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A Phase II Study of Binimetinib in Combination with Encorafenib in Adults with Recurrent BRAF V600-Mutated High-Grade Astrocytoma or other Primary Brain Tumor

A Protocol of the Adult Brain Tumor Consortium (ABTC)

Coordinating Center: ABTC Central Operations Office,
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Study Chair
Karisa Schreck, MD, PhD
Sidney Kimmel Comprehensive Cancer Center
201 North Broadway
Viragh 9th Floor, Box 3
Baltimore, MD 21231
Phone: 410-614-9916
Fax: 410-614-9335
Email: ksolt1@jhmi.edu

Study Co-Chair
Stuart Grossman, MD
Sidney Kimmel Comprehensive Cancer Center
201 North Broadway201 North Broadway
Viragh 9th Floor, Box 3
Baltimore, MD 21231
Phone: 410-955-8837
Fax: 410-614-9335
Email: grossman@jhmi.edu

Imaging Chair
Benjamin M. Ellingson, PhD
University of California Los Angeles
924 Westwood Blvd, Suite 615
Los Angeles, CA 90024
Phone: 310-481-7572
Email: bellingson@mednet.ucla.edu

Biostatistician
Xiaobu Ye, MD, MS
Johns Hopkins University
600 N. Wolfe Street/ Meyer 8-181D
Baltimore, MD 21287
Phone: 410-614-6261
Email: xye3@jhmi.edu

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PARTICIPATING INVESTIGATORS:
Adult Brain Tumor Consortium participating members

Nursing Contact
Michaella Iacoboni, RN
Johns Hopkins University
Phone: 410-955-4009
Fax: 410-614-9335
Email: msheeh13@jhmi.edu

Pharmacy Contact
Anne Delisa, PharmD, BCOP
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Phone: 410- 502-1036
Email: adelisa@jhmi.edu

ABTC Manager
Joy Fisher
Johns Hopkins University
Phone: 410-955-3657
Email: jfisher@jhmi.edu

ABTC Project Manager
Serena Desideri
Johns Hopkins University
Phone: 410-614-4400
Email: sdeside1@jhmi.edu

Protocol Development Coordinator
Eleni Kostalas-Lentis
Johns Hopkins University
Phone: 410-502-5973
Email: ekostal1@jh.edu

ABTC Programmer Analyst
Neeraja Danda
Johns Hopkins University
Phone: 410-502-5929
Email: ndanda1@jhmi.edu

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1.0 OBJECTIVES

Primary Objective

Estimate the efficacy of combination treatment with encorafenib and binimetinib, as measured by response rate (RANO criteria), in patients with recurrent BRAF V600E/K-mutated malignant glioma (MG) and anaplastic pleomorphic xanthoastrocytoma (PXAs).

Secondary Objectives

1. Estimate efficacy as measured by progression-free survival in subjects with recurrent malignant glioma or anaplastic PXA containing a BRAF-V600E/K mutation who receive drug.
2. Evaluate duration of response in subjects who have a partial or complete response.
3. Quantify the time-to-response among subjects who have a radiologic response.
4. Estimate efficacy as measured by overall survival in subjects with recurrent malignant glioma or anaplastic PXA containing a BRAF-V600E/K mutation who receive drug.
5. Characterize the toxicity profile of the combination of encorafenib and binimetinib in this patient population.

Exploratory Objectives

1. Estimate efficacy as measured by response rate, progression free survival, and overall survival in study participants with tumors other than MG and anaplastic PXA (cohort 3).
2. Estimate encorafenib and binimetinib concentrations in enhancing brain tissue and cerebrospinal fluid from a surgical cohort.
3. Explore putative mechanisms of resistance to encorafenib and binimetinib in BRAF-V600E/K mutated gliomas from an upfront surgical cohort and in patients who progress on study and undergo a clinically-indicated surgery.
4. Analyze the functional inhibition of the ERK signaling pathway in tumor tissue from a surgical cohort of patients treated with encorafenib and binimetinib, and correlate serum concentrations with changes in pathway activity.
5. Measure BRAF-V600 DNA mutant fraction in CSF and plasma over time while participants are receiving treatment.

2.0 BACKGROUND AND RATIONALE

2.1 BRAF Mutations in Gliomas

BRAF is one of 3 RAF-kinase isoforms (the others are ARAF and CRAF). All three are activated by dimerization, and induce MEK1 and MEK2 (MEK1/2) phosphorylation, which then activates ERK1 and ERK2 (ERK1/2). ERK1/2 translocates into the nucleus and regulates targets associated with proliferation, differentiation, and survival.(1) BRAF can be constitutively activated by point mutations removing the need for dimerization or by fusions with other kinases (KIAA1549-BRAF).(2) The *BRAF* V600 point mutation in particular is located within the kinase domain and allows constitutive activation of the kinase by removing inhibitory domain and prerequisite of dimerization for activity. This results in increased activation of the ERK signaling pathway and leads to cell proliferation and survival.(2)

While BRAF fusions are relatively common in pediatric gliomas, *BRAF* V600 mutations are also present in some adult gliomas. *BRAF* V600 mutations have been described in a variety of adult and pediatric gliomas including pleomorphic xanthoastrocytomas (PXA) (60-80%), gangliogliomas (20-70%), pilocytic astrocytomas (9-10%), low grade gliomas (5-15%) and glioblastomas (GBM) (1-5%).(3-5) While mutation is less common in adult GBM, it is relatively enriched for in the epitheliod subtype of GBM,(5, 6) and possibly in low grade astrocytomas as well (5-15%).(7) Despite a relatively low incidence in adults, the potential for targeted therapy makes *BRAF* V600 mutations in recurrent gliomas significant, as prognosis is poor and treatment options are very limited.

Current treatment for high-grade gliomas in adults is maximal safe surgical resection, followed by radiation with concurrent temozolomide, then adjuvant temozolomide. (8) Low-grade gliomas may be treated with an alternative chemotherapy regiment or radiation alone. Despite this, the average life expectancy for patients with glioblastoma is less than 18 months even with standard therapy, which was approved by the FDA thirteen years ago. While there is a significant amount of research underway for novel treatments, overall these have been disappointing to date. Recent advances in molecular diagnostics have revealed different glioblastoma subtypes that may have different driver mutations. (9)

The overall effect of *BRAF* mutations on the natural history of gliomas is unclear. A retrospective study of young adults (age 18-35) with GBM found BRAF mutations are associated with improved prognosis as compared to BRAF-WT tumors.(10) A similar result was found in a recent meta-analysis, which found BRAF-V600 mutations correlated with improved overall survival for young adults and low grade gliomas, but have no effect on prognosis in GBM in adults >35 years old, though the sample size was quite small.(11) In PXAs, BRAF mutations are associated with a longer overall survival in one analysis,(12) though not in another.(13)

2.2 Encorafenib

Encorafenib [methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3(methanesulfonamido) phenyl] -1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino] propan-2yl}carbamate] is a potent BRAF kinase inhibitor that is orally bioavailable and FDA approved in combination with binimetinib for the treatment of unresectable or metastatic melanoma with BRAF V600E or K mutations. It inhibits all RAF isoforms, but is most potent against the *BRAF* V600E mutations (IC_{50} = 0.35 nM), but also against wild-type (wt) BRAF and CRAF (IC_{50} 0.47 nM and 0.3 nM, respectively) in *in vitro* cell-free assays. (14)

Clinical Pharmacokinetics (PK) and Drug-drug Interactions of Encorafenib

The pharmacokinetics (PK) of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a *BRAF* V600E or K mutation. After repeat once-daily dosing, steady-state conditions were reached within 15 days, exposure being approximately 50% lower compared to Day 1, with a median half-life ~4 hours, and moderate intersubject variability (percent coefficient of variation [%CV]) of area under the curve (AUC; 12.3% to 68.9% over a range of doses). The PK of encorafenib has been shown to be approximately dose proportional after multiple doses, with any deviation from dose proportionality likely due to auto-induction of CYP3A4.

The human ADME study in healthy subjects showed that encorafenib is at least 86% absorbed and has a preferential distribution to plasma as compared to blood. Encorafenib was mainly eliminated via metabolism, with low levels of unchanged encorafenib detected in urine and feces. The dose was equally recovered in urine and feces (47.2% in each matrix) and the renal clearance was estimated to be 1.8%.

Results from a food-effect clinical study in healthy subjects have indicated that the influence of food on the PK of encorafenib is mild and not clinically relevant; therefore, encorafenib can be taken without regard to food. In combination studies, when administered with binimetinib, PK parameters of encorafenib were similar to those observed in the single-agent study.

2.3 Binimetinib

Binimetinib is an adenosine triphosphate (ATP)-uncompetitive inhibitor of MEK1 and MEK2. In cell-free systems, binimetinib inhibits MEK1 and MEK2 with half maximal inhibitory concentration (IC_{50}) values of 12 nM and 46 nM, respectively, on purified enzymes. The IC_{50} value of the active metabolite of binimetinib, AR00426032, was 7.1 nM. It is approved by the FDA in combination with encorafenib for the treatment of unresectable or metastatic melanoma with BRAF V600E or K mutations. (15)

Clinical Pharmacokinetics (PK) and Drug-Drug Interactions of Binimetinib

The PK of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. Binimetinib has been shown to be approximately dose proportional (Clinical Study Pfizer -162-111). The human ADME study indicated that approximately 50% of binimetinib dose was absorbed. The

primary metabolic pathways include glucuronication (up to 61.2% via UGT1A1), N-dealkylation (up to 17.8% via CYP1A2 and CYP2C19) and amide hydrolysis. The excretion route was 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib was 6.3% of total dose. The impact of UGT1A1 inhibitors or inducers has not been clinically assessed.

Food-effect clinical studies have indicated that the influence of food on the PK of binimetinib is mild and not clinically relevant; therefore, binimetinib can be taken with food.

2.4 Combination Therapy

Mathematical models support the fact that resistance to two different drugs, given serially, emerges faster than to the two drugs given simultaneously. (16) Unfortunately, resistance to BRAF inhibitors emerges in an average of 5-7 months in patients with melanoma. (17, 18) This occurs by a variety of different mechanisms including secondary mutations in BRAF, truncations, upregulation of other RAS/RAF family members, PI3K activation, PTEN loss, or RTK upregulation. (19-23) There have been attempts to avoid resistance by blocking MEK1/2, which is immediately downstream of BRAF, thereby making it more difficult for tumors to escape inhibition. Early studies showed that if a BRAF inhibitor is followed by a MEK inhibitor at the time of tumor progression, there is only a marginal improvement in survival (1.8mo). (24) More recently, the upfront combination of BRAF and MEK inhibitors has resulted in improved progression free survival as compared to monotherapy, and three different combinations of BRAF and MEK inhibitors are approved by the FDA for advanced-stage melanoma, including encorafenib and binimetinib (Table 1). (25-27) Encorafenib and binimetinib are approved by the FDA for combination therapy in patients with advanced or metastatic melanoma with an E or K mutation. (14, 15) The phase 3 COLUMBUS trial in advanced / metastatic melanoma with BRAF V600E or K mutations compared encorafenib plus binimetinib against vemurafenib alone and showed a progression free survival rate of 14.9 versus 7.3 months. (27) Overall survival was also favorable in the combination group, with median survival of 33.6 months with combination treatment and 16.9 months with vemurafenib alone. (28)

Study	Population	Therapy
CMEK162X2110, Phase 1b/2 (n=189)	BRAF V600E/K mutated advanced solid tumor	Encorafenib plus binimetinib
CLGX818X2109, Phase 2 (n=158)	Advanced melanoma with BRAF V600 mutation	Encorafenib plus binimetinib
CMEK162B2301, Phase 3 (n=921)	Advanced melanoma with BRAF V600 mutation	Encorafenib plus binimetinib vs. vemurafenib or encorafenib

Table 1: Compilation of clinical trials assessing encorafenib and binimetinib in patients with advanced cancer.

Clinical Pharmacokinetics (PK) of Combination Therapy

Administration of 45 mg binimetinib twice daily with escalating doses of daily encorafenib showed no distinct trend towards change in Cmax or AUC of binimetinib or encorafenib (compared to single-agent PK studies), per investigator brochure.

Blood Brain Barrier Penetration of Encorafenib and Binimetinib

Encorafenib is a P-glycoprotein (P-gp) substrate and an inhibitor of breast cancer resistance protein (BCRP), while binimetinib is a P-gp and BCRP substrate. Due to the function of the blood-brain barrier, the penetration of a drug into the brain depends on its intrinsic membrane permeability and its susceptibility to active efflux.(29) Although encorafenib and binimetinib have high intrinsic membrane permeability, efflux transporters may result in reduced brain concentrations for both.

Animal models have limited utility in predicting the effect of efflux transporter proteins on human brain concentrations. (29, 30) For example, dabrafenib and trametinib are efflux transporter substrates thought to have limited brain penetration based on nonclinical data, yet the combination had clinical activity in patients with melanoma brain metastasis in the COMBI-MB study. (31-33)

2.5 Rationale in Brain Tumors

BRAF Inhibitor Monotherapy in Brain Tumors

In pediatric brain tumors, BRAF inhibitor PLX4720 was able to inhibit MEK and ERK phosphorylation, as well as downstream AKT phosphorylation, in BRAF-V600E mutated astrocytoma cell lines, but not wild type tumor cell lines. It also prolonged survival of mice with xenografts from BRAF mutant brain tumors but not wild type tumors. (34)

BRAF inhibitors are being evaluated in gliomas with encouraging results. There have been several case reports of targeted treatment with BRAF inhibitors in adults with BRAF-V600 mutated primary brain tumors (Table 2). A recent basket study of vemurafenib monotherapy included adults with primary brain tumors and demonstrated positive responses to monotherapy in malignant gliomas (MG; 1/11 PR, 3/11 SD $\geq$ 6mo) and pleomorphic xanthoastrocytomas (PXAs; 4/7 radiographic responses PR or greater). (35) This is noteworthy, as response rates in recurrent glioblastoma trials are typically 3-8% for treatments that are non-efficacious (Table 1). Unfortunately, the average time to progression on BRAFi monotherapy was 5.3-5.7 months, similar to the results in melanoma. These results suggest that BRAF-V600 mutant brain tumors are sensitive to BRAFi, but develop resistance over time.

Age/ Sex	Histology	Prior Rx	BRAF Rx	Time on Txt	Best Outcome	Reference
34/F	PXA	RT, TMZ, PCV	Vemurafenib	4 mo	Stable disease	Chamberlain (36)
47/F	PXA	RT, TMZ, PCV	Vemurafenib	10 mo	PR	Chamberlain
53/M	PXA	RT+TMZ, PCV	Vemurafenib	10 mo	PR	Chamberlain
43/M	Anaplastic PXA	RT+TMZ, PCV	Vemurafenib	6 mo	Progression	Chamberlain
26/M	Epithelioid GBM	None	Vemurafenib	1 week	PR	Leaver (37)
39/M	Anaplastic PXA	RT	Vemurafenib	2 mo	CR	Leaver
41/M	Anaplastic PXA	TMZ, RT + TMZ	Vemurafenib	3 mo	PR	Lee (38)
35/F	PXA	None	Dabrafenib	3 mo	PR	Usubalieva (39)
25/M	HGG from ganglioglioma	RT+TMZ, adjuvant TMZ	Dabrafenib + TTFields	24+ mo	CR	Meletath (40)
21/F	Anaplastic PXA	RT, Vemurafenib	Dabrafenib	16+ mo	CR	Brown (41)

Table 2: Published reports of BRAF-directed therapy in adults. Legend: PXA = pleomorphic xanthoastrocytoma; GBM = glioblastoma; HGG = high grade glioma; RT = radiation therapy; TMZ = temozolomide; PCV = procarbazine, lomustine and vincristine; CR = complete response; PR = partial response.

BRAF / MEK Inhibitor Combination Therapy in Brain Tumors

Anecdotal clinical experience in the form of case reports suggests that combined BRAF and MEK inhibition (BRAFi/MEKi) can lead to sustained clinical and radiographic responses in some patients with recurrent BRAF V600-mutated recurrent high grade gliomas (HGG) in whom multiple previous therapies had failed (Table 3). (42-45)

Age/Sex	Histology	Prior Rx	BRAF/MEK	Time on Txt	Best Outcome
31/M	Anaplastic PXA	XRT+ TMZ, XRT,	Dabrafenib/ trametinib	14 mo	PR
35/F	Epitheliod GBM	XRT+TMZ, gliadel	Dabrafenib/ trametinib	30 mo	PR
28/F	Epitheliod GBM	None	Dabrafenib/ trametinib	11 mo	PR
32/F	Anaplastic PXA	XRT, vem+bev, Bev+CCNU	Dabrafenib/ trametinib	8 mo	PR
21/F	Anaplastic PXA	XRT, Vem, Dab	Dabrafenib/ trametinib	3 mo	PR
48/F	Anaplastic PXA	XRT, PCV, TMZ, Carboplatin	Dabrafenib/ trametinib	11 mo	PR
24/M	Anaplastic PXA	XRT+TMZ, Bev	Dabrafenib/ trametinib	3 mo	PR

Table 3: Published reports of BRAF/MEK inhibitor combined therapy in adults with high grade glioma. Legend: PXA = pleomorphic xanthoastrocytoma; GBM = glioblastoma; RT = radiation therapy; TMZ = temozolomide; PCV = procarbazine, lomustine and vincristine; Bev = bevacizumab; Vem = vemurafenib, Dab = dabrafenib; CCNU = lomustine; PR = partial response.

2.6 Correlative Studies Background

<u>BRAF-V600 DNA Mutant Fraction in CSF and Plasma</u>

Circulating tumor DNA (ctDNA) detected in plasma is becoming a powerful tool for detecting remission or progression in systemic cancers. (46-50) However, ctDNA is a generally insensitive tool for brain tumors. Our collaborators have demonstrated that cerebrospinal fluid (CSF) may be a more sensitive means of detecting circulating DNA (CSF-tDNA) than blood (Figure 2). (47) We intend to determine how sensitively and reliably ctDNA mutations can be detected in patients undergoing a uniform treatment regimen. ctDNA will be quantified from both CSF and plasma, and analyzed over time in patients who contribute multiple samples.

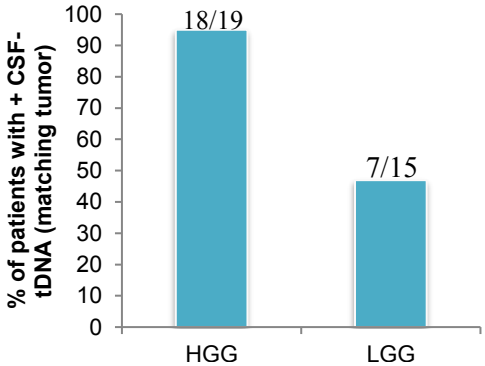


Figure 2: Detection of CSF-tDNA from primary brain tumors as derived from ventricular or lumbar CSF. Detected in 18/19 HGG and 8/15 LGG

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Patient Sample

Sample Size:

Minimum: 28 patients / Maximum: 62 patients

Accrual Rate:

1 patient per month

Gender:

Male and female

Age:

Patients must be at least 18 years of age.

Race:

Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	5	0	0	**7**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	5	0	0	**9**
White	14	21	3	8	**46**
More Than One Race	0	0	0	0	**0**
Total	**20**	**31**	**3**	**7**	**62**

3.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet all the following criteria within 30 days unless otherwise specified:

1. Subjects must have histologically confirmed high-grade glioma at diagnosis or recurrence (including but not limited to glioblastoma (GBM), anaplastic astrocytoma (AA), and gliosarcoma), or other high-grade primary brain tumor [including but not limited to anaplastic pleomorphic xanthoastrocytoma (aPXA), anaplastic ependymoma, and anaplastic ganglioglioma (AG)], that is recurrent after irradiation.
2. Patients must have a previously documented BRAF-V600 E or K mutation as performed by PCR or next generation sequencing in a CLIA-approved laboratory (including but not limited to Caris and FoundationOne).
3. Patients must have measurable (defined by at least 1 cm x 1 cm) contrast-enhancing disease by MRI imaging within 30 days of starting treatment.
4. The following intervals from previous treatments are required to be eligible:
    - 12 weeks from the completion of radiation.
    - 16 weeks from an anti-VEGF therapy
    - 4 weeks from a nitrosourea chemotherapy
    - 3 weeks from a non-nitrosourea chemotherapy
    - 2 weeks or 5 half-lives from any investigational (not FDA-approved) agents
    - 2 weeks from administration of a non-cytotoxic, FDA-approved agent (e.g., erlotinib, hydroxychloroquine, etc.)
5. Patients must be 18 years of age or older.
6. Patients must have a Karnofsky Performance (KPS) Status ≥ 60%.
7. Patients must have the following organ and marrow function within 30 days of starting treatment:

Absolute neutrophil count	≥1,000/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥ 9 g/dL
Total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN) OR total bilirubin >1.5 × ULN with direct bilirubin < 1.5 × ULN;
AST (SGOT)/ALT (SGPT)	≤ 3 x institutional ULN
Creatinine	≤ 1.5 x institutional ULN
	OR
Creatinine clearance	≥ 50 ml/min/1.73m^2 for patients with creatinine levels above institutional normal
APTT or PTT	≤ 1.5 x institutional ULN; subjects on anticoagulation may be permitted to participate
LVEF	≥ 50% as determined by MUGA or ECHO
QTc Interval	< 480 ms per triplicate averaged baseline ECG.

8. Patients must be able to provide written informed consent.
9. Women of childbearing potential must have a negative serum pregnancy test prior to study start. Women of childbearing potential must agree to use adequate contraception (intrauterine device, barrier, or other *non*-hormonal method of birth control; or abstinence) and not to donate ova from screening through 30 days after the last dose of study drug. Male participants must also agree to use adequate contraception and not to donate sperm from screening until 90 days after the last dose of study drug.
10. Patients must be maintained on a stable or decreasing dose of systemic corticosteroid regimen (no increase for 5 days) prior to baseline MRI. Topical and inhaled steroid treatment is allowed.
11. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with other malignancies must be disease-free for ≥ 2 years.
12. Patients must be able to swallow tablets and capsules.
13. Patients must have a tumor tissue form completed and signed by a pathologist; sites must agree to provide this form within 14 days after treatment start (see Section 9.6.4). The tumor tissue form must indicate availability of archived tissue. The archived tissue should be from the most recent tumor resection, demonstrating active tumor when sufficient tissue is available. If sufficient tissue is not available from the most recent surgery, then tissue from an earlier surgery is acceptable, if available, including from the initial resection at diagnosis.

3.3 Exclusion Criteria

Patients meeting any of the following criteria are excluded from the study:

1. Patients receiving any other standard or investigational agents are ineligible.
2. Patients with history or current evidence of the following conditions are excluded: neuromuscular disorder with associated elevated CK (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy), pancreatitis, retinal vein occlusion, uncontrolled HIV, or Hepatitis B/C. An exception will be made for (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months and for subjects with cleared HBV and HCV infections, who may enroll in the study.
3. Known hypersensitivity or contraindication to any component of binimetinib or encorafenib or their excipients
4. Current use of a prohibited medication (including herbal medications, supplements, or foods), as described in Section 4.4, or use of a prohibited medication ≤ 7 days prior to the start of study treatment.
5. Patient has not recovered to ≤ Grade 1 non-hematologic toxic effects of prior therapy before starting study treatment. ***Note:*** Stable chronic conditions (≤ Grade 2) that are not expected to resolve (such as neuropathy, myalgia, alopecia, prior therapy-related endocrinopathies) are exceptions and may enroll.

6. Impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, any of the following:

   - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) ≤ 180 days prior to start date;
   - Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2);
   - Left ventricular ejection fraction (LVEF) < 50% as determined by MUGA or ECHO;
   - Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg despite current therapy;
   - History or presence of clinically significant cardiac arrhythmias (including resting bradycardia, uncontrolled atrial fibrillation or uncontrolled paroxysmal supraventricular tachycardia);
   - Triplicate average baseline QTc interval ≥ 480 ms.

7. Impairment of gastrointestinal function or disease which may significantly alter the absorption of study drug (e.g., active ulcerative disease, uncontrolled vomiting or diarrhea, malabsorption syndrome, small bowel resection with decreased intestinal absorption), or recent (≤ 90 days) history of a partial or complete bowel obstruction, or other conditions that will interfere significantly with the absorption of oral drugs.

8. History of recent (≤ 90 days) thromboembolic or cerebrovascular event such as transient ischemic attack, cerebrovascular accident, or hemodynamically significant (massive or sub-massive) deep vein thrombosis or pulmonary emboli (DVT/PE). *Note*: Patients with DVT/PE that does not result in hemodynamic instability may enroll as long as they are anticoagulated for at least 4 weeks. *Note:* Patients with DVT/PE related to indwelling catheters or other procedures may enroll.

9. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.

10. Pregnant women are excluded from this study because the effects of encorafenib and/or binimetinib on a fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with encorafenib or binimetinib, breastfeeding should be discontinued if the mother is treated with encorafenib and/or binimetinib.

11. Patients who previously received BRAF or MEK inhibitors are excluded (including but not limited to dabrafenib, vemurafenib, encorafenib, sorafenib, trametinib, binimetinib, cobimetinib, or selumetinib).

12. Patients will be excluded if their tumor harbors a known RAS activating mutation. This does not need to be specifically tested for eligibility.

3.4 Additional Inclusion Criteria for Surgical Arm

Patients must meet the above inclusion / exclusion criteria for consideration with one exception. Patients with a BRAF-V600 E or K mutated low-grade glioma for whom there is a strong clinical suspicion of progression to high-grade would also be eligible for this arm. Additionally:

1. Patients must have a clinical indication for a tumor surgery.

2. No *a priori* contraindication to biospecimen collection (blood, tumor, CSF).

4.0 TREATMENT PLAN

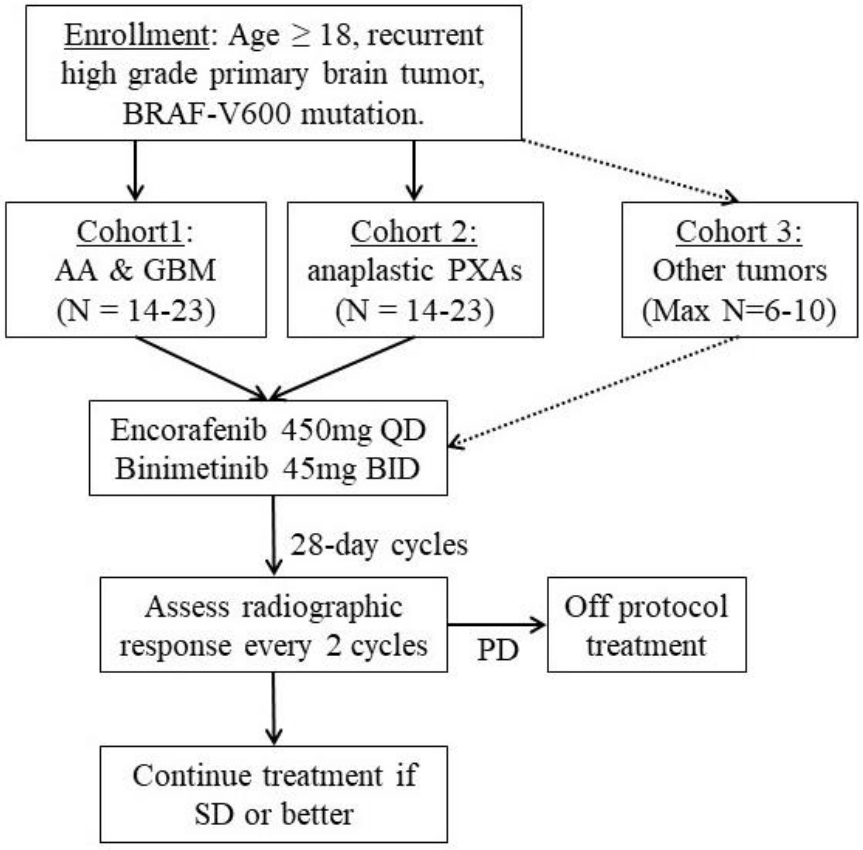
This is a Phase II, open-label, multicenter efficacy study of encorafenib in combination with binimetinib in adult patients with recurrent BRAF-V600E/K mutated high-grade primary brain tumors. The goal of this study is to estimate the efficacy of encorafenib and binimetinib as measured by radiographic response in recurrent high-grade primary brain tumors.

There are two arms: medical and surgical. All subjects on the medical arm must have histologically confirmed high-grade glioma (including but not limited to glioblastoma (GBM), anaplastic astrocytoma (AA), and gliosarcoma), anaplastic pleomorphic xanthoastrocytoma (aPXA) or other high-grade primary brain tumor (including but not limited to anaplastic ganglioglioma (AG), and anaplastic ependymoma) that is recurrent after first-line treatment. Subjects on the surgical arm must have a high-grade glioma or a known BRAF-mutated low-grade glioma with high clinical suspicion for progression to high-grade.

4.1 Treatment Schema

Medical Arm Treatment Schema

Following enrollment, patients will receive encorafenib and binimetinib at the FDA-approved dose of 450 mg of encorafenib once daily and the FDA-approved dose of 45 mg of binimetinib twice daily separated by 12 hours, continuously in 28-day cycles until progression or unacceptable toxicity. Patients will be followed by routine blood work, and general and neurological examination. A brain MRI will be performed prior to every odd-numbered cycle (every 8 weeks). Response will be assessed by RANO criteria (Section 8.1). Patients may remain on study and receive treatment until progression or as otherwise determined in Section 10.1.

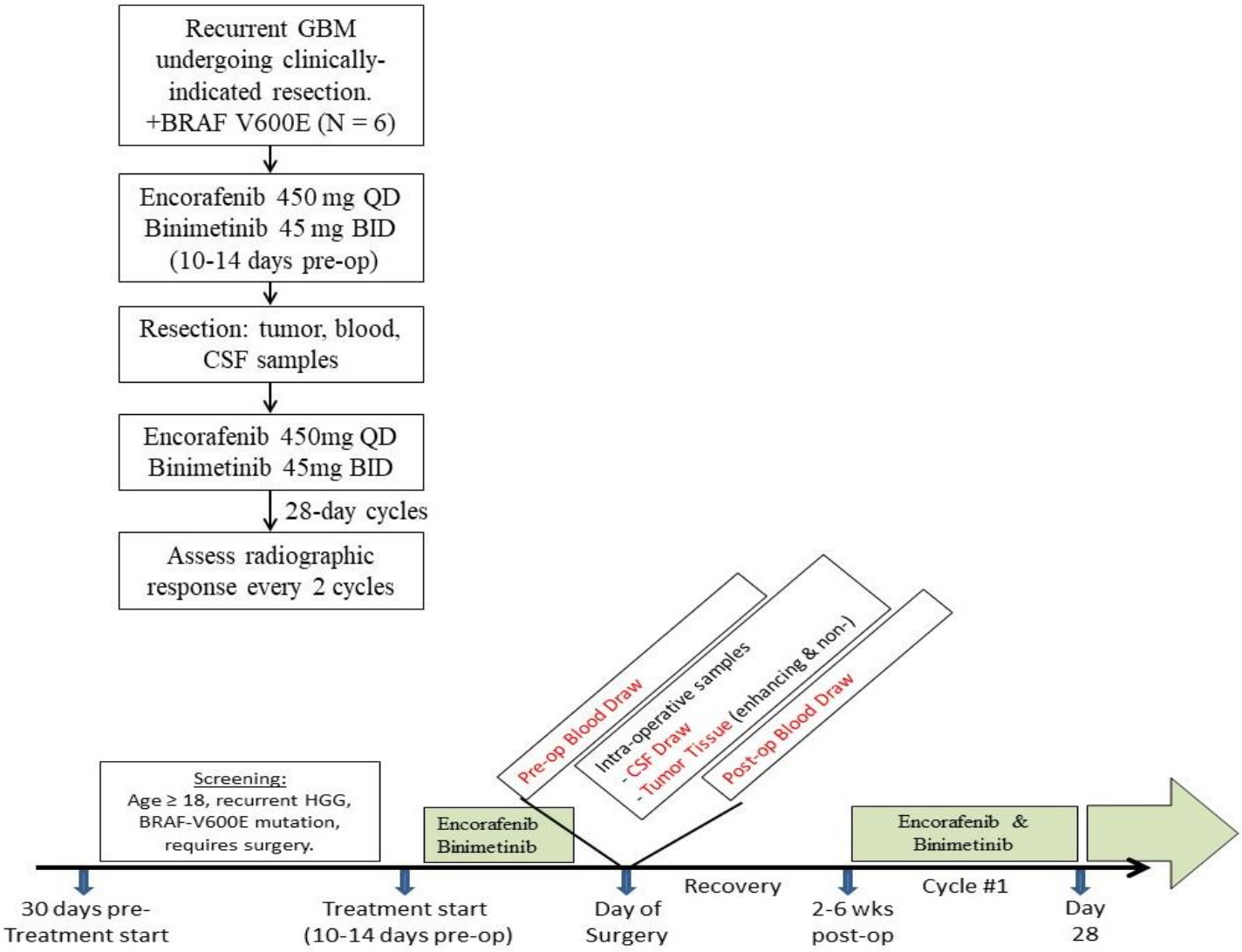


Surgical Arm Treatment Schema

Subjects in the surgical cohort must be candidates for a clinically-indicated surgery and must have a BRAF V600E/K-mutated high-grade glioma or a low-grade glioma with high clinical suspicion for progression to high-grade. These subjects will take encorafenib and binimetinib in combination at their FDA-approved doses (see Section 4.3 for administration details) for 10-14 days prior to surgery, with a preference for 14 days, though a minimum of 10 days is acceptable. The last dose of both drugs will be administered two hours prior to surgery. Specimens will be collected as described in Section 9.6 and processed as described in the **Laboratory Manual**.

After surgery, the subjects will not take further encorafenib or binimetinib until a study visit to assess their neurological exam, physical exam (or telemedicine physical evaluation), and performance status, at 2-6 weeks post-operatively. At time of restarting combination treatment, subjects will follow the schedule listed above for the medical cohort, and will continue treatment as defined in Section 10.1.

Patients with histopathology inconsistent with high-grade glioma (either treatment effect or low grade glioma) will be replaced. Overall survival will be assessed from the first day that patient receives drug to death from any cause.



Required Ophthalmology Exam for the Medical and Surgical Arms

A full ophthalmic examination will be performed by an ophthalmologist at Screening, and include best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and Ocular Coherence Tomography (OCT). Examination of the retina is required, especially to identify findings associated with serous retinopathy and RVO. On study, patients receiving binimetinib should be assessed at every physical examination for decreased visual acuity using a gross perimetry test (as opposed to automated visual field testing) in person or by telemedicine evaluation. Symptomatic patients should be referred for a full ophthalmic consultation.

- For patients with clinical suspicion of retinal abnormalities of any grade (e.g., serous retinopathy, RVO, photopsia, metamorphopsia, impairment of visual acuity), these additional assessments should be mandatory:

Non-vascular abnormalities: spectral domain OCT recommended Vascular abnormalities: fluorescein angiography of the central 30 degrees.

4.2 Treatment Requirements for subsequent cycles

If patients do not meet stopping criteria for encorafenib or binimetinib, and their study drugs are not being held based on their adverse events (per CTCAE version 5.0 defined in Section 5.1), they will proceed with the next cycle.

4.3 Encorafenib and Binimetinib Administration

Encorafenib will be administered in combination with binimetinib using the FDA approved doses. The dose of encorafenib is 450 mg orally once daily, taken with binimetinib. The dose of binimetinib is 45 mg orally twice daily, taken approximately 12 hours apart. It is recommended that both study drugs be taken in the morning rather than the evening. The study drugs may be taken with or without a meal.

Medical Arm patients: Encorafenib and binimetinib are taken every day for each 28 day cycle.

Surgical Arm patients: Encorafenib and binimetinib are taken for 10-14 days prior to surgery (preferably 14 days, though a minimum of 10 days is acceptable). The last dose of both drugs will be taken two hours prior to surgery. Following recovery from surgical resection (2-6 weeks), encorafenib and binimetinib are taken every day for each 28 day cycle.

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

If a subject misses a dose of binimetinib, the subject may take the dose immediately if the next dose is scheduled for at least 6 hours later. If the next scheduled dose of binimetinib

is due in less than 6 hours, the subject should skip the dose and resume binimetinib dosing at the next scheduled dose.

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

Treatment will generally be administered on an outpatient basis. Patients will be provided with medication diaries (Appendix I-IV) and instructed in their use. Patients will be instructed to bring all unused medication and their diaries to each study visit for assessment of compliance.

Because study treatment is intended for self-administration, if coming to the clinic presents a safety risk, it is permitted to ship the study drug and the appropriate medication diaries to the patient's residence before the scheduled cycle Day 1. The study drug should be shipped by a secure delivery method with package tracking and a delivery confirmation. The regulatory requirements for maintaining investigational product remain and should be addressed and documented.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

4.4 General Concomitant Medication and Supportive Care Guidelines

4.4.1 Permitted Concomitant Therapy Requiring Caution and/or Action

Encorafenib has been identified in vitro to be metabolized by CYP3A4 and to a lesser extent by CYP2C19. Concomitant use of moderate CYP3A4 inhibitors while on study should be avoided. If use of moderate CYP3A4 inhibitors is unavoidable and no alternatives are available, short-term use (≤ 30 days) is permitted with accompanying dose reduction to one-half of the encorafenib dose prior to use of moderate CYP3A4 inhibitors (or as close as can be achieved without exceeding the target dose). The encorafenib dose that was taken prior to initiating the CYP3A4 inhibitor may be resumed after the inhibitor has been discontinued for 3 to 5 elimination half-lives. Strong inhibitors of CYP2C19 should be used with caution when co-administered with encorafenib.

Encorafenib is a reversible inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP3A4 and UGT1A1. It is also a time-dependent inhibitor of CYP3A4, and induced CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C9, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index.

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal

contraception is required for females of childbearing potential during participation in this study. Caution should be used in participants receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

In vitro data showed that encorafenib is a substrate of the transporter P-gp. Thus, drugs that are known to inhibit or induce P-gp should be used with caution. Encorafenib is also a potent inhibitor of the renal transporters, OAT1, OAT3 and OCT2, and the hepatic transporters OATP1B1 and OATP1B3. The co-administration of drugs that are known to be sensitive or narrow therapeutic index substrates of OAT1, OAT3, OCT2, OATP1B1 or OATP1B3 should be used with caution.

In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation through UGT1A1. Binimetinib has also been shown to be a substrate of P-gp and BCRP. It is advised that inhibitors and inducers of UGT1A1, P-gp or BCRP transporters should be taken with caution when co-administered with binimetinib.

For a listing of examples of substrates, inhibitors and inducers to be used with caution, please consult with the FDA website: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Note that this list is not exhaustive.

Investigators should use caution when administering encorafenib or binimetinib with concomitant medications with a known, conditional or possible risk to prolong the QT interval and/or induce TdP. Subjects receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication, and may require dose titration of the concomitant medication. See the CredibleMeds® website for examples: Combined List of Drugs That Prolong QT and/or cause Torsades de Pointes (TDP). Note that this list is not exhaustive.

4.4.2 Prohibited Concomitant Medications During Study

Patients may receive other medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, anti-neoplastic biological therapy or other investigational agents. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study.

Per FDA labeling, administration of encorafenib along with a strong or moderate CYP3A4 inhibitor increases encorafenib plasma concentrations and may increase adverse reactions. The use of strong inhibitors of CYP3A4 is prohibited. Concomitant administration of encorafenib with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations and decrease encorafenib efficacy. Use of moderate and strong inducers of CYP3A4 is prohibited. Similarly, concomitant administration of encorafenib with sensitive CYP3A4 substrates my result in increased toxicity or decreased efficacy. Specifically, co-administration of encorafenib with hormonal contraceptives (CYP3A4 substrates) can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid

hormonal contraceptives.

The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use thereof.

4.4.3 Corticosteroids

The lowest required corticosteroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Alternatively, corticosteroid dose may be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

4.4.4 Herbal and Non-Traditional Medications

No data exist regarding the interaction of encorafenib and binimetinib with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving encorafenib and binimetinib therapy.

4.5 Lifestyle Considerations

4.5.1 Contraception

Female participants of childbearing potential must agree to take appropriate precautions to avoid pregnancy from Screening through 30 days after the last dose of study drug/ treatment. In addition, female participants must refrain from donating ova during the study through 30 days after the end of systemic exposure of study drug/treatment. Male participants should use a condom during treatment and through 90 days after the end of systemic exposure to study drug/treatment. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of systemic exposure to study drug/treatment. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of systemic exposure of study drug/treatment. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are **not** considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy

- Documented bilateral oophorectomy
  For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
  Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

4.5.2 Contraception Guidance:

NOTE: There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study.

The contraception guidelines outlined below are adapted from the recommendations related to contraception and pregnancy testing in clinical trials guidance document (Clinical Trials Facilitation Group Guidelines 2014). Participants must agree to use highly effective methods of contraception if it is mandated locally or when, in the judgment of the Investigator, compliance with acceptable methods is likely to be suboptimal.

The following methods have been classified as being highly effective (i.e., failure rate < 1% per year when used consistently and correctly) in preventing a pregnancy:

- Complete abstinence from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner (considered highly effective provided the vasectomized male has received medical assessment of surgical success and that the male is a female participant's sole sexual partner)

Acceptable birth control methods characterized as having a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

4.5.3 Meals and Dietary Restriction

Participants must avoid consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study drugs, due to potential CYP3A4 interaction with encorafenib. Orange juice is allowed.

4.5.4 Activity

Strenuous physical activities, such as competitive sports, can result in significant increases in CK levels while on binimetinib treatment. Participants should be cautioned not to start a new strenuous exercise regimen after first dose of study treatment.

5.0 DOSING DELAYS/DOSE MODIFICATION FOR TOXICITY

Clinically significant adverse events or abnormal laboratory values assessed as unrelated to disease progression, intercurrent illness, or concomitant medications may require dose delay and/or dose modification. Such toxicities must have an attribution of possible, probable, or definite to encorafenib and/or binimetinib (see Section 9.3). If multiple toxicities occur, dose modification decisions should be based on the most severe toxicity. If there is any question or clarification required concerning a toxicity, the treating site should contact the ABTC Central Office to determine patient's toxicity status. The ABTC Central Office, with the Study Chair (who may consult with Pfizer) will make the final decision.

5.1 Dose Modification for Encorafenib and Binimetinib

The dose levels and the general approach to encorafenib and/or binimetinib dose modification on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly recorded on the case report form.

Dose modifications are required for any clinically significant toxicity and are defined below.

- **In general, if toxicity occurs that is attributed to only one of the agents, only that agent should be dose-reduced/modified.**
- **If administration of binimetinib is interrupted, administration of encorafenib may be continued, but at a maximal dose of 300 mg per day.**

- **If administration of encorafenib is interrupted, administration of binimetinib may be continued at the same dose**
- **If either binimetinib or encorafenib are permanently discontinued, the other drug should also be discontinued and the patient removed from the study.**

If there is any question, Serena Desideri (sdeside1@jhmi.edu) or Neeraja Danda (ndanda1@jhmi.edu) at the ABTC Central Office and the Study Chair should be contacted.

Dose Reduction Schedule for Encorafenib

Dose Level	Encorafenib Dose/Schedule
0	450 mg daily
-1	300 mg daily
-2	225 mg daily
-3	150 mg daily

Dose Reduction Schedule for Binimetinib

Dose Level	Binimetinib Dose/Schedule
0	45 mg twice daily
-1	30 mg twice daily
-2	15 mg twice daily

Recommended Encorafenib Dose Modifications *

*For adverse events that may be related to both encorafenib and binimetinib, guidance is provided for the other agent also.

For patients with pre-existing disorder resulting in AE >1, the new event must resolve to at least the pre-existing baseline to resume treatment following the prescribed rules as outlined in the Modification Table.

Severity of Adverse Event	Dose Modifications
New Primary Malignancies	
Non-cutaneous *RAS* mutation-positive malignancies	Permanently discontinue.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold encorafenib and binimetinib for up to 6 weeks. • If improved, resume encorafenib and binimetinib at same or one reduced dose. • If not improved, permanently discontinue encorafenib and binimetinib.
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Eye Disorders (i.e., non-Uveitis Events	

Severity of Adverse Event	Dose Modifications
Grade 1–2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at one reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring (refer to footnote 18 of Table 9-1) until stabilization or resolution.
QTc Prolongation	
QTc > 500 ms and ≤ 60 ms increase from baseline	1st - 2nd occurrence: • Temporarily interrupt dosing of encorafenib until QTc < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: • Permanently discontinue encorafenib.
QTc > 500 ms and > 60 ms increase from baseline	Permanently discontinue.

Severity of Adverse Event	Dose Modifications
Hepatotoxicity	
Grade 2 AST or ALT	Maintain encorafenib dose. • If no improvement within 2 weeks, withhold encorafenib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions
Dermatologic (Except Hand-foot Skin Reactions)	
Grade 2	Initiate supportive measures: • Avoid unnecessary sunlight, apply broad-spectrum sunscreen at least twice daily. • Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g., clindamycin) OR oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID) If no improvement within 2 weeks, withhold encorafenib until Grade 0-1. Resume at same dose if first occurrence or reduce one dose level if recurrent.
Grade 3	Initiate supportive measures above. Withhold encorafenib until Grade 0-1. Resume at same dose if first occurrence or reduce one dose level if recurrent.
Grade 4	Permanently discontinue encorafenib.
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome (Dose Adjustment for Encorafenib ONLY)	
Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.
Grade 2	1st occurrence: • Maintain dose of encorafenib and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤ 14 days, interrupt dosing of encorafenib until resolved to Grade ≤ 1. Resume treatment with encorafenib at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Additional occurrence:

Severity of Adverse Event	Dose Modifications
	• Treatment with encorafenib may be maintained or interrupted based upon the Investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. If interrupted dosing of encorafenib per Investigator's judgment, interrupt until resolved to Grade ≤ 1. Resume treatment with encorafenib at the same dose level or one reduced dose level based upon the Investigator's discretion.
Grade 3	1st or additional occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. Then resume treatment at one reduced dose level of encorafenib. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. > 3nd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at one reduced dose level or permanently discontinue encorafenib should be based upon the Investigator's discretion.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at one reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at one reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including renal, hemorrhage).	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold encorafenib for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at one reduced dose level. • If no improvement, permanently discontinue.
First occurrence of any Grade 4	Permanently discontinue encorafenib or withhold for up to 4 weeks.

Severity of Adverse Event	Dose Modifications
	• If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at one reduced dose level. • If no improvement, permanently discontinue.
Recurrent Grade 3	Consider permanently discontinuing.
Recurrent Grade 4	Permanently discontinue.

Recommended Binimetinib Dose Modifications *

*For adverse events that may be related to both encorafenib and binimetinib, guidance is provided for the other agent also.

For patients with pre-existing disorder resulting in AE >1, the new event must resolve to at least the pre-existing baseline to resume treatment following the prescribed rules as outlined in the Modification Table.

Severity of Adverse Event	Dose Modifications
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of > 10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at one reduced dose level if the following are present: • LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib.
Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of > 20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib. • If improves to Grade 0-1, resume at one reduced dose level. • If no improvement, permanently discontinue binimetinib.
Life threatening PE	Permanently discontinue binimetinib.
Serous Retinopathy	
Symptomatic serous retinopathy/ Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at one reduced dose level or permanently discontinue binimetinib.
Retinal Vein Occlusion (RVO)	

Severity of Adverse Event	Dose Modifications
Any Grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and encorafenib for up to 6 weeks. • If improved, resume at same or one reduced dose level. • If not improved, permanently discontinue binimetinib and encorafenib.
Grade 4	Permanently discontinue binimetinib and encorafenib.
Other Eye Disorders (i.e., Non-retinal Events, non-Uveitis Events	
Grade 1-2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at one reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Interstitial Lung Disease	
Grade 2	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0-1, resume at one reduced dose level. • If not resolved within 4 weeks, permanently discontinue.
Grade 3 or Grade 4	Permanently discontinue.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
Grade 4 asymptomatic CPK elevation or Any Grade CPK elevation with symptoms or with	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at one reduced dose level.

Severity of Adverse Event	Dose Modifications
renal impairment	• If not resolved within 4 weeks, permanently discontinue binimetinib.
Dermatologic	
Grade 2	Implement supportive measures as above under encorafenib, dermatologic. If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or at one reduced dose level if recurrent.
Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce one dose level if recurrent.
Grade 4	Permanently discontinue.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at one reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgment of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at one reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue encorafenib and binimetinib.
Other Adverse Reactions (including hemorrhage)	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at one reduced dose level. • If no improvement, permanently discontinue.
First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at one reduced dose level. • If no improvement, permanently discontinue.
Recurrent Grade 3	Consider permanently discontinuing.
Recurrent Grade 4	Permanently discontinue.

5.2 Encorafenib and Binimetinib Dose Re-Escalation Guidelines

The lowest recommended dose level of encorafenib is 150 mg QD and the lowest recommended dose level of binimetinib is 15 mg BID. When the AE that resulted in a dose reduction improves to and remains stable at the patient's baseline level for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re-escalated, however:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTc ≥ 501 msec
- No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction
- No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.

Please refer to Dose Modification Table for recommended dose modifications for encorafenib and/or binimetinib, if applicable, based on the occurrence of treatment-related AEs. If a patient is re-escalated on a drug, please note this clearly on the case report forms and notify the ABTC Central Office that re-escalation is taking place.

5.3 Major Events

Major Events are non-treatment-related grade 3 and 4 hematologic and non-hematologic toxicities. Treatment should be delayed for major events if encorafenib and binimetinib may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline). If toxicity is not resolved in ≤ 6 weeks, the patient may be removed from treatment, pending discussion with the ABTC Central Office. The ABTC Central Office should be consulted if you are not clear on whether to continue or delay treatment.

5.4 Use of Hematologic Growth Factors

During the first 28 days of treatment, granulocyte colony stimulating factor (G-CSF) should be administered only for severe or prolonged neutropenia or for neutropenic sepsis. There will be no constraint on the use of growth factors during subsequent treatment; however, prophylactic use is discouraged and adherence to the American Society of Clinical Oncology (ASCO) guidelines is recommended (JCO, 12, 1994: pp 2471-2508). Patients should receive all necessary supportive care, including blood products, transfusions, antibiotics, pain medications, bisphosphonates, and replacement hormonal therapies (insulin, thyroid hormones, estrogen/progesterone).

5.5 Toxicity Criteria

All toxicities will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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). See also Section 9.3, Recording of Adverse Events.

6.0 PHARMACEUTICAL INFORMATION

6.1 Encorafenib

Other Names: Braftovi, LGX818

Information: Encorafenib is manufactured by Pfizer and is supplied as hard gelatin capsules in a dosage strength of 75 mg. Encorafenib capsules consist of encorafenib drug substance, copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, colloid silicon dioxide, crospovidone, and magnesium stearate of vegetable origin. The capsule shell is commercially available and contains gelatin and titanium dioxide as well as iron oxide red and yellow, ferrosoferric oxide, and monogramming ink. The capsule has a beige cap with a stylized "A" and a white body on which is written "LGX 75mg".

Encorafenib capsules should be stored at room temperature, not above 25°C and protected from moisture. Capsules are packaged in square, high-density polyethylene bottles that are induction sealed and closed with a polypropylene, child-resistant screw cap. Each bottle contains 90 capsules of Encorafenib. Encorafenib bottles will be labeled, at a minimum, with the lot number, contents (number of tablets), dosage strength, and storage conditions. Encorafenib should be dispensed to patients in the bottles provided by Pfizer and should not be repackaged at the site or pharmacy.

Stability: Refer to documentation enclosed with each shipment for expiration date. This is not included on the label for this product but will be provided with each shipment.

Route of Administration: Oral administration. Take encorafenib by mouth once daily with or without food. If a dose is missed, the dose can be taken if it is more than 12 hours until the next dose, otherwise it should be skipped.

6.2 Binimetinib

Other Names: Mektovi, MEK162

Information: Binimetinib is manufactured by Pfizer and is supplied as film-coated tablets in a dosage strength of 15 mg. The film-coated tablets consist of binimetinib drug substance, colloidal silicon dioxide/silica colloidal anhydrous, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose/cellulose, microcrystalline, and a commercial film coating. The tablet is ovaloid biconvex (capsule shaped), yellow to dark yellow in color with a stylized "A" on one side and "15" on the other side.

Binimetinib film-coated tablets should be stored at room temperature, not above 25°C and protected from light. Tablets are packaged in square, high-density polyethylene bottles that are induction sealed and closed with a polypropylene, child-resistant screw cap. Each bottle contains 180 tablets of Binimetinib. Binimetinib bottles will be labeled, at a minimum, with the lot number, contents (number of tablets), dosage strength, and storage conditions. Binimetinib should be dispensed to patients in the bottles provided by Pfizer and should not be repackaged at the site or pharmacy.

Stability: Refer to documentation enclosed with each shipment for expiration date. This is not included on the label for this product but will be provided with each shipment.

Route of Administration: Oral administration. Take binimetinib by mouth twice daily with or without food approximately 12 hours apart. If a dose is missed, the dose can be taken if it is more than 6 hours until the next dose, otherwise it should be skipped.

6.3 Agent Ordering

The investigator or those named as sub-investigators on the Statement of Investigator Form 1572 agree to supply study drugs only to those subjects enrolled in the study. The investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by Pfizer. The study site will maintain a dispensing log.

Once a site has submitted all required regulatory documents to ABTC (Forms 1572, *curriculum vitae* (CV), licenses, Institutional Review Board (IRB) protocol approval) an initial supply of drug can be ordered. An ABTC drug order form, which can be found on the ABTC website (ABTConsortium.org), should be emailed to the ABTC Central Office to initiate sending drug. The ABTC Central Office will forward the drug order form to Pfizer. Please allow 7 days from the receipt of the drug order at Pfizer for drug shipment.

6.4 Agent Accountability

Each institutional investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from Pfizer, using the NCI Oral Drug Accountability Record Form (Oral DARF).

Upon termination of the study the investigator or designee must complete a final inventory of supplies. Unused study drug should be disposed of per institutional pharmacy policy and noted in the record.

6.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

7.1 CTEP Registration Procedures

Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN)

or Rave or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

7.2 Site Registration Requirements – Institutional Review Board Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization

- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your NCI # and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does

not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

7.3 Patient Registration

Patient enrollment will be facilitated using OPEN. All site staff will use OPEN. OPEN is a web-based registration system available for ABTC studies from 9 a.m. to 4:30 p.m. Eastern Time. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Since this study includes a Phase I component, patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the registration system on OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll patients to this study.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role (or equivalent) on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Upon completion of the registration process in OPEN, sites must contact the ABTC Central Office to obtain confirmation of the patient's registration and dose assignment.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.0 RESPONSE ASSESSMENT / SAFETY AND QUALITY ASSURANCE

8.1 Criteria for Response Assessment

Patients with measurable enhancing disease will be assessed by the high grade glioma (HGG) RANO (radiographic assessment in neuro-oncology) criteria[54], while patients with no measurable enhancing mass and only T2/FLAIR abnormalities will be assessed using the low grade glioma (LGG) RANO criteria[55]. For the purposes of this study, subjects should be re-evaluated at the end of every 2 cycles (approximately every 8 weeks) with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below.

Measurable Disease on HGG RANO. Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal size of 1 cm x 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. If there are >2 lesions (multifocal) at baseline, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Complete Response – CR (requires *all* of the following):

a) Complete disappearance of all enhancing measurable and non-measurable disease, including T2 or FLAIR hyperintense lesions, sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No new lesions.
c) All measurable and non-measurable lesions, including T2/FLAIR hyperintense lesions, must be assessed using the same techniques as baseline.
d) Subjects must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved non-enhancing (T2/FLAIR) lesions.
f) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response – PR (requires *all* of the following):

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions (HGG RANO) or T2 hyperintense lesions (LGG RANO), sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No progression of non-measurable disease if HGG RANO is used.
c) No new enhancing or non-enhancing lesions.
d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan if using HGG RANO.
g) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease – SD (requires *all* of the following):

a) Does not qualify for CR, PR, or progressive disease (PD).
b) The designation of stable disease requires a minimum of 4-week duration.
c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
e) Stable clinically.

Progressive Disease – PD (defined by *any* of the following):

a) **For HGG RANO:** ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
b) Any new enhancing or non-enhancing lesion.
c) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.
d) Failure to return for evaluation due to death or deteriorating condition.
e) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

8.2 Assessment of Response

Assessment of response will begin with the MRI performed just prior to *every odd-numbered* treatment cycle. If during any scheduled MRI, the subject has a Complete Response or Partial Response, the MRI should be repeated prior to the next cycle. All scans are to be compared to the smallest measurement scan to date. The subject will then return to the every odd-numbered cycle schedule. This is required to confirm the duration of response. Subjects will be classified as responders if they have a minimum duration of response for 4 weeks at any time after the first cycle of encorafenib and binimetinib. MRI scans of subjects showing tumor response (PR or CR) as determined locally will be centrally reviewed by a neuroradiologist who will independently assess tumor size, compute percent tumor regression, and provide the final determination of tumor response.

8.3 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, pregnancy testing (in women of childbearing potential), regular measurement of vital signs, and the performance of physical/neurological, ophthalmic, and dermatologic examinations; ECGs and other cardiac monitoring may be performed as necessary.

8.4 Quality Assurance

Adherence to protocol therapy: Screening/baseline source documentation will be submitted/uploaded into CTEP's iMedidata Rave system and will be reviewed by the ABTC Central Office. As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on

each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Table of Required Observations - Medical Arm and Surgical Arm

Table 9.1 Required Observations – Medical and Surgical Arms. Encorafenib and Binimetinib (28-Day Cycles)

	Base line	Pre-Surgery (surgical arm only)	Day of Surgery (surgical arm only)	Post-Surgery (surgical arm only)	Pre-Cycle 1 (surgical arm only)	Days 1-28 of every cycle	Pre Cycle 2	Pre Cycle 3	Pre Cycle 4	Pre Cycle 5	Pre Cycle 6	Pre-Cycle 7	Pre Even Cycles after Cycle 7	Pre-Odd Cycles after Cycle 7	Off Treat-ment	30 Days Post-final Dose
Encorafenib		6	6			6										
Binimetinib		7	7			7										
Glucocorticoids Dose Evaluation	1			24	5		5	5	5	5	5	5	5	5	8	10
AE Evaluation	1		21	24	5		5	5	5	5	5	5	5	5	8,10	9, 10
MRI	1,13			24	5, 25			5, 13		5,13		5,13		5, 13	8	
H&P/Neuro Exam	1				5		5	5	5	5	5	5		5	8	
Ophthalmology Exam	18						5,18	5,18	5,18	5,18	5,18	5,18		5,18		
Dermatology Exam	1,19							5,19		5,19		5,19		5,19	19	10,19
KPS	1				5		5	5	5	5	5	5		5	8	
Vital Signs	1,2				2, 5		2, 5	2, 5	2, 5	2, 5	2,5	2, 5		2, 5	2,8	
Triplicate ECG	1,16,26															
ECHO or MUGA	1						17			17						
CBC, Diff, Platelets	1				5		5	5	5	5	5	5	5	5	8	
Serum Chemistry, CK, Troponin	1,3				3,5		3, 5	3, 5	3, 5	3, 5	3,5	3, 5	3, 5	3, 5	3,8	
APTT or PTT	1															
Serum Pregnancy Test	1,4															
Research CSF	5,15		5,15					5,15				5,15			5,15	
Research Blood	5,11		5,22					5,11				5,11			5,11	
Archived Tumor Tissue	14															
Tumor Tissue from Protocol Surgery			23												20	

1 – All baseline measurements must be done within minus 30 calendar days of treatment administration unless otherwise specified

2 – Including blood pressure, respiratory rate, heart rate, temperature, weight, height: height is required at baseline only; weight is required at each clinical evaluation.

3 – Including albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, creatinine, creatinine kinase, glucose, potassium, total protein, troponin, SGOT, SGPT, sodium.
4 – For women of child-bearing potential.
5 – Within minus 7 calendar days of cycle start.
6 – Surgical Arm: Pre-surgery, Encorafenib is administered once daily for 10-14 days prior to scheduled surgery, including the day of surgery (see Section 4.3). Patients are required to keep a medication diary (Appendix III).
Medical Arm and Surgical Arm (Post-Surgery): Encorafenib is administered orally once daily on Days 1-28 of each 28-day cycle (see Section 4.3). Patients are required to keep a medication diary (Appendix II).
7 – Surgical Arm: Pre-surgery, Binimetinib is administered orally twice daily for 10-14 days prior to scheduled surgery, including the day of surgery (see Section 4.3). Patients are required to keep a medication diary (Appendix III).
Medical Arm and Surgical Arm (Post-Surgery): Binimetinib is administered orally twice daily on Days 1-28 of each 28-day cycle (see Section 4.3). Patients are required to keep a medication diary (Appendix I).
8 – Evaluations done within +7 days of off treatment date unless indicated: do not repeat: if MRI within minus 14 days of off-treatment date; if H&P/neuro, KPS, labs within minus 5 days of off-treatment date.
9 – Adverse Events must be followed for at least 30 days from last dose of encorafenib and binimetinib.
10 – Perform within +14 days of the 30-day post-last dose date.
11 – Research blood for circulating tumor DNA (20 mL whole blood per time point) is to be collected at baseline, pre-Cycle 3, pre-Cycle 7, and at time of progression or off treatment. See Section 9.6.4.
12 – NA
13 – MRI with tumor measurements should be repeated every 8 weeks. See Section 4.1.
14 – Archived tumor tissue from the most recent tumor resection will be collected from patients when sufficient tissue is available. See Section 9.6.6.
15 – Surgical Arm: CSF will be collected during surgical procedure (required), prior to tumor disturbance. See Table 9.2.1 below and Section 9.6.4.
CSF donation at the following time points is optional in Medical Arm and Surgical Arm patients and requires additional, specific consent on consent form. In patients who consent, it should be collected at baseline, prior to cycle 3, prior to cycle 7, and at progression (6 mL per time point) or off treatment. It can be collected via Ommaya reservoir or lumbar puncture. See Section 9.6.4.
16 – ECG should be done prior to study enrollment, then as indicated clinically.
17 – Echocardiogram or MUGA scan should be performed prior to study enrollment, prior to Cycle 2, then every 3 cycles (i.e. cycle 5, 8, 11 etc..) thereafter unless indicated more frequently
18 – A full ophthalmic examination will be performed by an ophthalmologist at Screening, and include best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and Ocular Coherence Tomography (OCT). Examination of the retina is required, especially to identify findings associated with serous retinopathy and RVO. On study, patients receiving binimetinib should be assessed at every physical examination for decreased visual acuity using a gross perimetry test (as opposed to automated visual field testing) in person or

by telemedicine evaluation. Symptomatic patients should be referred for a full ophthalmic consultation.

* For patients with clinical suspicion of retinal abnormalities of any grade (e.g., serous retinopathy, RVO, photopsia, metamorphopsia, impairment of visual acuity), these additional assessments should be mandatory:
  - Non-vascular abnormalities: spectral domain OCT recommended
  - Vascular abnormalities: fluorescein angiography of the central 30 degrees.

19 – Dermatology evaluation should be performed by a study team member at baseline and every 8 weeks on trial, and for up to 6 months following discontinuation of encorafenib treatment.

20 – Flash-frozen tissue and 20 unstained FFPE slides following guidelines in Section 9.6.5 should be obtained from all patients who progress and have a clinically-indicated surgical resection at time of progression.

21 – Surgical Arm: patients should be seen on the day of surgery (prior to surgery) to evaluate for AEs.

22 – Surgical Arm (and Medical Arm patients undergoing a clinically-indicated surgery for their brain tumor while on study): See "Blood" in the Table of Additional Required Observations below (Table 9.2.1) for details and also Section 9.6.5.

23 – Surgical Arm (and Medical Arm patients undergoing a clinically-indicated surgery for their brain tumor while on study): See "Tumor Tissue" in the Table of Additional Required Observations below (Table 9.2.1) for details and also Section 9.6.5.

24 – Within 3 days post-surgery.

25 – Surgical Arm: Pre-Cycle 1 MRI does not need to be repeated if post-surgical MRI is within 21 days of Cycle 1 start.

26 – The ECG replicates should be extracted from the recordings at the predefined time points (5 minutes apart (+ 5min)

IMPORTANT: *The guidance below is subject to applicable local Institutional Policy on telemedicine. In the event that local Institutional Policy regarding telemedicine differs from this guidance, then please follow local Institutional Policy.*

Telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Required physical exams may be performed as a telemedicine physical evaluation, during telemedicine visits. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Additionally, informed consent should be obtained in person, but if deemed necessary, via telemedicine.

9.2 Table of Additional Required Observations - Surgical Arm

Patients on the surgical arm will be required to undergo all baseline observations as detailed for the medical arm in Section 9.1 prior to surgical resection with the exception of research CSF collection. Upon resumption of encorafenib and binimetinib after surgery (as detailed in Section 4.1), the Cycle 1-12 observations and off-treatment observations as detailed in the medical arm will also be observed. Observations listed below are additional on day of surgery.

Patients on the Medical Arm undergoing a clinically-indicated surgery for their brain tumor while on study should also adhere to specimen collection guidelines for Surgical Arm patients (below).

Table 9.2 Required Observations on Day of Surgery – surgical arm patients

	Means of Collection	2 hours prior to surgery	Just prior to surgery (after induction of anesthesia	Prior to tumor disturbance	During surgical resection	After closure
Encorafenib		1, 2				
Binimetinib		1, 2				
Blood	PD/Reistance/Circulating Tumor DNA: 10mL x 1		2,3			
	cTDNA:EDTA Lavender top 10mL x 2		2,3			
	PK: EDTA Lavender top 10mL x 1		2,3			2,3
Cerebrospinal Fluid	sterile container, 6mL			2,3		
Tumor Tissue	0.05-0.10 cm^3 contrast enhancing tumor				2,4	
	0.05-0.10 cm^3 non-enhancing tumor				2,4	
	0.5 cm^3 contrast enhancing tumor tissue				2,4	
	20 unstained slides					5
Documentation	On CRFs	2	2	2	2	2

1 – Encorafenib and Binimetinib should both be administered orally with a small quantity of water as necessary 2 hours before the patient's surgical time.
2 – Exact time for all drug administration and sample removal should be charted on case report forms (CRFs).
3 – The blood and CSF samples should be collected as close in time to the resection as possible. In the event that a specific blood tube is not available, a reasonable substitution (in volume only) may be made; however, the blood collected should not exceed that as outlined in the consent document. The same tube-type should be collected in all instances (e.g., two 6mL lavender top / EDTA tubes may be substituted for a 10mL tube).
4 – Three surgical specimens should be removed and flash-frozen. See Section 9.6.5.
5 - 20 unstained FFPE slides should be requested after tissue specimen is processed and final pathology report is complete. See Section 9.6.5. This is in addition to archival tumor tissue obtained for all study patients.

9.3 Adverse Events: Lists and Reporting Requirements

Patients will be evaluated for toxicity if they have received at least one dose of encorafenib and binimetinib.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 9.3.1) and the characteristics of an observed AE (Section 9.3.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

Adverse Events will be collected for at least 30 days following the last dose of study drug.

All adverse events must be reported to the ABTC Central Office and the NCI in the manner described and per the requirements of the investigative site's Institutional Review Board.

Adverse events will be entered into CTEP's iMedidata Rave database by the investigative site in a timely manner. See Section 12.0 – Records to be Kept.

9.3.1 Lists of AEs for encorafenib and binimetinib, alone and in combination

Table 9-3 Identified risks of single-agent encorafenib

MedDRA System Organ Class	Adverse Drug Reaction	Frequency Category	
Blood and Lymphatic System Disorders	Anemia	Common	
Ear and labyrinth disorders	Vertigo	Common	
Eye disorders	Iridocyclitis	Uncommon	
Gastrointestinal Disorders	Abdominal Pain	Common	
	Abdominal pain upper	Common	
	Constipation	Common	
	Pancreatitis	Uncommon	
	Pancreatitis Acute	Uncommon	
General disorders and administration site conditions	Xerosis	Common	
Immune System Disorders	Hypersensitivity	Common	
Investigations	Alanine aminotransferase increased	Common	
	Aspartate aminotransferase increased	Common	
	Blood alkaline phosphatase increased	Common	
	Blood creatinine increased	Common	
	Gamma-glutamyltransferase increased	Common	
Metabolism and nutrition	Decreased appetite	Very common	

disorders			
Musculoskeletal and connective tissue disorders	Muscle spasms	Common	
	Muscular weakness	Common	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Acanthoma	Uncommon	
	Basal cell carcinoma	Uncommon	
	Keratoacanthoma	Common	
	Melanocytic nevus	Common	
	Skin papilloma	Common	
	Squamous cell carcinoma	Common	
Nervous system disorders	Aguesia	Common	
	Dysguesia	Common	
	Dysaesthesia	Common	
	Hyperaesthesia	Common	
	Hypoaesthesia	Uncommon	
	Neuralgia	Common	
	Peripheral neuropathy	Very common	
Psychiatric disorders	Insomnia	Very common	
Skin and subcutaneous tissue disorders	Hair loss	Very common	
	Drug eruption	Uncommon	
	Dry skin	Very common	
	Hyperkeratosis	Very common	
	Itching	Very common	
	Palmar-plantar erythrodysaesthesia	Very common	
	Palmoplantar keratoderma	Very common	
	Rash follicular	Common	
	Rash generalized	Common	
	Rash macular	Common	
	Rash maculo-papular	Common	
	Rash papular	Common	
	Rash pruritic	Common	
	Skin redness	Very common	
	Urticaria	Uncommon	

Comprehensive Adverse Events and Potential Risks list (CAEPR)

for

Binimetinib (NSC 788187)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1374 patients.* Below is the CAEPR for Binimetinib.

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

Table 9-4 Identified risks of single-agent binimetinib

Version 2.1, September 11, 2019[1]

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (bradycardia)	
		Heart failure	
EYE DISORDERS			
	Blurred vision		***Blurred vision (Gr 2)***
		Eye disorders - Other (ocular hypertension)	
		Eye disorders - Other (retinal vascular occlusion)	
Eye disorders - Other (visual disorder)[2]			***Eye disorders - Other (visual disorder)[2] Gr 2)***
		Periorbital edema	
	Retinopathy[3]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema face		
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased[4]		***CPK increased[4] (Gr 2)***
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (myopathy)		
	Myalgia		***Myalgia (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash acneiform			***Rash acneiform (Gr 2)***
Rash[5]			***Rash[5] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (nail disorders)		
		Skin and subcutaneous tissue disorders - Other (severe cutaneous reaction)[6]	

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1374]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (skin fissures)		
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 2)***
	Thromboembolic event		
	Vascular disorders - Other (hemorrhage)[7]		

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

[2]Visual disorders may include visual disturbance, blurred vision, visual acuity reduced, flashing light, and floaters.

[3]Retinopathy may include chorioretinopathy, chorioretinitis, and retinal detachment.

[4]CPK increased may be associated with muscle pain and muscle weakness.

[5]Rash may include rash maculo-papular and erythematous rash.

[6]Severe cutaneous reactions may include bullous dermatitis, exfoliative dermatitis, erythema multiforme, and toxic skin eruptions.

[7]The majority of hemorrhage events were mild, although serious bleeding events in the eyes, GI tracts or lungs have rarely been reported.

Adverse events reported on binimetinib trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that binimetinib caused the adverse event:

Blood and lymphatic system disorders - Febrile neutropenia
Cardiac disorders - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (atrioventricular block); Cardiac disorders - Other (irregular heart rate); Cardiac disorders - Other (tachyarrhythmia); Cardiac disorders - Other (tachycardia); Myocardial infarction; Palpitations; Supraventricular tachycardia
Endocrine disorders - Hypothyroidism
Eye disorders - Dry eye; Eye disorders - Other (eye edema); Eye disorders - Other (visual field defect); Glaucoma
Gastrointestinal disorders - Abdominal distension; Ascites; Cheilitis; Colitis; Colonic obstruction; Dry mouth; Duodenal perforation; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (anorectal discomfort); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Hemorrhoids; Ileus; Pancreatitis; Small intestinal obstruction; Small intestinal perforation
General disorders and administration site conditions - Chills; Death NOS; Edema trunk; Flu like symptoms; General disorders and administration site conditions - Other (axillary pain);

General disorders and administration site conditions - Other (ulcer hemorrhage); Malaise; Multi-organ failure
Hepatobiliary disorders - Hepatobiliary disorders - Other (biliary colic); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic function abnormal)
Infections and infestations - Bacteremia; Bronchial infection; Kidney infection; Lung infection; Paronychia; Peritoneal infection; Sepsis; Shingles; Soft tissue infection; Upper respiratory infection; Urinary tract infection; Viremia
Injury, poisoning and procedural complications - Bruising
Investigations - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (C-reactive protein increased); Investigations - Other (electrocardiogram change); Investigations - Other (haptoglobin increased); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight gain; Weight loss
Metabolism and nutrition disorders - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus); Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
Musculoskeletal and connective tissue disorders - Arthritis; Flank pain; Muscle cramp; Neck pain; Pain in extremity
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Treatment related secondary malignancy; Tumor pain
Nervous system disorders - Akathisia; Dysgeusia; Headache; Nervous system disorders - Other (dropped head syndrome); Nervous system disorders - Other (myasthenic syndrome); Paresthesia; Presyncope; Somnolence; Spinal cord compression; Syncope; Transient ischemic attacks
Psychiatric disorders - Confusion; Hallucinations; Insomnia; Psychiatric disorders - Other (abnormal behavior); Suicide attempt
Renal and urinary disorders - Acute kidney injury; Hematuria; Proteinuria
Respiratory, thoracic and mediastinal disorders - Aspiration; Atelectasis; Cough; Hypoxia; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pneumothorax; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asthma); Wheezing
Skin and subcutaneous tissue disorders - Eczema; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (excoriation); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (rosacea); Skin and subcutaneous tissue disorders - Other (skin burning sensation); Urticaria
Vascular disorders - Hypotension; Lymphedema; Superficial thrombophlebitis; Vascular disorders - Other (aortic dilatation)

Note: Binimetinib in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Table 9-5 Identified risks of encorafenib in combination with binimetinib

MedDRA System Organ Class	Adverse Drug Reaction	Frequency Category	
Cardiac disorder	Diastolic dysfunction	Uncommon	
	Left ventricular dysfunction	Uncommon	
Eye disorders	Chorioretinopathy	Common	
	Detachment of retinal pigment epithelium	Very common	
	Iritis	Uncommon	
	Visual impairment	Very common	
Gastrointestinal disorders	Colitis	Uncommon	
	Gastrointestinal hemorrhage	Uncommon	
	Rectal haemorrhage	Uncommon	
Investigations	Ejection fraction decreased	Common	
Vascular disorders	Hypertension	Common	

9.3.2 Adverse Event Characteristics

Definition - Adverse Event (AE)

Adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Recording of Adverse Events - ABTC AE Form

- The investigator will monitor each patient closely for the development of adverse events and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.

- **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). You must use one of the CTCAE criteria to define your event.

  Adverse events not included in the CTCAE should be reported under "Other" within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New adverse events may be submitted to the CTEP Help Desk at ncictcaehelp@mail.nih.gov for annual evaluation by the CTCAE Change Management Committee.

- **Attribution of the AE:** The investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:

  - *Unrelated* – The AE is clearly not related to the investigational agent(s).
  - *Unlikely* – The AE is doubtfully related to the investigational agent(s).
  - *Possible* – The AE may be related to the investigational agent(s).
  - *Probable* – The AE is most likely related to the investigational agent(s).
  - *Definite* – The AE is clearly related to the investigational agent(s).

- All adverse events should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the investigator, constitute adverse events (even if not serious) should be followed.

9.4 Serious Adverse Events and Expedited Adverse Event Reporting

9.4.1 Definition – Serious Adverse Event (SAE)

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

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

9.4.2 Expedited Adverse Event Reporting

- **Use CTEP-AERS Web Application and Document on ABTC AE Form**

  - All SAEs must be documented on both the ABTC AE form and using the CTEP-AERS Web Application within 24 hours of learning of the event.

  - Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers). In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the ABTC Central Office by telephone at 410-614-4400 or 410-955-3657 or 410-599-4610. Once Internet connectivity is restored, the 24-hour notification must be entered electronically into CTEP-AERS by the original submitter at the site.

- When a serious adverse event (SAE) is reported through CTEP-AERS, the pharmaceutical company, Pfizer, will be notified by ABTC. This reporting must occur within twenty-four (24) hours of awareness of an SAE, or immediately upon awareness if the SAE is fatal or life-threatening. ABTC will utilize the secure SAE reporting email provided by Pfizer to submit this report. All SAEs will be documented and tracked by Pfizer as well as through the ABTC Central Office. Queries and follow up required for completing all SAEs will be conducted through Pfizer and the ABTC Central Office in a timely fashion. When an expedited report is required (15 days), a speedy resolution of queries will be expected in order to allow for on-time reporting to the FDA. ABTC is responsible for reporting all SAEs to the FDA.
- All SAEs (related or unknown relationship to study drug) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator.
- CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) of the Adult Brain Tumor Consortium (ABTC), the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions". Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.4.3 Other SAE Reporting

Any Serious Adverse Event, as described in Section 9.4.1, including death due to any cause, which occurs during this study must be **reported immediately (within 24 hours)** to the ABTC Central Office.

A phone call must be made to:

SERENA DESIDERI
ABTC DATA COORDINATOR
OFFICE: 410-614-4400
FAX: 410-614-9335
OR JOY FISHER, ABTC MANAGER: 410-955-3657 / 410-599-4610

These events also must be reported by the investigator to the appropriate Institutional Review Board (IRB).

Patients who are removed from study due to adverse events should be followed until the adverse event has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study, administration of study drug is to be discontinued immediately.

Pregnancies (both those of female patients and female partners of male patients) must be reported to Pfizer within 24 hours of the Investigator's knowledge. All pregnancies should be followed through to outcome and the outcome must be reported to Pfizer.

Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported following AE and SAE reporting guidelines.

Secondary Malignancy

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

Any secondary malignancies that occur following treatment with encorafenib and binimetinib should be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in Section 12.0.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

9.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions (Section 12.4).**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who

will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

9.6 Correlative Studies

9.6.1 Pharmacokinetic Assessment (All Surgical Patients): Exploratory

This correlative study is mandatory for all patients in the surgical arm. It is also optional for patients on the medical arm who progress while on treatment and undergo a clinically indicated resection while on study drugs.

Blood, cerebrospinal fluid, and tissue samples will be collected on the day of surgery at time points specified in Section 9.2. Details for the collection, processing, storage, and shipment of samples are provided in the **Laboratory Manual**.

We hypothesize tumor drug concentration will directly correlate with functional ERK inhibition, and may correlate with extent and duration of response in individual patients. Levels of total (protein-bound and unbound) encorafenib and binimetinib, as well as the active metabolite of each parent compound, will be measured as continuous variables using validated LC/MS methods in order to calculate the tumor-to-plasma ratio as an estimate of tumor permeability. (51) We will compare drug concentrations between enhancing and non-enhancing brain, and CSF. This assay will be performed by the ABTC-associated Applied Pharmacology Core at Johns Hopkins led by Dr. Michelle Rudek-Renaut.

9.6.2 Resistance Mechanisms (All Patients): Exploratory

There are two parts to this correlative study. Archival tumor tissue for genomic analysis will be obtained from all patients in the study (medical and surgical cohorts) as outlined in Section 9.1.

In the second component, FFPE post-treatment surgical tissue will be obtained from all patients in the surgical cohort (as described in the **Laboratory Manual**), and from patients who progress while on treatment and undergo an additional surgery. These slides will be obtained using the same procedure as described for archival tumor tissue.

A significant proportion of patients with melanoma or glioma treated with BRAF/MEK inhibitors develop therapeutic resistance over time as defined by relative insensitivity to targeted therapy leading to progressive disease. Thus, determination of resistance mechanisms is critical for future drug development. Putative mechanisms of resistance are defined as genomic or expression level changes that are likely to confer resistance, either because they have already been defined as such in other cancers, or because they are predicted to have a protein-level effect decreasing sensitivity to BRAF/MEK inhibitors. There are many known examples in other tumor types including mutations in *BRAF*, RAS, overexpression of COT, BRAF, CRAF, or YAP1, activation of receptor tyrosine kinases, or loss of NF1, PTEN, or STAG2/3.

Whole exome sequencing (WES) and RNA sequencing (RNAseq) will be performed to compare mutations in pre- and post-treatment samples (Illumina HiSeq 2500). WES & RNAseq will also be performed on unpaired baseline specimens from patients on the medical arm who do not respond to treatment with the assumption that a *de novo* mechanism of resistance exists in these tumors. We will use whole blood for comparison to filter out germline SNPs in all patients. Germline mutations will not be identified or reported. Results will have variant calling through standard procedures associated with the Computational Biology Core at Johns Hopkins. We will manually examine remaining variants to exclude sequencing errors and ensure sufficient coverage depth of at least 20x. We will compare candidate mutations against published genomic alterations conferring resistance, such as second-site mutations in *BRAF*, RAS mutations, and loss of *PTEN* and/or *NF1*. (20-23) For RNAseq results, we will use pathway analysis of the differentially expressed genes to identify potential alterations responsible for acquired resistance within individual patients and across the entire cohort. This assay will be performed by the laboratory of Drs. Schreck and Pratilas at Johns Hopkins.

9.6.3 Pharmacodynamic studies (All Surgical Patients): Exploratory

This correlative study is mandatory for all patients in the surgical arm. It is also optional for patients on the medical arm who progress while on treatment and undergo a clinically indicated resection while on study drugs.

Blood and tissue samples will be collected on the day of surgery at time points specified in Section 9.2.1. Details for the collection, processing, storage, and shipment of samples are provided in the **Laboratory Manual**.

Functional inhibition of ERK signaling will be measured by relative expression levels of phospho-ERK and p90 Ribosomal S6K (RSK) as quantified on immunoblot using standard procedures for quantification in the software ImageJ (https://imagej.nih.gov/ij/index.html). The ratios of phospho-ERK to total ERK and RSK to total ERK will be quantified as continuous variables. ERK inhibition will be measured as the fold-change in functional ERK activity (pERK/tERK and RSK/tERK, separately) between baseline (derived from archival tissue) and the surgical specimen. Functional inhibition will be correlated with peak serum concentrations separately for pERK and RSK to determine whether there is any correlation. This assay will be performed by the laboratory of Drs. Schreck and Pratilas at Johns Hopkins.

9.6.4 Circulating Tumor DNA (All Patients): Exploratory

This correlative study is mandatory for all patients, but there are two stages.

All patients on the medical and surgical arms will have a blood specimen (20 mL whole blood per time point) collected at pre-specified time points (see below). The blood samples will be collected, processed, stored, and shipped as described in the **Laboratory Manual**.

Cerebrospinal fluid donation is optional (other than the CSF collected during surgery for surgical arm patients, which is required) and requires additional, specific consent on consent form from patients on the medical and surgical arms. In patients who consent, it should be collected at the pre-specified time points below, same as for blood. It can be collected via Ommaya reservoir or lumbar puncture at the discretion of the treating physician (6 mL per time point). A patient does not need to consent to all these time points, but may elect to donate CSF for only one of these time points. Cerebrospinal fluid will be collected, processed, stored, and shipped as described in the **Laboratory Manual**.

Time Points:

- Baseline
- Pre-Cycle 3
- Pre-Cycle 7
- Off Treatment

Tumor-specific circulating DNA distinguishes from normal DNA by the occurrence of point mutations in tumor derived DNA. Tumor-specific circulating DNA can be detected in CSF as well as blood. (46) We will use Safe-SeqS, a next-generation sequencing assay that enables the detection of tumor specific DNA in a high background of normal DNA with high sensitivity and specify. (52) In this study, the BRAF V600E or K mutation is used to identify and monitor the fraction of tumor DNA. Tumor-specific circulating DNA as measured by the Safe-SeqS assay will be a continuous variable and shall be represented as a ratio between the mutant and wild-type allele evaluated (mutant fraction). The development of techniques to analyze genetic alterations in blood and CSF of patients is a rapidly changing field. The methods used to adequately detect mutated DNA and to differentiate it from wild type DNA will be adjusted and modified as appropriate on an ongoing basis. This assay will be performed by the laboratory of Dr. Chetan Bettegowda at Johns Hopkins.

9.6.5 Overview of Biospecimen Collection on Surgical Arm

Patients with a history of BRAF-V600E/K mutated glioma who are planning to undergo surgical tumor resection and are eligible to participate in this study (based on inclusion/exclusion criteria in Sections 3.2 and 3.3**)** may participate in the surgical arm. Patients on the medical arm who experience likely progression and require a clinically indicated surgery are also eligible if they continue drug until the day of surgery. All patients in this cohort should take their last dose of binimetinib and encorafenib two hours prior to surgery. At the time of this clinically indicated surgery, biospecimens will be collected, after the induction of general anesthesia, in the following order:

1) Prior to tumor manipulation: Whole blood (total of 40 mL) and cerebrospinal fluid (6 mL).

    a. Blood will typically be obtained from an arterial line and/or venous line placed as part of standard of care, placed immediately on wet ice, and processed as described in the **Laboratory Manual**.

b. CSF will be obtained in one of three ways per discretion of the neurosurgeon ± principal investigator, placed immediately on wet ice, and processed as described in the **Laboratory Manual**. Determination as to the method of CSF extraction (specifically, whether or not a lumbar puncture is indicated) will be determined prior to surgery and patient will confirm on consent form.
    i. By Ommaya reservoir access prior to the surgical procedure.
    ii. By lumbar puncture after the induction of anesthesia so as to induce no additional discomfort to the patient.
    iii. During surgery, from cisternal aspiration, if the cistern were to be opened as part of the planned surgical procedure.
    iv. During surgery, from ventricular aspiration, if the ventricle were to be encountered as part of the planned surgical procedure.

2) At tumor manipulation: Enhancing and non-enhancing brain tumor tissue.

    a. After frozen section confirmation of glioma and confirmation with the pathologist that sufficient material has been obtained for clinical diagnostic processing (grading, sub classification, and the relevant genetic testing), additional tumor specimens will be obtained for this study and processed as described in the **Laboratory Manual**.
    b. The specimen locations will be determined by the neurosurgeon based on MRI and tissue appearance with one intended to be in enhancing and the other in non-enhancing brain per MRI-contrast pre-operative image. The sample location will be noted with MRI wand and correlated with pre-operative MRI scan.

3) At closure: Whole blood (10 mL), obtained as above.

4) After tissue is processed: 20 unstained FFPE slides from current resection.

    20 unstained slides from the repeat resection should be requested and processed as outlined in the **Laboratory Manual** and shipped, along with a copy of the associated pathology report.

9.6.6 Archival Tumor Tissue: Exploratory

Archived tumor tissue from the most tumor recent resection demonstrating active tumor will be collected from all patients, when sufficient tissue is available. If sufficient tissue is not available from the most recent surgery, then tissue from an earlier surgery is acceptable, if available, including from the initial resection at diagnosis.

At the time of registration, prior to beginning treatment, a tumor tissue form indicating availability must be completed and signed by a pathologist for each study participant. This form provides written documentation of the availability of tissue for this study and the pathologist's agreement to send it as described below.

20 unstained slides, preferentially from the most recent tumor resection, will be requested. The associated pathology report from the institution of collection should be shipped with the slides.

Details for the collection and shipment of tissue samples are provided in the **Laboratory Manual**.

10.0 OFF TREATMENT/OFF STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The investigator may discontinue any subject's participation for any reason, including adverse event or failure to comply with the protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason must be stated on the case report form, and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for adverse events (AEs) for at least 30 days from the last dose of encorafenib and binimetinib.

10.1 Off Treatment Criteria

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

- Disease progression on MRI as determined by the local site
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

10.2 Off Study Criteria

Patients will only be off study at the time of death. All patients will be followed for survival every 2 months for the first two years from the off-treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit). Please note that additional survival status reports will be required twice yearly for ABTC Central Office reporting.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/ Endpoints:

This is a non-randomized, open-label, multicenter study of evaluating treatment efficacy and safety of encorafenib in combination with binimetinib in adult patients with recurrent BRAF-V600 mutated high-grade primary brain tumors. The study includes a total of four study cohorts. The Cohort 1 includes patients with high-grade glioma (including but not limited to glioblastoma (GBM), anaplastic astrocytoma (AA), and gliosarcoma. The Cohort 2 includes patients with anaplastic PXA that is recurrent after first-line treatment. The cohort 3 includes patients with recurrent high-grade brain tumor that is not included in the cohort 1 and 2, and the cohort 4 is a surgical cohort. All subjects must have histologically confirmed high-grade primary brain tumors.

The three treatment cohorts are independent subtypes of the high-grade primary brain tumors. No randomization is required for patient allocation on to each cohort.

The primary objective of the study is to evaluate efficacy of encorafenib in combination with binimetinib to treat patients with recurrent BRAF V600E/K-mutated malignant glioma (MG) and anaplastic pleomorphic xanothastrocytoma (PXAs).

The primary endpoint is tumor radiographic response per RANO criteria (Section 8.1) for the three treatment cohorts.

11.2 Sample Size Justification

Sample size consideration for cohort 1 malignant gliomas (MG) and cohort 2 anaplastic PXAs:
Based on the information from prior clinical trials (Scientific rational), the investigators consider the primary cohorts 1 (patients with AA or GBM) and 2 (Anaplastic PXAs) to share a similar null hypothesis of tumor response rate at 10% to be considered not clinically meaningful treatment effect and an alternative of 30% tumor response rate to be clinically desired treatment effect. A total of 23 patients is required per individual primary cohort 1 and cohort 2.
Cohort sample size estimation was based on a 2-stage design (minimax) with a futility analysis at end of first stage. Fourteen patients will be enrolled onto first stage. If no more than 1 response (7%) was observed among the initial 14 patients in a cohort, the cohort

would be terminated early and declared negative. Otherwise, nine more patients will be enrolled. If at least 5 responses (at least 22%) were observed among the 23 evaluable patients, the regimen would be considered worthy of further testing in this disease and the patient population. This design yields at least 85% power to detect a true response rate of at least 30% at a false positive rate of 10%. It yields at least 0.9 probability of a negative result if the true response rate is no more than 10%, with at least 0.58 probability of early negative stopping. The 2 primary cohorts will be evaluated independently.

The maximum total sample size for the two primary cohorts is 46 patients (23+23).

The sample size for the cohort 3 is 6 to 10 patients (other types of high-grade brain tumor that are not included in the primary cohort 1 or 2). This sample size is not based on statistical rationale but due to clinical feasibility. Patient enrollment will be considered completed at the time of completion of the enrollment in the cohort 1 and the cohort 2.

In the correlative studies, there is a surgical cohort of 6 patients who are clinically surgical indicated for tissue PK study after initial treatment prior to surgery. There is no clinical or trial decision will be made based on outcome of the surgical cohort. Currently, prior information on mount of drug concentration in tumor tissue are lacking, especially with this combination treatment. However, 6 patients will have 90% power to detect an 80% true probability of BBB penetration, with .93 likelihood of rejecting a 30% true probability of BBB penetration.

Data analysis will be performed for each cohort independently. Tumor response rate will be estimated as proportion of number of tumor responders over number of patients in a cohort, as a binomial distribution (exact method) with 80% and 90% confidence intervals.

Accrual Rate: The expected accrual rate is one patient per month among 11 ABTC institutions.

Slow Accrual Plan:
The study will be monitored for accrual starting quarter 6. If study accrual is ≤ 50% on the MG arm at the end of quarter 6 (9 patients) or every 2 quarters afterwards, we will add additional study centers by offering this study to a larger NCTN consortium such as Alliance or NRG Oncology in order increase accrual.

Stratification Factors: NA

11.3 Analysis of Secondary End Points:

Data analysis will be conducted for each cohort independently.

1. Progression-free survival: progression-free survival time is defined as the time from a date of treatment start to a date of the initial scan deemed tumor progression while patient is alive or death if there is no more than two missing imaging scans prior to death. The data will be censored if progressive disease was not observed at the time

of data cut-off for analysis. Probability of progression-free survival and median time of progression-free survival will be estimated using Kaplan-Meier method along with 95% confidence intervals.

2. Overall survival: survival time is defined as the time from a date of treatment started to a date of death. The data will be censored if patient was alive at the time of data cut-off for analysis. Overall survival (OS) and median OS will be estimated using Kaplan-Meier method along with 95% confidence interval.

3. Duration of response: duration of response is defined as the time from date of tumor response/per imaging to date of progression. The duration of the response will be summarized using descriptive statistics.

4. Time-to-response: time to response is defined as the time from date of treatment started to date of response per imaging among subjects who have a radiologic response. The duration of the time to response will be summarized using descriptive statistics.

5. Toxicity: NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used for scoring toxicity and adverse events. The severity and frequency of toxicity will be tabulated using descriptive statistics. The proportions of subjects who experienced grade 3 or above toxicities will be estimated, along with 95% confidence intervals by each type of toxicity.

11.4 Analysis of Exploratory Endpoints:

1. Clinical outcomes such as tumor response rate, progression-free survival, and overall survival for cohort 3 (recurrent BRAF-V600 mutated high-grade primary brain tumors not included in the cohort 1 and cohort 2). The standard definitions of these outcomes will be used as described above. The outcomes will be summarized and presented descriptively.
2. Encorafenib and binimetinib concentrations in enhancing brain tissue and cerebrospinal fluid (surgical cohort): descriptive summary on mean and standard deviation of drug will be reported. Additional analyses are summarized in Section 9.6.1.
3. Putative mechanisms of drug resistance are defined as identified genomic or functional alterations in post-treatment tissue that are not present, or are present in a much smaller variant allele frequency (VAF), in pre-treatment tissue, and that could contribute to decreased drug sensitivity. Candidate mutations will be measured using the methods described in Section 9.6.2. These results will be manually curated and confirmed against known gene lists.
4. Functional inhibition of the ERK signaling pathway: the functional inhibition of the ERK signaling pathway is defined by the measurements of phospho-ERK and RSK protein, quantitated relative to total ERK. Due to the exploratory nature, the pathway changes after drug exposure will be reported using descriptive summary.

5. BRAF-V600 DNA mutant fraction: the mutant fraction is measured as the number of BRAF V600E or –K transcripts relative to BRAF wild-type transcripts, corrected for differences in sequencing efficiency and the quantity of starting material. The mutant fraction in CSF and plasma will be collected over multiple time points during the study. The fraction change overtime will be presented as a liner or non-linear trend after data checking. Descriptive summary at each individual time point and multiple time points will be presented graphically.

   A more detailed description of exploratory correlatives are provided in Section 9.6.

12.0 STUDY ADMINISTRATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

12.1 Investigator's Study File

The Investigator's Study File must contain all essential documents as required by ICH E6, including IRB and governmental approvals with correspondence, informed consent forms, patient enrollment and identification logs, drug accountability records, staff *curriculum vitae*, authorization forms and other appropriate documents/correspondence etc.

12.2 Source Data/Documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include for example, patient hospital/clinic records, original laboratory reports, ECG read-outs, MRI reports, pathology and special assessment reports, etc.

Source documents are part of the study documents and must be maintained, and direct access to source documents made available upon request, for monitoring visits, IRB review, audits or inspections. All source documents used to verify answers on CRFs will be uploaded to RAVE, including all documentation to prove eligibility criteria was meet.

12.3 Document Retention and Archiving

The Investigator must keep all study documents on file for at least 5 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to local regulations.

These files must be made available for inspection, upon reasonable request, to authorized representatives of Sponsor or regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

12.4 Data Collection/Reporting

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

- All data are due within 14 days of evaluation time point. Please see Section 9.1 for evaluation time points. Note: Source documentation to verify each CRF must be uploaded into Rave.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION 9.3

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.5 Study Monitoring

The ABTC Study Monitor (Sponsor) will remotely monitor the Investigator and study team on a regular basis throughout the study to verify the adherence to Good Clinical Practice (GCP), the protocol and the completeness, consistency and accuracy of the data being entered into the CRFs. The Study Monitor will also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Study Monitor will only conduct target on-site monitoring (See ABTC Monitoring plan for details). If on-site monitoring is necessary, the Investigator shall ensure that the study monitor has direct access to all required study data (source documents) during the visits. This includes all patient records needed to verify the entries in the CRFs, regulatory documents, pharmacy records or any other documents of concern.

The Investigator agrees to cooperate with the Study Monitor and ABTC to ensure that any deviations or issues detected in the course of monitoring visits are resolved.

12.6 Audits and Inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP and regulatory requirements. These audits may also be conducted for quality assurance to ensure that complete and accurate data are submitted and that adverse events, complications and/or adverse reactions are being identified and reported.

The study may also be inspected by health authority inspectors, after appropriate notification. In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

13.0 REFERENCES

1.Lavoie H and Therrien M, Regulation of RAF protein kinases in ERK signalling. *Nat.Rev.Mol.Cell Biol.* 2015;16:281-298.

2.Davies H, Bignell GR, Cox C, et al., Mutations of the BRAF gene in human cancer. *Nature.* 2002;417:949-954.

3.Schindler G, Capper D, Meyer J, et al., Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma. *Acta Neuropathol.* 2011;121:397-405.

4.Dahiya S, Emnett RJ, Haydon DH, et al., BRAF-V600E mutation in pediatric and adult glioblastoma. *Neuro Oncol.* 2014;16:318-319.

5.Behling F, Barrantes-Freer A, Skardelly M, et al., Frequency of BRAF V600E mutations in 969 central nervous system neoplasms. *Diagn.Pathol.* 2016;11:55-016-0506-2.

6.Kleinschmidt-DeMasters BK, Aisner DLandForeman NK, BRAF VE1 immunoreactivity patterns in epithelioid glioblastomas positive for BRAF V600E mutation. *Am.J.Surg.Pathol.* 2015;39:528-540.

7.Chi AS, Batchelor TT, Yang D, et al., BRAF V600E mutation identifies a subset of low-grade diffusely infiltrating gliomas in adults. *J.Clin.Oncol.* 2013;31:e233-6.

8.Stupp R, Mason WP, van den Bent MJ, et al., European organization for research and treatment of cancer brain tumor and radiotherapy groups: National cancer institute of canada clinical trials grop. radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. 2005;352 (10):987-996.

9.Brennan CW, Verhaak RG, McKenna A, et al., The somatic genomic landscape of glioblastoma. *Cell.* 2013;155:462-477.

10.Zhang RQ, Shi Z, Chen H, et al., Biomarker-based prognostic stratification of young adult glioblastoma. *Oncotarget.* 2016;7:5030-5041.

11.Vuong HG, Altibi AMA, Duong UNP, et al., BRAF mutation is associated with an improved survival in glioma-a systematic review and meta-analysis. *Mol.Neurobiol.* 2017;

12.Ida CM, Rodriguez FJ, Burger PC, et al., Pleomorphic xanthoastrocytoma: Natural history and long-term follow-up. *Brain Pathol.* 2015;25:575-586.

13.Tabouret E, Bequet C, Denicolai E, et al., BRAF mutation and anaplasia may be predictive factors of progression-free survival in adult pleomorphic xanthoastrocytoma. *Eur.J.Surg.Oncol.* 2015;41:1685-1690.

14.Anonymous Braftovi (encorafenib) [package insert]. morrisville, NC: Array BioPharma; june 2018.

15.Anonymous Mektovi (binimetinib) [package insert]. morrisville, NC: Array BioPharma; june 2018.

16.Sosman JA, Kim KB, Schuchter L, et al., Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N.Engl.J.Med.* 2012;366:707-714.

17.Hauschild A, Grob JJ, Demidov LV, et al., Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2012;380:358-365.

18.Chapman PB, Hauschild A, Robert C, et al., Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N.Engl.J.Med.* 2011;364:2507-2516.

19.Poulikakos PI, Persaud Y, Janakiraman M, et al., RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature.* 2011;480:387-390.

20.Wang J, Yao Z, Jonsson P, et al., A secondary mutation in BRAF confers resistance to RAF inhibition in a BRAF V600E-mutant brain tumor. *Cancer.Discov.* 2018;pii.

21.Nazarian R, Shi H, Wang Q, et al., Melanomas acquire resistance to B-RAF(V600E) inhibition by RTK or N-RAS upregulation. *Nature.* 2010;468:973-977.

22.Paraiso KH, Xiang Y, Rebecca VW, et al., PTEN loss confers BRAF inhibitor resistance to melanoma cells through the suppression of BIM expression. *Cancer Res.* 2011;71:2750-2760.

23.Whittaker SR, Theurillat JP, Van Allen E, et al., A genome-scale RNA interference screen implicates NF1 loss in resistance to RAF inhibition. *Cancer.Discov.* 2013;3:350-362.

24.Kim KB, Kefford R, Pavlick AC, et al., Phase II study of the MEK1/MEK2 inhibitor trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. *J.Clin.Oncol.* 2013;31:482-489.

25.Long GV, Stroyakovskiy D, Gogas H, et al., Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: A multicentre, double-blind, phase 3 randomised controlled trial. *Lancet.* 2015;386:444-451.

26.Larkin J, Ascierto PA, Dreno B, et al., Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N.Engl.J.Med.* 2014;371:1867-1876.

27.Dummer R, Ascierto PA, Gogas HJ, et al., Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018;19:603-615.

28.Dummer R, Ascierto PA, Gogas HJ, et al., Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): A multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2018;19:1315-1327.

29.Di L, Umland JP, Chang G, et al., Species independence in brain tissue binding using brain homogenates. *Drug Metab.Dispos.* 2011;39:1270-1277.

30.Syvanen S, Lindhe O, Palner M, et al., Species differences in blood-brain barrier transport of three positron emission tomography radioligands with emphasis on P-glycoprotein transport. *Drug Metab.Dispos.* 2009;37:635-643.

31.Mittapalli RK, Vaidhyanathan S, Dudek AZandElmquist WF, Mechanisms limiting distribution of the threonine-protein kinase B-RaF(V600E) inhibitor dabrafenib to the brain: Implications for the treatment of melanoma brain metastases. *J.Pharmacol.Exp.Ther.* 2013;344:655-664.

32.Vaidhyanathan S, Mittapalli RK, Sarkaria JNandElmquist WF, Factors influencing the CNS distribution of a novel MEK-1/2 inhibitor: Implications for combination therapy for melanoma brain metastases. *Drug Metab.Dispos.* 2014;42:1292-1300.

33.Davies MA, Saiag P, Robert C, et al., Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): A multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol.* 2017;18:863-873.

34.Nicolaides TP, Li H, Solomon DA, et al., Targeted therapy for BRAFV600E malignant astrocytoma. *Clin.Cancer Res.* 2011;17:7595-7604.

35.Kaley T, Touat M, Subbiah V, et al., BRAF inhibition in BRAF(V600)-mutant gliomas: Results from the VE-BASKET study. *J.Clin.Oncol.* 2018;JCO2018789990.

36.Chamberlain MC, Salvage therapy with BRAF inhibitors for recurrent pleomorphic xanthoastrocytoma: A retrospective case series. *J.Neurooncol.* 2013;114:237-240.

37.Leaver KM, Zhang N, Ziskin JL, Vogel H, Recht LandThomas RP, Response of metastatic glioma to vemurafenib. *Neurooncol Pract.* 2016;3:268-271.

38.Lee EQ, Ruland S, LeBoeuf NR, Wen PYandSantagata S, Successful treatment of a progressive BRAF V600E-mutated anaplastic pleomorphic xanthoastrocytoma with vemurafenib monotherapy. *J.Clin.Oncol.* 2016;34:e87-9.

39.Usubalieva A, Pierson CR, Kavran CA, et al., Primary meningeal pleomorphic xanthoastrocytoma with anaplastic features: A report of 2 cases, one with BRAF(V600E) mutation and clinical response to the BRAF inhibitor dabrafenib. *J.Neuropathol.Exp.Neurol.* 2015;74:960-969.

40.Meletath SK, Pavlick D, Brennan T, et al., Personalized treatment for a patient with a BRAF V600E mutation using dabrafenib and a tumor treatment fields device in a high-grade glioma arising from ganglioglioma. *J.Natl.Compr.Canc Netw.* 2016;14:1345-1350.

41.Brown NF, Carter TandMulholland P, **Dabrafenib in BRAFV600-mutated anaplastic pleomorphic xanthoastrocytoma**. *CNS Oncol.* 2016;6:

42.Schreck KC, Guajardo A, Lin DDM, Eberhart CGandGrossman SA, Concurrent BRAF/MEK inhibitors in BRAF V600-mutant high-grade primary brain tumors. *J.Natl.Compr.Canc Netw.* 2018;16:343-347.

43.Johanns TM, Ferguson CJ, Grierson PM, Dahiya SandAnsstas G, Rapid clinical and radiographic response with combined dabrafenib and trametinib in adults with BRAF-mutated high-grade glioma. *J.Natl.Compr.Canc Netw.* 2018;16:4-10.

44.Brown NF, Carter T, Kitchen NandMulholland P, Dabrafenib and trametinib in BRAFV600E mutated glioma. *CNS Oncol.* 2017;6:291-296.

45.Migliorini D, Aguiar D, Vargas MI, Lobrinus AandDietrich PY, BRAF/MEK double blockade in refractory anaplastic pleomorphic xanthoastrocytoma. *Neurology.* 2017;88:1291-1293.

46.Bettegowda C, Sausen M, Leary RJ, et al., Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci.Transl.Med.* 2014;6:224ra24.

47.Wang Y, Springer S, Zhang M, et al., Detection of tumor-derived DNA in cerebrospinal fluid of patients with primary tumors of the brain and spinal cord. *Proc.Natl.Acad.Sci.U.S.A.* 2015;112:9704-9709.

48.De Mattos-Arruda L, Mayor R, Ng CK, et al., Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. *Nat.Commun.* 2015;6:8839.

49.Li Y, Pan W, Connolly ID, et al., Tumor DNA in cerebral spinal fluid reflects clinical course in a patient with melanoma leptomeningeal brain metastases. *J.Neurooncol.* 2016;128:93-100.

50.Momtaz P, Pentsova E, Abdel-Wahab O, et al., Quantification of tumor-derived cell free DNA(cfDNA) by digital PCR (DigPCR) in cerebrospinal fluid of patients with BRAFV600 mutated malignancies. *Oncotarget.* 2016;7:85430-85436.

51.Nijenhuis CM, Haverkate H, Rosing H, Schellens JHandBeijnen JH, Simultaneous quantification of dabrafenib and trametinib in human plasma using high-performance liquid chromatography-tandem mass spectrometry. *J.Pharm.Biomed.Anal.* 2016;125:270-279.

52.Kinde I, Wu J, Papadopoulos N, Kinzler KWandVogelstein B, Detection and quantification of rare mutations with massively parallel sequencing. *Proc.Natl.Acad.Sci.U.S.A.* 2011;108:9530-9535.

14.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The investigator is responsible for the retention of the patient log and patient records.

APPENDIX I – PATIENT MEDICATION DIARY - BINIMETINIB

(**Binimetinib** twice daily, every day in 28-day cycles)

Patient Name_____ **Patient Study ID** _____ **Cycle #** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **Binimetinib _____ mg (___ tablets) twice per day on Days 1- 28 of every 28-day cycle**. Take doses about 12 hours apart at approximately the same times each day. You may take binimetinib with or without a meal. Tablets should be swallowed whole, do not chew or crush.
2. Record the date and the time you took each **Binimetinib** dose.
   Record missed or skipped dose(s). If you miss a dose you may make up that dose if you take it within 6 hours of the time you normally take it. There must be at least 6 hours before the next dose.
   If you vomit a dose, do not re-take the study drug. Take the next dose at the time that you normally take the next scheduled dose.
3. Bring this form and any remaining **Binimetinib** tablets when you return for each appointment.

Week	Day	Date	Time of morning dose	# of 15 mg tablets	Time of evening dose	# of 15 mg tablets	Comments
1	1						
	2						
	3						
	4						
	5						
	6						
	7						
2	8						
	9						
	10						
	11						
	12						
	13						
	14						
3	15						
	16						
	17						
	18						
	19						
	20						
	21						
4	22						
	23						
	24						
	25						
	26						
	27						
	28						

Patient's Signature _____ **Date** _____

Nurse's Signature _____ **Date** _____

APPENDIX II – PATIENT MEDICATION DIARY - ENCORAFENIB

(**Encorafenib** once every day in 28-day cycles)

Patient Name_____ **Patient Study ID** _____ **Cycle #** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **Encorafenib _____ mg (___ capsules) once daily on Days 1- 28 (daily) of every 28-day cycle**. Take Encorafenib with one of your daily doses of Binimetinib. **Encorafenib** may be taken with or without a meal. Capsules should be swallowed whole, do not open or crush.
2. Record the date and the time you took each **Encorafenib** dose.
   Record missed or skipped dose(s). If you miss a dose you may make up that dose if you take it within 12 hours of the time you normally take it. There must be at least 12 hours before the next dose.
   If you vomit a dose, do not re-take the study drug. Take the next dose at the time that you normally take the next scheduled dose.
3. Bring this form and any remaining **Encorafenib** tablets when you return for each appointment.

Week	Day	Date	Time of dose	# of 75 mg capsules		Week	Day	Date	Time of dose	# 75 of mg capsules
1	1					3	15			
	2						16			
	3						17			
	4						18			
	5						19			
	6						20			
	7						21			
2	8					4	22			
	9						23			
	10						24			
	11						25			
	12						26			
	13						27			
	14						28			

Patient's Signature _____ **Date** _____

Nurse's Signature _____ **Date** _____

APPENDIX III – PRE-SURGICAL TREATMENT MEDICATION DIARY

Encorafenib (once daily) and Binimetinib (twice daily) for 10-14 days prior to surgery.

Patient Name _____ **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **Encorafenib _____ mg (___ capsules) every day in the morning starting 10-14 days prior to surgery**. Also take encorafenib **2 hours before your scheduled surgery** with a small amount of water.
2. You will take **Binimetinib _____ mg (___ tablets) twice per day starting 10-14 days prior to surgery.** Also take binimetinib **2 hours before your scheduled surgery** with a small amount of water.
3. **Encorafenib** and **Binimetinib** may each be taken with or without a meal. Pills should be swallowed whole, do not chew or crush. Encorafenib can be taken at the same time as binimetinib. If you miss a dose of encorafenib you may make up that dose if you take it within 12 hours of the time you normally take it. There must be at least 12 hours before the next dose of encorafenib. If you miss a dose of binimetinib you may make up that dose if you take it within 6 hours of the time you normally take it. There must be at least 6 hours before the next dose of binimetinib. If you vomit a dose of either study drug, do not re-take the study drug. Take the next dose of each study drug at the time that you normally take the next scheduled dose.
4. Record the date and the time you took each **Encorafenib** or **Binimetinib** dose and the number of pills you took. Record any missed or skipped dose(s). If you vomit a dose, do not re-take the study drug.
5. Bring this form and any remaining **Encorafenib** and **Binimetinib** pills when you return for each surgery.

Day	Date	Timeframe	Time of Dose	# pills of binimetinib	# pills of encorafenib	Comments
13 days prior to surgery		Morning				
		Evening			---	
12 days prior to surgery		Morning				
		Evening			---	
11 days prior to surgery		Morning				
		Evening			---	
10 days prior to surgery		Morning				
		Evening			---	
9 days prior to surgery		Morning				
		Evening			---	
8 days prior to surgery		Morning				
		Evening			---	
7 days prior to surgery		Morning				
		Evening			---	
6 days prior to surgery		Morning				
		Evening			---	
5 days prior to surgery		Morning				
		Evening			---	
4 days prior to surgery		Morning				
		Evening			---	
3 days prior to surgery		Morning				
		Evening			---	
2 days prior to surgery		Morning				
		Evening			---	
1 days prior to surgery		Morning				
		Evening			---	
(add'l day if surgery delayed)		Morning				
		Evening			---	
(add'l day if surgery delayed)		Morning				
		Evening			---	
Day of Surgery: 2 hours prior to surgery		Morning				
		Evening			---	

Patient's Signature _____ **Date** _____

Nurse's Signature _____ **Date** _____

APPENDIX IV – PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:	
Diagnosis:	
Study Doctor:	
Study Doctor Phone #:	
NCI Trial #:	ABTC-1802
Study Drug(S): **Encorafenib** **Binimetinib**	

For more information: 1-800-4-CANCER

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