

Phase II trial of CH5424802 (alectinib hydrochloride) for recurrent or refractory ALK-positive anaplastic large cell lymphoma: study protocol for a non-randomized non-controlled trial

Hirokazu Nagai^{1,3}, Reiji Fukano², Masahiro Sekimizu³, Akiko Kada³, Akiko M. Saito³, Ryuta Asada^{3,4} and Tetsuya Mori⁵

¹*Department of Hematology and Oncology Research, National Hospital Organization Nagoya Medical Center, Aichi, Japan*

²*Department of Pediatrics, National Kyushu Cancer Center, Fukuoka, Japan*

³*Clinical Research Center, National Hospital Organization Nagoya Medical Center, Aichi, Japan*

⁴*Innovative and Clinical Research Promotion Center, Gifu University Hospital, Gifu, Japan*

⁵*Department of Pediatrics, St. Marianna University School of Medicine Hospital, Kanagawa, Japan*

ABSTRACT

Currently, a standard therapy has not been established for recurrent or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. While there are many treatment options, such as hematopoietic stem cell transplantation, patients with resistant disease to conventional chemotherapies have particularly poor prognosis. There is urgent need to develop new drugs because of the lack of a standard therapy and poor prognoses. This phase II trial is designed for evaluating the efficacy and safety of alectinib hydrochloride for patients with recurrent or refractory anaplastic lymphoma kinase -positive anaplastic large cell lymphoma. The primary endpoint is the response rate according to the Revised Response Criteria for Malignant Lymphoma. The secondary endpoints are pharmacokinetics, safety in children, complete response rate, response duration, progression-free survival, event-free survival, overall survival, and adverse events. The results of this trial will be the pivotal data for the drug approval of alectinib hydrochloride for recurrent or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma.

Keywords: phase II trial, anaplastic large cell lymphoma, efficacy, safety

Abbreviations: ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; PD, progressive disease; CR, complete remission; PR, partial remission; PS, performance status; G-CSF, granulocyte colony-stimulating factor; ULN, upper limit of normal; ALT, alanine aminotransferase

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Corresponding author: Masahiro Sekimizu, M.D., Ph.D.

Clinical Research Center, National Hospital Organization Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya, Aichi 460-0001, Japan

Phone: +81-52-951-1111, fax: +81-52-212-7360, e-mail: masahiro.sekimizu@nnh.go.jp

INTRODUCTION

Anaplastic lymphoma kinase (ALK) positive anaplastic large cell lymphoma (ALCL) is an extremely rare large T-cell lymphoma that features CD30 antigen-positive large cells. Most cases demonstrate t(2;5)(p23;q35) chromosomal translocation. The formation of ALK/nucleophosmin fusion proteins (p80) due to this translocation has been shown to be at the core of the pathophysiology of this disease¹.

The standard initial treatment for ALK-positive ALCL in adults is the multi-agents combined chemotherapy of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or the CHOP-like regimens². Patients with relapsed or recurrent disease are treated with multi-agent combination chemotherapies similar to those used to treat recurrence of other types of aggressive lymphomas. Recently, the drug of anti-CD30 antibody, brentuximab vedotin, has been reported to be effective³. High-dose chemotherapy and allogeneic hematopoietic stem cell transplantation are also performed to some cases, but a standard therapy for recurrent or refractory ALCL has not yet to be established.

For pediatric ALCL, ALCL99 protocol is now the standard therapy for this disease which was conducted as an international joint clinical trial in Europe and Japan. The ALCL99 trial used multi-agent combination chemotherapy with dexamethasone, cyclophosphamide, high-dose methotrexate, ifosfamide, etoposide, cytarabine, and doxorubicin^{4,5}. Among the 352 registered patients, the 2-year event-free survival rate was 74.1% and the 2-year overall survival rate was 92.5%⁴. While the pediatric patients with ALCL have generally favorable prognosis, about 30% of cases require further treatments due to recurrence. Retrospective analysis suggests that allogeneic hematopoietic stem cell transplantation could be effective in chemotherapy-resistant cases⁶. However, a standard therapy has not been established for recurrent or refractory ALK-positive ALCL in children.

