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EAY131-H

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol H: Phase II Study of Dabrafenib and Trametinib in Patients with Tumors with BRAF V600E or V600K Mutations (Excluding Melanoma, Thyroid Cancer, Colorectal Adenocarcinoma, and Non-Small Cell Lung Cancer)

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Rev. Add29

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NOTE: This subprotocol (EAY131-H) 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.

Rev. Add19

Rev. Add13

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Addendum #19
Addendum #21
Addendum #25
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Addendum #34
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Dabrafenib	IND Sponsor: DCTD, NCI IND #: [redacted]	763760	NCI Supplied

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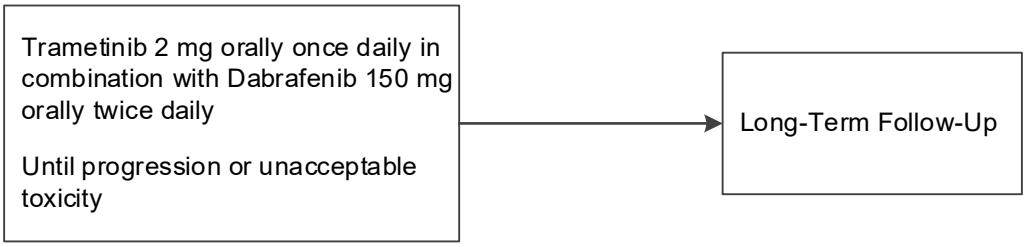

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1. Introduction

1.1 Dabrafenib and Trametinib

The RAF/MEK/ERK pathway plays a critical role in multiple cellular functions. Oncogenic activation of this pathway can result from deregulated activation or mutations of upstream receptor tyrosine kinases and RAS, or upregulation/mutations in RAF and MEK. BRAF is one of 3 structurally related RAF-kinase isoforms involved in signal transduction. Upon activation, RAF activates MEK1 and MEK2 (collectively referred to as MEK1/2), which in turn phosphorylate the activation loop of their effectors ERK1 and ERK2 (ERK1/2). Once activated, ERK1/2 translocate into the nucleus and phosphorylate a number of effector proteins, including transcription factors, while they also activate/inactivate a variety of cytosolic targets to regulate cell proliferation, motility, differentiation, and survival.[1]

Somatic BRAF mutations were first identified in a screen of cancer cell lines in 2002, where it appeared that a high percentage of melanomas had a mutation.[2] Mutations were noted in other malignancies as well, though at lower frequencies. All of the mutations identified in this study were within the kinase domain at exons 11 or 15, with the vast majority being due to a single point mutation at amino acid position 600, which resulted in the substitution of a glutamic acid for valine, V600E.[3] Mutation of BRAF in melanoma and other tumors leads to a constitutive activation of the RAF/MEK/ERK pathway, and is now validated as a major oncogenic driver and viable therapeutic target. In melanoma, more than 80% of the BRAF mutations cause a substitution of the amino acid glutamate (E) for valine (V) at position 600 (V600E) of the BRAF protein, whereas approximately 3-20% of melanoma mutations are a substitution of lysine (K) for valine at position 600 (V600K).[4-6] In addition, a substitution of arginine or aspartate for valine at position 600 also occurs albeit at a relatively low frequency.[7] BRAF V600E mutations occur at a variable frequency in cancer, including approximately 60% of melanoma,[2] 30 to 50% of papillary thyroid, 5 to 20% of colorectal, 30% of ovarian cancer, [8] and less than 5% of non-small cell lung cancers.[9]

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Dabrafenib [4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole] is an orally bioavailable, potent and selective RAF kinase inhibitor of human wild type BRAF and CRAF enzymes as well as the mutant forms of the BRAF enzyme, BRAF V600E, BRAF V600K, and BRAF V600D. A recent report has also demonstrated the efficacy of dabrafenib for metastatic melanoma patients harboring BRAF V600R.[10] The mode of action of dabrafenib is consistent with competitive inhibition of adenosine triphosphate (ATP) binding. Dabrafenib has demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated ERK1/2 [pERK1/2]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, and achieved biomarker suppression and tumor regression in BRAF mutation-positive xenograft models [GSK2118496 Investigator's Brochure version 06 09-JUL-2014]. Targeted inhibition of the RAF/MEK/ERK pathway with BRAF inhibitors dabrafenib or vemurafenib, as compared with chemotherapy, improved the progression-free and overall survival of patients who have metastatic melanoma with BRAF V600

mutations, leading to approval by the Food and Drug Administration (FDA) for both of these agents.[11,12]

While the introduction of BRAF inhibitors represent a significant advance in the treatment of BRAF V600 mutation-positive metastatic melanoma patients,[11] limitations of this novel therapy have already been identified, including rapid resistance and paradoxical activation of the RAF/MEK/ERK pathway resulting in secondary cancers.[13] Several distinct mechanisms of resistance to BRAF-inhibition have been proposed and include alterations that restore RAF/MEK/ERK pathway activation that render cells susceptible to MEK-inhibition.[14] Trametinib is a highly potent non-ATP competitive allosteric inhibitor of MEK1/2 (IC_{50} of 0.7 and 0.9 nM against MEK1 and MEK2, respectively) and is provided as a dimethyl sulfoxide solvate.[15] Trametinib inhibits not only MEK1/2 kinase activity for ERK1/2 phosphorylation but also prevents RAF-dependent MEK phosphorylation, producing very effective and prolonged ERK1/2 inhibition. BRAF-mutant Colo205, A375P F11s, and HT-29 human tumor xenograft mouse models showed significant mean tumor growth inhibition with multiple complete and partial tumor regressions [GSK1120212 Investigator's Brochure version 05 25-SEP-2013]. In a phase 3 trial, single-agent trametinib, compared to chemotherapy, improved the overall survival of patients with BRAF V600 mutation–positive metastatic melanoma leading to FDA approval for this indication.[16]

1.2 Supporting Preliminary Data

Given the efficacy of dabrafenib and trametinib monotherapy, preclinical work began to explore the anti-tumor activity of the combination. Experimental data generated with a BRAF- and MEK-inhibitor administered in combination in BRAF-mutant melanoma cell lines *in vitro* and xenografts *in vivo* demonstrated the efficacy combination therapy in models of acquired dabrafenib resistance. More importantly, superior anti-tumor activity of the BRAF- and MEK-inhibitor combination as compared to each agent as monotherapy was also observed in BRAF-sensitive models [GSK1120212 and GSK2118496 Investigator's Brochure version 03 23-JUN-2014]. This finding was confirmed in a randomized, phase 2 study of a combination of dabrafenib and trametinib, as compared with dabrafenib alone in patients with metastatic BRAF V600E and V600K mutated melanoma. In this trial, the investigators demonstrated a longer progression free survival with the combination (9.4 vs 5.8 months), as well as less squamous skin carcinoma (7% vs 19%).[17] Based on this study, the combination is now FDA approved for the treatment of V600E or V600K BRAF mutant melanoma. Recently, a double-blind, randomized, phase 3 study without crossover was published comparing the combination of dabrafenib and trametinib to dabrafenib plus placebo as first-line therapy in patients who had metastatic melanoma with BRAF V600E or V600K mutations.[13] The median progression-free survival was 9.3 months in the dabrafenib–trametinib group and 8.8 months in the dabrafenib-only group (P=0.03). The overall response rate was 67% in the dabrafenib–trametinib group and 51% in the dabrafenib-only group (P=0.002). At 6 months, the interim overall survival rate was 93% with dabrafenib–trametinib and 85% with dabrafenib alone (P=0.02). Available efficacy data of dabrafenib and trametinib in patients with solid tumors are listed in Table 1.

Table 1. Efficacy data from clinical trials evaluating the combination of trametinib with dabrafenib in patients with cancer

Study	Population	Therapy	RR, %	PFS	OS
Long et al; phase III (n=423)[13]	Metastatic melanoma with BRAF V600E or V600K mutations	Dabrafenib plus trametinib vs. dabrafenib plus placebo	67% vs. 51%	9.3 months vs. 8.8 months	Median OS not yet reached at time of analysis
Flaherty et al; phase I/II (n=162)[17]	Metastatic melanoma with BRAF V600E or V600K mutations	Dabrafenib monotherapy vs. Dabrafenib plus trametinib (1 mg dose) vs. Dabrafenib plus trametinib (2 mg dose)	54% vs. 50% vs. 76%	5.8 months vs. 9.2 months vs. 9.4 months	Median OS not yet reached at time of analysis
Phase I; (n=43)[18]	Metastatic colorectal patients with BRAF V600 mutations	Dabrafenib plus trametinib	7%	3.5 months	8.7 months

Over 1000 subjects, primarily with BRAF V600-mutated melanoma, have received the combination therapy regimen of dabrafenib and trametinib [GSK1120212 and GSK2118496 Investigator's Brochure version 03 23-JUN-2014]. In the phase III study, Long et al[13] report pyrexia, fatigue, headache, nausea, chills, arthralgias, diarrhea, rash, and hypertension as the most common adverse events (AEs) observed with these two agents. Grade 3 or 4 AEs occur in up to 35% of patients receiving combination therapy. Grade 3 or 4 AEs occurring in >1% of the study population included pyrexia, hypertension, neutropenia, AST/ALT increase, syncope, fatigue, and hyperglycemia. Life threatening and fatal AEs were observed, however, most were judged to not be related to treatment with dabrafenib and trametinib. Long et al[13] reported 4 deaths related to adverse events occurred in the dabrafenib–trametinib group: 3 from cerebral hemorrhage (2 during receipt of study treatment and one 5 days after cessation) and one from pneumonia (22 days after cessation of treatment). All 4 events were considered by the investigator to be unrelated to study treatment. The incidence of squamous cell carcinoma and squamous cell carcinoma of skin were lower when trametinib was added to dabrafenib compared to dabrafenib alone (2% vs. 9% respectively). Fewer patients in the dabrafenib–trametinib group than in the dabrafenib-only group had cutaneous squamous-cell carcinoma or cutaneous hyperkeratoses (3% vs. 32%).[13] Similar toxicity data were reported in other studies with melanoma, colorectal, and non-small cell lung cancer patients [GSK1120212 and GSK2118496 Investigator's Brochure version 03 23-JUN-2014].

Rationale: Targeting the RAF/MEK/ERK pathway in BRAF V600-mutated melanoma has led to improved outcomes and new standard of care options for this disease. Dual MEK and BRAF inhibition has demonstrated superior response rates and progression free survival when compared to BRAF monotherapy in advanced melanoma. This provides a strong rationale to assess the activity of combination therapy in other malignancies with limited treatment options with a BRAF V600E, V600K, V600D, or V600R mutation.

1.3 Dabrafenib Mesylate (GSK2118436B)

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by molecular alterations including BRAF activating mutations. Approximately 90% of all identified BRAF mutations in human cancer consist of a T1799 transversion mutation in exon 15, which results in a V600 E/D/K (T1799A) amino acid substitution. This mutation appears to mimic regulatory phosphorylation and increases BRAF activity approximately 10-fold compared to wild type (wt). RAF is a validated target in BRAF V^{600E}-containing melanoma. In August 2011, the FDA approved vemurafenib (PLX4032, Zelboraf®), an ATP-competitive selective RAF inhibitor for the treatment of late-stage $BRAF^{V600E}$ melanoma. In the pivotal phase III trial of vemurafenib *vs.* dacabazine (Chapman *et al.,* 2011), vemurafenib demonstrated significant improvement in overall survival (OS) (6-month OS of 84% *vs.* 64%, hazard ratio [HR]=0.37; *P*<0.001), progression-free survival (PFS) (estimated median PFS of 5.3 months *vs.* 1.6 months (HR=0.26; *P*<0.001]), and overall response rate (ORR) (48% *vs.* 5%). However, in patients with colorectal cancer (CRC) bearing the BRAF V600E mutation, there was only one partial response (PR) among 20 patients treated (ORR 5%) and four minor responses (Kopetz *et al.,* 2010).

Dabrafenib mesylate (GSK2118436B, Tafinlar®; referred to as dabrafenib hereafter), a 4-(3-aminosulfonylphenyl)-5-(pyrimidin-3-yl) thiazole, is an ATP-competitive, selective inhibitor of RAF kinase currently in clinical development. On May 29, 2013, the U.S. FDA approved dabrafenib for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test (FDA, 2013). On January 10, 2014, the FDA granted accelerated approval to dabrafenib and MEK inhibitor trametinib for use in combination to treat patients with unresectable or metastatic melanoma with either $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation as detected by an FDA-approved test (FDA, 2014).

