NOVARTIS

Novartis Research and Development

DRB436

Clinical Trial Protocol CDRB436J12301 / NCT04940052

A randomized, double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with locally advanced or metastatic, radio-active iodine refractory BRAFV600E mutation-positive Differentiated Thyroid Cancer

Document type:	Amended Protocol Version
EUDRACT number:	Not Applicable
Version number:	03 (Clean)
Clinical Trial Phase:	III
Release date:	28-Feb-2023

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
ATC	anaplastic thyroid cancer
ATP	Adenosine Triphosphate
AUC	Area under the curve
BID	bis in die/twice a day
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CDx	Companion Diagnostics
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMO&PS	Chief Medical Office and Patient Safety
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DoR	Duration of Response
DTC	Differentiated Thyroid Cancer
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of Treatment
ERCP	Endoscopic retrograde cholangiopancreatography
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration

FDG-PET	Fluorodeoxyglucose positron emission tomography
FFPE	Formalin fixed paraffin embedded
FPFV	First patient first visit
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
HBsAg	Hepatitis B Virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGRAC	Human Genetic Resource Administration of China
HIV	Human immunodeficiency virus
HLH	Hemophagocytic Lymphohistiocytosis
HR	Hazard Ratio
[redacted]	[redacted]
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IVD	In vitro diagnostic
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LPLV	Last patient last visit
LVEF	Left-ventricular-ejection-fraction
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MKI	Multi-targeted tyrosine Kinase Inhibitor
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
MUGA	Multigated acquisition
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OCT	Optical Coherence Tomography
ORR	Overall Response Rate
OS	Overall Survival

PD	Progressive Disease
PFS	Progression Free Survival
[redacted]	[redacted]
PR	Partial Response
[redacted]	[redacted]
[redacted]	[redacted]
PS	Performance Status
PT	Prothrombin Time
PTA	Post Trial Access
PTC	Papillary Thyroid Carcinoma
PTT	Partial Thromboplastin Time
QD	Once a day/quaque die
QTcF	QT interval corrected by Fridericia's Formula
R Value	ALT/ALP x ULN
RAI	Radio Active Iodine
RAP	The Report and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RPED	Retinal pigment epithelial detachment
RPSFT	Rank Preserving Structural Failure Time
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCAR	Severe cutaneous adverse reactions
SD	Stable disease
SOD	Sum of diameter
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tg	Thyroglobulin
TgAb	Thyroglobulin Antibody
TSH	Thyroid Stimulating Hormone
TTP	Time to progression
ULN	Upper Limit of Normal
VEGFR	Vascular Endothelial Growth Factor
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
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 patient
Cohort	A specific group of patients fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
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. Electronic Data Capture includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain 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	A trial patient (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Patient information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.

Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
[redacted]	[redacted]
Randomization number	A unique identifier assigned to each randomized patient
Screen Failure	A patient who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient
Study drug	Dabrafenib or Trametinib
Study treatment	Dabrafenib/Trametinib combination or placebo combination
Study treatment discontinuation	When the patient permanently stops taking any of the study treatments prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 3 (28-Feb-2023)

As of 28-Feb-2023, 70 patients have been enrolled and treated in study CDRB436J12301.

Amendment rationale

The main purpose of this amendment is (1) to add Section 6.5.1.13 Guideline dose modifications and management of HLH (Hemophagocytic Lymphohistiocytosis), (2) to revise Section 6.2.1.1 "Permitted concomitant therapy requiring caution and/or action.

(1) In post marketing experience, hemophagocytic lymphohistiocytosis (HLH) has been observed with dabrafenib and trametinib combination therapy. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be permanently discontinued and appropriate management of HLH should be initiated.

(2) Currently the use of live vaccines is left at investigators best clinical judgement considering the potential immuno-compromised state of cancer patients. This statement was updated to indicate that live vaccines are prohibited for patients at participating sites in South Korea.

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.

Section 2.2 Secondary estimands wording was updated for clarity.

Section 5.2 Exclusion criteria number 4 and 5 wording was updated for clarity.

Section 6.2.1 Duplicate sentence was deleted under concomitant therapy.

Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action was updated to prohibit the use of live vaccines at participating sites in South Korea.

Section 6.5.1 Dose modification was revised to clarify that the mandatory study drug discontinuation due to a dose interruptions of > 28 days only apply to adverse events related to study drug. Also, wording was revised for clarity.

Section 6.5.1.13 was added to indicate the guideline dose modification and management for HLH (Hemophagocytic Lymphohistiocytosis).

Section 6.5.2.1 Follow up on potential drug-induced liver injury (DILI) cases wording was updated for clarity.

Section 8.3.1 Tumor assessments under Baseline imaging assessments, statement was revised to clarify that brain MRI or CT should be completed at baseline.

Section 11.3 Duplicate sentence was deleted under site monitoring section.

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 and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent Form. The Informed Consent for this study was already updated to reflect the hemophagocytic lymphohistiocytosis (HLH) safety measure after the IB updates, in 2022

Amendment 2 (20-Apr-2022)

As of 20-Apr-2022, 17 patients have been enrolled and treated in this CDRB436J12301.

Amendment rationale

The main purpose of this amendment is (1) to revise the renal function inclusion criterion with serum creatinine, (2) to clarify Brain imaging language, (3) to specify the visual field examination for ophthalmic exam, (4) to clarify the conditions when unblinding may be needed/can be done and [redacted]

(1) The previous renal inclusion criterion was based on creatinine clearance of ≥ 50 ml/min using the Cockcroft-Gault (CG) formula [(140-age) x weight] / [72 x Serum creatinine]. The CG formula can be influenced by older age and lower body weight which can lead to underestimation of the renal function (Michels WM, 2010). In the current study, the CG formula resulted in the exclusion of some elderly patients not able to meet the creatinine clearance of ≥ 50 ml/min, whilst having normal serum creatinine. Considering that there is no dose adjustment for mild to moderate renal impairment for either agent on the label, a more flexible inclusion criteria using serum creatinine will be used as this has already been implemented in one of the study in the program. Therefore, the inclusion criterion is being changed to Serum Cr <1.5 mg/dl, which ensures patient's safety while also not excluding elderly patients due to underestimation of the renal function.

(2) The description of brain imaging was updated in order to clarify that Brain MRI is preferred for all patients, unless MRI contrast is contraindicated. If MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.

(3) The visual field examination was specified, an automated static perimetry covering 60 degrees (e.g. a 30-2 perimetry), in order to ensure consistency and interpretability of the data. Consistent perimetry assessment is to be performed per patient throughout the duration of the study to enable for evaluation of progression.

(4) The description of unblinding for determination of subsequent treatment was updated to clarify the conditions when unblinding may be needed/ can be done at the time of progressive disease confirmed by BIRC, to determine the optimal subsequent treatment for the patient.

[redacted]

Other clarifications, corrections, and administrative changes are also applied 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 underlined for insertions.

Updated Section 4.5: Risk and Benefit section has been updated to add language for Risk of Inaccurate BRAF results.

Updated Section 5.1 and Section 6.1.5.2: Inclusion criterion 11 to enter to the trial and criterion to cross over were changed from Creatinine Clearance based on Cockcroft-Gault criteria (≥ 50ml/min) to Serum Creatinine ≤ 1.5 mg/dl.

Updated Section 5.2: Exclusion criterion 21 wording was updated for clarity

Updated Section 6.2.1: Concomitant therapy section has been updated to clarify the use of palliative radiotherapy during the trial.

Updated Section 6.4 and Section 6.6.2 to clarify when the unblinding for determination of subsequent treatment is to be used.

Section 6.8 has been added to describe the management of overdose.

Updated Section 7: The list of informed consents included in this study was updated.

Updated Section 8: Added clarification in case of delegation to an off-site healthcare professional during Public Health emergency.

[redacted]

Updated Section 8.1.3: Definition of screen failure has been further clarified including the reason why minimal data are collected for these patients.

Updated Section 8.3.1 and Table 8-3: Criteria to perform Brain MRI or CT scan has been clarified.

Updated Ophthalmic Exam of Table 8-4: Visual field examination process has been detailed here, automated static perimetry covering 60 degrees (e.g. a 30-2 perimetry) is to be used. The same perimeter is to be used on a given patient throughout the duration of the study to enable evaluation of progression.

Updated Section 8.4.3: Assessment of Fertility wording has been updated to improve clarity.

[redacted]

Updated Section 9.1.2: Section has been clarified withdrawal of consent including use of data and/or biological samples.

Updated Section 9.1.3: Section has been updated to clarify lost to follow patient definition.

Updated Section 9.2: Section has been updated to clarify timelines for the primary analysis by adding that all randomized patients should complete approximately 16 weeks of follow-up or have discontinued before to conduct primary analysis.

Updated Section 10: Some rewording to improve clarity.

Updated Section 11.3: Site monitoring section has been clarified to improve clarity.

Newly added Data Protection as Section 13.5.

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 and Health Authority approval 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.

Amendment 1 (08-Nov-2021)

As of 08-Nov-2021, FPFV has not occurred yet in study CDRB436J12301.

Amendment rationale

The main purpose of this amendment is (1) to update the mandatory dose modification and recommended clinical management guidelines for suspected treatment-related pyrexia, [redacted] (3) to extend mitigation procedures related to public health emergencies throughout the protocol, and (4) to clarify exclusion criterion 16 to add left ventricular ejection fraction (LVEF) < lower limit of institutional normal (LLN) as assessed by ECHO or MUGA scan.

Dose modification guidelines for suspected treatment-related pyrexia were updated in order to align with the updated information available in dabrafenib and trametinib Investigator's Brochure Edition 13.

[redacted]

Exclusion criterion 16 was clarified to align the cardiovascular risk exclusion criteria related to LVEF with other dabrafenib/trametinib combination studies.

Further, recommendation about vaccines as concomitant therapy was added, and further administrative changes from the latest global protocol template were implemented.

Other clarifications and corrections are also applied 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 underlined for insertions.

[redacted]

Section 4.6: Rationale for Public Health Emergency mitigation procedures Section was included in the protocol for public health emergencies. Mitigation procedures in case of public health emergencies were included in specific protocol sections: study treatment home delivery in Section 6.7, remote informed consent procedure in Section 7, alternative methods of providing continuing care in Section 8, alternative methods for safety assessments and safety monitoring in Section 8.4, [redacted].

Updated Section 5.1: Inclusion criterion 4.d) FDG-avid lesion was clarified and SUV maximum was updated to higher or equal to 3 (≥3).

Updated Section 5.2: Exclusion criterion 16 was updated to align the cardiovascular risk exclusion criteria related to LVEF with other dabrafenib/trametinib combination studies.

Updated Table 6-1 in Section 6.1.1: description updated to reflect availability of placebo pack types for each study drug strengths.

Updated Section 6.2.1.1: vaccines were added as permitted concomitant therapy requiring caution.

Updated Section 6.5.1.1 and Table 6-6: Pyrexia symptoms were clarified, further, dose modification guidelines for pyrexia were updated: dabrafenib and trametinib must be interrupted if the patient's is temperature ≥ 38°C (100.4°F)). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia.

[redacted]

Updated Section 8.1.1 and [redacted] option was included to provide 5 additional FFPE slides from Chinese patients to support CDx development if adequate approval from relevant Chinese authorities has been obtained. FFPE sample requirements were slightly updated.

Updated Section 10.1.3: Immediate reporting of SAEs was clarified and to align with Health Authority requirements.

Updated Section 10.1.4: Consenting process of pregnant patient to collect and report information regarding the pregnancy was clarified.

Section 13.6: Patient Engagement Section was included.

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 and Health Authority approval 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.

Protocol summary

Protocol number	CDRB436J12301
Full Title	A randomized, double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with locally advanced or metastatic, radio-active iodine refractory BRAFV600E mutation-positive Differentiated Thyroid Cancer (DTC)
Brief title	Study of efficacy and safety of dabrafenib in combination with trametinib in previously treated patients with metastatic, radio-active iodine refractory BRAF V600E mutation-positive differentiated thyroid cancer
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of dabrafenib in combination with trametinib for the treatment of adult patients with locally advanced or metastatic, BRAFV600E mutation-positive DTC who are refractory to radioactive iodine treatment (RAI-r), and have progressed following 1 or 2 prior VEGFR (Vascular Endothelial Growth Factor) targeted therapies.
Primary Objective(s)	The primary objective of this study is to compare the progression free survival by RECIST 1.1 (response evaluation criteria) assessed by Blinded Independent Review Committee between dabrafenib in combination with trametinib versus placebo.
Secondary Objectives	The secondary objectives are: • To compare the overall response rate (ORR), overall survival (OS), duration of response (DoR) of dabrafenib plus trametinib versus placebo • To characterize the safety and tolerability of dabrafenib plus trametinib • To assess trametinib associated serous retinopathy ocular events
Study design	This is a global, multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in adult patients with locally advanced or metastatic BRAFV600E mutation-positive, differentiated thyroid carcinoma who are refractory to radioactive iodine and have progressed following prior VEGFR targeted therapy. The scientific objective guiding the primary estimand is based on the Progression Free Survival (PFS) as per BIRC assessment using RECIST 1.1 criteria. Patients randomized in the placebo arm for whom disease progression as per RECIST 1.1 is confirmed by Blinded Independent Review Committee (BIRC) and who meet the eligibility criteria outlined in Section 6.1.5.2 will be given the option to crossover to the open-label dabrafenib plus trametinib treatment.
Study population	150 adult patients with locally advanced or metastatic BRAFV600E mutation-positive, differentiated thyroid carcinoma who are refractory to radioactive iodine and have progressed following prior VEGFR targeted therapy. Patients will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or placebo. Patients will be stratified by number of prior VEGFR targeted therapy (1 versus 2) and prior lenvatinib treatment (yes versus no).
Key Inclusion criteria	• Signed informed consent must be obtained prior to performing any protocol specific pre-screening and screening procedure. • Male or female≥ 18 years of age at time of informed consent. • Histologically or cytologically confirmed diagnosis of advanced/metastatic differentiated thyroid carcinoma. • Radioactive-iodine refractory disease • BRAFV600E mutation-positive tumor sample as per Novartis-designated central laboratory result • Has progressed on at least 1 but not more than 2 prior VEGFR targeted therapy • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

	• At least one measurable lesion as defined by RECIST v1.1.
Key Exclusion criteria	• Anaplastic or medullary carcinoma of the thyroid. • Previous treatment with a BRAF inhibitor and/or a MEK inhibitor. • Concomitant RET Fusion-Positive Thyroid Cancer. • Treatment with any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization. • Treatment with any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization. • Treatment with radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization. • A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy.
Study treatment	Dabrafenib (DRB436) oral administration, 150 mg twice daily. Trametinib (TMT212) oral administration, 2 mg once daily. See dosing regimen in Section 6.1.
Efficacy assessments	**Radiological tumor assessments:** Tumor assessment by RECIST 1.1 performed every 8 weeks through week 56, then every 12 weeks until PD (progressive disease) determined by investigator and confirmed by BIRC, death, lost to follow-up, withdrawal of consent or primary PFS analysis, whichever occurs first. **Survival status:** collected every 12 weeks after post-treatment follow-up, until death, lost to follow-up or withdrawal of consent.
Key safety assessments	• Collection of Adverse Events (AE) and Serious Adverse Events (SAE) • Laboratory assessments, including hematology, chemistry, urinalysis, coagulation, thyroid function • Physical examination • Vital signs • Height and weight • Dermatological exam • ECG (electrocardiogram)/ECHO (Echocardiogram) • Ophthalmic exam including Optical coherence tomography (OCT)
Other assessments	[redacted]
Data analysis	**Primary estimand (PFS):** The clinical question of interest is: what is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the time to progression or death, had the new antineoplastic therapies not occurred regardless of treatment discontinuation and any unforeseen events like a pandemic, epidemic or natural disaster, in patients with previously treated BRAFV600E mutation positive DTC. The primary variable of the estimand (PFS) will be analyzed at the primary analysis, tested using the log-rank test stratified by randomization stratification factors. The following null hypothesis will be tested at one-sided 2.5% level of significance. H_{01}: $\theta_1 \geq 1$ vs. H_{A1}: $\theta_1 < 1$ where θ_1 is the PFS hazard ratio (dabrafenib and trametinib versus placebo). The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS and PFS Kaplan-Meier estimate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arm. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test.

	Secondary estimands **Efficacy (ORR and OS)** One secondary clinical question of interest is: what is the treatment effect based on overall response rate between dabrafenib plus trametinib and placebo, regardless of treatment discontinuation and any unforeseen events like a pandemic, epidemic or natural disaster, for patients with BRAFV600E mutation-positive advanced/metastatic DTC. A hierarchical testing strategy will be used to control the overall type I error rate: ORR (primary variable of the secondary estimand) will only be formally tested and interpreted if the primary analysis of PFS is statistically significant. If the ORR achieves statistical significance, then OS (primary variable of the other secondary estimand) will be tested and interpreted. The following null hypothesis of no difference in ORR based on BIRC assessment using RECIST 1.1 between dabrafenib plus trametinib and placebo treatment arms will be tested using Cochran-Mantel-Haenszel (CMH) test at a 1-sided significance level of 0.025, stratified by the randomization stratification factors. H_{02}: $\theta_{1R} - \theta_{2R} = 0\%$ vs. H_{A2}: $\theta_{1R} - \theta_{2R} > 0\%$ where θ_{1R} and θ_{2R} are the ORR for the dabrafenib plus trametinib and placebo arms, respectively. ORR will be calculated based on the FAS (Full Analysis Set), according to the ITT (Intent To Treat) principle and strata assigned at randomization. The difference in ORR and its 95% confidence interval will be reported. ORR and its 95% confidence interval based on the exact binomial distribution will be presented by treatment group. One other secondary clinical question of interest is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the survival time, regardless of treatment discontinuation, new antineoplastic therapies, any unforeseen events like a pandemic, epidemic or natural disaster and crossover, for patients with BRAFV600E mutation-positive advanced/metastatic DTC. The following null hypothesis will be tested at one-sided 2.5% level of significance, provided the ORR achieves statistical significance : H_{03}: $\theta_2 \geq 1$ vs. H_{A3}: $\theta_2 < 1$ where θ_2 is the OS hazard ratio (dabrafenib plus trametinib versus placebo). The distribution of OS will be estimated using the Kaplan-Meier method and compared between the two treatment groups using a stratified log-rank test at one-sided cumulative 2.5% level of significance, based on the FAS population. The median OS and OS Kaplan-Meier estimate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arm. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of OS, along with 95% CI based on the Wald test. Recognizing potential confounding effect of crossover on OS, an attempt may be made to correct estimates with an appropriate model method, for example using Rank Preserving Structural Failure Time (RPSFT) model by Robins and Tsiatis AA. 1991. **Safety (serous retinopathy ocular events)** Incidence, type and severity of ocular events using serous retinopathy grouping term will be summarized by treatment arm using ocular event evaluable set and safety set. 95% confidence interval of the incidence of serous retinopathy event will be as well presented.
Key words	Differentiated Thyroid Cancer, DTC, BRAF, DRB436, dabrafenib, TMT212, trametinib, radio-active iodine refractory

1 Introduction

1.1 Background

Thyroid cancer is responsible for 567,233 new cases worldwide in 2018, ranking in ninth place for incidence. The global incidence rate in women of 10.2 per 100,000 is 3 times higher than in men. International comparisons are complex due to differences in diagnosis and ascertainment of the disease. The highest thyroid cancer incidence was in the Asia continent with 340,245 (60%) cases. There were 78, 418 new cases in Europe and 70, 547 new cases in North America diagnosed in 2018, Bray et al 2018 Goodarzi et al 2019.

Thyroid cancer accounts for 3.1% of all new cancer cases in the US and in 2020 there were approximately 52,890 patients newly diagnosed. Thyroid cancer is projected to be the fourth most common cancer in the United States by 2030 (Stacey et al 2019, Siegel et al 2020). Thyroid cancer is the fourth most commonly diagnosed cancer in Chinese females with 147,618 new cases (7.7%) Feng et al 2019. In Japan, thyroid cancer accounts for 2% of all new cancer cases, about 17,479 new cancer cases The Lancet 2018. The global incidence has been steadily rising over the last four decades, which has been attributed in part to improved detection of subclinical, indolent cancers.

Thyroid follicular epithelial-derived cancers are divided into three main histological types, (1) papillary thyroid carcinoma (PTC), (2) follicular thyroid carcinoma (FTC), and (3) anaplastic thyroid cancer (ATC). Papillary and follicular thyroid cancer are considered differentiated and are often treated similarly thus referred to as differentiated thyroid cancer (DTC).

DTC is typically treated with surgery and subsequent therapy is dependent on the risk of disease recurrence. Most patients will require suppressive hormone therapy to prevent hypothyroidism and to minimize tumor growth stimulation through Thyroid Stimulating Hormone (TSH). Radioiodine therapy may be administered to (1) ablate residual normal thyroid tissue, (2) to eliminate subclinical adjuvant therapy, or (3) to treat clinically apparent residual metastatic disease. The decision to treat with radioactive iodine (RAI) therapy is dependent on the risk of recurrence. For patients who present as recurrent metastatic disease RAI therapy is a critical mainstay of therapy.

