Academic and Community Cancer Research United (ACCRU)

BrafPanc: A Phase II Trial of Binimetinib in combination with Encorafenib in patients with Pancreatic Malignancies and a somatic BRAF^{V600E} mutation

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site ([redacted]).

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√ Study contributor(s) not responsible for patient care.

Drug Availability

Drug Company Supplied: Binimetinib and encorafenib IND Exempt

Research Coordinating Center

[redacted]

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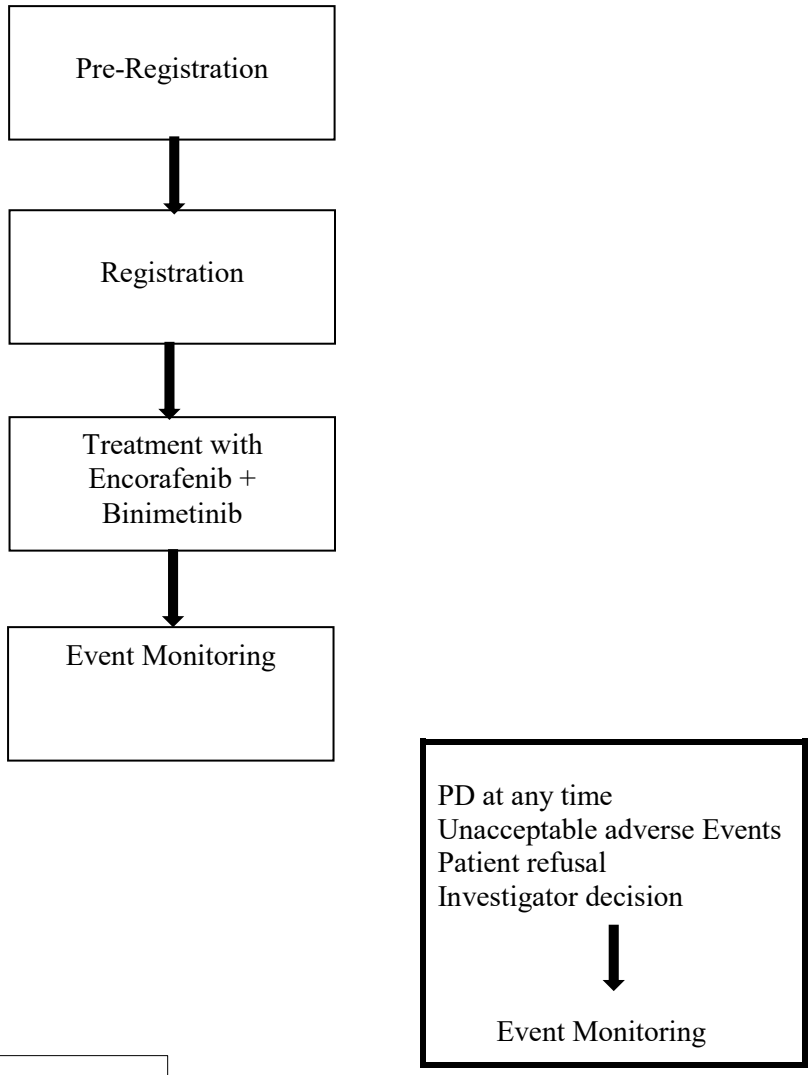
Schema



Generic name: Binimetinib Brand name(s): MEKTOVI Availability: Clinical Research Services	Generic name: Encorafenib Brand name(s): BRAFTOVI Availability: Clinical Research Services

1.0 Background

1.1 Treatment

1.11 Therapy for Pancreatic Cancer

While the treatments for metastatic pancreatic cancer have improved in the last decade, and modern chemotherapy regimens, including FOLFIRINOX and gemcitabine + nab-paclitaxel have improved survival times, the hard reality is that the vast majority of patients do not respond to standard chemotherapy. Specifically, the objective response rate (ORR) with front line FOLFIRINOX or gemcitabine + nab-paclitaxel are 32% and 23% respectively (Conroy *et al*, 2011; Von Hoff *et al*, 2013). In the 2nd line setting, those percentages drop considerably. For patients treated with the only FDA-approved second line therapy regimen, 5-flurouracil + nano-liposomal irinotecan, the ORR is only 17%, and the median progression-free (PFS) and overall survival (OS) was only 4 and 6 months, respectively (Wang-Gillam *et al*, 2016). Multiple other Phase II trials as 2nd line therapy for patients have yielded ORR of 2.5 to 24%, with a PFS typically of 2 – 4 months, and OS typically of 4 – 6 months (Boeck *et al*, 2008; Boeck *et al*, 2007; Cantore *et al*, 2004; Cereda *et al*, 2016; Cereda *et al*, 2011; Demols *et al*, 2006; Kim *et al*, 2012; Milella *et al*, 2004; Oettle *et al*, 2000; Tsavaris *et al*, 2005; Ulrich-Pur *et al*, 2003; Xiong *et al*, 2008; Zaniboni *et al*, 2012).

1.12 Predictive Biomarkers in Pancreatic Cancer, and BRAF mutations

There are no FDA approved targeted therapies for patients with pancreatic cancer. However, broad-based genetic sequencing efforts have consistently revealed that ≥25% of pancreatic cancers have potentially highly actionable molecular biomarkers with the definition of "highly actionable" being identified as a biomarker that predicts for a high response rate, or otherwise high degree of clinical activity for a therapy targeted to that biomarker, as defined in any cancer type (Aguirre *et al*, 2018; Bailey *et al*, 2016; Biankin *et al*, 2012; Collisson *et al*, 2011; Lowery *et al*, 2017; Pishvaian *et al*, 2018; Waddell *et al*, 2015; Witkiewicz *et al*, 2015). Two biomarkers that are clearly linked to a high degree of anti-cancer activity across tumors types include MSI-high or MMR deficient solid tumors, and NTRK fusions. Pembrolizumab and nivolumab are FDA approved for MSI-high or MMR deficient solid tumors (Le *et al*, 2015); while larotrectinib is FDA approved for tumors that harbor NTRK gene fusions (Drilon *et al*, 2018).

One such predictive biomarker is an activating mutation in the *BRAF* gene. In the population of pancreatic cancers lacking *KRAS* mutations, probable driver mutations have been identified including *BRAF, GNAS, CTNNB1,* as well as NRG1 fusions (Cancer Genome Atlas Research Network. Electronic address & Cancer Genome Atlas Research, 2017; Heining *et al*, 2018). *BRAF* mutations specifically have been previously identified in *KRAS* wild-type and mutant pancreatic cancer cell lines and patient tumors (Foster *et al*, 2016; Ishimura *et al*, 2003; Singhi *et al*, 2019).

BRAF alterations have also been identified in multiple cancer types including lung, colon, thyroid, and melanoma, as well as in non-Hodgkin lymphoma

(Davies *et al*, 2002; El-Osta *et al*, 2011). In pancreatic acinar cell carcinomas, rearrangements involving BRAF and RAF1 (CRAF) have been identified in approximately 23% of tumors (Chmielecki *et al*, 2014). Combined BRAF and MEK inhibition is now FDA approved for metastatic melanoma, non-small cell lung cancer and anaplastic thyroid cancer. In addition, targeting $BRAF^{V600}$ alterations with combinations of RAF/MEK inhibition with and anti-EGFR therapy has improved outcomes in colorectal cancer (Hyman *et al*, 2015; Planchard *et al*, 2016; Van Cutsem *et al*, 2019) and received breakthrough FDA status in 2018.

These alterations have been recently classified into 3 functional classes based on dependence of RAS activation, BRAF kinase activity, and signaling properties (Yaeger & Corcoran, 2019). Class I BRAF mutations result in RAS-independent kinase activation and signal as monomers (Poulikakos *et al*, 2010; Pratilas *et al*, 2009). To date, this class typically includes $BRAF^{V600E}$ mutations. Class II mutations are also RAS-independent but signal as heterodimers and do not commonly co-occur with other alterations in the MAPK pathway (Yao *et al*, 2015). This group includes activating *BRAF* mutations, several fusions, and in-frame deletions. Class III mutations are RAS-dependent and occur when these mutations heterodimerize with wild-type CRAF and amplify Ras signaling. Class III mutations often co-occur with activating *RAS* mutations, or NF1 loss-of-function mutations.

We recently evaluated several large pancreatic cancer next-generation sequencing (NGS) datasets, and we identified four categories of BRAF alterations: $BRAF^{V600}$ mutations, other missense mutations, in-frame deletions, and fusions all of which were evenly represented across patients (Table 1). Acinar cell carcinomas frequently harbored BRAF fusions (4/6, 67%); while patients with neuroendocrine tumors most frequently had $BRAF^{V600}$ mutations and non-canonical *BRAF* mutations (8/9, 89%). $BRAF^{V600E}$ mutations were also found in rare histologies, with one in a pancreatoblastoma and one in a solid and pseudopapillary neoplasm. The most common BRAF alterations in pancreatic acinar cell cancer patients were BRAF fusions (12/53), in-frame deletions (11/53, N486_P490del, ΔNVTAP) and the canonical $BRAF^{V600}$ mutation (11/53).

