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DRB436/dabrafenib and TMT212/trametinib

Clinical Trial Protocol CDRB436F2410 / NCT03551626

COMBI-APlus: Open-label, phase IIIb study of dabrafenib in COMBInation with trametinib in the Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm (Plus)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	*bis in diem*/twice a day
BUN	Blood Urea Nitrogen
CD-ROM	Compact Disc - Read Only Memory
CFR	Code of Federal Regulation
CI	Confidence Interval
CLDN	Complete Lymph Node Dissection
CRF	Case Report/Record Form (electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common Toxicity Criteria
cuSCC	Cutaneous Squamous Cell Carcinoma
DAR	Dose Administration Record
DBP	Diastolic Blood Pressure
DDI	Drug-drug Interaction
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DMFS	Distant Metastasis-Free Survival
DMSO	Dimethyl Sulfoxide
DOR	Duration of response
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EoT	End of Treatment
EoS	End of Study
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-M	Functional Assessment of Cancer Therapy–Melanoma
FDA	Food and Drug Administration
FFR	Freedom From Relapse
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQOL	Health-Related Quality Of Life
IA	Interim Analysis
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFNα	Interferon alfa
IRB	Institutional Review Board

IRT	Interactive Response Technology
LFT	Liver Function Test
LLN	Lower Limit of Normal
LPFV	Last Patient First Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical dictionary for regulatory activities
MUGA	Multigated acquisition scan
NSAID	Non-Steroidal Anti-Inflammatory Drugs
ORR	Overall response rate
OS	Overall Survival
PE	Pulmonary Embolism
PFS	Progression-free Survival
PHI	Protect Health Information
PP	Predictive Probability
PPES	Palmar-Plantar Erythrodysesthesia
PRO	Patient Reported Outcome
PS	Performance Status
QD/q.d.	*quauque die*/once daily
RPED	Retinal Pigment Epithelial Detachment
RFS	Relapse-free Survival
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SLNB	Sentinel Lymph Node Biopsy
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL	Total Bilirubin
TLND	Full therapeutic lymph node dissection
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic specimen	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient
Dosage	Dose of the study treatment given to the subject in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug".
Investigational treatment	All investigational drug(s) whose properties are being tested in the study. This includes approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage. Investigational treatment is synonymous with study treatment.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest for the study
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Subject number	A unique identifying number assigned to each patient who is consented in the study.
Relapse	Used interchangeably with recurrence to indicate the return of disease after treatment
Report and Analysis Plan	A regulatory document which provides evidence of preplanned analyses
Screen Failure	A subject who is screened but is not treated or randomized
Stage-related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment, in this case, refers to the investigational treatment.
Subject	An individual who has consented to participate in this study.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points.
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CDRB436F2410
Full Title	COMBI-APlus: Open-label, phase IIIb study of dabrafenib in COMBInation with trametinib in the Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorithm (Plus)
Brief title	Phase IIIb study for the effectiveness of an adapted pyrexia AE-management algorithm with dabrafenib in combination with trametinib in stage III BRAF V600 mutation-positive melanoma after complete resection
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The COMBI-AD study experienced a higher percentage of AEs leading to permanent study drug discontinuation than what has been historically seen in the previously pivotal studies of unresectable or metastatic melanoma. Pyrexia is the most frequently observed adverse event with dabrafenib and trametinib therapy. Pyrexia (Grade 3/4) led to hospitalization (11%) and permanent treatment discontinuation (9%) in the adjuvant COMBI-AD study. In the COMBI-APlus study, optimal management of pyrexia will be assessed to reduce adverse outcomes in pyrexia (Grade 3/4 pyrexia, hospitalization due to pyrexia, and permanent treatment discontinuation due to pyrexia). In fact, a recently published clinical guideline suggests that an improved algorithm for pyrexia management, which focuses on early detection of pyrexia, early interruption of dabrafenib and trametinib treatment, and recommended use of anti-inflammatory medications to prevent and treat pyrexia may reduce adverse outcomes in the management of dabrafenib and/or trametinib-induced pyrexia. The goal of this phase III study is to reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control from COMBI-AD study.
Primary Objective(s)	The primary objective of this study is to assess whether an adapted AE- management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control
Secondary Objectives	• Evaluate the Relapse-free survival (RFS) rate at 12 and 24 months • Evaluate the Overall survival (OS) rate at 12 and 24 months • Evaluation of pyrexia • Evaluate safety (AEs and SAEs) and tolerability: the overall AE rate leading to permanent treatment discontinuation by 12 months • Assess quality of life
Study design	This is an open-label Phase IIIb study of dabrafenib in combination with trametinib in the adjuvant treatment of melanoma after complete resection. Approximately 600 subjects will be enrolled to receive dabrafenib (150 mg BID) and trametinib (2 mg once daily) combination therapy for 12 months. At Day 1, subjects will be instructed on the pyrexia management algorithm. Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment. There will be an Interim Analysis (IA) of the primary endpoint and secondary efficacy endpoint RFS when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier). For this study, one study month is equal to 4 weeks or 28 days. This study consists of two Periods for Enrolled subjects: • Treatment Period - subjects will receive up to 12 months of treatment. • Follow-up Period - subjects will be followed through 24 months from their first dose date for relapse, and through end of study for overall survival. Follow-up will start once treatment is complete or is prematurely discontinued and continue through the end of the study, regardless of disease recurrence. Follow-up contact prior to disease recurrence will include clinic visits. Follow-up after disease recurrence will

	be limited to: Patient Reported Outcome information (through 24 months), new anti-cancer therapy initiated after treatment completion, and survival data.
Population	Approximately 600 subjects with completely resected, histologically confirmed, BRAF V600 E/K mutation-positive, high-risk [AJCC ed. 8 Stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC or IIID] cutaneous melanoma, over 18 years old, are expected to be enrolled in this study.

Key Inclusion criteria	The inclusion criteria are as follows:
	• ≥18 years of age
	• Signed informed consent must be obtained prior to participation in the study.
	• Completely resected histologically confirmed cutaneous melanoma stage IIIA (LN metastasis >1 mm), IIIB, IIIC, IIID [AJCC (ed 8)] no more than 12 weeks, from last surgery, before Day 1
	• V600E/K mutation positive using a validated local test
	• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
	• Subject has adequate bone marrow and organ function as defined by the following laboratory values without continuous supportive treatment (such as blood transfusion, coagulation factors and/or platelet infusion, or red/white blood cell growth factor administration) as assessed by laboratory for eligibility:
	  • Hematological
	  • Coagulation
	  • Renal
	  • Hepatic
	• Left ventricular ejection fraction (LVEF) ≥ lower limit of institutional normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan
	• 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

Key Exclusion criteria	The exclusion criteria are as follows: • Uveal or mucosal melanoma • Evidence of metastatic disease including unresectable in-transit metastasis • Received any prior adjuvant treatment, including but not limited to chemotherapy, checkpoint inhibitors, targeted therapy [e.g., BRAF and/or MEK inhibitors], biologic therapy, vaccine therapy, investigational treatment, or radiotherapy for melanoma • Taken an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to Day 1. • Current or expected use of a prohibited medications (other anticancer therapies, other investigational drugs, antiretroviral drugs, herbal remedies, and drugs that are strong inhibitors or inducers of CYP3A and CYP2C8). • Non-melanoma related major surgery or significant traumatic injury ≤ 2 weeks prior to start of study treatment. Minor surgical procedures should be completed 7 days prior to start of study treatment • Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO) • Subjects with known history for testing positive for Human Immunodeficiency Virus (HIV) • Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ • Cardiac or cardiac repolarization abnormality • A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy • History of clinically significant or active interstitial lung disease or pneumonitis • 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 subject's safety, obtaining informed consent, or compliance with study procedures

	• 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 or 2 weeks after stopping treatment with dabrafenib whichever is longer. • Women who are nursing during dosing and for 16 weeks after stopping study treatment • Male subjects (including those that have had a vasectomy) taking study treatment must use a condom during intercourse, and for 16 weeks after stopping treatment, and should not father a child during these periods
Study treatment	The combination of dabrafenib 150 mg twice a day and trametinib 2 mg once a day
Efficacy assessments	Tumor assessment by investigator's assessment measured at Month 3, 6, 12, 15, 18 and 24
Key safety assessments	• Physical examination • ECOG PS • Weight and vital signs • Ophthalmic examination • 12-lead ECGs • ECHO/MUGA • Laboratory assessments, including hematology, chemistry, and coagulation • Monthly pregnancy testing for women of child-bearing potential. • Adverse events (AEs), the severity, the relationship to study treatment and the seriousness
Other assessments	• Patient reported outcome assessment by Melanoma Subscale of the FACT M
Data analysis	• The data will be summarized with respect to demographic, baseline characteristics, safety observations and efficacy measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. • The primary analysis will be based on the calculation of the observed pyrexia event rate (composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia or permanent treatment discontinuation due to pyrexia) and its 95% two-sided exact confidence interval (Clopper and Pearson 1934) up to 12 months of therapy. • The study will meet its primary objective if the upper bound of the two-sided 95% CI is less than 20%. • The secondary endpoints RFS and OS distribution will be estimated by using Kaplan-Meier approach. • One IA for futility of the primary endpoint and the secondary endpoint RFS is planned for the study when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier.) • The sample size of 600 subjects has been chosen so that the study operating characteristics comply with the requirement to have a high probability (> 95%) to declare futility at IA if the true 12-month pyrexia event rate is ≥ 20%.
Key words	dabrafenib, trametinib, adjuvant, melanoma, combination treatment, pyrexia

Amendment 2 (12-Mar-2019)

As of 12-Mar-2019, 86 sites have been initiated, 311 subjects have enrolled into the study, and 234 subjects have started treatment in the study.

Amendment rationale

The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon review of the protocol. In addition, study population inclusion criteria was expanded, clarifications and corrections are made throughout the protocol, as well as editorial change to improve flow and consistency.

Changes to the protocol

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

- Protocol Summary Section updated to match the body of the protocol
- List of Abbreviations was updated
- Section 3 - Study Design: Treatment Period was clarified:
  - One study month is equal to 4 weeks or 28 days.
- Section 5.1 - Inclusion Criteria
  - Removed criteria that patients with unknown primary melanoma are not eligible
- Section 5.2 – Exclusion Criteria
  - Updated that women of child-bearing potential must use highly effective methods of contraception during dosing and for 2 weeks after stopping treatment with dabrafenib instead of 4
- Section 6.5.1.2 Other dose modifications and reductions
  - Added that for study treatment interruptions due to adverse events unrelated to dabrafenib and/or trametinib, approval from Novartis Medical Monitor is required to restart study treatments after ≥28 days interruption
- Table 6-7 Mandatory dose modifications and recommended clinical management guidelines for abnormal liver enzyme test
  - Updated Grade 3 and 4 mandatory dose modifications to indicate dabrafenib and trametinib must be interrupted until recovery to ≤ Grade 1 or baseline and if no recovery to ≤ Grade 1 within 4 weeks, permanently discontinue dabrafenib and trametinib.
- Removed following footnote as patients with metastatic disease are not eligible for study: For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increase by ≥ 50% relative to baseline and last for at least 1 week then the subject should be discontinue
- Table 6-8 Mandatory dose modifications and recommended clinical management guidelines for renal function alterations:
  - Updated recommended management guidelines for Grade 1 creatinine level increase to repeat serum creatinine within 24 hours for any increase in serum creatinine. If the increase in creatinine is confirmed, assess fluid status and consider fluid bolus and

monitor serum creatinine at least every 2 days until back to baseline. Mandatory treatment interruption
    - Updated recommended management guidelines for Grade 2 creatinine level to closely monitor serum creatinine
- Table 6-9 Mandatory dose modifications and recommended clinical management guidelines for rash
    - Guidelines updated for Grade 2 and Grade 3: AE resolution to ≤ Grade 1 or baseline must occur within a period of 4 weeks since a Grade 2 event has been identified
- Table 6-10 Mandatory dose modifications and recommended clinical management guidelines for pneumonitis
    - Guidelines updated for Grade 2: AE resolution to ≤ Grade 1 or baseline must occur within a period of 4 weeks since a Grade 2 event has been identified
- Table 6-11 General guidelines for dose modification for adverse events suspected to be related to dabrafenib and/or trametinib treatment
    - Dose modification language for Grade 4 updated to include restart with dabrafenib and trametinib reduced by one dose level per table 6-5 once toxicity resolved to ≤ Grade 1 or baseline or permanently discontinue dabrafenib and trametinib at the discretion of the investigator.
- Table 6-17 Mandatory dose modifications and recommended clinical management guidelines for diarrhea/colitis
    - Guidelines updated for Grade 3: AE resolution to ≤ Grade 1 or baseline must occur within a period of 4 weeks since a Grade 3 event has been identified
- Table 6-19 Mandatory dose modification and recommended clinical management for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment
    - Clarified for Grade 2-3 RPED, trametinib should only be restarted at a lower dose if improved to ≤ grade 1. If there is no improvement within 3 weeks, trametinib should be permanently discontinued.
- Table 8.1 Treatment Visit and Assessment Schedule
    - Added “X” for pre-screening visit to include molecular consent and demographic information collection
    - Added ECHO/MUGA scan at Month 9 visit
    - Added footnote to indicate Screening and Day 1 Hematology and Clinical Chemistry do not need to be repeated if screening labs are drawn within 3 days of Day 1
- Section 8.1.3 added Information to be collected on pre-screening failures
  Subjects who signed a Molecular Pre-screening Informed Consent Form but are not BRAF V600E/K mutation positive will be considered a pre-screen failure.
  The following eCRFs should be completed for pre-screen failures:
    - Demography
    - Molecular Informed Consent
    - Disposition, including reason for pre-screen failure
    - Biomarker Assessment - BRAF V600 Mutation Result

No other data will be entered into the clinical database for subjects who are pre-screen failures, unless the subject experienced a Serious Adverse Event during Pre-Screening (see Section 10 for SAE reporting details)

- Table 8-3 Follow-up (Post-Relapse) Assessment Schedule
  - Clarified post relapse data collection of disease information will be collected
- Section 10.1.4 Pregnancy Reporting
  - Corrected to reflect this study enrolls women who are considered to be of child-bearing potential using highly effective methods of contraception

IRBs/IECs

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

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

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

Amendment 1 (03-Dec-2018)

As of 30-Nov-2018, 47 sites have been initiated, 58 subjects have enrolled into the study, and 37 subjects have started treatment in the study.

Amendment rationale

The primary purpose of this protocol amendment is to implement clinically relevant feedback received from the Health Authorities and participating center's Ethics Committees upon review of the protocol. In addition, clarifications and corrections are made throughout the protocol as well as editorial change to improve flow and consistency.

Changes to the protocol

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

- Protocol Summary Section updated to match the body of the protocol
- List of Abbreviations was updated
- Glossary of terms: Patient, Personal Data and Withdrawal of study consent definitions updated to align with Novartis template language
- Table 2-1 Objectives and related endpoints, Section 3 Study Design, Section 4.1 Rationale for study design, Section 4.4 Purpose and timing of interim analyses/design adaptations, Section 4.5 Risks and benefits, Section 8.3.1 Efficacy Assessments, Section 10.3.1 Data Monitoring Committee and Section 12.5.1 Efficacy endpoints removed reference to "key" from secondary endpoints
- Section 3 Study Design, Section 4.4 Purpose and timing of interim analyses/design adaptions, Section 4.5 Risks and benefits, Section 10.2.3 Data Monitoring Committee, Section 12.5 Data analysis and statistical methods, and Section 12.7 Interim analyses: language regarding timing of interim analysis has been updated for consistency and clarification
- Section 3 Study Design, Section 5.1 Inclusion criteria number 3, Table 8-1 and Section 8.3 Efficacy, section 8.4.7 Laboratory evaluations: updated the term "enrollment" to "Day 1" or "First dose of study medication" for clarification at which timepoint specific accessments or procedure need to be completed
- Section 4.1 Rationale for study design and Section 6.5.1.1: replaced the term "treatment-related" pyrexia with pyrexia "occurring while on study treatment"
- Section 4.1 Rationale for study design and Section 12.4.1 Definition of Primary Endpoints added clarification detailing how the composite endpoint is calculated
- Section 5.1 Inclusion Criteria:
  - Inclusion Criteria 3: removed "(R0)"; updated to clarify the 12 week window is time from last surgery to Day 1; Patients who have previously had Stage III melanoma are not eligible; Complete nodal resection is not mandatory for microscopic (SNB) disease; Full therapeutic lymph node dissection (TLND) is required for macroscopic disease, as per established treatment guidelines.
  - removed hepatic laboratory requirements for patients with liver metastasis; patients with liver metastasis are not eligible
- Section 5.2 Exclusion Criteria:
  - Updated to exclude patients that have received prior neoadjuvant treatment

  - Updated the timeframe for which females must use highly effective methods of contraction after treatment discontinuation
  - For clarity, rephrased the sentence "Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject." to read "Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that subject"
  - Added hormonal intrauterine device as part of highly effective contraception methods allowed
  - Added "and/or trametinib" to the note on Hormonal-based methods
  - Removed the sentence "No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects" to algin with Novartis template language
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action:
  - Added "Moderate inhibitors or inducers of CYP3A and CYP2C8 are to be used with caution"
  - Clarified that strong inhibitors or inducers of CYP2C8 or CYP3A4 should be avoided and may only be used under special circumstances
  - Added list of the prohibited medications and of medications to be used with caution for reference
- Section 6.5.1 1 Mandatory dose modification and recommended clinical management for pyrexia suspected to be related to dabrafenib and/or trametinib treatment and Table 6-4 Mandatory dose modification and recommended clinical management for pyrexia suspected to be related to dabrafenib and/or trametinib treatment:
  - Added definition of pyrexia syndrome "defined as one or more of the following symptoms: chills/rigors/night sweats; flu-like symptoms" and it's distinction from pyrexia
  - Added "In a minority of cases the pyrexia was accompanied by symptoms such as severe rigors/chills, dehydration, hypotension, dizziness or weakness and required hospitalization"
  - Added "Subjects should be instructed to take non-steroidal anti-inflammatory drugs (NSAID) and/or paracetamol and/or metamizole, as appropriate, to control pyrexia syndrome (i.e. symptoms without documented temperature ≥ 38°C degrees)"
  - Added the use of oral corticosteroids should be considered to manage acute pyrexia refractory to dose interruption and anti-pyretics and to prevent further episodes of pyrexia in those with recurrent pyrexia events
  - Added "subjects experiencing pyrexia higher than 40°C (104°F), and/or pyrexia associated with rigors, severe chills, dehydration or hypotension, serum creatinine and other evidence of renal function should be monitored frequently. The frequency of monitoring must be adapted based on the individual clinical presentation."
  - Added dabrafeinib and trametinib can be interrupted in the presence of the pyrexia syndrome at investigators discretion for recurrent pyrexia and should be restarted upon improvement of symptoms at the same dose if symptom free for at least 24 hours.
  - Added for recurrent pyrexia that cannot be managed with dabrafeinib and trametinib interruption or prophylactic steroids, dose reductions are required

  - Added metamizole as a possible anti-pyretic treatment to be given to patients
- Table 6-8 Mandatory dose modifications and recommended clinical management guidelines for renal function alterations:
  - Updated to reflect NCI-CTCAE v4.03 for acute kidney injury
  - Remove language regarding initiation of steroid treatment from the recommended management guidelines for all grades
  - Added "hospitalization is indicated with frequent creatinine monitoring" for Grade 3 creatinine
- Section 6.5.1.3.14 Mandatory dose modification and management guideline for new malignancies suspected to be related to dabrafenib and/or trametinib treatment: Updated to say "Monitoring should follow institiuional guidelines and/or as clinically indicated"
- Section 6.5.1.3.15 Mandatory dose modification and management guideline for visual changes suspected to be related to dabrafenib and/or trametinib treatment, and Table 6-18: Added recommendation that an ophthalmological evaluation be performed within 24 hours for cases of patient-reported loss of vision or other visual disturbances
- Table 6-19 Mandatory dose modification and recommended clinical management for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment: updated mandatory dose modification requirements for Grade 2-3 RPED
- Tabe 8-1 Treatment Visit and Assessment Schedule:
  - Removed "enrollment" as an assessment from the table
  - Added one additional ECHO/MUGA assessment within eight weeks of initiating treatment (either at Month 1 or at Month 2), to align with product information for LVEF monitoring. Added footnote to clarify hepatitis screening is applicable only for subjects with a history of chronic HBV and/or HCV
  - Added footnote for ophthalmic examinations with reference to section 8.4.5 for details of ophthalmic exams needed and to Table 6-18 for management and dose guidelines
- Table 8-1 Treatment Visit and Assessment Schedule, Table 8-2 Follow-up (Pre-Relapse) Assessment Schedule and Table 8-4 Imaging assessments: Added footnote "CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scan if the CT frequency defined here is not permitted per country or ethics requirements or if CT contrast is contraindicated"
- Section 8.1.1 BRAF V600E/K pre-screening, removed "Verification of locally documented *BRAF* V600 mutation result must be completed prior to enrollment."
- Table 8-4 Imaging assessments and Section 8.3.1.1 Assessment Guideline: deleted "(only if MRI contraindicated or unavailable)"
- Table 8-5 Assessments and Specifications: updated title of table and vitals signs specifications to align with Novartis template language
- Table 8-7 Clinical laboratory parameters collection plan: added footnote making Bands optional test for hematology
- Section 8.4.8.1 Electrocardiogram (ECG) and Table 8-8 ECG collection plan for Treatment Period: removed requirement to collect ECGs in triplicates at Screening, Month 6 and Month 12
- Section 9.1.2 Withdrawal of informed consent: updated language to align with Novartis template language

- Section 10.1.3 SAE reporting: deleted the following sentence "complete the SAE Report Form in English, and submit the completed, signed form within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department" this study uses electronic SAE submission
- Section 12.1 Analysis sets, updated to clarify "the Full Analysis Set (FAS) and Safety Set are defined in the same way and comprise all subjects who received at least one dose of study treatment"
- Section 12.4.2 Statistical model, hypothesis, and method of analysis:
  - Revised the analysis of the primary endpoint will be based on the upper limit of the two-sided exact 95% confidence interval (Clopper and Pearson 1934)
  - Added Table 12-1 Exact 95% CI for different observed event rates at primary analysis
- Table 12-4 Operating Characteristics: added footnote clarifying that probabilities are calculated based on the exact binomial distribution
- Term "patient" was updated with "subject" when referring study participants to align with Novartis template language
- Added Appendix 16.1 with AJCC Melanoma Staging Eight Edition

IRBs/IECs

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1 Introduction

1.1 Background

Cutaneous melanoma is the most aggressive form of all skin cancers and has the highest rate of increasing incidence worldwide. The World Health Organization (WHO) estimated that 132,000 melanoma skin cancers occur globally each year (WHO 2017). In the United States (US), it was estimated that there would be 87,110 new cases of melanoma of the skin and an estimated 9,730 people would die of this disease in 2017 (SEER 2017). Surgical excision is the treatment of choice for early cutaneous melanoma and is curative in most cases. However, some patients will subsequently relapse with disseminated disease. High-risk features in the primary tumor (e.g., tumor thickness, ulceration, mitotic rate) and regional lymph node metastasis define patient subsets that are at increased risk for recurrent disease (Balch et al., 2009). Patients with positive Sentinel Lymph Node Biopsy (SLNB) are at higher risk of recurrence, and might be candidates for Complete Lymph Node Dissection (CLND) and/or adjuvant systemic therapy (NCCN V1, 2018). In addition to the recent results with drug therapies, it has been demonstrated by the DeCOG-SLT and the MSLT-2 trials CLND does not improve melanoma-specific survival (Leiter et al., 2016, Faries et al. 2017). It is anticipated that these findings will reduce the number of CLNDs in the management of melanoma (Eggermont et al., 2017).

The overall 5-year relapse-free survival (RFS) rates observed for Stage IIIA, IIIB, and IIIC patients were 63%, 32%, and 11%, respectively. The estimated 5-year survival rates for Stages IIIA, IIIB, and IIIC from the time of the first relapse were 20%, 20%, and 11%, respectively (Romano et al., 2010). According to a multivariate analysis, systemic relapse has been associated with shorter survival than regional relapse, particularly for older patients and patients experiencing a symptomatic relapse. Of note, more than 40% of patients with Stage III melanoma will present with systemic disease at first relapse (observed in 40%, 51%, and 61% of patients with Stage IIIA, IIIB, and IIIC disease, respectively) (Romano et al., 2010).

For patients with completely resected Stage III Melanoma, additional postoperative management options may include high-dose or pegylated IFN, High-dose Ipilimumab, Nivolumab or Dabrafenib/Trametinib for patients with BRAF V600 activating mutation. Selection of active adjuvant treatment in these patients depends on many factors, including patients preference, patient age and comorbidities, and risk of recurrence. (NCCN, V1, 2018)

Prior to the development of checkpoint inhibitor and BRAFV600 targeted therapies, high-dose interferon alfa (IFNα) was the only option for adjuvant treatment of high-risk melanoma that had demonstrated an improvement in overall survival (OS). The use of high-dose IFNα was supported by the results of the Eastern Cooperative Oncology Group (ECOG) 1684 and Intergroup E1694 trials (Kirkwood et al, 1996, Kirkwood et al, 2001, respectively) as well as a meta-analysis that included results from trials with various schedules and doses of IFNα (Kirkwood et al, 2013). Administration of adjuvant high-dose IFNα was associated with numerous serious side effects, including acute constitutional symptoms, chronic fatigue, myelosuppression, hepatotoxicity, and neurologic and psychologic effects, which were experienced to some degree by the majority of patients (Eggermont 2016). IFNα no longer has a well-defined role in the adjuvant setting for cutaneous melanoma. The use of high-dose IFNα for the high-risk node-negative disease may occasionally be an alternative, but its use should be discouraged in favor of clinical trial participation or observation.

Melanoma is a highly immunogenic tumor, initially suggested by observations of spontaneous remissions and identification of lymphocytic responses to primary melanoma (Kirkwood et al.,

2013). With the availability of new therapies (including immune checkpoint inhibitors, agents targeting the BRAF V600 activating mutation and MAPK pathway), significant progress has been made for the treatment of metastatic melanoma, translating into improved progression-free survival (PFS) and OS outcomes (Hodi et al, 2010; Larkin et al, 2015; Larkin et al, 2017; Robert et al, 2015; Long et al, 2015; Robert et al, 2016).

Adjuvant checkpoint inhibitors

Ipilimumab, an immune checkpoint inhibitor targeting CTLA-4, used at a dosage of 10 mg/kg, has shown significant RFS improvement in high-risk Stage III melanoma after complete resection [Hazard Ratio (HR)=0.76, 95% confidence interval (CI): 0.64, 0.89] which later translated into a survival benefit (HR=0.72, 95% CI: 0.58, 0.88) after a median follow-up of 5.3 years (Eggermont et al, 2015; Eggermont et al, 2016). Ipilimumab at a dosage of 10 mg/kg was approved in the adjuvant setting in the US in October 2015. Nivolumab versus ipilimumab have been assessed as adjuvant treatment in resected Stage IIIB, IIIC, or IV melanoma (Weber et al., 2017). The primary endpoint of RFS was met; showing a HR for disease recurrence or death of 0.65 (95 % CI, 0.51 to 0.83; P<0.001) favoring the nivolumab arm. The OS data is not yet mature. Nivolumab at a dosage of 240 mg every 2 weeks in the adjuvant setting was approved in the US in December 2017.

Adjuvant Targeted therapy

In the BRIM8 study, vemurafenib was evaluated as adjuvant treatment in patients with resected BRAF V600 mutant melanoma in two separate cohorts, Stage IIC-IIIB and Stage IIIC. The primary DFS endpoint in the Stage IIIC cohort was not met (HR=0.80; 95% CI 0.54-1.18; p=0.25); the DFS results in the Stage IIC-IIIB cohort showed clinical benefit (HR=0.54; 95%CI 0.37-0.78 p=0.001), although no formal testing was performed. The OS data was not yet mature (Lewis et al., 2017).

The COMBI-AD Study (Study BRF115532, Novartis code: DRB436F2301) evaluated the combination of dabrafenib and trametinib versus two placebos in the adjuvant treatment of advanced melanoma after complete resection. The study enrolled patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk (Stage IIIA, IIIB or IIIC) cutaneous melanoma.

The primary endpoint was RFS, and secondary endpoints included OS, distant metastasis-free survival (DMFS), freedom from relapse (FFR), and safety. The primary endpoint was met, with a 53% decrease in the relative risk of disease relapse or death observed with dabrafenib plus trametinib vs placebo (HR=0.47 [95% CI, 0.39-0.58]; P<0.001; median RFS, not reached in the dabrafenib+trametinib arm vs. 16.6 months in the placebo arm, respectively). RFS benefit with the combination treatment was observed across all patient subgroups analyzed, including BRAF mutation status, sex, age, disease stage, the presence of micro- or macrometastases and/or ulceration, and the number of nodal metastases. The OS results at the first interim analysis showed a favorable trend towards survival benefit in the dabrafenib + trametinib arm. Although the OS data was not mature, results favored the dabrafenib + trametinib arm, (HR, 0.57 [95% CI, 0.42-0.79]; P=0.0006); despite this low P value, the interim statistical significance threshold of P=1.9 × 10-5 was not reached. The combination treatment also resulted in DMFS and FFR improvements (49% and 53%, respectively) consistent with the RFS improvement observed (Long, 2017). In addition, the safety profile of the dabrafenib + trametinib combination in the COMBI-AD study was comparable to that observed in other approved indications, including unresectable/metastatic melanoma where it has been well characterized with consistent results

across two randomized Phase III studies. The AEs were manageable, and no new safety risks were identified.

In unresectable or metastatic melanoma, pyrexia is the most frequently observed adverse event with dabrafenib and trametinib therapy (63% in the COMBI-AD study and 54% in the COMBI-D [MEK115306] and COMBI-V [MEK116513] pooled metastatic melanoma data); the majority of the pyrexia events were of grade 1-2, with the same proportion of grade 3/4 (5%) in both settings. Pyrexia led to hospitalization in 11% of the patients in the adjuvant setting, and a similar proportion of hospitalization is observed in the metastatic setting (12% and 11% in the COMBI-D and COMBI-V, respectively). Pyrexia led to permanent treatment discontinuation in 9% of patients in the adjuvant setting while a lower proportion is observed in the metastatic setting (2% and 3% in the COMBI-D and COMBI-V, respectively). In the adjuvant COMBI-AD study, 87 of 435 patients (20%) in treatment arm experienced at least one of the following adverse outcomes of pyrexia (Grade 3/4 pyrexia, hospitalization due to pyrexia and permanent treatment discontinuation due to pyrexia).

The primary objective of this study is to assess whether an adapted AE-management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control from COMBI-AD study.

Introduction to study treatments

Dabrafenib (Tafinlar®) 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: BRAF V600E, V600K, and V600D. The mechanism of action of dabrafenib is consistent with competitive inhibition of ATP binding.

Dabrafenib was first approved by the FDA in 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with the BRAF V600E mutation. Dabrafenib is currently also approved in the EU, Switzerland, Canada, Australia and multiple other countries for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Prior to initiation of dabrafenib, patients must have confirmation of tumor BRAF V600 mutation. These approvals include the following limitation of use: dabrafenib is not indicated for the treatment of wild-type BRAF melanoma. 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 (Mekinist®) is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2. MEK proteins are critical components of the MAPK pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF and RAS signals through MEK1 or MEK2 proteins. Trametinib was first approved by the FDA in 2013 as a single-agent oral treatment for unresectable or metastatic melanoma in adult patients with BRAF V600 mutations. Trametinib is currently also approved in the EU, Canada, and Australia and multiple other countries for the treatment of adult patients with unresectable or metastatic melanoma. The recommended dose of trametinib is 2 mg once daily (QD).

Dabrafenib in combination with trametinib was first approved by the FDA in 2014 to treat unresectable or metastatic melanoma in adult patients with BRAF V600 mutations. Dabrafenib and trametinib are currently approved in more than 60 countries worldwide as monotherapies and in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. More recently, the combination was approved in the EU, the US,

and Switzerland for the treatment advanced non-small cell lung cancer with a BRAF V600 mutation, and applications for this indication are currently under review in other countries.

Based on the positive results of the COMBI-AD study, applications for the adjuvant treatment of patients with Stage III melanoma with a BRAF V600 mutation, following complete resection, are also being submitted worldwide, and are already under review by a number of health authorities.

Please refer to the local product information for details on the exact indications approved in a given country.

1.1.1 Clinical Experience

The below sections provide an overview on the clinical experience with dabrafenib and trametinib to date. For more details, please refer to the most current dabrafenib and trametinib Investigator's Brochures (IB).

1.1.1.1 Human Pharmacokinetics

Dabrafenib is absorbed orally with a median time to achieve tmax of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 94.5% (90% CI: 81 to 110%). Dabrafenib exposure (Cmax and AUC) increased in a dose-proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat BID dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Dabrafenib binds to human plasma protein and is 99.7% bound. The metabolism of dabrafenib is primarily mediated by cytochromes P450 (CYP) 2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Mean metabolite to parent AUC ratios following repeat dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant. Dabrafenib terminal half-life is 8 hours. Faecal excretion is the major route of elimination after oral dosing, accounting for 71% of a radioactive dose while urinary excretion accounted for 23% of radioactivity.

Trametinib is absorbed orally with a median time to achieve peak concentrations (tmax) of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72%. The increase in exposure (Cmax and AUC) was dose-proportional following repeat dosing. Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single oral dose administration. Steady-state was achieved by Day 15. In vitro and in vivo studies demonstrated that trametinib is metabolized predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolized by glucuronidation. The deacetylation is mediated by the carboxyl-esterases 1b, 1c and 2, with possible contributions by other hydrolytic enzymes. The drug-related material was excreted predominantly in the feces (≥ 81% of recovered radioactivity) and to a small extent in urine (≤20%). Less than 0.1% of the excreted dose was recovered as parent in urine.

Repeated co-administration of dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in a 16% increase in dabrafenib Cmax and a 23% increase in dabrafenib AUC. A small

decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when dabrafenib is administered in combination with trametinib using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib Cmax and AUC are considered not clinically relevant.

1.1.1.2 Drug-drug interaction

Effects of Other Drugs on Dabrafenib:

Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors of CYP3A4 or CYP2C8 may increase concentrations of dabrafenib. Substitution of strong inhibitors of CYP3A4 or CYP2C8 is recommended during treatment with dabrafenib. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) of CYP3A4 or CYP2C8 is unavoidable, patients should be closely monitored for adverse reactions when taking strong inhibitors.

Effects of Dabrafenib on Other Drugs:

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate). International normalized ratio (INR) levels should be monitored more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of dabrafenib with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of efficacy. It is recommended to substitute for these medications or monitor patients for loss of efficacy if the use of these medications is unavoidable.

Trametinib is an inducer of CYP3A4 *in vitro*. However, trametinib's efficacious dose of 2 mg once daily results in a low systemic maximal concentration (22.2 ng/mL or 0.036 μM), relative to its *in vitro* inhibition potency of CYP enzymes and transporters, rendering the risk of an inhibitory effect of trametinib on the PK of co-administered CYP or transporter substrates low.

Trametinib is eliminated primarily via deacetylation and possibly other hydrolases. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. Trametinib is also a substrate of P-gp and BSEP. However, due to its high passive permeability, these active transport processes are likely of limited relevance. Therefore, a clinically relevant effect of a co-administered P-gp or BSEP inhibitor on the PK of trametinib is unlikely.

No clinically relevant drug-drug interaction (DDI) was observed after repeat dosing dabrafenib 150 mg twice daily and trametinib 2 mg once daily.

1.1.1.3 Clinical safety in unresectable or metastatic melanoma

Safety data pooled from the dabrafenib and trametinib combination arms of 2 completed phase III studies in subjects (N=559) with melanoma [COMBI-D and COMBI-V] based on a cut-off date of 13-Mar-2015 are provided below. Data are in comparison to the dabrafenib monotherapy arm (N=211) of the COMBI-D and the vemurafenib monotherapy arm (N=349) of the COMBI-V study. The safety population consists of all subjects who received at least 1 dose of study treatment.

The median duration of follow-up, defined as the time from study start to last contact or death, was 19 months for the combination therapy group, 15 months for the vemurafenib group, and 16 months for the dabrafenib group.

The incidences of subjects with any on-therapy AE, study treatment-related AE, all SAEs, and study treatment-related SAE were similar between the treatment arms. The incidence of AEs leading to study treatment discontinuation, dose reductions, or dose interruptions was similar in the combination therapy group and the vemurafenib arm, and higher than in the dabrafenib monotherapy arm. The rate of fatal SAEs was higher in the combination therapy group compared to the two monotherapy groups. However, no subjects in the combination therapy group had fatal SAEs considered related to study treatment by the investigator.

Common Adverse Events [COMBI-D and COMBI-V studies]

The most commonly occurring AEs (>20%) in subjects treated with dabrafenib in combination with trametinib) were pyrexia, nausea, rash diarrhea, chills, headache, vomiting, hypertension, arthralgia, peripheral edema and cough and the most common Grade 3 or 4 AEs (≥5%) occurring in patients treated with the combination were hypertension and pyrexia.

The most common AEs leading to discontinuation (>1% of subjects) were pyrexia (2% and 3% in the COMBI-D and COMBI-V studies, respectively) and ejection fraction decreased in the combination therapy group.

Adverse events leading to dose reduction or interruption of study treatment [COMBI-D and COMBI-V studies]

In this pooled analysis, 55% of the patients had an AE leading to dose interruption, and 31% of the patients had an AE leading to dose reduction. The most common AEs leading to dose reduction (≥3% of subjects) were pyrexia, and ejection fraction decreased in the combination therapy group. Of the most common events, dose reductions due to pyrexia were more common in the combination therapy group compared with each monotherapy arm.

Of the most common AEs leading to dose interruption, dose interruptions due to pyrexia were more common in the combination therapy group compared with either monotherapy arm.

The incidences of pyrexia and neutropenia were higher (≥10% difference) in the combination therapy group compared with either monotherapy arm. In addition, the incidences of diarrhea, hepatic events, hypertension, and edema were higher (≥10% difference) in the combination therapy group compared with the dabrafenib monotherapy arm only, but similar to vemurafenib, and the incidence of bleeding events was higher in the combination therapy group compared with the vemurafenib monotherapy arm.

Skin Toxicities [COMBI-D and COMBI-V studies]

Skin adverse effects were less frequent in the combination therapy group, especially the events linked to a paradoxical activation of the MAPK pathway, including both benign and malignant skin tumors. This finding is in accordance with preclinical models showing that the addition of MEK inhibitors may down regulate the BRAF inhibitor-induced paradoxical activation of the MAPK pathway. Thus, secondary resistance and paradoxical activation of the MAPK pathway that occurr with BRAF inhibitor monotherapy, which translate into rapid tumor relapses and the emergence of skin cancers, respectively, are both improved by the combination therapy.

For more details, please refer to the most current dabrafenib and trametinib IBs and the approved product information.

1.1.1.4 Clinical efficacy in unresectable or metastatic melanoma

Both dabrafenib and trametinib have proven anti-tumor activity as monotherapy in *BRAF* V600 mutant metastatic melanoma (BREAK 3 and METRIC trials respectively) (Hauschild A, 2012; Schadendorf D, 2017).

The efficacy of dabrafenib and trametinib combination therapy vs. dabrafenib was initially assessed in a randomized Phase II study (BRF113220, Cohort C) (Flaherty et al., 2012). The combination therapy with dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily demonstrated superior PFS over dabrafenib monotherapy. The median PFS in the combination group was 9.4 months as compared with 5.8 months in the monotherapy group (HR=0.39; 95% CI: 0.25 - 0.62; P<0.001). The overall response rate (ORR) with combination therapy was 76%, as compared with 54% in the monotherapy group (P=0.03). At the updated 5-year OS analysis, 28% of patients treated with dabrafenib plus trametinib monotherapy and 13% of patients treated with dabrafenib monotherapy were alive (Long et al., 2017).

Two randomized Phase III trials confirmed the above results and showed that the combination of dabrafenib and trametinib improved OS, PFS, ORR, and duration of response (DOR) versus BRAF monotherapy (either dabrafenib or vemurafenib) in unresectable or metastatic melanoma (Long et al., 2014; Robert et al., 2015; Long et al., 2017).

The COMBI-D study assessed dabrafenib and trametinib versus dabrafenib in patients with untreated metastatic BRAF V600 mutated melanoma and demonstrated a 29% reduction in the risk of death for the combination therapy compared with dabrafenib monotherapy (HR=0.71, 95% CI: 0.55, 0.92; p=0.011) with a median OS of 25.1 months (95% CI: 19.2–not reached) in the combination arm versus 18.7 months (range: 15.2 to 23.7) in the dabrafenib arm. Clinical benefit was observed across all other efficacy parameters and sub-groups analyzed (Long et al., 2017). Additionally, the COMBI-V demonstrated a 31% reduction in the risk of death for the combination therapy compared with vemurafenib (HR=0.69, 95% CI: 0.53, 0.89; p=0.005). The median OS at the time of the analysis was not reached for the combination therapy arm relative to 17.2 months for the vemurafenib monotherapy arm and, as in COMBI-D, clinical benefit was observed across all efficacy parameters and subgroups analyzed (Robert et al, 2015). An updated 3-year efficacy and safety analysis has confirmed a superior efficacy and good tolerability profile supporting the long-term use of the combination across both of these trials (Robert et al, 2016).

1.1.1.5 Clinical efficacy in adjuvant melanoma

The COMBI-AD Study evaluated the combination of dabrafenib and trametinib versus two placebos in the adjuvant treatment of advanced melanoma after complete resection. The study enrolled patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk (Stage IIIA, IIIB or IIIC) cutaneous melanoma.

Please refer to Section 1.1 for details of efficacy study results.

1.1.1.6 Clinical safety in adjuvant melanoma

The safety profile of dabrafenib plus trametinib in the COMBI-AD study is in line with that reported in key trials of the combination in patients with BRAF V600E/K–mutant Stage IIIC unresectable or Stage IV metastatic melanoma (Flaherty et al., 2012; Long, 2017).

A total of 435 patients in dabrafenib+trametinib group and 432 patients in the placebo group were included in the safety analysis. The median daily dose received by the patients was close to the planned dose, indicative of high treatment compliance. The median duration of exposure

in the dabrafenib+trametinib arm was 11 months as compared to 10 months for placebo. Treatment interruptions and reductions were more frequent in the dabrafenib and trametinib arm compared to the placebo arm. Of the AEs that occurred in more than 10% of patients in the combination therapy group as compared to the placebo group, the most frequent were pyrexia (63% vs. 11%), fatigue (47% vs. 28%), nausea (40% vs. 20%), headache (39% vs. 24%), chills (37% vs. 4%) and diarrhea (33% vs. 15%). The percentage of patients with AEs suspected to be related to study treatment were higher in the dabrafenib+trametinib arm (91%) compared to the placebo arm (63%). Most of the AEs suspected to be related to study treatment were grade 1 or 2 in severity.

Grade 3/4 AEs were reported in 41% patients in the dabrafenib+trametinib treatment group and 14% in placebo group; the most frequently reported AEs in the dabrafenib+trametinib arm were hypertension (6%), pyrexia (5%), fatigue (4%), and elevated ALT (4%). Grade 3/4 AEs were not frequently reported in the placebo arm.

While SAEs were reported in both study arms, there was no particular AE that indicated a new safety signal. Pyrexia, chills, and decreased ejection fraction were the most common SAEs, reported in the dabrafenib+trametinib arm. Additionally, 1 patient had a fatal SAE of pneumonia; which was not suspected to be related to study drug.

Most of the deaths occurring during the study were due to disease progression: 90% (54/60) of all deaths in the dabrafenib + trametinib arm and 83% (77/93) in the placebo arm. On-treatment deaths occurred in 4 patients (<1%) in the dabrafenib+trametinib arm and 1 patient (<1%) in the placebo arm. In the dabrafenib+trametinib arm, 1 patient died due to pneumonia (fatal SAE), the 3 remaining deaths were due to disease progression.

Most patients in the combination arm completed the scheduled treatment duration (63% completed all scheduled dabrafenib treatment, and 64% completed all scheduled trametinib treatment); 26% of patients permanently discontinued treatment in the dabrafenib and trametinib arm vs. 3% in the placebo arm. The most common AEs leading to discontinuation common were pyrexia (9%), chills (4%), ALT increase (2%), and headache (2%) of patients.

The observed overall treatment discontinuation rate (26%) is higher than that observed with dabrafenib and trametinib combination in unresectable or metastatic melanoma (13% and 11% in the COMBI-D and COMBI-V studies, respectively) (Robert et al., 2015; Long et al., 2014). This increased discontinuation rate may be explained by a different threshold in patients' tolerability to side effects in the adjuvant setting. While in an adjuvant setting patients are considered cured, in the metastatic setting, the disease is active, and patients may experience symptoms; clinical deterioration is present with a shorter life expectancy. Similar observations have been made between other adjuvant and metastatic trials in melanoma and other tumor types (Hodi et al., 2010, Eggermont et al., 2015, Cuzick et al., 2014, Mehta et al., 2012, Yu et al., 2015, Slamon et al., 2001, Lewis et al. 2017).

Pyrexia-related events were the most frequently observed Adverse Events of Special Interest (AESIs); 67% patients in the dabrafenib and trametinib arm and 15% patients in the placebo arm, and were mostly grade 1 or 2 in severity. Events were managed by a combination of dose modifications and antipyretics, including corticosteroids.

Hepatic disorder-related AESIs were reported in 21% of patients in the dabrafenib and trametinib arm and 3% of patients in the placebo arm; events were primarily grade 1 or 2 increases in transaminases; AST or ALT increases of >5×ULN were reported in 7% of patients and >8×ULN in 2% of patients. Eight patients (2%) met protocol stopping criteria due to liver enzyme abnormalities. Three patients treated in the dabrafenib and trametinib arm had a

concomitant increase of ALT >3×ULN and bilirubin ≥2×ULN; however, confounding factors (including pre-existing liver conditions, high alcohol consumption, reactivation of EBV infection during treatment, and other concomitant medications) excluded these from meeting the criteria for drug-induced liver injury.

The AESI of treatment-emergent malignancies were infrequently reported in the dabrafenib and trametinib group. These comprised cutaneous squamous cell carcinoma (cuSCC) (including keratoacanthoma), non-cutaneous treatment-emergent malignancies, and new primary melanomas. cuSCC was reported in the same proportion in both arms (6 patients, 1%, in the dabrafenib and trametinib arm, and 5 patients, 1% in the placebo arm). Non-cutaneous malignancies were observed in 5 patients (1%) in the dabrafenib+trametinib group and 3 patients (<1%) in the placebo group. New primary melanomas were reported in 1 patient (<1%) in the dabrafenib+trametinib group compared to 6 patients (1%) in the placebo group. The incidence of treatment emergent malignancies was consistent with observations from other melanoma studies using the BRAF and MEK inhibitor combination therapy (Long et al., 2017; Robert et al., 2015).

No new safety signals emerged in the COMBI-AD study; the safety profile was comparable to that observed in other approved indications, with manageable AEs. This consistent safety profile further supports the use of this drug combination, as a more tolerable therapy is desirable in the adjuvant setting, and many healthcare providers are already experienced with the management of therapy-related AEs associated with dabrafenib and trametinib in the metastatic setting (Long, 2017).

The discontinuation rate observed in the COMBI-AD compares favorably to other published adjuvant studies where the discontinuation rates due to AEs were higher (PEGinterferon 37%; IFNα 37%, ipilimumab 52% (Eggermont et al., 2012; Kirkwood et al., 1996; Eggermont et al, 2015)

1.2 Purpose

In the dabrafenib plus trametinib arm of the COMBI-AD study (n=435), 114 patients (26.2%) experienced AEs leading to permanent study drug discontinuation, a higher percentage than what is historically seen in the pivotal studies in unresectable or metastatic melanoma studies (13% and 11% in the COMBI-D and COMBI-V studies, respectively (Robert et al., 2015; Long et al., 2014). In the COMBI-AD study, 289 patients (66%) had AEs leading to dose interruption, and 167 patients (38%) had AEs leading to dose reduction. A similar proportion of dose modifications were observed in the metastatic setting (55% for dose interruption and 31% for dose reductions). The most common AEs leading to treatment discontinuation in the dabrafenib and trametinib arm were pyrexia (9%), chills (4%), ALT increase (2%), and headache (2%).

In unresectable or metastatic melanoma, pyrexia is the most frequently observed adverse event with dabrafenib and trametinib therapy (63% in the COMBI-AD study and 54% in the COMBI-D and COMBI-V pooled metastatic melanoma data); the majority of the pyrexia events were of grade 1-2, with the same proportion of grade 3/4 (5%) in both settings. Pyrexia led to hospitalization in 11% of the patients in the adjuvant setting and a similar proportion of hospitalization is observed in the metastatic setting (12% and 11% in the COMBI-D and COMBI-V, respectively). Pyrexia led to permanent treatment discontinuation in 9% of patients in the adjuvant setting while a lower proportion is observed in metastatic setting (2% and 3% in the COMBI-D and COMBI-V, respectively). In the adjuvant COMBI-AD study 87 of 435 patients (20%) in treatment arm experienced at least one of the following adverse outcomes of

pyrexia (Grade 3/4 pyrexia, hospitalization due to pyrexia and permanent treatment discontinuation due to pyrexia).

Whilst a number of potential hypothesis for the increased permanent treatment discontinuation rates due to pyrexia in the adjuvant setting can be postulated (reduced tolerability threshold for AEs in the adjuvant setting vs metastatic; limited pyrexia AE-management experience at the time of the study conduct), the optimal management of pyrexia has also been the subject of expert discussion. In fact, a recently published clinical guideline suggests that an improved algorithm for pyrexia management, which focuses on early detection of pyrexia, early interruption of dabrafenib and trametinib treatment, and recommended use of anti-inflammatory medications to prevent and treat pyrexia may reduce adverse outcomes in the management of dabrafenib and/or trametinib-induced pyrexia (Atkinson 2016). However, this clinical guideline, including the effectiveness of anti-inflammatory medications to prevent and treat pyrexia, has not yet been prospectively studied.

The objective of this study is to assess whether an adapted AE-management algorithm for pyrexia (Fever $\geq$ 38 °C), will reduce adverse outcomes in pyrexia (Grade 3/4 pyrexia, hospitalization due to pyrexia, and permanent treatment discontinuation due to pyrexia). The targeted patient population for this study overlaps with the one enrolled in the COMBI-AD study and is defined by patients with high-risk [AJCC ed. 8 Stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC or IIID] BRAF V600E/K mutation-positive melanoma after complete resection.

2 Objectives and endpoints

Objectives and related endpoints are described in 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 assess whether an adapted AE- management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control	The composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia by 12 months in overall treated subjects
Secondary objective(s)	***Endpoint(s) for secondary objective(s)***
Secondary Objectives	
RFS rate at 12 and 24 months	RFS is defined as the time from the first dose of the study medication to disease recurrence or death from any cause at 12 and 24 months
OS rate at 12 and 24 months	OS is defined as the time from the first dose of study medication to date of death due to any cause at 12 and 24 months
Other Secondary Objectives	
To evaluate the life quality: Health-Related Quality Of Life (HRQOL) measures assessed using FACT-M	Changes in the HRQOL from baseline will be assessed using by FACT-M questionnaire
To evaluate the overall AE rate leading to permanent treatment discontinuation by 12 months	The proportion of subjects in the study who permanently discontinued treatment due to any Adverse event by 12 months
To evaluate pyrexia	Frequency, number of episodes, duration, AE management (including concomitant medications and study treatment modifications) due to pyrexia

Objective(s)	Endpoint(s)
To evaluate safety (AEs and SAEs)	Safety will be assessed by the frequency and severity of adverse events (AEs), serious AEs (SAEs) and laboratory abnormalities

3 Study design

This is an open-label Phase IIIb study of dabrafenib in combination with trametinib in the adjuvant treatment of melanoma after complete resection. Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [AJCC ed. 8 Stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC or IIID] cutaneous melanoma will be screened for eligibility.

The main purpose of the study is to assess whether an adapted AE-management algorithm for pyrexia (Fever (≥ 38 °C), Section 6.5.1.1), will reduce the incidence of Grade 3/4 pyrexia, hospitalization due to pyrexia and permanent treatment discontinuation due to pyrexia. The effectiveness of dabrafenib and trametinib therapy in this setting will also be assessed based on RFS and OS.

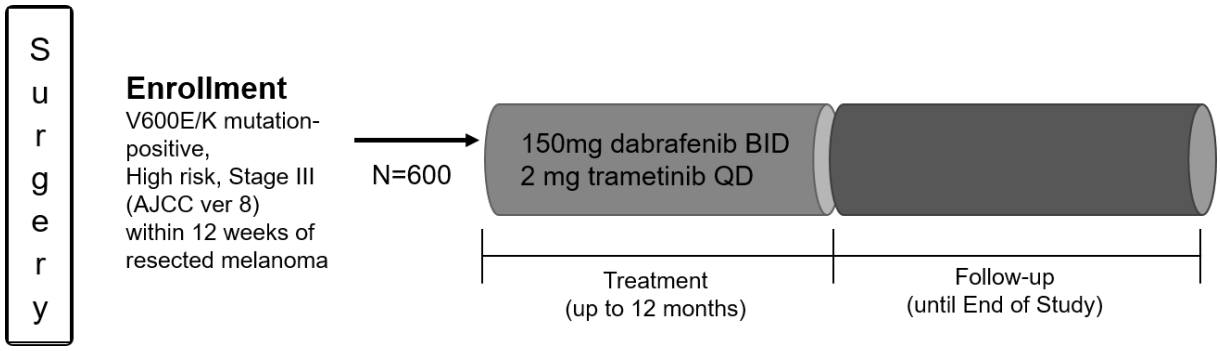
Approximately 600 subjects will be enrolled to receive dabrafenib (150 mg BID) and trametinib (2 mg once daily) combination therapy for 12 months. At Day 1, subjects will be instructed on the pyrexia management algorithm (refer to Section 6.5.1.1). Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment (Section 6.5.1.1). There will be an IA of the primary endpoint and secondary efficacy endpoint RFS when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier (see Section 4.4).

For this study, one study month is equal to 4 weeks or 28 days.

This study consists of two Periods for Enrolled subjects:

- Treatment Period – subjects will receive up to 12 months of treatment (refer to the schedule as noted in Table 8-1).
- Follow-up Period – subjects will be followed from treatment discontinuation through 24 months from their first dose date for relapse; and will be followed for overall survival through withdrawal, lost to follow-up, death, or the end of study (see definition in Section 9.2), whichever occurs first. Follow-up will start once: 1) treatment is completed; or 2) is prematurely discontinued and continue until withdrawal, lost to follow-up, death, or the end of study even if disease recurs. Follow-up contact prior to disease recurrence and through the 24 month assessment will include clinic visits (refer to the schedule as noted in Table 8-2). Follow-up after disease recurrence and until EoS should follow the schedule as noted in Table 8-3.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The COMBI-AD study demonstrated significant improvements with dabrafenib and trametinib in the adjuvant treatment of stage III BRAF V600E/K mutation-positive melanoma and this combination is already recommended in treatment guidelines as a new standard of care (NCCN 2017).

Considering that pyrexia is a common and well-characterized adverse event, it is observed early in the course of dabrafenib and trametinib treatment and presenting multiple occurrences in some patients. Therefore, an adapted pyrexia AE-management algorithm will be prospectively implemented in this single-arm, multicenter, phase IIIb study in order to evaluate the reduction of adverse outcomes of pyrexia (grade 3/4 pyrexia, hospitalization due to pyrexia, and permanent treatment discontinuation due to pyrexia).

This single-arm study does not have a control population. The COMBI-AD study will serve as a benchmark for the incidence of pyrexia over 12 months of treatment, an endpoint that is valid because most events were observed within this period. A phase IIIb, single-arm, non-randomized trial design for this study was chosen over a controlled study to compare AE management algorithms because of logistical issues, as it cannot be predicted which subjects will develop pyrexia while on study treatment. Also, unblinded randomization of different AE management algorithms in a controlled study would be subject to selection bias, and the COMBI-AD study provides a benchmark for historical comparison.

This study will consist of two periods for enrolled subjects: the Treatment period and the Follow-up period. The Treatment Period will enroll approximately 600 subjects with high-risk stage III BRAF V600E/K mutation-positive melanoma after complete resection. Subjects fulfilling the eligibility criteria will be enrolled to receive dabrafenib and trametinib for up to 12 months. The Follow-up Period will include all subjects from study treatment discontinuation through EoS, death, withdrawal of consent, or lost to follow-up, whichever occurs first.

The primary endpoint in the Treatment Period is the composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia among all treated subjects for up to twelve months of therapy.

The rate of the composite primary endpoint is defined as the total number of subjects experiencing at least one of the three components of the composite endpoint (i.e., Grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia), divided by the total number of subjects treated in the study. In the COMBI-AD study, 23 (5%)

subjects had grade 3/4 pyrexia, 46 (11%) subjects were hospitalized due to pyrexia and 38 (9%) subjects permanently discontinued due to pyrexia. In total, in COMBI-AD, 87 out of 435 subjects in the treatment arm (20%) developed either grade 3/4 pyrexia or hospitalization due to pyrexia or discontinued due to pyrexia. This rate of 20% will be used as the historical control rate for the assessment of pyrexia management algorithm in this study.

In the absence of control arm in the study, the composite rate due to adverse outcomes of pyrexia in the study will be compared with the 20% historical rate observed in COMBI-AD study.

As this is the first trial to prospectively test the algorithm, an IA of the primary endpoint and secondary efficacy endpoint RFS at 6 months is planned which will allow assessing the futility of the adapted algorithm. Please refer to Section 4.4.

The secondary endpoints of RFS and OS (12 and 24 months) will be assessed across both periods in the study based on efficacy assessment guidelines in the COMBI-AD study. Subjects will be followed up to EoS, death, withdrawal of consent, or lost to follow-up, whichever occurs first, but will only have on-study tumor assessments through 24 months after first dose of study treatment. Other secondary endpoints include the evaluation of the overall adverse events rate leading to permanent treatment discontinuation at 12 months, overall safety and tolerability, as well as patient-reported outcomes (FACT-M) through 24 months.

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dabrafenib dose

The dabrafenib dose is 150 mg BID (corresponding to a total daily dose of 300 mg) which is the approved dose for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations and the dose, which was tested in the adjuvant phase III study COMBI-AD.

Rationale for trametinib dose

Trametinib will be administered as 2 mg QD, which is the approved dose for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations and the dose which was tested in the adjuvant phase III study COMBI-AD.

Rationale for combination dose

The active biological dose range of trametinib and dabrafenib was established based on pharmacodynamics parameters, assessing dose-dependent tumor changes in phosphorylated ERK, Ki67, and p27 consistent with enzymatic pathway inhibition (Infante et al., 2012; Falchook et al., 2014). The randomized, Phase II doses of trametinib and dabrafenib as single agents were determined to be 2 mg once daily and dabrafenib 150 mg BID, respectively. According to pharmacodynamic models, these doses have shown near to maximum predicted target inhibition. The same doses were confirmed in the COMBI-D study for the trametinib +dabrafenib combination and implemented in pivotal studies in metastatic melanoma (Flaherty et al., 2012; Long et al., 2014; Robert et al., 2015).

The approved doses of dabrafenib 150 mg BID and trametinib 2 mg QD will be used in the Treatment Period of this study, and is aligned with the doses and treatment duration as used in the COMBI-AD trial.

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

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

One IA of the primary endpoint and secondary efficacy endpoint RFS is planned for the study when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier.) This analysis will allow assessing the effect of an adapted pyrexia treatment algorithm on the primary endpoint and RFS at 6 months. As this is the first trial to prospectively test the algorithm, the IA will allow for the assessment of futility of the adapted algorithm. Please refer to Sections 10.2.3 and 12.7.

4.5 Risks and benefits

The risk associated with participation in this study can be modeled after the results of the COMBI-AD study. In this study, a total of 435 patients in dabrafenib and trametinib group and 432 patients in the placebo group were included in the safety analysis. For details on the adverse events observed in the COMBI-AD study, refer to Section 1.1.1.5. For details of efficacy benefits observed, refer to Section 1.1.1.6.

Of the AEs that occurred in more than 10% of patients in the combination therapy group as compared to the placebo group, the most frequent were pyrexia (63% vs. 11%), fatigue (47% vs. 28%), nausea (40% vs. 20%), headache (39% vs. 24%), chills (37% vs. 4%) and diarrhea (33% vs. 15%). The percentage of patients with AEs suspected to be related to study treatment were higher in the dabrafenib and trametinib arm (91%) compared to the placebo arm (63%). Most of the AEs suspected to be related to study treatment were grade 1 or 2 in severity.

Grade 3/4 AEs were reported in 41% patients in the dabrafenib and trametinib treatment group and 14% in placebo group; the most frequently reported AEs in the dabrafenib and trametinib arm were hypertension (6%), pyrexia (5%), fatigue (4%), and elevated ALT (4%). Grade 3/4 AEs were not frequently reported in the placebo arm.

While SAEs were reported in both study arms, there was no particular AE that indicated a new safety signal. Pyrexia, chills, and decreased ejection fraction were the most common SAEs, reported in the dabrafenib and trametinib arm. Additionally, 1 patient had a fatal SAE of pneumonia; which was not suspected to be related to study drug.

In unresectable or metastatic melanoma, pyrexia is the most frequently observed adverse event with dabrafenib and trametinib therapy (63% in the COMBI-AD study and 54% in the COMBI-D and COMBI-V pooled metastatic melanoma data); the majority of the pyrexia events were of grade 1-2, with the same proportion of grade 3-4 (5%) in both settings. Pyrexia led to hospitalization in 11% of the patients in the adjuvant setting, and a similar proportion of hospitalization is observed in the metastatic setting (12% and 11% in the COMBI-D and COMBI-V, respectively). Pyrexia led to permanent treatment discontinuation in 9% of patients in the adjuvant setting while a lower proportion is observed in the metastatic setting (2% and 3% in the COMBI-D and COMBI-V, respectively). In the adjuvant COMBI-AD study 87 of 435 patients (20%) in treatment arm experienced at least one of the following adverse outcomes of pyrexia (Grade 3/4 pyrexia, hospitalization due to pyrexia and permanent treatment discontinuation due to pyrexia).

Besides the already demonstrated efficacy benefit of the adjuvant treatment with the combination of dabrafenib and trametinib, an additional potential benefit for the subjects participating in this study is that they will follow a recently published algorithm for pyrexia management, which may reduce adverse outcomes of dabrafenib and/or trametinib-induced pyrexia (Atkinson 2016). These potential benefits may lead to improved quality of life and may prevent subjects from prematurely discontinuing an efficacious treatment with a potential

negative impact on clinical outcome. Although this adapted algorithm has not been prospectively tested before, the algorithm is not anticipated to adversely impact patient outcomes.

This study incorporates routine safety monitoring and regularly scheduled safety assessments to identify and report any potential safety issues. All subjects must have routine safety evaluations through permanent discontinuation of study drug (See Table 8-1). Comprehensive dose modification, stopping rules and toxicity management plan for drug-related adverse events are provided in Section 6.5.1. Appropriate eligibility criteria as well as specific dose modification and stopping rules along with adverse event management guidelines Section 6.5.1.2, are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., skin toxicity and diarrhea are provided in Section 6.5.1.

The risk to subjects in this trial is further minimized by compliance with the eligibility criteria, study procedures, and close clinical monitoring. In summary, the data from phase I-III studies on the combination of dabrafenib and trametinib indicate that the majority of adverse events in patients receiving dabrafenib and trametinib combination have been manageable. In addition, prior to enrollment, this protocol will undergo appropriate review by local and regional governance bodies including ethics committees and drug regulatory bodies.

As the adverse event management algorithm for pyrexia is being tested prospectively for the first time in this study, an IA for futility has been included after the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier.) At the time of IA, if futility for the primary endpoint or secondary endpoint of RFS is reached, the independent Data Monitoring Committee (DMC) will recommend whether to continue, modify or terminate the trial. In the event the study is terminated due to futility, study subjects currently on treatment who are still deriving clinical benefit will be eligible to receive medication through a locally established Novartis program.

The safety profile of the combination of dabrafenib and trametinib reflects the safety profiles of the individual agents, with adverse events that are manageable with appropriate intervention, as described in the product labeling. No new safety signals were emerged in in the COMBI-AD study; the safety profile was comparable to that observed in other approved indications, with manageable AEs. As observed previously in the melanoma setting, pyrexia remains the most common AE and requires appropriate clinical management.

Taken together, the results of pivotal studies with dabrafenib and trametinib in the metastatic and adjuvant melanoma settings demonstrate the treatment benefit of the combination therapy with an acceptable safety profile with manageable AEs. Thus, the benefit-risk assessment remains positive.

Women of childbearing 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 subject will not reliably comply, they should not be entered or continue in the study.

5 Population

Approximately 600 subjects with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [AJCC ed. 8 Stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC or IIID] cutaneous melanoma, over 18 years old, are expected to be enrolled in this study. BRAF V600E/K mutation status will be determined locally with validated diagnostic kits. Subjects 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 subject who meet all of the inclusion and none of the exclusion criteria are entered into this protocol. Deviation from any entry criterion excludes a subject from enrollment into the study. Subjects will not be permitted to re-screen once they are deemed a screen failure. Subjects who discontinue the study will not be replaced.

5.1 Inclusion criteria

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

1. ≥18 years of age
2. Signed informed consent must be obtained prior to participation in the study.
3. Completely resected histologically confirmed cutaneous melanoma stage IIIA (LN metastasis >1 mm), IIIB, IIIC, IIID [AJCC (ed 8) *see appendix 16.1*] no more than 12 weeks, from last surgery, before Day 1
   a. Subjects presenting with initial resectable lymph node recurrence after a diagnosis of Stage I or II melanoma are eligible.
   b. Patients who have previously had Stage III melanoma at any time are not eligible
   c. Recovered from definitive surgery (e.g. no uncontrolled wound infections or indwelling drains).
   d. Complete nodal resection is not mandatory for microscopic (SNB) disease
   e. Full therapeutic lymph node dissection (TLND) is required for macroscopic disease, as per established treatment guidelines.
4. V600E/K mutation positive using a validated local test
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
6. Subject has adequate bone marrow and organ function as defined by the following laboratory values without continuous supportive treatment (such as blood transfusion, coagulation factors and/or platelet infusion, or red/white blood cell growth factor administration) as assessed by laboratory for eligibility:
   - Hematological
     - Absolute neutrophil count ≥ 1.5×10^9/L
     - Platelet count ≥ 100×10^9/L
     - Hemoglobin ≥ 9 g/dL
   - Coagulation
     - PT/INR and PTT ≤ 1.5 x ULN. Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to Day 1
   - Renal
     - Serum creatinine < 1.5 mg/dL
   - Hepatic

- Total bilirubin ≤ 1.5 x ULN except for subjects with Gilbert's syndrome who may only be included if the total bilirubin is ≤ 3.0 × ULN or direct bilirubin ≤ 1.5 × ULN
- Aspartate transaminase (AST) < 2.5 × ULN
- Alanine transaminase (ALT) < 2.5 × ULN
- Albumin ≥ 2.5 g/dL

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

5.2 Exclusion criteria

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

1. Uveal or mucosal melanoma
2. Evidence of metastatic disease including unresectable in-transit metastasis
3. Received any prior adjuvant or neoadjuvant treatment, including but not limited to chemotherapy, checkpoint inhibitors, targeted therapy [e.g., *BRAF* and/or MEK inhibitors], biologic therapy, vaccine therapy, investigational treatment, or radiotherapy for melanoma
4. Taken an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to Day 1.
5. Current or expected use of prohibited medications (other anticancer therapies, other investigational drugs, antiretroviral drugs, herbal remedies, and drugs that are strong inhibitors or inducers of CYP3A and CYP2C8).
6. Non-melanoma related major surgery or significant traumatic injury ≤ 2 weeks prior to the start of study treatment. Minor surgical procedures should be completed 7 days prior to start of study treatment
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO)
8. Subjects with known history for testing positive for Human Immunodeficiency Virus (HIV)
9. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ
10. Cardiac or cardiac repolarization abnormality, including any of the following:
    - History or current diagnosis of cardiac disease indicating a significant risk of safety for subjects 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)

11. 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 a risk factor for RVO or central serous retinopathy such as:
        - Evidence of new optic disc cupping;
        - Evidence of new visual field defects on automated perimetry;
        - Intraocular pressure >21 mmHg as measured by tonometry.
12. History of clinically significant or active interstitial lung disease or pneumonitis
13. 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 subject's safety, obtaining informed consent, or compliance with study procedures
14. Pregnant or nursing (lactating) women confirmed by a positive hCG laboratory test within 72 hours prior to initiating study treatment.
15. 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 or 2 weeks after stopping treatment with dabrafenib whichever is longer. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    c. Sterilization (at least 6 months prior to screening) for male partners. The vasectomized male partner should be the sole partner for that subject.
    d. Placement of a hormonal or non-hormonal intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.

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

16. Male subjects (including those that have had a vasectomy) taking study treatment must use a condom during intercourse, and for 16 weeks after stopping treatment, and should not father a child during these periods or donate sperm.

6 Treatment

6.1 Study treatment

The term 'study treatment' is used throughout the protocol to describe the combination of dabrafenib 150 mg BID and trametinib 2 mg QD. Study treatment may, therefore, refer to the individual study treatments or the combination of those study treatments.

6.1.1 Investigational and control drugs

Dabrafenib and trametinib will either be sourced as local commercial or provided as global clinical open-label supply. Global clinical open-label supply will be provided in bottles.

Trametinib will be provided as 0.5 mg and 2 mg tablets, and dabrafenib as 50 mg and 75 mg capsules for oral administration.

All dosages prescribed and dispensed to subjects and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF.

Table 6-1 Investigational drug

Investigational (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
dabrafenib 50 mg, 75 mg	Capsules	Oral use	Open-label subject packs; bottles	Novartis or locally
trametinib 0.5 mg, 2 mg	Tablets	Oral use	Open-label subject packs; bottles	Novartis or locally

6.1.2 Additional study treatments

No additional treatment beyond study treatment are included in this trial.

6.1.3 Treatment arms/group

There will be only one treatment arm in the study - dabrafenib 150mg BID (300mg/day) with trametinib 2mg QD. Subjects will be assigned treatment at Day 1.

6.1.4 Guidelines for continuation of treatment

Guidelines on management of common dabrafenib or trametinib associated toxicities and dose modification instructions are provided in Section 6.5.1.

6.1.5 Treatment duration

Subjects will receive study treatment for twelve months or until the subject experiences one of the following: disease recurrence by investigator's assessment, unacceptable toxicity, treatment is discontinued at the discretion of the investigator or the subject, start of a new anti-neoplastic therapy, withdrawal of consent, lost to follow-up, pregnancy, death, or study is terminated by the sponsor.

6.1.5.1 Treatment beyond disease relapse

Post relapse therapy will be permitted during the study in the Follow-up Period per Investigator discretion, but not provided or administered as study treatment.

6.2 Other treatment(s)

During study treatment and until disease relapse, subjects must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer.

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site of any new medication(s) he/she takes after start of study participation. All prescription medications, OTC drugs and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) taken within 28 days or 5 half-lives, whichever is shorter, including vitamins taken within one week prior to dosing must be recorded on the 'Concomitant Medications' or 'Prior or Concomitant non-drug therapies/procedures' eCRF. Prior antineoplastic surgery(ies) are to be recorded on the separate 'Prior Antineoplastic Surgery' eCRF page during screening. Medication entries must be specific to trade name, dose and units, frequency and route of administration, start and discontinuation dates, and reason for therapy. For medications administered one time, the frequency column may reflect "once".

Administration of certain concomitant medications may lead to the requirement for subject to be discontinued. Discussions regarding discontinuation of subjects requiring concomitant medication will be discussed with Novartis on a case-by-case basis.

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g., such as anti-emetics, anti-diarrhea) and safety of the subject are allowed except those prohibited in Section 6.2.2. Please refer to Section 6.5.1.1 for details of supportive care for pyrexia management.

Subjects are permitted to use the following medications during study treatment:

- Antivirus medications to manage HBV or HCV infection and/or prevent reactivation (e.g., tenofovir); supportive care.
- Medications to prevent or treat nausea or vomiting.
- Anti-diarrheal medications (e.g., loperamide) for subjects who develop diarrhea.
- Pain medication to allow the subject to be as comfortable as possible.
- Nutritional support or appetite stimulants (e.g., megestrol).
- Oxygen therapy and blood products or transfusions.
- Inactivated vaccines.
- The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study drug.

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

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

6.2.1.1.1 Dabrafenib

Effect of other drugs on dabrafenib

Based on *in vitro* studies, dabrafenib was shown to be primarily metabolized by CYP2C8 and CYP3A4. Medicinal products that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are likely to increase or decrease, respectively, dabrafenib concentrations. Alternative agents should be considered during administration with dabrafenib when possible. Moderate inhibitors or inducers of CYP3A and CYP2C8 are to be used with caution. See Table 6-3. Drugs that are strong inhibitors or inducers of CYP2C8 or CYP3A4 should be avoided and 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. See Table 6-2.

Effect of dabrafenib on other drugs

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

A partial list of the prohibited medications and of medications to be used with caution is provided in Table 6-2 and Table 6-3 respectively. The list may be modified based on emerging data.

Table 6-2 Prohibited Medications

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, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St. John's wort
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
Antiretroviral	Ritonavir, saguinavir, atazanavir
Hyperlipidemia	Gemfibrozil
Miscellaneous	Conivaptan

Table 6-3 Medication to be used with Caution

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**

USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
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. Consider substitution 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
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone

6.2.1.1.2 Trametinib

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

6.2.2 Prohibited medication

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

- Other anti-cancer therapies
- Other investigational drugs

Although not contraindicated/prohibited, certain medications drugs should be used with caution due to potential drug-drug interactions (see Section 6.2.1.1.1).

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of a subject to enter the study will be coordinated by the sponsor.

6.4 Treatment blinding

Not applicable

6.5 Dose modification

Guidelines on management of common dabrafenib or trametinib associated toxicities and dose modification instructions are provided in Section 6.5.1.

6.5.1 Dose modifications

The starting dose for subjects enrolled in the trial is set at 150 mg dabrafenib BID and 2 mg trametinib QD. Please refer to Section 4.2 for more details on the dose rationale.

6.5.1.1 Mandatory dose modification and recommended clinical management for pyrexia suspected to be related to dabrafenib and/or trametinib treatment

For the purpose of this study, pyrexia is defined as fever occurring while on study treatment (≥ 38°C) and pyrexia syndrome is defined as one or more of the following symptoms: chills/rigors/night sweats; flu-like symptoms. The incidence and severity of pyrexia are increased when dabrafenib is used in combination with trametinib compared to dabrafenib monotherapy. In a minority of cases the pyrexia was accompanied by symptoms such as severe rigors/chills, dehydration, hypotension, dizziness or weakness and required hospitalization.

Dabrafenib **and** trametinib must be interrupted promptly at the onset of pyrexia and should be restarted upon the improvement of symptoms at the same dose if symptom-free (temperature < 38°C) for at least 24 hours.

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

- a period of 4 weeks of treatment has elapsed since treatment is restarted at the lower dose level and there is no recurrence of the AE
- the subject is deriving clinical benefit

Subjects should be comprehensively educated and receive written guidance regarding febrile episodes before starting study drug treatment and also be instructed on the importance of immediately reporting febrile episodes or pyrexia syndrome.

Subjects should be instructed to take non-steroidal anti-inflammatory drugs (NSAID) and/or paracetamol and/or metamizole, as appropriate, to control pyrexia syndrome (i.e. symptoms without documented temperature ≥ 38°C degrees)

In the event of a fever (≥ 38°C).

- The subject should immediately stop both dabrafenib and trametinib
- The subject should be instructed to take non-steroidal anti-pyretics, as appropriate, to control fever.
- The use of oral corticosteroids should be considered to:
  - manage acute pyrexia refractory to dose interruption and anti-pyretics (paracetamol, NSAIDs)
  - prevent further episodes of pyrexia in those with recurrent pyrexia events i.e. prophylaxis
  - In subjects experiencing pyrexia higher than 40°C (104°F), and/or pyrexia associated with rigors, severe chills, dehydration or hypotension, serum creatinine and other evidence of renal function should be monitored frequently. The frequency of monitoring must be adapted based on the individual clinical presentation.
  - Clinical evaluation for infection and hypersensitivity is recommended for subjects experiencing pyrexia not resolving within 24 hours

Dabrafeinib and trametinib can be interrupted in the presence of the pyrexia syndrome (i.e. chills or rigors or night sweats or flu-like symptoms without documented temperature ≥ 38°C degrees) at investigators discretion for recurrent pyrexia and should be restarted upon improvement of symptoms at the same dose if symptom free for at least 24 hours.

If recurrent pyrexia cannot be managed with dabrafeinib and trametinib interruption or prophylactic steroids, dose reduce as per Table 6-5.

Pyrexia accompanied by hypotension, dehydration requiring intravenous fluids, renal insufficiency and/or severe (≥ Grade 3) rigors/chills in the absence of an obvious infectious cause should be reported as a SAE.

Guidelines for dose modification and management for pyrexia considered to be related to dabrafenib and/or trametinib are provided in Table 6-4.

Table 6-4 Mandatory dose modification and recommended clinical management for pyrexia suspected to be related to dabrafenib and/or trametinib treatment

Pyrexia (≥ 38°C)		
Occurrence	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
1st occurrence and subsequent occurrences	• Educate subject about pyrexia and its associated syndrome (chills or rigors or night sweats or flue like symptoms) to ensure prompt recognition and reporting • Clinical evaluation for infection and hypersensitivity [b] • Laboratory work-up [b] • Prompt administration of anti-pyretic treatment with non-steroidal anti-inflammatory drugs (NSAID) and/or paracetamol and/or metamizole at the onset of pyrexia [a] or of pyrexia syndrome • Recommend oral corticosteroids (i.e., prednisone 10 mg/d) for at least 5 days or as clinically indicated[c] • Optimize oral corticosteroid dose as clinically indicated for pyrexia that cannot be managed with dose interruptions[c] • Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.	• Dabrafenib and trametinib must be interrupted promptly at the very first observation of pyrexia and should be restarted upon resolution of pyrexia (temperature < 38°C) at the same dose if pyrexia free at least 24 hours*. • If recurrent pyrexia cannot be managed with interruption or prophylactic steroids, dose reduce as per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. • Note: proactive intermittent dosing is not allowed.

* Dabrafenib and Trametinib can be interrupted in the presence of pyrexia syndrome (i.e. symptoms without documented temperature ≥ 38°C degrees) at investigator discretion for recurrent pyrexia.

[a.] Anti-pyretic treatment should be started immediately at the onset of pyrexia or pyrexia syndrome, and prophylactic anti-pyretic treatment is recommended. Anti-pyretic treatment may include acetaminophen, ibuprofen, metamizole, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment is recommended to be discontinued after three days in the absence of pyrexia.

[b.] For subjects experiencing pyrexia not resolving within 24 hours, if clinically indicated by the treating physician, ~~a~~ clinical evaluation and laboratory work-up, thorough clinical examination for signs and symptoms of infection or hypersensitivity may be performed. 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.

[c.] Corticosteroids are recommended for recurrent pyrexia that cannot be managed with dose interruptions and anti-pyretic treatments and for pyrexia associated with complications. This recommendation may be superseded by local institutional guidelines where available, or the investigator's discretion on how to best manage a given subject.

6.5.1.2 Other dose modifications and reductions

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

Three dose reductions for dabrafenib and two dose reductions for trametinib are permitted. If more dose reductions of dabrafenib and trametinib are required, the subject must be permanently discontinued from that specific study treatment. Dose modification steps for dabrafenib and trametinib in Table 6-5 must be followed for the AEs presented in Section 6.5.1.

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

If treatment-related toxicities occur that are specific to combination treatment of dabrafenib and trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below:

Exception where dose modification is necessary for **only dabrafenib**:

- Uveitis (Table 6-18)

Exception where dose modifications are necessary for **only trametinib**:

- RVO (Table 6-18) and retinal pigment epithelial detachment (RPED) (Table 6-19)
- Left ventricular ejection fraction (LVEF) reduction (Table 6-15)

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

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

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

For study treatment interruptions due to adverse events unrelated to dabrafenib and/or trametinib, approval from Novartis Medical Monitor is required to restart study treatment after ≥28 days interruption.

Table 6-5 Dose modification steps for dabrafenib and trametinib

Dose reduction for dabrafenib [a, b]				
	Starting dose level	Dose level - 1	Dose level - 2	Dose level – 3
Dabrafenib	150 mg BID (300 mg/day)	100 mg BID (200 mg/day)	75 mg BID (150 mg/day)	50 mg BID (100 mg/day)
Dose reduction for trametinib [a, b]				
	Starting dose level	Dose level - 1	Dose level - 2	Dose level – 3
Trametinib	2 mg QD	1.5 mg QD	1.0 mg QD	-

BID: twice daily; QD: once daily

[a.] Dose modification should be based on the worst toxicity demonstrated at the last dose.

[b.] Dose reduction below 50 mg BID for dabrafenib and 1.0 mg QD for trametinib are not allowed.

6.5.1.3 Dose modification and management guideline for adverse events common to dabrafenib and trametinib

Adverse events that have been reported with dabrafenib in combination with trametinib in the adjuvant melanoma setting include, but are not limited to pyrexia, fatigue, nausea, headache, chills, diarrhea, vomiting, arthralgia, and rash. The most common adverse events for dabrafenib

and trametinib combination therapy include pyrexia, fatigue, nausea, headache, chills, diarrhea, rash, arthralgia, hypertension, vomiting, and cough.

Table 6-6 Reference of AEs and toxicity management guidelines

Adverse Events	dabrafenib	trametinib	Guideline
Pyrexia	X	X	Section 6.5.1.1 Table 6-4
Abnormal liver enzyme test	X	X	Section 6.5.1.3.2 Table 6-7
Renal Function Alterations	X	X	Section 6.5.1.3.3 Table 6-8
Skin rash	X	X	Section 6.5.1.3.4 Table 6-9
Serious skin reaction	X	X	Section 6.5.1.3.5
Pneumonitis	X	X	Section 6.5.1.3.6 Table 6-10
Hand foot skin reaction	X	X	Section 6.5.1.3.8 Table 6-12
Hematologic adverse events	X	X	Section 6.5.1.3.9 Table 6-13
Non-hematologic adverse events	X	X	Section 6.5.1.3.10 Table 6-14
LVEF	X	X	Section 6.5.1.3.11 Table 6-15
Hypertension	X	X	Section 6.5.1.3.12 Table 6-16
Diarrhea/colitis	X	X	Section 6.5.1.3.13 Table 6-17
New malignancies	X	X	Section 6.5.1.3.14
Visual changes	X (Uveitis)	X (RVO)	Section 6.5.1.3.15 Table 6-18, Table 6-19
RPED		X	Section 6.5.1.3.15 Table 6-19
Hyperglycemia	X		Section 6.5.1.3.16
Hemorrhage	X	X	Section 6.5.1.3.17
Thromboembolic events		X	Section 6.5.1.3.18
General	X	X	Section 6.5.1.3.7 Table 6-11
"X" indicates study treatment (s) that may need to be modified			

6.5.1.3.1 Guidance for corticosteroids tapering for management of adverse events common to dabrafenib and trametinib

Reduce prednisone dose by 2.5 to 5.0 mg decrements every 3–7 days until physiologic dose (5 to 7.5 mg of prednisone per day) is reached. Consider completing tapering over a period of at least 4 weeks. Slower tapering of corticosteroids therapy may be recommended if the adverse event is not showing improvement.

6.5.1.3.2 Mandatory dose modifications and recommended clinical management guidelines 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 6-7.

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

Table 6-7 Mandatory dose modifications and recommended clinical management guidelines for abnormal liver enzyme test

Abnormal liver enzyme tests/hepatitis		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 2: AST or ALT >3× ULN to ≤ 5× ULN and/or bilirubin > 1.5× ULN to ≤ 3× ULN	• Monitor hepatic laboratory tests more frequently(every 2-3 days) until returned to baseline values	• Interrupt, dabrafenib and trametinib until ≤ Grade 1, and then reinstate, dabrafenib and trametinib at the same dose level.

Grade 3 or 4: AST or ALT > 5× ULN and/or bilirubin > 3× ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until return to baseline values.
	• Consider appropriate consultation* with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary
	• If after 2-3 days new liver assessment shows worsening of laboratory test consider to initiate treatment with high dose steroids (1 to 2 mg/kg/day prednisone or equivalents)
	• Add prophylactic antibiotics for opportunistic infections
	• Start steroid taper as outlined in Section 6.5.1.3.1 if symptoms improve to Grade ≤1
	• If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given.
	• Infliximab is not recommended due to its potential for hepatotoxicity
		1st occurrence
		• Interrupt dabrafenib and trametinib until recovery to ≤ Grade 1 or baseline
		  • Reduce dabrafenib and trametinib to the next lower dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met
		  • If no recovery to ≤ Grade 1 within 4 weeks, permanently discontinue dabrafenib and trametinib.
		2nd occurrence
		• Interrupt dabrafenib and trametinib until ≤ Grade 1.
		  • Reduce dabrafenib and trametinib to the next lower dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met dose
		3rd occurrence
		• Permanently discontinue dabrafenib and trametinib

*Rule out viral hepatitis and other potential causes of liver injury

Note: For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.5.2.

6.5.1.3.3 Mandatory dose modifications and recommended clinical management guidelines for renal function alterations

Cases of renal insufficiency have occurred in adult patients receiving dabrafenib and the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications must be reviewed for the potential risk of inducing nephrotoxicity and concomitant medications may be modified if clinically possible.

Guidelines regarding management and dose reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in Table 6-8.

Table 6-8 Mandatory dose modifications and recommended clinical management guidelines for renal function alterations

NCI-CTCAE v4.03 for acute kidney injury

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 (Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline)	Repeat serum creatinine within 24 hours for any increase in serum creatinine >0.5 mg/dl • If the increase in creatinine is confirmed: a) Assess fluid status and consider fluid bolus b) Monitor serum creatinine at least every 2 days until back to baseline • If creatinine returns to baseline: a) resume routine creatinine monitoring per protocol • Promote hydration and cessation of nephrotoxic drugs.	• If the increase in creatinine is confirmed: a) Interrupt treatment • If creatinine returns to baseline: a) Continue dabrafenib and trametinib at the same dose.
Grade 2: (Creatinine 2 - 3 x above baseline)	• Closely monitor creatinine • Consult with specialist and consider renal biopsy • Promote hydration and cessation of nephrotoxic drugs.	**1st occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reinstate dabrafenib and trametinib at the same dose. **2nd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **4th occurrence** • Permanently discontinue dabrafenib and trametinib.

NCI-CTCAE v4.03 for acute kidney injury

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 3 (Creatinine > 3.0 x baseline or >4.0 mg/dL; hospitalization indicated)	• Hospitalization is indicated with frequent creatinine monitoring • Consult with nephrologist. • Promote hydration and cessation of nephrotoxic drugs.	**1st occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **2nd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence:** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline and then reduce dabrafenib and trametinib to the next lower dose, if available as dose level -2. If already at dose level-2 at time of occurrence, permanently discontinue dabrafenib and trametinib. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **4th occurrence:** Permanently discontinue dabrafenib and trametinib
Grade 4: Life-threatening consequences; dialysis indicated	• Consult with specialist and recommend renal biopsy. • Promote hydration and cessation of nephrotoxic drugs.	• Permanently discontinue dabrafenib and trametinib.

6.5.1.3.4 Mandatory dose modifications and recommended clinical management guidelines for skin rash

Guidelines for dose modification and management of skin rash considered to be related to study treatment by the investigator are provided in Table 6-9.

Table 6-9 Mandatory dose modifications and recommended clinical management guidelines for rash

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1: Rash covering < 10% body surface area	• Initiate prophylactic and symptomatic treatment measures. • Consider use of topical corticosteroids or urea containing creams in combination with oral antipruritics or moderate strength topical steroid (hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks	• Continue, dabrafenib and trametinib at the same dose.
Grade 2: 10-30% of body surface area	• If tolerable, as per Grade 1 • If intolerable, initiate systemic steroids (0.5 to 1 mg/kg/day prednisone or equivalents) • If symptoms persist or recur consider skin biopsy.	• If tolerable, continue dabrafenib and trametinib at the same dose. • If intolerable: **1st occurrence** • Interrupt, dabrafenib and trametinib until ≤ Grade 1, and then reinstate reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met • AE resolution to ≤ Grade 1 or baseline must occur within a period of 4 weeks since a Grade 2 event has been identified
Grade 3: More than 30% of body surface area	Obtain a skin biopsy and dermatology consult. Initiate therapy with high dose steroids (1 to 2 mg/kg/d prednisone or equivalents)	**1st occurrence** • Interrupt dabrafenib and trametinib until ≤ Grade 1, and reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met • AE resolution to ≤ Grade 1 or baseline must occur within a period of 4 weeks since a grade 3 event has been identified **2nd occurrence** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **3rd occurrence** • Interrupt dabrafenib and trametinib until ≤ Grade 1 or baseline. Once recovered, reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met

Rash Events (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
		4th occurrence • Permanently discontinue dabrafenib and trametinib.
Grade 4: Life-threatening	Same as Grade 3	Permanently discontinue dabrafenib and trametinib.

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

Withhold trametinib for intolerable or severe skin toxicity. Resume trametinib at reduced doses in subjects with improvement or recovery from skin toxicity within 3 weeks. In cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, permanently discontinue dabrafenib and trametinib and institute supportive care as per institutional guidelines.

6.5.1.3.6 Mandatory dose modifications and recommended clinical management guidelines for pneumonitis

Guidelines for dose modification and management of pneumonitis considered to be related to study treatment by the investigator are provided in Table 6-10.

Table 6-10 Mandatory dose modifications and recommended clinical management guidelines for pneumonitis

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1: Radiographic changes only- Asymptomatic	• CT scan (high-resolution with lung windows) recommended, with serial imaging to monitor for resolution or progression- re-image at least every 3 weeks • Monitor for symptoms every 2-3 days - Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse oximetry recommended • Consultation of pulmonologist recommended.	• Continue dabrafenib and trametinib at the same dose.
Grade 2: Symptomatic- medical intervention indicated; limits instrumental ADLs	• CT scan (high-resolution with lung windows) • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection • Consult pulmonologist • Pulmonary function tests - if normal at baseline, repeat every 8 weeks • Bronchoscopy with biopsy and/or BAL recommended	• Interrupt trametinib until recovery to ≤ Grade 1 or baseline. Dabrafenib may continue at the same dose. • Once recovered, reduce trametinib to the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. • If no recovery to ≤ Grade 1 within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue. • AE resolution to ≤ Grade 1 or baseline must occur within a period of 4

Pneumonitis (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
	• Symptomatic therapy including corticosteroids if clinically indicated (systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent as clinically indicated).	weeks since Grade 2 event has been identified.
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated	• CT scan (high-resolution with lung windows) • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL if possible • Treat with intravenous steroids (methylprednisolone 125 mg) as indicated. When symptoms improve to ≤ Grade 1, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours). • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider non-corticosteroid immunosuppressive medication (e.g., infliximab, cyclophosphamide, IVIG or mycophenolate mofetil).	• Interrupt trametinib until recovery to Grade ≤1 or baseline. Dabrafenib may continue. • Once recovered, trametinib may be restarted at the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met • If no recovery to Grade ≤ 1 or baseline within 4 weeks, permanently discontinue trametinib. Dabrafenib may continue.
Grade 4: Life-threatening respiratory compromise	Same as Grade 3	Same as Grade 3

6.5.1.3.7 Dose modification and management guideline for adverse events suspected to be related to dabrafenib and/or trametinib (other than Pyrexia)

For adverse events of special interest reported **only for dabrafenib and/or trametinib**, general guidelines for dose modification in Table 6-11 should be followed for dabrafenib and trametinib.

In general, if an AE resolves to Grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level.

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

Table 6-11 General guidelines for dose modification for adverse events suspected to be related to dabrafenib and/or trametinib treatment

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 or Grade 2 tolerable	• Monitor closely. • Provide supportive care according to institutional standards.	• Continue dabrafenib and trametinib at the same dose level.
Grade 2 (intolerable) or Grade 3	• Monitor closely. • Provide supportive care according to institutional standards.	• Interrupt dabrafenib and trametinib (except for cuSCC, keratoacanthoma, new primary melanoma, and basal cell carcinoma) • When toxicity resolves to ≤ Grade 1 or baseline, restart dabrafenib and trametinib reduced by one dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met • If the Grade 2 (intolerable) or Grade 3 toxicity recurs, interrupt dabrafenib and trametinib. • When toxicity resolves to Grade 1 or baseline, restart dabrafenib and trametinib reduced by another dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met

Grade	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 4	• Monitor closely. • Provide supportive care according to institutional standards.	• Interrupt dabrafenib and trametinib. • Restart with dabrafenib and trametinib reduced by one dose level per Table 6-5 once toxicity resolves to ≤ Grade 1 or baseline or permanently discontinue dabrafenib and trametinib at the discretion of the investigator. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met

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

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

- Prevention/prophylaxis: promote sunscreen use and avoidance of unnecessary sun exposure, use alcohol-free emollient creams, topical steroids and antibiotics as needed.
- Pruritic lesions: cool compresses and oral antihistamines
- Fissuring lesions: Monsel's solution, silver nitrate or zinc oxide cream
- Desquamation: thick emollients and mild soap
- Paronychia: antiseptic bath, local potent corticosteroids, antibiotics, surgery as needed
- Infected lesions: topical or systemic antibiotics
- Measures for PPES should include:
- Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles
- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g., urea 20-40% cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.

Guidelines for dose modification for hand-foot skin reaction considered to be related to study treatment by the investigator are provided in Table 6-12.

Table 6-12 Mandatory dose modifications and recommended clinical management guidelines for hand foot skin reaction (palmar-plantar erythrodysesthesia)

Hand foot skin reaction		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject's normal activities	• Recommend topical therapy for symptomatic relief.	• Continue dabrafenib and trametinib at the same dose.
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the subject's normal activities	• Recommend topical therapy for symptomatic relief	• Continue treatment and if no improvement within 7 days, see below. • No improvement within 7 days or 2nd or 3rd occurrence: • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 1 or baseline. • Reduce dabrafenib and trametinib at the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **4th occurrence:** • Discontinue dabrafenib and trametinib.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living	• Recommend topical therapy for symptomatic relief	**1stoccurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 1 or baseline. • Once recovered, reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **2nd occurrence**: • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 1 or baseline. • Once recovered, reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **3rd occurrence:** • Discontinue dabrafenib and trametinib.

6.5.1.3.9 Mandatory dose modifications and recommended clinical management guidelines for hematological adverse events

Guidelines for dose modification for hematologic adverse events suspected to be related to study treatment by the investigator are provided in Table 6-13.

Table 6-13 Mandatory dose modifications and recommended clinical management guidelines for hematological adverse events

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Neutropenia		
Grade 1, 2	NA	• Continue dabrafenib and trametinib at the same dose.
Grade 3, 4	• Monitor blood test more frequently (every 7 days for Grade 3, and 3-5 days for Grade 4).	**1st occurrence:** • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 2 or baseline. • Reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **2nd occurrence:** • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 2 or baseline. • Reduce dabrafenib and trametinib at the next dose level per Table 6-5. Re-escalation of the subject 's dose is recommended if criteria in Section 6.5.1.2 are met **3rd occurrence**: • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 2 or baseline. • Once recovered, reduce dabrafenib and trametinib to the next dose level per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **4th occurrence:** • Permanently discontinue dabrafenib and trametinib
Febrile Neutropenia	• Apply Institutional guidelines	• Follow modification guide for neutropenia Grade 4 (above).
Thrombocytopenia		
Grade 1, 2, 3 without clinically significant bleeding	• Grade 3: monitor blood test more frequently (every 7 days)	• Continue dabrafenib and trametinib at the same dose.

Hematologic suspected AEs (NCI-CTCAE v4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 3 with clinically significant bleeding Grade 4	• Grade 3: monitoring blood test more frequently (every 3-5 days)	**1st occurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 2 or baseline. • Restart dabrafenib and trametinib at same dose. **2nd occurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 2 or baseline. • Restart dabrafenib and trametinib at the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **3rd occurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 2 or baseline. • Restart dabrafenib and trametinib at another lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **4th occurrence:** • Interrupt dabrafenib and trametinib until toxicity resolves to ≤ Grade 2 or baseline. • Permanently discontinue dabrafenib and trametinib.

6.5.1.3.10 Mandatory dose modifications and recommended clinical management guidelines for non-hematological adverse events

Guidelines for dose modification for non-hematologic adverse events suspected to be related to study treatment by the investigator are provided in Table 6-14.

Table 6-14 Mandatory dose modifications and recommended clinical management guidelines for non-hematological adverse events

Non-Hematologic AEs (except Grade 2 alopecia, Grade 2 fatigue) (NCI-CTCAE v4.03)		
Grade	• Recommended adverse event management guidelines	• Mandatory dose modification requirements
Grade 1-2 tolerable	• Monitor closely. • Provide supportive care according to institutional standards.	• Continue, dabrafenib and trametinib at the same dose.
Grade 2 intolerable or Grade 3	• Monitor closely • Provide supportive care according to institutional standards	**1st or 2nd occurrence:** • Interrupt dabrafenib and trametinib until toxicity recovers to ≤ Grade 1 or baseline. • Restart dabrafenib and trametinib at the same dose. **3rd occurrence:** • Restart dabrafenib and trametinib at the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **4th occurrence:** • Permanently discontinue dabrafenib and trametinib.
Grade 4	Monitor closely Provide supportive care according to institutional standards	**1st occurrence:** • Interrupt dabrafenib and trametinib. • Dabrafenib and trametinib may be reinitiated at the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met **2nd occurrence:** • Permanently discontinue dabrafenib and trametinib.

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

Decreases of left-ventricular-ejection-fraction (LVEF) have been observed in patients receiving trametinib in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Visit Evaluation Schedule (Table 8-1). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-15.

Table 6-15 Mandatory dose modification and recommended clinical management for changes in LVEF suspected to be related to dabrafenib and/or trametinib treatment

Left Ventricular Ejection Fraction decrease (NCI-CTCAE v4.03)		
LVEF-drop (%) & clinical symptoms	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**

Asymptomatic:
Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN
	• Report as SAE.
	• Closely monitoring LVEF via ECHO, repeat ECHO within 2 weeks*.
	• If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN **and** absolute decrease ≤10% compared to baseline)
	  • Repeat ECHO 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter.
	• If repeat LVEF does not recover within 4 weeks.
	  • Consult with cardiologist
	  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution
		• Interrupt trametinib.
		• If the LVEF recovers, restart trametinib reduced by one dose level per Table 6-5.
		• More than two occurrence, permanently discontinue trametinib.
		• Permanently discontinue trametinib if repeat LVEF does not recover within 4 weeks.

Symptomatic: Resting LVEF 39-20% or >20% absolute reduction from baseline resting LVEF <20%	• Report as SAE. • Consult with cardiologist. • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.	• Permanently discontinue trametinib. • Interrupt dabrafenib • Restart dabrafenib if LVEF recovers including resolution of symptoms.
* If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later.		

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

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

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

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

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor

increased blood pressure can be scheduled independently from the per- protocol visits outlined in the Visit Evaluation Schedule (Table 8-1). Ideally, subsequent blood pressure assessments should be performed within one week.

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

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for dose modifications and management of hypertension are described below in Table 6-16.

Table 6-16 Mandatory dose modification and recommended clinical management for hypertension suspected to be related to dabrafenib and/or trametinib treatment

Hypertension (NCI-CTCAE 4.03)		
Severity	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
(Scenario A) Asymptomatic and persistent [a] SBP of >140 and <160 mmHg, or DBP >90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication. • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP[b] • If BP is not well controlled within 2 weeks, recommended to refer to a specialist and go to scenario (B).	Continue dabrafenib and trametinib at the same dose.
(Scenario B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP.	• Interrupt dabrafenib and trametinib if clinically indicated. • Once BP is well controlled, restart dabrafenib and trametinib reduced by one dose level per Table 6-5.
Symptomatic [c] hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment.	• Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended	• Interrupt dabrafenib and trametinib. • Once BP is well controlled, restart dabrafenib and trametinib reduced by one dose level per Table 6-5.
Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• Continue follow-up per protocol.	• Permanently discontinue dabrafenib and trametinib.

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

6.5.1.3.13 Mandatory dose modifications and recommended clinical management guidelines for diarrhea/colitis

Guidelines for dose modification and management for diarrhea 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 diarrhea/colitis

CTCAE v4.03	Recommended adverse event management guidelines	Mandatory dose modification requirements
Grade 1 diarrhea (increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline) OR Grade 2 diarrhea (increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline)	• Diet: stop all lactose containing products; eat small meals, BRAT diet (banana, rice, apples, toast) • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours; • Diarrhea > 24hr: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea > 48hr: loperamide 2 mg every two hours; maximum 16 mg/day. Consider other second-line therapies for diarrhea (e.g., octreotide, oral diphenoxylate, and oral antibiotics) • If Grade 2 and no improvement in 5 days consider oral steroids • If Grade 2 diarrhea persists >1 week consider gastroenterologist consultation and endoscopy to evaluate for colitis • If Grade 2 persists for 5 days and worsening of symptoms or diffuse ulcerations and bleeding seen on endoscopy, commence oral steroids at a dose 0.5 to 1 mg/kg/day prednisone equivalents and continue until symptoms improve to Grade 1. If no improvement occurs, manage as per Grade 3. • Lower GI endoscopy and biopsy should be considered and may assist in determining the duration of steroid taper based on the evidence of macroscopic and microscopic inflammation.	• Continue dabrafenib and trametinib at the same dose level. • If diarrhea is Grade 2, despite loperamide at 2 mg every two hours for > 48hr: • Interrupt dabrafenib and trametinib until ≤ Grade 1, and then reinstate, dabrafenib and trametinib at the same dose level.
Grade 3 diarrhea (increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL)	• Clinical evaluation and hospitalization mandatory; rule out bowel perforation and intravenous hydration. • Consider consultation with gastroenterologist and	**1st occurrence** • Interrupt, dabrafenib and trametinib until ≤ Grade 1, and then reinstate treatment (after appropriate steroid tapering) and reduce dabrafenib and trametinib to the next lower dose level per Table 6-

CTCAE v4.03	Recommended adverse event management guidelines	Mandatory dose modification requirements
	confirmation biopsy with lower GI endoscopy. • In addition to symptomatic treatment (diet, hydration, loperamide, antibiotics if indicated); initiate immediate treatment with intravenous steroids (methylprednisolone 1mg/kg/day) followed by high dose oral steroids (1 to 2 mg/kg/day prednisone equivalents) • When symptoms improve to ≤ Grade 1, steroid taper should be started and continued over no less than 4 weeks as per Section 6.5.1.3.1. • Taper over 6 to 8 weeks in subjects with diffuse and severe ulceration and/or bleeding. • If no improvement in 2-3 days: consider initiating infliximab 5 mg/kg and continue steroids. (Infliximab is contraindicated in subjects with sepsis or a perforation). Upon symptomatic relief initiate a prolonged steroid taper over 45 to 60 days. • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose followed by a more prolonged taper and administer infliximab. • If symptoms persist despite the above treatment, a surgical consult should be obtained.	5 Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. • AE resolution to ≤ Grade 1 or baseline must occur within a period of 4weeks since a grade 3 event has been identified **2nd occurrence** • Interrupt dabrafenib and trametinib until ≤ Grade 1, and then reduce dabrafenib and trametinib to the next lower dose per Table 6-5. Re-escalation of the subject's dose is recommended if criteria in Section 6.5.1.2 are met. **3rd occurrence** • Permanently discontinue dabrafenib and trametinib.
Grade 4: Life-threatening consequences; urgent intervention indicated	Same as Grade 3	Permanently discontinue, dabrafenib and trametinib.

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

New cutaneous malignancies:

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

Subjects should be instructed to immediately inform their physician if new lesions develop. Skin examination should be performed prior to initiation of study treatment and throughout therapy as detailed in the Visit Evaluation Schedule. Monitoring should follow institutional

guidelines and/or as clinically indicated following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

New non-cutaneous malignancies:

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

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

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

6.5.1.3.15 Mandatory dose modification and management guideline for visual changes suspected to be related to dabrafenib and/or trametinib treatment

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. If a subject reports loss of vision or other visual disturbancies, an urgent ophthalmological evaluation (within 24 hours) is recommended to detect potential retinal vein occlusion (RVO). However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination.

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

In subjects treated with trametinib, special attention should be given to retinal findings (e.g., RPED) 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 considered to be related to dabrafenib and/or trametinib are provided in Table 6-18 and Table 6-19.

Table 6-18 Mandatory dose modification and recommended clinical management for visual changes and/or ophthalmic examination findings suspected to be related to dabrafenib and/or trametinib treatment

Visual changes (Eye disorders – Other, CTCAE Version 4.03)		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
Grade 1 [a]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. Continue dabrafenib. • If RPED and RVO excluded, continue (or restart) trametinib at the same dose level. • **If RPED suspected or diagnosed:** see RPED dose modification in Table 6-19; **report as SAE if diagnosed**. • **If RVO diagnosed:** Permanently discontinue trametinib and report as SAE.
Grade 2 and Grade 3	• Consult ophthalmologist immediately, perform ophthalmological evaluation within 24 hours.	• Interrupt trametinib. Dabrafenib may be continued at the same dose [b]. If RPED and RVO excluded, restart trametinib at the same dose level. • **If RPED diagnosed**, see RPED dose modification in Table 6-19; **report as SAE**. • **If RVO diagnosed: Permanently discontinue trametinib and report as SAE.**
Grade 4	• Consult ophthalmologist immediately, perform ophthalmological evaluation within 24 hours.	• Interrupt trametinib. Dabrafenib may be continued at the same dose [b]. If RPED and RVO excluded, should consider restarting trametinib at same or reduced dose after discussion with study medical monitor. • If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE.

[a.] If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

[b.] Permanently discontinue dabrafenib for ≥ Grade 2 uveitis (including iritis and iridocyclitis) of > 6 weeks duration.

Table 6-19 Mandatory dose modification and recommended clinical management for retinal pigment epithelial detachments (RPED) suspected to be related to trametinib treatment

Retinal pigment epithelial detachments (RPED) CTCAE Version 4.03		
Grade	**Recommended adverse event management guidelines**	**Mandatory dose modification requirements**
• Grade 1 (Asymptomatic; clinical or diagnostic observations only)	• If RPED worsens follow instructions below.	• Continue treatment with retinal evaluation monthly until resolution.
• Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity).	• Retinal evaluation monthly.	• Interrupt trametinib for up to 3 weeks. • If improved to ≤ Grade 1, restart trametinib at a lower dose per Table 6-5. • If not improved to ≤ Grade 1 within 3 weeks, permanently discontinue trametinib

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

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

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

6.5.1.3.17 Mandatory dose modification and management guideline for hemorrhage

Hemorrhage, including major hemorrhage defined as symptomatic bleeding in a critical area or organ, can occur when dabrafenib is administered with trametinib. Permanently discontinue dabrafenib and trametinib for all Grade 4 hemorrhagic events and for any persistent Grade 3 hemorrhagic events. Withhold dabrafenib and trametinib for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

6.5.1.3.18 Mandatory dose modification and management guideline thromboembolic events

Advise subjects 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 subject will undergo specific laboratory and medical imaging studies to confirm it. The medical imaging study or studies selected will depend on the anatomic site or organ of involvement (e.g., Doppler ultrasound, venography, ventilation-perfusion lung scan, angiography, MRI). If the diagnosis is confirmed, appropriate medical care according to standard local clinical practice should be initiated immediately.

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

6.5.2 Follow-up for toxicities

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

Subjects with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI, and should be considered as clinically important events.

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

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

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

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

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

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

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 10.1.2) and reported as SAE using the term “potential drug-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 subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject’s safety and the validity of the study. The subject 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 tablet/capsule counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Subjects should record treatment compliance and pyrexia events on paper diaries, which should be verified at each monthly Treatment visit. These data should correspond to the information recorded on the eCRFs

6.7 Preparation and dispensation

No special preparation of the study treatments is required.

Dabrafenib and trametinib will be either sourced as local commercial supply or provided as global clinical open-label supply. Global clinical open-label supply will be provided in bottles.

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

When clinical supply is utilized, Investigator staff will identify the study medication kits to dispense to the subject 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 subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the IBs. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO 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 subject except for the medication number.

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

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

6.7.2 Instruction for prescribing and taking study treatment

Dabrafenib and trametinib should be taken as follows:

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

and 12 hours later for trametinib. Subject may then take the next dose at the scheduled time.

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

Table 6-20 Dose treatment and schedule

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

7 Informed consent procedures

Eligible subjects 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 subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents.

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

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

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 subjects 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. Subjects must be informed of the contraception requirements outlined in the Inclusion/Exclusion Criteria (Section 5).

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

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to

automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Subjects will receive study treatment for twelve months or until disease recurrence or early discontinuation of treatment. Subjects who discontinue study treatment prior to 12 months should complete an EoT visit. Subjects who complete 12 months of treatment and do not relapse will continue into the Follow-up Phase and follow assessments in Table 8-2 (i.e. beginning at the Month 15 assessment). In addition, subjects who permanently discontinue study treatment prior to 12 months without evidence of disease recurrence will complete an EoT visit and then will be followed for disease recurrence according to Table 8-2 until withdrawal of consent, lost to follow-up, death, or study completion (as defined in Section 9.2). Subjects will return for Follow-up visits starting at the next regularly scheduled disease assessment visit (i.e. Month 3, 6, or 12) and continue thereafter according to Table 8-2.

If a subject experiences disease recurrence, Follow-up visits should be conducted according to Table 8-3. Such follow-up assessments should start at the next scheduled assessment visit and continue thereafter according to Table 8-3. For example, if disease recurrence is observed at Month 6, the subject would complete the EoT visit, and then begin Follow-up assessments at Month 12 and continue according to the visit schedule in Table 8-3.

Follow-up for survival, new anti-cancer therapy (including radiotherapy) and response to new anti-cancer therapy will continue for all subjects beyond the 24 month assessment according to the schedule in Table 8-2 and Table 8-3 until the study is considered to be complete after which all protocol-required assessments and procedures will be discontinued. Follow-up contact to assess survival and new anti- cancer therapy may be made via clinic visit or another form of communication (e.g. phone, email, mail etc.).

Table 8-1 Treatment Visit and Assessment Schedule

Period	**Pre-Screening**	**Screening**	**Treatment Visits & Assessment Schedule[1]**													
Visit Name	**Pre-screening**	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**End of Treatment (EoT)[2]**
Informed consent	X	X														
Disposition Assessment (at the end of each study period)	X	X														X
Demography	X	X														
Inclusion / Exclusion criteria		X[4]														
Medical history/current medical conditions		X														
Disease Medical History		X														
Diagnosis and extent of cancer		X														
Prior Antineoplastic therapy		X														
IRT Registration		X														
IRT enrollment		X														
Ophthalmic Examination[11]		X														
BRAF V600E/K mutation testing	X[3]															

Period	**Pre-Screening**	**Screening**	**Treatment Visits & Assessment Schedule[1]**													
Visit Name	**Pre-screening**	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**End of Treatment (EoT)[2]**
Concomitant medications[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X	X[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry		X	X[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height		X														
Body Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel		X														
Hepatitis screen[8]		X														
Pregnancy Test (serum) [5]		X													X	X
Pregnancy (Urine)[5]				X	X	X	X	X	X	X	X	X	X	X		
Chest, abdomen & pelvic CT Scans[9]		X				X			X						X	X
Brain CT/MRI		X														
Dermatological Assessment		X				X			X						X	X
Electrocardiogram (ECG)		X							X						X	X

Period	Pre-Screening	Screening	Treatment Visits & Assessment Schedule[1]													
Visit Name	**Pre-screening**	**Screening**	**Day 1**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**End of Treatment (EoT)[2]**
ECHO/MUGA[10]		X			X[10]				X			X			X	X
Patient reported outcomes			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed[6]			X	X	X	X	X	X	X	X	X	X	X	X		
Study drug accountability[6]				X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. Screening procedures may be performed up to 28 days prior to start of study treatment (Day1). For monthly visits (i.e. Month 1, 2, 3, etc.) subjects should return to the clinic approximately every 4 weeks. A post baseline study visit window of +/-3 days is allowed for visits during treatment. A window of +/-7 days is permitted for some post baseline assessments, where noted in Section 8.3.1.1.

[2] If treatment is discontinued prior to Month 12, the treatment discontinuation visit (EoT) should be performed within 30 days of the subject's last dose. Laboratory assessments and other required assessments do not need to be repeated at the discontinuation visit if they were performed within 30 days of the discontinuation visit. Follow-up should occur until death or study completion according to the follow-up assessment schedule in Table 8-2 unless the subject withdraws from the study.

[3] A BRAF V600E/K mutation positive result must be confirmed via a validated local test prior to enrollment. Refer to Section 8.1.1.

[4] Complete resection of Stage III cutaneous melanoma must have occurred within 12 weeks of first dose (Day 1).

[5] For all women of childbearing potential, a serum pregnancy test will be required within 72 hours prior to start of study treatment (Day1). Subsequent tests may be urine tests, and should be performed monthly or at EoT if discontinuation occurs prior to Month 12. Additionally if study treatment is interrupted for more than 7 days, regardless of the reason for the disruption, a urine test must be performed to confirm the subject is not pregnant prior to re- starting study treatment.

[6] Dosing instructions must be provided to the subject. Subjects should start treatment as soon as possible but no later than 72 hours after drug being dispensed. Study treatment will be dispensed at Day 1 and monthly. Site must call IRT to register Enrollment. Treatment compliance will be assessed at all visits after Day 1 . To assess

compliance, subjects should be instructed to return study drug at each visit; compliance will be assessed by querying the subject and counting tablets/capsules. Dose reductions, dose interruptions/delays, and/or dose escalations must be recorded in the eCRF.

[7]All medications taken by the subject during the study from the time of Informed Consent until 30 days after the last dose of study treatment will be recorded; any new anti-cancer therapy, if taken after study treatment discontinuation will be recorded as detailed in Tables 8-2 and 8-3.

[8]Hepatitis screening only for subjects with a history of chronic HBV and/or HCV

[9]CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scan if the CT frequency defined here is not permitted per country or ethics requirements or if CT contrast is contraindicated.

[10]LVEF will be evaluated prior to initiation of study treatment, within eight weeks of initiating treatment (either at Month 1 or at Month 2), at Month 6, Month 9, Month 12, EoT and as clinically appropriate.

[11]Refer to section 8.4.5 for details of ophthalmic exams needed and to Table 6-18 for management and dose modification guidelines.

[12]Screening and Day 1 Hematology and Clinical Chemistry do not need to be repeated if screening labs are drawn within 3 days of Day 1

If early treatment discontinuation occurs due to reason other than disease relapse or a subject has completed treatment and has not relapsed, refer to Table 8-2.

Table 8-2 Follow-up (Pre-Relapse) Assessment Schedule

	Pre-Relapse Visit & Assessment Schedule[1]							
Visit Name	Month 3	Month 6	Month 12	Month 15	Month 18	Month 24	Survival Contact (every 3 mo)[2]	End of Study (EoS)[3]
Physical Examination	X	X	X	X	X	X		X[3]
ECOG Performance Status	X	X	X	X	X	X		X[3]
Chest, abdomen and pelvic CT scans[4]	X	X	X	X	X	X		X[3]
Dermatologic Assessment	X	X	X	X	X	X		X[3]
Patient reported outcomes	X	X	X	X	X	X		X[3]
Any anti-neoplastic therapy (including surgery, radiotherapy, medications) since discontinuation of study treatment including Best Response	X	X	X	X	X	X	X	X
Survival Follow Up	X	X	X	X	X	X	X	X
Disposition Assessment (at the end of each study period)								X

[1] Follow-up will start once treatment is completed or discontinued and should continue through EoS Visit, withdrawal or death, even if disease recurs. Follow-up visits prior to disease recurrence should follow Table 8-2, and should be clinic visits through the Month 24 Assessment. Follow-up visits after the Month 24 Assessment are not required to be clinic visits and the information collected will be limited to the following: any radiotherapy; surgical procedure or new anti-cancer therapy initiated until EoS visit, withdrawal or death; best response to any follow-up treatment; and survival data. For example, if a subject discontinues treatment at Month 2 for reason other than disease relapse, the EoT should be performed according to Table 8-1 and the follow-up assessments would start at Month 3 according to Table 8-2 until EoS, withdrawal or death. Follow-up after disease relapse should follow the schedule in Table 8-3.

[2] Survival follow-up after the Month 24 assessment should be conducted every 3 months until withdrawal, death, or study end (whichever occurs first), and can be done via phone contact.

[3]The EoS visit should be completed at withdrawal, lost to follow-up, death, or at the end of study (see definition in Section 9.2), whichever occurs first. If the EoS visit occurs after the Month 24 visit, a clinic visit is not required and the information collected will be limited to the following: anti-cancer therapy, best response to any follow-up treatment, and survival data

[4]CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scan if the CT frequency defined here is not permitted per country or ethics requirements or if CT contrast is contraindicated.

If relapse occurs, refer to Table 8-3.

Table 8-3 Follow-up (Post-Relapse) Assessment Schedule

	Post-Relapse Visit & Assessment Schedule[1]							
Visit Name	Month 3	Month 6	Month 12	Month 15	Month 18	Month 24	Survival Contact (every 3 mo)[2]	End of Study (EoS)[3]
Patient reported outcomes	X	X	X	X	X	X		X[3]
Any anti-neoplastic therapy (including surgery, radiotherapy, medications) and disease information since discontinuation of study treatment including Best Response	X	X	X	X	X	X	X	X
Survival Follow Up	X	X	X	X	X	X	X	X
Disposition Assessment (at the end of each study period)								X

[1] Follow-up will start once treatment is completed or discontinued and should continue through EoS Visit, withdrawal or death, even if disease recurs. Follow-up visits prior to disease recurrence should follow Table 8-2. Follow-up after disease relapse should follow the schedule in Table 8-3. For example, if a subject discontinues treatment at Month 2 due to disease relapse, the EoT should be performed according to Table 8-1 and the follow-up assessments would start at Month 3 according to Table 8-3 until EoS, withdrawal, lost to follow-up, or death.

[2] Survival follow-up after the Month 24 assessment should be conducted every 3 months until withdrawal, death, or study end (whichever occurs first), and can be done via phone contact.

[3]The EoS visit should be completed at withdrawal, lost to follow-up, death, or at the end of study (see definition in Section 9.2), whichever occurs first. If the EoS visit occurs after the Month 24 visit, a clinic visit is not required and the information collected will be limited to the following: anti-cancer therapy, best response to any follow-up treatment, and survival data

8.1 Screening

8.1.1 BRAF V600E/K pre-screening

Subjects will be enrolled based on local *BRAF* V600E/K mutation result as part of study inclusion criteria (Section 5). The *BRAF* V600 mutation will be assessed via a local institutional assay using a validated tissue-based molecular test for *BRAF* V600 mutations. Immunohistochemistry is not an accepted method and liquid biopsy based *BRAF* V600 results cannot be used to enroll subjects. If BRAF mutation results are not part of the patient's Medical History and must be completed as a study procedure to qualify for the study, the subject should first complete the Informed Consent.

The eCRF page for methods of local BRAF mutation testing must be completed.

8.1.2 Eligibility screening

Subject re-screening will not be permitted. Subjects should be registered in the Rave eCRF system for screening and subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the eCRF system. Please refer and comply with detailed guidelines in the CCG.

8.1.3 Information to be collected on pre-screening failures

Subjects who signed a Molecular Pre-screening Informed Consent Form but are not BRAF V600E/K mutation positive will be considered a pre-screen failure.

The following eCRFs should be completed for pre-screen failures:

- Demography
- Molecular Informed Consent
- Disposition, including reason for pre-screen failure
- Biomarker Assessment - BRAF V600 Mutation Result

No other data will be entered into the clinical database for subjects who are pre-screen failures, unless the subject experienced a Serious Adverse Event during Pre-Screening (see Section 10 for SAE reporting details)

8.1.4 Information to be collected on screening failures

Subjects who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure. Subjects who are found not eligible after signing the Informed Consent Form will be considered as screening failures.

The following eCRFs should be completed for screen failures:

- Demography
- Informed Consent
- Disposition, including reason for screen failure
- Inclusion/Exclusion Criteria
- Biomarker Assessment - BRAF V600 Mutation Local Result

No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during Screening (see Section 10 for SAE reporting details)

8.2 Subject demographics/other baseline characteristics

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

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

- Demography (age, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)

- Past and current medical conditions including cardiovascular medical history and risk factors
- Diagnosis and extent of cancer using AJCC edition 8
- Prior antineoplastic surgery(ies)
- Prior and current concomitant medications, surgical and medical procedures and significant non-drug therapies

Note: All other medications taken within 28 days or 5 half-lives, whichever is shorter before the first dose of study treatment is administered must be recorded on the Prior and current concomitant medication eCRF page and updated on an ongoing basis if there is new change to the medication.

Assessments to be performed at screening/baseline include;

- Physical examination (e.g. performance status (ECOG), height, weight, vital signs, ophthalmic and skin examination)
- Cardiovascular assessments (e.g., ECG, ECHO or MUGA)
- Laboratory assessments (e.g., hematology, chemistry, coagulation, serum pregnancy test, hepatitis test, if applicable)
- Imaging assessments (e.g., CT and MRI)
- Patient reported outcomes (FACT-M)

8.3 Efficacy

8.3.1 Efficacy Assessments

The secondary efficacy endpoints of this study are:

- RFS defined as the time from first dose of study medication to disease recurrence or death from any cause.
- OS defined as the interval from first dose of study medication to the date of death, irrespective of the cause of death; subjects still alive will be censored at the date of the last contact.

Tumor response will be assessed locally. The imaging assessment collection plan is presented in Table 8-4. The local investigator's assessment will be used for the primary Interim and endpoint RFS analysis and for treatment decision making, as well as the final OS analysis.

For subjects who continue on study without documented disease relapse, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed according to the schedule in Table 8-1, Table 8-2 and Table 8-4 (i.e. to Month 24 assessments) until documented disease relapse, death, lost to follow-up, withdrawal of consent, or EoS, whichever occurs first.

Table 8-4 Imaging assessments

Procedure	Screening	Treatment Period and Follow up Period
Chest, abdomen and pelvis CT or MRI (with contrast enhancement)*	Mandated	• Months 3, 6, 12, 15, 18, 24, regardless of whether subject is on treatment or not, until disease recurrence or start of new anti-cancer therapy.

		• EoT: if a scan was not conducted within 30 days prior to end of study treatment or when subject discontinues treatment. • EoS: if a scan was not conducted within 30 days prior to end of study for subjects who have not had disease recurrence or started other anti-cancer therapy.
Brain imaging (CT or MRI)	Mandated	Baseline MRI (preferred) or CT of the brain must be performed on all subjects. Post-baseline scans should be performed as clinically indicated.

*CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scan if the CT frequency defined here is not permitted per country or ethics requirements or if CT contrast is contraindicated

8.3.1.1 Assessment Guideline

Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline efficacy assessments Month 1 through Month 12, a window of ±3 days (physical exam) or ±7 days (CT scans, dermatologic skin assessment) is permitted to allow for flexible scheduling. After Month 12/EoT a post-baseline assessment window of ±14 days is permitted.

The following are required for efficacy assessment:

- Clinical examination
- Diagnostic quality, contrast-enhanced CT scan of the chest, abdomen and pelvis should be performed at baseline and subsequent timepoints as indicated in Table 8-1, Table 8-2, and Table 8-4. Intravenous contrast should be used for the CT scans preferably with oral contrast as well. CT contrast of the chest, with contrast-enhanced MRI of the abdomen and pelvis should be substituted for full CT scanning if the CT frequency prescribed in Table 8-1, Table 8-2, and Table 8-4 is not permitted per country or ethics requirements or if CT contrast is contraindicated. The method of imaging, including use of contrast, should be consistent throughout the study (i.e. if CT is done at screening, CT will be done at all future timepoints), where not contraindicated.
- A baseline MRI of the brain is required for all subjects. CT may be performed. Subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS recurrence). Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable.
- Biopsy of suspected recurrences is strongly recommended to confirm the diagnosis.
- Ultrasound is not a suitable modality of disease assessment for distant metastases. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- If clinically indicated, CT or MRI of other areas (e.g., neck) of disease as appropriate should be performed.
- Fluorodeoxyglucose positron emission tomography (FDG)-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion.
- If PET/CT is performed then the CT component can only be used for standard disease assessments if performed to diagnostic quality, which includes the required anatomical

coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical examination: New lesions detected by clinical examination must be biopsied, where possible, to confirm disease recurrence. If a biopsy cannot be obtained then CT/MRI must be done to confirm disease recurrence.

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. MRI is acceptable (refer to Section 8.3.1), but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type of disease.

Whenever possible the same scanner should be used.

Brain Scan: For the baseline brain scan and any post-baseline brain scans, contrast enhanced MRI is preferable to contrast enhanced CT.

8.3.1.2 Baseline imaging assessments

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

Any imaging assessments already completed during the regular work-up of the subject 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 Day 1 cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain CT or MRI

8.3.1.3 Post-baseline imaging assessments

Imaging assessments as described in Table 8-1, Table 8-2, and Table 8-4 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 according to Table 8-1, Table 8-2, and Table 8-4 until disease relapse, death, lost to follow-up, withdrawal of consent or the 24 month/ EoS assessment. Imaging assessments should be scheduled using Day 1 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, permanently discontinued, or unscheduled assessments performed.

Tumor assessments after start of new anti-neoplastic therapy post-relapse are recommended however not required. Best response to anti-neoplastic therapy after relapse will be collected on the eCRF.

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

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document relapse.

8.3.1.4 Study Completion Assessments

Prior to disease recurrence, if a subject withdraws from the study Day 1 through Month 24 and the last radiographic assessment was more than 3 months prior to withdrawal from study, a disease assessment should be obtained at the time of withdrawal from study.

8.4 Safety

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

Significant findings that were present prior to the signing of informed consent must be included in the 'Relevant Medical History/Current Medical Conditions' page on the subject's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the subject's CRF.

For details on AE collection and reporting, refer to Section 10.

Table 8-5 Assessments & Specifications

Assessment	Specification
Physical examination	• A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. • A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from Day 1, except for Month 12 or EoT, where a full physical exam is required. • Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the Relevant Medical History/Current Medical Conditions CRF. Significant findings made that begin *or* worsen after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event CRF.
Vital sign	• Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	• Height in centimeters (cm) at screening only and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and subsequent time points as specified in Table 8-1

8.4.1 Performance status

Performance status will be assessed as described in Table 8-1 and Table 8-2. More frequent examinations may be performed at the investigator's discretion, if medically indicated. ECOG Performance status scale will be used as described in the Table 8-6 below:

Table 8-6 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

8.4.2 Physical Exam

A complete physical examination will be performed at screening, Month 12 or EoT, and later as clinically indicated and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological assessments. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will be performed beginning at Day 1 as per schedule in Table 8-1 and will include the examination of general appearance, skin (including Dermatologic Exam), and vital signs (blood pressure and pulse).

8.4.3 Vital Signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature and will be measured at screening and at subsequent time points as specified in Table 8-1.

8.4.4 Height and Weight

Height will be measured at screening.

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1.

8.4.5 Ophthalmic examination

A standard ophthalmic examination by an ophthalmologist will be performed as per schedule in Table 8-1. The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities (dilation only required if clinically indicated). Optical coherence tomography is recommended at scheduled visits, and mandated if retinal

abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

More frequent examinations may be performed at the investigator's discretion, if medically indicated.

8.4.6 Dermatologic Examination

Dermatologic exams are required as per schedule in Table 8-1 and Table 8-2 through Month 24 or disease relapse. Exams 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. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.

8.4.7 Laboratory evaluations

Local laboratories will be used for routine safety assessments as outlined in Table 8-7 and the results will be recorded in the eCRF.

Novartis must be provided with a copy of the local laboratory's certification, and a tabulation of the normal ranges and units of each parameter collected for entry into the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a subject has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The Investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified lab normal range** at screening and/or at baseline, the assessment may be repeated to rule out laboratory error. If the repeat value remains outside of protocol-specified ranges during screening procedures, the subject must be excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the normal range for the center at screening and/or baseline, a decision regarding whether the result is of clinical significance or not must be made by the Investigator and should be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated as soon as possible, and in any case, prior to Day 1, to rule out laboratory error.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e. result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

Table 8-7 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands*, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Calcium, Magnesium, Phosphorus, Sodium, Potassium, Chloride, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Total Cholesterol, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting or non-fasting)
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy Test	A serum pregnancy test must be performed at screening (at the local laboratory) ≤ 72 hours before first dose of study treatment, and at treatment discontinuation (Month 12 or EoT) A local laboratory urine pregnancy test must be performed at day 1 and at Monthly visits during the treatment period.
Hepatitis markers (for subjects with a history of chronic HBV and/or HCV)	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR
*optional	

8.4.8 Cardiac Assessments

8.4.8.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed according to Table 8-1 and Table 8-8.

Standard 12 lead ECG will be performed after the subject has been resting for approximately 10 min prior to each ECG collection. Additional, unscheduled, ECGs may be performed at the discretion of the investigator at any time during the study as clinically indicated.

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment. All ECGs need to be collected and copies kept in the medical record for central review, if requested by the sponsor.

Any identifier details must be redacted (e.g. subject initials, date of birth).

Table 8-8 ECG collection plan for Treatment Period

Visit	Time	ECG Type	Number of ECG
Screening	Anytime	12 Lead	1
Month 6	Anytime	12 Lead	1
Month 12	Anytime	12 Lead	1
EoT	Anytime	12 Lead	1
Unscheduled	Anytime	12 Lead	1

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

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

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

8.4.9 Cardiac imaging – ECHO or MUGA scan

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

The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 6-15.

8.4.10 Pregnancy and assessments of fertility

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 will have serum pregnancy tests within 72 hours prior to the first dose of study treatment and at the Month 12 or the EoT visit. Monthly urine pregnancy tests will then be required to be performed beginning at Month 1 through Month 11. See Table 8-1 for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements.

Male subjects (including those that have had a vasectomy) taking study treatment must use a condom during intercourse from Day 1 through 16 weeks after stopping treatment, and should not father a child during these periods. In addition, male participants should not donate sperm from Day 1 to 16 weeks after last dose.

Refer to Section 5.2 for contraception requirements.

Women of child-bearing potential will be instructed to contact the site immediately at any time during the study and for 16 weeks after stopping treatment should they have a positive pregnancy test.

Refer to Section 10.1.4 for details on Pregnancy Reporting.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.5 Additional Assessments

8.5.1 Patient Reported Outcomes

The patient-reported outcomes (PRO) data will be collected using an electronic tablet device. All PRO assessments should be administered in the subjects' local language according to the Visit Evaluation Schedule in Table 8-1, Table 8-2, and Table 8-3, prior to any tests, treatments or receipt of results from any test to avoid biasing the subject's perspective.

Subjects should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, subjects should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all subjects, including from those who discontinue prior to the study evaluation completion visit, however, if subjects refuse to complete questionnaires, this should be documented in study source records. Subject's refusal to complete study questionnaires are not protocol deviations.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the subject, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in Section 10 of this protocol. Investigators should not encourage the subjects to change responses reported in questionnaires.

8.5.1.1 Functional Assessment of Cancer Therapy-Melanoma (FACT-M)

The Melanoma Subscale of the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, and global health status. The Melanoma Subscale of the FACT-M are recognized as reliable and valid measures (Cormier 2008) frequently used in clinical trials of patients with advanced or metastatic cancer.

The FACT-M quality of life questionnaire consists of the FACT-General (FACT-G) plus the Melanoma Subscale and the Melanoma Surgery Subscale, which complement the general scale with items specific to HRQOL in melanoma. Higher scores on all the FACT-M scales indicate a higher quality of life. In psychometric testing FACT-M questionnaire has been shown to be a reliable and valid instrument for subjects with melanoma that can be used for the assessment of

HRQOL in clinical trials (Cormier 2008). For the purpose of this study the 16 items that comprise the Melanoma Subscale of the FACT-M are used.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

- Disease relapse
- Unacceptable adverse event, including meeting stopping criteria as described in Sections 6.5.1 and 6.5.2.
- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Any situation in which study participation might result in a safety risk to the subject.

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

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

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. 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 (per assessment schedule in Table 8-2 or Table 8-3):

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

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

9.1.1.1 Replacement policy

Not applicable. Subjects will not be replaced on study.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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 subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information according to applicable law.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject 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 for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject (see also Section 9.2). 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Following twelve months of treatment or early treatment discontinuation, no further study treatment will be made available to a subject. All treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

Study completion is defined as 24 months after the first dose (Day 1) of the last subject enrolled, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Subjects will be followed on the study per the schedule of assessments (refer to Table 8-1, Table 8-2, Table 8-3). Each subject will complete their EoS visit 24 months after Day 1 of the last subject enrolled or at early withdrawal from the study, death, withdrawal of consent, or lost to follow-up.

Post relapse therapy will be permitted during the study in the Follow-up Period per Investigator discretion, but not provided or administered as study treatment.

The final OS analysis will be performed when the last subject completes their EoS visit (i.e. 24 months after LPFV). All available data from all subjects up to this cut-off date will be analyzed.

The study will be closed when all subjects have either died, withdrawn consent, are lost to follow-up, 24 months after Day 1 of last subject enrolled, or when the last EoS visit is completed, whichever occurs first.

In the event the study is terminated due to futility, study subjects currently on study treatment in the Treatment Phase and who are still deriving clinical benefit will be eligible to continue their adjuvant treatment (i.e. up to 12 months dabrafenib in combination with trametinib) through a locally established Novartis program.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign, symptom or disease) in a subject or clinical investigation subject 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.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

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

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

Adverse events that begin or worsen after informed consent must be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent must be recorded in the Medical History page of the subject's CRF. Adverse event monitoring must be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) must be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom must be reported as a separate Adverse Event.

Adverse events will be assessed 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, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the subject during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE v4.03 Grade 1-5)
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 subject
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.
6. 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

7. its outcome i.e., its recovery status or whether it was fatal

If the event worsened the event should be reported a second time in the CRF noting the start date when the even 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 subject.

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.

All adverse events must be treated appropriately. If a concomitant medication or non-drug therapy is given, this action must be recorded on the Adverse Event CRF.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Relapse or progression of malignancy (including fatal outcomes), confirmed via Investigator assessment, should not be reported as a serious adverse event.

Adverse events separate from the relapse or progression of malignancy (example, 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
- they are considered clinically significant
- they require therapy

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 subjects with the underlying disease.

Adverse events of special interest

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

AESIs are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the IB and a list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms to flag as AESI's will be included in the SAP.

AESI for the study drug include:

Table 10-1 Adverse events of special interest by study treatment

	trametinib	dabrafenib	dabrafenib and trametinib combination
Hepatic disorders	x		x
Pneumonitis/Interstitial lung disease	x		x
Skin toxicities (e.g., rash, dermatitis acneiform)	x		x
Bleeding events	x		x
Hypersensitivity	x	x	x
Pancreatitis		x	x
Neutropenia			x
Pulmonary embolism, deep vein thrombosis	x		x
Pre-renal and intrinsic renal failure		x	x
New primary melanoma		x	x
Non-Cutaneous Treatment-Emergent Malignancies		x	x
Hyperglycemia		x	x
Cardiac related events	x		x
Complicated pyrexia and/or Grade 3 and Grade 4 pyrexia		x	x
Uveitis		x	x
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment and uveitis)	x		x
Cutaneous squamous cell carcinoma including keratocanthoma		x	x
Hypertension	x		x

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 subject 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 subject'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 subject 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 subject 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.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease relapse of the study indication. Relapse of malignancy (including fatal outcomes), confirmed via Investigator assessment, should not be reported as a serious adverse event.

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 subject safety, every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 30 days after the subject has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Any additional information for the SAE including 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.

Any SAEs experienced after the 30 day safety evaluation follow-up period (or 5 half-lives, whichever is longer) must only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically

thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment). Instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) 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 drug 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.

10.1.4 Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for the investigational drug at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are considered to be of child-bearing potential using highly effective methods of contraception. In the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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, subject 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 collected in the DAR eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. 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.

Table 10-2 Guidance for capturing the study treatment errors including misuse/abuse

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

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

10.2 Additional Safety Monitoring

Not applicable

10.2.1 Liver safety monitoring

Please, refer to Section 6.5.1.3.2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Please refer to Section 6.5.1.3.3.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

10.2.3 Data Monitoring Committee

This study will include a DMC that will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in

the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data, and critical efficacy variables and recommend whether to continue, modify or terminate the trial. The DMC will be informed and convened quickly in the event of unexpected results that raise concerns to permit DMC evaluation and input. An IA for futility of the primary endpoint will be conducted when the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier) (see Section 12.7 and the DMC charter for details). At the time of this IA, the futility of a secondary efficacy endpoint RFS will also be assessed.

Responsibilities of the DMC and communication flow between the DMC and Novartis will be described in the DMC charter document. It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician.

10.2.4 Steering Committee

The steering committee will be established comprising investigators participating in the trial, i.e. not being members of the DMC 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 membership and role of the Steering Committee will be defined in a Steering Committee charter.

11 Data Collection and Database Management

11.1 Data collection

The 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 Principal investigator 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 subject 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT) for clinically supplied drug. 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. IRT will not be utilized to track study drug that is sourced as local commercial supply; this information will be recorded on local study drug accountability logs.

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

After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

11.3 Site monitoring

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

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

12 Data analysis and statistical methods

One IA for futility is planned for the study when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier.) Primary statistical analysis will be performed 12 months after LPFV. Final analysis of the study will be performed at the end of the study defined as 24 months after LPFV.

The data will be summarized with respect to demographic and baseline characteristics, and safety observations and efficacy measurements. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

12.1 Analysis sets

The Full Analysis Set (FAS) and Safety Set are defined in the same way and comprise all subjects who received at least one dose of study treatment.

The Safety Set includes all subjects who received at least one dose of study treatment.

12.2 Subject demographics and other baseline characteristics

Summary statistics of subject demographics and baseline characteristics will be provided using FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

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

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

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

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

12.4 Analysis of the primary endpoint(s)

To assess whether an adapted AE-management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is defined as the composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia or permanent treatment discontinuation due to pyrexia up to 12 months of therapy among overall treated subjects.

The rate of this composite endpoint is calculated as the total number of subjects experiencing at least one of the three components of the composite endpoint (i.e., grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia), divided by the total number of subjects in the FAS. The composite endpoint is assessed over a treatment period of 12 months.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be based on the calculation of the observed pyrexia event rate up to 12 months of therapy (primary endpoint) using the FAS. The observed pyrexia event rate will be summarized using descriptive statistics (N, %) along with its two-sided exact 95% confidence interval (Clopper and Pearson 1934).

In the COMBI-AD study, 87 out of 435 subjects in the treatment arm (20%) developed either grade 3/4 pyrexia or hospitalization due to pyrexia or discontinued due to pyrexia. This rate of 20% will be used as the historical control rate for the assessment of pyrexia management algorithm in this study.

Evidence of treatment effect (improvement in pyrexia event rate using the AE-management algorithm) will be concluded, if the upper bound of the two-sided 95% confidence interval is less than 20%.

The exact 95% confidence intervals for various observed event rates at the primary analysis are shown in Table 12-1. If 100 (16.7%) out of 600 subjects are observed with pyrexia event, then the upper bound of the 95% confidence interval will be less than 20%.

Table 12-1 Exact 95% CI for different observed event rates at primary analysis

N	r	Pyrexia event rate (%)	95% exact CI (%)*
600	100	16.7	13.8 – 19.9
600	101	16.8	13.9 – 20.1
600	102	17.0	14.1 – 20.2
600	103	17.2	14.2 – 20.4
600	104	17.3	14.4 – 20.6
600	105	17.5	14.5 – 20.8

N: Total numbers of subjects;

r: Number of subjects with pyrexia events at primary analysis

* Clopper and Pearson (1934)

In addition, the probability that the pyrexia even rate is below the threshold of 20% will be calculated from the posterior distribution. For illustration, as shown in Table 12-2, if 104 out of 600 subjects are observed with pyrexia events at primary analysis, then the posterior probability of observing an event rate of $< 20\%$ is 0.954 (probability ≥ 0.95).

Table 12-2 Posterior probability for a positive effect at primary analysis

N	r	Pyrexia event rate (%)	Posterior* Pr (event rate<20%|data)
600	100	16.7	0.983
600	101	16.8	0.977
600	102	17.0	0.971
600	103	17.2	0.963
600	104	17.3	0.954
600	105	17.5	0.943
600	110	18.3	0.854
600	115	19.2	0.703
600	120	20.0	0.508
600	125	20.8	0.313
600	130	21.7	0.161
600	135	22.5	0.068

N: Total numbers of subjects;

r: Number of subjects with pyrexia events at primary analysis

* A diffuse (highly non-informative) prior distribution of the composite rate with a skeptical expectation of 20%, namely Beta (0.25, 1) is assumed.

12.4.3 Handling of missing values/censoring/discontinuations

No missing data imputation rule will be applied to the primary analysis. For the primary endpoint, subjects who discontinued prematurely prior to 12 months without pyrexia will be counted as no event.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

The secondary endpoints are the RFS and OS rates at 12 and 24 months.

RFS is defined as the time from the date of first dose of the study medication to the date of disease recurrence or death due to any cause. Treatment emergent malignancies other than second melanomas will not be considered as events. RFS will be censored if no RFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-cancer therapy.

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

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

12.5.2 Safety endpoints

Other secondary objectives related to safety include:

- To evaluate overall AE rate leading to permanent treatment discontinuation by 12 months
- Frequency, number of episodes, duration, AE management (including concomitant medications and study treatment modifications) due to pyrexia
- To evaluate overall safety (AEs and SAEs)

For all safety analyses, the safety set will be used.

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

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

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse *events* and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

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.

The proportion of subjects in the study, who have permanently discontinued treatment due to any AE, will be estimated, along with 95% confidence intervals using Clopper Pearson exact method.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

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 v 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

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

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

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

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

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

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

12.5.3 Patient reported outcomes

Changes in HRQOL from baseline will be assessed using the FACT-M questionnaire. The summary table of change in HRQOL from baseline will be presented by using the FAS.

12.6 Analysis of exploratory endpoints

Not applicable

12.7 Interim analyses

One IA for futility of the primary endpoint is planned for the study when approximately the first 200 subjects dosed have been followed for 6 months (either completed 6 months of treatment or discontinued treatment earlier.) At the time of this IA, the futility of a secondary efficacy endpoint RFS will also be assessed. This analysis will allow assessing the impact of the adapted pyrexia AE-management algorithm on both the pyrexia event rate and the RFS rate at 6 months. The DMC will review the IA results and make a recommendation using the scenarios provided below. Any decision to stop or continue the pyrexia management algorithm will be made based on all data available at the IA cut-off taking the futility analysis into account.

From the COMBI-AD study that used the approved pyrexia management algorithm, the pyrexia event rate (composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia) at 12 month observed for dabrafenib + trametinib (N=435) was: 20% with 95% CI (16%, 24%). Under the new pyrexia treatment algorithm, an observed primary endpoint rate of at least 20% may indicate lack of improvement of the new algorithm. Assessment of futility for primary endpoint will be based on the calculated Bayesian predictive probabilities of the event that observed pyrexia event rate will be 20% or more in the FAS, if the study is continued beyond the interim (i.e. till the primary analysis).

The pyrexia event rate is assumed to be binary and the number of subjects with pyrexia events is assumed to follow a binomial distribution. Suppose the prior belief regarding the probability of event rate (π) is that it has a beta distribution with parameters a_0 and b_0. If there are x events out of n subjects, then the posterior distribution for π is beta with parameters $a_1 = a_0 + x$ and $b_1 = b_0 + n - x$. Now let Y represent the number of subjects with pyrexia events from m future observations, then the (posterior) predictive distribution of Y conditional on the observed data at the interim (x events out of n subjects) is a beta-binomial distribution described by

$$p(Y = y|x, n) = \binom{m}{y} \frac{B(a_0+x+y, b_0+n-x+m-y)}{B(a_0+x, b_0+n-x)}$$

where B(a, b) is the beta function.

A diffuse (highly non-informative) prior distribution of the composite rate with a skeptical expectation of 20%, namely Beta (0.25, 1) is assumed.

Under these assumptions, the DMC will be provided the predictive probability of observing pyrexia event rate of ≥ 20%, a criterion that may trigger consideration for stopping the study taking account of all available data and not just the pyrexia event rate data required for determination of futility.

Table 12-3 shows the predictive probabilities of observing pyrexia event rate ≥ 20% (n=200) under different interim results. For illustration, with 200 subjects at IA, if the observed pyrexia event rate is 22%, the probability of observing the pyrexia event rate ≥ 20% at primary analysis is > 80%. The DMC might interpret this scenario as an outcome where stopping the study for futility may be a sensible option. If the observed pyrexia event rate is 18% at IA, the probability of observing the pyrexia event rate ≥ 20% at primary analysis is < 20%.

Table 12-3 Predictive probability of observing composite pyrexia event rate greater or equal 20% (n=200) in the safety set at primary analysis (600 subjects) under different interim results

Observed rate at IA (n=200)		Predictive probability of observing pyrexia event rate ≥ 20% at primary analysis*
# of subjects with pyrexia events	%	
30	15	0.0135
32	16	0.0392
34	17	0.0943
36	18	0.1913
38	19	0.3318
40	20	0.5000
42	21	0.6673
44	22	0.8058
46	23	0.9015
48	24	0.9569
50	25	0.9838
52	26	0.9948
54	27	0.9986
56	28	0.9997
58	29	0.9999
60	30	1.0000

*prior distribution Beta (0.25, 1) is assumed.

At the time of this IA, the DMC will also be provided with interim results for the secondary endpoint RFS. Similar to the futility analysis for the primary endpoint, Bayesian predictive probabilities of the RFS rate will be provided.

From the COMBI-AD study, the Kaplan-Meier estimated RFS rate at 12 month for control group and treatment group were: 56% with 95% CI (51%, 61%) and 88% with 95% CI (85%, 91%), respectively. We consider the futility threshold of 12-month RFS rate of 61%, which is the upper bound 95% CI of control group, and calculate the predictive probability (PP) as follows:

PP = Prob. [Observed 12 month RFS rate ≥ 61% | x, n; x successes among n subjects]

The DMC will be provided the predictive probability of observing RFS of ≥ 61%, a criterion that may trigger consideration for stopping the study taking account of all available data and not just the RFS data required for determination of futility.

Table 12-4 shows the predictive probabilities of observing RFS rate ≥ 61% (n=200) under different interim results. For illustration, with 200 subjects at IA, if the observed RFS rate at 6-month is 65%, the probability of observing the RFS rate ≥ 61% at the primary analysis at 12 months is > 90%. If the observed RFS rate is 57%, the probability of observing the RFS rate ≥ 61% at the primary analysis is < 10%.

Table 12-4 Predictive probability of observing RFS rate greater or equal 61% (n=200) at the secondary analysis (600 subjects)

Observed rate at IA (n=200)	

# of relapse free	%	Predictive probability of observing RFS rate ≥ 61% at secondary analysis*
110	55	0.0163
112	56	0.0371
114	57	0.0760
116	58	0.1403
120	60	0.3550
122	61	0.4930
124	62	0.6321
128	64	0.8529
130	65	0.9201

*prior distribution Beta (0.37, 1) is assumed.

Subject enrollment will not be stopped for the IA. According to enrollment expectation, approximately 570 subjects are planned to be included in the study at the time of the IA cutoff.

12.8 Sample size calculation

The sample size calculation is based on the primary variable. The sample size of 600 has been chosen so that the study operating characteristics comply with the requirement to have a high probability (e.g. > 95%) for futility at IA if the true 12-month pyrexia event rate is > 20%, e.g., when the true pyrexia event rate is 27%, the probability is 95.5% for futility.

Operating characteristics are described below (see Table 12-5). For illustration, if the true 12-months pyrexia event rate is 30%, then there is a high chance (99.6%) of futility at the time of the IA, and the probability to continue the study and conclude success is lower than 0.001.

If the true pyrexia event rate is 20%, then the probability of observing a pyrexia event rate < 20% (i.e., study success for primary analysis) is 43.4%. If the true pyrexia event rate is lower (for example 18%), then there is 83.9% probability of declaring study success for primary analysis.

Table 12-5 Operating Characteristics

True 6 -month event rate	Probability to stop the study at IA	Probability of success at primary analysis (i.e., not stop at the IA and observe event rate < 20% at primary analysis)
16%	0.016	0.980
17%	0.040	0.939
18%	0.086	0.839
19%	0.161	0.661
20%	0.265	0.434
21%	0.391	0.228
22%	0.528	0.094
25%	0.856	0.001
26%	0.917	<0.001
27%	0.955	<0.001
28%	0.978	<0.001

True 6 -month event rate	Probability to stop the study at IA	Probability of success at primary analysis (i.e., not stop at the IA and observe event rate < 20% at primary analysis)
30%	0.996	<0.001

Probabilities are calculated based on the exact binomial distribution.

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 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, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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, EudraCT etc.) .

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol Amendments

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

Only amendments that are required for subject 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 subject 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.

Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

Atkinson V, Long GV, Menzies AM, et al (2016) Optimizing combination dabrafenib and trametinib therapy in BRAF mutation-positive advanced melanoma patients: Guidelines from Australian melanoma medical oncologists. Asia Pac J Clin Oncol. Dec;12 Suppl 7:5-12.

Cormier JN, Ross MI, Gershenwald JE, et al (2008). Prospective assessment of the reliability, validity, and sensitivity to change of the Functional Assessment of Cancer Therapy-Melanoma questionnaire. Cancer; 112:2249-2257

Cuzick J, Sestak J, Forbes J, et al (2014) Anastrozole for prevention of breast cancer in highrisk postmenopausal women (IBIS-II): an international, double-blind, randomised placebocontrolled trial. Lancet; 383: 1041-8.

Eggermont A, Suciu S, Testori A, et al (2012) Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer; 48:218-25.

Eggermont A, Chiarion-Sileni V, Grob JJ, et al (2015) Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol.;16(5):522-530.

Eggermont A, Suciu S, Rutkowski P, et al (2016) Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB-III cutaneous melanoma patients comparing intermediate doses of interferon- alpha-2b (IFN) with observation with ulceration of primary is key determinant for IFN- sensitivity. Eur J Cancer; 55:111-21.

Eggermont A, Dummer R (2017) The 2017 complete overhaul of adjuvant therapies for high-risk melanoma and its consequences for staging and management of melanoma patients. Eur J Cancer. Nov;86:101-105.

Falchook G, Long G, Kurzrock R, et al (2014) Dose Selection, Pharmacokinetics, and Pharmacodynamics of BRAF Inhibitor Dabrafenib (GSK2118436) Clin Cancer Res; 20: 4449-58.

Faries MB, Thompson JF, Cochran AJ, et al (2017) Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med. Jun 8;376(23):2211-2222.

Flaherty K, Infante JR, Daud A, et al (2012) Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. Nov 1;367(18):1694-703.

Flaherty K, Robert C, Hersey P, et al (2012) Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med; 367:107-14

Hauschild A, Grob JJ, Demidov LV, et al (2012) Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomized controlled trial. Lancet;380:358-65.

Hodi F, O'Day S, McDermott D, et al (2010) Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med; 363:711-23.

Infante J, Fecher L, Falchook G, et al (2012) Safety, pharmacokinetic, pharmacodynamic, and effi cacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol; 13:773-81.

Kirkwood J, Strawderman M, Ernstoff M (1996). Interferon Alfa-2b Adjuvant Therapy of High-Risk Resected Cutaneous Melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol; 14:7-17.

Kirkwood J, Ibrahim J, Sosman J, et al (2001) High-Dose Interferon Alfa-2b Significantly Prolongs Relapse-Free and Overall Survival Compared With the GM2-KLH/QS-21 Vaccine

in Patients With Resected Stage IIB-III Melanoma: Results of Intergroup Trial E1694/S9512/C509801. J Clin Oncol; 19: 2370-80.

Kirkwood J (2013) Adjuvant Immunotherapy of Melanoma, and Development of New Approaches Using the Neo- Adjuvant Approach in Melanoma. Clin Dermatol. 31: 237-50.

Larkin J, Chiarion-Sileni V, Gonzalez R, et al (2015) Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med; 373:23-34

Larkin J, Minor D, D'Angeloet S, et al (2017) Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol; 35.

Leiter U, Stadler R, Mauch C, et al (2016) German Dermatologic Cooperative Oncology Group (DeCOG). Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol. Jun;17(6):757-767.

Lewis K, Larkin J, Ribas A et al (2017) ESMO Abstract 1241P, Annals of Oncology, 28, sup5

Long G, 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 G, 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

Long GV, Eroglu Z, Infante J, et al (2017) Long-Term Outcomes in Patients With BRAF V600–Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib. *J Clin Oncol*.;74:1025.

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. Jul 1;28(7):1631-1639.

Long GV, Hauschild A, Santinami M, et al (2017) Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. Nov 9;377(19):1813-1823.

Mehta R, Barlow W, Albain K, et al (2012) Combination Anastrozole and Fulvestrant in Metastatic Breast Cancer. N Engl J Med; 367:435-44.

National Comprehensive Cancer Network (2017) – NCCN – Melanoma guidelines; version 1

National Comprehensive Cancer Network (2018) – NCCN – Melanoma guidelines; version 1

Robert C, Karaszewska B, Schachter J, et al (2015) Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. N Engl J Med; 372:30-9.

Robert C, Karaszewska B, Schachter J, et al (2016) ESMO Abstracts Annals of Oncology 27 (Supplement 6): vi552–vi587

Romano E, Scordo M, Dusza SW,et al (2010). Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol. Jun 20;28(18):3042-7.

Schadendorf D, Amonkar MM, Milhem M et al (2014) Functional and symptom impact of trametinib versus chemotherapy in BRAF V600E advanced or metastatic melanoma: quality-of-life analyses of the METRIC study. Ann Oncol. Mar;25(3):700-6.

SEER (2017). https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-andstatistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf.

Slamon D, Leyland-Jones B, Shak S, et al (2001) Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. N Engl J Med; 344:783-92.

Weber J, Mandala, M, Del Vecchio M, et al (2017) Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma, N Engl J Med. 2017 Nov 9;377(19):1824-1835

WHO (2017). Skin Cancer http://www.who.int/uv/faq/skincancer/en/index1.html accessed 11-Aug-2017.

Yu A, Yadav N, Lung B (2015) Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat; 149: 489-95.

16 Appendices

16.1 Appendix 1: AJCC Melanoma Staging Eight Edition

Table 16-1 Melanoma Stage III Subgroups Based on Primary Tumor (T) and Regional Lymph Nodes (N) categories

AJCC Eighth Edition
Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned

Legend	
A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

Table 16-2 Definition of Regional Lymph Node (N)

	EXTENT OF REGIONAL LYMPH NODE AND/OR LYMPHATIC METASTASIS	
N CATEGORY	NO. OF TUMOR-INVOLVED REGIONAL LYMPH NODES	PRESENCE OF IN-TRANSIT, SATELLITE, AND/OR MICROSATELLITE METASTASES
NX	Regional nodes not assessed (eg, sentinel lymph node [SLN] biopsy not performed, regional nodes previously removed for another reason); Exception: pathological N category is not required for T1 melanomas, use clinical N information	No
N0	No regional metastases detected	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or 3 tumor-involved nodes or any number of in-transit, satellite, and/or micro-satellite metastases with one tumor-involved node	
N2a	Two or 3 clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or 3, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Reproduced from Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.