Approximately 10–15% of patients do not trap iodine and are considered RAI-refractory. For these cases, the 10 year survival rate is 10% from the time of detection of metastasis, Gianoukakis et al 2018, Ancker et al 2020.

If disease progression cannot be controlled with local therapies such as surgery or radiotherapy, systemic therapy with chemotherapy can be considered. However, treatment with cytotoxic chemotherapy has shown disappointing results as complete remissions are rare and long-term responses are limited.

Advances in the understanding of the molecular pathogenesis of thyroid cancer have led to the development of targeted agents aimed at combating advanced disease. The novel treatment with multi-targeted tyrosine kinase inhibitors (MKIs) has shown favorable results in otherwise treatment-resistant thyroid cancer. The primary target for all of these effective tyrosine kinase inhibitors is angiogenic signaling in the tumor microenvironment, particularly the VEGFR family. The MKIs block signaling from the tyrosine kinase receptors, thus preventing phosphorylation and, ultimately angiogenesis and tumor growth. The first targeted agents which

have shown to improve PFS was the multikinase inhibitor, sorafenib, approved for use in patients with RAI-refractory DTC. Sorafenib is a protein kinase inhibitor with activity against multiple protein kinases, including VEGFR, PDGFR and RAF kinases. Of the RAF kinases, Sorafenib is more selective for C-Raf than B-RAF. In the DECISION trial, patients who had RAI-refractory locally advanced or metastatic DTC that had progressed within the past 14 months were randomly assigned to sorafenib or placebo. Median PFS was significantly longer in the sorafenib group (10.8 months) than in the placebo group (5.8 months; HR 0.59, 95%CI 0.45-0.76, p<0.0001). Improvement of PFS in the sorafenib group compared to the placebo group has been observed in all prespecified clinical and genetic biomarker subgroups. The partial response rate was 12.2 % and stable disease for 6 months or longer was achieved in 41.8% of patients Brose et al 2014. More recently, lenvatinib, another multi-kinase inhibitor, was approved for the treatment of locally recurrent or metastatic, progressive RAI-refractory DTC. Lenvatinib acts as a multi-tyrosine kinase inhibitor and inhibits vascular endothelial growth factor receptor family (VEGFR1–3), fibroblast growth factor receptor family (FGFR1–4), platelet-derived growth factor receptor-alpha (PDGFRα), tyrosine-kinase receptor (KIT) and rearranged during transfection receptor (RET). In the SELECT study, Lenvatinib was shown to prolong PFS compared with placebo (median 18.3 vs 3.6 months; hazard ratio (HR) 0.21; 99% CI 0.14–0.31) Schlumberger et al 2015. Cabozantinib is an oral multikinase inhibitor targeting MET in addition to VEGFR and is approved for medullary thyroid cancer. A single-arm open-label phase II study of cabozantinib in patients with metastatic, RAI-refractory DTC and evidence of progression on prior VEGFR-targeted therapy showed of the 25 patients, 10 (40%) had a partial response, 13 (52%) had stable disease, and two (8%) had non-evaluable disease. The median progression-free survival and overall survival were 12.7 months and 34.7 months, respectively Cabanillas et al 2017. Newly available targeted therapies show improvements in PFS for patients with RAI-refractory DTC. Sorafenib and lenvatinib are approved as first line indication in refractory RAI DTC in the US, China, Japan and other countries. Adverse effects of VEGFR-targeted therapy may include hypertension, renal toxicity, proteinuria, arthralgia/myalgia, headache, bleeding, myelosuppression, arterial thromboembolism, cardiotoxicity including prolonged QT intervals and risk for arrhythmia, thyroid dysfunction, cutaneous toxicity including hand-foot skin reaction, delayed wound healing, hepatotoxicity, nausea, vomiting, diarrhea, muscle wasting, fistula formation, osteonecrosis of the jaw.

BRAFV600E is the most common molecular abnormality in thyroid cancer. This mutation is frequently associated with tumor aggressiveness and poor prognosis because of the constitutive activation of downstream MAPK (Mitogen-Activated Protein Kinase) pathway, which drives cellular differentiation and cancer progression Dhillon et al 2007. This signaling pathway is an attractive therapeutic target because it is aberrantly activated in many human cancers. BRAFV600E is caused by T1799A mutations in the *BRAF* gene, which have been found in almost 50% of unresectable or metastatic melanomas and approximately 35-65% of patients with RAI-refractory DTC Aashiq et al 2019. The rate of BRAFV600E was reported around 71.2% and 70.6% in papillary thyroid cancer in China and Japan, respectively. Pooled Asian series of papillary thyroid cancer showed a higher prevalence of BRAFV600E than in Western series Rashid et al 2020. Clinically, BRAFV600E-mutation positive thyroid cancer cells exhibit primary resistance or poor response to RAI therapy due to the inhibition of radioiodine uptake and/or remodeling of metabolic pathways mediated by hyperactive BRAFV600E kinase. The genetic alterations related to the pathogenesis of thyroid cancer are also known to be associated with the silencing of various thyroid iodine-metabolizing genes, resulting in the failure of RAI

therapy Liu et al 2019. Hence, targeting V600E mutant BRAF is the next logical step in developing novel therapies for RAI-refractory DTC. No targeted therapy directed against BRAFV600E is available to date for the treatment of these patients.

Dabrafenib and Trametinib

Dabrafenib is an orally bioavailable, potent and selective RAF kinase inhibitor of human wild-type (WT) BRAF and CRAF enzymes as well as the mutant forms of the BRAF enzyme, BRAFV600E, BRAFV600K, and BRAFV600D. The mechanism of action of dabrafenib is consistent with competitive inhibition of adenosine triphosphate (ATP) binding.

The recommended dose of dabrafenib is 150 mg (two 75 mg capsules) twice daily (BID) (corresponding to a total daily dose of 300 mg).

Trametinib is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2. MEK proteins are critical components of MAPK pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF and RAS signal through MEK1 or MEK2. The recommended dose of trametinib is 2 mg once daily (QD).

While monotherapy with either dabrafenib or trametinib represented a significant advance in the treatment of BRAFV600 mutated, unresectable or metastatic melanoma, responses were not observed in all patients; underscoring the fact that intrinsic mechanisms of resistance were in place. The clinically relevant activity of the combination over BRAFV600 inhibitor monotherapy was confirmed across two randomized phase III studies where dabrafenib in combination with trametinib consistently demonstrated clinical benefit when compared to dabrafenib (COMBI-d) or vemurafenib monotherapy (COMBI-v). Statistically significant and clinically meaningful improvements were observed for OS, PFS, ORR, DOR and quality of life (QoL) with a manageable adverse events profile (Long et al 2014, Robert et al 2014, Schadendorf et al 2015, Long et al 2015, Long et al 2017, Robert et al 2019).

The combination of dabrafenib and trametinib has been approved for the following indications:

- The treatment of patients with unresectable or metastatic melanoma with BRAFV600E or V600K mutations.
- The adjuvant treatment of patients with melanoma with BRAFV600E or V600K mutations and involvement of lymph node(s), following complete resection.
- The treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAFV600E mutation .
- The treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAFV600E mutation.

In 2018, The U.S. Food and Drug Administration approved combination of dabrafenib and trametinib for the treatment of locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAFV600E mutation. Based on the results of a phase II clinical trial, investigator-assessed confirmed ORR was 67% (18/27; 95% CI, 46%-84%), with 8/18 responses ongoing at data cutoff. 12/18 patients (67%) had a DOR of ≥6 months. Median PFS and OS were 1.2 y (95% CI, 0.4-NR) and 1.7 y (95% CI, 0.7-NR). The overall safety profile of dabrafenib and trametinib was consistent with previous reports in advanced or metastatic melanoma and non small cell lung cancer. No new safety signals were detected Subbiah et al 2018 and Keam et al 2018.

Results from a randomized phase II study of patients with BRAF mutated RAI refractory papillary thyroid cancer who had evidence of disease progression, suggest that the combination of dabrafenib and trametinib vs. dabrafenib alone is safe and effective Shah et al 2017. Overall 53 patients were enrolled; 25% of patients had 1-3 prior therapy with multi-kinase inhibitors. Median follow up was 13 months. Preliminary efficacy results showed single agent dabrafenib, as well as combination of dabrafenib/trametinib are well tolerated therapies that result in similar high objective response rates, 50% and 54%, respectively. Median PFS was 15.1 months in the combination dabrafenib/ trametinib arm vs. 11.4 months in the single dabrafenib arm. Median DOR was 13.3 months in the combination dabrafenib/ trametinib arm vs. 15.6 months in the single dabrafenib arm in patients with progressive BRAF-mutated PTC. Based on the preliminary data, it is expected that dabrafenib in combination with trametinib will target the inhibition of radioiodine uptake and remodelling of metabolic pathways mediated by hyperactive BRAFV600E that could be beneficial for the patients.

Study CDRB436J12301 is a global, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of dabrafenib in combination with trametinib in RAI refractory patients with locally advanced or metastaticBRAFV600E mutation-positive DTC which have progressed following prior VEGFR-target therapies. In this study the combination of dabrafenib plus trametinib will be evaluated as (1) the combination has shown superior efficacy versus BRAF inhibitor monotherapy in other solid tumors, (2) the combination is already approved locally advanced or metastatic anaplastic thyroid cancer (ATC) with a BRAFV600E mutation, and (3) combination treatment was associated with a reduction in toxicities related to paradoxical activation of the MAPK pathway compared with BRAF inhibitor monotherapy, in particular, the incidence of secondary malignancies was decreased.

Further, data from study CDRB436J12301 will be used to estimate the incidence of trametinib associated serous retinopathy ocular events, to meet a Post Marketing Requirement.

Serous retinopathy is a rare ocular adverse reaction associated with trametinib and other MEK inhibitors, which manifests bilaterally within days of treatment initiation with a median time to onset of one month and in most cases resolves spontaneously within one to two months after dose interruption Stjepanovic and Velazquez-Martin JP and Bedard PL 2016. Study CDRB436J12301 will be used to estimate the incidence of, and to characterize trametinib-associated serous retinopathy ocular events.

1.2 Purpose

The purpose of this global, multicenter, randomized, double-blind, placebo-controlled phase III study is to evaluate the efficacy and safety of dabrafenib in combination with trametinib for the treatment of adult patients with locally advanced or metastatic, BRAFV600E mutation-positive DTC who are refractory to radioactive iodine treatment (RAI-r), and have progressed following 1 or 2 prior VEGFR targeted therapies.

In addition, the study will be used to estimate the incidence of, and to characterize trametinib-associated serous retinopathy ocular events.

2 Objectives and endpoints

The objectives and associated endpoints are presented in the Table 2-1 below:

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare PFS between dabrafenib plus trametinib versus placebo.	• PFS based on BIRC assessment using RECIST 1.1 criteria See Section 2.1 for Primary Estimand
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

• **Key efficacy secondary objectives:**
  • to compare ORR of dabrafenib plus trametinib versus placebo
  • to compare OS of dabrafenib plus trametinib versus placebo
Other efficacy secondary objective:
  • to evaluate DoR of dabrafenib plus trametinib versus placebo
	• ORR as per BIRC assessment using RECIST 1.1 criteria
	• OS including all deaths from any cause
	See Section 2.2 for Secondary Estimands.
	• DoR by BIRC assessment using RECIST v1.1 criteria

• To characterize the safety and tolerability of dabrafenib and trametinib	• Incidence and severity of AEs and SAEs, including changes in laboratory values, ECOG PS (performance status), and vital signs.
• To quantify trametinib associated serous retinopathy ocular events	• Incidence, type and severity of trametinib associated serous retinopathy ocular events.
[redacted]	

2.1 Primary estimands

The clinical question of interest is: what is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the time to progression or death, had the new antineoplastic therapies not occurred regardless of treatment discontinuation and any unforeseen events like a pandemic, epidemic or natural disaster, in patients with previously treated BRAFV600E mutation positive DTC.

The justification for targeting this treatment effect is that we wish to estimate the relative effect of the two treatments in the absence of potential confounding effect of any new antineoplastic

therapy that is not part of the assigned treatment strategy and that may potentially occur more frequently in the placebo arm than in the dabrafenib plus trametinib arm.

The primary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, (RAI-r, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2). Further details about the population are provided in Section 5.
- Primary variable: progression-free survival as assessed by BIRC, using RECIST v1.1, defined as the time from randomization to disease progression or death due to any cause, whichever occurs first.
- Treatment of interest: dabrafenib plus trametinib or placebo. Further details about the treatments are provided in Section 6.
- Handling of the remaining intercurrent events:
  - Treatment discontinuation due to any reason will be handled using treatment policy strategy since all PFS events will be considered as an event irrespective of the study treatment discontinuation reasons
  - Any unforeseen intercurrent events (e.g., pandemic, epidemic or natural disaster) will be handled using treatment policy strategy.
  - Initiation of any new antineoplastic therapy started before observing any PFS event will be handled using the hypothetical strategy, i.e. as if new anticancer therapy had not been available. New antineoplastic therapy has the potential to confound the interpretation of effect of the treatment strategy, especially if this occurs more frequently in placebo arm versus dabrafenib plus trametinib arm.
- The summary measure is the hazard ratio (HR) for PFS between the two treatment arms, estimated using a stratified Cox proportional hazard model.

Supplementary estimands to the primary estimand are defined in Section 12.

2.2 Secondary estimands

The following two key secondary estimands for efficacy are considered.

The secondary clinical question of interest is related to the treatment effect based on overall response rate between dabrafenib plus trametinib and placebo, regardless of treatment discontinuation and any unforeseen events (e.g., pandemic, epidemic or natural disaster), for patients with BRAFV600E mutation-positive advanced/metastatic DTC.

The secondary estimand linked to this secondary question is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2). Further details about the population are provided in Section 5.
- Primary variable: best overall response, defined as the best response recorded from the start of the treatment up to 30 days after the last dose of study treatment or disease progression as per BIRC using RECIST 1.1 criteria, whichever occurs first, with responses after the use of new antineoplastic therapy or after the start of open-label dabrafenib and

trametinib treatment following crossover for placebo patients considered as non-responses.

- Treatment of interest: dabrafenib plus trametinib or placebo. Further details about the treatments are provided in Section 6.
  - Handling of the remaining intercurrent events:
  - treatment discontinuation due to any reason will be handled using treatment policy strategy since all response assessments occurring after treatment discontinuation and during the 30-days post-treatment follow-up period will be considered for BOR derivation irrespective of the study treatment discontinuation reasons
  - any unforeseen intercurrent events (e.g., pandemic, epidemic or natural disaster) will be handled using treatment policy strategy

The summary measure is the difference in ORR of the two treatments (defined as the proportion of patients with confirmed best overall response (BOR) of complete response (CR) or partial response (PR) based on BIRC per RECIST 1.1) and its 95% confidence interval calculated using exact method.

One other secondary clinical question of interest is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the survival time, regardless of treatment discontinuation, new antineoplastic therapies, any unforeseen events (e.g., pandemic, epidemic or natural disaster) and crossover, for patients with BRAFV600E mutation-positive advanced/metastatic DTC

The secondary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2). Further details about the population are provided in Section 5.
- Primary variable: overall survival, defined as the time from randomization to death due to any cause.
- Treatment of interest: dabrafenib plus trametinib or placebo with or without any new antineoplastic therapy received post randomization as needed. Further details about the treatments are provided in Section 6.
- Handling of the remaining intercurrent events:
  - treatment discontinuation due to any reason will be handled using treatment policy strategy since all deaths will be considered as an event irrespective of the study treatment discontinuation reasons
  - any unforeseen intercurrent events (e.g., pandemic, epidemic or natural disaster) will be handled using treatment policy strategy
  - crossover of patients from placebo to dabrafenib plus trametinib will be handled using treatment policy strategy: all deaths will be considered as an event irrespective of the crossover
- The summary measure is the hazard ratio (HR) for OS between the two treatment arms, estimated using stratified Cox proportional hazard model.

Supplementary estimands to this secondary estimand (e.g., handling crossover intercurrent event using hypothetical strategy and appropriate model-based method to correct estimates recognizing potential confounding effect of crossover on OS for example using Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis) are defined in Section 12.

The following secondary estimand for safety is considered in the scope of a post-marketing requirement: what is the incidence of trametinib associated serous retinopathy ocular events while on-treatment, regardless of new antineoplastic therapies and any unforeseen events (e.g., pandemic, epidemic or natural disaster).

The secondary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2), who have received at least one dose of the study treatment and have at least two on-treatment OCT assessments.
- Primary variable: occurrence of serous retinopathy grouping event, reported in the AEs CRF (case report form) page, on-treatment, occurring from the start of study treatment and up to 30 days after last dose of study treatment, using specific case retrieval strategy for ocular events, listing the appropriate preferred terms falling into the definition of a serous retinopathy.
- Treatment of interest: dabrafenib plus trametinib
- Handling of the remaining intercurrent events:
    - treatment discontinuation of trametinib or dabrafenib at any time due to any reason will be handled using treatment policy strategy since all serous retinopathy events occurring on-treatment or up to 30 days after the last dose of study treatment will be considered irrespective of the trametinib or dabrafenib discontinuation reasons
    - any unforeseen intercurrent events (e.g. pandemic, epidemic or natural disaster) will be handled using treatment policy strategy
    - any new antineoplastic therapies received during treatment or during the 30-days post treatment follow-up period will be handled using treatment policy strategy : all serous retinopathy events will be considered regardless of the initiation of a new antineoplastic therapy
- The summary measure is the proportion of patients with at least one serous retinopathy grouping event occurring on-treatment, over the ocular-event set population.

One supplementary analysis of this safety secondary estimand will be done by changing the population of interest and the summary measure attributes, using the patients included in the safety set. Further details can be found in Section 12.

3 Study design

This is a global, multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in adult patients with locally advanced or metastatic BRAF V600E mutation-positive, differentiated thyroid carcinoma who are refractory to radioactive iodine and have progressed following prior VEGFR targeted

therapy. After eligibility assessment, patients will be randomized in a 2:1 ratio to either dabrafenib plus trametinib or placebo. Patients will be stratified by number of prior VEGFR targeted therapy (1 versus 2) and prior lenvatinib treatment (yes versus no). The scientific objective guiding the primary estimand is based on the PFS as per BIRC assessment using RECIST 1.1 criteria.

This study will enroll approximately 150 patients.

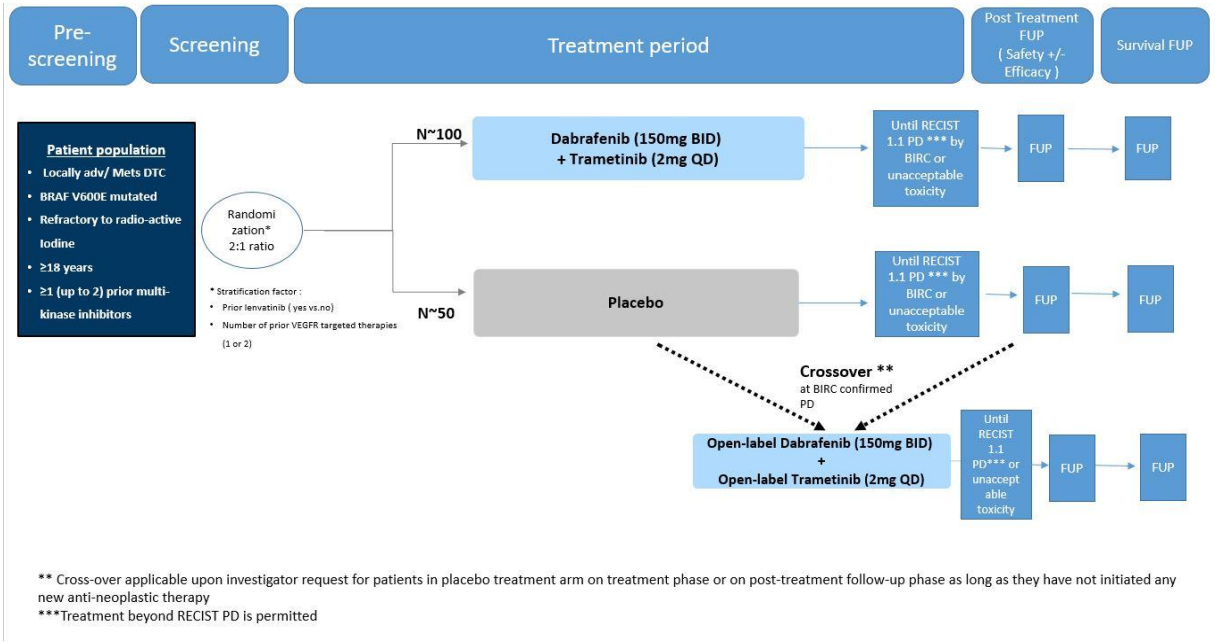
Patients randomized in the placebo arm for whom disease progression as per RECIST 1.1 is confirmed by BIRC and who meet the eligibility criteria outlined in Section 6.1.5.2 will be given the option to crossover to the open-label combination drug dabrafenib plus trametinib.

The treatment may be continued beyond RECIST 1.1 disease progression (confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit, and the patient wishes to continue on the study treatment (for additional details please refer to Section 6.1.5.1). In the case of discrepancy in the determination of progression between the site (local) and the BIRC (i.e., disease progression determined locally but not by BIRC), as long as it is clinically acceptable, the patient should not be discontinued from the study treatment until the disease progression has been determined by the BIRC or at a minimum, until at least one additional tumor assessment has been completed.

