August 19, 2020

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

Dear Ms. Kruhm:

Enclosed is Addendum #25 to EAY131-S2, *Phase II Study of Trametinib in Patients with Tumors with GNAQ or GNA11 Mutations*

This addendum is in response to Dr. Helen Chen's Request for Rapid Amendment for Trametinib dimethyl sulfoxide dated November 19, 2019, and also, Dr. Tali Johnson's Amendment Request for updates to specific protocol language for Trametinib dimethyl sulfoxide dated June 5, 2020

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

IRB Review Requirements:

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

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 Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.

Re: Review of Amendment #36 of Protocol #EAY131-S2: "MATCH Treatment Subprotocol S2: Phase II Study of Trametinib in Patients with Tumors with GNAQ or GNA11 Mutations." The following are ECOG-ACRIN's responses to the CTEP review comments dated 5/26/2020. Please note that the Principal Investigator's comments appear in bold below.

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	Title page	This protocol amendment has not completely updated the subprotocol chair's contact information according to CTEP's records. Our records indicate: • Jason Luke, MD (IVR – 47003) has relocated to University of Pittsburgh Cancer Institute. Please update his practice site including address. **PI Response: Dr. Luke's contact information, including the practice site address, has been updated.**

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

II. Additional Protocol Changes by Principal Investigator:

The following revisions to EAY131-S2 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated version date and addendum number.
2.	3.2.1	In second box, under "Pregnancies" revised language referencing "subject" to "female patient".
3.	3.3	Updated CAEPR list for Trametinib dimethyl sulfoxide with Version 2.6 October 10, 2019
4.	5	Updated Trametinib dimethyl sulfoxide supply language.
5.	Appendix IV	Updated patient drug information template format.

The following revisions to EAY131-S2 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated version date.
2.	What possible risks can I expect from taking part in this study?	Updated condensed risk list for Trametinib dimethyl sulfoxide with Version 2.6 October 10, 2019.

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

We request review and approval of this addendum to EAY131-S2 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

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

EAY131-S2

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol S2: Phase II Study of Trametinib in Patients with Tumors with GNAQ or GNA11 Mutations

TRAMETINIB TREATMENT SUBPROTOCOL CHAIR: Jason Luke, MD, FACP

Rev.5/16

TRAMETINIB TREATMENT SUBPROTOCOL CO-CHAIR: Hussein Tawbi, MD, PhD

TRAMETINIB TRANSLATIONAL CHAIR: Andrew Chi, MD, PhD

Version Date: August 19, 2020

Rev. Add13

Rev. Add19

NOTE: This subprotocol (EAY131-S2) should be used in conjunction with the MATCH Master Protocol (EAY131)

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

SUBPROTOCOL ACTIVATION DATE

February 25, 2016 (Incorporated in Addendum #2)

Addendum #3 – 5/16
Addendum #5 – 12/16
Addendum #6 – 1/17
Addendum #7 – 3/17
Addendum #13
Addendum #19
Addendum #25

Agent	IND#	NSC#	Supply
Trametinib dimethyl sulfoxide	IND Sponsor: DCTD, NCI IND#:	763093	NCI Supplied

Table of Contents

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Rev. Add25

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Rev.5/16

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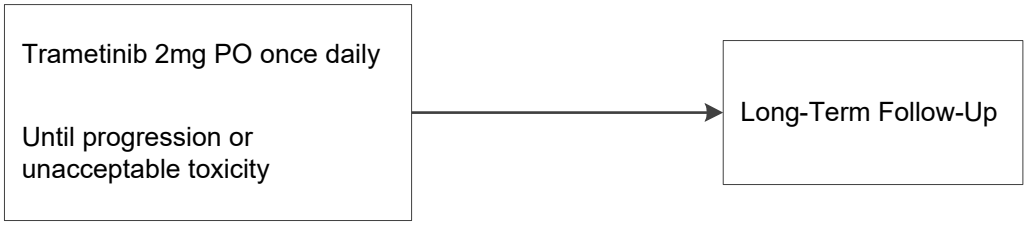
Schema



Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 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 kinase and activates MAPKK (MEK1/2), which in turn catalyze 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 Dimethyl Sulfoxide (hereafter, referred to as trametinib) is one of the 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 Amdinistration, 2013). On January 10, 2014, the FDA 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). Extensive research is underway to identify the patient selection markers and to 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). In addition, efforts have focused on identifying other upstream mutations in cancers like GNAQ and GNA11, which may benefit from selective MEK inhibition.

