MSK PROTOCOL COVER SHEET

Phase I/II Study of Binimetinib with Encorafenib in Patients with non-V600 Activating BRAF Mutant Advanced Malignancies

Dr. Rona Yaeger/Early Drug Development:

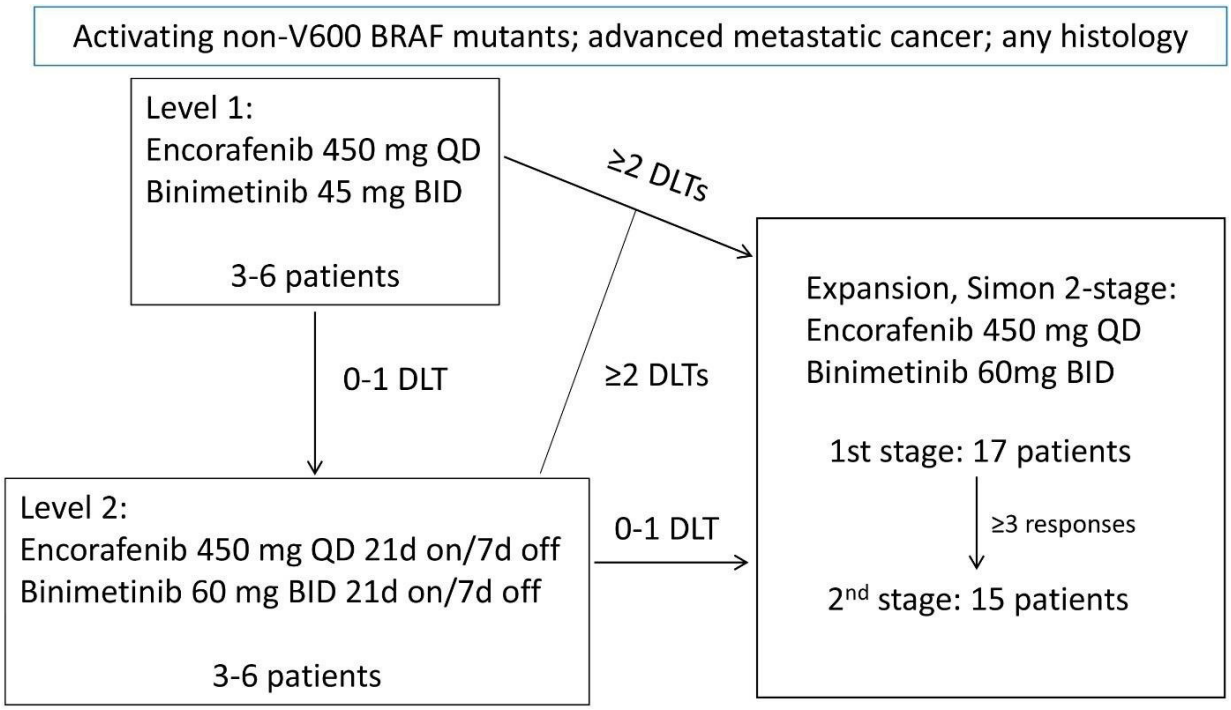
Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase I/II study of higher dose MEK inhibitor treatment together with RAF inhibitor treatment to target advanced cancers with non-V600 BRAF activating alterations. The goal of this trial is to test the safety and efficacy of an innovative combination aimed to more profoundly inhibit ERK signaling in tumors. In this regimen, the RAF inhibitor encorafenib serves to increase ERK pathway inhibition by (1) contributing a modest inhibition of mutant BRAF and by (2) opposing the toxicity of the MEK inhibitor binimetinib in normal tissues to allow treatment with a higher dose of binimetinib.

The trial includes an evaluation of the safety of the planned combination in a limited escalation followed by an efficacy evaluation of the dosing schedule that is deemed safe in a Simon's 2-stage design (**Figure 1**).

Figure 1. Study Schema



Abbreviations: QD, once daily; BID, twice daily; d, days; DLT, dose-limiting toxicity

Please note that the expansion phase includes initial patients treated at the level 2 dosing of encorafenib plus binimetinib on an intermittent schedule of 3 weeks on/ 1 week off and patients treated with amended, continuous dosing of study drugs. Drug dosing schedule was amended during the trial because several patients reported good tolerance of continuous

dosing during the first three weeks and symptomatic improvement but recrudescence of symptoms during the week off drug.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

Phase I: To evaluate the tolerability and safety profile of encorafenib 450 mg oral once daily (QD) with binimetinib 60 mg oral twice daily (BID) in patients with advanced malignancies harboring non-V600 activating BRAF alterations by evaluating dose-limiting toxicities (DLTs). Two dosing schedules will be evaluated. Initially patients were treated with intermittent dosing with treatment for 21 days on and 7 days off. Based on several patients reporting good tolerance of the continuous dosing and increased symptoms, including pain and fatigue, during the one week off and the absence of any dose limiting ophthalmologic toxicity, the dosing schedule was changed during the trial to a continuous schedule of encorafenib and binimetinib.

Phase II: To obtain preliminary evidence of efficacy measured by objective response rate .

2.2 Secondary Objectives

Phase II:

To determine progression free survival (PFS) for patients with advanced cancer with non-V600 activating BRAF mutations treated with encorafenib and binimetinib.

To determine overall survival (OS) for patients with advanced cancer with non-V600 activating BRAF mutations treated with encorafenib and binimetinib.

To determine safety, tolerability, and adverse event profile of this regimen.

2.3 Exploratory Objectives

Phase II:

2.31 To evaluate degree of ERK pathway inhibition with encorafenib and binimetinib in tumor tissue in day 7 on-treatment biopsies and correlate with objective response rate. Pharmacodynamic (PD) markers will consist of (1) RNA expression of the ERK transcriptional output genes DUSP6, SPRY2, and ETV1 and (2) immunohistochemical analysis of phosphorylated ERK expression.

2.32 To evaluate changes in mutant BRAF circulating free DNA (cfDNA) detection with treatment and correlate with the objective response rate.

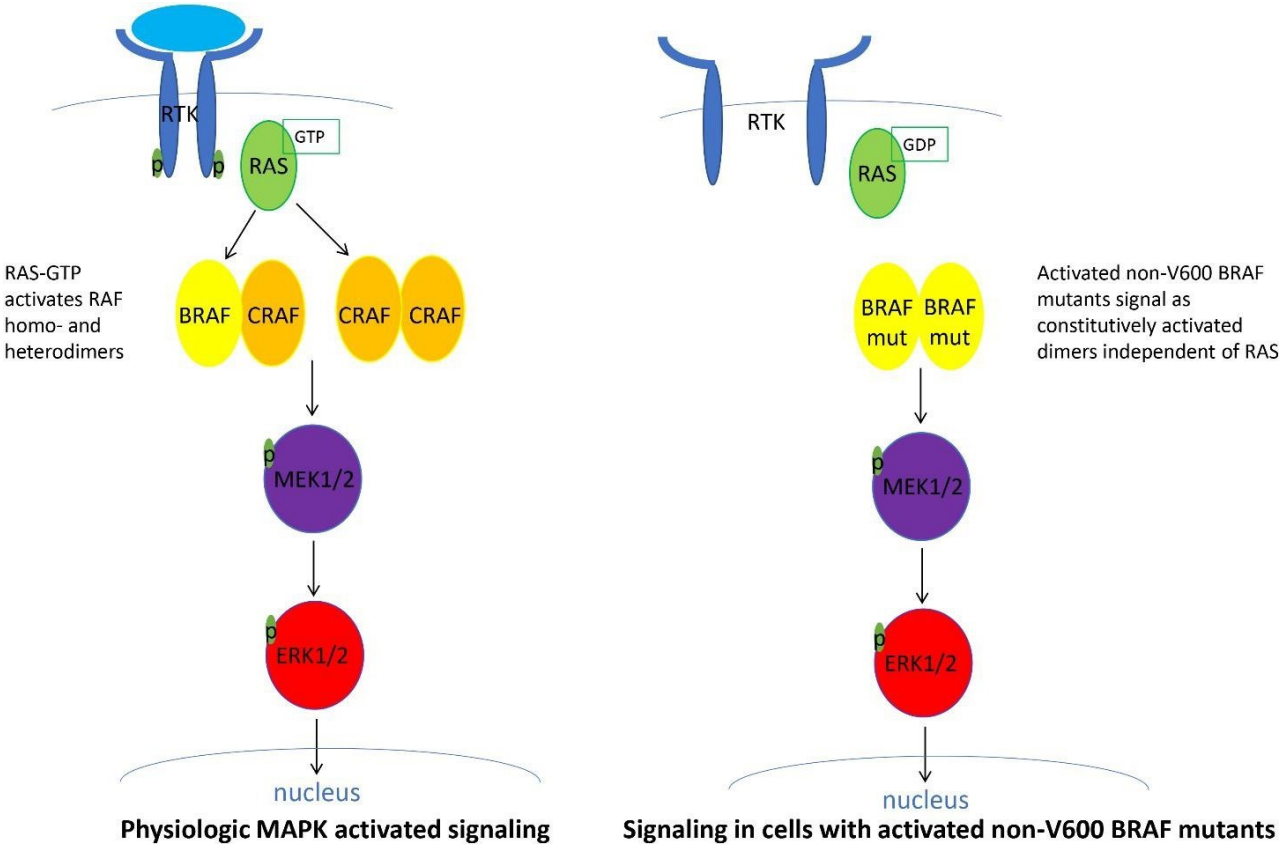
2.33 To evaluate the full tumor genomic profile with a multi-gene next-generation sequencing (NGS) assay and correlate with the objective response rate.

3.0 BACKGROUND AND RATIONALE

The MAPK (mitogen-activated protein kinase) signaling pathway is the most commonly activated oncogenic pathway in human cancer. Selective BRAF inhibitors have

revolutionized the treatment of BRAF V600 mutant tumors, including melanoma, lung cancer, and anaplastic thyroid cancers[1-3]. But the success of selective RAF inhibitors has been the exception, as the efficacy of MEK and ERK inhibitors has been limited by toxicity and inability to adequately inhibit the target[4, 5]. Non-V600 BRAF activating mutants, a heterogeneous group of genomic alterations, depend on ERK activation but are unaddressed by existing therapeutic strategies. Signaling in these tumors **(Figure 2)** consists of activated mutant BRAF dimers that turn on the MAPK cascade by activating MEK, which activates ERK, which then acts on cytosolic and nuclear targets to regulate cellular proliferation, survival, and differentiation.

Figure 2. Diagram for signaling in physiologic conditions versus in cells with activated non-V600 BRAF mutants

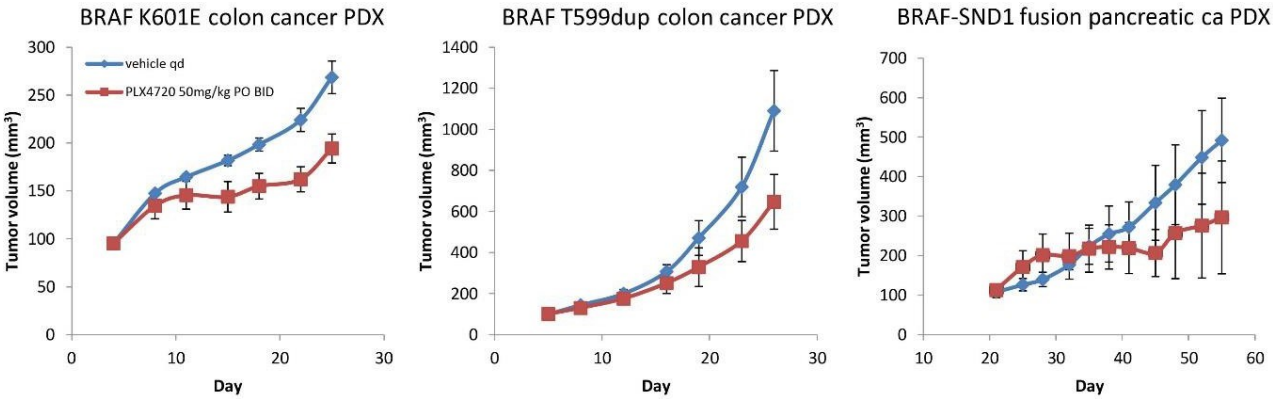


Non-V600 *BRAF* mutations and fusions are common in human cancer. In both published series and our own institutional sequencing effort, which has now profiled more than 20,000 cancers using the multi-gene exon-capture NGS platform MSK-IMPACT [Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets], among *BRAF* alterations, they account for approximately 75% of alterations in lung cancers, 10-20% in melanomas, and 30% in colorectal cancers[6]. In total, we have prospectively identified approximately 200 patients with non-V600 activating *BRAF* mutation or fusion, *RAS* wild-type tumors, through MSK-IMPACT analysis.

Pharmacodynamic analysis of tumor samples from patients with BRAF V600E melanoma treated in the phase 1 study of vemurfenib indicate that profound ERK inhibition is required for response to MAPK pathway inhibitors.[7] Inadequate continuous dosing of MAPK inhibitors leads to insufficient pathway inhibition for responses. A threshold of ERK inhibition is required for effect on tumor growth. This explains the limited activity seen with MEK or ERK inhibitors alone, where dose escalation is limited by a narrow therapeutic index.[4,9,15] To more effectively inhibit ERK signaling in these tumors, we plan to study a combination strategy that applies RAF inhibitors as a tool to oppose the toxicity of MEK inhibitors in normal tissues to titrate up the MEK inhibitor so as to better block ERK signaling in the tumor. Current RAF inhibitors (vemurafenib, dabrafenib, encorafenib) selectively inhibit BRAF V600 mutants, which signal as monomers in steady state. In RAF wild-type tissues, these drugs cause "paradoxical activation" and increase phosphorylated ERK levels by transactivation of one

protomer in the RAF dimer pair[7]. These drugs, however, do not cause paradoxical ERK activation in non-V600 activating BRAF mutants[8]. In these tumors, the mutant BRAF dimers are constitutively activated and thus not activated further by RAF inhibitors. Instead binding of RAF inhibitor to one site in the dimer pair, leads to inhibition of that protomer and a modest inhibition of ERK. Consistent with this understanding, treatment with the RAF inhibitor vemurafenib does not accelerate the growth of cell lines and patient derived xenografts (PDXs) with non-V600 *BRAF* alterations that we have generated from patients with activating non-V600 *BRAF* alterations **(Figure 3)**.

Figure 3. Effect of RAF inhibitor treatment on the growth of patient-derived xenografts (PDXs) with non-V600 activating BRAF mutants. Five mice are included in each arm.

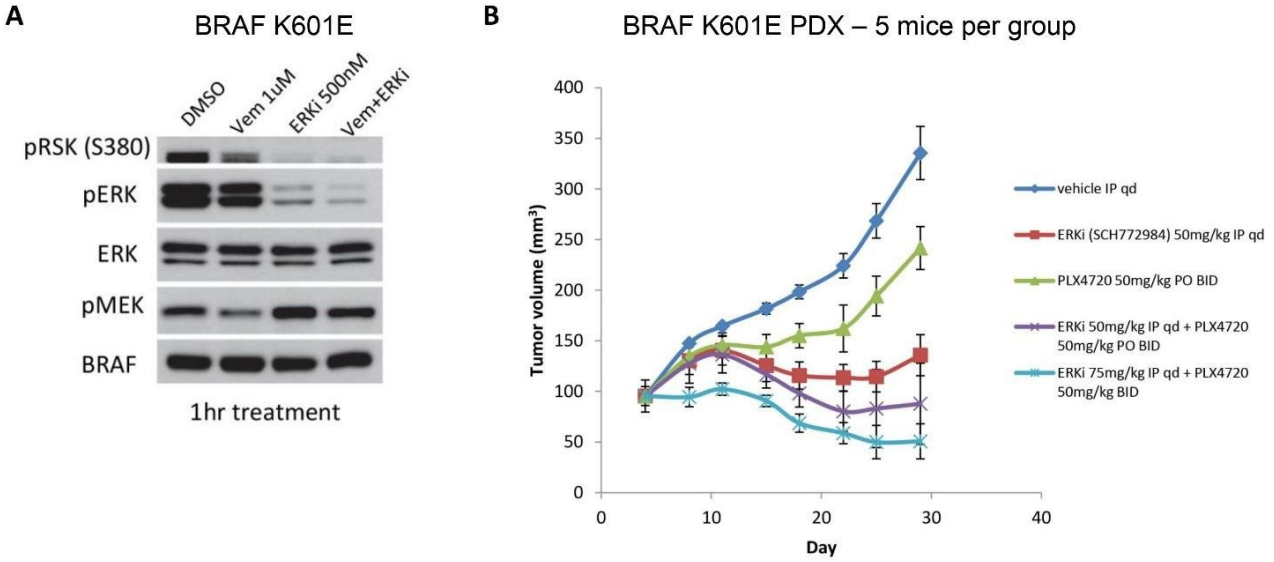


In the recent phase I trial of the ERK inhibitor BVD-523, treatment was associated with sporadic durable objective responses in patients with BRAF non-V600 mutant cancers, however, PD and pharmacokinetic (PK) data suggest that treatment exposure at maximally tolerated doses (MTDs) may be too low to effectively abrogate ERK signaling in many patients[9]. This narrow therapeutic window is likely the result of the lack of selectivity of ERK inhibition for mutant (cancerous) versus wild-type (healthy) tissues. These observations provide a strong rationale to leverage the paradoxical activation induced by first-generation BRAF inhibitors to oppose the inhibition of ERK in normal tissues with the goal of improving drug tolerance and therapeutic index. Therefore, we hypothesize that adding the RAF inhibitor encorafenib to the MEK inhibitor binimetinib will reduce toxicity related to inhibition of MAPK signaling in healthy tissue while having no deleterious effect on inhibiting MAPK signaling in non-V600 BRAF mutant or fusion tumors, allowing dose escalation to achieve a higher dose and better efficacy.

Preclinical data demonstrate the safety and efficacy of this approach. Treatment was tested in a cell line and xenograft generated from a patient's colon tumor with a BRAF K601E activating mutation. Exposure of the BRAF K601E colon cancer cells *in vitro* to vemurafenib does not change levels of phospho-ERK; exposure to the selective ERK inhibitor (Sch772984) leads to suppression of ERK signaling, with decreased levels of the activated downstream protein phospho-RSK; and combination treatment leads to continued inhibition of ERK signaling (**Figure 4A**). The PDX was expanded in mice for four treatment groups: vehicle control, vemurafenib, ERK inhibitor at the MTD in mice of 50 mg/kg daily, or the combination of these two drugs at these doses or with a high dose of the ERK inhibitor of 75 mg/kg daily, previously found to be too toxic in mice (**Figure 4B**). All treatments were well-

tolerated with no change in weight in the treated mice. Treatment with vemurafenib alone resulted in slowed but continued tumor growth, the ERK inhibitor prevented tumor growth, and combined ERK and RAF inhibition led to tumor regression. Notably, the combination of vemurafenib with the higher dose ERK inhibitor resulted in profound tumor regression in all mice treated. These data suggest that with concurrent RAF and ERK inhibitor treatment, we may be able to deliver an ERK inhibitor dose *in vivo* that sufficiently inhibits ERK signaling for tumor regression and improved clinical efficacy.

Figure 4. Effect of RAF and ERK inhibition on signaling and growth of BRAF K601E colon cancer patient derived cells.



Abbreviations: vem, vemurafenib; hr, hour; IP, intraperitoneal

Thus, the goal of this study is to increase ERK inhibition in non-V600 BRAF mutant tumors by using a RAF inhibitor to (1) oppose the effect of the MEK inhibitor in normal tissues (to allow uptitration of the MEK inhibitor) and (2) modestly inhibit ERK signaling and thus have an additive effect on pathway inhibition. In this study, for dose level 2, binimetinib will be administered in an intermittent schedule. Previous publications and our experiences in the clinic suggest that pulsatile dosing may maintain the MEK inhibitor dose to inhibit ERK sufficiently in the tumor and allow normal tissues to recover from toxic effects.[10,11] As profound ERK inhibition is required for tumor regression[7], an intermittent schedule may allow sufficient ERK inhibition in tumor tissue with time for recovery of normal tissues, rather than continuous inadequate target inhibition with a continuous lower-dose administration of MEK inhibitors.[10] The clinical experience with binimetinib is summarized in section 5.1. Because ocular toxicity, which is not clearly modulated by RAF inhibitors, limited continuous dosing at higher dose levels, dose level 2 consists of an intermitternt schedule of binimetinib. Encorafenib is also given on an intermittent schedule, so that dosing of encorafenib and binimetinib coincide. As the potential inhibitory effect of encorafenib likely varies by BRAF alterations, giving encorafenib on the same schedule as binimetinib will prevent unopposed RAF inhibitor therapy in these tumors and further limit the potential for ERK activation from encorafenib treatment. After four patients were treated at dose level 2, the dosing schedule was modified to continuous treatment of both binimetinib and encorafenib based on the

absence of dose limiting ophthalmologic symptoms and increased patient symptoms during the week off treatment.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This phase I/II study consists of a Phase I part followed by an efficacy analysis (Phase II) of the dosing schedule deemed safe in patients with advanced cancer with activating non-V600 BRAF mutant tumors. All patients must have had prior sequencing of their tumor with identification of activating non-V600 BRAF mutants. Patients will be initially enrolled to the approved dose of encorafenib 450 mg oral QD and binimetinib 45 mg PO BID, dose level 1. If we confirm this dose level is safely tolerated in the study population, we will then escalate treatment to dose level 2 with the novel dosing regimen of encorafenib 450 mg oral QD 21 days on/ 7 days off and binimetinib 60 mg oral BID 21 days on/7 days off.

Specifically three patients will be enrolled to dose level 1, If none of these patients experience a DLT in the first 28 days, then these three patients will start cycle 2 at dose level 2. If one patient experiences a DLT at dose level 1, then dose level 1 will be expanded with three additional patients. If there is 0-1 DLT in these six patients in the first 28 days, then we will enroll subsequent patients at dose level 2. If two of the three first patients enrolled to dose level 1 experience a DLT or if 2 of the 6 patients treated at dose level 1 experience a DLT, then we will not escalate treatment to dose level 2.

Three patients will be enrolled to dose level 2 and if 0 or 1 patient experiences a DLT in the first 28 days, then we will expand this dose level to include an additional three patients. If one or fewer patients experience DLTs in the first 28 day treatment cycle, then we will declare that this dose can be safely given in this population and phase II portion will proceed with this regimen. If 2 or more patients experience DLTs in the first 28 days, then the phase II portion will enroll patients at the dose 1 level.

The phase II part has a 2-stage design for efficacy assessment. Seventeen patients will be included in the first stage and if 3 or more responses are observed, then the second stage will proceed to enroll an additional 15 patients. As patients in the phase I part of the start will start at the lower dose level 1, they will not be included in the stage one efficacy cohort. At the end of the study, if 8 or more responses are observed the regimen would be considered promising for further study.

Safety will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5, based on recorded adverse events (AEs), physical examinations, and clinical laboratory assessments. Patients will be evaluated for response by computer tomography (CT) or MRI every 8 weeks. Response will be determined using RECIST (version 1.1 criteria). Clinical endpoints to be evaluated will include overall response rate (ORR), (PFS, OS, and AEs.

All patients will be asked to undergo an optional pre-treatment and day 7 optional on-treatment biopsy for planned PD and correlative studies. Additional research studies include blood collection every 4 weeks to monitor circulating tumor DNA (ctDNA) fraction.

We estimate that we will accrue about 1-2 patients per month and 16 patients a year. The trial recruitement will take 2-3 years.

4.2 Intervention

Treatment will consist of encorafenib 450 mg oral QD and binimetinib 60 mg oral BID . The dosing schedule was modified from intermittent dosing of 21 days on/ 7 days off after several patients reported good tolerance of continuous dosing during the first three weeks and symptomatic improvement but recrudescence of symptoms during the week off drug. A regimen of encorafenib 450 mg oral QD together with binimetinib 45 mg oral BID has already been found safe and is now approved by the United States Food and Drug Administration (FDA) as a treatment for BRAF V600 mutated melanoma. This trial aims to raise the MEK inhibitor dose by giving treatment together with a RAF inhibitor. Unlike in the treatment of BRAF V600 mutant tumors, the primary active drug in this trial of non-V600 activating BRAF mutants is the MEK inhibitor binimetinib. Patients will receive treatment until objective progression of disease or unacceptable toxicity. Patients may continue treatment beyond progression if they are receiving clinical benefit from treatment.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Patients will be treated with the combination of binimetinib and encorafenib.

5.1 Overview of Binimetinib

Binimetinib (also known as MEK162 or ARRY-438162) is a potent and selective allosteric, adenosine triphosphate (ATP)-uncompetitive inhibitor of MEK1/2. Binimetinib is currently being investigated as a single agent and in combination with a variety of other agents, including inhibitors of, BRAF, and cyclin-dependent kinase 4/6, Programmed cell death-1/programmed death-ligand 1(PD-1/PD-L1), and cytotoxic chemotherapy in patients with selected advanced or metastatic solid tumors, including melanoma, ovarian, and colorectal cancers.

Binimetinib is manufactured by Array BioPharma 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. 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 polyporplyene, child-resistant screw cap. Binimetinib bottles will be labelled, 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 Array BioPharma and should not be repackaged at the site or pharmacy.

<u>Binimetinib Nonclinical Safety Pharmacology and Toxicology</u>

Acute, subchronic, chronic and reproductive toxicity, genotoxicity and phototoxicity studies were completed in rats and monkeys to support the chronic administration of binimetinib to adult patients. There was no evidence of a genotoxic potential in vitro or in vivo. The adverse

effects of MEK inhibitors in humans are similar to those observed in rats and monkeys, with the exception of ocular findings and soft tissue mineralization (rats only). These adverse effects include gastrointestinal (GI) intolerance and diarrhea, rash (skin findings in rats only), retinal events (only seen in humans) and retinal vein occlusion (RVO) (rarely seen in humans). *In vitro* and *in vivo* phototoxicity studies conducted in mice indicate that binimetinib has a low risk of weak phototoxic potential at therapeutic doses. There has been no evidence of phototoxicity or photosensitivity in human beings treated with binimetinib for cancer or for rheumatoid arthritis. In the 6-month study in rats, there was a slight trend for increased kidney mineralization by mid-study onward at ≥ 1 mg/kg/day in females and ≥ 3 mg/kg/day in males. Treatment-related skin effects and kidney mineralization defined the lowest-observable-adverse-effect level (LOAEL) of 1 or 3 mg/kg (females and males, respectively). The MTD was defined by morbidity and mortality associated with dose-related increases in soft tissue mineralization and bone marrow atrophy-necrosis that occurred at doses of ≥ 100 mg/kg in the 28-day study. There were no observations on gross pathological examination; mineralization was only detected microscopically within the small arteries and arterioles in the affected organs.

Daily oral administration of binimetinib to juvenile Sprague-Dawley rats on postnatal Day 10 through 40 was not tolerated at doses ≥ 10 mg/kg/day. The MTD in juvenile rats was 3 mg/kg, and the no-observable-adverse-effect level (NOAEL) was 1 mg/kg/day. The exposure-based safety index attained at the MTD and NOAEL were very similar to those attained in adult rats.

Embryo-fetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and pulmonary trunk alterations) and reduced fetal body weight in rats and rabbits. Given these observed effects, binimetinib should not be used in pregnant women.

Clinical Experience with Binimetinib

As of 20 January 2018, a total of 2816 healthy subjects and patients have received binimetinib as monotherapy or in combination with other agents, including 229 healthy subjects, 17 subjects with hepatic dysfunction, 6 subjects with renal dysfunction, 164 patients with rheumatoid arthiritis, and 2400 patients with advanced cancer.Detailed information regarding clinical studies of binimetinib is presented in the Investigator's Brochure.

Clinical Pharmacokinetics

The PKs of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold and steady-state concentrations reached within 15 days, with a median terminal half-life ($t_{1/2}$) of approximately 9 hours. Food-effect clinical studies have indicated that the influence of food on the PK of binimetinib is mild and not clinically relevant. A drug-interaction study with the proton-pump inhibitor rabeprazole indicates binimetinib can be administered in the presence of stomach pH-altering agents. Binimetinib is primarily metabolized by glucuronidation pathways (mainly via uridine diphosphate glucuronosyl transferase [UGT]1A1, 1A3 and 1A9); however, the impact of UGT1A1 inhibitors or inducers has not been clinically assessed. *In vitro* studies also demonstrated that binimetinib is a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, but the effects of inhibitors of these substrates on the PK of binimetinib *in vivo* are unknown.

In vitro, binimetinib has the potential to inhibit CYP2B6; however, *in vivo* inhibition of CYP2B6 is anticipated to not be clinically significant. Binimetinib has also induced CYP3A in vitro, but this induction was not confirmed in a clinical drug-drug interaction (DDI) study.

In dedicated clinical studies to evaluate hepatic and renal impairment, an increase in binimetinib exposure was observed in subjects with moderate and severe hepatic impairment and in subjects with severe renal impairment.

Clinical data supporting binimetinib dose

The trial ARRAY-162-111, a phase I dose-escalation study in patients with advanced solid tumors followed by expansion cohorts in patients with advanced or metastatic biliary cancer or *KRAS*- or *BRAF*-mutant metastatic colorectal cancer, evaluated the safety and tolerability of increasing doses of binimetinib. In this study, 19 patients with advanced solid tumors received binimetinib in the dose escalation phase and 15 were evaluable for dose-escalation decisions. Dose levels and information about DLTs are listed in Table 1.

Table 1: Dose-Limiting Toxicities in the Phase I study of Binimetinib, ARRAY-162-111

Dose Level (no. of pts with DLTs/no. of evaluable patients in cohort)	**Dose-limiting Toxicity**
30 mg BID (0/3)	No DLT observed
45 mg BID (0/3)	No DLT observed
60 mg BID (0/6)	No DLT observed
80 mg BID (2/3)	Grade 3 dermatitis acneiform Grade 3 chorioretinopathy

Abbreviations: BID, twice daily; DLT, dose-limiting toxicity; mg, milligram(s); no., number; pts., patients

Based on the escalation, the MTD of binimetinib was declared to be 60 mg oral BID dosed continously. Following determination of the MTD in the dose-escalation phase, 74 patients were enrolled in the expansion phase, including 28 patients in the biliary cancer cohort, 31 patients in *KRAS*-mutant colorectal cancer cohort and 15 patients in the *BRAF*-mutant colorectal cancer cohort. After initiation of the expansion phase, a higher-than-expected frequency of ocular AEs affected the ability to treat patients continuously at the MTD, thus a reduced dose of 45 mg BID was implemented for the remainder of newly enrolled patients in the expansion phase cohorts. The ocular toxicity that limited dosing occurred after the first 28-days on treatment. Based on this toxicity profile, the current study initially tested an intermittent schedule of binimetinib at the higher dose of 60 mg to allow recovery from ocular effects during the fourth week of each cycle while binimetinib is held. However, the dosing schedule was changed to continuous treatement after several patients reported good tolerance of continuous dosing during the first three weeks and symptomatic improvement but recrudescence of symptoms during the week off drug.

Clinical Safety

Available clinical data indicate a predictable safety profile consistent with that reported for other allosteric MEK1/2 inhibitors. The most frequent treatment-emergent AEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term in patients receiving binimetinib

include rash, dermatitis acneiform, nausea, vomiting, diarrhea, peripheral edema, fatigue, and creatine kinase (CK) elevation. Other clinically relevant toxicities are retinal events, increased blood pressure, decreased ejection fraction, and noninfectious pneumonitis/interstitial lung disease, all of which should be monitored closely with appropriate diagnostic evaluations. These observed AEs are generally reversible and manageable by appropriate supportive medical care and/or dose modifications.

Pooled AE data from 2 single-agent clinical studies of binimetinib (CMEK162X2201 45 mg BID continuous dosing [N = 158] and CMEK162A2301 [N = 269]) are presented in Table in order to provide a detailed assessment of the safety of binimetinib in patients with metastatic melanoma (including *NRAS*-mutant and *BRAF*-mutant) naïve to prior MEK inhibitors who received single-agent binimetinib at the recommended single-agent dose of 45 mg BID ("binimetinib 45 mg population"; N = 427).

Table 2: Adverse Events Regardless of Causality Reported in ≥ 10.0% of Patients by Preferred Term (Pooled Data from Studies of Single-agent Binimetinib 45 mg BID in Patients with Melanoma)

	45 mg BID N = 427	
Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**
Any AE	427 (100)	285 (66.7)
Blood CK increased	191 (44.7)	89 (20.8)
Diarrhea	182 (42.6)	8 (1.8)
Dermatitis acneiform	177 (41.5)	11 (2.6)
Edema peripheral	174 (40.7	3 (0.7)
Rash	146 (34.2)	13 (3.0)
Nausea	128 (30.0)	5 (1.2)
Fatigue	114 (26.7)	15 (3.5)
Vomiting	84 (19.7)	8 (1.9)
Constipation	65 (15.2)	2 (0.5)
Hypertension	64 (15.0)	34 (8.0)
Asthenia	60 (14.1)	8 (1.9)
AST increased	59 (13.8)	9 (2.1)
Pruritus	58 (13.6)	4 (0.9)
Decreased appetite	55 (12.9)	2 (0.5)
Pyrexia	53 (12.4)	0
Dry skin	45 (10.5)	0
Dyspnoea	44 (10.3)	6 (1.4)
Ejection fraction decreased	44 (10.3)	15 (3.5)
Retinal detachment	44 (10.3)	0

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; CK, creatinine kinase; mg, milligram(s); n or N, number
Data cutoff date CMEK162X2201 06 Nov 2015; CMEK162A2301 18 Mar 2016

Further information can be found in the binimetinib Investigator's Brochure.

5.2 Overview of Encorafenib

Encorafenib (also known as LGX818) is a highly selective ATP-competitive small-molecule RAF kinase inhibitor, which suppresses the RAS/RAF/MEK/ERK pathway in tumor cells expressing BRAF V600E. Similar to other selective small-molecule RAF kinase inhibitors, encorafenib inhibits CRAF (half maximal inhibitory concentration [IC_{50}] = 0.30 nM), BRAF (IC_{50} = 0.47 nM), as well as BRAF V600E (IC_{50} = 0.35 nM) in cell-free assays. However, this class of inhibitor does not inhibit RAS/RAF/MEK/ERK signaling in cells expressing $BRAF^{wt}$. In the human melanoma cell line A375, which expresses BRAF V600E, encorafenib potently inhibits phospho-MEK (half maximal effective concentration [EC_{50}] = 2 nM), phospho-ERK (EC_{50} = 3 nM), and proliferation (EC_{50} = 4 nM), resulting in cell cycle arrest and apoptosis. Given the high degree of selectivity against other kinases, encorafenib has no antiproliferative activity in tumor cell lines that express wild-type BRAF and is highly selective for BRAF mutations in cell lines containing V600E/D/K, with the greatest sensitivity observed in BRAF V600E melanoma and colorectal cancer (CRC) lineages.

Encorafenib has been evaluated in multiple human tumor xenograft models grown in nude mice. Similar to the *in vitro* profile, the antitumor activity was restricted to tumors expressing BRAF V600E, while there was no antitumor effect in xenograft models expressing wild-type BRAF or CRAF. Nonclinical *in vivo* data suggest that encorafenib has a wide therapeutic index and that regression of BRAF V600E human melanoma tumor xenografts is associated with a strong and sustained inhibition of the RAF/MEK/ERK pathway.

Encorafenib is manufactured by Array BioPharma and is supplied as hard gelatin capsules in a dosage strength of 75 mg. Encorafenib capsules consist of encorafenib drug substance and the following excipients: 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, yellow or black depending on the particular strength. 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 polyporplyene, child-resistant screw cap. Encorafenib bottles will be labelled, 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 Array BioPharma and should not be repackaged at the site or pharmacy.

Nonclinical Safety Pharmacology and Toxicology

In 1- to 4-week toxicology studies in rats and cynomolgus monkeys, encorafenib was well tolerated at systemic exposures which result in tumor regression in mouse xenograft studies. Findings included hyperplasia and hyperkeratosis in the skin (plantar surface of feet) and non-glandular stomach in the rat. An absence of the later stages of spermatid maturation in male rats was also observed. Significant mortality/morbidity was observed mostly in female rats at the highest dose of 400 mg/kg/day, a dose well above the MTD in rats.

In the 13-week toxicology study in monkeys, the only test article-related finding was blister-like lesions identified over the macular region of the retina, observed in 2 monkeys treated at a dose of 60 mg/kg/day. Exposure (maximum area under the curve [AUC] from time 0 to 24 hours achieved in the study at any time point) in the 2 affected monkeys was 5- to 8-fold and

4- to 6-fold that achieved at the 300 and 450 mg QD dose levels, respectively, in humans at steady state in Clinical Study CLGX818X2101. One of the animals with this finding showed evidence of recovery. Histopathology examination of the affected eyes suggested that the findings were similar to the retinopathy associated with MEK inhibitors.

Nonclinical safety pharmacology results did not indicate a risk for QT prolongation based on: the findings of the Good Laboratory Practice (GLP) human ether-a-go-go-related gene assay, on electrocardiogram (ECG) evaluations in the GLP monkey cardiovascular telemetry study, and the GLP 4- and 13-week toxicology studies in monkeys. Also, there were no clinical signs in the 4-or 13-week GLP-compliant studies in the rat and monkey that would indicate an effect on the central nervous system or respiratory system.

The GLP Ames and chromosomal aberration assays as well as a rat micronucleus study indicated that encorafenib is not genotoxic.

Encorafenib showed a potential for phototoxicity in a screen 3T3 neutral red uptake in vitro assay. In patients treated with encorafenib, as a single-agent, in the range of doses of 300 to 450 mg QD, the incidence of photosensitivity was 2.9% and 5.6% in the melanoma and colorectal cohorts, respectively of Study CLGX818X2101 and 3.6% in the single-agent encorafenib arm of Clinical Study CMEK162B2301.

Pharmacokinetics and Metabolism

Encorafenib is a relatively potent reversible inhibitor of CYP2B6, CYP2C9, and CYP3A4/5 and a weak (IC_{50} ≥ 20 μM) reversible inhibitor of CYP1A2, CYP2C8, CYP2C19, and CYP2D6. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes and was found to potently induce CYP3A4 mRNA in vitro with EC_{50} values of 10.2 μM. Furthermore, encorafenib inhibits UGT1A1 and is a substrate of P-glycoprotein (P-gp) with high apparent passive permeability. It is also a weak inhibitor of breast cancer resistance protein (BCRP) (IC_{50}=10 to 25 μM). Finally, encorafenib inhibits the renal organic anion transporter (OAT) OAT1, OAT3, and OCT2 and the hepatic transporters, organic anion-transporting polypeptide (OATP)1B1 and OATP1B3.

Encorafenib is primarily metabolized by CYP3A4 (> 50%) and to lesser degrees by CYP2D6 and CYP2C19.

In a Phase I study in patients with locally advanced or metastatic *BRAF* V600E melanoma (Study CLGX818X2101, dose escalation phase), encorafenib was rapidly absorbed and plasma concentrations reached their peak on average at 2 hours postdose. Elimination was also rapid, with a terminal half-life ($t_{1/2}$) of 2 to 4 hours. Apparent systemic clearance (CL/F) and apparent volume of distribution (V_z/F) were moderate. After multiple QD administrations, steady-state appeared to have been reached by Day 15, with lower exposures than on Day 1, consistent with what would be expected with auto-induction of CYP3A4. At doses tested in the study (50, 100, 150, 200, 300, 450, 550 or 700 mg QD and 75, 100, and 150 mg BID), the average concentrations of encorafenib were above the predicted efficacious concentrations based on nonclinical xenograft models (0.135 μg/mL).

Additional details are provided in the encorafenib Investigator's Brochure.

Clinical Safety

The experience of encorafenib as a single agent includes 97 healthy subjects and 7 subjects with hepatic impairment in 5 studies (CLGX818A2101, ARRAY-162-105, ARRAY-818-101, ARRAY-818-102 and ARRAY-818-105) and 410 patients with cancer in 4 studies (CLGX818X2101, CLGX818X2102 [single-agent encorafenib part], CMEK162B2301 [single-agent encorafenib arm] and CLGX818AUS03). In single-agent studies, the most frequently reported AEs were dermatological, gastrointestinal, musculoskeletal, fatigue, asthenia and headache.

The largest encorafenib single-agent treatment population to date is from the Phase III Study CMEK162B2301 (also known as COLUMBUS)[12]. In the encorafenib arm, the most common AEs (> 25.0% of patients) were alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, nausea, hyperkeratosis, dry skin, myalgia, vomiting, headache, palmoplantar keratoderma and fatigue **(Table 3)**. Grade 3 or 4 AEs were reported for 127 patients (66.1%) in the encorafenib arm, the most common of which were palmar-plantar erythrodysesthesia syndrome (13.5%), myalgia (9.9%) and arthralgia (9.4%).

The most frequently observed AEs of special interest in patients in studies with encorafenib as a single-agent or in a dual combination are currently mostly characterized as acute renal failure events (including blood creatinine increased), dermatologic events (rash and skin events other than rash events), facial paresis, fatigue/asthenia events, GI events, headache events, heart rate increased (including atrial fibrillation and tachycardia), liver events, musculoskeletal disorders/pain events, ocular events (retinal events, vascular eye events and other eye events) and secondary neoplasms.

5.3 Overview of the Combination of Encorafenib and Binimetinib

Nonclinical Pharmacokinetics and Metabolism

Although the *in vitro* data suggest a potential for encorafenib to affect the PK of binimetinib-based inhibition of UGT1A1, no significant drug-drug interaction was observed up to the highest doses tested in Clinical Study CMEK162X2110 (800 mg QD encorafenib in combination with 45 mg BID of binimetinib).

Clinical Experience

In phase 1 studies, patients have received binimetinib at 45 mg PO BID, together with escalating doses of encorafenib (50, 100, 200, 400, 450, 600, or 800 mg QD). The recommended Phase 2 dose for encorafenib in combination with binimetinib was based on a Phase 1b/2 combination study (CMEK162X2110). In this trial, patients received binimetinib at 45 mg PO BID, together with escalating doses of encorafenib at the following dose levels: 50 mg (N=6), 100 mg (N=5), 200 mg (N=4), 400 mg (N=5), 450 mg (N=13), 600 mg (N=8), or 800 mg (N=6). Two separate dose combinations were recommended for the Phase 2 expansion in BRAF V600 mutated melanoma patients as was allowed per protocol with a total of 64 patients receiving 600 mg QD encorafenib as the starting dose and 15 patients receiving 450 mg QD as the encorafenib starting dose. Three patients receiving encorafenib 600 mg QD + binimetinib 45 mg BID experienced significant increases in creatinine levels. Although there were potential confounding factors in two of the patients that may have

contributed to the creatinine abnormalities, in the absence of strong evidence of better efficacy at the higher dose and observed responses at encorafenib doses as low as 50 mg QD, all patients were switched to or started on the lower recommended dose of encorafenib 450 mg QD + binimetinib 45 mg BID for the remainder of the Phase 2. Thirty-five patients had their encorafenib dose switched from 600 mg to 450 mg with this protocol change and an additional 8 patients had their doses reduced from 600 mg to 450 mg due to adverse effects.

The combination of encorafenib and binimetinib is now approved by the FDA for *BRAF* V600 mutated melanoma based on the COLUMBUS study (CMEK162B2301).

In this study, Combo 450 (encorafenib 450 mg QD plus binimetinib 45 mg BID) demonstrated a favorable efficacy and safety profile in patients with BRAF V600-mutant melanoma[10]. Combo 450 significantly improved PFS versus vemurafenib alone, with the median PFS being 14.9 months for Combo 450 versus 7.3 months for vemurafenib (hazard ratio [HR] [95% confidence interval (CI)], 0.54 [0.41, 0.71]; P<0.001). In addition, the median PFS of 14.9 months in the Combo 450 arm was improved compared with the encorafenib monotherapy arm in which the median PFS was 9.6 months (HR [95% CI], 0.75 [0.56, 1.00]; P=0.051). The local assessment of PFS in the Combo 450 and encorafenib monotherapy arms was consistent with the result by blinded independent assessment (HR [95% CI], 0.68 [0.52, 0.90]; P=0.006). Encorafenib 300 mg QD alone improved PFS vs vemurafenib (HR [95% CI], 0.68 [0.52, 0.90]; P=0.007). Objective response rate was greater in the Combo 450 arm (63.0% [55.8, 69.9]) compared with 50.5% (43.3, 57.8) in the encorafenib arm and 40.3% (33.3, 47.6) in the vemurafenib arm. The median duration of response was also greater in the Combo 450 arm (16.6 months [12.7, 20.4]) compared with 14.9 months (11.0, not evaluable) in the encorafenib arm and 12.5 months (6.9, 16.9) in the vemurafenib arm.

Maintenance of quality of life was improved with Combo 450 compared with vemurafenib alone and encorafenib alone as measured by the Functional Assessment of Cancer Therapy Melanoma scale and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (also known as EORTC QLQ-C30) Global Health Status score.

The tolerability profile of Combo 450 was favorable compared with monotherapy with vemurafenib or encorafenib alone, resulting in higher relative dose intensity for Combo 450. The most common AEs are summarized in **Table 3**.

Table 3: Adverse Events by Preferred Term (Study CMEK162B2301 Part 1)

	Combo 450 n=192 Median Duration of Exposure: 51 weeks		**Encorafenib 300 mg n=192 Median Duration of Exposure: 31 weeks**		**Vemurafenib n=186 Median Duration of Exposure: 27 weeks**	
Preferred Term	**Any Grade %**	**Grade 3/4 %**	**Any Grade %**	**Grade 3/4 %**	**Any Grade %**	**Grade 3/4 %**

Total	98	58	>99	66	>99	63
Nausea	41	2	39	4	34	2
Diarrhea	36	3	14	2	34	2
Vomiting	30	2	27	5	15	1
Fatigue	29	2	25	1	31	2
Arthralgia	26	1	44	9	45	6
Blood CK increased	23	7	1	0	2	0
Headache	22	2	27	3	19	1
Pyrexia	18	4	15	1	28	0
GGT increased	15	9	11	5	11	3
Alopecia	14	0	56	0	37	0
Hyperkeratosis	14	1	38	4	29	0
Dry skin	14	0	30	0	23	0
Myalgia	14	0	28	10	18	1
Rash	14	1	21	2	29	3
Hypertension	11	6	6	3	11	3
Palmoplantar keratoderma	9	0	26	2	16	1
Palmar-plantar erythrodysesthesia syndrome	7	0	51	14	14	1

Abbreviations: AE, adverse event; BID, twice daily; CK, creatinine kinase; Combo 450, encorafenib 450 mg QD + binimetinib 45 mg BID; GGT, gamma-glutamyltransferase; QD, once daily.

Note: All-cause AEs (>25% in any treatment group) or Grade 3/4 AEs (>5% in any treatment group) are shown.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Patients participating in this study will have advanced cancer with non-V600 BRAF activating alterations.

6.1 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient has signed the Informed Consent (ICF) prior to any screening procedures being performed and is able to comply with protocol requirements
2. Age ≥ 18 years at the time of informed consent
3. Metastatic or advanced-stage malignant tumors confirmed histologically for whom no standard therapy is considered to be appropriate by the investigator
4. Patients must have at least one other lesion that is measurable by RECIST criteria.

5. Patient's tumor must harbor an activating BRAF mutation (listed in **Table 4** or approved by the study Principal Investigator) or a fusion involving the kinase domain of BRAF

Table 4. Mechanistically validated activating non-V600 BRAF mutants

P367L/S
G464V/E
G469A/V/R
L485W
N486_A489delinsK
N486_P490del
E586K
L597Q/V/S
T599TT/TS
T599I/K
V600_K601delinsE
K601E/N/T
K601_S602delinsNT
BRAF kinase duplication
Fusions involving BRAF kinase domain

6. Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$ 2
7. Adequate bone marrow, organ function and laboratory parameters:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L,
   - Hemoglobin (Hgb) ≥ 8 g/dL with or without transfusions,
   - Platelets (PLT) ≥ 75 x 10^9/L without transfusions,
   - AST and/or ALT ≤ 2.5 × upper limit of normal (ULN); patient with liver metastases ≤ 5 ×ULN,
   - Total bilirubin ≤ 1.5 × ULN and < 2 mg/dL

     (Note: Patients who have a total bilirubin level > 1.5 x ULN will be allowed if their indirect bilirubin level is ≤ 1.5 x ULN)
   - Serum Creatinine ≤ 1.5 x ULN, or calculated creatinine clearance (determined as per Cockcroft-Gault) ≥ 50 mL/min at screening
8. Adequate cardiac function:
   - left ventricular ejection fraction (LVEF) ≥ 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram,
   - QTc interval ≤ 480 ms (preferably the mean from triplicate ECGs) ;
9. Able to take oral medications;
10. Patient is deemed by the Investigator to have the initiative and means to be compliant with the protocol (treatment and follow-up)
11. Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks, or must agree to take appropriate precautions to avoid pregnancy from screening through 30 days after the last dose of study drug/treatmentif of childbearing potential (Note: Permitted contraception methods listed in Section 9.3 should be communicated to the patients and their understanding

confirmed. For females of childbearing potential, the pregnancy test result must be negative at screening.)

12. Males must agree to take appropriate precautions to avoid fathering a child from screening through 90 days following the end of therapy. (Note: Permitted contraception methods listed in Section 9.3 should be communicated to the patients and their understanding confirmed.)

6.2 Subject Exclusion Criteria

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

1. Any symptomatic brain metastasis (Note: Patients previously treated or untreated for this condition who are asymptomatic in the absence of corticosteroid and anti-epileptic therapy are allowed. Brain metastases must be stable for ≥ 4 weeks, with imaging (e.g., magnetic resonance imaging [MRI] or computed tomography [CT]) demonstrating no current evidence of progressive brain metastases at screening.)
2. History or current evidence of retinal vein occlusion (RVO) or current risk factors to RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease
3. Leptomeningeal disease
4. Previous or concurrent malignancy within 2 years of study entry, with the following exceptions: adequately treated basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, early stage breast cancer, or other noninvasive or indolent malignancy
5. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
    - History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty, or stenting) < 6 months prior to screening,
    - Symptomatic chronic heart failure (i.e. Grade 2 or higher), history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality < 6 months prior to screening except atrial fibrillation and paroxysmal supraventricular tachycardia;
6. Uncontrolled hypertension defined as persistent elevation of systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 100 mmHg, despite current therapY.
7. Known positive serology for HIV (Human Immunodeficiency Virus), active hepatitis B, and/or active hepatitis C infection
8. Impaired GI function or disease that may significantly alter the absorption of encorafenib or binimetinib (e.g., ulcerative diseases, uncontrolled vomiting, malabsorption syndrome, small bowel resection with decreased intestinal absorption)
9. History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to the first dose of study treatment. Examples include transient ischemic attacks, cerebrovascular accidents, hemodynamically significant (i.e. massive or sub-massive) deep vein thrombosis or pulmonary emboli.

    Note: Patients with either deep vein thrombosis or pulmonary emboli that does not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for at least 4 weeks.

Note: Patients with thromboembolic events related to indwelling catheters or other procedures may be enrolled.Concurrent neuromuscular disorder that is associated with the potential of elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

10. Any other condition that would, in the Investigator's judgement, contraindicate the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medications, social/psychological issues, etc.
11. Patients who have undergone surgery ≤ 3 weeks prior to starting study drug or who have not yet recovered from side effects of such procedure
12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
13. Medical, psychiatric, cognitive, or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study
14. Prior treatment with any RAF, MEK, or ERK inhibitors (such as vemurafenib, dabrafenib, encorafenib; trametinib, cobimetinib, binimetinib, selumetinib; or BVD-523, respectively)

7.0 RECRUITMENT PLAN

As part of the Memorial Sloan Kettering-Integrated Mutation Profiling for Actionable Cancer Targets (MSK-IMPACT) initiative which started in 2014, every patient at MSK with advanced cancer has the opportunity for tumor NGS performed at our institution, generating routine information on BRAF alterations. Furthermore, samples without identified genomic drivers can be selected by pathology for further testing with the Archer FusionPlex assay, a NGS RNA-based methodology for fusion and alternative isoform testing. In this assay, cDNA libraries are made from RNA and subjected to anchored multiple PCRs (polymerase chain reactions) with primers for a set of kinase genes with potential activating structural variants. This allows for breakpoint identification and transcript sequencing, whether the partner gene is known or novel. The assay is thus designed to identify fusions, including fusions involving the BRAF gene. As of mid-year 2018, about 27,500 patient tumor samples have been analyzed by the MSK clinical molecular pathology laboratory with NGS. To facilitate accrual, a notification system will be set up where the investigators will be notified of all new cases of patients with appropriate BRAF alterations as potential candidates for this clinical trial. In total, we have prospectively identified at MSK approximately 200 patients with non-V600 activating *BRAF* mutation or fusion, *RAS* wild-type tumors, through MSK-IMPACT analysis. Therefore the maximal accrual of 38 patients should be highly feasible. We anticipate that accrual will take 2-3 years depending on the sample size in this 2-stage design. Every effort will be made to maximize recruitment of patients, including women and minorities. Patients will undergo formal informed consent process through designated consenting professionals on the study. Patients will be given time to understand and make informed decisions. A copy of the signed and dated consent form will be given to each patient to take home. Patients will not be paid for this study. The study drugs, encorafeninb and binimetinib, will be

delivered to patients without charge as Array BioPharma has agreed to provide treatment for the study.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process.The investigator/research staff may also review portions of their medical records at MSKCC in order tofurther assess eligibility. They will use the information provided by the patient and/or medical record toconfirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached.

8.0 PRETREATMENT EVALUATION

<u>Within 28 days prior to first dose of treatment:</u>

- Obtain informed consent
- Record BRAF alteration
- Verify all inclusion/exclusion criteria
- Record demographic information (age)
- Record current and past medical history
- Document prior anticancer treatments
- Record all medications/treatments that were administered/conducted within 28 days prior to Day 1

Baseline evaluations

- Complete physical examination including measured height and body weight
- Obtain full ophthalmic examination
- Obtain full dermatologic examination (may be done by treating physician or dermatologist)
- Assess vital signs (blood pressure, pluse, and temperature)
- Assess ECOG Performance Status
- Perform cardiac imaging by either ECHO or MUGA
- Triplicate ECG
- Collection of blood samples for the following:
  - Hematology (CBC with differential)
  - Chemistry (comprehensive chemistry panel, CK)
  - Magnesium
  - Serum pregnancy (females of childbearing potential only)
- Complete tumor assessments with appropriate radiological scans to document all suspected sites of disease, measurable or non-measurable, as defined by RECIST

9.0 TREATMENT/INTERVENTION PLAN

All patients will receive encorafenib and binimetinib. Encorafenib and binimetinib can be taken with or without food and can be taken together. Patients can self-administer doses at home on clinic days, as no PK studies are planned. Patients will receive a pill diary to record when they take the investigational agents.

Patients will continue to receive treatment until disease progression by RECIST Version 1.1, unacceptable toxicity, or until one of the criteria in Section 13.0 is met. Clinical assessments to evaluate tolerability will be performed on day 15 of cycle 1 and then day 1 of each subsequent cycle. Observed toxicities will be graded as per NCI-CTCAE Version 5. Standard safety evaluations will include laboratory analysis of blood samples, ECG, ECHO or MUGA, and ophthalmologic and dermatologic assessments. Standard tumor evaluations will consist of imaging studies with CT chest/abdomen/pelvis with contrast or, in patients unable to tolerate contrast, with non-contrast CT chest and MRI abdomen/pelvis every 8 weeks. Research evaluations include blood collection for cfDNA analysis every 4 weeks and mandatory tumor biopsy at baseline and on day 7 of treatment.

9.1 Dose levels

Patients will be monitored for AEs on an ongoing basis. The severity of AEs will be evaluated using the NCI-CTCAE, v.5. If a patient develops a toxicity, the dose may be modified as outlined in Table 5. The phase I portion of the study consists of two dose levels: level 1, binimetinib 45 mg BID plus encorafenib 450 mg QD, and level 2, binimetinib 60 mg BID 21 days on/ 7 days off plus encorafenib 450 mg QD 21 days on/ 7 days off. Patients participating in the phase I portion of the study will not have their drug dose reduced in the DLT period of the first 28 days unless they experience a DLT.

Table 5. Dose Levels for Dose Modifications

For dose level 1 (encorafenib 450 mg QD continuous + binimetinib 45 mg BID continuous):

	Encorafenib (mg QD)	Binimetinib (mg BID)
Starting dose	450	45
Dose level -1	300	30
Dose level -2	225	15
Dose level -3	150	Discontinue treatment

Abbreviations: QD, once daily; BID, twice daily.

For dose level 2 (encorafenib 450 mg QD 21 days on/ 7 days off + binimetinib 60 mg BID 21 days on/ 7 days off):

	Encorafenib (mg QD)	Binimetinib (mg BID)
Starting dose	450	60
Dose level -1	300	45
Dose level -2	225	30
Dose level -3	150	15

Abbreviations: QD, once daily; BID, twice daily.

9.2 Dose modifications

All dose modifications should be based on the worst preceding toxicity. Table 6 includes criteria for interruption and reduction of encorafenib and/or binimetinib. In general, doses should not be reduced or interrupted for Grade 1 AEs unless the AE is a specific ocular AE referred to in Table 6. Treatment to control symptoms should be provided as appropriate, if applicable.

When the AE that resulted in a dose reduction improves to and remains stable at the patient's Baseline 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 patients can have their dose reduced or re-escalated (in increments specified in Table 5); however:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction or prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.
- Patients may not remain on study if they have toxicity requiring discontinuation of one of the two drugs.

Table 6. Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
Eye Disorders - Retinal Events (including serous detachment of the retina), Posterior Uveitis[c] **Any visual acuity impairment at screening should be documented and should be considered as baseline.**	
Grade 1	Maintain dose levels of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days • If patient remains asymptomatic (Grade 1), maintain dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If patient becomes symptomatic (blurred vision, photophobia, etc.) or visual acuity assessment shows Grade 2, follow Grade 2 dose guidelines below
Grade 2	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days • If resolved to baseline or Grade ≤ 1, resume treatment at current dose level of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 1, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If posterior uveitis lasts > 6 weeks, permanently discontinue binimetinib and encorafenib.
Grade 3	Interrupt dosing of encorafenib and binimetinib and repeat ophthalmic monitoring including visual acuity assessment and OCT within 10 days: • If posterior uveitis resolves to Baseline or Grade ≤ 1 in < 6 weeks, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If posterior uveitis does not resolve to Baseline or Grade ≤ 1 in < 6 weeks, permanently discontinue binimetinib and encorafenib • If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol • If not resolved to baseline or Grade ≤ 2, continue the interruption and repeat the ophthalmic assessment in 10 days. o If resolved to baseline or Grade ≤ 2, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib and continue the schedule of visual assessments established per protocol o If remains Grade 3, permanently discontinue encorafenib and binimetinib
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring[c]
Eye Disorder - RVO[c]	

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
RVO of any grade	Permanently discontinue encorafenib and binimetinib and immediately follow-up with ophthalmic monitoring[c]
Other Eye Disorders (i.e., Non-retinal 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[c]: • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level[b] 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[c]
Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution[c]
Liver-related Adverse Events	
Grade 1 AST or ALT > ULN to 3 × ULN	Maintain dose level of encorafenib and binimetinib
Grade 2 AST or ALT > 3 to 5.0 × ULN or 3 × baseline value[d] AND blood bilirubin[g] ≤ 2.0 × ULN	Maintain dose level of encorafenib and interrupt dosing of binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, maintain dose level of encorafenib and binimetinib • If not resolved in ≤ 14 days, interrupt dose of encorafenib (in addition to prior binimetinib) until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib Treatment with encorafenib and binimetinib may be resumed sequentially at the Investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment
AST or ALT > 3.0 to 5.0 × ULN AND blood bilirubin[g] > 2.0 × ULN	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1, then: • If resolved in ≤ 7 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib • If not resolved in ≤ 7 days, permanently discontinue encorafenib and binimetinib

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
	Treatment with encorafenib and binimetinib may be resumed sequentially at the investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
Grade 3 AST or ALT > 5.0 to 8.0 × ULN) AND blood bilirubin[g] ≤ 2.0 × ULN	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then: • If resolved in ≤ 14 days, resume treatment at current dose level of encorafenib and binimetinib • If not resolved in ≤ 14 days, resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib Treatment with encorafenib and binimetinib may be resumed sequentially at the investigator's discretion, with encorafenib being resumed alone for one week before resuming binimetinib treatment If additional occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1 (or Grade ≤ 2 in case of liver metastasis), then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib
AST or ALT >8 × ULN AND blood bilirubin[g] ≤ 2.0 × ULN	Permanently discontinue encorafenib and binimetinib
AST or ALT > 5.0 × ULN AND blood bilirubin[g] > 2.0 × ULN	Permanently discontinue encorafenib and binimetinib
Grade 4 AST or ALT > 20.0 × ULN	Permanently discontinue encorafenib and binimetinib
Cardiac Disorders - Left Ventricular Systolic Dysfunction[a] (Dose Adjustment for Binimetinib ONLY)	
Asymptomatic absolute decrease of > 10% in LVEF compared to baseline and the LVEF is below the institution's LLN (e.g., a decrease of 60% to 48% is an absolute decrease of 12%)	Interrupt dosing of binimetinib and repeat evaluation of LVEF within 2 weeks • If the LVEF recovers (defined as LVEF ≥ 50% or ≥ LLN and absolute decrease ≤ 10% compared to baseline) ≤ 21 days, resume treatment at 1 reduced dose level[b] of binimetinib after approval of the Sponsor Principal Investigator. Monitor LVEF 2 weeks after resuming binimetinib, every 4 weeks for 12 weeks and subsequently as per protocolIf the LVEF does not recover in ≤ 21 days, permanently discontinue binimetinib. Closely monitor LVEF until resolution or for up to 16 weeks

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
Grade 3 – 4	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks Note: Copies of ECHO and/or MUGA scans could be requested for patients to be available to the Sponsor Investigator for patients with absolute decrease of >10% in LVEF compared to baseline and LVEF < 50% or LLN
CK Elevation	
Grade 1-2	Maintain dose of encorafenib and binimetinib. Ensure patient is adequately hydrated. Closely monitor CK and serum creatinine • If total CK ≥ 3 × ULN, measure CK isoenzymes and myoglobin in blood or urine
Grade 3 > 5.0 - 10.0 x ULN without renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dosing of encorafenib and binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine If symptomatic (muscle pain/spasms/muscle weakness), maintain dosing of encorafenib and interrupt dosing of binimetinib until resolved to NCI-CTCAE Grade ≤ 1 and monitor closely, then: • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib
Grade 4 without renal impairment (i.e., serum creatinine < 1.5 × ULN or 1.5 × baseline)	If asymptomatic, maintain dose of encorafenib and interrupt dosing of binimetinib. Ensure patient is adequately hydrated. Monitor and measure isoenzymes and myoglobin in blood or urine and serum creatinine • If resolved in ≤ 21 days, maintain dose of encorafenib and resume treatment at 1 reduced dose level[b] of binimetinib • If not resolved in ≤ 21 days, maintain dose of encorafenib and permanently discontinue binimetinib If symptomatic (muscle pain/spasms/muscle weakness), maintain dose of encorafenib and permanently discontinue binimetinib
Grade 3 or 4 with renal impairment (i.e., serum creatinine ≥ 1.5 × ULN or 1.5 × baseline)	Interrupt dosing of encorafenib and binimetinib until resolved to NCI-CTCAE Grade < 1 or baseline level. Ensure patient is adequately hydrated. Monitor closely and measure isoenzymes and myoglobin in blood or urine and serum creatinine, then: • If resolved in ≤ 21 days, consider resuming treatment at 1 reduced dose level[b] of encorafenib and binimetinib • If not resolved in ≤ 21 days, permanently discontinue encorafenib and binimetinib 2nd occurrence: • Permanently discontinue encorafenib and binimetinib
Cardiac Investigation – Prolongation of the QT interval QTcF value	

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
QTcF > 500 ms during treatment and change from pre-treatment value remains ≤ 60 ms	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib 2nd occurrence: • Temporarily interrupt dosing of encorafenib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level[b] of encorafenib 3rd occurrence: • Permanently discontinue encorafenib and patient will have to come off study
QTcF increase during treatment is both > 500 ms and > 60 ms change from pre-treatment values	Permanently discontinue encorafenib ~~and binimetinib~~
Rash	
Grade 1	Maintain dose level of encorafenib and binimetinib Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored
Grade 2	1st occurrence: • Maintain dose level of encorafenib and binimetinib • Initiate Initial Rash Treatment Regimen if it was not already started and rash should be closely monitored • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and binimetinib. For dermatitis acneiform, treatment with encorafenib may be maintained if, in the judgment of the investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib 2nd occurrence: • Reassess within ≤ 14 days. If rash worsens or does not improve, interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib and 1 reduced dose level[b] of binimetinib. For dermatitis acneiform rash, treatment with encorafenib may be maintained if, in the judgment of the investigator, the rash is considered to be unrelated to encorafenib. If treatment with encorafenib was maintained and no improvement within 8 days, interrupt dosing of encorafenib
Grade 3	1st occurrence:

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
	• Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Reassess weekly. Then resume treatment at current dose level of encorafenib and binimetinib. • Consider referral to dermatologist and manage rash per dermatologist's recommendation. 2nd occurrence: • Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of encorafenib and binimetinib. Resume treatment with encorafenib at the same dose level if, in the judgment of the Investigator, the rash is considered to be unrelated to encorafenib • Consider referral to dermatologist and manage rash per dermatologist's recommendation
Grade 4	Permanently discontinue encorafenib and binimetinib[f]
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome[e] (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: • 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 1 reduced dose level[b] at 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 1reduced dose level[b] of encorafenib • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
	> 3nd occurrence: • Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at 1 reduced dose level[b] or permanently discontinue encorafenib at the Investigator's discretion.
SCC, KA and any Other Suspicious Skin Lesion (Dose Adjustment for Encorafenib ONLY)	
Grade ≤ 3	Maintain dose of encorafenib (dose interruptions or modifications are not required). Treatment of SCC, KA, and any other suspicious skin lesion (eg. new primary melanoma) should occur based upon institutional practice.
Diarrhea	
Uncomplicated Grade 1-2	Maintain dose of encorafenib. Consider temporary interruption of binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of binimetinib
Complicated Grade 1-2	Consider temporary interruption of encorafenib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib Interrupt dosing of binimetinib until resolved to Grade ≤ 1. Then resume treatment at 1 reduced dose level[b] of binimetinib
Grade 3-4	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment at current dose level of encorafenib if, in the judgment of the Investigator, the toxicity is considered to be unrelated to encorafenib, or at 1 reduced dose level[b]. Resume treatment at 1 reduced dose level of binimetinib
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 1 reduced dose level[b] 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 1 reduced dose level[b]. 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.[f]
Interstitial Lung Disease/Pneumonitis	
Grade 1	Maintain dose level of encorafenib and binimetinib.
Grade 2	Maintain dose of encorafenib. Withhold binimetinib for up to 3 weeks. If improved to Grade 0 or 1, resume treatment at 1 reduced dose level of binimetinib. If not resolved within 3 weeks, permanently discontinue binimetinib.
Grade 3-4	Permanently discontinue binimetinib.
All Other Adverse Events (Suspected to be Related to Encorafenib and/or Binimetinib)	
Grade 1-2	If the event is a persistent Grade 2 AE not responsive to a specific therapy, consider interruption or reduction of encorafenib and binimetinib, as applicable

Worst toxicity NCI-CTCAE, v.5 Grade (unless otherwise specified[a])	**Recommended Dose Modifications for Encorafenib-related and/or Binimetinib-related Adverse Events**
Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤1 or to pretreatment/baseline level. If the event resolves ≤ 21 days, then study drug may be resumed at 1 reduced dose level[b] based upon the Investigator's discretion.
Grade 4	Permanently discontinue encorafenib and binimetinib.[f]

[a] Not according to NCI-CTCAE
[b] Dose reduction below 150 mg QD for encorafenib, and below 15 mg BID for binimetinib is not allowed.
[c] Ophthalmic monitoring mandated for retinal events, posterior uveitis, RVO: further evaluation with specialized retinal imaging (e.g. ocular coherence tomography, fluorescein angiography). Any diagnosis of retinal events must be supported by presence or absence of symptoms, visual acuity assessment and findings in OCT.
[d] For patients enrolled with liver metastases and baseline LFT elevations.
[e] Disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.
[f] A patient with a Grade 4 AE may resume treatment at the lower dose level if the AE recovers to Grade ≤ 1 within 28 days of discontinuing drug and, if in the opinion of the Sponsor Investigator, the event is not life-threatening and the patient can be managed and monitored for recurrence of AE. Any patients requiring a treatment interruption of duration > 28 days must discontinue study drug permanently.
[g] Refers to total bilirubin.

9.3 Permitted contraception methods

Female patients are either postmenopausal for at least 1 year, are surgically sterile for at least 6 weeks, or 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.

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[13]:

- 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

9.4 Concomitant medications

Appendix A lists concomitant medications to use with caution

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The following are the planned evaluations and interventions. The schedule is summarized in Figure 5. There is a 3 day +/- window for all interventions, except imaging assessments and

the pre-treatment biopsy, which have a +/- 7-day window. Each treatment cycle is defined as 28 days.

- Clinical assessment (physical examination-including assessment of visual acuity, complete blood count with differential, comprehensive chemistry profile, CK) at baseline, day 15 of cycle 1, and then day 1 of each subsequent cycle
- Research blood collection for cfDNA analysis at baseline and then day one of each subsequent cycle (two 10 mL streck tubes)
- ECG, done in triplicate, at baseline and then day 1 of each subsequent cycle
- ECHO/MUGA at baseline, 4 weeks (C2D1), and then every 8 weeks
- Ophthalmologic evaluation at baseline, Cycle 1 Day 21, Cycle 2 Day 21 and then Day 1 of every other Cycle (beginning with Cycle 5) and at anytime patients complains of visual symptoms or has decreased visual acuity.
- Dermatologic evaluations – can be performed by treating physician or dermatologist – at baseline and then every 8 weeks. It is recommended that patients have dermatologic evaluations for up to 6 months followind discontinuation of encorafenib.
- Imaging for tumor assessment with CT chest/abdomen/pelvis with contrast or, in patients unable to tolerate contrast, with CT chest and MRI abdomen/pelvis
- Optional tumor biopsy at baseline and at C1D7 of an accessible site, ideally at the same site for both biopsies. Pre-treatment biopsy, if completed, must be collected before the start of encorafenib and binimetinib.

An end-of-treatment evaluation will be performed between 28 and 42 days of the last dose (assessments/procedures for this visit outlined in Figure 5).

Patients will continue to be followed for overall survival after end-of-treatment. Where available, medical records will be reviewed or, if not available, patients will be contacted every 3 months to record survival status.

Figure 5. Study Calendar

Procedure or Assessment	**Screening**	**Cycle 1**				**Subsequent Cycles**				**Follow-up phase**
Day	Within 28 days prior to treatment	1	7	15	21	1	8	15	21	End of Treatment
Informed Consent	X									
Physical exam	X	X		X		X				X
Vital signs	X	X		X		X				X
ECOG Performance Status	X	X		X		X				X
Blood test (cbc w/diff, comprehensive chemistry profile, magnesium, CK)	X	X		X		X				X
Research blood test (cfDNA)		X				X				X
Pregnancy test (if able to become pregnant)	X	X				X				X
Triplicate ECG	X	X				X				
ECHO / MUGA	X					X*				X
Eye exam	X				X	X**			X**	X
Dermatology exam	X					X***				X
Tumor biopsy****	X		X							
Treatment (encorafenib)		QD oral medication								
Treatment (binimetinib)		BID oral medication								
Tumor assessments	X	every 8 weeks								
Concomitant Medications	X									
Adverse Events	X									

*ECHO/MUGA at baseline, 4 weeks (C2D1), and then every 8 weeks

**Ophthalmologic evaluation at baseline, Cycle 1 Day 21, Cycle 2 Day 21, and then Day 1 of every other cycle (beginning with Cycle 5) or anytime patient complains of visual symptoms or has decrease in visual acuity

*** Dermatologic evaluations – can be performed by treating physician or dermatologist – at baseline and then every 8 weeks. It is recommended that patients have dermatologic evaluations up to 6 months following discontinuation of encorafenib.

****Optional tumor biopsy at baseline and at C1D7. The pre-treatment biopsyhas a +/- 7 day window and the C1D7 biopsyhas a +/-3 day window.

Correlative studies

Planned correlative studies will evaluate PD markers for response and potential biomarkers for response/resistance. Tumor biopsy specimens collected immediately prior to treatment and on day 7 of treatment will be used to evaluate expression of phosphorylated ERK and of ERK transcriptional output genes. Immunohistochemical analysis will be used to determine phospho-ERK levels prior to treatment and on treatment, and RT-PCR (reverse transcription-polymerase chain reaction) will be used to measure expression of the ERK transcriptional output genes DUSP6, SPRY2, and ETV1. Plasma collected every 4 weeks on trial will be used for serial ctDNA analysis with treatment; cfDNA will be submitted for digital droplet PCR analysis for fraction of mutant BRAF and to track changes with treatment. Primers will be developed based on tumor BRAF alteration; primers for many of the recurrent activating non-V600 BRAF mutants are already available and the MSK Marie-Josée and Henry R. Kravis Center for Molecular Oncology can generate new primers using the patient's tumor as a positive control. Changes in expression level of phosphorylated ERK and the ERK output genes and, in cfDNA, BRAF mutant levels will be correlated with RECIST tumor assessments.

Baseline and end of treatment cfDNA will be subjected to NGS using the MSK cfDNA multi-gene assay to explore potential mechanisms of resistance.

Tumor genotyping by DNA analysis will be performed to identify somatic alterations in archived tissue from all cases, and genomic alterations will be correlated with response. All patients who did not undergo MSK-IMPACT genomic analysis of tumor tissue for detection of BRAF alterations will have pre-treatment tumor tissue sequenced with this assay to confirm the BRAF alteration. Patients will not be removed from the study if MSK-IMPACT analysis does not confirm the non-V600 activating BRAF alteration.

Additional biomarkers may be identified and measured as appropriate.

11.0 TOXICITIES/SIDE EFFECTS

The toxicity profile of encorafenib and binimetinib (alone and together) is summarized above in Section 5.

Toxicity should be assessed using the NCI-CTCAE, Version 5. A DLT is defined as an AE or abnormal laboratory value assessed as at least possibly related to the study medication, unrelated to disease, disease progression, intercurrent illness, or concomitant medications or therapies, which occurs within 28 days following the first dose of binimetinib or encorafenib. The event must occur during Cycle 1 of therapy and meet any of the criteria listed in the table below. The inability to deliver at least 75% of planned dose intensity due to toxicity in the first 21 days for binimetinib and in the first 28 days for encorafenib will also be considered a DLT. Whenever a patient experiences toxicity that fulfills the criteria for a DLT, treatment with the study drug will be interrupted and reduced per protocol, and the toxicity will be followed up.

Table 6. Criteria for Dose Limiting Toxicities

Cardiac disorders:

- Absolute decrease of LVEF > 10% compared to baseline and the LVEF is below the institution's LLN
- Left ventricular systolic dysfunction Grade ≥ 3
- Other cardiac disorders Grade ≥ 3

Vascular disorders:

- Grade 3 hypertension for > 14 consecutive days
- Grade 4 hypertension

General disordersand administration site conditions:

- Fatigue Grade 3 for ≥ 1 week

Respiratory disorders:

- Interstitial lung disease/ pneumonitis Grade ≥ 2

Skin and subcutaneous tissue disorders:

- Rash, HFSR, or photosensitivity NCI-CTCAE Grade 3 for > 14 consecutive days despite maximal skin toxicity treatment (as per local practice)
- Rash, HFSR, or photosensitivity NCI-CTCAE Grade 4

Gastrointestinal disorders:

- Diarrhea Grade 3 for ≥ 48 hours despite optimal use of antidiarrheal therapy
- Diarrhea Grade 4
- Nausea/vomiting Grade 3 for ≥ 48 hours despite optimal use of antiemetic therapy
- Nausea/vomiting Grade 4

Investigations:

- Total bilirubin Grade ≥ 3
- AST or ALT Grade ≥ 3 in conjunction with total bilirubin Grade ≥ 2 of any duration
- AST or ALT Grade 3 for > 7 consecutive days
- AST or ALT Grade 4
- Serum creatinine Grade ≥ 3
- CK elevation ≥ Grade 3 associated with an increase in creatinine ≥ 1.5 × the patient's baseline screening creatinine
- ANC Grade 4 for > 7 consecutive days
- Platelet count Grade 3 with signs of clinically significant bleeding
- Platelet count Grade 4
- QTcF prolonged ≥ Grade 3 (on at least 2 separate ECGs)

Eye disorders-Retinal:

- Retinopathy or retinal detachment Grade ≥ 3, confirmed by ophthalmic examination
- Retinal vascular disorder RVO, confirmed by ophthalmic examination

Eye disorders–Visual disturbances without ocular (retinal) changes:

- Blurred vision, flashing lights, floaters: Grade ≥ 3

Eye disorders – (other specify):

- Grade ≥ 3 for > 21 consecutive days
- Grade 4 confirmed by ophthalmic examination

Other hematologic and nonhematologic toxicities:

- Thrombocytopenia Grade 4 > 7 days
- Neutropenic fever
- Electrolyte abnormality Grade 3+ that lasts >72 hours, unless the patient has clinical symptoms, in which case all grade 3+ electrolyte abnormality regardless of duration should count as a DLT.
- Any other Grade ≥ 3 AE except:
    - Lymphocyte count decreased (lymphopenia) Grade ≥ 3 unless clinically significant
    - Isolated laboratory changes (e.g. alkaline phosphatase, cholesterol, lipase, serum amylase) or those due to sampling or laboratory errors without associated clinical signs or symptoms may be determined to not be DLTs upon discretion of the Investigator
    - Grade 3+ amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT.

Abbreviations: LVEF, left ventricular ejection fracture; LLN, lower limit of normal; HFSR, Hand-Foot Skin Reaction; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatinine kinase; ANC, absolute neutrophil count; ECG, electrocardiogram; QTcF, corrected QT interval by Fredericia; RVO, retinal vein occlusion; AE, adverse event; DLT, dose-limiting toxicity.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Radiologic tumor assessments will be performed in accordance with the Schedule of Procedures. CT and/or MRI will be used as appropriate for baseline tumor assessment which must be performed within 28 days prior to C1D1. Radiologic tumor assessments will be performed every 8 weeks +/- 7-day window. All target and non-target sites of active disease identified at screening must be followed for the duration of the study. Their presence and absence should be noted throughout follow-up. The same method of measurement (e.g. CT, MRI) and the same technique of assessment should be used to characterize each identified and reported lesion at baseline through to the final visit. Overall objective response for each patient is based on the combined results for target and non-target lesions. Tumor-based efficacy endpoints (i.e., PFS and ORR) will be based on tumor assessments performed by the radiologist and assessed by the Principal Investigator. Response and progression of disease will be evaluated using RECIST Version 1.1. Tumor assessments will be performed until the occurrence of documented disease progression or patient withdrawal from the study (e.g., progressive disease, lost to follow-up, withdrawal of consent, or death), whichever comes first. Additional tumor evaluations will be performed as clinically indicated. Missed tumor assessments must be performed as soon as possible.

The longest diameters (LDs) for all target lesions will be recorded (short axis for target pathological lymph nodes). The LD for all target lesions will be added and reported as the

baseline sum LD (SLD). Per RECIST Version 1.1, for determining complete response (CR) or partial response (PR), all post-baseline tumor measurements will be compared with the baseline SLD; for determining progressive disease (PD), the post-baseline measurement is compared with the smallest SLD recorded since initiation of treatment, including baseline. Patients who discontinue study treatment and do not have PD will be asked to remain on study for tumor evaluation per protocol and for determination of PFS.

All patients will be evaluable for toxicity from the time of their first treatment with encorafenib and binimetinib. Any patient who has received a dose of therapy with encorafenib and binimetinib will have their disease evaluated for radiographic response. Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease or unacceptable toxicity, he/she will be taken off study.

In addition, a subject should be withdrawn from the trial treatment, if, in the opinion of the investigator, it is medically necessary, or if it is the wish of the subject. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

Patients should be removed from therapy if any of the following occur:

- Tumor progression. This should be based on radiographic progression or a clinical deterioration thought by the clinical investigator to be secondary to tumor burden.
- The occurrence of other unacceptable toxicity indicating the need for cessation of treatment.
- The physician feels it is in the best interest of the patient to stop treatment.
- Patient refusal to continue with therapy.
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document subject outcome, if possible.
- Patient becomes pregnant.
- Termination of the study by investigator or Array BioPharma.

If the reason for withdrawal from the trial is the death of the patient, the two options for categorizing withdrawal are either progressive disease or an AE. More than one AE may be documented as a reason for withdrawal. Note that death is an outcome and not an AE.

Patients can continue treatment beyond progression if they are receiving clinical benefit from treatment.

14.0 BIOSTATISTICS

Phase I

Between 3 and 12 patients will be enrolled in the phase I portion of this study. We will first treat 3-6 patients at dose level 1, the approved dose of encorafenib 450 mg oral QD and binimetinib 45 mg PO BID, to evaluate the safety of this dose level in this population. If this dose level is found to be safe, up to 6 patients will be treated with dose level 2, encorafenib 450 mg oral QD continuous and binimetinib 60 mg oral BID 21 days on/7 days off. If one or fewer patients experience DLTs in the first 28 day treatment cycle, then we will declare that this dose can be safely given in this population and phase II portion will proceed with this regimen. In this case the six patients treated at dose level 2 in the Phase I portion will be included in the Phase II portion. If however 2 or more patients experience DLTs in the first 28 days, then the phase II portion will enroll patients at the dose 1 level of encorafenib 450 mg oral QD and binimetinib 45 mg oral BID. All patients will then be included in the efficacy endpoint. Patients who receive less than 75% of planned therapy in the first 28 days for reasons not related to adverse events will not be evaluated for DLTs and will be replaced.

Phase II

The primary endpoint of the phase II portion is the best objective response rate of the combination. Primary statistical analysis will be performed on data from the population comprising all patients receiving any dose of the investigational agents (encorafenib/binimetinib). Any patient who drops out prior to the 8 week assessment will be deemed a non-responder.

We infer a historical response rate (RR) of about 15% based on experience with ERK inhibitors in this population[9] and the activity of binimetinib in NRAS mutant melanoma[11]. These trials provide the only genomically annotated efficacy data for ERK pathway inhibitors in similar populations. With a total number of 32 patients, using a Simon's minimax 2 stage design, we can show a difference in RR from 15% to 35% with type I and II error rates of 0.1 each. We will enroll 17 patients in the first stage and if 3 or more responses are observed then an additional 15 patients will be enrolled for a total of 32 patients. Otherwise, if 2 or less responses are observed, the study will be terminated. Enrollment will pause after the first 17 patients enter the study to evaluate RR. If 3 or more patients already achieved a response, then the study will proceed to the second stage. If fewer than 3 RECIST responses are seen, then there will be a pause of up to 16 weeks from the start of treatment of the last enrolling patient to allow monitoring of treatment efficacy. Responses in the first stage do not need to be confirmed with repeat CT scan for the study to proceed to the second stage. At the end of the study, if 8 or more responses are observed then we would consider the study promising.

Secondary objectives: PFS will be calculated from the start of treatment until progression or death whichever occurs first. OS is defined as the interval between the time of initiation of therapy and the date of death from any cause. Patients who are alive at the time of study completion will be censored at the time the patient was last known to be alive. PFS and OS will be estimated using the Kaplan-Meier method.

Safety and tolerability will be summarized using descriptive statistics. All patients receiving any dose of the investigational agents (encorafenib/binimetinib) will be included in the analysis. We will also evaluate long-term tolerability as defined by percent of patients that require dose interruption, reduction, or discontinuation due to AEs. Please note three novel

dosing schedules were used in this protocol. The initial level 2 dose was encorafenib 450 mg QD continuous + binimetinib 60 mg BID 21 days on/ 7 days off. This dose was amended for intermittent dosing of both agents to limit unopposed RAF inhibitor treatment. The expansion dose was then amended to continuous treatment with both drugs after several patients reported good tolerance of continuous dosing during the first three weeks and symptomatic improvement but recrudescence of symptoms during the week off drug.

Exploratory objectives: Changes in RNA expression (continuous variables) between pre-treatment and day 7 of the ERK transcriptional output genes DUSP6, SPRY2, and ETV1 will be associated with response using Wilcoxon rank sum test while associations between response and immunohistochemical analysis of phosphorylated ERK expression (categorical) measured at pre-treament and day 7 post-treatment will be assessed using generalized estimating equations (GEE). The BRAF variant allelic fraction in cfDNA will be evaluated in plasma by droplet digital PCR to give a quantitative assessment. Associations between objective response rate and the changes in the proportion of detectable BRAF alterations between pre-treatment and week 4 will be assessed using the Wilcoxon rank sum test. Proportions of mutations identified by the next-generation sequencing assay will be estimated using binomial proportions along with exact 95% confidence intervals and associations between mutation status and objective response rate will be assessed using Fisher's exact test controlling the false discovery rate using Benjamini-Hochberg method to account for the multiple testing.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator(CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the study team. Medidata will be used for data collection. The data will be reported to the institution (MSK IRB) and the drug manufacturer (Array BioPharma) as appropriate. Tumor slides will be stored in the MSK Diagnostic Molecular Pathology Laboratory. Results from laboratory studies will include photomicrographs of immunohistochemistry (IHC) studies, computer files of sequencing data, and computer files from cfDNA analysis. These files will

be stores on the MSK Department of Medicine server. Documentation linking patient identifiers with patient samples and results will be securely maintained in the Medidata with access limited to study investigators.

16.1 Quality Assurance

Routine registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, and more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSK were approved by the National Cancer Institute (NCI) in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the MSK Office of Clinical Research. The MSK DSM Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control. Additionally, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: the *Data and Safety Monitoring Committee (DSMC)* for phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for phase III clinical trials, report to MSK's Research Council and IRB.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonisation (ICH) to the extent required by the FDA, and MSK policies. Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSK IRB guidelines. The study will protect the rights of all human subjects and the informed consent will clearly define the risks, benefits, toxicities, and side effects of treatment. We will also thoroughly explain the alternative options for treatment. The patients will be aware of the potential financial costs and burdens of enrolling on a clinical trial.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/PB.

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred

- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following o An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 Array SAE Reporting

All SAEs occurring in patients from the first dose of Array study drug until 30 days after the last dose of Array study drug must be reported to Array BioPharma Inc. within 24 hours of the Investigator's knowledge by faxing a completed SAE form to Array BioPharma Inc. at the number provided on the SAE form or fax cover sheet. SAEs occurring greater than 30 days after the last dose of Array study drug should be reported to Array BioPharma Inc. only if considered related to the Array product.

If new information becomes available for a previously reported SAE, a follow-up SAE report should be sent within 24 hours. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

Investigators must follow patients with SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, the patient is lost to follow up, or death OR until 30 days after the last dose of Array study drug, whichever occurs first. Ongoing treatment-related SAEs may be followed beyond this time period if clinically indicated.

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 Array BioPharma Inc. within 24 hours of the Investigator's knowledge. All pregnancies should be followed through to outcome and the outcome must be reported to Array BioPharma Inc.

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.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to

withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the IRB/PB of this Center. The consent form will include the following:

1. The nature and objectives, potential risks, and benefits of the intended study
2. The length of study and the likely follow-up required
3. Alternatives to the proposed study (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research-specific information. In addition to signing the IRB informed consent form, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

1. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* Jun 30 2011;364(26):2507-2516.
2. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med.* Aug 20 2015;373(8):726-736.
3. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. *J Clin Oncol.* Jan 1 2018;36(1):7-13.
4. Infante JR, Fecher LA, Falchook GS, et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. *Lancet Oncol.* Aug 2012;13(8):773-781.
5. Rinehart J, Adjei AA, Lorusso PM, et al. Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. *J Clin Oncol.* Nov 15 2004;22(22):4456-4462.
6. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med.* Jun 2017;23(6):703-713.
7. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature.* Mar 18 2010;464(7287):427-430.
8. Yao Z, Torres NM, Tao A, et al. BRAF Mutants Evade ERK-Dependent Feedback by Different Mechanisms that Determine Their Sensitivity to Pharmacologic Inhibition. *Cancer Cell.* Sep 14 2015;28(3):370-383.
9. Sullivan RJ, Infante JR, Janku F, et al. First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study. *Cancer Discov.* Dec 15 2017.

10. Xue Y., Martellotto L., Baslan T., Vides A., Solomon M., Mai T.T., Chaudhary M., Riely G., Li B., Scott K., et al. An approach to suppress the evolution of resistance in $BRAF^{V600E}$-mutant cancer. Nat. Med. 2017;23:929–937.

11. Yaeger, Rona, Zhan Yao, and Paul B. Chapman. "Intermittent Treatment with MEK Inhibitors in Patients with Oncogenic RAF-Driven Tumors: A Potential Strategy to Manage Toxicity and Maintain Efficacy." *JCO Precision Oncology*.2 (2018): 1-2

12. 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.* May 2018;19(5):603-615.

13. Trussell J. Contraceptive failure in the United States. *Contraception.* Aug 2004;70(2):89-96.

14. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* Apr 2017;18(4):435-445.

15. Flaherty, Keith T., et al. "Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma." *N Engl J Med* 367.2 (2012): 107-14.

20.0 APPENDICES

Appendix A. Concomitant medications to use with caution.

Appendix B. CT Biopsy Dose Analysis