After treatment discontinuation, all patients will be followed for safety and efficacy evaluations (as applicable) during the post-treatment follow-up period, and then the patient's status will be collected every 12 weeks as part of the survival follow-up (for additional details please refer to Section 8.3.2).

Refer to Figure 3-1 for an overview of the study design.

Figure 3-1 Study Design



** Cross-over applicable upon investigator request for patients in placebo treatment arm on treatment phase or on post-treatment follow-up phase as long as they have not initiated any new anti-neoplastic therapy
***Treatment beyond RECIST PD is permitted

Pre-Screening:

In order to be considered eligible for the study, patients must have BRAF V600E mutation confirmed by a Novartis-designated central laboratory (refer to Section 8.1.1). Depending on the availability of a local BRAFV600E result, patients may either enter pre-screening or directly to main screening as follows:

- Patients who do not have a local BRAF V600E result available as part of their medical record will be requested to sign and date an IRB/IEC (Institutional Review Board/Independent Ethics Committee) -approved molecular pre-screening informed consent form (ICF) before their tumor sample is sent for testing to a Novartis-designated central laboratory for BRAF V600E mutation testing and must wait for the BRAF V600E result before entering main screening.
- Patients who do have a local BRAF V600E result available as part of their medical record, will be authorized to enter main screening and undergo study specific screening procedures following signature of the main ICF.

A patient number (patient No.) will be assigned to each patient and the investigator or designated staff will provide the requested identifying information to register the patient in the Interactive Response Technology (IRT) system.

Screening:

Patients must sign an ICF prior to any study specific screening evaluations. All screening assessments must be performed within 28 days prior to start of treatment (Week 1 Day 1). Following completion of all required screening procedures (refer to Section 8.1) and verifying patient eligibility, the investigator or designated staff will confirm patient eligibility and randomize the patient via the IRT system.

Treatment period:

The treatment period begins when the first dose of study treatment is administered to the patient and ends when the patient meets reasons for treatment discontinuation as described in Section 9.1.1.

Patients may continue study treatment beyond disease progression by RECIST 1.1 as confirmed by the BIRC, if criteria stipulated in Section 6.1.5.1 are fulfilled. If the patient is continuing on study treatment, then all study procedures including tumor assessments must be followed as scheduled (Table 8-1 and Table 8-2).

An end of treatment (EOT) visit will be performed when patients permanently discontinue study treatment. For patients who crossover from placebo arm to receive open-label dabrafenib plus open-label trametinib, an additional subsequent EOT visit will be performed once they are discontinued from the open-label treatment (Table 8-2).

Post-Treatment Follow-Up (Efficacy and Safety):

All patients must be followed up for adverse events and serious adverse events up to 30 days after the last dose of study treatment (30 days safety call). Serious adverse events suspected to

be related to study drug will be recorded after the 30-day period following the last dose of study treatment and until study patient completion, death or withdrawn consent.

Patients who discontinue study treatment without disease progression as per BIRC, will continue efficacy assessments (Efficacy Follow-up) during the post treatment follow-up until disease progression documented by BIRC as per RECIST 1.1, death, lost to follow-up or withdrawal of consent.

Survival Follow-up:

Once patients completed the post-treatment follow-up after treatment discontinuation, their survival status will be collected every 12 weeks as part of the survival follow-up (via phone calls) see Section 8.3.2.

Every effort should be made to comply with the survival follow-up schedule and ensure collection of patient survival data.

Crossover:

Patients assigned to the placebo arm will be given the option to crossover to the open-label dabrafenib and trametinib combination treatment after BIRC confirmed RECIST 1.1 defined disease progression. Unblinding is permitted for crossover purpose upon investigator request (Section 6.1.5.2). Crossover is optional, at the investigator discretion and eligibility criteria must be confirmed prior to crossing over to open-label dabrafenib and trametinib combination treatment (Section 6.1.5.2).

After having completed the primary analysis, patients still receiving placebo may be allowed to receive open-label dabrafenib plus trametinib treatment immediately or later at the time of disease progression, as per investigator and patient discretions.

Open-label treatment period

Open-label treatment period will start on the day of first dose of dabrafenib and trametinib treatment for patients assigned to the placebo arm who crossover to the open-label dabrafenib plus trametinib treatment. Those patients will continue to be treated until disease progression based on investigator assessment or until unacceptable toxicity, withdrawal of consent, lost to follow-up or death. At this point, patients will be discontinued from the open-label study treatment (unless treatment can be continued beyond RECIST PD as per Section 6.1.5.1) and enter in the post-treatment follow-up period as described above.

Patients in the placebo arm who elect to crossover to open-label dabrafenib and trametinib treatment must follow the study assessments as per visit schedule in Table 8-2 of the Crossover Phase.

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study population	There is an unmet need in patients with advanced metastatic differentiated thyroid carcinoma who are refractory to radioactive iodine and have progressed following prior VEGFR targeted therapy.
Cross over at time of disease progression as confirmed by BIRC, or at the latest at time of primary analysis	This is done to allow patients treated with placebo benefiting as soon as possible of the investigational arm in a context of limited treatment options for this patients population. The fact that the crossover is only allowed at time of disease progression confirmed by BIRC (or at the latest at time of primary analysis) won't impact the primary PFS endpoint assessed by BIRC. However, it is acknowledged it will lead to confounding of OS as an endpoint.
Randomization 2:1, dabrafenib and trametinib vs. placebo	In absence of standard therapies in this population and setting, randomization 2:1 will increase the chance for patients to receive dabrafenib in combination with trametinib, with preliminary data (Shah et al 2017) suggesting efficacy, and to make the study more attractive for patients and investigators. The combination of dabrafenib with trametinib is used in this study, as the combination has shown clinically relevant superior outcomes across multiple tumor types and indications. Further, the combination has been associated with a reduction in toxicities related to paradoxical activation of the mitogen-activated protein kinase pathway compared with BRAF inhibitor (BRAFi) monotherapy.
Randomization stratification factors: • prior lenvatinib treatment (yes vs no) • number of prior VEGFR targeted therapies (1 vs 2)	The stratification factors have been selected to balance potential prognostic factors between the two treatment arms: • patients receiving prior lenvatinib treatment may observe a lower survival than others (Schlumberger et al 2015) • number of prior VEGFR targeted therapies may correlate with ORR (Cabanillas et al 2017)
Treatment beyond RECIST PD if there is clinical benefit for the patients and protocol specific criteria are met.	Treatment beyond RECIST progression is allowed because isolated progression is common with dabrafenib and trametinib where a single lesion has progressed and is still amenable to local therapy.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dabrafenib dose

The dabrafenib dose of 150 mg BID is the approved dose for patients with unresectable or metastatic and adjuvant melanoma, NSCLC, and ATC.

Rationale for trametinib dose

The trametinib dose of 2 mg QD, is the approved dose for patients with unresectable or metastatic and adjuvant melanoma, NSCLC, and ATC.

Rationale for combination dose

Dabrafenib 150 mg BID in combination with trametinib 2 mg QD are the approved doses for use in combination for patients with unresectable or metastatic and adjuvant melanoma, NSCLC and ATC.

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

Since there is no established standard of care treatment for patients with DTC who are RAI refractory and have progressed following prior VEGFR targeted therapy, placebo is chosen as comparator. There is a paucity of robust data to guide choice of agent to support improved outcomes with second-line therapy, on prior VEGFR targeted therapy, in DTC. The available option of treatment for these patients are the clinical trials.

The placebo patients will be allowed to crossover to the open-label dabrafenib and trametinib combination treatment as soon as RECIST 1.1 disease progression is confirmed by BIRC, or at the latest at time of primary analysis, upon investigator's request.

The combination of dabrafenib and trametinib is used in this study without including dabrafenib monotherapy as an additional arm for the following reasons:

- Dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) both inhibit the mitogen-activated protein kinase (MAPK) pathway. The combination demonstrated greater inhibition and decreased MAPK-driven acquired resistance, resulting in higher rate of tumor responses and longer duration of responses compared to dabrafenib (BRAF inhibitor) monotherapy alone. Eroglu Z and Ribas 2016
- Adding trametinib (MEK inhibitor) to dabrafenib (BRAF inhibitor) decreased the toxicities observed from the paradoxical MAPK pathway activation with BRAF inhibitor monotherapy. Eroglu Z and Ribas 2016

Thereby improving the benefit-risk profile for the combination of dabrafenib and trametinib compared to using dabrafenib monotherapy.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

This study is enrolling approximately 150 patients with locally advanced or metastatic BRAFV600E mutation-positive differentiated thyroid cancer. All patients are radio-active iodine refractory and progressed on anti-VEGFR treatment as part of their standard of care, thus placebo was selected as a comparator. Patients are randomized to either receive dabrafenib plus trametinib or placebo, until disease progression or death. To minimize exposure of patients to placebo, a 2:1 randomization is employed in this study. Further, placebo patients can crossover to receive dabrafenib plus trametinib at disease progression documented by investigator and

confirmed by BIRC, or at the latest at time of primary analysis. This approach is consistent with recent similar phase III studies in the same indication.

Dabrafenib and trametinib were first approved as monotherapy in 2013 and have since been approved in combination multiple indications (i.e., metastatic and adjuvant melanoma, NSCLC, and ATC) thus the safety profile is well established. As of Jun-2020, an estimated 8964 patients, primarily with BRAFV600 mutation-positive cancers, have received dabrafenib monotherapy or in combination with trametinib across the clinical development program. The combination of dabrafenib and trametinib has a well-established safety profile which reflects the safety profiles of the individual drugs. Adverse drug reactions are reversible and manageable with dose modifications (i.e., interruption and dose reduction), as described in the protocol, which are consistent with the product labelling.

The preliminary efficacy and safety of dabrafenib in combination with trametinib has been evaluated in a randomized phase II study in patients with BRAFV600 mutation-positive radioactive iodine refractory differentiated thyroid cancer. The combination was well tolerated and resulted in a clinical meaningful ORR (54%), with durable response (median DOR 13.3 months) and a median PFS of 15.1 months (Shah et al 2017). Further, the combination of dabrafenib and trametinib received FDA (Food and Drug Administration) approval for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options, based on the results on a single-arm phase 2 study trial demonstrating a clinically meaningful objective response rate, with durable responses and manageable safety profile (Subbiah et al 2018).

The central BRAF V600E mutation test used for enrollment is investigational. The test has been demonstrated to detect BRAF V600E however it has not been fully established to identify DTC patients who are most likely to benefit from dabrafenib plus trametinib or whether the benefits will outweigh any potential serious side effects or risks from the use of this test.

The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring, oversight and BRAF V600E mutation assay monitoring. As with any clinical study, there may be unforeseen risks with the study treatment, which could be serious. The specific risks for each compound are provided in the dabrafenib and trametinib Investigator's Brochures.

This study incorporates routine safety monitoring and regularly scheduled safety assessments to identify and report any potential safety issues. All patients must have safety evaluations for 30 days after the last dose of study drugs. Comprehensive dose modification, stopping rules and toxicity management plan for drug related adverse events are provided in the protocol. 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. The risk to patients in this trial are 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 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 patient will not reliably comply, then they should not be entered or continue in the study.

In addition, prior to enrollment, this protocol will undergo appropriate review by local and regional governance bodies including ethic committees and drug regulatory bodies.

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, mitigation procedures may be required to ensure patient safety and trial integrity are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Study Population

The study population will include approximately 150 previously treated adult patients with locally advanced /metastatic BRAFV600E mutation positive DTC which are refractory to radio-active iodine therapy and have had prior VEGFR targeted therapy.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to performing any protocol specific pre-screening and screening procedure.
2. Male or female≥ 18 years of age at time of informed consent.
3. Histologically or cytologically confirmed diagnosis of advanced/metastatic differentiated thyroid carcinoma.
4. Radioactive-iodine refractory disease by any of the following criteria:
   a) Total lifetime dose of radioactive iodine > 600 mCi.
   b) Absent or insufficient radioactive iodine uptake in either all lesions or an index lesion which has never been resected or received external beam radiation therapy as documented on a radioactive iodine scan (insufficient uptake must be confirmed by either an endocrinologist or nuclear medicine physician).
   c) Progression of disease (by imaging) within 12 months of radioactive iodine treatment.
   d) FDG-avid lesion (SUVmax ≥ 3) on a FDG-PET scan.
5. BRAFV600E mutation-positive tumor sample as per Novartis-designated central laboratory result.
6. Has progressed on at least 1 but not more than 2 prior VEGFR targeted therapy
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
8. At least one measurable lesion as defined by RECIST v1.1.

9. 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.
10. Women of childbearing potential must have a negative serum pregnancy test within 14 days before the first dose of study treatment and agree to use effective contraception during dosing and for 16 weeks after stopping study treatment with trametininb/placebo monotherpy or dabrafenib/placebo with trametinib/placebo, or 2 weeks after stopping treatment after last dose of dabrafenib/placebo, whichever is longer.
11. Patients must have adequate baseline organ function including the following local laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without growth factor support
    - Platelets $\geq 100 \times 10^9$/L
    - International Normalized Ratio (INR) and PTT $\leq$ 1.5 x ULN (upper limit of normal)
    - Hemoglobin (Hgb) $\geq$ 9 g/dL
    - Serum Creatinine $\leq$ 1.5 mg/dl
    - Total bilirubin (TBIL) $\leq$ 1.5 x ULN
    - Aspartate transaminase (AST) $\leq$ 2.5 x ULN
    - Alanine transaminase (ALT) $\leq$ 2.5 x ULN
12. Willing and able to comply with scheduled protocol visits, treatment plan and laboratory tests.

5.2 Exclusion criteria

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

1. Anaplastic or medullary carcinoma of the thyroid.
2. Previous treatment with a BRAF inhibitor and/or a MEK inhibitor.
3. Concomitant RET Fusion-Positive Thyroid Cancer.
4. Treatment with any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomization.
5. Treatment with any type of anticancer antibody (including investigational antibody) or systemic chemotherapy within 4 weeks before randomization.
6. Receipt of radiation therapy for bone metastasis within 2 weeks or any other radiation therapy within 4 weeks before randomization.
7. Major surgery (including radio surgery) or significant traumatic injury $\leq$ 2 weeks prior to start of study treatment. Minor surgical procedures should be completed 7 days prior to start of study treatment.
8. History of another malignancy <3 years prior to starting study treatment.
   Exceptions: Patients with history of completely resected skin cancer or patients with indolent second malignancies are eligible.
9. Patients with brain metastases are excluded if their brain 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])

10. Unresolved toxicity of Grade 2 or higher from previous anti-cancer therapy, except alopecia (using NCI-CTCAE version 4.03 (common terminology criteria for adverse event).
11. History or current interstitial lung disease or non-infectious pneumonitis.
12. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy including:
    - Presence of predisposing factors to RVO or central 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 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.
13. Patients with known history for testing positive for Human Immunodeficiency Virus (HIV).
14. Known Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be allowed).
15. Patients with local laboratory confirmed COVID-19 test are excluded if the risk benefit assessment by investigator is negative.

    Note: decision to enroll the patients must be confirmed with Medical monitor.
16. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History or current diagnosis of cardiac disease indicating a significant risk of safety for patients 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)
    - Left ventricular ejection fraction (LVEF) < lower limit of institutional normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan
17. Current use of a prohibited medication as described in Section 6.2.2.
18. 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 patient's safety, obtaining informed consent, or compliance with study procedures.

19. 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 dabrafenib in combination with trametinib
20. 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.
21. 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 patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy, 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 patient.
    - Placement of a hormonal or 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 trametinib monotherapy or dabrafenib in combination with trametinib and 2 weeks after stopping treatment with dabrafenib monotherapy, whichever is longer.

    If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

    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
    - 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 bilateral tubal ligation at least six weeks prior to enrollment on study. 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.

6 Treatment

6.1 Study treatment

In this study, the term “study treatment ” refers to Novartis study drug combination dabrafenib (DRB436) plus trametinib (TMT212) and to the placebo.

The term "study drug" refers to the individual components: dabrafenib (DRB436), trametinib (TMT212) and the placebo.

Study treatment will be provided as blinded clinical supply and 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 and control drugs

Investigational/control drugs (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
DRB436 50 mg / placebo DRB436 75 mg / placebo	Capsules	Oral use	Double Blind	Global
TMT212 2 mg / placebo TMT212 0.5 mg / placebo	Tablet	Oral use	Double Blind	Global

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF (electronic Case Report Form). Study treatment will be dispensed at the site during scheduled visits. In some exceptional situations the site may be allowed to send study treatment directly to the patient with prior sponsor approval.

6.1.2 Additional study treatments

No other treatment beyond the investigational drugs noted above are included in this trial.

6.1.3 Post-trial access

Patients who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator’s evaluation may receive post-trial access. Post Trial Access (PTA) means the provision of treatment to trial patients following their completion of trial participation. PTA will be provided via roll-over protocol until one of the following is met: patient no longer derives clinical benefit, launch or reimbursement (where applicable),

treatment fails to achieve registration in the trial patient's country, or the clinical program is discontinued for any other reason.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition patients onto locally available alternative treatment, or standard of care.

6.1.4 Treatment arms/group

Patients meeting all eligibility criteria will be randomized in a 2:1 ratio either to combination dabrafenib with trametinib or to placebo.

Study treatment will be double-blinded. Neither Novartis, the site nor the patient will know the treatment assignment.

Patients will be assigned at Week 1 Day 1 visit to one of the 2 treatment arms (dabrafenib 150 mg BID and trametinib 2 mg QD or dabrafenib placebo BID with trametinib placebo QD treatment arms), in a ratio of 2:1, respectively. All patients enrolled in the study will continue on treatment until disease progression as per RECIST 1.1 as confirmed by BIRC, unacceptable toxicity, pregnancy, loss of clinical benefit as determined by the investigator, withdrawal of consent, lost to follow-up, death, or study termination by the sponsor.

6.1.5 Treatment duration

Patients will receive dabrafenib in combination with trametinib or placebo until disease progression as per RECIST 1.1 as determined by investigator and confirmed by BIRC (and not meeting the criteria in Section 6.1.5.1) or loss of clinical benefit as determined by the investigator, death, unacceptable toxicity, pregnancy, withdrawal of consent, lost to follow-up, or early termination of the study by the sponsor.

Patients in the placebo arm will be allowed to receive open-label dabrafenib plus trametinib treatment after BIRC confirmed RECIST 1.1 defined disease progression. Criteria for crossover to open-label dabrafenib and trametinib combination treatment are described in Section 6.1.5.2.

6.1.5.1 Treatment beyond disease progression

For patients treated under the initial assigned treatment who have met the criteria for disease progression (PD) by local investigator according to RECIST v1.1 and confirmed by BIRC may continue to receive study treatment if the investigator believes the patient is receiving clinical benefit. For crossover patients, BIRC review is no longer required and open-label treatment may continue beyond local disease progression as per RECIST 1.1 at investigator's discretion.

Patients must meet the following below criteria to continue treatment beyond disease progression:

- Informed consent for treatment beyond disease progression is provided by the patient
- Clear evidence of clinical benefit assessed by the investigator
- Tolerance to study treatment
- Should not jeopardize critical interventions to treat/prevent severe complications, or prevent patients from receiving adequate care

- Patient performance status is stable
- No new antineoplastic therapy has been initiated

Patients who meet the above criteria and continue treatment beyond initial disease progression will continue all study procedures as outlined in the visit assessment schedule. 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. Patients with evidence of further disease progression on an imaging assessment or who are no longer deriving clinical benefit will be discontinued.

6.1.5.2 Crossover to dabrafenib and trametinib therapy

Patients randomized to the placebo treatment arm will be allowed to crossover to receive open-label combination dabrafenib and trametinib therapy only after BIRC confirmed RECIST 1.1 defined progressive disease. At time of primary PFS analysis, patients who are still under placebo treatment will be allowed to crossover to open-label combination dabrafenib and trametinib treatment immediately or later at time of disease progression.

If in the investigator judgement, the patient has any serious or unstable medical condition during the study that would prevent the patient from participating in the crossover phase, then the patient should be excluded.

In addition to the local disease progression as per RECIST 1.1 confirmed by BIRC, the following eligibility criteria must be confirmed prior to crossing over to dabrafenib and trametinib arm:

- Patients must not have an active medical condition of interstitial lung disease or non-infectious pneumonitis
- Patients with central nervous system (CNS) metastases must be neurologically stable
- Patients must have an ECOG PS of 0-2
- Patients must not be pregnant
- Patients must be compliant with the contraception guidelines outlined in Section 8.4.3.
- Patients must have adequate organ function including the following laboratory values prior to commencing treatment of dabrafenib and trametinib in the Crossover phase:
  - Serum Creatinine ≤ 1.5 mg/dl.
  - Total bilirubin (TBIL) ≤ 1.5 x ULN (upper limit of normal)
  - Aspartate transaminase (AST) ≤ 3 x ULN, except for patients with liver metastases, who may only be included if AST =< 5xULN
  - Alanine transaminase (ALT) ≤ 3 x ULN, except for patients with liver metastases, who may only be included if ALT =< 5xULN

If the patient has not undergone specific assessments defined below 7 days prior to commencing treatment of dabrafenib and trametinib in the Cross-over phase, they must complete via a baseline visit these following assessments in order to ensure the above criteria are met prior initiation of dabrafenib and trametinib treatment:

- ECOG-PS

- Vital signs and body weight
- Hematology labs
- Chemistry labs
- ECG
- Adverse events
- Concomitant medications

Placebo treatment arm patients who start new anti-neoplastic treatment during the treatment period or post-treatment follow-up phase will not be eligible to crossover.

