PROTOCOL AMENDMENT #5

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma; Correlation of Resistance with the Kinome and Functional Mutations

AMENDMENT INCORPORATES (check all that apply):
X_ Editorial, administrative changes
X_ Scientific changes (IRB approval)
X_ Eligibility Changes (IRB approval)

The purpose of this amendment is to allow the collection of progression biopsies from subjects who are withdrawn from the LCCC 1128 study for a variety of reasons including, but not limited to, a lack of tolerability, need to receive other therapy or completion of 3-years of study treatment without progression. The subset of the aforementioned subjects who are later re-challenged with dabrafenib and trametinib combination therapy and then progress while on this treatment, may be biopsied at the time of their clinical or radiological progression. These subjects are required to consent to this biopsy collection prior to being placed back on the LCCC 1128 clinical trial. Previously in protocol amendment #3, subjects who were withdrawn from study treatment due to an inability to tolerate the combination regimen, but who continued on BRAF inhibitor targeted therapy, were able to be consented, at the time of progression from single agent therapy, to undergo the a progression biopsy. As the protocol's objectives focus on combination therapy, the protocol is also currently being amended to remove this scenario. No subjects were biopsied who progressed solely on single agent therapy and thus this amendment will not affect previously collected data.

The following modifications were made to this protocol for amendment #5:

Editorial, Administrative Changes:
- Minor spelling grammar and formatting changes throughout the protocol
- Removal of Co-Investigators from the Face Page of the protocol
- Addition of the IND # to the Face Page of the Protocol
- IRB Reporting Requirements were updated in accordance with the UNC IRB SOPs (Section 7.3.3)
- FDA Expedited Reporting language was updated to better capture FDA guidance provided in 21CFR312.32 (IND Safety Reporting) (Section 7.3.3)
- Required documentation (Section 9.2) was updated to include financial disclosures
- Single Patient/Subject Exceptions (Section 9.5.2) was updated in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

Scientific Changes:
- Updated the study synopsis, study schema, biopsy section, Time and Events Table and correlative study procedures to indicate that former LCCC 1128 subjects who

progress on standard of care dabrafenib/trametinib off study are eligible for a progression biopsy (Section 1.1, 4.1, 4.2, 4.7, 6.1 and 6.7)

- The biopsy, duration of follow-up, Time and Events Table and follow-up assessments sections of the protocol were updated to indicate that subjects wo are placed back on study for the purposes of a progression biopsy will remain on study for safety monitoring, in relation to the biopsy procedure, for 30 days. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) related to the study procedure at 30 days will continue to be followed until the event is resolved or deemed irreversible by the investigator (Section 4.2, 4.7, 6.1 and 6.5).
- The assessment of primary endpoint and efficacy section (Section 6.9) was updated to clarify that analysis of progression biopsies from subjects placed back on study after progressing on standard of care dabrafenib/trametinib will be included in the analysis of the primary and correlative secondary objectives.
- The section on sample size and data analysis plans was updated to clarify that tumor samples from patients who progress on study and those who are removed from study and later progress on the combination treatment will be analyzed as one data set (Section 8.1).

Eligibility Criteria:

- Addition of inclusion criteria for off-study subjects who may be consented to come back on study for the purposes of a progression biopsy when they progress on standard of care dabrafenib and trametinib treatment (Section 3.3).
    - Subjects must have currently progressed while receiving trametinb and dabrafenib combination therapy.
    - Subjects must be willing to undergo a research biopsy
    - Subjects must have a tumor amenable to research biopsy
    - Subjects must provide informed consent
    - Subject must have been previously enrolled on the LCCC 1128 protocol.

THE ATTACHED VERSION DATED NOVEMBER 22, 2017 INCORPORATES THE ABOVE REVISIONS

PROTOCOL AMENDMENT #4

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma; Correlation of Resistance with the Kinome and Functional Mutations

AMENDMENT INCORPORATES (check all that apply):
X_ Editorial, administrative changes
X_ Scientific changes (IRB approval)
_ Eligibility Changes (IRB approval)

The following modifications were made to this protocol for amendment #4:

1) This amendment adds a requirement for annual ophthalmic exams while on treatment (see section 6.3.4 and time and events table)
2) Clarification of the duration follow-up period (see section 4.7 and 6.6). Regardless, of the reason that a patient comes off treatment, dermatologic exams will continue every 3 months for the first 6 months following discontinuation from dabrafenib, and may be done by a physician local to the patient. Only after these dermatologic exams are complete is the patient considered off follow-up, even if they do not require survival follow-up for this entire 6 month period.
3) This protocol amendment also clarifies that whether or not a subject enrolls in LCCC 1108, they will be asked to provide a single blood sample (approximately 8 mL) for research purposes. This blood sample may be collected at any point in the study, including during follow-up.
4) Section 7.3.3 has been updated with the new language in regards to Novartis reporting requirements.
5) Robert G. Dixon, MD, Hyeon Yu, MD, and Kathleen Gordon, MD have been added as co-investigators to the protocol title page
6) A line to provide the version of the protocol was added to the protocol signature page

In addition, the summary of changes for amendment #3 states that the sponsor changed from GSK to Novartis. Novartis is the funding source for this study and not the sponsor. No changes were made in protocol amendment #4 based on this clarification.

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THE ATTACHED VERSION DATEDAUGUST 1, 2016 INCORPORATES THE ABOVE REVISIONS

PROTOCOL AMENDMENT #3

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma; Correlation of Resistance with the Kinome and Functional Mutations

AMENDMENT INCORPORATES (check all that apply):
X Editorial, administrative changes
X_ Scientific changes (IRB approval)
X_ Eligibility Changes (IRB approval)

The following modifications were made to this protocol for amendment #3:
Eligibility criteria were modified to refine the definition of hypertension in exclusion criterion 3.2.6

1) At progression biopsy wording was changed to allow for attainment of biopsies in subjects withdrawn from study treatment due to lack of tolerability of the combination regimen and continued on BRAF inhibitor targeted therapy. These subjects should be re-consented so that progression biopsy can be obtained at the time of relapse on BRAF inhibitor targeted therapy (i.e., dabrafenib or vemurafenib). (Sections 4.2 and 6.7 and footnote #11 to Time and Events Table in section 6.1)
2) The frequency of tumor assessment scans was reduced to every 12 weeks for subjects responding to combination therapy after cycle 9

   AND

   The frequency of tumor assessment scans was reduced to every 6 months for subjects responding to combination therapy for > 2 years (Section 6.3.2 and footnote b added to Time and Events Table in Section 6.1)
3) The frequency of ophthalmic exams was reduced and are now only required at Screening and as clinically-indicated due to the presence of ocular symptoms (Section 6.3.2 and Time and Events Table in Section 6.1)
4) Sponsor changed from GlaxoSmithKline to Novartis
5) <u>Blood Sample:</u>
   For those patients who do not co-enroll into LCCC1108, we will ask for a blood sample (~8mLs) to ensure sufficient germline DNA in the event tissue samples are insufficient or request blood samples collected under LCCC9001 with IRB # 90-0573. This change is reflected in section 1.6, section 6.1 footnote #13, and 6.7
6) In anticipation of the pending switch from investigative product to commercial supply by the sponsor the following language was added: Trametinib/Dabrafenib commercially available product with auxiliary labeling will be provided by Novartis. The study drug should be administered and stored as per the instructions specified on the label (refer to the label, the PI or the IB for more detailed information). In addition, MSDS will now be available upon request from Novartis and not GSK (See sections 5.1.1, 5.1.2, 5.2.1, and 5.2.2
7) Sponsor SAE reporting requirements for GSK were deleted and replaced with SAE reporting requirements for Novartis in section 7.3.3.

THE ATTACHED VERSION DATED SEPTEMBER 15, 2015 INCORPORATES THE ABOVE REVISIONS

PROTOCOL AMENDMENT #2

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma; Correlation of Resistance with the Kinome and Functional Mutations

AMENDMENT INCORPORATES (check all that apply):
X Editorial, administrative changes
X_ Scientific changes (IRB approval)
X_ Eligibility Changes (IRB approval)

Minor editorial changes made throughout; changed biostatistician to Joseph Ibrahim, PhD; Requirement of tissue collection taking place at UNC have been removed as no other sites are involved in this study (sections 1.1, 1.7)

Safety and Efficacy
The 2 medications in the study were FDA approved in combination as of January 2014, and new Investigator Brochures were issued for dabrafenib, trametinib, and the combination. Based on these documents (including the updated package inserts), additional information on safety and efficacy on the combination has been incorporated into the protocol. These changes are reflected in sections 1.3, 1.4, 1.5, 5.1 and 5.2. Common AEs using combination therapy are listed in section 5.2.9. Section 1.7 was updated to include recent data indicating a possible survival benefit if patients are continued on BRAF inhibition post disease progression.

Eligibility
- Clarified that patients with elevated bilirubin due to Gilbert's disease will not be excluded (section 3.1.6)
- Clarified exclusion criteria 3.2.6 to "Patients with history of hypertension should have hypertension adequately controlled (BP < 140/90) with appropriate anti-hypertensive therapy or diet prior to study entry"
- Changed central serous retinopathy to new name: retinal pigment epithelial detachment (RPED) (section 3.2.13; also 1.5; 4.4.3)
- Revised section 3.1.3 to indicate that patients with $BRAFV^{600K}$ are also eligible in addition to $BRAFV^{600E}$, as the dabrafenib/trametinib combination is FDA approved in both populations.
- Added section 3.1.7 clarifying that prior anti-cancer treatment related toxicities must have resolved prior to enrollment.
- Detailed information added to section 3.1.9 on what constitutes effective contraception, and statement referencing this information added to inclusion criteria 3.1.10.
- Exclusion criteria 3.2.2 added (History of malignancy with confirmed activating RAS mutation at any time. *Note*: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility)
- Minor clarifications added to exclusion criteria 3.2.8, 3.2.11, and 3.2.14

Correlatives

Biopsies

Modified section 4.2 on timing of biopsies and removed statement that biopsy must be 'core' biopsy. (section 6.6 and 6.8) Clarified that biopsies may be delayed beyond point of disease progression if patient remains on therapy. The decision to continue therapy should be based on clinical benefit and safety considerations. Also updated in key to table of time and events (section 6.1, 6.4.1 and 6.7).

Deleted statement that maximum number of biopsy passes is 4. The maximum number of passes will be determined by treating physicians based upon considerations of safety.

Blood Sample

For those patients who do not co-enroll into LCCC1108, we will ask for a blood sample (~8mLs) to ensure sufficient germline DNA in the event tissue samples are insufficient. This change is reflected in section 1.6, section 6, 6.2 and 6.8

Management and Dose Modifications (section 4.4)

Deleted 'interstitial lung disease' as safety issues mostly for pneumonitis
Updated information on management based on most recent template language from GSK (section 4.4.3.1 on hypertension; 4.4.1.1 table on rash; 4.4.2 malignancies, 4.4.3.2 table on QTc prolongation; 4.4.3.3 reduced LVEF; 4.4.4 visual changes; section 4.4.5 pneumonitis; section 4.4.6 renal insufficiency; 4.4. 7 diarrhea; 4.4.8 pyrexia; 4.4.9.1 (liver chemistry stopping criteria) and added sections on new primary melanoma (4.4.2.2) non-cutaneous malignancies (4.4.2.3), pancreatitis (4.4.10) and hyperglycemia (4.4.11). Updated section 4.4.12 (non-specific toxicities attributable to drug therapy)

Concomitant Medications (section 4.5)

Added investigational drugs to the list of prohibited medications, and added section 4.5.3 on dabrafenib and radiation.

Time and Events Table

In footnotes to table (section 6.1) clarified biopsy timing and timing of tumor imaging. At recommendation of manufacturer, added additional ophthalmic exams at cycles 2, 8 and annually thereafter. Regardless of progression/non-progression, clarified that patients will be evaluated (receive mandated study assessments) every 2 cycles or 6 weeks after cycle 9. (sections 6.1, 6.3 and 6.3.5) Consolidated study assessments. Widened study window for lab screening assessments to within 21 days prior to therapy initiation. Widened study windows for cycle 9 and beyond to +/-5 days.

Safety reporting

Included information on trametinib overdose (section 5.1)
Added new toxicities that should be reported as an SAE (section 7.1)
Glaxo fax number updated: 610-200-1767
Appendix B: updated list of prohibited medications
Appendix G added: Ophthalmic Exam Worksheet for documentation of exam findings.
Appendix H added: safety information from ongoing randomized Phase 3 trial

THE ATTACHED VERSION DATED NOVEMBER 23 2014, INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #__1_

LCCC 1128: Open Label phase II trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma; Correlation of Resistance with the Kinome and Functional Mutations

AMENDMENT INCORPORATES (check all that apply):
X Editorial, administrative changes
X_ Scientific changes (IRB approval)
___Therapy changes (IRB approval)
X_ Eligibility Changes (IRB approval)

The main driver for this amendment was to increase the window of time for screening for all but the laboratory evaluations and baseline tumor biopsy from 1 week to 3 weeks, to expand/reorganize the T&E table so that we each study visit for the first 6 months is included in the table, to clarify the timing of the biopsies at progression, and to include specific information for affiliate sites as the study is changing to multicenter. These changes are reflected in sections 4.2, 6.0 (Time and Events table), and sections 6.2-6.7.

In addition, the 2 medications included in the study were FDA approved as of May 2013, and this information has been incorporated into the study. These changes are reflected in sections 1.1, 1.3, and 1.4.

Safety and drug interaction information: Since this trial was initially approved in 2012, new IBs for each individual agent were issued by the manufacturer. In addition, a new IB for the combination of trametinib and dabrafenib was issued in May of 2013. Updated safety information (including drug interaction information) from each of these documents was incorporated into the protocol. These changes are reflected in sections 1.4.1, 1.5, 4.4.2.2., 4.4.3, 4.4.4, 4.4.7, 4.5.2, 5.1.5, 5.2.5, 5.2.7, and 5.2.8, and Appendix C section 11.3.

Eligibility
Section 3.1.7 was revised to indicate that the pre-treatment biopsy required by the protocol should not be performed until all other eligibility criteria are confirmed.

Section 3.1.8: females of child-bearing potential must continue effective contraception until 16 (not 4 weeks) post the last dose of study medication. Men with a female partner of childbearing potential must agree to effective contraception from D1 of study treatment (not 14 days prior to D1 as written previously).

Biopsies:
Section 4.2, Time and Events footnote 11, and sections 6.4, 6.7.: These sections were revised to indicate that tissue at baseline does not have to be from the original diagnostic specimen, but from any site. If tissue is not available, a core biopsy can be obtained from any site, not restricted to target lesions. Repeat biopsies were already required at progression. However, the timing was clarified with amendment #1 to indicate they should be performed within 7 business days of documented progression, and optimally within 4 hours of that day's study medication. Post-treatment biopsies will be not required for patients removed from the study for reasons other than

disease progression. Sections 4.1, 4.2, 6.4 and 6.7 were revised to indicate that patients will be requested to stay on study medication until the post progression biopsy is performed.

Section 6.9.3 Evaluation of Target lesions:
A note was added to this section **NOTE:** Whenever possible, a biopsied lesion should not be considered a target lesion for RECIST tumor assessments. If the biopsied lesion is the only site of measurable disease, it may only be followed as a target lesion if a core biopsy was performed. Lesions that have been completely removed or subjected to excisional biopsy should not be followed as target lesions.

Time and Events:
In addition to the logistical changes and details on biopsies noted above, the footnotes were revise to specify that the end of treatment visit should be performed 30 days after the last dose of study medication, and to allow dermatologic evaluations to be performed at an MD office local to the patient if the patient is not scheduled to come to the clinic. It was also emphasized that a scan of the brain is not required post-baseline unless clinically indicated.

In addition, the following editorial changes were made:

The PI was changed from Frances Collichio, MD to Carrie Lee MD, MPH. Dr. Collichio remains as a co-investigator.

Section 4.3: This section was revised to indicate that if a patient misses a dose of dabrafenib, they may make this dose up, provided it is >6 hours until the next dose. If a patient misses a dose of trametinib, they may make this dose up, provided it is >12 hours until the next dose.

Sections 4.8 and 4.9 (Removal of Patients, Patient Replacement, and Study Withdrawal) were added to reconcile with the newest LCCC protocol template.

Section 6.9 was revised to emphasize that tissue at progression must be available to render a patient evaluable for the primary endpoint. The following statement was added: If a patient drops out of the study prior to progression, they may be replaced.

THE ATTACHED VERSION DATED JUNE 11, 2013, INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma: Correlation of Resistance with the Kinome and Functional Mutations

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Sponsor: Lineberger Comprehensive Cancer Center
IND: 115,704
Funding Source: Novartis
Version: November 22, 2017

LCCC 1128: Open Label Phase II Trial of the BRAF inhibitor (Dabrafenib) and the MEK inhibitor (Trametinib) in Unresectable Stage III and Stage IV BRAF Mutant Melanoma: Correlation of Resistance with the Kinome and Functional Mutations

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Carrie Lee, MD, MPH

PI Signature: _____

Date:_____

Version: November 22, 2017

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This multicenter phase II study in 20 patients with $BRAF^{V600}$mutant disease (specifically $BRAF^{V600E}$ or $BRAF^{V600K}$ designated as $BRAF^{V600E/K}$), unresectable stage III/IV melanoma is designed to explore the mechanisms by which tumors acquire resistance to the combination of a BRAF inhibitor (dabrafenib;Tafinlar®) and MEK inhibitor (trametinib;Mekinist®). Tissue will be collected at baseline and at progression. If a subject is removed from the study for one of a variety of reasons including, but not limited to, an inability to tolerate the combination of dabrafenib and trametinib, a need to receive other therapy or completion of 3-years of study treatment without progression, and the subject later receives, as part of his/her standard of care, the combination of dabrafenib and trametinib and progresses on the standard of care regimen, then the subject may be contacted by the treating physician to be put back on to the LCCC 1128 protocol and have a progression biopsy at this progression time point. Markers of resistance will be explored by performing near kinome-wide profiling on tumor samples, and in patients who co-enroll in institutional protocol LCCC1108, by sequencing tumors using NextGen DNA sequencing technology. Overall response rate and duration to this combination will also be assessed.

1.2 Melanoma

Melanoma is the sixth most common malignancy in the United States and its incidence is increasing faster than any other cancer [1, 2]. Patients with metastatic melanoma have a median life expectancy of only 8 months. In the extension cohort from a recent phase I trial of the BRAF inhibitor vemurafenib, 81% (26 of 32) of patients with $BRAF^{V600E/K}$ melanoma experienced at least 30% tumor shrinkage by RECIST with a complete response seen in two patients [3]. However, resistance to PLX4032 emerged after response durations of 2 to more than 18 months. Several key resistance mechanisms have been described and warrant further investigation. These mechanisms include new functional mutations in one of five established resistance genes (BRAF, NRAS, MEK1, MAP3K8 or COT, and PTEN).

MEK is a key protein integral to the RAS/RAF/MEK/ERK signaling pathway. In BRAF mutant melanoma, MEK activation drives disease proliferation. Therefore, it is hypothesized that the combination of BRAF and MEK inhibition is likely to have less downstream resistance than BRAF inhibition alone.

1.3 Trametinib

Trametinib is a reversible and highly selective allosteric inhibitor of MEK1/MEK2. These characteristics, along with its long half-life, small peak/trough ratio and limited inter-subject variability in its pharmacokinetic (PK) profile, render it an excellent MEK1/MEK2 inhibitor to evaluate in human trials.[4] Trametinib is approved as monotherapy and in combination with

dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

1.3.1 Effects in Humans

The effect of trametinib in subjects with a variety of cancers has been evaluated in a number of studies, and additional studies are ongoing.[4] Trametinib has been administered as monotherapy in at least 9 of these studies, and as combination therapy in at least 10 additional studies. Please also review the package inserts for trametinib and dabrafenib for updated background information on each product.

Preliminary trametinib pharmacokinetics (PK) was 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 at a dose of 2 mg of approximately 4 days.

In vitro, the metabolism of trametinib is mediated predominantly by non-CYP-mediated processes, via deacetylation alone, or with monooxygenation or in combination with glucuronidation biotransformation pathways. No formal clinical trials have been conducted to evaluate human cytochrome P450 (CYP) enzyme-mediated drug interactions with trametinib. Co-administration of trametinib (2mg per day) with the CYP3A 4 inducer dabrafeninb (150mg BID) resulted in no clinically relevant pharmacokinetic drug interactions (trametinib package insert; January 2014). This protocol prohibits or cautions against the use of medications with the potential for drug interactions with dabrafenib. See section 4.5 (Concomitant Medications) and section 11.2 (Appendices) for the categories of medications that are prohibited and/or to be used with caution.

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.

<u>Pharmacodynamics</u>

Pre- and post- (day 15) treatment tumor biopsies were performed for evaluation of pharmacodynamic (PD) markers in patients with metastatic melanoma in the first monotherapy trial of trametinib conducted (MEK111054). Doses remained stable for the 15 days of treatment and were 0.5, 1.0 or 2.0mg/day. PD markers evaluated included percent change from baseline of pERK, Ki67, and p27. Trough levels of trametinib were also obtained at day 15. PD responses in this study were dose-related, with minimal PD effects seen at 0.5mg/day, and robust changes reported at 2.0mg/day. The median change observed at a dose of 2 mg

daily was 62% inhibition of pERK, 83% inhibition of Ki67, and a 175% increase in p27, confirming inhibition of the MAPK/ERK pathway. Correlations were also reported between PD response and trough concentrations of trametinib on day 15. Monte Carlo simulations predict that 86% of subjects will exceed the target concentration of 10ng/mL at the 2mg/day dose.

Trametinib 2.0 mg once daily was administered in the Phase II and Phase III studies. After accounting for the effect of lactate dehydrogenase (LDH), a known prognostic marker in subjects with melanoma, subjects with exposure above the median value had longer progression-free survival (PFS) than those below the median exposure with hazard ratio (HR) <1. The relationship with exposure was more pronounced in the Phase II study compared to the Phase III study which may be related to the lower exposure observed in subjects enrolled in the Phase II study. The higher exposure in the Phase III study may suggest that the drug response is starting to plateau and data are less likely to show /an exposure-response.[4]

Safety and Efficacy

The most common adverse reactions in the trametinib arm (n=211) from the randomized, open-label study of trametinib versus chemotherapy in patients with BRAF ^{V600E} or $^{V600\ K}$ mutation –positive melanoma included the following: rash (57%), dermatitis acneiform (19%), dry skin (11%), pruritus (10%), paronychia (10%), diarrhea (43%), stomatitis (15%), abdominal pain (13%), lymphedema (32%), hypertension (15%), and hemorrhage (13%).

See section 5.1 and the trametinib Investigator's Brochure for additional safety information on trametinib and section 1.5 for safety and efficacy data when trametinib is combined with dabrafenib in BRAF mutant melanoma.

1.4 Dabrafenib

Dabrafenib is a potent and selective inhibitor of BRAF kinase, and inhibits phosphorylation of MEK and ERK *in vitro*, inhibits cell proliferation, and achieved tumor regression in xenograft cancer models that encode BRAF^{V600E}.[5] Dabrafenib is approved as monotherapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations, and in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600 K mutations

Dabrafenib is under development for the treatment of advanced cancer subjects with BRAF mutant tumors, which have been identified at a high frequency in specific cancers including approximately 40-60% of melanoma, 30 to 50% of papillary thyroid, 5 to 20% of colorectal cancer, and approximately 30% of ovarian cancer.

Please also review the latest version of the Investigator's Brochure for trametinib and dabrafenib for updated background information on each product and the number of clinical trials ongoing.

1.4.1 Effects in Humans

The effect of dabrafenib in subjects with a variety of cancers has been evaluated in a number of studies, and additional studies are ongoing. [5]

Pharmacokinetics

Two metabolites of dabrafenib were characterized and may contribute to the clinical activity of this drug. GSK2285403 (hydroxy-metabolite) pharmacokinetics paralleled that of parent while the 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.

Results following single dose administration showed a total recovery of radioactivity of 93.8 % of the dose with fecal excretion being the major route of elimination, accounting for 71.1% of the dose.

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.

Preliminary results of the effect of repeat dose administration of dabrafenib 150 mg BID on the single dose pharmacokinetics of midazolam, a CYP3A4 probe, showed a decrease in midazolam exposure, indicating that dabrafenib induces CYP3A4-mediated metabolism (moderate to potent). It may also induce other enzymes such as CYP2B6, CYP2C8, CYP2C9, and CYP2C19, as well as UDP glucuronosyl transferase (UGT) and transporters. Co-administration of dabrafenib and drugs that are affected by the induction of these enzymes may result in decreased concentrations and loss of efficacy. In preliminary studies, dabrafenib was a substrate for human P-glycoprotein (Pgp) and murine breast cancer resistant protein 1 (Bcrp1) *in vitro*. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a drug-drug interaction is minimal. [5]

In addition, CYP2C8, CYP3A4 and to a lesser extent CYP2C9 and CYP2C19 are involved in the oxidative metabolism of dabrafenib. *In vitro*, selective inhibitors of CYP 2C8 and CYP3A4 reduced the intrinsic clearance of dabrafenib. These results suggested that dabrafenib has the potential of being a victim of drug-drug interactions upon co-administration with strong CYP2C8 and CYP3A4 inhibitors and inducers.[5]

This protocol prohibits or caution against the use of medications with the potential for drug interactions with dabrafenib and/or trametinib. See section 4.5 (Concomitant Medications) and section 11.2 (Appendices) for the categories of medications that are prohibited and/or to be used with caution.

Pharmacodynamics

Based on results from the dose escalation part of Study BRF112680 (Part 1) in patients with V600 mutant-positive melanoma, 150mg BID is predicted to provide, on average, adequate inhibition of pERK (80%). [5]

Safety as Monotherapy

As summarized in the table below (from the dabrafenib 2014 IB)[5] the following adverse events were considered related to dabrafenib when administered as monotherapy across company-sponsored clinical trials (n=578). Approximately 30% of these patients received dabrafenib treatment for >6 months. Frequencies are as follows: very common (≥10%), common (≥1% and <10%), uncommon (≥0.01% and <1%), and rare (≥0.01% and <0.1%).

Frequency	Adverse Event
Very Common	Skin papilloma, papilloma
	Decreased appetite
	Headache
	Cough
	Nausea, vomiting, diarrhea
	Skin effects (rash, hyperkeratosis), alopecia, palmar-plantar erythrodysesthesia syndrome
	Arthralgia, myalgia, pain in extremity
	Asthenia, fatigue, pyrexia, chills
Common	Squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease), and keratoacanthoma Acrochordon (skin tags) Seborrhoeic keratosis
	Hypophosphataemia
	Constipation
	Skin effects (Actinic keratosis, Skin lesion, Dry skin, Erythema)
	Influenza-like illness
Uncommon	New primary malignant melanoma
	Hypersensitivity
	Uveitis
	Pancreatitis
	Renal failure, acute renal failure

See section 5.2.5 for additional safety information on dabrafenib and section 1.5 for safety and efficacy data when dabrafenib is combined with trametinib in BRAF mutant melanoma.

1.5 Safety and Efficacy when Dabrafenib Combined with Trametinib

To date over 1000 subjects, most with BRAF V600-mutated melanoma, have received the combination of these two drugs across the manufacturer's sponsored studies. Most of the safety data (as summarized in the June 2014 Investigator's Brochure of this combination) are from the randomized phase III double blind placebo controlled trial comparing this combination (n=209) to dabrafenib monotherapy (n=211), and study BRF113220. Study BRF113220 is designed to investigate the safety, PK and PD of dabrafenib in combination with trametinib in patients with BRAF V600 mutation positive solid tumors. The study consists of 4 parts: Part A evaluated the effect of repeat doses of trametinib on the PK of single-dose dabrafenib; Part B was a dose-escalation phase to determine the safety, tolerability and range of tolerated doses for the drugs in combination; Part C is a randomized phase II study to determine the clinical activity of the combination in patients with BRAF mutation positive melanoma; andPart D evaluated the PK of dabrafenib administered in combination with trametinib. Administration of dabrafenib and trametinib in combination had no clinically relevant effect on the exposure of trametinib or of dabrafenib relative to administration of either compound alone. [6]

1.5.1 Summary Safety Information of the Combination

Most subjects treated with combination therapy experienced an adverse event. In both studies, pyrexia was the most frequently reported AE, and the most frequently reported grade 3 event (presented with *) in subjects treated with combination therapy (51%/6%*) in Study MEK115306 and 57%/4%* in Study BRF113220). AEs that occurred in >30% of subjects treated with combination therapy in either study included pyrexia, fatigue, vomiting, chills, nausea, and headache.

Grade 4 AEs reported in more than a single subject treated with combination therapy included neutropenia (3 subjects in Study BRF113220) pyrexia (2 subjects in Study BRF113220). AEs leading to permanent discontinuation were reported in <10% of subjects treated with combination therapy in either study.

The most common SAEs in both studies were pyrexia and chills. Fatal SAEs have been reported in 4 subjects in the combination therapy arm in Study MEK115306 and 3 subjects in the 3 subjects in the 150mg/2mg combination therapy arm in the Study BRF113220 pooled combination therapy population. One fatal SAE was reported in 2 subjects in Study MEK115306 (cerebral hemorrhage).

In general, the overall profile of AEs of special interest observed in subjects treated with combination therapy is consistent with the known profiles of each separate drug. The most notable differences were the increase in Grade 3 pyrexia and hepatic events and the decrease in skin-related toxicities with combination therapy relative to monotherapy.

1.5.2 Special Warnings for the Combination

Ocular safety

Both trametinib and dabrafenib have been associated with ocular toxicities which appear to be class effects, including retinal pigment, papilledema, retinal pigment epithelial detachment (RPED; previously called central serous retinopathy or CSR) and retinal vein occlusion (RVO) associated with trametinib, and uveitis (including chorioretinitis, choroiditis, retinitis, vitritis, cyclitis, iridocyclitis, iritis, and uveitis) associated with dabrafenib. When all ocular events were considered together (blurred vision, dry eye, visual impairment and RPED), the incidence was 25%. With the exception of the single case of grade 3 RPED, all ocular events were grade 1 or 2. [6] In the MEK115306 study, ocular events occurred in 11% of patients in each arm, with no cases of RVO reported. Two subjects in the combination therapy arm had grade 3 ocular events (uveitis and iridocyclitis) considered related to study treatment.

Cutaneous squamous cell carcinoma (cuSCC)

In vitro experiments have demonstrated a paradoxical activation of MAP-kinase signaling in kerationcytes and potentially other cells harboring a wild-type BRAF kinase but a mutated RAS kinase upon exposure to a BRAF inhibitor. This paradoxical MAP-kinase pathway activation is potentially associated with a higher risk for the development of cuSCC induction.

Cases of cuSCC have been reported in patients treated with dabrafenib in combination with trametinib. In BRF113220 Part C, cuSCC occurred in 7% of subjects combination therapy arm at the dose used in LCCC1128 compared to 19% of subjects receiving dabrafenib monotherapy. In patients who received the combination dose of dabrafenib in combination with trametinib, events occurred later than with dabrafenib monotherapy with the median time to onset of 22 weeks. All patients on combination therapy who developed cuSCC continued on dabrafenib treatment without dose modification.

In the phase III study (MEK115306), the BRAF and MEK inhibitor combination was found to significantly reduce the incidence of secondary cuSCC which occurred in 9% of patients receiving dabrafenib monotherapy compared with 2% with the combination. The median time to onset of the first occurrence of cuSCC was 222 days in the combination arm and 57 days in the dabrafenib monotherapy arm.

Non-cutaneous secondary/recurrent malignancy

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

Pyrexia
The incidence and severity of pyrexia are increased when dabrafenib is combine with trametinib. When each drug is prescribe at its approved dose in combination, nearly half of the first occurrences of pyrexia occur within the first month of therapy, and ~ one-half of patients who experience this side effect had a single event. The majority of pyrexia events resolved in both arms[6].

Rash
In Part C of BRAF113220, 65% of subjects at the doses used in LCCC1128 experienced at least one event of skin-related toxicity. This incidence of skin-related events reported with the combination regimen appears to be lower than what has been observed in the trametinib monotherapy trials (~88%). The most frequent skin-related toxicities affecting over 10% of subjects in Part C were rash, dermatitis acneiform, erythema, and generalized rash. The incidence and severity of the majority of skin-related toxicities and especially those most often seen with either trametinib or dabrafenib therapy appear to be reduced when both compounds are combined.[6] In study MEK115306, the percentage of rash was similar between treatment arms (34% in the combination (none grade 3) and 30% (~20% grade 3) in the dabrafenib monotherapy arms). Dermatitis acneiform occurred with increased frequency in the combination arm (8%) as compared to 3% in the dabrafenib monotherapy arm.

1.5.3 Other Safety Considerations for the Combination

Pre-renal and Intrinsic Renal Failure
In Part C of study 113220, 1 subject (150mg/1mg) experienced grade 2 renal failure and 4 (at the 150mg/2mg doses) experienced grade 3 renal failure. In study MEK115306, the incidence of renal failure events was similar (3% in the combination and 2% for dabrafenib monotherapy).

Pancreatitis
Six subjects in BRF113220 had acute pancreatitis or pancreatitis, 3 of which were grade 4 and considered related to study treatment. [6] The time to onset to pancreatitis occurred at a median of 138 days. One event of pancreatitis was reported in each treatment arm of study MEK115306.

Hemorrhage
Combination treatment resulted in an increased incidence and severity of hemorrhagic events: 16% (9/55) of patients treated with the combination compared with 2% (1/53) of patients treated with dabrafenib alone. Intracranial hemorrhage was fatal in two (4%) patients receiving the combination.

Venous Thromboembolic Events
Treatment with the combination of trametinib and dabrafenib resulted in an increased incidence of deep vein thrombosis (DVT) and pulmonary embolism

(PE): 7% (4/55) of patients compared with none of the 53 patients treated with dabrafenib as a single agent. One (2%) patient receiving combination therapy experienced a fatal pulmonary embolism.

Hyperglycemia

Hyperglycemia may increase in occurrence when combination trametinib and dabrafenib are used. The incidence of Grade 3 hyperglycemia based on laboratory values was 5% (3/55) in patients treated with dabrafenib in combination with trametinib compared with 2% (1/53) in patients treated with dabrafenib as a single agent.

1.5.4 AEs of Special Interest

AEs of special interest were identified independently for both the dabrafenib and trametinib programs based on preclinical observations, the frequency of the events occurring in early clinical trials, and the potential association with the mode of action of BRAF or MEK inhibitors. AEs of special interest that are associated with trametinib (MEK category AEs) are:

- Skin-related toxicities (e.g., rash - generalized, macular, maculopapular,pruritic, erythematous; dermatitis acneiform; erythema; skin exfoliation; palmar-plantar erythrodysesthesia syndrome (PPES; also known as hand foot skin reaction or HFSR)
- Diarrhea
- Ocular events (e.g., RVO, chorioretinopathy)
- Hepatic events (e.g., aspartate aminotransferase [AST], ALT, and blood bilirubin increased)
- Cardiac-related events (e.g., LVEF decreased and left ventricular dysfunction)
- Hypertension
- Pneumonitis

AEs of special interest that are associated with dabrafenib (BRAF category AEs) are:

- Pyrexia
- Cutaneous squamous cell carcinoma • PPES
- Renal failure (renal failure, renal failure acute)
- Other treatment emergent malignancies
- New primary malignant melanoma
- Uveitis

In general, the overall profile of AEs of special interest observed with the combination in the Part C 150/2 group is consistent with the known profiles of each separate drug, the most notable differences being the increase in pyrexia and the decrease in skin-related toxicities with combination therapy relative to monotherapy. The incidence of MEK-related AEs of special interest in the Part C

150/2 group occurred at a rate (91%) that was similar to the incidence reported in the trametinib integrated summary of safety (ISS) population (94%) and higher than the incidence in the dabrafenib ISS population (55%).

MEK-related events of skin-related toxicities, diarrhea and hypertension appeared to be lower in the Part C 150/2 group compared with the trametinib ISS population, while the incidence rate of ocular events was higher relative to the trametinib ISS population.

For BRAF-related AEs of special interest, the incidence of any event in the Part C 150/2 group was higher (84%) than either the dabrafenib ISS population (49%) or the trametinib ISS population (19%). This increase is predominantly due to the increased incidence of pyrexia observed with combination treatment. Also noted were an increase in renal failure reports and a decrease in cuSCC and PPES reports when comparing the Part C 150/2 group to the dabrafenib ISS population.[6]

An overview of AEs of special interest at dose levels in Part C of BRF113220 is provided in the appendices, section 0.

Other AEs of special interest noted in the randomized phase III (MEK115306) trial (in addition to those listed above) included basal cell carcinoma, hemorrhages, deep vein thrombosis/pulmonary embolism, and neutropenia. An overview of AEs of special interest in MEK115306 is provided in the appendices, section 11.8.

1.5.5 Efficacy of Combination

The dose ranging trial (Part B of BRF113220) evaluated the safety and efficacy of 150mg dabrafenib twice daily plus trametinib (at doses of 2mg QD or 1 mg BID) versus dabrafenib150mg BID. A total of 162 patients with advanced melanoma and *BRAF V600E/K* mutations were randomized in a 1:1:1 ratio, with 54 patients in each arm who had not previously received BRAF or MEK inhibitors. Primary efficacy outcome was investigator–assessed ORR; median duration of follow-up was 14 months. In the trametinib 2 mg once daily arm, ORR was 76% versus 54% for dabrafenib monotherapy. Thus, the recommended combination dose is 150 mg dabrafenib twice daily plus 2mg trametinib once daily. The median duration of response was 10.5 months for combination therapy versus 5.6 months for patients on single-agent dabrafenib. See the package insert for further information.

In January 2014, the FDA approved the combination of trametinib and dabrafenib for treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. This indication is based upon demonstration of durable response rate.

The MEK115306 (COMBI-d) study of dabrafenib 150 mg BID and trametinib 2mgQD in combination versus single-agent dabrafenib sought to verify the clinical benefit of combination dabrafenib and trametinib. An analysis of investigator-assessed PFS after 211 (out of 423 patients) PFS events showed a 25% percent reduction in risk of progression or death (HR 0.75; 95% CI: 0.57, 0.99; per = 0.035). Median PFS for the combination therapy arm was 9.3 months compared with 8.8 months for the dabrafenib monotherapy arm.[6]

1.6 Correlative Studies

As described below, tumors will undergo near kinome-wide profiling using a mass-spectrometry-based, unbiased proprietary technology (Kinomining™) developed by Dr. Gary Johnson and colleagues at UNC. Tumor samples from patients who co-enroll in LCCC1108 will also be sequenced for approximately 150-200 genes of known importance in oncogenic signaling using NextGen DNA sequencing technology on the Illumina HiSeq platform. Both of these technologies can be performed with minimal amounts of patient sample. In addition, melanoma is a good disease for this study as the relatively young and otherwise healthy patients often have accessible disease and are good candidates for re-biopsy at the time of progression. At the time of consent, patients enrolled from affiliate sites will be informed that collection of their tumor tissue (both at baseline and at progression) is expected to take place at UNC whenever possible. For those patients who do not co-enroll into LCCC1108, we will ask for a blood sample (~8mLs) to ensure sufficient germline DNA in the event tissue samples are insufficient.

1.6.1 Kinomining™

Dr. Gary Johnson and colleagues have developed a chemical proteomics approach to define the activity of a significant percentage (60%) of the expressed kinome in cells and tumors.[7] The technique involves the use of pan kinase inhibitors immobilized on beads to capture a large percentage of expressed kinases in cells and tumors. The activation state of more than 60% of the expressed kinome, defined by RNA-seq, can be analyzed using mass spectrometry analysis of the captured kinases.

This technique has been used to study, and then rationally design a kinase inhibitor combination therapy for triple negative breast cancer (TNBC). Analysis of a patient TNBC tissue sample showed activated RAF-MEK1/2-ERK1/2 signaling, supporting MEK as a target in TNBC. In TNBC cells and tumors of a genetically engineered C3Tag mouse model (GEMM) of TNBC, MEK inhibition with the MEK inhibitor AZD6244 led to rapid reprogramming of the expression and activity of a group of Tyr and Ser/Thr kinases. This reprogramming bypassed the original MEK-ERK inhibition and demonstrated the resilient nature of the kinome. Mechanistically, we showed that acute MEK inhibitor treatment caused MEK-ERK activity loss resulting in rapid c-Myc degradation, inducing the expression of multiple receptor tyrosine kinases (RTKs) and ERK reactivation. RNAi knockdown of c-Myc induced RTK expression similarly to MEK

inhibition. Based on these results, we predicted and tested a novel small molecule combination therapy of MEK inhibitor and sorafenib for TNBC. The combination synergistically caused apoptosis and tumor regression in the C3Tag GEMM of basal-like/claudin-low TNBC, whereas the single agents of MEK inhibitor or sorafenib were largely ineffective. [7]

The research described above, along with siRNA screens of the kinome in cell lines, is identifying previously untargeted kinases essential for tumor growth and survival. Our belief is that the approach can be extended to human tumors.

1.6.2 UNCseq™

Clinical sequencing efforts at UNC have settled on the in solution hybrid capture methodology using the Illumina platform for downstream sequencing. This technology allows gene targets of interest to be isolated from genome-wide high-throughput sequencing libraries, reducing both sequencing costs and bioinformatic complexity downstream. This approach is also highly customizable, allow for changes in gene targets with little additional cost or need for re-optimization. At UNC in the Clinical Sequencing Program (UNCseq™), we are applying this technology to patients suffering from a diverse variety of malignancies with funds provided by the State of NC through the University Cancer Research Fund. UNCseq allows us to tailor therapy to a patient's cancer based on the tumor's molecular genetics, thereby improving response rate and decreasing the toxicity from exposure to ineffective agents.

We have an extensive unpublished experience in melanoma. For example, we have performed UNCseq on 52 melanoma samples with a capture approach restricted to 75 genes previously reported to harbor somatic mutations in this disease. These samples were run through a UNC-developed sample preparation and informatic pipeline to identify diverse kinds of genetic variants. This process was informed by UNC's efforts in the far-larger tumor sequencing program, the Cancer Genome Atlas, of which UNC is one of 8 participating centers in North America. Our results greatly surpassed gold standard Sanger sequencing. For example, we identified all validated BRAF V600 and NRAS Q61 codon mutations found by Sanger sequencing: (BRAF 46% of tumors; NRAS 17%). Deep sequencing also allowed identification of pathogenic mutations in many additional genes reported to be mutated in melanoma (KIT, CDKn2a, PTEN, LKB1); and identified novel functional mutations of BRAF and other kinases. In one BRAF/NRAS wild-type melanoma, we found a clear codon 12 activating KRAS mutation (Fig 1), which is reported to be present in ~1% of melanoma. KRAS mutation is not routinely assayed in melanoma at any major center, but would have clear implications for the testing of BRAF and MEK inhibitors.

Additionally, we found numerous frameshift (Fig 2), missense, nonsense and large deletion mutations in tumor suppressor genes (PTEN, CDKN2A, p53, LKB1). These mutations, found in many regions along the coding sequence,

would be difficult and expensive to assay by other technologies. We have also used normalized read counts to identify somatic Copy Number Variations (CNVs = deletions and amplifications) and potentially structural variation like chromosomal translocations without any modifications to the sample preparation pipeline. Data comparing X chromosome dosage in normal male and female tissues indicates that our approach can detect single copy loss with high statistical precision, suggesting most pathogenic CNVs will be obvious by this approach.

UNCseq offers a powerful new tool to assay known genetic factors for therapy and also to discover novel clinically relevant somatic mutations. The technique can effectively assay the diverse mutations that disable tumor suppressor genes, allowing an exploration of the clinical consequences of these genetic events which to date have been poorly characterized in other contexts. We expect this system will become indispensable to all stages of clinical care, including diagnosis, prognosis, treatment prediction, and drug discovery.

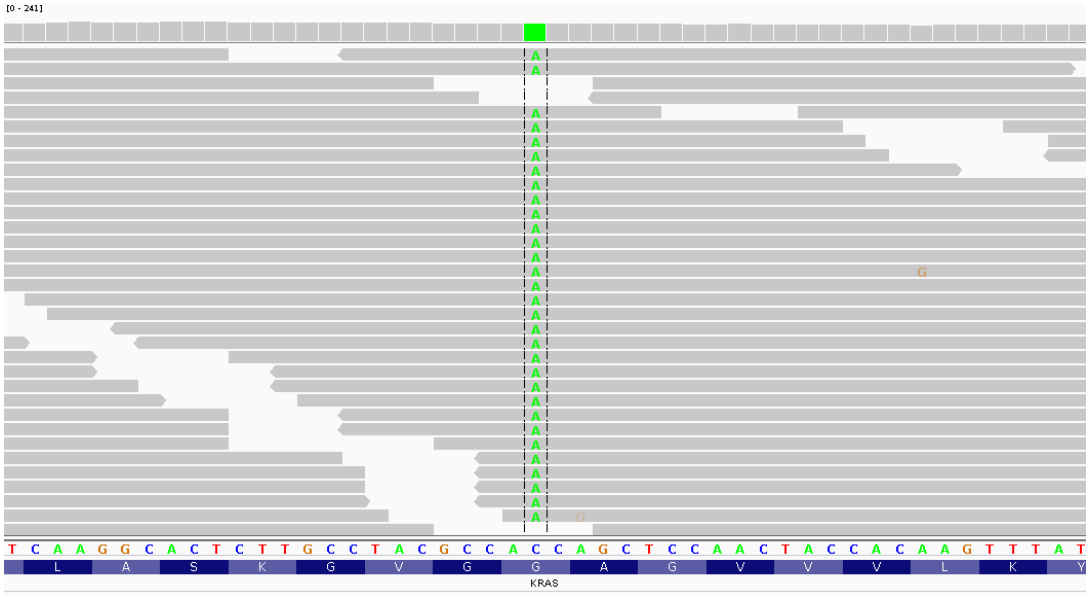


Figure 1: Sequencing results demonstrating a rare KRAS mutation in melanoma. This view uses Integrated Genome Viewer to show a subset of the deep sequencing reads mapping to the location (gray bars) and highlights locations with mutations (A bases where the reference nucleotide is C). Sequencing shows homozygous KRAS G12V constitutively active mutant.

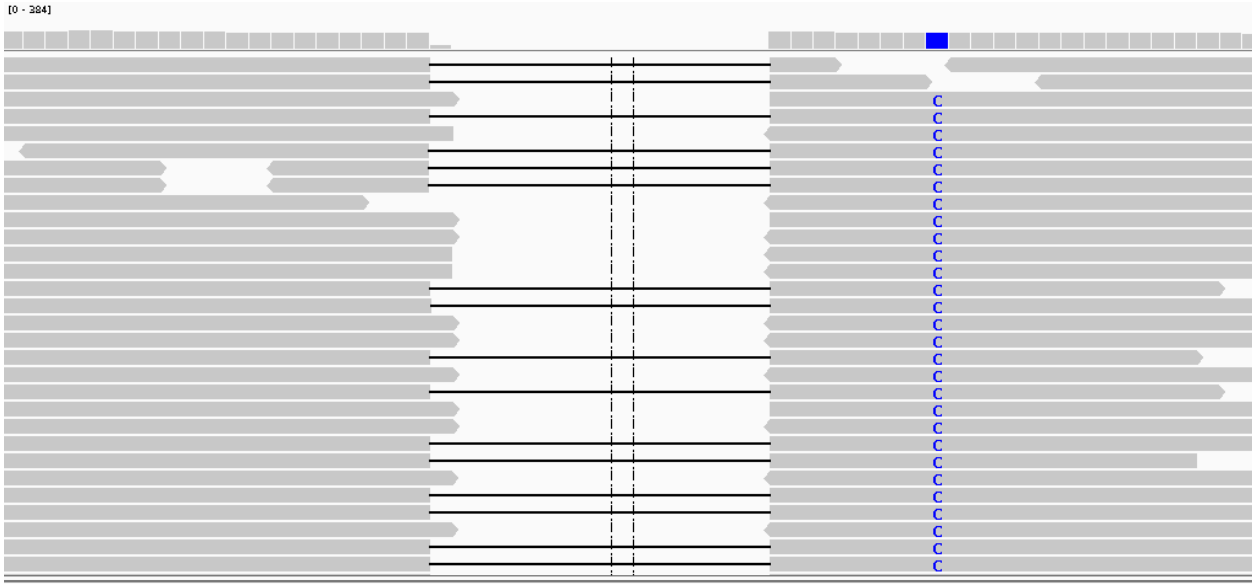


Figure 2: Sequencing results demonstrating a BRAF mutation novel to melanoma. Reads with deletions are marked by a black bar. Coverage at each base (noted along the top) shows complete drop within the deletion, suggesting that it is homozygous.

1.7 Rationale

BRF113220, the phase I/II trial of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in metastatic melanoma established the safety of this combination, and identified the recommended phase 2 doses (RP2D) for each agent. Expansion cohorts at the RP2D for these drugs in combination were included in the phase I to characterize the safety in more detail, and to explore the efficacy of this combination. The combination was well tolerated as described in section 1.5, with decreased frequency of rash compared to either agent alone.[5, 8] This study will utilize the RP2D determined in the Phase I/II study: trametinib 2mg QD and dabrafenib 150 mg BID. Despite a very promising overall response rate of 81%, these patients will also likely go on to develop resistance as a result of new resistance mutations, and given the cooperative signaling network of kinases that sense inhibition of key nodal kinases and induce compensatory responses that offset pharmacological intervention.

The present phase II study in 20 patients with $BRAF^{V600E/K}$ mutant, unresectable stage III/IV melanoma is designed to explore the mechanisms by which tumors acquire resistance to the combination of BRAF and MEK inhibition. Overall response rate and duration to this combination will also be assessed.

Tissue will be collected at baseline and at progression (clinical or radiological) or beyond progression pending the availability of sufficient tissue and considerations of patient safety. Patients may remain on treatment after progression (at the discretion of the investigator) as long as they are still experiencing clinical benefit, as targeted therapy post-progression may extend survival. A recent

analysis has shown that continuation on a BRAF inhibitor (dabrafenib or vemurafenib) as monotherapy after disease progression may improve survival. Among 36 patients who continued on treatment, post progression median PFS was 6.9 months versus 3.9 months among those (n=56) who discontinued treatment at progression (p=0.001). Furthermore, median OS was 17.8 months from start of BRAF therapy versus only 7.0 months in those who stopped treatment at progression (p<0.001). [9]

2.0 STUDY OBJECTIVES

2.1 Primary Objective

To identify kinases that are differentially expressed pre- and post-treatment with BRAF (dabrafenib) and MEK (trametinib) inhibitors, and to determine a kinome signature predictive of resistance to BRAF/MEK inhibition in stage III/IV melanoma

2.2 Secondary Objectives

2.2.1 To explore whether resistance to BRAF and MEK inhibition is associated with new functional mutations in the approximately 150 oncogenes / tumor suppressor genes that are assessed in more than 10% of the tumors (using NextGen DNA sequencing technology) in the subset of patients who co-enroll in LCCC1108, with particular focus on one of five established resistance genes (BRAF, NRAS, MEK1, MAP3K8 or COT, and PTEN)

2.2.2 To determine the overall response rate (ORR: complete response + partial response) as measured via RECISTv1.1

2.2.3 To estimate the duration of ORR as measured via RECISTv1.1

2.2.4 To estimate progression-free survival (PFS) as defined by RECISTv1.1

2.2.5 To estimate the rate of overall survival (OS) at 1 year from day 1 of treatment

2.3 Primary Endpoint

2.3.1 Kinome signature pathway will be based on comparison of kinome expression from pre- and post-treatment biopsies using Multiplexed Inhibitor Beads (MIBs) coupled with mass spectrometry

3.0 PATIENT ELIGIBILITY

3.1 Main Study Inclusion Criteria

Subject must meet all of the inclusion criteria to participate in this study:

3.1.1 Age ≥18 years

3.1.2 Signed written informed consent

3.1.3 Histologically confirmed V600E or V600K BRAF mutant melanoma

3.1.4 Unresectable Stage III/IV melanoma

3.1.5 ECOG PS 0-2

3.1.6 Normal organ function as defined by the following:

- Absolute neutrophil count $\geq 1.2 \times 10^9$/L
- Hemoglobin ≥9 g/dL, platelets $\geq 75 \times 10^9$/L
- PT/INR and PTT ≤1.5 x ULN (Note: subjects receiving anticoagulation treatment may enroll with INR established within the therapeutic range prior to D1 of treatment)
- Albumin ≥2.5 g/dL
- Total bilirubin ≤1.5 x ULN (patients with elevated bilirubin due to Gilbert's disease will not be excluded)
- AST and ALT ≤ 2.5× ULN
- CrCl ≥50mL/min per Cockcroft-Gault

3.1.7 Prior anti-cancer treatment related toxicities except alopecia and lab values as outlined in section 3.1.6 must be ≤ Grade 1 as per NCI CTCAEv4.

3.1.8 Willing to undergo biopsy for research purposes only (see section 6.6). **Note:** If possible, the pre-treatment biopsy should be performed after all other eligibility criteria are confirmed. Please also see the note in section 6.9.3 regarding assessment of biopsied lesions per RECIST v1.1.

3.1.9 Females of child-bearing potential: willing to use two forms of effective contraception, and to continue use for 16 weeks (4 months) post last dose of study medication. Effective contraception is defined as:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Male partner sterilization prior to the female subject's entry, and this male is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to enrollment, throughout study treatment, and for at least 4 months after the last dose of study treatment. Abstinence is only acceptable when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods, etc) and withdrawal are not acceptable methods of contraception.

- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

Note: Hormonal-based methods (e.g., oral contraceptives) are not permitted as contraception due to potential drug-drug interactions with dabrafenib.
Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 4 months following the last dose of study treatment.

Females of non-childbearing potential are those who are postmenopausal (defined as greater than 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone-replacement therapy (HRT). In questionable cases, the subject must have a follicle-stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (<140 pmol/L); or who have had a bilateral tubal ligation or tubal occlusion, bilateral oophoredtomy or hysterectomy. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described from D1 of treatment, throughout the treatment period, and for 16 weeks after the last dose of study treatment. If a subject becomes pregnant during the treatment period of the study, the study treatments should be stopped immediately.

3.1.10 In women of child-bearing potential, negative serum pregnancy test within 48 hours prior to day 1 of study treatment and agree to use effective contraception as outlined in section 3.1.9

3.1.11 Measurable disease as defined by RECIST v1.1

3.1.12 Able to swallow and retain oral medication

3.1.13 Left ventricular ejection fraction by ECHO ≥ institutional lower limit of normal

Patients with a history of hypertension MUST **have hypertension adequately controlled (BP < 140/90) with appropriate anti-hypertensive therapy or diet** prior to study entry. **Note:** To be eligible a subject must have an average of BP below 140/90 based on 3 separate measures. If the subject has a record of BP recordings taken at home, ≤ 20% of BPs taken should have numbers > 140/90.

3.2 Main Study Exclusion Criteria

Any subject meeting any of the following exclusion criteria at baseline will be ineligible for study participation:

3.2.1 Patients with a history of a prior malignancy are excluded unless they have been disease free for 3 or more years or unless they have a completely resected non-melanoma skin cancer, and/or subjects with indolent second malignancies.

3.2.2 History of malignancy with confirmed activating RAS mutation at any time. *Note*: Prospective RAS testing is not required. However, if the results of previous RAS testing are known, they must be used in assessing eligibility

3.2.3 Prior treatment with a BRAF inhibitor (including but not limited to dabrafenib (GSK2118436), vemurafenib, and LX281/BMS-908662) or a MEK inhibitor (including but not limited to trametinib (GSK1120212), AZD6244, and RDEA119); **NOTE:** There is no limit to the number of other prior therapies, and patients may be previously untreated.

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

3.2.5 Active GI or intracranial hemorrhage

3.2.6 History or evidence of cardiovascular risk including any of the following:

- QTc ≥ 480 msec;
- History or evidence of current clinically significant uncontrolled arrhythmias;
    - Exception: Subjects with controlled atrial fibrillation for >30 days prior to D1 of study treatment are eligible.
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to study entry;
- Patients with history of hypertension MUST have hypertension adequately controlled (BP < 140/90) with appropriate anti-hypertensive therapy or diet **prior to study entry**

Note: To be eligible a subject must have an average of BP below < 140/90 based on 3 separate measures. If the subject has a record of BP recordings taken at home and in their medical record, ≤ 20% of BPs taken should have numbers > 140/90.

- Patients with intra-cardiac defibrillators or permanent pacemakers;
- Known cardiac metastases;
- Abnormal cardiac valve morphology (≥grade 2) documented by echocardiogram (subjects with grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study.

3.2.7 History of known glucose-6-phosphate dehydrogenase (G6PD) deficiency

3.2.8 Brain metastases are excluded unless:

- All known lesions were previously treated with surgery or stereotactic surgery (whole-brain radiation is not allowed unless given after definitive treatment with surgery or stereotactic surgery), AND
- Brain lesion(s), if still present, must be confirmed stable (i.e., no increase in lesion size) for ≥ 12 weeks prior to D1 of study treatment (stability must be confirmed with two consecutive magnetic resonance image (MRI) or computed tomography (CT) scans with contrast, AND
- Asymptomatic with no corticosteroid requirements for ≥ 4 weeks prior to D1 of study treatment, AND
- Treatment with any CYP enzyme inducing anticonvulsants occurred < 4 weeks prior to D1 of study treatment

NOTE: if study subject has history of brain metastasis, but currently has no evidence of disease in brain (NED), confirmation by two consecutive scans separated by ≥6 weeks prior to D1 of treatment is required.

3.2.9 Pulmonary embolism on active therapy

3.2.10 History of interstitial lung disease or pneumonitis

3.2.11 Known HIV, Hepatitis B or C infection (with the exception of chronic or cleared HBV and HCV infection, which will be allowed provided the following tests are done at screening: viral hepatitis serology, Hepatitis B surface antigen and Hepatitis B core antibody (IgM) and/or Hepatitis C RNA)

3.2.12 Currently active GI disease, or prior surgery that may affect ability to absorb oral medications

3.2.13 History or current evidence/risk of retinal vein occlusion (RVO) or retinal pigment epithelial detachment (RPED):

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

3.2.14 Currently receiving cancer therapy (chemotherapy, radiotherapy, immunotherapy, or biologic therapy) NOTE: palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline provided total dose does not exceed 30 Gy; however, radiation skin injury has been reported with concurrent use of dabrafenib and radiation. See concomitant medications section 4.5.3 for recommendations when palliative radiation is prescribed.

3.2.15 Use of other prohibited medications within 5 half-lives or 14 days prior to the first dose of study drugs or requires any of these medications while receiving medication on this study (see section 4.5)

3.2.16 Pregnant or lactating female

3.3 Inclusion Criteria for Off-Study Subjects to Receive Progression Biopsy

3.3.1 Currently progressing on Trametinib/Deabrafenib Combination Therapy

3.3.2 Willing to undergo biopsy for research purposes only.

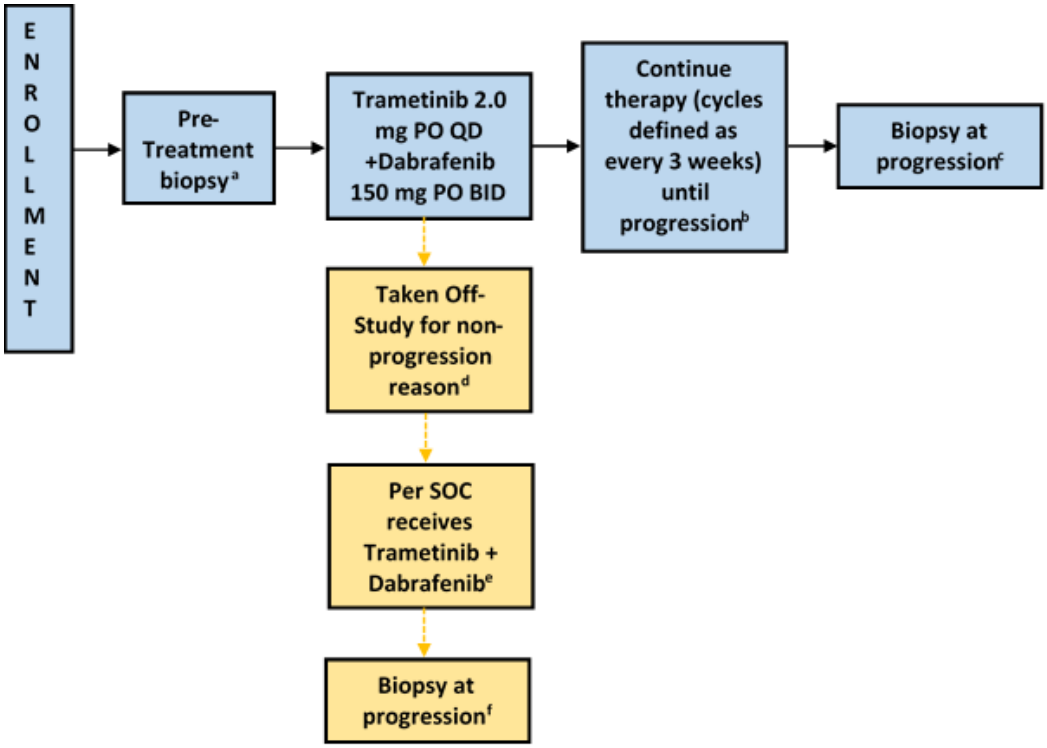
3.3.3 Tumor amenable to research biopsy.

3.3.4 Signed written informed consent to have a progression biopsy performed on the LCCC 1128 protocol.

3.3.5 Previously enrolled on the LCCC 1128 study and did not have a progression biopsy previously performed while on study.

4.0 TREATMENT PLAN

4.1 Schema



[a]Patient must have tumor accessible to biopsy to be eligible if frozen tissue from diagnostic specimen is not available.
[b]Patient may remain on treatment after progression if evidence of continuing clinical benefit
[c]Clinical or radiological
[d]Reasons may include, but are not limited to, inability to tolerate the combination of dabrafenib and trametinib, receiving other therapy, or completion of 3-years of study treatment without progression
[e]The subject may be placed back on the combination trametinib/dabrafenib therapy as part of his/her standard of care treatment plan
[f]The subject may have a progression biopsy taken after progression on standard of care treatment if the subject is eligible and consents to this biopsy. Progression can be defined clinically or radiologically.

This is an open label study of patients with unresectable stage III and stage IV melanoma with mutant V 600E/K melanoma and tumor that is accessible to biopsy. Patients can have had any number of prior lines of treatment (and may be previously untreated), but may not have previously received either a BRAF or MEK inhibitor for treatment of their melanoma.

Patients will receive the BRAF inhibitor dabrafenib and MEK inhibitor trametinib orally at the RP2D determined in the Phase I/II study (BRF113220): trametinib 2mg QD and dabrafenib 150 mg BID on a continuous basis. A cycle will be defined as 3 weeks in duration. Cycles will be repeated until disease progression (clinical or radiological). Patients may remain on treatment after progression (at the discretion of the investigator) as long as they are still experiencing clinical benefit**.** Patients will be requested to remain on study medication until the biopsy at progression is performed.

Patients will have a biopsy at baseline and at progression. Some subjects may be removed from study prior to progression for other reasons that include, but are not limited to, an inability to tolerate the combination of dabrafenib and trametinib, a need to receive other therapy, or completion of 3-years of study treatment without progression. If one of these subjects later receives the combination of dabrafenib and trametinib per his/her standard of care treatment plan, then the subject may re-consented for a biopsy upon progression. These subjects are required to consent to re-enter the study for the purposes of having a progression biopsy.

Kinomining™ and NextGen Sequencing (in patients who co-enroll into LCCC1108) will be done on baseline and progression biopsies to look for changes in kinome expression and mutations in resistance genes.

4.2 Biopsies

At baseline, if patient does not have frozen tissue available (see section 6.6) fresh tissue must be obtained. If possible, the pre-treatment biopsy should be performed after all other eligibility criteria are confirmed. Enough tissue will be collected for both kinomining and NextGen sequencing if available (see section 6.6). Fresh tissue collection of accessible tumor will be repeated **at progression (clinical or radiological)** whether patient continues treatment post progression or

not. In fact, patients will be requested to remain on study medication until the biopsy at progression is performed. For subjects who are withdrawn from study treatment, but are later placed back on the trametinib/dabrafenib combination therapy, a biopsy may be collected from the former study subject at the time of progression from the standard of care trametinib/dabrafenib therapy. These subjects must be consented and placed back on study to allow for attainment of a biopsy at progression. These subjects will then remain on study for safety monitoring, in relation to the biopsy procedure, for 30 days. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) related to the study procedure at 30 days will continue to be followed until the event is resolved or deemed irreversible by the investigator.

If possible, biopsies at progression should be performed within 7 business days of documented disease progression, and optimally within 4 hours of taking that day's study medication. If treating physician decides to continue treatment because the patient exhibits continued clinical benefit from therapy (and the patient agrees) then the biopsy can be delayed until the investigator deems the biopsy feasible as long as patient safety is not compromised. Post-treatment biopsies will not be required for patients removed for reasons other than disease progression; although, as mentioned above, if these subjects then go on to eventually receive the trametinib/dabrafenib combination in the future, as part of their standard of care, of the subject may be re-consented at the time of disease progression progression. See section 6.6 and laboratory manual. Please also see the note in section 6.9.3 regarding assessment of biopsied lesions per RECIST v1.1**.**

4.3 Treatment Dosage and Administration

Drug	Dose, Route & Schedule	Cycle
Trametinib	2 mg orally once daily	Every 3 weeks
Dabrafenib	150mg orally twice daily	Every 3 weeks

- After the pre-treatment biopsy is complete, patients will begin 2.0 mg of trametinib orally once per day in combination with dabrafenib 150mg PO BID.
- Patients will be instructed to take their dabrafenib at approximately the same time each day. The evening dose of dabrafenib should be administered approximately 12 hours after the morning dose.
- Both drugs should be administered under fasting conditions, either one hour before or 2 hours after a meal, and with approximately eight ounces of water.
- If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.
- If a patient misses a dose of dabrafenib, it should not be taken if it is less than 6 hours until the next dose. If a dose of trametinib is missed, the dose should only be taken if it is more than 12 hours until the next scheduled dose.

- Any missed dose should be noted on the patient diary (provided as a document separate from the protocol-see Appendices, section 11.6, for a model diary).

Note: loperamide should be made available prior to start of study treatment to patient so loperamide administration can begin at the first signs of diarrhea (see section 4.4.6).

4.4 Dose Modifications for Trametinib and Dabrafenib for Toxicity

See sections 5.1.5, 5.2.5, and appendices (section11.3), and the respective IBs for additional information on drug-related toxicities. Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed every 3 weeks for the development of any toxicity according to the Time and Events table (see Section 6.0). Toxicity will be assessed according to the NCI CTCAE, v 4.

If a patient experiences ≥2 or more AEs simultaneously that require different dose reductions, the lower dose should be used. Unless otherwise noted in the following sections, a maximum of 2 dose-level reductions for AEs are allowed on this protocol. If >2 dose reductions are required, protocol therapy is to be discontinued and patient is to be followed per protocol.

With the exception of decreased LVEF, both therapies should be reduced simultaneously in response to toxicities that are considered by the investigator to be treatment related. Note that if dabrafenib is permanently discontinued, trametinib will also be permanently discontinued.

Unless otherwise noted in the tables below, if an AE resolves to grade 1 or baseline at the reduced dose level, and no additional toxicities are seen after 4 weeks of study treatment at the reduced dose, the dose may be increased to the previous dose level in consultation with the study PI if so noted in the tables.

For AEs that require dose reductions, please refer to the dose levels in the following tables.

Trametinib Dose Levels for Toxicity		
Dose Levels	**Dose, Route and Schedule**	**Dosage Strength**
0	2 mg PO QD	2.0 mg tablets
-1	1.5 mg PO QD	0.5mg tablets
-2	1 mg PO QD	0.5mg tablets

Dabrafenib Dose Levels for Toxicity		
Dose Levels	**Dose, Route and Schedule**	**Dosage Strength**
0	150 mg PO BID	75 mg capsules
-1	100 mg PO BID	50 mg capsules
-2	75 mg PO BID	75 mg capsules

A dose reduction below 75 mg BID for dabrafenib and 1 mg once daily for trametinib is not allowed. If a dose reduction below 75 mg BID for dabrafenib is required, trametinib will also be permanently discontinued. If a dose reduction below 1.0 mg once daily for trametinib is required, then trametinib will be permanently discontinued, but these subjects will be allowed to continue dabrafenib.

4.4.1 Management and Dose Modifications for Skin Toxicities

Cutaneous AEs have been observed in subjects receiving dabrafenib, trametinib or both therapies in combination. See IBs for further information.[4, 5] In addition to dose modifications detailed below, please also see section 11.5 (Appendices) for supportive care measures for rash. See section 6.0; dermatologic evaluations will take place at baseline, during treatment and follow-up.

4.4.1.1 Rash

Rash is a frequent AE observed in subjects receiving trametinib, dabrafenib, or the combination of both therapies. See section 11.5 (Appendices) for recommended rash prophylaxis for the first 6 weeks of study treatment. Guidelines for management and dose reduction for rash considered related to study treatment are provided in the table below.

CTCAE Grade	Management of Rash	Action and Dose Modification for Dabrafenib and Trametinib
1	Initiate prophylactic regimen if not already started (recommended for the first 6 weeks of treatment (see section 11.5 (appendices). Treat with moderate strength topical steroid.* Reassess after 2 weeks	Continue current dose. If rash does not recover to baseline within 2 weeks despite best supportive care, reduce study treatment by one dose level
2	Initiate prophylactic regimen if not already started (recommended for the first 6 weeks of treatment (see section 11.5 (appendices)). Treat with moderate strength topical steroid.* Reassess after 2 weeks	Reduce study treatment by at least one dose level. If toxicity resolves to ≤ Grade 1 within 2 weeks, increase dose to previous dose level. If no recovery to ≤Grade 1 within 2 weeks, interrupt study treatment until ≤Grade 1. When restart, restart at the reduced dose level.
≥3	Treat with moderate strength topical steroid * PLUS oral methylprednisolone dose pack. Consider obtaining dermatology consultation	Interrupt study treatment until rash recovers to ≤Grade 2. Restart with study treatment reduced by one dose level. May consider escalating study treatment to previous dose level if no rash is evident 4 weeks after restarting treatment. If no recovery to grade ≤2 within 4 weeks, permanently discontinue study treatment.
*eg, hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream		

4.4.2 Malignancies

4.4.2.1 Squamous Cell Carcinoma (SCC)

Cutaneous SCC (cuSCC; include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib and the combination of dabrafenib and trametinib (see dabrafenib and trametinib combination IB)[6]. Approximately 70 % of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. These treatment-related cutaneous SCC should be surgically removed according to institutional practice. Dose modifications or interruptions of the study treatment are not required for cutaneous SCC. Occurrence of cutaneous SCC must be reported as an SAE (see Section 7.3.3).

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

4.4.2.2 New Primary Melanoma

New primary melanomas have been reported in patients treated with dabrafenib. These were identified primarily within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

4.4.2.3 Non-Cutaneous Malignancies

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

4.4.2.4 Palmar-plantar erythrodysaesthesia syndrome (PPES; also known as Hand-Foot-Skin-Reaction (HFSR))

Episodes of HSFR have been observed in subjects receiving dabrafenib. Guidelines for management of HFSR, and dose modifications for study treatment for HFSR potentially related to study treatment are listed in the table below. Management can differ from the guidelines below based on the clinical judgment of the investigator. The investigator should contact the overall PI to discuss skin toxicity as needed. Dermatologic exams should be performed by the Investigator as noted in the Time and Events Table, or may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.
A full-body skin examination and a removal of pre-existing calluses and keratotic skin is recommended prior to initiation of study treatment.

Life-style changes recommended for any grade of HFSR include the following:

- Reduce exposure of hands and feet to hot water,
- Avoid traumatic activity including vigorous exercise especially in the first 4 weeks after start of study treatment
- Avoid constrictive footwear
- Avoid excessive friction on the skin, when applying topical treatments
- Wear thick cotton socks and gloves, and shoes with padded insoles

Symptomatic treatments suggested for any grade of HFSR include the following:

- Use moisturizing creams frequently and especially on hands and feet
- Consider topical keratolytics: urea 20-40 % cream, or salicylic acid 6%, or tazarotene 0.1% cream, or fluorouracil 5% cream
- For erythematous areas: clobetasol propionate 0.05% ointment

- For pain: topical lidocaine 2%, and / or systemic pain medication such as nonsteroidal anti-inflammatory drugs, codeine, and pregabalin

Symptoms usually resolve within 2-4 weeks of treatment cessation.

CTCAE Grade	Management of HFSR	Action and Dose Modification for HFSR for Dabrafenib and Trametinib
1	Lifestyle changes recommended Initiate symptomatic treatment if clinically appropriate	Continue study treatment at current dose level
2	Lifestyle changes recommended Initiate symptomatic treatment	Interrupt study treatment until recovery to ≤grade 1 Recovery to ≤grade 1 within 7 days: Restart study treatment at previous dose level No recovery to grade ≤1 within 7 days or ≥ 2nd occurrence: **restart with study treatment reduced by one dose level[a]**
3	Lifestyle changes recommended Initiate symptomatic treatment Consider consulting dermatologist	Interrupt study treatment until recovery to ≤ grade 1 Restart with study treatment **reduced by one dose level[a]** If 3rd occurrence, discontinue study treatment permanently
[a]Escalation of study treatment to the previous dose level is allowed if no HFSR is observed in the 4 weeks subsequent to dose reduction.		

4.4.3 Management and Dose Modifications for Cardiac Toxicities

Cardiovascular adverse events have been seen in subjects receiving either dabrafenib, trametinib or both in combination. (See the IBs for additional information[4-6].

4.4.3.1 Hypertension

Increases in blood pressure have been observed in subjects receiving trametinib. Recommendations for blood pressure monitoring and management are provided below.

Monitoring of Hypertension

All blood pressure assessments should be performed under the following optimal conditions for the study subject:

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

- arm is supported so that the middle of the cuff is at heart level
- remains quiet during the measurement

In subjects with an initial blood pressure reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final blood pressure measurement. The averaged value should be recorded in the eCRF.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood pressure (DBP) > 90 mm Hg in three consecutive visits with blood pressure assessments from two readings collected as described above. Visits to monitor increased blood pressure can be scheduled independently from the per-protocol visits outlined in the Time and Events Table (see section 6.1). Ideally, subsequent blood pressure assessments should be performed within one week.

Asymptomatic hypertension is defined as an increase of SBP to >140 mm Hg and/or DBP >90 mm Hg in the absence of symptoms including headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension that resolve after the blood pressure is controlled within the normal range.

Management of Hypertension

For subjects experiencing an increase in systolic and/or diastolic blood pressure that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Hypertension	Action and Dose Modification for Dabrafenib and Trametinib
(Scenario A) Asymptomatic and persistent (terms defined above) SBP of >140 and <160 mmHg, or DBP >90 and <100 mmHg, **or** Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	Continue study treatment at the current dose Adjust current or initiate new antihypertensive medication Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled[a] BP If BP is not well controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(Scenario B) Asymptomatic SBP >160 mmHg, or DBP >100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A	Interrupt study treatment if clinically indicated Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication(s) during the next 2 weeks as indicated to achieve well-controlled BP[a] Once BP is well controlled[a], restart study treatment **reduced by one dose level[c]**
(Scenario C) Symptomatic[b] hypertension or Asymptomatic and persistent (term defined above) SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	Interrupt study treatment Adjust current or initiate new antihypertensive medication(s) Titrate antihypertensive medication during the next 2 weeks as indicated to achieve well-controlled BP[a] Referral to a specialist for further evaluation and follow-up is recommended Once BP is well controlled[a], restart study treatment **reduced by one dose level**
Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Permanently discontinue study treatment Continue follow-up per protocol.
[a]Well-controlled blood pressure defined as SBP ≤140 mm Hg and DBP ≤90 mm Hg in two separate readings during up to three consecutive visits. [b]Symptomatic hypertension defined as hypertension aggravated by symptoms (e.g., headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range. [c]Escalation of trametinib to previous dose level can be considered if BPs remain well-controlled for 4 weeks after restarting of trametinib. Approval from study PI is required.	

4.4.3.2 QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are provided in the following table. In studies to date, dabrafenib and trametinib do not exhibit an apparent potential to alter the QTc interval. The proportion of subjects with QTc interval >60 msec increases from baseline was higher in Part C

of study BRF113220 as compared to trametinib ISS and the dabrafenib ISS populations (13% compared to 3% and 3% respectively). [6]

QTc-Prolongation[a]	Action and Dose Modification for Dabrafenib and Trametinib
QTc≥501 msec **OR** uncorrected QT>600 msec **OR** QTc>530 msec for subjects with bundle branch block	Interrupt study treatment until QTc prolongation resolves to grade 1 or baseline Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits Review concomitant medication usage for a prolonged QTc Restart at current dose level[b] If event recurs, permanently discontinue study treatment
[a]Based on average QTc value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine if study treatments should be interrupted or discontinued. [b]If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the site investigator and study PI agree that the subject will benefit from further treatment.	

4.4.3.3 Reduced Left Ventricular Ejection Fraction

Decreases of the left ventricular ejection fraction (LVEF) have been observed in subjects receiving trametinib monotherapy and in combination with dabrafenib. Therefore, ECHOs must be performed to assess cardiac ejection fraction at regular intervals. ECHOs should be performed at baseline and at follow-up visit(s) See Time and Events table (section 6.1 for timing of follow-up ECHOs. Dose modification guidance and stopping criteria for LVEF decrease are provided in the table below.

LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic* Absolute decrease of >/=10% in LVEF compared to baseline and ejection fraction below the institution's LLN ***NOTE:** symptoms may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema	Interrupt study treatment (both drugs) and repeat ECHO within 2 weeks. If LVEF has not recovered in 2 weeks, repeat 2 weeks later. If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): • Restart with trametinib reduced by one dose level in consultation with study PI • Restart dabrafenib at previous dose level • Repeat ECHO 2 , 4 , 8 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter If LVEF **does not recover** within 4 weeks • Consult with cardiologist • **Permanently discontinue trametinib** • **Report as SAE** • Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution • Consult with study PI regarding restart of dabrafenib once LVEF recovers
Symptomatic* Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline	**Permanently discontinue trametinib. Discontinue dabrafenib.** **Report as SAE** **Consult with cardiologist**
Symptomatic Grade 4: resting LVEF <20%	Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution Consult with study PI regarding restart of dabrafenib once LVEF recovers

4.4.4 Management and Dose Modifications for Visual Changes

Episodes of visual changes have been observed in subjects receiving dabrafenib, trametinib or the combination of both therapies. Ocular adverse events are known to be related to trametinib. The causal relationship between a change in vision and the study treatment should be carefully explored and an ophthalmologist should be consulted. However, if the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Treatment with dabrafenib has been associated with the development of uveitis, including iritis. Monitor patients for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy. For adverse events of uveitis, no dose modifications are required as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, interrupt dabrafenib and hold until resolution of ocular inflammation. Then restart dabrafenib reduced by one dose level.

Special attention should be given to retinal problems (e.g., retinal pigment epithelium detachments (RPED)) or retinal vein abnormalities (e.g., RVO).

Refer to section 11.1 (Appendices) for grading of visual changes.

If visual changes develop, an eye exam is indicated. The exam will include best corrected visual acuity, tonometry, slit lamp biomicroscopic examination, visual field examination, and dilated indirect fundoscopy with special attention to retinal abnormalities. Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.

CTCAE Grade[a]	Management of Visual Changes	Action and Dose Modification for Dabrafenib and Trametinib
1[b]	Consult ophthalmologist within 7 days of onset Exclude RPED, and RVO Consult retinal specialist in case of RPED or RVO Continue follow up examination(s) by retinal specialist for RPED and RVO	If dilated fundus examination cannot be performed within 7 days of onset, interrupt study treatment until RPED and RVO can be excluded by retina specialist/ophthalmologist and symptoms resolve If RPED and RVO excluded, restart study treatment at same dose level RPED suspected or diagnosed and Grade 1(asymptomatic; clinical or diagnostic observations only)[a]: Continue treatment with retinal evaluation monthly until resolution. If it worsens follow instructions for grade.[a] RVO: **Permanently discontinue study treatment and report as SAE**
2 and 3	Consult ophthalmologist immediately Interrupt study treatment	If RPED and RVO excluded, restart study treatment at same dose level. If RPED diagnosed (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)[a], continue retinal evaluation monthly until resolves to ≤Grade 1. At that point, restart study treatment reduced by one dose level. RVO: **Permanently discontinue study treatment and report RVO as SAE**
4	Consult ophthalmologist immediately Interrupt study treatment	If RPED and RVO excluded, may consider restarting study treatment at same or reduced dose. If RVO or RPED diagnosed, **permanently discontinue study treatment and report as SAE.**

[a]Refers to CTCAE Version 4.0 'Eye disorders – Other, specify' (also see section 11.1 in Appendices); RPED graded as per CTCAE v4 "Retinopathy"
[b]If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.

4.4.5 Management and Dose Modifications for Pneumonitis

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

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

4.4.6 Management and Dose Modifications for Renal Insufficiency

Cases of renal insufficiency have occurred in subjects receiving dabrafenib and the combination of dabrafenib and trametinib.

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

reduction for renal insufficiency considered to be related to study treatment by the investigator are provided in the table below.

Serum Creatinine (SCr) Level	Management of Renal Insufficiency	Action and Dose Modification for Dabrafenib and Trametinib
SCr increase >0.2 mg/dL (18 µmol/L) **But** ≤0.5 mg/dL (44 umol/L) above baseline	Recheck SCr within 1 week SCr increase lasts > 1 week: contact Study PI; If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation. If pyrexia is present, treat pyrexia per guidelines[a]; please note NSAIDS can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluides	Continue study treatment at the same dose level
SCr increase >0.5 mg/dL (44 µmol/L) above baseline **Or** SCr >2 mg/dL (> 177 µmol/L)	Monitor SCr ≥ 2 times per week Hospitalization may be necessary if serum creatinine cannot be monitored at least twice weekly If pyrexia is present, treat pyrexia per guidelines[a] Consult nephrologist if clinically indicated Perform renal biopsy if clinically indicated, for example: Renal insufficiency persists despite volume repletion Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)	Interrupt study treatment until SCr recovers to baseline Restart with study treatment[b]

[a]NSAIDs can induce renal insufficiency, especially in subjects with dehydration; encourage oral fluids or consider intravenous fluids as clinically indicated. See guidelines for pyrexia in section 4.4.7

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

4.4.7 Management and Dose Modifications for Diarrhea

Episodes of diarrhea have occurred in subjects receiving dabrafenib, trametinib, or both therapies in combination. Other, frequent causes for diarrhea including concomitant medications (e.g., stool softeners, laxatives, antacids), infections by *C. difficile* or other pathogens, partial bowel obstruction, etc., should be clinically excluded. **Note:** loperamide should be made available prior to start of study treatment to patient so loperamide administration can begin at the first signs of diarrhea. Guidelines regarding management and dose reduction for diarrhea considered to be related to study treatment by the investigator are provided in the table below.

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

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

[b] **Complicated diarrhea** is diarrhea in the presence of symptoms noted under footnote (a)

[c] Escalation of study treatment to previous dose level is allowed after consultation with the PI and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

4.4.8 Management and Dose Modification Guidelines for Therapy-related Pyrexia

Pyrexia is defined as ≥38.5°Celsius or 101.3°Fahrenheit. Episodes of pyrexia have been observed in subjects receiving dabrafenib monotherapy and is increased in incidence and severity in subjects receiving dabrafenib in combination with trametinib. (Pyrexia is also a side effect of trametinib, but is less frequent than that associated with dabrafenib-see section 5.1.5). [6] In a minority of cases the pyrexia was accompanied by symptoms such as severe chills, dehydration, hypotension, dizziness or weakness. Pyrexia accompanied by hypotension, dehydration requiring IV fluids, or severe rigors/chills should be reported as an SAE (see section 7.3.3). Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take non-steroidal anti-pyretics (e.g., ibuprofen), acetaminophen or other suitable anti-pyretic medication as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. In subjects experiencing pyrexia associated with rigors, severe chills, dehydration, hypotension, etc., renal function should be monitored carefully.

For each episode of pyrexia (defined above), a thorough clinical examination (including blood pressure) for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full blood count, electrolytes, creatinine, BUN, CRP, liver function tests, blood culture, and urine culture. For subjects experiencing pyrexia complicated by rigors, severe chills, etc., a clinical evaluation and laboratory work-up is mandatory for each event; anti-pyretic treatment should be started immediately at the first occurrence and prophylactic anti-pyretic treatment is recommended. This prophylactic treatment may be discontinued after 3 days in the absence of pyrexia.

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

Pyrexia Management	Action and Dose Modification
1st Event Clinical evaluation for infection and hypersensitivity Laboratory work-up[a] Hydration as required Administer anti-pyretic treatment if clinically indicated and initiate prophylactic treatment[e] if fever associated with rigors, renal failure, dehydration or hypotension 2nd Event[b] Clinical evaluation for infection and hypersensitivity Laboratory work-up[a] Hydration as required Within 3 days of onset of pyrexia: Optimize anti-pyretic therapy Consider oral corticosteroids (i.e., prednisone 10 mg) for at least 5 days or as clinically indicated Subsequent Events: Clinical evaluation for infection and hypersensitivity Laboratory work-up[a] Hydration as required[d] Within 3 days of onset of pyrexia: Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia[b] If corticosteroids have been tapered and pyrexia recurs, restart steroids If corticosteroids cannot be tapered consult study PI	1st Event: Interrupt dabrafenib Continue trametinib (unless fever >104°F or fever complicated by rigors, hypotension, dehydration or renal failure, in which case trametinib should be withheld until fever resolves.) Resume at same or lower dose level. Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level**[l] 2nd Event: **Interrupt dabrafenib** Continue trametinib (unless fever >104°F or fever complicated by rigors, hypotension, dehydration or renal failure, in which case trametinib should be withheld until fever resolves.) Resume at same or lower dose level. Once pyrexia resolves to baseline, restart dabrafenib at the same dose level If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level** Subsequent Events: **Interrupt dabrafenib** Continue trametinib (unless fever >104°F or fever complicated by rigors, hypotension, dehydration or renal failure, in which case trametinib should be withheld until fever resolves.) Resume at same or lower dose level. Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level**[c] If dabrafenib must be reduced to <75 mg BID, permanently **discontinue both study treatments**

[a]To include CBC with diff, electrolytes, creatinine, BUN, CRP, liver function tests, blood culture, and urine culture.
[b]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 2nd event and doses should be gradually increased for subsequent events.
[c]Dabrafenib should be reduced by one dose level after three episodes of pyrexia complicated by rigors, severe chills, etc., which cannot be managed by best supportive care and increasing doses of oral steroids. Escalation of dabrafenib is allowed if no episode of pyrexia is observed in the 4 weeks subsequent to dose reduction.
[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]Prophylactic anti-pyretic treatment may be discontinued after 3 days in the absence of pyrexia

4.4.9 Dose Modifications for Liver Toxicities

Liver chemistry stopping criteria, follow up assessments and monitoring have been designed to assure subject safety and evaluate liver event etiology.

4.4.9.1 Definition of Liver Chemistry Stopping Criteria

Trametinib and dabrafenib will be permanently discontinued when any of the stopping criteria (1-5) listed below is met.

1. Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT≥3xULN **and** international normalized ratio [INR]>1.5, if INR measured.
    a. INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
    b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, discontinue study treatment, and **record presence of detectable urinary bilirubin on dipstick** indicating direct bilirubin elevations and suggesting liver injury. NOTE: Any case that meets these criteria and is considered to be drug related is considered to be an SAE by GSK. This is called "Hy's Law." If a Hy's Law case occurs but there is a potential explanation for it other than drug, please consult with the Study PI.
2. ALT ≥8xULN.
3. ALT ≥5xULN but <8 x ULN persists for ≥2 weeks.
4. ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
5. ALT ≥ 5xULN but <8 x ULN and cannot be monitored weekly for >2 weeks

4.4.9.2 Follow-up Action if Liver Chemistry Stopping Criteria are Met:

- **Immediately discontinue subject from study treatment**
- Report the event to GSK **within 24 hours** of learning of its occurrence (see section 7.3.3).
- Complete the liver event and SAE electronic case report form (eCRF) within Oncore® 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, termed 'Hy's Law', **must be reported as an SAE**
    - NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued 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 eCRFs if these tests are performed

- Perform liver event follow up assessments (see Appendices (section 11.4) and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- Follow-up is required until the toxicity is deemed irreversible or for 3 months, whichever comes first, following permanent discontinuation from study treatment for liver toxicity
- Do not re-challenge with study treatment without IRB approval (see appendices, sections 11.4.2 and 11.4.3.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to a clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (see appendices (section 11.4), 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.

In addition, for subjects meeting any of the criteria 2 - 5:

- Make every reasonable attempt to have subjects return to a clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see appendices (section 11.4)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values
- Subjects meeting criterion 5 should be monitored as frequently as possible

4.4.9.3 Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3xULN **but** <8xULN which exhibit a decrease to ALT ≥3xULN, but <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify study PI within 24 hours of learning of the abnormality to discuss subject safety
- Continue study treatment
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline values
- If at any time the subject meets any of the liver chemistry stopping criteria 1 – 5 (see section 4.4.8.1), proceed as described above in section 4.4.8.2)
- 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.

4.4.10 Pancreatitis

In the event of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected for confirmation of the diagnosis. Patients should be closely monitored when re-starting dabrafenib after an episode of pancreatitis.

4.4.11 Hyperglycemia

Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral therapy can occur with dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in subjects with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

4.4.12 Non-specified Toxicities Attributable to Drug Therapy

CTCAE Grade	Action and Dose Modification for Dabrafenib and Trametinib
1 or tolerable Grade 2	Continue study treatment at current dose level Monitor closely Provide supportive care according to institutional standards
1st, 2nd, or 3rd occurrence of intolerable Grade 2 or any Grade 3	Interrupt study treatment Monitor closely Provide supportive care according to institutional standards When toxicity resolves to ≤grade 1, restart study treatment **reduced by one dose level**
4th occurrence of intolerable Grade 2 or any Grade 3	Discontinue treatment
4	Interrupt study treatment Monitor closely Provide supportive care according to institutional standards Restart with study treatment **reduced by one dose level** once toxicity resolves to ≤grade 1 If the grade 4 toxicity recurs, once resolves to ≤grade 1, restart at two dose levels lower than the starting dose or **permanently discontinue study treatment** at discretion of the investigator For 3rd occurrence, discontinue treatment

4.5 Concomitant Medications/Treatments

4.5.1 Prohibited Medications, Herbal Supplements and Juices

The use of certain medications for 14 days or 5 half-lives prior to the first dose of study therapies and for the duration of the trial will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while treatment with study drug is interrupted, the PI can approve such use. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on treatment in this study
- Other investigational drugs
- The concurrent use of all herbal supplements is prohibited during the study (including but not limited to St. John's wort, kava, ephedra (ma

huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, or ginseng).

- Antiretroviral drugs. Subjects with known HIV are ineligible for study participation.
- Drugs that are clinically relevant strong inhibitors or inducers of CYP3A, CYP2C8, p-glycoprotein (Pgp) or breast cancer resistance protein (BCRP) transporter because they may alter dabrafenib and/or trametinib concentrations. These include but are not limited to those listed in section 11.2 (see Appendices); consider therapeutic substitutions for these medications. This list may be modified based on emerging data.

4.5.2 Drugs to be used with Caution

The following medications should be used with caution as their concentrations may be altered by dabrafenib or trametinib or they may alter dabrafenib or trametinib concentrations (see section 11.2.2 in appendices):

- Drugs that are mild/moderate inhibitors or inducers of CYP3A, CYP2C8, or Pgp or BCRP transporter.
- Drugs that are substrates of CYP2C8, CYP2C9, and CYP2C19 that are highly sensitive to inhibitors or that have a low therapeutic index. Dabrafenib has been shown to induce CYP3A4 in vivo and may induce CYP2B6. Other enzymes such as CYP2C8, CYP2C9, CYP2C19 and UGT may also be affected. Onset of induction is likely to occur after 3 days of repeat dosing with dabrafenib. Transient inhibition of CYP3A4 may be observed during the first few days of treatment. Upon discontinuation of dabrafenib, concentrations of these sensitive substrates may increase and subjects should be monitored for toxicity and dosage of these agents may need to be adjusted.[6]
- Co-administration of dabrafenib and medications that are affected by the induction of these enzymes (including warfarin, hormonal contraceptives, dexamethasone, antiretroviral agents or immunosuppressants) 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.
- Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When dabrafenib is coadministered with a proton pump inhibitor, H2-receptor antagonist or antacid, systemic exposure of dabrafenib may be decreased and the effect on its efficacy is unknown.

4.5.3 Dabrafenib and Radiation

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. To reduce this risk, it is recommended that dabrafenib be held for seven

days before and two days after radiation in subjects receiving dabrafenib in combination with trametinib.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression* (*Some patients may remain on treatment after progression (at the discretion of the investigator) as long as they are still experiencing clinical benefit
- In patients without progression, therapy may continue up to 3 years
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- 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.

4.7 Duration of Follow Up

Patients who come off therapy due to progression will enter the follow-up phase every 3 months for up to 1 year from study entry to document survival (no tumor measurement per study protocol will be necessary after progression).

Patients who come off therapy for reasons other than progression will enter the follow-up phase every 3 months for up to 1 year from study entry to document survival. If tumor assessments are available for patients who have not yet experienced progressive disease (PD), these evaluations will be documented in the eCRF until PD is confirmed. Regardless, of the reason that a patient comes off treatment, dermatologic exams will continue every 3 months for the first 6 months following discontinuation from dabrafenib, and may be done by a physician local to the patient. Only after these dermatologic exams are complete is the patient considered off follow-up, even if they do not require survival follow-up for this entire 6 month period.

Patients who come off therapy for reasons other than progression, later receive the dabrafenib/trametinib off-study and then progress on the combination therapy may be re-consented to undergo a progression biopsy. These subjects will then remain on study for safety monitoring, in relation to the biopsy procedure, for 30 days. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) related to the study procedure at 30 days will continue to be followed until the event is resolved or deemed irreversible by the investigator.

4.8 Removal of Patients from Protocol Therapy

Patients will be removed from study treatment when any of the criteria listed in Section 4.6 apply. Notify the Principal Investigator, and document the reason for removal from study treatment and the date the patient was removed in the

electronic Case Report Form (eCRF). The patient should be followed-up per protocol.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.9 Patient Replacement

If a patient drops out of the study prior to progression, they may be replaced after consultation with the manufacturer of trametinib and dabrafenib, GSK. We anticipate that ≤3 patients will fall into this category.

4.10 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Trametinib Description and Management

Details on this product may be found in the prescribing information (see www.accessdata.fda.gov) and the Investigator's Brochure.[4] Please also see sections 1.5 and the appendices (section 11.3) for additional information on safety when dabrafenib is combined with trametinib.

5.1.1 Supplier/How Supplied

Trametinib commercially available product with auxiliary labeling will be provided by Novartis. The study drug should be administered and stored as per the instructions specified on the label (refer to the label, the PI or the IB for more detailed information)

The drug substance (tablet) is blended with inert ingredients. It comes as 0.25, 0.5mg, 1 mg and 2 mg film coated tablets. For this trial it will be provided in 0.5 and 2.0 mg strengths.

5.1.2 Handling and Dispensing

A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

5.1.3 Dosage and Administration

See Section 4.3.

5.1.4 Return and Retention of Study Drug

Unused study drug returned by the subjects will be accounted for on site and will then be destroyed per UNC IDS drug destruction policy or per Affiliate institutional guidelines. Any study drug remaining after trial is complete will be destroyed per UNC IDS drug destruction policy or per Affiliate institutional guidelines.

5.1.5 Adverse Events (AEs) Associated with Trametinib

The data and guidance presented in this section is based on the nonclinical data and the safety profile seen in clinical studies involving trametinib to date, described in the trametinib Investigator's Brochures.[4]

Based on available AE data from the clinical studies to date, the most common toxicities ≥ 20% at the 2.0 mg/day dose are rash, diarrhea, fatigue, peripheral edema, nausea, vomiting, constipation, anemia, decreased appetite, dyspnea, pruritus, and abdominal pain. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and left ventricular ejection fraction (LVEF) reduction, although observed at lower frequencies, are also considered class effect toxicities as they have been observed with trametinib as well as other MEK inhibitors. Other very common toxicities (≥10% up to 19%) include alopecia, dermatitis acneiform, dry skin, pyrexia, hypertension, cough, and dry mouth; common toxicities (≥1% to <10%) include pneumonitis, dehydration, periorbital edema, blurred vision, vision impairment, left ventricular dysfunction, lymphedema, epistaxis, stomatitis, erythema, palmar-plantar erythrodysaesthesia syndrome, chapped skin, skin fissures, asthenia, facial edema, mucosal inflammation, cellulitis, folliculitis, paronychia, pustular rash, increases in ALT, AST, alkaline phosphatase, and serum creatinine, and decreased ejection fraction. Uncommon toxicities include hypersensitivity (which may present with symptoms such as fever, rash, increased LFTs, and visual disturbances), chorioretinopathy, papilloedema, retinal detachment, retinal vein occlusion, cardiac failure, pneumonitis, and interstitial lung disease.

The following Contraindications, Warnings and Precautions apply:

Contraindications:
Pregnancy:
There are no adequate and well-controlled studies of GSK1120212 in pregnant women. Animal studies have shown reproductive toxicity. In repeat dose studies

in rats given trametinib, there were ovarian effects that could likely affect female fertility. Therefore, the compound must not be administered to pregnant women or nursing mothers. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation. If GSK1120212 is used during pregnancy, or if the subject becomes pregnant while taking GSK1120212, the subject should be informed of the potential hazard to the fetus.

There are no adequate and well-controlled studies of GSK1120212 in pregnant women. Animal studies have shown embryofetal development toxicities, including teratogenic effects. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception during therapy and for 4 months following discontinuation. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception. If a female patient or a female partner of a patient becomes pregnant while the patient receives trametinib, the potential hazard to the fetus should be explained to the patient and partner (as applicable). Safety and efficacy in the elderly or pediatric populations have not been investigated.

Lactation
It is not known whether trametinib is excreted in human milk. Because many medicinal products are excreted in human milk, a risk to the nursing infant cannot be excluded. A decision should be made whether to discontinue nursing or to discontinue

Hypersensitivity
Any known hypersensitivity to the constituents of the vehicle would contraindicate trametinib use. Hypersensitivity to trametinib was reported by one subject 7 days after starting trametinib who experienced fever, asthenia, visual disturbance, and symptoms suggestive of a hypersensitivity reaction described by the investigator as “vascularity.” This subject also developed LFT elevations, lower limb nodules that by biopsy showed “dermo-hypodermatitis with plasmocyte and lymphocyte infiltrate.”

Precautions:
Pediatric Use
Trametinib should not be administered to pediatric populations and should be administered to elderly populations with caution.

Skin toxicities: Rash was a common toxicity in the FTIH study, and occurred at doses as low as 0.5 mg. At the 2.0 mg dose level in the FTIH study, 87% of the subjects experienced rash; most cases were Grade 1 or Grade 2 in severity; rash occurred as early as the first week of dosing, with the median onset on Day 15 of study treatment. In clinical studies overall, rash has been observed in about 60% of subjects. The majority of these cases was Grade 1 or 2 and did not require any dose interruptions or dose reductions.

Gastrointestinal toxicities: Diarrhea was a common toxicity, and occurred throughout the dose range. At the 2.0 mg dose level in the FTIH study, 56% of the subjects experienced diarrhea; most events were either Grade 1 or Grade 2 in severity.

Visual impairment:
Visual impairments, including chorioretinopathy, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and papilledema have been reported with trametinib.

Subjects with a history of RVO or risk factors of RVO should not receive trametinib. Exclusion criteria based on these risk factors, comprehensive stopping criteria, dose modifications, and ocular effects management guidelines have been incorporated into this protocol.[4]

Cardiomyopathy:
Cardiomyopathy, defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction (LVEF) has been reported with trametinib as well as with other MEK inhibitors in clinical development. Subjects with a history or evidence of cardiovascular risk including current ≥ Class II congestive heart failure as defined by New York Heart Association are not being enrolled in current studies. Subjects must have a normal LVEF on screening assessment. Comprehensive stopping criteria, dose modifications, and left ventricular dysfunction management guidelines have been incorporated into this study. In addition, there have been 9 cases of sudden death or cardiac arrest reported across the trametinib program. See the trametinib IB.[4]

Pneumonitis: Pneumonitis was seen in 6 out of 31 subjects (19%) treated with trametinib plus gemcitabine in Study MEK112111. Four of the 6 subjects were rechallenged with study drug, and while a relationship to trametinib could not be ruled out, all 4 subjects had no further pulmonary symptoms or evidence of pneumonitis on imaging studies. Investigators must use caution when using trametinib in combination with drugs that have been associated with or induced pneumonitis.

Drug Interactions
As trametinib is metabolized predominantly via deacetylation likely mediated by hydrolytic esterases, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. Based on *in vitro* and *in vivo* data, trametinib is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters.

Drug-Food Interactions
Administration of a single dose of trametinib with a highfat, high-calorie meal resulted in a 70% and 10% decrease in Cmax and AUC(0-∞), respectively

compared to fasted conditions. The recommendation is to administer trametinib on an empty stomach.

Renal Impairment
No dosage adjustment is required in subjects with mild or moderate renal impairment. There are no data in subjects with severe renal impairment; therefore, trametinib should be used with caution in subjects with severe renal impairment.

Hepatic Impairment
No dosage adjustment is required in subjects with mild hepatic impairment. There are no clinical data in subjects with moderate or severe hepatic impairment; therefore, trametinib should be used with caution in subjects with moderate or severe hepatic impairment.

Potential for Abuse and Dependence: Not known.

Overdose:
In BRF113220 study, 12 subjects experienced fourteen events of trametinib overdose as defined by the protocol (trametinib doses > 2mg in a day). All overdoses lasted for one day only. Five of these subjects took 2 tablets (4mg) trametinib and experienced 12 AEs, all within 3 days of taking the overdose. The adverse events were primarily grade 1 (chills, hot flash, diarrhea, low back pain, changes in hair texture, vomiting, weakness, and cough), with grade 2 pyrexia and chills, and grade 3 hyponatremia. One subject experienced mesenteric artery thrombosis identified as due to disease progression. No subjects required dose reduction or discontinuation. All subjects resumed trametinib treatment at the assigned dose.

In the event of a trametinib overdose, defined as administration of more than 3mg once daily (the maximum tolerated dose defined in the MEK111054 study), the investigator should contact the study PI immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. The investigator will use clinical judgment to treat any overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study PI based on the clinical evaluation of the subject.

There is no specific antidote for an overdose with trametinib. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status. Hemodialysis is not expected to enhance the elimination of trametinib as it is highly bound to plasma proteins. The most likely results of acute overdose with trametinib may include rash, nausea, vomiting, or diarrhea.

5.2 Dabrafenib Description and Management

Details on this product may be found in the prescribing information (see www.accessdata.fda.gov) and the Investigator's Brochure for dabrafenib.[5] Please also see sections 1.5 and the appendices (section 11.3) for additional information on the safety seen when dabrafenib is combined with trametinib.

5.2.1 Supplier/How Supplied

Dabrafenib commercially available product with auxiliary labeling will be provided by Novartis. The study drug should be administered and stored as per the instructions specified on the label (refer to the label, the PI or the IB for more detailed information).

Each capsule contains 25, 50 mg or 75 mg of dabrafenib. For this trial it will be provided in 50 and 75 mg strengths.

5.2.2 Handling and Dispensing

A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

5.2.3 Dosage and Administration

See Section 4.3.

5.2.4 Return and Retention of Study Drug

Unused study drug returned by the subjects will be accounted for on site and will then be destroyed per UNC IDS drug destruction policy or per Affiliate institutional guidelines. Any study drug remaining after trial is complete will be destroyed per UNC IDS drug destruction policy or per Affiliate institutional guidelines.

5.2.5 AEs Associated with Dabrafenib

As summarized in the table below (from the dabrafenib 2014 IB)[5] the following adverse events were considered related to dabrafenib when administered as monotherapy across company-sponsored clinical trials (n=578).
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%)

Eye Disorders
Uncommon

- Uveitis (including chorioretinitis, choroiditis, retinitis, vitritis, cyclitis, iridocyclitis, iritis, and uveitis)

Neoplasms benign and malignant (including cysts and polyps)
Very Common
- Skin papilloma, papilloma

Common
- Cutaneous squamous cell carcinoma (SCC), including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma
- Acrochordon (skin tags)
- Seborrheic keratosis

Uncommon
- New primary malignant melanoma

Immune System Disorders
Uncommon
- Hypersensitivity

Renal and urinary disorders
Uncommon
- Renal failure, acute renal failure

Respiratory, thoracic and mediastinal disorders
Very Common
- Cough

Metabolism and nutrition disorders
Very Common
- Decreased appetite

Common
- Hypophosphataemia

Nervous system disorders
Very Common
- Headache

Gastrointestinal disorders
Very Common
- Nausea
- Vomiting
- Diarrhea

Common
- Constipation

Uncommon
- Pancreatitis

Skin and subcutaneous tissue disorders
Very Common
- Skin effects (Rash, Hyperkeratosis)
- Alopecia
- Palmar-plantar erythrodysaesthesia syndrome

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
- Chills

Common
- Influenza-like illness

5.2.6 Contraindications

Drugs that are strong inhibitors or inducers of CYP3A or CYP2C8, Pgp or BCRP transporters, are contraindicated. See appendices and sections 4.5 and 11.2.1. Any known hypersensitivity to the constituents of the vehicle would contraindicate dabrafenib use.

5.2.7 Special Warnings and Special Precautions for Use

Dermatological effects:
Epidermal hyperplasia (acanthosis) and hyperkeratosis of the skin was seen in dogs and in rats. In clinical trials rashes have been observed, and in the monotherapy studies hyperkeratosis (29%), skin lesions including actinic keratosis (7%) and seborrheic keratosis (7%), hand-foot skin reactions (13%), rash (18%) and cutaneous SCC including keratoacanthomas (KA) (9%) have been observed. Approximately 70% of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. More than 90% of patients who developed cutaneous SCC continued on dabrafenib treatment without dose modification. Most events were Grade 1 with the exception of cutaneous squamous cell carcinomas, which were predominantly Grade 3. Dermatological changes are

being monitored in subjects through interim medical history, assessment of adverse events and physical examination including examination of the skin. Guidelines on management of HFSR and skin rashes have been provided in the protocol.

Non-cutaneous secondary/recurrent malignancy
Cases of RAS-driven malignancies have been seen with BRAF inhibitors. One case of RAS-mutation positive non-cutaneous malignancy (bile duct adenocarcinoma) has been identified to date in a subject receiving dabrafenib monotherapy. Patients should be monitored as clinically appropriate.

Ophthalmology effects:
Eye effects including blurred vision (2), uveitis/iritis (<1%), eye pain (<1%), visual impairment (<1%) and reduced visual acuity (<1%) have been infrequently observed in clinical studies to date, with events generally grade 1 or 2. An ophthalmologic consult is required for subjects developing symptoms associated with uveitis including blurry vision, eye pain or erythema.

Pyrexia:
In clinical studies, pyrexia was one of the most frequently occurring AEs (27%), most of which (64%) were considered to be related to study treatment. Events were primarily Grade 1 (55%) or Grade 2 (39%) in severity. The majority of events occurred early during study treatment, with a median time to onset of first occurrence of 3 weeks, and most cases (74% of first occurrences) were of short duration (5 days). The majority of subjects with pyrexia were managed without dose interruption or dose reduction.

Subjects should be evaluated for signs and symptoms of infection and work up considered as clinically indicated. Drug must be held for fever of 38.5°C or higher, and an absolute neutrophil count, serum creatinine and BUN must be drawn in the setting of fever. Subjects with fever should have a medical evaluation including measurement of blood pressure. Cases of fever with rigors or fever with hypotension should be reported as SAEs (regardless of whether or not hospitalization was required); see section 7.1.4.

Glucose-6-phosphate dehydrogenase:
Subjects with a history of known glucose-6-phosphate dehydrogenase (G6PD) deficiency may develop non-immune hemolytic anemia in response to dabrafenib which contains a sulfonamide, a potential risk factor for subjects with this deficiency (NOTE: patients with history of sulfa allergies do not need to be excluded from studies incorporating dabrafenib).

Hyperglycemia:
Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic agent therapy can occur with dabrafenib. The incidence of grade 3 hyperglycemia based on laboratory values was 6% in patients treated with dabrafenib compared to 0% in the dacarbazine group in the phase 3 randomized

trial that compared dabrafenib to dacarbazine. Some patients may require more intensive hypoglycemic therapy while taking dabrafenib. Monitor serum glucose levels as clinically appropriate during treatment with dabrafenib in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

Acute renal failure:
Acute renal failure/renal failure has been rarely reported (<1%) in patients receiving dabrafenib, and a case of granulomatous interstitial nephritis has also been reported in a clinical trial. In some cases complicated pyrexia may be associated with renal insufficiency/renal failure, possibly secondary to dehydration or hypotension. Renal function should be monitored carefully, especially in patients with pyrexia. Dabrafenib should be interrupted in patients with significantly elevated serum creatinine (creatinine rise > 0.5 mg/dL [44 μmol/L] above baseline or creatinine > 2.0 mg/dL [177 μmol/L]).

Pancreatitis:
Pancreatitis (<1%) and/or increased lipase/amylase (2%) have been reported at low frequency with dabrafenib, typically occurring within 14 days of starting therapy. For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be monitored locally.

New primary melanoma:
New primary melanomas have been reported in patients treated with dabrafenib. These were identified within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

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

Drug interactions:
Strong inhibitors or inducers of CYP3A or CYP2C8 are prohibited since they may increase or decrease dabrafenib concentrations. Mild or moderate inhibitor/inducers of these enzymes/transporters should be used with caution. Dabrafenib has been shown to induce CYP3A4 and CYP2C9, and,may induce CYP2C8, CYP2B6, CYP2C19 and UGT. Co-administration of dabrafenib and medications affected by the induction of these enzymes may result in decreased exposure of these medications and associated 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.

Drugs that affect gastric pH:
Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When dabrafenib is coadministered with a proton pump inhibitor, H2-receptor antagonist, or antacid, systemic exposure of dabrafenib may be decreased and the effect on its efficacy is unknown.

Drug-food interactions:
Administration of dabrafenib with a high-fat, high-calorie meal reduced the oral bioavailability of dabrafenib when compared to the fasted state with a decrease in Cmax and AUC of 51% and 31%, respectively, and delayed its absorption. The recommendation is to take dabrafenib on an empty stomach.

Pediatric population:
Safety and efficacy in the pediatric population has not been established, therefore, dabrafenib should not be administered to this population.

5.2.8 Other Considerations

Renal impairment
There are limited clinical data for dabrafenib in subjects with renal impairment. In clinical studies, 3% of subjects had baseline Grade 1 renal impairment.
Mild or moderate renal impairment is not expected to have a clinically relevant effect on dabrafenib pharmacokinetics given the low renal excretion of dabrafenib and metabolites. There are currently no data on which to base a dosing recommendation in subjects with severe renal impairment or end-stage renal disease. Dabrafenib should be administered with caution in this setting.

Hepatic impairment
There are limited clinical data for dabrafenib in subjects with hepatic impairment. In a population pharmacokinetic analysis, dabrafenib oral clearance and thus exposure was not significantly different in subjects with mild hepatic impairment compared to subjects with normal hepatic function. There are no PK data in subjects with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined. In clinical studies, mild elevations in AST or ALT were observed in 9% and 13% of subjects, respectively, at baseline. Based on preclinical and *in vitro* studies, hepatic metabolism and biliary secretion are likely to be the primary route of elimination. Dabrafenib concentrations may be increased in subjects with moderate and severe hepatic impairment. Dosage adjustment may be required, particularly in subjects with severe hepatic impairment.

Cardiovascular effects
Data from preclinical studies with dabrafenib suggest the potential for cardiovascular effects, including cardiac valve effects in the 28 day dog study, coronary vascular effects in the 7 day dog study, hepatic vascular effects in a 10 day rat study, increased incidence of minimal cardiomyopathy in male rats and mild increases in heart rate in single dose studies in dogs and rats. In addition, preliminary histological assessment of hearts from a 13-week oral toxicity study in dogs with dabrafenib revealed treatment-related right atrial wall thickening characterized microscopically by fibrovascular proliferation (transmural granulation tissue) associated with the right atrium/appendage.

Dabrafenib clinical protocols did not exclude subjects with risk factors for or known atherosclerotic coronary artery disease if cardiac function was stable, thus these conditions were frequently present at study entry, consistent with the expected incidence in the general population. Subjects with clinically significant baseline cardiac abnormalities were excluded from the studies. In the Phase III study BREAK-3 in which subjects with unresectable BRAFV600E mutation-positive melanoma received either dabrafenib or dacarbazine (DTIC) chemotherapy, none of the individual cardiac AEs of potential concern including decreased LVEF, valvular abnormalities, conduction abnormailities, or myocardial effects was seen at a higher incidence relative to DTIC than expected, when viewed in context of the 3:1 randomization and the longer exposure of dabrafenib treated patients (4.9 vs 2.8 months). Therefore, the preclinical findings regarding potential cardiovascular AEs have not been confirmed by clinical data.

Reproductive effects
In embryofetal development 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. In pregnant rats given dabrafenib, dose-dependent reductions in ovarian corpora lutea have been observed. Animal studies with dabrafenib have shown embryofetal developmental toxicities, including teratogenic effects. Dabrafenib must not be administrated to pregnant women or nursing mothers. Female subjects of childbearing potential are required to use effective methods of contraception from the time of a negative serum pregnancy test within 14 days prior to the first dose of study medication, until 4 weeks after the last dose of study medication.

In dogs and in rats, testicular degeneration/depletion has been observed in repeat dose studies (up to 13 weeks duration) with no clear evidence of recovery following off treatment periods of up to 4 weeks duration. Spermatid retention was observed in mice in a 14 day study. Male subjects enrolled or in follow-up in clinical trials are informed of the potential risk for impaired spermatogenesis, which may be irreversible. Male subjects must agree to use one of the

contraception methods in clinical protocols from the time of first dose of study medication until 16 weeks after the last dose of study medication.

Respiratory effects

Lobar bronchoalveolar inflammation has been observed in dogs, with shallow and/or labored breathing noted during the treatment phase in 2 dogs given dabrafenib for 13 weeks. Respiratory changes are being monitored through medical history and physical examination. Clinical trial investigators will be requested to consider performing a lung CT scan for cases of clinically significant respiratory symptoms. Adverse events classified as respiratory, thoracic or mediastinal disorders have been reported in studies of dabrafenib in subjects both with and without pulmonary metastases.The majority of these events were low grade and a consistent relationship to treatment was not observed. No pattern of specific events was observed; all adverse events in the integrated safety population (ISP) occurred at a frequency of <1% with the exceptions of cough (11%), dyspnoea (5%), oropharyngeal pain and productive cough (1% each).

Overdose

There has been a single report of dabrafenib overdose in study BRF112680 in which the patient ingested 300 mg three times daily (TID) (900 mg cumulative daily dose) instead of the intended dose of 100 mg TID (300 mg cumulative daily dose), for a period of 49 days. The patient did not experience any known adverse events related to the study medication.

There was one additional subject in BRF112680 who mistakenly took 225mg BID of dabrafenib for 11 days (22 doses) along with trametinib 2mg from study day 58 through day 68; this event was identified as an overdose by the site. On study day 58 the subject reported AEs of grade 1 blurred vision, grade 1 increase in GGT and grade 2 increase in alkaline phosphatase. The event of blurred vision did not resolve, the increased GGT and alkaline phosphatase both resolved. Only the increased GGT was considered related to study treatment. On study day 73 the subject reported AEs of Grade 1 diarrhea and Grade 1 seasonal allergies; neither resolved, the diarrhea was considered related to study treatment. There were no vital signs, laboratory studies, or cardiac assessments obtained during the event of overdose. The subject discontinued treatment on study day 226 due to disease progression.

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg daily (the highest dose tested in clinical studies to date), the investigator should contact the overall PI of the study immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. Hemodialysis is not expected to enhance the elimination of dabrafenib as it is highly bound to plasma proteins. The investigator will use clinical judgment to treat any overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study PI based on the clinical evaluation of the subject.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

5.2.9 Adverse Events (AEs) Associated with Dabrafenib in Combination with Trametinib

Per the dabrafenib (Tafinlar®) prescribing information January 2014, the most common adverse reactions (≥20%) reported when the two therapies are used in combination are pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. Based on the safety summary in the June 2014 IB of the combination, of the 420 patients enrolled in MEK115306, the most common adverse reactions (≥20%) when the two therapies are used in combination are pyrexia, fatigue, headache, nausea, chills, arthralgia, diarrhea, rash, hypertension and vomiting. See sections 1.5, 11.8, and the Investigator Brochures for additional details.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessment	**Pre-Study[1]** (≤ 21 days except where noted)	**D1 Cycle 1**	**D1 Cycle 2** (+/- 3 days)	**D1 Cycle 3** (+/- 3 days)	**D1 Cycle 4** (+/- 3 days)	**D1 Cycle 5** (+/- 3 days)	**D1 Cycle 6** (+/- 3 days)	**D1 Cycle 7** (+/- 3 days)	**D1 Cycle 8** (+/- 3 days)	**D1 Cycle 9 and every other cycle[2]** (+/- 5 days)	**D1 Cycle 9, and every 4th cycle[2]** (+/- 5 days)	**Yrly[3]**	**End of Treatment** (+/- 7 days)[4]	**Follow –up[4]**
Informed Consent	X													
History, PE[5]	X	X	X	X	X	X	X	X	X	X			X	
Dermatologic exam	X			X		X		X		X [6]			X[6]	X[6]
Ophthalmic exam	X[3]											X[3]		
ECOG PS	X	X	X	X	X	X	X	X	X	X			X	
Pregnancy Test[7]	X	Only if clinically appropriate[7]												
Hematology, serum chemistries, and LFTs[8]	X	X[1]	X	X	X	X	X	X	X	X			X	
Coagulation studies[9]	X													
ECG	X			X		X					X			
ECHO	X			X		X					X			
Patient Diary		Review throughout study												
Concomitant Meds	X	Review throughout study											X[4]	
Toxicity Assessment[10]	X	Review throughout study[10]											X[4]	X[10]
Tumor measurement[11]	X			X		X		X		X[12]				
Brain Scan[11]	X	Only if clinically indicated												
Tumor biopsy[13]	X[13]	At time of or after progression[13]												
LCCC1108 enrollment[14]	X													
Blood Sample[15]		See footnote #15												
Survival Status														X

Key to Time and Events Table 6.1 Footnotes

[1]Radiological assessments, physical, dermatologic and ophthalmic exams, EKG and ECHO, as well as laboratory evaluations including hematology, serum chemistries, and LFTs may be performed up to 3 weeks prior to day 1 of treatment. Screening labs performed within 48 hours prior to Cycle 1 Day 1 do not need to be repeated on C1D1.

[2]Treatment cycles are defined as every 21 days; study site visits are every other cycle after cycle 9. The study window for cycle 9 and beyond is +/-5 days. **Please note:** patients may remain on treatment after progression (at the discretion of the investigator) as long as they are still experiencing clinical benefit (see section 4.1). Patients may continue on study and receive treatment for up to 3 years or death (whichever occurs first) with clinic visits and tumor evaluations as noted in table.

[3] [a] Repeat ophthalmic exams annually while on treatment and if clinically-indicated due to the presence of ocular symptoms. The exams will be performed one year after the day 1 cycle 8 visit +/- 2 months and every year thereafter until the patient is off treatment. See Appendix G (section 11.7) for Ophthalmic Exam Worksheet.

[4]The end of treatment visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of study medication. All adverse events and concomitant medications should be followed up until the 30-day End of Treatment (EOT) visit. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at the EOT will continue to be followed until the event is resolved or deemed irreversible by the investigator. See section 6.5 for follow-up schedule for patients who discontinue study treatment due to progression or for other reasons.

[5]Complete history at baseline only, thereafter focused history on symptoms/toxicity; physical exam to include height (baseline only), weight, and vital signs

[6]Dermatologic exams will continue every 3 months for the first 6 months following discontinuation from dabrafenib, and should include monitoring for cutaneous and non-cutaneous secondary/recurrent malignancies.

[7]Serum B-HCG within 48 hours prior to first dose of study medication for WOCBP; serum B-HCG will be repeated only if clinically appropriate.

[8]**Hematology**: CBC with differential, Hgb, and platelet count; **Serum chemistries**: creatinine, sodium, potassium, calcium, magnesium, phosphorus, LDH and albumin. **Liver function tests:** total bilirubin, AST (SGOT) and ALT (SGPT). Also see sections 4.4.9.3 and 11.4 4 for required monitoring in event of liver toxicities, including possibility of blood draw for pharmacokinetics. If screening evaluations of these tests are performed within 48 hours prior to Day 1 of treatment, they do not need to be repeated.

[9]Coagulation profile includes prothrombin time or INR, and activated partial thromboplastin time.

[10]Toxicity assessment should include interrogation of the patient related to any visual changes they may be experiencing. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[11]Tumor imaging should remain consistent throughout study, and will include contrasted computed tomography (CT) scan of chest, abdomen and pelvis. These tests may be performed within 7 days prior to the study visit. At screening, a scan of the brain is required; MRI unless contraindicated, in which case a CT scan with contrast may be substituted. Beyond screening, a scan of the brain is not required but should be repeated if clinically indicated. For patients removed from treatment for reasons other than disease progression, follow-up tumor assessments (if available) should be documented until PD is confirmed.

[12] The frequency of tumor assessment scans reduced to every 12 weeks for subjects responding to combination therapy after cycle 9

AND

For subjects responding to combination therapy for > 2 years, reduce the frequency of disease assessment scans to every 6 months.

[13]At baseline, if frozen tissue is unavailable from any site of disease, fresh tissue must be obtained. If possible, the pre-treatment biopsy should be performed after all other eligibility criteria are confirmed. Fresh tissue collection of accessible tumor will be repeated **at progression** whether patient continues treatment post progression or not. If possible, biopsies at progression should be performed within 7 business days of documented disease progression, and optimally within 4 hours of taking that day's study medication. If treating physician decides to continue treatment because the patient exhibits continued clinical benefit from therapy (and the patient agrees) then the biopsy can be delayed until the investigator deems the biopsy feasible as long as patient safety is not compromised. Post-treatment biopsies will not be required for patients removed for reasons other than disease progression. See section 6.7 and laboratory manual. Please also see the note in section 6.9.3 regarding assessment of biopsied lesions per RECIST v1.1. **NOTE**: For subjects who are withdrawn from study treatment, but are later placed back on the trametinib/dabrafenib combination therapy, a biopsy may be collected from the former study subject at the time of progression from the standard of care trametinib/dabrafenib therapy. These subjects must be re-consented and placed back on study to allow for attainment of a biopsy at progression. These subjects will then remain on study for safety monitoring, in relation to the biopsy procedure, for 30 days. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) related to the study procedure at 30 days will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[14]Document status of LCCC1108--if patients consent to co-enroll into LCCC1108, the Study Coordinator of LCCC1128 should coordinate tissue collection during biopsies with Study Coordinator of LCCC1108. See section 6.6 for additional information.

[15] For those patients who do and do not co-enroll into LCCC1108, we will ask for a blood sample (~8mLs) to ensure sufficient germline DNA in the event tissue samples are insufficient or request blood samples collected under LCCC9001 with IRB # 90-0573. . This request and collection may take place at any point during the study, including during follow-up.

6.2 Pre-Study Assessments

Please see section 6.7 regarding collection of a single blood sample at some point over course of study for germline DNA.

Clinical evaluation: complete history, physical examination (to also include vital signs, height, and weight), dermatologic exam (including full body skin exam), ophthalmic exam (See Appendix G (section 11.7) for Ophthalmic Exam Worksheet), and ECOG performance status.

Laboratory studies:

- **Pregnancy Test**: A serum pregnancy test (β-HCG) is required for all women of childbearing potential at screening within 48 hours prior to the first dose of study treatment. Note: Postmenopausal women must have had amenorrhea for ≥12 months in order to be considered "of non-childbearing potential." This should be documented appropriately in the patient's medical history.
- **Hematology**: Hematology includes the following parameters: complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count.
- **Coagulation Profile**: The coagulation profile includes prothrombin time or INR, and activated partial thromboplastin time.
- **Serum Chemistries and LFTs**: These include the following parameters: creatinine, sodium, potassium, calcium, magnesium, phosphorus, LDH, albumin, total bilirubin, AST (SGOT) and ALT (SGPT)

Cardiac monitoring: 12-lead ECG, ECHO (preferred) or MUGA

Concomitant medications: Documentation of all concomitant medications, and in particular any prohibited drugs and drugs to be used with caution as listed in the appendices (see section 11.2). **NOTE**: Patients will be given a list of medications that are prohibited and/or should be used with caution as a separate document. Patients will be informed that these drugs may interact with trametinib or dabrafenib, and may increase or decrease their toxicity.

Patient Diary: Patients will be provided diary (as separate document) and instructed to record the time and date of each dose of study medication. Diary will be reviewed during study visits. See Appendices, section 11.6, for a model diary.

Toxicity assessment: Using NCI CTCAEv4 for baseline documentation

Tissue acquisition: Sufficient frozen tissue remaining from diagnostic biopsy or willing to undergo biopsy for research purposes. See section 6.7 and laboratory manual.

Tumor measurement: Tumor measurement or imaging should remain consistent throughout study, and will include contrasted computed tomography (CT) scan of chest, abdomen and pelvis. These tests may be performed ±7 days of the scheduled day. At screening, an MRI of the brain is required.

Brain scan: At screening, a scan of the brain is required; MRI unless contraindicated, in which case a CT scan with contrast may be substituted.

6.3 Treatment Assessments

6.3.1 Day 1 of each 3-week cycle until cycle 9, and then D1 of every odd numbered cycle thereafter

Clinical evaluation: focused history, physical examination (to also include vital signs, and weight), and ECOG performance status.

Laboratory studies:

- **Hematology**: Hematology includes the following parameters: complete blood count (CBC) with differential, hemoglobin (Hgb), and platelet count.
- **Serum Chemistries and LFTs:** These include the following parameters: creatinine, sodium, potassium, calcium, magnesium, phosphorus, LDH, albumin, total bilirubin, AST (SGOT) and ALT (SGPT).

Concomitant medications: Review any additions or deletions
Patient Diary: Review Diary
Toxicity Assessment: Using NCI CTCAEv4; toxicity assessment should include interrogation of the patient related to any visual changes they may be experiencing.

6.3.2 Day 1 of every other 3-week cycle starting with Cycle 3 until end of treatment

Clinical evaluation: Dermatologic exam
Tumor measurement: Tumor measurement or imaging should remain consistent throughout study, and will include contrasted computed tomography (CT) scan of chest, abdomen and pelvis. These tests may be performed ±7 days of the scheduled day.

Note: The frequency of tumor assessment scans reduced to every 12 weeks for subjects responding to combination therapy after cycle 9; For subjects responding to combination therapy for > 2 years, the frequency of disease assessment scans should be reduced to every 6 months.

6.3.3 Day 1 of Cycles 3, 5, 9, 13 and every 4th cycle thereafter

Cardiac monitoring: 12-lead ECG and ECHO

6.3.4 At screening, annually and as clinically indicated

Ophthalmic exam (See Appendix G (section 11.7) for Ophthalmic Exam Worksheet). The exams will be performed one year after the day 1 cycle 8 visit +/- 2 months and every year thereafter until the patient is off treatment.

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6.4 Continued Treatment after Disease Progression

See section 6.8, correlative study procedures for more information.

6.5 End of Treatment

This visit should occur in patients when they permanently stop treatment for any reason, and should be performed 30 days (+/-7 days) after the last dose of study medication.

Clinical evaluation: complete history, physical examination (to also include vital signs and weight), and ECOG performance status.
Laboratory studies:

- **Hematology**: Hematology includes the following parameters: CBC with differential, Hgb, and platelet count.
- **Serum Chemistries**: These include the following parameters: creatinine, sodium, potassium, calcium, magnesium, phosphorus, albumin, total bilirubin, AST (SGOT) and ALT (SGPT).

Concomitant medications: Review any additions or deletions
Patient Diary: Review Diary
Toxicity Assessment: Using NCI CTCAEv4; Patients who have an ongoing grade 4 or serious AE (SAE) at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator, and will then be followed-up per protocol. Toxicity assessment should include interrogation of the patient related to any visual changes they may be experiencing.
Tissue acquisition: Biopsy of accessible tumor will be done in patients who stop treatment due to progression, if possible within 7 business days of documented disease progression, and optimally within 4 hours of taking that day's study medication. Post-treatment biopsies will not be required for patients removed for reasons other than disease progression. See section 6.7 and laboratory manual.

6.6 Follow-up Assessments

Patients who come off therapy due to progression will enter the follow-up phase every 3 months for up to 1 year from study entry to document survival (no tumor measurement per study protocol will be necessary after progression). Patients who come off therapy for reasons other than progression will enter the follow-up phase every 3 months for up to 1 year from study entry to document survival. If tumor assessments are available for patients who have not yet experienced progressive disease (PD), enter the follow-up tumor evaluations in the eCRF until PD is confirmed. Regardless, of the reason that a patient comes off treatment, dermatologic exams will continue every 3 months for the first 6 months following discontinuation from dabrafenib, and may be done by a physician local to the patient. Only after these dermatologic exams are complete is the patient considered off follow-up, even if they do not require survival follow-up for this entire 6 month period.

Patients who have an ongoing ≥Grade 2 AE or SAE at the time of discontinuation from treatment will continue to be followed in clinic until the event is resolved or deemed irreversible by the investigator.

For subjects who are withdrawn from study treatment, but are later placed back on the trametinib/dabrafenib combination therapy, a biopsy may be collected from the former study subject at the time of progression from the standard of care trametinib/dabrafenib therapy. These subjects will then remain on study for safety monitoring, in relation to the biopsy procedure, for 30 days. Subjects who have an ongoing ≥grade 2 or serious AE (SAE) related to the study procedure at 30 days will continue to be followed until the event is resolved or deemed irreversible by the investigator.

6.7 Correlative Study Procedures

For both those patients who do and do not co-enroll into LCCC1108, we will ask for a blood sample (~8mLs in a yellow-top ACD tube) to ensure sufficient germline DNA in the event tissue samples are insufficient. This request and collection may take place at any point during the study, including during follow-up.

At baseline, if patient does not have frozen tissue available, fresh tissue must be obtained by biopsy. Biopsy of tumor will be repeated at or after progression (clinical or radiological) whether patient continues treatment post progression or not. If possible, biopsies at progression should be performed within 7 business days of documented disease progression, and optimally within 4 hours of taking that day's study medication. Please note that drug may be extended post progression (see section 4.1), and there is no need to hold drug for any length of time prior to the biopsy. In fact, patients will be requested to remain on study medication until the biopsy at progression is performed. If the treating physician decides to continue treatment at progression because the patient exhibits continued clinical benefit from therapy, the biopsy may be delayed until the investigator deems the biopsy feasible as long as patient safety is not compromised Post-treatment biopsies will not be required for patients removed for reasons other than disease progression. See laboratory manual.

Note: For subjects who are withdrawn from study treatment, but are later placed back on the trametinib/dabrafenib combination therapy, a biopsy may be collected from the former study subject at the time of progression from the standard of care trametinib/dabrafenib therapy. These subjects must be re-consented and placed back on study to allow for attainment of a biopsy at progression.

Biopsies may be obtained by punch biopsy, core biopsy, or surgical excision, and may be performed by clinical personnel trained to do biopsies for standard of care collections. The number of - passes made through tumor per biopsy will be determined by the treating physician and the physician performing the biopsy procedure with primary consideration being safety. The tissue collected will be divided into aliquots (depending on size of collection, up to 4 aliquots per collection). For patients who co-enroll into LCCC1108 for NextGen sequencing, enough tissue will be collected for both kinomining and NextGen sequencing by

coordinating with the Study Coordinator of LCCC1108. When insufficient tissue samples are available to achieve both kinomining and NextGen sequencing, priority will be given to kinomining. Additional details regarding processing, storing and handling tissue will be provided in a separate laboratory manual.

Biological samples collected for the study will be stored at the research laboratories at the Lineberger Comprehensive Cancer Center (LCCC), University of North Carolina at Chapel Hill, NC until the completion of the study. With patient consent, any remaining tumor tissue after protocol specific studies are complete will be stored for future research concerning melanoma.

6.7.1 Biopsy Risks

The risks of these procedures are associated with a small risk of pain, bleeding, infection, and damage to adjacent organs. The magnitude of this risk depends somewhat upon the site of the procedure.

Potential risks according to site are:

Skin/chest wall (punch biopsy or surgical excision):
Likely: local discomfort and minor bleeding.
Less likely: moderate or major bleeding, or infection

Lymph node or soft tissue (punch biopsy or surgical excision):
Likely: local discomfort and minor bleeding.
Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, pneumothorax, damage to adjacent organs. Additional risks may be present if intravenous conscious sedation (IVCS) is required (see below).

Liver (core needle biopsy):
Likely: local discomfort and minor bleeding
Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, bowel perforation or damage to adjacent organs
Additional risks may be present if IVCS is required (see below).

Breast (core biopsy): punch biopsy or surgical excision
Likely: local discomfort and minor bleeding.
Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, pneumothorax, damage to adjacent organs.

In order to minimize the risk of a biopsy, only qualified personnel will perform these procedures. Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant, answer any questions, and obtain a separate procedure consent. For biopsies of lesions that are not superficial and clearly palpable, imaging studies such as CT or ultrasound will be

used to guide the biopsy in order to minimize the risk of damage to adjacent structures. Patients receiving therapeutic anticoagulation, and patients with abnormal coagulation studies, neutropenia, or thrombocytopenia will not undergo biopsy until and unless these resolve because of the increased risk of potential complications under these circumstances. After lymph node biopsies, patients will be observed for approximately 2 hours (range 2-4 hours) after the procedure, or per institutional standard guidelines. After liver biopsies, patients will be observed for approximately 4 hours (range 4-6 hours) after the procedure, or per institutional standard guidelines. Less than the goal quantity of tissue is acceptable for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

6.7.2 Risks of Anesthesia

Local Anesthesia

All biopsy procedures require local anesthesia using lidocaine or related compounds. There is a small risk of an allergic reaction associated with these drugs.

In order to minimize the risk of local anesthesia, only qualified personnel will perform the biopsy procedure. Patients will be queried if they have had previous allergic reactions to local anesthetics.

Intravenous Conscious Sedation (IVCS)

Certain biopsy procedures, such as lymph node or liver biopsies, may require IVCS. IVCS is a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously and respond appropriately to physical stimulation and verbal commands. The medications used to induce conscious sedation include the benzodiazepine midazolam and the opioid agonist fentanyl, as per standard of care. IVCS is performed once over a 30-60 minute period, and may require administration of multiple doses of each agent over this time-frame. Rarely, IVCS will last longer than 60 minutes.

Midazolam:

See http://www.drugs.com/pro/midazolam-injection.html for complete prescribing information on midazolam, including complete information on risks associated with its use.

The risks of midazolam include respiratory depression and respiratory arrest, especially when used for sedation in non-critical settings. Respiratory arrest could require intubation. In very rare cases, when this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Other serious cardiorespiratory adverse events have occurred after administration of midazolam, including airway obstruction, oxygen desaturation, apnea, and cardiac arrest, rarely resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment,

particularly in patients with hemodynamic instability. Agitation, involuntary movements, hyperactivity and combativeness have been reported in adults patients treated with midazolam.

Concomitant use of midazolam with other respiratory depressants like fentanyl may increase the risk of hypoventilation, airway obstruction, desaturation or apnea, and may contribute to profound and/or prolonged drug effect. Prolonged sedation may also be seen midazolam is administered concomitantly with drugs known to inhibit the P450 3A4 enzyme system such as cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole.

Adverse effects reported after intravenous administration of a single dose when used as a sedative include the following (percentage is percentage of adult patients with adverse events): hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), and drowsiness (1.2%). In addition, the following local effects at the site of the injection have been reported: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), and phlebitis (0.4%). Additional rare (<1.0%) adverse events occurring when midazolam is used as a sedative include:
Respiratory **(**laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea);
Cardiovascular (bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm);
Gastrointestinal (acid taste, excessive salivation, retching);
CNS/Neuromuscular (retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia);
Special Senses (blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness);
Integumentary (hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site);
Hypersensitivity (allergic reactions including anaphylactoid reactions, hives, rash, pruritus);
Miscellaneous (yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma)

Fentanyl
See http://www.drugs.com/pro/fentanyl-injection.html for complete prescribing information on fentanyl (Duragesic®), including complete information on risks associated with its use.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. Skeletal muscle movements in the extremities, neck and external eye have also been reported with fentanyl; rarely, these have been strong enough to pose patient management problems. Fentanyl may also produce euphoria, miosis, bradycardia and bronchoconstriction, as seen with other narcotic analgesics. The most common serious adverse reactions reported with fentanyl include respiratory depression, apnea, rigidity, and bradycardia. If these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm and diaphoresis.

The risks of IVCS also include inhibition of the gag reflex and concomitant risk of aspiration and allergic reactions to the sedative or analgesic medications. The chances of serious risks from IVCS are small but real; for example, in a prospective study of 14,149 patients undergoing IVCS during upper gastrointestinal endoscopies, the rate of immediate cardiopulmonary events was 2 in 1000. The 30-day mortality was 1 per 2,000 cases. In this study, there was a strong association between lack of monitoring and use of high-dose benzodiazepines with adverse outcomes. There was also an association between the use of local anesthetic sprays to the oropharynx and the development of pneumonia.

In order to minimize the risk of IVCS, only qualified personnel (M.D. and R.N) will be responsible for conscious sedation. A minimum of two individuals will be involved in the care of patients undergoing conscious sedation—the physician performing the biopsy procedure, and the individual (R.N.) who monitors the patients and his/her response to both the sedation and the procedure, and who is capable of assisting with any supportive or resuscitative measures. The room where the procedure utilizing IVCS takes place in the interventional radiology suite will have adequate equipment to provide supplemental oxygen, monitor vital signs, and maintain an airway should this be necessary. An emergency cart will also be immediately accessible to the room where the procedure is to take place, and emergency support services will be available on page. Patients will be screened and evaluated for their fitness to undergo conscious sedation by a trained physician. Patients with active cardiac disease are excluded from this study. No local anesthetic spray to the oropharynx will be necessary, given that endoscopy is not a planned procedure. Following the procedure, patients will be observed closely in the recovery room according to standard institutional guidelines.

Risks of Imaging Studies

Some biopsy procedures require imaging studies, either to plan or guide the procedure. Imaging studies that may be used in obtaining tissue samples include CT scans and ultrasound. CT scans will expose study participants to controlled amounts of radiation. The total dose of radiation from these tests is not anticipated to cause any adverse effects. There is also a risk of an allergic reaction to the intravenous contrast dye used during CT imaging, as well as a risk

of experiencing feelings of anxiety or claustrophobia while undergoing a CT scan. There are no anticipated risks with the use of ultrasound.

In order to minimize these risks, patients will be queried, as per standard institutional practice, regarding their history of reactions to intravenous contrast dye. If a patient has had such a reaction, she/he will be premedicated, or dye will not be used, as per standard institutional practice. If a patient has previously experienced anxiety or claustrophobia while undergoing a CT scan, she/he will be encouraged to discuss this with her primary oncologist. Anxiolytics may be considered by the patient's primary oncologist as indicated.

6.8 Assessment of Safety

Any patient who receives at least one dose of study medication on this protocol will be evaluable for toxicity, with toxicity evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 available at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

6.9 Assessment of Primary Endpoint and Efficacy

Provided sufficient tumor tissue is available pre and post treatment (specifically at progression) to perform kinomining, data from the patient will be utilized to inform the primary objective. If a patient drops out of the study prior to progression, they may be replaced. See section 4.9 for additional information. For subjects who are withdrawn from study treatment, but are later placed back on the trametinib/dabrafenib combination therapy, a biopsy may be collected from the former study subject at the time of progression from the standard of care trametinib/dabrafenib therapy. Information from these biopsies will be included in the analysis of the primary objective and the correlative secondary objective.

Patients who have received at least 2 cycles of therapy and have their disease re-evaluated after 2 cycles will be evaluable for assessment of objective response. Patients who drop out of the study prior to this point will not be evaluable for response unless their disease progressed prior to this point.

6.9.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- $\geq$10mm by CT scan (CT scan slice thickness no greater than 5 mm)

- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

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

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.9.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

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, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

6.9.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: Whenever possible, a biopsied lesion should not be considered a target lesion for RECIST tumor assessments. If the biopsied lesion is the only site of measurable disease, it may only be followed as a target lesion if a core biopsy was performed. Lesions that have been completely removed or subjected to excisional biopsy should not be followed as target lesions.

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) target or no must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline 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 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.9.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and 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.

6.9.5 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. The best overall response will be defined according to the following table.

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.
[2] NE=inevaluable

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.
- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).**NOTE**: bilirubin fractionation is 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. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.
- Any new primary cancers and treatment emergent malignancies (including squamous cell carcinoma and new primary melanoma) with the exception of basal cell carcinoma (BCC). BCC should be reported as an AE or SAE based on the discretion of the investigator.
- Symptomatic LVEF decrease that meets stopping criteria or asymptomatic LVEF decrease that does not recover, as outlined as LVEF guidance (Section4.4.3.3)
- Retinal pigment epithelial detachment (RPED) or retinal vein occlusion (RVO)

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

In addition to the above, cases of fever with rigors or fever with hypotension should be reported as SAEs (regardless of whether or not hospitalization was required).

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Electronic Case Report Forms (eCRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. For Affiliate sites, an email must also be sent to the NCCN Study Coordinator indicating that an SAE or Serious SAR has been entered into Oncore (email contact will be provided at study start-up).

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

The UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.
- For affiliate sites relying on the UNC-IRB, the UNC IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Novartis Reporting Requirements:

The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) ***(For patients taking Novartis drugs)***.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form), if applicable

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be reported by the investigator to the Novartis Oncology Drug Safety and Epidemiology Department (DS&E) by fax **(fax: 877-778-9739)**. Pregnancy follow-up should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

FDA Expedited Reporting requirements for studies conducted under an IND:
A sponsor must report any suspected adverse reaction that is both serious and unexpected and related to the cellular product to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the cellular product and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with cell infusion exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with cellular product exposure, but is otherwise uncommon in the population exposed to the cellular product (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of cellular product therapy) that indicates those events occur more frequently in the cell infusion treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on a MedWatch form. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. For this study, the review division is the Center for Drug Evaluation and Research. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing cell infusion under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process

If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form should be submitted on MedWatch by the study coordinator.

The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500a, and not form 3500).

The MedWatch form should also be sent to the UNC Regulatory Associate and the IND Specialist within 48 hours of the sponsor being aware of the event. The Regulatory Associate with the aid of the IND Specialist will submit the IND Safety Report via IND serial submission to the FDA review division.

Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the cell infusion.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the cell infusion, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity t or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as study coordinators, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of

patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size and Data Analysis Plans

Our sample size justification is based on the primary objective to identify kinases which are differentially expressed between pre (just prior to treatment initiation) and post treatment (patients who developed resistance) after treatment with BRAF+MEK inhibition in melanoma patients.

The kinases will be profiled using Multiplexed Inhibitor Beads (MIBs) coupled with mass spectrometry. We anticipate this technique to capture between 50 – 100 kinases in melanoma patients. The kinase activity is reported as a quant ratio between the experimental and control samples. The Paragon algorithm[10] automatically identifies high confidence peptides that will contribute to the average quant ratio of a kinase. Our sample size justification is based on our ability to detect a meaningful difference in the kinase activity between pre and post treatment. The inherent matching of tumor by patient source pre and post treatment will provide a potential source of positive correlation that may be exploited to improve statistical power (e.g., using a paired t-test). However, in order to be conservative, we compute our statistical power using a two-tailed independent Mann-Whitney test in which the kinase activity is compared in the two groups. Based on preliminary data, we assume that 100 kinases are captured, of which 10% of them are truly differentially expressed between pre and post treatment and a common standard deviation of 0.95 (in $\log_2$ scale).

Table 1 summarizes the power to detect a true difference of D with a sample size of 20 tumors in each group (pre and post treatment) at FDR of 0.05 to account for multiple testings. For example, we achieve a power of 0.92 to detect a $\log_2$ difference of 1.32 (or a fold change of 2.5) for each kinase between pre and post treatment.

Table 1: Power calculation to detect kinase difference

D=Difference in log2 scale	1.00	1.32	1.58	1.81
Fold change (2^D)	2	2.5	3	3.5
Power	0.59	0.92	0.99	1.00

Data Analysis Plans

Exploratory tools such as heatmaps and two-way unsupervised hierarchical clustering will be utilized as visual representation of overall kinome activity. The

univariate analysis of kinase expression will be carried out to identify differentially expressed kinases after FDR adjustment. Since multiple kinases work in concert to regulate their functions, prediction analysis of microarrays (PAM) based on nearest shrunken centroid [9] will also be carried out to identify a subset of kinases that predicts resistance to BRAF+MEK inhibition. We also plan to utilize the kinome pathway as prior information in the analysis for identifying functionally related kinase sets to improve statistical power. Focusing on kinase sets may yield more reproducible and interpretable results.

Fisher's exact test will be carried out to test for association between the mutations at baseline to mutations upon the development of resistance to BRAF + MEK inhibition in each oncogene/tumor suppressor gene. Tumor samples from patients who progress while on study and those who are removed from study and who later progress on the combination treatment will be analyzed as one data set. The p-values will be adjusted via FDR to account for multiple comparisons.

The response rate will be estimated and 95% confidence interval will be computed. Progression-free survival will be evaluated using the Kaplan-Meier method. All demographic and analytic data will be summarized by descriptive statistics. Categorical data will be summarized using frequency tables whereas summary statistics such as means, medians, standard deviation and range will be provided for continuous data.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Financial Disclosures
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, please contact the UNCCN Study Coordinator to ensure there is an opening available on the study for the potential subject (direct line 919-966-7359), Monday through Friday, 9:00AM-5:00PM. To register a patient, please fax registration forms and eligibility documents to 919-966-4300.

9.4 Data Management and Monitoring/Auditing

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center compliance committee every six to twelve months depending on Affiliate site participation.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

9.5.3 Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy. .Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected

- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Study Coordinator within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:
Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Study Coordinator. The UNCCN Study Coordinator will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must

assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 REFERENCES

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8. Infante JR, F.G., Lawrence JS et al., *Phase I/II study to assess safety, pharmacokinetics, and efficacy of the oral MEK 1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral BRAF inhibitor GSK2118436 (GSK436).* J Clin Oncol, 2011. **29**(suppl; abst CRA8503).
9. Chan M, H.L., Menzies A et al., *Clinical characteristics and survival of BRAF-mutant (BRAF+) metastatic melanoma patients (pts) treated with BRAF inhibitor (BRAFi) dabrafenib or vemurafenib beyond disease progression (PD).* J Clin Oncol, 2013. **31**(suppl): p. abstract 9062.
10. Shilov, I.V., et al., *The Paragon Algorithm, a next generation search engine that uses sequence temperature values and feature probabilities to identify peptides from tandem mass spectra.* Mol Cell Proteomics, 2007. **6**(9): p. 1638-55.

11.0 APPENDICES

11.1 Appendix A Grading of Visual Changes

Grade*	Description
1	Asymptomatic or symptomatic but not limiting activities of daily living (ADL); clinical or diagnostic observations only; intervention not indicated
2	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL; local or noninvasive intervention indicated (e.g., topical or oral agents)
3	Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200 in the affected eye); Severe pain or medically significant but not immediately sight-threatening; operative intervention indicated; disabling; limiting self-care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye
*based on NCI CTCAE v4	

11.2 Appendix B Prohibited Drugs, and Drugs to be used with Caution

11.2.1 PROHIBITED MEDICATIONS (also see section 4.5.1)

- Anti-retroviral drugs (e.g., ritonavir, saquinavir, atazanavir)
- All herbal supplements including but not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, or ginseng. Grapefruit juice must also be avoided.

OTHER PROHIBITED MEDICATIONS[1]	
Strong CYP2C8/3A/Pgp/Bcrp Inhibitor/Inducer	**Therapeutic Area**
clarithromycin, telithromycin, rifamycin class agents (e.g. rifampin, rifabutin, rifapentine), troleandomycin	Antibiotics
itraconazole, ketoconazole, posaconazole, voriconazole	Antifungals
nefazodone	Antidepressants
gemfibrozil	Hyperlipidemia
carbamazepine, oxcarbamazepine, phenobarbital, amiodarone, phenytoin, s-mephenytoin, bosentan, mibefradil, modafinil, conivaptan, topiramate	Miscellaneous
pioglitazone, troglitazone	Antidiabetics
cyclosporine	Immunosuppressive agents
[1]This list may be modified based on emerging data.	

11.2.2 MEDICATIONS TO BE USED WITH CAUTION (also see section 4.5.2)

USE WITH CAUTION: since concentrations of dabrafenib may be increased	
Class/Therapeutic Area	**Mild/Moderate CYP3A, CYP2C8, Pgp or BCRP Inhibitors**
Antiarrhythmics	Diltiazem, verapamil
Antibiotic	Erythromycin, trimethoprim
Antifungal	Fluconazole
Miscellaneous	Aprepitant, cimetidine, montelukast, glitazones, quercetin
USE WITH CAUTION: Co-administration of these drugs with study treatment may result in loss of efficacy. Monitor subjects for loss of efficacy or substitute with another medication.	
Class/Therapeutic Area	**CYP3A4, CYP2B6, CYP2C8, CYP2C9, or CYP2C19 Substrates that May be Affected by Induction**
Analgesics	Alfentanil, buprenorphine, celecoxib, codeine, fentanyl, methadone, oxycodone
Antiarrhythmics	Disopyramide, dronedarone, mexiletine, propafenone, quinidine
Antibiotics	Chloramphenicol, doxycycline, erythromycin, moxifloxacin
Anticoagulants/ Antiplatelets	Cilostazole, warfarin
Anticonvulsants	Divalproex, lamotrigine, valproate, zonisamide
Antidepressants and Antipsychotics	Aripiprazole, bupropion, buspirone, desipramine, haloperidol, mirtazapine, pimozide, quetiapine, trazodone, amitriptyline, clomipramine, imipramine
Antidiabetics	Glyburide, saxagliptin, tolbutamide, nateglinide, pioglitazone, repaglinide, rosiglitazone
Antifungals	Caspofungin, fluconazole, terbinafine
Antihistamines	Astemizole, chlorpheniramine, ebastine
Antihypertensives	Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nilvadipine, nisoldipine, nitrendipine, propanalol, verapamil
Antimigraine Agents	Cafergot, diergotamine, eletriptan, ergotamine
Corticosteroids	Dexamethasone, hydrocortisone, methylprednisolone, oral budesonide
Erectile Dysfunction Agents	Sildenafil, tadalafil, vardenafil
HMG-CoA Reductase Inhibitors	Atorvastatin, cerivastatin, lovastatin, simvastatin
Hypnotics and Sedatives	Alprazolam, brotizolam, diazepam, estazolam, midazolam, triazolam, zolpidem, zopiclone
Immunosuppressants	Everolimus, sirolimus, tacrolimus
Miscellaneous	Aprepitant, cisapride, chloraquine, darifenacin, dextromethorphan, domperidone, disopyramide, finasteride, leflunomide, methohexital, nateglinide, ondansetron, oral contraceptives, pimoide, quinine, ranitidine, risperidone, salmetrol, solifenacin, sulfasalazine, testosterone, torisel, tramadol, tolvaptan, zaleplon, ziprasidone,
Selective Aldosterone Blockers	Eplerenone
Abbreviations: BCRP = breast cancer resistance protein; CYP = cytochrome P450; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; Pgp = p-glycoprotein.	

11.3 Appendix C AEs of Special Interest in Study BRF113220

	Combination Therapy		Monotherapy		
	Dabrafenib + Trametinib		Trametinib	Dabrafenib	
	Part C	Pooled	ISS	ISS	Part C
Dabrafenib	150mg PO BID	150mg PO BID		150mg PO BID	150mg PO BID
Trametinib	2mg PO QD	2mg PO QD	2mg PO QD		
N	55	202	329	586	53
Trametinib category, n (%)	50 (91)	146 (72)	308 (94)	323 (55)	40 (75)
Skin-related toxicities	36 (65)	107 (53)	288 (88)	262 (45)	36 (68)
Diarrhea	20 (36)	54 (27)	162 (49)	91 (16)	15 (28)
Ocular events	14 (25)	40 (20)	42 (13)	46 (8)	8 (15)
Hepatic events	8 (15)	29 (14)	42 (13)	36 (6)	2 (4)
Cardiac-related events	5 (9)	15 (7)	31 (9)	13 (2)	0
Hypertension	5 (9)	16 (8)	48 (15)	11 (2)	2 (4)
Pneumonitis	0	0	6 (2)	0	0
Dabrafenib category, n (%)	46 (84)	138 (68)	63 (19)	287 (49)	28 (53)
Pyrexia	42 (76)	127 (63)	48 (15)	194 (33)	17 (32)
CuSCC	4(7)	12 (6)	1 (<1)	64 (11)	10 (19)
PPES	4 (7)	10 (5)	12 (4)	81 (14)	0
Renal failure	4 (7)	8 (4)	6 (2)	7 (1)	0
Other treatment emergent malignancies	1 (2)	3 (1)	1 (<1)	6 (1)	0
New primary malignant melanoma	0	1 (<1)	0	7 (1)	1 (2)
Uveitis	0	2 (<1)	0	6 (1)	0

11.4 Appendix D Liver Events

11.4.1 Liver Event Follow Up Assessments

For subjects meeting any of the liver chemistry criteria 1 – 5 listed in Section 4.4.8, 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
  - 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 10 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. 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. If a PK analysis is required in the event of liver toxicity, GSK should be contacted immediately and supplies and instructions for collection will be sent as soon as possible.
- 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 eCRF. Please note that treatment with trametinib often associates with rash which is usually acneiform and affects the scalp, face, neck, chest, and upper back. Discuss with study PI as needed.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake eCRF

- The following assessments 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, and Type 1 anti-liver kidney microsomal antibodies
    - Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

11.4.2 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Treatment

Approval by Study PI for study treatment restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Institutional Review Board approval of study treatment restart/rechallenge must be obtained.
- If the restart/rechallenge is approved by the IRB, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Subjects must then return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

11.4.3 Drug Restart Following Transient Resolving Liver Events Not Related to Study Treatment

Approval by study PI for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Institutional Review Board approval of study treatment restart/rechallenge must be obtained, as required.
- If restart of study treatment is approved by the IRB, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Subjects must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated, and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study treatment must be stopped.

11.5 Appendix E Supportive Care and Preventive Measures for Rash

Type of Care	Action

Prevention/Prophylaxis[a]	• Avoid unnecessary exposure to sunlight
	• Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily.
	• Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
	• Topical steroids and antibiotics should be applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest, and upper back.
	  • Use mild-strength topical steroid (hydrocortisone 1% cream)
	  or
	  • topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)

Symptomatic Care[b]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

Abbreviations: BID = twice daily; SPF = skin protection factor
a. Rash prophylaxis is recommended for the first 6 weeks of study treatment
b. Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

11.6 Appendix F: Model Patient Diary for Compliance*

NOTE: For dabrafenib, please revise model to account for twice daily dosing:

Patient ID: ____________ Institution: ____________

Assigned Dose (mg): __________ Number of tablets per dose: _______

While you are on study, please record the date and time you take your ________ for each dose, and the number of tablets taken at each dose. Please bring this diary to each appointment with your study doctor. You should take your daily dose at the same time each day.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:
# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:
# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:
# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:	# pills taken ___ Time:

Patient Signature:__________________________________

*This diary may be revised per institutional guidelines or standards.

11.7 Appendix G. Ophthalmic Exam Source Worksheet

Subject Name:_____

Note to examiner: Please assess particularly for visible retinal pathology.
*** Optical coherence tomography is highly recommended** For patients in whom retinal abnormalities are noted, **color fundus photos, and fluorescein angiography if clinically indicated, are recommended.**

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

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

Signature of Examiner: _____
Printed Name: _____ Date: _____

11.8 Appendix H AEs of Special Interest in Study MEK115306

AEs of Special Interest Category	Dabrafenib+Trametinib (n=209)			Dabrafenib + Placebo (n=211)		
	Maximum Grade			Maximum Grade		
Subjects with Any Event	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
Pyrexia	13(6)	0	116(56)	4(2)	0	65(31)
Skin-related toxicities	0	0	84 (40)	4(2)	0	98(46)
Diarrhea	2(<1)	0	51(24)	2(<1)	0	30(14)
Hypertension	8(4)	0	46(22)	10(5)	0	29(14)
Edema	2(<1)	0	37(18)	1(<1)	0	12(6)
Hemorrhages	2(<1)	1(<1)	35(17)	3(1)		27(13)
Hepatic Events	10(5)	0	28(13)	2(<1)		15(7)
Ocular Events	2(<1)	0	22(11)	0		23(11)
Neutropenia	8(4)	1(<1)	22(11)	1(<1)		4(2)
Hypersensitivity	0	0	12(6)	0	0	6(3)
Hyperglycemia	4(2)	0	13(6)	1(<1)	0	2(<1)
Cardiac Related Events	1(<1)	0	9(4)	1(<1)	0	7(3)
Renal Failure	2(<1)	0	7(3)	0	0	4(2)
cuSCC	4(2)	0	5(2)	7(3)	1(<1)	20(9)
Basal Cell Carcinoma	3(1)	0	4(2)	5(2)	0	8(4)
Pneumonitis	0	0	1(<1)	0	0	0
Non-Cutaneous Treatment emergent malignancies	1(<1)	0	2(<1)	2(<1)	0	3(1)
New Primary melanoma	1(<1)	0	1(<1)	0	0	3(1)
Pancreatitis	0	0	1(<1)	1(<1)	0	1(<1)
DVT and PE	2(<1)	1(<1)	4(2)	1(<1)	0	2(<1)