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# Phase I/II study of alectinib in lung cancer with *RET* fusion gene : study protocol

Shinji Takeuchi[1], Toshinori Murayama[2,3], Kenichi Yoshimura[2], Takahiro Kawakami[2], Shizuko Takahara[2], Yasuhito Imai[2], Yoshikazu Kuribayashi[2], Katsuhiko Nagase[2], Koichi Goto[4], Makoto Nishio[5], Yoshinori Hasegawa[6], Miyako Satouchi[7], Katsuyuki Kiura[8], Takashi Seto[9], and Seiji Yano[1,2]

[1]*Division of Medical Oncology, Cancer Research Institute, Kanazawa University, Kanazawa, Japan,* [2]*Innovative Clinical Research Center (iCREK), Kanazawa University Hospital, Kanazawa, Japan,* [3]*Department of Clinical Development, Kanazawa University Hospital, Kanazawa, Japan,* [4]*Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan,* [5]*Thoracic Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan,* [6]*Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan,* [7]*Department of Thoracic Oncology, Hyogo Cancer Center, Akashi, Japan,* [8]*Department of Allergy and Respiratory Medicine, Okayama University Hospital, Okayama, Japan,* [9]*Department of Thoracic Oncology, National Kyusyu Cancer Center, Fukuoka, Japan*

**Abstract : Background : The rearranged during transfection (*RET*) fusion gene was discovered as a driver oncogene in 1-2% of non-small cell lung cancers (NSCLCs). Alectinib is an approved anaplastic lymphoma kinase (ALK) inhibitor that may also be effective for *RET* fusion-positive NSCLC. Methods/Design : *RET* fusion-positive NSCLC patients treated with at least one regimen of chemotherapy are being recruited. In step 1, alectinib (600 or 450 mg, twice daily) will be administered following a 3+3 design. The primary endpoint is safety. In step 2, alectinib will be administered at the recommended dose (RD) defined by step 1. The primary endpoint is the response rate of RET inhibitor treatment-naïve patients. Conclusion : This is the first study to investigate the safety and preliminary efficacy of alectinib in *RET* fusion-positive NSCLC patients. If successful, alectinib treatment may lead to substantial and important changes in the management of NSCLC with *RET* fusion genes.**
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***Keywords*** **:** *RET fusion gene, alectinib, non-small cell lung cancer*

## INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide and can be histologically subdivided into small cell lung cancer and non-small cell lung cancer (NSCLC). Several driver oncogenes, including epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*)-fusion genes, have been identified in NSCLC ; recently, individual therapy based on gene profiling with corresponding targeted drugs has been introduced into clinical practice (1-3).

Rearranged during transfection (*RET*) was discovered in 1985 as an oncogene that was produced by recombination during the transfection of NIH 3T3 cells with human lymphoma DNA (4). *RET* fusion genes are detected in 20-40% of papillary thyroid cancers (5, 6). Recently, they were also identified in some cases of NSCLCs (7-10). The most common fusion partner of *RET* is *KIF5B*, followed by *CCDC6*, *TRIM33*, and *NCOA4* (9, 11, 12). *RET* fusion is detected in 1-2% of NSCLCs and is mutually exclusive to the mutation or rearrangement of other commonly altered genes, including *EGFR*, *KRAS*, *ALK*, and *ROS1* (9). *KIF5B-RET* fusion transgenic mice were shown to develop lung adenocarcinoma (13), which indicated that *RET* fusion genes were one of the oncogenic drivers of lung adenocarcinoma.

Recent clinical trials of vandetanib or cabozantinib for *RET*-fusion positive NSCLC demonstrated a clinical response. Patients treated with vandetanib had a response rate of 53% (9/17 cases) and a progression-free survival (PFS) of 4.7 months (14) ; those treated with cabozantinib had a response rate of 28% (7/25 cases) and a PFS of 5.5 months (15). These results were not comparable to those in NSCLCs with *EGFR* mutations or *ALK* translocations treated with EGFR-tyrosine kinase inhibitors (TKIs) or ALK-TKIs, respectively, which indicated the need to develop more beneficial RET inhibitors for *RET* fusion-positive NSCLC.

