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TO: PHASE I SITES: U of CA LOS ANGELES (CA006), U OF SOUTHERN CALIFORNIA (CA011), U of CA SAN FRANCISCO (CA136), CALIFORNIA PACIFIC (CA222), U OF COLORADO (CO070), H. LEE MOFFITT CANCER CENTER (FL065), U OF MICHIGAN (MI014), OHIO STATE UNIV (OH007), CLEVELAND CLINIC (OH027), OREGON HEALTH SCIENCES UNIVERSITY (OR010), PROVIDENCE PORTLAND MC (OR014), U OF TENNESSEE – MEMPHIS (TN030), MD ANDERSON (TX035), U OF WASHINGTON (WA020)

PHASE II: SWOG

FROM: Danae Campos, Protocol Coordinator (E-mail- dcampos@swog.org)

RE: **S1221**, "Phase I/II Study of the Safety and Efficacy of the AKT Inhibitor GSK2141795 in Combination with Dabrafenib and Trametinib in Patients with BRAF Mutant Cancer." Study Chairs: Drs. A. Ribas, B. Chmielowski, R. Lo, and A Algazi.

REVISION #10

Study Chair: Antoni Ribas, M.D., Ph.D.
Phone Number: 310/206-3928
E-mail: aribas@mednet.ucla.edu

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Informed Consent changes
(√) Patient notification required (Patients currently receiving GSK2141795 must be reconsented.)

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes in this revision are effective upon approval by the local IRB; however, any changes to eligibility become effective 6 weeks after distribution of this notice.

REVISION #10

The following revisions have been made in the protocol referenced above:

1. Title Page: The version dates of the protocol and model consent form have been updated.

2. ICF: Page 13, under the section "What are the costs of taking part in this study", the paragraph beginning "If your disease progresses before the new drug supply", was deleted as there will be no additional supply of GSK2141795 available after 09/30/2018.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Syed Mahmood - Novartis

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated July 1, 2013

SWOG

PHASE I/II STUDY OF THE SAFETY AND EFFICACY OF THE AKT INHIBITOR GSK2141795 IN COMBINATION WITH DABRAFENIB AND TRAMETINIB IN PATIENTS WITH BRAF MUTANT CANCER

NCT #01902173

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AGENTS:

NCI-Supplied Investigational Agents:
Dabrafenib Mesylate (NSC-763760; IND-118705)
GSK2141795 (NSC-767034; IND-118705)
Trametinib (NSC-763093; IND-119432)

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PHASE II PORTION:

SWOG/SWOG

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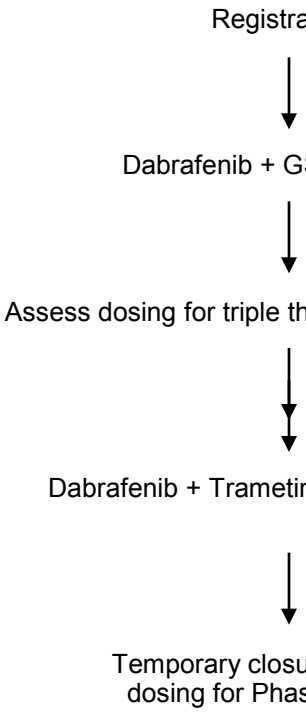
SCHEMA

Phase I portion (open to limited institutions as listed on the Title Page):



Phase II portion (open to all SWOG institutions):

A patient may be enrolled to either the Phase I portion or the Phase II portion, but not both.

1.0 OBJECTIVES

1.1 Primary Phase I Portion Objective

Dabrafenib + GSK2141795

The primary objective of the Phase I Portion will be to assess the safety of dabrafenib in combination with GSK2141795 and select the optimal dose of GSK2141795 for the Phase II Portion in patients with BRAF mutant cancer. Effective November 15, 2014, this trial will not proceed to the Phase II study of dabrafenib and GSK2141795, but will moving to an evaluation of triple therapy. See below)

Dabrafenib + Trametinib + GSK2141795

The primary objective of the Phase I portion will be to assess the safety of dabrafenib and trametinib and GSK2141795 in combination and select the optimal dose of the combination for the Phase II Portion in patients with BRAF mutant cancer.

1.2 Primary Phase II Portion Objective

The primary objective of the Phase II portion will be to evaluate the objective response rate (confirmed and unconfirmed, complete and partial responses) in patients with *BRAF*^{V600} mutant metastatic melanoma who have previously-have previously progressed on BRAFV600 inhibitor-based therapy (BRAFi), or BRAFi + MEK inhibitor-based therapy (MEKi).

1.3 Secondary Objectives

a. To estimate overall survival and progression-free survival.

b. To assess the toxicity profile of the recommended Phase II dose.

c. To assess response (complete and partial, confirmed and unconfirmed) of patients enrolled on each Phase I portion.

1.4 Translational Medicine Objective

a. The translational medicine objective is to explore the molecular mechanisms of acquired resistance to BRAF inhibitor therapy using available biopsies of lesions that progressed during prior BRAF inhibitor-based therapy. The analyses will include the following to detect MAPK-reactivation resistance: Detection of *BRAF*^{V600} amplification, *BRAF*^{V600} truncation, *NRAS*^{Q61} mutations and MEK mutations, which are the most validated and readily detectable acquired MAPK-reactivation resistance mechanisms. Additional analyses to detect other mechanisms of resistance, particularly those involving the AKT pathway, will be explored, as will be targeted sequencing of genes in the P13K/AKT pathway.

b. All patients participating in the Phase I portions of the study will have a limited PK sampling at baseline and at steady state on Days 15 and 29 before taking the study drugs on that day. In addition, three patients treated within the second cohort of each of the Phase I portions (D+G and D+T+G) will undergo an intense 15 day pharmacokinetic (PK) sampling for circulating levels of the study drugs. This will be performed to explore potential drug-drug interactions between dabrafenib and GSK2141795 leading to changes in the expected exposure with either agent compared to prior experience.

2.0 BACKGROUND

The BRAF inhibitors vemurafenib and dabrafenib confer objective response in about half of treated patients with *BRAF*^{V600} mutant metastatic melanoma, which is mediated by the inhibition of oncogenic MAPK signaling. Their clinical use is limited by the development of acquired resistance to single agent BRAF inhibitor therapies, which typically develops within 6 months of continuous therapy with dabrafenib or vemurafenib. *(1-7)*

Resistance to BRAF inhibitors does not follow the common pathways of resistance to other ATP-competitive targeted kinase inhibitors in that no mutations in the actual target kinase have been described that would make the drug binding ineffective. Notably, no mutations have been described in patient-derived samples that would correspond to the T315I resulting in resistance to imatinib in chronic myelogenous leukemia, or the T790M mutation resulting in resistance to gefitinib in non-small cell lung cancer. *(8,9)* Instead, a variety of mechanistically different resistance pathways have been described in subsets of acquired resistant tumor biopsies. These can be divided into two major groups when focusing on mechanisms reported to date in patient-derived samples:

1. **Reactivation of the MAPK pathway:** Despite the lack of identified secondary acquired mutations in BRAF to date, several alterations leading to reactivation of oncogenic signaling through the MAPK pathway result in acquired resistance to BRAF inhibitors. Of note, the resistant lesions universally maintain the *BRAF*^{V600} mutation. However, there can be other changes in BRAF itself, including amplifications of the mutant *BRAF*^{V600} gene and truncations in the BRAF protein through alternate splicing resulting in increased kinase activity due to increased dimerization. *(10,11)* Secondary mutations upstream or downstream of BRAF would also be predicted to result in resistance, and secondary mutations in *NRAS* and *MEK* have been described in patient-derived samples. *(12,13)* However, some patients with a concurrent mutation in *BRAF*^{V600} and *MEK*^{P124} at baseline can still have clinical responses to BRAF inhibitors. *(14)* Finally, overexpression of the MAPK protein COT without mutations has been suggested to also lead to acquired resistance. *(15)* Overall, data derived from analyzing tumor samples from baseline and at the time of acquired resistance, indicate that resistance due to reactivation of the MAP kinase pathway is present in 70% of the cases with a known or proposed resistance mechanism. *(16)* Most of these resistance mechanisms could be blocked by downstream MAPK pathway inhibition at the level of MEK or ERK. Combined BRAF and MEK inhibition has been tested in randomized Phase II and Phase III clinical trials using the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib. *(17,18)* Combination therapy substantially increases median PFS compared with dabrafenib alone and the FDA has approved the combination of dabrafenib and trametinib for the first line treatment of BRAF mutant melanoma. This combination is generally well tolerated and the addition of trametinib to dabrafenib actually reduced the incidence of several significant adverse effects of BRAF inhibitors. Based on the favorable adverse effect profile of dabrafenib with trametinib, triple therapy with dabrafenib, trametinib, and an additional agent may be feasible.

2. **MAPK-independent pathways:** In approximately one-fourth to one-third of the cases of acquired resistance, the BRAF inhibitor continues to demonstrate ability to block oncogenic BRAF^{V600} signaling, and the cell adapts to gain MAPK-independent oncogenic signaling often leading to overactivation of the PI3K pathway. *(12,16)* Mechanisms of resistance include overexpression or overactivation of receptor tyrosine kinases (RTKs), such as the platelet derived growth factor receptor beta (PDGFRb) the insulin-like growth factor receptor 1 (IGF-1R), or the epidermal growth factor receptor (EGFR). *(12,19,20)* Acquired resistance can also be induced by acquired activation mutations in PI3K pathway constituents including PIK3CA, PTEN, and PHLPP1. *(16)* Innate resistance to BRAF inhibitor therapy can be mediated by hepatocyte growth factor (HGF) binding to the RTK Met. *(21,22)* These RTKs share a common signaling hub, the PI3K-AKT pathway. In preclinical models this signaling can be inhibited by drugs that block PI3K, AKT or PI3K+TORC, restoring tumor responses in the acquired resistance setting.

(19,23-25) Unpublished data also suggest that acquired resistance to dual BRAF and MEK inhibition may lead to increased reliance on MAPK-independent pathways during drug escape and combined BRAF, MEK and AKT inhibition demonstrates substantial synergy preclinically in treatment-naïve models (*See Rationale for Triple Therapy*).

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

Data on 247 patients with metastatic melanoma and $BRAF^{V600}$ mutations participating in the Phase I/II 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 3.0.

Activity of dabrafenib + trametinib
In the Phase II 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. *(17)* All major efficacy endpoints were improved, including PFS, 12-month PFS, ORR, and duration of response (see table below).

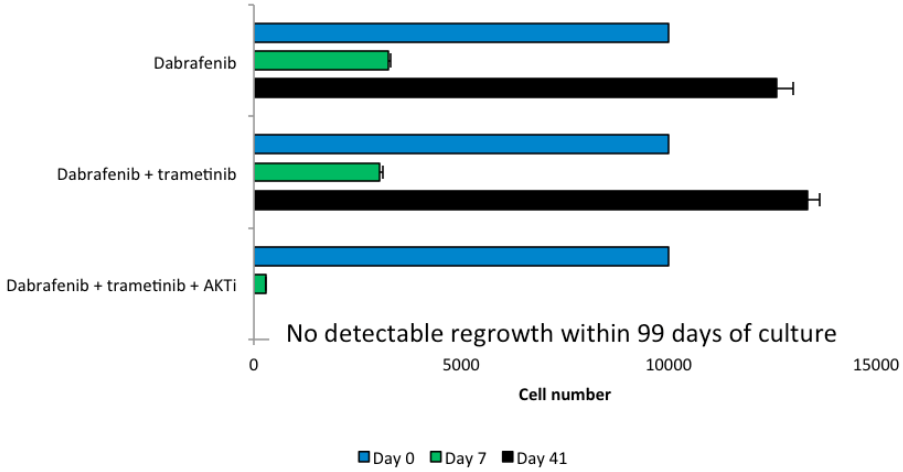
End Point (as assessed by the investigators)	Dabrafenib Monotherapy (n=54)	Combination 150/1 (n=54)	Combination 150/2 (n=54)
Progression-free Survival – months Median (95% CI)	5.8 (4.6-7.4)	9.2 (6.4-11.0)	9.4 (8.6-16.7)
Progression-free Survival at 12 mo. % (95% CI)	9 (3-20)	26 (15-39)	41 (27-54)
CR 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)

Safety data for trametinib in combination with GSK2141795

The combination of trametinib and GSK2141795 has been examined in Phase I and Phase II clinical trials. In Phase I testing, the most common adverse events (≥10%) were nausea (26%; G3/4 0%), AST elevation (22%; G3/4 9%), fatigue (22%; G3/4 0%), rash (22%; G3/4 0%), decreased appetite (17%; G3/4 0%), hypokalemia (17%; G3/4 0%), anemia (13%; G3/4 0%), confusional state (13%; G3/4 0%), dry mouth (13%; G3/4 0%), peripheral edema (13%; G3/4 0%), and vomiting (13%; G3/4 0%). *(26)* The recommended Phase II dose is trametinib 1.5 mg daily with GSK2141795 50 mg daily.

