Date Submitted: 4/10/2018

Alert Page

DF/HCC Protocol #: 17-526

Safety / Drug (includes preparation, administration, dose modifications, equations)

SAE Reporting: Please include Deb Knoerzer (dknoerzer@biomed-valley.com), Dean Welsch (dwelsch@biomed-valley.com) and Mary Varerasian (mvasrterasian@gmail.com) on ALL emails that are sent to Clinipace (safety@clinipace.com) regarding SAEs. The DFCI SAE form should be used in this submission.

Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)

DF/HCC Protocol #: 17-526

TITLE: A Phase II study of BVD-523 in Metastatic Uveal Melanoma

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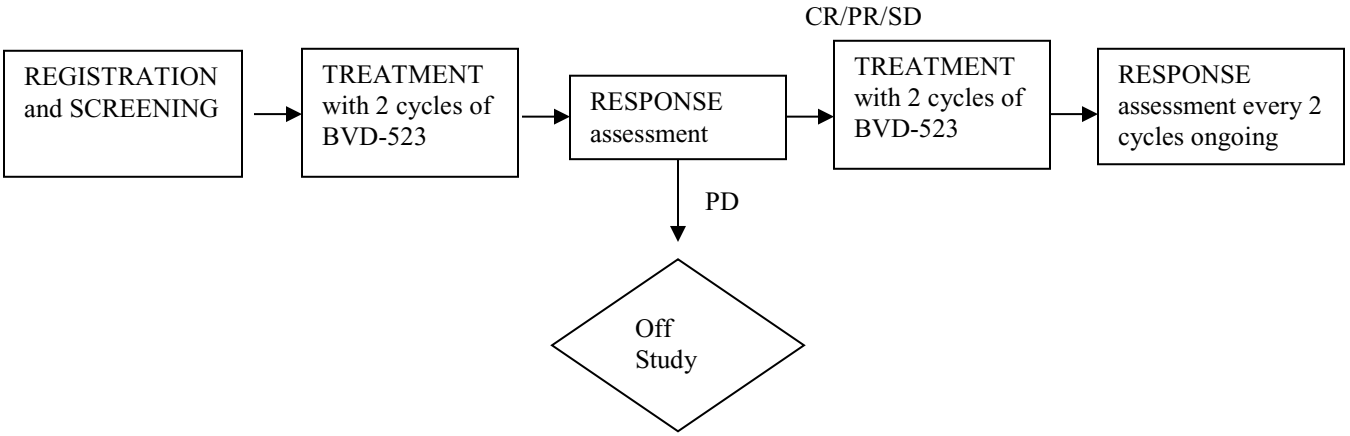
NCI-Supplied Agent(s): N/A
Other Agent(s): BVD-523 – BioMed Valley Discoveries, Inc.

IND #: 134771
IND Sponsor: DF/HCC Investigator Elizabeth Buchbinder, MD

Protocol Type / Version # / Version Date: Revised // 6 // January 23, 2019

SCHEMA


REGISTRATION and SCREENING
TREATMENT with 2 cycles of BVD-523
RESPONSE assessment
CR/PR/SD
TREATMENT with 2 cycles of BVD-523
RESPONSE assessment every 2 cycles ongoing
PD
Off Study

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OBJECTIVES

1.1 Study Design

A phase II trial of BVD-523 in patients with metastatic uveal melanoma. Patients will receive twice daily oral dosing of BVD-523 at the recommended phase II dose in 28-day treatment cycles until disease progression, unacceptable toxicity or other withdrawal criteria is met. Total enrollment for this phase II trial will be 13 or 25 patients.

1.2 Primary Objectives

1. To evaluate the overall response rate in uveal melanoma to ERK inhibitor therapy with BVD-523.

1.3 Secondary Objectives

1. To characterize the safety profile of ERK inhibitor therapy with BVD-523 when administered to adult patients with unresectable or metastatic uveal melanoma
2. To evaluate overall survival of patients with uveal melanoma treated with ERK inhibitor therapy with BVD-523.
3. To evaluate the pharmacodynamics of ERK inhibition on BVD-523 with a comparison of pre- and on-treatment biopsies.
4. To better understand the genetic variability of uveal melanoma through whole exome sequencing.

BACKGROUND

2.1 Study Disease(s)

In 2014 approximately 76,100 new cases of malignant melanoma were diagnosed in the United States.[1] While the majority of these arise from melanocytes of cutaneous origin, ocular melanomas comprise approximately 5% of all melanomas.[2] Uveal melanoma is a rare malignancy that arises from the iris, ciliary body or choroid of the eye. Ocular melanoma tumors may also arise in association with nevus of Ota.[3]

Management of uveal melanomas differs from that of cutaneous melanoma, as only inconsistent responses are seen to the therapies used most commonly for cutaneous melanoma, including ipilimumab, the anti-PD1 antibodies nivolumab and pembrolizumab, and chemotherapy. Despite the ability to achieve local control in the majority of patients, a quarter of patients will go on to die of metastatic disease.[4] The most common sight of initial metastasis is the liver due to hematogenous spread with an average survival of approximately one year after metastatic disease is diagnosed.[5]

Since uveal melanomas respond poorly to chemotherapy and immunotherapy no effective treatment options exist for this group of patients who develop metastatic disease. Most patients

with metastatic disease are considered for Phase I clinical trials as first line therapy. Unlike cutaneous melanoma, BRAF mutations are rarely (if ever) observed in uveal melanoma. However, greater than 80% of uveal melanomas have activating mutations in GNAQ or GNA11, genes that encode for G protein alpha subunits.[6-8] GNAQ and GNA11 mutations lead to downstream signaling through the MAPK pathway.

2.2 IND Agent

BVD-523 is a small molecule that potently inhibits both ERK1 and ERK2 protein kinases in the sub-nanomolar range, while not significantly inhibiting any of an array of kinases even at 1000-fold greater concentrations. BVD-523 potently inhibits growth and survival in cultured cancer cell lines; melanoma, colorectal and pancreatic lines harboring BRAF or RAS mutations are among those most susceptible to the drug. In animals bearing ectopic tumor xenografts, orally administered BVD-523 is effective as a single agent, again preferentially in cancers where activating mutations in the MAPK pathway cause abundant ERK kinase activation.

A phase I study of BVD-523 in patients with advanced malignancies (BVD-523-01) is currently ongoing and has demonstrated activity in patients with BRAF/MEK-inhibitor refractory, BRAF-mutant melanoma as well as in patients with NRAS-mutant melanoma. The dose-escalation phase of this study has been completed and the study has moved into a cohort-expansion part 2. This dose-escalation phase included dose levels ranging from 10 to 900 mg b.i.d. Single-patient cohorts were completed for dose levels of 10 mg, 20 mg, 40 mg, 75 mg, and 150 mg b.i.d. Subsequent cohorts included 4 patients (300 mg b.i.d.), 7 patients (600 mg b.i.d), 4 patients (750 mg b.i.d), and 7 patients (900 mg b.i.d.). Intra-patient dose escalation was permitted once the next higher dose had been declared tolerable; this occurred in 5 patients, including 4 patients who dose-escalated more than one time. The total duration of exposure has ranged from 23 to 804 days; the median duration of exposure to date is 93.0 days. The patient population in Part 1 included 14 males (52%) and 13 females (48%), ranging in age from 32 to 84 years old (mean age 59.7 years), diagnosed with a range of advanced solid tumors. In Part 1, the MTD and RP2D were determined to be 600 mg b.i.d., and this is the dose that is being tested in the cohort-expansion phase (Part 2) of the study. Two patients remained active on Part 1 study as of the cut-off date of 16th January 2016 and 48 patients have been enrolled and treated in Part 2 of Study BVD-523-01 which expands the 600 mg b. i. d. cohort to 7 groups of cancer patients with various BRAF, NRAS, MEK, and ERK mutations.

A second phase I study of BVD-523 in participants with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) also reached a MTD and RP2D of 600 mg b. i. d. The dose-escalation phase (Part 1) of this second study, BVD-523-02 has been completed, with 18 patients having been enrolled in this part of the study. This dose-escalation phase included dose levels ranging from 300 to 750 mg b.i.d. Cohorts evaluated included 5 patients (300 mg b.i.d.), 6 patients (600 mg b.i.d.), and 7 patients (750 mg b.i.d.). As of 16th January 2016, 3 patients (2 female, 1 male; age range 48 to 77 years old) have been enrolled into the cohort-expansion phase (Part 2) of Study BVD-523-02. As in Part 1, patients in Part 2 are required to have AML or MDS and are receiving BVD-523 at the dose of 600mg b. i. d. determined in Part 1.

BVD-523 will be administered at the RP2D of 600mg twice daily in 28 day cycles. The HCl salt of BVD-523 was selected for manufacture of drug product in capsule form.

More information is available in the Investigator's Brochure for BVD-523.

2.3 Rationale

The mitogen-activated protein kinase, or MAPK, pathway is a cell growth control pathway frequently aberrantly activated in malignancy. Surface receptors signal through RAS family GTPases to RAF family protein kinases, MEK and subsequently ERK family kinases. ERK kinases activate an array of effectors which lead to cell division and survival.[9] Many different components of the MAPK pathway can be mutated in cancer leading to activation of the pathway including members of the RAS family GTPase (KRAS, NRAS, and HRAS) and BRAF which is seen in over 50% of patients with advanced melanoma.[10, 11] Targeting the MAPK pathway has demonstrated efficacy in patients with mutations leading to increased MAPK signaling. Specifically there has been efficacy targeting BRAF in melanoma patients with a BRAF mutation[12] and even more efficacy when BRAF and MEK are targeted simultaneously.[13, 14]

Uveal melanomas have a high rate of activating mutations in GNAQ or GNA11 leading to downstream signaling through the MAPK pathway[6-8] This has led to therapeutic targeting of the MAPK pathway with MEK inhibition in patients with uveal melanoma. In a randomized phase II trial, 99 patients were randomized to receive the MEK inhibitor selumetinib or chemotherapy (investigator's choice of dacarbazine or temozolomide). Treatment with selumetinib was associated with a PFS of 15.9 versus 7 weeks with chemotherapy, and objective response rates of 14% and 0%, respectively.[15] Analysis of patients treated on this study supported a MAPK dependence which was reflected in MEK-Dependent gene expression changes in response to therapy.[16]

The ERK family kinases are MAPK signaling components downstream of MEK that have yet to be targeted in clinical practice, and ERK activation in Uveal melanoma has been observed in relation to GNAQ and GNA11 mutations. [6, 7] In addition ERK inhibition has been seen to overcome acquired resistance to MEK inhibitors in preclinical studies.[17] BVD-523 is a small – molecule inhibitor of ERK kinase currently in Phase I testing that has demonstrated activity in patients with BRAF/MEK-inhibitor refractory, BRAF-mutant melanoma as well as in a patient with NRAS mutant melanoma. Given the role of the MAPK pathway on development and growth of uveal melanoma and the initial activity in other MAPK dependent melanoma settings, there is a high probability that BVD-523 would have efficacy in this disease.

2.4 Correlative Studies Background

In order to evaluate the pharmacodynamics of ERK inhibition with BVD-523 we will obtain tissue samples from patients prior to enrollment and after approximately 15 days on treatment. These biopsies will be assessed by western blotting, to look at levels of ERK targets including DUSP, cyclin D, and others, and RNA seq to evaluate gene expression analysis. The goal of this correlative work is to determine if BVD-523 is appropriately inhibiting downstream signaling through ERK. In addition this testing will allow us to look at mechanisms of resistance to ERK

inhibition and predictors of response. In addition tumor will be assessed for the presence or absence of GNAQ and GNA11 mutations allowing for correlation with outcome.

Our understanding of the genetics of uveal melanoma is limited. A better understanding of the genetic diversity of uveal melanoma would be valuable to guide therapy and combinations of therapy in the future. We plan to perform whole exome sequencing in collaboration with the Broad Institute to gain a better understanding of the drivers of uveal melanoma

PARTICIPANT SELECTION

In this phase II study up to 25 patients with metastatic uveal melanoma will be enrolled to evaluate the efficacy of BVD-523. In the first stage 13 patients will be enrolled at which time an initial evaluation for efficacy will be performed. If sufficient efficacy is seen, we will enroll an additional 12 patients for a total of 25.

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed stage IV uveal melanoma.

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

3.1.3 Patients can have received any number of prior therapies for treatment of their uveal melanoma excluding prior treatment with an ERK inhibitor. Patients who have received prior MEK inhibition or other MAPK targeted agents will be allowed on study.

3.1.4 Age ≥ 18 years of age.

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

3.1.6 Life expectancy of greater than 6 months

3.1.7 Participants must have normal organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- hemoglobin ≥9.0 g/dL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤1.5 × institutional upper limit of normal
  AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal, unless there is known liver involvement in which case ≤5.0 × institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

3.1.8 Participants must have adequate cardiac function, e.g. left ventricular ejection fraction (LVEF) of >50% as assessed by multi-gated acquisition (MUGA) or ultrasound/echocardiography (ECHO); corrected QT interval (QTc) <470ms.

3.1.9 Presence of metastatic disease that would be amenable to the required biopsies. Ideally pre and post biopsies should be from the same lesion and otherwise from lesions in the same organ. If not possible, then biopsy of the lesions in different organs will be permitted. Archival tissue from a biopsy taken within 6 months prior to the first study treatment may be used in place of a pre-treatment biopsy at the discretion of the principal investigator.

3.1.10 The effects of BVD-523 on the developing human fetus are unknown. For this reason and because ERK inhibitors could potentially be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 4 months after completion of BVD-523 administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of BVD-523 administration.

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

3.2 Exclusion Criteria

3.2.1 Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C), small molecule targeted therapy (i.e. – kinase inhibitors) within 3 weeks or the last dose of antibody therapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Participants who are receiving any other investigational agents.

3.2.3 Major surgery within 4 weeks of the first dose of BVD-523. Tumor embolization procedure or ablation procedure within 2 weeks of first dose of BVD-523.

3.2.4 Participants with known brain metastases or evidence of leptomeningeal involvement are eligible only if these lesions are treated and both clinically and radiographically stable for at least four weeks. Patients are eligible if they are being treated with a stable dosage of steroids/anticonvulsants, requiring no dose increase for 4 weeks.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to BVD-523.