1.4 Mechanisms of Action and Preclinical Data with Dabrafenib

Dabrafenib potently inhibits all RAF isoforms, with the strongest potency against the V600 mutant, as compared to its activity against wt BRAF and CRAF (see below). In a panel of more than 270 kinases tested outside RAF isoforms, only 10 kinases were inhibited at a 50% inhibitory concentration (IC_{50}) <100 nM: LIM domain kinase 1 (LIMK1), activin receptor-like kinase 5 (ALK5)/ transforming growth factor (TGF)-beta receptor type-1 (TGFβ1R), Never In Mitosis Gene A (NIMA)-related kinase 11 (NEK11), salt-inducible kinase 1 (SIK1), salt-inducible kinase 2 (SIK2), polycystin-2 (PKD2), protein tyrosine kinase 6/breast tumor kinase (BRK), pancreatic eukaryotic initiation factor-2 alpha (eIF2α) kinase (PEK)/eIF2α kinase (PERK), endothelium-specific receptor tyrosine kinase 2 (TIE2) (R849W), and yeast casein kinase 1 (CK1) (IB, 2013a).

Inhibitory activity of dabrafenib on RAF

	$BRAF^{V600E}$	$BRAF^{V600K}$	$BRAF^{V600D}$	wt BRAF	CRAF
IC_{50}	0.65 nM	0.50 nM	1.84 nM	3.2 nM	5.0 nM

In a panel of > 110 human tumor cell lines with confirmed BRAF mutational status, dabrafenib potently inhibited proliferation of a majority (73%) of $BRAF^{V600E}$

mutant cell lines with growth IC_{50} (gIC_{50}) < 100 nM (IB, 2013a). In contrast, there was poor or no activity in other BRAF mutants or wt BRAF cell lines.

Dabrafenib given orally (PO) for 14 days at doses ranging from 0.1-300 mg/kg administered once daily (QD), twice daily (BID), or three times daily (TID) inhibited tumor growth in mice bearing $BRAF^{V600E}$ A375P F11s or Colo205 tumor xenografts. The effect was generally dose dependent up to 10 mg/kg/day (A375P F11s) or 30 mg/kg/day (Colo205), yielding 90-120% tumor reduction relative to untreated animals. However, cessation of treatment was associated with regrowth of the tumors. In A375P F11s melanoma xenografts, inhibition of pERK by > 50% in the tumor was seen at doses of ≥ 3 mg/kg. Based on the single-dose studies, ~100 nM (52 ng/mL) dabrafenib in blood at 6 h post-dosing was needed for effective pharmacodynamic biomarker inhibition in the tumor. At repeated dosing of 30 mg/kg/day, the tumor pERK levels were reduced by > 50% at 8 h after dosing (69% on Day 1 and 53% on Day 14). Levels of pERK returned to baseline 24 h post-dosing. Similar ↓pERK effects were seen in the ES-2 ovarian xenograft model, but pERK inhibition was weaker in the Colo205 xenograft model. Of note, concentrations of dabrafenib showing pharmacodynamic activity in xenografts did not cause a reduction in pERK/tERK levels in the normal intact brain.

1.5 Clinical Pharmacokinetics (PK) and Pharmacokinetics of Dabrafenib

Following single-dose oral administration of dabrafenib HPMC capsules, plasma concentrations peaked approximately 2.0 hours post-dose. Oral bioavailability is near complete (94.5%) relative to an intravenous (IV) microdose.

Dabrafenib is highly bound to plasma proteins (99.6%). Its volume of distribution after IV dosing is 45.5 L. Intravenous plasma clearance (12.0 L/hr) is low relative to liver blood flow, suggesting a low hepatic extraction ratio drug. Median terminal half-life is approximately 8 hours after a single oral dose.

Three metabolites of dabrafenib were characterized and may contribute to activity. GSK2285403 (hydroxy-metabolite [M7]) PK paralleled that of dabrafenib, while the carboxy- (GSK2298683 [M4]) and desmethyl- (GSK2167542 [M8]) metabolites exhibited a longer $t_{1/2}$ (21-22 hours) and accumulated following repeat dosing. M7 is the most abundant, accounting for 54% of the three metabolites. Similar to dabrafenib concentrations, exposure for all metabolites showed a less than dose proportional increase with repeat dosing.

Fecal excretion was a major route of dabrafenib elimination in humans, accounting for 71.1% of the dose administered, and renal excretion accounted for about 23% of drug elimination, recovered as metabolites only.

Administration of dabrafenib with a high-fat, high-calorie meal reduced the oral bioavailability of dabrafenib when compared to the fasted state with a decrease in C_{max} and AUC of 51% and 31%, respectively, and delayed its absorption. Therefore, the current recommendation is to administer dabrafenib under fasting conditions, either 1 h before or 2 h after a meal.

Drug-drug interactions for dabrafenib:

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate). Co-administration of

dabrafenib 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%. Co-administration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (a CYP3A4/CYP1A2 substrate) by 33%.

In vitro studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Co-administration of dabrafenib 75 mg twice daily and ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%. Co-administration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites. Dabrafenib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro.

Pharmacodynamic effect of dabrafenib:

Median tumor pERK inhibition was 83.9% (range: 38.0 to 93.3%) in BRAF mutant melanoma subjects receiving doses of 70 to 200 mg BID. The relationship between exposure and % pERK inhibition was characterized using a maximum response (E_{max}) model with 100% maximum inhibition and IC_{50} of 134 ng/mL (95% CI: 92.7, 155) based on the sum of the potency-adjusted parent and active metabolite concentrations. A dose-related decrease in pERK was predicted with total daily doses < 200 mg (100 mg BID) dabrafenib, with a plateau occurring beyond total daily doses of 200 mg thereafter.

Selection of the RP2D for dabrafenib monotherapy:

The single-agent MTD for dabrafenib was not reached. A dose of 150 mg BID was selected for further single-agent development, based on the following PK/pharmacodynamics, safety, and activity: a) dose increases beyond 150 mg BID yielded no increase in C_{max} and < 50% increase in AUC; b) incidence and severity of AEs was similar at 100-300 mg BID; c) pERK target suppression was > 80%; and d) the tumor response rate (RR) was 50% at 150 mg BID.

Antitumor Activity of Dabrafenib Monotherapy

Activity in patients with BRAF V600E or V600K melanoma in The FTIH monotherapy study (BRF112680). The study enrolled 114 patients with BRAF ^{V600} mutant melanoma in the dose escalation phase (Part 1), and 70 patients at the RP2D (150 mg BID) in Part 2. Within this study, a cohort of 10 patients with previously untreated asymptomatic brain metastasis was evaluated for intracranial response to dabrafenib (Long et al., 2011). All patients had decreases in the size of the brain metastasis; three patients achieved complete radiographic resolution of brain lesions as well as reduction in extracranial disease. The response rates in patients treated at 150 mg BID are shown below.

FTIH monotherapy study (BRF112680) response rates in melanoma patients

	Subgroup	Patient #	ORR
Part 1	V600E	77	50%
	V600K	14	20%
Part 2, Cohort A	V600E/K with brain mets	10	40%
	V600E/K without brain mets	20	55%

When dabrafenib was used at 50 mg BID (Part 2, Cohort C) in patients with BRAF ^{V600E} mutant melanoma, the response rate was only 17%.

Correlative studies in the phase 1 monotherapy trial:

Preliminary genomic analysis was performed on 37 patients with melanoma, using a Sequenom mutation analysis for 11 genes (AKT, BRAF, CDK4, CDKN2A, GNAQ, GNA11, Kit, MEK1, MEK2, and NRAS), and PTEN analysis by sequencing, comparative genomic hybridization (CGH), and multiplex ligation-dependent probe amplification (MPLA) (Nathanson *et al.,* 2011). Nine patients (24%) had PTEN genetic alterations including mutation, hemi-/homozygous deletion. PTEN deficiency was associated with lower responses (ORR of 11% and 54% in patients with and without PTEN alteration, respectively).

Phase III trial of dabrafenib versus chemotherapy in patients with advanced BRAFV600 mutant melanoma (BREAK3 Trial):

Patients with previously untreated, unresectable stage III or IV BRAF^{V600E}-mutated melanoma were randomized (3:1) and stratified by stage to dabrafenib (150 mg PO BID) or dacarbazine (DTIC) (1000 mg/m^2, IV, every 3 weeks [Q3W]). Of 250 patients 187 received dabrafenib and 63 received DTIC. The hazard ratio for PFS was 0.30 (95% CI: 0.18-0.53; $P < 0.0001$), with median PFS of 5.1 months for dabrafenib and 2.7 for DTIC. OS data were immature, with 30 deaths reported. Confirmed RR was 53% for dabrafenib and 19% for DTIC. Benefits in PFS and RR were observed in all subgroups evaluated.

Activity in BRAF ^{V600E} mutant tumors other than melanoma:

In phase 1 trial, 18 patients had cancers other than melanoma: CRC (7), papillary thyroid cancer (PTC) (13), NSCLC (1) and ovarian cancer (1). Confirmed PRs were seen in one patient with CRC, and in 5 patients with PTC; the patient with NSCLC had an unconfirmed PR at 6 weeks. Eleven patients (6 with PTC and 5 with CRC) had stable disease (SD) as their best response; the ovarian cancer patient had SD for approximately 36 weeks.

1.6 Clinical Experience with the Combination of **Dabrafenib + Trametinib**

Data on 247 patients with metastatic melanoma and BRAF^{V600} mutations participating in the phase 1/2 study of dabrafenib and trametinib, BRF113220, have been published (Flaherty *et al.*, 2012).

PK

Coadministration of dabrafenib 150 mg twice daily and trametinib 2 mg once daily resulted in no clinically relevant pharmacokinetic drug interactions.

RP2D for the combination of trametinib and dabrafenib

In the dose escalation portion (Part B) of study BRF113220, the MTD of the combination was not reached, and the RP2D was therefore 150/2 (Flaherty et al., 2012). Pyrexia, chills, and nausea were the most common reasons cited for dose reductions; pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions. Comprehensive safety data for the combination of dabrafenib and trametinib are presented in Section 1.7.

Activity of dabrafenib + trametinib

In the phase 2 portion of study BRF113220, among 162 patients with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive melanoma, were randomized to 3 arms: dabrafenib 150 mg BID + trametinib 2 mg QD, dabrafenib 150 mg BID + trametinib 1 mg QD, and single-agent dabrafenib 150 mg BID, efficacy analyses were performed in the intention-to-treat population, with a median follow-up of 14.1 months (Flaherty et al., 2012). All major efficacy endpoints were improved, including PFS, 12-month PFS, ORR, and duration of response (see table below).

End Point (as assessed by the investigators)	Dabrafenib Monotherapy (n=54)	Combination 150/1 (n=54)	Combination 150/2 (n=54)
Progression-free Survival – months Median (95% CI)	5.8 (4.6-7.4)	9.2 (6.4-11.0)	9.4 (8.6-16.7)
Progression-free Survival at 12 mo. % (95% CI)	9 (3-20)	26 (15-39)	41 (27-54)
CR or PR Patients (% [95% CI])	29 (54 [40-67])	27 (50 [36-64])	41 (76 [62-86])
Duration of response Median months (95% CI)	5.6 (4.5-7.4)	9.5 (7.4-NA)	10.5 (7.4-14.9)

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1.7 Safety profile of **Dabrafenib** or **Dabrafenib-Trametinib** Combination

Comprehensive Adverse Events and Potential Risks (CAEPR) lists using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms for dabrafenib and for trametinib are included in Section 3.3 and Section 3.4.

Based on available AE data from clinical studies involving **dabrafenib** to date, the most common drug-related AE was hyperkeratosis (29%). Other commonly reported (>15%) drug-related AEs included alopecia, arthralgia, fatigue, skin papilloma, pyrexia, and rash (IB, 2013).

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

Common Adverse Events of Dabrafenib Monotherapy Based on Phase III Trial of Dabrafenib vs. Dacarbazine in Patients with Advanced Melanoma (adapted from Dabrafenib Package Insert)

Adverse Reaction or Laboratory Abnormality	Dabrafenib (n=187)		Dacarbazine (n=59)	
	All Grades[a]	Grades 3 and 4[b]	All Grades[a]	Grades 3 and 4
Skin and subcutaneous tissue disorders				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA[f]	2	NA
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasm benign, malignant, and unspecified (including cysts and polyps)				
Papilloma[c]	27	0	2	0
cuSCC[d, e]	7	4	0	0
Respiratory, thoracic, and mediastinal				
Cough	12	0	5	0
Gastrointestinal disorders				
Constipation	11	2	14	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

[a] NCI CTCAE v4.
[b] Grade 4 adverse reactions limited to hyperkeratosis (n=1) and constipation (n=1).
[c] Includes skin pappiloma and papilloma.
[d] Includes squamous cell carcinoma of the skin and keratoacanthoma.
[e] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol.
[f] NA = not applicable.