Patients in the placebo arm who elect to crossover to open-label combination dabrafenib and trametinib therapy must follow the study assessments as per visit schedule in Table 8-2 in the Crossover Phase.

Patients must complete the EOT visit after permanent discontinuation of placebo. The next EOT visit will be performed for patients who crossover when they permanently discontinue open-label dabrafenib and trametinib treatment.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The investigator must be informed as soon as possible about any medication taken per visit evaluation schedule (Table 8-1 and Table 8-2). Any concomitant medication(s), including dietary supplements, taken during the study will be recorded in the Concomitant Medications eCRF. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, all prior/concomitant surgical procedures and significant non-drug therapies must be recorded on the appropriate Case Report Forms.

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

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted, however, caution should be exercised and additional INR monitoring is recommended when dabrafenib is used concomitantly with warfarin.

If palliative radiotherapy (only for analgesic purposes or for lytic lesions at risk of fracture) is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. Radiotherapy should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow (Section 16.1). Written approval from Medical Lead is required and study treatment should be interrupted during radiation treatment.

Radiotherapy is allowed after disease progression confirmed by BIRC and study treatment should be interrupted during radiation treatment.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

The following medications should be used with caution as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor patients for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 6-2.
- Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib- mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on Prothrombin Time (PT)/INR during and after treatment with dabrafenib. Prophylactic low dose warfarin may be given to maintain central catheter patency.
- Based on the mechanism of action of dabrafenib and trametinib, vaccines are not expected to have an interaction with these drugs, therefore they are not prohibited. However, investigators should use their best clinical judgement on the use of live vaccines considering the potential immuno-compromised state of cancer patients. In addition, it is recommended that vaccines are not administered on the first day of study drug administration. For certain countries live vaccines are prohibited based on their local regulations (e.g., South Korea).

Table 6-2 List of medications to be used with caution during study drug treatment

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor patients for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or Transporter Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin

Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin, rosuvastatin, pravastatin
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, digoxin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.	

6.2.2 Prohibited medication

The use of certain medications and illicit drugs within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study drug and for the duration of treatment will not be allowed.

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

- Other anti-cancer therapies;
- Other investigational drugs;
- Antiretroviral drugs;
- Herbal remedies (e.g., St. John's wort);
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibitor, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. The list may be modified based on emerging data.

Table 6-3 List of prohibited medications during study drug treatment

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine)
Anticonvulsant	Carbamazepine, phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Anti-retroviral	Ritonavir, Saquinavir, Atazanavir
Miscellaneous	Conivaptan

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

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

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed. If the patient fails to start treatment or is not randomized for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient did not receive study drug or was not randomized.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after the patient has screen failed, and the patient will be assigned a new Patient No.

6.3.2 Treatment assignment, randomization

Following completion of pre-screening and screening procedures, the investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. All eligible patients will be randomized via Interactive Response Technology (IRT) in a 2:1 ratio to one of the two treatment arms. The IRT will assign a randomization number to the

patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. First dose of study treatment should occur no more than three days from randomization.

The randomization will be stratified by prior lenvatinib treatment and number of prior VEGFR targeted therapies.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

A separate medication number list will be produced by or under the responsibility of Novartis GCS using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a patient, investigator, and sponsor-blinded study. Patients, investigator and designated site staff, persons performing the assessments, BIRC, local radiologists will remain blinded to the identity of the treatment from the time of randomization as defined below.

Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study except for the [redacted], modeler and modeling programmer. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples. The identity of the study treatment will be concealed by the use of study treatments (dabrafenib+trametinib or placebo) that are identical in packaging, labeling, schedule of administration, appearance, taste, and odor. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

At time of primary PFS analysis, investigators and patients may be unblinded and crossover of placebo patients may happen at the investigator's discretion. Further details on crossover eligibility can be found in Section 6.1.5.2. All patients will continue to be followed for OS until the final OS analysis.

Unblinding will only be permitted after disease progression confirmed by BIRC upon investigator request if this information is critical to determine the optimal subsequent treatment for the patient (cross-over, treatment beyond progression or subsequent treatment other than dabrafenib + trametinib), for regulatory reporting purposes, patient emergencies (Section 6.6.2).

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are permitted as described below.

6.5.1 Dose modifications

Mandatory dose modification and recommended management guidelines for treatment-related adverse events and for which no specific dose modification guidelines are available, are provided in Table 6-4 and Table 6-5.

If the patient requires a dose interruption of > 28 days (greater than 6 weeks for uveitis oriritis) from the previous dose for persistent grade 2 or greater dabrafenib and/or trametinib treatment related toxicity, then study treatment (dabrafenib and/or trametinib) must be discontinued for this patient.

All AEs are to be graded according to NCI-CTCAE v4.03 (National Cancer Institute-Common Terminology Criteria for Adverse Event v4.03), unless otherwise specified. Investigators should refer to the current dabrafenib and trametinib local prescribing information and/or Investigator's Brochure for further information.

Table 6-4 General Guidelines for dose modification

Grade	Recommended management	Mandatory dose modification
Grade 1 or Grade 2 tolerable	• Monitor closely • Provide supportive care according to institutional standards	• Continue dabrafenib/placebo and trametinib/placebo at the same dose level.
Grade 2 (intolerable) or Grade 3	• Monitor closely • Provide supportive care according to institutional standards	Interrupt dabrafenib/placebo and trametinib/placebo • When toxicity resolves to Grade 0 to 1, restart dabrafenib/placebo and trametinib/placebo reduced by one dose level per Table 6-5.
Grade 4	• Monitor closely • Provide supportive care according to institutional standards	Interrupt study treatment until Grade 0 to 1 and restart at next lower dose level or permanently discontinue study treatment • If the Grade 4 toxicity recurs, permanently discontinue study treatment.

Table 6-5 Dabrafenib/placebo and trametinib/placebo dose levels [a]

	Dabrafenib/placebo	Trametinib/placebo
Starting dose	150 mg twice daily	2 mg once daily
1st level dose reduction	100 mg twice daily	1.5 mg once daily
2nd level dose reduction	75 mg twice daily	1.0 mg once daily
3rd level dose reduction	50 mg twice daily	Not allowed
[a] Dose modification should be based on the worst toxicity demonstrated at the last dose		

A dose reduction below 50 mg twice daily for dabrafenib/placebo or, below 1 mg once daily for trametinib/placebo, is prohibited. If a dose reduction below 50 mg BID for dabrafenib/placebo is required, dabrafenib/placebo should be permanently discontinued but these patients will be allowed to continue trametinib/placebo. If a dose reduction below 1.0 mg once daily for trametinib/placebo is required, then trametinib will be permanently discontinued, but these patients will be allowed to continue dabrafenib/placebo. Patients on monotherapy will

discontinue dabrafenib/placebo or trametinib/placebo after the 3rd and 2nd dose level reduction, respectively.

If a patient's dose of dabrafenib and trametinib has been reduced per the dose modification instructions, dose re-escalation following the same dosing steps as de-escalation may be considered provided the following criteria are met:

- A period of 4 weeks (up to 6 weeks for uveitis) of treatment has passed since restarting dosing at the lower dose level and there is no recurrence of the AE.
- The patient is deriving clinical benefit

For patients who do not tolerate the protocol-specified dosing schedule, dose changes are permitted and must follow the following principles:

- If one of the combination drugs needs to be interrupted due to toxicity, the other may continue, if in the opinion of the investigator, the toxicity is clearly related to one of the drugs of the study treatment.
- Reduction of one of the drugs and not the other agent is appropriate following Section 6.5.
- If one of the study drugs is permanently discontinued, the other study drug ongoing can be continued.

6.5.1.1 Pyrexia

Pyrexia is a common AE in patients receiving dabrafenib and/or trametinib and it is important to educate patients comprehensively and adequately about these expected AEs and be instructed on the importance of immediately reporting pyrexia or pyrexia symptoms (chills, rigors, night sweats or flu like symptoms). In a minority of cases the pyrexia was accompanied by symptoms such as severe rigors/chills, dehydration, hypotension, dizziness or weakness and required hospitalization. Guidelines for mandatory dose modification and management for suspected treatment-related pyrexia are provided in Table 6-6.

Table 6-6 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]	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 6-5, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. For reescalation, refer to Section 6.5.1.

	• Oral hydration should be encouraged in patients without evidence of dehydration. Intravenous hydration is recommended in patients experiencing pyrexia complicated by dehydration/hypotension.	
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 patients 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.		

6.5.1.2 Rash

Rash is a very common AE observed in patients receiving dabrafenib and/or trametinib. Recommended prevention measures should be implemented. Guidelines for rash management are provided in Table 6-7 and Table 6-8.

Table 6-7 Rash prevention measures

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 sun 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.
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.
SPF = sun protection factor	

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided in Table 6-8.

Table 6-8 Mandatory dose modifications and recommended clinical management guidelines for suspected treatment-related rash

Rash Events		
Grade	**Recommended management**	**Mandatory dose modification**
Grade 1: Rash covering < 10% body surface area	• 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/placebo and trametinib/placebo at the same dose.
Grade 2: Rash covering 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 symptoms persist or recur consider skin biopsy	If tolerable, continue dabrafenib/placebo and trametinib/placebo at the same dose. If intolerable: • Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline, and then restart dabrafenib/placebo and trametinib/placebo at next lower dose level.
Grade 3: Rash covering >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 occurrence** • Interrupt dabrafenib/placebo and trematinib/placebo until ≤ Grade 1 or baseline, and then restart dabrafenib/placebo and trametinib/placebo at next lower dose level. **2nd occurrence** • Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline, and then restart dabrafenib/placebo and trametinib/placebo at next lower dose level. **3rd occurrence** • Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib/placebo and trametinib/placebo to the next lower dose level. **4th occurrence** • Permanently discontinue dabrafenib/placebo and trametinib/placebo.

Rash Events		
Grade	**Recommended management**	**Mandatory dose modification**
Grade 4: Life-threatening	• Same as Grade 3	• Permanently discontinue dabrafenib/placebo and trametinib/placebo.
NOTE: suspected cases of SCAR require permanent discontinuation of study treatment, see Section 6.5.1.3.		

6.5.1.3 Mandatory dose modifications and recommended clinical management of serious cutaneous adverse reactions irrespective of relationship to study treatment

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.

6.5.1.4 Dose modification and management guideline for new malignancies suspected to be related to dabrafenib and/or trametinib treatment

New cutaneous malignancies:

Dose modification or interruption is not required for cutaneous squamous cell carcinoma, keratoacanthomas, or new primary melanoma, however cuSCC (Cutaneous Squamous Cell Carcinoma) and new primary melanoma should be reported as a SAE.

New non-cutaneous malignancies.

In patients with a non-cutaneous malignancy that has a RAS mutation the benefits and risks should be considered before continuing treatment with dabrafenib and trametinib. Dose modification or interruption is not required for new non-cutaneous malignancies.

Non-cutaneous malignancies that are reported to the Investigator should be reported as an SAE.

6.5.1.5 Mandatory dose modifications and recommended clinical management guidelines for suspected treatment-related Acute Kidney Injury

Cases of renal insufficiency have occurred in patients 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 if required concomitant medications should be modified if clinically possible. Management and dose modification guidelines are provided in Table 6-9.

Table 6-9 Mandatory dose modifications and recommended clinical management guidelines for suspected treatment-related Acute Kidney Injury

Grade (NCI-CTCAE v4.03)	Recommended management	Mandatory dose modification
Grade 1 (Creatinine level increase of > 0.3 mg/dL; creatinine 1- 1.5 x above baseline)	If the increase in creatinine is confirmed: 1. Assess fluid status and consider fluid bolus 2. Monitor serum creatinine at least every 2 days until back to baseline If creatinine returns to baseline: 1. resume routine creatinine monitoring per protocol Promote hydration and cessation of nephrotoxic drugs.	If the increase in creatinine is confirmed: • Interrupt dabrafenib/placebo and trametinib/placebo If creatinine returns to baseline within 4 weeks: • Continue dabrafenib/placebo and trametinib/placebo at the same dose.
Grade 2: (Creatinine> 1.5 - 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/placebo and trametinib/placebo until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib/placebo and trametinib/placebo to the next dose level. **3rd occurrence:** • Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib/placebo and trametinib/placebo to the next dose level. **4th occurrence** • Permanently discontinue dabrafenib/placebo and trametinib/placebo.
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/placebo and trametinib/placebo until ≤ Grade 1 or baseline and then reduce dabrafenib/placebo and trametinib/placebo to the next lower dose. **2nd occurrence:**

Grade (NCI-CTCAE v4.03)	Recommended management	Mandatory dose modification
		• Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline and then reduce dabrafenib/placebo and trametinib/placebo to the next lower dose. **3rd occurrence:** • Interrupt dabrafenib/placebo and trametinib/placebo until ≤ Grade 1 or baseline and then reduce dabrafenib/placebo and trametinib/placebo to the next lower dose, if available as dose level -2. If already at dose level-2 at time of occurrence, permanently discontinue dabrafenib/placebo and trametinib/placebo. **4th occurrence:** • Permanently discontinue dabrafenib/placebo and trametinib/placebo.
Grade 4: Life-threatening consequences; dialysis indicated	• Consult with specialist and recommend renal biopsy. • Promote hydration and cessation of nephrotoxic drugs.	Permanently discontinue dabrafenib/placebo and trametinib/placebo.

6.5.1.6 Mandatory dose modification and management guideline for ocular adverse events

Episodes of visual changes have been observed in patients receiving trametinib, dabrafenib or the combination of dabrafenib/trametinib. An ophthalmologist should be consulted if changes in vision develop.

Treatment with dabrafenib has also been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy (refer to Table 6-10).

Table 6-10 Mandatory guidelines for dose modification for Uveitis

Uveitis, including iritis and iridocyclitis	For mild or moderate that respond to treatment, no dose modification required, for mild or moderate uveitis that does not respond to ocular therapy, or for severe uveitis, withhold dabrafenib/placebo for up to 6 weeks. • If improved to Grade 0-1, then resume dabrafenib/placebo at lower dose. • If not improved, permanently discontinue dabrafenib/placebo.
In patients treated with trametinib, special attention should be given to retinal findings (e.g., RPED (retinal pigment epithelial detachments) or retinovascular abnormalities (i.e., branch or central RVO). 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 and RPED considered to be related to dabrafenib and/or trametinib are provided in Table 6-11 and Table 6-12.

Table 6-11 Mandatory dose modification and recommended clinical management guidelines for suspected treatment-related visual changes and/or ophthalmic examination findings

Visual changes (Eye disorders – Other, CTCAE Version 4.03)		
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 6-12; 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/placebo. Dabrafenib/placebo may be continued at the same dose. If RPED and RVO excluded, restart trametinib at the same dose level. • If RPED diagnosed, see RPED dose modification in in Table 6-12; report as SAE. • If RVO diagnosed: Permanently discontinue trametinib/placebo and report as SAE.
Grade 4	Consult ophthalmologist immediately	• Interrupt trametinib/placebo. Dabrafenib/placebo may be continued at the same dose. If RPED and RVO excluded, should consider restarting trametinib/placebo 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.		

Table 6-12 Mandatory dose modification and recommended clinical management guidelines for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment

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

6.5.1.7 Guidelines for Pneumonitis/Interstitial Lung Disease (ILD)

Pneumonitis has been observed in patients receiving trametinib. Dose modification and supportive care guidelines for pneumonitis or interstitial lung disease (ILD) are described in Table 6-13.

Table 6-13 Mandatory dose Modifications and recommended clinical management guidelines for suspected treatment-related Pneumonitis or interstitial lung disease

Grade(NCI-CTCAE v4.03)	**Recommended management**	**Mandatory dose modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitor of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue dabrafenib/placebo and trametinib/placebo at current dose.
Grade 2	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • If pulmonary function test results are abnormal, repeat every 8 weeks until normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	Interrupt trametinib/placebo until toxicity recovers to Grade 0 to 1. Dabrafenib/placebo may continue. • Once recovered, restart trametinib/placebo at the next lower dose level. • If no recovery to grade ≤1 within 4 weeks, permanently discontinue trametinib/placebo. • Escalation to previous dose level after 4 weeks possible and consultation with Medical Lead.

Grade(NCI-CTCAE v4.03)	Recommended management	Mandatory dose modification
Grade 3	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • If pulmonary function test results are abnormal, repeat every 8 weeks until normal • Bronchoscopy with biopsy and/or BAL if possible • Symptomatic therapy including corticosteroids as clinically indicated	Interrupt trametinib/placebo until toxicity recovers to Grade 0 to 1. Dabrafenib/placebo may continue. • Once recovered, restart trametinib/placebo 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/placebo.
Grade 4	• Same as grade 3	Permanently discontinue trametinib/placebo Dabrafenib/placebo may continue
Abbreviations: BAL= bronchoalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events		

6.5.1.8 Guidelines dose modification and management for hypertension suspected to be related to dabrafenib and/or trametinib treatment

For patients experiencing an increase in systolic and/or diastolic blood pressure (DBP) that is persistent, recommendations for dose modifications and management of hypertension are described below in Table 6-14.

Table 6-14 Mandatory dose modification and recommended clinical management guidelines for suspected treatment-related hypertension

Severity	Recommended management	Mandatory dose modification
(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/placebo and trametinib/placebo 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 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/placebo and trametinib/placebo if clinically indicated. • Once BP is well controlled, restart dabrafenib/placebo and trametinib/placebo at next lower dose level.
(Scenario C) • Symptomatic [c] hypertension or	• Adjust current or initiate new antihypertensive medication(s)	• Interrupt dabrafenib/placebo and trametinib/placebo.

Severity	Recommended management	Mandatory dose modification
• Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment.	• 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	• Once BP is well controlled, restart dabrafenib/placebo and trametinib/placebo at next lower dose level.
(Scenario D) • Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• Continue follow-up per protocol.	• Permanently discontinue dabrafenib/placebo and trametinib/placebo.
Abbreviations: SBP= systolic blood pressure; DBP= diastolic blood pressure. [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.		

6.5.1.9 Mandatory dose modification and recommended management for suspected treatment-related left ventricular ejection fraction (LVEF) decrease

Decreases of left-ventricular-ejection-fraction (LVEF) have been observed in patients receiving trametinib monotherapy and in combination with dabrafenib. Therefore, Echocardiogram (ECHOs) or Multigated acquisition (MUGA) is recommended to assess cardiac function in regular intervals. Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-15.

Table 6-15 Mandatory dose modification and recommended clinical management guidelines for suspected treatment-related changes in LVEF

LVEF-drop (%) & clinical symptoms	Recommended management	Mandatory dose modification
Asymptomatic **and** absolute decrease of >10% in LVEF compared to baseline **and** ejection fraction below the institution's LLN (lower limit of normal)	• 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	• Interrupt trametinib/placebo. • If the LVEF recovers, restart trametinib/placebo at reduced next lower dose level and continue dabrafenib/placebo at the same dose level. • More than two occurrences, permanently discontinue trametinib/placebo. • Permanently discontinue trametinib/placebo if repeat LVEF does not recover within 4 weeks.

LVEF-drop (%) & clinical symptoms	Recommended management	Mandatory dose modification
	• Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution	
Symptomatic **or** Resting LVEF ≤ 39% **or**>20% absolute reduction from baseline	• Report as SAE. • Consult with cardiologist. • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.	• Permanently discontinue trametinib/placebo. • Interrupt dabrafenib/placebo. • Restart dabrafenib/placebo if LVEF recovers including resolution of symptoms.
* If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.		

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

6.5.1.11 Guideline dose modification and management venous thromboembolic events

Advise patient 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 patient must undergo specific laboratory and medical imaging studies for confirmation.

Table 6-16 Mandatory dose modifications and recommended clinical management guidelines for suspected treatment-related venous thromboembolic events

Uncomplicated DVT or PE	Withhold trametinib for up to 3 weeks. • If improved to grade 0-1, resume trametinib/placebo at lower dose. • If not improved, permanently discontinue trametinib/placebo.
Life-threatening PE	Permanently discontinue dabrafenib/placebo and trametinib/placebo.

6.5.1.12 Guideline dose modifications and recommended clinical management for abnormal liver enzyme test

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 6-17.

Table 6-17 Mandatory dose modifications and recommended clinical management guidelines for suspected treatment-related abnormal liver enzyme test

Grade (NCI CTCAE v4.03)	Recommended management	Mandatory dose modification
Grade 1		No modification
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/placebo and trametinib/placebo until Grade 0 to 1 and then reinstate dabrafenib and trametinib/placebo 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 & 2nd occurrence** • Interrupt dabrafenib/placebo and trametinib/placebo until recovery to Grade 0 to 1 • Reduce dabrafenib/placebo and trametinib/placebo to the next lower dose level per Table 6-5. If not recovery to Grade 0 to 1 within 4 weeks, permanently discontinue dabrafenib/placebo and trametinib/placebo. **3rd occurrence** • Permanently discontinue dabrafenib/placebo and trametinib/placebo.
*Rule out viral hepatitis and other potential causes of liver injury		

6.5.1.13 Guideline dose modifications 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 2021), 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 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 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists, etc., should be consulted as deemed necessary. All patients must be followed up for adverse events and serious adverse events for 30 days following the last

doses of dabrafenib/trametinib or placebo and must be followed up during the post treatment follow-up for SAE suspected to be related to the study treatment.

