CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study

Takashi Seto, Katsuaki Kiura, Makoto Nishio, Kazuhiko Nakagawa, Makoto Maemondo, Akira Inoue, Toyoaki Hida, Nobuyuki Yamamoto, Hiroshi Yoshioka, Masao Harada, Yuichiro Ohe, Naoyuki Nagami, Kengo Takeuchi, Tadashi Shimada, Tomohiro Tanaka, Tomohide Tamura

Summary

Background Currently, crizotinib is the only drug that has been approved for treatment of ALK-rearranged non-small-cell lung cancer (NSCLC). We aimed to study the activity and safety of CH5424802, a potent, selective, and orally available ALK inhibitor.

Methods In this multicentre, single-arm, open-label, phase 1–2 study of CH5424802, we recruited ALK inhibitor-naive patients with ALK-rearranged advanced NSCLC from 13 hospitals in Japan. In the phase 1 portion of the study, patients received CH5424802 orally twice daily by dose escalation. The primary endpoints of the phase 1 were dose limiting toxicity (DLT), maximum tolerated dose (MTD), and pharmacokinetic parameters. In the phase 2 portion of the study, patients received CH5424802 at the recommended dose identified in the phase 1 portion of the study orally twice a day. The primary endpoint of the phase 2 was the proportion of patients who had an objective response. Treatment was continued in 21-day cycles until disease progression, intolerable adverse events, or withdrawal of consent. The analysis was done by intent to treat. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264.

Findings Patients were enrolled between Sept 10, 2010, and April 18, 2012. The data cutoff date was July 31, 2012. In the phase 1 portion, 24 patients were treated at doses of 20–300 mg twice daily. No DLTs or adverse events of grade 4 were noted up to the highest dose; thus 300 mg twice daily was the recommended phase 2 dose. In the phase 2 portion of the study, 46 patients were treated with the recommended dose, of whom 43 achieved an objective response (93-5%, 95% CI 82.1–98.6) including two complete responses (4-3%, 0-5–14-8) and 41 partial responses (89-1%, 76-4–96-4). Treatment-related adverse events of grade 3 were recorded in 12 (26%) of 46 patients, including two patients each experiencing decreased neutrophil count and increased blood creatine phosphokinase. Serious adverse events occurred in five patients (11%). No grade 4 adverse events or deaths were reported. The study is still ongoing, since 40 of the 46 patients in the phase 2 portion remain on treatment.

Interpretation CH5424802 is well tolerated and highly active in patients with advanced ALK-rearranged NSCLC.

Funding Chugai Pharmaceutical Co, Ltd.

Introduction A fusion tyrosine kinase gene comprising the EML4 gene and the ALK gene has been identified in non-small-cell lung cancer (NSCLC) with inversion of chromosome 2p. Mouse 3T3 fibroblasts expressing EML4-ALK had increased transforming activity and tumorigenicity.1 Transgenic mice expressing EML4-ALK fusion gene in lung alveolar epithelial cells were generated and exhibited development of adenocarcinoma in lungs shortly after birth,2 suggesting that the EML4-ALK fusion gene could be a driver mutation for NSCLC and serve as a promising candidate for a therapeutic target.3 Therefore, the introduction of new ALK inhibitors is expected to improve the treatment of patients with ALK-rearranged NSCLC.4

