TITLE: A pilot study of Dabrafenib and Trametinib for patients with BRAF-mutated ameloblastoma

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PROTOCOL SYNOPSIS

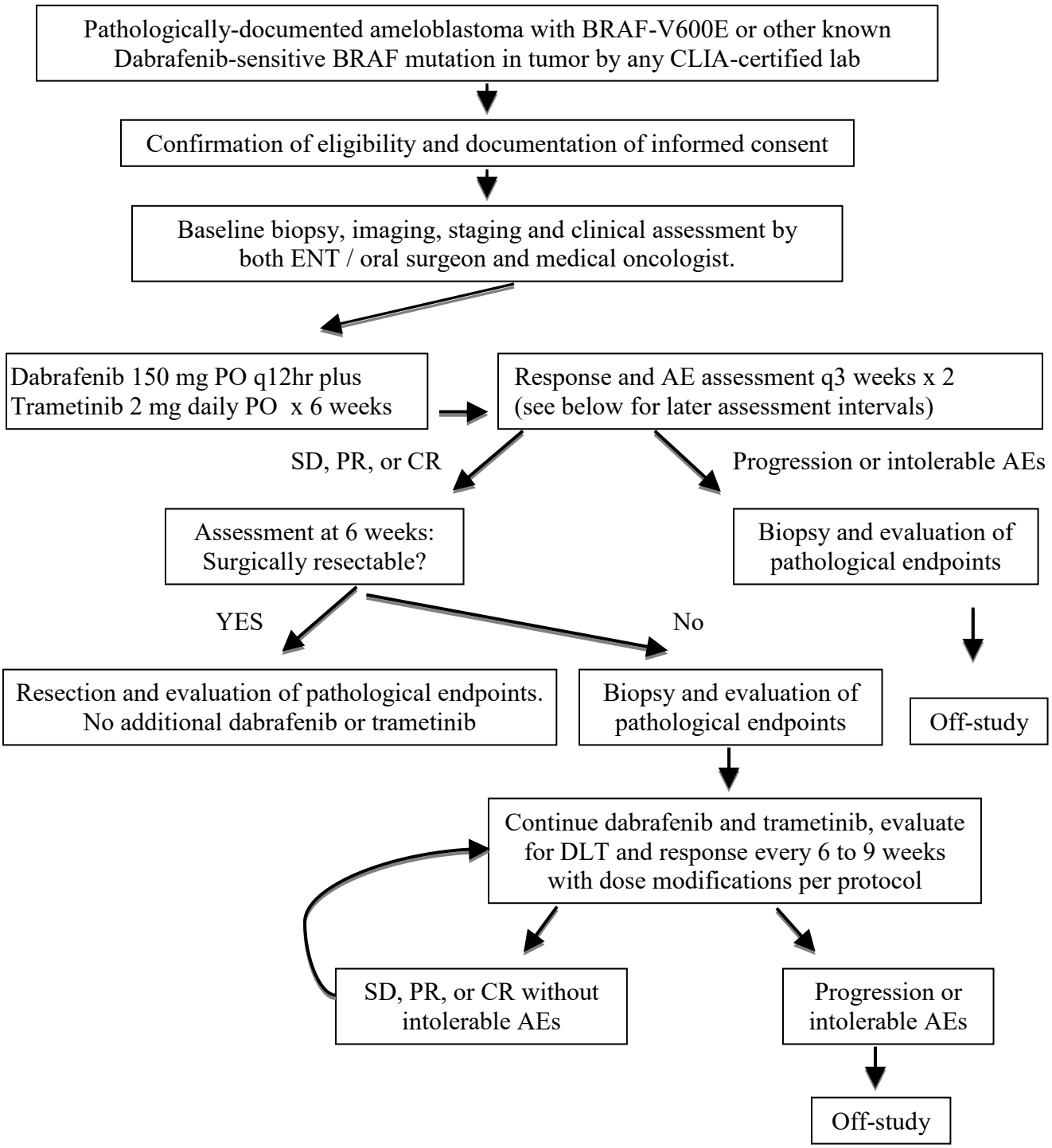
In the table below summarize the basic aspects of this research. This is to be used as a quick reference guide.

TITLE	A pilot study of Dabrafenib and Trametinib for patients with BRAF-mutated ameloblastoma
STUDY PHASE	Pilot
INDICATION	Ameloblastoma
INVESTIGATIONAL PRODUCT OR PROCEDURE	Dabrafenib and trametinib
PRIMARY OBJECTIVE(S)	Tumor response rate
SECONDARY OBJECTIVE(S)	Feasibility, safety, pathological response, evidence of molecular pathway inhibition
TREATMENT SUMMARY	Dabrafenib 150 mg po q 12 hours plus trametinib 2 mg once daily.
SAMPLE SIZE	17 evaluable patients
STATISTICAL CONSIDERATIONS	Simon Optimal 2 stage design

IRB application number: IRB-32275

By determination of the Principal Investigator and the IRB, this study is considered IND-Exempt.

SCHEMA


Pathologically-documented ameloblastoma with BRAF-V600E or other known Dabrafenib-sensitive BRAF mutation in tumor by any CLIA-certified lab
Confirmation of eligibility and documentation of informed consent
Baseline biopsy, imaging, staging and clinical assessment by both ENT / oral surgeon and medical oncologist.
Dabrafenib 150 mg PO q12hr plus Trametinib 2 mg daily PO x 6 weeks
Response and AE assessment q3 weeks x 2 (see below for later assessment intervals)
SD, PR, or CR
Progression or intolerable AEs
Assessment at 6 weeks: Surgically resectable?
Biopsy and evaluation of pathological endpoints
YES
No
Resection and evaluation of pathological endpoints. No additional dabrafenib or trametinib
Biopsy and evaluation of pathological endpoints
Off-study
Continue dabrafenib and trametinib, evaluate for DLT and response every 6 to 9 weeks with dose modifications per protocol
SD, PR, or CR without intolerable AEs
Progression or intolerable AEs
Off-study

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HTN	Hypertension
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell

1.0 OBJECTIVES

1.1 Primary Objectives

To observe the response rate of ameloblastoma to dabrafenib plus trametinib at 6 weeks.

1.2 Secondary Objectives

Secondary endpoints will include feasibility and safety in this patient population. Additionally, response will be assessed pathologically. Two main histologic assays for treatment response will be used: tumor necrosis and phosphorylated-MEK; phosphorylated-ERK; and Ki-67 levels as measured by immunohistochemistry.

2.0 BACKGROUND

2.1 Study Disease

Ameloblastoma is a rare, benign, slow-growing but locally-invasive neoplasm of odontogenic origin involving the mandible (80%) and maxilla with a high recurrence rate attributed to conservative treatment. The neoplasm was first described by Cusack in 1827. {Cusack, 1827} Etymologically, the name derives from the old French word "amel" which means enamel and the Greek word "blastos" meaning germ or bud. Over time, this tumor has been referred to by many different names including “cystosarcoma,” “adamantine epithelioma,” “adamantinoma,” and finally “ameloblastoma.” {Ivy, 1930; Malassez, 1885; Wedl, 1870; Brazis, 1995]

Ameloblastoma shows variable geographic prevalence, being the most common benign odontogenic tumor in China {Lu, 1998; Wu, 1985} and Africa {Anand, 1967; Mosadomi, 1975; Barnes, 2005}, while it is the second most common in the United States and Canada {Daley, 1994; Regezi, 1978} (odontoma being most common). Racial bias has also been observed, with African Americans at an overall five-fold increased risk of disease versus Caucasians. {Regezi, 1978} Global incidence has been estimated at 0.5 cases per million person years, with most cases diagnosed in the age range of 30 to 60 years. {Larsson, 1978}

Up to 80% of ameloblastoma cases occur in the mandible, with a particular predilection for the posterior mandibular region. {Reichart, 1995} Rare cases have been reported as primary to the sinonasal cavities. {Schafer, 1998} Often ameloblastoma can be associated with unerupted third molar teeth {Stanley, 1965; Gerzenshtein, 2006; Becelli, 2002} particularly in the unicystic type. Desmoplastic ameloblastomas often occur in the anterior or premolar regions of the mandible or maxilla. Ameloblastic carcinomas also favor the mandible (~2/3) over the maxilla. {Slootweg, 1984} Maxillary ameloblastomas also mostly occur in the posterior molar region.

Histopathologically, ameloblastoma resembles normal odontogenic/enamel epithelium and ectomesenchyme. Odontogenesis consists of chronographic and reciprocal interactions between the ectomesenchymal cells, which are derived from the neural crest, and the oral cavity lining epithelium. {Chai, 2000} The exact origin of ameloblastic epithelium has been hypothesized to arise from: (1) cells from the rests of enamel organ, (2) cells of the sheet of Hertwig’s or epithelial cell rest of Malassez, (3) epithelial boundary of an odontogenic cyst, particularly a dentigerous cyst, (4) basal cells of the oral mucosa, and (5)

heterotrophic epithelial from other parts of the body, perhaps pituitary. {Ritchie, 1990; Bhasker, 1981}

Until recently, little was known about the molecular aberrations driving ameloblastoma, due to the tumor's rarity and the fact that technologies to query the tumor genome do not work as efficiently in formalin-fixed paraffin-embedded tissue. However, in 2014, three separate reports, including one form our group at Stanford, profiling ameloblastoma via DNA sequencing were published, all showing the vast majority of tumors to contain somatic mutations impacting the mitogen-activated protein kinase (MAPK) signaling pathway (FGFR2-> RAS -> BRAF) that controls cell proliferation. {Kurppa, 2014; Sweeney, 2014; Brown, 2014}

In particular, all three studies reported a high frequency of BRAF-V600E (valine to glutamic acid substitution at amino acid 600) activating mutations at high allele frequencies in ameloblastomas. In each of these reports, the BRAF-mutated neoplasms were almost exclusively located in the mandible. Two of the three reports went on to characterize the sensitivity of BRAF-mutated ameloblastoma cells to vemurafenib, a V600E targeted small molecule inhibitor FDA-approved for metastatic melanoma. Both studies showed that AM-1, a mandibular-derived ameloblastoma cell line harboring the BRAF-V600E mutation, was exquisitely sensitive to vemurafenib at concentrations similar to BRAF-V600E mutated melanoma and colorectal cancer cell lines.

Surgery is the standard treatment for ameloblastomas. Historically, the extent of resection has been controversial, comprising of two surgical options: "conservative" *vs*. "radical". The former involves enucleation/curettage of the bony cavity, while the latter involves a radical operation with proper margins. Advantages of enucleation include the fact that it is an outpatient procedure able to be performed by many different service providers (Oral Surgeons and ENT), since it requires no reconstruction. Despite these facts, historical data on simple enucleation demonstrate recurrence rates 60 to 90% and this treatment modality is currently believed to play no role in the management of multicystic ameloblastomas.

The "radical" surgical option is the current standard of care for ameloblastoma, which includes enbloc resection with 1 to 2cm bone margins {Sham, 2009; Carlson, 2006; Gardner, 1980; Williams, 1993; Gortzak, 2006; Becelli, 2011; Pandya, 1972} and immediate bone reconstruction to help with speech and swallowing. {Sham, 2009; Vayvada, 2006; Tsai, 2006; Urken, 1991; Urken, 1998}

The bony margin is defined as the distance away from the radiographic margin predicted to be disease free and oncologically safe to perform osteotomies. Data from 82 ameloblastoma specimens showed microscopic tumor extension 2 to 8mm (mean of 4.5mm) beyond the radiographic boundaries of the tumor. {Carlson, 2006} Hence, the recommended bone margins are1 to 1.5cm for unicystic and 1.5 to 2cm for solid/multicystic histological types providing increased cure rates. {Wenig, 2007; Becelli, 2002; Carlson, 2006; Zwahlen, 2002; Ueno, 1989; Vayvada, 2006} Ameloblastic carcinoma requires 2 to 3cm bone margins with an elective neck dissection. {Ndukwe, 2010} Therefore surgery for ameloblastoma, when possible, tends to be radical and disfiguring.

Systemic chemotherapy has been attempted a number of times, with numerous agents and combinations being employed (see Table 1) {Gall, 1975; Eliasson, 1989; Ramadas, 1990;

Grunwald, 2001; Campbell, 2003; Amzerin, 2011; Van Dam, 2010}. Anecdotal reports have suggested that ameloblastoma may be sensitive to platinum based agents {Amzerin, 2011} although occasional reports highlight lengthy survival without chemotherapy. {Ciment, 2002; Hasim, 2007} Chemotherapy may also have a role in improvement of clinical symptoms in non-surgical patients. {Ciment, 2002} Much like radiotherapy though, only with continuous reporting of empirical case-based data will the role of systemic chemotherapy be evaluable in this rare entity.

Table 1: Anecdotal reports of Chemotherapy in Ameloblastoma

Case	Regimen	Response	Reference
1	Cyclophosphamide, Methotrexate, 5-Fluorouracil	None	Gall, *et al*, 1975
2	Vinblastine, Cisplatin, Bleomycin	PR	Eliasson, *et al*, 1989
3	Adriamycin, Cisplatin, Cyclophosphamide	PR	Ramadas, *et al*, 1990
4	1st line: 5-Fluorouracil and Cisplatin; 2nd line: Paclitaxel-Carboplatin	PR	Grünwald, *et al*, 2001
5	Cyclophosphamide	None	Campbell, *et al*, 2003
6	Doxorubicin and Cisplatin	PR	Amzerin, *et al*, 2011
7	Gemcitabine and Carboplatin	PR	Van Dam, *et al*, 2010

2.2 Study Agents

Dabrafenib is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC50 values of 0.65, 0.5, and 1.84 nM for BRAF-V600E, BRAF-V600K, and BRAF-V600D enzymes, respectively. It is manufactured in 50 and 75 mg capsules.

According to the FDA approved package insert, the safety of dabrafenib has been evaluated in 586 patients with BRAF-mutant melanoma, including 181 patients treated for at least 6 months and 86 additional patients for 12 months. The most commonly occurring adverse reactions in these patients treated with dabrafenib were, in order of decreasing frequency hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES). The most frequent adverse reactions leading to dose reduction of dabrafenib were pyrexia (9%); PPES (3%); chills (3%); fatigue (2%); and headache (2%).

Dabrafenib has been demonstrated to induce response rates of 52% with a duration median of 5.6 months, in patients with BRAF-mutant melanoma. There are presently no safety or efficacy data for dabrafenib in patients with BRAF-mutant ameloblastoma. Dabrafenib is not FDA approved for treatment of patients with ameloblastoma, therefore conduct of this study will be under either an IND or FDA authorized IND exemption.

Trametinib is a kinase inhibitor of MEK1 and MEK2 FDA-approved for use in patients with metastatic V600E mutated melanoma based upon a randomized control trial (RCT) of trametinib vs chemotherapy in which PFS (4.8 vs 1.5 mo) and RR (22% vs 8%) were

higher in patients treated with trametinib. {Flaherty, 2012} In January 2014, the combination of dabrafenib and trametinib was approved for the treatment of patients with BRAF-V600E mutant melanoma. This approval was based upon a RCT which demonstrated an improvement in survival in the combination (25.1 mo median OS) vs dabrafenib alone (18.7 mo median OS) with corresponding response rates of 69 vs 53% respectively. {Long, 2015} Treatment-related adverse events occurred in 181 (87%) of 209 patients in the dabrafenib and trametinib group and 189 (90%) of 211 patients in the dabrafenib only group; the most common was fever (108 patients, 52%) in the dabrafenib and trametinib group, and hyperkeratosis (70 patients, 33%) in the dabrafenib only group. Grade 3 or 4 adverse events occurred in 67 (32%) patients in the dabrafenib and trametinib group and 66 (31%) patients in the dabrafenib only group. Another RCT compared the combination of dabrafenib and trametinib vs vemurafenib, another TKI active against V600E mutant melanoma. {Robert, 2015} In that trial, the combination demonstrated improved PFS (11.4 vs 7.3 months), with similar AE and drug discontinuance rates.

Therefore, it appears that in melanoma with BRAF-V600E mutations, the combination is active and provides clinical benefit. More recently, this combination has also been shown to be active in other cancers with this BRAF mutation. {Williams, 2015; Brastianos, 2016; Escandell, 2015} Most relevant is a report of a dramatic response in a patient with BRAF-mutant ameloblastoma. {Kaye, 2015} Earlier this year we treated an ameloblastoma patient who declined major surgical resection off-label with single agent dabrafenib. After 2 months of treatment the patient decided to have the resection. We observed massive amounts of tumor necrosis in the specimen, a finding very atypical for untreated ameloblastoma (report accepted for publication, Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, 14 December 2015).

2.3 Rationale

Present accepted standard of care treatment for patients with ameloblastoma is limited to surgical resection and reconstruction. These operations for patients with advanced disease are morbid and disfiguring. There is no defined role for radiation or chemotherapy treatment for ameloblastoma patients at any stage.

Based on the recent discovery of potentially relevant BRAF mutations in ameloblastoma and preclinical data which suggest that BRAF-mutant ameloblastoma may respond to relevant mutant BRAF tyrosine kinase inhibition, we propose to ask in a pilot trial whether there is any evidence of anti- tumor activity against ameloblastoma in patients with advanced disease. Because of robust data with combined BRAF and MEK inhibition in BRAF-mutant melanoma, we plan to use dabrafenib and trametinib in combination. Novartis has agreed to supply both agents for this investigator-initiated study. Because most patients with advanced disease have significant mandibular bone involvement but do not have metastatic disease, we are proposing a trial which will focus on this group of patients. This allows us to ask in a preliminary way whether there is clinical, pathological, or microbiological evidence of anti-cancer activity of a relevant TKI, dabrafenib in combination with a MEK inhibitor, trametinib, in this situation. The design of the trial will facilitate collection of tissue at baseline and after 6 weeks of treatment to allow for assessment of the pathological and microbiological endpoints, but will also not unduly delay attempts at definitive surgical treatment for appropriate patients.

2.4 Study Design

This will be a single-group, single-arm, 2-stage, open non-randomized treatment study whose primary endpoint is tumor response rate with feasibility, safety, pathological and molecular biological secondary endpoints.

2.5 Correlative Studies Background

Activation of the Ras/Raf/MAPK signaling pathway begins with the binding of ligands to receptor-linked tyrosine kinases, such as epidermal growth factor receptor or fibroblast growth factor receptor. This leads to phosphorylation of tyrosine residues on the receptor that then recruits adaptor proteins (eg, GRB2 and SOS). This protein complex allows SOS to switch to an activated state that in turn leads to activation of Ras proteins by binding GTP. This turns on the activity of Raf serine/threonine kinases, including B-Raf (BRAF). The signaling transduction cascade then continues with the phosphorylation and activation of MEK1 and MEK2 tyrosine/threonine kinases. Through phosphorylation, the MEKs activate the Erk MAPKs which regulate transcriptional factors that influence differentiation, senescence, survival, and proliferation.

Mutations in the Ras/Raf/MAPK pathway are essential in a number of cancers including the majority of melanomas with ~50% exhibiting BRAF mutations and ~ 20% exhibiting NRAS mutations. In melanoma, these mutations appear at an early stage in tumorigenesis, including precursor lesions like benign nevi, and are preserved through progression. These are activating mutations which result in the Ras/Raf/MAPK pathway constitutively signaling for proliferation and survival. Inhibition of this pathway in tumors with BRAF mutations turns off this pathway and shuts down essential survival pathways resulting in cell death. BRAF inhibitor (dabrafenib; formerly GSK2118436) showed promising results with an approximately 2-fold increase in progression-free survival in a phase III trial, which is in a similar range as that of vemurafenib. {Hauschild, 2012}

Recent studies on ameloblastoma have found BRAF-V600E mutations to be present in the majority of cases arising in the mandible. Two studies have demonstrated that cell lines of ameloblastoma are responsive to V600E targeted small molecule inhibitors in cell proliferation assays.

Two main histologic assays for treatment response will be used: tumor necrosis and phosphorylated-MEK, phosphorylated-ERK, and Ki-67 levels as measured by immunohistochemistry. As mentioned above, since the activation of the Ras/Raf/MAPK pathway promotes cell proliferation and survival, blockade of this pathway will result in cell decrease in proliferation, death and necrosis. Furthermore, activation of the Ras/Raf/MAPK pathway leads to phosphorylation of several of the pathway components, including MEK and ERK. These assays for treatment response thus examine both early and late effects of Ras/Raf/MAPK pathway inhibition.

Routine Hemotoxylin-Eosin stained slides from both the pre-treatment biopsy as well as definitive resection specimens will be scored for the presence of tumor necrosis, which will be quantified. Additionally, unstained slides from both pre- and post- specimens from participating institutions will be sent to Stanford University for analysis of phospho-MEK/ERK and Ki-67 staining. Tumors will be scored, by at least two pathologists using percentage positive cells as the primary metric. The results of the

immunohistochemical analysis will be expressed as both raw data in addition to a ratio between pre- and post- treatment

We will also be consenting patients for permission to sequence the genome of their tumor, to publish in public databases anonymized sequence data and to attempt to establich cell cultures of tumor specimens if there is sufficient material to do so. These studies are exploratory and will only be done should there be sufficient specimen from the planned biopsies remaining after the tumor material for tumor necrosis and phosphorylation assays has been obtained.

3.0 PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

In order to reduce redundancy, we have incorporated the actual eligibility checklist into the body of the protocol.

3.1 Participant Eligibility Checklist

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note or a signed version of the eligibility checklist must be available in EPIC or other Electronic Medical Record for review.

Eligibility criteria in checklist form

I: Trial information

Protocol Title:	A pilot study of dabrafenib and trametinib for patients with BRAF-mutated ameloblastoma.
Protocol Number:	**IRB-32275 / ENT0043**
Principal Investigator:	A Dimitrios Colevas

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria	Yes	No	Supporting documents
1. Histological diagnosis of ameloblastoma. All stages are eligible. Patients must have evaluable disease by RECIST criteria	☐	☐	
2. BRAF-V600E or other known dabrafenib sensitive BRAF mutation in tumor by any CLIA-certified lab. May include, for example, Sanger sequencing, SNaPshot platform, immunohistochemistry, Foundation One tests, etc)	☐	☐	
3. At least 18 years old	☐	☐	
4. Life expectancy > 3 months	☐	☐	
5. ECOG performance status ≤ 2 (see Appendix C)	☐	☐	

6. *Lab values:* • *ANC > 1.5 x 10^9/L* • *PLT > 99 x 10^9/L* • *Hemoglobin > 8 g/dL* • *Tbili < 1.6 x ULN* o Except subjects with known Gilbert's syndrome • *AST, ALT and alk phos < 2.6 x upper limit of normal (ULN)* • *Serum creatinine ≤ 1.5 mg/dL, or if serum creatinine is > 1.5* mg/dL*, creatinine clearance must be ≥ 50 mL/min (*calculate creatinine clearance using the Cockcroft-Gault formula (see Appendix D). • *PR / INR and PTT ≤ 1.3 X ULN.* Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization	☐	☐	
7. Ability to understand and the willingness to sign a written informed consent document	☐	☐	
8. Patients of childbearing potential must agree to use effective contraception until at least 6 months after treatment with dabrafenib and trametinib. See exclusion criteria re pregnancy testing	☐	☐	
9. Able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels	☐	☐	
10. Left ventricular ejection fraction equal to or greater than normal within 1 month of enrollment. ECHO scans must be used throughout the study.	☐	☐	
Exclusion Criteria			
1. No prior treatment with agents targeting BRAF-mutant tyrosine kinases or MEK inhibitors or radiation of target lesions	☐	☐	

2. Invasive malignancy other than ameloblastoma within 3 years, excluding curatively treated basal cell carcinoma, and other highly curable cancers such as early stage cutaneous squamous cell carcinoma (T1 NO) cervical CIS, early stage prostate cancer, thyroid cancer, breast cancer or history of malignancy with confirmed activating RAS mutation at any time	☐	☐	
3. Uncontrolled hypertension (systolic blood pressure > 140 mm Hg and diastolic blood pressure of > 90 mm Hg which cannot be controlled by anti-hypertensive therapy), CHF, or other major medical illness.	☐	☐	
4. Prior allergic reactions attributed to compounds of similar chemical or biologic composition to dabrafenib or trametinib.	☐	☐	
5. Concomitant use of strong inhibitors (eg, ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 . For a full list of excluded drugs see Section 4.1.2 of the protocol	☐	☐	
6. Concomitant use of proton pump inhibitors, H2-receptor antagonists, antacids	☐	☐	
7. Known G6PD deficiency	☐	☐	
8. Pregnant or nursing patients. Women of childbearing potential must have a negative SERUM pregnancy test within 14 days of enrollment. Women of child-bearing potential must agree to use effective contraception for 14 days prior to enrollment, throughout the treatment period and for 4 to 6 months after the last dose of study treatment.	☐	☐	
9. EKG with QTcB (Bazett's formula) > 480 ms done within 14 days of enrollment	☐	☐	
10. Interstitial lung disease or pneumonitis.	☐	☐	
11. A history of retinal vein occlusion (RVO).	☐	☐	

12. Congestive heart fauilure NYHA Class III or worse (Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.)	☐	☐	
13. A history of acute coronary syndromes (including myocardial infarction or unstable angina), coronary angioplasty, or stenting within 6 months or a history or evidence of current clinically significant uncontrolled arrhythmias or intra-cardiac defibrillators or abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram. Subjects with Grade 1 abnormalities (ie, mild regurgitations/stenosis) may be entered. Subjects with moderate valvular thickening are not eligible. Subjects with atrial fibrillation controlled for > 30 days prior to dosing are eligible.	☐	☐	
14. Prior systemic anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy or investigational treatment within 3 weeks preceding first dose of study treatment, or chemotherapy without delayed toxicity within 2 weeks preceding first dose of study treatment.	☐	☐	
15. Any serious or unstable pre-existing medical conditions, psychiatric disorders or other conditions which could interfere with the subject's safety, obtaining informed consent, or compliance with study procedures.	☐	☐	
16. A history of Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection. Subjects with laboratory evidence of cleared HBV and/or HCV will be allowed.	☐	☐	

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

3.2 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.3 Study Timeline

Primary Completion:

We estimate the study will reach primary completion 27 months from the time the study opens to accrual.

Study Completion:

The study will reach study completion 36 months from the time the study opens to accrual.

4.0 TREATMENT PLAN

All patients will have a diagnosis of ameloblastoma pathologically confirmed by the participating institution's department of pathology. The mutational status of BRAF in the tumor must be determined by any CLIA-certified lab using standard techniques . These may include, for example, Sanger sequencing, SNaPshot platform, immunohistochemistry, Foundation One tests, etc.). While we are primarily expecting to identify V600 E mutations, other BRAF mutations known to confer sensitivity to dabrafenib are acceptable if approved by the study principal investigator.

Every patient must have baseline blood chemistries and counts and other eligibility criteria as defined in Section 3 done according to the schedule defined in the study calendar in Section 9. Baseline imaging used to define RECIST v1.1 {Eisenhauer, 2009} measurements are at the discretion of the local investigator. These will typically be either a contrast enhanced CT or MRI of the relevant anatomy, but PET-CT is also appropriate if the lesion is evaluable by PET-CT per RECIST v1.1 criteria. To maintain consistency of data and quality of science, whatever imaging modality is used at baseline for each patient should be used throughout the trial. Photographic documentation is encouraged but cannot substitute for imaging.

The starting dose for all patients will be:

Dabrafenib, 150 mg orally twice daily taken at least <u>1 hour before or at least 2 hours after a meal.</u> Dabrafenib comes as 75 mg and 50 mg capsules. Therefore the initial dose will be two 75 mg capsules as specified above. The second dose of dabrafenib (150 mg) should be administered approximately 12 hours after the morning dose.

Trametinib 2 mg once daily.

Take the once-daily dose of trametinib at approximately the same time each day with either the morning dose or the evening dose of dabrafenib. Study medications should be taken orally with approximately 200 mL of water under fasting conditions, **<u>either 1 hour before or 2 hours after a meal.</u>**

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

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

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

Patients whose tumors are amenable to surgical resection will continue dosing continuously for at least 6 weeks and proceed to surgery between weeks 6 and 7, without dose interruption. Patients undergoing surgical resection will continue dabrafenib and trametinib until it is necessary to take nothing by mouth in the hours preceding surgery, but **ideally the patients will be dosed with dabrafenib and trametinib within 12 hours of the surgical resection**. Patients whose tumors are grossly completely resected will not resume dabrafenib and trametinib. Patients whose tumors are not resected completely have the option to resume the dabrafenib and trametinib at the dose they were receiving immediately prior to surgery if ALL of the following criteria are met:

1. Prior to surgery the patient did not have AEs or progression which necessitated dabrafenib or trametinib cessation.
2. The patient has recovered from surgery without unexpected complication.
3. At least 1 week has passed since surgery.
4. The patient has evaluable residual tumor.
5. No more than 6 weeks has elapsed since surgery.

Patients whose disease is judged to be not amenable to resection will continue dabrafenib and trametinib indefinitely as long as there has not been tumor progression either by RECIST v1.1 or clinical progression criteria, there have not been unacceptable adverse events and the patient has not decided to discontinue for other reasons.

Clinical evaluations for protocol purposes will take place according to the schedule defined in Section 9. Dose modifications will be according to the guidelines in Section 6.

4.1 General Concomitant Medication and Supportive Care Guidelines

4.1.1 Permitted Medications and Non-Drug Therapies

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of investigational drug administration. Documentation of concomitant medication(s), including dietary supplements, taken during the study will be recorded in the patient medical record according to the schedule specified in Section 9. The minimum requirement is that drug name, dose, and the dates of administration are to be recorded.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional

guidelines. Use of anticoagulants such as **warfarin is permitted however, caution should be exercised** and additional International Normalized Ratio (INR) monitoring is recommended when dabrafenib is used concomitantly with warfarin. See Section 4.1.3 for guidelines concerning concomitant warfarin and dabrafenib administration.

Radiation skin injury has been reported with concurrent use of dabrafenib and radiation. It is recommended that dabrafenib and trametinib be held for 7 days before and 2 days after XRT.

Medicinal products that increase gastric pH should be used with caution when administered with dabrafenib. See Section 4.1.3 for details.

4.1.2 Prohibited Medications and Non-Drug Therapies

The use of certain medications (see Table 2 below) and illicit drugs within 28 days or 5 half-lives, whichever is shorter, prior to and during dabrafenib study treatment. will not be allowed.

The following medications or non-drug therapies are prohibited while on treatment in this study:

- Other anti-cancer therapies;
- Other investigational drugs;
- Herbal remedies (eg, St John's wort);
- Dabrafenib is metabolized primarily by Cytochrome P450 (CYP) 2C8 and CYP3A4. Co-administration of dabrafenib with ketoconazole, a CYP3A4 inhibitor, or with gemfibrozil, a CYP2C8 inhibitor, resulted in increases in dabrafenib AUC of 71% and 47%, respectively. Drugs that are strong inhibitors or inducers of CYP3A and CYP2C8 (see list in the table below) may only be used under special circumstances (e.g. as a single use for a procedure) while treatment with study drug is interrupted as they may alter dabrafenib concentrations; consider therapeutic substitutions for these medications. **Approval of the protocol principal investigator is required and must be documented in these situations**.

Table 2 : Prohibited Medications

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

4.1.3 Medications to be used with Caution

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

- Drugs that are moderate inhibitors or inducers of CYP3A and CYP2C8 as they may alter concentrations of dabrafenib.
- Dabrafenib has been shown to induce CYP3A4 and CYP2C9 in vivo using midazolam (CYP3A4 substrate) and S-warfarin (CYP2C9 substrate). Dabrafenib is an in vitro inducer of CYP2B6 and other enzymes such as CYP2C8, CYP2C19, UDP-glucuronyl transferases. Transporters may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes (including warfarin) and transporters may result in loss of efficacy. If co-administration of these medications is necessary, investigators should monitor subjects for loss of efficacy or consider substitutions of these medications. A partial list of these medications is provided in Table 2 above.
- Therapeutic level dosing of warfarin can be used with close monitoring of PT/INR by the site. Warfarin exposure has been shown to decrease (37% decrease) due to dabrafenib-mediated enzyme induction. Conversely, if dabrafenib dosing is reduced, interrupted, or discontinued, warfarin exposure may be increased. Thus, warfarin dosing may need to be adjusted based on PT/INR during and after treatment with dabrafenib. Prophylactic low dose warfarin may be given to maintain central catheter patency.

- InfromDabrafenib solubility is pH-dependent with decreased solubility at higher pH. Drugs such as proton pump inhibitors that inhibit gastric acid secretion to elevate gastric pH may decrease the solubility of dabrafenib and reduce its bioavailability. No clinical study has been conducted to evaluate the effect of pH on dabrafenib pharmacokinetics. In an ad-hoc analysis, no differences in C_{max} and AUC were noted between subjects who reported taking pH-elevating products relative to other subjects. Due to the theoretical risk that pH-elevating agents may decrease oral bioavailability and exposure to dabrafenib, these **medicinal products that increase gastric pH should be used with caution when administered with dabrafenib.**

4.2 Criteria for Removal from Study

Patients should have dabrafenib discontinued for unacceptable adverse events, clinically unacceptable or RECIST v1.1 defined progression, or patient withdraws of consent. For patients who stop dabrafenib because of unacceptable AEs or progression of disease, providers may proceed to surgical resection as clinically indicated. Patients who have not withdrawn consent to be studied should have all planned restaging and secondary tissues analyses performed per protocol prior to surgery and on the surgical specimens resected at the time of surgery. Patients should be followed for protocol related AEs for 4 weeks after the last dabrafenib dose unless another systemic anti- cancer agent has been initiated.

5.0 STUDY AGENT INFORMATION

5.1 Study Agents

Dabrafenib is a kinase inhibitor FDA approved for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. It comes in 50 mg and 75 mg capsules. Active ingredient: dabrafenib. Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose. Capsule shells contain: hypromellose, red iron oxide (E172), titanium dioxide (E171).

Trametinib is a FDA-approved kinase inhibitor for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E or -V600K mutations as detected by an FDA-approved test. Tablets are supplied as 0.5 mg and 2 mg tablets for oral administration. Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib non-solvated parent. Each 2 mg tablet contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated parent. The inactive ingredients are tablet core: mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal silicon dioxide; and coating: hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80 (2 mg tablets), iron oxide yellow (0.5 mg tablets), iron oxide red (2 mg tablets).

Dabrafenib and trametinib will be dosed as specified in Section 4 of this protocol, with dose modifications in Section 6.

5.2 Availability

Dabrafenib and trametinib will be obtained from Novartis and distributed to all investigational sites according to a pharmacy appendix to be developed prior to protocol activation.

5.3 Agent Ordering

Dabrafenib and trametinib will be ordered by site investigational pharmacies according to guidelines to be developed prior to protocol activation and included in the pharmacy appendix section.

5.4 Agent Accountability

Access to dabrafenib and trametinib will be restricted according to the standard operating procedures of the investigational pharmacies of each collaborating institution's pharmacy. Drug accountability will similarly be according to each institution's standard operating procedures.

5.5 Combination Dosage and Administration and Handling and Storage Guidelines

Dabrafenib and trametinib must be dispensed and administered in accordance with the protocol, and only to subjects enrolled in the study. Dabrafenib and trametinib must be stored in a secure area under the appropriate physical conditions for the product. Study medication is to be stored at the temperature specified on the label. Maintenance of a temperature log (manual or automated) is required. Access to and administration of dabrafenib and trametinib will be limited to the investigator and authorized site staff.

6.0 DOSE MODIFICATIONS

6.1 Dose Modification for General Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment and for which specific guidelines do not apply are provided in the table below. These guidelines are intended primarily for toxicities not easily managed with routine supportive care. For example, alopecia is not an indication for dose modification, nor is grade 2 nausea and vomiting that can be easily managed with anti-emetics.

Table 3: Recommended dabrafenib and trametinib dose level reductions

DABRAFENIB		TRAMETINIB	
Dose Level	**Dose/Schedule**	**Dose Level**	**Dose/Schedule**
Full dose	150 mg twice daily	Full dose	2 mg once daily
First reduction	100 mg twice daily	First reduction	1.5 mg once daily
Second reduction	75 mg twice daily	Second reduction	1 mg once daily
Third reduction	50 mg twice daily	Third reduction	0.5 mg once daily

Table 4: Dose Modification Guidelines - General

CTCAE Grade	Occurance	Action and Dose Modification [a,b]
Grade 1 or Grade 2 (tolerable)	N/A	Continue study treatment at same dose level (no dose modification) and monitor as clinically indicated
Grade 2 (Intolerable) or Grade 3	1st, 2nd or 3rd occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 then restart at next lower dose level
	4th or greater occurrence	Discontinue treatment
Grade 4	1st occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at next lower dose level or discontinue at discretion of investigator
	2nd occurrence	Interrupt study treatment until toxicity resolves to ≤ grade 1 or baseline then restart at two dose levels lower than the starting dose or discontinue at discretion of investigator and after discussion with the medical monitor.
	3rd occurrence	Discontinue treatment

a. Treatment should be discontinued if more than 3 dose reductions are required
b. Approval from the protocol PI is required to restart study treatment after ≥ 21 days

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered.

These are general guidelines and investigators should always use clinical judgment in determining dose adjustments for any individual patient. Some toxicities may require hospitalization for stabilization, additional work-up, and consultation with a specialist before treatment can be restarted. Specific adverse events and recommended management include the following:

6.2 Dose reductions for AEs of interest in patients taking dabrafenib and trametinib

6.2.1 Plantar- Palmar Erythrodysesthesia (Hand foot syndrome, PPES) – Measures for PPES should include:

Lifestyle modification: avoidance of hot water; traumatic activity; constrictive footwear; or excessive friction on the skin. Adopt the use of thick cotton socks and gloves, and shoes with padded insoles.

Symptomatic treatments: apply moisturizing creams frequently; topical keratolytics (eg, urea 20 to 40% cream; salicylic acid 6%; tazarotene 0.1% cream; fluorouracil 5% cream), clobetasol propionate 0.05% ointment for erythematous areas; topical lidocaine 2%; and/or systemic pain medication such as nonsteroidal anti-inflammatory drugs (NSAIDs); codeine; and pregabalin for pain.

Dose modification may also be required.

6.2.2 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.

6.2.3 Uveitis and ocular events (see below for specific guidelines)

Ophthalmological exams will be required at baseline, Week 6 and annually thereafter. Episodes of visual changes have been observed in subjects receiving trametinib, dabrafenib, and combination therapy. An ophthalmologist should be consulted if changes in vision develop. However, if the visual changes are clearly unrelated to study treatment (eg, 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. Special attention should be given to retinal findings (eg, retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (ie, branch or central retinal vein occlusions (RVO). Guidelines regarding management and dose reduction for visual changes and/or ophthalmic examination findings considered to be related to study treatment are provided in the below tables:

Table 5: Management and Dose Modification Guidelines for Visual Changes and/or Ophthalmologic Examination Findings

CTCAE Grade [a]	Adverse Event Management	Action and Dose Modification
Grade 1 [b]	• Consult ophthalmologist within 7 days of onset	• If dilated fundus examination cannot be performed within 7 days of onset, interrupt trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued • If RPED and RVO excluded, continue (or restart) trametinib at same dose level • If RPED suspected or diagnosed: see RPED dose modification table Y below; **report as SAE if diagnosed** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 2 and Grade 3	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued	• If RPED and RVO excluded, restart trametinib at same dose level • If RPED diagnosed, see RPED dose modification table below; **report as SAE** • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE**
Grade 4	• Consult ophthalmologist immediately • Interrupt trametinib. If subject is receiving trametinib/dabrafenib combination therapy dabrafenib may be continued	• If RPED and RVO excluded, may consider restarting trametinib at same or reduced dose after discussion with study medical monitor • **If RVO or RPED diagnosed, permanently discontinue trametinib and report as SAE**

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

Table 6: Recommended dose modifications for trametinib for retinal pigment epithelial detachments (RPED)

CTCAE Grade [a]	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib • Retinal evaluation monthly • If improved to ≤ Grade 1, restart trametinib at lower dose (reduced by 0.5 mg) or discontinue in patients taking trametinib 1 mg daily

e. Refers to CTCAE Version 4.0 'Retinopathy'

6.2.4 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.

Investigators should always err on the side of caution in these settings if treatment-related toxicity is a possibility.

6.2.5 Pyrexia

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. In a minority of cases the pyrexia was accompanied by symptoms such as severe chills; dehydration; hypotension; and dizziness or weakness.

Subjects should be instructed on the importance of immediately reporting febrile episodes. In the event of a fever, the subject should be instructed to take anti-pyretics (eg, ibuprofen or acetaminophen) as appropriate to control fever. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Monitor serum creatinine and other evidence of renal function during and following severe events of pyrexia.

Guidelines regarding management and dose modifications for pyrexia considered to be related to study treatment provided below.

Table 7: Management and Dose Modification Guidelines for Pyrexia

Adverse Event	Adverse Event Management	Action and Dose Modification
Pyrexia: [a]	All Events: • Clinical evaluation for infection and hypersensitivity [c] • Laboratory work-up [c] • Hydration as required [d] 1st Event [b]: • Administer anti-pyretic treatment as clinically indicated and initiate prophylactic treatment if associated with rigors, renal failure, dehydration or hypotension [e] 2nd Event [f] • Within 3 days of onset of pyrexia o Optimize anti-pyretic therapy o Consider oral corticosteroids (ie, prednisone 10 mg) for at least 5 days or as clinically indicated [f] Subsequent Events: • Within 3 days of onset of pyrexia: o Optimize oral corticosteroid dose as clinically indicated for recalcitrant pyrexia [f] o If corticosteroids have been tapered and pyrexia recurs, restart steroids o If corticosteroids cannot be tapered consult medical monitor	1st Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level [g]** 2nd Event: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib at the same dose level o If fever was associated with rigors, renal failure, dehydration or hypotension, **reduce dabrafenib by one dose level [g]** Subsequent Events: • **Interrupt dabrafenib** • Continue trametinib • Once pyrexia resolves to baseline, restart dabrafenib **reduced by one dose level [g]** • If dabrafenib must be reduced to < 50 mg BID, permanently **discontinue dabrafenib. Trametinib may be continued**

a. Pyrexia is defined as a body temperature equal to or above 38.5 Celsius or 101.3ºFahrenheit.
b. 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
c. Thorough clinical examination for signs and symptoms of infection or hypersensitivity is required; laboratory work-up should include full-blood-count, electrolytes, creatinine, blood urea nitrogen (BUN), C-reactive protein (CRP), liver-function tests, blood culture, and urine culture.
d. Oral hydration should be encouraged in subjects without evidence of dehydration. Intravenous hydration is recommended in subjects experiencing pyrexia complicated by dehydration/hypotension.
e. Anti-pyretic treatment may include acetaminophen, ibuprofen, or suitable anti-pyretic medication according to institutional standards. Prophylactic anti-pyretic treatment may be discontinued after three days in the absence of pyrexia
f. In subject experiencing pyrexia complicated by rigors, severe chills, etc., which cannot be controlled with anti-pyretic medication, oral corticosteroids should be started at the 2nd event and doses should be gradually increased for subsequent events.
g. 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.

6.2.6 Malignancies

Cutaneous squamous cell carcinoma (cuSCC)

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been observed in subjects treated with dabrafenib. Approximately 70 % of events occurred within the first 12 weeks of treatment with a median time to onset of 8 weeks. These should be surgically removed according to institutional practices. Dose modification or interruption of study treatment is not required for cuSCC or KA, however cuSCC should be reported as an SAE. In addition, a biopsy of the lesion should be taken, where possible, and a summary of the results submitted to the PI. Patients should be instructed to immediately inform their physician if new lesions develop. Skin examination should be performed prior to initiation of dabrafenib and during treatment with dabrafenib, every 2 months throughout therapy. Monitoring should continue every 2 months for 6 months following discontinuation of dabrafenib or until initiation of another anti-neoplastic therapy.

6.2.7 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.

6.2.8 Non-Cutaneous Malignancies

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling 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. A biopsy of the new malignancy should be taken, where possible, and submitted for further analyses with the results provided to the PI.

6.2.9 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 below.

Table 8: Management and Dose Modification Guidelines for Renal Insufficiency

Serum Creatinine Level	Adverse Event Management	Action and Dose Modification
Serum creatinine increase > 0.2 mg/dL (18 umol/L) but ≤ 0.5 mg/dL (44 umol/L) above baseline	• Recheck serum creatinine within 1 week • Serum creatinine increase > 1 week: contact Novartis Medical Monitor. If elevation persists beyond 4 weeks, recommend evaluation (consider renal biopsy) for etiology; consider nephrology consultation. • If pyrexia is present, treat pyrexia as per guidelines [a]	• Continue study treatment at the same dose level
Serum creatinine increase > 0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	• Monitor serum creatinine ≥ 2 times per week • Hospitalization may be necessary if serum creatinine cannot be monitored frequently • If pyrexia is present, treat pyrexia per guidelines [a] • Consult nephrologist if clinically indicated • Perform renal biopsy if clinically indicated, for example: o Renal insufficiency persists despite volume repletion o Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count)	• Interrupt study treatment until serum creatinine 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 Section

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.

6.2.10 Guidelines for Prolonged QTc

Guidelines for dose modification and stopping criteria due to QTC-prolongation are below.

Table 9: Withholding and Stopping Criteria for QTcB-Prolongation

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

Abbreviations: msec = milliseconds; QTc = QT interval on electrocardiogram

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

b. *If the QTc prolongation resolves to grade 1 or baseline, the subject may resume study treatment if the investigator and Novartis medical monitor agree that the subject will benefit from further treatment*

6.2.11 Guidelines 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, evaluated with imaging and functional tests. Dose modification and supportive care guidelines for pneumonitis are described below.

Table 10: Management and Dose Modification Guidelines for Pneumonitis

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended • Clinical evaluation and laboratory work-up for infection • Monitoring of oxygenation via pulse-oximetry recommended • Consultation of pulmonologist recommended	• Continue trametinib at current dose
Grade 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 BAL recommended • Symptomatic therapy including corticosteroids if clinically indicated	• Interrupt trametinib until recovery to grade ≤1 • Restart with trametinib reduced by one dose level • Escalation to previous dose level after 4 weeks and consultation with medical monitor possible • If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment
Grade 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 trametinib until recovery to grade ≤1 • After consultation with medical monitor, study treatment may be restarted reduced by one dose level • If no recovery to grade ≤1 within 4 weeks, permanently discontinue study treatment
Grade 4	• Same as grade 3	• Permanently discontinue trametinib

6.2.12 Guidelines for Cardiomyopathy

Across clinical trials of trametinib at the recommended dose 11% of patients developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF ≥ 10% below baseline) and 5% demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥ 20% below baseline.

Assess LVEF before initiation of trametinib, one month after initiation and then at 3-month intervals while on treatment. Withhold treatment if absolute LVEF value decreases by 10% from pre-treatment values and is less than the lower limit of normal. Permanently discontinue for symptomatic cardiomyopathy or persistent, asymptomatic LVEF dysfunction that does not resolve within 4 weeks

Table 11: Combination Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinic	LVEF-drop (%) or CTCAE grade	Action and Dose Modification

Asymptomatic	Absolute decrease of > 10% in LVEF compared to baseline and ejection fraction below the institution's LLN	• Interrupt trametinib and repeat ECHO within 2 weeks [a,b]
		• If the LVEF **recovers** within 4 weeks (defined as LVEF ≥ LLN and absolute decrease ≤ 10% compared to baseline)
		  • Consult with Novartis medical monitor and request approval for re-start
		  • If approved, re-start treatment with TMT reduced by one dose level
		• Repeat ECHO at 2, 4, 8, and 12 weeks after re-start, continue at intervals of 12 weeks
		• 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

Symptomatic [c]	Grade 3: resting LVEF 39 to 20% or > 20% absolute reduction from baseline Grade 4: resting LVEF < 20%	• **Permanently discontinue trametinib** • **Interrupt dabrafenib [d]** • **Report as SAE** • **Consult with cardiologist** • **Repeat ECHO after 2, 4, 8, 12, and 16 weeks, or until resolution [b,d]**

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction;

a. If ECHO does not show LVEF recovery after 2 weeks, repear ECHO two weeks later.
b. If recurrent episodes of LVEF reduction occur in subjets receiving DRB monotherapy, consult medical monitor.
c. Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.
d. Once LVEF recovers, including resolution of symptoms, restart of dabrafenib monotherapy only can be considered in consultation with Novartis medical monitor.

6.2.13 Treatment of Study Treatment Overdose

In the event of a dabrafenib overdose, defined as administration of more than 300 mg as a single dose or 600 mg per day (the highest dose tested in clinical studies to date), and/or a trametinib overdose, defined as administration of more than 3.0 mg once daily the investigator should closely monitor the subject for AEs/SAEs and laboratory abnormalities. The investigator will use clinical judgment to treat any overdose. Hemodialysis is not expected to enhance the elimination of either dabrafenib or trametinib as both are highly bound to plasma proteins.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the 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 case report forms.

7 ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1 Dabrafenib potential adverse effects

Please see the FDA package insert for dabrafenib. Additional information can also be found in the Investigator Brochure section titled "Summary of Data and Guidance for the Investigator." Below are tables from the 2015 package summarizing anticipated AEs:

Table 12: Selected Common Adverse Reactions Occurring in > 10% (All Grades) or ≥ 2% Grades 3 or 4) of Patients Treated with dabrafenib N = 187

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

[a] Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

[c] Includes skin papilloma and papilloma.

[d] cuSCC = cutaneous squamous cell carcinoma, includes squamous cell carcinoma of the skin and keratoacanthoma.

[e] Cases of cuSCC were required to be reported as Grade 3 per protocol.

[f] NA = not applicable.

Table 13: Incidence of Laboratory Abnormalities Increased from Baseline Occurring at a Higher Incidence in Patients Treated with dabrafenib (Tafinlar) in a single agent melanoma trial [Between-Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3 or 4)][a]

Test	TAFINLAR N = 187		DTIC N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6[b]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Adverse drug reactions, reported using MedDRA and graded using NCI CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in less than 10% of patients (N = 586) treated with TAFINLAR were:

Gastrointestinal Disorders: Pancreatitis

Immune System Disorders: Hypersensitivity manifesting as bullous rash

Renal and Urinary Disorders: Interstitial nephritis

Other clinically important adverse reactions observed in < 10% of patients (N = 586) treated with dabrafenib were:

- Gastrointestinal Disorders: Pancreatitis.
- Immune System Disorders: Hypersensitivity manifesting as bullous rash
- Renal and Urinary Disorders: Interstitial nephritis.

Table 14: Select Adverse Reactions Occurring in ≥10% (All Grades) of Patients Treated with dabrafenib(tafinlar) in Combination with Trametinib

Adverse Reactions	Pooled TAFINLAR plus Trametinib N = 559		Trial 2			
			TAFINLAR plus Trametinib N = 209		TAFINLAR N = 211	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General disorders and administrative site conditions						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Gastrointestinal disorders						
Constipation	13	0.2	13	0.5	10	0
Nervous system disorders						
Headache	30	0.9	33	0.5	30	1.4
Dizziness	11	0.2	14	0	7	0
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	25	0.9	26	0.9	31	0
Myalgia	15	0.2	13	0.5	13	0
Skin and subcutaneous tissue disorders						
Rash[c]	32	1.1	42	0	27	1.4
Dry skin	10	0	12	0	16	0
Respiratory, thoracic, and mediastinal disorders						
Cough	20	0	21	0	21	0
Infections and infestations						
Nasopharyngitis	12	0	12	0	10	0

[a] NCI CTCAE version 4

[b] Grade 4 adverse reactions limited to headache (n = 1).

[c] Includes rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, rash maculo-papular, and rash folliculitis.

Table 15: Select Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) of Patients Receiving dabrafenib (Tafinlar) in combination with trametinib.

Test	Pooled TAFINLAR plus Trametinib N = 559[a]		Trial 2			
			TAFINLAR plus Trametinib N = 209[b]		TAFINLAR N = 211[b]	
	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Liver Function Tests						
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypophosphatemia	38	6	38	3.8	35	7
Hyponatremia	25	8	24	6	14	2.9

[a] For these laboratory tests the denominator is 556.

[b] For these laboratory tests the denominator is 208 for the combination arm, 208-209 for the TAFINLAR arm.

[c] Grade 4 adverse reactions limited to hyperglycemia (n = 4), hyponatremia and hypophosphatemia (each n = 1), in the pooled combination arm; hyperglycemia (n = 1) in the Trial 2 combination arm; hypophosphatemia (n = 1) in the TAFINLAR arm.

7.1.2 Trametinib potential adverse effects

Please see the FDA package insert for trametinib. Additional information can also be found in the Investigator Brochure section titled "Summary of Data and Guidance for the Investigator". Below are tables from the 2015 package insert summarizing anticipated AEs

Table 16: Selected Adverse Reactions Occurring in ≥10% of Patients Receiving trametinib (Mekinist) and at a Higher Incidence (≥ 5%) than in the Chemotherapy Arm or ≥ 2% (Grades 3 or 4) Adverse Reactions

Adverse Reactions	MEKINIST N = 211		Chemotherapy N = 99	
	All Grades[a]	Grades 3 and 4[b]	All Grades[a]	Grades 3 and 4[b]
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Acneiform dermatitis	19	<1	1	0
Dry skin	11	0	0	0
Pruritus	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis[c]	15	2	2	0
Abdominal pain[d]	13	1	5	1
Vascular disorders				
Lymphedema[e]	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage[f]	13	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[b] Grade 4 adverse reactions limited to rash (n = 1) in trametinib arm and diarrhea (n = 1) in chemotherapy arm.
[c] Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.
[d] Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
[e] Includes lymphedema, edema, and peripheral edema.
[f] Includes epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage.

Other clinically important adverse reactions observed in less than or equal to 10% of patients (N = 329) treated with Mekinist (trametinib) were:
Cardiac Disorders: Bradycardia
Gastrointestinal Disorders: Dry mouth
Infections and Infestations: Folliculitis, rash pustular, cellulitis
Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis
Nervous System Disorders: Dizziness, dysgeusia
Ocular Disorders: Blurred vision, dry eye

Table 17: Percent-Patient Incidence of Laboratory Abnormalities Occurring at a Higher Incidence in Patients Treated With trametinib (Mekinist) in Trial 1 [Between Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3 or 4) [a]]

	MEKINIST N = 211		Chemotherapy N = 99	
Test	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Increased aspartate aminotransferase (AST)	60	2	16	1
Hypoalbuminemia	42	2	23	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

[a] No Grade 4 events were reported in either treatment arm.

Table 18: Incidence of Adverse Reactions Occurring in ≥10% (All Grades) of Patients Receiving trametinib (MEKINIST_ with Dabrafenib and at a Higher Incidence* than in Patients Receiving Single-Agent Dabrafenib

	Pooled MEKINIST plus Dabrafenib N = 559		Trial 2			
			MEKINIST plus Dabrafenib N =209		Dabrafenib N = 211	
Adverse Reactions	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General disorders and administrative site conditions						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Edema peripheral[b]	21	0.7	25	1.4	11	0.5
Gastrointestinal disorders						
Nausea	35	0.4	34	0.5	27	1.4
Diarrhea	31	1.3	30	1.4	16	0.9
Vomiting	27	1.1	25	1.0	14	0.5
Abdominal pain[c]	18	0.9	26	1.0	14	2.4
Nervous system disorders						
Dizziness	11	0.2	14	0	7	0
Vascular disorders						
Hypertension	26	11	25	6	16	6
Hemorrhage[d]	18	2.0	19	1.9	15	1.9
Skin and subcutaneous tissue disorders						
Rash[e]	32	1.1	42	0	27	1.4

* ≥5% for All Grades or ≥2% for Grades 3–4 incidence in patients receiving MEKINIST with dabrafenib compared with patients receiving dabrafenib as a single agent

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

[b] Includes peripheral edema, edema, lymphedema, localized edema , and generalized edema.

[c] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

[d] Most common events (≥1%) include epistaxis, hematochezia, decreased hemoglobin, purpura, and rectal hemorrhage. Grade 4 events were limited to hepatic hematoma and duodenal ulcer hemorrhage (each n = 1 in the pooled combination arm).

[e] Includes rash, generalized rash, pruritic rash, erythematous rash, papular rash, vesicular rash, macular rash, maculo-papular, and folliculitis rash.

Other clinically important adverse reactions for trametinib observed in less than 10% of patients receiving trametinib in combination with dabrafenib (N = 559) were:

Cardiac Disorders: Bradycardia

Musculoskeletal Disorders: Rhabdomyolysis

Table 19: Treatment-Emergent Laboratory Abnormalities Occurring at ≥ 10% (All Grades) of Patients Receiving trametinib (Mekinsit) with Dabrafenib and at a Higher Incidence* than in Patients Receiving Single-Agent Dabrafenib

	Pooled MEKINIST plus Dabrafenib N = 559[a]		MEKINIST plus Dabrafenib N = 209[b]		Dabrafenib N = 211[b]	
Test	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)	All Grades (%)	Grades 3 and 4[c] (%)
Hematology						
Neutropenia	46	7	50	6	16	1.9
Anemia	43	2.3	43	2.4	38	4.3
Lymphopenia	32	8	38	9	28	7
Thrombocytopenia	21	0.7	19	0.5	10	0.5
Liver Function Tests						
Increased AST	59	4.1	60	4.3	21	1.0
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Increased ALT	48	4.5	44	3.8	28	1.0
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypoalbuminemia	48	1.1	53	1.4	27	0
Hyponatremia	25	8	24	6	14	2.9

* ≥5% for All Grades or ≥2% for Grades 3–4 incidence in patients receiving MEKINIST with dabrafenib compared with patients receiving dabrafenib as a single agent

AST = Aspartate aminotransferase; ALT = Alanine aminotransferase.

[a] For these laboratory tests the denominator is 556.

[b] For these laboratory tests the denominator is 208 for the combination arm, 207-209 for the dabrafenib arm.

[c] Grade 4 adverse reactions limited to lymphopenia and hyperglycemia (each n = 4), increased ALT and increased AST (each n = 3), neutropenia (n = 2), and hyponatremia (n = 1), in the pooled combination arm; neutropenia, lymphopenia, increased ALT, increased AST, hyperglycemia (each n = 1) in the Trial 2 combination arm; neutropenia, thrombocytopenia, increased ALT, and increased AST (each n = 1) in the dabrafenib arm.

7.2 Adverse Event Reporting

For detailed guidance on reporting adverse events, refer to the adverse event SOP (Appendix B)

Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main 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.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE 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.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. 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 by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original 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, an 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 recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Adverse events will be graded according to CTCAE v4.03. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each

Adverse Event (AE) to determine whether it is unexpected according to Section 7.1 of the protocol and related to dabrafenib and trametinib.

SAEs and all subsequent follow-up reports will be reported to the CCTO Safety Office regardless of the event's relatedness to the investigation. Following review by the CCTO Safety Officers, any events meeting the IRB definition of "Unanticipated Problem" will be reported to the IRB using eProtocol within 10 working days of the review, or within 5 working days for deaths or life-threatening experiences. **SAEs will be relayed back to Novartis.**

7.2.1 SAE definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

7.3 Pregnancy

Pregnancy Testing and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (ie, physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy), bilateral tubal ligation or tubal occlusion, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, eg, 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).

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum β-human chorionic gonadotropin (HCG) pregnancy test performed within 14 days prior to randomization. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use an effective contraception method as described below throughout study treatment and until 4 months after the last dose of study treatment.

Novartis acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- 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 (eg, 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 (eg, 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.

If a subject becomes pregnant during the treatment period of the study, the study treatments should be stopped immediately.

8 CORRELATIVE/ SPECIAL STUDIES

8.1 Laboratory Correlative Studies

8.1.1 Collection of Specimen(s)

Biopsy specimens will be collected per normal institutional methods for biopsy and surgical resection procedures.

8.1.2 Handling of Specimens(s)

At the time of the baseline biopsy, endpoint biopsy, and/or resection specimen, the tissue will be handled and processed by routine tissue protocol at the pathology laboratory of the institution performing the procedure. Standard morphologic assessment of the tissue (including H&E stain) will be performed by the pathology laboratory of the institution performing the procedure with an emphasis to avoid decalcification of the tumor material, if possible.

8.1.3 Shipping of Specimen(s)

The archived biopsy or representative portions of the resection specimen, including formalin fixed paraffin embedded block and matching H&E slide, will be sent to the laboratory of Dr Robert West at the Site Performing Correlative Study (Stanford Cancer Institute) by overnight courier at room temperature. Once archived, the tissue is stable at room temperature.

8.1.4 Site(s) Performing Correlative Study

The Site Performing Correlative Study is the laboratory of Dr Robert West at the Stanford Cancer Institute at the Stanford University Medical Center. Dr West's laboratory will be responsible for all the correlative study tests.

8.1.5 Coding of specimens for privacy protection

The specimens will be coded at the time of receipt in the laboratory of Dr Robert West. The specimen will be given a 5-digit number with no relationship to the subjects' HIPPA data. The key for the coded specimens and the patient data will be kept by Dr Robert West in a locked office.

9 STUDY CALENDAR

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off-Study [d]
Dabrafenib		Dabrafenib will be administered twice daily as specified in Section 4 until surgical resection						FOR SUBJECTS **NOT** UNDERGOING SURGICAL RESECTION: dabrafenib will continue until disease progression or intolerance						
Trametinib		Trametinib will be administered daily as specified in Section 4 until surgical resection						FOR SUBJECTS **NOT** UNDERGOING SURGICAL RESECTION: trametinib will continue until disease progression or intolerance						
Informed consent	X													
Demographics	X													
Medical history	X													
Biopsy of tumor for correlative studies	X							X [g]						
Surgical resection for patients with resectable tumors, and tissue collection for correlative studies								X						
Concurrent meds	X	X						X [a]						
Physical exam	X			X			X			X [a]			X [a]	X
Vital signs	X			X			X			X [a]			X [a]	X
Height	X													
Weight	X													
Performance status	X													
CBC w/diff, plts	X			X			X			X [a]			X [a]	X
Serum chemistry [b]	X			X			X			X [a]			X [a]	X
EKG within 14 days of enrollment	X													
ECHO cardiogram within 1 month of enrollment	X			X									X [f]	

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off-Study [d]
Adverse event evaluation. See Section 7 for expected AEs and Section 6 for dose modification rules.	X			X			X			X [a]			X [a]	X [a]
Tumor measurements	X	Tumor measurements are repeated every 6 weeks. After Week 7, tumor measurements are repeated every 6 to 9 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X [d]
Radiologic evaluation (CT, MRI, X-ray)	X	Tumor measurements are repeated every 6 weeks. After Week 7, tumor measurements are repeated every 6 to 9 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X [d]
Serum Pregnancy testing within 14 days of enrollment	X													
Ophthalmologic examination. See Section 6 on guidelines for visual changes and exam source sheet in appendix	X						X [e]							

a: Only for patients continuing on dabrafenib and/ or trametinib who have not undergone surgery.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, AST, ALT, sodium.
d: Off-study evaluation.
e: Ophthalmologic exams to be repeated annually.
f: Every 3 months while on trametinib.
g. For subjects not undergoing surgical resection.

10 MEASUREMENTS

Primary Outcome Measure: Response rate according to RECIST v1.1 at 6 weeks

- RECIST v1.1 response rate, specifically, the sum of CR and PR per RECIST v1.1
- **Time Frame**: 6 weeks
- **Safety Issue:** Not a safety issue primary endpoint

10.1 Primary and Secondary Outcome measures

The primary endpoint will be tumor response rate (CR + PR) at 6 weeks. We intend to use modified RECIST v1.1 criteria {Eisenhauer, 2009}, knowing that since this patient population will include presurgical subjects, we will be unable to obtain response confirmation following the surgical resection of tumors. {Eisenhauer, 2009 #311}

10.1.1 Measurement Definition

The definition we will use for the primary endpoint of response will be per the RECIST v1.1 criteria, with the exception that for patients undergoing surgical resection there will be no confirmatory imaging as this would be irrelevant following surgical resection. CR, PR, SD, PR are all defined in the cited RECIST reference and are widely available and therefore will not be repeated here.

10.1.2 Measurement Methods

Standard CT or MRI scans and physical exam, per RECIST v1.1 criteria, will be used to measure tumors for purposes of response assessment. To maintain consistency of data and quality of science, whatever imaging modality is used at baseline for each patient should be used throughout the trial.

10.1.3 Measurement Time Points

Initial response evaluation for the primary endpoint will be at 6 weeks. For patients not undergoing surgical resection, follow-up imaging will be every 6 to 9 weeks, which we consider to be standard of care.

10.2 Secondary Outcome

10.2.1 Tumor necrosis

One secondary outcome will be percent of tumor necrosis at the time of endpoint biopsy or surgical resection. We intend to use this outcome with criteria established for treatment response in other tumors.

10.2.2 Measurement Definition

The definition we will use for the first secondary endpoint of response will be evaluation of extent of tumor necrosis by H&E slide review. This will be performed on either the endpoint biopsy or the resection specimen.

10.2.3 Measurement Methods

Routine H&E slide review will be used to measure extent of tumor necrosis for purposes of response assessment. Percentage of tumor necrosis by volume will be assessed as routinely done with other solid tumors such as osteosarcoma. The biopsy slide or multiple slides of the resection specimen will be examined and the volume of the necrosis compared to the volume of the total tumor will be determined by the centrally reviewing pathologists and percentage readouts of tumor necrosis, in increments of 10%, will be determined. In addition to measuring tumor necrosis the slide review will also estimate therapy effect on intact cells by estimating the percent cells with therapy-associated nuclear atypia.

10.2.4 Measurement Time Points

Tumor necrosis evaluation for this secondary endpoint will be at the time of the endpoint biopsy or the surgical resection.

10.2.5 Response Review

Tumor necrosis evaluation will be centralized review by the study co-investigator, Robert West, and at least one designee with substantial experience with tumor necrosis evaluation. Disagreements concerning response assessment between the PI and the second reviewer will be adjudicated by a board certified pathologist with tumor necrosis evaluation experience.

10.3 Secondary Outcome – Proliferation index

A second secondary outcome will be proliferation index as measured by Ki67 percent positivity at the time of endpoint biopsy or surgical resection. We intend to use this outcome as measured with immunohistochemistry with criteria established for assessment of proliferation index for other tumors.

10.3.1 Measurement Definition

The definition we will use for the second secondary endpoint of response will be evaluation of percent proliferation index by Ki67 immunohistochemistry. This will be performed on the initial pre-treatment biopsy and either the endpoint biopsy or the resection specimen.

10.3.2 Measurement Methods

Proliferation index evaluation will be performed in the laboratory of Dr. Robert West on the initial pre-treatment biopsy and either the endpoint biopsy or the resection specimen. Ki-67 immunohistochemistry will be scored by at least two pathologists using percentage positive cells as the primary metric. The results of the immunohistochemical analysis will be expressed as both raw data in addition to a ratio between pre- and post- treatment. All pathological evaluations will be done centrally by the pathology co- investigators, Robert West and Jonathan Pollack or their designees.

10.3.3 Measurement Time Points

Proliferation index evaluation for this secondary endpoint will be at the time of the endpoint biopsy or the surgical resection.

10.3.4 Response Review

Proliferation index evaluation will be centralized review by the study co-investigator, Robert West and Jonathan Pollack and at least one designee with substantial experience with proliferation index evaluation. Disagreements concerning response assessment between the PI and the second reviewer will be adjudicated by a board certified pathologist with proliferation index evaluation experience.

10.4 Secondary Outcome – Phosphorylation of MEK/ERK

A second secondary outcome will be expression of phosphorylation of MEK and ERK as measured by phospho-MEK/ERK positivity at the time of endpoint biopsy or surgical resection. We intend to use this outcome as measured with immunohistochemistry using antibodies specific for phospho-MEK/ERK and total MEK/ERK (either phosphorylated or

un-phosphorylated) with criteria established for assessment of protein expression by immunohistochemistry for other tumors.

10.4.1 Measurement Definition

The definition we will use for the second secondary endpoint of response will be evaluation of protein expression by immunohistochemistry. This will be performed on the initial pre-treatment biopsy and either the endpoint biopsy or the resection specimen.

10.4.2 Measurement Methods

Immunohistochemistry evaluation for MEK/ERK will be performed in the laboratory of Dr. Robert West on the initial pre-treatment biopsy and either the endpoint biopsy or the resection specimen. Immunohistochemistry will be scored by at least two pathologists using percentage positive cells and intensity of staining as the primary metrics. The results of the immunohistochemical analysis will be expressed as both raw data in addition to a ratio between pre- and post- treatment. All pathological evaluations will be done centrally by the pathology co- investigators, Robert West and Jonathan Pollack or their designees.

10.4.3 Measurement Time Points

Immunohistochemistry evaluation for MEK/ERK for this secondary endpoint will be at the time of the endpoint biopsy or the surgical resection.

10.4.4 Response Review

Immunohistochemistry evaluation for MEK/ERK will be centralized review by the study co-investigator, Robert West and Jonathan Pollack and at least one designee with substantial experience with protein expression evaluation. Disagreements concerning response assessment between the PI and the second reviewer will be adjudicated by a board certified pathologist with protein expression evaluation experience.

11 REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators. All participating sites will similarly have the informed consent document and protocol reviewed and approved by their local IRB and scientific review committee. There is to be only one version of the protocol to be used across all participating sites and no site can individually modify or amend the protocol at their site alone. That is, all protocol amendments and modifications must be reviewed and approved by all institutions' relevant review boards.

11.2 Data and Safety Monitoring Plan:

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may

include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRBs of all participating institutions and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

11.3.1 Data Collection

Data collection for this study will be via REDCap, a password protected HIPAA compliant web- based electronic data capture system. Prior to opening this study at any site, case report forms for the collection of all relevant required data will be developed and relevant site staff trained on the access and use of REDCap. Eligibility for each patient enrolled will be confirmed by the PI or designee centrally before authorization to enroll and patient number assignment is made via REDCap. The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. At each participating site, that site's PI or designee is responsible for collecting and storing in one central location copies of all primary clinical documents and be prepared to transmit these documents via secure electronic means for remote audit and review. All sites should also be able to readily access actual primary documentation, either electronically or in paper form, for on-site audit purposes.

11.3.2 Data Submission responsibility

It is the responsibility of each site PI to ensure that all investigators and designees at that site understand and are trained in all the relevant procedures for data collection and submission. For the purposes of site data submission compliance, data will be considered delinquent and such delinquency reported to that site's IRB if the data for any required routine evaluation is not submitted within 4 weeks after the relevant visit, test, or assessment has been completed or resulted.

11.3.3 Multicenter Guidelines

The overall PI is responsible for distribution of all IND action letters and safety reports to all participating institutions.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical Design and primary analysis

We propose a two stage Optimal design per Simon, *et al*. (Simon R ,1989. *Controlled Clinical Trials*. 10:1-10), and using the UNC calculator:

http://www.cscc.unc.edu/cscc/aivanova/SimonsTwoStageDesign.aspx

The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 9 evaluable patients will be accrued. If there is less than one response (defined in Section 10.1) in these 9 patients, the study will be stopped. If at the time of the 9th patient's enrollment there has not been at least one centrally documented response, accrual will stop until responses have been centrally determined for the first nine patients. Otherwise, 8 additional evaluable patients will be accrued for a total of

17 evaluable patients. The null hypothesis will be rejected if 3 or more responses are observed in 17 patients. We will allow for up to 11 patients in the first stage and up to 10 patients in the second stage to account for patient drop-out / uneavaluable patients. This design yields a type I error rate of 0.0466 and power of 0.8122 when the true response rate is 0.25. We believe that anything below a response rate of 25% would not be clinically meaningful given the potential risks of dabrafenib and trametinib. The likelihood of stopping early if the null hypothesis is true will be 0.63. A response rate of 25% or higher, in the context of other promising secondary endpoint results such as a high % of tumor necrosis, would warrant further study.

12.2 Secondary Analysis

We will determine secondary responses for: 1) tumor necrosis; 2) proliferation index; and 3) ERK/MEK phosphorylation. These assays will be exploratory and not subjected to a prospective statistical plan for analysis. Tumor necrosis % will be estimated according the standard surgical pathology techniques. Proliferation index will be measured by percentage of cells in mitosis and Ki 67 staining per standard surgical pathiology assays. The ratio of unphosphorylated to phosphorylated ERK and MEK will be done using standard phosphorylation specific antibodies on tumor tissue specimens in Dr West's lab according to his lab's SOPs. See Section 10 for details.

12.3 Sample Size

11 to 21 patients (9 to 17 evaluable pateints). See Section 12.1

12.4 Accrual estimates

We estimate 3 to 6 patients will be accrued among collaborating institutions annually. This is a very rare disease, incidence 0.5/ million estimated. Stanford sees and evaluates outside pathology on about 5 cases per year and our collaborating centers estimate about the same.

12.5 Feasibility and safety assessment

Because this is a very rare disease, our assumptions concerning the ability to accrue in a timely way are considerably uncertain. Therefore, at each annual review, should the accrual in the preceding year be less than 3 patients, we will re-evaluate the feasibility of conducting this protocol and either modify the protocol or close the protocol. Also as part of that annual review, if the cumulative rate of completion of 6 weeks of dabrafenib and trametinib treatment as specified in Section 4 is not achieved in at least 2/3 of all subjects , we will review the feasibility of administering treatment on this study and modify or close the protocol.

Safety data, collected as specified in the study calendar in section nine, will be summarized in tabular form using the CTCAE v4.03 for AE description and grading. Cumulative safety data and all SAE reports will be reviewed by investigators both annually and at the end of the first stage of accrual. Should less than 2/3 of patients enrolled at any of these annual reviews or first stage analysis not complete the protocol treatment as stipulated in this protocol, the protocol will either be amended to address these safety issues or the protocol will be closed to further accrual. High-grade AEs alone are not to be construed as an indication to stop accrual or amend the protocol as long as treatment of those AEs per standards of care and modifications per Section 6 allow for completion of treatment as specified in Section 4. Reporting of SAEs is covered in Section 7.2.

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Appendix A: Medication guide / Patient Information for patients:

Dabrafenib capsules

The current Medication Guide for Tafinlar (dabrafenib) dated November 2015 is attached to the eProtocol IRB-32275 application.

Trametinib Tablets

The current Patient Information for Mekinist (trametinib) is provided in the package insert dated November 2015, attached to the eProtocol IRB-32275 application.

Appendix B: Stanford Cancer Institute Standard Operating Procedures

Standard Operating Procedures (SOPs) for the Stanford Cancer Institute (SCI) pertaining to risks to subjects and safety reporting are available on the SCI Cancer Clinical Trials Office website (http://med.stanford.edu/ccto/services/regulatory.html).

Appendix C: ECOG performance status

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

Appendix D: Cockcroft-Gault formula:

CCr={((l 40–age) x weight)/(72xSCr)}x 0.85 (if female)

Appendix E: Ophthalmic exam source sheet

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 Subject name/ MRN:			
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 (eg, Humphrey 24-2 or 30-2 or equivalent if using a non-Humphrey instrument)			
Indicate normal or specify any abnormalities	OD:	OS:	
OPTICAL COHERENCE TOMOGRAPHY (strongly recommended)			
Indicate normal or specify any abnormalities	OD:	OS:	
COLOR FUNDUS PHOTOS (recommended if retinal abnormalities are noted)*			
Indicate normal or specify any abnormalities	OD:	OS:	
FLORESCEIN ANGIOGRAPHY (suggested if retinal abnormalities are noted and test clinically indicated)*			
Indicate normal or specify any abnormalities	OD:	OS:	
Were any of the following noted on ocular history or exam?		Yes	No
• History of CSR?			
• Evidence of new optic disc cupping?			
• Evidence of new visual field defects?			
EXCLUSION CRITERIA		Yes	No
• History of RVO? o *If yes, patient is not eligible for the study.*			

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