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

Patients with transaminase increase combined with elevation of total bilirubin may be indicative of potentially severe DILI. These events should be considered as clinically important and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

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

- For patients with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For patients with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 x baseline] OR [ALT or AST > 8.0 x ULN], whichever occurs first, combined with [total bilirubin > 2.0 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, GGT (Gamma-glutamyl transferase), LDH (Lactate dehydrogenase), prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, MRI, or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP (Alkaline Phosphatase) elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of the liver-specific ALP isoenzyme in patients 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 clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-18 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT (liver function test) abnormalities.

Table 6-18 Clinical and diagnostic assessments in case of LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

Other causes should also be considered based upon patients' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" i.e., >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates *probably caused* by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

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," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient 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 patient. This information should be captured in the source document at each visit. All study treatments dispensed and returned must be recorded on the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- Protocol number
- Patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study treatment must be discontinued once emergency unblinding has occurred. The patient will have an End of Treatment (EOT) visit completed and will continue to be followed for progression (if applicable) or survival as specified in the protocol.

6.7 Preparation and dispensation

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section.

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

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the 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 patient'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 patient is no longer appropriate or possible, and that it is in the interest of the patient's health to administer the study treatment even without performing an on-site visit. The dispatch of study treatment from the site to the patient's home remains under the accountability of the Investigator. Each shipment/provisioning will follow the IRT dispensation schedule as per Table 8-1 and Table 8-2. In this case, regular phone calls or virtual contacts will occur as per Investigator discretion between the site and the patient for instructional purposes, safety monitoring, investigation of any adverse events, ensuring patients continue to benefit

from treatment, and discussion of the patient's health status until the patients can resume visits at the study site.

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.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization 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 patient except for the medication number.

The investigator or designated site staff 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. Patients 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.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, 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

Patients will receive either 150 mg of dabrafenib administered orally, twice daily with trametinib administered orally, once daily at a dose of 2 mg; or placebo of dabrafenib 150 mg administered orally, twice daily with placebo of trametinib 2 mg, administered orally, once daily. Dabrafenib/placebo is available as capsules and trametinib/placebo is available as tablets.

Table 6-19 Dose and treatment schedule

Investigational / Control Drug	Dose	Frequency
DRB436/placebo	150 mg /0 mg	BID
TMT212/placebo	2 mg /0 mg	QD

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

- Dabrafenib/placebo will be administered twice daily (150 mg BID, corresponding to a total daily dose of 300 mg).
- Trametinib/placebo will be administered once daily (2 mg).

- Trametinib/placebo should be taken in combination with dabrafenib/placebo once daily, preferably in the morning.
- Dabrafenib/placebo capsules and trametinib/placebo tablets should be taken with approximately 120-240 mL of water.
- Study treatment should be administered under fasting conditions, at least 1 hour before or 2 hours after a meal.
- If it is not possible for a patient to tolerate the fasting conditions noted above, study treatment/placebo may be administered with a small non-fat meal (e.g. small amount of apple juice/sauce, a piece of dry toast). Patients should be advised to avoid administering study drug with milk or high-fat, high-calorie foods.
- If a patient vomits after taking study drug, the patient should be instructed not to retake the dose and wait for the next scheduled dose.
- If a patient misses a dabrafenib/placebo dose, they should be instructed not to double the next regularly scheduled dose. However, patients may take the missed dose immediately if the next scheduled dose is at least 6 hours later. Patients may then take the next dose at the scheduled time.
- If a patient misses a trametinib/placebo dose, they should be instructed not to double the next regularly scheduled dose. However, patients may take the missed dose immediately if the next scheduled dose is at least 12 hours later. Patients may then take the next dose at the scheduled time.
- The total daily dose of dabrafenib/placebo will not exceed 300 mg (150 mg BID).
- The total daily dose of trametinib/placebo will not exceed 2 mg.

6.8 Management of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the patient to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities until DRB436 and TMT212 can no longer be detected systemically (at least 8 days).
- Document the quantity of the excess dose as well as the duration of the overdose.

7 Informed consent procedures

Eligible patients 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 patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given

his/her level of understanding. If the patient 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 patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP (Good Clinical Practice) 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 side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and CDS (core data sheet). This information will be included in the patient informed consent and should be discussed with the patient 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 patient.

The following informed consents are included in this study:

- Pre-screening (when applicable)
- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female patients or the female partners of any male patients who took study treatment
  - Patient information sheet for female partners of any male participants who took study treatment
- As applicable, Treatment beyond progression consent

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 patients 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.

Declining to participate in these optional assessments will in no way affect the patient's ability to participate in the main research study.

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

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 ICFs by trial patient and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Visit Assessment Schedule (Table 8-1 and Table 8-2) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 or Table 8-2 for crossover patients) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue from the study treatment for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the end of treatment visit (EOT or Crossover EOT) will be performed. At this final visit, all dispensed study treatment should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the patient's source documentation and do not need to be recorded in the clinical database.

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 consultation) or visits by site staff/ off-site healthcare professional(s) to the patient´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the patient to visit the site again.

If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule

Period	Category[1]	Pre-screening	Screening period	Treatment period						Follow-up	
Visit Name	**Category**	**Pre-screening**	**Screening**	**Week 1 Day 1**	**Week 4**	**Week 8**	**Week 12 and on[2]**	**Week 56 and on (next visit after week 56 is week 68)**	**End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**-**	**-28 to -1**	**1**	**28 ±7**	**56 ±7**	**84 ±7**	**392 ±7**		**±14**	**±14**
Pre-screening Informed Consent	D	X									
Informed Consent	D		X								
Informed Consent for post progression treatment while on study treatment	D			At time of disease progression							
IRT Registration[3]	S	X									
IRT Randomization	S			X							
Inclusion / Exclusion criteria	D		X								
Demography	D		X								
Central determination of BRAF V600 [3]	D	X									
Relevant medical history/current medical conditions	D		X								
Prior/Concomitant Medications	D		Continuously until 30 days after end of treatment								
Prior/concomitant non-drug therapies and procedures	D		Continuously until 30 days after end of treatment								
Diagnosis and extent of cancer	D		X								

Period	**Category[1]**	**Pre-screening**	**Screening period**	**Treatment period**						**Follow-up**	
Visit Name	**Category**	**Pre-screening**	**Screening**	**Week 1 Day 1**	**Week 4**	**Week 8**	**Week 12 and on[2]**	**Week 56 and on (next visit after week 56 is week 68)**	**End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**-**	**-28 to -1**	**1**	**28 ±7**	**56 ±7**	**84 ±7**	**392 ±7**		**±14**	**±14**
Prior antineoplastic therapy (Medication, Radiation, Surgery)	D		X								
Physical Examination (Complete)	S		X	As clinically indicated					X		
Physical examination (Brief)	S			X	Every 4 weeks through week 56 then every 12 weeks					X	
Vital Signs and body weight	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X	X	
Height	D		X								
Dermatological Assessment	S		X	X	Every 4 weeks through week 56 then every 12 weeks				X	X	
Ophthalmic Examination	D		X		X	X	Week 12, Week 20 then every 12 weeks and as clinically indicated		X	X	
Optical Coherence Tomography (OCT)	D		X		X	X	Week 12, Week 20 then every 12 weeks and as clinically indicated		X		
Electrocardiogram (ECG)	D		X	X	X	Every 12 weeks through week 52		Week 56 then every 12 weeks	X		

Period	Category[1]	Pre-screening	Screening period	Treatment period						Follow-up	
Visit Name	**Category**	**Pre-screening**	**Screening**	**Week 1 Day 1**	**Week 4**	**Week 8**	**Week 12 and on[2]**	**Week 56 and on (next visit after week 56 is week 68)**	**End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**-**	**-28 to -1**	**1**	**28 ±7**	**56 ±7**	**84 ±7**	**392 ±7**		**±14**	**±14**
ECHO or MUGA	D		X		X	Every 12 weeks through week 52		Week 56 then every 12 weeks	X		
ECOG Performance Status	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Hematology	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Blood Chemistry	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Blood collection for thyroid testing (TSH, thyroglobulin, thyroglobulin antibody)	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Urinalysis	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Coagulation Panel	D		X	X	Every 4 weeks through week 56 then every 12 weeks				X		
Hepatitis testing[4]	D		X								
[redacted]											
Serum pregnancy test	S		X						X		
Urine pregnancy test	S			X	Every 4 weeks through week 56 then every 12 weeks						
CT scan or MRI of neck, chest and abdomen[5]	D		X	Every 8 weeks until Week 56, then every 12 weeks thereafter until determination of progressive disease							

Period	**Category[1]**	**Pre-screening**	**Screening period**	**Treatment period**						**Follow-up**	
Visit Name	**Category**	**Pre-screening**	**Screening**	**Week 1 Day 1**	**Week 4**	**Week 8**	**Week 12 and on[2]**	**Week 56 and on (next visit after week 56 is week 68)**	**End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**-**	**-28 to -1**	**1**	**28 ±7**	**56 ±7**	**84 ±7**	**392 ±7**		**±14**	**±14**
Brain Imaging (CT or MRI)[6]	D		X	If clinically indicated or positive at screening follow the same schedule as neck, chest, abdomen CT scan/MRI							
Whole body bone scan[6]	D		X	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 neck, chest or abdomen CT or MRI)[6]	D		For any lesions on whole body bone scan that are not visible on the neck, chest, abdomen scans	If clinically indicated or positive at screening follow same schedule as neck, chest, abdomen CT scan/MRI							
CT or MRI of other metastatic sites[6]	D		If other metastatic sites are suspected	If clinically indicated or positive at screening follow same schedule as neck, chest, abdomen CT scan/MRI							
Adverse Events	D		Continuously until 30 days after end of treatment								
Serious Adverse Events	D		Continuously until 30 days after end of treatment							X[7]	X[7]
IRT dispensation of dabrafenib/trametinib/placebo	S			X	Every 4 weeks through week 56 then every 12 weeks						
Administration of dabrafenib/placebo	D			Continuously b.i.d							
Administration trametinib/placebo	D			Continuously q.d.							
[redacted]											

Period	Category[1]	Pre-screening	Screening period	Treatment period						Follow-up	
Visit Name	**Category**	**Pre-screening**	**Screening**	**Week 1 Day 1**	**Week 4**	**Week 8**	**Week 12 and on[2]**	**Week 56 and on (next visit after week 56 is week 68)**	**End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**-**	**-28 to -1**	**1**	**28 ±7**	**56 ±7**	**84 ±7**	**392 ±7**		**±14**	**±14**
[redacted]											
Antineoplastic therapies since discontinuation of study treatment	D									X	X
Disposition Assessment	D	X	X						X	X[8]	
[redacted]											
Survival Patient Status											X

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] D refers to information collected in the Novartis database (eCRF); S refers to information only collected in the source documentation
[2] Visits will continue every 4 weeks from Week 12 until Week 56 then will be every 12 weeks.

Period	Category[1]	Pre-screening	Screening period	Treatment period						Follow-up	
Visit Name	Category	Pre-screening	Screening	Week 1 Day 1	Week 4	Week 8	Week 12 and on[2]	Week 56 and on (next visit after week 56 is week 68)	End of Treatment (within 7 days of discontinuation of study treatment)	Post treatment Follow-up (every 3 months)	Survival Follow-Up
Days	NA	-	-28 to -1	1	28 ±7	56 ±7	84 ±7	392 ±7		±14	±14

[3] Patients who have local BRAF V600E confirmation will be able to go directly to the screening phase but central confirmation of the mutation is required prior to enrollment. Some patients may have IRT Registration and central confirmation of BRAF V600E mutation completed during screening instead of pre-screening.
[4] To be completed only if patient has a history of hepatitis
[5] Tumor assessment at End of Treatment (EoT) only for patients without documented RECIST 1.1 PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment. Please refer to Section 8.3.
[6] Please refer to Section 8.3 for details.
[7] Only SAEs suspected to be related to study drug will be recorded after 30 days post study treatment
[8] Disposition will be completed at the last post treatment follow up visit only (not every 3 months)

[redacted]

Table 8-2 Assessment Schedule, Cross-over Patient (ONLY applicable for patients randomized to placebo treatment arm who have crossed over to the dabrafenib and trametinib combination treatment arm)

Period	**Category[1]**	**Cross-over treatment**						**Follow-up**	
Visit Name	**Category**	**Cross-over Baseline[2]**	**Cross-over Week 1 Day 1**	**Cross-over Week 4**	**Cross-over Week 8**	**Cross-over Week 12 and on**	**Cross-over End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**NA**	**1**	**28 ±7**	**56 ±7**	**84 ±7**		**±14**	**±14**
Crossover eligibility criteria	D	X							
IRT Update	S	X							
Concomitant Medications	D	Continuously until 30 days after end of treatment							
Concomitant non-drug therapies and procedures	D	Continuously until 30 days after end of treatment							
Physical Examination (complete)	S	X	As clinically indicated				X		
Physical examination (Brief)	S		X	Every 4 weeks through week 56 then every 12 weeks				X	
Vital Signs and body weight	D	X	X	Every 4 weeks through Week 56 then every 12 weeks			X	X	
Dermatological Assessment	S	X	X	Every 4 weeks through week 56 then every 12 weeks			X	X	
Ophthalmic Examination	D	X		X	X	Week 12, Week 20 then every 12 weeks and as clinically indicated	X	X	

Period	**Category[1]**	**Cross-over treatment**						**Follow-up**	
Visit Name	**Category**	**Cross-over Baseline[2]**	**Cross-over Week 1 Day 1**	**Cross-over Week 4**	**Cross-over Week 8**	**Cross-over Week 12 and on**	**Cross-over End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**NA**	**1**	**28 ±7**	**56 ±7**	**84 ±7**		**±14**	**±14**
Optical Coherence Tomography (OCT)	D	X		X	X	Week 12, Week 20 then every 12 weeks and as clinically indicated	X		
Electrocardiogram (ECG)[3]	D	X		X	Every 12 weeks through Week 52, at Week 56 and then every 12 weeks		X		
ECHO or MUGA[3]	D	X		X	Every 12 weeks through Week 52, at Week 56 and then every 12 weeks		X		
ECOG Performance Status	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		
Hematology	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		
Blood Chemistry	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		
Blood collection for thyroid testing (TSH, thyroglobulin, thyroglobulin antibody)	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		
Urinalysis	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		
Coagulation Panel	D	X	X	Every 4 weeks through week 56 then every 12 weeks			X		

Period	**Category[1]**	**Cross-over treatment**						**Follow-up**	
Visit Name	**Category**	**Cross-over Baseline[2]**	**Cross-over Week 1 Day 1**	**Cross-over Week 4**	**Cross-over Week 8**	**Cross-over Week 12 and on**	**Cross-over End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**NA**	**1**	**28 ±7**	**56 ±7**	**84 ±7**		**±14**	**±14**
Serum pregnancy test	S	X					X		
Urine pregnancy test	S		X	Every 4 weeks through week 56 then every 12 weeks					
CT scan or MRI of neck, chest and abdomen[4]	D	X	Every 8 weeks until week 56 then every 12 weeks						
Brain Imaging (CT or MRI)[4]	D	X	If clinically indicated or positive at screening follow the same schedule as neck, chest, abdomen CT scan/MRI						
Whole body bone scan[4]	D	X	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 neck, chest or abdomen CT or MRI)[4]	D	For any lesion lesions on whole body bone scan that are not visible on the neck, chest, abdomen scans	If clinically indicated or positive at screening follow the same schedule as neck, chest, abdomen CT scan/MRI						
CT or MRI of other metastatic sites[4]	D	If other metastatic sites are suspected	If clinically indicated or positive at screening follow the same schedule as neck, chest, abdomen CT scan/MRI						
Adverse Events	D	Continuously until 30 days after end of treatment							
Serious Adverse Events	D	Continuously until 30 days after end of treatment						X[5]	X[5]
IRT dispensation of dabrafenib/trametinib	S		X	Every 4 weeks through week 56 then every 12 weeks					
Administration of dabrafenib	D		Continuously b.i.d.						
Administration of trametinib	D		continuously q.d.						

Period	**Category[1]**	**Cross-over treatment**						**Follow-up**	
Visit Name	**Category**	**Cross-over Baseline[2]**	**Cross-over Week 1 Day 1**	**Cross-over Week 4**	**Cross-over Week 8**	**Cross-over Week 12 and on**	**Cross-over End of Treatment (within 7 days of discontinuation of study treatment)**	**Post treatment Follow-up (every 3 months)**	**Survival Follow-Up**
Days	**NA**	**NA**	**1**	**28 ±7**	**56 ±7**	**84 ±7**		**±14**	**±14**
Antineoplastic therapies since discontinuation of study treatment	D							X	X
Disposition Assessment	D	X					X	X[6]	
[redacted]									
Optional fresh biopsy collection[8]	D		At time of disease progression						
Survival Patient Status									X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] D refers to information collected in the Novartis database (eCRF); S refers to information only collected in the source documentation
[2] Please refer to Section 6.1.5.2
[3] ECG, ECHO or MUGA assessments must be performed within 4 weeks prior to the first dose of dabrafenib and trametinib therapy.
[4] At time of re-baselining and prior to crossover to combination therapy, a new disease assessment is required if the most recent disease assessment was performed more than 8 weeks prior to crossover.
[5] Only SAEs suspected to be related to study drug will be recorded after 30 days post study treatment
[6] Disposition will be completed at the last post treatment follow up visit only (not every 3 months)
[7] [redacted]
[8] [redacted].

8.1 Screening

8.1.1 Molecular pre-screening

In order to be considered eligible for the study, patients must have the presence of a BRAFV600E mutation confirmed by the Novartis-designated central laboratory.

If the results of this study are submitted for health authority registration, an *in vitro* diagnostic (IVD) assay may be required to be filed in accordance with local health authority requirements and the centralized BRAFV600E testing data (positive or negative) would be an essential part of the IVD registration. IVD registration may involve collaboration with a Novartis-designated partner company.

Patients who do not have a local BRAFV600E result available as part of their medical record will be asked to sign and date an IRB/IEC-approved molecular pre-screening ICF before their tumor sample is sent for testing to a Novartis-designated central laboratory for BRAFV600E mutation testing. A tissue sample may be submitted for central BRAFV600E testing at any time prior to main screening, including if the patient is receiving prior therapy, after the patient has signed an IRB/IEC-approved molecular pre-screening ICF. The result confirming the presence of a BRAFV600E mutation from the Novartis-designated central laboratory must be obtained prior to the patient proceeding to study specific screening procedures following signature of the main ICF.

Patients who have a local BRAFV600E result available will be able to proceed for study specific screening procedures following signature of the main ICF, as long as the result is documented as part of their medical record. The local test result, test methodology information and laboratory information, to the extent known, must be entered in the CRF. Local test results must not be used to determine BRAFV600E mutation status for eligibility. The presence of a BRAFV600E mutation must be confirmed by the Novartis-designated central laboratory in order for the patient to be considered eligible for the study.

BRAFV600E test results may take up to 1 week (5 business days) to be provided once the sample is received at the Novartis-designated central laboratory for testing. If the sample provided is insufficient for testing, another sample will be requested. Therefore, it is recommended that the tissue sample be sent to the central Novartis-designated laboratory at least 2 weeks ahead of randomization to ensure the result is received in time. A newly obtained tumor biopsy or archival tumor tissue sample will be accepted for central BRAFV600E testing. The most recent archival sample is strongly preferred; however, archival tumor tissue obtained at the time of diagnosis of DTC or any time since diagnosis is acceptable. The tissue sample should consist of a formalin fixed paraffin embedded (FFPE) tumor block or freshly cut tissue slides. Tissue samples should contain ample tumor content as tissue samples with low tumor content (i.e. less than 50% tumor content) may not be evaluable for BRAFV600E analysis. Fine-needle aspiration and bone biopsy samples are not acceptable. For patients entering pre-screening in China, a maximum of freshly cut 5 tissue slides are to be submitted. 5 additional FFPE slides may be collected for CDx development upon approval from health authorities, ethics committees and/or equivalent (e.g. HGRAC). [redacted]

Results from central testing will be communicated directly to the respective study center.

For all pre-screen failure patients outside of China, remaining tissue material after BRAFV600E testing can be returned to the site upon request, after some tissue is retained. The retained tissue sample will remain under the control of Novartis, to support the development of diagnostic test(s). For pre-screen failure patients from China, the slides required for pre-screening and associated remnant materials will be handled in accordance with local regulation.

[redacted]

8.1.2 Eligibility screening

Following registering in the IRT for screening, patient 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.

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed. Laboratory and radiological evaluations which were performed as part of the patient's clinical standard of care within the acceptable screening window can be used and do not need to be repeated.

