Official Title: A Phase III, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With Completely Resected Stage IB (Tumors Equal to or Larger Than 4 cm) to Stage IIIA Anaplastic Lymphoma Kinase Positive Non-Small Cell Lung Cancer

NCT Number: NCT03456076

Document Date: Protocol Amendment Version 7: 16-December-2021

PROTOCOL

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUVANT ALECTINIB VERSUS ADJUVANT PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE Ib (TUMORS≥4 cm) TO STAGE IIIa ANAPLASTIC LYMPHOMA KINASE–POSITIVE NON–SMALL-CELL LUNG CANCER**
PROTOCOL NUMBER:	BO40336
VERSION NUMBER:	*7*
EUDRACT NUMBER:	2017-004331-37
IND NUMBER:	111,723
TEST PRODUCT:	Alectinib (RO5424802)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
16-Dec-2021 22:27:11	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
6	10 March 2021
5	26 November 2019
4	8 November 2019
3	23 April 2018
2 (E.U.)	10 April 2018
1	5 February 2018

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol BO40336 has been amended primarily to update the management guidline of hemolytic anemia for patients treated with alectinib. Changes to the protocol, along with a rationale for each change, are summarized below:

- Management guideline of hemolytic anemia for patients treated with alectinib has been updated (Section 5.1.7.3).
- Hematologic findings from alectinib toxicity studies in animals have been provided to the section describing the risks associated with alectinib (Section 5.1.1.3).
- Management guidelines of bradycardia for patients treated with alectinib has been updated in line with the alectinib label (Section 5.1.7.3).
- Benefit-risk assessment for COVID-19 infection and COVID-19 vaccines has been included (Section 1.3.1).
- Text relating to the collection of radiographic images and the potential independent review by an imaging review facility have been added (Section 4.5.6, Section 7.5, Section 9.5, Appendix 1 and Appendix 2).
- Any references to the Medical Monitor's approval of the protocol-specific criteria or procedures are removed from the protocol. The Medical Monitor may be consulted for advice or clarification, but all medical decisions are the responsibility of the Investigator (Section 4.1.2, Section 4.3.2.2, and Section 5.1.7.2).
- The minimum requirement of Creatinine Clearance (CrCL) has been clarified when the pemetrexed is given to the patient together with cisplatin. The patient's CrCl must be $\geq$ 60 mL/min before the next dose of cisplatin admistration due to its dose-related and cumulative renal insufficiency (Section 4.3.2.2).
- Vinorelbine preparation by syringe has been removed from the protocol following United States Prescribing Information (USPI) update, in order to reduce the potential for unintended intrathecal administration which causes death or severe neurological injury (Section 4.3.2.2).
- Text relating to data reporting of COVID-19 vaccination in the medical history and/or in the concomitant medication section has been added (Section 4.5.2, Appendix 1 and Appendix 2).
- It has been clarified that, if the patient stops disease assessment, the patient will be contacted for disease recurrence status if no recurrence occurs as long as the patient hasn't withdrawn from the study (Section 4.6.1).
- The most common adverse effects for pemetrexed has been updated in line with the updated pemetrexed EU Summary of Product Characteristics, where multiple tables of adverse drug events have been consolidated into one table containing data from the pivotal clinical trials and the post marketing period (Section 5.1.4).
- It has been clarified that Long-Term Follow-Up should be conducted after the first documented disease recurrence or new primary NSCLC, until death, loss to follow-up, or study termination by the Sponsor (Appendix 1 and Appendix 2).

Additional minor changes have been made to improve clarity and consistency.
Substantive new information for Version 7 appears in Book Antiqua italics.
This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUVANT ALECTINIB VERSUS ADJUVANT PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE Ib (TUMORS≥4 cm) TO STAGE IIIa ANAPLASTIC LYMPHOMA KINASE–POSITIVE NON–SMALL-CELL LUNG CANCER**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ADJUVANT ALECTINIB VERSUS ADJUVANT PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH COMPLETELY RESECTED STAGE Ib (TUMORS≥4 CM) TO STAGE IIIa ANAPLASTIC LYMPHOMA KINASE–POSITIVE NON–SMALL-CELL LUNG CANCER**
PROTOCOL NUMBER:	BO40336
VERSION NUMBER:	*7*
EUDRACT NUMBER:	2017-004331-37
IND NUMBER:	111,723
TEST PRODUCT:	Alectinib (RO5424802)
PHASE:	III
INDICATION:	Anaplastic Lymphoma Kinase–Positive Non–Small-Cell Lung Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors≥4 cm) to Stage IIIa, anaplastic lymphoma kinase (ALK)–positive non–small-cell lung cancer (NSCLC). Specific objectives and corresponding endpoints for the study are outlined below.

The primary and secondary efficacy objectives will be analyzed in the intent-to-treat (ITT) population of randomized patients with resected Stage Ib (tumors ≥4 cm) to Stage IIIa NSCLC and in the subpopulation of patients with resected Stage II–IIIa NSCLC.

Disease-free survival (DFS) as an endpoint does not distinguish between the location of the first documented recurrence of disease or new primary NSCLC. Descriptive statistics (i.e., frequencies and percentages) will be used to explore the first site of recurrence of disease or new primary NSCLC.

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• DFS, defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC—as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status—or death from any cause, whichever occurs first
Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• OS, defined as the time from randomization to death from any cause

Exploratory Efficacy Objectives	Corresponding Endpoints
• To evaluate DFS rates for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• DFS rates at landmark timepoints of 3, 4, and 5 years
• To evaluate the effects of demographics and baseline prognostic characteristics on duration of DFS for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• Effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) on duration of DFS by subgroup analyses
• To evaluate the location of the first documented recurrence of disease or new primary NSCLC for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• The location of the first documented recurrence of disease or new primary NSCLC
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• Incidence of adverse events, with severity determined through use of NCI CTCAE v*5*.0 • Safety laboratory values • Vital signs • ECG
Pharmacokinetic Objectives (Alectinib Arm Only)	**Corresponding Endpoint**
• To characterize the pharmacokinetics of alectinib and its major metabolite(s) in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC • **At Japanese sites only:** To characterize the pharmacokinetics of alectinib and its major metabolite(s) in Japanese patients	• Plasma concentrations of alectinib and its major metabolite(s) at specified timepoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To investigate molecular mechanisms of resistance to alectinib in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage III, ALK-positive NSCLC	• Relationship between biomarkers in blood and tumor tissue and efficacy (DFS)
Exploratory Patient-Reported Outcome Objectives	**Corresponding Endpoints**
• To document the impact of alectinib compared with platinum-based chemotherapy on patients' quality of life and daily function • To document health utilities for pharmacoeconomic modeling	• Mean change from baseline in PCS, MCS, and the PF scale as measured by their corresponding scores of the SF-36v2® • Health utilities as evaluated through the EQ-5D-5L

ALK = anaplastic lymphoma kinase; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; MCS = mental component summary; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non–small-cell lung cancer; OS = overall survival; PCS = physical component summary; PF = physical function.

Study Design

Description of Study

This randomized, active-controlled, multicenter, open-label, Phase III study is designed to investigate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting. The primary endpoint of the study is DFS as assessed by investigator, while OS is a secondary endpoint.

This study will comprise approximately 200 centers in around 30 countries worldwide. Central randomization will be performed via an interactive voice or Web-based response system (IxRS). Randomized patients will be stratified by extent of disease (Stage Ib [tumors $\geq$4 cm] vs. Stage II vs. Stage IIIa) and ethnicity (Asian vs. non-Asian). Relevant instruction will be provided to each study site by the IxRS provider.

Patients with completely resected (negative margins), histologically-confirmed Stage Ib (tumors $\geq$4 cm) to Stage IIIa NSCLC as per the Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) 7th edition with documented ALK-positive disease as assessed by a U.S. Food and Drug Administration (FDA)-approved and Conformité Européenne (CE)-marked test and meeting all required eligibility criteria, will be randomized in a 1:1 fashion.

Staging must occur in accordance with the UICC/AJCC 7th edition and not the 8th edition. Patients with Stage Ib NSCLC with tumors $\geq$4 cm per the 7th edition classification have been shown to experience more modest benefit from adjuvant chemotherapy treatment than patients with Stage II–IIIa NSCLC, and this has been taken into consideration for recruitment capping, stratification, and statistical analysis of the primary endpoint.

Patients in the experimental arm will receive alectinib at 600 mg orally twice a day (BID) taken with food for 24 months.

Patients in the control arm will receive one of the protocol-specified platinum-based chemotherapy regimens (including all required premedications and permitted concomitant medications) according to the local prescribing information. Protocol-defined platinum-based chemotherapy regimens include:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

Platinum-based chemotherapy will be provided for 4 cycles, with each cycle lasting 21 days. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the above combinations.

Post-operative radiation therapy (PORT) is not allowed as a treatment option. Therefore, patients with Stage IIIa N2 NSCLC who, in the investigator's opinion, should receive PORT, are excluded from the study.

Study drug (alectinib or platinum-based chemotherapy) will be administered until completion of treatment period (24 months for alectinib and 4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Patients who complete a study treatment regimen or discontinue treatment prior to disease recurrence (e.g., due to unacceptable toxicity) will continue to be followed until disease recurrence. After disease recurrence, patients will be treated at the discretion of the investigator according to local clinical practice. No crossover in the adjuvant setting will be allowed between the 2 arms.

Approximately 255 patients will be enrolled into the study over a planned competitive recruitment period of approximately 38 months. Patients inappropriately randomized into the study will not be replaced. The primary DFS analysis will be conducted after approximately 89 DFS events in the Stage II–IIIa subpopulation have been observed. This is expected to occur approximately 60 months after the first patient is randomized. Data collection will continue for each patient until death or study closure, whichever occurs first.

An independent Data Monitoring Committee (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.

All randomized patients will undergo regular, scheduled visits until disease recurrence, death, withdrawal from the study, or study termination, whichever occurs first. Regular safety assessments will be performed for both arms during treatment. The safety follow-up visit will be performed 28 days after last dose of alectinib or 28 days after the end of the last cycle of platinum-based chemotherapy. For the first 12 weeks (3 months), regular safety assessment visits will be scheduled at baseline and every 3 weeks (i.e., 1 chemotherapy cycle) for both arms. Additional visits will be scheduled for patients in the alectinib arm at Weeks 2, 4, 8, and 10 to allow for more frequent CPK and liver function assessments. Phone calls for safety monitoring of patients in the chemotherapy arm will be performed at the same timepoints (Weeks 2, 4, 8, and 10). From Week 12, patients in the alectinib arm will continue to be monitored for safety until treatment discontinuation every 6 weeks until Week 48 and every 12 weeks from Week 49–96. Scheduled disease assessments will be performed for both arms at baseline, every 12 weeks for the first 2 years, every 24 weeks during Years 3–5, and annually thereafter until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. If clinically indicated, unscheduled assessments can be performed at any time. Positive efficacy results at an interim analysis will not influence the timing of disease assessments during the study.

For all patients, plasma samples for exploratory biomarker research will be obtained at baseline, every 3 weeks for the first 12 weeks, every 12 weeks from Weeks 13–96, every 24 weeks during years 3–5, and annually thereafter until disease recurrence. Tumor samples will be obtained at study entry and upon disease recurrence for biomarker analysis.

Plasma samples will also be obtained for patients randomized to the alectinib arm pre-dose at baseline, every 3 weeks for the first 12 weeks, and every 12 weeks until Week 96 for pharmacokinetic (PK) analysis. At participating Japanese sites that can perform serial/intensive PK sampling, serial/intensive PK samples will be collected from a subset of Japanese patients receiving alectinib (approximately the first 6 patients who consent to participate to the serial/intensive PK sample collection) to facilitate the PK assessment in this population. The option to participate in the intensive Japanese PK profiling will be offered to these patients until at least 6 evaluable patients, as per protocol, have provided a reliable and complete PK profile. Therefore, more than 6 patients may participate in the serial/intensive PK assessment. However, the study team will make all efforts to provide complete profiles to the sites within the shortest timeframe.

Number of Patients

Approximately 255 patients are expected to enroll in this study in approximately 200 sites globally.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 at time of signing Informed Consent Form
- Complete resection of histologically-confirmed Stage Ib (tumor ≥ 4 cm) to Stage IIIa (T2–3 N0, T1–3 N1, T1–3 N2, T4 N0–1) NSCLC as per UICC/AJCC, 7th edition, with negative margins, at 4–12 weeks before enrollment

    Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

    Resection by segmentectomy or wedge resection is not allowed.

    N3 disease is not allowed.
- If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will have occurred

    Systematic sampling is defined as removal of at least 1 representative lymph node at specified levels.

    Complete mediastinal lymph node dissection (MLND) is preferred. Mediastinal lymph node dissection entails resection of all lymph nodes at those same levels.

For patients who have undergone a right thoracotomy, sampling or MLND is required at Levels 4 and 7; for those who have undergone a left thoracotomy, sampling or MLND is required at Levels 5 and/or 6 and 7.

Exceptions will be granted for the following situations:

If patients have documented N2 disease in 1 level (per the UICC/AJCC staging system, 7th edition), not all levels need to be sampled.

If the preoperative staging imaging results (contrast computed tomography [CT] and positron emission tomography [PET] scans) do not suggest evidence of disease in the mediastinum, the patient may be considered eligible even if N2 nodal sampling was not performed per surgeon's decision.

- Documented ALK-positive disease according to an FDA-approved and CE-marked test
- Eligible to receive a platinum-based chemotherapy regimen according to the local labels or guidelines
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate hematologic function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:

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

  ANC $\geq 1500/\mu L$

  Hemoglobin ≥ 9 g/dL
- Adequate renal function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:

  Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) and

  Creatinine clearance (CrCl) ≥ 60 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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.

  Women of childbearing potential must have a negative serum pregnancy test result prior to randomization (maximum of -3 days) and within 10 days of the first dose of study drug. First dose of study drug (alectinib or chemotherapy) must be administered within 7 days from randomization.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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.

- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy
- Prior adjuvant radiotherapy for NSCLC

  Radiotherapy in the neo-adjuvant setting is allowed and must be completed at least 4 weeks prior to initiation of study treatment.
- Prior exposure to systemic anti-cancer therapy

  Anti-cancer therapy for an early stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment, may be allowed. The Medical Monitor could be consulted.
- Prior exposure to ALK inhibitors
- Stage IIIa N2 patients that, in the investigator's opinion, should receive PORT are excluded from the study

  Post-operative radiation therapy is not allowed in the study.
- Known sensitivity to any component of study drug (alectinib or planned chemotherapy) to which the patient may be randomized

  This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.
- Malignancies other than NSCLC within 5 years prior to enrollment, except for curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer, or any cured cancer that is considered to have no impact on DFS or OS for the current NSCLC
- Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post–major bowel resection
- Liver disease characterized by any of the following:

  ALT and AST $\geq 3 \times$ ULN

  or

  Impaired excretory function or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, or bleeding from esophageal varices

  or

  Active viral or active autoimmune, alcoholic, or other types of acute hepatitis.

  Active viral hepatitis B is defined as having positive hepatitis B surface antigen (HBsAg).

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (hepatitis B core antibody [HBcAb] – HbcAb-positive, but negative HBsAg) are eligible only if the HBV DNA test is negative.

Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.

- Japanese patients participating in the serial/intensive PK sample collection only: administration of strong/potent CYP450 3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib up to Week 3
- Any exclusion criteria based on local labels or guidelines for chemotherapy
- Patients with symptomatic bradycardia
- History of organ transplant
- Known HIV positivity or AIDS-related illness
- Any clinically significant concomitant disease or condition that could interfere with—or for which the treatment might interfere with—the conduct of the study or the absorption of oral medications or that would pose an unacceptable risk to the patients in this study, in the opinion of the Principal Investigator
- 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.

End of Study

This study is event-driven with a recruitment period of approximately 3 years. The required number of events for the primary analysis of the primary endpoint is expected to occur approximately 60 months after the first patient has been enrolled. Patients are to be treated until completion of the treatment period (24 months for alectinib and 4 cycles [21-day cycles] of platinum-based chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

Length of Study

The final survival follow-up analysis will be conducted at approximately 5 years after the last patient is enrolled. The study will formally end once the final survival follow-up analysis has been completed.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are alectinib and platinum-based chemotherapies.

Test Product (Investigational Drug)

Alectinib 600 mg (four 150-mg capsules) should be administered orally BID with food in the morning and evening. First dose of study drug should be administered as soon as possible after randomization and no later than 7 days after randomization. Treatment will continue until completion of treatment period (24 months), disease recurrence, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time. Patients should not take two doses at the same time to make up for a missed dose.

The patient will record their daily dose and time in a diary (Patient Dosing Diary).

Comparator

Platinum-based chemotherapy will be provided for 4 cycles, with each cycle lasting 21 days. Investigators can choose one of the permitted platinum-based chemotherapy regimens, which include the following:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

First dose of study drug should be administered as soon as possible after randomization, taking required premedication into account, and no later than 7 days after randomization. Treatment will continue until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

Institutions should follow their standard administration regiments (e.g., administration sequence or time) for the chemotherapy treatment. Patients must receive adequate premeditations, anti-emetic treatments, and IV hydration for platinum-based treatments according to the local standard of care and prescribing information.

Platinum-based chemotherapy cycles may be delayed for safety reasons; however, if interrupted for more than 21 days = 1 cycle), the cycle is considered a skipped cycle. This does not prevent investigator from completing 4 cycles.

The selected cisplatin-based chemotherapy regimen should remain the same for all cycles. For patients who experience unacceptable toxicity with cisplatin, carboplatin can be used. *The investigator should inform the Medical Monitor of t*he switch from a cisplatin-based regimen to a carboplatin-based regimen.

Statistical Methods

Primary Analysis

The primary and secondary efficacy analyses will be performed for all randomized patients (ITT population) and for the Stage II–IIIa subpopulation. The same analysis methods will be applied for both the ITT population and the Stage II–IIIa subpopulation.

Safety analyses will be performed on all randomized patients who received at least 1 dose of study medication.

Determination of Sample Size

Approximately 255 patients are expected to be randomized into the study. The number of Stage Ib patients will be capped at 25% to ensure that at least 75% of all randomized patients will have Stage II–IIIa disease. The resulting ITT population of all patients randomized will include a minimum of 191 patients in the Stage II–IIIa subpopulation.

Recruitment is assumed to happen at a rate of 0.034 patients per site per month, with a total of approximately 200 sites. Detailed recruitment is as follows:

- Months 1–2: 1 patient per month
- Month 3: 2 patients per month
- Month 4: 3 patients per month
- Months 5–6: 4 patients per month
- Months 7–9: 5 patients per month
- Months 10–12: 7 patients per month
- Month 13 onwards: 8 patients per month

Based on these assumptions, enrollment will take approximately 38 months to complete.

The sample size and the number of events required to demonstrate efficacy with regard to the primary efficacy endpoint DFS at the primary analysis are based on the following assumptions:

- Overall 2-sided significance level of 0.05 in the Stage II–IIIa subpopulation and the ITT population
- 80% power to detect a hazard ratio (HR) = 0.55, corresponding to an improvement in median DFS from 30–55 months for patients receiving alectinib compared with chemotherapy in the Stage II–IIIa subpopulation
- 80% power to detect an HR = 0.58 corresponding to an improvement in median DFS from 36–62 months for patients receiving alectinib compared with chemotherapy in the ITT population
- One interim analysis for DFS when approximately 67% of the total DFS events have occurred, with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries

Based on these assumptions, the primary DFS analysis will be conducted after approximately 89 DFS events in the Stage II–IIIa subpopulation have been observed. This is predicted to occur approximately 60 months (5 years) after the first patient is randomized.

The focus of this clinical trial is hypothesis testing, testing superiority of alectinib compared with chemotherapy with respect to DFS. To control the overall level of significance at a 2-sided error rate of 0.05, comparisons with respect to DFS between the alectinib and chemotherapy arms within the Stage II–IIIa subpopulation and the ITT population will be conducted hierarchically as follows:

- Disease-free survival (DFS) in the Stage II–IIIa subpopulation will be first tested at an overall 2-sided α-level of 0.05. If the 2-sided p-value corresponding to the stratified log-rank test is less than 0.0464 at the primary analysis (in order to adjust for 1 interim analysis for efficacy), the null hypothesis will be rejected, and it will be concluded that alectinib prolongs duration of DFS relative to chemotherapy in the Stage II–IIIa subpopulation. Stopping boundaries will be adjusted depending on the actual number of DFS events.
- If alectinib significantly prolongs DFS in the Stage II–IIIa subpopulation, then DFS in the ITT population will be tested at an overall 2-sided α-level of 0.05. If the 2-sided p-value corresponding to the stratified log-rank test is less than 0.0463 at the primary analysis (in order to adjust for 1 interim analysis for efficacy), the null hypothesis will be rejected, and it will be concluded that alectinib prolongs duration of DFS relative to chemotherapy in the ITT population. Stopping boundaries will be adjusted depending on the actual number of DFS events.

If alectinib has no significant effect on DFS in the Stage II–IIIa subpopulation, then DFS in the ITT population will not be tested.

Interim Analyses

There is 1 interim analysis for efficacy planned in the study for DFS. The interim analysis will be conducted after approximately 67% of events have been observed in the Stage II–IIIa subpopulation. Based on the assumptions described in the protocol, this relates to approximately 59 DFS events for the Stage II–IIIa subpopulation. This is predicted to occur approximately 44 months after the first patient is randomized (i.e., approximately 16 months before the primary analysis), although the exact timing of this analysis will depend on the actual number of DFS events in the Stage II–IIIa subpopulation, but irrespective of the number of DFS events observed in the ITT population.

To control the type I error, the stopping boundaries for the DFS interim and primary analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries. In the Stage II–IIIa subpopulation, the stopping boundary for early rejection of the null hypothesis for an overall 2-sided 5% significance level is $HR \leq 0.52$ ($p \leq 0.0118$). In the ITT population, the stopping boundary for early rejection of the null hypothesis for an overall 2-sided 5% significance level is $HR \leq 0.55$ ($p \leq 0.0121$). If less than 67% of DFS events in the ITT population have been observed at the time of reaching the required events for the interim analysis in the Stage II–IIIa subpopulation, the stopping boundaries will be adjusted depending on the actual number of DFS events observed in the ITT population. However, the ITT interim analysis would only take place in the case of early rejection of the null hypothesis in the Stage II–IIIa subpopulation.

An external iDMC will evaluate safety data on an ongoing basis and review the data from the interim analysis. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Board (IRB)/Ethics Committee (EC). A detailed plan will be included in the iDMC Charter.

Positive efficacy results at the interim analysis will not change the conduct of the study and timing of disease assessments.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ARDS	acute respiratory distress syndrome
AUC	area under the concentration–time curve
BID	twice a day
BICR	blinded independent central review
C_{max}	maximum observed concentration
CE	Conformité Européenne (European Conformity)
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CT	computed tomography (scan)
DAT	direct anti-globulin test
DFS	disease-free survival
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ESMO	European Society for Medical Oncology
EU-SmPC	Summary of Product Characteristics (European Union)
FDA	U.S. Food and Drug Administration
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
HUS	hemolytic-uremic syndrome
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Abbreviation	Definition
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRC	Independent Review Committee
IRF	Independent Review Facility
ITT	intent-to-treat (population)
IxRS	interactive voice or Web-based response system
KRAS	Kirsten rat sarcoma viral oncogene homolog
LACE	Lung Adjuvant Cisplatin Evaluation
MCS	mental component summary
MET	mesenchymal-epithelial transition factor
MLND	mediastinal lymph node dissection
MN	mobile nursing
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PCS	physical component summary
PET	positron emission tomography (scan)
P-gp	P-glycoprotein
PFS	progression-free survival
PK	pharmacokinetic
PORT	post-operative radiotherapy treatment
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
QTcF	QT interval corrected with use of Fridericia’s formula
RBR	Research Biosample Repository
RP2D	recommended Phase II dose
SAP	Statistical Analysis Plan

Abbreviation	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDF	survival distribution function
SLS	sodium lauryl sulfate
UK-SmPC	Summary of Product Characteristics (United Kingdom)
TKI	tyrosine kinase inhibitor
t_{max}	time to maximum observed concentration
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
USPI	United States Prescribing Information
WES	whole-exome sequencing
WGS	whole-genome sequencing

1. BACKGROUND

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

Cancer is a major cause of death worldwide and was responsible for 8.8 million deaths in 2015 according to the World Health Organization (WHO 2017), with non–small-cell lung cancer (NSCLC) being the leading cause of cancer-related mortality worldwide.

The highest estimated age-standardized incidence rates of NSCLC in men are reported in Central and Eastern Europe as 53.5 per 100,000 and in Eastern Asia as 50.4 per 100,000. In women, the incidence rates are generally lower, with the highest estimated rates in Northern America (33.8 per 100,000), Northern Europe (23.7 per 100,000), and Eastern Asia (19.2 per 100,000; GLOBOCAN 2012).

Survival rates for lung cancer tend to be lower than other common cancers because of its late diagnosis and limited availability of effective treatments. Around 60% of patients diagnosed with NSCLC already have advanced (Stage IIIb) or metastatic (Stage IV) disease, whereas approximately 30% are diagnosed with early-stage disease (Stage I or II) and approximately 10% with Stage IIIa. The 5-year survival rate for advanced and metastatic disease is very poor with the reported range between 1%–5%. For early stages, the 5-year survival rates are reported to be higher, ranging between 14%–70%, depending on the extent of the disease at diagnosis and available treatment options (Ravdin and Davis 2006; American Cancer Society [ACS] 2016; Cancer Research UK 2017).

Conventional anti-cancer therapies are far from satisfactory, and there is an unmet medical need for the development of new therapies for NSCLC. Progress in the identification of genetic mutations or chromosomal rearrangements in epidermal growth factor receptor (*EGFR)*, Kirsten rat sarcoma viral oncogene homolog (*KRAS*), mesenchymal-epithelial transition (*MET*) factor, and other genes has provided new opportunities to use targeted therapeutic agents for the treatment of advanced and metastatic NSCLC, when the tumor is identified as having these mutations (Katayama et al. 2011; Doebele et al. 2012).

Approximately 4%–5% of NSCLC cases have been shown to harbor the echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (*ALK*) fusion gene as a result of a chromosomal inversion at 2p21 and 2p23 (Choi et al. 2010; Ou et al. 2012; Paik et al. 2012; Blackhall et al. 2014).

In the advanced and metastatic setting, there are currently 4 approved treatments for patients with ALK-positive NSCLC that have been shown to provide clinical benefit and favorable tolerability compared with the previously used standard of care, platinum–based chemotherapy for patients with ALK-positive NSCLC.

Crizotinib (Xalkori®; Pfizer, Inc.) was the first ALK inhibitor approved and registered for the treatment of advanced and metastatic ALK-positive NSCLC (Sahu et al. 2013; Shaw et al. 2013). Crizotinib was granted approval for first-line treatment of patients with ALK-positive NSCLC with advanced or metastatic disease based on the results of the Phase III PROFILE 1014 study, which showed a significantly longer progression-free survival (PFS) for patients treated with crizotinib as compared with platinum-based chemotherapy (median PFS: 10.9 months vs. 7.0 months) in patients with previously untreated ALK-positive NSCLC. Since then, second-generation ALK inhibitors like alectinib, ceritinib, and brigatinib have been granted marketing authorization as first- or second-line treatment for advanced and metastatic ALK-positive NSCLC.

Despite advancements in the use of targeted therapies in advanced and metastatic NSCLC, none of the currently available targeted treatments have been approved in the adjuvant setting. For patients diagnosed with early-stage NSCLC (Stages I–IIIa), complete resection of the tumor is the preferred treatment option. For patients with resected Stage Ib (tumors $\geq$4 cm) to IIIa, adjuvant therapy has been shown to be of benefit following complete resection (Pignon et al. 2008). In this setting, the current standard of care is platinum-based chemotherapy according to the National Comprehensive Cancer Network (NCCN 2017) and European Society for Medical Oncology (ESMO) guidelines (Postmus et al. 2017).

1.2 BACKGROUND ON ALECTINIB

Alectinib (also referred to as RO5424802 or CH5424802) is a small-molecule, highly selective and potent oral next-generation ALK inhibitor with a benzo[b]carbazole scaffold.

The clinical development program for alectinib to date includes 2 single-arm Phase I/II studies in patients with advanced or metastatic ALK-positive NSCLC who have failed crizotinib treatment: Study NP28761/AF-002JG (hereafter referred to as Study NP28761), which was conducted in United States and Canada, and Study NP28673, which was conducted globally.

The clinical development program also includes the following randomized Phase III studies. The ALUR study (Study MO29750) was conducted globally and compares alectinib head-to-head with chemotherapy in patients who have failed both platinum-based chemotherapy and crizotinib treatment. In addition, 3 studies are being conducted to compare alectinib head-to-head with crizotinib in treatment-naive patients with advanced or metastatic disease: 1) the ALEX study (Study BO28984), being conducted globally, 2) the J-ALEX study, being conducted in Japan, and 3) the ALESIA study, being conducted in China.

1.2.1 Study NP28761

Study NP28761 was a multicenter, open-label, 2-part study of alectinib in patients with Stage IIIb–IV, ALK-positive NSCLC who had progressed on crizotinib therapy. A total of

134 patients were enrolled in the study, including 47 patients in the Phase I dose-escalation portion and 87 patients in the Phase II portion. In Phase I, alectinib administered at 600 mg twice a day (BID) was chosen as the recommended Phase II dose (RP2D) on the basis of safety, tolerability, pharmacokinetic (PK), and efficacy data (Gadgeel et al. 2014).

The study met its primary objective of demonstrating a clinically meaningful and statistically significant Independent Review Committee (IRC)-assessed objective response rate (ORR). The results of other secondary endpoints were supportive of the primary analyses, including investigator-assessed ORR (Shaw et al. 2016).

1.2.2 Study NP28673

Study NP28673 was a multicenter, open-label study of alectinib in patients with NSCLC who had progressed on crizotinib therapy. During the conduct of Part 1 (Phase I) of this study, the RP2D was confirmed to be 600 mg BID in Study NP28761. Therefore, Part 1 was not concluded, and patients enrolled in Part 1 were merged into Part 2 (Phase II). A total of 138 patients with Stage IIIb–IV, ALK-positive NSCLC were enrolled in the Phase II part of the study.

The study met its primary objective of demonstrating a clinically meaningful and statistically significant ORR based on IRC assessments. The co-primary objective of IRC-assessed ORR in the subgroup of chemotherapy-pretreated patients, although not met, was clinically meaningful. The results of other secondary endpoints were supportive of the primary analyses, including investigator-assessed ORR (Ou et al. 2016).

Updated safety and efficacy data were generated using a data cutoff date of 22 January 2016 for Study NP28761 and 1 February 2016 for Study NP28673 and confirmed the results from the primary analysis for all endpoints (see Table 1).

In the pooled safety data analysis from Studies NP28761 and NP28673, almost all patients (98.8%) reported at least 1 adverse event. Adverse events occurring with an incidence of ≥20% of patients were constipation (36%), fatigue (32%), peripheral edema (29%), myalgia (25%), nausea (22%), and cough (21%). There were 100 of 253 patients (39.5%) with at least 1 adverse event Grade ≥3. The following Grade ≥3 events were reported in ≥2% of the patients: increased blood CPK (4%), dyspnea (4%), increased ALT (3%), increased AST (3%), hypertriglyceridemia (2%), and anemia (2%). For additional details, refer to the Alectinib Investigator's Brochure.

Table 1 Summary of Efficacy Results from Studies NP28761 and NP28673

Endpoint	Study (Cutoff Date)	
	NP28761 Phase II (22 January 2016)	NP28673 Phase II (1 February 2016)
ORR (IRC) in RE population	N = 67 [a]	N = 122 [a]
No. responders (%)	35 (52.2%)	62 (50.8%)
95% CI [b]	(39.7%, 64.6%)	(41.6%, 59.9%)
ORR (Investigator) in RE population	N = 87	N = 138
No. responders (%)	46 (52.9%)	71 (51.4%)
95% CI [b]	(41.9%, 63.7%)	(42.8%, 60.0%)
C-ORR (IRC) in patients with measurable CNS lesions at baseline based on RECIST	N = 16	N = 34
No. responders (%)	12 (75.0%)	20 (58.8%)
95% CI	(47.6%, 92.7%)	(40.7%, 75.4%)
PFS (IRC)	N = 87	N = 138
Median, months	8.2	8.9
95% CI	(6.3, 12.6)	(5.6, 12.8)

C-ORR = CNS objective response rate; IRC = Independent Review Committee; ORR = objective response rate; PFS = progression-free survival; RE = response evaluable; RECIST = Response Evaluation Criteria in Solid Tumors.

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

[b] Equivalent to a test of the null hypothesis that the ORR was equal to 35% vs. the alternative hypothesis that the ORR was not equal to 35% (lower boundary of CI > 35%), using an exact Clopper-Pearson CI.

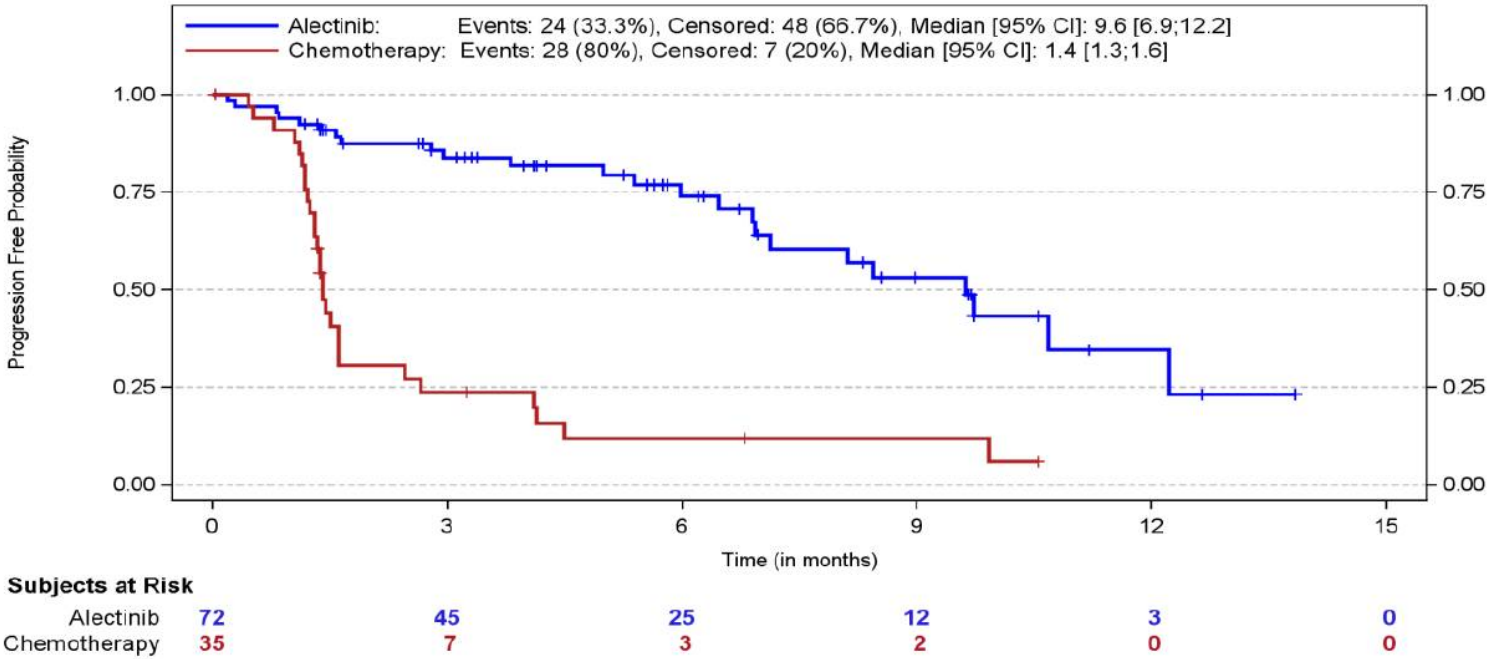
1.2.3 Study MO29750 (ALUR)

Study MO29750 (ALUR) was a randomized, multicenter, open-label, Phase III study of alectinib versus standard chemotherapy (pemetrexed or docetaxel) in patients with advanced, recurrent, or metastatic ALK-positive Stage IIIb–IV NSCLC previously treated with platinum-based chemotherapy and crizotinib. At the time of the primary analysis of ALUR (data cutoff: 26 January 2017), 107 patients had been randomized, 72 patients to alectinib and 35 patients to chemotherapy (2:1 randomization).

The ALUR study met its primary endpoint of demonstrating a statistically significant and clinically meaningful improvement in investigator-assessed PFS with alectinib compared with chemotherapy in the intent-to-treat (ITT) population (see Figure 1). Treatment with alectinib reduced the risk of disease progression or death by 85% compared with

chemotherapy, as shown by a stratified hazard ratio (HR) = 0.15 (95% CI: 0.08 to 0.29; $p < 0.001$). The estimated median PFS was 8.2 months longer in the alectinib arm (9.6 months vs. 1.4 months for chemotherapy).

Figure 1 Primary Efficacy Endpoint: Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival in ALUR—ITT Population



ITT = intent-to-treat.

The results for the secondary endpoints were in line with those for the primary endpoint. In particular, for the key secondary endpoint of the study, alectinib demonstrated a statistically significant and clinically meaningful improvement in IRC-assessed CNS ORR for patients with measurable CNS metastases at baseline.

In spite of a median treatment duration in the alectinib arm that was 3 times longer than the chemotherapy arm, a lower proportion of alectinib-treated patients experienced adverse events (any grade: 77% alectinib vs. 85% chemotherapy). In addition, when compared with patients who received chemotherapy, fewer patients treated with alectinib experienced severe adverse events (Grade ≥ 3), adverse events leading to discontinuation of study drug, and adverse events leading to dose reduction; however, more patients treated with alectinib experienced adverse events leading to dose interruption.

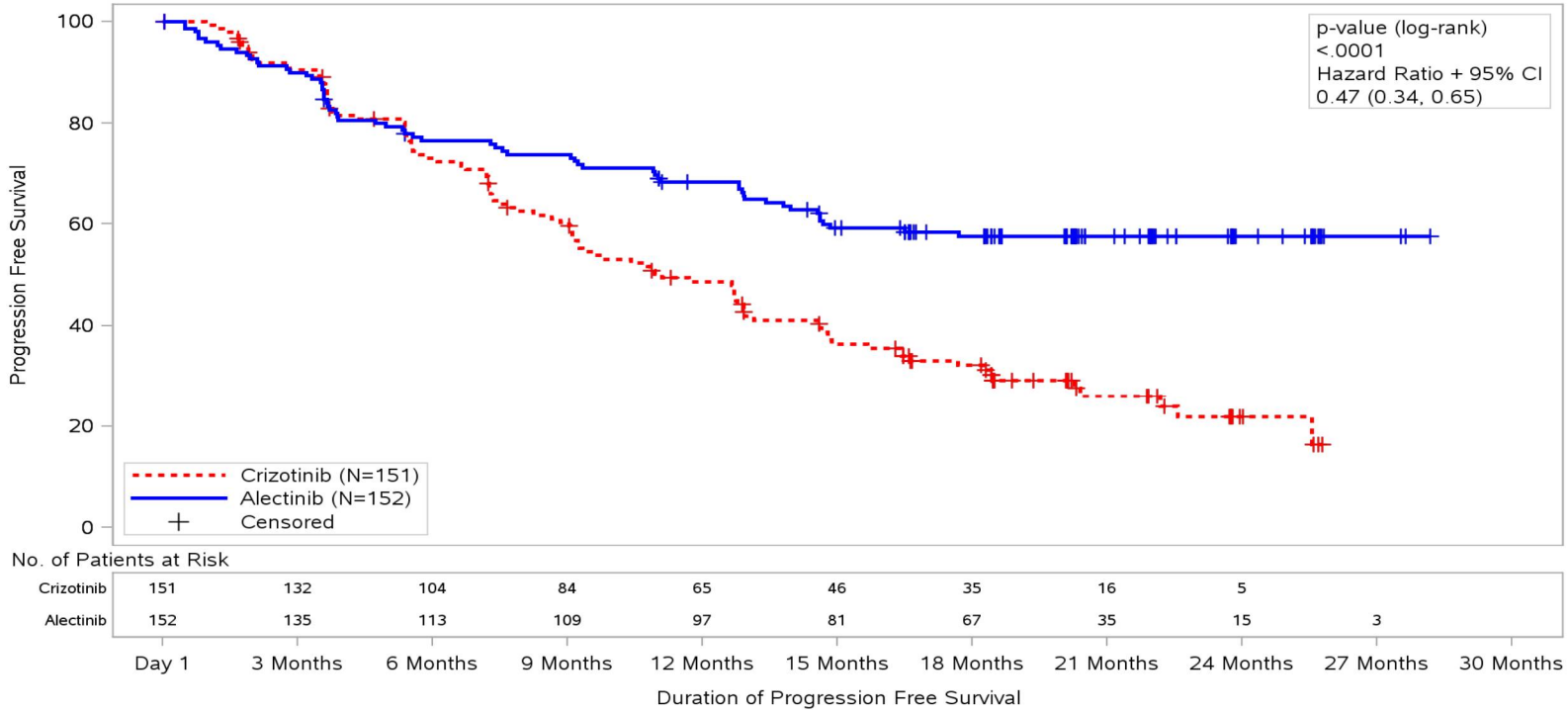
Refer to the Alectinib Investigator's Brochure for details on nonclinical and clinical studies.

1.2.4 Study BO28984 (ALEX)

Study BO28984 (ALEX) was a randomized, multicenter, open-label, Phase III head-to-head trial comparing alectinib and crizotinib in patients with treatment-naive, ALK-positive advanced or recurrent (Stage IIIb) or metastatic (Stage IV) NSCLC. A total of 303 patients were randomized to crizotinib (N = 151) or alectinib (N = 152).

The study met its primary objective (data cutoff: 9 February 2017) to demonstrate superiority of alectinib over crizotinib with respect to investigator-assessed PFS in the first-line setting of advanced ALK-positive NSCLC (see Figure 2). Alectinib significantly reduced the risk of disease progression or death by 53% compared with crizotinib, as shown by a stratified HR = 0.47 (95% CI: 0.34 to 0.65; $p < 0.0001$). At the time of the cutoff, median duration of PFS was 11.1 months with crizotinib and had not been reached with alectinib.

Figure 2 Primary Efficacy Endpoint: Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival in ALEX—ITT Population



Hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates Race (Asian vs Non-Asian) and CNS metastases at baseline by IRC.
Data cutoff: 09 February 2017.
Program: /opt/BIOSTAT/prod/cdpt7853/bo28984/g_ef_km.sas Output: /opt/BIOSTAT/prod/cdt7853t/t28984a/reports/g_ef_km_PFS_INV_IT.pdf 10APR2017 14:34

IRC = Independent Review Committee; ITT = intent-to-treat.

Notes: Hazard ratio was estimated by Cox regression. Stratified hazard ratio and p-value are stratified for covariates race (Asian vs. non-Asian) and CNS metastases at baseline by IRC.

Data cutoff: 9 February 2017.

The key secondary efficacy endpoints of IRC-assessed PFS and time to CNS progression, tested in the pre-specified hierarchy, were statistically significant with a HR = 0.50 (95% CI: 0.36 to 0.70) for IRC-assessed PFS and a cause-specific HR = 0.16 (95% CI: 0.10 to 0.28) for time to CNS progression by IRC.

Based on case reports from ALEX, acute kidney injury and increased weight have been identified as new adverse drug reactions for alectinib. Despite the longer treatment duration in the alectinib arm compared with the crizotinib arm, alectinib appeared to be tolerated better than crizotinib, as shown by the lower incidence of adverse events that were treatment-related, Grade ≥ 3 in severity, and led to treatment interruptions and dose reductions. For additional details, refer to the Alectinib Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Over 40% of patients with newly diagnosed NSCLC present with an early stage of disease (Stage I–IIIa). For these patients, resection of the tumor, if clinically feasible, is preferred. Despite complete resection, recurrence develops in up to 70% of patients (Ponn et al. 2005). For patients with Stage II–IIIa disease and among a subset of patients with Stage Ib disease in whom the tumor is ≥ 4 cm in size at baseline, adjuvant platinum-based chemotherapy administered following resection has been shown to provide additional, although limited, benefit. Over a median follow-up period of 5.2 years, comparing chemotherapy with no chemotherapy, the HR for overall survival (OS) was 0.89 (95% CI: 0.82 to 0.96; p = 0.005), corresponding to a 5-year survival benefit of 5.4% from chemotherapy and a 5-year disease-free survival (DFS) benefit of 5.8% over best supportive care (Pignon et al. 2008).

However, platinum-based chemotherapy has consistently been associated with significant toxicity, such as febrile neutropenia, myelosuppression, nausea, alopecia, nephropathy, and neuropathy. Thus, in addition to the modest treatment benefit reported for the platinum-based chemotherapy, the regimens are generally not well-tolerated, resulting in issues with treatment compliance (Pignon et al. 2008).

In the metastatic setting, targeted therapies such as erlotinib and gefitinib for patients with *EGFR*-mutated proteins and crizotinib and alectinib for patients with ALK-positive NSCLC have replaced the less efficacious and more toxic chemotherapy regimens in molecularly selected populations (Solomon et al. 2014; Ou et al. 2016; Shaw et al. 2016; Peters et al. 2017). In the adjuvant setting, the CTONG 1104 trial conducted in patients with *EGFR*-activating mutations was successful in demonstrating benefit with adjuvant gefitinib over platinum-based chemotherapy, suggesting that targeted therapies can provide meaningful clinical benefit in adjuvant NSCLC when administered to properly selected patient populations (Wu et al. 2017).

In a randomized double-blind Phase III trial (ADAURA), patients with resected EGFR mutation–positive NSCLC who received osimertinib had significantly longer DFS than those who received placebo (Wu et al. 2020). The ADAURA study results led to the U.S. Food and Drug Administration's (FDA) approval of osimertinib as the adjuvant therapy for EGFR mutation–positive NSCLC after tumor resection. In addition, a study of adjuvant crizotinib (Xalkori) is ongoing in patients with Stage Ib–IIIa, resected, ALK-positive NSCLC, as part of the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) scheme. No data from the ALCHEMIST study are available to report at this time.

Primary analysis of 2 global Phase III studies in ALK-positive advanced or metastatic (Stage IIIb–IV) NSCLC revealed a statistically significant and clinically meaningful benefit of alectinib compared with crizotinib in the first-line setting (ALEX) and compared with docetaxel or pemetrexed following recurrence on prior platinum-based chemotherapy and crizotinib (Study MO29750 [ALUR]; Novello et al. 2017; Peters et al. 2017). Both studies met their primary endpoints of investigator-assessed PFS. These results demonstrate a robust clinical benefit of alectinib, with a 53% and 85% reduction in the risk of a PFS event versus the comparator in ALEX and ALUR, respectively. Alectinib was better tolerated than crizotinib in ALEX and chemotherapy (docetaxel or pemetrexed) in ALUR, despite a substantially longer duration of treatment in the alectinib arm in both studies.

More detailed background information on the clinical efficacy of alectinib is presented in Section 1.2. Background information on the clinical safety of alectinib is presented in Section 1.2, Section 5.1, and the Alectinib Investigator's Brochure in more detail.

Identified and potential risks associated with alectinib treatment will be closely monitored throughout the clinical program. Patients' safety during the study is ensured by targeting the most appropriate patient population through inclusion/exclusion criteria, stringent safety monitoring by the Sponsor, and an independent Data Monitoring Committee (iDMC), as well as by protocol-specified study drug modification criteria (see Section 5.1.7).

In summary, a high unmet need remains for novel therapies that can provide greater clinical benefit with a more favorable safety profile than the current standard of care of platinum-based chemotherapy in the adjuvant setting. Overall, alectinib has shown meaningful benefit as well as an acceptable safety profile in a diverse population of advanced or metastatic ALK-positive NSCLC, including in patients who are treatment-naive and patients who have not received benefit from crizotinib treatment with or without prior chemotherapy. Furthermore, given the emerging data from targeted therapies in the post-operative setting of NSCLC, alectinib shows a potential of being beneficial for the adjuvant treatment of ALK-positive NSCLC. This would be consistent with the current treatment paradigm observed in the metastatic setting where, in the presence of actionable mutations or rearrangements of oncogene drivers such as *EGFR*

and *ALK*, targeted therapy is the recommended treatment of choice and has replaced chemotherapy by providing superior efficacy and a more tolerable safety profile.

1.3.1 *COVID-19 Benefit–Risk Assessment*

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how cancer therapies such as chemotherapy and targeted therapy impact the incidence or severity of COVID-19. Based on its safety profile and mechanism of action, it is not anticipated that the treatment used in this study will increase the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical trials with the treatment in this study have been ongoing during this pandemic and, although the study numbers are small, enrolled patients have not shown any increased risk of developing COVID-19 symptoms.

1.3.2 *COVID-19 Vaccines*

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

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

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib

(tumors ≥4 cm) to Stage IIIa, ALK–positive NSCLC. Specific objectives and corresponding endpoints for the study are outlined in Table 2.

The primary and secondary efficacy objectives will be analyzed in the ITT population of randomized patients with resected Stage Ib (tumors ≥4 cm) to Stage IIIa NSCLC and in the subpopulation of patients with resected Stage II–IIIa NSCLC.

Disease-free survival as an endpoint does not distinguish between the location of the first documented recurrence of disease or new primary NSCLC. Descriptive statistics (i.e., frequencies and percentages) will be used to explore the first site of recurrence of disease or new primary NSCLC.

Table 2 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥4 cm) to Stage IIIa, ALK-positive NSCLC	• DFS, defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC—as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status—or death from any cause, whichever occurs first
Secondary Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥4 cm) to Stage IIIa, ALK-positive NSCLC	• OS, defined as the time from randomization to death from any cause
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate DFS rates for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• DFS rates at landmark timepoints of 3, 4, and 5 years
• To evaluate the effects of demographics and baseline prognostic characteristics on duration of DFS for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• Effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) on duration of DFS by subgroup analyses

Table 2 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate the location of the first documented recurrence of disease or new primary NSCLC for patients in the alectinib arm compared with patients in the platinum-based chemotherapy arm	• The location of the first documented recurrence of disease or new primary NSCLC
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of alectinib compared with platinum-based chemotherapy in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• Incidence of adverse events, with severity determined through use of NCI CTCAE v5.0 • Safety laboratory values • Vital signs • ECG
Pharmacokinetic Objectives (Alectinib Arm Only)	**Corresponding Endpoint**
• To characterize the pharmacokinetics of alectinib and its major metabolite(s) in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC • **At Japanese sites only:** To characterize the pharmacokinetics of alectinib and its major metabolite(s) in Japanese patients	• Plasma concentrations of alectinib and its major metabolite(s) at specified timepoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To investigate molecular mechanisms of resistance to alectinib in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC	• Relationship between biomarkers in blood and tumor tissue (listed in Table 3) and efficacy (DFS)
Exploratory Patient-Reported Outcome Objectives	**Corresponding Endpoints**
• To document the impact of alectinib compared with platinum-based chemotherapy on patients' quality of life and daily function • To document health utilities for pharmacoeconomic modeling	• Mean change from baseline in PCS, MCS, and the PF scale as measured by their corresponding scores of the SF-36v2® • Health utilities as evaluated through the EQ-5D-5L

ALK = anaplastic lymphoma kinase; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; MCS = mental component summary; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non–small-cell lung cancer; PCS = physical component summary; PF = physical function.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This randomized, active-controlled, multicenter, open-label, Phase III study is designed to investigate the efficacy and safety of alectinib compared with platinum-based chemotherapy in the adjuvant setting. The primary endpoint of the study is DFS as assessed by the investigator, while OS is a secondary endpoint.

This study will be conducted at approximately 200 centers in around 30 countries worldwide. Central randomization will be performed via an interactive voice or Web-based response system (IxRS). Randomized patients will be stratified by extent of disease (Stage Ib [tumors $\geq$ 4 cm] vs. Stage II vs. Stage IIIa) and ethnicity (Asian vs. non-Asian). Relevant instructions will be provided to each study site by the IxRS provider.

Patients with completely resected (negative margins), histologically-confirmed Stage Ib (tumors $\geq$ 4 cm) to Stage IIIa NSCLC as per the Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) 7th edition (Detterbeck et al. 2009), with documented ALK-positive disease as assessed by a FDA–approved and Conformité Européenne (CE)-marked test and meeting all required eligibility criteria, will be randomized in a 1:1 fashion.

Staging must occur in accordance with the UICC/AJCC 7th edition and not the 8th edition. Patients with Stage Ib NSCLC with tumors $\geq$ 4 cm per the 7th edition classification have been shown to experience more modest benefit from adjuvant chemotherapy treatment than patients with Stage II–IIIa NSCLC, and this has been taken into consideration for recruitment capping, stratification, and statistical analysis of the primary endpoint.

Patients in the experimental arm will receive alectinib at 600 mg orally BID taken with food for 24 months.

Patients in the control arm will receive one of the protocol-specified platinum-based chemotherapy regimens (including all required premedications and permitted concomitant medications) according to the local prescribing information. Protocol-defined platinum-based chemotherapy regimens include:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

Platinum-based chemotherapy will be provided for 4 cycles, with each cycle lasting 21 days. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the above combinations.

Post-operative radiation therapy (PORT) is not allowed as a treatment option. Therefore, patients with Stage IIIa N2 NSCLC who, in the investigator's opinion, should receive PORT, are excluded from the study.

Study drug (alectinib or platinum-based chemotherapy) will be administered until the completion of the treatment period (24 months for alectinib and 4 cycles for chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Patients who complete a study treatment regimen or discontinue treatment prior to disease recurrence (e.g., due to unacceptable toxicity) will continue to be followed until disease recurrence. After disease recurrence, patients will be treated at the discretion of the investigator according to local clinical practice. No crossover in the adjuvant setting will be allowed between the 2 arms.

Approximately 255 patients will be enrolled into the study over a planned competitive recruitment period of approximately 38 months. Patients inappropriately randomized into the study will not be replaced. The primary DFS analysis will be conducted after approximately 89 DFS events in the Stage II–IIIa subpopulation have been observed. This is expected to occur approximately 60 months after the first patient is randomized. Data collection will continue for each patient until death or study closure, whichever occurs first.

An iDMC will be established to monitor the progress of the study and ensure that the safety of patients enrolled in the study is not compromised (see Section 5.1).

All randomized patients will undergo regular, scheduled visits until disease recurrence, death, withdrawal from the study, or study termination, whichever occurs first. Regular safety assessments will be performed for both arms during treatment. The safety follow-up visit will be performed 28 days after the last dose of alectinib or 28 days after the end of the last cycle of platinum-based chemotherapy. For the first 12 weeks (3 months), regular safety assessment visits will be scheduled at baseline and every 3 weeks (i.e., 1 chemotherapy cycle) for both arms. Additional visits will be scheduled for patients in the alectinib arm at Weeks 2, 4, 8, and 10 to allow for more frequent CPK and liver function assessments. Phone calls for safety monitoring of patients in the chemotherapy arm will be performed at the same timepoints (Weeks 2, 4, 8, and 10). From Week 12, patients in the alectinib arm will continue to be monitored for safety until treatment discontinuation every 6 weeks until Week 48 and every 12 weeks from Week 49–96. Scheduled disease assessments will be performed for both arms at baseline, every 12 weeks for the first 2 years, every 24 weeks during Years 3–5, and annually thereafter until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. If clinically indicated, unscheduled assessments can be performed at any time. Positive efficacy results at an interim analysis, as described in Section 6.9, will not influence the timing of disease assessments during the study.

For all patients, plasma samples for exploratory biomarker research will be obtained at baseline, every 3 weeks for the first 12 weeks, every 12 weeks from Weeks 13–96, every 24 weeks during Years 3–5, and annually thereafter until disease recurrence. Tumor samples will be obtained at study entry and upon disease recurrence for biomarker analysis (see Table 3).

Plasma samples will also be obtained for patients randomized to the alectinib arm pre-dose at baseline, every 3 weeks for the first 12 weeks, and every 12 weeks until Week 96 for PK analysis. At participating Japanese sites that can perform serial/intensive PK sampling, serial/intensive PK samples will be collected from a subset of Japanese patients receiving alectinib (approximately the first 6 patients who consent to participate in the serial/intensive PK sample collection) to facilitate the PK assessment in this population (see Appendix 3). The option to participate in the intensive Japanese PK profiling will be offered to these patients until at least 6 evaluable patients, as per protocol, have provided a reliable and complete PK profile. Therefore, more than 6 patients may participate in the serial/intensive PK assessment. However, the study team will make all efforts to provide complete profiles to the sites within the shortest timeframe.

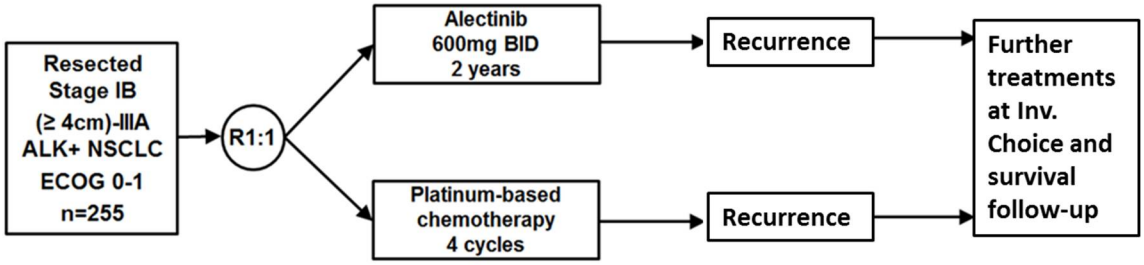
Table 3 Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Biomarkers
Plasma	At baseline and every 3 weeks for the first 12 weeks, every 12 weeks from Weeks 13–96, every 24 weeks during Years 3–5, and annually thereafter until disease recurrence	*ALK* rearrangements/mutations and other genes and gene mutations involved in resistance, and circulating tumor nucleic acids for MRD and early recurrence
Tumor tissue	At study entry and at disease recurrence	Confirmatory central ALK testing (at baseline only), and *ALK* rearrangements/mutations and other genes and gene mutations involved in resistance

ALK = anaplastic lymphoma kinase; MRD = minimal residual disease.

Figure 3 presents an overview of the study design. A schedule of activities is provided in Appendix 1 and Appendix 2.

Figure 3 Study Schema



ALK+ = anaplastic lymphoma kinase positive; BID = twice a day; ECOG = Eastern Cooperative Oncology Group (Performance Status); Inv. = investigator; NSCLC = non–small-cell lung cancer; R1:1 = 1:1 randomization.

3.2 END OF STUDY AND LENGTH OF STUDY

This study is event-driven with a recruitment period of approximately 3 years. The required number of events for the primary analysis of the primary endpoint is expected to occur approximately 60 months after the first patient has been enrolled. Patients are to be treated until completion of the treatment period (24 months for alectinib and 4 cycles [21-day cycles] of platinum-based chemotherapy), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

The final survival follow-up analysis will be conducted at approximately 5 years after the last patient is enrolled. The study will formally end once the final survival follow-up analysis has been completed.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Alectinib Dose and Schedule

The 600 mg BID dosing regimen of alectinib was established as the RP2D based on safety, tolerability, PK, and anti-tumor activity from the dose-escalation part of the Phase I/II Study NP28761. This dosing regimen has been approved in most countries, based on the results of the pivotal Phase II Studies NP28761 and NP28673 in the crizotinib-progressed or intolerant population. The justification of the global alectinib 600 mg BID clinical dosing regimen in the ALK inhibitor–naive population is supported by the observed efficacy and safety results (Peters et al. 2017) and the cumulative available data on alectinib pharmacokinetics and exposure-response from the global patient population in the ALEX study (Hsu et al. 2017).

The protocol-defined 2-year treatment duration is supported by efficacy and safety data reported from the ALEX study, in which alectinib was compared with crizotinib in the first-line metastatic setting. In this trial, IRC-assessed median PFS in the alectinib arm was shown to be 25.7 months [95% CI: 19.9 months, NE], whereas investigator-assessed median PFS was not reached at the time of primary analysis.

The median treatment duration with alectinib was 17.9 months at the time of the data cutoff, with 55% of patients in the alectinib arm still receiving treatment (Peters et al. 2017). It is anticipated that the mature median treatment duration will exceed 24 months. The safety analysis from ALEX was consistent with that reported in previous studies and compared favorably with that of crizotinib despite the long treatment duration (Ou et al. 2016; Shaw et al. 2016). The results were confirmed at the time of an updated analysis, reporting a median alectinib exposure of 20.6 months (range: 0–32 months). Despite the longer duration of treatment, the overall characteristics, types, and severities of adverse events from the updated analysis were consistent with those from the primary analysis, and no new or unexpected safety findings were identified.

Various clinical trials have been initiated in the adjuvant setting for NSCLC, comparing tyrosine kinase inhibitors (TKIs) with either placebo or chemotherapy. The TKI treatment duration in these trials is typically 2 or 3 years (Goss et al. 2013; Kelly et al. 2015). Most recently, results of the Phase III trial CTONG 1104, which compared gefitinib administered for 24 months versus 4 cycles of cisplatin plus vinorelbine in patients with *EGFR* mutation–positive NSCLC in the adjuvant setting, showed that targeted therapies can be of benefit in a properly selected NSCLC population. In the trial, patients experienced significantly longer DFS in the gefitinib arm compared with platinum-based chemotherapy, with a HR = 0.60 (95% CI: 0.42 to 0.87; p = 0.005). In addition, Grade ≥ 3 adverse events were less common with gefitinib than with platinum-based chemotherapy (12.3% vs. 48.3%, respectively), allowing for the conclusion that the 2-year treatment duration with gefitinib was beneficial and safe in the adjuvant setting in this molecularly-selected population (Wu et al. 2017).

Cumulatively, alectinib 600 mg BID administered with food has been chosen as the optimal therapeutic dose level with the best balance between efficacy and safety. Clinical data from the metastatic setting have shown that patients can be effectively and safely treated with alectinib for 2 years, and results from clinical trials of TKI treatment for NSCLC in the adjuvant setting have shown that a 2-year treatment duration is effective and shows a favorable safety profile in comparison with platinum-based chemotherapy.

Therefore, the protocol-defined experimental treatment will be 600 mg alectinib BID with food for 24 months administered orally.

3.3.2 Rationale for Open-Label Design of the Study

The open-label design of the study was chosen because alectinib is administered orally, whereas the comparator chemotherapies are administered intravenously. Furthermore, infusion times for the different chemotherapy regimens may vary. Blinding of treatments in this scenario would place undue burden on both patients and investigators.

3.3.3 Rationale for Patient Population and Analysis Groups

The study population will consist of patients who have undergone complete resection with negative margins (R0) of histologically-confirmed Stage Ib (tumors $\geq$ 4 cm) to Stage IIIa NSCLC as per UICC/AJCC, 7th edition. Patients will be randomized to receive either alectinib or platinum-based chemotherapy.

Post-operative radiotherapy treatment will not be allowed in the study. Post-operative radiotherapy treatment for patients with Stage I and II NSCLC has not been shown to provide additional benefit, while for patients with Stage IIIa N2 disease (R0), the benefit of PORT is not fully established. This is reflected in the recently published American Society of Clinical Oncology/Cancer Care Ontario guidelines on the use of PORT in the adjuvant setting where radiotherapy for patients with Stage IIIa N2 (R0) is not recommended for routine use, and it is advised that the benefits and risks of providing PORT for these patients should be carefully evaluated on a case-by-case basis (Kris et al. 2017).

In addition, PORT is associated with side effects that can appear during the treatment itself and/or up to 3–6 months after completion of treatment (Saynak et al. 2010; Patel et al. 2014; Radiology.org 2017). As per NCCN guidelines, PORT for patients with Stage IIIa N2 disease (R0) should only be provided following completion of adjuvant treatment, as its administration before or during adjuvant treatment could significantly delay, if not compromise, the planned adjuvant therapy.

However, because of the 24-month treatment duration for patients randomized to alectinib in the current study, delivery of PORT following adjuvant treatment may delay radiotherapy by at least 2 years, which may not be clinically meaningful. Thus, to prevent a potential under-treatment of patients randomized to the alectinib arm, as well as potential imbalances in efficacy and safety reporting between the 2 treatment arms, patients with Stage IIIa N2 disease that, in the investigator's opinion, could benefit from PORT, should not be enrolled in the study.

Patients will have ALK-positive disease as determined in accordance with local testing using an FDA-approved and CE-marked test, and ALK positivity will also be confirmed retrospectively by central testing. If local ALK testing is not available, patients can be tested centrally using the Ventana immunohistochemistry (IHC) assay.

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, comparing outcomes of adjuvant platinum-based treatment with best supportive care following complete resection of NSCLC, identified a variation in the magnitude of benefit between the different disease stages. The results indicated that patients with Stages II and III NSCLC (HR = 0.83 for each) experienced notable treatment benefit, while a more moderate effect was observed for patients with Stage Ib (HR = 0.93) and a potential deleterious effect in Stage Ia (HR = 1.40; Pignon et al. 2008). In the Cancer and Leukemia Group B 9633 study of adjuvant platinum-based chemotherapy in

Stage Ib NSCLC, a survival advantage was not observed with platinum-based chemotherapy in the ITT (Stage Ib) population. However, an exploratory analysis demonstrated a survival difference in favor of adjuvant chemotherapy for patients who had tumors ≥ 4 cm in diameter (HR = 0.69 [95% CI: 0.48 to 0.99]; Strauss et al. 2008).

Due to the potential variation in benefit with disease stage, with the strongest effect seen in Stages II and III and more moderate effects observed in earlier stages, the primary efficacy endpoint of investigator-assessed DFS will be tested using a hierarchical fixed-sequencing approach, testing patients with Stage II–IIIa first, followed by the ITT population, which includes patients with Stage Ib (tumors ≥ 4 cm) to IIIa (per UICC/AJCC, 7th edition). Stratification based on disease stage will be performed at randomization to ensure an equal distribution of patients with different disease stages between the treatment arms. In addition, efforts will be taken to ensure that at least 75% of the patients will have Stage II–IIIa disease by capping the number of patients with Stage Ib disease (as per UICC/AJCC, 7th edition) at 25%, a ratio consistent with what has been reported for the distribution of early-stage NSCLC (Decision Resources Group 2014).

The study is a global trial and, in order to ensure the applicability of the study data to a global population, efforts will be taken to ensure that no more than 75% of the subjects are of Asian race. To assess the generalizability of data from an Asian ALK-positive NSCLC population to a global population, a comprehensive literature search was conducted to review and compare key demographic and clinical characteristics in studies conducted in Asian populations with those conducted in non-Asian patients. The overall results of the literature review suggest similar patterns in Asian and non-Asian cohorts with regard to main baseline characteristics of ALK-positive NSCLC. In line with the results of the literature review, a recent publication (Nishio et al. 2017) comparing outcomes for Asian vs. non-Asian subgroups from the crizotinib studies, PROFILE 1007 and 1014, indicates that the baseline characteristics for the 2 groups were similar.

Results from alectinib studies conducted in the metastatic setting indicate a comparable efficacy outcome, safety profile, and PK profile for alectinib in the Asian and non-Asian population. In the ALEX study evaluating alectinib versus crizotinib in the first-line setting, 138 of 303 patients (45%) enrolled were Asian. A subgroup analysis of the primary endpoint of investigator-assessed PFS showed very consistent results in the Asian and non-Asian populations with PFS HRs = 0.46 (95% CI: 0.28 to 0.75) and 0.49 (95% CI: 0.32 to 0.75), respectively. This consistency was confirmed in the PFS subgroup analysis according to the IRC, with HRs = 0.49 (95% CI: 0.30 to 0.79) and 0.56 (95% CI: 0.36 to 0.87) in the Asian and non-Asian populations, respectively. A total of 69 of 138 Asian patients (50%) enrolled in the ALEX study received alectinib treatment. The safety subgroup analysis showed that race did not substantially influence the type and rate of adverse events reported. The most common event terms reported in each subgroup (Asian and non-Asian) were consistent with the overall

population, and overall differences in the incidence rate between Asian and non-Asian populations were small (generally $<10\%$ absolute difference).

3.3.4 Rationale for Control Group

Platinum-based chemotherapy is considered the standard of care for adjuvant treatment of NSCLC following resection according to NCCN and ESMO guidelines (NCCN 2017; Postmus et al. 2017). In this comparative study, the control arm will receive one of the protocol-defined, platinum-based chemotherapies, which includes cisplatin plus vinorelbine, cisplatin plus gemcitabine, and cisplatin plus pemetrexed.
The platinum-based chemotherapy regimen for patients randomized to the control arm will be chosen by investigator from the protocol-defined regimens according to local clinical practice. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the above combinations. As per NCCN and ESMO guidelines, platinum-based chemotherapy will be provided for 4 cycles, with each cycle lasting 21 days. The chemotherapy doses defined in the protocol are in line with recommendations in the NCCN guidelines.

The benefit provided by platinum-based chemotherapy in the adjuvant setting has been shown in a number of adjuvant NSCLC trials and has been summarized in a pooled analysis performed by the LACE Collaborative Group (Pignon et al. 2008). Results from the pooled LACE analysis indicated an increase in DFS and OS benefit at 5 years of 5.8% and 5.4%, respectively, compared with best supportive care. No significant difference in benefit was seen between the various chemotherapy regimens used. However, the platinum-based treatments are associated with significant side effects that can result in poor compliance.

There remains a high unmet need in patients with resectable NSCLC for more effective adjuvant therapies with a manageable and well-tolerated safety profile. Considering the robust efficacy data and acceptable safety profile observed with for alectinib in the metastatic setting, a head-to-head comparison between alectinib and platinum-based chemotherapy is warranted.

3.3.5 Rationale for PK Sample Collection Schedule

To date, the pharmacokinetics of alectinib have been characterized in crizotinib-naive patients with NSCLC who have failed to benefit from chemotherapy (Study AF-001JP), in patients who have failed to benefit from both chemotherapy and crizotinib treatment (Studies NP28761 and NP28673), and in patients with previously untreated, advanced ALK-positive NSCLC (ALEX and J-ALE). To better understand the pharmacokinetics of alectinib by identifying variables affecting exposure and to further support the development of a robust population PK characterization of alectinib, pharmacokinetics will be assessed in this study. This study will include PK assessment of alectinib in patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa, ALK-positive NSCLC by collecting samples from all patients randomized to the alectinib arm. For a

subset of patients randomized at Japanese sites (approximately the first 6 patients), serial/intensive PK samples will be collected to facilitate the PK assessment in this population in support of the optimal use of alectinib in the Japanese population, including identification of the appropriate alectinib dosing regimen in the adjuvant population in Japan.

The data collected from this study will enable a more robust understanding of alectinib pharmacokinetics in this global population and support optimal use of alectinib therapy, including investigation and potential identification of sources of variability, influencing alectinib pharmacokinetics and/or response to alectinib therapy.

3.3.6 Rationale for Biomarker Assessments

Several molecular mechanisms of resistance to crizotinib and other ALK inhibitors have been reported in the literature: secondary mutations in the *ALK* gene (e.g., gatekeeper mutation), increased copy number of the *ALK* gene, increased expression of ALK mRNA, and ALK-independent resistance mechanisms through activation of other oncogenic genes and pathways such as *EGFR*, *cKIT*, *MET* or *KRAS* (e.g., increased copy number, increased phosphorylation, or point mutations; Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013; Lin et al. 2017). Recently, the effects of different ALK variants on the efficacy of crizotinib were explored (Yoshida et al. 2016).

To investigate molecular mechanisms of resistance to ALK inhibitors and the *ALK* mutation status, as well as to explore the effect on efficacy by different *ALK* variants, tumor samples will be collected before treatment and at the time of recurrence to perform targeted sequencing on nucleic acids. A panel of known cancer genes and *ALK* rearrangements will be used for targeted sequencing.

The amount of circulating tumor nucleic acids shed into the bloodstream by the tumor can be used to detect early tumor recurrence. Additionally, gene rearrangements and somatic mutations in cancer genes appearing from drug resistance in *ALK* and other cancer-related genes can be detected in circulating tumor nucleic acids and monitored in plasma (Forshew et al. 2012). Tumor nucleic acids are shed into circulation in amounts that allow direct sequencing. Plasma samples will be collected before treatment and at defined timepoints during treatment to monitor for circulating tumor nucleic acids, gene rearrangements, and mutations in *ALK* and other cancer-related genes likely to be involved in resistance to ALK inhibitors. Information from mutated genes in the tumor will be correlated with mutations detected in plasma circulating tumor nucleic acids.

Determination of ALK positivity will be performed at sites by an FDA-approved and CE-marked test or by central Ventana ALK IHC. Local ALK-positive test results will be confirmed retrospectively by central Ventana ALK IHC testing. For exploratory purposes, other methods to determine ALK positivity (e.g., reverse transcription-PCR) may also be used. Currently, ALK positivity for fusions can only be determined in tissue samples using assays such as fluorescence in situ hybridization, IHC, PCR, and

sequencing. As tissue sampling is difficult and tissue biopsy sample sizes from lung cancer patients are very small, testing of several important biomarkers is challenging. Many patients with NSCLC may not have enough tumor tissue available and therefore, cannot be tested for some biomarkers such as *ALK*. Plasma ALK assays analyzing circulating tumor nucleic acids will enable more patients with NSCLC to be tested for *ALK* fusions and may also be used to monitor changes in *ALK* rearrangements during ALK inhibitor treatment. Information from plasma ALK assays will be used to investigate the use of circulating tumor nucleic acids from plasma as a surrogate for tumor tissue for diagnostic purposes.

3.3.7 Rationale for Patient-Reported Outcome Assessments

The benefits associated with treatment in the post-resection adjuvant setting must be weighed with its residual short- and long-term impact on patients' health-related quality of life (HRQoL) and function (Myrdal et al. 2001; Brunelli et al. 2007; Ostroff et al. 2011).

In this study, patient-reported outcome (PRO) data will be collected from patients using the SF-36v2® Health Survey, which yields 2 component summary scores (i.e., physical and mental) and 8 health domains (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) that provide a generic assessment of HRQoL. In addition, in order to inform pharmacoeconomic modeling, health-status utility scores will be collected using the EQ-5D-5L Questionnaire.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this trial is approximately 255 patients with completely resected Stage Ib (tumors $\geq$4 cm) to Stage IIIa ALK–positive NSCLC.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 at time of signing Informed Consent Form
- Complete resection of histologically-confirmed Stage Ib (tumor $\geq$4 cm) to Stage IIIa (T2–3 N0, T1–3 N1, T1–3 N2, T4 N0–1) NSCLC as per UICC/AJCC, 7th edition, with negative margins, at 4–12 weeks before enrollment

  Accepted types of resection include any of the following: lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy.

  Resection by segmentectomy or wedge resection is not allowed.

  N3 disease is not allowed.

- If mediastinoscopy was not performed preoperatively, it is expected that, at a minimum, mediastinal lymph node systematic sampling will occurred

  Systematic sampling is defined as removal of at least 1 representative lymph node at specified levels.

  Complete mediastinal lymph node dissection (MLND) is preferred. Mediastinal lymph node dissection entails resection of all lymph nodes at those same levels.

  For patients who have undergone a right thoracotomy, sampling or MLND is required at Levels 4 and 7; for those who have undergone a left thoracotomy, sampling or MLND is required at Levels 5 and/or 6 and 7.

  Exceptions will be granted for the following situations:

  If patients have documented N2 disease in 1 level (per the UICC/AJCC staging system, 7th edition), not all levels need to be sampled.

  If the preoperative staging imaging results (contrast computed tomography [CT] and positron emission tomography [PET] scans) do not suggest evidence of disease in the mediastinum, the patient may be considered eligible even if N2 nodal sampling was not performed per the surgeon's decision.
- Documented ALK-positive disease according to an FDA-approved and CE-marked test
- Eligible to receive a platinum-based chemotherapy regimen according to the local labels or guidelines
- Eastern Cooperative Oncology Group (ECOG) Performance Status of Grade 0 or 1
- Adequate hematologic function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:

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

  ANC $\geq 1500/\mu L$

  Hemoglobin ≥ 9 g/dL
- Adequate renal function, defined by the following laboratory test results, obtained within 3 days prior to initiation of study treatment:

  Serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN) and

  Creatinine clearance (CrCl) ≥ 60 mL/min
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy

  A woman is considered to be of childbearing potential if she is post-menarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes,

and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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.

Women of childbearing potential must have a negative serum pregnancy test result prior to randomization (maximum of −3 days) and within 10 days of the first dose of study drug. First dose of study drug (alectinib or chemotherapy) must be administered within 7 days from randomization.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and 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.

- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the last dose of alectinib or according to local labels or guidelines for chemotherapy
- Prior adjuvant radiotherapy for NSCLC

  Radiotherapy in the neo-adjuvant setting is allowed and must be completed at least 4 weeks prior to initiation of study treatment.

- Prior exposure to systemic anti-cancer therapy

  Anti-cancer therapy for an early stage of malignancy with curative intent, provided that the last dose received was more than 5 years prior to enrollment, may be allowed. *The* Medical Monitor *could be consulted.*

- Prior exposure to ALK inhibitors
- Stage IIIa N2 patients that, in the investigator's opinion, should receive PORT are excluded from the study

  Post-operative radiation therapy is not allowed in the study.

- Known sensitivity to any component of study drug (alectinib or planned chemotherapy) to which the patient may be randomized

  This includes, but is not limited to, patients with galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption.

- Malignancies other than NSCLC within 5 years prior to enrollment, except for curatively treated basal cell carcinoma of the skin, early gastrointestinal (GI) cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer, or any cured cancer that is considered to have no impact on DFS or OS for the current NSCLC
- Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post–major bowel resection
- Liver disease characterized by any of the following:

  ALT and AST $\geq 3 \times$ ULN

  or

  Impaired excretory function or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, or bleeding from esophageal varices

  or

  Active viral or active autoimmune, alcoholic, or other types of acute hepatitis.

  Active viral hepatitis B is defined as having positive hepatitis B surface antigen (HBsAg).

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (hepatitis B core antibody [HBcAb] – HbcAb-positive, but negative HBsAg) are eligible only if the HBV DNA test is negative.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if PCR is negative for HCV RNA.

- Japanese patients participating in the serial/intensive PK sample collection only: administration of strong/potent CYP450 3A inhibitors or inducers within 14 days prior to the first dose of study treatment and while on treatment with alectinib up to Week 3 (see Appendix 5)
- Any exclusion criteria based on local labels or guidelines for chemotherapy

- Patients with symptomatic bradycardia
- History of organ transplant
- Known HIV positivity or AIDS-related illness
- Any clinically significant concomitant disease or condition that could interfere with—or for which the treatment might interfere with—the conduct of the study or the absorption of oral medications or that would pose an unacceptable risk to the patients in this study, in the opinion of the Principal Investigator
- 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 in which approximately 255 patients will be randomly assigned in a 1:1 allocation ratio to the two treatment arms via a block-stratified randomization procedure over a planned recruitment period of approximately 3 years.

Randomization will guard against systematic selection bias and should ensure the compatibility of the treatment groups. To assist balance in prognostic factors, randomization will be stratified by race (Asian vs. non-Asian) and disease stage (Stage Ib [tumors $\geq$4 cm] vs. Stage II vs. Stage III). Central randomization and drug allocation will be performed and managed via an IxRS. Relevant instruction will be provided to each study site by the IxRS provider.

Study site personnel and patients will be unblinded to treatment assignment information during the study. The Sponsor and its agents will be blinded to treatment assignment information, with the exception of individuals who require access to treatment assignments to fulfill critical tasks in their job roles to be performed during the clinical trial.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are alectinib and platinum-based chemotherapies.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Alectinib

Alectinib comes in a capsule dosage form containing the following active ingredient: 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 alectinib (as free base) along with lactose monohydrate, carboxymethylcellulose 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 (also known as sodium dodecyl sulfate) as an excipient. This excipient is known to be potentially associated with GI adverse events such as nausea, vomiting, diarrhea, and abdominal pain.

Alectinib will be supplied by the Sponsor as capsules in vials. For information on the formulation and handling of alectinib, see the Alectinib Investigator's Brochure.

4.3.1.2 Platinum-Based Chemotherapy

Cisplatin, pemetrexed, vinorelbine, gemcitabine, and carboplatin will be supplied by the Sponsor and used in the commercially available formulation where allowed by local regulations.

For information on the formulation, packaging, and handling of cisplatin, pemetrexed, vinorelbine, gemcitabine, and carboplatin, please refer to the United States Prescribing Information (USPI), Summary of Product Characteristics (SmPC), local prescribing information or local guidelines for each drug.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

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

Guidelines for dose reduction and treatment interruption or discontinuation for patients who experience adverse events are provided in Sections 5.1.7–5.1.12.

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 study drug should be administered as soon as possible after randomization and no later than 7 days after randomization. Treatment will continue until completion of treatment period (24 months), disease recurrence, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

If a planned dose of alectinib is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of alectinib, patients should take the next dose at the scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.

The patient will record their daily dose and time in a diary (Patient Dosing Diary).

4.3.2.2 Platinum-Based Chemotherapy

Platinum-based chemotherapy will be provided for 4 cycles, with each cycle lasting 21 days. Investigators can choose one of the permitted platinum-based chemotherapy regimens, which include the following:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

The first dose of study drug should be administered as soon as possible after randomization, taking the required premedication into account, and no later than 7 days after randomization. Treatment will continue until completion of treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

Institutions should follow their standard administration regimens (e.g., administration sequence or time) for the chemotherapy treatment. Patients must receive adequate premeditations, anti-emetic treatments, and IV hydration for platinum-based treatments according to the local standard of care and prescribing information.

Platinum-based chemotherapy cycles may be delayed for safety reasons; however, if interrupted for more than 21 days = 1 cycle), the cycle is considered a skipped cycle. This does not prevent investigator from completing 4 cycles.

The selected cisplatin-based chemotherapy regimen should remain the same for all cycles. For patients who experience unacceptable toxicity with cisplatin, carboplatin can be used. *The investigator should inform the Medical Monitor of the* switch from a cisplatin-based regimen to a carboplatin-based regimen.

Cisplatin plus Vinorelbine

Table 4 lists the doses and the suggested infusion times for vinorelbine plus platinum-based treatments at Cycle 1. Doses for subsequent cycles can be modified in case of toxicities. Chemotherapy infusion times may be adapted in accordance with local standard of care.

Table 4 Doses and Suggested Infusion Times for Administration of Vinorelbine in Combination with Cisplatin or Carboplatin

Chemotherapy	Dose/Route	Infusion
Vinorelbine plus Cisplatin	25 mg/m^2 IV 75 mg/m^2 IV	Over 6–10 minutes on Days 1 and 8 Q21D Over 6–8 hours on Day 1 Q21D
Vinorelbine plus Carboplatin [a]	25 mg/m^2 IV AUC 5 IV	Over 6–10 minutes on Days 1 and 8 Q21D Over approximately 30–60 minutes on Day 1 Q21D

AUC = area under concentration-time curve; Q21D = every 21 days.

[a] Only in case of intolerability, cisplatin can be replaced by carboplatin.

The vinorelbine injection must be diluted prior to infusion in a*n* IV bag. The following solutions may be used for dilution of vinorelbine in IV bag: 5% dextrose injection, 0.9% sodium chloride, 0.45% sodium chloride, 5% dextrose and 0.45% sodium chloride, Ringer's Injection, or Lactated Ringer's Injection. The administration of vinorelbine should be done in accordance with local practice and prescribing information.

It is very important that the IV needle or catheter is properly positioned before vinorelbine is injected. Leakage into surrounding tissue during IV administration of vinorelbine may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Because there are no established guidelines for the treatment of extravasation injuries with vinorelbine, institutional guidelines may be used.

A prophylactic bowel regimen should be instituted to mitigate potential constipation, bowel obstruction, and/or paralytic ileus, considering adequate dietary fiber intake, hydration, and routine use of stool softeners.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.8 for vinorelbine, Section 5.1.11 for cisplatin, and Section 5.1.12 for carboplatin.

Cisplatin plus Gemcitabine

Table 5 lists the doses and the suggested infusion times for gemcitabine plus platinum-based treatments at Cycle 1. Doses for subsequent cycles can be modified in case of toxicities. Chemotherapy infusion times may be adapted in accordance with local standard of care.

Table 5 Doses and Suggested Infusion Times for Administration of Gemcitabine in Combination with Cisplatin or Carboplatin

Chemotherapy	Dose/Route	Infusion
Gemcitabine plus Cisplatin	1250 mg/m^2 IV 75 mg/m^2 IV	Over 30 minutes on Days 1 and 8 Q21D Over 6–8 hours on Day 1 Q21D
Gemcitabine plus Carboplatin [a]	1000 mg/m^2 IV AUC 5 IV	Over 30 minutes on Days 1 and 8 Q21D Over approximately 30–60 minutes on Day 1 Q21D

AUC = area under the concentration–time curve; Q21D = every 21 days.

[a] Only in case of intolerability, cisplatin can be replaced by carboplatin.

The gemcitabine injection must be diluted prior to infusion. The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride injection without preservatives. The administration of gemcitabine should be done in accordance with local practice and the prescribing information; sites should follow their institutional standard of care for determining the gemcitabine dose for obese patients and for dose adjustment in the event of patient weight changes.

Renal and hepatic function must be monitored prior to initiation of therapy and periodically thereafter.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.9 for gemcitabine, Section 5.1.11 for cisplatin, and Section 5.1.12 for carboplatin.

Cisplatin plus Pemetrexed

Table 6 lists the doses and the suggested infusion times for pemetrexed plus platinum-based treatments at Cycle 1. Doses for subsequent cycles can be modified in case of toxicities. Chemotherapy infusion times may be adapted in accordance with local standard of care.

Table 6 Doses and Suggested Infusion Times for Administration of Pemetrexed in Combination with Cisplatin or Carboplatin

Treatment	Dose/Route	Infusion
Pemetrexed	500 mg/m^2 IV	Over ~10 minutes on Day 1 Q21D
Cisplatin	75 mg/m^2	Over 6–8 hours on Day 1 Q21D
Carboplatin [a]	AUC 5 or 6 IV [a]	Over ~30–60 minutes on Day 1 Q21D

AUC = area under the concentration-time curve; Q21D = every 21 days.

[a] Only in case of intolerability, cisplatin can be replaced by carboplatin.

Patients should receive steroid, folic acid, and vitamin B12 premedication for pemetrexed to reduce the severity of skin, hematologic, and GI toxicity. The choice of steroid and timing of premedication can be administered according to the local standard of care and prescribing information (see Table 7).

Table 7 lists the suggested premedication for the pemetrexed plus platinum-based chemotherapy.

Table 7 Premedication for Pemetrexed Plus Platinum-Based Chemotherapy

Premedication	Dose/Route	Treatment
Folic acid	350–1000 μg PO	Once daily beginning 5–7 days before Cycle 1, Day 1, and continuing until 21 days after discontinuation of pemetrexed or as per local standard of care
Vitamin B12	1000 μg IM	Q9W (i.e., every 3 cycles) beginning in the week prior to first dose of pemetrexed and continuing until 21 days after discontinuation of pemetrexed or as per local standard of care. Subsequent vitamin B12 injections may be given the same day as treatment with pemetrexed.
Dexamethasone (or equivalent to 4 mg dexamethasone)	4 mg PO	Twice daily the day prior to, the day of, and the day after each infusion of pemetrexed or as per local standard of care

IM = intramuscular; PO = by mouth; Q9W = every 9 weeks.

Note: Prophylactic anti-emetics per local practice.

Patients with mild-to-moderate renal insufficiency (CrCl 45–79 mL/min) should avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and acetylsalicylic acid (> 1.3 g daily) for:

- At least 2 days prior to pemetrexed administration if the NSAID has a short elimination half-life
- At least 5 days if the NSAID has a long elimination half-life
- On the day of pemetrexed administration
- At least 2 days following pemetrexed administration

Patients should be monitored more frequently for myelosuppression, renal toxicity, and GI toxicity if concomitant administration of ibuprofen cannot be avoided.

At the start of each cycle, the ANC must be ≥ 1500/μL, the platelet count must be ≥ 100,000/mm^3, and the CrCl must be ≥ 45 mL/min *(or CrCl must be ≥ 60 mL/min when pemetrexed is given together with cisplatin).*

The effect of third space fluid, such as pleural effusion or ascites, on pemetrexed is not fully defined. Thus, drainage of third space fluid collection prior to pemetrexed treatment should be considered but may not be necessary.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.10 for pemetrexed, Section 5.1.11 for cisplatin, and Section 5.1.12 for carboplatin.

General Guidance for Cisplatin and Carboplatin Administration

Cisplatin: Cisplatin should be administered by IV infusion approximately 30 minutes after completion of the vinorelbine, gemcitabine, or pemetrexed infusion at a dose of 75 mg/m² over 6–8 hours (see Table 4, Table 5, and Table 6, respectively). Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin. Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. Refer to local clinical practice guidelines for further details.

Prior to initiating therapy and prior to each subsequent cycle, safety laboratory tests (in particular serum creatinine, BUN, CrCl, magnesium, sodium, potassium, and calcium) should be assessed, and audiometric testing should be performed as per local clinical practice.

Peripheral blood counts and liver function should be monitored periodically, and neurologic examination should be performed regularly as per local clinical practice.

Carboplatin: Carboplatin should be administered by IV infusion at a dose of area under the concentration-time curve (AUC) 5 when given in combination with vinorelbine (see Table 4) or gemcitabine (see Table 5) or at a dose of AUC 5 or 6 when given in combination with pemetrexed (see Table 6), or after completion of the pemetrexed, gemcitabine, or vinorelbine infusion, with standard anti-emetics per local practice guidelines.

The carboplatin dose will be calculated using the Calvert formula (Calvert et al. 1989):

$$\text{Total dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. For the purposes of this protocol, the GFR is considered to be equivalent to the CrCl. The CrCl is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) using the following formula:

$$\text{CrCl} = \frac{(140 - \text{age})\ (\text{wt})}{72 \times S_{cr}} \quad (\text{x } 0.85 \text{ if female})$$

Where: CrCl = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
S_{cr} = serum creatinine in mg/dL

NOTE: For patients with an abnormally low serum creatinine level, estimate GFR using a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated on the basis of serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity caused by overdosing. On the basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \times \text{min/mL)} \times (\text{GFR} + 25 \text{ mL/min})$$

The maximum dose is based on a GFR estimate that is capped at 150 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg.

For a target AUC = 5, the maximum dose is $5 \times 150 = 750$ mg.

For a target AUC = 4, the maximum dose is $4 \times 150 = 600$ mg.

Refer to the FDA's communication regarding carboplatin dosing for more details at the following Web site:

https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ ucm228974.htm

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (alectinib and all chemotherapy drugs) will be provided by the Sponsor where required by local health authority regulations.
The study site will acknowledge receipt of IMPs supplied by the Sponsor using IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Investigational medicinal products will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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

Currently, the Sponsor does not have any plans to provide the Roche IMP (alectinib) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing alectinib in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug to the study drug discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Premedication with antihistamines, anti-pyretics, and/or analgesics may be administered at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice.
Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

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

4.4.1 Cautionary Therapy

4.4.1.1 Alectinib

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

- For medications that are substrates of P-glycoprotein (P-gp) transporter or breast cancer resistance protein transporter, the investigator should carefully assess the risks against benefits when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided.
  If co-administration cannot be avoided, it is recommended that drug levels and/or signs for toxicity are carefully monitored (see Appendix 5).

4.4.1.2 Protocol-Defined Platinum-Based Chemotherapy Regimens

Plasma levels of anti-convulsant agents may become subtherapeutic during cisplatin therapy. Caution should be exercised when are co-administered with cisplatin. For full details, refer to the current versions of the local product labels.

4.4.1.3 Medications Given with Precaution due to Effects Related to CYP450 Enzymes

Vinorelbine is metabolized by CYP3A4. Exercise caution in patients concurrently taking drugs known to inhibit drug metabolism by hepatic CYP450 isoenzymes in the CYP3A subfamily. Concurrent administration of vinorelbine with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of adverse reactions. Therefore, the medications listed below should be avoided. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor prior to concomitant administration with vinorelbine.

- CYP3A4 inhibitors, including, but not limited to, boceprevir, cobicistat conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole, ritonavir saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone(h), erythromycin, fluconazole fluvoxamine imatinib, tofisopam, verapamil

The above lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2 Prohibited Therapy

4.4.2.1 For Patients Receiving Either Alectinib or Protocol-Defined Chemotherapy Regimens

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

- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment). Probenecid is prohibited for patients receiving pemetrexed chemotherapy.
- Systemic anti-cancer therapy
- Additional investigational drug (except for during the follow-up period)

- Radiotherapy/radionuclide therapy
- For patients receiving pemetrexed:
  - Use of NSAIDs such as ibuprofen and acetylsalicylic acid should be avoided, in accordance with Section 4.3.2.2.

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

4.4.2.2 For Japan Only: Patients Receiving Alectinib

For Japanese patients participating in the serial/intensive PK sample collection only, use of potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St. John's wort [*Hypericum perforatum*]) and or potent inhibitors of CYP3A (e.g., ketoconazole) within 2 weeks or 5 half-lives (whichever is longer) should be avoided before the first dose of study drug treatment and while on treatment with alectinib up to Week 3 (see Appendix 5). This is included to minimize the impact of extrinsic factors such as CYP3A inducers/inhibitors, which could confound PK assessments of the individual analytes, alectinib, or its active metabolite, M4.

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

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

https://medicine.iupui.edu/clinpharm/ddis/table.aspx (for CYP450 drug interactions)

4.4.3 Prohibited Food

Use of the following foods is prohibited as described below for patients receiving alectinib:

- For Japanese patients participating in the serial/intensive PK sample collection: use of grapefruit or grapefruit juice for at least 14 days prior to the initiation of the study and while on alectinib treatment up to Week 3 due to its potent CYP3A inhibitory effect

Use of the following foods is prohibited as described below for patients receiving vinorelbine:

- Use of grapefruit or grapefruit juice for at least 14 days prior to the initiation of the study and while on platinum-based chemotherapy regimens with vinorelbine treatment due to its potent CYP3A inhibitory effect

4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities must be performed and documented for each patient.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a vendor that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. Once the patient completes the onsite visit for Week 1, MN visits could be scheduled on specified visit days, to allow relevant assessments to be performed by the MN professional. The MN may contact the investigators during the home visit if required. Further details will be provided in the MN and Site guidance package. These assessments may include ECOG Performance Status, biospecimen collection (biomarkers, chemistry, coagulation, hematology, PK, pregnancy test, urinalysis, as applicable), vital signs, weight, limited symptom-directed physical assessment requested by the Principal Investigator, assistance/supervision with completion of PROs (SF-36v2; EQ-5D-5L), ECG, and assessing changes in signs/symptoms and concomitant medications, etc.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening 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 enrollment. 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, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies, radiotherapy and surgery, size of the resected tumor and date the patient underwent surgery for complete resection), female reproductive status, and tobacco use history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to initiation of

study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

Details of any COVID-19 vaccination received before study enrollment should be captured in the medical history section, at screening, whereas details regarding the COVID-19 vaccine received during the study should be recorded in the concomitant medication section.

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. 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.

4.5.4 Vital Signs

Vital signs will include measurements of temperature, weight, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position.

4.5.5 Eastern Cooperative Oncology Group Performance Status

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

4.5.6 Disease Assessments

Patients must be disease-free at baseline and reassessed at each subsequent tumor evaluation once randomized into the study. The disease recurrence will be assessed by the investigator using an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status. Disease assessments are to be performed at the timepoints specified below and in Appendix 1 and Appendix 2.
During the treatment period, the disease assessment schedule should be kept, regardless of drug delays or interruptions.

Positive efficacy results at an interim analysis, as described in Section 6.8, will not influence the conduct and timing of disease assessments during the study.

Screening assessments will include:

- CT scan (with oral/IV contrast unless contraindicated) of the chest and abdomen (including liver and adrenal glands)
- Magnetic resonance imaging (MRI) of the brain to rule out CNS metastasis. If MRI is not available, CT scans (with oral/IV contrast unless contraindicated) can be performed instead.
- Patients with metastatic disease are to be excluded from this study. Patients who have clinical signs, symptoms, biochemical abnormalities (including, but not limited to, ALP, LDH, etc.), or radiological imaging that could be suggestive of bone metastases at baseline, must undergo further investigation to exclude the presence of bone metastases at study entry. Additional appropriate imaging techniques include but are not limited to PET imaging and isotope bone scans.
- CT/MRI scans (with oral/IV contrast unless contraindicated) of the pelvis and neck should be included if clinically indicated
- The radiological assessments performed as per standard of care prior to obtaining informed consent and within 28 days before randomization do not have to be repeated at screening

If a CT scan with contrast is medically contraindicated, a non–contrast-enhanced chest CT scan is acceptable. If contrast-enhanced MRI is contraindicated, then non–contrast-enhanced MRI will suffice.

Subsequent disease assessments will include CT scans (with oral/IV contrast unless contraindicated) of the chest, CT/MRI scan of abdomen (including liver and adrenal glands) and brain, every 12 weeks (±7 days) for the first 2 years, every 24 weeks (±14 days) during years 3–5, and annually thereafter (±28 days) until disease recurrence, death, loss to follow-up, consent withdrawal, or study termination by the Sponsor, whichever occurs first. Computed tomography/MRI scans of the pelvis and neck, and isotope bone scans (where imaging of the bone is medically appropriate) should be included if clinically indicated.

Brain imaging should be performed preferably using MRI, with the following image acquisition requirements.

Minimum sequences required:

- Pre-contrast T1, T2/FLAIR
- Post-contrast T1, with 2 orthogonal planes (or a volume acquisition) recommended

Recommended slice thickness ≤ 5 mm with no gap.

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

across visits. At the investigator's discretion, radiographic scans may be repeated at any time if disease recurrence or a new primary NSCLC is suspected.

For patients in both arms, a tumor sample should be obtained at the time of first radiographic confirmation of disease recurrence or confirmation of a new primary NSCLC unless not clinically feasible (within 30 days of disease recurrence or prior to start of the next anti-cancer therapy, whichever is sooner). Results of histological confirmation will be captured in the eCRF.

Radiographic images will be submitted to an IRF for a quality and completeness check, and for temporary storage prior to transfer to the Sponsor for long-term retention and potential independent reading.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

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 count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells)

  For patients randomized to the alectinib arm, reticulocytes and haptoglobin should be tested at baseline and a peripheral blood smear should be performed. In case of Grade $\geq$ 2 anemia as per NCI CTCAE v5.0 (hemoglobin $<$ 10 g/dL), hemoglobin, RBC count, reticulocytes, and haptoglobin should be tested. In addition, a peripheral blood smear and a direct Coombs test (direct anti-globulin test [DAT]) should be performed. This laboratory work-up should be conducted at each new occurrence of anemia of Grade $\geq$ 2 in patients receiving alectinib.
- Coagulation: PT (or INR), and aPTT (or PTT)
- Serum chemistry: sodium, potassium, chloride, bicarbonate (optional), fasting glucose, BUN or urea, creatinine and CrCl (calculated according to the method of Cockcroft and Gault [1976]), CPK, gamma-glutamyl transferase (GGT), calcium, total and direct bilirubin, total protein, albumin, ALT, AST, ALP, phosphorus, magnesium, thyroid-stimulating hormone, and uric acid

  For patients randomized to the alectinib arm, LDH should be tested at baseline. In case of Grade $\geq$ 2 anemia as per NCI CTCAE v5.0 (hemoglobin $<$ 10 g/dL), ALT, total and direct bilirubin and LDH should be tested. This laboratory workup should be conducted at each new occurrence of anemia of Grade 2 or higher in patients receiving alectinib.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood)
- Pregnancy test

  All women who are not postmenopausal ($\geq$ 12 months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening, within 3 days of dosing. Urine pregnancy tests will be performed at all safety

visits during the course of the study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Samples for PK analysis (see Section 4.5.7.1)
- Pretreatment tumor tissue sample obtained at screening for determination of ALK status for patient eligibility (see Section 4.5.7.2)
- Tumor tissue sample obtained at the time of recurrence, if deemed clinically feasible, for exploratory research on biomarkers (see Section 4.5.7.2)
- Plasma samples for exploratory research on biomarkers (see Section 4.5.7.2)

Biomarker plasma and tissue sampling will be in accordance with the Institutional Review Board (IRB)/Ethics Committee (EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (Section 4.5.10), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Tumor and plasma samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining tissue blocks [pretreatment and at recurrence] will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining pretreatment tissue blocks will be returned to the site no later than 6 months after eligibility determination. Slides will not be returned.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.7.1 Samples for Pharmacokinetic Assessments

Pharmacokinetic samples will be collected in all patients receiving alectinib treatment, as indicated in Appendix 1 and Appendix 2, and sent to a Sponsor-designated central laboratory for the analysis of alectinib and its major metabolite(s). All trough/pre-dose

PK samples should be collected within 2 hours before the morning doses of study medications.

Plasma concentrations for alectinib and its metabolite(s), if applicable, will be measured by specific and validated liquid chromatography tandem-mass spectrometry methods. For each sample, approximately 2 mL of venous blood will be collected for alectinib PK analysis at the timepoints specified in the PK schedule in Appendix 3. Patients who permanently discontinue alectinib will also discontinue from all PK sampling and assessments.

For Japanese patients on alectinib treatment participating in serial/intensive PK sample collection (approximately the first 6 patients who consented to participate to the serial/intensive PK sample collection), additional PK samples will be collected at the timepoints specified in Appendix 3. Serial/intensive PK is for the alectinib arm and only applies to Japanese patients.

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.

4.5.7.2 Samples for Biomarker Assessments

Exploratory biomarker research may include, but will not be limited to, the analysis of DNA from tumor tissue and of circulating tumor DNA, and genes (e.g., *ALK, KRAS, EGFR*) and gene signatures associated with tumor biology and may involve analysis of somatic mutations, rearrangements, and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of oncogenes. Next-generation sequencing methods will not include whole-genome sequencing (WGS) or whole-exome sequencing (WES).

Next-generation sequencing may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator may obtain results from these analyses by requesting an NGS report directly from Foundation Medicine. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet criteria for testing.

Pretreatment Tumor Tissue Samples

For ALK-positive patient samples tested locally, mandatory pretreatment tumor samples will be collected to centrally examine ALK status by Ventana IHC for retrospective confirmation.

For sites where local ALK testing with an FDA-approved and CE-marked ALK test is not feasible, tumor samples can be tested centrally with the Ventana ALK IHC assay to determine ALK status for enrollment.

Tumor blocks (formalin-fixed, preferred 10% neutral-buffered formalin) are the preferred source, but if blocks are not available, unstained slides (minimum of 5 slides for ALK IHC test and 5–10 slides for biomarker analysis, cut less than 3 months before screening) are also accepted. Remaining tumor blocks will be returned to the sites; slides will not be returned. Central ALK testing to confirm or to determine patient ALK status will be performed at a Sponsor-designated central laboratory. In addition, other ALK assays may be used for testing patient samples to establish performance characteristics of these assays for diagnostic development. Testing may be performed on all enrolled patients. These additional testing data will have no impact on eligibility, and testing will be performed only after eligibility is established for each patient. In addition, local ALK test information, baseline demographic, and disease-related characteristic data for all screened patients may be collected. Pretreatment tumor samples will be used for targeted tumor sequencing if in accordance with local laws and regulations.

Tumor Tissue Samples at Time of Recurrence

Patients from both treatment arms will undergo a mandatory tumor biopsy sample collection, unless not clinically feasible as assessed and documented by investigators, at the first evidence of radiographic disease recurrence. These data will be used to explore whether the radiographic findings are consistent with the presence of tumor. Biopsies to confirm recurrence should be performed within 30 days of radiographic detection of disease recurrence or prior to the next anti-cancer therapy, whichever is sooner, unless not clinically feasible.

Acceptable samples include:

- Core-needle biopsies for deep tumor tissue; at least 3 cores, embedded into a single paraffin block, should be submitted for evaluation
- Excisional, incisional, punch, or forceps biopsy specimens for cutaneous, subcutaneous, or mucosal lesions
- Tumor tissue resection

Histological confirmation of recurrence or the new primary NSCLC will be performed at study site's local laboratory according to local general practice.

Following local histological confirmation of recurrence or the new primary NSCLC, formalin-fixed blocks (preferred; or if block is not available, a minimum of 5–10 unstained slides) should be sent to the Sponsor-designated central laboratory. These samples will be used for targeted sequencing with a panel of cancer genes, including *ALK*, to explore and elucidate molecular mechanisms of resistance to ALK inhibitors.

Biomarker Plasma Samples

Mandatory plasma samples will be collected for the isolation of circulating tumor nucleic acids in order to detect early tumor recurrence and also to determine *ALK* rearrangements and mutation status in *ALK* and other escape genes (e.g., *EGFR, KRAS*) by targeted sequencing. It will require 20 mL of blood (2 tubes of 10 mL each) to be collected at baseline, at recurring scheduled visits during treatment (see Appendix 4 for detailed information), and at disease recurrence.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedules of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. 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.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected with use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. In the event that the ECG machine does not directly provide results for RR and/or QTcF, these parameters can be derived using the formulae provided in Appendix 7. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on 2 successive ECGs. Standard-of care treatment may be instituted per the discretion of the investigator. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

If any ECG abnormality is associated with an adverse event, it must be recorded and managed as described in Section 5.1.7.

4.5.9 Patient-Reported Outcomes

Patient-reported outcome questionnaires, namely the SF-36v2 and EQ-5D-5L, will be collected on paper at the investigational sites to more fully characterize the clinical profile of the study drugs. The questionnaires will be translated as required in the local language. Patient-reported outcome questionnaires scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results, or health record; before administration of study treatment; and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. The PRO questionnaires will be collected at baseline, every 3 weeks through Week 12; and every 12 weeks thereafter until recurrence of disease, withdrawal of consent, death, or Week 96, whichever occurs first. Patient-reported outcome will also be collected at the safety follow-up visit.

Patients whose native language is not available on the PRO instrument or who are deemed by the investigator incapable of completing their PRO assessment after undergoing appropriate training are exempted from completing all PRO assessments.

4.5.9.1 SF-36v2

The SF-36v2 is a generic health-status measure with 36 items comprising 2 health component summary scores (i.e., physical component summary [PCS] and mental component summary [MCS]) as well as 8 health domain scores (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health; Ware and Sherbourne 1992; Ware et al. 2007; Ware et al. 2008; see Appendix 8).

4.5.9.2 EQ-5D-5L

The EQ-5D-5L is a generic preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that is used to build a composite of the patient's health status (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013; see Appendix 9). An additional visual analogue scale is also used to measure health status, separately from the composite score.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) 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, storage, and analysis of RBR 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.

Remains of tissue and plasma samples for study-related or non–study-related procedures that are performed or collected during the study will be collected for RBR from patients who give specific consent to participate in this optional research. Research Biosample Repository specimens will be used to achieve the following objectives:

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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

No samples will be taken for RBR purposes only. However, any remaining tissue and plasma samples for study-related or non–study-related procedures that are performed or collected during the study may also be collected for RBR purposes. For all samples, date of consent should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ALK-positive NSCLC:

- Biomarker plasma samples collected according to Appendix 4
- Pretreatment tumor tissue samples collected at screening
- Tumor samples from site of recurrence collected at time of recurrence

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, WES, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the

genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

Research Biosample Repository specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR 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.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study -data publication.

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent 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 RBR 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 and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be handled as described in the signed Informed Consent Form and, when applicable, will be destroyed or will no longer be linked to the patient. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. 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 appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR 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 BO40336 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BO40336.

4.5.10.7 Monitoring and Oversight

Research Biosample Repository specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Inability to tolerate study medication on the basis of the investigator judgment

See guidelines for managing adverse events and for comprehensive guidance on study-drug discontinuation in Section 5.1.7.

Patients who discontinue study drug prematurely will be asked to return to the clinic for safety assessments at a safety follow-up visit, which occurs 28 days after the last dose of alectinib or 28 days after the end of the last cycle of chemotherapy (7 weeks after Day 1 of the last cycle). Disease assessments must continue until recurrence as per the schedule of activities (see Appendix 1 and Appendix 2).

Patients who discontinue treatment prior to completion of the protocol-defined treatment period will remain in the study and should continue to be followed for disease assessments until recurrence, and for OS, provided they have not withdrawn consent for the study.

If patients stop scheduled assessments after study drug discontinuation, they will be contacted via phone calls regularly*, as long as the patient hasn't withdrawn from the study,* for *disease recurrence status if no recurrence occurs, for* survival status*,* and *for* any new anti-cancer therapy(ies) until death, withdrawal from the study, or the Sponsor terminates the study.

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

4.6.2 Patient Discontinuation from Study

Patients will return to the clinic for a study completion visit at the time of consent withdrawal or study closure.

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
- Study termination or site closure

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent for the study has been withdrawn; however, if patient withdraws from the study, site may use a public information source (e.g., county records) to obtain information about survival status. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

After study completion visit, no further information will be collected.

4.6.3 Study 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.

4.6.4 Site Discontinuation

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 Council *on* Harmonisation *of Technical Requirements for Registration of pharmaceuticals for Human Use* (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients receiving alectinib in this study is based on clinical experience and results from completed and ongoing studies in the metastatic setting as well as postmarketing experience. For the comparator arm, warnings and precautions are based on product labels for the respective regimens. The anticipated safety risks for alectinib and comparator treatments are outlined below. For a complete summary of safety information, please refer to the Alectinib Investigator's Brochure and the current version of the local product labels for the comparator arm treatments.

An external iDMC will review the safety data collected during the conduct of the study and perform periodic review. Further details will be outlined in the iDMC Charter.

All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. A detailed plan will be included in the iDMC Charter.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Alectinib

Events described in Section 5.1.1 will be closely monitored and represent selected adverse events for this study.

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

5.1.1.1 Interstitial Lung Disease

Tyrosine kinase inhibitors, including ALK inhibitors crizotinib and ceritinib, have been associated with the occurrence of treatment-related interstitial lung disease (ILD)/pneumonitis (including fatalities). Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates.

Guidelines for management and follow-up of patients who develop ILD or pneumonitis are provided in Table 8.

5.1.1.2 Hepatotoxicity

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

Abnormal hepatobiliary laboratory test values, such as increased ALT, AST, or bilirubin levels, have been observed after alectinib administration. Aspartate aminotransferase, ALT, and total bilirubin levels temporarily increased in the initial stages of treatment and then improved. In patients with Grades 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 $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN, with normal ALP, occurred with uncommon frequency in patients treated in alectinib clinical trials.

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

Guidelines for management and follow-up of patients who develop hepatotoxicity are provided in Table 8.

5.1.1.3 Anemia

Hematologic findings were observed in both the rat and cynomolgus monkey 4- and 13-week toxicity studies with alectinib. *The f*indings were at or close to clinically relevant exposures. *Changes in RBC morphology (e.g., poikilocytosis, red cell fragmentation) and in other erythroid parameters (e.g., reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume) were seen with alectinib in these studies. However, the changes on the erythroid system were considered to be of little toxicological significance because they were slight (0.94- to 1.3-fold vs. baseline), considered reversible, and did not exacerbate with prolonged treatment with alectinib*.

Cases of anemia*, including hemolytic anemia,* have been reported in patients treated with alectinib; the majority of the events were Grades 1 and 2.

To further enhance the understanding of hemolytic anemia in patients treated with alectinib, specific laboratory parameters for hemolytic anemia (blood smear, reticulocytes, haptoglobin, and LDH) will be tested at baseline for patients randomized to the alectinib arm. In case of Grade $\geq$ 2 anemia as per NCI CTCAE v5.0 (hemoglobin $<$ 10 g/dL), laboratory tests including hemoglobin, RBC count, reticulocytes, haptoglobin, ALT, LDH, total and direct bilirubin, peripheral blood smear, and a direct Coombs test (DAT) should be performed.

Guidelines for management and follow-up of patients who develop anemia *(including* hemolytic anemia*)* are provided in Table 8.

5.1.1.4 Gastrointestinal Disorders

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

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

Guidelines for management and follow-up of patients who develop GI disorders are provided in Table 8.

5.1.1.5 Skin Disorders

Results of an in vitro phototoxicity study indicated that alectinib may have phototoxic potential. Skin rash has been reported with majority of TKIs including those targeting the ALK receptor (Hartmann et al. 2009).

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

Guidelines for management and follow-up of patients who develop skin disorders are provided in Table 8.

5.1.1.6 Vision Disorders

In the rat quantitative whole-body autoradiography study, tissue radioactivity disappeared over time, following a time course comparable with 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 blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia, have been reported with alectinib and were generally Grades 1 and 2.

Guidelines for management and follow-up of patients who develop vision disorders are provided in Table 8.

5.1.1.7 Edema

Most TKIs, including ALK inhibitor crizotinib, have been associated with edema. Events of edema (mainly peripheral edema) have been reported with alectinib, mostly Grades 1 and 2.

Guidelines for management and follow-up of patients who develop edema are provided in Table 8.

5.1.1.8 Bradycardia

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

In a preliminary non–Good Laboratory Practice telemetry study in conscious cynomolgus monkeys, there were no effects on ECG or heart rate.

Events of bradycardia have been reported with alectinib. Data based on ECG and pulse measurements from the ongoing alectinib clinical trials show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. In patients treated with other ALK inhibitors (crizotinib and ceritinib), bradycardia adverse events, as well as decreases in heart rate based on ECG and pulse measurements, have also been reported (Xalkori U.S. Package Insert; Zykadia™ U.S. Package Insert).

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.

In case of bradycardia adverse event related to alectinib, refer to adverse event grade-dependent rules for dose modification outlined in the first section of Table 8.

5.1.1.9 Abnormal Renal Function (Serum Creatinine Increased, Acute Kidney Injury)

In the 2-week, nonclinical primate study at 60 mg/kg alectinib, an increase in creatinine was observed but no changes were observed in histopathology. In all other nonclinical primate studies, no changes in creatinine were observed.

Serum creatinine increases have been reported with alectinib treatment with common frequency. Acute kidney injury, including fatal outcome, has been observed with uncommon frequency in patients treated in alectinib clinical trials.

Serum creatinine increases and/or decreases in GFR, renal failure, and/or renal impairment have been reported for other ALK inhibitors (crizotinib, ceritinib).

Guidelines for management and follow-up of patients who develop abnormal renal function are provided in Table 8.

5.1.1.10 Severe Myalgia and CPK Elevations

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

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

Guidelines for management and follow-up of patients who develop severe myalgia and CPK elevations are provided in Table 8.

5.1.1.11 Dysgeusia

Events of dysgeusia have been reported in clinical trials with alectinib and were generally of Grades 1 and 2 severity. All patients who experienced dysgeusia continued alectinib treatment without any modification.

In patients treated with other ALK inhibitors, such as crizotinib and ceritinib, dysgeusia has been reported.

In case of dysgeusia adverse event related to alectinib, refer to adverse event grade-dependent rules for dose modification outlined in the first section of Table 8.

5.1.1.12 Alkaline Phosphatase Increase

Cases of increased blood ALP have been observed after alectinib administration. The majority of the cases were of Grades 1 and 2 severity.

In patients treated with other ALK inhibitors, increased blood ALP has been reported.

In case of ALP increase adverse event related to alectinib, refer to adverse event grade-dependent rules for dose modification outlined in the first section of Table 8.

5.1.2 Risks Associated with Vinorelbine

For full details regarding risks, warnings, and precautions relating to vinorelbine treatment, refer to the current version of the local product label. Management of patients who experience adverse events related to vinorelbine is outlined in Section 5.1.8.

The most common adverse reactions (incidence $\geq$20%) of vinorelbine are neutropenia, anemia, liver enzyme elevation, nausea, vomiting, asthenia, constipation, injection-site reaction, and peripheral neuropathy.

5.1.2.1 Myelosuppression

Severe myelosuppression resulting in serious infection, septic shock, and death may occur. Myelosuppression manifested by neutropenia, anemia, and thrombocytopenia occur with vinorelbine as a single agent and in combination with cisplatin. Neutropenia is the major dose-limiting toxicity (DLT). Neutropenia nadirs occur between 7 and 10 days after dosing, with neutropenia count recovery usually occurring within the following 7−14 days.

5.1.2.2 Hepatotoxicity

Drug-induced liver injury manifested by elevations of AST and bilirubin can occur in patients receiving vinorelbine alone or in combination with cytotoxic agents.

5.1.2.3 Severe Constipation and Bowel Obstruction

Severe constipation and bowel obstruction, including necrosis and perforation, can occur. A prophylactic bowel regimen should be instituted to mitigate potential constipation, bowel obstruction, and/or paralytic ileus, considering adequate dietary fiber

intake, hydration, and routine use of stool softeners. Patients should be monitored for abdominal pain and severe constipation.

5.1.2.4 Extravasation and Tissue Injury

Extravasation can result in severe tissue injury, necrosis, and/or thrombophlebitis. If signs or symptoms of extravasation occur, administration of vinorelbine should be immediately stopped and the recommended management procedures instituted.

5.1.2.5 Neurologic Toxicity

Severe sensory and motor neuropathies, including severe neuropathies, can occur in patients receiving vinorelbine. Patients should be monitored for new or worsening signs and symptoms of neuropathy, such as paresthesia, hyperesthesia, hyporeflexia, and muscle weakness, while receiving vinorelbine.

5.1.2.6 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including severe acute bronchospasm, interstitial pneumonitis, acute respiratory distress syndrome (ARDS), and respiratory failure, can occur, including fatalities. The mean time to onset of interstitial pneumonitis and ARDS after vinorelbine administration was 1 week (range: 3–8 days). Patients should be monitored for respiratory disorders (dyspnea and bronchospasm).

5.1.2.7 Embryo-Fetal Toxicity

Vinorelbine can cause fetal harm when administered to a pregnant woman. Refer to the current version of the local label for detailed guidance on contraception as well as details of impact on fertility.

5.1.3 Risks Associated with Gemcitabine

For full details regarding risks, warnings, and precautions relating to gemcitabine treatment, refer to the current version of the local product label. Management of patients who experience adverse events related to gemcitabine is outlined in Section 5.1.9.

The most common (≥20%) adverse reactions for the single-agent treatment are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased ALP, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

5.1.3.1 Schedule-Dependent Toxicity

Gemcitabine infusion times that are longer than 60 minutes or gemcitabine administration that occurs more frequently than once a week have been shown to increase toxicity (occurrence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia). The half-life of gemcitabine is influenced by the length of the infusion.

Pulmonary toxicity has been reported with the use of gemcitabine. Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia has been reported with gemcitabine as a single agent or in combination with other cytotoxic drugs.

Hemolytic-uremic syndrome (HUS) and/or renal failure have been reported following 1 or more doses of gemcitabine. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Patients will be monitored for gemcitabine-related adverse events.

5.1.3.2 Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent, and the risks are increased when combined with other cytotoxic drugs. Monitor for myelosuppression prior to each cycle.

5.1.3.3 Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and ARDS, has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine.

5.1.3.4 Hemolytic-Uremic Syndrome

Hemolytic-uremic syndrome, including fatalities from renal failure or the requirement for dialysis, can occur in patients treated with gemcitabine. Renal function should be assessed prior to initiation of gemcitabine, and assessment should be repeated periodically during treatment. Consider the diagnosis of HUS in patients who develop anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN). Renal failure may not be reversible even with discontinuation of therapy.

5.1.3.5 Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration in patients with concurrent liver metastases or a preexisting medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine treatment and periodically during treatment.

5.1.3.6 Embryo-Fetal Toxicity

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Refer to the current version of local label for detailed guidance on contraception as well as details of impact on fertility.

5.1.3.7 Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not indicated for use in combination with radiation therapy. Severe and life-threatening toxicity may occur when gemcitabine is administered during or within 7 days of radiation therapy.

5.1.3.8 Capillary Leak Syndrome

Capillary leak syndrome with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents.

5.1.3.9 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Posterior reversible encephalopathy syndrome can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Diagnosis of PRES should be confirmed with MRI.

5.1.4 Risks Associated with Pemetrexed

For full details regarding risks, warnings, and precautions relating to pemetrexed treatment, refer to the current version of the local product label. Management of patients who experience adverse events related to pemetrexed is outlined in Section 5.1.10.

The most common*ly reported undesirable* adverse *effects related to* pemetrexed*, whether used* as *monotherapy or in combination,* are *anorexia*, nausea, vomiting, *diarrhea, constipation,* stomatitis*,* pharyngitis*, mucositis, neutropenia, anemia, leukopenia*, *and* thrombocytopenia.

5.1.4.1 Myelosuppression

Pemetrexed can cause severe bone marrow suppression resulting in cytopenia and an increased risk of infection, and may result in a requirement for transfusions. Myelosuppression is usually the DLT.

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 pretreatment with folic acid and vitamin B12 was administered. Therefore, all patients treated with pemetrexed must be instructed to take folic acid and vitamin B12 as a prophylactic measure to reduce treatment-related toxicity (see Section 4.3.2.2).

5.1.4.2 Renal Failure

Pemetrexed can cause severe, and sometimes fatal, renal failure. Do not administer when CrCl is $<$45 mL/min.

Due to the GI toxicity of pemetrexed given in combination with cisplatin, severe dehydration has been observed. Therefore, patients should receive adequate

anti-emetic treatment and appropriate hydration prior to and/or after receiving treatment (see Section 4.3.2.2).

5.1.4.3 Bullous and Exfoliative Skin Toxicity

Serious and sometimes fatal, bullous, blistering, and exfoliative skin toxicity, including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, can occur with pemetrexed. Skin reactions, such as rash, desquamation, alopecia, and pruritus, have been reported in pemetrexed-treated patients not pretreated with a corticosteroid.

5.1.4.4 Interstitial Pneumonitis

Serious interstitial pneumonitis, including fatal cases, can occur with pemetrexed treatment.

5.1.4.5 Radiation Recall

Radiation recall can occur in patients who received radiation weeks to years previously. Monitor patients for inflammation or blistering in areas of previous radiation treatment.

5.1.4.6 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 preexisting cardiovascular risk factors.

5.1.4.7 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.

5.1.4.8 Embryo-Fetal Toxicity

Based on findings from nonclinical studies and its mechanism of action, pemetrexed can cause fetal harm when administered to a pregnant woman. Refer to the current version of local label for detailed guidance on contraception as well as details of impact on fertility.

5.1.5 Risks Associated with Cisplatin

For full details regarding risks, warnings, and precautions relating to cisplatin treatment, refer to the current version of the local product label. Management of patients who experience adverse events related to cisplatin is outlined in Section 5.1.11.

Cumulative renal toxicity associated with cisplatin is severe. Other major dose-related toxicities are myelosuppression, nausea, and vomiting. Ototoxicity, which may be more pronounced in children and is manifested by tinnitus and/or loss of high-frequency hearing and occasionally deafness, is significant. Anaphylactic-like reactions to cisplatin have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension

may occur within minutes of cisplatin administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms.

5.1.5.1 Nephrotoxicity

Cisplatin causes severe cumulative nephrotoxicity. Dose-related and cumulative renal insufficiency, including acute renal failure, is the major DLT of cisplatin. Renal toxicity is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid, and/or a decrease in CrCl. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage.

The administration of cisplatin using a 6- to 8-hour infusion with IV hydration and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by pre-hydration with 2 L of an appropriate IV solution, and similar post-cisplatin hydration (recommended 2500 mL/m^2/24 hours).

5.1.5.2 Ototoxicity

Ototoxicity has been observed in patients treated with a single dose of cisplatin 50 mg/m^2 and is manifested by tinnitus and/or hearing loss in the high-frequency range (4000–8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated cisplatin doses. It is unclear whether cisplatin-induced ototoxicity is reversible. Vestibular toxicity has also been reported. Ototoxic effects may be related to the C_{max} of cisplatin. Ototoxicity can occur during treatment or be delayed. Audiometric monitoring should be performed according to the local prescribing information. The risk of ototoxicity may be increased by prior or simultaneous cranial irradiation, and it may be more severe in patients being treated with other ototoxic drugs (e.g., aminoglycosides and vancomycin) and in patients with renal impairment. Genetic factors (e.g., variants in the thiopurine *S*-methyltransferase gene) may contribute to cisplatin-induced ototoxicity, although this association has not been consistent across populations and study designs.

5.1.5.3 Hematologic Toxicities

Myelosuppression can occur in patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between Days 18–23 (range: 7.5–45 days), with most patients recovering by Day 39 (range: 13–62 days). Leukopenia and thrombocytopenia are more pronounced at higher doses (> 50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to

myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression.

In addition to anemia secondary to myelosuppression, a Coombs-positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis, and this risk should be weighed by the treating physician.

5.1.5.4 Gastrointestinal Toxicities

Marked nausea and vomiting occur in almost all patients treated with cisplatin and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1–4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea, and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of cisplatin therapy. Diarrhea has also been reported.

5.1.5.5 Vascular Toxicities

Vascular toxicities coincident with the use of cisplatin in combination with other anti-neoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud phenomenon occurring in patients treated with the combination of bleomycin and vinblastine with or without cisplatin. It has been suggested that hypomagnesemia developing coincident with the use of cisplatin may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

5.1.5.6 Serum Electrolyte Disturbances

Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with cisplatin and are probably related to renal tubular damage. Tetany has been reported in those patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing cisplatin. Inappropriate anti-diuretic hormone syndrome has also been reported.

5.1.5.7 Hyperuricemia

Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/m^2, and peak levels of uric acid generally occur between 3–5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

5.1.5.8 Neurotoxicity

Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4–7 months); however, neurologic symptoms have been reported to occur after a single dose.
Although symptoms and signs of cisplatin neuropathy usually develop during treatment, symptoms of neuropathy may begin 3–8 weeks after the last dose of cisplatin. Cisplatin therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy.

Lhermitte sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome have also been reported. Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated in patients receiving a relatively high cumulative dose of cisplatin and with a relatively advanced symptomatic stage of peripheral neuropathy.

5.1.5.9 Ocular Toxicity

Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin. Improvement and/or total recovery usually occurs after discontinuing cisplatin. Steroids with or without mannitol have been used; however, efficacy has not been established.

Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic examination is irregular retinal pigmentation of the macular area.

5.1.5.10 Anaphylactic-Like Reactions

Anaphylactic-like reactions have been reported in patients previously exposed to cisplatin. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration. Reactions may be controlled by IV epinephrine with corticosteroids and/or antihistamines as indicated.
Patients receiving cisplatin should be observed carefully for possible anaphylactic-like reactions, and supportive equipment and medication should be available to treat such a complication.

5.1.5.11 Hepatotoxicity

Transient elevations of liver enzymes, especially AST, as well as bilirubin, have been reported to be associated with cisplatin administration at the recommended doses.

5.1.5.12 Other Events

Cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported. Local soft tissue toxicity has been reported following extravasation of cisplatin. Severity of the local tissue toxicity appears to be related to the concentration of the cisplatin solution. Infusion of solutions with a cisplatin concentration greater than 0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

5.1.5.13 Embryo-Fetal Toxicity

Cisplatin can cause fetal harm when administered to a pregnant woman. Refer to the current version of local label for detailed guidance on contraception as well as details of impact on fertility.

5.1.5.14 Carcinogenic Potential

In humans, in rare cases the appearance of acute leukemia has coincided with use of cisplatin, which was in general associated with other leukemogenic agents. Cisplatin is a bacterial mutagen and causes chromosome aberrations in cultures on animal cells. Carcinogenicity is possible but has not been demonstrated. Cisplatin is teratogenic and embryotoxic in mice.

5.1.6 Risks Associated with Carboplatin

For full details regarding risks, warnings, and precautions relating to carboplatin treatment, refer to the current version of the local product label. Management of patients who experience adverse events related to carboplatin is outlined in Section 5.1.12 .

Carboplatin is known to cause bone marrow suppression including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Patients will be monitored for carboplatin-related adverse events.

5.1.6.1 Hematologic Toxicities

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose–dependent and is also the DLT. Peripheral blood counts should be frequently monitored during treatment with carboplatin and, when appropriate, until recovery is achieved. Median nadir occurs at Day 21 in patients receiving single-agent carboplatin. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered. The hematologic effects, although usually reversible, can result in infectious or hemorrhagic complications, including drug-related deaths. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed with carboplatin treatment. Since anemia is cumulative, transfusions may be needed during treatment with carboplatin, particularly in patients receiving prolonged therapy. Bone marrow

suppression is increased in patients who have received prior therapy, especially regimens including cisplatin.

Marrow suppression is also increased in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced, and blood counts should be carefully monitored between courses. The use of carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

5.1.6.2 Nephrotoxicity

Development of abnormal renal function test results is uncommon. Most of the reported abnormalities have been mild, and about one-half of them were reversible. Even though carboplatin has limited nephrotoxic potential, concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression.

5.1.6.3 Ototoxicity

Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

5.1.6.4 Gastrointestinal Toxicities

Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with anti-emetics. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to anti-emetic measures. Although no conclusive efficacy data exist with the following schedules of carboplatin, lengthening the duration of single IV administration to 24 hours or dividing the total dose over 5 consecutive daily pulse doses has resulted in reduced emesis. Other GI effects observed frequently are pain, diarrhea, and constipation.

5.1.6.5 Neurotoxicity

Peripheral neuropathies have been observed in patients receiving carboplatin, with mild paresthesias occurring most frequently. Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Preexisting cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving carboplatin as secondary treatment.

5.1.6.6 Ocular Toxicity

Loss of vision, which can be complete for light and colors, has been reported after the use of carboplatin with doses higher than those recommended. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

5.1.6.7 Allergic Reactions

As in the case of other platinum-coordination compounds, allergic reactions to carboplatin have been reported (rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension). These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy.

5.1.6.8 Hepatotoxicity

Abnormal liver function tests (total bilirubin, AST, ALP) have been reported. These abnormalities have generally been mild and reversible in about one-half of the cases. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported. High dosages of carboplatin (more than 4 times the recommended dose) have resulted in severe abnormalities of liver function tests.

5.1.6.9 Embryo-Fetal Toxicity

Carboplatin may cause fetal harm when administered to a pregnant woman. Refer to the current version of local label for detailed guidance on contraception as well as details of impact on fertility.

5.1.6.10 Other Toxicities

Changes in electrolyte serum values have been reported for sodium, potassium, calcium, and magnesium; these electrolyte abnormalities were rarely associated with symptoms. Injection-site reactions, including redness, swelling, and pain, have been reported; necrosis associated with extravasation has also been reported. Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred, including fatalities that did not appear to be related to chemotherapy. Cancer-associated HUS has been reported rarely. Malaise, anorexia, hypertension, dehydration, and stomatitis have been reported.

5.1.7 Management of Patients who Experience Adverse Events with Alectinib

5.1.7.1 Dose Modifications

The dose of alectinib can be reduced in steps of 150 mg up to 2 times for management of drug-related toxicities (i.e., from 600 mg BID to 450 mg BID and then from 450 mg BID to 300 mg BID).

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

If further dose reduction is indicated after 2 dose-reductions, the patient must discontinue alectinib. Administration of a dose below 300 mg BID is not allowed. Dose modification may occur per Table 8 guidelines.

5.1.7.2 Treatment Interruption

Alectinib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug as per guidance in Table 8.

If alectinib has been withheld for >21 days because of toxicity, the patient should be discontinued from alectinib. Alectinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) *at the investigator's discretion. The* Medical Monitor *should be informed* and *may be consulted, to* determine the acceptable length of treatment interruption.

5.1.7.3 Management Guidelines

Guidelines for management of specific adverse events with alectinib are outlined in Table 8.

Table 8 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib

Event	Action to Be Taken
All AEs related [a] to alectinib (unless otherwise specified in this table) + Hepatotoxicity AEs (irrespective of relatedness)	• **Grade 4**: Temporarily interrupt alectinib for a maximum of 21 days after which the drug must be permanently withdrawn. If improvement to Grade ≤ 1 or baseline does not occur within 3 weeks, permanently discontinue alectinib. First episode: If improvement to Grade ≤ 1 within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. Second episode: If improvement to Grade ≤ 1 within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID. Third episode: Permanently discontinue alectinib. Please note that dose should not be reduced below 300 mg BID. • **Grade 3**: Temporarily interrupt alectinib for a maximum of 21 days after which drug must be permanently withdrawn. First episode: If improvement to Grade ≤ 1 occurs within 10 days, alectinib may be restarted at the original dose or dose reduced by 150 mg (1 capsule) as per investigator discretion. If improvement to Grade ≤ 1 or baseline occurs after 10 days but within 21 days, the alectinib dose must be decreased by 150 mg (1 capsule BID). Second episode: If improvement to Grade ≤ 1 occurs within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. Third episode: Permanently discontinue alectinib. • **Grade 2**: To be managed at the investigator's discretion. Please note that alectinib cannot be interrupted for more than 21 days and cannot be dose reduced below 300 mg BID. • **Grade 1**: No action required.
Interstitial lung disease/ pneumonitis	Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease/pneumonitis. **Regardless of relatedness to alectinib**, study drug should be permanently discontinued in patients diagnosed with interstitial lung disease/pneumonitis of any grade.
Hepatotoxicity	Liver test laboratory abnormalities are to be reported as AEs only if fulfilling the criteria listed in Section 5.3.5.5 and Section 5.3.5.7. At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible.

Table 8 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
Hepatotoxicity (cont.)	**Regardless of relatedness to alectinib, the grade-dependent rules for dose interruptions and dose modification outlined in the first section of this table must be followed.** **In addition**, study drug treatment has to be permanently discontinued if any of the following occurs: • First observation of ALT or AST $>8\times$ ULN • ALT or AST $>5\times$ ULN for more than 2 weeks • First observation of ALT or AST $>3\times$ ULN and total bilirubin $>2\times$ ULN • First observation of ALT or AST $>3\times$ ULN and the appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [$>5\%$]) • Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pretreatment 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, stomatitis)	The events are expected to be minimized by taking the study drug with a meal. If GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. **In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**
Skin disorder AEs (e.g., phototoxicity, rash)	Patients should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Patients should also be advised to use a broad-spectrum sunscreen and lip balm of at least SPF 50 to help protect against potential sunburn during this period. **In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**
Vision disorders	Investigators should consider referring the patients for an ophthalmologic evaluation according to local clinical practice guidelines if vision disorders persist or worsen in severity and to advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder. **In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**

Table 8 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. **In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**
Abnormal renal function AEs	Kidney function laboratory abnormalities are to be reported as AEs if they fulfill the criteria listed in Section 5.3.5.5. If at any time during the study treatment serum creatinine increases by $\geq 2\times$ over the baseline visit value, the patient has to be carefully monitored. All 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 serum creatinine value that is increased by $\geq 2\times$ over the baseline visit-value requires repeat testing. • **For Grade 1 and Grade 2 AEs related to alectinib**, **follow the grade-dependent rules for dose interruption and modification outlines in the first section of this table**. • **For Grade 3 AEs related to alectinib, temporarily interrupt alectinib until serum creatinine recovers to Grade 1 or baseline, then resume at reduced dose.** • **For Grade 4 AEs related to alectinib, permanently discontinue study drug.**
Severe myalgia and CPK elevations	CPK laboratory abnormalities are to be reported as AEs if they fulfill 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. Creatinine phosphokinase levels should be monitored in patients reporting these symptoms. **In case of AEs related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**

Table 8 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken
Anemia (including hemolytic anemia)	Grade ≥ 2 anemia (regardless of clinical relevance): At the time of assessing hemoglobin level for routine monitoring of Grade ≥ 2 anemia, RBC count, reticulocytes, haptoglobin, ALT, LDH, and total and direct bilirubin should also be tested. In addition, peripheral blood smear and a direct Coombs test should be performed. This laboratory workup is to be conducted at each new occurrence of anemia of Grade ≥ 2 in patients receiving alectinib. *If hemolytic anemia is suspected, withhold alectinib. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (refer to the general dose modification table in Section 5.1.7.1) upon resolution with improvement of hemoglobin to Grade ≤ 1 or baseline, or permanently discontinue alectinib.* **In case of *anemia of non-hemolytic mechanism, assessed as* related to alectinib, follow the grade-dependent rules for dose interruption and modification outlined in the first section of this table.**
Bradycardia [b]	*Grade 2 or Grade 3* • *Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products.* • *If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery toGrade ≤ 1 (asymptomatic) bradycardia, or to a heart rate of ≥ 60 bpm.* *If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.* *Grade 4* • *Permanently discontinue if no contributing concomitant medicinal product is identified.* • *If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to Grade ≤ 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated.* *Permanently discontinue in case of recurrence.*

Table 8 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Event	Action to Be Taken

AE = adverse event; BID = twice a day; GI = gastrointestinal; ULN = upper limit of normal.

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

[a] Please refer to Section 5.3.4 to determine whether event should be assessed as related or unrelated.

[b] *Heart rate less than 60 bpm.*

5.1.8 Management of Patients who Experience Adverse Events with Vinorelbine

For full details regarding warnings, precautions, and dose modifications/delays relating to vinorelbine treatment, refer to the current version of the local product label. Please refer also to any additional dose recommendations required for cisplatin (Section 5.1.11) or carboplatin (Section 5.1.12), depending on the treatment combination used.

Patients should be monitored for abdominal pain and severe constipation, for new or worsening signs and symptoms of neuropathy such as paresthesia, hyperesthesia, hyporeflexia, and muscle weakness, as well as for respiratory disorders (dyspnea and bronchospasm).

5.1.9 Management of Patients who Experience Adverse Events with Gemcitabine

For full details regarding warnings, precautions, and dose modifications/delays relating to gemcitabine treatment, refer to the current version of the local product label. Please refer also to any additional dose recommendations required for cisplatin (Section 5.1.11) or carboplatin (Section 5.1.12), depending on the treatment combination used.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

5.1.10 Management of Patients who Experience Adverse Events with Pemetrexed

For full details regarding dose modifications relating to pemetrexed treatment, refer to the current version of the local product label. Please refer also to any additional dose recommendations required for cisplatin (Section 5.1.11) or carboplatin (Section 5.1.12),

depending on the treatment combination used. The dose modification guidelines are applicable for pemetrexed used in combination with cisplatin or carboplatin.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

5.1.10.1 Non-Hematologic Toxicity

At the start of each cycle, the CrCl must be ≥45 mL/min. For enrollment and dosing decisions, CrCl will be estimated using the standard Cockcroft and Gault formula (or GFR measured Tc99m-DPTA serum clearance model). The method of CrCl assessment used at baseline should be used throughout the study.

5.1.11 Management of Patients who Experience Adverse Events with Cisplatin

For full details regarding dose modifications relating to cisplatin treatment, refer to the current version of the local product label. Please refer also to any additional dose recommendations required for vinorelbine (Section 5.1.8), gemcitabine (Section 5.1.9), or pemetrexed (Section 5.1.10), depending on the treatment combination used.

5.1.12 Management of Patients who Experience Adverse Events with Carboplatin

For full details regarding warnings and precaution relating to carboplatin treatment, refer to the current version of the local product label. Please refer also to any additional dose recommendations required for vinorelbine (Section 5.1.8), gemcitabine (Section 5.1.9, or pemetrexed (Section 5.1.10), depending on the treatment combination used.

5.1.12.1 Hematologic Toxicities

Patients with CrCl values below 60 mL/min are at increased risk of severe bone marrow suppression.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and 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; see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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 NCI CTCAE;

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

Severity and seriousness need to be independently assessed for each adverse event recorded on the 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 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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

- 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 or 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 during treatment and until 28 days after last dose of alectinib or 28 days after end of last cycle of chemotherapy (7 weeks after day one of last cycle).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 (v5.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 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 (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding 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 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 (see also Table 10):

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

Table 10 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 1 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") 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 GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all 3 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., ALP and bilirubin 5 × 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 whether 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 ($>3\times$ULN) 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 $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN 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 an 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 recurrence of NSCLC should be recorded on the Death Attributed to Disease Recurrence eCRF. All other deaths that occur during the adverse event reporting period, 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 iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be

replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

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 Recurrence of NSCLC

Events that are clearly consistent with the expected pattern of disease recurrence should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The expected pattern of disease recurrence will be based on determination by the investigator after an integrated assessment of radiographic data, biopsy sample results (if available), and clinical status. Every effort should be made to document disease recurrence with use of radiographic data, confirmed by biopsy sample results as per protocol. If there is any uncertainty as to whether an event is due to disease recurrence, it should be reported as an adverse event.

Recurrence of disease should not be recorded as an adverse event or serious adverse event, since recurrence of disease will be captured as an efficacy endpoint. However in situations in which there is no confirmation, the underlying symptoms should be captured as adverse events and assessed accordingly for seriousness, severity, and causality until a diagnosis or cause for such events is established or until confirmation of NSCLC recurrence. If the symptoms are later confirmed to be due to recurrence of disease, then symptoms reported as adverse events should be retracted. Data for disease recurrence will be captured as efficacy assessment data only.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- 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 recurrence of NSCLC

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

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately 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). For alectinib or any protocol chemotherapy regimen, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with alectinib and any protocol chemotherapy regimen, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

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. Investigators and site staff are not expected to review the PRO data for adverse events.

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 (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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

Medical Monitor Contact Information for All Sites

Medical Monitor/Roche Medical Responsible: [redacted], M.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), 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 and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and 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 or procedures permitted by the protocol, should be reported. The paper Clinical Trial Adverse Event/Special *Situations* 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 e-mail address provided to investigators.

5.4.2.2 Events that Occur after Study Drug Initiation

After initiation of study drug, all adverse events (serious and non-serious adverse events and adverse events of special interest) will be reported until the safety follow-up visit (28 days after last dose of alectinib or 28 days after the end of last cycle of chemotherapy [7 weeks after day one of last cycle]). 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 paper Clinical Trial Adverse Event/Special *Situations* 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 e-mail 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 serious adverse events that occur outside the defined reporting period treatment 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 90 days after the last dose of alectinib or according to local label for chemotherapy. A paper Clinical Trial Pregnancy Reporting Form 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 e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

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 90 days after the last dose of alectinib or according to local label for chemotherapy. A paper Clinical Trial Pregnancy Reporting Form 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 e-mail address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.
An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to

support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo-fetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryo-fetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as 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.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, e-mail, and/or a monitoring visit

to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after last dose of alectinib or 28 days after end of last cycle of chemotherapy [7 weeks after Day 1 of the last cycle], see Section 5.3.1), all deaths, regardless of cause, should be captured on the Death during Disease Follow-Up eCRF. All deaths, regardless of cause, occurring after disease recurrence, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special *Situations* Form using the fax number or e-mail 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 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
- USPI for vinorelbine and gemcitabine
- EU-SmPC for pemetrexed
- UK-SmPC for cisplatin and carboplatin

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary and secondary efficacy analyses will be performed for all randomized patients (ITT population) and for the Stage II–IIIa subpopulation. The same analysis methods will be applied for both the ITT population and the Stage II–IIIa subpopulation.

Safety analyses will be performed on all randomized patients who received at least 1 dose of study medication.

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 255 patients are expected to be randomized into the study.
As mentioned in Section 3.3.3, the number of Stage Ib patients will be capped at 25% to ensure that at least 75% of all randomized patients will have Stage II–IIIa disease.
The resulting ITT population of all patients randomized will include a minimum of 191 patients in the Stage II–IIIa subpopulation.

Recruitment is assumed to happen at a rate of 0.034 patients per site per month, with a total of approximately 200 sites. Detailed recruitment is as follows:

- Months 1–2: 1 patient per month
- Month 3: 2 patients per month
- Month 4: 3 patients per month
- Months 5–6: 4 patients per month
- Months 7–9: 5 patients per month
- Months 10–12: 7 patients per month
- Month 13 onwards: 8 patients per month

Based on these assumptions, enrollment will take approximately 38 months to complete.

The sample size and the number of events required to demonstrate efficacy with regard to the primary efficacy endpoint DFS at the primary analysis are based on the following assumptions:

- Overall 2-sided significance level of 0.05 in the Stage II–IIIa subpopulation and the ITT population
- 80% power to detect an HR = 0.55, corresponding to an improvement in median DFS from 30–55 months for patients receiving alectinib compared with chemotherapy in the Stage II–IIIa subpopulation
- 80% power to detect an HR = 0.58 corresponding to an improvement in median DFS from 36– 62 months for patients receiving alectinib compared with chemotherapy in the ITT population
- One interim analysis for DFS when approximately 67% of the total DFS events have occurred, with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries (see Section 6.9.1)

Based on these assumptions, the primary DFS analysis will be conducted after approximately 89 DFS events in the Stage II–IIIa subpopulation have been observed. This is predicted to occur approximately 60 months (5 years) after the first patient is randomized.

The focus of this clinical trial is hypothesis testing, testing superiority of alectinib compared with chemotherapy with respect to DFS. To control the overall level of significance at a 2-sided error rate of 0.05, comparisons with respect to DFS between the alectinib and chemotherapy arms within the Stage II–IIIa subpopulation and the ITT population will be conducted hierarchically as follows:

- Disease-free survival (DFS) in the Stage II–IIIa subpopulation will be first tested at an overall 2-sided α-level of 0.05. If the 2-sided p-value corresponding to the stratified log-rank test is less than 0.0464 at the primary analysis (in order to adjust for 1 interim analysis for efficacy, as specified in Section 6.9.1), the null hypothesis will be rejected, and it will be concluded that alectinib prolongs duration of DFS relative to chemotherapy in the Stage II–IIIa subpopulation. Stopping boundaries will be adjusted depending on the actual number of DFS events.
- If alectinib significantly prolongs DFS in the Stage II–IIIa subpopulation, then DFS in the ITT population will be tested at an overall 2-sided α-level of 0.05. If the 2-sided p-value corresponding to the stratified log-rank test is less than 0.0463 at the primary analysis (in order to adjust for 1 interim analysis for efficacy, as specified in Section 6.9.1), the null hypothesis will be rejected, and it will be concluded that alectinib prolongs duration of DFS relative to chemotherapy in the ITT population. Stopping boundaries will be adjusted depending on the actual number of DFS events.

If alectinib has no significant effect on DFS in the Stage II–IIIa subpopulation, then DFS in the ITT population will not be tested.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for study termination will be summarized by treatment arm for the Stage II–IIIa subpopulation and the ITT population. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm for the Stage II–IIIa subpopulation and ITT population.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic characteristics, such as age, sex, race/ethnicity, and baseline disease characteristics (e.g., ECOG Performance Status), will be summarized by treatment arm for the Stage II–IIIa subpopulation and the ITT population. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of alectinib or starting the first cycle of chemotherapy in the randomized phase.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed for the Stage II–IIIa subpopulation followed by the ITT population, which is defined as all randomized patients. Patients will be analyzed in the treatment group to which they were randomized.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of alectinib compared with platinum-based chemotherapy on the basis of DFS. Disease-free survival is defined as the time from randomization to the first documented recurrence of disease or new primary NSCLC—as determined by the investigator through use of an integrated assessment of radiographic data, biopsy sample results (if clinically feasible), and clinical status—or death from any cause, whichever occurs first.

Patients who are not reported as experiencing disease recurrence, a new primary NSCLC, or death will be censored at the date of the last disease assessment. If no post-baseline data are available, patients will be censored at the date of randomization.

To control the overall level of significance at a 2-sided error rate of 0.05, comparisons with respect to DFS between the alectinib and chemotherapy arms within the Stage II–IIIa subpopulation and the ITT population will be conducted hierarchically as described in Section 6.1.

The null (H_0) and alternative (H_A) hypotheses regarding DFS in each population (the Stage II–IIIa subpopulation and the ITT population) can be phrased in terms of the DFS survival distribution function (SDF) in the alectinib arm and SDF in the control arm, respectively:

H_0: SDF (alectinib) = SDF (chemotherapy)
versus
H_A: SDF (alectinib) ≠ SDF (chemotherapy)

The HR in the Stage II–IIIa subpopulation will be estimated with use of a stratified Cox regression model with race as stratification factor, including 95% CIs. For the ITT population, all stratification factors specified for randomization will be used for the stratified Cox regression model. Strata with less than 20 patients will be pooled for analysis in the stratified Cox regression model. The unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm, and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment and control arms.

Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm.

In addition, the impact of loss to follow-up on DFS will be assessed depending on the number of patients who are lost to follow-up. If more than 5% of patients are lost to follow-up for DFS in either treatment arm, a sensitivity analysis ("worst-case" analysis) will be performed in which patients who are lost to follow-up will be considered to have recurrent disease at the date of the last disease assessment.

6.4.2 Secondary Efficacy Endpoints

Overall survival is defined as the time from the date of randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.
The methodology (as described in Section 6.4.1) used for DFS will be applied for OS.

Overall survival will be analyzed at the time of the DFS analyses and at the time of the final survival follow-up analysis, which will be conducted at approximately 5 years after the last patient is enrolled.

6.4.3 Exploratory Efficacy Endpoints

Analyses at landmark timepoints of 3, 4, and 5 years within the Stage II–IIIa subpopulation and the ITT population will be performed for DFS. Rates will be estimated using Kaplan-Meier methodology for each treatment arm, with 95% CIs calculated using Greenwood's formula.

The effects of demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) on duration of DFS will be examined by subgroup analyses. Summaries of DFS, including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median survival time will be produced separately for each level of the categorical variables.

Disease-free survival as an endpoint does not distinguish between the location of the first documented recurrence of disease or new primary NSCLC. Descriptive statistics (i.e., frequencies and percentages) will be used to explore the first site of recurrence of disease or new primary NSCLC.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all randomized patients who were enrolled during the global enrollment phase and received any amount of study drug, with patients grouped according to treatment received.
All patients who receive any dose of alectinib will be included in the alectinib treatment arm.

Drug exposure will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be mapped to thesaurus terms and graded according to NCI CTCAE v5.0. All adverse events that occur during or after the first study drug dose will be summarized using descriptive statistics (i.e., frequencies and percentages) by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. Adverse events will be described in individual listings and by body system, as well as by severity. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

Summaries of treatment-related serious adverse events, adverse events of special interest, and all listings of adverse events will include all events that occur during or after the first study drug treatment. Safety summaries of all other adverse events will include treatment-emergent adverse events with onset up to 28 days after the last dose of alectinib or up to 28 days after the end of last cycle of chemotherapy (7 weeks after Day 1 of the last cycle), or until patients receive another anti-cancer therapy, whichever comes first.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized in shift tables. Changes in vital signs and ECGs will be summarized by treatment arm. Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

Subgroup analyses will be performed to evaluate the safety profile within subgroups of patients, including by sex, age (< 65 years vs. ≥ 65 years), race (non-Asian vs. Asian), and for the subpopulation of patients with Stage II–IIIa NSCLC. Furthermore, safety analyses will also be performed within the subgroups of patients by disease stage (Stage Ib vs. II vs. IIIa).

An external iDMC will evaluate safety data on an ongoing basis. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities.
Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. A detailed plan will be included in the iDMC Charter.

6.6 PHARMACOKINETIC ANALYSES

The serial/intensive PK analysis population (if Japan will participate in the study) will consist of the subset of Japanese patients who underwent serial/intensive PK sampling with sufficient data to enable estimation of key parameters (e.g., AUC, time to C_{max} [t_{max}], C_{max}, and half-life).

The sparse PK-evaluable population will consist of all patients who had at least 1 post-baseline quantifiable PK sample available.

Standard non-compartmental analysis may be conducted for PK data collected from patients participating in serial/intensive PK collections for relevant analytes, as data allow, as appropriate, and if needed. Pharmacokinetic parameters including, but not limited, to AUC, C_{max}, and t_{max} will be calculated on the basis of the available data as appropriate and where data allow.

Additional PK parameters may be calculated as deemed appropriate.

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

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

Results of PK and/or any PK/pharmacodynamic analyses may be reported outside the Clinical Study Report.

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

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

6.7 EXPLORATORY BIOMARKER ANALYSIS

Anaplastic lymphoma kinase tumor tissue and plasma assays (e.g., next-generation targeted sequencing, PCR) will be used as exploratory assays for all enrolled ALK-positive patients. Results from these analyses will be used to understand

resistance mechanisms to alectinib and the relevance of ALK rearrangement variant or fusion partner. Minimal residual disease after surgery, early recurrence, and changes in the mutational profile of the tumor by monitoring circulating tumor nucleic acids in plasma during treatment or at recurrence compared with baseline will be explored. Tumor mutations, tumor mutation allele frequencies, and circulating tumor nucleic acid amounts may be correlated with clinical efficacy. Efficacy analysis of different ALK tumor and ALK plasma subpopulations maybe performed.

Results from the exploratory biomarker analyses from baseline and recurrence tumor samples and from plasma samples at baseline, on treatment, and post-recurrence will be communicated outside the main Clinical Study Report.

6.8 EXPLORATORY PATIENT-REPORTED OUTCOME ANALYSES

The SF-36v2 and EQ-5D-5L will be scored per authors' guidelines. Completion and compliance rates will be summarized by number and proportion of patients among those expected to complete each questionnaire at each timepoint by treatment arm. Reasons for non-completion will be summarized at each timepoint by treatment arm.

In the ITT population, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) and the mean changes from baseline will be reported for the PCS score, MCS score, and each health domain from the SF-36v2 by visit and by treatment arm.

A single summary index from the EQ-5D-5L health states will be used in this study for economic modeling.

Furthermore, PRO analyses will also be performed in the subpopulation of patients with Stage II-IIIa NSCLC.

These results may not be reported in the Clinical Study Report.

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

There is 1 interim analysis for efficacy planned in the study for DFS. The interim analysis will be conducted after approximately 67% of events have been observed in the Stage II–IIIa subpopulation. Based on the assumptions described in Section 6.1, this relates to approximately 59 DFS events for the Stage II–IIIa subpopulation. This is predicted to occur approximately 44 months after the first patient is randomized (i.e., approximately 16 months before the primary analysis), although the exact timing of this analysis will depend on the actual number of DFS events in the Stage II–IIIa subpopulation, but irrespective of the number of DFS events observed in the ITT population.

To control the type I error, the stopping boundaries for the DFS interim and primary analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundaries. In the Stage II–IIIa subpopulation, the stopping boundary for early rejection of the null hypothesis for an overall 2-sided 5% significance level is HR $\leq$ 0.52 (p $\leq$ 0.0118). In the ITT population, the stopping boundary for early rejection of the null hypothesis for an overall 2-sided 5% significance level is HR $\leq$ 0.55 (p $\leq$ 0.0121). If less than 67% of DFS events in the ITT population have been observed at the time of reaching the required number of events for the interim analysis in the Stage II–IIIa subpopulation, the stopping boundaries will be adjusted depending on the actual number of DFS events observed in the ITT population. However, the ITT interim analysis would only take place in the case of early rejection of the null hypothesis in the Stage II–IIIa subpopulation.

An external iDMC will evaluate safety data on an ongoing basis and review the data from the interim analysis. All summaries and analyses by treatment arm for the iDMC's review will be prepared by an external independent data coordinating center. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification to the IRB/EC. A detailed plan will be included in the iDMC Charter.

Positive efficacy results at the interim analysis will not change the conduct of the study and timing of disease assessments, as described in Section 4.5.6.

6.9.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one additional interim efficacy analysis. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC Charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy, as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is

maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study to be stopped for positive efficacy may be added to the iDMC Charter. If the study continues beyond the interim analysis, the critical value at the primary DFS analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

Positive efficacy results at an optional interim analysis will not change the conduct of the study and timing of disease assessments, as described in Section 4.5.6.

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 and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

Patient-reported outcome data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

To facilitate source data verification and review, 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.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, 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.

Radiographic images will be submitted to an IRF for a quality and completeness check, and for temporary storage prior to transfer to the Sponsor for the long-term retention for potential independent reading.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

Biomarker plasma and tissue sampling will be conducted in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Pregnant Partner Authorization Form or Mobile 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.

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the 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 9.7).

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of 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 (see definition of end of study in Section 3.2).

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity during Q4 2019. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks.
Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Where required, specific-site management activities may be delegated to a contract research organization.

Approximately 200 sites globally will participate to enroll approximately 255 patients. Randomization will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

If testing for the study inclusion criteria of ALK-positive NSCLC cannot be performed locally, central testing will be offered. This will be performed at Sponsor's designated central laboratories and assessed by a Ventana IHC test.

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

An Independent Review Facility (IRF) will collect, store, and potentially review imaging data. It may perform a blinded independent central review (BICR) of images and other clinical data as needed. In the event that such review is undertaken, BICR membership and procedures will be detailed in a separate BICR charter.

9.6 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:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

9.7 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

[ACS] American Cancer Society. Non–small-cell lung cancer survival rates, by stage [resource on the Internet]. 2016 [cited 14 November 2017]. Available from: https://www.cancer.org/cancer/non-small-cell-lung-cancer/detection-diagnosis-staging/survival-rates.html.

Beal SL, Boeckmann AJ, Sheiner LB. NONMEM Project Group. NONMEM users guides. Version 5 ed. San Francisco, CA: University of California at San Francisco. 1999.

Blackhall FH, Peters S, Bubendorf L, et al. Prevalence and clinical outcomes for patients with ALK-positive resected stage I to III adenocarcinoma: results from the European Thoracic Oncology Platform Lungscape Project. J Clin Oncol 2014;32:2780–7.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Brunelli A, Socci L, Regai M, et al. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. Ann Thorac Surg 2007;84:410–6.

Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.

Cancer Research UK. Lung cancer incidence statistics [resource on the Internet]. Last reviewed February 2017 [cited 15 November 2017]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#ref-5.

Choi YL, Soda M. Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010;363:1734–9.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

Decision Resources Group. Non-small-cell lung cancer [resource on the Internet]. 2014 [cited 12 December 2017]. Available from: https://decisionresourcesgroup.com/report/246121-biopharma-non-small-cell-lung-cancer-2014/.

DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260–71.

Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. Cin Cancer Res 2012;18:1472–82.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Forshew T, Mertaza M, Parkinson C, et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. Sci Transl Med 2012;4:136ra68.

Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizoitinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119–28.

GLOBOCAN. Lung Cancer: estimatedincidence, mortality, and prevalence worldwide in 2012. 2012. Accessed December 2017. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=lung

Goss GD, O'Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol 2013;31:3320–6.

Hartmann JT, Haap M, Kopp HG, et al. Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. Curr Drug Metab 2009;10:470–81.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Hohenegger M. Drug induced rhabdomyolysis. Curr Opin Pharmacol 2012;12:335–9.

Hsu JC, Jaminion F, Guerini E, et al. Population pharmacokinetics (popPK) and exposure-response (ER) analyses bridge J-ALEX to the global population with an alectinib (ALC) 600 mg BID dosing regimen [abstract]. J Clin Oncol 2017;35(Suppl 15):e20616.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Katayama R. Khan TM, Benes C, 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;108:7535–40.

Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. J Clin Oncol 2015;33:4007–14.

Kim S, Kim TM, Kim DW, et al. Heterogeneity of genetic changes associated with acquired crizotinib resistance in ALK-rearranged lung cancer. J Thorac Oncol 2013;8:415–22.

Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for Stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. J Clin Oncol 2017;35:2960–74.

Lin JJ, Riely GJ, Shaw AT. Targeting ALK: precision medicine takes on drug resistance. Cancer Discov 2017;7:137–55.

Myrdal G, Gustafsson G, Lambe M, et al. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. Eur J Cardiothorac Surg 2001;20:694–9.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non–small-cell lung cancer, version 8 [resource on the Internet]. 2017 [cited 20 August 2017]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Nishio M, Kim DW, Wu YL, et al. Crizotinib versus chemotherapy in Asian patients with advanced ALK-positive non–small cell lung cancer. Cancer Res Treat 2017; doi: 10.4143/crt.2017.280 [ePub ahead of print].

Novello S, Mazieres J, Oh I, et al. Primary results from the phase III ALUR study of alectinib vs. chemotherapy in previously treated ALK+ non–small-cell lung cancer (NSCLC). Ann Oncol 2017;28(Suppl 5):v605–49.

Ostroff JS, Krebs P, Coups EJ, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. Lung Cancer 2011;71:103–8.

Ou SH, Ahn JS, DePetris L, et al. Alectinib in crizotinib-refractory ALK-rearranged non–small-cell lung cancer: a Phase II global study J Clin Oncol 2016;34:661–8.

Ou SH, Bartlett CH, Mino-Kenudson M, et al. Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology. Oncologist 2012;17:1351–75.

Paik JH, Choi CM, Kim H, et al. Clinicopathologic implication of ALK rearrangement in surgically resected lung cancer: a proposal of diagnostic algorithm for ALK-rearranged adenocarcinoma. Lung Cancer 2012;76:403–9.

Patel SH, Ma Y, Wernicke AG, et al. Evience supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer. Lung Cancer 2014;84:156–60.

Peters S, Camidge DR, Shaw AT et al. Alectinib versus crizotinab in untreated ALK-positive non–small-cell lung cancer. N Engl J Med 2017;377:829–38.

Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552–9.

Ponn RB, Lo Cicero J III, Daly BDT. Surgical treatment of non–small cell lung cancer. In: Shields TW, Lo Cicero III J, Ponn R, et al., editors. General Thoracic Surgery (6th edition). Philadelphia: Lippincott Williams & Wilkins, 2005:1548–87.

Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann of Oncol 2017;28(Suppl 4):iv1–21.

RadiologyInfo.org. Lung cancer treatment [resource on the Internet]. 2017 [updated 1 February 2017; cited 14 April 2018]. Available from: https://www.radiologyinfo.org/en/info.cfm?pg=lung-cancer-therapy.

Ravdin PM, Davis G. Prognosis of patients with resected non-small cell lung cancer: impact of clinical and pathologic variables. Lung Cancer 2006;52:207–12.

Sahu A, Prabhash K, Noronha V, et al. Crizotonib: a comprehensive review. South Asian J Cancer 2013;2:91–7.

Saynak M, Higginson DS, Morris DE, et al. Current status of postoperative radiation for non–small-cell lung cancer. Semin Radiat Oncol 2010;20:192–200.

Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non–small cell lung cancer: a single-group, multicentre, Phase 2 trial. Lancel Oncol 2016;17:234–42.

Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385–94.

Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.

Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043–51.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. Med Care 1992;30:473–83 (abstract)

Ware J, Kosinski M, Bjorner J, et al. User's Manual for the SF-36v2® Health Survey. Lincoln (RI): QualityMetric Incorporated; 2007:151–185.

Ware JE Jr., Kosinski M, Bjorner JB, et al. SF-36v2 health survey: administration guide for clinical trial investigators. Lincoln, Rhode Island: QualityMetric, Incorporated, 2008.

WHO. Cancer fact sheet [resource on the Internet]. 2017 [cited December 2017]. Available from: http://www.who.int/mediacentre/factsheets/fs297/en/.

Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non–small-cell lung cancer. N Engl J Med 2020;383:1711–23

Wu YL, Zhong W, Wang Q, et al. Gefitinib (G) versus vinorelbine + cisplatin (VP) as adjuvant treatment in stage II–IIIA (N1–N2) non–small-cell lung cancer (NSCLC) with *EGFR*-activating mutation (ADJUVANT): a randomized, Phase III trial (CTONG 1104) [abstract]. J Clin Oncol 2017;35(Suppl 15):8500.

Xalkori® (crizotinib, capsules for oral use). U.S. Package Insert, Pfizer. February 2012 [cited December 2017]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s002lbl.pdf.

Yoshida T, Oya Y, Tanaka K, et al. Differential crizotinib response duration among ALK fusion variants in ALK-positive non-small-cell lung cancer. J Clin Oncol 2016;34:3383–9.

Zykadia® (certinib, capsules for oral use). U.S. Package Insert, Novartis Pharmaceuticals Corporation. November 2017 [cited December 2017]. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zykadia.pdf.

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Appendix 1 Schedule of Activities: Alectinib Arm

Assessment	Screening		Treatment Period				Safety FU Visit [b]	Disease Recurrence Visit [c]	Long-Term Follow-Up [d]
			Weeks 1–12 [a]		Weeks 13–48	Weeks 49–96			
	Day –28 to –1	Day –3 to –1	Baseline	Q3W (± 3 Days)	Q6W (± 3 Days)	Q12W (± 5 Days)			
Informed consent [e]	x								
Demographic data	x								
Medical history, baseline conditions	x								
ECOG Performance Status	x		x	x	x	x	x		
Vital signs [f]	x		x	x	x	x	x		
Weight	x		x	x	x	x	x		
Height	x								
Complete physical examination [g]	x		x						
Limited physical examination [h]				x	x	x	x		
ECG	x [i]		x	At Weeks 3, 24, and 60			x		
Additional mandatory safety assessments			Every 2 weeks for the first 12 weeks [a]						
Hematology [j, k]	x [i]		x	x	x	x	x		
Coagulation [j]	x [i]		x	x	x	x	x		
Chemistry [l, k]	x [i]		x	x	x	x	x		
Pregnancy test [m]		x	To be repeated at all scheduled safety visits and as clinically indicated						
Urinalysis, dipstick	x		x	x	x	x	x		
Alectinib dispensing [n]			x	Every 3 weeks until Week 12 and every 12 weeks thereafter					

Appendix 1 Schedule of Activities: Alectinib Arm (cont.)

Assessment	Screening		Treatment Period				Safety FU Visit [b]	Disease Recurrence Visit [c]	Long-Term Follow-Up [d]
			Weeks 1–12 [a]		Weeks 13–48	Weeks 49–96			
	Day –28 to –1	Day –3 to –1	Baseline	Q3W (± 3 Days)	Q6W (± 3 Days)	Q12W (± 5 Days)			
Disease assessment (including MRI of the brain) [o]	x [p]		x	Every 12 weeks for the first 2 years, every 24 weeks during Years 3 to 5 and annually thereafter until recurrence					
Plasma PK sample (2 mL) [q]	See Appendix 3								
Plasma sample for biomarker analysis [r]	See Appendix 4								
Tumor tissue sample for biomarker analysis [s]	See Appendix 4								
Mandatory biopsy from site of recurrence [t]								x [t]	
Concomitant medications [u]	x [u]		x	x	x	x	x		
Adverse events [v]	x [v]		x	x	x	x	x		
Subsequent therapy and SFU [d]									x
Patient-Reported Outcome [w]			x [x]	x	x [w]	x [w]	x		

ALK = anaplastic lymphoma kinase; BID = twice a day; *COVID-19 = coronavirus disease 2019;* CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FU = follow-up; GGT = gamma-glutamyl transferase; *IRF = Independent Review Facility;* MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; *NSCLC = non-small-cell lung cancer;* PET = positron emission tomography; PK = pharmacokinetic; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; Q12W = every 12 weeks; RBR = Research Biosample Repository; SFU = survival follow-up.

Notes: The screening period is within 28 days prior to randomization. Baseline (Week 1) occurs when the first dose is administered. The first dose should be administered as soon as possible after randomization and no later than 7 days after randomization. All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For patients at participating sites who have provided written informed consent to participate in the mobile nursing visits, assessments normally performed by a nurse at the sites may be performed by a trained nursing professional at the patient's home or another suitable location, for visits after Week 1.

Appendix 1 Schedule of Activities: Alectinib Arm (cont.)

[a] Additional mandatory safety assessments include CPK at Weeks 2 and 4 and ALT, AST, ALP, and total and direct bilirubin at Weeks 2, 4, 8, and 10.

[b] The safety follow-up visit will take place 28 (±3) days after last dose of alectinib.

[c] The disease recurrence visit should be scheduled within 30 days after diagnosis of recurrence for a mandatory biopsy.

[d] Required follow-up information (e.g., survival status and information on further cancer therapies and procedures [radiotherapy, surgery]) will be collected *after the first documented disease recurrence or new primary NSCLC,* via telephone calls or clinic visits every 6 months (±14 days) until death, loss to follow-up, or study termination by the Sponsor.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[f] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Results of laboratory tests and ECG performed within 3 days of first dose can be used as baseline assessments.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Peripheral blood smear, reticulocytes, and haptoglobin should be tested at baseline and in case of Grade 2 or higher anemia as per NCI CTCAE v5.0 (hemoglobin $<$10 g/dL). Coagulation includes PT (or INR) and aPTT (or PTT).

[k] In case of Grade 2 or higher anemia as per NCI CTCAE v5.0 (hemoglobin $<$ 10 g/dL), laboratory tests including hemoglobin, RBC count, reticulocytes, haptoglobin, ALT, LDH, total and direct bilirubin, peripheral blood smear, and a direct Coombs test (DAT) should be performed. This laboratory workup is to be conducted at each new occurrence of anemia at Grade 2 or higher.

[l] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (optional), fasting glucose, BUN or urea, creatinine, creatinine clearance (calculated according to the method of Cockcroft and Gault), GGT, total protein, albumin, phosphorus, magnesium, calcium, total and direct bilirubin, ALP, CPK, ALT, AST, uric acid, and thyroid-stimulating hormone. Lactate dehydrogenase should be tested at baseline and in case of Grade 2 or higher anemia as per NCI CTCAE v5.0 (hemoglobin $<$ 10 g/dL).

[m] For all women of childbearing potential, a negative serum pregnancy test result must be available prior to randomization (maximum of −3 days) and within 10 days of the first dose of alectinib. The first dose of alectinib must be administered within 7 days from randomization. Urine

pregnancy tests should be performed at scheduled safety visits throughout the study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[n] Alectinib will be administered BID until completion of the 24-month treatment period, recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first. Alectinib will be dispensed on Week 96 for an additional 8 weeks of treatment in order to complete the 24-month treatment period (until Week 104).

[o] Screening disease assessments consist, at minimum, of a CT scan of chest, CT/MRI scan of abdomen (including liver and adrenal glands), as well as an MRI of the brain (a CT scan may be used if MRI is not feasible). Patients who have clinical signs, symptoms, biochemical abnormalities (including, but not limited to, ALP, LDH, etc), or radiological imaging that could be suggestive of bone metastases at baseline, must undergo further investigation to exclude the presence of bone metastases at study entry. Subsequent assessments consist, at minimum, of a CT of the chest, CT/MRI scan of abdomen (including liver and adrenal glands) and brain. In case of suspicion of disease recurrence based on clinical or laboratory findings, a disease assessment should be performed as soon as possible before the next scheduled evaluation. If disease assessments continue after the treatment period, visit windows are as described in Section 4.5.6. *Images will be submitted and stored at an IRF.*

[p] A screening disease assessment done within 28 days of randomization will be counted as the baseline assessment.

[q] Predose PK (2 mL) sampling for all patients on alectinib treatment will be performed at baseline, every 3 weeks until Week 12, and every 12 weeks thereafter until recurrence of disease, unacceptable toxicity, withdrawal of consent, death, or Week 96, whichever occurs first. The predose PK samples should be taken immediately (within 2 hours) before intake of study medication at specified study visits. Remind the patient not to take the daily dose at home on the day of the scheduled study visit. For Japan sites only (if Japan will participate in the study), a subset of Japanese patients on alectinib treatment (approximately the first 6 patients) participating in serial/intensive PK sample collection, additional PK samples will be collected at Week 3 predose (within 2 hours before intake of study medication), 0.5, 1, 2, 4, 6, 8, 10, and 12 hours (optional) postdose. See Appendix 3 for a detailed schedule.

[r] Residual plasma samples can be used for the RBR if the patient has provided written informed consent to participate. See Appendix 4 for a detailed schedule.

[s] Mandatory tumor sample obtained at study entry and taken at disease recurrence (if clinically feasible) for biomarker analysis (confirmatory central ALK testing [at baseline only] and ALK rearrangements/mutations and other genes and gene mutations involved in resistance). Residual tissue samples can be used for the RBR if the patient has provided written informed consent to participate.

[t] Mandatory biopsy (if clinically feasible) for confirmation of diagnosis of recurrence within 30 days from the time of recurrence. A tumor tissue for biomarker analysis will be obtained from the mandatory biopsy at recurrence.

[u] Concomitant medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug until safety follow-up visit. *Details of regarding the COVID-19 vaccine received should be recorded in the concomitant medication section.*

Appendix 1 Schedule of Activities: Alectinib Arm (cont.)

[v] 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. After initiation of study drug, all adverse events will be reported until the safety follow-up visit at 28 days after last dose of alectinib. After the adverse event reporting period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment. 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.

[w] The PRO questionnaires (SF-36v2® and EQ-5D-5L) will be completed by patients at the investigational site within the window (−3 days) specified for the clinic visit prior to any assessment at: baseline, every 3 weeks through Week 12, and every 12 weeks thereafter until recurrence of disease, withdrawal of consent, death, or Week 96, whichever occurs first. Patient-reported outcome will also be collected at the safety follow-up visit.

[x] Patient-reported outcome at baseline can be performed within -3 days of the first dose if not possible during the baseline (Week 1) visit. Patient-reported outcome must be collected at the clinic visit prior to any visit assessments.

Appendix 2 Schedule of Activities: Patients Randomized to Chemotherapy

Assessments	Screening		Treatment Period		Safety FU Visit [c]	Disease Recurrence Visit [d]	Long-Term Follow-Up [e]
			Weeks 1–12 [a]				
	Day –28 to –1	Day –3 to –1	Baseline	Q3W (±3 Days)			
Informed consent [f]	x						
Demographic data	x						
Medical history and baseline	x						
ECOG Performance Status	x		x	x	x		
Vital signs [g]	x		x	x	x		
Weight	x		x	x	x		
Height	x						
Complete physical examination [h]	x		x				
Limited physical examination [i]				x	x		
ECG	x [u]		x	At Week 3	x		
Hematology [j]	x [u]		x	x	x		
Coagulation [j]	x [u]		x	x	x		
Chemistry [k]	x [u]		x	x	x		
Pregnancy test [l]		x	To be repeated at all scheduled safety visits and as clinically indicated				
Urinalysis, dipstick	x		x	x	x		
Chemotherapy administration [b]			x	x			

Appendix 2 Schedule of Activities: Patients Randomized to Chemotherapy (cont.)

Assessments	Screening		Treatment Period		Safety FU Visit [c]	Disease Recurrence Visit [d]	Long-Term Follow-Up [e]
			Weeks 1–12 [a]				
	Day –28 to –1	Day –3 to –1	Baseline	Q3W (±3 Days)			
Disease assessment (including MRI of the brain) [m]	x [n]		x	Every 12 weeks for the first 2 years, every 24 weeks during Years 3–5 and annually thereafter until recurrence			
Plasma sample for biomarker analysis [o]	See Appendix 4						
Tumor tissue sample for biomarker analysis [p]	See Appendix 4						
Mandatory biopsy from site of recurrence [q]						x [q]	
Concomitant medications [r]	x		x	x	x		
Adverse events [s]	x		x	x	x		
Subsequent treatment and SFU [e]							x
PROs [t]			x [v]	x	x		

ALK = anaplastic lymphoma kinase; *COVID-19 = coronavirus disease 2019;* CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FU = follow-up; GGT = gamma-glutamyl transferase; *IRF = Independent Review Facility;* MRI = magnetic resonance imaging; *NSCLC = non-small-cell lung cancer;* PET = positron emission tomography; PRO = patient-reported outcome; Q3W = every 3 weeks; RBR = Research Biosample Repository; SFU = survival follow-up.

Appendix 2 Schedule of Activities: Patients Randomized to Chemotherapy (cont.)

Notes: The screening period is within 28 days prior to randomization. Baseline (Week 1) occurs when the first dose of platinum-based chemotherapy is administered. The first dose should be administered as soon as possible after randomization and no later than 7 days after randomization. All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. For patients at participating sites who have provided written informed consent to participate in the mobile nursing visits, assessments normally performed by a nurse at the sites may be performed by a trained nursing professional at the patient's home or another suitable location, for visits after Week 1.

[a] Additional mandatory phone calls at Weeks 2, 4, 8, and 10 need to be conducted for safety monitoring.

[b] Platinum-based chemotherapies will be administered until the completion of the treatment period (4 cycles), recurrence of disease, unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

[c] The safety follow-up visit will take place 28 days after the end of the last cycle of chemotherapy (7 weeks after Day 1 of the last cycle ± 3 days).

[d] The disease recurrence visit should be scheduled within 30 days after a diagnosis of recurrence for mandatory biopsy.

[e] Required follow-up information (e.g., survival status and information on further cancer therapies and procedures [radiotherapy, surgery] will be collected *after the first documented disease recurrence or new primary NSCLC,* via telephone calls and/or clinic visits every 6 months (± 14 days) until death, loss to follow-up, or study termination by the Sponsor.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[g] Includes respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, absolute count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). Coagulation includes PT (or INR) and aPTT (or PTT).

[k] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, bicarbonate (optional), fasting glucose, BUN or urea, creatinine, creatinine clearance (calculated according to the method of Cockcroft and Gault), GGT, total protein, albumin, phosphorus, magnesium, calcium, total and direct bilirubin, ALP, CPK, ALT, AST, uric acid, and thyroid-stimulating hormone.

[l] For all women of childbearing potential, a negative serum pregnancy test result must be available prior to randomization (maximum of −3 days) and within 10 days of the first dose of chemotherapy. The first dose of chemotherapy must be administered within 7 days from randomization. Urine pregnancy tests should be performed at all safety visits throughout the study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Appendix 2 Schedule of Activities: Patients Randomized to Chemotherapy (cont.)

[m] Screening disease assessments consist, at minimum, of a CT scan of chest, CT/MRI scan of abdomen (including liver and adrenal glands), as well as an MRI of the brain (CT scan may be used if MRI is not feasible). Patients who have clinical signs, symptoms, biochemical abnormalities (including but not limited to ALP, LDH, etc), or radiological imaging that could be suggestive of bone metastases at baseline, must undergo further investigation to exclude the presence of bone metastases at study entry. Subsequent assessments consist, at minimum, of a CT of the chest, CT/MRI scan of abdomen (including liver and adrenal glands) and brain. In case of suspicion of recurrence of disease based on clinical or laboratory findings, a disease assessment should be performed as soon as possible before the next scheduled evaluation. If disease assessments continue after the treatment period, visit windows are as described in Section 4.5.6. *Images will be submitted and stored at an IRF.*

[n] A screening disease assessment done within 28 days of randomization will be counted as the baseline assessment.

[o] Residual plasma samples can be used for RBR if patient has provided written informed consent to participate. See Appendix 4 for a detailed schedule.

[p] Mandatory tumor sample obtained at study entry and taken at disease recurrence (if clinically feasible) for biomarker analysis (confirmatory central ALK testing [at baseline only] and *ALK* rearrangements/mutations and other genes and gene mutations involved in resistance). Residual tissue samples can be used for the RBR if the patient has provided written informed consent to participate.

[q] Mandatory biopsy (if clinically feasible) for confirmation of a diagnosis of recurrence within 30 days from time of recurrence. Tumor tissue for biomarker analysis will be obtained from the mandatory biopsy at recurrence.

[r] Concomitant medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug until safety follow-up visit. *Details of regarding the COVID-19 vaccine received should be recorded in the concomitant medication section.*

[s] 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. After initiation of study drug, all adverse events will be reported until the safety follow-up visit at 28 days after the end of the last cycle of chemotherapy (7 weeks after Day 1 of the last cycle). After the adverse event reporting period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment. 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.

[t] The PRO questionnaires (SF-36v2® and EQ-5D-5L) will be completed by patients at the investigational site within the window (–3 days) specified for the clinic visit prior to any assessment at: baseline, every 3 weeks through Week 12, and every 12 weeks thereafter until recurrence of disease, withdrawal of consent, death, or Week 96, whichever occurs first. PROs will also be collected at the safety follow-up visit.

[u] Results of laboratory tests and ECG performed within 3 days of first dose can be used as baseline assessments.

[v] Patient-reported outcome baseline questionnaires can be performed within –3 days of the first dose if not possible during the baseline (Week 1) visit. Patient-reported outcome must be collected at the clinic visit prior to any visit assessments.

Appendix 3 Schedule of Pharmacokinetic Assessments for Patients Randomized to Alectinib

Visit	Timepoint	Sample Type
Baseline	Predose (within 2 hours before first administration of alectinib)	Plasma
Weeks 3, 6, 9, 12, 24, 36, 48, 60, 72, 84, and 96	Predose (within 2 hours before intake of alectinib)	Plasma
Week 3 [a]	Predose (within 2 hours before intake of alectinib), 0.5, 1, 2, 4, 6, 8, 10, and 12 (optional) hours	Plasma

PK = pharmacokinetic.

[a] Japan only (if Japan participates in the study): Japanese patients participating in the serial/intensive PK sample collection only.

Appendix 4 Schedule of Biomarker Samples

Visit	Timepoint	Sample Type	Biomarkers
Baseline	At visit	Plasma	*ALK* rearrangements/mutations and other genes and gene mutations involved in resistance and circulating tumor nucleic acids for MRD and early recurrence
	From prior sampling	Tumor tissue	Confirmatory central ALK testing, *ALK* rearrangements/mutations and other genes and gene mutations involved in resistance
Scheduled visits until recurrence	Every 3 weeks until Week 12, every 12 weeks between Weeks 13–96, every 24 weeks during Years 3–5, and annually thereafter until disease recurrence	Plasma	*ALK* rearrangements/mutations and other genes and gene mutations involved in resistance and circulating tumor nucleic acids for MRD and early recurrence
At disease recurrence visit	At disease recurrence	Plasma	*ALK* rearrangements/mutations and other genes and gene mutations involved in resistance and circulating tumor nucleic acids for MRD and early recurrence
		Tumor tissue [a]	*ALK* rearrangements/mutations and other genes and gene mutations involved in resistance

ALK = anaplastic lymphoma kinase; MRD = minimal residual disease.

[a] A tumor tissue for biomarker analysis will be obtained from the biopsy collected at recurrence.

Appendix 5 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	
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan	

Source: Levien and Baker 2003; Zhang 2010.

This information in this appendix is adapted from Levien and Baker 2003, Zhang 2010, and the FDA's Guidance on Drug–Drug Interactions.

Also see:

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

REFERENCES

Levien TL, Baker DE. Cytochrome P450 drug interactions. Therapeutic Research Center Pharmacist's Letter/Prescriber's Letter [resource on the internet]. 2003 [cited November 2017]. Available from: https://www.pharmacistletter.com.

Zhang L. Transporter mediated drug–drug interactions (DDIs). FDA. Clinical Pharmacology Advisory Committee Meeting Topic 4: Transporter-Mediated Drug–Drug Interactions. Atlanta, GA: 17 March 2010.

Appendix 6 Eastern Cooperative Oncology Group Performance Status Scale

Grade	ECOG Performance Status
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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 7 Formulae for the Calculation of QTcF and RR

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

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

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

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

Appendix 8 SF-36v2® Health Survey

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Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐1	☐2	☐3	☐4	☐5

Appendix 8 SF-36v2® Health Survey (cont.)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h. Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i. Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

Appendix 8 SF-36v2® Health Survey (cont.)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

Appendix 8 SF-36v2® Health Survey (cont.)

6. **During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix 9 EuroQol 5-Dimension, 5-Level Questionnaire

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Health Questionnaire

English version for the USA

Appendix 9 EuroQol 5-Dimension, 5-Level Questionnaire (cont.)

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 9 EuroQol 5-Dimension, 5-Level Questionnaire (cont.)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