Histology	Dataset	#Altered / # Total	Fraction mutated	Alterations
Pancreatic adenocarcinoma	GENIE	13 / 587	0.022	N486_P490del (4); V600_K601delinsE (2); Y633H; *767Cext*3; V600E; L485F; D391N; G469S; H766Y
	ICGC	4 / 572	0.007	V471I; V487S; P334L; D594G
	KYT	23 / 926	0.026	N486_P490del (6); V600E (4); SND1-BRAF fusion (3); V600_K601>E; deletion exons 2-10 + S467L; G596R; T310I; MKRN1-BRAF fusion; TMEM9-BRAF fusion; V600E + deletion exons 2-10 (after developing resistance to BRAF-targeted therapy); G469A; rearrangement; D594G; V487_P492>A
	MSK	7 / 383	0.018	BRAF-SND1 fusion (2); BRAF-LUC7L2 fusion; V600R; V600E; BRAF-JHDM1D fusion; V600E + BRAF-SND1 fusion
	TCGA	3 / 150	0.02	T488_Q493delinsK; N486_P490del; R462T
	UTSW	3 / 109	0.028	V600E (3)
	Total	**53 / 2,727**	**0.019**	
Pancreatic acinar cell carcinoma	GENIE	3 / 11	0.273	X327_splice; V600E; GLI2-BRAF fusion
	MSK	3 / 13	0.231	BRAF-SND1 fusion (2); GIPC2-BRAF fusion
	Total	**6 / 24**	**0.25**	
Pancreatoblastoma	KYT	1 / 1	1	V600E
Solid pseudopapillary neoplasm	GENIE	1 / 7	0.143	V600E

Table 1. BRAF alterations in pancreatic cancers

1.13 BRAF Mutant Cell Lines are Responsive to MEK and RAF Inhibitors
NIH/3T3 cells with stable expression of either *BRAF* ^{V600E} or *BRAF*$^{\Delta NVTAP}$ were treated with varying concentrations of vemurafenib ($BRAF^{V600E}$ inhibitor), PLX8394 (BRAF inhibitor), LY300912 (pan-RAF inhibitor), trametinib (MEK inhibitor), or dabrafenib (BRAF inhibitor) and analyzed for ERK phosphorylation (Figure 1). All of the RAF and MEK inhibitors demonstrates significant single agent activity in the *BRAF* ^{V600E} mutant cell lines (Figure 1C). In the *BRAF*$^{\Delta NVTAP}$ mutant lines, there appeared to be decreased sensitivity to vemurafenib and LY300912, and otherwise anti-tumor activity across other RAF and MEK inhibitors.

Cell viability studies of BA/F3 populations expressing *BRAF* ^{V600E} or *BRAF*$^{\Delta NVTAP}$ were performed with varying concentrations of different RAF or MEK inhibitors

(Figure 1, E-H). These studies confirmed single agent activity across the RAF and MEK inhibitors, again with enhanced activity of the *BRAF*$^{\Delta NVTAP}$ mutant to all treatments.

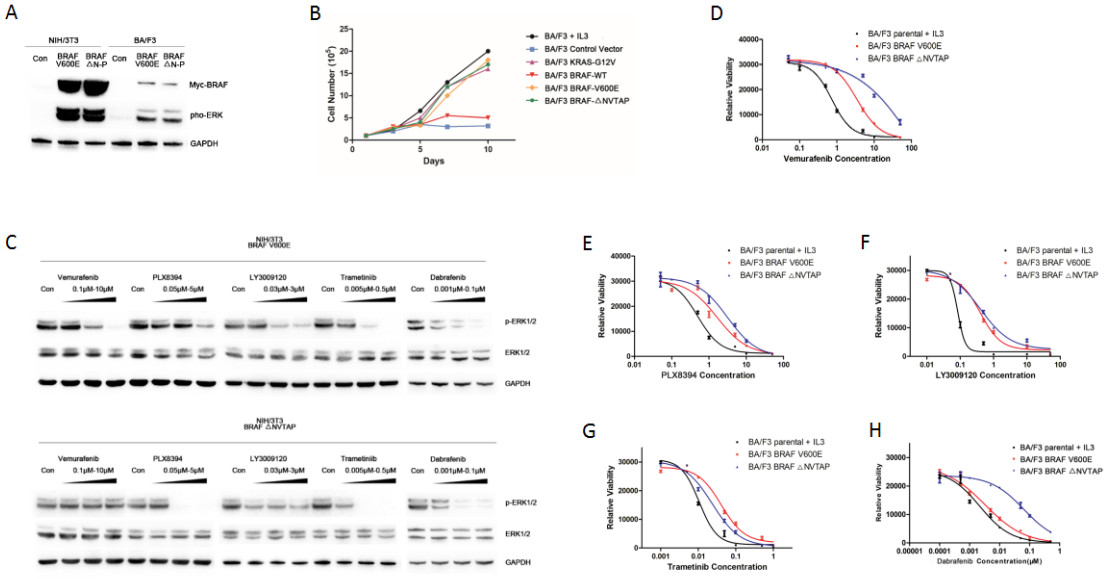


Figure 1. BRAF Mutant Cell Lines are Responsive to MEK and RAF Inhibitors. (A) Western blot analysis from stable expression of the indicated *BRAF* mutants in NIH/3T3 and BA/F3 cells. The mutants include *BRAF* ^{V600E} and *BRAF*$^{\Delta NVTAP}$. (B) BA/F3 cell growth curve from stable expression of the indicated constructs including control vector, *KRAS*^{G12V}, *BRAF*^{WT}, *BRAF* ^{V600E}, and *BRAF*$^{\Delta NVTAP}$. (C) Western blot of lysates from NIH/3T3 cells with *BRAF* ^{V600E} or *BRAF*$^{\Delta NVTAP}$ after treatment with the indicated concentration of different RAF or MEK inhibitors for 2 hours. (D – H) Viability of BA/F3 populations with *BRAF* ^{V600E} or *BRAF*$^{\Delta NVTAP}$ after 72 hour treatment with the indicated concentration of different RAF or MEK inhibitors. Error bars indicate +/- SD.

1.14 A retrospective case series of BRAF mutated pancreatic cancer

In a retrospective case series of pancreatic cancer patients with clinically annotated data, we identified 81 patients with BRAF alterations (Table 1). The histologies were as follows: 65/81 adenocarcinoma, 13/81 acinar cell cancer or mixed acinar/neuroendocrine, 4/81 IPMN and 1 pancreaticoblastoma. Median age was 64 (42 – 86) and 40/81 were women. 69 of the 81 patients (85%) were KRAS wild-type. 18/81 of patients had a V600E, 19/81 non-canonical, 20/81 deletion, and 25/81 fusion abnormalities. The majority of the cohort presented with advanced disease 61/81 (75%) and 20/81 (25%) presented with earlier stage disease. The median overall survival of the cohort was 1.92y [95%CI=1.36-2.44]. The median number of lines of therapy was 2.

In our 81 patients with BRAF alterations, KRAS alterations were only found in 12 (15%) patients. Additional genomic alterations involving the targeted genes of the various sequencing panel were identified in genes such as *TP53* (43%), *CDKN2A/B* (36%), and *SMAD4* (19%).

Of the patients with *BRAF*^{V600E} alterations, 15/18 were in pancreatic

adenocarcinomas and 3/18 in acinar cell tumors, median age was 63, and 13/17 were women. One had a *KRAS*^{G12V} alteration and 9 had alterations in p53, and 5 alterations in CDKN2A and 4 with alterations in SMAD4.

We then classified these alterations into functional categories using available literature regarding their activity and their response to BRAF targeted therapy. Of the 17 *BRAF*^{V600E} alterations, 13 were placed in class 1 (13/17). If there were additional alterations in BRAF, KRAS, or other potential driving alterations they were placed in class 3 (4/17). In our cohort, co-existing alterations occurred in *NTRK*^{fusion}, *KRAS*^{G12V}, *BRAF*^{Q609L}, and *SND1-BRAF*^{fusion}. Class 2 alterations included fusion abnormalities and in-frame deletions which were placed in separate categories. Our last category included Class 3 alterations, and those with multiple driver mutations. Of those with multiple drivers outside of the BRAF gene, 13/15 were KRAS alterations an NTRK fusion, and a RAF mutation. 3 patients had 2 alterations in the BRAF gene; BRAF^{V600E} + SND-1-BRAF^{Fusion}, BRAF^{V600E} + BRAF^{Q609L}, and BRAF^{S467L} + Exon 2-10^{deletion}.

An overall survival analysis was performed for each of these functional BRAF categories. Patients with IPMN's and resected disease were excluded. Class 1 median overall survival was 1.3 years (N=8); Class 2 (fusion) was 1.9 years (N=18) and Class 2 (non-fusion) was 1.2 (n=12); and class 3 1.6 years (n=15). There were no significant differences found between these categories of BRAF alterations.

1.15 MEK and RAF inhibitors have activity in the patients with KRAS wild-type and BRAF-mutated pancreatic cancers

In our case series, 17 patients were treated with BRAF directed therapy (Figure 2). This includes 6 patients treated with combination BRAF and MEK and 8 patients with MEK inhibitor therapy alone. 2 patients were treated with pan-RAF inhibitors. The median lines of previous therapy was 2 (1-4). In evaluable patients, median weeks of therapy was 21 (7-110).

Responses to BRAF targeted therapy were evaluated based the recently described functional classification system previously described. All patients with Class-1 alterations had significant responses to BRAF targeted therapy. This included 2 BRAF^{V600E} alterations with durable partial responses of 48 weeks and over 2 years and in 1 patient with *BRAF*$^{\Delta NVTAP}$ had stable disease after 21 weeks. In class 2 BRAF fusions there was significant activity to single agent MEK inhibitors. 4/6 patients had a treatment response to single agent trametinib. 2 with partial responses; one lasting 73 weeks and the other ongoing at 21 weeks. 2 with stable disease; one lasting 30 weeks and the other 12 weeks. In patients with class 2 BRAF in-frame deletions, 2 out of 5 had therapeutic responses. There was a partial response to single agent MEK inhibition lasting 24 weeks and stable disease on MEK and BRAF combination lasting 21 weeks and on-going. Patients with class 3 alterations did not derive benefit form BRAF targeted therapy in our cohort (N=3).

