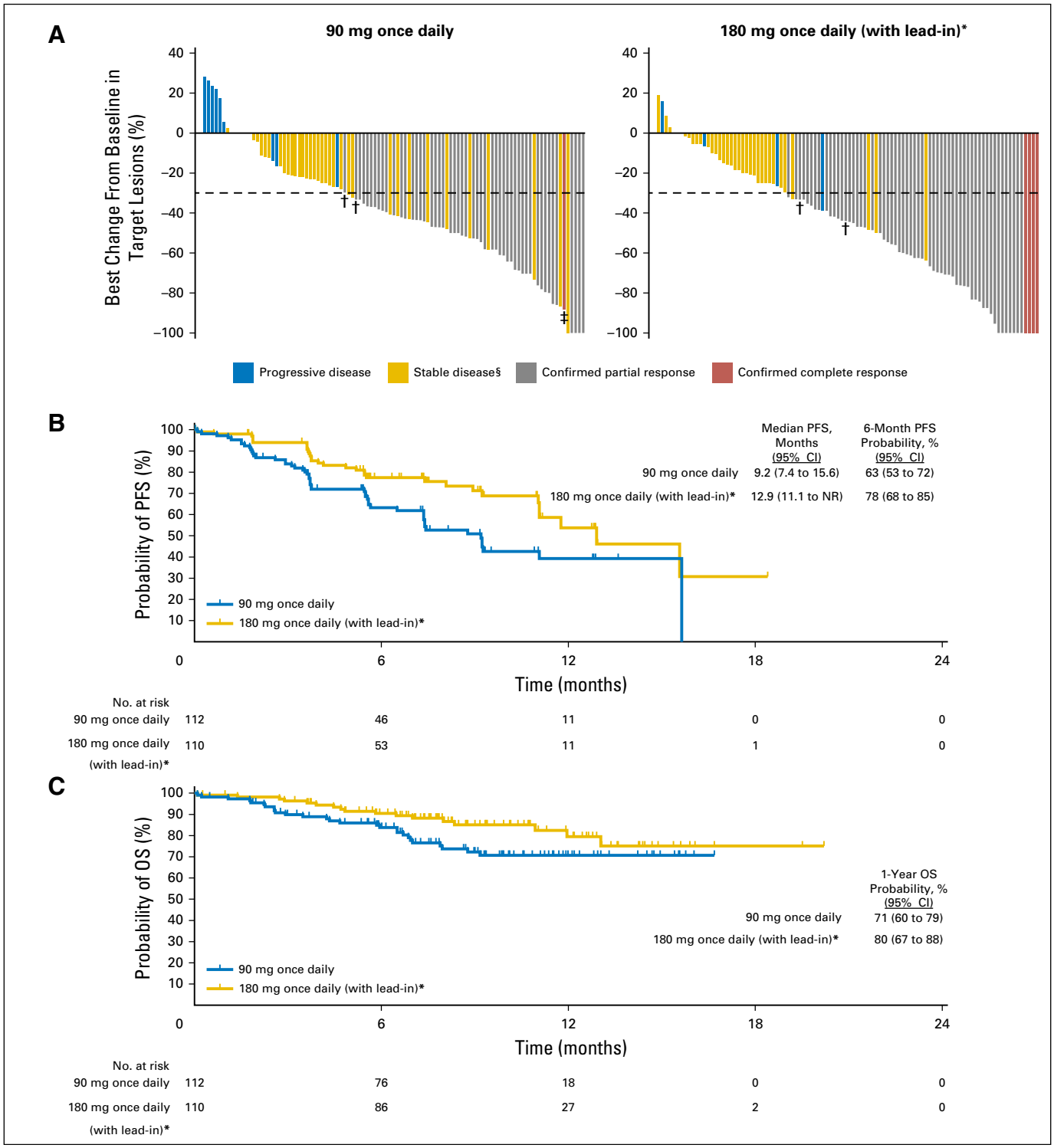

Fig 2. Brigatinib whole-body efficacy in crizotinib-refractory ALK-positive NSCLC by arm. (A) The best percentage change from baseline in the sum of the longest diameters of target lesions is reported in patients who had a follow-up scan and were evaluable for response (n = 101, arm A; n = 100, arm B), on the basis of investigator assessment. All study assessments were used in these calculations. The dotted line at −30% indicates the threshold for partial response per RECIST v1.1. The percentages of patients with no reduction, > 0% to 25% reduction, > 25% to 50% reduction, > 50% to 75% reduction, and > 75% to 100% reduction in target lesions were 13%, 20%, 35%, 20%, and 13% in arm A, respectively, and 7%, 23%, 29%, 19%, and 22% in arm B, respectively. (B) Investigator-assessed PFS is shown for the intention-to-treat population. Of the 112 patients in arm A, 50 (45%) had an event; of the 110 patients in arm B, 31 (28%) had an event. (C) Preliminary OS is shown for the intention-to-treat population. Of the 112 patients in arm A, 27 (24%) had an event; of the 110 patients in arm B, 17 (15%) had an event. ALK-positive, anaplastic lymphoma kinase gene–rearranged; NR, not reached; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. (*) 180 mg once daily with 7-day lead-in at 90 mg. (†) Single response awaiting confirmation. (‡) Patient had a lymph node target lesion that resolved to < 10 mm shortest diameter (complete response per RECIST v1.1). (§) Category includes single responses that were not confirmed.

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Table 3. Independent Review Committee–Assessed Intracranial Response Rates by Arm

Variable	Patients With Measurable (≥ 10 mm) Brain Metastases		Patients With Measurable (≥ 10 mm), Active* Brain Metastases	
	Arm A, 90 mg Once Daily	Arm B, 180 mg Once Daily (with lead-in)†	Arm A, 90 mg Once Daily	Arm B, 180 mg Once Daily (with lead-in)†
No. of patients	26	18	19	15
Confirmed intracranial ORR, No. (%)	11 (42)	12 (67)	8 (42)	11 (73)
