STATISTICAL ANALYSIS PLAN

STUDY TITLE: **A PHASE II, OPEN-LABEL, SINGLE-ARM DECENTRALIZED HOME-BASED APPROACH STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ALECTINIB IN LOCALLY ADVANCED OR METASTATIC ALK-POSITIVE SOLID TUMORS**

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STATISTICAL ANALYSIS PLAN APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document Version 2, 26 October 2020.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
1	see electronic date stamp on title page	Version 4, 24 November 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
ALK	anaplastic lymphoma kinase
BICR	blinded independent center review
BID	twice a day
CI	confidence interval
CNS	central nervous system
CR	complete response
COVID-19	corona virus disease 2019
CUP	cancer of unknown primary (site)
DNA	deoxyribonucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for the Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5-Dimension, 5-Level
FMI	Foundation Medicine Inc.
F1HEME	FoundationOneHeme test on blood
F1CDx	FoundationOne CDx test on tissue
F1LCDx	FoundationOne Liquid CDx test on blood
ICH	International Council on Harmonization
IMC	Internal Monitoring Committee
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PR	partial response
PFS	progression-free survival
PRO	patient-reported outcomes
PK	pharmacokinetic
QoL	quality of life
GHS/QoL	Global health status
QLQ-C30	Quality of Life Questionnaire
QTcF	QT interval corrected through use of Fridericia's formula
RANO	Response Assessment in Neuro-Oncology

RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	serious adverse events
SAP	Statistical Analysis Plan
SMQs	standardized MedDRA queries

1. INTRODUCTION

This study will evaluate the efficacy and safety of alectinib in patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic solid tumors other than lung cancer. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

1.1 OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints

Efficacy Objectives and Endpoints patients with anaplastic lymphoma kinase (ALK) fusion Solid Tumors (excluding Enrolled Patients with CUP and CNS Primary Tumors)	
Primary Objective	**Corresponding Endpoint**
• To demonstrate a clinically relevant response to alectinib treatment	• Confirmed objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or a partial response (PR) confirmed ≥ 28 days after initial response, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)
Secondary Objectives	**Corresponding Endpoints**
• The same as the primary endpoint	• According to the blinded independent center review (BICR)
• To evaluate the duration of response (DOR)	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as determined by both the investigator and by BICR according to RECIST v1.1
• To evaluate progression-free survival (PFS)	• PFS, defined as the time from first dose of alectinib treatment to disease progression or death from any cause, as determined by both the investigator and BICR according to RECIST v1.1
• To evaluate overall survival (OS)	• OS, defined as the time from first dose of study drug to death from any cause
Efficacy Objectives and Endpoints patients with other Disease Characteristics	
• To evaluate central nervous system (CNS) response in patients with measurable CNS metastases at baseline	• CNS ORR, defined as objective tumor response rate (a CR or a PR) of CNS lesions by BICR according to RECIST v1.1

Table 1 Objectives and Corresponding Endpoints (cont.)

• To evaluate the CNS duration of response	• CNS DOR, defined as the time from the first observation of CNS response until the first observation of CNS progression or death from any cause by BICR according to RECIST v1.1
• To evaluate the efficacy of alectinib in ALK fusion−positive patients with primary CNS tumors according to Response Assessment in Neuro-Oncology (RANO) criteria	• ORR, DOR, and PFS as determined by both the investigator and BICR • OS
• To evaluate the efficacy of alectinib in patients with solid tumors without ALK fusions, harboring defined ALK mutations (R1275Q, F1245C, F1174X, with X being any other amino acid)	• ORR, DOR, and PFS as determined by both the investigator and BICR according to RECIST v1.1 • CNS ORR and DOR in patients with CNS metastases at baseline by BICR according to RECIST v1.1 • OS
• To evaluate the efficacy of alectinib in patients with cancer of unknown primary (site) (CUP)	• ORR, DOR, and PFS as determined by both the investigator and BICR according to RECIST v1.1 • CNS ORR and DOR in patients with CNS metastases at baseline, as determined by BICR according to RECIST v1.1 • OS
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of alectinib in patients with ALK-positive CUP and non-CUP solid tumors	• ORR, DOR, and PFS as determined by both the investigator and BICR according to RECIST v1.1 • CNS ORR and DOR in patients with CNS metastases at baseline, as determined by BICR according to RECIST v1.1 • OS
• To evaluate the function, disease/treatment-related symptoms, and health-related quality of life	• Change from baseline in QLQ-C30 scores during study treatment

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of alectinib in all dosed patients	• Incidence and severity of adverse events, including serious adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic (PK) Objective	**Corresponding Endpoints**
• To characterize the alectinib PK profile	• Plasma concentrations of alectinib and its metabolite(s) as applicable at specified time points
Exploratory Biomarker Objectives	**Corresponding Endpoints**
• To identify and/or evaluate biomarkers that are associated with primary or acquired resistance to alectinib in the biomarker-evaluable population • To evaluate the impact of levels of circulating free DNA (cfDNA)	• Relationship between biomarkers found in circulating deoxyribonucleic acid (DNA) in blood and tumor tissue, with efficacy endpoints • Relationship between levels of cfDNA at baseline and changes in levels of cfDNA at different timepoints during treatment with efficacy endpoints
Health Status Utility Objective	**Corresponding Endpoint**
• To evaluate health status utility scores	• Change from baseline in EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-based and Visual Analog Scale (VAS) scores during study treatment

1.1.1 Expression of Objectives and Endpoints using the Estimand Framework

The primary study objective and corresponding endpoint, as well as the main secondary efficacy objective and the corresponding secondary efficacy endpoints, 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 demonstrate a clinically relevant response to alectinib treatment	• Population: Patients with ALK fusion solid tumors (excluding enrolled patients with CUP and CNS primary tumors) with measurable disease at baseline who have a baseline tumor assessment per the investigator according to RECIST v1.1 and receive at least one dose of alectinib (response-evaluable population) • Variable: Confirmed ORR, defined as the proportion of patients with a CR or a PR ≥ 28 days after initial response in patients with solid tumors, as determined by the investigator according to RECIST v1.1 • Treatment: Experimental: alectinib at the dose of 600 mg BID until disease progression, death, or withdrawal for any other reasons • Intercurrent events: • Start of additional or alternative therapy • Early discontinuation from study treatment for any reason or withdrawal from study • Handling of intercurrent events: A treatment policy with regards to the intercurrent events listed above will be applied for the primary analysis. • Summary measure: Confirmed ORR
Main Secondary Efficacy Objective	**Estimand Definition**
• To demonstrate a clinically relevant response to alectinib treatment	• According to the blinded independent center review (BICR)

ALK= anaplastic lymphoma kinase; BID=twice a day; CR=complete response; CNS=central nervous system; CUP=cancer of unknown primary (site); ORR=objective response rate; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumors.

1.2 STUDY DESIGN

This Phase II, open-label, single-arm study is designed to investigate the efficacy and safety of alectinib in patients with locally advanced or metastatic solid tumors (excluding lung cancer) that are determined to be ALK-positive per the Foundation Medicine Inc. (FMI) next-generation sequencing (NGS) test on tissue or blood (FoundationOne CDx [F1CDx] or FoundationOne Liquid CDx [F1LCDx] or FoundationOneHeme [F1HEME]).

ALK positivity determined per local accredited laboratory NGS-validated testing on tissue or blood may be accepted.

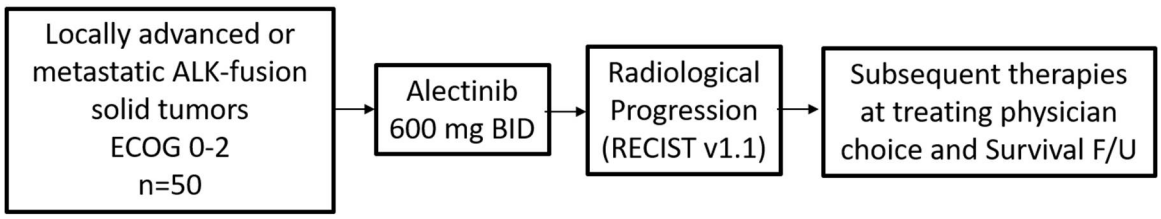
Patients can be identified by means of one of the two following enrollment pathways:

