

**Official Title:** RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS CRIZOTINIB IN ASIAN PATIENTS WITH TREATMENT-NAIVE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

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**STATISTICAL ANALYSIS PLAN**

**TITLE:** RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL  
STUDY OF ALECTINIB VERSUS CRIZOTINIB IN ASIAN  
PATIENTS WITH TREATMENT-NAIVE ANAPLASTIC  
LYMPHOMA KINASE-POSITIVE ADVANCED  
NON-SMALL CELL LUNG CANCER

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**STATISTICAL ANALYSIS PLAN APPROVAL**

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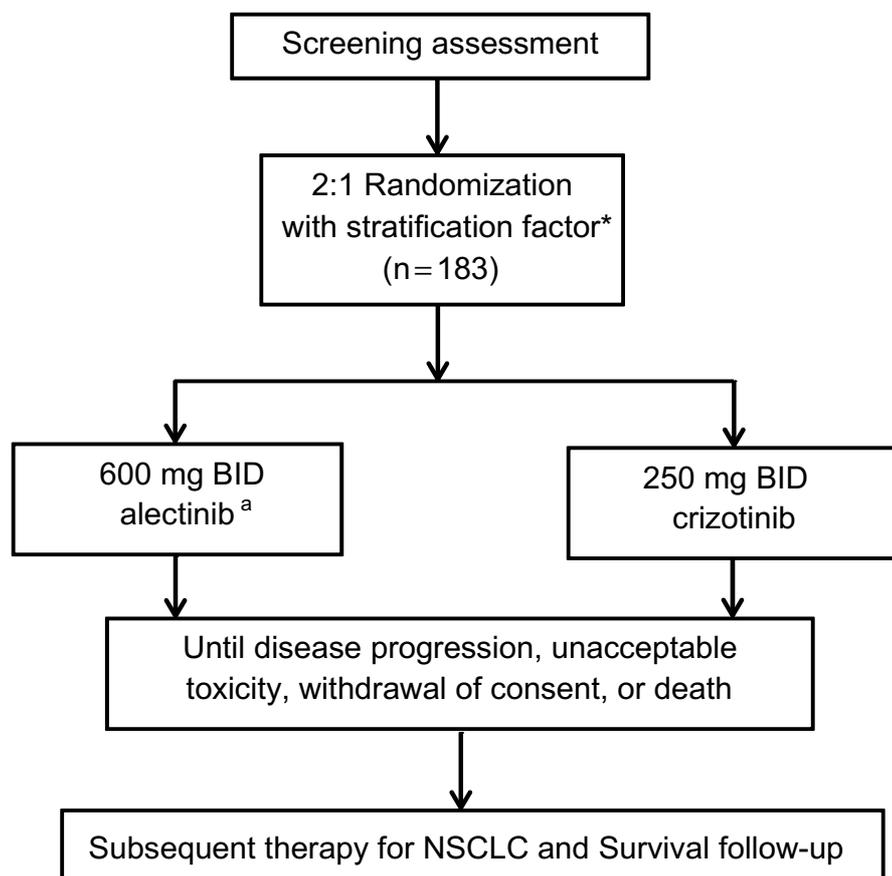
## 1. BACKGROUND

Alectinib is a small molecule that is highly selective and a potent inhibitor of anaplastic lymphoma kinase (ALK). Alectinib is currently being developed for the treatment of patients who have ALK-positive non-small cell lung cancer (NSCLC).

## 2. STUDY DESIGN

This is a randomized, active-controlled, multicenter, Phase III, open-label study in patients with treatment-naïve ALK-positive advanced NSCLC. All patients are required to provide pretreatment tumor tissue to confirm the presence of ALK rearrangement (by immunohistochemistry [IHC] test). Patients will be randomized 2:1 into one of the two treatment arms to receive either alectinib or crizotinib.

**Figure 1 Summary of Study Design**



\*: ECOG PS at baseline (0/1 vs. 2) and CNS metastases at baseline by investigator (yes vs. no)

<sup>a</sup> Frequent blood sampling will be performed in a subset of 20 Chinese patients enrolled to receive alectinib treatment to facilitate the characterization of alectinib pharmacokinetics.

## **2.1 PROTOCOL SYNOPSIS**

The Protocol Synopsis is in Appendix 1.

## **2.2 DETERMINATION OF SAMPLE SIZE**

The primary endpoint of investigator-assessed PFS was used to determine the sample size of the study. The primary objective of the study is to reliably determine whether the benefit (in terms of investigator-assessed PFS) of administering alectinib in this study is consistent with the benefit observed in the global pivotal study ALEX (BO28984). Consistency is defined as maintaining  $\geq 50\%$  of risk reduction from ALEX. That is, assuming the estimated PFS HR for study ALEX is 0.65 (i.e., 35% risk reduction), if the point estimate of HR from study YO29449 is less than 0.83, then the study's primary objective to demonstrate consistency is met.

Based on the assumption of PFS HR = 0.65, a total of 97 PFS events are required to achieve approximately 87% probability to show consistency. In this study, 183 patients will be enrolled in a 2:1 randomization allocation. Based on the assumption that the median PFS is 10.9 months for the crizotinib arm and 16.8 months for the alectinib arm (HR = 0.65) and patients are to be enrolled over approximately 13 months; the primary PFS analysis is expected to occur approximately 23 months after the first patient is enrolled.

No interim analysis for efficacy or futility is planned.

The first survival analysis will be performed together with the primary PFS analysis. The final survival analysis will be performed once approximately 55% of patients have died. The median OS in the crizotinib arm is assumed to be 24 months, and the expected median OS in the alectinib treatment arm is 30 months, equating to an HR of 0.8. The survival follow-up analysis is expected to occur approximately 41 months after the first patient has been enrolled.

## **2.3 ANALYSIS TIMING**

The number of PFS events required to show consistency depends on the HR observed in ALEX. The required number of PFS events to achieve approximate 87% probability to meet consistency criteria is listed as below.

**Table 1 Required Number of PFS Events to Show Consistency**

HR Observed in ALEX	Consistency Criteria (HR)	No. of PFS Events Required
0.65	0.83	97
0.6	0.8	70
0.55	0.78	50
0.5	0.75	35

HR = hazard ratio; PFS = progression-free survival.