CH5424802 (alectinib) is a second generation ALK-TKI that also displayed active against ALK with a L1196M gatekeeper mutation (16). In a phase I clinical trial, although the maximum tolerated dose was not determined, alectinib showed remarkable efficacy, with a response rate of 93.5% and PFS greater than 27 months, and 300 mg alectinib twice daily has been approved for the treatment of *ALK*-positive NSCLC in Japan (17). Although alectinib is thought to be a highly selective inhibitor of ALK relative to other compounds such as crizotinib and ceritinib, which have been approved for *ALK*-positive NSCLC, it also has a high activity against RET (18). A global trial showed the efficacy and safety of alectinib 600 mg twice daily and the U.S. Food and Drug Administration (FDA) approved this regime for *ALK*-positive NSCLC (19, 20). Recently, Lin *et al.* reported the compassionate or off-label use of alectinib in patients with NSCLC harboring a *RET*-fusion gene (21). In this report, alectinib demonstrated preliminary antitumor activity and suggested the importance of conducting prospective studies.

Therefore, we are conducting a phase I/II trial to assess the efficacy of alectinib in *RET* fusion-positive NSCLC patients (ALL-RET trial : Alectinib in lung cancer with *RET* fusion) (UMIN000020628).

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Address correspondence and reprint requests to Shinji Takeuchi, Division of Medical Oncology, Cancer Research Institute, Kanazawa University, 13-1, Takaramachi, Kanazawa, Ishikawa, 920-0934, Japan and Fax : +81-76-234-4524, and Toshinori Murayama, Department of Clinical Development, Kanazawa University Hospital, 13-1, Takaramachi, Kanazawa, Ishikawa, 920-0934, Japan and Fax : +81-76-234-4281.

## METHODS AND DESIGN

*Purpose*

The primary objective in the phase I portion (step 1) is to evaluate the safety, tolerability, pharmacokinetic parameters, maximum tolerated dose (MTD), and efficacy of CH5424802 (alectinib) in patients with advanced NSCLC harboring a RET fusion gene. In the phase II portion (step 2), it is to evaluate the efficacy and safety of CH5424802 at the MTD in patients with advanced NSCLC harboring a *RET* fusion gene.

*Study design*

This study is an open-label, multi-institutional phase I/II study ; as of January 2017, the participating institutions included seven specialized centers in Japan. These institutions are listed in Table 1.

*Ethical considerations and registration*

This study will be conducted in accordance with the International Committee for Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. The study protocol was approved by the institutional review boards of all participating institutions. Informed consent will be obtained from all patients before registration. This study was registered with UMIN Clinical Trials Registry (UMIN000020628).

*Endpoint*

The primary endpoints are dose-limiting toxicity (DLT), safety, and pharmacokinetic parameters in the phase I portion (step 1), and objective response rate (ORR) in RET-TKI naïve patients according to central review in the phase II portion (step 2). Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. DLT is defined as follows : grade ≥ 4 thrombopenia ; grade ≥ 3 febrile neutropenia ; grade ≥ 4 neutropenia lasting 4 days or more ; grade ≥ 3 any non-hematologic toxicity except for controllable electrolyte abnormality, nausea, vomiting, and diarrhea. DLT will be evaluated during the first cycle (21 days) of therapy.

The secondary endpoints are response rate according to review by investigators, PFS, disease control rate, overall survival, ORR in patients previously treated with RET-TKIs, subgroup efficacy in patients with different *RET* fusion partners, and safety.

## ELIGIBILITY CRITERIA

*Inclusion criteria*

Prior to enrolment in the study, patients must fulfill all of the following criteria : provision of written informed consent ; aged 20 years or older ; histologically or cytologically diagnosed NSCLC with unresectable locally advanced or metastatic disease ; tumor samples that tested positive for a *RET* fusion gene and negative for an *EGFR* mutation and an *ALK* fusion gene ; failure to respond to a course (or multiple courses) of chemotherapy or progression of NSCLC after a course (or multiple courses) of chemotherapy ; life expectancy of 3 months or longer ; Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 ; not pregnant ; have adequate bone marrow, liver, renal, and respiratory functions that meet the levels stated below :

