

Original Article

Phase 3 study of ceritinib vs chemotherapy in *ALK*-rearranged NSCLC patients previously treated with chemotherapy and crizotinib (ASCEND-5): Japanese subset

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Abstract

Background: In the global, Phase 3, ASCEND-5 study, ceritinib improved progression-free survival (PFS) vs chemotherapy in patients with anaplastic lymphoma kinase (*ALK*)-rearranged non-small cell lung cancer (NSCLC) who had previously progressed on crizotinib and platinum-based chemotherapy. Here, we report efficacy and safety in a subset of Japanese patients from the ASCEND-5 study.

Methods: Patients with advanced *ALK*-rearranged NSCLC received oral ceritinib 750 mg/day or chemotherapy (intravenous pemetrexed 500 mg/m² or docetaxel 75 mg/m² [investigator's choice], every 21 days).

Results: Among the 231 patients, 29 were Japanese, of which, 11 were treated with ceritinib and 18 were treated with chemotherapy (5 with pemetrexed and 13 with docetaxel). All the patients received prior crizotinib and one or two lines of prior chemotherapy for advanced disease. Median follow-up time was 16.6 months for ceritinib arm and 16.4 months for chemotherapy arm in the overall population. The median PFS by blinded independent review committee was 9.8 months (95% CI, 4.3–14.0) in ceritinib arm vs 1.6 months (95% CI, 1.4–3.0) in chemotherapy arm. Grade 3 or 4 adverse events, suspected to be study drug related, were reported in 36.4% of ceritinib arm and 72.2% of chemotherapy arm, respectively. No Grade 3 or 4 events of diarrhea, nausea and vomiting were reported in both the treatment arms. Adverse events leading to study drug discontinuation were reported in one patient in each arm: Grade 3 central-nervous system metastases in ceritinib-treated patient and Grade 3 febrile neutropenia in chemotherapy-treated patient.

Conclusions: Consistent with overall population, ceritinib demonstrated better efficacy compared with the standard second-line chemotherapy in Japanese patients with crizotinib-resistant *ALK*+ NSCLC.

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Key words: ceritinib, Japanese, *ALK*+, NSCLC

Introduction

Traditionally, patients with advanced non-small cell lung cancer (NSCLC) have been mainly treated with chemotherapy. Improved knowledge of NSCLC biology has led to the identification of molecular subsets of patients with NSCLC who may be candidates for targeted therapy. Anaplastic lymphoma kinase (*ALK*)-rearranged (*ALK*+) NSCLC is one such distinct molecular subset occurring in ~3–7% of patients with NSCLC (1, 2). Crizotinib, an oral small-molecule tyrosine kinase inhibitor of *ALK*, *MET* and *ROS1* kinases was the first *ALK*-targeted drug approved in patients with *ALK*+ NSCLC. Data from the two Phase 3 trials comparing crizotinib to chemotherapy have demonstrated that crizotinib was more effective than chemotherapy in patients with *ALK*+ NSCLC in both the first-line and second-line settings (3, 4). However, most of the patients on crizotinib develop resistance and progressive disease (5); the most common site of progression being the brain (6).

Ceritinib (LDK378; Novartis, East Hanover, NJ, USA), a next-generation, selective oral *ALK* inhibitor, has 20-fold greater potency than crizotinib in enzymatic assays (7). In rats, ceritinib has been demonstrated to cross the blood–brain barrier with a brain-to-blood exposure ratio of ~15% (8). Results from the Phase 1 ASCEND-1 study (9, 10) and Phase 2 ASCEND-2 study (11) demonstrated consistent, high and durable antitumor efficacy of ceritinib 750 mg/day in patients with *ALK*+ NSCLC who were previously given chemotherapy and crizotinib (the median progression-free survival [PFS] of 6.9 months [95% confidence interval (CI), 5.6–8.7] in ASCEND-1 and 5.7 months [95% CI, 5.4–7.6] in ASCEND-2 study). The most common adverse events (AEs) were gastrointestinal related (diarrhea, nausea and vomiting), majority of which were Grade 1 to 2 in severity (10, 11). Additionally, Phase 1 (NCT01634763) Japanese study (12) and Japanese subset in ASCEND-2 study (13) with *ALK*+ NSCLC patients showed a tolerable safety profile and clinical activity similar to that reported in ASCEND-1 and ASCEND-2 studies. The Phase 1 (NCT01634763) Japanese study also showed that pharmacokinetics and maximum tolerated dose were consistent with the global study (9). In randomized, global, Phase 3 trial, ceritinib demonstrated a statistically significant and clinically meaningful improvement in PFS vs chemotherapy in patients with advanced *ALK*+ NSCLC who were previously treated with crizotinib and 1–2 prior chemotherapy regimens (ASCEND-5 study). The overall safety of ceritinib was consistent with that reported in the previous studies (ASCEND-1 and ASCEND-2), with no new safety signals reported. Here, we describe the efficacy and safety results for the subpopulation of 29 Japanese patients enrolled in the ASCEND-5 study (14).

Materials and methods

Patient population

Eligible patients were adults with locally advanced or metastatic *ALK*+ NSCLC confirmed locally by FDA-approved Vysis *ALK* Break Apart Fluorescent In Situ Hybridization (FISH) Probe test (Abbott Molecular, Des Plaines, IL, USA). If the documentation of

ALK rearrangement was unavailable, a confirmatory FISH assay was performed on a new tumor biopsy (obtained prior to the first dose of study treatment or prior to study enrollment) at a Novartis-designated central laboratory. For the enrollment, patients must have been previously treated with cytotoxic chemotherapy (including a platinum-based doublet) and crizotinib (≥ 21 days, any time prior to the study enrollment) for advanced disease regardless of the sequence of prior treatment. More than one prior course of crizotinib was allowed, and all the patients must have demonstrated disease progression at the study entry. The other key inclusion criteria for this study included a World Health Organization (WHO) performance status of 0 to 2 and ≥ 1 measurable lesion as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients could have asymptomatic central-nervous system (CNS) disease that was neurologically stable and did not require increasing doses of steroids within 2 weeks of the study start. Additionally, patients must have recovered from all the toxicities related to prior anticancer therapies (Common Terminology Criteria for Adverse Events [CTCAE] v4.03) to Grade ≤ 1 , adequate laboratory test results, and a life expectancy of ≥ 12 weeks.

Patients were considered not eligible if they had received any previous *ALK*-inhibitor therapy other than crizotinib. Patients with an impairment of gastrointestinal (GI) function or GI disease were excluded, as it might have significantly altered the absorption of ceritinib. Further key exclusion criteria included the following: any patient with the history of carcinomatous meningitis, pancreatitis, interstitial lung disease, or pneumonitis, other malignant disease (besides NSCLC that was diagnosed and/or required therapy within the past 3 years). Patients with a clinically significant uncontrolled heart disease and/or recent cardiac event (within 6 months) and who had a major surgery within 4 weeks before starting the study were not eligible.

The protocol was approved by the local institutional review board for each site that participated in the study, and the written consent was obtained from all the patients before screening. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization.

Study design and treatment plan

ASCEND-5 is an open-label, randomized, Phase 3 study conducted across 20 countries including Japan in patients with *ALK*+ NSCLC who were previously treated with chemotherapy and crizotinib. Patients were randomly assigned in an 1:1 ratio to receive either ceritinib 750 mg/day (fasted, in continuous 21-day treatment cycles) or chemotherapy (intravenous pemetrexed 500 mg/m² or docetaxel 75 mg/m² [investigator choice], every 21 days) using an interactive response technology. Randomization was stratified by WHO performance status (0 vs 1–2) and the presence of brain metastases at screening (yes vs no). Treatment with ceritinib or chemotherapy continued until disease progression. Patients who progressed while receiving either ceritinib or chemotherapy could continue beyond

progression at the investigators' discretion if any evidence existed on continued clinical benefit. Patients who discontinued chemotherapy treatment because of disease progression (confirmed by blinded independent review committee [BIRC]) were allowed to cross over to the ceritinib treatment. For the patients treated with ceritinib, a maximum of three dose reductions (150 mg per reduction, to a lowest dose of 300 mg/day) were allowed. For patients treated with chemotherapy, the dose reductions were done based on approved local product labels or guidelines.

The primary endpoint of this study was PFS, defined as the time from randomization to the first radiologically documented disease progression (according to RECIST 1.1) per BIRC assessment or death due to any cause. The key secondary endpoint was overall survival (OS), defined as the time from randomization to date of death due to any cause. The other secondary endpoints included the following: PFS by investigator; overall response rate (ORR, defined as the proportion of patients with the best overall response of complete response or partial response) and disease control rate (DCR, defined as the proportion of patients with the best overall response of complete response or partial response or stable disease or non-complete response or non-progressive disease) by the investigator and BIRC; overall intracranial response rate (OIRR) and intracranial disease control rate (IDCR) as assessed by BIRC-neuroradiologist, and safety.

Study assessments

Efficacy analysis

All tumor responses (both whole-body and intracranial) were assessed by investigator and BIRC based on RECIST 1.1. At baseline, the following assessments were performed: computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest

and abdomen; whole-body bone scan. Computed tomography scan or MRI of the brain and photography of all the skin lesions were performed at baseline, and were repeated post-baseline if clinically indicated or positive at baseline. Tumor evaluation was performed at baseline and then every 6 weeks (2 cycles) after Cycle 1 Day 1 through month 18, and every 9 weeks (3 cycles) thereafter and at end of treatment for response determination. The intracranial tumor response was assessed by an independent neuroradiologist using modified RECIST 1.1, which allowed selecting up to five measurable brain lesions as target lesions for all the patients with known baseline brain metastasis.

Safety analysis

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious adverse events and pregnancies, the regular monitoring of hematology, serum chemistry, urinalysis, routine monitoring of vital signs (sitting pulse, sitting blood pressure and body temperature), weight, WHO performance status, electrocardiogram and physical condition. Assessments were performed at baseline/screening, at varying frequencies in every treatment cycle, and at end of treatment. Apart from the scheduled time points the assessments were repeated at any time when clinically indicated at the discretion of the Investigator. All AEs reported were recorded and graded according to the Common Terminology Criteria for AEs, v4.03.

Statistical analyses

This is a subgroup analysis of patients enrolled in the ASCEND-5 study at the investigational sites situated in Japan. The efficacy endpoints were analyzed in all the patients who were assigned with the study treatment (ceritinib or chemotherapy) by randomization according to the intention-to-treat principle, and the safety outcomes

Table 1. Baseline patient and disease characteristics

	Ceritinib N = 11	Chemotherapy N = 18
Age		
Median (range), years	52.0 (32.0–68.0)	50.0 (31.0–72.0)
Sex, n (%)		
Female	8 (72.7)	10 (55.6)
Race, n (%)		
Asian	11 (100)	18 (100)
WHO performance status, n (%)		
0	5 (45.5)	6 (33.3)
1	4 (36.4)	11 (61.1)
2	2 (18.2)	1 (5.6)
Smoking history, n (%)		
Current smoker	0	1 (5.6)
Ex-smoker	3 (27.3)	6 (33.3)
Never smoker	7 (63.6)	8 (44.4)
Missing	1 (9.1)	3 (16.7)
Disease stage at study entry, n (%)		
IV	11 (100)	18 (100)
Histology/cytology, n (%)		
Adenocarcinoma	11 (100)	17 (94.4)
Squamous cell carcinoma	0	1 (5.6)
Brain metastases, n (%)	7 (63.6)	10 (55.6)
Prior crizotinib treatment, n (%)	11 (100)	18 (100)
Prior chemotherapy treatment, n (%)		
One line	11 (100)	17 (94.4)
Two lines	0	1 (5.6)

WHO, World Health Organization.

in all the patients who received at least one dose of study treatment. PFS and OS were estimated using the Kaplan–Meier method, with their median value and the corresponding 95% confidence interval (CI) calculated by the Brookmeyer and Crowley method (15). A Cox regression model stratified by randomization factors (WHO performance status: 0 vs 1–2; presence or absence of brain metastases) was used to estimate the hazard ratio (HR) and the corresponding 95% CI. ORR, DCR, OIRR and IDCR were reported with the exact binomial 95% CI (Clopper–Pearson method) (16). The data cutoff date for this subgroup analysis was 26 January 2016. A complete and detailed description of the overall study design and sample size calculation for the primary endpoint has previously been published (14).

Results

Patients

Among the 231 patients with *ALK*-rearranged NSCLC randomized in the ASCEND-5 study, 29 were randomized in Japan. Of these 29 Japanese patients, 11 were treated with ceritinib 750 mg/day in the fasted state and 18 were treated with chemotherapy (5 with pemetrexed and 13 with docetaxel). All the patients had metastatic disease at the study entry, and majority of the patients had a WHO PS of ≤ 1 (nine patients [81.8%] in the ceritinib arm and 17 patients [94.4%] in the chemotherapy arm). Seven of the 11 patients (63.6%) in the ceritinib arm and 10 of the 18 patients (55.6%) in the chemotherapy arm had brain metastases at the study entry. All the patients had received at least one prior line of both chemotherapy and crizotinib in both the treatment arms, with 5.6% ($n = 1$) receiving 2 prior lines of chemotherapy in chemotherapy arm (Table 1). At the data cutoff, 8 of 11 patients (72.7%) in the ceritinib arm vs 18 of 18 patients (100%) in the chemotherapy arm had discontinued, while three patients (27.3%) continue to receive ceritinib treatment. The primary reason for discontinuation in ceritinib arm and chemotherapy arm was disease progression, which occurred in 7 (63.6%) vs 17 patients (94.4%), respectively. Among the chemotherapy-treated patients, 16 of 18 (88.9%) received ceritinib after discontinuation of chemotherapy in the extension phase.

Efficacy

At the data cutoff, in the overall population, the median follow-up time (duration between randomization and cutoff date) was 16.6 months (range, 2.8–30.1) for the ceritinib arm and 16.4 months (range, 2.9–30.9) for the chemotherapy arm. In the Japanese patient subgroup, with 9 of 11 patients (81.8%) having an event in the ceritinib arm vs 15 of 18 (83.3%) in the chemotherapy arm, the median PFS by BIRC was 9.8 months (95% CI, 4.3–14.0) in ceritinib arm vs 1.6 months (95% CI, 1.4–3.0) in the chemotherapy arm (HR, 0.17 [95% CI, 0.05–0.61]; Fig. 1; Table 2). These results were consistent with the investigator-assessed PFS data, for which, the median PFS was 9.8 months (95% CI, 2.9–18.9) in the ceritinib arm vs 1.7 months (95% CI, 1.3–3.2) in the chemotherapy arm.

In the overall population, since the PFS by BIRC was statistically significant favoring ceritinib, the preplanned interim analysis for OS was performed at the time of primary analysis for PFS (14). In the Japanese patient subgroup, with five deaths (45.5%) in the ceritinib arm and eight deaths (44.4%) in the chemotherapy arm, the median OS was similar between both treatment arms at the data cutoff: 23.9 months (95% CI, 6.6–NE) in ceritinib arm vs 22.8 months (95% CI, 8.3–NE) in chemotherapy arm (HR, 0.88 [95% CI,

0.27–2.82]). The 24-month OS even-free rate was 38.8% (95% CI, 6.9–71.5) in the ceritinib arm and 40.0% (95% CI, 12.4–66.8) in chemotherapy arm. There were no responders in the chemotherapy arm (0% [95% CI, 0.0–18.5]), but ceritinib was associated with high ORR (54.5% [95% CI, 23.4–83.3]). Similarly, the disease control rate was higher in the ceritinib arm than in the chemotherapy arm: 90.9% (95% CI, 58.7–99.8) vs 33.3% (95% CI, 13.3–59.0). The best percentage change from baseline in the sum of tumor diameters in individual patients is shown in Fig. 2.

Intracranial responses in patients with brain metastases at baseline

As per BIRC-neuroradiologist, 15 patients had brain metastases (measurable and/or non-measurable disease) at baseline (five patients in the ceritinib arm and 10 patients in the chemotherapy arm). The OIRR in these patients with brain metastases at baseline was 20.0% (95% CI, 0.5–71.6) with ceritinib and 0% (95% CI, 0.0–30.8) with chemotherapy. IDCR was 60.0% (95% CI, 14.7–94.7) with ceritinib and 70% (95% CI, 34.8–93.3) with chemotherapy (Table 2). In the ceritinib arm, four patients had measurable brain metastasis at baseline, of which one patient showed a partial response.

Safety

For the Japanese patients, the median duration of treatment exposure was 48.1 weeks (range, 0.3–122.9 weeks) for ceritinib and 6.2 weeks (range, 3.0–48.0 weeks) for chemotherapy. The median relative dose intensity was 71.9% (range, 35.4–100.0%) for ceritinib, 100% (range, 92.1–100.0%) for pemetrexed, and 85.3% (range, 54.6–101.8%) for docetaxel. Adverse events requiring dose adjustment were 36.4% (no Grade 3 or 4 AEs) in the ceritinib arm and 50.0% (all were Grade 3 or 4 AEs) in the chemotherapy arm. Adverse events requiring dose interruption/delay were reported in 9 of 11 patients (81.8%) in the ceritinib arm and 4 of 18 patients (22.2%) in the chemotherapy arm (Table 3).

In both the treatment arms, 100% of patients reported an AE (regardless of study drug relationship), of which, 63.6% of AEs in the ceritinib arm and 77.8% of AEs in the chemotherapy arm were of Grade 3 or 4. Adverse events suspected to be drug related were reported in 90.9% of the ceritinib arm and in 100% of the chemotherapy arm. The most frequent any-grade AEs (regardless of study drug relationship) in the ceritinib arm were diarrhea (81.8%), nausea and vomiting (each 63.6%). Alopecia, neutropenia (each 38.9%) and febrile neutropenia (33.3%) were more frequently seen in the chemotherapy arm than in the ceritinib arm, see Table 3. Adverse events leading to the study drug discontinuation were reported in one patient in each arm: Grade 3 CNS metastases in ceritinib-treated patient and Grade 3 febrile neutropenia in chemotherapy-treated patient. CNS metastasis was considered as an AE because the patient received ceritinib beyond confirmed progressive disease and later discontinued permanently in the context of disease progression. No patients in either arm discontinued due to GI AE. Grade 3 or 4 AEs, suspected to be study drug related, were reported in 36.4% of the ceritinib arm and 72.2% of the chemotherapy arm. No Grade 3 or 4 events of diarrhea, nausea and vomiting were reported in both the treatment arms. Most frequent ($\geq 10\%$) Grade 3 or 4 AE in ceritinib arm was gamma-glutamyltransferase increased (27.3%). Neutropenia, febrile neutropenia (each 33.3%), leukopenia and neutrophil count decreased (each 16.7%) were the most frequently reported Grade 3 or 4 AEs in the chemotherapy

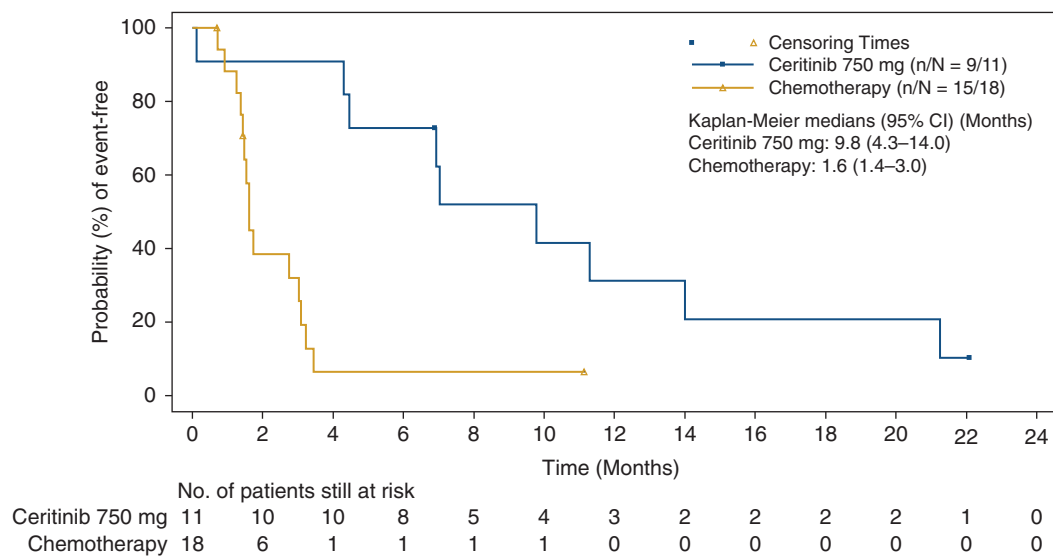


Figure 1. Kaplan-Meier curve showing progression-free survival of ceritinib ($n = 11$) vs chemotherapy ($n = 18$) in the Japanese patients ($N = 29$) (per BIRC assessment).

Table 2. Whole-body and intracranial responses based on BIRC assessments

	Ceritinib 750 mg $N = 11$	Chemotherapy $N = 18$
PFS, median [95% CI] (months)	9.8 [4.3–14.0]	1.6 [1.4–3.0]
OS, median [95% CI] (months)	23.9 [6.6–NE]	22.8 [8.3–NE]
ORR, n (%) [95% CI]	6 (54.5) [23.4–83.3]	0 [0.0–18.5]
Best overall response, n (%)		
PR	6 (54.5)	0
SD	4 (36.4)	5 (27.8)
PD	0	10 (55.6)
Non-CR/Non-PD ^a	0	1 (5.6)
Unknown	1 (9.1)	2 (11.1)
DCR, n (%) [95% CI]	10 (90.9) [58.7–99.8]	6 (33.3) [13.3–59.0]
Intracranial responses in patients with measurable and/or non-measurable disease brain metastases at baseline		
	Ceritinib 750 mg $N = 5$	Chemotherapy $N = 10$
OIRR, n (%) [95% CI]	1 (20.0) [0.5–71.6]	0 [0.0–30.8]
Best overall response, n (%)		
PR	1 (20.0)	0
SD	1 (20.0)	2 (20.0)
PD	1 (20.0)	2 (20.0)
Non-CR/Non-PD ^a	1 (20.0)	5 (50.0)
Unknown	1 (20.0)	1 (10.0)
IDCR, n (%) [95% CI]	3 (60.0) [14.7–94.7]	7 (70.0) [34.8–93.3]

^aNon-CR/Non-PD refers to best overall responses that are neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.

CR, complete response; DCR, disease control rate; IDCR, intracranial disease control rate; OIRR, overall intracranial response rate; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

arm (Table 4). Serious AEs regardless of study drug relationship were similar in both the arms (27.3% in the ceritinib arm and 22.2% in the chemotherapy arm) and none were of the predominant type. No patients reported interstitial lung disease (ILD) in the ceritinib arm. One patient (5.6%) in the chemotherapy arm reported ILD. Among important known AEs of ceritinib, electrocardiogram QTc prolongation occurred in three patients (all three were Grade 1) treated with ceritinib vs none treated with chemotherapy. In the ceritinib arm, one patient died during on-treatment period,

which was not attributable to ceritinib. The cause of the death was determined to be the underlying disease (NSCLC).

Discussion

The efficacy results from the Japanese patient subset of the ASCEND-5 study were consistent with those observed in the overall population. In the Japanese patients, ceritinib demonstrated better

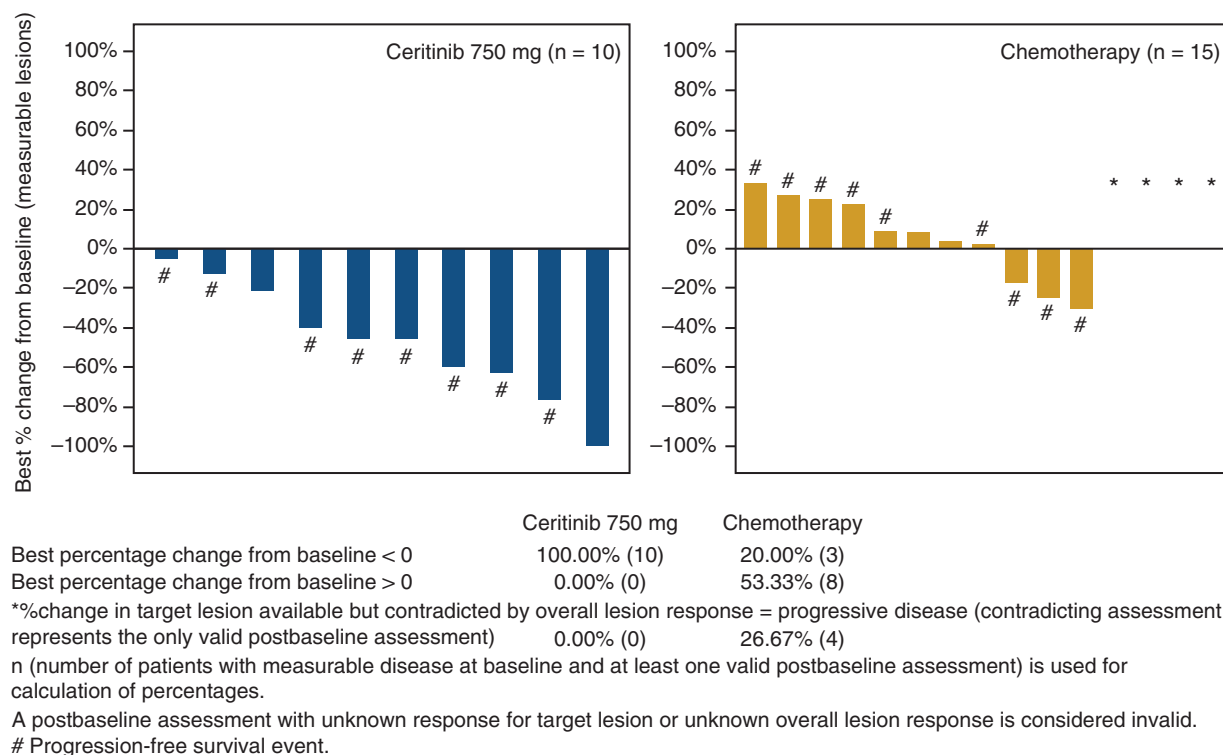


Figure 2. Best percentage change from baseline in sum of diameters per BIRC assessment.

efficacy compared with the chemotherapy in *ALK*-rearranged patients who were pretreated with chemotherapy and crizotinib. The median PFS by BIRC was numerically higher with ceritinib in the Japanese population (9.8 months [95% CI, 4.3–14.0]) than in the overall population (5.4 months [95% CI, 4.1–6.9]), whereas the median PFS with chemotherapy was similar with overlapping CIs between the Japanese patients (1.6 months [95% CI, 1.4–3.0]) and the overall population (1.6 months [95% CI, 1.4–2.8]) (14). In the ASCEND-2 Japanese population ($N = 24$), the median PFS was 6.6 months (95% CI, 3.7–9.3) (13). This numerical higher PFS in ASCEND-5 Japanese population need to be interpreted with caution because of the small sample size of the Japanese subgroup and overlapping 95% CIs. Other reason for better PFS in ASCEND-5 Japanese population may be attributed to the number of prior regimens received. In the ceritinib-treated overall population of ASCEND-5 study (14), 11% of patients received 2-lines of chemotherapy compared to none in the ASCEND-5 Japanese subgroup, whereas in the ASCEND-2 Japanese population, 54.2% of patients received ≥ 3 lines of prior regimen (chemotherapy/targeted therapy) (13). The median OS was similar between both the treatment arms (23.9 months [95% CI: 6.6–NE] for ceritinib vs 22.8 months [95% CI, 8.3–NE] for chemotherapy), which was consistent with the overall population (18.1 months [95% CI, 13.4–23.9] and 20.1 months [95% CI, 11.9–25.1] for ceritinib and chemotherapy, respectively, from the ASCEND-5 overall population) (14). Overall, the OS data are immature and the number of patients ($n = 16$ of 18) who crossed-over to ceritinib treatment from chemotherapy could be a confounding factor.

Other efficacy endpoints (ORR = 54.5% and DCR = 90.9%) were also higher with ceritinib compared to chemotherapy (ORR = 0% and DCR = 33.3%), which was also observed in the ASCEND-5 overall population (14). The ORR and DCR observed in the

ASCEND-5 Japanese patients were consistent with the previously reported Phase 2 (ASCEND-2) Japanese subgroup data in similar patient populations who had previously received crizotinib and chemotherapy (13). The safety profile of ceritinib in the ASCEND-5 Japanese subgroup was acceptable and consistent with the established safety profile of ceritinib with no new safety signals observed (10, 11, 13, 14). There were no remarkable differences in the safety profile of ceritinib, between the Japanese subset and overall population (14). Overall, AEs requiring dose interruption or delay were higher with ceritinib vs chemotherapy. Adverse events requiring dose adjustments and dose interruption/delay with ceritinib in the Japanese population were also consistent with the overall population (36.4% vs 36.5% and 81.8% vs 73.0%, respectively; data on file). Gastrointestinal AEs were most frequently reported with ceritinib also in the Japanese population, but none of them were of Grade 3 or 4, and no patients discontinued due to GI AE. While GI AEs were common and also commonly lead to dose interruption, these were generally manageable. Thus, to prevent dose interruptions and/or discontinuations, it is important to proactively manage GI toxicities (17). In the ceritinib treatment arm, three patients reported electrocardiogram QTc prolongation (all three were Grade 1) but none of these patients discontinued the study. ILD was not reported in patients treated with ceritinib but was reported in one patient treated with chemotherapy (docetaxel). Overall, AEs in the ceritinib arm were manageable in the Japanese population.

Recently, it was demonstrated that ceritinib 450 mg administered with food had comparable exposure to ceritinib 750 mg fasted in patients with *ALK*+ NSCLC with a more favorable safety profile (less frequent/severe GI toxicity and dose modifications resulting higher treatment exposure) in both treatment naive and pretreated patients (18) and promising emerging efficacy in treatment-naïve patients with *ALK*+ metastatic NSCLC (19). The result suggests

Table 3. Summary of adverse events occurring in >15% of patients at all grades and at Grades 3 or 4

Preferred term	Ceritinib 750 mg N = 11		Chemotherapy N = 18	
	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Summary of AEs				
All deaths ^a	5 (45.5)		8 (44.4)	
On-treatment deaths	1 (9.1)		0	
Total number of patients experiencing ≥ 1 AE	11 (100)	7 (63.6)	18 (100)	14 (77.8)
AEs suspected to be drug related	10 (90.9)	4 (36.4)	18 (100)	13 (72.2)
SAEs	3 (27.3)	3 (27.3)	4 (22.2)	4 (22.2)
SAEs suspected to be drug related	0	0	2 (11.1)	2 (11.1)
AEs leading to discontinuation	1 (9.1)	1 (9.1)	1 (5.6)	1 (5.6)
AEs requiring dose adjustment	4 (36.4)	0	9 (50.0)	9 (50.0)
AEs requiring dose interruption/delay	9 (81.8)	5 (45.5)	4 (22.2)	2 (11.1)
AEs occurring in >15% of patients				
Diarrhea	9 (81.8)	0	6 (33.3)	0
Nausea	7 (63.6)	0	7 (38.9)	0
Vomiting	7 (63.6)	0	1 (5.6)	0
Blood alkaline phosphatase increased	6 (54.5)	0	1 (5.6)	0
Alanine aminotransferase increased	5 (45.5)	1 (9.1)	3 (16.7)	0
Decreased appetite	5 (45.5)	0	5 (27.8)	1 (5.6)
Abdominal pain upper	4 (36.4)	0	1 (5.6)	0
Aspartate aminotransferase increased	4 (36.4)	1 (9.1)	3 (16.7)	0
Blood creatinine increased	4 (36.4)	0	0	0
Gamma-glutamyltransferase increased	4 (36.4)	3 (27.3)	1 (5.6)	0
Malaise	4 (36.4)	1 (9.1)	5 (27.8)	0
Constipation	3 (27.3)	0	3 (16.7)	0
Electrocardiogram QT prolonged	3 (27.3)	0	0	0
Hepatic function abnormal	3 (27.3)	0	1 (5.6)	0
Pneumonia	3 (27.3)	1 (9.1)	1 (5.6)	0
Rash	3 (27.3)	0	5 (27.8)	0
Arthralgia	2 (18.2)	0	5 (27.8)	0
Back pain	2 (18.2)	0	1 (5.6)	0
Blood albumin decreased	2 (18.2)	0	0	0
Bronchitis	2 (18.2)	0	0	0
Creatinine renal clearance decreased	2 (18.2)	0	0	0
Dry skin	2 (18.2)	0	0	0
Influenza	2 (18.2)	0	0	0
Nasopharyngitis	2 (18.2)	0	0	0
Pyrexia	2 (18.2)	0	5 (27.8)	0
Subcutaneous abscess	2 (18.2)	0	0	0
Weight decreased	2 (18.2)	0	1 (5.6)	0
Anemia	1 (9.1)	0	5 (27.8)	0
Fatigue	1 (9.1)	0	3 (16.7)	0
Leukopenia	1 (9.1)	0	5 (27.8)	3 (16.7)
Neutropenia	1 (9.1)	0	7 (38.9)	6 (33.3)
Pruritus	1 (9.1)	0	3 (16.7)	1 (5.6)
Stomatitis	1 (9.1)	0	3 (16.7)	0
White blood cell count decreased	1 (9.1)	0	3 (16.7)	2 (11.1)
Alopecia	0	0	7 (38.9)	0
Febrile neutropenia	0	0	6 (33.3)	6 (33.3)
Neutrophil count decreased	0	0	3 (16.7)	3 (16.7)

^aAll deaths, including those after the end of the on-treatment period.

AE, adverse event; SAE, serious adverse event.

that lower dose of ceritinib with food may be a preferred regimen with improved GI tolerability and high antitumor activity.

There are several limitations for this subgroup analysis. The small sample size of ASCEND-5 Japanese patients and the difference in number of patients between the ceritinib and chemotherapy arms due to stratification as part of a larger overall population (that included non-Japanese patients) may have affected outcomes. The ASCEND-5 Japanese subgroup results demonstrate that patients treated with ceritinib, a more potent ALK inhibitor, showed better efficacy after failure of both

crizotinib and chemotherapy, which was consistent in the ASCEND-5 overall population (14). Overall, these results confirm better clinical benefit with ceritinib vs chemotherapy in this Japanese patient population.

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Table 4. Summary of adverse events suspected to be study drug related occurring in >15% of patients at all grades and at Grade 3 or 4

Preferred term	Ceritinib 750 mg N = 11		Chemotherapy N = 18	
	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Total	10 (90.9)	4 (36.4)	18 (100)	13 (72.2)
Diarrhea	8 (72.7)	0	6 (33.3)	0
Nausea	7 (63.6)	0	6 (33.3)	0
Vomiting	7 (63.6)	0	1 (5.6)	0
Blood alkaline phosphatase increased	6 (54.5)	0	1 (5.6)	0
Alanine aminotransferase increased	5 (45.5)	1 (9.1)	3 (16.7)	0
Decreased appetite	5 (45.5)	0	5 (27.8)	0
Aspartate aminotransferase increased	4 (36.4)	1 (9.1)	3 (16.7)	0
Blood creatinine increased	4 (36.4)	0	0	0
Gamma-glutamyltransferase increased	4 (36.4)	3 (27.3)	1 (5.6)	0
Malaise	4 (36.4)	1 (9.1)	5 (27.8)	0
Electrocardiogram QT prolonged	3 (27.3)	0	0	0
Hepatic function abnormal	3 (27.3)	0	1 (5.6)	0
Rash	3 (27.3)	0	3 (16.7)	0
Abdominal pain upper	2 (18.2)	0	1 (5.6)	0
Creatinine renal clearance decreased	2 (18.2)	0	0	0
Pneumonia	2 (18.2)	1 (9.1)	1 (5.6)	0
Weight decreased	2 (18.2)	0	0	0
Anemia	1 (9.1)	0	5 (27.8)	0
Leukopenia	1 (9.1)	0	5 (27.8)	3 (16.7)
Neutropenia	1 (9.1)	0	7 (38.9)	6 (33.3)
Pruritus	1 (9.1)	0	3 (16.7)	1 (5.6)
Stomatitis	1 (9.1)	0	3 (16.7)	0
White blood cell count decreased	1 (9.1)	0	3 (16.7)	2 (11.1)
Alopecia	0	0	7 (38.9)	0
Arthralgia	0	0	4 (22.2)	0
Febrile neutropenia	0	0	6 (33.3)	6 (33.3)
Neutrophil count decreased	0	0	3 (16.7)	3 (16.7)
Pyrexia	0	0	5 (27.8)	0

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Conflict of interest statement

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