Rationale for triple therapy

Preclinical Rationale:
Activating mutations in the PI3K pathway have been described in 22% of tumors that acquired resistance to BRAF inhibitors, most frequently in combination with activating mutations of the MAPK pathway. *(16)* There are emerging data suggesting that the PI3K pathway plays a pivotal role in the survival of senescent tumor cells after maximal response to MAPK pathway inhibitors (Roger Lo, unpublished data). In preclinical testing, combined BRAF/MEK/AKT inhibition leads to profound decreases in BRAF mutant melanoma cell survival.



Lassen et al. Molecular Cancer. 2014.

Despite the improved PFS with dabrafenib and trametinib in the first line compared with dabrafenib alone, the addition of the MEK inhibitor trametinib alone to the BRAF inhibitor dabrafenib after disease progression on dabrafenib alone yields only modest clinical benefits with an objective response rate of only 9-15% and a median progression-free survival of only 3.6 months. *(27)* As a result, the combination of dabrafenib and trametinib after disease progression on a BRAF inhibitor has not been FDA approved and the vast majority of BRAF mutant melanoma patients treated with BRAF inhibitor monotherapy have no effective targeted therapy options after disease progression on these agents (median PFS 5-6 months). *(3,4)* The current study will examine the safety and efficacy of combined BRAF, MEK, and AKT inhibition based on preclinical data suggesting that resistance to MAPK inhibitors may be mediated by activating PI3K pathway mutations and non-mutational activation of the PI3K pathway. *(12,16,19-25)* Phase II testing of this combination in treatment naïve patients is based on data suggesting that 1. PI3K activity may be essential for the survival of senescent cells after maximal tumor killing from dabrafenib and trametinib and 2. The molecular evolution of surviving tumors in patients with disease progression on BRAF inhibitors may make the addition of additional oncogenic pathway inhibitors less effective at the time of progression than at the time of the initiation of BRAF inhibitor therapy (Roger Lo, unpublished data).

The rationales for the **S1221** treatment arms are summarized below:

Treatment arm	Prior treatment	Rationale
D + G Phase I ($BRAF^{V600X}$ solid tumors)	Any	Identify MTD.
D + T + G Phase I ($BRAF^{V600X}$ melanoma)	Any	Identify MTD, Early response signal.
D + T + G Phase II ($BRAF^{V600X}$ melanoma)	Prior PD on BRAFi or BRAFi + MEKi	Allows early assessment of benefit (ORR). Clinical need: Addition of MEKi alone after progression on BRAFi only modestly beneficial.
	No prior BRAFi or MEKi	Preclinical data suggests potential for more durable benefit due to targeting of senescent cells and prevention of emergence of resistance due to PI3K pathway activation.

Study outline

Dabrafenib + GSK2141795:
Phase I dose escalation will be performed according to a standard 3+3 scheme to identify the maximum tolerated dose (MTD) of dabrafenib with GSK795 prior to Phase 1 testing of dabrafenib, trametinib, and GSK2141795. The dabrafenib + GSK795 combination without trametinib will not continue to Phase 2 testing under the current protocol.

Dabrafenib + Trametinib + GSK2141795:
3 + 3 dose escalation will be performed to identify the MTD of dabrafenib, trametinib, and GSK2141795 in combination. Phase II testing will then be performed to obtain additional safety information and preliminary efficacy data in two populations: 1. Patients with prior disease progression on a BRAF inhibitor alone or a BRAF + MEK inhibitor combination and 2. Patients with no prior exposure to BRAF or MEK inhibitors.

Hypothesis

- The AKT inhibitor GSK795 can be combined safely with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.
- In patients with prior disease progression on BRAFi monotherapy or a BRAFi + MEKi combination, the addition of GSK795 and trametinib to dabrafenib will increase the overall response rate compared with historical controls treated with standard of care chemotherapy.
- Triple therapy with dabrafenib, trametinib, and GSK795 will increase the overall response rate in BRAFi/MEKi naïve patients compared with historical controls treated with dabrafenib and trametinib without a PI3K pathway inhibitor.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category			
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	32	62	94
Total Ethnic	34	63	97
Racial Category			
American Indian or Alaskan Native	2	0	2
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	32	63	95
Racial Category: Total of all Subjects	34	63	97

3.0 DRUG INFORMATION

Investigator's Brochures:

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, dabrafenib mesylate, trametinib, and GSK2141795 are investigational and are being provided under an IND held by the National Cancer Institute. The Investigator Brochures may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 240/276-6575.

3.1 Dabrafenib mesylate (GSK2118436B) (NSC-763760) (CTEP IND# 118705)

a. DESCRIPTION

Chemical Name:	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt
Other Names:	GSK2118436, GSK2118436A (free base)
Classification:	BRAF inhibitor
CAS Registry Number:	1195768-06-9
Molecular Formula:	$C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$
Molecular Weight:	615.68 (mesylate salt)

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.

b. TOXICOLOGY

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Below is the CAEPR for Dabrafenib mesylate (GSK2118436B).

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

Version 2.3, May 20, 2016[1]

Adverse Events with Possible Relationship to Dabrafenib mesylate (GSK2118436B) (CTCAE 4.0 Term) [n= 1291]			**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)***
EYE DISORDERS			
		Eye disorders - Other (iritis)[4]	
		Uveitis[4]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	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[5]		***Edema limbs[5] (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
Fever[6]			***Fever[6] (Gr 2)***
	Flu like symptoms		***Flu like symptoms (Gr 2)***
	General disorders and administration site conditions - Other (hemorrhage)[7]		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[8]	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (nasopharyngitis)		

INVESTIGATIONS			
	Creatinine increased[3]		***Creatinine increased[3] (Gr 2)***
	Neutrophil count decreased[3]		***Neutrophil count decreased[3] (Gr 2)***
	Platelet count decreased[3]		***Platelet count decreased[3] (Gr 2)***
	White blood cell decreased[3]		***White blood cell decreased[3] (Gr 2)***
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 2)***
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) - Other (squamous cell carcinoma or keratoacanthoma)[9]		***Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (squamous cell carcinoma or keratoacanthoma)[9] (Gr 2)***
	Treatment related secondary malignancy (non-SCC)[10]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
Headache			***Headache (Gr 2)***
		Syncope	

RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal failure)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		***Pruritus (Gr 3)***
Rash[11]			***Rash[11] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (abnormal hair texture)		***Skin and subcutaneous tissue disorders - Other (abnormal hair texture) (Gr 2)***
Skin and subcutaneous tissue disorders - Other (hyperkeratosis)			***Skin and subcutaneous tissue disorders - Other (hyperkeratosis) (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (neutrophilic panniculitis)[12]	
Skin and subcutaneous tissue disorders - Other (skin papilloma)			***Skin and subcutaneous tissue disorders - Other (skin papilloma) (Gr 2)***

VASCULAR DISORDERS			
	Vascular disorders - Other (venous thromboembolic event)[13]		

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

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

[6] 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 mesylate (GSK2118436B) is used in combination with trametinib dimethyl sulfoxide (GSK1120212B).

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

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

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

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

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

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

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

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

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Heart failure; Left ventricular systolic dysfunction; Mitral valve disease; Myocardial infarction; Sinus tachycardia
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Eye disorders - Other (amaurosis fugax); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual impairment); Eye disorders - Other (vitreous detachment); Floaters; Photophobia; Retinopathy
GASTROINTESTINAL DISORDERS - Colitis; Colonic perforation; Dry mouth; Dyspepsia; Gastritis; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Localized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic pain
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
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 loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hypernatremia; Hypocalcemia; Hypoglycemia; Hypomagnesemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (mycosis fungoides)
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysgeusia; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (intracranial pressure increased); Paresthesia; Seizure; Somnolence
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Hematuria; Renal calculi; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Menorrhagia; Reproductive system and breast disorders - Other (hematospermia)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Nasal congestion; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sore throat; Stridor; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Photosensitivity; Purpura; Skin and subcutaneous tissue disorders - Other (palmoplantar keratoderma)
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension

Note: Dabrafenib mesylate (GSK2118436B) 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.

c. PHARMACOLOGY

How Supplied: 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.

1. Each investigationally-labeled bottle is white, opaque, high density polyethylene (HDPE) with child-resistant closure and contains 28 capsules.

   - 50 mg capsule is Swedish orange, size 2 with markings of four black bars.
   - 75 mg capsule is pink, size 1 with markings of four black bars.

   Capsule excipients include microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide. Shell composition consists of an opaque hypromellose capsule, composed of red iron oxide (E172), titanium dioxide (E171), and hypromellose (E464). Four black bars are printed on the hypromellose capsules using black ink. The black ink contains black iron oxide (E172), shellac, propylene glycol, and ammonium hydroxide.

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

   - 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).

Storage: Store between 15°C to 30°C (59°F to 86°F).

Stability: Shelf-life studies of dabrafenib mesylate (GSK2118436B) are ongoing.

Route of Administration: Oral administration. Patients should take dabrafenib at least one hour prior to or two hours after a meal due to a potential food effect on dabrafenib absorption. A food effect study showed that food may decrease the dabrafenib C_{max} and $AUC_{(0-\infty)}$ by 60% and 33% respectively. If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.

Potential Drug Interactions**:** Dabrafenib mesylate (GSK2118436B) induces CYP3A4, 2C9 and possibly 2B6, 2C8, and 2C19 enzymes. Use caution in patients who are taking substrates that are metabolized in these enzyme pathways, such as warfarin.

Dabrafenib mesylate (GSK2118436B) metabolism appears to be mediated by CYP3A4 and CYP2C8. Use caution if strong inducers or inhibitors of CYP2C8 or 3A4 are co-administered with dabrafenib.

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.

Patient Care 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.

d. SUPPLIER

Dabrafenib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Dabrafenib is provided to the NCI under a Collaborative Agreement between Novartis and the DCTD, NCI.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recovered by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

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 a.m. and 4:30 p.m. Eastern time or by emailing PMBAfterHours@mail.nih.gov anytime.

3.2 GSK2141795 (GSK2141795C) (NSC-767034) (CTEP IND #118705)

a. DESCRIPTION

Chemical Name: N-[(1S)-2-amino-1-[(3,4 difluorophenyl)methyl]ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

Other Names: GSK2141795C

Classification: pan-AKT inhibitor

CAS Registry Number: 1047634-65-0

Molecular Formula: $C_{18}H_{16}Cl_2F_2N_4O_2$

Molecular Weight: 429.25 g/mol

Approximate Solubility: Very slightly soluble in water at room temperature (0.18 mg/mL). Solubility decreases as pH increases; for example solubility in gastric fluid at 37° C is >11 mg/mL.

Mode of Action: GSK2141795 is an ATP competitive pan-AKT inhibitor. AKT, a serine/threonine protein kinase with three isoforms, is active in several pathways that regulate survival, proliferation, tissue invasion and metabolism. Since AKT-mediated pathways are important in tumor proliferation and survival, AKT kinases are promising targets for therapeutic intervention. Hyperactivation of the AKT pathway can also correlate with chemotherapy resistance and poorer prognosis.

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks list (CAEPR) for GSK2141795 (NSC 767034)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm for further clarification. Frequency is provided based on 150 patients. Below is the CAEPR for GSK2141795.

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

Version 2.1, July 26, 2013[1]

Adverse Events with Possible Relationship to GSK2141795 (CTCAE 4.0 Term) [n= 150]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Esophagitis		
	Gastrointestinal mucositis[2]		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to GSK2141795 (CTCAE 4.0 Term) [n= 150]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypoglycemia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Respiratory mucositis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be disbuted 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] Gastrointestinal mucositis may include Anal mucositis, Mucositis oral, Rectal mucositis, or Small intestinal mucositis under the GASTROINTESTINAL DISORDERS SOC.

[3] Respiratory mucositis may include Laryngeal mucositis, Pharyngeal mucositis, or Tracheal mucositis under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC

Also reported on GSK2141795 trials but with the relationship to GSK2141795 still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Cardiac arrest, Left ventricular systolic dysfunction, Ventricular tachycardia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Wound infection
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Ejection fraction decreased; GGT increased
METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hyponatremia, Hypophosphatemia
NERVOUS SYSTEM DISORDERS - Dysgeusia; Dysphasia
RENAL AND URINARY DISORDERS - Acute kidney injury
VASCULAR DISORDERS - Thromboembolic event

Note: GSK2141795 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.

c. PHARMACOLOGY

How Supplied: GSK2141795 capsules are supplied by GlaxoSmithKline and distributed by the DCTD, NCI. The 25 mg capsule is a size 2 Swedish orange opaque body and Swedish orange opaque cap with no markings. The capsule contains active pharmaceutical ingredient, microcrystalline cellulose, and magnesium stearate. The capsules are packaged in white high density polyethylene (HDPE) bottles with white plastic, induction-seal, child-resistant caps. Each bottle contains 35 capsules.

Storage: Store bottles at 2-8° C (36-46° F).

Stability: Shelf life studies of GSK2141795 are on-going.

Route of Administration: Oral administration. Capsules must be taken fasting one hour following a meal and two hours before the next meal. These are the recommendations from the pharmaceutical collaborator.

Potential Drug Interactions: *In vitro* data suggest GSK2141795 is a substrate of CYP450 3A4. Potent inhibitors and inducers of 3A4 are prohibited. GSK2141795 appears to be a moderate inhibitor of CYP 2C8 and 3A4 by in vitro testing. Drugs that are substrates of these isoenzymes should be used with caution and ones with a narrow therapeutic index should be avoided.

GSK2141795 is a substrate of p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). It is also an inhibitor of BCRP and OATP1B1. Administration of sensitive BCRP substrates should be prohibited, such as topotecan.

d. SUPPLIER

GSK2141795 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. GSK2141795 is provided to the NCI under a Collaborative Agreement between GlaxoSmithKline, Inc. and the DCTD, NCI.

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

Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recovered by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

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 a.m. and 4:30 p.m. Eastern time by emailing PMBAfterHours@mail.nih.gov anytime.

3.3 Trametinib Dimethyl Sulfoxide (GSK1120212B) (NSC-763093) (IND-119432)

a. PHARMACOLOGY

Mechanism of Action: Trametinib 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 interferes with cellular signal-transduction and inhibits proliferation by inducing cell apoptosis, with selective activity towards B-RAF serine/threonine protein kinase (BRAF) and v-ras oncogene homolog GTPase (RAS) mutant cancer cell lines and hematopoietic cancer cells from acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) origins.

b. PHARMACOKINETICS

Absorption: Peak plasma concentrations are observed at 1.5 hours following single dose oral administration of trametinib under fasted conditions in humans. Administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in the maximum concentration (Cmax) and 10% decrease in the area under the concentration curve (AUC) compared to fasted conditions. Therefore, it is recommended that trametinib be administered under fasting conditions. The absolute oral bioavailability of a 2 mg tablet is moderate to high (72%) relative to a co-administered IV microdose (5 micrograms).

Distribution: Trametinib is highly bound to plasma proteins (97.4%), and has a high volume of distribution (Vd) of 1060 L.

Metabolism: Following single dose oral administration in humans, approximately 50% of plasma radioactivity is present as the parent compound. Trametinib is primarily metabolized via deacetylation mediated by hydrolytic esterases, such as carboxylesterases or amidases, with secondary oxidation or in combination with glucuronidation biotransformation pathways. The high absolute bioavailability and low clearance relative to liver blood flow (3.21 L/hr) suggest low hepatic extraction of trametinib in addition to low first-pass metabolism.

Elimination: Trametinib has a long terminal half-life of 5.3 days and accumulates with repeat once daily dosing. Fecal excretion is the major route of elimination accounting for >80% of excreted radioactivity recovered. Urinary excretion accounted for <19% of excreted radioactivity recovered (<10% of the radioactive dose).

c. ADVERSE EFFECTS

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1,111 patients.* Below is the CAEPR for trametinib dimethyl sulfoxide (GSK1120212B).

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

Version 2.4, October 7, 2016[1]

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 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 2)***
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
	Sinus bradycardia		
EYE DISORDERS			
	Blurred vision		
	Dry eye		
		Eye disorders - Other (chorioretinopathy also known as retinal pigment epithelial detachment)	
		Eye disorders - Other (retinal vein occlusion)	

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
EYE DISORDERS (contd.)			
	Eye disorders - Other (visual disorders)[2]		
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 2)***
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)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Paronychia		***Paronychia (Gr 2)***
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased		
	Ejection fraction decreased		

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypoalbuminemia		
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		***Hyponatremia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	
	Periorbital edema		
	Pruritus		***Pruritus (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (folliculitis)		***Skin and subcutaneous tissue disorders - Other (folliculitis) (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)[4]			***Skin and subcutaneous tissue disorders - Other (rash)[4] (Gr 3)***

Adverse Events with Possible Relationship to Trametinib dimethyl sulfoxide (GSK1120212B) (CTCAE 4.0 Term) [n= 1111]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 2)***
Vascular disorders - Other (edema)[5]			***Vascular disorders - Other (edema)[5] (Gr 2)***
	Vascular disorders - Other (hemorrhage)[6]		

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Myocardial infarction; Restrictive cardiomyopathy; Sinus tachycardia
EYE DISORDERS - Corneal ulcer; Eyelid function disorder; Flashing lights; Floaters; Glaucoma; Papilledema; Photophobia; Retinal detachment
GASTROINTESTINAL DISORDERS - Anal hemorrhage; Ascites; Duodenal ulcer; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Gastric hemorrhage; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other

(pneumatosis intestinalis); Gastrointestinal fistula; Gingival pain; Hemorrhoidal hemorrhage; Ileus; Lower gastrointestinal hemorrhage; Obstruction gastric; Pancreatitis; Rectal hemorrhage; Small intestinal obstruction; Upper gastrointestinal hemorrhage

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

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

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

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

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

METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Metabolism and nutrition disorders - Other (hyperphosphatemia)

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

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain

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

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

RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (dysuria); Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal fistula; Vaginal hemorrhage

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

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

VASCULAR DISORDERS - Hematoma; Hot flashes; Hypotension; Thromboembolic event (venous)

2. Pregnancy and Lactation: There are no adequate and well-controlled studies of trametinib in pregnant women. Animal studies have shown reproductive toxicity, decreased maternal and fetal weight, fetal malformations, and early termination of pregnancy. Therefore, trametinib should not be administered to pregnant women. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation. If trametinib is used during pregnancy, or if the subject becomes pregnant while taking trametinib, the subject should be informed of the potential hazard to the fetus.

   It is not known whether trametinib is excreted in human milk. Because of the potential for drugs to be excreted in human milk, the risk to the nursing infant cannot be excluded and therefore trametinib should not be administered to nursing mothers.

3. Drug Interactions: *In vitro* studies suggest that trametinib may be a substrate for CYP3A4 metabolism and consideration should be used when trametinib is given in combination with a strong CYP3A4 inducer or inhibitor. Trametinib is a weak CYP2C8 inhibitor and may affect medications that are substrates of CYP2C8. Trametinib is not a substrate for human P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), OATP1B1, or OATP1B2 transporters.

   Patients who are taking concomitant medications that have the potential to interact with trametinib may continue taking them, but should be monitored for additional toxicities.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Administration Instructions: Administer orally, on an empty stomach, either 1 hour before or 2 hours after food.

e. PREPARATION, STORAGE & STABILITY

Store tablets at 2°C – 8°C in the original bottle. Do not package tablets or remove desiccant. Bottles should be stored in the manufacturer's package carton for light protection. Protect from moisture. Shelf life surveillance of the intact bottles is ongoing.

Patient Storage Instructions:

- Study drug can be transported home in the bottle(s) that were dispensed to the patient at room temperature. Avoid exposing the bottle(s) to prolonged temperature extremes (i.e. do not leave bottle(s) in a hot car while doing errands)
- At home, store the study drug in the refrigerator, 2°C – 8°C (36°F - 46°F). Do not freeze the bottles.
- Keep the tablets in the original bottle(s). Do not remove tablets from the bottle(s) and put them in a pill box or daily dispenser.
- Keep desiccant cylinder in the bottles in order to keep tablets dry.

f. HOW SUPPLIED

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

a. Investigationally labeled bottles each contain 32 tablets packaged in high density polyethylene bottles with child-resistant closures including an induction seal liner.

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

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated. Aqueous film coating consists of Opadry Yellow 03B120006 (hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow).

- 2 mg tablets are pink, round, biconvex and film-coated. Aqueous film coating consists of Opadry Pink YS-1-14762-A (hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80, iron oxide red).

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

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

- 0.5 mg tablets are yellow, modified oval, biconvex and film-coated with 'GS' debossed on one face and 'TFC' on the opposing face. Aqueous film coating consists of hypromellose, titanium dioxide, polyethylene glycol, iron oxide yellow.

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

2. Supplied by: Trametinib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Dabrafenib is provided to the NCI under a Collaborative Agreement between Novartis and the DCTD, NCI.

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

Drug may be requested by submitting agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

4. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recovered by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

5. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

6. Contact 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 a.m. and 4:30 p.m. Eastern time or by emailing PMBAfterHours@mail.nih.gov anytime.

4.0 STAGING CRITERIA (AJCC 7th Edition, 2010)

Stage IIIC	**Colon**	
T4a	N2a	M0
T3-T4a	N2b	M0
T4b	N1-N2	M0

Stage IIIC	**Ovarian**	
T3c	N0	M0
Any T	N1	M0

STAGE IIIC	**Melanoma**	
T1-4b	N1b	M0
T1-4b	N2b	M0
T1-4b	N2c	M0
Any T	N3	M0

Stage IV	**Melanoma**	
Any T	Any N	M1

Distant Metastasis (M)

M1	Distant metastasis
M1a	Metastases to skin, subcutaneous or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

NOTE: for all other disease sites Stage IV is defined as any distant metastasis for this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

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 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

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

5.1 Phase I Portion Eligibility Criteria

_____ a. Patients must have *BRAF*^{V600} mutant metastatic cancer irrespective of the histology or prior therapy. *BRAF*^{V600} mutant status must be documented by a CLIA-certified laboratory. Use of an FDA-approved test is preferred although other BRAF tests at a CLIA-certified laboratory may also be accepted.

_____ b. Patients must have locally advanced unresectable Stage IIIC or metastatic Stage IV cancer with either progression to prior therapy or a newly diagnosed cancer that does not have an available treatment with curative intent. See Section 4.0 for staging criteria.

_____ c. Patients must have a complete physical examination and medical history within 28 days prior to registration.

_____ d. Patients must have measurable or non-measurable disease as defined in Section 10.1. All measurable lesions must be assessed (by physical examination, CT, or MRI scan) within 28 days prior to registration. Tests to assess non-measurable disease must be performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

_____ e. All patients must undergo a CT or MRI of the brain within 42 days prior to registration. Patients with asymptomatic brain metastases or previously treated brain metastases that are stable (i.e. not requiring corticosteroids) at the time of registration will be eligible.

_____ f. Patients may have received prior systemic therapy (chemotherapy, immunotherapy, biologic therapy, or combination regimens). All adverse events associated with prior treatment must have resolved to $\leq$ Grade 1 prior to registration.

SWOG Patient No. _____

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

_____ g. Patients progressing on a prior BRAF inhibitor-based therapy will be eligible, as are patients naïve to BRAF inhibitor therapy. Resistance to BRAF inhibitor-based therapy will be defined as progressive disease by RECIST 1.1 criteria while receiving therapy with a BRAF inhibitor (vemurafenib or dabrafenib, alone or in combination with a MEK inhibitor). This may be innate resistance (patients who never achieved a tumor response while on BRAF inhibitor therapy) or acquired resistance (progression after having a tumor response to BRAF inhibitor therapy). There will not be a period of break between progression on the prior BRAF inhibitor-based therapy and the start of dabrafenib, trametinib and GSK2141795.

_____ h. Patients may have received prior surgery (for both the primary and Stage IV disease). All adverse events associated with prior surgery must have resolved to ≤ Grade 1 prior to registration.

_____ i. Patients may have received prior radiation therapy. All adverse events associated with prior radiation therapy must have resolved to ≤ Grade 1 prior to registration.

_____ j. Patients must be willing to submit blood for pharmacokinetics (see Section 15.3). Sites must order **S1221** PK kit immediately after registration (see Section 18.6). The SWOG patient ID number must be provided on the **S1221** PK Kit Request Form.