Common Adverse Events of Dabrafenib-Trametinib Combination vs. Dabrafenib Monotherapy. The phase 2 portion of study BRF113220 (referred to as Part C) included 3 arms: dabrafenib 150 mg BID + trametinib 2 mg QD, dabrafenib 150 mg BID + trametinib 1 mg QD, and single-agent dabrafenib 150 mg BID. The most common AE resulting in permanent discontinuation was pyrexia (4%). AEs led to dose reductions in 49% and dose interruptions in 67% of patients treated with dabrafenib in combination with trametinib. The table below presents selected adverse reactions and treatment-emergent laboratory abnormalities in this study.

Selected AEs and Laboratory Abnormalities Occurring in ≥ 10% at (All Grades) or ≥ 5% (Grades 3 or 4) of Patients Treated With Dabrafenib in Combination With Trametinib

Adverse Reaction or Laboratory Abnormality	Dabrafenib + Trametinib 2mg (n=55)		Dabrafenib + Trametinib 1mg (n=54)		Dabrafenib (n=53)	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritis	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Metabolism and nutritional disorders						
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Vascular disorders						
Hemorrhage[d]	16	5	11	0	8	2

Renal and urinary disorders						
Renal failure[e]	7	7	2	0	0	0
Hematology						
Leukopenia	62	5	46	4	21	0
Neutropenia	55	13	37	2	9	2
Liver function tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						
Hyperglycemia	58	5	67	6	49	2
Hyponatremia	55	11	48	15	36	2
Hypophosphatemia	47	5	41	11	40	0
Increased creatinine	24	5	20	2	9	0

[a] NCI CTCAE v4.

[b] Includes the following terms: peripheral edema, edema, and lymphedema.

[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash popular, rash vesicular, rash macular, rash maculo-papular.

[d] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.

[e] Includes the following terms: renal failure and renal failure acute.

AEs of special interest:

The following events observed with dabrafenib monotherapy and for dabrafenib plus trametinib are discussed in further detail because they may represent a class effect of BRAF and/or MEK inhibitor compounds, and/or are potentially life-threatening. AEs of special interest associated with dabrafenib or trametinib individually are listed in the table below:

AEs of special interest that are associated with dabrafenib (BRAF category AEs) are:	AEs of special interest that are associated with trametinib (MEK category AEs)
• Skin-related toxicities • Pyrexia • Malignancies • Renal failure (renal failure, renal failure acute) • Uveitis • Hyperglycemia • Pancreatitis	• Skin-related toxicities (e.g., rash – generalized, macular, maculopapular, pruritic, erythematous, etc; dermatitis acneiform; erythema; skin exfoliation • Diarrhea • Ocular events (e.g., RVO, RPED (previously termed CSR) • Hepatic events (e.g., aspartate aminotransferase [AST], ALT, and blood bilirubin increased) • Cardiac-related events (e.g., LVEF decreased and left ventricular dysfunction) • Hypertension • Pneumonitis (pneumonitis, interstitial lung disease) • Hemorrhages

In general, the overall profile of "AEs of special interest" observed with the combination of trametinib-dabrafenib is consistent with the known profiles of each separate drug, the most notable differences being the increase in pyrexia and the decrease in skin-related toxicities with combination therapy relative to monotherapy.

For "MEK-related AEs of special interest," the overall incidence in the dabrafenib-trametinib combination arm in trial BRF113220 was 91%, which was similar to the incidence reported with trametinib ISS monotherapy (94%), but higher than the incidence in the dabrafenib alone arm. However, MEK-related skin toxicities, diarrhea and hypertension appeared to be lower in the combination arm, as compared with the trametinib-only treated population. The incidence rate of ocular events was higher relative to the trametinib ISS population.

For "BRAF-related AEs of special interest," the incidence of any event in combination arm was higher (84%) than either the Dabrafenib ISS population (49%) or the trametinib ISS population (19%). This increase is predominantly due to the increased incidence of pyrexia observed with combination treatment. Also noted were an increase in renal failure and a decrease in cuSCC and PPES when comparing the combination to dabrafenib ISS population.

The following sections provide more detailed description of the AEs of Special Interest.

Dermatologic toxicities (dabrafenib or dabrafenib-trametinib):

Dabrafenib monotherapy has been associated with skin-related toxicities including hyperkeratosis, skin papilloma, rash, seborrheic keratosis, acrochordon as well as rash and pruritis and cutaneous squamous cell carcinoma.

With the combination of dabrafenib-trametinib at 150/2 (Part C of the phase II trial), skin-related toxicity occurred in 65% of subjects (IB, 2013). This incidence was lower than observed in the trametinib ISS population (88%, 288 out of 329 subjects). The most frequent skin-related toxicities (affecting >10% treated with combination) were rash, dermatitis acneiform, erythema, and rash generalized. The incidence and severity of the majority of skin-related toxicities and especially those most often seen with either trametinib- or dabrafenib therapy alone appear to be reduced when both compounds are combined.

Malignancies (dabrafenib or dabrafenib-trametinib**):**

Cutaneous SCC and keratoacanthomas*:* SCC and proliferative skin toxicities are considered a class effect of BRAF inhibitors such as vemurafenib and sorafenib (Long *et al.,* 2011). SCC was treated with local excision, and treatment with dabrafenib was continued. Most SCCs of the skin have been localized and generally treated with curettage, and have been without significant clinical sequelae.

Across clinical trials of dabrafenib monotherapy (n=586), the incidence of cutaneous SCC was 11%. Of those patients who developed new SCC, approximately 33% developed one or more SCC with continued administration of dabrafenib.

In randomized trial with dabrafenib vs. dabrafenib-trametinib combination (BRF113220), the incidence of cutaneous SCC/keratocanthoma was statistically lower with150/2 combination therapy relative to dabrafenib alone (7 vs. 19%).

The median time to the first occurrence of keratoacanthoma/cuSCC was 152 days in the combination treatment group as compared to 30.5 days in the dabrafenib alone arm.

New primary malignant melanoma: In the randomized trial for dabrafenib-trametinib combination (BRF113220), new primary melanoma occurred in 2% (1/53) on dabrafenib monotherapy [similar to the dabrafenib ISS population (1%)] and in none of 55 patients receiving dabrafenib + trametinib (IB, 2013). The overall frequency of new primary melanomas observed with dabrafenib treatment approximates that expected for untreated subjects with antecedent melanoma.

Other treatment-emergent malignancies: Non-cutaneous secondary malignancies have also been reported in patients receiving dabrafenib or dabrafenib-trametinib combination. In patients receiving dabrafenib-trametinib combination, five cases out of 365 subjects (1%) were identified as having non-cutaneous malignancies: KRAS mutation-positive pancreatic adenocarcinoma (n=1), recurrent NRAS mutation-positive CRC (n=1), head and neck carcinoma (n=1), glioblastoma (n=1), and pre-existing renal cell carcinoma (n=1) (FDA label). No increase was detected in the overall frequency of treatment emergent malignancies in melanoma subjects receiving dabrafenib and trametinib treatment in Study BRF113220 as compared to the dabrafenib safety population. Dabrafenib should be permanently discontinued for RAS mutation-positive non-cutaneous malignancies.

Pyrexia (dabrafenib or dabrafenib-trametinib): Pyrexia and pyrexia-related events, including influenza-like illness, cytokine release syndrome, and systemic inflammatory response syndrome are common side effects associated with dabrafenib. In dabrafenib- trametinib combination study BRAF113220 Part C, pyrexia and related events in the combination arm (150/2) were increased in frequency and severity (76%; 5% grade 3, no grade 4), as compared with dabrafenib monotherapy ISS population (33%; 2% grade 3, no grade 4). Eleven percent of subjects in the combination group required hospitalization for episodes of serious pyrexia (IB, 2013). Approximately 50% of the pyrexia-related events in the Part C 150/2 arm resulted in dose interruption and/or dose reduction, a higher proportion than in the dabrafenib ISS population (15% to 30%). The majority of subjects (>80%) who dose-reduced dabrafenib due to AEs were able to be dose re-escalated.

All SAEs of pyrexia-related events (pyrexia, influenza-like illness, cytokine release syndrome, and systemic inflammatory response syndrome) were manually reviewed to identify cases described as having experienced **serious non-infectious febrile events** with complications of hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology (*e.g.*, infection). Ten such subjects were identified among 404 subjects (2.5%) in the entire combination therapy population as compared to 1% in the dabrafenib ISS population; 9 of these subjects were hospitalized. All of these subjects required dose interruption(s) and/or dose modification(s); one subject permanently discontinued study drug after experiencing fever, muscle weakness, dehydration, and hyponatremia. All subjects responded to symptomatic therapy with either NSAIDs, paracetamol, or corticosteroids and best supportive care including IV fluids.

Renal failure (dabrafenib or dabrafenib-trametinib): Renal failure was observed in the dabrafenib ISS population (<1%; <1% grade 3/4) and trametinib ISS population (2%; no grade 3, <1% grade 4), and was increased in incidence and severity in the combination arm in study BRF113220 (7%, all grade 3) (IB, 2013). Most cases of acute renal failure presented as a secondary event in the setting of pyrexia where dehydration appeared to be a contributing factor and/or in concert with other risk factors such as hemolytic uremic syndrome (HUS), antibiotic toxicity, or hypercalcemia. There was one case of advanced renal failure which may have been drug-induced but whose precise etiology was not clear. The renal events led to permanent discontinuation of study drugs in one subject, and to dose interruptions in three subjects.

Hypertension (dabrafenib-trametinib): Hypertension has been associated with trametinib therapy. In the combination study of dabrafenib-trametinib, the combination arm had a higher rate of hypertension compared to the dabrafenib ISS population (9% vs. 2%); however, this rate was lower than that in the trametinib ISS population (15%) (IB, 2013).

In either the combination or the dabrafenib monotherapy population, there were no SAEs related to hypertension, and hypertension did not lead to treatment discontinuation, dose reduction or dose interruption in any of the patients.

Cardiac valvular abnormalities (dabrafenib or dabrafenib-trametinib)*:* Data from preclinical studies suggested that dabrafenib has the potential to cause cardiac valve abnormalities. In a 28-day dog toxicology study, high doses (50 mg/kg/day; approximately 40-fold over the therapeutic dose) of dabrafenib in 1 dog (n=10) resulted in hypertrophy of the right atrio-ventricular valve (tricuspid valve). Therefore, this was monitored in clinical trials with echocardiograms.

Cardiomyopathy (dabrafenib-trametinib)**:** Cardiomyopathy has been associated with trametinib use and therefore the incidence was increased in the dabrafenib-trametinib combination compared to dabrafenib alone. Cardiac-related AEs occurred in 9% of subjects in the Part C 150/2 group, which is the same incidence as in the Trametinib ISS population (9%), but a higher incidence compared with the Dabrafenib ISS population (2%) (IB, 2013). Decreased ejection fraction was the only AE reported in the Part C 150/2 group, and all reports were either grade 1 or 2.

Ocular adverse events: Ocular events occurred at a higher frequency in study BRF113220 Part C 150/2 combination group (25%) compared to trametinib (13%) and dabrafenib (8%) monotherapy ISS populations (IB, 2013). Blurred vision, dry eye, and visual impairment were the most commonly reported ocular events in the Part C 150/2 group. All ocular events in Part C 150/2 were grade 1 to 2 with the exception of one case of grade 3 retinal pigment epithelial detachment (RPED).

***RPED and RVO** (dabrafenib-trametinib):* These two events are associated with trametinib therapy and therefore were observed in the combination of dabrafenib and trametinib. Of 365 subjects in Study BRF113220, the incidence of RPED remained at 1% and is thus similar to the frequency observed in the overall trametinib development program so far. Thus, the addition of dabrafenib appears to have no impact on the frequency or severity of RPED previously reported for trametinib.

RVO has not been reported as an AE in the dabrafenib ISS population of 586 subjects. Addition of dabrafenib to trametinib in the combination treatment regimen in Study BRF113220 did not increase the frequency of RVO observed thus far with trametinib monotherapy.

Uveitis, iritis, and iridocyclitis (dabrafenib or dabrafenib-trametinib): Uveitis and iritis can occur when dabrafenib is administered as a single agent or in combination with trametinib. In the 365 subjects with melanoma treated on the dabrafenib-trametinib combination arm in Study BRF113220, the incidence of ocular events including uveitis, iritis, or iridocyclitis was 2%, and responded to symptomatic therapy, which included primarily the use of topical corticosteroids. This rate is slightly higher than in the dabrafenib ISS population (1%). In addition, the severity of the inflammatory ocular events also appeared to be slightly increased, with 2 cases of uveitis Grade 3 and 1 case of Grade 4.