ALK inhibitors are drugs that directly inhibit ALK, which plays a central role in the pathology of ALK-positive ALCL, thus these agents are expected to be developed for this disease. The first-generation ALK inhibitor crizotinib has been found to have high efficacy against ALK fusion gene-positive lung cancer, and now it becomes to be a widely used agent⁷. Crizotinib was reported to be effective against ALK-positive ALCL in the Children's Oncology Group trial (ADVL0912 trial)⁸. The subjects of this trial were 79 children with recurrent malignant disease. Although most of the patients who were registered had neuroblastoma, there were 9 cases of ALK-positive ALCL. Overall response rate was 89% (8/9) with 78% (7/9) complete response in patients with ALK-positive ALCL. These results suggest that ALK inhibitors could be highly effective against ALK-positive ALCL.

CH5424802 (alectinib hydrochloride) is an orally administered second-generation ALK inhibitor manufactured at Chugai Pharmaceutical's Kamakura laboratory. Its antitumor effect is exerted through the selective inhibition of ALK, which leads to the inhibition of proliferation and the induction of apoptosis of ALK positive tumor cells⁹. In Japan, it is currently indicated for ALK fusion gene-positive non-small cell lung cancer¹⁰. We have planned a multi-institutional phase II clinical trial (UMIN000016991) to investigate the efficacy and safety of alectinib hydrochloride for patients with recurrent or refractory ALK-positive ALCL. Based on the results of this trial, we plan to apply for a drug approval of alectinib hydrochloride to recurrent or refractory ALK-positive ALCL.

METHODS/DESIGN

CH5424802 300 mg is administered orally twice a day after the morning and evening meals, repeated for 21 days. One cycle consists of 21 days. Patients who weigh less than 35 kg will be administered 150 mg twice a day after the morning and evening meals. Administration can be continued for a maximum of 16 cycles. From cycle 17 onwards, administration can be continued for patients who would have benefits of further treatment of CH5424802 according to investigators' assessments (see Fig. 1).

This is a single arm, open-label, multicenter phase II trial. We chose a single group, open-label design because a standard treatment for recurrent or refractory ALK-positive ALCL has not been established in Japan or overseas, therefore an appropriate control arm does not exist.

