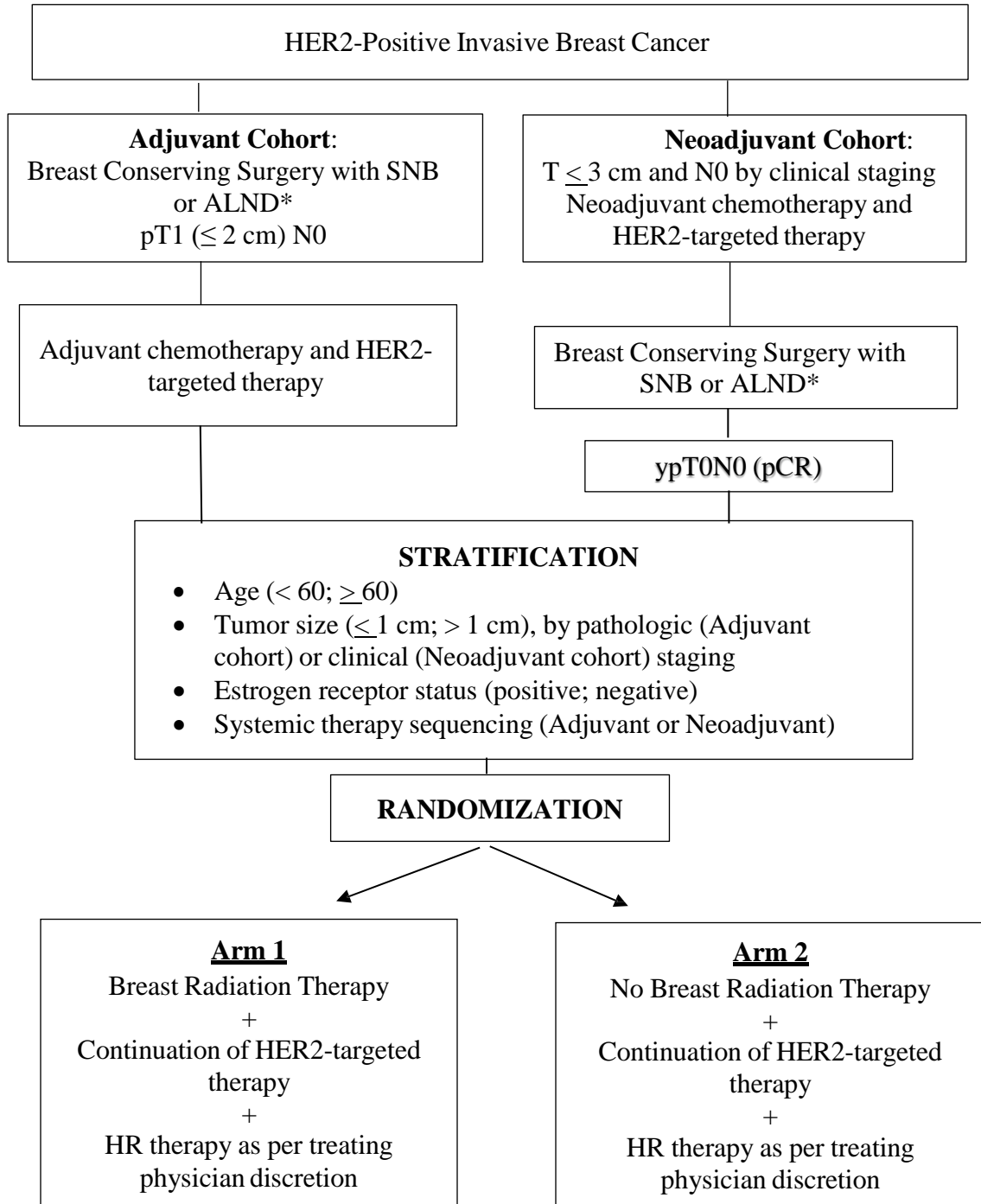


**Figure 1.  
NRG-BR008 SCHEMA**



\*Sentinel node biopsy (SNB) or axillary lymph node dissection (ALND)

### 3. 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 Coordinating Department (CCD).

#### On Study Guidelines:

- Assessment of cardiac function by echocardiogram or MUGA scan should occur within 12 months prior to randomization per the standard of care for HER2-directed agents.
- In patients assigned to radiation therapy, treatment should start  $\leq 12$  weeks from surgery on the Neoadjuvant cohort and  $\leq 8$  weeks from the completion of chemotherapy on the Adjuvant cohort. Patients should continue HER2-targeted therapy during assigned study treatment (radiation or observation).

#### 3.1 Eligibility Criteria

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

- 3.1.1** 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 permitting release of personal health information.
- 3.1.2** The trial is open to female and male patients who have undergone **breast conserving surgery** and completed a **minimum of 4 cycles (12 weeks) of neoadjuvant or adjuvant chemotherapy** in combination with HER2-targeted therapy.
- 3.1.3** The patient must be  $\geq 40$  years of age.
- 3.1.4** The patient must have an ECOG performance status of 0, 1, or 2/Karnofsky performance status above 60. (See [Appendix A](#)).
- 3.1.5** Histologically or cytologically confirmed invasive breast carcinoma.
- 3.1.6** The tumor must have been determined to be HER2-positive by current ASCO/CAP guidelines based on local testing results.
- 3.1.7** The tumor must have ER and PgR status assessed locally using current ASCO/CAP Guidelines.
- 3.1.8** Patient must have undergone axillary staging, either sentinel node biopsy (SNB) or axillary lymph nodal dissection (ALND). In neoadjuvant patients, SNB following neoadjuvant therapy is strongly recommended. SNB prior to neoadjuvant therapy is discouraged, but patients are permitted if node negative (pN0).
- 3.1.9** The following staging criteria must be met according to AJCC 8<sup>th</sup> edition criteria:  
Adjuvant cohort
- By pathologic evaluation, the patient's primary tumor must be  $\leq 2$  cm and ipsilateral nodes must be pN0. Surgical lumpectomy margins must be negative for invasive cancer and ductal carcinoma in situ (no ink on tumor).

### Neoadjuvant cohort

- Prior to neoadjuvant therapy, the patient's primary tumor must be  $\leq 3$  cm by imaging studies, with negative axillary nodes (cN0) based on axillary U/S, CT, PET or MRI. Physical examination is not sufficient documentation of cN0 status.
  - Must be ypT0N0 at surgery (lumpectomy); patients with residual non-invasive disease (DCIS) in the surgical specimen (ypTis), are NOT eligible.
- 3.1.10** For the Adjuvant cohort, adjuvant therapy must have consisted of a minimum of 4 cycles (12 weeks) of chemotherapy in combination with HER2-targeted therapy.
- 3.1.11** For the Neoadjuvant cohort, neoadjuvant therapy must have consisted of a minimum of 4 cycles (12 weeks) of chemotherapy in combination with HER2-targeted therapy.
- Patients who did not receive chemotherapy in the neoadjuvant setting are not eligible, even if they achieved pCR with their preoperative treatment; nor would these patients become eligible by receiving chemotherapy after surgery.
- 3.1.12** In patients assigned to radiation therapy, treatment should start  $\leq 12$  weeks from surgery on the Neoadjuvant cohort and  $\leq 8$  weeks from the completion of chemotherapy on the Adjuvant cohort. Patients should continue HER2-targeted therapy during assigned study treatment (radiation or observation).
- 3.1.13** Bilateral mammogram or MRI within 52 weeks prior to randomization.
- 3.1.14** HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of randomization are eligible for this trial.

### **3.2 Ineligibility Criteria**

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

- 3.2.1** Definitive clinical or radiologic evidence of metastatic disease.
- 3.2.2** On the Adjuvant cohort, patients with a primary tumor  $>2$  cm on pathologic examination of the surgical specimen. On the Neoadjuvant cohort, patients with a primary tumor  $> 3$  cm or with abnormal or suspicious ipsilateral axillary nodes by pretreatment imaging, unless demonstrated to be negative by cytologic or histologic examination.
- 3.2.3** Pathologically positive axillary nodes at any time including of pN0<sub>(i+)</sub> or pN0<sub>(mol+)</sub> ypN0<sub>(i+)</sub> or ypN0<sub>(mol+)</sub> disease.
- 3.2.4** Patient planning for or status-post mastectomy.
- 3.2.5** Radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes, unless there is histological confirmation that these nodes are negative for metastatic disease.
- 3.2.6** Suspicious microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast), or mass or non-mass enhancement on MRI (if performed) aside from the known cancer, unless biopsied and found to be benign.
- 3.2.7** Non-epithelial breast malignancies such as sarcoma or lymphoma.
- 3.2.8** Multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by  $\geq 4$  centimeters. If multifocal, all foci should be confined to a maximum tumor bed of 3 cm determined by pathological assessment.

- 3.2.9 Paget's disease of the nipple.
- 3.2.10 Synchronous (unilateral or bilateral) invasive breast cancer or DCIS. (Patients with synchronous and/or previous contralateral LCIS are eligible.)
- 3.2.11 On the Adjuvant cohort, surgical margins that cannot be microscopically assessed or are positive at pathologic evaluation. (If surgical margins are rendered free of disease by re-excision, the patient is eligible).
- 3.2.12 Treatment plan that includes regional nodal irradiation.
- 3.2.13 Prior ipsilateral breast or thoracic RT for any condition (contralateral RT for DCIS  $\geq$  10 years prior to randomization is permitted).
- 3.2.14 Patients treated for a prior invasive breast malignancy are excluded. Contralateral DCIS  $\geq$  10 years prior to enrollment is permissible.
- 3.2.15 Patients with a prior or concurrent 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.
- 3.2.16 Patients on oral, transdermal, or subdermal estrogen replacement (including all estrogen only and estrogen-progesterone formulas) are not eligible unless discontinued prior to randomization.
- 3.2.17 Active collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active systemic lupus erythematosus, or scleroderma.
- 3.2.18 Clinicians should consider whether any conditions would make this protocol unreasonably hazardous for the patient.
- 3.2.19 Pregnancy or lactation at the time of randomization or intention to become pregnant during treatment. (*Note: Pregnancy testing according to institutional standards for patients of childbearing potential must be performed within 14 days prior to randomization.*)
- 3.2.20 Use of any investigational product within 30 days prior to randomization.

### 3.3 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>.