NRG-BR009: A phase III trial evaluating addition of adjuvant chemotherapy to *O*varian *F*unction *S*uppression + *E*ndocrine *T*herapy in premenopausal women with pN0-1, HR+/HER2– breast cancer and Oncotype Recurrence Score (RS) ≤25 (OFSET)

Sandra M. Swain,[1] Gong Tang,[2] Shannon L. Puhalla,[3] Patricia A. Ganz,[4] N. Lynn Henry,[5] Reena S. Cecchini,[2] Sonya A. Reid,[6] Priya Rastogi,[3] Charles E. Geyer, Jr.,[3] Julia R. White,[7] Amy S. Clark,[8] Tufia C. Haddad,[9] Gregory A. Vidal,[10] Norman Wolmark,[3,11] Eleftherios P. Mamounas[12]

[1]Georgetown Lombardi Comprehensive Cancer Center (CCC), Georgetown University Medical Center, MedStar Health, Washington, DC; [2]NRG Oncology SDMC, Department of Biostatistics and Health Data Science, Pittsburgh, PA; [3]UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]David Geffen School of Medicine at UCLA; UCLA Fielding School of Public Health; UCLA Jonsson CCC, Los Angeles, CA; [5]University of Michigan Medical School, Ann Arbor, MI; [6]Vanderbilt University Medical Center, Nashville, TN; [7]University of Kansas Medical Center CCC, Kansas City, KS; [8]Perelman School of Medicine, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; [9]Mayo Clinic CCC, Rochester, MN; [10]West Cancer Center and Research Institute, Germantown, TN; [11]NSABP Foundation, Inc.; [12]AdventHealth Cancer Institute, Orlando, FL

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BACKGROUND

Women who are <35 years of age at diagnosis are more likely to die from their disease than older counterparts following standard treatments. Several studies have evaluated the role of ovarian suppression compared to chemotherapy.

TAILORx
- No benefit with chemo endocrine therapy (CET) *vs* endocrine therapy (ET) in postmenopausal patients with pN0/RS 11–25.
- Significant benefit with CET *vs* ET in premenopausal patients with pN0/RS 16–20 (and high clinical risk) or RS 21–25.

RxPONDER
- No benefit with CET *vs* ET in postmenopausal patients with pN1/RS 0–25.
- Significant benefit with CET *vs* ET in premenopausal patients with pN1/RS 0–25 (high clinical risk by definition).

SOFT
- Significant benefit with ovarian function suppression (OFS) + exemestane *vs* tamoxifen alone in high-risk premenopausal patients who also received adjuvant chemotherapy.

Neoadjuvant chemotherapy studies in ER+/HER2- pts
- Low pCR in patients with low/intermediate RS irrespective of menopausal status.

Mechanism of benefit from adjuvant chemotherapy could be an indirect endocrine effect of ovarian suppression from chemotherapy, a direct cytotoxic effect of chemotherapy, or a combination of both effects. The only way to isolate the potential benefit of the cytotoxic effect of chemotherapy in this population is to compare outcomes of adding adjuvant chemotherapy to ET + OFS vs ET + OFS alone.

OBJECTIVES

Primary

To determine whether adjuvant chemotherapy added to OFS plus ET is superior to OFS plus ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal, early-stage breast cancer patients with ER-positive, HER2-negative tumors and 21-gene RS between 16–25 (for pN0 patients) and 0–25 (for pN1 patients).

Secondary
- Invasive disease-free survival
- Overall survival
- Distant recurrence-free interval
- Breast cancer-free interval
- Menopausal symptom burden
- Pain severity

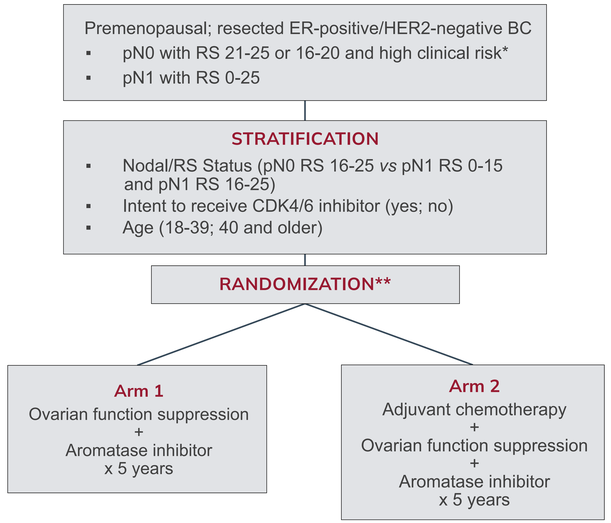
HYPOTHESIS

The addition of adjuvant chemotherapy to ovarian function suppression plus endocrine therapy will improve invasive breast cancer-free survival among the study population.

STUDY DESIGN

ARM 1	Aromatase inhibitor co-administered with a GnRH agonist for 5 years.
ARM 2	Adjuvant chemotherapy per physician's choice followed by an aromatase inhibitor co-administered with a GnRH agonist for 5 years.
ALL PATIENTS	Specific GnRH agonist and aromatase inhibitor per physician's choice. GNRH agonist every three months recommended. Radiation therapy per standard guidelines.

NRG-BR009 SCHEMA



* High clinical risk defined as:
1) low histologic grade with primary tumor size >3 cm, OR
2) intermediate histologic grade with primary tumor size >2 cm, OR
3) high histologic grade with primary tumor size >1 cm

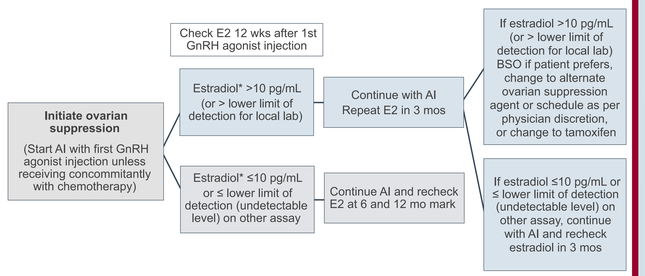
** Randomization is 1:1

NCT #: NCT05879926

PRO INSTRUMENTS

Outcome of Interest	Instrument	# of items
Primary Outcomes		
Menopausal symptom burden	FACT-ES ESS	19
Pain severity	PROMIS-29 Profile v2.1	1
Secondary Outcomes		
Vasomotor symptoms	FACT-ES ESS	-
Vaginal symptoms	FACT-ES ESS	-
Depression	PROMIS-29 Profile v2.1	4
Cognitive function	PROMIS-Short Form v2.0 Cognitive Function 4a	4
Fatigue	PROMIS-29 Profile v2.1	4
Pain interference	PROMIS-29 Profile v2.1	4
Adherence	Extent of Non-adherence Questionnaire (Voils)	3
Symptom burden	FACT-G GP5	1
Neuropathy	PRO-CTCAE	2

MONITORING ESTRADIOL



ELIGIBILITY

- Premenopausal women age ≥18 years.
- ECOG performance status of ≤2 (or Karnofsky ≥60%).
- Status post-lumpectomy with negative margins (no ink on tumor).
- Status post-axillary nodal staging (SNB or AND) – pN0 or pN1.
- ER and/or PR positive by ASCO/CAP.
- HER2-negative by ASCO/CAP.
- Oncotype DX Recurrence Score (RS) of ≤25 on diagnostic core biopsy or resected specimen for pN1; for pN0: RS 21–25 or RS 16–20 with high clinical risk.

STATISTICAL PLAN

- With a one-sided alpha level at 0.025, we would have 80% power to detect a 25% reduction in the instantaneous hazard rate from the additional adjuvant chemotherapy to OFS + ET when 380 IBCFS events are observed (Schoenfeld 1983).
- We anticipate that we can enroll 45 patients (20 pN1 and 25 pN0) per month at peak and complete the accrual of 3,960 patients in seven years and seven months.

STUDY STATUS

- Currently open in the USA, Canada, and approved international sites.
- Interested international sites that are participating members of NCTN groups are encouraged to contact their Member Group Operations Office.
- Accrual is 453/3,960 as of November 21, 2025.

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

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