Loco-Regional Irradiation in Patients with Biopsy-Proven Axillary Node Involvement at Presentation Who Become Pathologically Node-Negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

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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 patients with early-stage breast cancer (BC) who undergo breast-conserving surgery (BCS). However, the magnitude of benefit of RT is less clear in BCS patients with low-risk disease who receive effective systemic therapy. Among patients with early-stage HER2-positive (HER2+) BC, 10-year locoregional recurrence has been reported as low as 1.5% following BCS, adjuvant chemotherapy and HER2-targeted therapy, and RT. Given these exceedingly favorable outcomes, with the addition of HER2-directed therapy, we seek to evaluate the feasibility of omitting RT among patients with early-stage HER2+ BC following BCS and appropriate systemic therapy. Methods: This is a phase III randomized trial for patients ≥40 years with early-stage, node-negative HER2+ (IHC/FISH) BC treated with BCS with negative margins and sentinel lymph node biopsy or axillary dissection. Patients undergoing primary surgery must have pathologic T1 (< 2 cm) N0 disease, while patients receiving neoadjuvant therapy must have clinical T1-2 (with radiographically T< 3.0 cm) N0 disease and exhibit a pathologic complete response (ypT0N0) at surgery. All patients must receive cytotoxic chemotherapy and HER2-targeted therapy, either
in the adjuvant or neoadjuvant setting. Stratification is by age (< 60; ≥60), tumor size (≤1 cm; >1 cm), estrogen-receptor status (positive; negative), and systemic therapy sequencing (adjuvant vs neoadjuvant). Patients will be randomized to standard breast RT in addition to continuation of trastuzumab to complete a year of treatment (Arm 1), or trastuzumab alone (Arm 2).

Endocrine therapy will be recommended for patients with hormone-receptor positive tumors. The primary endpoint is the recurrence-free interval (RFI). Secondary endpoints include the time to ipsilateral breast recurrence, locoregional recurrence, disease-free survival, and overall survival, in addition to the 7-year ipsilateral breast recurrence rate among those not receiving RT. A health-related quality of life sub-study will assess differences in patient-reported breast pain and worry. We estimate a 7-year RFI of 97.5% with RT and allow for a clinically acceptable decrement of 3.63% without RT (7-year RFI of 93.87%; HR 2.5) to establish omission of RT as non-inferior. NRG-BR008 aims to enroll 1,300 patients over 4.5 years, yielding 80% power to detect the non-inferiority of RT omission with a one-sided α=0.05. We expect to observe the required 38 RFI events within 6 years of additional follow-up. The NRG-BR008/HERO trial opened to accrual in March, 2023. NCT05705401. Support: U10CA180868, -180822, UG1CA189867, U24CA196067; Susan G. Komen Foundation (JR)