95% CI	23 to 63	41 to 87	20 to 67	45 to 92
Confirmed intracranial CR, No. (%)	2 (8)	0	2 (11)	0
Confirmed intracranial PR, No. (%)	9 (35)	12 (67)	6 (32)	11 (73)
Intracranial disease control rate, No. (%)	22 (85)	15 (83)	16 (84)	14 (93)
95% CI	65 to 96	59 to 96	60 to 97	68 to 100

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response.
*Active brain metastases were defined as lesions without prior radiotherapy or those with investigator-assessed progression after prior radiotherapy.
†180 mg once daily with 7-day lead-in at 90 mg.

pneumonia (3%/5%, arms A/B), and increased lipase (4%/3%, arms A/B).

Pulmonary AEs with early onset. A subset of pulmonary AEs with early onset (median time to onset, 2 days [range, 1 to 9 days]) that included dyspnea, hypoxia, cough, pneumonia, or pneumonitis occurred in 14 patients (6%); seven patients (3%) had grade ≥ 3 events (Data Supplement). These AEs occurred at 90 mg, in both arms, and no such events occurred after escalation to 180 mg. They were managed with dose interruption and successful reintroduction of brigatinib in six of 14 patients, and one patient continued treatment with resolution of symptoms after dose reduction to 60 mg once daily without needing interruption. Seven patients discontinued treatment, including one patient who died on day 7, after experiencing dyspnea, cough, and pneumonia. This patient's autopsy revealed lymphangitic carcinomatosis, widespread lung scarring, and diffuse alveolar damage. Pathologist-reported causes of death were lung cancer, adhesive pericarditis, and respiratory failure. A multivariable analysis evaluated the impact of baseline risk factors on the development of pulmonary AEs with early onset (Data Supplement). Older age and shorter interval (< 7 days) between the last crizotinib dose and the first brigatinib dose were significantly associated with an increased event rate. Baseline characteristics for patients receiving crizotinib < 7 versus ≥ 7 days before brigatinib are shown in the Data Supplement.

