TITLE PAGE

Division: Worldwide Development
Information Type: Clinical Protocol

Title:	[A Phase II Open-Label, Two-Arm Study of the MEK Inhibitor, Trametinib, To Investigate the Safety and Anti-Cancer Activity in Subjects with Melanoma with BRAF non-V600 Mutations]

Compound Number(s): GSK1120212

Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center Protocol Number: **VICC MEL 1457**

Development Phase: II

Description: This study is a Phase II, open-label, multi-site two-arm study designed to determine the activity and safety of orally administered MEK inhibitor trametinib (GSK1120212), in subjects with melanoma harboring mutations in *BRAF* at locations other than codon 600 (BRAFnonV600^{MUT}) or BRAF fusions. The study will also evaluate the effect of therapy on tumor biomarkers. All patients will receive trametinib 2mg orally administered once daily. Cohort A will consist of subjects with melanoma harbouring mutations which have high or intermediate intrinsic catalytic activity and/or which previously been described sensitive to MEK inhibitors in pre-clinical and/or clinical studies (L597, K601E, G469A, E586K, F595L) as well as BRAF fusions. Cohort B will consist of subjects with melanoma harbouring mutations that have previously been shown to have low affinity for MEK phosphorylation and low intrinsic catalytic activity and/or low sensitivity to MEK inhibitors from previous studies (D594V, G466V, G496R etc), or for which the catalytic activity and effects on sensitization to MEK inhibitors is unknown. The primary endpoint is objective response rate to trametinib for patients in Cohort A; secondary endpoints include objective response rates in Cohort B, safety, progression free survival and overall survival in both treatment arms.

Subject: MEK inhibitor, trametinib, GSK1120212, BRAFV600 wild type, BRAF non-V600 mutant, NRAS wild type, cutaneous melanoma

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Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK1120212	Exempt	

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Title: [A Phase II Open-Label, Two-Arm Study of the MEK Inhibitor, Trametinib, To Investigate the Safety and Anti-Cancer Activity in Subjects with Melanoma with BRAF non-V600 Mutations]

Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center Protocol Number: VICC MEL 1457

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-Human Chorionic Gonadotropin
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CfDNA	Circulating cell free DNA
CI	Confidence Interval
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetic Modeling and Simulation
CPSR	Clinical Pharmacology Study Report
CR	Complete response
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CTA	Clinical Trial Authorization
CTR	Clinical Trial Registry
CV	Coefficient of variance
DBP	Diastolic blood pressure
DILI	Drug Induced Liver Injury
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FTIH	First time in humans
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyltransferase
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	International Data Standards Library
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International normalization ratio
IP	Investigational Product
IRB	Institutional Review Board
IRC	Independent Review Committee
IU	International Unit
IV	Intravenous
IVRS	Interactive voice response system
Kg	Kilogram
L	Liter
LFTs	Liver function tests
LLN	Lower limit of normal
Ln	Naperian (natural) logarithm
LOQ	Limit of quantification
LLQ	Lower limit of quantification
LSLV	Last subject's last visit
LVEF	Left Ventricular Ejection Fraction
µg	Microgram
µL	Microliter
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRS	Magnetic resonance spectroscopy
MRT	Mean residence time
MSDS	Material Safety Data Sheet

Msec	Milliseconds
MTD	Maximum tolerated dose
MUGA	Multigated (radionuclide) angiogram
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
PD	Progressive disease or pharmacodynamic
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic
PR	Partial response
QC	Quality control
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RCR	Recommended Combination Regimen
RNA	Ribonucleic acid
RPED	Retinal Pigment Epithelial Detachment
RVO	Retinal Vein Occlusion
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation or stable disease
SOP	Standard Operating Procedure
T	Time of last observed quantifiable concentration
t1/2	Terminal phase half-life
T	Dosing interval
Tlag	Lag time before observation of drug concentrations in sampled matrix
Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
UPC	Urine protein creatinine
US/USA	United States/United States of America
Vd/F	Apparent volume of distribution after extravascular (e.g., oral) administration
VICC	Vanderbilt-Ingram Cancer Center
WBC	White blood cells

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1. INTRODUCTION

1.1. Background

Cutaneous melanoma is the most aggressive form of all skin cancers. Worldwide, it is currently expected that approximately 132,000 people will be diagnosed with melanoma each year and some 37,000 people are expected to die of the disease annually. Untreated, the median survival time for patients with Stage IV melanoma is approximately 6 months with 26% of subjects alive at 1-year (Korn 2008); the estimated 5-year survival rate is < 10% (Huncharek 2001). Median progression-free survival (PFS) is also short at 1.7 months and only 14.5% of subjects are progression-free at 6 months (Korn 2008).

Much has changed in the treatment landscape of cutaneous melanoma recently, but with the exception of ipilimumab, significant advancements have been made exclusively for patients with mutations in a specific locus of the BRAF protein (BRAFV600) that causes constitutive activation of the RAS/RAF/MEK/ERK (MAPK) pathway. BRAF is part of the RAS/RAF/MEK/ERK (MAPK) pathway, which is a critical proliferation pathway in melanoma. Normally, the MAPK pathway is activated by the binding of extracellular growth factors to membrane-bound growth factor receptors which then recruit intracellular proteins to the cell membrane, leading to the activation of the small guanosine triphosphate (GTP)-binding protein RAS. As a result, RAS adopts an activated conformation which in turn activates RAF, which phosphorylates MEK on two regulatory serine residues. Activated MEK then phosphorylates threonine and tyrosine residues on its only known substrates, the MAP kinases ERK1 and ERK2. Phosphorylated ERK dimerizes and translocates to the nucleus, where it plays a critical role in cellular proliferation, nuclear transport, deoxyribonucleic acid (DNA) repair, messenger ribonucleic acid processing, and translation.

Approximately 40% of cutaneous melanomas harbor a BRAFV600 mutation (BRAF $V600^{MUT}$). These mutations increase the intrinsic serine-threonine kinase activity of the BRAF protein (Davies 2002). The presence of a BRAF $V600^{MUT}$ in a melanoma correlates with increased activity of, and functional dependence upon, the MAPK pathway. Most importantly, the presence of BRAF $V600^{MUT}$ also correlates with clinical benefit in patients to treatment with small molecule inhibitors of the V600-mutant BRAF protein and MEK inhibitors. Vemurafenib (BRAFi, Genentech), dabrafenib (BRAFi, GlaxoSmithKline), and trametinib (MEKi, GlaxoSmithKline) have all gained regulatory approval for the treatment of stage IV or unresectable stage III melanoma patients with BRAF $V600^{MUT}$ melanoma. However, these agents are not approved for use in patients without a mutation. As these patients represent > 50% of cutaneous melanoma patients, and a much higher proportion of patients with non-cutaneous melanomas, there is a critical need to identify additional effective therapeutic approaches.

Approximately 5% of all melanomas harbour mutations in BRAF in loci other than V600 (BRAF nonV600 ^{MUT}). These mutations are often not detected by many testing platforms which are commonly used in clinical practice that assess only codon 600. However, they are detected by testing platforms that assess for other regions of the *BRAF* gene that are known to be affected by somatic mutations, as well as platforms that sequence the entire *BRAF* gene. Many of these BRAF nonV600 ^{MUT} result in increased kinase activity of the

BRAF protein in vitro ("high activity group" including L597V, K601E, G469A) (Wan 2004). In addition, other mutations that do not increase the catalytic activity of BRAF ("low activity/unknown" group, including G466E, D594V, G596R) (Wan 2004) appear to be able to increase MAPK pathway activity through protein-protein interactions with other components of this pathway. Furthermore, BRAF fusions have been recently identified in a small percentage of melanomas which activate MAPK signaling (Botton 2013; Hutchinson 2013). MEK inhibitors have demonstrated activity in vitro in melanomas with high activity non-V600 BRAF mutations and individual patients with these mutations have demonstrated significant clinical responses to treatment with MEK inhibitors. Thus, MEK inhibitors may have value as a targeted therapy in this population. Although there is evidence that low-activity BRAF mutations activate MEK and ERK signaling, the clinical benefit of MEK inhibition in melanomas with such mutations is poorly defined. In addition, multiple somatic mutations in BRAF have been identified that have yet to be functionally characterized (Wan 2004).

1.2. Trametinib

1.2.1. Trametinib Background

Trametinib is a potent, highly selective, allosteric inhibitor of MEK1 and MEK2, is non-competitive towards ATP, and inhibits both MEK activation and kinase activity. Trametinib interferes with cellular signal transduction and induces apoptosis in human tumor cell lines both *in vitro* and in xenograft mouse models. Activity was most extensive in cell lines and models that contained activating BRAF mutations (Gilmartin 2011; Jing 2012).

Trametinib was first dosed in humans in 2008 in MEK111054 (Infante 2012). This first-in-human study identified the recommended monotherapy dose for trametinib (2 mg once daily continuous dosing); established the safety, PK, and PD profiles; and demonstrated clinical activity in several tumor types including $BRAF^{WT}$ melanoma (Falchook 2012). As of 23 June 2012, trametinib has been administered to more than 1700 subjects in 20 studies, including 10 monotherapy studies [**Novartis,** 2016. Trametinib was approved by the United States Food and Drug administration on 29 May 2013, under the brand name Mekinist, as a monotherapy in the setting of $BRAFV600^{MUT}$ melanoma.

Trametinib has also been evaluated in combination with dabrafenib in $BRAFV600^{MUT}$ melanoma. In BRF113220, this combination appeared more efficacious than dabrafenib alone, prolonging progression-free survival and increasing objective response rates (Flaherty 2012) Although trametinib has been most extensively tested in $BRAFV600^{MUT}$ melanoma, studies combining trametinib with other antineoplastic molecules are opening in other melanoma subtypes. The study described here is the first study in which trametinib or any molecularly targeted therapy will be evaluated specifically in $BRAFnonV600^{MUT}$ melanoma.

1.2.2. Pharmacokinetics of Trametinib in Humans

Peak plasma trametinib concentrations were observed 1.50 hours following single-dose administration of trametinib tablets under fasted conditions. The absolute oral bioavailability of the trametinib 2.0 mg tablet is moderate to high (72%) relative to a coadministered IV microdose [**Novartis,** 2016]. Trametinib is highly bound to plasma proteins (97.4%), has a high volume of distribution (Vd; 1060 L) and a long terminal half-life (5.3 days), and accumulates with repeat once daily dosing.

The metabolism of trametinib has been investigated using a series of *in vitro* and *in vivo* studies. Trametinib is metabolized via deacetylation to form M5 (deacetylation alone) and deacetylation in combination with mono-oxygenation to form M7 (mono-oxygenation and deacetylation). M5 can be N-glucuronidated to form M6 (N-glucuronidation of M5) while M7 undergoes O-glucuronidation to form M9 (O-glucuronidation of M7), a minor pathway in humans. Trametinib is metabolized predominantly via deacetylation (non-CYP450 mediated) alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. Although the specific enzyme responsible has not been identified, deacetylation is likely mediated by hydrolytic esterases, such as carboxyl-esterases or amidases.

1.2.3. Clinical Safety of Trametinib

The adverse events (AEs) observed in the pivotal, Phase III registration study (Flaherty 2012) was consistent with that seen across trametinib monotherapy studies and is summarized here. The Phase III study demonstrated that the 2 mg, continuous, once daily dose of trametinib has an acceptable safety profile. Adverse events occurring in ≥15% of subjects that received at least one dose of trametinib (N=211) were rash (57%), diarrhea (43%), peripheral edema (26%), fatigue (26%), dermatitis acneiform (19%), nausea (18%), alopecia (17%), and hypertension (15%). Less than 8% of the subjects had grade 3 or 4 rash (including only one patient with grade 4), and no grade 3 or 4 diarrhea was observed. Decreased ejection fraction or ventricular dysfunction occurred in 7% of the subjects, and <1% (n=2) had grade 3 cardiac-related events that were considered trametinib related and led to permanent discontinuation of the study treatment. Ocular events, most of which were grade 1 or 2, occurred in 9% of the subjects. Blurred vision was the most frequent ocular event (4%), and there was one case of reversible chorioretinopathy. Retinal vein occlusion, an AE that has been associated with MEK inhibitors, was observed only extremely rarely. Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest for trametinib because they are either known class effects (i.e. were observed with other MEK inhibitors) or are potentially life-threatening.

1.2.4. Clinical Activity of Trametinib

Trametinib has demonstrated significant clinical activity with an acceptable safety profile in Phase I-III studies (Falchook 2012; Flaherty 2012; Infante 2012; Kim 2013). In $BRAFV600^{MUT}$ melanoma, the Phase III study of trametinib demonstrated improved rates of progression-free survival and overall survival (Flaherty 2012). In this study,

trametinib demonstrated an overall response rate of 22% and a median PFS of 4.8 months. The duration of response was 5.5 months.

BRAFV600^{WT} melanoma has been evaluated in the trametinib first-in-human study (Infante 2012). This study enrolled 39 subjects with BRAFV600^{WT} cutaneous melanoma, of which 4 (10%) had confirmed objective responses (Falchook 2012). The median PFS for these 39 subjects was 2.0 months (95% CI 1.7-3.7 months; (Falchook 2012)). Subjects who were both BRAFV600^{WT} and NRAS^{WT} (n=20) had a higher response rate (20%) than those who were wild type only at BRAF (n=11; response rate= 0%). Moreover, a higher proportion of patients that were wild type for both genes, compared to those that were wild type for only BRAF, were on study treatment at week 24 (40% versus 18%; p=0.26) and at 1 year (30% versus 0%; p=0.07). Importantly, 2 patients with BRAFnonV600^{MUT} melanoma (L597V and G469A) were treated in this study with one achieving a partial response and the other with temporary stabilization of melanoma growth (see section 1.3.1). These results demonstrate that trametinib has clinical activity in subgroups other than BRAFV600^{MUT} melanoma.

1.3 Rationale in study population

1.3.1 Rationale for targeted therapy in BRAF nonV600^{MUT} melanoma

BRAF alterations in loci other than codon V600 occur in 4-6% of advanced melanomas in several published reports (Berger 2012; Dahlman 2012; Krauthammer 2012; Botton 2013). Some of these recurrent alterations constitutively activate MAPK signaling and may be exploited therapeutically. Direct inhibition of mutant BRAF with vemurafenib or dabrafenib appears ineffective in this population, although modest in vitro activity and a brief partial response have been reported for vemurafenib (Dahlman 2012; Bahadoran 2013). By contrast, in the preclinical setting and in occasional patients treated in clinical trials, MEK inhibition appears to be a more active therapeutic approach. For example, BRAF L597^{MUT} and K601E ^{MUT} melanoma demonstrated in vitro sensitivity to trametinib (Dahlman 2012).

Clinical corroboration has been demonstrated by several patients who have achieved a response to MEK inhibitors. For example, a patient with BRAF L597S^{MUT} melanoma had a dramatic response to an experimental MEK inhibitor (TAK-733) (Dahlman 2012). Furthermore, in the phase I trial of trametinib, a patient with BRAF L597V ^{MUT} melanoma experienced a prolonged partial response and remained on study for more than 2 years (Falchook 2012). An additional patient with a BRAF G469A mutation had a best response of stable disease. Finally, in a trametinib phase II study, a patient with BRAF K601E ^{MUT} melanoma experienced a prolonged partial response (Kim 2013). MEK inhibition in this population has not been studied in a systematic fashion and has never been evaluated prospectively. There is strong rationale to systematically evaluate MEK inhibition in the BRAF nonV600E^{MUT} melanoma population as this is a significant subgroup without current approved targeted therapy options.

1.3.2 Rationale for study cohorts

Subjects with BRAF nonV600E^{MUT} melanoma may be further classified by the functional effects of each particular mutation on BRAF kinase activation and subsequent MEK

phosphorylation. All well-characterized BRAF mutations in the kinase domain activate MAPK signaling, although the mechanisms vary. Many of the more common mutations, including V600, L597, K601 (see appendix 1 for full mutation list), robustly activate MAPK signaling through MEK phosphorylation and are predicted to be sensitive to MEK inhibition (Cohort A, "high activity") (Wan 2004). However, other observed mutations including G469E and D594G may signal through other effectors which may confer resistance to MEK inhibition, although the clinical experience with these melanomas is extremely limited (Smalley 2009). Together with additional mutations of unclear significance, (including S467L and P731S), we have labelled this group as cohort B, the "low activity/unknown" group. Additionally, BRAF nonV600 mutations may occur coincidentally with activating NRAS or BRAF V600E mutations. The functional significance of these mutations is not clear. It is hypothesized that these play a secondary role in these tumors; therefore these patients will not be included in our study.

Insight into the relative frequencies of these groups can be obtained from a large group of melanomas which were subjected to whole exon sequencing as part of the melanoma TCGA effort. Among the first 266 tumors, all of which were primaries or metastases of non-acral cutaneous melanomas, 17 (6.3%) harbored somatic BRAF nonV600 mutations and were $NRAS^{WT}$ and $BRAF\ V600^{WT}$. Of these, 10 (3.8%) could be classified as "high activity," with the additional 7 melanomas (2.6%) in the "low activity/unknown" group (3 with low activity, 4 with unknown activity). Our primary study group of interest is cohort A: the "high activity" group, as there is known pre-clinical and clinical rationale to study this population. However, there may be additional patients who will benefit from trametinib in the "low activity/unknown" group (cohort B); therefore this group will also be eligible to receive therapy in an exploratory fashion.

Approximately 1% of melanomas harbor fusions in the *BRAF* gene. (Botton 2013; Hutchinson 2013). These rearrangements fuse the BRAF kinase domain with a partner gene which leads to constitutive activation of the MAPK pathway. BRAF fusions are a frequent recurrent event in pilocytic astrocytomas and other cancers and were recently identified in melanoma and melanocytic tumors (Ciampi 2005; Jones 2008; Palanisamy 2010). BRAF fusion melanoma appears to confer resistance to vemurafenib. By contrast, trametinib strongly inhibited MAPK signaling *in vitro* and is predicted to have clinical activity in BRAF fusions (Hutchinson 2013). Therefore, patients with identified BRAF fusions will be included in cohort A.

2. OBJECTIVES AND ENDPOINTS

Table 1 lists the objectives and corresponding endpoints.

Table 1 Objectives and Endpoints

	Objectives	Endpoints
Primary	1. To determine the clinical efficacy of trametinib in advanced BRAF $nonV600^{MUT}$ melanoma ("high activity" group)	1. Overall response rate (primary statistical endpoint), duration of response, clinical benefit (CR+PR+SD) per RECIST v. 1.1.
Secondary	1. To characterize the safety of trametinib 2. To evaluate the	1. Safety and tolerability as measured by clinical assessments including vital signs and physical examinations, 12-lead

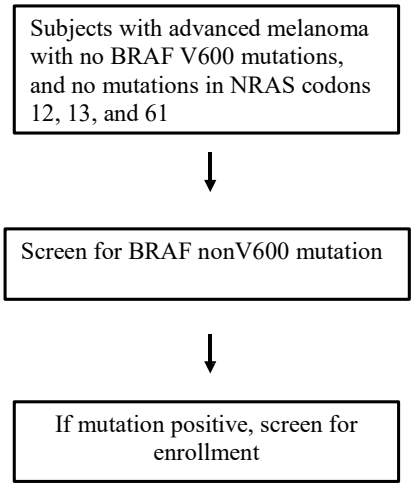
	time to progression (TTP) and overall survival (OS) of trametinib in advanced BRAF nonV600^{MUT} melanoma	electrocardiograms (ECG), echocardiogram (ECHO) or Multi Gated Acquisition (MUGA) scans, chemistry and hematology laboratory values, and adverse events (AEs). 2. TTP and overall survival.
Exploratory	1. To determine the clinical efficacy of trametinib in advanced BRAF nonV600^{MUT} melanoma ("low activity/unknown" group) 2. Identify mechanisms of resistance to trametinib in this patient population	1. Overall response rate, duration of response, clinical benefit (CR+PR+SD) per RECIST v. 1.1. 2. Assess molecular characteristics of patient samples, including archival samples, pre-treatment, early while on treatment, and/or at the time of progression

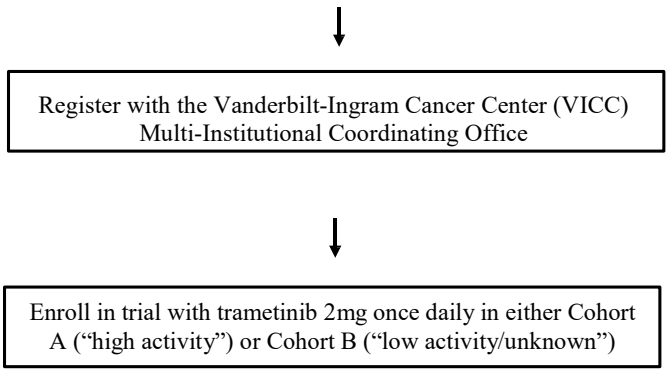
3. INVESTIGATIONAL PLAN

3.1. Discussion of Study Design and Study Schematic

This is a Phase II, open-label, multi-center study in subjects with advanced BRAFnonV600^{MUT} melanoma stratified by activity of genetic alterations. Cohort A will be patients with "high activity" BRAF mutations or BRAF fusion events (see appendix A); cohort B is an exploratory group with BRAF mutations of "low activity/unknown" significance. The study is designed to evaluate the response rate to trametinib at the dose approved by the Food and Drug Administration (FDA) for BRAF V600^{MUT} melanoma in the BRAFnonV600^{MUT} population. Safety will also be assessed.

Figure 1: Study Schematic





Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (see Section 7.1), are essential.

Enrollment Procedures

All patients MUST be registered with the Vanderbilt-Ingram Cancer Center (VICC) Multi-Institutional Coordinating Office prior to the start of protocol treatment. Each participating site must also be registered with their own institution according to their institutional guidelines prior to start of protocol treatment. Prior to the first patient registration, a copy of IRB approval at the respective sites will be requested and on file at the VICC Coordinating Center.

Patients will be centrally registered by sending the completed enrollment packet to the VICC Multi-Institutional Coordinating Office as outlined in the instructions provided on the enrollment form. The enrollment packet must include the following documents:

- Copy of the patient's signed and dated Informed Consent
- Eligibility Checklist
- Coordinating Center enrollment form

3.2. Treatment Schedule

The dose and schedule of trametinib is 2.0 mg administered orally once daily. Alterations to the dose and schedule of trametinib may be incorporated based on toxicity for individual patients. However, the dose level and schedule will not exceed 2.0 mg once daily. Dosing with start with Treatment period 1, Day 1 and the subject may continue treatment with trametinib until the Treatment Discontinuation Criteria are met (Section

6.3).

3.3. Genetic Analysis

Prior to enrolment, subjects will be required to provide archived tumor tissue or undergo tumor biopsy if archived tumor tissue is not available. Evaluation of BRAF mutational status may be performed at any laboratory with Clinical Laboratory Certification Amendment (CLIA) certification status. Most commonly performed diagnostics of BRAF mutations assess only mutations found at codon 600. Therefore, BRAF nonV600 mutations will likely be identified by either next generation sequencing methods (for example, FoundationOne™ assay which assesses the entire coding region of BRAF as well as functional rearrangements in BRAF). Targeted polymerase chain reaction assays may also be performed (for example, MD Anderson Cancer Center performs PCR-based mutational analysis in codons 444, 464, 466, 469, 471, 581, 586, 587, 592, 594, 595, 596, 597, 599, 600, 601, and 605). Patients with detected alterations in BRAF at known or previously unknown loci will be included. Prior testing results from a CLIA-certified laboratory that meet molecular entry criteria (presence of a non-V600 BRAF mutation or BRAF gene fusion; no mutation in codon 600 of BRAF; no mutation in codons 12, 13, and 61 of NRAS) will be sufficient for patient enrolment in the study without further testing.

3.4. Product dosing/administration

Product name	Trametinib	
Formulation description:	The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate), and compressed into tablets. The tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable)	
Dosage form :	Tablet	
Unit dose strength(s)/ Dosage levels	0.5mg	2mg
Physical Description:	White, oval , biconvex film coated tablet, 4.8mm x 8.7 mm	Pink, round biconvex film coated-tablets 8.0 mm in diameter.
Route/Duration	Oral/ Until treatment discontinuation criteria are met	
Dosing Instructions:	Trametinib should be taken fasting, at least 1 hour before or 2 hours after a meal. Trametinib will be administered with approximately eight ounces of water. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.	

3.5. Rationale

3.5.1. Rationale for Study

Trametinib has demonstrated clinical activity in subjects with BRAFV600^{WT} cutaneous melanoma (Falchook 2012). In patients with BRAFnonV600^{MUT} melanoma, several clinical responses have been described to MEK inhibition, including one lasting over two years from trametinib (Dahlman 2012; Falchook 2012). Finally, in vitro evidence supports that inhibition of MAPK signaling through MEK inhibition in BRAFnonV600^{MUT} melanoma, including those with BRAF fusions, is an effective treatment strategy.

3.5.2. Rationale for Population

Subjects with BRAFnonV600^{MUT} melanoma may respond to targeted therapy although as yet there have been no trial specifically enrolling this group. This patient population has an unmet medical need and trametinib monotherapy has achieved objective responses in such subjects. We are subdividing subjects based on the predicted activity of BRAF alterations into Cohort A ("high activity" BRAF mutations and BRAF fusion events) and Cohort B ("low activity/unknown" BRAF mutations) as defined by Wan et al published in Cell 2004; complete list is in appendix 1. This predetermined stratification will allow for improved definition of which subjects are likely to benefit from trametinib.

3.5.3. Rationale for Dose

The starting regimen of trametinib will be 2 mg continuous, once daily. This dose has demonstrated an acceptable safety profile (see Section 1.2.3), clinical activity, and a pharmacodynamic effect in subjects with BRAFV600^{MUT}melanoma (Falchook 2012; Infante 2012). This dose is also the FDA approved dose for subjects with BRAFV600^{MUT} melanoma.

3.5.4. Rationale for Endpoints

The primary endpoint is to determine the clinical efficacy of trametinib in BRAFnonV600^{MUT} melanoma for Cohort A ("high activity" mutations and BRAF fusions). Response criteria based on RECIST 1.1 will be used to assess complete or partial responses, stable disease, or progressive disease. Safety for both cohorts is a secondary endpoint and as such clinical assessments including vital signs and physical examinations, 12-lead ECG, ECHO, chemistry and hematology laboratory values, retinal exams as needed, and AEs will be monitored and evaluated. Progression free survival and overall survival will be additional secondary endpoints.

The exploratory endpoint is to determine the clinical efficacy of trametinib in Cohort B ("low activity/unknown" group). Response criteria based on RECIST 1.1 will be used to assess complete or partial responses, stable disease, or progressive disease (Eisenhauer 2009). PFS and OS for this cohort will be additional exploratory endpoints.

3.6. Study Treatment

All patients will receive trametinib 2 mg orally once daily

3.7. Dosage and Administration of Study Treatment

Trametinib should be administered once per day, continuously; and should be taken at about the same time each day. The study treatment should be administered together with approximately eight ounces of water. Trametinib should be taken fasting, at least 1 hour before or 2 hours after a meal. If a subject vomits after taking study medication, the subject should be instructed **not** to retake the dose and should take the next scheduled dose. A subject may take a dose within 12 hours of the scheduled time. If a dose is missed, a subject should not take a dose within 12 hours of their next scheduled dose of trametinib. Trametinib may not be crushed, chewed, or dissolved in water.

3.7.1. Meals and Dietary Restrictions

Study treatment(s) will be administered under fasting conditions (see Section 3.7).

Fasting will consist of avoiding the oral ingestion of calorie-containing products; ingestion of water is permitted. Any ongoing, usual concomitant medications may be administered while fasting.

3.7.2. Blinding

This is an open-label study.

3.8. Safety Management Guidelines

The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 4.0. The severity of AEs will be graded using the CTCAE, version 4.0. The section includes:

- general guidelines for clinically significant toxicities related to study treatments and
- specific guidelines for adverse events of special interest, which include but are not limited to events that have been observed with higher frequency or severity in subjects receiving trametinib.

Subjects should be carefully evaluated for evidence of drug-related toxicity. The investigator should use clinical judgment to determine which drug may be contributing to the treatment emergent toxicity and make the appropriate dosing adjustments. This may include interruption and/or reducing the dose of one or both treatments. Guidelines for toxicity and dose modifications are provided. Investigators should also refer to the trametinib Investigator Brochure [**Novartis,** 2016].

3.8.1. Dose Levels of trametinib

The dose levels for this study are provided in Table 2.

Table 2 Dose Level Reduction Guidelines

Dose Levels	Trametinib once daily
Full dose	2 mg
1st Dose reduction	1.5 mg
2nd Dose reduction	1.0 mg

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after four weeks of study treatment at the reduced dose, the dose of trametinib may be increased to the previous dose level. If a dose reduction below 1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued.

3.8.2. General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and which do not have specific guidelines (see Table 2) are provided in Table 3.

Table 3 Dose Modification Guidelines for Events Considered Related to Study Treatment

CTCAE Grade	Action and Dose Modification
Grade 1	• Continue study treatment at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Interrupt study treatment if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to grade 1 or baseline, restart study treatment at current dose level

CTCAE Grade	Action and Dose Modification
Grade 3	• Interrupt study treatment • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level** • If the grade 3 toxicity recurs, interrupt study treatment • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by another dose level**
Grade 4	• Interrupt study treatment • Monitor closely • Provide supportive care according to institutional standards • **Discontinue trametinib** OR if the subject is clinically benefiting, discuss continuation of the study treatment with the medical monitor once toxicity resolves to grade 1 or baseline. If continued, **reduce by one dose level**. • If the grade 4 toxicity recurs, **permanently discontinue study treatment**

Treatment with trametinib may be delayed for up to 21 days to allow resolution of toxicity, scheduling difficulties, or investigator discretion. Approval to restart a subject after >21 day delay will require consultation with the medical monitor. Laboratory abnormalities that are not clinically significant (i.e. creatinine phosphokinase levels) but are grade 3 or 4 do not automatically require dose reduction or discontinuation of study drug. They should be discussed in detail with the medical monitor.

3.9. Dose Modification Guidelines for Trametinib Adverse Events of Special Interest

3.9.1. Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in subjects receiving trametinib; (see the trametinib IB [**GlaxoSmithKline,** 2012] for additional information). Guidelines for LVEF decreases and hypertension are provided in Sections 3.9.1.1 and 3.9.1.2, respectively.

3.9.1.1. Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib. Therefore, ECHOs (preferred) or MUGA's must be performed to assess cardiac ejection fraction. The procedure performed at baseline must be performed at all subsequent visits as outlined in the Time and Events Table (see Section 7.1). Electronic copies of all ECHO/MUGA scans will be collected by Vanderbilt for review.

Dose modification guidance and stopping criteria for LVEF decrease are provided (Table 4).

Table 4 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification

Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• **Interrupt trametinib** and repeat ECHO/MUGA within 2 weeks[a]
		• If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline)
		  • Consult with the medical monitor and request approval for restart
		  • Restart treatment with trametinib at reduced dose by one dose level
		  • Repeat ECHO/MUGA 2 , 4 , 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter
		• If LVEF **does not recover** within 4 weeks[c]
		  • Consult with cardiologist
		  • **Permanently discontinue trametinib**
		  • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution

Symptomatic[b]	Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline Grade 4: resting LVEF <20%	• **Permanently discontinue trametinib.** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; ; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MUGA=Multi-gated acquisition a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.

b. Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

c. If dose is delayed more than 21 days, discussion with the medical monitor is required to resume therapy.

3.9.1.2. Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided.

Monitoring 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 appropriate cuff size has been selected
- the subjects 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 Time and Events Table (see Section 7.1). 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 mm Hg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension.

Management 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 the clinical management of hypertension are described in Table 5.

Table 5 Management and Dose Modification Guidelines for Hypertension

Hypertension	Action and Dose Modification
(Scenario A) • Asymptomatic and persistent[a] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or • Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Continue trametinib at the current dose • Adjust current or initiate new antihypertensive medication • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[b] BP • If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or • Failure to achieve well-controlled BP within 2 weeks in Scenario A	• **Interrupt trametinib** if clinically indicated • Adjust current or initiate new antihypertensive medication(s) • Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP • Once BP is well controlled[b], restart study treatment **reduced by one dose level**
(Scenario C) • Symptomatic[c] hypertension or • Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• **Interrupt trametinib** • 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 • Once BP is well controlled, restart trametinib **reduced by one dose level**
(Scenario D) • Refractory hypertension unresponsive to above interventions or hypertensive crisis.	• **Permanently discontinue trametinib** • Continue follow-up per protocol. • If hypertension resolves to ≤Grade 1, trametinib may be restarted with permission from the medical monitor

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; mmHg = millimetres mercury; SBP = systolic blood pressure;

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

3.9.2. Guidelines for Visual Changes

Episodes of visual changes have been observed in subjects receiving trametinib. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. Special attention should be given to retinal (e.g., RPED) or retinal vein abnormalities (e.g., RVO).

Guidelines regarding management and dose reduction for visual changes considered to be related to study treatment are provided (see Table 6 and 7).

Table 6 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• 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. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table 7 below; **report as SAE if diagnosed.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib •	• If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE** •
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib • Report as SAE • •	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RVO or RPED diagnosed, permanently discontinue trametinib**

Abbreviations: RPED = retinal pigment epithelial detachment; CTCAE = Common Terminology Criteria for Adverse Events;
RVO= retinal vein occlusion; SAE = serious adverse event

a. Refers to CTCAE Version 4.0 'Eye disorders – Other, specify'
b. If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

Table 7 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

c. Refers to CTCAE Version 4.0 'Retinopathy'

3.9.3. Pneumonitis Management Guidelines

Pneumonitis has been observed in subjects receiving trametinib. To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described (see Table 8).

Table 8 Pneumonitis Guidelines for Trametinib

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue trametinib at current dose
Grade 2	• 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 recommended • Symptomatic therapy including corticosteroids if clinically indicated	• **Interrupt trametinib** until recovery to grade ≤1 • Restart treatment with trametinib **reduced by one dose level** • Escalation to previous dose level after 4 weeks and consultation with medical monitor possible • If no recovery to grade ≤1 within 4 weeks, **permanently discontinue trametinib**
Grade 3	• 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 • Symptomatic therapy including corticosteroids as clinically indicated	• **Interrupt trametinib** until recovery to grade ≤1 • After consultation with medical monitor, treatment with trametinib may be restarted **reduced by one dose level** • If no recovery to grade ≤1 within 21 days, **permanently discontinue trametinib**
Grade 4	• Same as grade 3	• **Permanently discontinue trametinib**

Abbreviations: BAL= bronchioalveolar lavage; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events

3.10. Dose Modifications for Trametinib and supportive care

3.10.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT) ≥3 X (times) upper limit of normal (ULN) and bilirubin ≥2 Xs ULN (or ALT ≥3 X ULN and international normalization ratio [INR] >1.5)

NOTE: Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

2. ALT ≥5 X ULN.
3. ALT ≥3 X ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. ALT ≥3 X ULN persists for ≥4 weeks.
5. ALT ≥3 X ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 X ULN **and** <5 Xs ULN **and** bilirubin <2 X ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. As with other causes of dose holding, discussion with the medical monitor is required if trametinib is held for >21 days. See following section for details on weekly follow-up procedures for these subjects.

3.10.1.1. Liver Chemistry Follow-up Procedures

Refer to the diagram in Appendix 5 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.10.1:

- Immediately and permanently withdraw the subject from study treatment.
- Notify the Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event electronic case report forms (eCRFs). If the event also meets the criteria of a serious adverse event (SAE) (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

- Monitor subjects **weekly** until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and INR >1.5):

- **This event is considered an SAE** (see Section 8.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for <u>all</u> subjects with ALT ≥3 times ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C ribonucleic acid (RNA).
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody (if subject resides outside the United States (US) or Canada, or has traveled outside US or Canada in past 3 months).
- Serum creatine phosphokinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥2 times ULN.
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, on the AE eCRF.
- Record use of concomitant medication(s), acetaminophen, herbal remedies, other over-the-counter medication(s), or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.

