

**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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## PROTOCOL

**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

**PROTOCOL NUMBER:** YO29449

**VERSION NUMBER:** 3

**TEST PRODUCT:** Alectinib (RO5424802)

**MEDICAL MONITOR:** [REDACTED], M.D.

**SPONSOR:** F. Hoffmann-La Roche Ltd

**DATE FINAL:** 22 January 2015

**DATE AMENDED:** Version 2: 4 February 2016  
Version 3: See electronic date stamp below.

## PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[REDACTED]	Company Signatory (Clinical)	23-Mar-2017 23:55:35

## CONFIDENTIAL

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## **PROTOCOL AMENDMENT, VERSION 3: RATIONALE**

Protocol YO29449 has been amended to revise the primary analysis timepoint and the tumor and response assessment.

The major changes to the protocol are as follows:

- Tumor and response assessment: deleted the requirement for confirmation of response in Section 4.5.7, as described below:

An objective response should be confirmed by repeat assessments 4 weeks after the initial documentation. It is recommended that the confirmatory tumor assessment not be left until the next scheduled CT scan, but be performed as soon as possible following the 28-day interval from the initial documentation of response.

- Safety-related changes:

In Section 4.4.2, restrictions related to concomitant medications known to prolong the QT interval have been modified. The restriction is no longer required for alectinib-treated patients on the basis of the detailed evaluation of the pooled electrocardiogram (ECG) data from the two pivotal Studies NP28761 and NP28673 and ECG data from the supportive Study AF-001JP, which showed no evidence that alectinib caused any clinically relevant QTcF prolongation. Furthermore, there was no apparent correlation between the change in QTcF and alectinib plasma concentration. For crizotinib-treated patients, this restriction still applies. For the same reason, the guideline for management of specific adverse events related to QT prolongation in alectinib-treated patients has been removed from Table 3.

In Section 5.1.2.3, the section title “Hematologic Abnormalities” has been changed to “Anemia.” This aligns with the alectinib Investigator’s Brochure (IB), Version 7. The guideline for management of specific adverse events related to hematological abnormalities in alectinib-treated patients has been removed accordingly. Should adverse events be categorized as “hematological abnormalities,” appropriate management of the adverse events is already covered by the guideline “Other AEs or Laboratory Abnormalities,” also included in Table 3.

- In Section 6.1, the primary analysis timepoint was revised, as described below:

The primary objective of the study is to determine whether the benefit (in terms of investigator-assessed progression-free survival [PFS]) of administering alectinib in this study is consistent with the benefit observed in the global Study BO28984 (ALEX). Consistency is defined as maintaining  $\geq 50\%$  of risk reduction from Study ALEX. The number of PFS events required to show consistency depends on the hazard ratio (HR) observed in the ALEX trial. The primary analysis of PFS will occur when as early as required PFS events show that consistency has occurred. 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. The first survival analysis will be performed together with the primary PFS analysis. A survival follow-up analysis will be performed when approximately 55% of patients have died.

Other minor changes have been made to improve clarity and consistency and/or to align language with the updated model document (Sections 5.3.5.7, 5.3.5.10, 9.2, and 9.5). Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

## PROTOCOL AMENDMENT, VERSION 3: SUMMARY OF CHANGES

### GLOBAL CHANGES

The Medical Monitor was changed from [REDACTED] M.D., Ph.D. to [REDACTED] M.D., throughout.

### PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

### SECTION 2.1: EFFICACY OBJECTIVES

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).

### SECTION 2.5: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To investigate detection of mutations in ALK and other genes ~~involved in cancer in plasma~~, refer to Appendix 12 for detailed information.

### SECTION 3.1: DESCRIPTION OF STUDY

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 ~~44~~ 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 final~~ primary* analysis that will evaluate the primary endpoint of investigator-assessed PFS is expected to occur approximately ~~24~~ 23 months after the first patient has been enrolled when approximately 97 PFS events have occurred.

#### SECTION 3.1.1: Independent Review Committee

An IRC will be established to perform an independent review of all radiological scans for the ~~final-primary~~ analysis and to determine the response and disease progression on the basis of the RECIST v1.1 in addition to the local investigator's review of radiographs.... The IRC's assessment will only be used in the ~~final-primary~~ analysis.

Sites will submit radiological files to the centrally located IRC's data review facility during the study on an ongoing basis or at the Sponsor's request for ~~final primary~~ analysis. For the ~~final-primary~~ analysis, the IRC will perform an independent review of the computed tomography (CT) and magnetic resonance imaging (MRI) scans on the basis of a prespecified Charter to determine the response and disease progression on the basis of the RECIST v1.1.

## **SECTION 3.2: END OF STUDY**

~~This study is event driven, with a recruitment period of approximately 14 months. The required number of 97 PFS events for the final analysis of the primary endpoint is expected to occur approximately 24 months after the first patient has been enrolled. Follow-up for survival information will continue until the survival follow-up analysis or the Sponsor decides to end the study, whichever occurs first. A survival follow-up analysis will be performed when approximately 50% of the patients have died, which is estimated to occur approximately 40 months after the first patient has been enrolled.~~

*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.*

~~Only serious adverse events will be reported after the survival follow-up analysis has been completed.~~

### **SECTION 3.3.4: Rationale for Open-Label Design**

These include performing sensitivity analyses to demonstrate the robustness of the primary endpoint, defining disease progression with the use of established response evaluation criteria (RECIST v1.1), performing tumor assessment at the same frequency in both treatment arms, adhering to protocol-defined schedules, and finalizing the strategy for the ~~final~~ primary analysis of the primary endpoint before initiating this study, which include predefined methods for handling missing data and censoring rules. Efficacy analyses will be performed only at the prespecified analysis timepoints in the protocol (~~final~~ primary analysis will be performed when 97 PFS events have occurred, and survival follow-up analysis will be performed when ~~92~~ 101 OS events have occurred)

### **SECTION 4.1.1: Inclusion Criteria**

Patients must meet the following criteria for study entry:

- ... Examples of ~~non-hormonal~~ 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....

### **SECTION 4.1.2: Exclusion Criteria**

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

- Administration of agents with potential QT-prolonging effects within 14 days prior to receiving the first dose of study drug ~~and during treatment~~ (see Section 4.4.2 for further details)...

- Pregnant or lactating *women*

#### **SECTION 4.4.2: Prohibited Therapy**

... Exceptions to the below listed concomitant therapies restrictions (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) may be made only if the rationale is discussed and documented between the investigator and the Sponsor's Clinical Pharmacologist.

- Any concomitant medications known to affect QT interval duration, including but not limited to the following drugs: amiodarone, cisapride, clarithromycin, methadone, and quinidine within 2 weeks prior to the first dose of study drug treatment, ~~during for all patients, and while on treatment with study drugs, and~~ through the end of the study *for crizotinib-treated patients only*

#### **SECTION 4.5.7: Tumor and Response Evaluations**

Disease burden must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator based on physical examinations. ~~Clinical lesions will be, radiographic imaging, and other modalities, and~~ documented by color photography (with caliper measurement for measurable lesions) *or measurements by CT scans, and other modalities (e.g., MRI, brain scans), with the use of RECIST v1.1 (see Appendix 4). An objective response should be confirmed by repeat assessments  $\geq 4$  weeks after the initial documentation. It is recommended that the confirmatory tumor assessment not be left until the next scheduled CT scan, but be performed as soon as possible following the 28-day interval from the initial documentation of response.*

#### **SECTION 4.5.8.1: Laboratory Assessments**

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count *or percentage* [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells, *etc.*])
- Serum chemistry (sodium, potassium, chloride, bicarbonate *or total CO<sub>2</sub>*, fasting glucose...

#### **SECTION 4.5.8.2: Pretreatment Tumor Samples (Mandatory)**

Tumor blocks (formalin-fixed, preferred 10% neutral-buffered formalin) are the preferred source, but if blocks are not available, 7 unstained 5- $\mu$ m slides cut <3 months before screening are ~~also accepted~~ *acceptable for ALK IHC testing.*

*For cases where tumor blocks have been submitted, an additional 8 6 slides (optional sample collection) will be cut from blocks submitted for randomized patients. For cases where slides have been submitted for screening, an additional 6 slides are desired for tumor nucleic acid sequencing. Pretreatment tumor samples may be used for DNA and/or RNA extraction to investigate mechanisms of enable Next Generation*

~~Sequencing (NGS) to identify somatic mutations that are associated with disease progression or acquired resistance to ALK inhibitors, alectinib and to add to researchers' understanding of disease pathobiology. These samples will not be collected in countries/sites where the regulatory agency or the Institutional Review Board (IRB) does not allow this testing. Any remaining tumor blocks of from screen-failed patients will be returned to the sites within 3-4 months of receipt at Sponsor-designated central laboratory, and any remaining tumor blocks from randomized screen-failed patients will be returned to the sites before the final closure of the clinical database; slides will not be returned....~~

~~Pretreatment tumor samples may be used for DNA and/or RNA extraction to enable Next Generation Sequencing (NGS) to identify somatic mutations that are associated with disease progression or acquired resistance to alectinib and to add to researchers' understanding of disease pathobiology.~~

### **SECTION 4.5.8.3: Post-Treatment Tumor Samples (Optional)**

These samples may allow a greater understanding of the molecular mechanisms of resistance to ALK inhibitors and genes involved in cancer. *Any remaining tumor blocks of randomized patients will be returned to the sites before the final closure of the clinical database. Slides will not be returned.*

### **SECTION 4.5.8.4: Blood and Plasma Samples**

Mandatory plasma samples for biomarker analysis will be obtained to determine:

- ALK rearrangement determination by plasma ALK quantitative reverse transcription polymerase chain reaction. *This will require 20 mL of blood at screening from all screened patients.*
- ~~Mutations~~ *Mutation* status in ALK and other escape genes (e.g., EGFR, KRAS). *This will require 20 mL of blood (two tubes of 10 mL each) to be collected at baseline, at Treatment Visit 7 (Week 16), and subsequently at every second treatment visit (every 16 weeks) [see Appendix 1 for detailed information] until and at disease progression (CNS and during treatment post-/or systemic disease progression in case of isolated, asymptomatic progression of disease in the CNS. For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual.—) or treatment discontinuation for any reasons.*
- These samples will not be collected in countries/or sites where the regulatory agency or the IRB does not allow genetic testing.

~~For biomarkers, a maximum of 20 mL of blood will be collected at screening (for determination of ALK rearrangement), and a maximum of 20 mL of blood will be collected at baseline, at Visit 7 (Week 16), subsequently at every second visit (every 16 weeks), and at disease progression (CNS and/or systemic disease progression). These plasma samples (baseline and subsequent visits) will be used for determination of mutation status in ALK and other escape genes.~~

All the biomarker samples described in Sections 4.5.8.2, 4.5.8.3, and 4.5.8.4 will be stored for 5 years after the date of final closure of the associated clinical database.

#### **SECTION 4.5.9: Electrocardiograms**

To have a consistent approach for the RR and QTcF, it was decided that the calculation of RR and QTcF will be done by the Sponsor using the formulae provided in Appendix 11. The results will be populated in the eCRF for use by the investigator.

If any ECG abnormality is associated with an adverse event, it must be recorded and managed as described in Section 5. ~~Management of QT interval prolongation should be performed according to the guidance provided in Section 5.1.3.~~

If considered appropriate by the Sponsor, ECG recordings may be analyzed retrospectively at a central laboratory. ~~Guidance for abnormal ECG test results (QT prolongation) is provided in Table 3.~~

#### **SECTION 5.1.2.3: ~~Hematologic Abnormalities~~ Anemia**

~~Hematologic abnormalities~~ Cases of neutropenia, leukopenia, thrombocytopenia, and anemia have been reported in patients treated with alectinib administration. ~~Neutrophil counts generally decreased early and remained stable thereafter; the majority of the events were Grade 1 or 2.~~

#### **SECTION 5.1.2.8: ~~Cardiovascular Effects~~ Bradycardia**

~~QT interval prolongation appears to be an off-target class effect of some TKIs, including the ALK inhibitor crizotinib and ceritinib (Shah et al. 2013; XALKORI<sup>®</sup> U.S. Package Insert; ZYKADIA<sup>™</sup> U.S. Package Insert). Many TKIs have been associated with bradycardia and hypertension.~~

~~In an in vitro study of the cardiovascular system, alectinib inhibited the human *Ether a-go-go* Related Gene (hERG) current (IC<sub>20</sub>: 58 ng/mL; IC<sub>50</sub>: 217 ng/mL). Because plasma protein binding by alectinib is ≥99%, the plasma concentration of alectinib that is required to induce the same inhibition in vivo would be ≥100 times greater than the concentration required in vitro. In the monkey telemetry study, there were no effects on the ECG or any of the other cardiovascular parameters or body temperature at doses of up to 15 mg/kg (mean C<sub>max</sub>: 279 ng/mL).~~

#### **SECTION 5.1.3: Management of Specific Adverse Events with Alectinib**

##### **Table 3: Guidelines for Management of Specific Adverse Events with Alectinib**

Table 3 has been updated to reflect changes to the protocol.

#### **SECTION 5.3.5.7: Deaths**

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be

reported. The term "**sudden death**" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "**sudden death**" should not be used unless combined with the presumed cause of death (e.g., "**sudden cardiac death**").

#### **SECTION 5.3.5.10: Hospitalization or Prolonged Hospitalization**

~~The following hospitalization scenarios are not considered to be adverse events:~~ *An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:...*

~~The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:~~ *An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:...*

#### **SECTION 5.4.1: Emergency Medical Contacts**

##### **Medical Monitor (Roche Medical Responsible) Contact Information**

Medical Monitor: [REDACTED], M.D., Ph.D.

Email: [REDACTED]

Telephone No.: (office) [REDACTED]

Mobile Telephone No.: [REDACTED]

#### **SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

*The primary objective of the study is to determine whether the benefit (in terms of investigator-assessed PFS) of administering alectinib in this study is consistent with the benefit observed in global study ALEX. Consistency is defined as maintaining  $\geq 50\%$  of risk reduction from ALEX. ~~The final analysis of~~ number of PFS events required to show consistency depends on the HR observed in the ALEX trial. The required number of PFS events to achieve approximate 87% probability to meet consistency criteria is listed as below.*

~~The primary endpoint analysis of PFS will occur when as early as 97 required PFS events to show consistency have occurred, based on the investigators' assessments. On the basis of the assumptions outlined in Section 6.1, this is estimated to occur approximately 24 months after.~~ *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.*

~~The first patient has been enrolled. survival analysis will be performed together with the primary PFS analysis. A survival follow-up analysis will be performed when approximately 50% of patients (i.e., 92 55% patients) have died, which is estimated to occur approximately 40 months after the first patient has been enrolled.~~

### **Table 7: Required Number of PFS Events to Show Consistency**

Table 7 has been added to reflect changes to the protocol.

### **SECTION 6.1: DETERMINATION OF SAMPLE SIZE**

...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, assuming the estimated PFS HR for ~~Study BO28984~~ the *ALEX trial* is 0.65 (i.e., 35% risk reduction), if the point estimate of HR from *Study YO29449* ~~this study~~ 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 44 13 months; the final PFS analysis is expected to occur approximately 24 23 months after the first patient is enrolled.*

*The first survival analysis will be performed together with the primary PFS analysis. A survival follow-up analysis will be performed once approximately 50 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. At the time of the final analysis of the primary endpoint of investigator-assessed PFS, on the basis of the above assumptions, 61 OS events are expected to have occurred. The survival follow-up analysis is expected to occur approximately 40 41 months after the first patient has been enrolled.*

### **SECTION 6.4.1: Primary Efficacy Endpoint**

...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 ~~Study BO28984~~ the *ALEX trial*).

The treatment comparison of PFS will also be assessed and tested based on a stratified log-rank test ~~at the 5% level of significance (two-sided)~~ to demonstrate the strength of consistent trend....

## **SECTION 6.4.2: Secondary Efficacy Endpoints**

### ***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.*

## **SECTION 6.4.3: Sensitivity Analyses**

The following sensitivity ~~analyses~~ *analysis* will be performed on the primary endpoint of PFS:

- The effect of non-protocol-specified anti-cancer therapy before progression will be assessed by censoring patients at the last adequate tumor assessment before the start of non-protocol-specified anti-cancer therapy.
- ~~The effect of missing tumor assessments will be assessed if the number of missing assessments in either arm is >5%. For patients with progression determined following one or more missing tumor assessments, the progression will be backdated to the first missing tumor assessment.~~
- ~~The effect of patient's loss to follow up will be assessed depending on the number of patients who are lost to follow up. If >5% of patients are lost to follow up for PFS in either treatment arm, a "worst-case" analysis will be performed in which patients who are lost to follow up will be considered to have progressed at the last date they were known to be progression-free.~~

## **SECTION 6.7.1: Time to Deterioration of Patient-Reported Lung Cancer Symptoms**

*Additional details regarding the TTD analyses will be included within the SAP.*

## **SECTION 6.7.2: Additional Patient-Reported Outcomes**

*Additional details regarding the PRO analyses will be included within the SAP.*

## **SECTION 8.2: INFORMED CONSENT**

~~The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.~~

## **SECTION 9.2: PROTOCOL VIOLATIONS**

*The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

## **SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>  
[http://www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)

## **APPENDIX 1: Schedule of Assessments**

Appendix 1 has been modified to reflect the changes to the protocol.

## **SAMPLE INFORMED CONSENT FORM**

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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**PROTOCOL AMENDMENT ACCEPTANCE FORM**

**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

**PROTOCOL NUMBER:** YO29449

**VERSION NUMBER:** 3

**TEST PRODUCT:** Alectinib (RO5424802)

**MEDICAL MONITOR:** [REDACTED] M.D.

**SPONSOR:** F. Hoffmann-La Roche Ltd

**I agree to conduct the study in accordance with the current protocol.**

\_\_\_\_\_  
Principal Investigator's Name (print)

\_\_\_\_\_  
Principal Investigator's Signature

\_\_\_\_\_  
Date

Please retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

## PROTOCOL SYNOPSIS

**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

**PROTOCOL NUMBER:** YO29449

**VERSION NUMBER:** 3

**TEST PRODUCT:** Alectinib (RO5424802)

**PHASE:** III

**INDICATION:** Anaplastic lymphoma kinase-positive non-small cell lung cancer

**SPONSOR:** 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 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.

## **LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
BID	twice daily
C <sub>max</sub>	maximum plasma concentration observed
C-DOR	CNS duration of response
C-ORR	CNS objective response rate
C-PR	CNS progression rate
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
DOT	duration of treatment
EC	Ethics Committee
eCRF	electronic Case Report Form
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-associated protein-like 4
EORTC	European Organization for the Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HR	hazard ratio
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IRB	Institutional Review Board
IRC	Independent Review Committee

Abbreviation	Definition
ITT	intent-to-treat
IxRS	interactive voice/Web response system
KRAS	Kirsten rat sarcoma viral oncogene homolog
MDRD	modification of diet in renal disease
MET	mesenchymal-epithelial transition factor
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCA	non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NSCLC	non-small cell lung cancer
NGS	Next Generation Sequencing
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
QD	once daily
QLQ-C30	Quality-of-Life Questionnaire–Core
QLQ-LC13	Quality-of-Life Questionnaire–Lung Cancer module
QOL	quality of life
QTcF	Fridericia's formula
RANO	Response Assessment in Neuro Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RON	recepteur d'origine nantais
ROS1	c-ros oncogene 1
SAP	Safety Analysis Population
SD	stable disease
TKI	tyrosine kinase inhibitor
TTD	time to deterioration

Abbreviation	Definition
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal

## 1. **BACKGROUND**

### 1.1 **BACKGROUND ON ANAPLASTIC LYMPHOMA KINASE-POSITIVE NON-SMALL CELL LUNG CANCER**

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide. Lung cancer was estimated to cause 160,300 deaths in the United States in 2012, accounting for 28% of all cancer-related deaths according to a report from the American Lung Association (2014). In China, lung cancer is also the leading cause of cancer-related mortality, accounting for 25.2% of all malignant tumors in 2009 (Chen et al. 2013); the prevalence and mortality rate are 53.6 and 45.6 per 100,000, respectively. Survival rates for lung cancer tend to be much lower than other common cancers because of the late diagnosis and limited effective therapy of lung cancer in the advanced stage. The expected 5-year survival rate for all patients who receive a diagnosis of lung cancer is 16.3% compared with 65.2% for colon cancer, 90.0% for breast cancer, and 99.9% for prostate cancer (Siegel et al. 2012). Conventional anti-cancer therapies are far from satisfactory, and there is an unmet medical need for the development of new therapies for NSCLC.

Recent progress in the identification of genetic mutations or chromosomal rearrangements in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), mesenchymal-epithelial transition factor (MET), and other genes has provided new opportunities to use targeted therapeutic agents for the treatment of NSCLC, when the tumor is identified as having these mutations (Katayama et al. 2011; Doebele et al. 2012).