i) Neutrophil count ≥ 1,500/mm$^3$
ii) Hemoglobin level ≥ 9.0 g/dL
iii) Platelet count ≥ 100,000/mm$^3$
iv) Serum creatinine level ≤ 1.5 mg/dL
v) ALT, AST, and ALP levels ≤ 3-fold of the upper limit of the reference value at each institution
vi) Serum bilirubin level ≤ 1.5-fold of the upper limit of the reference value at each institution
vii) SpO2 ≥ 92% ;

and, for the phase II portion (step 2) : have one or more measurable lesions in accordance with the revised RECIST guidelines (version 1.1).

*Exclusion criteria*

Patients will be excluded for any of the following reasons : previous receipt of CH5424802 ; a history of hypersensitivity to additives contained in CH5424802 ; infection requiring systemic administration of antibiotics or antivirals ; positive laboratory tests for the hepatitis B antigen or anti-hepatitis C virus antibodies ; presence of unstable brain metastases or spinal cord compression that require treatment ; any condition that would preclude receipt of the study treatment ; a QTc interval greater than 480 ms, a history of long QT syndrome, a history of clinically significant ventricular arrhythmia, currently in receipt of antiarrhythmic drugs, or have an implanted defibrillator ; interstitial lung disease or a history of that disease ; poorly controlled diabetes or hypertension that cannot be managed with medication ; difficulty in receiving oral medication ; exhibition of adverse reactions to prior treatment of severity of grade 2 or higher ; if the following times have not elapsed since prior treatment or the conclusion of such treatment to the date of enrolment in the study :

i) Surgery or radiation therapy : 4 weeks
ii) Bronchoscopic treatment : 2 weeks
iii) Chemotherapy : 4 weeks
iv) Lenvatinib or vandetanib : 3 weeks
v) Nitrosourea or mitomycin C : 6 weeks
vi) Endocrine therapy or immunotherapy : 2 weeks
vii) Transfusion or hematopoietic growth factor : 2 weeks
viii) Other trial medications : 4 weeks ;

pleural effusion, pericardial effusion, or ascites that requires

Table 1. Participating Institutions and Coordinating Investigators

Coordinating Investigators
Shinji Takeuchi and Seiji Yano, Kanazawa University Hospital

| Participating Institution | Principal Investigator |
|---|---|
| 1. Kanazawa University Hospital | Shinji Takeuchi |
| 2. National Cancer Center Hospital East | Koichi Goto |
| 3. The Cancer Institute Hospital of JFCR | Makoto Nishio |
| 4. Nagoya University Hospital | Yoshinori Hasegawa |
| 5. Hyogo Cancer Center | Miyako Satouchi |
| 6. Okayama University Hospital | Katsuyuki Kiura |
| 7. National Kyushu Cancer Center | Takashi Seto |

treatment ; deep vein thrombus or pulmonary thromboembolism that requires treatment ; multiple malignancies with differing histologies ; a history of other malignancies in the past 5 years ; or patients deemed ineligible for participation in this study by an investigator for any other reason.

*Patient registration*

The investigators will send a patient registration form to the independent data center at Innovative Clinical Research Center in the Kanazawa University Hospital. Patient registration began on February 2016 and shall continue until January 2018.

*Treatment*

In the phase I portion (step 1), CH5424802 (cohort 1 : 600 mg ; cohort 2 : 450 mg) will be administered orally twice daily in a 21-day cycle. Three to six patients will be enrolled in each cohort. The recommended dose (RD) or maximum tolerated dose (MTD) of CH5424802 will be determined using a de-escalation scheme (Figure 1). In the phase II portion (step 2), the RD/MTD of CH5424802 in a cycle of 21 days will continue until the criteria for a respite, dosage reduction, or discontinuation of the protocol treatment are met.

*Follow-up*

After completion of the scheduled treatment, follow-up of the patients will occur until January 2019. The clinical outcomes for each patient will be measured at 24-week intervals after confirmation of disease progression or initiation of post-study treatment.

*Sample size determination*

In the phase I portion (step 1), the sample size was determined based on a conventional 3+3 phase I design for oncology drugs. In the phase II portion (step 2), the planned sample size of 17 RET-TKI-naïve patients was determined to reject a null ORR of 30% at a onesided significance level of 0.05 under an expected ORR of 60% with a power of 0.80. A maximum of 10 patients previously treated with other RET-TKIs (vandetanib and/or lenvatinib) will also be enrolled for exploratory analysis in the phase II portion (step 2).

*Statistical analysis*

In the phase I portion (step 1), the population analyzed for the primary endpoint will include the enrolled patients with complete safety data on the DLT. In the phase II portion (step 2), the analysis population for efficacy is the full analysis set, and we will estimate the confidence interval (CI) of the ORR using an exact binomial distribution with a one-sided significance level of 5%. A treatment will be declared promising if the estimated lower limit of the ORR exceeds the threshold value of 30%.

## RESULTS AND DISCUSSION

This is the first study to investigate the safety and preliminary efficacy of alectinib in *RET* fusion gene-positive NSCLC patients. To identify 20 *RET* fusion-positive NSCLC cases, we will screen 2000 NSCLC patients participating in the nationwide gene screening network, LC-SCRUM-Japan ; as of August 2016, the network contained more than 200 participating institutions.

In *ALK* fusion-positive NSCLC, alectinib activity has been shown against crizotinib-resistant *ALK* mutations, including L1196M and C1156Y (16). Moreover, alectinib has activity against *RET* mutations, including V804L and V804M (18), which are resistant to other RET-TKIs such as vandetanib and cabozantinib, and is expected to have clinical efficacy in patients who are refractory to other RET-TKIs. In the ALL-RET study, we will also evaluate the preliminary efficacy (the response rate) of alectinib in patients with *RET* fusion-positive NSCLC who are refractory to other RET-TKIs (vandetanib and/or lenvatinib).

If the trial is successful, alectinib may yield substantial and important changes in the management of patients with *RET* fusion gene positive NSCLC.

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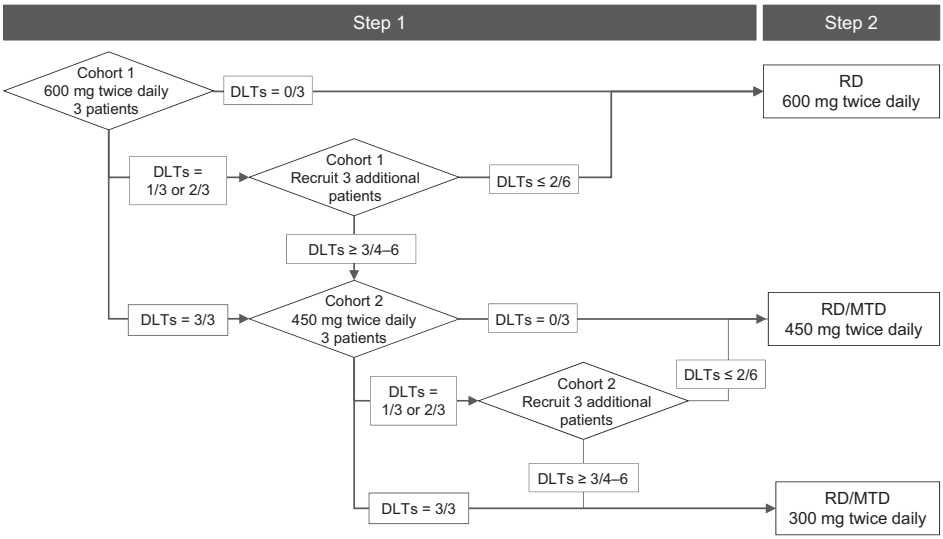


DLTs, dose-limiting toxicities. MTD, maximum tolerated dose. RD, recommended dose.

Figure 1. Study design.

## CONFLICTS OF INTEREST

Seiji Yano, Koichi Goto, Makoto Nishio, Yoshinori Hasegawa, Miyako Satouchi, Katsuyuki Kiura, and Takashi Seto have received speaker honoraria and research funding from Chugai Pharmaceutical Co, Ltd. All remaining authors have declared no conflicts of interest.

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