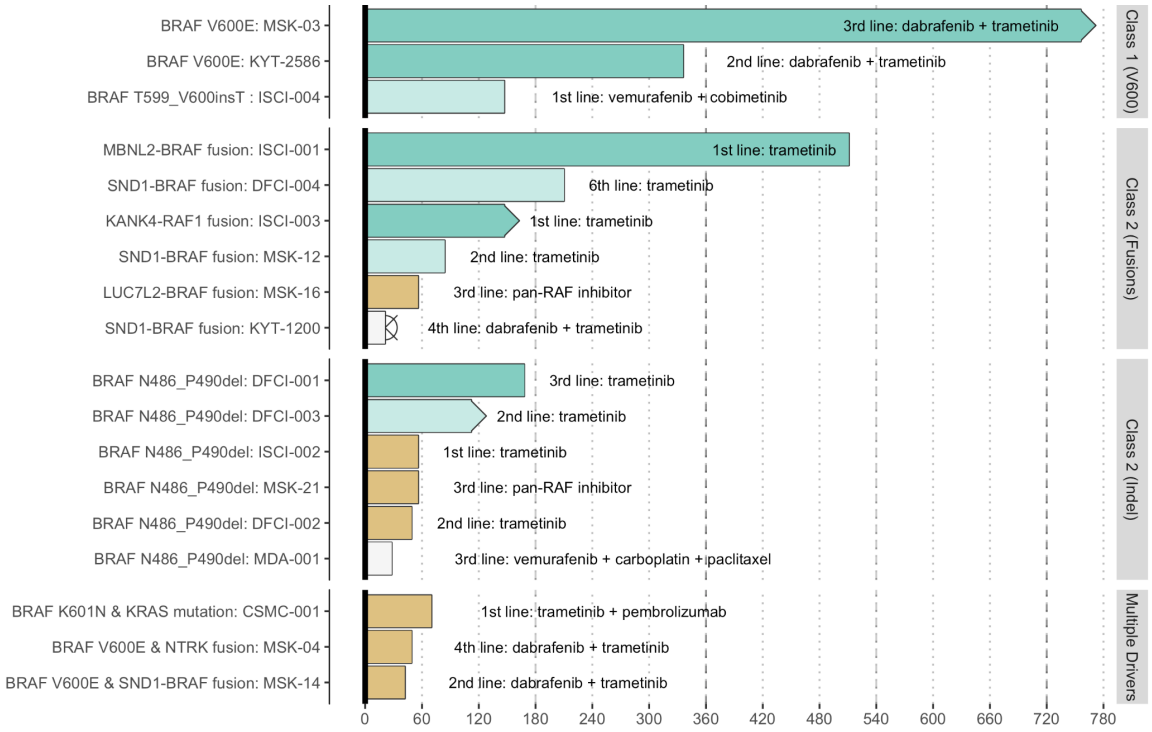
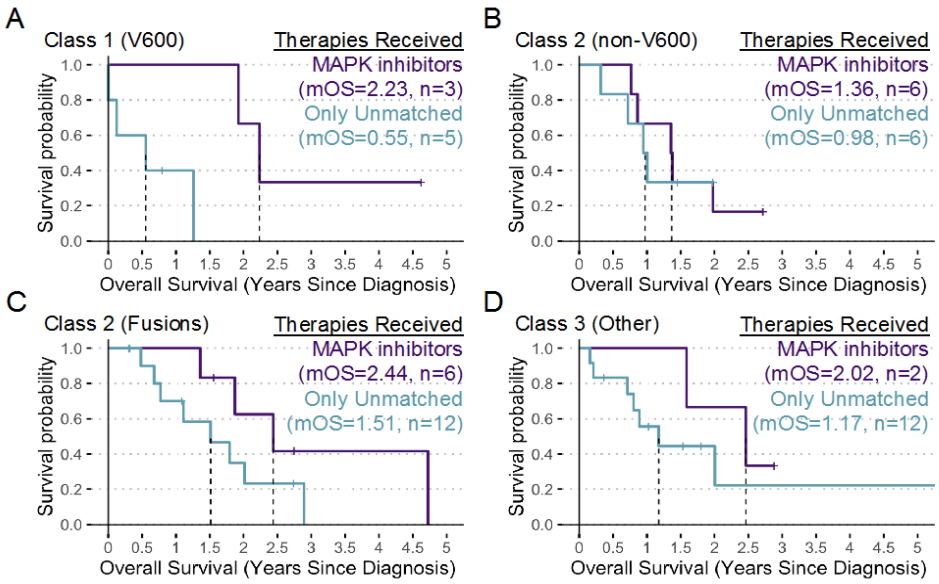


Figure 2. Therapeutic activity of BRAF targeted agents. Responses to 17 patients treated with BRAF directed therapy categorized by BRAF class, including 6 patients treated with combination BRAF and MEK and 8 patients with MEK inhibitor therapy alone. Each horizontal bar represents the time on therapy. Green bars represent patients with partial response as best response, light green are patients with stable disease, copper bars are patients with no response, and white bars indicate unevaluable subjects. Arrows indicate that patients continue on therapy.

1.16 Patients receiving BRAF directed therapy have improved outcomes

Using a multivariate model including BRAF alteration type, we compared overall survival between *patients with BRAF* alterations (delineated by BRAF subclass) who received a molecularly-matched therapy targeting the MAPK signaling pathway (e.g. a BRAF, pan-RAF, MEK, or ERK inhibitor) vs patients with *BRAF* alterations did not. There was a significant survival benefit, matched vs unmatched: ($p = 0.02068$, HR = 0.36 [0.15-0.86]). The extent of the survival benefits with targeted BRAF therapy were associated with functional class.



Overall survival analyses comparing patients with BRAF alterations (delineated by BRAF subclass) who received a molecularly-matched therapy (any treatment setting) targeting the MAPK signaling pathway (e.g. a BRAF, pan-RAF, MEK, or ERK inhibitor) vs patients with BRAF alterations (delineated by BRAF subclass) who did not. Matched Therapy vs Unmatched: 0.02068 (0.36 [0.15-0.86])

OS since Initial Diagnosis for the Advanced Cohort
Class 1 (V600), matched (mOS=2.23, n=3)
Class 1 (V600), unmatched (mOS=0.55, n=5)
Class 2 (Fusion), matched (mOS=2.44, n=6)
Class 2 (Fusion), unmatched (mOS=1.51, n=12)
Class 2 (non-V600), matched (mOS=1.36, n=6)
Class 2 (non-V600), unmatched (mOS=0.98, n=6)
Other, matched (mOS=2.02, n=2)
Other, unmatched (mOS=1.17, n=12)

Figure 3. Overall survival of pancreatic cancers with BRAF alterations

2.0 Goals

2.1 Primary Goal
To determine the efficacy of the combination of binimetinib and encorafenib as ≥ 2nd line of treatment for patients with metastatic pancreatic cancer with $BRAF^{V600E}$ mutation.

2.11 Primary Endpoint
Objective response rate at 24 weeks post-registration, as defined by RECIST 1.1.

2.2 Secondary Goals
To determine in patients treated with the combination of binimetinib and encorafenib as ≥ 2nd line of treatment for patients with metastatic pancreatic cancer with $BRAF^{V600E}$ mutation:

2.21 The median progression-free survival
Endpoint: The median time from study registration to clinical or radiographic disease progression or death, whichever occurs first, as defined by RECIST 1.1.

2.22 The median overall survival
Endpoint: The median time from study registration to death.

2.23 Duration of Response
Endpoint: The median duration of time from first documentation of an objective response to the earliest date progression is documented.

2.24 Time to Response
Endpoint: The median duration of time from study registration to the first documentation of an objective response.

2.25 The safety and tolerability
Endpoint: The rate of grade 3+ Adverse Events as defined by NIH CTCAE v5.0.

2.3 Correlative Research Goal

2.31 To determine the mechanisms of resistance, either primary or acquired through real time monitoring of the BRAF mutational profile evolution.

2.32 Endpoint:
Additional mutations in BRAF or in other related genes as determined by next-generation sequencing from plasma samples.

3.0 Patient Eligibility
NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Pre-registration – Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of a pancreatic malignancy as confirmed by the local pathology lab

3.13 Patients whose disease has progressed on (or who were intolerant of) at least one line of therapy for metastatic disease

3.14 Patients whose disease has recurred with metastatic disease ≤12 weeks of completion of neoadjuvant or adjuvant systemic chemotherapy; or patients with locally advanced disease whose disease progressed to metastatic disease on, or ≤12 weeks after completion of systemic chemotherapy would also be eligible

3.15 Provide informed written consent ≤28 days prior to pre-registration.

3.16 Central electronic/paper confirmation of the presence of a $BRAF^{V600E}$ mutation (Section 6.16). This review is mandatory prior to pre-registration to confirm eligibility.

Results from a CLIA/CAP certified testing lab (commercial or institutional) that confirm the presence of a $BRAF^{V600E}$ mutation in the patient's tumor must be submitted for central review.

3.2 Registration – Inclusion Criteria

NOTE: Registration must occur ≤ 30 days after pre-registration.

3.21 Confirmation of the presence of $BRAF^{V600E}$ mutation in the patient's tumor (Section 6.2).

3.22 Measurable disease as defined in Section 11.0.

3.23 ECOG Performance Status (PS) 0, 1, or 2. (Form is available on the ACCRU web site)

3.24 The following laboratory values obtained ≤ 14 days prior to registration.

NOTE: If your site laboratory reports use different units of measurements than what is required by the protocol eligibility requirements, please use the "Lab Test Unit Conversion Worksheet" available on the ACCRU website under "General Forms".

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥9.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN)
- Aspartate transaminase (AST) ≤ 2.5 x ULN; in participants with liver metastases ≤5 x ULN
- Aminotransferase (ALT) ≤ 2.5 x ULN; in participants with liver metastases ≤5 x ULN
- Calculated creatinine clearance must be ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.25 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.26 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

Note: During the **Active Monitoring** Phase of a study (i.e., active treatment), participants must be willing to return to the consenting institution for follow-up.

3.27 Ability to swallow the investigational product tablets and capsules.

3.28 Willing to provide tissue and blood samples for correlative research purposes (see Sections 6.0, 14.0 and 17.0).

3.3 Registration – Exclusion Criteria

3.31 Patients whose tumor harbors a *BRAF non-V600E* mutation or a BRAF fusion.

3.32 Prior therapy with BRAF inhibitor (e.g., encorafenib, dabrafenib, vemurafenib) and/or a MEK inhibitor (e.g., binimetinib, trametinib, cobimetinib).

3.33 Known hypersensitivity or contraindication to any component of binimetinib or encorafenib or their excipients.

3.34 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

NOTE: Female participants of childbearing potential must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix II, and to not donate ova from Screening until 30 days after the last dose of study drug.

NOTE: Male participants must agree to use methods of contraception that are highly effective or acceptable, as described in Appendix II, and to not donate sperm from Screening until 90 days after the last dose of study drug.

3.35 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.36 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

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

3.38 History of acute coronary syndromes (including myocardial infarction, unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting) < 6 months prior to registration.

3.39a Left ventricular ejection fraction (LVEF) ≤50% as determined by MUGA or ECHO.

3.39b Uncontrolled hypertension defined as persistent systolic blood pressure ≥ 150/100 mmHg or diastolic blood pressure ≥100 mmHg despite current therapy.

3.39c Triplicate average baseline QTc interval ≥480 ms.

3.39d Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.39e Patients who have had another active malignancy within the past two years are ineligible EXCEPT FOR patients with cervical cancer in situ, in situ carcinoma of the bladder, non-melanoma carcinoma of the skin, or patients who have had therapy with curative intent for breast or prostate cancer, but remain on adjuvant hormonal therapy.

3.39f Received anticancer therapy including chemotherapy, immunotherapy, or antineoplastic biologic therapy (e.g., erlotinib, cetuximab, bevacizumab etc.), ≤14 days (≤ 28 days for an antibody-based therapy) prior to registration.

3.39g Patients who have undergone major surgery (e.g., in-patient procedures) ≤ 6 weeks prior to registration or who have not recovered from side effects of such procedure.

3.39h Patients who have had radiotherapy ≤14 days prior to registration or who have not recovered from side effects of such procedure. NOTE: Palliative radiation therapy must be complete 7 days prior to the first dose of study treatment.

3.39i Patient has not recovered to ≤ Grade 1 from toxic effects of prior therapy before registration.

EXCEPTIONS: Stable chronic conditions (≤ Grade 2) that are not expected to resolve (such as neuropathy, myalgia, alopecia, prior therapy-related endocrinopathies).

3.39j Uncontrolled or symptomatic brain metastases or leptomeningeal carcinomatosis that are not stable, require steroids, are potentially life-threatening or have required radiation ≤28 days prior to registration.

NOTE: Patients with previously treated brain metastases may participate provided they are stable (e.g., without evidence of progression by radiographic imaging for ≤28 days prior to registration and neurologic symptoms have returned to baseline), and have no evidence of new or enlarging brain metastases or CNS edema, and does not require steroids at least 7 days before the first dose of study treatment.

3.39k Impairment of gastrointestinal function or disease which may significantly alter the absorption of study drug (e.g., active ulcerative disease, uncontrolled vomiting or diarrhea, malabsorption syndrome, small bowel resection with decreased intestinal absorption), or recent (≤12 weeks) history of a partial or complete bowel obstruction, or other condition that will interfere significantly with the absorption or oral drugs.

3.39l Known history of acute or chronic pancreatitis.

3.39m Concurrent neuromuscular disorder that is associated with elevated CK (e.g., inflammatory myopathies, muscular dystrophy, amytrophic lateral sclerosis, spinal muscular atrophy).

3.39n History or current evidence of RVO or current risk factors for RVO (e.g., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.

3.39o Current use of prohibited medication (including herbal medications, supplements, or foods), as described in Section 9.6, or use of prohibited medication ≤ 7 days prior to registration.

3.39p History of thromboembolic or cerebrovascular events ≤ 12 weeks prior to registration. 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 emobli that do not result in hemodynamic instability are allowed to enroll as long as they are on a stable dose of anticoagulants for ≤4 weeks prior to registration.

NOTE: Patients with thromboembolic events related to indwelling catheters or other procedures may register.

3.39q Evidence of Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection.

NOTE: Patients with laboratory evidence of cleared HBV or HCV infection may

register.

NOTE: Patients with no prior history of HBV infection who have been vaccinated against HBV and who have a positive antibody against hepatitis B surface antigen as the only evidence of prior exposure may register.

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase						
	≤28 Days Prior to Pre-reg	≤14 days prior to reg	Baseline (Prior to Cycle 1 Day 1 treatment)	C1D15 ±3 days	C2 and Beyond (±5 days)	At PD, withdrawal, or removal	30 Days after last dose
History and exam, weight, ECOG PS		X		X	X	X	X
Height		X					
Adverse event assessment				X	X	X	X
Informed Consent	X						
ECHO/MUGA[R, 9]		X			X	X	
Hematology: CBC/ differential		X	X	X	X	X	X
Chemistry: AST, ALT, alk phos, T. bili, creatinine, calcium, glucose, Na, K		X	X	X	X	X	X
CPK and troponin[10]			X		X		
Ophthalmic exam [R, 5, 6]		X					
Imaging (CT/PET CT or MRI) and tumor measurement[1]		X			X[4]	X	
Urine pregnancy test[2]		X					
Central electronic/paper confirmation of a $BRAF^{V600E}$ mutation[7]	X						
Mandatory tissue sample (see Section 17.0)[R,8]			X				
Mandatory blood sample (see Section 14.0)[R]			X		X	X	
Patient Medication Diary (Appendix I)[3]				X	X	X	

1 CT scans – chest, abdomen, and pelvis with IV and PO contrast; in the case of iodine contrast allergies an MRI of the abdomen and pelvis with gadolinium + a non-contrast chest CT is appropriate. Use same imaging throughout the study. Imaging at PD should only be repeated if not done within 28 days prior.

2 For women of childbearing potential only. Must be done ≤ 7 days prior to registration.

3 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned at the end of every cycle to the treating institution.

4 To be completed prior to cycle 2 and prior to 3rd cycle and subsequent odd cycles (±5 days)

5 A full ophthalmic exam will be performed by an ophthalmologist at screening, and as needed during on-study treatment phase and include best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and Ocular Coherence Tomography (OCT). Examination of the retina is required, especially to identify findings associated with serous retinopathy and RVO.

6 After baseline, patients receiving **binimetinib** should be assessed at every physical examination for decreased visual acuity using a gross perimetry test (as opposed to automated visual field testing). Symptomatic patients should be referred for a full ophthalmic consultation.

7 Results from a CLIA/CAP certified testing lab (commercial or institutional) that confirm the presence of a $BRAF^{V600E}$ mutation in the patient's tumor must be submitted for central review after the patient is pre-registered. See section 6.16 for detailed instructions.

8 Receipt of archival tumor tissue is not required for study registration and initiation of therapy. However, it is mandatory to receive the required tissue within 30 days from registration. See section 17.0.

9 ECHO/MUGA scans are to be performed at screening, on Cycle 2 Day 1, then every 12 weeks and at the end of treatment.

10 CPK and Troponin levels to be completed Cycle 1 Day 1 and Cycle 2 Day 1.

R Research funded (see Section 19.*0)*

5.0 Stratification Factors OR Grouping Factor:
N/A

6.0 Registration/Randomization Procedures

6.1 Pre-Registration (Step 0)

6.11 To pre-register a patient, access the ACCRU web page at [redacted] go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Users should refer to the section titled "Pre-Registration Components" for details on how to pre-register a patient to a study. At the time of pre-registration the patient will receive an ACCRU patient identification number. This number is to be used when submitting paper confirmation of the presence of a $BRAF^{V600E}$ mutation for the study. Patient pre-registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was pre-registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted]; click on "Registration, Installation & Entry Instructions".

6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.13 Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.14 Pre-registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.15 Submission of central electronic/paper confirmation of the presence of a $BRAF^{V600E}$ mutation.

6.151 Once the patient has completed the pre-registration step, sites will complete the top portion of the central review form and email it to [redacted] along results from a CLIA/CAP certified testing lab (commercial or institutional) that confirm the presence of a $BRAF^{V600E}$ mutation in the patient's tumor for central review.

6.2 Registration (Step 1)

Upon completion of the patient's central review, the person provided on the central review form will be contacted by email with the results approximately one week after submission. If based upon the review the subject is approved for registration, the site will send the central review form to the ACCRU Registration Office via fax [redacted] or email [redacted] The pre-registering institution must register the subject to the protocol.

6.21 To register a patient, access the ACCRU web page at [redacted], go to the Application section and click on "Registration" and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Users should refer to the section titled "Pre-Registration Component" for details on how to register a patient on step 2 of a study that has a pre-registration and registration step. The instructions for the registration/randomization application are available using the Help button. Prior to initiation of protocol treatment, this process must be completed in its entirety and an ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted] If the patient was pre-registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Application Training" at [redacted] click on "Registration, Installation & Entry Instructions".

6.22 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.0, 14.0 and 17.0).

6.23 Prior to accepting the registration, the registration/randomization application will verify the following:
- Patient eligibility

6.24 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her blood sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her tissue sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.

6.25 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist.

6.26 Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.27 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.28 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.29a Blood draw kit is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule
Starting Day 1 of Cycle 1 (28 day Cycles), patient will self-administer:
- Encorafenib 450 mg orally daily
- Binimetinib 45 mg orally twice daily

7.2 Anti-cancer treatment by a local medical doctor (LMD) is not allowed. However, symptom management that cannot wait until the next visit to the study site can be handled by the LMD.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.2 and 8.3), if applicable – This is potentially different information than what is found in the tables in Section 7.0.

Dose Level	Encorafenib	Binimetinib
0	450 mg	45 mg
-1	300 mg	30 mg
-2	225 mg	15 mg

* Dose level 0 refers to the starting dose.

The lowest recommended dose level of encorafenib is 225 mg QD and the lowest recommended dose level of binimetinib is 15 mg BID. When the AE that resulted in a dose reduction improves to and remains stable at the patient's baseline level for a minimum of 14 days, the dose can be re-escalated to the next dose level at the discretion of the Investigator, provided there are no other concomitant toxicities that would prevent drug re-escalation. There is no limit to the number of times the patient can have their dose reduced or re-escalated, however:

- No dose re-escalation of encorafenib is allowed after a dose reduction due to prolonged QTcF ≥ 501 msec
- No dose re-escalation of binimetinib is allowed after a dose reduction due to LVEF dysfunction
- No dose re-escalation of binimetinib or encorafenib is allowed after a dose reduction due to retinal toxicity ≥ Grade 2.
- If binimetinib is withheld, consider reducing encorafenib to a maximum dose of 300 mg daily until binimetinib is resumed.

Please refer to Dose Modification Table for recommended dose modifications for encorafenib and/or binimetinib, if applicable, based on the occurrence of treatment-related AEs.

8.2 Recommended Encorafenib Dose Modifications

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified*** ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**
BASED ON INTERVAL ADVERSE EVENT		
	Non-cutaneous RAS mutation-positive malignancies	Permanently discontinue
Eye Disorder	Uveitis	
	Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold encorafenib and binimetinib for up to 6 weeks
	Grade 4	Permanently discontinue encorafenib and binimetinib
	Eye disorders-Other, specify	
	Grade 1-2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
	Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.
	Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Investigations	Electrocardiogram QT corrected interval prolonged	
	QTcF > 500 ms and ≤ 60 ms increase from baseline	1st occurrence: • Temporarily interrupt dosing of encorafenib until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 2nd occurrence: • Temporarily interrupt dosing of encorafenib treatment until QTcF < 500 ms. Then resume treatment at 1 reduced dose level of encorafenib. 3rd occurrence: • Permanently discontinue encorafenib.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	QTcF > 500 ms and > 60 ms increase from baseline	Permanently discontinue encorafenib.
	Alanine aminotransferase or aspartate aminotransferase increased	
	Grade 2	Maintain encorafenib dose. • If no improvement within 4 weeks, withhold encorafenib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
	Grade 3 or 4	See Other Adverse Reactions
	Investigations-Other, specify	
	Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue encorafenib.
	First occurrence of ay Grade 4	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue encorafenib.
	Recurrent Grade 3	Consider permanently discontinuing encorafenib and binimetinib.
	Recurrent Grade 4	Permanently discontinue encorafenib and binimetinib.
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	
	Grade 1	Maintain dose of encorafenib. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	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 based upon the Investigator's discretion.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Grade 3	1st or additional occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤ 1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the patient weekly. Then resume treatment at one reduced dose level of encorafenib. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. > 3nd occurrence: Interrupt dosing of encorafenib until resolved to Grade ≤ 1, decision to resume treatment with encorafenib at one reduced dose level or permanently discontinue encorafenib should be based upon the Investigator's discretion.
	Skin and subcutaneous tissue disorders-Other, specify	
	Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
	Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
	Grade 4	Permanently discontinue encorafenib.
Gastrointestinal disorders	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 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. 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.

* [redacted]

** Use the following to describe actions in the Action column:

- Modified=A modification indicates a change in dose level during the current cycle. However, if a modification was issued after the last dose was received in the current cycle, the modification should be reported on the subsequent cycle. "Yes, planned" should be selected if the dose level was changed according to protocol guidelines (i.e. due to adverse events, lab values, etc.); "Yes, unplanned" should be selected if the dose level change was not a part of protocol guidelines (e.g. vacation, mistake, etc.). Held doses (including omissions and delays) should not be reported as modifications.

- Omitted=An omission indicates a dose was skipped and not made up, or that the drug was discontinued.

- Delayed=A delay indicates dose was postponed or not received when expected.

8.3 Recommended Binimetinib Dose Modifications

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified*** ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT		
Eye Disorders	Retinopathy and Retinal detachment	
	Grade 2 or above	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib.
	Retinal Vein Occlusion (RVO)	
	Any Grade	Permanently discontinue binimetinib.
	Eye disorders-Other, specify	
	Grade 1-2	Maintain dose level of encorafenib and binimetinib and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
	Grade 3	Interrupt dosing of encorafenib and binimetinib and refer patient to ophthalmologist within 7 days. • If resolved to Grade ≤ 1 in ≤ 21 days, resume treatment at 1 reduced dose level of encorafenib and binimetinib. • If not resolved to Grade ≤ 1 in ≤ 21 days, permanently discontinue encorafenib and binimetinib and close follow-up with ophthalmic monitoring until stabilization or resolution.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Grade 4	Permanently discontinue encorafenib and binimetinib and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
	Uveitis	
	Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and encorafenib for up to 6 weeks. • If improved, resume at same or reduced dose. If not improved, permanently discontinue binimetinib.
	Grade 4	Permanently discontinue encorafenib and binimetinib.
Cardiac Disorders	Heart Failure and Left ventricular systolic dysfunction	
	Grade 1	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if the following are present: • LVEF is at or above the LLN and • Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib.
	Grade 3-4	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Respiratory, thoracic and mediastinal disorders	Pneumonitis, pulmonary fibrosis	
	Grade 2	Withhold binimetinib for up to 4 weeks. • If improves to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue.
	Grade 3 or Grade 4	Permanently discontinue binimetinib.
Investigations	Alanine aminotransferase or aspartate aminotransferase increased	

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Grade 2	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
	Grade 3 or 4	See Other Adverse Reactions
	CPK increased	
Investigations	Grade 4 asymptomatic or Any Grade with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
	Investigations-Other, specify	
	Recurrent Grade 2 or First occurrence of any Grade 3	Withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
	First occurrence of any Grade 4	Permanently discontinue or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue encorafenib and binimetinib.
	Recurrent Grade 3	Consider permanently discontinuing encorafenib and binimetinib.
	Recurrent Grade 4	Permanently discontinue.
Gastrointestinal disorders	Nausea/Vomiting	
	Grade 1-2	Maintain dose level of encorafenib and binimetinib. Promptly institute antiemetic measure.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION****
	Grade 3	Interrupt dosing of encorafenib and binimetinib until resolved to Grade ≤ 1. Then resume treatment as 1 reduced dose level of encorafenib. Resume treatment with binimetinib at the current dose if, in the judgement of the Investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of encorafenib and binimetinib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
	Grade 4	Permanently discontinue encorafenib and binimetinib.
Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders-Other, specify	
	Grade 2	If no improvement within 2 weeks, withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
	Grade 3	Withhold until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
	Grade 4	Permanently discontinue encorafenib and binimetinib.

* [redacted]

** Use the following to describe actions in the Action column:

- Modified=A modification indicates a change in dose level during the current cycle. However, if a modification was issued after the last dose was received in the current cycle, the modification should be reported on the subsequent cycle. "Yes, planned" should be selected if the dose level was changed according to protocol guidelines (i.e. due to adverse events, lab values, etc.); "Yes, unplanned" should be selected if the dose level change was not a part of protocol guidelines (e.g. vacation, mistake, etc.). Held doses (including omissions and delays) should not be reported as modifications.

- Omitted=An omission indicates a dose was skipped and not made up, or that the drug was discontinued.

- Delayed=A delay indicates dose was postponed or not received when expected.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO), Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 Permitted Concomitant Therapy Requiring Caution and/or Action

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

There is a potential for encorafenib to induce CYP3A4, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least 1 form of non-hormonal contraception is required for females of childbearing potential during participation in this study. Caution should be used in participants receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

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

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

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

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

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

9.6 Prohibited Concomitant Therapy

Concomitant strong systemic CYP3A4 inhibitors and strong or moderate systemic CYP3A4 inducers are likely to significantly increase or decrease encorafenib exposure, respectively, and thus should not be used during this study.

10.0 Adverse Event (AE) Reporting and Monitoring

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms
Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be

downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.4 Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the Serious Adverse Event (SAE) Form to the ACCRU SAE Coordinator via fax [redacted] The ACCRU SAE Coordinator will forward to the encorafenib and binimetinib manufacturer as per the current reporting instructions.
- The ACCRU SAE Coordinator will forward to ACCRU IND Coordinator [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

Reporting of Serious Adverse Events to Array BioPharma, Inc.

All serious adverse events must be reported by the ACCRU SAE Coordinator by facsimile within 1 business day of notification to Array Drug Safety. [redacted]

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 sending the SAE report to Array or designee via facsimile or email transmission, as described on the Array provided SAE cover page. 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.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.521 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.522 Second Malignancy

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

10.523 Pregnancy

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

Pregnancies (both those of female patients and female partners of male patients) must be reported to 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.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [redacted] the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.53 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Eye disorders	Blurred vision	X	X
	Flashing lights	X	X
	Floaters	X	X
	Retinal vascular disorder	X	X
Investigations	Ejection fraction decreased	X	X
Musculoskeletal and connective tissue disorders	Arthralgia	X	X
	Myalgia	X	X
Skin and	Photosensitivity	X	X

subcutaneous tissue disorders	Rash acneiform	X	X
	Rash maculo-papular	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal disorders	Diarrhea	# stools per day	X

10.54 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable)

10.541 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.542 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.543 Grade 5 AEs (Deaths)

10.5431 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5432 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.55 Late occurring adverse events are any adverse event that occurs during Event Monitoring reporting period. These are reported in compliance with Section 4.0 and Section 18.0.

10.56 Monthly Report: Research Coordinating Center will provide Array BioPharma, Inc. with accrual report on a monthly basis.

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions

and the short axis measurements in the case of lymph nodes are used in the RECIST guideline (Eisenhauer *et al*, 2009).

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

    b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal FDG-PET scan.

iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained not less than 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6-8 weeks (see Section 11.44).

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

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.

  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node

that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST

v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 ECOG Performance Status: 0 vs. 1 vs. 2

12.2 2^{nd} line vs. $\geq 3^{rd}$ line

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol for a maximum of 36 cycles. After 36 cycles, patients will go to event monitoring.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 Patients who develop non-CNS PD at any time should go to event monitoring. These patients should be treated with alternative chemotherapy if their clinical status is good enough to allow further therapy.

13.5 Event monitoring is every 3 months (±14 days) for 5 years after registration. If the patient is still alive 5 years after registration, no further follow up is required.

13.6 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *major violation* if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted.

14.0 Body Fluid Biospecimens

14.1 Blood/Blood Products Handling

14.11 Kits are required for this study.

14.111 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.112 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning and Processing (BAP) Receiving or the BAP Shared Resource. Note: Expired tubes may be replaced with site stock if available.

14.113 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the shipping boxes.

14.114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.12 All samples must be collected **Monday-Friday ONLY.**

14.13 Label specimen tube(s) with protocol number, ACCRU patient ID number, and time and date blood is drawn.

14.14 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to Be Collected for

This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Baseline Prior to Treatment	Every 4 weeks Prior to Treatment	Off study or Progression	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
Mandatory	STRECK (black/tan)	10 ml (2)	Platelet poor plasma	X	X	X	No	Ambient (room tempera-ture cold packs)
Mandatory	EDTA (purple top)	10mL (2)	Plasma and White Blood Cells (buffy coat)	X	X	X	No	Refrig-erate (cold packs)

1. After all samples have been processed according to kit instructions, ship all specimens According to shipping instructions (see Section 14.25 for detailed shipping instructions.)
2. Blood draws should not be collected and submitted until after the patient is registered onto the study.

14.15 Shipping

14.151 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit) *(if applicable)*], and specimen collection labels are completed and filled in correctly.

14.152 Specimens must be shipped the same day they are drawn.

14.153 Specimens will be shipped in a dual-temperature shipping container. Place the refrigerated EDTA tubes with a properly prepared cold pack in one compartment. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen. Place the STRECK tubes with an ambient cold pack in the other compartment of the dual-temperature shipping container.

14.154 Ship specimens via Priority Overnight service, **Monday – Friday ONLY,** to BAP Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

14.155 The BAP kits will include a smart shipper label (3x5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by ACCRU if the shipping box provided with the BAP kit is used for shipping specimens to BAP Receiving.

Ship blood samples to:

BAP Freezer will receive the samples for ACCRU.

14.2 Study Methodology and Storage Information

14.21 Blood/blood product samples will be collected for the following research

14.211 DNA extraction and storage of DNA for future research (e.g., for genetic polymorphisms or cfDNA sequence and analysis) Plasma/cells/DNA will be stored frozen at -70ºC by BAP and at the end of the trial all specimens will be sent to Dana-Farber Cancer Institute, according to patient consent information (see Section 6.22) until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of ACCRU studies.)

ACCRU will ship samples to:

14.212 As part of ongoing ACCRU research, we will collect plasma for future research studies, according to patient consent information (see Section 6.24), on molecular determinants of efficacy and tolerability. Samples will be stored frozen at -70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for ACCRU and IRB review and approval.

14.3 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of

research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

IND exempt

- Investigator brochure available on the ACCRU website.

15.1 Binimetinib (MEK162, ARRY-438162, ONO-7703)

15.11 **Background**: Binimetinib is an orally bioavailable, selective and potent MEK1 and MEK 2 inhibitor. As a MEK inhibitor, this compound has the potential to benefit patients with advanced cancers by inhibiting the MAPK (mitogen-activated protein kinases) pathway.

15.12 **Formulation**: Binimetinib drug product is supplied as film-coated tablets in a dose strength of 15 mg. The film coated-tablets consist of binimetinib, 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.

15.13 **Preparation and storage**: Binimetinib film-coated tablets should not be stored above 25°C and should be protected from light. Tablets are packaged in plastic bottles acceptable for pharmaceutical use.

15.14 **Administration:** Binimetinib is administered twice daily with water, approximately 12 hours apart with or without meals. Tablets should be swallowed whole and should not be chewed.

15.15 **Pharmacokinetic information**:
Absorption: The pharmacokinetics of binimetinib are characterized by moderate to high variability, accumulation of approximately 1.5-fold, and steady state concentrations reached within 15 days. The human ADME study CMEK162A2102 indicated that approximately 50% of binimetinib dose was absorbed.

Distribution: Binimetinib is more distributed in plasma than blood. The blood-to-plasma concentration ratio of binimetinib in humans is 0.718. It is highly bound to plasma proteins (humans: 97.2%).

Metabolism: The primary metabolic pathways include glucuronidation (up to 61.2% via UGT1A1), N-dealkylation (up to 17.8% via CYP1A2 and CYP2C19) and amide hydrolysis.

Excretion: The excretion route was 31.7% of unchanged binimetinib in feces and 18.4% in urine. Estimated renal clearance of unchanged binimetinib was 6.3% of total dose.

15.16 **Potential Drug Interactions**:

Overall, the risk for binimetinib to be a cause of or be affected by significant drug-drug interactions is predicted to be low. However, given the predominant role of UGT1A1 in the metabolism of binimetinib, and because the effect of a UGT1A1 inhibitor or inducer has not been evaluated in a formal clinical study, special consideration should be taken for co-administration of drugs that are UGT1A1 inhibitors or inducers, and administration of binimetinib to patients with low UGT1A1 activity.

Binimetinib has been shown to be a substrate for P-gp and BCRP in vitro. The impact of P-gp/BCRP inhibitors on the PK of binimetinib in vivo is unknown; therefore, it is recommended that P-gp and BCRP inhibitors are dosed with caution.

15.17 **Known potential toxicities**:
Very Common (≥ 10%) - diarrhea, nausea, vomiting, fatigue, peripheral edema, increased AST, increased blood creatine phosphokinase, dermatitis acneiform, dry skin, pruritus, rash, decreased ejection fraction
Common (≥1% - <10%) - chorioretinopathy, dry eye, macular edema, retinal detachment, retinal vein occlusion, retinopathy, serous retinal damage, blurred vision, reduced visual acuity, visual impairment, abdominal pain, constipation, dyspepsia, gastroesophageal reflux disease, asthenia, facial edema, edema, malaise, pyrexia, folliculitis, paronychia, pustular rash, increased ALT, increased amylase, increased blood alkaline phosphatase, increased blood creatinine, increased GGT, lipase increased, arthralgia, muscular weakness, myalgia, dizziness, dysgeusia, epistaxis, alopecia, xerosis, nail disorder, palmar-plantar erythrodysesthesia syndrome, eczema, erythema, erythematous rash, papular rash, macular rash, maculo-papular rash, skin fissures, hypertension, neutropenia, pneumonitis
Uncommon (≥0.1 - <1%) – anemia, left ventricular dysfunction, eye edema, gastritis, gastrointestinal hemorrhage, colitis, general physical health deterioration, infection, skin infection, cellulitis, erysipelas, irregular heart rate, hypoglycemia, musculoskeletal pain, rhabdomyolysis, dropped head syndrome, ageusia, pulmonary embolism, xeroderma, follicular rash, pruritic rash, deep vein thrombosis, hypertensive crisis, hypotension

15.18 **Nursing Guidelines:**

15.181 Agent can cause decreased LVEF function. Instruct patients to report any lower extremity swelling, shortness of breath, and/or chest pain to study team.

15.182 Diarrhea and other gastrointestinal side effects are common. Treat symptomatically and monitor for effectiveness of intervention.

15.183 Rash is common and is usually acneiform in nature. Instruct patient to report any rash immediately.

15.184 Bleeding including serious and/or fatal hemorrhage can be seen. Instruct patient to report any bleeding to study team.

15.185 Monitor LFT's.

15.186 Rarely interstitial lung disease can be seen. Instruct patient to report any cough, dyspnea to the study team.

15.187 Rhabdomyolysis is a rare but serious side effect of this agent. Instruct patients to report any weakness, muscle pain, or just feelings or unwellness to the study team immediately.

15.188 Rarely ocular complications can occur, including chorioretinopathy, serous retinal damage, retinal detachment and other visual disturbances. Instruct patients to report any visual disturbances and/or eye pain to the study team immediately.

15.189a Strenuous physical activities, such as competitive sports, can results in significant increases in CK levels while on binimetinib treatment. Instruct patients to not start a new strenuous exercise regimen after first dose of study treatment.

15.19a **Drug procurement:** Drug procurement: Array BioPharma, Inc will supply the drug to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of binimetinib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19b Temperature excursions that occur at the site should be reported by the site to Clinical Research Services, a division of Rx Crossroads by McKesson via email to: [redacted] Any shipment deviations (those not occurring at the site) should be reported to Clinical Research Services, a division of Rx Crossroads by McKesson, via email to: [redacted] Clinical Research Services, a division of Rx Crossroads by McKesson, will report any temperature and shipment deviations (those not occurring at the site) to Array BioPharma Inc. via email to: [redacted]

15.19b1 When reporting a temperature excursion to Clinical Research Services, please include the following information as required by Array:

- Study/protocol number
- Name and contact information
- Site location and address
- Array lot and kit numbers affected (if applicable)
- High/low temperature recorded for event
- Duration of the event
- All supporting data or charts (Temp Log, TempTale, etc.)
- Temperature deviation event form (if site has their own)

Following temperature deviation, the affected material should be physically quarantined by the site until a response is received from Array regarding the disposition of the affected materials.

15.2 **Encorafenib (LGX818, ONO-7702, Braftovi®):**

15.21 **Background:** Encorafenib is a potent and selective ATP-competitive inhibitor of BRAF V600-mutant kinase.

15.22 **Formulation**: The encorafenib drug product is supplied as a hard gelatin capsule in dosage strengths 75 mg. The dosage forms for each strength have identical formulations which are packaged in different colored capsules:

- 75 mg capsule (FMI): Size #00 hard gelatin capsules; flesh opaque cap and white opaque body, with the markings "NVR" or stylized "A" on the cap and "LGX 75mg" on body.

The capsules consist of encorafenib drug substance, copovidone, poloxamer 188, succinic acid, microcrystalline cellulose, colloid silicon dioxide, crospovidone, and magnesium stearate of vegetable origin.

15.23 **Preparation and storage**: Encorafenib hard gelatin capsules should not be stored above 25°C and should be protected from moisture. Capsules are packaged in plastic bottles acceptable for pharmaceutical use and should not be repackaged at the site.

15.24 **Administration:** Encorafenib capsules are intended for oral administration with water; capsules should be swallowed whole and should not be chewed. Encorafenib capsules may also be opened and the powder mixed with sweetened applesauce; the soft food preparation is intended for oral administration with water. Encorafenib can be administered without regard to food.

15.25 **Pharmacokinetic information**:
Absorption: At least 86% of the dose is absorbed
Metabolism: N-dealkylation is the primary metabolic pathway; CYP3A4 (primary), CYP2C19, and CYP2D6 (minor) contribute to total oxidative clearance in human liver microsomes
Half-life elimination: 6.32 hours (range 3.74 to 8.09 hours)
Excretion: Feces (39%); urine (47.2%)

15.26 **Potential Drug Interactions**:
Since encorafenib is mainly metabolized by CYP3A, the co-administration of CYP3A inducers might decrease the exposure of encorafenib in clinical practice. Thus, long term co-administration of strong and moderate inducers of CYP3A with encorafenib should be avoided.

Clinical results from a dedicated DDI study with encorafenib and CYP3A inhibitors indicated concomitant administration of encorafenib with strong or moderate CYP3A inhibitors may increase encorafenib plasma concentration. If co-administration with strong or moderate CYP3A inhibitors cannot be avoided, dose reduction of encorafenib may be warranted.

Since no clinical data are available, caution should be used for co-administering substrates of CYP3A4 and UGT1A1.

Based on in vitro transporter studies, encorafenib can potentially inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 at clinical concentrations. Co-administration of encorafenib with drugs that are substrates for these enzymes and/or transporters may alter the exposure of the co-administered medication.

15.27 **Known potential toxicities**:
Very Common (≥10%)
Gastrointestinal: diarrhea
Metabolism and nutrition: decreased appetite
Nervous system: peripheral neuropathy
Psychiatric: insomnia
Skin and subcutaneous: hair loss, dry skin, hyperkeratosis, pruritis, Palmar-plantar erythrodysesthesia syndrome, palmoplantar keratoderma, erythema
Vascular: flushing
Common (≥1% - <10%)
Blood and lymphatic: anemia
Cardiac: tachycardia
Ear and labyrinth: vertigo
Eye: iridocyclitis
Gastrointestinal: nausea, vomiting, abdominal pain, constipation, dyspepsia, stomatitis
General: asthenia, fatigue, pyrexia, xerosis, chills, face edema, peripheral edema
Immune system: hypersensitivity
Investigations: AST and ALT increased, blood alkaline phosphatase increased, blood creatinine increased, gamma-glutamyltransferase increased, amylase increased, lipase increased, electrocardiogram QT prolonged
Metabolism and nutrition: dehydration, hyponatremia
Musculoskeletal and connective tissue: arthralgia, musculoskeletal pain, myalgia, muscle spasms, muscular weakness
Neoplasms benign, malignant and unspecified: keratoacanthoma, melanocytic nevus, skin papilloma, squamous cell carcinoma, dysplatic nevus, malignant melanoma
Nervous system: facial paralysis, facial paresis, ageusia, dysgeusia, dysesthesia, hyperesthesia, neuralgia

Renal and urinary: acute kidney injury, renal failure
Skin and subcutaneous: rash, photosensitivity reaction, skin exfoliation, skin hyperpigmentation
Uncommon (≥0.1% - <1%)
Eye: uveitis
Gastrointestinal: pancreatitis
Metabolism and nutrition: hyperglycemia
Musculoskeletal and connective tissue: back pain, pain in extremity
Neoplasms benign, malignant and unspecified: acanthoma, basal cell carcinoma
Nervous system: hypoaesthesia
Skin and subcutaneous: drug eruption, urticarial

15.28 **Nursing Guidelines:**

15.281 Diarrhea and nausea are common. Treat symptomatically and monitor for effectiveness.

15.282 Warn patients of possibility of secondary skin cancers. Instruct patients to report any new lesions to study team immediately.

15.283 Monitor LFT's, especially in combination therapy.

15.284 Agent may cause arthralgias. Treat symptomatically and monitor for effectiveness.

15.285 Agent causes QTc prolongation. Instruct patients to discuss any new medications with the study team, prior to starting such agents.

15.286 Agent can cause peripheral edema.

15.287 Rarely ocular toxicity can occur including retinitis, uveitis, and retinal vein occlusion. Instruct patients to report any vision changes and/or eye pain to the study team.

15.288 Monitor renal function, encourage patients drink adequate fluids.

15.289a Rash can be seen. Instruct patient to report rash to study team.

15.289b Agent can cause pyrexia, especially in combination with binimetinib. Instruct patient to report any fever to the study team.

15.29a **Drug procurement:** Drug procurement: Array BioPharma, Inc will supply the drug to Clinical Research Services, a division of Rx Crossroads by McKesson. Each participating ACCRU treating location will order the drug from Clinical Research Services, a division of Rx Crossroads by McKesson. Submit the Drug Order Request Form (found on the ACCRU web site) to:

Clinical Research Services, a division of Rx Crossroads by McKesson

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of encorafenib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29b Temperature excursions that occur at the site should be reported by the site to Clinical Research Services, a division of Rx Crossroads by McKesson via email to: [redacted] Any shipment deviations (those not occurring at the site) should be reported to Clinical Research Services, a division of Rx Crossroads by McKesson, via email to: [redacted] Clinical Research Services, a division of Rx Crossroads by McKesson, will report any temperature and shipment deviations (those not occurring at the site) to Array BioPharma Inc. via email to: [redacted]

15.29b1 When reporting a temperature excursion to Clinical Research Services, please include the following information as required by Array:

- Study/protocol number
- Name and contact information
- Site location and address
- Array lot and kit numbers affected (if applicable)
- High/low temperature recorded for event
- Duration of the event
- All supporting data or charts (Temp Log, TempTale, etc.)
- Temperature deviation event form (if site has their own)

Following temperature deviation, the affected material should be physically quarantined by the site until a response is received from Array regarding the disposition of the affected materials.

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16.0 Statistical Considerations and Methodology

16.1 Overview

This is a single-arm phase II study designed to assess the efficacy of binimetinib and encorafenib in patients with advanced pancreatic cancer and somatic $BRAF^{V600E}$ mutation. Overall response rate (ORR) will be used as the primary endpoint. Based on historical data and clinical experience, an ORR of 10% or less would be of no interest (null hypothesis), and an ORR of 30% or more would be of interest (alternative hypothesis). In addition to ORR, progression-free survival (PFS), overall survival (OS), and adverse event rates will be of specific interest. Analysis of acquired BRAF alterations will be performed as correlative research.

Investigation of the “Know Your Tumor” database shows that this subgroup of BRAF

mutations has an approximate prevalence of 15-20% in KRAS wild type pancreatic cancers. Other studies have found that approximately 2% of pancreatic cancers have activating alterations in BRAF.

To pre-register for this study, patients must have documentation indicating a $BRAF^{V600E}$ mutation. Successful registration to this trial requires that this document be centrally reviewed to confirm the existence of the $BRAF^{V600E}$ mutation. Therefore, we do not expect the number of patients pre-registered to the trial to be notably larger than the number of patients who eventually register to the trial.

16.2 Statistical Design

A Simon two-stage optimal design with relaxed futility stopping will be used (Ivanova, *et al*, 2016). The largest success proportion where the proposed treatment regimen would be considered ineffective is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. Rates of maintaining stable disease throughout the first 24 weeks on treatment are expected to be between 30% and 60%. The following two-stage design uses 10 or 26 evaluable patients to test the null hypothesis that the true success proportion in this given patient population is at most 10%.

16.21 Primary Endpoint

The primary endpoint in this trial is objective response rate (ORR) at 24 weeks post-registration. An objective response is defined as a complete or partial response with a confirmation scan not less than 4 weeks after the initial scan. Disease status will be assessed using RECIST v. 1.1 criteria. Evaluable patients are defined as those who are eligible, consented, and received any protocol treatment.

16.211 STAGE 1:

Enter 10 evaluable patients into the study. If three or fewer patients experience an objective response or maintain stable disease within the predefined time period, we will consider this treatment ineffective in this patient population, and terminate the study. Otherwise, if four or more patients experience an objective response or maintain stable disease, we will proceed to Stage 2.

16.212 STAGE 2:

Enter an additional 16 patients into the study. If five or fewer patients among the 26 total evaluable patients accrued experience an objective response within the predefined time period, we will consider this treatment ineffective in this patient population. If 6 or more patients out of the 26 total evaluable patients accrued experience an objective response, we may recommend further testing of this regimen in subsequent studies.

16.213 NOTE:

Accrual will not be suspended between stages to allow the first 10 patients to become evaluable, unless undue toxicity is observed.

16.22 Power and Sample Size

This two-stage study design outlined in 16.21 assumes the number of successes is binomially distributed, the null success proportion is 0.1, and the alternative success proportion is 0.3. Additionally, we assume the rate of stable disease has a uniform distribution *U(0.3, 0.6)* under the null hypothesis. Given these, the exact type 1 error rate (alpha) is 0.0397, and the exact power is 80.4% when the true response rate is 30%.

A minimum of 10 and maximum of 26 evaluable patients are required under the stated assumptions, unless undue toxicity is observed. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is therefore 29 patients. All sample size calculations were computed using PASS 15 software.

16.23 Operating Characteristics

The probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is:	0.10	0.15	0.20	0.25	0.30
then the probability of declaring that the regimen warrants further studies is:	0.04	0.18	0.42	0.66	0.84

16.24 Accrual Time and Study Duration

The anticipated accrual rate is 1-2 patients per month. Therefore, the accrual period for the first stage of this study is expected to be approximately 10 months. If patients are accrued to the second stage, the total accrual period is expected to be approximately 26 months. Should the study continue to full accrual, the primary analysis can begin approximately 32 months after the trial begins; as soon as the last patient has either experienced a confirmed objective response, or been observed for 24 weeks.

16.3 Analysis Plan

16.31 Primary Endpoint Analysis

The analysis for this trial will begin at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary and correlative endpoints, and the level of data maturity.

16.311 Definition

The primary endpoint for this study is defined in section 16.21. The final ORR point estimate and corresponding 95% confidence interval will be reported.

16.312 Estimation

The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Clopper and Pearson.

16.313 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. However, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.32 Secondary Endpoint Analysis

16.321 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from registration to the first of either disease progression or death from any cause, where disease progression is determined based on RECIST 1.1 criteria. PFS will be estimated using the Kaplan-Meier method. The median PFS and corresponding 95% confidence interval will be reported. Patients who do not experience disease progression or death while on protocol will be censored at the last disease assessment date.

16.322 Overall Survival

Overall survival (OS) is defined as the time from registration to death from any cause. Analysis of this endpoint will mirror that of PFS (section 16.321).

16.323 Duration of Response

Duration of response is defined as the duration of time from first documentation of an objective response (defined in 16.21) to the earliest date disease progression is documented or death from any cause. Analysis of this endpoint will mirror that of PFS (Section 16.321).

16.324 Time to Response

Time to response is defined as the duration of time from registration to the first documentation of an objective response (defined in 16.21). Analysis of this endpoint will mirror that of PFS (section 16.321).

16.325 Adverse Event Rate

All patients who have initiated treatment will be considered evaluable for adverse event analyses. The rate of patients experiencing a grade 3+ adverse event will be reported. Further analyses of adverse event rates will be considered exploratory.

16.33 Correlative Research

16.331 Additional mutations in BRAF or in other related genes as determined by next-generation sequencing from plasma samples will be used to investigate the mechanisms of resistance, either primary or acquired through real time monitoring of the BRAF mutational profile evolution.

16.322 Changes in tumor biomarker

The absolute change and percentage change from baseline at each assessment of CA19-9 of CEA levels will be investigated.

16.4 Safety Monitoring

16.41 Adverse Event Stopping Rule(s)

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time, we observe events considered to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

If at any time, 3 of the initial 10 treated patients or 30% or more of all patients (when accrual is greater than 10 patients) have experienced a non-hematologic grade 4 or 5 adverse event. .

We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Data Monitoring and Reporting

16.51 DSMB Reporting

The study chair(s) and the study statistician will review the study at least twice

per year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice per year, based on reports provided by the MCCC Statistical Office.

Additionally, during the first Simon Stage, if and as soon as two patients have experienced a confirmed partial or complete response to therapy, then the study chair(s) and the study statistician will review the study to determine if the study can be opened for full accrual.

16.52 CT.gov Reporting

Expected durations and timelines for certain events (e.g. accrual) and endpoints for CT.gov reporting purposes can be found in sections 16.24 and 16.3 respectively.

Expected durations and timelines for certain events (e.g. accrual) and endpoints for CT.gov reporting purposes can be found in sections 16.24 and 16.3 respectively.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Tissue Biospecimen Submission

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for biospecimen submission**
Formalin-fixed paraffin-embedded (FFPE) tissue blocks with corresponding H&E (OR twenty (23) 5µM unstained slides with corresponding H&Es)	Mandatory	≤**30** days after registration	Correlative studies (Section 17.5)	Section 17.3

17.2 Paraffin Embedded Tissue Blocks/Slides

17.21 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block with largest amount of invasive tumor (at least 1 cm of tumor for cases of surgical resection) (from original) surgery. **A corresponding H&E slide for each submitted block must be provided** to permit quality assessment of each tissue block

17.22 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut 23 five micron sections and mount on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections.** H&E stain every tenth slide (i.e., slides labeled 1, 11, 21, etc.). These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality. The remaining unstained slides will be processed as described in 17.5. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. **Do not bake or place covers slips on the slides. Labeling with sticky labels is not acceptable.**

17.23 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Paraffin embedded tissue blocks with corresponding H&E slide (OR 23 unstained slides with corresponding H&E(s)).
- Specimen Submission: Tissue form
- Pathology Reports
- Somatic Genetic Testing Results (e.g. Foundation Medicine, Caris or similar panel testing)
- Operative Report *(optional)*

- **Note: Please include the ACCRU patient ID number on all materials listed above.**

17.24 The block/slides must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials. During warm weather months, paraffin blocks should be shipped using a refrigerant pack to avoid heat that may melt paraffin and damage blocks.

17.25 Tissue specimens must be shipped ≤**30** days after registration.

17.26 Verify that the appropriate sections of the Specimen Submission: Tissue form are completed and filled in correctly. Enter information from the Specimen Submission: Tissue form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.27 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.3 Study Methodology and Storage Information

17.31 Submitted tissue samples will be analyzed as follows:

17.311 At the completion of the study, any unused/remaining material will be shipped to Dana-Farber Cancer Institute and stored for future research according to the patient consent permission (see Section 6.24). Potential future research may include immunohistochemistry (IHC) analyses to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events. When a protocol is developed, it will be presented for IRB review and approval.

ACCRU will ship samples to:

[redacted]

17.312 Banking of tumor tissue, according to the patient consent permission (see Section 6.245), is for future research. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU melanoma studies).

17.313 The institutional pathologist will be notified by the Pathology Coordinator if the block may be depleted.

17.314 Blocks requested to accommodate individual patient management will be returned promptly upon request.

17.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions ([redacted]).

18.1 Submission Timetable

Pre-Registration Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Screening	Complete for ALL patients
Supporting Documentation: Baseline[1]	See Section 6.0 (for central review, eligibility, etc. confirmation prior to Registration)

1. Results from a CLIA/CAP certified testing lab (commercial or institutional) that confirm the presence of a $BRAF^{V600E}$ mutation in the patient's tumor.

Initial Material(s) -

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤2 weeks after registration
On-Study	
On-Study: Prior Surgery[1]	
On-Study: Prior Systemic Therapy[1]	
On-Study: Prior Radiation[1]	
Adverse Event: Baseline	
RECIST Measurements: Baseline	
Supporting Documentation: Baseline[2]	
Specimen Submission: Blood (Baseline) (see Section 14.0)	
Specimen Submission: Tissue (Baseline) (see Section 17.0)	
Patient Status: Baseline	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
ACCRU Deviation Form[1]	Submit only if applicable during ***all*** **phases** of the study (initial, active)

1. Submit only if applicable.
2. Upload via the Supporting Documentation: Baseline form. Central Review Form. Imaging report confirming measureable disease.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention)	X	X
Treatment (Intervention): Dose Modifications, Omissions and Delays[1]	X	X
Adverse Events: Solicited	X	X
Adverse Events: Other[1]	X	X
RECIST Measurements[2]	X	X
Supporting Documentation[2]	X	X
Specimen Submission: Blood (see Section 14.0)	X	X
Patient Status: Treatment (Intervention)	X	X
Consent Withdrawal (choose appropriate form)[1] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up	X	X
Off Treatment		X
ACCRU Deviation[1]	X	X
Lost to Follow-up[1,3]		

1. Submit only if applicable.
2. Upload documentation of response or progression on the Supporting Documentation form.
3. Patients are eligible to be confirmed lost to follow-up after 2 years of unsuccessful contact with the patient.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]			
	q. 3 months until PD	At PD	After PD q. 3 mos.	Death
Patient Status: Survival and Disease Status Follow-Up/Event Monitoring	X[2]	X[2]	X	X
Adverse Events: Late[3]				
Supporting Documentation[2, 3]				
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-Up				
Lost to Follow-Up[3,4]				
ACCRU Deviation Form[3]	X[3]	X[3]	X[3]	X[3]

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.

3. Submit only if applicable.
4. Patients are eligible to be confirmed lost to follow-up after 2 years of unsuccessful contact with the patient.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

20.0 References

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Appendix I: ACCRU-GI-1907 SUBJECT MEDICATION DIARY

Name:	Subject ID Number:
Cycle:	
You will take:	

ORAL MEDICATION DIARY

Subject Instructions

- Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should continue or stop taking your medication.
- To correct a mistake, please make a single line through that entry and write your initials and the date next to the mistake.
- Please indicate on the calendar on the next page that you took your study medication by recording the date and dose taken on the line under the date.
- If you miss a dose, place a "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- If you miss a dose, do not make up the dose. Wait until your next dose is due.

ACCRU-GI-1907 SUBJECT MEDICATION DIARY

Study Drug/Dose	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Encorafenib/__mg							
Binimetinib (AM)/__mg							
Binimetinib (PM)/__mg							

Study Drug/Dose	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Encorafenib/__mg							
Binimetinib (AM)/__mg							
Binimetinib (PM)/__mg							

Study Drug/Dose	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Encorafenib/__mg							
Binimetinib (AM)/__mg							
Binimetinib (PM)/__mg							

Study Drug/Dose	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Encorafenib/__mg							
Binimetinib (AM)/__mg							
Binimetinib (PM)/__mg							

Date:_____ Subject's Signature_____

Area Below Only To Be Completed only by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					

Appendix II: Contraception

Female participants of childbearing potential must agree to take appropriate precautions to avoid pregnancy from Screening through 30 days after the last dose of study drug/treatment. In addition, female participants must refrain from donating ova during the study through 30 days after the end of systemic exposure of study drug/treatment.

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

Definitions:

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female

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

Contraception Guidance:

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

required for females of childbearing potential during participation in this study.

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

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

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

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

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