Hyperglycemia (dabrafenib or dabrafenib-trametinib): Hyperglycemia can occur when dabrafenib is used as a monotherapy or in combination with trametinib. In study BRF112680 (dabrafenib monotherapy), 5/12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking dabrafenib; the incidence of grade 3 hyperglycemia was 6% (12/187) in patients treated with dabrafenib compared with none of the dacarbazine-treated patients. In study BRF113220 (combination with trametinib), the incidence of hyperglycemia was 5% (3/55) in patients treated with dabrafenib-trametinib compared with 2% (1/53) in patients treated with dabrafenib (FDA label).

Pancreatitis (dabrafenib or dabrafenib-trametinib): Pancreatitis (<1%) and/or increased lipase/amylase (2%) have been reported at low frequency with dabrafenib. In the phase 2 combination study BRAF113229, AEs of acute pancreatitis or pancreatitis occurred in six (1%) subjects on the dabrafenib-trametinib arm (IB, 2013), and none with dabrafenib monotherapy. The time to onset of pancreatitis ranged from Study Day 21 to 292 (median: 138 days). At the data cut-off, 4 subjects had recovered from the event of pancreatitis. Discontinuation of study drugs due to pancreatitis was not deemed necessary by the investigators in any of the 6 cases. The incidence of pancreatitis was <1% in the dabrafenib ISS population (2 subjects) and in the trametinib ISS population (1 subject).

Hepatic events (dabrafenib-trametinib combination): In the Part C 150/2 group, 15% of subjects experienced hepatic AEs as compared to 13% of subjects in the trametinib ISS population and 6% of subjects in the dabrafenib ISS population (IB, 2013). Of the hepatic AEs, increased ALT and AST were the most common events in all groups, and most were either grade 1 or 2. No cases of Hy's law (propensity for fatal drug induced liver injury given severe transaminase elevations with or without hyperbilirubinemia) were observed among any of the subjects in the BRF113220 study.

Diarrhea (dabrafenib-trametinib combination): The proportion of subjects in the Part C 150/2 group who experienced diarrhea was 36% compared with 49% in the trametinib ISS population and 16% in the dabrafenib ISS population (IB, 2013). Most subjects across the monotherapy and combination therapy dabrafenib and trametinib clinical programs reported grade 1 or grade 2 diarrhea.

Pneumonitis (dabrafenib-trametinib combination): Pneumonitis was not reported as an AE in the 365 subjects enrolled in Study BRF113220

(Investigators Brochure, 2013). However, pneumonitis was the most common drug-related SAE (1% of subjects) Trametinib ISS population. Overall, the addition of dabrafenib to trametinib does not appear to increase the frequency or severity of pneumonitis previously observed with trametinib monotherapy.

Hypersensitivity: There has been a single report of hypersensitivity (blisters) to dabrafenib, occurring on the same day as the 1st dose of study drug as well as upon rechallenge (IB, 2013). The subject recovered after interruption and then discontinuation of dabrafenib. Grade 1 AEs of blisters on limbs (4 subjects) and drug hypersensitivity (rash, 1 subject) have been reported in previous studies with dabrafenib. However, the precise etiology of these events is unclear.

Hypersensitivity to trametinib was reported by one subject 7 days after starting trametinib who experienced fever, asthenia, visual disturbance, and symptoms suggestive of a hypersensitivity reaction described by the investigator as "vascularity." This subject also developed LFT elevations, lower limb nodules that by biopsy showed "dermo-hypodermatitis with plasmocyte and lymphocyte infiltrate." The subject recovered after discontinuation of trametinib.

Hemorrhages (dabrafenib-trametinib combination): Hemorrahge is an AE identified with the dabrafenib-trametinib combination therapy. Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with dabrafenib plus trametinib combination therapy (FDA label). In study BRF113220, treatment with dabrafenib in combination with trametinib resulted in an increased incidence and severity of any hemorrhagic event: 16% (9/55) of patients treated with trametinib in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. The major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with trametinib in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial hemorrhage was fatal in two (4%) patients receiving the combination of trametinib and dabrafenib.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency (dabrafenib or dabrafenib-trametinib combination): Dabrafenib, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with G6PD deficiency; these patients should be closely observed for signs of hemolytic anemia.

Embryofetal toxicity: Based on the mechanisms of action, dabrafenib and/or trametinib can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose.

1.8 Clinical pharmacology of trametinib:

Trametinib is absorbed rapidly with median T_{max} generally occurring 1.50 hours after single oral administration of trametinib under fasting conditions. The absolute oral bioavailability of a single trametinib 2 mg tablet is moderate to high (72%) relative to a co-administered IV microdose.

Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once daily of 5.97 and a terminal half-life of 5.3 days. Steady state is achieved by Day 15.

Trametinib has a high volume of distribution (Vd) of 1060 L. Fecal excretion is the major route of elimination after [^{14}C] trametinib oral dose, accounting for > 80% of excreted radioactivity recovered (or 39.2 and 35.0% of the radioactive dose in 2 subjects) while urinary excretion accounted for < 19% of excreted radioactivity recovered (< 10% of the radioactive dose).

Rev. Add13

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

Rev. Add25

1.9 Arm Expansion

1.9.1 Arm H has accrued 35 patients and met the primary endpoint of the trial with 33% response rate (A. Salama et al, American Society of Clinical Oncology, Chicago, IL, 2019). This led to consideration of filing with the FDA for approval of this combination for a tumor agnostic indication. This was discussed with CTEP and the pharma company, Novartis, who strongly supported the recommendation. It was decided that the NCI-MATCH trial should attempt to improve confidence intervals around the response rate to this combination by expanding the accrual of this arm by 50 additional patients. The final accrual for this arm will therefore be 85 patients. This part of the trial will exclude cholangioncarcinoma as there is activity of the combination in this tumor type and it will likely be pursued for regulatory approval as a single histology. Accrual will stop on December 31, 2022.

Rev. Add31

It is expected that a total of ~80 patients will be analyzable (eligible and treated). It is also of interest to perform the analysis within the subset of patients with assay results from the designated outside laboratories that could be confirmed by the MATCH assay, and it is estimated that ~56 analyzable patients will be in this cohort, including 22 patients from the screening cohort (of the first 35 accrued patients, 11 were accrued based on results from outside labs, among whom results for 6 (55%) were confirmed by the MATCH assay (MATCH assay could not be performed for 4 patients due to lack of sample or assay failure, and results for 1 patient could not be confirmed)). The table below gives the 95% confidence interval, assuming 56, 68, or 80 analyzable patients, and an observed response rate of 33%.

Number of confirmed responders / Number of analyzable patients	**18/56**	**22/68**	**26/80**
95% CI	(20.3%, 46.0%)	(21.5%, 44.8%)	(22.4%,43.9%)

2. Selection of Patients

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

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

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (https://dctd.cancer.gov/research/ctep-trials/memos/protocol-deviations.pdf). 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 the relevant treatment consent form

Rev. 8/15

2.1 Eligibility Criteria

Rev.2/16

_____ 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. 8/15
Rev. Add13

_____ 2.1.2 Patients must have a BRAF V600E or, V600K, V600R or V600D mutation, or another aberration, as identified via the MATCH Master Protocol and described in Appendix IV. See Appendix IV for information on the targeted mutations and the corresponding Levels of Evidence (LOE).

Rev. 8/15

_____ 2.1.3 Patients with a diagnosis of metastatic melanoma from a cutaneous, acral, mucosal, or unknown primary site are excluded.

_____ 2.1.4 Patients with a diagnosis of papillary thyroid cancer are excluded.

Rev.5/16

_____ 2.1.5 Patients with a diagnosis of colorectal adenocarcinoma are excluded.

Rev. Add13

_____ 2.1.6 Patients with a diagnosis of non-small cell lung cancer are excluded.

_____ 2.1.7 Patients with a diagnosis of cholangiocarcinoma are excluded

_____ 2.1.8 Patients with a diagnosis of low grade serous ovarian cancer are excluded

Rev.5/16 _____ 2.1.9 Patients must have normal organ and marrow function as defined below:

- Prothrombin time (PT)/International normalized ratio (INR) and partial thromboplastin time (PTT) ≤ 1.3x institutional ULN; subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to registration to treatment.

Rev. 8/15, 2/16 _____ 2.1.10 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: _____

_____ 2.1.11 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have NONE of the following cardiac criteria:

Rev. 8/15

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

Date of ECG: _____

Rev. 8/15 _____ 2.1.12 Patients with a history of interstitial lung disease or pneumonitis are excluded.

_____ 2.1.13 Patients must not have known hypersensitivity to dabrafenib and trametinib or compounds of similar chemical or biologic composition or to dimethyl sulfoxide (DMSO).

Rev. 8/15 _____ 2.1.14 Patients must not have a history or current evidence/risk of retinal vein occlusion (RVO). An eye exam is required at baseline. See Appendix III for the Trametinib Ophthalmic Exam Form.

Rev. 8/15 _____ 2.1.15 Patients who previously received MEK inhibitors (including, but not limited to, trametinib, binimetinib, cobimetinib, selumetinib, RO4987655 (CH4987655), GDC-0623 and pimasertib) will be excluded.

Rev. 8/15 _____ 2.1.16 Patients who previously received BRAF inhibitors (including, but not limited to, dabrafenib (Tafinlar), vemurafenib (PLX-4720) (Zelboraf), RAF265, LGX818 (encorafenib), RO5212054 (PLX3603), ARQ 736, XL281 (BMS-908662), CEP-32496, and the BRAF/MEK dual inhibitor RO5126766) will be excluded.

_____ 2.1.17 Patients with prior exposure to dabrafenib or trametinib on another treatment subprotocol of the MATCH trial are excluded.

_____ 2.1.18 Current use of a prohibited medication. Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8 are ineligible. Current use of, or intended ongoing treatment with: herbal remedies (e.g., St. John's wort), or strong inhibitors or inducers of P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1) should also be excluded. See Appendix II for a list of these prohibited medications.

_____ 2.1.19 Patients who previously received monoclonal antibody therapy (eg. Ipilimumab and others) must have stopped the prior therapy for 8 or more weeks before starting on trametinib and dabrafenib.

_____ 2.1.20 Patients with a history of Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection are excluded. An exception will be patients with cleared HBV and HCV infection which will be allowed on study.

_____ 2.1.21 Patients with history of RAS mutation-positive tumors are not eligible regardless of interval from the current study.

NOTE: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility.

_____ _____

Physician Signature Date

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

3. Trametinib/Dabrafenib Treatment Plan

3.1 Administration Schedule

Dabrafenib will be administered in combination with trametinib. The dose of dabrafenib is 150 mg orally twice daily, taken approximately 12 hours apart in combination with trametinib 2 mg given orally once daily for a 28 days cycle.

When dabrafenib and trametinib are administered in combination, take the once-daily dose of trametinib at approximately the same time each day with either the morning dose or the evening dose of dabrafenib. The second dose of dabrafenib should be administered approximately 12 hours after the morning dose. Study medication should be taken orally with approximately 200 mL of water under fasting conditions, either 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 dose as originally scheduled.

If administration of trametinib is interrupted or permanently discontinued, administration of dabrafenib may be continued. If administration of dabrafenib is interrupted or permanently discontinued, administration of trametinib may continue.

If a subject misses a dose of dabrafenib, the subject may take the dose immediately if the next dose is scheduled for at least 6 hours later. If the next scheduled dose of dabrafenib is due in less than 6 hours, the subject should skip the dose and resume dabrafenib dosing at the next scheduled dose. If a subject misses a dose of trametinib, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later.

3.2 Adverse Event Reporting Requirements

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

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

Rev.2/16

3.2.1 Additional adverse event reporting instructions, requirements and exceptions for EAY131 – Subprotocol H

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events, 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 H specific expedited reporting requirements:

- **LVEF Changes:** If any of the following circumstances occur, the event(s) must be reported immediately (within 24 hours of learning of the event) as an initial report in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the table in Section 5.3.7 of the MATCH Master Protocol.
  - Asymptomatic: Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN and LVEF **does not recover** within 4 weeks
  - Symptomatic: Grade 3-4 LVEF

  Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for LVEF Decrease
- **Visual Changes:** If RPED (retinal pigment epithelial detachments) or RVO (retinal vein occlusion) are diagnosed, the event(s) must be reported immediately (within 24 hours of learning of the event) as an initial report in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the table in Section 5.3.7 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 immediately (within 24 hours of learning of the event) as an initial report in CTEP-AERS. Complete the full CTEP-AERS report within the timeframes outlined in the table in Section 5.3.7 of the MATCH Master protocol.
  - ALT ≥ 3xULN **and** bilirubin ≥ 2x ULN or > 35% direct bilirubin
  - ALT ≥ 3xULN **and** INR ≥ 1.5, if INR measured (INR threshold does not apply if subject is on anticoagulant)

  Please refer to the dose modification instructions for further information regarding Treatment Modification and Management Guidelines for Liver Chemistry Changes
- **Pregnancies:** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the patient is on Dabrafenib or Trametinib, or within 90 days of the patient's last dose of Dabrafenib or Trametinib, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported immediately (within 24 hours of learning of the event) as an initial report in CTEP-AERS. Complete the full CTEP-AERS report within 5 calendar days. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the

occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol H specific expedited reporting exceptions:

For Subprotocol H, the adverse events listed below **do not** require expedited reporting in 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. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

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 on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy,

   NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
3. Report the diagnosis via CTEP-AERS, regardless of attribution, at https://ctepcore.nci.nih.gov/ctepaers

4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

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

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

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

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

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

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

Rev. 1/17
Rev. Add19
Rev. Add25

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' https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf for further clarification. Frequency is provided based on 1111 patients. Below is the CAEPR for Trametinib.

Rev. 2/16

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

Rev. Add29

NOTE: Any event listed in the EAY131-H specific expedited reporting requirements in Section 3.2.1 must be reported in CTEP-AERS, even if the event is listed as an exception in the green column below.

Version 2.7, July 25, 2025[1]

Adverse Events with Possible Relationship to Trametinib (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			
		Cardiac disorders - Other (atrioventricular block)[2]	
		Cardiac disorders - Other (bundle branch block)[3]	
		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)	

Adverse Events with Possible Relationship to Trametinib (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (retinal vein occlusion)	
	Eye disorders - Other (visual disorders)[4]		
		Papilledema	
	Periorbital edema		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
Generalized edema[5]			***Generalized edema[5] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[6]		
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[7]	
INFECTIONS AND INFESTATIONS			
	Folliculitis		***Folliculitis (Gr 2)***
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 3)***
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)***

Adverse Events with Possible Relationship to Trametinib (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<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)***
		Tumor lysis syndrome[8]	
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)***
	Nervous system disorders - Other (peripheral neuropathy)		
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)[9]			***Skin and subcutaneous tissue disorders - Other (rash)[5] (Gr 3)***

Adverse Events with Possible Relationship to Trametinib (CTCAE 5.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Stevens-Johnson syndrome[10]	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event (venous)	
	Vascular disorders - Other (hemorrhage)[11]		

[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] Atrioventricular block includes Atrioventricular block complete, Atrioventricular block first degree, Mobitz type II atrioventricular block.

[3] Bundle branch block includes Bundle branch block right and Bundle branch block left, Conduction disorder; Mobitz type I.

[4] 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.

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

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

[7] Hemophagocytic lymphohistiocytosis is observed in combination with dabrafenib which also has this adverse event.

[8] Tumor lysis syndrome: Cases of tumor lysis syndrome, including fatal cases, have been reported in patients treated with trametinib in combination with dabrafenib.

[9] 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, seborrheic dermatitis, dermatitis psoriasiform, rash follicular, skin fissures, and skin chapped.

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

[11] 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 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that trametinib caused the adverse event:

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

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (cardiac stenosis); Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired

ENDOCRINE DISORDERS - Hypothyroidism

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

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colonic ulcer; Duodenal ulcer; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric ulcer; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (abdominal visceral perforation); Gastrointestinal disorders - Other (bowel obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal disorders - Other (parotid gland swelling); Gastrointestinal fistula; Gingival pain; Ileus; Obstruction gastric; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Flu-like symptoms; Gait disturbance; General disorders and administration site conditions - Other (axillary pain); General disorders and administration site conditions - Other (systemic inflammatory response syndrome); Localized edema; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS

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

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

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Blood bilirubin increased; Blood lactate dehydrogenase increased; Cardiac troponin I increased; Cardiac troponin T increased; CD4 lymphocytes decreased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased

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

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Flank pain; Generalized muscle weakness; Muscle cramp; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (compression fracture); Musculoskeletal and connective tissue disorder - Other (proximal upper extremity weakness and neck extensor weakness); Myalgia; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage[11] Tumor pain

NERVOUS SYSTEM DISORDERS - Amnesia; Cognitive disturbance; Dysarthria; Dysgeusia; Edema cerebral; Encephalopathy; Intracranial hemorrhage[11]; Lethargy; Muscle weakness left-sided; Nervous system disorders - Other (ascending polyneuropathy); Nervous system disorders - Other (diplopia); Nervous system disorders - Other (leptomeningeal disease); Nystagmus; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Personality change; Psychiatric disorders - Other (altered mental status); Psychosis; Suicidal ideation

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Dysuria; Hematuria; Proteinuria; Renal and urinary disorders - Other (nephrotic syndrome); Renal colic; Urinary incontinence; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage[11]

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage[11]; Epistaxis; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pleural effusion; Pneumothorax; Productive cough; Pulmonary hypertension; Respiratory failure; Sinus disorder; Sore throat

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

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension

NOTE: Trametinib 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.

Rev.12/16
Rev. Add21
Rev. Add25
Rev. Add34

3.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Dabrafenib mesylate (GSK2118436B, NSC 763760)

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' https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf for further clarification. *Frequency is provided based on 1374 patients.* Below is the CAEPR for Dabrafenib (GSK2118436B).

Rev.2/16

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER. Since this protocol uses multiple investigational agents, if an AE is listed on both SPEERs, use the lower of the grades to determine if expedited reporting is required.

NOTE: Any event listed in the EAY131-H specific expedited reporting requirements in Section 3.2.1 must be reported in CTEP-AERS, even if the event is listed as an exception in the green column below.

Version 2.7, January 17, 2025[1]

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2,3]		***Anemia[2,3] (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Left ventricular systolic dysfunction[4]	
EYE DISORDERS			
		Eye disorders - Other (iritis)[5]	
		Uveitis[5]	
		Vision decreased	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
		Colitis	
		Colonic perforation	
	Constipation		***Constipation (Gr 3)***

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Diarrhea		***Diarrhea (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs[6]		***Edema limbs[6] (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever[7]			***Fever[7] (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[8]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH))[9]	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Creatinine increased[3]		***Creatinine increased[3] (Gr 2)***
	Neutrophil count decreased[3]		***Neutrophil count decreased[3] (Gr 3)***
	Platelet count decreased[3]		***Platelet count decreased[3] (Gr 2)***
	White blood cell decreased[3]		***White blood cell decreased[3] (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia[3]		***Hyperglycemia[3] (Gr 2)***
	Hypokalemia[3]		***Hypokalemia[3] (Gr 2)***
	Hyponatremia[3]		***Hyponatremia[3] (Gr 3)***
	Hypophosphatemia[3]		***Hypophosphatemia[3] (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia			***Arthralgia (Gr 3)***
	Back pain		***Back pain (Gr 3)***
	Myalgia		***Myalgia (Gr 3)***
	Pain in extremity		***Pain in extremity (Gr 3)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Neoplasms benign, malignant and unspecified (incl cysts and polyps) -		***Neoplasms benign, malignant and unspecified (incl cysts***

Adverse Events with Possible Relationship to Dabrafenib (GSK2118436B) (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	Other (squamous cell carcinoma or keratoacanthoma)[10]		***and polyps) - Other (squamous cell carcinoma or keratoacanthoma)[10] (Gr 2)***
	Skin papilloma		***Skin papilloma (Gr 2)***
		Treatment related secondary malignancy (non SCC)[11]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
Headache		Syncope	***Headache (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Hair texture abnormal		***Hair texture abnormal (Gr 2)***
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
Hyperkeratosis			***Hyperkeratosis (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		***Pruritus (Gr 3)***
Rash[12]			***Rash[12] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms (DRESS))	
		Skin and subcutaneous tissue disorders - Other (neutrophilic panniculitis, panniculitis)[13]	
		Stevens-Johnson syndrome	
VASCULAR DISORDERS			
	Hypertension		
	Thromboembolic event[14] Vascular disorders - Other (hemorrhage)[15]		

[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] The incidence of anemia is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[3] The frequencies of these events are based upon laboratory findings rather than being due to patient-reported outcomes.

[4] The incidence of left ventricular systolic dysfunction is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[5] Dabrafenib (GSK2118436B) has been associated with ocular toxicities including chorioretinitis, retinitis, iridocyclitis, iritis, and uveitis.

[6] Edema limbs (peripheral edema) is a risk associated when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B) compared to dabrafenib (GSK2118436B) alone.

[7] Fever (pyrexia) can be associated with hypotension and/or (in rare cases) syncope. The frequency of fever and serious febrile events is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[8] Manifestations of allergic reactions (hypersensitivity) to dabrafenib (GSK2118436B) may include bullous rash (bullous dermatitis).

[9] The incidence of hemophagocytic lymphohistiocytosis (HLH)) is increased when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[10]Squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease), and keratoacanthoma have been observed.

[11] New non-SCC malignancies have been reported including primary melanoma, basal cell carcinoma, and non-cutaneous malignancies.

[12] Rash includes the terms: rash, rash acneiform, rash papular, rash maculo-papular, and erythema.

[13] Recurrent neutrophilic panniculitis has been observed in at least one patient treated with dabrafenib (GSK2118436B) in combination with the MEK inhibitor trametinib dimethyl sulfoxide (GSK1120212B).

[14] Venous thromboembolic events (including deep vein thrombosis and pulmonary embolism) is a risk associated when dabrafenib (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

[15] Treatment with dabrafenib (GSK2118436B) in combination with trametinib dimethyl sulfoxide

(GSK1120212B) resulted in an increased incidence and severity of hemorrhagic events compared to patients treated with dabrafenib (GSK2118436B) as a single agent. Sites of hemorrhage may include, but are not limited to, intracranial, reproductive tract, respiratory tract, and gastrointestinal hemorrhage.

Adverse events reported on Dabrafenib (GSK2118436B) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Dabrafenib (GSK2118436B) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Heart failure; Mitral valve disease; Myocardial infarction; Pericardial effusion; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain

ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism

EYE DISORDERS - Blurred vision; Eye disorders - Other (amaurosis fugax); Eye disorders - Other (vitreous detachment); Floaters; Photophobia; Retinal detachment; Retinopathy

GASTROINTESTINAL DISORDERS - Dry mouth; Dyspepsia; Gastritis; Stomach pain

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS - Death NOS; Disease progression; Gait disturbance; Localized edema; Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain

INFECTIONS AND INFESTATIONS - Bacteremia; Bronchial infection; Catheter related infection; Device related infection; Gallbladder infection; Infections and infestations - Other (bacterial peritonitis); Infections and infestations - Other (blood culture positive); Infections and infestations - Other (croup infectious); Infections and infestations - Other (Epstein-Barr virus infection); Infections and infestations - Other (respiratory tract infection); Lung infection; Otitis media; Pharyngitis; Rash pustular; Rhinitis infective; Sepsis; Skin infection; Urinary tract infection; Viremia

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Injury, poisoning and procedural complications - Other (complication associated with device); Injury, poisoning and procedural complications - Other (device occlusion); Injury, poisoning and procedural complications - Other (radiation injury, stroke-like migraine attacks after radiation therapy); Seroma

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Lipase increased; Lymphocyte count decreased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypernatremia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain

NEOPLASMS, BENINGN, MALIGNANT AND UNSPECIFIED (INCL CYST AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acrochordon); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (bile duct adenocarcinoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (mycosis fungoides)

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Hydrocephalus; Lethargy; Nervous system disorders - Other (expressive aphasia); Nervous system disorders - Other (intracranial pressure increased); Paresthesia; Seizure; Somnolence; Stroke

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria; Renal calculi; Urinary frequency; Urinary retention

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Menorrhagia; Prostatic obstruction; Reproductive system and breast disorders - Other (hematospermia)

RESPIRATORY, THORACIC AND MEDAISTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Dyspnea; Hypoxia; Nasal congestion; Oropharyngeal pain; Pleuritic pain; Productive cough; Pulmonary edema; Respiratory failure; Rhinorrhea; Sore throat; Stridor; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS- Bullous dermatitis[8]; Eczema; Erythroderma; Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (palmoplantar keratoderma); Skin and subcutaneous tissue disorders - Other (sunburn); Skin hyperpigmentation

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension

NOTE: Dabrafenib 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.

3.5 Dose Modifications

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NOTE: Patients who interrupt trametinib and dabrafenib 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 (https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events).

The table below outlines the dose levels to be used for any necessary dabrafenib and trametinib dose modifications in studies which include the combination:

Dose Level	Dabrafenib Dose/Schedule
0	150 mg BID
-1	100 mg BID
-2	75 mg BID
-3	50 mg BID

Dose Level	Trametinib Dose/Schedule
0	2 mg QD
-1	1.5 mg QD
-2	1.0 mg QD

Dabrafenib and Trametinib Dose Modification Guidelines

If an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level. A dose reduction below 50 mg BID for dabrafenib is not allowed. For dabrafenib-trametinib combination, dose below 1 mg once daily for trametinib is not allowed; however, if dabrafenib will be permanently discontinued for dabrafenib-related toxicities, the patients will be allowed to continue trametinib. Conversely, if trametinib is permanently discontinued for trametinib-related toxicities, patients will be allowed to continue dabrafenib.

The dose modifications may involve one or both agents, and should be based on the nature, severity and attributions of the AEs. General guidelines are provided in Tables below, with details stipulated in subsequent sections. The CTEP drug monitors should be consulted if there are questions about the attribution of AEs and how the doses should be modified.

3.5.1 Dabrafenib-Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections

Dabrafenib-Trametinib Dose Modification for Toxicities Not Specified in Subsequent Sections	
CTCAE Grade	**Action and Dose Modification**
Grade 1 **Grade 2 (tolerable)**	• Continue study treatment at same dose level (no dose modification). • Monitor closely. • Provide supportive care according to institutional standards.
Grade 2 (intolerable) **Grade 3**	• Interrupt study treatment. • Monitor closely. • Provide supportive care according to institutional standards. • When toxicity resolves to grade 1 or baseline, restart study treatment **reduced by one dose level**. • If the grade 2 (intolerable) or grade 3 toxicity recurs, interrupt study treatment. • When toxicity resolves to grade 1 or baseline, **restart study treatment reduced by another dose level**.
Grade 4	• Permanently discontinue, or interrupt, study treatment. • Monitor closely. • Provide supportive care according to institutional standards. • If study treatment was interrupted, restart study treatment **reduced by one dose level** once toxicity resolves to grade 1 or baseline.
* If the AEs are thought to be due to one of the two agents, resumption of the other agents may be considered if the first agent is discontinued due to toxicities and treatment interruption is < 14 days. The subprotocol Study Chair should be consulted for resumption of single agent.	

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3.5.2 Dabrafenib-Trametinib Dose Modification for Pyrexia

- Pyrexia is defined as a body temperature equal to or above 38.5° Celsius or 101.3° Fahrenheit
- Pyrexia is an adverse event associated with dabrafenib and is increased in frequency and severity in subjects receiving dabrafenib in combination with trametinib. In a minority of cases, pyrexia was accompanied by symptoms such as severe chills/rigors, dehydration, hypotension, dizziness or weakness and required hospitalization.
- Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take anti-pyretics (e.g. ibuprofen or acetaminophen/paracetamol) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia

Dabrafenib-Trametinib dose Modification and Management Guidelines for Pyrexia		
Event	**Management Guideline**	**Dose Modification**
Work up: • Clinical evaluation for infection and hypersensitivity, especially if pyrexia is complicated by rigors, severe chills, dehydration, *etc.* • Laboratory work-up (should include full-blood-count, electrolytes, creatinine, BUN, CRP, liver-function tests, blood and urine culture). ***Management***: • Anti-pyretic treatment should be started immediately at the first occurrence. Anti-pyretic treatment may include acetaminophen (paracetamol), ibuprofen, or suitable anti-pyretic medication per institutional standards. • Oral hydration is encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended if pyrexia is complicated by dehydration/hypotension. • In subject experiencing pyrexia complicated by rigors, severe chills, *etc.*, which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started. • Prophylactic anti-pyretic treatment is recommended after the 2nd event, or after the 1st event if complicated by rigors or severe chills. Prophylactic anti-pyretics may be discontinued after three days in absence of pyrexia		
Rev. 12/16 1st Event:	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up • Hydration as required • Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment	• Interrupt dabrafenib. • Continue trametinib. • Upon recovery to baseline, restart dabrafenib at the same dose level. If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**.
2nd Event	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up • Hydration as required • Within 3 days of onset of pyrexia: – Optimize anti-pyretic therapy. – Consider oral corticosteroids (*i.e.*, prednisone 10 mg) for at least 5 days or as clinically indicated.	• **Interrupt dabrafenib.** • Continue trametinib • Upon recovery to baseline, restart dabrafenib at the same dose level. If fever was associated with dehydration or hypotension, **reduce dabrafenib by one dose level**.
Subsequent Events:	• Clinical evaluation for infection and hypersensitivity • Laboratory work-up • Hydration as required • Blood sample for cytokine analysis • Within 3 days of onset of pyrexia: – Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia. – If corticosteroids have been tapered and pyrexia recurs, restart steroids. – If corticosteroids cannot be tapered, consult the subprotocol Study Chair.	• **Interrupt dabrafenib.** • Continue trametinib. • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level**. • If dabrafenib must be reduced to < 50 mg BID, permanently **discontinue dabrafenib**.
Rev. 8/15 Dabrafenib should be reduced by one dose level after three episodes of pyrexia which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.		

3.5.3 Dabrafenib-Trametinib Dose Modification for Rash

Rash is a frequent AE observed in patients receiving trametinib, dabrafenib, or the combination of both agents. Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors and EGFR inhibitors[32,33]

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.

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Dabrafenib-Trametinib Supportive care and Dose Modification for Rash		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Supportive care: **Prevention:** • Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥ 15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID) **Symptom management:** • 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 * Rash prophylaxis is recommended for the first 6 weeks of study treatment * Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management		
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue study treatment. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce study treatment with both drugs by one dose level**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce study treatment with both drugs 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 study treatment with both drugs at reduced dose level.**[3]
Grade ≥ 3	• Use moderate strength topical steroids PLUS oral methyl-prednisolone dose pack.[2] • Consult dermatologist.	• Interrupt study treatment until rash recovers to ≤ grade 1. • **Restart study treatment with both drugs reduced by one dose level.**[3,4] • If no recovery to ≤ grade 2 within 14 days, **permanently discontinue study treatment**.

1. Rash prophylaxis is recommended for the first 6 weeks of study treatment.
2. Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone propionate concentration 0.05% cream.
3. Study treatment may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.

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3.5.4 Dabrafenib-Trametinib Dose Modification for palmar-plantar erythrodysesthesia syndrome (PPES)

- Lifestyle modification: avoidance of hot water, traumatic activity, constrictive footwear, or excessive friction on the skin and the use of thick cotton socks and gloves, and shoes with padded insoles
- Symptomatic treatments: apply moisturizing creams frequently, topical keratolytics (e.g. urea 20-40 % cream, salicylic acid 6%, tazarotene 0.1% cream, fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas, topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin for pain.
- Dose modification may also be required. – Refer to table for dose modification for non-specific AEs

3.5.5 Dabrafenib-Trametinib Treatment Modification for New Primary/ Recurrent Malignancies

3.5.5.1 Cutaneous SCC and New Primary Melanoma

Dermatologic skin assessments for subjects on treatment should be performed by the treating physician before initiation of dabrafenib, then every 2 months through treatment. For protocols that start after June 2014, it is also recommended that skin exams, per institutional standards, should continue every 2-3 months for 6 months after discontinuation of dabrafenib or initiation of another anti-neoplastic therapy. Report any new primary/recurrent malignancies as SAE through CTEP-AERS if it meets the reporting requirements outlined in Section 3.2.2.

Cutaneous Squamous Cell Carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma [KA] or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib. Approximately 70 % of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks.

These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reported as an SAE (if it meets the reporting requirements outlined in Section 3.2.2). In addition, a biopsy of the lesion should be taken, where possible, and a summary of the results submitted to CTEP through the SAE reporting.

Patients should be instructed to immediately inform their physician if new lesions develop.

New Primary Melanoma

New primary melanomas have been reported in patients treated with dabrafenib. These were identified primarily within the first 5 months of therapy and did not require treatment modification other than excision. New primary melanoma should be reported as SAE through CTEP-AERS if it meets the reporting requirements outlined in Section 3.2.2.

3.5.5.2 Non-Cutaneous Malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with dabrafenib. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. Patients should be monitored as clinically appropriate.

Permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies. If used in combination with trametinib, trametinib may continue.

Following discontinuation of dabrafenib, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

New non-cutaneous malignancies should be reported as a SAE if it meets the reporting requirements outlined in Section 3.2.2. In addition, a biopsy should be taken, where possible, and a summary of the results submitted to CTEP through the SAE reporting. Testing of these biopsies should include RAS mutation analysis and may include analysis of genomic alterations, which include but not limited to DNA, RNA and protein analysis of these biopsy specimens, and would analyze the biological pathways known to be associated with, and relevant to, BRAF-mutant tumor activation.

3.5.6 Dabrafenib-Trametinib Dose Modification for Hemorrhages

Dabrafenib-Trametinib Treatment Modifications for Hemorrhage	
Grade 3	Hold dabrafenib-trametinib for up to 2 weeks If improved, resume the drugs at one dose reduction If no improvement, permanently discontinue dabrafenib-trametinib
Grade 4	Permanently discontinue dabrafenib or dabrafenib-trametinib

3.5.7 Dabrafenib-Trametinib Dose Modification for Pancreatitis

In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis. For changes in treatment, please refer to *Dose Modification for Toxicities Not Specified in Subsequent Sections* Section 3.5.1

3.5.8 Dabrafenib-Trametinib Dose Modification for Hyperglycemia

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination. For changes in treatment, please refer to *Dose Modification for Toxicities Not Specified in Subsequent Sections* Section 3.5.1

3.5.9 Dabrafenib-Trametinib Dose Modification for Renal Insufficiency

Cases of renal insufficiency have occurred in patients receiving the combination of dabrafenib and trametinib. Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and modified if clinically possible.

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Dabrafenib-Trametinib Dose Modification for Renal Insufficiency		
Serum Creatinine Level	**Management Guideline**	**Action and Dose Modification**
Serum creatinine increase > 0.2 mg/dL (18 mcmol/L) ***BUT*** ≤ 0.5 mg/dL (44 mcmol/L) above baseline	• Recheck serum creatinine within 1 week. • •Serum creatinine increase >1 week: contact the subprotocol Study Chair. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation. • If pyrexia is present, treat pyrexia as per guidelines.[a]	Continue study treatment at the same dose level.
Serum creatinine increase > 0.5 mg/dL (44 mcmol/L) **ABOVE NORMAL** ***OR*** > 2 mg/dL (> 177 mcmol/L)	• Monitor serum creatinine ≥ 2-times per week. • Hospitalization may be necessary if serum creatinine cannot be monitored frequently. • If pyrexia is present, treat pyrexia per guidelines. • Consult nephrologist if clinically indicated. • Perform renal biopsy if clinically indicated, for example: – Renal insufficiency persists despite volume repletion. – Patient has new rash or signs of hypersensitivity (such as elevated eosinophil count).	• Interrupt study treatment for up to 2 weeks until serum creatinine recovers to baseline. • Restart study treatment.[b]

[a] NSAIDs can induce renal insufficiency, especially in patients with dehydration; ;encourage oral fluids or consider IV fluids as clinically indicated. See guidelines for pyrexia Section 3.5.2.

[b] Investigator may restart at either the same or a reduced dose level. Escalation of study treatment to previous dose level is allowed if another episode of renal insufficiency does not occur after 4 weeks of dose reduction. Consultation with the subprotocol Study Chair is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

3.5.10 Dabrafenib-Trametinib Dose Modification for Reduced Left Ventricular Ejection Fraction

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

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Dabrafenib - Trametinib Treatment Modification and Management Guidelines for LVEF Decrease		
Clinic	**LVEF-drop (%) or CTCAE grade**	**Dose Modification**
Asymptomatic	Absolute decrease of > 10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib. Dabrafenib may continue • Repeat ECHO 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 trametinib and dabrafenib at reduced doses by one dose level. – Repeat ECHO 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** – Resumption of dabrafenib may be considered after consultation with the subprotocol Study Chair. – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
Rev. Add13 **Symptomatic[b]**	• Grade 3: resting LVEF 39-20% or > 20% absolute reduction from baseline • Grade 4: Resting LVEF < 20%.	• **Permanently discontinue trametinib. Report as SAE** • **Hold dabrafenib until LVEF improves. Consult the subprotocol Study Chair for resumption of dabrafenib** • Consult with cardiologist. • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
[a] If ECHO does not show LVEF recovery after 2 weeks, repeat ECHO 2 weeks later. [b] Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.		

