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# A Randomized Phase 2 Study of single agent Dabrafenib (BRAFi) vs. combination regimen Dabrafenib (BRAFi) and Trametinib (MEKi) in patients with BRAF mutation or BRAF gene fusion defect in thyroid carcinoma

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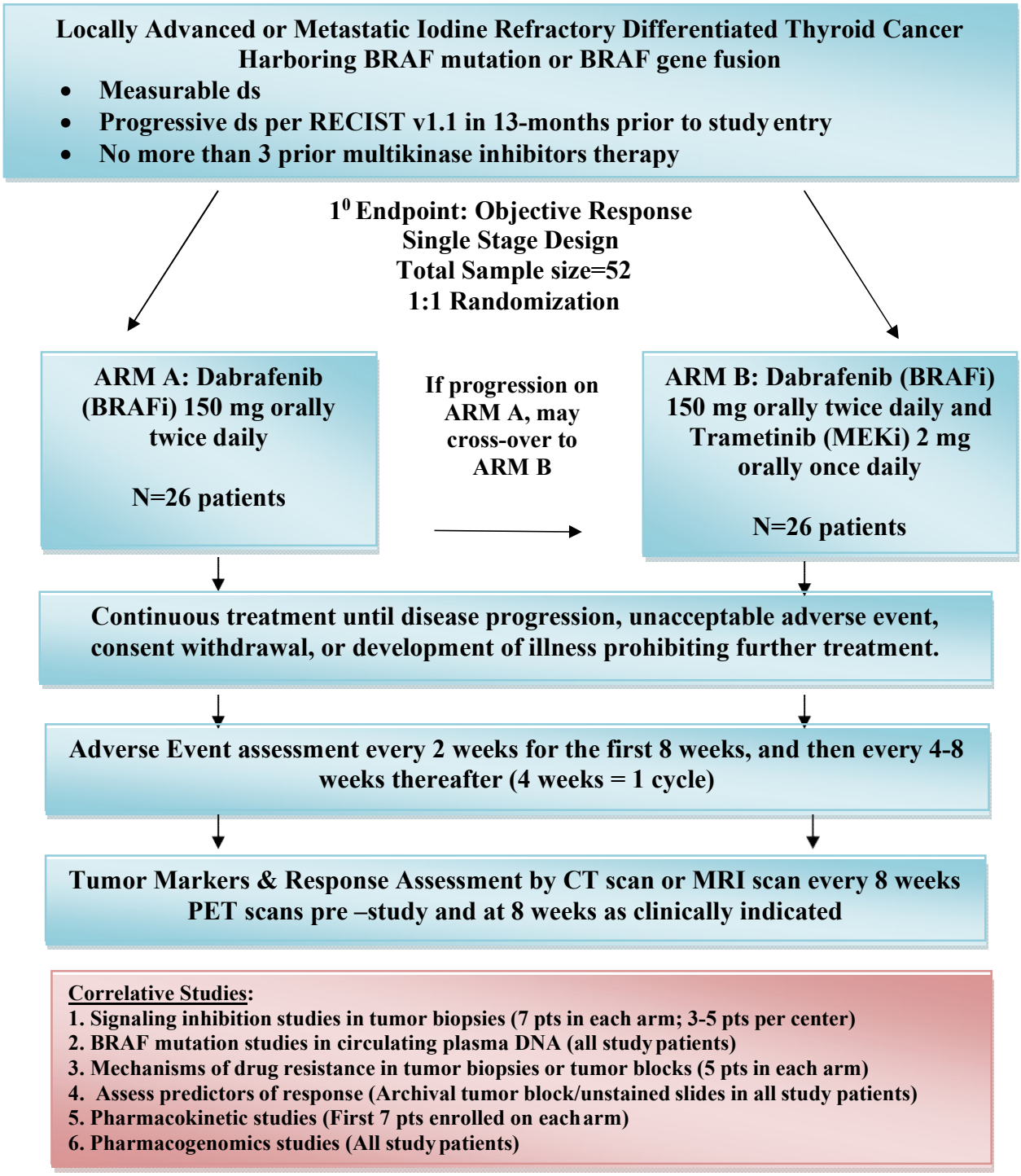
## SCHEMA

# A Randomized Phase 2 Study of single agent Dabrafenib (BRAFi) vs. combination regimen Dabrafenib (BRAFi) and Trametinib (MEKi) in patients with BRAF mutation or BRAF gene fusion defect in thyroid carcinoma



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# 1. OBJECTIVES

## 1.1. Primary Objectives

a. To screen two different regimens [Dabrafenib (BRAFi) as a single agent versus the combination regimen of Dabrafenib (BRAFi) and Trametinib (MEKi)] and identify which regimen is more promising for subsequent testing in a Phase III trial in radioiodine refractory BRAF-mutation or BRAF gene fusion defect positive differentiated thyroid cancer (DTC) patients.

The primary endpoint for each of the treatment arms of this trial is overall response rate, defined as the proportion of patients who have a minor response, partial response, or complete response within the first 6 cycles of therapy.

## 1.2. Secondary Objectives

a. To understand duration of objective response, progression-free survival and overall survival for each treatment group.

b. To assess tolerability and adverse events of Dabrafenib (BRAFi) as a single agent and the tolerability and adverse events of Dabrafenib (BRAFi) and Trametinib (MEKi) in combination, in patients with DTC.

b. To evaluate impact of experimental drugs on serum tumor marker thyroglobulin and its correlation with overall response rate.

d. To understand pharmacokinetic, pharmacogenetics and pharmacodynamics of experimental drugs using serial tumor biopsies, tumor blocks and peripheral blood.

# 2. BACKGROUND

## 2.1 Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy, accounting for 96% of all endocrine cancers. There are an estimated 56,000 new thyroid cancer cases in the United States in 2012 (1). Distant metastases occur in less than 10% of patients with differentiated thyroid cancer (DTC), but represent the most common cause of thyroid cancer related death. DTC comprises 90% of all thyroid cancer cases and includes the histological groups of papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC).

Based on the results of placebo-controlled international multicenter phase III trial, sorafenib was approved through the FDA in Nov. 2013 for the treatment of locally recurrent or metastatic, progressive differentiated thyroid cancer that does not respond to radioactive iodine treatment. Median progression free survival for

patients on sorafenib was 10.8 months compared to 5.8 months for participants receiving a placebo. Given the modest benefits and significant side effect profile of sorafenib, several new targeted therapies are being explored in early phase clinical trials. BRAF plays critical role in pathogenesis of thyroid cancer and this trial evaluates the role of potent BRAF inhibitor in the treatment of such cancers.

In this population of patients, the expected survival declines rapidly (2-4) with reports of 10% survival at 10 years in patients without any initial $I^{131}$ uptake as compared to 92% survival rate in patients with $I^{131}$ uptake who achieve negative studies after treatment (4). Currently, patients with progressive and metastatic iodine refractory thyroid cancer are offered treatment with clinical trial, small molecule kinase inhibitors including sorafenib, sunitinib, or pazopanib, or best supportive care.

## 2.2 The role of BRAF gene defects in thyroid cancer

RAS/RAF/MEK/ERK or the "MAPK pathway" is an intracellular signaling pathway that plays a critical role in transmission of cell signals to the cell nucleus, where it mediates cell differentiation, proliferation, apoptosis, and survival. The MAPK pathway is activated in a variety of human malignancies, often through gain-of-function mutations in components of the RAS and RAF family. RAF is a cytoplasmic serine-threonine kinase with three isoforms: ARAF, BRAF, and CRAF. The BRAF gene, found of chromosome 7, is the strongest activator of the MAPK pathway. Furthermore, constitutive activation of the BRAF gene by point mutations is a well-described and common genetic event in many human cancers, including melanoma, papillary thyroid carcinoma, colon cancers and ovarian cancers (5-7). As depicted below in Figure 1, the MAPK-signaling cascade is initiated through activation of the receptor tyrosine kinase, which in turn activates RAS. RAS then facilitates homo- or heterodimerization of wild-type BRAF. Activated BRAF phosphorylates MEK, which in turn phosphorylates ERK, leading to multiple cellular effects that are critical to cell proliferation and survival. Mutated BRAF can bypass RAS activation and directly dimerize and activate BRAF. BRAF can also form a heterodimer with CRAF and result in downstream activation of MEK/ERK pathway. KSR, or kinase suppressor of RAS, is able to trigger BRAF activation through side-to-side heterodimerization, further highlighting the complexity of this pathway (8).

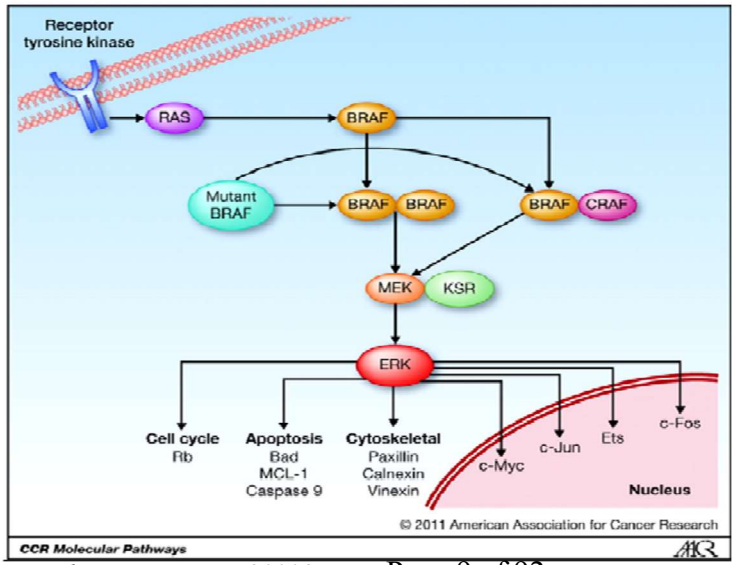


**Figure 1**. Mutant BRAF and its role in the MAPK pathway.

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*Res* 2011

The prevalence of BRAF mutations in papillary thyroid cancer (PTC) ranges from 29% to 83%, with an average frequency of 44% (7). PTC is the most common histologic subtype of thyroid cancer, accounting for greater than 80% of all cases. Substitution of glutamic acid for valine in the 600 position of BRAF protein, or V600E, is characteristic of the mutation found in PTC, but also is found in poorly differentiated and anaplastic thyroid cancer derived from PTC (9). The oncologic activity of BRAF V600E mutation as an initiating event in thyroid cancer development has been demonstrated in studies of BRAF V600E positive transgenic mice. Transgenic mice developed invasive PTC and poorly differentiated thyroid cancer with progressive local invasion (10, 11). Further, PTC in human tumors with BRAF mutations are present with greater frequency in the advanced setting, and have been associated with older age, extra thyroidal extension, and more frequent presentation at Stage III and IV (12).

**BRAF Gene Fusion as a Molecular Target for RAF and MEK inhibitors**

Analogous to a *mutation* in the BRAF gene causing constitutive activation of this kinase in melanoma and thyroid cancer (BRAF V600E), *gene fusions* involving BRAF and a number of different upstream partners have been shown to activate the kinase activity of BRAF. Although genetically the BRAF gene is wild type in these fusions, the end result of elevated kinase activity can be considered the same as in an activating mutation.

Background on BRAF Fusions. Work by Ciampi et al. published in 2005 revealed an intrachromosomal inversion that generated a AKAP9-BRAF fusion in papillary thyroid carcinoma. Further characterization of this fusion gene predicted loss of the N-terminal autoinhibitory domains of BRAF, however the kinase domain remained intact. *In vitro* experiments showed the kinase activity of the AKAP9-BRAF fusion to be greater than that of the well characterized $BRAF^{V600E}$ mutant. Additionally, the downstream MAPK target ERK was shown to be elevated in cells expressing the BRAF fusion gene.

Our group has observed presence of another BRAF fusion gene defect in patient with thyroid cancer. KLHL7-BRAF gene fusion involves KLHL7 and BRAF genes on chromosome 7, translocating to form a new gene fusion, with intact gene structure or open reading frame. This is predicted to have similar structure and function as other gene fusions, where loss of an inhibitory domain of the BRAF gene leads to persistence activation of the kinase.

Fusions involving BRAF and other N-terminal partners have been observed in multiple other malignancies including an AGTRAP-BRAF fusion in gastric cancer and SLC45A3-BRAF fusion in prostate cancer. In both cases, the inhibitor domain is lost and the kinase domain of BRAF is retained[2]. Expression of the SLC45A3-BRAF fusion in prostate

epithelial cells induced both MEK and ERK phosphorylation and these cells became sensitive to treatment with the RAF inhibitor Sorafenib and the MEK inhibitor U0126.

More recently, BRAF fusions were identified in melanocytic neoplasms and were found to have several different N-terminal fusion partner[3]. Analysis of six melanocytic tumors and a cutaneous melanoma cell line once again revealed retention of an intact kinase domain in these BRAF fusions. Further study using the melanoma cell line confirmed previous results by demonstrating constitutive activation of the MAPK pathway. Both p-ERK and p-MEK levels were elevated to levels similar to two $BRAF^{V600E}$ mutant melanoma cell lines, and were shown to be decreased upon treatment with the RAF inhibitor Sorafenib.

RAF Inhibitors. Importantly, only agents that inhibit wildtype BRAF have pre-clinical activity or are predicted to have activity, including Sorafenib and Dabrafenib.

**Summary.** Due to the similar kinase activity found in the context of both BRAF mutation and BRAF fusion genes, using a RAF inhibitor such as Dabrafenib or a MEK inhibitor such as Trametinib is a rational choice for treatment of tumors containing these fusion genes. Combination therapy with Dabrafenib and Trametinib would also be a rational consideration.

## 2.3 Dabrafenib (BRAFi)

Dabrafenib is an orally bioavailable potent and selective inhibitor of BRAF kinase with a mode of action consistent with adenosine triphosphate (ATP)-competitive inhibition. Dabrafenib has demonstrated suppression of downstream pharmacodynamic biomarker, phosphorylated ERK (pERK) in tumor cell lines, anti-proliferative activity against multiple BRAF mutant tumor cell lines and achieved biomarker suppression and tumor regression in BRAF mutant xenograft models (Investigator Brochure). Results from early phase clinical studies suggest that Dabrafenib has a favorable pharmacologic and toxicologic profile.

### 2.3.1 Mechanism of Action

The mechanism of action of Dabrafenib is consistent with competitive inhibition of ATP binding. It is most potent at inhibiting mutant $BRAF^{V600E}$ and mutant $BRAF^{V600K}$, and less potent at inhibiting $BRAF^{V600D}$.

### 2.3.2 Nonclinical Studies

Dabrafenib is a potent and selective RAF kinase inhibitor against human wild type (WT) BRAF and CRAF enzymes with $IC_{50}$ values of 3.2 and 5.0 nM, respectively, as well as against the mutant forms $BRAF^{V600E}$, $BRAF^{V600K}$, and $BRAF^{V600D}$, having $IC_{50}$ value of 0.65, 0.5, and 1.85 nM, respectively. Dabrafenib was highly selective for inhibition of $BRAF^{V600E}$ with a selectivity of at least 375-fold for $BRAF^{V600E}$ in

panels of >270 protein and lipid kinases, with the exception of 8 kinases, for which $IC_{50}$ values of Dabrafenib were <100 nM. Two of the three active metabolites of Dabrafenib [GSK2285403 (M7) and GSK2167542 (M8)] demonstrated similar selectively against a small panel of kinases.

Dabrafenib caused a dose-dependent decrease in pERK and phosphorylated MEK (pMEK), with $IC_{50}$ of 3 nM, in ES-2 human ovarian carcinoma cell lines with a $BRAF^{V600E}$ mutation. It also decreased pERK in other $BRAF^{V600E}$ cell lines with similar potency ($IC_{50}$ of 3 - 120 nM), while cell lines with WT BRAF or RAS mutations were much less sensitive to Dabrafenib (pERK $IC_{50}$ values >900 nM). In $BRAF^{V600E}$ cell lines, Dabrafenib induced a concentration-dependent cell cycle arrest in G0/G1 phase at 24 hours followed by apoptosis. In a panel of 110 human tumor cell lines, Dabrafenib potently ($IC_{50}$ <100 nM) inhibited proliferation of 73% of $BRAF^{V600E}$ containing cell lines, with generally little or no growth inhibition in tumor cell lines with WT BRAF or in cell lines containing activated RAS.

### 2.3.3 Nonclinical Pharmacokinetics and Metabolism

In mouse, rat, and dog, oral bioavailability of Dabrafenib (from solution formulation) was moderate to high (46-82%). Blood clearance was moderate in the mouse, rat and monkey (32-50% of liver blood flow), but low in the dog (12% of liver blood blow) and volume of distribution was moderate to low (1.4 to 0.6 times total body water).

Preclinical in vitro studies showed that Dabrafenib was primarily metabolized by CYP2C8 and CYP3A4. Dabrafenib is also substrate of human P-glycoprotein (Pgp) and murine breast cancer resistant protein 1 (Bcrp1) in vitro. However, the relative contribution of these various pathways is yet to be elucidated.

### 2.3.4 Animal Toxicology

The principal dose-limiting toxicity seen in animal toxicology studies conducted with Dabrafenib was gastrointestinal side effects. These effects were dose-dependent effects in rats and dogs with doses > 10 mg/kg/day and included infrequent emesis, changes in fecal consistency, decreased food consumption and body weight loss.

In Dogs, Dabrafenib minimally inhibited hERG repolarization (IC25 of 11.7 μM; 6.1 μg/mL) and its principal metabolites did not significantly inhibit hERG (IC50 >30 μM). There was no prolongation of QTc interval or other ECG changes in dogs; therefore, Dabrafenib administration has a low potential for QTc prolongation in humans.

### 2.3.5 Clinical Studies

Dabrafenib is an experimental oral drug that is being studied in patients with various types of cancers. There are multiple ongoing, concluded or completed phase I, II or III studies in patients with solid tumor including following studies: There are four

Phase I studies, including the First-time-in-Human (FTIH) study (BRF112680), a food effect/particle size evaluation study with two different capsule shells (BRF113468), a human mass balance study (BRF113463) and an absolute bioavailability study (BRF113479). In addition, there are four Phase II studies (BRF113710, BRF113928, BRF 113929 and BRF114144), one Phase III study (BRF113683), and a Phase 1/2 combination study (BRF113220) with Trametinib, a MEK inhibitor.