Approximately 5% of NSCLC cases have been shown to harbor the echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) fusion gene as a result of a chromosomal inversion at 2p21 and 2p23 (Choi et al. 2010; Ou et al. 2012). The formation of the ALK fusion protein results in activation and dysregulation of the gene's expression and signaling, which may contribute to increased cell proliferation and survival in tumors that express these genes. The formation of the ALK fusion protein is further supported by reports that the *TFG* and *KIF5B* genes may also serve as ALK fusion partners in some patients with NSCLC. Expression of these ALK fusion genes in mouse 3T3 fibroblasts causes their transformation and enhanced proliferation. ALK gene alterations are generally in a mutually exclusive relationship with mutations in EGFR or KRAS (Soda et al. 2007; Inamura et al. 2008; Inamura et al. 2009; Wong et al. 2009), although EGFR mutations may develop as a resistance mechanism after treatment with crizotinib (XALKORI<sup>®</sup>, U.S. Package Insert) (Doebele et al. 2012). Inhibition of ALK activity in Ba/F3 cells that were transfected with the EML4-ALK fusion protein resulted in inhibition of cell growth (Ou et al. 2012), whereas a small molecule inhibitor of ALK demonstrated anti-tumor efficacy in two xenograft models in athymic mice, namely, the H3122 NSCLC and Karpas299 anaplastic large cell lymphoma models harboring the EML4-ALK and nucleophosmin-ALK fusion proteins, respectively. Hence,

ALK appears to be a suitable therapeutic target for NSCLC with ALK gene rearrangements.

Wild-type ALK is hardly expressed at all in most normal human tissues, being expressed at higher levels in a few limited types of tissue such as developing and mature nervous system tissue (glial cells, neurons, endothelial cells, and pericytes) (Pulford et al. 1997). By contrast, an aberrant ALK with constitutively active kinase results from the formation of the EML4-ALK fusion gene by chromosomal translocation.

Currently, the first approved medicine for treatment-naive ALK-positive NSCLC is crizotinib, an inhibitor of receptor tyrosine kinases including ALK, hepatocyte growth factor receptor (HGFR; also known as c-Met), recepteur d'origine nantais (RON), and c-ros oncogene 1 (ROS1) (Sahu et al. 2013).

Crizotinib was first granted accelerated approval by the U.S. Food and Drug Administration (FDA) in August 2011 for the treatment of patients with locally advanced or metastatic NSCLC that is positive for ALK as detected by an FDA-approved test. The approval was based on two single-arm studies. The primary endpoint for both studies was the objective response rate (ORR) as assessed by the investigator. In one study, the ORR was 50% (95% CI: 42%, 59%) with a median response duration of 42 weeks, and in the other study, the ORR was 61% (95% CI: 52%, 70%) with a median response duration of 48 weeks (Camidge et al. 2012; Kim et al. 2012). In November 2013, the FDA granted regular approval for crizotinib on the basis of the demonstration of superior progression-free survival (PFS) and ORR for crizotinib compared with chemotherapy in patients with ALK-positive NSCLC whose disease progressed after platinum-based doublet chemotherapy (Study PROFILE 1007). Study PROFILE 1007 was an open-label active-controlled multinational randomized study that enrolled 347 patients with ALK-positive metastatic NSCLC. Patients were required to have disease progression following platinum-based chemotherapy. The study demonstrated significantly prolonged PFS in patients who were treated with crizotinib compared with patients who received chemotherapy (hazard ratio [HR]=0.49 [95% CI: 0.37, 0.64],  $p < 0.0001$ ). Median PFS was 7.7 months for patients treated with crizotinib and 3.0 months for patients treated with chemotherapy. The ORR was significantly higher for patients treated with crizotinib compared with patients who received chemotherapy (65% vs. 20%, respectively), with median response durations of 7.4 months for patients treated with crizotinib and 5.6 months for patients treated with chemotherapy. No difference in overall survival (OS) was noted between the two groups in a planned interim analysis (HR = 1.02 [95% CI: 0.68%, 1.54%]) (Shaw et al. 2013a). Common adverse reactions in clinical studies with crizotinib, occurring at an incidence of 25% or higher, included visual disorders, nausea, diarrhea, vomiting, constipation, edema, elevated transaminases, and fatigue (National Cancer Institute 2013). Study PROFILE 1014, a Phase III study of crizotinib compared with standard pemetrexed-platinum-based chemotherapy, met its primary objective of prolonging PFS in patients with ALK-positive non-squamous NSCLC who were previously untreated, with

a median PFS of 10.9 and 7.0 months (HR: 0.45; 95% CI: 0.35, 0.60;  $p < 0.0001$ ) for crizotinib and pemetrexed-platinum-based chemotherapy, respectively (Solomon et al. 2014). Objective response rates were 74% and 45%, respectively ( $P < 0.001$ ). Median OS was not reached in either group (HR for death with crizotinib: 0.82; 95% CI: 0.54, 1.26;  $P = 0.36$ ) (Solomon et al. 2014).

These results showed that an ALK inhibitor is effective in patients with NSCLC whose disease harbors ALK fusion genes. Crizotinib has subsequently been approved in other countries, such as Japan, Korea, Canada, Switzerland, and China. In the European Union, crizotinib was conditionally approved in October 2012 for the treatment of adults with previously treated ALK-positive NSCLC.

Although substantial benefit has been observed with crizotinib therapy, relapse typically occurs. Studies with patients who had disease progression while receiving crizotinib treatment reveal two main reasons for treatment failure: the development of resistance to treatment because of secondary (e.g., gatekeeper) mutations (predominantly in ALK or occasionally in other genes, such as EGFR, cKIT, or KRAS) (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013) and CNS relapse (crizotinib has impaired control of brain metastases in comparison with other sites of systemic disease). The CNS is the primary site of initial treatment failure in 46% of patients with ALK-positive NSCLC who are treated with crizotinib (Costa et al. 2011; Chun et al. 2012). Significant morbidity is associated with brain metastases as a function of brain involvement and because of the treatment required for disease control (e.g., corticosteroids, surgery, and radiation).

The second approved treatment for ALK-positive NSCLC (approved in the United States, currently under development in China) is ceritinib (ZYKADIA™, U.S. Package Insert), which is an inhibitor of receptor tyrosine kinases that include ALK and insulin-like growth factor 1. Ceritinib was granted accelerated approval by the FDA in 2014 for the treatment of patients with ALK-positive metastatic NSCLC who experienced disease progression while receiving crizotinib treatment or whose disease was intolerant to crizotinib therapy. This indication was approved on the basis of tumor response rate and duration of response (DOR) in a Phase I single-arm study (Shaw et al. 2013b).

One hundred thirty-one patients were enrolled in the ceritinib Phase I study (38% male, median age 53 years), including 59 patients in the dose-escalation phase (Shaw et al. 2013b). The maximum tolerated dose (MTD) of 750 mg administered once daily (QD) was established, and 72 patients in an expanded cohort received the MTD. Among the 88 evaluable patients with NSCLC who received 400–750 mg ceritinib QD, the ORR was 70%, with 40 confirmed and 22 unconfirmed responses. In the subset of 64 crizotinib-resistant patients, the ORR was 73%, with 31 confirmed and 16 unconfirmed responses. As of 8 November 2012, 50% of patients with unconfirmed responses continued to receive ceritinib treatment. Responses were observed in patients with different crizotinib-resistance mutations as well as in patients without a detectable mutation. Responses were also observed in patients with untreated CNS

metastases. Among patients with NSCLC who had a confirmed response, the median DOR was 7.4 months (95% CI: 6.7, not reached) and 78% had a DOR of  $\geq 6$  months. In all of the 123 patients with NSCLC, the median PFS was 8.6 months (95% CI: 4.3, 19.3 months). In the subset of 83 crizotinib-naive patients, the ORR was 72.3% (95% CI: 61.4%, 81.6%), median PFS was 18.4 months (95% CI: 11.1, non-estimable) and median DOR was 17.0 months (95% CI: 11.3, non-estimable) (Felip et al. 2014). The most common adverse events that were reported were nausea (72%), diarrhea (69%), vomiting (50%), and fatigue (31%). The most common Grade 3 or Grade 4 adverse events that were reported were ALT elevation (12%), diarrhea (7%), and AST elevation (6%).

A new generation of ALK inhibitors may have the potential to overcome these two major limitations of crizotinib treatment to offer patients a better chance of prolonged remission and to minimize the development of CNS metastases and the attendant comorbidity.

## 1.2 BACKGROUND ON ALECTINIB

Alectinib (also known as RO5424802, CH5424802, or AF802) is a newly developed small molecule, highly selective, and potent oral next-generation ALK inhibitor with a benzo[b]carbazole scaffold. In enzyme inhibition assays performed in vitro, this compound has been shown to selectively inhibit ALK. The compound also shows high anti-tumor activity both in vitro and in vivo against tumor cell lines with some type of ALK gene alteration, including NSCLC and anaplastic large cell lymphoma lines harboring an ALK translocation and a neuroblastoma line harboring an amplified ALK gene.

Nonclinical pharmacology studies showed that alectinib is efficacious in a model of tumors that express an ALK fusion and bear the L1196M mutation, which is associated with resistance to crizotinib, and alectinib is effective in mouse NCI H2228 NSCLC xenografts that are already maximally suppressed by crizotinib. Alectinib also prolongs survival in an intracerebral NCI H2228 implantation model, and it reduces tumor growth in an intracranial model monitored with the use of bioluminescence.

To date, the clinical development program for alectinib is comprised of three ongoing Phase I/II studies in patients with ALK-positive NSCLC. The ongoing Phase I/II studies consist of the following: Study AF-001JP, which is being conducted in Japan; Study NP28761/AF-002JG, which is being conducted in North America; and Study NP28673, which is being conducted globally.

The first-in-human Study AF-001JP is an open-label Phase I/II study being conducted in Japan. This study's objective is to assess the pharmacokinetics, safety, and efficacy of alectinib in Japanese patients with ALK-positive NSCLC who are crizotinib-naive and have had disease progression after receiving at least one line of chemotherapy. This study has completed enrollment, but it is still ongoing. A total of 70 patients were enrolled in the study (24 patients in the Part I portion and 46 patients in the Part 2 portion of the study). In the Part 1 portion of the study, at the data cutoff date of 14

February 2014, 24 patients were treated with alectinib doses ranging from 20 to 300 mg administered twice daily (BID). No dose-limiting toxicities (DLTs) or adverse events of Grade 4 severity were observed at up to the highest dose tested (i.e., 300 mg BID); the dosage of 300 mg BID was further evaluated in the Part 2 portion of the study without further dose escalation. In the Part 2 portion of the study, 46 patients were treated with the highest evaluated alectinib dosage of 300 mg BID, of whom 43 patients achieved an objective response (93.5%; 95% CI: 82.1%, 98.6%) and 9 patients (20%) experienced a complete response (CR) based on the review and assessment of patient radiographs by an Independent Review Committee (IRC) for the 12-month follow-up analysis (data cutoff date for response data, 31 January 2013). The median PFS was 27.7 months (95% CI: 26.9–not evaluable) based on the 31 January 2014 data cutoff date (Tamura et al. 2014).

Table 1 and Table 2 show the ORR and PFS results from patients participating in Part 2 of Study AF-001JP. The majority of patients (86%) had a time to response of  $\leq 6$  weeks after administration of the first dose.

**Table 1 Response Rates from Patients Participating in Part 2 of Study AF-001JP**

Response	IRC Assessment (%) (n=46)
Complete response	9 (20)
Partial response	34 (74)
Stable disease	1 (2)
Progressive disease	0 (0)
Not evaluable	2 (4.3)
Complete and partial responses [95% CI]	43 (93.5 [82.1, 98.6])

IRC = Independent Review Committee; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Note: Radiographs reviewed and assessed by an IRC with the use of RECIST v1.1 (data cutoff date, 2 April 2014).

**Table 2 Progression-Free Survival Results from Patients Participating in Part 2 of Study AF-001JP**

Result	No. (%) of Patients n=46
Median duration of treatment, months	22.4
No. (%) of patients with PFS events	12 (26)
Median PFS, months (95% CI)	27.7 (26.9, not estimable)
Percent of patients with 2-year PFS (95% CI)	76 (60, 86)

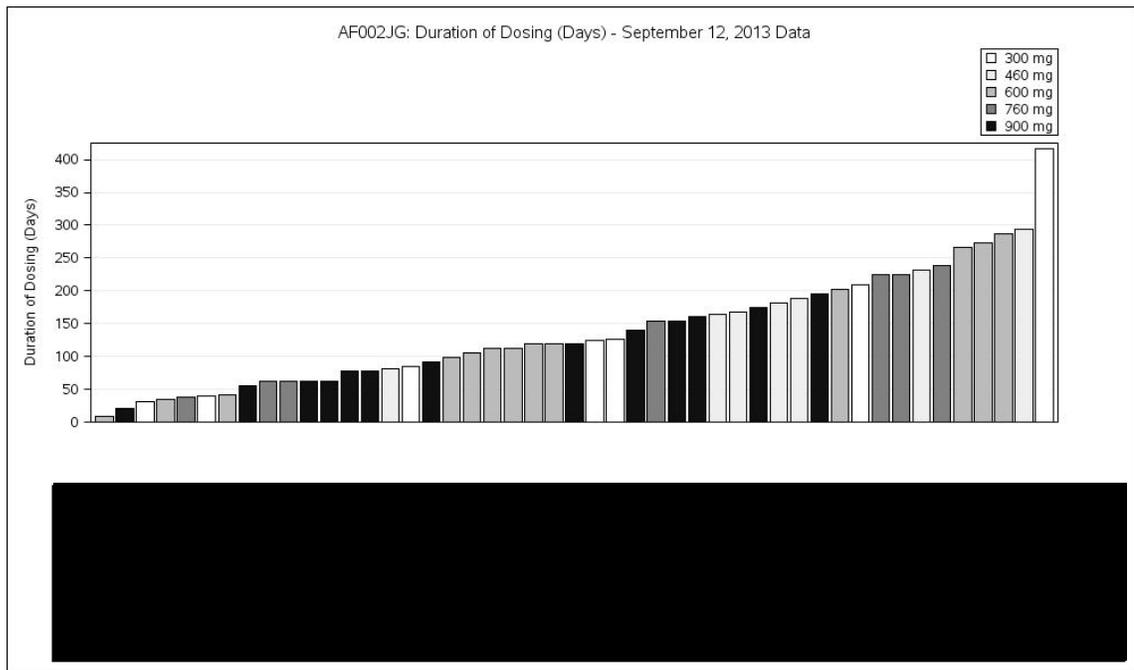
IRC=Independent Review Committee; PFS=progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

Notes: Radiographs reviewed and assessed by an IRC with the use of RECIST v1.1 (data cutoff date, 2 April 2014). The data in [Table 2](#) have not changed since the previous data cutoff date, 14 February 2014 (Chugai data on file). The maximum median PFS CI interval could not be estimated because the maximum was not reached.

In Study NP28761/AF-002JG (patients with ALK-positive NSCLC who had experienced crizotinib therapy failure), the Part 1 portion has completed enrollment. Two “bridging” cohorts of patients that received alectinib 600 and 900 mg BID, with the use of a 150-mg capsule, were included in Study NP28761/AF-002JG to transition and facilitate the planned formulation for the Phase II studies. A total of 47 patients were enrolled in Part 1. There was no substantial difference in pharmacokinetics between the two formulations (20 or 40-mg capsule and the 150-mg capsule) at the 600-mg BID dosage on the basis of the available data.

The radiological imaging analysis that was performed in 44 evaluable patients who had a baseline scan and at least one follow-up scan (data cutoff date, 12 September 2013) showed that 2 of 7 patients in the 300-mg BID dosage cohort, 5 of 7 patients in the 460-mg BID dosage cohort, 4 of 10 patients in the 600-mg BID dosage cohort, and 4 of 13 patients (including 1 patient with CR) in the 900-mg BID dosage cohort had achieved a confirmed partial response (PR), as assessed by the investigator. Three of 10 patients in the 600-mg BID dosage cohort, 2 of 7 patients in the 760-mg BID dosage cohort, and 4 of 13 patients in the 900-mg BID dosage cohort had achieved a PR as assessed by the investigator; these results have yet to be confirmed by a second tumor assessment. Three patients (all in the 600-mg BID dosage cohort) were unevaluable (tumors could not be evaluated at baseline). The ORR was 54.5% (i.e., 24 of 44 evaluable patients who had a baseline scan and at least one post-treatment scan available to determine overall response, or who had a best overall response of progressive disease [PD] determined by the investigator, on the basis of symptomatic progression [3 patients]), including unconfirmed responses across all dose cohorts. Thirty-three of the 47 treated patients (70%) were still receiving study treatment. The durations of dosing by cohort are shown in [Figure 1](#).

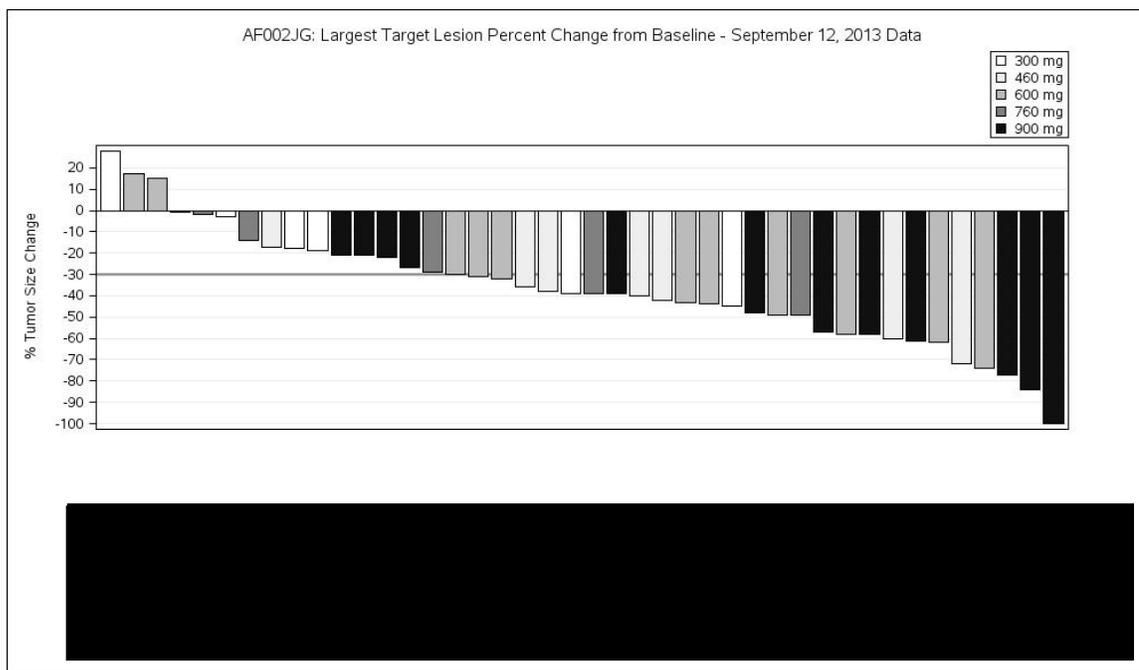
**Figure 1 Duration of Dosing by Cohort for Patients in Part 1 of Study NP28761/AF-002JG**



Note: Data cutoff date, 12 September 2013.

The waterfall plot for the 42 patients who had a radiological tumor assessment performed after baseline is shown in [Figure 2](#); 27 patients experienced tumor shrinkage of >30%, of whom 23 patients were assessed as experiencing a PR (9 of these PRs had yet to be confirmed by a second tumor assessment).

**Figure 2 Maximum Percent Change from Baseline in Target Lesion Size as Assessed by the Investigator for Patients in Part 1 of Study NP28761/AF-002JG**



Note: Data cutoff date, 12 September 2013.

Study NP28673 began enrolling patients on 20 June 2013, and the efficacy/safety data was published on 2015 American Society of Clinical Oncology (ASCO) annual meeting (see Alectinib Investigator's Brochure for more details).

The benefit of alectinib, with regard to CNS activity, has been described by the DOT (before disease progression) or ORR in patients with brain metastases at baseline in the two active studies: Study AF-001JP, conducted in Japan and Study NP28761/AF-002JG conducted in North America. In Part 2 of Study AF-001JP, 14 of 46 crizotinib-naïve patients (30%) had documented CNS lesions before being enrolled into the study. Three of these 14 patients were asymptomatic and had not received any prior CNS radiation. At the time of the clinical cutoff date of 31 January 2014, 9 of 14 patients who had brain metastases at baseline remained in the study without disease progression in the CNS or systemic disease progression.

