Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

Fast Facts

A ComboMATCH Treatment Trial
EAY191-N2: PHASE 2 TRIAL OF FULVESTRANT AND BINIMETINIB IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE METASTATIC BREAST CANCER WITH A FRAMESHIFT OR NONSENSE MUTATION OR GENOMIC DELETION IN NF1

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 CoordinatingDepartment (CCD).

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

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

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 numberand allele frequency cutoff as per the Registration Protocol.

2. Patients must have disease that can be safely biopsied and agree to a pre-treatment biopsyor, 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. 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 permittingrelease of personal health information.
4. Age ≥ 18.
5. ECOG performance status 0-2 (see Appendix A).
6. Histologically or cytologically confirmed invasive breast carcinoma.
7. Confirmed metastatic disease by either imaging or tissue diagnosis.
8. Measurable disease by RECIST 1.1 and one additional lesion that can be biopsied(primary, metastatic both allowed).

9. Patients must have inactivating or inferred inactivating NF1 alterations detected in tumor as determined by the ComboMATCH screening assessment.
10. The tumor must have been determined to be ER and/or PgR positive assessed by currentASCO/CAP Guideline Recommendations for hormone receptor testing. Patients with ≥ 1% ER or PgR staining by IHC are considered positive.
11. The tumor must have been determined to be HER2-negative by current ASCO/CAPguidelines.
12. Prior therapy:
    - Prior use of CDK4/6i is required.
    - Prior use of fulvestrant regardless of duration.is allowed and will determine treatmentassignment.
    - Up to one line of chemotherapy in metastatic setting is allowed.
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
14. Adequate renal function defined as:

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

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

15. Adequate hepatic function defined as follows:
    - Total bilirubin level ≤ institutional upper limit of normal.
    - AST and ALT must be ≤ 5.0 x ULN.
16. For patients who will be assigned to Cohort 2 (fulvestrant-resistant), 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 besubstituted based on institutional/situational preferences.)
17. Patients with a prior or concurrent malignancy whose natural history or treatment doesnot have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
18. HIV-infected patients on effective anti-retroviral therapy with undetectable viral loadwithin 6 months of registration are eligible for this trial.

Ineligibility Criteria

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

1. Concurrent anticancer therapy.
2. Active autoimmune disease requiring systemic treatment within the past 3 months, documented history of clinically severe autoimmune disease, or a syndrome that requiressystemic steroids or immunosuppressive agents.
3. Active brain metastasis. Brain metastases that have been stable for at least 1 month after completion of treatment are not an exclusion criterion.
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.
5. Patients will be excluded if they currently have the following risk factors for RVO thatare 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.

6. Cardiac history:

- Patients with baseline QTc > 500 ms, either induced by medication or congenital longQT 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 cardiacfunction using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

7. Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ Grade 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 ofthe results or render the patient at high risk from treatment complications.
9. Other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interferewith interpretation of study results.
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 ofchildbearing potential.)***

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

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

Eligibility Criteria for Cohort 1, Treatment Regimen 2 Patients who Transition toCohort 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.

1. Patient's willingness to migrate to Cohort 2 affirmed.
2. The patient must have an ECOG performance status of 0-2 (see Appendix A).
3. Adequate hematologic function defined as follows:
    - Absolute neutrophil count ≥ 1,500/mm3
    - Platelet count ≥ 100,000/ mm3
    - Hemoglobin level ≥ 10 g/dL

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.

5. Adequate renal function defined as:

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

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

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.).

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

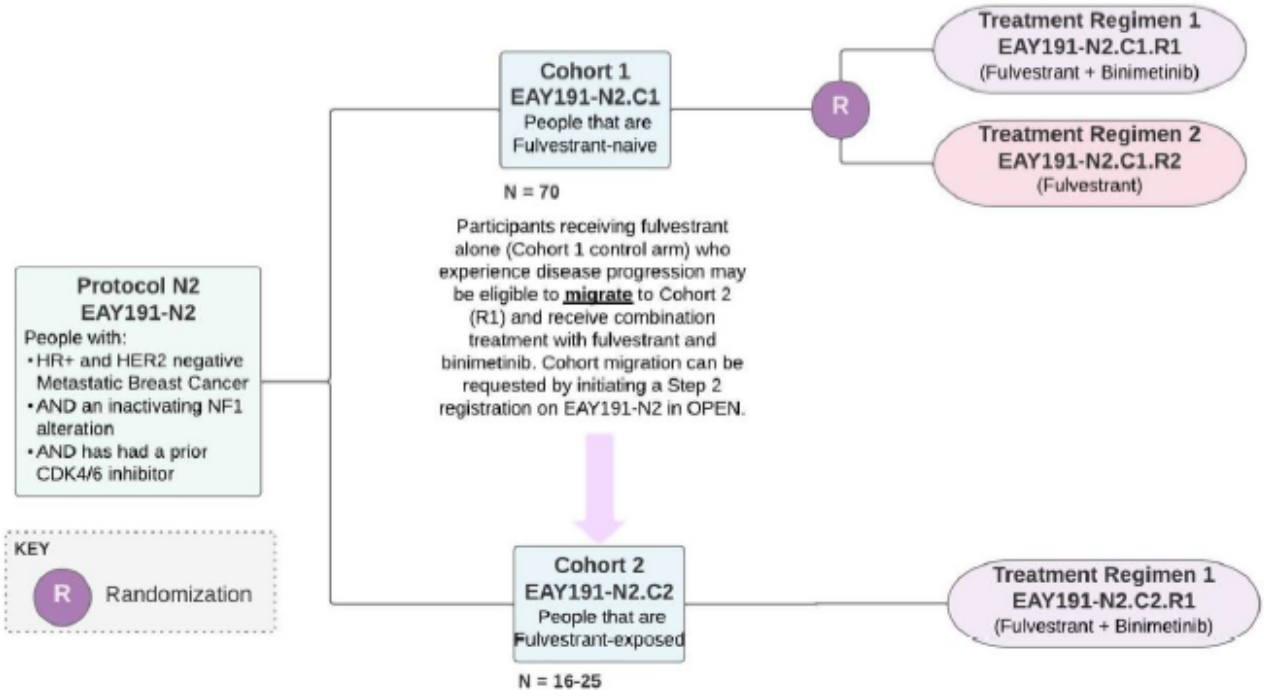
Ineligibility Criteria for Cohort 1, Treatment Regimen 2 Patients who Migrate to Cohort 2

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

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.

A ComboMATCH Treatment Trial EAY191-N2 SCHEMA



For Cohort 1, randomization is 1:1.

Table of Abbreviations

NF1	Neurofibromin type 1