So far, crizotinib, a multi-targeted receptor tyrosine kinase inhibitor of ALK, MET, and ROS1 oncogene,5 is the only agent that has been approved for ALK-rearranged NSCLC in the USA, European Union, Japan, and other countries. In the phase 1 trial of crizotinib in patients with ALK-rearranged NSCLC, 87 of 143 evaluable patients had an objective response (60-8%, 95% CI 52.3–68.9). Median progression-free survival (PFS) was 9-7 months.6 In a retrospective study7 comparing survival outcomes in crizotinib-treated patients enrolled in the phase 1 trial and crizotinib-naive controls screened during the same period, crizotinib therapy was associated with better survival. However, resistance to crizotinib occurs by a number of mechanisms, including ALK gene alterations, such as ALK point mutations and copy number gain, and other oncogenes.8,9 Additionally, poor penetration of crizotinib across the blood–brain barrier is thought to be associated with a higher incidence of brain involvement if relapse occurs.10 In the crizotinib phase 2 trial, the most common site for single organ disease progression was the brain.11
CH5424802 (RO5424802; Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) is a novel, highly selective oral ALK inhibitor. In-vitro kinase assays showed that this compound selectively inhibits ALK. CH5424802 also shows high anti-tumour activity both in vitro and in vivo against tumour cell lines with some type of ALK gene alteration, such as NSCLC and anaplastic large-cell lymphoma lines harbouring an ALK fusion gene and a neuroblastoma line harbouring amplified ALK gene. More importantly, CH5424802 yielded potential anti-tumour activity against the gatekeeper Leu1196Met mutation in EML4-ALK, which has been identified in tumour cells refractory to crizotinib.

We report the results of a phase 1–2 study of CH5424802 (AF-001JP study) that was designed to identify the maximum tolerated dose (MTD) and pharmacokinetic parameters of the drug, and subsequently to assess its activity and safety in ALK inhibitor-naive patients with ALK-rearranged NSCLC.

Methods
Study design and patients
This study was a multicentre, single-arm, open-label, phase 1–2 trial (AF-001JP). Patients were eligible if they were aged 20 years or older; had histologically or cytologically confirmed advanced or metastatic ALK-rearranged stage IIIIB, IV, or recurrent NSCLC; had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; had measurable lesions as defined by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) (for the phase 2 portion only); received two or more (phase 1 portion) or one or more (phase 2 portion) previous chemotherapy regimens; and had adequate haematological, hepatic, and renal function. We excluded patients who had received previous treatment with any ALK inhibitor. Other exclusion criteria included symptomatic brain metastases or brain metastases requiring treatment, history of serious cardiac dysfunction, clinically significant gastrointestinal abnormality that would affect the absorption of the study drug, and pregnant or lactating women.

To identify whether patients were positive for ALK fusion gene expression, formalin-fixed paraffin-embedded sections from previous diagnostic or surgical procedures were sent to the laboratory in the Cancer Institute, Japanese Foundation for Cancer Research, Tokyo, Japan, and screened using anti-ALK immunohistochemistry with iAEP method (ALK Detection Kit, Nichirei Bioscience, Tokyo, Japan). In patients who were positive by immunohistochemistry, the fluorescence in-situ hybridisation (FISH) test was subsequently done for confirmation. An experienced pathologist (KT) judged these tests. Additionally, we did a multiplex RT-PCR method (SRL, Tokyo, Japan) on samples of cells or frozen cancer tissue sections. We deemed patients to be positive for ALK fusion gene expression when either FISH or RT-PCR showed positive results. In this study, patients gave written informed consent for ALK assessment by a central laboratory. If tumours were confirmed to be ALK positive, patients signed another informed consent form for enrolment into this trial. Patients participating in the study were treated at 13 hospitals in Japan. The study was approved by the institutional review board at each participating institution, and done in accordance with the Declaration of Helsinki and Good Clinical Practices.

Procedures
In the phase 1 portion of this study, patients received CH5424802 orally twice daily (once in the morning and once in the evening) in an open-label, sequential-cohort, dose-escalation study. We did the dose escalation with an accelerated titration design under fasting conditions from 20 mg to 300 mg twice daily. We determined a dose of 300 mg twice daily as the highest planned dose on the basis of the available safety information about the additive formulation in Japan. Patients fasted for 2 h before administration and 1 h after administration. We predefined dose-limiting toxicities (DLTs) as a treatment-related adverse event that occurs during the DLT assessment period (from day 1 to day 3 in cycle 0 and from day 1 to day 21 in cycle 1) and met any of the following criteria: grade 4 thrombocytopenia, grade 4 neutropenia continuing for 4 days or more, non-haematological toxic effects of grade 3 or worse (excluding transient electrolyte abnormalities and diarrhoea, nausea, or vomiting that recovers to grade 2 or lower with appropriate treatment), and events that required suspension of treatment for at least 7 days. The recommended dose was to be determined after taking into consideration tumour response in addition to the MTD, safety, and pharmacokinetic parameters under fasting conditions. While this fasting part was ongoing with DLT assessment in the cohort of patients given 300 mg twice daily, we amended the study to conduct a non-fasting part at doses of 240 mg and 300 mg twice daily by a traditional 3+3 design. We assessed the effect of food by comparing results under fasting and non-fasting conditions at both doses in the two groups of patients.

