NOVARTIS

Clinical Development

DRB436E/Dabrafenib/Tafinlar®

CDRB436ECN01/ NCT04452877

An Open-Label, Single-arm Study to Evaluate the Safety and Efficacy of Dabrafenib in Combination with Trametinib in Chinese Patients with BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final
Release date:	15-Oct-2024
Number of pages:	31

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Aug-2020	Prior to DB lock	Creation of initial version	N/A - First version	NA
13-Apr-2021	Prior to DB lock	Changes needed for primary analyes as per protocol and to implement changes to LVEF analyses	The definition of baseline was updated to specify the baseline for PRO analyses. The definition of full analysis set was updated to align with definition in the protocol. ECG and cardiac imaging data section LVEF analyses were updated to incorporate clinical evaluations. Heading of section 2.10 and section 2.9 were fixed.	2.1.1.4 Baseline 2.2 Analysis set 2.7.4.1 ECG and cardiac imaging data 2.9 PD and PK/PD analyses 2.10 Patient-reported outcomes
15-Oct-2024	Prior to Final DB lock	Changes needed for final analyses as per protocol	Updated the version of the study protocol for which the SAP is based on. [redacted]	1 Introduction [redacted]

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study DRB436ECN01, a single-arm, open label, multicenter phase II, study of dabrafenib in combination with trametinib in Chinese subjects with *BRAF* V600E mutation-positive, stage IV NSCLC (AJCC staging 8th edition).

The content of this SAP is based on protocol DRB436ECN01Amendment 4, dated 13-Mar-2023. All decisions regarding final analysis, as defined in this SAP document, have been made prior to database lock.

1.1 Study design

This is a single arm, open label, multicenter phase II study evaluating the efficacy and safety of dabrafenib in combination with trametinib in Chinese subjects with BRAF V600E mutation-positive AJCC v8 stage IV NSCLC.

Subjects with stage IV BRAF V600E mutant NSCLC confirmed by local qualified assay (NMPA and/or MOH-approved) will be enrolled in this study. Central testing for BRAF V600E will be performed. This study will enroll subjects:

1. who have not received any prior systemic anti-cancer therapy for metastatic disease (i.e. dabrafenib/trametinib will be the 1st line treatment for metastatic disease)
2. who have relapsed or progressed on at least one prior platinum based chemotherapy prior to enrollment but cannot have received more than 3 prior systemic therapies for metastatic disease (i.e. dabrafenib/trametinib will be no less than second line treatment for metastatic disease).

All subjects must not have been previously exposed to a BRAF or MEK inhibitor. Subjects will receive the recommended dose of both drugs (dabrafenib 150 mg twice daily and trametinib 2 mg once daily).

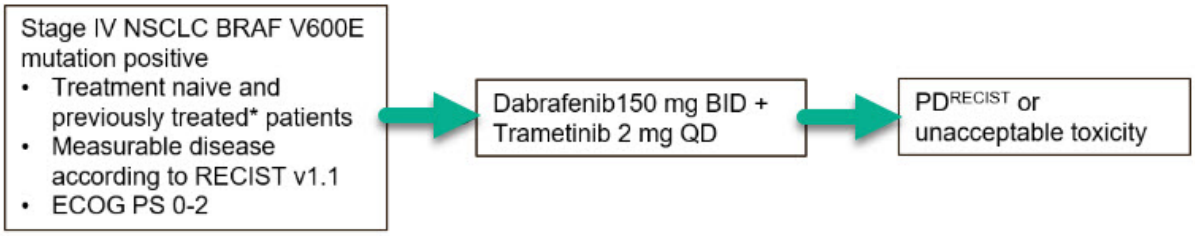
The primary endpoint for the study is ORR as determined by central independent review using Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Approximately 40 Chinese patients over 18 years old will be enrolled in this study and will receive dabrafenib (150 mg BID) and trametinib (2 mg once daily) combination therapy until disease progression by RECIST 1.1 as determined by investigator, unacceptable toxicity, start of a new antineoplastic therapy, pregnancy, withdrawal of consent, lost to follow-up, physician's decision, death, or if study is terminated by the sponsor. Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment.

Treatment beyond disease progression per RECIST 1.1 as determined by investigator is allowed if protocol specific criteria are met. The tumor assessments will be performed every 6 weeks until Week 36, and every 12 weeks thereafter until disease progression, death, lost of follow-up, or withdrawal of consent. Survival and new anti-cancer therapy follow-up will continue until study completion.

No interim analysis will be conducted for this study.

Figure 1-1 Study Design



*For previously treated patients: up to three systemic treatments for metastatic disease with at least one prior approved platinum-based regimen will be allowed.

1.2 Study objectives and endpoints

Objectives and related endpoints are provided in Table 1-1.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the objective response rate (ORR) by central independent review	• ORR, defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) by central independent review as per RECIST 1.1 criteria.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess overall response rate (ORR), progression-free survival (PFS), duration of response (DoR) by investigator assessment	• ORR, defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST 1.1 criteria. • PFS, defined as the interval between first dose and the earliest date of disease progression or death due to any cause. • DoR, defined for the subset of subjects with confirmed CR or PR, as the time from first documented evidence of CR or PR until time of first documented disease progression or death due to any cause.
• To evaluate overall survival (OS)	• OS, defined as the time from first dose until death due to any cause.
• To characterize the safety and tolerability of dabrafenib in combination with trametinib in Chinese patients with *BRAF* V600E mutation-positive stage IV NSCLC	• Measurements used to evaluate safety will include AEs, physical and dermatological examinations, ophthalmic examination, vital signs, 12-lead ECGs, ECHO, and clinical laboratory tests.
• To characterize PK of dabrafenib, dabrafenib metabolites, and trametinib	• Trough concentrations of dabrafenib, dabrafenib metabolites, and trametinib at Visits of week 3, 6, and 12.

Objective(s)	Endpoint(s)
• To characterize quality of life as measured by the EORTC-QLQ C30, LC13 and the EQ-5D-5L	• Change from baseline in EORTC QLQ-C30/LC13, and EQ-5D-5L.
[redacted]	

2 Statistical methods

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The data from all centers that participate will be combined in the analyses.

Primary analysis will be conducted when all enrolled subjects have had at least two post-baseline tumor assessments or have discontinued study earlier for any reason prior to the second post-baseline disease assessment, and the final analysis will occur at the end of the study.

2.1 Data analysis general information

All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings. If it is required to impute an end date to be able to perform a specific analysis (e.g. for a dose administration record for dabrafenib or trametinib drugs with missing end date or end date after the cut-off date, the cut-off date needs to be imputed as an end date to allow for calculation of treatment exposure duration and dose intensity), the imputed date will be displayed and flagged in the listings.

All data will be analyzed by Novartis using Novartis clinical data standards (NCDS). Analysis data sets and statistical outputs will be produced using the SAS system Version 9.4 or higher (UNIX environment) in the global programming & statistical (GPS) environment.

Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

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

The primary efficacy and safety analysis will be conducted when all enrolled subjects have had at least two post-baseline tumor assessments or have discontinued study earlier for any reason prior to the second post-baseline tumor assessment. Any additional data collected past this time, as allowed by the protocol, will be further summarized in a final study report once these subjects completed the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1.1 General definitions

2.1.1.1 Study drug and study treatment

Study drug and study treatment both refer to Dabrafenib in Combination with Trametinib.

2.1.1.2 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 is administered and recorded on the exposure form. For the sake of simplicity, the date of first administration of study drug will also be referred 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 is administered and recorded on the exposure form. This date is also referred as last date of study drug.

2.1.1.3 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, 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 data listings.

2.1.1.4 Baseline

Baseline will be defined as the most recent non-missing value during the screening period prior to the first dose of study treatment. For Patient Reported Outcomes (PRO), baseline date will be the same as Cycle 1 Day 1 for each participant given ePROs will be completed prior to any other assessments and treatments on Cycle 1 Day 1. For laboratory data, baseline will be

defined as the most recent non-missing value from a laboratory during the screening period prior to the first dose of study treatment. If patients have no value as defined above, the baseline results will be considered missing.

2.1.1.5 Last contact date

Last contact date will be used for the censoring of patients in the analysis of overall survival.

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

- Last contact date collected on the 'Survival information' eCRF.
- All assessment dates (e.g. tumor assessment, laboratory/PK collection dates, vital signs assessment, performance status, ECG assessment). Note, only a true on study assessment date or patient contact date will be used. If there is a visit date without evidence of any actual assessment performed that date will not be used. No dates post cut-off will be used.
- Medication dates including study medications, concomitant medications, and anti-cancer therapies administered after study treatment discontinuation.
- Adverse event dates.

Note: The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date.

2.1.1.6 Treatment periods

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

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects who received at least one dose of study drug from enrollment up to the cut-off date. This population will be the primary population for efficacy and safety analysis.

The Pharmacokinetic Analysis Set (PAS) will consist of those subjects in the FAS for whom a pharmacokinetic sample is obtained and analyzed.

2.2.1 Subgroup of interest

Not applicable.

2.3 Patient disposition, 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 presented overall and listed by treatment group (previously treated and treatment naive) and overall. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, smoking history, ECOG performance status, etc.) will be summarized by frequency count and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, BMI, etc.) will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer at initial diagnosis, diagnosis of disease, BRAF mutation status, details of tumor histology/cytology, stage at study entry per AJCC Edition 8, time since initial diagnosis, time from initial diagnosis to first recurrence/progression (in months), time since most recent relapse/progression to randomization (in months), presence/absence of target and non-target lesions, sum of lesion diameter for target lesions at baseline, number and type of metastatic sites involved. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page. Tumor (T) stage at study entry, lymph nodes (N) stage at study entry, and metastases (M) at study entry will be further listed in the Subject disease history listing.

Medical history

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

Prior anti-cancer therapy

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

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized.

Prior anti-neoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens of anticancer medications. Prior antineoplastic medications will also be summarized by ATC class, and preferred term.

Screen failures

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

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

All screen failure patients with reasons for screen failure will be listed. Violations of inclusion/ exclusion criteria leading to screen failures will be summarized by criteria.

2.3.1 Patient disposition

The number (%) of screened and not-randomized subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

A summary of the number of subjects in FAS and PAS will be provided. A listing of subjects excluded from analysis populations will also be provided. Anyone who had a randomization ID but without a study treatment will be excluded from FAS. Anyone who do not have PK sample will be excluded from PAS.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who discontinued study treatment, has treatment ongoing or completed the study, and a summary of the primary reasons for discontinuation of study treatment or death. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF.

A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The FAS will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in months to Dabrafenib and Trametinib respectively, as well as actual cumulative dose, the dose intensity (DI) (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (RDI) (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose changes, reductions or interruptions, and the reasons, will be summarized.

Dose exposure and intensity

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

- Duration of exposure (days): last date of study drug − first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a patient in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- Average daily dose (mg/day): cumulative dose (mg)／number of dosing days (days)
- DI (mg/day): cumulative dose (mg)／duration of exposure (days)
- RDI (%): 100 × [DI (mg/day)／planned dose]

The number of subjects with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized.and all dosing data will be listed.

Summary statistics of time to first dose reduction / interruption will also be presented.

Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

Dose reductions, interruptions or permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized.

‘Dose changed’, ‘Dose interrupted’, and ‘Dose permanently discontinued’ fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields ‘Reason for dose change/dose interrupted’ and ‘Reason for permanent discontinuation’ will be used to summarize the reasons.

A dose change is either ‘change in prescribed dose level’ or ‘dosing error’ where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Number of reductions will be derived programmatically based on the change and the direction of the change.

The number of subjects who continue treatment beyond RECIST1.1 progression according to local investigators assessment based on protocol specified criteria will be summarized. It includes all subjects who received any study treatment (i.e. at least one dose of any component of the study treatment) after RECIST 1.1 progression assessed by local investigators. Those subjects will be identified using the field "Will the subject continue treatment beyond disease progression as per RECIST1.1?" on the Verification for Treatment beyond RECIST1.1 PD CRF pages.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery, will be summarized by treatment group and overall. Prior anti-neoplastic medications will be summarized by therapy type (e.g. chemotherapy, hormonal therapy, immunotherapy etc.) and setting (e.g. adjuvant, metastatic, etc.). Summaries will also include total number of regimens, time from last treatment to progression for the last therapy, type of therapy received at any time or as last systemic therapy for metastatic lung cancer prior to enrollment, excluding radiotherapy and surgery, best response to last systemic therapy based on RECIST v1.1. The medication therapy type of any combination therapy will be classified based on the types of treatment taken at each regimen. For example, a combination therapy of targeted therapy and immunotherapy will be classified in both categories with appropriate sub-types.

