BRE038 (Inclusion Criteria)

Inclusion Criteria:

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Women or men ≥18 years of age at time of signing Informed Consent Form
- If female, patients must meet at least one of the following definitions:

o Postmenopausal, as defined by at least one of the following criteria:

- Age ≥ 60 years
- Age < 60 years and 12 months of amenorrhea plus follicle-stimulating hormone and plasma estradiol levels within postmenopausal range by local laboratory assessment in the absence of oral contraceptive pills, hormone replacement therapy, or gonadotropin-releasing hormone agonist or antagonist
- Documented bilateral oophorectomy (≥ 14 days prior to first treatment on Day 1 of Cycle 1 and recovery to baseline)

o Premenopausal or perimenopausal (i.e., not meeting the criteria for postmenopausal) and meeting the following criterion:

- Treatment with luteinizing hormone-releasing hormone (LHRH) agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment

- If male, recommendation of treatment with LHRH agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- Histologically or cytologically confirmed adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or radiation therapy with curative intent
- Documented ER-positive and/or progesterone receptor-positive tumor according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, defined as ≥ 1% of tumor cells stained positive based on the most recent tumor biopsy and assessed locally

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- Documented HER2-negative tumor according to ASCO/CAP guidelines, defined as a HER2 immunohistochemistry (IHC) score of 0 or 1+, or an IHC score of 2+ accompanied by a negative fluorescence, chromogenic, or silver in situ hybridization

test indicating the absence of HER2 gene amplification, or a HER2/CEP17 ratio of < 2.0 based on the most recent tumor biopsy and assessed locally

- Confirmation of biomarker eligibility: valid results from either central testing of blood or local testing of blood or tumor tissue documenting PIK3CA-mutant tumor status

Eligible PIK3CA mutations are defined as follows:

H1047D/I/L/N/P/Q/R/T/Y G1049A/C/D/R/S

E545A/D/G/K/L/Q/R/V E453A/D/G/K/Q/V

E542A/D/G/K/Q/R/V K111N/R/E

Q546E/H/K/L/P/R G106A/D/R/S/V

N345D/H/I/K/S/T/Y G118D

C420R R88Q

M1043I/T/V

The central test for identification of eligible PIK3CA mutations is the FoundationOne Liquid Clinical Trial Assay performed at Foundation Medicine, Inc.

All patients are required to submit a freshly collected pre-treatment blood sample, whether patients are enrolled by local or central test results.

Local tests of blood or tumor tissue may only be performed using a Sponsor pre-approved PCR- or NGS-based assay at a CLIA-certified or equivalent laboratory. The full laboratory report of the PIK3CA mutation result must be available and submitted for confirmation.

o Local test results reported from blood should be from a blood specimen representative of patient's metastatic disease state, collected after conclusion of patient's most recent anti-cancer therapy.

o Local test results reported from tumor tissue should be from the patient's metastatic disease state whenever possible.

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- Consent to provide fresh (preferred) or archival tumor tissue specimen. It is preferred that the specimen be from the most recently collected and available tumor tissue, and whenever possible, from a metastatic site of disease. See the laboratory

manual for specimen requirements.

- Patients must have progressed during adjuvant endocrine treatment or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen

  o If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, progression event must be > 12 months since completion of CDK4/6 inhibitor portion of neoadjuvant or adjuvant therapy.

- Measurable disease per RECIST v1.1

  o Patients with bone-only disease are not eligible, even if a bone lesion qualifies as a measurable lesion.

- Treatment with endocrine-based therapy (e.g., palbociclib and fulvestrant) is recommended at time of entry into the study, as per national or local treatment guidelines

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 60 days after the final dose of study treatment. Based on local prescribing information for

fulvestrant, patients may be advised to use an effective means of contraception for up to 1 year after the final dose of fulvestrant. Women must refrain from donating eggs during this same period.

  o A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator

(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

o Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

o The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

o With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 98 days after the final dose of study treatment to avoid exposing the embryo. Based on local prescribing information for fulvestrant, patients may be advised to use an effective means of contraception for up to 1 year after the final dose of fulvestrant. Men must refrain from donating sperm during this same period.

o The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

- ECOG Performance Status of 0 or 1
- Life expectancy of > 6 months
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, defined by the following:

- Absolute neutrophil count ≥ 1500/µL
- Hemoglobin ≥ 9 g/dL
- Platelet count ≥ 100,000/µL
- Fasting glucose <126 mg/dL or < 7.0 mmol/L and HbA1c < 5.7%

o For patients with fasting glucose ≥ 100 mg/dL or ≥ 5.5 mmol/L (i.e., threshold for pre-diabetes) at baseline, recommend lifestyle changes according to American Diabetes Association guidelines; that is, dietary advice (e.g., small frequent meals, low carbohydrate content, high fiber, balanced carbohydrate intake over the course of the day, three small meals and two small snacks rather than one large meal) and exercise. Consultation with an endocrinologist or diabetologist is highly

recommended.

- Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (< 3 × ULN if Gilbert's disease)
- Serum albumin ≥ 2.5 g/dL or 25 g/L
- AST and ALT ≤ 2.5 × ULN with the following exception:

  o Patients with documented liver metastases may have AST and/or ALT ≤ 5.0 × ULN
- ALP ≤ 2.5 × ULN with the following exception:

  o Patients with documented liver or bone metastases may have ALP ≤ 5.0 × ULN
- Creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft−Gault glomerular filtration rate estimation
- INR < 1.5 × ULN and aPTT < 1.5 × ULN

o For patients requiring anticoagulation therapy with warfarin, a stable INR between 2 and 3 is required. If anticoagulation is required for a prosthetic heart valve, then stable INR between 2.5 and 3.5 is permitted. Consult the local prescribing information for fulvestrant.

- Ability, in the investigator's judgment, and willingness to comply with all study-related procedures, including completion of patient-reported endpoints