Patients will be evaluated against all study inclusion and exclusion criteria and safety assessments (refer to Table 8-1) within 28 days prior to start of treatment (Week 1 Day 1). Screening assessments must be repeated if performed outside of the specified screening window. Patients must meet all inclusion and none of the exclusion criteria at screening in order to be eligible for the study.

Laboratory assessments of hematology/chemistry performed as part of the screening evaluations done within 7 days prior to Week 1 Day 1 will not be required to be repeated on Week 1 Day 1, unless deemed clinically necessary by the investigator. Serum pregnancy test is preferentially within 72 hours prior to treatment start. Urine pregnancy test on Week 1 Day 1 will not be required if serum pregnancy test is done within 72 hours prior to Week 1 Day 1. Laboratory test result(s) or symptoms that do not satisfy the eligibility criteria may be repeated or treated during the screening visit window. In the event that the repeated laboratory test(s) cannot be performed within 28 days from the original screening visit, or do not meet the eligibility criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screening failure.

Re-screening of a patient who has failed screening may be allowed. In such cases, a new ICF must be signed. A new patient number will be assigned to the patient. The re-screen form will have to be completed in the eCRF and in IRT to provide the original patient number. All required screening assessments must be repeated if they do not meet the allowed time window for screening when the patient is re-screened for participation in the study. An individual patient can only be re-screened once for the study. Once the number of patients enrolled is likely to

ensure target number of treated patients, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen.

For patients who are screened and eligibility confirmed in IRT system, but fail to start treatment for any reason, the reason should be recorded on the appropriate disposition eCRF.

8.1.3 Information to be collected on screening failures

A screen failure occurs when a patient who consents to participate in the clinical study is subsequently found to be ineligible and therefore not randomly assigned to study treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

The following eCRF pages must be completed for screening failure patients:

- Tumor samples collection (archival or newly obtained) for central BRAFV600E testing
- Mutation status
- Differentiated Thyroid Cancer diagnosis and extent of disease, including:
  - Date of diagnosis and stage of DTC
  - Site of active disease
  - Characteristics of disease
- Screening phase disposition
- Demography (age, gender, race)
- Informed consent
- Inclusion/Exclusion Criteria
- Withdrawal of consent (if applicable)
- Death (if applicable)

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced an SAE during the screening phase (see SAE section for reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure (i.e. tumor biopsy collection) will be reported to the Novartis Safety group.

8.2 Patient demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Patient race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Patient demographic and baseline characteristic data are to be collected on all patients. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the

appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Patient demographic and baseline characteristic data that need to be collected on all Patients at screening include:

- Demography (age, gender, race)
- Other background or relevant medical history
- Cancer characteristics including diagnosis, history, extent of cancer, prior antineoplastic therapies (medication, radiation, surgeries), and the date of progression prior to study entry
- Tumor imaging assessments
- Other assessments to be completed for the purpose of determining eligibility (ECOG performance status, complete physical examination, vital signs, hematology, chemistry, coagulation studies, urinalysis, HIV testing [only recorded in source documentation], serum pregnancy test for women of child-bearing potential [only recorded in source documentation], and 12-Lead ECG)
- Prior and current concomitant medications and surgical and medical procedures

8.3 Efficacy

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 (Section 16.1) based on RECIST 1.1 Eisenhauer et al 2009. The imaging assessment collection plan is presented in Table 8-3.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. The central review of the scans will be carried out in a blinded fashion. Details of the central review process will be described in the independent review charter.

The central (BIRC)'s assessment will be used for the primary analysis and for treatment decision making as long as it's clinically acceptable. Central review will stop once patients in the randomized treatment group have crossed over to the dabrafenib and trametinib combination arm or after final primary analysis completion. Local investigator assessment will be used for sensitivity analysis purpose.

Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at 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.

Although the study will use an Independent Central Radiology Review to measure tumor response, the decision to enroll the patient will be made based on the judgment of the investigator and local radiologist. Once the patient is enrolled, the baseline imaging data should be sent within the time window specified in the imaging manual by the study site to the Independent Central Radiology.

8.3.1 Tumor assessments

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 Week 1 Day 1). Any imaging assessments already completed during the regular work-up of the patient 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 randomization cannot be considered baseline images. Assessments required are described in Table 8-1 and Table 8-2.

If a patient is known to have a contraindication to CT intravenous (i.v.) 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 should be performed.

Brain MRI or CT should be completed at baseline. 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-99m 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 neck, chest, abdomen or brain CT/MRI.

If clinically indicated, CT or MRI of other areas of disease, as appropriate, should be performed. Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessments

Imaging assessments as described in Table 8-3 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing. Imaging assessments for response evaluation will be performed starting at Week 8, every 8 weeks (+/- 7 days) thereafter through Week 56 and then every 12 weeks thereafter (all ± 7 days) until disease progression per RECIST 1.1 as per BIRC, death, lost to follow-up, withdrawal of consent or primary PFS analysis, whichever occurs first. Imaging assessments should be scheduled using the date of randomization 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. If an unscheduled imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a patient, 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 and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent.

All study imaging (including any off-schedule imaging studies) up to crossover or to primary PFS analysis should be submitted to the designated imaging CRO for quality control and BIRC review.

For patients who crossover to open-label combination dabrafenib and trametinib treatment, the next disease progression will be further determined based on investigator assessment and imaging assessment will follow the local practice and institutional guidelines.

After primary PFS analysis, imaging assessment will follow the local practice and institutional guidelines and be captured in the appropriate eCRF RECIST pages, up to RECIST 1.1 disease progression as per local investigator assessment, death, lost to follow-up or withdrawal of consent.

Timepoints at which progression is determined locally

All patients who have disease progression determined by the local investigator require an expedited tumor response review by the BIRC. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically, e.g. via the Internet. In all instances, the process at the imaging CRO will ensure that the BIRC reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The investigator seeking an expedited review must indicate this request to the imaging CRO on a designated form or by alternative means. The imaging will undergo expedited BIRC review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the BIRC review will be communicated to the site. While the investigator is awaiting the results of the BIRC review, it is preferable that the patient continue on study treatment. However, during this time, the investigator should do whatever is medically necessary for his/her patient.

If the BIRC determines disease progression, then the patient should discontinue study treatment (except for those who would fulfill criteria for treatment beyond RECIST PD, see Section 6.1.5.1) and subsequent tumor assessments are no longer required. Patients randomized in the placebo arm will be allowed to receive dabrafenib and trametinib combination treatment after meeting criteria, as described in Section 6.1.5.2.

If the BIRC does not determine disease progression, the patient should continue receiving the study treatment, unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy, until disease progression has been determined by the BIRC or at a minimum, until at least one additional tumor assessment has been completed.

Patients will continue to have imaging performed as per protocol (Table 8-3) until the BIRC determines disease progression.

The imaging vendor will ensure that the BIRC reviewers involved are blinded to the expedited status of the reading.

Timepoints without locally determined progression

All imaging time points without locally determined progression will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

End of treatment imaging assessments

At end of treatment, imaging assessments will be done for all patients without prior documented RECIST 1.1 PD as per the BIRC and who do not enter the efficacy follow-up phase provided the last imaging assessment was not conducted within 30 days prior to the end of study treatment.

Efficacy follow-up imaging assessments

All patients who discontinue study treatment **without** prior documented disease progression RECIST 1.1 as per the BIRC will continue these efficacy imaging assessments, in the efficacy follow-up phase of the post-treatment period, until documented disease progression by RECIST 1.1 as per the BIRC, withdrawal of consent, pregnancy, lost to follow up, or death irrespective of start of new anti-neoplastic therapy.

Patients who crossover to open-label combination dabrafenib and trametinib treatment and who discontinued the drugs without documented disease progression RECIST 1.1 as per investigator, will continue efficacy imaging assessments as per Table 8-2 in the efficacy follow-up phase of the post-treatment period, until documented disease progression by RECIST 1.1 as per investigator, withdrawal of consent, pregnancy, lost to follow up, death, or primary PFS analysis, whichever occurs first.

Table 8-3 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Neck, chest, abdomen CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 8 weeks (+/- 7 days) from Week 8 until Week 56, then every 12 weeks (+/- 7 days) after Week 56 until documented disease progression per RECIST 1.1 per BIRC, death, lost to follow-up or withdrawal of consent, or primary PFS analysis whichever occurs first Refer to Section 8.3.1 for details on additional tumor assessments to perform to allow further central analysis
Brain CT or MRI	Mandated	If clinically indicated or If lesions were documented at screening follow the same schedule as neck, chest, abdomen CT Scan/MRI
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 neck, chest, abdomen CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of neck, chest, and abdomen or if clinically indicated

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI of other metastatic sites (e.g. pelvis)	If other metastatic sites are suspected	If lesions were documented at baseline, follow same schedule as CT/MRI of neck, chest, and abdomen or if clinically indicated

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, the collection of images may be modified by Novartis and will be communicated to the investigator.

8.3.2 Survival assessment

All patients will enter the survival follow-up period once they completed the post-treatment follow-up (e.g., safety and efficacy follow-up, if applicable) after treatment discontinuation. Survival status will be collected every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up.

Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim analysis to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

Information on all subsequent therapies received for DTC, if any, after study treatment has been completed, will be collected (including start date, stop date, and date of progression if any).

8.3.3 Appropriateness of efficacy assessments

Tumor assessment every 8 -12 weeks are consistent with the standard clinical practice. The median PFS is expected to be approximately 5 months for patients receiving placebo and 11 months for patients receiving dabrafenib plus trametinib. Conducting tumor evaluation more than 8 weeks apart may expose a patient to an unnecessary active or not active treatment if disease progression event takes place between the infrequent assessments or prevent from earlier identification of progression lesions and appropriate treatment.

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.

Safety will be monitored by assessing physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, ECG, ECHO/MUGA, laboratory assessments including hematology, chemistry, urinalysis, coagulation as well as collecting AEs at every visit. Clinically relevant findings that were present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant new findings that begin or worsen after informed consent which meet the definition of an AE must be recorded as an AE. For details on AE collection and reporting, refer to AE Section 10.1.1.

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 patient´s health status until it is safe for the patient to visit the site again.

Table 8-4 Summary of Safety Assessments

Assessment	Specification
Physical examination	A complete physical examination will be performed at screening and at treatment discontinuation per Table 8-1 and Table 8-2 and will include the examination of general appearance, neck (including thyroid), 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 complete physical examination can be performed at other visits as clinically indicated. A brief physical examination will include the examination of general appearance, vital signs and body weight. A brief physical examination will be performed at all visits (except screening and treatment discontinuation) as per schedule in Table 8-1 and Table 8-2. 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. In the event of a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, the brief physical exam can be conducted by the investigator via telemedicine or may be performed via home nursing. Each request must be reviewed and approved by the Novartis Global Team.
Vital signs and body weight	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, body temperature and body weight. Vital signs and body weight will be measured at screening and subsequent time points as specified in Table 8-1 and Table 8-2.
Height	Height in centimeters (cm) will be measured as specified in Table 8-1.
Dermatological	Dermatological examinations may be performed by the investigator as part of the Physical Exam or may be referred to a dermatologist, at the discretion of the investigator. It 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 and Table 8-2). 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 deidentified pathology reports of new lesions or lesions that change during the study must be obtained and forwarded to Novartis or designee. In the event of a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, dermatological assessment may be done remotely. Each request must be reviewed and approved by the Novartis Global Team.
Ophthalmic Exam	Episodes of visual changes related to retinal pigment epithelial detachments (RPED) have been observed in patients receiving trametinib, dabrafenib, and combination therapy. A standard ophthalmic examination by an ophthalmologist will be performed at screening, Week 4, Week 8, Week12, Week 20 and every 12 weeks after Week 20 and as clinically indicated as per schedule in Table 8-1 and Table 8-2. The exam will include best corrected visual acuity, tonometry, slit lamp examination, visual field examination utilizing automated static perimetry covering 60 degrees (e.g. a 30-2 perimetry). The same perimetry is to be used whenever possible on any one patient throughout the duration of follow up to enable for evaluation of progression and indirect fundoscopy with special attention to retinal abnormalities.

Assessment	Specification
	Optical coherence tomography (OCT) is mandated at screening, Week 4, Week 8, Week12, Week 20 and every 12 weeks after Week 20 and as clinically indicated as per schedule in Table 8-1 and Table 8-2. OCT images will be reviewed centrally. In the event of a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, patient would be allowed to have opthalmologic exams performed at a facility other than the study site. In this case every effort should be made to share the OCT images with the study site and send to the Novartis vendor. Each request must be reviewed and approved by the Novartis Global Team.

Performance status:

ECOG Performance status scale will be used as described in Table 8-5.

Table 8-5 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 the analysis of all scheduled hematology, chemistry, coagulation, urinalysis and serum pregnancy test to assess the patient's eligibility and safety monitoring (as detailed in Table 8-1 and Table 8-2).

Additional time points should be added as deemed necessary as per the investigators best judgment to make sure dose adjustments are performed to safeguard the safety of the patient.

Additional results from unscheduled laboratory evaluations should be recorded in the appropriate Unscheduled Visit eCRF.

Laboratory assessments of hematology/chemistry performed as part of the screening evaluations done within 7 days prior to Day 1 will not be required to be repeated on Day 1, unless deemed clinically necessary by the investigator. Serum pregnancy test is preferentially within 72 hours prior to treatment start. Urine pregnancy test on Day 1 will not be required if serum pregnancy test is done within 72 hours prior to Day 1. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Table 8-1 and Table 8-2) except as stated above.

The investigator is responsible for reviewing all laboratory reports for patients and evaluating any abnormalities for clinical significance.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory

until normalization of the result(s) or until the result is no longer considered to be clinically significant.

In the event of a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, an alternate local laboratory may be used and/or laboratory samples may be collected via home nursing. Each request must be reviewed and approved by the Novartis Global Team.

Table 8-6 Local Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, 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	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leucocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen). If dipstick is abnormal, then perform local laboratory Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid	TSH, Thyroglobulin (Tg), Thyroglobulin Antibody (TgAb)
Hepatitis markers	HBV-DNA, HBsAb, HBcAb, HCV RNA-PCR
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. Pregnancy tests during treatment period may be urine tests (refer to 'Pregnancy and assessments of fertility' section).

8.4.2 Electrocardiogram (ECG)

A standard 12-lead ECG (single) will be performed according to the relevant Visit Evaluation Schedule (Table 8-1 and Table 8-2). Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. 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) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility according to the following formula:

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

Single 12-lead ECGs are collected and results are entered into the appropirate eCRF pages. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

Table 8-7 Local ECG collection plan

Week (or Cycle)	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12-Lead
Week 1 Day1	1	Anytime	12-Lead
Week 4 and every 12 weeks after through week 52. Then week 56 and every 12 weeks after.	1	Anytime	12-Lead
EOT		within 7 days of discontinuation of study treatment	12-Lead
Unscheduled (as clinically indicated)		Anytime	12-Lead

Each ECG tracing must be labeled with study number, patient initials (where regulations permit), patient number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF.

Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study to ensure patient eligibility. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

8.4.2.1 Echocardiogram (ECHO)

Decreases of the LVEF have been observed in patients 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 and Table 8-2).

The same procedure (ECHO or MUGA) should be performed at screening/cross over baseline and at follow-up visit(s). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-15.

8.4.3 Pregnancy and assessments of fertility

Male patients

A condom is required for all sexually active male patients 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) must use a condom during intercourse while on study treatment, and for 16 weeks after stopping treatment with trametinib/placebo monotherapy or dabrafenib/placebo in combination with trametinib/placebo

and 2 weeks after stopping treatment with dabrafenib/placebo monotherpay, whichever is longer, and should not father a child during these periods.

In addition, male patients 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 trametinib/placebo or dabrafenib/placebo in combination with trametinib/placebo and 2 weeks after stopping treatment with dabrafenib/placebo monotherapy, whichever is longer. Highly effective contraception methods include:

1. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
2. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral 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.
3. Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that patient.
4. 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.

NOTES:

- 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.
- 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 bilateral 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 childbearing potential.

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 patients cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant patients can perform the urine pregnancy test at home and report the result to the site. It is important that patients 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 patient so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of Fertility

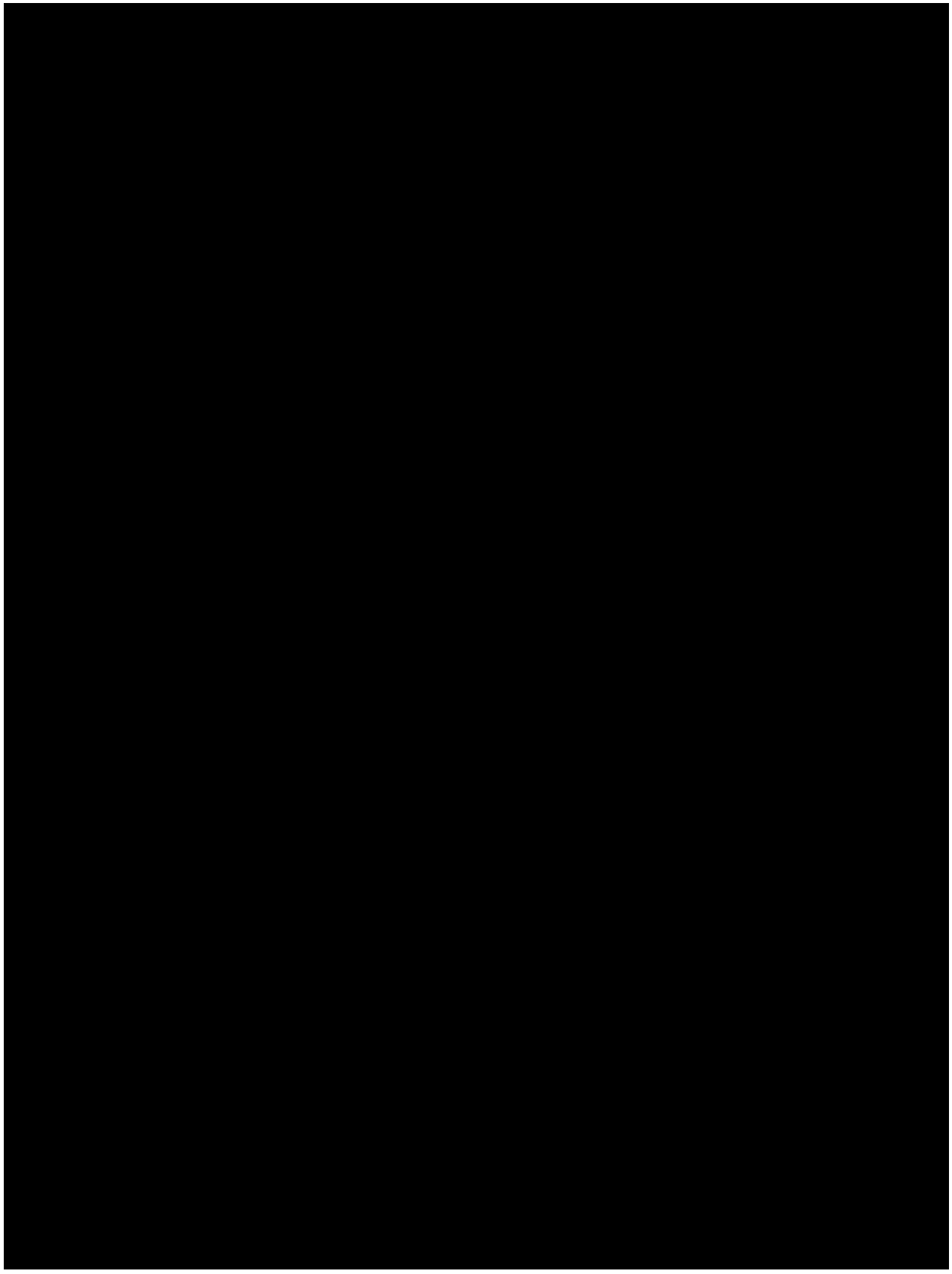
A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source documents.

