Non-Interventional Study Protocol
B7461038

Retrospective, Multicenter, Observational Study to Evaluate Clinical Real World Outcomes of Lorlatinib after Alectinib in *ALK*-positive NSCLC Japanese Patients

Statistical Analysis Plan
(SAP)

Version: 3

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1 AMENDMENTS FROM PREVIOUS VERSIONS

This statistical analysis plan (SAP) for Study B7461038 is based on the protocol dated 15APR2021.

Table 1 Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 08APR2021	Version 1 19MAR2021	NA	NA
2 08SEP2021	Version 2 15APR2021	Incorporate amended content of the protocol	• Add the observation period in Section 2.1 • Clarify that the time to failure of subsequent other treatment will be summarized by each line of lorlatinib therapy in Section 7.2.1
3 12MAY2022	Version 2 15APR2021	Add the ad-hoc analysis following advisory board meeting results	• Add time to last treatment failure in Section 5.1.4. • Add the analysis method for time to last treatment failure in Section 7.

2 INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7461038. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1 STUDY DESIGN

This study is a post-approval, company-sponsored, observational study and a multicenter, non-interventional, retrospective, chart review of patients with anaplastic lymphoma kinase (ALK) positive (+) non-small cell lung cancer (NSCLC) patients treated using lorlatinib as the second-line or later therapy in Japan after failure of alectinib treatment as the first-line therapy from 20th November 2018.

All decisions regarding clinical management and treatment of participating patients were made by an investigator as a part of standard care in real-world clinical setting and were not contingent upon patient's participation in the study. Data will be collected if available per study site. Patients in this study are those who started treatment with lorlatinib from 1st May 2019 to 31st December 2020 in clinical practice.

The observation period will be from the start date of alectinib to 15th October 2021.

2.1.1 Study Population

The study population includes Japanese patients with *ALK*+ NSCLC who received lorlatinib as the second-line or later therapy after failure of alectinib treatment as the first-line therapy from 20th November 2018.

The expected number of patients will be approximately 50 patients treated with lorlatinib in total. The number of patients who received lorlatinib as the second-line therapy will be 30 patients, but this should be considered flexible.

2.1.2 Data Source

As this is a retrospective study, all data will be collected from medical records at the participating study site.

2.1.3 Treatment/Cohort Labels

Patients receiving lorlatinib as the second-line and the third-line therapy may be labeled, respectively, "2L" and "3L" for the purpose of reporting if necessary.

2.2 STUDY OBJECTIVES

The primary objective is to describe the demographic characteristics of patients with *ALK*+ NSCLC patients treated with lorlatinib as the second-line or later therapy after failure of alectinib as the first-line therapy in a real-world clinical setting, clinical usage and observed effectiveness of lorlatinib.

The secondary objectives are as follows:

- To describe treatments received including alectinib as the first-line therapy prior to lorlatinib
- To describe treatment pattern after lorlatinib as the second-line or later therapy

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

Null and alternative hypotheses in variable selections described in Section 7.2.1 are as follows:

H_0: a regression parameter related to an interesting variable is zero, and

H_1: a regression parameter related to an interesting variable is not zero.

3.2 STATISTICAL DECISION RULES

Two-sided 5% significance level will be used in variable selections described in Section 7.2.1.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET

A full analysis set (FAS) will consist of patients who meet the inclusion criteria and do not meet the exclusion criteria.

INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Histologically or cytologically confirmed NSCLC, with any TNM stage.

2. Confirmed *ALK* gene rearrangement by any validated tests.

3. Confirmed the treatment with alectinib in the first-line setting as systemic therapy in a medical record.

4. Confirmed the start of treatment with lorlatinib as the second-line or later therapy from 1st May 2019 to 31st December 2020.

5. Availability of clinical information from a medical record.

6. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

   (1) Written consent is not required for patients who were transferred to a hospital, and registration with verbal consent is acceptable.

   (2) Opt-out enrollment is allowed for patients who have already died.

EXCLUSION CRITERIA

Patients meeting the criterion below will not be included in the study:

1. Participating on any clinical trials of which final results has not yet been reported during the study period.

4.2 SUBGROUPS

A subgroup analysis will be considered, including but not limited to subgroup by the line of therapy with regard to lorlatinib.

5 ENDPOINTS AND COVARIATES

5.1 EFFICACY/EFFECTIVENESS ENDPOINTS

5.1.1 Time to Treatment Failure

Time to treatment failure (TTF) is the time from the first date of interest treatment (either alectinib or lorlatinib) to the date of any-cause treatment discontinuation including disease progression, treatment toxicity and death.

5.1.2 Combined TTF

Combined TTF is defined as sum of the time from the first date of alectinib to the date of any-cause alectinib discontinuation, the time from the first date of lorlatinib to the date of lorlatinib discontinuation and the time from the first date of the other subsequent treatment to the date of other subsequent treatment discontinuation.

5.1.3 Objective Response

Objective response (OR) based on an investigator assessment is defined as complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 from the first date of interest treatment (either alectinib or lorlatinib) until the date of treatment discontinuation. Repeat assessments were not required to confirm CR and PR due to a nature of real-world clinical setting.

5.1.4 Time to Last Treatment Failure

Time to last treatment failure (TLTF) is the time from the first date of alectinib to the date of any-cause treatment discontinuation including disease progression, treatment toxicity and death in the last treatment.

5.2 SAFETY ENDPOINTS

There are no safety endpoints in this study.

5.3 OTHER ENDPOINTS

5.3.1 Baseline Characteristics

The following patient characteristics at baseline (the first date of alectinib treatment) and/or the first date of lorlatinib treatment will be collected.

- Age (continuous and categorical [<65 years, ≥65 years])
- Sex
- Weight
- Height
- Body mass index (BMI) (continuous and categorical [<18.5 kg/m^2, 18.5 -<25 kg/m^2, ≥25 kg/m^2])
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Histological type
- Number and site of metastases

- Complications/medical history (related to history of treatment for *ALK*+ NSCLC)
- Smoking history
- Brinkman index
- ALK test result including ALK testing method and the date of test result/diagnosis
- Number of treatment regimens administered to the target disease prior to the start of lorlatinib treatment

5.3.2 Reason for Discontinuation

Reason for discontinuation of each line will be collected.

5.4 COVARIATES

Potential covariates are, but not limited to, the followings:

- baseline characteristics, and
- reason for discontinuation of lorlatinib treatment.

6 HANDLING OF MISSING VALUES

No imputation for missing values will be performed.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

All analyses described in this section will be conducted using the FAS.

7.1 STATISTICAL METHODS

Continuous variables will be summarized using the number of patients, mean, standard deviation (SD), interquartile range (IQR), minimum, median and maximum. Categorical variables will be summarized using the frequency and percentage. Time-to-event endpoint will be summarized using the Kaplan-Meier method. A confidence interval (CI) of a specific percentile will be derived by the Brookmeyer and Crowley method. A CI of survival probability will be estimated using Greenwood's formula. Cox proportional hazards model may be performed to examine the association between time-to-event endpoint and covariates if data allows.

7.2 STATISTICAL ANALYSES

7.2.1 Time to Treatment Failure

TTF will be summarized using the Kaplan-Meier method with the Kaplan-Meier plot. Percentiles of survival curve (25%, median and 75%) with their 2-sided 95% CIs will be estimated. Yearly rates with their 2-sided 95% CI will also be provided. If patients

continue a treatment at the date of data entry, TTF will be censored at the available last date of treatment or the study end period.

TTF will be evaluated by each treatment below:

- TTF of alectinib as the first-line therapy,
- TTF of lorlatinib as the second-line therapy,
- TTF of lorlatinib as the third-line or later therapy,
- TTF of lorlatinib across the line of therapy, and
- TTF of subsequent other treatment (e.g., chemotherapy and other TKIs) by each line of lorlatinib therapy

If data allows, Cox proportional hazards model may be performed. Variable selection in Cox proportional hazard model may be performed. Candidates for covariate will be selected by an univariate selection at first. If more than 2 variables are selected in the univariate selection, a stepwise selection will be performed using candidates for covariate after the univariate selection.

7.2.2 Combined TTF

Combined TTF will be summarized using the Kaplan-Meier method. Percentiles of survival curve (25%, median and 75%) with their 2-sided 95% CIs will be estimated. Yearly rates with their 2-sided 95% CI will also be provided. Censor rule is the same as that described in Section 7.2.1.

7.2.3 Objective Response

A best overall response (BOR) will be assessed based on reported overall responses at different evaluation time points from each initiation of treatment therapy until discontinuation. An objective response rate (ORR) is defined as the percentage of patients with the BOR of either CR or PR according to RECIST v1.1. Patients without CR or PR will be considered as non-responders.

The ORR will be estimated by dividing the number of patients with BOR of either CR or PR by the number of patients in the FAS. The corresponding exact 2-sided 95% CIs will be provided.

The ORR will be evaluated by each treatment below:

- ORR of alectinib as the first-line therapy,
- ORR of lorlatinib as the second-line therapy, and

- ORR of lorlatinib as the third-line or later therapy.

7.2.4 Time to Last Treatment Failure

TLTF will be summarized using the Kaplan-Meier method. Percentiles of survival curve (25%, median and 75%) with their 2-sided 95% CIs will be estimated. Yearly rates with their 2-sided 95% CI will also be provided. Censor rule is the same as that described in Section 7.2.1.

7.2.5 Baseline Characteristics

Baseline characteristics will be summarized descriptively. Similarly, patient's characteristics at the start of lorlatinib treatment will be summarized descriptively.

The third-line or later regimen data will be listed if the lorlatinib treatment is the second-line therapy. Similarly, the second-line regimen data will be listed if the lorlatinib treatment is the third-line or later therapy.

7.2.6 Reason for Discontinuation

Reason for discontinuation will be summarized.