The following are required for subjects with ALT ≥3 times ULN **and** bilirubin ≥2 times ULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT] scan) to evaluate liver disease.
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [**CTCAE,** 2009]).
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793.

3.10.2. Guidelines for Prolonged QTc

Investigators should review concomitant medication usage for those that cause a prolonged QTc. Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided (see Table 9).

Table 9 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥501 msec	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b,c] • **If event recurs, permanently discontinue study treatments**

Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using the Bazett's formula

a. Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.
b. If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and medical monitor agree that the subject will benefit from further treatment.
c. If dose is delayed more than 21 days, discussion with the medical monitor is required to resume therapy.

3.10.3. Guidelines for Rash

Rash is a frequent AE observed in subjects receiving trametinib (see the Investigator's Brochures [**GlaxoSmithKline,** 2012] for more information). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula 2011; Lacouture 2011) and are provided (see Table 10 and Table 11).

Commented [d1]: Change to Novartis 2016?

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the Medical Monitor may be required.

Table 10 Guidelines for Supportive Care of Rash

Type of Care	Action

Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight
	• Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily.
	• Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
	• Topical steroids and antibiotics should be applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest, and upper back.
	  • Use mild-strength topical steroid (hydrocortisone 1% cream)
	  or
	  • topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)

Symptomatic Care[b]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

Abbreviations: BID = twice daily; SPF = sun protection factor

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided (see Table 11).

Table 11 Management and Dose Modification Guidelines for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures[a] • Use moderate strength topical steroid[b] • Reassess after 2 weeks	• Continue study treatment • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level[c]**

Grade 2	• Initiate prophylactic and symptomatic treatment measures
	• Use moderate strength topical steroid[b]
	• Reassess after 2 weeks
		• **Reduce trametinib by one dose level**
		  • If rash recovers to ≤grade 1 within 2 weeks, increase dose to previous dose level
		  • If no recovery to ≤grade 1 within 2 weeks, interrupt study treatment until recovery to ≤grade 1
		• **Restart trametinib at reduced dose level[c]**

Grade≥3	• Use moderate strength topical steroids[b] PLUS oral methyl-prednisolone dose pack • Consult dermatologist	• Interrupt trametinib until rash recovers to grade ≤1 • **Restart[c] trametinib reduced by one dose level[d]** • If no recovery to grade ≤2 within 4 weeks**, permanently discontinue trametinib**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of medical monitor is required to restart study treatment after >21 days of interruption.
d. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

3.10.4. Guidelines for Diarrhea

Episodes of diarrhea have occurred in subjects receiving trametinib (see the Investigator Brochures [**Novartis, 2016**] for more information). Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, etc., should be clinically excluded.

Guidelines regarding management and dose reduction for diarrhea considered to be related to trametinib by the investigator are provided (see Table 12).

Table 12 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea[a] Grade 1 or 2	• Diet: stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics	• Continue trametinib • If diarrhea is grade 2 for > 48h, interrupt trametinib until diarrhea resolves to grade ≤1 • Restart trametinib at the same dose level[d]
Uncomplicated Diarrhea[a] Grade 3 or 4 Any Complicated Diarrhea[b]	• Clinical evaluation mandatory • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Oral antibiotics and second-line therapies if clinically indicated • Hydration: intravenous fluids if clinically indicated • Antibiotics (oral or intravenous) if clinically indicated • Intervention should be continued until the subject is diarrhea free for ≥ 24 hours • Intervention may require hospitalization for subjects at risk of life-threatening complications	• Interrupt trametinib until diarrhea resolves to grade ≤1 • Restart with trametinib reduced by one dose level[d,e] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

a. **Uncomplicated diarrhea** defined by the absence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution
b. **Complicated diarrhea** defined by the presence of symptoms such as, cramping, nausea/vomiting ≥grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥3, frank bleeding, and/or dehydration requiring intravenous fluid substitution
c. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea
d. If dose is delayed more than 21 days, discussion with the medical monitor is required to resume therapy.
e. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

4. INVESTIGATIONAL PRODUCT(S)

The term 'study treatment' is used throughout the protocol to describe any combination of investigational product(s) (IP) received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatment or the combination of those study treatments.

4.1. Description of Investigational Product(s) and/or Comparators/Placebo

4.1.1. Trametinib

Trametinib will be provided as 0.5 mg and 2.0 mg tablets. Each tablet will contain 0.5 mg or 2.0 mg of trametinib parent (present as the DMSO solvate).

Trametinib commercial available supply with auxiliary label will also be provided by Novartis. The study drug should be administered and stored according to the instructions specified on the drug labels (refer to label, PI, and IB for detailed information).

Trametinib will be shipped to sites by the Clinical Research Management Group. The contents of the label will be in accordance with all applicable regulatory requirements.

4.2. Preparation/Handling/Storage of Trametinib

Handling

Under normal conditions of handling and administration, investigational products (IPs) are not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

In the case of unintentional occupational exposure notify the study monitor, the Medical Monitor and/or the study manager.

Storage

Study treatments must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the study treatments will be limited to the investigator and authorized site staff. Study treatments must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Study medication is to be refrigerated and stored at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required.

4.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of study treatments dispensed and/or administered to study subjects, the amount returned by study

subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study. See Appendix 8 for medication diary.

4.4. Treatment Compliance

Treatment compliance will be assessed through querying the subject during the site visits and documented in the source documents, electronic case report form (eCRF), and the medication diary. A record of the number of trametinib tablets capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the eCRF. Investigators must make every effort to bring non-compliant subjects into compliance.

4.5. Treatment of Investigational Product Overdose

In the event of an overdose defined as administration of more than 3.0 mg once daily for trametinib (the maximum tolerated dose defined in the MEK111054 Study), the investigator should:

- contact the Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities
- obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the electronic case report form (eCRF).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

5. STUDY POPULATION

5.1. Number of Subjects

The number of subjects enrolled will be dependent on the early response rate. In stage I, 15 subjects will be enrolled in cohort A and if less than one response is confirmed, the trial will be terminated. If one or more responses are observed, an additional 10 subjects will be enrolled. For cohort B, we will enroll patients concurrently. In stage I we will enroll up to 15 patients. If no responses are seen, this arm will be terminated. If one or more responses occur, we will accrue up to 10 additional patients. However, this exploratory study arm will close at the completion of cohort A accrual.

5.2. Subject Selection Criteria

5.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the study treatments that may impact subject eligibility is provided in the Investigator Brochures and Supplements [**Novartis, 2016**].

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

1. ≥18 years old.
2. Signed written informed consent.
3. Histologically or cytologically confirmed diagnosis of melanoma.
4. BRAF mutation in loci other than V600 (BRAF nonV600 MUT) or BRAF fusion detected by genetic testing of the primary tumor or regional/distant metastasis.
5. Subjects must provide either a fresh or archived tumor sample for correlative study analyses.
6. For subjects with melanoma, archived or freshly biopsied tumor tissue (preferred) must be obtained prior to enrollment. Tissue shipment tracking information should be provided before administration of study treatment is initiated. However, if shipping will be delayed and tissue shipment tracking information is unavailable, study drug may be administered prior to tissue receipt pending discussion with principal investigator.
7. Measurable disease (i.e., present with at least one measurable lesion per RECIST, version 1.1 (Eisenhauer 2009).
8. All prior anti-cancer treatment-related toxicities (except alopecia and laboratory values as listed on Table 12) must be ≤ grade 1 according to the Common Terminology Criteria for Adverse Events version 4 (CTCAE version 4.0; **CTCAE,** 2009) at the time of randomization. Subjects with endocrinopathies (e.g. hypopituitarism, hypothyroidism, hypoadrenalism) caused by immune therapies currently on adequate hormone replacement WILL be permitted.
9. Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
10. Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to randomization and agree to use effective contraception as defined (see Section 7.3.9).
11. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1.2.
12. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Refer to Appendix for details.

13. Adequate baseline organ function as defined in Table 13.

Table 13 Definitions for Adequate Baseline Organ Function

System	Laboratory Values
Hematologic	
ANC	≥ 1.0 × 10^9/L
Hemoglobin	≥ 9 g/dL
Platelet count	≥ 75 x 10^9/L
PT/INR[a] and PTT	≤ 1.3 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
Total bilirubin	≤ 1.5 x ULN
ALT	≤ 2.5 x ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[b]	≥50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO, >50% if not specified

Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; INR = international normalized ratio; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a. Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization. PT and PTT > 1.3 x ULN are permitted in these subjects.

b. Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix). Creatinine clearance must be ≥50 mL/min to be eligible.

5.2.2. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. No prior therapy with inhibitors affecting the MAPK pathways at any level (BRAF, MEK, NRAS, ERK inhibitors) for unresectable stage IIIC of Stage IV (metastatic) melanoma. No limit to other therapies (immunotherapy or chemotherapy). Prior systemic treatment in the adjuvant setting is allowed. (Note: Ipilimumab treatment must end at least 8 weeks prior to Study Day 1).
2. BRAFV600 mutation positive.
3. NRAS codon 12, 13, or 61 mutation.
4. Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to Study Day 1, or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to Study Day 1.
5. Taken an investigational drug within 28 days or 5 half-lives (minimum 14 days), whichever is shorter, prior to Study Day 1.
6. Current use of a prohibited medication as described (see Section 10).

7. History of another malignancy

   Exception: Subjects who have been disease-free for 3 years, or subjects with a history of completely resected, non-melanoma skin cancer, or subjects with indolent second malignancies are eligible. T1a melanoma and melanoma in situ are permitted. Consult Medical Monitor if unsure whether second malignancies meet requirements specified above.

8. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.

9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (subjects with laboratory evidence of cleared HBV and HCV infection will be permitted).

10. History of leptomeningeal disease or spinal cord compression secondary to metastasis.

11. Brain metastasis, unless previously treated with surgery or stereotactic radiosurgery and the disease has been confirmed stable (i.e., no increase in lesion size) for at least 6 weeks with two consecutive MRI scans using contrast prior to Study Day 1 (the first MRI may be prior to surgical resection or radiation).

12. A history or evidence of cardiovascular risk including any of the following:

    a. A QT interval corrected for heart rate using the Bazett's formula (QTc; Appendix 6) ≥480 msec;

    b. A history or evidence of current clinically significant uncontrolled arrhythmias;

       Exception: Subjects with atrial fibrillation controlled for > 30 days prior to Study Day 1;

c. History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to Study Day 1;

d. A history or evidence of current □Class I congestive heart failure as defined by the New York Heart Association (NYHA) guidelines (Appendix 2);

e. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;

f. Patients with intra-cardiac defibrillators or permanent pacemakers;

g. Known cardiac metastases;

13. A history or current evidence of RVO including:

a. History of RVO or

b. Visible retinal pathology as assessed by ophthalmic examination that is considered a risk factor for RVO such as:

- Evidence of new optic disc cupping;
- Evidence of new visual field defects;
- Intraocular pressure >21 mmHg as measured by tonography.

14. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide (DMSO).

15. History of interstitial lung disease or pneumonitis.

16. Females who are pregnant or nursing (see Section 11.2).

6. COMPLETION OR WITHDRAWAL OF SUBJECTS

6.1. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to the Coordinating Center.

6.2. Subject Completion Criteria

A completed subject is one who has discontinued study treatment for reasons listed in Section 6.3 and completed a post-treatment follow-up visit or has died while receiving study treatment.

6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.10.1. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol

- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- a dose delay of > 21 days unless the investigator or Medical Monitor agree that further treatment may benefit the subject
- intercurrent illness that prevents further administration of study treatment(s)
- subject is lost to follow-up or study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF).

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the electronic case report form (eCRF).

Once a subject has permanently discontinued from trametinib, the subject will not be re-administered with the discontinued study treatment.

All subjects who discontinue from both study treatments will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1).

6.4. Study Completion

Study will be completed having met the study objectives, approximately 24 month s after last subject first visit, or when all subjects have withdrawn from the study, whichever occurs first.

6.5. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not the Coordinating Center is providing specific post-study treatment.

After study participation is completed or terminated, subjects may either:

- Transition to a future rollover study if eligible and continue receiving their current treatment with trametinib

OR

- Complete a follow-up visit within approximately 28 days of the last dose of study treatments if the subject:
  - chooses not to enter the roll-over study, or
  - is withdrawn due to an adverse event (AE) considered related to study treatment, or
  - is considered ineligible to enter the rollover study.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed.

The timing of each assessment is listed in the Time and Events Table (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the following assessments: safety, pharmacokinetic (PK), pharmacodynamics (PD)/biomarker or other assessments. The change in timing or addition of time points for any of the planned study assessments listed above must be approved and documented by the Coordinating Center, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 100 ml of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

This section consists of the Time and Events Table (Table 14) and supplemental footnotes to describe assessment windows and sequencing of study-specific assessments and procedures.

Table 14 Time and Events

STUDY PHASES[1]	SCR[2]	TREATMENT-One Cycle=28 days			Follow up[3]	
		D1	D15[21]	Continuation	EOT	Post EOT FU
Visit Window (Days)	-28	N/A	±3	±3	± 3	±7
CLINICAL ASSESSMENTS						
Informed Consent[4]	X					
Baseline demographics	X					
Medical History	X					
Interim Medical History				Day 1 of each cycle		
Disease Characteristics	X					
Prior Anti-Cancer Therapy	X					
ECOG Performance Status	X	X[5]		Day 1 of each cycle	X	
SAFETY ASSESSMENTS						
Physical Exam, Weight, Height[17]	X	X[5]		Day 1 of each cycle	X	
Ophthalmologic Exam[6]	X (≤35 days)			As clinically warranted	As clinically warranted	
Vital Signs[7]	X	X	X	Day 1 of each cycle	X	X
12-lead ECG[8]	X			Cycle 2 day 1, cycle 4 day 1, then every 12 weeks thereafter; more frequently if clinically warranted		X
ECHO or MUGA[9]	X (≤35 days)			Cycle 2 day 1, cycle 4 day 1, then every 12 weeks thereafter; more frequently if clinically warranted		X[18]
Adverse Events[10]	X	Continuous				X
Concomitant Medications	X	Continuous				X
LABORATORY ASSESSMENTS						
Hematology/Chemistry[22]	X (≤14days)	X[5]	X	Day 1 of each cycle or more often as clinically warranted	X	X
Coagulation/Urinalysis	X			As clinically warranted		X
Serum Pregnancy Test[11]	X (≤14 days)			Cycle 3, day 1, then every 8 weeks		X
Hepatitis B and Hepatitis C[16]	X					
EFFICACY ASSESSMENTS						
Disease assessment/imaging studies	X[14]			Every 8 weeks through week 56 then every 12 weeks thereafter (+/- 7 days)		X[15]

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STUDY PHASES[1]	SCR[2]	TREATMENT-One Cycle=28 days			Follow up[3]	
		D1	D15	Continuation	EOT	Post EOT FU
Visit Window (Days)	-28	N/A	±3	±3	± 3	±7
EXPLORATORY ASSESSMENTS						
Archival tumor tissue [19]	X					
Optional Pre-Dose/Post-Dose Biopsies[12]	X (≤28 days)		X[20]			
Blood Biomarkers	X		X			
Optional Post-Progression Tumor Biopsy[13]					X	

SCR=Screening, D=Day

1. All assessments mandated throughout the study should be performed on the visit day prior to administration of study treatments unless otherwise indicated. Dose modifications of any nature for either study treatment must not alter the pre-planned schedule of visits starting with the first dose of study treatment on Cycle 1, day 1. The start of a Cycle is defined as the day when trametinib administration begins. If a cycle is delayed by one week or less, assessments need not be repeated if results were not clinically significant.
2. Assessments within 28 days prior to the first dose of study treatment unless otherwise noted.
3. For subjects meeting permanent study treatment withdrawal criteria (Section 6.3), perform follow-up visit approximately 28 days after withdrawal from study treatment. For subjects eligible to continue study treatments in a rollover protocol at study end (Section 6.5), perform follow-up visit just prior to the start of dosing in the rollover trial. Assessments completed at this end of study follow-up visit may be used as baseline values for the rollover trial, provided that these assessments are collected within 14 days of the first dose of study treatment.
4. Informed consent may be obtained at any time prior to commencement of screening procedures and does not expire.
5. If completed within 72 hrs prior to the first dose of study treatment, this assessment need not be repeated unless clinically indicated. If labs are obtained, inclusion criteria remain the same and subjects may not begin therapy if laboratory parameters have changed outside study limits.
6. An ophthalmic examination will be performed as described (see Section 7.3.8).
7. Vital signs include temperature, respiratory rate, blood pressure, and pulse rate (see Section 7.3.3).
8. For ECG collection, the subject should rest in a semi-recumbent or supine position for at least 5 minutes prior to digital ECG acquisition (see Section 7.3.4).
9. LVEF is measured with either ECHO (preferred) or MUGA. The method used to initially document the subject's baseline status must be used consistently throughout the study (see Section 7.3.5).
10. From the time of consent until first dose of study treatment: only collect SAEs related to study participation or a Novartis concomitant medication. From Day 1 of study treatment to 28 days after the last dose: collect all AEs and SAEs regardless of causality. From 29 days post treatment and onward, if available: only collect SAEs related to study participation, study treatment, or a Novartis concomitant medication.
11. Perform only in women of childbearing potential. Serum testing is required at screening; serum or urine pregnancy test may be used at subsequent time points (see Section 7.3.9).
12. If available and with their consent, subjects may choose to provide fresh tumor tissue samples at the times indicated (see Section 0). Samples collected on Day 15 should be collected prior to dosing. Tissue may be obtained through excisional, incisional, core needle, or punch biopsies (or by other methods after discussion with medical monitor.)
13. Post-progression tumor tissue collection is optional and should be performed on all consenting subjects within 28 days of disease progression.

14. Baseline CT with contrast (or MRI if CT is contraindicated) should be performed within 28 days of the first dose of study treatment. The method (CT or MRI) used to document the subject's baseline status must be used consistently throughout the study. Subjects with melanoma must also have head MRI to fulfil eligibility criteria. (See Section 7.3.6 details.)
15. Required only if previous assessment was more than 8 weeks prior to follow-up visit.
16. Subjects must be negative for Hepatitis B surface antigen and Hepatitis C antibody at the screening visit. False positive patients may be cleared for enrollment based on RNA-based assays (see Section 7.3.7).
17. Height will be collected at screening only.
18. ECHO/MUGA not required at Follow-up visit if all other on-study LVEF assessments were normal and treating physician feels it is not indicated.
19. Archival tumor tissue (10 unstained slides, 5 micron thickness) will be collected if available for further research if a baseline biopsy is not performed. Efforts should be made to obtain the archival tissue prior to receiving drug; if a plan to receive the tumor tissue is in place, however, day 1 should not be delayed.
20. Optional early on-treatment biopsy may occur on day 15 +/- 3 days.
21. Day 15 visit only for cycle 1; thereafter patients will be seen every 28 days (+/- 3 days).
22. See Table 15 for required laboratory tests.

7.2. Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth, gender, race and ethnicity.

Medical/medication history assessed as related to the eligibility criteria listed in Section 5.2.

Baseline (Screening) assessments obtained will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs: blood pressure, temperature, respiratory rate, pulse rate
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests: hematology, clinical chemistry and urinalysis
- Serum beta-human chorionic gonadotropin (β-HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan
- Brain magnetic resonance imaging (MRI) with contrast or a computed tomography (CT) scan (with/without contrast) if MRI is contraindicated for all subjects with cutaneous melanoma
- Ophthalmic exam by an ophthalmologist
- Review of concomitant medications

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.2.1. Critical Baseline Assessments

Critical baseline assessments include height, weight, blood pressure, smoking history, medical conditions and family history of cardiovascular disease and risk factors, and stage of disease at screening.

7.3. Safety Evaluations

Planned time points for all safety assessments are provided in the Time and Events Table (Section 7.1).

7.3.1. Physical Examinations

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

7.3.2. ECOG Performance Status

The performance status will be assessed using the Eastern Cooperative Oncology Group (ECOG) scale (Appendix 4) as specified in the Time and Events Table (see Section 7.1).

7.3.3. Vital Signs

Vital sign measurements will include (i.e., systolic and diastolic blood pressure, temperature, respiration rate and pulse rate). Vital signs should be measured after resting for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated.

7.3.4. Electrocardiogram (ECG)

A single 12-lead ECG will be obtained at designated time points during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-recumbent or supine position.

The QT interval should be corrected for heart rate by Bazette's formula (QTcB; see Appendix 6). Refer to Section 3.10.2 for QTc stopping criteria and additional information.

7.3.5. Echocardiogram (ECHO) and/or Multi-gated Acquisition (MUGA) Scans

An ECHO (preferred) or a MUGA scan will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility, as specified in the Time and Events Table (see Section 7.1). Additional ECHO or MUGA assessments may be performed if clinically warranted. The procedure used to document the subject's baseline LVEF status should be used consistently throughout the study. If possible, the interpretation of LVEF status should be performed consistently by the same reviewer throughout the study. The evaluation of the echocardiographer should include

an evaluation for left ventricular ejection fraction (LVEF) and both right and left-sided valvular lesions.

Copies of all ECHO or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF < institutional lower limit of normal (LLN) may be required by the Coordinating Center for review.

7.3.6. Brain MRI and/or CT Scan

A magnetic resonance imaging (MRI) with contrast will be performed at Screening (see Time and Events Table, Section 7.1) to rule out any new untreated brain metastases and to verify stability of brain metastases if present for all subjects with cutaneous melanoma. A computed tomography (CT) scan with and without contrast may be performed if a MRI is contraindicated.

7.3.7. Laboratory Assessments

All protocol required laboratory assessments should be performed according to the Time and Events Table (see Section 7.1).

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

If laboratory assessments for screening are completed within 72 hours of the first dose, they do not have to be repeated on cycle 1, day 1. If labs are obtained on the first day, values are still required to meet inclusion criteria (Table 13).

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinical significant by the Investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF.

All laboratory tests with abnormal values that are considered clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the possible etiology should be identified and the Coordinating Center notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 15:

Table 15 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count		MCV	Neutrophils
White blood cell (WBC) Count (absolute)		MCH	Lymphocytes
		MCHC	Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
International Normalized Ratio (INR; at screening only)[a]			
Prothrombin time (PT; at screening only)[a]			
Partial thromboplastin time (PTT; at screening only)[a]			
Clinical Chemistry			
Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Creatinine[b]	Chloride	Alanine aminotransferase (ALT)	
Glucose, (random)	Total carbon dioxide (CO_2)		Albumin
Sodium	Calcium	Alkaline phosphatase	
Lactate Dehydrogenase (LDH)		Potassium	
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other screening tests			
Human Immunodeficiency virus (HIV) [c]			
Hepatitis B (HBsAg)			
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA® immunoblot assay should be reflexively performed **on the same sample** to confirm the result)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

a. Coagulation panel to be done at Screening only
b. If serum creatinine is > 1.5 mg/dL, creatinine clearance should be calculated using the standard Cockroft-Gault formula (Appendix)
c. HIV testing is optional

7.3.8. Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination performed by an ophthalmologist at the times described (Section 7.1). At certain time points in the trial and if visual changes develop, an eye exam is indicated. (Refer to Table 6 for visual changes stopping criteria). 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. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and

fluorescein angiography are also recommended if clinically indicated.

7.3.9. Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum β-HCG pregnancy test performed within 14 days prior to the first dose of study treatment(s). Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described (Section 11.1.1) during the study until four months following the last dose of study treatment(s).

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to the Coordinating Center within two weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event (AE) or serious adverse event (SAE). Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment(s), must be promptly reported to the Coordinating Center.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the Coordinating Center as described above.

7.4. Baseline Assessment of Target and non-target lesions

All baseline lesion assessments must be performed within 28 days of enrollment.

- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions; however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

7.5. Efficacy Assessments

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [Eisenhauer, 2009].

See the Time and Events Table (Section 7.1) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays.

The following are required at baseline:

- Computed tomography (CT) scan with contrast (e.g., chest, abdomen, and/or pelvis as appropriate for a given subject) for assessment of baseline disease burden within four weeks of enrollment. All post- treatment assessments require CT imaging of disease sites identified by these baseline scans.
  NOTE: Although CT is preferred, MRI may be used as an alternative method of baseline disease assessment, especially for those subjects where CT is contraindicated (i.e., allergy), provided that the method used to document baseline status is used consistently throughout study treatment to facilitate direct comparison.
- A baseline brain scan is required for all subjects for assessment of CNS disease within four weeks of enrollment. Head CT with contrast or magnetic resonance imaging (MRI) are both acceptable methods of CNS disease assessment, but contrast enhanced MRI is preferred. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (i.e., symptoms suggestive of CNS progression). Subjects demonstrating brain metastasis at baseline must have the baseline scan compared to an earlier scan performed (preferably 6 weeks earlier) to demonstrate that the metastasis is stable. Stable is defined as no increase in lesions between the two scans. The radiologist reports and the primary investigator's analysis for these scans must be sent to the medical monitor for approval. Timing between the baseline scan and original scan is described above.

NOTE: For subjects with CNS disease at baseline, a brain scan is required every eight weeks or as clinically indicated.

NOTE: The method used to document baseline status should be used consistently throughout study treatment to facilitate direct comparison

For subjects with palpable/superficial lesions, clinical disease assessments by physical examination should be performed at baseline and throughout study treatment as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than four weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g., evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

7.5.1 Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- FDG-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scan 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 response 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 electronic CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin

lesions, documentation by color photography, including a ruler or calipers to measure the size of the lesion, is required.

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended.
Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used (Eisenhauer 2009).

X-ray: Should not be used for target lesion measurements owing to poor lesion definition.
Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray.

Brain Scan: If brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

7.5.2 Measurable and Non-measurable Definitions

A measurable lesion is a non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if:

- ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured (Eisenhauer 2009).

A non-measurable lesion is:

- All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal

masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques (Eisenhauer 2009).

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

7.5.3 Response Criteria

7.5.3.1 Target Lesions

Definitions for assessment of response for target lesion(s) are as follows:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
  - **Not Applicable (NA):** No target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the five preceding definitions.

NOTE:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

7.5.3.2 Non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- **Complete Response (CR):** The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non- pathological (e.g. <10 mm short axis).
- **Non-CR/Non-PD:** The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.
- **Not Applicable (NA):** No non-target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the four preceding definitions.

NOTE:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

7.5.3.3 New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment.

If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

7.5.3.4 Evaluation of overall response

Table 16 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 16 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

NOTE:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

7.5.3.5 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by the study investigator.

- To be assigned a status of SD, the post-baseline disease assessment must have met the SD criteria at least once after study Day 1.

- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:
To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 28 days after the criteria for response are first met. Electronic scans will be required for independent review.

7.6. Translational Research

Performance of these investigations may be conditional on the results of the clinical trial, and samples may be selected for analysis on the basis of the clinical outcome. A table of samples to be collected for translational research, whether the samples are mandatory or optional, and the primary purpose for collection is provided (see Table 17).

Comparative examination of pre-dosing profiles of subjects may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with trametinib or provide new insights into cancer and medically related conditions. Comparative examination of post-dosing profiles in conjunction with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate to the action of trametinib in this patient population.

All samples may be retained for a maximum of 15 years after the last subject's last visit of the follow-up period. Future research may be performed on available sample with an IRB-approved protocol.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with cancer or medically related conditions and/or the action of trametinib may be identified by application of:

- DNA/gene, RNA, and protein analysis of tumor tissue and blood/plasma.

Table 17 Table of Samples for PD and Translational Research

Samples	Mandatory/Optional	Archived/Fresh tumor tissue	Primary Purpose
Tumor tissue for genetic analysis	Mandatory[1]	Either	For genetic analysis
Pre-dose and post-	Optional	Fresh	For PD analysis of protein biomarkers via IHC

dose tumor tissue biopsies			or other analyses.
Post-progression tumor biopsy	Optional	Fresh	For evaluation of DNA, RNA and proteins related to drug response and resistance

[1]Patients without available tumor tissue with genetic analysis may be included if previous next generation sequencing panels that have already assessed genetic biomarkers of interest have been performed. Discussion with the principle investigator is required.

7.6.1. Tumor Tissue for Genetic and Protein Biomarker Analysis

Molecular inclusion for the trial include: (1) The presence of a mutation in BRAF at a codon other than V600, or a BRAF gene fusion event; (2) The documented absence of a mutation at BRAFV600 (i.e., $BRAFV600^{WT}$) in tumor tissue; and (3) The documented absence of a mutation in codons 12, 13, and 61 of NRAS. These molecular criteria for inclusion may be met by previously performed molecular testing performed in a CLIA-certified laboratory. Alternatively, archival or fresh tissue must be provided for testing of BRAF and NRAS. In addition to these required molecular tests, archival specimens are required to allow for testing of additional molecular alterations that may correlate with sensitivity or resistance to treatment with trametinib. Such alterations include, but are not limited to, gene mutations (MEK1, MEK2, KRAS, HRAS, NF1, PTEN, PIK3CA, AKT, TP53, CDKN2A, CDK4), gene deletions (PTEN, CDKN2A), gene amplifications (BRAF, CDK2, CCND1, MITF), and/or changes in gene or protein expression (growth factor receptors, p-ERK, p-AKT, PTEN, CDKN2A).

During the screening period prior to enrollment, all subjects with melanoma will be required to provide archived tumor tissue or to undergo tumor biopsy if archived tumor tissue is not available. New biopsy samples must be taken from lesions not required for disease assessment.

Optional tumor biopsies may also be performed to allow for assessment of the pharmacodynamics effects of trametinib treatment. Such biopsies may be performed within 28 days of the start of treatment, and on Cycle 1 Day 15 (+/- 3 days to allow for scheduling conflicts). Assessment of these samples will include, but are not limited to, changes in the activation status of components of the MAPK pathway and other compensatory signaling pathways implicated in melanoma (i.e. PI3K-AKT pathway).

Optional tumor biopsies may also be collected after documented disease progression from subjects that have provided appropriate consent. Samples will be used to investigate the molecular mechanisms of treatment resistance. Exact methodologies and markers examined will be determined by the Principal Investigators at the time the samples are available for analysis, based on existing knowledge about resistance and melanoma; the nature and amount of the biopsy material, and the molecular analysis platforms available at that time. Analyses may include, but are not limited to, changes in DNA, RNA, and/or protein, and the establishment of cell lines and/or xenografts.

Investigators are highly encouraged to collect tumor biopsies at baseline (in the absence of sufficient archival tissue) and day 15 (+/- 3 days) following initiation of therapy, with an optional tumor biopsy conducted at the time of disease progression. The pre-treatment biopsy will be obtained within 28 days of starting therapy. As noted, archival tissue within one year of starting therapy of sufficient quantity will preclude the need for an initial biopsy. Issues that would cause treatment delays should be discussed with the PI who may grant permission on a case-by-case basis to analyze tissue from a protocol pre-treatment biopsy that has occurred greater than 28 days prior to study treatment. The post-treatment biopsy will be performed at day 15 ± 3 days prior to the morning dose of the study medications. An optional third tumor biopsy will be requested of these patients at the time of tumor progression, with particular efforts made at obtaining such biopsies in patients who have developed progression after achieving a radiographic response to treatment or after prolonged disease control (i.e., greater than 4 months). All biopsies may be obtained through excisional, incisional, core-needle, or punch biopsy methods. Up to eight core samples will be obtained with each biopsy (in the case of a core biopsy), providing sufficient tissue for the correlative studies.

Tissue will be divided such that a portion (one core in the case of core needle biopsy procedures) is formalin fixed and designated for immunohistochemistry (IHC) and the remainder flash frozen in liquid nitrogen or embedded in optimal cutting temperature (OCT) compound. When limited tissue is available, flash frozen/OCT tissue will generally be prioritized.

Fresh tumor biopsy samples should be snap-frozen using liquid nitrogen or a dry ice slurry, or embedded in OCT. The tissue must be processed as soon as possible after biopsy to minimize any form of degradation and to avoid risking the viability of the tissue. The following procedures may be used or standard operating procedures (SOPs) for each institution may be used after discussion with the principal investigator.

Snap-Freezing in Liquid Nitrogen:

- Label cryogenic vial(s) with the subject's study identification number, the date of collection, time point (baseline, day 15, or progression) and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.
- Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.
- Remove the cryogenic vial from the liquid nitrogen.
- Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

Freezing Procedure with Dry Ice Slurry

- Materials required include: 5 lbs dry ice, alcohol (ethanol or comparable), basin, long forceps

- Place at least 5 lbs of dry ice into a basin and pour one liter of alcohol over the ice.
- Label cryogenic vial(s) with the subject's study identification number, the date of collection, and the study center performing the biopsy. Ensure that the label adheres to the vial and does not come off when placed in liquid nitrogen. Labels cannot be adequately affixed to the vials after freezing.
- Immediately place the freshly obtained tissue into the labelled cryogenic vial. Place the vial with tissue in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue. Tumor cores should be frozen individually in separate cryovials as collected in order to minimize the time between removal and freezing.
- Pace the lower half of the sealed cryotube containing tissue into the solution for at least 2 minutes until frozen solid.
- Store the sample in a -80°C freezer (-65°C to -80°C is acceptable) until ready for shipping.

Archival tumor tissue should be obtained as 10 unstained slides with 5 micron thickness.

7.6.2. Blood Biomarkers

Blood samples (3X 10 ml) will be collected as indicted in the Time and Events Table (see Section 7.1). Blood will be processed to isolate both PBMCs and serum for future biomarker analyses at the conclusion of the study, as to be determined by the investigators based on the state of knowledge at that time, and available molecular analysis platforms. Possible analyses include, but are not limited to, immune cell populations, circulating free DNA (cfDNA), circulating miRNA, and proteins/cytokines.

Three 10 ml sodium heparin tubes will be collected from patients prior to treatment, and at day 15. Samples will be subsequently stored for future correlative studies. The samples drawn prior to treatment can be drawn on C1W1 prior to initiation of study drug.
Process samples in the following manner. If institutional standards differ for PBMC or plasma processing, other processing methods may be acceptable pending discussion with the principal investigator.

•

Processing – Plasma

1. Centrifuge the tubes at 609 x g or equivalent speed for 10-15 minutes with low brake. Centrifuge at 4 °C.
2. Use a transfer pipette to transfer the plasma into cryovials in 1mL aliquots. Store cryovials in -80 °C freezer until shipped.
3. Save remaining sample for PBMC processing.

Processing - Peripheral Blood Mononuclear Cells

1. Remove the Ficoll from the refrigerator and aliquot 12mls of Ficoll into two separate 50mL centrifuge tubes (or prepare Ficoll for underlay using pre-measured transfer packs).
2. Dilute remaining sample from plasma processing above (white and red blood cells) with 1:1 1XPBS. Wash the original green-top blood tubes with the diluent prior to mixing in the empty 50mL tube. Mix the PBS and blood well.

3. Slant the 50mL tube containing Ficoll being careful not to spill. Carefully pour the diluted blood on top of the Ficoll so as to not disturb the Ficoll layer. Discard the now empty 50mL tubes as well as the original blood tubes.
4. Spin at 609 x g or equivalent speed for 20 minutes, no brake. Centrifuge at 4ºC.
5. Aspirate the PBMC layer at the interface above the density gradient (white layer/buffy coat) including a small amount of plasma but as little Ficoll as possible.
6. Transfer to a sterile, 50mL centrifuge tube. Add sufficient 1X PBS to bring the fluid volume to 50mls in each tube. Spin at 343 x g or equivalent speed for 15 minutes.
7. Pour off supernatant, flick tube to re-suspend cells (repeat steps 7-8 two more times to give a total of three washes.)
8. After third wash, add 10mL 1X PBS and count cells. Record cell count and cell viability.
9. Spin at 343 x g or equivalent speed for 15 minutes. Pour off supernatant.
10. Prepare a 10% DMSO in 100% FBS (1:10 dilution) for freezing solution. Ensure the FBS is chilled before adding the DMSO.
11. Suspend cell pellet in enough freezing media to ensure 1 mL aliquots of $5.0x10^6$ cells.
12. Make 1mL aliquots into cryovials, and store at -80 °C until shipment.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE) as outlined in Section 8.1 and Section 8.2, respectively.

