PROTOCOL

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**
PROTOCOL NUMBER:	BO41929
VERSION NUMBER:	4
EUDRACT NUMBER:	2021-002352-36
IND NUMBER:	111,723
NCT NUMBER:	04644315
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
24-Nov-2021 23:50:48	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	See electronic date stamp on title page
3	17 August 2021
2	9 June 2021
1	2 October 2020

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol BO41929 has been amended primarily to update information related to the risk of anemia associated with alectinib and to introduce management guidance related to hemolytic anemia, in line with the Dear Investigator Letter on hemolytic anemia dated 28 October 2021 Additional changes have been made to clarify language in the protocol and to align process between the two possible operational approaches that can be employed to conduct the study (i.e., Virtual site and/or Physical site approach). The changes to the protocol, along with a rationale for each change, are summarized below:

Safety-related changes

- Benefit-risk assessment of COVID-19 vaccine and efficacy of alectinib has been moved to Section 1.4.2.1.
- Additional information has been included regarding hemolytic anemia (Section 5.1.1.3) and dose modification guidance for the management of hemolytic anemia adverse reaction with alectinib (Section 5.1.2.3, Table 1) in line with the Dear Investigator Letter on hemolytic anemia dated 28 October 2021.

Clarifications and process-related changes

- Information related to Alectinib approval status and associated clinical practice have been removed in section 1.4.1 since it was redundant with information presented earlier in the section.
- Language has been simplified regarding patient ALK+tumors identification in Section 3.3.1.
- Language on Investigator Oversight of Study Personnel has been adjusted to clearly specify in which country virtual and/or physical site operational approach can be used and clarify reason of offering the two approaches. (Section 3.3.1 and Appendix 9).
- The data collection approach for virtual sites was adjusted to enable entry of eCRF data through EDC (RAVE) directly instead of Science 37 platform to be transferred in RAVE, and align with data entry approach for Physical site as well as to add clarification to indicate that, in addition to virtual site, the approach with physical study sites (e.g., hospital, clinic, or oncology institution) can be used in the United States (Sections 3.3.1, 4.6.6, 7.1, 7.2, 7.3.1, Appendix 9).
- Language has been adjusted for inclusion criteria regarding prior treatment to clarify that alectinib as second line is acceptable once Standard of Care (SoC) fails. There is no need to exhaust all SoC alternatives before initiating alectinib (Section 4.1.1).
- The responsibilities of the Principal Investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 4.5.3,4.6.6, 5.1.2.2).

- For clarity, language has been adjusted regarding when physical examinations are performed in patient homes (Sections 5.1 and 5.3.1.1).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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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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 to the Sponsor.

PROTOCOL SYNOPSIS

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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VERSION NUMBER:	4
EUDRACT NUMBER:	2021-002352-36
IND NUMBER:	111,723
NCT NUMBER:	04644315
TEST PRODUCT:	Alectinib (RO5424802)
PHASE:	Phase II
INDICATION:	Anaplastic lymphoma kinase–positive solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

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 below.

Primary Efficacy Objective

The primary efficacy objective is to demonstrate a clinically relevant response to experimental treatment on the basis of the following endpoint:

- Confirmed objective response rate (ORR) (defined as the proportion of patients with a complete response [CR] or a partial response [PR]) ≥28 days after initial response, in patients with solid tumors as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

The primary efficacy objective of the trial is to evaluate alectinib at the dose of 600 mg BID until disease progression, death, or withdrawal for any other reasons in patients with ALK fusion solid tumors (excluding enrolled patients with cancer of unknown primary (CUP) site and central nervous system [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).

The primary evaluation will be made regardless of whether patients withdraw from treatment, withdraw consent, or receive additional or alternative therapy.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of alectinib in patients with ALK-positive solid tumors in the response-evaluable population, defined according to the investigator or by blinded independent center review (BICR), depending on who is assessing the endpoint, on the basis of the following endpoints:

- Confirmed ORR, defined as the proportion of patients with a CR or PR ≥28 days after initial response by BICR according to RECIST v1.1

- Duration of response (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
- Progression-free survival (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
- CNS ORR, defined as objective tumor response rate (a CR or a PR) of CNS lesions in patients with measurable CNS metastases at baseline by BICR according to RECIST v1.1
- 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
- Overall survival (OS), defined as the time from first dose of study drug to death from any cause

For patients with primary CNS tumors with measurable disease at baseline who have a baseline tumor assessment per the investigator according to Response Assessment in Neuro-Oncology (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

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

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

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of alectinib in patients with ALK-positive CUP and non-CUP solid tumors who receive at least one dose of alectinib on the basis of the following endpoints:

- 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

Safety Objectives

The safety objective for this study is to evaluate the safety of alectinib in all dosed patients on the basis of the following endpoints:

- 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 Objective

The pharmacokinetic (PK) objective for this study is to characterize the alectinib PK profile on the basis of the following endpoint:

- Plasma concentrations of alectinib and its metabolite(s) as applicable at specified timepoints

Exploratory Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To identify and/or evaluate biomarkers that are associated with primary or acquired resistance to alectinib in the biomarker-evaluable population by analyzing the relationship between biomarkers found in circulating DNA in blood and tumor tissue, with efficacy endpoints
- To assess relationship between levels of circulating free DNA (cfDNA) at baseline, and changes in levels of cfDNA at different timepoints during treatment, with efficacy endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with alectinib on the basis of the following endpoint:

- Change from baseline in QLQ-C30 scores during study treatment
- Change from baseline in EQ-5D-5L index-based and Visual Analog Scale scores during study treatment

Study Design

Description of Study

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 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.

For eligible and enrolled patients, the tumor tissue sample must be submitted for retrospective analysis by FMI using the F1CDx assay.

The nature of the approach makes it impossible to predict at which clinical sites these patients will be identified. Therefore, a decentralized, home-based approach will be implemented using mHCPs that have professional qualifications as per local requirements. The mHCPs will attend to the patient at home, and the investigator will interact with the patient using telemedicine. This approach minimizes the need for on-site visits for patients, thus making clinical trials more accessible to patients regardless of location. 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 RECIST v1.1 have been recruited, regardless of the number of enrolled patients with primary CNS tumors (evaluable according to RANO criteria), with CUP or ALK mutations. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of up to two screenings per participant) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. The investigator will record reasons for screen failure in the screening log.

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.

The primary endpoint will be based on the response-evaluable population with ALK fusion solid tumors that are assessed according to RECIST v1.1.

The primary objective of the study is confirmed ORR as per investigator assessment in solid tumors assessed according to RECIST v1.1. Secondary endpoints include ORR by BICR, DOR, and PFS as per investigator assessment and BICR, CNS ORR, and DOR as per BICR, OS, and for patients with primary CNS tumor, the ORR, DOR and PFS as per investigator assessment and BICR according to RANO criteria. BICR procedures will be detailed in the BICR Charter.

The efficacy in patients with solid tumors harboring ALK mutations, with CUP, or with primary CNS tumors evaluable according to RANO criteria will be assessed as secondary endpoints.

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.

Patients will receive alectinib at the dose of 600 mg BID, taken with food, until disease progression, death, or withdrawal for any other reasons. Treatment beyond radiological progression is possible in the event of isolated lesion progression if, in the investigator’s opinion, there is evidence of ongoing clinical benefit.

All enrolled patients will undergo regular, scheduled visits until disease progression, death, withdrawal from the study, or study termination, whichever occurs first. For patients receiving alectinib beyond radiological progression, scheduled visits (including tumor assessments), will continue to be performed until treatment permanently discontinues.

For the first 12 weeks (3 months), regular safety assessments will be scheduled at baseline and every 2 weeks to allow for more frequent liver function and CPK assessments as per alectinib label. After Week 12, patients will undergo regular safety visits every 4 weeks.

Tumor assessments will be performed during screening and every 8 weeks (calculated from baseline) during study conduct and will consist of computed tomography (CT) and brain magnetic resonance imaging (MRI) scans (or brain CT scans if MRI is not feasible). Brain scans will be mandatory at baseline and during study conduct for patients with primary CNS tumors or brain metastases at baseline. For patients without brain metastases at baseline, brain scans will be performed as clinically indicated during study conduct. A safety follow-up will occur during the treatment discontinuation visit 28 days (4 weeks) after the final dose of alectinib.

Plasma samples will be obtained for biomarker analysis at baseline, Week 8, Week 36, and upon disease progression, and for PK analysis at baseline and every 4 weeks at scheduled visits during the treatment period.

Internal Monitoring Committee

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.

Number of Patients

Approximately 50 patients with ALK-fusion solid tumors will be enrolled in this study.

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.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Histologically confirmed locally advanced or metastatic solid tumor excluding lung cancer
- ALK-positive tumor per FMI NGS (NGS F1CDx, F1LCDx, or F1HEME) or per local accredited laboratory using validated NGS testing of tumor tissue or peripheral blood:
  - ALK fusion
  - The following ALK-activating mutations: R1275Q, F1245C, or F1174X
  - Local ALK test report (only for cases with local ALK testing)
- *Disease progression on prior treatment, or previously untreated disease with no available acceptable treatment*
- Other prior cancer therapies are allowed, including investigational drugs, if any treatment-related toxicities (excluding alopecia) have resolved to Grade 1 or better and laboratory values as defined in inclusion criteria, and meet the following washout criteria prior to first dose of alectinib:
  - At least 4 weeks must have elapsed since the last dose of the prior cytotoxic chemotherapy or antibody-directed therapy.
  - At least 7 days must have elapsed since prior tyrosine kinase inhibitor therapy.
  - At least 14 days must have elapsed since prior radiotherapy.
- Measurable disease at baseline, as assessed by investigator (by RECIST v1.1, or according to RANO criteria for patients with primary CNS tumors)

  For primary CNS tumors, only MRI scans will be accepted. If the local radiology facility cannot perform MRI, the patient will be excluded from the study.
- Life expectancy of at least 12 weeks in the opinion of the investigator
- Eastern Cooperative Oncology Group Performance Status of 0–2
- Adequate hematologic function:
  - Platelet count $\geq 100 \times 10^9$/L

- Absolute neutrophil count $\geq 1500/\mu L$
- Hemoglobin ≥ 9 g/dL

- Adequate hepatic function:
  - ALT (SGPT) and AST (SGOT) $\leq 2.5 \times$ upper limit of normal (ULN) ($\leq 5 \times$ ULN for patients with concurrent liver metastasis)
  - Bilirubin ≤ 2 mg/dL
- Adequate renal function:
  - Serum creatinine $< 2 \times$ ULN
  - Calculated creatinine clearance of ≥ 60 mL/min (Cockroft-Gault formula)
- Patients with primary CNS tumors are eligible
- Patients with CUP tumors are eligible
- Patient with brain or leptomeningeal metastasis are allowed in the study if asymptomatic and if they meet the following criteria:
  - No neurological signs and clinically stable for at least 2 weeks without corticosteroid treatment for brain metastasis prior to first dose of alectinib
  - If previously treated with whole-brain radiotherapy or gamma-knife radiosurgery, treatment must have been completed at least 2 weeks prior to first dose of alectinib
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
- Willingness to comply with home-based approach and visits by mHCPs
- Ability to swallow alectinib capsules intact (without chewing, crushing, or opening)
- Women of childbearing potential must have a negative serum pregnancy test result during screening and a negative urine pregnancy test at baseline before first dose of study drug is administered (unless a negative serum test was obtained within 10 days of first dose of study drug, in which case the urine pregnancy test is not required)
- 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. Women must refrain from donating eggs during this same period.

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and at least 90 days after the final dose of alectinib. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 least 90 days after the final dose of alectinib. 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 final dose of alectinib 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.

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 3 months after the final dose of alectinib
- Lung cancer
- Patients with one of the following ALK point mutations: I1171X, G1202R, V1180L
- Prior therapy with an ALK inhibitor
- Liver disease characterized by any of the following:
  - 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
  - Acute 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 polymerase chain reaction is negative for HCV RNA.
- Known HIV infection
- Patients with symptomatic bradycardia
- Patients with symptomatic or unstable brain metastasis

  Patients with primary CNS tumors are allowed.
- Malabsorption syndrome or any other condition that would interfere with enteral absorption
- Incomplete recovery from any surgery prior to treatment
- Any other malignancies within 5 years prior to enrollment, except the following:
  - Curative treated basal cell carcinoma of the skin, early gastrointestinal cancer by endoscopic resection, in situ carcinoma of the cervix, ductal carcinoma in situ, papillary thyroid cancer
  - Any cured cancer that is considered to have no impact on PFS or OS for the current ALK-positive solid tumor
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History of hypersensitivity to alectinib or any of its excipients

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

End of 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.

Length of Study

The end of the study is expected to occur approximately in the year 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.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product (IMP) for this study is alectinib.

Alectinib will be supplied by the Sponsor as a capsule dosage form containing the active ingredient 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6,11-dihydro-5Hbenzo[b]carbazole-3-carbonitrile hydrochloride.

Each capsule contains 150 mg of alectinib (as free base) along with lactose monohydrate, carboxymethylcellulose calcium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate as excipients.

Alectinib will be supplied by the Sponsor as capsules in bottles. Alectinib capsules should be stored in accordance with the storage instructions on the label.

Alectinib 600 mg (four 150-mg capsules) is to be administered orally BID with food. The capsules should not be opened and the contents of capsules should not be dissolved.

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

Patient will be treated until disease progression, unacceptable toxicity, withdrawal from treatment, or death. Treatment beyond radiological progression is possible in the event of isolated lesion progression if, in the Investigator's opinion, there is evidence of ongoing clinical benefit.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Cases of accidental overdose or medication error, overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in the protocol.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is ORR as assessed by investigator per RECIST v1.1, defined as the proportion of patients with an objective response. An objective response is defined as a CR or a PR per RECIST v1.1. Confirmation of objective response is required (confirmed $\geq$ 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.

An estimate of the ORR and its 95% CI using the Clopper-Pearson method will be calculated.

The primary efficacy analysis population consists of 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.

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 CR or PR, unless they progressed or withdrew from sooner from the study.

Determination of Sample Size

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 (evaluable according to RANO criteria), with CUP, or ALK mutations).

This sample size has been chosen so that for the primary analysis the lower limit of the two-sided 95% 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 the following table.

ORR Scenarios with Associated 95% CIs

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)

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%.

Interim Analysis

A non-binding interim analysis will be performed after 15 RECIST v1.1 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
BID	twice a day
BICR	blinded independent center review
CDx	companion diagnostic
cfDNA	circulating free DNA
COVID-19	coronavirus disease 2019
CR	complete response
CRC	clinical research coordinator
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
CUP	cancer of unknown primary (site)
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for the Research and Treatment of Cancer
DOR	duration of response
F1CDx	FoundationOne CDx
F1LCDx	FoundationOne Liquid CDx
FDA	(U.S.) Food and Drug Administration
FMI	Foundation Medicine, Inc.
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IMT	inflammatory myofibroplastic tumors
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
mHCP	mobile health care professional

Abbreviation	Definition
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
QTcF	QT interval corrected through use of Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SLS	sodium lauryl sulfate
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
VAS	Visual Analog Scale

1. BACKGROUND

1.1 BACKGROUND ON ALK-POSITIVE SOLID TUMORS

1.1.1 Background on ALK-Oncogene and ALK-Inhibitor Development

Anaplastic lymphoma kinase (ALK) is a cytoplasmatic membrane tyrosine kinase receptor protein encoded by the *ALK* gene. While wild-type ALK is expressed at very low levels in most normal human tissues, and its physiological expression is limited to neuronal cells (glial cells, neurons, endothelial cell, and pericytes) (Pulford et al. 1997), the *ALK* gene has been found to be rearranged, mutated, or amplified in a series of tumors (Ardini et al. 2010). In particular, chromosomal rearrangements result in ALK fusion proteins that have been shown to be constitutively active leading to increased signaling of pathways that drive uncontrolled cell growth, survival, and ultimately tumorigenesis.

Expression of these *ALK* fusion genes in mouse 3T3 fibroblasts cause cell transformation and enhanced proliferation. Inhibition of ALK activity in Ba/F3 cells transfected with the EML4-ALK fusion protein resulted in inhibition of cell growth (Ou et al. 2012). In addition, inhibition of ALK signaling demonstrated anti-tumor efficacy in two xenograft models in athymic mice, namely, the H3122 non–small cell lung cancer (NSCLC) and Karpas299 anaplastic large cell lymphoma models harboring the EML4-ALK and nucleophosmin ALK fusion proteins, respectively (Koivunen et al. 2008; Webb et al. 2009).

In NSCLC, ALK fusions are observed with a frequency of approximately 5%. In solid tumors other than NSCLC, many different ALK-fusion partners have been identified in a variety of malignancies, including, but not limited to, Spitz tumors, inflammatory myofibroplastic tumors (IMTs), thyroid cancer, digestive tract cancer, ovarian cancer, and renal cell carcinoma (Hallberg and Palmer 2013; Cao et al. 2019). However, outside of NSCLC, the frequency of ALK rearrangements in solid tumors is extremely low and estimated at about 0.2% (Ross et al. 2017). In addition to ALK fusion proteins, activating mutations in the ALK kinase domain have been found in different tumor types, including familial and sporadic cases of neuroblastoma (Lamant et al. 2000; Mossé et al. 2008; Wood et al. 2009).

Given the relatively high prevalence of ALK alterations in NSCLC, ALK inhibitor development in solid tumors has been largely limited to this indication, and to date several ALK inhibitors have been approved for advanced or metastatic ALK-positive NSCLC (Serritella and Bestvina 2020). 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 compared with platinum-based chemotherapy (median PFS: 10.9 vs. 7.0 months) in patients with previously untreated ALK-positive NSCLC (Solomon et al. 2014). Since then, next-generation ALK inhibitors, such as alectinib, ceritinib, and brigatinib, have been granted market authorization as first- or second-line treatment for advanced and metastatic ALK-positive NSCLC (Serritella and Bestvina 2020).

Studies of patients who had progression with crizotinib treatment revealed two main reasons for treatment failure: development of resistance because of secondary mutations predominantly in *ALK* or occasionally in other genes, such as *EGFR* or *KRAS* (Katayama et al. 2011; Doebele et al. 2012; Kim et al. 2013), and CNS relapse or progression. The CNS is the primary site of initial treatment failure in approximately 46% of patients with ALK-positive NSCLC treated with crizotinib due to its poor CNS penetration (Costa et al. 2011; Chun et al. 2012; Weickhardt et al. 2012). Significant morbidity is associated with brain metastases as a direct consequence of the pathophysiology of brain metastases and as a result of the side effects of treatment required to control CNS disease, such as corticosteroids, surgery, and radiation.

1.2 BACKGROUND ON ALECTINIB

1.2.1 Background on Tumor-Agnostic Drug Development

In recent years, there has been a shift in cancer treatment practices based on improved understanding of oncogenic signaling processes, as opposed to an "all-comers" approach (Gambardella et al. 2020). Molecular alterations in specific kinases often result in constitutive activation of cell proliferation and survival pathways, which can drive the initiation and progression of malignancy. This is particularly evident in NSCLC, for which numerous targeted therapies have been approved and adopted in clinical practice for specific molecularly defined populations, such as patients with NSCLC harboring EGFR-activating mutations, ALK fusions, and ROS1 rearrangements (National Comprehensive Cancer Network [NCCN] 2020).

More recently, this biomarker-driven treatment paradigm has gone beyond the confines of histologically defined tumors to be applied more broadly, regardless of tumors site of origin, in the so-called tumor-agnostic setting. This approach considers treatment based on known oncogenic drivers/genomic alterations to be more relevant than histology for the purpose of defining treatment strategies.

The tumor-agnostic setting has been recently validated by the U.S. Food and Drug Administration's (FDA's) approvals of NTRK inhibitors, such as larotrectinib and entrectinib in metastatic solid tumors expressing the TRK fusion oncogene, regardless of tumor's primary origin and histology. The efficacy of larotrectinib was investigated in 55 adult and pediatric patients across 17 unique TRK fusion–positive tumor types (Drilon et al. 2018). The response rate across multiple tumor types was 75% (95% CI: 61% to 85%) by independent review and 80% (95% CI: 67% to 90%) by investigator assessment (Drilon et al. 2018). Entrectinib was investigated in 54 patients across

10 different tumor types and 19 different histologies (Doebele et al. 2020). The response rate across tumor types was 57% (95% CI: 43% to 71%), and median duration of response (DOR) was 10 months (95% CI: 7.1 months to not estimable).

In addition, pembrolizumab, a PD-1 inhibitor, has received FDA approval in the tumor-agnostic setting in microsatellite instability–high or mismatch repair–deficient metastatic solid tumors. The efficacy of pembrolizumab was investigated across five single-arm clinical trials in 149 patients with 15 different solid tumor types that were microsatellite instability high or mismatch repair deficient positive (Marcus et al. 2019). The overall objective response rate (ORR) was 39.6% (95% CI: 32% to 48%), with DOR ranging from 1.6 months to 22.7 months.

These approvals demonstrate that therapies aimed at well-characterized oncogenic markers can deliver significant benefit and represent promising personalized treatment option regardless of tumor's site of origin and histological type.

1.2.2 Alectinib

Alectinib (also referred to as RO5424802 or CH5424802) is an oral small molecule, highly selective and potent next-generation ALK inhibitor with benzo[b]carbazole scaffold. In enzyme inhibition assays performed in vitro, this compound has been shown to selectively inhibit ALK and RET. Alectinib also shows in vitro and in vivo anti-tumor activity against tumor cell lines harboring ALK translocations, ALK alterations, and neuroblastoma lines harboring ALK-activating mutations. Alectinib is not a substrate of efflux transporters (such as P-glycoprotein [P-gp]) in the blood–brain barrier and is therefore able to distribute into and be retained within the CNS leading to high levels of CNS drug exposure.

Alectinib was approved in the United States, Canada, the European Union, and several other countries at a dose of 600 mg twice a day (BID) for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication was approved by the FDA on the basis of the ORR and DOR observed in two single-arm pivotal studies (NP28761 and NP28673), demonstrating a combined ORR of 51% in this crizotinib-failed population and median DOR of 14.9 months (Yang et al. 2017). Efficacy in the CNS was also assessed in these trials, with a combined CNS response rate of 64% observed in patients with measurable CNS disease at baseline (Gadgeel et al. 2016). The most common adverse events (occurring in $>$20% of patients) observed in the combined analysis were constipation (38%), fatigue (34%), peripheral edema (28%), myalgia (25%), nausea (23%), cough (21%) and headache (21%). Reported adverse events were mostly of Grade 1 or Grade 2 severity, and no Grade $\geq$3 adverse event occurred with a frequency of more than 5%, the most common being increased blood CPK (4%), dyspnea (4%), increased ALT (3%), and increased AST (3%). Adverse events leading to dose modification or interruptions occurred in 33% of patients, whereas adverse events leading to treatment withdrawal were reported in 6% of patients (Yang et al. 2017).

Alectinib has also been approved in the first-line setting on the basis of the data observed in BO28984 (ALEX), a randomized, open-label Phase III study of alectinib versus crizotinib in treatment-naive patients with ALK-positive NSCLC. The study showed a clinically meaningful and statistically significant improvement in investigator-assessed PFS of alectinib compared with crizotinib. At the updated data cutoff (1 December 2017), the PFS stratified hazard ratio was 0.43 (95% CI: 0.32 to 0.58) and median PFS with alectinib was 34.8 months (95% CI: 17.7 months to not evaluable) versus 10.9 months (95% CI: 9.1 to 12.9 months) with crizotinib (Camidge et al. 2019). Alectinib has also shown considerable activity in the CNS, with CNS response rates of 81% in patients with measurable CNS disease at baseline (Peters et al. 2017), and a median PFS in patients with CNS metastases at baseline of 27.7 versus 7.4 months for crizotinib (hazard ratio=0.35; 95% CI: 0.22 to 0.56) (Camidge et al. 2019). The safety profile of alectinib was consistent with that previously observed in trials conducted in patients who had previously received treatment with crizotinib. At the primary analysis, despite the longer treatment duration in the alectinib arm compared with the crizotinib arm (17.9 months and 10.7 months, respectively), alectinib appeared to be better tolerated than crizotinib, as shown by the lower incidence of patients with adverse events that were Grade $\geq$3 in severity (41% vs. 50%), leading to treatment interruptions (19% vs. 25%) and dose reductions (16% vs. 21%) (Peters et al. 2017).

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

1.3 BACKGROUND ON THE DECENTRALIZED STUDY MODEL

Clinical trials have made rapid advances in terms of digitalization and decentralization (Laegemiddelstyrelsen 2021). Digital tools have reduced the need for patients to attend appointments at a hospital or similar clinical setting. Such tools enable digital consent and electronic consultations, and can include electronic data collection systems, wearables, and other medical devices. These advances make it possible to conduct decentralized clinical trials that promote health service equality, allowing patients to participate in clinical trials, regardless of their mobility or proximity to hospitals. This ensures a wider representation of trial participants, which is likely to facilitate the recruitment and retention of patients in clinical trials.

The benefit of a decentralized study model is that patients can be treated at home. This eliminates the need for them to travel long distances for clinic visits and provides an opportunity for patients with rare diseases to participate in a clinical trial. In this model, the investigator can treat and monitor the patient remotely (via telemedicine) in the physical presence of a mobile health care professional (mHCP). Protocol assessments can be conducted at the patient’s home by the mHCP with the investigator present via telemedicine. In this model, the mHCP can collect and prepare all samples for shipment to the analytical lab, with imaging investigations being conducted at a facility identified and set up for the study close to the patient’s home. The investigator can make referrals

to a specialist if additional investigations are needed to ensure patient safety, as in the traditional clinical trial model. The logistics of conducting a decentralized study may differ according to local requirements and investigator preference.

In the context of the current study, ALK positivity may be determined using local or centralized testing results, making it is impossible to predict where identified patients will be located. Therefore, given the targeted population, the rarity of ALK positivity, and the approach used to identify patients, a decentralized approach has been chosen for this study.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This trial will assess the efficacy and safety of alectinib in ALK-positive solid tumors other than lung cancer. For the purposes of this study, ALK positivity is defined as ALK fusions or the selected ALK-activating mutations R1275Q, F1245C, F1174X (with X being any other amino acid). Patients enrolled in this study will represent a population with a high-unmet medical need because patients will be eligible only if they have either exhausted or are unsuitable to receive the standard-of-care treatment for their diagnosed malignancy.

Alterations in ALK have been shown to be an important mechanism of oncogene addiction in many tumor types (Hallberg and Palmer 2013; Ross et al. 2017), and although these alterations are rare in non-NSCLC tumors, evidence of clinical benefit from ALK inhibitors in a variety of ALK-driven malignancies exists. Efficacy of ALK inhibitors have been reported in nonclinical models of neuroblastoma harboring ALK-activating mutations, such as F1174L, F1245C, and R1275Q (Trigg and Turner 2018). In addition, clinical benefit has been described with alectinib in a patient with small cell carcinoma of the prostate harboring the F1174C ALK mutation (Carneiro et al. 2018).

Clinical benefit has also been reported with ALK inhibitors in patients with various solid tumors harboring ALK fusions, such as cancer of unknown primary (CUP) site, IMT, colorectal cancer, and thyroid cancer (Amatu et al. 2015; Godbert et al. 2015; Yakirevich et al. 2016; Gambacorti-Passerini et al. 2018), and with alectinib in papillary renal cell carcinoma (Pal et al. 2018), metastatic IMT (Saiki et al. 2017; Honda et al. 2019) and large cell neuroendocrine carcinoma (Shimizu et al. 2019). Of note, while most of the efficacy data for alectinib, particularly in the clinical setting, are based on inhibition of the EML4-ALK fusion protein (the most abundant fusion protein observed in NSCLC), evidence of alectinib activity in other types of ALK fusion proteins exist. In the ALEX trial of alectinib versus crizotinib in treatment-naive patients with ALK-positive NSCLC, 11 patients enrolled in the alectinib arm were identified to harbor fusion partners other than EML4 (KLC1, BCL11A, FTO, KIF5B, BRE, MAP4K3 LM07, and ORC5). Of these, 10 patients achieved a best overall response of a partial response (PR), and one experienced stable disease (Roche data on file).

In patients with ALK-positive NSCLC, alectinib has proven to be a potent, well tolerated, brain-penetrant ALK inhibitor at the approved dosage of 600 mg BID, and there is no reasonable expectation that the safety profile observed with alectinib in patients with ALK-positive NSCLC should differ significantly when administered to patients with other solid tumors. Therefore, it is expected that alectinib in the population enrolled in this study will show a favorable benefit–risk profile.

Identified and potential risks associated with alectinib treatment will be closely monitored throughout the clinical program. Patients' safety during the study is optimized by targeting the most appropriate patient population through inclusion and exclusion criteria, stringent safety monitoring by the Sponsor, and protocol-specified study drug modification criteria (see Section 5.1.2).

The role of ALK alterations in different tumor types, combined with the promising clinical activity described above in non-NSCLC tumors, supports further investigation of alectinib in the tumor-agnostic setting for patients with solid tumors harboring ALK fusions or selected ALK-activating mutations (such as the one described in neuroblastoma), for whom no alternative standard therapy is suitable.

1.4.1 Trial-Specific Risk Assessment

Alectinib is an approved drug in NSCLC. In this setting, it is prescribed by oncologists and taken by patients at home BID. If this was a traditional study rather than a decentralized study, patients would be asked to take alectinib at home as per investigator instructions. Moreover, the safety assessments to be completed at the patient's home in this study are the same as those that would be completed at an in-clinic visit. More frequent safety visits are scheduled during the first 3 months in order to closely monitor initial patient exposure to alectinib. In addition, patients will be instructed to take the first dose in the presence of an mHCP.

This study allows both virtual and physical study sites (see Appendix 9 and Section 3.3.1).

The following elements are associated with the decentralized nature of the study:

- Telemedicine
  - The investigator and clinical research coordinator (CRC) will be in remote contact with the patient.
  - An mHCP will perform protocol-mandated assessments and will collect and prepare all samples for shipment to an analytical laboratory.
  - *A smartphone* will be provided to the patients with an application that facilitates connection with the investigator and CRC.
- Electronic ICF
- At-home investigational medicinal product (IMP) delivery
- Local imaging center close to the patient's home

Overall, based on the expected favorable benefit–risk profile of alectinib in this study, the decentralization elements stated above, the patient population to be enrolled, the well-characterized and tolerated safety profile of alectinib and its route of administration along with the standard practice, the risks associated with decentralization are expected to be similar to those in a *traditional* study.

In this decentralized study, all included elements have been designed to enable operating as close as possible to the level of a non-decentralized study.

- Investigator and Sponsor have exactly the same responsibilities, as outlined in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; E6R2).
- Safety management performed remotely will follow the same approach as management for a non-decentralized trial.
  - There will be more frequent safety visits during the first 3 months in order to closely monitor initial patient exposure to alectinib.
  - Patients will be instructed to take the first dose in the presence of an mHCP.
  - The investigator will make arrangements for referrals to a specialist if additional investigations to the study protocol are needed to ensure patient safety.
- All drug shipments will be temperature controlled and bottles pre-labelled for clinical trial use. The mHCP will check bottle integrity and label and provide instruction to patient on how to take the medicine.
- The mHCP will be a trained, experienced, and qualified healthcare professional. Assessments and supervision of the mobile healthcare professional will be performed in the remote presence of the investigator.

1.4.2 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.

Study BO41929 is home based, utilizing mHCPs*, who would continue to observe the applicable epidemiologic/public health and hygiene measures,* and telemedicine visits with the investigator.

1.4.2.1 COVID-19 Vaccines

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).

Although there is no specific requirement regarding the timing of vaccine administration, the vaccination should ideally be at least commenced before study enrollment and initiation of study drug, whenever possible.

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.

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 and to appropriately identify and assess potential adverse reactions (e.g., nausea, diarrhea, myalgia) possibly shared by vaccines and study drugs.

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.

2. OBJECTIVES AND ENDPOINTS

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

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective is to demonstrate a clinically relevant response to experimental treatment on the basis of the following endpoint:

- Confirmed ORR, defined as the proportion of patients with a complete response [CR] or a PR $\geq$28 days after initial response in patients with solid tumors, as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

The primary efficacy objective of the trial is to evaluate alectinib at the dose of 600 mg BID until disease progression, death, or withdrawal for any other reasons in 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).

The primary evaluation will be made regardless of whether patients withdraw from treatment, withdraw consent, or receive additional or alternative therapy.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of alectinib in patients with ALK-positive solid tumors in the response-evaluable population, defined according to the investigator or by blinded independent center review (BICR), depending on who is assessing the endpoint, on the basis of the following endpoints:

- Confirmed ORR, defined as the proportion of patients with a CR or PR $\geq$28 days after initial response by BICR according to RECIST v1.1
- Duration of response (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
- Progression-free survival (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
- CNS ORR, defined as objective tumor response rate (a CR or a PR) of CNS lesions in patients with measurable CNS metastases at baseline by BICR according to RECIST v1.1
- 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
- Overall survival (OS), defined as the time from first dose of study drug to death from any cause

For patients with primary CNS tumors with measurable disease at baseline who have a baseline tumor assessment per the investigator according to Response Assessment in Neuro-Oncology (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

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

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

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of alectinib in patients with ALK-positive CUP and non-CUP solid tumors who receive at least one dose of alectinib on the basis of the following endpoints:

- 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, as determined by BICR according to RECIST v1.1
- OS

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of alectinib in all dosed patients on the basis of the following endpoints:

- 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)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the alectinib PK profile on the basis of the following endpoint:

- Plasma concentrations of alectinib and its metabolite(s) as applicable at specified time points

2.4 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To identify and/or evaluate biomarkers that are associated with primary or acquired resistance to alectinib in the biomarker-evaluable population by analyzing the relationship between biomarkers found in circulating DNA in blood and tumor tissue, with efficacy endpoints
- To assess relationship between levels of circulating free DNA (cfDNA) at baseline and changes in levels of cfDNA at different timepoints during treatment with efficacy endpoints

2.5 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with alectinib on the basis of the following endpoint:

- Change from baseline in QLQ-C30 scores during study treatment
- Change from baseline in EQ-5D-5L index-based and Visual Analog Scale (VAS) scores during study treatment

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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.

For sample requirements, see Section 4.6.6 and Appendix 2, Table 3.

For eligible and enrolled patients, the tumor tissue sample must be submitted (see Section 4.6.6 and Appendix 2, Table 3) for retrospective analysis by FMI using the F1CDx assay.

The nature of the approach makes it impossible to predict at which clinical sites these patients will be identified. Therefore, a decentralized, home-based approach will be implemented using mHCPs that have professional qualifications as per local requirements. The mHCPs will attend to the patient at home, and the investigator will interact with the patient using telemedicine. This approach minimizes the need for on-site visits for patients, thus making clinical trials more accessible to patients regardless of location. 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 RECIST v1.1 have been recruited, regardless of the number of enrolled patients with primary CNS tumors (evaluable according to RANO criteria), with CUP or ALK mutations. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of up to two screenings per participant) at the investigator's discretion. Patients must re-sign the Informed Consent Form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 4.6.1).

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.

The primary endpoint will be based on the response-evaluable population with ALK fusion solid tumors that are assessed according to RECIST v1.1.

The primary objective of the study is confirmed ORR as per investigator assessment in solid tumors assessed according to RECIST v1.1 (see Appendix 5). Secondary endpoints include ORR by BICR, DOR, and PFS as per investigator assessment and by BICR, CNS ORR, and DOR as per BICR, OS, and for patients with primary CNS tumor, the ORR, DOR and PFS as per investigator assessment and BICR according to RANO criteria. BICR procedures will be detailed in the BICR Charter.

The efficacy in patients with solid tumors harboring ALK mutations, with CUP, or with primary CNS tumors evaluable according to RANO criteria will be assessed as secondary endpoints.

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.

Patients will receive alectinib at the dose of 600 mg BID, taken with food, until disease progression, death, or withdrawal for any other reasons. Treatment beyond radiological progression is possible in the event of isolated lesion progression if, in the investigator's opinion, there is evidence of ongoing clinical benefit.

All enrolled patients will undergo regular, scheduled visits until disease progression, death, withdrawal from the study, or study termination, whichever occurs first. For patients receiving alectinib beyond radiological progression, scheduled visits (including tumor assessments), will continue to be performed until treatment permanently discontinues.

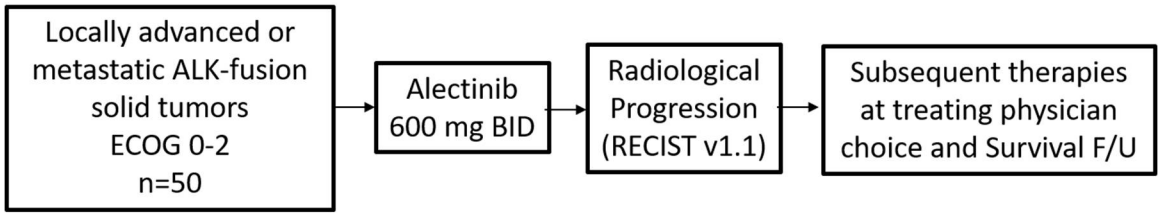
For the first 12 weeks (3 months), regular safety assessments will be scheduled at baseline and every 2 weeks to allow for more frequent liver function and CPK assessments as per alectinib label. After Week 12, patients will undergo regular safety visits every 4 weeks. See Appendix 1 for the schedule of activities.

Tumor assessments will be performed during screening and every 8 weeks (calculated from baseline) during study conduct and will consist of computed tomography (CT) and brain magnetic resonance imaging (MRI) scans (or brain CT scans if MRI is not feasible). Brain scans will be mandatory at baseline and during study conduct for patients with primary CNS tumors or brain metastases at baseline. For patients without brain metastases at baseline, brain scans will be performed as clinically indicated during study conduct. A safety follow-up will occur during the treatment discontinuation visit 28 days (4 weeks) after the final dose of alectinib.

Plasma samples will be obtained for biomarker analysis at baseline, Week 8, Week 36, and upon disease progression, and for PK analysis at baseline and every 4 weeks at scheduled visits during the treatment period.

Figure 1 presents an overview of the study design. The schedule of activities is provided in Appendix 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.

3.1.1 Internal Monitoring Committee

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.

3.2 END OF STUDY AND LENGTH OF 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 the year 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.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Single-Arm Decentralized Design

This study will be a single-arm trial with ORR as the primary endpoint. The choice of a single-arm design is driven by the extremely low frequency of the target population (estimated at around 0.2%) (Ross et al. 2017). Having a matched control would be difficult in this tumor-agnostic population, as it is impossible to predict which tumor types will be enrolled, and in what proportion relative to the overall number of patients recruited. Adding to the complexity of finding a suitable control arm is the requirement

for enrolled patients to have exhausted standard therapy or to be unsuitable to receive the standard of care for their diagnosed malignancy. This will mean that patients included in this trial will receive alectinib in different lines of therapy, further increasing the difficulty of finding a matched control group.

The low prevalence of ALK-positive patients in solid tumors other than NSCLC (Ross et al. 2017) does not lend itself to traditional recruitment approaches. It is estimated that more than 25,000 patients would need to be screened in order to identify 50 potentially eligible patients.

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 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.

For sample requirements, see Section 4.6.6 and Appendix 2, Table 3.

For eligible and enrolled patients, the tumor tissue sample must be submitted (see Section 4.6.6 and Appendix 2, Table 3) for retrospective analysis by FMI using the F1CDx assay.

For more information, see Section 4.6.6.

Site activation following patient identification is not a viable approach since this would take several weeks to be completed, resulting in significant delays to the start of treatment. For these reasons, a decentralized design will be adopted using telemedicine. The infrastructure platform for this particular approach will be provided if it is not yet available for the investigator.

Patient visits will be home-based, conducted by a mHCP and remotely by the investigator via telemedicine. Visit assessments will be conducted by the mHCP with remote supervision from the investigator whenever required. The mHCP must be licensed to perform the assessments according to country regulations. Study materials (including study drug) will be shipped either to the patient's home or brought to the patient's home via an alternative process (e.g., via the mHCP). See the country-specific operations manual for details. For tests that cannot be performed at home (such as

scans for tumor assessments), arrangements will be made for patients to visit the nearest local facility that can perform the required tests.

In this decentralized study, the patient's care is provided by the mHCP and investigator. As in any clinical trial, the relevant patient health care providers will be kept informed about the patient to ensure continuity of care outside the study. The investigator will participate in all scheduled, home-based visits via telemedicine. The responsibilities of the investigator in the oversight of study personnel are described in Appendix 9.

In order to allow flexibility to participate in the study *there are* two *operational* approaches *that can be used for study conduct as outlined below*:

- Investigators who are associated with a physical study site (e.g., hospital, clinic, or oncology institution) that is involved in the study conduct
- Investigators who are not associated with a physical study site

  A third-party vendor, such as Science 37, will be involved in the study conduct (virtual study site).

Implementation of the elements cited above will depend on local requirements as well as the site scheme foreseen in the country where the study is being conducted. The investigators will be informed about the approach used in their country. Please refer to the country-specific operations manual *(see Appendix 9 for further details)*.

3.3.2 Rationale for Alectinib Dose and Schedule

The 600-mg BID dosing regimen of alectinib was established as the recommended Phase 2 dose based on safety (Section 1.4), tolerability, PK, and anti-tumor activity from the dose-escalation part of Phase I/II Study NP28761 (Gadgeel et al. 2014). This dosing regimen was then approved in the ALK-positive, crizotinib refractory or intolerant advanced NSCLC on the basis of the positive benefit–risk profile observed in the pivotal Phase II Studies NP28761 and NP28673. In addition, the 600-mg BID dosing regimen has also been approved in the ALK-positive, treatment-naive, advanced NSCLC population on the basis of the efficacy and safety results reported in the ALEX trial (Peters et al. 2017), as well as the cumulative PK, exposure–response and exposure-safety data observed with alectinib (Morcos et al. 2018; Smart et al. 2019).

Tumors driven by a particular oncogene tend to become addicted to that pathway and can greatly benefit from its targeted inhibition (Pagliarini et al. 2015). As shown in ALK-positive NSCLC, alectinib is a potent and well-tolerated brain-penetrant ALK-inhibitor, and case reports exist describing its efficacy in the treatment of patients with ALK-positive solid tumors other than NSCLC when dosed at 600 mg BID (see Section 1.2). In addition, there is no reasonable expectation that the safety profile observed with alectinib in ALK-positive NSCLC at this dose should differ significantly when administered to patients with other solid tumors. Therefore, it is expected that

600-mg BID dose of alectinib in this population will demonstrate a favorable benefit–risk profile.

3.3.3 Rationale for Patient Population and Analysis Groups

The study population consists of patients with ALK-positive locally advanced or metastatic solid tumors other than lung cancer who have either exhausted or are unsuitable to receive the standard of care for their diagnosed malignancy.
See Section 1.1 for details on ALK fusions and ALK alterations and Section 1.4 for more information about the study population.

The primary analysis will be performed on ALK fusion solid tumors (excluding patients with CUP and CNS primary tumors) that are measurable at baseline, as assessed by the investigator according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST), which is expected to be the main population recruited in the study.

Patients with CUP are also allowed in the study, and data will be analyzed separately from the data in the primary analysis. This will be done to preserve the primary analysis population of patients with ALK fusion solid tumors. Analyzing patients with CUP as a part of the primary analysis population would lead to increased risk of enrolling patients with misdiagnosed ALK-positive lung cancer.

Patients with primary CNS tumors are allowed in the study, and data will be analyzed separately as their disease is assessed using a different set of criteria (i.e., the RANO criteria).

Patients with tumors harboring selected ALK-activating mutations are also allowed in the study. However, data will be analyzed separately from data in the primary analysis because evidence of benefit with ALK inhibitors in these tumors is less robust than for ALK fusion–driven malignancies and is primarily limited to neuroblastoma.

3.3.4 Rationale for Biomarker Assessments

Cancer is a heterogeneous disease, and ALK-positive tumors as defined in this study can occur in different forms, depending on the type of ALK fusion partner or ALK-activating mutation driving the malignancy (Hallberg and Palmer 2013). ALK fusion partners, ALK fusion variants, and ALK mutations, or mutations in tumor-related genes occurring before or during alectinib treatment may influence treatment efficacy. ALK mutations and mutations in cancer-related genes can appear as a result of biologic selection pressure on tumor cells induced by the treatment. Therefore, patients enrolled in the study may not be equally likely to benefit from treatment with alectinib. Biomarker samples collected prior to dosing will be assessed in an effort to identify those patients most likely to respond to alectinib. Biomarker samples collected during study conduct will be assessed to investigate possible correlation between levels of cfDNA with activity of alectinib or progression during treatment, and samples collected at progression will be analyzed in an effort to identify acquired resistance mechanisms to alectinib.

Validated and approved diagnostic tests are required to identify patients with ALK-positive tumors who are eligible for alectinib treatment across tumor types. Currently available companion diagnostic tests for alectinib are approved only for NSCLC. Therefore, approved tissue and plasma NGS assays to detect ALK-positive patients for alectinib treatment across tumor types are needed. Patients may not have enough tumor tissue available to be tested for rare biomarkers such as ALK by tissue. Plasma ALK assays that analyze circulating tumor nucleic acids will enable more patients to be tested for ALK positivity. Data generated in this study may support a possible registration of tissue and plasma NGS assays as CDx for alectinib across tumor types.

3.3.5 Rationale for Pharmacokinetic Sample Collection

To date, the pharmacokinetics of alectinib have been characterized in ALK-positive NSCLC patients. The data collected from this study will enable the understanding of alectinib pharmacokinetics in this tumor-agnostic population and will allow researchers to investigate potential sources of variability influencing alectinib and/or response to alectinib therapy.

3.3.6 Rationale for Patient-Reported Outcome Assessments

The benefits associated with alectinib treatment in this patient population must be weighed with its potential impact on patients' health-related quality of life and function.

Patient-reported outcomes (PROs) provide a unique understanding of patients' experience with the disease and associated treatment. Therefore, the aim of the PRO endpoints in this study is to complement traditional efficacy and safety endpoints to inform the benefit–risk profile of alectinib in the tumor-agnostic setting.

The focus will be on capturing patients' experience with symptoms commonly experienced as result of treatment intake or clinical progression. Data will be collected using the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Aaronson et al. 1993). In addition, in order to inform pharmacoeconomic modeling, health status utility scores will be collected using the EQ-5D-5L Questionnaire will be used (EuroQol Group 1990; Herdman et al. 2011; Janssen et al. 2013; Devlin and Brooks 2017).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 50 patients with ALK-fusion solid tumors will be enrolled. In addition, patients with CUP, CNS primary tumor, and tumors harboring ALK mutations will be allowed in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Histologically confirmed locally advanced or metastatic solid tumor excluding lung cancer
- ALK-positive tumor per FMI NGS (NGS F1CDx, F1LCDx, or F1HEME) or per local accredited laboratory using validated NGS testing of tumor tissue or peripheral blood:
  - ALK fusion
  - The following ALK-activating mutations: R1275Q, F1245C, or F1174X
  - Local ALK test report (only for cases with local ALK testing; see Section 4.6.5.3)
- *Disease progression on prior treatment, or previously untreated disease with no* available *acceptable treatment*
- Other prior cancer therapies are allowed, including investigational drugs, if any treatment-related toxicities (excluding alopecia) have resolved to Grade 1 or better and laboratory values as defined in inclusion criteria, and meet the following washout criteria prior to first dose of alectinib:
  - At least 4 weeks must have elapsed since the last dose of the prior cytotoxic chemotherapy or antibody-directed therapy.
  - At least 7 days must have elapsed since prior tyrosine kinase inhibitor (TKI) therapy.
  - At least 14 days must have elapsed since prior radiotherapy.
- Measurable disease at baseline, as assessed by investigator (by RECIST v1.1, or according to RANO criteria for patients with primary CNS tumors)

  For primary CNS tumors, only MRI scans will be accepted. If the local radiology facility cannot perform MRI, the patient will be excluded from the study.
- Life expectancy of at least 12 weeks in the opinion of the investigator
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–2 (see Appendix 3)
- Adequate hematologic function:
  - Platelet count ≥ 100×10^9/L
  - Absolute neutrophil count ≥ 1500/μL
  - Hemoglobin ≥ 9 g/dL
- Adequate hepatic function:
  - ALT (SGPT) and AST (SGOT) ≤ 2.5 × upper limit of normal (ULN) (≤ 5 × ULN for patients with concurrent liver metastasis)
  - Bilirubin ≤ 2 mg/dL

- Adequate renal function:
  - Serum creatinine $< 2 \times$ ULN
  - Calculated creatinine clearance of ≥ 60 mL/min (Cockcroft-Gault formula)
- Patients with primary CNS tumors are eligible
- Patients with CUP tumors are eligible
- Patient with brain or leptomeningeal metastasis are allowed in the study if asymptomatic and if they meet the following criteria:
  - No neurological signs and clinically stable for at least 2 weeks without corticosteroid treatment for brain metastasis prior to first dose of alectinib
  - If previously treated with whole-brain radiotherapy or gamma-knife radiosurgery, treatment must have been completed at least 2 weeks prior to first dose of alectinib
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures
- Willingness to comply with home-based approach and visits by mHCPs
- Ability to swallow alectinib capsules intact (without chewing, crushing, or opening)
- Women of childbearing potential must have a negative serum pregnancy test result during screening and a negative urine pregnancy test at baseline before first dose of study drug is administered (unless a negative serum test was obtained within 10 days of first dose of study drug, in which case the urine pregnancy test is not required)
- 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. Women must refrain from donating eggs during this same period.

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and at least 90 days after the final dose of alectinib. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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 adequate methods of contraception.

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

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile 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 least 90 days after the final dose of alectinib. 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 final dose of alectinib 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.

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 3 months after the final dose of alectinib
- Lung cancer
- Patients with one of the following ALK point mutations: I1171X, G1202R, V1180L
- Prior therapy with an ALK inhibitor
- Liver disease characterized by any of the following:
  - 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
  - Acute 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 polymerase chain reaction (PCR) is negative for HCV RNA.
- Known HIV infection
- Patients with symptomatic bradycardia

- Patients with symptomatic or unstable brain metastasis
- Patients with primary CNS tumors are allowed
- Malabsorption syndrome or any other condition that would interfere with enteral absorption
- Incomplete recovery from any surgery prior to treatment
- Any other malignancies within 5 years prior to enrollment, except the following:
  - Curative 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
  - Any cured cancer that is considered to have no impact on PFS or OS for the current ALK-positive solid tumor
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History of hypersensitivity to alectinib or any of its excipients

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

4.2 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one screening opportunities (for a total of two screenings per individual) at the investigator's discretion. The investigator will *maintain a* record *of* reasons for screen failure (see Section 4.6.1).

4.3 METHOD OF 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.

The decentralized study design minimizes the need for on-site visits for patients, thus making clinical trials more accessible to patients regardless of location.

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 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.

For sample requirements, see Section 4.6.6 and Appendix 2, Table 3.

For eligible and enrolled patients, the tumor tissue sample must be submitted (see Section 4.6.6 and Appendix 2, Table 3) for retrospective analysis by FMI using the F1CDx assay.

Replacement of patients with ALK-fusion solid tumors assessed according to RECIST v1.1 will be allowed for enrolled patients that have not taken any dose of alectinib.

4.4 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is alectinib.

4.4.1 Study Treatment Formulation and Packaging

4.4.1.1 Alectinib

Alectinib will be supplied by the Sponsor as a capsule dosage form containing the active ingredient 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6, 11-dihydro-5Hbenzo[b]carbazole-3-carbonitrile hydrochloride.

Each capsule contains 150 mg of alectinib (as a free base) along with lactose monohydrate, carboxymethylcellulose calcium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate as excipients.

Alectinib will be supplied by the Sponsor as capsules in bottles. Alectinib capsules should be stored in accordance with the storage instructions on the label.

For more information on the formulation and handling of alectinib, see the latest Alectinib Investigator's Brochure.

4.4.2 Study Treatment Dosage, Administration, and Compliance

Alectinib 600 mg (four 150-mg capsules) is to be administered orally BID with food. The capsules should not be opened, and the contents of capsules should not be dissolved.

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

Patient will be treated until disease progression, unacceptable toxicity, withdrawal from treatment, or death. Treatment beyond radiological progression is possible in the event

of isolated lesion progression if, in the investigator's opinion, there is evidence of ongoing clinical benefit.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for dose modification and treatment interruption or permanent discontinuation for patients who experience adverse events are provided in Section 5.1.2.

4.4.3 Investigational Medicinal Product Handling and Accountability

The IMP required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mHCP]) is responsible for maintaining records of IMP delivery, IMP inventory, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received. See the country-specific operations manual for additional details.

In order to ensure patient anonymization, the Sponsor will ship the IMP to a licensed pharmacy, which could be an independent vendor or the central site pharmacy. The licensed pharmacy will dispense the IMP after investigator's prescription and manage the IMP and associated shipments to the patient's home; the process will be detailed in the country-specific operations manual as per local requirements.

The study site should follow all instructions included with each shipment of IMP. The licensed pharmacy used for the study will acknowledge receipt of IMPs supplied by the Sponsor by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The depot must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring of the IMP. The IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to authorized staff.

Investigator or delegate will be responsible for coordinating the shipment of IMP to the patient's home prior to the date and time of the visit. Upon delivery, a telemedicine visit with the patient or patient caregiver will be conducted by the investigator or delegate to confirm that appropriate temperature conditions have been maintained during transit and that the IMP was received in good condition (i.e., no damage and unopened) according to the process described in the country-specific operations manual.

Appropriate packaging will be delivered to patients' homes, or as per local regulations, in order to return unused IMP after IMP accountability is performed by an mHCP or at the site, whichever is in agreement with the local requirements. The returned IMP will be stored at the depot until final disposition is confirmed by the study monitor or Sponsor.

4.4.4 Continued Access to Alectinib

The Sponsor will offer continued access to Roche IMP (alectinib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (alectinib) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (alectinib) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for the indication explored in this study
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for the indication explored in this study
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

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

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

4.5 CONCOMITANT THERAPY

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 treatment discontinuation visit occurring 28 days after last dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Details about the product and the

number of doses will be reported for COVID-19 vaccines and for COVID-19 infection mitigation.

4.5.1 Permitted Therapy

The medications and/or treatments below are permitted:

- Premedication with analgesics and/or anti-emetics may be administered at the discretion of the investigator.
- Local therapy (e.g., stereotactic radiotherapy or surgery) may be given in patients with isolated asymptomatic CNS progression (e.g., new CNS oligometastases) after consultation with the Sponsor.
- In certain instances, palliative radiotherapy to bone lesions and for purposes of pain control may be permitted, provided it does not interfere with the assessment of tumor target/non-target lesions, and is considered to be medically necessary by the investigator. The sponsor must be notified if palliative radiotherapy is started.
- If palliative radiation is indicated, palliative radiation may start within 24 hours of the last dose of alectinib, unless, in the judgment of the investigator, patient safety will require a longer washout period prior to palliative therapy. Dosing of alectinib may resume with the resolution of any radiation toxicity to Grade 1 or better.
- Inactivated vaccines are allowed.

4.5.2 Cautionary Therapy

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

- For medications that are substrates of P-gp transported 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 those 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 4).

4.5.3 Prohibited Therapy

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

- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents

  Note: The use of systemic corticosteroids for the management of CNS metastases may be permitted after discussion with the Medical Monitor.
- Additional investigational drug (excluding post-progression during survival follow-up)

- Radiotherapy/radionuclide therapy, except for palliative radiotherapy to bone lesions or for pain control
- If palliative radiation is indicated, alectinib should be interrupted for at least 24 hours before start of radiation treatment

    Dosing of alectinib may resume with the resolution of any radiation toxicity to Grade 1 or better.

The list of medication provided above is not necessarily comprehensive. If in doubt, the investigator *may* consult with the Medical Monitor when prescribing concomitant medications.

4.6 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

In this decentralized model, all scheduled study activities, from signing of informed consent to scheduled safety visits and study closeout, will be executed remotely whenever possible. Home-based visits and assessments will be performed by the investigator via telemedicine sessions, facilitated by mHCPs attending to the patient's home. Investigator will be responsible for ensuring that all mHCPs are licensed, qualified, in good standing per applicable country-specific regulations and requirements, and that appropriate background checks have been performed. The responsibilities of the investigator in the oversight of study personnel are described in Appendix 9.

During scheduled visits, the mHCP will perform study assessments as directed remotely by the investigator. In addition, as per schedule of activities (see Appendix 1), blood samples for hematological and chemistry laboratory assessments, as well as plasma samples for biomarker and PK analysis, will be obtained, processed, and sent to one or several laboratories or to the Sponsor or a designee for analysis. The mHCP will also perform a dipstick urinalysis at the patient's home. The mHCP will document results as per local requirements.

Remote visits may be facilitated by the CRC. For virtual sites, the CRC will be the Science 37 CRC, while for physical sites, the investigator may delegate the CRC responsibilities to the mHCP or site personnel. The CRC will be responsible for scheduling the home-based visits.

For tests that cannot be performed at home (such as scans for tumor assessments), arrangements will be made by the investigator, mHCP, or CRC for patients to visit a local facility that can perform the required tests.

All source data relevant to the study, including efficacy and safety parameters, will be kept at the site or captured using a validated platform (i.e., the Science 37 Platform) (see Section 7 for additional details). The study data entered will be available in the eCRF

database (RAVE) to allow the Sponsor's study team to perform data management and medical review, and generate queries accordingly. Queries will be answered by the investigator or designee. Details related to source data, data capture, and cleaning can be found in the country-specific operations manual.

On-Study Visits: Assessments and Procedures

Study visits will be performed at patients' homes according to the schedule of activities as outlined in Appendix 1.

All necessary study supplies, including the study drug, will be shipped by secure courier to the patient's home (or, alternatively, see Section 4.4.3) ahead of the scheduled study visits. Return labels will be included so patients can return supplies to vendor once study participation is completed or upon discontinuation.

The CRC will schedule visits taking into consideration the patients' availability and the allowed visit windows and will notify the investigator and mHCP, as applicable. The coordinating responsible will set up the appointment for the investigator to perform the telemedicine remote visits and remind the patient of upcoming visits and procedures that will take place during the visit. In addition, the coordinating responsible will provide remote coordination and technical assistance during all visits. The patient will be provided with a mobile device for the duration of the study to facilitate interactions with the investigator, the mHCP, and the coordinating responsible. See the country-specific operations manual for more details.

For tests that cannot be performed at home (such as scans for tumor assessments), arrangements will be made for patients to visit a local facility that can perform the required tests.

Unscheduled visits will also be performed at patients' homes if possible. However, it may be necessary that patients visit a local laboratory/specialist or the local oncologist for safety reasons, as needed. Records generated from these visits will be obtained and sent to investigator or uploaded into the relevant data capture system for documentation and the investigator's review.

For details on procedures and assessments to be performed at each visit, see the schedule of activities in Appendix 1.

The local oncologist or current treating physician will be informed in writing according to local requirements of all clinically relevant updates to the status of the patient by the CRC, in addition to communication between the investigator and the local oncologist or current treating physician when necessary. This is to ensure continuity of care should the investigator require that the patient visits the local oncologist for safety reasons.

If the investigator determines that the patient requires an in-person consultation with a medical provider (e.g., there is a new symptom or an adverse event that warrants an in-person evaluation), the patient will be referred to his or her oncologist or relevant specialist for an in-person examination. With the patient's medical records release authorization, designated study personnel will contact the facility that performed the in-person examination to obtain the resulting medical records and transcribe them on the eCRF for the investigator to review.

In the event that a scheduled home-based visit cannot be performed within the allowed window (see Appendix 1), the visit should be-rescheduled as soon as possible. Should this not be feasible, the patient may be asked to visit his or her local oncologist to perform the necessary procedures (including laboratory tests) to ensure continuity of care.

4.6.1 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 by the site. This study may use an electronic informed consent process if allowed by local regulations as described below.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a *detailed* record of all patients screened and *document* eligibility or record reasons for screening failure, as applicable.

This log will be maintained as described above.

Informed Consent Process

Patients will be asked to provide informed consent to allow screening procedures to begin. Electronic signature or wet ink signature is acceptable as per local requirements. Electronic signature details can be found in the country-specific operations manual.

The potential study patient will review the documents (paper or electronic) and discuss them with the investigator via a telemedicine visit, during which all their questions about the study will be answered and all elements of the informed consent process will be covered. Study coordinators will also facilitate the review of the inform consent with the patients. During this discussion, the investigator will be able to evaluate the potential patient's understanding by querying them about the objectives of the study, risks of participation, expectations, and other information present in the informed consent. The investigator will provide clarifications and further explanation as needed.

After this discussion, the patient will be given the opportunity to independently consider participation in the study. If willing to participate, the patient will provide a handwritten

signature directly recorded electronically in the designated signature block using a computer mouse, touchscreen, or stylus depending on the capability of his or her device or wet ink signature, as per local regulations. The investigator will countersign in the same manner, also as per local regulations and in a timely manner. The patient will be provided with a copy (electronic or paper) of the fully executed informed consent documents, and the informed consent process will be documented and maintained at the site as part of source documentation as required per regulation.

In addition, if consented patients are located in the United States, the patient will sign the Authorization to Use and Disclose Protected Health Information and, for patients in California, an Experimental Research Subject Bill of Rights document. An equivalent document may apply to other countries and will be used accordingly (see the country-specific operations manual for details).

A screening visit will be scheduled after inform consent is obtained. The CRC will register the patient in the Sponsor-provided system. A mHCP will complete screening procedures at the patient's home, with the investigator participating via a telemedicine and a coordinating responsible providing remote coordination and technical assistance during the visit if applicable and required (see country-specific operations manual for details). Various procedures may be completed on different days to accommodate the patient's and mHCP's schedules, as long as they are completed within the screening visit window. Specific screening procedures and assessments are outlined in the schedule of activities (see Appendix 1).

The investigator, mHCP, and the CRC will enter data collected during screening on the eCRF, and the investigator will review the data to confirm the patient's eligibility according to the inclusion and exclusion criteria (see Section 4.1).

4.6.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), female reproductive status, and smoking 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.

4.6.3 Physical Examinations

A complete physical examination, performed during 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 as baseline condition should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified baseline and 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 eCRF.

For patients with primary CNS tumors, a neurological examination must be performed at each tumor assessment visit and compared to the neurological examination performed at the time of the previous disease assessment. This will allow the evaluation of responses in these patients according to RANO criteria. Definition of clear neurological worsening is difficult to describe because progression in the CNS can present in numerous ways. Accordingly, evaluation of neurological function at each disease assessment will be based purely on the mHCP's and investigator's assessment of the patient's neurological state compared with the neurological function at the time of the previous disease assessment. Neurological status will be recorded as "stable or improved" or "worsened" on the RANO response pages.

Telemedicine Physical Examinations (if applicable)

Physical examinations for this study will be conducted via telemedicine, which is permitted in the recruitment countries/states selected for this study. The investigator, assisted by a mHCP, will conduct physical examinations of study patients via telemedicine during a videoconference session.

As part of this examination, under the direction of the investigator present over telemedicine, a mHCP will assist in performing the physical examination required per protocol at the patient's home.

4.6.4 Vital Signs

Vital signs will be reported on the eCRF and will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, weight, and temperature. New or worsened clinically significant abnormalities will be reported as adverse events on the eCRF.

Vital sign measurement will be performed by an mHCP professional.

4.6.5 Tumor and Response Evaluations

All known and suspected sites of disease must be assessed and documented at screening and re-assessed at each subsequent tumor evaluation according to the schedule of activities (see Appendix 1) until investigator-assessed radiographic disease progression (or loss of clinical benefit in case treatment continues beyond disease

progression), withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

Tumor assessments will be performed during screening and every 8 weeks (calculated from baseline) during study conduct and will consist of CT and brain MRI scans (or brain CT scans if MRI is not feasible).

Because imaging scans cannot be performed at home, arrangements will be made for patients to visit a local imaging facility that can perform the required tests. Patients will use the same imaging facility for the duration of their participation in the study. The CRC will coordinate with the patient and imaging facility to schedule imaging procedures according to the schedule of activities (see Appendix 1). The local imaging facilities will be instructed regarding and if required, trained on the methodology required for disease assessments to be performed according to RECIST v1.1 or RANO criteria, as applicable.

Methods:

- CT scans: CT scans should be performed with oral or IV contrast unless contraindicated and have a maximum slices thickness of 5 mm
- MRI scans, with minimum sequences consisting of the following:
  - Pre-contrast T1, T2/fluid-attenuated inversion recovery
  - Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended
- Recommended slice thickness: $\leq$5 mm with no gap

Imaging facilities should perform scans according to requirements specified above and should apply the same radiographic procedure used to define measurable disease at screening throughout the study for consistency. The scans and radiology report will be submitted to Science 37 and the investigator as soon as possible to allow treatment decisions in a timely manner.

Response will be assessed by the investigator on the basis of the CT and MRI scans according to RECIST v1.1 (see Appendix 5) or, for patients with primary CNS tumors, RANO criteria, which include neurological examination and corticosteroid use (see Appendix 6).

In addition, scans will be sent for 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.

Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days prior to the first dose may be considered as baseline assessment if they satisfy the protocol criteria.

Scheduled tumor assessments should be kept according to the original scheduled based on the date of first dose administration, regardless of clinical visits delays and drug interruptions. At the investigator's discretion, tumor assessment may be repeated at any time if progressive disease is suspected (for example, in case of symptomatic deterioration).

An objective response should be confirmed by repeat assessments at least 4 weeks after initial documentation. No additional assessment is planned for 4 weeks after the initial response, but every effort should be made to obtain confirmation of response, even if a patient who has initially responded is withdrawn from study treatment for any reasons other than progression or death.

Patients who discontinue study treatment for any reason other than progression of disease or death should continue to have regular disease assessments every 8 weeks per the schedule of assessments (see Appendix 1) until progression.

4.6.5.1 Non-Primary CNS Tumors Assessments

Screening assessments for non-primary CNS tumors should include CT scans (with oral or IV contrast unless contraindicated) of the chest, abdomen, and pelvis (if applicable), and be consistent with standard imaging required for the malignancy under consideration. An MRI scan of the head must be performed at screening to assess CNS metastases. Patients with known or suspected bone metastases should undergo radionuclide bone scan at screening. Bone scans, positron emission tomography (PET) scans, or plain films are not considered adequate imaging techniques to measure bone lesions and do not need to be repeated routinely but can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques, such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.

In the event that a CT PET/CT scanner is used for tumor assessments, the CT portion of the PET/CT scan must meet the criteria for diagnostic quality.

In the event that the local imaging facility cannot perform MRI, CT scans of the head may be performed instead.

Patients without brain or bone disease at baseline do not need brain or bone scans at subsequent tumor assessments unless clinically warranted.

4.6.5.2 Primary CNS Tumors Assessments

For patients with primary CNS tumors, all assessments must be performed by MRI. If the local radiology facility cannot perform MRI, the patient cannot be enrolled in the study.

4.6.5.3 Corticosteroid Use for Primary CNS tumors

For patients with primary CNS tumors, corticosteroid intake should be captured at all tumor assessment visits and compared with corticosteroid intake at the time of the previous tumor assessment. The changes will be recorded as "stable or decreased" or "increased" on the RANO response pages. Increases and decreases in corticosteroid intake should be clinically justified. Increases in corticosteroid dose for reasons other than for CNS disease control do not need to be taken into consideration when making this comparison.

4.6.6 Laboratory, Biomarker, and Other Biological Samples

The following laboratory tests will be performed centrally or locally (refer to the country-specific operations manual):

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Coagulation: PT or INR, and aPTT or PTT
- Chemistry panel: Sodium, potassium, chloride, glucose, creatinine, creatinine clearance (according to Cockcroft and Gault method), gamma-glutamyl transferase, total protein, albumin, phosphorus magnesium, calcium, total and direct bilirubin, ALP, CPK, ALT, AST, uric acid, and BUN or urea
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. A urine pregnancy test must also be obtained at baseline before first dose of study drug is administered (unless a negative serum test was obtained within 10 days of first dose of study drug, in which case the urine pregnancy test is not required). Urine pregnancy tests will be performed at specified subsequent visits as per the schedule of activities (see Appendix 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Urinalysis, using dipstick (pH, specific gravity, glucose, protein, ketones, blood)

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

- Plasma sample for PK analysis

  PK plasma samples will be taken during screening or before the first dose. At subsequent visits, the time of sample draw and the time of the last dose must be captured in the $eCRF$. 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 2. Patients who permanently

discontinue alectinib will also discontinue from all PK sampling and assessments. Plasma concentrations of alectinib and its metabolite(s), as applicable, will be measured by a specific, validated liquid chromatography-tandem mass spectrometry assay.

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.

- Plasma samples for exploratory research on biomarkers

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

  Plasma samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools. Blood will be collected to prepare for cfDNA analysis at the required timepoints (see Appendix 2).

- Tumor tissue sample from patients with F1LCDx and F1HEME results will be analyzed retrospectively by F1CDx tissue NGS (see Appendix 2, Table 3).
- Tumor tissue sample from patients enrolled with local ALK-positive NGS testing will be analyzed retrospectively by F1CDx tissue NGS. Plasma may be accepted in absence of tissue for the analyses. The Medical Monitor *is available to advise as needed*. Information about the local laboratory report (laboratory name, sample type, date, test type, result) will be collected (see Appendix 2, Table 3).
- Tumor tissue for the prospective determination of the ALK status in case of an unacceptable per protocol criteria local ALK test result

The tumor samples must be formalin-fixed, paraffin-embedded (FFPE) tissue blocks with greater than 20% tumor content. Blocks are preferred. If blocks cannot be sent, 11 slides cut at 4–5um thick may be submitted. *The Medical Monitor is available to advise as needed*.

Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected by means of resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

NGS may be performed by Foundation Medicine if local ALK testing is not under the protocol criteria (i.e., by immunohistochemistry). If performed by means of prospective testing by Foundation Medicine, the investigator may obtain an NGS report through Foundation Medicine's web portal. 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 purposes of guiding future treatment decisions. Results will not be available for samples that do not meet criteria for testing.

Using FMI for retrospective analysis of tissue, the CDx program will be performed according to local regulations.

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 (see Section 4.6.9), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tumor and plasma samples (and their derivatives) 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 archival tissue blocks will be returned upon request or no later than the time of final closure of the study database, whichever occurs first.

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.

Given the complexity and nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to 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.

Special Considerations for Blood Sampling

An mHCP, who may be a phlebotomist, will draw blood and process samples at the patient's home per laboratory manual using the laboratory kits provided by the central laboratory (at scheduled or unscheduled home visits). Samples will be centrifuged as necessary and shipped to the central laboratory for analysis, along with the original

completed laboratory transmittal form (a copy of the form will be sent to Science 37, and a photograph of the original will be uploaded into the Science 37 Platform).

Sharps and used tubes will be placed into sharps containers and shipped by the mHCP for appropriate destruction. Results reported by the central laboratory will be uploaded into the eCRF for review, assessment, and documentation by the investigator.

In the event that local laboratories are used (for example if patient is required to visit local specialists or the local oncologist), the results will be obtained and uploaded on the eCRF by the CRC for documentation and the investigator's review.

4.6.7 Electrocardiograms

Single ECG recordings will be obtained at screening, baseline, and at the treatment discontinuation visit. ECGs will also have to be obtained if bradycardia with a resting heart rate below 60 bpm is observed and during study conduct as clinically indicated.

The mHCP will perform an ECG at the patient's home per the schedule of activities, including handling electrodes and leads placement, confirming lead quality tracing with the investigator, and capturing the ECG tracing. After the mHCP performs the ECG, the tracing is automatically captured by the vendor's ECG portal.

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. ECG 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). 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.

The investigator will assess the quality of the tracing in real time by accessing the ECG portal. The CRC will upload the final report in the eCRF for final sign-off by the investigator. The following should be recorded in the eCRF: 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, together with any morphologic waveform changes or other ECG abnormalities. The investigator may consult with a cardiologist as required. Copies of ECG tracings will be kept in the Science 37 Platform as part of the patient's permanent study files. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If 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 two successive ECGs. Standard-of-care treatment

may be instituted per the discretion of the investigator. The investigator should 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 5.1.2.

4.6.8 Clinical Outcome Assessments

PRO questionnaires will be completed to assess the treatment benefit of alectinib. In addition, PRO questionnaires will allow to capture each patient's direct experience with alectinib.

PRO data will be collected through use of the following instruments: EORTC QLQ-C30 and EQ-5D-5L.

4.6.8.1 Data Collection Methods for Clinical Outcome Assessments

PRO questionnaires will be collected on paper by the mHCP at the patient's home during the visit as per scheduled of activities (Appendix 1). The completion of the questionnaire will be performed independently by patients at the start of the visit, before discussion with patients about any results, or health status, and prior to any other study assessments that could bias patient's responses to ensure validity of the questionnaire is not compromised and that data quality meets regulatory requirements.

The PRO questionnaires will be collected at baseline and subsequently as per schedule of activities until the treatment discontinuation visit, withdrawn of consent, death, or study termination, whichever occurs first.

PRO questionnaires will be made available in different languages and will be provided by the Sponsor.

Patients should be given the following instructions for completing PRO questionnaires at home:

- Patients should complete the instruments in a quiet area with minimal distractions and disruptions.
- Patients should answer questions to the best of their ability; there are no right or wrong answers.
- Patients should not obtain advice or help from others (e.g., mHCP, family members, or friends) when completing the instruments.

4.6.8.2 Description of Clinical Outcome Assessment Instruments

EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 7).

There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated, reliable self-reported questionnaire (Aaronson et al. 1993) (see Appendix 8). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea) and global health/quality of life, with a recall period of the previous week. The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

4.6.9 Optional Samples for Research Biosample Repository

4.6.9.1 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 biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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

4.6.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by the IRB/EC and, if applicable, an appropriate regulatory body. Only if the IRB/EC has

granted approval for RBR sampling, this section of the protocol (Section 4.6.9) will be applicable.

4.6.9.3 Sample Collection

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 solid tumors, diseases, or drug safety:

- Leftover plasma collected for biomarkers and leftover tissue samples (with the exception of remaining archival tissue blocks, which will be returned) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS 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 or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples 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.

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

All RBR samples 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).

4.6.9.4 Confidentiality

All RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples 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 samples, data derived from these analyses will generally not be provided to 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 samples 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.

4.6.9.5 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 samples. 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 samples and data will continue to be used as part of the RBR research.

4.6.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples 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 RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the study, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.6.9.7 Monitoring and Oversight

All RBR samples 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 samples 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. 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.

4.7 TREATMENT, PATIENT, AND STUDY DISCONTINUATION

Patients will continue on study treatment until disease progression, discontinuation, withdrawal of consent, or death, whichever occurs first.

Treatment beyond radiological progression is possible in the event of isolated lesion progression if, in the investigator’s opinion, there is evidence of ongoing clinical benefit.

In the event of a patient’s voluntary withdrawal of consent, the investigator will make a reasonable effort to document the reported reason for consent withdrawal in the eCRF. All efforts will be made to complete the assessments prior to study withdrawal, as detailed in the protocol.

For patients whose status is unclear because they fail to communicate with the study personnel without confirming discontinuation or withdrawal, study personnel will show due diligence by documenting all actions taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.).

Patients will not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

4.7.1 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 determination that treatment discontinuation is in the best interest of the patient
- Pregnancy

- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Any event that meets stopping criteria defined in Section 5.1.2

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients with ALK-fusion tumors who are enrolled in the study and do not receive any dose of study treatment will be replaced.

The mHCP will perform a treatment discontinuation visit 28 days after the final dose of alectinib for safety assessments as described in the schedule of activities (see Appendix 1).

If alectinib is prematurely discontinued for reasons other than disease progression, off-treatment disease assessments must continue until radiological progression of the disease as per schedule of activities (see Appendix 1). Following progression, patient status, and subsequent therapies will be captured as long-term follow-up every 3 months until death, patient withdrawal of consent, or termination of the study, whichever occurs first.

4.7.2 Patient Discontinuation from the Study

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 patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination
- Adverse event
- Patient loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the eCRF.

Patients who wish to discontinue alectinib prematurely remain in the study. If patients wish to stop scheduled assessments after alectinib discontinuation, they will be asked to be contacted regularly for long-term follow-up.

If a patient requests to be withdrawn from the study completely, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.7.3 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.

4.7.4 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 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 with patients with NSCLC. For a complete summary of safety information, refer to the Alectinib Investigator's Brochure.

During the study visits conducted in the patient's homes, the following parameters will be evaluated and the investigator will use results of these procedures to assess safety throughout the study:

- Physical examinations (directed by the investigator via videoconference with the assistance of a mHCP)
- Vital signs and weight
- Laboratory tests
- ECGs

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 study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, dosage modification and treatment interruption or discontinuation are provided below.

5.1.1 Risks Associated with Alectinib

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

5.1.1.1 Interstitial Lung Disease and Pneumonitis

Cases of interstitial lung disease and pneumonitis, some leading to acute respiratory distress syndrome or death, have been associated in patients receiving TKIs, including ALK inhibitors. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at higher risk of pulmonary events.

Guidelines for management and follow-up of patients who develop ILD or pneumonitis are provided in Table 1.

5.1.1.2 Hepatotoxicity

Hepatobiliary findings were observed in both rat and monkey 4- and 13-week toxicity studies with alectinib at or close to clinically relevant exposures. Hepatobiliary effects included increased hepatic ALP, direct bilirubin, gamma-glutamyl transferase and liver weight, vacuolation, degeneration, and necrosis of the 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 in patients. AST, ALT, and total bilirubin levels temporarily increased in the initial stages of treatment and then improved. In patients with Grade 3 and 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 1.

5.1.1.3 Anemia*, Including Hemolytic Anemia*

Hematologic findings were observed in both rat and cynomolgus monkey 4- and 13-week toxicity studies with alectinib. *The* findings were at or close to clinically relevant exposures. *Changes in red blood cell morphology (e.g., poikilocytosis, red cell fragmentation) and in the erythroid system's other parameters (e.g., reticulocyte count, hemoglobin, hematocrit, mean corpuscular volume) were seen with alectinib, but these changes were very slight, considered reversible*, and *did not exacerbate with prolonged alectinib administration*.

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

Guidelines for *anemia (including hemolytic anemia)*, adverse event*s'* management, and follow-up are provided in Table 1.

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.

Sodium lauryl sulfate (SLS) 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 due to SLS is not because of systemic toxicity but is a consequence of local irritation to the GI tract. In general, tolerability is improved when SLS is administered together with food.

Guidelines for management and follow-up of patients who develop GI disorders are provided in Table 1.

5.1.1.5 Skin Disorders

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

Results of an in vitro phototoxicity study indicated that alectinib may have phototoxic potential, and cases of skin rash and photosensitivity (generally Grades 1 and 2) have been reported with alectinib.

Guidelines for management and follow-up of patients who develop skin disorders are provided in Table 1.

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 with 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 1.

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 1.

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 alectinib.

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

Events of bradycardia have been reported with alectinib. Data based on ECG and pulse measurements from 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 Table 1.

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 glomerular filtration rate, renal failure, and/or renal impairment have been reported for other ALK inhibitors.

Guidelines for management and follow-up of patients who develop abnormal renal function are provided in Table 1.

5.1.1.10 Severe Myalgia and CPK Elevations

Post-marketing 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 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 1.

5.1.1.11 Dysgeusia

Events of dysgeusia have been reported with ALK inhibitors. With alectinib, these are generally of Grades 1 and 2 severity. All patients who experienced dysgeusia continued alectinib treatment without any dose modification.

In case of dysgeusia adverse event related to alectinib, refer to adverse event grade-dependent rules for dose modification outlined in Table 1.

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 1.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

The dose of alectinib can be reduced in steps of 150 mg up to two times for the 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 two dose reductions, the patient must discontinue alectinib. Administration of a dose below 300 mg BID is not allowed in this study.

5.1.2.2 Treatment Interruption

Alectinib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If alectinib has been withheld for >21 days because of toxicity, the patient should be discontinued from alectinib, unless resumption of treatment is *approved by the* investigator *following consultation* with the Medical Monitor *if needed.* Alectinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures), *at the investigator's discretion,* following consultation with the Medical Monitor *if needed*. The investigator *may consult the Medical Monitor to determine* the acceptable length of treatment interruption.

5.1.2.3 Management Guidelines

Table 1 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 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. Second episode: If improvement to Grade ≤ 1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID. Third episode: Permanently discontinue alectinib. 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 or baseline occurs within 10 days alectinib may be restarted at the original dose or dose reduced by 150 mg (1 capsule) at the investigator's discretion. If improvement to Grade ≤ 1 or baseline occurs after 10 days but within 21 days then alectinib dose must be decreased by 150 mg (1 capsule BID). Second episode: If improvement to Grade ≤ 1 or baseline 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 5.3.5.4 and Section 5.3.5.6. At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible.

Table 1 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× ULN • ALT or AST >5× ULN for more than 2 weeks • First observation of ALT or AST >3× ULN and total bilirubin >2×ULN • First observation of ALT or AST >3× 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 1 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 5.3.5.4. If at any time during the study treatment serum creatinine increases by ≥2× 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 ≥2× 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 outlined 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 5.3.5.4. Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK 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 1 Guidelines for Management of Risks, Adverse Events, and Selected Laboratory Abnormalities with Alectinib (cont.)

Bradycardia [b]	Grade 2 or Grade 3 • Temporarily withhold for a maximum of 21 days (after which the drug must be permanently withdrawn) until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia, or to a heart rate of ≥ 60 bpm. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, resume at reduced dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Grade 4 • Permanently discontinue if no contributing concomitant medicinal product is identified. • If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm within 21 days, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
Hemolytic anemia	*If hemoglobin concentration is <10 g/dl (Grade ≥2) and hemolytic anemia is suspected, withhold alectinib and initiate appropriate laboratory testing in accordance with local clinical practice guidelines. If hemolytic anemia is confirmed, resume alectinib at a reduced dose (see the general dose modification table, Section 5.1.2.1) 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.*

AE = adverse event; BID = twice a day; CPK = creatine phosphokinase; 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.

5.2 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 Section 5.3.5.8, Section 5.3.5.9 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 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; 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 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator and site designee (e.g., the mHCP or CRC) are 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 communicated by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF by the investigator.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

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

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.1.1 Special Considerations Related to Decentralized Study Design

Supervision of patients during trial conduct includes identifying, managing, and assessing safety events. Patients will agree, as a part of the consenting process, to report potential adverse events as soon as possible to study personnel (investigator, mHCP, or clinical trial coordinator), with the study issued smartphone facilitating communication between the patient and the investigator and study personnel.

Adverse events may be reported in a variety of ways, including but not limited to: spontaneous communication by the patient; observations via telemedicine by study personnel or the investigator; observations by the mHCP who visits the patients' homes; communications to study personnel from the patients' health care providers or specialists; and/or documentation of events in medical records provided by patients' health care providers or specialists.

As soon as a patient communicates a possible adverse event, or study personnel are alerted to a possible adverse event through laboratory results or review of medical records, the investigator will evaluate the patient. The investigator will call or have a videoconference with the patient to evaluate the adverse event and determine the course of action. The investigator will use his or her medical judgment and dose modification rules as described in the protocol to determine the appropriate care needed to address the adverse event. Examples of actions that could be taken include, but are not limited to, management via telemedicine, referral to the patient's local oncologist, referral to specialist physician (such as neurologist or cardiologist) or urgent care, immediate referral to a local emergency department, and/or request to call *a local emergency number (e.g., 911 in the United States)* immediately, as appropriate.

Additionally, during the study visits conducted in the patients' homes, the following will be evaluated, and the investigator will use results of these procedures to assess safety throughout the study:

- Physical examinations (directed by the investigator via videoconference with the assistance of a mHCP
- Vital signs and weight
- Laboratory tests, including urine pregnancy test
- ECGs

As soon as study personnel become aware of a safety event, the investigator will assess the event according to medical practice, the protocol, the Alectinib Investigator's Brochure, and IRB requirements. The assessment can occur in a multitude of ways, including review of medical records, communication with study patients, communication with other medical providers, and communication with study personnel. Events assessed as serious adverse events or adverse event of special interest (see Section 5.4.1), as well as pregnancy (see Section 5.4.3), will be reported to the Sponsor within the required 24-hour window (see Section 5.2.2). The investigator is responsible for informing and updating study personnel regarding safety events and for reporting adverse events and serious adverse events to the Sponsor, as required.

Sponsor or Sponsor designee will prepare and submit reports of all safety events, including serious adverse events, to the IRB per the IRB reporting requirements.

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 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 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: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether 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 3):

- 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 3 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 re-challenge.
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).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.

- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe 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 three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × 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

(adverse event of special interest or serious 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 5.3.5.4) 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).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the malignancy under study should be recorded on the Death Attributed to Progressive Disease 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 IMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. 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.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of ALK-Positive Tumor

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 (or RANO criteria for primary CNS tumors). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 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
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

5.3.5.11 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 or qualifies as an adverse event of special interest, 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, 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, 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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 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. The mHCPs are expected to review the PRO data to make sure all questions have been completed before leaving the patient's home. Investigators 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)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for All Science 37 Locations

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

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. These events will be entered on the Adverse Event eCRF immediately (i.e., no more than 24 hours after learning of the event).

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of alectinib. 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. A report will be generated and sent to Roche Safety Risk Management by the electronic data capture (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 email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 28 days after the final dose of study 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of study drug. 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 final dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or 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, 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 embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as 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 the final dose of study drug), all deaths, regardless of cause, 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 through use of the reference safety information in the document listed below:

Drug	Document
Alectinib	Alectinib Investigator's Brochure

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 following populations are defined:

- The response-evaluable population is defined as all patients with ALK fusion (excluding patients with CUP and CNS primary tumors) solid tumors with measurable disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study drug.
- All populations are defined according to the investigator or by blinded independent center review (BICR), depending on who is assessing the endpoint.
- The response-evaluable population with measurable CNS disease at baseline is defined as all patients with measurable CNS disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study drug.
- The primary CNS tumor response-evaluable population is defined as 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.
- The CUP response-evaluable population is defined as all patients with CUP with measurable disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study drug.
- The ALK-mutations response-evaluable population is defined as all patients with ALK mutations with measurable disease at baseline evaluable according to RECIST v1.1 who receive at least one dose of study drug.

The primary analysis will be performed on the response-evaluable population.

Secondary analyses will be performed on the response evaluable population, the measurable CNS disease at baseline response-evaluable population, the primary CNS tumor response evaluable population, the CUP response-evaluable population, and the ALK mutation response-evaluable population, separately. The DOR will be assessed in the patients with confirmed or unconfirmed objective response, as appropriate.

Safety analyses will be performed on all enrolled patients who receive at least one dose of study drug.

Details of all above analyses will be provided in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

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% 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 4.

Table 4 ORR Scenarios with Associated 95% CI

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

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%.

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment, study treatment administration, reasons for discontinuation from study treatment, and reasons for premature study discontinuation will be listed and summarized, including any related to COVID-19. Reasons for screen failure will be extracted from the Science 37 Platform, listed, and summarized. Major protocol deviations, including major deviations of inclusion/exclusion criteria, as well as any related to the COVID-19, will be reported and summarized.

6.3 SUMMARIES OF DEMOGRAPHIC 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 proportions for categorical variables, as appropriate.

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

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR as assessed by investigator per RECIST v1.1, defined as the proportion of patients with an objective response. An objective response is defined as a CR or a PR per 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.

An estimate of the ORR and its 95% CI using the Clopper-Pearson method will be calculated.

The primary efficacy analysis population consists of 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.

An interim analysis will be performed as described in Section 6.9.

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 CR or PR, unless they progressed or withdrew from sooner from the study.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are presented in Section 2.1.2.

6.4.2.1 Secondary Endpoint Definitions

The secondary endpoint definitions are as follows.

Confirmed Objective Response Rate

Proportion of patients with a confirmed objective response by BICR. An objective response is defined as a CR or a PR per 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 non-responders.

An analysis of this endpoint will also be performed on the basis of RANO criteria assessed by investigator and BICR in patients with primary CNS tumors. Confirmation of objective response is not required for patients with ALK mutations.

Duration of Response

Duration of response 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 method will be used to estimate the median DOR with 95% CIs.

An analysis of this endpoint will also be performed on the basis of RANO criteria assessed by the investigator and BICR in patients with primary CNS tumors. Confirmation of objective response is not required for patients with ALK mutations.

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 Kaplan-Meier method will be used to estimate the median PFS with 95% CIs.

An analysis of this endpoint will also be performed on the basis of RANO criteria assessed by investigator and BICR in patients with primary CNS tumors.

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. CNS CR and PR will be assessed by BICR. The analysis method is the same as for the primary endpoint. Confirmation of objective response is not required.

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 method is the same as for the DOR defined above. Confirmation of objective response is not required.

Overall Survival

OS 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 Kaplan-Meier method will be used to estimate the median OS with 95% confidence limits.

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

6.4.3 Exploratory Biomarker Endpoints

The following exploratory biomarker endpoints are described in Section 2.4:

- Relationship between biomarkers found in circulating 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

The primary analysis will be repeated for the subgroups of patients with results from FMI tests and with results from non-FMI tests, respectively.

6.5 SAFETY ANALYSES

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

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

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms and graded according to NCI CTCAE v5.0. All adverse events that occur on or after the first study drug dose (treatment-emergent adverse events) will be summarized using descriptive statistics (i.e., frequencies and percentages) by mapped term, appropriate thesaurus level, and severity grade (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

modification 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 experience the same event on more than one occasion will be counted only once in the calculation of the event frequency.

Summaries of all adverse events considered to be treatment-related (serious adverse events, adverse events of special interest, and all listings of adverse events) will include all events that occur on or after the first study drug treatment. On the other hand, summaries of adverse events considered by the investigator to be unrelated to treatment will include treatment-emergent adverse events with onset up to 28 days after the final dose of alectinib 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. Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion or discontinuation 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), and race.

6.6 PHARMACOKINETIC ANALYSES

The 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®) (Beal et al. 1999) 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.

6.7 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 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 characteristic 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.

6.8 HEALTH STATUS UTILITY ANALYSES

The QLQ-C30 and EQ-5D-5L questionnaires will be used to assess the impact of alectinib on patients' quality of life and daily function. Completion and compliance rates will be summarized by number and proportion of patients among those expected to complete each questionnaire at each timepoint.

The QLQ-C30 and EQ-5D-5L questionnaires 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. Reasons for non-completion will be summarized at each timepoint.

Summary statistics (mean, standard deviation, median, and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

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.

6.9 INTERIM ANALYSIS

A non-binding interim analysis will be performed after 15 RECIST v1.1 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.

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.

The home-based decentralized study can be conducted by investigators with the investigator's institution as the study site or with investigators without institution involvement; if there is no institution involvement, a central virtual study site such Science 37 will be used.

For countries using a virtual study site (i.e., Science 37):

The Science 37 Platform will be used in this trial for countries without investigator's institution (physical study sites) or for countries with no other required or mandated alternatives for the collection and management of source data. The Science 37 Platform complies with Code of Federal Regulations Title 21 Part 11 regulation and is validated and maintained in a validated state throughout the lifecycle of the system. In this trial, the Science 37 Platform will serve as an electronic source documentation tool.

At a minimum, source documents consistent with the type and level of detail that are commonly recorded at study sites will be developed in the Science 37 Platform.

Common for both approaches *(i.e., virtual and physical sites):*

Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system (RAVE). 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 (RAVE).

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

Common for both approaches (i.e., virtual and physical sites):

All eCRFs are to be completed through the *EDC system (RAVE),* which is *Medidata's* designated EDC system. Study personnel will receive training and have access to a manual for appropriate eCRF completion. *All* eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained staff. The Sponsor eCRF database (RAVE) should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, *investigator/*Science 37 *(depending on the approach)* will receive a copy of the RAVE eCRF patient data in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

7.3.1 Virtual Study Sites

In countries with virtual study sites, the Science 37 Platform will be used for source documentation. Patients' medical records, including laboratory reports from central and local laboratories, ECG reports, pathology reports, tumor genetic profiling reports, including local NGS ALK testing report, etc., obtained during the study will be uploaded in the Science 37 Platform. Other records media, such as CDs containing images, will be maintained in a secure location as part of the patient research file.

A study monitor will perform source data verification to confirm that protocol data are accurate, complete, and verifiable from source documents. Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan.

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.

Source documents that are required to verify the validity and completeness of data entered into the Science 37 Platform 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, Science 37 and designated vendors (i.e., for IMP management) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. Science 37 and designated vendors must also allow inspections by health authorities.

7.3.2 Physical Study Sites

In countries with physical study sites, 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 15 years, after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

Roche will retain study data for 25 years after the final 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 applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms) 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.

In this study, informed consent may be obtained electronically using a validated system approved by local regulations. See Section 4.6.1 for details on the process.

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.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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. For the 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, the 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 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 (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, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

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. Prior

to study initiation, 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 prior to study initiation. 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 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.

Approximately 50 patients will be enrolled in this study.

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

- The Precision Enrollment approach offered by FMI. 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
- Patients with ALK-positive NGS test results obtained outside FMI's Precision Enrollment 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.

For sample requirements, see Section 4.6.6 and Appendix 2, Table 3.

For eligible and enrolled patients, the tumor tissue sample must be submitted (see Section 4.6.6 and Appendix 2, Table 3) for retrospective analysis by FMI using the F1CDx assay.

A decentralized, home-based approach will be adopted that minimizes the need of on-site visits for patients, thus making clinical trials more accessible to patients regardless of location. 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 4.6. Accredited local laboratories may be used for patient safety follow-up; local laboratory ranges will be collected.

BICR of tumor assessments will be conducted to determine the secondary endpoints of confirmed ORR, DOR, PFS, CNS ORR, and CNS DOR, all according to RECIST v1.1. In addition, BICR of tumor assessments of primary CNS tumors will be conducted according to the RANO criteria.

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

An IMC will monitor patient safety throughout the study, focusing on death cases and interim futility analysis.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to health care professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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).

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Appendix 1
Schedule of Activities

Assessment	Screening	Treatment Period			Treatment Discontinuation Visit (28 days after Final Dose of Study Drug [±5 days])	Off-Tx Visits [b]	Long-Term Follow-Up [c]
	Days −28 to −1	Baseline (Week 1)	Q2W (±3 days) for the First 12 Weeks [h]	Q4W thereafter until PD, Death, or Withdrawal from Study [a] (±3 days)			
Informed consent	x						
Demographic data	x						
Medical history, baseline conditions	x						
ECOG Performance Status	x	x		x	x		
Vital signs	x	x		x	x		
Weight	x	x		x	x		
Height	x						
Physical examination [d]	x	x		x	x		
ECG	x	x		As clinically indicated	x		
Coagulation [e]	x	x		As clinically indicated	x		
Hematology [f]	x	x		x	x		
Chemistry [g]	x	x		x	x		
Urinalysis, dipstick	x	x		x	x		

Appendix 1: Schedule of Activities

Assessment	Screening	Treatment Period			Treatment Discontinuation Visit (28 days after Final Dose of Study Drug [±5 days])	Off-Tx Visits [b]	Long-Term Follow-Up [c]
	Days −28 to −1	Baseline (Week 1)	Q2W (±3 days) for the First 12 Weeks [h]	Q4W thereafter until PD, Death, or Withdrawal from Study [a] (±3 days)			
Additional mandatory laboratory assessments [h]			x				
Plasma PK sample (2 mL) [i]		x		x			
Plasma sample for biomarkers (10 mL) [j]		x		Only at Week 8, Week 36, and at progression			
Tumor tissue sample [k]	x [l]	x					
Pregnancy test	x [m]	x [n]		Urine pregnancy test Q4W and as clinically indicated	x		
Alectinib dispensing		x		x			
Disease assessment (CT scans)	x			Q8W (±5 days)		Q8W (± 5 days)	
MRI or CT scan of the brain [o]	x			x [p]		x [p]	
Radionuclide bone scan [q]	x						
Concomitant medications	x	x		x	x		
Adverse events	x	x		x	x		
Patient-reported outcomes [r]		x		x	x		
Subsequent therapy and SFU							x

CPK = creatine phosphokinase; CT = computed tomography (scan); eCRF = electronic Case Report Form; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin fixed, paraffin embedded; FMI = Foundation Medicine, Inc.; GGT = gamma-glutamyl transferase; MRI = magnetic resonance imaging; NA = not applicable; NGS = next-generation sequencing; PD = progressive disease; PK = pharmacokinetic; PRO = patient-reported outcome; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RBR = Research Biosample Repository; SFU = survival follow-up; Tx = treatment; WES = whole exome sequencing; WGS = whole genome sequencing.

Notes: Results of laboratory tests and ECG performed within 3 days before first dose of study drug can be used as baseline assessments.

[a] Treatment beyond radiological progression is possible in the event of isolated lesion progression if in the investigator's opinion there is evidence of ongoing clinical benefit. For patient receiving study drug beyond radiological progression, scheduled visits (including disease assessments) will continued to be performed until treatment discontinuation.

[b] For patients who discontinue study treatment prematurely for reasons other than disease progression, tumor assessments should continue until progression.

[c] Required follow-up information (e.g., survival status and information on further cancer therapies and procedures [radiotherapy, surgery]) will be collected via telephone calls every 3 months (±14 days) until death, loss to follow-up, or study termination by the Sponsor. More frequent calls may be required when clinical data cut-offs are performed.

[d] Complete physical examination (head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems). Baseline and post-baseline visits: limited physical examination, symptom-directed, and as clinically indicated. For patients with primary CNS tumors, a neurological examination must be performed at each tumor assessment visit and compared with the neurological examination performed at the time of the last disease assessment.

[e] Coagulation includes PT (or INR) and aPTT (or PTT).

[f] Includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[g] Includes sodium, potassium, chloride, glucose, 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, BUN, or urea.

[h] Additional mandatory laboratory assessments include CPK at 2 weeks after baseline and liver enzymes (ALT, AST, ALP, and total and direct bilirubin) 2, 6, 10, and 12 weeks after baseline. These are in addition to the regular assessments performed Q4W.

[i] Plasma sample for PK to be taken during screening or before first dose of study drug at baseline. At subsequent visits, time of sample draw and last dose of alectinib must be captured. See Appendix 2 for details.

[j] See Appendix 2 for details.

[k] Available (most recent) FFPE tissue block or 11 unstained slides 4–5 μm thick. Tissue sample is not required if ALK positivity was determined by FMI using tissue. A tissue block or 11 unstained slides are also required for all patients who have local ALK-positive test by NGS.

[l] Tumor tissue sample for prospective testing at FMI if local ALK test result is not acceptable for enrollment as specified by the protocol.

[m] During screening, a negative serum pregnancy test must be obtained.

[n] At baseline a negative urine pregnancy test must be obtained before first dose of study drug is administered (unless a negative serum test was obtained within 10 days of first dose of study drug).

[o] For primary CNS tumors, at all tumor assessment visits, corticosteroid use for CNS disease must be compared with the corticosteroid intake at the time of the last disease assessment. Changes in corticosteroid dose for reasons other than for CNS tumor control do not need to be taken into consideration when making this comparison.

[p] As clinically indicated (mandatory Q8W [±5 days] for primary CNS tumors or for patients with CNS metastases at baseline).

[q] A radionuclide bone scan is required at screening for patients with known or suspected bone metastasis.

[r] The PRO questionnaires QLQ-C30 and EQ-5D-5L will be completed by patients at home during the scheduled visits performed by the mobile health care professional. Questionnaires are to be completed before any other visit-related assessment is performed.

Appendix 2
Schedule of Pharmacokinetic and Biomarker Samples

Table 1 Pharmacokinetic Schedule of Activities

Visit	Timepoint	Sample Type
Baseline (Week1)	Predose	Plasma
Week 4 and every 4 weeks thereafter during the treatment period	Record time: drawn plasma and last dose of alectinib	Plasma

Table 2 Biomarker Schedule of Activities

Visit	Sample Type
Screening	Available (most recent) tumor tissue [a]
Baseline (Week 1) [b]	Plasma for biomarkers
Week 8	Plasma for biomarkers
Week 36	Plasma for biomarkers
Disease progression [c]	Plasma for biomarkers

ALK = anaplastic lymphoma kinase; FMI = Foundation Medicine, Inc.

[a] Not necessary if ALK positivity was already determined by FMI on tissue. It includes patients identified outside FMI Precision Enrollment. Plasma may be acceptable after consultation with the Medical Monitor.

[b] Sample to be collected predose.

[c] Plasma for disease progression biomarker will be collected within 30 days of disease progression per investigator's assessment according to Response Evaluation Criteria in Solid Tumors, Version 1.1 or, for patients with primary CNS tumors, Response Assessment in Neuro-Oncology criteria.

ANAPLASTIC LYMPHOMA KINASE (ALK)–POSITIVE TESTS AND REQUIREMENTS FOR TISSUE

Data generated may support possible registration of tissue and plasma next-generation sequencing assays as a companion diagnostic for alectinib across tumor types.

The tests for determination of ALK positivity and tissue requirements are presented in Table 3.

Table 3 ALK-Positive Tests and Tissue Requirements

ALK-Positive Result on	Tumor Tissue Sample	Retrospective Testing
F1CDx	Not applicable	—
F1LiquidCDx	Required	F1CDx
F1HEME	Required	F1CDx
Local NGS testing except FMI F1CDx [a, b]	Required	F1CDx

ALK = anaplastic lymphoma kinase; CDx = companion diagnostic; F1 = Foundation One; FMI = Foundation Medicine, Inc.; NGS = next-generation sequencing.

[a] If tissue is not available, blood may be acceptable after consultation with the Medical Monitor.

[b] If local NGS test is from FMI but is not listed in the table, tissue is also required.

Appendix 3
ECOG 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 4
List of P-gp Substrates

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 benefit–risk assessment 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.

P-gp Substrates
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan

P-gp = P-glycoprotein.

For additional information, please refer to:

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

Appendix 5
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009; Schwartz et al. 2016), are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride PET scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

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

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not-evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm

but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter-measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm

there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, non-CR/non-PD or NE	No	PR
SD	CR, non-CR/non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR	NED [b]	No	CR
PR	NED [b]	No	PR
SD	NED [b]	No	SD
NED [a]	Non-CR/non-PD	No	Non-CR/non-PD
NED [a]	CR	No	CR
NED [a]	NE	No	NE
NED [a]	NED [b]	No	NED
Any non-PD	Any non-PD	NE	NE

CR = complete response; NE = not evaluable; NED = non-evaluable disease; PD = progressive disease; PR = partial response; SD = stable disease,

[a] No target lesions identified at baseline

[b] No non-target lesions identified at baseline.

Table 2 Criteria for Overall Response in Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Timepoint Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
NE	No	NE
Unequivocal progression	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.
Note: Non-CR and non-PD are used instead of stable disease because no lesion can be measured.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table 1 and Table 2.

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

Fluorodeoxyglucose positron emission tomography (FDG PET) is not validated for the use in clinical trials to determine response but can be used to identify new lesions and

may benefit clinical decision-making. Use of FDG-PET imaging to identify new lesions is presented in Table 3.

Table 3 Use of FDG-PET Imaging to Identify New Lesions

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT or MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT or MRI	Additional follow-up CT or MRI scans are needed to determine if there is truly progression occurring at that site. If so: new lesion (PD) with date of PD being the date of the initial abnormal FDG-PET scan date If not: not a new lesion
None	Positive FDG-PET that corresponds to a preexisting site of disease on CT or MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG- = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography; PD = progression disease.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Schwartz LH, Litiére S, de Vries E, et al. RECIST 1.1—update and clarification: from RECIST Committee. Euro J Cancer 2016;62:132–7.

Appendix 6
Response Assessment in Neuro-Oncology (RANO) Criteria

The Response Assessment in Neuro-Oncology (RANO) terminology used for the RANO criteria for characterizes lesions as measurable versus non-measurable and target versus non-target lesions in the brain. Measurable lesions are ones that can be assessed quantitatively. From among the measurable lesions, up to five target lesions will be selected at baseline (to be followed through a patient's treatment course). Once a lesion is selected as a target lesion, it remains a target lesion, even if it falls below the size limits for what is considered as measurable at baseline. The remaining lesions (additional measurable and/or non-measurable lesions) will be categorized as non-target lesions and do not require measurement, only qualititative assessment. For patients with primary CNS disease, any metastases outside the brain are extremely rare. In the event this does occur, the patient will be assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 5) (as a non-target lesion at baseline or new lesion post-baseline).

The parameters for image acquisition are to follow the consensus guidelines and standardized Brain Tumor Imaging Protocol (BTIP) (Ellingson et al. 2015).

RESPONSE ASSESSMENT IN NEURO-ONCOLOGY CRITERIA FOR HIGH-GRADE GLIOMA

Anti-tumor activity will be assessed based on clinical and radiographic evidence as specified by the RANO criteria.

All measurable and non-measurable lesions should be assessed using the same techniques as at baseline. Ideally, patients should undergo imaging using the same magnetic resonance imaging (MRI) scanner or MR scanner of at least the same magnet strength for the duration of the study to reduce difficulties in interpreting changes.

Measurable disease is defined as contrast enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. If there are multiple contrast-enhancing lesions, up to five of the largest lesions that are suitable for reproducible measurements should be selected as target lesions and the sum of the products of the perpendicular diameters of such lesions should be determined. If the MRI is performed with thicker slices (>5 mm), the minimum size of a measurable lesion at baseline should be two times the slice thickness. If there are interslice gaps, the perpendicular diameters must be at least two times the sum of the slice thickness and interslice gap for lesions to be considered measurable at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered non-measurable unless there is a nodular component measuring ≥ 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Lesions with a necrotic component can be selected as target lesions if they are the only lesion(s) present, otherwise they should be selected as non-target lesions.

Non-measurable disease is defined as either other enhancing measurable lesions, masses with margins not clearly defined (non-enhancing FLAIR or T2 lesions) or enhancing lesions with maximal perpendicular diameters less than the minimum size for measurability (e.g., 10 mm).

Radiographic response should be determined in comparison to the tumor measurements obtained at pretreatment baseline (see Table 1). The smallest tumor measurements at either pretreatment baseline or after initiation of therapy should be used for determination of progression. Target lesion response categories are defined by changes in enhancing tumor measurements; non-target lesions are assessed qualitatively (see Table 2). Target lesion, non-target lesion (both enhancing and non-enhancing), and new lesion status are combined as the radiologic (MRI) timepoint response (see Table 3). The MRI timepoint response is combined with clinical status and corticosteroid use to derive the overall response per the RANO criteria.

Table 1 Target Lesion Response Categories

Response	Definition
CR	Disappearance of all target lesions
PR	≥ 50% decrease in SPD of longest diameters, taking as reference the baseline SPD with no evidence of progressive disease
SD	Neither sufficient shrinkage to qualify for a PR, nor sufficient increase to qualify for PD
PD	≥25% increase in the SPD of the longest diameters and the greatest perpendicular diameter of target lesions compared with the smallest recorded sum (nadir) during the study
NE	One or more target lesions cannot be assessed or accurately determined or were excised or irradiated and have not re-appeared or increased. If in the event of one or more NE target lesions, the remainder of the evaluable target lesions compute to a response of PD (a 25% increase in the SPD of the longest diameters), then the target response will be PD (not NE). If there is a change in modalities and the reader is not confident that the images are truly comparable or reflect underlying biology, NE should be selected unless there is visually clear progression of these lesions.

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; SPD = sum of products of perpendicular diameters.

Table 2 Radiologic (MRI) Timepoint Response Categories in RANO Criteria for HGG

Target Lesions	Non-Target Lesions			New Lesions	MRI Timepoint Response
	Contrast Enhancing (T1)	Non-Contrast Enhancing (FLAIR T2)	Combined		
CR	Complete disappearance	Stable or improved	CR	No	CR
CR	Stable or NE	Stable or improved	SD	No	PR
PR	No unequivocal progression	Stable or improved	SD	No	PR
SD	No unequivocal progression	Stable or improved	SD	No	SD
NE	No unequivocal progression	Stable or improved	SD	No	NE
PD	Any	Any	—	Any	PD
Any	Unequivocal progression	Any	PD	Any	PD
Any	Any	Unequivocal progression	PD	Any	PD
Any	Any	Any	—	Yes	PD
NA [a]	Complete disappearance or stable	Stable or improved	CR or SD	No	SD
NA [a]	NA [b]	Not worse	SD	No	NED

CR = complete response; FLAIR = fluid-attenuated inversion recovery; HGG = high-grade glioma; MRI = magnetic resonance imaging; NA = not applicable; NE = not evaluable; NED = no evidence of disease; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.

[a] No target lesions identified at baseline.

[b] No non-target lesions identified at baseline.

Table 3 RANO Criteria: Incorporating MRI and Clinical Factors

Response	Criteria for High-Grade Glioma
CR	Requires all of the following: • Confirmed CR on MRI (response sustained for at least 4 weeks with no signs of progression) sustained for at least 4 weeks • Patients must be off corticosteroids (or on physiological replacement doses only) • Clinical status is stable or improved Note: Patients with non-measurable disease at baseline only cannot have a CR; the best response possible is SD.
PR	Requires all of the following: • Confirmed PR on MRI (response sustained for at least 4 weeks with no signs of progression) • Same or lower dose of corticosteroids compared to baseline • Clinical status is stable or improved Note: Patients with non-measurable disease only cannot have a PR; the best response possible is SD.
SD	Requires both of the following: • SD on MRI • Clinical status is stable or improved Note: In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: • PD on MRI • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose • Failure to return for evaluation due to death or deteriorating condition

CR = complete response; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology.

MEASURING LESIONS THAT SPLIT OR COALESCE ON TREATMENT

In case of lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

MEASURING LESIONS THAT BECOME TOO SMALL TO MEASURE

During the study, all target lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions that are recorded as target lesions at baseline become so faint that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be selected and added to the sum of the SPD

Increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have progression. The date of progression should be the first time point at which corticosteroid increase was necessary.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the Karnofsky or Lansky Performance Status from 100 or 90 to 70 or less, a decline in Performance Status of at least 20 from 80 or less, or a decline in Performance Status from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose.

Patients with non-measurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of $\geq$ 10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0-mm skip) will also be considered to have experienced progression. The transition from a non-measurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9×9 mm lesion [non-measurable] increasing to a 10×11 mm lesion [measurable]). Ideally, the change should be significant ($>$ 5 mm increase in maximal diameter or $\geq$ 25% increase in the sum of the products of perpendicular diameters of enhancing lesions).

In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the patient may continue treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the timepoint at which this issue was first raised.

REFERENCES

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 2010;8:1963–72.

Wen PY, Chang SM, Van den Bent M, et al. Response Assessment in Neuro-Oncology Clinical Trials; J Clin Oncol 2017;35:2439–49.

RANO CRITERIA FOR LOW-GRADE GLIOMA

To be assessed using same methodology as described above for HGG assessed according to the RANO criteria with the exception that RANO LGG assessments will focus on FLAIR T2-weighted MRI sequences for analysis (see Table 4). However, progression will also include evidence of enhancement (T1-weighted MRI sequences).

Table 4 Radiology Lesion Timepoint Response Categories in RANO Criteria for LGG

Target Lesions (FLAIR T2)	Non-Target Lesions (FLAIR T2)	New Lesions (FLAIR T2, T1)	Timepoint Response
CR	CR	No	CR
CR	SD or NE	No	PR
PR	Any non-PD or NE	No	PR
MR	Any non-PD or NE	No	MR
SD	Any non-PD or NE	No	SD
NE	Any non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NA [a]	CR or SD	No	SD
NA [a]	NA [b]	No	NED

CR = complete response; FLAIR = fluid-attenuated inversion recovery; LGG = low-grade glioma; MR = minor response; NA = not applicable; NE = not evaluable; NED = no evidence of disease; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.

[a] No target lesions identified at baseline.

[b] No non-target lesions identified at baseline.

Table 5 Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria for Low-Grade Glioma
Complete response	Requires all of the following criteria compared with the baseline scan: • Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely) • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients must be off corticosteroids or only receiving physiological replacement doses. • Patients should be stable or improved clinically.
Partial response	Requires all of the following criteria compared with the baseline scan: • A ≥ 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Minor response	Requires the following criteria compared with baseline: • A decrease of the area of non-enhancing lesion on T2 or FLAIR magnetic resonance imaging between 25% and 50% compared with baseline • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Stable disease	Is present if the changes do not qualify for complete, partial, or minor response, or progression and requires: • Stable area of non-enhancing abnormalities on T2 or FLAIR imaging • No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement • Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan and should be stable or improved clinically
Progression	Defined by any of the following: • Development of new lesions or increase of enhancement (radiological evidence of malignant transformation) • A 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events • Definite clinical deterioration not attributable to other causes apart from the tumor or decrease in corticosteroid dose • Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders

FLAIR = fluid-attenuated inversion recovery; MRI = magnetic response imaging; RANO = Response Assessment in Neuro-Oncology.

Note: Adapted from Wen et al. 2012.

REFERENCES

Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro Oncol 2015;17:1188–98. doi:10.1093/neuonc/nov095.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. J Clin Oncol 2012;28:1963–72.

Appendix 7
EQ-5D-5L

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Health Questionnaire

English version for the USA

Appendix 7: EQ-5D-5L

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

MOBILITY

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

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

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

PAIN / DISCOMFORT

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

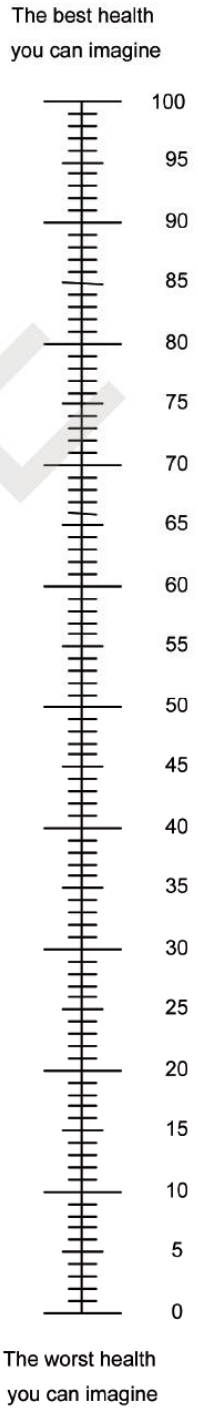
ANXIETY / DEPRESSION

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

Appendix 7: EQ-5D-5L

- 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 = ☐



Appendix 8
European Organisation for the Research and Treatment of Cancer QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9 Investigator Oversight of Study Personnel

All sites

All investigators for this study are qualified and licensed oncologists who are responsible for patient care and execution of the study. The investigator may use the infrastructure and delegate study-related activities to personnel at their site or external vendors as necessary. The investigators will need to fulfill their responsibilities as per Good Clinical Practice, including oversight of all health care providers and vendors who perform study-related activities delegated to them by the investigator.

The description of the operational processes for the specific format of the study conduct applicable to the site (physical site or virtual site) is described in detail in the county-specific operational manual.

In order to allow flexibility to participate in the study there are two *operational* approaches that *can* be used for study conduct *as outlined below.*

Virtual sites in the United States (Science 37 Metasites)

In the United States, these investigators will be geographically dispersed throughout the country. Investigators will sign a U.S. Food and Drug Administration (FDA) Form 1572.

The Science 37 study team is composed of investigators, mobile health care professionals (mHCPs), clinical research coordinators (CRCs), and the clinical study lead (CSL) who provides project management for the study. In addition to the study team members described above, Science 37 will use service providers for the conduct of the study (e.g., investigational medicinal product [IMP] management by a preferred IMP depot service provider).

All study-team members will receive protocol-specific training from Science 37 and the Sponsor. At the beginning of the study, a study protocol start-up/kickoff meeting will be held via teleconference to prepare the study team for conducting the study and to ensure the team is familiar with the study documentation, administrative procedures, responsibilities, and other relevant study information. The study team will complete additional protocol-specific training, if the protocol changes during the study.

The Science 37 study team will hold regular internal meetings via teleconference to discuss Science 37 operations and study execution. Topics for these meetings may include study status, regulatory updates, adverse events, changes to the protocol or other procedures, and any study-related information that may affect the patient or workflows. The frequency of meetings will be adjusted as necessary. The CSL will be responsible for planning, scheduling, and leading these meetings and will be supervised by the investigators. Meeting minutes will be distributed to ensure all staff are aware of what was discussed and the decisions made during the meeting.

Appendix 9: Investigator Oversight of Study Personnel

Investigator responsibilities for providing supervision in this remote decentralized study are the same as they are in a conventional study and are consistent with those outlined in 21 CFR 312 and ICH E6 (R2) guidance.

Investigators will ensure that the study is conducted according to the investigational plan and that all applicable regulations for protecting the rights, safety, and welfare of patients are followed. The Science 37 Platform enables ongoing communication between all members of the study team. Investigators will communicate directly with the CSL, mHCP, and CRCs via teleconference, email, phone, text, or any appropriate and convenient mode of communication throughout the study as necessary. In addition, investigators will have real-time access to study $source$ data within the Science 37 Platform.

Investigators in this study will delegate certain study-related tasks to other members of the study team. When an investigator delegates study-related tasks, he or she is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator will ensure that all study staff adhere to the study protocol (i.e., inclusion and exclusion criteria, safety assessments, safety monitoring, assessment of adverse events and reporting of serious adverse events, reporting of unanticipated problems, etc.). Investigators will oversee mHCP activities by monitoring study-visit data within the Science 37 Platform, as well as during live study telemedicine interactions.

Study data will be collected during protocol-defined visits and entered $manually$ into the $eCRF$. Investigators will complete protocol assessments and document directly into the platform. The responsibility for transcribing selected data into the $eCRF$ may also be delegated to the study's CRC. In instances where the data are not directly entered into the $eCRF$ by an investigator, the information will be made available for review during routine core study team meetings and via routine study activities/status update reports to be provided as part of the ongoing oversight process:

- Quality assurance reporting will be provided for investigator review addressing data types focused on the study-specific primary objectives and the data required to answer those objectives.
- Data entry and documentation that require regulatory submissions will be reviewed and signed off by the investigator (protocol deviations, Investigator's Brochure submissions, protocol amendments, etc.).

Any issues related to study operations and study personnel will be discussed during regularly scheduled meetings or escalated ad hoc as necessary. Relevant meeting discussions and decisions will be documented in meeting minutes, circulated for reference, and filed in the Investigator Site File.

Issues related to the IMP that take place during delivery between Roche and the IMP depot or during storage at the depot will be reported to Roche by the IMP depot and/or Science 37 upon identification, in line with Roche's reporting requirements directed in the IMP management manual. The IMP depot will keep records of the communication and will inform Science 37 in a timely manner. IMP issues taking place after study drugs are shipped to the patients' homes will be documented in the Science 37 Platform and reported to Roche as instructed in the study protocol and IMP management manual.

The study team will ensure that all communication and records associated with this study, including those that demonstrate appropriate and required oversight, will be saved and archived. All research records will be available for inspection by authorized representatives of federal regulatory agencies, the Sponsor, and/or the Institutional Review Board. Each investigator will ensure that the following records in the Investigator Site File are maintained by Science 37, and the investigator will have access to review these documents in real time:

- A list of qualified persons to whom the investigator has delegated significant research-related duties
- All records submitted to the Institutional Review Board with evidence of approval
- All records of the disposition of the IMP
- Current curriculum vitae of the investigator and study personnel
- Appropriate documentation regarding study-specific Science 37 Platform access distinguishing all persons and roles authorized to make entries or corrections on data collection forms
- Reports to document findings of study monitoring

Physical Sites (Investigator-Associated Institutions) *in all countries, including the United States*

Science 37 may not be involved. The investigator will use the hospital infrastructure to conduct the study.

When physical study sites are used:

- There will be no Science 37 coordinator; rather, the site coordinator will conduct activities delegated by the investigator.

  The site coordinator will liaise with the mHCP vendor to coordinate visits to the patient's home and set up the telemedicine sessions with the investigator and the patient.
- The investigational medicinal product can be managed by the hospital's pharmacy or by another licensed pharmacy if necessary.
- Safety samples can be analyzed by a central or a local lab (investigator's site).

- The investigator will make arrangements for imaging assessments to be completed as per-protocol at a facility, ideally one that is close to the patient's home or to the investigator's site.
- The patient will be visited by a licensed mHCP who has been delegated to perform the assessments as per protocol.
- The investigator will use the hospital medical records as the source documents, including completed patient-reported outcomes and informed consent forms. The mHCPs will share their notes with the investigator as detailed in the country-specific operations manual. Data will be reported in RAVE by the investigator *or investigator delegate* as in the traditional clinical trial model, and on-site monitoring will take place at the investigator's site.