1.1.1 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.

1.1.2 Clinical Pharmacokinetics (PK) and Activity of Trametinib

Phase 1 Trial of Trametinib Monotherapy (MEK111054)

There were 3 parts in this industry sponsored study. Part 1: The dose-escalation portion involved 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 study has been completed and all parts, other than FDG-PET results, have been reported

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., 2012).

PK and metabolism of trametinib:

PK measurements were conducted under fasting conditions. After a single dose (Day 1), AUC_{0-24} 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_{0-24} 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_{0-24} 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 dimethyl sulfoxide is a weak CYP2C8 inhibitor and weak CYP3A4 inducer. Drug-drug interactions with sensitive substrates of 2C8 and 3A4 are not anticipated. 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 phase 1 trial:

In the 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 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)	0.47 (0.34, 0.65)	
P value (log-rank test)	*P* < 0.0001	
Confirmed Tumor Responses		
Objective Response Rate (95% CI)	22% (17, 28)	8% (4, 15)
CR, n (%)	4 (2%)	0
PR, n (%)	43 (20%)	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/m^2 weekly $\times$7 for 8 weeks, then weekly $\times$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.

The guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and guanine nucleotide-binding protein subunit alpha-11 (GNA11) are large GTPases of the Gαq family (Van Raamsdonk et al., 2009; Van Raamsdonk et al., 2010). Recurrent activating mutations in GNAQ (3.3% of 8778 cancer samples in COSMIC v63) or GNA11 (2.3% OF 6237 cancers in COSMIC v62) have been identified in cancers. Most of these mutations result in defective GTPase activity and render the proteins constitutively active (O'Hayre et al., 2013). Activating mutations ultimately lead to downstream activation of MAPK signaling (Hubbard and Hepler, 2006; Griner and Kazanietz, 2007). The highest prevalence of GNAQ and GNA11 mutations are found in uveal melanoma (33% AND 39% respectively), blue nevi (32% and 3-5%, respectively) and cutaneous melanoma (1.4% and 1.3%, respectively), but are also found in colon adenocarcinoma at about 2%.(Shoushtari AN et al GNAQ and GNA11 mutations in uveal melanoma. Melanoma Res 2014; 24: 525-534). MEK inhibitors can be active in melanomas with GNAQ or GNA11 mutations. Preclinical activity of the MEK 1 and 2 inhibitor selumetinib has been published

(Ambrosini et al. Identification of unique MEK dependent genes in GNAQ mutant uveal melanoma involved in cell growth, tumor cell invasion and MEK resistance. Clin Cancer Res 2012; 18: 3552-3561). A subsequent randomized phase II trial of investigator's choice chemotherapy with or without selumetinib in metastatic uveal melanoma showed, in an unplanned analysis, a significant improvement in PFS for the selumetinib group (Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM,

Kudchadkar RR, et al. Effect of selumetinib vs chemotherapy on progressionfree survival in uveal melanoma: a randomized clinical trial. JAMA 2014; 311:2397–2405). In a phase I study of trametinib in patients with melanoma, combined exploratory and clinical genotyping of patients who entered the trial with uveal melanoma revealed 6 patients with GNAQ or GNA11 mutations. 50% had response of stable disease and one patient with a GNA11 mutation remained on trametinib for more than 40 weeks (Falchook GS et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose escalation trial. Lancet Oncol 2012; 13: 782-89).

1.2 Supporting Preliminary Data

***GNAQ / GNA11* Biology and Targeted Therapy**

The guanine nucleotide-binding protein G(q) subunit alpha (GNAQ) and guanine nucleotide-binding protein subunit alpha-11 (GNA11) are two closely related large GTPases of the Gαq family (Van Raamsdonk et al., 2009; Van Raamsdonk et al., 2010). Mutations in GNAQ or GNA11 are likely to be present in 1.6 - 2% of the population of cancer patients based on the cBIO Portal database. Mutations in *GNAQ* or *GNA11* eliminate the activity of the heterotrimeric G protein α subunits $G_{\alpha q}$ and $G_{\alpha 11}$ GTPase, leading to hyperactivation of signaling downstream of the GNAQ and GNA11 (O'Hayre et al., 2013). The oncogenic activity of GNAQ was initially revealed as part of a systematic analysis of the transforming potential of G proteins and their coupled receptors (Kalinec et al., 1992). The best-described signaling event downstream of Gαq involves activation of phospholipase C (PLC) with subsequent increase in inositol 1,4,5-trisphosphate (IP3), and diacylglycerol (DAG) (Hubbard and Hepler, 2006). IP3 increases cytoplasmic Ca2+ levels leading to modulation of multiple calcium-regulated pathways. Together with DAG, this stimulates classical protein kinase C (PKC) isoforms (Griner and Kazanietz, 2007). GNAQ thus utilizes PLC to stimulate MAPK.

Based upon the finding that uveal melanoma (UM) is characterized by functionally active mutations in GNAQ or GNA11 (Ivey et al., 2003; Onken et al., 2008; Raamsdonk et al., 2008), as well as preclinical findings demonstrating antitumor effects of MEK inhibition in *GNAQ/GNA11* mutant UM (Ambrosini et al., 2012), a randomized trial of the MEK inhibitor selumetinib versus temozolomide was performed in patients with UM. The primary endpoint of the study, progression-free survival, was doubled as compared with chemotherapy. A hazard ratio for progression of 0.46 in favor of selumetinib was observed (Carvajal et al., 2013). The overall response for patients whose tumors harbored *GNAQ/GNA11* mutations was 15%. The overall response rate was zero in patients who crossed over to selumatinib after failure of temozolomide. Patients experiencing RECIST responses and tumor shrinkage form baseline were found

to harbor mutations in the Q209L; Q209P; Q209H; and Q209R of exon 5 as well as R183 of exon 4 of *GNAQ* (personal communication from Richard Carvajal, MD)

The preliminary success of the MEK inhibitor selumetinib in targeting *GNAQ/GNA11* suggests that MAPK inhibition is a reasonable therapeutic target in UM and other *GNAQ/11* mutant cancers. Two approaches may be considered in improving the clinical outcome of patients then including adding a second signaling inhibitor to a MEK inhibitor or alternatively, more completely suppressing MAPK signaling with a more potent MEK inhibitor. In considering combination approaches, it is important to make note that signaling downstream of *GNAQ/GNA11* is mediated through PKC isoforms, this molecule has been of interest for targeted therapy development in this molecular model. Inhibitors of PKC such as sotrastaurin and related compounds, selectively block the proliferation of melanoma cell lines with mutations in *GNAQ* or *GNA11* (Wu et al., 2012a; Wu et al., 2012c). Similar results are observed with human melanoma cell lines with *GNAQ* or *GNA11* mutations. While MEK inhibitors suppress the growth of UM cell lines, they show no selectivity compared to melanoma cell lines with mutations in other oncogenes such as RAS or BRAF. By contrast, in UM with *GNAQ* or *GNA11* mutations, a combination of PKC inhibition and MEK inhibitors leads to a highly synergistic effect. These results suggest that combined inhibition of PKC and MEK may represent a rational combination to be evaluated in *GNAQ* and *GNA11* mutant cancers.

Combination approaches of MEK inhibition with other pathway inhibitors have also been examined in *GNAQ* or *GNA11* mutant uveal melanoma. Based upon preclinical data demonstrating enhancement of MEK inhibitor-induced antitumor effects by concurrent inhibition of AKT or PI3K (Ambrosini et al., 2013; Khalili et al., 2012), a phase II trial of trametinib in combination with GSK2141795, an oral AKT inhibitor, was launched (NCI 9445). Furthermore, building upon preclinical data demonstrating the enhanced susceptibility of tumor cells to chemotherapy with concurrent MEK inhibition (Holt et al., 2012), as well as the greater PFS observed with the combination in a study of cutaneous melanoma (Holt et al., 2012; Robert et al., 2013), a phase II trial of DTIC with or without selumetinib has also begun accrual (NCT01974752).

To date, combination approaches of molecular inhibitors have proved to be toxic relative to expectations for targeted therapies (Bendell et al., 2014). Therefore, consideration of MAPK suppression by a higher potency MEK inhibitor would be reasonable. As above, selumetinib demonstrated a clinically significant response rate of 15% in UM. Selumetinib in a MEK1/2 inhibitor with MEK1 IC_{50} of 10 ηM. Other MEK inhibitors are available including the MEK1/2 inhibitor trametinib, which demonstrates a MEK1 IC_{50} of 0.7 ηM (Luke et al. 2014). Trametinib has not been evaluated in UM or *GNAQ/11* mutant tumors in a robust manner. In the single agent phase I study of trametinib (Infante et al., 2012), 16 patients with UM were treated without identification of any partial response. However, the *GNAQ/11* mutational status of these patients was not disclosed. Whereas in the selumetinib phase II trial, patients were untreated, in the trametinib phase I study the median number of prior therapies was 3. This likely impacted on the result. Of the 16 patients treated, best response included 8 patients with stable disease with 4 patients on treatment greater than 16 weeks. This decrease in efficacy of MEK inhibition after further lines of therapy is consistent with what was seen in the selumetinib trial. In that study, no patients who received chemotherapy first

had a response to selumetinib after crossing over on the study. The molecular mechanism underpinning this change in biology is unknown though it has been postulated that perhaps the essential signaling pathways in UM can change after chemotherapy. An on-going study is evaluating trametinib with and without an AKT inhibitor in untreated advanced UM. This prior experience with MEK inhibitors suggests that treatment with trametinib for UM and *GNAQ/11* mutant tumors may be efficacious and is an important clinical question to explore. Trametinib is chosen for this study in place of selumatinib because of its better efficacy based on cross trial comparison for similar patient population (BRAFV600E melanoma).

2. Selection of Patients

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

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

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

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

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

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

2.1 Eligibility Criteria:

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

Rev. Add13

_____ 2.1.2 Patients must have GNAQ or GNA11 mutations, or another aberration, as determined via the MATCH Master Protocol and according to Appendix III. See Appendix III for information on the targeted mutations and corresponding Levels of Evidence.

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

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

Date of ECG: _____

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

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

Date of ECHO/nuclear study: _____

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

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

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

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

_____ 2.1.10 Patients with glioblastoma must have histologically or radiographically confirmed recurrent or progressive WHO Grade 4 glioma (glioblastoma).

NOTE: All baseline and post-baseline disease assessments must be performed using contrast-enhanced cranial MRI or contrast-enhanced CT for subjects who cannot have MRI performed.

_____ 2.1.11 Patients with uveal melanoma are excluded.

_____ _____

Physician Signature Date

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

3. Treatment Plan

3.1 Administration Schedule

All patients will receive trametinib 2mg daily continuously until intolerable toxicity, disease progression, or the end of the study.

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

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

Trametinib should be stored at 2-8°C (36-46°F). Refrigerate. Do not freeze.

3.2 Adverse Event Reporting Requirements

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

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

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3.2.1 Additional instructions, requirements and exceptions for protocol EAY131-Subprotocol S2.

Additional Instructions

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

EAY131- Subprotocol S2 specific expedited reporting requirements:

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

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

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

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

EAY131-S2 specific expedited reporting exceptions:

For study Subprotocol S2, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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

3.2.2 Second Primary Cancer Reporting Requirements

NOTE: The MATCH Master Protocol outlines the standard requirements for the reporting of second primaries. Please be aware that there are additional requirements for this subprotocol. Please adhere to the guidelines outlined below for the reporting of second primaries on this subprotocol.

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

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

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

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

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

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

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

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated

pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

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

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

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

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

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			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (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%)**	
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[1]			***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.

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3.4 Dose Modifications

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

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

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

3.4.1 Dose Modification Guidelines for Trametinib Adverse Events of Special Interest

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

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

Table 1 Dose Level Reduction Guidelines

3.4.2

If an AE resolves to grade 1 or lower (or baseline) and remains grade 1 or lower at the reduced dose level and the subject does not experience any additional AEs requiring dose hold or reductions, then after 4 weeks of the study treatment at reduced dose, the dose of trametinib may be increased one dose level. If a dose reduction below 1 mg once daily for trametinib is required, then trametinib will be permanently discontinued.

3.4.3 Guidelines for Cardiovascular Adverse Events

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

3.4.3.1 Left Ventricular Ejection Fraction (LVEF)

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

Dose modification guidance and stopping criteria for LVEF decrease are provided (Table 2).

Table 2 Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• **Interrupt trametinib** and repeat ECHO/MUGA within 2 weeks[a] • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥ LLN and absolute decrease ≤ 10% compared to baseline): - Consult with the subprotocol Study Chair and request approval for restart - Restart treatment with trametinib at reduced dose by one dose level[b] - Repeat ECHO/MUGA 2, 4, 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter • If LVEF **does not recover** within 4 weeks - Consult with cardiologist - **Permanently discontinue trametinib** - Report as SAE - Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution - Consult with the subprotocol Study Chair.[c]
Rev. Add13 Symptomatic[b]	Grade 3: resting LVEF 39-20% or > 20% absolute reduction from baseline	• **Permanently discontinue trametinib.** • **Report as SAE** • **Consult with cardiologist** • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution
	Grade 4: resting LVEF < 20%	

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

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

3.4.3.2 Hypertension

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

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

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

- Restrictive clothing has been removed from the cuff area and the appropriate right 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 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg 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 one week.

Table 3 Management and Dose Modification Guidelines for Hypertension

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		
(Scenario A) Asymptomatic and persistent SBP of ≥ 140 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue trametinib at the current dose.

Management and Trametinib Dose Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
(Scenario B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt trametinib if clinically indicated. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario C) Symptomatic hypertension or Persistent SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, despite antihypertensive medication and dose reduction of trametinib	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt trametinib. • Once BP is well-controlled, restart trametinib **reduced by one dose level**.[a]
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	**Permanently discontinue trametinib**.
a. Escalation of trametinib to previous dose level can be considered if BPs remain well controlled for 4 weeks after restarting of trametinib. Approval from the subprotocol Study Chair is required.		

3.4.4 Guidelines for Visual Changes

Trametinib is known to be associated with visual adverse events. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions [RVO]).

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

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

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

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

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

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

Table 5 Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)[a]

CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily • **If no recovery within 4 weeks, permanently discontinue trametinib**

3.4.5 Pneumonitis Management Guidelines

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

Table 6 Pneumonitis Guidelines for Trametinib

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

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

3.5 Dose Modifications for Trametinib and supportive care

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3.5.1 **Trametinib Dose Modification for Liver Chemistry Changes**

Table 7: Trametinib Dose Modification for Liver Function Test Abnormalities

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

Event	Treatment modifications and assessment/monitoring
	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.[5] • 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 unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) (Le Gal *et al.*, 2005).

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3.5.2 Guidelines for Prolonged QTc

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

Table 8 Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
• QTcB ≥ 501 msec, or • Uncorrected QT > 600 msec, or • QTcB > 530 msec for subjects with bundle branch block	• Interrupt all study treatments until QTcB prolongation resolves to grade 1 or baseline • Test serum potassium, calcium, phosphorus and magnesium. If abnormal correct per routine clinical practice to within normal limits. • Review concomitant medication usage for a prolonged QTc. • Restart at current dose level[b] • **If event does not resolve or recurs after restarting, permanently discontinue study treatments.**

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

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

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

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3.5.3 Guidelines for Rash

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

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

Table 9 Guidelines for Supportive Care of Rash

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

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

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

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

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

Table 10 Management and Dose Modification Guidelines for Rash

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

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

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

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Moderate-strength topical steroids: hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream
c. Approval of subprotocol Study Chair is required to restart study treatment after > 2 weeks of interruption.
d. Escalation of study treatment to previous dose level may be considered if no rash is evident 4 weeks after restarting study treatment

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3.5.4 Guidelines for Diarrhea

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

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

Table 11 Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea[a] Grade 1 or 2	• Diet: stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended • Hydration: 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Diarrhea > 24h: loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics • Diarrhea > 48h: loperamide 2 mg every two hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics	• Continue trametinib • If diarrhea is grade 2 for > 48h, interrupt trametinib until diarrhea resolves to grade ≤1 • Restart trametinib at the same dose level • If treatment delay is > 14 days, discontinue trametinib.
Uncomplicated Diarrhea[a] Grade 3 or 4 Any Complicated Diarrhea[b]	• Clinical evaluation mandatory • Loperamide[c]: initially 4 mg, followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea free for 12 hours • Oral antibiotics and second-line therapies if clinically indicated • Hydration: intravenous fluids if clinically indicated • Antibiotics (oral or intravenous) if clinically indicated • Intervention should be continued until the subject is diarrhea free for ≥ 24 hours • Intervention may require hospitalization for subjects at risk of life-threatening complications	• Interrupt trametinib until diarrhea resolves to grade ≤1 • Restart with trametinib reduced by one dose level[d] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

a. **Uncomplicated diarrhea** defined by the absence of symptoms such as, cramping, nausea/vomiting ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥ 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

b. **Complicated diarrhea** defined by the presence of symptoms such as, cramping, nausea/vomiting ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia grade ≥ 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution

c. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea

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

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3.5.5 Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Table 12 Trametinib Treatment Modification for Clinically Significant Toxicities Deemed Related to Trametinib

(This section is not for specific AEs such as hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, or visual changes. Refer to other sections for these specific AEs).		
CTCAE v4 Grade	**Management Guideline**	**Dose Modification**
Grade 1	Monitor as clinically indicated. Provide supportive care according to institutional standards.	Continue trametinib at current dose level.
Grade 2 (tolerable)		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution, restart treatment at current dose level.
Grade 2 (intolerable) and Grade 3		• Interrupt treatment until resolution to grade 1 or baseline. • Upon resolution to baseline or grade 1, restart with one level of dose reduction. • If the Grade 3 toxicity recurs, interrupt trametinib; When toxicity resolves to Grade 1 or baseline, restart trametinib **reduced by another dose level.**
Grade 4		If event resolves to grade 1 or baseline discuss potential continuation of trametinib with the subprotocol Study Chair; if continuation of treatment agreed then restart trametinib at dose **reduced by one dose level**. If event does not resolve, permanently discontinue trametinib.
Trametinib should be discontinued if treatment delay is ≥14 days due to toxicities. If the investigator concludes that continued trametinib will benefit a patient, the subprotocol Study Chair may be consulted for the possibility of resuming trametinib, provided that toxicities have resolved to baseline or grade 1.		

3.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

3.7 Duration of Agent-specific treatment

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

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

3.8 Duration of Follow-Up

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

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4. Study Parameters

4.1 Therapeutic Parameters for Trametinib Treatment

NOTE: In addition to the study parameters listed in the main screening protocol, the below parameters must also be performed for patients receiving Trametinib treatment.

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

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

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

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

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

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

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

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

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

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

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

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

I. As clinically indicated.

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

K. Within 8 weeks of treatment assignment.

L. Cardiac monitoring with ECG and either ECHO or Nuclear Study (MUGA or First Pass) is needed at week 5, week 13, and every 12 weeks thereafter unless clinically indicated sooner. The same modality should be used at baseline and thereafter.

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5. Drug Formulation and Procurement

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

Availability

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

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

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

NCI Supplied Agent(s) – General Information

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

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

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

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

5.1 Trametinib dimethyl sulfoxide (NSC 763093)

5.1.1 Other Names

Trametinib, GSK1120212B, TMT212-NXA, JTP-74057, JTP-78296, JTP-75303, Mekinist®

5.1.2 Classification

MEK inhibitor

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5.1.3 Mode of Action

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

5.1.4 Storage and Stability

Storage: Store tablets at 2°C -8°C (36° F to 46° F) in the original bottle and dispense unopened bottles. Do not open bottles or repackage tablets or remove desiccant. Bottles should be protected from light and moisture.

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

Stability: 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.

Storage: Refer to the package label for expiration.

5.1.5 Dose Specifics

Trametinib will be given continuous dosing 2mg daily.

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5.1.6 Preparation

Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Each investigationally-labeled bottle contains 32 tablets with a desiccant.

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

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. 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.