The primary analysis of PFS will occur when the required number of PFS events is expected approximately 22 months after the first patient has been enrolled. If number of PFS events is not enough for the estimation of median PFS, an updated PFS analysis will be done when approximately 55% of patients have had PFS events.

The first survival analysis will be performed together with the primary PFS analysis. The final survival analysis will be performed when approximately 55% patients have died.

The study will formally end when the survival follow-up analysis is complete and the last patient has permanently discontinued treatment with alectinib and performed the Study Completion or Study Treatment Discontinuation assessments (Post-Treatment Visit).

### **3. STUDY CONDUCT**

#### **3.1 RANDOMIZATION ISSUES**

Patients will be randomly assigned in a 2:1 allocation ratio to one of the two treatment arms to receive either alectinib or crizotinib via a block stratified randomization procedure.

Randomization will guard against systematic selection bias and should ensure the comparability of treatment groups. To assist balance in important prognostic factors, randomization will be stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS; 0/1 vs. 2), and CNS metastases at baseline (yes vs. no).

#### **3.2 INDEPENDENT REVIEW FACILITY**

An independent imaging group will be used to evaluate tumor assessments for determination of progression and response rate according to Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 for the secondary efficacy endpoint of PFS analysis. Imaging studies (computed tomography [CT]/magnetic resonance imaging [MRI]/bone scans) will be acquired according to a standard protocol and will be forwarded to the independent reviewers. In addition, relevant cytologic and medical data (e.g., relevant cytology reports documenting malignant pleural effusions, bone marrow aspirations, cerebral spinal fluid, CNS symptoms, corticosteroid use, etc.) may be forwarded, if available, to the independent reviewers to aid with assessment of progressive disease (PD) and response. Investigator tumor assessments will not be reconciled with the Independent Review Committee (IRC) tumor assessments. Further

details are included in the IRC Charter. Details of imaging handling procedures are also described in a separate laboratory manual.

For evaluation of the CNS endpoints, the IRC will perform an assessment of scans based on RECIST v1.1 and Response Assessment in Neuro-Oncology (RANO) criteria. More details are given in the IRC charter.

#### **4. STATISTICAL METHODS**

The analyses outlined in this Statistical Analysis Plan (SAP) supersede those specified in the protocol for the purpose of a regulatory filing.

#### **4.1 ANALYSIS POPULATIONS**

##### **4.1.1 Intent-To-Treat Population**

The primary analysis population for efficacy is the intent-to-treat (ITT) population, defined as all randomized patients. Patients will be assigned to the treatment group to which they were randomized.

##### **4.1.2 Safety Population**

The primary analysis population for safety is the Safety Population, defined as all patients who received at least one dose of study medication. Patients will be assigned to treatment groups as treated, and all patients who received any dose of alectinib will be included in the alectinib treatment arm.

##### **4.1.3 Pharmacokinetic Evaluable Population**

The PK Evaluable Population is defined as all patients who received any dose of alectinib and who had at least one quantifiable post-baseline PK sample available.

The Frequent PK Evaluable Population is defined as the patients who underwent frequent PK sampling at Visit 0 (Baseline) on Day 1 and Visit 2 (Week 4) in the PK Evaluable Population and provided sufficient PK timepoints to perform the NCA PK analysis.

#### **4.2 ANALYSIS OF STUDY CONDUCT**

Study enrollment, patient disposition, reasons for discontinuation from the study treatment, and reason for study termination will be summarized for all patients in the ITT population.

Protocol deviations, including deviations of inclusion/exclusion criteria and deviations during study conduct will be reported and summarized.

#### **4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY**

Demographic, baseline disease characteristics, and lung cancer history, including prior brain radiation, will be compared descriptively between both treatment arms for the ITT population. Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive baseline summaries of discrete data will present the category counts as frequencies and percentages.

A summary of concordance of stratification factors determined by electronic Case Report Form (eCRF) versus interactive voice or Web-based response system (IxRS) will also be reported.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of study medication.

Previous and concomitant cancer therapy will also be summarized, including radiotherapy and surgery, as well as subsequent anti-cancer therapy. Previous and concurrent diseases and medications will also be summarized.

## **4.4 EFFICACY ANALYSIS**

### **4.4.1 Primary Efficacy Endpoint**

PFS is defined as the time from date of randomization to the date of first documented disease progression or death, whichever occurs first. The primary endpoint of PFS will be determined on the basis of investigator assessment of progression using RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the last tumor assessment date either during study treatment or during follow-up. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

Patients who discontinue treatment prior to disease progression (e.g., due to toxicity) will continue in the study and will be followed until disease progression and for OS regardless of whether they subsequently receive anti-cancer therapy.

The Kaplan-Meier method will be used to estimate the median PFS for each treatment arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. A stratified Cox proportional hazard regression model will be used including treatment in order to provide an estimate of the treatment effect expressed as an HR (alectinib vs. crizotinib), as well as a 95% CI. The stratification factors are the randomization stratification factors: ECOG PS (0/1 vs. 2) as recorded on the eCRF, and CNS metastases at baseline (yes vs. no) as assessed by IRC unless otherwise specified. The stratification factors will be included in the analysis as long as an individual stratum includes > 10% of the ITT population. Point estimate of the adjusted HR will be compared with the consistency threshold (observed HR of 0.47 in study ALEX).

The treatment comparison of PFS will also be assessed based on a stratified log-rank test to demonstrate the strength of consistent trend. However, p-values will be for descriptive purpose. Results from an unstratified log-rank test will also be presented as a supportive analysis.

### **4.4.2 Secondary Efficacy Endpoints**

All secondary efficacy endpoints will be analyzed in the ITT population unless otherwise specified. The stratification factors will be the same as for the analysis of the primary efficacy endpoint. Results from unstratified tests will also be presented as supportive analyses.

## **PFS by IRC**

An analysis of PFS on the basis of the IRC assessments will be performed using the same methodology as specified for PFS on the basis of investigator assessment.

A concordance analysis between the IRC-determined and the investigator-determined PD status (yes vs. no) will be provided by treatment arm together with a summary of agreement between the IRC-determined and the investigator-determined PD dates. The early discrepancy rate (investigator assessed prior to IRC) and the late discrepancy rate (investigator assessed after IRC) will be calculated for each treatment arm and the differential discordance calculated as the rate on the alectinib arm minus the rate on the crizotinib arm ([Amit et al. 2011](#)).

## **Time to CNS Progression by IRC RECIST Criteria**

Time to CNS progression is defined as the time from randomization until first radiographic evidence of CNS progression by independent review. An independent central radiological review will be performed for all patients, and the analysis of CNS progression will be based on the data from the independent review. All ITT patients will be included in the analysis regardless of their baseline status of CNS metastases. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of preexisting baseline CNS lesions. On the basis of RECIST v1.1, this is defined as a new post-baseline CNS/brain lesion(s) and/or an increase of  $\geq 20\%$  in the sum of longest diameters of the measurable baseline CNS lesions compared with nadir and/or unequivocal progression of non-measurable baseline CNS lesions.

Non-CNS progression without prior CNS progression and death without prior CNS or non-CNS progression are regarded as competing risks for CNS Progression. In order to account for the competing risks inherent in the comparison of CNS progression between alectinib and crizotinib, a stratified two-sided log-rank test will be computed on the basis of a cause-specific hazard function. Cause-specific hazard ratios and corresponding 95% CI will be derived from stratified cause-specific Cox proportional regression models. Results from unstratified tests will also be presented as supportive analyses.

The probability of CNS progression, non-CNS progression, and death by treatment group with 95% CIs will each be estimated using cumulative incidence functions. Gray's test to compare the risk of CNS progression between alectinib and crizotinib will also be performed as a supportive analysis.

Similar analyses of CNS progression based on IRC RANO criteria will be performed.

## **Objective Response Rate**

ORR, on the basis of investigator assessment, is defined as the percentage of ITT patients with measurable disease at baseline who attain a complete response (CR) or partial response (PR). Per RECIST v1.1, confirmation of objective response is not required for this secondary endpoint. Patients without a post-baseline tumor assessment will be considered non-responders, as will patients with a best overall response of stable disease (SD), PD, or not evaluable (NE).

An estimate of ORR and its two-sided 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. Response rates in the treatment groups will be compared using a stratified Mantel-Haenszel test, including the randomization stratification factors. Results from unstratified tests will also be presented as supportive analyses. The difference in ORR between the two treatment arms will be presented together with a two-sided 95% CI on the basis of a normal approximation to the binomial distribution.

ORR by IRC will be analyzed similarly as a supportive analysis in the population of patients identified to have measurable disease at baseline according to the IRC.

### **Duration of Response**

For patients with measurable disease at baseline who have experienced an objective response (CR or PR) during the study as assessed by the investigator, duration of response (DOR) is defined as the duration from the first tumor assessment that supports the patient's objective response (CR or PR, whichever is first recorded) to first documented disease progression or death due to any causes, whichever occurred first. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date. DOR will be estimated using Kaplan-Meier methodology and an HR and its 95% CI on the basis of a Cox proportional regression model with stratification factors will be calculated.

### **Overall Survival**

OS is defined as the time from the date of randomization to the date of death due to any cause. Patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Patients who do not have post-baseline information will be censored at the date of randomization. OS will be analyzed using the same methodology as specified for the primary endpoint. A survival follow-up analysis will be performed based on more mature data.

### **CNS Objective Response Rate (CORR) according to RECIST v1.1 and RANO criteria by IRC**

CORR will be summarized by treatment group in the subgroup of patients in the ITT population who have measurable CNS lesions at baseline as determined by the IRC. These summaries will be provided for both RECIST v1.1 and RANO. CNS responses according to RECIST v1.1 do not have to be confirmed, whereas confirmation is incorporated into the RANO criteria.

CORR will be summarized by treatment group in the subgroup of patients in the ITT population who have measurable and non-measurable CNS lesions at baseline as determined by the IRC. For this analysis, patients with non-measurable CNS disease at baseline by IRC who experience a CR in CNS lesions will be included as responders.

In addition, a subgroup analysis of CORR will be performed according to prior brain radiation status (yes vs. no) for the two analysis populations above if applicable, i.e. at least 10% patients had prior brain radiation .

### **CNS Duration of Response (CDOR) according to RECIST v1.1 and RANO criteria by IRC**

This analysis will be performed including all patients in the ITT population who have measurable CNS lesions at baseline as determined by the IRC who had a CNS response (CR or PR). CDOR is time from CNS response to CNS PD by IRC.

#### **4.4.3 Sensitivity Analyses**

A sensitivity analysis will be performed on the primary endpoint of PFS with the following changes from the primary analysis:

- Censor patients at the last adequate tumor assessment prior to the start of non-protocol-specified anti-cancer therapy received prior to observing progression.

#### **4.4.4 Subgroup Analyses**

PFS by investigator and IRC assessments will be presented separately for important subgroups including age (< 65, ≥ 65), sex, smoking status, and baseline prognostic characteristics including baseline ECOG PS, CNS metastases at baseline as determined by IRC, and prior brain radiation (in patients with CNS metastases at baseline). The HR including a 95% CI will be presented separately for each level of the categorical variables.

### **4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES**

Frequent PK analyses will be based on the Frequent PK Evaluable Population. All the other PK analyses will be based on the PK Evaluable Population.

Standard non-compartmental analysis (NCA) will be conducted for PK data collected from patients participating in serial/intensive PK collections for relevant analytes. PK parameters, including but not limited to area under the concentration-time curve (AUC), maximum concentration (C<sub>max</sub>), and time to maximum concentration (t<sub>max</sub>), will be calculated on the basis of the available data as appropriate and where data allow. Additional PK parameters may be calculated as deemed appropriate.

Individual and mean plasma concentrations at each sampling timepoint and/or PK parameters for alectinib and metabolite(s) will be listed, as appropriate. Summary statistics (e.g., means, standard deviation, coefficient of variation percent, geometric means, medians, and ranges) for plasma concentrations and/or PK parameters for alectinib and metabolite(s) will be presented by nominal collection times (plasma concentrations only), as appropriate. Additional plots or summary statistics may be constructed or calculated, as appropriate.

The results of frequent PK analyses as well as other PK analyses based on the PK Evaluable Population have already been reported in the separate PK CSR and will not be included in this primary CSR.

Non-linear mixed-effects modeling (with software NONMEM) will be used to analyze the sparse and/or serial/intensive plasma concentration-time data for alectinib. The PK data from this study may be pooled with data from other studies. Population and individual PK parameters will be estimated and the influence of various covariates (such as age, sex, and body weight) on these parameters will be investigated. Exploratory analyses will be conducted to investigate the relationship between alectinib PK exposure and efficacy/safety parameters.

Results of the mixed-effects modeling and exploratory analyses will be reported in a document separate from the CSR.

## **4.6 SAFETY ANALYSES**

All safety analyses will be performed on the Safety Population; that is, all patients who receive any dose of study medication (see Section 4.1.2) by treatment arm, and as such, all patients who received any dose of alectinib will be included in the alectinib treatment arm.

### **4.6.1 Exposure of Study Medication**

Study treatment (alectinib and crizotinib) exposure, including treatment duration, dose intensity, number of doses, missed dose, and total cumulative dose will be summarized with descriptive statistics.

### **4.6.2 Adverse Events**

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). All adverse events occurring during or after the first study treatment will be listed and summarized by mapped term, appropriate thesaurus level and NCI CTCAE grade.

Summary tables of the following will be provided:

- All adverse events
- Serious adverse events
- Severe adverse events (Grade 3 or higher)
- Adverse events leading to study treatment discontinuation
- Adverse events leading to dose reduction
- Adverse events leading to dose interruption
- Treatment-related adverse events
- Adverse events leading to death
- Adverse events by highest NCI CTCAE grade
- Selected adverse events relating to ALK inhibitors and/or the tyrosine kinase inhibitor class and alectinib data

A summary table of common adverse events, that is, those occurring in at least 10% of patients, will be provided.

A summary table of adverse events with a difference in incidence of 5% of patients between treatment arms will be provided.

Selected adverse events are defined as follows and are subject to change for any updates at program level:

#### **Gastrointestinal (GI) tract AEs**

- MedDRA SOC: *GI disorders*
- Stomatitis
  - MedDRA PTs: stomatitis and mouth ulceration
- Muscular AEs and creatine phosphokinase (CPK) elevations
  - MedDRA HLGTS: Musculoskeletal and connective tissue disorders not elsewhere classified (NEC), Enzyme investigations NEC, and Muscle disorders
  - Myalgia
    - MedDRA PTs: myalgia and musculoskeletal pain
- Hepatocellular and cholestatic damage, liver AEs, and abnormal liver laboratory tests
  - MedDRA SMQ: *Drug related hepatic disorders, narrow*
  - Bilirubin increased
    - MedDRA PT: Blood Bilirubin Increased, Hyperbilirubinaemia, Bilirubin Conjugated Increased
- Skin disorders
  - MedDRA SOC: *Skin and subcutaneous tissue disorders*
  - Rash
    - MedDRA PTs: rash, rash maculo-papular, dermatitis acneiform, erythema, rash generalised, rash macular, rash papular, exfoliative rash, and rash pruritic
  - Photosensitivity
    - MedDRA PT: photosensitivity reaction
- Vision disorders
  - MedDRA SOC: *Eye disorders*
- Abnormal kidney function AEs
  - MedDRA SMQ: *Acute renal failure, narrow*
  - MedDRA SOC: *Renal and urinary disorders*
  - MedDRA HLGTS: Renal and urinary tract investigations and urinalyses
- Hematologic abnormalities
  - MedDRA SMQ: *Haematopoietic cytopenias, wide*
  - Anemia
    - MedDRA PTs: anaemia and haemoglobin decreased
- Interstitial lung disease (ILD)
  - MedDRA SMQ: Interstitial Lung Disease, narrow
  - Interstitial lung disease and pneumonitis

MedDRA PTs: ILD and pneumonitis

- QT interval prolongation
  - MedDRA SMQ: *Torsade de Pointes QT Prolongation, narrow*
- Edema
  - MedDRA PTs: oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema, and localised oedema
- Bradycardia
  - MedDRA PTs: bradycardia and sinus bradycardia
- Dysgeusia
  - MedDRA PTs: dysgeusia and hypogeusia
- Weight increased
  - MedDRA PT: weight increased

Rates of each selected adverse event group will be summarized including incidence of all grades events, Grade 3 or higher events, serious adverse events, and adverse events leading to treatment discontinuation or dose modification.

Multiple occurrences of the same event will be counted once at the maximum severity.

All deaths and causes of death will be summarized.

Adverse events by sex, age (< 65 years vs. ≥ 65 years), and CNS metastases at baseline (yes vs. no) will be presented.

#### **4.6.3 Laboratory Data**

Laboratory data will be classified according to NCI CTCAE v4.0 and will be summarized descriptively over time, including change from baseline. Highest NCI CTCAE grade after baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as ALT or AST increases above 3-fold the ULN with concomitant total bilirubin increases above 2-fold the ULN.

#### **4.6.4 Vital Signs**

Vital signs will be summarized descriptively by treatment group over time, including change from baseline. Pulse rate and ECOG PS will also be presented as shift tables from baseline to the worst value and best value during post-baseline study period by treatment group.

#### **4.6.5 Electrocardiograms**

The following parameters are captured on the eCRF and will be summarized by treatment group over time: heart rate; RR (time from one R wave to next R wave); PR, QRS and QT duration; and QT interval corrected using Fridericia's formula.