### 2.3.5.1 Pharmacology in Clinical Studies

Single and Repeat Dose Pharmacokinetics (PK)

Following single dose oral administration of Dabrafenib in gelatin capsules, plasma concentrations peaked approximately 1.0 to 2.5 hours post-dose and decreased thereafter following a bi-exponential decline. Median terminal half-lives ranged from 4.0 to 6.8 hours following administration of single doses ranging from 12 to 300 mg. Increases in maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) were generally dose-proportional following single doses up to 300 mg, but less than dose proportional to dose following repeat-dosing. A 2-fold increase in dose (150 mg BID vs. 300 mg BID) resulted in a 43% increase in AUC (0-τ) and no increase in predose concentrations (Cτ). There was no accumulation with daily doses ranging from 12 mg to 600 mg administered using twice- daily administration; mean accumulation AUC Day 15/Day 1 ratios were <1.0 for all cohorts. Following administration of Dabrafenib 150 mg BID, AUC was 37% lower on Day 18 relative to Day 1. The decrease in exposure noted with repeat dosing of Dabrafenib was likely due to induction of its own metabolism.

Metabolism and Excretion

Based on preclinical and in vitro studies, hepatic metabolism and biliary secretion are likely to be the primary route of elimination of GSK2118436. Dabrafenib concentrations are likely to be increased in subjects with hepatic impairment and dosage adjustment may be required.

In human hepatocytes, Dabrafenib produced dose-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. The single-dose exposure to midazolam, a CYP3A4 substrate was reduced by 74 % with co administration of Dabrafenib150 mg BID following repeat-dose administration. Thus, Dabrafenib induces CYP3A4-mediated metabolism and may induce other enzymes such as CYP2B6 and CYP2C family (2C8, 2C9, and 2C19). Co-administration of Dabrafenib and drugs which are primarily metabolized by these enzymes may result in decreased concentrations and loss of efficacy.

Dabrafenib inhibited CYPs 2C8, 2C9, 2C19 and 3A4 in human liver microsomes with $IC_{50}$ values in the range of 8 to 32 μM. Drugs that are substrates of CYP2C8, CYP2C9, and CYP2C19 that are highly sensitive to inhibitors or that have a low therapeutic index should be used with caution.

Three metabolites of Dabrafenib were characterized and may contribute to clinical activity. GSK2285403 (hydroxy-metabolite) pharmacokinetics paralleled that of parent while the carboxy- (GSK2298683) and desmethyl- (GSK2167542) metabolites exhibited a longer half-life and accumulated following repeat dosing. Similar to parent concentrations, exposure for all metabolites showed a less than dose proportional increase with repeat dosing. Preliminary results following single dose administration showed a total recovery of radioactivity of 93.8 % of the dose with faecal excretion being the major route of elimination, accounting for 71.1% of the dose.

Relative Bioavailability and Food Effect Evaluation

The relative bioavailability of single dose of Dabrafenib administered in an hydroxypropyl methylcellulose (HPMC) capsule relative to the same formulation in a gelatin capsule was evaluated in a non-randomized fashion across 2 separate cohorts of subjects enrolled in Study BRF113468. Preliminary results obtained in 14 out of 28 subjects (7 per cohort) showed higher exposure with HPMC relative to gelatin capsule with geometric least squares mean ratios (90% CI) for Cmax and AUC(0-∞) of 3.24 (2.08, 5.05) and 2.20 (1.31, 3.67), respectively. HPMC capsules are currently being used in the clinical studies BRF113683 (Phase 3) and BRF113929 (Phase 2 study with brain metastases) while gelatin capsules are being used in Study BRF113710 (Phase 2).

The current recommendation is to administer Dabrafenib under fasting conditions, either one hour before or 2 hours after a meal. Preliminary results of the food effect study showed a decrease in Dabrafenib Cmax and AUC (0-∞) after single dose administration.

Drug Drug Interaction

Preliminary results of the effect of repeat dose administration of Dabrafenib150 mg BID on the single dose pharmacokinetics of midazolam, a CYP3A4 probe, showed a decrease in midazolam exposure. The geometric least squares mean ratio (90% CI) for Cmax and AUC of midazolam with Dabrafenib vs. midazolam alone is 0.388 (0.241, 0.626) and 0.258 (0.210, 0.318), respectively, indicating that Dabrafenib induces CYP3A4-mediated metabolism. Co-administration of Dabrafenib and drugs which are affected by the induction of these enzymes may result in decreased concentrations and loss of efficacy. If co-administration of these medications is necessary, monitor subjects for loss of efficacy or consider substitutions of these medications.

**2.3.5.2 Safety data in Clinical Studies**

Safety data provide below for various studies are updated as of 25 March 2011.

Dabrafenib (BRAFi) Monotherapy Studies:

Preliminary safety data are available for the BRF112680 FTIH study and the

BRF113710 phase II monotherapy study in metastatic melanoma.

In the BRF112680 first time in human (FTIH) study, 184 patients have received at least one dose of study drug. Doses ranged from 12 mg QD to 300 mg BID and patients have received study drug up to a maximum of 626 days. A total of 127 subjects (69%) have withdrawn from the study as of 25 March 2011, primarily due to progression of disease (121 subjects, 66%). Across all 184 subjects, 98% experienced at least 1 AE of any grade. The most common AEs experienced by ≥20% subjects were fatigue, pyrexia, headache, nausea, hyperkeratosis, skin papilloma, pain in extremity, rash, decreased appetite, diarrhea, vomiting and alopecia. Most AEs were grade 1 or 2. Seventy seven subjects (42%) experienced a grade 3 adverse event, and 15 subjects (8%) experienced grade 4 adverse events; the most common grade 3 or 4 AEs experienced by ≥4% subjects were squamous cell carcinoma, anemia, hyponatremia, hypophosphatemia and lymphopenia. Sixty six (36%) subjects reported SAEs; the most common SAEs were SCC (11%), pyrexia (5%), and urinary tract infection (3%). No subjects have permanently discontinued study drug due to AEs/SAEs. Fifty seven subjects (31%) had study drug interrupted due to the occurrence of AEs, primarily due to pyrexia (9%). Thirty deaths due to the progression of disease under study have been reported. No fatal AEs/SAEs (grade 5) have been reported.

In the phase II BRF113710 study, 92 patients have received at least one dose of study drug (150 mg BID). The majority of the subjects (94%) have received 6 months or less of study treatment. Across all 92 subjects 87% have experienced at least 1 AE of any grade. AEs were primarily grade 1 or 2. The most common AEs experienced by ≥15% subjects were arthralgia, hyperkeratosis, pyrexia, fatigue, nausea and headache. Sixteen subjects (17%) experienced a grade 3 adverse event, and 7 subjects (8%) experienced a grade 4 adverse event; grade 3 AEs experienced by more than 1 subject include anemia, hyperphosphatemia, lymphopenia, squamous cell carcinoma and headache. Sixteen (17%) subjects reported SAEs, SAEs reported by more than 1 subject include SCC, anemia and vomiting. No subjects have permanently discontinued study drug or withdrawn from the study due to AEs/SAEs. Twenty-six subjects (28%) had study drug interrupted due to the occurrence of AEs, primarily due to hyperphosphatemia (5%). Eight deaths due to the progression of disease under study have been reported. No fatal AEs/SAEs (grade 5) have been reported.

<u>Dabrafenib (BRAFi) in Combination with Trametinib (MEKi)</u>

As of 25 March 2011, there is 1 ongoing combination study, the Phase I/II study BRF113220 in which Dabrafenib has been administered as monotherapy or in combination with Trametinib. One hundred and thirty seven subjects have been enrolled. A total of 15 subjects (11%) have withdrawn from the study primarily due to lack of effect and progression of disease (9%). Thirty two (23%) patients have experienced SAEs, with the most common SAEs being pyrexia (n=7, 5%), hypotension (n=5, 4%) and nausea (n=4, 3%). Overall, 106 (77%) of patients experienced AEs, with the most common AEs experienced by ≥20% subjects being pyrexia (n=36, 26%), fatigue (n=35, n=26%) and nausea (n=28, 20%). Two subjects

have permanently discontinued study drug due to AEs (retinal vein occlusion, cerebrovascular accident). Four deaths have been reported in the study, 3 due to the progression of disease a 1 death from complications following surgery.

## 2.4 Trametinib (MEKi)

Trametinib is an orally bioavailable reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Trametinib is non-competitive towards ATP and inhibits activation of MEK by RAF kinases as well as MEK kinase activity. Trametinib has demonstrated suppression of downstream pharmacodynamic biomarkers, phosphorylated MEK (pMEK) and phosphorylated ERK (pERK) in tumor cell lines, anti-proliferative activity against multiple BRAF or RAS mutant tumor cell lines and achieved biomarker suppression and tumor regression in BRAF or RAS mutant xenograft models (Investigator Brochure). Results from early phase clinical studies suggest that Trametinib has a favorable pharmacologic and adverse event profile.

### 2.4.1 Mechanism of Action

Trametinib is an allosteric inhibitor of MEK1 and MEK2. Inhibition of MEK1 and MEK2 is expected to reduce proliferation of cells that are dependent on the MAPK pathway for growth.

Phosphorylation of ERK by MEK enzyme in presence of ATP (2.5, 5, 10 and 20 μM) and Trametinib (0.125, 0.25 and 0.5 μM) demonstrated that the inhibition constants (Ki values) were 0.38 μM and 0.29 μM against phosphor-MEK (pMEK) and the pMEK-ATP complex, respectively. These data demonstrate that Trametinib is an inhibitor of pMEK activity and is not competitive with ATP binding, as Ki values were similar in the absence or presence of ATP.

Trametinib demonstrated equal potency against activated MEK1- and MEK2-mediated phosphorylation of ERK (sequence identity of 85% across the whole protein and 100% in the active site for humans). Trametinib demonstrated preferential inhibition of Raf-mediated MEK1 activation (IC50 = 0.60 nM) over pMEK1 kinase activity (IC50 = 13 nM). Trametinib exerted no effect on B-RAF or c-Raf kinase activity, as Trametinib (0.1 to 10 μM) did not affect the phosphorylation of myelin basic protein mediated by B-RAF or c-Raf. Phospho-mapping identified that Trametinib blocks phosphorylation by activated Raf kinase of Ser218 and not Ser222 on MEK.

### 2.4.2 Nonclinical Studies

Trametinib is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are critical components of the extracellular signal-related kinase (ERK) pathway which is

commonly hyperactivated in tumor cells. Oncogenic mutations in both B-RAF and RAS signal through MEK1 and MEK2. Trametinib is non-competitive towards ATP and inhibits activation of MEK by RAF kinases as well as MEK kinase activity. The specificity of Trametinib to MEK1 and MEK2 was confirmed against a panel of 183 kinases, including MEK5, the closest kinase homolog to MEK1 and MEK2, and no significant inhibitory activity was measured.

In vitro, 80% of cell lines carrying activating mutations of B-Raf and 72% of Ras mutant cancer cell lines were sensitive to Trametinib in cell proliferation assays, and a majority (83%) of hematopoietic cancers from acute or chronic myeloid leukemia (AML or CML, respectively) origins were also very sensitive.

**Anti-tumor Activity *in vitro***
Cancer cells expressing high constitutive levels of activated ERK (pERK) tended to be more sensitive to Trametinib than those with lower levels of pERK, suggesting that tumors with B-RAF or RAS mutations and/or high levels of pERK may respond to Trametinib treatment. In all cell lines, pERK was strongly inhibited following treatment with Trametinib and was independent of their proliferative response, suggesting that pERK inhibition is necessary but not sufficient to inhibit cell proliferation. In cell lines that were sensitive to the anti-proliferative activity of Trametinib, the response was associated with arrest in G1 phase of the cell cycle, accumulation of p27, reduction of cyclin D1 and phospho-retinoblastoma protein. Induction of apoptosis was demonstrated in some cell lines. Inhibition of pERK and inhibition of cancer cell proliferation were fully reversible following compound removal, suggesting that sustained exposure to Trametinib, or potential combination with other drugs, may be required for full activity.

When Trametinib was combined with standard of care drugs against human cancer cell lines in vitro, an additive effect was observed for pancreatic cancer with gemcitabine or erlotinib and for colon cancer with 5-FU or irinotecan. The combination of Trametinib with rapamycin, ara-C, bexarotene or sorafenib produced an additive effect against most AML cell lines tested. In addition, combination of Trametinib with an investigational phosphoinositide 3-kinase (PI3K) inhibitor, as well as with a Centromer Protein-E (CENP-E) inhibitor, was synergistic on inhibition of cell growth in various cancer (pancreas, colon, lung) cells. Additionally, the combination of Trametinib and a CENP-E inhibitor increased caspase activity, indicating enhanced apoptosis in colon cancer cell lines.

While many proliferating human cells are sensitive to Trametinib in vitro, Trametinib did not affect non-dividing normal cells and did not completely inhibit bone marrow progenitor cells at concentrations demonstrating anti-proliferative activity on very sensitive cancer cell lines.

**Anti-tumor Activity *in vivo***
Trametinib was orally bioavailable in mice, and doses as low as 1 mg/kg reached blood concentrations that caused sustained reductions of pERK, an accumulation of

p27, and a decrease of Ki67 in tumor xenografts; brain exposure levels were ~10% of those in blood, and no significant pERK inhibition was measured in brain tissue. In mice, exposure to Trametinib produced dose- and schedule-dependent anti-tumor responses correlating with blood levels. Typically, B-RAF--mutant xenografts responded with tumor regression while K-RAS-mutant xenografts responded with tumor growth inhibition. In vivo combination studies testing Trametinib together with various other anticancer drugs showed good potential for synergistic effects.

### 2.4.3 Non-clinical Pharmacokinetics and Metabolism

Trametinib exhibited low plasma clearance among nonclinical species (mouse, rat, dog and monkey) with varied but generally long half-lives. Oral bioavailability ranged between 42% and 100%. Since Trametinib is a low solubility, high permeability molecule, its absorption is likely limited by solubility and dissolution.
Plasma protein binding was high in nonclinical species and human (>95%) and blood cell association was low. Consistent with high permeability, Trametinib had moderate to high volume of distribution among the nonclinical species studied and drug-related material (DRM) was widely distributed into rat tissues.

No apparent human-specific metabolite was observed in the in vitro cross-species [14C] Trametinib metabolism study. [14C]Trametinib was also found to metabolize predominantly via a non-cytochrome P450 (CYP) mediated deacetylation with secondary oxidation or glucuronidation biotransformation pathways. CYP3A4 was implicated in the in-vitro formation of M7, a metabolite mediated by both non-CYP and CYP pathways. The relative contribution of CYP3A4 to the total metabolic clearance of Trametinib in human in vivo is not currently understood and, therefore, the possibility of a metabolic drug interaction cannot be eliminated. Elimination of DRM in rat and dog after oral administration occurred predominantly via the feces (>60% of dose), with urinary excretion (<7% of dose) representing a minor route.

Trametinib was found to be an in vitro inhibitor of CYP2C8, CYP2C9 and 2C19, inducer of CYP3A4 and inhibitor of the transporters (OATP1B1, OATP1B3, Pgp and BCRP), the low clinical Trametinib systemic exposure relative to these in vitro inhibition values suggests a low potential for Trametinib as a perpetrator in clinical drug-drug interactions. However, drugs with a narrow therapeutic index that are substrates of CYP2C8, the CYP with the lowest inhibition IC50, should be used with caution. There was no evidence of time-dependent inhibition with any of the CYP enzymes investigated. In addition, Trametinib was not found to be an in vitro substrate of the transporters Pgp and human breast cancer resistance protein (BCRP).

### 2.4.4 Animal Toxicology

Systemic toxicity of Trametinib has been evaluated following oral dosing in rats and dogs for up to 13 weeks. In the most sensitive nonclinical species, rat, the principal adverse effects seen in oral toxicity studies of up to 13 weeks with daily dosing were skin and stomach erosions, skin ulcerations, which were secondary to reduced

proliferation, altered phosphate homeostasis that resulted in soft tissue mineralization, hepatocellular necrosis, bone marrow degeneration/necrosis and ovarian perturbations.

Trametinib inhibited hERG channel repolarization in HEK293 with an IC50 of 1.54 μM (950ng/mL). In a rabbit left ventricular wedge assay, Trametinib had no significant effect on QT interval at concentrations up to 30 μM (18450 ng/mL; limit of solubility). In addition, single oral doses up to 1.5 mg/m2 in dogs produced no changes in arterial blood pressure, heart rate, body temperature or ECG intervals, including QTc. While Trametinib affected cardiac electrophysiology in vitro, no effects were observed in vivo at doses that were maximally tolerated in dogs. This difference in responses is likely related to the very low Cmax (~10 ng/mL total drug) at tolerated doses in dogs and the high protein binding (97% in dogs) of Trametinib. The concentrations at which effects were seen in these in vitro studies are significantly higher than the free fraction observed in nonclinical toxicology studies or the clinical dose (2 mg). These results suggest a low risk for cardiovascular effects in the clinic.

### 2.4.5. Clinical Studies:

The effect of Trametinib in subjects with a variety of refractory cancers is currently under evaluation in 14 ongoing clinical studies. Following clinical data derived from these studies are updated as of April 14 2011.

Trametinib has been administered as monotherapy in 6 of these studies, and as combination therapy in the other 8 studies. As of 14 April 2011, 657 subjects with cancer have received at least one dose of Trametinib in the 13 ongoing Phase I/II/III clinical studies. This number does not include subjects from 2 randomized trials (MEK113487 and MEK114267), from the blinded part of the combination trial (BRF113220), and from another combination trial (P3K113794).

#### 2.4.5.1 Pharmacology in Clinical Studies

Preliminary Trametinib pharmacokinetics were determined after single- and repeat dose oral administration of Trametinib tablets in subjects with solid tumors. Trametinib is absorbed rapidly with median Tmax generally occurring within 1-3 hours after oral administration of Trametinib under fasting conditions. Following repeat-dosing the mean area under the curve (AUC0-τ) and maximum concentrations (Cmax) increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean effective half life of approximately 5 days.

