BRE038 (Exclusion Criteria)

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from study entry:

- Metaplastic breast cancer
- Any history of leptomeningeal disease or carcinomatous meningitis
- Any prior systemic therapy for metastatic breast cancer
- Prior treatment with fulvestrant or any selective estrogen-receptor degrader
- Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action is to inhibit the PI3K-AKT-mTOR pathway
- Appropriate for treatment with cytotoxic chemotherapy at time of entry into the study, as per national or local treatment guidelines (e.g., patients with visceral crisis)
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following

criteria:

- Measurable disease outside the CNS
- No ongoing requirement for corticosteroids as therapy for CNS metastases, with corticosteroids discontinued for ≥ 2 weeks prior to enrollment and no ongoing symptoms attributed to CNS metastases
- Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic assessments
- Screening CNS radiographic assessments ≥ 4 weeks since completion of radiotherapy
- No history of intracranial hemorrhage or spinal cord hemorrhage

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently

  o Indwelling pleural or abdominal catheters may be allowed, provided the patient has adequately recovered from the procedure, is hemodynamically stable and symptomatically improved, and has prior approval from the Medical Monitor

- Serious infection requiring IV antibiotics within 7 days prior to Day 1 of Cycle 1

- Any concurrent ocular or intraocular condition (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, would require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition

- Active inflammatory (e.g., uveitis or vitritis) or infectious (e.g., conjunctivitis, keratitis, scleritis, or endophthalmitis) conditions in either eye or history of idiopathic or autoimmune-associated uveitis in either eye

- Requirement for daily supplemental oxygen

- Symptomatic active lung disease, including pneumonitis

- History of or active inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)

  o Patients currently receiving immunosuppressants for inflammatory bowel disease (e.g., sulfasalazines) are considered to have active disease and are therefore ineligible.

- Any active bowel inflammation (including diverticulitis)

- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  o Bisphosphonate and denosumab therapy for bone metastases or osteopenia/osteoporosis is allowed.

- Clinically significant and active liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis

- Known HIV infection

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic, or infectious disease) or any other diseases, active or uncontrolled pulmonary dysfunction, 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, that may affect the interpretation of the results, or that renders the patient at high risk from treatment complications

- Chemotherapy, radiotherapy, or any other anti-cancer therapy within 2 weeks before randomization
- Investigational drug(s) within 4 weeks before randomization
- Prior radiotherapy to ≥ 25% of bone marrow, or hematopoietic stem cell or bone marrow transplantation
- Unresolved toxicity from prior therapy, except for hot flashes, alopecia, and Grade ≤ 2 peripheral neuropathy
- History of other malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer
- History of or active clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment
  - History of myocardial infarction within 6 months prior to first dose of study treatment
  - New York Heart Association Class III or IV cardiac disease or congestive heart failure requiring medication
  - Uncontrolled arrhythmias, history of or active ventricular arrhythmia requiring medication
  - Coronary heart disease that is symptomatic or unstable angina
  - Congenital long QT syndrome or QT interval corrected through use of Fridericia's formula > 470 ms demonstrated by at least two ECGs > 30 minutes apart, or family history of sudden unexplained death or long QT syndrome
- Clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

BRE038 (Exclusion Criteria)

- Allergy or hypersensitivity to components of the GDC-0077/placebo, palbociclib, or fulvestrant formulations
- Treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors within 1 week or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Pregnant, lactating, or breastfeeding, or intending to become pregnant during the study or within 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 last dose of fulvestrant)

  o Women of childbearing potential (including those who have had a tubal ligation) must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Major surgical procedure, or significant traumatic injury, within 28 days prior to Day 1 of Cycle 1 or anticipation of the need for major surgery during the course of study treatment
- Minor surgical procedures < 7 days prior to first dose of study treatment

  o Patients must have sufficiently recovered from surgery, including adequate wound healing.