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*Clinical Study Protocol*

# A Phase I/II Study of Crizotinib for Recurrent or Refractory Anaplastic Lymphoma Kinase-Positive Anaplastic Large Cell Lymphoma and a Phase I Study of Crizotinib for Recurrent or Refractory Neuroblastoma: Study Protocol for a Multicenter Single-arm Open-label Trial

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**Crizotinib is an inhibitor of multiple tyrosine kinases, including the anaplastic lymphoma kinase (ALK). Responses to crizotinib have also been reported in patients with ALK-positive anaplastic large-cell lymphoma (ALCL) and solid tumors with ALK-mutation, including neuroblastoma. Optimal treatment for patients with recurrent or refractory ALK-positive ALCL and neuroblastoma has not been established. There is a need to develop new drugs for these patients. The objectives of this trial are to evaluate the tolerability and safety of crizotinib in Japanese patients with recurrent/refractory ALK-positive ALCL or neuroblastoma (phase I) and its efficacy in recurrent/refractory ALK-positive ALCL (phase II).**

**Key words:** crizotinib, recurrent, refractory, anaplastic large cell lymphoma, neuroblastoma

Standard treatment for recurrent or refractory anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) has not been established. Various treatments, including hematopoietic cell transplantation, have been performed, but the prognosis of conventional chemotherapy-resistant patients is particularly poor. ALCL accounts for approximately 10-15% of children with non-Hodgkin lymphoma (NHL) and 1-2% of adult patients with NHL. Since the number of adult patients with NHL has been reported as 17,000 per year in Japan <National Cancer Center for Cancer Control and Information Services. http://ganjoho.ncc.go.jp/public/index.html (In Japanese). (Accessed October 4, 2017.)>, the number of adult patients with ALCL is estimated to be 170 to 340 per year. The incidence of pediatric ALCL in Japan is reported as approximately 20 cases per year. <National Center for Child Health and Development. https://www.ncchd.go.jp/hospital/sickness/children/lymphoma.html (In Japanese) (Accessed March 15, 2018.)> In children and adolescents, more than 90% of cases are ALK-positive [1] compared to only 40-50% of adult patients [2]. Since the event-free survival (EFS) rate of ALK-positive ALCL is about 70% for both adults and children, the incidence of relapsed/refractory cases is estimated to be 20% to 30%. From the above, it is estimated that the number of ALK-ALCL patients with relapsed/refractory disease is

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20 to 50 per year.

There is no standard treatment for recurrent or refractory neuroblastoma, and this is a serious disease with an unfavorable prognosis; therefore, new drugs should be promptly developed. There is also no standard established treatment for recurrent or refractory ALK-positive ALCL. Crizotinib is a selective adenosine triphosphate (ATP)-competitive small molecule oral inhibitor of the anaplastic lymphoma kinase (ALK), c-Met/hepatocyte growth factor receptor (HGFR), and ROS1 receptor tyrosine kinases and their oncogenic variants (*e.g.*, c-Met/HGFR mutations and ALK or ROS1 fusion proteins). Although clinical studies in the United States have demonstrated the tolerability and safety of crizotinib in childhood patients with malignant neoplasms [3], there have been no clinical trials in Japan investigating the safety and efficacy of crizotinib in young Japanese patients. Thus the appropriate dose for young Japanese patients is unclear. We therefore planned an investigator-initiated phase 1/2 study to examine the tolerability and safety of this drug in Japanese patients with recurrent/refractory ALK-positive ALCL or recurrent/refractory neuroblastoma (phase I) and its efficacy in Japanese patients with recurrent/refractory ALK-positive ALCL (phase II).

***Trial design.*** This is a multicenter, single-arm, open label, phase I dose-escalation study for ALCL and neuroblastoma followed by a phase II study. This study has been registered in the Clinical Trial Registry (UMIN000028075). The trial was approved by the institutional review boards of each participating institution. Since optimal treatment for recurrent/refractory ALK-positive ALCL has not been established, there is no adequate control group for this study. Therefore, the phase II is a single-arm, open label study. The number of patients with recurrent/refractory ALK-positive ALCL/neuroblastoma is limited; therefore, a multicenter study was designed. Since the upper age limit was set as 21 years old in the previous report of an overseas clinical trial (ADVL 0912), we adopted the same setting in this trial for purposes of safety.

## Endpoints

In the phase I, the primary endpoints are dose-limiting toxicity (DLT) and adverse events, while the secondary endpoints are pharmacokinetics and response. In the phase II, the primary endpoint is the response rate evaluated by the Central Evaluation Committee, while the secondary endpoints are the complete remission (CR) rate, duration of response, progression-free survival (PFS), event-free survival (EFS), and adverse events.

In the analysis set, the proportion of patients with CR or partial response as the best response is regarded as the response rate. In addition, the proportion of patients with CR as the best response is regarded as the CR rate.

The duration of response refers to a period from the first day of CR or PR evaluation until the first day of PD evaluation or day of death (earlier). The patients who continued study participation until the analysis without showing PD, those who received anti-tumor treatments other than the test treatment and stem cell transplantation, and those excluded from this study before CR or PR evaluation were censored at the last day of image assessment.

The PFS refers to a period from the start of treatment (Day 1 of Cycle 1) until the first day of PD evaluation or day of death (earlier). The patients who continued study participation until the analysis without showing PD, those who received anti-tumor treatments other than the test treatment, and those excluded from this study before CR or PR evaluation were censored at the last day of image assessment.

The EFS refers to a period from the start of treatment (Day 1 of Cycle 1) until the first day of PD evaluation, the day of toxicity-related permanent test-treatment discontinuation, the day of permanent test-treatment discontinuation based on the patient's will, the first day of a new treatment other than stem cell transplantation in the absence of PD verification, the day of secondary-cancer onset, or the day of death (earlier). The patients who continued study participation until the analysis without showing PD, those who underwent stem cell transplantation, and those excluded from this study before CR or PR evaluation, are censored at the last day of image assessment.

## Eligibility Criteria

***Inclusion criteria***

Phase I:

1) Aged 1 to 21 years upon provision of informed consent by the patient and/or their guardian.
2) Histologically confirmed recurrent/refractory

ALK-positive ALCL or recurrent/refractory neuroblastoma at the initial diagnosis or relapse.
3) Capable of providing histopathology tissues or slides of lymphoma for central review.
4) Measurable or evaluable disease.
5) A Karnofsky performance status of 50% to 100% for those aged ≥ 17 years and a Lansky performance status of 50% to 100% for those aged ≤ 16 years.
6) Full recovery from the acute toxic effects of all prior anti-cancer therapy, except for alopecia.
7) Fulfillment of the organ function requirement defined in the protocol.

Phase II:
1) Aged 1 to 21 years upon provision of informed consent by the patient and/or their guardian.
2) Histologically confirmed recurrent/refractory ALK-positive ALCL at the initial diagnosis or relapse.
3) Capable of providing histopathology tissues or slides of lymphoma for central review.
4) Measurable disease.
5) A Karnofsky performance status of 50% to 100% for those aged ≥ 17 years and a Lansky performance status of 50% to 100% for those aged ≤ 16 years.
6) Full recovery from the acute toxic effects of all prior anti-cancer therapy, except for alopecia.
7) Fulfillment of the organ function requirement defined in the protocol.

***Exclusion criteria***

Phase I/II:
1) Central nervous system disease.
2) Primary cutaneous ALCL.
3) Pregnant or breast-feeding women.
4) Reproductive potential together with refusal of an effective contraception method.
5) Any of the following concomitant medications:
   - Therapeutic corticosteroids for lymphoma
   - Other investigational drugs
   - Anticancer agents
   - CYP3A4 substrates with a narrow therapeutic index (*e.g.*, pimozide, aripiprazole, triazolam, ergotamine, or halofantrine)
   - Strong CYP3A4 inhibitors (*e.g.*, ketoconazole, itraconazole, miconazole, clarithromycin, erythromycin, ritonavir, indinavir, nelfinavir, saquinavir, amprenavir, delavirdine, nefazodone, diltiazem, verapamil, or grapefruit juice)
   - Strong CYP3A4 inducers (*e.g.*, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, tipranavir, ritonavir, or St. John's wort)
6) Current interstitial fibrosis or interstitial lung disease or a known history of either condition.
7) Current myocardial infarction or cerebrovascular disorder or a known history of either condition.
8) An uncontrolled infectious disease.
9) Potential inability to comply with the safety monitoring requirements of the study in the opinion of the investigator.
10) Inability to swallow capsules or oral solution. Patients receiving an oral solution using a feeding tube are allowed.

## Treatment Methods

***Interventions.*** Crizotinib is given orally twice a day. A cycle of therapy is considered to be 28 days. The main analysis is performed after 6 cycles in Phase I and 12 cycles in Phase II. The dose of crizotinib should be adjusted with the body surface area determined based on the height and body weight. As a rule, only in the first cycle, crizotinib should be administered with hospitalization.

***Dose.*** A phase I clinical study involving children with solid tumors in the United States (ADVL0912) [4] demonstrated the tolerability of this drug at a dose of 280 mg/m$^2$ administered twice a day. Further, there was no appearance of DLT at any dose, with the exception of brain tumor-associated DLT at 215 mg/m$^2$. Based on these data, the initial dose of this drug might have been established as 280 mg/m$^2$ in this trial, since we did not enroll brain tumor patients, but this dose exceeds the body surface area-converted value (165 mg/m$^2$) of the dose approved for Japanese adults. Therefore, the initial dose was established as 165 mg/m$^2$, in consideration of safety, and two-stage dosimetry was adopted.

The dose of crizotinib should be adjusted with the body surface area determined based on the height and body weight measured within 1 week before the start of a cycle. Even when subjects are obese or thin, correction with the standard body weight will not be performed. Even if there are changes in the height or body weight after the start of administration, dose regulation by the re-calculation of the body surface area will not be conducted during the cycle. The body surface area should be calculated using the following formula (the height is expressed as a value obtained by rounding off

the first decimal place, and the body weight is expressed as a value obtained by rounding off the second decimal place):

body surface area ($m^2$) = square root of {height (cm) x body weight (kg)/3,600} (values are rounded off to two decimal places).

1) Phase I (See Tables 1-3 for details. )

- Cohort 1 (dose level: 0): 165 mg/$m^2$/dose
- Cohort 2 (dose level: +1): 280 mg/$m^2$/dose
- Reduced dose level from +1: 215 mg/$m^2$/dose

2) Phase II

The recommended doses for the phase II established in the phase I should be adopted. (*See DLT assessment/recommendation doses for the phase II.*)

***DLT assessment/recommendation doses for the phase II.*** DLT should be evaluated from Day 1 of Cycle 1 until Day 28 in the phase I. DLT is defined as the following events possibly/probably/definitely related to this drug. The grade of DLT should be assessed according to the Common Terminology Criteria for Adverse Events v4.03.

1) Non-hematological DLT

i. All Grade 4 non-hematological toxicities.

ii. All Grade 3 non-hematological toxicities, excluding the following:
- Grade 3 nausea/vomiting persisting for < 3 days.
- Grade 3 abnormal alanine aminotransferase/aspartate aminotransferase values that recover to the baseline during a 14-day period of dose interruption and do not recur after the resumption of administration.
- Grade 3 fever/infection persisting for < 5 days.
- Grade 3 hypophosphatemia/-kalemia/-calcemia/-magnesemia responding to oral supplementation.

iii. Grade 2 allergic reactions requiring temporal dose interruption are not regarded as DLT.

iv. All Grade 2 non-hematological toxicities persisting for ≥ 7 days and requiring temporal dose interruption due to intolerance.

v. All adverse events requiring temporal dose interruption for ≥ 15 days or that recur after the resumption of drug administration.

2) Hematological DLT

Grade 4 peripheral blood neutropenia and Grade 4 thrombocytopenia.

In this trial, 3 to 6 patients will be assigned to each cohort. The coordinating investigator must assess the tolerability of the dose/administration method based on the incidence of DLT during the DLT assessment period, and evaluate whether switching to the next cohort or Phase II is possible. If none of the 3 patients in Cohort 1 experience DLT, the dose/administration method should be evaluated as tolerable, and escalation to Cohort 2 should be performed. If 1 patient experiences DLT, 3 more patients should be added to the same cohort to examine a total of 6 patients. If ≤ 1 of the 6 patients experiences DLT, the dose/administration method should be evaluated as tolerable, and escalation to Cohort 2 should be performed. However, if 2 or more patients experience DLT, the coordinating investigator must determine the tolerability of the dose/administration method and whether escalation to Cohort 2 is possible in conference with the Efficacy/

**Table 1** Dose assignment: Dose Level 0, crizotinib 165 mg/$m^2$/dose BID

| Dose assignment: Dose Level 0, crizotinib 165 mg/$m^2$/dose BID | | | | | |
|---|---|---|---|---|---|
| Body surface area ($m^2$) | Total daily dose (mg/day) | Capsule formulation (150, 200, 250 mg) | | Oral solution (25 mg/ml) | |
| | | mg/dose, PO, BID | | ml/dose, PO, BID | |
| 0.30–0.38 | 100 | – | – | 2 | 2 |
| 0.39–0.53 | 150 | – | – | 3 | 3 |
| 0.54–0.68 | 200 | – | – | 4 | 4 |
| 0.69–0.83 | 250 | – | – | 5 | 5 |
| 0.84–0.98 | 300 | 150 | 150 | 6 | 6 |
| 0.99–1.13 | 350 | 200 | 150 | 8 | 6 |
| 1.14–1.28 | 400 | 200 | 200 | 8 | 8 |
| 1.29–1.43 | 450 | 250 | 200 | 10 | 8 |
| 1.44–1.66 | 500 | 250 | 250 | 10 | 10 |
| 1.67– | 600 | 300 | 300 | 12 | 12 |

**Table 2** Dose assignment: Dose Level +1, crizotinib 280 mg/$m^2$/dose BID

| Dose assignment: Dose Level +1, crizotinib 280 mg/$m^2$/dose BID | | | | | |
|---|---|---|---|---|---|
| Body surface area ($m^2$) | Total daily dose (mg/day) | Capsule formulation (150, 200, 250 mg) | | Oral solution (25 mg/ml) | |
| | | mg/dose, PO, BID | | ml/dose, PO, BID | |
| 0.30–0.40 | 200 | – | – | 4 | 4 |
| 0.41–0.49 | 250 | – | – | 5 | 5 |
| 0.50–0.58 | 300 | 150 | 150 | 6 | 6 |
| 0.59–0.67 | 350 | 200 | 150 | 8 | 6 |
| 0.68–0.80 | 400 | 200 | 200 | 8 | 8 |
| 0.81–0.98 | 500 | 250 | 250 | 10 | 10 |
| 0.99–1.16 | 600 | 300 | 300 | 12 | 12 |
| 1.17–1.33 | 700 | 350 | 350 | 14 | 14 |
| 1.34–1.51 | 800 | 400 | 400 | 16 | 16 |
| 1.52–1.69 | 900 | 450 | 450 | 18 | 18 |
| 1.70–1.87 | 1,000 | 500 | 500 | 20 | 20 |
| 1.88– | 1,100 | 550 | 550 | 22 | 22 |

Safety Evaluation Committee. If none of the 3 patients in Cohort 2 experience DLT, the dose/administration method should be evaluated as tolerable, and Dose level+1 should be defined as the recommended dose for Phase II. If 1 of the 3 patients in Cohort 2 experiences DLT during the DLT assessment period, 3 patients should be added to the same cohort to examine a total of 6 patients. If ≤1 patient experiences DLT in Cohort 2, Dose level+1 should be defined as a recommendation dose for Phase II. When ≥2 patients experience DLT in Cohort 2, Dose level 0 should be defined as a recommended dose for the Phase II, provided that 6 patients comprise Cohort 1. When 2 or more patients experience DLT in Cohort 2 and 3 patients comprise Cohort 1, 3 patients should be added to Cohort 1 and Dose level 0 should be defined as the recommended dose for Phase II, provided that ≤1 of the 6 patients experiences DLT. If 2 or more patients experience DLT in Cohort 2 and 2 or more patients experience DLT in Cohort 1, to which 3 patients were added, the coordinating investigator must determine the tolerability of the dose/administration method in conference with the Efficacy/Safety Evaluation Committee. For switching to Phase II, data on the tolerability/safety from Cohorts 1 and 2 of this trial must be comprehensively reviewed in cooperation with the Efficacy/Safety Evaluation Committee.

***Efficacy assessment.***

1. Neuroblastoma

In this trial, the modified Response Evaluation Criteria in Solid Tumors version 1.1 [5] will be used when evaluating the treatment response. For evaluable lesions, the responses of MIBG-positive lesions must be evaluated using the Curie scale [6], and others should be evaluated in the same manner as at baseline.

2. ALCL

In this trial, the Revised Response Criteria for Malignant Lymphoma [7] will be used when evaluating the treatment response.

**Table 3** Dose assignment: Reduced dose Level from+1, crizotinib 215 mg/m$^2$/dose BID

| Dose assignment: Reduced Dose Level from+1, crizotinib 215 mg/m$^2$/dose BID | | | | | |
|---|---|---|---|---|---|
| Body surface area (m$^2$) | Total daily dose (mg/day) | Capsule formulation (150, 200, 250 mg) | | Oral solution (25 mg/ml) | |
| | | mg/dose, PO, BID | | ml/dose, PO, BID | |
| 0.30–0.40 | 150 | – | – | 3 | 3 |
| 0.41–0.52 | 200 | – | – | 4 | 4 |
| 0.53–0.63 | 250 | – | – | 5 | 5 |
| 0.64–0.80 | 300 | 150 | 150 | 6 | 6 |
| 0.81–0.98 | 350 | 200 | 150 | 8 | 6 |
| 0.99–1.16 | 400 | 200 | 200 | 8 | 8 |
| 1.17–1.33 | 500 | 250 | 250 | 10 | 10 |
| 1.34–1.51 | 600 | 300 | 300 | 12 | 12 |
| 1.52–1.69 | 650 | 350 | 300 | 14 | 12 |
| 1.70–1.87 | 700 | 350 | 350 | 14 | 14 |
| 1.88– | 800 | 400 | 400 | 16 | 16 |

## Statistical Considerations

***Sample size.*** The scheduled number of patients to be registered is 6-12 in the phase I. The number of patients per cohort was established as 3 to 6 with reference to the "Guidelines for the clinical assessment of antitumor drugs". <Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. https://www.pmda.go.jp/files/000206740.pdf (In Japanese). (Accessed October 4, 2017)>.

The scheduled number of patients to be registered is 11 in the phase II. 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 ALCL. < National Cancer Center for Cancer Control and Information Services. http://ganjoho.jp/child/cancer/neuroblastoma/index.html (In Japanese). (Accessed October 4, 2017).> In addition, the PROPEL trial for recurrent or refractory peripheral T-cell lymphoma showed a 35% (6/17 cases) objective response rate for ALCL (both ALK-positive and -negative) patients using Pralatrexate [8]. Referencing these reports, the threshold response rate for purposes of the present trial was determined as 50%. Crizotinib showed a response rate of 89% (8/9 cases) [4] in a trial of pediatric recurrent or refractory ALCL patients. 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 [9]. Other studies have reported response rates of 80% or higher [10] < National Cancer Center for Cancer Control and Information Services. http://ganjoho.ncc.go.jp/public/index.html (In Japanese). (Accessed October 4, 2017.)>, <National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. (Accessed July 19, 2017. )>. We expected that our drug would elicit response rates comparable to these drugs, and thus set the expected response rate as 85%. Since a

statistical power of 78% could be obtained using 11 cases with an alpha level of 0.05 (one-tailed), the sample size was 11.

***Statistical analysis.***

*Analysis set*

The Full Analysis Set (FAS) consists of patients registered in this trial and treated with the investigational drug. However, cases where it has been found that there is a Good Clinical Practice (GCP) violation after registration, and cases which are found to be ineligible after registration are excluded. In the FAS, a population without serious protocol violations, meeting the protocol regulations, is regarded as a Per Protocol Set. In this study, the FAS is the primary analysis set of efficacy. Patients registered in this trial and treated with the investigational drug at least once are regarded as the safety analysis set.

Patients to be analyzed for DLT are defined as follows:

- Patients with 1 or more episode of DLT during the DLT assessment period (from Day 1 of Cycle 1 until the time of administration on Day 1 of Cycle 2).

  or

- Those to whom a specific dose (≥75%) of crizotinib was administered in Cycle 1 and in whom observation during the DLT assessment period was completed.

Patients, registered in this trial, with pharmacokinetic data at least one are regarded as a population to be analyzed for the pharmacokinetics.

The response rate, the CR rate and their 90% confidence intervals will be calculated.

To estimate the duration of response, PFS, and EFS, the Kaplan-Meier method will be used. The 90% confidence interval of these values will be calculated using Greenwood's formula. The incidence of DLT will be calculated with respect to the dose levels. The incidence of adverse events/reactions to the investigational drug will be calculated with respect to the events, grade, and severity.

## Discussion

This is an exploratory study pursuant to the performance of a multinational study. The objectives of this study are to evaluate the tolerability and safety of this drug in Japanese patients with recurrent/refractory ALK-positive ALCL or recurrent/refractory neuroblastoma (phase I) and its efficacy in Japanese patients with recurrent/refractory ALK-positive ALCL (phase II).

Competing interests. Investigational drugs will be provided by Pfizer Inc. free of charge.

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