#### 2.4.5.2 Safety data in Clinical Studies

Based on the adverse events (AEs) observed in the dose escalation phase of the first-time in-human (FTIH) study MEK111054, the maximum tolerated dose was

established at 3.0 mg once daily (QD), and the recommended Phase II dose (RP2D) of Trametinib was identified as 2.0 mg QD.

Of the 241 subjects in the 2.0 mg dose group in the 3 monotherapy trials (MEK111054, MEK111759, and MEK113583), 99% to 100% of subjects experienced at least one AE, and 26% to 71% of all subjects experienced SAEs. Of the 241 subjects, 4% to 23% permanently discontinued study treatment due to AEs. In these trials, the most common AEs experienced were rash, diarrhea, nausea, fatigue, vomiting, anemia, peripheral edema, abdominal pain, constipation, dermatitis acneiform, decreased appetite, pruritus, dyspnea, pyrexia, pneumonia, febrile neutropenia, AST increased, ALT increased, and dry skin.

In the 5 combination therapy trials of Trametinib for which data are available (MEK112110, MEK112111, MEK113486, open-label parts of BRF113220, and TAC113886), 89% to 100% of all 296 subjects in any dose group experienced at least one AE and 21% to 45% of all 388 subjects in any dose group experienced at least one SAE. Of these 296 subjects, 4% to 10% permanently discontinued study treatment due to AEs. In the 5 combination trials for which data are available, the most common AEs experienced were nausea, fatigue, diarrhea, vomiting, decreased appetite, pyrexia, rash, constipation, neutropenia, dry skin, dermatitis acneiform, anemia, mucosal inflammation, stomatitis, exfoliative rash, thrombocytopenia, peripheral edema, abdominal pain, cough, chills, and AST increased.

## 2.5 Rationale

Differentiated thyroid cancer (DTC) accounts for 95% of all endocrine cancers and papillary thyroid carcinoma (PTC) is the most common (85%) type of DTC. There is no standard treatment for patients with metastatic, radioiodine resistant DTC. Aberrant signaling through the RAS/RAF/MEK/ERK pathway has been identified in many human malignancies (13). BRAF mutations are present in approximately 44% of PTC cases, and with greater frequency in the advanced setting (12, 14). The role of BRAF in development of PTC is well established(8).

BRAF or MEK inhibitors in PTC: Our group reported significant biologic and clinical activity of sorafenib, an orally active multi-kinase inhibitor targeting BRAF and angiogenesis, in patients with advanced PTC (15). While we showed drastic >95% decrease in pERK in tumor biopsies obtained from the PTC patients treated with sorafenib, the mechanism of action remains unclear. Of note, we also observed significant anti-angiogenic effect (dramatic decline in pVEGFR in tumor biopsies and in tumor perfusion in index lesions in dynamic contrast enhanced-MRIs).(16) Clinically, sorafenib has efficacy with objective response rates of 15-25% in phase 2 trials (16-18) and is now recommended by NCCN for the treatment of advanced iodine-refractory DTC. In a phase I trial of PLX4032, a selective ATP competitive BRAF inhibitor, one patient with PTC had a partial response (PR) and 2 patients had stable disease (SD) with response ranging 8 to 13 months (19). Single agent MEK inhibitor, AZD6244 has been tested in a phase 2 clinical trial in patients with iodine-

refractory PTC (20). Of a total of 39 individuals enrolled in the trial, best response was evaluable in 32 patients of whom 1 had a PR (3%) and 21 had SD (54%). Of note, a relatively high frequency of progressive disease (PD) (43%) was seen in this study.

Dabrafenib and Trametinib in solid tumors: Dabrafenib is a highly potent and selective ATP competitive BRAF inhibitor with selectivity for mutant BRAF over wild type BRAF. In the first time in human (FTIH) study (21), the recommended phase 2 dose (RP2D) was defined as 150 mg twice daily. Trametinib is a potent, highly selective allosteric inhibitor of MEK1 and MEK 2. In the FTIH study (22), the maximum tolerated dose (MTD) was defined as 2 mg daily. Both of these agents were well tolerated and resulted in >90% pERK inhibition in tumors of patients with melanoma. While dramatic objective responses in melanoma are observed with both single agents, benefit of BRAF inhibitor was restricted to patients with BRAF mutated melanoma. Dramatic antitumor activity has been demonstrated with the combination of Trametinib and Dabrafenib a phase I/II trial of patients with BRAF mutated solid tumors (23). The RP2D was Trametinib 2 mg daily in combination with Dabrafenib 150 mg twice daily. Adverse events included rash, neutropenia, pyrexia, vomiting, fatigue and sepsis like syndrome. No cutaneous squamous cell carcinoma (SCC) was observed. In 10 patients who received Dabrafenib 150 mg twice daily and Trametinib >1mg daily, 9 had PR and 1 SD.

Pre-clinical data in thyroid cancer: In preclinical thyroid models, BRAF V600E mutation confers preferential sensitivity to both BRAF and MEK inhibition (24, 25). Singly, BRAF and MEK inhibitors effectively reduced MAPK signaling in BRAF mutated thyroid cell lines by decreasing pERK, and inhibited growth of BRAF mutated xenograft tumors (Figure 2) (26-28). Mechanisms of acquired resistance to BRAF inhibition, including RAF isoform switching and overexpression of PDGFR, N-RAS, or COT, have been described in preclinical melanoma studies (29-31). MEK inhibition with Trametinib was shown to prevent ERK activation and proliferation in a melanoma cell line resistant to BRAF inhibition (29).

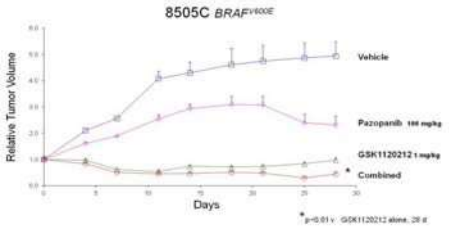



**Figure 2. Trametinib causes durable responses in DTC xenograft tumors**. $5x10^6$ cells from the indicated line, suspended in matrigel were injected into the right flank of 4 to 6 week old athymic nu/nu mice. After tumors reached 0.1 $cm^3$, they were randomized in groups of 13 to receive Trametinib 1mg/kg or pazopanib 100 mg/kg, both drugs combined, or vehicle control by oral lavage.

Given the above preclinical and clinical data, we hypothesize that single agent Dabrafenib will have efficacy in the treatment of advanced, BRAF mutated DTC and that combination therapy with Dabrafenib and Trametinib will result in greater clinical efficacy than Dabrafenib alone, through vertical inhibition of the RAS/RAF/MEK/ERK pathway and mitigation of potential mechanisms of resistance.

## 2.6 Correlative Studies Background

26.1 Tumor pharmacodynamics (PD) evaluation: Mutations in BRAF, specifically the BRAF V600E mutation, are the most commonly described mutations in DTC (7, 12, 32, 33). Preclinical models have confirmed that these mutations are oncogenic (10) and result in constitutive activation of the MAPK (RAS/RAF/MEK) pathway (34). Inhibition of BRAF and other signaling molecules in the MAPK pathway is thus conceptually appealing and early clinical trials evaluating BRAF inhibitors have been promising in patients with advanced thyroid cancer (35). Our primary hypothesis is that combination therapy with Dabrafenib (BRAFi) and Trametinib (MEKi) in patients with BRAF-mutant DTC will accentuate the vertical blockade of the MAPK pathway when compared to GSK2118438 alone, and that MAPK blockade will be associated with response to therapy. We propose using fine needle aspiration (FNA) tumor biopsies for PD monitoring. We have previously demonstrated in our study of sorafenib (a multikinase inhibitor with relatively weak BRAF inhibition) in papillary thyroid cancer that FNAs, obtained serially prior to and during treatment, can be used for PD monitoring of treatment with BRAF inhibitors (16). We performed immunohistochemistry (IHC) in biopsy specimens and tested for pERK, pAKT and pVEGFR. Monitoring of the same pharmacodynamics markers was also used with the potent and selective BRAF inhibitor PLX4032 in patients with metastatic melanoma (19). In the phase I PLX4032 trial, tumor biopsies obtained at baseline and day 15 was available for seven patients. Tumor levels of pERK, cyclin D1, and Ki-67 were markedly reduced at day 15 as compared with baseline in all specimens tested. These studies support the hypothesis that decreases in tumor pERK and Ki-67 will be seen with treatment, reflecting down regulation of MAPK. Increases in the levels of the sodium-iodine symporter (NIS) may also be seen, as BRAF activation suppresses NIS expression, leading to a loss of RAI sensitivity (36).

26.2 BRAF V600E quantification in circulating plasma DNA: Several investigators have demonstrated the ability to detect the BRAF V600E mutation in circulating plasma DNA samples from patients with $BRAF^{V600E}$ mutant neoplasms, including melanoma (37-39) and thyroid cancer (40). With the emergence of new technology, it is now possible to develop highly sensitive assays to detect and obtain absolute concentrations of rare mutant alleles (41). We hypothesize that plasma levels of mutant BRAF alleles can be correlated to radiographic response as defined by RECIST, with improved sensitivity and specificity in comparison to traditional serologic correlates such as thyroglobulin (Tg), potentially allowing for the early detection of disease progression and resistance to therapy.

26.3 Tumor mutation screening: Third, we propose to study the potential mechanisms of resistance to BRAFi and MEKi in a subset of patients with initial response to therapy followed by subsequent progression. Several mechanisms of resistance to BRAF inhibitors have been described in melanoma, including BRAF-independent activation of the MAPK pathway (e.g., NRAS mutations), as well as upregulation of alternative signaling pathways that are independent of MAPK (e.g., PDGFRβ, COT) (30, 31). However, it is unclear if these same pathways can be implicated in the development of resistance in thyroid carcinoma. Patterns of resistance are anticipated to differ in

patients treated with both BRAFi and MEKi as opposed to BRAFi alone: we expect that additional activating mutations of the MAPK pathway (e.g., NRAS) will be restricted to patients treated with BRAFi alone. IHC and tumor mutational screening will be performed at baseline and at progression as part of this analysis.

2.6.4. Predictive markers of response: Pre-clinical studies show that Trametinib responds better in tumors that have high levels of pERK expression. If we observe significant clinical response, we will evaluate levels of pERK, pAKT, pMEK expression in archival tumor samples. Alternative mechanism of funding will be sought.

2.6.5 Pharmacokinetics (PK): We will evaluate PK of both Dabrafenib (BRAFi) and Trametinib (MEKi). A recent study reported no drug-drug interactions between these two agents in a population of melanoma patients (23). Therefore, we will not evaluate the potential for drug-drug interaction. However, it will be important to characterize the PK of both agents, as well as the PK of GSK2285403 and GSK2167542, the active metabolites of GSK2118436.

2.6.6 Pharmacogenetics (PGx): Finally, we will assess the impact of PGx on drug disposition (absorption, distribution, metabolism, and elimination) in this patient population. An alternative source of funding will support PGx studies.

## 3. PATIENT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed papillary thyroid cancer, follicular thyroid cancer (Tall cell variant, insular thyroid cancer, follicular variant of papillary thyroid cancers, poorly differentiated thyroid cancer or any of the above mixed histology will be allowed). Patients with anaplastic thyroid cancer are excluded.

3.1.2 Presence of BRAF mutation or genes fusions involving BRAF in tumor tissue.

3.1.3 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan, MRI, or calipers by clinical exam. Malignant lymph nodes will be considered measurable if they are ≥ 15 mm in short axis. See Section 11 for the evaluation of measurable disease.

3.1.4 Patients must have progressive disease within the thirteen months prior to study enrollment. Progressive disease is as defined in RECIST 1.1, which is at least a 20% increase in the sum of diameters of target lesions and the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progressive disease.

3.1.5 Patients must have disease that is refractory (unresponsive) to radioactive iodine (RAI) treatment as defined by one of the following:

a. One or more measurable lesions that do not demonstrate RAI uptake
b. One or more measurable lesions progressive by RECIST 1.1 within 12-months of prior RAI therapy and/or the appearance of one or more new lesion within 12 months of prior RAI therapy.
c. Cumulative RAI dose of >600 mCi.
d. Measurable disease that is Fludeoxyglucose (18F) PET scan positive.

3.1.6 Prior therapy allowed:

3.1.6.1 Patients may have been previously treated with up to three regimens of oral multikinase inhibitors, including sorafenib, sunitinib and pazopanib.
3.1.6.2 Patients may have been previously treated with external beam radiation or cytotoxic chemotherapy therapy.

3.1.7 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of Dabrafenib or Trametinib, each respectively as monotherapy or as combination therapy in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

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

3.1.9 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Total bilirubin ≤1.5 X institutional upper limit of normal (unless due to Gilbert's disease)
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal
- Serum creatinine ≤1.5 X institutional upper limit of normal
- Left ventricular EF ≥ 50%

3.1.10 Patient must have a calcium phosphate product (CPP) $\leq 4.0 mmol^2/L^2$ or 50 $mg^2/dL^2$).

3.1.11 Female patients of childbearing potential are required to have a negative serum pregnancy test within 14 days prior to the first dose of study medication.

a. Females are required to use an effective method of contraception from the time of negative serum pregnancy test, throughout the study duration, and for

4 months after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to study enrollment, for the duration of study participation, and for 16 weeks after completion of the last dose of study drug.

b. Specific contraception requirements for females: Female subjects of childbearing potential must not become pregnant and are required to be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%. Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception. Contraceptive methods with a failure rate of < 1% include the following:

• Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% failure rate as stated in the product label,

• Male partner sterilization (vasectomy with documentation of Azoospermia) prior to the female subject's entry into the study, and this male is patient's sole sexual partner. For this definition, "documented" refers to the outcome of the investigator's/qualified physician designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.

• Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

c. Specific contraception requirements for males: To prevent pregnancy in a female partner or to prevent exposure of any partner to the investigational product from a male subject's semen, male subjects must use one of the
following contraceptive methods during the study and for a total of 16 weeks following the last dose of study drug (based upon the lifecycle of sperm):

• Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject for 14 days prior to first dose of study drug, through the dosing period, and for at least 16 weeks after the last dose of study drug. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

• Condom *(during non-vaginal intercourse with any partner - male or female)* **OR**

• Condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) *(during sexual intercourse with a female)*

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

## 3.2 Exclusion Criteria

3.2.1 Patients who have had external beam radiotherapy, cytotoxic chemotherapy, or oral multikinase inhibitors within 4 weeks prior to study enrollment.

3.2.2 Patients who have been treated with radioactive iodine within 24 weeks prior to study enrollment (radioactive iodine within 24 weeks will be allowed if negative post-treatment scan or progressive disease defined by RECIST 1.1).

3.2.3 Patients that have not recovered from adverse events related to prior chemotherapy, radiation therapy or multikinase inhibitors to CTCAE 4.0 grade 1 or less except for alopecia.

3.2.4 Patients previously treated with potent BRAF inhibitor or MEK inhibitor, including PLX4032/vemurafenib, ARQ 736 for more than 10 days. Previous treatment with sorafenib is permitted.

3.2.5 Patients that are receiving any other investigational agent.

3.2.6 Patients that are currently taking any prohibitive medication. (Appendix B). Patients on therapeutic dose of warfarin. This is due to potential for significant interactions between warfarin and study agents.

3.2.7 Patients with a known history of infection with Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV).

3.2.8 Patients with a history of other malignancy. Patients who have been disease-free from other malignancy for 5 years or greater, or patients with a history of resected non-melanoma skin cancer, or patients with a history of treated in situ carcinoma will be allowed.

3.2.9 Patients with uncontrolled brain metastases. Patients who are on a stable dose of corticosteroids for more than 1 month or off corticosteroids for 2 weeks prior to study enrollment can be enrolled. Enzyme-inducing anti-epileptic drugs are not permitted.

3.2.10 Patients with a known history of retinal vein occlusion (RVO) or central serous retinopathy (CSR) or predisposing factors to RVO or CSR (e.g.

uncontrolled
glaucoma or ocular hypertension, uncontrolled systemic disease such as
hypertension, diabetes mellitus, or history of hyper viscosity or hypercoagulability syndromes).

3.2.11. Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO or CSR such as:

a. Evidence of new optic disc cupping
b. Evidence of new visual field defects
c. Intraocular pressure > 21 mm Hg as measured by tonography

3.2.12 Patients with Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.

a. Abnormal cardiac valve morphology (subjects with minimal abnormalities, can be entered on study with approval).

3.2.13 QTc interval greater than or equal to 480 msecs (≥ 500 msec for subjects with Bundle Branch Block).

3.2.14 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.15 Pregnant women and nursing women are excluded from this study because Dabrafenib has the potential for teratogenic or abortifacient effects. In embroyfetal developmental studies in rats, developmental toxicities including reduced fetal body weight, embryo-lethality, cardiac ventricular septal defect malformations, delayed skeletal development and variation in thymic shape have been observed.

3.2.16 HIV-positive patients or those on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Dabrafenib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.17 Subjects with a history of pneumonitis or interstitial lung disease.

3.2.18 History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to study enrollment.

3.2.19 History of uncontrolled arrhythmias. Subjects with controlled atrial fibrillation for >1 month prior to study enrollment are not excluded.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

### 4.1 General Guidelines

OSU patients will be registered by the OSU research coordinator.

Subsite patients will have eligibility verified and will be entered on study centrally at the Ohio State University by the Study Coordinator. All subsites should call the Subsite Coordinator, Jennifer Sexton, at 614-366-5642 to verify slot availabilities. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

Following registration, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator and Subsite Coordinator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Subsite Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order study agents directly from Novartis. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

### 4.2 Registration Process

To register a subsite patient, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Subsite Coordinator:

- Copy of all required laboratory and radiologic tests per the protocol calendar. Screening tests must be within the specified window.
- Signed patient consent form
- HIPAA authorization form
- Eligibility Criteria Checklist
- Registration Form
- Source documents verifying every inclusion & exclusion criteria
- Emails and other signed forms used as source documentation

The subsite research nurse or data manager at the participating site will then call or email the Subsite Coordinator to verify eligibility. To complete the registration process, the Coordinator will:

- assign a patient study number
- register the patient on the study
- randomize the patient to treatment ARM A or ARM B
- advise if patient will need Pharmacokinetic studies (as it is restricted to first 10 pts on each arm)
- fax or e-mail the patient study number and assigned treatment ARM to the participating site

### 4.3 Cross-over from Arm A to Arm B

- At the treating physician's discretion, patients that experience disease progression on ARM A, may cross over from ARM A to ARM B. Each participating center needs to re-register the patient by contacting the coordinating center with the following data: Progressive disease documentation form (e.g. local Tumor Measurement Form)
- Reports of relevant CT/MRI scans including baseline and on study until progression

Patients that cross over to ARM B will not be eligible to participate in the Pharmacokinetics (PK) or the Pharmacogenetics (PGx) correlative studies.

## 5. TREATMENT PLAN

### 5.1 Agent Administration

Patients will receive treatment depending on which treatment ARM patients are randomized to (see Figure 3. Treatment Schema). Please review entire Section 5.0 to review treatment of study agents as well as caution with concomitant medications.

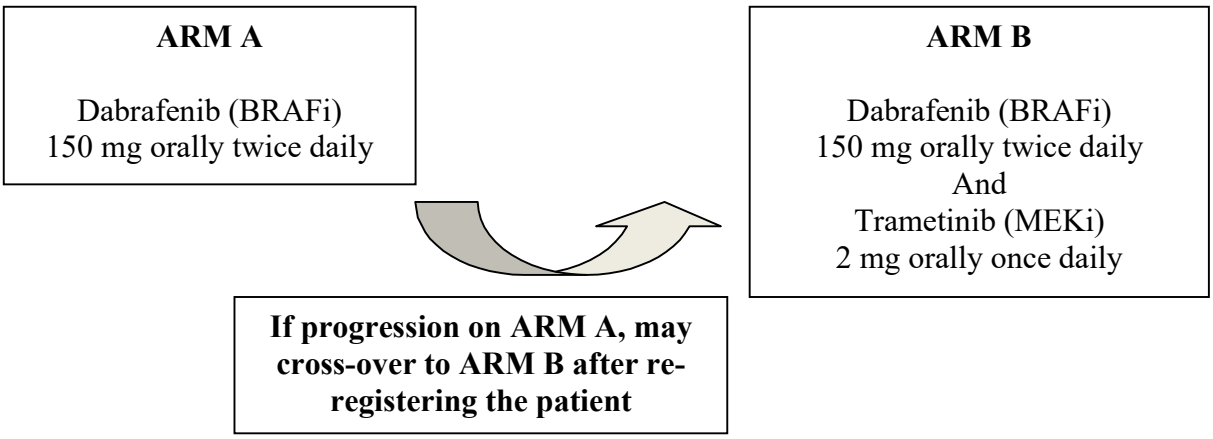
Treatment will be administered on an outpatient, continuous basis. One cycle is defined as 28 days. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies may be administered with the intent to treat the patient's thyroid cancer.

The patient will be requested to maintain a medication diary documenting the dose of medication(s) and the date and time of each dose taken. The medication diary will be returned to clinic staff at the end of each cycle.

It is preferred that patients take all planned study agent on day 1 of each new cycle. Patients should be instructed to take scheduled doses on clinic visit days. Any dose delayed > 1 hour from scheduled time on day 1 of a new cycle due to pending safety assessments may still be taken so long as there is at least 12 hours between doses (per IBs). Alternatively, one dose of Trametinib and/or one or more doses of Dabrafenib may be missed on day 1 of a new cycle, if per local standard practice patients are

instructed by the treating physician to hold all dosing on clinic days until after the safety assessments have been completed. All missed doses and reasons are to be clearly documented in the source records and study case report forms.

**Figure 3. Treatment Schema**




### 5.1.1. Administration of Dabrafenib (BRAFi) [For ARM A and ARMB]

Dabrafenib will be taken on an outpatient basis at the dose of 150 mg orally twice a day, or approximately every twelve hours, and on a continuous basis. Dabrafenib capsules are supplied as 50 mg, and 75 mg capsules for oral administration.

Dabrafenib should be taken under fasting conditions, either one hour before a meal or 2 hours after a meal. It should be taken with approximately 240 mL (8 fluid ounces) of water at approximately the same time each day. Patients should abstain from ingestion of Seville oranges, grapefruit or grapefruit juice, pummelos, or exotic citrus fruits or grapefruit hybrids while on the study, and avoid ingestion of such fruit(s) for at least 24 hours prior to the start of dosing, due to potential increased plasma Dabrafenib concentrations due to inhibition of intestinal CYP3A4.

If a patient vomits after taking study medication, the patient should be instructed not to retake the dose and should take the next scheduled dose.

Medication should be taken within a two hour window of the scheduled dose. If a patient misses the dose (falls outside of the scheduled 2 hour window) of study medication for some reason, the patient should just skip that dose and should take the next scheduled dose.

### 5.1.2 Administration of Trametinib (MEKi) [For ARM B ONLY]

Trametinib will be taken on an outpatient basis at the dose of 2 mg orally once daily in the morning and on a continuous basis. Trametinib tablets are supplied as 0.5 mg, and 2 mg (as free base) tablets for oral administration.

Trametinib should be administered under fasting conditions, either one hour before or 2 hours after a meal, at approximately the same time each day. It should be taken with approximately 240 mL (8 fluid ounces) of water. If a patient vomits after taking study medication, the patient should be instructed not to retake the dose and should take the next scheduled dose.

Trametinib should be taken within a two hour window of the scheduled dose. If a patient misses the dose (falls outside of the scheduled 2 hour window) of study medication for some reason, the patient should just skip that dose and should take the next scheduled dose.

Trametinib and the morning dose of Dabrafenib may be taken at the same time.

Patients who are selected for pharmacokinetics (PK) blood draws will take Dabrafenib (BRAFi) only once in the morning (instead of twice) on C1D1 and C2D1. On these days, patients on ARM B will take their daily dose of Trametinib (MEKi) in the morning. These patients will be instructed to bring and take their study drug(s) in the clinic on C1D15 for a pre-dose PK sample. Patients will take study med(s) in the clinic on C1D1 and C2D1, as timed for PK sampling.

## 5.2 General Concomitant Medication and Supportive Care Guidelines

### 5.2.1 General Concomitant Medication Use

Because there is a potential for interaction of Dabrafenib or Trametinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

### 5.2.2 Supportive Care Guidelines

Anti-emetics and anti-diarrheal treatment are not recommended for prophylactic use. Specific guidelines for management of adverse events are described in Section 6.

Proton Pump Inhibitors (PPIs) or H2 Blockers (acid reducers) may be used as supportive care for early symptoms of nausea and/or heartburn as nausea/heartburn might indicate early symptoms of gastritis/peptic ulcer that might be associated with study drugs.

## 5.3 Prohibited Medications

Dabrafenib induces CYP3YA-mediated metabolism, and administration of Dabrafenib with drugs that are affected by the induction of these enzymes, may result in decreased concentrations and loss of efficacy of the study drug. Drugs that are strong inhibitors or inducers of CYP3A or CYP2C8, Pgp or Bcrp transporters are contraindicated. These prohibited medications can be found in Appendix B.

## 5.4 Cautionary Medications

The following medications should be used with caution: (see Appendix C for a listing of these medications)

- Drugs that are substrates of CYP2C8, CYP2C9, and CYP2C19 that are highly sensitive to inhibitors or that have a low therapeutic index because concentrations of these substrates may be altered by Dabrafenib.
- Drugs that are mild/moderate inhibitors or inducers of CYP3A, CYP2C8, or Pgp or Bcrp transporter because they may alter Dabrafenib concentrations.
- Additionally, Dabrafenib may induce CYP3A4 and CYP2B6. Other enzymes such as CYP2C8, CYP2C9, and CYP2C19 may be affected as well. Co-administration of Dabrafenib and medications that are affected by the induction of these enzymes 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. The list may be modified based on emerging data.
- Patients that are taking Anti-Platelets or Anti-Coagulants such as: Aspirin, Clopidogrel, Dabigatran, Warfarin, Enoxaparin, or any other blood thinning agent, will need to have a CBC every 2 weeks during the first 4 months for close monitoring as GI haemorrhage has been seen with study drugs and above agents might increase such risk.

## 5.5 Duration of Therapy

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

- Disease progression for patients on ARM B (Patients who develop progression on ARM A may be crossed-over to ARM B after re-registering patient with coordinating center). Disease progression in this case is defined as 20% increase in sum of index lesions compared with baseline (not the best response); or unequivocal diagnosis of new non-bony tumor lesion. Patients who are noted to have ‘new’ or ‘worsening’

bony lesions can stay on treatment if the patient has clinical benefit (it has been challenging to diagnose bony metastasis response/progression while patients are treated with such new class of drugs).

- Off of study drug continuously for more than 28 days for any reason.
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) or meets any dose stopping criteria (Section 6)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 5.6 Duration of Follow Up

Patients will either be seen in the clinic, or contacted by phone every 3 months for 1 year post study treatment.

Follow up data to be collected:

- Survival status
- Disease status (progressed/stable)
- If any additional cancer therapy was initiated (name & start date)

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

### 5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

### 6.1 Dabrafenib Delays/Modifications (applicable to ARM A and ARM B patients):

For Arm B patients, please see section 6.2 also.

#### 6.1.1 Guidelines for Dabrafenib Dose Modification and Treatment of Adverse Events

The severity of adverse events will be graded utilizing the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Dose modifications of Dabrafenib will be made according to the dose levels outlined in **Table 1.**

| Table 1. Dabrafenib Dose Levels | |
|---|---|
| **Dose Level** | **Dabrafenib Dose/Schedule** |
| 0 | 150 mg BID |
| - 1 | 100 mg BID |
| - 2 | 75 mg BID |
| - 3 | 50 mg BID |

Guidelines for dose modifications and interruptions for management of toxicities associated with the study treatment other than those pertaining to neutropenia, fever, rash, hand foot skin reactions (HFSR), renal insufficiency, liver chemistry abnormalities, left ventricular ejection fraction (LVEF) are provided in **Table 2.**

Dose modifications specifically for neutropenia are outlined in **Table 3**. Prophylactic antibiotics are recommended for treatment of neutropenic fever (defined as a single fever >38.3ºC (101ºF), or a sustained temperature >38ºC (100.4ºF) for more than one hour in a patient with absolute neutrophil count (ANC) <500 cells/microL, or <1000 cells/microL with a predicted nadir of <500 cells/microL). The choice of antibiotic for neutropenic fever is per the treating physician and the institution's hospital policy**.**

Dose modifications for fever are provided in **Table 4.** Antipyretic use is permitted for symptomatic relief of fever. In the absence of severe neutropenia, the use of antibiotics is at the clinical discretion of the examining physician/investigator. For complicated fever, defined as Grade ≥3 fever or any grade with signs and symptoms including; rigors, dehydration, hypotension, dizziness or weakness, the administration of both Dabrafenib and Trametinib should be interrupted/held.

Dose modifications for rash and general recommendations for rash management are provided in **Table 5.**

Dose modifications for hand foot skin reaction (HFSR) are provided in **Table 6.** Treatment of squamous cell carcinoma (SCC), keratoacanthoma (KA), and actinic keratosis (AK) lesions should be based upon institutional practice. Dose interruptions or modifications are usually not required for SCC/KA. Biopsies of any new skin lesions suspicious for malignancy and pre-malignancy (SCC, AK, KA) are recommended.

Dose modifications for renal insufficiency are outlined in **Table 7.**

| Table 2. Dose Modification Table for Toxicities Other Than **Neutropenia, Fever, Rash, HFSR, LVEF, renal insufficiency or liver chemistry abnormalities | |
|---|---|
| **Non-hematologic and hematologic Toxicity (except**)** | **Dose Modification Algorithms[a, b, d, e]** |
| Grade 1 | Continue Dabrafenib at full dose, monitor as clinically indicated. |
| Grade 2 | **For Grade 2 Diarrhea with accompanying risk factors[c]** Hold Dabrafenib until return to ≤ Grade 1, provide supportive care.<br><br>**All other toxicities:** Consider holding Dabrafenib until resolution to Grade 1 or baseline; provide supportive care as clinically indicated. Monitoring of laboratory values should occur as clinically indicated.<br><br>**For Grade 2 or higher respiratory symptoms (i.e. cough, dyspnea, hypoxia etc.),** evaluation by a CT scan is recommended. |
| Grade 3 | **For Grade 3 toxicity,** hold Dabrafenib until toxicity is Grade 1 or baseline then reduce dose of Dabrafenib by 1 dose level. The subject may be continued at the same dose if, **in the judgment of the investigator, the toxicity is considered to be unrelated to Dabrafenib.** Continue to monitor as clinically indicated.<br><br>**If any Grade 3 toxicity recurs,** hold dosing until Grade 1 or baseline, then reduce current dose of Dabrafenib by one dose level. |
| Grade 4 | Discontinue Dabrafenib. Continue to monitor as clinically indicated, and provide supportive care as needed<br><br>If in the investigator's judgment the toxicity is unlikely to recur then, hold until toxicity is Grade 1 or baseline, then reduce dose of Dabrafenib by 1 dose level. If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug with the PI. |

** Neutropenia, Fever, Rash, HFSR, LVEF, renal insufficiency or liver chemistry abnormalities

a. The minimum dose is 50 mg BID. If a subject requires dose reduction below 50 mg BID then the subject must be discontinued from study medication.
b. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
c. Risk factors for cancer treatment-induced diarrhea include: fever, orthostatic symptoms (i.e. dizziness), abdominal pain/cramping, or weakness.
d. If the patient has a Grade 3 or 4 laboratory abnormality, that in the judgment of the investigator, is not considered clinically significant, dose modification is not required.
e. For subjects who develop symptoms associated with uveitis including blurry vision, eye pain or erythema ophthalmologic consult is required.

**Table 3. Dose Modification Table for Neutropenia**

| Grade | ANC value /mm3 | Management of Neutropenia | Dabrafenib Dose Adjustment |
|---|---|---|---|
| 1 | 1500-LLN | • Monitor per protocol time and events table | Continue at current dose |
| 2 | 1000-<1500 | • Re-check ANC in 1 week. If improvement to grade 1, continue to monitor per protocol time and events table.<br>• If stable at grade 2, monitor ANC every 2 weeks until resolution to grade 1 or until stable for 4 weeks<br>• If worsens to grade 3 or 4 follow below. | Any occurrence: continue at current dose |
| 3 | 500-<1000 | • Re-check ANC at least weekly during dose interruption.<br>• If resolved to grade 1, re-check ANC 3 days after rechallenge with Dabrafenib and then 1 week later. | • Any occurrence: hold until return to grade 1, then reduce one dose level<br>• 1st recurrence: Discontinue Dabrafenib or hold until return to grade 1, then reduce one dose level<br>• 2nd recurrence: Discontinue Dabrafenib. |
| 4 | <500 | • Re-check ANC at least weekly<br>• If resolved to grade 1, re-check ANC 3 days after rechallenge with Dabrafenib and then 1 week later. | • Discontinue or hold until return to grade 1, then reduce Dabrafenib by one dose level.<br>• 1st recurrence: discontinue Dabrafenib. |

**Table 4. Dose Adjustments for Fever (Pyrexia)** [a, b]

| Occurrence | Management | Study drug adjustment |
|---|---|---|
| **1st event** | • Clinical evaluation for infection and hypersensitivity[c]<br>• Laboratory work-up[c]<br>• Hydration as required[d] | • Administer anti-pyretic treatment if clinically indicated[e]<br>• **Continue or Interrupt dabrafenib depending on severity of pyrexia and associated conditions**-for example, if fever was associated with dehydration, hypotension, or renal insufficiency, hold dabrafenib and reduce dabrafenib by one dose level when restarted.<br>• Once pyrexia resolves to baseline, restart dabrafenib at the same dose if dabrafenib was held. |
| **2nd event** | • Work-up at physicians' discretion | • **Same as for 1st event <u>and:</u>**<br>• Administer anti-pyretic treatment if clinically indicated[f]<br>• Consider oral corticosteroids (i.e., prednisone 10 mg/d) for at least 5 days or as clinically indicated[f] |
| **Subsequent events** | • Work-up at physicians' discretion | • **Same as for 1st event <u>and:</u>**<br>• Administer anti-pyretic treatment if clinically indicated[e]<br>• Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[f]<br>• If corticosteroids have been tapered and pyrexia recurs, restart steroids<br>• If corticosteroids cannot be tapered or escalating doses are required, consult protocol chair.<br>• **If associated with dehydration, hypotension or renal insufficiency (on 2 or more occasions), reduce dabrafenib by one dose level** |
| | | |

BUN = blood urea nitrogen;

a. Fever (pyrexia) is defined as a body temperature equal to or above 38.5° Celsius or 101.3°Fahrenheit.

b. For subjects experiencing fever (pyrexia) complicated by rigors, severe chills, etc., a clinical evaluation is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended

c. Thorough clinical history for symptoms of infection or hypersensitivity is required; laboratory work-up may include complete-blood-count, electrolytes, creatinine, BUN, liver-function tests, blood culture, and urine culture.

d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.

e. Anti-pyretic treatment may include acetaminophen (paracetamol), ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia

f. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2$^{nd}$ event and prednisone doses should be gradually increased for subsequent events.

**Table 5. Dose Modification for Skin Rash**

| Skin Toxicity Grade (CTCAE v 4.0) | Guideline for Management | Dose Reduction[a] |
|---|---|---|
| 1 | Topical corticosteroids (mometasone, betamethasone, or fluocinonide creams) | None |
| 2 | Topical steroids with the addition of diphenhydramine 50 mg bid, consider oral prednisone[b] (short course) | None: if unacceptable to subject or medically concerning then hold until recovery to ≤Grade 1. Restart at same dose. |
| ≥3 | | Hold until recovery to ≤Grade 1. Then reduce the dose by one dose level.<br><br>For subjects with Grade 3 or 4 extensive or symptomatic dermatologic event, or chronic, persistent or recurring lower grade skin events, dermatology consult is encouraged. |

a. If no recovery after 2 weeks of holding drug, subjects must be withdrawn from study treatment unless in the opinion of the investigator there is a reason to believe that the subject will experience clinical benefit from future treatment.

b. The use of topical corticosteroids are preferred except in the event of severe skin toxicity(ies) to avoid the potential drug-drug interaction between the investigational agents and corticosteroids; at physician's discretion

**Table 6. Dose Modifications for Hand-Foot Skin Reaction (HFSR)**

| HFSR Grade | Occurrence | Dose Modification[a] |
|---|---|---|
| 1 | Any occurrence. | Continue treatment with Dabrafenib and start topical therapy[b] for symptomatic relief. |
| 2 | 1st occurrence. | Continue treatment with Dabrafenib and start topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c]<br>If no improvement within 28 days, see below |
| | No improvement within 28 days or additional occurrence. | Interrupt Dabrafenib treatment until toxicity resolves to Grade 0-1.[d]<br>When resuming treatment, decrease Dabrafenib dose by one dose level. Continue topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c] |
| Grade 3 or intolerable grade 2 | 1st or 2nd occurrence. | Interrupt Dabrafenib treatment until toxicity resolves to Grade 0-1. [d.]<br>When resuming treatment, decrease Dabrafenib dose by one dose level. Continue topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c] |
| | 3rd occurrence. | Discontinue Dabrafenib treatment. |

a. No dose adjustment is required on the basis of subject age, gender, or body weight.
b. Topical therapy includes the following options; keratolytics (e.g. urea 40%), high potency corticosteroids (fluocinonide, clobetasol), oral analgesia (NSAIDs or narcotics)
c. Lifestyle modifications include; avoidance of excessive temperatures, exercise, and ill-fitting clothing/shoes. Use of soft slippers (Tempurpedic or Crocs), friction-relieving measures (calfskin, gels).
d. HSFR usually resolves within 2-4 weeks of drug cessation.

**Table 7. Dose Modifications and Guidelines for Renal Insufficiency**

| Serum Creatinine | Guidelines for Management |
|---|---|
| For subjects with serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤0.5 mg/dL (44 umol/L) above baseline: | 1. Continue Dabrafenib and re-check serum creatinine within 1 week<br>2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); encourage oral fluids<br>3. If elevation in serum creatinine persists beyond 1 week, please contact study coordinator |
| For subjects with serum creatinine rise >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L) | 1. Interrupt Dabrafenib<br>2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration<br>3. Follow serum creatinine at least twice weekly (or consider hospitalization if serum creatinine cannot be monitored frequently)<br>4. Consider renal consultation<br>5. If serum creatinine returns to baseline, may restart study treatment at the same dose, or reduced by one dose level at the investigator's discretion.<br>6. Consider renal biopsy if clinically indicated, for example:<br>a. Renal insufficiency persists despite volume repletion<br>b. Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)<br>7. Approval of PI is required to re-initiate therapy if<br>c. Subject's serum creatinine has not returned to baseline<br>d. There is evidence of thrombotic microangiopathy |

### 6.1.2 Dose Stopping Safety Criteria

#### 6.1.2.1 Liver Chemistry Stopping Criteria

Dabrafenib will be stopped if any one of the following criteria is met:

- ALT ≥ 3 times (x) upper limit of normal (ULN) and bilirubin ≥ 2 x ULN (Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury)
- ALT ≥ 5 x ULN
- ALT ≥ 3 x ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia)
- ALT ≥ 3 x ULN and persists for ≥ 4 weeks

- ALT ≥ 3 x ULN and cannot be monitored weekly for ≥ 4 weeks

Patients with ALT ≥ 3 x ULN and <5 x ULN and bilirubin < 2 x ULN, and who do not have hepatitis symptoms or rash, can continue study drug Dabrafenib as long as liver enzymes can be monitored weekly for 4 weeks.

**When any of the liver chemistry stopping criteria 1-5 is met, do the following:**

• Immediately withdraw investigational product for that subject
• Report the event within 24 hours of learning its occurrence
• Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
**NOTE:** If serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
• Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
• Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
• Withdraw the subject from the study (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
• Do not re-challenge with investigational product.

**In addition, for criterion 1:**

• Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
• A specialist or hepatology consultation is recommended
• Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values for criteria 2, 3, 4 and 5:
• Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
• Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks
• Notify within 24 hours of learning of the abnormality to discuss subject safety.
• Can continue investigational product must return weekly for repeat liver chemistries

(ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline)
• If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
• If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

**For criteria 1-5, make every attempt to carry out the liver event follow up assessments described below**:
• Viral hepatitis serology including:
• 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
• Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product 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. Instructions for sample handling and shipping are in the SPM
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form
• Record use of concomitant medications, acetaminophen, herbal remedies, and other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
• Record alcohol use on the liver event alcohol intake case report form

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:
• 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 (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week (James LP. Drug Metab Disp 2009; 37:1779–1784).
• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

#### 6.1.2.2 Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

ECHO or MUGA must be performed at baseline and at follow-up visit(s) per the schedule in the Study Calendar. Subjects who have an asymptomatic, absolute decrease of > 10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue Dabrafenib and have a repeat evaluation of LVEF within 1 week. ECHO or MUGA should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline

If the LVEF recovers (defined as ≥ LLN and absolute decrease ≤ 10% compared to baseline) at any time during the next 4 weeks, the subject may be restarted on Dabrafenib at reduced dose level, after consultation and approval of the Protocol Chair. For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.

If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue Dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue Dabrafenib. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart Dabrafenib at a reduced dose after consultation and approval of the Protocol Chair.

#### 6.1.2.3 Valvular Toxicity Stopping Criteria

Subjects who have an asymptomatic, moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity per CTC AE v4.0) should temporarily discontinue Dabrafenib and have a repeat evaluation by ECHO within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until valve recovery to baseline.

If the valve recovers to baseline any time during the next 4 weeks, the subject may be restarted on Dabrafenib at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol

If repeat ECHO does not reveal valve recovery to baseline within 4 weeks, then the subject should permanently discontinue Dabrafenib. The valve should continue to be monitored via ECHO every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 valvular toxicity (symptomatic, severe regurgitation/stenosis by imaging, with symptoms controlled by medical intervention) must discontinue Dabrafenib. Valvular toxicity should continue o be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (return to baseline via imaging AND symptom resolution) within 4 weeks, the

subject may restart Dabrafenib at a reduced dose after consultation and approval of the Protocol Chair.

#### 6.1.2.4 QTc Stopping Criteria

If QTc corrected (QTcB) is greater than or equal to 530 milliseconds[1], the study drug Dabrafenib will be held.

[1] If ECG demonstrates greater than 500 millisecond QTc (grade 3 or 4), obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine if averaged QTc greater than or equal to 530 millisecond. If that is the case, the subjects should have study medication withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study medication if after the Protocol Chair agrees that the subject will benefit from further treatment.

### 6.2 Trametinib Delays/Modifications (applicable to patients on ARM B):

Given that there are several overlapping AEs between Dabrafenib and Trametinib, dose modification/stopping guidelines for all patients on ARM B must follow guidelines for Dabrafenib. In each of those categories, dose reduction, dose holding or dose continuation of Trametinib must follow similar criteria as for Dabrafenib. If there is discrepancy between two guidelines for a given AE, please follow guidelines for Dabrafenib for patients on ARM B. Diarrheas, peripheral/periorbital edema, acneiform rash, please follow guidelines given in section 6.2.

**Table 8. Trametinib Dose Levels**

| Dose Level | Trametinib Dose |
|---|---|
| 0 | 2 mg once a day |
| - 1 | 1.5 mg once a day |
| - 2 | 1 mg once a day |

A maximum of two Trametinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued. If a dose reduction of Trametinib is required, but the toxicity resolves and no additional toxicities are seen after two cycles of treatment, the dose of Trametinib may be re-escalated but should not exceed 2 mg once a day.

Trametinib dose modification guidelines are outlined in Table 9 for clinically significant toxicities that are deemed related to Trametinib (i.e. peripheral and periorbital edema).

Dose modification guidelines for rash are outlined in Table 10.

**Table 9. Dose Delay and Modification for Trametinib related AEs (for peripheral edema, periorbital edema)**

| Toxicity Grade[a] | Dose Modification of Trametinib |
|---|---|
| Grade 1 | Continue at current dose level. |
| Grade 2 | Interrupt treatment until toxicity resolves to Grade 1 or baseline. Upon resolution, restart treatment at current dose level with supportive care as clinically indicated. Consider dose reduction by at least one dose level. |
| Grade 3 | Interrupt treatment until toxicity resolves to Grade 1 or baseline. Upon resolution, consider dose reduction by at least one dose level. |
| Grade 4 | Permanently discontinue Trametinib |

Treatment with Trametinib may be interrupted for up to 21 days to allow resolution of toxicity, or based on investigator discretion. If the investigator concludes that continued treatment will benefit a subject who has experienced a treatment delay >21 days, then the subject may continue Trametinib therapy.

**Table 10. Dose Modification Rash Management Guidelines for Trametinib**

| Step | Rash grading | Rash severity | Management of Rash | Trametinib Dose Adjustment |
|---|---|---|---|---|
| 1 | Mild | Localized<br>Minimally symptomatic<br>No impact on ADL<br>No sign of superinfection | Initiate prophylactic regimen if not already started.<br>Consider using moderate strength topical steroid.*<br><br>Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2 | Continue current dose.<br><br>Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2 |
| 2 | Moderate | Generalized<br>Mild symptoms (eg, pruritis, tenderness)<br>Minimal impact on ADL<br>No sign of superinfection | Initiate prophylactic regimen if not already started, using moderate strength topical steroid.*<br><br>Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3 | Reduce dose by at least one dose level or consider interrupting treatment until resolution to Grade 1. If toxicity resolves, can consider re-escalation to initial dose level.<br><br>Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3 |
| 3 | Severe | Generalized<br>Severe symptoms (e.g., pruritis, tenderness)<br>Significant impact on ADL<br>Sign of or potential for superinfection | Initiate prophylactic regimen if not already started, using moderate strength topical steroids PLUS methylprednisolone dose pack.<br><br>Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation. | Interrupt treatment until rash improves (moderate, mild) or resolves, then follow steps outlined for the appropriate grading.<br><br>Reassess after 2 weeks; if rash worsens or does not improve, permanently discontinue treatment with Trametinib. |

*e.g., hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream

### 6.2.1 Diarrhea Management/Dose Modifications

Consider other concomitant causes. These include medications (e.g., stool softeners, laxatives, antacids, etc), infection by *C. difficile or other pathogens*, partial bowel obstruction etc.

**6.2.1.1 Supportive care guidelines for <u>uncomplicated Grade 1 to 2 diarrhea</u>** (i.e., mild to moderate and defined as CTCAE Grade 1-2 with no complicating signs or symptoms):

- Dietary modifications: stop all lactose containing products and eat small meals. A BRAT (banana, rice, apples, toast) diet can be helpful
- Hydration: drink 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth)
- Consider administration of standard dose of loperamide (subjects should have loperamide available in order to start at the first signs of diarrhea):
- Initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool; maximum 16mg/day.
- Continuation of loperamide is suggested until diarrhea free for 12 hours.
- Consider interruption of treatment with Trametinib until symptoms have resolved to baseline or Grade 1. Re-treatment with Trametinib may then be resumed at the same dose level or at the reduced dose. If dose was reduced, re-escalation may be considered if toxicity resolves.
- If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every two hours; maximum 16mg/day. Consider adding oral antibiotics.
- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, start budesonide or other second-line agents (octreotide, or tincture of opium). Consider adding oral antibiotics.

**6.2.1.2 Supportive care guideline for <u>Grade 3 to 4 diarrhea or complicated Grade 1 to 2 diarrhea</u>** (i.e., cramping, nausea/vomiting ≥Grade 2, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration):

- The subject must call the investigator immediately for any complicated severe diarrhea event.
- Interrupt treatment with Trametinib until symptoms resolve to ≤Grade 1 or baseline. Re-start therapy at a reduced dose level. Re-escalation may be considered if toxicity resolves.
- If loperamide has not been initiated, initiate loperamide immediately. Initial dose 4 mg followed by 2 mg every two hours or after every unformed stool; maximum 16mg/day.

- For dehydration, use intravenous fluids as appropriate; if severe dehydration, administer octreotide.
- Administer antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to 4 neutropenia.
- Intervention should be continued until the subject is diarrhea free for at least 24 hours.
- Intervention may require hospitalization for subjects most at risk for life-threatening complications.

### 6.2.2 Dose modification for Visual Changes

#### 6.2.2.1 CTCAE v 4.0 Eye Disorders

| Grade | Description |
|---|---|
| 1 | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL |
| 3 | Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL |
| 4 | Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye |

For all visual changes, regardless of grade, a blood sample for pharmacokinetics analysis must be drawn as close as possible to the time of the event.

#### 6.2.2.2 Grade 1 visual change:

- If the changes are clearly not due to retinal or retinal vein abnormalities or are clearly unrelated to study drug (e.g. conjunctivitis), Trametinib treatment may continue with close observation.
- If drug attribution or etiology is unclear, immediately refer the subject for ophthalmic exam; if an ophthalmic exam cannot be performed within 7 days, interrupt treatment with Trametinib until exam can be performed.
- If a retinal abnormality is noted, interrupt treatment with Trametinib immediately and consider referral to a retinal specialist, if available, for further evaluation
    - If RVO is diagnosed, report as SAE and permanently discontinue treatment with Trametinib.

- If CSR is diagnosed, interrupt treatment with Trametinib until signs and symptoms have resolved. Resume treatment with Trametinib at reduced dose by one dose level.
- If there is no evidence of RVO or CSR, resume treatment with Trametinib at the same dose level.

**6.2.2.3 Grade 2 or Grade 3 visual changes:**

- Immediately interrupt treatment with Trametinib and refer subject to an ophthalmologist for evaluation with an ophthalmic exam.
- For all subjects with findings consistent with RVO or CSR based on the ophthalmic exam, referral to a retinal specialist, if available, should be considered for further evaluation.
  - If RVO is diagnosed, report as SAE and permanently discontinue Trametinib.
  - If CSR is diagnosed, interrupt treatment with Trametinib until signs and symptoms have resolved and then resume treatment with Trametinib at reduced dose by at least one dose level.
  - If there is no evidence of RVO or CSR, interrupt treatment with Trametinib until signs and symptoms have returned to Grade 1 or resolved. Resume treatment with Trametinib at reduced dose by one dose level. Treatment with Trametinib at the same dose level may be considered if visual changes are clearly unrelated to study drug.

**6.2.2.4 Grade 4 visual changes** require permanent discontinuation of treatment with Trametinib.

### 6.2.3 Supportive Care Measures for Respiratory Symptoms

For Grade 2 or higher respiratory symptoms (i.e., cough, dyspnea, hypoxia, etc.), evaluation by a CT scan is recommended.

### 6.2.4 Supportive Care Measures for Abdominal Pain or Suspected Pancreatitis

For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.

### 6.2.5 Supportive Care Measures for Anemia

For patients that develop Grade 2 anemia, or patients with preexisting Grade 2 anemia that experience a drop in hemoglobin of 1g/dL, A GI bleed work up should be considered, e.g.: EGD (Esphagogastroduodenoscopy) and a colonoscopy.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

## 7.1. Expected Adverse Events for Dabrafenib (BRAFi)

Presented below are AEs considered related to dabrafenib treatment, observed in
subjects with unresectable and metastatic melanoma treated with dabrafenib (150 mg
BID), including subjects in BREAK-2 (data cut-off 7 July 2011), BREAK-MB (data cutoff 28 November, 2011), the randomized arm of BREAK-3 (data cut-off 19 December2011), the monotherapy arm of BRF113220 (data cut-off 1 September 2011), and specific cohorts in the first-time-in-human study BRF112680 (data cut-off 25 March 2011). The total number included in this analysis is 578 subjects. Approximately 30 % of patients received treatment with dabrafenib for more than 6 months. Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

**Very common: ≥ 1/10 (≥ 10%)**
**Common: ≥1/100 and <1/10 (≥ 1% and <10%)**
**Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)**
**Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)**

| Table 11. Adverse Events for Dabrafenib (BRAFi) as monotherapy | |
|---|---|
| **MedDRA SOC** | **Preferred Term** |
| ***Neoplasms benign and malignant (including cysts and polyps)*** | **Very Common:** Skin papilloma, papilloma<br>**Common:** Squamous cell carcinoma (SCC), including SCC of the skin and<br>SCC in situ (Bowen's disease) and keratoacanthoma<br>Acrochordon (skin tags)<br>Seborrhoeic keratosis<br>**Uncommon:** New primary malignant melanoma or other non-skin type malignancies. |
| ***Blood and the lymphatic system disorders*** | **Very Common:** Anemia<br>**Common:** Leukopenia, Neutropenia |
| ***Vascular disorders*** | **Uncommon:** Venous thromboembolism, Pulmonary Embolism |
| ***Immune System Disorders*** | **Uncommon:** Hypersensitivity |
| ***Metabolism and nutrition disorder*** | **Very Common:** Decreased appetite<br>**Common:** Hypophosphatemia |
| ***Nervous system disorders*** | **Very Common:** Headache<br>**Rare:** Encephalopathy |
| ***Eye Disorders*** | **Uncommon: Uveitis** |
| ***Respiratory, thoracic and mediastinal disorders*** | **Very Common:** Cough |
| ***Gastrointestinal disorders*** | **Very Common:** Nausea, Vomiting, Diarrhea<br>**Common:** Constipation, Gastrointestinal Bleeding, Peptic Ulcer, Gastrointestinal Ulcer<br>**Uncommon:** Pancreatitis |
| ***Skin and subcutaneous tissue disorders*** | **Very Common:** Skin effects (rash, hyperkeratosis) Alopecia, Palmar-plantar erythrodysaesthesia syndrome<br>**Common:** Skin effects (Actinic keratosis, Skin lesion,Dry skin, Erythema) |
| ***Musculoskeletal, connective tissue and bone disorders*** | **Very Common:** Arthralgia, Myalgia, Pain in extremity |
| ***General disorders and administration site conditions*** | **Very Common:** Asthenia**,** Fatigue, Pyrexia (some cases have been associated with hypotension and/or syncope), Chills<br>**Common:** Influenza like illness |
| ***Renal and urinary disorders*** | **Uncommon:** Renal failure, Acute renal failure |
| ***Reproductive System*** | Impaired spermatogenesis, potentially irreversible |

### 7.2 Expected Adverse Events for Trametinib (MEKi)

The following undesirable effects have been observed in subjects with metastatic melanoma receiving trametinib 2 mg once daily in the integrated safety population as of 25 June 2012 cutoff date (n=329). Of these 329 subjects, 211 were from MEK114267 (Phase III randomized open label study), 97 were from MEK113583 (Phase II study), and 21 were from MEK111054 (FTIH study). The most common adverse reactions (≥ 20 %) for trametinib include rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical trials with trametinib,

adverse reactions of diarrhoea and rash were managed with appropriate supportive care. Adverse reactions are listed below by MedDRA body system organ class. The following convention has been utilized for the classification of frequency:
**Very common: ≥ 1/10 (≥ 10%)**
**Common: ≥1/100 and <1/10 (≥ 1% and <10%)**
**Uncommon: ≥1/1,000 and <1/100 (≥0.1% and <1%)**
**Rare: ≥1/10,000 and <1/1,000 (≥0.01% and <0.1%)**

Categories have been assigned based on frequencies of AEs (considered related to trametinib) observed in the integrated safety summary (ISS) data (n=329).

**Table 12: Adverse Events for Trametinib as monotherapy**

| MedDRA SOC | Preferred Term |
|---|---|
| ***Neoplasms benign and malignant (including cysts and polyps)*** | **Uncommon:** New primary malignant melanoma or other non-skin type malignancies. |
| ***Hepatobiliary disorders*** | **Very Common:** Aspartate aminotransferase (AST)increased<br>**Common:** Alanine aminotransferase (ALT) increased, Blood alkaline phosphatase(ALP) increased |
| ***Immune system disorders*** | **Common:** Hypersensitivity (*May present with symptoms such as fever, rash, increased LFT's, and visual disturbances.* |
| ***Blood and the lymphatic system disorders*** | **Common:** Anemia |
| ***Cardiac disorders*** | **Common:** Left ventricular dysfunction, Ejection fraction decreased<br>**Uncommon:** Cardiac failure |
| ***Vascular disorders*** | **Very Common:** Hypertension<br>**Common:** Lymphoedema<br>**Uncommon:** Venous thromboembolism, Pulmonary Embolism |
| ***Respiratory, thoracic, and mediastinal disorders*** | **Very Common:** cough, dyspnea<br>**Common:** Epistaxis, pneumonitis<br>**Uncommon:** Interstitial lung disease |
| ***Metabolism and nutrition disorder*** | **Common:** Dehydration, Hyperglycemia |
| ***Eye Disorders*** | **Common:** Periorbital oedema, Vision blurred, Visual impairment<br>**Uncommon:** Retinal Pigment Epithelial Detachment (RPED), Papilloedema, retinal vein occlusion, retinal detachment |
| ***Gastrointestinal disorders*** | **Very Common:** Dry mouth, Diarrhea, Nausea, Vomiting, Constipation, Abdominal pain<br>**Common:** Stomatitis, Gastrointestinal Bleeding, Peptic Ulcer, Gastrointestinal Ulcer |
| ***Skin and subcutaneous tissue disorders*** | **Very common:** Alopecia, Rash (macular, maculopapular, erythematous or pruritic), Dermatitis acneiform rash, Pruritus, Dry skin<br>**Common:** Erythema, palmar-plantar erythrodysaesthesia syndrome, skin chapped, skin fissures |
| ***Musculoskeletal, connective tissue and bone disorders*** | **Common:** Blood creatinine phosphokinase increased (CPK) increased |
| ***General disorders and administration site conditions*** | **Very Common:** Fatigue, peripheral edema, Pyrexia<br>**Common:** Asthenia, Facial edema, Mucosal inflammation |
| ***Infections and infestations*** | **Common:** Cellulitis, Folliculitis, Paronychia, Rash pustular |

### 7.3 Expected Adverse Events for Dabrafenib and Trametinib

The safety of Dabrafenib and Trametinib have been studied in the combination study BRF113220data cutoff 25 May 2012; n=365). AEs associated with combination therapy are outlined in Table 13. In general, skin cancers such as keratoacanthoma are less common in patients treated with combination therapies as opposed to Dabrafenib monotherapy.

AEs associated with individual study drug can occur in patients treated with combination therapy (See sections 7.1 and 7.2). Included in the table below and marked by an asterisk (*) are events considered related to study drug treatment based on analysis of monotherapy data, but which were not observed in Part C subjects receiving combination therapy (dabrafenib 150 mg BID +trametinib 2 mg QD).

Adverse events for Dabrafenib and Trametinib in combination are listed in Table 13, by MedDRA body system organ class and preferred term, with associated frequency categories:

**Very common: ≥ 1/10 (≥ 10%)**
**Common: ≥ 1/100 and <1/10 (≥ 1% and <10%)**
**Uncommon: ≥ 1/1,000 and <1/100 (≥ 0.1% and <1%)**
**Rare: ≥ 1/10,000 and <1/1,000 (≥ 0.01% and <0.1%)**

**Table 13. Adverse Events for Dabrafenib in combination with Trametinib**

| MedDRA SOC | Preferred Term |
|---|---|
| ***Neoplasms benign and malignant (including cysts and polyps)*** | **Common:** Squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, Skin papilloma, papilloma<br>Acrochordon (skin tags)<br>Seborrhoeic keratosis<br>**Uncommon:** New Primary Malignant Melanoma* |
| ***Blood and the lymphatic system disorders*** | **Very Common:** Neutropenia, Anemia<br>**Common:** Thrombocytopenia<br>**Uncommon:** Leukopenia** |
| ***Immune systems disorders*** | **Common:** Drug hypersensitivity |
| ***Metabolism and nutrition disorders*** | **Very Common:** Dehydration, Decreased appetite<br>**Common:** Hyponatremia, Hypophosphatemia* |
| ***Nervous system disorders*** | **Very Common:** Headache, Dizziness |
| ***Eye disorders*** | **Common:** Vision blurred, Visual impairment, Chorioretinopathy, Papilloedema<br>**Uncommon:** Retinal Vein Occlusion*, Uveitis* |
| ***Cardiac disorders*** | **Uncommon:** Cardiac Failure* |

| | |
|---|---|
| ***Vascular disorders*** | **Common:** Hypertension, Hypotension, Lymphoedema |
| ***Musculoskeletal, connective tissue and bone disorders*** | **Very Common:** Arthralgia, Myalgia, Pain in extremity, Muscle spasms<br>**Rare:** Rhabdomyolysis |
| ***Renal and urinary disorders*** | **Common:** Renal failure, acute renal failure |
| ***Respiratory, thoracic, and mediastinal disorders*** | **Very Common:** Cough<br>**Common:** Dyspnoea, Epistaxis<br>**Uncommon:** Pneumonitis** |
| ***Gastrointestinal disorders*** | **Very Common:** Abdominal pain (including abdominal pain upper), Constipation, Diarrhea, Nausea, Vomiting, Dry Mouth<br>**Common:** Stomatitis, Pancreatitis, Gastrointestinal Bleeding, Peptic Ulcer, Gastrointestinal Ulcer |
| ***Skin and subcutaneous tissue disorders*** | **Very Common:** Dry skin, Pruritus, Rash (including rash generalized, rash maculopapular), Dermatitis acneiform Erythema, Actinic keratosis, Night sweats<br>**Common:** Hyperkeratosis, Alopecia, Palmar-plantar erythrodysaesthesia syndrome, Skin chapped Skin lesion, Hyperhidrosis<br>**Uncommon:** Rash Pustular* |
| ***General disorders and administration site conditions*** | **Very Common:** Fatigue, Oedema peripheral (including face oedema and periorbital oedema), Pyrexia, Chills<br>**Common:** Asthenia, Mucosal inflammation, Influenza-like illness<br>**Rare:** Panniculitis |
| ***Infections and infestations*** | **Very Common:** Urinary tract infection<br>**Common:** Cellulitis, Folliculitis, Paronychia |
| ***Investigations*** | **Common:** Alanine aminotransferase increased, Aspartate aminotransferase increased<br>Blood alkaline phosphatase increased<br>Gamma-glutamyltransferase increased<br>Ejection fraction decreased<br>**Uncommon:** Blood creatine phosphokinase increased* |

***Events considered related to study drug treatment based on analysis of monotherapy data, but which were not observed in Part C subjects receiving combination therapy (dabrafenib 150 mg BID +trametinib 2 mg QD).**

****Frequency was based on total subjects enrolled in dabrafenib/trametinib combination studies.**

## 7.4 Adverse Event Characteristics

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

**Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

## 7.5 Expedited Adverse Event Reporting

Expedited AE reporting for this study must be submitted to the institutional review board (IRB), to coordinating sites as well as to study collaborators including NCCN and Novartis.

### 7.5.1 Reporting to Institutional Review Board (IRB) and Data Safety Monitoring Board (DSMB)

Investigators and research staff are responsible for reporting to their local IRB and DSMB per institutional guidelines about unanticipated problems involving risks to subjects or others. The convened IRBs are responsible for making the final determination that a reported event (e.g., adverse event) is an unanticipated problem involving risks to subjects or others. (http://orrp.osu.edu/irb/osupolicies/documents/EventReporting.pdf)

**Serious adverse event (SAE)**: An adverse event that is fatal or life threatening, disabling or incapacitating, requires or prolongs hospitalization, or results in significant disability, congenital anomaly, or birth defect or which may require intervention to prevent the previously stated outcomes.

All Serious Adverse Events (SAE) should be reported to the IRB using the Event Reporting Form version 3.0 (http://orrp.osu.edu/irb/event/index.cfm) within 10 days of the Investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of study activities by the Investigator or funding organization to avoid potential harm to participants should be reported immediately (within 48 hours) whenever possible.

**NOTE: Subsite Institutions are not permitted to report directly to the OSU IRB. All subsite SAEs are to be reported to the Principal Investigator and Subsite Coordinator. The Subsite Coordinator will submit subsite SAEs to the OSU IRB.**

### 7.5.2 Reporting to Coordinating Center (Ohio State University), NCCN (National Comprehensive Cancer Network) and Novartis.

Member Institution shall report **only SAEs** arising during the Study in subjects exposed to the Novartis Study Drug(s) to Ohio State University,

NCCN and Novartis **within twenty-four (24) hours of first becoming aware of the event.** Neither Ohio State University, NCCN nor Novartis require non-serious AEs to be reported, as they will be reviewed by local institution's IRB and/or DSMB.

SAE's should be reported using MedWatch forms (http://www.fda.gov/Safety/_MedWatch/HowToReport/ucm085568.htm)

Send MedWatch forms to Ohio State University (ATTN: Jennifer Sexton) at Fax: 614-366-4721 or secure email Jennifer.sexton@osumc.edu.

Send MedWatch forms to the oncology Novartis DS&E department with the appropriate fax cover sheet via Fax # 1-877-778-9739 (Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: usdrugsafety.operations@novartis.com).
**You must include the Novartis study identifier on the form or cover sheet: CDRB436DUS17T.**

Send MedWatch forms to NCCN at fax # 215-358-7699 or email ORPreports@nccn.org. **Please include the NCCN study identifier: NCCNGSK20008.**

### 7.5.3 Reporting to Food and Drug Administration (FDA)

Coordinating site (Ohio State University) team will send SAE report to FDA using MedWatch form to the FDA in accordance with applicable regulations. Note: Subsite Institutions are NOT permitted to report directly to the FDA. Subsite SAEs are to be reported to the Principal Investigator and Subsite Coordinator. The Subsite Coordinator will submit subsite SAEs to the FDA.

## 7.6 Specific Reporting of Pregnancy

**7.6.1. Time period for collecting pregnancy information**: Pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing, and until at least 30 days after the last dose of study medication. The time period for collecting information on whether a pregnancy occurs is from the Screen Visit to the Final Study Visit. Information on pregnancies identified prior to study drug administration does not need to be reported to the project contact for pregnancy receipt. Pregnancies detected between the first dose of study drug and the Final Study Visit will be followed to determine the outcome of the pregnancy.

**7.6.2. Action to be taken if pregnancy occurs in a female subject**: The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The subject will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. While pregnancy itself is not considered to be an AE or SAE, any

pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a SAE through spontaneous reporting. Any female subject who becomes pregnant while participating will discontinue study medication or be withdrawn from the study.

**7.6.3. Action to be taken if pregnancy occurs in a female partner of a male study subject:** The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The partner will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

# 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.

## 8.1 Dabrafenib (BRAFi)

### 8.1.1 Pharmaceutical Description

Dabrafenib Capsules are supplied as 50 mg and 75 mg capsules for oral administration. The 50 mg capsule is a dark red capsule imprinted with 'GS TEW' and '50 mg'. The 75 mg capsule is a dark pink capsule imprinted with 'GS LHF' and '75 mg'.

The product is packaged into white, opaque, high density polyethylene (HDPE) bottles with child-resistant closures.

### 8.1.2 Physical and Chemical Properties of the Drug

**Approved Name**: Tafinlar (Dabrafenib)

**Chemical and Structural Formula:** Dabrafenib mesylate is a kinase inhibitor. The chemical name for dabrafenib mesylate is N-{3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, methanesulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68.

**Physical Form**: Dabrafenib mesylate is a white to slightly colored solid with three $pK_a$s: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

### 8.1.3 Storage Requirements

The recommended storage conditions, and expiry date where required, are stated on the product label.

### 8.1.4 Route of administration

The route of administration is oral.

**Drug-drug interactions/ Drug-food interactions**

Drugs that are strong inhibitors or inducers of CYP3A or CYP2C8, Pgp or Bcrp transporters, are prohibited because they may increase or decrease, respectively Dabrafenib concentrations (Appendix B). Mild or moderate inhibitor/inducers of these enzymes/transporters should be used with caution.

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 adhoc analysis, no differences in Cmax 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. See section 5.2.2 re: supportive care when necessary.

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. Subjects should abstain from ingestion of Seville oranges, grapefruit or grapefruit juice, pummelos, or exotic citrus fruits or grapefruit hybrids while on the study, and avoid ingestion of such fruit(s) for at least 24 hours prior to the start of the first dose due to potential increased plasma Dabrafenib concentrations due to inhibition of intestinal CYP3A4.

## 8.2 Trametinib (MEKi)

### 8.2.1 Pharmaceutical Description

Trametinib Tablets are supplied as, 0.5 mg, and 2 mg (as free base) tablets for oral administration. Trametinib

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

Trametinib Tablets, 2 mg (as free base) are pink, round, biconvex, film-coated tablets. Trametinib Tablets are packaged into a high density polyethylene (HDPE) bottle that contains desiccant with a child-resistant closure that includes an induction seal liner.

### 8.2.2 Physical and Chemical Properties of the Drug

**Novartis Code**: TMT212-NXA The suffix NXA denotes the dimethyl sulfoxide solvate form.

**Approved Name**: Mekinist (Trametinib) dimethyl sulfoxide (USAN)

**Other Names**: JTP-74057, JTP-78296, JTP-75303

**Chemical and Structural Formula:** GSK1120212B, a MEK 1/2 inhibitor, is a polycyclic, nitrogen containing heterocycle also possessing aromatic halide and amide functionality, and is a dimethyl sulfoxide solvate.
Molecular formula: $C_{26}H_{23}FIN_5O_4C2H6OS$
Molecular weight: 693.53

**Physical Form**: White to almost white solid

**Solubility**: Practically insoluble in the pH range of 2-8 in aqueous media.

#### 8.2.3 Storage Requirements

Trametinib is to be refrigerated at 36-46°F. The recommended storage conditions, and expiry date where required, are stated on the product label, and on the storage and dosage cards dispensed to the patient with their medication.

#### 8.2.4 Route of administration

The route of administration is oral.

## 9. CORRELATIVE STUDIES

### 9.1 Tumor pharmacodynamics (PD) evaluation (Tumor Biopsies pre-study and on-study)

**9.1.1 Collection and Handling of Specimen(s):** Fine needle aspiration (FNA) or core biopsy of tumor will be obtained at baseline and on C1D15 (+/- 5 days), for 7 patients in each arm of the study (14 patients total: "Biopsy cohort") who provide informed consent and have tumor lesions that are deemed by the study investigators to be accessible for biopsy. If funding permits, pre-study and on-study (C1D15) biopsies can be done in additional 6 patients on the trial. Optional biopsy/FNA will also be performed at progression in up to 5 patients in each arm of the FNA cohort who provide informed consent and who demonstrate initial radiographic response to therapy followed by radiographic progression. While these FNA/biopsies are invasive and will be done for research purpose, such procedures are routinely done for diagnostic purpose in clinical setting and are well tolerated in patients with thyroid cancer.

Biopsy/FNAs of accessible tumor will only be obtained under ultrasound or CT-guidance (unless palpable tumors) by medical personnel (e.g. cytologist, endocrinologist, surgeon, radiologist) with expertise in performing biopsy/FNA. Clinical trial research team member will be present bedside at time of biopsy to collect and process biopsy material. Detailed instructions describing this procedure will be included in a separate Study Lab Manual.

To assure that 10 evaluable paired FNA/biopsies are obtained from patients on each ARM of the study (total 20 patients), each participating center (total of 4 centers) will be required to enroll at least 5 patients who have paired biopsies. It is possible that 10 patients have pre-study biopsies but some of these patients might not be able to have 2nd on-study biopsy. Such case will be considered in-evaluable and additional patients will be recruited.

**9.1.2 Shipping of Specimen(s):** Frozen FNA samples will be batch shipped on dry ice to the Solid Tumor Translational Science (STTS) Resource at The Ohio State University Comprehensive Cancer Center along with the whole blood specimen and the frozen plasma samples collected for BRAF mutation testing. After the C2D1collection time point. Shipping address and days of shipment details will be provided in the Lab Manual.

**9.1.3 Site(s) Performing Correlative Study**: Laboratory of Dr. Daniel A. Haber at Massachusetts General Hospital Cancer Center.

