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

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STATISTICAL ANALYSIS PLAN

STUDY 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

STUDY NUMBER: BO40336

STUDY NAME: ALINA

VERSION NUMBER: 2

ROCHE COMPOUND(S): Alectinib (RO5424802)

EUDRACT NUMBER: 2017-004331-37

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PLAN PREPARED BY: [redacted], MSc

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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DATE FINAL: See electronic date stamp on the last page of the document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This statistical analysis plan (SAP) was developed based on Roche SAP model document v2.0 (28 February 2022).

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2	see electronic date stamp on title page	Version 7, 16 December 2021
1	15 March 2018	Version 1, 5 February 2018

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
All	The structure of the document has been updated and the estimand framework has been introduced	In line with the latest Roche SAP model document
5.3.2	The following sentence, “Strata with less than 20 patients will be pooled for analysis in the stratified Cox regression model.”, has been removed	Keep the factors used for randomization. Removing Race will still lead to low number of events in Stage IB (<10% of patients), removing Disease Stage will create heterogeneity.
5.3.3	Addition of potential sensitivity analyses	To assess the impact of the following on the primary endpoint: stratification errors, missing disease assessments, IRF assessments, Ukraine crisis.
5.5.3	Time to Central Nervous System (CNS) Recurrence or Death has been added as an exploratory endpoint	Endpoint judged clinically relevant

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AJCC	American Joint Committee on Cancer
AE	adverse event
ALK	anaplastic lymphoma kinase
AUC	area under the concentration-time curve
BICR	blinded independent central review
CI	confidence interval
CNS	central nervous system
COVID	coronavirus disease
CSR	Clinical Study Report
DFS	disease-free survival
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
HR	hazard ratio
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IRF	Independent Review Facility
ITT	intent to treat
IxRS	interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
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
PRO	patient-reported outcomes
PD	pharmacodynamic
PK	pharmacokinetic
SAE	serious adverse events
SAP	Statistical Analysis Plan
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study BO40336 (ALINA), 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 (ALK)-positive non-small-cell lung cancer (NSCLC). More detailed background information for the study can be found in the protocol.

1.1 OBJECTIVES, ENDPOINTS AND ESTIMANDS

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 as per the Union Internationale Contre le Cancer (UICC)/American Joint Committee on Cancer (AJCC) 7th edition (Detterbeck et al. 2009). Specific objectives and corresponding endpoints for the study are outlined in Table 1.

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.

In this SAP, the term "study treatment" refers to all protocol-mandated treatments assigned to patients as part of this study and includes alectinib and protocol-defined platinum-based chemotherapy regimens: cisplatin plus vinorelbine, cisplatin plus gemcitabine and cisplatin plus pemetrexed. In case of intolerability to a cisplatin-based regimen, carboplatin can be administered instead of cisplatin in one of the above combinations.

Table 1 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	• Disease-free survival (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	• Overall survival (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 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 of the protocol) 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.

1.1.1 Expression of Objectives and Endpoints Using the Estimand Framework

The primary study objective and corresponding endpoint, as well as the secondary efficacy objective and corresponding secondary efficacy endpoint, are expressed using the estimand framework in Table 2, in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020).

Table 2 Objectives and Estimands

Primary Efficacy Objective	Estimand Definition

• 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	• Population: patients with completely resected Stage II–IIIa ALK-positive NSCLC (Stage II-IIIa population)
	• Variable: Time from randomization to the first occurrence of a DFS event (as defined in Table 1)
	• Treatments:
	  ○ Experimental: alectinib 600 mg orally BID taken with food for 24 months
	  ○ Control: protocol-specified platinum-based chemotherapy regimens 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 below combinations.
	  ○ 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
	• Intercurrent events:
	  ○ Start of non-protocol adjuvant anti-cancer therapy prior to a DFS event
	  ○ Early discontinuation from study treatment for any reason prior to a DFS event
	• Handling of intercurrent events: A treatment policy with regards to the intercurrent events listed above will be applied for the primary analysis
	• Summary measure: Hazard ratio for DFS
	If alectinib significantly prolongs DFS in the Stage II–IIIa subpopulation, then DFS will be tested in the ITT population. The corresponding estimand is defined similarly as above but with the population as defined below:
	• Population: patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa ALK-positive NSCLC (ITT population)

Secondary Efficacy Objective	Estimand Definition

• 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	• Population: patients with completely resected Stage II–IIIa ALK-positive NSCLC (Stage II-IIIa population)
	• Variable: Time from randomization to death from any cause
	• Treatments:
	  ○ Experimental: alectinib 600 mg orally BID taken with food for 24 months
	  ○ Control: protocol-specified platinum-based chemotherapy regimens 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 below combinations.
	  ○ 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
	• Intercurrent events:
	  ○ Start of non-protocol adjuvant anti-cancer therapy
	  ○ Early discontinuation from study treatment for any reason
	• Handling of intercurrent events: A treatment policy with regards to the intercurrent events listed above will be applied for the analysis
	• Summary measure: Hazard ratio for OS
	
	OS will also be analyzed in the ITT population. As a consequence, an alternative estimand for OS is defined similarly as above but with the population as defined below:
	• Population: patients with completely resected Stage Ib (tumors ≥ 4 cm) to Stage IIIa ALK-positive NSCLC (ITT population)

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.

1.2 STUDY DESIGN

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 disease-free survival (DFS) as assessed by investigator, while OS is a secondary endpoint.

Patients with completely resected (negative margins), histologically confirmed Stage Ib (tumors ≥ 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 anaplastic lymphoma kinase (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 (Figure 1).

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.

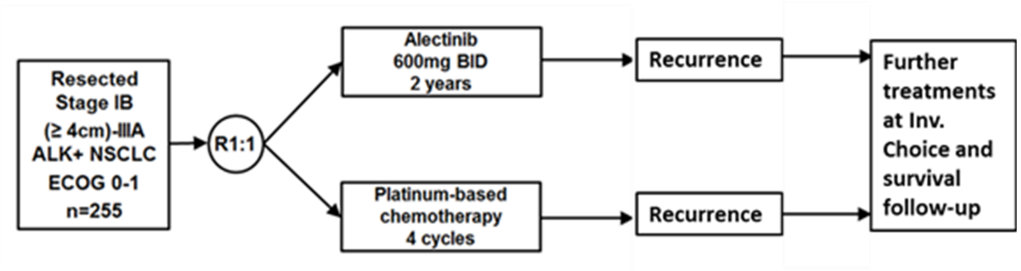
Protocol-defined platinum-based chemotherapy regimens include:

- 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.

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 two arms.

Figure 1 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.

1.2.1 Treatment Assignment

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 IIIa). Central randomization and drug allocation will be performed and managed via an interactive voice or Web-based response system (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.

1.2.2 Independent Review Facility

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.

1.2.3 Data Monitoring

An external independent Data Monitoring Committee (iDMC) will be established to monitor the progress of the study, 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 (Institutional Review Board/ Ethics Committee) IRB/EC. A detailed plan will be included in the iDMC Charter.

An 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 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.

2. STATISTICAL HYPOTHESES

The primary efficacy objective for this study is to evaluate the efficacy of alectinib compared with platinum-based chemotherapy on the basis of DFS.

To control the overall level of significance at a two-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 3.1.

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)

3. SAMPLE SIZE DETERMINATION

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 intent-to-treat (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 approximately 200 sites. Detailed recruitment is as follows:

- Months 1–2: 1 patient per month
- Month 3: 2 patients per month
- Months 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 two-sided significance level of 0.05 in the Stage II–IIIa subpopulation and the ITT population
- 80% power to detect an hazard ratio (HR) of 0.55, corresponding to an improvement in median DFS from 30 months to 55 months for patients receiving alectinib compared with chemotherapy in the Stage II–IIIa subpopulation
- 80% power to detect an HR of 0.58 corresponding to an improvement in median DFS from 36 months to 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 (for details see Section 5.8.1)

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.

3.1 TYPE 1 ERROR CONTROL

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 two-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:

- DFS in the Stage II–IIIa subpopulation will be first tested at an overall two-sided α level of 0.05. If the two-sided p-value corresponding to the stratified log-rank test is less than 0.0464 at the primary analysis (in order to adjust for one interim analysis for efficacy, as specified in Section 5.8.1), 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 two-sided α level of 0.05. If the two-sided p-value corresponding to the stratified log-rank test is less than 0.0463 at the primary analysis (in order to adjust for one interim analysis for efficacy, as specified in Section 5.8.1), 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.

4. ANALYSIS SETS

The analysis sets for this study are defined in Table 3 below:

Table 3 Analysis Sets

Population	Definition
ITT	All randomized participants, whether or not the participant received the assigned treatment. Participants will be grouped according to the treatment assigned at randomization by the IxRS.
Stage II-IIIa	All participants in the ITT population with Stage II-IIIa NSCLC as per IxRS data.
Safety-Evaluable	All participants who received at least one dose of study treatment. Participants will be assigned to treatment groups as treated, and all participants who received any dose of alectinib will be included in the alectinib treatment arm.
PK-Evaluable	All participants who received at least one dose of study treatment and had at least one post-baseline quantifiable PK sample available.

ITT = intent-to-treat; IxRS = interactive voice or web-based response system; PK = pharmacokinetic.

5. STATISTICAL ANALYSES

The analyses described in this SAP will supersede those specified in the protocol for the purposes of a regulatory filing.

5.1 GENERAL CONSIDERATION

All efficacy analyses will be performed for the Stage II–IIIa subpopulation followed by the ITT population, unless otherwise specified. Participants will be analyzed according to the treatment assigned at randomization by IxRS.

All safety analyses will be performed in the safety-evaluable population, unless otherwise specified. Participants will be analyzed according to the treatment they actually received. Specifically, a patient will be included in the alectinib arm in safety analyses if the patient receives any amount of alectinib, regardless of the initial treatment assignment by the IxRS.

Unless otherwise stated, baseline values are the last available data obtained prior to the patient receiving the first dose of study treatment (or at screening, for patients who were not treated).

Continuous variables will be summarized using means, standard deviations (SD), medians, ranges, and inter-quartile ranges (Q1 and Q3). Categorical variables will be summarized by frequencies and percentages.

Throughout the statistical analysis, two-sided tests will be performed at a significance level of 5%, unless otherwise stated. A testing hierarchy will be used to control the overall type I error rate at 5% with regards to DFS in the Stage II-IIIa subpopulation and

ITT population, as specified in Section 3.1. Adjustment for multiplicity will be applied as well for DFS due to the conduct of one interim analysis for efficacy. All other p-values and 95% confidence intervals (CIs) will be given in an exploratory manner.

5.2 PARTICIPANT DISPOSITION

Study enrollment and reasons for discontinuation from the study will be summarized by treatment arm for the Stage II–IIIa subpopulation and the ITT population. Study treatment disposition and reasons for discontinuation from study treatment will be summarized for the safety-evaluable set.

5.3 PRIMARY ENDPOINT ANALYSIS

5.3.1 Definition of Primary 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. DFS 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.

Data for 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, data for these patients will be censored at the date of randomization plus 1 day. In addition, in case of patients with baseline disease, data for such cases will be censored at the date of randomization plus 1 day.

As mentioned previously, a testing hierarchy will be used and DFS will be first tested in the Stage II–IIIa subpopulation. The primary estimand is defined as indicated in Table 2.

If alectinib significantly prolongs DFS in the Stage II–IIIa subpopulation, then DFS will be tested in the ITT population. The corresponding estimand is defined similarly as the primary one but with a different population (see Table 2).

5.3.2 Main Analytical Approach for Primary Endpoint

- The treatment comparison of DFS will be based on a stratified log-rank test, according to the protocol-defined stratification factors as entered in the IxRS:
  - Race (Asian vs. non-Asian) for the analysis in the Stage II–IIIa subpopulation,
  - Race (Asian vs. non-Asian) and disease stage (Stage Ib [tumors ≥ 4 cm] vs. Stage II vs. Stage IIIa) for the analysis in the ITT population
- Cox proportional hazards model, stratified by the protocol-defined stratification factors as entered in IxRS, as shown above, will be used to estimate the HR between the two treatment arms and its 95% confidence interval (CI).

- Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm, and the Kaplan-Meier curves 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 (Brookmeyer and Crowley 1982).

5.3.3 Sensitivity Analyses for Primary Endpoint

5.3.3.1 Unstratified Analysis

To assess the impact of stratification, results from an unstratified log-rank test and the unstratified HR will also be provided.

5.3.3.2 Stratification Errors

The analysis of DFS may be repeated by using the stratification factors as entered in the electronic Case Report Form (eCRF).

5.3.3.3 Loss to Follow-Up

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.

5.3.3.4 Missing Disease Assessments

The impact of missing scheduled tumor assessments on DFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis methods.

For each patient, the left and the right boundaries of the interval will be derived based on the following rules:

Table 4 Rules for Interval Censoring

Situations	Left Boundary	Right Boundary
Patients who had disease recurrence or new primary NSCLC prior to death	The date of the last assessment that showed a disease-free* status	The date of the first assessment that showed disease recurrence or new primary NSCLC
Patients who died without disease recurrence or new primary NSCLC	The date of the last assessment that showed a disease-free* status	Death date
Patients who did not die nor had disease recurrence nor new primary NSCLC	The date of the last assessment that showed a disease-free* status	Not applicable (Missing)

* For patients who did not have any post-baseline assessment with disease-free status, the left boundary is the date of randomization.

The DFS survival curves will be estimated using the nonparametric maximum likelihood estimate (NPMLE, Turnbull 1976) for each treatment arm. The median DFS of each treatment arm will be reported and its 95% confidence interval will be constructed based on the Brookmeyer-Crowley method (Brookmeyer and Crowley 1982).

Hypothesis testing will be performed based on the stratified log-rank test proposed by Sun (Sun 1996) to compare the DFS in the treatment arms. The treatment effect will be estimated using a stratified proportional hazard regression model (Finkelstein 1986) with a parametric assumption of piecewise Exponential distribution for the baseline hazard function (Friedman 1982, Royston and Parmar 2002). Results from an unstratified analysis will also be provided.

5.3.3.5 DFS by IRF

An analysis of DFS on the basis of IRF assessments may be performed after centralized, independent review of response endpoints by the IRF using the same analyses as specified for DFS on the basis of investigator assessment.

5.3.3.6 Ukraine Crisis

Due to the potential inability to conduct site inspections or source data verification in Russia and/or Ukraine, a sensitivity analysis may be performed on DFS by censoring data from sites in Russia and/or Ukraine at the onset of the crisis, which was 24 February 2022.

5.3.4 Supplementary Analyses for Primary Endpoint

5.3.4.1 Subgroup Analyses for Primary Endpoint(s)

The generalizability of DFS results when comparing alectinib to chemotherapy will be investigated by estimating the treatment effect in subgroups based on key baseline demographics (e.g., age, sex, and race/ethnicity) and disease characteristic (e.g., disease stage, smoking history, and ECOG Performance Status). Summaries of DFS by these subgroups will be provided in forest plots including unstratified HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of the median provided separately for each level of the subgroups.

5.4 SECONDARY ENDPOINT ANALYSES

5.4.1 Overall Survival

OS 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, data for these patients will be censored at the date of randomization plus 1 day.

The estimand for OS is defined as indicated in Table 2. OS will also be analyzed in the ITT population. As a consequence, an alternative estimand for OS is defined similarly as above but with a different population (see Table 2).

The methodology (as described in Section 5.3.2) 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.

5.5 EXPLORATORY ENDPOINTS ANALYSIS

5.5.1 DFS Rates at Selected Time Points

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

5.5.2 Location of First Documented recurrence or New Primary NSCLC

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.

5.5.3 Time to Central Nervous System (CNS) Recurrence or Death

Time to CNS recurrence or death is defined as the time from randomization to the first documented recurrence of disease in the CNS or death from any cause, whichever occurs first. Patients who are not reported as experiencing disease recurrence in the CNS or death will be censored at the date of the last disease assessment. Of note, data for patients who experienced non-CNS recurrence prior to an eventual CNS recurrence will be censored at the date of non-CNS recurrence in this analysis. If no post baseline data are available, data for these patients will be censored at the date of randomization plus 1 day.