8.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/serious adverse event [SAE]).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

8.2. Definition of an SAE

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are adverse events (AEs). If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or

surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, 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 drug dependency or drug abuse.

g. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and international normalization ratio (INR) >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

  NOTE: Bilirubin fractionation is performed if testing is available. If testing is not available, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 times ULN, then the event is still reported as a serious adverse event (SAE). If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- Any new primary cancers
- LVEF that meets stopping criteria (see Section 3.9.1.1)
- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion

8.2.1. Sentinel Events

A Sentinel Event is a Novartis-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated by the Supporter. The medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current Novartis-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

8.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., electrocardiogram [ECGs], radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an adverse event (AE) or serious adverse event (SAE), in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

8.3.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

8.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a serious adverse event (SAE). Death due to disease under study is to be recorded on the Death electronic case report form (eCRF). However, if the underlying disease (i.e.,

progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

8.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an adverse event (AE) or serious adverse event (SAE).

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or Novartis concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to Coordinating Center within 24 hours, as indicated in Section 8.5.1.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

8.5.1. Prompt Reporting of SAEs and Other Events

Serious adverse events (SAEs), pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator on a Vanderbilt Serious Adverse Event Form and the centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore [redacted] as described (Table 18) in the following table once the investigator determines the event meets the protocol definition for that event. SAEs should also be sent to Novartis and the NCCN as listed below:

All Events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a 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), complete the SAE Report Form in English, and send the completed, signed form by fax to ([redacted] within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets and to NCCN via email to [redacted]

Table 18 Rules for Reporting SAE, Cardiovascular, Pregnancy and Liver Function Abnormalities

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. Coordinating Center is to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

8.5.2. Regulatory reporting requirements for SAEs

Prompt notification of serious adverse events (SAEs) by the investigator to the Coordinating Center is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. All serious adverse events must be reported to the Coordinating Center within 1 business day after the treating institution becomes aware of the event. Events should be reported using the Vanderbilt Serious Adverse Event Form.

Follow-up information must also be reported within 1 business day of receipt of the information by the investigator.

The Coordinating Center has a legal responsibility to notify the local regulatory authority, the FDA and other regulatory agencies about the safety of a product under clinical investigation. The Coordinating Center will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/ethics committee (EC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

Food and Drug Administration (FDA)

In this trial, unexpected adverse events believed to be definitely, probably, or possibly related to the medications will be reported to the Food and Drug Administration via MedWatch Form 3500A Mandatory Reporting Form (using the online form available at: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf by telephone 1-800-FDA-1088; or by fax 1-800-FDA-0178 using form available at:
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085692.htm.
The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

9. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

9.1. Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 3.10.1, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology, including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)

- Hepatitis C RNA
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, then obtain heterophile antibody or monospot testing)
-

- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2 X upper limit of normal (ULN).

- Obtain a complete blood count (CBC) with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE eCRF.
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication eCRF.
- Record alcohol use on the liver event alcohol intake eCRF.

The following assessments are required for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT]) to evaluate liver disease.

9.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3 X ULN **but** <5X ULN **and** bilirubin <2 X ULN, without symptoms indicative of hepatitis or rash, and who can be monitored safety for 4 weeks, the following actions should be taken:

- Notify the Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Continue administration of study drug(s).
- Evaluate liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) weekly until they resolve, stabilize or return to within baseline levels.
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5 (Section 3.10.1), then proceed as described in Section 9).
- If, after 4 weeks of monitoring, ALT <3X ULN and bilirubin <2 X ULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

9.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Drug(s)

Approval by the Medical Monitor to restart/rechallenge study drug(s) may be considered where:

- The subject is receiving compelling benefit, the benefit exceeds the risk, and no effective alternative therapy is available. Approval of restart/rechallenge by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must be obtained, as required.

- If the restart/rechallenge is approved by Coordinating Center in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the Medical Monitor.
- Subjects approved by the Coordinating Center for restart/rechallenge of study drug(s) must return to the clinic twice a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.

9.4. Drug Restart Following Transient, Resolving Liver Events Not Related to Study Drug(s)

Approval by the Medical Monitor to restart study drug(s) may be considered where:

- Liver chemistry abnormalities have a clear underlying cause (e.g., biliary obstruction, hypotension) and liver chemistries have improved to normal or are within 1.5 X baseline and ALT <3X ULN. Approval of restart by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may be required.
- If the restart/rechallenge is approved by Coordinating Center in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the Medical Monitor.
- Subjects approved by the Coordinating Center for restart/rechallenge of study drug(s) must return to the clinic once a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.
- If protocol-defined stopping criteria for liver chemistry abnormalities are met, study drug(s) administration must stop.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF). Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by the Coordinating Center and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

As trametinib is metabolized predominantly via deacetylation likely mediated by hydrolytic esterases, its PK is unlikely to be affected by other agents through metabolic interactions. Trametinib repeat-dose exposure was not affected by co-administration with a CYP3A4 inducer.

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

Any questions regarding concomitant medications should be directed to the Medical Monitor for clarification.

10.1. Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and hematopoietic growth factors as appropriate.

10.2. Prohibited Medications and Non-Drug Therapies

The use of certain medications prior to the first dose of study treatment (refer to inclusion and exclusion criteria, Section 5.2) and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while treatment with study treatment is interrupted, the Medical Monitor can approve such use.

The following medications or non-drug therapies are prohibited:

- Anticancer agents: Additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy will be prohibited.
- Herbal therapies: Subjects will abstain from using herbal preparations/medications within 14 days prior to the first dose of Trametinib and throughout the study until the end of treatment visit. These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

The investigator should contact the Medical Monitor before initiating treatment with any herbal preparation.

11. LIFESTYLE AND/OR DIETARY RESTRICTIONS

11.1. Contraception

11.1.1. Female Subjects

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicular stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

Abstinence

Sexual inactivity by abstinence must be consistent 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.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least four months after the last dose of study treatment.

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptives (either combined or progesterone only) if not contraindicated for this subject population or per local practice.
- Estrogenic vaginal ring if not contraindicated for this subject population or per local practice.
- Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice.
- Implants of levonorgestrel if not contraindicated for this subject population or per local practice.
- Injectable progesterone if not contraindicated for this subject population or per local practice.

- Intrauterine device or intrauterine system that meets the <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

11.1.2. Male Subjects

To prevent pregnancy in a female partner, male subjects must use one of the following contraceptive methods from the beginning of the study until 90 days after the last dose of study treatment:

- ☐ Abstinence, defined as sexual inactivity consistent 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.
- ☐ Condom *(during non-vaginal intercourse with any partner - male or female)* **OR**
- ☐ Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) *(during sexual intercourse with a female)*

11.2. Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for four months following the last dose of study treatment.

12. DATA MANAGEMENT

Each participating institution will be collaborating with Vanderbilt on patient accrual. Data will be collected using a centralized electronic case report form called ON-line Clinical Oncology Research Environment = Oncore [redacted]Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management

functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. Also the system is capable in storing basic protocol information (e.g., IRB approval dates, dates for annual renewals, etc.) and clinical trials research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. OnCore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. OnCore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage all VICC clinical trials data. OnCore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Specified members at each participating site will submit all pertinent regulatory documents to the Coordinating Center team member, who will upload it on Oncore.

The Principal Investigator or designee will inform the sponsor within 24 hrs of any serious adverse event, and will inform the IRB in accordance with each institution's IRB policy. The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting, and report AEs and SAEs, as detailed in the protocol. Furthermore, the investigator will be required to provide periodic (monthly) safety updates on the conduct of the study at his/her site and notification of study closure to the SRC/IRB. If any problem is identified related to the conduct of this research, the VICC Data Safety and Monitoring Committee (DSMC) will be formally asked to review the study and the situation that required DSMC intervention.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypothesis

The primary objective is to determine wither trametinib is an effective targeted therapy in BRAF nonV600^{MUT} melanoma. The hypothesis described below will apply to cohort A ("high activity" mutations and fusion events). The null hypothesis is that the objective response rate (ORR; percentage of patients achieving a confirmed CR or PR is not attractive (defined as ≤5%). The alternative hypothesis is that the response rate is of interest for further development (defined as ≥25%).

The final analysis of the overall response rate will be performed using one sided test with α=0.05. It is calculated that at least 4 responses are needed out of a total of 25 patients to reject the null hypothesis.

To allow early termination of the trial due to lack of efficacy, the trial will be conducted in two stages per Simon's Minimax Design. If no responses are demonstrated in the first 15 patients, then the trial will be terminated early for futility. If ≥1 responses are observed,

enrollment will continue to 25 patients.

For the experimental arm (cohort B), the trial will also be conducted in two stages. If no responses are demonstrated in the first 15 patients, then the cohort will be terminated early for futility. If ≥1 responses are observed, enrollment will continue to a maximum of 25 patients. Additionally, when cohort A accrual has completed, cohort B will close and not accrue further patients.

Given the rapid changes in melanoma therapies, we will also have the option of closing either cohort if the clinical activity is low. If one or two responses occur in cohort A from the first 15 patients, the principal investigators and Coordinating Center will have the option of closing the trial at the interim analysis. The principal investigators must be in universal agreement for this to occur.

13.2. Sample Size Assumptions

To determine the overall sample size and the interim sample size, a two stage Simon's Minimax design was evaluated. To test the hypotheses (ORR=5% vs. 25%), 1 response from the first 15 subjects would be required to progress to stage 2 and a total of 25 subjects will be needed to achieve the desired type I (<5%) and type II error rate (Power>90%). The risk of incorrectly stopping the trial after stage I if the drug is effective is <1.5%.

Table 20: Sample size calculations

If the True Response Rate to trametinib is: (%)	Probability of Early Termination after Stage I	Probability of Rejecting the Null Hypothesis
5%	0.463	0.034 (type 1 error)
10%	0.206	0.234
15%	0.087	0.525
20%	0.035	0.762
25%	0.013	0.901
30%	0.005	0.965

13.3. Data Analysis Considerations

Data will be listed and summarized according to Novartis integrated data standards library (IDSL) reporting standards where applicable. Complete details will be provided in the Reporting and Analysis Plan (RAP). Analyses will be performed for each cohort.

13.3.1. Interim Analysis

An interim analysis will be performed for each cohort after 15 subjects have completed their first post-dose disease assessment at 8 weeks. The primary analysis of this includes a boundary for early decision on futility.

By the Simon Optimal design, it is calculated that at least 1 response of 15 subjects are needed to further progress enrolment. There is no early stopping boundary for efficacy, however if ≥4 patients experience CR or PR, then further planning of additional development may occur.

Core members of the Novartis clinical team will be notified of the results of the interim analysis. Investigators will be informed as to whether or not the study will be stopped prematurely.

13.3.2. Final Analysis

13.3.2.1. Primary Analysis

The primary comparison of interest (and primary endpoint) is to determine whether the objective response rate to trametinib in cohort A ("high affinity" group) is less than or equal to a null hypothesized response rate of 5% versus an alternative response rate of 25%. No comparisons between treatments will be performed as there is a single arm in each cohort. The primary analysis of ORR will be performed following treatment of all patients for at least 8 weeks or have discontinued therapy.

13.3.2.2. Secondary Analyses

13.3.2.2.1. Cohort B

Overall response rate will be assessed in cohort B as defined by RECIST 1.1 criteria and will be reported in a descriptive fashion. No statistical comparisons will be performed.

13.3.2.2.2. Overall Survival and Progression-Free Survival for both cohort A and B

Overall survival, defined as the time from Day 1 of the trametinib therapy to death from any cause. Progression free survival, defined as the time from Day 1 of trametinib therapy to progression of disease as defined by RECIST 1.1 criteria or death, will be reported for each arm. We will also perform subset analysis for PFS stratified by baseline characteristics including LDH level, metastatic stage, and previous therapy (particularly whether a subject has received immune-based therapy).

13.3.2.2.3. Safety

Adverse events (AEs) will be coded using the standard MedDRA and grouped by system organ class. Adverse events (AEs) will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4.0).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, serious adverse events (SAEs) and AEs leading to discontinuation of study treatment. Adverse events (AEs), if listed in the NCI-CTCAE (version 4.0) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

Characteristics (e.g. number of occurrences, action taken, grade, etc.) of the following AEs of special interest will be summarized separately.

The incidence of deaths and the primary cause of death will be summarized.

13.3.2.2.4. Biomarkers and Pharmacodynamic Analyses

The study will analyze tumor tissue and/or blood to understand genetic mechanism of MEK inhibitor response and resistance. As data warrant, correlation analysis will be performed to explore the relationship between patient's biomarker and PD data (e.g. change from baseline) to patient's tumor response. As data warrant, additional analysis will be conducted on cfDNA data. Full details will be provided in RAP prior to study initiation.

Molecular characterization of tumor tissue will be performed to identify markers that correlate with clinical responsiveness to treatment with trametinib. Analysis will incorporate detection of DNA-based alterations in other genes known to be altered in melanoma, including (but not limited to) genes in the MAPK pathway (i.e. MEK1/2, NF1), PI3K-AKT pathway (i.e. PIK3CA, AKT, PTEN), cell cycle regulators (i.e. CDKN2A, CDK4, CCND1), and/or broader molecular testing. Analysis of RNA and protein may also be performed for tumors with sufficient material available to assess functional networks and pathways. The exact methodologies used will be selected based on the DNA/RNA/protein amounts, technologies, and information available at the time the analyses will be performed. Analyses will be performed on pre-treatment and/or archival samples to identify predictors of treatment outcomes. Optional on-treatment biopsies will be used to evaluate pharmacodynamic and other molecular effects of

treatment, which will be compared to clinical outcomes. Optional post-progression samples will be analyzed to identify mechanisms of resistance.

13.3.3. Withdrawal

Reason for subject withdrawal will be listed.

13.3.4. Missing Data

Missing data will not be imputed. Where appropriate, available data will be summarized over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.

13.3.5. Protocol Violations

A summary and listing of protocol violations will be provided.

13.3.6. Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

13.3.7. Other Issues

Data from participating centers will be pooled prior to analysis. It is anticipated that subject accrual may be limited across centers and summaries of data by center would likely not be informative. Therefore, these summaries will not be provided.

Demographic and baseline characteristics will be summarized.

13.4. Key Elements of Analysis Plan

Data will be listed and summarized according to the Novartis reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be information, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

13.4.1. Pharmacodynamic Analyses

13.4.1.1. Translational Research Analyses

The results of translational research investigations may be reported separately from the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Further details on the translational research analyses will be addressed in the Reporting and Analysis Plan (RAP).

13.4.1.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main clinical study report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

14.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, the Coordinating Center will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional review board (IRB)/ethics committee (EC) review and approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

The Coordinating Center will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair (or his designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating sites.

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to the Coordinating Center before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to the Coordinating Center.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each site must be kept informed of such administrative changes.

Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the Investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

14.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Coordinating Center, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Coordinating Center will work with the investigator to ensure the Institutional review board (IRB)/ethics committee (EC) is notified.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP) and the Coordinating Center procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and the Coordinating Center requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the electronic case report form (eCRF) will serve as the source document.

During the course of the study, the Coordinating Center will routinely monitor sites for protocol compliance, compare CRFs with individual subjects' original source documents, assess drug accountability, and ensure that the study is being conducted according to the pertinent regulatory requirements. The review of subjects' medical records will be performed in a manner to ensure that subjects' confidentiality is maintained. Investigators must agree to cooperate with the Coordinating Center to ensure that any problems detected are resolved.

Quarterly safety and monitoring reports are available to the Data and Safety Monitoring Committee (DSMC). The DSMC reviews all serious adverse events reported during the previous quarter for all clinical trials active at the VICC and makes recommendations to address concerns of patient safety.

A Quality Assurance auditor under the direction of the DSMC will audit this clinical trial quarterly for compliance with adverse event reporting, regulatory and studies requirements, and data accuracy and completion. Audit reports detailing the findings are provided to the DSMC.

14.5. Quality Assurance

To ensure compliance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable regulatory requirements, the Coordinating Center may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures, recruitment material, etc.), each participant's informed consent, enrollment form, eligibility checklist, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

14.6. Study and Site Closure

The end of the study will be defined as the date of the last visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, International Conference on Harmonization Good Clinical Practice (ICH GCP), and the Coordinating Center Standard Operating Procedures.

The Coordinating Center reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) unsatisfactory enrollment, GCP noncompliance, inaccurate or incomplete data collection, falsification of records, safety issues, ethical issues, or noncompliance. If the Coordinating Center determines that such action is required, the Coordinating Center will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, the Coordinating Center will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, the Coordinating Center will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. The Coordinating Center will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/EC promptly and provide the reason(s) for the suspension/termination.

The Coordinating Center may also close study sites which fail to recruit subjects within a predefined timeframe.

14.7. Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the Investigator at each site at such time that the records may be destroyed.

The investigator must notify the Coordinating Center of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

14.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Novartis will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Novartis Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

15. REFERENCES

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APPENDICES

Appendix 1 BRAF mutations by Cohort

Cohort A – "High Activity"*	**Cohort B – "Low Activity/Unknown"**	**Excluded**
R462I	G466E	Concurrent BRAF V600E mutation
I463S	G466V	Concurrent NRAS codon 12, 13, or 61 mutation
G464V	D594V	
G464E	G596R	
G466A	**All other BRAF mutations**	
G469A		
G469E		
N581S		
E486K		
F595L		
L597V		
L597S		
L597R		
L597Q		
T599I		
K601E		
A728V		
BRAF fusions/truncations		
*Defined by affinity for MEK phosphorylation in Wan et al, Cell 2004. Mutations with documented responses to MEK inhibitors are also included		

Appendix 2 : NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Reference:

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

Appendix 3 : COCKCROFT-GAULT FORMULA

ClCr (mL/min) = $\frac{Q \times (140 - age[yr]) \times ideal\ body\ weight\ [kg]^*}{72 \times serum\ creatinine\ [mg/dL]}$

Q = 0.85 for females
Q = 1.0 for males

OR

ClCr (mL/min) = $\frac{K \times (140 - age[yr]) \times ideal\ body\ weight\ [kg]^*}{Serum\ creatinine\ [umol/L]}$

K = 1.0 for females
K = 1.23 for males

*Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]
Ideal body weight:

Males =	50.0 kg + (2.3 kg x each inch over 5 feet) or 50.0 kg + (0.906 kg x each cm over 152.4 cm)
Females =	45.5 kg + (2.3 kg x each inch over 5 feet) or 45.5 kg + (0.906 kg x each cm over 152.4 cm)
Example:	Male, actual body weight = 90.0 kg, height = 68 inches Ideal body weight = 50.0 + (2.3) (68-60) = 68.4 kg.

This subject's actual body weight is >30% over ideal body weight. Therefore, in this case, the subject's ideal body weight of 68.4 kg should be used in calculating estimated CrCl.

Reference

Devine, BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacology Case Studies. Drug Intelligence and Clinical Pharmacy. 1974; 8:650-655

Appendix 4: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Reference:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 5: Liver Safety Drug Restart Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

Background Information on Drug Restart/Rechallenge

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies.**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin≥2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3].

Drug Restart/Rechallenge Process (also see Figure 1)

1. Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.
2. Medical Monitor & Clinical Safety Physician.to review the subject's restart/rechallenge risk factors & complete checklist (Table 1).

Table 1. Checklist for drug restart/rechallenge for critical medicine

(Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

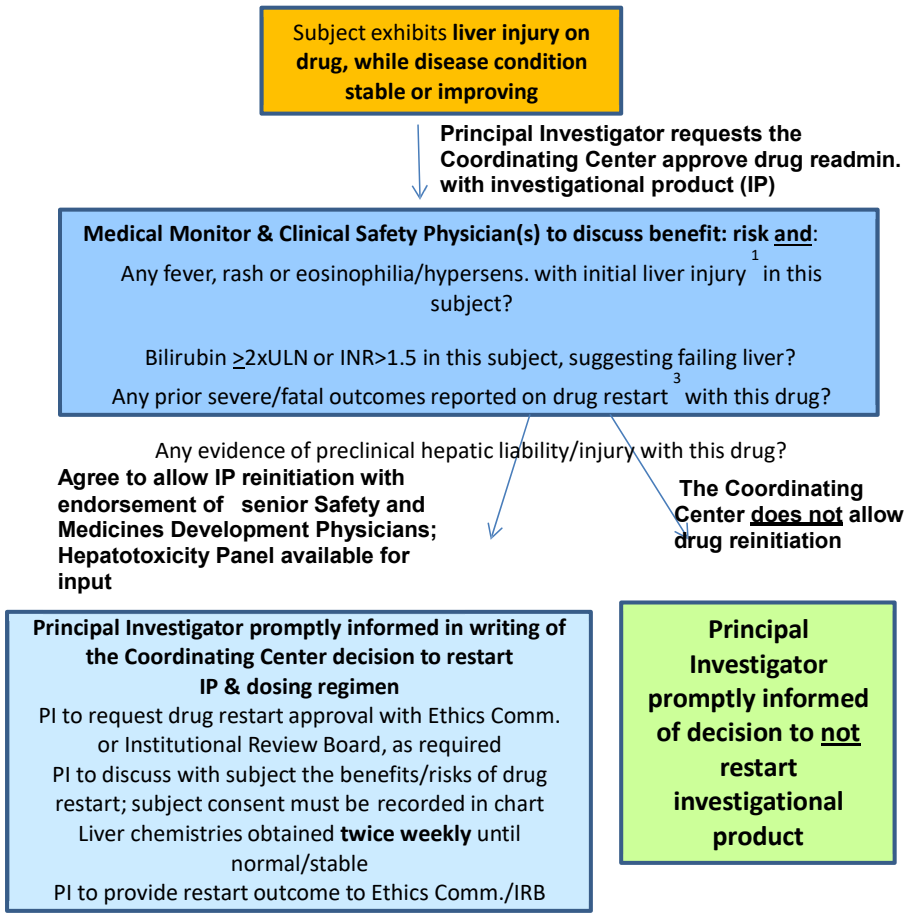
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug restart/rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin≥2xULN (direct bilirubin >35% of total)		
• Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**:		

• IP associated with known preclinical hepatic liability/ injury		

3. If the Coordinating Center provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:

   - The PI is to obtain Ethics Committee or Institutional Review Board review of drug re-initiation, as required.
   - PI must discuss the possible benefits and risks of drug re-initiation with the subject.
   - The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.
   - The drug must be reinitiated at approved dose(s).
   - Subjects approved by the Coordinating Center for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
   - The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.
   - The Coordinating Center is to be notified of any adverse events, as per Section 8.5.1.

Novartis process for drug restart after possible drug-induced liver injury



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3. Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. Hepatology 2010;52:2216–2222

Appendix 6 : QT interval on electrocardiogram corrected using the Bazett's formula (QTcB)

Bazett's formula used to correct QT interval for heart rate is:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, *measured in seconds*, often derived from the heart rate (HR) as 60/HR, and QT is the QT interval *measured in milliseconds*.

Reference

Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353-370.

Appendix 7 – Medication Diary

Patient Name:_____ Study ID:_____MRN:_____
Number of Trametinib Tablets Given: __ ___ Pill Bottle(s) returned: Circle **Yes** or **No**
Total Daily Dose of Trametinib: _____ Number of Trametinib tablets returned _____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT

SPECIAL INSTRUCTIONS

1. Trametinib should be taken by mouth on an empty stomach one hour before a meal or two hours after a meal with water only.
2. Trametinib tablets should be refrigerated.
3. If a dose of Trametinib is missed for more than 12 hours after a scheduled dose, wait until the next scheduled dose. Doses can be "made up" prior to the 12 hour limit.

Cycle #:_____ # of Weeks_____

Day	Medication	Date	Time	# of 2mg tablets taken	# of 0.5mg tablets taken	Comments
Example	Trametinib	01/01/2014	9:00 AM	1	0	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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24						
25						
26						
27						
28						

Patient Signature: _____ Date: _____

Consenting Professional/Research RN Signature _____ Date: _____

Consenting Professional/Research RN Comments:

_____
_____
_____
_____