3.2.6 Participants receiving any medications or substances that are known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4 or strong inducers of CYP3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

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

3.2.8 Pregnant women are excluded from this study because BVD-523 is an ERK with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with BVD-523 breastfeeding should be discontinued if the mother is treated with BVD-523.

3.2.9 Gastrointestinal (GI) condition which could impair absorption of study medication or inability to ingest study medication.

3.2.10 A history of current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)

3.2.11 Concomitant malignancies or previous malignancies with less than 2 years of disease-free interval at the time of enrollment (except non-melanoma skin cancer, cervical cancer in situ, prostate cancer with undetectable PSA). Other concurrent malignancies must be discussed with the medical monitor prior to enrollment.

3.2.12 Patients with melanoma of cutaneous, mucosal or acral-lentiginous origin or of unknown primary.

3.3 Inclusion of Women and Minorities

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

REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the DF/HCC Clinical Trial Management System

(CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed

TREATMENT PLAN

5.1 Treatment Regimen

BVD-523 is to be taken twice daily orally for 28 consecutive days at 12 ±2 hour intervals. This will be dosed at the recommended phase 2 dose (RP2D) of 600mg twice daily. This study drug dose will be supplied to participants in four 150 mg capsules 28 consecutive days will be defined as a treatment cycle. Treatment will be administered on an outpatient basis. The study medication should be taken with 8 ounces of water (Juice, coffee, tea or soda is not allowed) at the same time each day on an empty stomach i.e., fasting (30-60 minutes before food or 2 hours after food). At this time, there are no identified foods that participants should avoid while taking study drug. All capsules, if more than one is taken at each dosing time, should be taken within 10 minutes. Patients will be instructed NOT to take a substitute capsule if vomiting occurs after self-dosing at home. In clinic doses are only required on days when PK samples are collected. Dosing initiates the clock for PK collections.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

5.2.1 Screening visit

All participants must sign an informed consent document prior to the initiation of any study related procedures. The informed consent document must be signed within 30 days of Cycle 1 Day 1. The remaining screening procedures (with the exception of the scans

and pre-treatment biopsy) are to be conducted within 21 days of Cycle 1 Day 1.

- Review of study eligibility criteria
- Physical Examination, including height and weight
- Medical History
- Record concomitant medications taken up to 14 days prior to Cycle 1 Day 1
- Vitals [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR)]
- ECOG Performance Status evaluation
- Laboratory Assessments
    - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count
    - Serum chemistry: sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, creatine phosphokinase, and albumin
    - Serum lipase and amylase
    - Serum pregnancy test for women of childbearing potential (WOCBP)
    - Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
    - Urinalysis
- Echocardiogram (ECHO)
    - Unscheduled ECHOs can be completed as clinically indicated.
- 12-lead ECG. If an ECG shows QTc prolongation (>470 milliseconds), the ECG must be repeated twice to obtain values in triplicate.
- Ophthalmology examination: an ophthalmologist, or designated member of the clinical team, will check the participants vision and measure the pressure level in their eyes at baseline.
- Radiologic imaging studies to evaluate tumor status must include: Magnetic Resonance Imaging (MRI) of the brain and contrast Computed Tomography (CT) of the chest, abdomen, and pelvis. MRI of the chest, abdomen and/or pelvis may be used in place of a CT scan at baseline, but the same type of imaging modality must then be used throughout the course of the study (e.g. MRI of the pelvis performed at baseline, therefore, MRI of pelvis must be done at subsequent visits). Additional imaging may be obtained as clinically indicated. Baseline scans must be done $\leq$4 weeks prior to the start of study treatment.
- Tumor biopsy 1 – 28 days prior to receiving the first dose of study treatment. Archival tissue from a biopsy taken within 6 months prior to the first study treatment may be used in place of a pre-treatment biopsy at the discretion of the PI.

5.2.2 Cycle 1, Day 1

- Physical exam
- Vital signs (temperature, HR, BP and RR)
- Weight
- Performance status
- Record concomitant medications
- Laboratory Assessments*
    - Hematology
    - Serum chemistry
    - Serum lipase and amylase
    - Serum pregnancy test for WOCBP
- 12-lead ECG. If an ECG shows QTc prolongation (>470 milliseconds), the ECG must be repeated twice to obtain values in triplicate.
- BVD-523 dosing
- Dispensing of study medication for the remainder of the 28 day cycle with drug diary.
- Record AEs

***NOTE:** C1D1 laboratory assessments are not required to re-meet eligibility criteria. If there is a cause for concern related to eligibility or scheduled C1D1 laboratory assessments the investigator should use their discretion.

5.2.3 Cycle 1, Day 15

- Tumor biopsy between days 12-18 while on treatment.
- Collection of research blood sample for PK analysis prior to dosing.

5.2.4 Cycle 2, Day 1

- Physical exam
- Vitals (temperature, HR, BP and RR)
- Weight
- Performance status
- Record concomitant medications
- Laboratory Assessments
    - Hematology

  - Serum chemistry
  - Serum lipase and amylase
  - PT and aPTT
  - Urinalysis
  - Serum pregnancy test for WOCBP
- 12-lead ECG. If an ECG shows QTc prolongation (>470 milliseconds), the ECG must be repeated twice to obtain values in triplicate.
- BVD-523 dosing
- Dispensing of medication for the remainder of the 28 day cycle with drug diary.
- Record AEs
- Eye examination

5.2.5 Cycle 2, Days 22 – 28

- Radiologic imaging studies: CT or MRI of chest, abdomen and pelvis followed by response evaluation to evaluate tumor status are required at each tumor assessment visit, even if sites of disease were not identified in this region at baseline. MRI scan of the brain and additional imaging may be obtained as clinically indicated.

5.2.6 Cycle 3, Day 1 and beyond

Participants continuing BVD-523 dosing past Cycle 2 will repeat the schedule of events for Cycle 2, Day 1 with all required assessments with the following exceptions:

- Radiological imaging studies to evaluate tumor status will be repeated **during the last week (Days 22 to 28) of every second cycle** (e.g., Cycles 4, 6, 8, etc. only). Radiologic measurements should be performed every 8 weeks from C1D1 and this schedule should not be adjusted due to dose delay/modifications.

5.2.7 End of Treatment Visit

To be completed 20 to 30 days after the last dose of study drug.

- Physical examination
- Vitals (temperature, HR, BP and RR)
- Weight
- Performance status
- Record concomitant medications
- Laboratory Assessments

  - Hematology
  - Serum chemistry
  - Serum lipase and amylase
  - PT and aPTT
  - Urinalysis
  - Serum pregnancy test for WOCBP
- 12-lead ECG. If an ECG shows QTc prolongation (>470 milliseconds), the ECG must be repeated twice to obtain values in triplicate.
- Radiologic imaging studies: CT or MRI of chest, abdomen and pelvis followed by response evaluation to evaluate tumor status if the last scans were performed more than 4 weeks prior. MRI scan of the brain and additional imaging may be obtained as clinically indicated.
- Record AEs
- Eye Examination, will be performed by an ophthalmologist, or designated member of the clinical team, to check the participants vision and measure the pressure level in their eyes.

5.3 Agent Administration

5.3.1 BVD-523

BVD-523 is to be taken twice daily orally for 28 days, at 12 ±2 hour intervals at a dose of 600mg BID. This study drug dose will be supplied to participants in four 150 mg capsules. The study medication should be taken with 8 ounces of water (juice, coffee, tea or soda is not allowed) at the same time each day on an empty stomach (e.g. fasting or 30-60 minutes before food or 2 hours after food). Water is permitted during this period. At this time, there are no identified foods that participants should avoid while taking study drug. All capsules, if more than one is taken at each dosing time, should be taken within 10 minutes. Crushing, chewing, or dissolution in water is not advised. It is strongly preferred that participants take the medication as whole capsules. A participant that is observed to vomit an intact capsule after dosing in the clinic may receive a substitute dose of drug. However, participants should be instructed NOT to take a substitute capsule if vomiting occurs after self-dosing at home.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of BVD-523 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Medications which are known to be strong inhibitors of CYP3A4, CYP2D6, and CYP1A2, or strong inducers of CYP3A4, are not permitted during the study (for list of non-permitted drugs see Appendix 1)

The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Medications taken within 14 days prior to Cycle 1, Day 1 and during the study will be collected on the participant's case report form. The following are the supportive care guidelines for the study:

- No other antineoplastic agents will be permitted during this study
- No concurrent radiation treatment will be permitted during this study, except for palliation or symptom relief on case by case basis following discussion with Principal Investigator
- No treatment with chronic immunosuppressants (e.g., cyclosporine following transplantation or systemic steroids for treatment of autoimmune disease) will be permitted during this study; however, use of inhalant steroids and steroids given for antiemetic purposes or supportive therapy for brain metastases are permitted
- The use of erythropoietin or other specific red blood cell growth factors and red blood cell transfusions will be permitted as clinically indicated during the study
- The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated
- Other concomitant medications may be given as clinically indicated
- Caution should be exercised when concomitant medications that are cleared predominantly by the CYP1A2, CYP2D6 and CYP3A4 pathways are administered.

The above information is precautionary only. Investigators are encouraged to discuss the use of individual medications with the Principal Investigator on a case-by-case basis.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or willingness to comply with the oral medication regimen and/or documentation requirements.
- Participant decides to withdraw from the protocol therapy.
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgement of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off-treatment, on follow-up, or off-study, the relevant off-treatment/off-study information will be updated in OnCore

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Elizabeth Buchbinder, MD at (617) 632-6588 or pager # 40221.

5.6 Duration of Follow Up

Participant survival information will be collected, preferably via office visit or telephone contact, every 4 weeks (± 1 week) from the date of last dose of study drug until the participant's death or until the participant is lost to follow-up, or until study closure (approximately 6 months after the last participant terminates treatment). A participant will be determined to be lost to follow-up only after at least 3 attempts to contact him/her have been made over a 4-month period. At least two of these attempts to contact must be made through certified letters.

The following information will be collected:

- The participant's survival status, and if deceased, the date of death.
- The method by which the survival status was assessed and the date it was assessed.
- Any subsequent anti-cancer therapy received after discontinuation from study drug.

In addition, survival participants removed from study for unacceptable adverse events will be followed for resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

Participants that receive protocol therapy will not be replaced in this trial.

DOSING DELAYS/DOSE MODIFICATIONS

6.1 Criteria for dose delays/dose modifications

In general, participants experiencing **Grade 1 and 2** drug related toxicities should not have the dose of BVD-523 modified. However, appropriate supportive care should be provided for the management of drug related toxicities. Grade 2 toxicities may require dose or schedule modifications (delaying or omitting individual doses) due to potentially greater clinical significance; however, this should occur after discussion with Principal Investigator.

Dosing of BVD-523 must be delayed if a participant experiences a **Grade 3 non-hematologic** toxicity. If the toxicity resolves (returned to baseline or decreased to Grade ≤ 1) within 14 days, dosing of BVD-523 may be resumed with a 25% dose reduction. Exceptions to this rule are as follows:

- Grade 3 fatigue persistent for ≤ 7 days
- Grade 3 nausea, vomiting, or diarrhea persisting ≤ 72 hours with maximum supportive care
- Grade 3 electrolyte events if they are resolved with replacement within 24 hours
- Lymphopenia regardless of grade
- The following grade 3 laboratory abnormalities will not be considered dose limiting if they return to baseline within 7 days: elevated bilirubin, AST, ALT, cholesterol, amylase, lipase, creatinine and hypertriglyceridemia

Dosing of BVD-523 must be delayed if a participant experiences the following **Grade 2 hematologic** toxicities:

- thrombocytopenia (< 50,000/μL)
- neutropenia (< 1,000/μL) lasting > 7 days

Dosing of BVD-523 must be delayed if a participant experiences the following **Grade 3 hematologic** toxicities:

- hemoglobin decrease (< 8.0 g/dL)
- grade 3 or 4 febrile neutropenia (defined as temperature ≥ 101°F with a neutrophil count ≤ 1,000 cells/μL).

If the toxicity resolves (returned to baseline or decreased to Grade ≤ 1) within 14 days, dosing of BVD-523 may be resumed with a 25% dose reduction

In the case of **Grade 4 hematologic or non-hematologic** (except alopecia) toxicity, **or persistent Grade 3** toxicity despite one dose level reduction, the dose level will be reduced by a

total of 50 %. BVD-523 dose should not be reduced by more than 50 %. Participants unable to tolerate BVD-523 at a dose level of 50%, or whose drug related toxicity has not returned to baseline or Grade ≤ 1 within 14 days, will be discontinued from study, unless clinical benefit has been demonstrated and a lower dose might, in the opinion of the PI, maintain clinical benefit.

Dose Level	BVD-523 Dose
-2	300mg, BID
-1	450mg, BID
0	600mg, BID

Nausea	**Management/Next Dose for BVD-523**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Diarrhea	**Management/Next Dose for BVD-523**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Management/Next Dose for BVD-523**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	**Management/Next Dose for BVD-523**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

Rash	**Management/Next Dose for BVD-523**
≤ Grade 1	No change in dose; topical antibiotics, steroids, and moisturizers indicated
Grade 2	No change in dose; Oral antibiotics indicated, oral steroids should be considered
Grade 3	Hold until ≤ Grade 1. Resume at same dose level. Oral antibiotics and steroids indicated
Grade 4	Hold until ≤ Grade 1. Resume at one dose level lower if indicated **
*Participants requiring a delay of >2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	
Rash should be initially treated with topical steroids and topical clindamycin or doxycycline. If these do not sufficiently control the rash then would consider adding oral antibiotic therapy with doxycycline or minocycline. If rash is still not responding to therapy would consider adding a short course of oral steroids.	

ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, without any judgment about causality.

7.1.2 Serious adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, regardless of causality, that results in ANY of the following outcomes:

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

7.2 Adverse Event List for BVD-523

In the following sections a short summary of preclinical data is provided. Detailed information is presented in the BVD-523 Investigator's Brochure.

Events Not Considered SAEs:

- Previously planned surgeries (prior to signing the ICF)
- Non-disease related elective surgeries
- Pre-planned hospitalizations or procedures for pre-existing conditions
- Death due to disease progression

Preliminary evidence from *in vitro* and *in vivo* toxicological assessments of BVD-523 suggests the molecule has a safety profile supportive of its development as an anti-cancer therapeutic. Additionally, human clinical trials have been conducted using other drugs known to affect the MAPK pathway and findings from these studies may provide information regarding possible safety risks that are mechanistically attributable to MAPK pathway inhibition.

Thus, BVD-523's risk profile may potentially include the following:

Dermatological Lesions
Dermatological lesions have been seen in rodent GLP toxicology studies of BVD-523. Several of the following findings displayed exposure-dependent increases in incidence and/or severity: non-specific dermal inflammation, pustular dermatitis, epidermal ulceration and acanthosis. These toxicities appeared to be associated with predominantly reversible pharmacodynamics, as the majority of findings were mild and/or of low incidence in animals that underwent dose cessation.

In clinical studies, other drugs that inhibit components of the MAPK pathway exhibit cutaneous toxicity. Multiple investigational inhibitors of MEK1/2 kinases exhibit exposure dependent, dose-limiting and reversible skin toxicities in a proportion of patients. Specific toxicities include: non-specific rash and pruritus, acneiform dermatitis, epidermal fissure and paronychia. Additionally, clinical experience with both investigational agents and approved drugs that primarily target BRAF kinase have displayed exposure-dependent and reversible skin toxicities in a proportion of treated patients; relevant lesions here include keratoacanthoma-type squamous cell carcinomas, non-cancerous hyperkeratosis and actinic keratosis.

A similar pattern of cutaneous toxicity was observed in the first 18 patients in the FIM Phase 1 study BVD-523-01, with two thirds of patients experiencing rash and 1 patient with a history of squamous cell carcinoma developing a squamous cell carcinoma while on treatment with BVD-523. Rash has been treated with topical or oral agents, and dose reductions/interruptions as needed. Patients in this study of BVD-523 will be monitored for signs of dermatological toxicities.

Phototoxicity
BVD-523 exhibits an absorbance peak in the range of UV-A/UV-B light, specifically at ~320 nM. Clinical studies of other drugs that modulate MAPK pathway components have exhibited skin phototoxicity, and photosensitization has been reported in 1 patient on a low dose of BVD-523 (20 mg b.i.d) in the FIM Phase 1 study.
Beyond dermatological monitoring (above), potential risks of direct phototoxicities induced by BVD-523 should be further minimized by advising that patients minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients should be informed that relevant sun exposure may occur even through glass, such as while driving.

Ophthalmological Effects
Preclinical toxicology studies of BVD-523 have not revealed any exposure-dependent ophthalmological toxicities; however, clinical studies of MEK1/2 kinase inhibitors highlight ocular toxicities that may reflect mechanistically attributable risks observable in a proportion of patients. Of particular concern are the following dose-limiting toxicities comprising exposure-dependent, serious adverse events during clinical studies: retinal vein occlusion, retinal detachment and related vision abnormalities. In the ongoing FIM Phase 1 study to date (1st April 2014) a single AE of vision changes has been reported in 1 patient on a low dose of BVD-523 (20 mg b.i.d). While it is not definitively understood whether ocular toxicities reflect primary pharmacology associated with global inhibition of the MAPK pathway specific management and exclusion criteria are defined in this clinical protocol.

Gastrointestinal Toxicity
Preclinical toxicity studies of BVD-523 provided evidence of exposure-related, reversible gastrointestinal toxicities, and these toxicities have also been observed at high frequency if the first 18 patients in the ongoing FIM Phase 1 study, in one case leading to an SAE of renal insufficiency secondary to dehydration. The severity and reversibility of these nonclinical and clinical toxicities, while not meriting a specific monitoring or treatment plan, warrant

active routine monitoring of patients for this toxicity.

QTc Prolongation
The balance of preclinical evidence suggests BVD-523 has low, but observable, potential to cause QT prolongation. Given potentially unique species sensitivity, as well as possibly unknown consequences following chronic dosing, patients dosed with BVD-523 are being monitored for potential QTc prolongation and any other related cardiotoxicities, including 12 hour Holter monitoring after the 1st and 3rd dose. No cardiac AEs have been reported in the first 18 patients treated with BVD-532 in doses up to 900 mg BID.

Tissue Mineralization
Tissue mineralization has been observed in rodent toxicology studies of BVD-523. The incidence and severity of mineralization was dose-dependent, and effects were observed in 1 or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium was seen; these effects were not observed in animals in which there was no mineralization.

Tissue mineralization has been reported in rodents with other compounds that target the MAPK pathway and published studies suggest that the MAPK pathway is a negative regulator of matrix mineralization both *in vitro* and *in vivo*.

Routine clinical laboratory tests, including blood chemistry analyses for calcium and inorganic phosphate, will be performed and any indication of abnormalities may result in further investigations. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway.

Hematological Effects
Hematological effects observed in a rat repeat dose study included lowered reticulocyte counts, mean corpuscular volume, platelet counts (in females only) and increased neutrophil, monocyte, basophil and large unstained cell counts. In dogs the clinical pathology findings were consistent with inflammation (increased white blood cell count, neutrophils, fibrinogen and globulin) and decreased albumin and hemorrhage (decreased red cell mass).

In order to monitor for potential hematologic toxicity in humans, routine clinical laboratory hematology tests, should be performed and any indication of abnormalities may result in further investigations.

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the first dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. Study personnel must alert the Overall PI as soon as possible (**no later than 24 hours of the investigator learning of the SAE**).

7.4.2 Any serious adverse event (SAE) that occurs after the first dose of study treatment, during treatment, or within 30 days of the last dose of treatment should also be reported to BVD via Clinipace using the local institutional SAE form. Please include Deborah Knoerzer (dknoerzer@biomed-valley.com), Dean Welsch (dwelsch@biomed-valley.com) and Mary Varterasian (mvarterasian@gmail.com) on all emails that are sent to Clinipace (safety@clinipace.com) regarding SAEs.

7.4.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.2.

8.1 BVD-523

8.1.1 Description

When BVD-523 was characterized using *in vitro* screens against 66 receptors and ion channels no toxicologically significant interactions were identified. Additionally, BVD-523 was negative in bacterial mutation and *in vivo* micronucleus screening assays, so BVD-523 is not considered to have a significant genetic toxicology risk.

While BVD-523 modestly inhibits the hERG current (IC50 3.4 μM), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10 μg/mL, and no significant cardiovascular findings were observed upon acute oral dosing of the compound at dose levels up to 50 mg/kg in dogs (Cmax = 17.3 μM). Thus BVD-523 is considered to have a low potential to cause QT prolongation in patients, but, as stated, the study will monitor for signs of cardiovascular effects of BVD-523 in humans.
No significant cytochrome P450 (CYP) inhibition has been observed with the compound. *In vitro* studies suggest that the compound is metabolized primarily via oxidation by multiple CYPs, including 3A4, 2D6, and 1A2. Furthermore, no significant CYP induction was observed after up to 14 days drug treatment in rats, nor during *in vitro* studies with human hepatocytes. These data suggest a limited potential for drug-drug interactions.
BVD-523 HCl salt is orally available in multiple species (absolute bioavailability %F = 23% in dog to 100 % in monkey) when formulated as a simple suspension in 1% carboxymethylcellulose (CMC) and has a half-life of 2−4 hours across all species.
BVD-523 was administered to male and female Sprague-Dawley rats in several toxicology studies: a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; for up to 14 days at dose levels up to 100 mg/kg twice daily; and for up to 5 days at dose levels up to 150 mg/kg/dose once daily. The incidence and severity of mineralization seen in these studies was dose-dependent and effects were observed in 1 or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen; these effects were not observed in animals in which there was no mineralization. Therefore, the risk of tissue mineralization can be assessed by serum phosphorus and calcium monitoring. A

clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway because those compounds likewise elicited mineralization in rodents.

When BVD-523 was administered to male and female Sprague-Dawley rats for up to 28 days at a dose level of 25 or 50 mg/kg twice daily, it was poorly tolerated. Although most clinical signs and clinical pathology findings reversed following 4 weeks of recovery, skin lesions and histopathology findings persisted in many tissues at both dose levels after the recovery phase. Based on these findings, 25 and 50 mg/kg twice daily dose levels were considered severely toxic. Administration of 12.5 mg/kg twice daily for 28 days was generally welltolerated by rats of both sexes; however, this dose level was associated with test articlerelated findings that included: swelling in the neck; decreased forelimb strength; multiple clinical pathology findings; enlarged lymph nodes, spleen, and mammary gland. Based on these findings, the severely toxic dose in 10% of the animals (STD10) for BVD-523 when administered for up to 28 days in Sprague-Dawley rats is 12.5 mg/kg given twice daily (25 mg/kg/day). On Day 28 of the dosing phase, this dose level corresponded with a Cmax of 28700 and 15323 ng/mL and AUC0-12 of 264868 and 124341 hr.ng/mL for males and females, respectively.

BVD-523 was administered to male and female beagle dogs for up to 28 days at dose levels of 15, 5, or 2 mg/kg twice daily. Initial analysis of the toxicity profile observed shows that BVD-523 was well tolerated in dogs. The rat was designated the most sensitive species and rat data were used to calculate the starting dose in man.

BVD-523 has a measured UV absorbance at 320 nm, which means that it can absorb both UV-A and UV-B. BVD-523 may therefore act as a photosensitizing agent in man. Based on the data accumulated to date, BVD-523 possesses a toxicology profile which presents no impediment to its development as an anti-cancer agent.

For further information, please refer to the BVD-523 Investigator's Brochure.

8.1.2 **Form**

The BVD-523 drug product is an oral capsule containing BVD-523 drug substance encapsulated in a hard gelatin capsule. The capsule dose strength intended for the clinical studies is 150 mg (yellow) as the free base content. The capsules will be provided in 30-count white HDPE bottles.

8.1.3 **Storage and Stability**

Bottles of BVD-523 will be stored at controlled room temperature (15^{o}C-25^{o}C) environment under temperature monitoring in a location with access limited to authorized study personnel.

BVD-523 drug product lots retest dates are driven by real-time stability. BioMed Valley Discoveries, Inc. will provide a note to file stating the retest date for each lot shipped. The site will be responsible to manage inventory and track retest dates. When a new retest date is due, the site will request to BioMed Valley Discoveries, Inc. or designee to issue an updated retest

date note to file to the site

8.1.4 **Compatibility**

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 **Availability**

BVD-523 drug product is stored at Catalent Pharma Solutions (CPS) in Kansas City, MO and will be shipped from this location to the clinical investigational site(s). All drug product remaining at the site will be destroyed at the end of the study in accordance with the site local guidelines and policies."

8.1.7 **Preparation**

30-count bottles of BVD-523 drug product capsules will be distributed.
Site pharmacies will be responsible for:

1. Dispensing enough drug product to each subject.
a. Cycles 1-2: 1 extra day of drug.
b. After Cycle 2: 2 extra days of drug.
2. Affixing an appropriate label to the bottles of BVD-523 dispensed to enrolled subjects.
a. The label must contain a pharmacy-dispensed unique bottle number (as per their institution's policy).

8.1.8 **Administration**

BVD-523 drug product will be taken orally by enrolled study subjects twice a day at the dose and as outlined on dosing instruction sheets provided to each subject. BVD-523 should be taken at the same time each day on an empty stomach (i.e., fasting), either 30-60 minutes before food or 2hrs after food, with 8 oz of water (juice, coffee, tea or soda is not allowed.). All capsules should be consumed in 10 minutes or less.

8.1.9 **Ordering**

As each site is initiated, the investigator or appropriate investigator-designee will order adequate supply of capsules (150 mg) to allow for dose escalations/reductions, as appropriate. Sites may request resupply of study drug as needed.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful

record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

Any opened bottles of BVD-523 will be destroyed according to local policies and guidelines. Unopened, unused bottles containing the 30-count capsules will be destroyed at the end of the study in accordance with institutional SOPs.

BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.0 **LABORATORY CORRELATIVE STUDIES**

BVD-523 is expected to inhibit downstream signaling through ERK. Tumor biopsies are expected to be obtained 7-28 days prior to the first treatment and 12-16 days following the initial treatment in order to facilitate ERK signaling analysis, mutation analysis, sequencing, and cell line development.

The sequence as to preference of site selection for the pre- and post- treatment biopsies is: (1) biopsies of the same lesion, (2) different sites within the same organ, (3) different organs. While incisional or excisional biopsies are preferred, we anticipate that many patients will need to undergo imaging guided core needle biopsies of organs such as the liver. Sufficient biopsy material to provide at least 23 unstained paraffin embedded slides and extra fresh tissue from the pre- treatment biopsy and 13 unstained paraffin embedded slides and extra fresh tissue from the post-treatment biopsy is required. If imaging guided core needle biopsies are necessary, three to four specimens using an 18-gauge needle are required to obtain sufficient biopsy material from the pre-treatment biopsy. Two to three specimens using an 18-gauge needle are required to obtain sufficient biopsy material from the post-treatment biopsy. Blocks or sufficient unstained slides may be sent for processing; blocks are preferred. If the patient had a previous biopsy, material from that biopsy can be used for GNAQ and GNA11 testing (10 slides needed) and only enough biopsy material for 13 unstained paraffin embedded slides and extra fresh tissue is required from the pre-treatment biopsy.

Archival tissue from a biopsy taken within 6 months prior to the first study treatment may be used in place of a pre-treatment biopsy at the discretion of the PI

The biopsy specimens will be used for the following pharmacodynamic correlates:

1. Analysis of changes in ERK signaling such as pRSK, DUSP, cyclin D and others. This will be performed in conjunction with Ryan Sullivan's lab at MGH.

2. Determination of the presence or absence of GNAQ and GNA11 activating mutations in the metastatic tumor. This will be performed on unstained paraffin embedded material derived from pre treatment biopsy or the initial biopsy confirming metastatic disease by a combination of PCR, HPLC and DNA sequencing.

3. Whole exome sequencing and RNA seq. This will be performed in collaboration with the Broad institute. There is a lack of knowledge about the genetic drivers of Uveal melanoma and this study will allow for an exploration of these on and off MAPK targeted therapy.

4. Routine histopathology (H+E staining)

5. Development of PDX: Tissues obtained from fresh biopsies will be used to generate patient derived xenografts and cell lines to evaluate mechanisms of drug resistance.

Procedure:

Ideally pre-and post-biopsies should be from the same lesion and otherwise from lesions in the same organ. If not possible, then biopsy of the lesions in different organs will be permitted.

One specimen of fresh tissue sample should be sent to Dr. Rizwan Haq at DFCI Medical Oncology Labs as soon as possible after tissue is available. It will be necessary to coordinate with Dr. Haq (Rizwan_haq@dfci.harvard.edu and copy priyas_pancholi@dfci.harvard.edu) for each biopsy in order to ensure that the sample can be processed immediately after the biopsy. The rest of the tissue specimens (fixed) should be sent to Ryan Sullivan's lab at MGH for further analysis. Tissue processing at the MGH Med Onc lab will require sufficient biopsy material to provide at least 23 unstained paraffin embedded slides from the pre- treatment biopsy and 13 unstained paraffin embedded slides from the post-treatment biopsy. If imaging guided core needle biopsies are necessary, three to four specimens using an 18-gauge needle are required to obtain sufficient biopsy material from the pre-treatment biopsy. Two to three specimens using an 18-gauge needle are required to obtain sufficient biopsy material from the post-treatment biopsy.

Please refer to the Sample Collection Information Sheet for sample destination and shipping details.

DFCI:
Study teams will also refer to the Cross-Sectional Interventional Radiology (CSIR) Service Biopsy Protocol for this study.

Non-DFCI Sites:
Study teams will follow institutional procedures for scheduling, obtaining, and transporting biopsy specimens. All specific requirements related to DFCI personnel are limited to patients at DFCI and are not required to be completed for subjects enrolled at other sites.

Breakdown:

Pre-Treatment

Set	Needle	# Samples	Preparation (Media)	Destination
1	18G	3-4 specimens	1 specimen DMEM	DFCI Med Onc Labs (Haq)
			2-3 specimens 10% neutral formalin	MGH Med Onc Labs (Sullivan)

Post-Treatment

Set	Needle	# Samples	Preparation (Media)	Destination
1	18G	2-3 specimens	1 specimen DMEM	DFCI Med Onc Labs (Haq)
			1-2 specimens 10% neutral formalin	MGH Med Onc Labs (Sullivan)

STUDY CALENDAR

10.1 Study Calendar

Baseline evaluations are to be conducted within 21 days prior to start of protocol therapy. The informed consent document must be signed within 30 days of Cycle 1 Day 1. Scans and pre-treatment biopsy may be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of study therapy. **Note:** Cycle 1 Day 1 labs do not need to re-meet eligibility.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

		Cycle 1[B]		Cycle 2[B]		Cycle 3+ [B]	Off Treatment/ Follow-up
	Pre-Study	Day 1	Day 15	Day 1	Days 22 to 28	Day 1	EOT[e]
BVD-523		A	A	A	A	A	
Informed consent	X						
Demographics	X						
Medical history	X						
Concomitant Medications	X	X					X
Physical exam	X	X		X		X	X
Vital signs[a]	X	X		X		X	X
Height	X						
Weight	X	X		X		X	X
Performance status	X	X		X		X	X
Hematology[b]	X	X		X		X	X
Serum chemistry[c]	X	X		X		X	X
Serum lipase and amylase	X	X		X		X	X
PT and apTT	X			X		X	X
Urinalysis	X			X		X	X
B-HCG[d]	X	X		X		X	X
PK blood sample			X[h]				
ECG[f]	X	X		X		X	X
MUGA/ECHO	X	X[g]					
Adverse event evaluation		X					X
Tumor measurements	X	*Tumor measurements will be repeated every 8 weeks ± 1 week from C1D1.*					X

Radiologic evaluation	X	*Radiological imaging studies to evaluate tumor status will be repeated every 8 weeks ± 1 week from C1D1.*					X
Tumor Biopsy	X[i]		X				
Eye Exam[j]	X	*Eye Exams should be performed every 5 weeks (±1 week) from C1D1.*					X[j]

A: *BVD-523*: Dose as assigned; *dispensed on this day, drug taken twice daily every 12 hours (±2 hours).* On C1D15 the morning dose will be in-clinic due to PK sampling and it is allowable to have that dose out of the 12 (±2) hour window. Dosing should resume at the normal time that evening.

B: Window of ±3 days for all study visits. See Section 5 for study visit details.

a: Vital signs to include heart rate, blood pressure, temperature, respiratory rate

b: Hematology Labs: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count.

c: Serum Chemistry Labs: Sodium, potassium, chloride, bicarbonate, magnesium, calcium, phosphorus, blood urea nitrogen, creatinine, glucose (random), total bilirubin, LDH, total protein, ALP, ALT, AST, creatine phosphokinase, and albumin.

d: Serum pregnancy test (women of childbearing potential only)

e: End of Treatment: Evaluation to be completed within 20 to 30 days after the last dose of study drug. After this visit, participant survival information will be collected, preferably via office visit or telephone contact, every 4 weeks (± 1 week) from the date of last dose of study drug until the participant's death or until the participant is lost to follow-up, or until study closure (approximately 6 months after the last participant terminates treatment).

f: 12-lead ECG. If an ECG shows QTc prolongation (>470 ms), the ECG must be repeated twice to obtain values in triplicate. Bazett's formula is acceptable to use to calculate the heart rate-corrected QT interval.

g: Unscheduled ECHOs can be completed as clinically indicated.

h: A blood sample for PK analysis will be drawn at time 0 (shortly before dosing). Refer to the Sample Collection Information Sheet for PK processing instructions.

i: The pre-treatment biopsy must be performed 1 – 28 days prior to receiving the first dose of study treatment. Archival tissue from a biopsy taken within 6 months prior the first study treatment may be used in place of a pre-treatment biopsy at the discretion of the PI. The on-treatment biopsy should be performed within Days 12 – 18 of the study.

j: There is a window of ± 1 week for eye exams. The EOT eye exam should occur 5 weeks (±1 week) after the last dose of study drug.

MEASUREMENT OF EFFECT

As response is the primary endpoint of this trial, participants with measurable and/or non-measurable disease will be assessed by RECIST criteria. For the purposes of this study, participants should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained no earlier than 4 weeks following initial documentation of an objective response.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every *8* weeks.

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

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

the short axis will be measured and followed.

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

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

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

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

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

11.1.3 Methods for Evaluation of Disease

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

The same method of assessment and the same technique should be used to characterize

each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent

fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

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

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of

20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

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

response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from first treatment to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from first treatment to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from first treatment to progression, or censored at date of last disease evaluation for those without progression reported.

DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or

data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

I. Primary Objectives

a. To evaluate the overall response rate in uveal melanoma to ERK inhibitor therapy.

II. Secondary Objectives

a. To characterize the safety profile of ERK inhibitor therapy when administered to adult patients with unresectable or metastatic uveal melanoma
b. To evaluate overall survival of patients with uveal melanoma treated with ERK inhibitor therapy.
c. To evaluate the pharmacodynamics of ERK inhibition with a comparison of pre- and on-treatment biopsies.

13.2 Sample Size, Accrual Rate and Study Duration

We would consider ERK inhibition therapy effective in the treatment of uveal melanoma if a 25% response rate was observed. To assess this, we will conduct a two-stage design comparing a null rate of 5% against the alternative rate of 25%. Thirteen patients will be enrolled into the first stage of the trial and if one or fewer responses are observed the trial will be terminated for lack of efficacy. If two or more responses are seen, an additional 12 patients will be enrolled into the second stage of the trial. If a total of three or more of the 25 total patients

have a response the treatment would be considered promising. With this number of patients there is a 1 sided type-1 error of 8% (target 10%) and 87% power (target 85%). If the true response rate is 5% then the probability is 0.86 of stopping at the end of the first stage.

Uveal melanoma, similar to cutaneous melanoma, is a disease which is predominantly found in patients of Caucasian descent. Thus our study will not have many patients from racial categories other than White with a few patients who are Hispanic or Latino.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	8	+	12	=	20
Ethnic Category: Total of all subjects	10	+	15	=	25
Racial Category					
American Indian or Alaskan Native		+		=	
Asian		+		=	
Black or African American		+		=	
Native Hawaiian or other Pacific Islander		+		=	
White	10	+	15	=	
Racial Category: Total of all subjects	10	+	15	=	25
	(A1 = A2)		(B1 = B2)		(C1 = C2)

13.3 Stratification Factors

There are no planned stratification factors.

13.4 Interim Monitoring Plan

Enrollment will be paused at 13 patients to determine if there is sufficient efficacy to continue as outlined above.

13.5 Analysis of Primary Endpoints

The primary endpoint for this study is overall response rate in uveal melanoma by standard solid

tumor response criteria. The proportion of patients with best response of CR or PR will be presented with a 90% confidence interval estimated using the method of Atkinson and Brown, which allows for the two stage design.

13.6 Analysis of Secondary Endpoints

Secondary endpoints for this study include the rate of disease control, time to tumor progression, duration of response, safety of BVD-523, overall survival and correlative studies looking at drug effect and association of response with GNAQ and GNA11 mutation.

Disease control rate. The proportion of patients with best response of CR, PR, or SD lasting at least 24 weeks will be presented with a 90% exact binomial confidence interval. For a sample of size 25, the confidence interval will be no wider than 0.35.

Overall survival. Overall survival (OS) is the time interval between the start of treatment and death from any cause. OS will be censored at the date of the last follow-up visit for patients who become lost to follow-up.

Time to tumor progression. Time to tumor progression (TTP) is the time interval between the dates of the start of trial treatment and first documentation of progressive disease. In the absence of documented progressive disease, follow-up will be censored at date of last disease assessment.

Duration of response. Duration of response (DoR) is defined among patients with objective response (confirmed CR or PR as best overall response) as the interval between dates of first documentation of objective response and first documentation of progressive disease. In the absence of documented progressive disease, follow-up will be censored at date of last disease assessment.

The time-to-event endpoints will each be summarized using the method of Kaplan-Meier. Point estimates for each endpoint will be presented with 90% confidence intervals derived using log(-log(endpoint)) methodology.

Safety and Tolerability. All adverse events recorded during the trial will be summarized. The incidence of events that are new or worsening from the time of first dose of treatment will be summarized according to system organ class and/or preferred term, severity (based on CTCAE grade), type of adverse event, and relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by primary system organ class, and type of adverse event.

Association between GNAQ mutation and outcome. To explore the association between GNAQ mutation and clinical outcome, tumors will be classified according to whether or not there is GNAQ mutation and compared with therapeutic response The relationship between GNAQ mutation and progression-free survival will be explored using the method of Kaplan-Meier. Time to disease progression will be calculated, stratified by GNAQ mutation status.

Association between changes in levels of GNAQ, GNA11 or ERK effectors and outcome. Changes

in GNAQ or GNA11 expression, or change in ERK targets, will be documented with immunohistochemistry of tumor. Biopsies and blood/serum samples will be collected pre-treatment and 12-16 days after first treatment. Pre-treatment levels will be considered as predictors of clinical efficacy; changes in expression between pre- and post-treatment samples will also be related with clinical outcome. Pre-treatment levels and percent changes will be summarized using descriptive statistics.

For the analysis of association between change in biomarkers levels and response, we anticipate that approximately 90% of patients will have tissue for analysis at pre-treatment and again at 12-16 days, resulting in a potential sample size of 23 patients with paired biopsies. For a response rate of 0.25, this would result in six patients with response and 17 non-responders. Comparisons of biomarker change measured on a continuous scale will be based on two-sided Wilcoxon rank-sum tests with a type-I error of 0.1. There will be at least 80% power to detect differences in biomarker change that are approximately 1.35 times the common standard deviation of the change.

13.7 Reporting and Exclusions

All safety data will be summarized using descriptive statistics and presented in patient data listings. Information on study treatment will be summarized by dose and cumulative dose using descriptive statistics. Adverse event data will be presented in frequency tables (overall and by intensity) by body system. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion will be counted only once in the calculation of the event frequency. The worst grade of an event will be reported for any patient.

Laboratory data will be summarized for each assessment time using descriptive statistics for patients with marked abnormalities during study treatment based on NCI-CTCAE Version 5.0 criteria. Vital signs and physical examinations will be summarized for each assessment time using descriptive statistics and reported in patient data listings.

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

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

PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX 1 NON-PERMITTED CONCOMITANT MEDICATIONS

INHIBITORS	INHIBITORS	INHIBITORS
3A4	2D6	1A2
indinavir	bupropion	fluvoxamine
nelfinavir	fluoxetine	ciprofloxacin
ritonavir	paroxetine	enoxacin
atazanavir	quinidine	
clarithromycin		
itraconazole		
ketoconazole		
voriconazole		
nefazodone		
saquinavir		
telithromycin		
boceprevir		
conivaptan		
posaconazole		
telaprevir		

INDUCERS
3A4
carbamazepine
phenytoin
rifabutin
avasimibe
St. John's Wort

Strong Inhibitors: ≥ 5-fold increase in AUC or > 80% decrease in CL
Strong Inducers: ≥ 80% decrease in AUC
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit Accessed 4-1-15 Table dated 7-28-11

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol # : Insert DFCI IRB protocol number
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: BVD-523
How Much: Your dose is _____
How Often: You will take each dose twice a day
When: You should take your dose ….

SPECIAL INSTRUCTIONS:

1. Complete one form for each cycle (28 days)
2. Swallow capsules whole with 8 oz. of water. Do not chew, crush, or break the capsules
3. BVD-523 must be taken on an EMPTY stomach, either 30-60 minutes before food or 2 hours after food.
4. BVD-523 is to be taken twice daily orally for 28 days, at 12 +/- 2 hour intervals.
5. All capsules, if more than one is taken at each dosing time, should be taken within 10 minutes.
6. On visit dates, doses should be taken in the clinic.
7. Always ask the study personnel before taking another drug, including herbs.
8. Do not change the study drug dosage
9. If you miss or vomit a dose do not take another one.
10. Any missed or vomited doses should be reflected in this diary. Record the date, the number of tablets you too, and
11. Ensure that the study personel are informed if you are hospit