Figure 1
NSABP B-51/RTOG 1304 Schema

Clinically T1–3, N1 Breast Cancer
Documented Positive Axillary Nodes by FNA
or by Core Needle Biopsy

Minimum of 12 Weeks of Standard Neoadjuvant Chemotherapy
Plus Anti-HER2 Therapy for Patients with HER2-Positive Tumors

Definitive Surgery with Histologic Documentation of Negative Axillary Nodes
(Either by Axillary Dissection or by Sentinel Node Biopsy ± Axillary Dissection)

STRATIFICATION
- Type of surgery (mastectomy, lumpectomy)
- Hormone receptor status (ER-positive and/or PgR-positive;
  ER- and PgR-negative)
- HER2 status (negative, positive)
- Adjuvant chemotherapy (yes, no)
- pCR in breast (yes, no)

RANDOMIZATION

Arm 1
(Groups 1A and 1B)*, **
No Regional Nodal XRT
- Group 1A Lumpectomy: No regional nodal XRT with WBI
- Group 1B Mastectomy: No regional nodal XRT and no chestwall XRT

Arm 2
(Groups 2A and 2B)*, **
Regional Nodal XRT
- Group 2A Lumpectomy: Regional nodal XRT with WBI
- Group 2B Mastectomy: Regional nodal XRT and chestwall XRT

* Patients will be randomized to one of the following:
  - **Arm 1**
    - Radiation therapy for Group 1A
      Whole breast irradiation + boost
    - No radiation therapy for Group 1B
  - **Arm 2**
    - Radiation therapy for Group 2A
      Whole breast irradiation + boost and regional nodal irradiation
    - Radiation therapy for Group 2B
      Chest wall and regional nodal irradiation

** All patients will receive additional systemic therapy as planned (i.e., hormonal therapy
for patients with hormone receptor-positive breast cancer and trastuzumab or other
anti-HER2 therapy for patients with breast cancer that is HER2-positive).
NSABP B51 / RTOG 1304/LU205322: A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post- Lumpectomy Regional Nodal XRT in patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy.
Dr. T. Thomas

Eligibility:

1. The patient must be ≥ 18 years old.
2. The patient must have an ECOG performance status of 0 or 1
3. Patient must have clinically T1-3, N1 breast cancer at the time of diagnosis (before neoadjuvant therapy). Clinical axillary nodal involvement can be assessed by palpation, ultrasound, CT scan, MRI, PET scan, or PET/CT scan.
4. Patient must have had pathologic confirmation of axillary nodal involvement at presentation (before neoadjuvant therapy) based on either a positive FNA (demonstrating malignant cells) or positive core needle biopsy (demonstrating invasive adenocarcinoma). The FNA or core needle biopsy can be performed either by palpation or by image guidance. Documentation of axillary nodal positivity by sentinel node biopsy (before neoadjuvant therapy) is not permitted.
5. Patients must have had ER analysis performed on the primary breast tumor before neoadjuvant therapy according to current ASCO/CAP Guideline Recommendations for hormone receptor testing. If negative for ER, assessment of PgR must also be performed according to current ASCO/CAP Guideline Recommendations for hormone receptor testing (http://www.asco.org).
6. Patients must have had HER2 testing performed on the primary breast tumor before neoadjuvant chemotherapy according to the current ASCO/CAP Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer (http://www.asco.org). Patients who have a primary tumor that is either HER2-positive or HER2-negative are eligible.
7. Patient must have completed a minimum of 12 weeks of standard neoadjuvant chemotherapy consisting of an anthracycline and/or taxane-based regimen.
8. For patients who receive adjuvant chemotherapy after surgery, a maximum of 12 weeks of intended chemotherapy may be administered but must be completed before randomization. (If treatment delays occur, chemotherapy must be completed within 14 weeks.) The dose and schedule of the adjuvant chemotherapy are at the investigator’s discretion. Note: It is preferred that all intended chemotherapy be administered in the neoadjuvant setting.
9. Patients with HER2-positive tumors must have received neoadjuvant trastuzumab or other anti-HER2 therapy (either with all or with a portion of the neoadjuvant chemotherapy regimen), unless medically contraindicated.
10. At the time of definitive surgery, all removed axillary nodes must be histologically free from cancer. Acceptable procedures for assessment of axillary nodal status at the time of surgery include:
    - axillary node dissection;
    - sentinel node biopsy alone provided that at least 2 sentinel lymph nodes are removed.
• Removal of at least 3 sentinel lymph nodes and use of dual tracer for lymphatic Mapping are strongly recommended; or
• sentinel node biopsy followed by axillary node dissection.

Note: Patients are eligible whether there is residual invasive carcinoma in the surgical breast specimen or whether there is evidence of pathologic complete response

11. Patients with pathologic staging of ypN0(i+) or ypN0(mol+) are eligible.
12. Patient who have undergone either a total mastectomy or a lumpectomy are eligible. (Patients who have had a nipple-sparing mastectomy are eligible.)
13. For patients who undergo lumpectomy, the margins of the resected specimen or re-excision must be histologically free of invasive tumor and DCIS as determined by the local pathologist. Additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. (Patients with margins positive for LCIS are eligible without additional resection.)
14. For patients who undergo mastectomy, the margins must be histologically free of residual (microscopic or gross) tumor.
15. The interval between the last surgery for breast cancer (including re-excision of margins) and randomization must be no more than 56 days. Also, if adjuvant chemotherapy was administered, the interval between the last chemotherapy treatment and randomization must be no more than 56 days.
16. The patient must have recovered from surgery with the incision completely healed and no signs of infection.
17. If adjuvant chemotherapy was administered, chemotherapy-related toxicity that may interfere with delivery of radiation therapy should have resolved.
NSABP PROTOCOL B-51/RTOG PROTOCOL 1304/LU 205322

A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy

Exclusion Criteria:

Patients with one or more of the following conditions are NOT eligible for this study:

1. Definitive clinical or radiologic evidence of metastatic disease.
2. Tumors including inflammatory breast cancer.
3. Documentation of axillary nodal positivity before neoadjuvant therapy by sentinel node biopsy alone.
4. N2 or N3 disease detected clinically or by imaging.
5. Patients with histologically positive axillary nodes post neoadjuvant therapy.
6. Patients with microscopic positive margins after definitive surgery.
7. Synchronous or previous contralateral invasive breast cancer or DCIS. (Patients with synchronous and/or previous contralateral LCIS are eligible.)
8. Any prior history, not including the index cancer, of ipsilateral invasive breast cancer or ipsilateral DCIS treated with radiation therapy. (Patients with synchronous or previous ipsilateral LCIS are eligible.)
9. 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 randomization.
10. Any radiation therapy for the currently diagnosed breast cancer prior to randomization.
11. Any continued use of sex hormonal therapy, e.g., birth control pills, ovarian hormone replacement therapy. Patients are eligible if these medications are discontinued prior to randomization (see Section 5.1).
12. Prior breast or thoracic RT for any condition.
13. Active collagen vascular disease, specifically dermatomyositis with a CPK level above normal or with an active skin rash, systemic lupus erythematosus, or scleroderma.
14. Pregnancy or lactation at the time of study entry. (Note: Pregnancy testing must be performed within 2 weeks prior to randomization according to institutional standards for women of childbearing potential.)
15. Other non-malignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow-up.
16. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements.