UCSF Helen Diller Family Comprehensive Cancer Center

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Phase II trial to evaluate trametinib in patients with advanced *NF1*-mutant non-small cell lung cancer

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Protocol Signature Page

Protocol No.: 166521 **Version Date:** 06-20-2018

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.
6.

UCSF Principal Investigator / Study Chair

Collin Blakely, MD PhD

Printed Name

_____ _____

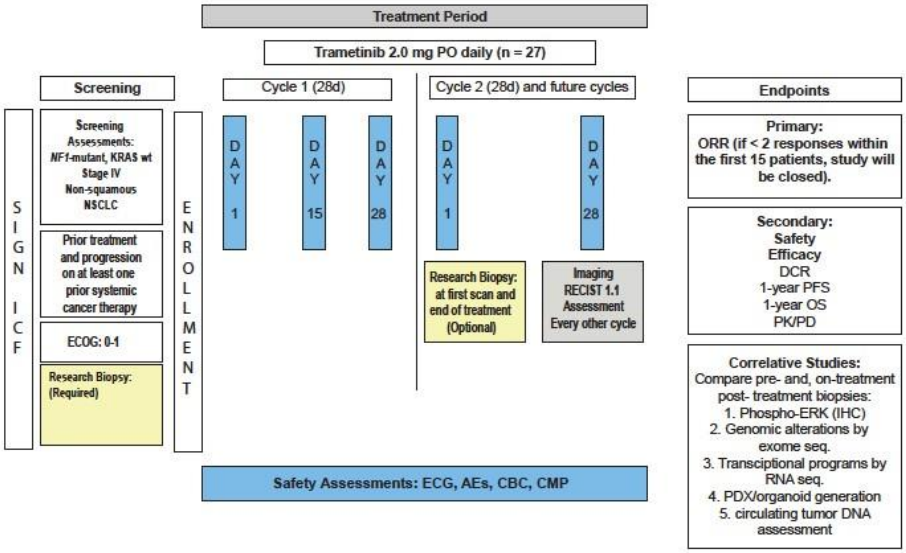
Signature Date

Participating Site(s)

Site Name: University of California, Davis **Principal Investigator:** Jonathan Riess, MD [redacted]	**Site Name:** University of California, San Diego **Principal Investigator**: Hatim Husain, MD [redacted]
Signature:	Signature:

Abstract

Title	Phase II trial to evaluate trametinib in patients with advanced *NF1*-mutant non-small cell lung cancer
Patient population	Patients with metastatic or unresectable locally advanced non-squamous, non-small cell lung cancer (NSCLC) whose tumors harbor a non-synonymous *NF1* mutation, with progressive disease on at least one prior line of therapy.
Rationale for Study	*NF1* is a tumor suppressor gene, which encodes a RAS GTPase activating protein (GAP), which facilitates the hydrolysis of RAS-GTP to the inactive RAS-GDP.[7-9] Germline *NF1* inactivating mutations are associated with both pediatric and adult malignancies.[10] Somatic mutations in *NF1* have been associated with adenocarcinoma of lung,[11] malignant melanoma,[12] glioblastoma,[13] as well as myelodysplastic syndrome.[10] *NF1* loss in melanoma cell lines that were wild-type for BRAF/RAS resulted in elevated RAS-GTP levels and MAPK signaling activation. Treatment of these cells with the MEK inhibitor trametinib resulted in sustained ERK inhibition and suppression of tumor cell proliferation.[12] Likewise, leukemias have been shown to arise from either germline or somatic loss of *NF1*[14] and treatment of autochthonous myeloid malignancies driven by engineered *NF1* loss in the mouse have been shown to be sensitive to MEK inhibition in preclinical models.[15] We hypothesize that patients with advanced NSCLC whose tumors harbor non-synonymous somatic mutations in *NF1* will exhibit tumor dependence upon the MAPK signaling pathway and will be sensitive to treatment with the potent and selective MEK inhibitor trametinib.[16]
Primary Objective	To evaluate the efficacy of trametinib in patients with advanced, non-squamous NSCLC who have progressed on at least one prior line of systemic cancer therapy (i.e. platinum doublet, anti-PD1/PDL1 or appropriate EGFR, ALK, or ROS-1 targeted therapy), and whose tumors harbor a non-synonymous mutation in *NF1* and is negative for an activating mutation in *KRAS*.
Secondary Objectives	• To evaluate secondary measures of clinical efficacy in advanced NSCLC patients treated with trametinib. • To evaluate the safety and tolerability of trametinib using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.03. • To describe the pharmacokinetics associated with trametinib. • To assess tissue and blood-based biomarkers that may be predictive of response or primary resistance to trametinib. • To determine subsets of advanced NSCLC in whom MEK inhibition is especially effective. (e.g., specific *NF1* mutations).

Study Design	This is a phase II, single-arm, open-label, multicenter clinical trial evaluating the efficacy and safety of trametinib monotherapy in patients with advanced non-squamous NSCLC whose tumors non-synonymous *NF1* mutations and are *KRAS wildtype*. Eligible patients must have documented disease progression either during or after treatment with platinum doublet chemotherapy or most recent therapy and may not have received prior treatment with a MEK inhibitor. Patients with activating alterations in EGFR, ALK, and ROS-1 must also have received appropriate TKI treatment. Patients who meet eligibility criteria will receive trametinib monotherapy and followed for the primary endpoint of objective response rate and additional secondary endpoints. 
Number of patients	A total of 27 patients will be enrolled into the study, with the goals of obtaining 24 evaluable patients. Using a Simon 2-stage design, if we do not observe at least 2 responses within the first 15 patients, enrollment will be stopped due to lack of efficacy.
Duration of Therapy	Patients may continue treatment until disease progression or up to 24 months from the time of study entry or until the study is closed.
Duration of Follow up	All patients will be followed for 12 months.
Duration of study	The study is estimated to reach completion 4 years from the time the study opens to accrual.

Study Drugs	Trametinib is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2 activation and kinase activity. Trametinib will be administered as 2 mg orally once daily.
Safety Assessments	Safety assessments will be based on events occurring during the on-study period, defined as from the first dose of trametinib to 30 days after the last dose of trametinib or until resolution for serious adverse events. Safety will be assessed by reviewing adverse events (AEs), laboratory evaluations, physical examination, and imaging or procedures when clinically indicated. Toxicity will be graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03).
Efficacy Assessments	Efficacy measures will include tumor assessments by CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST Version 1.1. Brain imaging (CT/MRI) is required at baseline and follow-up scans should include the brain in patients with baseline brain lesions. All sites of disease should be followed and the same imaging methodology should be used throughout the study. Tumor assessments will be carried out at screening and every 8 weeks ± 1 week from the time of trametinib initiation and thereafter until tumor progression. Patients are required to have an end-of-treatment tumor scan using the same methodology used at screening unless: • The patient has radiographic evidence of disease progression while on study, or • It has been < 2 weeks since their last on-study scan Patients who discontinue trametinib without progression should continue to be scanned per standard of care until disease progression occurs.

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DCR	Disease control rate
DFS	disease-free survival
DLT	dose limiting toxicity
DR	Duration of Response
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board

List of Abbreviations

IV	Intravenous
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	disease progression
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PFS	progression Free Survival
PR	partial response
PRC	Protocol Review Committee (UCSF)
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
WBC	white blood cell (count)

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1 Introduction

1.1 Background on Indication

The RTK-RAS-MAPK pathway is central in the initiation and maintenance of non-small cell lung cancer (NSCLC). Canonical mutations in *KRAS*, *EGFR* or fusions in *ALK*, *ROS1*, or *NRTK1* are present in about 50% of NSCLC of the adenocarcinoma subtype.[24] In two studies of approximately 400 NSCLC patients by The Cancer Genome Atlas (TCGA) Research Network, the frequency of mutations in *NF1* became apparent.[1,25] These mutations are typically mutually exclusive from *KRAS*, *EGFR,* or BRAF mutations (**Figure 1.1).**

We hypothesize that patients with advanced non-squamous NSCLC whose tumors harbor re-current non-synonymous somatic mutations in *NF1* will exhibit tumor dependence upon the MAPK signaling pathway and will be sensitive to treatment with the potent and selective MEK inhibitor trametinib.[16]

Figure 1: Mutations in *BRAF* and *NF1* are mutually exclusive from *EGFR* or *KRAS* mutations in lung adenocarcinoma (Source: Cancer Genome Atlas Research Network[1])

1.2 Background on the Compounds

1.2.1 Non-clinical pharmacology

Trametinib (GSK1120212) is a selective MEK1 and MEK2 inhibitor with selective activity towards BRAF and RAS mutant cancer cell lines and hematopoietic cancer cells from acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) origins. Trametinib inhibited the proliferation of most of the BRAF mutant melanoma cell lines tested (22 of 25) and it effectively inhibited the growth of BRAF mutant melanoma xenografts in vivo alone or in combination with dabrafenib. It causes inhibition of ERK phosphorylation leading to Gap-1 (G1) cell cycle arrest and tumor xenograft growth.

There were no clinically relevant findings in single dose safety pharmacology studies in rats and dogs evaluating the cardiovascular, respiratory and central nervous systems conducted with trametinib. Left ventricular ejection fraction decrease is a common adverse event in patients taking trametinib. Mice given trametinib at ≥ 0.25 mg/kg/day for 3 weeks (3-times the clinical area under the plasma concentration-time curve [AUC] at steady state) had decreased ventricular function, lower heart rates and lower heart weight in the absence of cardiac histopathology. Importantly, there was no diminution of dobutamine-induced contractility. An in vitro investigative study demonstrated that the echocardiography effects were not likely to be due to acute myocardial toxicity or inhibition of mitochondrial function.

1.2.2 Pharmacokinetics and Product Metabolism in Animals

The nonclinical pharmacokinetics (PK) of trametinib were similar across the species (mouse, rat, dog and monkey). Low plasma clearance relative to liver blood flow and generally long half-lives (t1/2) likely contribute to the accumulation upon repeat dosing which is consistent with observations in humans. Upon achieving steady-state, by 7 days for mice and by 3 weeks for rats and dogs (based on sparse sampling study design), the exposure of trametinib generally increased dose proportionally, which is consistent with observations in humans (steady state appeared to be achieved by Day 15).

The volume of distribution of trametinib was generally greater than total body water for all species, consistent with the observed wide distribution to tissues in the rat. There was no selective association of drug-related material with melanin containing tissues. Plasma protein binding was high in nonclinical species and humans (>95%). In vitro blood cell association in humans was concentration dependent with a high blood to plasma ratio (ranged from 3 to 8) at the clinically relevant trametinib concentrations of 1 and 10 ng/mL. Nonclinical species, including rats and dogs, showed protracted elimination of DRM (Drug Related Material) consistent with a high volume of distribution, long half-life, and the PK data of trametinib in subjects with solid tumors.

Absorption and systemic availability in nonclinical species and humans was moderate to high (>40% to approximately 100%). The fecal route of elimination was the major excretory pathway in humans, rats, dogs, and mice. Trametinib has a high passive permeability and is not an in vitro substrate for human P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), multi-drug resistance protein 2 (MRP2) and multidrug and toxin extrusion protein 1 (MATE1). Therefore, the risk for an effect of other drugs on trametinib via these mechanisms is low. Trametinib is a weak in vitro substrate of the efflux transporter bile salt export pump (BSEP). The current literature suggests that BSEP mostly transports endogenous bile salts[26] and is unlikely to play a major role in drug disposition and hence poses a low risk in drug-drug interactions.[27] In humans, trametinib is eliminated predominantly by hydrolytic deacetylation, either deacetylation alone (M5) or in combination with mono-oxygenation M7). The enzymes involved are likely hydrolytic enzymes, such as esterases or amidases that are not generally associated with drug interaction risks.

For the nonclinical species (rat and dog), trametinib was the major circulating component (> 60% of DRM) in plasma at all sampling time points. In humans, trametinib partitions in red blood cells and the majority of the circulating radioactivity is present as trametinib in blood (78-95% of DRM). Three minor metabolites M5, M6 and M7 were identified with the deacetylated metabolite (M5), which was shown to have similar in vitro pharmacological activity as parent, accounting for ≤11% of plasma (rat and dog) or blood DRM (human). In an earlier investigation of plasma metabolites in humans following repeat dosing, the metabolites do not appear to accumulate to the same degree as parent. Qualitatively, all of the major metabolites of trametinib observed in humans have been detected in the nonclinical species.

Based on in vitro studies, trametinib is not an inhibitor of cytochrome P450 enzymes including CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. Although trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and 2C19, inducer of CYP3A4 and inhibitor of the organic anion transporting polypeptide (OATP) transporters (OATP1B1, OATP1B3), Pgp, BCRP, organic anion transporter (OAT)1, OAT3, organic cation transporter 2 (OCT2), and MATE1), its low efficacious dose, and low clinical systemic concentration (22.2 ng/mL or 0.04 □M at 2 mg)

relative to the in vitro inhibition/induction potency suggests an overall low potential for drug-drug interactions.

1.2.3 Pharmacokinetics in humans

Trametinib pharmacokinetics were determined after single- and repeat-dose oral administration of trametinib tablets in subjects with solid tumors. Trametinib is absorbed rapidly with median time to maximum plasma concentration (tmax) generally occurring 1.50 hours after single oral administration of trametinib under fasting conditions. The absolute oral bioavailability of a single trametinib 2.0 mg tablet is moderate to high (72%) relative to a co-administered intravenous (IV) microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in Cmax, a 24% decrease in area under the concentration-time curve from time zero (predose) to last time point (AUC[0-t]) and a 10% decrease in AUC extrapolated to infinity (AUC [0-□]) compared to fasted conditions.

Following repeat-dosing the mean area under the curve from 0 hours to the time of next dosing (AUC[0-□]) and Cmax increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97 and a terminal half-life of 5.3 days determined after single dose administration. Steady state appears to be achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (C □), Cmax and area under the concentration-time curve from time zero (pre-dose) to 24 hrs (AUC[0-24]) between Days 15 and 21.

Trametinib is a low extraction ratio drug based on plasma IV clearance of 3.21 L/hr, which represents approximately 1% of liver blood flow. Trametinib has a high volume of distribution (Vd) of 1060 L determined following an IV microdose.

Fecal excretion is the major route of elimination after [14C] trametinib oral dose, accounting for >80% of excreted radioactivity recovered (or 39.2% and 35.0% of the radioactive dose in 2 subjects) while urinary excretion accounted for <19% of excreted radioactivity recovered (<10% of the radioactive dose). Following a single dose of [14C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound. However, based on metabolite profiling after repeat dosing of trametinib, ≥75% of drug-related material in plasma is the parent compound.

In vitro and in vivo data suggest that trametinib is unlikely to affect the PK of other drugs and that the PK of trametinib is unlikely to be affected by other drugs. Trametinib is metabolized predominantly via deacetylation which is likely mediated by hydrolytic esterases which are not generally associated with drug interaction risk, nor is it a substrate of Pgp or BCRP.

1.2.4 Trametinib Efficacy

Efficacy results from the MEK114267 (melanoma) study and the supporting studies MEK113583 (melanoma), MEK111054 (solid tumors or lymphoma), and MEK114653 (non-small cell lung carcinoma; NSCLC) indicated:

- Substantial evidence of effectiveness in unresectable *BRAF* V600 mutation positive melanoma as evidenced by prolongation of progression-free survival (PFS) and overall survival (OS). Updated long term results from MEK114267 study also consolidated the OS benefit of trametinib treatment over chemotherapy in this patient population.
- The clinical activity of trametinib observed in melanoma subjects whose tumors harbor *BRAF* V600K mutations is comparable to the activity seen in *BRAF* V600E mutations
- Comprehensive efficacy data to support the recommended dose of trametinib of 2 mg once daily for all subjects
- The efficacy of trametinib in melanoma across all demographic (e.g., age, gender) and prognostic factors (e.g., tumor stage, Eastern Cooperative Oncology Group Performance Status [ECOG PS], lactate dehydrogenase (LDH) levels, history of brain metastases).

1.2.5 Safety

Based on the adverse events (AEs) observed in the dose escalation phase of the first-time-in-human (FTIH) study MEK111054, the maximum tolerated dose was established at 3.0 mg once daily, and the RP2D of trametinib was identified as 2.0 mg once daily.

In the 11 monotherapy studies of trametinib for which data are available (MEK111054, MEK111759, MEK113583, MEK113708, MEK113709, MEK114267, MEK114375, MEK115064, MEK114653, MEK114655, and MEK115892), all studies except MEK113708 had AEs.

In the studies with AEs, 50% to 100% of all subjects in any dose group had at least 1 AE, and 0% to 70% of all subjects in any dose group had at least 1 serious adverse event (SAE). Of the studies with discontinuations or withdrawals, 3% to 26% of subjects receiving trametinib permanently discontinued study treatment or withdrew due to AEs.

Of the > 700 subjects (including crossover subjects) in the 2.0 mg dose group, in 8 monotherapy studies with AEs (MEK111054, MEK111759, MEK113583, MEK113709, MEK114267, MEK115064, MEK114655, and MEK114653), 50% to 100% of subjects had at least 1 AE, and 0% to 70% of all subjects had SAEs. Of the studies with discontinuations or withdrawals (MEK111054, MEK113583, MEK114267, MEK114653, and MEK111759), 3% to 24% in the 2.0 mg does group permanently discontinued study treatment or withdrew from the study due to AEs. Data from studies with the combination of trametinib and dabrafenib (GSK2118436) are included in another IB [GlaxoSmithKline Document Number 2011N126811_02]. In the 2.0 mg dose group across all completed monotherapy studies with AEs, the most common AEs had were rash, diarrhea, fatigue, edema peripheral, nausea, dermatitis acneiform, vomiting, constipation, anemia, pruritus, alopecia, hypertension, decreased appetite, dyspnea and dry skin.

1.3 Rationale for the Proposed Study

Recent genomic studies, including the Cancer Genome Atlas (TCGA), have identified >140 different recurrent somatic mutations in *neurofibromin-1* (*NF1*) in human NSCLC[17,18]. These *NF1*-mutants are present in ~10% of NSCLC patients and often occur in the absence of another known genetic driver event, suggesting a potential driver role for mutant NF1[17,18]; thus, *NF1*-mutant NSCLC comprises an emerging distinct genetic subtype of NSCLC and the largest population of *NF1*-mutant patients across all tumor types. *NF1* is a tumor suppressor that is genetically inactivated in several tumor types including melanoma, glioblastoma, certain

leukemias, and the hereditary syndrome neurofibromatosis[12,19-23]. NF1 is a GTPase activating protein (GAP) for RAS GTPases, which require GTP binding to signal to downstream effector pathways such as the RAF-MEK-ERK cascade[20]. NF1 enhances the intrinsic rate of GTP hydrolysis of RAS, thereby switching RAS off. Loss of NF1 activity enhances RAS-GTP levels to promote RAF-MEK-ERK signaling, cellular proliferation and growth, and oncogenesis[12,20,23].

There are currently no FDA-approved targeted therapy options for patients with advanced non-squamous NSCLC whose tumors harbor *NF1* mutations and have failed treatment with first-line platinum-containing cytotoxic chemotherapy or appropriate EGFR, ALK, or ROS-1 targeted therapies. After progression on first-line platinum doublet chemotherapy or second-line immunotherapy, single-agent cytotoxic chemotherapy in the second or third-line setting has limited efficacy[28]. . This highlights the ongoing unmet need for patients with advanced NSCLC with *NF1* mutations.

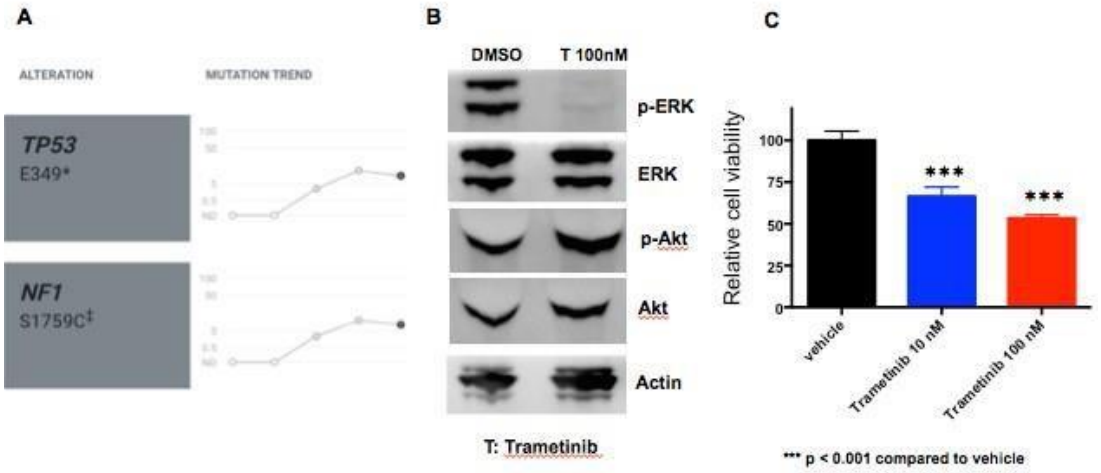

Figure 1.4. Relative sensitivity of *NF1*-mutant patient-derived lung adenocarcinoma cell line to the MEK inhibitor trametinib. (A) Detection of cell-free DNA by Guardant 360 assay in a patient with known, metastatic NF1-mutant lung adenocarcinoma (A) Western blot showing a decrease in ERK phosphorylation upon trametinib treatment of cell lines derived from the patient's tumor. (B) Cell viability assay showing a ~ 50 % reduction in cell viability upon trametinib treatment of *NF1* mutant lung adenocarcinoma cells.

NF1 is a tumor suppressor gene, which encodes a RAS GTPase activating protein (GAP), which facilitates the hydrolysis of RAS-GTP to the inactive RAS-GDP.[7-9] Germline *NF1* inactivating mutations are associated with both pediatric and adult malignancies.[10] Somatic mutations in *NF1* have been associated with adenocarcinoma of lung,[11] malignant melanoma,[12] glioblastoma,[13] as well as myelodysplastic syndrome.[10] *NF1* loss in melanoma cell lines that were wild-type for BRAF/RAS resulted in elevated RAS-GTP levels and MAPK signaling activation. Treatment of these cells with the MEK inhibitor trametinib resulted in sustained ERK inhibition and suppression of tumor cell proliferation.[12] Likewise, leukemias have been shown to arise from either germline or somatic loss of NF1[14] and treatment of autochthonous myeloid

malignancies driven by engineered *NF1* loss in the mouse have been shown to be sensitive to MEK inhibition in preclinical models.[15]

We have generating a non-small cell lung cancer cell line from a patient whose only know somatic mutations were in *TP53* E349* and *NF1* S1759C. Notably, the frequency of these mutations detectable by cell-free DNA from the patients' blood have increased as the lung cancer progressed radiographically (Figure 1.4A). MEK activity, as determined by ERK phosphorylation is rapidly decreased upon treatment of these cells with trametinib (Figure 1.4B). Meanwhile, cell viability decreases by ~50 % upon trametinib treatment (Figure 1.4C). With demonstrated activity against and *NF1* mutant melanoma[12] and myeloid malignancy[31] and lung adenocarcinoma preclinical models (Figure 1.4), we hypothesize that trametinib will provide an effective and tolerable therapy for patients with *NF1*-mutant NSCLC. The goals of the current study are to determine the anti-tumor efficacy and safety of oral single-agent trametinib in patients with *NF1* mutated advanced non-squamous NSCLC after failure of at least one prior line of chemotherapy including a platinum doublet, and appropriate treatment with an EGFR, ALK, or ROS-1 inhibitor in patients whose tumors harbor activating alterations in those genes.

1.4 Correlative Studies

1.4.1 Whole exome and transcriptome sequencing.

We will use whole exome and transcriptome deep sequencing (WES; RNAseq) in the pre-treatment, on treatment, and post-resistance samples to uncover somatic genetic alterations (mutations and copy number alterations) and transcriptional events associated with clinical resistance (either de novo or acquired), using our methods and with a minimum depth of WES coverage of 100X to capture events occurring down to ~1% frequency. This approach will enable identification and/or validation of RNA signatures of potential resistance events, such as ERK1/2 transcriptional output. The analysis of samples from patients with de novo resistance and of matched paired tumor samples acquired from individual patients before treatment and at acquired resistance (based on standard radiographic assessment in the trial, such as RECIST criteria) will be prioritized for study to facilitate the clinical correlation of the genetic findings with bona fide clinical resistance. Orthogonal validation of specific findings will be done using individualized assays in the clinical specimens (e.g. direct sequencing, SNP arrays, fluorescence in situ hybridization for DNA alterations; q-RT-PCR, IHC for RNA and protein abundance changes) and associated circulating free DNA, where feasible.

1.4.2 IHC for phospho-ERK and downstream effectors:

We will evaluate whether trametinib effectively shuts down the MEK signaling axis by performing IHC analysis on pre-treatment and on-treatment biopsy specimens. YAP-TAZ signaling will also be evaluated, given that its upregulation is associated with resistance to MAPK pathway inhibitors[32].

1.4.3 Patient-derived xenografts and organoids

When possible, patient derived xenografts or organoids will be generated from patient biopsy specimens. Alterations discovered in the clinical specimen analysis will be functionally studied using our standard cell-based assays. We will test if activation or suppression of the candidate resistance gene (as indicated by whether the gene is increased or decreased in resistance)

promotes MEK inhibitor resistance, in vitro and in vivo in tumor xenograft and organoid studies.

1.4.2 Cell-Free DNA

Blood samples for circulating tumor DNA (ctDNA) will be collected pre-treatment and post-resistance tissue biopsy to identify mechanisms of resistance. Concordance of ctDNA with pre- and post- tissue biopsy will be assessed. 20ml of whole blood for ctDNA analysis will be collected at the time of pre-treatment biopsy, monthly until tumor progression, and at the time of post-resistance biopsy to monitor dynamic changes in the quantity of ctDNA for the specific *NF1* mutations. The rate of ctDNA clearance of the specific *NF1* mutations will be serially tracked and will be compared to radiologic change on CT scans. Acquired somatic mutations in, *NF1* or off-target genes qualitatively evaluated to identify second site mutations that may confer resistance to therapy.

2 Objectives of the Study

2.1 Primary

To evaluate the efficacy of trametinib in patients with advanced, non-squamous NSCLC who have progressed on at least one prior systemic anti-cancer therapy (i.e. platinum doublet chemotherapy, anti-PD1 or anti-PDL1 immunotherapy, or appropriate EGFR, ALK, and ROS-1 targeted therapy) and whose tumors harbor a non- synonymous mutation in *NF1* and is negative for activating mutations in *KRAS.*

2.2 Secondary

- To evaluate secondary measures of clinical efficacy in advanced NSCLC patients treated with trametinib.
- To evaluate the safety and tolerability of trametinib using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.03.

2.3 Exploratory Objectives, Other Assessments

- Determine whether specific mutations in *NF1* identified in pretreatment tumor samples correlate with response and/or resistance to trametinib.
- To identify biomarkers of clinical benefit and mechanisms of resistance (de novo resistance, incomplete response, and acquired resistance) to trametinib therapy in *NF1* mutant NSCLC.
- Assess circulating tumor DNA (ctDNA) for biomarkers of response and/or resistance to trametinib.

2.4 Endpoints

2.4.1 Primary Endpoints

- Objective Response Rate (ORR) according to RECIST Version 1.1 criteria as determined by investigator assessment. The ORR is defined as the best overall response recorded from the start of the treatment until disease progression or recurrence from the start of treatment.

2.4.2 Secondary Endpoints

- Efficacy: DR, DCR, PFS, and OS according to RECIST Version 1.1 criteria as determined by investigator assessment.
  - The DR for CR and PR will be measured from the date that the best response if first recorded until the date that PD is documented. For patients who continue treatment post progression, the date of PD documentation will be used for analysis.
  - DCR will be defined as the percentage of patients who have achieved CR, PR, or SD for at least 12 weeks.
  - PFS will be calculated as 1+ the number of days from the first dose of study drugs to documented radiographic progression or death due to any cause over a period of 1 year. For patients who continue treatment post-progression, the date of radiographic progression will be used for PFS analysis.
  - OS will be calculated as 1+ the number of days from the first dose of study drugs to death due to any cause over a period of 1 year.

- Safety and tolerability:
  - All treatment-emergent AEs
  - Treatment-emergent AEs by CTCAE grade
  - Grade 3 or greater treatment-emergent AEs
  - Treatment-related, treatment-emergent AEs
  - Dose-limiting toxicity AEs
  - Serious treatment-emergent AEs
  - Treatment-emergent AEs with an outcome of death
  - Treatment-emergent AEs leading to discontinuation of trametinib.
  - Treatment-emergent AEs resulting in interruption or reduction or delay of trametinib.

2.4.3 Exploratory Endpoints

- Specific mutations in *NF1* identified in pretreatment tumor samples correlated with response and/or resistance to trametinib.
- Circulating cell free DNA (cfDNA) biomarkers associated with response and/or resistance to trametinib.
- RNA and DNA changes in samples during therapy and at progression.

3 Study Design

3.1 Characteristics

This is a Phase II, open-label, multicenter clinical trial evaluating the efficacy and safety of

a non-synonymous *NF1* mutation and are wildtype for activating mutations in KRAS. Eligible patients must have documented disease progression either during or after treatment with appropriate EGFR, ALK, or ROS-1 inhibitors (in patients with EGFR activating mutations, or ALK or ROS-1 fusions) and platinum doublet chemotherapy (or inability to tolerate) or most recent therapy and must not have received prior treatment with a MEK inhibitor.

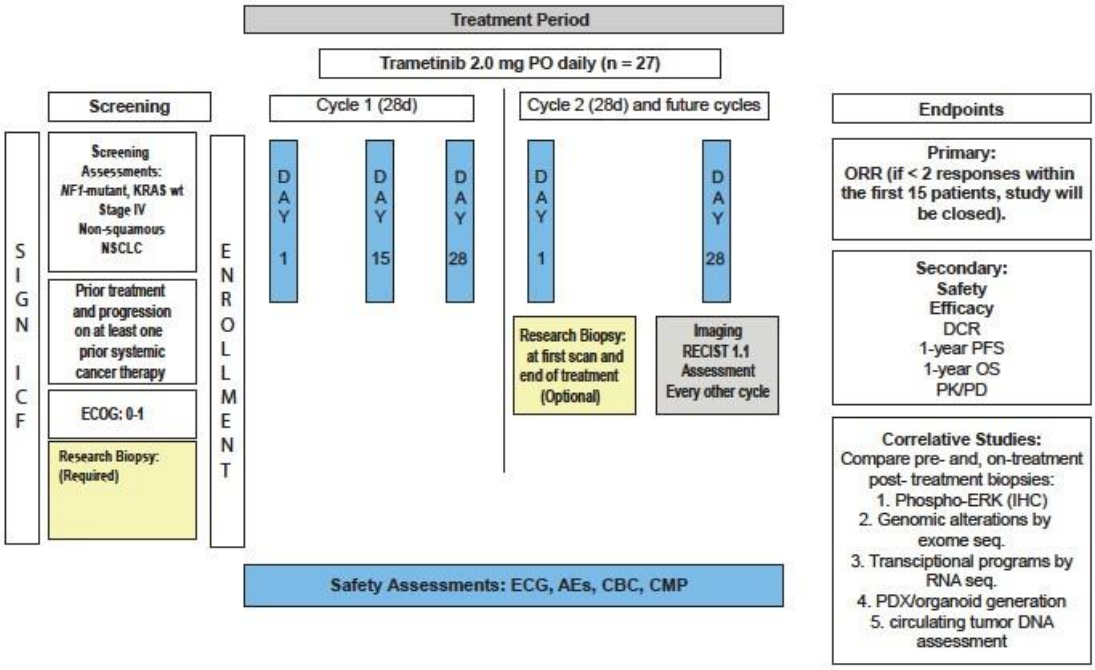

Figure 3.1. Study schema

Patients will receive trametinib monotherapy in 28-day cycles. The primary outcome is objective response rate.

3.2 Number of Subjects

A total of 27 patients will be enrolled in the study, with the goal of obtaining 24 evaluable patients. This will provide 80% power to detect a 30% ORR with trametinib compared to the null hypothesis of a 10% ORR. Using a Simon 2-stage design, if we do not observe at least 2 responses within the first 15 patients, enrollment will be stopped due to lack of efficacy.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained

from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Histologically or cytologically confirmed metastatic or unresectable locally advanced, non-squamous, NSCLC.
2. Documented non-synonymous somatic mutation in *NF1* in any tumor specimen or cell-free DNA assay by CLIA-approved laboratory.
3. Received at least one prior line of cancer therapy for the treatment of NSCLC. This should include at least one of the following: platinum (carboplatin or cisplatin) doublet chemotherapy (acceptable combinations include: paclitaxel, docetaxel, abraxane, pemetrexed, gemcitabine, vinorelbine, or etoposide), anti-PD1/PDL1 therapy (pembrolizumab, nivolumab, or atezolizumab), or appropriate targeted therapy in patients with activating EGFR (osimertinib, erlotinib, gefitinib, or afatinib), ALK (alectinib, crizotinib, ceritinib, brigatinib, or loralatinib), or ROS-1 (crizotininb or entrectinib) alterations. Therapy may be given as monotherapy or in combination with other cancer therapy (e.g. bevacizumab, ipilumimab)
4. Patients with a known activating mutation in EGFR (Exon 19 deletion, G719A, S768I, V769L, T790M, L833F, L858R, L861Q), must have progressed or been intolerant to treatment with a first-line EGFR TKI (erlotinib, afatinib, gefitinib or osimertinib). Patients whose tumors were found to have an EGFR T790M mutation must also have progressed or been intolerable to treatment with osimertinib.
5. Patients with a known ALK-rearrangement must have progressed or been intolerant to treatment with at least one ALK TKI: crizotinib, ceritinib, alectinib, brigatinib, or loralatinib.
6. Patients with a known ROS-1- rearrangement must have progressed or been intolerant to treatment with crizotinib or entrectinib.
7. Patients with PDL1 level of ≥ 50%, who do not have an ALK-rearrangement or EGFR-mutation, must have progressed or been intolerant to treatment with anti-PD1/PDL1 therapy (pembrolizumab, nivolumab, or atezolizumab).
8. Documented disease progression or intolerance to treatment either during or after treatment with most recent therapy.
9. Willingness to undergo research biopsy.
10. Measurable disease defined by RECIST 1.1 criteria.
11. Life expectancy of at least 3 months.
12. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
13. Age ≥ 18 years.
14. Resolution of all acute toxic effects of prior chemotherapy, immunotherapy, radiotherapy or surgical procedures to NCI CTCAE Version 4.03 grade 1.
15. Adequate baseline organ function defined in Table 3.1.

Table 3.1 Definitions for adequate baseline organ function

System	Laboratory Values
Hematologic	
Absolute neutrophil count	≥ 1.2×10^9/L
Hemoglobin	≥ 9 g/dL
Platelets	≥ 100×10^9/L
PT/INR and PTT	≤ 1.5 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
Total bilirubin	≤ 1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine **or**	≤ 1.5 ULN
Calculated creatinine clearance[a]	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or MUGA[b]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; PT = prothrombin time; PTT= partial thromboplastin time; ULN = upper limit of normal; LLN = lower limit of normal

a. Calculated by the Cockcroft-Gault formula.

b. Same method as used at baseline must be use throughout the study

16. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to study enrollment. The effects of trametinib on the developing human fetus are unknown. For this reason and because animal studies with trametinib have shown reproductive toxicity, women of child-bearing potential and men must agree to use effective methods of contraception (hormonal or barrier method of birth control) prior to study entry, for the duration of study participation, and for 4 months following discontinuation of trametinib. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of study drug administration.

17. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.

18. All prior treatment- related toxicities must be CTCAE (Version 4.03) ≤ Grade 1 (except alopecia) at the time of randomization

19. Ability to understand a written informed consent document, and the willingness to sign it.

3.3.2 Exclusion Criteria

Patients eligible must not meet **any** of the following criteria:

1. Known mutation in KRAS at position G12, G13, or Q61.
2. Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression. Treated brain metastases are allowed as long as they are stable for at least 28 days post-treatment.
3. Pregnant women are excluded from this study because trametinib is a MEK inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with trametinib, breastfeeding should be discontinued if the mother is treated with trametinib.
4. 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 and/or subjects with indolent second malignancies are eligible.
5. Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
6. The subject has received cytotoxic chemotherapy, molecular targeted therapy, or immunotherapy within 21 days before the first dose of study drug (trametinib).
7. Prior treatment with MEK inhibitor.
8. History of interstitial lung disease or pneumonitis.
9. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drug, or excipients or to dimethyl sulfoxide (DMSO).
10. Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy, or immunotherapy within 21 days prior to study enrollment and/or daily or weekly chemotherapy without the potential for delayed toxicity within 14 days prior to study enrollment.
11. History of retinal vein occlusion (RVO).
12. 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).
13. History or evidence of cardiovascular risk including any of the following:
    - LVEF< LLN
    - A QT interval corrected for heart rate using the Bazett's formula (QTcB) 480 msec;
    - History or evidence of current clinically significant uncontrolled arrhythmias.

- **Clarification:** Subjects with atrial fibrillation controlled (defined as not requiring change in cardiac drug dosing, emergency room visit, or hospital admission) for >30 days prior to dosing are eligible.
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to study enrollment.
- History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).
- 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;
- Patients with intra-cardiac defibrillators.

3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 24 months or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.
- The study is closed by the sponsor or investigator.

Patients who are continuing to respond to the study drug after 24 months of therapy will be provided with continued access to the drug by Novartis.

3.5 Duration of Follow Up

Patients will be followed for 30 days after completion of treatment or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

3.6 Study Timeline

3.6.1 Primary Completion

It is expected that the study will reach primary completion 36 months from the time the study opens to accrual.

3.6.2 Study Completion

It is expected that the study will reach full completion 48 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug

Trametinib tablets are provided as immediate release tablets for oral administration containing trametinib dimethyl sulfoxide (GSK1120212B) equivalent to 0.5 mg or 2 mg of trametinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the trametinib Investigator's Brochure for a list of excipients.

The trametinib tablets are packaged in high-density polyethylene bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

Classification

Cytotoxic drug: molecular targeted cytotoxic drug

Mechanism of Action

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 256 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are 257 upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes 258 cellular proliferation.

Metabolism

Trametinib is metabolized predominantly via deacetylation alone or with mono282 oxygenation or in combination with glucuronidation biotransformation pathways in vitro. 283 Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases. 284 Following a single dose of [14C]-trametinib, approximately 50% of circulating radioactivity is 285 represented as the parent compound. However, based on metabolite profiling after repeat dosing 286 of trametinib, ≥ 75% of drug-related material in plasma is the parent compound.

Contraindications

None.

Availability

Trametinib will be supplied by Novartis.

Storage and handling

Trametinib tablets should be stored refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

Side Effects

The following undesirable effects have been observed in subjects with metastatic melanoma receiving trametinib 2 mg once daily in the integrated safety population as of 25 June 2012 cutoff date (n=329). Of these 329 subjects, 211 were from MEK114267 (Phase III randomized open label study), 97 were from MEK113583 (Phase II study), and 21 were from MEK111054 (FTIH study). The most common adverse reactions (≥ 20%) for trametinib include rash, diarrhea, fatigue, edema peripheral, nausea, and dermatitis acneiform. In clinical trials with trametinib, adverse reactions of diarrhea and rash were managed with appropriate supportive care.

Adverse reactions are listed below by MedDRA body system organ class. The following convention has been utilized for the classification of frequency:
Very common ≥1 in 10 (≥ 10%)
Common ≥ 1 in 100 and < 1 in 10 (≥ 1% and <10%)
Uncommon ≥ 1 in 1,000 and < 1 in 100 (≥ 0.1% and <1%)
Rare ≥ 1/10,000 and <1/1,000 (≥ 0.01% and <0.1%)

Categories have been assigned based on frequencies of AEs (considered related to trametinib) observed in the integrated safety summary (ISS) data (n=329).

Infections and Infestations

Very Common:	Urinary tract infection
	Nasopharyngitis
Common:	Folliculitis
	Paronychia
	Cellulitis
	Rash pustular

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common:	Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease), and keratoacanthoma
	Papilloma including skin papilloma
	Seborrhoeic keratosis
	Acrochordon (skin tags)
Uncommon:	New primary melanoma

Blood and lymphatic system disorders

Very Common:	Neutropenia
Common:	Anemia
	Thrombocytopenia
	Leukopenia

Immune system disorders

Uncommon:	Hypersensitivity
	May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances

Metabolism and Nutrition Disorders

Very Common:	Decreased appetite
Common:	Dehydration
	Hyponatraemia
	Hypophosphataemia
	Hyperglycemia

Nervous system disorders

Very Common:	Headache
	Dizziness

Eye disorders

Common:	Vision blurred
	Periorbital edema
	Visual impairment
Uncommon:	Chorioretinopathy (also known as Retinal Pigment Epithelial Detachment (RPED))
	Uveitis
	Retinal vein occlusion
	Papilledema
	Retinal detachment
	Peiorbital oedema

Cardiac disorders

Common:	Left ventricular dysfunction
	Ejection fraction decreased
Uncommon:	Cardiac failure

Vascular disorders

Very common:	Hypertension
	Hemorrhage. The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial hemorrhages have been reported.
Common:	Lymphedema
	Hypotension

Respiratory, thoracic and mediastinal disorders

Very common:	Cough
	Dyspnea
Common:	Epistaxis
	Pneumonitis
Uncommon:	Interstitial lung disease

Gastrointestinal disorders

Very common:	Diarrhea
	Nausea
	Vomiting
	Constipation
	Abdominal pain

	Dry mouth
Common:	Stomatitis
Uncommon:	Pancreatitis

Hepatobiliary disorders

Very Common:	Aspartate aminotransferase increased
	Alanine aminotransferase increased
Common:	Blood alkaline phosphatase increased
	Gamma-glutamyltransferase increased

Skin and subcutaneous tissue disorders

Very common:	Rash
	Dermatitis acneiform
	Dry skin
	Pruritus
	Alopecia
Common:	Skin chapped
	Erythema
	Palmar-plantar erythrodysaesthesia syndrome
	Skin fissures
	Actinic keratosis
	Night sweats
	Hyperkeratosis
	Hyperhidrosis
	Skin lesion
	Panniculitis

Musculoskeletal and connective tissue disorder

Very Common:	Arthralgia
	Myalgia
	Pain in extremity
Common:	Blood creatine phosphokinase increased
	Muscle spasms

Renal Disorders

Uncommon:	Renal Failure
	Nephritis

General disorders

Very Common:	Fatigue
	Edema peripheral
	Pyrexia
	Chills
	Asthenia
Common:	Face edema
	Mucosal inflammation
	Influenza-like illness

Complete and updated adverse event information is available in the Investigational Drug Brochure and product package insert.

4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

4.3 Drug Ordering

UCSF will obtain trametinib directly from pharmaceutical company as study supply.

4.4 Packaging and Labeling of Study Drugs

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

5 Treatment Plan

5.1 Dosage and Administration

Treatment will be administered on an outpatient basis.

Table 5.1 Regimen Description

Study Drug	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Trametinib	Take with a full glass of water, without food, at least 1 hour before or 2 hours after a meal.	2 mg, once daily	Oral	Days 1-28	4 weeks (28 days)

If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each 28 day cycle.

5.1.1 Other Modalities or Procedures

No other modalities will be used in this study.

5.2 Dose Modifications and Dosing Delays

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation.

Table 5.2 Dose Modifications and Dosing Delays

Dose Level	Dose of Study Drug
-2	1 mg daily
-1	1.5 mg daily
1	2 mg daily

Dose adjustment for trametinib below 1 mg QD is not recommended.

A maximum of two trametinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued.

If a dose reduction of trametinib is required, but the toxicity resolves and no additional toxicities are seen after two cycles of treatment, the dose of trametinib may be re-escalated but should not exceed 2 mg once daily.

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03.

Table 5.3 Dose Delay and Modification for Events Considered Related to Trametinib

CTCAE Grade	Action and Dose Modification
Grade 1	• Continue trametinib at current dose level • Monitor closely • Provide supportive care according to institutional standards
Grade 2	• Interrupt trametinib if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart trametinib at current dose level
Grade 3	• Interrupt trametinib if clinically indicated • Monitor closely • Provide supportive care according to institutional standards • When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by one dose level** • If the Grade 3 toxicity recurs, interrupt trametinib • When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by another dose level**
Grade 4	• Interrupt trametinib • Monitor closely • Provide supportive care according to institutional standards • If event resolves to Grade 1 or baseline discuss potential continuation of trametinib with investigator-sponsor; if continuation of treatment agreed then restart trametinib at dose **reduced by one dose le**vel • **If event does not resolve permanently discontinue trametinib**

Note: Approval from the investigator-sponsor is required to restart study treatment after ≥ 28 days of interruption.

Trametinib dose modification guidelines are outlined in Table 5.2 and Table 5.3 for clinically significant toxicities that are deemed related to trametinib (i.e. peripheral and periorbital edema) with the exception of the **following events of special interest:**

- rash (Section 5.2.1)
- diarrhea (Section 5.2.2),
- ejection fraction changes (Section 5.2.3),
- hypertension (Section 5.2.4)
- prolonged QTc (Section 5.2.5)
- pneumonitis (Section 5.2.6),
- visual changes (Section 5.2.7),
- liver chemistry elevation (Section 5.2.8)

For these, refer to the relevant sections for dose modification guidelines for adverse events of special interest.

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

5.2.1 Guidelines for Rash

Rash is a frequent AE observed in subjects receiving trametinib (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors[33] and EGFR inhibitors[34] and are provided in Table 5.4 and Table 5.5.

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 investigator-sponsor may be required.

Table 5.4 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 in Table 5.5.

Table 5.5 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 trametinib • 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 trametinib 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, after discussion with study PI. • **Restart[c] with 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 the investigator-sponsor is required to restart study treatment after >4 weeks 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

5.2.2 Guidelines for Diarrhea

Episodes of diarrhea have occurred in subjects receiving trametinib (see the Investigator Brochures 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 in Table 5.6.

Table 5.6 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
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] • 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. 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.

5.2.3 Guidelines for Ejection Fraction Changes

Left Ventricular Ejection Fraction (LVEF)
Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib. Therefore, ECHO/MUGAs must be performed to assess cardiac ejection fraction in regular intervals as outlined in the Time and Events Table (Table X).

The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Electronic copies of all ECHO/MUGA scans will be collected by Novartis for review. Instructions for submission of ECHO/MUGA scans are provided in the Study Procedures Manual (SPM).

Dose modification guidance and stopping criteria for LVEF decrease are provided in Table 5.7.

Table 5.7 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 Novartis medical monitor and request approval for restart • Restart treatment with trametinib reduced dose by one dose level[b] • 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 • Consult with cardiologist • Permanently discontinue trametinib • Report as SAE

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction;

a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
b. Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from Novartis Medical Monitor is required.
c. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.

5.2.4 Guidelines for Hypertension

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

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 right 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 Schedule of Study Procedures and Assessments (Table 6.1). 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 5.8:

Table 5.8 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 DBP still <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 to achieve well-controlled BP Once BP is well controlled[b], restart trametinib **reduced by one dose level[c]**
(Scenario C) Symptomatic[d] hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of trametinib	Interrupt trametinib Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication during the next 2 weeks 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[c]**
(Scenario D) Refractory hypertension unresponsive to above interventions or having hypertensive crisis.	**Permanently discontinue trametinib** Continue follow-up per protocol.

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. Escalation of trametinib to previous dose level can be considered if BPs remains well-controlled for 4 weeks after restarting

of trametinib. Approval from Novartis Medical Monitor is required.

d. 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.

5.2.5 Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in

Table 5.9 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
QTcB ≥501 msec or uncorrected QT>600 msec or QTcB>530 msec for subjects with bundle branch block	Interrupt study treatment 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] **If event recurs, permanently discontinue study treatment**

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 Novartis medical monitor agree that the subject will benefit from further treatment.

5.2.6 Guidelines for Pneumonitis

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 in Table 5.10.

Table 5.10 Management and Dose Modification Guidelines for Pneumonitis

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 of 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 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 study treatment
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, study treatment may be restarted reduced by one dose level • If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment
Grade 4	• Same as grade 3	• Permanently discontinue trametinib

5.2.7 Guidelines for Visual Changes or Specified Ophthalmic Examination Findings

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO)).

Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in Table 5.11.

Table 5.11 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 • <u>If RPED suspected or diagnosed:</u> see RPED dose modification table Y below; **report as SAE.** • <u>If RVO diagnosed:</u> **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 • <u>If RPED diagnosed</u>, see RPED dose modification table below; **report as SAE.** • <u>If RVO diagnosed:</u> **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 4.03 'Eye disorders – Other, specify'

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

Table 5.12 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

a. Refers to CTCAE Version 4.03 'Retinopathy'

5.2.8 Guidelines for Liver Chemistry Elevation

Table 5.13

Grade of Event	Management/Next Dose for Trametinb
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 Resume at same dose level
Grade 3	Hold* until ≤ Grade 1 Resume at one dose level lower, if indicated**
Grade 4	Off protocol therapy

5.2.9 Guidelines for other toxicity

Table 5.14

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for trametinib**
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 in ≤ 7 days, maintain dose level If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then ↓dose level
PULMONARY Notes: • Withhold trametinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. • During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for trametinib**
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from study.
CARDIAC INVESTIGATIONS	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit dose until QTC is less than 481 ms, then ↓dose level Perform an analysis of serum potassium, and if below lower limit of normal, correct with supplements to within normal limits. -Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms -Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTc ≥ 501 or > 60ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from trametinib.

Table 5.15

Worst toxicity (CTCAE 4.03 Grade)*	Dose Modifications for trametinib
BRADYCARDIA	
Grade 1 or Grade 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia and adjust the dose of trametinib
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume trametinib at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue trametinib
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥3 (> 2.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Note: Withhold trametinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	

5.3 Monitoring and Toxicity Management

Each patient receiving trametinib will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in Section 6 Study Procedures and Observations. Toxicity will be assessed according to the NCI CTCAE v4.03. Dose adjustments will be made according to the system showing the greatest degree of toxicity.

We will monitor for potential adverse effects including but not limited to fatigue, dehydration, cytopenias, leukocytosis, nausea, vomiting, signs and symptoms of infection. In addition, we will monitor specifically for the following adverse events of special interest (please see corresponding subsections in Section 5.2 for acute toxicity management and dose modifications):

- Diarrhea (Section 5.2.2),
- Ejection fraction changes (Section 5.2.3),
- Hypertension (Section 5.2.4)
- Prolonged QTc (Section 5.2.5)
- Pneumonitis (Section 5.2.6),
- Visual changes (Section 5.2.7),
- Liver chemistry elevation (Section 5.2.8)

Acute toxicity will be managed by supportive care and/or delay of dose. Further management will depend upon the judgment of the treating clinician and may include dose reduction. Patients will also be monitored for visual changes and change in cardiac function and QTc as described below.

Ophthalmic Examination

Subjects are required to have a standard ophthalmic examination conducted by an ophthalmologist at baseline, week 4/Month 1 (prior to commencement of cycle 2), Month 6 and then annually thereafter unless clinically indicated sooner.

The exam will include visual acuity (best corrected), tonometry (intraocular pressure measurement), visual field examination, slit lamp biomicroscopy of the anterior segment (with special attention to inflammation) and the posterior segment, and indirect fundoscopic examination with special attention to possible retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected or noted. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

Cardiac monitoring

LVEF will be assessed by echocardiogram or multigated acquisition (MUGA) scan within 28 days prior to initiation of trametinib. The same cardiac monitoring procedure (either echocardiogram or MUGA scan) will be repeated at one month after initiation of trametinib, and then at every 3 month intervals while on treatment.

An electrocardiogram will be performed within 28 days prior to initiation of trametinib to assess QTc. An electrocardiogram will be repeated on Cycle 1 Day 1, at one month after initiation of trametinib, and then at every 3 month intervals while on treatment.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6 Schedule of Study Procedures and Assessments. Screening assessments must be performed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. All on-study visit procedures are allowed **a window of ± 3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

6.1.1 Pretreatment Period

6.1.1.1 Screening Assessments

Visit Windows: The Screening procedures and assessments must be completed within 28 days of the Day 1 Visit.

- Physical examination
- Vital signs
- Complete medical history including history of prior treatments and any residual toxicity relating to prior treatment
- Baseline conditions assessment
- Performance status
- Disease assessment including imaging (CT or MRI) of chest/abdomen/pelvis and brain for tumor/lesion assessment
- Baseline medications
- Research tumor biopsy for biomarker analysis (to be paid for by study), unless deemed medically unsafe
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessments, including:

  Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate.

- Coagulation assessment, including prothrombin time, partial thromboplastin time, international normalized ratio (PT/PTT/INR)
- Urinalysis
- Serum or urine pregnancy test within 3 days prior to the start of study drug for patients of child-bearing potential.
- Electrocardiogram (ECG) in triplicate
- Cardiac assessment (MUGA or TTE)
- Ophthalmic exam
- Specimen collection for biomarkers and banking

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Cycle 1, Day 1

Visit Windows: Screening laboratory tests completed within 3 days of Cycle 1 Day 1 do not need to be repeated

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:

  Alkaline phosphatase, ALT/AST, total bilirubin, BUN, creatinine, fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Urinalysis
- Serum or urine pregnancy test
- Electrocardiogram (ECG) in triplicate
- Administration of Trametinib in clinic
- Blood collection for ctDNA and cfDNA biomarkers

6.1.2.2 Study Procedures Cycle 1 Day 8

- Evaluation of adverse events
- Concomitant medications
- Administration of Trametinib in clinic
- Blood collection for ctDNA and cfDNA biomarkers

6.1.2.3 Study Procedures Cycle 1 Day 15

- Evaluation of adverse events
- Concomitant medications
- Administration of Trametinib in clinic
- Blood collection for ctDNA and cfDNA biomarkers
- Ophthalmic exam prior to cycle 2 day 1

6.1.2.4 Study Procedures Cycle 2 and beyond

Visit Windows: Lab tests must be completed within 3 days of Day 1 and imaging studies must be completed within 7 days of Day 1.

- Disease assessment including imaging (CT or MRI) of chest/abdomen/pelvis for tumor/lesion assessment – Cycles 3, 5, 7, and every other cycle thereafter
- If known lesions, brain imaging (CT or MRI) – Cycles 3, 5, 6, and every other cycle thereafter
- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessments, including:

  Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate
- Coagulation assessment, including PT/PTT/INR
- Urinalysis
- Serum or urine pregnancy test
- Brain imaging, if known metastases for tumor/lesion assessment (every other cycle, starting with cycle #3)
- Electrocardiogram (ECG) in triplicate
- Cardiac Assessments (TTE or MUGA) Cycle 2 day 1, and then every 3 cycles
- Blood collection for ctDNA and cfDNA biomarkers
- Optional Biopsy (at best response to therapy) for biomarkers and banking
- Ophthalmic exam prior to cycle 2 day 1, again at 6 months, and then annually thereafter unless clinically indicated sooner.

6.1.3 End-of-Treatment Study Procedures

To be completed within 30 days of the last dose of study drug.

- Disease assessment including imaging (CT or MRI) of chest/abdomen/pelvis, and brain (if lesions found in screening), for tumor/lesion assessment
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- Hematology labs (other than CBC with diff)
- Complete blood count (CBC) with differential and platelet count
- Blood chemistry assessment, including:
- Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate,
- Coagulation assessment, including PT/PTT/INR
- Urinalysis
- Electrocardiogram (ECG)
- Blood collection for ctDNA and cfDNA biomarkers
- Optional tumor biopsy for biomarker analysis and exploratory studies.

6.1.4 Post-treatment/Follow Up Visits

Patients will be followed every 3 months +/- 14 days for up to 18 months after enrollment or until disease progression.

The following procedures will be performed at the Follow Up Visit(s):

- Disease assessment including imaging (CT or MRI) of chest/abdomen/pelvis, and brain (if lesions found in screening) for tumor/lesion assessment. Scans would only be completed in follow-up for patients whose disease has not yet progressed since entering the study.
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- Hematology labs (other than CBC w/ Diff)
- CBC with differential and platelet count
- Blood chemistry assessment, including:

  Alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate,
- Coagulation assessment, including PT/PTT/INR

- Urinalysis

6.1.5 Long Term/Survival Follow-up Procedures

6.1.6 Discontinuation of Therapy

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

Table 6.1 Schedule of Study Procedures and Assessments

Period/Procedure	Screening[a]	Cycle 1					Cycle 2 and future Cycles					End of Treatment visit	Follow-up visits
Study Day/Visit Day	**-28 to 0 (+/- 3)**	**1 (+/- 3)**	**8 (+/- 3)**	**15 (+/- 3)**	**22 (+/- 3)**	**29 (+/- 3)**	**1 (+/- 3)**	**8 (+/- 3)**	**15 (+/- 3)**	**22 (+/- 3)**	**29 (+/- 3)**	**30d after last dose of study drug**	**FU every 3 months (+/- 14d)**
Informed consent	X												
Baseline conditions[b]	X												
AE assessment		X	X	X			X					X	X
Concomitant medications	X	X	X	X			X					X	X
Blood collection for biomarkers	X	X	X	X			X					X	
Required Research Biopsy)[c]	X												
Optional Research Biopsy							X +/- 7d (C2only)					X	
Treatment/Drug Administration													
Trametinib[d]		X	X	X			X						
Clinical procedures													
Physical exam	X	X					X					X	X
Vital signs	X	X					X					X	X
Medical history[e]	X						X					X	X
Disease assessment[f]	X						X					X	X
Performance status	X	X					X					X	X
Laboratory procedures[g]													
CBC w/ Diff	X	X					X					X	X
Blood chemistry	X	X					X					X	X

Period/Procedure	**Screening[a]**	**Cycle 1**					**Cycle 2 and future Cycles**					**End of Treatment visit**	**Follow-up visits**
Study Day/Visit Day	**-28 to 0 (+/- 3)**	**1 (+/- 3)**	**8 (+/- 3)**	**15 (+/- 3)**	**22 (+/- 3)**	**29 (+/- 3)**	**1 (+/- 3)**	**8 (+/- 3)**	**15 (+/- 3)**	**22 (+/- 3)**	**29 (+/- 3)**	**30d after last dose of study drug**	**FU every 3 months (+/- 14d)**
Coagulation	X	X					X					X	X
Urinalysis	X	X					X					X	
Pregnancy test (HCG)	X	X					X						
Imaging procedure[h]													
Imaging (CT or MRI) [h]	X						X					X	X
Cardiac Assessment (ECHO, MUGA)	X						X						
ECG/EKG (in triplicate)	X	X					X					X	
Ophthalmology Exam	X					X							

a. Screening procedures and assessments must be completed -28d of Day 1 visit. Screening labs completed within 3 days of C1D1 need not be repeated.

b. Baseline conditions include all ongoing medical conditions at time of consent.

c. **Archival tissue collection** and research biopsy during screening and for exploratory biomarker assessments. Biopsy will be CT guided (or via bronchoscopy if unable to obtain) unless deemed medically unsafe.
Optional tumor biopsy: for exploratory analyses, best response and resistance (C2D1 +/- 7d and at end of treatment visit).

d. Trametinib will be taken with a full glass of water, without food, at least 1 hour before or 2 hours after a meal, 2mg, once a day. See section 5.0 Table 5.1 for treatment regimen details. Safety assessments (AE assessments and concomitant medication check) to be completed during clinic visits.

e. Medical history documentation of past conditions or procedures that have been resolved.

f. Disease assessment documentation at screening (presence of measurable disease) and on trial includes restaging (per RECIST), which will occur q2 cycles beginning cycle #3. During Follow-up visits, scans would only be completed in follow-up for patients whose disease has not yet progressed since entering the study

g. **Blood chemistry labs**: alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate

Coagulation labs: PT/PTT/INR

Serum or urine pregnancy test must be negative within 3 days prior to start of C1D1.

h. **Imaging exams**: if known lesions, brain imaging every other cycle starting with cycle #3.

Cardiac assessments to be completed every 3 months after cycle #2.

Ophthalmology exams to be completed prior to cycle 2 day 1, again at 6 months, and then annually thereafter unless clinically indicated sooner.

6.2 Usage of Concurrent/Concomitant Medications

No formal drug interaction studies have been conducted with trametinib. There is a low likelihood of drug-drug interactions with trametinib.

Trametinib has a high passive permeability and is eliminated primary via deacetylation, which is mediated by hydrolytic enzymes that are generally not associated with drug interaction risks. It is also not an in vitro substrate for human Pgp, BCRP, MRP2 and MATE1. In addition, due to trametinib's low efficacious dose and low systemic maximal concentration (22 ng/mL or 0.04 μM) relative to its in vitro CYP inhibition/induction potency. Therefore, the risk of a drug-drug interaction by trametinib as both perpetrator or as a victim is low. See also Section 4.3.6 for detailed discussion.

6.3 Dietary Restrictions

Trametinib should be taken with a full glass of water, without food, at least 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70%, 24%, and 10% decrease in Cmax, AUC(0-t), and AUC(0-∞), respectively compared to fasted conditions.

6.4 Prohibited Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor controls not permitted during the study; however, radiotherapy or procedures for symptom management is allowed.

Subjects are prohibited from receiving antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.

Bisphosphonates or denosumab are allowed for patients with bone metastases.

Growth factor support may be considered for patients with neutropenia after discussion with the study PI.

Avoid concurrent use of strong CYP3A inhibitors during treatment.

Medications known to produce QT prolongation should be avoided during treatment of patients with and trametinib. See http://crediblemeds.org/ for the most up-to-date reference lists of QT-prolonging medications. Please note that the lists contain common supportive medications, such as anti-emetics (ondansetron [and other 5HT3 antagonists], metoclopramide, hydroxyzine), antibiotics (azithromycin, ciprofloxacin, metronidazole) and anti-depressants (escitalopram).

Medications to consider for nausea that are not associated with QT prolongation include:

- Steroids (dexamethasone, methylprednisolone)
- Benzodiazepines
- Aprepitant
- Select anticholinergic agents (scopolamine)
- Trimethobenzamide
- Cannabinoids

7 Reporting and Documentation of Results

7.1 Evaluation of Efficacy (or Activity)

7.1.1 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

7.1.1.1 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will 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). A sum of the longest diameter (LD) for all target lesions will be

calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable. (e.g., PSA, CA-125, CA19-9, CEA)

7.1.1.2 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI

Spiral CT scans should be performed using a 5 mm contiguous reconstruction algorithm.

7.1.1.3 Response Criteria

Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes). There can be no appearance of new lesions.

Partial Response (PR)

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD)

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD)

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

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

Table 7.1 Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Duration of Response

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, [redacted]

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator- sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator- sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.03.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family

Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will

review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and

discussed at DSMC meetings, which take place every six weeks.

For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 2 or 3 Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 4 Multicenter Institutional Studies.

7.7 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Reporting to Pharmaceutical Companies providing Study Drug

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment

of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Warnings and precautions

Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

See Section 2.4 for study endpoints.

This is a Phase II, open-label, multicenter clinical trial evaluating the efficacy and safety of trametinib monotherapy in patients with advanced non-squamous NSCLC whose tumors harbor a non-synonymous *NF1* mutation and are wildtype for KRAS. Patients will receive trametinib monotherapy in 28 day cycles.

8.1.1 Randomization

This is a single-arm, open-label phase II study without any randomization.

8.1.2 Unblinding Subjects

Study is open-label so unblinding subjects is not applicable.

8.1.3 Stratification Factors

None

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

The primary endpoint is objective response rate (ORR). To provide 80% power to detect a 30% ORR compared to the null hypothesis of a 10% ORR in each cohort, 27 patients will be enrolled, with the goal of obtaining 24 evaluable patients. Using a Simon 2-stage design, if we do not observe at least 2 responses within the first 15 patients, enrollment will be stopped due to lack of efficacy.

The primary efficacy analysis will be based on one-sided exact binomial test comparison of the observed ORR in patients receiving at least one dose of study treatment to the null-hypothesized value of 10%, using the 5% significance level. Secondary time-to-event endpoints (DR, PFS and OS) will be summarized using Kaplan-Meier estimates with associated 95% confidence limits. The secondary DCR endpoint will be summarized as a proportion with an exact binomial 95% confidence interval. Safety analyses will be descriptive summaries of AEs by patient and type.

8.2.2

Replacement Policy

All patients who receive a dose of trametinib will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced after discussion with the Principal Investigator. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to grade 2 or lower; however, they will not be replaced.

8.2.3

Accrual estimates

At UCSF, UC Davis, and UC San Diego we see > 200 patients per month with advanced NSCLC, 80% of whom have non-squamous histology. Based on The Cancer Genome Atlas (TCGA) Research Network studies described in Section 1.1, we predict that about,11% of lung adenocarcinomas will harbor *NF1* mutations.[17] Conservatively, we expect that 10 patients per month will harbor one of these mutations and that 1-2 patients per month will be eligible and will consent to participate in the study.

Interim Analyses and Stopping Rules
Using a Simon 2-stage design, if we do not observe at least 2 responses within the first 15 patients in a given cohort, enrollment to that arm would be stopped due to lack of efficacy.

8.3 Analyses Plans

8.3.1 Analysis Population

All patients who receive a dose of trametinib will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving any dose of study therapy may be replaced after discussion with the investigator sponsor. Subjects who have received any dose of study therapy will not be replaced.

Demographic and baseline characteristics will be summarized by each cohort and overall. In general, frequency distribution and percentage will be used to summarize categorical measurements, while mean with standard deviation and median with interquartile range will be used to describe symmetric and skewed continuous measurements, respectively. Univariate analysis among variables will be assessed using the two-sample t-test, Wilcoxon-rank-sum test, Chi-square test, as appropriate.

8.3.2 Primary Analysis (or Analysis of Primary Endpoints)

The ORR is defined as the best overall response recorded from the start of the treatment until disease progression or recurrence as assessed over a 1-year period from the start of treatment. The frequency and percentages of patients with a best overall response rate of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) will be determined. We will test the hypothesis that the ORR is greater than the null hypothesis of 10% using the Fisher's exact test.

8.3.3
Secondary Analysis (or Analysis of Secondary Endpoints)

Definition and analytical plan for secondary efficacy endpoints:

(a) Duration of response (DR): The DR for CR and PR will be measured from the date that the best response if first recorded until the date that PD is documented over the period of 1 year. For patients who continue treatment post progression, the date of PD documentation will be used for analysis. The DR will be summarized using descriptive statistics (N, mean, standard deviation, minimum, and maximum).

(b) Disease control rate (DCR): DCR will be defined as the percentage of patients who have achieved CR, PR, or SD for at least 12 weeks. The DCR will be summarized using descriptive statistics (N, mean, standard deviation, minimum, and maximum).

(c) Progression-free Survival (PFS): PFS will be calculated as 1+ the number of days from the first dose of study drugs to documented radiographic progression or death due to any cause over a period of 1 year. For patients who continue treatment post-progression, the date of radiographic progression will be used for PFS analysis. The Kaplan-Meier analysis will be used to calculate the median PFS with 95% confidence interval.

(d) Overall Survival (OS): OS will be calculated as 1+ the number of days from the first dose of study drugs to death due to any cause over a period of 1 year. The Kaplan-Meier analysis will be used to calculate the median OS with 95% confidence interval.

(3) Definition and analytical plan for safety and tolerability endpoints: The safety population will consist of all subjects who receive any amount of study treatment. Safety will be assessed by evaluation of AEs. All safety analyses will be performed using the safety population. Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Seriousness, severity grade and relationship to study treatment will be assessed by the investigator. Severity grade will be defined by the National Cancer Institute (NCI) CTCAE v4.03. Listings of AEs will be provided.

Separate tables will present the following by dose group and study phase:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Dose-limiting toxicity AEs
- Serious treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of trametinib.
- Treatment-emergent AEs resulting in interruption or reduction or delay of trametinib.

8.3.4 Other Analyses/Assessments

Exploratory Analysis: Understanding the mechanisms of response and resistance to trametinib therapy will be critical to identifying patients who may preferentially benefit the most from this therapy. We propose to investigate this by:

(a) Assess pre-treatment, at time of first scan to assess response, trametinib resistant tumors (in optional biopsy specimens) for evidence MAPK pathway activation. IHC will be performed to assess ERK1/2 phosphorylation. Phosphorylation will be scored in a continuous manner, and difference in phosphorylation between pre-treatment, best response, and post-resistant specimens will be determined by a two-tailed T-test.

(b) We will use whole exome and transcriptome deep sequencing (WES; RNAseq) in the pre-treatment, at time of first scan to assess response (optional), and post- progression (optional) tumor biopsy samples to uncover somatic genetic alterations (mutations

and copy number alterations) and transcriptional events associated with clinical resistance (either de novo or acquired), with a minimum depth of WES coverage of 100X to capture events occurring down to ~10% frequency. We will use tumor microdissection to maximize tumor purity and peripheral leukocytes as normal/germline controls, with appropriate standard correction of the genetic findings for cancer cell fraction. This unbiased analysis is warranted to ensure we capture resistance events that are anticipated (e.g. secondary BRAF or MEK pathway mutations or ERK1/2 upregulation, or HIPPO-YAP pathway upregulation[32,35] and unexpected and coordinated changes (e.g. genomic amplification + concordant RNA overexpression of a resistance gene). This approach will enable identification and/or validation of RNA signatures of potential resistance events (such as ERK1/2 transcriptional output). The analysis of samples from patients with de novo resistance and of matched paired tumor samples acquired from individual patients before treatment and at acquired resistance will be prioritized for study to facilitate the clinical correlation of the genetic findings with bona fide clinical resistance. For instance, we may find that genetic mutation/amplification or transcriptional upregulation of ERK1/2 is present in tumors from patients with de novo or acquired trametinib resistance. All statistical and genomic analyses will be done with custom scripts and extensively developed pipelines in the R statistical computing framework [redacted]). Descriptive statistics and graphical methods will be used to analyze the data. Orthogonal validation of specific findings will be done using individualized assays in the clinical specimens (e.g. direct sequencing, SNP arrays, fluorescence in situ hybridization for DNA alterations; q-RT-PCR, IHC for RNA and protein abundance changes) and associated circulating free DNA, where feasible.

(c) When possible, we will generate patient-derived organoids and/or patient-derived xenografts from biopsy specimens from patients that participate in the trial in order to fully interrogate pathways of response and resistance in a highly clinically relevant system. We will use these models to perform pre-clinical trials aimed at overcoming mechanisms of resistance with rationally designed polytherapy.

(d) Circulating cell free DNA (cfDNA) will be assessed for biomarkers of resistance that are identified above. Descriptive statistics and graphical methods will be used to analyze the data.

8.4 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The frequencies of individual toxicities thought to be probably, possible, or definitely related to study drug will be reported as well as the incidence of any grade 3, 4, and 5 toxicities regardless of attribution. Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (UCSF Institutional Review Board). Prior to obtaining IRBIRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case Report Forms (CRFs)

The Principal Investigator, and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

9.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

9.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment.

The following issues will be discussed as appropriate: Enrollment information

- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations

- Other issues affecting the conduct of the study

Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.9 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.10 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Institutional Review Board (IRB). Prior to implementing this protocol at the participating sites, approval for the UCSF IRB approved protocol must be obtained from the participating site’s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 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 2 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active 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	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) for both IND and IND-exempt trials.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. Single Site (HDFCCC) Therapeutic Essential Regulatory Documents:

Documents Filed in iRIS:

- Current and prior versions of the Informed Consent Form(s) (ICFs).
- IRB approvals for initial submission of application, all modifications, and continuing annual renewals.
- Current and prior approved protocol versions.
- Current IRB roster
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event (SAE) Reports.
- Subject diary and handouts (if applicable).
- Single Patient Exception (SPE) Report(s) to the IRB with Approval Letter(s) from IRB.
- Protocol Violation (PV) Reports with acknowledgement from the IRB.

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial).
- Protocol signature page(s) with PI signature(s) for all protocol versions.
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC) document.
- Screening/enrollment log.
- Data and Safety Monitoring Committee (DSMC) monitoring reports.
- DSMC dose escalation approvals with study status summary forms.
- Case Report Form (CRF) completion manual.
- Drug Destruction Standard Operating Procedure (SOP).

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature.
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training Documents (i.e., Collaborative Institute Training Initiative (CITI), etc.).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center.
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor.
- Drug Destruction Standard Operating Procedure (SOP).
- For all laboratories listed on the FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CV(s) and Medical License(s) of Lab Director(s), and laboratory reference ranges.

Documents Filed in Regulatory Binder:

- Delegation of Authority Log with signatures (to be scanned in OnCore once the trial is complete).

2. Additional Essential Documents for Therapeutic Multicenter Trials for the Coordinating Center (filed in OnCore or Zip Drive):

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act {HIPAA) Consent Form for the Participating Site(s).
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s), will need Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for investigational New Drug Application).
- Site Initiation Visit (SIV) minutes and correspondence with the Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s).
- Protocol Violations (PV) Reports to IRB with acknowledgement from IRB for Participating Site(s).
- Single Patient Exception (SPE) Reports to IRB with IRB Approval Letters for Participating Site(s).
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s).
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s).
- For all laboratories listed on FDA 1572, will need CUA certifications, CAP certifications, lab licenses, CVs and Medical License(s) of Lab Director(s), and laboratory reference ranges for the Participating Site(s).
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study).
- Serious Adverse Event (SAE) forms submitted to the IRB for the Participating Site(s).

3. *Required Multicenter Essential Regulatory Document Checklist for Therapeutic and Non-Therapeutic Trials (For Start-Up Only):*

- See attached checklist(s).

4. Required Essential Regulatory Documents for Single Site and Multicenter Therapeutic IND-Exempt Studies (filed in OnCore):

- For IND Exempt studies, the Essential Regulatory Documents for UCSF would include all documents in Section #1 of this policy. The Essential Regulatory Documents from the participating site(s) for Multicenter Trials when UCSF is the Coordinating Center would only include the signed protocol signature page, CV of the PI, and the IRB approval letters. All other documents in Section #2 of this policy would be the responsibility of the Participating Site(s).

5. Required Essential Regulatory Documents for Single Site Non-Therapeutic Studies (filed in OnCore):

- For Single Site non-therapeutic trials, all Regulatory Documents in Section #1 of this policy are required except for: current and prior versions of the Investigator Brochure (IB), package insert (if the study drug is commercial), DSMC dose escalation approvals with study status summary forms, approvals for Biosafety Committee, Radiation Committee, and Infusion Center, and drug destruction SOPs.

6. Required Essential Regulatory Documents for Multicenter Non-Therapeutic Studies (filed in OnCore):

- For Multicenter non-therapeutic trials with UCSF as the Coordinating Site, all required Regulatory Documents listed above in Section #5 for Single Site non-therapeutic trials are required for the Coordinating Site. The only required Regulatory Documents from the Participating Site(s) will be: IRB approval letters, IRB roster, and ICF and HIPAA consent forms, the Delegation of Authority Log (with NIH or CITI human subject protection training certificates or GCP training certification), Protocol Violations and Single Patient Exception (SPE) reports to the IRB with supporting fax documentation (if applicable), Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor, and the Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s). If applicable, a copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study) will be required.

Alternate Procedures

There are no alternate procedures to the HDFCCC policy for requirements for Essential Regulatory Documents for Multicenter Investigator-Initiated Oncology Clinical Trials.

References

- ICH Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance (current version).

- International Conference on Harmonization: Good Clinical Practice: Consolidated Guideline (current version).
- International Conference on Harmonization: Essential Documents for the Conduct of a Clinical Trial (current version).
- 21CFR50
- 21 CFR56.11
- 45CFR46
- 21 CFR312

Required Regulatory Documents for Sub-sites Participating in Therapeutic UCSF Investigator Initiated Multicenter trial

Directions: Scan the documents in a zip drive and upload to OnCore.

1572

☐ PI and Sub investigators:
- CV and Medical license
- Financial disclosure form
- NIH or CITI human subject protection training certification

☐ Laboratories:
- CLIA &CAP and Lab Licenses
- CV and Medical License of Lab Director
- Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents
- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log
- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy
- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

Appendix 4 Data Safety Monitoring Plan for a Multicenter Study (Phase II or III study)

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all HDF CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Monitoring every six months (depending on patient accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

All institutional Phase II or III therapeutic studies are designated with a moderate risk assessment (see Appendix H). The data is monitored by a DSMC Monitor twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Adverse Events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol Violations.
- Other issues affecting the conduct of the study.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines listed in Appendix H. The data (i.e., copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol and FDA regulations.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), regardless of being unexpected or considered to be associated with the use of the study drug will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse Events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:

- **Definite** – The adverse event is clearly related to the investigational agent(s) or medical procedure.
- **Probable** – The adverse event is likely related to the investigational agent(s) or medical procedure.
- **Possible** – The adverse event may be related to the investigational agent(s) or medical procedure.
- **Unlikely** – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
- **Unrelated** – the adverse event is clearly not related to the investigational agent(s) or medical procedure.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled monthly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an Adverse Event is defined as a Serious Adverse Event (SAE) according to the following criteria:

- Death.
- Life-threatening (i.e. results in an immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Permanent or significant disability/incapacity.
- Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
- Event occurring in a gene therapy study.
- Event that changes the risk/benefit ratio of a study.
- Any other event the Principal Investigator judges to be serious or which would

suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:

www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All Serious Adverse Events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 1 business days of becoming aware of the event. The SAEs are reviewed and monitored by the UCSF Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore®.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e- mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day and the IRB must be notified within 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

[redacted]

DSMC Monitors
Box 0128
UCSF HDFCCC
San Francisco, CA 94143

Appendix 5 Prohibited Medications

Medications to Avoid

CC# pending: A Phase II Trial to Evaluate Trametinib in Molecular subpopulations of patients with advanced non-small cell lung cancer

The following is a list of medications to avoid while you are participating in this study. If you go to any medical visit, please take this list with you for the doctor's reference.

Before you begin treatment, Dr. Blakely or one of his associates will review all medications you are taking. Make sure you talk with Dr. Blakely before you start or stop taking any medications. This list contains only the most common drugs that are known to interact with the drugs used in this study. It is very important to discuss all medications that you are taking with your study doctor. This information will be reviewed at each study visit.

Strong inducers of CYP3A or CYP2C8		**Strong inhibitors of CYP3A**	
Generic Name	**Brand Names ®**	**Generic Name**	**Brand Names ®**
Rifampin	Rifadin	Clarithromycin	Biaxin
Rifabutin	Mycobutin	Telithromycin	Ketek
Rifapentine	Priftin	Troleandomycin	
Carbamazepine	Tegretol, Carbatrol, Equetro	Nefazodone	Serzone
Oxcarbazepine	Trileptal	Itraconazole	Sporanox, Onmel
Phenobarbital		Ketoconazole	Nizoral, Xolegel, Extina
Phenytoin	Dilantin, Phenytek, Dilantin-125, Cerebyx	Posaconazole	Noxafil
s-mephenytoin		Voriconazole	Vfend
Bosentan		Ritonavir	Norvir
St. John's Wort		Saguinavir	
		Atazanavir	Reyataz
		Gemfibrozil	Lopid
		Conivaptan	Vaprisol

Appendix 6 Specimen Collection

Sampling and shipping information

For the purposes of this study, a whole blood sample is collected by standard phlebotomy procedures. Blood should be drawn in the morning prior to drug administration. Aliquots of 5-10 ml of venous blood will be drawn from each patient using PPT and SST vacutainers and or PAXGene tubes.

1) Two Plasma Preparation (EDTA) Tubes (PPT, 6-10ml)
2) One Serum Separator Tube (SST, 8.5ml)
3) In cases in which sequencing to be performed immediately by the Bivona lab, one PAXGene tube will be collected for transport

These samples will be used by the clinical coordinator to generate:

1) 6 x 300 µl of plasma aliquots, frozen at -80^{o} Celsius
2) 6 x 300 µl of sera aliquots, frozen at -80^{o} Celsius
3) 4 x 1.5ml whole blood aliquots, frozen at -80^{o} Celsius
4) Two “Crude Buffy Coat” aliquots

Processing of the samples will be carried out using following protocols:

Plasma and Crude Buffy Coat Preparation SOP

- Gently inverts the Plasma Preparation Tube 8 -10 times following venipuncture
- The sample will be hold at room temperature (RT) until processing. Processing should occur within 2 hours of the blood draw.
- The sample will be centrifuged at 1,100 x g for 10 minutes at RT in a swing out rotor.
- Plasma aliquots will be transferred from the vacutainer to cryo vials
- Plasma samples will be frozen and archived at -80C^{o} Celsius.
- The “Crude” Buffy Coat is removed with a transfer pipette and two equal aliquots are generated in 1.8 ml cryovial.
- The cryo vials are immediately placed in a –80^{0} Celsius freezer (no transfer in slow freezing chamber).
- The clinical coordinator transfers samples into a Tissue Core–80^{0} Celsius freezer for temporary storage, the time when the samples have been frozen will be noted.

Serum Preparation SOP

- Inverts the Serum Preparation Tube 5 times following venipuncture and records the blood draw time
- Hold sample at room temperature. Wait for blood to clot 30 - 45 minutes after blood collection in order to ensure that proper blood clotting occurred. Blood processing should occur within 2 hours of blood draw.
- Centrifuge at 1,100 x g for 10 minutes at room temperature in a swing out rotor.
- Serum aliquots will be transferred from the vacutainer to the cryo vials using a 200 µl transfer pipette.
- Serum samples will be frozen and archived at -80^{o} Celsius.

Whole Blood Preparation SOP

- The EDTA tube is inverted 5 – 10 times before 4 x 1500 µl aliquots are transferred into 1.8 ml cryo vials.
- The vials are immediately placed in a –80^{0} Celsius freezer (no transfer in slow freezing chamber).

PaxGene tube Blood Preparation SOP

- The PaxGene tube is inverted 5 – 10 times.
- The tube is stored at room temperature for up to 2 hours.

If not picked up or delivered to the Bivona lab within 2 hours, the tube is temporarily stored at –20 Celsius freezer for up to 72 hours

Sample shipment instructions

For each shipment, an inventory of the samples should accompany the shipment. This inventory should include the study ID, subject ID, sample number, visit number scheduled time of collection.

Clearly indicate any missing specimens. The original inventory will be retained at the site in the Investigator's file.

All samples will be kept at the temperature specified up to and during the shipment. Unless instructed otherwise, the samples will be packed carefully with suitable packing material and dry ice to keep them frozen.

All shipments should be sent (Monday through Wednesday **only**) by a carrier guaranteeing overnight delivery. The following items should be considered:

- Advise the carrier of the type of service desired, need for personalized door-to-door pickup, and delivery guaranteed within 24 hours.

- Advise the carrier of the nature of the shipment's contents (human biological specimens) and label the package accordingly.
- Indicate Novartis drug code and Study No. on the face of the parcel to be shipped. The parcel also must carry a "dangerous goods" label because of the dry ice (labels supplied by the courier).
- The carrier must be asked to store the parcel(s) in a freezer if shipment is delayed and to replace exhausted dry ice before transportation continues.

Instructions for shipment of biological samples

Samples have to be packed according to the ICAO/IATA-Packing-Instructions in an insulated box. To guarantee that the samples remain deep frozen during transport, use about **10 kg of dry ice** per box which will keep the samples frozen during the whole duration of the transport (air freight). Send the parcel to the following.

A shipping log must be included with the shipment.

Ship to:

Helen Diller Family Comprehensive Cancer Center

Tissue Core

C/O Collin Blakely

[redacted]

Please notify the addressee *in advance* of the shipment and indicate:

- Number of the airbill
- The time and date of shipping and approximate time of arrival
- To whom the shipment is addressed, the study number, carrier and the shipping form number (or equivalent airbill number)
- The sender's name, telephone number and alternative contact personnel
- The total number of cartons and unit weight of each carton

Also notify the Clinical Trial Leader [redacted] when a shipment has been scheduled.

The samples should be sent at the beginning of a week in order to arrive no later than Thursday.