NOVARTIS

Clinical Development

LDK378

CLDK378A1201 / NCT02450903

A phase II, multi-center, open-label, single-arm study to evaluate the efficacy and safety of oral LDK378 treatment for patients with ALK-positive non-small cell lung cancer previously treated with alectinib

RAP Module 3 – Detailed Statistical Methodology

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Version	Date	Changes
1.0	29-Oct-2015	N/A; First version.
Amendment 1	13-Jun-2017	Section 1.2 Objectives: [redacted] Section 2.1 Data analysis: Reporting strategy was clarified. Subgroup analysis of key efficacy endpoints by prior ALK inhibitor (alectinib only, alectinib and crizotinib) was added since a patient previously treated with crizotinib (in addition to alectinib) was allowed to enroll in the study as per protocol amendment 3. In addition, subgroup by best response to prior alectinib (CR/PR, SD/PD/UNK) was newly defined. Section 2.3 Patient demographics and other baseline characteristics: Analysis of prior antineoplastic therapy was updated to include prior crizotinib therapy as per protocol amendment 3. Section 2.8.1 Efficacy: Protocol deviation code was specified to identify further antineoplastic therapies. Section 2.8.2 Safety: Summary of treatment-related serious AESIs was added. AE analysis for clinical trial safety disclosure was updated according to the current guidance/standards. Laboratory parameters for summaries were modified to align with other LDK378 studies. Drug-induced liver injury was added as part of safety assessments based on protocol amendment 2. Section 4.6 Dose interruptions and dose changes: Specification for reporting of dose interruption/change was clarified to support programming.

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1 Introduction

This Reporting and Analysis Plan (RAP) module describes the planned statistical methods for all safety, efficacy, [redacted] analyses for study CLDK378A1201.

1.1 Study design

This is a single-arm, open-label, multi-center, phase II study to evaluate the efficacy and safety of the ALK inhibitor LDK378 when used as a single agent in patients with ALK-rearranged, stage IIIB or IV NSCLC previously treated with alectinib. A total of approximately 20 patients will be enrolled into the study. Treatment with LDK378 will continue until the patient experiences disease progression as determined by the investigator according to RECIST 1.1, unacceptable toxicity that precludes further treatment, pregnancy, start of a new anticancer therapy, discontinuation of treatment at the discretion of the patient or investigator, lost to follow-up, death, or termination of the study by Sponsor. LDK378 may be continued beyond RECIST-defined progressive disease (PD) as assessed by the investigator if, in the judgment of the investigator, there may be clinical benefit with continued treatment. In these patients, tumor assessments should continue as per the schedule of assessments until treatment with LDK378 is permanently discontinued. Patients who discontinue the study medication in the absence of progression will continue to be followed with tumor assessments until the time of PD as assessed by the investigator.

1.2 Objectives

The objectives and related endpoints are listed in Table 1-1.

Table 1-1 Objectives and related endpoints

	Objective	Endpoint
Primary	To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment per RECIST 1.1.	ORR, defined as the proportion of patients with a best overall confirmed response of CR or PR in the whole body as assessed per RECIST 1.1 by the investigator.
Key secondary	To evaluate disease control rate (DCR).	DCR, calculated as the proportion of patients with best overall response of CR, PR, or SD.
	To evaluate time to tumor response (TTR).	TTR, calculated as the time from first dose of LDK378 to first documented response (CR or PR) for patients with confirmed CR or PR.
	To evaluate duration of response (DOR).	DOR, calculated as the time from the date of the first documented response (CR or PR) to the first documented disease progression or death due to any cause for patients with confirmed CR or PR.

	Objective	**Endpoint**
Other secondary	To evaluate progression free survival (PFS).	PFS, calculated as the time from first dose of LDK378 to date of first documented disease progression (per RECIST 1.1) or date of death due to any cause.
	To evaluate overall survival (OS).	OS, calculated as the time from first dose of LDK378 to death from any cause.
	To evaluate overall intracranial response rate (OIRR).	OIRR, calculated as the proportion of patients with a best overall confirmed response of CR or PR in the brain assessments for patients having measurable brain metastases at baseline.
	To evaluate the safety profile.	AEs, ECGs and laboratory abnormalities.

All tumor-response related endpoints will be evaluated using tumor responses assessed by investigator according to RECIST 1.1.

2 Statistical methods

This section and its subsections will be imported to Section 9.7 of the Clinical Study Report (CSR) after the analyses have been conducted. This section of the RAP follows the CSR template structure of Section 9.7 as of the release date of this document.

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.

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 CLDK378A1201 protocol, which will be available in Appendix 16.1.1 of the 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® 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 informed consent in centers that participate in this study will be combined and 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 cut-off date, determined prior to database lock.

The analysis cut-off date for the primary analysis of study data will be around 168 days after the first dose of study drug for the last patient enrolled corresponding to when all patients have either completed at least 6 cycles of treatment, i.e., 168 days (1 cycle = 28 days), or discontinued earlier. The results from primary analysis will be reported in the primary (interim) CSR. Following the primary analysis time point, the study will remain open. Patients still being followed on the study will continue as per the schedule of assessments. The analysis cut-off date for the final analysis of study data will be established at the end of the study when at least 75% of deaths have occurred. The results from final analysis will be reported in the final CSR. Note that the analysis cut-off date and reporting strategy may be changed according to the development and/or NDA submission status of LDK378.

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).

Subgroup analysis

Key efficacy endpoints (best overall response, ORR, and DCR) will be summarized for the following subgroups:

- Brain metastases at baseline: (presence, absence)
  Note: for the subgrouping the brain metastases are defined as measurable or non-measurable disease in the brain at baseline. List of lesion locations considered to be brain metastases is provided in Section 4.7.3.
- Prior ALK inhibitor: (alectinib only, alectinib and crizotinib)
- Best response to prior alectinib: (CR/PR, SD/PD/UNK)

2.2 Analysis sets

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

Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of LDK378. The FAS will be used for summaries of baseline characteristics and all efficacy analyses, unless otherwise specified.

Safety Set

The Safety Set will include all patients who receive at least one dose of LDK378. All safety data will be analyzed using the Safety Set. In this non-randomized study the FAS and Safety Set are identical.

Frequency counts and percentages (using FAS as denominator) of patients in each of the above defined analysis sets will be summarized. In addition, a listing of patients included in each of the analysis sets will be provided.

Section 4.2 provides further details regarding the derivation the analysis sets.

2.3 Patient demographics and other baseline characteristics

The FAS will be used for all patient demographic and baseline characteristic summaries and listings with the exception of screen failures.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age category; <65 and ≥65 years, race, ethnicity, WHO performance status, smoking history) will be summarized by frequency count and percentages. Continuous data (e.g. age, weight, height, body mass index) 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, as appropriate, for diagnosis and extent of cancer based on the data collected on the electronic Case Report Form (eCRF) including diagnosis of disease, predominant histology/cytology, histological grade, time (in months) since initial diagnosis to start date of study drug, stage at initial diagnosis, stage at time of study entry, time (in months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression to start date of study drug, current extent of disease (metastatic sites), number of metastatic sites at baseline, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion (based on the data collected on the RECIST eCRF page). A listing will also be provided including the information such as the ones above.

ALK status

ALK status at screening, collected on the [ALK Translocation status] eCRF page, will be listed.

Medical history

Medical history and current medical conditions will be summarized and listed. Separate summaries will be presented for medical history and current medical conditions. The summaries will be presented by primary system organ class and preferred term.

A medical condition that is not active at the study entry (i.e., 'Ongoing' is 'No' on the [Medical History] eCRF page) is classified as medical history (historical medical conditions). A medical condition that is active at the study entry (i.e., 'Ongoing' is 'Yes' on the [Medical History] eCRF page) is classified as current medical conditions. Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Prior antineoplastic therapy

Prior antineoplastic (anticancer) therapy will be listed in three separate categories: (i) medications, (ii) radiotherapy, and (iii) surgery.

The number and percentage of patients who received any prior antineoplastic therapy (including medication, radiotherapy or surgery), prior antineoplastic medication, prior antineoplastic radiotherapy or prior antineoplastic surgery will be summarized.

All patients must have received alectinib for inclusion in the study; reason for alectinib discontinuation, best response on alectinib, duration of best response, and time from start of

last alectinib treatment to progression (date of progression on alectinib – start date of last alectinib treatment + 1) will be summarized. Prior crizotinib therapy will be summarized in a similar way to alectinib for patients previously treated with crizotinib.

Prior antineoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens, prior anticancer medications (including alectinib, crizotinib, cisplatin, carboplatin, pemetrexed, docetaxel, gemcitabine, bevacizumab, erlotinib, vinorelbine, gefitinib, paclitaxel, and others), therapy type at last treatment, and setting at last treatment. Prior antineoplastic medications will also be summarized by ATC class and preferred term.

Prior antineoplastic radiotherapy will be summarized by locations, setting at last radiotherapy, and time since end of last radiotherapy to start date of study drug (by category).

Prior antineoplastic surgery will be summarized by procedure at last surgery and time since last surgery to start date of study drug (by category).

Screen failures

Screen failures are patients who have been enrolled and have failed to meet inclusion and/or exclusion criteria. These patients are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled (screened) patients as follows:

- Number (%) of patients who completed screening phase (based on the presence of 'Date of study phase completion' and 'Next phase entered' is 'Treatment' (or 'Will the subject continue into the next phase of the trial?' is 'Yes') on the [End of Screening Phase Disposition] eCRF page);
- Number (%) of patients who discontinued during screening phase (based on the presence of 'Date of discontinuation', 'Subject status (i.e., reason for discontinuation)' entered, and 'Will the subject continue into the next phase of the trial?' is 'No' on the [End of Screening Phase Disposition] eCRF page);
    - Primary reasons for screening phase discontinuation (based on the 'Subject status (i.e., reason for discontinuation)' recorded on the [End of Screening Phase Disposition] eCRF page for patients who discontinued during screening phase).

All screen failures (i.e., patients who discontinued during screening phase) will be listed along with the relevant information such as reason(s) for screening phase discontinuation and the inclusion/exclusion criteria leading to screen failure. The eCRF data reported in screen failures will not be included in any data analyses, but it will be presented in separate listings as needed.

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. All protocol deviations will be listed for the FAS.

The full list of potential CSR-reportable protocol deviations is documented separately in the Study Specification Document (SSD). All protocol deviations will be reviewed during the study and finalized before database lock.

2.5 Patient disposition

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

Treatment phase:

- Number (%) of patients who are still on-treatment (based on the absence of [End of Treatment Phase Disposition] eCRF page);
- Number (%) of patients who discontinued study treatment (based on the completion of [End of Treatment Phase Disposition] eCRF page with the 'Date of discontinuation' and 'Subject status (i.e., reason for discontinuation)' entered);
    - Number (%) of patients who entered post-treatment efficacy follow-up (based on the 'Next phase entered' is 'Post-treatment follow-up' (or 'Will the subject continue into the next phase of the trial?' is 'Yes') on the [End of Treatment Phase Disposition] eCRF page for patients who discontinued study treatment);
    - Number (%) of patients who entered survival follow-up (based on the 'Will the subject continue into the next phase of the trial?' is 'No' and 'Will the subject be followed for survival?' is 'Yes' on the [End of Treatment Phase Disposition] eCRF page for patients who discontinued study treatment);
    - Number (%) of patients who discontinued from study (based on the 'Will the subject continue into the next phase of the trial?' is 'No' and 'Will the subject be followed for survival?' is 'No' on the [End of Treatment Phase Disposition] eCRF page for patients who discontinued study treatment);
- Primary reasons for study treatment discontinuation (based on the 'Subject status (i.e., reason for discontinuation)' recorded on the [End of Treatment Phase Disposition] eCRF page for patients who discontinued study treatment);

Post-treatment efficacy follow-up phase:

- Number (%) of patients who are still in the post-treatment efficacy follow-up phase (based on the presence of [End of Treatment Phase Disposition] eCRF page and the absence of [End of Post Treatment Phase Disposition] eCRF page for patients who entered post-treatment efficacy follow-up);
- Number (%) of patients who discontinued from the post-treatment efficacy follow-up (based on the completion of [End of Post Treatment Phase Disposition] eCRF page with the 'Date of discontinuation' and 'Subject status (i.e., reason for discontinuation)' entered for patients who entered post-treatment efficacy follow-up);
    - Number (%) of patients who entered survival follow-up (based on the 'Will the subject be followed for survival?' is 'Yes' on the [End of Post Treatment Phase Disposition] eCRF page for patients who discontinued from the post-treatment efficacy follow-up);

  - Number (%) of patients who discontinued from study (based on the 'Will the subject be followed for survival?' is 'No' on the [End of Post Treatment Phase Disposition] eCRF page for patients who discontinued from the post-treatment efficacy follow-up);
- Primary reasons for discontinuation from the post-treatment efficacy follow-up (based on the 'Subject status (i.e., reason for discontinuation)' recorded on the [End of Post Treatment Phase Disposition] eCRF page).

The patient disposition will be listed for the FAS. The informed consent data will be listed for the screen failures as well as the FAS.

2.6 Treatments (study drug, concomitant therapies, compliance)

The Safety Set will be used for all medication data summaries and listings unless otherwise specified.

Study drug and study treatment

Study drug and study treatment both refer to LDK378 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 page. 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 page. This date will also be referred to as last date of study drug.

Study day

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, and dose interruption) 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:

Study day = Event date – 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:

Study day = Event date – Start date of study drug.

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

Dose exposure and intensity

Definitions of study drug exposure variables, as well as intermediate calculations, are provided in Table 2-1.

Table 2-1 Study drug exposure variables

Variable	Definition
Duration of exposure (days):	Last date of study drug − Start 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 (days) − Number of zero dose days
% of actual days dosed (%):	100 x Number of dosing days / Duration of exposure (days)
% of days received full dose (%):	100 x Number of days received full (planned) dose / Duration of exposure (days)
Average daily dose (mg/day):	Cumulative dose (mg) / Number of dosing days
Dose intensity; DI (mg/day):	Cumulative dose (mg) / Duration of exposure (days)
Relative dose intensity; RDI (%):	100 x DI (mg/day) / Planned dose (i.e., 750 mg/day)

Note:
Given the planned dose of 750 mg/day, the planned dose intensity (PDI) can be calculated as:
PDI (mg/day) = Cumulative planned dose (mg) / Duration of exposure (days),
where
Cumulative planned dose (mg) = Planned dose of 750 (mg) x Duration of exposure (days).
Then, RDI (%) which is calculated as (100 x DI / PDI) can be simplified as shown above.

Duration of exposure to study drug, cumulative dose, average daily dose, DI and RDI will be summarized. In addition, the duration of exposure to study drug and RDI will be categorized and the frequency counts and percentages of patients in each category will also be presented.

Frequency counts and percentages of patients who have dose changes, reductions or interruptions, and the corresponding reasons, will be summarized. In addition, descriptive statistics will also be presented for the % of actual days dosed, % of days received full dose, number of dose changes, and number of dose interruptions.

Time to first dose reduction, defined as the time from the first dose of study drug to the first reduction of study drug, will be summarized in 2 month-intervals. Summary statistics of time to first dose reduction will also be presented. Time to first dose interruption, defined as the time from the first dose of study drug to the first interruption of study drug, will be summarized in a similar way.

Listings of all doses of the study drug along with dose change and dose interruption reasons will be produced. The derived exposure variables will also be listed by patient.

Section 4.6 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 pages, respectively.

Concomitant medications will be coded using the WHO Drug Reference List (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the MedDRA terminology.

All summaries will be tabulated using frequency counts and percentages. Concomitant medications will be summarized by ATC class and preferred term. These summaries will include: 1) medications starting on or after the start of study drug and starting no later than 30 days after last dose of study drug and 2) medications starting prior to the start of study drug and continuing after the start of study drug. Surgeries or procedures will be summarized by primary system organ class and preferred term in a similar way.

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

Note patients who receive the prohibited concomitant therapies will be reported as a protocol deviation.

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.

Antineoplastic therapies initiated after discontinuation of study drug will be listed in three separate categories: (i) medications, (ii) radiotherapy, and (iii) surgery.

All summaries will be tabulated using frequency counts and percentages. Antineoplastic medications initiated after discontinuation of study drug will be summarized by ATC class and preferred term.

2.7 Analysis of the primary variable

The primary objective is to demonstrate the antitumor activity of LDK378, as measured by ORR by investigator assessment per RECIST 1.1, in patients with ALK-positive NSCLC previously treated with alectinib.

2.7.1 Variable

The primary efficacy endpoint is the ORR which is defined as the proportion of patients with a best overall confirmed response of CR or PR, as assessed per RECIST 1.1 by the investigator.

2.7.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be performed on the FAS.

The primary efficacy endpoint ORR, as assessed per RECIST 1.1 by the investigator, will be estimated and the exact 95% confidence interval (CI) will be provided (Clopper and Pearson, 1934). Exact CIs 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. Refer to Section 4.7.5 for additional details of CI calculation.

No statistical hypothesis testing is planned in this study.

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 ORR, irrespective of the number of missed assessments before response.

Patients with a best overall response of 'Unknown' per RECIST 1.1 will be considered as non-responders in estimating the ORR.

Patients who have disease progression and continue to receive the study treatment after progression will qualify for PD at the time of first documented progression. Tumor assessments performed after the first documented progression will not be considered for ORR. This will apply to secondary efficacy endpoints as well.

2.7.4 Supportive analyses

Best overall response will be listed by patient and summarized along with the ORR.

ORR will be summarized by subgroup (as defined in Section 2.1).

Waterfall plots representing the best percentage change from baseline in the sum of the tumor measured diameters for target lesions will be produced. Refer to Section 4.7.1 for additional details.

2.8 Analysis of secondary variables

2.8.1 Efficacy

The key secondary and other secondary efficacy endpoints are provided in Table 1-1. All tumor response related endpoints under the secondary efficacy objectives (DCR, TTR, DOR, PFS, and OIRR), as well as the primary efficacy endpoint ORR, will be analyzed based on the investigator assessments as per RECIST 1.1. Confirmation of response is required for all response endpoints, as per RECIST 1.1.

The definitions and details on the derivation of the efficacy endpoints are given in Section 15 (Appendix 2) of the CLDK378A1201 protocol. Further details and rules needed for programmatic implementation of RECIST 1.1 guidelines are provided in Section 4.7.1.

All secondary efficacy endpoint analyses will be performed based on the FAS, unless otherwise specified. All efficacy data, such as tumor assessments and respective efficacy endpoints, will be listed by patient.

Best overall response and DCR will be summarized by subgroup (as defined in Section 2.1) as well as the primary efficacy endpoint ORR.

Best overall response

Best overall response (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. If there is only one confirmatory assessment available which has been performed earlier, the status PR or CR will not be assigned. Unconfirmed PR and unconfirmed CR are considered as SD if >6 weeks after start of study drug, otherwise considered as UNK. 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 for a CR).
- SD = at least one SD assessment (or better) >6 weeks after start of study drug (and not qualifying for CR or PR).
- PD = progression ≤12 weeks after start of study drug (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e., not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks)

Only tumor assessments performed before the start of any further antineoplastic therapies (i.e., any additional secondary antineoplastic therapy or anticancer surgery) will be considered in the assessment of BOR. If a patient receives any further antineoplastic therapy while on study, any subsequent tumor assessments will be excluded from the BOR determination. Further antineoplastic therapies will be identified via protocol deviations (deviation code: COMDxx for use of prohibited concomitant therapy including other anticancer therapy, where xx is a serial number, e.g. COMD01, COMD02) or from the data collected on the [Antineoplastic Therapy Since Discontinuation of Study Treatment] eCRF pages, as appropriate. Clinical deterioration will not be considered as documented disease progression.

For patients with BOR of UNK, the reason for having unknown status will be listed. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New antineoplastic therapy started before first post-baseline assessment
- SD too early (≤6 weeks after start date of study drug)
- PD too late (>12 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’.

Frequency counts and percentages of patients with each BOR will be reported along with ORR and DCR.

Disease control rate

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR or SD, as assessed per RECIST 1.1 by the investigator.

DCR will be estimated and the exact 95% CI will be provided.

Time to response

Time to response (TTR) is defined as the time from the start date of study drug to the date of first documented response (PR or CR, which must be confirmed subsequently) for patients with a confirmed response (PR or CR) as assessed per RECIST 1.1 by the investigator.

TTR will be summarized using descriptive statistics for patients with a confirmed response (PR or CR). In addition, TTR will be summarized in 2-month intervals.

Duration of response

Duration of response (DOR) is defined as the time from the date of first documented response (PR or CR) to the date of first documented disease progression (PD) or death due to any cause among patients with a confirmed response (PR or CR) as assessed per RECIST 1.1 by the investigator.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy in the absence of disease progression, DOR will be censored at the date of last adequate tumor assessment before the earlier of the cut-off date or the start date of new anticancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. The censoring and event date options to be considered for the main analysis are presented in Table 2-2.

Table 2-2 Outcome and event dates for DOR and PFS analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	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	Date of last adequate assessment	Censored

Situation	Date	Outcome

[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.

DOR will be described in tabular and graphical format using Kaplan-Meier methods. The Kaplan-Meier estimate of the distribution function will be constructed. The number of patients at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles, will be reported. (Brookmeyer and Crowley, 1982; Klein and Moeschberger, 1997). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice, 2002) at several time points (including at least 4, 8, 12, 15, 18 months) will be summarized.

Refer to Section 4.7.4 for further details regarding derivation of Kaplan-Meier estimates.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the start date of study drug to the date of first documented disease progression (PD) or death due to any cause.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy in the absence of disease progression, PFS will be censored at the date of last adequate tumor assessment before the earlier of the cut-off date or the start date of new anticancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. Refer to Table 2-2 for censoring and event date options and outcomes for PFS.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments (see Section 4.7.1). See also Section 4.6.1 describing the special case of a missing baseline tumor assessment.

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles with 95% CIs, and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 4, 8, 12, 15 and 18 months). Censoring reasons will also be summarized.

In addition, the supportive analysis of PFS with censoring rule modified by ignoring further anticancer therapy ('F' in Table 2-2) will be considered when the percentage of patients censored due to the initiation of new anticancer therapy in the main analysis (for censoring reason classification, see Section 4.7.1) is equal to or more than 25% of the FAS (i.e., ≥5 out of 20 patients). In this supportive analysis, data from tumor assessments performed after the start of further anticancer therapy will also contribute to the determination of censoring and event date for PFS. Except for further anticancer therapy, the same censoring rule used for the main analysis will be followed. PFS will be described in a similar way, as needed.

Overall survival

Overall survival (OS) is defined as the time from the start date of study drug to the date of death due to any cause. If a patient is alive at the date of the analysis cut-off or lost to follow-

up, OS will be censored at the last contact date prior to the cut-off date (see Section 4.3 for further details on derivation of last contact date).

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles with 95% CIs, and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 4, 8, 12, 15 and 18 months). Censoring reasons will also be summarized.

Overall intracranial response rate

Overall intracranial response rate (OIRR) is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline (i.e., at least one target lesion in the brain). OIRR is defined as the ORR based on target, non-target and new lesions in the brain and defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain, as assessed per RECIST 1.1 by the investigator. Refer to Section 4.7.3 for additional details.

OIRR will be estimated and the exact 95% CI will be provided. In addition, best overall intracranial response and intracranial disease control rate (i.e., BOR and DCR based on target, non-target and new lesions in the brain) will be summarized. These analyses will be conducted for patients with measurable brain metastases at baseline.

Duration of Follow-up and Gap Analyses

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

- Duration between the start date of study drug and the 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 outcome (event or censoring). Date of censoring is defined as the date of last adequate tumor assessment for PFS or the last contact date (when the patient is known as alive) for OS.

Descriptive statistics (including 25th and 75th percentiles) will be tabulated for the duration and the follow-up times for PFS/OS.

Summaries will also be tabulated for the gap time for PFS/OS follow-up compared to the cut-off date. Gap analysis is the summary of gap time (months) for PFS/OS follow-up as compared to the cut-off date. Gap time for PFS/OS is defined as follows

- For patients who are censored regardless of follow-up status,
  Gap time = (Cut-off date – Censoring date) / 30.4375 (months).
- For patients who completed study phase or prematurely discontinued from the study due to certain reasons, e.g., withdraw consent and lost to follow-up,

Gap time = (min(Cut-off date, Study termination date) – Censoring date) / 30.4375 (months).

- For patients who are censored but still in follow-up,
  Gap time = (Cut-off date – Censoring date) / 30.4375 (months).

Median, 25th and 75th percentiles, minimum and maximum, as well as the frequency counts and percentages of patients in each of <4, 4-<8, 8-<12, 12-<18, ≥18 months, will be reported for PFS and OS gap times for patients who were censored.

All summaries will be reported in months (see Section 4.4). Date of censoring is the same as defined for the PFS and OS analysis.

2.8.2 Safety

All safety analyses will be performed based on the Safety Set. All listings and tables will be presented for all patients, unless otherwise specified.

Baseline

Baseline is the result of an investigation describing the "true" uninfluenced state of the patient. The last available assessment before or on the start date of study drug is defined as "baseline" value or "baseline" assessment. If an assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time or first dose time is not collected or is missing. If assessment time and first dose time are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments before the start date of study drug will be used in the determination of baseline. See Section 4.8.2 for further details on derivation of baseline for laboratory data and ECGs.

Patients who start study treatment and discontinue from the study on the same day may have 2 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.

Grouping for the analyses

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: from day of first dose of study drug to 30 days after last dose of study drug (Note: 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, i.e., assessments collected no later than 30 days after last dose of study drug and assessments collected before or on the data cut-off date for ongoing patients, unless otherwise specified.

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

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

Adverse events

Adverse events (AEs) will be coded using the latest version of MedDRA available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist 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 [Death] eCRF page.

As described previously, AE summary tables will include only AEs observed during the on-treatment period (i.e., treatment-emergent AEs). All AE summaries will be tabulated (frequency counts and percentages) by primary system organ class and/or preferred term, and severity grades, 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 summary tables will be produced:

- AEs, regardless of study drug relationship
- AEs, suspected to be study drug related
- Deaths (on-treatment deaths, all deaths during the study)
- Serious AEs, regardless of study drug relationship
- Serious AEs, suspected to be study drug related
- AEs leading to study drug discontinuation, regardless of study drug relationship
- AEs requiring dose adjustment, regardless of study drug relationship
- AEs requiring dose interruption, regardless of study drug relationship
- AEs requiring dose adjustment or interruption, regardless of study drug relationship
- AEs requiring additional therapy, regardless of study drug relationship

All AEs will be listed along with any other information (e.g., start/end dates, duration, severity, causality, action taken and outcome) as appropriate. Additional listings will be produced separately for deaths, serious AEs, AEs leading to study drug discontinuation, AEs requiring dose adjustment, AEs requiring dose interruption, AEs requiring dose adjustment or interruption, and AEs requiring significant additional therapy.

Adverse events of special interest

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

- Hepatic toxicity
- Interstitial lung disease/pneumonitis
- QTc prolongation

- Hyperglycemia
- Bradycardia
- Pancreatitis
- Gastrointestinal toxicity (nausea, vomiting and diarrhea)

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 list of preferred terms will be finalized in a separate document (i.e., case retrieval strategy). These AESIs will be summarized for each grouping, by preferred term, as follows:

- AESIs, regardless of study drug relationship
- CTC grade 3/4 AESIs, regardless of study drug relationship
- AESIs, suspected to be study drug related
- Serious AESIs, regardless of study drug relationship
- Serious AESIs, suspected to be study drug related
- AESIs leading to study drug discontinuation, regardless of study drug relationship
- AESIs requiring dose adjustment, regardless of study drug relationship
- AESIs requiring dose interruption, regardless of study drug relationship
- AESIs requiring dose adjustment or interruption, regardless of study drug relationship

AESIs will be listed by grouping.

Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment AEs (i.e., treatment-emergent AEs) which are not serious AEs with an incidence greater than 5% and on on-treatment serious AEs and serious AEs suspected to be related to study treatment will be provided by primary system organ class and preferred term.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and preferred term:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one serious AE / serious AE suspected to be related to study treatment / non-serious AE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one serious AE is occurring, then one occurrence is calculated for that serious AE.

The number of deaths resulting from serious AEs suspected to be related to study treatment and serious AEs irrespective of study treatment relationship will be provided by primary system organ class and preferred term.

Laboratory data

Local laboratories will be used for laboratory evaluations in this study. Laboratory data will be classified (by Novartis Oncology Statistical Programming personnel) into CTC grades according to the CTCAE version 4.03. 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 CTC 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 CTC 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 grading of baseline value and for the grading of post-baseline values with missing baseline value, the grade will be derived using the criteria based only on the normal range as per CTCAE version 4.03. A CTC grade of 0 will be assigned when the post-baseline value is ≤ULN (for hyper) or ≥LLN (for hypo).

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

As described previously, laboratory summary tables will include only laboratory assessments collected during the on-treatment period. Shift tables may use data from pre-treatment period for baseline calculations. The following summaries will be produced separately for the hematology and biochemistry (including hormones) 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 laboratory parameters listed in Table 2-3 will be summarized as above stated. For bi-directional parameters, both hyper and hypo summaries will be presented.

Table 2-3 Laboratory parameters for summaries

Category	Parameter with CTC grades	Parameter without CTC grades
Hematology	absolute lymphocytes [hyper, hypo]	basophils
	absolute neutrophils [hypo]	eosinophils
	hemoglobin [hypo]	monocytes
	platelet counts [hypo]	RBC
	WBC [hyper, hypo]	
Biochemistry	albumin [hypo]	blood urea nitrogen (BUN) or urea
	alkaline phosphatase [hyper]	direct bilirubin
	ALT (SGPT) [hyper]	

Category	Parameter with CTC grades	Parameter without CTC grades
	amylase [hyper]	
	AST (SGOT) [hyper]	
	corrected calcium* [hyper, hypo]	
	creatinine [hyper]	
	creatinine clearance [hypo]	
	GGT [hyper]	
	glucose [hyper, hypo]	
	lipase [hyper]	
	magnesium [hyper, hypo]	
	phosphate (inorganic phosphorus) [hypo]	
	potassium [hyper, hypo]	
	sodium [hyper, hypo]	
	total bilirubin [hyper]	
Hormones (males only)		follicle stimulating hormone (FSH)
		luteinizing hormone (LH)
		testosterone, free
		testosterone, total (free and bound)

*Corrected for albumin. See Section 4.8.3 for details on calculation of parameter.

Laboratory parameters for urinalysis, coagulation and pregnancy listed below will be presented in listings and will not be summarized.

- Urinalysis: macroscopic panel (dipstick) (color, bilirubin, blood, glucose, ketones, pH, protein, specific gravity, urobilinogen), microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells).
- Coagulation: international normalized ratio (INR), pro-thrombin time (PT) or quick test.
- Pregnancy: serum pregnancy test, urinary pregnancy test.

The following listings will be produced for the laboratory data for all laboratory parameters.

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4 (for laboratory parameters where CTC grades are defined)
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory normal ranges.

In addition, laboratory normal ranges will be listed by laboratory identification number and laboratory category.

Box plot of laboratory data by time point (scheduled visit) will be produced for each of all laboratory parameters with the exception of qualitative data such as urine dipstick glucose.

Liver function tests

Liver function tests (LFTs) of interest for LDK378 are total bilirubin (TBILI), ALT, AST and alkaline phosphatase (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 values for the categories:

  - TBILI ≤ 2xULN, TBILI > 2xULN and missing TBILI
  - ALT ≤ 3xULN, ALT > 3xULN and missing ALT
  - AST ≤ 3xULN, AST > 3xULN and missing AST
  - ALP < 2xULN, ALP ≥ 2xULN and missing ALP
- Frequency counts and percentages of patients with worst post-baseline 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 ≥ 2xULN

  Note the concurrent measurements are those occurring on the same date.
- Scatter plot of maximum post-baseline TBILI/ULN-normalized values vs. maximum post-baseline AT/ULN-normalized values.

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. Individual patient profiles with ULN-normalized LFT values for patients with a post-baseline TBILI > 2xULN, ALT > 3xULN or AST > 3xULN will be described graphically.

ECGs

ECG data will be analyzed based on local laboratory reported results. At each scheduled time-point, the triplicate ECGs will be taken as per protocol and the summary (mean) of their values for each ECG parameter will be collected in the [12 Lead ECG Evaluation – Local Analysis] eCRF page.

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. For this analysis, the Bazett's correction formula defined as QTcB = QT/SquareRoot(RR) and the Fridericia's correction formula defined as QTcF = QT/CubeRoot(RR), where RR (in seconds) = 60/HR, will be used for QT correction.

As described previously, ECG summary tables will include only ECG assessments collected during the on-treatment period. Shift tables, change from baseline summaries, and change score generation may use data from pre-treatment period for baseline calculations. The following summaries will be produced for each applicable ECG parameters.

- For each of ECG parameters (HR, and QT, QTcB, QTcF, 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 QT/QTc intervals (QT, QTcB, QTcF), shift tables based on notable parameter categories (≤450, >450 – ≤480, >480 – ≤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/QTcB/QTcF increase from baseline >30 ms, >60 ms
  - Newly occurring post-baseline QT/QTcB/QTcF >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 ≤220 ms, >220 ms
  - QRS increase from baseline >25% and value >110 ms
  - Newly occurring post-baseline QRS >110 ms and ≤120ms, >120 ms

  Note the denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. 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.

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 shift table analysis of notable QT/QTc intervals and the analysis of notable ECG changes.

All ECG parameters will be listed and the notable values will be flagged in the listing. In addition, patients with notable ECG values will be listed separately.

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), systolic and diastolic blood pressure (mmHg).

As described previously, vital sign summary tables will include only vital sign assessments collected during the on-treatment period. Shift tables, change from baseline summaries, and change score generation may use data from pre-treatment period for baseline calculations. The following summaries will be produced for each of vital sign parameters (weight, body temperature, pulse rate, systolic and diastolic blood pressure).

- Descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point.
- Shift table based on values classified as notable low, normal, notable high, or notable (high and low) at baseline and the worst post-baseline value observed.

Clinically notable elevated values are defined as:

- Systolic BP: ≥160 mmHg and an increase ≥20 mmHg from baseline
- Diastolic BP: ≥100 mmHg and an increase ≥15 mmHg from baseline
- Body temperature: ≥39.1°C
- Weight: increase from baseline of ≥10%
- Pulse rate: ≥120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values are defined as:

- Systolic BP: ≤90 mmHg and a decrease ≥20 mmHg from baseline
- Diastolic BP: ≤50 mmHg and a decrease ≥15 mmHg from baseline
- Body temperature: ≤35°C
- Weight: decrease from baseline of ≥10%
- Pulse rate: ≤50 bpm with decrease from baseline of ≥15 bpm

All vital sign parameters (including height and BMI at screening) will be listed and the notable values will be flagged in the listing. In addition, patients with notable vital sign values will be listed separately.

ECOG (WHO) performance status

The ECOG (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 2-4, ranging from 0 (most active) to 5 (dead):

Table 2-4 ECOG (WHO) performance status scale

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

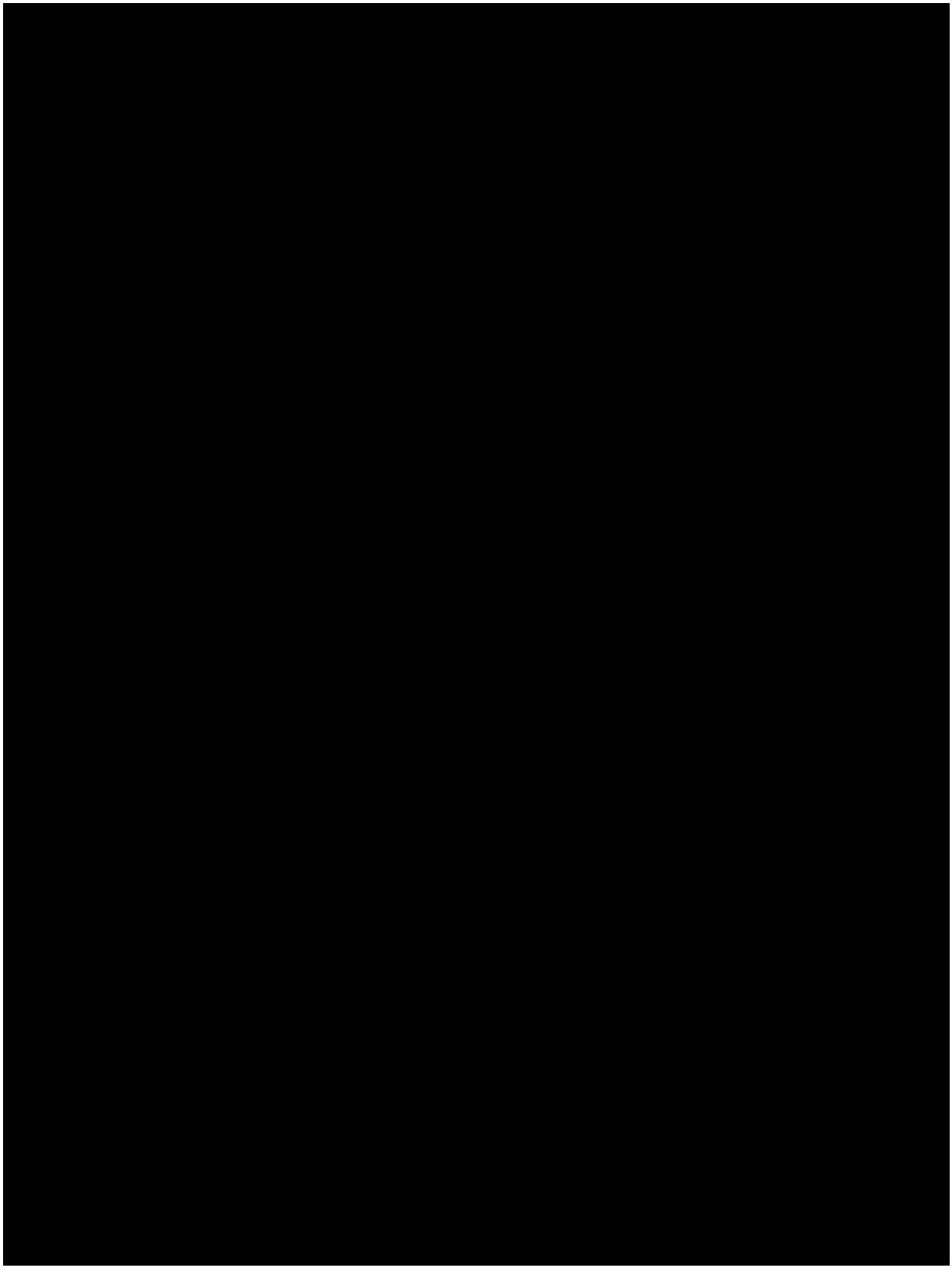
The following summaries will be produced for the FAS.

- Shift table of ECOG performance status at baseline to worst post-baseline status by score
- Shift table of ECOG performance status at baseline to best post-baseline status by score

ECOG performance status will be listed for the FAS.

Drug-induced liver injury

For patients meeting the potential drug-induced liver injury (DILI) criteria specified in the protocol, further follow-up and data collection related to liver events (e.g., detailed history, medication, laboratory test, liver exams/tests) will be required by using the [Liver Events] eCRF pages as appropriate. All DILI-related data will be listed if available.



2.9 Sample size calculation

The study does not include formal statistical hypothesis testing and the sample size (N=20) is not derived based on power considerations.

A response rate of 10% or less is considered as an insufficient level of activity for the proposed patient population. With a sample size of 20 patients, there is an approximately 58.4% chance that the exact 95% CI will exclude an insufficient response rate of 10% when the true ORR is 30%. The probability increases to 75.5% and 87.4%, when the true ORRs are 35% and 40%, respectively. For an observed response rate of 30.0% (6 responders in 20 patients), the exact 95% CI is (11.9%, 54.3%). The operating characteristics of this study are summarized in Table 2-5.

Table 2-5 Operating characteristics for various ORRs when N=20 patients

True ORR	Probability that exact 95% CI excludes an insufficient level of 10% *	Expected number of responders	Observed ORR and exact 95% CI
30%	58.4%	6	30.0% (11.9%, 54.3%)
35%	75.5%	7	35.0% (15.4%, 59.2%)
40%	87.4%	8	40.0% (19.1%, 63.9%)

*Of 20 patients at least 6 responders are required to meet the criteria (i.e., exact 95% CI excludes an insufficient level of 10%), thus it is calculated as a binomial probability that ≥6/20 responders are observed given the true ORR.

2.10 Power for analysis of key secondary variables

Not applicable.

2.11 Interim analysis

No interim analysis is planned in this study.

3 Changes to protocol specified analyses

No changes are made.

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 programing 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 of study data after all patients have either completed at least 6 cycles of treatment or discontinued earlier; final analysis of study data once at least 75% of patients have died) will include the data with an assessment date or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the analysis cut-off date. For example, if the cut-off date is 30DEC2008, an AE starting on 28DEC2008 will be reported, whereas an AE starting on 31DEC2008 will not be reported.

4.2 Patient classification into analysis sets

This section provides additional details to those included in Section 2.2.

Patients are excluded from the analysis sets based on the protocol deviations entered in the database and/or on specific patient classification rules as shown in Table 4-1 below.

Table 4-1 Patient classification rules

Analysis set	Protocol deviation ID* leading to exclusion	Additional patient classification rules leading to exclusion
Full Analysis Set	INCL13 (Patients who do not provide the written informed consent prior to any screening procedures), TRT02 (Patients who do not receive at least one dose of study drug without the withdrawal of informed consent after continuing into the treatment phase)	
Safety Set	INCL13, TRT02	
[redacted]		

*Protocol deviation IDs are from the 'PD Specs and Edit Checks' sheet of Study Specification Document (SSD) final version 1.0. If the SSD (protocol deviation IDs) is updated during the study, refer to the corresponding IDs provided in the latest SSD at the time of analysis.

4.3 Last contact date

The last contact date is used for censoring in OS analyses and will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

- All patient assessment dates (e.g., blood draws, vital signs, performance status, ECG, tumor assessments).
- Start and end dates of antineoplastic therapies administered after study drug discontinuation.
- AE start and end dates.
- From the [Survival information] eCRF page,
  - Last known date subject 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 subject alive nor date of assessment is used.
- Study drug start and end dates.
- Date of discontinuation collected on the [End of Treatment Phase Disposition] and/or the [End of Post Treatment Phase Disposition] eCRF pages.

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 analysis cut-off date will not be applied to the last contact date.

4.4 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.

4.5 Age derivation

Age will be calculated based on the date when the patient signed the main study informed consent from the date of birth.

4.6 Dose interruptions and dose changes

This section provides additional details to those included in Section 2.6.

All reporting of dose interruptions and dose changes are based on the dose actually taken by the patient and flags for dose interruption/change recorded on the [DAR] eCRF page.

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*).

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.

Dose reductions are a subset of dose changes where dose changes to higher than protocol planned dose are excluded.

4.7 Efficacy endpoints

For further details on efficacy endpoints, see Section 15 (Appendix 2) of the CLDK378A1201 protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator according to RECIST 1.1.

Response and progression evaluation will be performed according to the Novartis RECIST 1.1 guidelines, included in Section 15 (Appendix 2) of the protocol.

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

4.7.1 Implementation of RECIST guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method as per RECIST 1.1 (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 [RECIST New Lesion] eCRF page 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 an UNK (unknown) overall lesion response assessment. However, a response assessment other than the Novartis calculated UNK response may be accepted from the investigator 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 review process.

Determination of missing adequate tumor assessments

For the computation of ORR, 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. 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 15 (Appendix 2) of the protocol, 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 $D_2 = (8 \times 2) + 2 = 18$ 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
3. Withdrew consent
4. Adequate assessment no longer available
5. New cancer therapy added prior to disease progression
6. Event after ≥2 missing tumor assessments

PFS censoring reason is then derived by the following sequence of rules.

- If patient is considered to have a PFS event then PFS censoring reason is set to missing.
- Else if patient has had no baseline tumor assessment then PFS censoring reason = 4.
- Else if start date of new anti-neoplastic therapy is before any PFS event which is less than D_2 distance after date of last adequate tumor assessment (LATA), i.e., if (PFS event date – LATA date ≤ D_2), then PFS censoring reason = 5.
- Else if patient has a PFS event after two or more missing assessments, i.e., if (PFS event date – LATA date > D_2) and PFS event is before min date, then PFS censoring reason = 6.
- Else if min date = date of withdrawal of consent and (date of withdrawal of consent – LATA date ≤ D_2) then PFS censoring reason = 3.

- Else if min date = date of treatment discontinuation and (date of treatment discontinuation – LATA date ≤ D_2) and date of discontinuation reason in the [End of Treatment Phase Disposition] eCRF page = 'Lost to follow-up' then PFS censoring reason = 2.
- Else if min date = analysis cut-off date and (analysis cut-off date – LATA date ≤ D_2) then PFS censoring reason = 1.
- Else PFS censoring reason = 4.

where min date = minimum of non-missing (analysis cut-off date, start date of further anti-neoplastic therapy, date of withdrawal of consent, date of discontinuation due to loss to follow-up).

Non-measurable disease at baseline

As specified in Section 15 (Appendix 2) of the protocol, the RECIST 1.1 criteria imply that only patients with measurable disease at baseline 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 the 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 Section 15 (Appendix 2) of the protocol, overall lesion response can be derived for patients without measurable disease at baseline as follows (Table 4-2).

Table 4-2 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 *	No	Non-CR/Non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

* 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 15 (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 study drug. This rule, however, only applies to the 'PD component' of the PFS or DOR assessment.

Patients without baseline tumor assessment who die within D_2 distance from start date of study drug 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 diameters 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 lesion 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) as needed.

All possible assessment scenarios are described in Table 4-3.

Table 4-3 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	Non-CR/Non-PD	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:
   a. 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 b.
   b. Check the overall lesion response. If PD, then go to step c. Otherwise, go to step d.
   c. Check target response. If PD, then go to step d. Otherwise flag the assessment *.
   d. 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.

Investigator assessment will be used in the construction of waterfall plot.

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.

In addition, patients with a PFS event will be represented by the flag '#' below or above the vertical bars.

4.7.2 Sources for overall lesion response

The tumor-response related endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. In this study, the overall lesion response at a given assessment/time point will be provided from single source, i.e., investigator (local radiology) reported overall lesion responses. No blinded independent review committee (BIRC) is established for independent tumor assessments. Therefore the evaluation of tumor-response related endpoints will be based only on investigator assessments in this study.

4.7.3 BOIR calculations in patients with measurable brain metastases at baseline

A patient with measurable brain metastases at baseline is defined as a patient having at least one target lesion in the brain. Inclusion of response assessments based on lesion locations in the brain for each assessment, including baseline to identify whether patients have measurable brain metastases, uses the following list of terms collected based on investigator reported tumor data ('Lesion Location' collected on the [RECIST] eCRF pages):

- Brain
- CNS: Infratentorial
- CNS: Supratentorial
- Cerebral cortex
- Meninges
- Spinal cord
- CNS - not otherwise specified
- Leptomeningeal
- Cerebellum

For all lesion locations above, 'Lesion Type' should be 'Non-nodal' for the inclusion of response assessments. This list may be updated based on actual data of the lesion locations

(and the description of lesion) at the time of analysis, as per scientific judgment of the medical expert. Especially when the lesion location is 'Other', the description of lesion will be considered.

The following steps will be taken to calculate the best overall intracranial response (BOIR) for patients with measurable brain metastases at baseline:

1. If only target lesion in brain and no non-target lesions in brain are identified at baseline, calculate the sum of the measured diameters from all target lesions in the brain (selected from list above), and use new lesions in brain (if any, based on the list) to derive responses per assessment. Non-target lesion response status is not considered since no non-target lesions were identified in the brain at baseline.
2. If both target and non-target lesions in the brain are identified at baseline, calculate the sum of the measured diameters from all target lesions in the brain (selected from list above), use all non-target lesion response status in the brain (selected from list above) and new lesions in the brain (if any, based on the list) to derive responses per assessment.
3. For each assessment, derive overall intracranial response.
4. For the whole set of derived overall intracranial responses, calculate BOIR.

For this subset of patients, calculate the OIRR.

4.7.4 Kaplan-Meier estimates

To analyze time-to-event endpoints (DOR, PFS and OS) an estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option (see example below). The median time to event and estimated event rates at different time points will be estimated, along with associated 95% two-sided CIs derived based on the complementary log-log transformation. This will be conducted via the SAS procedure LIFETEST. 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 time to event will be obtained along with two-sided 95% CIs calculated from PROC LIFETEST output using the method of Brookmeyer and Crowley, 1982.

Kaplan-Meier estimates with two-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 endpoint. The CIs will be constructed using Greenwood's formula (Collet, 1994, p.23) for the standard error of the Kaplan-Meier estimate.

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

4.7.5 Confidence interval for response rate

ORR, DCR and OIRR 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 x (1 – two-sided alpha level of 0.05)) two-sided Pearson-Clopper CI. These estimates are obtained as follows:

```
PROC FREQ DATA=dataset;
   TABLE binary-event / BINOMIAL(LEVEL='Yes') ALPHA=0.05;
   EXACT BINOMIAL;
RUN;
```

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 lower confidence limit (LCL) and the upper confidence limit (UCL) of a 0% response rate are calculated as follows:

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

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

4.8 Safety evaluations

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

4.8.1 Multiple assessments within post-baseline visits

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

Laboratory Data

Local laboratories will be used for laboratory evaluations in this study. However, if laboratory assessments are collected from both local and central laboratories on the same date, analyses are as follows. 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

ECG data will be analyzed based on local laboratory reported results. At each scheduled time-pint, the triplicate ECGs will be taken as per protocol and the summary (mean) of their measurements for each ECG parameter will be collected in the [12 Lead ECG Evaluation – Local Analysis] eCRF page. Thus the mean of measurements associated with the scheduled time point will be used for the analyses.

4.8.2 Baseline

As defined in Section 2.8.2, the last available assessment before or on the start date of study drug is defined as 'baseline' value or 'baseline' assessment.

Laboratory data

Local laboratories will be used for laboratory evaluations in this study. However, if both local and central laboratory assessments are 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 mean of the pre-dose replicate measurements on the baseline day. For the calculation of the mean, unscheduled assessments will not be combined with scheduled assessments. The mean will be calculated separately for scheduled and unscheduled. Note in this study the mean of replicate measurements at each time point is collected on the [12 Lead ECG Evaluation – Local Analysis] eCRF page and thus individual measurements are not entered in the database.

Study day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration. 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. Unscheduled assessments on study day 1 will be considered as post-baseline.

4.8.3 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.

Handling of test values below LLOQ and above HLOQ

For numeric laboratory parameters, test values below the lower limit of quantification (LLOQ) and above the higher limit of quantification (HLOQ) may show '<n' (or '<=n') and '>n' (or '>=n') in the database respectively, where n can be any number. The classification of the CTC grades and the low/normal/high groups will follow a data handling rule: a value which shows '<n' (or '<=n') will be handled as zero; a value which shows '>n' (or '>=n') will be handled as n. These values will be presented in the listing as it is.

Hematology

Hematologic tests include hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), and differential counts (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):

NEU count = (WBC count) x (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 absolute range is NOT missing (% range is or is not missing), then use the absolute range provided by the site.
- If % range is NOT missing and absolute range is 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) x (LLN for NEU%value / 100),

  ULN for NEU count = (ULN for WBC count) x (ULN for NEU%value / 100)

Biochemistry

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

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

The normal limits (LLN and ULN) for corrected Ca will also be derived using the above formula with the corresponding normal limits for total Ca and serum albumin.

4.9 Handling of missing or partial dates

For patients not known to have died prior to the analysis 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 to the min (analysis cut-off date, death date, 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.

4.9.1 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 DDMMMYYYY 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:

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

The following Table 4-4 explains the abbreviations used.

Table 4-4 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 4-5 describes the possible combinations and their associated imputations. In the 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 4-5 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 4-6 is the legend to the above table.

Table 4-6 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 4-7 gives a few examples.

Table 4-7 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

4.9.2 Incomplete dates of initial diagnosis, first recurrence/progression and most recent relapse/progression

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

4.9.3 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.

4.9.4 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 1st 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.

4.9.5 Incomplete date for death or last contact

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

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

- Missing day: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day is missing from the date of last contact, it will be imputed to the 15th day of the month and year of last contact only if derived from the survival page.

4.9.6 Incomplete date for disease progression on alectinib prior to the start of study drug.

If day of progression associated with the [Prior Antineoplastic Therapy – Alectinib] eCRF page is missing then the imputed PD date is:

= min (midpoint between the end date of the prior alectinib medication and the end of the month, start date of LDK), if end date of prior alectinib medication is in the same month as the PD date.

= min (15th of the month of the PD date, start date of LDK), if end date of prior alectinib medication is in a month prior to the PD date.

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

If both day and month of progression associated with the [Prior Antineoplastic Therapy – Alectinib] eCRF page is missing then the imputed PD date is:

= min (midpoint between the end date of the prior alectinib medication and the end of the year, start date of LDK), if end date of prior alectinib medication is in same year as the PD date.

= min (July 1 of the year of the PD date, start date of LDK), if end date of prior alectinib medication is in a year prior to the PD date.

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

Completely missing PD dates will not be imputed. For the midpoint calculation, if odd days in between (e.g., last dose of alectinib is 27 June 2012, and end of the month is 30 June 2012), then use the next day from the midpoint calculation (e.g., midpoint is 29 June 2013).

4.9.7 Incomplete date for last dose of study drug

Scenario 1

If the last date of study drug is after the analysis cut-off date or is completely missing and there is no [End of Treatment Phase Disposition] eCRF page and no death date, the patient should be considered to be on-going and use the cut-off 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 Phase Disposition] 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 Year = Year of min (EOT visit date, death date) and Month < the month of min (EOT visit date, death date)

= 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.

5 Reference:

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