Official Title: **RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOCETAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**

NCT Number: NCT02604342

Document Date: Protocol Version 7.1: 01-Dec-2017

PROTOCOL

TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOCETAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**
PROTOCOL NUMBER:	MO29750
VERSION NUMBER:	7.1
EUDRACT NUMBER:	2015-000634-29
IND NUMBER:	111723
TEST PRODUCT:	Alectinib (RO5424802)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1.0: 28 May 2015
DATE AMENDED	Version 2.0: 26 Nov 2015 Version 3.0: Not submitted (due to typos) Version 4.0: 20 May 2016 Version 5.0: 7 December 2016 Version 6.0: 20 June 2017 (Hong Kong and Turkey) Version 7.1: See electronic stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	01-Dec-2017 18:49:16

PROTOCOL AMENDMENT, VERSION 7.1: RATIONALE

Specific changes in Version 7.1 and their rationale are as follows:

- Subsequent to its primary completion date (January 26, 2017), Study MO29750 was found to have met its primary objective, i.e., median PFS assessed by the investigator was 9.6 months for alectinib (95% CI: 6.9–12.2 months) versus 1.4 months for chemotherapy (95% CI: 1.3–1.6; p<0.001).[1] Furthermore, the safety profile for alectinib was consistent with previous studies and compared favorably with chemotherapy. Given these results—as well as the fact that participants now have access to alectinib by other means, either as a marketed and reimbursed drug (per prescription) (Alecensa®), in a Roche Post-Trial Access program or in a roll-over extension study (BO39694), depending on the drug approval and reimbursement status in the country—the number of assessments and patient visits during the follow-up period has been reduced in an effort to improve patient convenience. Specifically, the follow-up period after last patient randomized has been reduced from 24 months to 14 months.
- Efficacy analyses of Study MO29750 also showed that median PFS assessed by the IRC was 7.1 months for alectinib versus 1.6 months for chemotherapy (HR=0.32, 95% CI 0.17–0.59; p<0.001). As the primary objective has now been addressed, and as both the investigator and IRC assessments found similar highly significant benefits of alectinib relative to chemotherapy, the protocol has been amended such that it no longer mandates ongoing IRC review. To ensure that all patients are captured in final analyses (a small number of participants [n=12] enrolled after the primary analysis cut-off date), the IRC will continue its review for up to 12 weeks after the last patient in. This will allow the IRC to analyze one baseline scan and two on-treatment scans for each patient who enrolled after the primary analysis date, which is deemed adequate for assessment of alectinib efficacy.
- In prior versions of the protocol, the post treatment study visit occurred 3 months after the last administration of study drug. This choice was made based on the known safety profiles of pemetrexed and docetaxel. However, with the observed difference in PFS between test agents, it is expected that very soon all remaining patients in the trial will be from the alectinib arm exclusively. Thus, the post treatment visit has been changed in Version 7 to occur 4 weeks after last administration of study drug to align more closely to other alectinib clinical trials.

Additional minor changes, including removal of an inadvertent link to an internal Roche list of contact numbers (Section 5.4.1), have been made to improve clarity, consistency, and accuracy. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

---

[1] Novello, S et al. Primary results from the phase III ALUR study of alectinib versus chemotherapy in previously treated ALK+ non-small-cell lung cancer (NSCLC). Presented at: ESMO 2017 Congress; 2017 Sept 8-12. Abstract #1299O.

PROTOCOL AMENDMENT, VERSION 7.1:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

Section 3.2: END OF STUDY

The end the of study will occur when each patient is followed up for OS for up to ~~24~~ *14* months or when 50% of randomized patients have died, whichever occurs first.

Section 5.4.1: Emergency Medical Contacts

Toll-free numbers for the Help Desk as well as Medical Monitor contact information will be distributed to all investigators. ~~The list can be generated using contact numbers found at the following link: http://gcpcenter.roche.com/synergy/portal/view/pdq-spi/gcpcenter/34-64711453.~~

Section 9.4: ADMINISTRATIVE STRUCTURE

An IRC will review the tumor assessments to determine the secondary endpoints. *IRC assessments will continue until 12 weeks after the last patient in, after which time the IRC assessments will be halted.*

Appendix 1: Schedule of Assessments

Footnote c: ~~Three months~~ *Four weeks* after permanent treatment discontinuation for patients who do not receive alectinib treatment beyond progression, or at the end of randomized treatment for patients who enter the post progression period.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOCETAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**
PROTOCOL NUMBER:	MO29750
VERSION NUMBER:	7.1
EUDRACT NUMBER:	2015-000634-29
IND NUMBER:	111723
TEST PRODUCT:	Alectinib (RO5424802)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy (as instructed by XX ***[e.g., your local study monitor, the CRO]***) ***[or]*** (to the contact provided below).

(Name)
(Address)

PROTOCOL SYNOPSIS

TITLE:	**RANDOMIZED, MULTICENTER, PHASE III, OPEN-LABEL STUDY OF ALECTINIB VERSUS PEMETREXED OR DOECTAXEL IN ANAPLASTIC LYMPHOMA KINASE-POSITIVE ADVANCED NON -SMALL CELL LUNG CANCER PATIENTS PREVIOUSLY TREATED WITH PLATINUM-BASED CHEMOTHERAPY AND CRIZOTINIB**
PROTOCOL NUMBER:	MO29750
VERSION NUMBER:	7.1
EUDRACT NUMBER:	2015-000634-29
IND NUMBER:	111723
TEST PRODUCT:	Alectinib (RO5424802)
PHASE:	III
INDICATION:	Anaplastic lymphoma kinase-positive (ALK-positive) non-small cell lung cancer (NSCLC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is as follows:

- To evaluate and compare between treatment groups the efficacy of alectinib versus chemotherapy in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy and crizotinib (progressed or intolerant to crizotinib), as measured by investigator-assessed progression-free survival (PFS)

Key Secondary Efficacy Objective

The key secondary efficacy objective for this study is as follows:

- To evaluate and compare between treatment groups the central nervous system (CNS) objective response rate (C-ORR) in patients with measurable CNS metastases at baseline, as assessed by an Independent Review Committee (IRC)

Other Secondary Efficacy Objectives

Other secondary efficacy objectives for this study are to evaluate and compare between treatment arms:

- PFS (assessment by IRC)
- Objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) in all patients according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (assessment by investigator and IRC)
- PFS in patients with baseline CNS metastases (assessment by investigator and IRC)
- Time to CNS progression in all patients, patients with baseline CNS metastases and patients without baseline CNS metastases (assessment by IRC)

- CNS duration of response (C-DOR), CNS disease control rate (C-DCR) and C-ORR for all patients with baseline CNS metastasis (assessment by IRC)
- C-DOR and C-DCR for patients with baseline measurable CNS metastasis (assessment by IRC)
- Overall survival (OS)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of alectinib compared with chemotherapy in all patients and patients with CNS metastases at baseline

Pharmacokinetics Objective

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

Patient-Reported Outcomes Objectives

- 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 (single item) pain in arm/shoulder and fatigue as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13), as well as TTD in a composite of three symptoms (cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain) To evaluate and compare patient-reported outcomes (PROs) of health-related quality of life (HRQoL), patient functioning and side effects of treatment, as measured by the EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L

Exploratory Objectives

The exploratory objectives for this study may include but are not limited to the following:

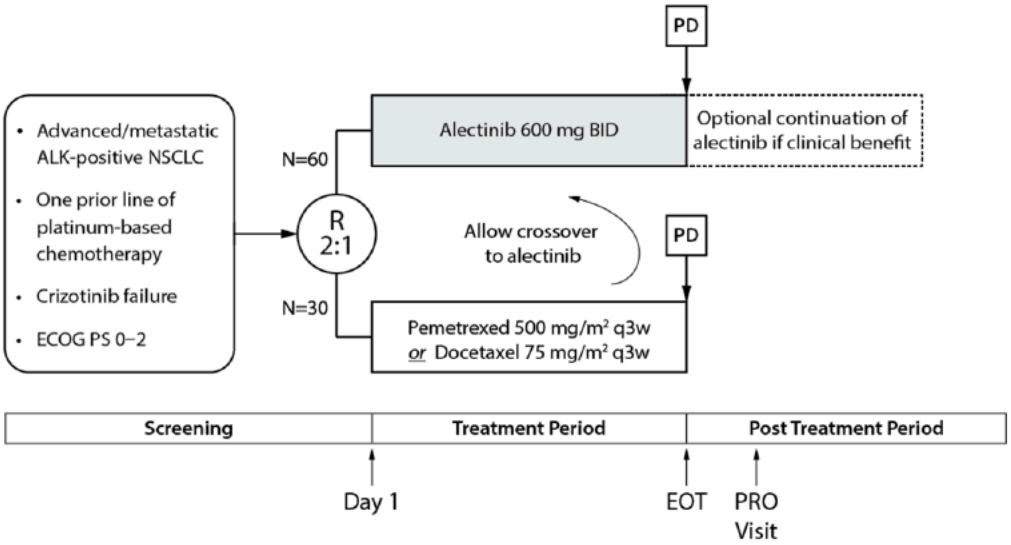
- To evaluate and compare PROs of patients with CNS metastases, as measured by specific questions from the EORTC QLQ-BN20 questionnaire
- Need and dosing for corticosteroids in case of CNS metastasis
- To assess exploratory biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to ALK genetic alterations) and their association with disease status, clinical outcome, efficacy and safety
- To investigate molecular mechanisms of resistance to ALK inhibitors
- To develop biomarker or diagnostic assays to detect ALK mutations/fusions in plasma/tumor and to establish performance characteristics of these assays

Study Design

Description of Study

This will be a randomized active-controlled multicenter Phase III open-label study. The study will consist of a Screening Period, a Treatment Period and a Post Progression and Post Treatment Period (Synopsis Figure). Day 1 (baseline) will be defined as the first day a patient receives study medication. The Post Treatment Period for patients who do not receive crossover treatment or treatment beyond progression will include one additional clinic visit where patients will complete PRO questionnaires. This visit will be conducted within the Post Progression period for patients who do cross over or receive treatment beyond progression. The study will be conducted in approximately 60 centers located in approximately 15 countries worldwide.

Synopsis Figure. Study Schema.



ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; NSCLC = non-small cell lung cancer; PD = progressive disease; R = randomization.

Note: To ensure comparability between treatment groups, patients will be randomized using the following stratification factors: ECOG PS (0/1 vs. 2); and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no). Enrolment caps will be used to ensure that at least 50% of randomized patients will have baseline CNS metastases.

To be eligible, patients must have advanced or recurrent Stage IIIB ALK-positive NSCLC that is not amenable for multimodality treatment or metastatic Stage IV ALK-positive NSCLC. In addition, the patients must have received two prior systemic lines of therapy for their NSCLC, consisting of one platinum-based chemotherapy regimen and crizotinib. The NSCLC must be positive for ALK as determined by ALK immunohistochemistry (IHC) or ALK fluorescence in situ hybridization (FISH). Testing must be validated and in line with published national or international guidelines.

Patients will be randomized 2:1 into one of two treatment arms to receive either alectinib or chemotherapy (pemetrexed or docetaxel). 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)
- CNS metastases at baseline (yes vs. no)

  In addition, patients with baseline CNS metastases will be stratified by history of radiotherapy (yes vs. no)

Enrollment caps will be used to ensure that at least 50% of randomized patients will have baseline CNS metastases. An IxRS manual containing relevant information will be provided to each study site.

Following randomization, the experimental arm will receive oral alectinib at a dosage of 600 mg twice daily (BID), taken with food. The control arm will receive chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. The first dose of the study drug (and the required premedication, when applicable) should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

Patients on both arms will be treated with study drug (including those who cross over from chemotherapy to alectinib) until disease progression, unacceptable toxicity, withdrawal of consent or death. At the discretion of the patient and the investigator, patients on the alectinib arm who show radiological progression per RECIST v1.1 will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on the control (chemotherapy) arm who do not have any safety-related issues that might render the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will be allowed to cross over to receive alectinib treatment. Patients with any safety-related issues rendering the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will have the possibility to cross over after the safety-related issues have resolved or normalized. Upon progression on cross-over treatment with alectinib, patients will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until further disease progression, no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on either arm who opt not to continue or to cross over to alectinib will be treated at the discretion of the investigator according to local practice.

In all patients, information regarding the type and duration of subsequent therapies following disease progression, as well as overall survival follow-up, will be collected. Patients who discontinue treatment prior to disease progression (e.g., due to unacceptable toxicity) will continue to be followed until disease progression and for OS, regardless of whether they subsequently receive non-study anti-cancer therapy.

The assessments to be conducted in this study are described below and will be carried out at the time points designated in the Schedule of Assessments (Appendix 1 and 2).

- Disease progression will be assessed using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). The primary efficacy objective will be investigator-assessed PFS, and the key secondary efficacy objective will be IRC-assessed C-ORR. Other secondary objectives will include the following assessments by the IRC: PFS; PFS in patients with CNS metastases at baseline; time to CNS progression in all patients and in patients with and without baseline CNS metastases; and C-DOR and C-DCR in all patients with baseline CNS metastases and in patients with measurable CNS metastases. The IRC and the investigator will evaluate ORR, DCR and DOR. Finally, OS will be determined
- Safety will be monitored by assessing serious and non-serious adverse events (AEs), safety laboratory tests, vital signs and electrocardiogram (ECG). The incidence, nature and severity of all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety tests will include hematology and blood chemistry. Vital sign assessments will include blood pressure and pulse rate; additional vital signs will be collected only if clinically warranted. In addition, the study will have a baseline urinalysis assessment (dipstick); additional urinalyses will be conducted only if clinically warranted
- Pharmacokinetic (PK) parameters for alectinib and its major metabolite(s) will be assessed on sparsely collected pre-dose blood samples. The specific PK parameters will be determined as appropriate, where data allow
- HRQoL will be assessed using three PRO instruments: the EORTC QLQ-C30, the EORTC QLQ-LC13, and the EuroQoL 5D-5L. PRO scores will be determined for all patients and for patients with CNS metastases at baseline and will be compared across treatment groups
- Finally, the study will have exploratory analyses examining biomarkers and assessing the HRQoL effects of brain metastases in patients with CNS metastases at baseline. The latter PRO assessments will be based on two selected questions from the EORTC QLQ-BN20, a QoL instrument specific for brain neoplasms

An independent data monitoring committee (iDMC) is planned for this study to review safety data periodically. More details will be provided in the iDMC charter.

Number of Patients

At least 90 and a maximum of 120 patients (as per previous protocol) will be randomly assigned in a 2:1 allocation ratio to the two treatment arms) via a block-stratified randomization procedure and over a planned recruitment period of approximately 12 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) and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. 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. ALK positivity must have been determined by a validated FISH test (recommended probe, Vysis ALK Break-Apart Probe) or a validated IHC test (recommended antibody, clone D5F3)
2. Patient had received two prior systemic lines of therapy for advanced or metastatic disease (stage IIIB or IV), which must have included one line of platinum-based chemotherapy and one line of crizotinib (progression on or intolerability to crizotinib)
3. Prior CNS or leptomeningeal metastases allowed if asymptomatic. 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 and local treatment is indicated, patients need to complete the local treatment (surgery or radiotherapy). In all cases, radiation treatment must be completed at least 14 days before enrollment and patients must be clinically stable
4. Patients with symptomatic CNS metastases for whom radiotherapy is not an option will be allowed to participate in this study
5. Measurable disease (by RECIST v1.1) prior to the administration of study treatment (Appendix 5)
6. Age ≥18 years old
7. Life expectancy of at least 12 weeks
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 (Appendix 6)
9. Adequate hematologic function:
    - Platelet count ≥ 100 $x10^9$/L
    - Absolute neutrophil count (ANC) ≥ 1500 cells/µL
    - Hemoglobin ≥ 9.0 g/dL
10. 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 (Appendix 8)
11. 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
12. For all females of childbearing potential, a negative pregnancy test must be obtained prior to randomization and within 3 days before starting study treatment

13. 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, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices
14. For men: agreement to remain abstinent or use a contraceptive method that results 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 (in addition, refer to the local label for pemetrexed and docetaxel). 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
15. Able and willing to provide written informed consent prior to performing any study related procedures and to comply with the study protocol, including being willing and able to use the electronic patient-reported outcome device

<u>Exclusion Criteria</u>

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

1. 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 or in situ carcinoma of the cervix)
2. Patients who have received any previous ALK inhibitor other than crizotinib
3. Any GI disorder that may affect absorption of oral medications, such as mal-absorption syndrome or status post-major bowel resection
4. Liver disease characterized by:
   - Alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) > 2.5 x upper limit of normal (ULN) (> 5 x ULN for patients with concurrent liver metastases) 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 or bleeding from esophageal varices

     OR
   - Acute viral or active autoimmune, alcoholic or other types of acute hepatitis
5. NCI CTCAE v4.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication
6. Any exclusion criteria based on local label of pemetrexed or docetaxel
7. History of organ transplant
8. Patients with baseline QTc > 470 ms or symptomatic bradycardia
9. Administration of strong/potent CYP3A4 inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib or docetaxel
10. History of hypersensitivity to any of the additives in the alectinib drug formulation (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, sodium lauryl sulfate [SLS] or magnesium stearate)
11. History of severe hypersensitivity reaction to pemetrexed or docetaxel or any known excipients of these drugs

12. Patients not eligible for treatment with docetaxel or pemetrexed according to the local labels
13. Pregnant or lactating women
14. Known HIV positivity or AIDS-related illness
15. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study
16. 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.

Length of Study

The time from the first patient randomized to the end of study (defined below) will be up to 26 months (includes 12 months of recruitment period and a maximum of 14 months of follow up for OS for all participants). Since a maximum of 120 patients may be enrolled as per previous protocol version, this may result in an extension of the 12-month recruitment period.

End of Study

The end the of study will occur when each patient is followed up for OS for up to 14 months or when 50% of randomized patients have died, whichever occurs first.

Patients who are receiving and benefitting from study treatment at the end of the study may be offered the possibility of rolling over into a long-term extension study, following the approval of this extension study by Competent Authorities and the Ethics Committees of the respective investigational sites. During the long-term extension study, minimum data will be collected and SAE's will be reported to Roche and entered into the Roche safety data base. Study MO29750 will be closed and an updated analysis performed once all patients have either withdrawn or enrolled in the extension study.

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurs first. Similar definitions of PFS will be used by the investigator (primary endpoint) and the IRC. Patients without an event will be censored at the last tumor assessment. Patients with no post-baseline assessments will be censored at the date of randomization. PFS for patients with CNS metastasis at baseline will be defined in a similar way, taking into account all lesions in the body
- Overall response rate (ORR) is defined as the percentage of patients who attain complete response (CR) or partial response (PR), as determined using RECIST v1.1. Similar definitions of ORR will be used by the investigator and the IRC. Patients without any post-baseline assessments will be regarded as non-responders. ORR for patients with CNS metastasis at baseline (C-ORR) will be defined in a similar way for lesions in the CNS. (It should be noted that patients with non-measurable disease can achieve only CR and not PR)
- Disease control rate (DCR) is defined as the percentage of patients who attain complete response (CR), partial response (PR) or stable disease (SD) of at least 5 weeks, as determined using RECIST v1.1. Similar definitions of DCR will be used by the investigator and the IRC. Patients without any post-baseline assessments will be regarded as non-responders. CNS DCR (C-DCR) for patients with CNS metastasis at baseline will be defined in a similar way for lesions in the CNS. (It should be noted that patients with non-measurable disease can achieve only CR or SD and not PR).

- Duration of response (DOR) 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. Similar definitions of DOR will be used by the investigator and the IRC. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement. DOR for patients with CNS metastasis at baseline (C-DOR) will be defined in a similar way for lesions in the CNS, taking into account all lesions in the body
- Overall survival (OS) 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
- Time to CNS progression is defined as the time from randomization to the first documented disease progression in the CNS

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Serious and non-serious AEs
- Safety laboratory tests
- Vital signs
- ECG

The incidence, nature and severity of all AEs events will be graded according to NCI CTCAE v.4.0.

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE 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

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 AE.

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are the following:

- Sparse (pre-dose) PK samples for measurement of alectinib and its major metabolite(s) will be collected in all study patients receiving alectinib treatment
- 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, as appropriate. The potential influence of covariates that contribute significantly to the between-patient differences in PK parameters of alectinib will also be explored and quantified, as appropriate

Additional PK parameters may be calculated as deemed appropriate.

Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows (see Appendix 7):

- EORTC QLQ-C30 and EORTC QLQ-LC13 scores to determine the impact of alectinib compared with chemotherapy in the overall population, as well as in patients with CNS metastases, as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms (e.g. cough, chest pain (single item) dyspnea (single item and multi-item scales)pain in chest, pain in arm/shoulder and fatigue), and as well by TTD for the composite of three symptoms (cough, dyspnea(multi-item subscales QLQ-LC13) and chest pain).
- The EORTC QLQ-C30 and EORTC QLQ-LC13 scores to measure PROs of HRQoL, patient functioning and side effects of therapy compared between patients treated with alectinib and those treated with chemotherapy. The comparison will be done for the overall patient population, as well as in patients with CNS metastases at baseline
- The EuroQoL 5 Dimension (EQ-5D-5L) questionnaire score to will be used for the overall patient population, as well as for patients with CNS metastases at baseline, to assess patients' health status and generate utility scores for use in pharmacoeconomic models for reimbursement purposes only

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows (additional exploratory parameters may be assessed as deemed appropriate):

- Scores from three specific questions extracted from the EORTC QLQ-BN20 questionnaire, a QoL instrument specific to brain neoplasms. The three questions are as follows: "Do you have headaches?"; "Do you have problems with coordination/balance?"; and "Did you have trouble communicating your thoughts?" Each of the three questions will be scored on a 4-point scale (1, Not at all; 2, A little; 3, Quite a bit; 4, Very much), which will subsequently be linearly transformed to a 0–100-point scale
- To assess exploratory biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to ALK genetic alterations) and their association with disease status, clinical outcome, efficacy and safety
- To investigate molecular mechanisms of resistance to ALK inhibitors
- To develop biomarker or diagnostic assays to detect ALK mutations/fusions in plasma/tumor and to establish performance characteristics of these assays

Investigational Medicinal Products

Test Product (Investigational Drug)

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

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

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

Alectinib 600 mg (four 150-mg capsules) should be administered orally BID with food in the morning and evening. 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. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death.

If a dose is missed, patients can make up that dose unless the next dose is due within 6 hours. If the time is less 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 5.1.2.

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

Comparators

For information on administration of pemetrexed (Alimta®) and docetaxel (Taxotere®), refer to the local prescribing information.

Guidelines for dosage modifications and treatment interruptions or discontinuation due to specified adverse events on pemetrexed or docetaxel are provided in Section 5.1.2.

Non-Investigational Medicinal Products

In addition to the test product or comparators, all patients in this study will receive standard-of-care therapy for advanced NSCLC, as assessed by the investigator.

Statistical Methods

Primary Analysis

The main primary endpoint is PFS assessed by the investigator as defined above.

The main efficacy analysis will be based on the intent-to-treat (ITT) population that includes all randomized patients. The per protocol (PP) population will be defined as the subset of the ITT population who have received at least one dose of study medication and have at least one post baseline tumor assessment with no major protocol violations (which will be defined in the statistical analysis plan).

The main analysis for investigator assessed PFS will be a stratified Cox model analysis that will include a treatment group variable and stratification factors, defined as:

- ECOG PS (0/1 vs. 2),
- CNS metastases at baseline (yes vs. no)

  In addition, patients with baseline CNS metastases will be stratified by history of radiotherapy (yes vs. no)

The un-stratified Cox model analysis for PFS and also stratified with stratification factors recorded in the eCRF will also be provided as sensitivity analyses.

Estimates for the survivor function for PFS will be obtained by the Kaplan-Meier approach. The p-value of log-rank test will be displayed together with estimated hazard ratios and associated 95% confidence intervals (CIs).

Hypotheses testing for the primary endpoint:

- H_0: the distribution of the PFS time is the same in the two treatment groups
- H_1: the distribution of the PFS time is different in the two treatment groups.
- If the hazard ratio (HR) of the investigational arm compared with the control arm with respect to PFS is assumed to be constant over time (λ), then the null (H_0) and alternative hypotheses (H_1) are: H_0: $\lambda=1$ vs. H_1: $\lambda \neq 1$

Unless otherwise specified, all tests will be performed at two-sided alpha of 5%.

Safety endpoints will be analyzed for the safety population, which will include all patients who received at least one dose of study medication. For analysis purposes, patients will be assigned to treatment groups based on actual received study medication. More details are provided in Section 6.5.

PK data will be analyzed with summary statistics (e.g., means, standard deviation, coefficient of variation %, geometric means, medians and ranges). Further details are provided in Section 6.6.

The PRO measures, EORTC QLQ-C30, EORTC QLC-LC13, and EQ-5D 3L and questions specific to CNS metastases (a part of EORTC BN20 questionnaire) will be summarized using descriptive statistics. Selected single or multi-item subscales will be graphically presented and difference between two treatment groups over time will be explored using mixed models. The Cochran-Mantel-Haenszel statistic test will be applied to take the ordinal nature of a variable EORTC QOQ-BN20. More details will be specified in the SAP.

Descriptive analysis for biomarkers will be provided and further association between biomarkers and clinical endpoints (e.g. PFS, OS, ORR, etc.) will be explored using Cox regression model or logistic model. More information will be provided in the SAP.

Determination of Sample Size

The sample size estimation was performed using EAST Software, Version 6.0, based on the statistical hypotheses in Section 6.4.

Synopsis Table: Summary of Determination of Sample Size

Primary endpoint	***Median Time to PFS (Chemo vs. Alectinib) Months/HR***	***Number of Patients/Events***	***Number of Patients Per Treatment arm (Chemo vs Alectinib)***
PFS	3 vs. 7/0.43	90/50	30 vs. 60
Key Secondary endpoint	***Response (Chemo vs. Alectinib)***	***Number of Patients***	
C-ORR [b]	15% vs. 55%	24	8 vs. 16

a. 80% power, two sided alpha test at 0.05; 2:1 randomization.

b. Patients with measurable CNS metastases at baseline, 70% power, one-sided test at 0.05.

Assuming an accrual period of 12 months and a primary analysis with at least 50 PFS events planned approximately after 13 months, a sample size of 90 patients (60 patients in the experimental arm [alectinib] and 30 patients in the control arm [chemotherapy]) with at least 50 PFS events will provide 80% power to detect a significant improvement in the median time of the primary endpoint from 3 to 7 months (i.e., HR of 0.43), based on a two-sided log-rank test at an alpha level of 0.05. In the pivotal Profile 1007 trial (Shaw et al. 2013), median PFS in the chemotherapy arm among 174 patients previously treated with one platinum-based chemotherapy regimen and treated in second line with either pemetrexed or docetaxel was 3 months (95% CI, 2.6–4.3). Hence, a median PFS of 3 months for the chemotherapy arm (control arm) has been assumed.

The objective response (Shaw et al. 2013) was reported in the chemotherapy group as 20% (95% CI, 14%–26%). Also, we expect that at least 25% of patients with measurable CNS metastases at baseline will be randomized in 2 treatment arms in this study. Approximately 24 patients with measurable CNS metastases at baseline (8 patients in control and 16 patients in experimental arm) will provide power of 70% (one-sided 5% alpha test) to detect clinically meaningful difference in C-ORR of 40%, assuming C-ORR in control arm of 15%.

If superiority for the PFS endpoints is concluded, subsequent hierarchical testing for the key secondary endpoint, C-ORR in patients with measurable CNS metastases at baseline, will be performed.

Interim Analyses

No interim analyses for efficacy or futility are planned. Safety review of data will be performed as explained in the iDMC charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AGC	absolute granulocyte count
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
BID	twice daily
BOR	best overall rate
C-DCR	CNS disease control rate
C-DOR	CNS duration of response
CI	confidence interval
C_{max}	maximum (peak) concentration of drug in blood plasma
CNS	central nervous system
CPK	creatine phosphokinase
C-ORR	CNS objective response rate
CR	complete response
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
DOT	duration of treatment
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D-5L	EuroQoL 5 Dimension questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Definition
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GGT	gamma glutamyl transferase
GI	gastrointestinal
HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent data monitoring committee
IHC	immunohistochemistry
INR	international normalized ratio
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
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal epithelial transition factor
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PP	per protocol
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
QLQ-C30	Quality of Life Questionnaire Core
QLQ-LC13	Quality of Life Questionnaire Supplemental Lung Cancer Module
QoL	quality of life
RBC	red blood cell
RE	response-evaluable
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
ROS1	ROS proto-oncogene 1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SHBG	sex hormone-binding globulin
SLS	sodium lauryl sulfate
SOC	system organ class
SPF	skin protection factor
TBP	treatment beyond progression
TKI	tyrosine kinase inhibitor
T_{max}	time after drug administration at which peak plasma concentration occurs
TTD	time to deterioration
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. BACKGROUND

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

It is estimated that nearly 1.6 million people perish from lung cancer every year, making it the leading cause of cancer-related mortality worldwide (GLOBOCAN 2012). In the European Union, 313,000 new cases of lung cancer were diagnosed in 2012 (214,000 men and 99,000 women) and 268,000 people died of the disease (186,000 men and 82,000 women). An estimated 158,040 US citizens are expected to die from lung cancer in 2015, accounting for approximately 27 percent of all cancer deaths (American Lung Association 2015). The primary form of lung cancer is non-small cell lung cancer (NSCLC), which occurs in approximately 85% of all lung cancer cases (the other forms include small cell lung cancer [10%–15%] and lung carcinoid tumor [5%]) (Molina et al. 2008). The two predominant histologic types of NSCLC are adenocarcinoma (more than half of cases) and squamous cell carcinoma (approximately 25% of cases) (Langer et al. 2010; Travis et al. 2011).

Survival rates are lower for NSCLC than for other common cancers. Thus, the expected 5-year survival rate in NSCLC 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). The overall 5-year survival rate for advanced NSCLC, is 2%−4% depending on geographic location (Cetin et al. 2011). Poor prognostic factors for survival in patients with NSCLC include advanced stage of disease at the time of initial diagnosis, poor Eastern Cooperative

Oncology Group (ECOG) performance status (PS) and a history of unintentional weight loss. More than half of patients with NSCLC present with distant metastatic disease at the time of initial diagnosis, which directly contributes to poor survival prospects.

Approximately 5% of patients with NSCLC 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 (Rikova et al. 2007; Soda et al. 2007; Soda et al. 2008; Kwak et al. 2010). Presence of the ALK rearrangement is observed predominantly in non-smoking younger female patients with adenocarcinoma, especially those diagnosed in the advanced stages of NSCLC (Fan et al. 2014; Wang et al. 2014; Zhao et al. 2015). NSCLC patients with ALK rearrangements rarely have mutations in the epidermal growth factor receptor (EGFR) or the Kirsten rat sarcoma viral oncogene homolog (KRAS), suggesting that these genetic alterations tend to be mutually exclusive (Fan et al. 2014; Wang et al. 2014; Zhao et al. 2015). However, EGFR mutations may develop as a resistance mechanism following treatment of ALK-positive NSCLC with crizotinib (see below) (Doebele et al. 2012).

Few studies have assessed the activity of chemotherapy specifically against ALK-positive advanced NSCLC, although some retrospective studies suggested that ALK rearrangements may be associated with enhanced sensitivity to pemetrexed-based regimens (Camidge et al. 2011; Lee et al. 2011). Two recent randomized Phase III studies, however, compared chemotherapeutic regimens in patients with advanced ALK-positive NSCLC (Shaw et al. 2013; Solomon et al. 2014) (Table 1).

Table 1 Randomized Phase III Trials in ALK-Positive Advanced NSCLC

	ORR (%)	Median PFS (months)	Median OS (Months)
First-line therapy (PROFILE 1014) [a]			
Pemetrexed plus cisplatin or carboplatin (n=171)	45	7.0	NR
Crizotinib (n=172)	74	10.9	NR
Second-line therapy following a platinum-based regimen (PROFILE 1007) [b]			
Pemetrexed or docetaxel (n=174)	20	3.0	22.8
Crizotinib (n=173)	65	7.7	20.3

NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

a. Solomon, B. J., T. Mok, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-2177.

b. Shaw, A. T., D. W. Kim, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-2394..

In the PROFILE 1014 study (Solomon et al. 2014), 342 patients with advanced ALK-positive nonsquamous NSCLC who had received no previous systemic treatment for advanced disease were randomized 1:1 to one of two treatments. The first group (n=171) received pemetrexed plus cisplatin or carboplatin every 3 weeks for up to 6 cycles, a standard therapeutic regimen for first-line treatment of advanced ALK-positive NSCLC. The second group (n=172) received twice-daily crizotinib, an oral small-molecule tyrosine kinase inhibitor of ALK, MET and ROS1 kinases (Kwak et al. 2010; Ou et al. 2011; Bergethon et al. 2012). Progression-free survival (PFS) was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001). Objective response rates (ORRs) were 74% and 45%, respectively (P<0.001). Median overall survival (OS) was not reached in either group; the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, diarrhea, nausea and edema, and the most common events with chemotherapy were nausea, fatigue, vomiting and decreased appetite. As compared with chemotherapy, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in quality of life (QoL).

In the PROFILE 1007 study (Shaw et al. 2013), 347 patients with locally advanced or metastatic ALK-positive lung cancer who had received one prior platinum-based regimen were randomized 1:1 to one of two treatments. The first group (n=174) received pemetrexed or docetaxel every 3 weeks, a standard therapeutic regimen for second-line treatment of advanced NSCLC (Reck et al. 2014). The second group (n=173) received twice-daily crizotinib. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group. The response rates were 65% (95% CI, 58% to 72%) with crizotinib, as compared with 20% (95% CI, 14% to 26%) with chemotherapy (P<0.001). An interim analysis of OS showed no significant improvement with crizotinib as compared with chemotherapy. Common adverse events associated with crizotinib were visual disorder, gastrointestinal side effects and elevated liver aminotransferase levels, whereas common adverse events with chemotherapy were fatigue, alopecia, and dyspnea. Patients reported greater reductions in symptoms of lung cancer and greater improvement in global QoL of life with crizotinib than with chemotherapy.

The previous studies make two key points related to treatment of advanced ALK-positive NSCLC:

- First, response to standard chemotherapy (platinum-based regimens, pemetrexed, docetaxel, etc., and their combinations) appears to be relatively similar in advanced ALK-positive NSCLC patients compared to a general population of unselected advanced NSCLC patients, although very subtle differences in outcomes may be observable (compare Table 1 vs. Table 2 and 3) (Fossella et al. 2000; Shepherd et al. 2000; Schiller et al. 2002; Hanna et al. 2004; Shepherd et al. 2005; Sandler et al. 2006; Pirker et al. 2009; Ramlau et al. 2012). Thus, to a first approximation,

treatment outcomes with standard chemotherapy are similar in advanced ALK-positive NSCLC and other types of advanced NSCLC.

- Second, ALK inhibitor therapy appears to be superior to standard chemotherapy in ALK-positive NSCLC patients (Table 1). Based on these and other data, crizotinib was approved in 2011 in the US in 2011, where it is currently indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test (US Food and Drug Administration). Crizotinib was approved in 2012 in the EU, where it is indicated for the treatment of adults with previously treated ALK-positive advanced NSCLC (European Medicines Agency).

Table 2 Randomized Phase III Trials in Previously Untreated Patients With Advanced NSCLC

First-Line Therapy Regimen	ORR (%)	Median PFS (months)	Median OS (Months)
Chemotherapy [a]			
Cisplatin and paclitaxel (n=288)	21	3.4	7.8
Cisplatin and gemcitabine (n=288)	22	4.2	8.1
Cisplatin and docetaxel (n=289)	17	3.7	7.4
Carboplatin and paclitaxel (n=290)	17	3.1	8.1
Chemotherapy and bevacizumab [b]			
Carboplatin and paclitaxel (n=444)	15	4.5	10.3
Carboplatin, paclitaxel and bevacizumab (n=434)	35	6.5	12.3
Chemotherapy and cetuximab [c]			
Cisplatin and vinorelbine (n=568)	29	4.8	10.1
Cisplatin, vinorelbine and cetuximab (n=557)	36	4.8	11.3

ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

a. Schiller JH, Harrington D, Belani CP, et al. Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92−8.

b. Sandler A, Gray R, Perry MC, et al. Paclitaxel–carboplatin alone or with bevacizumab for non−small-cell lung cancer. N Engl J Med 2006;355:2542−50.

c. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. Lancet 2009;373:1525−31.

Table 3 Randomized Phase III Trials of Second-Line Therapy for Advanced NSCLC

First-Line Therapy Regimen	ORR (%)	Median OS (months)	1-Year OS (%)
TAX 317 (2000) [a]			
Docetaxel 100 mg/m^2, q3w	7.1	5.9	19
Docetaxel 75 mg/m^2, q3w	7.1	7.5	37
Best supportive care	NA	4.6	11
TAX 320 (2000) [b]			
Docetaxel 100 mg/m^2, q3w	10.8	5.5	21
Docetaxel 75 mg/m^2, q3w	6.7	5.7	32
Vinorlebine or ifosfamide	0.8	5.6	19
JMEI (2004) [c]			
Docetaxel 75 mg/m^2, q3w	8.8	7.9	29.7
Pemetrexed 500 mg/m^2, q3w	9.1	8.3	29.7
BR.21 (2004) [d]			
Erlotinib 150 mg, QD	8.9	6.7	31
Best supportive care	NA	4.7	21
VITAL (2012) [e]			
Docetaxel 75 mg/m^2, q3w	8.9	10.4	NA

NA = not applicable; ORR = overall response rate; OS = overall survival; q3w = every 3 weeks; QD = every day.

Note: This table is adapted from Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. Oncologist 2008;13:28–36.

a. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103.

b. Fossella FV, DeVore R, Kerr RN, et al. Randomized Phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354–63.

c. Hanna Nasser, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non–small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589–97.

d. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated nonsmall-cell lung cancer. N Engl J Med 2005;353:123–32.

e. Ramlau R, Gorbunova V, Ciuleanu TE, et al. Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non–small-cell lung cancer: a randomized, controlled Phase III trial. J Clin Oncol 2012;30:3640– 7.

Although substantial benefit has been observed with crizotinib therapy, relapse remains the norm. Studies with patients who had progression on crizotinib treatment reveal three potential reasons for treatment failure: 1) development of resistance due to 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); 2) CNS progression; and 3) an as yet unknown mechanism. CNS progression may be particularly important for crizotinib-treated patients as the CNS is the primary site of initial treatment failure in 46%–60% of patients with ALK-positive NSCLC treated with this agent (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et al. 2015). Since significant morbidity is associated with CNS metastases due to the CNS involvement and to the standard forms of treatment (corticosteroids, surgery and radiation), an unmet medical need exists in this setting for chemotherapeutic agents with better activity in the CNS.

1.2 BACKGROUND ON ALECTINIB

Alectinib (also RO5424802 or CH5424802) is a newly developed highly-selective CNS-active 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 alterations, including NSCLC and anaplastic large cell lymphoma lines harboring an ALK translocation and a neuroblastoma line harboring an amplified ALK gene.

Nonclinical pharmacology studies showed that alectinib was efficacious in a model of tumors expressing an ALK fusion bearing the L1196M mutation, which is associated with resistance to crizotinib, and alectinib was effective in mouse NCI H2228 NSCLC xenografts that were already maximally suppressed by crizotinib. Alectinib also prolonged survival in an intracerebral NCI H2228 implantation model, and it reduced tumor growth in an intracranial model monitored using bioluminescence.

The clinical development program for alectinib, to date, comprises three ongoing Phase I/II studies in patients with ALK-positive NSCLC and two ongoing phase III studies:

The ongoing Phase I/II studies include:

- Study AF-001JP, a supportive first-in-human study conducted in Japan in crizotinib-naive patients with locally advanced or metastatic ALK-positive NSCLC who have progressed on at least one line of chemotherapy
- Study NP28761, conducted in the United States and Canada, in patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib
- Study NP28673, conducted globally, in patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib; the study also included a drug-drug interaction sub-study, where a single oral dose of midazolam was administered alone and in combination with multiple doses of alectinib

The enrollment of patients in the Phase I/II studies is complete and follow-up is ongoing.

The ongoing phase III studies include:

- Study BO28984 (ALEX), conducted globally, is comparing alectinib to crizotinib in treatment-naive ALK-positive NSCLC patients
- J-ALEX, conducted in Japan, is comparing alectinib to crizotinib in ALK-positive NSCLC patients who have progressed on prior chemotherapy

Results from the Phase III trials are not available to report at this time.

Please refer to the current Investigators Brochure for the most recent updates.

1.2.1 Study AF-001JP

1.2.1.1 Efficacy

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-naïve and have disease progression after at least one line of chemotherapy. AF-001JP has completed enrollment but 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, 24 patients were treated at doses of 20–300 mg twice daily (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 escalation of the dose.

In the Phase II portion of the study, 46 patients were treated with alectinib 300 mg BID. As of 31 January 2014, 43 patients (93.5%; 95% CI: 82.1% to 98.6%) achieved an objective response and 9 patients (19.6%; 95% CI: 9.4% to 33.9%) had a CR on the basis of an independent radiological review (Table 4). Median PFS was 27.7 months (95% CI: 26.9 months, NR) and the 2-year OS rate was 79% (95% CI: 63%, 89%). Thirty-one patients remained on alectinib at the cut-off date.

Table 4 Overall Response Rates and Time to Response in Patients in Part 2 of Study AF-001JP (Data Cutoff Date: 31 January 2014)

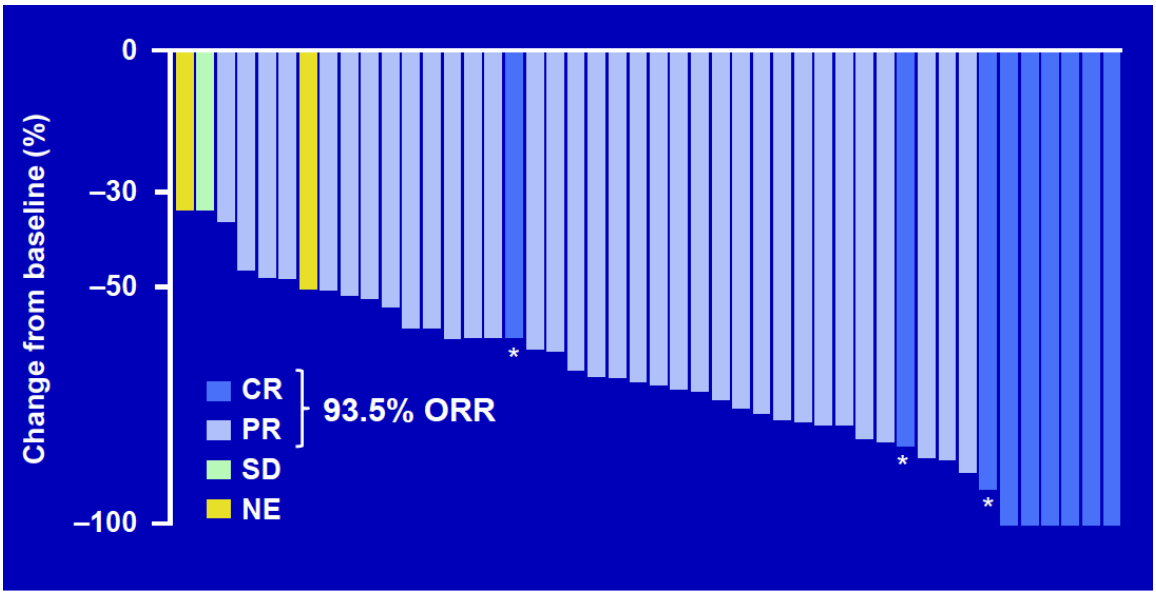
Response (n=46)	n (%)	95% CI (%)
CR	9 (19.6)	9.4–33.9
PR	34 (73.9)	58.9–85.7
SD	1 (2.2)	0.1–11.5
PD	0 (0.0)	0.0–7.7
Not evaluated	2 [a]	–
ORR (CR + PR)	43 (93.5)	82.1–98.6
Disease control (CR + PR + SD)	44 (95.7)	–

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

a. One patient withdrew early due to an AE (brain edema) and so had no response data; one had investigator-assessed PD that was later determined not to be PD by the IRC

Figure 1 shows the waterfall plot of the best change from baseline in the size of target lesions in Study AF-001JP, as determined by independent radiological review.

Figure 1 Change in Size of Target Lesions as Assessed by the IRC in Part 2 of Study AF-001JP Using RECIST v1.1 (Data Cutoff Date: 31 January 2014)

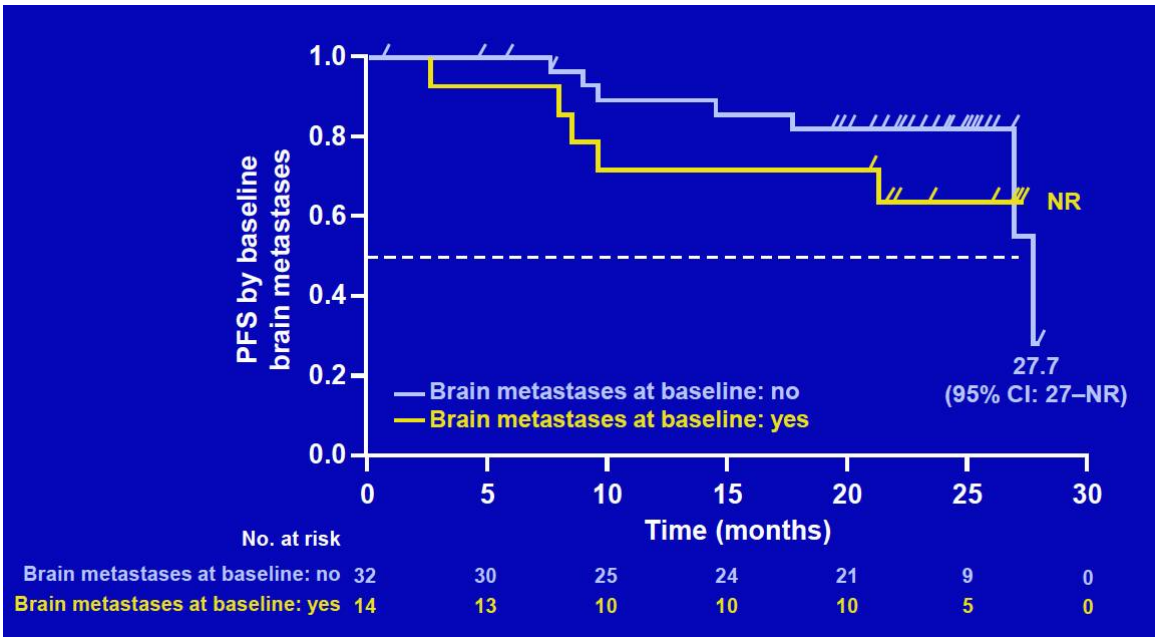


CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

* Three of 9 patients who were assessed as having a CR had lymph nodes as the target lesions. Per RECIST 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, they were assessed as having CR, although their tumor change from baseline was less than 100%.

PFS was favorable regardless of the presence or absence of CNS metastases at baseline (Figure 2).

Figure 2 Comparison of PFS in Patients With and Without CNS Metastases at Baseline in Study AF-001JP (Data Cutoff Date: 31 January 2014)



1.2.1.2 Safety

The safety results of Study AF-001JP, conducted in Japan, were consistent with the results observed in the pivotal Studies NP28761 and NP28673 (see next section). Refer to the Alectinib Investigator's Brochure for more details.

1.2.2 Studies NP28761 and NP28673

1.2.2.1 Primary Efficacy

In Phase II of Study NP28761, the study met its primary objective of demonstrating a clinically meaningful and statistically significant ORR based on IRC assessments (52.2%; 95% CI: 39.7%, 64.6%) in patients with ALK-positive advanced NSCLC whose disease had progressed on crizotinib treatment. The result of the secondary endpoint, investigator-assessed ORR (50.6%; 95% CI: 39.6%, 61.5%), was consistent with the primary endpoint.

In Study NP28673, the study met its main objective of demonstrating a clinically meaningful and statistically significant ORR based on IRC assessments (50.8%; 95% CI: 41.6%, 60.0%) in patients with ALK-positive advanced NSCLC whose disease had progressed on crizotinib treatment. The co-primary objective of IRC-assessed ORR in

the subgroup of chemotherapy pretreated patients, although not statistically significant, was clinically meaningful (44.8%; 95% CI: 34.6%, 55.3%). Due to the hierarchical order of testing, the overall study was considered positive as the first co-primary endpoint met statistical significance. The result of the secondary endpoint, investigator-assessed ORR (50.7%; 95% CI: 42.1%, 59.3%), was supportive of the primary endpoints.

An overview of efficacy results from Studies NP28761 and NP28673 are shown in following table.

Table 5 Overview of Efficacy Results From Studies NP28761 and NP28673 (Cutoff Date: 27 April 2015)

	Alectinib 600 mg BID	
	NP28761 Phase II	**NP28673 Phase II**
Primary Efficacy Parameters		
ORR (IRC) in RE population	n=67[a]	N=122[a]
Responders, n (%)	35 (52.2)	62 (50.8)
[95% CI[b]]	[39.7, 64.6]	[41.6, 60.0]
ORR (IRC) in patients pre-treated with chemotherapy[c]	N=52	N=96
Responders, n (%)	30 (57.7)	43 (44.8)
[95% CI[b]]	[43.2, 71.3]	[34.6, 55.3]
Secondary Efficacy Parameters		
ORR (investigator) in RE population	N=87	N=138
Responders, n (%)	44 (50.6)	70 (50.7)
[95% CI[b]]	[39.6, 61.5]	[42.1, 59.3]
ORR (investigator) in patients pre-treated with chemotherapy	N=64	N=110
Responders, n (%)	33 (51.6)	54 (49.1)
[95% CI[b]]	[38.7, 64.3]	[39.4, 58.8]
Exploratory Efficacy Parameters		
DCR (IRC) in RE population	N=67[a]	N=122[a]
CR + PR + SD, n (%)	43 (64.2)[d]	78 (63.9)[e]
[95% CI[b]]	[51.5, 75.5]	[54.8, 72.4]

	Alectinib 600 mg BID	
	NP28761 Phase II	**NP28673 Phase II**
DCR (investigator) in RE population	N=87	N=138
CR + PR + SD, n (%)	41 (61.2)[d]	95 (68.8)[e]
[95% CI[b]]	[48.5, 72.9]	[60.4, 76.5]
DOR (IRC) in RE population	N=67	N=122
Median time to event, months	13.5	14.1
[95% CI[f]]	[6.7, NE]	[10.9, NE]
DOR (investigator) in RE population	N=87	N=138
Median time to event, months	11.1	11.2
[95% CI[f]]	[8.8, NE]	[9.6, NE]
PFS (IRC) in safety population	N=87	N=138
Median time to event, months	8.1	8.9
[95% CI[f]]	[6.2, 12.6]	[5.6, 12.8]
PFS (investigator) in safety population	N=87	N=138
Median time to event, months	8.4	9.3
[95% CI[f]]	[5.5, 12.3]	[7.4, 12.8]

BID = twice daily; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IRC = independent review committee; NE = not estimated; ORR = objective response rate; PFS = progression-free survival; PR = partial response; RE = response-evaluable; SD = stable disease.

a There were 20 patients (NP28761) and 16 patients (NP28673) who did not have measurable disease at baseline according to the IRC and therefore were not included in the IRC RE population.

b 95% CI for rates were constructed using Clopper-Pearson method.

c Primary efficacy parameter only in Study NP28673.

d DCR is defined as the percentage of patients with a BOR of CR, PR, or SD lasting for at least 12 weeks after the first dose of alectinib.

e DCR is defined as the percentage of patients with a BOR of CR, PR, or SD lasting for at least 16 weeks.

f 95% CI for median was computed using the method of Brookmeyer and Crowley.

1.2.2.2 Central Nervous System Response

CNS response on the basis of radiological imaging was examined in a pooled analysis that included patients from Phase I [600 mg BID] and II of Study NP28761, as well as Phase II and the midazolam drug-drug interaction sub-study of Study NP28673. Among 50 pooled and evaluable patients who had either measurable or non-measurable CNS lesions at a baseline scan and at least one follow-up scan, 11 patients achieved a confirmed CR, 21 achieved PR, 13 achieved SD and 3 achieved PD in the IRC-

assessed population (data cutoff date: 27 April 2015). Two patients were unevaluable. The CNS DCR in this group was 90.0% (i.e., 45 of the 50 total evaluable patients).

Similarly, in 136 patients who had either measurable or non-measurable CNS lesions at a baseline scan, 37 patients achieved a confirmed CR, 58 achieved SD and 12 achieved PD in the IRC-assessed population. Twenty-one patients were noted as achieving PR (*NB*, patients with only non-measurable lesions cannot achieve PR). Eight patients were unevaluable. The CNS DCR was 85.3% (116 of the 136 total evaluable patients).

The median CNS DOR for evaluable patients with measurable CNS lesions at baseline in the pooled analysis was 10.8 months (95% CI: 7.6, 14.1 months). The median CNS DOR for evaluable patients with measurable and non-measurable CNS lesions at baseline was 11.1 months (95% CI: 10.3, NE months).

1.2.2.3 Safety

In Study NP28761, no DLTs were observed in the dose-escalation cohorts up to a dose of 900 mg BID. However, 2 patients in the subsequent 900-mg BID bridging cohort experienced a DLT, one each of Grade 3 headache and Grade 3 neutrophil count decreased, and both patients continued study treatment at reduced dose of 600 mg BID. On the basis of efficacy, safety, and PK data, the recommended Phase 2 dose was 600 mg BID.

Safety findings were consistent between the pivotal Studies NP28761 and NP28673 and overall findings are summarized here.

In a pooled safety analysis (includes patients from Phase I [600 mg BID] and II of Study NP28761 and Phase II and the midazolam drug-drug interaction sub-study of Study NP28673), almost all patients (98.4%) reported at least one AE as of the cutoff date of 27 April 2015. The most commonly reported AEs were constipation (33.6%), fatigue (30.0%), peripheral edema (26.1%), and myalgia (24.1%). The majority of AEs were of Grade 1 or 2 severity. Grade ≥ 3 AEs occurred in 86 of 253 patients (34.0%), with the most commonly reported being increased blood CPK (3.6%), dyspnea (3.6%), increased ALT (3.2%), and increased AST (2.8%).

Forty-nine of 253 patients (19.4%) in the pooled analysis had at least one SAE. The majority of the SAEs were single cases, and no SAE was reported in more than 3 patients. Of the 74 of 253 patients (29.2%) who died in the pooled analysis, the majority (66 patients [89.2% of the deaths]) were due to disease progression. Seven of 253 patients (2.8%) had an AE with fatal outcome. Rates of AEs leading to study drug withdrawal (5.9%), interruption (26.9%), or dose reduction (11.5%) indicated that alectinib treatment was well tolerated.

Selected AEs were defined in the study protocols based on potential risks identified from clinical and non-clinical data with alectinib and from data with ALK inhibitors. Selected

AEs that were reported in ≥ 10% of patients were constipation (34%); myalgia (24%); nausea (18%); diarrhea and AST increased (each 16%); ALT increased and anemia (each 14%); and vomiting, rash, blood CPK increased, and back pain (each 12%).

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

In patients with advanced NSCLC who lack an EGFR activating mutation or ALK gene rearrangement (~85% of all cases), standard first-line treatment is platinum-based chemotherapy (in patients with PS 0–2), although addition of bevacizumab improved outcome over platinum-based chemotherapy alone (Reck et al. 2014). Following treatment failure on first-line agents, patients with advanced NSCLC lacking EGFR/ALK alterations are then recommended to receive either pemetrexed or docetaxel as second-line therapy (Reck et al. 2014).

NSCLC patients with ALK gene rearrangements have an additional therapeutic option in the EU, where crizotinib is indicated for previously-treated ALK-positive advanced NSCLC (European Medicines Agency). Approval for this indication was based largely on the results from the PROFILE 1007 study (Shaw et al. 2013). In this randomized Phase III study, 347 patients with locally advanced or metastatic ALK-positive lung cancer who had received one prior platinum-based regimen were randomized 1:1 to one of two treatments. The first group (n=174) received pemetrexed or docetaxel every 3 weeks. The second group (n=173) received twice-daily crizotinib. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group. The response rates were 65% (95% CI, 58% to 72%) with crizotinib, as compared with 20% (95% CI, 14% to 26%) with chemotherapy (P<0.001). An interim analysis of OS showed no significant improvement with crizotinib as compared with chemotherapy. Patients also reported greater reductions in symptoms of lung cancer and greater improvement in global QoL of life with crizotinib than with chemotherapy.

Although substantial benefit has been observed with crizotinib therapy, relapse nonetheless eventually occurs. This is thought to happen for three potential reasons: 1) the development of drug resistance due to a secondary (e.g., gatekeeper) mutation(s), 2) CNS progression; and 3) an as yet unknown mechanism(s) (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013). The CNS relapse is most likely attributable to the fact that crizotinib is a P-glycoprotein (P-gp) substrate and, thus, may not be retained at significant levels in brain tissue. Consequently, in ALK-positive NSCLC, crizotinib exhibits impaired control of CNS metastases relative to other sites of systemic disease, with 46%–60% of progressions in patients treated with crizotinib involving the CNS (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et

al. 2015). In other words, the CNS becomes a sanctuary site for ALK-positive NSCLC treated with crizotinib—a physiologic and anatomic mechanism of drug resistance.

As crizotinib provides a median of 7.7 months of PFS following failure of platinum-based therapies, it becomes vitally important to identify optimal rescue therapies following failure of both platinum-based therapy and crizotinib. In the EU, current options in this setting include pemetrexed and docetaxel (Reck et al. 2014), with pemetrexed being favored by a recent ESMO consensus statement (Besse et al. 2014). Nonetheless, as shown in PROFILE 1007 (Shaw et al. 2013), the latter two agents have very poor efficacy as second-line agents (ORR, 20%; PFS, 3 months), and there is no reason to expect that the same is not true in the third-line setting.

The purpose of this study is therefore to determine whether alectinib, an ALK-specific TKI, provides more clinical benefit than pemetrexed or docetaxel in advanced ALK-positive NSCLC following relapse on platinum-based chemotherapy and crizotinib. The study will examine the effects of alectinib in all eligible patients, as well as in the subgroup of patients with CNS metastases at baseline.

Several prior observations predict that alectinib may be efficacious in both of these patient populations:

- Nonclinical data for alectinib suggest that it may be active in NSCLC even after progression on prior crizotinib therapy when the mechanism of resistance is due to acquired mutation in the ALK gene (Alectinib Investigator's Brochure for details)
- Alectinib is lipophilic and not a substrate for P-gp or the ABC transporter breast cancer resistance protein, known efflux transporters at the blood-brain barrier. Indeed, promising efficacy within the CNS has been observed with alectinib in pivotal Phase 2 studies in patients who have progressed on prior crizotinib therapy (see Section 1.2.2 and Alectinib Investigator's Brochure for details)
- In NSCLC patients treated with alectinib, PFS was favorable regardless of the presence or absence of CNS metastases at baseline (see Sections 1.2.2 and 1.2.2)

Finally, this study will also carry out PK, PRO and exploratory biomarker assessments. The rationales for these latter assessments are presented in detail in Sections 3.3.6, 3.3.7 and 3.3.8.

1.3.2 Benefit-Risk Assessment

Overall, the efficacy and safety data from the pivotal Studies NP28761 and NP28673 and the supporting studies show a favorable benefit/risk ratio for alectinib treatment, when administered at a dose of 600 mg BID (1200 mg/day), in patients with ALK-positive advanced NSCLC. The compound has been well tolerated in clinical studies in which patients with locally advanced or metastatic ALK-positive NSCLC have been treated with multiple doses of up to 760 mg BID.

Identified and potential risks associated with alectinib treatment will continue to be closely monitored throughout this study. Patient safety will be ensured by targeting the appropriate patient population (advanced ALK-positive NSCLC with and without CNS metastases at baseline) using carefully chosen inclusion/exclusion criteria, by stringent safety monitoring carried out by the Sponsor and Independent Data Monitoring Committee (iDMC) and by protocol-specified study drug interruption criteria.

With the above safety precautions in place, the estimated benefits of alectinib treatment outweigh the risks in this study, especially given the potential of alectinib—and the dearth of effective chemotherapeutic agents currently available—in patients with advanced ALK-positive NSCLC who have failed on prior platinum-based therapy and crizotinib.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study are as follows:

- To evaluate and compare between treatment groups the efficacy of alectinib versus chemotherapy in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy and crizotinib (progressed or intolerant to crizotinib), as measured by investigator-assessed progression-free survival (PFS)

The key secondary efficacy objective for this study is as follows:

- To evaluate and compare between treatment groups the central nervous system (CNS) objective response rate (C-ORR) in patients with measurable CNS metastases at baseline, as assessed by an Independent Review Committee (IRC)

Other secondary efficacy objectives for this study are to evaluate and compare between treatment arms:

- PFS (assessment by IRC)
- Objective response rate (ORR), disease control rate (DCR) and duration of response (DOR) in all patients according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (assessment by investigator and IRC)
- PFS in patients with baseline CNS metastases (assessment by investigator and IRC)
- Time to CNS progression in all patients, patients with baseline CNS metastases and patients without baseline CNS metastases (assessment by IRC)
- CNS duration of response (C-DOR), CNS disease control rate (C-DCR) and C-ORR for all patients with baseline CNS metastasis (assessment by IRC)
- C-DOR and C-DCR for patients with baseline measurable CNS metastasis (assessment by IRC)
- Overall survival (OS)

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of alectinib compared with chemotherapy in all patients and patients with CNS metastases at baseline

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of alectinib and its major metabolites

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

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

- To evaluate and compare time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, chest pain (single item), dyspnea (single item and multi-item subscales), pain in arm/shoulder and fatigue, as measured by the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13), as well as by a composite of three symptoms (cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain). Analysis will be performed for all patients, as well as in the subgroup of patients with CNS metastases
- To evaluate and compare patient-reported outcomes (PROs) of health-related quality of life (HRQoL), patient functioning and side effects of treatment, as measured by the EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L. Analysis will be performed for all patients, as well as in the subgroup of patients with CNS metastases

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study may include but are not limited to the following:

- To evaluate PROs of patients with CNS metastases, as measured by specific questions from the EORTC QLQ-BN20 questionnaire
- To assess exploratory biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to ALK genetic alterations) and their association with disease status, clinical outcome, efficacy and safety
- To investigate molecular mechanisms of resistance to ALK inhibitors
- To develop biomarker or diagnostic assays to detect ALK mutations/fusions in plasma/tumor and to establish performance characteristics of these assays

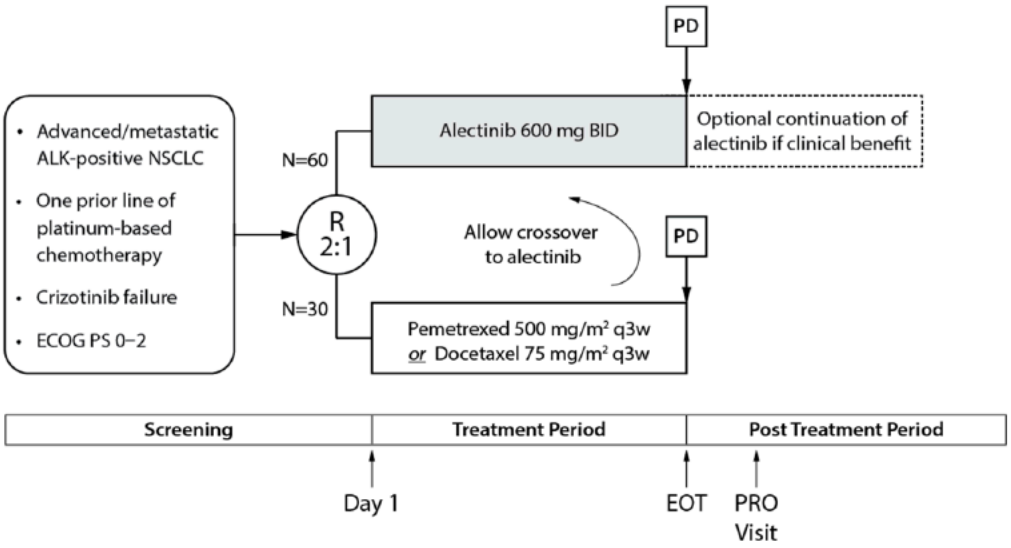
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This will be a randomized active-controlled multicenter Phase III open-label study. The study will consist of a Screening Period, a Treatment Period and a Post Progression and Post Treatment Period (Figure 3). Day 1 (baseline) will be defined as the first day a patient receives study medication. The Post Treatment Period for patients who do not

receive crossover treatment or treatment beyond progression will include one additional clinic visit where patients will complete PRO questionnaires. This visit will be conducted within the Post Progression period for patients who do cross over or receive treatment beyond progression. The study will be conducted in approximately 60 centers located in approximately 15 countries worldwide.

Figure 3 Study Schema



ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = End of Treatment; NSCLC = non-small cell lung cancer; PD = progressive disease; R = randomization.

Note: To ensure comparability between treatment groups, patients will be randomized using the following stratification factors: ECOG PS (0/1 vs. 2); and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no). Enrolment caps will be used to ensure that at least 50% of randomized patients will have baseline CNS metastases.

To be eligible, patients must have advanced or recurrent Stage IIIB ALK-positive NSCLC that is not amenable for multimodality treatment or metastatic Stage IV ALK-positive NSCLC. In addition, the patients must have received two prior systemic lines of therapy for their NSCLC, consisting of one platinum-based chemotherapy regimen and crizotinib. The NSCLC must be positive for ALK as determined by ALK immunohistochemistry (IHC) or ALK fluorescence in situ hybridization (FISH). Testing must be validated and in line with published national or international guidelines.

Patients will be randomized 2:1 into one of two treatment arms to receive either alectinib or chemotherapy (pemetrexed or docetaxel). 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)

- CNS metastases at baseline (yes vs. no)

    In addition, patients with baseline CNS metastases will be stratified by history of radiotherapy (yes vs. no)

Enrollment caps will be used to ensure that at least 50% of randomized patients will have baseline CNS metastases. An IxRS manual containing relevant information will be provided to each study site.

Following randomization, the experimental arm will receive oral alectinib at a dosage of 600 mg twice daily (BID), taken with food. The control arm will receive chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks. The first dose of the study drug (and the required premedication, when applicable) should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

Patients on both arms will be treated with study drug (including those who cross over from chemotherapy to alectinib) until disease progression, unacceptable toxicity, withdrawal of consent or death. At the discretion of the patient and the investigator, patients on the alectinib arm who show radiological progression per RECIST v1.1 will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on the control (chemotherapy) arm who do not have any safety-related issues that might render the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will be allowed to cross over to receive alectinib treatment. Patients with any safety-related issues rendering the patient ineligible to receive alectinib treatment (as per safety-based inclusion criteria of the study) will have the possibility to cross over after the safety-related issues have resolved or normalized. Upon progression on cross-over treatment with alectinib, patients will be allowed to continue receiving alectinib beyond disease progression if he or she is clinically benefitting from the drug until further disease progression, no further clinical benefit is to be expected, unacceptable toxicity, withdrawal of consent or death. Patients on either arm who opt not to continue or to cross over to alectinib will be treated at the discretion of the investigator according to local practice.

In all patients, information regarding the type and duration of subsequent therapies following disease progression, as well as overall survival follow-up, will be collected. Patients who discontinue treatment prior to disease progression (e.g., due to unacceptable toxicity) will continue to be followed until disease progression and for OS, regardless of whether they subsequently receive non-study anti-cancer therapy.

The assessments to be conducted in this study are described below and will be carried out at the time points designated in the Schedule of Assessments (Appendix 1 and 2):

- Disease progression will be assessed using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). The primary efficacy objective will be investigator-assessed PFS, and the key secondary efficacy objective will be IRC-assessed C-ORR. Other secondary objectives will include the following assessments by the IRC: PFS; PFS in patients with CNS metastases at baseline; time to CNS progression in all patients and in patients with and without baseline CNS metastases; and C-DOR and C-DCR in all patients with baseline CNS metastases and in patients with measurable CNS metastases. The IRC and the investigator will evaluate ORR, DCR and DOR. Finally, OS will be determined
- Safety will be monitored by assessing serious and non-serious adverse events (AEs), safety laboratory tests, vital signs and electrocardiogram (ECG). The incidence, nature and severity of all AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety tests will include hematology and blood chemistry. Vital sign assessments will include blood pressure and pulse rate; additional vital signs will be collected only if clinically warranted. In addition, the study will have a baseline urinalysis assessment (dipstick); additional urinalyses will be conducted only if clinically warranted
- Pharmacokinetic (PK) parameters for alectinib and its major metabolite(s) will be assessed on sparsely collected pre-dose blood samples. The specific PK parameters will be determined as appropriate, where data allow
- HRQoL will be assessed using three PRO instruments: the EORTC QLQ-C30, the EORTC QLQ-LC13, and the EuroQoL 5D-5L. PRO scores will be determined for all patients and for patients with CNS metastases at baseline and will be compared across treatment groups
- Finally, the study will have exploratory analyses examining biomarkers and assessing the HRQoL effects of brain metastases in patients with CNS metastases at baseline. The latter PRO assessments will be based on two selected questions from the EORTC QLQ-BN20, a QoL instrument specific for brain neoplasms

An independent data monitoring committee (iDMC) is planned for this study to review safety data periodically. More details will be provided in the iDMC charter.

3.2 END OF STUDY

The end the of study will occur when each patient is followed up for OS for up to 14 months or when 50% of randomized patients have died, whichever occurs first.

Patients who are receiving and benefitting from study treatment at the end of the study may be offered the possibility of rolling over into a long-term extension study, following the approval of this extension study by Competent Authorities and the Ethics Committees of the respective investigational sites. During the long-term extension study, minimum data will be collected and SAE's will be reported to Roche and entered into the

Roche safety data base. Study MO29750 will be closed and an updated analysis performed once all patients have either withdrawn or enrolled in the extension study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Design Features

This Phase III study design is based on the hypothesis that, in advanced ALK-positive NSCLC patients who have failed prior platinum-based therapies and crizotinib, treatment with alectinib will prolong investigator-assessed PFS compared to treatment with pemetrexed or docetaxel. Its key secondary hypothesis is that treatment with alectinib will improve IRC-assessed C-ORR compared to pemetrexed and docetaxel in the same patient population. Results from this randomized prospective study will help regulatory agencies decide whether alectinib is an effective post-progression therapy in advanced ALK-positive NSCLC patients who have failed prior platinum-based therapies and crizotinib.

The open-label design is necessitated by the fact that alectinib is administered orally, whereas the comparator chemotherapies are administered intravenously. Furthermore, pemetrexed is normally administered over 10 minutes and docetaxel is administered over an hour. Blinding of treatments in this scenario would therefore place undue burden on both patients and investigators.

Patients will be randomized 2:1 into one of two treatment arms to receive either alectinib or chemotherapy (pemetrexed or docetaxel). To ensure comparability between treatment groups, patients will be randomized using the following stratification factors: ECOG PS (0/1 vs. 2); and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no). Enrollment caps will be used to ensure that 50% of randomized patients will have baseline CNS metastases and, in the comparator group, 50% of patients will use each type of chemotherapy.

3.3.2 Rationale for Study Population

Crizotinib is indicated in the EU as second-line therapy for advanced ALK-positive NSCLC after relapse on first-line chemotherapy (European Medicines Agency 2015), which is typically a platinum doublet chemotherapy. However, as it only provides a median of 7.7 months of PFS in this setting, it is vitally important to ascertain an optimal rescue therapy. The purpose of this study is to directly determine whether alectinib, an ALK-specific TKI, provides more clinical benefit than standard chemotherapy (pemetrexed or docetaxel) in this specific study population, i.e., in advanced ALK-positive NSCLC following relapse on platinum-based chemotherapy and crizotinib.

Efforts will be taken to ensure that at least 50% of patients enrolled have CNS metastases. Furthermore, the key secondary efficacy objective of the study is to determine C-ORR. This focus on CNS metastases reflects the fact that 46%–60% of

progressions in patients treated with crizotinib involve the CNS, i.e., that the CNS becomes a sanctuary site for ALK-positive NSCLC treated with crizotinib (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et al. 2015). Hence, in determining the efficacy of alectinib in this setting, a fully representative sample of patients must contain this difficult-to-treat class.

3.3.3 Rationale for Alectinib Dose and Schedule

Selection of the alectinib dose for the study is based on the clinical safety, efficacy and PK data observed in the pivotal Phase I/II studies, NP28761/AF-002JG and NP28673, and supportive nonclinical data for alectinib.

Phase I of Study NP28761 evaluated escalating doses of alectinib from 300 to 900 mg BID using a modified 3+3 design to determine the RP2D. The starting dose in Study NP28761 was the highest dosage evaluated in Study AF-001JP, 300 mg BID. Alectinib was generally well tolerated across the doses tested and was well tolerated in the study population. Dose escalation revealed two patients with DLTs at 900 mg; both patients resumed treatment at a reduced dose of 600 mg where no further DLTs were observed. These clinical safety data, together with PK data and available efficacy data from Phase I of Study NP28761 showing promising antitumor activity of alectinib 600 mg BID supported the selection of the 600 mg BID dosing regimen as the RP2D.

Phase II of Study NP28761 and Study NP28673 confirmed the selection of the 600 mg BID dosing regimen, as the primary efficacy endpoint was met, and the dosing regimen was generally well tolerated in the crizotinib-progressed patient population.

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

Thus, on the basis of nonclinical and clinical data, a dosing regimen of 600 mg BID of alectinib has been chosen as the clinical dose level for this crizotinib-progressed patient population.

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

3.3.4 Rationale for Control Group

In this comparative study, the control group will receive either pemetrexed or docetaxel. According to a recent ESMO consensus report, patients with ALK-positive NSCLC are recommended to receive a platinum-based chemotherapy in the first-line setting and crizotinib in the second-line setting (Besse et al. 2014). Following progression on second-line crizotinib, the ESMO guidelines then recommend third-line pemetrexed in patients with nonsquamous NSCLC. Pemetrexed may therefore be considered the standard therapeutic option in the third-line setting and will thus be used as one control agent in this trial.

In addition to pemetrexed, current ESMO guidelines recommend docetaxel following failure of first-line platinum-based doublets in general populations of advanced NSCLC patients (which are largely ALK-negative) (Reck et al. 2014). Consequently, since many practicing oncologists may view it as a standard option following failure of platinum-based therapies and crizotinib, docetaxel will be used as the other control agent in this trial.

3.3.5 Rationale for Efficacy 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 efficacy endpoint for this trial. PFS 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. The trial will test the hypothesis that alectinib will significantly improve PFS from 3 months—the currently expected value in advanced ALK-positive NSCLC patients who receive pemetrexed or docetaxel following failure of platinum-based therapies and crizotinib—to 7 months, which is considered a clinically significant improvement over the dismal norm. The total number of planned patients, i.e., 60 in the alectinib arm and 30 in the chemotherapy arm with at least 50 overall observed PFS events, will provide 80% power to detect a significant improvement in the primary endpoint from 3 months to 7 months (HR of 0.43) for a two-sided log-rank test at an alpha level of 0.05.

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 = 0.43) and study assessments that will allow 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).

If superiority for the PFS endpoints is concluded, subsequent hierarchical testing for the key secondary efficacy endpoint, CNS objective response rate (C-ORR) in patients with measurable CNS metastases at baseline, will be performed. In ALK-positive NSCLC, crizotinib has been shown to exhibit impaired control of CNS metastases relative to other sites of systemic disease, with 46%–60% of progressions in patients treated with crizotinib involving the CNS (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et al. 2015). Preliminary evidence of CNS benefit with alectinib has been observed in patients in the two ongoing Phase II studies (see Section 1.2 and Alectinib Investigator's Brochure for additional details). Thus, a direct assessment of the efficacy of alectinib in advanced ALK-positive patients who have failed on platinum-based therapies and crizotinib will have high clinical significance.

3.3.6 Rationale for Pharmacokinetics Assessments

To date, the pharmacokinetics of alectinib have been characterized in chemotherapy-failed, crizotinib-naïve 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. To better understand the pharmacokinetics of alectinib and to further characterize exposure-response relationships for alectinib, this study will seek to better understand, identify and characterize variables that may lead to potential changes in exposure of alectinib in patients with advanced ALK-positive NSCLC. Results from these analyses will enable a more robust understanding of alectinib pharmacokinetics, including the identification of potential sources of variability influencing alectinib pharmacokinetics and/or response to alectinib therapy, and will inform and confirm optimal use of alectinib.

3.3.7 Rationale for PRO 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. Therefore, this study will collect PRO data from patients at the time points described in the Schedule of Assessments (Appendix 1 and 2). The validated instruments used will include the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Core-30 (EORTC QLQ-C30), the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer-13 (EORTC QLQ--LC13 and the EuroQoL 5 Dimension 5 level (EQ-5D-5L) (Appendix 7). In addition, on an exploratory basis, this study will assess scores from two selected questions on the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Brain Neoplasm-20 (EORTC QLQ-BN20) (see Section 3.3.8). The scientific and clinical rationales for choosing these instruments are provided below and in the next section (Section 3.3.8).

3.3.7.1 EORTC QLQ-C30 and QLQ-LC13

The EORTC Study Group on Quality of Life has developed a modular system for assessing the quality of life of cancer patients in clinical trials that is composed of two basic elements: 1) a core quality of life questionnaire, the EORTC QLQ-C30, covering general aspects of health-related quality of life; and 2) additional disease- or treatment-specific questionnaire modules (Bergman et al. 1994). The disease-specific module focusing on lung cancer, the EORTC QLQ-LC13, will be used in this study. Together, these two instruments can provide assessments of patient-reported quality of life related to cancer generally and lung cancer specifically.

Pain (chest and arm/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 (10 points) improvements 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 functioning, except for the domain measuring cognitive functioning, 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).

3.3.7.2 EQ-5D-5L

The EQ-5D-5L questionnaire will be used in this study to assess patients' general health status, as well as to assist in generating utility scores for use in pharmacoeconomic models for reimbursement. The EQ-5D-5L is a generic preference-based health utility measure that provides a single index value for health status. The instrument consists of two parts. The first part, health-state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second part, consisting of a visual analog scale, will not be used in this study.

The EQ-5D-5L was used previously in the PROFILE 1007 study, which compared crizotinib with pemetrexed or docetaxel in ALK-positive NSCLC patients who had progressed on a prior platinum-based chemotherapy regimen (Blackhall et al. 2014), #0}. In the PROFILE 1007 study population, the overall mean health utility index scores (95% CI) on treatment were significantly greater ($p < 0.05$) for crizotinib (0.82 [0.79−0.85]) than for chemotherapy (0.73 [0.70−0.77]; 0.74 [0.70−0.79] for pemetrexed and 0.66 [0.58−0.74] for docetaxel). Within groups, a significant overall improvement from baseline in general health status (EQ-5D VAS) was observed for crizotinib compared with a significant overall deterioration for chemotherapy. Significant overall deterioration from baseline was also observed for the pemetrexed and docetaxel subgroups. A greater overall improvement in general health status from baseline was observed in the crizotinib arm compared with either pemetrexed (estimated difference

[95% CI]: 8.74 [4.47, 13]; p < 0.001) or docetaxel (estimated difference [95% CI]: 14.50 [7.82, 21.17]; p < 0.001)

3.3.8 Rationale for Exploratory Assessments

3.3.8.1 Selected Questions From the EORTC QLQ-BN20

Approximately 46%–60% of progressions in patients treated with crizotinib involve the CNS (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012; Costa et al. 2015; Gainor et al. 2015). In Phase I/II clinical trials, alectinib exhibited significant activity against CNS metastases (see Section 1.2). Therefore, since significant morbidity is associated with CNS metastases due to the CNS involvement and to the standard forms of treatment (corticosteroids, surgery, and radiation), it becomes of real interest to determine whether the improvement in objective responses with alectinib translates into improvements in CNS PROs.

To address this issue, all patients in the study will complete three questions extracted from the EORTC QLQ-BN20 questionnaire, a QoL instrument specific to brain neoplasms, at the time points indicated in the Schedule of Assessments (Appendix 1 and 2). The three questions are as follows:

1. Do you have headaches?
2. Do you have problems with coordination / balance?
3. Did you have trouble communicating your thoughts?

Since the EORTC QLQ-LC13 will be used to assess the impact of lung cancer on patient quality of life in the two treatment groups, the complete EORTC QLQ-BN20 cannot also be included among the assessments, as the two instruments invalidate each other. Thus, to directly assess the quality-of-life impact of brain metastases on patients in the trial, which is of significant interest given that the CNS can be a sanctuary for crizotinib-resistance, the above three questions were chosen from the EORTC QLQ-BN20. These questions were selected based on information from literature searches and were agreed upon by the MO29750 Study Committee. Because this approach has not been validated in NSCLC patients with CNS metastases, the proposed analyses will of necessity be conducted in an exploratory fashion.

3.3.8.2 Biomarkers

There are several molecular mechanisms of resistance to crizotinib 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 like 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, optional 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 may be used: 1) targeted sequencing of a panel of genes known to be

involved in cancer, and/or 2) unbiased genomic sequencing. Analyses aiming to further characterize the molecular tumor microenvironment may be added.

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 polymerase chain reaction and sequencing. Plasma samples will be collected before treatment and at certain time points during treatment to monitor mutations in ALK and other genes. Similar analyses will be performed in tumor tissue and will be correlated with results from the analysis of plasma samples.

For exploratory assessments, other methods besides IHC and FISH will be used to determine ALK positivity (e.g., reverse transcription polymerase chain reaction, nucleic acids sequencing). Information from plasma ALK assays will be used to investigate the use of circulating tumor nucleic acids for diagnostic purposes.

A rationale for the RCR biomarker samples is provided in Section 4.5.11.1.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression, as determined using RECIST v1.1, or death from any cause, whichever occurs first. Similar definitions of PFS will be used by the investigator (primary endpoint) and the IRC. Patients without an event will be censored at the last tumor assessment. Patients with no post-baseline assessments will be censored at the date of randomization. PFS for patients with CNS metastasis at baseline will be defined in a similar way, taking into account all lesions in the body
- Overall response rate (ORR) is defined as the percentage of patients who attain complete response (CR) or partial response (PR), as determined using RECIST v1.1. Similar definitions of ORR will be used by the investigator and the IRC. Patients without any post-baseline assessments will be regarded as non-responders. ORR for patients with CNS metastasis at baseline (C-ORR) will be defined in a similar way for lesions in the CNS. (It should be noted that patients with non-measurable disease can achieve only CR and not PR)
- Disease control rate (DCR) is defined as the percentage of patients who attain complete response (CR), partial response (PR) or stable disease (SD) of at least 5 weeks, as determined using RECIST v1.1. Similar definitions of DCR will be used by the investigator and the IRC. Patients without any post-baseline assessments will be regarded as non-responders. CNS DCR (C-DCR) for patients with CNS metastasis at baseline will be defined in a similar way for lesions in the CNS. (It should be noted that patients with non-measurable disease can achieve only CR or SD and not PR).

- Duration of response (DOR) 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. Similar definitions of DOR will be used by the investigator and the IRC. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement. DOR for patients with CNS metastasis at baseline (C-DOR) will be defined in a similar way for lesions in the CNS, taking into account all lesions in the body
- Overall survival (OS) 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
- Time to CNS progression is defined as the time from randomization to the first documented disease progression in the CNS

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Serious and non-serious AEs
- Safety laboratory tests
- Vital signs
- ECG

Incidence, nature and severity of all adverse events will be graded according to NCI CTCAE v.4.0

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE 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

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 AE.

3.4.3 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

- 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, as appropriate. The potential influence of covariates that contribute significantly to the between-patient differences in PK parameters of alectinib will also be explored and quantified, as appropriate

Additional PK parameters may be calculated as deemed appropriate.

3.4.4 Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows (see Appendix 7):

- EORTC QLQ-C30 and EORTC QLQ-LC13 scores to determine the impact of alectinib compared with chemotherapy in the overall patient population, as well as in patients with CNS metastases at baseline, as measured by time to deterioration (TTD) in patient-reported lung cancer symptoms (e.g., cough, chest pain (single item) dyspnea (single item and multi-item scales], pain in chest, pain in arm/shoulder and fatigue)as well as measured by a composite of three symptoms (cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain)The EORTC QLQ-C30 and EORTC QLQ-LC13 scores to measure PROs of HRQoL, patient functioning and side effects of therapy compared between patients treated with alectinib and those treated with chemotherapy. The comparison will be done for the overall patient population, as well as in patients with CNS metastases at baseline

- The EuroQoL 5 Dimension (EQ-5D-5L) questionnaire score will be used for the overall patient population, as well as for patients with CNS metastases at baseline, to assess patients' health status and generate utility scores for use in pharmacoeconomic models for reimbursement purposes only

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows (additional exploratory parameters may be assessed as deemed appropriate):

- Scores from three specific questions extracted from the EORTC QLQ-BN20 questionnaire, a QoL instrument specific to brain neoplasms. The three questions are as follows: "Do you have headaches?"; "Do you have problems with coordination/balance?"; and "Did you have trouble communicating your thoughts?" Each of the three questions will be scored on a 4-point scale (1, Not at all; 2, A little; 3, Quite a bit; 4, Very much), which will subsequently be linearly transformed to a 0–100-point scale
- Need and dosing for corticosteroids in case of CNS metastasis
- To assess exploratory biomarkers relevant in NSCLC biology and alectinib mechanism of action (including but not limited to ALK genetic alterations) and their association with disease status, clinical outcome, efficacy and safety
- To investigate molecular mechanisms of resistance to ALK inhibitors

- To develop biomarker or diagnostic assays to detect ALK mutations/fusions in plasma/tumor and to establish performance characteristics of these assays

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. 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. ALK positivity must have been determined by a validated FISH test (recommended probe, Vysis ALK Break-Apart Probe) or a validated IHC test (recommended antibody, clone D5F3)
2. Patient had received two prior systemic lines of therapy for advanced or metastatic disease (stage IIIB or IV), which must have included one line of platinum-based chemotherapy and one line of crizotinib (progression on or intolerability to crizotinib)
3. Prior CNS or leptomeningeal metastases allowed if asymptomatic. 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 and local treatment is indicated, patients need to complete the local treatment (surgery or radiotherapy). In all cases, radiation treatment must be completed at least 14 days before enrollment and patients must be clinically stable
4. Patients with symptomatic CNS metastases for whom radiotherapy is not an option will be allowed to participate in this study
5. Measurable disease (by RECIST v1.1) prior to the administration of study treatment (Appendix 5)
6. Age ≥18 years old
7. Life expectancy of at least 12 weeks
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 (Appendix 6)
9. Adequate hematologic function:
   - Platelet count ≥ 100 $x10^9$/L
   - Absolute neutrophil count (ANC) ≥ 1500 cells/µL
   - Hemoglobin ≥ 9.0 g/dL
10. 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 (Appendix 8)
11. 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

12. For all females of childbearing potential, a negative pregnancy test must be obtained prior to randomization and within 3 days before starting study treatment
13. 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, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices
14. For men: agreement to remain abstinent or use a contraceptive method that results 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 (in addition, refer to the local label for pemetrexed and docetaxel). 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
15. Able and willing to provide written informed consent prior to performing any study related procedures and to comply with the study protocol, including being willing and able to use the electronic patient-reported outcome device

4.1.2 Exclusion Criteria

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

1. 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 or in situ carcinoma of the cervix)
2. Patients who have received any previous ALK inhibitor other than crizotinib
3. Any GI disorder that may affect absorption of oral medications, such as mal-absorption syndrome or status post-major bowel resection
4. Liver disease characterized by:
   - Alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) > 2.5 x upper limit of normal (ULN) (> 5 x ULN for patients with concurrent liver metastases) 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 or bleeding from esophageal varices

     OR
   - Acute viral or active autoimmune, alcoholic or other types of acute hepatitis

5. NCI-CTCAE v4.0 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication
6. Any exclusion criteria based on local label of pemetrexed or docetaxel
7. History of organ transplant
8. Patients with baseline QTc > 470 ms or symptomatic bradycardia
9. Administration of strong/potent CYP3A4 inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib or docetaxel
10. History of hypersensitivity to any of the additives in the alectinib drug formulation (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, sodium lauryl sulfate [SLS] or magnesium stearate)
11. History of severe hypersensitivity reaction to pemetrexed or docetaxel or any known excipients of these drugs
12. Patients not eligible for treatment with docetaxel or pemetrexed according to the local labels
13. Pregnant or lactating women
14. Known HIV positivity or AIDS-related illness
15. Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study
16. 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 3.3. At least 90 and a maximum of 120 patients (as per previous protocol version) will be randomly assigned in a 2:1 allocation ratio to the two treatment arms) via a block-stratified randomization procedure and over a planned recruitment period of approximately 12 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) and CNS metastases at baseline (yes vs. no). In addition, patients with baseline CNS metastasis will be stratified by history of radiotherapy (yes vs. no).

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

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Alectinib

Alectinib 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.

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

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

4.3.1.2 Pemetrexed

For information on the formulation, packaging and handling of pemetrexed (Alimta®), refer to the local prescribing information. Pemetrexed should only be used for treatment of patients non-squamous NSCLC histology in this study.

4.3.1.3 Docetaxel

For information on the formulation, packaging and handling of docetaxel (Taxotere®), refer to the local prescribing information.

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. 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. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death.

If a dose is missed, patients can make up that dose unless the next dose is due within 6 hours. If the time is less 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 5.1.2.1.

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

4.3.2.2 Pemetrexed

Pemetrexed will be administered according to the locally approved label. The starting dose of pemetrexed will be 500 mg/m^2 q3w. The first dose of the study drug should be administered as soon as possible after randomization starting with the required premedication, preferably within 24 hours, and no later than 48 hours after randomization. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death.

Premedication for Pemetrexed

All patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity. To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of and the day after pemetrexed administration. The premedication doses administered should be in compliance with the local label.

Folic Acid

Patients will obtain folic acid in one of the following forms, with preference in order from Option 1 to Option 3:

1. 350 to 600 µg folic acid
2. A multivitamin containing folic acid in the range of 350 to 600 µg (acceptable only if Option 1 is not available)
3. A dose of folic acid between 600 and 1000 µg (acceptable only if neither Option 1 nor Option 2 is available)

For purposes of this trial, all patients should take oral folic acid daily according to local label, starting the week preceding the first infusion of pemetrexed and continuing daily until 21 days after discontinuation of pemetrexed.

Vitamin B_{12}

Vitamin B_{12} will be prescribed by the investigator and administered as a 1000 µg intramuscular injection. A vitamin B_{12} injection must be administered according to local practice for pemetrexed administration, starting the week preceding the first pemetrexed infusion and should be repeated approximately every 9 weeks. Equivalent subcutaneous administration is permitted.

Dexamethasone

Dexamethasone 4 mg (or an equivalent corticosteroid and dose) will be given orally twice per day, the day before, the day of and the day after each dose of pemetrexed.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.2.

4.3.2.3 Docetaxel

Docetaxel will be administered according to the locally approved label. The first dose of docetaxel should be administered as soon as possible after randomization starting with the required premedication, preferably within 24 hours, and no later than 48 hours after randomization at a starting dose of 75 mg/m^2 q3w. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent or death.

Vital signs will be collected for docetaxel infusions according to Section 4.5.5. For further details, see the local prescribing information for docetaxel.

All patients randomized to receive docetaxel should be premedicated with corticosteroids according to local practice (e.g., oral dexamethasone at 16 mg per day [8 mg twice daily] for 3 days, starting a day prior to administration) to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions.

Anti-emetic prophylaxis may be administered at the treating physician's discretion according to local practice.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.3.

For further details, see the local prescribing information for docetaxel.

4.3.3 Investigational Medicinal Product Accountability

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or 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 Continued Access to Alectinib

The Sponsor will offer continued 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 completing 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 completing 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 advanced ALK-positive NSCLC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for advanced ALK-positive NSCLC
- Provision of study drug is not permitted under the laws and regulations of the country in which the patient is being treated

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

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from screening to the study completion/discontinuation visit. All such 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.

4.4.1.1 Alectinib

Caution should be exercised when the following treatments or procedures are co-administered or performed during treatment with alectinib:

- For medications that are substrates of P-gp transporter or breast cancer resistance protein transporter, the investigator should use caution and monitoring when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration cannot be avoided, it is recommended that signs for toxicity are carefully monitored (see Appendix 4)
- Acetaminophen up to 2 g/day
- Local therapy (e.g., stereotactic radiotherapy or surgery) may be given to patients who progress on alectinib with required treatment interruption as per section 4.4.2.1 prior to continuing treatment beyond progression

4.4.1.2 Pemetrexed

For full details regarding permitted therapies with pemetrexed treatment, refer to the current version of the local product label.

4.4.1.3 Docetaxel

For full details regarding permitted therapies with pemetrexed treatment, refer to the current version of the local product label.

4.4.2 Prohibited Therapy

4.4.2.1 Alectinib

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 alectinib, unless otherwise specified below.

- 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 4).
- 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 4)
- 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 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 ≤ Grade 1

- Additional investigational drug (except for during the follow-up period)

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

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

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

4.4.2.2 Pemetrexed

For full details regarding prohibited therapies with pemetrexed treatment, refer to the current version of the local product label.

4.4.2.3 Docetaxel

Docetaxel is a CYP3A4 substrate. Patients randomized to receive docetaxel must avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors.

In addition, concomitant treatment with CYP3A4 inducers may decrease plasma concentrations of docetaxel. Therefore, concomitant medications that are CYP3A4 inducers should be used with caution.

Granulocyte colony-stimulating factor treatment is permitted for patients in the docetaxel arm. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), EORTC, and European Society of Medical Oncology (ESMO) guidelines; namely, in patients who are ≥ 60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

Anti-emetics, anti-allergic measures and other treatments for concomitant docetaxel toxicities may be used at the discretion of the investigator, taking into account precautions from local prescribing information.

See the local prescribing information for docetaxel for all boxed warnings and contraindications.

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 alectinib because it is a potent CYP3A inhibitor and may increase plasma concentration of alectinib or docetaxel.

For full details regarding prohibited therapies with pemetrexed and docetaxel treatment, refer to the current version of the local product label.

4.5 STUDY ASSESSMENTS

All study assessments will be carried out at the time points described in the Schedule of Assessments (Appendix 1 and 2) and the Schedule of Pharmacokinetic Assessments (Appendix 3).

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 screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), 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 Medication Use for Control of Pain

Type, dose and frequency of medications used for the control of pain will be collected in this study

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.

4.5.5 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressures while the patient is in a seated position. Other vital signs (e.g., respiratory rate, oxygen saturation and temperature) may be collected at the discretion of the investigator if clinically warranted. Only abnormal findings will be recorded in the eCRF.

4.5.6 ECOG Performance Status

ECOG PS will be measured using the ECOG Performance Status Scale (see Appendix 6). It is recommended, where possible, that a patient's PS be assessed by the same person throughout the study.

4.5.7 Tumor and Response Evaluations

Disease burden must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, computed tomography (CT) scans and other modalities (e.g., MRI, brain scans), using RECIST v1.1 (Appendix 5). 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 (Appendix 5).

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

CT/MRI scans of chest and abdomen and MRI scans of the brain should be performed for all patients as described in Schedule of Assessments (Appendix 1 and 2). CT/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 ≤ 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 if the soft tissue component and to meet the definition of measurability and so should be followed by cross-sectional imaging.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

4.5.8.1 Laboratory Assessments

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

- **Hematology** (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells])
- **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 8]; CPK; gamma-glutamyl transferase (GGT); calcium; total and direct bilirubin; total protein; albumin; ALT; AST; alkaline phosphatase [ALP]; phosphorus; Urinalysis (dipstick: mandatory at baseline; additional urinalyses if clinically indicated)
- **Pregnancy test (baseline)**. 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. Results must be available prior to randomization. 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 Biomarker Assessments

The following samples will be sent to the Sponsor or a designee for analysis:

- From patients who consent to undergo optional biopsy pre-treatment or at the time of disease progression, biopsies (formalin-fixed, paraffin-embedded) will be taken for exploratory research as defined in the Schedule of Assessments (Appendix 1 and 2)
- Plasma (10 ml) obtained baseline, week 6, week 12 and every 6 weeks until disease progression, along with other routine laboratory or PK collection

- Mandatory submission of residual tumor tissue (an FFPE tissue block, or 10–15 unstained slides) from an archived tumor sample collected prior to exposure to crizotinib and preferably from primary tissue

The goal of tumor collections will be to sequence ALK gene and other genes relevant in NSCLC biology or the tumor microenvironment to determine molecular mechanisms of resistance to ALK inhibitors.

These specimens will be used for research purposes to identify biomarkers useful for predicting and monitoring response to alectinib treatment, identifying biomarkers useful for predicting and monitoring alectinib safety, assessing pharmacodynamic effects of alectinib treatment and investigating mechanism of therapy resistance. Additional markers may be measured in case a strong scientific rationale for these analyses develops. Additional analyses may include but are not limited to immunohistochemistry and/or gene expression studies.

Unless a patient gives specific consent for leftover specimens to be stored for optional exploratory research (see Section 4.5.11), these specimens will be destroyed within 5 years after the date of final closure of the clinical database, with the following exception:

- Archival tumor blocks (mandatory) will be returned at the latest by the end of the study, or earlier if requested by the site

Other residual tissue material (slides, extracts, etc.) will be destroyed within 5 years after the date of final closure of the clinical database.

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

4.5.8.3 Samples for Pharmacokinetic Assessments

PK samples will be collected in all patients on alectinib treatment as indicated in Appendix 1, 2 and 3 for the analysis of alectinib and its major metabolite(s) (RO5468924, and/or others, if applicable, appropriate and 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.

PK samples will be analyzed as needed. 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.

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 Clinical Study Report 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.

4.5.9 Electrocardiograms

An ECG will be recorded at specified timepoints as outlined in the Schedule of Assessments (Appendix 1 and 2). 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. ECG 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.

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. Guidance for abnormal ECG results (QT prolongation) is provided in Table 6.

4.5.10 Patient-Reported Outcomes

PROs (EORTC QLQ-C30, QLQ-L13, EQ-5D-5L and three questions from the EORTC QLQ-BN20) 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 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. The ePRO device and instructions for completing the PRO questionnaires 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.

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 this optional research. RCR 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 Institutional Review Board or Ethics Committee (IRB/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. Remaining tissue and plasma samples from study-related or non-study-related procedures that are performed during the study may also be stored for RCR purposes.

For all samples, dates 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.

RCR 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 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.

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 or not 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 RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO29750 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 MO29750.

4.5.11.7 Monitoring and Oversight

RCR 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. However, patients will not be followed for any reason after consent 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's judgment
- NSCLC disease progression, although treatment beyond PD will be allowed at the discretion of the patient and the investigator

See guidelines for managing adverse events and for comprehensive guidance on study drug discontinuation in Section 5.1.2.

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 and 2).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment 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 on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). An iDMC has also been incorporated into the trial design to periodically review aggregate safety data (see the iDMC Charter for a detailed monitoring plan).

5.1.1 Risks Related to Study Drugs

5.1.1.1 Adverse Events Relating to ALK Inhibitors and Alectinib Data

Events described in this section (Section 5.1.1.1) will be closely monitored and represent selected AEs for this study.

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

Interstitial Lung Disease

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

See Section 5.1.2.1 for management and follow-up.

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 upper limit of normal (ULN) and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred with uncommon frequency in patients treated in alectinib clinical trials.

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

See Section 5.1.2.1 for management and follow-up.

Anemia

Hematologic 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. Findings were at or close to clinically relevant exposures. Hematologic adverse effects such as anemia, thrombocytopenia, bleeding and neutropenia have been observed with most TKIs, including ALK inhibitor crizotinib.

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

See Section 5.1.2.1 for management and follow-up.

Gastrointestinal Disorders

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

SLS (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 AEs 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.

See Section 5.1.2.1 for management and follow-up.

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 5.1.2.1 for management and follow-up.

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 5.1.2.1 for management and follow-up.

Edema

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

See Section 5.1.2.1 for management and follow-up.

Bradycardia

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 to likely be caused by vasodilatation induced by L type Ca2+ channel inhibition.

Events of bradycardia have been reported with alectinib. Heart rate data evaluation (based on ECG and pulse measurements) from the pivotal 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.

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 5.1.2.1 for management and follow-up.

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 5.1.2.1 for management and follow-up.

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 AEs 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 5.1.2.1 for management and follow-up and Table 6 for guidelines for managing AEs.

5.1.1.2 Risks Associated With Pemetrexed

For full details regarding warnings and precaution relating to pemetrexed treatment, refer to the current version of the local product label.

Myelosuppression

Pemetrexed can suppress bone marrow function as manifested by neutropenia, thrombocytopenia and anemia (or pancytopenia). Myelosuppression is usually the dose-limiting toxicity (DLT).

Skin Reactions

Skin reactions, such as rash, desquamation, alopecia and pruritus, have been reported in pemetrexed-treated patients not pre-treated with a corticosteroid.

Renal Insufficiency

An insufficient number of patients has been studied with CrCl < 45 mL/min. Therefore, the use of pemetrexed in patients with CrCl < 45 mL/min is not recommended. Patients with **mild to moderate renal insufficiency** (CrCl from 45 to 79 mL/min) should avoid taking NSAIDs such as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration. All patients eligible for pemetrexed treatment should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration.

Serious **renal events**, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in

whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes.

The effect of third-space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third-space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Cardiovascular Events

Serious cardiovascular events, including myocardial infarction and cerebrovascular events have been uncommonly reported during clinical studies with pemetrexed, usually when given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.

Immunosuppression

An immunosuppressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever which is contraindicated) is not recommended.

5.1.1.3 Risks Associated With Docetaxel

For full details regarding warnings and precaution relating to docetaxel treatment, refer to the current version of the local product label.

Risks associated with docetaxel are provided in Table 6.

Table 6 Side Effects Associated With Docetaxel

Most Common Side Effects	Less Common Side Effects (but may be Severe or Life Threatening)
• Myelosuppression ± infection or bleeding (may be severe)	• Secondary malignancy/leukemia
• Hypersensitivity reaction (may be severe)	• Cardiotoxicity, arrhythmia
• Fluid retention (may be severe)	• Pneumonitis
• Neuropathy (may be severe)	• Gastrointestinal obstruction, perforation, hemorrhage
• Cutaneous Effects (including nails, may be severe)	• Venous thromboembolism
• Alopecia	• Arterial thromboembolism
• Gastrointestinal (nausea, vomiting, stomatitis, diarrhea)	• Disseminated intravascular coagulation
• Fatigue	• Seizures
• Musculoskeletal pain	• Hepatotoxicity
• Lacrimation/tear duct obstruction	

Due to the ethanol (also known as alcohol) content in the docetaxel formulation, some patients may experience intoxication during and after treatment. Refer also to the warnings and precautions of the local prescribing information for docetaxel. Other specific instructions can be found in Sections 4.4.1.3, 4.4.2.3 and 5.1.2.3.

5.1.2 Management of Specific Adverse Events

5.1.2.1 Management of Specific Adverse Events with Alectinib

Management of symptomatic adverse events may require temporary interruption, dose reduction, or treatment discontinuation of alectinib. General dose modification advice for alectinib is provided in Table 7.

Table 7 Dose Reduction Schedule

Dose reduction schedule	Dose level
Starting Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Alectinib treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose reduction or if dose interruption exceeds 21 days.

Guidelines for managing specific adverse events with alectinib are provided in Table 8.

Table 8 Guidelines for Management of Specific Adverse Events with Alectinib

Event	Action to Be Taken
Interstitial lung disease	• Patients should be monitored for pulmonary symptoms indicative of pneumonitis • Study drug should be permanently discontinued in patients diagnosed with interstitial lung disease
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.4 and 5.3,5.7 • If ALT or AST $> 3 \times$ baseline, repeat testing of ALT, AST, ALP and total bilirubin within 48–72 hours, with inquiry about symptoms. If upon repeat testing the transaminases remain $> 3 \times$ baseline, but are not $> 5 \times$ baseline or not accompanied with bilirubin increases or do not match any other rule for permanent discontinuation, then monitoring can continue as per investigator judgment, and dose modification is not necessary • At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible. • 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
Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea)	The events are expected to be minimized by taking the study drug with meal. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and not tolerable, treatment with study drug should be temporarily interrupted until recovery to Grade 1 or lower.
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 5 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sun screen and lip balm of at least SPF > 50 to help protect against potential sunburn.

Event	Action to Be Taken
Vision disorders	Investigators should consider referring the patients for an ophthalmological evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity.
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines
Abnormal kidney function AEs	Kidney function laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.5 • 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 If, at the repeat test, the eGFR decrease is still $>50\%$ of the baseline visit value, the treatment with alectinib should be interrupted • Alectinib treatment may be resumed with caution if the eGFR value has increased to approximately the baseline visit value

Event	Action to Be Taken
Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.5 • 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. CPK levels should be assessed in patients reporting these symptoms • At the first occurrence of any asymptomatic CPK values ($>10\times$ULN, symptomatic CPK $>5\times$ULN, or in the presence of severe muscular symptoms with CPK $>$ ULN but $\leq 5\times$ULN) at any time during the study treatment, the patient requires monitoring of the CPK values until they are normalized to pre-treatment levels or a reasonable explanation for the CPK elevation and the symptoms is established
Other AEs (including bradycardia, anemia and CPK elevation) or laboratory abnormalities:	• Grade 3 or 4: Temporarily interrupt alectinib for a maximum of 21 days 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 (450 mg 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 (300 mg BID) Third episode: Permanently discontinue alectinib • Grade 2 (except any symptoms and signs that can be corrected with supportive care): Temporarily interrupt alectinib and resume if recovering to Grade ≤ 1 or baseline if clinically indicated First episode: If improvement to Grade ≤ 1 or baseline within 10 days, continue same dose of alectinib. If improvement occurs after 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID when resuming treatment (450 mg BID) Second episode: If improvement to Grade ≤ 1 or baseline within 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID (450 mg BID or 300 mg BID if after first episode dose was reduced to 450 mg BID). Third episode: Permanently discontinue alectinib. • Grade 1: no action required

eGFR = estimated glomerular filtration rate.

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.

5.1.2.2 Management of Specific Adverse Events With Pemetrexed

For full details regarding warnings and precaution relating to pemetrexed treatment, refer to the current version of the local product label.

Myelosuppression

Patients should be monitored for myelosuppression during treatment and pemetrexed should not be given to patients until ANC returns to ≥ 1500 cells/mm^3 and platelet count returns to ≥ 100,000 cells/mm^3. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-hematological toxicity seen from the previous cycle.

Less toxicity and reduction in grade 3/4 hematological and non-hematological toxicities such as neutropenia, febrile neutropenia and infection with grade 3/4 neutropenia were reported when pre-treatment with folic acid and vitamin B_{12} was administered. Therefore all patients treated with pemetrexed must be instructed to take folic acid and vitamin B_{12} as a prophylactic measure to reduce treatment-related toxicity.

Skin Reactions

Pre-therapy with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions. A corticosteroid should be given the day prior to, on the day of and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice per day, the day before, the day of, and the day after each dose of pemetrexed.

Renal Insufficiency

An insufficient number of patients has been studied with CrCl < 45 mL/min. Therefore, the use of pemetrexed in patients with CrCl < 45 mL/min is not recommended. Patients with **mild to moderate renal insufficiency** (CrCl from 45 to 79 mL/min) should avoid taking NSAIDs such as ibuprofen, and aspirin (> 1.3 g daily) for 2 days before, on the day of, and 2 days following pemetrexed administration. All patients eligible for pemetrexed treatment should avoid taking NSAIDs with long elimination half-lives for at least 5 days prior to, on the day, and at least 2 days following pemetrexed administration.

Serious **renal events**, including acute renal failure, have been reported with pemetrexed alone or in association with other chemotherapeutic agents. Many of the patients in whom these occurred had underlying risk factors for the development of renal events including dehydration or pre-existing hypertension or diabetes.

The effect of third-space fluid, such as pleural effusion or ascites, on pemetrexed is unknown. In patients with clinically significant third-space fluid, consideration should be given to draining the effusion prior to pemetrexed administration.

Due to the gastrointestinal toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate antiemetic treatment and appropriate hydration prior to and/or after receiving treatment.

Immunosuppression

An immunosuppressed status is common in cancer patients. As a result, concomitant use of live attenuated vaccines (except yellow fever which is contraindicated) is not recommended.

5.1.2.3 Management of Specific Adverse Events With Docetaxel

Guidelines for docetaxel dose modifications to manage general toxicities are shown in Table 9. Guidelines for the management of hepatotoxicity for docetaxel-treated patients are shown in Table 10. Guidelines for the management of edema for docetaxel-treated patients are shown in Table 11. Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions or other Grade 3/4 nonhematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. Patients who develop Grade ≥ 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Table 9 Guidelines for Management of Specific Docetaxel-Related Adverse Events

Adverse Event (Worst Grade in Previous Cycle)	Action to be Taken
Febrile neutropenia/Grade 4 AGC ≥ 7 days	Hold docetaxel until symptoms resolve [a] Reduce docetaxel to 75% of previous dose (e.g., from 75 mg/m^2 to 55 mg/m^2)
Grade 3 skin/neuropathy/major organ/ non-hematologic toxicity	Hold docetaxel until symptoms resolve Reduce docetaxel to 75% of previous dose
Grade 4 skin/neuropathy/major organ/ non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction	Discontinue docetaxel treatment

AGC = absolute granulocyte count.

a. Do not repeat until AGC ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L and toxicity ≤ Grade 2.

Table 10 Guidelines for Management of Hepatotoxicity in Docetaxel-Treated Patients

	AST/ALT		ALP		Bilirubin	Docetaxel Dose
Mild to moderate	> 1.5 × ULN	AND	2.5 × ULN			75%
Severe	> 3.5 × ULN	AND	> 6 × ULN	OR	> ULN	Do not treat. Discontinue if treatment already started.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Other Specific Docetaxel Toxicities Not Requiring Dose Adjustment

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm or, very rarely, fatal anaphylaxis have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required.

Severe fluid retention has also been reported following docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each docetaxel infusion to reduce the incidence and severity of fluid retention (see Section 4.3.2.3). Patients with preexisting effusions should be closely monitored from the first dose for the possible exacerbation of the effusions. See Table 10 for the management of edema.

Table 11 Guidelines for the Management of Edema in Docetaxel-Treated Patients

Edema	Severity	Effusion
Asymptomatic	Mild, Grade 1	Asymptomatic, no intervention needed
Symptomatic	Moderate, Grade 2	Symptomatic, may require intervention
Symptomatic, resulting in interruption of treatment	Severe, Grade 3	Symptomatic, urgent intervention required

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 subject 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 or not 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), except as described in Section 5.3.5.10
- 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 5.3.5.11)

- 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 National Cancer Institute Common Terminology Criteria for Adverse Events (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 include 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 5.3.5.7)
- 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 prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 12 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 12 Adverse Event Severity Grading Scale for Events Not Specifically Listed in 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: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[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 oneself, 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 or not 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/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 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), 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.

5.3.5.3 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.

5.3.5.4 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.

5.3.5.5 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 adverse events.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ 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 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 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 (as defined by Hy's law). 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 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

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

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

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Non-Small Cell Lung Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 criteria (Appendix 5). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of 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.

5.3.5.11 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 a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- 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

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

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

5.3.5.13 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.

5.3.5.14 Adverse Events in Individuals Not Enrolled in the Study

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical 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 (see Section 5.4.2 for further details)
- Non-serious adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week.

Toll-free numbers for the Help Desk as well as Medical Monitor contact information will be distributed to all 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form 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 to immediately inform the investigator if they become pregnant during the study or within 3 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. 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.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), 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.

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 (in addition, refer to the local label for pemetrexed and docetaxel). A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. 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 Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to

follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

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

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

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

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

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

- Alectinib Investigator's Brochure
- Local prescribing information for pemetrexed and docetaxel

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

6.1 DETERMINATION OF SAMPLE SIZE

The sample size estimation was performed using EAST Software Version 6.0 based on the statistical hypotheses in Section 6.4.

Table 13 Summary of Determination of Sample Size [a]

Primary endpoint	Median Time to PFS (Chemo vs. Alectinib) months/HR	Number of Patients/Events	Number of Patients Per Treatment arm (Chemo vs Alectinib)
PFS	3 vs. 7/0.43	90/50	30 vs. 60
Key Secondary endpoint	**Response (Chemo vs. Alectinib)**	**Number of Patients**	
C-ORR [b]	15% vs. 55%	24	8 vs. 16

a. 80% power, two sided alpha test at 0.05; 2:1 randomization.
b. Patients with measurable CNS metastases at baseline, 70% power, one-sided test at 0.05.

Assuming an accrual period of 12 months and a primary analysis with at least 50 PFS events planned approximately after 13 months, a sample size of 90 patients (60 patients in the experimental arm [alectinib] and 30 patients in the control arm [chemotherapy]) with at least 50 PFS events will provide 80% power to detect a significant improvement in the median time of the primary endpoint from 3 to 7 months (i.e., HR of 0.43), based on a two-sided log-rank test at an alpha level of 0.05. In the pivotal Profile 1007 trial (Shaw et al. 2013), median PFS in the chemotherapy arm among 174 patients previously treated with one platinum-based chemotherapy regimen and treated in second line with either pemetrexed or docetaxel was 3 months (95% CI, 2.6–4.3). Hence, a median PFS of 3 months for the chemotherapy arm (control arm) has been assumed.

The objective response (Shaw et al. 2013) was reported in the chemotherapy group as 20% (95% CI, 14%–26%). Also, we expect that at least 25% of patients with measurable CNS metastases at baseline will be randomized in 2 treatment arms in this study. Approximately 24 patients with measurable CNS metastases at baseline

(8 patients in control and 16 patients in experimental arm) will provide power of 70% (one-sided 5% alpha test) to detect clinically meaningful difference in C-ORR of 40%, assuming C-ORR in control arm of 15%.

If superiority for the PFS endpoints is concluded, subsequent hierarchical testing for the key secondary endpoint, C-ORR in patients with measurable CNS metastases at baseline, will be performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

All randomized patients will be summarized by treatment arms, country and investigators. Major protocol violations will be summarized by frequency tables.

Median follow up on treatment and study will be summarized and estimates with corresponding 95% confidence interval (CI) provided using the Kaplan-Meier approach.

Patients who cross over from chemotherapy to alectinib will be censored at the time of cross-over (additional censoring rules will be provided in the SAP).

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Formal statistical hypotheses for the primary endpoint is in Section 6.4.

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, maximum and 25th–75th quartiles. 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 subsequent anti-cancer therapy by treatment arms. Previous and concurrent diseases and medications will also be summarized.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The main primary endpoint is PFS, as defined in Section 3.4.1.

The main efficacy analysis will be based on the intent-to-treat (ITT) population that includes all randomized patients. The per protocol (PP) population will be defined as the subset of the ITT population who have received at least one dose of study medication with no major protocol violations (which will be defined in the statistical analysis plan [SAP]).

The main analysis for investigator assessed PFS will be a stratified Cox model analysis that will include a treatment group variable and stratification factors, defined as:

- ECOG PS (0/1 vs. 2),
- CNS metastases at baseline (yes vs. no)

  In addition, patients with baseline CNS metastases will be stratified by history of radiotherapy (yes vs. no)

Further details for this analysis will be specified in the Statistical Analysis Plan. The un-stratified Cox model analysis for PFS will also be provided as sensitivity analyses.

Estimates for the survivor function for PFS will be obtained by the Kaplan-Meier approach. The p-value of log-rank test will be displayed together with estimated hazard ratios and associated 95% confidence intervals (CIs).

Hypotheses testing for primary endpoint:

- H_0: the distribution of the PFS time is the same in the two treatment groups
- H_1: the distribution of the PFS time is different in the two treatment groups
- If the hazard ratio (HR) of the investigational arm compared with the control arm with respect to PFS is assumed to be constant over time (λ), then the null (H_0) and alternative hypotheses (H_1) are: H_0: $\lambda=1$ vs. H_1: $\lambda\neq1$

Unless otherwise specified, all tests will be performed at two-sided alpha of 5%.

6.4.2 Secondary Efficacy Endpoints

The key secondary endpoint is C-ORR in patients with measurable CNS metastases at baseline as per IRC assessment.

If superiority for the PFS endpoints is concluded, subsequent hierarchical testing for the key secondary endpoint, C-ORR in patients with measurable CNS metastases at baseline (IRC assessment), will be performed between the two treatment groups. The difference in C-ORR in patients with measurable CNS metastases at baseline per IRC assessment will be displayed with associated 90 and 95% CI using the Hauck-Anderson approach and p-value for the Chi-square test (test at a one-sided alpha level of 0.05). Logistic analysis will be used to assess the influence of stratification factors and baseline covariates in an exploratory manner. Also, 95% Clopper-Pearson CI for each treatment arm will be displayed.

There will be no multiplicity adjustments for testing of other secondary endpoints.

This study is not powered for OS, so adequately powered statistical testing for this endpoint will not be possible. However, Kaplan-Meier estimates and a log rank test will be provided in an exploratory manner to assess the difference between treatment arms for OS. Unless otherwise specified, other time-to-event endpoints will be analyzed in a similar way to PFS and OS.

The C-ORR and ORR will be summarized by the number and proportion of responders and non-responders in each treatment group, together with two-sided 95% Clopper-Pearson CI. The difference in C-ORR (or ORR) will be displayed with associated CI using the Hauck-Anderson approach and p-value for the Chi-square test. Logistic analysis will be used to assess the influence of stratification factors and baseline covariates in an exploratory manner. Also, 95% Clopper-Pearson CI for each treatment arm will also be displayed.

DCR will be summarized in a similar way to the C-ORR and ORR.

Median duration of response for each treatment arm will be estimated using the Kaplan-Meier approach. The hazard ratio between the two arms with associated 95% CI will also be estimated using Cox model analysis. Time to response will be analyzed in a similar way to duration of response.

Time to CNS progression is defined as the time from randomization to the first documented disease progression in the CNS.

In order to account for the competing risks inherent to the analysis of this endpoint, HR and corresponding 95% CI and two-sided log-rank test will be computed on the basis of cause-specific hazard functions to compare the risk of CNS progression between the alectinib and chemotherapy treatment groups. The probability of CNS progression, non-CNS progression and death will each be estimated using cumulative incidence functions.

These time to CNS progression analyses will be provided using all patients regardless of their baseline status of CNS metastases, and also when number of patients with CNS progression events allows, on the subgroups of patients with baseline CNS and patients without baseline CNS.

Analysis methods for time-to-event endpoints, such as OS or PFS assessed by the IRC, are the same as those described for the primary endpoint.

The number (percentage) of patients who received chemotherapy at the time of progression, and who also agreed to cross-over to receive alectinib, will be summarized. The following methodologies may be used as appropriate to explore the impact of cross-over on the Overall Survival difference between treatment arms, in addition to the ITT analysis: censoring at time of cross-over or treatment switch, exclusion of patient switching treatment from the OS analysis, discount methods, or more advanced methods, such as for example Rank Preserving Structural Failure Time (RPSFT) methodology. More details on these methodologies, different censoring rules and models for these types of data will be provided in the Statistical Analysis Plan (SAP).

6.5 SAFETY ANALYSES

Safety endpoints will be analyzed for the safety population, which will include all patients who received at least one dose of study medication. For analysis purposes, patients will be assigned to treatment groups based on actual received study medication during study treatment period, defined in figure 3. Safety summary for patients that cross over to receive alectinib upon progression on chemotherapy or who continue in treatment beyond progression on alectinib, will be presented separately, starting from the first day of alectinib treatment for patients randomized to chemotherapy and switching to Alectinib, and starting first day of treatment beyond progression for patients randomized to Alectinib and continuing Alectinib beyond progression.

The incidence of AEs and SAEs will be summarized according to the primary system organ class (SOC), and within each SOC by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. AE data will be presented in frequency tables (overall and by intensity) by body system and treatment groups. SAEs, AEs with NCI CTCAE Grade 3 or higher and AEs that cause premature discontinuation from study medications will be analyzed in a similar way. Listing of deaths and cause of deaths will be provided.

Selected laboratory parameters will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade for each treatment cycle and overall, and graphically presented over time via box-plots split by treatment groups.

Information on study medication will also be summarized by duration on treatment, interruptions using descriptive statistics.

Premature withdrawal and reasons for premature withdrawal from study and study medication will be summarized by frequency tables.

Summaries described in this section will be also repeated for patients with CNS metastasis at baseline.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean plasma concentrations at each sampling time point 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) will be presented, as appropriate. Additional plots or summary statistics may be constructed or calculated, as appropriate.

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, as needed and if appropriate. 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, as needed and if appropriate.

Details of the mixed-effects modeling and exploratory analyses will be reported in a document separate from the clinical study report. Results of PK and/or any PK/pharmacodynamics analyses may be reported outside the clinical study report.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

The PRO measures, EORTC QLQ-C30, EORTC QLC-LC13, EQ-5D-5L and questions specific to CNS metastases (a part of EORTC QLQ-BN20 questionnaire), will be summarized using descriptive statistics. Selected single or multi-item subscales will be graphically presented and difference between two treatment groups over time will be explored using mixed models.

Evaluation and comparison of time to deterioration (TTD) in patient-reported lung cancer symptoms of cough, chest pain (single-item) dyspnea (single item and multi-item subscales), pain in shoulder/arm, and fatigue is a very important endpoint based on data collected via EORTC QLQ-C30 and EORTC QLC-LC13. TTD in patient-reported lung cancer symptoms of cough, chest pain, dyspnea (single item and multiple item), pain in arm/shoulder and fatigue as well as TTD for a composite of three symptoms (cough, dyspnea (multi-item subscales QLQ-LC13 and chest pain) will be analyzed as a time-to-event endpoint, as described for PFS or using descriptive statistics if not recorded as a time-to-event endpoint.

The EQ-5D-5L 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 pharmacoeconomic models for reimbursement purposes only.

The Cochran-Mantel-Haenszel statistic test will be applied to take the ordinal nature of a variable EORTC QOQ-BN20. More details will be specified in the statistical analyses plan.

More details will be specified in the SAP.

6.8 BIOMARKER ANALYSES

Descriptive analysis for biomarkers will be provided and further association between biomarkers and clinical endpoints (e.g., PFS, OS, ORR, etc.) will be explored using Cox regression model or logistic model. More information will be provided in the SAP.

6.9 INTERIM ANALYSES

No interim analyses for efficacy or futility are planned. Safety review of data will be performed as explained in the iDMC charter.

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 through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

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

ePRO 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 U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR 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

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

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

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

7.3 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, patient-reported outcomes, 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 Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Home Nursing 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative 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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written 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

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 U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including 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.

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.

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, 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. IDMC review meetings will be held in a blinded manner to the Sponsor.

An IRC will review the tumor assessments to determine the secondary endpoints. IRC assessments will continue until 12 weeks after the last patient in, after which time the IRC assessments will be halted.

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor 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).

10. REFERENCES

Aapro, M. S., J. Bohlius, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011;47:8-32.

Aaronson, N. K., S. Ahmedzai, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-376.

American Lung Association. (2015). "Lung Cancer Fact Sheet." Retrieved March 2015, from http://www.lung.org/lung-disease/lung-cancer/resources/facts-figures/lung-cancer-fact-sheet.html.

Bergethon, K., A. T. Shaw, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

Bergman, B., N. K. Aaronson, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A:635-642.

Besse, B., A. Adjei, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol 2014;25:1475-1484.

Bezjak, A., D. Tu, et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2006;24:3831-3837.

Blackhall, F., D. W. Kim, et al. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer. J Thorac Oncol 2014;9:1625-1633.

Camidge, D. R., S. A. Kono, et al. Anaplastic lymphoma kinase gene rearrangements in non-small cell lung cancer are associated with prolonged progression-free survival on pemetrexed. J Thorac Oncol 2011;6:774-780.

Cetin, K., D. S. Ettinger, et al. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. Clin Epidemiol 2011;3:139-148.

Chun, S. G., K. S. Choe, et al. Isolated central nervous system progression on Crizotinib: an Achilles heel of non-small cell lung cancer with EML4-ALK translocation? Cancer Biol Ther 2012;13:1376-1383.

Costa, D. B., S. Kobayashi, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011;29:e443-445.

Costa, D. B., A. T. Shaw, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. J Clin Oncol 2015;

Crawford, J., C. Caserta, et al. Hematopoietic growth factors: ESMO recommendations for the applications. Ann Oncol 2009;20 Suppl 4:162-165.

Crinò, L., D. Kim, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005. J Clin Oncol 2011;29:(suppl; abstr 7514).

Doebele, R. C., A. B. Pilling, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Clin Cancer Res 2012;18:1472-1482.

European Medicines Agency. (2015). "Xalkori (crizotinib)." Retrieved March 2015, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124.

Fan, L., Y. Feng, et al. Clinicopathological and demographical characteristics of non-small cell lung cancer patients with ALK rearrangements: a systematic review and meta-analysis. PLoS One 2014;9:e100866.

Fossella, F. V., R. DeVore, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362.

Gainor, J. F., C. A. Sherman, et al. Alectinib salvages CNS relapses in ALK-positive lung cancer patients previously treated with crizotinib and ceritinib. J Thorac Oncol 2015;10:232-236.

GLOBOCAN 2012. "Lung Cancer: Estimated Incidence, Mortality and Prevalence Worldwide in 2012." Retrieved March 2015, from http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Hanna, N., F. A. Shepherd, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

Hartmann, J. T., M. Haap, et al. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. Curr Drug Metab 2009;10:470-481.

Hohenegger, M. Drug induced rhabdomyolysis. Curr Opin Pharmacol 2012;12:335-339.

Hopwood, P. and R. J. Stephens. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. Br J Cancer 1995;71:633-636.

Hyde, L. and C. I. Hyde. Clinical manifestations of lung cancer. Chest 1974;65:299-306.

Katayama, R., T. M. Khan, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci U S A 2011;108:7535-7540.

Kim, S., T. M. Kim, et al. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. J Thorac Oncol 2013;8:415-422.

Kwak, E. L., Y. J. Bang, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-1703.

Langer, C. J., B. Besse, et al. The evolving role of histology in the management of advanced non-small-cell lung cancer. J Clin Oncol 2010;28:5311-5320.

Lee, J. O., T. M. Kim, et al. Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. J Thorac Oncol 2011;6:1474-1480.

Molina, J. R., P. Yang, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-594.

Ou, S. H., E. L. Kwak, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.

Pirker, R., J. R. Pereira, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531.

Ramlau, R., V. Gorbunova, et al. Aflibercept and Docetaxel versus Docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. J Clin Oncol 2012;30:3640-3647.

Reck, M., S. Popat, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39.

Rikova, K., A. Guo, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190-1203.

Sandler, A., R. Gray, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-2550.

Sarna, L., S. Swann, et al. Clinically meaningful differences in patient-reported outcomes with amifostine in combination with chemoradiation for locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. Int J Radiat Oncol Biol Phys 2008;72:1378-1384.

Schiller, J. H., D. Harrington, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98.

Shaw, A. T., D. W. Kim, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-2394.

Shepherd, F. A., J. Dancey, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-2103.

Shepherd, F. A., J. Rodrigues Pereira, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132.

Siegel, R., C. DeSantis, et al. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012;62:220-241.

Smith, T. J., J. Khatcheressian, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-3205.

Soda, M., Y. L. Choi, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-566.

Soda, M., S. Takada, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-19897.

Solomon, B. J., T. Mok, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-2177.

Travis, W. D., E. Brambilla, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: international multidisciplinary classification of lung adenocarcinoma: executive summary. Proc Am Thorac Soc 2011;8:381-385.

US Food and Drug Administration. (2015). "XALKORI - crizotinib capsule." Retrieved March 2015, from http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2a51b0de-47d6-455e-a94c-d2c737b04ff7.

Wang, Y., S. Wang, et al. Clinicopathologic features of patients with non-small cell lung cancer harboring the EML4-ALK fusion gene: a meta-analysis. PLoS One 2014;9:e110617.

Weickhardt, A. J., M. S. Rothman, et al. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer. Cancer 2012;118:5302-5309.

Zhao, F., M. Xu, et al. Clinicopathological Characteristics of Patients with Non-Small-Cell Lung Cancer Who Harbor EML4-ALK Fusion Gene: A Meta-Analysis. PLoS One 2015;10:e0117333.

Appendix 1
Schedule of Assessments – Alectinib Arm (cont.)

Appendix 1
Schedule of Assessments – Alectinib Arm

Assessment	Screening		Treatment Period [a] (± 7 Days for Visits; ± 3 Days for Safety Visits)									Post Treatment Visit [c]	Post-progression visits on alectinib treatment in case of TBP (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Visit 0 Baseline Wk 0	Safety Visit [b] Wk 2	Visit 1 Wk 3	Safety Visit [b] Wk 4	Visit 2 Wk 6	Safety Visit [b] Wk 8	Safety Visit [b] Wk 10	Visit 3 Wk 12	All subsequent visits (every 6 weeks until PD, death, or withdrawal from study prior to PD)			
Informed consent	x													
Demographics	x													
Medical history	x													
Pregnancy test [d]		x	Repeated only if necessary											
Physical examination [e]	x		x	Only if clinically necessary										
Vital signs (BP, pulse) [f]	x		x		x		x			x	x		x	
ECOG PS	x		x		x		x			x	x	x	x	
ECG [g]			x [h]							x	Week 24, every 12 weeks thereafter and at PD		x [i]	
Hematology [j]	x		x [h]		x		x			x	x		x	

Appendix 1
Schedule of Assessments – Alectinib Arm (cont.)

Assessment	Screening		Treatment Period [a] (± 7 Days for Visits; ± 3 Days for Safety Visits)									Post Treatment Visit [c]	Post-progression visits on alectinib treatment in case of TBP (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Visit 0 Baseline Wk 0	Safety Visit [b] Wk 2	Visit 1 Wk 3	Safety Visit [b] Wk 4	Visit 2 Wk 6	Safety Visit [b] Wk 8	Safety Visit [b] Wk 10	Visit 3 Wk 12	All subsequent visits (every 6 weeks until PD, death, or withdrawal from study prior to PD)			
Biochemistry [j]	x		x [h]	x [k]	x	x [k]	x	x [k]	x [k]	x	x		x	
Urinalysis	x		x [h]	Only if clinically necessary									x [i]	
Concomitant medications	x		x	x	x	x	x	x	x	x	x		x	
Optional tumor sample [l]			x								At PD			
Mandatory archival tumor sample (as many as available) [m]			x											
Plasma for detection of exploratory biomarkers, including ALK mutations (20 mL of blood)			x				x			x	x			
Tumor assessment [n]	x [o]		x [o]				x			x	x [p]			

Appendix 1
Schedule of Assessments – Alectinib Arm (cont.)

Assessment	Screening		Treatment Period [a] (± 7 Days for Visits; ± 3 Days for Safety Visits)									Post Treatment Visit [c]	Post-progression visits on alectinib treatment in case of TBP (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Visit 0 Baseline Wk 0	Safety Visit [b] Wk 2	Visit 1 Wk 3	Safety Visit [b] Wk 4	Visit 2 Wk 6	Safety Visit [b] Wk 8	Safety Visit [b] Wk 10	Visit 3 Wk 12	All subsequent visits (every 6 weeks until PD, death, or withdrawal from study prior to PD)			
MRI scan of the brain	x [o]		x [o]				x			x	x [p]			
PK samples (2 mL blood) [q]			x		x		x							
PRO (EORTC QLQ-C30/LC13/BN 20, EQ-5D-5L) [r]			x		x		x			x	x	x		
Alectin b [s]			600 mg BID										600 mg BID	
Adverse events [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Subsequent therapy for NSCLC												x		x
Alectin b dispensing (bottles to dispense) [u]			1		1		2			3	3 bottles every 12 weeks, starting from Visit 3			

Appendix 1
Schedule of Assessments – Alectinib Arm (cont.)

Assessment	Screening		Treatment Period [a] (± 7 Days for Visits; ± 3 Days for Safety Visits)									Post Treatment Visit [c]	Post-progression visits on alectinib treatment in case of TBP (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Visit 0 Baseline Wk 0	Safety Visit [b] Wk 2	Visit 1 Wk 3	Safety Visit [b] Wk 4	Visit 2 Wk 6	Safety Visit [b] Wk 8	Safety Visit [b] Wk 10	Visit 3 Wk 12	All subsequent visits (every 6 weeks until PD, death, or withdrawal from study prior to PD)			
Alectin b accountability [v]			x		x		x			x	Every 12 weeks, starting from Visit 3	x	x	
Blood Sample for Roche Clinical Repository (10 mL)			x											

ALK = anaplastic lymphoma kinase; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-BN20 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Brain Neoplasm-20; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Core-30; EORTC QLQ-LC13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer-13; EQ-5D-5L = EuroQoL 5 Dimension 5 level; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; TBP, treatment beyond progression; Wk, Week.

[a] The first dose of alectin b should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

[b] Assessment of liver values (ALT/AST/total bilirubin/direct bilirubin/ALP every 2 weeks for the first 3 months of treatment) and CPK (every 2 weeks for the first month of treatment) should be performed at clinic visits.

[c] Four weeks after permanent treatment discontinuation for patients who do not receive alectinib treatment beyond progression, or at the end of randomized treatment for patients who enter the post progression period.

[d] Screening serum pregnancy test results should be available prior to randomization. After randomization, to be repeated as necessary (urine or serum).

[e] Including an ophthalmologic examination if clinically indicated.

Appendix 1
Schedule of Assessments – Alectinib Arm (cont.)

[f] Vital signs will include measurements of pulse rate and systolic and diastolic blood pressures while the patient is in a seated position. Other vital signs (e.g., respiratory rate, oxygen saturation and temperature) may be collected at the discretion of the investigator if clinically warranted. Only abnormal findings will be recorded in the eCRF.

[g] Refer to Section 4.5.9.

[h] Screening assessments done within 3 days can be counted as the baseline assessment.

[i] As clinically needed.

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

[j] Refer to section 4.5.8.1

[k] Blood will be drawn in the clinic to assess liver function (AST/ALT/total bilirubin/direct bilirubin/ALP on Weeks 2, 4, 8 and 10) and CPK (on Weeks 2 and 4).

[l] Optional formalin-fixed, paraffin-embedded (FFPE) samples. The baseline sample can be taken from the FFPE tumor block obtained at screening. At progression, optional biopsy should be taken from the progressing lesion only.

[m] Collected prior to exposure to crizotinib and preferably from primary tissue.

[n] 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 a kaline phosphatase $> 1.5 \times$ ULN) of bone metastasis should undergo radionuclide bone scan. Post-baseline assessments are to be performed within ± 1 week for the scheduled 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.

[o] Screening tumor assessment done within 28 days will be counted as the baseline assessment.

[p] 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.

[q] Pre-dose PK (2 mL) sampling for all patients on alectinib treatment will be performed at baseline and at specified visits during the treatment period. The pre-dose PK samples should be taken immediately before (within 2 hours) intake of study medication at the specified study visits. Remind the patient not to take a daily dose at home on the day of scheduled study visit. See also Appendix 3.

[r] Further guidelines on PRO questionnaire administration will be provided in the study manual.

[s] Refer to Section 4.3.2.1.

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

[u] Refer to Section 4.3.3.

[v] Accurate records of all investigational medicinal products (IMPs) received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log. IMPs will either be disposed 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.

Appendix 2
Schedule of Assessments – Chemotherapy Arm (cont.)

Appendix 2
Schedule of Assessments – Chemotherapy Arm

NOTE: If considered to be of clinical benefit for the patient and if there is no safety risk, patients on the chemotherapy arm can cross over to receive alectinib at the discretion of the patient and investigator prior to documentation of PD per RECIST v1.1. Patients who cross over in the first treatment period should follow the visit schedule as in the first treatment period, i.e., tumor assessments every 6 weeks until PD, death, or withdrawal from study prior to PD.

	Screening		Treatment Period [a] (Patients should report to the hospital every 3 weeks ± 3 days for chemotherapy administration) [b] (For Chemo Cycle Only administration beyond Wk 12, which will occur every 3 weeks, refer to the Wk 9 column for required assessments. Every 6 weeks, a visit will occur for assessments according to Wk 12)												
Assessment	Days –28 to 0	Days –3 to 0	Chemo Cycle & Visit 0 Baseline Wk 0	Safety Call [c] Wk 2	Chemo Cycle & Visit 1 Wk 3	Safety Call [c] Wk 4	Chemo Cycle & Visit 2 Wk 6	Safety Call [c] Wk 8	Chemo Cycle Only [d] Wk 9	Safety Call [c] Wk 10	Chemo Cycle & Visit 3 Wk 12	All subsequent visits Every 6 weeks thereafter until PD, death, or withdrawal from study prior to PD)	Post Treatment Visit [e]	Post-progression visits on alectinib treatment in case of cross over (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal [f]	Survival follow-up and subsequent NSCLC treatment (every 3 months)
Informed consent	x														
Demographics	x														
Medical history	x														
Pregnancy test [g]		x	Repeated only if necessary												
Physical examination [h]	x		x	Only if clinically necessary											
Vital signs (BP, pulse) [i]	x		x		x		x				x	x		x	
ECOG PS	x		x		x		x				x	x	x	x	

Appendix 2
Schedule of Assessments – Chemotherapy Arm (cont.)

Assessment	Screening		Treatment Period [a] (Patients should report to the hospital every 3 weeks ± 3 days for chemotherapy administration) [b] (For Chemo Cycle Only administration beyond Wk 12, which will occur every 3 weeks, refer to the Wk 9 column for required assessments. Every 6 weeks, a visit will occur for assessments according to Wk 12)										Post Treatment Visit [e]	Post-progression visits on alectinib treatment in case of cross over (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal [f]	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Chemo Cycle & Visit 0 Baseline Wk 0	Safety Call [c] Wk 2	Chemo Cycle & Visit 1 Wk 3	Safety Call [c] Wk 4	Chemo Cycle & Visit 2 Wk 6	Safety Call [c] Wk 8	Chemo Cycle Only [d] Wk 9	Safety Call [c] Wk 10	Chemo Cycle & Visit 3 Wk 12	All subsequent visits Every 6 weeks thereafter until PD, death, or withdrawal from study prior to PD)			
ECG [i]			x [k]								x	Week 24, every 12 weeks thereafter and at PD		x [l]	
Hematology [m]	x		x [k]		x		x				x	x		x	
Biochemistry [m]	x		x [k]		x		x				x	x		x	
Urinalysis	x		x [k]	Only if clinically necessary										x [l]	
Concomitant medications	x		x	x	x	x	x	x	x	x	x	x		x	
Optional tumor sample [n]			x									At PD			
Mandatory archival tumor sample (as many as available) [o]			x												

Appendix 2
Schedule of Assessments – Chemotherapy Arm (cont.)

Assessment	Screening		Treatment Period [a] (Patients should report to the hospital every 3 weeks ± 3 days for chemotherapy administration) [b] (For Chemo Cycle Only administration beyond Wk 12, which will occur every 3 weeks, refer to the Wk 9 column for required assessments. Every 6 weeks, a visit will occur for assessments according to Wk 12)										Post Treatment Visit [e]	Post-progression visits on alectinib treatment in case of cross over (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal [f]	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Chemo Cycle & Visit 0 Baseline Wk 0	Safety Call [c] Wk 2	Chemo Cycle & Visit 1 Wk 3	Safety Call [c] Wk 4	Chemo Cycle & Visit 2 Wk 6	Safety Call [c] Wk 8	Chemo Cycle Only [d] Wk 9	Safety Call [c] Wk 10	Chemo Cycle & Visit 3 Wk 12	All subsequent visits Every 6 weeks thereafter until PD, death, or withdrawal from study prior to PD)			
Plasma for detection of exploratory biomarkers, including ALK mutations (20 mL of blood)			x				x				x	x			
Tumor assessment [p]	x [q]		x [q]				x				x	x [r]			
MRI scan of the brain	x [q]		x [q]				x				x	x [r]			
PRO (EORTC QLQ-C30/LC13/BN20, EQ-5D-5L) [s]			x		x		x				x	x	x		
Adverse events [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Subsequent therapy for NSCLC													x		x
Chemotherapy dispensing and accountability [u]			x		x		x		x		x	x [v]			

Appendix 2
Schedule of Assessments – Chemotherapy Arm (cont.)

Assessment	Screening		Treatment Period [a] (Patients should report to the hospital every 3 weeks ± 3 days for chemotherapy administration) [b] (For Chemo Cycle Only administration beyond Wk 12, which will occur every 3 weeks, refer to the Wk 9 column for required assessments. Every 6 weeks, a visit will occur for assessments according to Wk 12)										Post Treatment Visit [e]	Post-progression visits on alectinib treatment in case of cross over (q6w, ± 7 days) until PD, unacceptable toxicity or withdrawal [f]	Survival follow-up and subsequent NSCLC treatment (every 3 months)
	Days –28 to 0	Days –3 to 0	Chemo Cycle & Visit 0 Baseline Wk 0	Safety Call [c] Wk 2	Chemo Cycle & Visit 1 Wk 3	Safety Call [c] Wk 4	Chemo Cycle & Visit 2 Wk 6	Safety Call [c] Wk 8	Chemo Cycle Only [d] Wk 9	Safety Call [c] Wk 10	Chemo Cycle & Visit 3 Wk 12	All subsequent visits Every 6 weeks thereafter until PD, death, or withdrawal from study prior to PD)			
Blood Sample for Roche Clinical Repository (10 mL)			x												

ALK = anaplastic lymphoma kinase; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-BN20 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Brain Neoplasm-20; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Core-30; EORTC QLQ-LC13 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire—Lung Cancer-13; EQ-5D-5L = EuroQoL 5 Dimension 5 level; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; TBP, treatment beyond progression; Wk, Week.

[a] The first dose of the study drug (and the required premedication, when applicable) should be administered as soon as possible after randomization, preferably within 24 hours, and no later than 48 hours after randomization.

[b] The chemotherapy cycle should always occur every 21 ± 3 days. Thus, if there is a delay in chemotherapy administration (e.g., for an AE), the next chemotherapy administration should occur every 21 ± 3 days thereafter, even if this administration schedule does not align with the prespecified study assessment visits. In other words, Investigators should not shorten the chemotherapy cycle in order to re-align with the assessment schedule.

[c] New AEs and new treatment(s) since last visit, by phone interview.

[d] Specific eCRFs will be available at the chemo-only visits.

[e] Four weeks after permanent treatment discontinuation for patients who do not cross over to alectinib.

Appendix 2
Schedule of Assessments – Chemotherapy Arm (cont.)

[f] Refer to Appendix 1 for the Schedule of Assessments for patients who cross over to alectinib therapy, including drug dispensation, accountability and safety visits. Please note that the first full assessment visit and re-supply of study drug for patients who cross over will be after 6 weeks (and not at 3 weeks, as with patients who are randomized to the alectin b study arm).

[g] Screening serum pregnancy test results should be available prior to randomization. After randomization, to be repeated as necessary (urine or serum).

[h] Including an ophthalmologic examination if clinically indicated.

[i] Vital signs will include measurements of pulse rate and systolic and diastolic blood pressures while the patient is in a seated position. Other vital signs (e.g., respiratory rate, oxygen saturation and temperature) may be collected at the discretion of the investigator if clinically warranted. Only abnormal findings will be recorded in the eCRF.

[j] Refer to Section 4.5.9.

[k] Screening assessments done within 3 days can be counted as the baseline assessment.

[l] As clinically needed

[m] Refer to section 4.5.8.1

[n] Optional formalin-fixed, paraffin-embedded (FFPE) samples. The baseline sample can be taken from the FFPE tumor block obtained at screening. At progression, optional biopsy should be taken from the progressing lesion only.

[o] Collected prior to exposure to crizotinib and preferably from primary tissue.

[p] 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 a kaline phosphatase $> 1.5 \times$ ULN) of bone metastasis should undergo radionuclide bone scan. Post-baseline assessments are to be performed within ± 1 week for the scheduled 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.

[q] Screening tumor assessment done within 28 days will be counted as the baseline assessment.

[r] 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.

[s] Further guidelines on PRO questionnaire administration will be provided in the study manual.

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

[u] Refer to Section 4.3.3. Note that only information related to drug supply will be captured in the interactive web-based response system. Any new AEs or concomitant medications at chemotherapy cycle visits should be captured on the eCRF.

[v] Chemotherapy will be re-supplied every 3 weeks.

Appendix 2
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

Appendix 3
Schedule of Pharmacokinetic Assessments

Visit	Timepoint
Visit 0 (baseline) [a]	Pre-dose (within 2 hours before intake of alectinib)
Visit 1 (Week 3)	Pre-dose (within 2 hours before intake of alectinib)
Visit 2 (Week 6)	Pre-dose (within 2 hours before intake of alectinib)

PK = pharmacokinetics

a. Before the first dose of alectinib.

Appendix 4
List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters (cont.)

Appendix 4
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

This information in this appendix is adapted from Levien and Baker 2003[2], Zhang 2010[3], and FDA Guidance on Drug-Drug Interactions.

Also see:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

---

[2] Levien TL, and Baker DE Cytochrome P450 Drug Interactions. Therapeutic Research Center Pharmacist's Letter/Prescriber's Letter [resource on the Internet]. 2003. Available from: www.pharmacistsletter.com and www.prescribersletter.com.

[3] Zhang L. Transporter Mediated Drug-Drug Interactions. FDA. Clinical Pharmacology Advisory Committee Meeting Topic 4: Transporter-Mediated Drug-Drug Interactions Atlanta, GA, March 17, 2010.

Appendix 4
List of Substrates, Inhibitors, and Inducers of Drug-Metabolizing Enzymes and Transporters (cont.)

- 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 AUC of a concomitantly administered CYP3A substrate. These are based on the available published literature and, thus, are not considered exhaustive or inclusive. See FDA Guidance on Drug-Drug Interactions for further detail.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

Appendix 5
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 CT or 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 ≥ 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 ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include

---

[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.

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.

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.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

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 skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray

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

CT, MRI

CT 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. MRI is also acceptable.

If, prior to enrollment, it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision 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.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

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.

- CR: Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

- 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.

- 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.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

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 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 2 is to be used.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

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

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

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [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.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR 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
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.

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

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 in Table 1 to Table 3.

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

In studies for which patients with advanced disease are eligible (i.e., primary disease 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
Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1: Excerpt from Original Publication (cont.)

Appendix 6
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 7
EORTC QLQ-C30/LC13 and EQ-5D-5L Questionnaires

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

Appendix 7
EORTC QLQ-C30/LC13 and EQ-5D-5L Questionnaires (cont.)

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe 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 doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 7
EORTC QLQ-C30/LC13 and EQ-5D-5L Questionnaires (cont.)

Appendix 8
Modification of Diet in Renal Disease (MDRD) Formula

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

$$\text{eGFR [mL/min/1.73 m}^2\text{]} = 175 \times \text{SCRT}^{-1.154} \times \text{AGE}^{-0.203} \text{ [× 0.742 if female] [× 1.212 if African American] (conventional units)}$$

where SCRT = serum creatinine in conventional units, i.e. mg/dL.

The following conversion factor should be used in case the serum creatinine value is provided by the lab in µmol/L units:

Serum creatinine [mg/dL] ・・Serum creatinine [µmol/L] ・・0.0113

Miller WG. Estimating glomerular filtration rate. Clin Chem Lab Med 2009;47(9):1017−9.
Heil W., Koberstein R, Zawta B. Reference Ranges for Adults and Children−Pre-Analytical Considerations. Roche Diagnostics GmbH 2014, 8th edition, p.159.