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ORIGINAL REPORT

Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With *ALK*-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2

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ABSTRACT

Purpose

Phase I data (ASCEND-1) showed ceritinib efficacy in patients with *ALK*-rearranged non–small-cell lung cancer (NSCLC), regardless of brain metastases status and with or without prior therapy with an inhibitor of the ALK protein. Data are presented from a phase II trial (ASCEND-2) in which ceritinib efficacy and safety were evaluated in patients who had *ALK*-rearranged NSCLC previously treated with at least one platinum-based chemotherapy and who had experienced progression during crizotinib treatment as their last prior therapy.

Patients and Methods

Patients with advanced *ALK*-rearranged NSCLC, including those with asymptomatic or neurologically stable baseline brain metastases, received oral ceritinib 750 mg/d. Whole-body and intracranial responses were investigator assessed (according to RECIST version 1.1). Patient-reported outcomes were evaluated with the Lung Cancer Symptom Scale and European Organisation for Research and Treatment of Cancer surveys (the core-30 and the 13-item lung cancer–specific quality-of-life questionnaires).

Results

All 140 patients enrolled had received two or more previous treatment regimens, and all patients had received crizotinib. The median duration of exposure and the follow-up time with ceritinib were 8.8 months (range, 0.1 to 19.4 months) and 11.3 months (range, 0.1 to 18.9 months), respectively. Investigator-assessed overall response rate was 38.6% (95% CI, 30.5% to 47.2%). Secondary end points, all investigator assessed, included disease control rate (77.1%; 95% CI, 69.3% to 83.8%), time to response (median, 1.8 months; range, 1.6 to 5.6 months), duration of response (median, 9.7 months; 95% CI, 7.1 to 11.1 months), and progression-free survival (median, 5.7 months; 95% CI, 5.4 to 7.6 months). Of 100 patients with baseline brain metastases, 20 had active target lesions at baseline; investigator-assessed intracranial overall response rate was 45.0% (95% CI, 23.1% to 68.5%). The most common adverse events (majority, grade 1 or 2) for all treated patients were nausea (81.4%), diarrhea (80.0%), and vomiting (62.9%). Patient-reported outcomes showed a trend toward improved symptom burden. The global quality-of-life score was maintained during treatment.

Conclusion

Consistent with its activity in ASCEND-1, ceritinib treatment provided clinically meaningful and durable responses with manageable tolerability in chemotherapy- and crizotinib-pretreated patients, including those with brain metastases.

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INTRODUCTION

The discovery of oncogenic-driver alterations and the subsequent development of targeted therapeutics against these mutations have been key advancements in the treatment of non–small-cell lung cancer (NSCLC).[1] *ALK* rearrangements, most commonly *EML4-ALK* fusion, occur in approximately 2% to 7% of patients with NSCLC, and clinical data have demonstrated the success of therapeutic approaches targeting the ALK protein

in this patient group.[2-5] The first ALK-targeted agent approved in patients with *ALK*-rearranged NSCLC was crizotinib, which has become a standard of care in this group after results from two phase III trials showed its superiority compared with chemotherapy in both the first- and second-line settings.[2,5,6] However, despite these promising results, patients eventually experience disease progression because of acquired resistance through secondary *ALK* mutations (eg, gatekeeper L1196 mutation) and alternative oncogenic pathways.[7-9] The rate of brain metastases in *ALK*-positive patients with NSCLC, 30% to 50%,[10,11] is poorly understood[12]. In chemotherapy-pretreated patients without baseline brain metastases who receive crizotinib, approximately 20% experience progression in the brain as a new site of disease.[12]

Strategies to overcome crizotinib-resistant disease, including highly potent, structurally distinct, second-generation ALK inhibitors, are being developed. Among these, ceritinib was granted accelerated approval by the US Food and Drug Administration in April 2014 for the treatment of patients with *ALK*-positive metastatic NSCLC who have experienced progression during treatment with or who are intolerant to crizotinib.[13] Ceritinib has since been approved by the European Medicines Agency[14] and in numerous countries worldwide. Other second-generation agents include alectinib[15,16] and brigatinib (AP26113)[17]; promising clinical outcomes have been reported in patients with *ALK*-rearranged NSCLC for each agent; importantly, all have shown evidence of intracranial efficacy.[16,18,19]

Ceritinib (LDK378, Novartis) is a selective oral inhibitor of ALK with a 20-fold greater potency than crizotinib in enzymatic assays. In vivo analyses with a rat model demonstrated penetration of ceritinib across the blood–brain barrier, with a brain-to-blood exposure (area under the curve from 0 to infinity) ratio of approximately 15%.[20] Results from the phase I dose-escalation/dose-expansion ASCEND-1 study demonstrated robust antitumor efficacy (intracranially and extracranially) in heavily pretreated patients with *ALK*-rearranged NSCLC, including both ALK inhibitor–naïve and ALK inhibitor–pretreated patients.[4,13,21] Ceritinib activity was observed in patients with or without crizotinib resistance mutations.[4]

The efficacy and safety results for ceritinib 750 mg/d in a heavily pretreated patient population are reported for 140 patients with *ALK*-rearranged NSCLC enrolled in the ASCEND-2 (NCT01685060) phase II study. Patients enrolled had received two or more prior lines of antineoplastic therapy, including platinum-based chemotherapy, and all patients had experienced progression during crizotinib treatment as the last therapy before starting ceritinib. Ceritinib activity is also reported for patients with asymptomatic or neurologically stable brain metastases at study entry.

PATIENTS AND METHODS

Patients

Eligible patients had locally advanced/metastatic *ALK*-rearranged NSCLC confirmed by US Food and Drug Administration–approved fluorescent in situ hybridization (FISH) assay at local sites (confirmation by Novartis-designated central laboratory was required when *ALK* documentation was unavailable). Other key inclusion criteria included a WHO performance status (PS) of 2 or less and measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1. All patients must have received prior treatment with at least one platinum-based chemotherapy regimen and crizotinib. Prior treatment with any ALK inhibitor other than crizotinib was not permitted, and crizotinib must have been the last systemic antineoplastic therapy prior to ceritinib initiation. Progression during crizotinib treatment, or within 30 days of last dose, was required.