Time to CNS recurrence or death will be analyzed in the Stage II–IIIa subpopulation and the ITT population, and the same methodology (as described in Section 5.3.2) used for DFS will be applied.

5.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the safety-evaluable set (see Section 4), with participants grouped according to whether any alectinib was received.

5.6.1 Extent of Exposure

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

5.6.2 Adverse Events

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 collected.

After initiation of study drug, all adverse events should be collected 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).

After the end of the adverse event reporting period, serious adverse events that are believed to be related to prior exposure to study drug should be collected.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms (MedDRA), and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, selected adverse events, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries.

Subgroup analyses will be performed to evaluate the safety profile within subgroups of patients, including by sex, age ($<$ 65 years vs. $\geq$ 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 (Ib vs. II vs. IIIa).

AEs associated with coronavirus disease 2019 (COVID--19) will be summarized and listed.

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.

5.6.3 Laboratory Data

Summary tables of shifts in NCI CTCAE v5.0 grades from baseline to the worst post baseline value will be presented by treatment arm for relevant laboratory data.

Potential Hy's law patients will be listed based on the laboratory data only: elevated ALT or AST ($>$ 3 $\times$ upper limit of normal [ULN]) in combination with elevated total bilirubin ($>$ 2 $\times$ ULN).

5.6.4 Vital Signs

Changes in vital signs will be summarized by treatment arm and visit. A summary of abnormalities will be presented as well.

5.6.5 ECGs

Changes from baseline in the following ECGs parameters will be summarized by treatment arm and visit: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings.

5.7 OTHER ANALYSES

5.7.1 Summaries of Conduct of Study

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.

COVID-19 and Ukraine crisis related major protocol deviations will be summarized by treatment arm, as well.

5.7.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Demographics (e.g., age, sex, and race/ethnicity) and baseline prognostic characteristics (e.g., disease stage, smoking history, and ECOG Performance Status) will be summarized descriptively by treatment arm for the Stage II–IIIa subpopulation and the ITT population.

A summary of concordance of stratification factors determined by eCRF versus IxRS will also be reported.

5.7.3 Pharmacokinetic Analyses

PK analyses will be conducted in the PK-evaluable populations.

A separate PK cut-off date may be established prior to the interim analysis clinical cut-off date to ensure expedient sample analyses. An earlier PK cut-off date will only be applied when there is sufficient PK sample data available to adequately characterize PK.

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. PK parameters including, but not limited, to area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), and time to maximum plasma concentration (t_{max}) will be calculated on the basis of the available data as appropriate and where data allow.

Additional PK parameters may be calculated as deemed appropriate.

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

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

Additional PK/pharmacodynamic analyses may be reported outside the Clinical Study Report (CSR).

As appropriate, nonlinear mixed-effects modeling (with software NONMEM) (Beal et al. 1999) may be used to analyze the sparse and/or serial/intensive plasma concentration–-time data for alectinib, estimate population and individual PK parameters, and explore the influence of various covariates (such as age, gender, and body weight) on these parameters. Exploratory analyses may be conducted to investigate the relationship between alectinib PK exposure and efficacy/safety parameters. Details of the mixed-effects modeling and exploratory analyses, if performed, will be reported in a document separate from the CSR.

The PK data from this study may be pooled with data from other studies for PopPK analysis.

5.7.4 Exploratory Biomarker Analyses

ALK 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 CSR.

5.7.5 Exploratory Patient-Reported Outcome Analyses

The SF-36v2 and EuroQol 5-Dimension, 5-Level Questionnaire (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 and the mean changes from baseline will be reported for the Physical component summary (PCS) score, Mental component summary (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, patient-reported outcome (PRO) analyses will also be performed in the subpopulation of patients with Stage II–IIIa NSCLC.

These results may not be reported in the CSR.

5.8 INTERIM ANALYSES

5.8.1 Planned Interim Analyses

There is one 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 3, 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 two-sided 5% significance level is HR $\leq$0.52 ($p \leq 0.0118$). In the ITT population, the stopping boundary for early rejection of the null hypothesis for an overall two-sided 5% significance level is HR ≤ 0.55 ($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.

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

5.8.2 Optional Interim Analyses

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 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.

6. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document.

7. REFERENCES

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