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Local Protocol #: SARC033

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Summary of changes Memo

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1. Updated Section 8.1.1.
2. Updated Patient Clinical Trial Wallet Card

NCI Protocol #: 10015

Local Protocol #: SARC033

ClinicalTrials.gov Identifier: NCT03148275

TITLE: A Non-Randomized, Open-Label, Phase 2 Study of Trametinib in Patients with Unresectable or Metastatic Epithelioid Hemangioendothelioma

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NCI-Supplied Agent(s): Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Other Agent(s):
Not applicable

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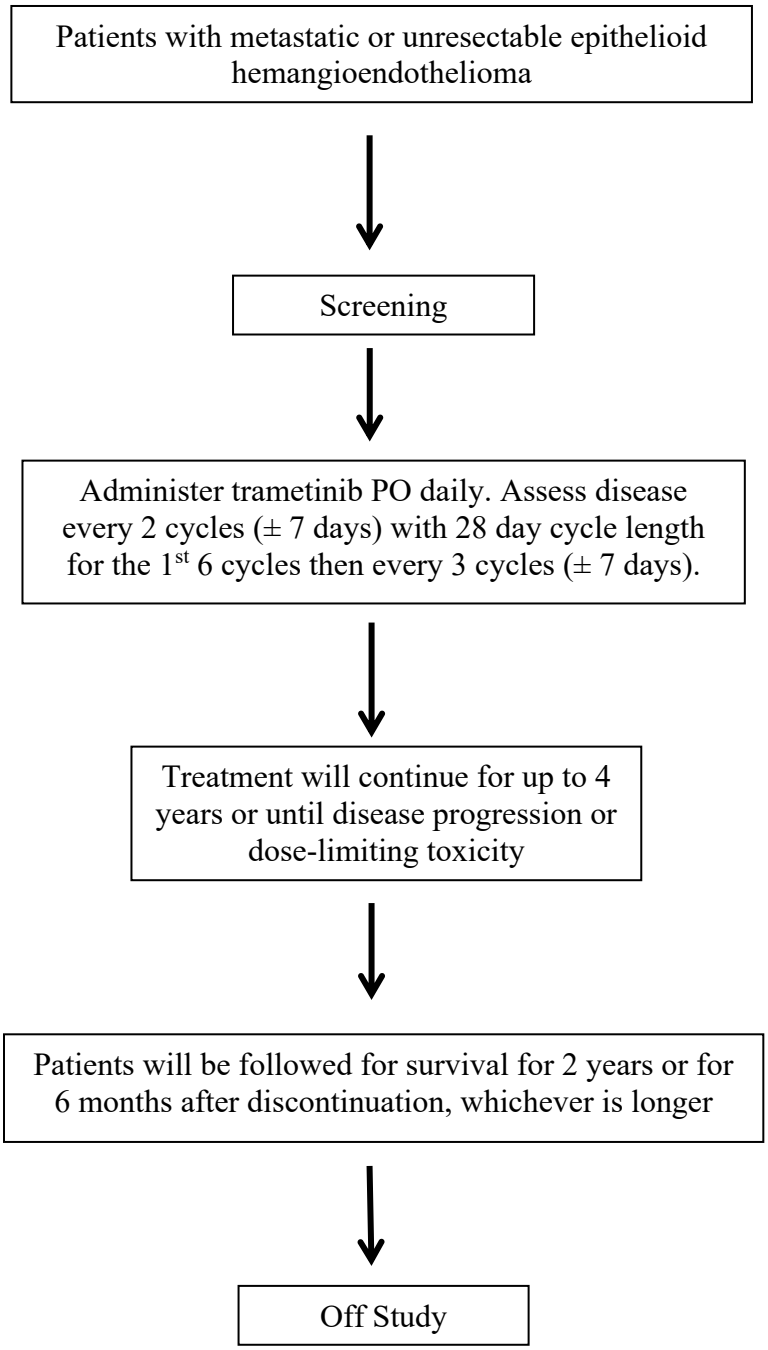
SCHEMA


Patients with metastatic or unresectable epithelioid hemangioendothelioma
Screening
Administer trametinib PO daily. Assess disease every 2 cycles (± 7 days) with 28 day cycle length for the 1st 6 cycles then every 3 cycles (± 7 days).
Treatment will continue for up to 4 years or until disease progression or dose-limiting toxicity
Patients will be followed for survival for 2 years or for 6 months after discontinuation, whichever is longer
Off Study

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1. OBJECTIVES

1.1 Primary Objectives

- Estimate the objective response rate (ORR) using RECIST 1.1

1.2 Secondary Objectives

- Estimate the 6-month and median progression free survival (PFS) rates
- Estimate the 2-year and median overall survival (OS) rates
- Evaluate the safety of trametinib in patients with epithelioid hemangioendothelioma
- Evaluate patient-reported symptoms using NIH PROMIS global health; pain intensity, interference and behavior short form inventories prior to, after 4 weeks and after 6 months (if stable or better disease) of treatment, and on evidence of disease progression

1.3 Exploratory Objectives

- Compare the rates of epithelioid hemangioendothelioma progression prior to starting trametinib to rates on treatment by central review of radiology images
- Evaluate the effect of trametinib on change in tumor volume and compare to RECIST1.1 response through central imaging review
- Evaluate the effect of trametinib on markers of inflammation including c-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and plasma connective tissue growth factor (CTGF).

2. BACKGROUND

2.1 Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is a rare sarcoma that shows vascular (endothelial) differentiation. It usually presents with widespread metastases. Although metastatic disease can be stable for years, it inevitably progresses rapidly and without warning, is highly lethal and has no effective treatment. EHE can occur at any age, but peaks in adulthood (Weiss & Enzinger, 1982). Five-year disease-specific mortality is 40% and 65% for EHE that arises in the lung and liver, respectively (Weiss & Goldblum, 2008). Although localized EHE can often be treated with surgery and radiation, systemic therapy options are limited for patients with metastatic disease in which the median survival is less than 4 years.

Due to the rarity of this disease, there is no consensus on standard systemic therapy and data is limited to single-institution case reports or retrospective case series. Cioffi et al. (Cioffi et al., 2011) reported a retrospective study of 42 patients with metastatic EHE. Thirty-four patients received systemic chemotherapy including conventional doxorubicin-containing regimens (n=16), other chemotherapy regimens (n=6), and anti-angiogenesis agents or tyrosine kinase inhibitors (TKI, n=12). There were no objective responses although 14 patients had stable disease for at least 6 months. Of those with stable disease, 4 patients received doxorubicin-containing chemotherapy, 4 received other chemotherapy and 6 received angiogenesis targeting agents or TKIs. Median PFS was 4.8 months and median OS was 41 months.

Mehrabi et al. published a comprehensive review of patients with malignant hepatic EHE comprised of 434 patients (Mehrabi et al., 2006). The most common treatment was liver transplantation (44.8%), followed by observation (24.8%) and chemotherapy or radiotherapy (21%). One-year and five-year patient survival rates were 73.3% and 30%, respectively, for patients who received treatment with chemotherapy or radiotherapy. Chemotherapeutic regimens were diverse and included thalidomide, doxorubicin, 5-fluorouricil, epirubicin plus dacarbazine and interferon-alpha. Based on the data presented as a retrospective observational analysis, the effectiveness of the different chemotherapy treatments used cannot be inferred.

There have been few clinical trials that have prospectively investigated drug therapies for patients with EHE. For example, a phase II study evaluated bevacizumab in seven patients with locally advanced or metastatic EHE (Agulnik et al., 2013). Two patients had a partial response and four patients demonstrated stable disease with one patient experiencing progressive disease at first evaluation. The mean number of cycles received was 17.3 (52 weeks). Median PFS was 39.1 weeks and median OS was 142.6 weeks. Given the small number of patients in this study, further conclusions cannot be made.

A phase II study by the French Sarcoma Group evaluated the efficacy of sorafenib (800 mg daily) in 15 patients with progressive EHE with a primary endpoint of 9-month PFS (Chevreau et al., 2013). Twelve patients had metastatic disease at the time of enrollment. The 2-month, 4-month, 6-month and 9-month progression free rates were 84.6%, 46.4%, 38.4% and 30.7%, respectively. Median follow-up was 12 months, with a median PFS of 6 months. Median overall survival was not reached at the time of analysis. Two partial responses were noted and lasted 2 months and 9 months. The median treatment duration was 124 days with seven patients requiring dose reductions or transient treatment discontinuation due to toxicity including hand-foot syndrome, diarrhea and mucositis with anorexia. Previously reported treatment and trials have used chemotherapy, immunotherapy, multi-kinase inhibitors or anti-vascular endothelial growth factor inhibitors with marginal benefit; therefore, standard drug therapy for patients with locally advanced or metastatic unresectable EHE has not been established.

Recently, a disease-defining *TAZ-CAMTA1* gene fusion has been identified in EHE. This is a balanced, reciprocal translocation that results in the fusion of *TAZ* (also known as *WWTR1*), to *CAMTA1*, dysregulating the Hippo pathway (Tanas et al., 2016; Tanas et al., 2011). Importantly, this fusion is found in more than 90% of EHE tumors, and EHE tumors have no other consistent genetic alterations, suggesting that the fusion is an early and important genetic event and that EHE cells are highly dependent on TAZ-CAMTA1 (Tanas et al., 2011). TAZ-CAMTA1 drives oncogenic transformation through a TAZ-like transcriptional program and the Hippo pathway is unable to regulate TAZ-CAMTA1 (Tanas et al., 2016). Thus, this fusion unleashes an otherwise tightly controlled transcriptional program resulting in EHE oncogenesis. Rubin et al. have studied signal transduction downstream of TAZ-CAMTA1, identifying connective tissue growth factor (CTGF) and MAP kinase signaling as key pathways and potential therapeutic targets (unpublished data). Most of the clinical studies discussed above predate the discovery of this gene fusion. The limited success of systemic therapies as demonstrated in these reports underscores the need for further research to identify more effective treatments.

2.2 CTEP IND Agent

2.2.1 Trametinib Dimethyl Sulfoxide (GSK1120212B, MEKINIST)

The RAF-MEK-ERK pathway plays a critical role in multiple cellular functions. Activation of the pathway can result from activation/mutations of the upstream receptor tyrosine kinases (RTKs) and RAS, or upregulation/mutations in RAF and MEK. Upon activation, RAF acts as the MAPK kinase and activates MAPKK (MEK1/2), which in turn catalyzes activation of the effectors ERK1/ERK2. Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins and transcriptional factors that regulate cell proliferation, motility, differentiation, and survival.

Trametinib is one of several MEK inhibitors in clinical development. On May 29, 2013, the U.S. Food and Drug Administration (FDA) approved trametinib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutations as detected by an FDA-approved test (U.S. Food and Drug Administration, 2013). On January 10, 2014, the Food and Drug Administration granted accelerated approval to trametinib and dabrafenib for use in combination to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test (U.S. Food and Drug Administration, 2014).

Experience to date indicates that MEK is a valid target. In a phase 3 trial comparing trametinib with dacarbazine or paclitaxel in patients with BRAF V600E or V600K mutant metastatic melanoma, trametinib demonstrated a significantly better response rate, progression-free survival, and overall survival (Flaherty *et al.*, 2012). However, single agent activities are limited. Extensive research is underway to identify the patient selection markers and develop rational combination strategies. Preclinical studies have provided strong rationale and proof of principle for combination of MEK inhibitors with RTK inhibitors (EGFR or IGF-1R) (Gopal *et al.,* 2010; Ebi *et al.,* 2011), PI3K/AKT inhibitors (Engelman *et al.,* 2008; Hoeflich *et al.,* 2009), and mTOR inhibitors. On the other hand, the optimal dose/schedule and patient selection criteria for combination regimens have not been defined. Phase 1 results for a number of combinations have been reported, including AZD6244 + MK2206 (Tolcher *et al.,* 2011) and GDC-0973 + GDC-094 (MEK + PI3K inhibitor) (Bendell *et al.,* 2011).

The most up-to-date preclinical and clinical study information for trametinib can be found in the GSK1120212 (trametinib) Investigator's Brochure (August 10, 2018).

2.2.1.1 Mechanisms of Action and Preclinical Data with Trametinib

Trametinib is a dimethyl sulfoxide (DMSO) solvate compound (ratio 1:1) with potent, allosteric and ATP non-competitive inhibition of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) (Gilmartin *et al.,* 2011). Trametinib inhibited MEK1/2 kinase activity and prevented RAF-dependent MEK phosphorylation (S217 for

MEK1), producing prolonged pERK1/2 inhibition. Trametinib showed better potency against unphosphorylated MEK1/2 (u-MEK1/2) when compared with preactivated diphosphorylated MEK (pp-MEK), suggesting that u-MEK affords a higher affinity binding site for trametinib than does pp-MEK.

The specificity of trametinib was confirmed against a panel of 183 kinases, including MEK5 (the closet kinase homolog to MEK1/2), CRAF, BRAF, ERK1, and ERK2 (Yamaguchi *et al.,* 2011). Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of RAF-mediated MEK1 activation (IC_{50} = 0.60 nM) over pMEK1 kinase activity (IC_{50} = 13 nM) (Investigator's Brochure, 2012a).

BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed the most significant mean tumor growth inhibition (TGI) (80% to 87%) at 3.0 mg/kg trametinib, with multiple complete and partial tumor regressions. In the Colo205 model, tumor regression was observed even at a dose of 0.3 mg/kg (Yamaguchi *et al.,* 2011). Two KRAS-mutant xenograft models, HCT-116 and A549, also showed significant TGI (83% and 75%) but without significant tumor regressions (Gilmartin *et al.,* 2011). As predicted by cell proliferation assays, tumor xenograft lines with wild-type (wt) RAF/RAS (PC3, BxPC3, and BT474) were much less sensitive, showing only modest TGI (44-46%) with no tumor regressions.

Pharmacodynamic studies were performed in mice treated with trametinib for 14 days (Gilmartin *et al.,* 2011). In the A375P F11s xenograft model, the first dose of trametinib (3 mg/kg) significantly reduced pERK for more than 8 hours on Day 1. pERK inhibition was more sustained (over 24 hours) after the Day 7 dose, probably due to an increase in the steady-state levels of trametinib after repeated doses. The average C_{max} in blood was 1,410 nM on Day 7, with an estimated half-life ($t_{1/2}$) of 33 hours. In addition, immunohistochemistry (IHC) also confirmed inhibition of cell proliferation (reduced Ki67) and G1 cell cycle arrest (elevated p27Kip1/CDKN1B) following 4 days of treatment.

2.2.1.2 Clinical Pharmacokinetics (PK) and Activity of Trametinib

FTIH Phase 1 Trial of Trametinib Monotherapy (MEK111054)
There are 3 parts in this study. Part 1: The dose-escalation portion involves administration of trametinib (repeat doses of 0.125 mg to 4.0 mg) to patients with solid tumors or lymphoma in one of three schedules - (1) QD for 21 days followed by 7 days without drug, (2) loading dose on Day 1 or Day 1-2, followed by QD with the designated dose, or (3) QD dosing without a drug holiday. Part 2: cohort expansion at the recommended phase 2 dose (RP2D) for pancreatic cancer, melanoma, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or any BRAF mutation-positive cancer. Part 3: expansion to characterize the biologically active range of trametinib via analysis of pharmacodynamic biomarkers (biopsies or FDG-PET).

The MTD of trametinib was established as 3 mg QD, but the recommended phase 2 dose (RP2D) was chosen at 2 mg QD based on tolerability of repeated cycles (Infante *et al.,* 2010).

Trametinib treatment in children
A 3 part phase 1/2, open-label, multicenter study of trametinib in pediatric subjects with recurrent or refractory tumors (NCT02124772) is underway. Unpublished results from the part A, dose escalation portion of the study which included 38 subjects is complete. The recommended phase 2 dose in children 6 years of age or older is 0.025 mg/kg per day with the total dose not to exceed 2 mg per day. A dose of 0.04 mg/kg per day (corresponding to a dose of 2 mg per day in a subject weighing 50 kg) was associated with skin related dose-limiting toxicities. Pharmacokinetic steady state drug concentration target was met in children 6 years of age or older using a dose of 0.025 mg/kg per day. (confidential information from Novartis)

PK and metabolism of trametinib:
PK measurements were conducted under fasting conditions. After a single dose (Day 1), $AUC_{0\text{-}24}$ and C_{max} values were dose-proportional up to 6 mg, lower than dose proportional following 8 mg, and greater than dose proportional following the 10 mg dose. Median T_{max} was 1.5 hours.

After repeat doses (Day 15), trametinib accumulated with a mean accumulation ratio of 6.6 at the RP2D of 2 mg QD. Between-subject variability in exposure ranged from 27-50% for C_{max} and 20-41% for $AUC_{0\text{-}24}$ across all dosing regimens. The effective $t_{1/2}$ was approximately 4.5 days, and steady state was reached by approximately Day 15. Trametinib had a small peak:trough ratio of ~2 (Infante *et al.,* 2010). At 2 mg QD on Day 15, mean $AUC_{0\text{-}24}$ was 376 ng•h/mL and C_{max} 23 ng/mL, and the mean trough concentrations ranged from 10.0 to18.9 ng/mL. The long half-life and small peak:trough ratio of trametinib allowed constant target inhibition within a narrow range of exposure.

Drug-drug interactions:
Trametinib is metabolized predominantly via deacetylation (non-cytochrome P450 [CYP450]-mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways (Investigator's Brochure, 2012a). The deacetylation is likely mediated by hydrolytic esterases, such as carboxylesterases, or amidases. Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP3A4. Trametinib has an overall low potential for drug-drug interactions.

Pharmacodynamic effect and biomarkers:
The relationship between dose and tumor biomarkers such as pERK, Ki67, and p27, were evaluated in patients with BRAF or NRAS mutation-positive metastatic melanoma (Investigator's Brochure, 2012a). In general, increasing exposures and/or doses provided greater pharmacodynamic effects. The median change observed at a dose of 2 mg QD was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27.

Antitumor Activity in the FTIH phase 1 trial:
In the FTIH phase 1 trial, 14 patients with BRAF-mutant melanoma received trametinib at 2 mg QD. The overall objective response rate (ORR) was 43% (6/14), including 2 complete responses (CRs) (Investigator's Brochure, 2012a). In 9 patients with BRAF wt melanoma, 2 patients achieved a partial response (PR), and 3 patients with stable disease (SD) (Infante *et al.,* 2010). In 26 evaluable pancreatic cancer patients, there were 2 PRs (1 PR was KRAS mutation-positive) and 11 SD (2 achieved ≥20% tumor reduction) (Messersmith *et al.,* 2011). Among the 27 CRC patients (without selection of RAS or RAF mutations), 8 SD were observed.

Antitumor Activity in Melanoma

Phase 3 trial of trametinib vs. chemotherapy in advanced V600 mutant melanoma:
In a phase 3 trial, patients with unresectable stage IIIC or IV cutaneous melanoma with a BRAF V600E or V600K mutation were randomized (2:1) to trametinib (2 mg, PO, QD) or chemotherapy (dacarbazine or paclitaxel) (Flaherty *et al.*, 2012; MEKINIST, 2013). There were 322 patients in the intention-to-treat (ITT) population, of whom 273 (85%) were in the primary efficacy population (patients with $BRAF^{V600E}$-positive cancer who did not have brain metastases at baseline). Of the patients, 214 were randomized to receive trametinib, and 108 were randomized to receive chemotherapy. Investigator-assessed efficacy data are summarized as follows:

	Trametinib (n=214)	**Chemotherapy (DTIC) (n=108)**
PFS Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR (95% CI) *P* value (log-rank test)	0.47 (0.34, 0.65) *P*<0.0001	
Confirmed Tumor Responses Objective Response Rate (95% CI) CR, n (%) PR, n (%)	 22% (17, 28) 4 (2%) 43 (20%)	 8% (4, 15) 0 9 (8%)
Duration of response Median, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)
CI = confidence interval; CR = complete response; HR = hazard ratio; NR = not reached; PFS = progression-free survival; PR = partial response		

The 6-month OS rate was 81% in the trametinib group and 67% in the chemotherapy group. Mature data on OS are pending.

Experience with Trametinib in Metastatic Melanoma Following BRAF Inhibitor Therapy

The clinical activity of single-agent trametinib was evaluated in a single-arm, multicenter, international trial in 40 patients with BRAF V600E or V600K mutation-

positive, unresectable, or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received trametinib at a dose of 2 mg PO QD until disease progression or unacceptable toxicity. None of the patients achieved a confirmed PR or CR.

Antitumor Activity of Trametinib in Cancer Other Than Melanoma

In a phase 1/2 monotherapy study, acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) patients were given trametinib at dose levels from 1-2 mg QD. Drug-related AEs in 45 patients were similar to that observed in patients with solid tumors, and 2 mg PO QD was selected for further investigation in this patient population. Twelve patients (23%) withdrew due to an AE, including cardiac failure (2) and infection (2). Efficacy was reported in 39 patients (Borthakur *et al.,* 2010). The best response in 13 patients with KRAS or NRAS mutations included 3 CRs (23%), 7 SD (54%), and 1 PD (progressive disease) (5%). In 26 patients with wild-type RAS or an unknown mutation, there were 2 PRs (8%).

In a multicenter phase 2 study, NSCLC patients with KRAS mutant tumors were randomized 2:1 to receive trametinib (2 mg QD) or docetaxel (75 mg/m^2 IV every 3 weeks) (Blumenschein *et al.*, 2013). A total of 134 pts were randomized to trametinib (89) or docetaxel (45); 129 patients had KRAS-mutant NSCLC. The hazard ratio for PFS was 1.14 (95% CI, 0.75-1.75; *P*=0.5197) with a median PFS of 11.7 versus 11.4 weeks for trametinib versus docetaxel. The overall response rate (ORR) was 12% for trametinib and 12% for docetaxel.

In a double-blind, phase 2 study evaluating the combination of gemcitabine with trametinib, untreated pancreatic cancer patients were randomized to receive gemcitabine (1000 mg/m2 weekly ×7 for 8 weeks, then weekly ×3 every 4 weeks) plus either trametinib 2mg or placebo QD (Infante *et al.*, 2013). Median OS was 8.4 months with trametinib compared to 6.7 months with placebo. Median PFS was 16 weeks versus 15 weeks, and ORRs and median duration of responses were 22% and 23.9 weeks and 18% and 16.1 weeks on trametinib and placebo; the median OS and ORR in the subgroup of patients with KRAS mutations (143/160) was similar to OS and ORR for all randomized patients.

Trametinib has not been formally evaluated in patients with EHE or soft tissue sarcoma. We do not expect drug pharmacokinetics or adverse events rates to differ significantly from the experience of trametinib in treatment of metastatic melanoma or non-small cell lung cancer.

2.2.1.3 Trametinib Safety Profile

A **Comprehensive Adverse Events and Potential Risks (CAEPR)** list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in Section 7.1 of the protocol.

Based on available AE data from clinical studies involving trametinib to date, the most common toxicities are rash and diarrhea. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with trametinib as well as other MEK inhibitors.

AEs of special interest:
Rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis are considered AEs of special interest because they are either known class effects (*i.e.*, have been observed with other MEK inhibitors) or are potentially life-threatening (Investigator's Brochure, 2013). The following sections provide integrated summaries for these AEs across different clinical trials, with emphasis on trials using trametinib as monotherapy, especially at the RP2D of 2 mg.

Refer to dose modification guidelines for the toxicities for which they are addressed in Section 6.

Rash: Rash was a common AE observed across different dose levels and in different combinations (Investigator's Brochure, 2013). At the 2 mg dose, rash was seen in 27% to 78% of patients in different trials. Of the ~370 subjects with rash AEs at the 2 mg monotherapy dose (including crossover subjects) in five studies, the majority of rash AEs were grades 1 or 2 (24% to 73%); 0% to 9% of patients experienced grade 3 rash AEs, and four patients had a grade 4 rash AE.

In a randomized phase 3 trial of trametinib vs. chemotherapy, the overall incidence of skin toxicity (including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema) was 87% in patients treated with trametinib and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients on the trametinib arm, most commonly for secondary infections of the skin The median time to onset of skin toxicity was 15 days (range: 1 to 221 days), and median time to resolution was 48 days (range: 1 to 282 days). Dose reduction was required in 12% for skin toxicities, and permanent discontinuation of trametinib was required in 1% of patients.

Diarrhea: At the 2 mg monotherapy dose, 33% to 58% of patients in five trials had diarrhea (Investigator's Brochure, 2013). Of ~320 subjects (including crossover subjects) with diarrhea at this dose, the majority of diarrhea AEs were grade 1 or 2 in severity (33% to 56% of all study patients); 17 patients had grade 3 diarrhea, and none had grade 4 diarrhea.

Visual disorders: At the 2 mg monotherapy dose, 4% to 21% of the patients in five trials experienced visual disorders (Investigator's Brochure, 2013). Of the 85 total subjects (including crossover subjects) experiencing visual disorders at this dose level, the

majority of visual disorders were grades 1 or 2 (4% to 20% of all study patients); six patients experienced grade 3 visual disorders, and one patient experienced a grade 4 visual disorder.

- *Retinal Pigment Epithelial Detachment (RPED):* Also known as chorioretinopathy, RPED is a visual impairment due to fluid accumulation under the retina and causes blurry vision. There were five cases of RPED, previously termed central serous retinopathy, reported from the integrated trametinib safety population consisting of subjects treated with trametinib 2 mg once daily from five studies (Investigator's Brochure, 2013). As of 23 June 2013, 14 cases of RPED were reported across the entire trametinib program amongst subjects treated with trametinib either as monotherapy or in combination with other anti-cancer agents (including cases from a MEK/BRAF combination study).

- *Retinal vein occlusion (RVO):* As of 23 June 2013, a total of four cases of RVO were reported across the entire trametinib program (including one case from a MEK/BRAF combination study) (Investigator's Brochure, 2013). All cases of RVO occurred in one eye only. Study drug was stopped at time of diagnosis in all cases. There was a decrease of visual acuity in two subjects with central RVO (CRVO) while the other two subjects had no meaningful decrease of visual acuity. In the two subjects with CRVO, local treatment with intravitreal injections of anti-VEGF antibodies was initiated within 2 weeks after RVO diagnosis, and visual acuity improved in one subject and restored to baseline conditions in another subject, at the time of the data cutoff. Three of these four cases were considered related to study treatment by the investigators.

Hepatic disorders: Abnormalities of liver enzymes and bilirubin have been observed with administration of trametinib (Investigator's Brochure, 2013). However, assessment of these cases was often confounded by co-morbid conditions (such as biliary obstruction), concomitant use of other potentially hepatotoxic drugs, and liver metastases. At the 2 mg monotherapy dose, 8% to 34% of patients in five trials had LFT abnormalities. Of the 96 total patients (including crossovers) with LFT changes, the majority were grade 1 or 2 in severity (4% to 20% of all study patients); 26 had grade 3 events, and 6 patients had grade 4 events.

Cardiac-related AEs: At the 2 mg monotherapy dose, 3% to 21% of the subjects in six studies had cardiac-related AEs (Investigator's Brochure, 2013). Of the 65 total subjects (including crossover subjects) experiencing cardiac-related AEs at the 2.0 mg monotherapy dose in five of the studies, the majority of cardiac-related AEs were grades 1 or 2 in severity (0% to 16% of all study subjects); 18 subjects had grade 3 cardiac-related AEs, and no subjects had Grade 4 cardiac-related AEs in any study. No subject in one study, which evaluated the effect of repeat oral dosing of trametinib 2 mg QD on cardiac repolarization in subjects with solid tumors, had cardiac-related AEs. One study subject receiving trametinib 2 mg QD had grade 5 (fatal) acute cardiac failure, with evidence of massive tumor invasion of the heart; this AE was considered not drug-related by the investigator.

In the phase 3 trial of trametinib vs. chemotherapy in patients with melanoma (MEK114267), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased LVEF) occurred in 7% (14/211) of patients treated with trametinib, and in no patients in the chemotherapy arm. Cardiomyopathy was identified within the first month of treatment in five of these 14 patients; median onset of cardiomyopathy was 63 days (range: 16 to 156 days). Cardiomyopathy resolved in 10 of these 14 (71%) patients. Cardiac monitoring should be included in trametinib protocols, to include LVEF assessment by echocardiogram or MUGA scan at baseline, one month after initiation of trametinib and then at 2- to 3-month intervals while on treatment. Refer to dose modification guidelines for cardiac AEs in the event of LVEF decline or symptomatic cardiac AEs.

Pneumonitis: At the 2 mg monotherapy dose, 0% to 4% of the subjects in five studies had pneumonitis (Investigator's Brochure, 2013). Of the nine total subjects (including crossovers) experiencing pneumonitis AEs at this dose, three subjects had grade 1 or 2 pneumonitis and six subjects had grade 3 pneumonitis.

Embryofetal toxicity: Based on its mechanism of action, trametinib can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Incidence of common AEs reported from a phase III trial of trametinib vs. chemotherapy in patients with advanced melanoma:

Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded from this trial. Selected adverse reactions (AR) occurring in patients receiving trametinib as compared to patients in the chemotherapy arm are listed as below:

Table: Selected adverse reactions (ARs) occurring in ≥10% of patients receiving trametinib AND at a higher incidence than in the chemotherapy arm (high in the trametinib arm compared with chemotherapy by ≥5% in overall incidence or by ≥2% grade 3 or 4 AEs)

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Adverse Reactions	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritis	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				

Diarrhea	43	0	16	2
Stomatitis	15	2	2	0
Abdominal pain	13	1	5	1
Vascular disorders				
Lymphedema	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage	13	<1	0	0

Table: Percent-patient incidence of laboratory abnormalities occurring at a higher incidence in patients treated with trametinib versus chemotherapy (between-arm difference of ≥5% [all grades] or ≥2% [grades 3 or 4])

	Trametinib (n=211)		**Chemotherapy (n=99)**	
Preferred term	**All Grades**	**Grades 3 and 4**	**All Grades**	**Grades 3 and 4**
Increased aspartate aminotransferase (AST)	60	2	16	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

Other clinically important adverse reactions observed in ≤10% of patients (n=329) treated with trametinib were: nervous system disorders (dizziness, dysgeusia), ocular disorders (blurred vision, dry eye), infections and infestations (folliculitis, rash pustular, cellulitis), cardiac disorders (bradycardia), gastrointestinal disorders (xerostomia), and musculoskeletal and connective tissue disorders (rhabdomyolysis).

2.3 Rationale

The MAPK pathway is activated downstream of the *TAZ-CAMTA1* gene fusion seen in over 90% of EHE tumors and pre-clinical studies demonstrated that MEK activation correlates with the ability of TAZ-CAMTA1-expressing cells to grow as colonies in soft agar or in suspension. Exposure of these cells to either the selective MEK inhibitor PD325901 or trametinib inhibited colony formation in agar and in suspension establishing a role of MAP kinase pathway in growth and survival of cells dependent on TAZ-CAMTA1 mediated oncogenesis and MEK as a potential tumor-dependent target for therapy. The IC50 for trametinib inhibition of tumor growth in vitro was less than 10 nM, which is a therapeutically achievable dose.

2.4 Correlative Studies Background

2.4.1 Fluorescence In-situ Hybridization (FISH) for *TAZ-CAMTA1* gene fusion
We believe EHE most likely to respond to MEK inhibition are tumors that harbor the *TAZ-CAMTA1* translocation because MEK activation requires TAZ-CAMTA1 expression (see section 2.4.2). In pathology review of tumors that morphologically resembled EHE, over 90% of the tumors contained *TAZ-CAMTA1* gene fusion detected by FISH (Tanas et

al. 2011). Therefore, we believe most, if not all, patients enrolled in this trial will have tumor that contains *TAZ-CAMTA1* gene fusion. A fusion FISH test has been developed at Cleveland Clinic and will be used to evaluate the presence of the *TAZ-CAMTA1* gene fusion in tumor from patients enrolled in the trial. Archival formalin-fixed, paraffin-embedded tumor samples will be collected and processed by the SARC SPORE pathology core. Representative H&E stained sections will be reviewed by the pathology core as a central review of the diagnosis. Fusion FISH for *TAZ-CAMTA1* will be performed on unstained sections from diagnostic tissue using the CLIA-certified FISH laboratory at Cleveland Clinic after enrollment (See section 9.1). Tumors with at least 10% fused gene signals will be considered positive for *TAZ-CAMTA1* gene fusion and will be scored as *TAZ-CAMTA1* fusion detected. Tumors with less than 10% fused gene signals will be scores as *TAZ-CAMTA1* fusion not detected. Tumor in which the fusion FISH test is not informative for technical reasons including lack of sufficient tumor tissue in the sample/slide will be scored as test failed.

2.4.2 Ability of trametinib to inhibit MAP kinase signaling in EHE

EHE tumor samples prior to treatment with trametinib demonstrate activation of the MAP kinase pathway and administration of trametinib to patients with EHE in standard clinical doses will result in inactivation of the MAP kinase pathway resulting in a decrease in the level of phosphorylation of ERK. In pre-clinical studies, NIH/3T3 cells stably expressing TAZ-CAMTA1 were grown in suspension and the MAPK and PI3K pathways were examined. NIH/3T3 cells containing empty vector, which do not proliferate in suspension, were used as a control. Phospho-ERK, which is emblematic of MAPK pathway activation, was sustained in TAZ-CAMTA1-expressing cells (7 day-13 day lanes) while cells expressing vector alone lost ERK phosphorylation over time (Fig. 1A). This suggests that TAZ-CAMTA1 maintained MAPK activation in these cells. In contrast, phospho-AKT, a surrogate of PI3K pathway activation was activated both in cells with empty vector and cells expressing TAZ-CAMTA1, suggesting that it was MAPK pathway activation and not PI3K activation that was driving proliferation of NIH/3T3-expressing cells in suspension (Fig. 1A). Phospho-ERK has been detected in protein lysates of snap-frozen EHE tumor samples (Fig 1B) and in EHE tumor cells by immunohistochemistry using a phospho-specific anti-ERK antibody (Fig 1 C-D). Based on these observations, we hypothesize that tumor response to clinically administered doses of trametinib will be accompanied by suppression of the MAPK pathway signaling detected by loss of phosphorylated ERK. Fresh tumor tissue will be obtained by core needle biopsy in patients who consent to the optional biopsies prior to treatment and approximately 4 weeks after start of treatment with trametinib for the analysis of MAP kinase pathway activation. The analysis will be performed by a research laboratory at Cleveland Clinic.

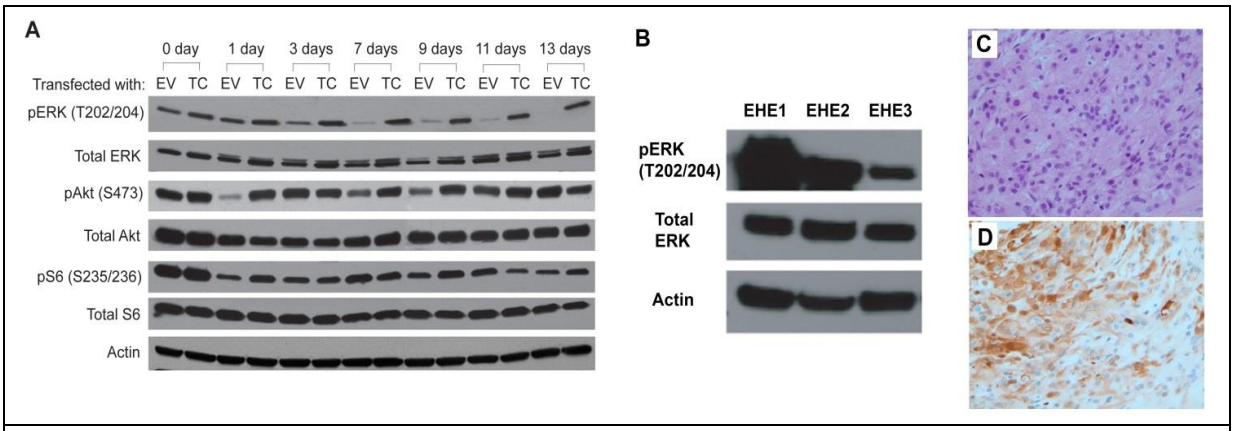
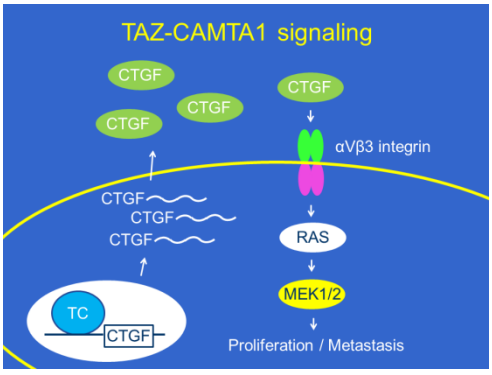


Fig. 1. MAPK/ERK is activated in EHE. A. NIH/3T3 cells stably transfected with either TAZ-CAMTA1 (TC) or empty vector (EV) were cultured on HEMA-coated plates, which prevent attachment and so force the cells to grow in suspension. Cell lysates were prepared at various time points, fractionated on PAGE and western blotted with antibodies to total ERK, pERK (T202/204), total AKT, pAKT (S473), total S6, and phospho-S6 (S235/236), and actin. Note that at later time points pERK is elevated in TC cells while it is lost in EV cells, suggesting that pERK/MAPK activation is driving proliferation in suspension. **B.** Protein lysates from three different frozen EHE tumor samples from three separate patients were fractionated on PAGE and western blotted with antibodies to pERK (T202/204), total ERK, and actin demonstrating abundant phospho-ERK in all tumor samples. EHE histological section **(C)** with pERK (T202/204) immunohistochemistry **(D)** revealing abundant cytoplasmic positivity in tumor cells but not admixed inflammatory cells.

2.4.3 Biomarkers of EHE activity in patients treated with trametinib

Plasma CTGF levels may be a useful biomarker of EHE survival as CTGF is a secreted protein whose gene is an immediate downstream target of TAZ-CAMTA1 (Tanas et al., 2016). CTGF is secreted and binds to αIIbβ3 integrin on the cell surface, leading in an autocrine fashion to downstream activation of RAS and MAP kinase pathways. This signal transduction pathway drives TAZ-CAMTA1-mediated NIH/3T3 cell transformation. Inhibition of any portion of this pathway inhibits transformation. This pathway is summarized in Figure 2. Preliminary studies have shown that CTGF is produced at high levels and secreted into culture media by cells that express TAZ-CAMTA1.



CTGF is secreted by EHE and can be quantified in plasma from EHE patients using enzyme-link immunosorbent assay (ELISA). If trametinib results in EHE cell death and objective tumor response, we hypothesize that CTGF plasma levels will decline. Alternatively, if trametinib blocks growth of EHE by inhibiting MEK but does not result

in cell death, we expect CTGF plasma levels will remain unchanged because the production and secretion of CTGF is upstream of the RAS and MAP kinase pathways. Additionally, patients with advanced EHE have elevated c-reactive protein levels and erythrocyte sedimentation rate in the blood (unpublished observation) which may be related to tumor production of CTGF. Blood from patients will be obtained prior to starting trametinib, approximately 4 weeks and 6 months after start of treatment with trametinib, and at the time objective tumor response or progression is identified to explore the relationship between trametinib treatment, plasma levels of circulating CTGF, c-reactive protein levels and erythrocyte sedimentation rate. ELISA for CTGF quantification will be performed by a central reference laboratory and CRP and ESR will be determined by local CLIA-certified laboratories using standard methods.

2.4.4 Tumor volume

We hypothesize that a change in volume of EHE will correlate with EHE response to treatment. Analysis of change in tumor volume identified more patients than RECIST 1.1 with response and correlated with survival in a retrospective analysis of Ewing sarcoma treated with anti-insulin-like growth factor therapy (Koshkin et al., 2016). Dr. Lawrence Schwartz has experience in determining tumor volume using Columbia University's semi-automated solid tumor segmentation software (Koshkin et al., 2016). Digital radiology files will be obtained from treating centers and sent to Dr. Schwartz for analysis. Tumor volume will be determined for up to 3 dominant lesions per patient and change in volume over time will be calculated. Tumor response by volume will be compared to response by RECIST 1.1 and correlated with survival. Based on prior studies, increase in tumor volume of 100% or more will be scored as progression and decrease in volume of 45% or more will be scored as response (Koshkin et al., 2016).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. Baseline imaging must be obtained within 30 days of Day 1 of study. See Section 11 for the evaluation of measurable disease.

3.1.2 Patients must have histologically confirmed epithelioid hemangioendothelioma which is metastatic or locally advanced (unresectable), and tumor tissue (paraffin-embedded tissue block or tumor tissue on unstained glass slides) available for fusion FISH analysis at Cleveland Clinic. Patient tumor tissue stored in pathology archives may be used for fusion FISH; a new biopsy is not mandatory.

3.1.3 Patients must have evidence of disease progression per RECIST1.1 prior to enrollment or have evidence of cancer-related pain requiring symptom management with narcotic analgesics.

3.1.4 Because there is no established standard or approved drug therapy for treatment of EHE, patients previously untreated or treated with drug therapy for EHE are eligible. There is no limit on the number of prior regimens used to be eligible.

3.1.5 Age ≥15 years. EHE is very unlikely to arise before the age of 15 years.

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.7 Life expectancy of greater than 6 months.

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

3.1.9 All prior treatment-related toxicities must be CTCAE v5 grade ≤1 (**except alopecia**) at the time of enrollment.

3.1.10 Patients must have normal organ and marrow function as defined below within 2 weeks of patient registration (for blood results) and 30 days of registration for LVEF assessment:

- Absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L
- Hemoglobin ≥9 g/dL, patients may receive transfusion to meet criterion
- Platelets $\geq 75 \times 10^9$/L
- Albumin ≥2.5 g/dL
- Total bilirubin ≤1.5x institutional upper limit of normal (ULN). **NOTE**: patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate in the study
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5x institutional ULN
- Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min *OR* 24-hour urine creatinine clearance ≥50 mL/min
- Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal (LLN) by ECHO or MUGA

3.1.11 Criteria related to reproductive issues.
Trametinib can cause fetal harm when administered to a pregnant woman. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study participation, and for four months after the last dose of the drug. Women of child-bearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and agree to use effective contraception throughout the treatment period and for 4 months after the last dose of study treatment. Should a woman become pregnant or

suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.12 HIV-Patients positive for human immunodeficiency virus (HIV) are NOT excluded from this study, however HIV-positive patients must meet the following criteria:

- A stable regimen of highly active anti-retroviral therapy (HAART)
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
- A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test

3.2 Exclusion Criteria

3.2.1 Prior systemic therapy with a MEK inhibitor

3.2.2 History of another malignancy.
Exception: Patients who have been disease-free for 3 years or patients with a history of completely resected non-melanoma skin cancer and/or patients with indolent secondary malignancies, are eligible. Consult the CTEP Medical Monitor if unsure whether second malignancies meet the requirements specified above.

3.2.3 History of interstitial lung disease or pneumonitis requiring supplemental oxygen or treatment with oral or intravenously administered corticosteroids.

3.2.4 Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity (e.g. doxorubicin), biologic therapy, or immunotherapy within 21 days prior to enrollment and/or daily or weekly chemotherapy (e.g. sunitinib, sorafenib and pazopanib) without the potential for delayed toxicity within 14 days prior to enrollment.

3.2.5 Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of trametinib and during the study.

3.2.6 Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression.

3.2.7 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trametinib, or excipients or to dimethyl sulfoxide (DMSO).

3.2.8 Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:
- Other anti-cancer therapy while on study treatment. (note: megestrol [Megace] if used as an appetite stimulant is allowed).
- Concurrent treatment with bisphosphonates is permitted; however, treatment must be

initiated prior to the first dose of study therapy. Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.
- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

3.2.9 History or current evidence/risk of retinal vein occlusion (RVO).

3.2.10 History or evidence of cardiovascular risk including any of the following:
- A QT interval corrected for heart rate using the Bazett's formula QTcB ≥480 msec.
- History or evidence of current clinically significant uncontrolled arrhythmias (Exception: patients with controlled atrial fibrillation for >30 days prior to randomization are eligible).
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to randomization.
- History or evidence of current ≥ Class II congestive heart failure as defined by the New York Heart Association (NYHA) functional classification system.
- 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.
- Patients with intra-cardiac defibrillators.
- Known cardiac metastases.

3.2.11 Known Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (patients with chronic or cleared HBV and HCV infection are eligible).

3.2.12 Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.

3.2.13 Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception. If a female patient or a female partner of a patient becomes pregnant while the patient receives trametinib, the potential hazard to the fetus should be explained to the patient and partner (as applicable).

3.2.14 Inability to comply with protocol-required procedures.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Epithelioid hemangioendothelioma is slightly more prevalent in females than males. There is no known predilection of the disease for a particular race or ethnic background. The study is open to eligible males and females of all races and ethnicity and enrollment will not discriminate on the basis of race or ethnicity. Because of the rarity of locally advanced or metastatic EHE and the need to complete accrual to the trial in a timely manner, patients will be enrolled as they consent and are determined to be eligible to participate. The study will not target enrollment to meet a predefined goal for accrual for any particular gender, race or ethnicity.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions about Investigator Registration, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order

for the SSW approval to the processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *NCI protocol #10015* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or click on the By Lead Organization folder to expand, then select *EDDO-MI014*, and protocol #*10015.*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For #*10015* Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, and IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal(Note: The use of the Regulatory Submission Portal will become **mandatory** in early 2017)
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration tab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with RIB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 Patient Enrollment Instructions

The SARC Research Project Manager (RPM) must be notified before patients are consented and begin eligibility screening for enrollment in the study. The RPM may be notified by phone: 734-930-7600, fax: 734-930-7557, or email: SARC033@sarctrials.org. The SARC RPM will inform the site if an enrollment slot is available based on the total number of patients with *TAZ-CAMTA1* gene fusion positive EHE enrolled in the trial. Patients must not be consented until the site has been informed that an enrollment slot is available. An enrollment slot will only be opened (made available) if a patient enrolled in the trial and started on trametinib does not have *TAZ-CAMTA1* gene fusion positive EHE confirmed after testing by FISH at the central/reference laboratory. After obtaining patient consent, the site should provide the SARC RPM the date informed consent was obtained, patient initials, patient age, and whether the patient has agreed to participate in the optional tumor biopsies for research. This information will be used by the SARC office to track enrollment and assist sites with shipment of the biologic samples for the correlative research studies.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Trametinib

Trametinib 2 mg will be taken orally once daily with a cycle length of 28 days. The effect of food on trametinib absorption is unknown. The current recommendation is to administer trametinib on an empty stomach, 1 hour before or 2 hours after a meal; the recommendation to administer trametinib on an empty stomach may change based on

emerging data. Patients will be instructed to take the medication at approximately the same time each day with a full glass of water. If a dose is missed, the patient will be instructed to take it as soon as they remember. If the next scheduled dose is within 12 hours, they will skip the missed dose. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary should be returned to and/or reviewed by clinic staff at each scheduled clinic visit during the course of treatment.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Trametinib	Take 1 or more hours before or 2 or more hours after food. Take with at least 8 ounces of water	2 mg	PO	once daily	28 days (4 weeks)

5.2 Definition of Dose-Limiting Toxicity
Not Applicable

5.3 Dose Expansion Cohorts
Not Applicable

5.4 General Concomitant Medication and Supportive Care Guidelines

Routine supportive care for management of nausea, anorexia, diarrhea, rash and hypertension are allowed. Additional supportive care recommendations are provided below in section 6. Trametinib is highly bound to plasma proteins (97.3%) and has the potential to interfere with other highly protein-bound drugs. Use caution in patients taking concomitant drugs that are highly protein-bound and have narrow therapeutic ranges. Trametinib is an in vitro inhibitor of CYP 2C8, 2C9, 2C19 and is anticipated to have overall low potential for drug interactions. It is also a weak CYP 2B6 and 3A4 inducer and expected to have little clinical effect on sensitive substrates.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 52 cycles or until one of the following criteria applies:

- Disease progression per RECIST,
- Clinical progression,
- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients with clinical progression or disease progression per RECIST who are benefitting from trametinib in reduction of tumor-related symptoms may continue on treatment with trametinib after discussion with the Study PI and CTEP Medical Monitor and approval.

5.6 Duration of Follow Up

Patients will be followed for 24 months after initiation of trametinib unless the patient remains on active treatment beyond 24 months. In that case, follow-up will be continued until 6 months after discontinuation of treatment or until death, whichever occurs first. If the patient discontinues therapy prior to 24 months, follow-up will continue for 6 months after discontinuation or 24 months after initiation of trametinib, whichever is longer. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study if they decide to withdraw from the study or die. Patient participation in the study will conclude when they complete study follow-up described in section 5.6. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Trametinib Dose Modifications

The table below outlines the dose levels to be used for any necessary trametinib dose modifications:

Dose Level	Trametinib Dose/Schedule
0	2 mg once daily
-1	1.5 mg once daily
-2	1 mg once daily

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

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

Dose modification and AE guidelines are outlined in the sections below for AEs that are deemed possibly related to trametinib:

- AEs not otherwise specified
- Rash
- Visual changes
- Diarrhea
- Liver chemistry elevation
- Ejection fraction changes
- Hypertension
- Prolonged QTc
- Pneumonitis

6.1.1 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

<table>
<tr><th colspan="3">Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib
(This section is <u>not</u> for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, or visual changes. Refer to <u>other</u> sections for these specific AEs).</th></tr>
<tr><th>CTCAE v5 Grade</th><th>Management Guideline</th><th>Dose Modification</th></tr>
<tr><td>Grade 1</td><td rowspan="4">Monitor as clinically indicated.
Provide supportive care according to institutional standards.</td><td>Continue trametinib at current dose level.</td></tr>
<tr><td>Grade 2 (tolerable)</td><td>• Interrupt treatment until resolution to grade 1 or baseline.
• Upon resolution, restart treatment at current dose level.</td></tr>
<tr><td>Grade 2 (intolerable) and Grade 3</td><td>• 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.</td></tr>
<tr><td>Grade 4</td><td>If event resolves to grade 1 or baseline discuss potential continuation of trametinib with Medical Monitor; if continuation of treatment agreed then restart trametinib at dose reduced by one dose level.
If event does not resolve, permanently discontinue trametinib.</td></tr>
<tr><td colspan="3">Trametinib should be discontinued if treatment delay is <u>≥</u>21 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the study chair and CTEP Medical Monitor may be consulted for the possibility of resuming trametinib, provided that toxicities have resolved to baseline or grade 1.</td></tr>
</table>

6.1.2 Trametinib Dose Modification for <u>Rash</u>

Rash is a frequent AE observed in patients receiving trametinib (Investigator's Brochure, 2012a). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors (Balagula *et al.*, 2010; Lacouture *et al.*, 2011).

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 study chair or the CTEP Medical Monitor may be required.

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 antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.
[a] Rash prophylaxis is recommended for the first 6 weeks of study treatment. [b] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Trametinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level**.[3]

Trametinib Dose Modification Guidelines and Management for Rash		
Rash Severity	**Management Guideline**	**Dose Modification**
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ grade 1. • **Restart trametinib at reduced dose level**.[3]
Grade ≥3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt trametinib until rash recovers to ≤ grade 1. • **Restart with trametinib reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 4 weeks, **permanently discontinue trametinib**.
1. Rash prophylaxis is recommended for the first 6 weeks of study treatment. 2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream. 3. Approval of CTEP Medical Monitor is required to restart study treatment after >4 weeks of interruption. 4. Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

6.1.3 Trametinib Dose Modifications 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 the table below.

Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings		
Event CTCAE Grade	**Management Guideline**	**Dose Modification**
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold 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/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 or RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the CTEP Medical Monitor. • **If RVO or RPED, permanently discontinue trametinib**.
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

Trametinib Dose Modification for RPED	
Event 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 with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

6.1.4 Trametinib Dose Modification for Diarrhea

Episodes of diarrhea have occurred in patients receiving trametinib (Investigator's Brochure, 2012a). Other frequent causes of diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by C. difficile or other pathogens, or partial bowel obstruction should be clinically excluded.

Guidelines regarding management and dose modification for diarrhea considered related to trametinib are provided in the table below.

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] 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[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hous: Loperamide 2 mg every 2 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 > 48 h, interrupt trametinib until diarrhea resolves to grade ≤1. • Restart trametinib at the same dose level • If treatment delay is >4 weeks, discontinue trametinib.

Management and Trametinib Dose Modification Guidelines for Diarrhea		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 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.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**. • If treatment delay is >4 weeks, discontinue trametinib.
1. **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. 2. **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. 3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea. 4. Escalation of trametinib to previous dose level is allowed after consultation with the medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.		

6.1.5 Trametinib Dose Modification for Liver Chemistry Changes

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).
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]	• Immediately discontinue study treatment. • Do not restart/rechallenge unless approved by CTEP trametinib medical monitor. • 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

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
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 5. ALT ≥3x ULN and cannot be monitored weekly for 4 weeks 6. ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	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] • If possible, obtain blood sample for PK analysis.[5] • 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 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.[6] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.
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	

Trametinib Dose Modification for Liver Function Test Abnormalities	
Event	**Treatment modifications and assessment/monitoring**
unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody 5. PK sample is desired if feasible. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. 6. 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).	

6.1.6 Trametinib Dose Modification for Pneumonitis

Pneumonitis has been observed in patients receiving trametinib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms and evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described in the tables below.

Pneumonitis Guidelines for Trametinib Monotherapy		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • 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. • 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	• **Permanently discontinue trametinib if pneumonitis is related to treatment.**
Grade 3	• Same as grade 2	• **Permanently discontinue trametinib**
Grade 4	• Same as grade 2	• **Permanently discontinue trametinib**

6.1.7 Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHO/MUGAs must be performed in regular intervals outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s).

Trametinib 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 CTEP trametinib medical monitor 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 CTEP trametinib medical monitor.[c]
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib**. • **Report as SAE**. • **Consult with cardiologist**. • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.
[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 CTEP trametinib medical monitor is required. [c] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

6.1.8 Trametinib Dose Modification for QTc Prolongation

Trametinib Withholding and Stopping Criteria for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥501 msec, or • Uncorrected QT >600 msec, or • QTcB >530 msec for subjects with bundle branch block	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level.[b] • **If the event does not resolve or recurs after restarting, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTcB = QT interval on electrocardiogram corrected using 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 CTEP trametinib medical monitor agree that the subject will benefit from further treatment.	

6.1.9 Trametinib Dose Modification for 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.

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 Medical Monitor is required.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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

The Comprehensive Adverse Event 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 via CTEP-AERS (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 (GSK1120212B).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, October 10, 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		
GASTROINTESTINAL DISORDERS			

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%)**	
	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		
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)***

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%)**	
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 (drug reaction with eosinophilia and systemic symptoms [DRESS])	
Skin and subcutaneous tissue disorders - Other (rash)[5]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***
		Stevens-Johnson syndrome[6]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[7]		

[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, rash acneiform, 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]Stevens-Johnson syndrome has been observed in patients treated with trametinib and dabrafenib combination.

[7]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[7]; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage[7]; 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[7]; Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage[7]; 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[7]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage[7]; 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.

7.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not Applicable

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported**

expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported to SARC033@sarctrials.org.

Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required – to be determined by SARC.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Trametinib dimethyl sulfoxide (GSK1120212B) (NSC 763093)

Chemical Name (IUPAC): equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl}phenyl)acetamide with (methylsulfinyl)methane

Other Names: trametinib, GSK1120212, MEKINIST™, JTP-74057, JTP-78296, JTP-75303

CAS Registry Number: 1187431-43-1

Classification: MEK inhibitor

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$

M.W.: 693.54 (dimethyl sulfoxide solvate), 615.41 (anhydrous parent)

Approximate Solubility: Trametinib dimethyl sulfoxide is almost insoluble in water (<0.0001 mg/mL at 25° C)

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.

Description: Trametinib dimethyl sulfoxide is a white to almost white powder.

How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes 0.5 mg and 2 mg (as free base) tablets. Each investigationally-labeled bottle contains 32 tablets.
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. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.
- 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

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

If a storage temperature excursion is identified, promptly return trametinib to 2ºC -8ºC

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: Stability studies are ongoing. Tablets are only stable for 32 days once bottle has been opened. If multiple bottles are dispensed to a patient in the same visit, please advise the patient to open only one bottle at a time.

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.

Potential Drug Interactions

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). Trametinib is a substrate for P-gp and BSEP, but this is not expected to be clinically relevant due to trametinib's high permeability..

Trametinib dimethyl sulfoxide is an *in vitro* inhibitor of CYP 2C8, 2C9, 2C19 and is anticipated to have overall low potential for drug interactions as a perpetrator. It is also a weak CYP 2B6 and 3A4 inducer and expected to have little clinical effect on sensitive substrates. Trametinib is not an inhibitor of CYP 1A2, 2A6, 2B62D6 and 3A4 and not an inhibitor of MRP2 or BSEP, but an in vitro inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1. No clinically relevant inhibition by trametinib is predicted in the liver or kidney and a low risk of intestinal drug-drug interaction is possible with BCRP.

Trametinib is highly bound to plasma proteins (97.3%) and has the potential to interfere with other highly protein-bound drugs. Use caution in patients taking concomitant drugs that are highly protein-bound and have narrow therapeutic ranges.

Patient Care 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. Refer to the protocol document for specific guidance.

Availability

Trametinib dimethyl sulfoxide (GSK1120212B) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Trametinib dimethyl sulfoxide (GSK1120212B) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent 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). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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.

Starter supplies are not being provided. Subjects must be enrolled prior to submitting the clinical drug request in OAOP.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests 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 and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.2.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx

- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

8.1.2.4 Investigator Brochure Availability

The current versions of the IBs for the 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 and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Integral Laboratory or Imaging Studies

None.

9.2 Integrated Studies

9.2.1 Evaluate tumor for presence of *TAZ-CAMTA1* gene fusion by fluorescence in-situ hybridization.

9.2.1.1 FISH for *TAZ-CAMTA1* gene fusion

The presence of *TAZ-CAMTA1* gene fusion may be detected by fluorescence in situ hybridization (FISH) or polymerase chain reaction. FISH probes have been developed using a red fluorophore to the 5' end of *TAZ (WWTR1* gene) and a green fluorophore to the 3' end of *CAMTA1* gene. Cells containing translocation of *TAZ (WWTR1*) on chromosome 3 with *CAMTA1* on chromosome 1 can be detected by fusion of the red and green fluorescent signals in nuclei. After processing tissue for FISH, at least 50 nuclei will be examined. Tumor with at least 10% of the nuclei containing a fused signal will be scored as containing the *TAZ-CAMTA1* translocation.

9.2.1.2 Collection of Specimen(s)

The registering site should submit the required specimen for FISH within 2 weeks of patient registration/enrollment. Formalin-fixed, paraffin-embedded archival tumor tissue may be submitted for FISH analysis. Tissue may be from core needle biopsy or excision of an EHE lesion. An adequate amount of tissue should be available to produce 12 slides containing 4 micron thick sections of tumor tissue for FISH and at least 1 slide for hematoxylin and eosin staining. Sites may submit 1 H&E stained slide of representative tumor tissue and either 12 slides containing four micron-thick unstained tumor sections or a paraffin block containing tumor tissue. Unstained sections should be placed on charged

slides and NOT baked.

9.2.1.3 Handling of Specimens(s)
Routine handling of patient tissue at ambient room temperature.
Tumor block and/or slides will be shipped to:

Cleveland Clinic
Department of Pathology
ATTN: Dr. Brian Rubin
2119 East 93rd Street, L15
Cleveland OH 44106
Contact: Barbara Bailey or Brian Rubin (216)445-5551

Notification of shipment should be sent to SARC RPM at SARC033@sarctrials.org

9.2.1.4 Site performing integrated study

Cleveland Clinic CLIA-certified FISH laboratory

9.3 Exploratory/Ancillary Correlative Studies

9.3.1 Plasma Connective Tissue Growth Factor (CTGF) Level
Plasma CTGF levels may be a useful biomarker of EHE survival as CTGF is a secreted protein whose gene is an immediate downstream target of TAZ-CAMTA1 (Tanas et al., 2016). CTGF is secreted and binds to αIIbβ3 integrin on the cell surface, leading in an autocrine fashion to downstream activation of RAS and MAP kinase pathways. This signal transduction pathway drives TAZ-CAMTA1-mediated NIH/3T3 cell transformation. Inhibition of any portion of this pathway inhibits transformation. Preliminary studies have shown that CTGF is produced at high levels and secreted into culture media by cells that express TAZ-CAMTA1. CTGF is expressed in human EHE as demonstrated by anti-CTGF western blot of patient tumor lysates. CTGF is secreted by EHE and can be quantified in plasma from EHE patients using standard ELISA. Fibrogen (San Francisco) has supplied a CTGF-specific monoclonal antibody to CTGF that performs well in ELISA. If trametinib results in EHE cell death and objective tumor response, we hypothesize that CTGF plasma levels will decline. Alternatively, if trametinib blocks growth of EHE by inhibiting MEK but does not result in cell death, we expect CTGF plasma levels will remain unchanged.

9.3.1.1 Collection of Specimen(s)
Samples (3-5 mL blood) will be obtained prior to treatment, after 4 weeks and 6 months (in patients with stable or better disease) of treatment, at the time of objective tumor response and upon determination of EHE radiologic or clinical progression.

9.3.1.2 Handling of Specimens(s)
Blood will be drawn in sodium or potassium-EDTA collection tubes and processed

within 60 minutes of collection. After collection of blood into collection tubes, the tubes should be gently inverted 4-6 times to ensure proper mixing of blood with EDTA. The tubes should be centrifuged at 1,000 – 2,000 x gravity at 4 degrees centigrade for 15-20 minutes to separate plasma. After centrifugation, 1-2 mL of plasma should be removed using a clean pipet and placed into two 1.5 mL Eppendorf (or similar) collection vials, labeled with the date of collection, patient ID and study ID or similar specimen tracking information and immediately frozen at -80ºC. Specimens should be stored frozen at -80ºC or colder until shipped on dry ice.

9.3.1.3 Shipping of Specimen(s)

Samples should be batched for shipping. The site may batch all aliquots from each time point from each study participant in one shipment to avoid unnecessary shipping expense. Samples must be kept frozen and shipped on dry ice via overnight delivery service for arrival to the laboratory on Monday through Friday. Samples should not arrive on Saturday, Sunday or recognized Federal holiday. Samples should be sent to:

Lisa Denero
Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA 1340
Columbus OH 43205
Phone: 614-355-2799

Notification of shipment should be sent to SARC RPM at SARC033@sarctrials.org

9.3.1.4 Site(s) Performing Correlative Study

Dr. Brian Rubin's research laboratory at Cleveland Clinic.
Department of Pathology
2119 East 93rd Street, L15
Cleveland OH 44106

9.3.2 Assessment of MAP kinase pathway signaling

In pre-clinical studies, NIH/3T3 cells stably expressing the *TAZ-CAMTA1* gene fusion were grown in suspension and the MAPK pathway was examined. NIH/3T3 cells containing empty vector were used as control. Phospho-ERK, which is emblematic of MAPK pathway activation was sustained in TAZ-CAMTA1 expressing cells while cells expressing vector alone lost ERK phosphorylation over time. This suggests that TAZ-CAMTA1 maintained MAPK activation. Furthermore, phospho-ERK has been detected in protein lysates of snap-frozen EHE tumor samples and localized phospho-ERK in EHE tumor cells by immunohistochemistry with a phospho-specific anti-ERK antibody which demonstrated strong activation specifically in tumor cells. We hypothesize that tumor responses to clinically administered doses of trametinib will be accompanied by suppression of the MAPK pathway signaling.
Formalin-fixed paraffin-embedded samples will undergo quality review by the SARC SPORE Pathology core and tumor tissue will be analyzed for ERK phosphorylation by

semi-quantitative immunohistochemistry using phospho-ERK (Thr202/Tyr204)-specific antibody (Cell Signaling #4370) and quantitative immunochemistry by AQUA. If ERK is no longer suppressed in tumor progression, MEK 1/2 will be sequenced to identify genetic mechanisms of resistance. Frozen tumor tissue will be reserved for primarily for protein studies of intracellular protein kinase signaling studies, if needed. For example, if IHC suggests that ERK is inhibited, then the snap frozen tissue will be used to make protein lysates for phospho-proteomic arrays (R&D systems) which will provide a panel of anti-phospho-protein antibodies targeting proteins involved in a variety of intracellular signaling pathways to identify activation of alternative signaling pathways that mechanistically could drive progression.

9.3.2.1 Collection of Specimens

Optional tumor biopsy will be performed prior to starting trametinib and after approximately 4 weeks of trametinib treatment (+/- 7 days), and upon progression in patients who previously had objective tumor response. It is encouraged that biopsies be performed to collect tumor tissue for correlative research studies to evaluate the effect of trametinib on MEK signaling. Patients will be provided the option of participating in biopsy of tumor prior to treatment an on treatment with trametinib. If treatment is interrupted in a patient, the biopsy should be delayed until drug is restarted and taken daily for at least 7 days. At a minimum, biopsy should consist of 4 core biopsies using 14 to 16 gauge needles at least 8-10 mm in length. Two core biopsies should be immediately placed in formalin and processed using standard methods in paraffin for standard immunohistochemistry. The remaining cores should be immediately flash frozen in liquid nitrogen or embedded in OCT (optimal cutting temperature) compound and frozen at -80 degrees Celsius.

9.3.2.2 Handling of Specimens

Paraffin-embedded samples should be labeled with date of biopsy, subject ID and Study ID and kept at ambient temperature. Tissue frozen in liquid nitrogen should be kept frozen in an Eppendorf (or similar) clean collection vial labeled with the date of biopsy, subject ID and study ID and stored at -80 degrees Celsius until shipped to Cleveland Clinic on dry ice.

9.3.2.3 Shipping of Specimens

Paraffin-embedded samples should be shipped at ambient temperature. Frozen samples may be batched for shipping. The site may batch all frozen tissue biopsies from each time point from each study participant in one shipment to avoid unnecessary shipping expense. Samples must be kept frozen and shipped on dry ice via overnight delivery service for arrival to the laboratory on Monday through Friday. Samples should not arrive on Saturday, Sunday or recognized Federal holiday. Samples should be sent to:

Lisa Denero
Biopathology Center
Nationwide Children’s Hospital
700 Children’s Drive, WA 1340

Columbus OH 43205

Notification of shipment should be sent to SARC RPM at SARC033@sarctrials.org

9.3.2.4 Sites Performing Correlative Study
Dr. Brian Rubin's research laboratory, Cleveland Clinic
Department of Pathology
ATTN: Dr. Brian Rubin
2119 East 93rd Street, L15
Cleveland OH 44106

9.4 Special Studies

9.4.1 Tumor Volume

9.4.1.1 Measure: Change in volume of EHE on treatment with trametinib. In a retrospective analysis, a change in tumor volume identified more patients than RECIST 1.1 with response and correlated with survival in a prospective trial of Ewing sarcoma treated with anti-insulin-like growth factor. We will assess changes in tumor volume over time, compare this to response by RECIST 1.1 criteria and correlate with survival. An increase in tumor volume of 100% or more will be scored as progression and decrease in volume of 45% or more will be scored as response.

9.4.1.2 Assessment

9.4.1.2.1. Sites of tumor will be imaged by CT or MRI using standard protocols.

9.4.1.2.2. Imaging tumor will occur within 30 days prior to starting drug, after cycles 2, 4 and 6 and thereafter approximately every 12 weeks. For patients will evidence of disease progression prior to enrollment, CT or MRI scans documenting progression will also be reviewed.

9.4.1.3 Data Recording

9.4.1.3.1. The TRIAD software anonymizes, encrypts and validates the images as they are transferred. Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account. To submit images, the site TRIAD user must be on the site's affiliate rosters and be assigned the TRIAD site user role on the CTSU roster. Users should contact the site's CTSU Administrator of Data Administrator to request assignment of the TRIAD site user role. After the user receives a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be

able to submit the image files. TRIAD installation documentation can be found at the link https://triadinstall.acr.org/triadclient/. This process can be done in parallel to obtaining the CTEP-IAM account username and password. If you have questions regarding this information, please send an email to the TRIAD Support mailbox at TRIAD-Support@acr.org. For support with the TRIAD application, please send an email to TRIAD-Support@ACR.org. Participating sites that are unable to use or access TRIAD may submit digital images through QARC's secure FTP site or in DICOM files on CD/DVD. For questions regarding diagnostic imaging submission, please contact SARC@QARC.org or 401-753-7600.

9.4.1.3.2. Timing of Recording. Sites will submit images of CT or MRI obtained prior to starting trametinib within 4 weeks after enrollment. Sites will submit images of CT or MRI performed during the treatment period within 4 weeks of completion of the radiology scan.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to patient registration. Tumor imaging, cardiac evaluation and ophthalmology evaluations must be done within 30 days prior to patient registration. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The window for cycle visits is +/- 7 days.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk[i] 12	Off Treatment
Trametinib Daily		A	A	A	A	A	A	A	A	A	A	A	A	
Informed consent	X													
Archival tumor tissue sent for TAZ-CAMTA1 FISH	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------X												
Physical exam	X	X		X		X				X				X
Vital signs	X	X				X				X				X
Height	X													
Weight	X	X				X				X				X
Performance status	X	X				X				X				X
CBC w/diff, plts	X	X		X		X				X				X
Serum chemistry[a]	X	X		X		X				X				X
ESR, CRP[b]	X					X								
Plasma collection for CTGF[b]	X					X								
EKG	X													
Echocardiogram or MUGA[c]	X	Every 12 weeks (+/- 14 days) (use same methodology for baseline and follow up).												
Ophthalmology exam[d]	X													
Adverse event evaluation		X----------X												X
Tumor measurement[e]	X	Tumor measurements are repeated every 8 weeks (± 7 days) for first 24 weeks, then every 12 weeks (± 7 days). Digital files of radiology images sent to QARC.												X
Radiologic evaluation[f]	X	Radiologic measurements should be performed every 8 weeks (± 7 days) for first 24 weeks, then every 12 weeks (± 7 days).												X
Pregnancy test[g]	X													
Optional fresh biopsy of tumor	X				X									
NIH PROMIS Questionnaire[h]	X				X									

A: Trametinib: Dose as assigned; to be taken daily

a: Comprehensive metabolic panel. The panel should include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

b: Biomarker assessment: ESR-westergren method preferred and CRP, to be performed by local lab prior to therapy, after 4 weeks and 6 months of treatment (for patients with stable for better disease), at time of objective response and at progression. Plasma for

determination of CTGF level to be obtained at the same time points and sent to central lab for analysis.

c: The same modality (ECHO or MUGA) should be used at baseline and at follow-up

d: Ophthalmology exams should be obtained at baseline, and if clinically indicated, during study. Opthalmology exam should include Ocular Coherence Tomography, fundoscopy, tonometry, visual field examination, and corrected visual acuity assessments.

e: Tumor digital files to be sent to QARC for tumor volume assessment.

f: Tumor measurements do not need to be repeated if patient ends treatment because of documented tumor progression by imaging.

g: Blood or urine pregnancy test (women of childbearing potential).

h: NIH PROMIS global health, pain intensity, interference and behavior short form inventories to be obtained prior to trametinib treatment, after 1 month and 6 months of treatment, and on evidence of disease progression or response.

i: For patients remaining on treatment after week 12, evaluations will include physical exam, weight, performance status, complete blood count with differential and platelet count, and serum chemistry at least once per cycle.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (± 7 days) for the first 24 weeks, then every 12 weeks (± 7 days). In addition to a baseline scan, confirmatory scans should also be obtained 4 to 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

11.1.1 Definitions

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

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

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable only if demonstration of progression of the lesion has occurred following radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]) or MRI. At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the

beginning of treatment and never more than 30 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers are not available for EHE and cannot be used to assess response.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Confirmation is required in this protocol.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of

treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

CT and MRI scans performed to document patient tumor progression prior to study enrollment and response to treatment with trametinib will be electronically sent via TRIAD to IROC Rhode Island (QARC). Digital images will be transferred to Dr. Lawrence Schwartz at Columbia University for review and independent assessment of tumor response. The decision to continue a patient on treatment with trametinib will be based on the treating investigator or site assessment of tumor response.

11.2 Antitumor Effect – Hematologic Tumors N/A

11.3 Other Response Parameters – N/A

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the study, the SARC office will help monitor patient enrollment, treatment and adverse events including reasons for discontinuation of treatment. A running list of patient accrual, duration of therapy, reason for drug discontinuation and SAEs will be maintained and reviewed during the conference calls. Any unexpected AEs that are felt to be clinically significant will also be reviewed. SARC Clinical Trials review calls occur monthly with the study PI, SARC medical officer, study statistician and SARC staff. This process is standard for all SARC clinical trials. The Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Site Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of the Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the

appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

*For studies assigned for **CTMS Routine** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines - N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can

Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the

Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

Not applicable.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint is the objective response rate using RECIST 1.1. Tumor response assessed by the local site investigator or delegate will be used to assess the objective response rate. Tumor response will be centrally reviewed by Dr. Lawrence Schwartz but the local site assessment will be used to determine patient treatment and tumor response outcome.

A Simon minimax sampling two-stage design will be used to estimate the objective response rate with a goal of at least 20% of patients to be considered as having preliminary evidence of activity and less than 5% indicating that trametinib is ineffective as a potential EHE treatment. Thirteen patients with EHE will be enrolled in stage I, and if there is at least one objective response as defined by RECIST 1.1, additional patients with EHE will be enrolled until 27 patients with EHE in which *TAZ-CAMTA1* translocation is detected by fusion FISH in archival tumor tissue have been registered and started treatment. The diagnosis of EHE will be determined by the local site, but the presence of *TAZ-CAMTA1* translocation will be determined by the Cleveland Clinic FISH laboratory. If four or more objective tumor responses are documented among 27 patients with *TAZ-CAMTA1* translocation positive EHE, trametinib will be considered to have activity in EHE. With a type 1 error of 5%, this design will have a power of approximately 80% and will have a 51% probability of terminating after the first step if the response rate is 5%. The ORR, 6-month PFS and 2-year OS rates will be calculated along with their 95% confidence intervals. PFS and OS will be estimated by the Kaplan-Meier method.

In stage I enrollment, the presence of *TAZ-CAMTA1* translocation was not detected in 3 tumor samples and in one case there was insufficient tumor tissue available for the analysis. The rate of *TAZ-CAMTA1* translocation negative EHE is higher than the expected rate of less than 10%, and because we anticipate activation of the MAP kinase pathway to occur in tumor with expression of TAZ-CAMTA1 but not in tumor without the translocation, the protocol is amended to enroll at least 27 patients with EHE containing *TAZ-CAMTA1* translocation.

Secondary objectives of the 6-month PFS rate, median PFS, and 2-year OS rate will be determined from analyses of patients with *TAZ-CAMTA1* translocation positive EHE. Evaluation of the safety of trametinib, and patient reported symptoms using NIH-PROMIS questionnaires will be determined from analyses of all patients who started treatment with trametinib.

Progression-free survival will be calculated from time of first dose of study medication to occurrence of radiologic tumor progression per RECIST1.1, clinical progression based on treating physician's assessment or death from any cause. Overall survival will be calculated from the time of first dose of study drug to occurrence of death from any cause. Patients who are registered and are determined to be eligible for study treatment but do not start study drug will be replaced. All patients who receive study drug for any period of time will be evaluable for toxicity. The rates of adverse events occurring in at least 5% of subjects and rates of grade 3-5 adverse events will be tabulated by system and term using Common Terminology Criteria of Adverse Events (CTCAE). For dose adjustment schedule see Section 6.1. PROMIS questionnaires will be scored according to recommended standardized system and t-scores generated. A mixed model will be used to analyze change in t-scores over time. Whether or not having evidence of disease progression will be used as a time-dependent variable in the mixed model with adjustment of other potential confounding variables.

13.2 Sample Size/Accrual Rate

This study will be conducted in a two-stage process. In stage I, 13 patients with EHE will be enrolled. If there is at least 1 objective response, additional patients will be enrolled in stage II until there is evidence that a total of 27 patients with EHE with *TAZ-CAMTA1* translocation detected by fusion FISH have been registered and started treatment. After 27 patients have been enrolled and started treatment, enrollment of additional patients will be held until FISH testing is performed on available tissue from the enrolled patients. One enrollment slot will be opened for each case of FISH result of *TAZ-CAMTA1* translocation "not detected", "test failed", or "test not performed" (no tumor tissue in sample) until a total of 27 patients have enrolled and started treatment with FISH result of *TAZ-CAMTA1* translocation "detected". Enrollment in the second stage will be held until at least 1 objective response has occurred. Enrollment for stage I is anticipated to be complete within the first 12 months of study activation. Enrollment for stage II is anticipated to be complete within 18 months of proceeding to stage II. We anticipate that on average, 1 patient per month will be accrued to the study. The study is open to all eligible persons at least 15 years of age. Because of the very rare nature of the disease under study, we will not restrict enrollment based on sex, race or ethnicity in order to complete accrual within 2-3 years.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	3	2	0	0	**5**
White	9	6	2	1	**18**
More Than One Race	1	1	0	0	**2**
Total	**14**	**10**	**2**	**1**	**27**

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13.3 Stratification Factors

None.

13.4 Analysis of Exploratory Endpoints

Exploratory correlative studies will evaluate rates of EHE growth prior to starting trametinib to growth rates on treatment, the change in c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), plasma connective tissue growth factor (CTGF) and tumor volume as potential biomarkers of EHE activity, and the effect of trametinib on MAP kinase activation.

Digital files of cross-sectional radiology images (CT and MRI) will be provided to Lawrence Schwartz (Columbia University, NY) to evaluate the change in rate of EHE growth pre-trametinib therapy and on trametinib. Evidence of tumor progression per RECIST will be required for enrollment of patients (except in setting of severe tumor-related pain); therefore, longitudinal pre-treatment radiology images will be available in the majority of cases for comparison. A 50% or more reduction in the change in tumor size/unit of time following start of treatment with trametinib will be considered clinically significant. McNemar test will be used to compare the number of patients with EHE progression prior to starting trametinib to the number

of patients with EHE progression during treatment.

Patient CTGF samples collected at indicated time points will be run in triplicate and average values used for the comparison. The CTGF, CRP and ESR levels over time will be used as time-dependent variables in a Cox model to determine the association with EHE survival.

The agreement of change in tumor volume and in tumor size assessed by RECIST will be summarized with a scatterplot. The Pearson correlation coefficient (or Spearman, if more appropriate) will be assessed to determine the strength of the agreement. Agreement of the tumor classifications (response versus no response) will be summarized as the raw agreement and with a Kappa Statistic. The association of the change in tumor volume with survival will be evaluated in two ways. The first will be to use the change in tumor volume as a time dependent variable in a Cox model. The second will be a landmark analysis (done at either the first radiographic assessment or at the second radiographic assessment) to compare the survival of patients classified as a responder (based on tumor volume) to those who have not responded by the selected landmark time. Patients who died prior to the landmark time point will be omitted from analysis.

Evaluation of MAP kinase activation is an exploratory analysis on relatively few samples. In another multicenter SARC phase II clinical trial (SARC028) that required paired pre-treatment and on-treatment tumor biopsy, matched samples were obtained in 75% of the cases and tumor biopsy was performed in about 50% of patients at the time of progression. We estimate a similar success rate in obtaining matched tumor tissue. Descriptive statistics will be generated, and estimates for the proportion of samples with demonstrated inhibition of MAPK signaling post-treatment compared to pre-treatment will be generated along with 95% confidence intervals. Likewise, the proportion of patients with demonstrated MAPK signaling inhibition at time of disease progression will be determined with the corresponding 95% confidence interval. These are exploratory analyses and all available data will be used.

Evaluation of presence of *TAZ-CAMTA1* gene fusion will be performed by FISH. Tumor in which at least 10% of nuclei are scored as having a fused signal will be counted as EHE with presence of *TAZ-CAMTA1* translocation. The number and percent of *TAZ-CAMTA1* gene fusion positive EHE will be reported.

13.5 *For phase 2 protocols only:* **Reporting and Exclusions**

13.5.1 Evaluation of Toxicity

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

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be

assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria and took at least 1 dose of trametinib will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX C BIOASSAY TEMPLATES

*If the protocol includes any **integral** biomarker studies using* in situ *hybridization (ISH), immunohistochemistry (IHC), and/or DNA-based mutation assays, you may fill out the appropriate template (found at http://www.cancerdiagnosis.nci.nih.gov/diagnostics/templates.htm) and attach to this protocol submission as separate Appendices.*

If the laboratory or laboratories performing the studies has an alternatively-formatted document that supplies the same level of information regarding validation, materials and methods, etc*., it may be used instead of the templates.*

Not applicable

APPENDIX D SARC033 STUDY DRUG DIARY PATIENT INITIALS: _____ SUBJECT STUDY ID# _____

- Please complete this chart each time you take study drug.
- Trametinib should be taken at approximately the same time each day.
- Each dose should be taken on an empty stomach everyday approximately1 hour before or 2 hours after a meal with a full glass of water.
- If you forget to take your dose at the scheduled time, please take as soon as you remember. If the next scheduled dose is within 12 hours, please skip the missed dose.
- If you vomit your dose of trametinib, do not take that dose again. Mark the vomited dose in this diary. Take the next day's dose as
- schedule.
- Bring any unused trametinib, all containers (empty and full), and this diary to each clinic visit.
- The study staff will make sure you have an adequate supply of drug to take home at the end of each clinic visit.
- You must inform the study doctor of any medication you take (prescription, or over-the-counter).
- You must not take any new medicines unless you/your child talk to your study doctor first.
- You must not take any other medicines to treat you cancer, unless specifically allowed by your/your child's study doctor.

Please select study drug dose (once daily): ☐ **2 mg** ☐ **1.5 mg** ☐ **1 mg**

Day	Date	Time	Dose	Comment / Symptom*	Day	Date	Time	Dose	Comment / Symptom*
Day 1					Day 15				
Day 2					Day 16				
Day 3					Day 17				
Day 4					Day 18				
Day 5					Day 19				
Day 6					Day 20				
Day 7					Day 21				
Day 8					Day 22				
Day 9					Day 23				
Day 10					Day 24				
Day 11					Day 25				
Day 12					Day 26				
Day 13					Day 27				
Day 14					Day 28				

*what to describe at the next office visit. Note: You/your child can ask the study doctor questions about symptoms or side effects at any time.

FOR OFFICE USE

Date Dispensed: _____ # of pills/tabs dispensed: _____

Date Returned:_____ # of pills/tabs returned: _____

Total # pills/tabs that should have been taken: _____

Discrepancy Notes: Staff Initials:

Patient's Signature: _____

Date: _____

PROMIS Item Bank v.1.0 – Pain Intensity – Short Form 3a

Pain Intensity – Short Form 3a

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no pain	Mild	Moderate	Severe	Very severe
PAINQU6	How intense was your pain at its worst?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQU8	How intense was your average pain?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		No pain	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU21	What is your level of pain right now?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Interference – Short Form 4a

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
1	How much did pain interfere with your day to day activities?.....	☐	☐	☐	☐	☐
2	How much did pain interfere with work around the home?	☐	☐	☐	☐	☐
3	How much did pain interfere with your ability to participate in social activities?	☐	☐	☐	☐	☐
4	How much did pain interfere with your household chores?	☐	☐	☐	☐	☐

Global Health

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

PROMIS v1.1 Item Bank – Pain Behavior –
Short Form 7a

Pain Behavior – Short Form 7a

Please respond to each item by marking one box per row

	In the past 7 days....	**Had no pain**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
PAINBE2	When I was in pain I became irritable.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE3	When I was in pain I grimaced	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE8	When I was in pain I moved extremely slowly……..……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE24	When I was in pain I moved stiffly ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE25	When I was in pain I called out for someone to help me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE37	When I was in pain I isolated myself from others.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
PAINBE45	When I was in pain I thrashed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