_____ k. Patients must have available and be willing to submit baseline tissue taken at the time of disease progression to prior BRAF inhibitor-based therapy (either fresh frozen [preferred], or paraffin-embedded tumor blocks) OR must have a site of disease that can be biopsied within this study for translational medicine studies outlined in Section 15.4 and Section 18.2. Tissue may be from an archival biopsy or a new biopsy after the patient has been registered to the protocol. Since patients are referred to this protocol after progression on prior BRAF inhibitor-based therapy, the biopsy taken at the time of progression will be used as the baseline biopsy for this study. Patients must be willing to submit plasma and whole blood for translational medicine studies as outlined in Section 15.4 and Section 18.2.

_____ l. Patients must have Zubrod Performance Status ≤ 1 (see Section 10.4).

_____ m. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,200/ul; platelets ≥ 100,000/ul; and hemoglobin ≥ 9 g/dL. These results must be obtained within 28 days prior to registration.

_____ n. Patients must have adequate liver function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (or ≤ 2.5 x ULN for patients with Gilbert's syndrome), and AST and ALT ≤ 2.5 x IULN (or < 5 x IULN for patients with known liver metastases). Patients must have a serum albumin ≥ 2.5 g/dL. These results must be obtained within 28 days prior to registration.

SWOG Patient No. _____

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

_____ o. Patient must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ 1.5 mg/dL OR measured or calculated creatinine clearance ≥ 50 mL/min. This result must have been obtained within 28 days prior to registration.

Estimated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$

_____ p. Patient must have a left ventricular ejection fraction ≥ institutional lower limit of normal (LLN) by ECHO or MUGA within 28 days prior to registration.

_____ q. Patients must not have a corrected QT (QTc) interval ≥ 480 msecs within 28 days prior to registration

_____ r. Patients must not have a history of acute coronary syndromes (including unstable angina), myocardial infarction within 6 months, coronary angioplasty, or stenting within the past 24 weeks; Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system (see Appendix 18.6); or history of known cardiac arrhythmias (such as atrial fibrillation) unless it has been stably controlled for > 30 days prior to registration. Abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram (subjects with Grade 1 abnormalities [i.e., mild regurgitation/stenosis]) can be entered on study. Subjects with moderate valvular thickening are not eligible.

_____ s. Patients with melanoma must have a serum lactate dehydrogenase (LDH) test performed within 28 days prior to registration.

_____ t. Patients with HIV are eligible if they are not on antiviral agents and have adequate CD4 counts (≥ 500 mm^3).

_____ u. Patients receiving anticoagulation treatment are allowed to participate with INR established within the therapeutic range. (See Section 7.2b).

_____ v. At the time of registration, patients must not be receiving any medications or substances that are strong inhibitors or inducers of CYP3A or CYP2C8. Patients must not be planning to use herbal remedies (e.g., St. John's wort), or strong inhibitors or inducers of P-glycoprotein (Pgp) or breast cancer resistance protein 1 (Bcrp1). See Appendix 18.4 for list of medications.

_____ w. Women of childbearing potential must have a negative pregnancy test within 14 days of registration.

SWOG Patient No. _____

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

_____ x. Patients must not be pregnant or nursing due to unknown teratogenic side effects. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. Hormonal contraception is not allowed due to drug interactions which can render hormonal contraceptives ineffective. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ y. Patient must not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, previously diagnosed Type 1 diabetes mellitus/Type 2 diabetes, psychiatric illness/social situations, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, that would limit compliance with study requirements. Patients must not have any evidence of mucosal or internal bleeding. Patients must not have a history of pneumonitis or interstitial lung disease. Patients must not have received any major surgery within four weeks prior to registration.

_____ z. Patients must not have an active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection.

_____ aa. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib or other agents used in this study including dimethyl sulfoxide (DMSO).

_____ bb. Patients must be able to retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels. Patients who have feeding tubes can enroll in the study provided that the capsules do not need to be modified.

_____ cc. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ dd. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

_____ ee. Patients must be ≥ 18 years of age.

_____ ff. Patients must have a serum albumin ≥ 2.5 g/dL within 28 days prior to registration.

SWOG Patient No. _____

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

_____ gg. Patients with known history or current evidence of retinal vein occlusion (RVO) are not eligible:

- History of RVO, or predisposing factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
- Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO such as:
  - Evidence of new optic disc cupping
  - Evidence of new visual field defects
  - Intraocular pressure > 21 mmHg

- NOTE: Ophthalmic exam is required for all patients. Exam must be obtained within 28 days prior to registration.

_____ hh. Patients must not have uncontrolled hypertension (defined as systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg which cannot be controlled by anti-hypertensive therapy),

5.2 Phase II Portion Eligibility Criteria

All the same criteria from Section 5.1 above, but eligibility will be restricted to the following:

_____ a. Patients must have histologically confirmed melanoma with *BRAF*^{V600} mutation. Patients must have Stage IIIC or Stage IV disease as outlined in Section 4.0.

_____ b. Patients must have received prior BRAF inhibitor therapy (e.g. dabrafenib, vemurafenib) within 56 days prior to registration. Prior trametinib therapy is permitted. Patients are not required to interrupt BRAF or MEK inhibitor therapy prior to the initiation of three agent combination therapy on study.

_____ c. Patients must have measurable disease as defined in Section 10.1. All measurable lesions must be assessed (by physical examination, CT, or MRI scan) within 28 days prior to registration. Tests to assess non-measurable disease must be performed within 42 days prior to registration. Patients whose only measurable disease is within a previous radiation therapy port must demonstrate clearly progressive disease (in the opinion of the treating investigator) prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (RECIST 1.1).

_____ d. Patients must have Zubrod Performance status ≤ 2 (see Section 10.4).

_____ e. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years. 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.

6.0 STRATIFICATION FACTORS

This section is not applicable.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Ribas at 310/206-3928 or Dr. Algazi at 415/353-7552. For dosing principles or questions, please consult SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

NOTE: GSK2141795 will not be available after September 30, 2018. At that time, patients remaining on protocol treatment may continue with dabrafenib and trametinib alone.

7.1 Treatment Overview

The study will be conducted in two sequential parts. A patient may be enrolled to either the Phase I Portion or the Phase II Portion, but not both.

Phase I Dabrafenib plus GSK2141795 (D+G) Details are in Section 7.3 **and Dabrafenib and Trametinib plus GSK2141795 (D+T+G) Portion** – Details are in Section 7.4.

Phase II Portion – Details are in Section 7.5.

7.2 General Concomitant Medication and Supportive Care Guidelines

a. The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study treatment. Because there is a potential for interaction of the study drugs with other concomitantly administered drugs through the cytochrome P450 system, the concurrent use of all other drugs, over-the-counter medications, or alternative therapies must be recorded in the clinical chart. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior surgical procedures will be recorded in the clinical chart. The Study Chair should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes (see Section 18.4). Appendix 18.6 contains a patient information sheet that can be used for this specific protocol and presented to the patient.

Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibition, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in Section 18.4) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications.

b. Warfarin exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus dose monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter potency.

c. Patients should have a baseline fasting glucose level within the institutional upper limit of normal (IULN). This result should be obtained within 28 days prior to registration. Given the known metabolic toxicities of GSK2141795, patients with prior diabetes mellitus or problems in glucose control should have an HgA1c ≤ 7% within 28 days prior to registration. The same criterion will be used in patients with confirmed diagnosis of diabetes mellitus who have been on a stable dietary or therapeutic regimen for this condition in the last three months.

d. 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.

e. Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. Any radiation therapy should be completed at least two days prior to registration.

7.3 Treatment - Phase I Dabrafenib + GSK2141795 (D+G)

a. Dose Escalation Scheme for D + G

Effective November 15, 2014, this trial will not proceed to the Phase II study of dabrafenib and GSK2141795, in favor of evaluation of triple therapy. (See Section 7.4).

This will be a dose-escalation clinical trial using a standard 3+3 design. There will be 2 dose levels. The starting dose level is 1. No patients will be enrolled in the next dose level until the toxicity is fully assessed after the completion of 2 cycles in at least 3 patients enrolled at the previous dose level. The maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of dose-limiting toxicities (DLT) is < 33%. The cohort of the MTD (or proposed dose for Phase II Portion if MTD not reached) will be at least 6 patients.

Dose escalation scheme for D+G:

Dose Level	Dabrafenib (twice a day)	GSK2141795 (once a day)
1	150 mg	50 mg
2	150 mg	75 mg
2+	12/1/15	12/1/15

NOTE: The drug regimen will be given on an outpatient basis. A cycle equals 28 days.

In the case that the PK sampling suggests that there is a drug-drug interaction between dabrafenib and GSK2141795 resulting in decreased exposure of one or both of the study drugs, a cohort 2+ will be open with dosing increased over cohort 2 with goal of reaching the full dose plasma levels of both agents based on the prior single agent experience with each of them.

Patients enrolled at a lower dose cohort can have their doses of GSK2141795 increased to the next cohort level if DLT is < 33% and at least 3 patients have gone through the full DLT assessment period of 2 months.

b. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.3c.

2. Only DLTs occurring during Cycles 1 and 2 will be used to guide dosing determination of GSK2141795.

3. Patients will be considered evaluable for DLT if they fulfill one of the following criteria:

   - They experience a DLT or
   - They received GSK2141795 at the assigned dose for at least 11 days during Cycle 1, and at least 28 days combined of dabrafenib over Cycles 1 and 2 or
   - They received GSK2141795 at the assigned dose for at least 11 days during Cycle 1 and at least 50% of dabrafenib during Cycle 1.

   Patients who do not meet at least one of these criteria will be considered not evaluable for DLT and will be replaced.

4. The following dosing scheme will be used for dose determination:

   a. Begin at Dose Level 1 (see Dose Escalation Scheme above):

      1) Enroll 3 patients and evaluate for toxicity. Enroll additional patients as required until 3 evaluable patients have been enrolled.

      2) If 0 of the initial 3 patients experience a DLT stop enrollment at this dose and continue to Dose Level 2.

      3) If only 1 of the initial 3 evaluable patients at the current dose level experience a DLT, expand enrollment until 6 evaluable patients have been enrolled or a second patient experiences a DLT.

      4) If 1 of 6 patients experiences a DLT, continue to Dose Level 2.

      5) If 2 or more patients experience a DLT, lower dose levels may be investigated to find the recommended dose for the Phase II Portion or the study may be permanently closed.

   b. At Dose Level 2 (see Dose Escalation Scheme above):

      1) Enroll 3 patients and evaluate for toxicity. Enroll additional patients as required until 3 evaluable patients have been enrolled.

      2) If 0 or 1 patients experience a DLT, expand enrollment until 6 evaluable patients have been enrolled or a second patient experiences a DLT.

      3) If 0 or 1 of 6 patients experiences a DLT, Dose Level 2 is the MTD.

      4) If 2 or more patients experience a DLT,

         a) If 6 patients have been enrolled in Dose Level 1, Dose Level 1 is the MTD.

         b) If 3 patients have been enrolled in Dose Level 1, expand enrollment to 6 evaluable patients.

            1. If 0 or 1 patients of 6 patients experience a DLT, Dose Level 1 is the MTD.

            2. If 2 or more patients experience a DLT, lower dose levels may be investigated to find the recommended dose for the Phase II Portion or the study may be permanently closed.

c. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0.

Dose-limiting toxicities (DLT) apply only during Cycles 1 and 2 and should be drug-related (possible, probable or definite). The following events are considered dose limiting:

1. Febrile neutropenia,

2. Grade 4 neutrophil count decrease for more than 7 days duration,

3. Grade 4 platelet count decrease,

4. Grade 3 or 4 skin rash, fevers and hyperglycemia that do not recover within 14 days with adequate medical management as described in Section 8.0,

5. Grade 3 or 4 non-hematologic toxicity that does not recover within 7 days with adequate medical management.

7.4 Treatment - Phase I Dabrafenib + Trametinib + GSK2141795 (D + T + G)

a. Dose Escalation Scheme of D + T + G:

Phase I portion: The primary objective is to assess the safety of dabrafenib, trametinib, and GSK2141795 in combination and to determine the dosing of the 3 drug combination for the Phase II portion. Dose escalation of dabrafenib, trametinib, and GSK2141795 will be initiated after completion of the dabrafenib + GSK2141795 phase I dose escalation. This three drug dose escalation will follow a standard 3+3 design. There will be 4 dose levels. No patients will be enrolled in the next dose level until the toxicity is fully assessed after the completion of 2 cycles in at least 3 patients enrolled at the previous dose level. The maximum tolerated dose (MTD) is defined as the highest dose studied in which the incidence of dose-limiting toxicities (DLT) is < 33%. The MTD cohort (or proposed dose for Phase II portion if MTD not reached) will include at least 6 patients.

Dose escalation scheme for D+T+G

Dose Level	Dabrafenib (mg PO BID)	Trametinib (mg PO daily)	GSK2141795 (mg PO daily)
1	150	1.5	25
2	150	1.5	50
3	150	1.5	75
4	150	2	75

b. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.4c.

2. Only DLTs occurring during Cycles 1 and 2 will be used to guide dosing determination of the study combinations.

3. Patients will be considered evaluable for DLT if they fulfill one of the following criteria:

- They experience a DLT or
- They received GSK2141795 at the assigned dose for at least 11 days during Cycle 1, at least 28 days combined of trametinib over Cycles 1 and 2, and at least 28 days of dabrafenib over Cycles 1 and 2 or
- They received GSK2141795 at the assigned dose for at least 11 days during Cycle 1, at least 50% of trametinib during Cycle 1 and at least 50% of dabrafenib during Cycle 1.

.

Patients who do not meet at least one of these criteria will be considered not evaluable for DLT and will be replaced.

4. The following dosing scheme will be used for dose determination:

a. Begin at Dose Level 1 (see Dose Escalation Scheme above):

1) Enroll 3 patients and evaluate for toxicity. Enroll additional patients as required until 3 evaluable patients have been enrolled.

2) If 0 of the initial 3 patients experience a DLT stop enrollment at this dose and continue to the next higher dose level. If the current dose level is Dose Level 4, then expand enrollment until 6 evaluable patients have been enrolled or two patients experience a DLT.

3) If 0-1 out of 6 patients experience a DLT on Dose Level 4, then Dose Level 4 is the MTD.

4) If only 1 of the initial 3 evaluable patients at the current dose level experience a DLT, expand enrollment until 6 evaluable patients have been enrolled or a second patient experiences a DLT.

5) If 1 of 6 patients experiences a DLT, continue to the next highest dose level. If 2 or more patients have already experienced a DLT at the next highest level or if the current dose level is Dose Level 4 then the current dose level is the MTD.

6) If 2 or more patients experience a DLT, stop enrollment at the current dose level and continue to the next lowest dose level. If 6 patients have already been enrolled at the next lowest dose level then that dose level is the MTD. If the current dose level is Dose Level 1 lower dose levels may

be investigated to find the recommended dose for the Phase II Portion or the study may be permanently closed.

c. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0.

Dose-limiting toxicities (DLT) apply only during Cycles 1 and 2 and should be drug-related (possible, probable or definite). The following events are considered dose limiting:

1. Febrile neutropenia,
2. Grade 4 neutrophil count decrease for more than 7 days duration,
3. Grade 4 platelet count decrease,
4. Grade 3 or 4 skin rash, fevers and hyperglycemia that do not recover within 14 days with adequate medical management as described in Section 8.0,
5. Grade 3 or 4 non-hematologic toxicity that does not recover within 7 days with adequate medical management.

7.5 Treatment - Phase II Portion of the Study

Agent	Dose	Route	Schedule*
Dabrafenib	150 mg	PO	Twice a day
Trametinib	determined in Phase I portion	PO	Once a day
GSK2141795	determined in Phase I portion	PO	Once a day

* Note: One cycle = *28* days

Patients will continue treatment until disease progression or other reason for discontinuation of protocol treatment (see Section 7.9).

7.6 Guidelines for Administration

When dabrafenib, trametinib and GSK2141795 are administered in combination, take the once-daily dose of trametinib and GSK2141795 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. Study drugs may be delivered to patients with feeding tube as long the capsules and tablets are not modified.

If administration of drug is interrupted or permanently discontinued, administration of the other drugs may be continued.

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 or GSK2141795, the subject may take the dose immediately if the next dose is scheduled for at least 12 hours later.

7.7 Drug Compliance Documentation

Drug compliance will be recorded by patients on the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.8 Full CDUS Reporting Requirements

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4c, the **S1221** Treatment Form, and the **S1221** Adverse Event Form). A cycle is defined as **28** days.

7.9 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2d. However, the patient may continue to stay on protocol treatment as long as in the opinion of the treating investigator the patient is continuing to clinically benefit from treatment. This may be if there are lesions that continue to respond to the therapy despite others progressing, or if there is symptomatic relief of symptoms on therapy.

b. Symptomatic deterioration (as defined in Section 10.2e).

c. Unacceptable toxicity.

d. Treatment delay of both protocol drugs for any reason > 8 weeks.

e. The patient may withdraw from the study at any time for any reason.

7.10 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.11 Follow-Up Period

All patients will be followed until death or ***3*** years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Dose Modification Considerations

a. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reductions.

b. No dose escalation or re-escalation is allowed.

8.3 Dose Modifications for Dabrafenib, Trametinib, and GSK2141795

The table below outlines the dose levels to be used for any necessary dabrafenib, trametinib and GSK2141795 dose modifications:

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

Dose Level	GSK2141795 Dose/Schedule
0	75 mg QD
-1	50 mg QD
-2	25 mg QD

Dabrafenib, Trametinib, and GSK2141795 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. Dose reduction below 1 mg once daily for trametinib is not allowed. Dose reduction below 25 mg once daily for GSK2141795 is not allowed. However, if dabrafenib, trametinib, or GSK2141795 is permanently discontinued due to an agent specific toxicity (see below), the patient will be allowed to continue on the remaining agent(s).

Study Chair approval is required to restart study treatment after ≥ 28 days of dose interruption.

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. Study Chair should be consulted if there are questions about the attribution of AEs and how the doses should be modified.

a. 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 <28days. CTEP monitor should be consulted for resumption of single agent.	

b. 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

Dose Modification and Management Guidelines for **Pyrexia**[a]

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		
1st Event[b]:	• Cinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] • Administer anti-pyretic treatment if clinically indicated and continue prophylactic treatment[f]	• Interrupt dabrafenib. • Continue trametinib and GSK2141795. • 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[c] • Laboratory work-up[c] • Hydration as required[d] • 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.[f]	• **Interrupt dabrafenib.** • Continue trametinib and GSK2141795 • 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**.

Dose Modification and Management Guidelines for **Pyrexia**[a] (contd)

Event	Management Guideline	Dose Modification
Subsequent Events:	• Clinical evaluation for infection and hypersensitivity[c] • Laboratory work-up[c] • Hydration as required[d] • Blood sample for cytokine analysis[e] • Within 3 days of onset of pyrexia: – Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia.[g] – If corticosteroids have been tapered and pyrexia recurs, restart steroids. – If corticosteroids cannot be tapered, consult medical monitor.	• **Interrupt dabrafenib.** • Continue trametinib and GSK2141795. • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level**.[h] • If dabrafenib must be reduced to <50 mg BID, permanently **discontinue dabrafenib**.
[h] 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.	–	

c. Dose Modification for **Rash**

Rash is a frequent AE observed in patients receiving trametinib, dabrafenib, and GSK2141795.

The institutional standards for the management of skin-related AEs can differ from these guidelines. In this case, best clinical judgment should be applied and a consultation with the study chair or the CTEP Medical Monitor may be required.

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)		

Supportive Care and Dose Modification for Rash

CTCAE Grade	Adverse Event Management	Action and Dose Modification
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 a. * 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 by one dose level (all agents)**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce study treatment 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 at reduced dose level (all agents).**[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 reduced by one dose level (all agents).**[3,4] • If no recovery to ≤ grade 2 within 28 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 priopionate 0.5% cream. 3. Approval of Study Chair is required to restart study treatment after >28 days of interruption. 4. Study treatment may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.		

d. 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

e. Treatment Modification for **New Primary/ Recurrent Malignancies:**

Cutaneous SCC and New Primary Melanoma
Dermatologic skin assessments for subjects on treatment should be performed before initiation of dabrafenib, then every 2 months through treatment. *(For protocols that start after June 2014, it is also recommended that skin exams 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.**

- *Cutaneous SCC*
  Cases of cuSCC (which include those classified as keratoacanthoma 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. 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.

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. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses with the results provided to CTEP via 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.

f. Dose Modification for **Hemorrhages**

Grade 3	• Hold dabrafenib, trametinib and GSK2141795 for up to 3 weeks • If improved, resume the drugs at one dose reduction • If no improvement, permanently discontinue dabrafenib or dabrafenib-trametinib
Grade 4	• Permanently discontinue dabrafenib or dabrafenib-trametinib

g. 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.

h. 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. See Section 8.4a for GSK2141795 dose modification instructions.

i. Dose Modification for **Renal Insufficiency**

Prior to start of study treatment, concomitant medications should be reviewed for the potential risk of inducing nephrotoxicity and modified if clinically possible.

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 CTEP Medical Monitor. 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) ***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 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 6.1.2.

[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 Study Chair is required before restarting study treatment if there is evidence of thrombotic microangiopathy.

j. Dose Modification for **Reduced Left Ventricular Ejection Fraction**

Decreases of the left ventricular ejection fraction (LVEF) have been observed in patients receiving trametinib. Therefore, ECHO/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).

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 Study Chair and request approval for restart. – Restart trametinib 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** – Continuation of dabrafenib and GSK214175 may be considered after consultation with Study Chair. – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
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 and GSK2141795 until LVEF improves. Consult Study Chair for resumption of dabrafenib and GSK2141795** • 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.		

k. Dose Modification for **<u>Hypertension</u>**

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.

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]**.

Treatment Modification for Hypertension

Event	Management Guideline	Dose Modification
(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 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

l. Dose Modification for **QTc Prolongation and Valvular Changes**

Dose 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 investigator and CTEP medical monitor agree that the subject will benefit from further treatment.

Dose modifications for valvular changes	
Asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTC AE v4.0)	• Hold study therapy. Repeat ECHO within 1 week, and every 1-2 weeks for 4 weeks. • If abnormality recovers within 4 weeks, resume study therapy with one dose level reduction. For such subjects, continue ECHO monitoring 2 and 4 weeks after rechallenge, then every 4 weeks for 12 weeks and then per protocol. • If no recovery by 4 weeks, discontinue the study drug. Follow up with echocardiogram as above
Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention)	• Permanently discontinue GSK2118436. • Continue echocardiogram every 4 weeks for 16 weeks or until resolution.
Resumption of the study agent may be considered in patients who were benefiting and have recovered from the valvular toxicities, but would require approval by the study sponsor (CTEP) and study chair)	

m. Dabrafenib or 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 or Dabrafenib-Trametinib **Treatment Modification and Management Guidelines for Diarrhea**

CTCAE Grade	Management Guideline	tion 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.

Dabrafenib or Dabrafenib-Trametinib **Treatment Modification and Management Guidelines for Diarrhea**

CTCAE Grade	Management Guideline	tion and Dose Modification
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea[2]**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea-free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life-threatening complications.	• Interrupt 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 medical monitor and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

n. 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.

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]). For events of visual changes regardless of severity but for which an ophthalmic examination is conducted, a blood sample for PK analysis is encouraged when feasible, and the blood sample should be drawn as close as possible to the time of the event.

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.

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 and GSK2141795 may be continued. • If RPED and RVO excluded, restart trametinib at same dose level • 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 and GSK2141795 may be continued. • If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor. • 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.		

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 and GSK2141795 treatment is not affected
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. Continue dabrafenib and GSK2141795 • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

Dabrafenib or 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 continue.

o. 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.

CTCAE Grade
Grade 1
Grade 2
Grade 3
Grade 4

p. Dose Modification for **Liver Chemistry Changes**

Dabrafenib or 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).
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 5. ALT ≥3x ULN **and** cannot be monitored weekly for 4 weeks 6. ALT ≥3x ULN associated with symptoms[3] (new or worsening) believed to be related to liver injury or hypersensitivity	• **Immediately discontinue study treatment.** • **Do not restart/rechallenge** unless approved by 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] • If possible, obtain blood sample for PK analysis.[5] • Serum CPK and LDH. • Fractionate bilirubin, if total bilirubin ≥2x ULN. •

Event	Treatment modifications and assessment/monitoring
(Contd.)	• CBC with differential to assess eosinophilia. • Record clinical symptoms of liver injury, or hypersensitivity on AE CRF. • Record concomitant medications (including acetaminophen, herbal remedies, other over the counter medications). • Record alcohol use. *Additional work up for patient stopping for criteria 1-2 (with abnormal TB and INR, indicating potentially more significant liver toxicities)*: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (in subjects with likely acetaminophen use in the preceding). • If there is underlying chronic hepatitis B (e.g. positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody.[6] • Liver imaging (ultrasound, MRI, CT) and /or liver biopsy.

Footnotes:

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

q. 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 3 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.

8.4 Dose Modifications for GSK2141795

a. **GSK2141795 Dose Modification for Hypo- or Hyperglycemia**

Management and Dose Modification Guidelines for Hypo- or Hyperglycemia		
Criteria	**Management Guidelines**	**Study Drug Modification**
(For management purposes, refer to mild, moderate and severe intensity criteria; however for eCRF reporting use NCI-CTCAE version 4.0 Grades 1-5)		
Mild Fasting blood glucose > 150mg/dL	Monitor fasting and preprandial glucose.	**Continue study drug**
Moderate to Severe Fasting blood glucose <70 mg/dL OR any blood glucose > 250mg/dL	• If a blood glucose >250 mg/dL, monitor for ketoacidosis as clinically indicated. • When managing hyperglycemia associated with GSK2141795, be aware that the action of insulin or other antihyperglycemic agents (*e.g.*, sulfonylureas, biguanides, *etc.*) may be substantially blocked by the study agent. However the action of antihyperglycemic agents would be restored as GSK2141795 is cleared. The patient should be observed closely for rebound hypoglycaemia as GSK2141795 is held/or discontinued. • Intravenous insulin treatment is recommended.	Hold GSK2141795 and notifyinvestigator immediately. Continue dabrafenib and trametinib. The investigator should discuss intervention and possible resumption of GSK2141795 with the Study Chair.

8.5 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Ribas at 310/206-3928 or Dr. Algazi at 415/353-7552.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.1 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Study Calendar – Phase I D+G Portion

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow-Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
PHYSICAL																
H & P	X	X		X		X		X		X				X	X	X
Wt & PS	X	X		X		X		X		X						X
Baseline Abnormality Assessment	X															
Tox Notation		X		X		X		X		X				X≠	X≠	X≠
Eye Exam√√	X															
Derm Exam**	X													X**	X**	X**
Disease Assessment ¥	X									X				X	X	
Review Intake Calendar						X				X						
LAB ∏																
CBC/ Diff/PLT /Hg	X	X		X		X		X		X						X
Serum Bilirubin	X	X		X		X		X		X						X
AST & ALT	X	X		X		X		X		X						X
Serum Creat or CrCl	X	X		X		X		X		X						X
Serum Glucose	X	X		X		X		X		X						
Serum albumin	X	X		X		X		X		X						
Amylase/Lipase+	X	X		X		X		X		X						
PT/INR, PTT Δ	X															
LDH Ω	X															
Pregnancy test (women of child bearing potential)	X															

Section 9.1 Study Calendar continues on next page. Click here for footnotes.

9.1 Study Calendar – Phase I D+G Portion (contd.)

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow-Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
X-RAYS & SCANS																
Brain CT or MRI	X															X
CT or MRI ¥	X									X				X£	X	
ECHO or MUGA	X									Xπ				Xπ		
ECG	X															
SPECIMEN SUBMISSION																
Blood for PK ∝	X			X		X										
Paraffin-Embedded Tissue/Slides (Fresh Frozen Tissue if Available)	X			XΦ											X	
Plasma and buffy Coat ®	X									X					X	
TREATMENT																
Dabrafenib ∑		X	X	X	X	X	X	X	X	X	X	X	X			
GSK2141795 ⌐		X	X	X	X	X	X	X	X	X	X	X	X			

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

¥ For the first two years after registration, disease assessments must be performed after every two cycles of treatment using the same method as baseline and must be documented on the Follow-Up Tumor Assessment Form (RECIST 1.1). A response must be confirmed by a second determination at least 4 weeks after a complete or partial response has been noted. After two years (measured from time of registration), the frequency of disease assessment, CT, and MRI may be reduced to once every 12 weeks.

√√ Ophthalmic exam must be performed at baseline. Follow-up exams should be performed as clinically indicated.

** Dermatology exams are required every 2 months throughout treatment, and every 2 months through 6 months after discontinuation of dabrafenib or until the start of another anti-neoplastic therapy.

π On treatment echocardiogram (or MUGA) should be obtained every 2 months for all patients in the Phase I portion.

∏ Patients known to be HIV + must not be on antiviral agents and must have CD34 counts ≥ 500 mm^3 (see Section 5.1t).

Δ See Sections 5.1u and 7.2b.

B Protocol treatment assessments will continue on this schedule until any one of the criteria in Section 7.8 is met.

£ Once off protocol treatment, disease assessments must be performed every 8 weeks until disease progression. After two years (measured from time of registration), the frequency of disease assessments, CT and MRI may be reduced to once every 12 weeks.

Ψ After disease progression (see Section 10.2), follow-up for survival status must be performed every 3 months for the first year, then every 6 months for a total of 3 years from the date of registration or death, whichever is first.

≠ Assessments should continue until resolution of all acute adverse events. Patients with AEs at progression should be followed at frequencies appropriate for the nature and duration of the events, until the AE has resolved or is deemed irreversible.

∑ To be taken twice daily.

⌐ To be taken once a day.

Ω For melanoma patients only.

∝ Required at baseline and prior to dosing on Days 15 and 29. Three patients treated within the second cohort of the Phase I Portion (D+G) will have more extensive PK sampling at baseline, pre-dose and +1, +2, +4, and +8 hours on Day 15, and pre-dose Day 29.

Φ Optional biopsy between Day 15-28.

® Plasma and buffy coat must be submitted at baseline, before the start of Cycle 3 and at the time of progression.

+ As clinically indicated to evaluate adverse events (i.e., abdominal pain, pancreatitis, etc).

9.2 Study Calendar – Phase I D+T +G Portion

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow-Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
PHYSICAL																
H & P	X	X		X		X		X		X				X	X	X
Wt & PS	X	X		X		X		X		X					X	X
Baseline Abnormality Assessment	X															
Tox Notation		X		X		X		X		X				X≠	X≠	X≠
Eye Exam√√	X															
Derm Exam**	X													X**	X**	X**
Disease Assessment ¥	X									X				X	X	
Review Intake Calendar						X				X						
LAB ∏																
CBC/ Diff/PLT /Hg	X	X		X		X		X		X						X
Serum Bilirubin	X	X		X		X		X		X						X
AST & ALT	X	X		X		X		X		X						X
Serum Creat or CrCl	X	X		X		X		X		X						X
Serum Glucose	X	X		X		X		X		X						
Serum albumin	X	X		X		X		X		X						
Amylase/ Lipase +	X	X		X		X		X		X						
PT/INR, PTT Δ	X															
LDH Ω	X															
Pregnancy test (women of child bearing potential)	X															

Section 9.2 Study Calendar continues on next page. Click here for footnotes.

9.2 Study Calendar – Phase I D+T +G Portion (contd.)

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow-Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
X-RAYS & SCANS																
Brain CT or MRI	X															X
CT or MRI ¥	X									X				X£	X	
ECHO or MUGA	X									Xπ				X π		
ECG	X															
SPECIMEN SUBMISSION																
Blood for PK ∝	X			X		X										
Paraffin-Embedded Tissue/Slides (Fresh Frozen Tissue if Available)	X			XΦ											X	
Plasma and Buffy Coat ®	X									X					X	
TREATMENT																
Dabrafenib ∑		X	X	X	X	X	X	X	X	X	X	X	X			
Trametinib ⌐		X	X	X	X	X	X	X	X	X	X	X	X			
GSK2141795 ⌐		X	X	X	X	X	X	X	X	X	X	X	X			

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

¥ For the first two years after registration, disease assessments must be performed after every two cycles of treatment using the same method as baseline and must be documented on the Follow-Up Tumor Assessment Form (RECIST 1.1). A response must be confirmed by a second determination at least 4 weeks after a complete or partial response has been noted. After two years (measured from time of registration), the frequency of disease assessments, CT and MRI may be reduced to once every 12 weeks.

√√ Ophthalmic exam must be performed at baseline. Follow-up exams as clinically indicated.

** Dermatology exams are required every 2 months throughout treatment, and every 2 months through 6 months after discontinuation of dabrafenib or until the start of another anti-neoplastic therapy.

π On treatment echocardiogram should be obtained every 2 months for all patients in the Phase I portion.

∏ Patients known to be HIV + must not be on antiviral agents and must have CD34 counts ≥ 500 mm^3 (see Section 5.1t).

Δ See Sections 5.1u and 7.2b.

B Protocol treatment assessments will continue on this schedule until any one of the criteria in Section 7.8 is met.

£ Once off protocol treatment, disease assessments must be performed every 8 weeks until disease progression. After two years (measured from time of registration), the frequency of disease assessments, CT and MRI may be reduced to once every 12 weeks.

Ψ After disease progression (see Section 10.2), follow-up for survival status must be performed every 3 months for the first year, then every 6 months for a total of 3 years from the date of registration or death, whichever is first.

≠ Assessments should continue until resolution of all acute adverse events. Patients with AEs at progression should be followed at frequencies appropriate for the nature and duration of the events, until the AE has resolved or is deemed irreversible.

∑ To be taken twice daily.

⌐ To be taken once a day.

Ω For melanoma patients only.

∝ Required at baseline and prior to dosing on Days 15 and 29. Three patients treated within the second cohort of the Phase I Portion (D+G) will have more extensive PK sampling at baseline, pre-dose and +1, +2, +4, and +8 hours on Day 15, and pre-dose Day 29.

Φ Optional biopsy between Day 15-28.

® Plasma and buffy coat be submitted at baseline, before the start of Cycle 3 and at the time of progression.

+ As clinically indicated to evaluate adverse events (i.e., abdominal pain, pancreatitis, etc).

9.3 Study Calendar – Phase II D+T+G

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
PHYSICAL																
H & P	X	X				X				X				X	X	X
Wt & PS	X	X				X				X						X
Baseline Abnormality Assessment	X															
Tox Notation		X				X				X				X≠	X≠	X≠
Disease Assessment ¥	X									X				X£	X	
Eye Exam √√	X															
Dermatology Exam**	X													X**	X**	X**
Review Intake Cal						X				X						
LAB ∏																
CBC/Diff/PLT/Hg	X	X				X				X						X
Serum Bili	X	X				X				X						X
AST & ALT	X	X				X				X						X
Serum Cr or CrCl	X	X				X				X						X
Serum Glucose	X					X				X						
Serum Albumin	X	X				X				X						
Amylase /Lipase +	X					X				X						
PT/INR, PTT ∆	X					X				X						
LDH	X															
Pregnancy test (women of child bearing potential)	X															

Section 9.3 Study Calendar continues on next page. Click here for footnotes.

9.3 Study Calendar – Phase II D+T+G (contd.)

		Cycle 1				Cycle 2				Cycle 3 + β				Follow-Up Prior to Progression	At Time of Progression	Post-Progression Follow Up Ψ
REQUIRED STUDIES	PRE-STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12			
X-RAYS & SCANS																
CT or MRI Scan of the brain	X															
CT or MRI ¥	X									X				X£	X	
ECHO or MUGA	X									Xπ						
ECG	X															
SPECIMEN SUBMISSION																
Paraffin-Embedded Tissue/Slides (Fresh Frozen Tissue If Available)	X			XΦ											X	
Plasma and Buffy Coat ®	X									X					X	
TREATMENT																
Dabrafenib ∑		X	X	X	X	X	X	X	X	X	X	X	X			
Trametinib ⌐		X	X	X	X	X	X	X	X	X	X	X	X			
GSK2141795 ⌐		X	X	X	X	X	X	X	X	X	X	X	X			

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

Footnotes:

¥ Disease assessments must be performed after every two cycles of treatment using the same method as baseline and must be documented on the Follow-Up Tumor Assessment Form (RECIST 1.1). A response must be confirmed by a second determination at least 4 weeks after a complete or partial response has been noted.

√√ Ophthalmic exam must be performed at baseline. Follow-up exams are to be performed as clinically indicated.

** Dermatology exams are required every 2 months throughout treatment, and every 2 months through 6 months after discontinuation of dabrafenib or until the start of another anti-neoplastic therapy.

π On treatment echocardiogram should be obtained every 2 months for all patients.

∏ Patients known to be HIV + must not be on antiviral agents and must have CD34 counts ≥ 500 mm^3 (see Section 5.1t).

Δ See Sections 5.1u and 7.2b.

B Protocol treatment assessments will continue on this schedule until any one of the criteria in Section 7.8 is met.

£ Once off protocol treatment, disease assessments must be performed every 8 weeks until disease progression.

Ψ After disease progression (see Section 10.2), follow-up for survival status must be performed every 3 months for the first year, then every 6 months for a total of 3 years from the date of registration or death, whichever is first.

≠ Assessments should continue until resolution of all acute adverse events. Patients with AEs at progression should be followed at frequencies appropriate for the nature and duration of the events, until the AE has resolved or is deemed irreversible.

∑ To be taken twice daily.

⌐ To be taken once a day.

Ω For melanoma patients only.

∝ Required at baseline and prior to dosing on Days 15 and 29. Three patients treated within the second cohort of the Phase I Portion (D+T+G) will have more extensive PK sampling at baseline, pre-dose and +1, +2, +4, and +8 hours on Day 15, and pre-dose Day 29.

Φ Optional biopsy between Day 15-28.

® Plasma and buffy coat must be submitted at baseline, before the start of Cycle 3 and at the time of progression.

+ As clinically indicated to evaluate adverse events (i.e., abdominal pain, pancreatitis, etc).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

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

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

   Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

   1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

   2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g., CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. **Objective status notes:**

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (see Section 10.2e), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goals

This study will initially be open to limited institutions, with an expected accrual of 3-12 patients in the D+G Phase I Portion and 6-18 patients in the D+T+G Phase I Portion. The Phase II Portion of the trial will be open Group-wide and will require 10-33 eligible patients. Assuming that 10% of patients enrolled will be ineligible or not evaluable,

approximately 70 patients will be required. Based on data from previous studies in similar patient populations the estimated accrual rate is 2-3 patients per month.

11.2 Evaluation of Dabrafenib + GSK2141795 (D+G)

a. Analysis of Phase I Portion

Section 7.3 provides the details of the study design for the Phase I Portion of the study. The Phase I Portion will be a limited dose-escalation.

The primary objective of the Phase I Portion will be to determine the maximum tolerated dose (MTD) of GSK2141795 and dabrafenib in patients with BRAF mutant locally advanced or metastatic cancer. The regimen will be considered safe and the MTD determined if the dose-limiting toxicity rate is ≤ 33%.

Prior to implementation of the Phase II Portion, a temporary closure will occur in order to assess dose and to evaluate the safety profile more fully.

b. Analysis of Phase II Portion

Note: Effective November 15, 2014, this trial will not proceed to the Phase II study of dabrafenib and GSK2141795, but will be moving to an evaluation of triple therapy.

The study will be conducted in two sequential parts. Patients enrolled to the Phase I Portion will not be included in the analysis of the Phase II Portion.

The primary objective of the Phase II Portion of this study is to evaluate the objective response rate (confirmed and unconfirmed, complete and partial responses) of GSK2141795 used in combination with dabrafenib in patients with Stage IV or unresectable Stage III melanoma who have acquired resistance to BRAF inhibitor-based therapy. Resistance to BRAF inhibitor-based therapy will be defined as progressive disease by RECIST 1.1 criteria while receiving therapy with a BRAF inhibitor (vemurafenib or dabrafenib, alone or in combination with a MEK inhibitor). This may be innate resistance (patients who never achieved a tumor response while on BRAF inhibitor therapy) or acquired resistance (progression after having a tumor response to BRAF inhibitor therapy).

It is assumed that this regimen will not be of further interest if the true response rate is less than 5% (null) and that a true response rate of 25% or more would be of considerable interest for further investigation (alternative).

Parallel patient enrollment will be implemented for two strata (prior therapy with BRAF-inhibitor only versus prior therapy with both a BRAF-inhibitor and a MEK-inhibitor), and a two-stage design will proceed separately for each stratum as follows: In the first step, 9 eligible patients will be accrued. If necessary, the study may be temporarily closed while response data matures. If zero responses are observed, the study will be closed with the conclusion that this regimen does not warrant further study. If at least one response is observed, an additional 15 eligible patients will be accrued. Three or more responses out of 24 will be considered evidence that this regimen warrants further study, provided other factors such as overall survival and adverse events also appear favorable. This design has 90% power with a one-sided alpha of 10%.

11.3 Evaluation of Dabrafenib + Trametinib + GSK2141795 (D+T+G)

a Analysis of Phase I Portion

Section 7.4 provides the details of the study design for the Phase I Portion of the study. The Phase I Portion will be a limited dose-escalation.

The primary objective of the Phase I Portion will be to determine the maximum tolerated dose (MTD) of GSK2141795, dabrafenib and trametinib in patients with BRAF mutant locally advanced or metastatic cancer. The regimen will be considered safe and the MTD determined if the dose-limiting toxicity rate is ≤ 33%.

Prior to implementation of the Phase II Portion, a temporary closure will occur in order to assess dose and to evaluate the safety profile more fully.

b Analysis of Phase II Portion

The study will be conducted in two sequential parts. Patients enrolled to the Phase I Portion will not be included in the analysis of the Phase II Portion.

The primary objective of this portion study is to evaluate the objective response rate (confirmed and unconfirmed, complete and partial responses) of GSK2141795 used in combination with dabrafenib and trametinib in patients with Stage IV or unresectable Stage III melanoma who have acquired resistance to BRAF inhibitor-based therapy. Resistance to BRAF inhibitor-based therapy will be defined as progressive disease by RECIST 1.1 criteria while receiving therapy with a BRAF inhibitor (vemurafenib or dabrafenib, alone or in combination with a MEK inhibitor). This may be innate resistance (patients who never achieved a tumor response while on BRAF inhibitor therapy) or acquired resistance (progression after having a tumor response to BRAF inhibitor therapy).

It is assumed that this regimen will not be of further interest if the true response rate is less than 15% (null) and that a true response rate of 35% or more would be of considerable interest for further investigation (alternative).

A two-stage design will be used for patient accrual. In the first step, 10 eligible patients will be accrued. If necessary, the study may be temporarily closed while response data matures. If 0-1 responses are observed, the study will be closed with the conclusion that this regimen does not warrant further study in the Group A population. If at least 2 responses are observed, an additional 23 eligible patients will be accrued. Eight or more responses out of 33 will be considered evidence that this regimen warrants further study, provided other factors such as overall survival and adverse events also appear favorable. This design has 87% power with a one-sided alpha of 0.9%.

11.4 Analysis of Secondary Endpoints

The Phase II Portion will include estimating overall survival, progression-free survival, and toxicity rates. Assuming 33 eligible patients are enrolled, this will be sufficient to estimate overall survival, progression-free survival, and toxicity rates to within ± 17% (95% confidence interval). Assuming 33 eligible patients overall, any toxicity with at least a 5% chance of occurring has a 82% chance of being observed at least once. In addition, to assess safety and feasibility in both the Phase I and Phase II Portions of the trial, descriptive statistics will be presented for the number of patients requiring dose reduction, interruption or discontinuation and the percentage of dose delivery.

11.5 Analysis of Translational Medicine Component

This analysis will include those patients enrolled to the Phase I or II Portion of the study with adequate specimens. Every attempt will be made for pre-study collection of blood and tissue specimens. Blood and tissue specimens from accessible metastatic lesions will be requested from two other time points: 1) after start on therapy (approximately Day 15-30), and 2) at the time of progression on this study.

For the pre-study time point, for each of the categorical markers listed in Section 18.2, we will estimate the prevalence of the marker in this patient population. For binary markers, the prevalence will be able to be estimated and exact binomial confidence interval will be calculated. The association between these categorical markers and clinical outcomes will be explored in a preliminary manner, using Fisher's exact test to compare response and a logrank test to compare Kaplan-Meier estimates of OS and PFS between marker positive and marker negative groups.

For the quantitative markers in the previous section, we will estimate median and range values in this patient population. The association between quantitative markers and clinical outcomes will be explored in a preliminary manner, using the Wilcoxon-rank sum

test to assess response and Cox regression to assess PFS and OS. In addition, we may explore dichotomizing the patients into two groups by splitting at the median (or other cutpoints may be explored) and applying the methods specified above for the categorical markers.

For patients with samples at more than one time we will examine changes in marker status over time. This analysis will be very exploratory.

For patients enrolled on the Phase I Portion, PK sampling steady state should be taken at baseline, pre-dose Day 15 and pre-dose Day 29. In addition, three patients treated within the second cohort of each of the Phase I Portions (D+G and D+T+G) will have more extensive PK sampling at baseline, pre-dose and +1, +2, +4, and +8 hours on Day 15, and pre-dose Day 29.

11.6 Data and Safety Monitoring

See Section 15.0, description of conference calls for safety monitoring of the Phase I Portion and selection of the recommended Phase II dose.

There is no formal data and safety monitoring committee for single arm Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Chair at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than eight working days prior to planned start of treatment). If enrolling a patient onto the Phase I portion, sites must order **S1221** PK kit immediately after registration (see Section 18.6). The SWOG patient ID number must be provided on the **S1221** PK Kit Request Form. Allow up to five working days for the PK kit to arrive.

13.2 Slot Reservation

Patients planning to enroll on this study must first have a slot reserved in advance of the registration, even if the site plans to enroll right away. All site staff will use OPEN to create a slot reservation. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench. Please refer to the 'Slot Reservation Quick Reference Site User Guide' within the OPEN tab on the CTSU members' website under 'Training and Demonstration Materials' for detailed instructions.

The individual making the slot reservation for the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Patient Initials

e. Patient's Date of Birth

f. ZIP Code

g. Gender (select one):
- Female Gender
- Male Gender

Slot reservations expire within 28 calendar days. A warning e-mail will be sent 48 hours before the expiration date. The reservation can be renewed any time before it expires as long as at least 1 slot is still available. After it expires, a new slot reservation must be created for the patient before they can be enrolled to this trial. Reservations may also be withdrawn at any time. If you withdraw a reservation, please notify the Statistical Center at melanomaquestion@crab.org.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org, or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.

- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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

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

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data Collection

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

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

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a

separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION FOR ALL PATIENTS SUBMIT:

S1221 Onstudy Form

Baseline Tumor Assessment Form (RECIST 1.1)

S1221 Baseline Abnormalities Form

Radiology reports from all scans performed to assess disease at baseline

Pathology report from a CLIA certified lab documenting BRAF mutation status

ALSO SUBMIT WITHIN 7 DAYS OF REGISTRATION FOR PATIENTS ENROLLED ON THE PHASE II PORTION:

Pathology report documenting histologic confirmation of malignant melanoma.

b. SUBMIT WITHIN 14 DAYS AFTER REGISTRATION:

Pre-study specimens as outlined in Section 15.4.

c. WITHIN 7 DAYS AFTER COMPLETION OF EVERY CYCLE (1 CYCLE = 28 DAYS), SUBMIT:

S1221 Treatment Form

S1221 Adverse Event Form **(Submit every 14 days during Cycles 1 and 2 of Phase I Portion, see Section 15.1 for Rapid Reporting requirements):**

d. WITHIN 7 DAYS AFTER EVERY TUMOR ASSESSMENT (INCLUDING BOTH ON TREATMENT AND OFF TREATMENT PRIOR TO DISEASE PROGRESSION) (see Section 9.0 for Disease Assessment Schedule) SUBMIT:

Follow-Up Tumor Assessment Form

Radiology reports from all scans performed to assess disease. Physician must note tumor measurement in patient records.

e. WITHIN 14 DAYS OF PROGRESSION SUBMIT:

NOTE: IF PATIENT REMAINS ON TREATMENT FOLLOWING PROGRESSION (SEE SECTION 7.9a, CONTINUE TO SUBMIT THE **S1221** ADVERSE EVENT FORM AND **S1221** TREATMENT FORM AFTER EVERY CYCLE OF TREATMENT AS OUTLINED IN SECTION 14.4c).

Follow-Up Tumor Assessment Form (RECIST 1.1)

Radiology reports from all scans performed to assess disease. Physician must note tumor measurement in patient records.

S1221 Treatment Form and **S1221** Adverse Event Form (if the patient was still on protocol treatment) or

Follow-Up Form (if patient was off treatment) documenting date, site and method for determining progression.

f. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT SUBMIT:

Off Treatment Notice

S1221 Treatment Form

S1221 Adverse Event Form.

g. AFTER OFF TREATMENT, SUBMIT EVERY 3 MONTHS FOR 1 YEAR AND 6 MONTHS UP TO 3 YEARS FROM DATE OF REGISTRATION:

Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH SUBMIT:

Notice of Death **and all of the items listed in Section 14.4f (**if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Phase I Portion: Rapid Reporting

RAPID REPORTING OF TREATMENT-RELATED DOSE-LIMITING TOXICITIES FOR PHASE I PORTION OF TRIAL

Participation in the Phase I Portion of the trial requires that Adverse Events be reported every 14 days for patients who have initiated treatment.

Institutional participation in the Phase I Portion of the trial requires the identification of a contact CRA and back-up CRA. **Prior to registration of the first patient, each institution must provide the contact and back-up CRA names, e-mail addresses, and phone numbers to the SWOG Data Operations Center.** Institutions will be responsible for keeping this information up-to-date and must notify the study Data Coordinator (Jennie Barrett; jennieb@crab.org; 206/652-2267) of any changes.

The contact CRA and back-up CRA will receive weekly e-mails including a list of the Adverse Event and Treatment forms that are overdue, currently due, or due in the next week. These e-mails will include a reply-to address and phone number to contact the Data Operations Center when questions arise.

15.2 Phase I Portion: Mandatory Conference Calls

A mandatory conference call for study teams with active patients will take place twice a month. The call will update participants on the current status of the trial and will include representatives from the study team, investigators from all participating institutions and representatives from GSK. At this time any serious toxicities encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of important study decisions via e-mail.

15.3 Phase I Portion: Mandatory Pharmacokinetic (PK) Sampling

a Pharmacokinetic (PK) kits will not be provided for this submission; sites will use institutional supplies. NOTE: Kits are no longer being supplied by the SWOG Biospecimen Repository.

b. In all Phase I Portion patients PK sampling will be obtained at baseline, pre-dose Day 15, and pre-dose Day 29.

At each time point, collect 3 mL whole blood PK sample into a properly labeled 2 mL K2EDTA evacuated blood collection tube. Record the date and time each sample is collected.

Immediately after collection, gently invert (DO NOT SHAKE) the evacuated blood collection tube 8-10 times to mix the K2EDTA anticoagulant with the whole blood, blood samples should remain at room temperature prior to centrifugation and should be processed within 30 minutes of collection. Centrifuge the sample at 2500 to 3000 rpm for 10 to 15 minutes at room temperature to achieve a clear plasma layer over the red cells. The speed and time may be varied according to the make and model of centrifuge used. Immediately transfer plasma into two (2)

corresponding pre-labeled 1.8 mL NUNC tubes (each containing approximately 0.75 mL of plasma) and store at - 20°C until shipped. The Covance Bioanalytical study number for S1221 is 8290125. The GSK study number is BRA117182. Please include either the GSK or Covance study number along with the SWOG protocol number in all correspondence.

PK samples will be shipped to:

Lab #207: Covance BioanalyticalLaboratory Services Inc.
Sample Management-bioanalytical (Rm 131D 1S)
3301 Kinsman Boulevard
Madison, WI 53704 -2523
Attn: Principal Investigator: John banach
Tel 608/310-2939
E-mail: John.Banach@covance.com

Covance require an electronic manifest to be sent with each PK shipment. By logging your shipment in the SWOG Specimen Tracking system, an electronic manifest will be automatically emailed to Covance for you.

c. During each of the Phase I portions (D+G and D+T+G) a more intense PK sampling schedule will be followed for three patients of cohort 2, or as an extension to cohort 1 if it is identified as the MTD, (and additional ones if needed to further define potential drug-drug interactions). These patients will have PK sampling at baseline, pre-dose and +1, +2, +4, +8 hours on Day 15, and pre-dose Day 29.

15.4 Phase I & II Portions: Mandatory Specimen Submission for Translational Medicine

Specimens for Translational Medicine Studies and Banking submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201 (required for patients):

a. Specimens must be submitted at the following times (see Section 9.0):

1. Submit entire block of paraffin-embedded tissue (and if available entire fresh-frozen tumor) or 20 unstained slides (if site cannot send tissue block) at baseline, at anytime during Days 15-28 of Cycle 1 (optional), and at time of progression.

2. Submit four separate purple-top EDTA tubes each containing four ml of whole blood at baseline, prior to the start of Cycle 3 and at time of progression. Follow guidelines on the SWOG Specimen Webpage for collecting, processing and shipping buffy coat and plasma specimens. Batch ship frozen plasma and buffy coat specimens to the SWOG Specimen Repository.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S1221** protocol abstract page on the SWOG website (www.swog.org).

c. Avoid refrigerated storage overnight before liquid nitrogen immersions; instead the tissue must be completely immersed in RNALater and then liquid nitrogen immediately after biopsy and must be maintained cryopreserved. The specimens must be shipped in dry ice.

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

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

1. Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to the Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

   Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 CFR Part 164.

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

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

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

   E-mail: ncicteppubs@mail.nih.gov

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

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program (CTEP) Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations office electronically via the CTEP-AERS web-based application located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in Phase I and Phase II of this study are dabrafenib and GSK2141795 If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Dabrafenib, Trametinib, and GSK2141795 (Phase I and Phase II)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: **Investigators MUST immediately report to the sponsor (NCI) ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)**

An adverse event is considered serious if it results in ANY of the following outcomes:

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or Section 16.1f.

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

May 5, 2011

f. Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase I and Early Phase II Studies Utilizing an Agent under a CTEP IND:

Group-specific instructions: Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical source documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

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

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

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Translational Medicine

18.3 Intake Calendar

18.4 Strong inducers/inhibitors of CYP3A, CYP2C8, Pgp, Bcrp and possibly 2C8/9 and 2C19

18.5 New York Heart Association Classifications

18.6 Information on Possible Drug Interactions

18.7 Patient Information – Wallet Card

18.8 Instructions for Patients for Storage of Trametinib Tablets

18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 Translational Medicine

Pre-study (after failing frontline BRAF inhibitor therapy) blood and tissue specimens will be required. Blood and tissue specimens will be requested from two other time points: 1) prior to starting first line BRAF inhibitor therapy (initial diagnosis) and 2) at the time of progression on this study.

Studies will be done in blood, formalin-fixed paraffin embedded (FFPE) tissues, and if available in fresh cryopreserved tissues.

From FFPE the following studies will be done:
- NRAS, MEK1/2, PI3K and AKT1 mutations by Sanger sequencing
- Mutant BRAF amplification by genomic DNA (gDNA) Q-PCR
- pERK and pAKT by IHC
- PDGFRβ, EGFR, cKIT, cMET by IHC
- HGF by IHC

From blood, the following studies will be done:
- Growth factor (HGF) levels
- Extraction of gDNA for validation of somatic alterations in collected tumors

From fresh frozen tissue (when available), the following studies will be done:
- NRAS, MEK1/2, PI3K and AKT1 mutations by Sanger sequencing (if available and if any assay above fails or the results of which is equivocal)
- Mutant BRAF amplification by genomic DNA (gDNA) Q-PCR (if available and if any assay above fails or the results of which is equivocal)
- Mutant BRAF truncation by cDNA Q-PCR
- RTK (PDGFRβ, EGFR, cKIT, cMET) by cDNA Q-PCR

Phosphorylation of receptor tyrosine kinases (RTKs) may be analyzed by a reverse phase protein array assay.

In cases a fresh tissue sample of sufficient size is available, whole-exome sequencing and RNA-Seq will be attempted, with parallel testing of peripheral blood cells. Fresh tissues cryoperserved in RNALater are expected to provide more reliable cDNA Q-PCR assay performance. Highly pigmented tissues will be processed by an established protocol to reduce melanin in gDNA and RNA/cDNA during sample processing.

18.3 Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #_____**

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____

18.4 Strong inducers/inhibitors of CYP3A, CYP2C8, Pgp, Bcrp and possibly 2C8/9 and 2C19

Prohibited Medications

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

The following medications should be used with caution as their concentrations may be altered by dabrafenib or they may alter dabrafenib concentrations:

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases, and transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 1 and in the SPM.
- Dabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.

- **A list of medications that should be used with caution are listed in the table below:**

Table 1 Medications to be used with Caution	
USE WITH CAUTION: Moderate inhibitors of CYP3A, or CYP2C8 since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Moderate CYP3A and CYP2C8 Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin
Antifungal	Fluconazole
Miscellaneous	Aprepitant
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil
Antimigraine Agents	Diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, lovastatin, simvastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone
Selective Aldosterone Blockers	Eplerenone
USE WITH CAUTION: Co-administration of drugs that increase gastric pH should be used with caution when administered with dabrafenib..	
pH altering agents	dexlansoprazole. esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole, ranitidine

Abbreviations: CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A.

* Therapeutic level dosing of warfarin can be used with approval by the medical monitor and close monitoring of PT/INR by the site. Exposure may be decreased due to enzyme induction when on treatment, thus warfarin dosing may need to be adjusted based upon PT/INR. Consequently, when discontinuing dabrafenib, warfarin exposure may be increased and thus close monitoring via PT/INR and warfarin dose adjustments must be made as clinically appropriate. Prophylactic low dose warfarin may be given to maintain central catheter patency.

Because the list of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/main-table/; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Section 18.6 is a patient information sheet that can be used for this specific protocol and presented to the patient.

18.5 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.6 Information on Possible Drug Interactions

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times.]

The patient is enrolled on a clinical trial using the experimental agents **dabrafenib, trametinib, and GSK2141795.** *This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

Drug Interactions:
Dabrafenib, trametinib, and GSK2141795 interact with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's Wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Liver Enzyme Interactions:
Dabrafenib, trametinib, and GSK2141795 interact with certain specific enzymes in your liver.

- The enzymes in question are ***CYP450 3A4, 2C8, 2C9, 2C19, 2B6, P-gp, BCRP and OATP1B1.*** Dabrafenib, trametinib, and GSK2141795 levels are affected by some of these enzymes and can alter the levels of other medicines you take.

- Dabrafenib, trametinib, and GSK2141795 must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.

- Other medicines may also affect the activity of the enzyme.

- Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of one or more of the drugs, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the drugs, increasing the chance of harmful side effects. Dabrafenib mesylate should not be taken with any other drugs that are strong inducers or inhibitors of CYP 3A4 or 2C8. Prohibited medications include azole antifungals, some antiepileptic drugs, some antibiotics and some immunosuppressants. Please check with the study investigator before prescribing or dispensing strong inhibitors/inducers of CYP 3A4 or 2C8. Mild/moderate inhibitors/inducers should be used with caution.

- Dabrafenib mesylate is considered an inducer of CYP 3A4, 2B6 and possibly 2C8/9 and 2C19, meaning that it can decrease the levels of other drugs that are processed by these enzymes. This can lead to harmful side effects and/or reduce the effectiveness of those medications.

- GSK2141795 is a moderate inhibitor of CYP 2C8 and 3A4. Drugs that are substrates of these CYP 2C8 and 3A4 should be used with caution and ones with a narrow therapeutic index should be avoided.

- GSK2141795 is a substrate of p-glycoprotein (P-gp) and breast cancer protein (BCRP). It is also an inhibitor of BCRP and OATP1B1. Administration of sensitive BCRP substrates should be prohibited, such as topotecan.

You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.

Before you start the study, your study doctor will work with your regular prescriber to switch any prohibited medicines that are considered strong inducers/inhibitors or substrates of ***CYP 3A4, CYP, 2C8, P-gp, or BCRP***.

Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.

Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

Be careful:

- If you take acetaminophen regularly: You should not take more than 3 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.

  Speak to your doctor about any medications you think may contain acetaminophen in order to find a dose that is safe for you.

- If you take herbal medicine regularly: You should not take St. John's wort while you are taking dabrafenib mesylate.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is and he or she can be contacted at _____.

18.7 Information on Possible Drug Interactions – Patient Wallet Card

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agents **dabrafenib mesylate, trametinib DMSO, and GSK2141795.** This clinical trial is sponsored by the NCI. Dabrafenib mesylate interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Dabrafenib mesylate interacts with a specific liver enzymes called **CYP 3A4 and 2C8**, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any prohibited medicines that are considered "strong inducers/inhibitors or substrates of **CYP 3A4 and 2C8**."
- GSK2141795 is a moderate inhibitor of CYP 2C8 and 3A4. Drugs that are substrates of these CYP 2C8 and 3A4 should be used with caution and ones with a narrow therapeutic index should be avoided.
- GSK2141795 is a substrate of p-glycoprotein (P-gp) and breast cancer resistant protein (BCRP). It is also an inhibitor of BCRP and OATP1B1. Administration of sensitive BCRP substrates should be prohibited, such as topotecan.
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspxfor a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

18.8 Instructions for Patients for Storage of Trametinib Tablets

Patient Storage Instructions:

- Study drug can be transported home in the bottle(s) that were dispensed to the patient at room temperature. Avoid exposing the bottle(s) to prolonged temperature extremes (i.e. do not leave bottle(s) in a hot car while doing errands)

- At home, store the study drug in the refrigerator, 2°C – 8°C (36°F - 46°F). Do not freeze the bottles.

- Keep the tablets in the original bottle(s). Do not remove tablets from the bottle(s) and put them in a pill box or daily dispenser.

- Keep desiccant cylinder in the bottles in order to keep tablets dry.