3.5.11 Dabrafenib-Trametinib Dose Modification for Hypertension

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

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

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

- Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the study calendar. Ideally, subsequent blood pressure assessments should be performed within 1 week.
- Persistent hypertension is defined as an increase of systolic BP (SBP) > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg in three consecutive visits with blood pressure assessments from two readings.
- Asympomatic hypertension is defined as an increase of SBP > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting, or other symptoms indicative of hypertension.

Dabrafenib-Trametinib Treatment Modification for Hypertension		
Event	**Management Guideline**	**Dose Modification**
(Scenario A) Asymptomatic and persistent[a] SBP of ≥ 140 and < 160 mmHg, or DBP ≥ 90 and < 100 mmHg OR • Clinically significant increase in DBP of 20 mmHg (but DBP still below 100 mmHg)	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled[b] BP. • If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	• Continue study treatment.
(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 study treatment if clinically indicated. • Once BP is well-controlled[b], restart study treatment reduced by one dose level[c]
(Scenario C) Symptomatic[d] hypertension OR • Persistent SBP ≥ 160 mmHg, or DBP ≥ 100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• 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 study treatment • Once BP is well controlled, restart study treatment **reduced by one dose level**[c].
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	• Permanently discontinue study treatment.

a. Hypertension detected in two separate readings during up to three consecutive visits
b. Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits.
c. Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from the subprotocol Study Chair is required.
d. Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range

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3.5.12 Dabrafenib-Trametinib Dose Modification for QTc Prolongation

Dabrafenib - Trametinib modification for QTc Prolongation	
QTc Prolongation[a]	**Action and Dose Modification**
• QTcB ≥ 501 msec	• Interrupt study treatment until QTcB prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • Review concomitant medication usage for agents that prolong QTc. • If the event resolves, restart study treatment at current dose level[b]. • **If the event does not resolve, permanently discontinue study treatment. Consider evaluation with cardiologist.** • **If the event recurs, permanently discontinue study treatment. Consider evaluation with cardiologist.**
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 subprotocol Study Chair agrees that the subject will benefit from further treatment.	

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3.5.13 Dabrafenib-Trametinib Dose Modification for **Diarrhea**

Episodes of diarrhea have been observed in patients receiving dabrafenib, trametinib, or both therapies in combination. Other, frequent causes for diarrhea including concomitant medications (*e.g.*, stool softeners, laxatives, antacids, *etc.*), infections caused by *C. difficile* or other pathogens, partial bowel obstruction, *etc.*, should be clinically excluded.

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

1. **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.
2. **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.
3. Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea.
4. Escalation of study treatment 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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3.5.14 Dabrafenib-Trametinib Dose Modification for Visual Changes

Episodes of visual changes have been observed in patients receiving dabrafenib, trametinib, or the combination of both therapies. 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.

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Uveitis and iritis have been associated with dabrafenib, while RPED and RVO have been associated with trametinib therapy. Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy. 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 of the anterior segment (with special attention to inflammation) and the posterior segment, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography, and fluorescein angiography may also be indicated as determined by clinical exam.

Guidelines regarding event management and dose reduction for visual changes considered to be related to study treatment are provided in the table below.

Dabrafenib-Trametinib **Treatment Modification for Visual Changes**		
CTCAE Grade	**Management Guideline**	**Action and Dose Modification**
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ ophthalmologist. Dabrafenib may be continued. • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If Uveitis/Iritis, refer to table below for Iritis/Uveitis • If RPED suspected or diagnosed, refer to RPED dose modification table below; **report as SAE if diagnosed**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib. Dabrafenib may be continued. • 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 Uveitis/Iritis, refer to table below for Uveitis/Iritis • If RPED diagnosed, see RPED dose modification table below; **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**.
Grade 4	• Consult ophthalmologist immediately.	• Interrupt trametinib. Dabrafenib may be continued. • If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with the subprotocol Study Chair. • If Uveitis/Iritis, refer to table below • **If RVO or RPED diagnosed, permanently discontinue trametinib** and report as SAE.
Abbreviations: RPED = retinal pigment epithelial detachments; RVO = retinal vein occlusion; SAE = serious adverse event *If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

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Dabrafenib-Trametinib **Dose Modification for RPED**	
Event CTCAE Grade	**Action and Dose Modification**
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue trametinib with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below. • Dabrafenib treatment is not affected
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. Continue dabrafenib • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

Dabrafenib-Trametinib **Dose Modification for Uveitis and Iritis**	
CTCAE Grade	**Action and Dose Modification**
Uveitis and Iritis	• Continue study treatment • Control ocular inflammation with local therapies • If not improved to grade ≤ 1 within 1 week, interrupt dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level • If no recovery within 4 weeks, permanently discontinue dabrafenib. Trametinib may be continued.

3.5.15 Dabrafenib-Trametinib Dose Modification for **Pneumonitis**

Pneumonitis has been observed in patients receiving trametinib in combination with dabrafenib. To reduce the risk of pneumonitis, patients will be monitored closely for symptoms, evaluated with imaging and functional tests when appropriate.

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Dabrafenib-Trametinib Treatment Modification for **Pneumonitis**		
CTCAE Grade	**Adverse Event Management**	**Action and Dose Modification**
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation with pulmonologist recommended	• Continue study therapy 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 trametinib reduced by one dose level • Escalation to previous dose level after 4 weeks may be considered after consultation with the subprotocol Study Chair. • 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 • Resumption of trametinib at one dose level reduction may be considered after consultation with the subprotocol Study Chair. • If no recovery to grade ≤1 within 2 weeks, **permanently discontinue trametinib.**
Grade 4	• Same as grade 2	• **Permanently discontinue trametinib.**

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3.5.16 Dabrafenib-Trametinib Dose Modification for **Liver Chemistry Changes**

Dabrafenib-Trametinib **Dose Modification for Liver Chemistry Changes**	
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 treatment**. • Report as SAE if CTEP-AERS reporting criteria is met. • If **liver chemistry stopping criteria** are met any time, proceed as described below. **MONITORING:** Repeat LFT (ALT, AST, ALK, bilirubin) until they return to normal/baseline or stabilise (LFT may be every 2 weeks after 4 weeks if ALT < 3x ULN and TB < 2 ULN). If baseline ALT and Tbili already meet these criteria, then monitoring is required only if ALT or TB rises after initiation of study therapy.
Rev. 8/15 **Criteria for discontinuing study drug:** When any of the liver stopping criteria below is met, discontinue trametinib **and dabrafenib** 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). **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 hours** • Monitor subjects weekly until LFTs return to normal/baseline or stabilize. **ASSESSMENT and WORKUP:** • Viral hepatitis serology.[4] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. • CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total 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).

3.5.17 Dabrafenib-Trametinib Dose Modification for **Venous Thromembolism (VTE)**

Event	Dabrafenib	Trametinib (When Used in Combination)
Uncomplicated DVT or PE	Do not modify the dose.	Withhold trametinib for up to 2 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
Life Threatening PE	Permanently discontinue dabrafenib	Permanently discontinue trametinib.

3.6 General Concomitant Medication and Supportive Care Guidelines

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

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. If radiation therapy is permitted on protocol, it is recommended that dabrafenib be held for 7 days before and 2 days after XRT in subjects.
Because there is a potential for interaction of trametinib and dabrafenib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

3.7 Duration of Agent-specific treatment

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

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

3.8 Duration of Follow-Up

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

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4. Study Parameters

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4.1 Therapeutic Parameters for Dabrafenib plus Trametinib Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol at Step 0, the below parameters must also be performed for patients receiving Dabrafenib plus 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
Rev.5/16 PT/INR and PTT	X				
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X				
Toxicity Assessment[G]		X		X	X[F]
Pill Count/Diary[H]		X		X	
ECG[K,L]	X	X[L]			
Rev. 8/15 Echocardiogram or Nuclear Study[L]	X	X[L]			
Dermatologic Exam[M]	X		X[M]	X	X[M]
Rev. 8/15 Eye Exam	X	X[I]			
Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

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

Rev. 8/15, 2/16 B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium, and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with 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.

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

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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.

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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.

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

M. Test can be done by the treating physician and should be done every 2 months during study treatment, and every 2-3 months for 6 months following discontinuation of study treatment or until initiation of other anti-neoplastic agent. Refer to Section 3.5.5 for further instructions.

Rev. Add13 **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 (https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management).

Rev. 12/16 **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 (https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

Rev. 3/17 **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

Rev. Add25 registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

5.1 Trametinib (NSC 763093)

5.1.1 Other Names

Rev. 8/15 Trametinib, GSK1120212B, TMT212-NXA, JTP-74057, JTP-78296, JTP-75303, Mekinist®

5.1.2 Classification

MEK inhibitor

Rev. 12/16 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

Rev. 8/15 **Storage:** Store tablets at 2°C -8°C 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.

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.

5.1.5 Dose Specifics

2 mg orally once daily

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How Supplied: Novartis supplies and CTEP, NCI, DCTD distributes trametinib as 0.5 mg and 2 mg (as free base) tablets. Tablets may be provided in investigationally-labeled bottles or commercially-labeled bottles.

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

The aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow (0.5 mg tablet), iron oxide red (2 mg tablet) and polysorbate 80 (2 mg tablet).

Each investigationally-labeled bottle contains 32 tablets with a desiccant:

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

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

- 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

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- 2 mg tablets are pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red.

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5.1.7 Route of Administration

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

5.1.8 Incompatibilities

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

Trametinib 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 patients of childbearing potential to use effective contraception while receiving study treatment and for 4 months after the last dose of trametinib. Advise patients not to breastfeed while receiving study

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

5.2 Dabrafenib (NSC 763760)

5.2.1 Other Names

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GSK2118436, GSK2118436A (free base); Tafinlar

5.2.2 Classification

BRAF inhibitor

5.2.3 Mode of Action

Dabrafenib mesylate (GSK2118436B) is a potent and selective BRAF kinase inhibitor. This inhibition suppresses downstream activity of pERK, a biomarker, and has antiproliferative activity against BRAF mutant tumors. The mode of action is consistent with ATP-competitive inhibition.

5.2.4 Storage and Stability

Storage: Store between 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]

If a storage temperature excursion is identified, promptly return dabrafenib mesylate (GSK2118436B) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to the package label for expiration.

5.2.5 Dose Specifics

150 mg orally twice daily

5.2.6 Preparation

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Dabrafenib mesylate (GSK2118436B) capsules are supplied by Novartis and distributed by the DCTD, NCI as 50 mg and 75 mg capsules (equivalent to the free-base) for oral administration.

Each commercially-labeled bottle contains 120 capsules and a silica gel desiccant.

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- 50 mg capsule is dark red and imprinted with ‘GS TEW’ and ‘50 mg.’
- 75 mg capsule is dark pink and imprinted with ‘GS LHF’ and ‘75 mg.’

Capsule excipients include microcrystalline cellulose, magnesium stearate (vegetable source), and colloidal silicon dioxide. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

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5.2.7 Route of Administration

Oral administration. Take dabrafenib mesylate (GSK2118436B) by mouth one hour prior or two hours after a meal. If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.

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5.2.8 Incompatibilities

In vivo data shows that metabolism of dabrafenib mesylate (GSK2118436B) and its metabolites is mediated by CYP3A4 and CYP2C8. Use caution if strong inducers or inhibitors of CYP2C8 or 3A4 are co-administered with dabrafenib. Although *in vitro* studies indicate dabrafenib mesylate and its metabolites are substrates for P-glycoprotein (P-gp) and BCRP transporters, the apparent high oral bioavailability and permeability indicate modulation of efflux transporters will have minimal impact on dabrafenib pharmacokinetics.

Dabrafenib mesylate (GSK2118436B) and its metabolites showed moderate inhibition of CYP 2C8, 2C9, 2C19 and 3A4 in human microsomes studies. Use caution in patients who are taking sensitive substrates of these enzymes. Additionally, dabrafenib and its metabolites showed inhibition of OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 transporter systems and weak to moderate inhibition of BCRP. Neither dabrafenib nor its metabolites show inhibition of P-gp *in vitro*.

Dabrafenib mesylate (GSK2118436B) induces CYP3A4, 2C9 and possibly 2B6, 2C8, 2C19 enzymes, UDP glucuronosyltransferase and P-gp. Use caution in patients who are taking substrates of these pathways, such as warfarin or hormonal contraceptives.

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Dabrafenib solubility is pH-dependent and experiences decreased solubility at higher pH. Use caution in patients who are taking drugs that elevate gastric pH due to the theoretical risk of decreasing oral bioavailability of dabrafenib.

5.2.9 Side Effects

See Section 3.4 for side effects.

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5.2.10 Nursing/Patient Implications

In the case of overdose, patients should be treated symptomatically since there is no specific antidote. Hemodialysis is likely to be ineffective since dabrafenib mesylate is highly bound to plasma proteins.

