Pharmacologic study (JP28927) of alectinib in Japanese patients with ALK+ non-small-cell lung cancer with or without prior crizotinib therapy

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We report pharmacokinetics, efficacy and safety data for a new 150-mg alectinib capsule in *ALK*+ non-small-cell lung cancer in a multicenter, open-label pharmacologic study (JP28927). Eligible patients (≥20 years, locally advanced/metastatic *ALK*+ disease, ALK inhibitor-naïve and -pretreated [including crizotinib refractory]) were randomized 1:1 to receive one of two sequences of alectinib 300 mg twice daily (comprising different schedules of 20/40-mg and 150-mg capsules) until investigator-determined lack of clinical benefit. Co-primary endpoints were: bioequivalence of alectinib 20/40 mg *vs* 150 mg; food effect with 150 mg; and safety. Thirty-five patients were enrolled; median treatment duration was 13.1 months (range 1.1−15.0). Under fasting conditions, exposure of the two formulations was similar; mean AUC_{last} ± standard deviation 3230 ± 914 h·ng/mL *vs* 3710 ± 1040 h·ng/mL, respectively, for 150-mg *vs* 20/40-mg capsules. Food effect with 150 mg alectinib was negligible. Treatment-related adverse events in >20% of patients were constipation (31.4%), dysgeusia (25.7%), and decreased white blood cell and neutrophil count (22.9% each). No treatment-related grade 4/5 events occurred. Median time to response was 1.2 months (95% CI 1.1−2.1). For the full analysis set (*n* = 35) and crizotinib-failure subpopulations (*n* = 23), the overall response rate was 70.0% (95% CI 50.6−85.3) and 65.0% (95% CI 40.8−84.6), and median progression-free survival was 13.9 months (95% CI 11.1−not reached) and 12.9 months (95% CI 3.9−not reached), respectively. The 150-mg capsule had a similar exposure profile to 20/40-mg capsules. Alectinib demonstrated promising efficacy and was well tolerated.

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] However, recent advances in knowledge of the molecular genotype of lung tumors have led to a revolution in the diagnosis and treatment of the disease. The anaplastic lymphoma kinase (*ALK*) gene is frequently involved in translocations that lead to gene fusions in a variety of malignancies, including lung cancer. It is estimated that *ALK* gene rearrangements occur in 4–5% of all patients with advanced non-small-cell lung cancer (NSCLC).[2]

Transforming rearrangements of the *ALK* gene were initially identified in anaplastic large-cell lymphoma.[3] In 2007, a novel fusion oncogene that resulted in the expression of EML4-ALK fusion proteins was identified in NSCLC.[4–6] *ALK*+ tumor cells displayed oncogenic behavior, being dependent on signaling from ALK fusion proteins for their survival.[5,7] This observation formed the basis of targeting *ALK* as a therapeutic approach for the treatment of *ALK*+ NSCLC.

In 2011, the ALK inhibitor crizotinib was approved by the US Food and Drug Administration for the first-line treatment of advanced *ALK*+ NSCLC.[8] Approval was partly based on a phase I study that reported an overall response rate (ORR) of 57% and a 6-month progression-free survival (PFS) rate of 72%.[9] In 2014, ceritinib was granted accelerated approval in the USA for patients with *ALK*+ NSCLC who experienced disease progression (PD) or who were intolerant to crizotinib; approval was based on ORR of 58% (crizotinib naïve) and 56% (crizotinib pretreated) and a median PFS of 7.0 months.[10]

In 2014, alectinib, a central nervous system-penetrant and highly selective ALK inhibitor, was granted approval by the Japanese Ministry of Health, Labour and Welfare for the treatment of *ALK*+, unresectable, advanced or recurrent NSCLC in Japan. Approval was based on data from ALK inhibitor-naïve patients with *ALK*+ NSCLC who received alectinib 300 mg

twice daily in a phase I/II study (AF-001JP). Alectinib was well tolerated and highly active, with >90% (43/46) of patients achieving an objective response.[11] Follow-up is ongoing and, to date, 19.6% of patients have achieved a complete response (CR) and the 2-year PFS rate is 76%.[12,13]

Patients given alectinib in 20/40-mg capsules must take eight capsules to reach the recommended clinical dose of 300 mg.[11] As this can be burdensome and could decrease compliance, we undertook the current study to demonstrate the bioequivalence of a new 150-mg capsule of alectinib *vs* the 20/40-mg capsules in patients with *ALK+* NSCLC. We also investigated the safety and efficacy of alectinib in *ALK+* NSCLC, including patients who had failed on crizotinib.

Patients and Methods

This multicenter, open-label, randomized study (JP28927) examined the bioequivalence and the effect of food on the bioavailability of 150-mg and 20/40-mg capsules of alectinib under fasting conditions in patients with *ALK+* NSCLC (JapicCTI-132186).

Patients were randomly assigned using a permuted block randomization method in a 1:1 ratio to one of two groups to receive alectinib 300 mg twice daily in cycle 1 (30 days). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed and approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all patients.

Treatment. Patients in group A received alectinib 20/40-mg capsules for 10 days (fasting), followed by 150-mg capsules for 10 days (fasting), then 150-mg capsules for 10 days (non-fasting state) (Fig. S1). Patients in group B received alectinib 150-mg capsules for 10 days (fasting), followed by 20/40-mg capsules for 10 days (fasting), then 150-mg capsules for 10 days (non-fasting state). A washout period of 2 weeks was required between the last dose of crizotinib/prior ALK inhibitor and the first dose of alectinib. After cycle 1, patients received 150-mg alectinib capsules until investigator-determined lack of clinical benefit.

Patients. Eligible patients were aged ≥20 years, had histologically or cytologically confirmed advanced or metastatic *ALK*-rearranged, stage IIIB/IV, or recurrent NSCLC, and an Eastern Cooperative Oncology Group performance status of 0–1. Prior treatment, including other ALK inhibitors, was allowed. Patients with meningeal or symptomatic brain metastases, or those who had received prior alectinib treatment, were excluded.

Endpoints. The primary endpoints were to evaluate: the bioequivalence of 300 mg twice-daily alectinib with 20/40-mg capsules *vs* 150-mg capsules under fasting conditions; the effect of food on the pharmacokinetics of alectinib after repeated oral administration of the 150-mg capsule after meals; and safety. Secondary endpoints included investigator-assessed ORR, PFS, time to response, duration of response and disease control rate (DCR). Efficacy and safety analyses were also undertaken in a subgroup of patients who had failed prior crizotinib.

Assessments. Blood samples for pharmacokinetic analysis were collected pre-dose and at 0.5, 1, 2, 4, 6, 8 and 10 h post-dose. Plasma alectinib concentrations were quantified using a liquid chromatography–mass spectrometry method with a lower limit of quantification of 0.10 ng/mL.[11]

Tumor response and progression were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline, days 31 and 59, and then every 56 days. ORR was defined as the percentage of patients with a CR or partial response (PR) according to RECIST. Time to response was calculated from the first administration of alectinib until the date when the criteria for PR/CR were first met, with duration of response calculated from the date of first meeting the criteria for PR/CR until the date of confirmed PD/death, whichever occurred first. DCR comprised CR, PR and stable disease according to RECIST. PFS was calculated from the date of first administration of alectinib until the date of first PD or death, whichever occurred first. Adverse events (AE) were graded according to NCI-CTCAE version 4.03. The full analysis set (FAS) included all patients who were treated and eligible; all patients who received at least one dose of alectinib were included in the safety analysis population.

Anaplastic lymphoma kinase status was confirmed using FISH. A multiplex RT-PCR test was also carried out on cells or frozen tissue sections. Patients were deemed to be positive for *ALK* fusion gene expression when FISH and/or RT-PCR showed positive results.

Statistical analysis. Sample size was determined using the intra-individual variability of trough concentration data from the phase I/II parts of study AF-001JP.[11] The population pharmacokinetics model used in AF-001JP was also employed; the sample size, which had 80% power to detect bioequivalence in the area under the plasma concentration–time curve from time zero to the time of last alectinib concentration (AUC_{last}) and the maximum concentration (C_{max}), was estimated to be 30 patients.

Pharmacokinetic parameters for individual plasma concentration data were estimated using a non-compartmental method (Phoenix WinNonlin version 6.2; Certara, Cary, NC, USA); estimates and 90% confidence interval (CI) geometric mean ratios were derived from a mixed model (SAS version 9.2; SAS institute, Cary, NC, USA). Kaplan–Meier methodology was used to estimate the distribution of time to response, duration of response, and PFS. No formal comparisons were made between the FAS and crizotinib-failure populations.

Time to response, ORR, duration of response, and DCR were analyzed using data from patients who had measurable disease at baseline.

Results

Patients were enrolled between July and September 2013 (Fig. S2). Data are presented as of 6 November 2014 (the last patient's last visit). Thirty-five patients with *ALK+* NSCLC were recruited and randomly assigned to the two groups (Figs S1,S2); all were eligible for the FAS and safety populations. Twenty-nine patients (82.9%) had received at least one prior ALK inhibitor. Of 28 patients who had received previous crizotinib treatment, 23 were defined as crizotinib failures.

Median patient age was 45 years (range 21–78) for the FAS population and 43 years (range 21–64) for the crizotinib-failure population (Table 1). All patients had adenocarcinoma and most patients had received two or more prior chemotherapy regimens.

Bioequivalence. Under fasting conditions, exposure of the 150-mg alectinib capsule was similar to that of the 20/40-mg capsules: mean $C_{max} \pm SD$, 390 ± 103 ng/mL *vs* 460 ± 122 ng/mL; $AUC_{last} \pm SD$, 3230 ± 914 h·ng/mL *vs* 3710 ± 1040 h·ng/mL, respectively (Fig. S3a). The ratios of geometric mean were 0.868 (90% CI 0.801−0.941) for AUC_{last} and 0.846 (90% CI 0.784−0.913) for C_{max} for the 150-mg capsule

Table 1. Baseline characteristics of the full analysis set and the crizotinib-failure population

Characteristic	FAS population (n = 35)†		Crizotinib failure‡ (n = 23)§	
	Number of patients	%	Number of patients	%
Age, years				
Median	45.0		43.0	
Range	21−78		21−64	
Gender				
Male	16	45.7	10	43.5
Female	19	54.3	13	56.5
ECOG PS				
0	15	42.9	10	43.5
1	20	57.1	13	56.5
Smoking status				
Never	21	60.0	15	65.2
Current	1	2.9	1	4.3
Former	13	37.1	7	30.4
Adenocarcinoma	35	100.0	23	100.0
Number of prior ALK inhibitors				
0	6	17.1	−	−
1	23	65.7	19	82.6
2	6	17.1	4	17.4
Number of prior chemotherapy regimens				
0–1	6	17.1	−	−
2	11	31.4	7	30.4
≥3	18	51.4	16	69.6

†28/35 patients were crizotinib pretreated (of which, 5 patients also received ceritinib and 1 patient also received ASP3026); 1 patient received only ceritinib treatment. ‡Failure: patients experienced disease progression on crizotinib. §Including 3 patients who failed on ceritinib. ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set.

Table 2. Bioequivalence analysis of 20/40-mg alectinib capsules *vs* the 150-mg capsule

PK parameter	Number of patients	Geometric LSM		Ratio of geometric LSM		
		20/40-mg capsule	150-mg capsule	Estimate	90% CI	
					Lower	Upper
AUC, h·ng/mL	34	3570	3100	0.868	0.801	0.941
C_{max}, ng/mL	34	445	377	0.846	0.784	0.913

AUC, area under the curve; CI, confidence interval; C_{max}, maximum plasma concentration; LSM, least squares mean; PK, pharmacokinetics.

vs the 20/40-mg capsules (Table 2). Although the lower limit of the C_{max} 90% CI was slightly below the criteria for bioequivalence (0.80–1.25),[14] the AUC_{last} met the criteria.

Food effect. Exposure (C_{max} and AUC_{last}) from the 150-mg capsule in the non-fasting state was approximately 20% higher than that in the fasting state, but this difference was within the interindividual variability range, and the effect of food on the pharmacokinetics of alectinib was considered negligible (Fig. S3b).

Safety. For patients taking the 20/40-mg and 150-mg capsules, all grade treatment-related AE occurring in >20% of patients were constipation (31.4%), dysgeusia (25.7%), and a

Table 3. All-grade treatment-related adverse events in 10% or more of patients in the safety population and the crizotinib-failure population

Adverse event	Safety population (n = 35)†		Crizotinib failure (n = 23)	
	Number	%	Number	%
Constipation	11	31.4	7	30.4
Dysgeusia	9	25.7	7	30.4
WBC count decreased	8	22.9	5	21.7
Neutrophil count decreased	8	22.9	4	17.4
Vomiting	5	14.3	3	13.0
Rash	5	14.3	3	13.0
Blood bilirubin increased	5	14.3	2	8.7
AST increased	5	14.3	1	4.3

†Treatment-related grade 3 adverse events were observed in 3 patients; pulmonary thrombosis (n = 1), decrease in lymphocyte cell count (n = 1), and hypophosphatemia (n = 1). Data are presented as of 6 November 2014, which was the last patient's last visit. AST, aspartate aminotransferase; WBC, white blood cell.

decrease in white blood cell (WBC) (22.9%) and neutrophil cell count (22.9%) (Table 3). Grade 3 treatment-related AE were observed in three patients (pulmonary thrombosis, decrease in lymphocyte cell count, and hypophosphatemia). No treatment-related grade 4/5 AE were reported. Alectinib was interrupted or discontinued due to AE in 20% and 5.7% of patients, respectively. There were two cases of grade 1 interstitial lung disease including pneumonitis. Treatment-related nausea was experienced by 8.6% of patients in the safety population. In the crizotinib-failure population, all grade treatment-related AE reported in >20% of patients were constipation (30.4%), dysgeusia (30.4%), and a decrease in WBC count (21.7%).

Efficacy. For patients taking the 20/40-mg and 150-mg capsules, median treatment duration was 13.1 months (range 1.1−15.0); treatment duration by individual patient is shown in Fig. S4. Of 30 patients in the FAS response-evaluable (RE) population who had measurable lesions, 22 demonstrated tumor shrinkage of >30% (Fig. S5). ORR in this group was

Table 4. Response rates with alectinib in the overall and crizotinib-failure populations

Response, n	Total (n = 30)†	Crizotinib failure (n = 20)‡
Complete response	0	0
Partial response	21	13
Stable disease	4	3
Progressive disease	5	4
ORR, %	70.0	65.0
95% CI	50.6–85.3	40.8–84.6
DCR, %	83.3	80.0
95% CI	65.3–94.4	56.3–94.3
Median time to response, months	1.2	1.2
95% CI	1.1–2.1	1.1–1.3

†24/30 patients were crizotinib pretreated (of which, 4 patients also received ceritinib and 1 patient also received ASP3026); 1 patient received only ceritinib treatment. ‡Including 3 patients who failed on ceritinib. Data are presented as of 6 November 2014, which was the last patient's last visit. CI, confidence interval; DCR, disease control rate; ORR, overall response rate.
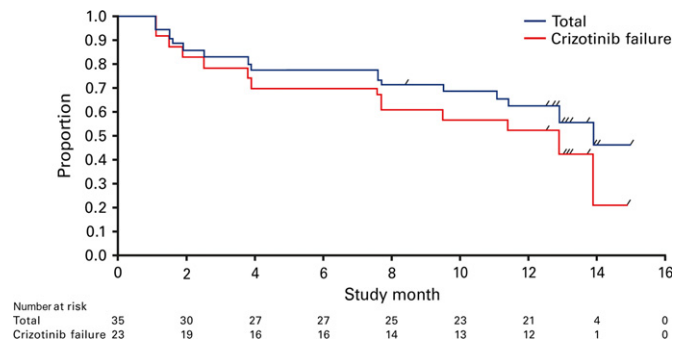
Fig. 1. Progression-free survival in the full analysis set and crizotinib-failure populations.

70.0% (95% CI 50.6−85.3) and DCR was 83.3% (95% CI 65.3−94.4), with a median time to response of 1.2 months (95% CI 1.1−2.1). In the crizotinib-failure RE population ($n = 20$), ORR was 65.0% (95% CI 40.8−84.6) and DCR was 80.0% (95% CI 56.3−94.3) (Table 4); median time to response was 1.2 months (95% CI 1.1−1.3). Overall, 21 patients in the FAS RE population and 13 patients in the crizotinib-failure RE population had a PR; no patient achieved a CR. The median duration of response was not estimable in either the FAS or crizotinib-failure populations (range 2.5–14.1 months).

Median PFS was 13.9 months (95% CI 11.1−not reached [NR]) for all patients and 12.9 months (95% CI 3.9−NR) for the crizotinib-failure population (Fig. 1). A PFS event was observed in 14 patients who had experienced PD with crizotinib; no events occurred in patients who had discontinued crizotinib for reasons other than PD.

Discussion

Alectinib is approved by the Japanese Ministry of Health, Labour and Welfare for the treatment of *ALK+*, unresectable, advanced or recurrent NSCLC at a dose of 300 mg twice daily given in eight capsules (20/40 mg).[11] In the present study, a new 150-mg alectinib capsule showed similar bioequivalence to the 20/40-mg capsules, and its food effect was negligible. These findings suggest that the 150-mg capsule could be a good substitute for eight 20/40-mg capsules, providing increased treatment administration choice for patients with *ALK+* NSCLC.

Alectinib was well tolerated and had an acceptable safety profile with no treatment-related grade 4/5 AE or gastrointestinal toxicities leading to treatment withdrawal. These results are in line with the AF-001JP study and two phase II studies of alectinib in *ALK+* NSCLC patients who had failed on crizotinib, despite the use of different alectinib doses.[11,15,16]

Although crizotinib is approved for the front-line treatment of *ALK+* NSCLC, many patients who initially respond well undergo a relapse within 1 year of treatment.[17,18] In this study, alectinib 300 mg twice daily showed favorable response rates in patients with *ALK+* NSCLC, including those who had failed on prior crizotinib. These results are in line with preclinical studies in which alectinib led to tumor size reduction in models of crizotinib resistance.[19] Even though the treatment dose was different, ORR in our study is also in agreement with data from the NP28761 study (ORR: 47.8%; DCR: 79.7%) and the NP28673 study (ORR: 50.0%; DCR 78.7%).[15,16] In addition, favorable median PFS of 13.9 and 12.9 months was observed in the FAS and crizotinib-failure populations, respectively, although these estimates could be unstable because of

the distribution of censored patients. Our study is, however, limited by the small sample size and larger studies are required to validate the observed results.

This study demonstrated that a new 150-mg alectinib capsule has a similar pharmacokinetic profile to the existing 20/40-mg capsules, providing an additional therapeutic option for patients with *ALK+* NSCLC. Furthermore, alectinib has promising efficacy and is well tolerated in patients with *ALK+* NSCLC who have progressed on prior ALK inhibitors, including those with crizotinib-treatment history and crizotinib failures. It is of note that superior PFS with alectinib *vs* crizotinib has been recently demonstrated in a randomized phase III study of Japanese patients with ALK inhibitor-naïve, *ALK+* NSCLC (J-ALEX; JapicCTI-132316).[20]

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig. S1. JP28927 study design.

Fig. S2. Trial profile of patient disposition.

Fig. S3. Pharmacokinetic assessment of (a) the bioequivalence of 20/40-mg capsules *vs* a 150-mg capsule of alectinib and (b) the effect of food on the 150-mg alectinib capsule.

Fig. S4. Treatment duration by individual patient (full analysis set).

Fig. S5. Maximum percentage change in tumor size from baseline (FAS response-evaluable population).