For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized. For prior surgery, time since last surgery and procedure will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery. Palliative antineoplastic radiotherapy administered during the treatment phase may also be summarized.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Concomitant medications

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

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

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

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

2.5 Analysis of the primary objective

The primary objective is to assess the ORR of dabrafenib in combination with trametinib in Chinese patients with *BRAF* V600E mutation-positive metastatic NSCLC by central independent assessment.

2.5.1 Primary endpoint

The primary endpoint of the study is overall response rate (ORR), defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR), as per central independent review assessment and according to RECIST 1.1.

2.5.2 Statistical hypothesis, model, and method of analysis

This study will pursue an estimation approach rather than formal hypothesis testing. The ORR will be summarized along with its exact 95% confidence intervals.

2.5.3 Handling of missing values/censoring/discontinuations

Subjects in the study who are of unknown clinical response will be treated as non-responders.

2.6 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives in this study are: To assess overall response rate (ORR), progression-free survival (PFS), duration of response (DoR) and overall survival (OS) by investigator assessment.

2.6.1 Secondary endpoints

All secondary efficacy assessments (ORR, PFS, DoR, OS) will be analyzed as per investigator assessment. Confirmation of response is required for all response endpoints, as per RECIST 1.1.

All secondary efficacy analyses will be performed based on the FAS.

The secondary efficacy endpoints are:

- ORR

- PFS
- DoR
- OS

2.6.2 Statistical hypothesis, model, and method of analysis

ORR is defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) by investigator assessment as per RECIST 1.1 criteria. ORR will be analyzed in the FAS population. ORR will be summarized along with its exact 95% confidence intervals.

PFS is defined as the time from the date of first dose to the date of the first documented progression or death due to any cause. PFS will be assessed via local review according to RECIST 1.1. PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-neoplastic therapy.

PFS will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented, if appropriate.

Duration of response (DoR) only applies to subjects whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data per local review. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. Subjects continuing without progression or death will be censored at the date of their last adequate tumor assessment. DoR will be listed and summarized for all subjects in the FAS with confirmed BOR of CR or PR.

OS is defined as the time from date of first dose to date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

OS will be analyzed in the FAS population. The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented, if appropriate.

2.6.3 Handling of missing values/censoring/discontinuations

For subjects who have not progressed or died at the time of the PFS, OS or DoR analysis, censoring will be performed using the date of the last adequate disease assessment or first dose for subjects without any adequate post baseline assessments. In addition, subjects with a loss to follow-up prior to a PFS or death event will be censored at the date of the last adequate disease assessment prior to the loss to follow-up for PFS or OS, respectively. Subjects who start new anti-cancer therapy prior to a PFS event will be censored for PFS and DoR (if this subject is a responder). In these cases, an adequate assessment is defined as an assessment where the investigator determined response is CR, PR, or SD.

2.7 Safety analyses

All safety analyses will be performed based on the FAS.

2.7.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding (using the latest version available prior to clinical database lock) by maximum severity (based on Common Terminology Criteria for Adverse Events [CTCAE] grades version 4.03), and relation to study drug. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency.

AEs will be coded using MedDRA using the latest version available locket the time of analysis and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death) is not used; rather, ‘fatal’ is collected as AE outcome and death information is also collected on a separate (e)CRF page.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- On-treatment deaths, by primary system organ class and preferred term
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs associated with discontinuation of study drug
- AEs requiring dose adjustment or study drug interruption
- AEs requiring significant additional therapy
- AEs excluding SAEs

All AEs regardless of study drug relationship will be summarized.

2.7.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESI are discussed in detail in the Investigator Brochure, and a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms to flag as AESI's will be exported from the eCRS.