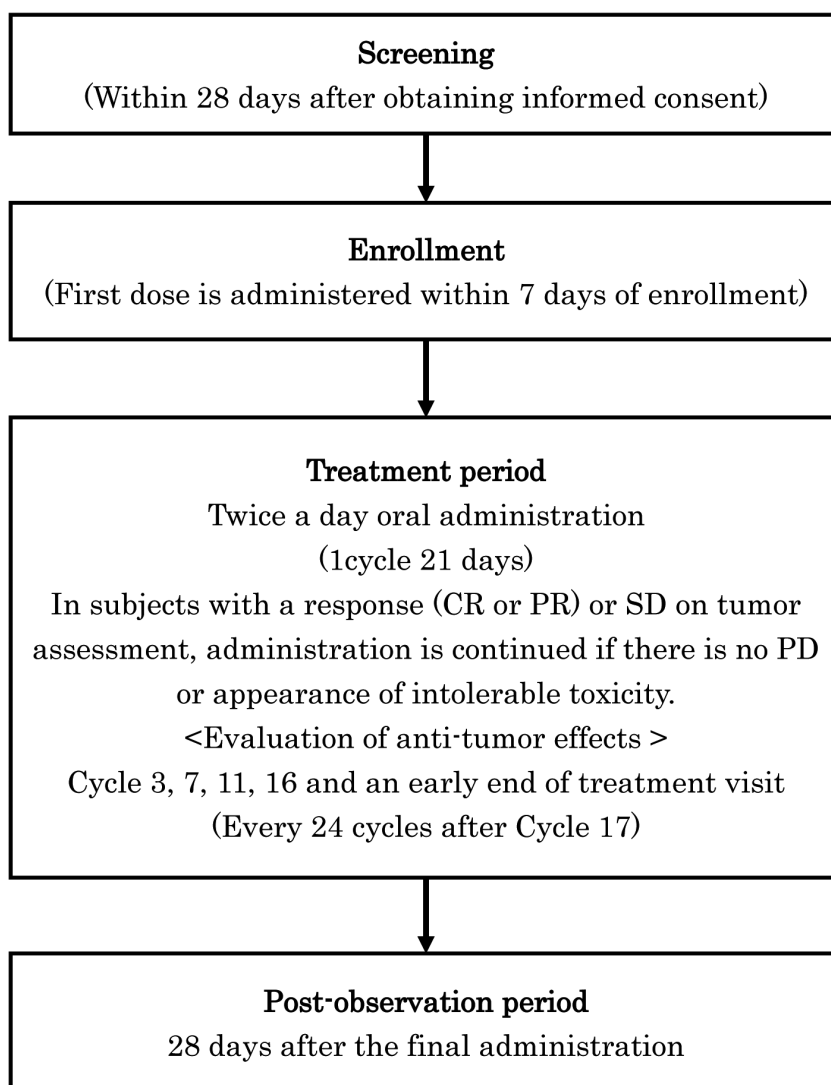


Fig. 1 Entire design of this trial

Participants

Patients with a minimum age limit of 6 years suffering from recurrent or refractory ALK-positive ALCL are included in this study.

Eligibility criteria

Inclusion criteria

- 1) Aged 6 years or older at consent and judged by the investigator/subinvestigator to be able to take capsules.
- 2) Definitively diagnosed with ALK-positive ALCL by histological examination.
Note: ALK-positive ALCL is confirmed by immunohistochemical staining of tissues collected at the initial diagnosis or relapse.
- 3) Being able to provide pathological tissues of lymphoma for central review.
- 4) With progressive disease (PD) during standard chemotherapy, without achieved complete remission (CR) /partial remission (PR) after standard chemotherapy, or with recurrence or progression after standard chemotherapy.
- 5) Having measurable lesions defined by the Revised Response Criteria for Malignant Lymphoma.
- 6) With an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0–2.
- 7) Expected to survive for 3 months or longer at the time of consent.
- 8) Fulfilling all the following criteria on the clinical laboratory tests at the screening examination, and having not been administered granulocyte colony-stimulating factor (G-CSF) or having not received blood transfusion within 1 week before examination of the neutrophil and platelet counts and retain normal functions of major organs.
 - Neutrophil count: $\geq 1,500/\mu\text{L}$
 - Platelet count: $\geq 75,000/\mu\text{L}$
 - Serum bilirubin level: ≤ 1.5 times the upper limit of normal (ULN) of the facility
 - Serum creatinine level: ≤ 1.5 times the ULN
 - Alanine aminotransferase (ALT) and aspartic aminotransferase levels: ≤ 2.5 times the ULN
- 9) Provided written consent to participate in this clinical trial has been given by the subject in person or by a legal guardian (when the subject is younger than 20 years at consent).

Exclusion criteria

- 1) Diagnosed with primary cutaneous ALCL in the latest (with other organs invaded by the disease and in a similar condition to systemic ALCL: considered eligible).
- 2) Observed active viral, bacterial, or fungal infection within 2 weeks before the first administration of alectinib hydrochloride.
- 3) With poorly controlled diabetes (a hemoglobin A1c [HbA1c] level of $\geq 7.0\%$ on the screening examination).
- 4) With a history or complication of another malignant neoplasm that has not been a remission status for 3 years or longer, although the following are excluded:
 - a. Non-melanoma skin cancer
 - b. Radically treated localized prostate cancer
 - c. Carcinoma *in situ* of the uterine cervix
- 5) With central nervous system lesions.
- 6) Showing signs or symptoms suggestive of progressive multifocal leukoencephalopathy.
- 7) With a history of severe hypersensitivity or allergy.
- 8) Positive for human immunodeficiency virus antibody, hepatitis B virus surface antigen, hepatitis B surface antibody, hepatitis B core antibody, or hepatitis C virus antibody at the

screening examination. Positive for HBs antibody with previous hepatitis vaccination are not excluded.

9) With liver cirrhosis.

10) Having received autologous hematopoietic stem-cell transplantation within 12 weeks before the first administration of alectinib hydrochloride.

11) Having received allogeneic hematopoietic stem-cell transplantation.

