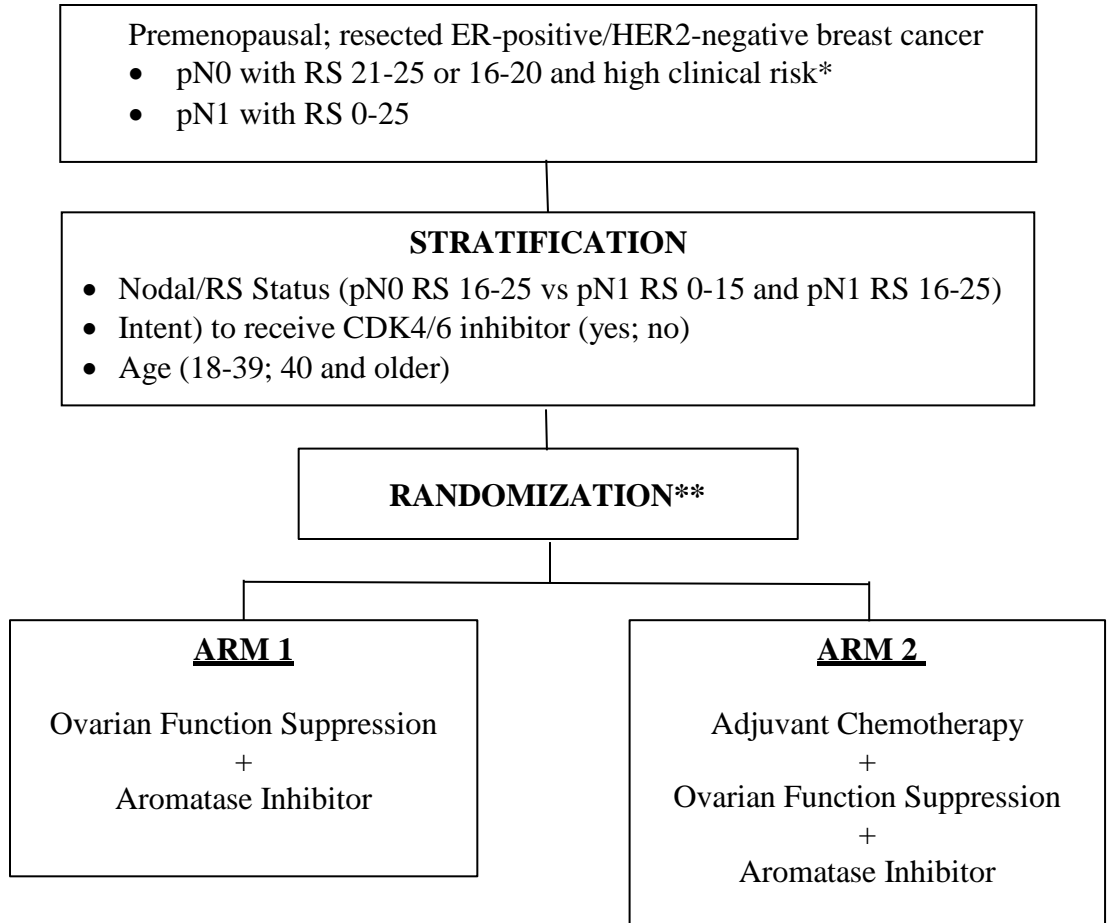


Figure 1. NRG-BR009 Schema



* **High clinical risk defined as:**

- 1) low histologic grade with primary tumor size > 3 cm, OR
- 2) intermediate histologic grade with primary tumor size > 2 cm, OR
- 3) high histologic grade with primary tumor size > 1 cm

** Randomization is 1:1.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD [see protocol cover page]).

3.1 Patient Pre-Entry and Randomization

For the NRG-BR009 study, patients who meet eligibility based on a “Low Risk” or “MPI” result on MammaPrint® testing must have an Oncotype DX Recurrence Score® assay done. A tissue sample must be sent to Genomic Health for a Recurrence Score (RS) to determine eligibility, and the result must fall into categories required for the Recurrence Score. For these patients, Genomic Health will cover the cost of the additional test. *If MammaPrint High Risk or MP2, these patients are not eligible.*

3.1.1 Step 1/Pre-entry (*ALL patients*)

- Step 1: *All patients must be registered in NRG-BR009 before being randomized.*
- The authorized site staff must obtain a signed **consent form** from potential patients before any study-specific procedures are performed.
- The authorized site staff must determine patient eligibility prior to Step 1/Pre-entry, (except for an Oncotype Recurrence Score for patients who meet eligibility based on a MammaPrint result). See [Sections 3.2](#) and [3.3](#).
- During registration in OPEN, patients will be assigned a unique patient identifier which will be used to identify the sample to be sent for central Oncotype DX Recurrence Score testing (only required for those patients who meet eligibility based on a MammaPrint result and need to have an Oncotype Recurrence Score to be eligible), the eCRFs in Medidata RAVE, and any other trial-related communications. See [Section 10](#) and the NRG-BR009 Pathology and Correlative Science Instructions for ordering the Oncotype DX Recurrence Score test kit. *An Oncotype DX RS must be performed on core biopsy specimen obtained prior to initiation of neoadjuvant endocrine therapy if received.*
- If a patient has a MammaPrint assay result, the patient must meet all BR009 eligibility criteria to be eligible for the study.

3.1.2 Step 2 Study Entry/Randomization (*ALL patients*)

- Step 2: The authorized site staff will randomize the patient using OPEN.
- OPEN will randomly assign treatment to Arm 1 or Arm 2.

3.2 Eligibility Criteria

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

3.2.1 The patient or a legally authorized representative must provide study-specific informed

consent prior to pre-entry and, for patients treated in the U.S., authorization permitting release of personal health information.

- 3.2.2** Female patients must be ≥ 18 years of age.
- 3.2.3** Patients must be premenopausal (evidence of functioning ovaries) at the time of pre-entry. For study purposes, premenopausal is defined as:
- Age 50 years or under with spontaneous menses within 12 months; *or*
 - Age > 50-60 years with spontaneous menses within 12 months plus follicle-stimulating hormone (FSH) **and** estradiol levels in the premenopausal range; *or*
 - Patients with amenorrhea due to IUD or prior uterine ablation must have FSH **and** estradiol levels in the premenopausal range; *or*
 - Patients with prior hysterectomy must have FSH **and** estradiol levels in the premenopausal range.
- 3.2.4** The patient must have an ECOG performance status of ≤ 2 (or Karnofsky $\geq 60\%$).
- 3.2.5** Patients may have ipsilateral or contralateral synchronous breast cancer if the highest stage tumor meets entry criteria, and the other sites of disease would not require chemotherapy or HER2-directed therapy.
- 3.2.6** Patients may have multicentric or multifocal breast cancer if the highest stage tumor meets entry criteria, and the other sites of disease would not require chemotherapy or HER2-directed therapy.
- 3.2.7** Patient may have undergone a total mastectomy, skin-sparing mastectomy, nipple-sparing mastectomy, or a lumpectomy.
- 3.2.8** For patients who undergo a lumpectomy, the margins of the resected specimen or re-excision must be histologically free of invasive tumor and DCIS with no ink on tumor as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional excisions may be performed to obtain clear margins. Positive posterior margin is allowed if surgeon deems no further resection possible. (Patients with margins positive for LCIS are eligible without additional resection.)
- 3.2.9** For patients who undergo mastectomy, the margins must be free of residual gross tumor. (Patients with microscopic positive margins are eligible if post-mastectomy RT of the chest wall will be administered.)
- 3.2.10** Patient must have undergone axillary staging with sentinel node biopsy (SNB), targeted axillary dissection (TAD), or axillary lymph node dissection (ALND).
- 3.2.11** The following staging criteria must be met postoperatively according to AJCC 8th edition criteria:
- By pathologic evaluation, primary tumor must be pT1-3. (If N0, must be T1c or higher.)
 - By pathologic evaluation, ipsilateral nodes must be pN0 or pN1 (pN1mi, pN1a, pN1b, pN1c).
 - Patients with positive isolated tumor cells (ITCs) in axillary nodes will be considered N0 for eligibility purposes.

- Patients with micrometastatic nodal involvement (0.2-2 mm) will be considered N1.

3.2.12 Oncotype DX RS requirements*:

- If node-negative:
 - Oncotype DX RS must be RS 21-25, *or*
 - Oncotype DX RS must be 16-20 and disease must be high clinical risk, defined as: low histologic grade with primary tumor size > 3 cm, intermediate histologic grade with primary tumor size > 2 cm, or high histologic grade with primary tumor size > 1 cm.
- If 1-3 nodes involved:
 - Oncotype DX RS must be < 26.

* Patients with a “Low Risk” or “MP1” *MammaPrint result* must have eligibility assessed with an Oncotype DX RS at pre-entry (see [Section 3.1](#)). Blocks or unstained slides must be sent to the Genomic Health centralized laboratory for testing at no cost to these patients. ***If MammaPrint High Risk or MP2, these patients are not eligible.***

3.2.13 The tumor must be ER and/or PgR-positive by current ASCO/CAP guidelines based on local testing results. Patients with $\geq 1\%$ ER and/or PgR staining by IHC will be classified as positive.

3.2.14 The tumor must be HER2-negative by current ASCO/CAP guidelines based on local testing results.

3.2.15 The interval between the last surgery for breast cancer (including re-excision of margins) and pre-entry must be no more than 16 weeks.

3.2.16 Short course of endocrine therapy of less than 6 weeks duration before pre-entry is acceptable either as neoadjuvant or adjuvant therapy. An Oncotype DX RS must be performed on core biopsy specimen obtained prior to initiation of neoadjuvant endocrine therapy if received.

3.2.17 Patients with a prior or concurrent non-breast 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. This would include prior cancers treated with curative intent.

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

3.2.19 Radiation therapy should be used according to standard guidelines; the intended radiation therapy should be declared prior to pre-entry.

3.3 Ineligibility Criteria

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

3.3.1 Definitive clinical or radiologic evidence of metastatic disease.

3.3.2 pT4 tumors, including inflammatory breast cancer.

3.3.3 History of ipsilateral or contralateral invasive breast cancer. (Patients with synchronous

and/or previous DCIS or LCIS are eligible.)

- If prior ipsilateral DCIS was treated with lumpectomy and XRT, a mastectomy must have been performed for the current cancer.
- 3.3.4** Life expectancy of < 10 years due to co-morbid conditions in the opinion of the investigator.
- 3.3.5** Known results from most recent lab studies obtained as part of routine care prior to study entry showing **ANY** of the following values:
- ANC < 1200/mm³;
 - Platelet count < 100,000/mm³;
 - Hemoglobin < 10 g/dL;
 - Total bilirubin > ULN for the lab or > 1.5 x ULN for patients who have a bilirubin elevation due to Gilbert's disease or similar syndrome involving slow conjugation of bilirubin;
 - AST(SGOT)/ALT(SGPT): > 3 × institutional ULN;
 - Renal function of GFR < 30 mL/min/1.73m².
- 3.3.6** 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.
- 3.3.7** Non-epithelial breast malignancies such as sarcoma or lymphoma.
- 3.3.8** Any treatment with radiation therapy, chemotherapy, or biotherapy administered for the currently diagnosed breast cancer prior to pre-entry. (Patients with prior ET of more than 6 weeks duration for treatment of this cancer are not eligible.) Prior tamoxifen given for breast cancer prevention is allowed. Prior AI or GnRH for fertility preservation is allowed.
- 3.3.9** Hormonally based contraceptive measures must be discontinued prior to pre-entry (including progestin/progesterone IUDs).
- 3.3.10** Patients with evidence of chronic hepatitis B virus (HBV) infection are ineligible unless the HBV viral load is undetectable on suppressive therapy. Patients with a history of hepatitis C virus (HCV) infection are ineligible unless they have been treated and cured or have an undetectable HCV viral load if still on active therapy.
- 3.3.11** Pregnancy or lactation at the time of pre-entry. (*Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 2 weeks prior to pre-entry.*)
- 3.3.12** 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.