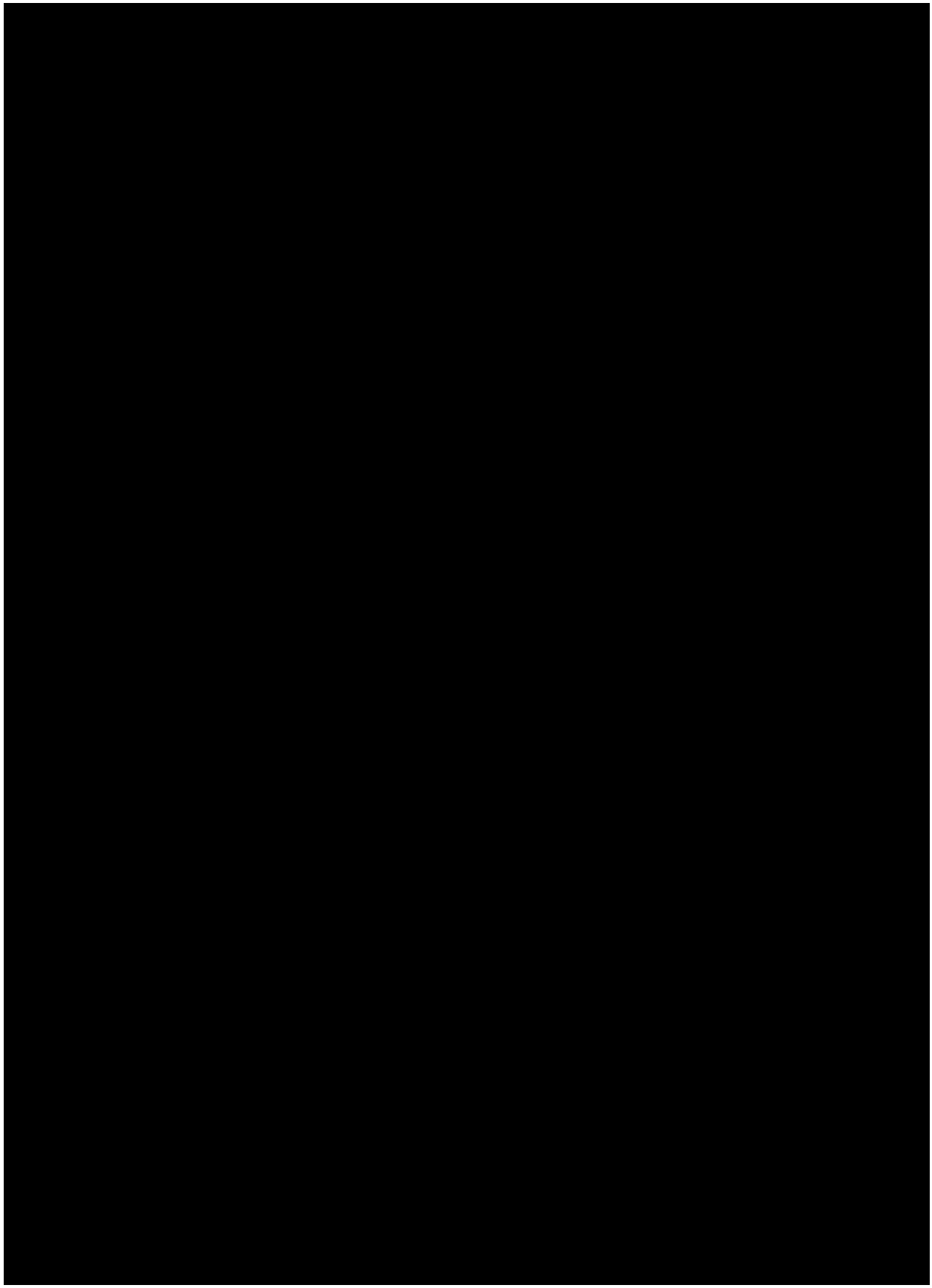
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

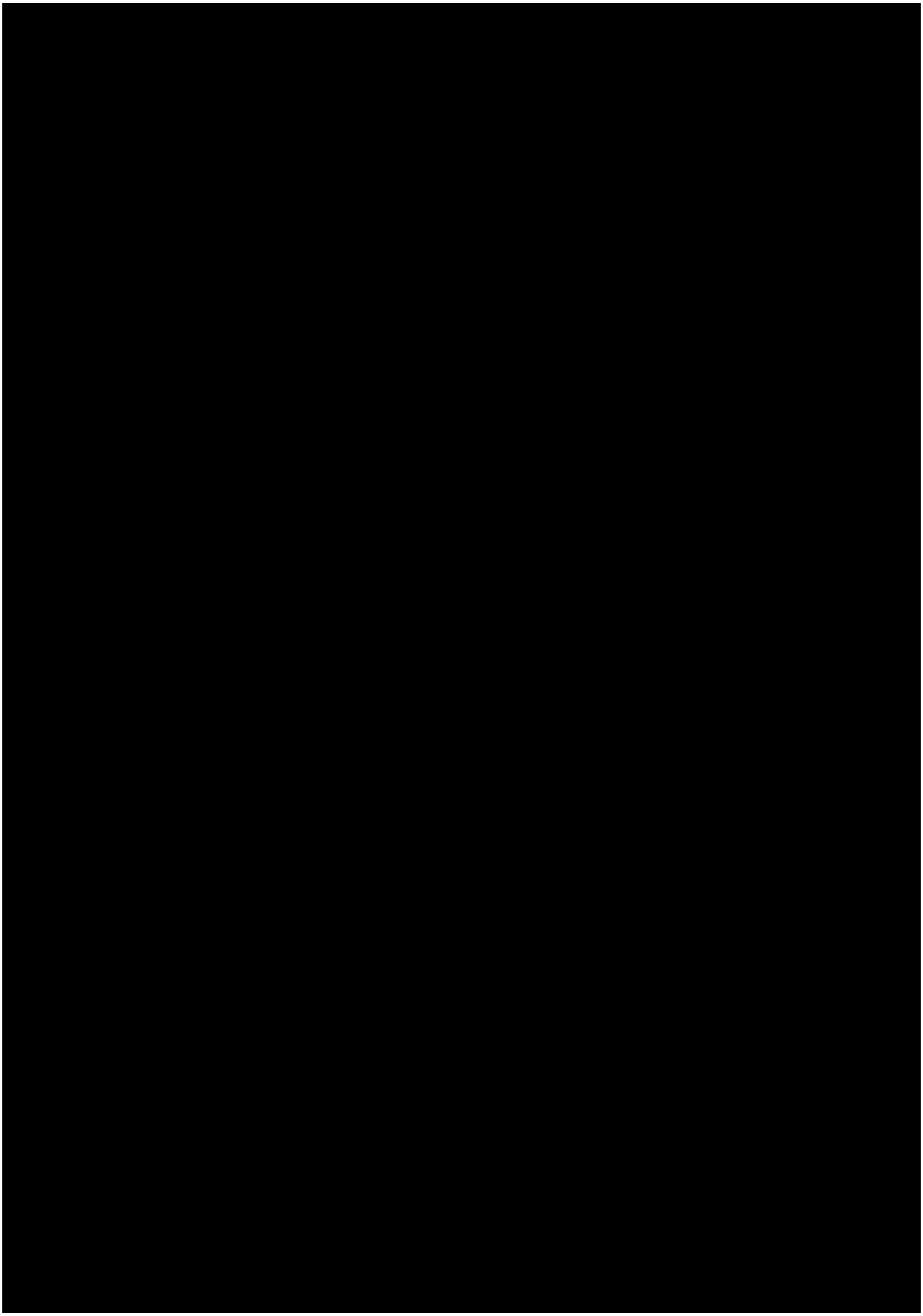
In absence of medical documentation, confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

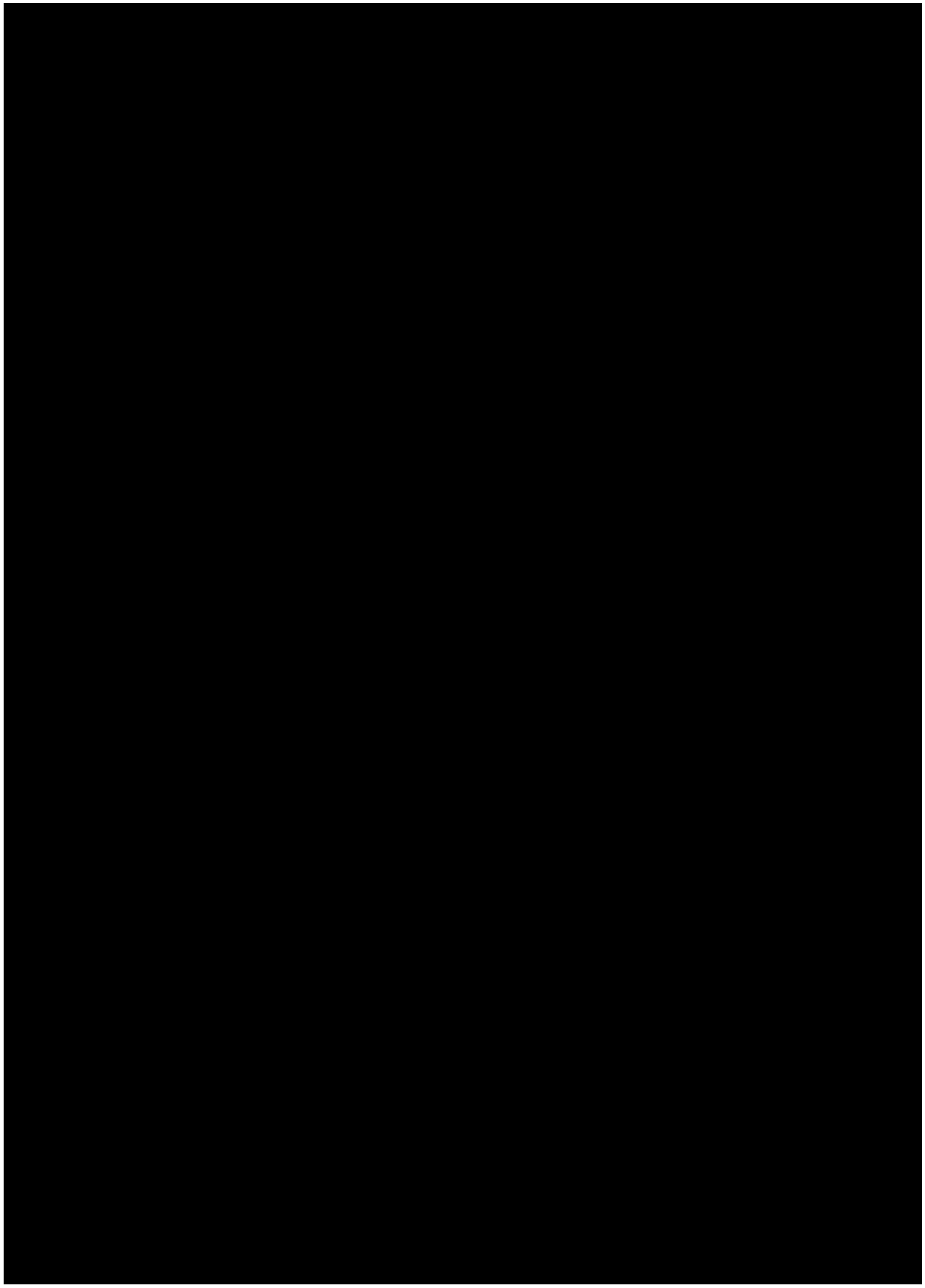
8.4.4 Appropriateness of safety measurements

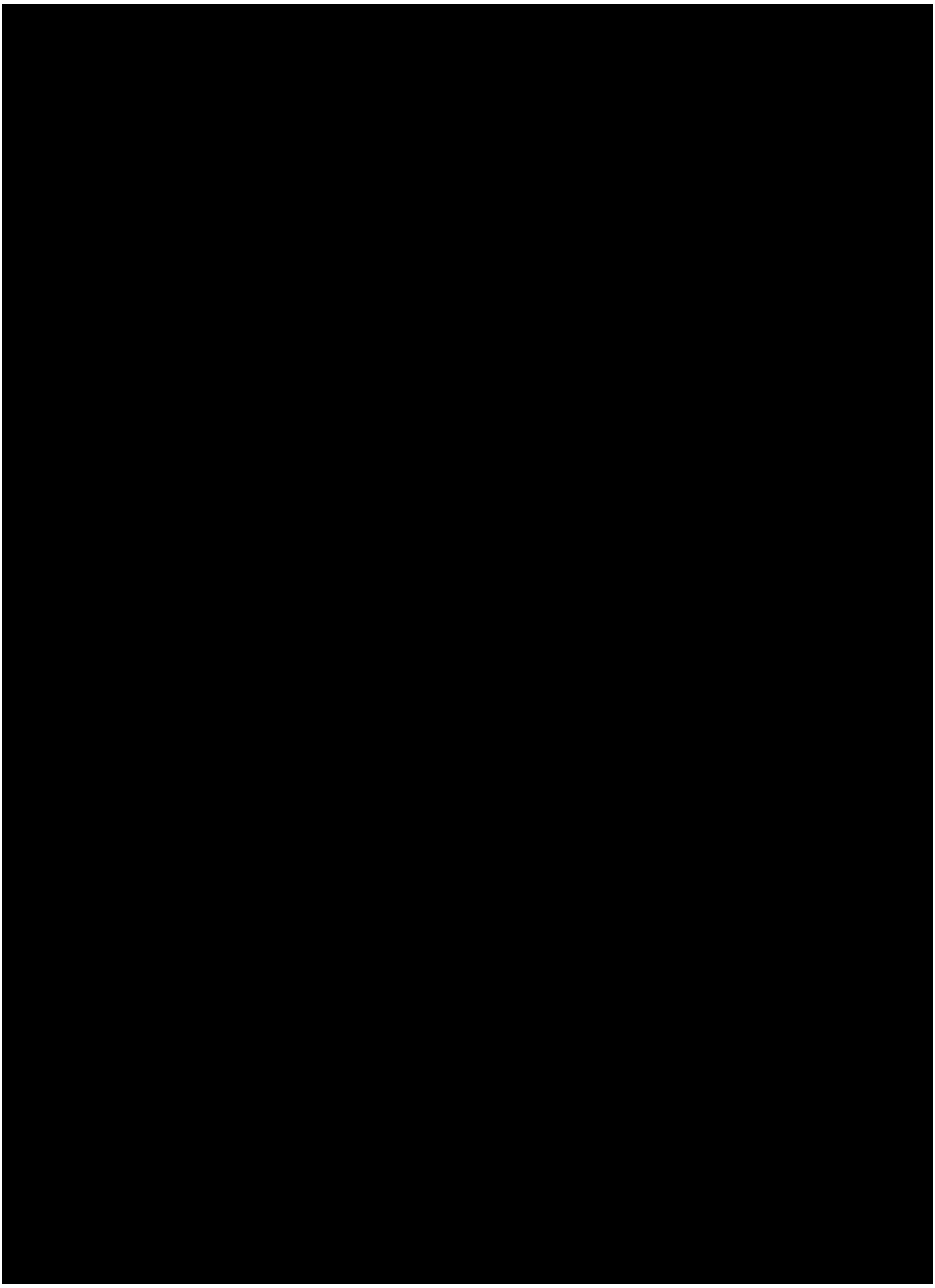
The safety assessments selected are standard for this indication/patient population.











9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued under the following circumstances:

- Patient/guardian decision
- Physician decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the patient
- Following emergency unblinding
- Disease progression per RECIST 1.1 (as assessed by the investigator confirmed by BIRC). In some circumstances, patients may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1, refer to Section 6.1.5.1.
- Study terminated by the sponsor

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient’s premature discontinuation of study treatment and record this information.

Patients 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 'Withdrawal of Informed Consent' section). **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 patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section (Section 6.6.2).

For patient's who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent as applicable, tumor assessments must continue to be performed until documented disease progression as determined by investigator and confirmed by BIRC, death, lost to follow-up, or withdrawal of consent as applicable.

In some circumstances patients may be allowed to continue to receive study treatment beyond disease progression as per RECIST criteria. These patients will continue assessments as outlined in the assessments section, and will complete the EOT visit only after permanent discontinuation of study treatment.

9.1.2 Withdrawal of informed consent

Withdrawal of consent/opposition to use of data/ and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data,

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 as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her/exercise data/privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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 patient 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 withdrawal of consent/exercise data/privacy rights should be made as detailed in the assessment table.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent, (or exercise other participants' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to patients enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 patient's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

The primary analysis will occur when approximately the required number of 95 PFS events as per BIRC assessment is reached and all randomized patients have completed approximately 16 weeks of follow-up or have discontinued before (refer to the Section 12). At this time, the primary clinical study report (CSR) will be produced. After the primary analysis of PFS, the study will remain open provided the PFS demonstrates treatment benefit. Patients still being followed on the study after the primary analysis time point will continue as per the schedule of assessments.

The study will end at the time of the LPLV, once the final OS analysis is performed approximately when all patients have been followed for at least 3 years (i.e. 3 years after last

patient first treatment) or when statistical significance is reached for OS analysis (see Section 12.5.1.1 and Section 12.7) whichever occurs first and the final analysis of study data is conducted. All available data from all patients up to this cutoff date will be analyzed.

At the end of the study, every effort will be made to continue provision of study treatment outside this study through PTA (see Section 6.1.3) for patients who in the opinion of the Investigator are still deriving clinical benefit. If the primary analysis of PFS does not demonstrate treatment benefit, the follow-up for OS will end.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation patient 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 patient and identifying adverse events.

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

For patients who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

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

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 Common Toxicity Criteria (CTC) AE grade (version 4.03). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life threatening, and death related to the AE corresponding respectively to Grade 1 - 5, will be used
2. 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 underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. 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
6. Its outcome

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 patient.

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 following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered /not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (as per RECIST 1.1 criteria), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

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 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,
- are considered clinically significant,

- require therapy, or require change in study medication(s).

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with the underlying disease.

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 patient 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
- 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 patient'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 patient 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 patient 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 new 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.

All reports of intentional misuse and abuse of the study treatment are also considered serious adverse events irrespective of whether a clinical event has occurred.

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 patient safety, every SAE, regardless of causality, occurring after the patient 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 obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE (with paper backup) Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the patient has provided informed consent (e.g Pre-Screening, Screening) until the time the patient is deemed a Screen Failure must be reported to Novartis.

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 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.

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.

For patients with unknown BRAF V600 mutation status and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (e.g. molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known BRAF V600 mutation status who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial patient becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial patient. The patient must be given adequate time to read, review and sign the pregnancy consent form. The consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure patient 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. The collection of this information could last for up to 12 months following the birth of the child.

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 patient 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, patient 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.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate 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.

10.2 Additional Safety Monitoring

10.2.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

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 patient 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 (or designated CRO) 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 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.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who

will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) 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 **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Describe procedures for the identification of data to be recorded directly on the CRF considered as source data. Source documents provide evidence for the existence of the patient, and substantiate the integrity of data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in, e.g. source data acknowledgment or monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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 CRA organization. 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 patient 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 patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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 patients will be disclosed.

12 Data analysis and statistical methods

The primary analysis including safety and efficacy data will be conducted after approximately 95 PFS events have been reported as per BIRC assessment and all randomized patients have completed approximately 16 weeks of follow-up (e.g. corresponding to the second scheduled post-baseline tumor assessment) or have discontinued earlier. The final OS analysis will be performed once all patients will be followed for at least 3 years.

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 patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

The Safety Set includes all patients who received at least one dose of any component of the study treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The crossover population may be used to summarize the analyses performed on data collected after the crossover, if applicable: it includes all patients who received at least one dose of any component of the open-label study treatment.

The ocular event evaluable set comprises all patients from the safety set who have at least two on-treatment optical coherence tomography (OCT) assessments.

[redacted]

12.2 Patient demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS and Safety set.

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, by treatment group.

12.3 Treatments

The Safety set 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 exposure related analyses will be presented by treatment group.

The duration of exposure in weeks to study treatment and for each study drug (dabrafenib, trametinib) will be presented. 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 for each study drug component by means of descriptive statistics.

The number of patients with dose adjustments (reductions, interruptions, or permanent discontinuation) and the reasons will be summarized for each study drug, by treatment group. All dosing data will be listed.

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary estimand

The primary variable of the primary estimand, PFS, is defined as the time from the date of randomization to the date of the first documented progression according to RECIST 1.1 based on BIRC assessment, or death due to any cause. In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment before the start of a new antineoplastic therapy, if any, if no PFS event is observed prior to the analysis cut-off date using the censoring options from Table 16-5 of the appendix Section 16.1 based on options A(1), C2(1), D(1), E(1), and F(2). Censoring conventions (e.g. handling of missing values, censoring, discontinuation, crossover) are provided in Section 12.4.3.

12.4.2 Statistical model, hypothesis, and method of analysis

The following null hypothesis will be tested at one-sided 2.5% level of significance.

$H_{01}: \theta_1 \geq 1$ vs. $H_{A1}: \theta_1 < 1$

where θ_1 is the PFS hazard ratio (dabrafenib and trametinib versus placebo).

The primary endpoint of PFS will be analyzed at the primary analysis, tested using the log-rank test stratified by randomization stratification factors.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS and PFS Kaplan-Meier estimate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arm. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test.

12.4.3 Handling of remaining intercurrent events of primary estimand

The intercurrent events for the primary estimand and handling strategies are described in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

In the primary analysis, PFS will be censored at the last adequate tumor assessment before the start of a new antineoplastic therapy, if any, and performed on or before the analysis cut-off date, if no PFS event is observed prior to the analysis cut-off date. Clinical deterioration will not be considered as documented disease progression.

If a PFS event is observed after two or more missing tumor assessments, then PFS will be censored at the last adequate tumor assessment (prior to the first missing assessment and before the PFS event). If a PFS event is observed after the start of a new antineoplastic therapy, then PFS will be censored at the last adequate tumor assessment prior to the start of the new antineoplastic therapy. Patients without any post-baseline tumor assessment and who did not die will be censored at the time of randomization. Censoring rules for PFS follow the censoring options from Table 16-5 of the appendix Section 16.1 based on options A(1), C2(1), D(1), E(1), and F(2).

12.4.5 Sensitivity analyses for primary estimand

As a sensitivity analysis, PFS as per local investigator assessment will be analyzed using the same analytical conventions as the primary analysis.

To assess the impact of stratification, the hazard ratio and 95% confidence interval for PFS based on BIRC assessment will be obtained using the unstratified Cox regression model.

Additional sensitivity analyses may be detailed in the SAP.

