March 11, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #19 to EAY131-R, *Phase II Study of Trametinib in Patients with BRAF Fusions, or with Non-V600E, Non-V600K BRAF Mutations.*

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

This addendum has been reviewed and approved by the Central IRB, which is the sole IRB of record for this study. Local IRB review and approval is unnecessary.

Implementation of this addendum must occur on the activation date. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

This addendum is in response to Dr. Helen Chen February 22, 2019 Request for Rapid Amendment for Trametinib dimethyl sulfoxide.

The following revisions to EAY131-R protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	Cover Page	In second note, removed second sentence, ”Please reference activation memo for the addendum activation date.”
3.	3.3	Updated the Trametinib CAEPR list with version 2.5, February 1, 2019.

The following revisions to EAY131-R Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the possible risks language and the Trametinib risk list with version 2.5 February 1, 2019.

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If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-R so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

Enclosure

CC:

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-R

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol R: Phase II Study of Trametinib in Patients with BRAF Fusions, or with Non-V600E, Non-V600K BRAF Mutations

TRAMETINIB TREATMENT SUBPROTOCOL CHAIR: Douglas B. Johnson, MD, MSCI
TRAMETINIB TREATMENT SUBPROTOCOL CO-CHAIR: Marcus Noel, MD
TRAMETINIB TRANSLATIONAL CHAIR: Gregory Riely, MD, PhD

Version Date: March 11, 2019
NCI Update Date: August 12, 2015

Rev. Add13
Rev. Add19

NOTE: This subprotocol (EAY131-R) should be used in conjunction with the MATCH Master Protocol (EAY131).

NOTE: As of 11/17, all protocol changes will be noted by addendum number.

ACTIVATION DATE
August 12, 2015
PRE-ACTIVATION DATE
May 29, 2015
Update #1 – Incorporated Prior to Activation
Addendum #1 – 8/15
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #6 – 1/17
Addendum #7 – 3/17
Addendum #13
Addendum #19

Agent	IND#	NSC#	Supply
Trametinib			NCI Supplied

Rev. 12/16

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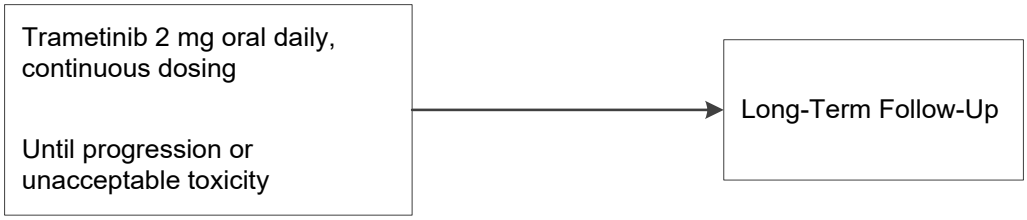
Schema



Cycle = 28 days
Accrual Goal: 35

*

1. Introduction

1.1 Trametinib

1.1.1 Background

Trametinib is a potent, highly selective, allosteric inhibitor of MEK1 and MEK2, is non-competitive towards ATP, and inhibits both MEK activation and kinase activity. Trametinib interferes with cellular signal transduction and induces apoptosis in human tumor cell lines both in vitro and in xenograft mouse models. Activity was most extensive in cell lines and models that contained activating BRAF mutations [1, 2].

Trametinib was first dosed in humans in 2008 in MEK111054 (NCT00687622) [3]. This first-in-human study identified the recommended monotherapy dose for trametinib (2 mg once daily continuous dosing); established the safety, PK, and PD profiles; and demonstrated clinical activity in several tumor types including BRAF wild type melanoma [3]. Trametinib has been administered to > 1700 subjects in 13 studies, which are complete and 9 additional studies which are ongoing. Trametinib has been administered as monotherapy in 12 studies and in combination in the other 10, two additional trials are ongoing as part of the compassionate use program [4]. Trametinib was approved by the United States Food and Drug administration on May 29, 2013, under the brand name Mekinist, as a monotherapy in the setting of $BRAF^{V600}$ mutant melanoma.

1.1.2 Pharmacokinetics of Trametinib in Humans

Peak plasma trametinib concentrations were observed 1.5 hours following single-dose administration of trametinib tablets under fasted conditions. The absolute oral bioavailability of the trametinib 2.0 mg tablet is moderate to high (72%) relative to a coadministered IV microdose [4]. Trametinib is highly bound to plasma proteins (97.4%), has a high volume of distribution (Vd; 1060 L), a long terminal half-life (5.3 days), and accumulates with repeat once daily dosing.

The metabolism of trametinib has been investigated using a series of in vitro and in vivo studies. Trametinib is metabolized via deacetylation to form M5 (deacetylation alone) and deacetylation in combination with mono-oxygenation to form M7 (mono oxygenation and deacetylation). M5 can be N-glucuronidated to form M6 (N glucuronidation of M5) while M7 undergoes O-glucuronidation to form M9 (O glucuronidation of M7), a minor pathway in humans. Trametinib is metabolized predominantly via deacetylation (non-CYP450 mediated) alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. Although the specific enzyme responsible has not been identified, deacetylation is likely mediated by hydrolytic esterases, such as carboxyl-esterases or amidases [4].

1.1.3 Safety

The adverse events (AEs) observed in the pivotal, Phase III registration study of trametinib in $BRAF^{V600}$ mutant melanoma [5] were consistent with that seen across trametinib monotherapy studies and is summarized here. The Phase III study demonstrated that the 2 mg, continuous, once daily dose of trametinib has an acceptable safety profile. Adverse events occurring in ≥15% of subjects that received at least one dose of trametinib (N=211) were rash (57%), diarrhea (43%), peripheral edema (26%), fatigue (26%), dermatitis acneiform (19%), nausea (18%), alopecia (17%), and hypertension (15%). Less than 8% of the subjects had grade 3 or 4 rash (including only one patient with grade 4), and no grade 3 or 4 diahrrea was observed. Decreased ejection fraction or ventricular dysfunction occurred in 7% of the subjects, and <1% (n=2) had grade 3 cardiac-related events that were considered trametinib related and led to permanent discontinuation of the study treatment. Ocular events, most of which were grade 1 or 2, occurred in 9% of the subjects. Blurred vision was the most frequent ocular event (4%), and there was one case of reversible chorioretinopathy. Retinal vein occlusion, an AE that has been associated with MEK inhibitors, was observed only extremely rarely. Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest for trametinib because they are either known class effects (i.e.,were observed with other MEK inhibitors) or are potentially life-threatening.

