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A ComboMATCH Treatment Trial

EAY191-N2: PHASE 2 TRIAL OF FULVESTRANT AND BINIMETINIB IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE METASTATIC BREAST CANCER WITH INACTIVATING OR INFERRED INACTIVATING NF1 ALTERATIONS

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Participating Organizations
ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
SWOG/SWOG

Participating Sites
☒ U.S.
☐ Canada
☐ Approved International Member Sites
☐ Limited Participation

Protocol Agents:

Agent	Supply	NSC#	IND#	IND Sponsor
Binimetinib	CTEP	788187	[redacted]	DCTD, NCI
Fulvestrant	Commercial	719276	N/A	N/A

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Amendment 2	**February 12, 2024**
Amendment 1	**May 22, 2023**
Initial	**February 02, 2023**

STUDY TEAM

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STUDY SPECIFIC CONTACTS AND RESOURCES	
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Data Management For questions concerning data submission	NRG Statistics and Data Management Center – Pittsburgh Phone: 412-624-2666 E-mail: support@NRGOncology.org

Regulatory Affairs For questions concerning protocol and informed consent versions & amendments, IRB review, and informed consent	NRG Oncology – Pittsburgh Phone: 412-339-5300 E-mail: NRG-Pitt-Regulatory@nrgoncology.org
Biospecimen Bank	ComboMATCH Biobank *See Protocol Section 10.*
STUDY SPECIFIC CONTACTS AND RESOURCES	
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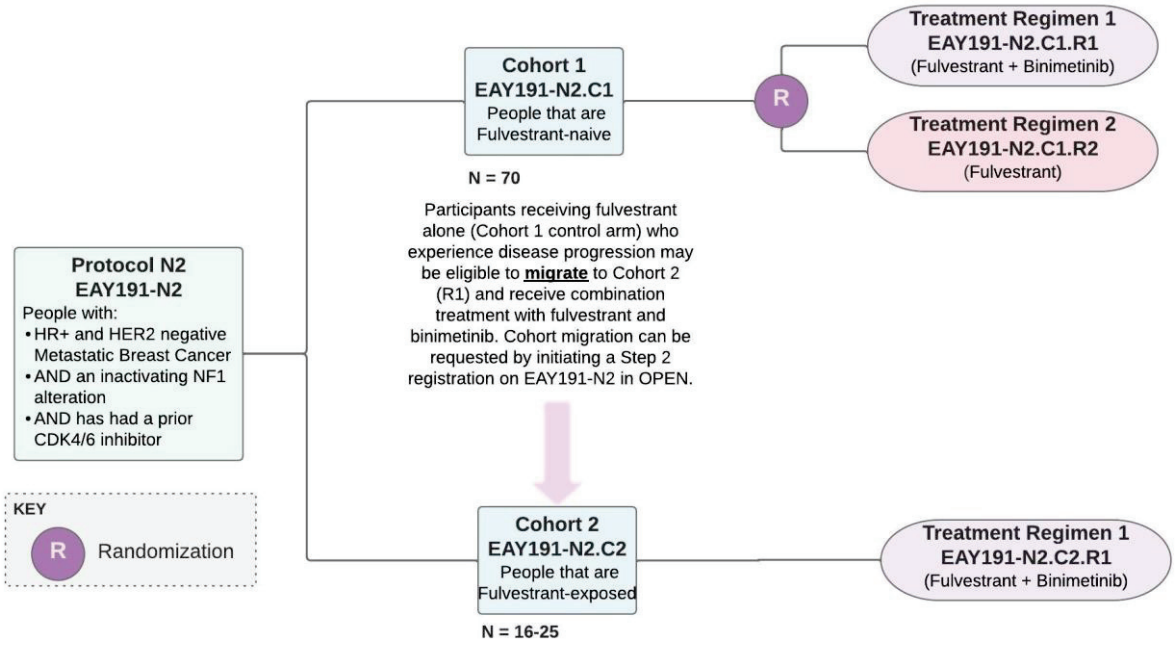
CANCER TRIALS SUPPORT UNIT CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU(2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or e-mail: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related), contact the Clinical Coordinating Department at NRG Oncology at 1-800-477-7227 or by email at ccdPGH@NRGOncology.org.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

TABLE OF CONTENTS

A ComboMATCH Treatment Trial EAY191-N2 SCHEMA



For Cohort 1, randomization is 1:1.

Table of Abbreviations

NF1	Neurofibromin type 1

1. OBJECTIVES

1.1 Primary Objective

Cohort 1: To determine whether the combination of fulvestrant and binimetinib improves progression-free survival (PFS) compared to treatment with fulvestrant alone in patients not previously treated with fulvestrant.

Cohort 2: To determine whether overall response rate (ORR) within 4 months in patients who have previously progressed on a fulvestrant-containing regimen is greater than 10%, as a historical comparison, when these patients receive combination fulvestrant and binimetinib therapy.

1.2 Secondary Objectives

1.2.1 To estimate ORR at any time after the start of the treatment for Cohort 2 and separately for the two arms in Cohort 1.

1.2.2 To estimate PFS distribution in Cohort 2.

1.2.3 To estimate clinical benefit rate separately for the two arms in Cohort 1 and Cohort 2.

1.2.4 To determine the safety and toxicity profile in both cohorts.

1.2.5 To estimate the overall survival (OS) in both cohorts.

1.2.6 Collect tissue and provide it to the ComboMATCH Registration Protocol to assess concordance between the diagnostic tumor mutation profile generated by the Designated Laboratories, the pre-treatment biopsy mutation profile, and the pre-treatment ctDNA mutation profile from plasma, as described in ComboMATCH Registration Protocol. For this treatment substudy, the outcome objective will be to report the proportion of cases providing sufficient tissue for that integrated scientific activity in the ComboMATCH Registration Protocol.

1.3 Exploratory Biomarker Objective

1.3.1 To analyze the cfDNA at progression to determine the changes in cfDNA profile in order to understand blood-based mutation dynamics.

1.3.2 To analyze RNAseq at progression to determine potential pathways that are altered that may contribute to the sensitivity/resistance.

1.3.3 To discover/detect novel biomarkers using microscaled proteogenomics by analyzing the proteins and phosphor-proteins along with genomics to determine potential pathways that may correlate with the response to the combination treatment.

1.3.4 To detect the loss of NF1, using immunohistochemistry staining to precisely measure the level of the NF1 protein.

1.3.5 To determine the variant allele frequency (VAF) of mutant NF1 measuring by using droplet digital polymerase chain reaction (ddPCR) for the targeted NF1 gene level.

2. BACKGROUND

2.1 Hormone Receptor-Positive Metastatic Breast Cancers

Approximately 80% of breast cancers are positive for estrogen receptor-α (ER+), a ligand-dependent transcription factor that is activated by estradiol (E2) (Feng 2014). The E2-liganded ER recruits co-activators (such as steroid-receptor co-activators, SRC-1-3) to estrogen-responsive elements (EREs) in ER-regulated genes. Tamoxifen, a selective ER modulator (SERM), is predominantly antagonistic in breast cancer cells, hence its therapeutic effect. When tamoxifen binds to ER, co-activators are displaced by corepressors in the ER- ERE complex (Shang 2000). Established ER corepressors bind ER via their leucine/isoleucine-rich motifs, and substitutions of L or I with an A can disrupt binding (Hu 1999). Interactions are also mediated by electrostatic interactions (Heldring 2007, Shiau 1998). Despite the development of novel therapeutics such as CDK 4/6 inhibitors, cancers eventually develop resistance to endocrine therapy, leading to breast-cancer-caused mortality. There is a great need for novel ways to target this emerging resistance to endocrine therapy.

2.2 NF1 Loss Correlates with Poor Patient Outcome in ER+ Breast Cancer

While NF1 mutation frequencies are low in primary ER+ breast cancer (2% in TCGA [TCGA, 2014], as shown in Figure 1A, and 4% in the patient cohort investigated by the Baylor College of Medicine [BCM] researchers [Griffith 2018]), NF1 mutation frequency is higher in metastatic ER+ breast cancer patients (n = 535) (Lanman 2015, Zill 2018). Neurofibromin (NF), a tumor suppressor and Ras-GAP (GTPase-activating protein), is also an estrogen receptor-α (ER) transcriptional corepressor through leucine/isoleucine-rich motifs that are functionally independent of GAP activity. However, GAP activity, in turn, does not affect ER binding of NF1. Similar enrichment of NF1 mutations in metastatic hormone receptor (HR)-positive breast cancer has been reported by others (TCGA 2014, Bertucci 2019, Meric-Bernstam 2014, Pearson 2020, Razavi 2018). These observations suggest that somatic NF1 events are an essential class of mutations causing breast cancer progression.

To investigate the consequences of NF1 depletion on ER+ breast cancer, MCF-7 ER+ breast cancer cells were engineered to harbor lentiviruses expressing one of two doxycycline (DOX)-inducible small hairpin RNA (shRNA) clones (C5 and C6). Upon DOX addition (+DOX), NF1 protein levels were reduced by ~70% as detected by a monoclonal antibody (mAb) raised by BCM investigators. Remarkably, when NF1 expression was suppressed (+DOX) in MCF-7 cells as well as in two more ER+ breast cancer cell lines—ZR-75B and T47D—in vitro growth was consistently stimulated by 4-hydroxy-tamoxifen (4-OHT) under E2-deprived conditions (charcoal-stripped serum) (Figure 1D), in comparison with the non-silenced control (–DOX) or the scrambled shRNA +DOX control, indicating an NF1-loss-mediated transition from 4-OHT antagonism to agonism. Furthermore, NF1-silenced cells proliferated at lower concentrations of E2 than controls, and higher E2 concentrations paradoxically inhibited cell growth, indicating E2 hypersensitivity (Figure 1E). Two pools of NF1 ‘‘knockout’’ (KO) MCF-7 cells were independently created by CRISPR-Cas9 with results similar to the shRNA data (Figures 1D and 1E).

MDA-MB-231 cells are ER–, and NF1 expression is barely detectable (Sokol 2019) due to a frameshift mutation (NF1-T467fs) (Ogata 2001). These NF1 low cells were unresponsive to 4-OHT or E2, which was validated by 4-OHT agonism in an MCF-7-based xenograft mouse model, when NF1 is silenced (Figure 1F, left). Interestingly, these tumors grew better than control tumors even at a lower dose of E2 (0.05 mg dose) (Figure 1F, right).

Figure 1. NF1 loss promotes tamoxifen agonism and E2 hypersensitivity leading to poor patient outcome in HR+ breast cancer

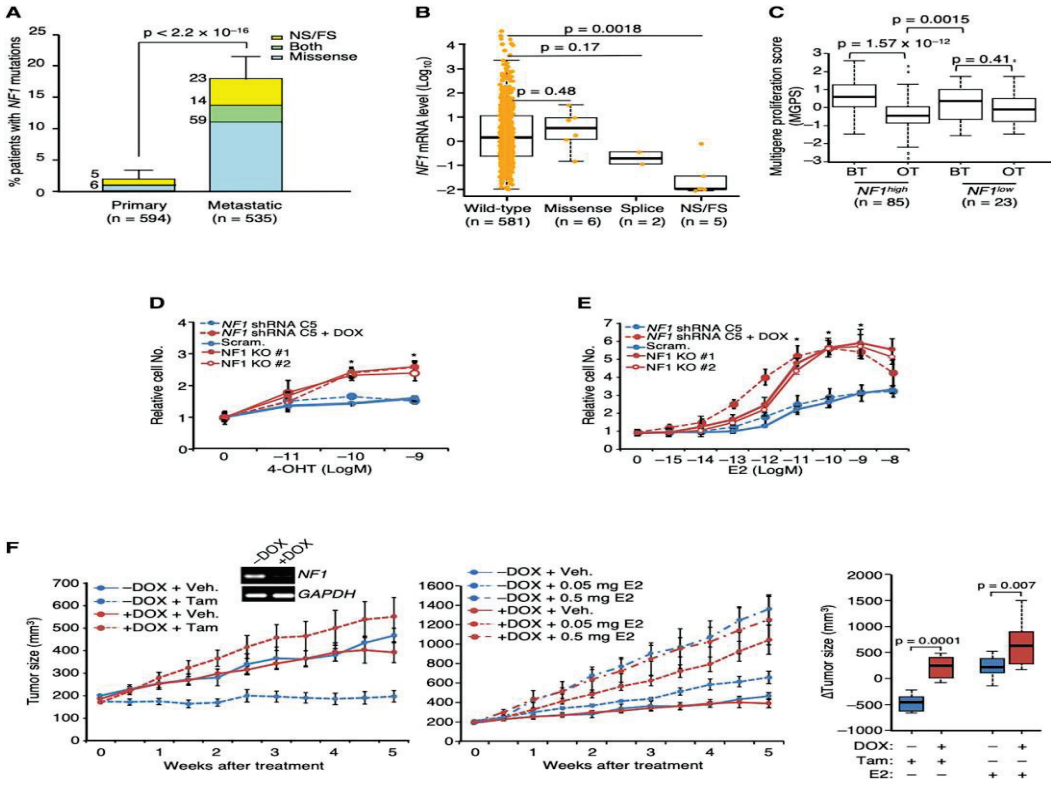


Figure 1. *NF1* Loss Promotes Tamoxifen Agonism and E2 Hypersensitivity Leading to Poor Patient Outcome in HR+ Breast Cancer

(A) The percentages of ER+ primary versus metastatic breast cancers carrying NF1 mutations were analyzed by Fisher's exact test. NS and FS stand for nonsense and frameshift, respectively. The number of patients carrying a particular type of NF1 mutation is shown at the upper left side of each column. (B) Boxplot analysis of NF1 mRNA levels in ER+ breast tumors carrying different NF1 mutations in the RNA-seq database of TCGA. p value by Wilcoxon rank-sum test. The line in the middle of the box is the median. The box edges are the 25th and 75th percentiles and the whiskers denote 1.5 times the interquartile range. (C) Patient samples were stratified by NF1 mRNA levels according to TCGA definitions of high versus low expression (mean, 1.5 3 SD). The boxplot analysis was similarly performed as in (B) to compare multigene proliferation score (MGPS) in tumors before treatment (BT) and on treatment (OT) with AI. The differences in MGPS before and during treatment in each NF1 group were analyzed by the Wilcoxon signed-rank test. The differences in MGPS as a result of treatment between the two NF1 groups were further analyzed by Wilcoxon rank-sum test. (D) DOX-inducible gene silencing using NF1 shRNA clone C5 and CRISPR-mediated NF1-KO were performed in MCF-7 cells. These cells were seeded in E2- deprived medium, to which 4-OHT was added, and cultured for 6 days. Cell numbers relative to vehicle control are plotted. Experiments were conducted as biological triplicates (n = 3 experiments), except for MCF-7 cells carrying NF1 shRNA C5 (n = 8 experiments). (E) Cell growth in response to E2 was similarly analyzed as in (D). n = 3 experiments, except for MCF-7 cells carrying NF1 shRNA C5 (n = 8 experiments). (F) MCF-7 cells carrying DOX-inducible NF1 shRNA were transplanted into the mammary fat pads of ovariectomized nude mice, supplemented by an E2 capsule. When tumors appeared, the original E2 capsule was removed, and the resulting mice were randomized, DOX or vehicle treated. Each set was then treated by either tamoxifen (5 mg/mouse, left), or E2 (at two doses, middle). For NF1+ (–DOX) tumors, n = 10, 12, 12, and 8 mice per group for treatment of vehicle, 0.05 mg E2, 0.5 mg E2, and tamoxifen; for NF1KD (+DOX) tumors, n = 10, 13, 11, and 8 mice per group. The inset shows NF1-silencing validation by qPCR 2 weeks post-DOX addition. On the far right, ''D tumor volumes'' between vehicle and either tamoxifen or E2 treated were analyzed by boxplot as in (C). Data are reported as mean ± SEM. *p < 0.05, **p < 0.01 by pairwise two-tailed Student's t test, unless otherwise indicated.

2.3 NF1 Depletion Globally Enhances ER Transcriptional Activity, and the Survival Differs Between Types of Mutations

Because the abnormal E2 and tamoxifen responses observed in NF1-depleted cells are ER dependent, BCM researchers investigated whether NF1 depletion affects ER-dependent transcription. To examine the effects of NF1 on gene expression in a genome-wide fashion, RNA sequencing (RNA-seq) experiments were performed in control (–DOX) and NF1 knockdown (+DOX, KD) MCF-7 cells with and without E2 stimulation. Overall, E2 altered expression from 540 genes in the control NF1+ cells and 955 genes in NF1KD cells (Figure 2A). Aside from a predominance of additional E2-regulated genes, a K-Ras-dependent gene expression signature was also observed (Figure 2A). To determine whether the E2-induced gene expression patterns shown in Figure 2A could be replicated in patient samples, differentially expressed genes according to NF1 status (with or without NF1 nonsense/frameshift mutation) METABRIC and TCGA ER+ datasets were identified, and pathway enrichments were similarly assessed. The results were compared with the two MCF-7 E2-regulons described above. Supporting the conclusion that NF1 depletion dramatically affects the expression of E2-responsive genes in clinical ER+ specimens, E2-responsive pathway terms were most significantly modulated by NF1 mutation status, followed by the K-Ras signature (Figure 2B). Next, it was determined that neurofibromin can interact with ER via an ER-binding motif that is independent of Ras/GAP activity. The Ras-Raf signaling was not critical for estrogen-sensitive HR+ breast cancer cells or the ER-dependent gene expressions. Among two commonly clinically observed corepressor motifs, I417M (coexisted with NF1 nonsense mutation as the biallelic event) and R1362Q (located in GAP domain, increased NF1 gain of expression by mutation), the I417M motif mutation increased the level of estrogen-responsive genes, regardless of Ras-Raf inhibition by MEK inhibitor treatments but not R1362Q (Figure 2A). This finding suggested that the estrogen hypersensitivity mediated by NF1 is not dependent on the interaction with GAP. In light of all of this, NF1 loss should be considered an attractive therapeutic target in ER+ breast cancer—always keeping in mind, however, that not all the mutations are the same.

Figure 2. NF1 depletion globally enhances ER transcriptional activity

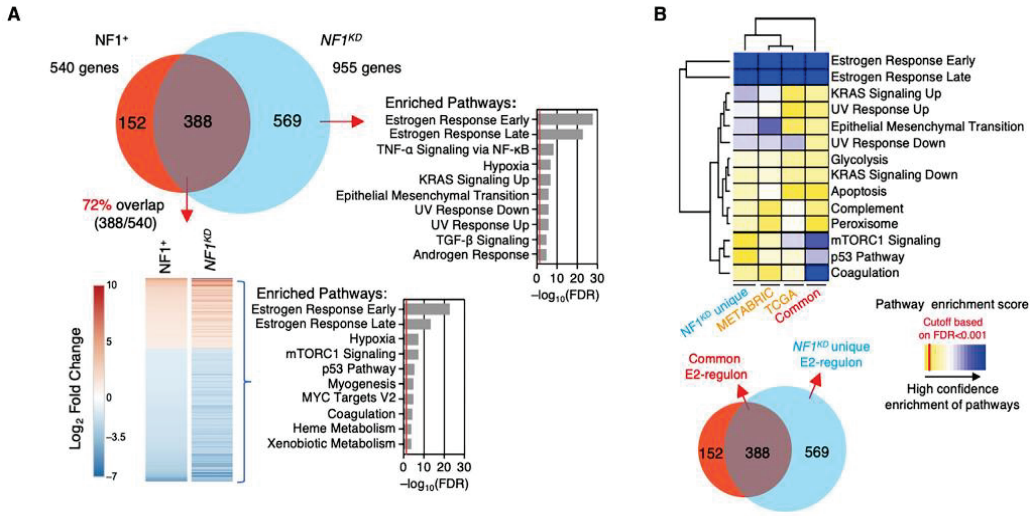


Figure 2. *NF1* depletion globally enhances ER transcriptional activity

(A) RNA-seq was performed on $NF1^{+}$ or $NF1^{KD}$ MCF-7 cells treated with E2 or vehicle. A Venn diagram depicts the number of E2-mediated differentially expressed genes in $NF1^{+}$ (red), $NF1^{KD}$ cells (blue), and those that overlap (common E2-regulon, purple). The common E2-regulon genes identified in $NF1^{+}$ and $NF1^{KD}$ cells were ranked by (Log_2) fold-change in gene expression, and enrichment for Hallmark Pathways by GSEA is shown to the right (red line marks a false discovery rate cutoff at 0.05). GSEA analysis was also performed to examine Hallmark Pathways selectively enriched in $NF1^{KD}$ cells ("$NF1^{KD}$ unique E2-regulon"). (B) Genes identified in (A) were examined in the TCGA and METABRIC ER^{+} breast cancer cases to identify those genes that are differentially expressed between tumors with wild-type *NF1* and *NF1* frameshift/nonsense mutations. The enriched Hallmark Pathways in the patient data are presented along with the results of the two E2-regulons identified in MCF-7 cells.

Previously, BCM researchers showed the survival data from the patient samples using the UBC-TAM study (Griffith 2018) that only nonsense/frameshift mutation without interaction with GAP but causing the loss of NF1 activity, was associated with worse survival outcomes (Figure 3).

Figure 3. NF1 loss of function mutations drive poor outcomes.

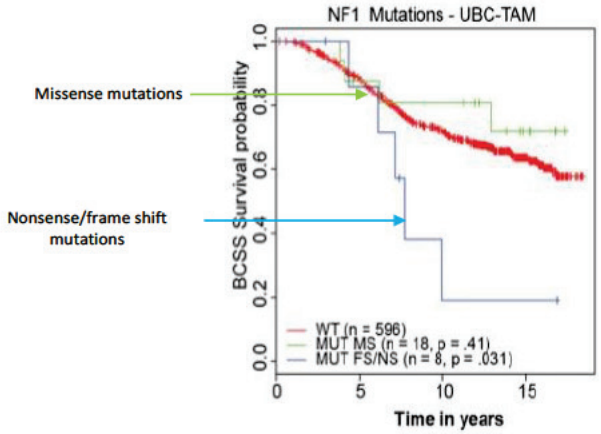


Figure 3. NF1 loss of function mutations drive poor outcomes
Kaplan–Meier plots of candidate gene mutations in discovery and validation cohorts. Kaplan–Meier graphs showing the prognostic role of NF1mutations, separated by variant type—Missense (MUT MS, green), Frameshift/Nonsense (MUT FS/NS, blue) in ER+breast cancer patients from UBC-TAM dataset.

2.4 SERD Activity Against NF1 Loss HR+ Positive Breast Cancers and Synergistic Tumor Growth Inhibition of Combination Therapy (SERD + MEK inhibitor)

NF1 KO HR+ breast cancer cells showed tamoxifen or AI agonism in published data of the analysis from samples of patients treated with tamoxifen, UBC-TAM dataset (Griffith 2018). However, these cells data remain sensitive to the SERD, fulvestrant. In other words, NF1 loss did not result in the resistance to the SERD. However, even with treatment of NF1-silenced breast cancer cells with fulvestrant (SERD), we have observed more of Ras-Raf-MEK-ERK pathway genes. Thus, in NF1 loss ER+ breast cancer cells, the Ras activation does play a role in acquired SERD resistance, which can be reversed upon MEK inhibitor addition. Indeed, the combination of MEK inhibitors, selumetinib and binimetinib, with fulvestrant successfully inhibited NF1 low ER+ breast cancer PDX (Figure 4). An initial in vivo assessment of dabrafenib-trametinib in WHIM16 suggested activity for Ras-dependent kinase inhibition with fulvestrant over that observed for fulvestrant alone (data not shown here), but longer-term exposure was limited by weight loss and diarrhea. BCM researchers therefore replaced the dabrafenib-trametinib combination with selumetinib-laced chow and conducted a four-arm study to compare single-agent efficacy versus the combination. These data demonstrate that when selumetinib was combined with fulvestrant, efficient and long-term inhibition/regression of the tumor was achieved, (Figure 4A) despite only 50% inhibition of ERK activity. In contrast, selumetinib alone slowed growth but did not induce tumor regression. Western blot confirmed ER degradation by fulvestrant and pERK inhibition by selumetinib (Figure 4B). Selumetinib did not reduce ER phosphorylation at S118, suggesting the MEKi efficacy cannot be easily explained on this basis. Binimetinib, another shorter half-life and better-tolerated MEKi, also efficiently inhibited tumor growth when combined with fulvestrant (Figures 4A and 4B).

Figure 4. Co-targeting Ras and ER to treat NF1-deficient ER+ breast cancer.

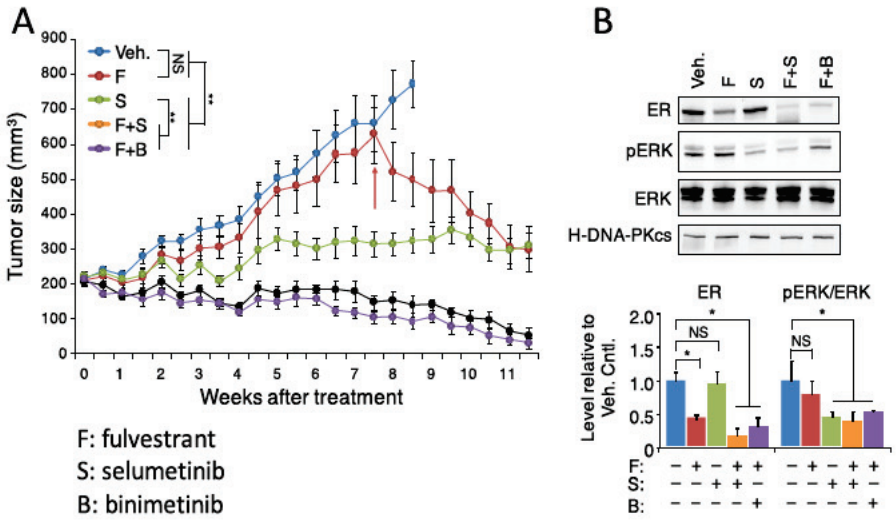


Figure 4. Co-targeting Ras and ER to Treat NF1-Deficient ER⁺ Breast Cancer
(A) WHIM16 tumors were transplanted into cleared mammary fat pads of mice and later randomized to receive treatment (n = 15 per treatment arm) when tumor volumes reached 200 mm3. Tumor volume comparison was performed at 52 days post-treatment by t test between indicated treatment groups, and at the same time, binimetinib (B) was added to the fulvestrant-only arm (marked by the black arrow). After 84 days (gray arrow), treatments were withdrawn from all treatment groups expect the group receiving late binimetinib after initial fulvestrant monotherapy. (B) WHIM16 tumors from each treatment arm at week-4 post-treatment in (C) were analyzed by immunoblot (one representative tumor shown on the left), and the results relative to those treated by the vehicle control were quantified on the right (n = 3 tumors).

2.5 Single-Agent Activity of Fulvestrant and Binimetinib

The Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON) study compared the efficacy of single agent fulvestrant to the previous standard of care aromatase inhibitor (Neve 2016, Ellis 2015, Robertson 2016). This was the first study that confirmed the higher efficacy of fulvestrant, showing the hazard ration of PFS of fulvestrant to anastrozole as 0.797, 95% confidence interval 0.637-0.999, p=0.486). The median PFS of fulvestrant was 16.6 months, 3 months longer compared to 13.8 months with anastrozole. As a result, fulvestrant has been considered to be the most potent anti-estrogen therapy. In the clinic, no prospective study has been done to selectively treat NF1 lost ER+ breast cancer. Therefore, the potential clinical activity of single agent fulvestrant can be extrapolated from the BCM pre-clinical data.

As summarized in the previous section, fulvestrant has initial efficacy in NF1 lost ER+ breast cancer; however, soon the resistance occurs by compensatory activation of the Ras-Raf-MEK-ERK pathway. This emerging resistance to single agent fulvestrant can be overcome by the addition of a MEK inhibitor as shown in Figure 4A. While single agent selumetinib showed some efficacy (Figure 4A), a MEK inhibitor without endocrine therapy has never been tested as a single agent given the importance of companion endocrine therapy in any ER+ breast cancer targeted therapies. Cohort 1 will clearly address both fulvestrant single agent activity and the combination of fulvestrant + binimetinib to address these unanswered clinical questions.

Taken together, BCM researchers designed this exciting finding into a Phase 2 Trial of Fulvestrant and Binimetinib in Patients with HR-Positive Metastatic Breast Cancer with inactivating or inferred inactivating NF1 alterations.