Advise patients of childbearing potential to use effective non-hormonal contraception methods while receiving study treatment and for 16 weeks after the last dose of dabrafenib. Hormonal contraceptives can be ineffective when taken concurrently with dabrafenib.

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 H: Trametinib/Dabrafenib

Appendix I

Rev. 12/16, 3/17

Patient Pill Calendars

Pill Calendar Directions

1. Take your scheduled dose of each tablet or capsule.
2. If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next dose.
3. If a dose of trametinib is missed, only take the dose if it is more than 12 hours until the next scheduled dose.
4. Please bring the empty bottle or any leftover tablets or capsules and your pill calendar to your next clinic visit.
5. Take dabrafenib mesylate (GSK2118436B) twice daily by mouth either 1 hour before or two hours after a meal.
6. Take trametinib (GSK1120212) once daily by mouth either 1 hour before or 2 hours after a meal.
7. Swallow dabrafenib capsules whole. Do not crush, chew, or open capsules.
8. Swallow trametinib tablets whole. Do not crush or chew tablets.
9. Store dabrafenib at room temperature.
10. Store trametinib in the refrigerator. Do not freeze.

Patient Pill Calendar

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

Trametinib

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

Patient Signature: _____ Date: _____

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules 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 capsules and your completed pill calendar to your doctor's visits.

Dabrafenib

DAY	Date			Time capsules taken		Number of capsules 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	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
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22								
23								
24								
25								
26								
27								
28								

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol H: Trametinib/Dabrafenib

Appendix II

CYP3A4/CYP2C8 Inducers and Inhibitors

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agent on these lists.

PROHIBITED – strong inducers of CYP3A or CYP2C8, since concentrations of dabrafenib may be decreased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Rifamycin class agents (e.g., rifampin, rifabutin, rifapentine),
Anticonvulsant	Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin
Miscellaneous	bosentan, St. John's wort
PROHIBITED – Strong inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Drugs/Agents**
Antibiotics	Clarithromycin, telithromycin, troleandomycin
Antidepressant	Nefazodone
Antifungals	Itraconazole, ketoconazole, posaconazole, voriconazole
Hyperlipidemia	Gemfibrozil
Antiretroviral	ritonavir, saquinavir, atazanavir
Miscellaneous	Conivaptan

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol H: Trametinib/Dabrafenib

Appendix III

Rev. 8/15

Trametinib Ophthalmic Exam Form

Subject Name: _____

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

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

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

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

Signature of Examiner: _____

Printed Name: _____ **Date:** _____

Molecular Analysis for Therapy Choice (MATCH)
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Rev. Add13

Appendix IV

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BRAF Mutations Eligible for Inclusion

Gene Name	Variant ID	Variant Type	Variant Description	Level of Evidence Code
BRAF	COSM1127	SNV	p.V600R	2
BRAF	COSM1583011	SNV	p.V600R	2
BRAF	COSM308550	SNV	p.V600D	2
BRAF	COSM473	SNV	p.V600K	1
BRAF	COSM474	SNV	p.V600R	2
BRAF	COSM476	SNV	p.V600E	1
BRAF	COSM477	SNV	p.V600D	2

Other novel BRAF V600 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 H: Trametinib/Dabrafenib

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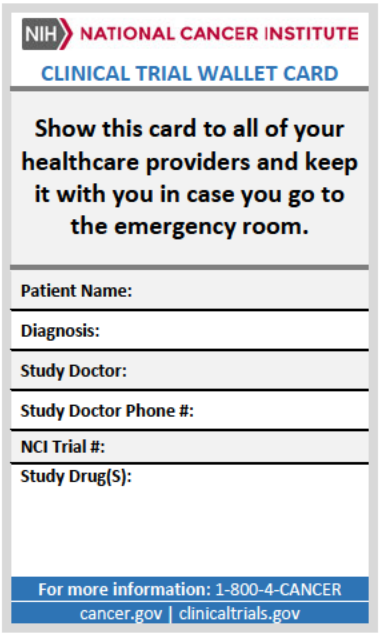
Appendix V

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

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol H: Trametinib/Dabrafenib

Rev. Add30

Appendix VI

CS-MATCH-0021

Bridging concordance study for a BRAF V600E companion diagnostic to support submission in a tumor agnostic indication based on Novartis ROAR clinical trial (NCT02034110) data and data from NCI-MATCH study, subprotocol H, with positive signal for the activity of dabrafenib in combination with trametinib in rare tumors with BRAFV600E mutations

Principal Investigators:
PRINCIPAL INVESTIGATORS: Connie Wong, PhD

I. Introduction

This proposal is a request for tissue samples collected via NCI-MATCH subprotocol H to enable a CDx bridging study in support of a tumor agnostic claim application for dabrafenib (Tafinlar®) in combination with trametinib (Mekinist®). Mature results from all cohorts of the Novartis ROAR Study (NCT02034110), along with mature results from Arm H of the NCI MATCH study, will be submitted to Health Authorities, including FDA, in support of the use of dabrafenib in combination with trametinib in patients with BRAF V600E mutation-positive solid tumors (e.g., a tissue agnostic claim). Collectively, these data show important benefit, as demonstrated by clinically meaningful response rates and durability of response, across a number of BRAF V600 mutation-positive, rare and ultra-rare cancers, which have no effective treatment available (8 and 17 indications studied in ROAR and NCI-MATCH, respectively). As a part of the regulatory path, a companion diagnostic test (CDx) is required by the FDA. A bridging study is needed to support CDx development which will require as many tissue samples as possible from patients with rare histologies treated with dabrafenib in combination with trametinib. If this application is supported, tissue samples collected via NCI-MATCH subprotocol H would be tested with a comparator assay (e.g., THxID) and the proposed CDx in order to determine the agreement between the two assays. In addition, the results of the NCI-MATCH central Oncomine Ampliseq NGS test may be compared to the proposed CDx results. While Novartis estimates that a concordance study between THxID and the CDx will suffice, the FDA may require that the efficacy be calculated in the CDx-evaluable population. Discussions with FDA are planned to define the requirements for the CDx bridging study. This project will be performed in partnership with an undisclosed diagnostic company (information is currently confidential until contracting is completed).

II. Objectives

A. Primary objective: To evaluate the concordance between the bioMerieux THxID test (comparator) and the proposed CDx test for BRAF V600E in solid, rare cancer tissue specimens representative of the ROAR and NCI-MATCH subprotocol H studies.

III. Methodology

Summary:

Novartis ROAR Study (NCT02034110) with a median follow-up of 13.8 months are available. These data show important benefit as demonstrated by clinically meaningful

response rates and durability of response across eight BRAF V600 mutation-positive, rare and ultra-rare cancers which have no effective treatment available. In addition, there are now data available from NCI-MATCH study, subprotocol H, which show promising efficacy of dabrafenib in combination with trametinib across 17 distinct rare histologies with a BRAFV600E mutation, in patients who have exhausted prior treatment options. In consideration of these results, Novartis has a regulatory path forward to support the labeled tissue agnostic use of dabrafenib and trametinib in the treatment of patients with rare BRAF V600E mutation-positive tumors.

Novartis and ECOG/ACRIN (on behalf of NCI-MATCH) have entered a collaboration and are in the process of formalizing an agreement to provide Novartis with the NCI-MATCH data in support of the regulatory submission described above.

The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers. This pathway can be constitutively activated by alterations in specific proteins, including BRAF, which phosphorylates MEK on 2 regulatory serine residues. Over 45 cancer-associated mutations have been identified in BRAF (1). BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50 to 60% of melanoma (2), Approximately 90% of all identified BRAF mutations that occur in human cancer are a T1799A transversion mutation in exon 15, which results in a V600E amino acid substitution (3). This mutation appears to mimic regulatory phosphorylation, locks the BRAF kinase in its active status, and increases BRAF activity approximately 10-fold compared to wild type (2). T1799A alteration (V600E mutation) accounts for 70 to 90% of BRAF mutant melanoma patients. In addition, the T1799A alteration could be associated with a second nucleotide mutation (G1798A) and leads to a V600K mutation in an additional ~6% to 29% of patients with a BRAF mutation (4). Dabrafenib is a selective inhibitor of BRAF kinase activity and trametinib is a selective inhibitor of MEK activity for tumors that carry T1799A and/or GT1798-1799AA alterations in the BRAF gene. The clinical utility of this kit is to evaluate the BRAF (V600E / K) (T1799A / GT1798-1799AA) mutation status in order to screen patients for treatment with the dabrafenib or trametinib.

The THxID™-BRAF kit allows detection of the V600E and V600K mutations of the BRAF gene from FFPE sections. For this, the THxID™-BRAF kit makes use of 2 major processes:

- Nucleic acid isolation from FFPE sections through extraction / purification steps:
    - The paraffin is removed. The sample is lysed then heated to reverse formalin crosslinking. The DNA is bound to a membrane. After washing, concentrated DNA is eluted from the membrane.
- Real time PCR amplification and detection of target DNA (BRAF gene) present in the total nucleic acids:
    - Amplification Refractory Mutation Specific System (ARMS) (5) PCR technology is used. In the PCR reaction, primers specific for the BRAF gene allow the amplification of a non-polymorphic gene area, which is used as an internal control. The primers specific for the mutations V600E and V600K allow the amplification of mutated fragments leading to the identification of BRAF mutations. Target specific probes bind instantaneously to the newly synthesized complementary DNA.

      In the THxID™-BRAF kit, 2 different probes labeled with 2 different dyes allow the simultaneous detection of the BRAF internal control and a BRAF mutation.

Kinetic analysis of the fluorescent signals and delta Ct (Crossing threshold) calculation reveal the presence of potential BRAF mutations.

IV. Statistical Considerations

A. Endpoints: The endpoints for the concordance analyses are the PPA and NPA between the bioMerieux THxID test (comparator) and the proposed CDx test for BRAF V600E status.

B. Analysis plan:

To evaluate the concordance between the bioMerieux THxID test (comparator) and the proposed CDx test for BRAF V600E, the PPA and NPA will be estimated.

As shown below in Table 1, point estimates of PPAs, with and without invalid results included, will be calculated as the probability of detecting a BRAF V600E mutation by the CDx Test given the samples are tested as BRAF V600E mutation positive by the comparative method, THxID Test. Similarly, NPAs, with and without invalid results included, will be estimated as the probability of a sample being tested negative for a BRAF V600E mutation by the CDx Test given that the samples are tested as BRAF mutation negative by the THxID Test. The associated two-sided 95% Wilson Score confidence interval (CI) will be calculated and reported along with the point estimates of the PPA and NPA. Samples with invalid or missing THxID results and/or missing CDx Test results will be excluded from the analysis.

BRAF V600E mutation (CDx)	ThxID (Comparative method)		
	Positive	Negative	Total
Positive	a	b	a + b
Negative	c	d	c + d
Invalid	e	f	e + f
Total	a + c + e	b + d + f	a + b + c + d + e + f

$$PPA(invalid\ excluded) = \frac{a}{a+c} \times 100\%$$

$$PPA(invalid\ included) = \frac{a}{a+c+e} \times 100\%$$

$$NPA(invalid\ excluded) = \frac{d}{b+d} \times 100\%$$

$$NPA(invalid\ included) = \frac{d}{b+d+f} \times 100\%$$

C. Rationale for the sample size estimate:

The clinical concordance study will test all available solid tissue samples (or DNA isolated from tissue samples) with sufficient material, from patients from solid tumor

cohorts in the ROAR trial (141 patients from 6 cohorts) and the subprotocol H (33 patients with 15 cancer types) using the proposed CDx test for BRAF V600E. Accounting for 95% concordance between CDx and THxID, a sample size of 172 BRAF V600E positive patients determined by THxID are needed. A sample size of approximately 100 specimens with BRAF V600E negative status, determined by THxID will be needed. Negative samples will be commercially sourced. 172 BRAF V600E positive patients and 100 BRAF V600E negative patients, determined by THxID, will be tested by the proposed CDx test for concordance analysis.

The NPA and PPA for the CDx test are expected to be 95% or higher with a PCR comparator test, such as THxID. The acceptance criterion of the study requires that the lower limit of the two-sided 95% Wilson Score CI for PPA and NPA must be greater or equal to 85%. If a true PPA of 95% is assumed, a sample size of 146 positive samples affords 98.5% power to detect the lower limit of 85% for the associated 95% confidence interval. If a true NPA of 95% is assumed, a sample size of 85 negative samples affords 86.7% power to detect the lower limit of 85% for the associated 95% confidence interval. Considering the possibility of invalid results in approximately 15% of cases, the sample size above (172 positives and 100 negatives) is expected to provide sufficient statistical power to meet the acceptance criterion.

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