**9.1.4 Methods for Analysis of Tumor Pharmacodynamics studies:** Prior to staining, tumor biopsy samples will be thawed and deposited onto at least 3 glass slides by centrifugation (Cytospin), and briefly dried. Slides can be stored at 4ºC covered in PBS until staining. The samples with be stained with antibodies to anti-thyroglobulin antibodies (thyroid cancer cells), CD45 (white blood cells), panCytokeratins, DAPI (nuclei), and one PD biomarker (pERK, NIS, pAKT, p-p70S6K or Ki67), followed by appropriate secondary antibodies, utilizing immunofluorescence staining protocols developed by S. Michael Rothenberg in Daniel Haber's laboratory at Massachusetts General Hospital Cancer Center. Additional proteins that provide information on tumor biology or pharmacodynamics may be tested as deemed appropriate by investigators. Immunofluroescence based cellular analysis has the primary advantages over traditional immunohistochemistry of: multiplexed analysis (e.g. simultaneous staining with three-four markers); sensitivity to scant samples; and the potential ability to quantify the results. Stained slides will be scanned within 48 hrs of staining on a Duet-3 automated scanning system (Bioview). Candidate tumor cells will be automatically scored according to pre-defined thresholds (e.g. CD45-negative, DAPI-positive, Cytokeratin-positive), and then visually inspected to confirm both cell morphology and specificity of staining. For pharmacodynamic analysis of the FNAs, the distribution of fluorescence intensities corresponding to pERK, pAKT, p-p70S6K, NIS and Ki67 will be determined and compared in pre- and on- treatment samples. The percentage change of tumor cell pERK, pAKT, p-p70S6K, NIS and Ki67 levels from pretreatment levels (both mean fluorescence intensity and number of pixels above predefined thresholds as assessed by antibody staining) will be calculated. When patient-derived samples are analyzed, control cell lines, to consist of cultured BRAF-mutant thyroid cancer cells untreated or treated with the same agents, will be analyzed simultaneously and in

parallel. Day to day variations in assay performance will be accounted for by comparing the data derived from such control samples.

**9.2 BRAF mutation quantification in circulating plasma DNA (Peripheral Blood pre-study, on-study and at progression)**:

**9.2.1 Collection and handling of Specimen(s):** All patients with a documented BRAF mutation at enrollment (up to 52 patients) will have 10 mL of whole blood collected in EDTA tubes on day 1 of each cycle for the first 6 cycles and then every other cycle (alternating with CT/MRI scan) after that while patients remain on study (C8D1, C10D1 etc.). If a patient goes off study due to disease progression, a sample will be collected at that time. Details on the processing of these samples are included in the Study Lab Manual.

**9.2.2 Shipping of Specimen(s):** Frozen plasma samples for cycles 1-2 will be shipped on dry ice to the Solid Tumor Translational Science (STTS) Resource at The Ohio State University Comprehensive Cancer Center along with FNA tumor biopsies (if applicable) and whole blood specimens. Specimens collected at cycle 3-7 will be held and batch shipped after cycle 7. The remaining samples will be stored at the individual sites and batched shipped either every 6 months or when the patient goes off study. Shipping address and days of shipment details will be provided in the Study Lab Manual.

**9.2.3 Site(s) Performing Correlative Study:** Solid Tumor Translational Science Resource (STTS) at the Ohio State University Comprehensive Cancer Center. For method validation, one sample of plasma may be shipped to Molecular Diagnostics Co.

**9.2.4 Methods for Analysis of BRAF mutation quantification in circulating plasma DNA:** DNA will be extracted from 1 mL of plasma, using the QIAamp Circulating Nucleic Acid kit (Qiagen) and quantitated using the Nanodrop 3300 Fluorospectrometer with PicoGreen (Thermo Scientific). The BRAF V600E mutation will be detected in purified plasma DNA by running a highly sensitive allele-specific TaqMan assay on the 7500 FAST Real Time PCR System (Applied Biosystems). DNA concentration will be normalized across samples using the delta-Ct value of the wild-type BRAF allele. Copy number of the BRAF V600E allele will be determined by comparing plasma samples results to a standard curve for BRAF V600E consisting of eight dilutions (100%, 50%, 20%, 10%, 1%, 0.1%, 0.02% and 0% mutated alleles) obtained by mixing purified wild-type and mutant linearized plasmid DNA.

**9.3 Tumor mutation screening/Mechanisms of drug-resistance (Tumor biopsy at Progression)**

**9.3.1 Collection and handling of Specimen(s):** Tumor mutational analysis to determine mechanisms of drug-resistance will be performed in at least 5 patients

in each arm of the study (10 patients total) who 1) provide informed consent 2) demonstrate initial radiographic response followed by documented disease progression while on study and 3) have biopsy/FNA accessible tumors. DNA will be extracted from tissue taken at the time of progression and compared to DNA extraction from baseline tissue. Ideally these samples would be from patients enrolled in the "Biopsy cohort" for PD biomarker evaluation (section 9.1.1) in order to obtain the status of these biomarkers at progression; however, this may not be possible given the limited number of these patients. Baseline tissue can be from either the FNA samples taken at baseline (if the patient was in this cohort and sufficient material is available) or from archival formalin-fixed paraffin-embedded (FFPE) tumor tissue. FNA samples will be collected and processed as described in section 9.1.1 and 9.1.2. For archival tumor samples, please see section 9.4.

**9.3.2 Shipping of Specimen(s):**
From archival tumor sample shipment, please see section 9.4. Frozen FNA samples will be shipped on dry ice to the Solid Tumor Translational Science (STTS) Resource at The Ohio State University Comprehensive Cancer Center with any remaining frozen plasma samples for BRAF mutations analysis. Shipping address and days of shipment details will be provided in the Study Lab Manual.

**9.3.3 Site(s) Performing Correlative Study:** Solid Tumor Translational Science Resource (STTS) at The Ohio State University Comprehensive Cancer Center.

**9.3.4 Methods for Analysis of Tumor Mutation/Mechanisms of resistance studies:**
For DNA purification from archival FFPE tissue, an H&E slide will be prepared and tumor percentage and location will be determined by a pathologist. Tumor tissue will then be macro dissected from several matching 4-5 micron unstained slides and DNA will be extracted using the Recover All Total Nucleic Acid Isolation Kit for FFPE (Ambion) according to the manufacturer protocol. For the FNA/biopsy samples, cells will pelleted by centrifugation, supernatant removed, and DNA extracted using the same kit listed above minus the deparaffinization step. Quality and quantity of DNA will be assessed using the Nanodrop 1000 Spectrophotometer. The status of >700 hot spot mutations across 46 common cancer genes, including MEK and members of the PI3K pathway, will be determined using the Ion AmpliSeq Cancer Panel on the Ion PGM sequencer. Sequence variants will be evaluated using the Torrent Suite Software.

## 9.4 Predictive markers of response (Archival Tumor Blocks):

**9.4.1 Collection and handling of Specimen(s):** Archival formalin-fixed paraffin-embedded (FFPE) tumor tissue if available from prior surgery or biopsy will be collected for all patients on the study. Tumor blocks will be collected and at least 5 unstained slides containing 4-5 micron sections of tumor block or part of tumor block will be provided.

**9.4.2 Shipping of Specimen(s):** From archival tumor sample, at least 5 unstained slides containing 4-5 micron sections of tumor block or part of tumor block will be shipped at room temperature. This can be shipped with the first shipment after cycle 2 samples are collected (plasma, blood and tumor biopsies, as applicable) to the Solid Tumor Translational Science (STTS) Resource at The Ohio State University Comprehensive Cancer Center. Shipping address and days of shipment details will be provided in the Study Lab Manual.

**9.4.3 Site(s) Performing Correlative Study**: Solid Tumor Translational Science Resource (STTS) at the Ohio State University Comprehensive Cancer Center.

**9.4.4 Methods for Analysis of predictive biomarkers:** If significant clinical response is demonstrated in the study, we will perform immunohistochemistry and/or tumor genotyping studies to examine levels of relevant protein expression (such as pERK, pMEK) and/or microRNA profile or tumor genetics.

## 9.5 Pharmacokinetics (PK) (Peripheral Blood/plasma)

**9.5.1 Collection and handling of Specimen(s):** First 7 patients enrolled on each arm of the clinical trial (14 patient's total) at the times specified below for pharmacokinetic assessment.

Two mL of whole blood into tubes containing K2EDTA as an anticoagulant will be collected from subjects at the time points specified below. If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, will be kept patent with normal saline or heparin solution, and will be removed after the last blood sample is collected or earlier if the subject requests. Importantly, in order to avoid artificial dilution of the PK samples by the saline or heparin, 1 mL of whole blood will be collected and discarded before each whole blood PK 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 and place the sample(s) on ice or in a refrigerator. Within 1 hour of sample collection, separate the plasma by refrigerated (4° C) centrifugation at 1,500 to 2,000 x g for a minimum of 10 minutes. Transfer 400-500 microliters (0.4 - 0.5 mL) of plasma into one (1) 1.8-mL NUNC tubes.
If vital signs, safety ECGs and PK sample collection are scheduled for the same nominal time, the ECG will be obtained first, followed by vital signs, and then PK sample collection. Collect each PK sample as close as possible to the planned time relative to dosing.

Store the plasma samples **within 60 minutes of the sampling time*** at -20°C or lower, in an upright position, to keep the plasma in the bottom of the tube. Keep the samples frozen in a freezer set at approximately -20°C or lower until shipped.

* It is acceptable to store the plasma samples within 90 minutes of collection provided that the collection tube was stored on wet ice until centrifugation.

Pre-labeled collection and transport tubes will be supplied in kits.

Time Points for PK Blood Collection: Samples will be drawn on:

- Cycle 1, Day 1: Prior to drug administration and at 1, 2, 3, 4, 6, 8±1 and 22±2 hours after drug administration.
- Cycle 1, Day 15: Pre-dose sample
- Cycle 2, Day 1: Prior to drug administration and at 1, 2, 3, 4, 6, 8±1 and 22±2 hours after drug administration.
- C4D1, C6D1 and C12D1 – Pre-dose specimen.

Patients will be instructed NOT to take their study drugs on the day of the clinic visit so the pre-dose samples on (C1D1, C1D15, C2D1, C4D1, C6D1, and C12D1) can be drawn. Patients who are selected for pharmacokinetics (PK) blood draws will take Dabrafenib (BRAFi) only once in the morning (instead of twice) on C1D1 and C2D1. On these days, patients on ARM B will take their daily dose of Trametinib (MEKi) in the morning. Dabrafenib and Trametinib should be taken under fasting conditions with 8 fluid ounces of water (either one hour before a meal or 2 hours after a meal). If a patient were to eat before their appointment, there should be at least a 2-hour time lapse between the food ingestion and the administration of the study medication(s).

**9.5.2 Shipping of Specimen(s):** Frozen plasma samples for PK analysis will be shipped on dry ice to Covance.
Refer to the study Lab manual for specific shipping schedule and directions on shipping.

**9.5.3 Site(s) Performing Correlative Study:** Pharmacoanalytical Shared Resource at the Ohio State University Comprehensive Cancer Center will perform the pharmacokinetic analysis of plasma concentration-time data.

**9.5.4 Methods for Analysis of Pharmacokinetics:** A liquid chromatography-tandem mass spectrometry assay for simultaneous quantification of Dabrafenib and Trametinib will be done by methods standardized and validated by team at Novartis.

**9.6 Pharmacogenetics (PGx)**

**9.6.1 Collection and handling of Specimen(s):** A 6-mL whole blood sample will be collected into an EDTA containing tube prior to dosing on day 1 of cycle 1 from all patients enrolled in the clinical trial. After collection, the whole blood samples will be split into two 2-3 mL cryovials, immediately frozen and stored at -70ºC or -80 ºC until shipping.

**9.6.2 Shipping of Specimen(s):** Frozen blood samples will be shipped on dry

ice to the Solid Tumor Translational Science (STTS) Resource at The Ohio State University Comprehensive Cancer Center along with tumor biopsies (if applicable) and with frozen plasma for BRAF mutation analysis. Shipping address and days of shipment details will be provided in the Lab Manual.

**9.3 Site(s) Performing Correlative Study:** Pharmacoanalytical Shared Resource at the Ohio State University Comprehensive Cancer Center

**9.4 Methods for Analysis of Pharmacogenetics:** DNA will be extracted from frozen blood. Analysis for polymorphisms in drug metabolizing enzymes and transporter genes will be done using appropriate drug disposition (absorption, distribution, metabolism, elimination) genotyping panel(s). Dabrafenib is a substrate and inducer of CYP3A4 and information on the clearance pathways for Trametinib is limited.

## 10. STUDY CALENDAR:

| | Pre-therapy[a] (Days -28 to Day 0) | | On-therapy[b] | | | | Off-therapy[c] |
|---|---|---|---|---|---|---|---|
| | | Day 1 Cycle 1[l] | Day 7 Cycles 1,2,3,4 | Day 15 Cycles 1, 2 | Day 1 Cycles 2, 4, 6[l] Only first 18 Cycles[p] | Day 1 Cycles 3, 5, 7[lp] | |
| **Study Drug (s)** | | | **See Section 5.0 for details** | | | | |
| **History/Physical Exam** | X | X | | X | X | X | X |
| **Vital signs/Weight** | X | X | | X | X | X | X |
| **Concurrent Medications** | X | X | | X | X | X | X |
| **Adverse Event Evaluation** | | X | | X | X | X | X |
| **Patient diary Submission** | | | | | X | X | X |
| **CBC w/diff, platelets[m]** | X | X[a] | | X | X | X | X |
| **Serum Chemistry[d]** | X | X[a] | | X | X | X | X |
| **Serum β-HCG[e]** | X | | | | | | |
| **Serum Thyroglobulin (Tg), anti-Tg antibody and TSH** | X | | | | | X | X |
| **Dermatology Exam** | X[j] | | | | | X[j] | |
| **Ophthalmologic Exam** | X[k] | | | | | | |
| **Electrocardiogram (EKG)[q]** | X | | | | | X | |
| **CT or MRI scan of neck/chest/abdomen[f]** | X[f] | | | | | X[f] | |
| **PET scan (only if clinically indicated)[g]** | X[g] | | | | | X[g] | |
| **Transthoracic Echocardiogram or MUGA[h]** | X[h] | | | | | X[h] | |
| **Phone Call Visit[o]** | | | X | | | | |
| | ***Following Correlative tests may be done in selected group of patients ONLY. (See Section 9 and Lab Manual)*** | | | | | | |
| **6-mL blood for Pharmacogenetics (*Section9 .6*)[n]** | | X | | | | | |
| **2-mL blood per time point for pharmacokinetics (*Section 9.5*)[n]** | | **Please see Section 9.5 for details of time points** | | | | | |
| **Paraffin tumor block (*Section 9.4*)** | X | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **10-mL blood for BRAF mutations in circulating plasma *(Section 9.2)*** | | **X** | | | **X[r]** | **X (Cycles 3 and 5 only)** | **X Only if PD** |
| **Tumor Pharmacodynamics Tumor Biopsy(*Section 9.1*)** | **X** | | | **X[i] +/- 5 days** | | | |
| **Tumor Mutation Screening Tumor Biopsy (*Section 9.3*)** | | | | | | | **X Only if PD** |

| | |
|---|---|
| | **a. If pre-study labs (CBC/diff, Chemistry) are drawn within 14 days of study entry, such labs do not have to be repeated on C1D1.**<br><br>**b. All on-study visits can be performed within +/-3 days. For cycles 8 to 18, please follow same schedule as for even and odd cycles as Cycles 2, 4, 6 or Cycles 3, 5, 7 respectively. Please review all footnotes as some testing is not required as frequently after 1st 6 cycles.**<br>**c. Off-therapy evaluations are to be conducted within 4 weeks after last dose of study drug (s). Labs do not need to be repeated if done within 2 weeks.**<br><br>**d. Sodium, Potassium, Chloride, Bicarbonate, Creatinine, BUN, Glucose, Calcium, Phosphorus, Total protein, Albumin, Total bilirubin, SGOT (AST), SGPT (ALT), Alkaline phosphatase, lactate dehydrogenase (LDH).**<br><br>**e. Pregnancy test (sensitivity of at least 50 mIU/mL) will be performed for all women of childbearing potential before beginning study drug (s).**<br><br>**f. CT or MRI scans as determined by investigators to assess the response per RECIST v1.1 criteria. CTs or MRIs with IV contrast are encouraged but will be done per investigator's discretion. Scans can be done within 7 days prior to day 1 of cycles 3, 5, 7 and subsequent odd number of cycles. If CT abdomen is negative at baseline, they only need to be repeated if clinically indicated during the study period.**<br><br>**g. PET scans are performed only as clinically indicated at pre-study, every 8 weeks and off study as determined by treating physicians.**<br><br>**h. Echo or MUGA will be done pre-study and every 2 cycles for 6 cycles and then every 4 cycles x 18 months and then only if clinically indicated. Scans can be done within 7 days prior to day 1 of cycles 3, 5, 7 and subsequent odd number of cycles.**<br><br>**i. This can be done any time +/- 5 days from C1D15. Not required during C2D15 time point.**<br><br>**j. Patients on both ARMs must have a dermatologic exam to monitor and manage side effects on the skin.**<br>**k. All patients must have ophthalmologic exam at pre-therapy. Patients randomized to or crossed over to ARM B (combination treatment arm) should have these as clinically indicated. Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline, and as clinically warranted per protocol's guidance (Refer to Section 6.2.2 for visual changes stopping criteria). The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy, with special attention to retinal abnormality that are predisposing factors for RVO or CSR. For patients with clinical suspicion of RVO or CSR, fluorescein angiography and/or optical coherence tomography are highly recommended.**<br><br>**l. Each cycle start is allowed a +/- 3 day window**<br><br>**m. Patients taking Antiplatelets or Anticoagulants need to have a CBC every 2 weeks for the first 4 months.**<br><br>**n. Patients that cross over from ARM A to ARM B are not eligible for the PK or PGx correlative studies.**<br><br>**o. All patients will receive a follow up phone call a week after each clinic visit for the first 4 months of treatment. The team will confirm with the patient that they are taking the correct amount of study medication, and that they have enough study medication to last until their next clinic visit.**<br><br>**p. After the completion of the 18th cycle, visits will be extended to every 8 weeks. All exams, tests, and scans listed for the odd cycle visits will be completed.**<br><br>**q. Electrocardiogram (EKG) will be done pre-study and every 2 cycles for 6 cycles and then every 4 cycles x 18 months and then only if clinically indicated.**<br><br>**r. After completion of the 18th cycle, visits will be extended to every 8 weeks. BRAF research labs will be drawn at every other visit (every 16 weeks) and at time of progression.** |

Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Four weeks (28 days) is considered one cycle. A member of the study team will be making a follow up phone call to each patient a week after each clinic visit for the first 4 months of treatment. The team will confirm with the patient that they are taking the correct amount of study medication, and that they have enough study medication to last until their next clinic visit.