The benefiting target patients will be determined by identifying the mutation of NF1 that leads to the loss of the function of NF1. This novel fulvestrant and binimetinib combination will be studied in patients with metastatic HR positive breast cancer, with known/confirmed neurofibromin loss by inactivating or inferred inactivating NF1 alterations.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD).

Patients who meet the eligibility and ineligibility criteria and are **fulvestrant-naïve** will be randomized after registration to receive either fulvestrant and binimetinib or fulvestrant alone.

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

A ComboMATCH Treatment Trial EAY191 Eligibility Criteria

3.1.1 The patient must be enrolled on the ComboMATCH Master Registration Trial EAY191.

Note: Patients must fulfill all eligibility criteria outlined in Section 3 of the ComboMATCH Registration Trial EAY191 at the time of registration to EAY191-N2. This includes submission of NGS data from one of the NCI credentialed Designated laboratories for all potential patients prior to treatment trial assignment. Copy number and allele frequency cutoff as per the Registration Protocol.

3.1.2 Patients must have disease that can be safely biopsied and agree to a pre-treatment biopsy or, if disease cannot be safely biopsied, have archival tissue available from within 12 months prior to the date of registration on the ComboMATCH Registration Trial (EAY191).

Please note the current actionable marker of interest (aMOI)/actionable alteration list for this treatment trial can be found on the CTSU ComboMATCH Registration Protocol page.

Please note novel/Dynamic aMOI can be submitted for review per the process described in the ComboMATCH Registration Protocol.

A ComboMATCH Treatment Trial EAY191-N2 Eligibility Criteria

3.1.3 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.1.4 Age ≥ 18.

3.1.5 ECOG performance status 0-2 (see Appendix A).

3.1.6 Histologically or cytologically confirmed invasive breast carcinoma.

3.1.7 Confirmed metastatic disease by either imaging or tissue diagnosis.

3.1.8 Measurable disease by RECIST 1.1 and one additional lesion that can be biopsied (primary, metastatic both allowed).

3.1.9 Patients must have inactivating or inferred inactivating NF1 alterations detected in tumor as determined by the ComboMATCH screening assessment.

3.1.10 The tumor must have been determined to be ER and/or PgR positive assessed by current ASCO/CAP Guideline Recommendations for hormone receptor testing. Patients with ≥ 1% ER or PgR staining by IHC are considered positive.

3.1.11 The tumor must have been determined to be HER2-negative by current ASCO/CAP guidelines.

3.1.12 Prior therapy:

- Prior use of CDK4/6i is required.
- Prior use of fulvestrant regardless of duration.is allowed and will determine treatment assignment.
- Up to one line of chemotherapy in metastatic setting is allowed.

3.1.13 Adequate hematologic function defined as follows:

- Absolute neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/ mm^3
- Hemoglobin level ≥ 10 g/dL

3.1.14 Adequate renal function defined as:

Creatinine clearance (CrCL) of ≥ 30 mL/min by the Cockcroft-Gault formula.

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

3.1.15 Adequate hepatic function defined as follows:

- Total bilirubin level ≤ institutional upper limit of normal.
- AST and ALT must be ≤ 5.0 x ULN.

3.1.16 For patients who will be assigned to Cohort 2 (fulvestrant-resistant), a LVEF assessment must be performed within 12 weeks prior to registration. The LVEF must be ≥ 50% regardless of the cardiac imaging facility's lower limit of normal. (LVEF assessment performed by echocardiogram is preferred; however, MUGA scan may be substituted based on institutional/situational preferences.)

3.1.17 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.18 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Concurrent anticancer therapy.

3.2.2 Active autoimmune disease requiring systemic treatment within the past 3 months, documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

3.2.3 Active brain metastasis. Brain metastases that have been stable for at least 1 month after completion of treatment are not an exclusion criterion.

3.2.4 History of or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for neurosensory retinal detachment/central serous, chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration.

3.2.5 Patients will be excluded if they currently have the following risk factors for RVO that are documented prior to the enrollment:

- Known uncontrolled glaucoma with intra-ocular pressures ≥ 21 mmHg.
- Known serum cholesterol ≥ Grade 2.
- Known hypertriglyceridemia ≥ Grade 2.
- Known hyperglycemia (fasting) ≥ Grade 2.

3.2.6 Cardiac history:

- Patients with baseline QTc > 500 ms, either induced by medication or congenital long QT syndrome will be excluded due to known side effects of binimetinib.
- Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.2.7 Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ Grade 2.

3.2.8 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

3.2.9 Other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interfere with interpretation of study results.

3.2.10 Pregnancy or lactation at the time of registration or intention to become pregnant during the study. ***(Note: Pregnancy testing according to institutional standards for patients of childbearing potential.)***

- For binimetinib, highly effective contraception should be used for at least 30 days after the last dose, and patients should not breastfeed for 3 days after the last dose.
- For fulvestrant, highly effective contraception should be used for 1 year after the last dose, and patients should not breastfeed for 1 year after the last dose.

3.2.11 Use of any investigational product within 30 days prior to study entry.

3.3 Eligibility Criteria for Cohort 1, Treatment Regimen 2 Patients who Migrate to Cohort 2

Cohort Migration

Patients treated with control treatment fulvestrant who experience disease progression

may be eligible to migrate to Cohort 2 and receive combination treatment with binimetinib and fulvestrant. Patients who choose to do so must meet laboratory values and performance status requirements below and should begin treatment within 28 days.

3.3.1 Patient's willingness to migrate to Cohort 2 affirmed.

3.3.2 The patient must have an ECOG performance status of 0-2 (see Appendix A).

3.3.3 Adequate hematologic function defined as follows:

- Absolute neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/ mm^3
- Hemoglobin level ≥ 10 g/dL

3.3.4 Adequate hepatic function defined as follows:

- Total bilirubin level ≤ institutional upper limit of normal (ULN).
- AST and ALT must be ≤ 5.0 x ULN.

3.3.5 Adequate renal function defined as:

Creatinine clearance (CrCL) of ≥30 mL/min by the Cockcroft-Gault formula.

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

3.3.6 A LVEF performed within the last 3 months must be ≥ 50% regardless of the cardiac imaging facility's lower limit of normal. (LVEF assessment performed by echocardiogram is preferred; however, MUGA scan may be substituted based on institutional/situational preferences.).

3.3.7 Pregnancy test according to institutional standards must be negative (for patients of childbearing potential only).

3.4 Ineligibility Criteria for Cohort 1, Treatment Regimen 2 Patients who Migrate to Cohort 2

3.4.1 Not a candidate for binimetinib in the opinion of the treating investigator.

3.5 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 Pre-Treatment Assessment

Table 1. Pre-treatment assessments

Assessments See Section 10 for Biospecimen Submission Information	**Prior to Registration on EAY191-N2**		**Prior to Treatment (within 3 calendar days) (Cycle 1, Day 1)**
Consent form signed by the patient	X		
Central NF1 testing results ***(determined by ComboMATCH screening assessment)***	X		
Confirm any known documentation of risk factors for RVO (see 3.2.4)[a]	X		
History and physical exam[b]	X	Within 4 weeks	X
Performance status (see Appendix A)[l]	X		
Height and weight	X		
Assessment of BP	X		X
Assessment of concomitant medications[c]	X		X
CBC/differential/platelet count[l]	X	Within 14 days	X
Total bilirubin/AST/ALT/alkaline phosphatase[l]	X		X
Calcium, fasting blood glucose, albumin, sodium, potassium[l]	X		X
Tumor markers[d]	X		X
Creatinine clearance [l]	X		X
Pregnancy test[e,j]	X		X
Echocardiogram (or MUGA scan)[f,l]	X	X Within 12 weeks for patients in **Cohort 2**	X Within 12 weeks for patients in **Cohort 1, Treatment Regimen 1)**
12-Lead ECG (if clinically indicated)[g]	X	Within 12 weeks	
Imaging of chest/abdomen/pelvis[h]	X	Within 5 weeks	
Bone scan[i]	X		
Neuroimaging[j]	X		

Table continued on next page.

Table 1. Pre-treatment assessments *(continued)*

Assessments See Section 10 for Biospecimen Submission Information	**Prior to Registration on EAY191-N2**	**Prior to Treatment (within 3 calendar days) (Cycle 1, Day 1)**
Submission of fresh tumor core biopsy **OR** archival FFPE if within 12 months of registration on the ComboMATCH Registration Trial (EAY191)**k**		X (if submitting fresh tumor core biopsy
Submission of whole blood for cfDNA, WES, and NF1 VAF**k**		X (After registration before treatment begins)

a While the known risk factors of RVO including previously documented glaucoma are exclusion criteria, eye exams and blood tests to identify risk factors for RVO will be conducted as clinically indicated (physician discretion) and are not required by the study.

b History and physical by a physician or other healthcare professional.

c Include all prescribed and over-the-counter medications, supplements, herbal therapies (see Section 5.2.1).

d Tumor marker testing is not a study requirement. The results of tumor markers (e.g., CA15-3, CEA, CA27.29) will be collected if they are ordered as part of standard care.

e For patients of childbearing potential: Pregnancy testing should be performed according to institutional standards prior to registration.

f Patients in Cohort 2 must have a LVEF ≥ 50% as stated in the binimetinib package insert prior to registration. Patients in Cohort 1 who are randomized to Treatment Regimen 1 must have a LVEF ≥ 50% as stated in the binimetinib package insert prior to starting treatment. ***Echocardiogram is the preferred method for assessment of LVEF.*** However, LVEF assessment by MUGA scan is permitted. All subsequent LVEF assessments should be performed by the same method (echocardiogram or MUGA scan) that was performed at baseline.

g ECGs will be conducted as clinically indicated and **are not** mandated.

h The same method (CT or MRI) used for baseline tumor measurements should be used at all other tumor measurement time points. If patient is unable to receive CT contrast, an MRI of the abdomen/pelvis and non-contrast chest CT should be performed. PET/CT ***is not*** an acceptable alternative contrast enhanced imaging method.

i If PET/CT was previously performed within the 5 weeks prior to registration and demonstrated no evidence of bone metastases, baseline bone scan is recommended but not required.

j MRI of the brain (or contrast CT scan of the brain if patients are unable to undergo MRI) is required if symptoms suggest possible CNS metastatic disease. However, neuroimaging is also recommended in asymptomatic patients.

k Samples are to be collected and submitted as outlined in Section 10 and Appendix D. Kits are available for the collection and shipment of blood specimens (see Section 10.3 for kit information). To order kits, complete the EAY191 Collection and Shipping Kit Order Form (see Appendix D).

l These assessments must be completed prior to registration to Cohort 2 for patients in Cohort 1, Treatment Regimen 2 who progress on fulvestrant alone. Patient's willingness to migrate to Cohort 2 must be affirmed.

4.2 **Assessments During Treatment**

Table 2. Assessments during treatment

Assessments *(See footnotes **a, b, and c**)*	**Time Points**				
	C1D1	**C1D15**	**C2D1**	**Day 1 of each cycle until off study therapy** *(from registration)*	**30 days after last dose of binimetinib**
History & physical exam[d] (≤ 3 days)	X	X	X	X	
Vital signs (≤ 3 days)	X	X	X	X	
Adverse event assessment (≤ 3 days)	X	X	X	X	X
Concomitant medication assessment[f] (≤ 3 days)	X	X	X	X	
CBC/differential/platelet count[g] (≤ 3 days)	X	X	X	X	
Total bilirubin/AST/ALT/alkaline phosphatase (≤ 3 days)	X	X	X	X	
Creatinine, calcium, glucose, albumin, sodium, potassium (≤ 3 days)	X	X	X	X	
Tumor markers[h]	X		X	X	
Imaging of chest/abdomen/pelvis for disease assessment[i,j] (+/- 7 days)	X (every 8 weeks)				
Echocardiogram (or MUGA scan)[k] (+/- 14 days)				X (every 3 cycles starting at Cycle 4 Day 1)	
12-Lead ECG	X (as clinically indicated)				
Eye exam[l]	X (as clinically indicated)				
Bone scan (+/- 28 days)	X (every 6 months from registration)				

Table continued on next page.

Table 2. Assessments during treatment *(continued)*

Assessments *(See footnotes **a, b, and c**)*	**Time Points**				
	C1D1	**C1D15**	**C2D1**	**Day 1 of each cycle until off study therapy** *(from registration)*	**30 days after last dose of binimetinib**
Optional submission of whole blood for cfDNA and NF1 VAF		X	X		
	X (at progression or end of treatment)				
Optional submission of FFPE sections for WES, RNAseq, and microscaled proteogenomics**m**	X (at progression or end of treatment)				

a History and physical, blood tests, x-rays, scans, and other testing may be performed more frequently at the discretion of the investigator.

b See Section 4.3 for required assessments in follow-up. See Section 6.1 for treatment management and modifications.

c While tests, exams, and assessments, are not required following disease progression, survival status continues to be required every 6 months for 5 years. (See Section 7 for adverse event reporting requirements.)

d History and physical with exams (by physician or other healthcare professional) appropriate for therapy-related assessments and follow-up evaluations.

e See Section 7 for instructions regarding adverse event reporting.

f Include all prescribed and over-the-counter medications, supplements, herbal therapies (see Section 5.2.1).

g CBC/differential/platelet count may be checked more frequently per institutional policy.

h Tumor marker testing is not a study requirement. The results of tumor markers (e.g., CA15-3, CEA, CA27.29) will be collected if they are ordered as part of standard care.

i The same method (CT or MRI) used for baseline tumor measurements should be used at all other tumor measurement time points. Scans may be performed within 14 days of the scheduled scan.

j At the time of progression, patients should have imaging of the chest/abdomen/pelvis, preferably with a CT scan, and a bone scan performed to document extent of disease. **Note:** In the event of declining renal function or dye allergy, chest CT may be performed without contrast and MRI of abdomen and pelvis may be substituted for CT scan.

k Due to the known cardiac effect of binimetinib, patients in Cohort 1, Treatment Regimen 1 and patients in Cohort 2 will have an echocardiogram performed every 3 cycles. Patients in Cohort 1, Treatment Regimen 2 may have an echocardiogram or MUGA performed if clinically indicated. Echocardiogram is the preferred method for assessment of LVEF. However, LVEF assessment by MUGA scan is permitted. All LVEF assessments should be performed by the same method (echocardiogram or MUGA scan) that was performed at baseline.

Table continued on next page.

Table 2. Assessments during treatment *(continued)*

l	While the risk factor of RVO including previously documented glaucoma are exclusion criteria, eye exams will be conducted as clinically indicated and not mandated.
m	A new biopsy will not be required for migration, but the optional biopsy at disease progression should be encouraged.

4.3 Assessments in Follow-Up

Patients who discontinue protocol therapy for reasons other than disease progression should continue tumor assessments and tissue and blood sample submissions outlined on Table 2 until progression is documented or non-protocol therapy initiated. The frequency of imaging will be at the investigator's discretion until progression is documented or non-protocol therapy initiated.

Following disease progression, protocol-specified tests, exams, and assessments, are not required, and survival status should continue every 6 months for 5 years. (See Section 7 for adverse event reporting requirements.)

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Fulvestrant/Binimetinib Therapy

Study treatment should begin within 2 weeks after registration. The first dose of fulvestrant can be administered while waiting for the PMB-supplied binimetinib to be received at the site.

Treatment will continue in the absence of progression or toxicity.

5.1.1 Cohort 1 (fulvestrant-naïve): Patients are randomized 1:1 between fulvestrant + binimetinib (Treatment Regimen 1) and fulvestrant alone (Treatment Regimen 2).

- Fulvestrant will be administered intramuscularly (500 mg intramuscularly into gluteal area slowly [1-2 minutes per injection] as two 5 mL injections) on Day 1 and Day 15 of Cycle 1 and Day 1 of each 28-day cycle afterwards.
- Binimetinib 45 mg (3 tablets) is taken twice daily on Days 15-28 of Cycle 1 and then twice daily for 28 days starting with Cycle 2 and beyond. A cycle is 28 days. Binimetinib will be administered orally twice daily on a fixed schedule unless the side effects warrant dose reduction. The use of a binimetinib medication diary is recommended (see Appendix E).

  For patients with known metastasis in the liver and have a baseline grade 1 or grade 2 liver enzymes abnormality (AST, ALT), patients are required to start with the dosage of 30 mg (2 tablets) orally taken twice daily. If patients have known liver metastasis but have normal liver function test, they will start with the normal dose.

- Patients in Cohort 1, Treatment Regimen 2 who progress on fulvestrant alone may migrate to Cohort 2 if they meet the EAY191-N2 eligibility/ineligibility criteria in Sections 3.3 and 3.4. Migration to Cohort 2 should take place within one month of progression, with no non-protocol intervening anti-cancer therapy given. Patients not willing to migrate to Cohort 2 will have further therapy at the investigator's discretion.

Cohort Migration

Patients receiving fulvestrant who experience disease progression may be eligible to migrate to Cohort 2 and receive combination treatment with binimetinib and fulvestrant upon documentation of disease progression.

A new biopsy will not be required for migration, but the optional biopsy at disease progression should be encouraged.

5.1.2 Cohort 2 (fulvestrant-resistant): Patients will receive fulvestrant + binimetinib.

- Fulvestrant will be administered intramuscularly (500 mg intramuscularly into gluteal area slowly [1-2 minutes per injection] as two 5 mL injections) on Day 1 of Cycle 1 and Day 1 of each 28-day cycle afterwards.

  Note: If a fulvestrant-containing regimen was not administered immediately prior to

enrolling on this study, reload fulvestrant on Day 1 and Day 15 of Cycle 1. If the patient has progressed on fulvestrant and the EAY191-N2 treatment is the next line of therapy, **or** if patients receiving fulvestrant alone in Cohort 1, Treatment Regimen 2 progress, the Day 15 loading dose of fulvestrant will be omitted, while the study visits and labs will still be conducted.

- Binimetinib 45 mg (3 tablets) is taken twice daily on Days 15-28 of Cycle 1 and then twice daily for 28 days starting with Cycle 2 and beyond. A cycle is 28 days. Binimetinib will be administered orally twice daily on a fixed schedule unless the side effects warrant dose reduction. The use of a binimetinib medication diary is recommended (see Appendix E).

  For patients with known metastasis in the liver and have a grade 1 or grade 2 liver enzymes abnormality (AST, ALT), patients are required to start with the dosage of 30 mg (2 tablets) orally taken twice daily. If patients have known liver metastasis but have normal liver function test, they will start with the normal dose.

5.1.3 Route of Administration of Binimetinib

Binimetinib can be taken orally with or without food. Tablets should be swallowed whole. If a dose of binimetinib is missed, take it if there is > 6 hours until the next dose. If it is within 6 hours of the next scheduled dose, skip this dose and take the next dose at the scheduled time. Do not make up for the missed dose. If a dose is vomited, skip the dose. Take the next dose at the scheduled time.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Supportive Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Herbal and Nutritional Supplement

The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, the use of general nutritional foundation supplements including calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins, L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding registration and the treatment discontinuation visit. If the patient is taking any prohibited medications as of the day of consent, they will be instructed to discontinue the drug and alternatives will be discussed with the patients.

See Section 9.1 for potential drug interactions with binimetinib. See Appendix F for a Patient Clinical Trial Wallet Card.

5.2.2 Participation in Other Trials

Patients are not to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g., imaging trials, quality of life, etc.).

5.3 Duration of Therapy

Treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression (see Section 13),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6,
- Patient decides to withdraw consent for participation in the study,
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
- Death
- Pregnancy
  - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a female patient or the partner of a male patient participating in the study.

Note:

- Patient has the right to refuse further treatment, but that does not necessitate withdrawing consent for participation in the study (e.g., follow-up) (See Section 8.2.2 regarding study consent withdrawal)
- See Section 6 to determine if individual treatment components can be stopped independently.
- If all protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Dose Modifications

- The CTCAE v5.0 must be used to grade the severity of AEs. Refer to http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- Dose reductions for binimetinib must be based on the AE requiring the greatest modification.
- Binimetinib doses that have been reduced may be escalated at investigator discretion.
- There are no dose reductions for fulvestrant.
- Binimetinib cannot be given as single agent therapy.
- If binimetinib is discontinued due to toxicity and in the absence of progression in Cohort 1, Treatment Regimen 1 or Cohort 2 patients, fulvestrant doses should be continued until progression if the patient is benefitting from the fulvestrant.
- Patients in Cohort 1, Treatment Regimen 2 who progress may migrate to Cohort 2 (see Section 3.3) as long as the accrual of Cohort 2 is not finished.
- Binimetinib and fulvestrant must be discontinued at the time of progression for patients in Cohort 1, Treatment Regimen 1 or Cohort 2 patients.
- If necessary, the timing of fulvestrant in both cohorts may be adjusted to 2 days earlier or 2 days later than the scheduled date of treatment.
- Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 28 days of the scheduled interruption. The reason for interruption should be documented in the patient's study record.
- When rescheduling study therapy for non-medical adjustments, refer to the memo posted under Supplemental Documents on the protocol-specific page located on the CTSU members' website (https://www.ctsu.org) for information regarding treatment over holidays/vacations and other non-medical delays (e.g., physician or patient schedules). This memo is updated annually.

Table 3. Dose levels for binimetinib (Cohort 1, Treatment Regimen 1 or Cohort 2)

	Dose Level 0 ***Starting Dose***	**Dose Level -1**	**Dose Level -2**
Binimetinib	45 mg orally twice daily	30 mg orally twice daily	Permanently discontinue if unable to tolerate binimetinib 30 mg orally twice daily
Binimetinib ***(For patients with known metastasis of the liver)***	30 mg orally twice daily	Permanently discontinue if unable to tolerate binimetinib 30 mg orally twice daily	N/A

6.2 Management of Binimetinib Treatment-Related Events

Available clinical data for binimetinib indicate a predictable safety profile consistent with those reported for other allosteric MEK1/2 inhibitors including the characteristic class effects of ocular toxicities, elevations of CK that are mostly asymptomatic, liver function test abnormalities (elevation of AST, ALT and total bilirubin), left ventricular dysfunction, skin toxicities including rash and acneiform dermatitis, hypertension, thromboembolic events, diarrhea, edema and hemorrhage. The majority of these toxicities are generally reversible and manageable by appropriate supportive medical care and/or dose modifications or discontinuation. Refer to Table 4 for binimetinib dose modifications.

If binimetinib must be held for more than 2 cycles (8 weeks) due to toxicity, the patient will be taken off study therapy.

Table 4. Dose modifications for binimetinib

CTCAE v5.0 Adverse Event	Management
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is also below lower limit of normal (LLN)	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 lower limit of normal, and • Absolute decrease from baseline is 10% or less, and • Patient is asymptomatic. If the LVEF does not recover within 4 weeks permanently discontinue binimetinib.
Symptomatic congestive heart failure **OR** absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Permanently discontinue binimetinib.
Venous Thromboembolism	
Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Withhold binimetinib. • If improved to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life-threatening PE	Permanently discontinue binimetinib.

Table continued on next page.

Table 4. Dose modifications for binimetinib *(continued)*

CTCAE v5.0 Adverse Event	Management
Serous Retinopathy	
Symptomatic serous retinopathy/Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib.
Retinal Vein Occlusion	
Any grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib.
Grade 4	Permanently discontinue binimetinib.
Interstitial Lung Disease	
Grade 2	Withhold binimetinib 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.
Grade 3 or Grade 4	Permanently discontinue binimetinib.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain binimetinib dose. • If no improvement within 2 weeks, withhold binimetinib until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See **Other Adverse Reactions**
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations	
• Grade 4 asymptomatic CPK elevation **OR** • Any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib 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.

Table continued on next page.

Table 4. Dose modifications for binimetinib *(continued)*

CTCAE v5.0 Adverse Event	Management
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue binimetinib.
Other Adverse Reactions	
• Recurrent Grade 2 **OR** • First occurrence of any Grade 3	Withhold binimetinib 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 binimetinib.
First occurrence of any Grade 4	Permanently discontinue binimetinib, **OR** Withhold binimetinib 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 binimetinib.
Recurrent Grade 3	Consider permanently discontinuing binimetinib.
Recurrent Grade 4	Permanently discontinue binimetinib.

6.3 Management of Fulvestrant Treatment-Related Events

There are no planned dose modifications for fulvestrant. If a patient experiences an unanticipated grade 3 or 4 toxicity that is considered at least possibly related to fulvestrant, the fulvestrant should be discontinued. Patients who discontinue fulvestrant and are also receiving binimetinib, must also discontinue binimetinib. Binimetinib cannot be given as single agent therapy. The patient should continue tumor assessments and tissue and blood sample submissions outlined on Table 2 until progression is documented or non-protocol therapy initiated. The frequency of imaging will be at the investigator's discretion until progression is documented or non-protocol therapy initiated.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent (binimetinib) administered in EAY191-N2, which is being made available under an IND sponsored by the NCI, CTEP. For patients receiving binimetinib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.6.2.

Commercial Agents

The commercial agent in EAY191-N2 is fulvestrant. For patients receiving fulvestrant, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.6.2.

7.2 Adverse Event Reporting Requirements

Complications associated with the prior to start of treatment or end-of-treatment/progression research biopsy will be reported and tracked as protocol-related AEs within Medidata Rave on the relevant ComboMATCH Treatment Trial. No AE reporting will be reported via the ComboMATCH Registration Trial.

7.3 Adverse Events and Serious Adverse Events

7.3.1 Adverse Event Characteristics

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.3.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study patient must be reported via CTEP-AERS in an expedited manner.

7.4 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Binimetinib (NSC 788187)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted in Table 5). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1521 patients.* Below is the CAEPR for Binimetinib.

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

Table 5. Comprehensive Adverse Events and Potential Risks (CAEPR) List for Binimetinib

Version 2.2, April 12, 2023[1]

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1521]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (bradycardia)	
		Cardiac disorders – Other (left ventricular dysfunction [cardiomyopathy])	
		Heart failure	
EYE DISORDERS			
	Blurred vision		***Blurred vision (Gr 2)***
		Eye disorders - Other (ocular hypertension)	
	Retinopathy[3]		
Eye disorders - Other (visual disorder)[2]			***Eye disorders - Other (visual disorder)[2] Gr 2)***
		Periorbital edema	
		Retinal vascular disorder	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1521]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Skin infection		***Skin infection (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	CPK increased[4]		***CPK increased[4] (Gr 2)***
	Ejection fraction decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Generalized muscle weakness		***Generalized muscle weakness (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (myopathy)		
	Myalgia		***Myalgia (Gr 2)***
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash acneiform			***Rash acneiform (Gr 2)***
Rash[5]			***Rash[5] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (nail disorders)		
		Skin and subcutaneous tissue disorders - Other (severe cutaneous reaction)[6]	

Adverse Events with Possible Relationship to Binimetinib (CTCAE 5.0 Term) [n= 1521]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (skin fissures)		
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 2)***
	Thromboembolic event		
		Vascular disorders - Other (hemorrhage)[7]	

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

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

[3]Retinopathy may include chorioretinopathy, chorioretinitis, and retinal detachment. Retinal events includes, retinal pigment epitheliopathy, retinoschisis, retinal oedema, chorioretinopathy, retinopathy, and retinal exudates, eye oedema

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (atrioventricular block); Cardiac disorders - Other (irregular heart rate); Cardiac disorders - Other (tachyarrhythmia); Cardiac disorders - Other (tachycardia); Myocardial infarction; Palpitations; Supraventricular tachycardia
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Dry eye; Eye disorders - Other (chalazion); Eye disorders - Other (change in visual acuity); Eye disorders - Other (detachment of retinal pigment epithelium); Eye disorders - Other (eye edema); Eye disorders - Other (eyelid oedema); Eye disorders - Other (irritation); Eye disorders - Other (retinal exudates); Eye disorders - Other (retinal vein thrombosis); Eye disorders - Other (visual field defect); Eye disorders

- Other (subretinal fluid); Glaucoma; Vision decreased.
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Cheilitis; Colitis; Dry mouth; Duodenal perforation; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (anorectal discomfort); Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal disorders - Other (hematochezia); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (pneumatosis intestinalis); Hemorrhoids; Ileus; Pancreatitis; Small intestinal obstruction; Small intestinal perforation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Edema trunk; Flu like symptoms; General disorders and administration site conditions - Other (axillary pain); General disorders and administration site conditions - Other (hemorrhagic cyst); General disorders and administration site conditions - Other (ulcer hemorrhage); Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (biliary colic); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic function abnormal)
INFECTIONS AND INFESTATIONS - Bacteremia; Bronchial infection; Kidney infection; Lung infection; Paronychia; Peritoneal infection; Sepsis; Shingles; Soft tissue infection; Upper respiratory infection; Urinary tract infection; Viremia
INJURY, POISONING AND PROCEDURAL COMPLICATIONS – Bruising; Injury, poisoning and procedural complications - Other (toxic skin eruption)
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (C-reactive protein increased); Investigations - Other (electrocardiogram change); Investigations - Other (haptoglobin increased); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus); Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Flank pain; Muscle cramp; Myositis; Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (skin papilloma, papilloma); Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Akathisia; Dysgeusia; Headache; Nervous system disorders - Other (dropped head syndrome); Nervous system disorders - Other (myasthenic syndrome); Paresthesia; Presyncope; Somnolence; Spinal cord compression; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Hallucinations; Insomnia; Psychiatric disorders - Other (abnormal behavior); Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Menorrhagia;

Reproductive system and breast disorders - Other (polymenorrhea); Reproductive system and breast disorders - Other (metrorrhagia); Reproductive system and breast disorders - Other (hematospermia); Reproductive system and breast disorders - Other (uterine hemorrhage)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Atelectasis; Cough; Hypoxia; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pneumothorax; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asthma); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Eczema; Erythema multiforme; Erythroderma; Hyperhidrosis; Nail discoloration; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Skin and subcutaneous tissue disorders - Other (excoriation); Skin and subcutaneous tissue disorders - Other (panniculitis and erythema nodosum); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (rosacea); Skin and subcutaneous tissue disorders - Other (skin burning sensation); Urticaria
VASCULAR DISORDERS - Hypotension; Lymphedema; Superficial thrombophlebitis; Vascular disorders - Other (aortic dilatation)

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

7.5 Adverse Events for Commercial Study Agent (Fulvestrant)

Refer to the current FDA-approved package insert for detailed pharmacologic and safety information for fulvestrant.