1. The Precision Enrollment approach offered by FMI. Briefly, when non−lung cancer samples are determined by FMI central testing to be positive for ALK, an FMI medical oncologist will contact the ordering physician (local oncologist) and provide information about the trial. If this is of interest to both the physician and the patient, enrollment procedures will begin.
2. Patients with ALK-positive NGS test results obtained outside FMI'S Precision Enrollment approach may be identified and the local ALK NGS test report will be made available (see Section 4.6.6) and will be assessed by the investigator for eligibility. The study team and Medical Monitor are to be consulted. If ALK positivity is not accepted per the criteria, prospective FMI testing is required and the patient may be enrolled if assessed to be ALK-positive by FMI.

Patients with both ALK-fusion and selected ALK mutations will be enrolled in the study. Enrollment will end once approximately 50 patients with ALK fusion solid tumors evaluable by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) have been recruited, regardless of the number of enrolled patients with primary central nervous system (CNS) tumors (evaluable according to Response Assessment in Neuro-Oncology [RANO] criteria), with cancer of unknown primary (site) (CUP) or ALK mutations.

The study schema is shown in Figure 1.

Figure 1 Study Schema



ALK = anaplastic lymphoma kinase; BID = twice a day; ECOG = Eastern Cooperative Oncology Group; F/U = follow-up; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

An interim, non-binding analysis will be performed once the first 15 RECIST v1.1 investigator-assessed response-evaluable patients with ALK fusions (excluding patients with primary CNS tumors and patients with CUP) have a response evaluation at 8 weeks available (unless they progressed or discontinued earlier from the study). If the analysis result shows that the response rate does not achieve at least 25% (4 responders), the study may be terminated due to futility.

The primary analysis will take place once all patients have been followed for a minimum of 24 weeks (i.e., three tumor assessments) to allow confirmation of any observed complete response (CR) or partial response (PR), unless they progressed or withdrew from sooner from the study.

The end of this study is defined as the date when the last patient, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately in 2026.

In addition, the Sponsor may decide to terminate the study at any time.

The length of the study is expected to be approximately 5 years.

1.2.1 Treatment Assignment

This is a Phase II, open-label, single-arm study. Patients with both ALK fusion and selected ALK mutations will be enrolled in the study.

1.2.2 Blinded Independent Center Review

Scans will be sent for blinded independent center review (BICR) for assessment of responses according to RECIST v1.1 and, for patients with primary CNS tumors, according to RANO criteria.

Assessments performed by BICR will not be shared with the investigator and will have no impact on the management of the patient. Further details are included in the BICR Charter.

1.2.3 Data Monitoring

An internal monitoring committee (IMC) will monitor patient safety throughout the study, focusing on death cases and interim futility analysis. The IMC will include Sponsor's representatives from Clinical Science, Clinical Safety, and Biostatistics. The IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, the protocol should be amended, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the Committee's composition, frequency and timing of meetings, and members' roles and responsibilities are provided in the IMC Charter.

2. STATISTICAL HYPOTHESES

It will be tested that the confirmed ORR is greater than 30% which is assumed to be the minimal clinically relevant response rate.

3. SAMPLE SIZE DETERMINATION

Patients with both ALK fusion and selected ALK mutations will be enrolled in the study. Enrollment will end once around 50 patients with ALK fusions solid tumors evaluable according to RECIST v1.1 have been recruited (regardless of the number of enrolled patients with primary CNS tumors, CUP, or harboring selected ALK mutations).