Similar CNS responses were observed in Study NP28761/AF-002JG, although the data (n=47 patients) are more limited due to the shorter follow-up duration implemented in this study. Of the 47 patients for whom crizotinib therapy had failed who enrolled in the study (data cutoff date, 12 September 2013), 21 patients (45%) were known to have brain metastases at baseline, of whom 17 patients had received prior radiation before enrolling in the study and 4 had not received any prior radiation therapy. Seventeen of

the 21 patients are continuing on study treatment, and 4 patients discontinued study treatment due to progressive disease. All 4 patients who did not have prior brain irradiation before enrolling in the study remain in the study with durations of 77, 77, 154 and 196 days, as of 12 September 2013.

Study BO28984 (ALEX) is the pivotal Phase III study to evaluate alectinib versus crizotinib in patients with treatment-naïve advanced ALK-positive NSCLC. This study is ongoing. The results from Study BO28984 will determine whether alectinib treatment has superior efficacy compared with crizotinib.

Study JO28928, with a design similar to Study BO28984 in patients with ALK-positive NSCLC who are treatment-naïve or have received one line of standard chemotherapy, is ongoing in Japan.

See the Alectinib Investigator's Brochure for additional details on nonclinical and clinical studies.

### **1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

Over the past 10 years, the treatment of NSCLC has become increasingly focused on guiding treatment based on the presence or absence of an actionable mutation. Numerous oncogenes have now been identified in NSCLC, including mutations in the genes that code for EGFR, KRAS, phosphoinositide-3-kinase, catalytic,  $\alpha$  polypeptide, and human EGFR 2 (Pao and Girard 2011). As described in previous sections, a translocation in the gene that encodes the receptor tyrosine kinase ALK that leads to the expression of ALK fusion proteins was identified as an oncogenic driver in a subset of patients with NSCLC (Soda et al. 2007). ALK rearrangements are found in approximately 4.6% of unselected patients with NSCLC (Koivunen et al. 2008; Takeuchi et al. 2008; Boland et al. 2009; Wong et al. 2009; Bang 2011; Kim et al. 2011; Paik et al. 2011; Cardarella et al. 2012; Dai et al. 2012; Fukui et al. 2012).

Crizotinib is the first ALK inhibitor that is currently approved, and it has been registered in multiple countries worldwide including China for the treatment of ALK-positive NSCLC. Crizotinib is an oral, small-molecule, multi-targeted tyrosine kinase inhibitor (TKI) that targets ALK, MET, RON, and ROS1 tyrosine kinases (Sahu et al. 2013; Shaw et al. 2013a). Study PROFILE 1014, a Phase III study of crizotinib compared with standard pemetrexed-platinum-based chemotherapy, was presented at the ASCO 2014 congress (Mok et al. 2014). The study met its primary objective of prolonging PFS in patients who were previously untreated with ALK-positive non-squamous NSCLC with a median PFS of 10.9 and 7.0 months (HR: 0.45; 95% CI: 0.35, 0.60;  $p < 0.0001$ ) for crizotinib and pemetrexed-platinum-based chemotherapy, respectively (Solomon et al. 2014).

Although substantial benefit has been observed with crizotinib therapy, relapse eventually occurs. Two main reasons for this are the development of resistance

because of secondary (e.g., gatekeeper) mutations or because of CNS relapse (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013). This could be because of the fact that crizotinib is a P-glycoprotein (P-gp) substrate and has a low penetration in the CNS. Thus, patients with ALK-positive NSCLC that are treated with crizotinib experienced impaired control of brain metastases relative to other sites of systemic disease; 46% of progressive disease in patients who are treated with crizotinib involves the CNS (Costa et al. 2011). The CNS becomes a sanctuary site for ALK positive NSCLC that is treated with crizotinib—a physiologic and anatomic mechanism of drug resistance.

The second approved treatment for ALK-positive NSCLC is ceritinib (ZYKADIA™ U.S. Package Insert), an inhibitor of receptor tyrosine kinases including ALK and IGF-1. Ceritinib was granted accelerated approval by the FDA in 2014 for the treatment of patients with ALK-positive metastatic NSCLC who have had disease progression during treatment with crizotinib or are intolerant to crizotinib therapy.

Alectinib was granted approval in Japan on 4 July 2014 for the treatment of patients with ALK fusion gene-positive, unresectable, recurrent or advanced NSCLC.

Alectinib is a highly selective and potent, oral next-generation ALK inhibitor. Clinical data from the Part 2 portion of ongoing Study AF-001JP assessing alectinib in patients with ALK-positive NSCLC who are crizotinib-naive and have disease progression after at least one line of chemotherapy reported that the median treatment duration in the study has passed 23 months (range: 1-33). The ORR was 93.5% (95% CI: 82.1, 98.6) with a complete response rate of 19.6% (9 patients), and the 2-year PFS was 76% (95% CI: 60, 86) (Tamura et al. 2014).

Moreover, alectinib is a lipophilic drug and not a P-gp substrate, which may support its accessibility through the blood-brain barrier. This has been demonstrated in the nonclinical setting on the basis of the prolongation of survival in a mouse model with implanted CNS lesions and in a tissue-distribution study with a single oral dose of [<sup>14</sup>C]-alectinib of 1 mg/kg to albino rats (Ou et al. 2013). Preliminary clinical data from the Phase I and II studies demonstrate the consistent therapeutic efficacy of alectinib in brain metastases.

The clinical efficacy data are compelling, demonstrating that alectinib has a longer disease progression-free interval and improved activity with regard to the CNS, thus delaying the impact of CNS metastases on neurologic function and the morbidities associated with treatments required for disease control such as brain radiation, surgery, and corticosteroid use. The currently available clinical safety data support an acceptable safety and tolerability profile for alectinib. These data suggest the importance of comparing alectinib with crizotinib as a therapeutic option for ALK-positive advanced or advanced NSCLC.

In this proposed Phase III study, treatment-naive Asian patients with ALK-positive advanced NSCLC will be enrolled and randomized to receive either crizotinib or alectinib treatment. The results of this study will determine whether alectinib treatment has similar efficacy to which was demonstrated in Study BO28984.

The first Phase I dose-escalation study of alectinib was conducted in Japan (Study AF001-JP) and demonstrated that alectinib was generally well tolerated without dose-limiting toxicities at dosing regimens up to 300 mg BID. Of the 58 patients who received treatment with the highest evaluated dosage, 300 mg BID alectinib in Study AF 001JP, 27 experienced Grade 3 adverse events and 9 experienced serious adverse events. No deaths were reported during the study or during the 28 days after study drug treatment was discontinued. There were 5 adverse events that led to treatment discontinuation in Part 2 of the study (brain edema, sclerosing cholangitis, interstitial lung disease [ILD], increased ALT, and tumor hemorrhage). Alectinib was well tolerated at all doses investigated in this study. Alectinib's adverse event profile was consistent with the known adverse event profile associated with ALK inhibitors. In Part 1 of Study NP28761/AF-002JG, alectinib was well tolerated, with no DLTs or treatment-related dose modifications for doses through 600 mg BID. Two DLTs were reported in a bridging cohort of patients treated at 900 mg BID. Therefore, the recommended alectinib Phase II dosage of 600 mg BID was chosen as having the best balance among clinical safety, efficacy, and pharmacokinetic (PK) data observed in the Phase I and II studies (see Section 3.3.1).

On the basis of available preliminary data, the estimated benefits of alectinib treatment outweigh the risks, specifically:

- Available nonclinical and clinical data demonstrate that alectinib is active in patients with NSCLC who are either crizotinib-naive or have had disease progression during crizotinib therapy
- Clinical safety data from patients treated with alectinib up to and including 900 mg BID demonstrated that safety profile of alectinib is consistent with the known safety profile associated with ALK inhibitors.

Identified and potential risks associated with alectinib treatment will continue to be closely monitored throughout the clinical program. Patient safety during the alectinib program is facilitated by targeting the most appropriate patient population and by using protocol-specified study drug interruption criteria.

## **2. OBJECTIVES**

### **2.1 EFFICACY OBJECTIVES**

The primary efficacy objective for this study is to evaluate and compare the efficacy of alectinib with that of crizotinib in Asian patients with treatment-naive ALK-positive advanced NSCLC, as measured by investigator-assessed 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 ORR and DOR by treatment arm
- To evaluate and compare the time to disease progression in the CNS on the basis of review of patient radiographs by an 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 IRC by treatment arm
- To evaluate and compare the OS by treatment arm

## **2.2 SAFETY OBJECTIVE**

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

## **2.3 PHARMACOKINETIC OBJECTIVE**

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

## **2.4 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 and/or 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, see [Appendix 7](#)), the supplemental EORTC Quality-of-Life Questionnaire–Lung Cancer module (QLQ-LC13, see [Appendix 8](#)), and a composite of the following three symptoms: cough, dyspnea, and 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 (see [Appendix 7](#) and [Appendix 8](#), respectively)

## 2.5 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.*

## 3. STUDY DESIGN

### 3.1 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; D5F3 antibody, catalog reference number 790-4794, CE IVD: 06679072001, 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 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 BID, taken with food. The control arm will receive crizotinib administered orally at 250 mg BID, taken either 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 on the basis of RECIST v1.1, and subsequent treatment 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 the 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

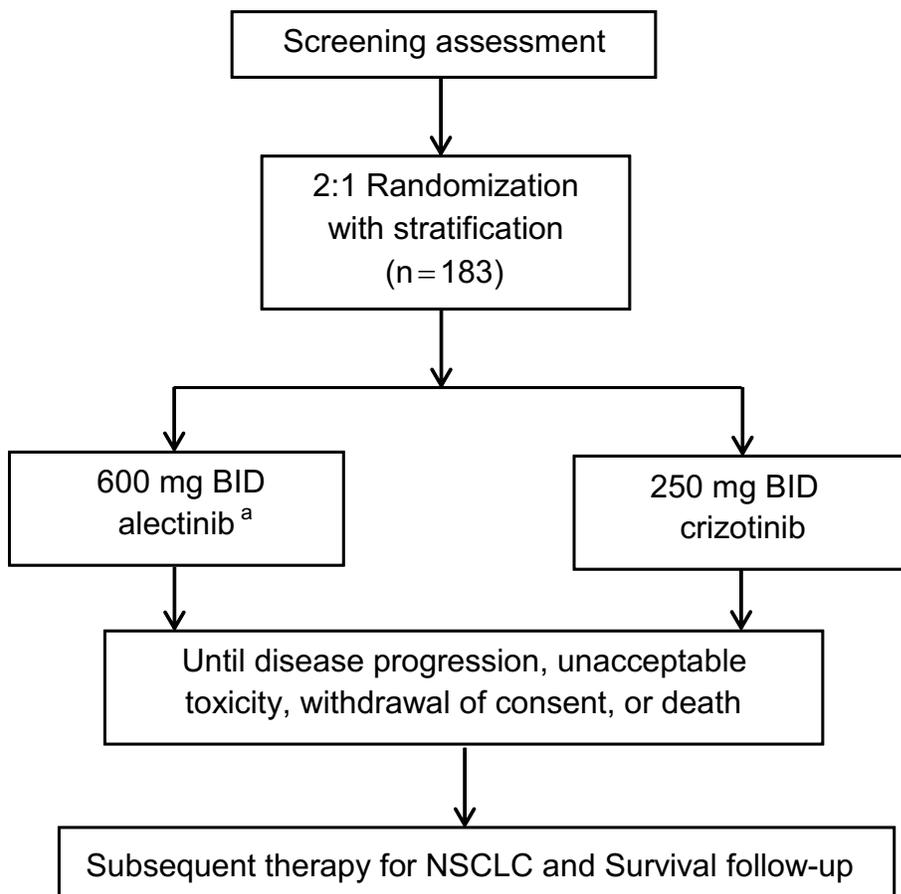
disease progression in the CNS is at the investigator's discretion for patients who may continue to benefit from their respective study drug treatment.

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.

A summary of the study design is shown in [Figure 3](#), and a schedule of assessments is provided in [Appendix 1](#).

**Figure 3 Summary of Study Design**



BID=twice a day; NSCLC=non-small cell lung cancer.

<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.

### **3.1.1 Independent Review Committee**

An IRC will be established to perform an independent review of all radiological scans for the *primary* analysis and to determine the response and disease progression on the basis of the RECIST v1.1 in addition to the local investigator's review of radiographs. Only the results from the investigator's review of radiographs will be used to determine whether patients should be enrolled or should remain in the study. The IRC's assessment will only be used in the *primary* analysis. All decisions made during the performance of the study will be on the basis of the local investigator's review and assessment of radiographs.

Sites will submit radiological files to the centrally located IRC's data review facility during the study on an ongoing basis or at the Sponsor's request for *primary* analysis. For the *primary* analysis, the IRC will perform an independent review of the computed

tomography (CT) and magnetic resonance imaging (MRI) scans on the basis of a prespecified Charter to determine the response and disease progression on the basis of the RECIST v1.1. Details are provided in the IRC Charter.

For evaluation of the CNS endpoints, the IRC will perform an assessment of scans on the basis of RECIST and RANO criteria. Details are provided in the IRC Charter.

### **3.2 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.*

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).

### **3.3 RATIONALE FOR STUDY DESIGN**

#### **3.3.1 Rationale for Alectinib Dosage**

Selection of the alectinib dose used in this study is based on the clinical safety, efficacy, and PK data observed in the Phase I/II studies (Study AF-001JP and Study NP28761/AF-002JG) and the supportive nonclinical data for alectinib.

The first-in-human study (Study AF-001JP) evaluated escalating doses of alectinib in Japanese patients in an accelerated titration scheme to rapidly identify the MTD. All doses, including the highest evaluated dosage in the study (300 mg BID), were well tolerated, and no DLTs were observed. The highest tested dosage, 300 mg BID, was further evaluated in the Part 2 portion of the study and demonstrated promising early efficacy and good safety with an ORR, as assessed by an IRC, of 93.5% (43/46 patients; 95% CI: 82.1%, 98.6%).

With no MTD determined in Study AF-001JP, dose escalation progressed in the North American Study NP28761/AF-002JG with the use of a modified 3+3 design, where 3 patients were assessed for DLTs, and additional patients were enrolled for PK evaluation. The starting dosage in Study NP28761/AF-002JG was 300 mg BID (the highest dosage evaluated in Study AF-001JP), and dose escalation progressed with evaluation of higher dosages of alectinib through 900 mg BID. Following multiple dosages of alectinib at 300 mg BID in Study NP28761/AF-002JG, the median alectinib exposure (area under the concentration–time curve from 0 to 10 hours [AUC<sub>0-10</sub>]) appeared to be approximately 2-fold lower compared with that in patients from

Study AF-001JP. The mechanisms underlying the observed exposure differences are not entirely clear; however, they suggest that a proportion of patients may not achieve exposures that demonstrated robust efficacy and safety in Study AF-001JP.

In Study NP28761/AF-002JG, no DLTs were observed in the dose escalation cohorts, up to a dosage-level of 900 mg BID. However, 2 patients in the subsequent 900-mg BID bridging cohort experienced a DLT (1 patient experienced a Grade 3 headache, and 1 patient Grade 3 neutropenia) and continued study drug treatment at a reduced dosage of 600 mg BID. Overall, alectinib was well tolerated in the study population.

Importantly, administration of alectinib at 600 mg BID provides systemic exposures that meet or exceed exposures that were achieved in patients receiving 300 mg BID in Study AF-001JP, demonstrating robust efficacy and safety in patients who are crizotinib-naïve. Further, in Study NP28761/AF-002JG, the 600-mg BID regimen has demonstrated promising activity in patients who are crizotinib-resistant and in patients who have CNS metastases; this regimen is also well tolerated in this patient population. Limited PK data from the 600-mg BID dose level are available from Study NP28673 across populations and illustrate that the mean alectinib steady-state exposures are only approximately 30%–40% higher in Asian (Taiwanese/South Korean) patients compared with Caucasian (European) patients in the within-study evaluation of Study NP28673. During cross-study evaluations that were relative to Study NP28761/AF-002JG, mean exposure differences ranged from 30% to 100% between Asian and non-Asian patients. The underlying mechanism for the differences remains to be determined; however, analyses of clinical safety data from the ongoing Phase II Study NP28673 demonstrated that the safety and tolerability profiles of alectinib administered at 600 mg BID are comparable between Asian and non-Asian patients and show good tolerability in the Asian population receiving the 600 mg BID dosing regimen, indicating that the clinical relevance of any observed differences in PK are limited.

On the basis of available nonclinical data, administration of alectinib 600 mg BID provides systemic exposures within the expected range (on the basis of regression of available data) for tumor regression observed in mouse xenograft models. See the Alectinib Investigator's Brochure.

Thus, the available clinical efficacy, safety, and PK and PK/PD data from ongoing clinical studies along with the supportive nonclinical data support the dosing regimen of 600 mg BID of alectinib as the recommended dosing regimen for evaluation in this study.

### **3.3.2 Rationale for Patient Population**

The study population will be composed of patients with non-resectable, locally advanced and metastatic NSCLC who have been shown to be ALK-positive by an IHC test performed at central laboratories specially designated for the study. Patients should not have received any previous treatment for advanced NSCLC (i.e., are treatment-naïve).

Both experimental (alectinib) and control (crizotinib) treatments are ALK-targeted therapies. The clinical practice guidelines recommend targeted treatment for patients with metastatic, oncogene-driven disease as first-line systemic therapy (i.e., EGFR-inhibitors for EGFR-positive NSCLC and ALK-inhibitors for ALK-positive NSCLC) ([NCCN 2014](#)).

To be eligible to participate in this study, determination of ALK positivity will be performed at a central laboratory with the use of an IHC assay (see [Appendix 10](#)). IHC is faster, easier to perform in local laboratories, and requires less equipment compared with the fluorescence in situ hybridization (FISH) assay. In addition, IHC has high concordance with FISH and a lower false-negative rate ([Kim et al. 2011](#)), and Ventana Medical Systems has been approved in China ([China Food and Drug Administration 2013, 2014](#)).

### **3.3.3 Rationale for Control Group**

Targeted therapy (including ALK-targeted therapy) is likely to have a greater anti-tumor effect than standard chemotherapy, offering patients a higher response rate and longer durability of response with less toxicity compared with any potential chemotherapy options ([Mok et al. 2009](#); [Rosell et al. 2012](#); [Sequist et al. 2013](#); [Shaw et al. 2013a](#)).

Crizotinib is an oral small-molecule multi-targeted TKI targeting ALK, MET, RON, and ROS1 tyrosine kinases ([Sahu et al. 2013](#); [Shaw et al. 2013a](#)). It is the first-generation ALK inhibitor that has been approved in multiple countries worldwide for the treatment of ALK-positive NSCLC.

In November 2013, crizotinib was granted regular approval in the United States for use in an ALK-positive NSCLC setting, regardless of treatment line ([XALKORI® U.S. Package Insert](#)), whereas in Europe, crizotinib is currently approved conditionally for patients with previously treated ALK-positive NSCLC ([Crizotinib SmPC](#)).

Crizotinib was also approved in China in February 2013 and became standard of treatment for ALK-positive NSCLC.

The National Comprehensive Cancer Network (NCCN) guidelines recommend crizotinib as first-line therapy for patients with advanced ALK-positive NSCLC ([NCCN 2014](#)).

The randomized Phase III Study PROFILE 1014 was conducted to assess the efficacy of crizotinib versus standard platinum-based chemotherapy (pemetrexed plus cisplatin or carboplatin) as first-line treatment for patients with ALK-positive, non-squamous NSCLC. The study met its primary objective of prolonging PFS in previously untreated patients with ALK-positive non-squamous NSCLC with median PFS of 10.9 and 7.0 months (HR: 0.45; 95% CI: 0.35, 0.60;  $p < 0.0001$ ) for crizotinib and pemetrexed-platinum-based chemotherapy, respectively ([Solomon et al. 2014](#)). The authors concluded that these

findings establish crizotinib as the standard of care for patients with previously untreated advanced ALK-positive non-squamous NSCLC (Solomon et al. 2014).

Crizotinib will be dosed as per standard dose recommendations from prescribing information—patients in the crizotinib arm will receive crizotinib at 250 mg orally BID with or without food until disease progression, unacceptable toxicity, withdrawal of consent, or death.

### **3.3.4 Rationale for Open-Label Design**

An open-label study design is more appropriate for patients enrolled in this particular study for a number of reasons defined below and with the ultimate goal to ensure patient compliance as much as possible.

For a blinded study design, all enrolled patients would be required to take five large capsules BID. This high pill count results from the difference in capsule size between crizotinib (size 0) and alectinib (size 1). Each dose would consist of one-250 mg capsule of crizotinib or matching placebo, and four-150 mg capsules of alectinib or matching placebo. In order to maintain blinding, crizotinib capsules would be required to be over-encapsulated which would increase the size of the capsule from size 0 to size 00 (double zero). The size 00 capsule is the largest capsule size administered orally to humans. For some patients, the size 00 capsules are too large to swallow. The high pill count per dose, combined with this large capsule size, is considered to be a significant burden to patients that increases the risk of non-compliance.