Common adverse events (> 20%) include: cough; infection; anemia; thrombocytopenia; constipation, diarrhea, nausea, vomiting, anorexia; pain, fatigue; flushing; headache

Occasional events (<= 20%) include: arrhythmia; peripheral edema; dyspnea; thromboembolic event; alanine aminotransferase increased, aspartate aminotransferase increased; allergic reaction

Rare but serious events (< 3%) none.

7.6 Expedited Reporting of Adverse Events

For studies that utilize the Rave-CTEP-AERS integration, expedited reports are initiated via Rave; **see Section 14.3 for important operational details/information about Rave-CTEP-AERS Integration** and how to obtain the CTSU Expedited Safety Reporting Rules Evaluation User Guide.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

7.6.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a **CTEP-AERS-24-hour notification** must be submitted within 24 hours of learning of the AE. Each CTEP-

AERS 24-hour notification must be followed by a complete report within **5 calendar days**.

- **CTEP-AERS 10 Calendar Day Report** requires that a complete report is electronically submitted within 10 calendar days of learning of the AE (see Table 6).
- Supporting source documentation is requested by CTEP and by NRG as needed to complete adverse event review. Deidentified supporting source documentation should be uploaded to the CTSU Source Document Portal via the CTEP-AERS integration.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action not recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.6.2 Expedited Reporting Requirements for Adverse Events

Table 6. Late Phase 2 and Phase 3 Studies: Expedited reporting requirements for adverse events that occur on studies under an IND within 30 days of the last administration of the investigational agent (binimetinib) and/or commercial agent (fulvestrant)[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the study therapy (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 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 NCI via electronic submission 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">10 Calendar Days</td><td rowspan="2">24-Hour, 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: ***Protocol-specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR for binimetinib.***

Expedited AE reporting timelines are defined as:

- "24-Hour, 5 Calendar Days" – The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent and/or commercial agent and has an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report with 5 calendar days for:

- All Grade 4 and Grade 5 AEs

Expedited 10 calendar days reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

7.6.3 Reporting to the Site IRB

Investigators will report unanticipated problems to the NCI CIRB according to the NCI CIRB SOPs. In addition, investigators must report serious adverse events to the local Institutional Review Board (IRB) responsible for the oversight of the patient if required by institutional policy.

7.6.4 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.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined Section 7.7.

7.6.5 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 AE reporting unless otherwise specified.

7.7 Routine Reporting Requirements for Adverse Events

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

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.8 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's

partner from the time of consent to 30 days after the last dose of binimetinib or one year after the last dose of fulvestrant must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes six person registration types.

- Investigator (IVR) - MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) - advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Non-Investigational New Drug (IND)/Non-Treatment (NINT) - (e.g., MD, DO, NP, PA, PharmD, PhD, EdD) investigators who wish to exclusively participate in non-IND/non-treatment studies flagged for NINT participation;
- Associate Plus (AP) - clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) - other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) - individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	NINT	AP	A	AB
CTEP-IAM Account with ID.me credentials	✓	✓	✓	✓	✓	✓
FDA Form 1572 • Practice sites, IRBS, and labs	✓	✓				
Financial Disclosure Form	✓	✓	✓	✓		
NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal statement, memberships, honors, publications, research support)	✓	✓	✓	✓		
NINT Investigator Acceptance Form • Practice sites, IRBS, and labs • NINT Biosketch (education, licensure, ABMS certification, GCP Training)	✓	✓	✓			
GCP Training Certificate (mandatory upload file)	✓	✓	✓	✓		
Agent Shipment Form (if applicable)	✓					
CV (optional file upload)	✓	✓	✓	✓		
Annual Re-registration	✓	✓	✓	✓	✓	✓

IVRs, NPIVRs, and NINTs must list all clinical practice sites and Institutional Review

Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Note that NINTs may only participate on studies flagged for NINT participation and cannot hold any active task on a DTL.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB

approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB approval record:

- Have an active CTEP status;
- Have active status at the site(s) on the IRB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *NRG* and protocol number [*EAY191-N2*].
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at by phone or email: 1-866-651-

CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List. Persons with Non-Investigational New Drug/Non-Treatment (NINT) registration type cannot be assigned any task on the DTL.

8.2 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study; the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study; the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

To assign a Non-Investigational New Drug (IND)/Non-Treatment (NINT) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, NINTs must list all clinical practice sites, Institutional Review Boards, and labs covering their practice sites on the NINT Investigator Acceptance Form in RCR. NINTs may only participate on studies flagged for NINT participation.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.2.2 Cohort Migration Registration Procedure

Patients receiving fulvestrant who experience disease progression may be eligible to migrate to Cohort 2 and receive combination treatment with binimetinib and fulvestrant (see Section 5.1.2). Cohort migration can be requested by initiating Step 2 registration on the treatment trial in OPEN.

Click "Request" to confirm the patient is eligible for and determine whether a slot is available for the patients to migrate; click "Cancel" to withdraw a request. Determination of slot availability might be delayed < 24 hours for review if trial eligibility criteria has changed since the patient's initial enrollment.

Patient Migration steps:

- Log into the Treatment Trial in the OPEN registration system and select the appropriate patient.
- Cohort migration can be requested by initiating a Step 2 registration on the treatment trial in OPEN. Complete Cohort/Stratum Migration Request question in OPEN by clicking "Request."
- Once a slot in Cohort 2 has been confirmed, the patient can be migrated to Cohort 2.
- Once a patient is assigned to Cohort 2 via migration, they must be enrolled within 14 days, or the slot will be automatically released, and the process must be repeated to request a new slot on Cohort 2 for this patient.
- Cohort Migration is dependent on slot availability.
- If the patient opts not to migrate after the request has been made, the request can be cancelled in OPEN by clicking "cancel."
- Please note: Once the patient has been registered to Cohort 2, they must start treatment within 14 days – therefore total time from migration request to start of treatment is a maximum of 28 days.
- A new biopsy will not be required for migration, but the optional biopsy at disease progression should be encouraged.
- If assistance is needed with this process, contact the ComboMATCH Help Desk.

8.2.3 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow up data to be submitted to NRG Oncology), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal.

NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed (see Section 5.3).

9. DRUG INFORMATION

General Patient Care Implications

Patients must use highly effective contraception because the study treatment may be teratogenic. Highly effective contraception is defined as hormonal contraceptives (oral contraceptives, Nuvaring, Depo Provera), intrauterine device, true abstinence, two barrier methods of birth control including condoms with cervical cap or diaphragm, patient has received surgical sterilization, patient is monogamous with a post-menopausal partner.

9.1 Investigational Study Agent: Binimetinib (MEK162, ARRY-438162) (NSC# 788187, IND#[redacted]

Chemical Name or Amino Acid Sequence: 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1Hbenzimidazole-6-carboxamide

Other Names: MEK162, ARRY-438162

Classification: MEK 1/2 inhibitor

CAS Registry Number: 606143-89-9

Molecular Formula: C17H15BrF2N4O3 **M.W.:** 441.23

Approximate Solubility: Binimetinib's solubility is pH dependent. At pH 1 solubility is 0.993 mg/mL. At pH 7.4 solubility is 0.012 mg/mL.

Mode of Action: Binimetinib is a potent, selective, allosteric small-molecule inhibitor of mitogen-activated protein (MAP) kinase kinase (MEK 1 and MEK 2) that is uncompetitive with adenosine triphosphate (ATP).

How Supplied: Array Biopharma Inc., a wholly owned subsidiary of Pfizer Inc. supplies and CTEP, NCI, DCTD distributes binimetinib as 15 mg film-coated tablets in bottles containing 180 tablets. The tablets are yellow to dark yellow, unscored biconvex oval shaped and the size is 0.2 x 0.48 inches. The tablets are debossed with a stylized "A" on one side and "15" on the other side. The film-coated tablets consist of binimetinib drug substance; colloidal silicon dioxide; croscarmellose sodium; lactose monohydrate; magnesium stearate; microcrystalline cellulose; polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, and ferrosoferric oxide.

Storage: Store at 20°C - 25°C, excursions permitted between 15°C and 30°C, protect from light.

> If a storage temperature excursion is identified, promptly return binimetinib to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Refer to label for shelf life dating. Tablets should be dispensed in the original packaging.

Route and Method of Administration: Orally with or without food. Tablets should be swallowed whole. If a dose of binimetinib is missed, take it if there is > 6 hours until the next dose. If it is within 6 hours of the next scheduled dose, skip this dose and take the next dose at the scheduled time. Do not make up for the missed dose. If a dose is

vomited, skip the dose. Take the next dose at the scheduled time.

Potential Drug Interactions: *In vitro*, binimetinib is metabolized primarily by glucuronidation mainly via UGT1A1 but also UGT1A3 and 1A9. Binimetinib is a substrate of CYP1A1, 1A2, 2C19, 3A4 *in vitro* but the potential for a clinical drug interaction is expected to be minimal. Binimetinib is also a substrate of P-gp and BCRP. Binimetinib is not a substrate of OATP1B1, 1B3, 2B1, or OCT1. Inhibitors or inducers of UGT1A1, P-gp, and BCRP should be co-administered with caution.

In vitro, binimetinib reversibly inhibited CYP2B6 and is a weak inhibitor of CYP1A2 and 2C9. However *in vivo* no clinically significant inhibition is expected with CYP2B6. Binimetinib is not a time-dependent inhibitor of CYP1A2, 2C9, 2D6, and 3A4/5. It has little or no inhibition of CYP2A6, 2C8, 2C19, 2D6, 2E1, and 3A4/5. Binimetinib is a weak inhibitor of UGT1A-mediated SN-38 conjugation *in vitro*. Binimetinib was not found to be an *in vitro* inhibitor of BCRP, P-gp, or OCT1 but is a weak inhibitor of OCT2. There is a low potential for binimetinib to cause a clinical drug interaction with substrates mainly cleared by OATP and OCT2.

Binimetinib is an *in vitro* inducer of CYP3A4 but this was not confirmed clinically. Slight induction of CYP2C9 mRNA was also found but did not translate into induction of activity.

Binimetinib is highly protein bound (97.2%). Use caution in patients who are receiving concomitant medications that are also highly protein-bound.

Drugs with a conditional, possible, or known risk to induce Torsades de Pointes or QT prolongation should be co-administered with caution. Patients that take these medications should be monitored frequently or according to protocol.

Patient Care Implications: There is some data that suggest binimetinib exposure may be associated with reproductive toxicity. Binimetinib must not be used in pregnant women during treatment and for 30 days after last dose. Women should not breastfeed during treatment and for 3 days after last dose.

9.1.1 Procurement of binimetinib

- Binimetinib will be supplied free of charge by Array Biopharma Inc., a wholly owned subsidiary of Pfizer Inc., and will be distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).
- NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.
- No starter supplies will be provided for this study. Orders can be placed after

enrollment and randomization and include the patient ID# when placing the order. Submit binimetinib requests through the PMB online agent order processing (AURORA) application (https://ctepcore.nci.nih.gov/aurora). Access to AURORA requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/index.jsp) and the maintenance of an "active" account status, a "current" password, and active person registration status

- For questions about drug orders, transfers, returns, or accountability call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.1.2 PMB Useful Links and Contacts

- *CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/*
- *NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov*
- *PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm*
- *PMB online agent order processing (AURORA) application:* https://ctepcore.nci.nih.gov/aurora
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp*
- *CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov*
- *IB Coordinator: IBCoordinator@mail.nih.gov*
- *PMB email: PMBAfterHours@mail.nih.gov*
- *PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)*

9.1.3 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

9.1.4 Investigator Brochure Availability

The current version of the binimetinib IB will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the

establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

9.1.5 Material Safety Data Sheets

The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

9.2 Commercial Agent: Fulvestrant

Sites must refer to the FDA package insert for detailed pharmacologic and safety information.

Product description: FASLODEX is supplied as two 5 mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of FASLODEX solution for intramuscular injection and fitted with a tamper evident closure. The single-dose prefilled syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Solution preparation: Refer to the current FDA-approved package insert for 'standard' preparation instructions, handling, and storage.

Route of administration: The recommended dose of FASLODEX is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock. Discard each syringe after use.

Agent Ordering: Fulvestrant is commercially available.

10. PATHOLOGY/BIOSPECIMEN

10.1 Biomarker Testing

Table 7. Biomarker Table

Priority	Biomarker Name [a]	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose [b]	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]	Funding Source(s) [d]
Tissue-based Biomarkers								
1	Whole Exome **(REQUIRED)**	Whole Exome Sequencing CLIA: No	Integrated To compare with Designated Laboratory assay To identify markers of response and resistance to binimetinib and fulvestrant	Fresh tumor core biopsy (preferred) or archival paraffin-embedded tumor tissue	Pre-treatment and at progression or end of treatment	Pre-treatment Mandatory Post treatment Optional	MoCha Laboratory (FNLCR) P. Mickey Williams	Molecular Diagnostic Network (MDNet) Contract (Lyndsay Harris, NCI Contact)
2	Whole Transcriptome (RNAseq) **(REQUIRED)**	RNA sequencing CLIA: No	Exploratory To identify markers of response and resistance to binimetinib and fulvestrant.	Fresh tumor core biopsy (preferred) or archival paraffin-embedded tumor tissue	Pre-treatment and at progression or end of treatment	Pre-treatment Mandatory Post-treatment Optional	MoCha Laboratory (FNLCR) P. Mickey Williams	Molecular Diagnostic Network (MDNet) Contract (Lyndsay Harris, NCI Contact)
3	NF1 protein	IHC CLIA: No	Exploratory To identify markers of response and resistance to binimetinib and fulvestrant, by comparing with baseline	Fresh tumor core biopsy or archival paraffin-embedded tumor tissue	Pre-treatment	Optional	Baylor College of Medicine (BCM) Laboratory George Miles	BCM SPORE
4	NF1 protein and related biomarkers	Microscaled proteogeno-mic assay CLIA: No	Exploratory To identify markers of response and resistance to binimetinib and fulvestrant	Fresh tumor core biopsy, frozen	Pre-treatment and at progression or end of treatment	Optional	Baylor College of Medicine (BCM) Laboratory Eric Chang	BCM SPORE

Table continued on next page.

Table 7. Biomarker Table *(continued)*

Priority	Biomarker Name [a]	Assay (CLIA: Y/N)	Use in the Trial (Integral, Integrated, or Exploratory) AND Purpose [b]	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI [c]	Funding Source(s) [d]
Blood-based Biomarkers								
1	Germline Whole Exome **(REQUIRED)**	Whole Exome Sequencing (WES) CLIA: No	Integrated Germline genomic control for tissue WES	Whole blood	Pre-treatment	Mandatory	MoCha Laboratory (FNLCR) P. Mickey Williams	Molecular Diagnostic Network (MDNet) Contract (Lyndsay Harris, NCI Contact)
2	Cell-free DNA **(REQUIRED)**	TSO500® for cfDNA CLIA: No	Integrated To compare with WES and Designated Laboratory assay Exploratory To explore serial changes in cfDNA alterations over course of treatment	Plasma	Pre-treatment, C1D15, C2D1, and at progression or end of treatment	Pre-treatment Mandatory Progression Optional	MoCha Laboratory (FNLCR) P. Mickey Williams	Molecular Diagnostic Network (MDNet) Contract (Lyndsay Harris, NCI Contact) BCM SPORE
3	NF1 VAF	ddPCR CLIA: No	Exploratory To detect Variant Allele Fraction (VAF) of NF1 and co-mutations	Plasma	Pre-treatment, C1D15, C2D1, and at progression or end of treatment	Optional	Baylor College of Medicine (BCM) Laboratory George Miles	BCM SPORE

10.1.1 Integrated Biomarkers

Integrated and exploratory molecular profiling assays will be performed within the research setting in the Molecular Diagnostics Network (MDNet) laboratories. Integrated whole exome sequencing and exploratory sequencing of RNA and ctDNA will use massively parallel sequencing (next generation sequencing) on an Illumina sequencer.

10.1.1.1 Whole Exome

Whole exome sequencing analyzing tissue samples collected prior to start of therapy will be performed in order to assess the concordance of the central molecular characterization of the pre-treatment biopsy samples with the genetic readouts from the

designated outside laboratories (dOLs). Whole blood will also be sequenced to compare to tumor sequence.

Please refer to the ComboMATCH registration protocol for further information.

10.1.1.2 Pre-Treatment Circulating Tumor DNA (ctDNA)

DNA sequencing will be performed at MDNet laboratories on circulating tumor DNA in blood samples collected prior to start of therapy in order to assess how the registration diagnostic tumor mutation profile and pre-treatment biopsy profile compare to the ctDNA mutation profile from plasma.

Please refer to the ComboMATCH registration protocol for further information.

10.1.2 Exploratory Biomarkers

10.1.2.1 Whole Transcriptome

RNA sequencing will be performed on tumor tissue samples collected prior to start of therapy in order to investigate molecular features that may have influence on response or lack of response to the treatment. Tumor RNA and DNA sequences obtained at progression or end of treatment will be assessed for potential resistance mechanisms.

Please refer to the ComboMATCH registration protocol for further information.

10.1.2.2 NF1 Protein and Related Biomarkers

Immunohistochemical (IHC) staining will be performed to measure the level of NF1 protein loss. Microscaled proteogenomics assays will be performed to determine the phosphoproteome of ER+ NF1-depleted tumors. See Appendix C for further information.

10.1.2.3 Digital Droplet PCR

Digital Droplet PCR (ddPCR) will be used to assess longitudinal changes in the Variant Allele Fraction (VAF) of NF1 and co-mutations in ctDNA. See Appendix C for further information.

10.2 Specimen collection and submission

Samples are to be submitted as outlined in Appendix D. Tissue and blood will be collected at the time points listed below.

Table 8. Specimen Collection

Specimen Type	Intended Assay(s)	Archival	Baseline	On Study	Progression[1]	Ship to:
Fresh tumor core biopsy	WES RNAseq IHC	N/A	Two cores in formalin for paraffin embedding[2] (Mandatory)[3]	N/A	Two cores in formalin for paraffin embedding (Optional)	Central Biorepository and Pathology Facility
Fresh tumor core biopsy	Microscaled proteogenomics	N/A	Two cores in OCT (Optional)	N/A	Two cores in OCT (Optional)	
FFPE tumor	WES RNAseq IHC	FFPE block or unstained slides (Mandatory)[3]	N/A	N/A	N/A	
Whole blood[4]	WES germline control, ctDNA	N/A	4 Streck tubes (Mandatory)	4 Streck tubes C1D15, C2D1 (Optional)	4 Streck tubes (Optional)	

1. Collect samples at progression or end of treatment only if patient has been on study therapy for 6 months or more.
2. It is requested that two core biopsies 16-18 gauge in diameter and at least 1 cm in length are obtained. Note that for the prior to start of treatment submissions, FFPE tissue collected within 12 months prior to registration to the EAY191 Registration Trial may be an acceptable alternative submission based on treatment status of the patient. See Appendix D for specific instructions.
3. Per Section 3.1.2, "Patients must have disease that can be safely biopsied and agree to a pre-treatment biopsy or have archival tissue available from within 12 months prior to registration."
4. Collect blood prior to start of treatment, on C1D15, on C2D1, and at end/discontinuation of ComboMATCH treatment (or progression, whichever is earlier)

10.3 Kit information for collections

Samples are to be submitted as outlined in Appendix D. Kits are available for the collection and shipment of blood specimens. To order kits, complete the EAY191 Collection and Shipping Kit Order Form (see CTSU website) and fax to 713-563-6506. All samples submitted on the ComboMATCH Treatment Trials must follow the same logging and tracking process. ComboMATCH will initially leverage a manual paper-based process. The paper-based process will subsequently be replaced with the Precision Medicine Specimen Tracking Forms within Rave and submitted with a Rave generated

shipment manifest and local pathology group information. Sample tracking and biopsy collection procedures are described in Appendix D. For pathology materials it is strongly recommended that full patient names be provided.

11. SPECIAL STUDIES (NON-TISSUE) NOT APPLICABLE

12. CENTRAL QUALITY/ENDPOINT REVIEWS NOT APPLICABLE

13. ASSESSMENT OF DISEASE STATUS

Tumor response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer 2009) except in the documentation of progressive disease (PD).

13.1 Definition

13.1.1 Evaluable Toxicity

All patients will be evaluable for toxicity from the time of their first administration of protocol therapy.

13.1.2 Evaluable for Objective Response

Patients who have measurable disease present at baseline and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of the first 3 weeks of treatment will also be considered evaluable.)

13.2 Disease Parameters

13.2.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) ≥ 10 mm by CT scan with slice thickness no greater than 5 mm, MRI, or calipers in clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The same method (CT or MRI) used at baseline should be used at all other tumor measurement time points.

In rare instances in which none of the metastatic sites can be used as a measurable lesion, the breast primary, if intact, can be used as a measurable lesion. If it meets the criterion of ≥ 10 mm, it can be monitored on serial chest CT or on breast imaging techniques (e.g., mammography, ultrasound). The breast primary should not be used as a site of measurable disease if other sites of measurable disease have been identified. This should only be done when resection of the breast primary is not anticipated.

13.2.2 Malignant Lymph Nodes

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

13.2.3 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm

or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

13.2.4 Special Considerations Regarding Tumor Measurability

- **Bone lesion measurability**

  When evaluating bone lesions, the following should be considered:

  – Bone scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

  – Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

  – Blastic bone lesions are non-measurable.

- **Cystic lesions**

  – Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  – Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are presented in the same patient, these are preferred for selection as target lesions.

- **Tumors with prior local treatment**

  – Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

13.2.5 Target Lesions

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

13.2.6 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes which are not used as target lesions should be identified as non-target lesions and should also be recorded at baseline. All sites of non-target lesions must be assessed along with the target lesions. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.2.7 Lesions

If new lesions appear and there is clinical doubt as to whether a lesion is new or an inflammatory change, follow-up scans are required in no less than 6 weeks. If the new lesion is confirmed as unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to be something other than the tumor by a scan obtained at least 6 weeks after the initial scan), the date of progression is taken to be the date on which the new lesion was first detected. If a lesion reappears after disappearing in a patient previously declared to have a CR, PD is declared. However, if such a lesion behaves in this manner in a patient with SD or PR, confirmation as stated above defines the response or progression.

13.2.8 Pseudoprogression

Delayed responses after a tumor flare have been reported in patients who have received immune-based therapy. Caution must be exercised not to confuse a possible tumor flare with PD. In scenarios where pseudoprogression of previously targeted or not-targeted lesions is suspected, follow-up scans are required in 4 to 6 weeks. Based on that repeating imaging, if there is confirmatory evidence of tumor progression, the date of PD will be documented as the initial evaluation. However, if subsequent response is confirmed, no progression is documented, and the imaging schedule reverts to that otherwise stated in the protocol.

13.3 **Response Criteria**

13.3.1 Evaluation of Target Lesions

- *Complete response (CR)*

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

- *Partial response (PR)*

  At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

- *Progressive disease (PD)*

  At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on

study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.)

- *Stable disease (SD)*

  Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

13.3.2 Evaluation of Non-Measurable/Non-Target Lesions

- *Complete response (CR):* Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- *Non-CR/Non-PD:* Persistence of one or more non-target lesion(s).
- *Progressive disease (PD):* Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

13.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Refer to Table 9 and Table 10 for a summary of the criteria that contribute to the determination of response.

Table 9. Time point response: patients with target (± non-target) disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-CR/Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion (Eisenhauer 2009).
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Table 10. Time point response: patients with non-target disease only

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

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

13.5 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping protocol therapy.

13.6 Duration of Response

13.6.1 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met

for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

13.6.2 Duration of Stable Disease

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

13.7 **Progression-Free Survival**

Progression-free survival is defined as the time from randomization to the first documented progressive disease, as determined using the current RECIST 1.1 criteria, or death from any causes, whichever occurs first.

14. DATA AND RECORDS

14.1 Data Management/Collection

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Investigational New Drug (IND)/Non-Treatment (NINT), NonPhysician Investigator (NPIVR), or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. NINTs will only have write access in Rave for studies flagged for NINT participation.

This study has a Delegation of Tasks Log (DTL). Therefore, those individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user.

Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management* > *Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

14.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.6 and 7.7 for information about expedited and routine reporting.

14.3 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event Form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westatctsucontact@westat.com.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents > Protocol Related Documents > Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information > User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

14.4 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

14.5 **Global Reporting/Monitoring**

DMU Light *monitoring:*

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable.

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

15. STATISTICAL CONSIDERATIONS

15.1 Abstract

This is a phase II study of binimetinib in combination with fulvestrant in patients with metastatic hormone receptor positive HER2 negative breast cancers with a non-functional mutation (inactivation or inferred inactivation) in NF1. This trial includes two cohorts: the fulvestrant naïve cohort (Cohort 1: randomized) and the fulvestrant resistant cohort (Cohort 2: single arm).

15.2 Primary Endpoints

15.2.1 Cohort 1

Progression free survival (PFS) defined as the duration between randomization and progression or death from all cause, whichever happens first.

15.2.2 Cohort 2

Overall response rate (ORR) within 4 months defined as the percentage of patients who reaches a complete or partial response (defined by RECIST v1.1) within 4 months of the start of the treatment.

15.3 Secondary Endpoints

- ORR for each study arm of Cohort 1. ORR is defined as the percentage of patients who reach a complete or partial response (defined by RECIST v1.1) any time after the start of the treatment.
- ORR for Cohort 2 is defined as the percentage of patients who reach a complete or partial response (defined by RECIST v1.1) any time after the start of the treatment.
- Clinical benefit rate, defined as proportion of patients who achieved a CR, PR, or stable disease (SD) defined by RECIST criteria any time after the start of the treatment.
- PFS for patients of Cohort 2. PFS as defined in Section 15.2.1.
- Overall survival (OS) defined as the duration between randomization and death of all causes.
- Toxicity by study arm for Cohort 1 and toxicity for Cohort 2.

15.4 Randomization and Stratification

Cohort 1 patients will be randomized in 1:1 ratio to fulvestrant + binimetinib or fulvestrant only arm by permuted block randomization. Block size 4, 6, and 8 will be used. No stratification will be considered.

15.5 Patient Population for Analysis

15.5.1 Per Protocol Population

The per protocol (PP) population includes all patients who completed the study according to the protocol. For Cohort 1, the PP analysis will be performed for the primary endpoints. For Cohort 2, all patients who have started the experimental therapy will be analyzed for the primary outcomes.

15.5.2 Safety Population

For both study cohorts, patients who received at least one dose of the study regiment will be included in the safety population. Safety population will be used for the analysis of safety endpoints. Patients will be analyzed according to the treatment received.

15.6 Primary Endpoint(s), Sample Size, and Analysis Plan

15.6.1 Sample Size and Power Calculations

Cohort 1

A total of 70 fulvestrant naïve patients will be randomized in a 1:1 ratio to receive either fulvestrant + binimetinib or fulvestrant only. Patients who progressed on the fulvestrant only arm will have the choice to consent to join the Cohort 2 study. The primary endpoint for Cohort 1 is progression-free survival (PFS). It is estimated that the median PFS for the patients on the fulvestrant alone arm will be around 6 months (H0). A HR of 0.5 or smaller (HA) is considered worth further investigation of the regimen, which will require a total number of 55 events to reach 90% power with a 1-sided log rank test (α=0.1). The estimated monthly accrual for this cohort is 1.5/month, thus the accrual will be finished in 47 months. The average lost to follow-up rate is 1% per year. With the above assumptions, we will need to follow up the patients for an additional 6 months to reach the number of events needed. The total study time after the first patient is randomized on the trial will be 53 months.

One interim analysis for futility will be performed when 28 events are obtained (about 31 months after the first patient is randomized on the trial). If the PFS hazard ratio at the interim is in the wrong direction (favoring control arm), then the study will be stopped for futility (Wieand 1994), this rule is binding. The probability of stopping the trial for futility under the null is 0.5 and under the alternative is 0.033. The overall power for the definitive analysis is 89%.

Cohort 2 (n=16 or 25)

This is the cohort for fulvestrant exposed patients (as single agent or combination). The primary endpoint of this cohort is ORR (best response rate within 4 months). Our targeted rate is 30% or higher (HA), as compared to the expected 10% for the patients eligible for the study (H0). We base our study size based on a Simon 2-stage mini-max design in which 16 patients will be treated initially. If 2 or more patients responded, an

additional 9 patients (total n=25) will be treated. If 5 or more patients responded by the end of the second stage, we will consider the regimen to be potentially worthy of further investigation. The type I and type II errors of the study are both set at 10%.

That is, if the true rate is 30% or higher, we will have over 90% power to declare the regimen effective. If the response rate is 10%, the probability of stopping at the first stage is 51%, and the overall probability of false positive is controlled at 10%. The expected sample size under null is 20.37.

Accrual/Study Duration

Cohort 1: The estimated monthly accrue for Cohort 1 is 1.5 patients/month, thus the accrue will be finished in 47 months.

Cohort 2: We expect the accrual rate for Cohort 2 to be approximately 1 patient per month. Accounting for a potential up to a 4-month hiatus between the two stages, we will finish the accrual of 25 patients in 29 months.

Stopping guideline for insufficient accrual for both cohorts:

Monitoring will be done separately for each cohort.

If at one year after activation, the accrual is less than 35% of what was projected in the protocol for one year of accrual, consideration will be given to amendment of the statistical section or terminating that cohort of insufficient accrual.

If at two years after activation, the accrual is less than 50% of what was projected in the protocol for two years of accrual, consideration will be given to amendment of the statistical section or terminating that cohort of insufficient accrual.

15.7 Analysis Plan

15.7.1 Analysis of Primary Endpoints

Cohort 1: PFS of the two study arms will be compared by log-rank test (1-sided, α=0.1). Kaplan-Meir plot will be provided. HR and the corresponding 95% confidence interval (CI) will be estimated by Cox proportional model using treatment as covariate. The primary analysis will be based on PP population.

Cohort 2: ORR will be calculated as the proportion of patients achieved PR or CR within 4 months after the initiation of the treatment. ORR will be reported with corresponding 95% exact CI. Patients who have withdrawn from the study before starting the experimental therapy will be considered non-evaluable for clinical response and hence replaced.

15.7.2 Analysis of Secondary Efficacy Endpoints

- ORR in Cohort 1: ORR for each study arm will be calculated with corresponding 95% exact CI. Fisher exact test will be used to compare the ORR of the two study arms.
- PFS in Cohort 2: PFS for Cohort 2 will be summarized using the Kaplan-Meir's

method. Median PFS with corresponding 95% CI will be provided.

- Clinical benefit rate will be analyzed for each arm of Cohort 1 and Cohort 2 as described for ORR above.
- OS: OS for Cohort 1 will be analyzed as described for PFS in Cohort 1 in Section 15.6.1. OS for Cohort 2 will be analyzed as described for PFS in Cohort 2 above.

15.7.3 Analysis of Safety Endpoints

The grade of toxicity measurement will follow CTCAE version 5.0. The distribution by treatment group of the highest grade of each CTCAEs experienced by each patient categorized will be tabulated. The tabulations will also be reviewed on a semi-annual basis by the Data Monitoring Committee (DMC). These tabulations will include summaries by system organ class and summaries by term under each system organ class.

15.7.4 Analysis of Integrated and Exploratory Biomarkers

A separate Statistical Analysis Plan (SAP) will be developed for the integrated and exploratory biomarker analysis.

Concordance of diagnostic tumor mutation profile generated by the Designated Laboratory, the pre-treatment biopsy mutation profile, and the pre-treatment ctDNA mutation profile will be assessed. Details are provided in the statistical plan of the ComboMATCH Registration Protocol.

15.8 Monitoring/Oversight Committee

NRG Oncology Data Monitoring Committee (DMC)

The NRG Oncology DMC will review the study twice a year with respect to patient accrual and AEs. The DMC also will review the study for protocol-specified interim analyses and on an "as needed" basis.

NRG Oncology Early Phase Oversight Committee

Study reports focusing on accrual, adverse event, and DLT data will be prepared regularly, and the PI/NRG study team will have regular conference calls (biweekly) to review the accrual/safety data, which will be summarized by the study chair. Summaries from these calls will be reviewed quarterly by the NRG Oncology Early Phase Oversight Committee.

Safety monitoring

The grade of toxicity measurement will follow CTCAE v5.0. Dose limiting toxicity (DLT) are defined as hematologic toxicity grade 3 or 4; Grade 4 neutropenia or thrombocytopenia > 7 days, Grade 3 thrombocytopenia with bleeding; non-hematologic toxicity grade ≥ 2 that, in the judgement of the investigator, was dose limiting; rash grade ≥ 3 requiring dose reduction; treatment delay of ≥ 14 days because of unresolved toxicity. ≥Grade 3 electrolyte abnormality that lasts >72 hours, unless the patient has clinical

symptoms, in which case all ≥ Grade 3 electrolyte abnormality regardless of duration should count as a DLT. For patients with hepatic metastases, AST or ALT > 8 x ULN or AST or ALT > 5 x ULN for ≥ 14 days is considered a DLT. Non-hematologic DLT will be defined as a treatment-related grade 3 or greater nonhematologic toxic effect other than nausea, vomiting, or fatigue; a drug-related grade 3 or greater clinically significant laboratory abnormality including CBC determined by the site PI (and discussion with the study PI if there is a consult needed), liver and kidney function, electrolyte that does not return to grade 1 or less or baseline within 1 week; grade 3 nausea/vomiting or diarrhea related to study drug treatment that is not controlled after > 72 hours with adequate antiemetic and other supportive care ; or ≥ Grade 3 fatigue ≥ 1 week related to study drug treatment. A drug-related grade 2 toxicity persistent over 2 weeks requiring a dose reduction will be considered a DLT if the treating physician and the PI concur. The threshold for allowable Grade 3 events is < 72 hours. A previously reported DLT of binimetinib, including cardiac issues or retinal issues, will be further investigated for its effect on cardiac complication and will be considered a DLT as it is even if no other cardiac sequels are detected on investigation. The observation period of the DLT is 1 cycle.

Bayesian analysis will be used by the study investigators to monitor the DLT rate in the first 15 patients of the combination arm in Cohort 1 and Cohort 2 to ensure that the underlying DLT rate does not exceed 20%. For this purpose, a posterior probability (PPr) will be calculated from the study's accumulating data on DLT or absence thereof, and a weak prior distribution of a beta distribution with parameters $\alpha = 0.5$ and $\beta = 0.5$ is used. If PPr (DLT rate>0.2) > 0.90, i.e., there is a 90% or higher chance that more than 20% of patients will experience serious adverse events, then enrollment will be suspended pending a review of both the data and the study's implementation.

The enrollment suspension rule using the Bayesian analysis mentioned above can be represented as a table of possible outcomes for DLTs, as shown below.

Bayesian rule for suspending enrollment	
Suspend accrual if > =n patients experience a DLT	in N patients treated
2	2-4
3	5-7
4	8-11
5	12-14
6	15

The operating characteristics of this study design can be expressed in terms of probability of early suspending the enrollment for a study arm under the assumptions of various true rates of DLT. The following table calculated these probabilities for a single dose level based on the simulation of 10,000 hypothetical trials. Simulations are done using the web tool provided at https://www.trialdesign.org/one-page-shell.html#BTOX.

Frequentist properties of Bayesian rule for suspending enrollment	
Probability of DLT	Probability of suspending the enrollment
0.05	0.016
0.1	0.0686
0.15	0.162
0.2	0.289
0.3	0.584
0.5	0.822

15.9 Project Optimus Contingency

If any of the cohorts in this trial meet a primary or secondary clinical benefit endpoint, the totality of the dosing experience of all experimental cohorts in this trial will be reviewed by the study team in collaboration with CTEP. If 30% or more of the patients on this trial assigned to treatment with the experimental regimen require a dose discontinuation, reduction or delay due to toxicity at any point during treatment, then an additional cohort maybe added by amendment after consideration and review to the trial to explore a lower dose. The lower dose will be determined based on toxicities observed, and the totality of what is known about the pharmacokinetics and target engagement of the agents in the experimental regimen.

15.10 Gender/Ethnicity/Race Distribution

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	0	1	0	2
Asian	8	0	1	0	9
Native Hawaiian or Other Pacific Islander	1	0	1	0	2
Black or African American	8	0	1	0	9
White	59	1	7	0	67
More Than One Race	3	0	3	0	6
Total	80	1	14	0	95

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APPENDIX A
ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90-100%
1	Restricted in physically strenuous activity but ambulatory	70-80%
2	Ambulatory and capable of self-care; but unable to carry out any work activities	50-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30-40%
4	Completely disabled	10-20%

2.0 ACTIVITIES OF DAILY LIVING

The following definitions for activities of daily living (ADL) should be used when the CTCAE v5.0 grading criteria are based on ADL:

- *Instrumental ADL* refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- *Self-care ADL* refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX B
CTEP COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

- Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agent(s) contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

- For a clinical protocol where there is an investigational Agent used in combination with (an) other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    - NCI will provide all Collaborator(s) with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    - Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    - Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

- Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and

disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

- When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

- Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

- Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX C
EXPLORATORY BIOSPECIMEN RESEARCH

Refer to Master Registration (screening) protocol for methods for MDNet WES and ctDNA.

1. NF1 immunohistochemistry (IHC)

Immunohistochemistry (IHC) is one of the key methods to detect, monitor, and select the predictive biomarker in cancer therapeutics even in the modern oncology. A robust biomarker detection by IHC is critical in the translational development of such biomarkers. Thus, BCM researchers developed an IHC assay of the neurofibromin (NF1) staining using the section of the pre-treatment tumors and core biopsies. Given large size and multiple function of the NF1 gene, it is rare to have both alleles to be deleted or mutated, and yet functionally, one allele alteration sufficiently alters the function of the NF1 protein. Our preliminary study using the PDX model study confirmed this finding. As part of the Baylor Breast SPORE project, the IHC antibodies have been established and continue to optimize to test the NF1. This is a novel approach since this has not been done in other NF1 relevant disease.

2. Microscaled Proteogenomics Assay

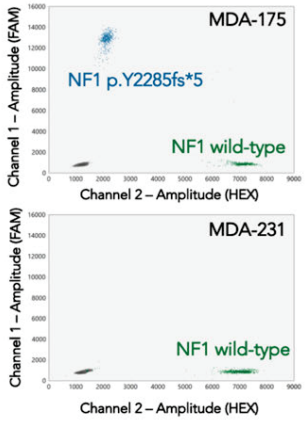
Cancer proteogenomics integrates data from cancer genomics and transcriptomics along with cancer proteomics to provide deeper insights into cancer biology and therapeutic vulnerabilities. Both by improving the functional annotation of genomic aberrations and through insights into pathway activation, this multi-dimensional approach to the characterization of human tumors shows promise for application to precision oncology. However real-life translation of proteogenomic approach is limited by the requirement of large sample acquisition. For example, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) requires at least 100 mg of tumor tissue, which typically yields quantitative information on > 10,000 proteins and > 30,000 phosphosites per sample. To reduce these tissue requirements, BCM researchers developed methods to generate high-quality DNA, RNA and protein for deep-scale DNA and RNA sequencing and proteome and phosphoproteome analysis from a single 14 G core needle biopsy (Biopsy Trifecta Extraction, (BioTExt)) and a microscaled liquid chromatography-mass spectrometry (LC-MS/MS)-based proteome and phosphoproteome analysis pipeline (MiProt) that requires only 25 μg peptide per sample. Using this approach, BCM researchers successfully identified a downregulated ERBB2 protein, and the perturbation in phosphosite signature that correlated with lack of pCR, in ERBB2 targeted therapeutic trials. Based on the success of proof-of-concept trial data, the plan is to apply this novel assay to this ComboMATCH trial pre-treatment sample. BCM researchers hope to identify a phosphosite signature that is specific to the therapeutic sensitivity of FuBi combination and associated ER and Ras/MAPK pathway proteogenomic signatures.

Details of the assay can be further found in our recent paper:
https://www.nature.com/articles/s41467-020-14381-2

3. ctDNA ddPCR assay – four time points

Digital PCR affords the ability to determine ultrasensitive measurements of mutated and wild type copies of DNA over tens of thousands of individual droplets based on emission of HEX and FAM-labeled primer probes. An automated water-emulsion droplet generator (QX200DG, BioRad) creates tens of thousands of individual droplets that partition analyte molecules and detection probes into separate PCR reactions. A typical starting sample of 20 µL should yield up to 20,000 droplets. The QX200 can process and analyze up to 96 samples per run, yielding and counting approximately 1.5 million droplets per 96-well plate. Such microfluidics-based sample partitioning and statistical analyses of up to millions of droplets provide absolute quantification of target DNA or RNA molecules for probe-based detection at high sensitivity without the need for standard curves. Completed droplet reactions are streamed single file through a specialized reader for fluorescence analysis using a multi-pixel photon counter. Positive droplets exhibit increased fluorescence of target (mutant) probes compared to negative droplets (wild type), and the fraction of PCR-positive droplets are quantitated according to Poisson distribution. Thus, the fractional abundance of the mutant allele can be calculated by the ratio of the number of mutant-FAM probe copies per droplet over the total DNA concentration of the reaction.

A



B

PIK3CA E545K			KRAS G12D		
Measured VAF (%)	Expected VAF (%)	Acceptance Criteria (Manufacturer)	Measured VAF (%)	Expected VAF (%)	Acceptance Criteria (Manufacturer)
6.50	6.30	2.2%CV (30% Horizon) PASS	5.14	6.30	14.3%CV (30% Horizon) PASS
1.24	1.30	3.3%CV (40% Horizon) PASS	1.16	1.30	8%CV (40% Horizon) PASS
0.15	0.13	10%CV (50% Horizon) PASS	0.08	0.13	34%CV (50% Horizon) PASS
0	0	0	0	0	0

Figure 1. Representative mutation analysis by ddPCR. (A) Detection of the frameshift mutation NF1 p.Y2285fs*5 in MDA-175 cells (top panel) and its absence in MDA-231(bottom panel) using custom-–designed ddPCR primer/probes. Positive detection of the NF1 mutation is identified by the cluster of blue dots (FAM channel, y axis), where the green dots (HEX channel, x axis) indicate wild type. Quadrant thresholds that discriminate probe signals were calculated using the BioRad QuantaSoft® software package. The fractional abundance or allelic frequency of the NF1 mutant is ~51%, consistent with the heterozygous nature of this alteration. (B) Table inset. Representative data from commercial cfDNA reference standards prepared in synthetic plasma that were extracted using Promega ctDNA extraction chemistry followed by digital droplet PCR. Two independent mutations at varying mutant allelic fractions (VAF%) were examined by ddPCR are demonstrated to be within range of acceptable (%CV) published manufacturer criteria.

For ddPCR the mutations to be detected must be known a priori, as unlike next generation sequencing panels, the method is specific to confirming the presence or absence of a mutation at specific locus. Qualifying mutations for the longitudinal ctDNA analysis by ddPCR will be selected from the sequenced surgical tissue samples with mutations prioritized by likely clonal/driver status. For each mutant allele, a custom ddPCR probe set (BioRad) will be designed and used for serial ctDNA monitoring across blood collection timepoints in the study. Digital droplet construction will be performed

on the BioRad AutoDG QX200 (automatic droplet generator) ddPCR system with assays utilizing TaqMan hydrolysis chemistry with custom and/or commercially available primer-probe sets (BioRad). The partitioned PCR droplet assays will be subjected to amplification using a C1000 Touch™ thermal cycler (BioRad) and fluorometrically assessed on the QX200 droplet reader. The fraction of positive droplets will be fitted to a Poisson distribution using available QuantaSoft Pro software (BioRad) to calculate the number of mutant and wild-type (WT) copies of DNA in the sample. BCM researchers demonstrated that custom probes can be designed and used to detect specific mutations, as illustrated in Figure 1A above for a frame-shift alteration in NF1 (NF1 p.Y2285fs*5). BCM researchers previously confirmed that high sensitivity and specificity can be achieved on this platform using commercially available ctDNA reference standards prepared in synthetic plasma (Horizon Discovery) (Figure 1B). This assay platform will be utilized in collaboration with Dr. George Miles to monitor abundance of ctDNA isolated from blood plasma at sampled timepoints outlined in this proposed study to combine fulvestrant and binimetinib. It is believed that this preliminary data and track record of developing and applying ddPCR-based serial monitoring of ctDNA justifies the NF1 mutant allele detection to monitor the therapy induced clonal/ subclonal changes incorporated into the ComboMATCH fulvestrant + binimetinib study.

As noted, all these three exploratory assays will be supported as a part of newly funded Baylor Breast SPORE2020.

APPENDIX D
RESEARCH BIOSPECIMEN SUBMISSION GUIDELINES

I. Kit Ordering [Kit Order Form located on the CTSU website]

II. Tissue Submissions

The relevant pathology and surgical reports and the following forms must accompany all tissue submissions:

- Copy of the REDACTED diagnostic or surgical pathology report associated with the submitted tissue
- The original diagnostic pathology report
- Other immunologic and cytologic reports
- Initial Activation: EA Generic Specimen Submission Form 2981 (CTSU website)
- Post-Activation Transition: Rave-generated Samples Tracking and Manifest Form
- Initial Activation: Local Pathology Group Information Form (CTSU website)
- Post-Activation Transition: Rave-generated Local Pathology Group Information Form
- A copy of all pathology and cytologic reports should be uploaded via the EAY191 OPEN Registration
- For initial activation, fax EA Generic Specimen Submission Form and Local Pathology Group Information Form to MD Anderson TQL 713-745-4925

NOTE: The CLIA Submission Form available in Rave is NOT required for ComboMATCH.

A. Fresh Research Biopsy Samples

The biopsies are to occur:

- After registration to the Treatment Trial, prior to initiation of treatment (MANDATORY).
- At end of treatment or progression if the patient has been on protocol treatment for 6 or more months and there is a lesion amenable to a minimal risk biopsy (OPTIONAL).

NOTE: The EOT may serve as the 'prior to start of treatment' research biopsy for a subsequent cTT.

The biopsies must be minimal or less than minimal risk (no more than 2% risk of serious complication requiring hospitalization). If it is determined during or just prior to the biopsy procedure that it would be greater than minimal risk, no biopsy is to be performed with no impact on patient participation in the treatment trial.

The following specimens are to be submitted:

- Two core biopsies, 16-18 gauge in diameter and at least 1 cm in length. Place each core between sponges in a cassette, snap the cassette lid in place, place the cassette into the formalin-filled container, secure the container lid, and place the container into the shipping kit.

- Two cores embedded in OCT.
  - Use 14- or 16-gauge needle to obtain 2 replicate cores. Quality of the collected core specimens is essential. Cores containing tumor appear white and dense. Cores containing fat are not suitable for analysis and should be recollected. If uncertain, cores can be immersed briefly (< 30 seconds) in saline. Tumor containing cores sink, whereas predominantly fatty cores float.
  - Place two, square, clear plastic cryomolds on pre-cooled metal platform. Keep metal platform on dry ice. Place two cores (one core/mold) fully extended into cryomolds and immediately cover each core with 4 mL OCT from provided pre-filled 10 mL OCT syringe.
  - Allow OCT to freeze completely. OCT is frozen when it is completely white and chalky in appearance. Once frozen, push on back of the cryomold to eject OCT pellet into a white cryomold cassettes (1 pellet per cryomold cassette). Close cryomold cassettes.
  - Place cryomold cassettes in frozen specimen bag and seal.

B. Research Biopsy Guidelines

These instructions are for patients that are undergoing fresh tumor biopsy rather than using archival tissue that is less than 12 months old.

1. If a non-cutaneous lesion site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigator, patient and Interventional Radiologist an attempt at biopsy will be made. All internal organ biopsies will be done by the Interventional Radiologist with a percutaneous approach, or during a clinically necessary surgical/endoscopic procedure, including craniotomy for brain metastasis or primary tumor.
2. No endoscopic, laparoscopic, or surgical procedure will be done solely to obtain a biopsy for this protocol.
3. The choice of imaging modality to be used to facilitate tissue acquisition during the biopsy procedure will be decided by members of the Interventional Radiology team at the clinical site and may include ultrasound, CT scan, or MRI. Tumor biopsies will be performed only if they are considered to be of low risk (< 2% major complication rate) to the participant as determined by the investigator and Interventional Radiologist. Biopsies will be performed under local anesthesia and/or sedation.

C. FFPE Tissue Block

FFPE tumor tissue may be submitted in lieu of the "Prior to start of treatment" fresh tissue biopsy if it meets the following requirements:

- Tissue must have been collected within 12 months prior to registration to the EAY191 Registration Trial.
- Patient may have received treatment after tissue collection; however, lack of response must be documented prior to registration to EAY191.

The optimal block is 70% tumor tissue with:

- Surface area: 25mm^2 is optimal. Minimum is 5 mm^2
- Volume: 1mm^3 optimal. Minimum volume is 0.2 mm^3; however, the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block is not available, the following is to be submitted:

- One (1) H&E slide, AND
- Ten (10) to twenty (20) or more recently cut 4-5 micron unstained sections on positively charged slides

D. Peripheral Blood Submissions:

Research bloods must be collected and submitted "prior to start of treatment," on days C1D15 and C2D1 of treatment and at "end of treatment/progression."

Streck tube:

a. Draw 10mL peripheral blood into each of 4 vacutainers (2 vacutainers on C1D15 and C2D1) for plasma and buffy coat. Gently invert 8-10 times.
b. Ship at ambient temperature the day of collection.

E. Shipping Procedures

The tissue and blood specimens are to be shipped at ambient temperature (use a cool pack in warm weather). The Rave-generated shipping manifest must accompany the samples.

Ship to:

MD Anderson Cancer Center CTO TQL
ATTN: For ComboMATCH Clinical Trial
1515 Holcombe Blvd.
G1.3598
Houston, TX 77030

Phone: Toll Free 844-744-2420 (713-745-4901 Local or International Sites)
Fax: 713-745-4925

F. Precision Medicine Specimen Tracking Manifest Form and Pathology Group Form

Once the Rave-based Forms become available, it is required (barring special circumstances) that all samples submitted on this trial be entered and tracked in the Screening Instance of Rave. A Rave-generated shipping manifest must be generated and shipped with all sample submissions. Additionally, a Pathology Group Form should be completed for submitted tissue reviewed by a local pathologist.

Please direct your questions or comments pertaining to the specimen tracking system to combo-match-support@nih.gov or https://service.cancer.gov/ComboMATCH.

If Rave is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the Rave generated shipping manifest (see the CTSU website). Additionally, the paper version of the Pathology Group Form should also be completed (see the CTSU website). The completed forms are to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate lab on the submission form:

MD Anderson Cancer Center CTO TQL: 713-745-4925

Retroactively enter all specimen collection and shipping information when Rave is available.

G. Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via Rave/CSMS and receipt verified by the receiving laboratory. Sites will be contacted by the receiving laboratory or ComboMATCH Help Desk if usability issues arise. Inventories of specimens forwarded and utilized for the study will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

APPENDIX E
MEDICATION DIARY

Protocol: EAY191-N2/Cohort 1, Treatment Regimen 1 or Cohort 2 **Page 1**
Study Medication: Binimetinib

Prescribed dose: (insert number) tablets (**15 mg** each) orally twice each day

- Please record information daily.
- Take binimetinib in the morning and evening (with or without food) approximately 12 hours apart.
- Tablets should be swallowed whole.
- If a dose of binimetinib is missed, take it if there is > 6 hours until the next dose. If it is within 6 hours of the next scheduled dose, skip this dose and take the next dose at the scheduled time. Do not make up for the missed doses.
- If a dose is vomited, skip the dose. Take the next dose at the scheduled time.
- Please remember to bring this diary (all pages) and your binimetinib containers (even if they are empty) to each visit with your study team.

Cycle 1 (Start binimetinib on Day15)	**Date**	**Time taken/Dose**		**Notes Include any side effects that you are having.**
		AM/dose	**PM/dose**	
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's name: _____

Physician's office will complete this section:

Total number of binimetinib 15 mg tablets taken this reporting period: _____

Research Staff Signature: _____ Date: _____

Protocol: EAY191-N2/Cohort 1, Treatment Regimen 1 or Cohort 2 **Page 1**
Study Medication: Binimetinib

Prescribed dose: *(insert number)* tablets (15 mg each) orally twice each day

- Please record information daily.
- Take binimetinib in the morning and evening (with or without food) approximately 12 hours apart.
- Tablets should be swallowed whole.
- If a dose of binimetinib is missed, take it if there is > 6 hours until the next dose. If it is within 6 hours of the next scheduled dose, skip this dose and take the next dose at the scheduled time. Do not make up for the missed doses.
- If a dose is vomited, skip the dose. Take the next dose at the scheduled time.
- Please remember to bring this diary (all pages) and your binimetinib containers (even if they are empty) to each visit with your study team.

Cycle *(insert cycle #)* Day	**Date**	**Time taken/dose**		**Notes Include any side effects that you are having.**
		AM/dose	**PM/dose**	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				

Protocol: EAY191-N2/Cohort 1, Treatment Regimen 1 or Cohort 2 **Page 2** **Study Medication: Binimetinib**				
Cycle ***(insert cycle #)*** **Day**	**Date**	**Time taken/dose**		**Notes** **Include any side effects that you are having.**
		AM/dose	**PM/dose**	
20				
21				
22				
23				
24				
25				
26				
27				
28				

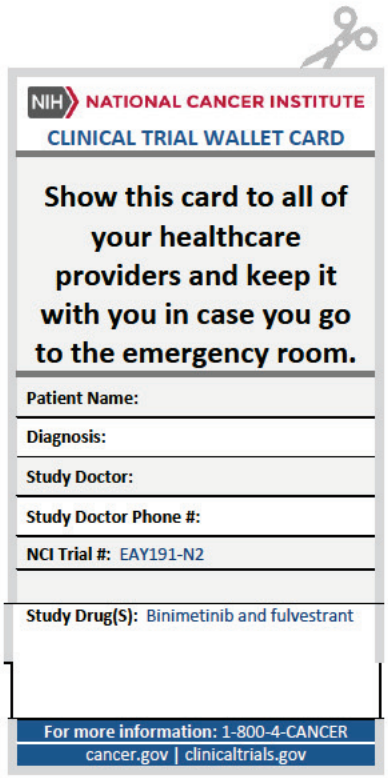
Patient's name: _____

Physician's office will complete this section:

Total number of binimetinib 15 mg tablets taken this reporting period: _____

Research Staff Signature: _____Date: _____

APPENDIX F
PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: EAY191-N2

Study Drug(S): Binimetinib and fulvestrant

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov