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Phase I Study of Ceritinib (LDK378) in Japanese Patients with Advanced, Anaplastic Lymphoma Kinase-Rearranged Non–Small-Cell Lung Cancer or Other Tumors

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Introduction: Anaplastic lymphoma kinase (ALK)-rearranged non–small-cell lung cancer (NSCLC) is sensitive to ALK inhibitors, but resistance develops. This study assessed the maximum-tolerated dose, safety, pharmacokinetics (PK), and antitumor activity of ceritinib, a novel ALK inhibitor (ALKi), in Japanese patients with *ALK*-rearranged malignancies.

Methods: This phase I, multicenter, open-label study (NCT01634763) enrolled adult patients with *ALK*-rearranged (by fluorescence in situ hybridization and/or immunohistochemistry) locally advanced/metastatic malignancy that had progressed despite standard therapy. The study comprised two parts: dose escalation and dose expansion. Ceritinib (single-dose) was administered orally in the 3-day PK run-in period, then once daily, in 21-day cycles. Adaptive dose escalations were guided by a Bayesian model.

Results: Twenty patients (80% with ALKi treatment history [ALKi-pretreated]; 19 NSCLC; one inflammatory myofibroblastic tumor) received ceritinib 300 to 750 mg (19 during dose escalation, one in dose expansion). Two dose-limiting toxicities occurred: grade 3 lipase increase (600 mg); grade 3 drug-induced liver injury (750 mg). The most common adverse events were gastrointestinal (nausea: 95%; diarrhea, vomiting: 75%). Ceritinib PK profile was dose proportional across 300 to 750 mg dosages; steady state was reached by day 15. Overall response rate was 55% (11 of 20 patients). Among patients with NSCLC, partial response was observed in two of four ALKi-naive patients, five of nine crizotinib-pretreated patients, two of four alectinib-pretreated patients, and one of two crizotinib and alectinib/ASP3026 pretreated patients. The ASP3026-pretreated inflammatory myofibroblastic tumor patient achieved partial response.

Conclusions: Ceritinib maximum-tolerated dose was 750 mg once daily in Japanese patients. Antitumor activity was observed irrespective of prior ALKi treatment history. Dose expansion, examining the activity of ceritinib in alectinib-resistant patients, is ongoing.

Key Words: *ALK* rearranged, non–small-cell lung cancer, Ceritinib, Alectinib.

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Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase first discovered in anaplastic large cell lymphoma.[1] *ALK* gene rearrangements occur in a variety of human malignancies, including non–small-cell lung cancer (NSCLC).[2,3] Overall, 2% to 7% of patients with NSCLC have *ALK* genetic alterations, with higher prevalence among nonsmokers, younger patients, and patients with adenocarcinomas.[4–6] *ALK* gene rearrangement can trigger oncogenic signaling pathways, principally the extracellular signal-regulated kinase and signal transducer and activator of transcription 3 pathways.[2] Inhibition of ALK by a tyrosine kinase inhibitor could lead to suppression of potential oncogenic drivers.

Crizotinib (Xalkori; Pfizer, Mission, KS) is an oral inhibitor of ALK, c-MET, and ROS1 receptor tyrosine kinases, effective in patients with advanced, *ALK*-rearranged NSCLC, with overall response rates (ORRs) of approximately 60% across all studies, and median progression-free survival (PFS) of 8 to 10 months.[7–9] In an open-label phase III study, crizotinib was superior to standard chemotherapy in patients with previously treated, advanced, *ALK*-rearranged NSCLC (ORR, 65% versus 20%; median PFS, 8 versus 3 mo, with crizotinib versus chemotherapy).[9] Although crizotinib has demonstrated therapeutic efficacy, the majority of patients progress, typically within 12 months, with the development of resistance.[10] Acquired resistance has been observed in about one third of patients with *ALK*-rearranged NSCLC involving mutations within the ALK tyrosine kinase domain and/or amplification of the *ALK* fusion gene and/or activation of EGFR, KRAS, or c-KIT.[10–13]

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Alectinib (CH5424802/RO5424802; Chugai/Roche) is a selective, orally available ALK inhibitor.[14] In a phase I/II study of alectinib in Japanese patients with *ALK*-rearranged NSCLC, an ORR of 93.5% was reported in patients who had not previously received an ALK inhibitor, with no dose-limiting toxicities (DLTs) at the maximally administered dose of 300 mg twice daily.[15] Another phase I study, conducted in the United States, evaluated alectinib in patients with crizotinib-refractory *ALK*-rearranged NSCLC, demonstrating an ORR of 55% (all cohorts), including both confirmed and unconfirmed responses, with DLTs occurring in the 900 mg twice-daily cohort.[16] The recommended phase II dose for alectinib was determined as 600 mg twice daily in the non-Japanese population[16] and 300 mg twice daily in Japanese patients.[15]

Ceritinib (LDK378; Novartis Pharmaceuticals) is a novel, potent, orally active, small-molecule tyrosine kinase inhibitor of ALK. In enzyme-based assays, ceritinib inhibited ALK with a half maximal inhibitory concentration (IC_{50}) value of 0.20 nM. In an enzyme panel of 30 kinases, only three other kinases (IGF-1R [IC_{50} = 8 nM], InsR [IC_{50} = 7 nM], and STK22D [IC_{50} = 23 nM]) showed biochemical inhibition below 100 nM, demonstrating the potency and high selectivity of ceritinib. At the cellular level, in a panel of 18 kinases, ceritinib inhibited ALK with an IC_{50} value less than 100 nM, confirming its high potency.[17] Furthermore, ceritinib was found to be 20-fold more potent compared with crizotinib in inhibiting ALK, and unlike crizotinib, it did not inhibit the kinase activity of c-MET. Ceritinib demonstrated marked antitumor activity in echinoderm microtubule-associated protein-like 4 (EML4)-ALK xenograft models of NSCLC, including those exhibiting crizotinib resistance.[18] These preclinical results suggested that ceritinib might exhibit antitumor activity in patients with *ALK*-rearranged NSCLC with crizotinib-resistant and crizotinib-naive disease.

Accordingly, results from a first-in-human, dose-escalation, phase I study of ceritinib (ASCEND-1; NCT01283516) in patients with *ALK*-rearranged malignancies have recently been published. The maximum-tolerated dose (MTD) of oral ceritinib was established as 750 mg once daily.[19] Ceritinib demonstrated substantial clinical activity in patients with NSCLC treated at doses of 750 mg once daily, reporting PFS of 18.4 months (95% confidence interval, 11.1, nonestimable) in patients who were ALK inhibitor naive (n = 83) and 6.9 months (95% confidence interval, 5.6, 8.7) in patients previously treated with crizotinib (n = 163).[20] The ORR was 61.8% in all patients (n = 246), 72.3% in patients who were ALK inhibitor naive, and 56.4% in patients previously treated with crizotinib.[20]

More recently, ceritinib activity has also been shown against cell lines harboring alectinib-resistant mutations, including a patient-derived cell line.[21] Further, ceritinib treatment of a patient who had progressed on alectinib following an initial response resulted in significant tumor regression, with a confirmed partial response (PR) more than 7 months.[21] These data suggest that ceritinib may show activity in patients who relapse on this second-generation ALK inhibitor, as well as in patients who are resistant to crizotinib.

This phase I, multicenter, open-label study (NCT01634763) was conducted to determine the MTD, safety, pharmacokinetics (PK), and antitumor activity of ceritinib in Japanese patients with *ALK*-rearranged NSCLC or other tumors harboring an *ALK* gene alteration. In addition, given the recent data in the literature on ceritinib efficacy in alectinib-resistant tumors and consequent interest in the potential for sequential therapy with ALK inhibitors,[21] further details on efficacy and safety in patients who had previously relapsed during treatment with alectinib are provided.

PATIENTS AND METHODS

Study Population

Adult patients (≥18 yr) with locally advanced or metastatic malignancy harboring genetic alterations in *ALK*, which had progressed despite standard therapy or for which no effective standard therapy exists, were included in this study. Genetic translocation in *ALK* was detected by fluorescence in situ hybridization (FISH) in at least 15% of tumor cells in patients with NSCLC; in other tumors, overexpression of ALK protein by immunohistochemistry was considered indicative of a genetic alteration in *ALK*. Other eligibility criteria included measurable or nonmeasurable disease and Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with NSCLC that had progressed during prior therapy with alectinib were enrolled to the dose-expansion part of the study.

Key exclusion criteria included patients with uncontrolled or symptomatic central nervous system metastases requiring increasing doses of steroids; patients with uncontrolled nausea, vomiting, or diarrhea of Common Terminology Criteria for Adverse Events (version 4.03) grade more than 1; and history of or current second malignancy and/or interstitial lung disease.

The study protocol and all amendments were reviewed by the institutional review board for each investigational site. This study was conducted according to the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. Institutional review board–approved informed consent was obtained from each patient in writing at screening.

Study Design

The primary objective of this study was to determine the MTD and/or the recommended dose (RD) of oral ceritinib in Japanese patients with *ALK*-rearranged tumors. Secondary objectives included assessment of the overall safety, tolerability, and single- and multiple-dose PK profile of ceritinib, as well as investigation of its preliminary antitumor efficacy at MTD/RD.

The study was divided into two parts: dose escalation and dose expansion at the MTD/RD. In each dose cohort of the dose-escalation part, three to six patients were to be enrolled, with at least six patients at the MTD/RD. In addition, at least six patients were to be enrolled in the dose-expansion part, after determination of the MTD/RD. Dose-escalation decisions, including MTD/RD determination, were made by the Principal Investigators and Novartis study personnel, based on available toxicity information (including DLTs and other adverse events [AEs] during cycle 1), PK information,

and recommendations from the Bayesian logistic regression model (BLRM). Updated safety data from ongoing patients, including data in later cycles, were also considered.

Ceritinib was administered orally as a single dose in the 3-day PK run-in period, followed by once-daily dosing in continuous 21-day cycles. Based on the available safety and efficacy data from the global, first-in-human, ASCEND-1 study at the time of protocol writing, ceritinib was well tolerated at doses up to 500 mg once daily, with no DLTs at the 300 mg once-daily dose. Furthermore, based on predictions from the BLRM, the MTD was more than 700 mg once daily, with a low probability of overdose at the 600 mg once-daily dose. Therefore, the starting dose of ceritinib selected for this study was 300 mg once daily. Patients continued treatment until unacceptable toxicity, disease progression, or withdrawal of consent. Treatment beyond disease progression was permitted if there was evidence of clinical benefit, as assessed by the principal investigator, such as disease shrinkage at other sites or symptomatic improvement.

To further address the safety, antitumor activity, and PK profile of ceritinib treatment in patients previously treated with alectinib, the dose-expansion part of this study is focused on patients with *ALK*-rearranged NSCLC who progressed on alectinib treatment.

Assessments

DLTs were assessed during the first cycle (including the PK run-in period) of ceritinib treatment in the dose-escalation part. AEs were assessed according to Common Terminology Criteria for Adverse Events version 4.03. Blood samples were collected for the assessment of PK parameters following ceritinib treatment. Tumor response evaluations were performed by local investigators using computerized tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.1 at baseline and subsequently on day 1 of every odd cycle (within –3 to +14 days), except for cycle 1 day 1, until discontinuation from the study. Brain magnetic resonance imaging or head computerized tomography were performed in all patients with NSCLC due to the high incidence of brain metastases; metastatic disease sites were followed at scheduled visits using appropriate imaging, as clinically indicated.

Statistical Analysis

An adaptive BLRM employing the escalation with overdose control (EWOC) principle was used to make dose recommendations and estimate the MTD/RD.[22] According to the EWOC principle, the potential doses recommended for the successive cohort in the dose-escalation part and the estimated MTD/RD for the dose-expansion part must have less than 25% posterior probability of DLT in the excessive toxicity interval (≥33% to ≤100%). After each cohort of patients in the dose-escalation part, the posterior distributions for the probabilities of DLT at different dose levels were obtained using the BLRM, and in general, the dose recommended for the successive cohort or estimated as MTD/RD was the one with the highest posterior probability of DLT rate falling in the targeted toxicity interval (≥16% to <33%), among the doses fulfilling the EWOC principle.

Safety data were summarized for all patients (*ALK*-rearranged NSCLC and other tumors) who received at least one dose of ceritinib. The PK analysis was summarized for all patients who received at least one dose of ceritinib and had at least one evaluable PK sample. Efficacy data were analyzed for all patients with NSCLC who had received the first dose of ceritinib at least 18 weeks before the analysis cutoff date. Data from patients enrolled in the dose-expansion part were pooled with data from patients receiving the same dose level in the dose-escalation part of the study. The ORR and disease control rate were summarized along with the exact (Clopper–Pearson) 95% confidence intervals. The data cutoff date was July 4, 2014, for safety and efficacy data. For PK analyses, the data cutoff date was August 2, 2013, including only patients in the dose-escalation part of the study. Enrollment for the dose-expansion part is ongoing.

RESULTS

Patient Disposition

A total of 19 patients were enrolled and treated with ceritinib at doses of 300 mg (n = 3), 450 mg (n = 6), 600 mg (n = 4), and 750 mg (n = 6), in the dose-escalation part of this study. In addition, one patient was enrolled in the dose-expansion part of the study and is included in the 750-mg group for all analyses presented, apart from PK analyses. Median duration of exposure to ceritinib was 32.1 weeks (range, 0.1–86.7 weeks). At the time of data cutoff, 19 patients (95%) had discontinued treatment. The most common reason for discontinuation was progression (12 patients [60%]—includes patients with response prior to disease progression), eight of whom were treated at doses less than 750 mg once daily. AEs led to discontinuation in a further two patients (10%). One patient discontinued treatment due to drug-induced liver injury that was reported as a DLT; the other patient discontinued due to cholangitis and increased hepatic enzyme, both of which were considered to be related to biliary stent malfunction, but not to the study drug. Two patients died during the study, due to disease progression; neither of the deaths was considered related to the study drug. Both patients had metastatic *ALK*-rearranged NSCLC at study entry. At the time of death, one patient had ongoing hydrocephalus; the other patient had respiratory failure.

Demographics and Baseline Disease Characteristics

Overall, 55% of patients were female, and 90% had an Eastern Cooperative Oncology Group performance status of up to 1 (Table 1). Nineteen patients (95%) had NSCLC, and one patient (5%) had inflammatory myofibroblastic tumor (IMT). ALK positivity was confirmed by immunohistochemistry in the patients with IMT; *ALK* rearrangement was confirmed by FISH in all 19 patients with NSCLC. Among 19 patients with NSCLC, 17 (89%) were diagnosed with adenocarcinoma. The majority of patients (80%) had received prior ALK inhibitors: 45% crizotinib only; 25% other ALK inhibitor (alectinib or

TABLE 1. Baseline Characteristics

	Ceritinib Dose				
	300 mg Once Daily	450 mg Once Daily	600 mg Once Daily	750 mg Once Daily	All Patients
Demographic Variable	***n* = 3**	***n* = 6**	***n* = 4**	***n* = 7**	**N = 20**
Age, yr					
Median (range)	51 (45–56)	37 (29–67)	39 (34–61)	45 (38–68)	44 (29–68)
<65, *n* (%)	3 (100)	5 (83)	4 (100)	6 (86)	18 (90)
≥65, *n* (%)	0	1 (17)	0	1 (14)	2 (10)
Sex, *n* (%)					
Female	3 (100)	5 (83)	2 (50)	1 (14)	11 (55)
Male	0	1 (17)	2 (50)	6 (86)	9 (45)
ECOG performance status, *n* (%)					
0	2 (67)	2 (33)	1 (25)	3 (43)	8 (40)
1	1 (33)	2 (33)	3 (75)	4 (57)	10 (50)
2	0	2 (33)	0	0	2 (10)
Baseline brain metastases, *n* (%)	1 (33)	4 (67)	3 (75)	0	8 (40)
Prior ALK inhibitor, *n* (%)					
Crizotinib only	1 (33)	4 (66)	2 (50)	2 (29)	9 (45)
Other ALK inhibitor only	1 (33)	0	1 (25)	3 (43)	5 (25)
Both crizotinib and other ALK inhibitor	0	1 (17)	1 (25)	0	2 (10)
ALK inhibitor naive	1 (33)	1 (17)	0	2 (29)	4 (20)
Median time since last dose of prior ALK inhibitor to start of treatment, days (range)	80 (20–140)	73 (16–110)	16 (16–17)	17 (15–34)	17 (15–140)
Prior ALK inhibitor as last therapy, *n* (%)	1 (33)	3 (50)	4 (100)	5 (71)	13 (65)
Type of *ALK*-rearranged tumors					
NSCLC	3 (100)	6 (100)	4 (100)	6 (86)	19 (95)
IMT	0	0	0	1 (14)	1 (5)

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; IMT, inflammatory myofibroblastic tumor; NSCLC, non–small-cell lung cancer.

ASP3026); and 10% both crizotinib and other ALK inhibitor. All 19 patients with NSCLC had measurable disease according to Response Evaluation Criteria In Solid Tumors v 1.1.

Dose Escalation and Toxicity

During dose escalation, two DLTs were reported in two patients. Grade 3 lipase increase (>2.0–5.0 × upper limit of normal [ULN]) occurred in one patient treated with ceritinib 600 mg once daily. The patient experienced nausea, vomiting, and gastrointestinal pain before and during the grade 3 lipase increase; however, the investigator assessed that these events were not the symptoms of pancreatitis. The event resolved without medication, after ceritinib was interrupted. Ceritinib was resumed at a dose of 450 mg once daily. Grade 3 drug-induced liver injury (elevated bilirubin [>3.0–10.0 × ULN], ALP, alanine aminotransferase [ALT], and aspartate transaminase [>5.0–20.0 × ULN]) occurred in one patient treated with ceritinib 750 mg once daily; the condition improved after ceritinib was permanently discontinued. Based on these findings, the MTD of ceritinib in Japanese patients was established as 750 mg once daily. The posterior probability of DLT rate being in the excessive toxicity interval (≥33% to ≤100%) at the 750-mg once-daily dose was 7.3%, which fulfilled the EWOC principle (<25%).

All patients experienced one or more drug-related AE. The most common AEs were nausea (95%), diarrhea (75%), and vomiting (75%) (Table 2). Sixteen patients (80%) reported grade 3/4 AEs, the most common of which were increased ALT and tumor pain, each of which occurred in two patients. Ten patients (50%) reported grade 3/4 AEs suspected to be drug related, the most common of which was increased ALT (two patients [10%]) (Table 2). Aside from DLTs, no other drug-related AEs lead to discontinuation from the study. Nine patients (45%) experienced at least one dose reduction and 11 patients (55%) at least one dose interruption due to AEs, with most occurring in patients treated at 750 mg dose (5 of 9 and 5 of 11, respectively) (Supplementary Digital Content 1, http://links.lww.com/JTO/A838, shows dose amendments due to AEs according to dose). Overall, ceritinib had an acceptable tolerability profile in Japanese patients, with no treatment-related deaths reported.

Pharmacokinetics

PK analyses revealed that ceritinib exposure increased with dose across the 300 to 750 mg once-daily range (Table 3). In the PK run-in period, the relationship between ceritinib dose and PK parameters (maximum plasma concentration [C_{max}] and area under plasma

TABLE 2. Adverse Events (≥20% for All Grades) Considered to Be Study Drug Related

	Ceritinib Dose									
	300 mg Once Daily (*n* = 3)		450 mg Once Daily (*n* = 6)		600 mg Once Daily (*n* = 4)		750 mg Once Daily (*n* = 7)		All Patients (N = 20)	
Preferred Term	All Grades, *n* (%)	Grade 3/4, *n* (%)	All Grades, *n* (%)	Grade 3/4, *n* (%)	All Grades, *n* (%)	Grade 3/4, *n* (%)	All Grades, *n* (%)	Grade 3/4, *n* (%)	All Grades, *n* (%)	Grade 3/4, *n* (%)
Nausea	3 (100)	0	6 (100)	0	4 (100)	0	6 (86)	1 (14)	19 (95)	1 (5)
Diarrhea	3 (100)	0	2 (33)	0	4 (100)	0	6 (86)	0	15 (75)	0
Vomiting	1 (33)	0	6 (100)	0	4 (100)	0	4 (57)	0	15 (75)	0
Increased blood creatinine	3 (100)	0	3 (50)	0	1 (25)	0	5 (71)	0	12 (60)	0
Decreased appetite	0	0	3 (50)	0	3 (75)	0	4 (57)	0	10 (50)	0
Fatigue	0	0	2 (33)	0	3 (75)	0	3 (43)	0	8 (40)	0
Abdominal pain	2 (67)	0	1 (17)	0	0	0	2 (29)	0	5 (25)	0
Increased alanine aminotransferase	0	0	2 (33)	0	1 (25)	1 (25.0)	1 (14)	1 (14)	4 (20)	2 (10)
Increased aspartate aminotransferase	0	0	2 (33)	0	1 (25)	1 (25.0)	1 (14)	0	4 (20)	1 (5)
Abnormal hepatic function	0	0	0	0	1 (25)	0	3 (43)	1 (14)	4 (20)	1 (5)
Hyperuricemia	0	0	0	0	0	0	4 (57)	0	4 (20)	0
Neutropenia	2 (67)	0	2 (33)	0	0	0	0	0	4 (20)	0
Rash	0	0	3 (50)	0	0	0	1 (14)	0	4 (20)	0
Maculopapular rash	1 (33)	0	1 (17)	0	1 (25)	0	1 (14)	0	4 (20)	0
Stomatitis	1 (33)	0	2 (33)	0	1 (25)	0	0	0	4 (20)	0

concentration versus time curve over a dosing interval [AUC_{0-24}]) was analyzed. Although interindividual variability was observed, C_{max} and AUC_{0-24} increased in an approximately dose proportional manner, with exponent near unity (0.909 and 1.04, respectively) in a power model assuming a natural log (ln)-normal distribution: ln(parameter) = exponent × ln(dose) + constant (Graph a, Supplementary Digital Content 2, http://links.lww.com/JTO/A838, showing the dose relationship of AUC_{0-24}). In addition, in cycle 1 day 8 and cycle 2 day 1, C_{max} and AUC_{0-24} tended to increase with ascending dose (Table 3). The elimination half-life calculated at each dose in the 3-day PK run-in period was 22 to 33 hours. Median time to reach maximum plasma concentration (T_{max}) was 2 to 7 hours across the tested doses and profile days. Based on trough concentration versus time profiles, at cycle 1 day 15, ceritinib plasma concentration appeared to reach steady state (data not shown). Graph b (Supplementary Digital Content 2, http://links.lww.com/JTO/A838) shows the steady-state ceritinib plasma concentration versus time profile (cycle 2 day 1). At the ceritinib MTD of 750 mg, AUC_{0-24} was 26,400 ng·hr/mL (Graph, Supplementary Digital Content 2, http://links.lww.com/JTO/A838) (Table 3). Geometric mean for the accumulation ratio was 5.41 to 19.5 at cycle 1 day 8 and 6.78 to 21.5 at cycle 2 day 1.

Efficacy

Efficacy of ceritinib treatment in all patients.

Based on investigator assessment across all dose groups, the ORR and disease control rate among patients with NSCLC were 10 of 19 (53%) and 13 of 19 (68%), respectively (Table 4). Of four patients with *ALK*-rearranged NSCLC not previously treated with an ALK inhibitor, two patients had a confirmed PR.

Fifteen patients with *ALK*-rearranged NSCLC had previously received an ALK inhibitor (crizotinib, alectinib, or ASP3026), with a median time from last dose of prior ALK inhibitor to ceritinib treatment of 17 days (range, 15–140). All patients discontinued at least one prior ALK inhibitor due to disease progression; the patient who had received both alectinib and crizotinib discontinued alectinib due to disease progression and crizotinib due to an unknown reason, while the patient receiving ASP3026 and crizotinib discontinued both drugs due to disease progression. Among the 15 patients previously treated with ALK inhibitors, eight (53%) had PR, including five of nine patients previously treated with crizotinib only, two of four patients previously treated with alectinib only, and one of two patients previously treated with both crizotinib and either alectinib or ASP3026 (the patient with PR was previously treated with crizotinib and ASP3026). The patient with IMT in the ceritinib 750 mg once-daily group, who was previously treated with ASP3026, achieved PR.

Among 19 patients with *ALK*-rearranged NSCLC who had measurable disease at baseline, 16 patients had at least one valid postbaseline assessment. In the remaining three NSCLC patients, a valid postbaseline assessment was unavailable due to early withdrawal from the study (n = 2) or a change in imaging modality (n = 1). Of the 16 evaluable patients, 15 showed a reduction in the size of target lesions (Fig. 1). Responses occurred regardless of the type of prior ALK inhibitor administered (crizotinib, alectinib, or ASP3026).

TABLE 3. Pharmacokinetic Parameters of Ceritinib

Dose (mg Once Daily)	Day	*n*	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$T_{1/2}$ (hr)
300 (*n* = 3)	PK run-in	2	5.10	168 (3)	2760 (33)	22.1 (3.4)
	Cycle 1 day 8	3	3.00	537 (208)	10,700 (4950)	NA
	Cycle 2 day 1	2	5.98	867 (59)	NA	NA
450 (*n* = 6)	PK run-in	5	5.88	76 (68)	1030 (963)	26.0 (6.3)[a]
	Cycle 1 day 8	5	3.97	858 (215)	18,400 (4010)[b]	NA
	Cycle 2 day 1	5	5.95	982 (102)	20,900 (3990)[c]	NA
600 (*n* = 4)	PK run-in	4	5.97	215 (196)	3710 (3590)	30.7 (3.6)
	Cycle 1 day 8	4	3.44	1060 (633)	16,600 (10,500)[c]	NA
	Cycle 2 day 1	4	4.93	1150 (592)	21,400 (15,300)[a]	NA
750 (*n* = 6)	PK run-in	6	5.98	206 (75)	3590 (1680)	33.4 (4.3)[d]
	Cycle 1 day 8	6	6.96	1220 (212)	25,700 (4440)[d]	NA
	Cycle 2 day 1	3	1.93	1470 (375)	26,400 (5810)[a]	NA

Values represent median for T_{max} and mean (SD) for C_{max}, AUC_{0-24}, and $T_{1/2}$.
[a]*n* = 2.
[b]*n* = 4.
[c]*n* = 3.
[d]*n* = 5.
AUC_{0-24}, area under the plasma concentration versus time curve over the dosing interval; C_{max}, maximum plasma concentration; NA, not applicable; PK, pharmacokinetic; $T_{1/2}$, half-life; T_{max}, time at which maximum plasma concentration is achieved.

TABLE 4. Best Overall Response with Ceritinib in Patients with *ALK*-Rearranged NSCLC (RECIST Version 1.1)

	Ceritinib Dose			
	300 mg Once Daily	450 mg Once Daily	600 mg Once Daily	750 mg Once Daily
Best Overall Response, *n* (%)	*n* = 3	*n* = 6	*n* = 4	*n* = 6
CR	0	0	0	0
PR	3 (100)	3 (50)	2 (50)	2 (33)
Stable disease[a]	0	1 (17)	0	2 (33)
Progressive disease	0	1 (17)	2 (50)	0
Unknown	0	1 (17)	0	2 (33)
ORR (CR + PR)	3 (100)	3 (50)	2 (50)	2 (33)
95% CI	29.2–100.0	11.8–88.2	6.8–93.2	4.3–77.7
Disease control rate (CR or PR or stable disease)	3 (100)	4 (67)	2 (50)	4 (67)
95% CI	29.2–100.0	22.3–95.7	6.8–93.2	22.3–95.7

[a]Two of three patients achieved an unconfirmed PR (one treated with 450 mg once daily and one with 750 mg once daily).
ALK, anaplastic lymphoma kinase; CI, confidence interval; CR, complete response; NSCLC, non–small-cell lung cancer; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy of ceritinib treatment in patients previously treated with alectinib.

PRs were observed in two of five patients previously treated with alectinib, neither of whom had brain metastases at baseline. Patient 2002 had a duration of response of 4.2 months, with ceritinib administered at a dose of 300 mg once daily for 6.1 months. Figure 2 shows preceritinib and 5 months postceritinib treatment scan images, illustrating regression of the target lesion. Ceritinib was permanently discontinued after 6.1 months due to progression in nontarget lesions (bone) and pleural effusion. Patient 3008 also achieved PR, with a duration of response of 9.5 months. Ceritinib was administered for 18.1 months at a dose of 750 mg once daily. Treatment was discontinued due to progressive disease. Clinical benefit with stable disease was also achieved in one patient, 3009, treated at 750 mg once daily. The patient, who did not have baseline brain metastases, was treated for 3.9 months before discontinuing due to progression of a new lesion in the brain (Supplementary Digital Content 3, http://links.lww.com/JTO/A838, which shows the demographics, disposition, and efficacy results in patients previously treated with alectinib).

Two of the five patients pretreated with alectinib had progressive disease following ceritinib treatment (1003 and 3004). Patient 1003 received ceritinib 600 mg once daily for 1.4 months before discontinuing due to progression of nontarget lesion (hilar lymph node) at day 45. Of note, ceritinib treatment was temporarily interrupted in this patient (day 25–36) due to grade 3 lipase increase. Patient 3004 had progressive disease

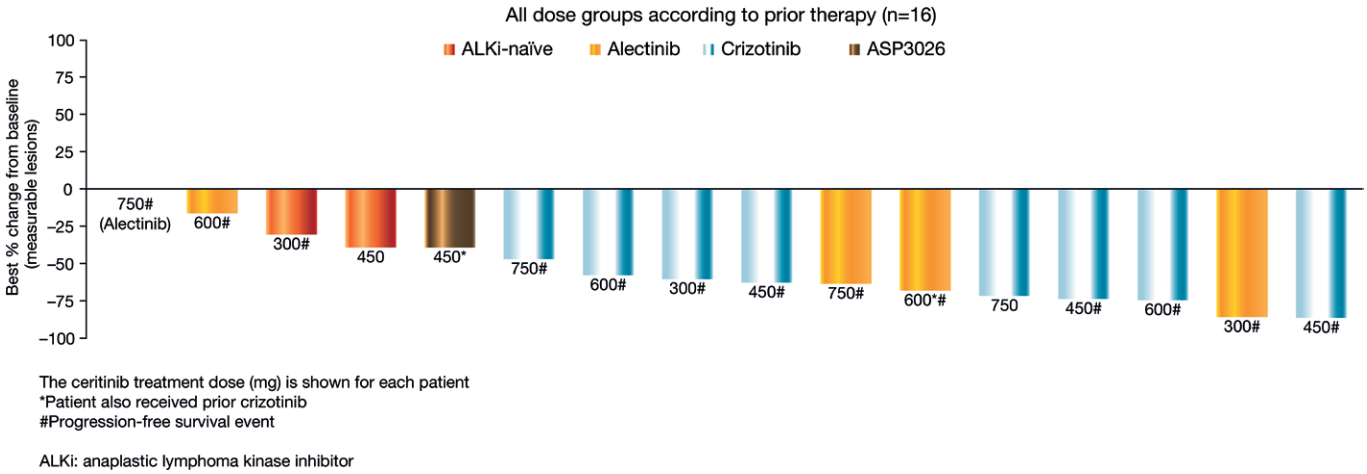

FIGURE 1. Best percentage change from baseline with ceritinib, by dose group.

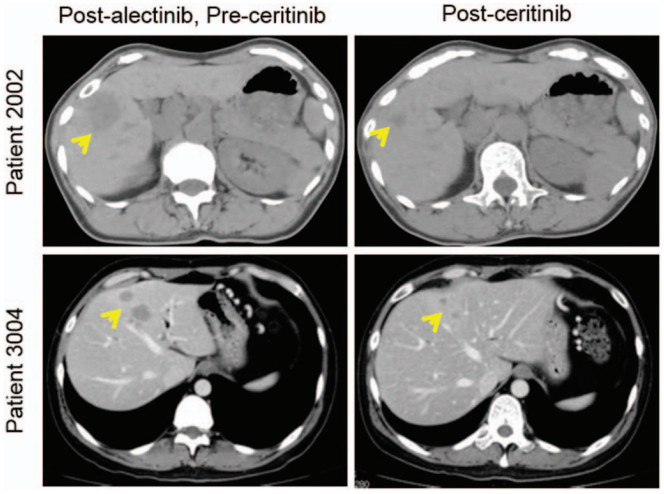

FIGURE 2. Pre- and postceritinib treatment scan images in two patients previously treated with alectinib.

in a brain metastasis (nontarget lesion) after 1.7 months of treatment. Nevertheless, this patient was benefitting from treatment and continued on ceritinib for a further 6.8 months before discontinuing after a total of 8.5 months of ceritinib (600 mg once daily for 6.3 mo and 450 mg once daily for 2.2 mo). Of note, the brain lesion was present at ceritinib treatment onset, and the patient received no treatment for brain metastases during the study. Figure 2 shows scan images of the target lesion preceritinib and 12 weeks postceritinib, demonstrating some regression in the target lesion, despite progression in the brain. This patient discontinued treatment due to AEs (Supplementary Digital Content 3, http://links.lww.com/JTO/A838).

DISCUSSION

The results of this phase I study established the MTD of ceritinib at 750 mg once daily in Japanese patients with *ALK*-rearranged tumors, including 19 patients with NSCLC and one with IMT. Ten of 19 patients with NSCLC (53%) achieved PR; furthermore, the patient with IMT also achieved PR.

Overall, the safety profile of ceritinib was acceptable, with no treatment-related deaths. The safety profile (all grades) of ceritinib in Japanese patients was similar to that seen in the Asian subset of patients from the ASCEND-1 study of ceritinib, with gastrointestinal AEs (nausea, diarrhea, and vomiting) having the highest incidence, though most were grade 1 to 2. Gastrointestinal AEs (including nausea, diarrhea, and vomiting) were also common (39–56%) with crizotinib.[7] The incidence of drug-related grade 3/4 AEs was 50% in this study, 49% in the ASCEND-1 study of ceritinib,[19] and 24% with crizotinib.[7]

In this study, ceritinib plasma concentration appeared to reach steady state by day 15, and its PK profile was dose proportional for the 300 to 750 mg once-daily dose range. In the ASCEND-1 study, there were no significant ethnic differences in PK parameters between Asian and non-Asian patients, although ceritinib showed a modest increase (<30%) in exposure in Asian patients compared with non-Asian patients.[23] In this study, exposure was numerically higher (<30%) compared with the Asian patients in ASCEND-1; however, patient numbers were limited ($n = 3$).

The ORR with ceritinib in Japanese patients with *ALK*-rearranged NSCLC (10 of 19 patients, 53%) appeared lower compared with that observed in a subset of Asian patients from the ASCEND-1 study of ceritinib (56 of 82 patients, 68%). However, the numbers of patients are small, and there were differences in baseline characteristics between the Asian population of ASCEND-1 and Japanese patients with NSCLC enrolled in this study (e.g., >3 prior antineoplastic medications: 40% versus 26%; ALK inhibitor pretreatment: 57% versus 80%, for Asian patients in ASCEND-1 versus Japanese patients).[23]

In this study, ceritinib demonstrated clinical benefit in three (two PR and one stable disease) of five Japanese patients with recurrence or relapse after alectinib. In a phase I/II study of alectinib in Japanese patients with advanced, *ALK*-rearranged NSCLC who were ALK inhibitor naive (ALK confirmed by both immunohistochemistry and FISH), ORR was 93.5%.[15] Ceritinib efficacy in alectinib-resistant patients could be a consequence of specific mutations that impair alectinib binding to ALK, but

not ceritinib, which is structurally distinct.[21] Consistent with this, specific ALK resistance mutations have been shown to differentially alter the IC_{50} values for different ALK inhibitors, such that one inhibitor shows greater activity over others.[18,21]

Ceritinib also demonstrated activity in this study in Japanese patients who had relapsed on crizotinib treatment. Ceritinib clinical activity in Japanese patients with crizotinib-resistant *ALK*-rearranged tumors was consistent with the ASCEND-1 study.[9] This may reflect the greater potency of ceritinib compared with crizotinib, which was observed in preclinical studies,[18] and its ability to inhibit *EML4-ALK* harboring kinase-domain mutations known to be resistant to crizotinib, including L1196M.[17,24]

In patients with NSCLC treated with ALK inhibitors, acquired resistance is an ongoing challenge, potentially limiting the transformative impact of these drugs on patients.[10,21,25] Resistance occurs due to secondary mutations in the ALK tyrosine kinase domain and *ALK* gene amplification.[10,11,24] Most notably, the gatekeeper L1196M substitution has been shown to confer resistance to crizotinib.[10,11,26] There may be differences in the efficacy of different ALK inhibitors for treating patients with certain resistance mutations; for example, alectinib was relatively less potent against L1196M, G1202R, and 1151Tins *EML4-ALK* than against S1206Y *EML4-ALK*,[10] and ASP3026 was less potent compared with crizotinib and alectinib against wild-type *EML4-ALK* but relatively more potent against G1202R.[10] These data suggest that patients who develop resistance to one or two ALK inhibitors through particular ALK mutations may still respond to other ALK inhibitors, such as ceritinib, with differing specificity for ALK. As a result of these considerations, although specific resistance mutations for each patient were not identified in this study, the study protocol was amended to focus on patients with NSCLC that has progressed since treatment with alectinib in the dose-expansion part. The observed ceritinib activity in patients previously treated with alectinib reported here supports this approach.

The results of this study suggest that ceritinib is active in Japanese patients with tumors harboring ALK rearrangements, including those patients who have received prior treatment with other ALK inhibitors.

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