AESI for dabrafenib include:

- Hypersensitivity
- Complicated pyrexia and/or Grade 3 and Grade 4
- New primary/secondary malignancy
- Pre-renal and intrinsic renal failure
- Uveitis
- Hyperglycemia
- Pancreatitis
- AESI for trametinib include:
- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders
- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Hypersensitivity
- Venous thromboembolism (VTE)
- AESI for dabrafenib in combination with trametinib include:
- Skin related toxicities
- Ocular events
- Cardiac related events
- Hepatic disorders

- Pneumonitis/interstitial lung disease
- Bleeding events
- Hypertension
- Hypersensitivity
- Pyrexia
- New primary/secondary malignancy
- Pre-renal and intrinsic renal failure
- Uveitis
- Hyperglycemia
- Venous thromboembolism (VTE)
- Pancreatitis
- Neutropenia

2.7.2 Deaths

On-treatment and all deaths will be separately summarized based on the number and percentage of subjects. The summary will include primary cause of death (disease under study, SAE related to study treatment, or other).

All deaths will be listed, post-treatment deaths will be flagged.

2.7.3 Laboratory data

The summaries will include all assessments collected no later than 30 days after study drug discontinuation. All assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings.

All laboratory data will be listed by subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v4.03 grades if applicable and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by CTCAE v4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v4.03 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE v4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

2.7.4 Other safety data

The summaries will include all assessments collected no later than 30 days after study drug discontinuation. All assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings.

2.7.4.1 ECG and cardiac imaging data

All ECG parameters will be listed by subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Separate listing will be provided for QTcF. Average value will be used for time points with triplicate measurements, and will be included in the listing. Separate listings of QTcF will be produced for subjects with any QTcF>500 msec and/or QTcF change from baseline >60msec. In all listings, baseline value will be specified for each subject.

All ECG parameters change from baseline will be listed. Separate listing will be provided for QTc change from baseline.

Numeric values of ECG parameters will be summarised at baseline, planned visit and worst case post-baseline. Summary statistics will include count, mean, median, standard deviation, minimum, and maximum.

Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced (by treatment group).

QTcF shifts from baseline category will be produced for worst case post-baseline. The following categories will be used:

- <450msec
- 450-480 msec
- 481-500 msec
- >500 msec

Worst case post-baseline increase from baseline to the following categories will be summarized for QTcF:

- Any Grade Increase
- Increase to Grade 1 (450-480 msec)
- Increase to Grade 2 (481-500 msec)
- Increase to Grade 3/4 (>500 msec)

Note: 'Any Grade Increase' will include increase to Grade 1 (450-480), increase to Grade 2 (481-500), and increase Grade 3/4 (>=501).

QTcF increases from baseline of 31-60 msec and >60 msec will be summarized for worst-case post-baseline. Subjects with missing baseline values will be excluded from this summary.

All ECG findings will be listed. The worst-case post-baseline ECG findings will be summarised by frequency and percentage.

LVEF Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst case post baseline. Only the post baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- Any increase
- No change
- Any decrease
- >0 - < 10 Decrease
- 10 - 19 Decrease
- >= 20 Decrease

LVEF results will also be listed with subject level details including absolute change from baseline.

Note: If there is any change in the methodology used throughout the study compared to baseline, the post-baseline values for which the methodology differs from baseline will be discarded in the tables presenting comparisons to baseline.

A listing of patients with newly occurring clinically significant abnormality will be produced.

2.7.4.2 Vital signs

Vital sign data (blood pressure, heart rate, temperature, etc.) and change from baseline will be listed for each subject by treatment and visit/time. Baseline value will be specified in the listing of vital sign data.

Value of vital signs will be summarized using mean, median, standard deviation, minimum and maximum for baseline and worst-case post-baseline. The change from baseline at each planned visit and worst-case post-baseline will be summarized similarly.

