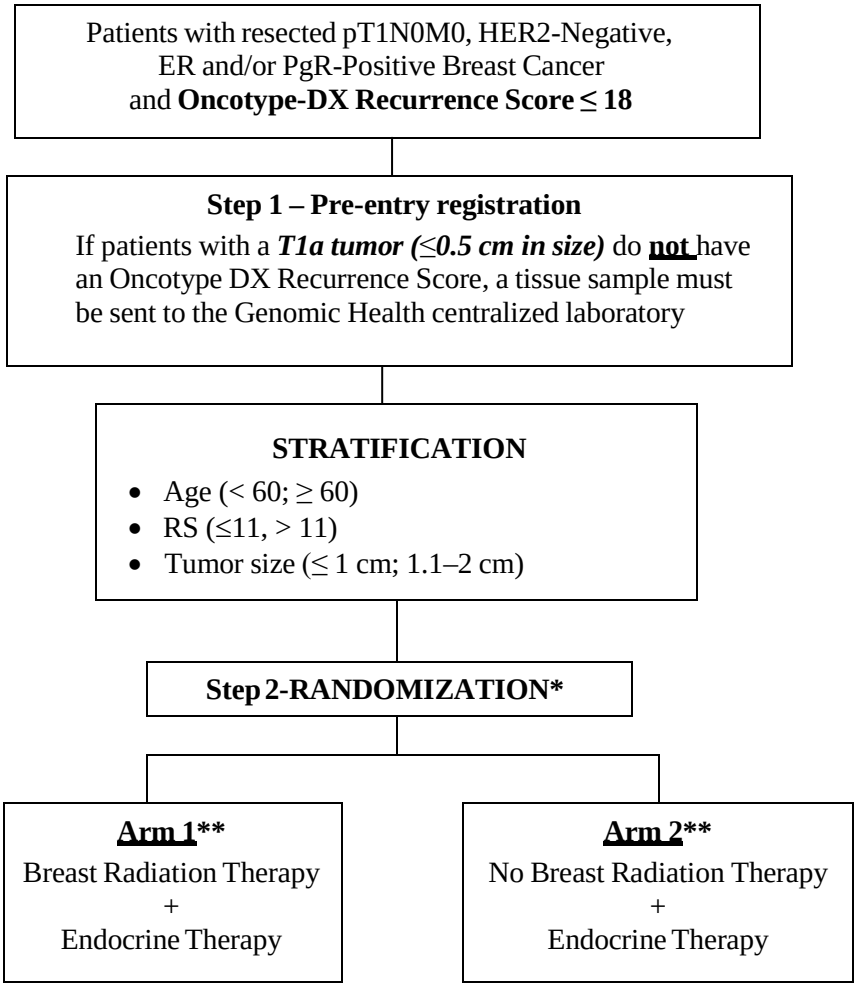
Figure 1.
NRG-BR007 SCHEMA



* Randomization is 1:1.
** See Section 5.0 for radiation therapy and endocrine therapy information.

3.1 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]). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.2 Patient Pre-Entry and Randomization

For the NRG-BR007 study, patients with a ***T1a tumor (≤0.5 cm in size)*** who do **not** have an Oncotype DX Recurrence Score must have a tissue sample sent to Genomic Health for a Recurrence Score to determine eligibility. For these patients, Genomic Health will cover the cost of the test.

3.2.1 Pre-Entry *(ALL patients)*

- Step 1: ***All patients will have to be registered in NRG-BR007 before being randomized.***
- The authorized site staff must obtain a signed **consent form** from the potential patients before any study specific procedures are performed.
- The authorized site staff must determine patient eligibility. See Sections 3.2 and 3.3.
- During Pre-Entry 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 (for patients with a ***T1a tumor (≤0.5 cm in size)*** who have not had a Recurrence Score), the eCRFs in Medidata RAVE, and any other trial-related communications. See Section 10.0 and the NRG-BR007 Pathology and Correlative Science Instructions for ordering the Oncotype DX Recurrence Score test.
- Patients who already have a Recurrence Score result of ≤ 18, will be registered in Step 1 and go straight to randomization in Step 2.
- When a Recurrence Score result of ≤ 18 is received on central testing for patients with a ***T1a tumor (≤ 0.5 cm in size)***, the patient should be randomized. Patients who do **not** have a Recurrence Score result of ≤ 18 by central testing will not be randomized, will be treated per investigator discretion, and will not be followed on BR007.

3.2.2 Randomization (*ALL patients*)

- Step 2: If a patient meets all eligibility requirements, the authorized site staff will randomize the patient using OPEN.
- OPEN will randomly assign treatment (breast radiation therapy + endocrine therapy or no breast radiation + endocrine therapy).

3.3 Eligibility Criteria

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

3.3.1 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.

3.3.2 The patient must be ≥ 50 years and < 70 years of age.

3.3.3 The trial is open to female and male patients.

3.3.4 The patient must have an ECOG performance status of 0 or 1.

3.3.5 The patient must have undergone a lumpectomy and 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. (Patients with margins positive for LCIS are eligible without additional resection.)

3.3.6 The tumor must be unilateral invasive adenocarcinoma of the breast on histologic examination.

3.3.7 Patient must have undergone axillary staging (sentinel node biopsy and/or axillary node dissection).

3.3.8 The following staging criteria must be met postoperatively according to AJCC 8th edition criteria:

- By pathologic evaluation, primary tumor must be pT1 (≤ 2 cm).
- By pathologic evaluation, ipsilateral nodes must be pN0. (Patients with pathologic staging of $pN0_{(i+)}$ or $pN0_{(mol+)}$ are <u>NOT</u> eligible.)

3.3.9 Oncotype DX Recurrence Score of ≤ 18 on diagnostic core biopsy or resected specimen.**

** For patients with a ***T1a tumor (≤ 0.5 cm in size)*** who do not already have an Oncotype DX Recurrence Score at study entry, a specimen (unstained blocks or slides) must be sent to the Genomic Health centralized laboratory.

3.3.10 The tumor must have been determined to be ER and/or PgR positive assessed by current ASCO/CAP Guideline Recommendations for hormone receptor testing. Patients with ≥ 1% ER or PgR staining by IHC are considered positive.

3.3.11 The tumor must have been determined to be HER2-negative by current ASCO/CAP guidelines.

3.3.12 Patients may be premenopausal or postmenopausal at the time of study entry. For study purposes, postmenopausal is defined as:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry; or a documented hysterectomy; or
- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard; or
- Documented bilateral oophorectomy.

3.3.13 The interval between the last surgery for breast cancer (including re-excision of margins) and study entry must be no more than 70 days.

3.3.14 The patient must have recovered from surgery with the incision completely healed and no signs of infection.

3.3.15 Bilateral mammogram or MRI within 6 months prior to study entry.

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

3.3.17 Patients must be intending to take endocrine therapy for a minimum 5 years duration (tamoxifen or aromatase inhibitor). The specific regimen of endocrine therapy is at the treating physician's discretion.

3.4 Ineligibility Criteria

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

3.4.1 Definitive clinical or radiologic evidence of metastatic disease.

3.4.2 pT2 - pT4 tumors including inflammatory breast cancer.

3.4.3 Pathologic staging of $pN0_{(i+)}$ or $pN0_{(mol+)}$, pN1, pN2, or pN3 disease.

3.4.4 Patient had a mastectomy.

3.4.5 Palpable or radiographically suspicious ipsilateral or contralateral axillary, supraclavicular, infraclavicular, or internal mammary nodes, unless there is histologic confirmation that these nodes are negative for tumor.

3.4.6 Suspicious microcalcifications, densities, or palpable abnormalities (in the ipsilateral or contralateral breast) unless biopsied and found to be benign.

3.4.7 Non-epithelial breast malignancies such as sarcoma or lymphoma.

3.4.8 Proven multicentric carcinoma (invasive cancer or DCIS) in more than one quadrant or separated by 4 or more centimeters. (Patients with multifocal carcinoma are eligible.)

3.4.9 Paget's disease of the nipple.

3.4.10 Any history, not including the index cancer, of ipsilateral invasive breast cancer or ipsilateral DCIS treated or not treated. (Patients with synchronous or previous ipsilateral LCIS are eligible.)

3.4.11 Synchronous or previous contralateral invasive breast cancer or DCIS. (Patients with synchronous and/or previous contralateral LCIS are eligible.)

3.4.12 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.)

3.4.13 Treatment plan that includes regional nodal irradiation.

3.4.14 Any treatment with radiation therapy, chemotherapy, biotherapy, and/or endocrine therapy administered for the currently diagnosed breast cancer prior to study entry. (Short course endocrine therapy of < 6 weeks duration is acceptable post core biopsy pre surgery if the Oncotype DX Recurrence Score is assessed on the biopsy core and is $\leq$18.)

3.4.15 History of non-breast malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to study entry.

3.4.16 Current therapy with any endocrine therapy such as raloxifene (Evista®), tamoxifen, or other selective estrogen receptor modulators (SERMs), either for osteoporosis or breast cancer prevention. (Short course endocrine therapy of < 6 weeks duration is acceptable post core biopsy pre surgery if the Oncotype DX Recurrence Score is assessed on the biopsy core and is $\leq$18.)

3.4.17 Patients intending to continue on oral, transdermal, or subdermal estrogen replacement (including all estrogen only and estrogen-progesterone formulas) are not eligible. Patients that discontinue oral, transdermal, or subdermal estrogen replacement prior to registration are eligible.

3.4.18 Prior breast or thoracic RT for any condition.

3.4.19 Active collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosis, or scleroderma.

3.4.20 Pregnancy or lactation at the time of study entry or intention to become pregnant during treatment. ***(Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 2 weeks prior to study entry.)***

3.4.21 Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of study therapy or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

3.4.22 Psychiatric or addictive disorders or 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.

3.4.23 Use of any investigational product within 30 days prior to study entry.