

Clinical Development

LDK378 (Ceritinib)

LDK378A2205 / NCT02336451

**A Phase II, multi-center, open-label, five-arm study to evaluate the efficacy and safety of oral ceritinib treatment for patients with ALK-positive non-small cell lung cancer (NSCLC) metastatic to the brain and/or to leptomeninges**

**RAP Module 3 (SAP) – Detailed Statistical Methodology**

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**Document History – Changes compared to previous version of RAP module 3.**

Version	Date	Changes
Draft 1.0	05-Aug-2015	Original version
Amendment 1.0	11-Mar-2019	<p>Section 1:</p> <ul style="list-style-type: none"><li>Standard languages added to clarify that the SAP should be finalized before database lock</li></ul> <p>Section 1.1:</p> <ul style="list-style-type: none"><li>Details added describing the study design with regards to each study arm</li><li>Timeline for primary and final analysis updated to align with protocol amendment 6</li></ul> <p>Section 1.2:</p> <ul style="list-style-type: none"><li>Details added for the definition of primary endpoint in Section 1.2.1</li><li>Details and clarification added for other secondary objectives for endpoints and study arms in Section 1.2.2</li></ul> <p>Section 2.1:</p> <ul style="list-style-type: none"><li>Study arms used with regard to the general presentation of descriptive summaries updated</li><li>Subgroup analysis removed</li></ul> <p>Section 2.2:</p> <ul style="list-style-type: none"><li>Per-protocol set was removed</li><li>[REDACTED]</li></ul> <p>Section 2.3:</p> <ul style="list-style-type: none"><li>By prior radiation to the brain and by prior ALK inhibitor use analyses removed</li><li>Details of summaries of diagnosis and extent of cancer, medical history, and prior anti-cancer therapy were updated to align with eCRF</li></ul> <p>Section 2.4:</p> <ul style="list-style-type: none"><li>Summary of major protocol deviations leading to exclusion from PPS removed</li></ul> <p>Section 2.5:</p> <ul style="list-style-type: none"><li>By prior radiation to the brain and by prior ALK inhibitor use analyses removed</li><li>Details of summaries of disposition were updated to align with eCRF</li></ul> <p>Section 2.6:</p>

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Version	Date	Changes
		<ul style="list-style-type: none"><li>• Baseline definitions for general efficacy and safety evaluations moved from Section 2.8.2</li><li>• Exposure by prior radiation to the brain and by prior ALK inhibitor use analyses removed</li><li>• Kaplan-Meier analysis for dose reduction or interruption removed</li></ul>
		Section 2.7: <ul style="list-style-type: none"><li>• Definition and derivation algorithm of best overall response moved from Section 2.8.1.2 to Section 2.7.1. The cut-off for SD too early and PD too late was updated based on tumor assessment schedule.</li><li>• Subgroup analysis and PPS analysis were removed from Section 2.7.4</li></ul>
		Section 2.8: <ul style="list-style-type: none"><li>• Description of secondary efficacy endpoints moved from Section 2.8.1 to Section 2.8.1.2</li><li>• Table 2-1 updated to remove supportive analysis and subgroup analysis. IDCR and EDCR at week 8 and week 16 added.</li><li>• PPS analysis and subgroup analysis removed from Section 2.8.1.1</li><li>• OIRR, TTIR and DOIR analyses based on all patients added in Section 2.8.1.2</li><li>• IDCR and EDCR at week 24 updated to at week 8 and week 16. Algorithms on derivation of IDCR and EDCR at 8 and 16 weeks added. Similar analyses based on patients with measurable brain metastases added for IDCR in Section 2.8.1.2</li><li>• Methods used for TTIR, TTER and TTR analyses changed from KM method to descriptive summary in Section 2.8.1.2</li><li>• The strategy of handling start of new anticancer therapy updated from censoring to the new standard of ignoring for DOIR, DOER, DOR and PFS analyses in Section 2.8.1.2.</li><li>• Supportive and PPS analyses for ORR and DCR per BIRC removed in Section 2.8.1.2</li><li>• Gap analyses removed from Section 2.8.1.2</li><li>• On treatment deaths, by primary SOC and PT, AESI leading to study drug discontinuation, two safety disclosure tables added and subgroup analysis for AEs removed in Section 2.8.2</li></ul>

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Version	Date	Changes
		<ul style="list-style-type: none"><li>• Lab parameter updated to include RBC and direct bilirubin; Urinalysis listings were removed; Categories for liver function tests updated in Section 2.8.2</li><li>• The denominator used for the percentage calculation for ECG abnormality was further clarified; respiration rate removed from vital sign analysis; Clarification for the analysis of WHO PS added in Section 2.8.2.1</li><li>• [REDACTED]</li><li>• [REDACTED]</li><li>• Sample size calculation and power analysis updated to align with protocol amendment in Section 2.9 and Section 2.10</li><li>• A preliminary interim analysis for arm 5 added in Section 2.11</li></ul>
		Section 3: <ul style="list-style-type: none"><li>• Table 3 added to include the changes to protocol specified analyses</li></ul>
		Section 4: <ul style="list-style-type: none"><li>• Patient classification into analysis sets removed</li><li>• Further details were added for the derivation of last contact date in Section 4.2</li><li>• Age derivation added as Section 4.4</li><li>• “New anticancer therapy will defined for whole body, intracranial, and extracranial separately” added; PFS censoring reasons updated in Section 4.6.1.</li><li>• Details of PROC LIFETEST added in Section 4.6.4</li><li>• Baseline ECG definition updated in Section 4.7</li><li>• Imputation rule for death date updated in Section 4.8.6</li><li>• Imputation rule for concomitant medication date added as Section 4.8.2 and imputation incomplete dates for disease progression prior to start of study drug added as Section 4.8.8</li></ul>

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## 1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical methods for all safety, efficacy, [REDACTED], [REDACTED] analyses for study LDK378A2205 final clinical study report.

The content of this SAP is based on [LDK378A2205](#) study protocol [Amendment 6](#). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

### 1.1 Study design

This is a phase II, multi-center, open-label, five-arm study in which the efficacy and safety of oral ceritinib treatment will be assessed in patients with NSCLC metastatic to the brain and/or to leptomeninges harboring an ALK rearrangement using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria). The study will enroll approximately 160 patients globally.

Patients with ALK-positive NSCLC and active metastases to the brain and/or to leptomeninges will be included in this study. Patients without evidence of leptomeningeal carcinomatosis (LC) will be allocated into 1 of the 4 arms taking into account the patient's history of prior therapy: prior radiation therapy (whole brain or stereotactic radiation therapy) to the brain (yes/no) and prior treatment with an ALK inhibitor (ALKi) (yes/no) ([Table 1-1](#)). The allocation of patients into the five study arms are described below.

**Table 1-1 Allocation into Study Arms based on prior radiation to brain (yes/no) and prior treatment with ALK inhibitor (yes/no)**

	Prior Radiation to the brain: YES	Prior Radiation to the brain: NO
Prior treatment with a ALKi <sup>1</sup> : YES	Arm 1	Arm 2
Prior treatment with a ALKi: NO	Arm 3	Arm 4
Leptomeningeal disease <sup>1</sup>	Arm 5	

<sup>1</sup>Previous treatment with ALK inhibitors other than crizotinib is not allowed in Arms 1, 2 and 5.

The description of patients in each of the five study arms is as follows:

- Arm 1 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain and with prior exposure to an ALKi.
- Arm 2 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain but with prior exposure to an ALKi.
- Arm 3 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously treated with radiation to the brain but with no prior exposure to an ALKi.
- Arm 4 will include patients with metastases in the brain without evidence of leptomeningeal carcinomatosis, previously untreated with radiation to the brain and with no prior exposure to an ALKi.



- Arm 5 will include any patients with leptomeningeal carcinomatosis with or without evidence of active lesion at the baseline Gadolinium-enhanced brain MRI.

All patients will receive the same treatment regimen regardless of the arm to which they are allocated. Treatment with ceritinib will continue until the patient experiences disease progression (in the brain, outside of the brain or both) as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinues treatment at the discretion of the patient or investigator, lost to follow-up, death, or study is terminated by the Sponsor.

Tumor response will be evaluated starting from the first day of treatment with ceritinib until the time of disease progression according to RECIST 1.1 as determined by investigator, withdrawal of consent for further follow-up, loss to follow-up or death. This schedule of tumor assessments must continue regardless of dose interruptions. In patients who discontinue treatment in the absence of progression, tumor assessments will continue every 8 weeks until progression of disease, withdrawal of consent for further follow-up, loss to follow-up or death.

Primary analysis of any of the study arms or overall will occur only after enrollment in the specific study arms or overall is complete and all patients have completed at least 24 weeks of treatment with ceritinib or have discontinued earlier respectively. The study will end when both of the following conditions are met:

1. At least 24 weeks after last patient treated in the study.
2. At least 75% of patients have died, have been lost to follow-up, or have withdrawn consent for survival follow-up, **or** the last patient will be able to enter into a separate rollover study and/or other options for continued treatment, whichever comes first.

If the end of study criteria is met before the primary analysis is conducted, a single final analysis and study report may be performed. If the end of the study criteria is not met by the time that the primary analysis is conducted, a final CSR will be produced reporting all available data collected up to last patient last visit (LPLV) including the additional study data collected after the primary analysis.

## **1.2 Objectives**

### **1.2.1 Primary objective**

The primary objective is to evaluate the antitumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1. The primary endpoint is the overall response rate (ORR) defined as the proportion of patients with a best overall confirmed response of complete response (CR) or partial response (PR) in the whole body as assessed per RECIST 1.1 by the investigator.

### **1.2.2 Key secondary and other secondary objectives**

The key secondary objective is to evaluate Disease Control Rate (DCR) in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges based on investigator assessment per RECIST 1.1. The DCR is defined as the proportion of patients with a best overall response of CR, PR or SD in the whole body, as assessed by the investigator per RECIST 1.1.

Other secondary objectives are:

- To evaluate intracranial tumor-response related endpoints (OIRR, IDCR, TTIR and DOIR) as assessed by investigators and Blinded Independent Review Committee (BIRC) (using modified RECIST 1.1 criteria)
- To evaluate extracranial tumor-response related endpoints (OERR, EDCR, TTER and DOER) as assessed by investigators and BIRC (using RECIST 1.1 criteria)
- To evaluate whole body tumor-response related endpoints as assessed by investigators (TTR, DOR and PFS) and BIRC (ORR, DCR, TTR, DOR and PFS) (using RECIST 1.1 criteria)
- To evaluate overall survival (OS) in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges
- To evaluate safety in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges

### 1.2.3 Exploratory objectives

- To evaluate intracranial endpoints for patients with measurable brain metastases at baseline in Arms 1 to 4 (OIRR, TTIR and DOIR) and for patients with active brain lesions at baseline in Arms 1 to 4 (IDCR) using the Response Assessment in Neuro-Oncology (RANO) criteria for high grade gliomas (Wen et al 2010) by investigators and BIRC.

## 2 Statistical methods

This section and its subsections will be imported to [Section 9.7](#) of the CSR after the analyses have been conducted.

The text will be changed to the past tense when imported into the CSR; references to [Section 4](#) of the RAP, where additional details are provided for programming implementation, may be removed in the CSR.

In what follows, study drug refers to LDK378 (certinib).

## 2.1 Data analysis

Data will be analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis [Section 10](#) of the LDK378A2205 protocol, which will be available in [Appendix 16.1.1](#) of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided, as applicable, in [Section 4](#) from which [Appendix 16.1.9](#) of the CSR will be extracted.

SAS<sup>®</sup> version 9.4 (or later version if available at time of database lock) will be used in all analyses.

Data from all patients who signed main informed consent in centers that participate in this study will be used in the analysis. Data collected after withdrawal of informed consent will not be reported. Due to expected small size of enrollment at individual centers, no center effect will be assessed. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock. Data collected after patients' withdrawal of informed consent for further participation in the study will not be reported (except for death date, which might be obtained from public records).

[Section 4.1](#) provides further details regarding data to be included in the analyses.