12.4.6 Supplementary analysis

As supplementary analyses performed in the FAS, the hazard ratio and 95% confidence interval for PFS based on independent review will be obtained from:

- A stratified and covariate-adjusted Cox model including as potential covariate the following: ECOG ((1 and 2) vs 0). The final covariates will be pre-specified in the SAP.

An additional supplementary analysis will handle the intercurrent event of a new antineoplastic therapy started using treatment policy strategy: all PFS events will be considered regardless of the start of a new antineoplastic therapy. The target population, the primary variable, other intercurrent events and summary measure will be the same in this supplementary analysis as for the primary estimand.

If the primary analysis of PFS is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed for the following subgroups:

- Gender (male vs female)
- Age (<65 vs. ≥ 65 years)
- Region (Asia vs North America vs rest of the world)

- Type of prior treatment received (lenvatinib vs others)
- Number of prior VEGFR targeted therapies (1 vs 2)
- Baseline TSH (≤0.5 vs >0.5 mIU per liter)
- Baseline thyroglobulin (≤10 vs. >10 ng/ml)

Additional subgroup analyses with different definition or variables as well as additional supplementary analyses (e.g., handling potential impact of any unforeseen events like a pandemic, epidemic or natural disaster on treatment effect) may be conducted for PFS. Details will be specified in the SAP.

12.4.7 Supportive analyses

As a supportive analysis, the number of patients censored and reason for censoring will be summarized by treatment group using descriptive statistics, presented separately for BIRC and local assessment.

As supportive analysis, PFS based on investigator assessment may be performed on the population of placebo patients who crossover to dabrafenib plus trametinib treatment, if sufficient number of patients, and will be defined as the time from the day of the first dose of dabrafenib and trametinib treatment to the date of the first documented disease progression according to RECIST 1.1 as per investigator assessment, or death due to any cause. Further details may be found in the statistical analysis plan.

12.5 Analysis of secondary endpoints/estimands

The secondary objectives in this study are to compare the two treatment groups with respect to ORR, OS, and to evaluate the DOR and safety.

Overall Response Rate and OS are identified as the key secondary endpoints. A hierarchical testing strategy will be used to control the overall type I error rate : ORR will only be formally tested and interpreted if the primary analysis of PFS is statistically significant. If the ORR achieves statistical significance, then the OS will be tested and interpreted. Please refer to Section 12.7 for full description of the ORR and OS testing strategy.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Key secondary estimands/endpoints

The key secondary estimands are defined in Section 2.2 and as below.

Overall Response rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per BIRC assessment and according to RECIST 1.1 (see Section 16.1 for details). Of note, tumor assessments after the start of open-label dabrafenib and trametinib treatment following crossover for placebo patients are not considered in the BOR derivation .

The following null hypothesis of no difference in ORR based on BIRC assessment using RECIST 1.1 between dabrafenib plus trametinib and placebo treatment arms will be tested using

Cochran-Mantel-Haenszel (CMH) test at a 1-sided significance level of 0.025, stratified by the randomization stratification factors.

H_{02}: $\theta_{1R} - \theta_{2R} = 0\%$ vs. H_{A2}: $\theta_{1R} - \theta_{2R} > 0\%$ where θ_{1R} and θ_{2R} are the ORR for the dabrafenib plus trametinib and placebo arms, respectively. ORR will be calculated based on the FAS, according to the ITT principle and strata assigned at randomization.

The difference in ORR and its 95% confidence interval will be reported.

ORR and its 95% confidence interval based on the exact binomial distribution will be presented by treatment group.

As a supportive analysis, ORR per local investigator assessment will be analyzed using the same method as ORR by BIRC.

Overall Survival

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

The following null hypothesis will be tested at one-sided 2.5% level of significance:

H_{03}: $\theta_2 \geq 1$ vs. H_{A3}: $\theta_2 < 1$

where θ_2 is the OS hazard ratio (dabrafenib plus trametinib versus placebo).

The distribution of OS will be estimated using the Kaplan-Meier method and compared between the two treatment groups using a stratified log-rank test at one-sided cumulative 2.5% level of significance, based on the FAS population. The median OS and OS Kaplan-Meier estimate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arm. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of OS, along with 95% CI based on the Wald test.

Recognizing potential confounding effect of crossover on OS, an attempt may be made to correct estimates with an appropriate model method, for example using Rank Preserving Structural Failure Time (RPSFT) model by Robins and Tsiatis AA. 1991. Further details will be provided in the statistical analysis plan.

12.5.1.2 Other secondary efficacy endpoints

Duration of response (DOR)

Duration of response only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST 1.1 based on BIRC assessment. 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. Patients continuing without progression or death due to any cause will be censored at the date of their last adequate tumor assessment before the start of new antineoplastic therapy, if any. Of note, the definition of DOR uses the same end date and censoring than for PFS analysis, which is different from the definition reported in Section 16.1. DOR will be listed and summarized by treatment group for all patients in the FAS with confirmed BOR of CR or PR. The distribution function of DOR will be

estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment group.

As supportive analyses, DOR may be performed as per local investigator review using the same analytical approach than for the analyses based on BIRC assessment.

12.5.2 Safety endpoints

For all safety analyses except ocular event analyses, the safety set will be used. For the ocular event analyses, both safety set and ocular event evaluable set will be used. All listings and tables will be presented by treatment group.

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

1. Pre-treatment period: from day of patient's informed consent to the day before first administration of the study treatment
2. On-treatment period: from day of first administration of the study treatment to the earlier of
    - 30 days after date of last administration of the study treatment
    - day prior to the start of open-label dabrafenib and trametinib treatment following crossover from placebo
3. Post-treatment period: starting at day 31 after last administration of study treatment or at the first day of open label dabrafenib and trametinib treatment.

Additional observation period may be defined for patients who would crossover from placebo and for which safety data may be summarized for that period. Further details will be provided in the statistical analysis plan.

Adverse events

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

- By treatment, primary system organ class and preferred term.
- By treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

Serious adverse events, non serious adverse events and adverse events of special interest (AESI) during the on treatment period will be tabulated. AESIs will be defined based on the case retrieval strategy (CRS) available at the time of analysis.

As a secondary estimand and supplementary of secondary estimand, incidence, type and severity of ocular events using serous retinopathy grouping term will be summarized by treatment arm using ocular event evaluable set and safety set. 95% confidence interval of the incidence of serous retinopathy event will be as well presented. Serous retinopathy will be defined based on a specific case retrieval strategy for ocular events, listing the appropriate preferred terms falling into the definition of a serous retinopathy.

Analyses using optical coherence tomography data (OCT) as per local and central review may be provided as appropriate. Further details may be found in the SAP.

All deaths (on-treatment and post-treatment) will be summarized overall and separately.

Any adverse events which will be counted for a specific treatment period (like after the crossover timing for patients from placebo) may be summarized and further details may be found in the statistical analysis plan.

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

All vital signs data will be tabulate and listed by treatment group, visit, notable values will be flagged. Summary statistics will be provided by treatment group.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment group. 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 listings/summaries will be generated separately for hematology, and biochemistry tests:

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

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

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

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

Primary endpoint: Progression free survival (PFS)

There is no interim analysis (IA) for PFS. The primary analysis will be performed after approximately 95 PFS events have been reported as per BIRC assessment and all randomized patients have completed approximately 16 weeks of follow-up or have discontinued before. Formal testing of the primary endpoint with full alpha will be performed at the primary analysis.

Key secondary endpoints: Overall Response Rate (ORR) and Overall Survival (OS)

A hierarchical testing procedure will be adopted and the statistical test for ORR will be performed only if the primary analysis of PFS is statistically significant. OS will be tested only if the primary analysis of PFS and key secondary ORR endpoint are statistically significant.

For ORR, there is no interim analysis planned. The analysis will be performed at the time of the primary analysis for PFS (and provided PFS is significant).

For OS, a maximum of two analyses are planned:

- At the time of the primary analysis for PFS (and provided PFS and ORR are significant), at which point a total of approximately 39 deaths are expected (around 31 months from first patient randomized)
- At the time of final analysis for OS when all randomized patients will be followed for at least 3 years.

The type I error rate for OS testing will be controlled by using a one-sided 2-look group sequential design. Specifically, an α-spending function according to Lan-DeMets (Pocock) as implemented in East (6.4) Lan and DeMets DL 1983 to spend sufficient alpha and increase the chance to be positive at interim (given later confounding of OS analysis due to crossover), along with the testing strategy outlined above will be used to maintain the overall type I error probability. This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses at the interim and the final analysis Glimm et al 2010.

The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS and key secondary endpoint ORR have already been shown to be statistically

significant favoring the test treatment arm. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of the earlier interim analysis.

The projected timing of interim and final OS analysis is summarized in Table 12-1.

At the time of primary analysis, PFS, ORR and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment as much as possible and if patients do not crossover to dabrafenib and trametinib arm. All patients will continue to be followed for OS until the final OS analysis.

Table 12-1 Estimated timelines for interim and final OS analyses

Months after randomization of the first patient (approximation)	# PFS Events	Cumulative Power against a PFS hazard ratio of 0.455	# OS events	Cumulative[b] Power against OS hazard ratio of 0.7
31	95 (100%)	96.2%	39 (47.6%) [a]	15.1%
62	-	-	82 (100%) [a]	31.1%
a: Interim/final analysis for OS will only be performed if the final analysis for PFS and key secondary ORR analysis are significant b: Power conditional on PFS and ORR being significant				

NOTE: Simulation is performed in East (6.4) with number of simulations = 10,000 and randomization seed =1234, under alternative hypothesis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the question of interest related to the primary estimand. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on Lenvatinib (Schlumberger et al 2015) and Sorafenib data (Brose et al 2014), including mostly naïve patients (without receiving any prior treatment regimen), the median PFS in the control arm is expected to be around 5 months for this study population.

Under the assumption that the median PFS in the control arm is 5 months, it is expected that treatment with dabrafenib and trametinib will result in a 55% reduction in the PFS hazard rate (corresponding to an increase in median PFS from 5 months to 11 months under the exponential model assumption). If the true HR=0.455 (under the alternative hypothesis), a total of approximately 95 PFS events are required to have 95% power at a one-sided 2.5% level of significance to reject the null hypothesis (HR=1) using a log-rank test. Considering a recruitment period of approximately 26 months from the start of the study with an accrual rate of 1 patient/month for first 4 months, 3 patients/month from 4 to 8 months, 6 patients/month for 9 to 11 months and 8 patients/month thereafter, along with an assumed 8% dropout rate/year, approximately 150 patients will need to be randomized to the two treatment arms in a 2:1 ratio. Given the above assumptions, it is estimated that the 95th PFS event will be observed at approximately 31 months from the date of the first patient randomized in the study. Of note, to achieve 90% power only 77 PFS events would have been needed under the same assumptions.

However, sample size needed to be increased to fulfill the ocular-event analysis regulatory requirement. This results in an increase of the power to ensure also that all patients have been randomized and followed for a minimum follow-up time, at time of primary analysis. The sample size calculation was conducted with software package East 6.4.

12.8.2 Secondary endpoint(s)

Serous retinopathy ocular events incidence

In order to fulfill regulatory requirement, patients will be followed for serous retinopathy ocular events assessment (set of AEs previously reported in patients taking trametinib). No comparison with placebo arm will be done, only the incidence of serous retinopathy events will be provided for the two treatment arms, with specific interest for dabrafenib and trametinib arm, as part of a secondary endpoint. The sample size of 150 total patients randomized will provide acceptable precision for these serous retinopathy ocular events rates. Approximately 100 patients would be randomized in dabrafenib and trametinib arm to get 90 evaluable patients in dabrafenib and trametinib arm assuming a dropout rate of ~10%. With 90 evaluable patients, if the true serous retinopathy ocular events rate with dabrafenib and trametinib treatment is 10% or less, there will be at least 71.3% probability to show that the upper bound of the 95% CI is below 20% (e.g. current serous retinopathy ocular events rate reported for other MEK-inhibitors treatments). Table 12-2 below shows various scenario for the serous retinopathy ocular event rates (and corresponding number of observed events), exact Clopper-Pearson 95% confidence intervals among 90, 150 evaluable patients (as defined in Section 12.1). These calculations were made using R3.4.3.

Table 12-2 95% confidence intervals for serous retinopathy ocular events rates among 90 evaluable patients

# of patients evaluable in dabrafenib and trametinib arm	# of patients with events	Event rate (%)	95% CI (%)
90	4	4.4	(1.2 - 11.0)
	7	7.8	(3.2 - 15.4)
	9	10.0	(4.7 - 18.1)
	10	11.1	(5.5 - 19.5)
	11	12.2	(6.3 - 20.8)
	14	15.6	(8.8 - 24.7)
	18	20.0	(12.3 - 29.8)
150	5	3.3	(1.1 - 7.6)
	10	6.7	(3.2 - 11.9)
	15	10.0	(5.7- 16.0)
	20	13.3	(8.3 - 19.8)
	30	20.0	(13.9 - 27.3)

Overall response rate

Overall response rate, as one the key efficacy secondary objectives, will be formally statistically tested, provided that the primary analysis of PFS is statistically significant. Based on phase II study (Shah et al 2017), it is hypothesized that dabrafenib and trametinib would result in an

overall response rate of 35%. Overall response rate in placebo arm is expected to be around 1%. The number of patients planned to be enrolled (e.g. 150 patients), will provide sufficient power (>99%) to reject the null hypothesis of no difference in overall response rate between treatment arms, using a Cochran-Mantel-Haenszel (CMH) test at a 1-sided significance level of 0.025. The overall response rate analysis will be performed at the time of the primary analysis. These calculations were made using the software package East 6.4.

Overall survival

Overall survival, as one of the key secondary objectives, will be formally statistically tested, provided that the primary analysis of PFS and key secondary ORR endpoint are statistically significant and using a 2-look group sequential design with Lan-DeMets (Pocock) alpha spending function. Based on data (Schlumberger et al 2015, Cabanillas et al 2017), the median OS in the control arm is expected to be around 24 months. It is hypothesized that treatment with dabrafenib and trametinib will result in a 30% reduction in the hazard rate for OS, i.e., an expected hazard ratio of 0.70 (which corresponds to an increase in median OS to 34.3 months under the exponential model assumption). This study is not designed to be powered for overall survival and considering the confounding of OS due to crossover of placebo patients to the dabrafenib and trametinib arm early at time of disease progression (confirmed by independent review), there will be only a low chance (29%) to reject the null hypothesis of OS hazard ratio = 1. Based on the number of patients planned to be enrolled to provide sufficient power for the primary estimand (i.e. 150 patients), assuming 10% drop-out rate per treatment arm per year, and to align with the primary PFS analysis timing after around 31 months from first patient randomized, it is estimated that approximately 39 OS events will be observed. The final analysis will be driven by calendar time and will be performed once all patients will be followed for at least 3 years. These calculations were made using the software package East 6.4.

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 ICH (International Council for Harmonization) 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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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 results website and all required Health Authority websites (e.g. Clinicaltrials.gov, 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.

13.5 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.6 Patient Engagement

The following patient engagement initiatives are included in this study and will be provided, as available, for distribution to study patients at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter

- Plain language trial summary - after CSR publication
- Individual study results - after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients 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 patients.

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 patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient 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.

15 References

References are available upon request

Aashiq M, Silverman DA, Na'ara S, et al (2019) Radioiodine-Refractory Thyroid Cancer: Molecular Basis of Redifferentiation Therapies, Management,and Novel Therapies . Cancers. 11, 1382.

Ancker OV, Krüger M, Wehland M, et al (2020) Multikinase Inhibitor Treatment in Thyroid Cancer. Int J Mol Sci. 21,10

[redacted]

Bray F, Ferlay J, Soerjomataram I, et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424.

Brose MS, Nutting CM, Jarzab, et al (2014) Sorafenib in locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet. 384: 319–328.

Cabanillas ME, de Souza JA, Geyer S, et al (2017) Cabozantinib As Salvage Therapy for Patients With Tyrosine Kinase Inhibitor-Refractory Differentiated Thyroid Cancer: Results of a Multicenter Phase II International Thyroid Oncology Group Trial. J. Clin. Oncol. 17: 3315-3321.

Dhillon AS, Hagan S, Rath O, et al (2007) MAP kinase signalling pathways in cancer. Oncogene 26: 3279-90.

[redacted]

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

Eroglu Z and Ribas A (2016) Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. Ther Adv Med Oncol. 8: 48–56.

Feng RM, Zong YN, Cao SM, et al (2019) Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics. Cancer Commun 39: 22.

Gianoukakis AG, Dutcus CE, Batty N, et al (2018) Prolonged duration of response in lenvatinib responders with thyroid cancer. Endocr. Relat. Cancer 25: 699-704.

Glimm E, Maurer W, Bretz F (2010) Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine, 29: 219– 28.

Goodarzi E, Moslem A, Feizhadad H, et al (2019) Epidemiology, Incidence and Mortality of Thyroid Cancer and their Relationship with the Human Development Index in the World: An Ecology Study in 2018. Advances in Human Biology. Volume 9, Issue 2 . p. 162-167.

Keam B, Kreitzman RJ, Wainberg ZA, et al (2018) Updated efficacy and safety data of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E–mutated anaplastic thyroid cancer (ATC). p. Annals of Oncology, Vol 29, Suppl 8.

Kikuchi A, Singh K, Gars E & Ohgami R S (2022) Histopathology 80, 616–626. https:doi.org/10.1111/his.14591.

Lan KKG, DeMets DL (1983) Discrete sequential boundaries for clinical trials. Biometrika, 70: 659-63.

Liu J, Liu Y, Lin Y, et al (2019) Radioactive Iodine-Refractory Differentiated Thyroid Cancer and Redifferentiation Therapy. Endocrinol Metab (Seoul) 34: 215-25.

Long GV, Flaherty KT, Stroyakovskiy D, et al (2017) Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann. Oncol. 28: 1631-39.

Long GV, Stroyakovskiy D, Gogas H, et al (2014) Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N. Engl. J. Med. 371: 1877-88.

Long GV, Stroyakovskiy D, Gogas H, et al (2015) Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 386: 444-51.

Michels WM, Grootendorst DC, et al (2010) Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010 Jun;5(6):1003-9.

[redacted]

Rashid FA, Munkhdelger J, Fukuoka J, et al (2020) Prevalence of BRAFV600E mutation in Asian series of papillary thyroid carcinoma a contemporary systematic review. Gland Surg. 5:1878-1900.

Robert C, Grob JJ, Stroyakovskiy D, et al (2019) Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma. N. Engl. J. Med. p. 626-636.

Robert C, Karaszewska B, Schachter J, et al (2014) Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 372: 30-9.

Robins JM, Tsiatis AA. (1991) Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun. Statist.-Theory Meth. 20 (8): 2609-31.

Schadendorf D, Amonkar MM, Stroyakovskiy D, et al (2015) Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur. J. Cancer 51 (7): 833-40.

Schlumberger M, Tahara M, Wirth LJ, et al (2015) Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N. Engl. J. Med. 372(7): 621-30.

Shah MH, Wei L, Wirth LJ, et al (2017) Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma. Journal of Clinical Oncology. Vol 35: Issue 15 Suppl.

Siegel RA, Miller KD, Jemal A (2020) Cancer Statistics 2020. Cancer J Clin 69 (1):7-347–30.

Stacey A, Byfield D, Adejoro O, et al (2019) Real-World Treatment Patterns Among Patients Initiating Small Molecule Kinase Inhibitor Therapies for Thyroid Cancer in the United States. Adv Ther. 36(4):896–915.

Stjepanovic N, Velazquez-Martin JP and Bedard PL (2016) Ocular toxicities of MEK inhibitors and other targeted therapies. Annals of Oncology 27: 998–1005.

Subbiah V, Kreitman RJ, Wainberg ZA, et al (2018) Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600–Mutant Anaplastic Thyroid. Cancer. J Clin Oncol. 1:7-13..

The Lancet (2018) GLOBOCAN 2018: counting the toll of cancer. Lancet 392:985.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J. Natl. Cancer Inst. 92(3): 205-16.

16 Appendices

16.1 Appendix 1: RECIST 1.1: 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

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.

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 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 10 mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5 mm 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.
  - '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, 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 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 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 subject 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.

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 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.

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. ³ 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.

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 ³ 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.

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) > 7 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression < or = 17 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 7 weeks or early progression within the first 17 weeks)

The time durations specified in the SD/PD/UNK definitions above are based on a 8 week tumor assessment frequency. E.g. if the assessment occurs every 8 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 7 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 (³30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ³20% 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)

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 medication 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.

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 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.

16.1.3.2.6 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. Fist Patient First Visit (FPFV) to Last Patient Last Visit (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.

16.1.3.2.7 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 will be used as the start date.

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

- 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.

16.1.3.2.8 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 be incorporated in an appropriate manner as described below.

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.

16.1.3.2.9 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 (Report and analysis plan) 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:

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)	As per above situations Censored Censored Event

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
		(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	
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.

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.

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 specification 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
- Patient/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:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Patient/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.

16.1.5 Programming rules

The following should be used for programming of efficacy results:

16.1.5.1 Calculation of "time to event" validation

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

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.

16.1.5.2 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.

16.1.5.3 Incomplete assessment 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.

16.1.5.4 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)'.

16.1.5.5 Study/project specific programming

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

16.1.5.6 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 16-2)
- 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.