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Novartis Research and Development

DRB436

Clinical Trial Protocol 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

Document type:	Amended Protocol Version
EUDRACT number:	N/A
Version number:	04 (Clean)
Clinical Trial Phase:	II
Release date:	13-Mar-2023

Clinical Trial Protocol Template Version 2.0 dated 01-Aug-2018

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CSCO	Chinese Society of Clinical Oncology
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DoR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EGFR	epithelial growth factor receptor
FDA	Food and Drug Administration
FPFV	First patient first visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLQ	lower limit of quantification
LPLV	Last patient last visit
MedDRA	Medical dictionary for regulatory activities

[redacted]

mg	milligram(s)
mL	milliliter(s)
MOH	Ministry of Health
NMPA	National Medical Products Administration
NSCLC	Non-small cell lung cancer
o.d.	once a day
ORR	Overall response rate
OS	Overall survival
p.o.	oral
PD	pharmacodynamic(s)
PFS	Progression-free survival
PK	pharmacokinetic(s)
PTA	Post-trial access
REB	Research Ethics Board
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SCAR	Serious cutaneous adverse reaction
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	upper limit of normal
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A specific group of participants fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Enrollment number	A unique identifier assigned to each enrolled participant
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial participants, regardless of randomization group, rescue medication, active drug run-ins etc.)

[redacted]

Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen Failure	A participant who is screened but is not treated or enrolled
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the participant as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date
Participant	An individual who has consented to participate in this study. The term Participant may be used to describe either a healthy volunteer or a patient.
Participant number	A number assigned to each participant who enrolls in the study. When combined with the center number, a unique identifier is created for each participant in the study. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed participant, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 4 (13-Mar-2023)

Amendment rationale

As of the release date of this amendment, 34 participants have been enrolled and treated in this study. China NMPA provided NDA conditional approval on 22-Mar-2022 Tafinlar (Dabrafenib Mesylate Capsules) in combination with Mekinist (Trametinib Tablets) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600 mutation.

The main purpose for this amendment is to add updated safety information, hemophagocytic lymphohistiocytosis (HLH) observed with dabrafenib and trametinib combination therapy, obtained from post marketing experience.

This amendment also introduces the following changes:

- Align the dose modification section of the protocol for hemophagocytic lymphohistiocytosis (HLH) with the dabrafenib Investigator's Brochure (IB) edition 15 and trametinib IB edition 15.
- Clarify description of the requirements for central BRAF V600 E mutation testing
- Update the rescreening procedure for screen failure subjects.
- Clarify the study completion and post-study treatment requirements
- Clarify the safety endpoint description for Adverse Events.
- Clarify the use of platinum-based treatment as mandatory for pre-treated subjects
- Wording changes to align with new Novartis protocol template v5.0 language:
    - Add new section on reference to treatment of overdose
    - Add sentence to clarify that data and samples collected from participants prior to screen failures may still be analyzed
    - Clarify the documentation of efficacy assessment in Central Imaging
    - Update the wording for women of child-bearing potential
    - Add text that eCOA assessments will not be reviewed by the Investigator/ study personnel.
    - Update the Pregnancy reporting language
    - Clarify the reporting of study treatment errors including misuse/abuse
    - Removal of text relating to the withdrawal of consent in certain countries where consent is not required for the use of personal and coded data

In addition, editorial revisions, corrections are made throughout the protocol to improve consistency.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Updated List of abbreviations

Updated Glossary of terms

Protocol summary: Updated to align with the amended protocol

Section 5.1 Inclusion Criteria

- Clarified the inclusion criteria wording regarding BRAF central lab testing. Inclusion criteria 3: the term "fresh tumor tissue sample" changed to "new tumor tissue sample" (to align with Section 8.5.3)
- Clarified the text of the Inclusion Criteria 4 for the use of platinum-based treatment as mandatory for pre-treated subjects (to align with Table 3-1)

Section 6.5.2.10 Guideline dose modification and management for hemophagocytic lymphohistiocytosis (HLH)

- Added the guideline dose modification and management for hemophagocytic lymphohistiocytosis (HLH)

Section 6.6.2 Treatment of overdose

- Added new section on reference to treatment of overdose

Section 8.1 Screening

- Updated the rescreening procedure for screen failure subjects to enable the rescreening of all the subjects regardless of the initial screen failure reason (i.e CT /MRI results have expired (>28 days prior to enrollment) due to unexpected administrative issues or unexpected drug supply issue
- Clarification that a new sample is not needed if participant already provided the tumor tissue samples for central testing of BRAF V600E mutation.

Section 8.1.2 Information to be collected on screening failures

- Added sentence to clarify that data and samples collected from participants prior to screen failures may still be analyzed

Section 8.3.1 Efficacy assessments

- Clarified the documentation of efficacy assessment in Central Imaging

Section 8.4.3 Pregnancy and assessments of fertility

- Updated the wording for women of child-bearing potential

Section 8.5.1 Clinical Outcome Assessments (COAs)

- Added text that eCOA assessments will not be reviewed by the Investigator/ study personnel.

Section 8.5.3 Biomarkers

- Updated description of the requirements for central BRAF V600 E mutation testing

[redacted]

Section 9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

- Removed text related to the withdrawal of consent in certain countries where consent is not required for the use of personal and coded data

Section 9.2 Study completion and post-study treatment

- Clarified the study completion date from 'approximately' 17 months to 17 months and separated from post-study treatment requirements

Section 10.1.4 Pregnancy Reporting

- Updated the Pregnancy reporting language

Section 10.1.5 Reporting of study treatment errors including misuse/abuse

- Clarified the reporting of study treatment errors including misuse/abuse

Section 12.5.2 Safety Endpoints

- Clarified the safety endpoint description for Adverse Events.

Section 15 References

- Updated list of references

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do not affect the Informed Consent. The Informed Consent for this study was already updated to reflect the hemophagocytic lymphohistiocytosis (HLH) safety measure after the IB updates in 2022.

Amendment 3 (15-Oct-2021)

Amendment rationale

As of the release date of this protocol amendment, 20 participants have been enrolled and treated in this study. A primary analysis has been conducted with a cut-off date of 11-Mar-2021.

The main purpose for this amendment is to increase the sample size from 20 to 40 participants to further investigate the efficacy and safety of dabrafenib and trametinib in Chinese patients with *BRAF* V600E mutation-positive metastatic non-small cell lung cancer (NSCLC). As per China National Medical Products Administration (NMPA) guidance, the sample size was increased.

This amendment also introduces the following changes :

- Align the dose modification section of the protocol for pyrexia with the dabrafenib Investigator's Brochure (IB) edition 13 and trametinib IB edition 13.
- Removed the carboxy-dabrafenib metabolite from the pharmacokinetic (PK) analysis. Based on exposure, relative potency, and PK properties, the activity of carboxy-dabrafenib is not likely to be clinically relevant. Analysis of carboxy-dabrafenib will be discontinued and PK of this metabolite for the additional patients will not be performed.
- Include a section related to Public Health Emergency mitigation procedures.
- Update the permitted concomitant therapy section of the protocol with a clarification on the use of vaccines.
- Include pandemic disruption proofing language under protocol sections 6.7, 7, 8, 8.3.1, 8.4, 8.4.1, 8.4.3, and 8.5.1.
- Update the withdrawal of informed consent language to align with the new Novartis protocol template version 4.0.
- Update the end of study definition.
- Replace "subjects" with term "participants" throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of abbreviations: updated the ORR definition, and added CRP/IB/ICF/MOH/PTA abbreviations

Glossary of terms: updated withdrawal of study consent definition

Protocol summary: updated to align with the amended protocol

Section 1.2 Purpose

- Updated the additional number of patients to be enrolled
- Updated the additional number of previously treated, and treatment naive patients to be enrolled

Section 2 Table 2-1 Objectives and related endpoints

[redacted]

- Updated the ORR defined form
- Clarified dabrafenib metabolites

Section 3 Study design

- Updated the total number of patients to be enrolled

Section 4.1 Rationale for study design

- Updated the additional number of patients to be enrolled as well as the enrolment period
- Removed the follow-up period for Study BRF113928

Section 4 Rationale

- Added new sub-section 4.6 Rationale for Public Health Emergency mitigation procedures

Section 6.2.1 Concomitant therapy

- Removed "Inactivated vaccines" as a clarification is provided under section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action

- Clarified the use of vaccines

Section 6.5.2.1 Pyrexia

- Updated dose modification guidelines for cases of pyrexia

Section 6.5.2.1 Table 6-5 Mandatory dose modification and recommended clinical management guidelines for suspected treatment-related pyrexia

- Updated requirement for suspected treatment-related cases of pyrexia

Section 6.7 Preparation and dispensation

- Added disruption proofing language

Section 7 Informed consent procedures

- Added disruption proofing language

Section 8 Visit schedule and assessments

- Added disruption proofing language

Section 8.3.1 Table 8-2 Imaging Assessment collection Plan

- Added disruption proofing language

Section 8.4 Safety

- Added disruption proofing language

Section 8.4.1 Laboratory evaluations

- Added disruption proofing language

Section 8.4.3 Pregnancy and assessments of fertility

- Added disruption proofing language

Section 8.5.1 Clinical Outcome Assessments (COAs)

- Added disruption proofing language

[redacted]

Section 8.5.2.1 Pharmacokinetic blood collection and handling

- Removed the carboxy-dabrafenib metabolite from the PK analysis

Section 8.5.2.2 Analytical method

- Removed the carboxy-dabrafenib metabolite from the PK analysis

Section 8.5.3 Biomarkers

- Clarified local testing of *BRAF* V600E mutation status.

Section 9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

- Updated the withdrawal of informed consent language

Section 9.2 Study completion and post-study treatment

- Updated the end of study definition

Section 10.1.3 SAE Reporting

- Clarified SAE reporting timeframe

Section 12 Data analysis and statistical methods

- Clarified the timeframe of primary analysis occurrence

Section 12.5. Analysis of secondary endpoints

- Clarified dabrafenib metabolites

Section 12.5.3 Pharmacokinetics

- Clarified dabrafenib metabolites

[redacted]

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The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2 (08-Jun-2020)

Amendment rationale

As of the release date of this protocol amendment, no patients have been screened or treated in this study.

The main purpose for this amendment is to reduce the amount of tumor material required for central BRAF V600E testing, following Human Genetic Resource Administration of China (HGRAC) recommendation and data obtained during the assay testing by the central laboratory. In order to complete the BRAF V600E testing at the central lab, the number of formalin-fixed paraffin-embedded (FFPE) tumor slides is reduced from minimum 10, to minimum 3 to maximum 5 slides, and tumor blocks are no longer needed.

This amendment also introduces the following changes:

- Update to exclusion criteria #1 in order to exclude patients with leptomeningeal metastases (LM) under the same conditions as patients with brain metastases: patients with non-small cell lung cancer (NSCLC) experience LM in 3-9% of cases. Because overall survival (OS) and performance status of those patients with LM are very poor, they are mostly excluded from clinical trials. In order to avoid confounding efficacy results, exclusion criteria #1 has been updated.
- An ophthalmic evaluation is added at Week 3, in accordance with the median time to onset of MEK inhibitor associated retinopathy. Retinopathy is a known adverse event seen with MEK inhibitor therapy, including trametinib.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Protocol summary: updated to align with the amended protocol

Section 3 Study design

- Clarification regarding central BRAF V600E testing

Section 5.1 Inclusion criteria

- Clarification regarding central BRAF V600E testing

Section 5.2 Exclusion criteria

- Added leptomeningeal metastases to exclusion criteria #1

Section 6.5.2.10 Mandatory dose modification and management guideline for visual changes

- Added information regarding MEK inhibitor associated retinopathy

Section 7 Informed consent procedures

- Updated common adverse effects

Section 8 Visit schedule and assessments

- Clarification about assessments to record in the subject's source documentation

Table 8-1 Assessment schedule

[redacted]

- Clarification about assessments to record in the subject's source documentation
- Harmonized presentation of assessments to perform at week 15 and every 3 weeks thereafter
- Clarification of period and visit names for post treatment follow-up phase
- Added ophthalmic assessment at Week 3

Section 8.1 Screening

- Updated the requirements for assigned subject number in case of subject re-screening
- Updated number of tumor slides to minimum 3 to maximum 5
- Clarification regarding central BRAF V600E testing
- Removed tumor block for BRAF V600E testing
- Removed sentence regarding centrally confirmed BRAF V600E

Section 8.3.1. Efficacy assessments

- Updated to Novartis guideline version 3.2 based on RECIST 1.1
- Added information regarding cytology and histology report form shared with imaging CRO

Table 8-2 Imaging Assessment Collection Plan

- Clarified assessments may be performed if clinically indicated

Section 8.5.3 Biomarkers and Table 8-8 Biomarker sample collection plan

- Clarification regarding central BRAF V600E testing
- Removed tumor block for BRAF V600E testing
- Updated number of tumor slides to minimum 3 to maximum 5

Section 10.1.1 Adverse Events

- Updated list of AESI for trametinib

Section 15 References

- Added two references

Section 16 Appendices

- Updated Appendix 1 to reflect Novartis guideline version 3.2 based on RECIST 1.1

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1

Amendment rationale

As of the release date of this protocol amendment, no patients have been screened or treated in this study.

The main purpose for this amendment is to:

1. Change the primary endpoint of this study from investigator assessment of Overall Response Rate (ORR) to central independent review of ORR. This change was mandated by the China National Medical Products Administration. ORR by investigator assessment will be a secondary endpoint.
2. Align the dose modification section of the protocol for severe cutaneous adverse reaction(s) (SCAR(s)) with the dabrafenib Investigator's Brochure (IB) version 11 and trametinib IB version 11.
3. Clarify inclusion and exclusion criteria related to prior treatment regimen requirements for pre-treated patients, based on current standard of care for Chinese patients with metastatic NSCLC.

[redacted]

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following sections of the protocol were changed:

Updated the list of abbreviations

Protocol summary: updated to aligned with the amended protocol

Section 1.1. Background

- Updated to clarify recent approval of pembrolizumab as single agent or in combination in China

Section 1.2 Purpose

- Updated to clarify results for study DRB436E2201
- Updated to clarify number of pre-treated and treatment naive patients

Table 2-1 Objectives and related endpoints

- Updated to reflect the changes in study endpoints

[redacted]

Section 3 Study design

- Updated to ORR by central independent review
- Updated to disease progression determined by investigator

[redacted]

Section 4.1 Rationale for study design

- Updated to ORR by central independent review

Section 5.1 Inclusion criteria

- Updated inclusion criteria #4 for pre-treated subjects

Section 5.2 Exclusion criteria

- Updated exclusion criteria #4 for previous chemotherapy

Section 6.1.4 Treatment duration

- Updated to disease progression determined by investigator

Table 6-7 Mandatory dose modifications and recommended clinical management guidelines for rash

- Added requirement for suspected cases of serious skin reactions section

Section 6.5.2.3 Mandatory dose modifications and recommended clinical management of serious skin reactions

- Added dose modification guidelines and clinical management for cases of SCARs

Table 8-1 Assessment schedule

- Clarified tumor follow-up phase and efficacy follow-up schedule
- Added survival follow-up period
- Added requirements for patient reported outcome at week 15 and every 3 weeks thereafter

Section 8.1 Screening

- Clarified BRAF V600E mutation testing requirements at screening

Section 8.3.1 Efficacy assessments

- Updated to tumor assessment by investigator and by central independent review
- Updated to reflect the use of a central independent review
- Updated requirement for whole body scan at baseline

Table 8-2 Imaging assessment collection plan

- Updated requirement for whole body scan

Section 8.3.2 Transmission of efficacy data to central independent review

- New section added to describe the process for sharing images with the imaging CRO and timepoints for central independent review

Table 8-5 Clinical laboratory parameters collection plan

- Removed Bands from the laboratory parameters

[redacted]

Section 9.1.1 Discontinuation of study treatment

- Added timeframe for preventing to repeat assessments at EOT
- Updated to disease progression determined by investigator

[redacted]

Section 9.1.2 Survival follow-up

- New section added to describe the survival follow-up visit and timelines

Section 10.1.1 Adverse events

- Updated CTCAE to version 4.03

Section 12.4.1 Definition of primary endpoint(s)

- Updated to ORR by central independent review

Section 12.5.1 Efficacy endpoints

- Added definition of ORR

[redacted]

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The changes described in this amended protocol require IRB/IEC approval and Health Authority notification according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CDRB436ECN01
Full Title	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
Brief title	Study of efficacy, safety, and pharmacokinetic of dabrafenib in combination with trametinib in Chinese patients with *BRAF* V600E mutation-positive metastatic Non-Small Cell Lung Cancer (NSCLC)
Sponsor and Clinical Phase	Novartis/Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the safety and efficacy of dabrafenib in combination with trametinib in Chinese patients with BRAF V600E mutation-positive metastatic NSCLC. The general study design has been discussed and agreed with Chinese Health Authority and is applying a similar design used for global pivotal phase II study (BRF113928).
Primary Objective(s)	The primary objective of this study is to assess ORR by central independent review.
Secondary Objectives	• To assess overall response rate, progression-free survival, duration of response and overall survival by investigator assessment. • To characterize the safety and tolerability of dabrafenib in combination with trametinib. • To characterize PK of dabrafenib, dabrafenib metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib • To characterize quality of life as measured by the EORTC-QLQ C30, LC13 and the EQ-5D.
[redacted]	[redacted]
Study design	This is a single-arm, open label, multicenter phase II, study of dabrafenib in combination with trametinib in Chinese participants with *BRAF* V600E mutation-positive, stage IV NSCLC (AJCC staging 8th edition). Approximately 40 Chinese adults will be enrolled in this study. Patients will be treated with dabrafenib in combination with trametinib until disease progression, start of a new anti-neoplastic therapy, unacceptable toxicity, pregnancy, withdrawal of consent, lost to follow-up, physician's decision, death, or if study is terminated by the sponsor.
Population	Adults with previously treated and untreated *BRAF* V600E mutation-positive NSCLC.
Key Inclusion criteria	Key inclusion criteria are listed below, please refer to the protocol for the full list of inclusion criteria: • Signed informed consent must be obtained prior to performing any screening procedure • Male or female ≥ 18 years of age at time of informed consent • Histologically or cytologically confirmed diagnosis of metastatic (NSCLC (using AJCC 8th edition) that is BRAF V600E mutation-positive by local test result from a qualified assay (NMPA and/or MOH-approved). • An archival or new tumor tissue sample should be available at the time of enrollment for central testing of BRAF V600E status (see Section 8.5.3 for details). • Previously treated or untreated for metastatic NSCLC: • Participants previously treated should have received no more than 3 prior systemic therapies for metastatic disease, with at least one prior platinum based chemotherapy, and should have documented disease progression on a prior treatment regimen (i.e. RECIST 1.1)

[redacted]

	• Participants who have received prior therapy with checkpoint inhibitor therapy (i.e. anti-PD-1/PD-L1) as the last treatment regimen must have had a confirmed disease progression while on or after this therapy prior to enrollment. • Participants with EGFR or ALK mutation who have previously received therapy with EGFR or ALK inhibitor(s) respectively are eligible.

Key Exclusion criteria	Key exclusion criteria are listed below, please refer to the protocol for the full list of exclusion criteria:
	• Participants with brain or leptomeningeal metastases are excluded if these metastases are:
	  • Symptomatic OR
	  • Treated (surgery, radiation therapy) but not clinically and radiographically stable 3 weeks after local therapy (as assessed by contrast enhanced magnetic resonance imaging [MRI] or computed tomography [CT]), OR
	  • Asymptomatic and untreated but >1 cm in the longest dimension
	• Previous treatment with a BRAF inhibitor or a MEK inhibitor.
	• All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 8-5) must be Grade 2 or less according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.03; NCI, 2009) at the time of enrollment.
	• Prior systemic anti-cancer treatment (chemotherapy, radiotherapy, biologic therapy, vaccine therapy, or investigational treatment) within the last 2 weeks, and prior treatment with immune checkpoint inhibitor within 4 weeks preceding the first dose of the combination.

Study treatment	Dabrafenib (DRB436), and trametinib (TMT212)
Efficacy assessments	Radiological tumor response will be assessed by investigator assessment and in addition independently assessed by central review using RECIST version 1.1. The following assessments are required at screening/baseline: • Chest, abdomen, and pelvis CT or MRI • Brain CT or MRI • Whole body bone scan • Localized bone CT, MRI, or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI • Color photography including a metric ruler to measure the size of the lesion for any skin lesions present • CT or MRI of other metastatic sites (e.g. neck), if clinically indicated Post-baseline imaging assessments will be performed every 6 weeks until week 36, and then every 12 weeks until disease progression per RECIST version 1.1 (as assessed by the investigator), death, lost to follow-up or withdrawal of consent.
Pharmacokinetic assessments	Pharmacokinetics of dabrafenib, dabrafenib metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib.
Key safety assessments	• Adverse events • Physical examination • Weight and vital signs • Dermatological examination, skin biopsy, photography • Eastern Cooperative Oncology Group (ECOG) performance status • Laboratory assessments including hematology, chemistry, urinalysis, coagulation, hepatitis markers, and pregnancy test • 12-lead ECG • Echocardiogram • Ophthalmic examination

[redacted]

Other assessments	• Patient reported outcomes (PROs) assessments by the European Organization for Research and Treatment of Cancer core quality of life (EORTC QLQ-C30 and EORTC QLQ-LC13) and EuroQoL (EQ-5D-5L) questionnaires. • Biomarkers: archival or new tumor biopsy sample for BRAF V600E mutation testing.
Data analysis	The primary endpoint of the study is overall response rate (ORR), defined as the proportion of participants with best overall response (BOR) of complete response (CR) or partial response (PR), as per central independent review and according to RECIST 1.1. The ORR will be summarized along with its exact 95% confidence intervals.
Key words	Metastatic Non-Small Cell Lung Cancer (NSCLC), Chinese patients, dabrafenib (DRB436), trametinib (TMT212), BRAF V600

[redacted]

1 Introduction

1.1 Background

Lung cancer is one of the most frequently diagnosed cancer globally, with an estimated 1.8 million new cases worldwide in 2012 and represents the leading cause of cancer-related deaths globally, with approximately 1.6 million deaths in 2012 (Ferlay et al 2015). Lung cancer is also the most prevalent cancer in China, with about 733,000 new cases per year and the leading cause of cancer-related death (Chen et al 2015). The prognosis for patients with metastatic disease remain extremely poor, with 5 years survival rates reported as less than 5% (Lu et al 2019).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer diagnoses and approximately 70% of patients present with advanced disease (Molina et al 2008, Siegel et al 2015). Driver oncogene mutation have been identified in a subset of patients with NSCLC (Hirsch et al 2017). The more common targetable mutation are epidermal growth factor receptor (EGFR)-activated mutation or anaplastic lymphoma kinase (ALK) gene fusion. EGFR mutations occur in 10–20% of patients not of east Asian descent with NSCLC and in about 40% of Asian patients, while ALK-driven tumors represent 2–7% of NSCLCs and are more frequent in the Asian population (Hirsch et al 2017). With the completion of genomic analysis in lung cancer by The Cancer Genome Atlas (TCGA) Research Network, more and more sensitizing molecular alterations have been identified in genes such as KRAS, ROS1, RET,BRAF, HER2, MET exon 14, and PIK3CA that could potentially be targeted in NSCLC (The Cancer Genome Atlas Research Network 2014).

BRAF, one of the serine/threonine protein kinase, belongs to the RAF kinase family in the RAS-RAF-MEK-ERK signaling pathway (Caparica et al 2016, Sánchez-Torres et al 2013). When activated by mutations, BRAF activates MEK and this leads to the activation of the ERK signaling pathway to promote cell growth, proliferation, and survival (Pao and Girard 2011). The most common mutation in BRAF is the valine (V) to glutamate acid (E) substitution at residue 600 (*BRAF* V600E), which results in a mutant *BRAF* protein that no longer requires dimerization for its activity and is constitutively active and transforming in vitro (Dankort et al 2007, Davies et al 2002, Ji et al 2007,Yang et al 2010). Somatic mutations in *BRAF* are found in several kinds of cancers, including melanoma, ovarian carcinomas, colorectal cancers, papillary thyroid cancers, and lung cancers. *BRAF* mutations are observed in 1–3% of NSCLC (Cardarella et al 2013, Marchetti et al 2011, Pratilas et al 2008).

Surgery is the treatment of choice for participants with NSCLC stages I through IIA, while participants with stage IIIB and IV NSCLC without targetable oncogenic drivers are usually treated with chemotherapy. The median overall survival of patients treated with platinum-based doublet chemotherapy is only 8-10 months, with approximately 50-70% of patients having disease stabilization or tumor shrinkage in response to first line chemotherapy (Scagliotti et al 2002, Scagliotti et al 2008, Schiller et al 2002). For NSCLC patients with known genetic alterations, such as EGFR, ALK, BRAF, or ROS-1 target therapies have been approved and completely transformed the treatment landscape and life expectancy for lung cancer (Barlesi et al 2016, National Health Commission of the People's Republic of China 2019). More recently immune checkpoint inhibitors have been introduced for the treatment of locally advanced and metastatic NSCLC patients without a targetable mutation monoclonal

antibodies targeting PD-1 and PD-L1 (nivolumab, durvalumab, pembrolizumab, and atezolizumab) have each demonstrated significant activity as monotherapy and superiority over single agent chemotherapy in pretreated NSCLC either PD-L1 selected or unselected and have been recently approved by the Health Authorities in this setting (Antonia et al 2017, Barlesi et al 2016, Langer et al 2016).

In China, the current standard of care for advanced NSCLC without targetable oncogenic drivers remain systemic chemotherapy with platinum-based regimens despite the recent approval of pembrolizumab as single agent or in combination with platinum-based doublet chemotherapy in first-line NSCLC. Second line choices for systemic therapy include docetaxel, pemetrexed, and EGFR-TKIs. Recently, PD-1 inhibitor became available in China as a new second-line choice for patients with metastatic NSCLC with intolerance to or progression after previous platinum-based chemotherapy (National Health Commission of the People's Republic of China 2019). According to the Chinese Society of Clinical Oncology (CSCO), EGFR and ALK tyrosine kinase inhibitors could be used as first line systemic therapy in patients with EGFR and ALK sensitizing mutation and gene fusion that are documented before the application of first line therapy (National Health Commission of the People's Republic of China 2019).

Currently in China no target therapy is available for patients with BRAF mutation. The prevalence of *BRAF* V600 mutation in Chinese population with NSCLC is approximatively 1.7% - 1.8% which is similar to the rate seen globally (Ding et al 2017, Gao et al 2018). Data on Chinese patients with BRAFV600-mutant NSCLC are inadequate as the majority of the studies have been conducted in Caucasian and enrolled patients mainly from Europe and America (Ding et al 2017). In a recent study the clinicopathologic features and outcomes of Chinese patients with NSCLC and BRAF mutations have been analyzed. Compared to patients with non-V600E mutations, patients with V600E-mutated tumors had a shorter progression-free survival (PFS) to first-line chemotherapy, and BRAF mutation was more likely to be associated with adenocarcinoma and never smokers. Those finding further highlight the urgent need for novel and effective drugs inhibiting the BRAF pathway for Chinese patients with BRAF mutated NSCLC (Ding et al 2017).

Dabrafenib is a potent and selective inhibitor of BRAF kinase activity. Dabrafenib has demonstrated inhibition of a downstream pharmacodynamic biomarker (phosphorylated ERK [pERK]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutant tumor cell lines. Trametinib is a reversible, highly selective, allosteric inhibitor of MEK1 and MEK2. Trametinib is non-competitive towards adenosine triphosphate (ATP) and inhibits both MEK activation and kinase activity. BRAF and MEK are in the same pathway, and because MEK is a substrate of activated BRAF, inhibiting both proteins simultaneously rather than individually could provide more effective pathway inhibition. In addition emerging data indicate that acquired resistance to BRAF-inhibitors is often associated with reactivation of the MAPK pathway, which might render BRAF-inhibitor resistant melanoma cells susceptible to the combination of BRAF and MEK inhibition (Alcalá and Flaherty 2012). Moreover, combining a MEK and BRAF inhibitor may attenuate BRAF inhibitor-mediated hyperproliferative skin toxicities (Hatzivassiliou et al 2010).

Combination of dabrafenib and trametinib have been approved in United States (US), the European Union (EU), Japan and many other countries as treatments in patients with BRAF

[redacted]

mutated metastatic and adjuvant melanoma and non-small cell lung cancer (NSCLC). This combination is also approved for *BRAF* V600E mutated anaplastic thyroid carcinoma (ATC) in United States (US).

1.2 Purpose

The purpose of this single arm, open label, multicenter phase II study is to evaluate the efficacy and safety of dabrafenib in combination with trametinib in Chinese patients with *BRAF* V600E mutation-positive metastatic NSCLC.

As of today, no targeted therapy for advanced NSCLC with *BRAF* V600E mutation has been approved in China. The current standard therapy for *BRAF* V600E mutant advanced NSCLC remains chemotherapy, which is considered not effective (National Health Commission of the People's Republic of China 2019).

In a global phase II study (DRB436E2201) of 57 patients with previously treated, advanced NSCLC with *BRAF* V600E mutation (cohort B), the combination of dabrafenib plus trametinib was associated with an ORR of 63% in 52 evaluable patients, and the disease control rate was 79%. The median PFS was 9.7 months. In another cohort (cohort C) of the same phase II study, 36 previously untreated patients with *BRAF* V600E mutation positive advanced NSCLC were treated with dabrafenib plus trametinib. The ORR was 64% and included two patients with a complete response and 21 with a partial response. The median PFS was 10.9 months as assessed by investigators. The side effect profile in both cohorts was consistent with that observed in unresectable or metastatic melanoma (Planchard et al 2016, Planchard et al 2017). Based on the results of this study, dabrafenib in combination with trametinib was approved for the treatment of patients with *BRAF* V600E mutant advanced NSCLC in the US, EU, Japan and other countries.

This study was originally conducted in 20 *BRAF* V600E mutated NSCLC patients (approximately 10 previously treated and 10 treatment naive patients) with the aim to provide evidence of efficacy of dabrafenib and trametinib treatment in Chinese patients. Following primary analysis cut-off on 11-Mar-2021, approximately 20 additional patients will be enrolled (approximately 10 previously treated and 10 treatment naive patients) to further investigate the efficacy and safety of dabrafenib and trametinib in Chinese patients with *BRAF* V600E mutation-positive metastatic NSCLC.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the overall response rate (ORR) by central independent review	• ORR, defined as the percentage of participants 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 participants with a confirmed complete response (CR) or partial response

[redacted]

Objective(s)	Endpoint(s)
• To evaluate overall survival (OS)	(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 participants 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. • 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 (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib	• Trough concentrations of dabrafenib, dabrafenib metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib at Visits of week 3, 6, and 12.
• 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]	

3 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 participants with *BRAF* V600E mutation-positive AJCC v8 stage IV NSCLC.

Participants 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 participants:

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 participants must not have been previously exposed to a BRAF or MEK inhibitor. Participants 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).

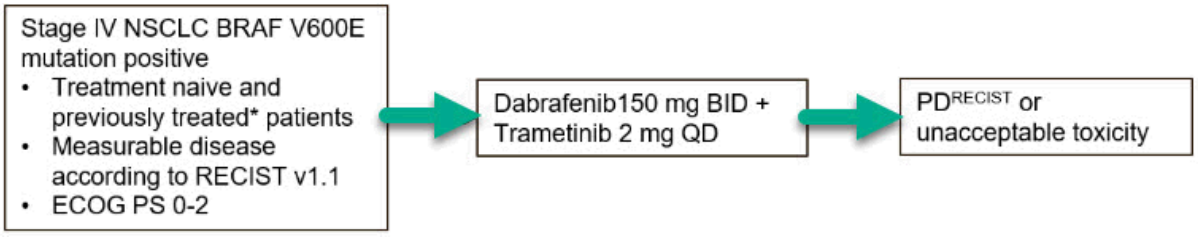
Approximately 40 Chinese patients over 18 years old will be enrolled in this study and will receive dabrafenib (150 mg BID) and trametinib (2 mg once daily) combination therapy until

[redacted]

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 (Section 6.5).

Treatment beyond disease progression per RECIST as determined by investigator is allowed if protocol specific criteria are met (see Section 6.1.4.1). The tumor assessments will be performed every 6 weeks until Week 36, and every 12 weeks thereafter (See Table 8-2) 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.

Figure 3-1 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.

4 Rationale

4.1 Rationale for study design

The study is an open-label, single arm design with ORR by central independent review as the primary endpoint. The general study design has been discussed and agreed with China National Medical Products Administration (NMPA) and is using a similar design used in the global pivotal phase II study (BRF113928). The initial enrollment period was planned to last approximately 12 months (for the first 20 patients); the enrollment period for the 20 additional patients is also planned to last approximately 12 months.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dabrafenib and trametinib combination dose

The starting dose in this study will be dabrafenib 150 mg twice daily (BID) and trametinib 2 mg once-daily (QD) will be used in the study. These are the approved combination doses in EU and US for patients with advanced NSCLC with *BRAF* V600E mutation, based on results from Studies BRF113928, MEK115306, MEK116513, and MEK115532. No significant ethnic difference is found in Asian patients with respect to PK, safety and efficacy for both dabrafenib and trametinib.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

[redacted]

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

The efficacy of dabrafenib and trametinib combination therapy for BRAF V600E mutation positive non-small cell lung cancer has been demonstrated in study BRF113928, based on the positive risk/benefit profile, and is an accepted treatment option globally for the population studied (Anguera and Majem 2018).The safety profile of dabrafenib in combination with trametinib is well characterized, and in study BRF113928 the observations were mostly consistent with the previously described safety profile in the melanoma Phase III studies (Hauschild et al 2012, Long et al 2015, Long et al 2014, Robert et al 2015). Adverse events primarily driven by the underlying lung cancer, such as cough, dyspnea, pleural effusion were more frequently reported in this study than those seen in the melanoma studies. Neutropenia was also more frequently reported in the Combination Second-Line Plus population (any grade: 21%, grade 3/4: 11%) than melanoma studies. Neutropenia was less frequent with less severity in Combination First-Line population (any grade: 11%, grade 3/4: 8%). Overall, in study BRF113928 the safety profile was similar between the First-Line and Second-Line Plus Population except for neutropenia, as discussed above. The most frequently reported AEs of any grade with dabrafenib in combination with trametinib were: pyrexia, nausea, diarrhea, edema peripheral, dry skin, fatigue, and vomiting (Clinical Study Report Study No. CDRB436E2201). In this study we do not expect a different risk/safety profile compared to the one observed in the global study due to absence in ethnic sensitivity for BRAF and MEK inhibitors.

The study incorporates routine safety monitoring and regularly scheduled safety assessments to identify and report any potential safety issues. All participants must have safety evaluations for 30 days after the last dose of study drug. Comprehensive dose modification, stopping rules and toxicity management plan for drug related adverse events are provided in the protocol in Section 6.5. The risk to these stage IV NSCLC patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

The Investigator's Brochure fully characterizes both efficacy and safety aspects of dabrafenib and/or trametinib treatment to enable its appropriate use to maximize benefit while minimizing risks to patients.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be

[redacted]

discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

Deviation from any eligibility criterion below excludes a patient from enrollment into the study. Patients who discontinue the study will not be replaced. Participants eligible in this study must meet **all** inclusion and **none** of the exclusion criteria:

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to performing any screening procedure.
2. Male or female ≥ 18 years of age at time of informed consent.
3. Histologically or cytologically confirmed diagnosis of Stage IV NSCLC (according to AJCC 8th edition) that is *BRAF* V600E mutation-positive by local test result from a qualified assay (NMPA and/or MOH-approved).
   - An archival or new tumor tissue sample should be available at the time of enrollment for central testing of *BRAF* V600E status (see Section 8.5.3 for details).
4. Previously treated or untreated for metastatic NSCLC (prior systemic treatment in the adjuvant setting is allowed)
   - Participants previously treated should have received no more than 3 prior systemic therapies for metastatic disease, with at least one prior platinum based chemotherapy, and should have documented disease progression on a prior treatment regimen (i.e. RECIST 1.1)
   - Participants who have received prior therapy with checkpoint inhibitor therapy (i.e. anti-PD-1/PD-L1) as the last treatment regimen must have had confirmed disease progression (i.e. RECIST 1.1) while on or after this therapy prior to enrollment.
   - Participants with EGFR or ALK mutation who have previously received therapy with EGFR or ALK inhibitor(s) respectively are eligible.
5. Measurable disease per RECIST 1.1.
6. Anticipated life expectancy of at least 3 months.
7. ECOG performance status ≤ 2.
8. Adequate bone marrow and organ function as defined by the following laboratory values without continuous supportive treatment (such as blood transfusion, coagulation factors and/or platelet infusion, or red/white blood cell growth factor administration) as assessed by local laboratory for eligibility:

   Hematological

   - Hemoglobin ≥ 9 g/dL
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Platelets ≥ 100×10^9/L

[redacted]

Coagulation

- PT/INR and PTT ≤ 1.5 x ULN. Participants receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to enrollment.

Renal

- Serum creatinine < 1.5 mg/dL

Hepatic

- Total bilirubin ≤ 1.5 × ULN (upper limit of normal) except for participants with Gilbert's syndrome who

  may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
- AST and ALT ≤ 2.5 × ULN, except for participants with liver metastasis, who may only be included if AST/ALT ≤ 5.0 × ULN
- Albumin ≥ 2.5 g/dL

9. Left ventricular ejection fraction (LVEF) ≥ lower limit of institutional normal (LLN) as assessed by ECHO or MUGA scan
10. Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Participants with brain or leptomeningeal metastases are excluded if these metastases are:
   - Symptomatic OR
   - Treated (surgery, radiation therapy) but not clinically and radiographically stable 3 weeks after local therapy (as assessed by contrast enhanced magnetic resonance imaging [MRI] or computed tomography [CT]), OR
   - Asymptomatic and untreated but >1 cm in the longest dimension
2. Previous treatment with a BRAF inhibitor or a MEK inhibitor.
3. All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 8-5) must be Grade 2 or less according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.03; NCI, 2009) at the time of enrollment.
4. Prior anti-cancer treatment (chemotherapy, radiotherapy, biologic therapy, vaccine therapy, or investigational treatment) within the last 2 weeks, and prior treatment with immune checkpoint inhibitors within 4 weeks preceding the first dose of the study treatment.
5. Current use of a prohibited medication as described in Section 6.2.2.
6. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

[redacted]

7. Participants with known history for testing positive for Human Immunodeficiency Virus (HIV)
8. History of another malignancy <3 years prior to starting study treatment or any malignancy with confirmed activating RAS-mutation. Note: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

   Exceptions: participants with any of the following malignancies within 3 years (does not include malignancies with confirmed activating RAS-mutation) are eligible: (a) a history of completely resected skin cancer, (b) successfully treated in situ carcinoma, (c) chronic lymphocytic lymphoma (CLL) in stable remission, or (d) indolent prostate cancer (definition: clinical stage T1 or T2a, Gleason score ≤ 6, and prostate specific antigen [PSA] <10 ng/mL) requiring no or only anti-hormonal therapy with histologically confirmed tumor lesions that can be clearly differentiated from lung cancer target and non-target lesions are eligible
9. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History or current diagnosis of cardiac disease indicating a significant risk of safety for participants participating in the study such as uncontrolled or significant cardiac disease, including any of the following:
     - Recent (within last 6 months) myocardial infarction
     - Unstable angina (within last 6 months),
     - Uncontrolled congestive heart failure
     - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third-degree atrioventricular block without a pacemaker)
10. A history or current evidence/risk of retinal vein occlusion (RVO) or serous retinopathy including:
    - Presence of predisposing factors to RVO or serous retinopathy (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes); or
    - Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO or central serous retinopathy such as:
      - Evidence of new optic disc cupping;
      - Evidence of new visual field defects on automated perimetry;
      - Intraocular pressure >21 mmHg as measured by tonometry.
11. History or current interstitial lung disease or non-infectious pneumonitis.
12. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that, in the opinion of the investigator, could interfere with the participant's safety, obtaining informed consent, or compliance with study procedures.
13. Pregnant or nursing (lactating) women. Female patients who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

[redacted]

14. Women of childbearing potential, women physiologically capable of becoming pregnant, must use highly effective methods of contraception like:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant) Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that participant.
    - Placement of a non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with documented failure rate of less than 1% per year.

    Above measures for effective contraception must be applied for the following period of time: during dosing and for 16 weeks after stopping treatment with dabrafenib in combination with trametinib.

    Note(s):
    - Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository) are not considered highly effective methods of contraception
    - Hormonal-based methods (e.g., oral contraceptives) are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib and/or trametinib
    - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
15. Sexually active males (including those that have had a vasectomy) must use a condom during intercourse and should not father a child during this period. The amount of time a patient must use a condom after last treatment is as follows:
    - 16 weeks post treatment discontinuation of dabrafenib in combination with trametinib
16. Participants with active Hepatitis B infection (HbsAg positive) will be excluded.

    Note: Participants with antecedent of Hepatitis B (anti-HBc positive, HbsAg and HBV-DNA negative) are eligible.
17. Participants with positive test for hepatitis C ribonucleic acid (HCV RNA)

    Note: Participants in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA $\geq$ 6 months (with the use of IFN-free regimes) or $\geq$ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible

[redacted]

18. Concurrent participation in other clinical trials using experimental therapies.

6 Treatment

6.1 Study treatment

Study treatment includes the investigational drugs dabrafenib (DRB436) using 50 mg and 75 mg capsules and trametinib (TMT212) using 2 mg and 0.5 mg tablets. Study treatment will be provided as global clinical open-labeled supply or commercially sourced supply. Global supplies will be packed and labeled under the responsibility of Novartis Global Clinical Supply (GCS).

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
DRB436 75 mg	Capsule	Oral use	Open label participant packs; bottle	Sponsor (global or local)
DRB436 50 mg	Capsule	Oral use	Open label participant packs; bottle	Sponsor (global or local)
TMT212 2 mg	Tablet	Oral use	Open label participant packs; bottles	Sponsor (global or local)
TMT212 0.5 mg	Tablet	Oral use	Open label participant packs; bottles	Sponsor (global or local)

Dispense a 3 week supply of the study treatment with instructions. Allow for +/- 7 day visit window. Record dose reductions, dose interruptions/delays, and/or dose escalations in CRF.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

This is a single arm study. Participants meeting all eligibility criteria as defined in Section 5 will receive dabrafenib 150 mg BID in combination with trametinib 2 mg once daily, starting from Day 1.

6.1.4 Treatment duration

Study treatment will be administered until the participant experiences one of the following: disease progression by RECIST 1.1 as determined by investigator assessment (and not meeting the criteria in Section 6.1.4.1), unacceptable toxicity, pregnancy, treatment discontinuation at

[redacted]

the discretion of the investigator or the participant, start of a new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, death, or study termination by the sponsor.

6.1.4.1 Treatment beyond disease progression

Participants will be permitted to continue study treatment beyond disease progression per RECIST 1.1 as assessed by investigator review provided they meet all the following criteria:

1. Informed consent for treatment beyond disease progression is provided by the participant
2. The participant experienced a confirmed tumor response according to RECIST 1.1 while receiving study treatment or disease under study has remained no worse than stable for a period of at least 3 months while receiving study treatment.
3. Absence of signs and symptoms of clinical disease progression despite disease progression based on RECIST 1.1 criteria.
4. No treatment-related AEs of CTCAE grade 4 or serious AEs (SAEs) have occurred during the last 4 weeks of study treatment
5. Participant remains with stable performance status.
6. Continuation of treatment beyond progression should not delay critical interventions to treat/prevent severe complications of disease progression (e.g, CNS metastases), or prevent participants from receiving adequate care.

Participants who meet the above criteria are permitted to continue study treatment and continue all study procedures as outlined in Table 8-1. The reasons for the participant continuing treatment beyond progression will be documented in the eCRF.

In case of clinical deterioration or suspicion of disease progression, a follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Participants with evidence of further disease progression on an imaging assessment or who are no longer deriving clinical benefit will be permanently discontinued.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must instruct the participant to notify the study site of any new medication(s) he/she takes after start of study participation.

Prior antineoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate prior antineoplastic therapy Case Report Forms during screening.

All medications, procedures, and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms. Medication entries must be specific to trade name, dose and units, frequency and route of administration, start and discontinuation dates, and reason for therapy. For medications administered one time, the frequency column may reflect “once.”

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before

[redacted]

allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the participant are allowed except those prohibited in Section 6.2.2. Participants are permitted to use the following medications during study treatment:

- Limited-field palliative radiotherapy to non-target lesion(s) may be allowed after documented discussion with Novartis study physician as concomitant therapy such as local therapies administered during the study treatment. Any radiotherapy must be listed on the appropriate eCRF. In case of palliative radiotherapy, the participant should interrupt dabrafenib and trametinib for fractionated radiotherapy and stereotactic radiosurgery before and after radiotherapy as outlined below (Anker et al 2016).
  - Interrupt dabrafenib and trametinib ≥ 3 days before and after fractionated radiation
  - Interrupt dabrafenib and trametinib ≥ 1 day before and after stereotactic radiosurgery (SRS)
- Antivirus medications to manage HBV or HCV infection and/or prevent reactivation (e.g., tenofovir); supportive care.
- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for participants who develop diarrhea.
- Pain medication to allow the participant to be as comfortable as possible.
- Bone targeted therapies (e.g., bisphosphonates, denosumab) to treat bone metastases or to prevent skeletal related events.
- Nutritional support or appetite stimulants (e.g., megestrol).
- Oxygen therapy and blood products or transfusions.
- The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study drug

All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered after the participant signed consent and through 30 days after the last dose of study treatment must be listed on the Concomitant Medications or the Procedures and Surgical and Medical Procedures eCRF.

Any anti-neoplastic therapy (including surgery, radiotherapy, medications) administered in the Follow-up Period after discontinuation of study treatment must be listed on Antineoplastic Medication Since Discontinuation eCRF pages including best response to therapy, if available.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Dabrafenib

Effect of other drugs on dabrafenib

Based on in vitro studies, dabrafenib was shown to be primarily metabolized by CYP2C8 and CYP3A4. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Use caution if

[redacted]

strong inhibitors (e.g ketoconazole, nefazodone, clarithromycin, ritonavir, gemfibrozil) or inducers (e.g rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP2C8 or CYP3A4 are co-administered with dabrafenib.

Effect of dabrafenib on other drugs

Dabrafenib induces CYP3A4 and CYP2C9 mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19 and UDP glucoronosyltransferases (UGT). Dabrafenib may also induce transporters (e.g P-glycoprotein [P-gp]).Co-administration of dabrafenib and medicinal products which are affected by the induction of CYP3A4 or CYP2C9 such as hormonal contraceptives, warfarin or dexamethasone may result in decreased concentrations and loss of efficacy. If co-administration of these medications is necessary, monitor participants for loss of efficacy or consider substitutions of these medicinal products. Use caution if co-administration of CYP2C or CYP3A4 substrates with narrow therapeutic index is required. Refer to the Tafinlar label for further information.

Trametinib

Based on in vitro and in vivo data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters.

Dabrafenib and trametinib
Based on the mechanism of action of dabrafenib and trametinib, vaccines are not expected to have an interaction with these drugs, therefore are not prohibited. However, investigators should use their best clinical judgment on the use of live vaccines considering the potential immunocompromised state of cancer patients.

6.2.2 Prohibited medication

The following medications or non-drug therapies are also prohibited while on treatment in this study:

- Other anti-cancer therapies
- Other investigational drugs

Although not contraindicated/prohibited, certain medications drugs should be used with caution due to potential drug-drug interactions (see Section 6.2.1.1).

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Subject Number (Subject No.), that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Subject No. available.

[redacted]

6.3.2 Treatment assignment, randomization

Not applicable.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in Table 6-2. These guidelines are intended primarily for toxicities not easily managed with routine supportive care. For example, alopecia is not an indication for dose modification, nor is grade 2 nausea and vomiting that can be easily managed with anti-emetics.

The following section(s) address the specific instructions for mandatory dose modifications and recommended management for AEs considered suspected to be related to study treatment. For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions or modifications are mandated in order to allow participants to continue study treatment.

If treatment related toxicities occur when dabrafenib and trametinib are used in combination, then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below:

Exception where dose modification is necessary for only dabrafenib:

- Uveitis (Table 6-14)

Exception where dose modifications are necessary for only trametinib:

- Retinal vein occlusions (RVO) (Table 6-14) and retinal pigment epithelial detachment (RPED) (Table 6-15)
- Left ventricular ejection fraction (LVEF) reduction (Table 6-13)
- Pneumonitis and ILD (Table 6-10)

Table 6-2 Dose Modification Guidelines - General

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 or Grade 2 tolerable	• Monitor closely • Provide supportive care according to institutional standards	• Continue dabrafenib and trametinib at the same dose level.
Grade 2 (intolerable) or Grade 3	• Monitor closely. • Provide supportive care according to institutional standards	• Interrupt dabrafenib and trametinib • When toxicity resolves to ≤ Grade 1 or baseline, restart dabrafenib and trametinib

[redacted]

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
		reduced by one dose level per Table 6-3. • If the Grade 2 (intolerable) or Grade 3 toxicity recurs, interrupt dabrafenib and trametinib. • If following an interruption of dabrafenib and trametinib, the AE doesn't recover to ≤ Grade 1 or baseline within 3 weeks, dabrafenib and trametinib must be discontinued • Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met.
Grade 4	• Monitor closely. • Provide supportive care according to institutional standards	• Interrupt study treatment until =< Grade 1 and restart at next lower dose level or permanently discontinue study treatment • If the Grade 4 toxicity recurs, permanently discontinue study treatment

6.5.1.1 Dose Reduction

Deviations to mandatory dose interruptions and/or reductions are not allowed. A maximum of two trametinib dose level reductions and three dose level reduction for dabrafenib are allowed. Steps for dose modifications for trametinib and dabrafenib are listed in Table 6-3.

Table 6-3 Dose Modification steps for dabrafenib and trametinib

	Dabrafenib	Trametinib
Starting dose[a]	150 mg BID	2 mg once daily
1st level dose reduction	100 mg BID	1.5 mg once daily
2nd level dose reduction	75 mg BID	1 mg once daily
3rd level dose reduction	50 mg BID	Not allowed
[a] Dose modification should be based on the worst toxicity demonstrated at the last dose		

A dose reduction below 50 mg BID for dabrafenib or below 1 mg QD for trametinib is not allowed. If a dose reduction below 50 mg BID for dabrafenib is required, dabrafenib will be permanently discontinued but these participants will be allowed to continue trametinib. If a dose reduction below 1.0 mg QD for trametinib is required, then trametinib will be permanently discontinued, but these participants will be allowed to continue dabrafenib.

6.5.1.2 Dose Re-escalation

If a participant's dose of dabrafenib and trametinib has been reduced per the dose modification instructions, re-escalation of the participant's dose is recommended provided the following criteria are met:

[redacted]

- A period of 4 weeks of treatment has passed since restarting dosing at the lower dose level and there is no recurrence of the AE
- The participant is deriving clinical benefit

6.5.1.3 Dose Delay

For dabrafenib and/or trametinib related adverse events: if following an interruption of dabrafenib and trametinib, an AE doesn't recover to ≤ Grade 1 or baseline within 4 weeks, dabrafenib and trametinib must be discontinued.

Approval from the Medical Lead is required to restart study treatment after 4 weeks.

Table 6-4 provides a list of AEs of special interest and relevant sections where detailed dose modification and management requirements for relevant AEs can be found. All AEs are to be graded according to NCI-CTCAE v4.03, unless otherwise specified. Investigators should refer to the current dabrafenib and trametinib local prescribing information and/or Investigator's Brochure for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues not specifically mentioned in this protocol.

Table 6-4 Reference of AEs and toxicity management guidelines

Adverse Events	dabrafenib	trametinib	Guideline
General	X	X	X
Pyrexia	X	X	X
Rash	X	X	X
Serious skin reactions	X	X	X
Hand foot skin reactions	X	X	X
Diarrhea	X	X	X
Pneumonitis / ILD		X	X
Renal function alterations	X	X	X
Hypertension	X	X	X
LVEF decrease	X	X	X
Visual changes	X (Uveitis)	X (RVO)	X
RPED		X	X
Hyperglycemia	X		X
Hemorrhage	X	X	X
Thromboembolic events		X	X
New malignancies	X	X	X
Abnormal liver enzyme tests	X	X	X

6.5.2 Dose Modification Guidelines - Adverse Events of Special Interest

6.5.2.1 Pyrexia

Pyrexia is a common AE in patients receiving dabrafenib and/or trametinib, and the incidence and severity of pyrexia is increased with combination therapy. Pyrexia may be accompanied by severe rigors, dehydration and hypotension, which in some cases can lead to acute renal

[redacted]

insufficiency. Pyrexia often occurs within the first month of treatment, and participants may experience more than one event.

Before starting study drug treatment, participants should be comprehensively educated and receive guidance regarding pyrexia and be instructed on the importance of immediately reporting pyrexia or pyrexia symptoms (chills, rigors, night sweats or flu-like symptoms).

Guidelines for dose modification and management for pyrexia considered to be related to dabrafenib and/or trametinib are provided in Table 6-5.

Table 6-5 Mandatory dose modification and recommended clinical management guidelines for suspected treatment-related pyrexia

Occurrence	Recommended management	Mandatory dose modification
First occurrence	• Clinical evaluation for infection and hypersensitivity[a] • Laboratory work-up[a] • Prompt administration of anti-pyretic treatment [b] • Oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient, • i.e.prednisone 10 mg/d for at least 5 days or as clinically indicated[c] • Optimize oral corticosteroid dose as clinically indicated for pyrexia that cannot be managed with dose interruptions[c] • Oral hydration should be encouraged in participants without evidence of dehydration. Intravenous hydration is recommended in participants experiencing pyrexia complicated by dehydration/hypotension.	Dabrafenib and trametinib must be interrupted promptly at the very first observation of pyrexia (temperature ≥ 38° C (100.4° F)). Dabrafenib and trametinib should be restarted if patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level per Table 6-3, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. For re-escalation, refer to Section 6.5.1.2.
Subsequent occurrences	Same as above	In case of recurrence, dabrafenib and trametinib can be interrupted at the first symptom of pyrexia (presence of pyrexia symptoms chills, rigors, night sweats or flu-like symptoms) without documented temperature ≥ 38°C (100.4°F).

a. Laboratory work-up may include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture. In participants experiencing pyrexia higher than 40° C (104° F), and/or pyrexia associated with rigors, severe chills, dehydration or hypotension, renal function should be monitored frequently. The frequency of monitoring must be adapted based on the individual clinical presentation.
b. Anti-pyretic treatment should be started immediately at the onset of pyrexia or pyrexia symptoms. Anti-pyretic treatment may include acetaminophen, ibuprofen, metamizole, or suitable anti-pyretic medication according to institutional standards.
c. Corticosteroids are recommended for recurrent pyrexia that cannot be managed with dose interruptions and anti-pyretic treatments and for pyrexia associated with complications as per local institutional guidelines where available, or investigator's discretion.

[redacted]

6.5.2.2 Rash

Rash is a frequent AE observed in participants receiving trametinib, dabrafenib, or the combination of both therapies. Recommended guidelines for rash management are provided below tables (Table 6-6, Table 6-7).

Table 6-6 Guidelines for Supportive Care of Rash

Type of Care	Action
Prevention/Prophylaxis: Start from Day 1	• Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Prevention/Prohylaxis: Start from Day 29 and implement for a total of 6 weeks	• Topical steroids and antibiotics should be applied at least twice daily starting on Day 29 of study treatment and to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream and topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)
Symptomatic Care	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics
Abbreviations: BID = twice daily; SPF = sun protection factor	

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 6-7.

Table 6-7 Mandatory dose modifications and recommended clinical management guidelines for rash

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1: Rash covering < 10% body surface area	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks	• Continue dabrafenib and trametinib at the same dose.
Grade 2: 10-30% of body surface area	• If tolerable, as per Grade 1 • If intolerable, initiate systemic steroids (0.5 to 1 mg/kg/day prednisone or equivalents)	• If tolerable, continue dabrafenib and trametinib at the same dose. • If intolerable:

[redacted]

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
	• If symptoms persist or recur consider skin biopsy.	**1st and subsequent occurrences** • Interrupt dabrafenib and trametinib until ≤ Grade 1, and then restart dabrafenib and trametinib at next lower dose level.
Grade 3: More than 30% of body surface area	• Obtain a skin biopsy and dermatology consult. • Initiate therapy with high dose steroids (1 to 2 mg/kg/d prednisone or equivalents)	**1st 2nd, and 3rd occurrences** • Interrupt dabrafenib and trametinib until ≤ Grade 1, and then restart dabrafenib and trametinib at next lower dose level. **4th occurrence** Permanently discontinue dabrafenib and trametinib.
Grade 4: Life-threatening	• Same as Grade 3	• Permanently discontinue dabrafenib and trametinib.
NOTE: suspected cases of SCAR require permanent discontinuation of study treatment (see Section 6.5.2.3)		

6.5.2.3 Mandatory dose modifications and recommended clinical management of serious skin reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with dabrafenib in combination with trametinib. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, dabrafenib and trametinib should be permanently discontinued.

6.5.2.4 Mandatory dose modifications and recommended clinical management guidelines for hand-foot reaction (palmar-plantar erythrodysesthesia)

In general, management of hand-foot skin reactions include:

- Prevention/prophylaxis: promote sunscreen use and avoidance of unnecessary sun exposure, use alcohol-free emollient creams, topical steroids and antibiotics as needed.
- Pruritic lesions: cool compresses and oral antihistamines
- Fissuring lesions: Monsel's solution, silver nitrate or zinc oxide cream
- Desquamation: thick emollients and mild soap
- Paronychia: antiseptic bath, local potent corticosteroids, antibiotics, surgery as needed
- Infected lesions: topical or systemic antibiotics
- Measures for PPES should include:
    - Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles

[redacted]

- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g., urea 20-40% cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.

Guidelines for dose modification for hand foot skin reaction considered to be related to study treatment by the investigator are provided in Table 6-8.

Table 6-8 Mandatory dose modifications and recommended clinical management guidelines for hand foot skin reaction (palmar-plantar erythrodysesthesia)

Hand foot skin reaction (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	• Recommend topical therapy for symptomatic relief.	• Continue dabrafenib and trametinib at the same dose.
Grade 2: Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	• Recommend topical therapy for symptomatic relief	• Continue treatment and if no improvement within 7 days, see below. • No improvement within 7 days or 2nd or 3rd occurrence: • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 1 or baseline. • Reduce dabrafenib and trametinib at the next lower dose. **4th occurrence:** • Discontinue dabrafenib and trametinib.
Grade 3: Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	• Recommend topical therapy for symptomatic relief	**1stoccurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 1 or baseline. • Once recovered, restart dabrafenib and trametinib at the next lower dose level. **2nd occurrence:** • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 1 or baseline. • Once recovered, restart dabrafenib and trametinib at the next lower dose level. **3rd occurrence:** • Discontinue dabrafenib and trametinib.

[redacted]

6.5.2.5 Guidelines for Diarrhea

Episodes of diarrhea have occurred in participants receiving dabrafenib, trametinib, or both therapies in combination. Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by C. difficile or other pathogens, partial bowel obstruction, etc., should be clinically excluded. Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatment by the investigator are provided in Table 6-9.

Table 6-9 Management and Dose Modification Guidelines for Diarrhea

Diarrhea (NCI-CTCAE v4.03)		
CTCAE Grade	**Adverse Event Management**	**Mandatory dose modification requirements**
Grade 1 diarrhea (increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Grade 2 diarrhea (increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline)	• Diet: stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide[a]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics	• Continue dabrafenib and trametinib • If diarrhea is grade 2 for > 48h, interrupt dabrafenib and trametinib until diarrhea resolves to grade ≤1 • Restart dabrafenib and trametinib at the same dose level
Grade 3 diarrhea (increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)	• Clinical evaluation mandatory • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Oral antibiotics and second-line therapies if clinically indicated • Hydration: intravenous fluids if clinically indicated • Antibiotics (oral or intravenous) if clinically indicated	• Interrupt dabrafenib and trametinib until diarrhea resolves to grade ≤1 • Restart with dabrafenib and trametinib reduced by one dose level[b] • If 3 dose reductions of study treatment are clinically indicated, permanently discontinue dabrafenib and trametinib

[redacted]

Diarrhea (NCI-CTCAE v4.03)		
CTCAE Grade	**Adverse Event Management**	**Mandatory dose modification requirements**
	• Intervention should be continued until the participant is diarrhea free for ≥ 24 hours • Intervention may require hospitalization for participants at risk of life-threatening complications	
Grade 4: (Life-threatening consequences; urgent intervention indicated)	• Same as Grade 3	• Permanently discontinue, dabrafenib and trametinib.
Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events a. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea b. Escalation of study treatment to previous dose level is allowed after consultation with the Medical Lead and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.5.2.6 Guidelines for Pneumonitis

Pneumonitis has been observed in participants receiving trametinib. To reduce the risk of pneumonitis, participants will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in Table 6-10.

Table 6-10 Management and Dose Modification Guidelines for Pneumonitis

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Adverse Event Management**	**Mandatory dose modification requirements**
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue dabrafenib and trametinib at current dose
Grade 2	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt trametinib until toxicity recovers to ≤ Grade 1 or baseline. Dabrafenib may continue • Once recovered, restart trametinib at the next lower dose level. • Escalation to previous dose level after 4 weeks possible and consultation with Medical Lead

[redacted]

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Adverse Event Management**	**Mandatory dose modification requirements**
		• If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue
Grade 3	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated • Oxygen indicated	• Interrupt trametinib until toxicity recovers to ≤ Grade 1 or baseline. Dabrafenib may continue • Once recovered, restart trametinib at the next lower dose level after consultation with medical lead. • Escalation to previous dose level after 4 weeks and consultation with Medical Lead is possible • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue
Grade 4	• Life-threatening respiratory compromise; urgent intervention indicated (e.g. tracheotomy or intubation)	• Permanently discontinue trametinib. Dabrafenib may continue
Abbreviations: BAL= bronchoalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events		

6.5.2.7 Guidelines for Renal Insufficiency

Cases of renal insufficiency have occurred in participants receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications should be modified if clinically possible. Management and dose modifications guidelines are provided in Section 6.2. Close monitoring of serum creatinine, treatment associated pyrexia (see Table 6-5), and treatment interruption for increased serum creatinine > 2 mg/dL (or > 0.5 mg/dL above baseline). Nephrology consultation should also be obtained in absence of obvious cause for persistent creatinine elevation (e.g volume depletion).

Table 6-11 Mandatory dose modifications and recommended clinical management guidelines for renal insufficiency

Acute kidney injury (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1 (Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline)	• If the increase in creatinine is confirmed: a. Assess fluid status and consider fluid bolus b. Monitor serum creatinine at least every 2 days until back to baseline	• If the increase in creatinine is confirmed: a. Interrupt dabrafenib and trametinib • If creatinine returns to baseline:

Acute kidney injury (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
	c. If creatinine returns to baseline: a.resume routine creatinine monitoring per protocol • Promote hydration and cessation of nephrotoxic drugs	a.Continue dabrafenib and trametinib at the same dose.
Grade 2: (Creatinine 2 - 3 x above baseline)	• Closely monitor creatinine • Consult with specialist and consider renal biopsy • Promote hydration and cessation of nephrotoxic drugs.	**1st occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reinstate dabrafenib and trametinib at the same dose. **2nd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **4th occurrence** • Permanently discontinue dabrafenib and trametinib.
Grade 3 (Creatinine > 3.0 x baseline or >4.0 mg/dL; hospitalization indicated)	• Hospitalization is indicated with frequent creatinine monitoring • Consult with nephrologist. • Promote hydration and cessation of nephrotoxic drugs.	**1st occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **2nd occurrence:**

[redacted]

Acute kidney injury (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
		• Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose, if available as dose level -2. If already at dose level-2 at time of occurrence, permanently discontinue dabrafenib and trametinib. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **4th occurrence:** Permanently discontinue dabrafenib and trametinib
Grade 4: Life-threatening consequences; dialysis indicated	• Consult with specialist and recommend renal biopsy. • Promote hydration and cessation of nephrotoxic drugs.	• Permanently discontinue dabrafenib and trametinib.

6.5.2.8 Mandatory dose modification and management guideline for hypertension suspected to be related to dabrafenib and/or trametinib treatment

Increases in blood pressure have been observed in participants receiving trametinib. For adequate monitoring and management of hypertension, all blood pressure assessments should be performed under the following optimal conditions:

- the participant has been seated with back support, ensuring that legs are uncrossed and flat on the floor
- the participant is relaxed comfortably for at least 5 minutes
- restrictive clothing has been removed from the cuff area and the right cuff size has been selected
- the participant's arm is supported so that the middle of the cuff is at heart level
- the participant remains quiet during the measurement.

In participants with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the eCRF.

[redacted]

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per- protocol visits outlined in the Visit Evaluation Schedule (Table 8-1). Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP >140 mm Hg and/or DBP >90 mmHg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

For participants experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for dose modifications and management of hypertension are described below in Table 6-12.

Table 6-12 Mandatory dose modification and recommended clinical management for hypertension suspected to be related to dabrafenib and/or trametinib treatment

Severity	Recommended adverse event management guidelines	Mandatory dose modification requirements
(Scenario A) • Asymptomatic and persistent [a] SBP of >140 and <160 mmHg, or DBP >90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication. • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled [b] BP • If BP is not well controlled within 2 weeks, recommended to refer to a specialist and go to scenario (B).	• Continue dabrafenib and trametinib at the same dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP.	• Interrupt dabrafenib and trametinib if clinically indicated. • Once BP is well controlled, restart dabrafenib and trametinib at next lower level
• Symptomatic [c] hypertension or • Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment.	• Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended	• Interrupt dabrafenib and trametinib. • Once BP is well controlled, restart dabrafenib and trametinib at next lower level.
• Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• Continue follow-up per protocol.	• Permanently discontinue dabrafenib and trametinib.

a. Hypertension detected in two separate readings during up to three consecutive visits.
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range.

[redacted]

6.5.2.9 Mandatory dose modification and management guideline for changes in LVEF suspected to be related to dabrafenib and/or trametinib treatment

Decreases of left-ventricular-ejection-fraction (LVEF) have been observed in participants receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Visit Evaluation Schedule (Table 8-1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-13.

Table 6-13 Mandatory dose modification and recommended clinical management for changes in LVEF

Clinical symptoms & LVEF drop (%) or CTCAE grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Asymptomatic, absolute decrease of >10% in LVEF compared to baseline **and** ejection fraction below the institution's LLN	• Report as SAE. • Closely monitoring LVEF via ECHO, repeat ECHO within 2 weeks*. • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN **and** absolute decrease ≤10% compared to baseline) • Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If repeat LVEF does not recover within 4 weeks. • Consult with cardiologist • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution	• Interrupt trametinib. Dabrafenib may continue • If the LVEF recovers, restart trametinib reduced next lower level and continue dabrafenib at the same dose level. • More than two occurrence, permanently discontinue trametinib. • Permanently discontinue trametinib if repeat LVEF does not recover within 4 weeks.
Symptomatic or • Resting LVEF 39-20% or >20% absolute reduction from baseline (CTCAE grade 3) • Resting LVEF <20% (CTCAE grade 4)	• Report as SAE. • Consult with cardiologist. • Intervention indicated. • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.	• Permanently discontinue trametinib. • Interrupt dabrafenib • Restart dabrafenib if LVEF recovers including resolution of symptoms.
* If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.		

6.5.2.10 Guideline dose modification and management for hemophagocytic lymphohistiocytosis (HLH)

In post marketing experience, hemophagocytic lymphohistiocytosis (HLH) has been observed with dabrafenib and trametinib combination therapy. Since post-marketing adverse drug reactions are reported from a population of uncertain size, the exact frequency of HLH in patients receiving dabrafenib and trametinib is unknown. HLH is a rare, life-threatening condition caused by an overactive, abnormal response of the immune system (Kikuchi et al 2022), HLH is associated with a constellation of multiple clinical and laboratory features that may include fever, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, high serum ferritin, multilineage cytopenias and hemophagocytosis. If HLH is suspected, treatment

[redacted]

should be interrupted. If HLH is confirmed, treatment should be permanently discontinued and appropriate management of HLH per institutional standards should be initiated.

6.5.2.11 Mandatory dose modification and management guideline for visual changes

Episodes of visual changes have been observed in participants receiving trametinib, dabrafenib or the combination of dabrafenib/trametinib. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor participants for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. Permanently discontinue dabrafenib for persistent ≥ Grade 2 uveitis (including iritis and iridocyclitis) of > 6 weeks duration. No dose modification of trametinib is required when taken in combination with dabrafenib.

In participants treated with trametinib, special attention should be given to retinal findings (e.g., RPED) or retinovascular abnormalities (i.e., branch or central RVO). Retinopathy is a known adverse drug reactionseen with MEK inhibitor therapy, including trametinib. MEK inhibitor associated serous retinopathy typically manifests bilaterally within days of treatment initiation with a median time to onset of one month (Cruz-Merino et al 2017, Francis et al 2017). Treatment emergent cases of RVO and RPED should be reported as SAEs.

Guidelines for dose modification and management for visual changes and/or ophthalmic examination findings considered to be related to dabrafenib and/or trametinib are provided in Table 6-14 and Table 6-15.

Table 6-14 Mandatory dose modification and recommended clinical management for visual changes and/or ophthalmic examination findings

Visual changes (Eye disorders – Other, CTCAE Version 4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1 [a]	Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. Continue dabrafenib. • If RPED and RVO excluded, continue (or restart) trametinib at the same dose level. • If RPED suspected or diagnosed: see RPED dose modification in Table 6-15; report as SAE if diagnosed. • If RVO diagnosed: Permanently discontinue trametinib and report as SAE.
Grade 2 and Grade 3	Consult ophthalmologist immediately	• Interrupt trametinib. Dabrafenib may be continued at the same dose [b].If RPED and RVO excluded, restart trametinib at the same dose level. • If RPED diagnosed, see RPED dose modification in Table 6-15; report as SAE.

[redacted]

Visual changes (Eye disorders – Other, CTCAE Version 4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
		• If RVO diagnosed: Permanently discontinue trametinib and report as SAE.
Grade 4	Consult ophthalmologist immediately	• Interrupt trametinib. Dabrafenib may be continued at the same dose [b].If RPED and RVO excluded, should consider restarting trametinib at same or reduced dose after discussion with study medical monitor. • If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE.
[a.] If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required. [b.] Permanently discontinue dabrafenib for ≥ Grade 2 uveitis (including iritis and iridocyclitis) of > 6 weeks duration.		

Table 6-15 Mandatory dose modification and recommended clinical management for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment

Retinal pigment epithelial detachments (RPED)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
• Grade 1 (Asymptomatic; clinical or diagnostic observations only)	• If RPED worsens follow instructions below.	• Continue dabrafenib and trametinib with retinal evaluation monthly until resolution.
• Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity).	• Retinal evaluation monthly.	• Interrupt trametinib and continue dabrafenib. • If improved to ≤ Grade 1, restart trametinib at next lower level • If not improved to ≤ Grade 1 within 3 weeks, permanently discontinue trametinib

6.5.2.12 Monitoring guideline for hyperglycemia suspected to be related to dabrafenib treatment

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in participants with pre-existing diabetes or hyperglycemia.

Advise participants to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

6.5.2.13 Mandatory dose modification and management guideline for hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when dabrafenib is administered with trametinib. Permanently discontinue dabrafenib and trametinib for all Grade 4 hemorrhagic events and for any persistent Grade 3

[redacted]

hemorrhagic events. Withhold dabrafenib and trametinib for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

6.5.2.14 Mandatory dose modification and management guideline thromboembolic events

Advise patients to immediately seek medical care if they develop symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), such as shortness of breath, chest pain, or arm or leg swelling. If any signs or symptoms of venous thromboembolism are present, the participant will undergo specific laboratory and medical imaging studies to confirm it. The medical imaging study or studies selected will depend on the anatomic site or organ of involvement (e.g., Doppler ultrasound, venography, ventilation perfusion lung scan, angiography, MRI). If the diagnosis is confirmed, appropriate medical care according to standard local clinical practice should be initiated immediately.

Permanently discontinue trametinib for life threatening PE. Withhold trametinib for uncomplicated venous thromboembolism for up to 3 weeks; if improved, trametinib may be resumed at a lower dose level.

6.5.2.15 Mandatory dose modification and management guideline for new malignancies suspected to be related to dabrafenib and/or trametinib treatment

New cutaneous malignancies:

Cutaneous squamous cell carcinoma (CuSCC), keratoacanthomas (KA) and new primary melanomas have been observed in participants treated with dabrafenib and dabrafenib/trametinib combination therapy. These treatment-related lesions should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for CuSCC, KA, or new primary melanoma, however CuSCC and new primary melanoma should be reported as a SAE. In addition, a biopsy of the lesion should be taken, where possible, and submitted for further analyses and a summary of the results submitted to Novartis.

Participants should be instructed to immediately inform their physician if new lesions develop. Skin examination should be performed prior to initiation of study treatment and throughout therapy as detailed in the Visit Evaluation Schedule. Monitoring should continue every month for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

New non-cutaneous malignancies:

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling in *BRAF* wild type cells with RAS mutations when exposed to *BRAF* inhibitors, which may lead to increased risk of non-cutaneous malignancies in participants treated with dabrafenib. Cases of RAS-driven malignancies have been seen with *BRAF* inhibitors, including dabrafenib. Participants should be monitored as clinically appropriate. Consider the benefits and risks before continuing treatment with dabrafenib in participants with a non-cutaneous malignancy harboring a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib.

[redacted]

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

New cutaneous and non-cutaneous malignancies that are reported to the Investigator should be reported as a SAE. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses including RAS mutation status. Testing of these biopsies may include analysis of genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens, and would analyze the biological pathways known to be associated with, and relevant to, *BRAF*-mutant tumor activation.

6.5.2.16 Mandatory dose modifications and recommended clinical management guidelines for abnormal liver enzyme

Guidelines for dose modification and management of abnormal liver enzyme functions considered to be related to study treatment by the investigator are provided in Table 6-16.

In addition to the instructions below, participants with normal baseline transaminases and bilirubin who experience sudden elevations even within Grade 1, should be monitored more closely.

Table 6-16 Mandatory dose modifications and recommended clinical management guidelines for abnormal liver enzyme test

Abnormal liver enzyme tests/hepatitis		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 2: AST or ALT >3× ULN to ≤ 5× ULN and/or bilirubin > 1.5× ULN to ≤ 3× ULN	• Monitor hepatic laboratory tests more frequently(every 2-3 days) until returned to baseline values	• Interrupt, dabrafenib and trametinib until ≤ Grade 1, and then reinstate, dabrafenib and trametinib at the same dose level.
Grade 3 or 4: AST or ALT > 5× ULN and/or bilirubin > 3× ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until return to baseline values. • Consider appropriate consultation* with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary.	**1st and 2nd occurrences** • Interrupt dabrafenib and trametinib until recovery to ≤ Grade 1 or baseline • Reduce dabrafenib and trametinib to the next lower dose level per Table 6-3. Re-escalation of the participant's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence** • Permanently discontinue dabrafenib and trametinib
Rule out viral hepatitis and other potential causes of liver injury **For participants with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increase by ≥ 50% relative to baseline and last for at least 1 week then the participant should be discontinued		

[redacted]

Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with an elevation of total bilirubin (TBIL) may be indicative of potential DILI. These events should be considered as clinically important and managed accordingly.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and TBIL value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For participants with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in participants without bone metastasis, or elevation of ALP liver fraction in participants with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury).

In the absence of cholestasis, these participants should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g., biliary tract) may be warranted.
4. Additional testing for other hepatotropic viral infection (e.g., CMV, EBV, Adenovirus, HSV, HHV6, HIV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 10) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

[redacted]

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with dabrafenib, metabolites of dabrafenib and trametinib, as detailed in pharmacokinetics section.

6.6.2 Treatment of overdose

Investigators should refer to the current dabrafenib and trametinib local prescribing information and/or Investigator's Brochure for additional information regarding overdose.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational drug section.

A unique medication number is printed on the study treatment label.

As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant. The study treatment has a 2-part label (base plus tear-off label), immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant's source document.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), that limits or prevents on-site study visits, delivery of study treatment directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of study treatment from the site to the participant's home remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

[redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.2 Instruction for prescribing and taking study treatment

Dabrafenib and trametinib should be taken as follows:

- Dabrafenib will be administered orally twice daily (BID) during the treatment period.
- Trametinib will be administered orally once daily (QD) during the treatment period.
- Participants should be instructed to take the dabrafenib and trametinib concurrently in the morning, at approximately the same time every day. The second (evening) dose of dabrafenib (150 mg) should be administered approximately 12 (± 4) hours apart from the first dose (morning) of dabrafenib.
- Dabrafenib and trametinib should be taken with approximately 120-240 mL of water under fasting conditions, at least 1 hour before or 2 hours after a meal.
- Participants should be instructed to swallow whole capsules of dabrafenib and not chew or open them.
- If a participant vomits after taking study drug, the participant should be instructed not to retake the dose and wait for the next scheduled dose. The occurrence and frequency of any vomiting during treatment must be noted in the AE section of the eCRF.
- If a participant misses a scheduled dose not due to interruption for any AE, he/she should be instructed not to double the next regularly scheduled dose. However, participant may take the missed dose immediately if the next scheduled dose is at least 6 hours later for dabrafenib and 12 hours later for trametinib. Participant may then take the next dose at the scheduled time.

[redacted]

- Global clinical open-label supply kits of study treatment assigned by the IRT will be recorded in the IRT system.

Table 6-17 Dose treatment and schedule

Study treatment	Pharmaceutical form and route of administration	Strength	Frequency and/or Regimen	Dose
Dabrafenib	Capsules for oral use	50 mg, 75 mg	BID	150 mg BID (300 mg/day)
Trametinib	Tablets for oral use	0.5 mg, 2 mg	QD	2 mg/day

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICHE6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common adverse drug reactions already known about the investigational drug can be found in the Investigator's Brochure (IB) and/or Core Data Sheet (CDS). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate informed consent forms (ICFs) by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All assessment (marked as "X") should be recorded in the clinical database or received electronically from a vendor. All data obtained from these assessments must be supported in the participant's source documentation. Other assessments (marked as "S") will be recorded in the participant's source documentation only.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment Phase**							**Post-treatment Follow-up Phase**	**Survival Follow-up**	**Study Completion**
Visit Name	**Screening**	**Day 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 15 and every 3 weeks thereafter**	**End of Treatment (to be completed within 7 days of permanent discontinuation of study treatment)**	**Post treatment follow-up**		**End of Study (EoS)**
Days	**-28 to -1**	**Day 1**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**EoT**	**FU visit**	**Survival**	**EoS**
Informed consent	X										
Enrollment		X									
Inclusion / Exclusion criteria	X										
Demography	X										
BRAF V600E mutation testing	X										
Tumor sample collection for central BRAF V600E testing. Note: if local BRAF V600E mutation result is not available, sample should be sent for central testing by Day -20	X										

[redacted]

Period	**Screening**	**Treatment Phase**							**Post-treatment Follow-up Phase**	**Survival Follow-up**	**Study Completion**
Visit Name	**Screening**	**Day 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 15 and every 3 weeks thereafter**	**End of Treatment (to be completed within 7 days of permanent discontinuation of study treatment)**	**Post treatment follow-up**		**End of Study (EoS)**
Days	**-28 to -1**	**Day 1**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**EoT**	**FU visit**	**Survival**	**EoS**
Serum pregnancy test and menstrual history	S							S			
Medical history/current medical conditions	X										
IRT Registration	S	S	S	S	S	S	S	S			
Diagnosis and extent of cancer	X										
Prior Antineoplastic Therapy (Medication, Radiation, Surgery)	X										
Hepatitis screen	X										
Family history	S										
Smoking history	X										
Alcohol Consumption	X										

[redacted]

Period	**Screening**	**Treatment Phase**							**Post-treatment Follow-up Phase**	**Survival Follow-up**	**Study Completion**
Visit Name	**Screening**	**Day 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 15 and every 3 weeks thereafter**	**End of Treatment (to be completed within 7 days of permanent discontinuation of study treatment)**	**Post treatment follow-up**		**End of Study (EoS)**
Days	**-28 to -1**	**Day 1**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**EoT**	**FU visit**	**Survival**	**EoS**
Physical Examination	S	S	S	S	S	S	S	S			
Vital Signs	X	X	X	X	X	X	X	X			
Body Weight	X	X	X	X	X	X	X				
Dermatological Assessment	S		S	S	S	S	S	S			X
Ophthalmic Examination	X		X	X		Week 12 and every 12 weeks thereafter		X			
Electrocardiogram (ECG)	X		X	X			Week 15 and every 9 weeks thereafter	X			
Echocardiogram	X			X			Week 15 and every 9 weeks thereafter	X			
Concomitant medications	X	X	X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X			X

[redacted]

Period	**Screening**	**Treatment Phase**							**Post-treatment Follow-up Phase**	**Survival Follow-up**	**Study Completion**
Visit Name	**Screening**	**Day 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 15 and every 3 weeks thereafter**	**End of Treatment (to be completed within 7 days of permanent discontinuation of study treatment)**	**Post treatment follow-up**		**End of Study (EoS)**
Days	**-28 to -1**	**Day 1**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**EoT**	**FU visit**	**Survival**	**EoS**
ECOG Performance Status	X	X	X	X	X	X	X	X			
Hematology	X	X	X	X	X	X	X	X			
Clinical Chemistry	X	X	X	X	X	X	X	X			
Urinalysis	X	X	X	X	X	X	X	X			
Coagulation Panel	X										
PK blood collection			X	X		X					
Pregnancy (Urine)		S	S	S	S	S	S				
Tumor Assessment (Imaging)	X			X		Every 6 weeks until Week 36, and then every 12 weeks			Every 6 weeks until Week 36, and then every 12 weeks		

[redacted]

Period	**Screening**	**Treatment Phase**							**Post-treatment Follow-up Phase**	**Survival Follow-up**	**Study Completion**
Visit Name	**Screening**	**Day 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**	**Week 15 and every 3 weeks thereafter**	**End of Treatment (to be completed within 7 days of permanent discontinuation of study treatment)**	**Post treatment follow-up**		**End of Study (EoS)**
Days	**-28 to -1**	**Day 1**	**21 ±7**	**42 ±7**	**63 ±7**	**84 ±7**	**105 ±7**	**EoT**	**FU visit**	**Survival**	**EoS**
Fluid/Tissue collection results (if available)	As clinically indicated			As clinically indicated		As clinically indicated			As clinically indicated		
Patient reported outcomes		X	X	X	X	X	X	X			
Study drug administration		X	X	X	X	X	X				
Study treatment discontinuation								X			
Survival Follow Up										X	
Antineoplastic therapies since discontinuation of study treatment									X	X	X

[redacted]

8.1 Screening

Participants must sign an informed consent form (ICF) prior to any study specific screening evaluations, within 28 days prior to the first dose of study treatment. The screening phase begins once written informed consent is provided and ends after 28 days or when participant receives the first dose of study treatment. Following completion of screening procedures and verifying participant eligibility based on assessments, the participant will be enrolled via the Interactive Response Technology (IRT) system. Laboratory results from the local laboratory will be used to determine participant's eligibility to the study. Refer to Table 8-1 for additional details.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. Participants who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Each case must be discussed and agreed with Novartis on a case-by-case basis.

All required screening assessments must be repeated if they do not meet the allowed time window for screening, when the subject will be rescreened for participation in the study.

If the participant already provided the ~~archival~~ tumor tissue samples for central testing of BRAF V600E mutation status it is not required to submit a new sample

Procedure for re-screening is as follows:

- Site must register the patient as a screen failure in IRT
- Subject number will be different from the initial screening

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in Medical History CRF. CRA is to review and confirm patient‘s eligibility for re-screening with the site. Patients may be re-screened only once and must be enrolled within 28 days after the recorded rescreening date. All evaluations including original assessments and repeated assessments must be collected on the eCRF.

Participants will be enrolled based on a positive *BRAF* V600E mutation test performed using an NMPA/MOH-approved assay as part of study inclusion criteria (Section 5.1).

- Patients with local *BRAF* V600E mutation performed by an NMPA/MOH-approved assay at screening will be enrolled based on local testing results. Local *BRAF* V600E mutation result should be locally documented and verified by a Novartis monitor and testing method should be recorded in the eCRF. For these patients it is required to provide an archival tumor tissue sample (minimum 3 to maximum 5 tumor slides) at screening but central testing of *BRAF* V600E mutation status is not required prior to enrollment. These patients will not be excluded if centralized testing is later found to be discordant or uninformative (e.g. inadequate sample).
- Patients who do not have locally documented *BRAF* V600E results available, or have *BRAF* V600E results based on NMPA/MOH unapproved assays at screening will be enrolled based on central *BRAF* testing results. For these patients, a tumor sample

[redacted]

(minimum 3 to maximum 5 tumor slides, see Section 8.5.3) for prospective central testing must be submitted during screening, performed prior to enrollment. A positive *BRAF* V600E mutation result must be obtained prior to enrollment.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition Case Report Form. Data and samples collected from participants prior to screen failures may still be analyzed (i.e. specifically, mutation test for BRAF from either Central or Local Lab collected from participants prior to screen failure.)

8.2 Participant demographics/other baseline characteristics

The data to be collected on participant characteristics at screening includes:

- Demography (age, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Past and current medical conditions including cardiovascular medical history and risk factors
- Diagnosis and extent of cancer using AJCC edition 8
- Alcohol history
- Smoking history
- HIV history
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and current concomitant medications, surgical and medical procedures and significant non-drug therapies. Note: All other medications taken within 28 days or 5 half-lives, whichever is shorter before the first dose of study treatment is administered must be recorded on the Prior and current concomitant medication eCRF page and updated on an ongoing basis if there is new change to the medication.

Assessments to be performed at screening/baseline include:

- Physical examination (e.g. performance status (ECOG), height, weight, vital signs, ophthalmic and skin examination)

[redacted]

- Cardiovascular assessments (e.g., ECG, ECHO or MUGA)
- Laboratory assessments (e.g., hematology, chemistry, thyroid function, coagulation, urinalysis, serum pregnancy test)
- Tumor assessment (RECIST 1.1, color digital photography including metric ruler for skin lesions, etc.)

8.3 Efficacy

8.3.1 Efficacy assessments

Tumor response will be assessed locally and by independent central review according to the Novartis guideline version 3.2 (Section 16) based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-2. Details of the central review process will be described in the independent review charter.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The central independent review's assessment will be used for the primary endpoint analysis and local investigator's assessment will be used for treatment decision making.

Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline images. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Information regarding cytology/histology results should be transmitted to the imaging CRO via the cytology and histology report form for all visits, when applicable, for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Day 1).

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after enrollment cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen, and pelvis CT or MRI
- Brain CT or MRI
- Whole body bone scan
- Localized bone CT, MRI, or x-ray, for any lesions identified on the whole body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI
- Color photography including a metric ruler to measure the size of the lesion for any skin lesions present

[redacted]

- CT or MRI of other metastatic sites (e.g. neck), if clinically indicated

If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts; however, if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

A brain MRI or CT should be completed for all participants to identify brain metastases. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

A whole body bone scan should be performed per institutional standard of care [e.g. Tc-99 bone scan, whole body bone MRI, Fluorodeoxyglucose positron emission tomography (FDG-PET), or sodium fluoride (NaF) PET]. Localized CT, MRI, or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan, which are not visible on the chest, abdomen, and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g. neck) of disease as appropriate should be performed.

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 8-2 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing (see Table 8-1). Imaging assessments for response evaluation will be performed every 6 weeks (+/- 7 days) for the first 36 weeks, and every 12 weeks (+/- 7 days) thereafter until disease progression , death, lost to follow-up or withdrawal of consent. Imaging assessments should be scheduled using the enrollment date as the reference date (not the date of the previous tumor assessment), and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local

[redacted]

radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 1).

Table 8-2 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 6 weeks (+/- 7 days) until Week 36, and every 12 weeks (+/- 7 days) thereafter
Brain CT or MRI	Mandated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis, or if clinically indicated
Whole body bone scan	Mandated	If clinically indicated
Localized bone CT, MRI, or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis, or if clinically indicated
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis, or if clinically indicated
CT or MRI of other metastatic sites (e.g. neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis, or if clinically indicated
During a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic, or natural disaster, that limits or prevents on-site study visits, the collection of images may be modified by Novartis and will be communicated to the investigator		

8.3.2 Transmission of radiological data to central independent review

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging vendor designated by Novartis. Rapid image transmission to the central imaging vendor will be accomplished by transferring the images acquired by the investigator electronically in a secured website (e.g.: via the internet).

All imaging timepoints will be read on an ongoing basis as detailed in the imaging manual to be provided by the designated imaging vendor and independent review charter. In all instances, the process at the imaging vendor will ensure that the central reviewers remain blinded to the results of the local assessment. Results of these readings will not be communicated to the sites.

In case patients continue treatment beyond disease progression as outlined in Section 6.1.4.1, images should still be sent to the imaging vendor.

[redacted]

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-3 Physical Examination, Vital Signs, Height and Weight & Specifications

Assessment	Specification
Physical examination	A complete physical examination will be performed at screening and later as clinically indicated and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be performed at all visits starting from visit 3 as per schedule in Table 8-1 except where a complete physical examination is required. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature. Vital signs will be measured at screening and at subsequent time points as specified in Table 8-1
Height and weight	Height in centimeters (cm) will be measured at screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1.
Dermatological Examination/Skin Biopsy/Photography	A full body dermatological examination will be performed by a dermatologist (or suitably qualified medical personnel) to identify abnormal skin lesions. All findings will be photographed and identified during screening. Dermatological examinations should include examination of skin and assessment of any skin changes. Dermatological examinations will be obtained at each time point as noted in the Assessment Schedule (Table 8-1). Wherever possible, the same individual should perform these examinations. Biopsy in or around skin lesions that change during the study may be obtained if clinically indicated. Skin photography and de-identified pathology reports of new lesions or lesions that change during the study must be obtained and forwarded to Novartis or designee.

ECOG Performance status:

Performance status will be assessed as described in the Table 8-1. More frequent examinations may be performed at the investigator's discretion, if medically indicated. ECOG Performance status scale will be used as described in Table 8-4:

Table 8-4 ECOG 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 housework, 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

8.4.1 Laboratory evaluations

Local laboratory will be used for analysis of scheduled hematology, biochemistry, and other blood specimens collected as part of safety monitoring (as detailed in Table 8-5). The frequency of the assessments is indicated in the Table 8-1.

For assessment of participants' eligibility to the study, laboratory results from local laboratory will be used.

The results of the local laboratory will be recorded in the eCRF.

The CRA will obtain the local laboratory reference ranges and a copy of the laboratory certification for all laboratory results that are entered into the eCRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab collection site may be used.

Table 8-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Other (absolute value preferred , %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT , AST, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Cholesterol, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting)
Urinalysis	Microscopic Panel: Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (at baseline and as clinically indicated)

[redacted]

Test Category	Test Name
Pregnancy Test	A serum pregnancy test must be performed at screening (at the local laboratory) ≤ 14 days before first dose of study treatment, and at EOT. Subsequent tests may be urine tests (refer to 'Pregnancy and assessments of fertility' section).

8.4.2 Cardiac assessments

8.4.2.1 Electrocardiogram (ECG)

A standard 12 lead ECG (single or triplicate) will be performed according to the relevant Visit Evaluation Schedule (Table 8-1). Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline/according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. Additional, unscheduled, ECGs may be performed at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate ECGs should be recorded approximately 2 minutes apart. The mean QTcF value should be calculated from each of the triplicate ECGs assessments. All ECGs need to be collected and copies kept in the medical record for central review, if requested by the sponsor.

Twelve (12)-lead ECGs will be obtained using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTcF intervals. ECG data will be read and interpreted locally.

Any identifier details must be redacted e.g. participant initials, date of birth.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

Table 8-6 ECG collection plan

Week (or Cycle)	Day	Time	ECG Type	Number of ECG
Screening	-28 to -1	Anytime	12 Lead	3
3	1	Anytime	12 Lead	3
6	1	Anytime	12 Lead	3
Week 15 and every 9 weeks thereafter and at EoT	1	Anytime	12 Lead	3
Unscheduled (as clinically indicated)		Anytime	12 Lead	1 (3 if clinically significant)

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), subject number, date, and kept in the source documents at the study site.

Clinically significant abnormalities present when the participant signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened

[redacted]

clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

8.4.2.2 Echocardiogram (ECHO)

Decreases of the LVEF have been observed in participants receiving trametinib. Therefore, ECHO or MUGA (ECHO is preferred) must be performed to assess cardiac ejection fraction in regular intervals according to the relevant schedule (Table 8-1).

The same procedure (ECHO or MUGA) should be performed at baseline and at follow-up visit(s). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-13.

8.4.3 Pregnancy and assessments of fertility

Male participants

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

Male patients (including those that have had a vasectomy) taking the dabrafenib and trametinib combination therapy must use a condom during intercourse, and for 16 weeks after stopping treatment, and should not father a child during these periods.

In addition, male participants should not donate sperm for the time period specified above.

Women of child-bearing potential

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during dosing and for 16 weeks after stopping treatment with dabrafenib and trametinib combination therapy. Highly effective contraception methods include:

a. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

c. Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that participant.

d. Placement of a hormonal or non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.

[redacted]

Notes:

a. Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository) are not considered highly effective methods of contraception.

b. Hormonal-based methods (e.g. oral contraceptives) are not considered as highly effective methods of contraception due to potential drug-drug interactions with dabrafenib and/or trametinib

c. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

As per Section 4.6, changes in safety assessments can be added as one of the risk mitigation procedure during public health emergency declared by local or regional authorities. If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.4 Hepatitis marker

Hepatitis panels listed in Table 8-5 will be performed at screening and as clinically indicated while on study treatment.

HBV-DNA serology (including HBV-DNA, HBsAg, HBsAb, HBcAb) and HCV RNA-PCR test will be performed at baseline/screening (≤ 28 days prior to start of study treatment) and as clinically indicated (hepatitis markers should be evaluated for precautionary safety monitoring of viral re-activation while on study treatment).

During the screening period, participants must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all participants to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc.), and any past or present HBV symptoms (e.g., jaundice, dark urine, light colored stools, right upper quadrant pain).

After start of the study treatment and until 150-day safety follow-up, testing for HBV and HCV should be performed if clinically indicated (for example: rule out viral causality in case of DILI).

[redacted]

8.4.5 Ophthalmic examination

Episodes of visual changes have been observed in participants receiving trametinib, dabrafenib, and combination therapy.

A standard ophthalmic examination by an ophthalmologist will be performed as per schedule in Table 8-1. The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities (dilation only required if clinically indicated). Optical coherence tomography is mandated if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient Reported Outcomes

The impact of treating BRAF+ NSCLC with dabrafenib in combination with trametinib on health-related quality-of-life (QoL), physical functioning, lung cancer symptoms, treatment-related side effects, global health status, and utilities will be assessed with the the European Organization for Research and Treatment of Cancer core quality of life questionnaire (EORTC-QLQ-C30), it's lung cancer specific module (QLQ-LC13), and the EuroQoL 5-level instrument (EQ-5D-5L, tablet version) (Aaronson et al 1993, Bergman et al 1994, Rabin and de Charro 2001):

PRO data will be recorded by participants onto an electronic tablet device maintained at the study site. Investigators or study personnel should provide technical assistance but should not encourage the participants to change responses reported in questionnaires. All ePRO assessments should be administered in the participant's local language according to the assessment schedule in Table 8-1, prior to any assessments (including imaging assessments), treatments, or receipt of results from any test to avoid biasing the participant's perspective.

The ePROs will be completed prior to any other assessments on Cycle 1 Day 1 prior to enrollment, then at every visit (with and without dosing) while the patient is on treatment until treatment discontinuation and/or at the End of Treatment visit (EOT).

Participants should be given sufficient space and time to complete all study questionnaires. The responses stored electronically on the database will be considered the source file. If missing responses are noted, the tablet will alert participants of any missing responses. Attempts should be made to collect questionnaires for all participants. If participants refuse to complete questionnaires, this should be documented in the source documents. A participant's refusal to complete study questionnaire(s) are not protocol deviations. Please refer to the study ePRO manual for detailed instructions for completion and handling of the ePROs.

The participant should be made aware that completed questionnaires are not reviewed by the Investigator/ study personnel.

[redacted]

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely.

8.5.2 Pharmacokinetics

8.5.2.1 Pharmacokinetic blood collection and handling

Blood samples (2 mL) for pharmacokinetic analysis of dabrafenib and metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib) and trametinib will be collected during the study visits in Week 3, Week 6, and Week 12 shown in Table 8-1 and Table 8-7. For each visit, participants will be instructed to withhold their morning dose prior to the study visit, and a pharmacokinetic sample will be obtained prior to study treatment administration (between 8-14 hours after the evening dose of the previous day). The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the CRF. Sampling problems will be noted in the relevant field of the CRF.

For events of visual changes regardless of severity, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Details of pharmacokinetic blood sample collection (including volume to be collected, timing of samples, recording of pharmacokinetic sample information), processing, storage and shipping procedures are provided in the Laboratory Manual.

Table 8-7 Sample log table for the evaluation of pharmacokinetics of trametinib , dabrafenib, and related metabolites

Weeks	Scheduled Time	Dose Reference ID for trametinib	Dose Reference ID for dabrafenib	PK Sample Number	Volume (mL)
3	0 h (pre-dose)[a]	101/1001[b]	201/2001[c]	1	2
6	0 h (pre-dose)[a]	102/1002[b]	202/2002[c]	2	2
12	0 h (pre-dose)[a]	103/1003[b]	203/2003[c]	3	2
NA	Unscheduled[d]	NA	NA	1001+[d]	2

[a]Samples will be collected prior to the morning dose of trametinib and dabrafenib (between 8-14 hours after the evening dose of the previous day).

[b]The first Dose Reference ID for trametinib is for current dose, while the second PK collection number is for last dose the participant received prior to the collection of the PK sample

[c]The first Dose Reference ID for dabrafenib is for current dose, while the second PK collection number is for last dose the participant received prior to the collection of the PK sample

[d]For events of visual changes regardless of severity, a blood sample for PK analysis must be drawn as close as possible to the time of the event, sequentially numbered 1001, 1002, etc.

8.5.2.2 Analytical method

Plasma analysis will be performed under the control of PK Sciences, the details of which will be included in the Lab Manual. Concentrations of dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib and trametinib will be quantified in one validated assay. Raw data will be stored in the Good Laboratory Practice (GLP) Archives.

[redacted]

Once the plasma has been analyzed for dabrafenib and its metabolites and trametinib, any remaining plasma may be analyzed for other compound-related metabolites and the results reported.

8.5.3 Biomarkers

Central *BRAF* V600E mutation testing

For this study, biomarker analysis is limited to central *BRAF* V600E mutation testing in tumor tissue samples. If available, it is mandatory to provide an archival specimen obtained at or since the time of diagnosis for central *BRAF* V600E mutation testing. A sample from the most recent biopsy is preferred. Tumor tissue samples will be provided as a minimum of 3 to a maximum of 5 formalin-fixed paraffin-embedded (FFPE) tumor slides. Every effort should be made to submit freshly cut tissue sectioned onto tumor slides. Slide cut date is required on sample requisition form. CNS and bone are excluded organs for new biopsy.

If a suitable archival tumor tissue sample is not available, minimum 3 to maximum 5 slides from a newly acquired biopsy sample can be accepted, if a new biopsy is medically feasible.

Table 8-8 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Archival or new tumor biopsy sample for central *BRAF* V600E mutation testing	Minimum 3 to maximum 5 tumor slides freshly cut from FFPE archival tumor sample or from new tumor biopsy sample. Fine needle aspirates are not acceptable.	Screening	At C1D1 with local *BRAF* V600E result or by screening Day -20, if local *BRAF* V600E result not available.

Tumor biopsy samples will be tested to centrally confirm the *BRAF* V600E status at the Novartis-designated laboratory. Provision of a minimum of 3 to a maximum of 5 freshly cut tumor slides is indicated in order to allow for sufficient material for central *BRAF* V600E mutation testing, as described below:

- If local documentation of *BRAF* V600E mutation status by local test result from a qualified assay (NMPA and/or MOH-approved) is available, *BRAF* V600E mutation results will be subjected to retrospective central testing by a Novartis designated laboratory with a MOH/NMPA approved assay.
- In cases where an acceptable local result for *BRAF* V600E mutation is not available, a tumor sample for central prospective testing must be submitted during screening, prior to enrollment. To allow sufficient time for testing, the tumor sample should be sent to a Novartis designated central laboratory for testing by screening Day -20.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Disease progression
- Adverse events, abnormal laboratory values, or abnormal test result that indicate a safety risk to the participant as described in Section 6.5.2.
- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Any situation in which study participation might result in a safety risk to the participant

If a participant discontinues study treatment at a scheduled visit, the assessments performed at that visit can be used to fulfil the treatment discontinuation visit requirements. Laboratory assessments and other required assessments do not need to be repeated at the discontinuation visit if they were performed within 14 and 30 days, respectively, of the discontinuation visit. If the last efficacy assessment was >6 weeks prior to study withdrawal and disease progression had not been documented, efficacy assessment should be obtained.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in Section 9.1.3. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the participant’s discontinuation from study treatment.

For participants who discontinue treatment for reasons other than documented disease progression as determined by investigator, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 6 weeks until Week 36 and then every 12 weeks until documented disease progression as determined by investigator, death, lost to follow-up, or withdrawal of consent.

[redacted]

In some circumstances participants may be allowed to continue to receive study treatment beyond disease progression as per RECIST criteria as determined by investigator. These participants will continue assessments as outlined in the assessments section, and will complete the EOT visit only after permanent discontinuation of study treatment. After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact (per assessment schedule in Table 8-1)

- new / concomitant treatments including any radiotherapy, surgical procedure or new anticancer therapy
- adverse events/Serious Adverse Events
- survival status

Monthly safety follow up should continue for up to 6 months or until initiation of another anti-neoplastic therapy for monitoring for patients with cutaneous and non-cutaneous malignancies.

9.1.2 Survival follow-up

All patients who discontinued from tumor assessments will subsequently be followed for survival information every 3 months until death, lost to follow-up or withdrawal of consent for survival. The investigator or his/her designee will collect this survival information and any new anti-neoplastic therapies for all patients until the final survival analysis.

Follow-up can be done via a phone contact. Antineoplastic therapies will be captured on the relevant eCRF page following the last dose of the study treatment.

9.1.3 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

In the event that a participant withdraws consent and/or opposes the use of data/biological samples, study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up. If the participant agrees, a final evaluation at the time of the participant's

[redacted]

withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come for a final visit) and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Following discontinuation of study treatment, all participants are to be followed as specified in Section 9.1. The End of Study eCRF should only be completed when a participant is no longer being followed.

The primary analysis was conducted when the first 20 enrolled participants 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. The primary analysis data will be summarized in

[redacted]

the primary clinical study report (CSR). Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing participants will continue to receive study treatment and be followed as per the schedule of assessments, as long as participants derive benefit from dabrafenib in combination with trametinib.

The study will end 17 months after the LPFV or when all participants have died or discontinued from the study, whatever occurs first.

At the end of the study, every effort will be made to continue provision of study treatment outside this study in alignment with local regulations through an alternative setting (e.g. another clinical study, Post Trial Access (PTA)) to participants who in the opinion of the Investigator are still deriving clinical benefit. The final analysis will occur at the end of the study. All available data from all participants up to this cut-off date will be analyzed and summarized in a final CSR.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a participant or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade OR the Common Toxicity Criteria (CTC) AE grade (version 4.03).
1. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of

[redacted]

underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

2. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
3. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
4. action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

1. its outcome (i.e. recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or end of study visit) following the last dose of study treatment.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

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

[redacted]

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 included in the SAP.

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

AESI for dabrafenib in combination with trametinib include:

- Neutropenia

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

[redacted]

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment (or longer, depending on the elimination half-life of the specific compound) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate Case Report Form (CRF) irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the

[redacted]

EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

[redacted]

12 Data analysis and statistical methods

It is planned that the data from all centers participating in the trial will be pooled for analysis. Novartis and/or a designated CRO will perform all analyses.

The primary efficacy and safety analysis will be conducted when the first 20 enrolled participants 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 participants completed the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants that received any study treatment.

Efficacy and safety analysis will be based on this analysis set.

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for FAS.

12.3 Treatments

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 the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

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

[redacted]

12.4 Analysis of the primary endpoint(s)

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.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of the study is overall response rate (ORR), defined as the proportion of participants 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 (see Section 16 for details).

12.4.2 Statistical model, hypothesis, and method of analysis

The ORR will be summarized along with its exact 95% confidence intervals.

12.4.3 Handling of missing values/censoring/discontinuations

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

Other missing data are simply noted as missing on appropriate tables/listings.

12.4.4 Sensitivity analyses

Not applicable.

12.5 Analysis of secondary endpoints

The secondary 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
- To characterize the safety and tolerability of dabrafenib in combination with trametinib
- To characterize PK of dabrafenib, dabrafenib metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib
- To characterize quality of life as measured by the EORTC-QLQ C30, LC13 and the EQ-5D-5L

12.5.1 Efficacy endpoint(s)

ORR is defined as the percentage of participants 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 (see Section 16 for further details). 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.

[redacted]

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 participants 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. Participants 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 participants 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 participant is not known to have died, then OS will be censored at the latest date the participant 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.

12.5.2 Safety endpoints

For all safety analyses, the FAS will be used.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study treatment
2. On-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
3. Post-treatment period: starting at 31 day after last dose of study treatment.

Adverse events

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study treatment or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and severity (based on CTCAE v 4.03)

[redacted]

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, adverse events of special interest (AESI), other significant adverse events leading to dose adjustment and discontinuation.

The list of AESI's will also include relevant events for dabrafenib and trametinib which will be defined in the SAP.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12-lead ECG

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted (centrally/locally).
2. Categorical Analysis of QT/QTc interval data based on the number of participants 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 participants will be produced (by treatment group).

All ECG data will be listed by participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by participant, 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:

[redacted]

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant 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.

12.5.3 Pharmacokinetics

Plasma concentration data of dabrafenib, dabrafenib metabolites (hydroxy-dabrafenib, and desmethyl-dabrafenib), and trametinib will be listed by participant, 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.

12.5.4 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, as appropriate.

[redacted]

12.7 Interim analyses

Not applicable.

[redacted]

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial

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results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

[redacted]

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

16.1 Appendix 1: Response Criteria; Response Evaluation Criteria in Solid Tumors (RECIST)

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

Document type:	TA Specific Guideline
Document status:	Version 3.2: February 11, 2016 Version 3.1: November 29, 2011 Version 3: October 19, 2009 Version 2: January 18, 2007 Version 1: December 13, 2002
Release date:	11-Feb-2016
Authors (Version 3.2):	[redacted]
Authors (Version 3.1):	[redacted]
Authors (Version 3):	[redacted]
Authors (Version 2):	[redacted]
Authors (Version 1):	[redacted]

16.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse, et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer, et al 2009).

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The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse, et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer, et al 2009) European Journal of Cancer; 45:228-247.

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 16.1.3.2.8

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

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- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.8.

16.1.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- 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 major 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 or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However,

[redacted]

another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  - Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
  - Physical exams: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
  - Ultrasound: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
  - Endoscopy and laparoscopy: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
  - Tumor markers: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic

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confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.1.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- Target lesions: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.1.2.1.1.
- **Nodal target**: See Section 16.1.2.1.1.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

16.1.2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These

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evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are participant to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

[redacted]

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
3. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit

[redacted]

is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2].

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail..
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

16.1.2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.1.2.2.

16.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 16.1.2.4.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

[redacted]

16.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response 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 where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

[redacted]

- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

[redacted]

The primary analysis of the best overall response will be based on the sequence of central blinded review/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study treatment for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

[redacted]

16.1.3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

16.1.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.1.3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

16.1.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

[redacted]

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

16.1.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

[redacted]

16.1.3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.1.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

16.1.3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement 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 progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

[redacted]

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.1.3.2.8).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

16.1.3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also

[redacted]

be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 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[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 16.1.2.4.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

16.1.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 16.1.3.2.7, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

[redacted]

Table 16-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

1. =Definitions can be found in Section 16.1.3.2.7.
2. =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7.
3. =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.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

[redacted]

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

[redacted]

16.1.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

16.1.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

16.1.4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which "*must*" lead to discontinuation of patient from trial.

16.1.4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

[redacted]

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

[redacted]

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

16.1.4.5.2 Incomplete assessment dates

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, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.1.3.2.7). 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 previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

16.1.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

16.1.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

16.1.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

16.1.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)

[redacted]

- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

16.1.5 References (available upon request)

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