1.1.4 Clinical Efficacy

Trametinib has demonstrated significant clinical activity with an acceptable safety profile in Phase I-III studies [3, 5-7]. In $BRAF^{V600}$ mutant melanoma, the Phase III study of trametinib demonstrated improved rates of progression-free survival and overall survival versus cytotoxic chemotherapy [5]. In this study, trametinib demonstrated an overall response rate of 22% and a median PFS of 4.8 months. The duration of response was 5.5 months.

$BRAF^{V600}$ wild type (WT) melanoma and other malignancies were evaluated in the trametinib first-in-human study [3]. This study enrolled 39 subjects with $BRAF^{V600}$ WT cutaneous melanoma, of which 4 (10%) had confirmed objective responses [6]. The median PFS for these 39 subjects was 2.0 months (95% CI 1.7-3.7 months). Subjects who were both $BRAF^{V600}$ WT and NRAS WT (n=20) had a higher response rate (20%) than those who were wild type only at BRAF (n=11; response rate= 0%). Moreover, a higher proportion of patients that were wild type for both genes, compared to those that were wild type for only BRAF, were on study treatment at week 24 (40% versus 18%; p=0.26) and at 1 year (30% versus 0%; p=0.07). Importantly, 2 patients with BRAF mutations at non-V600 codons (L597V and G469A) were treated in this study with one achieving a partial response and the other with temporary stabilization of melanoma growth (see Section 1.2.2). Among other malignancies, several patients experienced partial responses (see Section 1.2.3).

These results demonstrate that trametinib has clinical activity in subgroups other than $BRAF^{V600}$ mutant melanoma.

1.2 Supporting Preliminary Data

1.2.1 Frequency of non-V600 BRAF mutations

Mutatations in BRAF at codons other than V600 (non-V600) have been identified in 2.79% of all tissue samples in the cBIO repository, a biorepository that includes 69 next generation sequencing studies across 23 histologic subtypes of cancer [8, 9]. These widely vary across cancer types, for example, in melanoma, approximately 5% of tumors harbor these mutations. These alterations are present in 1-3% of lung adenocarcinomas, and 1% or less of ovarian carcinomas, gastric carcinomas, prostate cancer, lung squamous cell carcinomas, glioblastomas,

1.2.2 Frequency of BRAF fusions

The frequency and tumor type distribution of BRAF fusions has not been well described to this point. Several distinct BRAF fusions have been described in the majority of pediatric astrocytomas and low grade gliomas over the past several years [10-12]. In addition, these alterations have been identified in 7-30% of adult pilocytic astrocytomas, and nearly 10% of adult diffuse gliomas [13, 14]. BRAF fusions have also been recently appreciated in melanoma, with up to 10% of the non-BRAF, non-NRAS mutated melanomas (3-4% of all melanomas), and other melanocytic tumors [15-17]. BRAF fusions have also been described in prostate adenocarcinoma [18].

1.2.3 Rationale for trametinib in the BRAF non-V600 and BRAF fusion populations

Recurrent mutations in exon 11 and 15 of BRAF were initially identified by Davies et al in 2002 [19]. These mutations (notably V600E, L597V, G469A, G464V) were demonstrated to constitutively activate MAPK signaling and ERK phosphorylation many fold greater than wild type BRAF. Wan and colleagues then delineated high activity mutants, which directly activate ERK signaling through MEK activation, and low-activity, which activate ERK signaling through CRAF and protein-protein interactions [20]. Direct inhibition of mutant BRAF with vemurafenib or dabrafenib appears ineffective in the non-V600 population, although modest in vitro activity and a brief partial response have been reported for vemurafenib [21, 22]. By contrast, in the preclinical setting and in occasional patients treated in clinical trials, MEK inhibition appears to be a more active therapeutic approach.

Clinical corroboration has been demonstrated by several patients with melanoma who have achieved a response to MEK inhibitors. For example, a patient with $BRAF^{L597S}$ mutant melanoma had a dramatic response to an experimental MEK inhibitor (TAK-733) [21]. Furthermore, in the phase I trial of trametinib, a patient with $BRAF^{L597V}$ mutant melanoma experienced a prolonged partial response and

remained on study for more than 2 years [6]. An additional patient with a $BRAF^{G469A}$ mutation had a best response of stable disease. Finally, in a trametinib phase II study, a patient with $BRAF^{K601E}$ mutant melanoma experienced a prolonged partial response [7]. Patients with other cancers have also had tumor regression and/or partial responses with trametinib although the presence of a non-V600 BRAF mutation or BRAF fusion has not been determined in these patients [3]. MEK inhibition in this population has not been studied in a systematic fashion and has never been evaluated prospectively.

BRAF rearrangements fuse the BRAF kinase domain with a partner gene which leads to constitutive activation of the MAPK pathway [15, 16]. BRAF fusion melanoma appears to confer resistance to vemurafenib. By contrast, trametinib strongly inhibited MAPK signalling in vitro and is predicted to have clinical activity in BRAF fusions [15]. At this time, no patients with BRAF fusions have been treated with trametinib.

MEK inhibitors have been associated with occasional responses in other cancers. In these studies, it is unclear whether BRAF non-V600 mutations or fusions were present. MEK inhibitors have been studied in advanced biliary tract cancer, notably a second line phase II trial with selumetinib. No $BRAF^{V600E}$ mutations were found, however 12% of patients had a confirmed response and another 68% stable disease [23]. Selumetinib has also been investigated in non-small cell lung cancer (NSCLC). 87 patients were randomized to either selumetinib plus docetaxel or placebo plus docetaxel. There was a significant increase in progression free survival 5.3 months versus 2.1 months (HR 0.58 80% CI 0.42-0.79; p=0.014) and trend towards increased overall survival (9.4 months versus 5.2 months, HR 0.8-, 80% CI 0.56-1.14;p=0.21) in the selumetinib-containing arm [24]. A randomized phase II trial evaluated the MEK inhibitor AZD6244 versus pemetrexed in NSCLC. Among, 84 patients randomized, 2 patients in the AZD6244 arm had a partial response. Additional mutational analysis of the tumors was not available in this trial. Trametinib was evaluated in a phase 1 trial of advanced refractory solid tumors. Several patients experienced objective responses including two patients with pancreatic cancer (one with a KRAS mutation) and two with non-small cell lung cancer (NSCLC; both with KRAS mutations; one concurrently had a BRAF mutation) [3]. In addition, patients with colon, ovarian, and thyroid cancer also had some regression of their disease that did not reach a partial response. Of note, several patients harbored BRAF mutations although it was not reported whether these were V600 mutations. Another MEK inhibitor, BAY 86-9766, was evaluated as a single agent in a phase 1 trial, of 53 evaluable patients. One (colorectal) patient had a partial response, and 11 had stable disease [25].

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

Rev. 8/15

2.1 Eligibility Criteria

Rev.2/16

_____ 2.1.1 Patient must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. 8/15
Rev. Add13

_____ 2.1.2 Patients must have a BRAF non-V600 mutation or BRAF fusion, or another aberration, as identified via the MATCH Master Protocol and described in Appendix II. See Appendix II for information on the targeted mutations/fusions and the corresponding Levels of Evidence (LOE).

Rev. 8/15

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have NONE of the following cardiac criteria:

- Clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).
- Treatment-refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy.

Date of ECG: _____

Rev. 8/15

_____ 2.1.4 Patients with a history of interstitial lung disease or pneumonitis are excluded.

Rev. 8/15, 2/16

_____ 2.1.5 Patients must have an ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have a left ventricular ejection fraction (LVEF) < the institutional lower limit of normal (LLN). If the LLN is not defined at a site, the LVEF must be > 50% for the patient to be eligible.

Date of ECHO/nuclear study: _____

_____ 2.1.6 Patients must not have known hypersensitivity to trametinib or compounds of similar chemical or biologic composition or to dimethyl sulfoxide (DMSO).

Rev. 8/15

_____ 2.1.7 Patients must not have a history or current evidence/risk of retinal vein occlusion (RVO). An eye exam is required at baseline. See Appendix III for the Trametinib Ophthalmic Exam Form.

Rev. 8/15

_____ 2.1.8 Patients who previously received MEK inhibitors (including, but not limited to, trametinib, binimetinib, cobimetinib, selumetinib, RO4987655 (CH4987655), GDC-0623 and pimasertib) will be excluded.

_____ 2.1.9 Patients who previously received monoclonal antibody therapy (eg. ipilimumab, nivolumab, pembrolizumab and others) must have stopped the prior therapy for 8 or more weeks before starting on trametinib.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3 Trametinib Treatment Plan

3.1 Administration Schedule

Trametinib will be taken orally at a dose of 2mg once daily, continuously for each 28 day cycle. Patients will continue therapy until intolerable toxicity, disease progression, or the end of the study.

Trametinib should be administered once per day, continuously; and should be taken at about the same time each day. The study treatments should be administered together with approximately eight ounces of water. Trametinib should be taken fasting, at least 1 hour before or 2 hours after a meal. If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

If a dose of trametinib is missed, only take the dose if it is more than 12 hours until the next scheduled dose.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

Rev.2/16

3.2.1 Additional instructions, requirements and exceptions for EAY131 - Subprotocol R

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol R specific expedited reporting requirements:

- **LVEF Changes:** If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol
  - Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN and LVEF **does not recover** within 4 weeks
  - Symptomatic: Grade 3-4 LVEF

Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for LVEF Decrease

- **Visual Changes**: If RPED (retinal pigment epithelial detachments) or RVO (retinal vein occlusion) are diagnosed, the event(s) must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol. Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Visual Changes.
- **Liver Chemistry Changes**: If any of the following circumstances occur, the event(s) must be reported via CTEP-AERS according to the timeframes outlined in the AE table in section 5.3.6 of the MATCH Master protocol
  - ALT ≥ 3xULN **and** bilirubin ≥ 2x ULN or > 35% direct bilirubin
  - ALT ≥ 3xULN **and** INR ≥ 1.5, if INR measured (INR threshold does not apply if subject is on anticoagulant)

  Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Liver Chemistry Changes
- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on Trametinib, or within 28 days of the subject's last dose of Trametinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol R specific expedited reporting exceptions:

For Subprotocol R, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

3.2.2 Second Primary Cancer Reporting Requirements

NOTE: The MATCH Master Protocol outlines the standard requirements for the reporting of second primaries. Please be aware that there are additional requirements

for this subprotocol. Please adhere to the guidelines outlined below for the reporting of second primaries on this subprotocol.

All cases of second (second malignancy is a cancer that is unrelated to any prior anti-cancer treatment, including the treatment on this protocol) **and** secondary malignancies (secondary malignancy is a cancer caused by any prior anti-cancer treatment, including the treatment on this protocol), including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)], regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy,
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: **All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment.** All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.

Whenever possible, the CTEP-AERS report should include the following:

- tumor pathology
- history of prior tumors
- prior treatment/current treatment including duration
- any associated risk factors or evidence regarding how long the tumor may have been present
- when and how the tumor was detected
- molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- tumor treatment and outcome (if available).

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 2/16, 1/17

Rev. Add19

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Trametinib dimethyl sulfoxide (GSK1120212B, NSC 763093)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1111 patients.* Below is the CAEPR for Trametinib dimethyl sulfoxide (GSK1120212B).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 2.5, February 1, 2019[1]

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[2]		
		Papilledema	
	Periorbital edema		

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[3]			***Generalized edema[3] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[4]		
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	CPK increased		
	Ejection fraction decreased		

Adverse Events with Possible Relationship to Trametinib (GSK1120212B) (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Nail changes		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[6]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should

be included in the e-mail.

[2]Visual disorders include visual disturbance that can be associated with conjunctival hemorrhage, corneal graft rejection, cyclitis, eye nevus, halo vision, iritis, macular edema, retinal hemorrhage, visual acuity reduced, visual impairment, and vitreous detachment.

[3]Generalized edema includes edema, lymphedema, and edema limbs.

[4]Hypersensitivity (allergic reactions) may present with symptoms such as fever, rash, increased liver function tests, and visual disturbances.

[5]Skin and subcutaneous tissue disorders - Other (rash) may include rash, rosacea, erythematous rash, genital rash, rash macular, exfoliative rash, rash generalized, erythema, rash papular, seborrhoeic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

[6]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage), and fatal intracranial hemorrhages have been reported.

Adverse events reported on trametinib dimethyl sulfoxide (GSK1120212B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trametinib dimethyl sulfoxide (GSK1120212B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia

EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Photophobia

GASTROINTESTINAL DISORDERS - Ascites; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy)

INFECTIONS AND INFESTATIONS - Biliary tract infection; Catheter related infection; Device related infection; Endocarditis infective; Enterocolitis infectious; Hepatitis viral; Infections and infestations - Other (abscess limb); Infections and infestations - Other (necrotizing fasciitis); Infections and infestations - Other (oral infection); Pharyngitis; Sepsis; Upper respiratory infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (compression fracture); Myalgia; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (diplopia); Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (erythema nodosum); Skin ulceration; Urticaria

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

NOTE: Trametinib (GSK1120212B) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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3.4 Dose Modifications

NOTE: Patients who interrupt trametinib for > 2 weeks will be removed from this subprotocol, unless the interruption was for reduction in LVEF, visual changes or RPED with subsequent recovery as described in corresponding tables below.

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

3.4.1 Dose Modification Guidelines for Trametinib Adverse Events of Special Interest

The dose levels for this study are provided in Table 1.

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

Table 1 Dose Level Reduction Guidelines

3.4.2

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

3.4.3 Guidelines for Cardiovascular Adverse Events

Cardiovascular adverse events have been seen in subjects receiving trametinib [4]). Guidelines for LVEF decreases and hypertension are provided below.

3.4.3.1 Left Ventricular Ejection Fraction (LVEF)

Decreases of the left-ventricular-ejection-fraction (LVEF) have been observed in subjects receiving trametinib. Therefore, ECHOs (preferred) or MUGA's must be performed to assess cardiac ejection fraction. The procedure performed at baseline must be performed at all subsequent visits as outlined in the Time and Events Table (See Section 4.1). Electronic copies of all ECHO/MUGA scans will be collected by GSK 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 (Table 2).

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Table 2 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 subprotocol Study Chair and request approval for restart. – Restart treatment with trametinib at 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 the subprotocol Study Chair.[c]
Symptomatic[a]	Grade 3: resting LVEF 39-20% or > 20% absolute reduction from baseline Grade 4: resting LVEF < 20%	• **Permanently discontinue trametinib.** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution

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Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; GSK = GlaxoSmithKline; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MUGA=Multi-gated acquisition

a. If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.

b. Escalation of trametinib to previous dose level can be considered if LVEF remains stable for 4 weeks after restarting of trametinib. Approval from the subprotocol Study Chair is required.

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

3.4.3.2 Hypertension

Increases in blood pressure (BP) have been observed in patients receiving trametinib. Recommendations for BP monitoring and management are provided below.

Monitoring: All BP assessments should be performed under the following optimal conditions:

- The subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor.
- The subject is relaxed comfortably for at least 5 minutes.
- Restrictive clothing has been removed from the cuff

area, and the right cuff size has been selected.

- The subject's arm is supported so that the middle of the cuff is at heart level.
- The subject remains quiet during the measurement.
- In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
- Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mmHg and/or diastolic blood pressure (DBP) >90 mmHg in three consecutive visits with blood pressure assessments from two readings as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.

Table 3 Management and Dose Modification Guidelines for Hypertension

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) Asymptomatic and persistent SBP of ≥ 140 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.
(Scenario B) Asymptomatic SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) Symptomatic hypertension or Persistent SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from the subprotocol Study Chair is required.		

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3.4.4 Guidelines for Visual Changes

Trametinib is known to be associated with visual adverse events. 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]).

The ophthalmology exam will include best corrected visual acuity, visual field examination, tonometry, slit lamp biomicroscopic examination, and indirect fundoscopy. Optical coherence tomography is recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including visual field examination, fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in Tables 4 and 5.

Table 4 Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmic Examination Findings

CTCAE Grade[a,c]	Adverse Event Management	Action and Dose Modification
Grade 1[b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table below (following this table); **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately	• Hold trametinib • If RPED and RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 4 weeks, discontinue trametinib • If RPED diagnosed, see RPED dose modification table below; **report as SAE.** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Report as SAE	• Hold trametinib • If RPED and RVO excluded, may restart trametinib at same or reduced dose after discussion with the subprotocol Study Chair. • **If RVO or RPED diagnosed, permanently discontinue trametinib**

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Abbreviations: RPED = retinal pigment epithelial detachment; CTCAE = Common Terminology Criteria for Adverse Events;

RVO= retinal vein occlusion; SAE = serious adverse event

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

Table 5 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 • **If no recovery within 4 weeks, permanently discontinue trametinib**

3.4.5 Pneumonitis Management Guidelines

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

Rev. 8/15 **Table 6 Pneumonitis Guidelines for Trametinib**

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue trametinib at current dose
Grade 2	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Consult pulmonologist • Pulmonary function tests -if < normal, repeat every 8 weeks until ≥ normal • Bronchoscopy with biopsy and/or BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• **Interrupt trametinib** until recovery to grade ≤ 1 • Restart treatment with trametinib **reduced by one dose level** • Escalation to previous dose level after 4 weeks and consultation with the subprotocol Study Chair possible • If no recovery to grade ≤ 1 within 2 weeks, **permanently discontinue trametinib**
Grade 3	• Same as Grade 2	• **Interrupt trametinib** until recovery to grade ≤1 • After consultation with the subprotocol Study Chair, treatment with trametinib may be restarted **reduced by one dose level** • If no recovery to grade ≤ 1 within 2 weeks, **permanently discontinue trametinib**
Grade 4	• Same as grade 2	• **Permanently discontinue trametinib**

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

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3.5 Dose Modifications for Trametinib and supportive care

3.5.1 Trametinib Dose Modification for Liver Chemistry Changes

Table 7: Trametinib Dose Modification for Liver Function Test Abnormalities

Event	Treatment modifications and assessment/monitoring
ALT ≥ 3x ULN but < 5x ULN and TB < 2x ULN, without symptoms considered related to liver injury or hypersensitivity and who can be monitored weekly for 4 weeks	• May continue study drug. • Report as SAE if CTEP-AERS reporting criteria is met. • If liver chemistry stopping criteria are met any time, proceed as described below. MONITORING: Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT < 3x ULN and TB < 2 ULN). If baseline ALT and Tbili already meet these criteria, then monitoring is required only if ALT or TB rises after initiation of study therapy.
Rev. 8/15 Criteria for discontinuing study drug: When any of the liver stopping criteria below is met, discontinue trametinib 1. ALT ≥ 3xULN and bilirubin ≥ 2x ULN or > 35% direct bilirubin [1, 2] 2. ALT ≥ 3xULN and INR >1.5, if INR measured[2] (INR threshold does not apply if subject is on anticoagulant) 3. ALT ≥ 5x ULN 4. ALT ≥ 3x ULN persists for ≥ 4 weeks. However, if ALT was elevated 3-5x at baseline due to liver mets, then this criteria should not be used for treatment discontinuation UNLESS the ALT improves to <3x ULN and then subsequently rises. 5. ALT ≥ 3x ULN and cannot be monitored weekly for 4 weeks. However, if ALT was elevated 3-5x at baseline due to liver mets, then this criteria should not be used for treatment discontinuation UNLESS the ALT improves to < 3x ULN and then subsequently rises. 6. ALT ≥ 3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	• Immediately discontinue study treatment. • Do not restart/rechallenge unless approved by the subprotocol Study Chair. *[* • Report as SAE if: 1) CTEP-AERS reporting criteria are met, or 2) patients meet criteria 1-2. • Perform liver event ASSESSMENT AND WORKUP (see below). • Monitor the subject until liver chemistries resolve, stabilize, or return to baseline (see MONITORING below). • *[* MONITORING: *In patients stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities):* • Repeat liver chemistries (ALT, AST, ALK, bilirubin) and perform liver event follow-up assessments within 24 hours. • Monitor subjects twice weekly until LFT return to normal/baseline or stabilize. • A specialist or hepatology consultation is recommended. *In patients stopping for criteria 2-6:* • Repeat LFT and perform liver event follow up assessments within 24-72 hrs • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. ASSESSMENT and WORKUP: • Viral hepatitis serology.[4] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥ 2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total

Event	Treatment modifications and assessment/monitoring
	immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[5] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.

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Footnotes:

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, which indicates direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (> 35% direct bilirubin) or ALT ≥ 3x ULN and INR > 1.5 (if INR measured) may indicate severe liver injury (possible "Hy's Law"). INR measurement is not required, and the threshold value stated will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).

3.5.2 Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTc-prolongation are provided (see Table 8).

Table 8 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 all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • **If event does not resolve or recurs after restarting, permanently discontinue study treatments.**

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

A: Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued.

B: If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and the subprotocol Study Chair agree that the subject will benefit from further treatment.

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3.5.3 Guidelines for Rash

Rash is a frequent AE observed in subjects receiving trametinib (see the Investigator's Brochures [4]] for more information). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors [26, 27] and are provided (see Table 9 and Table 10).

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 the subprotocol Study Chair may be required.

Table 9 Guidelines for Supportive Care of Rash

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

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

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment

b. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

Guidelines for management and dose reduction for rash considered to be related to study treatment are provided (see Table 10).

Table 10 Management and Dose Modification Guidelines for Rash

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

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

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

Rev.2/16 b. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone propionate concentration 0.05% cream

Rev. 8/15 c. Approval of the subprotocol Study Chair is required to restart study treatment after > 2 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

3.5.4 Guidelines for Diarrhea

Episodes of diarrhea have occurred in subjects receiving trametinib (see the Investigator Brochures [4] for more information). Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *C. difficile* or other pathogens, partial bowel obstruction, etc., should be clinically excluded.

Guidelines regarding management and dose reduction for diarrhea considered to be related to trametinib by the investigator are provided (see Table 11).

Table 11 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 • If treatment delay is > 14 days, discontinue trametinib.
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

Rev. 8/15 d. Escalation of trametinib to previous dose level is allowed after consultation with the subprotocol Study Chair and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

3.5.5 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Rev. 8/15 **Table 12 Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib**

(This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards.	Continue trametinib at current dose level.
Grade 2 (tolerable)		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution, restart treatment at current dose level.
Grade 2 (intolerable) and Grade 3		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution to baseline or grade 1, restart with one level of dose reduction. • 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		If event resolves to grade 1 or baseline discuss potential continuation of trametinib with the subprotocol Study Chair; if continuation of treatment agreed then restart trametinib at dose **reduced by one dose level**. If event does not resolve, permanently discontinue trametinib.
Trametinib should be discontinued if treatment delay is ≥14 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the subprotocol Study Chair may be consulted for the possibility of resuming trametinib, provided that toxicities have resolved to baseline or grade 1.		

3.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. See adverse reaction sections, tables 9-12.

3.7 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.8 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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4. Study Parameters

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4.1 Therapeutic Parameters for Trametinib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol at Step 0, the below parameters must also be performed for patients on trametinib treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]			X
Performance status	X	X[J]			X
CBC w/diff, plts[B]	X	X[J]			X
Serum chemistry[B]	X	X[J]			X
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X				
Toxicity Assessment[G]		X		X	X[F]
Pill Count/Diary[H]		X		X	
ECG[K,L]	X	X[L]			
Rev. 8/15 Echocardiogram or Nuclear Study[L]	X	X[L]			
Rev. 8/15 Eye Exam	X	X[I]			
Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

Rev.2/16 B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium, and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with Rev. 8/15 creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

Rev.2/16 C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

Rev.2/16 D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

Rev. 3/17, Add13 E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

Rev.2/16 F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

I. As clinically indicated.

J. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

K. Within 8 weeks of treatment assignment.

Rev. 8/15 Rev. 2/16 L. Cardiac monitoring with ECG and ECHO/nuclear study (MUGA or First Pass) is needed at week 5, week 13, and every 12 weeks thereafter unless clinically indicated sooner. The same modality should be used at baseline and thereafter.

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5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

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5.1 Trametinib (NSC 763093)

5.1.1 Other Names

MEKINIST™, GSK1120212, JTP-74057, JTP-78296, JTP-75303

5.1.2 Classification

MEK inhibitor

5.1.3 Mode of Action

Trametinib dimethyl sulfoxide is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Tumor cells commonly have hyperactivated extracellular signal-related kinase (ERK) pathways in which MEK is a critical component. Trametinib dimethyl sulfoxide inhibits activation of MEK by RAF kinases and MEK kinases.

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5.1.4 Storage and Stability

Storage: Store tablets at 2°C -8°C in the original bottle. Do not repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

If a storage temperature excursion is identified, promptly return trametinib to 2°C -8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

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5.1.5 Dose Specifics

Trametinib will be given continuous dosing 2mg daily.

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5.1.6 Preparation

Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets.

Each commercially-labeled bottle contains 30 tablets with a desiccant.

The tablet core contains mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (non-animal), colloidal silicon dioxide and sodium lauryl sulfate.

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated with ‘GS’ debossed on one face and ‘TFC’ on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.
- 2 mg tablets are pink, round, biconvex and film-coated with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

5.1.7 Route of Administration

Oral. Take by mouth on an empty stomach, either 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.

5.1.8 Incompatibilities

In vitro studies suggest that trametinib dimethyl sulfoxide is not a substrate of CYP enzymes or of human BCRP, MRP2, OATP1B1, OATP1B3, OATP2B1, OCT1 or MATE1 transporters. Trametinib elimination by deacetylation to metabolite M5 is dependent on carboxylesterases (CES1b, CES1c and CES2). M5 is eliminated by CYP3A4 and other pathways, presenting the clinically relevant, albeit low, potential for drug-drug interaction. Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability.

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Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8, and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 and 3A4 and not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 MRP2 and MATE1.

5.1.9 Side Effects

See Section 3.3 for side effects.

5.1.10 Nursing/Patient Implications

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib.

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6. Translational Studies-TBD

Please refer to the MATCH Master Protocol for information on the Translational Studies.

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7. References

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol R: Trametinib

Appendix I

Rev. 12/16, 3/17

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each tablet.
2. If a dose of trametinib is missed, only take the dose if it is more than 12 hours until the next scheduled dose.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
4. Take trametinib (GSK1120212) once daily by mouth either 1 hour before or 2 hours after a meal.
5. Trametinib should be stored at 2-8°C (36-46°F). Refrigerate. Do not freeze.
6. Trametinib should not be crushed, dissolved, or chewed.
7. Do not take an additional dose as a replacement if vomiting were to occur after a dose of trametinib.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

Trametinib

DAY	Date: Month	Day	Year	Time tablets taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient Signature: _____ Date: _____

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol R: Trametinib

Appendix II

BRAF non-V600 Mutations Eligible for Inclusion

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	COSM1739329	SNV	p.L485W	2
BRAF	COSM478	SNV	p.K601E	3
BRAF	COSM6265	SNV	p.K601N	3
BRAF	COSM472	SNV	p.T599I	3
BRAF	COSM21549	SNV	p.A598V	3
BRAF	COSM1126	SNV	p.L597S	3
BRAF	COSM1125	SNV	p.L597Q	3
BRAF	COSM471	SNV	p.L597R	3
BRAF	COSM470	SNV	p.L597V	3
BRAF	COSM469	SNV	p.G596R	3
BRAF	COSM53198	SNV	p.F595L	3
BRAF	COSM468	SNV	p.F595L	3
BRAF	COSM21612	SNV	p.F595L	3
BRAF	COSM466	SNV	p.D594V	3
BRAF	COSM253330	SNV	p.D594E	3
BRAF	COSM144576	SNV	p.D594H	3
BRAF	COSM467	SNV	p.D594G	3
BRAF	COSM211600	SNV	p.D594N	3
BRAF	COSM1583010	SNV	p.D594A	3
BRAF	COSM27639	SNV	p.D594N	3
BRAF	COSM463	SNV	p.E586K	3
BRAF	COSM462	SNV	p.N581S	3
BRAF	COSM1133046	SNV	p.Y472C	3
BRAF	COSM459	SNV	p.G469V	3
BRAF	COSM460	SNV	p.G469A	3
BRAF	COSM461	SNV	p.G469E	3
BRAF	COSM451	SNV	p.G466V	3
BRAF	COSM453	SNV	p.G466E	3
BRAF	COSM452	SNV	p.G466A	3
BRAF	COSM253328	SNV	p.G466R	3
BRAF	COSM449	SNV	p.G464E	3
BRAF	COSM450	SNV	p.G464V	3
BRAF	COSM1448615	SNV	p.G464R	3

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	COSM1111	SNV	p.G464R	3
BRAF	COSM448	SNV	p.I463S	3
BRAF	COSM447	SNV	p.R462I	3
BRAF	AGAP3-BRAF.A9B9	Gene Fusion	BRAF Translocation	3
BRAF	AGAP3-BRAF.A10B11	Gene Fusion	BRAF Translocation	3
BRAF	AGK-BRAF.A2B8	Gene Fusion	BRAF Translocation	3
BRAF	AGTRAP-BRAF.A5B8.COSF828.1	Gene Fusion	BRAF Translocation	3
BRAF	AKAP9-BRAF.A7B11	Gene Fusion	BRAF Translocation	3
BRAF	AKAP9-BRAF.A21B10	Gene Fusion	BRAF Translocation	3
BRAF	AKAP9-BRAF.A22B9	Gene Fusion	BRAF Translocation	3
BRAF	AKAP9-BRAF.A28B9	Gene Fusion	BRAF Translocation	3
BRAF	AKAP9-BRAF.A8B9.COSF1013.1	Gene Fusion	BRAF Translocation	3
BRAF	AP3B1-BRAF.A22B9	Gene Fusion	BRAF Translocation	3
BRAF	ARMC10-BRAF.A4B11	Gene Fusion	BRAF Translocation	3
BRAF	ATG7-BRAF.A18B9	Gene Fusion	BRAF Translocation	3
BRAF	BAIAP2L1-BRAF.B12B9	Gene Fusion	BRAF Translocation	3
BRAF	BBS9-BRAF.B19B4	Gene Fusion	BRAF Translocation	3
BRAF	BCL2L11-BRAF.B3B10	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-AP3B1.B8A23	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-CIITA.B9C6	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-MACF1.B8M15	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-MRPS33.B1M2	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-SLC26A4.B3S7	Gene Fusion	BRAF Translocation	3
BRAF	BRAF-SUGCT.B1S13	Gene Fusion	BRAF Translocation	3
BRAF	BTF3L4-BRAF.B3B11	Gene Fusion	BRAF Translocation	3
BRAF	C7orf73-BRAF.C2B9	Gene Fusion	BRAF Translocation	3
BRAF	CCDC6-BRAF.C1B9	Gene Fusion	BRAF Translocation	3
BRAF	CCDC91-BRAF.C11B9	Gene Fusion	BRAF Translocation	3
BRAF	CCNY-BRAF.C1B10	Gene Fusion	BRAF Translocation	3
BRAF	CDC27-BRAF.C16B9.1	Gene Fusion	BRAF Translocation	3
BRAF	CEP89-BRAF.C16B9	Gene Fusion	BRAF Translocation	3
BRAF	CLCN6-BRAF.C2B11.COSF1440	Gene Fusion	BRAF Translocation	3
BRAF	CLIP2-BRAF.C6B11	Gene Fusion	BRAF Translocation	3
BRAF	CUL1-BRAF.C7B9	Gene Fusion	BRAF Translocation	3
BRAF	CUX1-BRAF.C10B9	Gene Fusion	BRAF Translocation	3
BRAF	DYNC1I2-BRAF.D7B10	Gene Fusion	BRAF Translocation	3
BRAF	EML4-BRAF.E6B10	Gene Fusion	BRAF Translocation	3

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	EPS15-BRAF.E22B10	Gene Fusion	BRAF Translocation	3
BRAF	ERC1-BRAF.E12B10	Gene Fusion	BRAF Translocation	3
BRAF	ERC1-BRAF.E17B8	Gene Fusion	BRAF Translocation	3
BRAF	FAM114A2-BRAF.F9B11	Gene Fusion	BRAF Translocation	3
BRAF	FAM131B-BRAF.F1B10.COSF1191	Gene Fusion	BRAF Translocation	3
BRAF	FAM131B-BRAF.F3B9.COSF1193	Gene Fusion	BRAF Translocation	3
BRAF	FAM131B-BRAF.F2B9.COSF1189.1	Gene Fusion	BRAF Translocation	3
BRAF	FCHSD1-BRAF.F13B9.COSF403	Gene Fusion	BRAF Translocation	3
BRAF	FXR1-BRAF.F13B10	Gene Fusion	BRAF Translocation	3
BRAF	GATM-BRAF.G2B11	Gene Fusion	BRAF Translocation	3
BRAF	GHR-BRAF.G1B10	Gene Fusion	BRAF Translocation	3
BRAF	GNAI1-BRAF.G1B10.COSF1442	Gene Fusion	BRAF Translocation	3
BRAF	GTF2I-BRAF.G4B10	Gene Fusion	BRAF Translocation	3
BRAF	HERPUD1-BRAF.H4B7	Gene Fusion	BRAF Translocation	3
BRAF	KCTD7-BRAF.K3B8	Gene Fusion	BRAF Translocation	3
BRAF	KCTD7-BRAF.K4B8	Gene Fusion	BRAF Translocation	3
BRAF	KDM7A-BRAF.K11B11	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K9B9	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K12B9.COSF1474	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K12B11	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K13B9	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K14B9.COSF483	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K14B11.COSF1226	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K16B10	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K17B10.COSF509	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K18B9.COSF511	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K15B9.COSF481.1	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K15B10.COSF1283.1	Gene Fusion	BRAF Translocation	3
BRAF	KIAA1549-BRAF.K15B11.COSF485.1	Gene Fusion	BRAF Translocation	3
BRAF	KLHL7-BRAF.K5B9	Gene Fusion	BRAF Translocation	3

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	LSM12-BRAF.L3B9	Gene Fusion	BRAF Translocation	3
BRAF	LSM14A-BRAF.L9B9	Gene Fusion	BRAF Translocation	3
BRAF	MACF1-BRAF.M60B9	Gene Fusion	BRAF Translocation	3
BRAF	MAD1L1-BRAF.M16B9	Gene Fusion	BRAF Translocation	3
BRAF	MAD1L1-BRAF.M17B10	Gene Fusion	BRAF Translocation	3
BRAF	MKRN1-BRAF.M4B9	Gene Fusion	BRAF Translocation	3
BRAF	MKRN1-BRAF.M4B11.COSF1444	Gene Fusion	BRAF Translocation	3
BRAF	MYRIP-BRAF.M16B9	Gene Fusion	BRAF Translocation	3
BRAF	MZT1-BRAF.M2B11	Gene Fusion	BRAF Translocation	3
BRAF	NUB1-BRAF.N3B9	Gene Fusion	BRAF Translocation	3
BRAF	NUDCD3-BRAF.N4B9	Gene Fusion	BRAF Translocation	3
BRAF	NUP214-BRAF.N21B10	Gene Fusion	BRAF Translocation	3
BRAF	PAPSS1-BRAF.P5B9.1	Gene Fusion	BRAF Translocation	3
BRAF	PLIN3-BRAF.P1B9	Gene Fusion	BRAF Translocation	3
BRAF	RAD18-BRAF.R7B10	Gene Fusion	BRAF Translocation	3
BRAF	RBMS3-BRAF.R11B11	Gene Fusion	BRAF Translocation	3
BRAF	RNF11-BRAF.R1B11	Gene Fusion	BRAF Translocation	3
BRAF	RNF130-BRAF.R3B9.COSF1483	Gene Fusion	BRAF Translocation	3
BRAF	RP2-BRAF.R3B10	Gene Fusion	BRAF Translocation	3
BRAF	SLC12A7-BRAF.S17B11	Gene Fusion	BRAF Translocation	3
BRAF	SLC45A3-BRAF.S1B8.COSF871	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S9B2	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S9B9	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S10B9	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S10B11	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S11B11	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S14B9	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S14B11	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S18B10	Gene Fusion	BRAF Translocation	3
BRAF	SND1-BRAF.S16B9.1	Gene Fusion	BRAF Translocation	3
BRAF	SOX6-BRAF.S5B9	Gene Fusion	BRAF Translocation	3
BRAF	SOX6-BRAF.S6B9	Gene Fusion	BRAF Translocation	3
BRAF	STRN3-BRAF.S3B10	Gene Fusion	BRAF Translocation	3
BRAF	TANK-BRAF.T4B9	Gene Fusion	BRAF Translocation	3
BRAF	TAX1BP1-BRAF.T8B11.1	Gene Fusion	BRAF Translocation	3
BRAF	TMEM178B-BRAF.T2B9	Gene Fusion	BRAF Translocation	3
BRAF	TMPRSS2-BRAF.T3B11	Gene Fusion	BRAF Translocation	3

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	TRIM4-BRAF.T6B10	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T3B10	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T3B11	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T5B8	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T10B9	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T11B2	Gene Fusion	BRAF Translocation	3
BRAF	TRIM24-BRAF.T9B9.1	Gene Fusion	BRAF Translocation	3
BRAF	UBN2-BRAF.U3B11	Gene Fusion	BRAF Translocation	3
BRAF	ZC3HAV1-BRAF.Z3B10	Gene Fusion	BRAF Translocation	3
BRAF	ZC3HAV1-BRAF.Z7B11	Gene Fusion	BRAF Translocation	3
BRAF	ZKSCAN5-BRAF.Z2B9	Gene Fusion	BRAF Translocation	3
BRAF	ZSCAN30-BRAF.Z3B10	Gene Fusion	BRAF Translocation	3

Other BRAF Fusion events or novel BRAF activating mutations not listed in the above table but identified by one of the designated outside laboratories as described in the MATCH Master Protocol will also be considered actionable mutations (aMOIs) at Level of Evidence Code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol R: Trametinib

Appendix III

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Trametinib Ophthalmic Exam Form

Subject Name: _____

Note to examiner: Please assess particularly for visible retinal pathology.

***Optical coherence tomography is highly recommended.** For patients in whom retinal abnormalities are noted, **color fundus photos, and fluorescein angiography if clinically indicated, are recommended.**

OPHTHALMIC EXAMINATION		
1. Date of Examination:	_ _/_ _ _ /_ _ _ _ dd / mmm / yyyy	
VISUAL ACUITY		
Enter corrected visual acuity	OD:	OS:
TONOMETRY		
Enter IOP (mmHg)	OD:	OS:
INDIRECT FUNDOSCOPY		
Indirect Exam: Indicate normal or specify abnormalities	OD:	OS:
CONFRONTATION VISUAL FIELD EXAM OR AUTOMATED PERIMETRY (e.g., Humphrey 24-2 or 30-2 or equivalent if using a non-Humphrey instrument)		
Indicate normal or specify any abnormalities	OD:	OS:
OPTICAL COHERENCE TOMOGRAPHY (strongly recommended)		
Indicate normal or specify any abnormalities	OD:	OS:
COLOR FUNDUS PHOTOS (recommended if retinal abnormalities are noted)*		
Indicate normal or specify any abnormalities	OD:	OS:
FLORESCEIN ANGIOGRAPHY (suggested if retinal abnormalities are noted and test clinically indicated)*		
Indicate normal or specify any abnormalities	OD:	OS:

Were any of the following noted on ocular history or exam?	Yes	No
• History of CSR?		
• Evidence of new optic disc cupping?		
• Evidence of new visual field defects?		
EXCLUSION CRITERIA	Yes	No
• History of RVO? o *If yes, patient is not eligible for the study.*		

Signature of Examiner: _____

Printed Name: _____ **Date:** _____

Molecular Analysis for Therapy Choice (MATCH)
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Appendix IV

Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Rev. 12/16 The patient _____ is enrolled on a clinical trial using the experimental study drug, **Trametinib**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Trametinib is a weak CYP2C8 inhibitor and weak CYP3A4 inducer.

Drug-drug interactions with any substrates of CYP2C8 and CYP3A4 are not anticipated.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

There is a very low risk that **Trametinib** may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

There is a very low risk of drug interaction when **Trametinib** is combined with other medicines that use certain liver enzymes to be effective or to be removed from your body. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that use the liver enzymes CYP2C8 and CYP 3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Your study doctor's name is

_____

and he or she can be contacted at

_____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial using the experimental agent **Trametinib.** This clinical trial is sponsored by the NCI. **Trametinib could** interact with drugs that affect the QT interval, a measurement of heart conductivity. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**Trametinib could lengthen the QT interval rarely** and must be used very carefully with other medicines that affect the QT interval. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered QT prolonging agents. ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/ for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.