Before starting ceritinib, all crizotinib-related toxicities had to have resolved to Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or lower. Patients with asymptomatic or neurologically stable brain metastases (for $\geq$ 2 weeks before study entry) were eligible. Prior radiotherapy to the brain must have been completed at least 2 weeks before ceritinib treatment started. Key exclusion criteria are provided in the Appendix Methods (online only).

Study Design

Eligible patients in this single-arm, open-label, multicenter, phase II study received ceritinib 750 mg/d on a continuous dosing schedule. Treatment continued until radiologically documented disease progression by investigator (RECIST, version 1.1), unacceptable toxicity, or withdrawal of consent occurred. Treatment beyond progression was permitted in patients who were still experiencing clinical benefit. The primary objective was to demonstrate antitumor activity measured by investigator-assessed overall response rate (ORR).

Secondary objectives included response-related end points assessed by investigator and blinded independent review committee (BIRC), overall survival (OS), safety, and patient-reported outcomes (PROs).

Prior to study initiation, the protocol was reviewed and approved by the local human investigations committee at each participating site. All patients provided written informed consent. The study was conducted in accordance with the ethics of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization.

Study Assessments

Efficacy analysis. Tumor assessments were performed at baseline and every 8 weeks ($\pm$ 1 week) from the start of ceritinib treatment, by using contrast-enhanced computerized tomography or magnetic resonance imaging. Scans of the chest, upper abdomen, and brain were performed in all patients at baseline; brain scans were only performed at subsequent assessments in patients with brain lesions at baseline. A consistent imaging modality was required throughout the study.

Investigator-assessed, whole-body (extra- and intracranial disease sites) tumor responses were determined per RECIST, version 1.1, for ORR, disease control rate (DCR), time to response (TTR), duration of response (DOR), and progression-free survival (PFS). OS was also calculated. Intracranial responses (overall intracranial response rate [OIRR] and intracranial disease control rate [IDCR]) were calculated in patients with baseline brain metastases when a target lesion in the brain was identified. Selection as a target lesion indicated that the lesion was active (a new or existing lesion that progressed after local therapy). As a result, patients with brain metastases previously treated with radiotherapy whose lesions had not subsequently progressed were not included in the analyses. Supporting analyses by BIRC were conducted for whole-body and intracranial responses.

Safety analysis. Safety was monitored at baseline and at every subsequent visit. Assessments of physical condition, ECG, PS, and laboratory parameters were performed. All adverse events (AEs) were recorded and graded according to the CTCAE (version 4.03).

PROs analysis. The European Organisation for Research and Treatment of Cancer core-30 quality-of-life questionnaire (QLQ-C30, version 3.0) and complementary 13-item lung cancer–specific questionnaire (QLQ-LC13, version 1.0), along with the Lung Cancer Symptom Scale (LCSS), were used to evaluate functioning, symptom impact, and treatment-related AEs. Details are provided in the Appendix Methods.

Statistical Analyses

Data sets. All patients who received at least one dose of ceritinib were included in the efficacy (full analysis set [FAS]) and safety (safety set) analyses. Supportive efficacy analyses were performed in the per-protocol set (PPS), which included patients who had no major protocol deviations (Appendix Table A1, online only) and who had adequate tumor assessments at baseline and follow-up (> 7 weeks after starting treatment, except when progressive disease [PD] was observed before 7 weeks, in which case the patient was always included in the PPS set).

The study objective was met at the time of the primary analysis, which was based on a data cutoff date of February 26, 2014. This is an updated analysis of the data that is based on a cutoff date of August 13, 2014.

Efficacy analysis. Per RECIST, version 1.1, confirmation of response at 4 weeks or more after initial documentation was required for determination of best overall response (BOR). On the basis of an exact binomial distribution, approximately 137 patients were required to test a null hypothesis of an ORR ≤ 25% versus a target ORR of ≥ 38%, with a one-sided α of .025 and 90% power. On the basis of 137 patients, if 45 or more responses were observed (estimated ORR of ≥ 32.8%), the null hypothesis would be rejected. Additional details are available in Appendix Methods.

PROs analysis. Details are available in Appendix Methods. For each survey, a change from the baseline score of 5 to 15 points was considered clinically meaningful.[22]

RESULTS

Patients

Across 51 global sites, from December 2012 to September 2013, 140 patients with *ALK*-rearranged advanced NSCLC were enrolled. All patients received at least one dose of ceritinib 750 mg/d. The median follow-up time was 11.3 months (range, 0.1 to 18.9 months; Appendix Table A2, online only). Baseline demographics and disease characteristics are listed in Table 1. Most patients were white or Asian and had a WHO PS of 1 or less. At study entry, 100 patients (71.4%) had brain metastases, 72.0% of whom had received prior brain radiation; the median time from completion of prior radiotherapy to the start of ceritinib was 6.2 months (range, 0.5 to 54.0 months). Patients were heavily pretreated; all patients had received two or more prior lines of therapy including crizotinib; 56.4% had received three or more prior lines of treatment. Crizotinib was the last therapy received prior to initiation of ceritinib treatment; all patients experienced progression on crizotinib.

Table 1. Patient Demographic and Disease Characteristics (by investigator, unless otherwise specified)

Characteristic	No. (%) of Patients With *ALK*-Rearranged NSCLC (N = 140)
Median (range) age, years	51 (29-80)
Sex	
Male	70 (50.0)
Female	70 (50.0)
Ethnicity	
White	84 (60.0)
Asian	53 (37.9)
Other	3 (2.1)
WHO/ECOG performance status	
0	42 (30.0)
1	78 (55.7)
2	20 (14.3)
Tumor histology/cytology	
Adenocarcinoma	129 (92.1)
Squamous cell carcinoma	3 (2.1)
Mucinous adenocarcinoma	2 (1.4)
Adenosquamous cell carcinoma	1 (0.7)
Bronchioalveolar carcinoma	1 (0.7)
Papillary serous	1 (0.7)
Undifferentiated carcinoma	1 (0.7)
Other	2 (1.4)
Stage IV at study entry	140 (100.0)
Site of metastasis	
Brain	100 (71.4)
Lung	47 (33.6)
Liver	52 (37.1)
Bone	81 (57.9)
No. of target lesions at baseline	
1	60 (42.9)
≥ 2	80 (57.1)
No. of target lesions at baseline (by BIRC)	
0	26 (18.6)
1	37 (26.4)
≥ 2	75 (53.6)
Missing baseline	2 (1.4)
No. of prior regimens (chemotherapy/ targeted therapy)	
2	61 (43.6)
3	48 (34.3)
> 3	31 (22.1)
Median (range) time since most recent relapse/progression, months	1.2 (0.2-15.9)
Prior radiotherapy to the brain*	
No prior radiotherapy	28 (28.0)
Prior radiotherapy	72 (72.0)
Time elapsed from prior radiotherapy to the brain to first dose of ceritinib, months	
Median (range)	6.2 (0.5-54.0)
≤ 3 months prior	21 (29.2)
> 3 months prior	51 (70.8)

Abbreviations: BIRC, blinded independent review committee; ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer.
*In patients with brain metastases at study entry (n = 100).

Efficacy

The investigator-assessed ORR was 38.6% (95% CI, 30.5% to 47.2%; Table 2). The DCR was 77.1% (95% CI, 69.3% to 83.8%). Among patients with measurable disease at baseline and at least one postbaseline assessment, tumor burden was reduced from baseline in 75.2% of patients (Fig 1A). Supportive analyses were performed with the PPS (n = 128), which excluded 12 patients (8.6%) who had major protocol deviations (exclusions listed in Appendix Table A1; efficacy data in Appendix Tables A3 and A4, online only). Supportive efficacy analyses were also performed with the FAS by BIRC assessment (N = 140) and with the PPS by BIRC assessment (n = 102), which, in addition to the 12 patients who had major protocol deviations, excluded 26 patients (18.6%) who did not have baseline target lesions and/or had no valid baseline tumor assessment (Appendix Table A1). The BOR with the FAS and the PPS by BIRC assessment was supportive of investigator assessments (Appendix Table A4).

Responses by investigator assessment were rapid (median TTR 1.8 months; range, 1.6 to 5.6 months) and durable (median DOR, 9.7 months; 95% CI, 7.1 to 11.1). The median investigator-assessed PFS was 5.7 months (95% CI, 5.4 to 7.6).

Table 2. Whole-Body Responses Based on Investigator Assessments

Response	Assessment		
	FAS (N = 140)	PPS (n = 128)	Brain Metastases at Study Entry (n = 100)
No. (%) of patients by best overall response			
CR	4 (2.9)	4 (3.1)	0
PR	50 (35.7)	50 (39.1)	33 (33.0)
SD	54 (38.6)	53 (41.4)	41 (41.0)
PD	19 (13.6)	17 (13.3)	16 (16.0)
UNK	13 (9.3)	4 (3.1)	10 (10.0)
ORR			
No. (%) of patients	54 (38.6)	54 (42.2)	33 (33.0)
95% CI	30.5 to 47.2	33.5 to 51.2	23.9 to 43.1
DCR			
No. (%) of patients	108 (77.1)	107 (83.6)	74 (74.0)
95% CI	69.3 to 83.8	76.0 to 89.5	64.3 to 82.3
DOR, months			
Median	9.7	—	9.2
95% CI	7.1 to 11.1		5.5 to 11.1
PFS, months			
Median	5.7	—	5.4
95% CI	5.4 to 7.6		4.7 to 7.2

Abbreviations: CR, complete response; DCR, disease control rate (CR + PR + SD); DOR, duration of response; FAS, full analysis set; ORR, overall response rate (CR + PR); PD, progressive disease; PFS, progression-free survival; PPS, per-protocol set; PR, partial response; SD, stable disease; UNK, unknown.

The median OS was 14.9 months (95% CI, 13.5 to not evaluable), and the 12-month OS rate was 63.8% (95% CI, 54.9% to 71.4%). Data from 81 patients (57.9%) were censored for OS; of these, 72 patients (51.4%) were alive at cutoff.

Efficacy in patients with brain metastases at baseline. A preplanned subgroup analysis of whole-body efficacy was conducted in patients with baseline brain metastases (n = 100). Investigator-assessed ORR in patients with baseline brain metastases was 33.0% (95% CI, 23.9% to 43.1%), the DCR was 74.0% (95% CI, 64.3% to 82.3%), the median DOR was 9.2 months (95% CI, 5.5 to 11.1 months), and the median PFS was 5.4 months (95% CI, 4.7 to 7.2 months; Table 2). BIRC assessment of efficacy in patients with baseline brain metastases was supportive of these outcomes (Appendix Table A4).

Intracranial responses in patients with active brain metastases at baseline. Intracranial responses were evaluated in 20 patients with investigator-assessed measurable brain lesions selected as active target lesions per RECIST, version 1.1, at study entry. Objective intracranial responses were reported in 45.0% (95% CI, 23.1% to 68.5%; as shown by the brain scans of two patients with intracranial response; Appendix Fig A1, online only), and an IDCR of 80.0% (95% CI, 56.3% to 94.3%) was achieved (Table 3). BIRC analysis of intracranial responses was supportive (Appendix Table A5, online only).

Treatment Exposure

The median duration of ceritinib exposure for all patients was 8.8 months (range, 0.1 to 19.4 months); the median relative dose intensity was 84.9% (range, 37.5% to 100.0%). The median duration of exposure was 8.6 months (range, 0.1 to 19.4 months) in patients with baseline brain metastases. Dose interruptions (for at least 1 day of treatment) occurred in 75.7% of patients, of which 85.8% were attributable to AEs. At least one dose reduction was required in 54.3% of patients, of which 84.2% were due to AEs. The median time to dose reduction was 1.6 months (range, 0.2 to 13.5 months), and reductions occurred throughout the dosing period.

Safety

Table 4 summarizes AEs reported by 20% or more of patients and grade 3 to 4 AEs reported by 2% or more of patients. All patients experienced at least one AE, suspected to be drug related in 96.4% of patients. AEs that resulted in treatment discontinuation were reported in 7.9%, but no single AE predominated. Common GI AEs (eg, nausea, diarrhea, and vomiting) were most prevalent; greater than 75% of patients experienced drug-related nausea or diarrhea. Most drug-related nausea, diarrhea, and vomiting were grade 1 or 2 and were reported at grade 3 or 4 in 5.7%, 6.4%, and 4.3% of patients, respectively. Only 2.1% discontinued ceritinib treatment because of nausea, diarrhea, and vomiting.