Additionally, a blinded study design would increase the complexity of standard dose reductions. Dose interruption or dose reduction may be required on the basis of individual safety and tolerability. The standard crizotinib dose reduction is 200 mg BID, which would require a different capsule (size 1), followed by 250 mg QD. However, dose reductions for alectinib would occur in 150 mg steps. In a double-blind study, these multiple-step dose reductions introduce a high level of complexity and potential for error.

To avoid a significant burden to patients associated with high pill count and increased risk of non-compliance because of capsule size and complexity of standard dose reductions, adequate steps have been taken to ensure the validity of the data in an open-label study design. These include performing sensitivity analyses to demonstrate the robustness of the primary endpoint, defining disease progression with the use of established response evaluation criteria (RECIST v1.1), performing tumor assessment at the same frequency in both treatment arms, adhering to protocol-defined schedules, and finalizing the strategy for the *primary* analysis of the primary endpoint before initiating this study, which include predefined methods for handling missing data and censoring rules. Efficacy analyses will be performed only at the prespecified analysis timepoints in the protocol (*primary* analysis will be performed when 97 PFS events have occurred, and survival follow-up analysis will be performed when 101 OS events have occurred).

### **3.3.5 Rationale for Primary Endpoint Selection**

The investigator-assessed PFS is the primary endpoint for this study.

PFS, as an endpoint, may reflect tumor growth and may be assessed before the determination of a survival benefit, and its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit-risk of the new study drug treatment compared with available therapies ([U.S. Department of Health and Human Services 2007](#); [European Medicines Agency 2012](#)). A PFS HR of 0.65 will be targeted, which constitutes a clinically meaningful benefit in this patient population because it will delay the use of platinum-based chemotherapy and potentially reduce both the frequency of CNS relapse and the morbidity associated with treating CNS metastases.

The assumed median PFS for patients in the alectinib treatment arm is 16.8 months, and an OS of more than 30 months is expected, which equates to a post-progression survival of at least 15 months. Patients with ALK-positive NSCLC who were treated with crizotinib in the second-line setting had a median PFS of 7.7 months and an interim median OS of 20.3 months ([Shaw et al. 2013a](#)), which equated to a post-progression survival of 12.6 months. This lengthy post-progression survival expected with alectinib treatment provides an opportunity for patients to receive subsequent treatments with other ALK inhibitors or several additional lines of chemotherapy or to participate in additional clinical studies.

Patients in both study arms who experience disease progression during study treatment will likely be treated with other subsequent treatment options, including ALK inhibitors. The availability of crizotinib on the market, the likely availability of other next-generation ALK TKIs, and the availability of other investigational agents in clinical studies offer potential treatment options to patients in this study who will eventually have disease progression. Subsequent therapies frequently confound the detection of an OS benefit, particularly in a setting with a long post-progression survival, such as ALK-positive NSCLC. This has been observed in studies for EGFR TKIs, in which strong PFS benefits were observed without evidence of OS benefit ([Rosell et al. 2009](#); [Fukuoka et al. 2011](#)).

The anticipated long post-progression survival and the confounding effects of subsequent lines of therapy indicate that it may be difficult to detect an OS benefit in this setting. Nevertheless, OS is one of the study's secondary endpoints. The crossover from crizotinib treatment to alectinib treatment will not be allowed in this study in order to preserve the study's ability to potentially demonstrate some degree of treatment benefit of alectinib in regards to OS, but, upon progression, patients will be treated at the investigator's discretion.

To ensure the consistency benefit with the global pivotal Study BO28984 (in terms of PFS), maintaining  $\geq 50\%$  of risk reduction from Study BO28984, a number of measures have been implemented, which include a substantial target magnitude of benefit (target HR=0.65) and study assessments that allow for a robust evaluation of benefit-risk (standard RECIST criteria used to define disease progression at fixed assessment intervals that are identical in both treatment arms and a robust definition of PFS along with prospectively defined methods to assess, quantify, and analyze PFS, which include censoring methods and sensitivity analyses).

### **3.3.6 Rationale for Secondary Endpoint of Time to CNS Progression**

Lung cancer is the most common type of cancer to spread to the brain, with at least 40% of people with lung cancer developing brain metastases at some point during their disease. ALK-positive NSCLC has a propensity to metastasize to the brain, and crizotinib has impaired control of brain metastases in comparison with other sites of systemic disease ([Chun et al. 2012](#)).

Delaying or preventing the development of CNS metastases would provide patients with a clinically meaningful benefit by avoiding consequences of neurological deficits from brain metastasis or by delaying or preventing long-term side effects associated with steroid use and brain irradiation.

Preliminary evidence of CNS benefit with alectinib has been observed in patients in the two ongoing Phase I/II studies. See Section 1.2 and the Alectinib Investigator's Brochure for additional details.

Time to CNS progression is defined as the time from randomization until radiographic evidence of CNS progression is documented. The aim of the prespecified analysis will be to evaluate whether alectinib significantly delays or prevents the development of CNS metastases.

Randomization of this Phase III study will be stratified by the presence or absence of CNS metastasis at baseline.

Imaging analysis with the use of uniform image acquisition technique (MRI scans) will be performed routinely at baseline and at subsequent follow-up assessments along with every systemic imaging tumor assessment or whenever clinically indicated (i.e., clinical suspicion of CNS metastasis) in order to achieve an accurate determination of time to CNS progression. This ensures that early brain metastatic lesions are detected and that assessment bias between the two treatment arms is avoided by having regularly scheduled MRI scans.

### **3.3.7 Rationale for Alectinib Pharmacokinetic Sample Collection Schedule**

To date, the pharmacokinetics of alectinib has been characterized in Study AF-001JP in patients with NSCLC who are crizotinib-naive and have had chemotherapy treatment fail and in Study NP28761/AF-002JG and Study NP28673 in patients who had both chemotherapy and treatment with crizotinib fail. In order to better understand the pharmacokinetics of alectinib in Chinese patients and to further support the development of a robust population PK model for alectinib, characterization of alectinib pharmacokinetics will be done in this study.

This study will include PK assessment of alectinib in patients with ALK-positive advanced NSCLC who are ALK inhibitor treatment-naive by collecting sparse samples from all patients receiving alectinib. Frequent blood sampling will be performed in a subset of 20 Chinese patients to facilitate the characterization of alectinib pharmacokinetics. The PK profile of alectinib after a single dose and at steady-state will be evaluated to determine accumulation index, area under the concentration–time curve (AUC), maximum plasma concentration observed ( $C_{max}$ ), time to maximum concentration ( $t_{max}$ ), etc.

The data from this study will provide a more robust understanding of alectinib pharmacokinetics in the crizotinib-naive patient population, including investigation and potential identification of sources of variability influencing alectinib pharmacokinetics or response to alectinib therapy. Results from the PK data collected in this study and analyses of these PK data may help support an optimal use of alectinib therapy.

### **3.3.8 Rationale for Biomarker Assessments**

There are several molecular mechanisms of resistance to crizotinib reported in the literature: increased copy number of the ALK gene, increased expression of ALK mRNA, secondary mutations in ALK (e.g., gatekeeper mutation), and changes (e.g., increased copy number, increased phosphorylation, or point mutations) in escape genes such as EGFR, cKIT, or KRAS (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013). In order to investigate molecular mechanisms of resistance to ALK inhibitors and ALK-mutation status, tumor samples will be collected before treatment and at the time of disease progression with the goal of sequencing nucleic acids.

Mutations in cancer genes appearing from drug resistance may be monitored in circulating nucleic acids in plasma (Forshew et al. 2012). Tumor nucleic acids are shed into circulation in amounts that allow direct amplification by polymerase chain reaction and analysis by sequencing. Plasma samples will be collected before treatment and at certain timepoints during treatment, to monitor mutations in ALK and other genes involved in resistance to ALK inhibitors. Information from mutated genes in the tumor will be correlated with mutations in plasma nucleic acids.

### 3.3.9 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to increase survival and palliate symptoms because disease symptoms have negative impacts on HRQOL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2008). This is especially true for studies that use PFS as a primary endpoint, where it is important to translate the delay in disease progression into an endpoint that is meaningful to patients.

Pain (chest; arm/shoulder), dyspnea, cough, and fatigue have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. Study BR.21 (erlotinib vs. chemotherapy in second- or third-line NSCLC) demonstrated that a longer TTD observed in the pain, dyspnea, and cough scales of the EORTC (QLQ-C30 and QLQ-LC13, see Appendix 7 and Appendix 8, respectively) was consistent with superior PFS, OS, and quality-of-life (QOL) benefits in the erlotinib treatment arm compared with the placebo treatment arm (Aaronson et al. 1993; Bergman et al. 1994; Bezzak et al. 2006). Additionally, patients in crizotinib Study PROFILE 1005 reported clinically significant (10 points) improvement in the pain, cough, dyspnea, and fatigue symptom scales as early as 2 weeks after starting treatment (Crinò et al. 2011).

The EORTC's QLQ-C30 and QLQ-LC13 scales (see Appendix 7 and Appendix 8, respectively) were used in Study PROFILE 1007, a Phase III study that compared second-line crizotinib versus chemotherapy. The study reported a significantly greater overall reduction from baseline in the symptoms of alopecia, cough, dyspnea, fatigue, chest pain, arm or shoulder pain, and pain in other parts of the body in patients treated with crizotinib compared with patients treated with chemotherapy ( $p < 0.001$  for all comparisons, without adjustment for multiple testing). Patients treated with crizotinib also had a significantly greater delay in the worsening of symptoms and significantly greater overall improvement from baseline in the global QOL versus those patients who received chemotherapy ( $p < 0.001$ ). In all domains measuring functioning, except for the domain measuring cognitive functioning, there was a significantly greater overall improvement from baseline among patients in the crizotinib treatment group versus patients in the chemotherapy group (Shaw et al. 2013a). In Study PROFILE 1014, a Phase III study of crizotinib compared with standard pemetrexed–platinum-based chemotherapy, there was a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib than among those who received chemotherapy ( $P < 0.001$ ). Crizotinib was also associated with a significantly greater overall improvement from baseline in physical, social, emotional, and role-functioning domains ( $P < 0.001$ ) (Solomon et al. 2014).

Therefore, to assess the QOL of patients in this study, PRO data will be collected from patients enrolled in this study with the use of validated EORTC questionnaires (QLQ-C30 and QLQ-LC13, see Appendix 7 and Appendix 8, respectively).

### **3.4 OUTCOME MEASURES**

#### **3.4.1 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 CR or PR as assessed by the investigators 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 a 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 who 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 they were known to be alive. Patients without any follow-up information will be censored at the date of randomization.

#### **3.4.2 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

### **3.4.3 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 PK of alectinib (and metabolite[s], if appropriate). See [Appendix 1](#) and [Appendix 2](#) for PK sampling times.
- Frequent blood sampling will be performed in a subset of 20 consenting Chinese patients enrolled to receive alectinib treatment. See [Appendix 1](#) and [Appendix 2](#) for PK sampling times.
- PK parameters will be determined as appropriate and where data allow
- NCA for alectinib (and metabolite[s], if appropriate) may 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.

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

The PRO questionnaires included 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 at every follow-up visit (every 8 weeks) after the Post-Treatment Visit for 6 months:

- The EORTC QLQ-C30 and EORTC QLQ-LC13 (see [Appendix 7](#) and [Appendix 8](#)) 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 (see [Appendix 7](#) and [Appendix 8](#)) 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.

### **3.4.5 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

## **4. MATERIALS AND METHODS**

### **4.1 PATIENTS**

Target population is patients with treatment-naïve ALK-positive non-resectable, locally advanced and metastatic NSCLC.

#### **4.1.1 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. The Ventana IHC test 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 determined with the use of 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 the 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 at  $\geq 14$  days before enrollment and be clinically stable.
- For all females of childbearing potential, a negative serum pregnancy test result must be obtained within 3 days prior to 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 of  $< 1\%$  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.

#### **4.1.2 Exclusion Criteria**

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

- A malignancy within the past 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 (NCI CTCAE v4.0) Grade 3 or higher toxicities due to 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 P450 (CYP) 3A inhibitors or inducers within 14 days prior to receiving the first dose of study treatment and during treatment with alectinib or crizotinib (see [Appendix 3](#))
- Administration of agents with potential QT-prolonging effects within 14 days prior to receiving the first dose of study drug (see Section 4.4.2 for further details)
- History of hypersensitivity to any of the additives in the alectinib drug formulation (see Section 4.3.1.1 for further details)
- History of hypersensitivity to any of the additives in the crizotinib drug formulation (see Section 4.3.1.2 for further details)
- 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

## **4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING**

This is an open-label study, for which the rationale is described in Section 3.3.4.

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 14 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).

Central randomization and drug pack number allocations will be performed and managed by an IxRS. Further details will be provided in an IxRS manual.

## **4.3 STUDY TREATMENT**

### **4.3.1 Formulation, Packaging, and Handling**

#### **4.3.1.1 Alectinib**

Alectinib is supplied 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 as excipients.

Alectinib capsules should be stored in accordance with the storage instructions on the label.

The formulation contains SLS as a surfactant excipient. This excipient is known to be associated potentially with GI adverse events such as nausea, vomiting, diarrhea, and abdominal pain.

For further details, see the Alectinib Investigator's Brochure.

#### **4.3.1.2 Crizotinib**

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.

## **4.3.2 Dosage, Administration, and Compliance**

### **4.3.2.1 Alectinib**

Alectinib 600 mg (four 150-mg capsules) should be administered orally BID with food in the morning and evening.

If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time.

Guidelines for dosage modifications and treatment interruptions or discontinuation because of specified adverse events are provided in Section 5.3.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

### **4.3.2.2 Crizotinib**

Crizotinib 250 mg (one 250-mg capsule) should be administered orally BID (in the morning and evening) with or without food.

If a dose is missed, the missed dose should be taken as soon as the patient remembers unless it is <6 hours until the next scheduled dose, in which case the patient should not take the missed dose. Patients should not take 2 doses at the same time to make up a missed for a missed dose. If vomiting occurs after taking a dose of crizotinib, the next dose should be taken as scheduled.

If dose reduction is necessary, then the dose of crizotinib should be reduced to 200 mg BID. If further dose reduction is necessary, then the dose should be modified to 250 mg taken QD. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4. Any overdose or incorrect administration of crizotinib should be noted on the crizotinib Administration eCRF. Adverse events associated with an overdose or incorrect administration of crizotinib should be recorded on the Adverse Event eCRF.

## **4.3.3 Investigational Medicinal Product Accountability**

All investigational medicinal products (IMPs) required for completion of this study (alectinib and crizotinib) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the

Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

#### **4.3.4 Post-Study Access to Alectinib**

The Sponsor will offer post-study access to the study drug alectinib free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for ALK-positive NSCLC.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for ALK-positive NSCLC.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

[http://www.roche.com/policy\\_continued\\_access\\_to\\_investigational\\_medicines.pdf](http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf)

### **4.4 CONCOMITANT THERAPY**

#### **4.4.1 Permitted Therapy**

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 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).

Caution should be exercised when the following are co-administered with alectinib:

- For medications that are substrates of P-gp transporter or breast cancer resistance protein transporter, the investigator should use caution and monitoring when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration cannot be avoided, it is recommended that signs for toxicity are carefully monitored (see [Appendix 3](#)).

Caution should be exercised when the following are co-administered with crizotinib:

- Crizotinib has been shown to be a moderate inhibitor of CYP3A. Dose reduction may be needed for co-administered drugs that are predominantly metabolized by CYP3A in patients receiving crizotinib. Concurrent use of CYP3A substrates with narrow therapeutic indices should be avoided (see [Appendix 3](#)).
- On the basis of an in vitro study, crizotinib is predicted to inhibit intestinal P-gp. Therefore, administration of crizotinib with medicinal products that are substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) may increase their therapeutic effect and adverse reactions (see [Appendix 3](#)). Close clinical surveillance is recommended when crizotinib is administered with these medicinal products.
- Bradycardia has been reported during clinical studies; therefore, the use of crizotinib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) should be avoided to the extent possible.

- In vitro studies in human hepatocytes indicated that crizotinib may induce pregnane X receptor and constitutive androstane receptor–regulated enzymes (e.g., CYP3A4, CYP2B6, CYP2C8, CYP2C9, UGT1A1). However, there was no observed induction in vivo when crizotinib was co-administered with the CYP3A probe substrate midazolam. Caution should be exercised in administering crizotinib in combination with medicinal products that are metabolized predominantly by these enzymes. Of note, the effectiveness of concomitant administration of oral contraceptives may be altered.
- In vitro studies indicated that crizotinib is an inhibitor of CYP2B6. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz).

#### **4.4.2 Prohibited Therapy**

Use of the following therapies (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) is prohibited during the study and for at least 14 days prior to initiation of study drug treatment (either alectinib or crizotinib), unless otherwise specified below. Exceptions to the below listed concomitant therapies restrictions (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) may be made only if the rationale is discussed and documented between the investigator and the Sponsor’s Clinical Pharmacologist.

- Potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St John’s wort [*Hypericum perforatum*]) within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug treatment and during treatment with study drugs (see [Appendix 3](#))
- Potent inhibitors of CYP3A (e.g., ketoconazole) within 2 weeks or 5 half-lives (whichever is longer) prior to the first dose of study drug treatment and during treatment with study drug (see [Appendix 3](#))
- Any concomitant medications known to affect QT interval duration, including but not limited to the following drugs: amiodarone, cisapride, clarithromycin, methadone, and quinidine within 2 weeks prior to the first dose of study drug treatment *for all patients, and while on treatment through the end of the study for crizotinib-treated patients only*
- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins during study treatment
- Systemic chemotherapy
- Radiotherapy/radionuclide therapy except for palliative radiotherapy to bone lesions or for pain control. If palliative radiation is indicated for bone metastases, palliative radiation may start within 24 hours after the last dose of alectinib unless, in the judgment of the investigator, patient safety will require a longer washout period before initiating palliative therapy. Alectinib dosing may resume after resolution of any radiation toxicity to a Grade  $\leq 1$ .
- Additional investigational drug (except during the follow-up period)

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication strongly inhibits or induces CYP3A. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications that are not listed above.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

<http://medicine.iupui.edu/clinpharm/ddis/table.aspx>

#### **4.4.3 Prohibited Food**

Ingestion of grapefruit or grapefruit juice should be avoided during the study and for at least 14 days prior to the initiation of study drug treatment (either alectinib or crizotinib) because it is a potent CYP3A inhibitor and may increase plasma concentration of either alectinib or crizotinib.

### **4.5 STUDY ASSESSMENTS**

See [Appendix 1](#) for the schedule of assessments performed during the study.

#### **4.5.1 Informed Consent Forms and Screening Log**

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm the patient meets all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

#### **4.5.2 Medical History and Demographic Data**

Medical history includes clinically significant diseases, surgeries, cancer history (including previous cancer therapies and procedures), reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

#### **4.5.3 Corticosteroid Use for CNS Metastases**

For patients with CNS metastases requiring corticosteroid use, the corticosteroid intake should be captured at all tumor assessment visits and compared with the corticosteroid intake at the time of the last disease assessment. The changes will be recorded as

increased, unchanged, or decreased. Increases and decreases in corticosteroid intake should be clinically justified. Increases in corticosteroid dose for reasons other than for CNS metastases control do not need to be taken into consideration when making this comparison.

#### **4.5.4 Physical Examinations**

A complete physical examination performed at screening and baseline should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems as well as height and weight. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Note: For patients with known CNS metastases, a neurological examination must be performed at each tumor assessment visit and be compared with the neurological examination performed at the time of the last disease assessment. Definition of clear neurological worsening is difficult to describe because progression in the CNS can present in numerous ways. Accordingly, evaluation of neurological function at each disease assessment will be made purely on the basis of the investigator's assessment of the patient's neurological state compared with the neurological function at the time of the last disease assessment. Neurological status will be recorded as improved, stable, or worsened.

#### **4.5.5 Vital Signs**

Vital signs will include measurements of respiratory rate, oxygen saturation, heart rate, and systolic and diastolic blood pressure (while the patient is in a seated position), and temperature.

#### **4.5.6 Eastern Cooperative Oncology Group Performance Status**

PS will be measured with use of the ECOG PS Scale (see [Appendix 6](#)). It is recommended, where possible, that a patient's PS be assessed by the same person throughout the study.

#### **4.5.7 Tumor and Response Evaluations**

Disease burden must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator based on physical examinations, *radiographic imaging, and other modalities, and* documented by color photography (with caliper measurement for measurable lesions) *or measurements by* CT scans and other modalities (e.g., MRI, brain scans), with the use of RECIST v1.1 (see [Appendix 4](#)).

To assess response in patients with measurable disease, the preferred radiologic tumor response assessment is CT scan with intravenous contrast. If intravenous contrast is contraindicated, a non-contrast-enhanced chest CT scan will be acceptable for chest lesions, and MRI may be used for non-chest lesions. If contrast-enhanced MRI is contraindicated, then non-contrast-enhanced MRI will suffice. Positron emission tomography (PET) scan, bone scan, and ultrasound cannot be used to measure lesions as per RECIST v1.1 (see [Appendix 4](#)).

The same radiographic procedure used to define measurable disease sites at screening must be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits.

CT and/or MRI scans of chest and abdomen and MRI scans of the brain should be performed for all patients as described in Schedule of Assessments (see [Appendix 1](#)) at screening, then every 8 weeks subsequently until disease progression and during post-progression on treatment visit in the case of isolated, asymptomatic progression of disease in the CNS, and at the Post-Treatment Visit (4 weeks after permanent treatment discontinuation). CT and/or MRI scans of the neck bones and pelvis should be included if clinically indicated. At the investigator's discretion, CT and/or MRI scans may be repeated at any time if PD is suspected.

Note: Brain imaging should be performed with the use of MRI with the following image acquisition requirements:

- Minimum sequences required:
  - Pre-contrast T1, T2/FLAIR
  - Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended
- Recommended slice thickness  $\leq 5$  mm with no gap

Patients with known or suspected bone metastases should undergo a radionuclide bone scan at screening. Bone scan, PET scan, or plain films are not considered to be adequate imaging techniques to measure bone lesions and do not need to be repeated routinely, but they can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI may be considered measurable lesions of the soft tissue component and meets the definition of measurability; these should be followed by cross-sectional imaging.

According to RECIST criteria, measurable skin metastases should be clinically assessed with caliper measurement. Documentation by color photography, including a ruler to estimate the size of the lesion, should be performed at screening then repeated at the scheduled tumor evaluations.

## **4.5.8 Laboratory, Biomarker, and Other Biological Samples**

### **4.5.8.1 Laboratory Assessments**

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count *or percentage* [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells, *etc.*])
- Coagulation (PT [or INR] and aPTT)
- Serum chemistry (sodium, potassium, chloride, bicarbonate *or total CO<sub>2</sub>*, fasting glucose, BUN or urea, creatinine [including an estimated eGFR calculated with the use of the MDRD formula; see [Appendix 9](#)], CPK, gamma-glutamyl transferase [GGT], calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase [ALP], phosphorus, magnesium, and thyroid-stimulating hormone.
- Urinalysis: Urine samples will be collected according to the schedule of assessments (see [Appendix 1](#)) (first morning urine sample for baseline and end-of-treatment/withdrawal visit spot urine sample for rest of the visits). Urine protein will be measured by dipstick test.
- Pregnancy test. All women who are not postmenopausal ( $\geq 12$  months of non-therapy induced amenorrhea) or surgically sterile will have a serum pregnancy test performed at screening (i.e., within 3 days prior to receiving first dose of study drug). Urine pregnancy tests will be performed anytime during the course of the study, as per investigator's discretion. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

### **4.5.8.2 Pretreatment Tumor Samples (Mandatory)**

Mandatory pretreatment tumor samples will be collected to centrally examine ALK status by IHC (eligibility criteria). Tumor blocks (formalin-fixed, preferred 10% neutral-buffered formalin) are the preferred source, but if blocks are not available, 7 unstained 5- $\mu$ m slides cut <3 months before screening are *acceptable for ALK IHC testing*.

*For cases where tumor blocks have been submitted, an additional 6 slides will be cut from blocks submitted for randomized patients. For cases where slides have been submitted for screening, an additional 6 slides are desired. Pretreatment tumor samples may be used for DNA and/or RNA extraction to enable Next Generation Sequencing (NGS) to identify somatic mutations that are associated with disease progression or acquired resistance to alectinib and to add to researchers' understanding of disease pathobiology. These samples will not be collected in countries/sites where the regulatory agency or the Institutional Review Board (IRB) does not allow this testing. Any remaining tumor blocks from screen-failed patients will be returned to the sites within 3–4 months of receipt at Sponsor-designated central laboratory, and any remaining tumor blocks from randomized patients will be returned to the sites before the final closure of the clinical database; slides will not be returned.*

For fresh tumor biopsy samples (guided by ultrasound or CT scan), acceptable methods include core biopsy samples for lung and liver lesions and bronchoscopic biopsy samples for lung lesions. The minimum size recommended for the biopsy needle is 20G.

For enrollment in the study, central ALK testing to determine or confirm patients' ALK status will be performed at a Sponsor-designated central laboratory with use of a Ventana ALK test by IHC (see [Appendix 10](#)).

For sample handling procedures, storage conditions and shipment instructions, see the laboratory manual.

#### **4.5.8.3 Post-Treatment Tumor Samples (Optional)**

Post-treatment tumor samples (preferably formalin-fixed blocks, but if not available a minimum of 9 unstained 5 µm slides) at the time of disease progression or permanent treatment discontinuation (at the last treatment or post-progression visit) may be collected, with proper informed consent. These samples may allow a greater understanding of the molecular mechanisms of resistance to ALK inhibitors and genes involved in cancer. *Any remaining tumor blocks of randomized patients will be returned to the sites before the final closure of the clinical database. Slides will not be returned.*

NGS **may be** performed by Foundation Medicine (ex-China) or a designated laboratory in China. If performed by Foundation Medicine or a designated lab in China, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by the FDA; results from these investigational tests should not be used to guide future treatment decisions.

On the basis of continual analysis of the data in this study and other studies, or on the basis of data from literature, collection of optional tumor samples with exploratory purposes may be stopped at any time if the data from the samples collected do not produce useful information.

#### **4.5.8.4 Blood and Plasma Samples**

Mandatory plasma samples *for biomarker analysis* will be obtained to determine:

- ALK rearrangement determination by plasma ALK quantitative reverse transcription polymerase chain reaction. *This will require 20 mL of blood at screening from all screened patients.*

- *Mutation* status in ALK and other escape genes (e.g., EGFR, KRAS). *This* will require 20 mL of blood (two tubes of 10 mL each) to be collected at baseline, at Treatment Visit 7 (Week 16), and subsequently at every second treatment visit (every 16 weeks) [see [Appendix 1](#) for detailed information] until *and at* disease progression (*CNS and/or systemic* disease progression) or *treatment discontinuation for any reasons*.
- These samples will not be collected in countries/*or sites* where the regulatory agency or the IRB does not allow genetic testing.

Details of sample handling procedures, sample storage, and shipment will be described in a separate laboratory manual.

On the basis of continual analysis of the data in this study and in other studies or on the basis of data from literature, the collection of plasma samples for exploratory purposes may be stopped at any time, if the data from the samples collected do not produce useful information.

*All the biomarker samples described in Sections [4.5.8.2](#), [4.5.8.3](#), and [4.5.8.4](#) will be stored for 5 years after the date of final closure of the associated clinical database.*

#### **4.5.8.5 Samples for Alectinib Pharmacokinetic Assessments**

Blood samples (approximately 2 mL of venous blood) collected from all patients treated with alectinib will be used for assessment of alectinib pharmacokinetics and major metabolites M4 (RO5468924) and other metabolites if appropriate (provided that assays for detection are available). Plasma concentrations for alectinib (and metabolite[s], if appropriate) will be measured by specific and validated liquid chromatography tandem mass spectrometry methods. These samples will be destroyed when the final clinical study report is complete.

Frequent blood sampling will be performed in a subset of 20 consenting Chinese patients randomized to alectinib treatment to ensure there are at least 16 patients with evaluable PK profiles on Visit 0 (baseline, after the first dose) and Visit 2 (Week 4) at the timepoints specified in [Appendix 2](#) for the non-compartmental PK analyses, as appropriate and where data allow.

Sparse blood samples will be collected from all patients receiving alectinib treatment and subsequently used for popPK analyses, as appropriate and where data allow.

See [Appendix 2](#) for the blood sample collection schedule. Residual samples following the PK analysis may be used to further evaluate the profile of alectinib metabolites.

All predose blood samples collected for PK analysis should be collected within 2 hours BEFORE the morning dose of any study medication.

Patients who permanently discontinue study drug treatment will also be discontinued from all PK assessments. The procedures for the collection, handling, storage, and shipping of plasma samples for the PK analysis are specified in the laboratory manual.

These samples will be destroyed when the final clinical study report is complete.

On the basis of continual analysis of the data in this study and other studies, collection of any sample type may be stopped at any time, if the data from the samples collected do not produce useful information or at the discretion of the Sponsor.

#### **4.5.9 Electrocardiograms**

An ECG will be recorded at specified timepoints as outlined in the schedule of assessments ([Appendix 1](#)) at screening, at Visit 0 (baseline), at Visit 2 (Week 4), at Visit 8 (Week 24), at Visit 12 (Week 56), and at the end of treatment/withdrawal visit and as clinically indicated throughout the study. All ECG recordings must be performed with the use of a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. All ECGs are to be obtained before other procedures, as well as meals, that are scheduled at that same visit (e.g., vital sign measurements, blood draws, study drug administration). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

Patients must have been in a supine or semi-supine position for at least 5 minutes before the ECG recording is obtained. The same recording position (supine or semi-supine) and the same equipment should be used for each patient throughout the study. The ECG printout must be 1) reviewed by a medically qualified member of the study team at the site, 2) annotated to indicate any clinical finding, and 3) dated and signed by this person and filed in the patient notes. ECG parameters will be entered on the ECG eCRF. The following parameters should be captured on the ECG eCRF: heart rate; PQ, QRS, and QT duration; and QT interval corrected with the use of Fridericia's formula (QTcF). In the event that the ECG machine does not directly provide results for RR and/or QTcF, these parameters can be derived using the formulae provided in [Appendix 11](#).

*To have a consistent approach for the RR and QTcF, it was decided that the calculation of RR and QTcF will be done by the Sponsor using the formulae provided in [Appendix 11](#). The results will be populated in the eCRF for use by the investigator.*

If any ECG abnormality is associated with an adverse event, it must be recorded and managed as described in [Section 5](#).

If considered appropriate by the Sponsor, ECG recordings may be analyzed retrospectively at a central laboratory.

#### **4.5.10 Patient-Reported Outcomes**

PROs (EORTC QLQ-C30 and EORTC QLQ-L13, see [Appendix 7](#) and [Appendix 8](#), respectively) will be collected to more fully characterize the clinical profile of alectinib. These instruments (questionnaires) will be translated as required, in the local language. To ensure instrument validity and to ensure that data standards meet health authority requirements, the PROs scheduled for administration during a clinic visit (EORTC QLQ-C30 and EORTC QLQ-L13, see [Appendix 7](#) and [Appendix 8](#), respectively) should be completed before the performance of non-PRO assessments and the administration of study treatment. Patients will also need to maintain a diary of daily drug intake (crizotinib arm)/drug intake with food (alectinib arm).

### **4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION**

#### **4.6.1 Patient Discontinuation**

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw consent for treatment should continue to be followed for tumor assessments until disease progression and for OS information, provided they have not withdrawn consent for the study. However, patients will not be followed for any reason after consent for the study has been withdrawn. Patients who withdraw from the study will not be replaced.

#### **4.6.2 Study Treatment Discontinuation**

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Inability to tolerate the study medication on the basis of the investigator's judgment

See guidelines for managing adverse events and for comprehensive guidance regarding study drug discontinuation in [Section 5.1.3](#).

Patients who discontinue study drug prematurely will be asked to return to the clinic for tumor assessments until disease progression as per the study schedule (see [Appendix 1](#)).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

#### **4.6.3 Study and Site Discontinuation**

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other related studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

### **5. ASSESSMENT OF SAFETY**

#### **5.1 SAFETY PLAN**

##### **5.1.1 Adverse Events Collection**

After informed consent has been obtained and before initiation of study drug treatment, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsy sample collections).

After the first dose of study treatment and through the 4-week follow-up after the last dose of study treatment, all adverse events will be collected regardless of seriousness, causality assessment, or actions taken and reported by the investigator or designated medically qualified study site personnel, as described below. At each visit, the investigator or designated medically qualified study personnel will ask the patient if any untoward medical event had occurred since the last visit. It is the investigator's responsibility to record all adverse events in the patient's medical records.

All serious and non-serious adverse events will be reported on the standard Adverse Event/Serious Adverse Event eCRF.

## **5.1.2 Adverse Events Relating to ALK Inhibitors and/or the Tyrosine Kinase Inhibitor Class and Alectinib Data**

Events described in Sections 5.1.2.1 through 5.1.2.10 will be closely monitored and will represent selected adverse events for this study.

A more detailed safety profile of alectinib is provided in the Alectinib Investigator's Brochure.

### **5.1.2.1 Interstitial Lung Disease**

TKIs, including the ALK inhibitors crizotinib and ceritinib, have been associated with the occurrence of treatment-related ILD (including fatalities).

See Section 5.1.3 for management and follow-up procedures.

### **5.1.2.2 Hepatotoxicity**

Hepatobiliary findings were observed in both the rat and monkey in 4- and 13-week toxicity studies with alectinib. The findings in the 13-week studies were similar to those of the 4-week studies. The findings were at or were close to clinically relevant exposures. Hepatobiliary effects included increased hepatic ALP, direct bilirubin, GGT, and liver weight; vacuolation/degeneration/necrosis of bile duct epithelium; inflammatory cell infiltration in Glisson's sheath; enlargement/focal necrosis of hepatocytes; and enlargement of Kupffer cells.

Abnormal hepatobiliary laboratory test values, such as increased ALT, AST, or bilirubin levels, have been observed after alectinib administration. AST, ALT, and total bilirubin levels temporarily increased in the initial stages of treatment and then improved (i.e., levels decreased or returned to normal). In patients with Grade 3-4 AST/ALT elevations, documented drug induced liver injury by liver biopsy was reported with uncommon frequency. Concurrent elevations in ALT or AST greater than or equal to three times the upper limit of normal (ULN) and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred with uncommon frequency in patients treated in alectinib clinical trials.

In patients treated with other ALK inhibitor drugs, abnormal liver function tests and drug-induced hepatotoxicity, including cases with fatal outcome have been reported.

See Section 5.1.3 for management and follow-up procedures.

### **5.1.2.3 *Anemia***

Hematologic findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib. The findings in the 13-week studies were similar to those of the 4-week studies. Findings were at or close to clinically relevant exposures. Hematologic adverse effects such as anemia, thrombocytopenia, bleeding, and neutropenia have been observed with most TKIs, including ALK inhibitors crizotinib and ceritinib.

*Cases of anemia have been reported in patients treated with alectinib; the majority of the events were Grade 1 or 2.*

See Section [5.1.3](#) for management and follow-up procedures.

#### **5.1.2.4 Gastrointestinal Disorders**

GI disorders such as nausea, vomiting, constipation, and diarrhea have been reported with alectinib. Similar GI disorders have been observed with other TKIs, including the ALK inhibitors crizotinib and ceritinib.

SLS (or the synthetic equivalent: sodium dodecyl sulfate) is a surfactant excipient in the clinical formulation at a concentration of 50% (w/w SLS to active pharmaceutical ingredient). This excipient is a known GI irritant and may be associated with GI adverse events including nausea, vomiting, diarrhea, and abdominal pain. Of note, GI tract toxicity as the safety determinant of SLS does not occur because of systemic toxicity, but is a consequence of local irritation to the GI tract. In general, when taken with food, higher levels of SLS—a known GI tract mucosal irritant—are tolerated versus gavage administrations.

See Section [5.1.3](#) for management and follow-up procedures.

#### **5.1.2.5 Skin Disorders**

Results of an in vitro phototoxicity study indicated that alectinib may have a phototoxic potential.

Skin rash has been reported with the majority of TKIs, including those that target the ALK receptor ([Hartmann et al. 2009](#)).

Cases of skin rash and photosensitivity have been reported with alectinib and were generally of Grade 1 or 2.

See Section [5.1.3](#) for management and follow-up procedures.

#### **5.1.2.6 Vision Disorders**

In the rat quantitative whole body autoradiography study, tissue radioactivity disappeared over time, following a time course comparable to that of plasma radioactivity, with the exception of melanin-containing tissues such as the uveal tract of the eyes, which had a much higher and more sustained exposure in pigmented rats. This is consistent with what is commonly observed for lipophilic basic drugs.

Vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters have been reported with several TKIs, including ALK inhibitors (crizotinib and ceritinib) ([Shaw et al. 2013a](#); ZYKADIA™ U.S. Package Insert).

Vision disorders, such as dry eye, blepharitis, conjunctivitis, blurred vision, and impaired vision have been reported with alectinib and were generally of Grades 1 and 2.

See Section 5.1.3 for management and follow-up procedures.

#### **5.1.2.7 Edema**

Most TKIs, including the ALK inhibitors crizotinib and ceritinib, have been associated with edema. Events of edema have been reported with alectinib, mostly of Grade 1 or 2.

See Section 5.1.3 for management and follow-up procedures.

#### **5.1.2.8 Bradycardia**

In the monkey telemetry study, there were no effects on the ECG or any of the other cardiovascular parameters or body temperature at doses of up to 15 mg/kg (mean  $C_{max}$ : 279 ng/mL).

In a preliminary telemetry study in conscious cynomolgus monkeys, a slight hypotensive effect (approximately 10 mmHg) was observed when alectinib was administered at 20 and 60 mg/kg orally with no effects on ECG or heart rate. The hypotensive effect of alectinib observed in monkeys was considered likely to have been caused by vasodilatation that was induced by L-type  $Ca^{2+}$  channel inhibition.

Events of bradycardia have been reported with alectinib. Preliminary heart rate data (based on ECG and pulse measurements) from the ongoing alectinib clinical studies show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. In patients treated with other ALK inhibitors (crizotinib and ceritinib), bradycardia adverse events, and decreases in heart rate based on ECG and pulse measurements, have also been reported.

In case of bradycardia, concomitant medications must be evaluated to identify those that are known to cause bradycardia, as well as anti-hypertensive medications; discontinuation or dose reduction of these concomitant medications must be considered.

See Section 5.1.3 for management and follow-up procedures.

#### **5.1.2.9 Abnormal Renal Function**

In a 2-week non-human primate study, alectinib was administered at 60 mg/kg. An increase in creatinine was observed but no changes were observed in histopathology. In all other non-human primate studies, no changes in creatinine were observed.

In a retrospective analysis conducted by the Chronic Kidney Disease Epidemiology Collaboration prediction equation, eGFR is reduced by treatment with crizotinib, but the majority of patients will recover their eGFR after the cessation of therapy. The early onset, size of the change, minimal cumulative effect, and rapid reversibility raise the

possibility that this may be a pharmacological and/or tubular creatinine secretion effect rather than a direct nephrotoxic effect ([Brosnan et al. 2014](#)).

Serum creatinine increases have been reported with ceritinib treatment and were generally of Grades 1 and 2 ([ZYKADIA™ U.S. Package Insert](#)). Serum creatinine increases have been reported with alectinib treatment and were generally of Grades 1 and 2.

See Section [5.1.3](#) for management and follow-up procedures.

#### **5.1.2.10 Severe Myalgia and CPK Elevations**

Postmarketing experience with some TKIs includes reports of myopathy and rhabdomyolysis ([Hohenegger 2012](#)).

Blood CPK increases, generally of Grades 1 and 2, and muscular adverse events have been reported with alectinib treatment. Grade 3 myalgia and CPK elevations have been reported with alectinib treatment and were reversible upon dose reduction and interruption.

See Section [5.1.3](#) for management and follow-up procedures and [Table 3](#) for guidelines for managing adverse events.

### 5.1.3 Management of Specific Adverse Events with Alectinib

**Table 3 Guidelines for Management of Specific Adverse Events with Alectinib**

Event	Action to Be Taken
Interstitial lung disease	<ul style="list-style-type: none"> <li>• Patients should be monitored for pulmonary symptoms that are indicative of pneumonitis.</li> <li>• Study drug should be permanently discontinued in patients who are diagnosed with interstitial lung disease.</li> </ul>
Hepatotoxicity	<p>Liver test laboratory abnormalities are to be reported as AEs only if they fulfill the criteria listed in Section 5.3.5.4 and Section 5.3.5.6.</p> <ul style="list-style-type: none"> <li>• If ALT or AST <math>&gt;3\times</math> baseline, repeat testing of ALT, AST, ALP, and total bilirubin within 48–72 hours, with inquiry about symptoms. If upon repeat testing, the transaminases remain <math>&gt;3\times</math> baseline, but are not <math>&gt;5\times</math> baseline or not accompanied with bilirubin increases or do not match any other rule for permanent discontinuation, then dose modification is not necessary and monitoring can continue as per investigator judgment.</li> <li>• At any time during the study treatment, if symptoms that are compatible with liver injury are observed, liver enzymes should be measured as soon as possible.</li> <li>• Study drug treatment must be permanently discontinued if any of the following occurs: <ul style="list-style-type: none"> <li>First observation of ALT or AST <math>&gt;8\times</math> ULN</li> <li>ALT or AST <math>&gt;5\times</math> ULN for <math>&gt;2</math> weeks</li> <li>First observation of ALT or AST <math>&gt;3\times</math> ULN and total bilirubin <math>&gt;2\times</math> ULN</li> <li>First observation of ALT or AST <math>&gt;3\times</math> ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [<math>&gt;5\%</math>]).</li> </ul> </li> <li>• Following study drug discontinuation, weekly monitoring of laboratory test values should continue until the abnormal test values have normalized to pretreatment levels and/or an adequate explanation of the abnormal test value is found.</li> <li>• Resumption of study drug is not allowed in patients who discontinue because of any of the above criteria.</li> </ul>

**Table 3 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)**

Event	Action to Be Taken
Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea)	The events are expected to be minimized by taking the study drug with a meal. If GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and are not tolerable, treatment with study drug should be temporarily interrupted until recovery to Grade 1 or lower.
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sun screen and lip balm of at least SPF 50 to help protect against potential sunburn.
Vision disorders	Investigators should consider referring the patients for an ophthalmological evaluation according to local clinical practice guidelines, if vision disorders persist or worsen in severity.
Edema	Physical examinations will be performed routinely during the study. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines

**Table 3 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)**

Event	Action to Be Taken
Abnormal kidney function AEs	<p data-bbox="489 406 1902 435">Kidney function laboratory abnormalities are to be reported as AEs only if they fulfill the criteria listed in Section <a href="#">5.3.5.4</a>.</p> <ul data-bbox="489 443 1902 735" style="list-style-type: none"><li data-bbox="489 443 1902 573">• If, at any time during the study treatment, eGFR decreases more than 50% over the baseline visit value, the patient must be carefully monitored. All of the underlying factors that may have acutely impacted serum creatinine levels must be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate, etc.).</li><li data-bbox="489 581 1902 670">• Any eGFR decrease more than 50% over the baseline visit value requires repeat testing. If, at the repeat test, the eGFR decrease remains &gt; 50% remains over the baseline visit value, the treatment with alectinib should be interrupted.</li><li data-bbox="489 678 1902 735">• Alectinib treatment may be resumed with caution if the eGFR value has increased to the approximate baseline visit value.</li></ul>

**Table 3 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)**

Event	Action to Be Taken
Severe myalgia and CPK elevations	<p>CPK laboratory abnormalities are to be reported as AEs only if they fulfill the criteria listed in Section <a href="#">5.3.5.4</a>.</p> <ul style="list-style-type: none"><li>• Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if it is accompanied by malaise or fever. CPK levels should be assessed in patients who report these symptoms.</li><li>• At the first occurrence of any of asymptomatic CPK values (<math>&gt; 10 \times \text{ULN}</math>), symptomatic CPK <math>&gt; 5 \times \text{ULN}</math>, or in the presence of severe muscular symptoms with CPK <math>&gt; \text{ULN}</math> but <math>\leq 5 \times \text{ULN}</math>) at any time during the study treatment, the patient will require monitoring of the CPK values until the values are normalized to pretreatment levels or a reasonable explanation for the CPK elevation and the symptoms is established.</li></ul>

**Table 3 Guidelines for Management of Specific Adverse Events with Alectinib (cont.)**

Event	Action to Be Taken
Other AEs (including bradycardia, anemia, and CPK elevation) or laboratory abnormalities:	<ul style="list-style-type: none"> <li>• Grade 3 or 4:               <ul style="list-style-type: none"> <li>Temporarily interrupt alectinib for a maximum of 3 weeks.</li> <li>If improvement to Grade <math>\leq 1</math> or baseline does not occur within 3 weeks, permanently discontinue alectinib.</li> <li>First episode: If improvement to Grade <math>\leq 1</math> or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID (decrease to 450 mg BID).</li> <li>Second episode: If improvement to Grade <math>\leq 1</math> or baseline occurs within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID (decrease to 300 mg BID).</li> <li>Third episode: Permanently discontinue alectinib.</li> </ul> </li> <li>• Grade 2 (except for any symptoms and signs that may be corrected with supportive care):               <ul style="list-style-type: none"> <li>Temporarily interrupt alectinib and resume if recover to Grade <math>\leq 1</math> or baseline if clinically indicated.</li> <li>First episode: If improvement to Grade <math>\leq 1</math> or baseline occurs within 10 days, continue the same dose of alectinib. If improvement occurs after 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID when resuming treatment (decrease to 450 mg BID).</li> <li>Second episode: If improvement to Grade <math>\leq 1</math> or baseline occurs within 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID (decrease to 450 mg BID, or 300 mg BID if the dose was reduced to 450 mg BID after the first episode. If improvement occurs after 10 days, decrease the current dose of alectinib by 300 mg (2 capsules) when resuming treatment (decrease to 300 mg BID or 150 mg BID if the dose was reduced to 450 mg BID after the first episode).</li> <li>Third episode: Permanently discontinue alectinib.</li> </ul> </li> <li>• Grade 1: no action required</li> </ul>

AE = adverse event; ALP = alkaline phosphate; BID twice daily; GI = gastrointestinal; SPF = sun protection factor; ULN = upper limit of normal.

Note: Diarrhea, nausea, and vomiting should be handled with supportive care practices before considering dose modification. Preexisting pleural effusion will not be considered an adverse event.

### 5.1.4 **Safety of Crizotinib and Management of Adverse Events**

Dosing interruption and/or dose reduction may be required on the basis of individual safety and tolerability. If dose reduction is necessary, then the dose of crizotinib should be reduced to 200 mg taken BID. If further dose reduction is necessary, then the dose should be modified to 250 mg taken QD on the basis of individual safety and tolerability (XALKORI® U.S. Package Insert; Crizotinib SmPC). Dose reduction guidelines for hematologic and non-hematologic toxicities are provided in Table 4 and Table 5.

**Table 4 Crizotinib Dose Modification—Hematologic Toxicities (Except Lymphopenia)**

NCI CTCAE Grade	Crizotinib Treatment
3	Withhold until recovery to Grade $\leq 2$ , then resume at the same dose schedule.
4	Withhold until recovery to Grade $\leq 2$ , then resume at 200 mg twice daily <sup>a</sup> .

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

<sup>a</sup> In the case of second episode, dosing should be withheld until recovery to Grade  $\leq 2$ , then dosing should be resumed at 250 mg once daily. Crizotinib must be permanently discontinued in the case of a third episode of Grade 4 hematologic toxicity.

**Table 5 Crizotinib Dose Modification—Non-Hematologic Toxicities**

NCI CTCAE Grade	Crizotinib Treatment
ALT or AST elevation $>5\times$ ULN with total bilirubin $\leq 1.5\times$ ULN	Withhold until recovery to baseline or $\leq 3\times$ ULN, then resume at reduced dose. Crizotinib must be permanently discontinued in case of recurrence.
ALT or AST elevation $>3\times$ ULN with concurrent total bilirubin elevation $>1.5\times$ ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue
Any grade drug-related pneumonitis <sup>a</sup>	Permanently discontinue
QTc $> 500$ ms on at least 2 separate ECGs	Withhold until recovery to baseline or $<481$ ms, then resume at reduced dose. Crizotinib must be permanently discontinued in case of recurrence (i.e., QTc $> 500$ ms on at least 2 separate ECGs).
QTc $> 500$ ms or $\geq 60$ ms change from baseline with torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue
Bradycardia (heart rate $< 60$ bpm, symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate $\geq 60$ bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If a contributing concomitant medication is identified and discontinued or its dose is adjusted, resume crizotinib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate $\geq 60$ bpm. If no contributing concomitant medication is identified, or if contributing concomitant medication is identified but not discontinued or its dose was not modified, resume crizotinib at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of $\geq 60$ bpm.

**Table 5 Crizotinib Dose Modification—Non-Hematologic Toxicities (cont.)**

NCI CTCAE Grade	Crizotinib Treatment
Bradycardia (heart rate < 60 bpm, life-threatening consequences, urgent intervention indicated)	Permanently discontinue If no contributing concomitant medication is identified or if contributing concomitant medication is identified but not discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to asymptomatic bradycardia or to a heart rate > 60 bpm, with frequent monitoring. Crizotinib must be permanently discontinued in case of recurrence.

bpm = beats per minute; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; QD = once daily.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

<sup>a</sup> Not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect. Crizotinib should be withheld if pneumonitis is suspected and must be permanently discontinued if treatment-related pneumonitis is diagnosed.

GI events were commonly reported with crizotinib in clinical studies. Nausea, diarrhea, vomiting, and constipation were the most commonly reported GI events and were primarily Grade 1 in severity. Supportive care for GI events may include standard anti-emetic or anti-diarrheal or laxative medicinal products ([XALKORI® U.S. Package Insert](#); [Crizotinib SmPC](#)). In clinical studies with crizotinib, events of gastrointestinal perforations were also reported ([XALKORI® U.S. Package Insert](#); [Crizotinib SmPC](#)).

Blood counts and liver function tests including ALT, AST, and total bilirubin should be monitored as per the local prescribing information for crizotinib.

See local prescribing information for further crizotinib safety information.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; performing of protocol-specified safety laboratory assessments; measuring of protocol-specified vital signs; and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

### **5.2.1 Adverse Events**

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient that is administered a pharmaceutical product, regardless of causal attribution. An adverse event may therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory test value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur before assignment of study treatment (e.g., screening invasive procedures such as biopsy sample collections)

### **5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)**

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that might have caused death had it occurred in a more severe form or was allowed to continue.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.9](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE;

see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the Adverse Event eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### **5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)**

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are the following:

- Cases of potential drug-induced liver injury which include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below:  
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

## **5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS**

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–Section 5.6. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### **5.3.1 Adverse Event Reporting Period**

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

**After informed consent** has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsy sample collections, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

**After initiation of study drug**, all adverse events will be reported until 4 weeks after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

### **5.3.2            Eliciting Adverse Event Information**

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### **5.3.3            Assessment of Severity of Adverse Events**

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in the NCI CTCAE**

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living <sup>a</sup>
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living <sup>b, c</sup>
4	Life-threatening consequences or urgent intervention indicated <sup>d</sup>
5	Death related to adverse event <sup>d</sup>

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

<sup>a</sup> Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>b</sup> Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

<sup>c</sup> If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

<sup>d</sup> Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

### **5.3.5 Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### **5.3.5.1 Diagnosis versus Signs and Symptoms**

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### **5.3.5.2 Adverse Events That are Secondary to Other Events**

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

#### **5.3.5.3 Persistent or Recurrent Adverse Events**

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the

Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

#### **5.3.5.4 Abnormal Laboratory Values**

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

Note: For oncology studies, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin  $5 \times$  ULN associated with cholestasis), the diagnosis only (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

#### **5.3.5.5 Abnormal Vital Sign Values**

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

#### **5.3.5.6 Abnormal Liver Function Tests**

The finding of an elevated ALT or AST ( $>3 \times$  baseline value) in combination with either an elevated total bilirubin ( $>2 \times$  ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST  $>3 \times$  baseline value in combination with total bilirubin  $>2 \times$  ULN (of which  $\geq 35\%$  is direct bilirubin)
- Treatment-emergent ALT or AST  $>3 \times$  baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

### **5.3.5.7 Deaths**

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed, by the investigator, solely to progression of NSCLC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other deaths that occur during the study, regardless of the relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "**sudden death**" should not be used unless combined with the presumed cause of death (e.g., "**sudden cardiac death**").*

During survival follow-up, deaths attributed to progression of NSCLC should be recorded only on the Survival eCRF.

### **5.3.5.8 Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

### **5.3.5.9 Lack of Efficacy or Worsening of Non–Small Cell Lung Cancer**

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 (see Appendix 4). In rare cases, the determination of clinical progression will be made on the basis of symptomatic deterioration. However, every effort should be made to document progression with use of objective criteria. If there is any uncertainty as to whether an event occurs because of disease progression, it should be reported as an adverse event.

### **5.3.5.10 Hospitalization or Prolonged Hospitalization**

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

*An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned before the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

*An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:*

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours
- Hospitalization to perform a planned measurement for the study

### **5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration**

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### **5.3.5.12 Patient-Reported Outcome Data**

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed with the use of PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

### **5.3.5.13 Adverse Events in Individuals Not Enrolled in the Study**

If an adverse event inadvertently occurs in an individual not enrolled in the study, the Adverse Event Form provided to investigators should be completed and submitted to Roche or its designee, either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

## **5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR**

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/Ethics Committee (EC).

### **5.4.1 Emergency Medical Contacts**

#### **Medical Monitor (Roche Medical Responsible) Contact Information**

Medical Monitor: [REDACTED] M.D.

Email: [REDACTED]

Telephone No.: [REDACTED]

Mobile Telephone No.: [REDACTED]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical

Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators Form").

## **5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest**

### **5.4.2.1 Events That Occur before Study Drug Initiation**

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators.

### **5.4.2.2 Events That Occur after Study Drug Initiation**

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 4 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section [5.6](#).

## **5.4.3 Reporting Requirements for Pregnancies**

### **5.4.3.1 Pregnancies**

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the investigator and submitted to the sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks

of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

#### **5.4.3.2 Pregnancies in Female Partners of Male Patients**

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the sponsor by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### **5.4.3.3 Abortions**

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

#### **5.4.3.4 Congenital Anomalies/Birth Defects**

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

### **5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS**

#### **5.5.1 Investigator Follow-Up**

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome may be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section [5.4.3.1](#).

### **5.5.2 Sponsor Follow-Up**

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## **5.6 POST-STUDY ADVERSE EVENTS**

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 4 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## **5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES**

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events with the use of the following reference documents:

- Alectinib Investigator's Brochure
- Local prescribing information for crizotinib

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

## **6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

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.

The primary analysis population for safety is the Safety Analysis Population (SAP) 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.

*The primary objective of the study is to determine whether the benefit (in terms of investigator-assessed PFS) of administering alectinib in this study is consistent with the benefit observed in global study ALEX. Consistency is defined as maintaining  $\geq 50\%$  of risk reduction from ALEX. The number of PFS events required to show consistency depends on the HR observed in the ALEX trial. The required number of PFS events to achieve approximate 87% probability to meet consistency criteria is listed as below.*

**Table 7 Required Number of PFS Events to Show Consistency**

<i>HR Observed in ALEX</i>	<i>Consistency Criteria (HR)</i>	<i>No. of PFS Events Required</i>
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 as early as required PFS events to show consistency have occurred. 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.

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

Further details of all analyses will be provided in the Statistical Analysis Plan.

## 6.1 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, assuming the estimated 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'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 final 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. A survival follow-up 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.*

## 6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination will be summarized by treatment arm for all randomized patients. Violations of inclusion and exclusion criteria will be reported and summarized by treatment arm.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Summaries of treatment group comparability will be based on the ITT population.

Demographic, baseline disease characteristics and lung cancer history will be summarized by treatment arm for all randomized patients, including the randomization stratification factors. Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequency and percentages.

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

## **6.4 EFFICACY ANALYSES**

The primary population for all primary and secondary efficacy analyses will be the ITT population.

### **6.4.1 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 according to 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 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) 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.

### **6.4.2 Secondary Efficacy Endpoints**

#### ***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.*

## **Time to CNS Progression**

Time to progression of disease in the CNS is defined as the time from the randomization date until radiographic evidence of progression of disease in the CNS. The analysis of progression of disease in the CNS or response will be based on the data from the IRC assessment. All patients will be included in the analysis regardless of their baseline status of CNS metastases. Progression of disease in the CNS is defined as progression due to newly developed CNS lesions or progression of preexisting baseline CNS lesions. On the basis of RECIST v1.1 and RANO, 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 or unequivocal progression of non-measurable baseline CNS lesions.

To account for the competing risks inherent in such an analysis, HRs, including statistical inference based on a two-sided log-rank test to compare the risk of progression of disease in the CNS between the alectinib and crizotinib treatment groups, will be computed on the basis of cause-specific hazard functions.

The probability of CNS disease progression, non-CNS disease progression, and death will each be estimated with the use of cumulative incidence functions.

For descriptive purposes, estimates of the CNS disease progression rates over time with 95% CIs will be presented on the basis of cumulative incidence functions. A Gray's test to compare the risk of progression of disease in the CNS between alectinib and crizotinib will also be performed as a supportive analysis.

In the subgroup of patients with measurable CNS lesions at baseline, an exploratory analysis of C-ORR, defined as the percentage of patients who achieve a best overall response of CR or PR in the CNS (defined by RECIST v1.1 as a 30% decrease in the sum of longest diameters of measurable CNS lesions referencing baseline), will also be performed. Duration of CNS response will be listed and may be analyzed if there are a sufficient number of CNS responses.

## **Objective Response Rate**

ORR, based on investigator assessment, is defined as the percentage of patients who attain a CR or PR based on RECIST v1.1. Confirmation of an objective response is not required for this secondary endpoint. Patients without a tumor assessment after baseline will be considered non-responders, as will patients with a best overall response of stable disease (SD), PD, or NE.

An estimate of ORR and its two-sided 95% CI will be calculated with use of the Clopper-Pearson method for each treatment arm. Response rates in the treatment groups will be compared with use of a stratified Mantel-Haenszel test on the basis of the randomization stratification factors. 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.

### **Duration of Response**

For patients who have experienced an objective response (CR or PR) during the study as assessed by the investigator, 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 cause, 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 with the use of Kaplan-Meier methodology, and a HR on the basis of a Cox proportional regression model will be calculated.

### **CNS Objective Response Rate**

This is defined as the objective tumor response rate (CR+PR) in CNS lesions in patients who have measurable disease in the CNS at baseline. An analysis by an IRC with the use of RECIST v1.1 and RANO criteria will be performed. An exploratory analysis of C-ORR in patients with measurable and/or non-measurable CNS disease at baseline will also be performed.

### **CNS Duration of Response**

This is defined as the time from the first observation of a CNS response until first observation of CNS progression or death from any cause. An analysis by an IRC with the use of RECIST v1.1 and RANO criteria will be performed. Duration of CNS response will be listed and may be analyzed if there are a sufficient number of CNS responses.

### **CNS Progression Rate**

The cumulative incidence of CNS progression will be plotted using a cumulative incidence curve and rates over time will be presented. CNS progression is defined as a new CNS lesion or progression of preexisting CNS lesions. An analysis by an IRC with the use of RECIST v1.1 and RANO criteria will be performed.

### **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 information after baseline will be censored at the date of randomization. OS will be analyzed with the use of the same methodology as specified for the primary endpoint. A survival follow-up will be performed based on more mature data.

### **6.4.3        Sensitivity Analyses**

The following sensitivity *analysis* will be performed on the primary endpoint of PFS:

- The effect of non-protocol-specified anti-cancer therapy before progression will be assessed by censoring patients at the last adequate tumor assessment before the start of non-protocol-specified anti-cancer therapy.

### **6.4.4        Subgroup Analyses**

Subgroup analyses of PFS will be performed for patients with baseline CNS metastases and for patients without baseline CNS metastases. In addition, a subgroup analysis of time to CNS progression will be performed, excluding patients who had pretreatment radiation therapy for CNS lesions.

All other subgroup analyses will be specified in the statistical analysis plan.

## **6.5            SAFETY ANALYSES**

The primary population for all safety analyses will be the SAP as defined in Section 6.

All safety parameters will be summarized in tables to evaluate and compare the safety profile of patients treated with alectinib versus crizotinib in terms of the following:

- Adverse events including adverse events leading to dose modifications or interruptions, study drug withdrawal, and death
- Severe, serious, and selected adverse events
- Deaths
- Laboratory parameters and abnormalities
- Vital signs
- ECGs
- ECOG PS

Adverse events will be coded with the use of MedDRA and will be summarized by mapped term and appropriate thesaurus level. All adverse events and routine laboratory parameters will be assessed according to the NCI CTCAE v4.0 grading system.

Adverse events will be described by individual listings, by body system, and by severity. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion will be counted only once in the calculation of the event frequency.

Laboratory values will be summarized by treatment arm, including summary tables for the shifts in grades from baseline to the worst grade observed during treatment.

Descriptive summary tables of change from baseline over time will be provided for vital signs, and descriptive statistics will be tabulated for ECOG PS. ECG findings over time will be summarized.

Study drug administration will be summarized by duration and cumulative dose. In addition, treatment exposure will be summarized and will include the number of doses received, dose intensity, and the planned dose percentage.

## **6.6 PHARMACOKINETIC ANALYSES**

Standard NCA may be conducted for PK data collected from patients who participate in the frequent blood sampling, as appropriate and if data allow. Blood samples will be used for PK analysis of relevant analytes, as data allow and where appropriate. PK parameters including but not limited to AUC,  $C_{max}$ , and  $t_{max}$ , 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.

A popPK analysis will be performed to describe the time course of plasma concentrations of alectinib (and/or metabolite(s), if available and appropriate), as appropriate and where data allow. The influence of covariates (e.g., body weight, age, sex, race, and concomitant medications) on PK parameters will be investigated, if necessary and appropriate. If necessary, the data may be pooled with data from previous studies.