5.1.7 Route of Administration

Oral. Take by mouth on an empty stomach, either 1 hour before or 2 hours after a meal. If a dose of trametinib is missed, the dose can be taken if it is more than 12 hours until the next scheduled dose.

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5.1.8 Incompatibilities

In vitro studies suggest that trametinib 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.

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

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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.

5.1.9 Side Effects

See Section 3.3 for side effects.

5.1.10 Nursing/Patient Implications

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Advise women not to breastfeed while receiving study treatment and for 4 months after the last dose of trametinib. Advise men study participants to use barrier contraception and not to father a child while taking study treatment and for 4 months after the last dose of trametinib.

6. Translational Studies

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

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol S2: Trametinib/GNAQ/GNA11

Appendix I

Rev. 12/16, 3/17

Patient Pill Calendar

Pill Calendar Directions

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

Patient Pill Calendar

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

Trametinib

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

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol S2: Trametinib/GNAQ/GNA11

Appendix II

Trametinib Ophthalmic Exam Form

Please use the form on the following page for documenting ophthalmic examinations as appropriate to the clinical situation.

Subject Name: _____

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

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

OPHTHALMIC EXAMINATION			
1. Date of Examination:	_ _/_ _ _/_ _ _ _ dd / mmm / yyyy		
VISUAL ACUITY			
Enter corrected visual acuity	OD:	OS:	
TONOMETRY			
Enter IOP (mmHg)	OD:	OS:	
INDIRECT FUNDOSCOPY			
Indirect Exam: Indicate normal or specify abnormalities	OD:	OS:	
CONFRONTATION VISUAL FIELD EXAM OR AUTOMATED PERIMETRY (e.g., Humphrey 24-2 or 30-2 or equivalent if using a non-Humphrey instrument)			
Indicate normal or specify any abnormalities	OD:	OS:	
OPTICAL COHERENCE TOMOGRAPHY (strongly recommended)			
Indicate normal or specify any abnormalities	OD:	OS:	
COLOR FUNDUS PHOTOS (recommended if retinal abnormalities are noted)*			
Indicate normal or specify any abnormalities	OD:	OS:	
FLORESCEIN ANGIOGRAPHY (suggested if retinal abnormalities are noted and test clinically indicated)*			
Indicate normal or specify any abnormalities	OD:	OS:	
Were any of the following noted on ocular history or exam?		Yes	No
• History of CSR?			
• Evidence of new optic disc cupping?			
• Evidence of new visual field defects?			
EXCLUSION CRITERIA		Yes	No
• History of RVO? o *If yes, patient is not eligible for the study.*			

Signature of Examiner: _____

Printed Name: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol S2: Trametinib/GNAQ/GNA11

Rev. Add13

Appendix III

Actionable Mutations for Sub-Protocol EAY131-S2

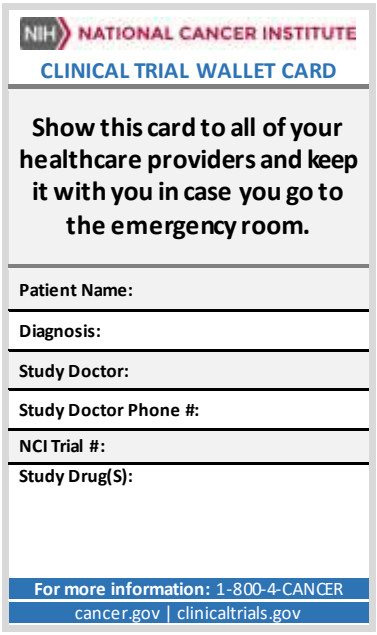
Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
GNA11	COSM52969	SNV	2	p.Q209L
GNA11	COSM52970	SNV	2	p.Q209P
GNAQ	COSM28757	SNV	2	p.Q209L
GNAQ	COSM28758	SNV	2	p.Q209P
GNAQ	COSM28760	SNV	2	p.Q209R
GNAQ	COSM52975	SNV	3	p.R183Q

Other novel GNAQ or GNA11 activating mutations not listed in the above table but identified by one of the designated outside laboratories as described in the MATCH Master Protocol will also be considered actionable mutations (aMOIs) at Level of Evidence Code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol S2: Trametinib/GNAQ/GNA11

Appendix IV:

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