### General presentation of descriptive summaries

Qualitative data (e.g., gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant population or subgroup, as the denominator.

Continuous data (e.g., age, body weight) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

All baseline characteristics, efficacy (except intracranial endpoints by RANO) and safety analyses will be presented by study arm (Arm 1, Arm 2, Arm 3, Arm 4 and Arm 5) and for all patients.

In addition, all efficacy endpoints, except intracranial endpoints by RANO, will be presented by prior radiation to the brain (Arms 1+3 vs. Arms 2+4) and by prior ALK inhibitor use (Arms 1+2 vs. Arms 3+4) and overall, for patients from Arms 1 through 4, unless otherwise specified. Intracranial endpoints by RANO will be presented by study arm for patients in Arm 1 to Arm 4 and overall, for patients from Arms 1 through 4.

## 2.2 Analysis sets

A patient is considered to be enrolled into the study if they have signed a study informed consent. Only patients who have signed a study informed consent will be included in the analysis data sets.

### Full Analysis Set

The Full Analysis Set (FAS) consists of all patients who received at least one dose of study drug.

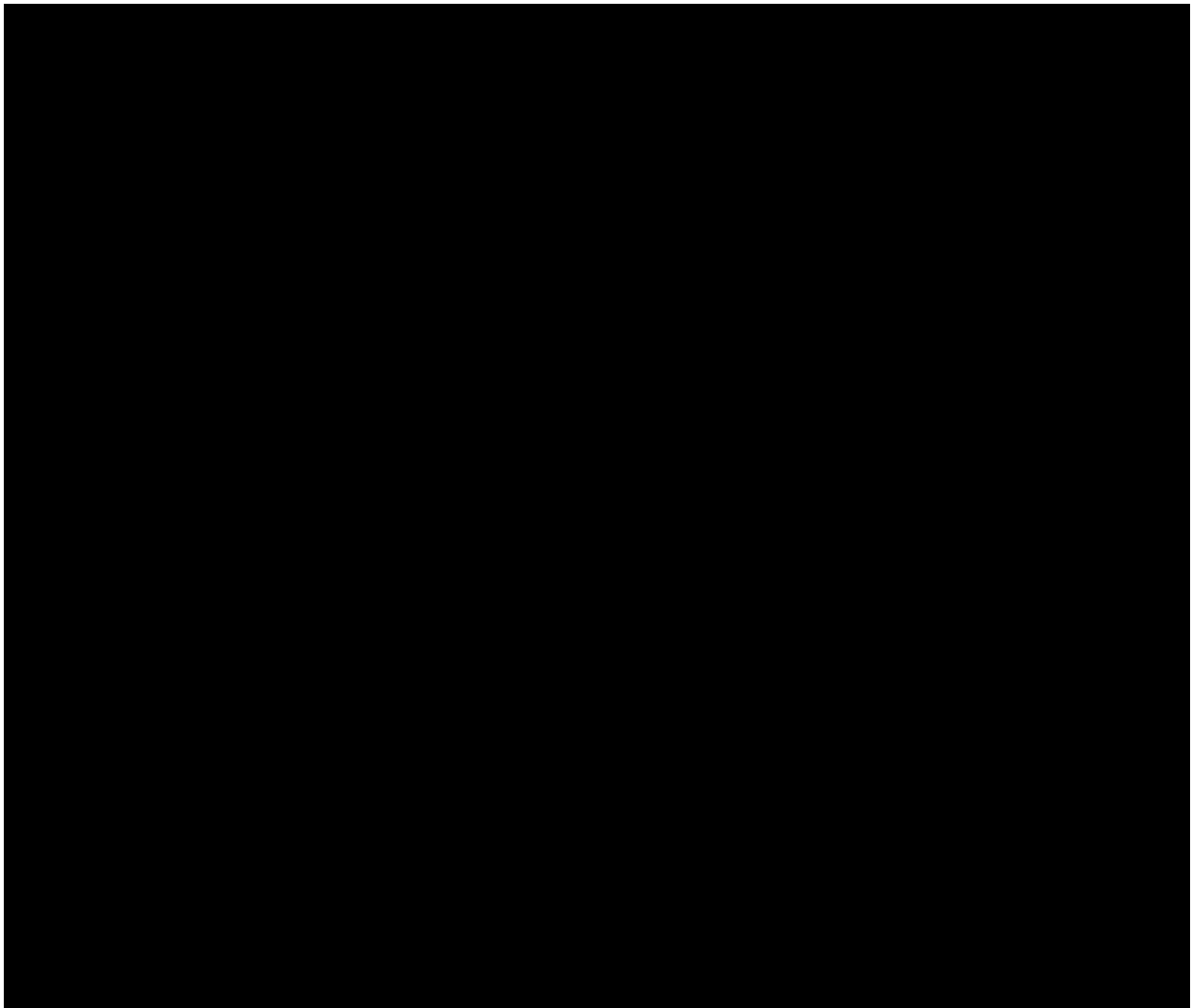
The FAS will be used for summaries of baseline characteristics and all efficacy analyses, unless otherwise specified.

The following endpoints will be analyzed on a subset of FAS:

Patients with measurable brain metastases: Overall intracranial response rate (OIRR), Time to intracranial tumor response (TTIR) and Duration of intracranial response (DOIR)

### **Safety Set**

The Safety Set consists of all patients who received at least one dose of study drug. All safety data will be analyzed using the Safety Set. The FAS and Safety Set in this study are identical.



### **2.3 Patient demographics and other baseline characteristics**

The FAS will be used for all patient demographic and baseline characteristic summaries and listings, unless otherwise specified. Summaries will be produced by study arm and for all patients. Listings will be produced by study arm.

## Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized by study arm and for all patients. Categorical data (e.g. gender, race, ethnicity, WHO performance status, age groups: <65, 65-<85, ≥85 years, smoking history) will be summarized by frequency count and percentages. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (as defined in [Section 2.1](#)).

## Diagnosis and extent of cancer

Descriptive statistics and frequency counts and percentages will be tabulated by study arm, as appropriate, for diagnosis and extent of cancer based on the data collected on the electronic Case Report Form (eCRF) including primary site of cancer, predominant histology/cytology, histological grade, time (in months) from initial diagnosis of primary site, stage at initial diagnosis, stage at time of study entry, time (in months) from initial diagnosis to first recurrence/progression, time (in months) from most recent relapse/progression, metastatic sites of cancer, number of metastatic sites of cancer, types of intracranial and extracranial lesions (target and non-target lesions) at baseline based on investigator and BIRC assessment, Intracranial lesion (target and non-target) location at baseline, disease burden (intracranial, extracranial and whole body) at baseline for target lesion based on investigator and BIRC (based on the data collected on the RECIST eCRF page).

## Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms, will be summarized and listed by study arm. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term, in each study arm and all patients. Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

## Prior anti-cancer therapy

Prior anti-neoplastic (anti-cancer) therapy will be listed in three separate categories: 1. medications, 2. radiotherapy, and 3. surgery.

The number and percentage of patients who received any prior anti-neoplastic medications, prior antineoplastic therapy Crizotinib, prior anti-neoplastic radiotherapy, prior anti-neoplastic radiotherapy to the brain, or prior anti-neoplastic surgery will be summarized by study arm and for all patients.

Prior anti-neoplastic medications will be summarized by study arm. Summaries will include chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens (crizotinib and other), therapy type, setting, best response at last treatment, time from last treatment start to progression and duration of last treatment best response. Prior antineoplastic medications will also be summarized by ATC class, preferred term and study arm. Prior antineoplastic therapy crizotinib will be summarized by study arm and includes setting, best response at last crizotinib treatment, time from last crizotinib treatment start to progression, duration of last crizotinib treatment best response and reason for discontinuation of last crizotinib treatment.

For radiotherapy and radiotherapy to the brain, time since last radiotherapy end to treatment start, locations, setting and method of last therapy will be summarized. For prior surgery, time since last surgery, procedure and residual disease at last surgery will be summarized. ATC class and preferred term will also summarize steroid use at the start of study drug.

## Screening phase disposition

A patient who signs study informed consent but fails to satisfy all of the eligibility criteria for any reason will be considered a screen failure. These patients are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled patients as follows:

- Number (%) of patients who completed screening phase (based on the presence of study phase completion date and the 'Next phase entered' is 'Treatment' in the 'Screening Phase Disposition' page);
- Number (%) of patients who discontinued during screening phase (based on the presence of date of discontinuation and discontinuation / "subject status" reason entered and 'Will the subject continue into the next phase of the trial' is 'No' in the 'Screening Phase Disposition' page);
- Reasons for screening phase discontinuation (based on reasons recorded in Screening Phase Disposition' page).

All screen failure patients with reasons for screen failure will be listed.

## 2.4 Protocol deviations

Frequency counts and percentages of patients in the FAS with any CSR reportable protocol deviations (related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be tabulated by the deviation category by study arm and for all patients.

All protocol deviations will be listed.

## 2.5 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated by study arm.

Related to the treatment phase:

- Number (%) of patients who are still on-treatment (based on the absence of the 'End of Treatment Disposition' page);
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment Disposition' page with date of discontinuation and reason of discontinuation/ 'Subject Status' entered);
- Number (%) of patients who entered post treatment follow-up phase from treatment phase (based on 'Next Phase Entered' is 'Post-treatment follow-up' on the 'End of Treatment Disposition' page for patients who discontinued treatment);
- Number (%) of patients who entered survival follow-up from treatment phase (based on 'Will the subject be followed for survival' is 'Yes' on the 'End of Treatment Disposition' page for patients who discontinued treatment);

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- Number (%) of patients who discontinued from study from treatment phase (based on ‘Will subject continue into the next phase of the trial’ is ‘No’ as entered on the ‘End of Treatment Disposition’ page for patients who discontinued treatment);
- Primary reasons for study treatment discontinuation (based on discontinuation reasons entered under ‘Subject Status’ in the ‘End of Treatment Phase Disposition’ page).

Related to the post-treatment follow-up phase:

- Number (%) of patients who are still in the post-treatment follow-up phase (based on presence of ‘End of Treatment Disposition’ and absence of ‘End of Post Treatment Phase Disposition’ page);
- Number (%) of patients who discontinued from the post-treatment follow-up (based on completion of ‘End of Post Treatment Phase Disposition’ page with date of discontinuation and discontinuation reasons entered under ‘Subject Status’);
- Number (%) of patients who entered survival follow-up (based on completion of ‘End of Post Treatment Phase Disposition’ page with date of discontinuation and discontinuation reasons entered under ‘Subject Status’ and ‘Will the subject be followed for survival’ is ‘Yes’ for patients who discontinued from the post-treatment follow-up);
- Number (%) of patients who discontinued from study (based on completion of ‘End of Post Treatment Phase Disposition’ page with date of discontinuation and discontinuation reasons entered under ‘Subject Status’ and ‘Will subject be followed for survival’ is ‘No’ for patients who discontinued from the post-treatment follow-up);
- Primary reasons for discontinuation from the post-treatment follow-up (based on discontinuation reasons entered under ‘Subject Status’ in the ‘End of Post Treatment Phase Disposition’ page).

## **2.6 Treatments (study drug, concomitant therapies, compliance)**

The Safety Set will be used for all medication data summaries and listings unless otherwise specified. Summaries will be produced by study arm and for all patients. Listing will be produced by study arm.

### **Study drug and study treatment**

Study drug and study treatment both refer to LDK378 (ceritinib) and will be used interchangeably.

### **Date of first/last administration of study drug**

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as start date of study drug.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on the DAR eCRF. This date will also be referred to as the last date of study drug.

### **Study day**

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The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

$$\text{Study Day} = \text{Date of the assessment/ Event date} - \text{start date of study drug} + 1.$$

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

$$\text{Study Day} = \text{Event date} - \text{start date of study drug}.$$

The study day will be displayed in the relevant data listings.

## Baseline

Baseline is the result of an investigation describing the “true” uninfluenced state of the patient.

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is taken as “baseline” value or “baseline” assessment.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken or “baseline” assessment.

If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first administration of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing.

If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. See [Section 4.7.2](#) for further details on derivation of baseline for laboratory data and ECGs.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reported to the end of treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

## Dose exposure and intensity

Definitions of duration of exposure, cumulative dose, average daily dose, dose intensity (DI), relative dose intensity (RDI), as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug – first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a patient in the study
- Number of dosing days (days): duration of exposure – number of zero dose days



- Average daily dose (mg/day): cumulative dose (mg)/ number of dosing days (days)
- DI (mg/day): cumulative dose (mg)/ duration of exposure (days)
- RDI (%):  $100 \times [\text{DI (mg/day)}/\text{planned dose intensity (750 mg/day)}]$

Note: given the planned ceritinib dose of 750 mg/day, the planned dose intensity can be calculated as:

$$\text{PDI (mg/day)} = \text{cumulative planned dose (mg)}/\text{Duration of exposure (days)},$$

where

$$\text{cumulative planned dose (mg)} = \text{Protocol planned dose of 750 (mg)} * \text{Duration of exposure.}$$

then, RDI (%) which is calculated as  $100 * \text{DI}/\text{PDI}$  can be simplified as shown above.

Duration of exposure to study drug, cumulative dose, average daily dose, DI and RDI will be summarized by study arm and for all patients. In addition, the duration of exposure to study drug will be categorized into time intervals and frequency counts and percentages of patients with exposure in each time interval will be presented. Frequency counts and percentages of patients who have dose changes, reductions or interruptions, and the corresponding reasons, will be summarized by study arm and for all patients. Time to first dose reduction and time to first dose interruption will be summarized by study arm and for all patients, using summary statistics along with frequency counts and percentages for pre-specified time intervals

Listings of all doses of the study drug along with dose change and dose interruption reasons will be produced.

[Section 4.5](#) provides further details on the definition of dose changes and interruptions.

### Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drug, prior antineoplastic treatments and blood transfusions), surgeries or procedures (including physical therapy) administered in the study and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All summaries will be tabulated using frequency counts and percentages by study arm.

Concomitant therapies will be summarized by ATC class and preferred term by study arm and for all patients. These summaries will include: 1) medications starting on or after the start of study drug but starting no later than 30 days after last dose of study drug; and 2) medications starting prior to the start of study drug but continuing after the start of study drug.

All concomitant therapies and surgeries and medical procedures will be listed. Any concomitant therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study drug will be flagged in the listings.

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## **Antineoplastic therapy after discontinuation of study drug**

The FAS will be used for all listings and summaries of antineoplastic therapies initiated after discontinuation of study drug. All summaries will be tabulated by study arm and for all patients, using frequency counts and percentages.

Antineoplastic medications initiated after discontinuation of study drug will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and listed.

Antineoplastic radiotherapy since discontinuation of study treatment will be summarized and listed.

Antineoplastic surgery since discontinuation of study treatment will be summarized by primary system organ class and preferred term and listed.

## **2.7 Analysis of the primary variable**

The primary objective is to evaluate the anti-tumor activity of ceritinib in patients with ALK-positive NSCLC metastatic to the brain and/or to leptomeninges.

### **2.7.1 Variable**

The primary endpoint used to evaluate the anti-tumor activity of ceritinib is the overall response rate (ORR), which is defined as the proportion of patients with a best overall confirmed response (BOR) of CR or PR in the whole body, as assessed per RECIST 1.1 by the investigator.

### **Best overall response**

The BOR will be assessed based on reported lesion responses at different evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response.

BOR for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression  
PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying as a CR)
- SD = at least one SD assessment (or better) > 7 weeks after start of study drug (and not qualifying as a CR or PR)
- PD = progression  $\leq$  17 weeks after start of study drug (and not qualifying as a CR, PR or SD)
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 7 weeks or progression within the first 17 weeks)

The cut-off for SD too early and PD too late were chosen based on tumor assessment schedule. Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or anti-cancer surgery) will be considered in

the assessment of BOR. If a patient receives any further anti-neoplastic therapy while on study, any subsequent assessments will be excluded from the BOR determination. Further anti-neoplastic therapies will be identified from the data collected on ‘Anti-neoplastic therapies since last date of study drug’ as appropriate. Clinical deterioration will not be considered as documented disease progression. Patients with BOR ‘unknown’ will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- Stable disease (SD) too early ( $\leq 7$  weeks after start date of study drug)
- PD too late ( $> 17$  weeks after start date of study drug).

Special (and rare) cases where BOR is ‘unknown’ due to both early SD and late PD will be classified as ‘SD too early’. In case, a patient had only a non-measurable disease at baseline, same cut-off ( $\leq 7$  weeks after start date of study drug) will be applied for a response of non - CR/non-PD too early.

### 2.7.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed on the FAS. This is an estimation based study and no statistical testing of hypothesis will be conducted.

The primary efficacy endpoint ORR per investigator in the whole body will be estimated and the 95% exact binomial (Clopper and Pearson 1934) confidence intervals (CIs) will be provided by study arm and for all patients. Exact binomial confidence intervals will be used since the confidence limits based on the normal approximation are not bounded by the [0, 1] interval, meaning that for rates close to 0 or 1, the upper limit of the normal approximation interval for the proportion could exceed 1 or the lower limit could be negative.

Additionally, the ORR in the whole body will also be summarized by prior radiation to the brain, prior ALK inhibitor use and overall using the data from Arms 1 through 4.

### 2.7.3 Handling of missing values/censoring/discontinuations

Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR, irrespective of the number of missed assessments before response.

Patients with a best overall response (BOR) of ‘Unknown’ per RECIST 1.1 will be considered as non-responders when estimating ORR. Patients who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of ORR and any other efficacy endpoints.

### 2.7.4 Supportive analyses

Waterfall plots representing the best percentage change from baseline in the sum of the tumor diameters for target lesions will be produced by prior ALKi use (Yes/No) for FAS. See [Section 4.6.1](#) for details on construction of waterfall graphs.

## 2.8 Analysis of secondary variables

### 2.8.1 Efficacy

Table 2-1 summarizes all tumor related endpoints and the population for analysis. The definitions and details on the derivation of the secondary endpoints are given in the following sections. Confirmation of response is required for all response endpoints, as per RECIST 1.1 and RANO. Further details and rules needed for programmatic implementation of RECIST 1.1 guidelines and RANO guidelines are provided in Section 4.6.1 and Section 4.6.2 respectively.

**Table 2-1 Summary of tumor-related efficacy endpoints and analysis populations**

Category	Efficacy endpoints *	By investigators or BIRC	Primary analysis population#
Primary endpoint	ORR	Investigators	FAS
Key secondary endpoint	DCR	Investigators	FAS
Other secondary endpoints			
Intracranial endpoints	OIRR	Both	FAS and FAS subset**
	IDCR	Both	FAS and FAS subset**
	IDCR at week 8 and week 16	Both	FAS
	TTIR	Both	FAS and FAS subset**
	DOIR	Both	FAS and FAS subset**
Extracranial endpoints	OERR	Both	FAS
	EDCR	Both	FAS
	EDCR at week 8 and week 16	Both	FAS
	TTER	Both	FAS
	DOER	Both	FAS
Whole body endpoints	ORR	BIRC	FAS
	DCR	BIRC	FAS
	TTR	Both	FAS
	DOR	Both	FAS
	PFS	Both	FAS
	OS	N/A	FAS
Exploratory endpoints			
Intracranial endpoints	OIRR by RANO	Both	FAS subset**
	TTIR by RANO	Both	FAS subset**
	DOIR by RANO	Both	FAS subset**
	IDCR by RANO	Both	FAS

#: Efficacy endpoints per RECIST or Modified RECIST will be analyzed 1) by study arm and for all patients and 2) by prior radiation to brain and prior ALK inhibitor use and overall for patients in arm 1-4. Efficacy endpoints per RANO will be analyzed by study arm and overall for patients in arm 1-4.

\*: Efficacy endpoints are evaluated by RECIST 1.1 or Modified RECIST 1.1 unless otherwise noted.

\*\* : FAS subset with measurable brain metastases at baseline.

### 2.8.1.1 Key secondary endpoint

The key secondary objective is to evaluate Disease Control Rate (DCR). The DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR or SD in the whole body, as assessed per RECIST 1.1 by the investigator.

DCR will be estimated and the exact binomial 95% CI (Clopper & Pearson, 1934) will be presented by study arm and for all patients.

### Supportive and sensitivity analyses

The DCR will also be summarized by prior radiation to the brain and by prior ALK inhibitor use.

### 2.8.1.2 Other secondary endpoints

The following intracranial, extracranial and whole body (for lesions **in and outside** the brain) tumor-response related endpoints will be assessed separately based on investigator assessment and BIRC assessment per RECIST 1.1 (OERR, EDCR, TTER, DOER, ORR, DCR, TTR, DOR and PFS) or Modified RECIST 1.1 (OIRR, IDCR, TTIR, DOIR).

#### 2.8.1.2.1 Intracranial endpoints

**Overall intracranial response rate (OIRR):** OIRR is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline. The OIRR is defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain as assessed per modified RECIST 1.1.

OIRR will be estimated and the exact binomial 95% CI will be presented by study arm and for all patients. OIRR will also be summarized by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4. OIRR by the investigator and by BIRC will be summarized separately.

Same analysis on OIRR will be conducted for patients having evaluable (measurable or non-measurable) brain metastases at baseline.

**Intracranial disease control rate (IDCR) at 8 and 16 weeks and overall:** IDCR is calculated based on response assessments in the brain for patients having evaluable (measurable or non-measurable) brain metastases at baseline. In what follows, CR, PR and SD are possible responses only for patients with measurable brain metastases at baseline, while non-CR/non-PD is a possible response only for patients without measurable brain metastases at baseline.

- The IDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR, SD or non-CR/non-PD assessment in the brain at Week 8 and Week 16 intracranial tumor evaluations respectively, taking into consideration 4-week window for each assessment, i.e., assessment done between study day 29 and 85 (both inclusive) for week 8 and study day 86 and 141 (both inclusive) for week 16, as per modified RECIST 1.1. If there are multiple tumor assessments within the defined window, the following rules should be used hierarchically to select the overall response contributing to the xx-week IDCR rate:
  - 1) PD - If at least one tumor assessment with overall response of PD;
  - 2) Unknown - if all tumor assessment with overall responses of unknown;

3) CR/PR/SD - Overall response from the latest tumor assessment within the window

The assessment of SD too early or PD too late will be considered as Unknown and following the same rule specified in SAP [Section 2.7.1](#).

- IDCR overall is defined as the proportion of patients with a best overall response of CR, PR, SD or non-CR/non-PD in the brain, as assessed per modified RECIST 1.1.

IDCR will be estimated and the exact binomial 95% CI will be presented by study arm and for all patients. IDCR will also be summarized by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4. IDCR by the investigator and by BIRC will be summarized separately.

Same analysis on overall IDCR will be conducted for patients having measurable brain metastases at baseline.

**Time to intracranial tumor response (TTIR):** TTIR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the brain as assessed per modified RECIST 1.1 criteria for patients with measurable brain metastases at baseline.

TTIR will be summarized by frequency counts in time intervals and using descriptive statistics for patients with confirmed CR or PR.

These analyses of TTIR will be performed separately based on investigator and BIRC assessment.

Same analysis on TTIR will be conducted for patients having evaluable (measurable or non-measurable) brain metastases at baseline.

**Duration of intracranial response (DOIR):** Among patients with measurable brain metastases at baseline and a confirmed response (PR or CR) in the brain per Modified RECIST 1.1, DOIR is defined as the time from the first documented response (PR or CR) in the brain to the date of the first documented disease progression in the brain or death due to any cause. If a patient has not had an event, DOIR is censored at the date of last adequate tumor assessment.

The censoring and event date options to be considered for the main analysis are presented in [Table 2-2](#). Please note that the intracranial/extracranial/whole body tumor assessments apply to intracranial (DOIR), extracranial (DOER) and whole body (DOR and PFS) endpoints, respectively.

**Table 2-2 Outcome and event dates for DOIR, DOER, DOR and PFS analyses**

	Situation	Date	Outcome
A	No baseline intracranial/extracranial/ whole body assessment	Date of first dose of study drug <sup>a</sup>	Censored
B	Progression at or before next scheduled intracranial/extracranial/ whole body assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing intracranial/extracranial/ whole body assessment	Date of progression (or death)	Progressed

	Situation	Date	Outcome
C2	Progression or death after two or more missing intracranial/extracranial/ whole body assessments	Date of last adequate intracranial/extracranial/ whole body assessment <sup>b</sup>	Censored
D	No progression	Date of last adequate intracranial/extracranial/ whole body assessment <sup>b</sup>	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above (ITT approach)	As per above situations

a The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

b After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in [Section 14.2.25](#) of (Appendix 2) of the LDK378A2205 protocol.

DOIR will be described by study arm using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25<sup>th</sup> and 75<sup>th</sup> percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-specified time points.

DOIR will also be summarized by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) using the data from Arms 1 through 4.

These analyses of DOIR will be performed separately based on investigator assessment and based on BIRC assessment.

Same analysis on DOIR will be conducted for patients having evaluable (measurable or non-measurable) brain metastases at baseline.

#### 2.8.1.2.2 Extracranial endpoints

**Overall extracranial response rate (OERR):** OERR is defined as the proportion of patients with a best overall confirmed response of CR or PR outside of the brain, as assessed per RECIST 1.1.

OERR will be estimated and the exact binomial 95% CI will be presented by study arm and for all patients. OERR will also be summarized by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

OERR by the investigator and by BIRC will be summarized separately.

#### **Extracranial disease control rate (EDCR) at 8 and 16 weeks and overall:**

- EDCR at 8 and 16 weeks is defined as the proportion of patients with CR, PR or SD outside of the brain at Week 8 and Week 16 extracranial tumor evaluations respectively, as assessed per RECIST 1.1. Same method will be used as for IDCR. See details in [Section 2.8.1.2.1](#).
- EDCR overall is defined as the proportion of patients with a best overall response of CR, PR or SD outside of the brain as assessed per RECIST 1.1.

EDCR will be estimated and the exact binomial 95% CI will be presented by study arm. EDCR will also be summarized by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

EDCR by the investigator and by BIRC will be summarized separately.

**Time to extracranial tumor response (TTER):** TTER is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) outside of the brain as assessed per RECIST 1.1 criteria.

TTER will be summarized by frequency counts in time intervals and using descriptive statistics for patients with confirmed CR or PR.

These analyses of TTER will be performed separately based on investigator assessment and based on BIRC assessment.

**Duration of extracranial response (DOER):** Among patients with a confirmed response (PR or CR) outside of the brain per RECIST 1.1, DOER is defined as the time from the first documented response (PR or CR) outside of the brain to the date of the first documented disease progression outside of the brain or death due to any cause.

DOER will be described by study arm using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25<sup>th</sup> and 75<sup>th</sup> percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-specified time points. .

Additionally, DOER will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

These analyses of DOER will be performed separately based on investigator assessment and based on BIRC assessment.

#### 2.8.1.2.3 Whole body endpoints

**ORR by BIRC:** The evaluation of ORR will be repeated based on BIRC assessment by study arm and for all patients. Additionally, ORR by BIRC will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

**DCR by BIRC:** The evaluation of DCR will be repeated based on BIRC assessment by study arm and for all patients. Additionally, DCR by BIRC will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

**Time to tumor response (TTR):** TTR is defined as the time from the date of the first dose of ceritinib to the date of the first documented response (CR or PR) in the whole body as assessed per RECIST 1.1 criteria.

TTR will be summarized by frequency counts in time intervals and using descriptive statistics for patients with confirmed CR or PR.



These analyses of TTR will be performed separately based on investigator assessment and based on BIRC assessment.

**Duration of response (DOR):** Among patients with a confirmed response (PR or CR) in the whole body per RECIST 1.1, DOR is defined as the time from the first documented response (PR or CR) to the date of the first documented disease progression or death due to any cause.

DOR will be described by study arm and for all patients using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25<sup>th</sup> and 75<sup>th</sup> percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-specified time points.

Additionally, DOR will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

These analyses of DOR will be performed separately based on investigator assessment and based on BIRC assessment.

**Progression-free survival (PFS):** PFS is defined as the time from the date of the first dose of ceritinib to the date of the first radiologically documented disease progression in the whole body per RECIST 1.1 or death due to any cause. A patient who has not progressed or died at the date of the analysis cut-off will be censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. By default, if disease progression or death for any reason is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death for any reason is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD. Refer to [Table 2-2](#) for censoring and event date options and outcomes for PFS. See also [Section 4.6.1](#) describing the special case of a missing baseline tumor assessment.

PFS will be described by study arm using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25<sup>th</sup> and 75<sup>th</sup> percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-specified time points. Censoring reasons will also be summarized.

These analyses will be performed separately based on investigator assessment and based on BIRC assessment. Additionally, PFS will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

**Overall survival (OS):** OS time is defined as time from the date of first dose of ceritinib to the date of death due to any cause. OS time for patients who are alive by the date of the analysis cut-off or are lost to follow-up will be censored at the date of last contact.

OS will be described by study arm using Kaplan-Meier methods, including estimated median (in months) with 95% CI, 25<sup>th</sup> and 75<sup>th</sup> percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at pre-specified time points. Censoring reasons will also be summarized.

OS will be analyzed by study arm using the data from study arms 1 through 5. However, Kaplan-Meier curves of OS will not be produced for Arm 5 alone if the number of patients enrolled in this arm is  $\leq 10$ .

Additionally, OS will also be presented by prior radiotherapy to the brain (yes, no) and prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4.

### Duration of Follow-up

Follow-up in the study will be summarized using the following methods to provide a comprehensive assessment of follow-up for all patients.

Summary of duration between start date of study drug and cut-off date, and follow-up times for PFS/OS, are defined as follows:

- Duration between start date of study drug and data cut-off date = (Cut-off date – Start date of study drug + 1) / 30.4375 (months).
- Follow-up time = (Date of event or censoring – Start date of study drug + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date (when the patient is known as alive) for OS.

All summaries will be reported in months (see [Section 4.3](#)). The calculations for PFS will be based on investigator assessment and BIRC assessment.

### Exploratory endpoints

[REDACTED]

**OIRR by RANO:** OIRR by RANO will be estimated and the exact binomial 95% CI will be presented by study arm. OIRR by the investigator and by BIRC will be summarized separately.

**IDCR by RANO:** IDCR by RANO will be estimated and the exact binomial 95% CI will be presented by study arm. IDCR by the investigator and by BIRC will be summarized separately.

**TTIR by RANO:** Similar to TTIR by Modified RECIST 1.1, TTIR by RANO will be analyzed using frequency count and descriptive statistics by study arm.

These analyses of TTIR will be performed separately based on investigator assessment and based on BIRC assessment.

**DOIR by RANO:** Similar to DOIR by Modified RECIST 1.1, DOIR by RANO will be analyzed using Kaplan-Meier methods by study arm.

[REDACTED]

### 2.8.2 Safety

All safety analyses will be performed based on the Safety Set by study arm (Arms 1 to 5) and all patients.

### Observation periods for the analyses

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The overall observation period will be divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study drug
- On-treatment period:
  - For discontinued patients, from day of first dose of study drug to 30 days after last dose of study drug
  - For ongoing patients, from day of first dose of study drug to the data cut-off date
- Post-treatment period: starting at day 31 after last dose of study drug

The safety summary tables will include only assessments collected during the on-treatment period.

For select items, shift tables or change from baseline summaries generated for laboratory, ECG, vital signs and change score (WHO PS) generation may use data from pre-treatment period for baseline calculations.

All data, regardless of observation period, will be listed and assessments collected during the pre-treatment and post-treatment period will be flagged in all the listings.

### **Adverse events (AEs)**

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading exists for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected on the "End of Treatment Disposition", "End of Post Treatment Phase Disposition" or "Death" eCRF pages.

All AE summaries will be summarized (frequency counts and percentages) by primary system organ class (SOC) and/or preferred term (PT), maximum severity grades, and relation to study drug except where otherwise noted. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- All deaths, by primary SOC and PT
- On treatment deaths, by primary SOC and PT
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs associated with discontinuation of study drug
- AEs requiring dose adjustment
- AEs requiring study drug interruption
- AEs requiring dose adjustment or study drug interruption
- AEs requiring significant additional therapy

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- AEs excluding SAEs

Per safety disclosure, two tables for on-treatment death/SAE and non-SAE will be summarized but not included in the CSR.

### **Adverse events of special interest**

Adverse events of special interest (AESIs) are defined as AEs within the following categories/groupings of preferred terms:

- Hepatotoxicity
- Interstitial lung disease/pneumonitis
- QTc prolongation
- Hyperglycemia
- Bradycardia
- GI toxicity (nausea, diarrhea, and vomiting)
- Pancreatitis

AESIs are defined at the project level and may be updated based on emergent data to reflect new AESIs at the time of analysis. The AESIs listed above will be identified based on a list of preferred terms. The final list of preferred terms is available in the electronic case retrieval strategy and will be presented in a separate annex of the document. These AESIs will be summarized for each grouping, by preferred term, as follows:

- All AESIs
- CTC grade 3/4 AESIs
- AESIs suspected to be study drug related
- CTC grade 3/4 AESIs suspected to be drug related
- Serious AESIs
- AESI leading to study drug discontinuation
- AESIs requiring dose adjustment or study drug interruption
- AESIs requiring dose adjustment
- AESIs requiring study drug interruption

### **Laboratory data**

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected in the on-treatment period. All laboratory assessments will be listed and those collected prior to first dose of study drug or later than 30 days after study drug discontinuation will be flagged in the listings.

Laboratory data will be classified (by Novartis Oncology Statistical Programming) into CTC grades according to the NCI CTCAE v4.03. For all reports, CTC grade is always obtained on the converted measurement in SI unit. Grade 5 will not be used. The CTC grade 0 will be assigned as below in different scenarios:

1. For laboratory parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
2. For laboratory, parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.
3. For laboratory parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline laboratory values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per CTCAE v4.03. A severity grade of 0 will be assigned when the post-baseline value is  $\leq$  ULN (for hyper) or  $\geq$  LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

The following summaries will be produced for the hematology and biochemistry laboratory data (by laboratory parameter):

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are not defined.

The following lab parameters will be summarized:

- Hematology: absolute lymphocytes, absolute neutrophils, hemoglobin (anemia), WBC, platelet counts, absolute basophils, absolute eosinophils, absolute monocytes, RBC.
- Biochemistry: alkaline phosphatase (ALP), SGPT (ALT), SGOT (AST), total bilirubin, amylase, lipase, potassium (hyper and hypo), sodium (hyper and hypo), creatinine, glucose (hyper and hypo), phosphate, albumin, calcium (corrected for albumin), magnesium, creatinine clearance, direct bilirubin, blood urea nitrogen (BUN) or urea, GGT.
- For bi-directional parameters, both hyper and hypo summaries will be presented.

All hematology and biochemistry will be listed as per protocol. Further, following laboratory parameters will be presented in listings and will not be summarized:

- Coagulation: INR, pro-thrombin time (PT) or Quick Test.

Other laboratory parameters collected and not described above may be summarized if clinically indicated.

The following listings will be produced for the laboratory data for all laboratory parameters where CTC grades are defined:

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4.
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Liver function tests (LFTs) of interest for ceritinib are total bilirubin (TBILI), ALT, AST and ALP. In what follows, AT refers to ALT or AST values. LFTs will be summarized as follows:

- Shift tables of baseline vs. worst post-baseline on-treatment values for the categories:
  - $TBILI \leq 2xULN$ ,  $TBILI > 2xULN$  and missing TBILI
  - $ALT \leq 3xULN$ ,  $ALT > 3xULN$  and missing ALT
  - $AST \leq 3xULN$ ,  $AST > 3xULN$  and missing AST
  - $ALP < 2xULN$ ,  $ALP \geq 2xULN$  and missing ALP
- Frequency counts and percentages of patients with worst post-baseline on-treatment values in the categories:
  - $ALT > 3xULN$ ,  $ALT > 5xULN$ ,  $ALT > 10xULN$ ,  $ALT > 20xULN$
  - $AST > 3xULN$ ,  $AST > 5xULN$ ,  $AST > 10xULN$ ,  $AST > 20xULN$
  - $AT > 3xULN$ ,  $AT > 5xULN$ ,  $AT > 10xULN$ ,  $AT > 20xULN$
  - $TBILI > 2xULN$
  - Concurrent  $ALT > 3xULN$  and  $TBILI > 2xULN$
  - Concurrent  $AST > 3xULN$  and  $TBILI > 2xULN$
  - Concurrent  $AT > 3xULN$  and  $TBILI > 2xULN$
  - Concurrent  $AT > 3xULN$  and  $TBILI > 2xULN$  and  $ALP < 2xULN$
  - Concurrent  $AT > 3xULN$  and  $TBILI > 2xULN$  and  $ALP \geq 2xULN$

Concurrent measurements are those occurring on the same date.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline  $TBILI > 2xULN$ ,  $ALT > 3xULN$  or  $AST > 3xULN$  will be provided.

### 2.8.2.1 Other safety data

#### ECGs

ECG data will be analyzed based on central laboratory reported results. The summaries will include all ECG assessments performed in the on-treatment period. All ECG assessments will be listed, and those collected prior to first dose of study drug or later than 30 days after study drug discontinuation will be flagged in the listing.

#### Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where RR represents the RR interval of the ECG, in seconds.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. An alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on linear or log-linear regression methods which yield, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model  $QT = a + b * RR$  to baseline data
- Use the estimated slope,  $\hat{b}$ , to correct QT
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b} * (1 - RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

#### ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate – denoted as HR in what follows, and QTc) as noted.

- Pearson correlation between QT and HR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments and separately using on-treatment assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- For each of the QTc and QT intervals, shift tables based on notable parameter categories ( $\leq 450$ ,  $>450 - \leq 480$ ,  $>480 - \leq 500$ ,  $>500$  ms) at baseline and the worst post-baseline value observed
- Frequency counts and percentages of patients having notable ECG values according to the following categories:
  - QT parameter (QT, QTc) increase from baseline  $>30$  ms,  $>60$  ms
  - Newly occurring post-baseline QT parameter  $> 450$  ms,  $> 480$  ms,  $> 500$  ms
  - HR increase from baseline  $> 25\%$  and value  $> 100$  bpm
  - HR decrease from baseline  $> 25\%$  and value  $< 50$  bpm
  - PR increase from baseline  $> 25\%$  and value  $> 200$  ms
  - Newly occurring post-baseline PR  $> 200$  ms and  $\leq 220$  ms,  $> 220$  ms
  - QRS increase from baseline  $> 25\%$  and value  $> 110$  ms
  - Newly occurring post-baseline QRS  $> 110$  ms and  $\leq 120$ ms,  $> 120$  ms

The denominator to calculate percentages for each category is the number of patients at risk for a specific category. For new abnormality post baseline values, this is the number of patients with both baseline and post baseline, and baseline not meeting the criteria. For abnormal change from baseline, this is the number of patients with both baseline and post baseline evaluations. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline

- Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages for any newly occurring ECG abnormality, each abnormality type and each individual finding is the number of patients with both a baseline and a post-baseline evaluation, and baseline being normal, i.e. those patients who are at risk of developing this abnormality. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed by patient, time point and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

## Vital signs

Vital sign assessments will be performed in order to characterize basic body function. The parameters collected are weight (kg), body temperature (°C), pulse rate (beats per minute), and sitting systolic and diastolic blood pressure (mmHg).

Clinically notable elevated values are defined as:

- Systolic BP:  $\geq 160$  mmHg and an increase  $\geq 20$  mmHg from baseline
- Diastolic BP:  $\geq 100$  mmHg and an increase  $\geq 15$  mmHg from baseline.
- Body temperature:  $\geq 39.1^{\circ}\text{C}$
- Weight: increase from baseline of  $\geq 10\%$
- Pulse rate:  $\geq 120$  bpm with increase from baseline of  $\geq 15$  bpm

Clinically notable below normal values are defined as:

- Systolic BP:  $\leq 90$  mmHg and a decrease  $\geq 20$  mmHg from baseline
- Diastolic BP:  $\leq 50$  mmHg and a decrease  $\geq 15$  mmHg from baseline
- Body temperature:  $\leq 35^{\circ}\text{C}$
- Weight: decrease from baseline of  $\geq 10\%$
- Pulse rate:  $\leq 50$  bpm with decrease from baseline of  $\geq 15$  bpm

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP.



Descriptive statistics will be tabulated by study arm for baseline and changes from baseline to worst post-baseline value for each vital sign measure.

Patients with clinically notable vital sign abnormalities will be listed by study arm. All vital sign assessments will be listed by study arm, patient and vital sign parameter.

In the listings, clinically notable values will also be flagged.

### WHO performance status

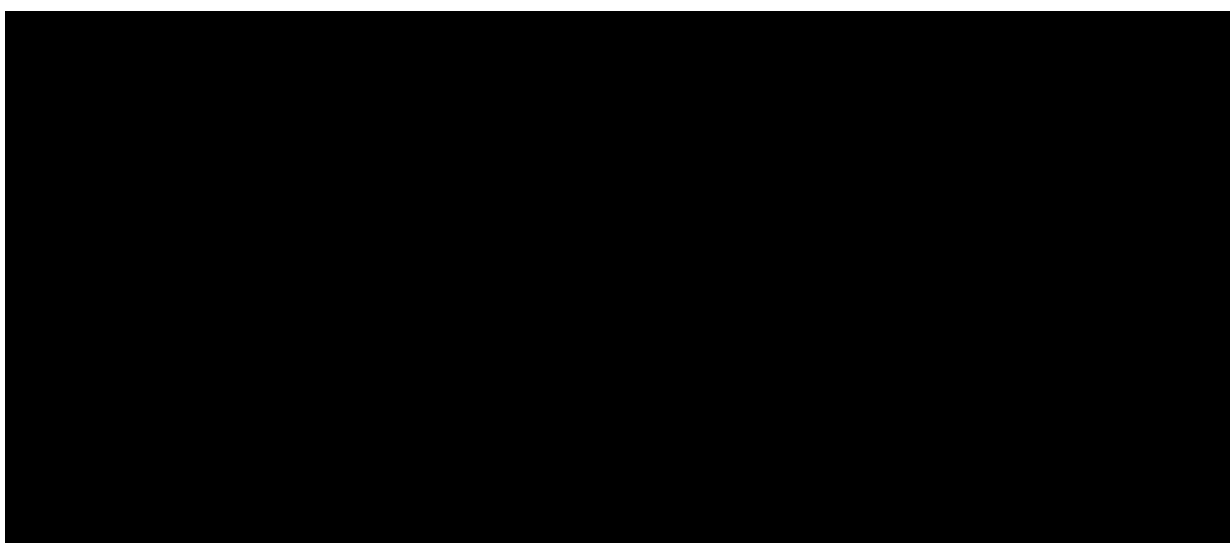
The WHO performance assessment allows patients to be classified as to their functional impairment, the definition of scores in relation to their performance status is provided in [Table 2-3](#), ranging from 0 (most active) to 5 (dead):

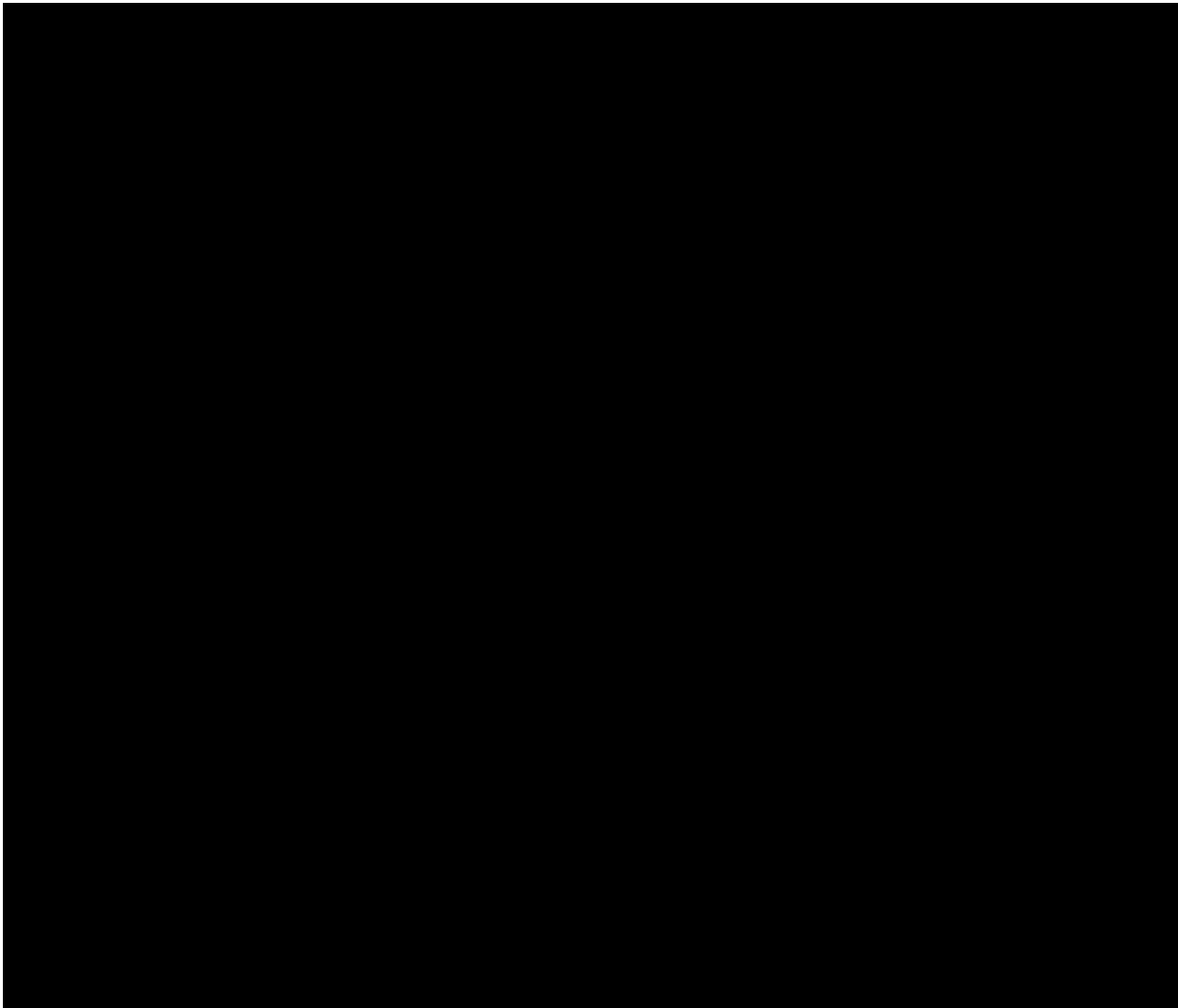
**Table 2-3 WHO performance scale**

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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

For all analyses regarding WHO, non-missing post-baseline questionnaire assessments within 30 days of last dose of study treatment, and before the start of any further anti-neoplastic therapies will be used.

Shift tables of WHO performance status at baseline to worst post-baseline WHO status by score will be provided; shift tables of WHO performance status at baseline to best post-baseline WHO status by score will also be provided. WHO performance status at each time point will be listed.

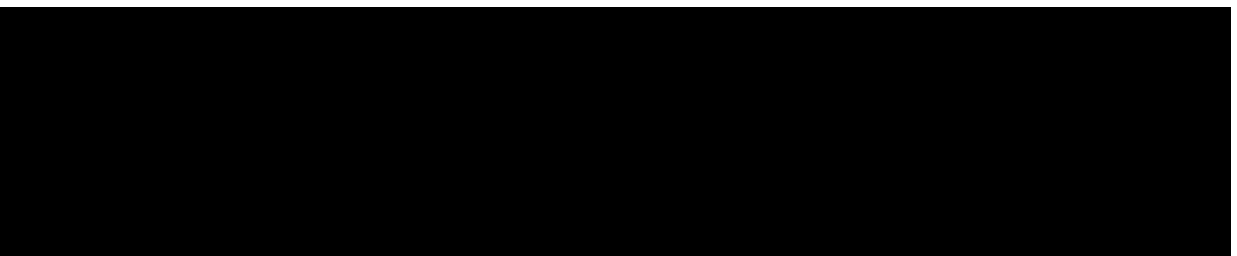


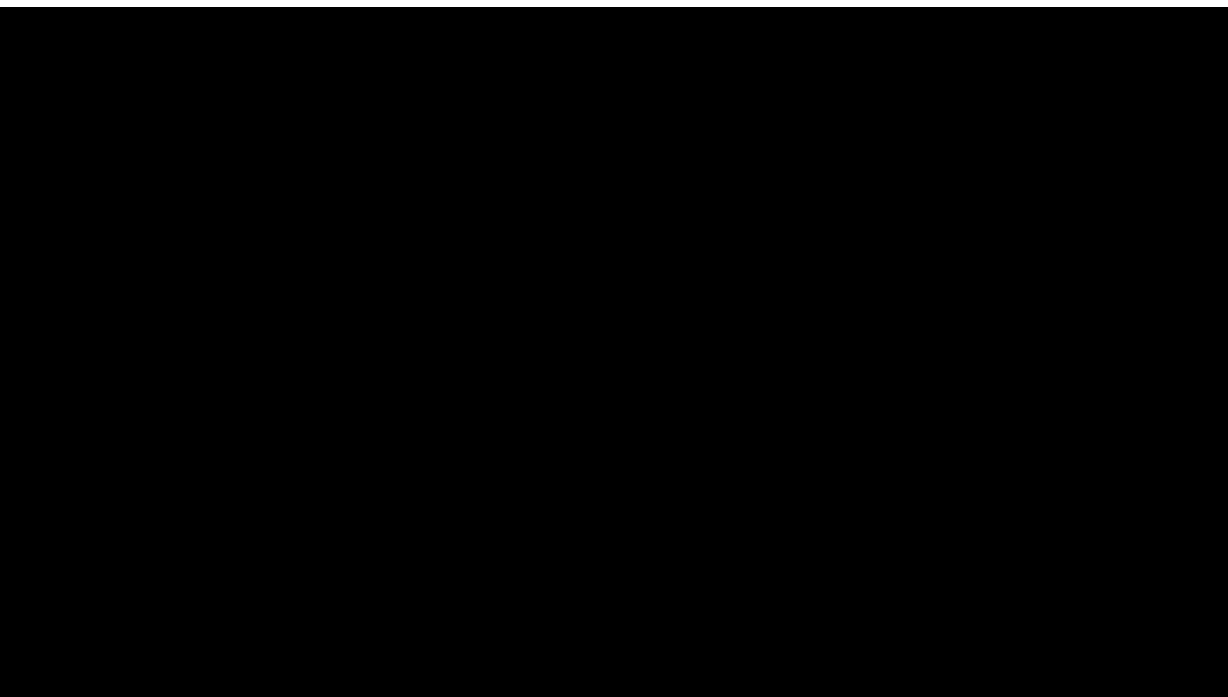


[Redacted text block]

**2.8.6 Patient-report outcomes**

Not applicable.





## 2.9 Sample size calculation

The study will enroll approximately 160 patients, with approximately 40 patients each in Arms 1 and 2 and ~30 patients each in Arms 3 and 4 and at least 20 patients in Arm 5 (See [Table 2-4](#)). It is assumed that 5% of the patients diagnosed with brain metastases have leptomeningeal carcinomatosis. Additional patients in Arm 4 may be enrolled in order to achieve approximately 60 patients in Arms 3 and 4 together (i.e. ALKi naïve patients) if enrollment rate in Arm 3 is slow.

An observed ORR of 50% in 140 patients planned for Arms 1-4 will result in an exact binomial 95% CI with a lower bound greater than 40% which is clinically meaningful and exceeds the ORR expected with available therapies ([Shaw 2012](#)). [Table 2-4](#) provides the exact binomial 95% CI for various observed ORRs for the 140 patients and for each of the strata.

**Table 2-4 Exact binomial 95% confidence intervals for various observed ORRs**

Sample Size	Observed ORR	Number of Patients with Confirmed PR or CR	Exact 95% CI
N=140 (overall Arms 1-4)	50%	70	(41.44%, 58.56%)
	60%	84	(51.39%, 68.18%)
N=80 (Arms 1 and 2)	40%	32	(29.20%, 51.56%)
	50%	40	(38.60%, 61.40%)
	60%	48	(48.44%, 70.80%)
N=40 (each of Arms 1 or 2)	40%	16	(24.87%, 56.67%)
	50%	20	(33.80%, 66.20%)
N=30 (each of Arms 3 or 4)	60%	18	(40.60%, 77.34%)
	70%	21	(50.60%, 85.27%)

## 2.10 Power for analysis of key secondary variables

Estimation of the DCR is the key secondary objective of the study. An observed DCR of 65% in 140 patients in Arms 1-4 will result in an exact binomial 95% CI with a lower bound greater than 55%. [Table 2-5](#) provides the exact binomial 95% CI for various observed DCRs for the 140 patients and for each of the strata.

**Table 2-5 Exact binomial 95% confidence intervals for various observed DCRs**

Sample Size	Observed DCR	Number of Patients with SD, PR or CR	Exact 95% CI
N=140 (overall Arms 1-4)	65%	91	(56.49%, 72.86%)
	75%	105	(66.98%, 81.93%)
N=80 (Arms 1 and 2)	60%	48	(48.44%, 70.80%)
	70%	56	(58.72%, 79.74%)
N=40 (each of Arms 1 or 2)	60%	24	(43.33%, 75.14%)
	70%	28	(53.47%, 83.44%)
N=30 (each of Arms 3 or 4)	70%	21	(50.60%, 85.27%)
	80%	24	(61.43%, 92.29%)

An additional secondary objective of the study is estimation of the OIRR for patients with measurable brain metastases at baseline. As described in [Section 4.1.1 of the study protocol](#), the study targets enrolling approximately 70 patients with measurable brain metastases: ~50 patients with prior ALKi treatment (Arms 1 and 2) and ~20 patients with no prior ALKi treatment (Arms 3 and 4). An observed OIRR of 50% in 70 patients with measurable brain metastases will result in an exact binomial 95% CI with a lower bound greater than 35%. An observed OIRR of 60% in 50 patients with measurable brain metastases previously treated with ALKi (Arms 1 and 2) will result in an exact binomial 95% CI with a lower bound greater than 45%. An observed OIRR of 60% in 20 patients with measurable brain metastases not previously treated with ALKi (Arms 3 and 4) will result in an exact binomial 95% CI with a lower bound greater than 36% ([Table 2-6](#)). The reported OIRR with crizotinib is 18% (95% CI: 5 - 40) for patients with measurable brain metastases and prior radiation therapy to the brain, and 33% (95% CI: 13 - 59) for patients without prior radiation to the brain; recent whole brain radiation was allowed ([Crino et al 2013](#)).

**Table 2-6 Exact binomial 95% confidence intervals for various observed OIRRs**

	Observed OIRR	Number of Patients with Confirmed PR or CR in the brain	Exact 95% CI
N=70 (Overall)	45%	32	(33.74%, 58.06%)

Arms 1-4)	50%	35	(37.80%, 62.20%)
	55%	39	(43.34%, 67.59%)
	60%	42	(47.59%, 71.53%)
N=50 (prior ALKi treatment, Arms 1+2)	40%	20	(26.41 %, 54.82 %)
	45%	23	(31.81 %, 60.68 %)
	50%	25	(35.53%, 64.47%)
	55%	28	(41.25%, 70.01%)
	60%	30	(45.18%, 73.59%)
N=20 (no prior ALKi treatment, Arms 3+4)	50%	10	(27.20%, 72.80%)
	55%	11	(31.53%, 76.94%)
	60%	12	(36.05%, 80.88%)
	65%	13	(40.78%, 84.61%)



### 3 Changes to protocol specified analyses

Table 3-1 summarizes the changes to protocol-specified analyses and associated rationale for inclusion in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR.

**Table 3-1 Changes to protocol specified analysis or descriptions and rationale**

Protocol Section	Protocol Description	Change
Section 10.5.2	The distribution function of TTIR will be estimated using the Kaplan-Meier method. The median TTIR along with 95% CI will be presented. TTIR will be summarized by prior radiotherapy to the brain (yes, no), prior ALK inhibitor use (yes, no) and overall using the data from Arms 1 through 4. Similar for TTER and TTR.	TTIR will be summarized by frequency counts in time intervals and using descriptive statistics for patients with confirmed CR or PR. This analysis is removed. This update was made because median value is not estimable using KM method due to low response rate. Descriptive statistics suggested median

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		values were consistent across study arms.
Section 10.5.2	A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the anticancer therapy date.	A patient who has not progressed or died at the date of the analysis cut-off will be censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. This update was made to align with the latest “Guidelines for response, duration of overall response, TTF, TTP, progression-free survival, and overall survival”.

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## 4 Additional details on implementation of statistical methodology

The sections below contain additional details on statistical methodology that will be included in [Appendix 16.1.9](#) (Documentation of Statistical Methods) of the CSR as well as rules details on programming rules that will be followed to implement the analyses described in [Section 2](#).

### 4.1 Data included in the analyses

This section provides additional details to those included in [Section 2.1](#).

Each analysis (primary analysis and final analysis) will include the data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date. For example, if the cut-off date is 30DEC2008, an AE starting on 28DEC2008 will be reported, whereas an adverse event starting on 31DEC2008 will not be reported.

### 4.2 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (e.g. blood draws (laboratory, [REDACTED]), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of antineoplastic therapies administered after study drug discontinuation (with non-missing medication/procedure term).
- AE start and end dates (with non-missing verbatim AE term present)
- From ‘Survival information’ eCRF:

- Last known date patient alive if answer to question ‘Is subject alive?’ is ‘lost to follow-up’;
- Date of assessment if answer to question ‘Is subject alive?’ is Yes  
Note: If answer to question ‘Is subject alive?’ is ‘unknown’, neither ‘last known date patient alive’ nor ‘date of assessment’ is used
- Study drug start and end dates from DAR with non-missing dose. Doses of 0 are allowed.
- Concomitant medications/Surgical and Medical Procedures start and end dates
- Date of discontinuation/study phase completion on the ‘End of treatment discontinuation’ and the ‘End of Post Treatment Phase Disposition’ eCRFs.

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

Only dates associated with patient visits or actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cutoff date will not be applied to the last contact date.

Partial date imputation is allowed for event (death)/censoring if the date is coming from ‘Survival information’ eCRF only. If the day is missing for the ‘Date of assessment’ when answer to question ‘Is subject alive?’ is Yes, or ‘Last known date patient alive’ when answer to question ‘Is subject alive?’ is ‘lost to follow-up’, it will be imputed to 1<sup>st</sup> day of the month and year. If imputed date is after cut-off date, then this date will not be applied to derive the last contact date.

### 4.3 Month derivation

For all derivations, a month will be calculated as  $(365.25 / 12) = 30.4375$  days. If duration is to be reported in months, duration in days will be divided by 30.4375.

### 4.4 Age derivation

Age for enrolled patients or screen failures will be calculated based on the date when the patient signed the main study informed consent from the date of birth.

### 4.5 Dose interruptions and dose changes

This section provides additional details to those included in [Section 2.6](#). Both dose interruption and dose change are analyzed based on CRF pages based on the dose actually taken by the patients.

An interruption is defined as a 0 mg dose taken on one or more days. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (*example: If the actual dose on days 1-3 is 750 mg and actual*

*dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1).*

- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (*example: If the actual dose on days 1-3 is 750 mg and actual dose on days 4-5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2).*
- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (*example: if the actual dose on days 1, 3 and 5, is 750 mg and actual dose on days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2).*

A dose change is defined as a change in dosing from one record to the next. However, a dose interruption will not be counted as a dose change. For example, for LDK378, in the sequence 750 mg – 0 mg – 600 mg, the 600 mg dose will be counted as a dose change (with reason documented), preceded by a 0 mg due to interruption (with reason documented). Dose reductions are a subset of dose changes where dose changes to higher than protocol planned dose are excluded.

## 4.6 Efficacy endpoints

For further details on efficacy endpoints, see [Section 14](#) (Appendixes 2 and 3) of the LDK378A2205 protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator and BIRC according to RECIST 1.1 with the exception of intracranial endpoints following Modified RECIST 1.1. Additionally, intracranial endpoints are also evaluated by investigator and BIRC as exploratory endpoints according to RANO criteria.

The text below gives more detailed instructions and rules needed for programming of the analyses described in [Sections 2.7](#) and [2.8.1](#).

### 4.6.1 Implementation of RECIST guidelines

#### Disease progression

PD should only be assigned if it is demonstrated by an objective assessment method as per RECIST 1.1 (whole body and extracranial) or Modified RECIST 1.1 (intracranial) (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions). If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST eCRF with appropriate method (or method='Other').

In particular, discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as PD in the determination of BOR, the derivation of any efficacy endpoint or efficacy analysis.

#### Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to



MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT and vice versa while keeping same contrast use (e.g. switching from spiral CT with contrast to CT with contrast) is not considered a change in imaging modality .

A change in methodology will result by default in a UNK (unknown) overall lesion response assessment. However, a response assessment other than the Novartis calculated UNK response may be accepted from the investigator or BIRC if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response reported by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be queried during the data validation process.

### **Determination of missing adequate tumor assessments**

For the computation of ORR (for primary analysis), patients without any radiological assessment after the start date of study drug will be counted as failure.

Partial or complete responses reported prior to any additional anticancer therapy will be considered for ORR computation irrespective of the number of missed assessments before response. The anticancer therapy will be defined for intracranial, extracranial and whole body separately: e.g., radiotherapy to the brain will only be considered as anticancer therapy for intracranial and whole body endpoints but not for extracranial endpoint. In this section, the ‘missing adequate assessment’ is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the ‘missing adequate assessment’ will also be referred as ‘missing assessment’.

As detailed in [Section 14](#) (Appendix 2) of the LDK378A2205 protocol and [Table 2-2](#) of SAP, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments. *For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment before the event date.*

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date.

If the distance is larger than threshold  $D_1$  or  $D_2$  then the analysis will assume one or two missing assessments, respectively. The threshold  $D_1$  will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold  $D_2$  is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. In this study, the protocol defined schedule of tumor assessment is every 8 weeks and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than  $D_1 = 8 + 2 = 10$  weeks means one missing assessment and any distance larger than  $D_2 = (2 * 8) + 2 = 18$  weeks means two missing assessments.

The same definition of  $D_2$  will be used to determine the PFS censoring reason.

Possible censoring reasons for PFS are:

1: Ongoing without event

2: Lost to follow-up

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- 3: Withdrew consent
- 4: Adequate assessment no longer available
- 5: Event after  $\geq 2$  missing tumor assessments

**Non-measurable disease at baseline**

As specified in Section 14 (Appendix 2) of the LDK378A2205 protocol, the RECIST 1.1 criteria imply that only patients with measurable disease at baseline (at least one extracranial measurable lesion as per inclusion criteria) should be included in the study. If a patient without measurable disease is enrolled, the intent-to-treat (ITT) principle requires including these patients in the analyses. Hence, analyses will be based on FAS including patients with either measurable or non-measurable disease. Therefore, a rule needs to be specified on how to handle these cases.

As specified in Table 3-1 of Section 14 (Appendix 2) of the LDK378A2205 protocol, overall lesion response can be derived for patients without measurable disease at baseline as follows (Table 4-1).

**Table 4-1 Overall lesion response at each assessment: patients with non-target disease only**

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD <sup>1</sup>	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

<sup>1</sup> In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination.

**Missing baseline tumor assessment**

As specified in Section 14 (Appendix 2) of the protocol, since the timing of PD cannot be determined for patients with missing baseline tumor assessment, these patients are censored in the PFS analysis at the start date of treatment. This rule, however, only applies to the ‘PD component’ of the PFS or DOR assessment.

Patients without baseline tumor assessment who die within D<sub>2</sub> distance from start date of treatment will be counted as having an event in the primary analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

**Construction of waterfall graphs**

The waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of the measured diameter of all target lesions for each patient. The proportions of patients with various degrees of tumor shrinkage or growth can then represent a useful efficacy metric.

However, caution needs to be paid to the assessments, where an occurrence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measurements obtained on target lesions. These assessments will not be displayed as bars in the graph. If such a “contradicting” assessment represents the only post-baseline assessment for a patient, then the patient will be represented by a special symbol (e.g. \*) in the waterfall graph.

The assessments with unknown target response and also assessments with unknown overall response will be excluded. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph needs to be shown and this number will be used as a denominator when calculating the percentages of patients with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in [Table 4-2](#).

**Table 4-2 Inclusion/exclusion of assessments used in waterfall graph**

Criteria for inclusion/exclusion			Possible source of contradictions	
Target response	Overall lesion response	Include in waterfall	Non-target response	New lesion?
CR/PR/SD	PD	Yes but as * only	PD	any
CR/PR/SD	PD	Yes but as * only	any	Yes
UNK	UNK or PD	No	any	any
CR/PR/SD	UNK	No	UNK	No
CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
PD	PD	Yes as a bar	any	any

The following algorithm will be used to construct the graph:

1. Select “valid” post-baseline assessments to be included, i.e. for each patient and each assessment repeat the following four steps:
  - 1.1. Check the target lesion response and overall lesion response at each assessment. If at least one of them is UNK then exclude the whole assessment. Otherwise, go to step 1.2.
  - 1.2. Check the overall lesion response. If PD, then go to step 1.3. Otherwise, go to step 1.4
  - 1.3. Check target response. If PD, then go to step 1.4. Otherwise flag the assessment \*.
  - 1.4. Calculate the % change from baseline in target lesions.
2. For each patient, go through all valid assessments identified in step 1 and find the assessment with best % change from baseline in target lesions. The “best” means best for the patient, i.e. the largest shrinkage or if a patient only has assessments with tumor growth take the assessment where the growth is minimal. (*Example 1*: Patient 1 has the following %

changes from baseline at assessments 1, 2, 3, 4 and 5, respectively: -10%; -25%; -13%; -4% and +6%. His/her best % change is then -25%. *Example 2:* Patient 2 has the following % changes from baseline at assessments 1, 2 and 3, respectively: +5%; +18% and +35%. His/her best % change is then +5%.

3. Construct the waterfall graph displaying the best % change from baseline for each patient. Patients having only ★ flagged assessment(s) will be displayed separately.

The recommended way of the display from left to right is:

1. Bars above the horizontal axis representing tumor growth
2. Bars under the horizontal axis representing tumor shrinkage
3. “Zero” bars with ★ symbol representing patients with contradiction

#### 4.6.2 Implementation of RANO guidelines (protocol Appendix 3)

As described in the protocol, intracranial endpoints (OIRR, IDCR, DOIR, and TTIR in the brain) will also be evaluated by RANO criteria as exploratory endpoints. This section provides some details on how to derive these intracranial endpoints by RANO and further details are included in the protocol Appendix 3.

##### RANO vs. RECIST 1.1

In this study, intracranial endpoints will be evaluated by both RECIST 1.1 and RANO. Measurable disease by RANO is defined as bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 10mm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm.

The major differences between RECIST 1.1 and RANO include:

- The measurability criteria for target lesion by RANO is based on two dimensions and is more stringent than the RECIST 1.1 criteria, therefore, the number of target lesions by RANO is no more than the number of target lesions by RECIST 1.1;
- In RECIST 1.1, only one diameter is recorded for each target lesion, while in RANO, two perpendicular diameters are measured for each target lesion;
- In RANO, corticosteroids use and clinical status are also considered for determining overall response;
- There are two types of non-target lesions by RANO: non-enhancing lesions and non-measurable enhancing lesions. Both types of non-target lesions contribute to the non-target lesion response.

##### Overall Lesion Response Collected on RANO eCRF page

Intracranial endpoints by RANO will be derived based on the collected overall lesion response on eCRF page “RANO Overall Lesion Response” (ZR domain, ZRCAT = “RESPONSE ASSESSMENT IN NEURO-ONCOLOGY”, and ZRSCAT = “OVERALL LESION RESPONSE”). The derivation of intracranial endpoints (OIRR, IDCR, DOIR, TTIR and TTP in the brain) by RANO is the same as by RECIST 1.1.

## Calculation of Overall Lesion Response by RANO

Overall lesion responses by RANO are also calculated from the following components:

1. Target lesion measurements;
2. Non-target lesion response;
3. New lesion present (Yes/No);
4. Corticosteroids use;
5. Clinical status.

All these components are collected on the following eCRF pages:

1. RANO target lesion - Measurable enhancing lesion (T1) (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "TARGET ENHANCING T1");
2. RANO non-target lesion - Non-measurable enhancing lesion (T1) (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "NON-TARGET ENHANCING T1");
3. RANO non-target lesion - Non-enhancing lesion (T2/FLAIR) (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "NON-TARGET NON ENHANCING T2/FLAIR");
4. RANO New Lesion (ZI domain, ZICAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "NEW");
5. Corticosteroids use and clinical status are collected on the Modified RANO Assessment (ZR domain, ZRCAT = "MODIFIED RANO CRITERIA FOR BRAIN METASTASES", ZISCAT = "RESPONSE ASSESSMENT").

Unlike in RECIST 1.1, each target lesion by RANO criteria has two perpendicular diameters collected. In order to calculate the target lesion response, the product of the two perpendicular diameters is calculated for each target lesion. Then the sum of the products of all target lesions is compared to the baseline or nadir to determine the target lesion response.

The non-target lesion response is collected on the field of "Non-target lesion present" in the Modified RANO Assessment page, and is evaluated based on both non-target lesion eCRF pages as shown above. However, no derivation will be performed from individual non-target lesion status to non-target lesion response.

The RANO response/progression criteria are summarized in [Table 4-3](#).

Please note that patients with non-measurable disease in brain at baseline are allowed to be enrolled in the study. According to RANO criteria, these patients with non-measurable disease in brain cannot have a response of CR or PR in the brain, and the best response they can achieve is stable disease (SD) in the brain.

**Table 4-3 Summary of the RANO response criteria**

	CR	PR	SD	PD
T1-Gd+ target lesions	None	≥50% decrease from baseline	<50% decrease from baseline but <25% increase from nadir	≥25% increase from nadir*
T1-Gd+ non-target lesions	Stable or improved	Stable or improved	Stable or improved	Increase*
T2/FLAIR	Stable or improved	Stable or improved	Stable or improved	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA**
Clinical Status	Stable or improve	Stable or improve	Stable or improve	Deterioration*
Requirement for Response	All	All	All	Any*
CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease *: Progression when this criterion is met **: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration				

Two fields in the Modified RANO Assessment page will not be used for any data analysis in the study: “New enhancement outside radiation field?”, “Tumor present in histopathology”.

As in RECIST 1.1, PD should only be assigned if it is demonstrated by an objective assessment method as per RANO. Discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence, will not be considered as PD.

As in RECIST 1.1, the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. The details of change in imaging modality are described in [Section 4.6.1](#).

The same principle will be followed for determining missing adequate tumor assessments, as described in [section 4.6.1](#).

### 4.6.3 Sources for overall lesion response

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point will be provided from different sources as illustrated in [Table 4-4](#).

**Table 4-4 Sources for overall lesion response**

Source 1	Investigator (local radiology) reported overall lesion response (intracranial, extracranial and whole body)
Source 2	BIRC (Blinded Independent review committee) reported overall lesion response (intracranial, extracranial and whole body)

In this study, Source 1 will be used for the primary endpoint ORR, the key secondary endpoint DCR and other secondary endpoint calculations based on investigator assessment (OIRR, IDCR, TTIR, DOIR, OERR, EDCR, TTER, DOER, DOR, TTR, and PFS). Source 2 will be used to calculate OIRR, IDCR, TTIR, DOIR, OERR, EDCR, TTER, DOER, ORR, DCR, DOR, TTR,

and PFS by BIRC. In addition, OIRR, TTIR, DOIR, and IDCR are also assessed according to RANO from both Source 1 and 2.

#### 4.6.4 Kaplan-Meier estimates

To analyze time to event variables (DOIR, TTIR, DOER, TTER, DOR, TTR, OS and PFS) an estimate of the survival function will be constructed using **Kaplan-Meier (product-limit) method** as implemented in SAS PROC LIFETEST with METHOD=KM option (see example below). The TIME statement will include a variable with survival times (*survtime* in the example below) and a (right) censoring variable (*censor* in the example below) with a value of 1, representing censoring:

```
PROC LIFETEST data = dataset  
    METHOD = KM  
    CONFTYPE=LOGLOG;  
TIME survtime*censor(1);  
RUN;
```

/\* *survtime* represents variable containing event/censor times;  
*censor* represents censoring variable (1 = censored, 0 = event); \*/

Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained along with 2-sided 95% CIs calculated from PROC LIFETEST output using the method of [Brookmeyer & Crowley, 1982](#).

Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. The time points can be expressed in weeks or in months depending on the time-to-event variable. The CIs will be constructed using Greenwood's formula [Collet, 1994, p.23] for the standard error of the Kaplan-Meier estimate.

The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The CONFTYPE option specifies the transformation applied to the survival function to obtain the point-wise confidence intervals and the confidence intervals for the quartiles of the survival times. The LOGLOG keyword specifies the complementary log-log transformation (Collett, 1994; Lachin, 2000)  $g(x)=\log(-\log(x))$  which ensures that the point-wise confidence intervals are always within interval [0,1]. Although the LOGLOG is the default option in SAS v 9.4, it should be explicitly shown.

The Kaplan-Meier graphs will be constructed using SAS software.

#### 4.6.5 Confidence interval for response rates

The estimate of the response rates (OIRR, IDCR, OERR, EDCR ORR, DCR) will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson, 1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided exact binomial CI. These estimates are obtained as follows:

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```
proc freq data = dataset;  
  table binary event /  
    binomial(  
      level = "Yes")  
      alpha = two-sided alpha level;  
  exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing `level="No"`. From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"} (\%) = 100\% - UCL_{LEVEL="No"} (\%)$$

$$UCL_{LEVEL="Yes"} (\%) = 100\% - LCL_{LEVEL="No"} (\%)$$

## 4.7 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the analyses described in [Section 2.8.2](#).

### 4.7.1 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, WHO performance status), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

#### Laboratory Data

For laboratory data, assessments can be collected from both local and central laboratory on the same date. For shift tables using CTC grades to compare baseline to the worst post-baseline value, the assessment with worst post-baseline value is used for analyses irrespective of the source. For LFT summaries, where concurrent measurements are used in the calculation of number and percentage of patients with worst post-baseline values, the assessment with worst post-baseline value is used (since worst values are based on the largest ratio of lab value to its ULN for each patient) although the worst values for the different parameters may be coming from different laboratories.

#### ECGs

For all patients, 3 ECGs are targeted to be measured at the protocol-defined (nominal) time-points. If a patient has more than one measurement at a nominal time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

### 4.7.2 Baseline

As defined in [Section 2.6](#), the last available assessment before or on the date of start of study drug is defined as “baseline” value or “baseline” assessment.

#### Laboratory data



If both central and local laboratory assessments were performed on the same date and corresponding to the baseline assessment date, then the central laboratory assessment will be used for the calculation of baseline.

## ECGs

Baseline for ECG measurement is the average of all available measurements (unscheduled, if applicable) taken prior to dosing on the date associated with the last available ECG measurement before or on the date of start of study treatment. To determine whether ECG measurement was taken prior to dosing, ECG time will be compared with dosing time, if available. Unscheduled assessments will be included in the calculation of the average if ECG time is before dosing time. Study day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time or ECG time is missing.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

For unscheduled assessments on study day 1,

- if dosing time is non-missing, then the assessment is classified as post-baseline if ECG time is later than dosing time.
- if dosing time is missing, the assessment is classified as post-baseline.

The same ECG assessments will be used for both qualitative and quantitative baseline evaluations.

### 4.7.3 Laboratory Parameters

This section provides further detail on the analysis of laboratory parameters that will be listed and summarized as described in [Section 2.8.2](#).

#### Hematology

Hematologic tests include: Hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly for neutrophils and lymphocytes, because CTC grading is based on the absolute counts).

The method to convert the value is straightforward: for each patient, the original lab value (%) is divided by 100 and multiplied by WBC count e.g. for neutrophils (NEU):

$$\text{NEU count} = (\text{WBC count}) * (\text{NEU\%value}/100)$$

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If % range missing and absolute range missing, then use pre-defined normal range reported in the Merck manual

- If % absolute range NOT missing (% range is or isn't missing), then use the absolute range provided by the site
- If % range NOT missing and absolute range missing, then the % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils NEU):  
LLN for NEU count = (LLN for WBC count)\* (LLN for NEU%value /100)  
ULN for NEU count = (ULN for WBC count)\*(ULN for NEU%value/100)

## Biochemistry

The following calculation will be applied for corrected calcium in SI unit:

Corrected calcium (mmol/L)=measured total Ca (mmol/L)+0.02 (40-serum albumin[g/L]),  
where 40 represents the average albumin level in g/L.

## 4.8 Handling of missing or partial dates

For patients not known to have died prior to the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date or after the date of withdrawal of informed consent will be reported as “continuing”.
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. for a dose administration record with missing end date or last date of study drug after the cut-off date), the end date will be imputed by the minimum of death date, cut-off date and withdrawal of informed consent date for the purpose of calculating duration of exposure to study drug and dose intensity. The imputed date will be displayed and flagged in the listings.

### 4.8.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following

It would not be possible to place the AE in time.

Therefore the treatment/dosage at the time of the event would be unknown.

Therefore the event could not be reported/summarized appropriately – if at all.

Therefore it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

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- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

The following [Table 4-5](#) explains the abbreviations used.

**Table 4-5 AE/treatment date abbreviations**

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix [Table 4-6](#) describes the possible combinations and their associated imputations. In the light grey boxes the upper\_text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

**Table 4-6 AE partial date imputation algorithm**

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The following [Table 4-7](#) is the legend to the above table.

**Table 4-7 AE/treatment date relationship and imputation legend**

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
( A )	01MONYYYY
( B )	TRTSTD+1
( C )	15MONYYYY
( D )	01JULYYYY
( E )	01JANYYYY

The following [Table 4-8](#) gives a few examples.

**Table 4-8 AE imputation example scenarios**

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	( D )	01JUL2000
ddmmm2002	20OCT2001	After	( E )	01JAN2002
ddmmm2001	20OCT2001	Uncertain	( B )	21OCT2001
ddSEP2001	20OCT2001	Before	( C )	15SEP2001
ddOCT2001	20OCT2001	Uncertain	( B )	21OCT2001
ddNOV2001	20OCT2001	After	( A )	01NOV2001

#### 4.8.2 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial concomitant medication end dates will not be imputed.

#### 4.8.3 Incomplete date of initial diagnosis of cancer, date of first recurrence/progression and date of most recent recurrence

Missing day is defaulted to the 15<sup>th</sup> of the month and missing month and day is defaulted to 01-Jan.

#### 4.8.4 Incomplete date for anti-neoplastic therapies

##### Prior therapies

###### Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study drug -1'.

###### End date:

Imputed date = min (start date of study drug, last day of the month), if day is missing;

Imputed date = min (start date of study drug, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

##### Post therapies

###### Start date:

Imputed date = max (last date of study drug + 1, first day of the month), if day is missing;

Imputed date = max (last date of study drug + 1, 01JAN), if day and month are missing.

End date: No imputation.

#### 4.8.5 Incomplete assessment dates for tumor assessment

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise, if overall lesion response is PD, the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1<sup>st</sup> of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

In case of multiple imaging scans performed within an evaluation, if some imaging dates for tumor assessment under the same evaluation for a patient are before as well as after cut-off, the entire evaluation will not be included for analyses based on the pre-specified cut-off.

#### 4.8.6 Incomplete date for death

All dates must be completed with day, month and year.

If the day or month is missing, death date will be imputed to the maximum of the full (non-imputed) last contact date (excluding the date of death) and the following:

- Missing day: 1<sup>st</sup> day of the month and year of death
- Missing day and month: Jan 1st of the year of death

#### 4.8.7 Incomplete dates for last dose of study drug

##### Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be on-going and use the cutoff date for the analysis as the last dosing date.

##### Scenario 2

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death date available then imputed last dose date:

= 31DECYYYY, if only Year is available and Year < Year of min (EOT visit date, death date)

= Last day of the month, if both Year and Month are available and EITHER

-- Year = Year of min (EOT visit date, death date) and Month < the month of min (EOT visit date, death date) OR,

-- Year < Year of min (EOT date, death date) irrespective of the month

= min (EOT visit date, death date), for all other cases.

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug;

Otherwise, use the imputed date.

#### 4.8.8 Incomplete dates for disease progression prior to start of study drug

If day of PD associated with prior antineoplastic medication is missing then imputed PD date:

= min (midpoint between the end date of the prior antineoplastic medication and the end of the month, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in the same month as the PD date,

= min (15th of the month of the PD date, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in a month prior to the PD date

= 15th of the month of the PD date, if end date of prior antineoplastic medication is in a month after the PD date.

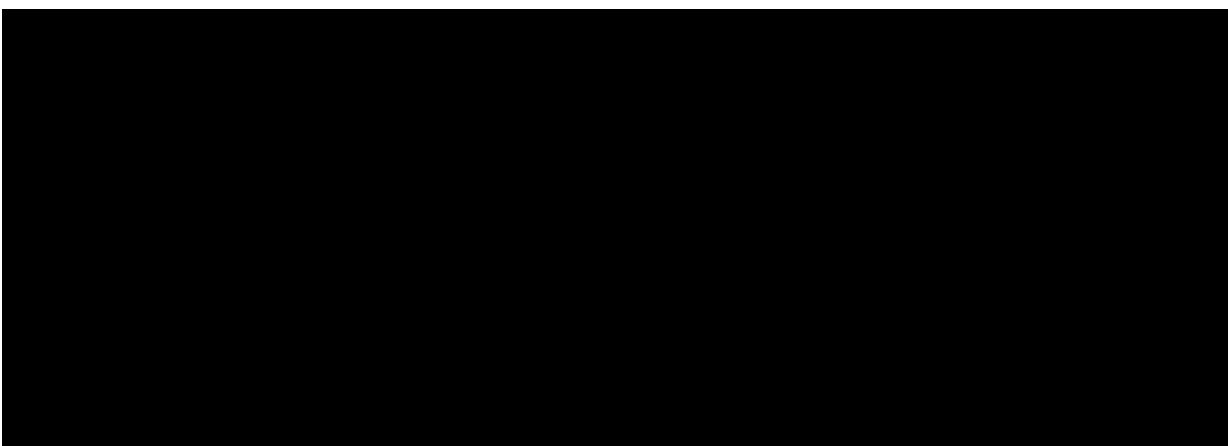
If both day and month of PD associated with prior antineoplastic medication are missing then imputed PD date:

= min (midpoint between the end date of the prior antineoplastic medication and the end of the year, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in the same year as the PD date

= min (July 1 of the year of the PD date, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in a year prior to the PD date

= July 1 of the year of the PD date, if end date of prior antineoplastic medication is in a year after the PD date

Completely missing PD dates will not be imputed. The start date of medication from the next regimen is based on the earliest start date of any medication(s) from the next regimen. For the mid-point calculation, if odd days in between, (e.g. last dose of medication is 27 June 2012, and end of the month is 30 June 2012), then use the next day from the midpoint calculation (e.g. mid-point is 29 June 2013).



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