## 4.7 PATIENT-REPORTED OUTCOME ANALYSES

Through the use of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-LC13, lung cancer symptoms, symptoms commonly associated with cancer treatments, and disease and treatment's impact on patients' functioning and health-related quality of life (HRQoL) will be collected at every study visit (week 4, week 8, and then after every 4 weeks) until disease progression and during post-progression treatment in case of isolated, asymptomatic CNS progression; at post-treatment visit (4 weeks after permanent treatment discontinuation); and at subsequent 8-weekly survival follow-up visits for 6 months. For patients who discontinue treatment for reasons other than disease progression and who progress within the first 6 months of survival follow-up, patient-reported outcome (PRO) measures will be administered every 4 weeks until disease progression and then decreased to every 8 weeks until 6 months post-treatment. For patients who discontinue treatment for reasons other than disease progression and have not yet progressed at 6 months post-treatment, PRO measures will be administered every 4 weeks until disease progression and will no longer be required thereafter.

For the following PRO analyses, there may be multiple PRO assessments completed within the same calendar day; the earliest assessment will be used for analysis. In the cases that there are multiple PRO assessments completed within the same cycle (for post-randomization Visits 1 and 2), the last PRO assessment will be chosen for analysis.

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be scored according to the EORTC scoring manual 3rd edition (Fayers et al. 2001). The QLQ-C30 and LC13 are composed of both multi-item scales and single-item measures including functional scales, symptom scales, and a global health status/QoL scale.

For multi-item subscales, if  $\leq 50\%$  of items within the multi-item subscale are missing at a given timepoint, the multi-item score will be calculated on the basis of the non-missing items. If  $> 50\%$  of items are missing or if a single-item measure is missing, the subscale is missing.

All of the scales and single-item measures will be linearly transformed so that each score will range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL; however, a high score for a symptom scale/item represents a high level of symptomatology/problems.

### 4.7.1 Time to Deterioration of Patient-Reported Lung Cancer Symptoms, Global Health Status, and Cognitive Function

Time to deterioration (TTD) analyses will be performed on lung cancer symptom scores, global health status scores, and cognitive function scale scores in the ITT population and will include all data collected through disease progression and survival follow-up.

TTD is defined as the time from randomization until the first permanent clinically meaningful deterioration. Permanent clinically meaningful deterioration in lung cancer symptoms is defined as a  $\geq 10$ -point increase from baseline in a symptom score that is not followed by a score below a  $\geq 10$  point increase from baseline at any subsequent time points (i.e.  $\geq 10$ -point increase must be held for all subsequent assessments). Conversely, confirmed clinically meaningful deterioration in global health status or cognitive function is defined as a  $\geq 10$ -point decrease from baseline in a score that is not followed by a score below a  $\geq 10$  point decrease from baseline at any subsequent time points (i.e.  $\geq 10$ -point decrease must be held for all subsequent assessments). A  $\geq 10$ -point change in the score is perceived by patients as being clinically significant (Osoba et al. 1998).

TTD will be documented for each of the following symptom, global health status, or cognitive function scale scores:

- Cough (Question 31 on the EORTC Quality of Life Questionnaire Lung Cancer Module [QLQ-LC13]),
- Dyspnea single item (Question 8 on the Core Quality of Life Questionnaire [QLQ-C30]),
- Dyspnea multi-item subscale (Questions 33-35 on the QLQ-LC13),
- Chest pain (Question 40 on the QLQ-LC13),
- Arm/shoulder pain (Question 41 on the QLQ-LC13), and
- Fatigue multi-item subscale (Questions 10, 12, and 18 on the QLQ-C30).
- Global Health Status scale (Questions 29 and 30 on the QLQ-C30)
- Cognitive Function Scale (Questions 20 and 25 on the QLQ-C30)

In addition to those single symptom endpoints, a 3-symptom composite endpoint will also be assessed. In this instance, permanent symptom deterioration will be determined as a  $\geq 10$ -point increase above baseline in any of the following lung cancer symptom scores, whichever occurs first (cough, chest pain, and dyspnea multi-item subscale). In the same manner as the single symptom endpoints, permanent symptom deterioration will need to be observed for the original symptom; a  $\geq 10$ -point increase from baseline in a symptom score that is not followed by a score below a  $\geq 10$  point increase from baseline at any subsequent time points (i.e.  $\geq 10$ -point increase in *cough score* must be held for all subsequent assessments of *cough score*).

Patients without baseline or post-baseline EORTC symptom or scale scores will be censored at the date of randomization. Patients without deterioration at the time of analysis will be censored at the last time they were known to have not deteriorated.

There will be no imputation for missing data for the TTD analysis.

TTD of the pre-specified symptoms will be summarized using the Kaplan-Meier method. The estimated Kaplan-Meier plots will be provided for each score previously described (including the 3-symptom composite score). A stratified log-rank test will be the primary method to compare the time to first deterioration between the treatment groups. The median time and two-sided 95% CI for the median will also be provided. Estimates of the treatment effect will be expressed as HRs with use of a stratified Cox model, including

95% CIs for the ITT population.

#### **4.7.2 Additional Patient-Reported Outcomes Analyses**

Only ITT patients with a baseline assessment and at least one post-baseline assessment (PRO-evaluable subset) will be included in the following analyses. Missing post-baseline items and subscales will not be imputed and will be summarized as observed.

Completion rates will be summarized by listing the number and proportion of patients in the PRO-evaluable subset who completed the PRO assessments at each timepoint by treatment arm. Reasons for non-completion will be summarized if available in the CRF.

All of the following analyses will be performed on all on-treatment timepoints as well as at the time of disease progression per RECIST v1.1 (PRO assessment completed within  $\pm 7$  days of date of radiographic pharmacodynamic), at the last dose of treatment, at the 4-week post-treatment discontinuation visit, and at the 8-weekly survival follow-up visits through 6 months.

- EORTC scores and change from baseline will be descriptively analyzed using means, standard deviations, medians, and range, by treatment arm at baseline and each of the timepoints previously defined.
- Graphs of the mean changes and standard errors over time from the baseline assessment of items and subscales will be provided for each treatment arm.
- The number and proportion of patients who improved, worsened, or remained stable compared with baseline score will be summarized for all item-score and subscale scores of the EORTC QLQ-C30 questionnaire and the QLQ-LC13 by treatment arm at baseline and each of the timepoints previously defined. A patient will be deemed improved at a timepoint if there is a  $\geq 10$  point decrease from baseline for any symptom or a  $\geq 10$  point increase from baseline for any function scales or global health status scale. A patient will be deemed worsened at that timepoint if they have a  $\geq 10$  point increase from baseline for any symptom or a  $\geq 10$  point decrease from baseline for any function scales or global health status scale. If patients do not fit the improved or worsened criteria, they will be defined as stable for that specific item/scale at that timepoint.
- The mean change from baseline and the proportion of patients who improved, worsened or remained stable analyses will also be performed within the subgroup of patients with CNS metastases at baseline for the global health status scale and cognitive function scales only

## **5.           REFERENCES**

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# Appendix 1 Protocol Synopsis

## PROTOCOL SYNOPSIS

<b>TITLE:</b>	<b>RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS CRIZOTINIB IN TREATMENT-NAIVE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER</b>
<b>PROTOCOL NUMBER:</b>	YO29449
<b>VERSION NUMBER:</b>	3
<b>TEST PRODUCT:</b>	Alectinib (RO5424802)
<b>PHASE:</b>	Phase III
<b>INDICATION:</b>	Anaplastic lymphoma kinase-positive (ALK-positive) non-small cell lung cancer (NSCLC)
<b>SPONSOR:</b>	F. Hoffmann-La Roche Ltd

### Objectives

#### **Efficacy Objectives**

The primary efficacy objective for this study is to evaluate and compare the efficacy of alectinib compared with crizotinib in Asian patients with treatment-naive anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC), as measured by investigator-assessed progression-free survival (PFS). This objective is to reliably determine whether the benefit (in terms of PFS) of administering alectinib in this study is consistent with the benefit observed in the global Study ALEX (BO28984).

The secondary efficacy objectives for this study are as follows:

- To evaluate and compare the objective response rate (ORR) and duration of response (DOR)
- To evaluate and compare the time to disease progression in the CNS on the basis of review of patient radiographs by an Independent Review Committee (IRC) with the use of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and Response Assessment in Neuro Oncology (RANO) criteria, as well as:
  - To evaluate the CNS objective response rate (C-ORR) in patients with CNS metastases who have measurable disease in the CNS at baseline
  - To assess the CNS duration of response (C-DOR) in patients who have a CNS objective response
  - To assess CNS progression rates (C-PR) at 6, 12, 18, and 24 months on the basis of cumulative incidence
- To evaluate and compare the PFS assessment by an independent review committee (IRC) by treatment arm
- To evaluate and compare the overall survival (OS) by treatment arm

### **Safety Objective**

The safety objective for this study is to evaluate the safety and tolerability of alectinib compared with crizotinib.

### **Pharmacokinetic Objective**

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of alectinib (and metabolite[s], if appropriate).

### **Patient-Reported Outcome Objectives**

The patient-reported outcome (PRO) objectives for this study are as follows:

- To evaluate and compare time to deterioration (TTD) with patient-reported lung cancer symptoms of cough, dyspnea (single item and multi-item subscales), chest pain, arm/shoulder pain, and fatigue as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Core (QLQ-C30), the supplemental EORTC Quality-of-Life Questionnaire–Lung Cancer module (QLQ-LC13), and a composite of the following three symptoms cough, dyspnea, chest pain.
- To evaluate and compare PROs regarding health-related quality of life (HRQOL), daily functioning, and side effects of treatment as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13.

### **Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To investigate molecular mechanisms of resistance to ALK inhibitors.
- To investigate detection of mutations in ALK and other genes, refer to Appendix 12 for detailed information.

## **Study Design**

### **Description of Study**

This is a randomized, active controlled, multicenter Phase III open-label study in Asian patients with treatment-naïve ALK-positive advanced NSCLC. All patients are required to provide a pretreatment tumor sample that will be used to confirm the presence of ALK rearrangement (by Ventana immunohistochemistry [IHC] test performed at a central laboratory). Patients will be randomized 2:1 into one of the two treatment arms to receive either alectinib or crizotinib, respectively.

This study will be conducted in approximately three other Asian countries in addition to China. The primary endpoint of the study is investigator-assessed PFS.

Central randomization will be performed via an interactive voice/Web response system (IxRS) with stratification by Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0/1 vs. 2) and CNS metastases at baseline (yes vs. no). An IxRS information manual will be provided to each study site.

The experimental arm will receive alectinib administered orally at 600 mg twice a day (BID) with food. The control arm will receive crizotinib administered orally at 250 mg BID, taken with or without food. The first dose of the study drug should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

Patients will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients should discontinue the study medication once progression of disease has been determined based on the use of RECIST v1.1 and subsequent treatments will be decided at the discretion of the investigator according to local practice. Information regarding the nature and the duration of subsequent therapies will be collected.

In the case of isolated asymptomatic disease progression in the CNS (e.g., new CNS oligometastases) localized treatment (e.g., stereotactic radiotherapy or surgery) may be provided followed by the continuation of patient's study treatment (either alectinib or crizotinib) until systemic disease progression or symptomatic disease progression in the CNS. The decision to continue the study treatment beyond the isolated, asymptomatic disease progression in the CNS is at the investigator's discretion for patients who may continue to benefit from respective treatment.

Patients who discontinue study drug treatment before disease progression (e.g., because of unacceptable toxicity) will continue to be followed to collect information regarding disease progression and OS information regardless of whether the patient subsequently received any non-study anti-cancer therapy. Data regarding subsequent anti-cancer therapy will be collected for the analysis of OS.

Approximately 183 patients (122 in the alectinib treatment arm and 61 in the crizotinib treatment arm) will be enrolled into the study over a planned recruitment period of 13 months. Patients who are inappropriately randomized into the study will not be replaced. With the current assumption that hazard ratio is 0.65, the primary analysis that will evaluate the primary endpoint of investigator-assessed PFS is expected to occur approximately 23 months after the first patient has been enrolled when approximately 97 PFS events have occurred. Data collection will continue for each patient until death or study closure, whichever occurs first.

### **Number of Patients**

Approximately 183 patients will be randomly assigned in a 2:1 allocation ratio to the two treatment arms (122 in the alectinib treatment arm and 61 in the crizotinib treatment arm) via a block stratified randomization procedure and over a planned recruitment period of 13 months.

Randomization will guard against systematic selection bias and should ensure the comparability of treatment groups. To assist the balance of important prognostic factors, randomization will be stratified by ECOG PS (0/1 vs. 2) and CNS metastases at baseline (yes vs. no).

### **Target Population**

#### **Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive as assessed by the Ventana IHC test. Sufficient tumor tissue available to perform ALK IHC is required. Ventana IHC testing will be performed at the designated central laboratory.
- Age  $\geq$  18 years
- Life expectancy  $\geq$  12 weeks
- ECOG PS of 0–2
- No history of receiving systemic treatment for advanced, recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC
- Adequate hematologic function:
  - Platelet count  $\geq$   $100 \times 10^9/L$
  - ANC  $\geq$  1500 cells/ $\mu L$
  - Hemoglobin  $\geq$  9.0 g/dL
- Adequate renal function:

An estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula of  $\geq 45$  mL/min/1.73 m<sup>2</sup>

- Patients must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before receiving the first dose of study treatment.
- Measurable disease (by RECIST v1.1) before administration of study treatment.
- Previous brain or leptomeningeal metastases are allowed if the patient is asymptomatic (e.g., diagnosed incidentally at study baseline). Asymptomatic CNS lesions may be treated at the discretion of the investigator as per local clinical practice. If patient has neurological symptoms or signs because of CNS metastasis, the patient must complete whole-brain radiation or gamma knife irradiation treatment. In all cases, radiation treatment must be completed  $\geq 14$  days before enrollment and disease must be clinically stable.
- For all females of childbearing potential, a negative serum pregnancy test result must be obtained within 3 days before starting study treatment.
- For women who are not postmenopausal ( $\geq 12$  months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus), agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of  $< 1\%$  per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate  $< 1\%$  per year. Barrier methods must always be supplemented with the use of a spermicide.
- For men, agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Able and willing to provide written informed consent before performing any study-related procedures and to comply with the study protocol.

### Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- A malignancy within the previous 3 years (other than curatively treated basal cell carcinoma of the skin, early gastrointestinal [GI] cancer by endoscopic resection, in situ carcinoma of the cervix, or any cured cancer that is considered to have no impact in PFS or OS for the current NSCLC).
- Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection.
- Liver disease characterized by:
  - ALT or AST  $> 3 \times$  the upper limit of normal (ULN;  $\geq 5 \times$  ULN for patients with concurrent liver metastases) confirmed on two consecutive measurements
  - OR

Impaired excretory function (e.g., hyperbilirubinemia), synthetic function, or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices

OR

Acute viral or active autoimmune, alcoholic, or other types of hepatitis

- National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 Grade 3 or higher toxicities because of any previous therapy (e.g., radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication.
- History of organ transplant
- Co-administration of anti-cancer therapies other than those administered in this study
- Baseline QTc > 470 ms or symptomatic bradycardia
- Administration of strong/potent cytochrome P4503A inhibitors or inducers within 14 days prior to the receiving the first dose of study treatment and during treatment with alectinib or crizotinib
- Administration of agents with potential QT-prolonging effects within 14 days prior to receiving the first dose of study drug.
- History of hypersensitivity to any of the additives in the alectinib drug formulation
- History of hypersensitivity to any of the additives in the crizotinib drug formulation
- Pregnant or lactating women
- Known HIV positivity or AIDS-related illness
- Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study
- Any psychological, familial, sociological, or geographical condition that potentially hampers compliance with the study protocol requirements or follow-up procedures; those conditions should be discussed with the patient before study entry

### **Length of Study**

The time from first patient screened to end of study, defined below, will be approximately 43 months.

### **End of Study**

This is an event-driven study. With the current assumption that the HR is 0.65 and the recruitment period is 13 months, the required 97 PFS events for primary efficacy analysis is expected to occur 23 months after the first patient has been enrolled. If the number of PFS events is not enough for the estimation of median PFS, an updated PFS analysis will be done when approximately 55% of patients have had PFS events. A survival follow-up analysis will be performed when approximately 55% of patients have died, which is estimated to occur 41 months after the first patient has been enrolled.

### **Outcome Measures**

#### **Efficacy Outcome Measures**

The efficacy outcome measures for this study are as follows:

- PFS, defined as the time from randomization to the first documentation of disease progression, as determined by the investigators (primary endpoint) or IRC (secondary endpoint) with the use of RECIST v1.1 or death from any cause, whichever occurs first. Patients without an event will be censored at the last tumor assessment either during

follow-up or during study treatment. Patients without any assessments performed after baseline will be censored at the date of randomization.

- ORR, defined as the percentage of patients who attain complete response (CR) or partial response (PR) as assessed by the investigator with the use of RECIST v1.1. Patients without any assessments will be regarded as non-responders.
- Time to progression of disease in the CNS, defined as the time from randomization to the first occurrence of disease progression in the CNS as determined by an IRC with the use of RECIST v1.1 and RANO (separate assessments and analyses), as well as C-ORR in patients with CNS metastases who have measurable disease in the CNS at baseline, C-DOR in patients who have a CNS Objective Response, and C-PR at 6, 12, 18, and 24 months.
- DOR, defined as the time from the initial documentation of response (CR or PR with the use of RECIST v1.1) to first documentation of disease progression with the use of RECIST v1.1 or death (whichever occurs first). This will be calculated only for patients who have a best overall response of CR or PR. Patients who do not have disease progression or die after they have had a response will be censored at the date of their last tumor measurement.
- OS, defined as the time from randomization to death from any cause. Patients without an event will be censored at the last date known to be alive. Patients without any follow-up information will be censored at the date of randomization.

#### **Safety Outcome Measures**

The safety outcome measures for this study are as follows:

- Serious and non-serious adverse events
- Safety laboratory test results
- Vital signs (blood pressure, heart rate), ECG
- Physical examination findings

#### **Pharmacokinetic Outcome Measures**

The PK outcome measures for this study are as follows:

- Sparse blood sampling will be performed in all patients receiving alectinib treatment to characterize the pharmacokinetics of alectinib (and metabolite[s], if appropriate).
- Frequent blood sampling will be performed in the first 20 consenting Chinese patients enrolled to receive alectinib treatment.
- PK parameters will be determined as appropriate and where data allow.
- Non-compartmental analysis for alectinib (and metabolite[s], if appropriate) will be conducted in patients undergoing frequent blood sampling, as appropriate and where data allow.

The sparse and frequent pharmacokinetics of alectinib (and metabolite[s], if appropriate) will be described, and the between-patient variability will be estimated with the use of a population PK approach. The potential influence of covariates that contribute significantly to the between-patient differences in PK parameters of alectinib will also be explored and quantified. If necessary, data may be pooled with data from other studies.

#### **Patient-Reported Outcome Questionnaires**

The PRO questionnaires for this study are as follows and will be administered to patients every 4 weeks until disease progression and during disease progression while receiving study drug treatment in the case of isolated, asymptomatic disease progression in the CNS at the Post-Treatment Visit (4 weeks after treatment discontinuation), and every follow-up visit (every 8 weeks) after the Post-Treatment Visit for 6 months:

- EORTC QLQ-C30 and the EORTC QLQ-LC13 will be used to determine the impact of alectinib compared with crizotinib as measured by TTD with patient-reported lung cancer symptoms (e.g., cough, dyspnea [single item and multi-item scales], pain in chest, pain in arm/shoulder, fatigue).
- The EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to measure PROs of HRQOL, patient functioning, and side effects of therapy compared between patients treated with alectinib and those treated with crizotinib.
- For patients who discontinue treatment for reasons other than disease progression and who progress within the first 6 months of survival follow-up, PRO questionnaires will be administered every 4 weeks until disease progression. Upon disease progression, PRO questionnaires will be provided every 8 weeks until 6 months post-treatment.
- For patients who discontinue treatment for reasons other than disease progression and who have not yet progressed at 6 months post-treatment, PRO questionnaires will be administered every 4 weeks until disease progression and will no longer be required thereafter.

### **Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- Baseline and post-progression tumor mutation status to study molecular mechanisms of resistance to ALK inhibitors
- ALK and other genes involved in cancer mutation and rearrangement status in plasma-circulating tumor nucleic acids to monitor efficacy, resistance, and disease progression

### **Investigational Medicinal Products**

#### **Test Product**

Alectinib comes in a hard capsule dosage form containing the following active ingredient:

Chemical name: 9-Ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6, 11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloride

Each capsule contains 150 mg of alectinib (as free base) along with lactose monohydrate, **carmellose calcium, hydroxypropyl cellulose, SLS, and magnesium stearate.**

Alectinib capsules should be stored in accordance with the storage instructions on the label. Alectinib capsules should be administered orally BID with food in the morning and evening.

#### **Comparator**

Crizotinib comes in a hard capsule dosage form. Each capsule contains 250 mg or 200 mg crizotinib. Crizotinib hard capsules should be stored in accordance with the storage instructions on the label. Crizotinib capsules should be administered orally BID.

For further details, see the local prescribing information for crizotinib (XALKORI<sup>®</sup>, U.S. Package Insert).

#### **Non-Investigational Medicinal Product**

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to screening to the Study Completion and Study Treatment Discontinuation Visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic case report form (eCRF).

All therapy and medication administered to manage adverse events should be recorded on the Concomitant Medications eCRF.

Permitted medications and treatments are listed below:

- Anticoagulants and anti-thrombotic agents (i.e., warfarin-derived anticoagulants, unfractionated heparin or low-molecular heparins, aspirin [ $\leq$  325 mg/day], and clopidogrel).

- Acetaminophen up to 2 g/day
- Gastric pH-elevating medications (such as proton pump inhibitors, H2 blockers, or antacids)
- Local therapy (e.g., stereotactic radiotherapy or surgery) may be given to patients with isolated asymptomatic CNS progression (e.g., new CNS oligometastases).

### **Statistical Methods**

#### **Primary Analysis**

PFS is defined as the time from date of randomization to the date of first documented disease progression or death, whichever occurs first. The primary endpoint of PFS will be determined based on investigator assessment of progression with the use of RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the last tumor assessment date either during study treatment or during follow-up. Patients without tumor assessments after baseline will be censored at the date of randomization.

Patients who discontinue treatment before disease progression (e.g., because of toxicity) will continue in the study and will be followed until disease progression and for OS regardless of whether they subsequently receive anti-cancer therapy.

The Kaplan-Meier method will be used to estimate the median PFS for each treatment arm with 95% confidence limits, and a Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms. A stratified Cox proportional regression model will be used including treatment in order to provide an estimate of the treatment effect expressed as a hazard ratio (HR) (alectinib vs. crizotinib), as well as a 95% CI. The stratification factors are the randomization stratification factors: ECOG PS (0/1 vs. 2) and CNS metastases at baseline (yes vs. no), as recorded on the eCRF. Point estimate of the adjusted HR will be compared with the consistency threshold (observed HR in the ALEX trial).

The treatment comparison of PFS will also be assessed and tested based on a stratified log-rank test to demonstrate the strength of consistent trend. However, this hypothesis testing is limited because statistically negative outcomes do not necessarily rule out clinically significant treatment effects.

#### **Determination of Sample Size**

The primary endpoint of investigator-assessed PFS was used to determine the sample size of the study. The primary objective of the study is to reliably determine whether the benefit (in terms of PFS) of administering alectinib in this study is consistent with the benefit observed in the global Study ALEX. Consistency is defined as maintaining  $\geq 50\%$  of risk reduction from Study ALEX. That is, assumed the PFS HR for the ALEX trial is 0.65 (i.e., 35% risk reduction), if the point estimate of HR from Study YO29449 is less than 0.83, then the study primary objective to demonstrate consistency is met.

Based on the assumption of PFS HR = 0.65, a total of 97 PFS events are required to achieve approximately 87% probability to show consistency. In this study, 183 patients will be enrolled in a 2:1 randomization allocation. Based on the assumption that median PFS is 10.9 months for the crizotinib arm and 16.8 months for the alectinib arm (HR = 0.65) and patients are to be enrolled over 13 months; the final PFS analysis is expected to occur approximately 23 months after the first patient is enrolled.

#### **Interim Analysis**

No interim analysis for efficacy or futility is planned.