Official Title: Randomized, Multicenter, Phase III, Open-Label Study of Alectinib Versus Crizotinib in Treatment-Naive Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer

NCT Number: NCT02075840

Document Date: Protocol Amendment Version 9: 15-Oct-2023

PROTOCOL

PROTOCOL TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS CRIZOTINIB IN TREATMENT-NAIVE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO28984
VERSION NUMBER:	9
TEST PRODUCT:	Alectinib (RO5424802)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIERS	IND Number: 111,273 EudraCT Number: 2013-004133-33 EU CT Number: 2023-506859-13-00 UTN Number: U111-1160-7882 NCT Number: NCT02075840
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
9	See electronic date stamp on the final page of this document	Canada	11	—
8	18 January 2022	Canada	10	18 January 2022
—	—	Canada	9	15 August 2021
7	22 June 2021	Canada	8	21 June 2021
6	4 November 2019	Canada	7	4 November 2019
5	4 June 2018	Canada	6	28 June 2018
4	15 April 2016	Canada	5	10 February 2017
3	14 May 2015	—	—	—
2	8 October 2014	—	—	—
1	10 February 2014	—	—	—

PROTOCOL AMENDMENT, VERSION 9:
RATIONALE

Protocol BO28984 has been amended primarily to update the formal end of study definition, to include guidance on photosensitivity for crizotinib, and to align the protocol with E.U. Clinical Trials Regulation (CTR) requirements.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Language has been included to provide flexibility for additional survival follow-up analyses to be performed (Section 3.2).
- The end of study definition has been updated so that patients can be followed up until the last patient has completed the study or when the Sponsor decides to end the trial, whichever occurs first (Section 3.2).
- Guidance on photosensitivity has been included under additional restrictions for concomitant therapies for alectinib to align with Management of Specific Adverse with Alectinib (Section 4.4.4).
- Instructions about patient withdrawal from the Roche Biosample Repository after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global.rcr-withdrawal@roche.com (Section 4.5.11.6).
- Guidance on photosensitivity has been included in Safety of Crizotinib and Management of Adverse Events to align with the Crizotinib Summary of Product Characteristics (Section 5.1.4).
- Adverse even reporting for hospitalization has been clarified (Section 5.3.5.10).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.3).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).

Changes related to E.U. CTR requirements have been made as follows:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1).
- The synopsis has been simplified to align with CTR and other guidelines.
- A section describing the duration of participation has been added to align with CTR requirements (Section 3.3).
- A comprehensive list of investigational medicinal products has been added to align with CTR requirements (Section 4.3 and Appendix 11).

- Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (Section 5.4.1).
- It has been made explicit that expedited safety reports are notified to Eudravigilance (Section 5.7).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS CRIZOTINIB IN TREATMENT-NAIVE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO28984
VERSION NUMBER:	9
TEST PRODUCT:	Alectinib (RO5424802)
SPONSOR NAME:	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 to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS CRIZOTINIB IN TREATMENT-NAIVE ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 111,723 EudraCT Number: 2013-004133-33 EU CT Number: 2023-506859-13-00 UTN Number: U1111-1160-7882 NCT Number: NCT02075840

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of alectinib, a novel highly selective anaplastic lymphoma kinase (*ALK*) inhibitor, in patients with treatment–naive *ALK*–positive advanced non–small cell lung cancer (NSCLC). At the commencement of this study, the only treatment option for *ALK*–positive treatment–naive NSCLC is crizotinib (Xalkori®, Pfizer, Inc.), an inhibitor of receptor tyrosine kinases including *ALK*, hepatocyte growth factor receptor (*HGFR, c–MET)*, recepteur d'origine nantais (*RON*), and c-ros oncogene 1 (*ROS1*). Although substantial benefit has been observed with crizotinib therapy, there continues to be a need for increasingly selective treatments with improved benefit–risk profiles that attenuate development of resistance, increase penetration into the CNS (a common site of metastases in disease progression), and improve the long-term prognosis in patients with *ALK*–positive NSCLC.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of alectinib compared with crizotinib in patients with treatment–naive *ALK*–positive advanced NSCLC. Specific objectives and corresponding endpoints are outlined in the following table.

Objectives and Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of alectinib compared with crizotinib	• Investigator-assessed PFS, defined as the time from randomization to the date of first documented disease progression (per RECIST v1.1), or death from any cause, whichever occurs first.
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of alectinib compared with crizotinib	• PFS on the basis of IRC assessments • Time to CNS progression, defined as the time from randomization to the first occurrence of disease progression in the CNS as determined by IRC using 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 OR, and C-PR at 6, 12, 18, and 24 months. • ORR, defined as percentage of patients who attain a CR or PR as determined by investigator assessment per RECIST v1.1. • DOR, defined as time from when response (CR or PR) was first documented to first documented disease progression or death (whichever occurs first). • 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.
• To evaluate the safety and tolerability of alectinib compared with crizotinib	• Serious and non-serious adverse events • Safety laboratory tests values • Vital signs (blood pressure, heart rate), ECG • Physical examination
• To characterize the pharmacokinetics of alectinib and metabolite(s)	• Sparse (pre-dose) PK samples for measurement of alectinib and its major metabolite(s) will be collected in all study patients receiving alectinib treatment. • Serial/intensive PK sampling will be collected in a subset of consenting patients enrolled to receive alectinib treatment (approximately 10%–15%), at least approximately n = 20) • PK parameters will be determined as appropriate and where data allow:

	The pharmacokinetics of alectinib (and metabolite[s], if appropriate) will be described, and the between-patient variability will be estimated using 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. Non-compartmental analysis may be conducted in patients undergoing serial/intensive PK sample collection, as appropriate and where data allow.
• To evaluate and compare TTD in patient–reported lung cancer symptoms of cough, dyspnea (single item and multi–item subscales), chest pain, arm and shoulder pain, and fatigue compared between patients treated with alectinib and those treated with crizotinib • To evaluate and compare PROs of HRQoL, patient functioning, and side effects of treatment compared between patients treated with alectinib and those treated with crizotinib	• The EORTC QLQ-C30 and EORTC QLQ-LC13 to determine the impact of alectinib compared with crizotinib as measured by TTD. • The EORTC QLQ-C30 and EORTC QLQ-LC13 to measure PROs of HRQoL, patient functioning, and side effects of therapy.
C-DOR = CNS duration of response; C-ORR = CNS objective response rate; C-PR = CNS progression rate; CR = complete response; DOR = duration of response; EORTC = European Organization for the Research and Treatment of Cancer; EORTC QLQ–30 = EORTC core quality of life questionnaire; EORTC QLQ–LC13 = supplement to the EORTC QLQ–30; HRQoL = health-related quality of life; IRC = Independent Review Committee; OR = objective response; ORR = objective response rate; OS = overall survival; PFS = progression–free survival; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; RANO = Revised Assessment in Neuro-Oncology; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; TTD = time to deterioration.	

OVERALL DESIGN AND STUDY POPULATION

Study BO28984 is a Phase III, randomized, active-controlled, multicenter, open-label study of alectinib as first-line systemic therapy in patients with treatment-naive *ALK*-positive advanced NSCLC. The study is designed to evaluate the efficacy, safety, and pharmacokinetics of alectinib compared with crizotinib as first-line therapy in treatment-naive patients with non-resectable, locally advanced, and metastatic *ALK*-positive NSCLC.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active–controlled	**Population Diagnosis or Condition**	Patients with histologically or cytologically confirmed diagnosis of advanced, recurrent, or metastatic *ALK*-positive non–small cell lung cancer

Phase:	Phase III	**Population Type:**	Adult patients
Interventional Model:	Parallel group	**Population Age:**	≥ 18 years
Test Product:	Alectinib	**Site Distribution:**	Multi-site, multi-region
Active Comparator:	Crizotinib	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to be Enrolled:**	286

STUDY TREATMENT

Alectinib 600 mg (four 150-mg capsules) should be administered orally twice a day (BID) with food in the morning and evening. Crizotinib at 250 mg (one 250-mg capsule) should be administered orally BID with or without food (in the morning and evening).

If dose reduction of alectinib is necessary, then the dose of alectinib should be reduced to 450 mg BID. If further dose reduction is necessary, then the dose should be modified to 300 mg BID.

If dose reduction of crizotinib 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 once a day.

DURATION OF PARTICIPATION

Treatment will continue until disease progression as stated in the protocol. The total duration of study participation for each individual is expected to range from 1 day to more than 144 months.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee, Independent Review Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
AUC	area under the concentration–time curve
BID	twice a day
C_{max}	maximum observed concentration
C-DOR	CNS duration of response
C-ORR	CNS objective response rate
C-PR	CNS progression rate
COVID-19	coronavirus disease 2019
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
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
ePRO	electronic patient-reported outcome
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat
IxRS	interactive voice or Web-based response system
KRAS	Kirsten rat sarcoma viral oncogene homolog
LH	luteinizing hormone
MET	mesenchymal-epithelial transition factor
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCA	non-compartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
QD	once a day
QTcF	QT interval corrected using Fridericia's formula
RANO	Revised Assessment in Neuro Oncology
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RON	recepteur d'origine nantais
ROS1	c-ros oncogene 1
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SDF	survival distribution function

Abbreviation	Definition
SHBG	sex hormone-binding globulin
SLS	sodium lauryl sulfate
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
USPI	U.S. Package Insert

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 160,340 deaths in the United States in 2012, accounting for 28% of all cancer-related deaths according to the report from the American Lung Association (American Lung Association 2014). There is an annual incidence of 310,000 cases of NSCLC in men in Europe with a mortality of 276,000 deaths (GLOBOCAN 2008). Among women in Europe, there is an annual incidence of 107,000 cases and a mortality of 91,000 deaths. In total, there are 417,000 cases of NSCLC and 367,000 deaths in Europe each year, which represents a major health problem. Survival rates for lung cancer tend to be much lower than other common cancers because of its late diagnosis and limited effective therapy in the advanced stage. The expected 5-year survival rate for all patients in whom lung cancer is diagnosed 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 resulting *ALK* fusion protein results in activation and dysregulation of the gene's expression and signaling, which can contribute to increased cell proliferation and survival in tumors expressing these genes. This is further supported by reports that the *TFG* and *KIF5B* genes can 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. The *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 (Doebele et al. 2012). Inhibition of *ALK* activity in Ba/F3 cells 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 2 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 expressed at very low levels in most normal human tissues, but is 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 only approved medicine for treatment-naive *ALK*-positive NSCLC is crizotinib (Xalkori®, Pfizer, Inc.), an inhibitor of receptor tyrosine kinases including *ALK*, hepatocyte growth factor receptor (*HGFR, 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) for the treatment of patients with locally advanced or metastatic NSCLC that is positive for *ALK* as detected by an FDA-approved test in August 2011. The approval was based on 2 single-arm trials. The primary endpoint of both trials was objective response rate (ORR) as assessed by the investigator. In one study, the ORR was 50% (95% CI: 42% to 59%) with a median response duration of 42 weeks, and, in the other study, the ORR was 61% (95% CI: 52% to 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 demonstrating 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 (PROFILE 1007 study). An open-label, active-controlled, multinational, randomized trial enrolled 347 patients with *ALK*-positive metastatic NSCLC. Patients were required to have disease progression following platinum-based chemotherapy. The trial demonstrated significantly prolonged PFS with crizotinib treatment compared with chemotherapy (hazard ratio [HR] = 0.49 [95% CI: 0.37 to 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 (65% vs. 20%), 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 (HR = 1.02 [95% CI: 0.68% to 1.54%]) in a planned interim analysis (Shaw et al. 2013). Common adverse reactions in clinical trials 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 [NCI] 2013). These results showed that an *ALK* inhibitor is effective in patients with NSCLC harboring *ALK* fusion genes. Crizotinib has subsequently been approved in other countries, such as Japan, Korea, Canada, and Switzerland. 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 remains the norm. Studies with patients who had progression with crizotinib treatment revealed two main reasons for treatment failure: the development of resistance 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 treated with crizotinib (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012). Significant morbidity is associated with brain metastases as a function of brain involvement, and because of treatment (corticosteroids, surgery, and radiation) required for disease control.

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

1.2 BACKGROUND ON ALECTINIB

Alectinib (also RO5424802 or CH5424802) 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 antitumor activity both in vitro and in vivo against tumor cell lines with some types of *ALK* gene alteration, including NSCLC and anaplastic large cell lymphoma lines harboring an *ALK* translocation and a neuroblastoma line harboring amplified *ALK* gene.

Nonclinical pharmacology studies showed that alectinib is efficacious in a model of tumors expressing an *ALK* fusion bearing 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 using bioluminescence.

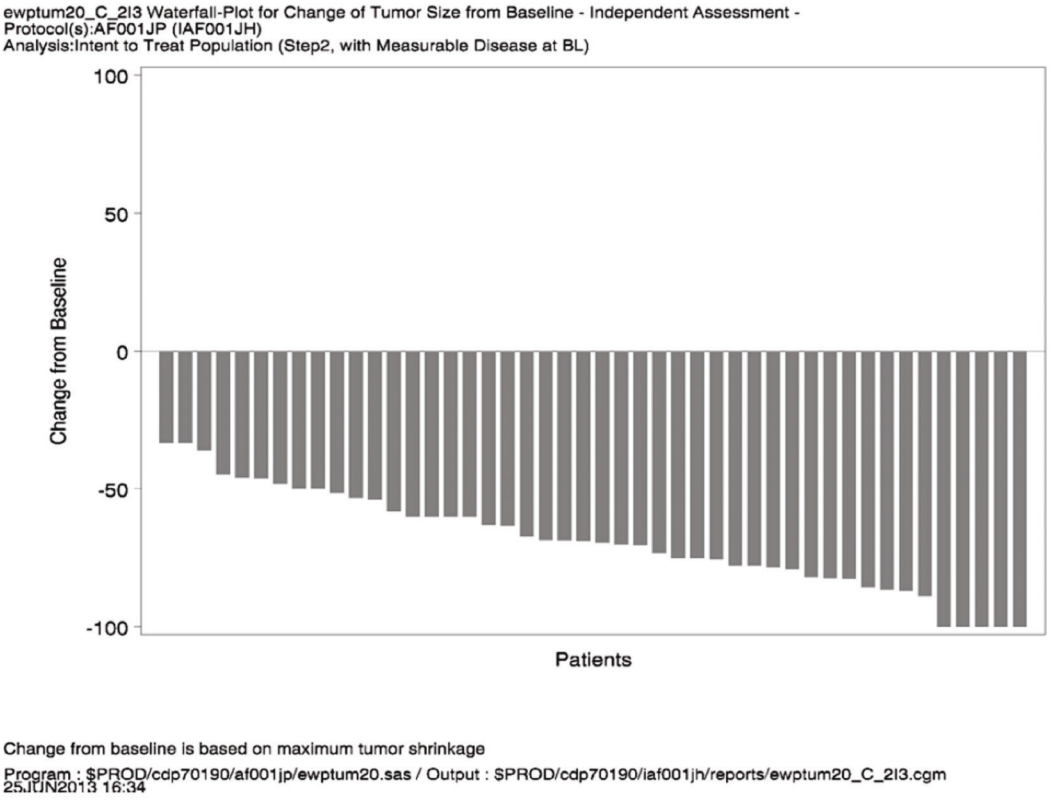
The clinical development program for alectinib, to date, comprises 3 ongoing Phase I/II studies in patients with *ALK*-positive NSCLC. The ongoing Phase I/II studies are as follows: Study AF-001JP, which is being conducted in Japan;
Study NP28761/AF-002JG, which is being conducted in United States and Canada; 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 is assessing the pharmacokinetics, safety, and efficacy of alectinib in patients with *ALK*-positive NSCLC who are crizotinib-naive and have disease progression after at least one line of chemotherapy. This study has completed enrollment, but it is still ongoing. A total of 70 patients were included (24 patients in the

Phase I portion and 46 patients in the Phase II portion of the study). In the Phase I portion of the study, at the data cutoff date of 31 July 2012, 24 patients were treated at doses of 20–300 mg twice a day (BID). No dose-limiting toxicities (DLTs) or adverse events of Grade 4 were noted up to the highest dose; thus, 300 mg BID was evaluated in the Phase II portion of the study without further escalating the dose. In the Phase II portion of the study, 46 patients were treated with the highest evaluated dose of 300 mg BID, of whom 43 achieved an objective response (93.5%; 95% CI: 82.1% to 98.6%) and 7 patients had a complete response (CR) on the basis of an independent radiological review in the 12-month follow-up analysis (data cutoff for response data: 18 April 2013). The median duration of treatment (DOT) in the study has not been achieved at that date because 86% of patients were still on treatment in the study, but the projected median DOT is more than 14 months as data mature.

Figure 1 shows the waterfall plot of the best change from baseline in the size of target lesions by an independent radiological review. Table 1 shows the ORR by time interval. The majority (86%) of patients had a time to response within 6 weeks after administration of the first dose.

Figure 1 Change in Size of Target Lesions as Assessed by the Independent Review Committee in Part 2 of Study AF-001JP Using RECIST v1.1 (Data Cutoff Date: 18 April 2013)



Two of 7 patients who were assessed as having a CR had lymph nodes as the target lesions. Per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 (v1.1), the percent change from baseline for patients with CR can be less than 100% when lymph nodes are identified as the target lesions. Therefore, these patients were assessed as having a CR, although their tumor change from baseline was less than 100%.

Table 1 Overall Response Rates and Time to Response in Patients in Part 2 of Study AF-001JP

Response (Data Cutoff Date: 18 April 2013)	IRC Assessment (N = 46)
Complete response	7
Partial response	36
Stable disease	1
Progressive disease	0
Not evaluable	2
Total response	43
Overall response rate (95% CI)	93.5% (82.1%, 98.6%)
Time to Response	**IRC Assessment (N = 43)**
0 to ≤ 3 weeks	22 (51%)
> 3 to ≤ 6 weeks	15 (35%)
> 6 to ≤ 9 weeks	3 (7%)
> 9 weeks	3 (7%)

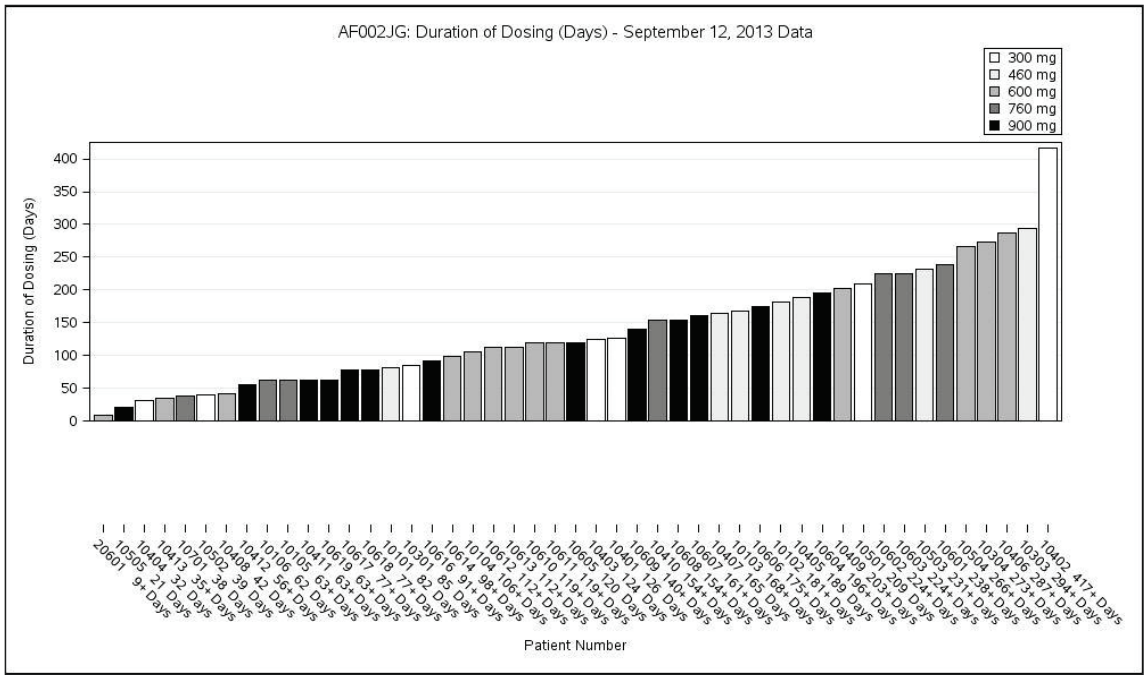
IRC = Independent Review Committee.

In Study NP28761/AF-002JG (patients with crizotinib-failed *ALK*-positive NSCLC), the Phase I portion has completed enrollment. Two 'bridging' cohorts of patients receiving alectinib using the 150-mg capsule at 600 and 900 mg BID were included in Study NP28761/AF-002JG to transition/facilitate the planned formulation for the Phase II trials. A total of 47 patients were enrolled in Phase I (Part 1). There did not appear to be any substantial difference in pharmacokinetics between the 2 formulations (20/40-mg capsule and the 150-mg capsule) at the 600-mg dose on the basis of available data.

The radiological imaging analysis performed in 44 evaluable patients who had a baseline scan and at least 1 follow-up scan (data cutoff date: 12 September 2013) has shown 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 have 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 achieved a PR, as assessed by the investigator, which is still to be confirmed. Three patients (all in the 600-mg BID dosage

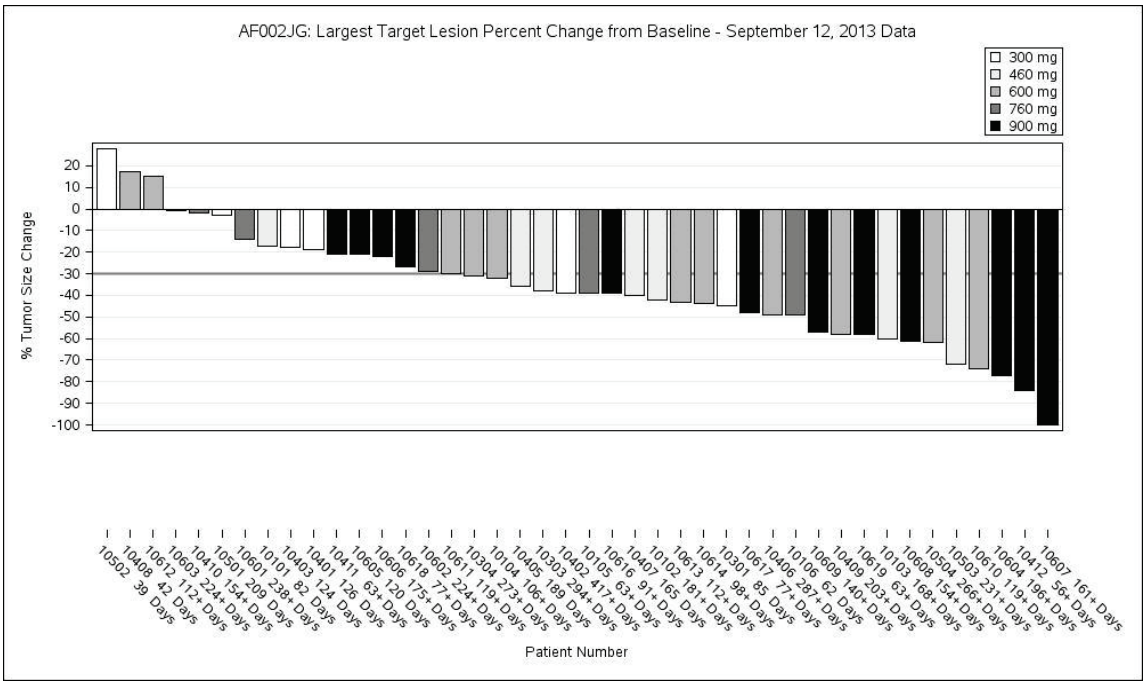
cohort) were unevaluable. The ORR was 54.5% (i.e., ORR was reported for 24 of 44 evaluable patients who had a baseline scan and at least 1 post-treatment scan available to determine overall response, or who had a best overall response of progressive disease [PD] determined by the investigator, on the basis of symptomatic progression [3 patients]), including unconfirmed responses across all dose cohorts. Thirty-three of the 47 (70%) treated patients were still receiving study treatment. The durations of dosing by cohort are shown in Figure 2.

Figure 2 Duration of Dosing by Cohort in Patients in Part 1 of Study NP28761/AF-002JG (Data Cutoff Date: 12 September 2013)



The waterfall plot for the 42 patients, with a post-baseline radiological tumor assessment, is shown in Figure 3. On the basis of the data analyzed at that date, 27 patients experienced tumor shrinkage of >30%, of whom 23 patients were assessed as experiencing PR (9 of whom are still to be confirmed by a second tumor assessment).

Figure 3 Best Percent Change in Size of Target Lesions from Baseline as Assessed by the Investigator in Patients in Part 1 of Study NP28761/AF-002JG (Data Cutoff Date: 12 September 2013)



Patients were enrolled in Study NP28673 starting on 20 June 2013 and no data are available to report at this time.

The benefit of alectinib on CNS activity has been described by the DOT (before progression) or ORR in patients with brain metastases at baseline in the two active studies: Study AF-001JP in Japan and Study NP28761/AF-002JG in the United States. In Phase II of Study AF-001JP, 14 of the 46 (30%) crizotinib-naive patients had documented CNS lesions before enrollment into the trial. Three of these 14 patients were asymptomatic and had not received prior CNS radiation. At the clinical cutoff date of 18 March 2013, 5 of the 14 patients were off-study because of systemic disease progression or an adverse event. Nine patients remain in the study with a DOT ranging from 10–18 months (none of these patients presented signs or evidence of systemic disease or CNS progression).

Similarly, in Study NP28761/AF-002JG, among the 47 patients enrolled (data cutoff date: 12 September 2013), 21 patients (45%) were known to have brain metastases at baseline. Of these 21 patients, 11 (52%) achieved an ORR as determined by Independent Review Committee (IRC; data cutoff date: 12 September 2013; Inoue et al. 2013). Moreover, of these 21 patients, 17 remained on active study treatment and 4 discontinued study treatment because of systemic PD (1 patient had

both systemic disease and CNS progression). No patient discontinued because of CNS progression alone.

In addition, 2 patients with leptomeningeal carcinomatosis received benefit from alectinib treatment. One patient with leptomeningeal spread in Study NP28761/AF-002JG achieved a PR after 6 weeks of treatment. Another patient with leptomeningeal carcinomatosis but without systemic lesions was treated under a single-patient Investigational New Drug (IND) application because of ineligibility to enter either of the 2 Phase II alectinib studies (because of the high intake of dexamethasone for symptom control). After 6 weeks of treatment, this patient achieved CR as demonstrated by complete disappearance of gadolinium enhancement on magnetic resonance imaging (MRI) and disappearance of positive cerebrospinal fluid cytology. This patient was able to reduce corticosteroids to the physiological replacement dose only.

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 coding for *EGFR*, *KRAS*, phosphoinositide-3-kinase (specifically, the catalytic α polypeptide), and *EGFR*2 (Pao and Girard 2011). As described in previous sections, a translocation in the gene encoding the receptor tyrosine kinase *ALK*, leading to the expression of *ALK* fusion proteins, was identified as an oncogenic driver in a subset of patients with NSCLC (Soda et al. 2007). The *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 has been approved and registered in multiple countries worldwide for the treatment of *ALK*-positive NSCLC. Crizotinib is an oral small-molecule multi-targeted tyrosine kinase inhibitor (TKI) targeting *ALK*, *MET*, *RON*, and *ROS1* tyrosine kinases (Sahu et al. 2013, Shaw et al. 2013). The previous clinical studies reported that the median PFS with crizotinib ranged from 7.7–9.7 months (Camidge et al. 2012; Kim et al. 2013; Shaw et al. 2013). The PROFILE 1014 study, a Phase III study of crizotinib compared with standard pemetrexed-platinum-based chemotherapy, was presented at the American Society of Clinical Oncology 2014 congress (Mok et al. 2014). The study met its primary objective of prolonging PFS in previously untreated patients with *ALK*-positive non-squamous NSCLC with a median PFS of 10.9 and 7.0 months (HR: 0.454; 95% CI: 0.346 to 0.596; $p < 0.0001$) for crizotinib and pemetrexed-platinum-based chemotherapy, respectively.

Although substantial benefit has been observed with crizotinib therapy, relapse eventually occurs. Two major reasons for this are the development of resistance because of secondary (e.g., gatekeeper) mutations, or CNS relapse (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013). This could be due to the fact that crizotinib is a P-glycoprotein (P-gp) substrate and has a low penetration in the CNS. Thus, *ALK*-positive NSCLC treated with crizotinib has impaired control of brain metastases relative to other sites of systemic disease, with 46% of progressions in patients treated with crizotinib involving the CNS (Costa et al. 2011; Weickhardt et al. 2012). The CNS becomes a sanctuary site for *ALK*-positive NSCLC treated with crizotinib—a physiologic and anatomic mechanism of drug resistance.

Alectinib is a highly selective and potent oral next generation *ALK* inhibitor. Clinical data collection from the Phase II portion is still 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 had not been achieved as 86% of patients were still active on the study, but the projected median DOT is estimated to be at least 14 months at the final point of data collection (Inoue et al. 2013).

Moreover, alectinib is a lipophilic drug and is not a P-gp substrate. Thus, it is able to penetrate the blood-brain barrier and has the potential to reach higher concentrations in the brain as compared with substrates of P-gp such as crizotinib. This has been shown 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 [^{14}C]-alectinib at 1 mg/kg in albino rats (Ou et al. 2013). Preliminary clinical data from the Phase I/II studies show consistent therapeutic efficacy of alectinib in brain metastases.

The clinical efficacy data is compelling given the demonstrated activity for a longer progression-free interval with alectinib treatment and improved activity in the CNS. This progression-free interval delays the impact of CNS metastases on neurologic function along with the morbidities associated with treatment like brain radiation, surgery and corticosteroid use required for disease control. The currently available clinical safety data is supportive of an acceptable safety and tolerability profile with alectinib. Altogether, it would be important to compare alectinib with crizotinib as a therapeutic option for patients with treatment-naive *ALK*-positive advanced NSCLC.

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

In this proposed Phase III study, treatment-naive patients with *ALK*-positive advanced NSCLC will be enrolled and will be randomized to receive either alectinib or crizotinib treatment. The results of this study will determine whether alectinib treatment has superior efficacy compared with crizotinib.

The first Phase I dose-escalation study of alectinib (Study AF001-JP, conducted only in Japan) with a dosing regimen of 20, 40, 80, 160, 240, and 300 mg BID orally showed that alectinib was generally well-tolerated without major toxicities. Of the 58 patients who received treatment with 300 mg BID alectinib in Study AF-001JP, 27 patients experienced Grade 3 adverse events and 9 experienced serious adverse events. No deaths were reported during this study and up to 28 days after treatment discontinuation. There were 5 adverse events leading to treatment discontinuation in Part 2 (brain edema, sclerosing cholangitis, interstitial lung disease [ILD], ALT increased, and tumor hemorrhage). Alectinib was well-tolerated at all doses investigated in this study. Its adverse event profile was consistent with the one known to be associated with TKIs. In the Phase II Study NP28761/AF-002JG, alectinib was well-tolerated with no DLTs or treatment-related dose modifications up to 600 mg BID. Two DLTs were reported at 900 mg BID. The recommended alectinib Phase II dosage of 600 mg BID was chosen as having the best balance between clinical safety, efficacy, and pharmacokinetic (PK) data as observed in the Phase I/II studies (see Section *3.4.1*).

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 crizotinib-naive patients with NSCLC as well as after progression on prior crizotinib therapy
- Clinical safety data in humans up to 900 mg BID demonstrate that its safety profile is consistent to the one known to be 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 ensured by targeting the most appropriate patient population, stringent safety monitoring by the Sponsor and independent Data Monitoring Committee (iDMC), and by protocol-specified study drug interruption criteria.

1.3.1 COVID-19 Benefit–Risk Assessment

No changes related to coronavirus disease 2019 (COVID-19) have been made to this protocol.

In the setting of the COVID-19 pandemic, patients with certain comorbidities, including those with cancer, are a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19 infection. However, it is unclear whether or how anti-cancer therapies such as chemotherapy or targeted therapy affect the incidence or severity of COVID-19 infections. Based on their safety profiles and mechanisms of action, it is not anticipated that the medicinal products used in this study will increase the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Other clinical trials with the medicinal products used in this study have

been ongoing during this pandemic and, although the numbers are small, patients have not shown any increased risk of developing COVID-19 symptoms.

1.3.2 COVID-19 Vaccine Benefit–Risk Assessment

Based on the published mechanism of action of the COVID-19 vaccines and the known mechanism of action of alectinib or crizotinib, there is no scientific rationale to expect that COVID-19 vaccines will affect the efficacy of alectinib and crizotinib. Based on a specific benefit-risk assessment, taking into account the available relevant information, the approved non-live COVID-19 vaccines may and should be administered to patients who are in the study, as long as there is no other contraindication (e.g., known hypersensitivity to a vaccine component).

Investigators should share with patients' primary healthcare providers relevant information regarding any potential effect of respective study drugs on the response to COVID-19 vaccination, as applicable. Also, patients should contact the investigators or site staff, when they are invited to receive a COVID-19 vaccine deployed in their region. The decision to vaccinate a patient should be based on a patient's SARS-CoV-2 infection/complication risk, general health condition, severity of underlying malignancy, and regional epidemiology of COVID-19. Coronavirus 2019 vaccines should be administered in accordance with their respective prescribing information and applicable immunization guidelines.

After COVID-19 vaccination, one should continue to observe the applicable epidemiologic/public health and hygiene measures, during the pandemic, along with per protocol safety measures and assessments, in order to minimize the risk, but also to appropriately identify and assess potential adverse reactions (e.g., nausea, diarrhea, myalgia) possibly shared by vaccines and study drugs.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is:

- To evaluate and compare the efficacy of alectinib compared with crizotinib in patients with treatment-naive *ALK*-positive advanced NSCLC, as measured by investigator-assessed PFS

The secondary efficacy objectives for this study are:

- To evaluate and compare the ORR and duration of response (DOR)
- To evaluate and compare the time to progression in the CNS on the basis of IRC review of radiographs by RECIST v1.1 and Revised Assessment in Neuro Oncology (RANO) criteria, as well as:
  - To evaluate CNS ORR (C-ORR) in patients with CNS metastases who have measurable disease in the CNS at baseline

  - To assess CNS DOR (C-DOR) in patients who have a CNS OR
  - 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 the IRC
- To evaluate and compare the OS

2.2 SAFETY OBJECTIVES

The secondary safety objective for this study is:

- To evaluate the safety and tolerability of alectinib compared with crizotinib

2.3 PHARMACOKINETIC OBJECTIVES

The secondary PK objective for this study is:

- To characterize the pharmacokinetics of alectinib and metabolite(s)

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

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

- To evaluate and compare time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, dyspnea (single item and multi-item subscales), chest pain, arm and shoulder pain, and fatigue as measured by the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the supplemental lung cancer module (QLQ-LC13) as well as a composite of 3 symptoms (cough, dyspnea, chest pain)
- To evaluate and compare PROs of health-related quality of life (HRQoL), patient functioning, and side effects of treatment as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are:

- To evaluate and compare patient's health status as assessed by the EQ-5D-3L questionnaire to generate utility scores for use in economic models for reimbursement
- To evaluate and compare the onset of hypogonadism in adult men by measuring total testosterone and free testosterone (either by direct measurement or by calculation using albumin and sex hormone-binding globulin [SHBG]), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels in blood
- To evaluate and compare efficacy in patients with treatment-naive *ALK*-positive NSCLC as assessed by the fluorescence in situ hybridization (FISH) Vysis® ALK Break Apart FISH Probe Kit (Abbott)
- To evaluate and compare efficacy and safety in patients having treatment-naive *ALK*-positive NSCLC as assessed by plasma *ALK* assays (polymerase chain reaction [PCR] and/or sequencing)

- To determine the correlation between *ALK* status as assessed by plasma *ALK* PCR and/or plasma *ALK* sequencing tests, with *ALK* status obtained using the Ventana ALK immunohistochemistry (IHC) and FISH Vysis ALK Break Apart FISH Probe Kit (Abbott)
- To investigate molecular mechanisms of resistance to *ALK* inhibitors
- To investigate detection of *ALK* mutations/fusions in plasma

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

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

This study will comprise approximately 180 centers, in around 30 countries worldwide.

The primary endpoint of the study is investigator-assessed PFS.

Central randomization will be performed via an interactive voice or Web-based response system (IxRS) using the following stratification factors: Eastern Cooperative Oncology Group Performance Status (ECOG PS; 0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no). An IxRS manual containing relevant information will be provided to each study site.

The experimental arm will receive alectinib 600 mg orally BID, taken with food.
The control arm will receive crizotinib 250 mg orally 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. After disease progression (as per RECIST v1.1), patients should discontinue the study medication. After disease progression, patients will be treated at the discretion of the investigator according to local practice. Information regarding the nature and the duration of subsequent therapies will be collected.

In case of isolated asymptomatic CNS progression (e.g., new CNS oligometastases), local therapy can be given (e.g., stereotactic radiotherapy or surgery) followed by continuation of either alectinib (in alectinib arm) or crizotinib (in crizotinib arm) until systemic disease progression and/or symptomatic CNS progression. The decision to continue the treatment beyond isolated, asymptomatic CNS progression is at the investigator's discretion for patients who can continue to benefit from their respective treatment.

Patients who discontinue treatment prior to disease progression (e.g., due to unacceptable toxicity or withdrawal of consent) will continue to be followed until disease progression and for OS regardless of whether they subsequently receive non-study anti-cancer therapy. Data for subsequent therapy will be collected for the analysis of OS.

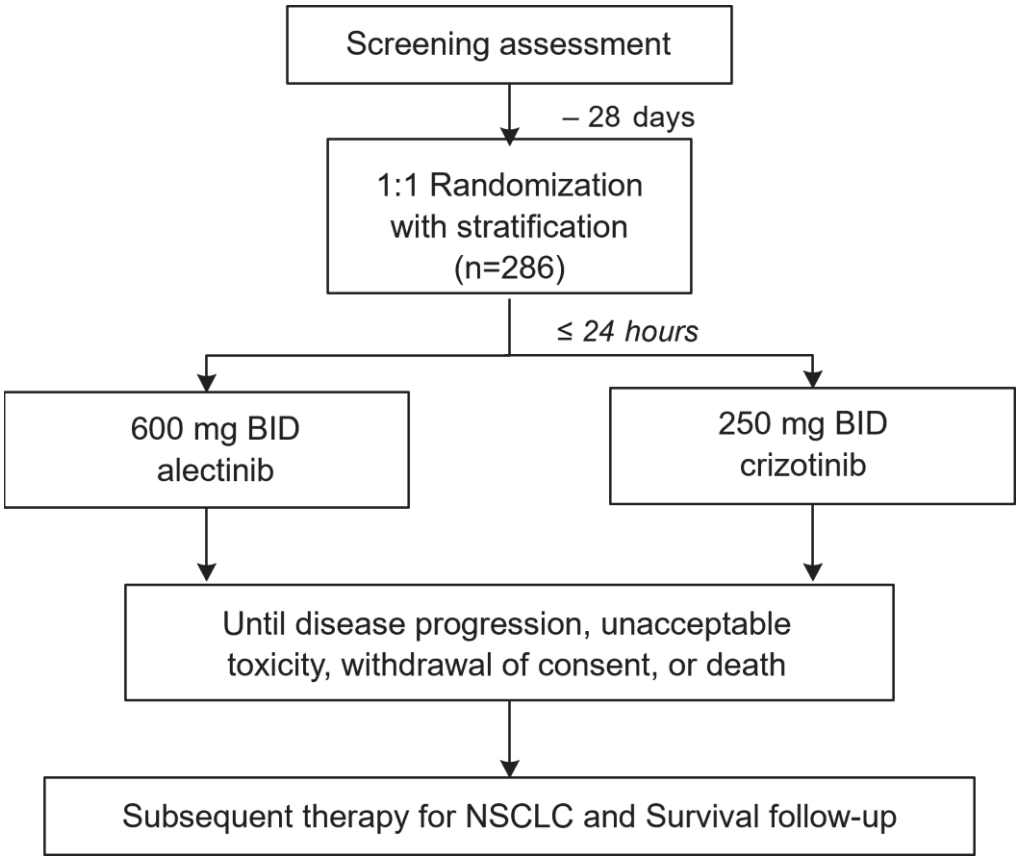
Approximately 286 patients (143 per treatment arm) will be enrolled into the study over a planned competitive recruitment period of 24 months. Patients inappropriately randomized into the study will not be replaced. The final analysis evaluating the primary endpoint of investigator-assessed PFS will occur when approximately 170 patients have progressed or died, which is expected to occur approximately 33 months after the first patient has been enrolled. Data collection will continue for each patient until death or study closure, whichever occurs first.

An iDMC will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised as outlined in Section 9.4.

A summary of the study design is shown in Figure 4.

A schedule of assessments is provided in Appendix 1.

Figure 4 Summary of Study Design



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

3.2 END OF STUDY *AND LENGTH OF STUDY*

This study is event-driven, with a recruitment period of approximately 24 months. The required number of events for the final analysis of the primary endpoint is expected approximately 33 months after the first patient has been enrolled. Patients are to be treated until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

A survival follow-up analysis will be performed when approximately 50% of patients have died, estimated to occur approximately 144 months (12 years) after the first patient has been enrolled. *Additional survival follow-up analyses may be performed.*

The study will formally end when the last patient has completed the study or when the Sponsor decides to end the trial, whichever occurs first.

3.3 *DURATION OF PARTICIPATION*

Treatment will continue until disease progression (as per RECIST v1.1), unacceptable toxicity, withdrawal of consent, or death (Section 3.1). The total duration of study participation for each individual is expected to range from 1 day to more than 144 months.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Alectinib Dosage

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

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

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

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

Importantly, administration of 600 mg BID provides systemic exposures that meet or exceed exposures achieved in patients receiving 300 mg BID in Study AF-001JP, demonstrating its robust efficacy and safety in crizotinib-naive patients. Furthermore, in Study NP28761/AF-002JG, the 600 mg BID regimen has demonstrated promising activity in crizotinib-resistant patients, including activity in patients with CNS metastases while being tolerated by patients. On the basis of available preclinical 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.

Thus, on the basis of nonclinical and clinical data, a dosing regimen of 600 mg BID of alectinib has been chosen as the optimal therapeutic dose level with the best balance between efficacy and safety.

Alectinib 600 mg should be administered orally BID with food in the morning and evening.

3.4.2 Rationale for Patient Population

The study population will comprise patients with non-resectable, locally advanced and metastatic NSCLC who have been shown to be *ALK*-positive by the Ventana IHC test performed at central laboratories specially designated for the study. Patients should not have received any prior treatment for advanced NSCLC (treatment-naive).

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; National Comprehensive Cancer Network [NCCN] 2014).

To be eligible for the study, determination of *ALK* positivity will be performed centrally using the IHC assay (see Appendix 8) that is being developed by Ventana Medical Systems as a companion diagnostic to alectinib. Immunohistochemistry may replace FISH-based identification of *ALK* rearrangement as the standard companion diagnostic in the future. Immunohistochemistry is faster, easier to perform in local laboratories, and requires less equipment compared with the FISH assay. In addition, IHC has high concordance with FISH and a lower false-negative rate (Kim et al. 2011).

3.4.3 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. 2013; Sequist et al. 2013; Shaw et al. 2013).

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

In the United States, in November 2013, crizotinib was granted a regular approval for the *ALK*-positive NSCLC setting regardless of treatment line (XALKORI U.S. Package Insert

[USPI]), whereas in Europe, crizotinib is currently only approved conditionally for patients with previously treated *ALK*-positive NSCLC (Crizotinib Summary of Product Characteristics [SmPC]).

The NCCN guidelines recommend crizotinib as a first-line therapy for patients with advanced *ALK*-positive NSCLC (NCCN 2014).

The randomized Phase III PROFILE 1014 study was conducted to assess the efficacy of crizotinib versus standard platinum-based chemotherapy (pemetrexed + 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 a median PFS of 10.9 and 7.0 months (HR: 0.454; 95% CI: 0.346 to 0.596; $p < 0.0001$) for crizotinib and pemetrexed platinum-based chemotherapy, respectively (Mok et al. 2014). The authors concluded that these findings support crizotinib as the standard of care for patients with previously untreated advanced *ALK*-positive non-squamous NSCLC (Mok et al. 2014).

Crizotinib will be dosed as per standard dose recommendations from the prescribing information; patients in the crizotinib arm will receive crizotinib 250 mg orally BID with or without food until disease progression, unacceptable toxicity, withdrawal of consent, or death. See Section 5.1.4 for criteria for dosing interruption and/or dose reduction for treatment with crizotinib.

3.4.4 Rationale for Open-Label Design

An open-label study design is more appropriate for patients enrolled in this particular trial for a number of reasons described 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 5 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 comprise one 250-mg capsule of crizotinib or matching placebo and four 150-mg capsules of alectinib or matching placebo. In order to blind, crizotinib capsules must be over-encapsulated. That further increases the size of a capsule from size 0 to size 00. Size 00 is usually the largest capsule size used orally for humans. For some patients, size 00 capsules are too large to swallow. This high pill count of large capsules is considered to be a significant burden to patients and increases the risk of non-compliance.

Additionally, a blinded study 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 dose reductions for crizotinib would be 200 mg BID (different capsule, size 1), followed by 250 mg once a day (QD). 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.

In order to avoid a significant burden to patients with high pill count, increased risk of non-compliance, 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 a supportive analysis of efficacy on the basis of determining progression by an IRC, performing sensitivity analyses to demonstrate the robustness of the primary endpoint, defining progression using established response evaluation criteria (RECIST v1.1), performing tumor assessment at the same frequency in both arms and adhering to protocol-defined schedules, and finalizing the strategy for the final analysis of the primary endpoint before trial start, including developing predefined methods for handling missing data and censoring rules. Efficacy analyses will only be performed at the pre-specified analysis timepoints in the protocol (final analysis once 170 PFS events have occurred and survival follow-up analysis after approximately 50% of patients have died).

3.4.5 Rationale for Primary Endpoint Selection

The investigator-assessed PFS (which will be supported by IRC-assessed PFS analysis, one of the secondary endpoints of the study) is the primary endpoint for this trial.

Progression free-survival, as an endpoint, can reflect tumor growth and can 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 risk-benefit of the new treatment compared with available therapies (FDA 2007; European Medicines Agency 2012). A PFS HR of 0.65 will be targeted, which constitutes a clinically meaningful benefit in this patient population as it will delay the use of platinum-based chemotherapy and will potentially reduce the frequency of CNS relapse and the morbidity associated with treating CNS metastases.

The assumed median PFS of 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 13 months. Patients with *ALK*-positive NSCLC 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. 2013), which equated to a post-progression survival of 12.6 months. This lengthy post-progression survival provides an opportunity for subsequent treatment with other *ALK* inhibitors, several additional lines of chemotherapy, or participation in additional clinical trials.

Patients in both study arms who experience disease progression on study treatment will likely be treated with other subsequent treatment options, including *ALK* inhibitors. The availability of crizotinib on the market, as well as the likely availability of other next-generation *ALK* TKIs, and the availability of other investigational agents in clinical trials offer potential treatment options to patients in the 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 trials for *EGFR* TKIs, in which strong PFS benefits were observed without evidence of OS benefit (Rosell et al. 2009; Fukuoka et al. 2011).

The long post-progression survival and the confounding effects of subsequent lines of therapy indicate that it would be difficult to detect an OS benefit in this setting. Nevertheless, OS is one of the study's secondary endpoints. The crossover from the crizotinib arm to alectinib will not be allowed in this study, with the aim of preserving the trial's ability to potentially demonstrate some degree of treatment benefit of alectinib in OS. However, the study will not be powered to demonstrate any statistically significant difference in the secondary endpoint of OS.

To ensure the validity of the PFS as the primary endpoint, a number of measures have been implemented: full IRC assessment to support the analysis of the primary endpoint, a substantial target magnitude of benefit (target HR = 0.65) and study assessments that will allow for a robust evaluation of risk-benefit (standard RECIST criteria to define progression with fixed assessment intervals that are identical in both treatment arms and a robust definition of PFS and prospectively defined methods to assess, quantify, and analyze PFS, including censoring methods and sensitivity analyses).

3.4.6 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. Anaplastic lymphoma kinase-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 clinically meaningful benefit by avoiding consequences of neurological deficits from brain metastasis or by delaying/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 2 ongoing Phase I/II studies. See Section 1.2 and 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 pre-specified analysis will be to evaluate whether alectinib significantly delays or prevents the development of CNS metastases.

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

Imaging analysis by consistently used 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 arms is avoided by having regularly scheduled scans.

An independent central radiological review will be performed for all patients and the analysis of time to CNS progression or response will be based on the data from the independent review. The review will be based on the standard RECIST v1.1 criteria to assess the CNS lesions, and a second independent review on the basis of the RANO criteria, which are typically used to assess brain tumors (Wen et al. 2010), will be performed. The assessment will be performed independently from the overall disease progression assessment.

3.4.7 Rationale for PK Sample Collection Schedule

To date, the pharmacokinetics of alectinib have been characterized in chemotherapy-failed, crizotinib-naive patients with NSCLC in Study AF-001JP and in patients who have failed chemotherapy and crizotinib treatment in Study NP28761/AF-002JG and Study NP28673. In order to better understand the pharmacokinetics of alectinib and to further support the development of a robust population PK model for alectinib in order to better understand, identify, and characterize variables which lead to changes in exposure, characterization of alectinib pharmacokinetics will be done in this study. This study will include PK assessment of alectinib in *ALK* inhibitor treatment-naive patients with *ALK*-positive advanced NSCLC by collecting trough samples from all patients receiving alectinib. Serial/intensive PK samples will be collected from a subset of patients (10%−15% [at least n = 20] of patients receiving alectinib) to facilitate the PK assessment. The data that will be collected from this study will enable more robust understanding of alectinib pharmacokinetics in the global crizotinib-naive population including investigation and potential identification of sources of variability influencing alectinib pharmacokinetics and/or response to alectinib therapy. Results from PK data collection in this study and analyses of PK data could help support optimal use of alectinib therapy.

3.4.8 Rationale for Biomarker Assessments

Several molecular mechanisms of resistance to crizotinib have been reported in the literature: increased copy number of *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. Two types of approaches will be used: 1) targeted sequencing of a panel of genes known to be involved in cancer and 2) unbiased genomic sequencing.

Mutations in cancer genes appearing from drug resistance can 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 PCR and 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 DNA.

Determination of *ALK* positivity will be initially performed by Ventana IHC (see Appendix 8). In addition, the Abbott Vysis FISH test will be used as an exploratory assay, after patients have been enrolled in this study. Results from these analyses will be used to quantify the degree of correlation between FISH and IHC for the detection of *ALK*-positive NSCLC. For exploratory purposes, other methods to determine *ALK* positivity (e.g., reverse transcription-PCR) may also be used. Currently, *ALK* positivity for fusions can only be determined in tissue samples using assays such as FISH, IHC or PCR. As tissue sampling is difficult and tissue biopsy sample sizes from lung cancer patients are very small, testing of several important biomarkers is challenging. Many patients with NSCLC may not have enough tumor tissue available and; therefore, cannot be tested for some biomarkers such as *ALK*. Plasma *ALK* assays analyzing circulating tumor nucleic acids will enable more patients with NSCLC to be tested for *ALK* fusions. Information from plasma *ALK* assays will be used to investigate the use of circulating tumor nucleic acids from plasma as a surrogate for tumor tissue for diagnostic purposes.

3.4.9 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to both 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 trials 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 and shoulder), dyspnea, cough, and fatigue have been regarded as the most frequent and clinically relevant disease-related symptoms experienced by patients with NSCLC. The BR.21 study (erlotinib vs. chemotherapy in second- or third-line NSCLC) demonstrated that longer TTD in the pain, dyspnea, and cough scales of the EORTC QLQ-C30 and QLQ-LC13 was consistent with superior PFS, OS, and quality-of-life benefits in the erlotinib arm as compared with the placebo arm (Aaronson et al. 1993; Bergman et al. 1994; Bezjak et al. 2006). Additionally, patients in the crizotinib PROFILE 1005 trial reported clinically significant improvements

(by 10 points) in the pain, cough, dyspnea, and fatigue symptom scales seen as early as 2 weeks on treatment (Crinò et al. 2011).

The EORTC QLQ-C30 and QLQ-LC13 were used in the Phase III PROFILE 1007 study (second-line crizotinib vs. chemotherapy). The study reported 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 with crizotinib than 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. There was also a significantly greater overall improvement from baseline in the global quality of life among patients who received crizotinib treatment than among those who received chemotherapy ($p < 0.001$). In all domains measuring function, except for the domain measuring cognitive function, there was a significantly greater overall improvement from baseline among patients in the crizotinib group than among patients in the chemotherapy group (Shaw et al. 2013).

Therefore, to assess the quality of life of patients in this trial, PRO data will be collected from patients enrolled in this study using the validated questionnaires EORTC QLQ-C30 and QLQ-LC13.

3.5 OUTCOME MEASURES

3.5.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- PFS, which is defined as the time from randomization to the first documented disease progression, as determined by the investigators (primary endpoint) or IRC (secondary endpoint) using 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 with no post-baseline assessments will be censored at the date of randomization.
- ORR, which is defined as the percentage of patients who attain a CR or PR, as determined by the investigators using RECIST v1.1. Patients without any assessments will be regarded as non-responders.
- Time to CNS progression, which is defined as the time from randomization to the first occurrence of disease progression in the CNS as determined by IRC using 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 OR, and C-PR at 6, 12, 18, and 24 months
- DOR, which is defined as the time from when response (CR or PR) was first documented to first documented disease progression or death (whichever occurs first). This will only be calculated for patients who have a best overall response of CR or PR. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement.

- OS, which is 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.

3.5.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

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

3.5.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Sparse (pre-dose) PK samples for measurement of alectinib and its major metabolite(s) will be collected in all study patients receiving alectinib treatment. See Appendix 1 and Appendix 2 for PK sampling times.
- Serial/intensive PK sampling will be collected in a subset of consenting patients enrolled to receive alectinib treatment (approximately 10%–15%, at least approximately n = 20). See Appendix 1 and Appendix 2 for PK sampling times.
- PK parameters will be determined as appropriate and where data allow:

  The pharmacokinetics of alectinib (and metabolite[s], if appropriate) will be described, and the between-patient variability will be estimated using 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.

  Non-compartmental analysis (NCA) may be conducted in patients undergoing serial/intensive PK sample collection, as appropriate and where data allow.

3.5.4 Patient-Reported Outcome Measures

The PRO measures included for this study are as follows and will be administered to patients every 4 weeks until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression; at the post-treatment visit (4 weeks after permanent treatment discontinuation); and every follow-up visit (every 8 weeks) after post-treatment visit for 6 months:

- The EORTC QLQ-C30 and EORTC QLQ-LC13 to determine the impact of alectinib compared with crizotinib as measured by TTD in 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 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 measures will be administered every 4 weeks until disease progression and then decreased to every 8 weeks until 6 months post-treatment.

For patients who discontinue treatment for reasons other than disease progression and have not yet progressed at 6 months post-treatment, PRO measures will be administered every 4 weeks until disease progression and will no longer be required thereafter.

3.5.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- EQ-5D-3L to generate utility scores for use in economic models for the purpose of reimbursement
- Total testosterone and free testosterone levels (either by direct measurement or by calculation using albumin and SHBG), FSH, and LH in blood to measure the onset of hypogonadism in adult men
- Results from the FISH Vysis® ALK Break Apart FISH Probe Kit (Abbott) to evaluate and compare efficacy in patients with treatment-naive NSCLC that is *ALK*-positive by FISH test
- *ALK* fusion status in circulating tumor nucleic acids from plasma to evaluate and compare efficacy and safety in patients with treatment-naive NSCLC that is *ALK*-positive by plasma *ALK* tests (PCR and/or sequencing) for diagnostic purposes
- Post-progression tumor mutation status to study molecular mechanisms of resistance to *ALK* inhibitors
- *ALK* mutation status in plasma DNA to monitor efficacy and disease progression

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population is patients with treatment-naive, *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 to perform *ALK* IHC and *ALK* FISH is required. Both tests will be performed at designated central laboratories.
- Age ≥ 18 years old
- Life expectancy of at least 12 weeks

- ECOG PS of 0–2
- No prior systemic treatment for advanced or recurrent NSCLC (Stage IIIB not amenable to multimodality treatment) or metastatic (Stage IV) NSCLC
- Adequate hematologic function:

  Platelet count $\geq 100 \times 10^9$/L

  ANC ≥ 1500 cells/μL

  Hemoglobin ≥ 9.0 g/dL
- Adequate renal function:

  An estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease equation of at least 45 mL/min/1.73 m^2
- Patients must have recovered from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment
- Measurable disease (by RECIST v1.1) prior to the administration of study treatment
- Prior brain or leptomeningeal metastases allowed if asymptomatic (e.g., diagnosed incidentally at study baseline). Asymptomatic CNS lesions might be treated at the discretion of the investigator as per local clinical practice. If patients have neurological symptoms or signs due to CNS metastasis, patients need to complete whole-brain radiation or γ knife irradiation treatment. In all cases, radiation treatment must be completed at least 14 days before enrollment and patients must be clinically stable.
- For all females of childbearing potential, a negative pregnancy test must be obtained within 3 days before starting study treatment
- For women who are not postmenopausal (≥ 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 only acceptable 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 and proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, 2 methods (e.g., 2 barrier methods such as condom and cervical cap use) 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 only acceptable 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 prior to performing any study-related procedures and to comply with the study protocol, including patients must be willing and able to use the electronic patient-reported outcome (ePRO) device.

4.1.2 Exclusion Criteria

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

- Patients with a previous malignancy within the past 3 years are excluded (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 and 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 $>3\times$ upper limit of normal (ULN; $\geq 5\times$ ULN for patients with concurrent liver metastasis) confirmed on two consecutive measurements

  OR

  Impaired excretory function (e.g., hyperbilirubinemia) or 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 acute hepatitis
- NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Grade 3 or higher toxicities due to any prior therapy such as 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
- Patients with baseline QTc >470 ms or symptomatic bradycardia
- Administration of strong/potent CYP3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib or crizotinib (see Appendix 3)
- Administration of agents with potential QT interval prolonging effects within 14 days prior to the first administration of study drug for all patients and while on treatment through the end of the study for crizotinib-treated patients only (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 investigator, pose an unacceptable risk to the patient in this study
- Any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol requirements and/or follow-up procedures; those conditions should be discussed with the patient before trial entry

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label trial, for which the rationale is described in *Section 3.4.4* .

Approximately 286 patients will be randomly assigned in a 1:1 allocation ratio to the two treatment arms via a block-stratified randomization procedure and over a planned recruitment period of 24 months.

Randomization will guard against systematic selection bias and should ensure the comparability of treatment groups. To assist balance in important prognostic factors, randomization will be stratified by ECOG PS (0/1 vs. 2), race (Asian vs. non-Asian), 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.

The independent review of scans for the secondary endpoints of PFS and time to CNS progression on the basis of IRC will be performed in a blinded fashion.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study include alectinib and crizotinib. Appendix 11 identifies all IMPs for this study.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Alectinib

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, sodium lauryl sulfate (SLS), and magnesium stearate as excipients.

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.

The formulation contains SLS as an excipient. This excipient is known to be potentially associated 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 (XALKORI USPI).

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 patient misses a dose, it can be taken within 6 hours of the scheduled time. If the time is greater than 6 hours, or if the patient vomits the dose, the patient should wait until the next scheduled time and take the next scheduled dose. Patients should not take two doses at the same time to make up for a missed dose.

Guidelines for dosage modifications and treatment interruptions or discontinuation due to specified adverse events are provided in Section 5.1.3.

Any dose modification should be noted on the study drug administration electronic Case Report Form (eCRF).

4.3.2.2 Crizotinib

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

If a dose is missed, then it should be taken as soon as the patient remembers unless it is less than 6 hours until the next 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 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 taken 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 study drug 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.

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

The Sponsor will offer post-trial 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 website:

https://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

The medications and/or treatments below are permitted:

- Anticoagulants and antithrombotic agents (i.e., coumadin-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, H_2 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)
- Approved COVID-19 vaccines and treatments (including those with emergency use authorizations)
  - Details regarding the COVID-19 vaccine received during the study should be recorded in the concomitant medication section

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 drug levels and/or 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, avoid using crizotinib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) 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, uridine diphosphate glucuronosyltransferase [UGT]1A1). 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 predominantly metabolized 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 coadministered drugs that are metabolized by CYP2B6 (e.g., bupropion, efavirenz)
- Physiologically based pharmacokinetic simulations predicted a 17% increase in crizotinib steady-state AUC after treatment with the moderate CYP3A inhibitors diltiazem or verapamil. Caution is recommended in case of co-administration of crizotinib with moderate CYP3A inhibitors.
- In vitro studies indicated that crizotinib is a weak inhibitor of UGT1A1 and UGT2B7. Therefore, crizotinib may have the potential to increase plasma concentrations of

co-administered drugs that are metabolized predominantly by UGT1A1 (e.g., raltegravir and irinotecan) or UGT2B7 (e.g., morphine, naloxone).

- Crizotinib is an inhibitor of organic cation transporter (OCT)1 and OCT2 in vitro. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of OCT1 or OCT2 (e.g., metformin and procainamide).

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 treatment (either alectinib or crizotinib), unless otherwise specified below. Exceptions to restrictions of the concomitant therapies listed below (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) may be made 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) before the first dose of study drug treatment and while on treatment with study drugs (see Appendix 3). For crizotinib only, the effect of a moderate inducer, including, but not limited to, efavirenz or rifabutin is not clearly established; therefore, their combination with crizotinib should be avoided.
- Potent inhibitors of CYP3A (e.g., ketoconazole) within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study drug treatment and while on 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 before 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 while on 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 of the last dose of alectinib, unless, in the judgment of the investigator, patient safety will require a longer washout period prior to palliative therapy. Dosing of alectinib may resume with the resolution of any radiation toxicity to $\leq$ Grade 1.
- Additional investigational drug (except for during the follow-up period)

The list of medications provided above is 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 not listed above.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

https://medicine.iupui.edu/clinpharm/ddis/table.aspx (for P450 drug interactions)

4.4.3 Prohibited Food

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

4.4.4 *Additional Restrictions*

Prolonged sun exposure should be avoided while taking study drugs and for at least 7 days after discontinuing alectinib. When outdoors, protective measures (e.g., use of protective clothing and/or sunscreen of at least 50 SPF) should be taken because of photosensitivity risk.

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 that patients meet all eligibility criteria before randomization. The investigator will maintain a detailed record of all patients screened and document eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes a record of clinically significant diseases, surgeries, cancer history (including prior 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 to 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 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 compared to 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 based purely on the investigator's assessment of the patient's neurological state compared to 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, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

4.5.6 ECOG Performance Status

Performance status will be measured using the ECOG PS Scale (see Appendix 5). It is recommended, where possible, that a patient's ECOG 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 on the basis of physical examinations. Clinical lesions will be documented by color photography (with caliper measurement for measurable lesions), computed tomography (CT) scans, and other modalities (e.g., MRI, brain scans), using RECIST v1.1 (see Appendix 4). For assessing 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 can 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 lesion 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.

Computed tomography/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 subsequently until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression and at the post-treatment visit (4 weeks after permanent treatment discontinuation). Computed tomography/MRI scans of the neck bone and pelvis should be included if clinically indicated. At the investigator's discretion, CT/MRI scans may be repeated at any time if PD is suspected.

Note: Brain imaging should be performed using 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 radionuclide bone scan at screening. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions and do not need to be repeated routinely but 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 can be considered

measurable lesions of the soft tissue component and meet the definition of measurability and should be followed by cross-sectional imaging.

4.5.8 Laboratory, Biomarker, and Other Biological Sample

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 [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells])
- Coagulation (PT [or INR], and aPTT)
- Serum chemistry (sodium, potassium, chloride, bicarbonate, fasting glucose, BUN or urea, creatinine [including calculated eGFR using the Modification of Diet in Renal Disease formula, see Appendix 7]; CPK; gamma-glutamyl transferase [GGT]; calcium; total and direct bilirubin; total protein; albumin; ALT; AST; ALP; phosphorus; magnesium; thyroid-stimulating hormone; and total testosterone and free testosterone [either by direct measurement or by calculation using, albumin and SHBG], FSH, and LH [for male patients only])
- Urinalysis. Urine samples will be collected according to the schedule of assessments (Appendix 1; first morning urine sample for baseline and end of treatment visit, spot urine for rest of visits). Urine protein will be measured by dipstick test.
- Pregnancy test. All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening, within 3 days of dosing. Urine pregnancy tests will be performed anytime during the course of the study, as per investigator's discretion. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

4.5.8.2 Pre-Treatment Tumor Samples (Mandatory)

Mandatory pre-treatment tumor samples will be collected to centrally examine *ALK* status by Ventana IHC (eligibility criteria) and Vysis FISH. Tumor blocks (formalin-fixed, preferred 10% neutral-buffered formalin) are the preferred source, but if blocks are not available, unstained slides (ten to fifteen 5-µm slides cut less than 3 months before screening) are also accepted. Remaining tumor blocks will be returned to the sites; slides will not be returned.

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

Central *ALK* testing to determine or confirm patient *ALK* status will be performed at a Sponsor designated central laboratory. After completion of *ALK* testing for enrollment with a pre-specified *ALK* test by Ventana IHC (Appendix 8), patient samples will also be

centrally tested by FISH Vysis® ALK Break Apart FISH Probe Kit (Abbott). Additionally, other *ALK* assays may be used for testing patient samples to establish performance characteristics of these assays for diagnostic development. Testing may be performed on all screened patients (screen- failed and enrolled). These additional testing data will have no impact on eligibility, and testing will be performed only after eligibility is established for each patient. In addition, local *ALK* test information, baseline demographic, and disease-related characteristic data for all screened patients may be collected in order to support potential registration of a companion diagnostic assay for alectinib.

The tumor sample may also be tested for the presence of *EGFR* mutations, if requested by the investigator.

Pre-treatment tumor samples may be used, after proper informed consent is obtained, for genomic sequencing.

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

4.5.8.3 Pre- and Fresh Post-Treatment Tumor Biopsies (Optional)

Pre-treatment tumor samples (preferably formalin-fixed blocks but if not available a minimum of 10–15 unstained 5 μm slides) for *ALK* testing is a mandatory requirement for this study. Optional additional pre-treatment tumor samples and fresh post-treatment tumor biopsy at disease progression or permanent treatment discontinuation (at the last treatment or post-progression visit) may be collected, with proper informed consent. These samples will be used to help to understand molecular mechanisms of resistance to *ALK* inhibitors by genomic sequencing. Remaining tumor blocks will be returned to the sites, slides will not be returned.

The remaining mandatory (Section 4.5.8.2) and optional specimens (Section 4.5.8.3) will be destroyed within 5 years after the date of final closure of the clinical database. Other residual tissue material (slides, extracts, etc.) will be destroyed within 5 years after the date of final closure of the clinical database.

On the basis of continuous analysis of the data in this study and other studies, or on the basis of data from literature, collection of optional tumor biopsies 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 will be obtained to determine:

- Mutation status in *ALK* and other escape genes (e.g., *EGFR*, *KRAS*). Circulating tumor DNA (ctDNA) can be isolated from plasma samples and will be analyzed using a targeted sequencing panel which measures clinically relevant

genomic alterations in commonly altered oncogenes. It will require 20 mL of blood (2 tubes of 10 mL each) to be collected at baseline, at the Visit 3 (Week 16) treatment, and subsequently at every second treatment visit. The last 20-mL blood sample will be taken at progression of disease, which includes isolated, asymptomatic CNS progression. For detailed information about *ALK* mutation sampling, see Appendix 1. For sample handling procedures, storage conditions and shipment instructions, see the laboratory manual.

- *ALK* rearrangement. This will require 20 mL of blood (2 tubes of 10 mL each) to be collected at baseline.

Mandatory blood samples will be obtained to determine:

- All patients who are randomized in alectinib arm will also participate in retrospective pharmacogenomic research to understand inter-individual variability of safety and pharmacokinetics of alectinib. For this purpose, a 3-mL blood sample will be drawn at baseline (see Section 4.5.8.4.1). Samples will not be obtained from patients at investigational sites in countries where the regulatory agency or Institutional Review Board (IRB) or Ethics Committee (EC) does not allow genetic testing.

Optional blood samples will be collected to obtain:

- Plasma. Centrally *ALK* negative tested patients (by Ventana ALK IHC) who agree to donate 10 mL plasma will be assessed by plasma *ALK* assays (PCR and/or sequencing) for the development of a plasma *ALK* diagnostic test
- A source of healthy tissue for patients who agreed to participate in the optional genomic sequencing assessment. For patients in the crizotinib arm, a 3-mL blood sample will be drawn at baseline. For patients in the alectinib arm, a source of healthy tissue will be used as a portion of the sample for the pharmacogenomics research (see Section 4.5.8.4.1)
- A portion of this blood sample will also be used as a source of healthy tissue for the patients on alectinib treatment who agree to participate in the optional genomic sequencing research.

For biomarkers, a maximum of 43 mL of blood will be collected at baseline (20 mL of blood for plasma purification and determination of mutation status in *ALK* and other escape genes, 20 mL of blood for plasma purification and detection of *ALK* rearrangements, and 3 mL blood for pharmacogenomics research). Twenty mL of blood (for plasma purification and determination of mutation status in *ALK* and other escape genes) will be collected at Visit 3 (Week 16) and subsequently at every second visit, and 20 mL will be collected at disease progression (CNS and/or systemic disease progression) for plasma purification, for determination of mutation status in *ALK* and other escape genes.

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

On the basis of continuous analysis of the data in this study and other studies, or on the basis of data from literature, collection of plasma with exploratory purposes may be stopped at any time if they are deemed not informative.

4.5.8.4.1 Samples for Pharmacogenomic Assessments

One sample (approximately 3 mL of whole blood) will be collected from all patients on alectinib treatment. Samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes including but not limited to CYP2C9, CYP3A4/5, and UGT1A1, and transporters (e.g., organic anion transporter polypeptide 1B1) and for genetic variants that could contribute to potentially drug-related liver safety assessments (including, but not limited to, human leukocyte antigen, see Appendix 9 for more details).

For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for collection of this genetic material for above evaluations can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the Clinical Study Report (CSR).

4.5.8.5 Samples for Pharmacokinetic Assessments

Pharmacokinetic samples will be collected in all patients on alectinib treatment, as indicated in Appendix 1 and Appendix 2 for the analysis of alectinib and its major metabolite(s) (RO5468924, RO5507197, and/or others, if applicable and if appropriate, and if assays are available). Residual samples following PK analysis may be used to evaluate profiling for alectinib metabolite(s).

All trough/pre-dose PK samples should be collected within 2 hours **before** the morning doses of study medications.

Serial/intensive samples will be collected in a subset of patients (10%–15% [at least approximately n = 20] of patients receiving alectinib) on Visit 0 (baseline, after the first dose) and Visit 1 (Week 4) at the timepoints specified in Appendix 2.

Plasma concentrations for alectinib and its metabolite(s), if applicable, will be measured by specific and validated liquid chromatography tandem mass spectrometry methods.

For each sample, approximately 2 mL of venous blood will be collected for alectinib PK analysis at the timepoints specified in the PK schedule in Appendix 1 and Appendix 2.

Patients who permanently discontinue from study drugs will also discontinue 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 CSR is complete.

On the basis of continuous analysis of the data in this study and other studies, any sample type collection 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.

The evaluation of PK was performed at the primary analysis. With implementation of the Version 6 of the protocol, PK sampling will be discontinued.

4.5.9 Electrocardiograms

An ECG will be recorded at specified timepoints as outlined in the schedule of assessments (Appendix 1) at screening, Visit 0 (baseline), Visit 1 (Week 4), Visit 4 (Week 24), Visit 8 (Week 56), and at the last treatment visit and as clinically indicated throughout the study. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, study drug administration) as well as prior to meals. 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 prior to the recording being taken. 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. Electrocardiogram parameters will be entered on the ECG eCRF. The following parameters should be captured on the eCRF: heart rate, RR, PQ, QRS and QT duration, and QT interval corrected using 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 10.

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, ECGs may be analyzed retrospectively at a central laboratory.

4.5.10 Patient-Reported Outcomes

Patient-reported outcomes (EORTC QLQ-C30, QLQ-L13, and EQ-5D-3L) will be collected to more fully characterize the clinical profile of alectinib. The instruments will be translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, the PROs scheduled for administration during a clinic visit (EORTC QLQ-C30, QLQ-L13, and EQ-5D-3L) should

be completed prior to the performance of non-PRO assessments and the administration of study treatment.

Patients will use an ePRO device to capture PRO data and maintain a diary of daily drug intake (crizotinib arm) or drug intake with food (alectinib arm). The ePRO device and instructions for completing the PRO questionnaires and diaries electronically will be provided by the investigator staff. The data will be transmitted via pre-specified transmission method (e.g., web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by appropriate study personnel securely via the Internet.

The evaluation of PROs was performed at the primary analysis. With implementation of the Version 5 of protocol, PRO measurements will be discontinued, and the ePRO device will no longer be used for capturing PRO data and maintaining a diary of daily drug intake.

The collection of PROs is no longer required. Collection of PRO data was discontinued with the implementation of the Version 5 of the protocol.

4.5.11 Samples for Roche Clinical Repository

4.5.11.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in optional research. Roche Clinical Repository specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed

Consent Form by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

For RCR purposes, 10 mL of blood will be collected. Any remaining tissue samples from study-related or non-study related procedures that are performed during the study may also be collected for RCR purposes. For all samples, date of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Roche Clinical Repository specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.11.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted.
The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.11.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. 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 provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.11.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the Subject Withdrawal Form during Study Conduct and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. *If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the site, the investigator must inform the Sponsor be emailing the study number and patient number to the following email address:*

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study BO28984 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BO28984.

4.5.11.7 Monitoring and Oversight

Roche Clinical Repository specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well

as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

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 progression and for OS, 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 study medication on the basis of the investigator judgment

See guidelines for managing adverse events and for comprehensive guidance on 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 progression as per study schedule (see Appendix 1).

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

All serious adverse events 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 Section 5.1.2.1 through Section 5.1.2.10 will be closely monitored and 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

Tyrosine kinase inhibitors, including *ALK* inhibitor crizotinib, have been associated with the occurrence of treatment-related ILD (including fatalities).

See Section 5.1.3 for management and follow-up.

5.1.2.2 Hepatotoxicity

Hepatobiliary findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib, and findings in the 13-week studies were similar to those of the 4-week studies. The findings were at or 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. In patients with Grade 3–4 AST/ALT elevations, documented drug-induced liver injury by liver biopsy was reported with uncommon frequency in alectinib pivotal clinical trials. Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal ALP, occurred with uncommon frequency in patients treated in alectinib clinical trials.

In patients treated with other tyrosine kinase *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.

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 were at or close to clinically relevant exposures. Changes in red blood cells morphology (e.g., poikilocytosis, red cell fragmentation) and in other erythroid parameters (e.g., reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume) were seen with alectinib in these studies. However, the changes on the erythroid system were considered to be of little toxicological significance because

they were slight (0.94- to 1.3- fold vs baseline), considered reversible, and did not exacerbate with prolonged treatment with alectinib.

Cases of anemia, including hemolytic 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 anemia (including hemolytic anemia) adverse events` management and follow-up.

5.1.2.4 Gastrointestinal Disorders

Gastrointestinal disorders such as nausea, vomiting, constipation, and diarrhea have been reported with alectinib. Similar GI disorders have been observed with other TKIs, including *ALK* inhibitor crizotinib.

Sodium lauryl sulfate (syn. 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 is not because of systemic toxicity, but a consequence of local irritation to the GI tract. In general, when mixed with diet, 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.

5.1.2.5 Skin Disorders

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

Skin rash has been reported with majority of TKIs including those targeting the *ALK* receptor (Hartmann et al. 2009).

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

See Section 5.1.3 for management and follow-up.

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, except for melanin-containing tissues such as uveal tract of eyes, which had 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; Shaw et al. 2013).

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

See Section 5.1.3 for management and follow-up.

5.1.2.7 Edema

Most TKIs, including *ALK* inhibitor crizotinib, have been associated with edema. Events of edema have been reported with alectinib, mostly Grade 1 or 2.

See Section 5.1.3 for management and follow-up.

5.1.2.8 Bradycardia

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

In a preliminary non-Good Laboratory Practice telemetry study in conscious cynomolgus monkeys, a slight hypotensive effect (approximately 10 mmHg) was seen 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 be caused by vasodilatation 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 trials 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, as well as decreases in heart rate based on ECG and pulse measurements, have also been reported (XALKORI USPI; ZYKADIA™ USPI).

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

See Section 5.1.3 for management and follow-up.

5.1.2.9 Abnormal Renal Function

In the 2-week non-human primate study 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.

Serum creatinine increases have been reported with alectinib treatment and were generally Grades 1 and 2.

See Section 5.1.3 for management and follow-up.

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 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 and Table 2 for guidelines for managing adverse events.

5.1.3 Management of Specific Adverse Events with Alectinib

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib

Event	Action to Be Taken
Interstitial lung disease	• Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis • Regardless of relatedness to alectinib, study drug should be permanently discontinued in patients diagnosed with interstitial lung disease of any grade
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4 and Section 5.3.5.6. • At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible Regardless of relatedness to alectinib, the grade-dependent rules for dose interruptions and dose modification outlined in the last section of this table must be followed. In addition, study drug treatment has to be permanently discontinued if any of the following occurs: – First observation of ALT or AST $>8\times$ULN – ALT or AST$>5\times$ULN for more than 2 weeks – First observation of ALT or AST$>3\times$ULN and total bilirubin$>2\times$ULN – First observation of ALT or AST$>3\times$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 [$>5\%$]) • Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found • Resumption of study drug is not allowed in patients discontinuing because of any of the above criteria

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities 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 meal. If GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
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 sunscreen and lip balm of at least SPF 50 to help protect against potential sunburn during this period. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
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, and to advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
Abnormal kidney function AEs	Kidney function laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4. • If, at any time during the study treatment, eGFR decreases by > 50% of the baseline visit value, the patient has to be carefully monitored. All of the underlying factors that may have acutely impacted serum creatinine levels need to 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.) Any eGFR decrease by > 50% of the baseline visit value requires repeat testing. • For Grade 1 and Grade 2 AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table • For Grade 3 AEs related to alectinib, temporarily interrupt alectinib until laboratory value recovers to Grade 1 or baseline, then resume at reduced dose. • For Grade 4 AEs related to alectinib, permanently discontinue study drug.
Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4. • Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Creatinine phosphkinase levels should be assessed in patients reporting these symptoms • In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table
Hemolytic anemia	If hemoglobin concentration is < 10 g/dl (Grade ≥ 2) and hemolytic anemia is suspected, withhold alectinib and initiate appropriate laboratory testing, in accordance with local clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (see Table 3 below) upon resolution with improvement of hemoglobin to Grade ≤ 1 or baseline, or permanently discontinue alectinib. In case of anemia of non-hemolytic mechanism, assessed as related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the last section of this table.

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
Bradycardia [b]	Grade 2 or Grade 3: • Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia, or to a heart rate of ≥ 60 bpm. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Grade 4: • Permanently discontinue if no contributing concomitant medicinal product is identified • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated. • Permanently discontinue in case of recurrence

Table 2 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
All AEs related [a] to alectinib (unless otherwise specified in this table) or Hepatotoxicity AEs (irrespective of relatedness)	• Grade 4: – Temporarily interrupt alectinib for a maximum of 21 days, after which drug must be permanently withdrawn. If improvement to Grade ≤1 or baseline does not occur within 3 weeks, permanently discontinue alectinib. – First episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule BID) – Second episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule BID) – Third episode: Permanently discontinue alectinib • Grade 3: – Temporarily interrupt alectinib for a maximum of 21 days, after which drug must be permanently withdrawn – First episode: If improvement to Grade ≤1 or baseline within 10 days, alectinib may be restarted at the original dose or with dose reduced by 150 mg (1 capsule BID) as per investigator discretion. If improvement occurs after 10 days but within 21 days, then decrease the current dose of alectinib by 150 mg (1 capsule BID) – Second episode: If improvement to Grade ≤1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule BID) – Third episode: Permanently discontinue alectinib • Grade 2: – To be managed at the investigator's discretion. Please note that alectinib cannot be interrupted for more than 21 days and cannot be dose reduced below 300 mg BID. • Grade 1: no action required

AE = adverse event; BID = twice a day; eGFR = estimated glomerular filtration rate
GI = gastrointestinal; ULN = upper limit of normal.

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

[a] To determine whether event should be assessed as related or unrelated, see Section 5.3.4.

[b] Heart rate less than 60 bpm.

Table 3 Alectinib Dose Modification

Dose Reduction Schedule	Dose Level
Dose	600 mg twice a day
First dose reduction	450 mg twice a day
Second dose reduction	300 mg twice a day

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 USPI; Crizotinib SmPC). For more details on dose reduction and permanent discontinuation for hematologic and non-hematologic toxicities, refer to the latest XALKORI USPI or Crizotinib SmPC or local prescribing information.

Gastrointestinal events were commonly reported with crizotinib in clinical trials. 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 antiemetic and/or antidiarrheal or laxative medicinal products. In clinical studies with crizotinib, events of GI perforations were reported (XALKORI USPI; Crizotinib SmPC).

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

In clinical studies of crizotinib in patients with either *ALK*-positive or *ROS1*-positive NSCLC, Grade 4 visual field defect with vision loss has been reported. Optic atrophy and optic nerve disorder have been reported as potential causes of vision loss. Ophthalmological evaluation consisting of best-corrected visual acuity, retinal photographs, visual fields, optical coherence tomography, and other evaluations as appropriate for new onset of severe visual loss, should be performed. In patients with new onset of severe visual loss (best-corrected visual acuity $<$ 6/60 in one or both eyes), crizotinib treatment should be discontinued.

In clinical studies with crizotinib and during post-marketing surveillance, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported. Patients with or without preexisting cardiac disorders receiving crizotinib should be monitored for signs and symptoms of heart failure (e.g., dyspnea, edema, rapid weight gain from fluid retention). Dosing interruption, dose reduction, or discontinuation should be considered as appropriate if such symptoms are observed.

Increased blood creatinine and decreased creatinine clearance were observed in patients in clinical studies with crizotinib. Renal failure and acute renal failure were reported in patients treated with crizotinib in clinical trials and during post-marketing surveillance. Cases with fatal outcome, cases requiring hemodialysis and cases of Grade 4 hyperkalemia were also observed (Crizotinib SmPC).

Photosensitivity has been reported in patients treated with crizotinib. Patients should be advised to avoid prolonged sun exposure while taking crizotinib and, when outdoors, to take protective measures (e.g., use of protective clothing and/or sunscreen).

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 protocol-specified safety laboratory assessments, measuring 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 where a patient is administered a pharmaceutical product, regardless of causal attribution. An adverse event can 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 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 prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

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:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is 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 had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- 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)
- Is a 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 criteria; 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 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 that 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 Sections 5.4–5.6. 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 biopsies, 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 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 events 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 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 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 [a]
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 [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

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

Note: On the basis of the most recent version of NCI CTCAE (v4.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] 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.

[d] 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, considering especially 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 and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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 gastrointestinal 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:

- 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 (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as an adverse event.

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 the ULN associated with cholestasis), only the diagnosis (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 one 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 an 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 on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

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 1 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.

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 criteria v1.1 (Appendix 4). In rare cases, the determination of clinical progression will be based on symptomatic deterioration.

However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to 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., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as an 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 even 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 prior to 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

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using 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.

5.4 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 trial. 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/EC.

5.4.1 *Medical Monitors and* Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur Prior to 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 Clinical Trial Adverse Event/ Special Situations 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 using 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 Clinical Trial Adverse Event/Special Situations 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 using the fax number or email

address provided to 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 in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form 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 immediately (i.e., no more than 24 hours after learning of the pregnancy) and send to Roche Safety Risk Management either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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 pregnant partner and the course and outcome of the pregnancy as it becomes available.
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

A spontaneous abortion should be classified as an 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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 an 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 event considered to be related to study drug or trial-related procedures until a final outcome can 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.

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, e-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 study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Clinical Trial Adverse Event/Special Situations 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.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs,, and investigators.

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

- Alectinib Investigator's Brochure
- Crizotinib Summary of Product Characteristics (European Union)

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 defined as all patients who received at least 1 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.

A secondary analysis population for efficacy is the FISH Positive Population (FPP). This is defined as all patients in the ITT population who were *ALK*-positive using the Vysis FISH assay. Patients will be assigned to the treatment group to which they were randomized. This analysis population will be used to perform a supportive analysis of the study data based on the Vysis FISH assay.

An analysis of the primary endpoint of investigator-assessed PFS based on the FPP will be performed at the time of the primary analysis. A major discrepancy between the Ventana IHC assay and the Vysis FISH assay may necessitate a follow-up analysis of the primary endpoint based on 170 PFS events observed in the FPP to ensure 80% power of the log-rank test under the assumption of a hazard ratio of 0.65 in this secondary population.

The final analysis of the primary endpoint of PFS will occur when 170 PFS events have occurred, on the basis of the investigators' assessments. On the basis of the assumptions outlined in Section 6.1, this is estimated to occur approximately 33 months after the first patient has been enrolled. A survival follow-up analysis will be performed once approximately 50% of patients have died, which is estimated to occur approximately 144 months (12 years) after the first patient has been enrolled.

Hypothesis tests will be two-sided with a significance level of 5% unless otherwise indicated.

The baseline value of any variable will be defined as the last available value recorded prior to the first administration of alectinib or crizotinib.

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

6.1 DETERMINATION OF SAMPLE SIZE

The focus of this clinical trial is hypothesis testing (Section 6.4.1), and the primary endpoint of PFS was used to determine the sample size of the study.

At the time of initially writing the protocol, there were no Phase III data available on crizotinib in the first-line setting in *ALK*-positive patients. The median PFS for crizotinib administered as second-line therapy from the global randomized Phase III PROFILE 1007 study was 7.7 months (95% CI: 6.0% to 8.8%). From the Phase II single arm study of patients who had received ≥ 1 line of chemotherapy (with 85% patients having received ≥ 2 prior chemotherapy regimens), the median PFS was 8.5 months (95% CI: 6.2% to 9.9%). The Phase III PROFILE 1014 study of crizotinib versus standard pemetrexed-platinum-based chemotherapy in previously untreated patients

with *ALK*-positive non-squamous NSCLC reported a median PFS of 10.9 months for crizotinib (Mok et al. 2014).

Thus, an initial assumption of median PFS of 9.8 months for the crizotinib arm has been reassessed based on data from the Phase III study PROFILE 1014 to 10.9 months. An HR of 0.65 for alectinib versus crizotinib (i.e., an increase from 10.9 months median PFS to 16.8 months) will be targeted.

In this study, 286 patients will be enrolled in a 1:1 randomization allocation. Enrollment will take approximately 24 months on the basis of an assumption of non-linear recruitment as follows:

- Month 1: 1 patient per month
- Month 2: 2 patients per month
- Month 3: 4 patients per month
- Month 4: 6 patients per month
- Month 5: 8 patients per month
- Month 6: 10 patients per month
- Month 7: 12 patients per month
- Months 8–12: 13 patients per month
- Months 13–14: 14 patients per month
- Month 15 onwards: 15 patients per month

A total of 170 PFS events are required to achieve 80% power at a 2-sided αlevel of 5%. This number of PFS events is estimated to occur approximately 33 months after the first patient has been enrolled.

No interim analysis for efficacy or futility is planned.

A survival follow-up analysis will be performed once approximately 50% 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 0.83. On the basis of the sample size (N = 286), the trial will not be powered to demonstrate any statistically significant difference in OS of this magnitude. At the time of the final analysis of the primary endpoint of PFS, on the basis of the above assumptions, 106 OS events are expected to have occurred. The survival follow-up analysis is expected to occur approximately 144 months (12 years) 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, on the basis of information captured on the eCRF, 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 using RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the last tumor assessment date either during study treatment or during follow-up. Patients with no post-baseline tumor assessment will be censored at the date of randomization.

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

The treatment comparison of PFS will be based on a stratified log-rank test at the 5% level of significance (2-sided). The stratification factors are the randomization stratification factors: ECOG PS (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no), as recorded on the eCRF. Results from an unstratified log-rank test will also be presented.

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 difference between the two treatment groups will be assessed and tested for the following hypothesis: the survival distribution function (SDF) of the alectinib treatment group is the same as for the crizotinib treatment group versus the alternative that the two distributions are different:

H_0: SDF (alectinib) = SDF (crizotinib)

versus

H_1: SDF (alectinib) $\neq$ SDF (crizotinib)

where SDF denotes the survival distribution function of the parameter PFS.

6.4.2 Secondary Efficacy Endpoints

If the primary endpoint of PFS is statistically significant at a 2-sided 5% significance level, the following secondary endpoints will be tested in the following sequential order, each at a 2-sided 5% significance level:

- PFS by IRC
- Time to CNS progression
- ORR
- OS

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

In order to account for the competing risks inherent in such an analysis, HRs, including statistical inference on the basis of a 2-sided log-rank test, to compare the risk of CNS progression between the alectinib and crizotinib treatment groups, will be computed on the basis of cause-specific hazard functions.

The probability of CNS progression, non-CNS progression, and death will each be estimated using cumulative incidence functions.

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

An exploratory analysis of CNS time to progression on the basis of RANO criteria will also be performed on the basis of the IRC assessments.

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 (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. Similar analyses will be performed in the subgroup of patients with measurable and/or non-measurable CNS lesions at baseline.
An exploratory analysis of these endpoints will also be performed on the basis of RANO criteria assessed by the IRC.

Objective Response Rate

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

An estimate of ORR and its two-sided 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. Response rates in the treatment groups will be compared using a stratified Mantel-Haenszel test 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 causes, whichever occurred first. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed. Duration of Response will be estimated using Kaplan-Meier

methodology and an HR on the basis of a Cox proportional regression model will be calculated.

Overall Survival

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

6.4.2.1 Sensitivity Analyses

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

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

6.4.2.2 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 pre-treatment radiation therapy for CNS lesions.

All other subgroup analyses will be specified in the Statistical Analysis Plan (SAP).

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:

- 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 using MedDRA and 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. For adverse events, the most extreme severity will be used for reporting. Adverse events will be described by individual listings and by body system, as well as by severity. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are 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. In order to evaluate and compare hypogonadism in the two treatment arms, testosterone levels in the blood will be summarized for males by treatment arm over time (for details, see Section 6.8).

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

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

Subgroup analyses will be performed to evaluate the safety profile within the subgroups of patients including by sex, age (<65 vs. ≥ 65 years), and race (non-Asian vs. Asian).

An iDMC will review the safety data collected during the conduct of the study. Safety monitoring will be performed periodically. Further details will be outlined in the iDMC Charter.

6.6 PHARMACOKINETIC ANALYSES

Standard NCA may be conducted for PK data collected from patients participating in serial/intensive PK collections for relevant analytes, as data allow, as appropriate, and if needed. PK parameters, including but not limited to AUC, C_{max}, and time to maximum concentration (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.

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

Summary statistics (e.g., means, standard deviation, coefficient of variation %, geometric means, medians and ranges) for plasma concentrations and/or PK parameters for alectinib and metabolite(s) 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/pharmacodynamic analyses may be reported outside the CSR.

Nonlinear mixed-effects modeling (with software NONMEM; Beal et al. 1999) will be used to analyze the sparse and/or serial/intensive plasma concentration-time data for alectinib. The PK data from this study may be pooled with data from other studies. Population and individual PK parameters will be estimated and the influence of various covariates (such as age, gender, and body weight) on these parameters will be investigated.

Exploratory analyses will be conducted to investigate the relationship between alectinib PK exposure and efficacy/safety parameters.

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

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

Time to deterioration from baseline will be assessed at every study visit (Week 4, Week 8, and then after every 4 weeks) until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression; at post-treatment Visit (4 weeks after permanent treatment discontinuation); and at subsequent 8-weekly survival follow-up visits for 6 months, for 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. Time to deterioration will be analyzed for the ITT population. If a baseline or post-baseline 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.

6.7.2 Additional Patient-Reported Outcomes

Patient-reported outcomes of HRQoL, lung cancer–related symptoms, and health status will be measured using the EORTC QLQ-C30 and EORTC QLQ-LC13.

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 questionnaire, and the QLQ-LC13 according to the EORTC scoring manual guidelines. 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.

6.8 EXPLORATORY ANALYSES

The EQ-5D-3L is a generic PRO instrument that is used for across diseases and indications cost-effectiveness analyses. This instrument quantifies the QoL of various health outcomes and is applicable to a wide range of health states. Analyses of this outcome will be exploratory and will generate utility scores for use in economic models for reimbursement purposes only. The PRO will be administered every 4 weeks until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression; at the post-treatment visit (4 weeks after permanent treatment discontinuation); and every follow-up visit (every 8 weeks) after post-treatment visit for 6 months (see Appendix 1).

It has been reported that crizotinib therapy triggers rapid suppression of testosterone levels in men causing rapid-onset hypogonadism. It is unknown if reductions in testosterone reflect an effect of crizotinib on *ALK* or on some combination of the drug's targets (i.e., c-MET; Weickhardt et al. 2012; 2013). Total testosterone and free testosterone levels (either by direct measurement or by calculation using albumin and sex hormone-binding globulin [SHBG] calculator: https://www.issam.ch/freetesto.htm) and FSH and LH levels in blood will be measured (see Appendix 1) in male patients enrolled in the study for exploratory analysis of an onset of hypogonadism. The recommended time of day to have a blood sample taken for this test is between 7 a.m. and 10 a.m.

The Abbott Vysis FISH test will be used as an exploratory assay after patients have been enrolled in this study. Results from these analyses will be used to quantify the degree of correlation between Vysis FISH and Ventana IHC for the detection of *ALK*-positive NSCLC.

The *ALK* plasma assays (PCR and/or sequencing) will be used as exploratory assays for *ALK*-positive and consented *ALK*-negative patients. Results from these analyses will be used to quantify the degree of correlation between *ALK* plasma tests and Ventana IHC and Vysis FISH for the detection of *ALK*-positive NSCLC. The *ALK* plasma assay population may be used for exploratory efficacy and safety analysis. This analysis population will be used to support diagnostic development. Assays from this population may be used for the registration of a plasma assay as a companion diagnostic. This analysis will be dependent on the successful technical development of a plasma *ALK* assay. Results of analyses related to those alternative diagnostic tests and exploratory analyses on post-progression tumor samples to measure molecular mechanisms of resistance to *ALK* inhibitors and plasma samples to measure *ALK* rearrangements in circulating tumor cells will be communicated outside the main CSR.

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 using 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, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

Electronic Case Report Forms 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.

Electronic PRO data will be collected through use of an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with the FDA regulations for electronic records (21 Code of Federal Regulations Part 11). The ePRO device data are available for view access only via secure access to a Web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. 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

Electronic Case Report Forms 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. Electronic Case Report Forms 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. Electronic Case Report Forms 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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use an ePRO device to capture PRO data. The data will be transmitted via pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be reviewed by site staff via secure access to a Web server.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 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 trial.

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 prior 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 7.6.

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

7.5 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 can 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the 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 prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the initial study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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). Studies conducted in the United States or under a United States

IND application will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014), and all other applicable local regulations.*

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 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.

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 prior to 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 using 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.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

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 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 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 IND 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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted CSRs and/*or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation and* will be provided upon request.

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 DEVIATIONS

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 trial, specifically study design, data interpretation, exploratory analyses, or alternate changes to the trial 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 Sponsor's designated central laboratories and assessed by Ventana IHC test.

An iDMC will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised. Details of the composition, roles, and responsibilities, and processes of the iDMC are documented in a separate iDMC charter. The iDMC will review safety data and can make recommendations to the Sponsor to stop or amend the study on the basis of safety findings. The frequency of these reviews as well as the data to be reviewed will be agreed with the iDMC and outlined in the separate iDMC charter. No stopping for early proof of efficacy will result from any of these regular safety reviews. Independent Data Monitoring Committee review meetings will be held in a blinded manner to the Sponsor.

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 DISSEMINATION 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, in clinical trial registries of the U.S. National Institutes of Health and the European Medicines Agency, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted CSRs and*/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical *Study information* at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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 CSR. 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 prior to 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 trials 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, and/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 on Treatment in Case of Isolated, Asymptomatic CNS Progression (Every 12 weeks)[v] Until Systemic Progression and/or Symptomatic CNS Progression	Post-Treatment Visit (4 weeks after Permanent Treatment Discontinuation) [a]	Subsequent Therapy for NSCLC; Survival follow-up [a]
	Days -28 to 0	Days -3 to 0	Visit 0 (Baseline)	Visit 1 (Week 4)	Visit 2 (Week 8)	All Subsequent Visits (Every 12 weeks)[v] Until PD, Death, or Withdrawal from Study prior to PD[a]			
Informed consent	x								
Demographics	x								
Medical history	x								
Pregnancy test [b]		x	To be repeated as necessary						
Physical examination [c]	x		x	x	x	x	x		
Vital signs	x		x	x	x	x	x		
ECOG PS	x		x	x	x	x	x		
ECG [d]	x		x [e]	x		x			
Hematology, Coagulation	x		x [e]	x	x	x	x		
Biochemistry	x		x [e]	x	x	x	x		
Urinalysis	x		x [e]	x	x	x	x		
Concomitant medications	x		x	x	x	x	x		

Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period				Post-Progression Visits on Treatment in Case of Isolated, Asymptomatic CNS Progression (Every 12 weeks)[v] Until Systemic Progression and/or Symptomatic CNS Progression	Post-Treatment Visit (4 weeks after Permanent Treatment Discontinuation) [a]	Subsequent Therapy for NSCLC; Survival follow-up [a]
	Days -28 to 0	Days -3 to 0	Visit 0 (Baseline)	Visit 1 (Week 4)	Visit 2 (Week 8)	All Subsequent Visits (Every 12 weeks)[v] Until PD, Death, or Withdrawal from Study prior to PD[a]			
Mandatory tumor sample for *ALK* testing [f]	x								
Optional plasma sample from centrally confirmed *ALK* negative patients (20 ml of blood)	x								
Optional tumor sample			x [g]			x [h]	x [h]		
Plasma sample for *ALK* fusion detection in nucleic acids (20 mL of blood)			x [i]						
Plasma for detection of *ALK* mutation status (20 mL of blood)			x			x [j]	x [j]		

Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period				Post-Progression Visits on Treatment in Case of Isolated, Asymptomatic CNS Progression (Every 12 weeks)[v] Until Systemic Progression and/or Symptomatic CNS Progression	Post-Treatment Visit (4 weeks after Permanent Treatment Discontinuation) [a]	Subsequent Therapy for NSCLC; Survival follow-up [a]
	Days -28 to 0	Days -3 to 0	Visit 0 (Baseline)	Visit 1 (Week 4)	Visit 2 (Week 8)	All Subsequent Visits (Every 12 weeks)[v] Until PD, Death, or Withdrawal from Study prior to PD[a]			
Blood sample for pharmacogenomics research at pre-dose (3 mL of blood) [k]			x						
Tumor assessment [l]	x [m]		x [m]		x	x [n]	x	x [o]	
MRI scan of the brain	x [m]		x [m]		x	x [n]	x	x [o]	
PK samples (2 mL blood) [p]			x	x	x	x			
PRO (EORTC QLQ-C30/LC13); EQ-5D [q]			x	x	x	x	x	x	
Total testosterone, (either by direct measurement or by calculation using albumin and SHBG), FSH, and LH [r]			x	x	x	x			
Adverse events [s]	x	x	x	x	x	x	x	x	

Appendix 1 Schedule of Assessments (cont.)

Assessment	Screening		Treatment Period				Post-Progression Visits on Treatment in Case of Isolated, Asymptomatic CNS Progression (Every 12 weeks)[v] Until Systemic Progression and/or Symptomatic CNS Progression	Post-Treatment Visit (4 weeks after Permanent Treatment Discontinuation) [a]	Subsequent Therapy for NSCLC; Survival follow-up [a]
	Days -28 to 0	Days -3 to 0	Visit 0 (Baseline)	Visit 1 (Week 4)	Visit 2 (Week 8)	All Subsequent Visits (Every 12 weeks)[v] Until PD, Death, or Withdrawal from Study prior to PD[a]			
Subsequent therapy for NSCLC							x	x	x [t]
Drug dispensing and accountability [u]			x	x	x	x	x	x (accountability only)	
Blood Sample for Roche Clinical Repository (10 mL)			x						

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 = European Organization for the Research and Treatment of Cancer; EQ-5D = EuroQoL 5 Dimension; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; NCI = National Cancer Institute; 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. Post-baseline assessments are to be performed within ± 1 week.

[a] For details on assessments when patient permanently discontinues from study treatment, see flowchart in Figure A1–1.

[b] Urine or serum, to be repeated as necessary.

[c] Including an ophthalmologic examination if clinically indicated.

[d] At screening, Visit 0 (baseline), Visit 1 (Week 4), Visit 4 (Week 24), Visit 8 (Week 56), last treatment visit, and as clinically indicated throughout the study.

[e] Screening laboratory assessment done within 3 days can be counted as the baseline assessment.

[f] Preferably blocks fixed in neutral buffered formalin; if blocks are not available, a minimum of 10 to 15 unstained 5-μm slides are required. Tumor *ALK* status will be assessed by central laboratory before randomization.

[g] Optional tumor sample could be taken from the tumor block obtained at screening.

[h] At the time of disease progression from progressive lesions.

[i] Mandatory blood sample (20 mL) for detection of *ALK* rearrangements in nucleic acids in plasma collected at baseline only.

[j] Blood sample (20 mL) to obtain plasma for analysis of mutation status in *ALK* and other escape genes will be collected at Visit 0 (baseline), during the study every second visit (i.e., every 24 weeks with the implementation of protocol version 6), and the last collected at progression of disease, which includes isolated, asymptomatic CNS progression (see Section 4.5.8.4).

[k] This sample is required in all patients in alectinib arm, and in those patients in the crizotinib arm who wish to participate in optional genomics sequencing.

[l] Tumor assessment consists at minimum of a CT/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 $>1.5\times$ ULN) of bone metastasis should undergo radionuclide bone scan. Clinical lesions should be assessed with caliper measurement and documented by color photography, including a ruler to estimate the size of the lesion. Post-baseline assessments are to be performed within ± 1 week for the 8 weekly assessments. If there is suspicion of disease progression on the basis of clinical or laboratory findings, a tumor assessment should be performed as soon as possible before the next scheduled evaluation.

[m] Screening tumor assessment done within 14 days will be counted as the baseline assessment.

[n] Tumor assessment can 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 prior to PD, regardless of whether they subsequently receive non-study, anti-cancer therapy.

[o] If treatment was permanently discontinued due to disease progression.

[p] Pre-dose 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 pre-dose 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. For a subset of patients on alectinib treatment (10%–15%, or at least approximately $n = 20$) participating in serial/intensive PK sample collection, additional PK will be collected on Visits 0 (baseline) and 1 (Week 4) at pre-dose (within 2 hours before intake of study medication), 1, 2, 4, 6, and 8 hours post-dose. With implementation of version 6 of the protocol, PK sampling is no longer required.

[q] PRO questionnaires are to be completed every 4 weeks until disease progression and during post-progression on treatment in case of isolated, asymptomatic CNS progression; at the post-treatment visit (4 weeks after permanent treatment discontinuation); and every follow up visit (every 8 weeks) after post-treatment visit for 6 months. Further guidelines on PRO questionnaire administration will be provided in the study manual. With implementation of Version 5 of the protocol, PRO measurement will no longer be performed.

[r] Male patients only, using institutional standard assay. The recommended time of day to have a blood sample taken for this test is between 7 a.m. and 10 a.m. Albumin and SHBG measurements are not required when a direct assessment of free testosterone is available. If free

testosterone level cannot be directly assessed, it will be calculated from albumin and SHBG using a free testosterone calculator: http://www.issam.ch/freetesto.htm.

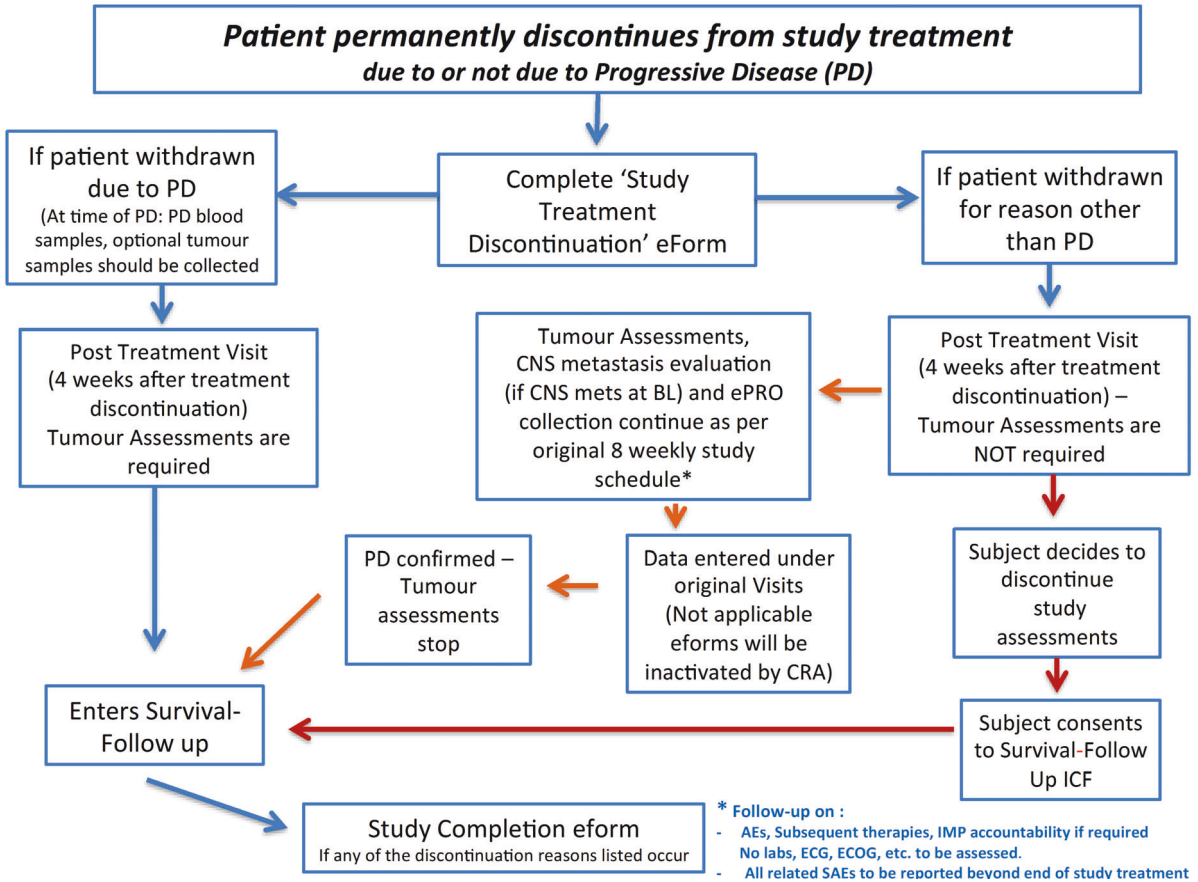
[s] Graded according to NCI CTCAE (version 4.0). Serious adverse events collection must start from first study-specific procedure.

[t] Performed every 8 weeks after post-treatment visit during the first 6 months and then every 12 weeks, via phone calls if no other in-person assessment is required.

[u] For details on drug dispensing and accountability, see Section 4.3.3.

[v] With implementation of version 6 of the protocol, (patients on treatment for more than 3 years) the study visit frequency decreases from every 8 weeks to every 12 weeks. The study treatment dispense is adjusted to the interval.

Figure A1–1 Flowchart for Patients who Permanently Discontinue Study Treatment



AEs = adverse events; ECOG = Eastern Cooperative Oncology Group; ePRO = electronic patient-reported outcome (not collected since protocol v5); ICF = informed consent form; IMP = investigational medicinal product; PD = progressive disease.

Appendix 2
Schedule of Alectinib Pharmacokinetic Assessments

Visit	Timepoint
Visit 0 (baseline)	Pre-dose (within 2 hours before intake of alectinib)
Visit 1 (Week 4)	Pre-dose (within 2 hours before intake of alectinib)
Visit 2 (Week 8)	Pre-dose (within 2 hours before intake of alectinib)
All subsequent visits (every 8 weeks) until PD or death/withdrawal from study prior to PD	Pre-dose (within 2 hours before intake of alectinib)
Visit 0 (baseline) and Visit 1 (Week 4)[a]	Pre-dose (within 2 hours before intake of alectinib), 1, 2, 4, 6, and 8 hours post-dose

PD = progressive disease; PK = pharmacokinetic.

[a] For patients participating in the serial/intensive PK sample collection only.

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 risk-benefit 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 Potent Inducers	CYP3A Potent Inhibitors
avasimibe, barbiturates, carbamazepine, efavirenz, ethosuximide, garlic supplements, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentine, St. John's wort, troglitazone	aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, 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, carbmazepine, 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, Zhang 2010, and FDA Guidance on Drug-Drug Interactions.

Also see:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Potent inhibitors of CYP3A are those considered to be “strong CYP3A inhibitors” previously shown to result in a ≥ 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.

References

Levien TL, Baker DE. Cytochrome P450 drug interactions. Therapeutic Research Center Pharmacist’s Letter/Prescriber’s Letter [resource on the Internet]. 2003. Available from:
https://www.pharmacistsletter.com and https://www.prescribersletter.com.

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 4
Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1: Excerpt from Original Publication

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

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/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 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 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.

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[1] 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.

[2] 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.

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 adequate imaging techniques for measuring bone lesions. However, these techniques 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, can be considered as 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) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can 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.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of clinical lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is required.

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.

CT, MRI

Computed tomography is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable.

If, prior to enrollment, it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to 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 under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to 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 prior studies if possible. Each case should be discussed with the radiologist to determine if the substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions because the same lesion may appear to have a different size using a new modality.

Ultrasound

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

Endoscopy, laparoscopy, tumor markers, cytology, 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 (albeit measurable) 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, but, in addition, the lesions should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 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 if 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 ≥ 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 involving the same organ as a single item on the Case Report Form (CRF; 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 short axis to < 10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum 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 shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special notes on the assessment of target lesions

Lymph nodes

Lymph nodes 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 on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met, since 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) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when 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 CRF, 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 BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when 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).

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, BML should not be ticked.

Lesions that split or coalesce on 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 in non-target disease in

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

This circumstance arises in some Phase III trials when 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 worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if 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 representing 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 seen, 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, some 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 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 its small size) continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using 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 A4–1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table A4–2 is to be used.

Table A4–1 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 A4–2 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 [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint unless a convincing argument can be made that the contribution of the individual missing 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 were not assessed either because the scan was not done or because the scan could not be assessed due to poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess”, except 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 where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Table A4–3 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 a
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

Table A4–3 Best Overall Response When Confirmation Is Required (cont.)

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.

[a] 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 (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed 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 in order not to overstate 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 CRF.

Patients with a global deterioration of health status requiring 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. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown Table A4–1, Table A4–2, and Table A4–3.

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 still 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 complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
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 6
EORTC QLQ-C30/LC13 and EQ-5D-3L Questionnaires

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

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

During the past week:	Not at All	A Little	Quite a Bit	Very Much
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

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

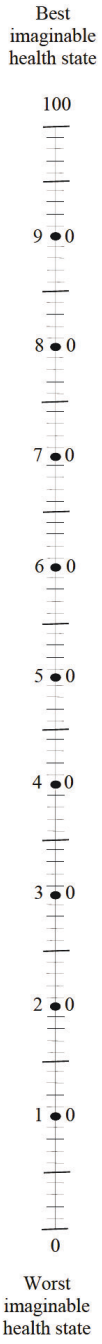
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

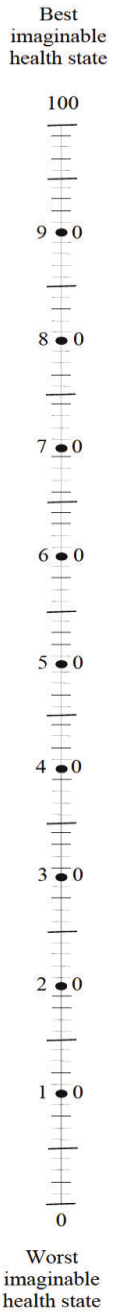
Your own health state today



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

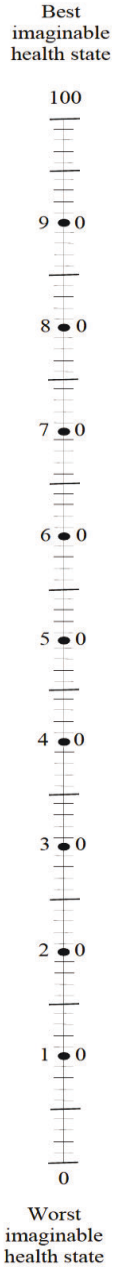
Your own health state today



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 7
Modification of Diet in Renal Disease (MDRD) Formula

The estimating glomerular filtration rate (eGFR) will be calculated on the basis of the following formula:

$$\text{eGFR [mL/min/1.73 m2]} = 175 \times \text{SCRT}^{-1.154} \times \text{AGE}^{-0.203} [\times 0.742 \text{ if female}] [\times 1.212 \text{ if African American}] \text{ (conventional units)}$$

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 lab in μmol/L units:

$$\text{Serum creatinine [mg/dL]} = \text{Serum creatinine [}\mu\text{mol/L]} \times 0.0113$$

REFERENCES:

Heil W, Koberstein R, Zawta B. Reference ranges for adults and children – considerations. Roche Diagnostics GmbH 2014, 8th edition, p.159.

Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med 2009;47:1017–9

Appendix 8
Anaplastic Lymphoma Kinase (*ALK*) Immunohistochemistry

Overview

The VENTANA anti-anaplastic lymphoma kinase (*ALK;* D5F3) Rabbit Monoclonal Primary Antibody (VENTANA anti-*ALK* [D5F3]) immunohistochemistry (IHC) assay will be used to determine *ALK* IHC status and to select patients with positive *ALK* for enrollment in Study BO28984. 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 BO28984, the VENTANA anti-*ALK* (D5F3) assay will be used for investigational purposes only.

The VENTANA anti-*ALK* (D5F3) is intended for laboratory use in the detection of the *ALK* protein in formalin-fixed, paraffin-embedded non–small cell lung cancer (NSCLC) tissue stained with using 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® 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 can 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 9
Drug Metabolism Enzymes, Transporters (DMET), and Liver Injury Polymorphisms

ABCB1	CHST13	CYP3A5	HNMT	SLC22A3	UGT1A4	ADRB3	HSP90A1	STAT6
ABCB11	CHST2	CYP3A7	MAOA	SLC22A4	UGT1A5	ALG10B	IGF1	TNF
ABCB4	CHST3	CYP46A1	MAOB	SLC22A5	UGT1A6	APOA1	IGF2	TNFRSF1B
ABCB7	CHST4	CYP4A11	MAT1A	SLC22A6	UGT1A7	APOC3	IL10	TXNIP
ABCC1	CHST5	CYP4B1	METTL1	SLC22A7	UGT1A8	ARHGAP24	IL22	UBC
ABCC2	CHST6	CYP4F11	NAT1	SLC22A8	UGT1A9	ATF3	IL4	UCP1
ABCC3	CHST7	CYP4F12	NAT2	SLC25A27	UGT2A1	ATIC	IL4R	VDR
ABCC4	CHST8	CYP4F2	NNMT	SLC28A1	UGT2B11	BIRC2	IL6	
ABCC5	CHST9	CYP4F3	NQO1	SLC28A2	UGT2B15	BIRC3	IL8	
ABCC6	COMT	CYP4F8	NR1I2	SLC28A3	UGT2B17	C3orf38	INSR	
ABCC8	CROT	CYP4Z1	NR1I3	SLC29A1	UGT2B28	CALCA	IRS1	
ABCC9	CYP11A1	CYP51A1	NR3C1	SLC29A2	UGT2B4	CASP9	IRS2	
ABCG1	CYP11B1	CYP7A1	ORM1	SLC5A6	UGT2B7	CD33	IRS4	
ABCG2	CYP11B2	CYP7B1	ORM2	SLC6A6	UGT8	CD36	ITPA	
ABP1	CYP17A1	CYP8B1	PGAP3	SLC7A5	VKORC1	CD44	JAK1	
ADH1A	CYP19A1	DCK	PNMT	SLC7A7	XDH	CDK4	JUN	
ADH1B	CYP1A1	DPYD	PON1	SLC7A8		CDK6	KCNIP4	
ADH1C	CYP1A2	EPHX1	PON2	SLCO1A2		CEBPB	KRT18	
ADH4	CYP1B1	EPHX2	PON3	SLCO1B1		CEP44	KRT8	
ADH5	CYP20A1	FAAH	POR	SLCO1B3		CES1	LEP	
ADH6	CYP21A2	FMO1	PPARD	SLCO2B1		CTLA4	LEPR	
ADH7	CYP24A1	FMO2	PPARG	SLCO3A1		CYP3A	LMX1A	
AHR	CYP26A1	FMO3	PPP1R9A	SLCO4A1		EGFR	LPL	

Appendix 9 Drug Metabolism Enzymes, Transporters (DMET), and Liver Injury Polymorphisms (cont.)

AKAP9	CYP26C1	FMO4	PRSS53	SLCO5A1	ETNK2	MCTP2
ALB	CYP27A1	FMO5	PTGIS	SPG7	FASLG	MT-CO2
ALDH1A1	CYP27B1	FMO6	QPRT	SPN	FMOD	MTHFR
ALDH2	CYP2A13	G6PD	RALBP1	SULT1A1	FOS	NFE2L2
ALDH3A1	CYP2A6	GSTA1	RPL13	SULT1A2	FPGS	NOS2
ALDH3A2	CYP2A7	GSTA2	RXRA	SULT1A3	GGH	NOS3
AOX1	CYP2B6	GSTA3	SERPINA7	SULT1B1	GPNMB	OR5H2
APOA2	CYP2B7P1	GSTA4	SLC10A1	SULT1C2	GPT	PARD3B
ARNT	CYP2C18	GSTA5	SLC10A2	SULT1C4	GPX1	PRKCZ
ARSA	CYP2C19	GSTM1	SLC13A1	SULT1E1	GPX3	RASGRP1
ATP7A	CYP2C8	GSTM2	SLC15A1	SULT2A1	GPX4	RB1
ATP7B	CYP2C9	GSTM3	SLC15A2	SULT2B1	GYS1	RDH5
CA5P	CYP2D6	GSTM4	SLC16A1	SULT4A1	GYS2	RIPK1
CBR1	CYP2E1	GSTM5	SLC19A1	TBXAS1	HCP5	SOCS3
CBR3	CYP2F1	GSTO1	SLC22A1	TPMT	HGF	SOD1
CDA	CYP2J2	GSTP1	SLC22A11	TPSG1	HLA-A	SOD2
CES2	CYP2S1	GSTT1	SLC22A12	TYMS	HLA-B	SPP1
CHST1	CYP39A1	GSTT2	SLC22A13	UGT1A1	HLA-DQA1	SQSTM1
CHST10	CYP3A4	GSTZ1	SLC22A14	UGT1A10	HLA-DQB1	ST6GAL1
CHST11	CYP3A43	HMGCR	SLC22A2	UGT1A3	HLA-DRB1	STAT1

Appendix 10
Formulae for the Calculation of QTcF and RR

QtcF – Fridericia's correction for QTc measurement (if not provided directly by the ECG machine):

$$QTcF\ (ms) = \frac{QT\ (ms)}{\sqrt[3]{RR(ms)/1000}}$$

RR Interval Formula (if not provided directly by the ECG machine):

RR (ms) = 60000/heart rate (bpm)

Appendix 11
Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A11–1 Investigational Medicinal Product Designations for European Economic Area and the United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in EEA and U.K.*	*Used within Marketing Authorization*
Alectinib (RO524802)	*IMP (test product)*	*Authorized*	*Yes*
Crizotinib	*IMP (test product)*	*Authorized*	*Yes*

EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

Signature Page for Protocol - BO28984 - ALECENSA - v9 - Global/Core - Published
System identifier: RIM-CLIN-502369

Approval Task	[redacted] Company Signatory 15-Oct-2023 17:49:28 GMT+0000