BRE045 Inclusion Criteria

Key Inclusion Criteria:

1. Both males and females
2. Pathologically documented breast cancer that:
    - Is advanced or metastatic
    - Has HER2-low expression (IHC 1+ or IHC 2+/ISH-) as determined by the central laboratory result from the most recently collected pre-randomization tumor sample (see inclusion criterion 3)
    - Was never previously reported as HER2-positive (IHC 3+ or ISH+) as per ASCO/CAP guidelines.
    - Is documented as HR+ (either ER and/or PgR positive [ER or PgR ≥1%]) per ASCO/CAP guidelines (Allison et al 2020). If a subject has had multiple ER/PgR results after metastatic disease, the most recent test result will be used to confirm eligibility.
3. Must have an adequate tumor tissue sample available for assessment of HER2 by central laboratory, preferably in FFPE blocks based on a mandatory FFPE tumor sample obtained at the time of metastatic disease or later*; the most recently collected pre-randomization tumor sample that meets the tissue requirements specified in protocol Section 8.6 is required.* If no archival specimens are available, a newly acquired biopsy specimen is acceptable. (See Section 8.6 and the laboratory manual for additional details).
4. ECOG performance status of 0 or 1
5. Must have had either:
    - Disease progression on endocrine therapy + CDK4/6 inhibitor within 6 months of starting first line treatment for metastatic disease and considered appropriate for chemotherapy as the next treatment by the investigator, OR
    - Disease progression on at least 2 previous lines of ET with or without a targeted therapy (such as CDK4/6, mTOR or PI3-K inhibitors) administered for the treatment of metastatic disease.

      Of note with regards to the ≥2 lines of previous ET requirement:

        - ✓ Single agent anti-CDK4/6 therapy for the treatment of metastatic disease is considered a line of therapy

- ✓ Disease progression on adjuvant ET or progression within 12 months of stopping ET can be treated as one prior line ET; these subjects will only require 1 additional line of ET in the metastatic setting
- ✓ Any progression >12 months after discontinuing adjuvant ET or completing a course of adjuvant ET will not be considered a line of therapy
- ✓ Single agent PARP inhibitor therapy is not considered a line of ET
- ✓ Changes in dosing schedules, or discontinuations/re-starting of the same drugs or the addition of a targeted therapy to an ET without progression (e.g., adding a CDK4/6 to a current aromatase inhibitor regimen) will not be considered separate lines of therapy.

6. No prior chemotherapy for advanced or metastatic breast cancer. Subjects who have received chemotherapy in the neo-adjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval (defined as completion of systemic chemotherapy to diagnosis of advanced or metastatic disease) of >12 months.
7. Subjects must have at least one measurable lesion as defined per RECIST v1.1 or have non-measurable, bone-only disease that can be assessed by CT or MRI or X-Ray. Lytic or mixed lytic bone lesions that can be assessed by CT or MRI or X-Ray in the absence of measurable disease as defined above is acceptable; subjects with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible.
8. Has LVEF ≥ 50% by either echocardiography (ECHO) or multiple-gated acquisition (MUGA) within 28 days before randomization.
9. Adequate organ and bone marrow function within 14 days before randomization. The most recent results available must be used to meet the inclusion criteria. No EPO, G-CSF, GM-CSF within 14 days and RBC, platelet transfusion within 7 days prior to the sampling
10. Has adequate treatment washout period before randomization