Individual and mean plasma concentrations at each sampling timepoint and/or PK parameters for alectinib (and metabolite[s], if appropriate) will be listed.

Summary statistics (e.g., means, standard deviation, coefficient of variation percentages, geometric means, medians, and ranges) for plasma concentrations and/or PK parameters for alectinib (metabolite[s], if appropriate) will be presented by treatment and nominal collection times (plasma concentrations only), as appropriate. Additional plots or summary statistics may be constructed or calculated, as appropriate.

Results of PK and/or any PK or PK/pharmacodynamic analyses may be reported outside the clinical study report.

Nonlinear mixed-effects modeling (with software NONMEM) ([Beal et al. 1999](#)) will be used to analyze the sparse and/or frequent 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.

Details of any mixed-effects modeling and exploratory analyses will be reported in a document separate from the clinical study report of this study.

## **6.7 PATIENT-REPORTED OUTCOME ANALYSES**

The following PRO endpoints will be analyzed and PRO data will be presented separately from adverse event data.

### **6.7.1 Time to Deterioration of Patient-Reported Lung Cancer Symptoms**

TTD from baseline will be assessed every 4 weeks until disease progression and during study treatment after disease progression in the case of isolated, asymptomatic progression of disease in the CNS; at Post-Treatment Visit (4 weeks after permanent treatment discontinuation); and at subsequent survival follow-up visits every 8 weeks for 6 months, for the following lung cancer symptoms: cough (Question 31 on the QLQ-LC13), dyspnea single item (Question 8 on the 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) for patients in each arm. Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. TTD will be analyzed for the ITT population. If a baseline or postbaseline PRO evaluation is not available, TTD will be censored at the date of randomization. If they have not deteriorated, patients will be censored at the last time when they completed an assessment for cough, dyspnea (single item), dyspnea (subscale items), chest pain, arm/shoulder pain, and fatigue.

*Additional details regarding the TTD analyses will be included within the SAP.*

### **6.7.2 Additional Patient-Reported Outcomes**

PROs of HRQOL, lung cancer-related symptoms, and health status will be measured with the use of the EORTC QLQ-C30 and EORTC QLQ-LC13 (see [Appendix 7](#) and [Appendix 8](#), respectively).

Summary statistics (mean, standard deviation, median, and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 and the QLQ-LC13 according to the EORTC scoring manual guidelines (see [Appendix 7](#) and [Appendix 8](#), respectively). Completion and compliance rates will be summarized at each timepoint by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

*Additional details regarding the PRO analyses will be included within the SAP.*

## **6.8 EXPLORATORY ANALYSES**

Results of exploratory analyses on post-progression tumor samples to measure molecular mechanisms of resistance to ALK inhibitors and plasma samples to measure ALK rearrangements and mutations in ALK and other genes involved in cancer will be communicated outside the main clinical study report.

## **6.9            OPTIONAL INTERIM ANALYSES**

No interim analysis for efficacy or futility is planned.

## **7.                DATA COLLECTION AND MANAGEMENT**

### **7.1                DATA QUALITY ASSURANCE**

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with the use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data or other electronic data will be sent directly to the Sponsor, with use of the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

### **7.2                ELECTRONIC CASE REPORT FORMS**

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

Acknowledgement of receipt of the compact disc is required.

### **7.3                SOURCE DATA DOCUMENTATION**

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of

transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no previous written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

#### **7.4 USE OF COMPUTERIZED SYSTEMS**

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record may serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

#### **7.5 RETENTION OF RECORDS**

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor before transferring any records to another party or moving them to another location.

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

### **8.2 INFORMED CONSENT**

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained with use of the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

### **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written Investigational New Drug safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

### **8.4 CONFIDENTIALITY**

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

### **8.5 FINANCIAL DISCLOSURE**

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

## **9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

### **9.1 STUDY DOCUMENTATION**

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

### **9.2 PROTOCOL VIOLATIONS**

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

### **9.3 SITE INSPECTIONS**

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

### **9.4 ADMINISTRATIVE STRUCTURE**

A Steering Committee is established to provide the study Sponsor with recommendations related to any aspect of the study, specifically study design, data interpretation, exploratory analyses, or alternate changes to the study that may assist in patient accrual, data collection, analysis, and interpretation of the study results. The Sponsor is ultimately responsible for all decisions regarding the study.

The test for the study inclusion criteria of ALK-positive NSCLC will be performed at the Sponsor's designated central laboratories and assessed by the Ventana IHC test.

An IRC will review the tumor assessments to determine the secondary endpoints of the overall disease PFS and time to CNS progression, both on the basis of RECIST v1.1. In addition to the secondary endpoint of time to CNS progression together with C-ORR, C-DOR, and CNS progression rate at 6, 12, 18, and 24 months, an IRC will review the tumor assessments on the basis of RANO criteria.

The independent review of MRI and CT scans will NOT determine either eligibility OR patient treatment. All treatment decisions will be made by the investigator using local assessments.

## **9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS**

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

*[http://www.roche.com/roche\\_global\\_policy\\_on\\_sharing\\_of\\_clinical\\_study\\_information.pdf](http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf)*

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor before submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## **9.6 PROTOCOL AMENDMENTS**

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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## Appendix 1 Schedule of Assessments

Assessment	Screening		Treatment Period							Post-Progression Visits during Treatment in the Case of Isolated, Asymptomatic Disease Progression in the CNS (Every 8 Weeks) until Systemic Disease Progression or Symptomatic Disease Progression in the CNS	End of Treatment/Withdrawal Visit <sup>d</sup>	Post-Treatment Visit (4 Weeks after Permanent Treatment Discontinuation)	Subsequent Therapy for NSCLC; Survival Follow-Up and PRO (EORTC QLQ-C30/QLQ-LC13)
	Days – 28 to 0	Days – 3 to 0	Visit 0 (Baseline)	Visit 1 (Week 2) <sup>a</sup>	Visit 2 (Week 4)	Visit 3 (Week 6) <sup>b</sup>	Visit 4 (Week 8)	Visit 5 (Week 10) and Visit 6 (Week 12) <sup>c</sup>	All Subsequent Visits (Every 8 Weeks, from Week 8 onward) until PD, Death, or Withdrawal from the Study before PD				
Informed consent	x												
Demographics	x												
Medical history and baseline conditions	x												
Pregnancy test <sup>e</sup>	x <sup>e</sup>	x <sup>e</sup>	To be repeated as necessary										
Physical examination <sup>f</sup>	x		x		x		x		x	x	x		
Vital signs	x		x		x		x		x	x	x		
ECOG PS	x		x		x		x		x	x	x		
ECG <sup>g</sup>	x		x <sup>h</sup>		x				x		x		

## Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period							Post-Progression Visits during Treatment in the Case of Isolated, Asymptomatic Disease Progression in the CNS (Every 8 Weeks) until Systemic Disease Progression or Symptomatic Disease Progression in the CNS	End of Treatment/Withdrawal Visit <sup>d</sup>	Post-Treatment Visit (4 Weeks after Permanent Treatment Discontinuation)	Subsequent Therapy for NSCLC; Survival Follow-Up and PRO (EORTC QLQ-C30/QLQ-LC13)
	Days – 28 to 0	Days – 3 to 0	Visit 0 (Baseline)	Visit 1 (Week 2) <sup>a</sup>	Visit 2 (Week 4)	Visit 3 (Week 6) <sup>b</sup>	Visit 4 (Week 8)	Visit 5 (Week 10) and Visit 6 (Week 12) <sup>c</sup>	All Subsequent Visits (Every 8 Weeks, from Week 8 onward) until PD, Death, or Withdrawal from the Study before PD				
Hematology, coagulation	x		x <sup>h</sup>		x		x		x	x	x		
Biochemistry	x		x <sup>h</sup>	x <sup>a</sup>	x	x <sup>b</sup>	x	x <sup>c</sup>	x	x	x		
Urinalysis	x		x <sup>h</sup>		x		x		x	x	x		
Concomitant medications	x		x	x	x	x	x	x	x	x	x		
Mandatory tumor sample for ALK testing <sup>i</sup>	x												
Tumor sample for sequencing (NGS)			x <sup>j</sup>							x <sup>k</sup>	x <sup>k</sup>		

## Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period							Post-Progression Visits during Treatment in the Case of Isolated, Asymptomatic Disease Progression in the CNS (Every 8 Weeks) until Systemic Disease Progression or Symptomatic Disease Progression in the CNS	End of Treatment/Withdrawal Visit <sup>d</sup>	Post-Treatment Visit (4 Weeks after Permanent Treatment Discontinuation)	Subsequent Therapy for NSCLC; Survival Follow-Up and PRO (EORTC QLQ-C30/QLQ-LC13)
	Days – 28 to 0	Days – 3 to 0	Visit 0 (Baseline)	Visit 1 (Week 2) <sup>a</sup>	Visit 2 (Week 4)	Visit 3 (Week 6) <sup>b</sup>	Visit 4 (Week 8)	Visit 5 (Week 10) and Visit 6 (Week 12) <sup>c</sup>	All Subsequent Visits (Every 8 Weeks, from Week 8 onward) until PD, Death, or Withdrawal from the Study before PD				
Plasma for detection of ALK rearrangements (20 mL, for all screened patients)	x												
Plasma for detection of ALK mutation status (20 mL of blood)			x						x <sup>i</sup>		x <sup>i</sup>		
Tumor assessment <sup>m</sup>	x <sup>n</sup>		x <sup>n</sup>				x		x <sup>o</sup>	x		x <sup>p</sup>	

## Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period							Post-Progression Visits during Treatment in the Case of Isolated, Asymptomatic Disease Progression in the CNS (Every 8 Weeks) until Systemic Disease Progression or Symptomatic Disease Progression in the CNS	End of Treatment/Withdrawal Visit <sup>d</sup>	Post-Treatment Visit (4 Weeks after Permanent Treatment Discontinuation)	Subsequent Therapy for NSCLC; Survival Follow-Up and PRO (EORTC QLQ-C30/QLQ-LC13)
	Days – 28 to 0	Days – 3 to 0	Visit 0 (Baseline)	Visit 1 (Week 2) <sup>a</sup>	Visit 2 (Week 4)	Visit 3 (Week 6) <sup>b</sup>	Visit 4 (Week 8)	Visit 5 (Week 10) and Visit 6 (Week 12) <sup>c</sup>	All Subsequent Visits (Every 8 Weeks, from Week 8 onward) until PD, Death, or Withdrawal from the Study before PD				
MRI scan of the brain	x <sup>n</sup>		x <sup>n</sup>				x		x <sup>o</sup>	x		x <sup>p</sup>	
PK samples for alectinib (2 mL blood) <sup>q</sup>			x		x		x		x				
PRO (EORTC QLQ-C30/QLQ-LC13) <sup>r</sup>			x		x		x		x	x		x	x <sup>s</sup>
Adverse events <sup>t</sup>	x	x	x	x	x	x	x	x	x	x	x	x	
Subsequent therapy for NSCLC										x		x	x <sup>s</sup>

## Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period							Post-Progression Visits during Treatment in the Case of Isolated, Asymptomatic Disease Progression in the CNS (Every 8 Weeks) until Systemic Disease Progression or Symptomatic Disease Progression in the CNS	End of Treatment/Withdrawal Visit <sup>d</sup>	Post-Treatment Visit (4 Weeks after Permanent Treatment Discontinuation)	Subsequent Therapy for NSCLC; Survival Follow-Up and PRO (EORTC QLQ-C30/QLQ-LC13)
	Days – 28 to 0	Days – 3 to 0	Visit 0 (Baseline)	Visit 1 (Week 2) <sup>a</sup>	Visit 2 (Week 4)	Visit 3 (Week 6) <sup>b</sup>	Visit 4 (Week 8)	Visit 5 (Week 10) and Visit 6 (Week 12) <sup>c</sup>	All Subsequent Visits (Every 8 Weeks, from Week 8 onward) until PD, Death, or Withdrawal from the Study before PD				
Drug dispensing and accountability <sup>u</sup>			x		x		x		x	x		x (accountability only)	

ALK=anaplastic lymphoma kinase; ALP=alkaline phosphatase; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire–Core; EORTC QLQ-LC15=European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire–Lung Cancer module; MRI=magnetic resonance imaging; NCI=National Cancer Institute; NGS=Next Generation Sequencing; NSCLC=non-small cell lung cancer; PD=progressive disease; PK=pharmacokinetic; PRO=patient-reported outcome; ULN=upper limit of normal.

Notes: First dose of study drug to be taken as soon as patient has been randomized and appropriate drug has been provided–within ≤ 24 hours. Assessments performed after baseline are to be completed within ± 1 week for the first two 4 weekly and subsequent 8 weekly assessments.

## Appendix 1 Schedule of Assessments (cont.)

- <sup>a</sup> The visit on Week 2 is only required for the specific monitoring of liver function tests, including ALT, AST, total bilirubin, direct bilirubin, *ALP*, and CPK for patients in the alectinib treatment arm, and for the specific monitoring of ALT, AST, *ALP*, total bilirubin, and direct bilirubin for patients in the crizotinib treatment arm. No other assessments are needed on this visit with the exception of any new records for adverse events and concomitant medications.
- <sup>b</sup> The visit on Week 6 is only required for the specific monitoring of liver function tests, including ALT, AST, total bilirubin, and direct bilirubin, *ALP* for patients in both the alectinib and crizotinib treatment arm. No other assessments are needed on this visit with the exception of any new records for adverse events and concomitant medications.
- <sup>c</sup> The visits on Week 10 and Week 12 are only required for the specific monitoring of liver function tests, including ALT, AST, *ALP*, total bilirubin, and direct bilirubin for patients in the alectinib treatment arm only. No other assessments are needed on this visit with the exception of any new records for adverse events and concomitant medications.
- <sup>d</sup> End of Treatment/Withdrawal: The visit that the investigators or patients decide to stop/withdraw study treatment permanently for progression, AE, or any other reason. Obtain these assessments, if not completed during the previous 4 weeks on study.
- <sup>e</sup> All women who are not postmenopausal ( $\geq 12$  months of non-therapy induced amenorrhea) or surgically sterile will have a serum pregnancy test performed at screening (i.e., within 3 days prior to receiving first dose of study drug). Urine pregnancy tests will be performed anytime during the course of the study, per the investigator's discretion. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.
- <sup>f</sup> Includes an ophthalmologic examination if clinically indicated.
- <sup>g</sup> ECG should be performed in 12-lead in triplicate and obtained within approximately 2–5 minutes at each specified timepoint, and each measurement should be separated  $\leq 2$  minutes. ECGs should be performed at screening, Visit 0 (baseline), Visit 2 (Week 4), Visit 8 (Week 24), Visit 12 (Week 56), end of treatment/withdrawal visit, and as clinically indicated throughout the study.
- <sup>h</sup> Screening laboratory assessment done within 3 days may be counted as the baseline assessment.
- <sup>i</sup> Preferably blocks fixed in neutral buffered formalin; if blocks are not available, a minimum of 7 unstained 5- $\mu$ m slides *cut less than 3 months before screening* are required. Tumor ALK status will be assessed by central laboratory before randomization.
- <sup>j</sup> Tumor sample could be taken from the tumor block obtained at screening and will be used for NGS. If blocks are not available, 6 unstained 5- $\mu$ m slides are desired.
- <sup>k</sup> Only one optional tumor sample to be collected at the time of disease progression from progressive lesions. Preferably blocks fixed in neutral buffered formalin; if blocks are not available, a minimum of 9 unstained 5- $\mu$ m slides are required.
- <sup>l</sup> Blood samples (20 mL) will be collected to obtain plasma used to test for exploratory biomarkers. Blood samples will be collected at Visit 0 (baseline), at every 16 weeks during the study, *until and at disease progression (CNS or systemic disease) or treatment discontinuation for any reasons*.

## Appendix 1 Schedule of Assessments (cont.)

- <sup>m</sup> Tumor assessment consists at minimum of a CT and/or MRI scan of chest and abdomen (for imaging of liver and adrenal glands). Patients who are known to have bone metastasis or who display clinical or laboratory signs (e.g., serum ALP > 1.5 × ULN) of bone metastasis should undergo radionuclide bone scan. Skin metastases should be clinically assessed with caliper measurement and documented by color photography, including a ruler to estimate the size of the lesion. Assessments performed after baseline must be completed within ± 1 week for the 8 weekly assessments. If there is a suspicion of disease progression on the basis of clinical or laboratory findings, a tumor assessment should be performed as soon as possible and before the next scheduled evaluation.
- <sup>n</sup> Screening tumor assessment performed within 14 days will be considered the baseline assessment.
- <sup>o</sup> Tumor assessment may be performed whenever clinically indicated. Brain assessment scans should be performed at every systemic imaging tumor assessment. Tumor assessment should continue until disease progression if a patient discontinues treatment before PD, regardless of whether they subsequently receive non-study anti-cancer therapy (a use of subsequent non-study, anti-cancer therapy before disease progression would be considered a protocol violation).
- <sup>p</sup> If treatment was permanently discontinued because of disease progression.
- <sup>q</sup> Predose PK (2 mL) sampling for all patients on alectinib treatment will be performed at each visit during the treatment period and at the final study visit. The predose PK samples should be taken immediately before (within 2 hours) intake of study medication at all study visits. Remind the patient not to take a daily dose at home on the day of scheduled study visit. Frequent blood sampling will be performed in a subset of 20 Chinese patients consenting to frequent sampling to ensure that at least 16 patients will have evaluable PK profiles at Visit 0 (baseline) and Visit 2 (Week 4) at predose (within 2 hours before intake of study medication), and at 1, 2, 4, 6, 8, 10, and 12 hours postdose. Sparse PK sampling will be collected from all patients enrolled onto alectinib treatment. See [Appendix 2](#) for further detail on alectinib PK sampling times.
- <sup>r</sup> PRO questionnaires are to be completed every 4 weeks until disease progression and during disease progression during study treatment for the case of isolated, asymptomatic disease progression in the CNS; at the Post-Treatment Visit (4 weeks after treatment discontinuation); and at every follow-up visit (every 8 weeks) after Post-Treatment Visit for 6 months. Further guidelines for the administration of the PRO questionnaires will be provided in the study manual.
- <sup>s</sup> Performed every 8 weeks after Post-Treatment Visit during the first 6 months and then every 12 weeks or performed as appropriate. The PRO assessments should be performed during the first 6 months.
- <sup>t</sup> Graded according to the NCI CTCAE (v4.0). Serious adverse event collection must start from the time of the first study-specific procedure.
- <sup>u</sup> For details on drug dispensing and accountability, see Section [4.3.3](#).

## Appendix 2

### Schedule of Alectinib Pharmacokinetic Assessments

Visit	Timepoint
Visit 0 (baseline)	Predose (within 2 hours before morning dose)
Visit 2 (Week 4)	Predose (within 2 hours before morning dose)
Visit 4 (Week 8)	Predose (within 2 hours before intake of alectinib)
Every 8 weeks until PD or death or withdrawal from the study before PD	Predose (within 2 hours before intake of alectinib)
Visit 0 (baseline) and Visit 2 (Week 4) <sup>a</sup>	Predose (within 2 hours before morning dose), 1, 2, 4, 6, 8, 10, and 12 <sup>b</sup> hours postdose

PD = progressive disease; PK = Pharmacokinetic.

Notes: Blood samples (approximately 2 mL of venous blood) collected from all patients.

<sup>a</sup> Only for the subset of 20 patients who participate in the frequent blood sample collections.

<sup>b</sup> The 12 hour PK samples should be taken before the evening dose; a sample collection time window of  $\pm 1$  hour is only considered for the 12-hour PK sample.

### Appendix 3

## List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters

This representative list is not intended to be an exhaustive list. Each patient's concomitant medications should be carefully considered by the investigator with regard to the benefit-risk for the particular patient and appropriate monitoring, including any concomitant medication, dose adjustment, or therapeutic alternatives, which should be determined by the investigator caring for the patient.

CYP3A Inducers		CYP3A Potent Inhibitors	
avasimibe, aminoglutethimide, barbiturates, carbamazepine, dexamethasone, efavirenz, ethosuximide, garlic supplements, glucocorticoids, glutethimide, griseofulvin, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentine, St John's wort, troglitazone		aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, verapamil, voriconazole	
P-gp			
Substrates		Inducers	
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan		avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir	
Dual UGT1A1/CYP3A			
Substrates	Inhibitors	Inducers	
buprenorphine, raltegravir	atazanavir	rifampin	

This information in this appendix is adapted from Levien and Baker 2003<sup>1</sup>, Zhang 2010<sup>2</sup>, and FDA Guidance on Drug-Drug Interactions.

Also see: <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>.

<sup>1</sup> Levien TL and Baker DE Cytochrome P450 Drug Interactions. Therapeutic Research Center Pharmacist's Letter/Prescriber's Letter [resource on the Internet]. 2003. Available from: [www.pharmacistsletter.com](http://www.pharmacistsletter.com) and [www.prescribersletter.com](http://www.prescribersletter.com).

<sup>2</sup> Zhang L. Transporter Mediated Drug-Drug Interactions. FDA. Clinical Pharmacology Advisory Committee Meeting Topic 4: Transporter-Mediated Drug-Drug Interactions Atlanta, GA, 17 March 2010.

### **Appendix 3**

## **List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters (cont.)**

Potent inhibitors of CYP3A are those considered to be “strong CYP3A inhibitors” previously shown to result in a  $\geq 5$ -fold increase in the area under the concentration–time curve of a concomitantly administered CYP3A substrate. These are based on the available published literature and, thus, are not considered exhaustive or inclusive. See FDA Guidance on Drug-Drug Interactions for further detail.

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication**

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,<sup>1</sup> are presented below, with slight modifications and the addition of explanatory text as needed for clarity.<sup>2</sup>

#### **MEASURABILITY OF TUMOR AT BASELINE**

##### **DEFINITIONS**

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

##### **Measurable tumor lesions**

###### **Tumor lesions**

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT and/or MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

###### **Malignant lymph nodes**

To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also the notes below on “Baseline Documentation of Target and Non-Target Lesions” for information on lymph node measurement.

##### **Non-measurable tumor lesions**

Non-measurable tumor lesions encompass small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast

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<sup>1</sup> Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). *Eur J Cancer* 2009;45:228–47.

<sup>2</sup> For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

#### **Special considerations regarding lesion measurability**

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

#### **Bone lesions**

Bone scan, positron emission tomography (PET) scan, or plain films are not considered to be adequate imaging techniques for measuring bone lesions. However, these techniques may be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that may be evaluated by cross-sectional imaging techniques, such as CT or MRI, may be considered measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

#### **Cystic lesions**

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases may be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

#### **Lesions with prior local treatment**

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

#### **TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS**

##### **Measurement of lesions**

All measurements should be recorded in metric notation, with use of calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start date and never more than 4 weeks before the beginning of the treatment.

##### **Method of assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

##### **Clinical lesions**

Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm in diameter as assessed with the use of calipers (e.g., skin nodules). Documentation of skin lesions by color photography, including a ruler to estimate the size of the lesion, is suggested.

##### **Chest X-ray**

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

##### **Computed tomography scan and magnetic resonance imaging**

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined the measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is  $\leq 5$  mm. When CT scans have a slice thickness  $> 5$  mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If, before enrollment, it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type that is under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is performed, the decision whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the previous studies if possible. Each case should be discussed with the radiologist to determine if the substitution of these other

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in the measurement and interpretation of target lesions of non-target disease or new lesions on a different modality because the same lesion may appear to have a different size with use of a new modality.

#### **Ultrasound**

Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

#### **Endoscopy, laparoscopy, tumor markers, cytology, and histology**

The utilization of these techniques for objective tumor evaluation cannot generally be advised.

### **TUMOR RESPONSE EVALUATION**

#### **ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE**

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

#### **BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS**

When more than one measurable lesion is present at baseline, all lesions, up to a maximum of five lesions total and a maximum of two lesions per organ, representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (even measurable lesions) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, and the lesions should also be available for repeated measurements. If measurement of the largest lesion is not reproducible, the next largest lesion that may be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomical structures that may be visible by imaging even if they are not involved by tumor. As noted above,

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge whether a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm  $\times$  30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis of  $< 10$  mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions or sites of disease, including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”

In addition, it is possible to record multiple non-target lesions that involve the same organ as a single item on the electronic Case Report Form (eCRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

## **RESPONSE CRITERIA**

### **Evaluation of target lesions**

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions  
Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to  $< 10$  mm.
- Partial response (PR): At least a 30% decrease in the sum of the diameters of the target lesions, using the baseline sum of diameters as a reference

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

- Progressive disease (PD): At least a 20% increase in the sum of the diameters of the target lesions using the smallest sum of the diameters during the study (nadir) as a reference, including baseline
  - In addition to the relative increase of 20%, the sum of the diameters must also demonstrate an absolute increase of at least 5 mm.
  - The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD, using the smallest sum of the diameters during the study as a reference.

#### **Special notes on the assessment of target lesions**

##### **Lymph nodes**

Lymph nodes that are identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm during the study. This means that when lymph nodes are included as target lesions, the sum of the lesions may not be zero even if CR criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

##### **Target lesions that become too small to measure**

During the study, all lesions (nodal and non-nodal) that are recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when they are very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the eCRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned, and the BML (below measurable limit) checkbox should not be checked. (Note: It is less likely that this rule will be used for lymph nodes because they usually have a definable size when they are normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned in this circumstance as well, and BML should also be ticked).

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

To reiterate: if the radiologist is able to provide an actual measure, this measurement should be recorded even if it is below 5 mm, and, in that case, the BML checkbox should not be checked.

#### **Lesions that split or coalesce during treatment**

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

#### **Evaluation of Non-Target Lesions**

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Whereas some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: Disappearance of all non-target lesions  
All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions
- PD: Unequivocal progression of existing non-target lesions  
The appearance of one or more new lesions is also considered progression.

#### **Special Notes on Assessment of Progression of Non-Target Disease**

##### **When the patient also has measurable disease**

In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening of non-target disease of a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

##### **When the patient has only non-measurable disease**

The circumstance arises in some Phase III studies in which it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that may be applied when assessing patients for unequivocal progression is to consider whether the increase in overall disease burden, on the basis of the change in non-measurable disease, is comparable in magnitude to the increase that would be required to declare PD for measurable disease. That is, an increase in tumor burden represents an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread. Examples may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is observed, the patient should be considered to have had overall PD at that point. Though it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

#### **New lesions**

The appearance of new malignant lesions denotes disease progression; therefore, comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (e.g., some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show PR or CR (e.g., necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not).

A lesion that is identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal (e.g., because of the small size) continued therapy and follow-up evaluation will clarify whether it represents truly new disease. If repeat scans confirm that there is definitely a new lesion, then progression should be declared with use of the date of the initial scan.

#### **EVALUATION OF RESPONSE**

##### **Timepoint response (overall response)**

It is assumed that at each protocol-specified timepoint, a response assessment occurs. [Table 1](#) provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

## Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

When patients have non-measurable (therefore non-target) disease only, [Table 2](#) is to be used.

**Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR= complete response; NE= not evaluable; PD= progressive disease; PR= partial response; SD= stable disease.

**Table 2 Timepoint Response: Patients with Non-Target Lesions Only**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR= complete response; NE= not evaluable; PD= progressive disease.

<sup>a</sup> “Non-CR/non-PD” is preferred over “stable disease” for non-target disease because stable disease is increasingly used as an endpoint for an assessment of efficacy in some studies; thus, assigning “stable disease” when no lesions may be measured is not advised.

### **Missing assessments and not-evaluable designation**

When no imaging or measurement is performed at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements is made at an assessment, the case is also usually considered not evaluable at that timepoint unless a convincing argument may be made that the contribution of the individual missing

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD (e.g., if a patient had a baseline sum of 50 mm with three measured lesions, and during the study, only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion).

If one or more target lesions was not assessed either because the scan was not performed or because the scan could not be assessed as a result of poor image quality or obstructed view, the response for target lesions should be “unable to assess” because the patient is not evaluable. Similarly, if one or more non-target lesion is not assessed, the response for non-target lesions should be “unable to assess,” except for where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except for where there is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

## Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

**Table 3 Best Overall Response When Confirmation Is Required**

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR <sup>a</sup>
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

<sup>a</sup> If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (because disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be reported when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

### **Special notes on response assessment**

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal to avoid overstating progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the eCRF.

Patients with a global deterioration of health status who require discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.

## **Appendix 4**

### **Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)**

The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in [Table 1–Table 3](#).

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If, at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease is still present or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication**

Selected sections from the manuscript by [Wen et al. \(2010\)](#)<sup>1</sup> describing the Response Assessment in Neuro-Oncology (RANO) criteria are presented below, with slight modifications to the original text and the addition of explanatory text as needed for clarity.

In 2010, the Response Assessment in Neuro-Oncology Working Group (RANO) published its consensus recommended criteria for evaluation of treatment in high-grade gliomas ([Wen et al. 2010](#)). These criteria offered an improvement over the frequently adopted Macdonald criteria ([Macdonald et al. 1990](#)<sup>2</sup>), based primarily on contrast-enhanced imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) and the two-dimensional World Health Organization (WHO) oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure. The RANO criteria mitigate some risks of false positive/negative response particularly those associated with anti-angiogenic therapies. The RANO criteria will be used in the current trial to assess tumor response.

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the non-enhancing component, should be performed. As with the Macdonald Criteria ([Macdonald et al. 1990](#)), the product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

#### **MEASUREABLE AND NON-MEASURABLE DISEASE FOR CONTRAST-ENHANCING LESIONS**

Measurable disease is defined as bi-dimensionally contrast-enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. As with Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, in the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be 2 times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. Such lesions should be considered non-measurable unless there is a nodular component measuring  $\geq 10$  mm in diameter. The cystic or surgical cavity should not be measured in determining response.

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<sup>1</sup> Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. *J Clin Oncol* 2010;28:1963–72.

<sup>2</sup> Macdonald DR, Cascino TL, Schold SC, et al. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–80.

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)**

Non-measurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximum perpendicular diameters of < 10 mm. Patients with measurable disease are required for study eligibility in Stage 2.

#### **NUMBER OF LESIONS**

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined, similar to the criteria proposed for systemic tumors in RECIST, v1.1. However, given the heterogeneity of high-grade gliomas and the difficulty in measuring some lesions, a maximum of five of the largest lesions may be measured. In general, the largest enlarging lesion(s) should be selected. However, emphasis should also be placed on lesions that allow reproducible repeated measurements. Occasionally, the largest lesions may not lend themselves to reproducible measurements, and the next largest lesions that can be measured reproducibly should be selected.

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions will be considered the target lesions for evaluation of response. The other lesions will be considered non-target lesions and should also be recorded. Rarely, unequivocal progression of a non-target lesion requiring discontinuation of therapy or development of a new contrast-enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes will qualify as progression.

About 20%–30% of patients develop pseudoprogression after chemoradiotherapy, especially within the first 3 months after completion of radiotherapy. Given the difficulty of differentiating pseudoprogression from true progression in the first 12 weeks after irradiation, such patients will be excluded from the clinical trial.

Patients are required to have a 25% increase in the sum of the products of the perpendicular diameters of the contrast-enhancing lesions, while on stable or increasing doses of corticosteroids, before they are considered to have progressive disease and are entered into a clinical trial for recurrent/progressive disease. Patients with new contrast-enhancing non-measurable disease may be considered for clinical trials in which progression-free survival (PFS) is the primary endpoint. Clinical deterioration or increase in corticosteroid dosing alone would not be sufficient to indicate progressive disease for entry in clinical studies.

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)**

A particularly difficult problem involves patients receiving first-line anti-angiogenic agents who develop predominantly non-enhancing disease at progression. This can be difficult to differentiate from treatment effects. If it seems clear that the non-enhancing changes represent tumor progression, these patients would also be eligible for enrollment in clinical trials for recurrent disease, although their tumor will be considered non-measurable. As noted previously, although it would be preferable to have a more objective measure of progressive non-enhancing recurrent disease similar to contrast-enhancing disease, the RANO Working Group felt that this was not possible at present given the limitations of current technology.

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement either at pretreatment baseline or after initiation of therapy should be used for determination of progression. Criteria for radiographic changes after therapy are listed below. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals.

If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents, such as anti-angiogenic therapies, that affect vascular permeability is particularly difficult.

In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease.

#### **DETERMINATION OF FIRST PROGRESSION**

RANO criteria for determination of first progression are summarized in [Table 11](#). Standard therapy for glioblastoma involves maximal safe tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide. Approximately 20%–30% of patients undergoing their first post-radiation MRI show increased contrast enhancement that eventually subsides without any change in therapy. This phenomenon, termed pseudoprogression, likely results from transiently increased permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide, and complicates the determination of tumor progression immediately after completion of radiotherapy. Pseudoprogression may be accompanied by progressive clinical signs and symptoms and seems to be more frequent in patients with a methylated *MGMT* gene promoter.

This treatment-related effect has implications for patient management and may result in premature discontinuation of effective adjuvant therapy. This limits the validity of a PFS

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)**

endpoint unless tissue-based confirmation of tumor progression is obtained. It also has significant implications for selecting appropriate patients for participation in clinical trials for recurrent gliomas. Failure to exclude patients with pseudoprogression from these studies will result in a falsely high response rate and PFS and the possibility that an agent will be incorrectly considered to be active. To address this issue, the RANO criteria provides that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease (see [Table 11](#)). It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment into trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

## Appendix 5 Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)

**Table 11 Criteria for Determining First Progression Depending on Time from Initial Chemoradiotherapy**

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., >70% tumor cell nuclei in areas], high or progressive increase in M12-A proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	<ol style="list-style-type: none"> <li>1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.</li> <li>2. Increase by ≥25% in the sum of the products of the perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.</li> <li>3. Clinical deterioration not attributable to concurrent medication or co-morbid conditions is sufficient to declare progression on current treatment but not for entry into a clinical trial for recurrence.</li> <li>4. For patients receiving anti-angiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and must not be a result of co-morbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).</li> </ol>

FLAIR = fluid-attenuated inversion recovery.

### RESPONSE ASSESSMENT

Criteria for response assessment are summarized in [Table 12](#). All measurable and non-measurable lesions should be assessed using the same techniques as at baseline. All patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

## Appendix 5 Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)

**Table 12 Summary of RANO Response Criteria**

	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥50% ↓	<50% ↓ but <25% ↑	≥25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑ <sup>a</sup>
New lesion	None	None	None	Present <sup>a</sup>
Corticosteroids	None	Stable or ↓	Stable or ↓	NA <sup>b</sup>
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↑ <sup>a</sup>
Requirement for response	All	All	All	Any <sup>a</sup>

↓ = decreased; ↑ = increased; CR = complete response; FLAIR = fluid-attenuated inversion recovery; NA = not applicable; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.

<sup>a</sup> Progression occurs when this criterion is present.

<sup>b</sup> Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

### COMPLETE RESPONSE

Complete response requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/fluid-attenuated inversion recovery [FLAIR]) lesions; and the patient must be off corticosteroids or on physiologic replacement doses only, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

### PARTIAL RESPONSE

Partial response requires all of the following: ≥50% decrease, compared with baseline, in the sum of the products of the perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non-measurable disease; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; and the patient must be on a corticosteroid dose not greater than the dose at the time of the baseline scan, and stable or improved clinically. In the absence of a confirming scan 4 weeks later, this response will be considered only stable disease.

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)**

#### **STABLE DISEASE**

Stable disease occurs if the patient does not qualify for complete response, partial response, or progression (see next section) and requires the following: stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and clinically stable status. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

#### **PROGRESSION**

Progression is defined by any of the following:  $\geq 25\%$  increase in the sum of the products of the perpendicular diameters of all enhancing lesions (compared with the smallest tumor measurement either at baseline [pretreatment] or after initiation of therapy [i.e., compared with baseline if no decrease]) on stable or increasing doses of corticosteroids; a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to co-morbid events; the appearance of any new lesions; clear progression of non-measurable lesions; or definite clinical deterioration not attributable to other causes apart from the tumor, or to a decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. Such patients should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first timepoint at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in Karnofsky Performance Status from 100 or 90 to 70 or less, a decline in Karnofsky Performance Status of at least 20 from 80 or less, or a decline in Karnofsky Performance Status from any baseline to 50 or less,

## **Appendix 5**

### **Response Assessment in Neuro-Oncology (RANO): Modified Excerpt from Original Publication (cont.)**

for at least 7 days, be considered neurologic deterioration unless attributable to co-morbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern

Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or from 2 to 3 would be considered neurologic deterioration.

Patients with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimum bi-directional diameter of  $\geq 10$  mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a  $9 \times 9$  mm lesion [non-measurable] increasing to a  $10 \times 11$  mm lesion [measurable]). Ideally, the change should be significant  $\geq 5$  mm increase in maximum diameter or  $\geq 25\%$  increase in the sum of the products of the perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression.

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, the date of progression should be the timepoint at which this issue was first raised. For multifocal lesions, progressive disease is defined as a  $\geq 25\%$  increase in the sum of the products of the perpendicular diameters of all measurable lesions compared with the smallest tumor measurements either at baseline or after initiation of therapy [Table 12](#)). The appearance of a new lesion or unequivocal progression of non-target lesions will also be considered progression. Partial response is defined as a  $\geq 50\%$  decrease, compared with baseline, in the sum of the products of the perpendicular diameters of all measurable lesions sustained for at least 4 weeks with stable or decreasing corticosteroid doses.

## Appendix 6

### Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

## Appendix 7 EORTC Quality-of-Life Questionnaire—Core 30



### EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
<b>During the past week:</b>				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4





## **Appendix 9**

### **Modification of Diet in Renal Disease Formula**

The estimated glomerular filtration rate (eGFR) will be calculated on the basis of the following formula:

$$\text{eGFR [mL/min/1.73 m}^2\text{]} = 175 \times \text{serum creatinine}^{-1.154} \times \text{AGE}^{-0.203} [\times 0.742 \text{ if female}]$$

[ $\times 1.212$  if African American] (conventional units)

Where SCRT = serum creatinine in conventional units (i.e., mg/dL), the following conversion factor should be used in case the serum creatinine value is provided by the laboratory in  $\mu\text{mol/L}$  units:

$$\text{Serum creatinine [mg/dL]} = \text{Serum creatinine } [\mu\text{mol/L}] \times 0.0113$$

Reference: Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med 2009;47:1017–9

Heil W., Koberstein R, Zawta B. Reference Ranges for Adults and Children—Pre-Analytical Considerations. Roche Diagnostics GmbH 2014, 8th edition, p.159

## **Appendix 10**

### **Anaplastic Lymphoma Kinase Immunohistochemistry**

#### **Overview**

The VENTANA anti-anaplastic lymphoma kinase (ALK) (D5F3) Rabbit Monoclonal Primary Antibody (VENTANA anti-ALK [D5F3]; catalog reference number 790-4794) immunohistochemistry (IHC) assay will be used to determine ALK IHC status and to select patients with positive ALK for enrollment in Study Y029449. The anti-ALK (D5F3) rabbit monoclonal antibody IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to Roche's ALK inhibitor, alectinib. For Study Y029449, the VENTANA anti-ALK (D5F3) assay will be used for investigational purposes only.

VENTANA anti-ALK (D5F3) is intended for laboratory use in the detection of the ALK protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue stained with use of a VENTANA automated slide stainer. It is indicated as an aid in identifying patients eligible for treatment with alectinib.

#### **Device Description**

The VENTANA anti-ALK (D5F3) IHC assay is an automated IHC staining assay system comprising a pre-diluted, ready to-use anti-ALK (D5F3) rabbit monoclonal primary antibody, the BenchMark<sup>®</sup> automated slide staining platform, OptiView DAB detection kit, OptiView Amplification kit, Rabbit Monoclonal Negative Control Ig, and VENTANA anti-ALK 2-in-1 cell line control slides or other appropriate system run control.

#### **Scoring System**

The IHC scoring system evaluates specific VENTANA anti-ALK (D5F3) staining in NSCLC tumor cells by the presence of a strong, granular, cytoplasmic staining pattern. Pathologists must rely on the Negative Reagent Control (NRC) slides to distinguish non-specific staining from specific ALK positivity. Samples must be assessed for morphological damage and the presence of viable tumor versus necrosis. Light, granular, cytoplasmic stippling in alveolar macrophages may occur on anti-ALK (D5F3) and/or NRC slides as an artifact of the detection system. This staining artifact should be noted on the Slide Evaluation Form comment field but should NOT be interpreted as ALK-positive staining. Some background staining has also been observed on normal mucosa in NSCLC specimens, as well as in necrotic tumor areas; this staining also should not be interpreted as ALK-positive staining. Case slide sets failing to show specific staining of the case tissue with VENTANA anti-ALK (D5F3) cannot be considered ALK-positive. Refer to VENTANA ALK Scoring Interpretation Guide for NSCLC for additional information.

## Appendix 11 Formulae for the Calculation of QTcF and RR

QTcF – Fridericia's correction for QTc measurement (if not provided directly by the ECG machine):

$$\text{QTcF (ms)} = \frac{\text{QT (ms)}}{\sqrt[3]{\text{RR (ms)} / 1000}}$$

RR Interval Formula (if not provided directly by the ECG machine):

$$\text{RR (ms)} = 60000 / \text{heart rate (bpm)}$$

## Appendix 12 FoundationOne Gene Panel

Genes									
ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4	KAT6A	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1	C11orf30	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYV	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL

## Appendix 12 FoundationOne Gene Panel (cont.)

AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRF1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	
Rearrangements									
ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	