In the phase 2 portion of this study, patients received CH5424802 at the recommended dose identified in the phase 1 portion of the study orally twice a day (once in the morning and once in the evening). The patients fasted for 2 h before administration and 1 h after administration. Treatment was continued in 21-day cycles until disease progression, intolerable adverse events, or withdrawal of consent.

Tumours were assessed every cycle until four cycles and every two cycles thereafter, with RECIST version 1.1. In the phase 2 portion, tumour assessment from brain to pelvis at baseline was mandatory. Tumour assessment in this trial was done with CT scans for chest and abdomen; with CT or MRI for head, neck, and pelvis; and with bone scintigraphy. PET, x-ray, CT, or MRI for bone. Adverse
events were monitored up to the 28th day after the final dose, and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). When vision disorders occurred during this trial, an ophthalmological examination was done.

If a patient had thrombocytopenia or neutropenia of grade 4 or a non-haematological toxic effect of grade 3 or higher occurred, treatment with CH5424802 would be suspended until the toxic effects improved to grade 1 or lower, or the baseline grade. If the period of suspension was 14 days or less, treatment with CH5424802 could be resumed at the same dose level. If the period of suspension was longer than 14 days, treatment with CH5424802 would be resumed at a reduced dose. Treatment with CH5424802 would be discontinued permanently if treatment could not be resumed within 21 days of suspension. Additionally to these criteria, at the initiation of every cycle, treatment with CH5424802 would commence after it had been confirmed that all the following criteria were met (neutrophil count ≥1500 cells per μL [this criterion was amended so that patients with a neutrophil count ≥1000 cells per μL could receive the next cycle of treatment], platelet count ≥7.5x10⁴ cells per μL; non-haematological toxic effects of grade ≤1 or grade at baseline with exception of investigator’s judgment).

Pharmacokinetics

In the phase 1 portion of the study, we obtained 2 mL blood samples at pre-dose, 0·5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 24 h, 32 h, 48 h, and 72 h after single oral administration of CH5424802, and at pre-dose, 0·5 h, 1 h, 2 h, 4 h, 6 h, 8 h, and 10 h at steady state under fasting and non-fasting conditions. The blood samples were centrifuged at 1500–2000×g for 10 min at 4°C. The plasma samples were then stored at –70°C or less. We measured drug concentrations in plasma by the liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry with limit of quantitation of 0·1 ng/mL.

Statistical analysis

The primary endpoint of the phase 1 portion was DLT, MTD, safety, and pharmacokinetic parameters. The primary endpoint of the phase 2 portion was the proportion of patients who had an objective response, as determined by an independent review committee, which was to be confirmed by a subsequent scan. Secondary endpoints included safety, the proportion of patients who achieved disease control, progression-free survival, overall survival, and pharmacokinetic parameters.

In the phase 1 portion of the study, we did all statistical analyses in a descriptive manner; and we thus did no formal hypothesis testing. We analysed plasma CH5424802 concentrations with Phoenix WinNonlin Version 6.2 (Pharsight Corporation, Mountain View, CA, USA). We directly obtained the maximum plasma concentrations (Cmax) from the plasma-concentration curves for every participant. We calculated the area under the plasma concentration-time curve (AUC) for every individual using the linear log trapezoidal method as implemented in Phoenix WinNonlin.