In general, patients are followed every 2 weeks for the first 8 weeks and then every 4 weeks until the completion of cycle 18 at which time visits will be extended to every 8 weeks while on study. Off therapy visit is done within 4 weeks after last dose of study drug. Additionally, patients will be seen in the clinic, or contacted by phone every 3 months for 1 year post study treatment.
Follow up data to be collected:

- Survival status
- Disease status (progressed/stable)
- If any additional cancer therapy was initiated (name & start date)

## 11. MEASUREMENT OF EFFECT

### 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response every 8 weeks. Subsequent scan done at 8 weeks will serve as confirmatory scans following initial documentation of objective response.

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

#### 11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Dabrafenib (ARM A) or from the time of their first treatment with Dabrafenib and Trametinib (ARM B).

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

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

### 11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable unless there is progression (per RECIST v1.1) in tumor lesions in the irradiated field and if radiation therapy is more than 8 weeks prior to study entry.

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

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

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

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

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

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

### 11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules).

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

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

situations (*e.g.* for body scans).

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

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic

images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

### 11.1.4 Response Criteria (Modified to define Minor Response and progressive disease category)

#### 11.1.4.1 Evaluation of Target Lesions

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

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

Minor Response (MR): 20%-29% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: unequivocal diagnosis of new non-bony tumor lesion is also considered progression. This is because it has been challenging to diagnose bony metastasis response/progression while patients are treated with such new class of drugs-i.e.: sometimes necrosis caused by

study drug is interpreted as 'progression of lytic component).

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

#### 11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

#### 11.1.4.3 Evaluation of Best Overall Response (Modified with confirmation of response required at 8 weeks rather than 4 weeks)

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

the achievement of both measurement and confirmation criteria.

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

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | CR | No | CR | >8 wks. Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥8 wks. Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| MR | Non-CR/Non-PD/not evaluated | No | MR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | Documented at least once ≥8 wks. from baseline** |
| PD | Any | Yes or No | PD | no prior SD, MR, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since

SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

### 11.1.5 Duration of Response

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

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

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

### 11.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

### 11.1.7 Response Review

Objective response review will be done by radiologists from each site where patient was treated.

## 12. DATA REPORTING REQUIREMENTS

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

### 12.1 Data Reporting

### 12.1.1 Method

This study will be monitored by Ohio State University (Coordinating site) per their institutional guidelines for Multicenter Trials. Cumulative protocol- and patient-specific data will be submitted via Case Report Forms to The Ohio State University within 2 weeks of patient completion of each cycle/study time point.

### 12.1.2 Case Report Forms:

Case Report forms will be provided by OSU. In addition to case report forms, relevant reports on source documents will be requested to verify objective response. Actual CT or MRI images might be requested to verify objective response.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Endpoints

#### 13.1.1 Study Overview

This is a randomized phase II study designed to screen two different regimens and identify which one is the more promising candidate for subsequent testing in a Phase III trial in metastatic, radioiodine-refractory differentiated thyroid cancer (DTC) patients with mutated BRAF. To determine this, this study will assess the proportion of patients who have any response (minor, partial, or complete) within 6 cycles of therapy. Patients will be randomized to receive one of the two treatment regimens with equal allocation. Randomization will be done using block randomization with varying block sizes.

#### 13.1.2 Primary Endpoint

The primary endpoint for each of the treatment arms of this trial is overall objective response rate, defined as the proportion of patients who have a minor response (MR), partial response (PR), or complete response (CR) within the first 6 cycles of therapy. All randomized patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

Complete response (CR) and partial response (PR) will be defined by RECIST 1.1, and minor response (MR) will be defined as 20-29% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Any patients who have received at least one dose of treatment will be considered evaluable for these analyses. Patients will be analyzed in the treatment arm to which they were randomized. If a patient progresses, they will have met the primary endpoint classification for the purposes of this protocol (i.e. they will have had a response prior to progression or not). Patients' statuses prior to progression will be used in the assessment of response rates when evaluating the

primary endpoints for the treatment arms. Data on patients who cross over and receive treatment per another arm after progression will not be used in the decision analyses.

Rationale for using minor response as a part of objective response: Currently, many targeted therapy trials show clinically meaningful responses that are most evident only when reviewing waterfall plots that show % of tumor shrinkage in each patient. We have learned that PR and CR do not provide accurate assessment of clinical benefit. While stable disease is included as part of objective response in many solid tumors, it is not interpretable in patients with thyroid cancer due to overall slow-growing nature of cancer in many patients. Per RECIST 1.1, > 20% increase in tumor target lesions is considered significant and objective response in this case is defined as progressive disease. We therefore believe that 20-29% shrinkage of tumor represents true shrinkage that is clinically meaningful and is not by chance or measurement variation. Thus, we include MR as a part of objective response even though MR is not conventionally included.

### 13.1.3 Statistical Design

To both evaluate whether or not each of these experimental treatment regimens are sufficiently active in this patient population as well as to screen these regimens for the most promising regimen to be carried forward to the phase III setting, this study utilizes a flexible screening design developed by Sargent and Goldberg (*Statistics in Medicine,* 2001). Overall, we have developed this study to be able to determine that one regimen is decidedly worth pursuing further over another if the true differential in the overall response rates between arms is 0.20. Overall, we have developed this study to be able to determine that one regimen is decidedly worth pursuing further over another if the true overall response rates are 15% versus 35%. This study design has 90% power to identify the correct regimen as most promising and thus the regimen to bring forward into larger and confirmatory studies. Based on these assumptions and constraints, 26 evaluable patients will be accrued to each arm to evaluate the regimens under the parameters specified. If our underlying assumptions regarding the true response rates associate with each of these arms is a little lower (e.g. 10% vs. 30%), we will have additional power for these analyses (i.e. >90%). Even if our true response rates corresponding to the treatment regimens being evaluated here are higher (e.g. 40% vs. 60%), we will still have sufficient power (>88%) to determine that one arm is more promising than another if it truly is with this number of patients per arm and the same rule for observed differential described below. The main decision rule is based on differential, and the above assumptions show a flexibility and sufficient power for identifying the most promising regimen even if our hypotheses regarding response rates are slightly off.

As part of this design, we define one treatment arm to be more promising than another if the actual observed overall response rate for each of the arms differ by 10% or more, in which case the regimen with the higher overall response rate will be recommended for further testing. If these rates differ by less than 10%, factors

other than the overall response rate will be considered.

- If one treatment arm has an overall response rate that is at least 0.10 higher than the other, then it will be deemed the most promising and carried forward to the phase III setting.
- If the rates of the arms fall within d = +/- 0.10 of each other, the results of the study are considered statistically ambiguous and the regimens are considered similar with respect to their respective overall response rates. In this case, other factors are allowed to be taken into consideration when deciding on which regimen to bring forward into definitive Phase III testing. For this trial, we will specifically evaluate differences in the toxicity, PR+CR rate, progression-free survival, and correlative markers that indicate if the inhibitor therapeutic agents are hitting their respective targets.
- In the event that the success rates fall within .10 of each other, this study design assumes that there is a 50/50 chance of choosing the correct regimen. However, the choice of "d" used to determine whether or not other factors are considered is decidedly wide in order to allow the incorporation of the toxicity, translational, and other efficacy endpoints to be taken into consideration in this complex patient population. If one is clearly more promising than the other regimens and thus surpasses the other by the stated "d", then it is less relevant to utilize other factors in this determination. The only potential exception is if the clearly most promising regimen has substantially more toxicity than the other regimen(s).

## 13.2 Sample Size/Accrual Rate

### 13.2.1 Sample Size

The one-stage screening design to be utilized as described in Section 13.1. A maximum of 26 evaluable patients will be accrued to each arm unless undue toxicity is encountered. Overall, a total of 52 patients will be accrued to this trial (26 to each of the two treatment arms).

### 13.2.1 Accrual Time and Study Duration

Based on previous studies conducted through this group in this patient population, we expect the annual accrual rate to be approximately 7 patients per quarter. Therefore, the accrual period for this trial is expected to be about 24 months. The total study duration is expected to be 4 years, in order to fully evaluate clinical outcomes.

The primary endpoint analysis will be done after the last accrued patient

has been followed for at 6 cycles. The primary endpoint analysis will be done after the last accrued patient has been followed for at 6 cycles.

### 13.3 Stratification Factors

None

### 13.4 Analysis of Secondary Endpoints

The MR+PR+CR response rate will be estimated for each treatment arm. In determining this rate, the number of patients with RECIST-based MR, PR or CR will be divided by the number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true PR+CR response rate will be calculated.

The Kaplan-Meier method will be used to estimate progression-free and overall survival. Each of these variables will be measured from the date of registration to the date of the event (i.e., death or disease progression) or the date of last follow-up to evaluate that event. We will also evaluate the proportion of patients who are progression-free and alive at one year.

Toxicity and Tolerability: Frequency and severity of adverse events and tolerability of the regimen in each of the treatment arms will be collected and summarized using descriptive statistics. As per NCI CTCAE v4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described. We will also assess tolerability of the regimens through assessing the number of patients who required dose modifications and/or dose delays. In addition, we will also capture the proportion of patients who go off treatment due to adverse reactions or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. These tolerability measures will be assessed within each of the treatment arms and we will explore differences in these measures between the arms. All patients who have received at least one dose of any of the therapeutic agents in a treatment arm will be evaluable for toxicity and tolerability.

In addition to the clinical outcomes of interest, we will also evaluate several correlative markers as well. Specifically, we will evaluate the serum thyroglobulin and assess how these levels correspond with achievement of response to treatment. We will assess this as between and across treatment arms; change in serum thyroglobulin levels will be evaluated between arms, and the impact of this change and how it is associated with response will be assessed using logistic regression analyses; we will look at how treatment arm and thyroglobulin levels are associated

with incidence of response. We will also evaluate differential levels using graphical methods (e.g. side-by-side boxplots) and two-sample t-tests (or nonparametric equivalent as necessary). We will also evaluate pharmacokinetic, pharmacogenetic, and pharmacodynamic markers. Differences in these markers and factors between patients who do vs. do not achieve response will be evaluated using chi-square statistics and two-sample t-tests depending on the type of marker/factor being compared based on clinical outcome group. Graphical analyses will also be used to assess potential trends and relationships between clinical response and these markers/factors.

## 13.5 Reporting and Exclusions

13.5.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with Dabrafenib on ARM A and from the time of their first treatment with Dabrafenib and Trametinib on ARM B.

13.5.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) minor response, 4) stable disease, 5) progressive disease, 6) early death from malignant disease, 7) early death from toxicity, 8) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 5-9 above should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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# APPENDIX A

## Performance Status Criteria

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

# APPENDIX B

**<u>Prohibited Medications</u>: Strong CYP2C8/3A/Pgp/Bcrp Inhibitor/Inducers of Dabrafenib**

| **Strong CYP2C8/3A/Pgp/Bcrp Inhibitor/Inducer** | **Therapeutic Area** |
|---|---|
| Clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine), troleandomycin, anti-retrovirals (ritonavir, indinavir, nelfinavir, saquinavir, amprenavir,atazanavir, efavirenz), | Antibiotics |
| Itraconazole, ketoconazole, posaconazole, voriconazole | Antifungals |
| Nefazodone | Antidepressants |
| Gemfibrozil | Hyperlipidemia |
| Amiodarone, Bosentan, mibefranil, conivaptan, ethosuximide, St John's Wort, grapefruit juice/extract | Miscellaneous |
| Cyclosporine | Immunosuppressive agents |
| Carbamazepine, oxcarbazepine phenobarbital, phenytoin, s-mephenytoin | Anticonvulsant |

## APPENDIX C

## Cautionary Medications: Listed medications should be used cautiously with Dabrafenib

| **USE WITH CAUTION: Concentrations of these drugs may be altered (increased or decreased) by GSK2118436.** | |
|---|---|
| **CYP2C8/C9/C19/Substrate** | **Therapeutic Area** |
| Cerivastatin | HMG-CoA Reductase Inhibitors |
| Tolbutamide, nateglinide, repaglinide | Antidiabetics |
| Amitriptyline, clomipramine, imipramine | Antidepressants |
| **USE WITH CAUTION: Potential for inhibitors of CYP3A, CYP2C8, Pgp and Bcrp since concentrations of Dabrafenib may be increased** | |
| **Mild/Moderate Inhibitor** | **Therapeutic Area** |
| Erythromycin | Antibiotic |
| Fluconazole | Antifungal |
| diltiazem, verapamil | Antiarrhythmics |
| aprepitant, cimetidine, montelukast | Miscellaneous |
| **USE WITH CAUTION: Monitor for loss of efficacy or substitute another medication** | |
| **Substrates of CYP3A4/CYP2B6/CYP2C8/CYP2C9/CYP2C19 that may be affected by induction** | **Therapeutic Area** |
| chloramphenicol, doxycycline, erythromycin, moxifloxacin | Antibiotics |
| Caspofungin, Fluconazole, terbinafine | Antifungals |
| Amlodipine, diltiazem, felodipine, nifedipine, nilvadipine, nisoldipine, verapamil | Antihypertensives |
| aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine | Antidepressants and Antipsychotics Agents |
| glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone | Antidiabetics |
| Lamotrigine, valproate, divalproex, zonisamide, | Anticonvulsants |
| alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone | Analgesics |
| aprepitant, cisapride, darifenacin, disopyramide, leflunomide, methohexital, oral contraceptives, quinine, ranitidine, solifenacin, sulfasalazine, tramadol, tolvaptan, chloroquine, zopiclone, dexlansoprazole, esomeprazole, famotidine, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole | Miscellaneous |
| alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone | Hypnotics and Sedatives |

| | |
|---|---|
| Diergotamine, ergotamine, eletriptan | Antimigraine agents |
| Everolimus, sirolimus, tacrolimus | Immunosuppressive agents |
| astemizole, chlorpheniramine, ebastine | Antihistamine |
| oral budesonide, methylprednisolone, dexamethasone | Corticosteroids |
| sildenafil, tadalafil, vardenafil | Erectile Dysfunction agents |
| Eplerenone | Selective Aldosterone Blockers |
| Disopyramide, dronedarone, mexiletine, propafenone, quinidine | Antiarrhythmics |
| lovastatin, atorvastatin, simvastatin | HMG-CoA Reductase Inhibitors |
| cilostazol, warfarin(excluded as therapeutic dosage), aspirin/anticoagulants | Anticoagulants and Antiplatelets |

## Appendix D: Sample Calendar

| | | | | | | |
|---|---|---|---|---|---|---|
| **OSU 12064** <u>Pre-therapy testing</u><br>History, Physical Exam, Skin exam, and Eye* Exam<br>Blood tests, EKG, Echo, CT or MRI scan<br>Tumor biopsy*; PET scan*<br>Obtain cancer specimen from prior biopsy or surgery | | | | **1** ***Cycle 1 Day 1***<br>History<br>Physical Exam<br>Blood tests<br>Blood tests up to 8 hours* | **2** ***Cycle 1 Day 2***<br>Blood tests* | **3** |
| **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| **11** | **12** | **13** | **14** | **9** ***Cycle 1 Day 15***<br>History<br>Physical Exam<br>Blood tests<br>Tumor biopsy* | **16** | **17** |
| **18** | **19** | **20** | **21** | **22** | **23** | **24** |
| **25** | **26** | **27** | **28** | **29** ***Cycle 2 Day 1***<br>History<br>Physical Exam<br>Blood tests<br>Submit pill diary<br>Blood tests up to 8 hours* | **30** ***Cycle 2 Day 2***<br>Blood tests* | **31** |
| **32** | **33** | **34** | **35** | **36** | **37** | **38** |
| **39** | **40** | **41** | **42** | **43** ***Cycle 2 Day 15***<br>History<br>Physical Exam<br>Blood tests | **44** | **45** |
| **46** | **47** | **48** | **49** | **50- 56**<br>CT or MRI scan, Echo*, PET scan*, Skin Exam | | |
| **Notes:**<br>1. Tests/items marked *will only be done when/if applicable to you.<br>2. Study drug (s) should be taken under fasting conditions, either one hour before a meal or 2 hours after a meal. It should be taken with approximately 240 mL (8 fluid ounces) of water.<br>3. Please fill out pill diary and bring it to every clinic visit. | | | | **57** ***Cycle 3 Day 1***<br>History<br>Physical Exam<br>Blood Tests<br>EKG<br>Submit pill diary | **58** | **59** |

**Appendix E: Patient Pill Diary.** [Note: Be sure to bring this pill diary and the pill bottles with you to your next study visit. Sign below. Thank you]

| Study #: |
|---|
| Patient ID: |

| Patient Name | | | | | | |
|---|---|---|---|---|---|---|
| Patient Signature | | Date | Day 1 of Cycle: | | | ***If you have any questions regarding your study medication, or if you feel you are going to run out of study medication, please call the study team right away.** |
| | | | Tafinlar (Dabrafenib) Morning Dose (mg) | Tafinlar (Dabrafenib) Evening Dose (mg) | Mekinist (Trametinib) Once daily dose (mg) | |
| Day Number | Day of Week | Date | Time/Dose | Time/Dose | Time/Dose | **Comments:** |
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**Appendix F: Novartis provided Storage & Dosing Instruction Cards to be dispensed to patients with Trametinib**

Instructions for taking study drug

Mekinist (Trametinib)

Keep Trametinib refrigerated at 36-46°F.

1. Take Trametinib at approximately the same time each day.
2. Take Trametinib either one hour before or two hours after a meal.
3. Take the amount of study drug indicated on the bottle once a day with approximately 8 ounces of water.
4. Trametinib should be taken within a two hour window of the scheduled dose. If you miss the dose (falls outside of the scheduled 2 hour window) for some reason, you should just skip that dose and should take the next scheduled dose.
5. If you vomit after taking study drug, do not retake the dose. Take the next dose as scheduled.

Novartis Study
Patient Dosing Instructions
V1.0 Nov 2010