Preoperative radiotherapy versus postoperative radiotherapy after NACT in high-risk breast cancer: a prospective, randomized, international multicentre Phase III trial — NeoRad

P3-10-22

Christiane Matuschek[1], Tanja Fehm[2], Maria Hufnagel[3], Vesna Bjelic-Radisic[4], Michael Untch[5], Michael Golatta[6,7], Danny Jazmati[8], Thorsten Kühn[9], David Krug[10], Jens Blohmer[11], Carsten Denkert[12], Beyhan Ataseven[13], Carolin Nestle-Krämling[14], Stefanie Corradini[15], Jens Huober[16], Bernd Gerber[17], Eugen Ruckhäberle[18], Andreas Hartkopf[19], Theresa Link[20], Kerstin Rhiem[21], Elmar Stickeler[22], Claus Hanusch[23], Joerg Heil[6,7], Christine Solbach[24], Mattea Reinisch[25], Inga Bekes[16], Johannes Holtschmidt[26], Valentina Nekljudova[26], Sibylle Loibl[26], Wilfried Budach[8]

1. Bielefeld University, Medical School and University Medical Center OWL, Klinikum Mitte, Department of Radiation Oncology; 2. Department of Gynecology and Obstetrics, University Hospital Duesseldorf, CIO[ABCD], Germany; 3. Brustzentrum Sana Klinikum Lichtenberg, Berlin, Germany; 4. Breast Unit, University Hospital Helios, University Witten Herdecke, Wuppertal, Germany; 5. Helios Klinikum Berlin-Buch, Berlin, Germany; 6. Department of Gynecology and Obstetrics, University of Heidelberg, Heidelberg, Germany; 7. Breast Center Heidelberg, Klinik St. Elisabeth, Heidelberg, Germany; 8. Department of Radiation Oncology, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Germany; 9. Department of Gynecology and Obstetrics, University of Ulm, Ulm, Germany; 10. Department of Radiotherapy and Radiation Oncology, University Medical Center Hamburg-Eppendorf, Germany; 11. Department of Gynecology with Breast Center, Charité Universitätsmedizin Berlin, Germany; 12. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 13. Department of Gynecology, Gynecologic Oncology and Obstetrics, Bielefeld University, Medical School and University Medical Center OWL, Klinikum Lippe, Detmold, Germany; 14. Department of Gynecology, Evangelisches Krankenhaus Düsseldorf Germany; 15. Department of Radiation Oncology, Ludwig Maximillian University, Munich, Germany; 16. Cantonal Hospital, Breast Center, St. Gallen, Switzerland; 17. Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany; 18. Department of Gynecology and Obstetrics, University Hospital Tübingen, Tübingen, Germany; 20. Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany; 21. Center for Familial Breast and Ovarian Cancer, University of Cologne, Cologne, Germany; 22. Department of Gynecology and Obstetrics, RWTH Aachen, Aachen, Germany; 23. Rotkreuzklinikum München, München, Germany; 24. Department of Gynecology and Obstetrics, University Hospital , Goethe University Frankfurt, Frankfurt, Germany; 25. Breast Unit, University Hospital Mannheim, Mannheim. Germany; 26. German Breast Group, Neu-Isenburg, Germany.

Background

Preoperative radiotherapy (PRT) is a well-established treatment for various tumor types (e.g., rectal cancer, sarcoma, bronchial carcinoma). While encouraging research on preoperative radiotherapy exists for breast cancer, most of these studies were either non-randomized or included old patient cohorts[1-3]. Contemporary investigations indicate that administering PRT is associated with better survival outcomes[4] and does not correlate with postoperative complications following mastectomy with or without immediate breast reconstruction[5]. There is evidence that the immunogenic effects of radiotherapy may lead to improved immune recognition of tumor cells (e.g., increased stromal TILs)[6]. In addition, PRT is associated with low grades of fibrosis, good to excellent long-term cosmetic outcomes, and comparable long-term general and breast-specific quality-of-life outcomes[7-8]. These potential advantages make PRT a promising modality in interdisciplinary cancer therapy, thereby necessitating its evaluation in a clinical trial setting.

Study Overview

NeoRad (NCT04261244, GBG116) is a multicenter, prospective, randomized phase III trial. Eligible patients with high-risk breast cancer and indication for NACT will be randomized to receive adjuvant radiotherapy after completion of NACT either prior to surgery (PRT) or after surgery.

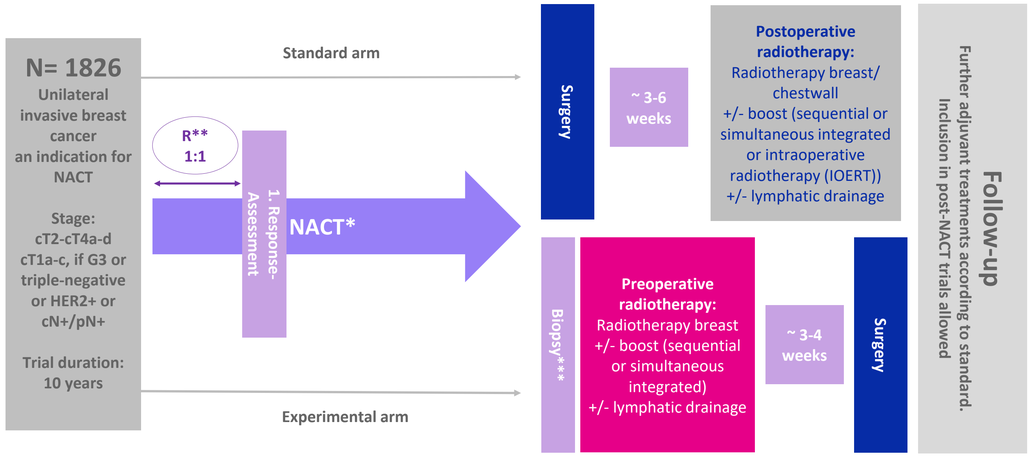
Patients should not have their first response assessment after start of NACT prior to randomization to avoid bias resulting from the assessment result. 1826 patients will be randomized 1:1 stratified by biological subtype, clinical nodal status, and type of planned breast surgery.

Standard arm: patients will undergo surgery, sentinel lymph node biopsy, and eventually (targeted) axillary dissection according to the latest S3/AGO guideline at the time of therapy. After surgery, patients will receive adjuvant radiotherapy and systemic treatment following S3/AGO guidelines.

Experimental arm: patients will receive whole breast irradiation (WBRT) with or without regional lymph node irradiation 2-4 weeks following NACT. A biopsy of the breast tumor +/- suspicious lymph nodes is highly recommended to evaluate pCR status after NACT and allows assignment to further postneoadjuvant treatments. Approximately 3-6 weeks after radiotherapy, patients will undergo surgery and eventually (targeted) axillary dissection.

In both arms, patients will receive further postneoadjuvant systemic treatment according to S3/AGO guidelines, if indicated.

Study Design



Stratification factors :
- Biological subtype
- cN0 vs cN+
- type of planned breast surgery

* Neoadjuvant chemotherapy (NACT) +/- anti-HER2-therapy, +/- immuno-therapy
** Randomization before first response assessment
*** Core needle biopsy breast tumor +/- lymph nodes (if ycN+) highly recommended

Modified according to: doi 10.1007/s00761-024-01568-1

Figure 1: Study design

Key Inclusion Criteria

1. Female patients with histologically proven invasive, unilateral breast cancer
2. Indication for NACT (+/- antibody treatment or other targeted therapies) in accordance with national and international guidelines
3. Indication for radiotherapy
4. T2-T4a-d (if T4d: max. 1 cm inflammation) or T1a-c (if G3, triple negative, HER2- positive, or cN+/pN+)
5. No restrictions on HR or HER2-status or grading (G1-3)
6. No pre-existing conditions that forbid study therapy

Key Exclusion Criteria

1. Male patients
2. Neoadjuvant treatment solely with endocrine therapy
3. Bilateral breast cancer
4. Distant metastases
5. Pregnancy or lactation
6. Prior radiotherapy of the affected or contralateral breast
7. Patients who have been previously assessed for chemotherapy response
8. Connective tissue disease, symptomatic chronic lung disease, cardiac comorbidities, lymphedema ≥ grade 2 of the ipsilateral arm, or any medical conditions that prohibit the administration of neoadjuvant radiotherapy
9. Other malignancies (except basalioma or in-situ-carcinomas in complete response)

Study Objectives

Primary objective: Superiority of PRT/experimental treatment schedule in terms of disease-free survival (DFS)

Key secondary objectives:
- Time to ipsilateral local recurrence (LR) as a first site of recurrence
- Time to regional recurrence (RR) as a first site of recurrence
- Distant disease-free survival (DDFS), overall survival (OS), and breast cancer specific survival (BCSS)
- Pathological complete response (pCR) defined as ypT0/is, ypN0
- Quality of life
- Acute and late toxicity

Safety: Interim analyses for surgical complications will be conducted: after 100 patients have received breast-conserving surgery or autologous flap reconstruction (in both arms combined); and after 40 and 100 patients have been reconstructed with an implant (also combined from both arms).

Sample Size Calculation

An improvement in 10-year DFS rate from 70% to 76.5% with PRT is assumed, corresponding to a hazard ratio of 0.75. Considering a cumulative drop out rate of 10% in 10 years, 2x913 patients have to be randomized to achieve a power of 80% for the two-sided log-rank test at level α=0.05 (calculated event count of 379).

Follow-up Visits

Study visits after whole breast radiotherapy (WBRT) begin in week 2 after completion of WBRT. In the standard treatment arm, this is followed by a visit 3 months after surgery and 6 months after WBRT. In the experimental arm, a visit 2 weeks after WBRT/110 days prior to surgery is performed, followed by a visit 3 and 6 months after surgery. Afterwards, visits will be repeated annually until year 10.

Recruitment

The first patients were enrolled in 02/24 at the University Hospital of Düsseldorf. A total of 1826 patients will be recruited across 40 centers within 4 years.

References

1. Poleszczuk J, Luddy K, Chen L, et al. Neoadjuvant radiotherapy of early-stage breast cancer and long-term disease-free survival. *Breast Cancer Res.* 2017;19(1):75.
2. Corradini S, Krug D, Meattini I, et al. Preoperative radiotherapy: A paradigm shift in the treatment of breast cancer? A review of literature. *Crit Rev Oncol Hematol.* 2019;141:102-111.
3. Matuschek C, Nestle-Kraemling C, Kühn T, et al. Neoadjuvant Radio(chemo)therapy for Breast Cancer: An Old Concept Revisited. *Breast Care (Basel).* 2020;15(2):112-117.
4. Brackstone M, Palma D, Tuck AB, et al. Concurrent Neoadjuvant Chemotherapy and Radiation Therapy in Locally Advanced Breast Cancer. *Int J Radiat Oncol Biol Phys.* 2017;99(4):769-776.
5. Baltodano PA, Reinhardt ME, Flores JM, et al. Preoperative Radiotherapy Is Not Associated with Increased Post-mastectomy Short-term Morbidity: Analysis of 77,902 Patients. *Plast Reconstr Surg Glob Open*. 2017;5(3):e1108.
6. Shaitelman SF, Le-Petross H, Raso MG, et al. PRECISE: Preoperative Radiation Therapy to Elicit Critical Immune Stimulating Effects - A Phase 2 Clinical Trial. *Int J Radiat Oncol Biol Phys.* 2014 [Online ahead of print].
7. Matuschek C, Nestle-Kraemling C, Haussmann J, et al. Long-term cosmetic outcome after preoperative radio-/chemotherapy in locally advanced breast cancer patients. Langfristiges kosmetisches Ergebnis nach neoadjuvanter Radio-/Chemotherapie bei lokal fortgeschrittenen Brustkrebspatientinnen. *Strahlenther Onkol.* 2019;195(7):615-628.
8. Haussmann J, Nestle-Kraemling C, Bölke E, et al. Long-term quality of life after preoperative radiochemotherapy in patients with localized and locally advanced breast cancer. *Strahlenther Onkol.* 2020;196(4):386-397.

Presented at: San Antonio Breast Cancer Symposium® - December 10-13, 2024

This study was supported by a grant from Deutsche Krebshilfe.