In the phase 2 portion of this study, initially, we used a threshold response rate of 25% for reference based on the response rate of a platinum doublet regimen that is a standard treatment for NSCLC, and an expected response rate of 70% based on the patients to crizotinib. Since 12 individuals are necessary to yield a statistical power of 80% with a two-sided significance of 5%, we calculated a target sample size of

<table>
<thead>
<tr>
<th>Phase 1 (n=24)</th>
<th>Phase 2 (n=46)</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>42·5 (28–67), 48·0 (26–75), 39·0–60·0, 37·5–54·5</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 13 (54%), 24 (52%), Male 11 (46%), 22 (48%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never 14 (58%), 27 (59%), Former 10 (42%), 18 (39%), Present 0</td>
</tr>
<tr>
<td>Histological findings*</td>
<td>Adenocarcinoma 22 (92%), 46 (100%), Squamous-cell carcinoma 1 (4%), 0, Large-cell carcinoma 1 (4%), 0</td>
</tr>
<tr>
<td>Clinical stage (at screening)</td>
<td>IIIB 0, 2 (4%), IV 14 (58%), 31 (67%), Postoperative recurrence 10 (42%), 13 (28%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 9 (38%), 20 (43%), 1 15 (63%), 26 (57%)</td>
</tr>
<tr>
<td>ALK diagnosis†</td>
<td>Immunohistochemistry and FISH 22 (92%), 39 (85%), RT-PCR 2 (8%), 7 (15%)</td>
</tr>
<tr>
<td>EGFR status*</td>
<td>Wild-type 22 (92%), 41 (89%), Mutation 0, 0, Unknown 2 (8%), 5 (21%)</td>
</tr>
<tr>
<td>Previous chemotherapy regimens for metastatic disease</td>
<td>0 0, 1 (2%), 1 1 (4%), 21 (46%), 2 10 (42%), 9 (20%), ≥3 13 (54%), 15 (32%)</td>
</tr>
</tbody>
</table>

Data are median (range, IQR) or number of patients (%). ECOG=Eastern Cooperative Oncology Group. FISH=fluorescence in-situ hybridisation. *Histological findings and EGFR status were reported by the investigator site. †ALK diagnosis was performed in two central reference laboratories (one for immunohistochemistry and FISH, and the other for RT-PCR). ‡Regarded as eligible for inclusion because relapse occurred within 6 months of completion of adjuvant chemotherapy.

Table 1: Demographics and baseline characteristics
15 patients to allow for dropouts. Subsequently, the response rate of crizotinib for patients with ALK-rearranged NSCLC was published.20 We amended this study to test the null hypothesis of a threshold response rate of 45% for the study drug, based on the reported response rate of crizotinib.

We did the analysis by intent to treat. The decision as to whether to reject the null hypothesis that the response rate of 45% or less was based on whether the lower limit of the 95% CI estimated using the Clopper-Pearson method exceeded 45%. We estimated the proportion of patients who achieved disease control together with an estimate of the CI with the Clopper-Pearson method. Additionally, we did a pot-hoc subgroup analysis of response rate with regard to the age, sex, ECOG PS, body-mass index (BMI), number of previous chemotherapy regimens for metastatic disease, history of treatment with pemetrexed, types of ALK diagnostic method, and status of brain metastasis. All analyses were done with SAS version 9.2. This study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-101264.

Role of the funding source
This study was designed and funded by the study sponsor (Chugai Pharmaceutical Co, Ltd) and monitored by a clinical research organisation (EPS Corporation). The clinical research organisation collected all data and the study sponsor did all data analysis and interpretation, with input from the authors and investigators. The initial draft of the report was reviewed and commented on by all authors, and by employees of Chugai Pharmaceutical Co, Ltd. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
The first patient identified with ALK-positive NSCLC was enrolled on Sept 10, 2010, and received their first dose on Sept 14, 2010. The last patient was enrolled on April 18, 2012, and received their first dose on April 18, 2012. Data cutoff for this report was July 31, 2012.

For both the phase 1 and phase 2 parts of this study, 436 patients were screened for ALK and 135 (31%) patients were identified as ALK-positive. 70 patients were enrolled and treated in either the phase 1 (24 patients) or the phase 2 portions (46 patients). The major reason for...
exclusion of the other 65 ALK-positive patients was because of other eligibility criteria, or a reason not specified by investigators.

Table 1 summarises the baseline characteristics of patients enrolled in this study. In the phase 1 portion of the study, 15 patients were treated with CH5424802 under fasting conditions in six cohorts (20–300 mg twice a day), and nine were treated under non-fasting conditions in two cohorts (240 mg and 300 mg twice a day).

All 24 patients in the phase 1 part of the study completed at least two cycles, and had at least one adverse event while on study. Eight (33%) of 24 patients had grade 3 adverse events. Four patients had six adverse events that were deemed to be related to the study treatment—neutropenia (three patients, 13%), blood bilirubin increased (one patient, 4%), hypophosphataemia (one patient, 4%), and leucopenia (one patient, 4%). We noted no grade 4 adverse events or deaths at any dose level. We noted no DLTs up to the highest dose (300 mg twice a day; table 2). One patient had a dose reduction due to rash at a dose of 300 mg twice a day in the phase 1 portion, but no patient needed drug discontinuation because of adverse events. Thus, we did not identify the MTD in this study.

Blood samples were taken from all 24 patients. Table 3 shows the pharmacokinetics parameters at steady state after multiple dosing (day 21 in cycle 1). \( T_{\text{ss}} \) was between 2.00 h and 4.61 h constantly throughout the dose range (20–300 mg twice daily), and the \( \text{AUC}_{0-10} \) increased in an approximately linear way within the dose range under the fasting condition. We compared the absorption of CH5424802 under fasting and non-fasting conditions at 240 mg and 300 mg twice daily. The plasma exposures at steady state were similar under fasting and non-fasting conditions, although it took longer to reach \( T_{\text{ss}} \) under non-fasting conditions.

Of the 24 patients, all 20 (83%) patients with measurable lesions based on RECIST criteria and treated with CH5424802 showed tumour shrinkage and 17 (85%) of 20 patients had a partial response by investigator’s assessment (figure 1). All 15 patients with measurable lesions treated at doses higher than 160 mg twice a day achieved a partial response (240 mg [six patients], and 300 mg [nine patients]). One patient (4%) with non-measurable lesions met the criteria of RECIST version 1.1 for a complete response. The mean duration of treatment was 11.8 months (range 3–18) with a median follow-up of 12.05 months (range 4.7–20.8). 16 (67%) patients enrolled during the phase 1 portion of this trial remained on study treatment as of July 31, 2012.

On the basis of these results, the planned highest dose (300 mg twice daily) was judged as acceptable to be the recommended dose in the phase 2 portion.

Of the 46 patients enrolled in the phase 2 portion of the trial (all of whom had measurable lesions), two patients (4.3%, 95% CI 0.5–14.8) achieved a complete response, 41 patients (89.1%, 76.4–96.4) had a partial response, and one patient (2.2%, 0.1–11.5) had stable disease by independent review committee assessment (figure 2). No
patient had progressive disease; two patients (4.3%) had an unknown response because of early withdrawal. Thus 43 patients (93.5%, 95% CI 82.1–98.6) had an objective response, and 44 (95.7%, 95% CI 85.2–99.5) achieved disease control. We noted no apparent differences in response when analysed by age, sex, ECOG PS, BMI, number of previous chemotherapy regimens for metastatic disease, history of treatment with pemetrexed, types of ALK test, and status of brain metastasis (data not shown).

Figure 2 shows a waterfall plot of the best percentage change in the size of target lesions from baseline. All patients had a reduction in tumour size of more than 30%. Response to treatment was noted early, and 30 (65%) of 46 patients reached the criteria for partial response within 3 weeks (cycle 1) and 40 (87%) patients did so within 6 weeks (cycle 2; figure 3).

The study is still ongoing; 40 (87%) of 46 patients remained on treatment as of data cutoff and more follow-up is needed for precise estimation of treatment duration and progression-free survival in the phase 2 portion. The median treatment duration as of data cutoff had already passed 7.1 months (range 1–11) with a median follow-up period of 7.6 months (3.4–11.3).

Of the 46 patients in the phase 2 portion, 15 (33%) patients had known brain metastases, of whom 12 (26%) had previous radiation for CNS metastases and three (7%) were clinically stable without symptoms at baseline. Seven patients had prolonged periods of disease control for more than 6 months on CH5424802 treatment (average 6.5 months, range 0.8–11.3). No progression of CNS lesions in any of the patients was noted by the time of data cutoff, although radiotherapy before treatment might have affected the natural history of brain disease. Of the patients with CNS lesions, 12 were on treatment at data cutoff, and three patients had discontinued treatment because of brain oedema, tumour haemorrhage, and progression of non-CNS tumour lesions. Two of the three patients who had baseline CNS lesion but no radiation continued the study medication for more than 300 days without progression of brain metastases.

Adverse events were recorded in all 46 patients included in the safety analysis. Grade 3 adverse events were reported in 17 (37%) patients, but no grade 4 adverse events or deaths were reported. Serious adverse events occurred in five (11%) patients (brain oedema, radius fracture, tumour haemorrhage, cholangitis sclerosing, and alveolitis allergic). Four (9%) patients discontinued treatment because of adverse events (brain oedema, tumour haemorrhage, interstitial lung disease, and sclerosing cholangitis), which were considered related to CH5424802 with the exception of brain oedema. 22 (48%) patients suspended treatment within the 21-day limit because of adverse events. No patients required dose reduction.

Table 4 shows treatment-related adverse events reported in 10% or more of patients enrolled in phase 2 (n=46).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All grades</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>14 (30%)</td>
<td>0</td>
</tr>
<tr>
<td>Increased AST</td>
<td>13 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td>13 (28%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>12 (26%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (26%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (24%)</td>
<td>0</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>10 (22%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>8 (17%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Increased blood CPK</td>
<td>7 (15%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7 (15%)</td>
<td>0</td>
</tr>
<tr>
<td>Increased blood ALP</td>
<td>6 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>6 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (13%)</td>
<td>0</td>
</tr>
</tbody>
</table>

AST=aspartate aminotransferase. ALT=alanine aminotransferase. CPK=creatine phosphokinase. ALP=alkaline phosphatase.

Figure 3: Number of patients who had tumour size reduction of 30% or more by treatment cycle in phase 2
*One cycle lasted 3 weeks.
Almost 94% of patients achieved an objective response, with a median treatment duration of 7.1 months. The high proportion of patients achieving an objective response rate was 60.8% and 53% in two separate early phase trials (panel). Although median progression-free survival has not yet been reached, the median treatment duration at the time of data cutoff had already passed 7.1 months, and 40 of 46 patients remained on treatment.

The activity of CH5424802 could be explained by its potency and highly selective inhibitory effect on ALK. Crizotinib, a first-in-class ALK inhibitor, has been shown to be effective in patients with ALK-rearranged non-small-cell lung cancer. ALK expression in normal tissue is very low, and might not be activated generally. CH5424802 is a selective ALK inhibitor and, therefore, allows a high exposure while limiting side-effects. The high proportion of patients achieving an objective response and the favourable effects on brain metastases suggest that CH5424802 is a promising ALK inhibitor.

Investigation of CH5424802 in patients who are resistant to crizotinib is ongoing (NCT01588028).

**Discussion**

The results of this phase 1–2 study showed that CH5424802, given at a dose of 300 mg twice daily, is safe and active in patients with ALK-rearranged NSCLC. Almost 94% of patients achieved an objective response, and early reductions in tumour size of at least 30% were noted in most patients within the first 6 weeks. The proportion of patients who achieved an objective response noted here for CH5424802 is substantially higher than that of crizotinib (60.8% and 53%) in two separate early phase trials (panel). Although median progression-free survival has not yet been reached, the median treatment duration at the time of data cutoff had already passed 7.1 months, and 40 of 46 patients remained on treatment.

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The activity of CH5424802 could be explained by its potency and highly selective inhibitory effect on ALK. Crizotinib, a first-in-class ALK inhibitor, has been shown to be effective in patients with ALK-rearranged non-small-cell lung cancer. ALK expression in normal tissue is very low, and might not be activated generally. CH5424802 is a selective ALK inhibitor and, therefore, allows a high exposure while limiting side-effects. The high proportion of patients achieving an objective response and the favourable effects on brain metastases suggest that CH5424802 is a promising ALK inhibitor.

Investigation of CH5424802 in patients who are resistant to crizotinib is ongoing (NCT01588028).

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results, suggesting that there might have been patients with false-positive results by FISH test. Therefore, the difference in the diagnostic methods might contribute to the observed difference in the activity between the two drugs, and this should be explored in future studies.

CH5424802 was generally well tolerated with manageable adverse events. Although four patients discontinued treatment because of adverse events in this study, all 42 patients continued treatment with CH5424802 without any dose modification at the time of data cutoff. No adverse events specific to CH5424802 leading to discontinuation were identified either. Among 43 events in 22 patients with drug suspension, 24 events (56%) were due to the strict cycle initiation criteria. Since this is a first-in-human trial and safety profile of ALK inhibitors were not well known at the initiation of this study, strict cycle initiation criteria were defined, in addition to treatment suspension and dose reduction criteria. Patients with grade 2 non-haematological toxic effects or decreased neutrophil count suspended CH5424802 until they resolved to grade equal to or lower than 1 or grade at baseline at the initiation of each following cycle. Symptoms such as visual and gastrointestinal disorders (diarrhea, vomiting, and nausea) that were frequently reported with crizotinib occurred at a low rate in this study. This could be related to the high selectivity of this compound to ALK kinase. The inhibitory activity against other kinases, such as MET and ROS1 by crizotinib, might be a reason for these side-effects of crizotinib.

Almost a third of the patients screened for ALK assessment were identified as ALK positive. This ALK-positive ratio is higher than that previously reported,1 which might be due to bias by selecting patients with negative EGFR mutations, younger age, or non-smoking status. Limitations of this study can include a lack of any EML4-ALK mutational data. The study was also limited by a rather small enrolment and short follow-up period, and by its non-randomised nature.

Based on the results of the present study, CH5424802 could be an effective and safe option for the treatment of ALK-rearranged NSCLC. Further studies to confirm the efficacy of the drug and to assess its activity in patients resistant to crizotinib are ongoing.

Contributors

All authors contributed to data analysis, data interpretation, and writing of the report.

Conflicts of interest

TSe has received lecture fees and research funding from Chugai, Pfizer, and Novartis. KK has received lecture fees from Chugai, Pfizer, Novartis, and Astellas, and research funding from Chugai and Pfizer. MN has received lecture fees from Chugai and Pfizer, and research funding from Chugai, Pfizer, and Novartis. KN has received lecture fees and research funding from Chugai, Pfizer, and Novartis. KN has received lecture fees and research funding from Chugai, Novartis, and research funding from Novartis. AI has received lecture fees and research funding from Chugai. TH has received lecture fees and research funding from Chugai, Pfizer, and Novartis. NY has received lecture fees from Chugai and Pfizer; research funding from Chugai, Pfizer, and Novartis; and advisory fee from Novartis. HY has received lecture fees from Chugai and Pfizer, and research funding from Chugai and Novartis. MH has received lecture fees from Chugai and Pfizer, and research funding from Chugai, YO has received lecture fees, research funding, and travel grants from Chugai, Pfizer, and Novartis. NN has received lecture fees and research funding from Chugai and Pfizer. KT has received lecture fees and research funding from Chugai and Nichirei, and advisory fee from Chugai and Nichirei. TSh and TTan are employees of Chugai Pharmaceutical Co, Ltd. TTan has received lecture fees from Chugai, Pfizer, and Novartis, and research funding from Chugai.

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