Dose modifications. Dose reduction as the result of any AE occurred in 7% (eight of 109) and 20% (22 of 110) of treated patients in arms A and B, respectively. Dose interruption (≥ 3 days) for any reason occurred in 18% (20 of 109) and 36% (40 of 110) of patients in arms A and B, respectively. The median dose intensity was 90 mg per day in arm A and 174 mg per day in arm B. The most common reasons for dose reduction were increased blood creatine phosphokinase (n = 2, arm A/n = 5, arm B), pneumonitis (n = 1, arm A/n = 2, arm B), and rash (n = 1, arm A/n = 2, arm B). Eight patients (4%) died within 30 days of the last dose (excluding those who died as a result of neoplasm progression, malignant pleural effusion, and metastases to meninges). Investigator-reported reasons for death included pneumonia (n = 2; one case was an early pulmonary AE), bacterial meningitis (n = 1), dyspnea (n = 1), pulmonary embolism (n = 1), respiratory failure (n = 1), sudden death (n = 1), and urosepsis (n = 1).

QoL

The mean transformed global health status/QoL score (on the basis of questions 29 and 30 of EORTC QLQ-C30) gradually increased through approximately month 7 and then slowly declined, but remained higher than baseline values (Data Supplement). No significant differences between arms were observed at baseline or during follow-up.

DISCUSSION

Brigatinib demonstrated substantial efficacy with both regimens. Objective response rates were high, and responses occurred quickly and were durable in both arms. Efficacy outcomes favored the higher dose, most notably in PFS and intracranial responses. At 180 mg (with lead-in at 90 mg), the confirmed ORR was 54% (59 of 110 patients), and the intracranial ORR was 67% for patients with measurable brain metastases. The median PFS was > 1 year by investigator assessment (12.9 months) and by IRC assessment (15.6 months), and the estimated 1-year OS was 80%.

Objective response rates for ALK inhibitors in the post-crizotinib setting (brigatinib, ceritinib, and alectinib) seem similar across most trials, at 50% to 56%,[13,15,16,25] although somewhat different patient populations and methods of assessment limit comparison. These response rates probably reflect comparable activity against dominant crizotinib-resistant clones. However, any differences among these drugs in their ability to suppress clinically relevant ALK mutations, including those that may not be dominant initially but could emerge later, are more likely to be reflected in PFS or duration of response.[12-16,21] In preclinical models, brigatinib had broader predicted mutation coverage, compared with ceritinib and alectinib.[21] Consistent with this observation, in the phase I/II trial of brigatinib, the median PFS of patients with advanced ALK-positive NSCLC who previously received crizotinib (most of whom received 180 mg per day, with or without lead-in at 90 mg) was recently reported as 12.9 months, across all doses tested.[22] This extended PFS, relative to ceritinib[12-14] and alectinib[15,16] results, is substantiated by the median PFS of > 1 year in arm B of ALTA. Additionally, a patient with the recalcitrant G1202R mutation had a confirmed PR, as predicted by preclinical data. A limitation

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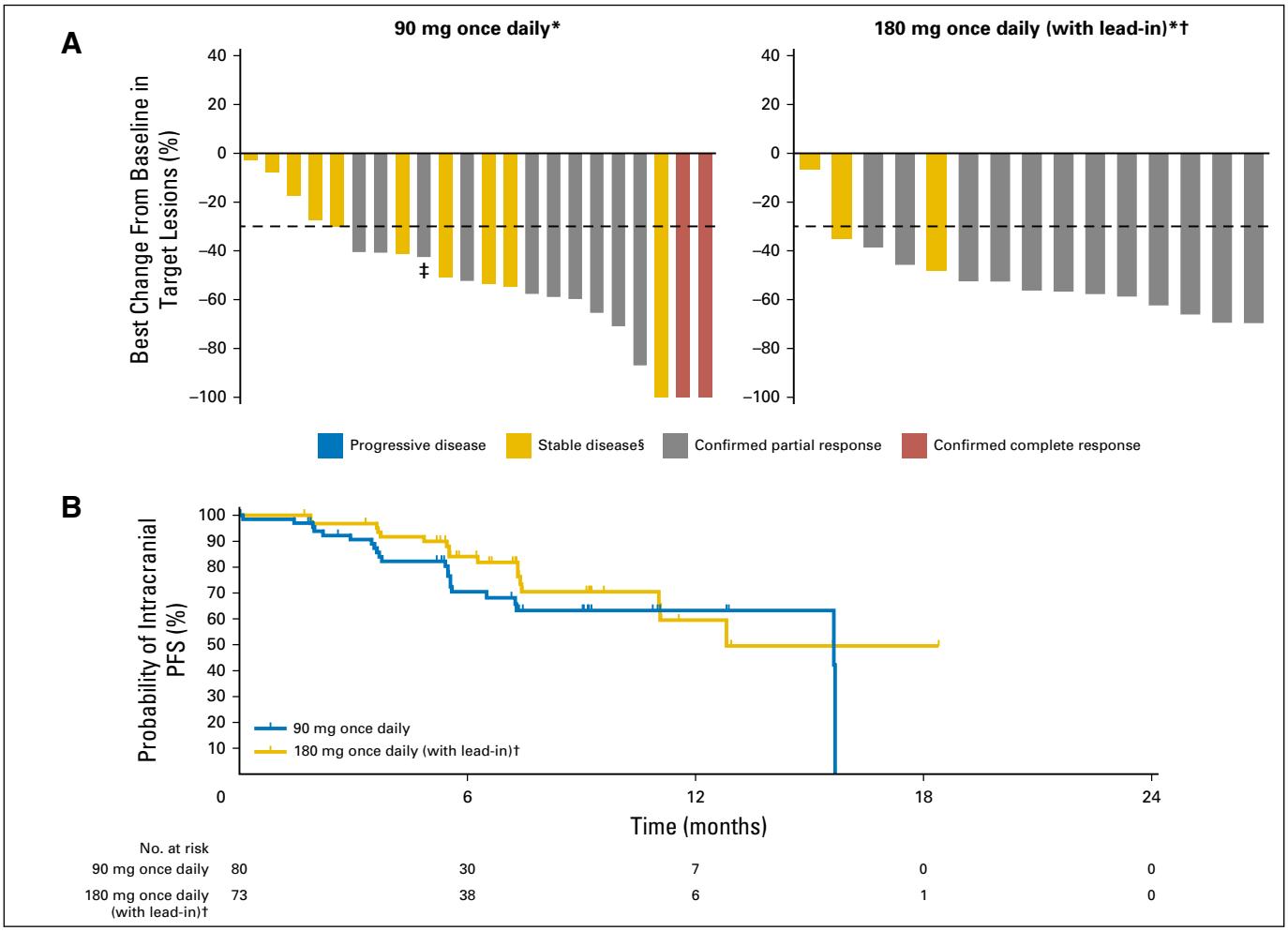

Fig 3. Brigatinib intracranial efficacy in crizotinib-refractory ALK-positive NSCLC by arm. (A) The best percentage change from baseline in the sum of the longest diameters of target lesions is reported in patients who had measurable brain metastases at baseline, as assessed by an independent review committee, and available data (22 of 26 patients in arm A, 15 of 18 patients in arm B). The dotted line at −30% indicates the threshold for partial response per RECIST v1.1. (B) Intracranial PFS is shown for patients with brain metastases at baseline, as assessed by an independent review committee (n = 80, arm A; n = 73, arm B). Of the 80 evaluable patients in arm A, 22 (28%) had an event; of the 73 evaluable patients in arm B, 17 (23%) had an event. ALK-positive, anaplastic lymphoma kinase gene–rearranged; NSCLC, non–small-cell lung cancer; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. (*) Includes patients with active brain metastases at baseline (90 mg once daily, n = 16; 180 mg once daily [with lead-in], n = 14). (†) 180 mg once daily with 7-day lead-in at 90 mg. (‡) Single response awaiting confirmation. (§) Category includes single responses that were not confirmed.

of the current study is that the randomized selection design did not include formal statistical PFS and OS comparisons between arms.

The safety profile in this study was consistent with that previously reported for brigatinib[22,23] and was acceptable in both arms. The frequency of any individual grade ≥ 3 AE was low in both arms. Dose modifications and discontinuations as the result of AEs were more common with 180 mg (with lead-in). Dose-reduction rates were 20% (arm B) versus 7% (arm A). In contrast, at the recommended starting doses of ceritinib and alectinib, reported dose-reduction rates are 58% and 23%, respectively.[26,27] Beyond tolerability, the impact of dose reductions on efficacy, particularly CNS efficacy, should be considered. The intracranial ORR of 67% in patients with measurable brain metastases who received 180 mg (with lead-in) in this study compares favorably with second-generation ALK-inhibitor data.[28,29] The CNS benefit seems to be sustained with a median intracranial PFS > 1 year in both arms and the median durations of intracranial response not being reached. Health-related QoL remained at or higher than baseline levels and did not differ between arms.

The current results confirm phase I/II observations regarding pulmonary AEs with early onset.[23] In the phase I/II trial, the frequency of these AEs seemed to be related to starting dose; a lead-in dose of 90 mg once daily for 1 week before escalation to 180 mg once daily seemed to reduce the risk of these AEs compared with starting at 180 mg once daily. In ALTA, all early pulmonary AEs occurred at 90 mg (in arm A or before dose escalation in arm B); no such events occurred after escalation to 180 mg in arm B. Therefore, the efficacy of 180 mg (with lead-in) was not associated with an increased risk of additional early pulmonary AEs, compared with 90 mg. Pulmonary toxicity, including pneumonitis and interstitial lung disease, has been observed with crizotinib, ceritinib, and alectinib in similar patient populations[26,27,30]; however, rapid onset in the small subset of brigatinib-treated patients with these AEs, and the potential to tolerize and continue dosing, suggest a different underlying etiology that is unknown. Patients

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Table 4. Treatment-Emergent Adverse Events Reported in ≥ 10% of All Patients

Treatment-Emergent Adverse Event	Arm A, 90 mg Once Daily, n = 109		Arm B, 180 mg Once Daily (with lead-in),* n = 110	
	Any Grade, No. (%)	Grade ≥ 3, No. (%)	Any Grade, No. (%)	Grade ≥ 3, No. (%)
GI disorders				
Nausea	36 (33)	1 (1)	44 (40)	1 (1)
Diarrhea	21 (19)	0	42 (38)	0
Vomiting	26 (24)	2 (2)	25 (23)	0
Constipation	21 (19)	1 (1)	17 (15)	0
Abdominal pain	18 (17)	0	9 (8)	0
Nervous system disorders				
Headache	30 (28)	0	30 (27)	1 (1)
General disorders				
Fatigue	22 (20)	1 (1)	30 (27)	0
Pyrexia	15 (14)	0	7 (6)	1 (1)
Respiratory, thoracic, and mediastinal disorders				
Cough	20 (18)	0	37 (34)	0
Dyspnea	23 (21)	3 (3)	23 (21)	2 (2)
Musculoskeletal and connective tissue disorders				
Muscle spasms	13 (12)	0	19 (17)	0
Arthralgia	15 (14)	1 (1)	15 (14)	0
Back pain	11 (10)	2 (2)	17 (15)	2 (2)
Investigations				
Increased blood creatine phosphokinase	12 (11)	3 (3)	33 (30)	10 (9)
Increased amylase	9 (8)	1 (1)	16 (15)	1 (1)
Increased aspartate aminotransferase	9 (8)	0	16 (15)	0
Skin and subcutaneous tissue disorders				
Rash	8 (7)	1 (1)	18 (16)	3 (3)
Metabolism and nutrition disorders				
Decreased appetite	24 (22)	1 (1)	17 (15)	1 (1)
Vascular disorders				
Hypertension	12 (11)	6 (6)	23 (21)	7 (6)

NOTE. The median time on treatment was 7.5 months in arm A and 7.8 months in arm B.
*180 mg once daily with 7-day lead-in at 90 mg.

treated with brigatinib should be monitored for new or worsening respiratory symptoms, particularly during the first week of treatment. Management of early pulmonary AEs should include dose interruption and prompt clinical evaluation.

In conclusion, efficacy and safety in the phase II ALTA trial support future trials with the 180-mg regimen (with lead-in at 90 mg). On the basis of these results, brigatinib seems to be a promising new treatment option for crizotinib-refractory ALK-positive NSCLC. Brigatinib is currently being investigated in a randomized, phase III trial of brigatinib (180 mg [with lead-in]) versus crizotinib in ALK inhibitor–naïve patients (ALTA-1L; ClinicalTrials.gov identifier: NCT02737501).

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Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial

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