This sample size has been chosen so that for the primary analysis the lower limit of the two-sided 95% confidence interval (CI) (using an exact Clopper-Pearson CI) around the point estimate of the confirmed ORR according to RECIST v1.1 will represent a clinically relevant response. With a sample size of 50 patients, an observed response rate of 46% (23 of 50 responses) would have a lower limit of the two-sided 95% CI of 31.8%, which is considered to be clinically relevant in this tissue-agnostic, biomarker-defined population with no available treatment options. With 50 patients, there is 70% power to detect a 16% increase in ORR from clinically relevant 30% to 46% at the 5% two-sided significance level.

Different ORR scenarios with their associated 95% CI are presented in Table 3.

Table 3 ORR Scenarios with Associated 95% CI

Expected ORR	Expected Number of Patients with a Response	95% CI for ORR [a]
46%	23	(31.81%, 60.68%)
48%	24	(33.66%, 62.58%)
50%	25	(35.53%, 64.47%)

CI=confidence interval; ORR=objective response rate.

[a] Using the Clopper-Pearson method and given a sample size of 50 patients.

With a sample size of 50 patients, an ORR of 46% will have an associated 95% CI of 31.81% to 60.68%.

4. ANALYSIS SETS

The following populations are defined:

Table 4 Analysis Populations

Population	Definition
Response-evaluable population	All patients with ALK fusion–positive solid tumors (excluding patients with CUP and primary CNS tumors) with measurable disease at baseline (who have a baseline tumor assessment) per the investigator according to RECIST v1.1 and have received at least one dose of study treatment.
Response-evaluable population with measurable CNS disease at baseline	All patients with measurable CNS disease at baseline evaluable per the investigator according to RECIST v1.1 who have received at least one dose of study treatment.
Primary CNS tumor response-evaluable population	All patients with ALK fusion CNS primary tumors with measurable disease at baseline evaluable according to RANO criteria who receive at least one dose of study treatment.
CUP response-evaluable population	All patients with CUP with measurable disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study treatment.
ALK-mutations response-evaluable population	All patients with ALK mutations with measurable disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study treatment.
Exploratory ALK-positive CUP and non-CUP response-evaluable population	All patients with ALK-positive CUP and non-CUP solid tumors who receive at least one dose of study treatment.
Responders	All patients with a response according to the specified endpoints for the analysis of the duration of response
PK-evaluable population	All patients who received any dose of study medication and who have at least one post-baseline PK sample available.
Safety-evaluable	All participants who received at least one dose of study treatment.

ALK=anaplastic lymphoma kinase; CUP=cancer of unknown primary (site); CNS=central nervous system; PK=pharmacokinetic; RANO=Response Assessment in Neuro-Oncology; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1.

All populations that are defined accordingly by the investigator assessment are defined in the same way by BICR, depending on who is assessing the endpoint.

Replacement of patients with ALK fusion solid tumors assessed according to RECIST v1.1 who discontinue their participation in the study will be allowed if enrolled patients have not received any dose of alectinib.

All patients must have measurable disease at baseline as assessed by investigator according to the inclusion criteria. Therefore, progression free survival (PFS) and overall survival (OS) will be assessed in the response-evaluable populations of the patients with

the respective disease characteristics. For PFS analyses by BICR the population defined by the investigator is taken into account.

5. STATISTICAL ANALYSES

5.1 GENERAL CONSIDERATION

The analyses outlined in this statistical analysis plan (SAP) supersede those specified in the protocol for the purpose of a regulatory filing.

ORR, duration of response (DOR), and PFS are determined by the investigator and by BICR according to RECIST v1.1 and RANO respectively. Secondary endpoint analyses for the endpoint by BICR are as well sensitivity analyses for that endpoint by investigator.

CNS ORR and DOR are determined in patients with CNS metastases at baseline only by BICR according to RECIST v1.1.

The analyses will be performed in the populations specified in Section 4.

5.2 PARTICIPANT DISPOSITION

The patient status (on treatment, off treatment, in long-term follow-up, lost-to-follow-up and dead) and the time of efficacy follow-up will be summarized.

5.3 PRIMARY ENDPOINT ANALYSIS

5.3.1 Definition of Primary Endpoint

The primary efficacy endpoint is confirmed ORR as determined by the investigator in patients with ALK fusion solid tumors (excluding enrolled patients with CUP and CNS primary tumors). An objective response is defined as a CR or a PR according to RECIST v1.1. Confirmation of objective response is required (confirmed ≥ 28 days apart in two separate tumor assessments). Patients not meeting this criterion (including patients without a post-baseline tumor assessment) will be considered as non-responders. ORR is defined as the proportion of patients with measurable disease at baseline who have an objective response in the response-evaluable population.

5.3.2 Main Analytical Approach for Primary Endpoint

An estimate of the confirmed ORR and its two-sided 95% CI using the Clopper-Pearson method will be calculated. The confirmed ORR will be tested against the minimal clinically relevant ORR of 30% in this tissue-agnostic, biomarker-defined population with no available treatment options at the 5% two-sided significance level, i.e., the lower limit of the Clopper-Pearson CI must be bigger than 30%.

5.3.3 Sensitivity Analyses for Primary Endpoint

see Section 5.1.

5.3.4 Supplementary Analyses for Primary Endpoint

5.3.4.1 Subgroup Analyses for Primary Endpoint

The generalizability of the confirmed ORR results will be investigated by estimating the effect in subgroups including by sex, age, and race.

5.4 SECONDARY ENDPOINTS ANALYSES

5.4.1 Key Secondary Endpoint

The key secondary efficacy endpoint is confirmed ORR as determined by the BICR in patients with ALK fusion solid tumors (excluding enrolled patients with CUP and CNS primary tumors). The same analyses as for the primary endpoint will be applied.

5.4.2 Supportive Secondary Endpoints

5.4.2.1 Duration of Response

DOR is defined as the time from the date of the first occurrence of a CR or a PR (whichever status is recorded first) to the date of the first documented disease progression or death due to any causes, whichever occurred first. The DOR will be assessed in patients who had a confirmed objective response during the study, as determined by the investigator or BICR per RECIST v1.1. Patients who have not progressed or died at the time of analysis will be censored at the last tumor assessment date. If no tumor assessments are performed after the date of the first occurrence of a CR or a PR, DOR will be censored at the date of the first occurrence of a CR or a PR. The Kaplan-Meier methodology will be used to estimate the median DOR and to construct survival curves. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DOR (Brookmeyer and Crowley 1982).

5.4.2.2 Progression-Free Survival

Progression free survival is defined as the time from the first date of treatment to the date of first documented disease progression or death, whichever occurs first. Disease progression will be assessed by the investigator or the BICR using RECIST v1.1. Patients who have not experienced disease progression or died at the time of analysis will be censored at the last tumor assessment date. Patients with no post-baseline tumor assessment will be censored at the first date of treatment. The analysis methods are the same as for the DOR defined above.

5.4.2.3 Overall Survival

Overall survival is defined as the time from the first date of treatment to the date of death due to any cause. Patients who are not reported as dead at the time of the analysis will be censored at the date when they were last known to be alive. If no post-baseline information is available, then OS will be censored at the date of the first treatment. The analysis methods are the same as for the DOR defined above.

5.4.2.4 CNS Objective Response Rate

For patients with ALK-fusion positive tumors (excluding patients with CUP and patients with CNS primary tumors), who present with measurable CNS metastases at baseline

an analysis of CNS ORR defined as the percentage of patients who achieve a best overall response of a CR or a PR of CNS lesion (defined according to RECIST v1.1) will also be performed in the response-evaluable population with measurable CNS disease at baseline. CNS CR and PR will be assessed by BICR. The analysis methods are the same as for the primary endpoint. Confirmation of objective response is not required.

5.4.2.5 CNS Duration of Response

For patients who had a CNS objective response during the study, an analysis of CNS DOR, defined as the time from the date of the first occurrence of CNS CR or PR (whichever status is recorded first) to the date of the first documented disease CNS progression or death due to any causes, whichever occurred first, will be conducted. CNS disease progression will be assessed by BICR using RECIST v1.1. The analysis methods are the same as for the DOR defined above. Confirmation of objective response is not required.

5.4.2.6 Efficacy in Patients with Primary CNS Tumors

For patients with primary CNS tumors with measurable disease at baseline who have a baseline tumor assessment per the investigator according to RANO criteria and receive at least one dose of alectinib:

- ORR, DOR, and PFS in all ALK fusion−positive patients who have measurable disease at baseline as determined by both the investigator and BICR
- OS

The analysis methods are the same as for the respective endpoints defined above.

5.4.2.7 Efficacy in Patients with Solid Tumors without ALK Fusions, Harboring Defined ALK Mutations (R1275Q, F1245C, F1174X, with X being any other amino acid)

For patients with solid tumors without ALK fusions, harboring defined ALK mutations (R1275Q, F1245C, F1174X, with X being any other amino acid) and receive at least one dose of alectinib:

- ORR, DOR, and PFS as determined by the investigator and by BICR according to RECIST v1.1
- CNS ORR and DOR in patients with CNS metastases at baseline by BICR according to RECIST v1.1
- OS

Confirmation of objective response is not required.

The analysis methods are the same as for the respective endpoints defined above.

5.4.2.8 Efficacy in Patients with CUP

For patients with CUP who receive at least one dose of alectinib:

- ORR, DOR, and PFS as determined by both the investigator and BICR according to RECIST v1.1
- CNS ORR and DOR in patients with CNS metastases at baseline, as determined by BICR according to RECIST v1.1
- OS

The analysis method is the same as for the respective endpoints defined above.

For some populations, depending on the number of patients, a formal analysis will not be produced; instead, listings or spider plots could be used.

5.5 EXPLORATORY ENDPOINTS ANALYSES

5.5.1.1 Efficacy in Patients with ALK-Positive CUP and Non-CUP Solid Tumors

For patients with ALK-positive CUP and non-CUP solid tumors who receive at least one dose of alectinib:

- ORR, DOR, and PFS as determined by both the investigator and BICR according to RECIST v1.1
- CNS ORR and DOR in patients with CNS metastases at baseline, as determined by BICR according to RECIST v1.1
- OS

The analysis methods are the same as for the respective endpoints defined above.

5.5.1.2 Patient Reported Outcomes: EORTC Data

The quality of life questionnaire core 30 (QLQ-C30) questionnaires will be used to assess the impact of alectinib on patients' quality of life and daily function. All patients who receive at least one dose of alectinib will be analyzed. Completion rates will be summarized by number and proportion of patients among those expected to complete each questionnaire at each timepoint. Reasons for non-completion will be summarized at each timepoint if available.

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (Version 3) data will be scored according to the EORTC scoring manual (Fayers et al. 2001). In the event of incomplete data, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed consistent with the scoring manual and validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing.

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean changes from baseline will be calculated for the function, disease/treatment-related symptom-, and Global Health Status (GHS)/Quality

of life (QoL) scales of the EORTC QLQ-C30 at each assessment timepoint. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported on patients with a baseline and at least one post-baseline assessment. Previously published minimally important differences will be used to identify meaningful change from baseline within the treatment group on the functional and GHS/QoL scales (Osoba et al. 1998; Cocks et al. 2011).

5.6 SAFETY ANALYSES

Safety analyses will be performed on the safety evaluable population, defined as all enrolled patients who received any amount of study drug

5.6.1 Extent of Exposure

Study drug exposure, including treatment duration, number of doses, dose intensity and total cumulative dose will be summarized with descriptive statistics.

5.6.2 Adverse Events

Verbatim description of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

After informed consent has been obtained but prior to initiation of study drug, only serious AEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) are collected.

After initiation of study drug, all adverse events will be collected until 28 days after the final dose of study drug.

After the end of the adverse event reporting period, all deaths, regardless of cause, and serious adverse events that are believed to be related to prior exposure to study drug are collected.

All AEs that occur on or after the first study drug dose (treatment-emergent AEs) will be reported. They will be summarized using descriptive statistics (i.e., frequencies and percentages) by Medical Dictionary for Regulatory Activities (MedDRA) term, appropriate MedDRA levels, and NCI CTCAE v5.0 grade, regardless of relationship to study drug as assessed by the investigator. For each patient, if multiple incidences of the same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately:

- AEs
- AEs leading to withdrawal of study drug
- AEs leading to dose reduction or interruption

- Grade 3/4 AEs, Grade 5 AEs, serious adverse events
- AEs of special interest

All deaths and causes of death will be summarized.

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

5.6.3 Laboratory Data

Clinically relevant shifts from baseline in NCI CTCAE v5.0 grade (defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post baseline) will be also provided. Of note, abnormal laboratory data that are clinically significant will be reported as AEs and summarized in the AE tables.

A Hy's Law analysis will be provided: the finding of an elevated ALT or AST (>3 · baseline value) in combination with either an elevated total bilirubin (>2 · upper limit of normal) 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).

5.6.4 Vital Signs

Change from baseline in selected vital signs will be summarized (diastolic/systolic blood pressure, pulse rate, temperature, respiratory rate).

5.6.5 ECGs

Changes from baseline in the following ECGs parameters will be summarized: 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

Study enrollment, reasons for discontinuation from study drug, and reasons for premature study discontinuation will be listed and summarized for all patients, including any related to Corona virus disease 2019 (COVID-19).

Major protocol deviations, including major deviations of inclusion/exclusion criteria, as well as any related to the COVID-19, will be reported and summarized.

5.7.2 Summaries of Demographics and Baseline Characteristics

For all patients, demographic and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, and medical history) will be summarized using means, standard deviations, medians, ranges, and interquartile ranges for

continuous variables, and frequencies and percentages for categorical variables, as appropriate.

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of alectinib.

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

5.7.3 Pharmacokinetic Analyses

The pharmacokinetic (PK)-evaluable population will consist of all patients who have at least one post-baseline quantifiable PK sample available.

Nonlinear mixed-effects modeling (with software NONMEM®) will be used to analyze the sparse plasma concentration−time data for alectinib and its metabolites, as applicable. 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.

5.7.4 Biomarker Analyses

ALK tumor tissue and plasma assays (e.g., next-generation targeted sequencing, polymerase chain reaction) will be used as exploratory assays for all enrolled ALK-positive patients. Results from these analyses along with clinical data collected in this study will be used to explore genomic variants (e.g., ALK rearrangement variants, fusion partners, mutations in ALK and other cancer related genes) that may be predictive of response to study drug or may be associated with progression to a more severe disease state. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored. Somatic mutations in ALK and other cancer related genes may be associated with acquired resistance to alectinib or can increase the knowledge and understanding of the disease biology. Tumor mutation allele frequencies and circulating tumor nucleic acid amounts may also be correlated with clinical efficacy. Efficacy analysis of different ALK tumor and ALK plasma subpopulations may be performed.

Information regarding the detection of ALK rearrangements from targeted DNA sequencing from tissue and plasma samples, and baseline demographic and disease-related characteristics for all enrolled patients in this study may be used for companion diagnostic development. These data may be used to support potential registration of a

companion diagnostic assay for alectinib in the tumor-agnostic setting and shared with health authorities.

Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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.

5.7.5 Health Status Utility Analyses

The EuroQol 5-Dimension Questionnaire 5-level version (EQ-5D-5L) questionnaires will be scored per authors' guidelines. A single summary index from the EQ-5D-5L health states will be used in this study for economic modeling.

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

5.8 INTERIM ANALYSES

A non-binding interim analysis will be performed after 15 RECISTv1.1 investigator-assessed response-evaluable patients with ALK fusions tumors (excluding patients with primary CNS tumors and patients with solid tumors of CUP) have at least a response-evaluation available at 8 weeks (unless they progressed or discontinued earlier from the study). During the period waiting for a response evaluation of these first 15 patients, the study will continue to enroll. If the analysis result shows that the response rate does not achieve at least 25% (4 responders), the study may be terminated due to futility.

Further details regarding the rules and guidelines of data review will be provided in the IMC Charter.

6. SUPPORTING DOCUMENTATION

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

7. REFERENCES

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