Overall, grade 3 to 4 AEs were reported in 71.4% of patients; 45.7% experienced grade 3 to 4 AEs suspected to be drug related. The most common drug-related grade 3 to 4 AEs were elevated ALT and γ-glutamyltransferase, which occurred in 15.7% and 9.3%, respectively. Serious AEs (SAEs) were reported in 40.7% of patients; 17.1% experienced SAEs suspected to be drug related. Pneumonitis and QTc prolongation (suspected to be drug related) occurred at any grade in 1.4% and 7.9% of patients, respectively; grade 4 pneumonitis and grade 3 QTc prolongation each occurred in one patient (0.7%). Other important known adverse drug reactions of ceritinib include hyperglycemia and bradycardia; no drug-related grade 3 or 4 occurrences were reported for either AE.

PROs

Compliance was high; greater than 90% of patients completed the QLQ-C30, QLQ-LC13, and LCSS questionnaires through cycle 13 of the study. Patients reported no worsening in cancer symptoms during treatment and trended toward improvement in lung-related symptoms (ie, cough, pain, and dyspnea) from baseline by LCSS; the mean change from baseline of symptom burden score ranged from −1.4 to −6.2 (Fig 2A). Results from the QLQ-LC13 were consistent with these data. The QLQ-C30 symptom score indicated that patients reported worse GI-related symptoms (from baseline) throughout treatment; mean changes from baseline ranged from −3.6 to +31.8 (Fig 2B). Diarrhea remained consistently worse from baseline throughout treatment (mean change from baseline QLQ-C30 symptom score, +24.5 to +31.8). Although nausea and vomiting were also consistently worse than baseline, an improvement in these symptoms was observed from early to late treatment cycles. Overall, health-related quality of life (QOL) was generally maintained during treatment, and no substantial change from baseline was observed in the QLQ-C30 global QOL (mean change from baseline, −1.5 to +4.6) or function scale score (Fig 2C).

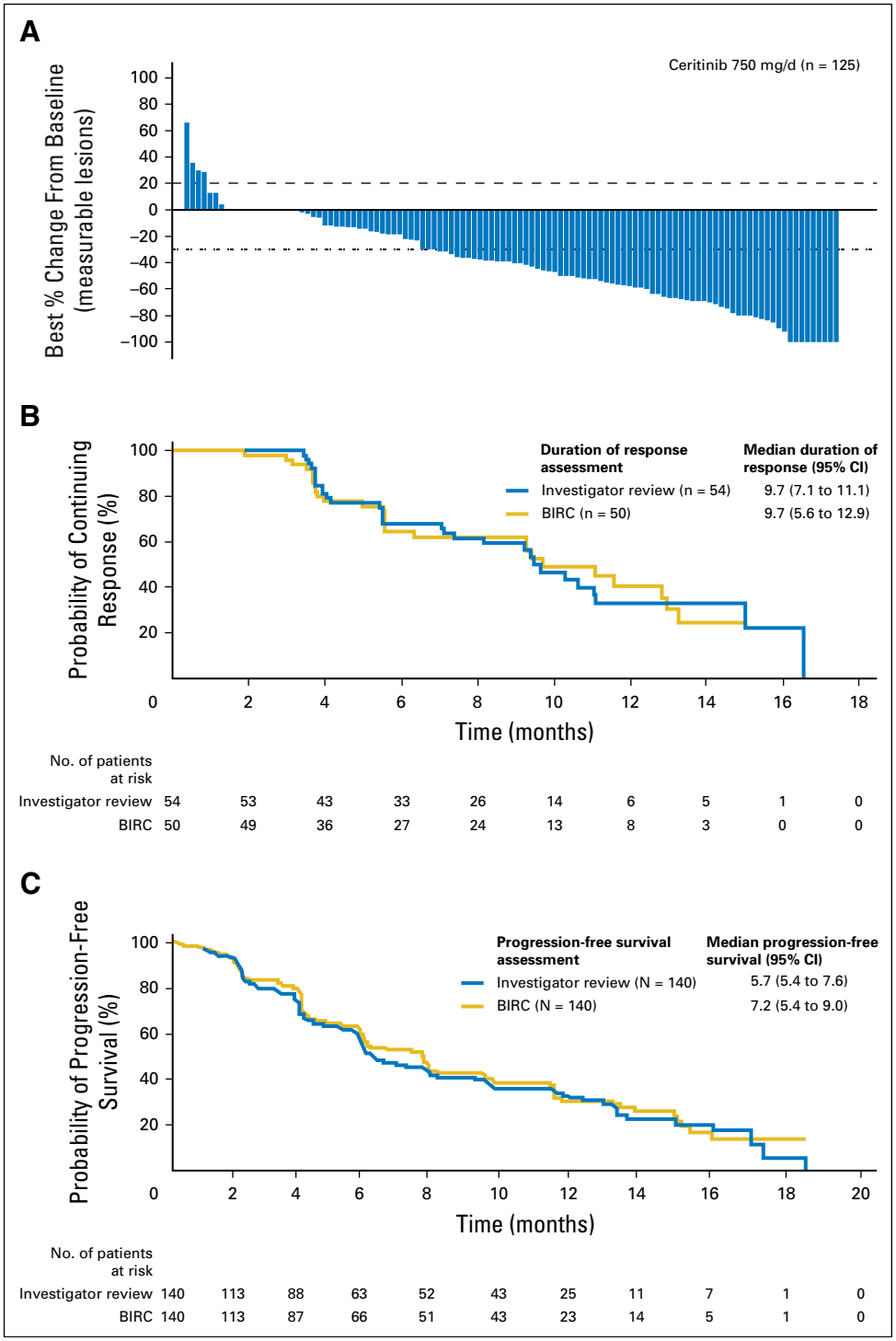

Fig 1. (A) Waterfall plot of best percentage change from baseline by investigator review (n = 125 with measurable disease at baseline and at least one postbaseline assessment without unknown response for target lesion or overall response [includes 114 patients with best percentage change from baseline data available, > 0%, < 0%, or 0%, shown in the figure and 11 patients, not shown, with a percentage change in the target lesion available but contradicted by overall lesion response, progressive disease]). (B) Duration of response in all patients with *ALK*-rearranged non–small-cell lung cancer (NSCLC) who responded to ceritinib treatment (n = 54 by investigator; n = 50 by blinded independent review committee [BIRC]). (C) Progression-free survival in all patients with *ALK*-rearranged NSCLC (N = 140).

DISCUSSION

Ceritinib resulted in significant and durable clinical activity in patients with *ALK*-rearranged NSCLC who had experienced treatment failure with multiple prior antineoplastic treatment regimens, including crizotinib.[2] Whole-body and intracranial responses were reported in those patients with brain metastases at study entry, including patients with target lesions in the brain. The incidence and type of AEs were consistent with those reported for the ASCEND-1 study, and no new or unexpected SAEs were reported.[4,21] GI AEs were the most prevalent; however, most were grade 1 or 2 and were manageable with dose interruption/reduction. In addition, PROs suggested an improvement in lung symptoms, and the global QOL score was maintained throughout therapy.

The results reported in this study support those reported for the group of 163 patients previously treated with crizotinib in ASCEND-1.[21] The investigator-assessed DCR was consistent

Table 3. Investigator-Assessed Intracranial Responses in Patients With Target Brain Lesions at Study Entry

Best overall response	No. (%) of Patients With Target Brain Lesions at Study Entry (n = 20)
CR	2 (10.0)
PR	7 (35.0)
SD	7 (35.0)
PD	3 (15.0)
UNK	1 (5.0)
OIRR*	9 (45.0)
IDCR*	16 (80.0)

Abbreviations: CR, complete response; IDCR, intracranial disease control rate; OIRR, overall intracranial response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.
*95% CI: OIRR, 23.1 to 68.5; IDCR, 56.3 to 94.3.

between the two studies (ASCEND-2: 77.1% [95% CI, 69.3% to 83.8%]; ASCEND-1: 74.2% [95% CI, 66.8% to 80.8%]).[23] The ORR in ASCEND-2 (38.6%; 95% CI, 30.5% to 47.2%) was lower than that reported in ASCEND-1 (56.4%; 95% CI, 48.5% to 64.2%), and both were investigator assessed.[24] However, both the median DOR in patients who achieved a response and the median PFS in all patients in ASCEND-2 (DOR, 9.7 months [95% CI, 7.1 to 11.1 months]; PFS, 5.7 months [95% CI, 5.4 to 7.6 months]) were similar to those reported for ASCEND-1 (DOR, 8.3 months [95% CI, 6.8 to 9.7 months]; PFS 6.9 months [95% CI, 5.6 to 8.7 months])[24]; each was investigator assessed in both studies, and CIs overlapped.

Table 4. Summary of Adverse Events (regardless of study drug relationship) Occurring in ≥ 20% of Patients at All Grades or ≥ 2% of Patients at Grades 3 or 4

Adverse Event	No. (%) of Patients by Grade	
	All Grades	Grades 3 or 4
Total	140 (100.0)	100 (71.4)
Nausea	114 (81.4)	9 (6.4)
Diarrhea	112 (80.0)	9 (6.4)
Vomiting	88 (62.9)	6 (4.3)
ALT increased	61 (43.6)	24 (17.1)
Decreased appetite	57 (40.7)	5 (3.6)
Fatigue	51 (36.4)	9 (6.4)
Weight decreased	48 (34.3)	6 (4.3)
AST increased	45 (32.1)	7 (5.0)
Abdominal pain	44 (31.4)	2 (1.4)
Constipation	40 (28.6)	3 (2.1)
Cough	30 (21.4)	0
Pyrexia	29 (20.7)	4 (2.9)
Dyspnea	29 (20.7)	8 (5.7)
γ-GT increased	25 (17.9)	17 (12.1)
Asthenia	25 (17.9)	6 (4.3)
Anemia	22 (15.7)	3 (2.1)
Blood ALP increased	21 (15.0)	4 (2.9)
Pneumonia	10 (7.1)	5 (3.6)
Hypokalemia	8 (5.7)	4 (2.9)
Hyperglycemia	7 (5.0)	4 (2.9)
Hypophosphatemia	7 (5.0)	3 (2.1)
Pericardial effusion	5 (3.6)	5 (3.6)
Dehydration	5 (3.6)	3 (2.1)
General physical health deterioration	4 (2.9)	4 (2.9)
Hepatic function abnormal	4 (2.9)	3 (2.1)

Abbreviations: ALP, alkaline phosphatase; γ-GT, γ-glutamyltransferase.

Results reported for ASCEND-2 and ASCEND-1 were generally consistent; however, several differences between the studies exist that do not facilitate their direct comparison. The proportion of patients evaluated with a single-target lesion at baseline was 42.9% in ASCEND-2 compared with 24.8% in ASCEND-1. Prior studies suggest that selection of fewer target lesions could result in a lower response compared with studies that included a higher number of target lesions,[25] as supported by the results reported here. All patients enrolled on ASCEND-2 had experienced progression during prior crizotinib treatment. Despite previous progression during treatment with an ALK inhibitor, the subsequent median investigator-assessed DOR with ceritinib treatment in these patients was 9.7 months.

Ceritinib achieved whole-body and intracranial responses in patients with baseline brain metastases, a common site of progression during crizotinib treatment.[12] Intracranial activity has been reported in crizotinib-treated patients; the OIRR in 22 patients with previously untreated measurable lesions in the brain was 18%, far lower than the systemic ORR of 53%; both were investigator assessed.[12] In contrast, in this study, the investigator-assessed OIRR after ceritinib treatment in 20 patients with baseline brain metastases was 45.0%, despite selection of active target lesions, and the IDCR was 80.0%; however, the two study populations cannot be fairly compared, because 14 of the 20 patients included in this analysis of intracranial efficacy had previously received local treatment, and the sample sizes were small, which also precluded investigation of efficacy as a function of prior radiotherapy. Furthermore, patients in this study had already experienced progression during crizotinib treatment, whereas those patients whose disease responded to crizotinib were ALK inhibitor naïve. These data, together with emerging evidence for intracranial efficacy with other second-generation ALK inhibitors,[16,18] suggest that patients who experience progression in the brain during crizotinib treatment may benefit from subsequent treatment with an alternative ALK-targeted therapeutic.

ALK-dependent crizotinib resistance through amplification of the *ALK* gene has been described, as have numerous ALK kinase domain mutations that prevent crizotinib-mediated inhibition of the ALK fusion protein.[7,26,27] Resistance to ALK inhibition can also result from *ALK*-independent mechanisms, including upregulation of alternative oncogenes/signaling pathways.[7,26,28] Specific crizotinib resistance mutations have not been defined for all patients in this study; nonetheless, it is likely that the antitumor activity observed with ceritinib encompassed patients who had a range of different crizotinib resistance mutations, including patients who had no known/defined resistance mechanism. The molecular profile after disease failure during prior crizotinib treatment was defined in a small patient cohort in ASCEND-1, which demonstrated tumor regression with ceritinib, irrespective of the cause of acquired resistance.[4] Similarly, a retrospective analysis of ceritinib in patients previously treated with crizotinib uncovered *ALK* resistance mutations in seven of 23 patients; no statistical relationship was observed between known *ALK* resistance mutations and response to ceritinib.[6,29]

In addition to antitumor activity, there was a trend toward a reduction in many patient-reported lung cancer–related

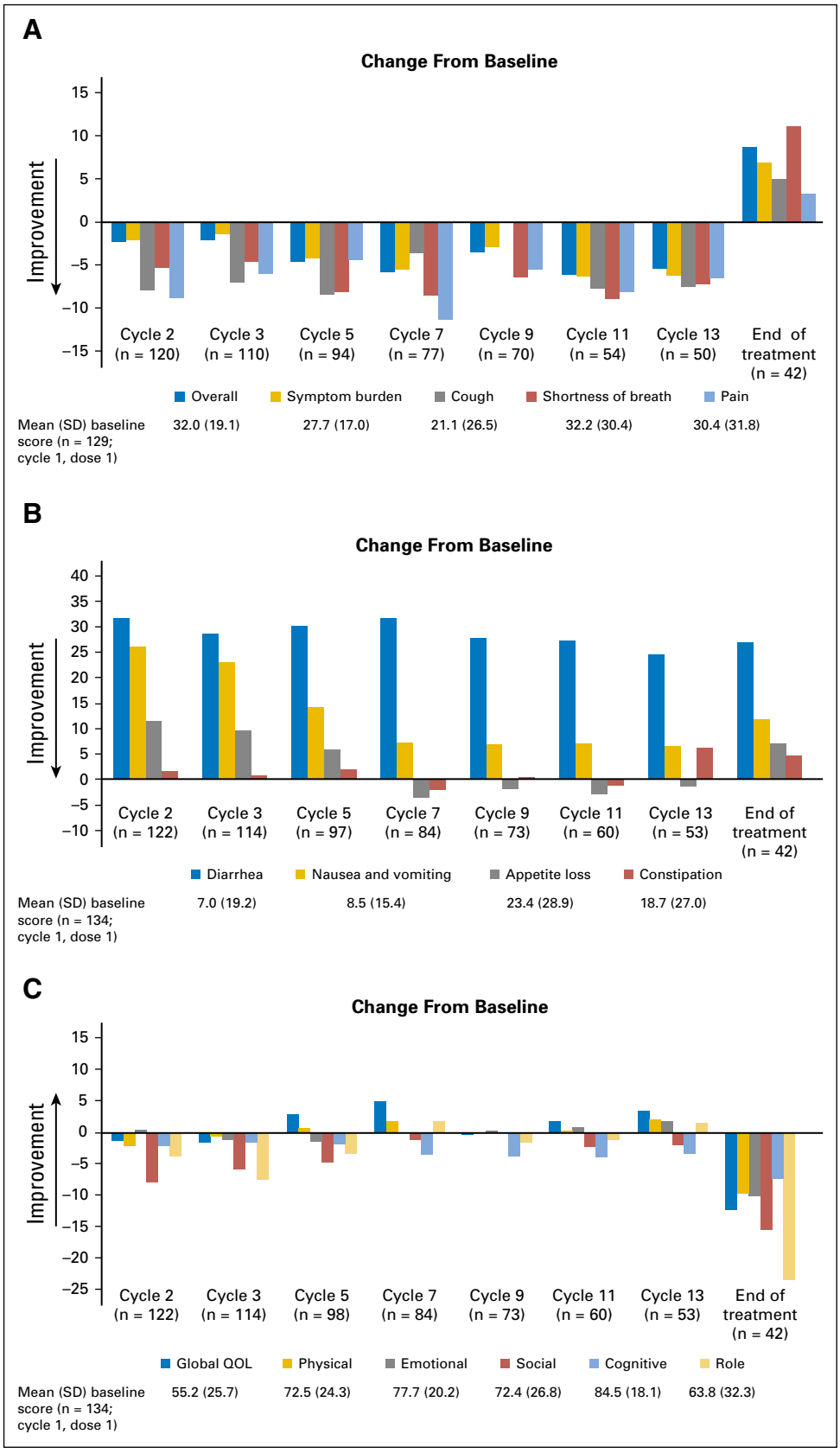

Fig 2. (A) Improvement from baseline in symptoms according to Lung Cancer Symptom Scale score. (B) Worsening GI-related symptoms from baseline according to the European Organisation for Research and Treatment of Cancer core-30 quality-of-life questionnaire (QLQ-C30) symptom score. (C) Maintenance of global health-related quality of life (QOL) according to the QLQ-C30 score. SD, standard deviation.

symptoms. Patients appeared to experience an early improvement in lung-related symptoms, which was maintained throughout treatment, but symptoms consistently worsened at the end of treatment visits, potentially because of disease progression. However, because these data are from a single-arm study with no comparator, PRO data should be considered with caution.

Considered together with results from ASCEND-1, these data are encouraging for heavily pretreated patients with advanced disease and high tumor burden, including those with disease progression in the brain. High and durable responses are observed when ceritinib is administered to patients who have already experienced disease progression during both chemotherapy and crizotinib. Safety analyses are consistent with those reported previously, and PROs were suggestive of improvement in lung cancer–related symptoms. These results support the positive benefit-risk profile of ceritinib compared with currently available therapies in patients with *ALK*-rearranged NSCLC who have experienced progression during crizotinib treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With ALK-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2

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Appendix

Supplemental Methods

Key exclusion criteria included hypersensitivity to any of the excipients of ceritinib; history of carcinomatous meningitis; the presence/history of a malignant disease other than non–small-cell lung cancer that has been diagnosed and/or required therapy within the past 3 years (exceptions to this exclusion included completely resected basal cell and squamous cell skin cancers and completely resected carcinoma of any type in situ); and clinically significant, uncontrolled heart disease. In addition, patients who had thoracic radiotherapy to lung fields 4 or fewer weeks prior to starting study treatment or who had not recovered from radiotherapy-related toxicities were excluded, as were patients who had major surgery within 4 weeks (2 weeks for resection of brain metastases) prior to the start of the study drug or who had not recovered from adverse events of such a procedure and patients with a history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis.

Study Assessments

The European Organisation for Research and Treatment of Cancer core-30 quality-of-life questionnaire (QLQ-C30) comprises 30 questions that incorporate multi-item scales (functional, symptom, and global health and quality of life), and the complementary quality-of-life lung cancer–specific questionnaire (QLQ-LC13) consists of a single multi-item scale to assess symptoms and adverse events. These surveys were used together with the visual analog Lung Cancer Symptom Scale (LCSS), which measures major symptoms for lung cancer, total symptom distress, normal activity status, and overall quality of life.

The questionnaires were self administered and were provided to patients at the first visit, on day 1 of cycles 2 and 3, and on day 1 of every second cycle thereafter. All responses were collected at the beginning of each visit, prior to any interaction with the study investigator.

Statistical Analyses

Efficacy analysis. On the basis of an exact binomial distribution, approximately 137 patients were required to test a null hypothesis of an overall response rate (ORR) of 25% or less versus a target ORR of 38% or greater with a one-sided α of .025 and 90% power. If 137 patients were enrolled, and if at least 45 responses were observed (estimated ORR, $\geq$ 32.8%), the null hypothesis would be rejected. The ORR (proportion of patients with a best overall response [BOR] of complete response [CR] or partial response [PR]) was calculated, along with exact binomial 95% CI; patients with a BOR of unknown were counted as nonresponders for ORR calculations. The disease control rate rate, with the corresponding exact binomial 95% CI, was estimated as the proportion of patients with a BOR of CR, PR, or stable disease (SD). The duration of response was defined as time from first documented response to first documented disease progression or death. The time to response was defined as time from first dose of ceritinib to first documented response. Progression-free survival (PFS) was defined as the time from the first dose of ceritinib to the first documented progressive disease (PD) or death. A patient who had not experienced progression or died at the date of the analysis cutoff or when he/she received any additional anticancer therapy in the absence of disease progression was censored at the time of the last adequate tumor evaluation before the earlier of the cutoff date or the date of anticancer therapy. By default, if disease progression or death was documented after one single missing tumor evaluation, the actual event date of disease progression/death was used for the PFS event date. If disease progression or death was documented after two or more missing tumor evaluations, the PFS time of these patients was censored at the date of the last adequate tumor evaluation without PD. Overall survival (OS) was defined as the time from the first dose of ceritinib to death. The OS time for patients who were alive at the end of the study or who were lost to follow-up was censored at the date of last contact. The median duration of response, time to response, PFS, and OS times, and the associated 95% CIs, were estimated with Kaplan-Meier methodology.

Intracranial responses were assessed as CR, PR, or SD (defined as non-CR/non-PD for patients with nonmeasurable brain lesions at baseline). The overall intracranial response rate was calculated as the proportion of patients with a BOR of CR or PR, and the intracranial disease control rate as the proportion of patients with a BOR of CR, PR, or SD.

Patient-reported outcomes analysis. For each of the surveys, summary scores were generated from the responses for each domain, per the respective scoring manuals. The change from baseline was assessed for each visit; patients with an evaluable baseline score and at least one evaluable postbaseline score were included in the change-from-baseline assessments.

Table A1. Protocol Deviations Leading to Exclusion From PPS

Protocol Deviation	No. (%) of Patients in FAS (N = 140)
No postbaseline tumor assessment	9 (6.4)
No local documentation of *ALK*-positive status using the FDA-approved FISH test	3 (2.1)
Additional protocol deviations leading to exclusion by BIRC	
No valid baseline tumor assessment*	2 (1.4)
No baseline target lesions†	26 (18.6)

Abbreviations: BIRC, blinded independent review committee; FAS, full analysis set; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization; PPS, per-protocol set.
*One patient was also included in the number of patients excluded because the patient had no local documentation of *ALK*-positive status with the FDA-approved FISH test.
†One patient was also included in the number of patients excluded because the patient had no postbaseline tumor assessment.

Table A2. Patient Disposition

Variable	No. (%) of Patients	
	FAS (N = 140)	Brain Metastases at Study Entry (n = 100)
Median (range) duration of follow-up, months	11.3 (0.1-18.9)	11.2 (0.2-18.9)
Treatment ongoing	51 (36.4)	34 (34.0)
Treatment discontinued	89 (63.6)	66 (66.0)
Reason for discontinuation		
Adverse event	10 (7.1)	7 (7.0)
Death	5 (3.6)	3 (3.0)
Disease progression	56 (40.0)	43 (43.0)
Physician/patient decision	17 (12.1)	12 (12.0)
Lost to follow-up	1 (0.7)	1 (1.0)

Abbreviation: FAS, full analysis set.

Table A3. Whole-Body Responses Based on Investigator Assessments for PPS of Patients

Best Overall Response	No. (%) of Patients in PPS (n = 128)
CR	4 (3.1)
PR	50 (39.1)
SD	53 (41.4)
PD	17 (13.3)
UNK	4 (3.1)
ORR*	54 (42.2)
DCR*	107 (83.6)

Abbreviations: CR, complete response; DCR, disease control rate (CR + PR + SD); ORR, overall response rate (CR + PR); PD, progressive disease; PPS, per-protocol set; PR, partial response; SD, stable disease; UNK, unknown.
*95% CI: ORR, 33.5 to 51.2; DCR, 76.0 to 89.5.

Table A4. Whole-Body Responses Based on BIRC Assessments

Best overall response	No. (%) of Patients by Assessment Type		
	FAS (N = 140)	PPS (n = 102)	Brain Metastases at Study Entry (n = 100)
CR	0	0	0
PR	50 (35.7)	50 (49.0)	32 (32.0)
SD	38 (27.1)	37 (36.3)	32 (32.0)
Non-CR/non-PD	22 (15.7)	0	15 (15.0)
PD	15 (10.7)	12 (11.8)	11 (11.0)
UNK	15 (10.7)	3 (2.9)	10 (10.0)
ORR	50 (35.7)	50 (49.0)	32 (32.0)
95% CI	27.8 to 44.2	39.0 to 59.1	23.0 to 42.1
DCR	88 (62.9)	87 (85.3)	64 (64.0)
95% CI	54.3 to 70.9	76.9 to 91.5	53.8 to 73.4

Abbreviations: BIRC, blinded independent review committee; CR, complete response; DCR, disease control rate (CR + PR + SD); FAS, full analysis set; ORR, overall response rate (CR + PR); PD, progressive disease; PPS, per-protocol set; PR, partial response; SD, stable disease; UNK, unknown.

Table A5. BIRC-Assessed Intracranial Responses in Patients With Target Brain Lesions at Study Entry

Best Overall Response	No. (%) of Patients With Target Brain Lesions at Study Entry (n = 33)
CR	1 (3.0)
PR	12 (36.4)
SD	15 (45.5)
PD	0
UNK	5 (15.2)
OIRR*	13 (39.4)
IDCR*	28 (84.8)

Abbreviations: BIRC, blinded independent review committee; CR, complete response; IDCR, intracranial disease control rate; OIRR, overall intracranial response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.
*95% CI: OIRR, 22.9 to 57.9; IDCR, 68.1 to 94.9.

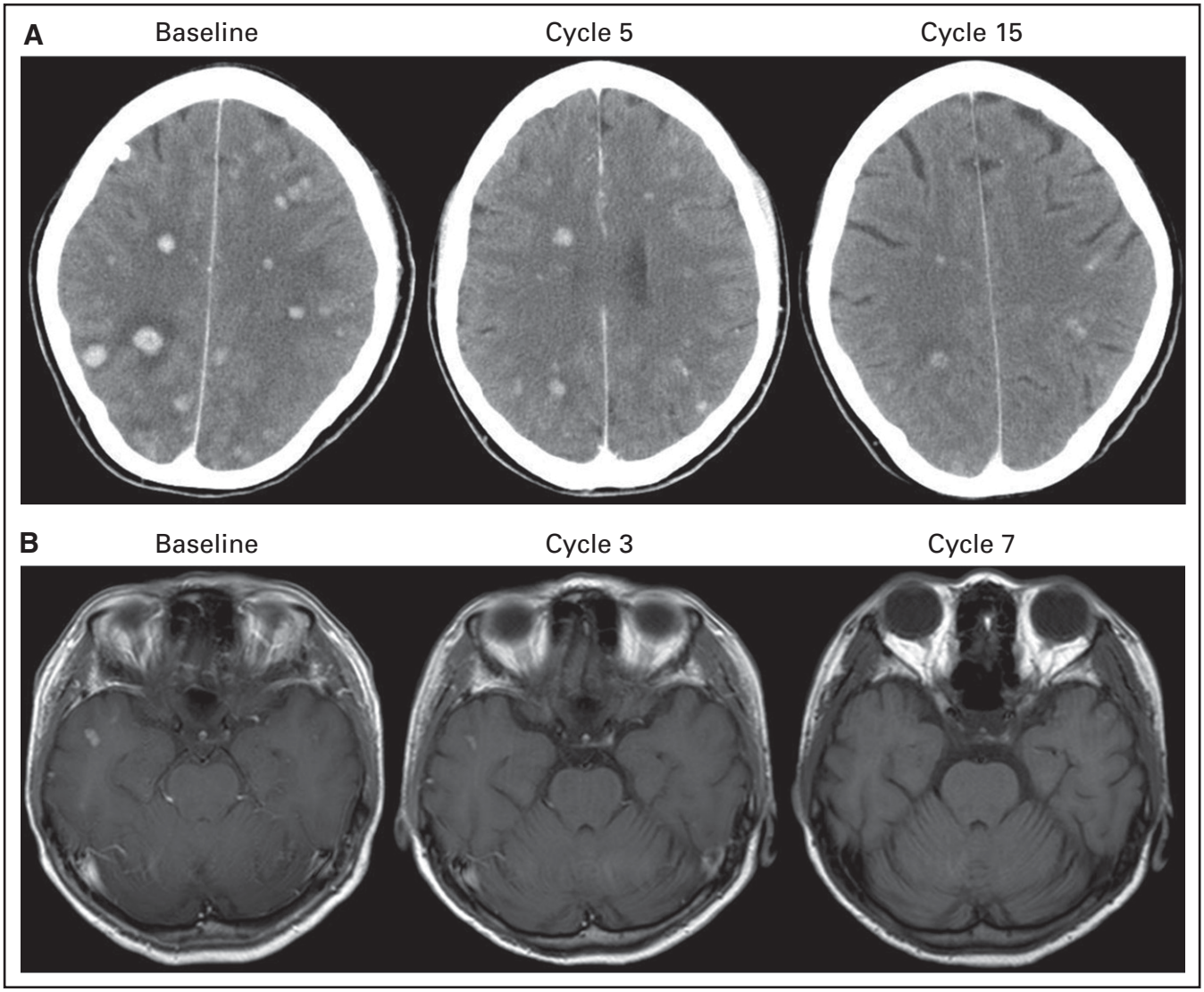

Fig A1. (A) Computed tomography scan image showing a partial response in the brain in a patient with brain metastases at baseline and at cycles 5 and 15 of ceritinib. The patient had received no prior radiotherapy to brain. After 422 days of ceritinib treatment, the patient discontinued treatment because of clinical progression. (B) Magnetic resonance imaging scan images showing a complete response in the brain in a patient with brain metastases at baseline and at cycles 3 and 7 of ceritinib. The patient had received no prior radiotherapy to the brain. After 358 days of ceritinib treatment, the patient remained on treatment.