12) Having received treatment for a malignant neoplasm (including radiation therapy, chemotherapy, and hormone therapy) within 4 weeks before the first administration of alectinib hydrochloride. However, patients diagnosed as PD after the last chemotherapy (excluding antibody therapy) administered in not less than 2 weeks ago are not excluded.

13) Having been administered an adrenocorticosteroid hormone preparation for the treatment of lymphoma within 7 days before the first administration of the investigational product. However, the administration of hydrocortisone at 2.5 mg/kg (100 mg at a maximum) for complications such as fever until 48 hours before the first administration of the investigational product is allowed.

14) Administered any investigational product or treated using an investigational device within 4 weeks before the first administration of alectinib hydrochloride.

15) Received a treatment specifically targeting ALK in the past.

16) Known to have hypersensitivity to additives contained in alectinib hydrochloride (lactose hydrate, crystalline cellulose, sodium lauryl sulfate, etc.).

17) Pregnant, breast-feeding, or may be pregnant, or without consent to contraception for 6 months after the last administration of alectinib hydrochloride.

18) Having a disability that impairs their ability to consent in writing or conform to the trial procedure.

19) Judged by the investigator/subinvestigator to be Inappropriate for participation in this clinical trial for other reasons.

Endpoints

The primary efficacy endpoint is response rate, which is defined as the proportion of patients who achieved CR or PR in overall best response. Overall response is assessed by a central review board according to the Cheson criteria (2007)¹¹⁾. The secondary endpoints are the evaluations of pharmacokinetics, safety in children, CR rate, response duration, progression-free survival, event-free survival, overall survival, and adverse events.

Interim analysis and monitoring

We do not plan the interim analysis to evaluate efficacy, because this is a single-arm trial and it is not appropriate to assess the efficacy based on preliminary data. To ensure the safety of the pediatric patients, the efficacy and safety committee meeting will be held to evaluate their safety after the registration of first 3 patients aged 6 to 15 years. To confirm that the trial is being conducted safely, appropriately, and in accordance with the trial protocol and any relevant laws and regulations, and to confirm the reliability of the data, monitoring will be performed by site visits to view source materials and case report forms directly. Monitoring will be performed by the clinical trial project department at the Clinical Research Center at Nagoya Medical Center.

Sample size

Ten cases.

A standard therapy has yet to be established for patients with recurrent or refractory ALCL. Past research indicates a long-term survival rate of 40–60% for recurrent or refractory ALCL¹²⁾.

In addition, the PROPEL trial for recurrent or refractory peripheral T-cell lymphoma showed a 35% (6/17 cases) objective response rate for ALCL patients using pralatrexate¹³). Referencing these reports, the threshold response rate was determined as 50%. Crizotinib showed a response rate of 89% (8/9 cases) in the trial of pediatric recurrent or refractory ALCL patients¹³). Reported response rates to brentuximab vedotin (recombinant) in recurrent or refractory ALCL patients were 100% (5/5 cases) in Japan and 86% (50/58 cases) overseas. Other studies have reported response rates of 80% or higher. We expected that our drug would elicit response rates comparable to these drugs, and put the expected response rate as 85%. Since statistical power of 79% could be obtained with 10 cases with alpha level of 0.05 (one-tailed), the target sample size was 10.

DISCUSSION

The results of this trial will be the pivotal data for the drug approval of alectinib hydrochloride for recurrent or refractory ALK-positive ALCL.

DECLARATIONS

Ethics approval and consent to participate

The trial was approved by the institutional review boards of each participating institution. Written informed consent is obtained from every patient prior to participation in the trial.

Competing interests

HN has received research funding from Janssen Pharmaceutical K. K., Mundipharma K.K., Celgene Corporation, Bayer Yakuhin Ltd., Abbvie G.K., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Esai Co., Ltd., and honoraria from Chugai Pharmaceutical Co., Ltd., Mundipharma K.K., Esai Co., Ltd., Sanofi K.K., and Janssen Pharmaceutical K. K.

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Authors' contributions

HN, TM, RF, MS and RA conceived of the study, and participated in its design and coordination and helped to draft the manuscript. AK participated in the design of the study and the statistical analysis plan. AS manages the data of this study.

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