# NRG-BR008: A phase III randomized trial of radiotherapy optimization for low-risk HER2-positive breast cancer (HERO*)

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## BACKGROUND

Breast radiotherapy (RT) is the standard of care for many patients with early-stage breast cancer (BC) who undergo breast-conserving surgery (BCS). However, the magnitude or RT benefit is less clear among patients undergoing BCS for low-risk disease following highly effective systemic therapy.

For patients with early-stage HER2-positive BC, 10-yr locoregional recurrence has been reported as low as 1.5% following BCS, adjuvant chemotherapy, HER2-targeted therapy, and RT.

Given these exceedingly favorable reports, we seek to evaluate the feasibility of foregoing RT among patients with early-stage HER2-positive BC following BCS and appropriate systemic therapy.

## HYPOTHESES

- If patients who are at low risk of local recurrence can be robustly identified, it may be acceptable for such patients to forego radiation.
- Patients in the omission-of-RT arm will report less pain, but greater worry about recurrence, at 3 yrs.
- The 7-yr IBR rate will be <7% for patients not receiving adjuvant breast RT.

## OBJECTIVES

### Primary

- To compare the recurrence-free interval (RFI) among patients with early-stage, low-risk HER2-positive BC who undergo BCS and receive HER2-directed therapy and are randomly assigned to not receive adjuvant RT *vs* those who are randomly assigned to receive adjuvant RT per the current standard of care.

### Secondary

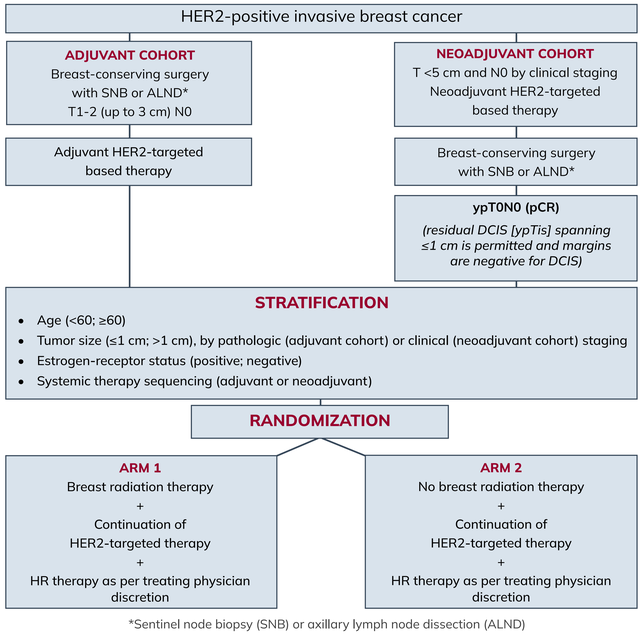
- 7-yr ipsilateral breast recurrence (IBR) rate in the omission-of-RT arm.
- Time to IBR by treatment arm.
- Time to local-regional recurrence (LRR) by treatment arm.
- Disease-free survival (DFS) by treatment arm.
- Overall survival (OS) by treatment arm.
- Patient-reported breast pain in patients who do and do not receive RT in Adjuvant and Neoadjuvant cohorts.
- Patient-reported worry about recurrence in patients who do and do not receive breast RT in Adjuvant and Neoadjuvant cohorts.

### Exploratory

- Explore measures of quality of life (QOL) that would reasonably be expected to vary by study arm, including cosmesis, breast-related functional status, fatigue, breast and skin symptoms, and global QOL.

## NRG-BR008 STUDY DESIGN

### SCHEMA




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

**NCT #: NCT05705401**

Clinical cohorts based on the sequencing of systemic therapy:

- The **Adjuvant cohort** includes all patients who receive adjuvant HER2-directed chemotherapy.
- The **Neoadjuvant cohort** includes all patients who receive neoadjuvant HER2-directed chemotherapy and achieve pCR at surgery (no residual invasive or in situ disease).

Patients are randomly assigned in 1:1 ratio to either receive or not receive adjuvant radiotherapy:

**Arm 1** Standard breast RT; continuation of HER2-directed therapy.

**Arm 2** No RT; continuation of HER2-directed therapy.

Support: U10 CA180868, -180822, UG1 CA189867, U24 CA196067

## PRO INSTRUMENTS

| Outcome of Interest | Instrument | # |
|---|---|---|
| **Primary Outcomes** | | |
| Breast Pain | BCTOS Breast Pain | 3 |
| Breast cancer worry about recurrence | Breast Cancer Worry | 3 |
| **Secondary Outcomes** | | |
| Cosmesis | BCTOS; Global Cosmesis Score | 8; 1 |
| Breast-related functional status | BCTOS | 7 |
| Fatigue | PROMIS Fatigue | 6 |
| Breast cancer treatment symptoms | Treatment-related Symptom Checklist (NSABP B-39/RTOG 0413) | 13 |
| Global Quality of Life | PROMIS Global | 10 |
| **Exploratory Outcomes** | | |
| Distress related to cancer recurrence | Quality of Life After Cancer | 4 |

## STATISTICAL CONSIDERATIONS

- 7-yr RFI in the RT group 97.5%.
- Clinically acceptable difference of 3.6%, corresponding to 7-yr RFI of 93.9% in the no-RT arm (max HR of clinical insignificance is 2.5).
- Statistical power to demonstrate non-inferiority as defined – 80%.
- Significance level – 0.05 (one-sided).
- Annual rate of loss-to-follow up – 1%.
- Total sample size 1,300 patients accrued over 7.25 yrs with 4.5 yrs of additional follow-up.
- Interim futility analysis when 19 RFI events are observed.
- Final analysis conducted when 38 RFI events are observed.

## ELIGIBILITY

### Both Cohorts

- Female or male patients who have undergone BCS and have completed min 8 wks of adjuvant or adjuvant systemic therapy with a HER2-targeted regimen. Patients treated with T-DM1 must have received at least 6 cycles of this treatment.
- Must be ≥18 yrs.
- ECOG 0-2/Karnofsky >60.
- Histologically or cytologically confirmed HER2+ invasive breast carcinoma.
- Any estrogen or progesterone receptor status.
- Patient must have undergone axillary staging, either SNB or ALND.

### Adjuvant cohort

- Primary tumor must be ≤3 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

- Must achieve pCR with HER2-targeted preoperative treatment.
- Prior to neoadjuvant therapy, the patient's primary tumor must be ≤5 cm with negative axillary nodes (cN0) based on axillary U/S, CT, PET, or MRI.
- Must be ypT0N0 at surgery (lumpectomy) — patients with residual non-invasive disease (DCIS) in the surgical specimen (ypTis), are only eligible if residual DCIS spans ≤1 cm, and surgical margins are negative for DCIS.

## STUDY STATUS

On July 17, 2025, CTEP determined that NRG-BR008 in its present form should be closed due to slower than anticipated accrual despite eligibility changes.

The trial was closed to accrual on August 4, 2025. Enrolled patients will continue in follow-up, and long-term data will be collected.

Efforts are underway to establish an alternate phase II single-arm study for radiotherapy omission among patients with early-stage HER2-positive breast cancer.

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