Summary of shift from baseline categories to worst case post-baseline categories will be provided for systolic blood pressure, diastolic blood pressure, temperature and heart rate. Both increase and decrease in the categories will be included. The following categories will be used for both baseline and worst-case post-baseline:

- Systolic blood pressure (mmHg): Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3/4 (>=160)
- Diastolic blood pressure (mmHg): Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3/4 (>=100)
- Heart rate: <60bpm, 60-100bpm, >100bpm
- Temperature: <=35 C, >35 to <38 C, >=38C

Summaries of worst-case post-baseline change from baseline by categories in systolic blood pressure, diastolic blood pressure, temperature and heart rate will be produced:

For heart rate change from baseline category, the following categories will be used:

- Decrease to <60bpm
- Change to normal or no change
- Increase to >100bpm

For temperature change from baseline category, the following categories will be used:

- Decrease to <=35
- Change to normal or no change
- Increase to >= 38

For systolic blood pressure shift from baseline categories, the following categories will be used:

- ‘Any Grade Increase’
- ‘Increase to Grade 1 (120-139 mmHg)
- ‘Increase to Grade 2 (140-159 mmHg)’
- ‘Increase to Grade 3/4 (>=160 mmHg)’

Note: ‘Any Grade Increase’ will include increase to Grade 1 (120-139 mmHg), increase to Grade 2 (140-159 mmHg), and increase to Grade 3/4 (>=160 mmHg).

For diastolic blood pressure change from baseline categories, the following categories will be used:

- ‘Any Grade Increase’
- ‘Increase to Grade 1 (80-89 mmHg)
- ‘Increase to Grade 2 (90-99 mmHg)’
- ‘Increase to Grade 3/4 (>=100mmHg)’

Note: 'Any Grade Increase' will include increase to Grade 1 (80-89 mmHg), increase Grade 2 (90-99 mmHg), and increase to Grade 3/4 (>=100 mmHg).

Body weight and change from baseline will be listed. The summary of body weight at baseline and end of study treatment along with percent change will be provided.

2.8 Pharmacokinetic endpoints

Plasma concentration data of dabrafenib, dabrafenib metabolites, and trametinib will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. PAS will be used for pharmacokinetics.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Quality of life, as measured by the EORTC-QLQ C30, LC13 and the EQ-5D-5L, will be listed. Descriptive summaries and change from baseline will be provided.

2.11 Biomarkers

No biomarker analyses will be presented in this analysis. [redacted]

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

No interim analysis is planned.

[redacted]

[redacted]

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

In general imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapse time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study time periods or for specific analysis purposes as outlined below.

The partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation. The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed.

Details on imputing partial dates for specific datasets are outlined in following sections.

5.1.1 Study drug

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

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will be reported as "continuing at the cut-off date".
- 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.

For patients known to have died prior to or on the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the death date.
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the imputed end date 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 cut-off 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.

5.1.2 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 explains the abbreviations used.

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

The following matrix describes the possible combinations and their associated imputations. In the light grey boxes the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

	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 is the legend to the above table.

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 gives a few examples.

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

5.1.3 Concomitant medication date imputation

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

5.1.3.1 Prior therapies date imputation

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.

5.1.3.2 Post therapies date imputation

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.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event; although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. The Novartis internal CTC grading document should be added as appendix to the SAP and to Section 16.1.9 of the CSR. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

Common Toxicity Criteria (CTC) grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for an xxx differential

$$xxx\ count = (WBC\ count) * \left(\frac{xxx\ \%\ value}{100}\right)$$

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

$$Corrected\ Calcium\ \left(\frac{mg}{dL}\right) = Calcium\left(\frac{mg}{dl}\right) - 0.8\left[Albumin\ \left(\frac{g}{dL}\right) - 4\right]$$

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Statistical models

5.4.1 Confidence interval and p-value for response rate

This sections provides the programming details to assess the antitumor activity of ceritinib as measured by ORR.

ORR 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 & Pearson,1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI.

5.4.2 Kaplan-Meier estimates

To analyze time to event variables (DoR, OS and PFS) an estimate of the survival function will be constructed using ***Kaplan-Meier (product-limit) method*** as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

6 Reference

Brookmeyer R and Crowley J (1982). A Confidence Interval for the Median Survival Time, Biometrics 38, 29 - 41.

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26, 404-413.

Collet D (1994). Modelling survival data in medical research. London, Chapman & Hall.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group (2001). The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels.