



# **AXSANA**

**(AXillary Surgery After NeoAdjuvant Treatment)**

**-EUBREAST 3-**

A prospective multicenter cohort study to evaluate different surgical methods of axillary staging (sentinel lymph node biopsy, targeted axillary dissection, axillary dissection) in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy

## **Study protocol**

Clinical Trials.gov  
NCT 04373655

Version 5.0.8  
13.03.2021  
18 pages

## **Table of Contents**

Study administration	3
Glossary and Abbreviations	7
Introduction / Rationale	8
Study design	10
Study aims	10
Inclusion and exclusion criteria	12
Registration and treatment	12
Evaluation of the quality of life	13
Study flowchart	14
Data management and analysis	15
Statistical considerations	15
Funding	15
Target accrual	15
Study duration	15
Amendments	16
References	17

## Study administration

The International Steering Committee is composed of members of the International Steering Board, the Organizing Committee and Heads of all National Steering Committees.

### International Steering Board

Prof. Dr. med. Thorsten Kühn Chair	Klinikum Esslingen GmbH Klinik für Frauenheilkunde und Geburtshilfe Department of Obstetrics and Gynecology Hirschlandstr. 97 73730 Esslingen, Germany Tel.: (+49) 711/3103-3051 Fax: (+49) 711/3103-3052
Ass. Prof. Jana de Boniface Co-Chair	Karolinska Institutet and Capio St. Göran's Hospital SE-17176 Stockholm, Sweden Tel.: (+46) (0)8-5177 0000
Dott. Oreste Gentilini Co-Chair	San Raffaele Hospital Milan Via Olgettina Milano, 60 20132 Milano MI, Italy Tel.: (+39) 0226433999
Univ.- Prof. Dr. med. Elmar Stickeler Co-Chair	Universitätsklinikum Aachen Pauwelsstraße 30 52074 Aachen, Germany Tel.: (+49) 241/90-88400 Fax: (+49) 241/80-82476

### Organizing Committee

Prof. Dr. med. Thorsten Kühn	Klinikum Esslingen GmbH Klinik für Frauenheilkunde und Geburtshilfe Department of Obstetrics and Gynecology Hirschlandstr. 97 73730 Esslingen, Germany
Priv.-Doz. Dr. Maggie Banys-Paluchowski	Department of Gynecology Asklepios Klinik Barmbek Rübenkamp 220 22307 Hamburg, Germany
Dr. Steffi Hartmann	Department of Gynecology and Obstetrics Klinikum Südstadt Rostock University of Rostock Südring 81 18059 Rostock, Germany

### Heads of the National Steering Committees (in alphabetical order)

Albania	Prof. As. Helidon Nina Oncology Hospital University Hospital Center “Nene Tereza” Tirania Albania
Austria	Univ.-Prof. Dr. Florentia Peintinger Medical University of Graz Neue Stiftingtalstraße 6 8010 Graz Austria
Azerbaijan	Ass. Prof. Hagigat Valiyeva Qanimat Azerbaijan Medical University Oncology Department Azerbaijan
Czech Republic	Lukas Dostalek, MD Gynecologic Oncology Center Department of Obstetrics and Gynecology First Faculty of Medicine Charles University General University Hospital Prague Czech Republic
Finland	Dr. Laura Niinikoski Breast Surgery Unit Comprehensive Cancer Center Helsinki University Hospital University of Helsinki Finland
France	Prof. Jean-Marc Classe Institut de cancerologie de l'Ouest Nantes Department of surgical oncology Bd. Jacques Monod – 44805 Saint Herblain France
Germany	Priv.-Doz. Dr. Maggie Banys-Paluchowski Department of Gynecology Asklepios Klinik Barmbek Rübenkamp 220 22307 Hamburg Germany
Greece	Prof. Dr. Michalis Kontos 1st Department of Surgery University of Athens, Laiko Hospital 17 Agiou Thoma Street 11527 Athens Greece
Hungary	Dr. habil. Zoltan Matrai National Institute of Oncology Rath Gy. u. 7-9., 1122 Budapest Hungary
India	Dr. Geeta Kadayaprath, MS FRCS Breast Surgical Oncology and Oncoplastic Surgery Max Institute of Cancer Care

	Max Healthcare Delhi India
Italy	Dott. Oreste Gentilini San Raffaele Hospital Milan Via Olgettina Milano, 60 20132 Milano MI Italy
Norway	Dr. Ellen Schlichting, M.D. Ph.D. Department for Breast and Endocrine Surgery Oslo University Hospital Oslo Norway
Poland	Prof. Dr. Dawid Murawa Collegium Medicum University of Zielona Gora ul. Zyty 28, 65-046 Zielona Góra Poland
Portugal	Dr. David Pinto Fundação Champalimaud Avenida Brasília 1400-038 Lisboa Portugal
Romania	Dr. Eduard-Alexandru Bonci Prof. Dr. Ion Chiricuta Institute of Oncology 34-36 Republicii street 400015 Cluj-Napoca Romania
Russia	Prof. Dr. Petr Krivorotko Petrov Research Institute of Oncology Pesochny, ul. Leningradskaya, 68 197758 Saint-Petersburg Russia
Spain	Dr. Isabel Rubio Breast Surgical Unit Clínica Universidad de Navarra Av. Marquesado de Santa Marta 1 28027 Madrid Spain
Sweden	Ass. Prof. Jana de Boniface Karolinska Institutet and Capio St. Göran's Hospital SE-17176 Stockholm, Sweden
Switzerland	Dr. Maria Luisa Gasparri Department of Gynecology and Obstetrics University of the Italian Switzerland Ente Ospedaliero Cantonale of Lugano Lugano, Switzerland
Turkey	Prof. Dr. Guldeniz Karadeniz Cakmak Zonguldak BEUN The School of Medicine General Surgery Department Breast and Endocrine Unit Kozlu/Zonguldak 67600 Turkey

### **Committee on Quality of Life and Arm Morbidity**

Ass. Prof. Jana de Boniface	Karolinska Institutet and Capio St. Göran's Hospital Stockholm, Sweden
Prof. Yvonne Wengström	Karolinska Institutet Stockholm, Sweden
Helena Ikonomidis Sackey	Karolinska Institutet and Karolinska University Hospital Stockholm, Sweden
Matilda Appelgren	Karolinska Institutet Stockholm, Sweden

### **Statistical analysis regarding oncological outcomes**

Prof. Dr. rer. nat. Michael Hauptmann  
Brandenburg Medical School Theodor Fontane  
Institut für Biometrie und Registerforschung, Campus Neuruppin, Haus O  
Fehrbelliner Straße 38  
16816 Neuruppin  
Germany

### **Data management**

EUBREAST (European Breast Cancer Research Association of Surgical Trialists)

Chairman: Prof. Dr. Thorsten Kühn  
Klinikum Esslingen  
Hirschlandstr. 97  
D-73730 Esslingen, Germany

EUBREAST Founding Location  
Via Monte Napoleone 29  
I 20121 Milano MI  
Italy

## Glossary and Abbreviations

<b>ACOSOG</b>	American College of Surgeons Oncology Group
<b>AGO</b>	German Working Group Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie)
<b>ALND</b>	axillary lymph node dissection
<b>cN0</b>	initial clinical node status negative
<b>cN+</b>	initial clinical node status positive
<b>CRF</b>	Case Report Form
<b>DFS</b>	disease-free survival
<b>FNR</b>	false-negative rate
<b>iDFS</b>	invasive disease-free survival
<b>NCCN</b>	National Comprehensive Cancer Network
<b>NACT</b>	neoadjuvant chemotherapy
<b>OS</b>	overall survival
<b>pCR</b>	pathological complete remission
<b>pN0</b>	pathological node status negative
<b>pN+</b>	pathological node status positive
<b>post-NACT</b>	status after neoadjuvant chemotherapy
<b>SLN</b>	sentinel lymph node
<b>SLNB</b>	sentinel lymph node biopsy
<b>TLN</b>	target lymph node = suspicious lymph node that has been marked
<b>TLNB</b>	target lymph node biopsy = targeted removal of the marked target node
<b>TAD</b>	targeted axillary dissection = TLNB + SLNB
<b>ycN0</b>	clinical node status after neoadjuvant chemotherapy negative
<b>ycN+</b>	clinical node status after neoadjuvant chemotherapy positive
<b>ypN+</b>	pathological node status after neoadjuvant chemotherapy negative
<b>ypN0</b>	pathological node status after neoadjuvant chemotherapy positive

## Introduction / Rationale

For many decades, axillary lymph node dissection (ALND) has been considered standard of care in breast cancer (BC) patients. The procedure aimed at assessing the pN status (diagnostic / staging) to guide adjuvant therapy decisions as well as ensuring adequate locoregional control (therapeutic). However, ALND is associated with high morbidity and may therefore lead to reduced quality of life in BC patients (1).

In women undergoing primary surgery, ALND as a staging tool has been replaced by the less invasive sentinel lymph node biopsy (SLNB) without compromising the disease-free or overall survival (DFS, OS). Since then, the therapeutic benefit of ALND in patients with clinically occult metastasis in the sentinel lymph node (SLN) has been challenged as well. According to the current national and international guidelines (e.g. ESMO, NCCN, German S3 guideline and AGO recommendations) completion ALND can be safely omitted in selected patients with 1-2 positive sentinel lymph nodes (2,3,4,5).

The feasibility and safety of the SLNB after neoadjuvant chemotherapy (NACT) has been controversially discussed, particularly regarding women who initially presented with positive lymph nodes (cN+) and converted to ycN0 following NACT. In these patients, two large prospective multicenter trials reported a false-negative rate (FNR) of 12 and 14%, respectively (6,7), thus exceeding the generally accepted (albeit arbitrarily chosen) cutoff of 10%. The clinical relevance of an FNR > 10% and its impact on oncological endpoints (DFS, OS) remains unclear. For this reason, numerous national guidelines still recommend ALND in these patients (3,4).

Possible ways to further reduce the FNR in cN+ patients have been extensively discussed in the recent years. In 2016, Caudle et al. reported on a novel surgical approach (TAD = targeted axillary dissection) that consists of inserting a marking (e.g. a clip or a radioactive tracer) into the metastatic lymph node before NACT. In patients in whom the marked lymph node (target lymph node = TLN) and the sentinel node had been successfully removed, the FNR was as low as 1.4% (8). These retrospectively analyzed data from a prospective register support the hypothesis that TAD can improve the relatively low success rates of SLNB and reduce the long-term morbidity of patients undergoing axillary surgery in the neoadjuvant setting.

The optimization of systemic treatment strategies has led to an increase in pathological complete remission (pCR) rates over the last years. pCR rates of up to 70% have been reached in subgroups (9). Conversion to negative lymph node status in patients receiving neoadjuvant



therapy who were initially diagnosed with nodal involvement can be observed in up to 50% of patients (7,10). Therefore, the number of patients undergoing ALND despite negative lymph nodes after NACT is increasing.

Various forms of axillary staging surgery after NACT are currently in use internationally with the aim to ensure oncological safety and to avoid over-therapy (ALND, TAD, SLNB). The choice of the appropriate technique generally depends on the recommendations issued by national panels/associations and surgeons.

According to an analysis of 12,965 women from the U.S. American National Cancer Database, the percentage of patients receiving SLNB alone in this setting increased between 2012 and 2015 from 22.8% to 42.2%. At the same time the number of removed nodes increased as well (> 2 nodes in 63.8% of cases), although the number of detectable sentinel nodes in previous large studies did not exceed two (11). These data show a lack of standardization in this patient subgroup. The surgical approach depends mostly on the personal preferences of the surgeon.

Although the use of TAD in clinical routine is increasing, data from prospective studies are still limited.

Hartmann et al. evaluated the identification rate of the TLN in a prospective single-center feasibility study including 30 patients (12). The TLN could be identified on ultrasound in 25 out of 30 patients (83.3%). In 9 out of 30 (30%) women clip removal could not be confirmed on radiography. The authors concluded that clip marking of the TLN is not a suitable technique for clinical routine due to low visibility and identification rate of the clipped node after NACT.

Siso et al. examined 46 patients undergoing clip marking of the biopsied TLN (13). In 2 out of 46 (4.3%) patients the clip could not be identified preoperatively. In 44 out of 46 patients the TLN was detected on ultrasound and removed. The false negative rate was 4.1%.

Several validating studies are still ongoing. The following studies aim at evaluating the reproducibility of TAD and the feasibility of different marking techniques (carbonic ink, clip, radioactive seed) (14):

<b>Study</b>	<b>Country</b>	<b>Marking technique</b>
RISAS (NCT 02800317)	The Netherlands	Radioactive seed
SENTA (NCT 03012307)	Germany	Clip
TATTOO (DRKS 00013169)	Germany/Sweden	Carbonic ink

GANEA 3 (NCT 01221688)	France	Clip
------------------------	--------	------

Several issues regarding currently used axillary staging techniques remain yet to be clarified. Based on the unclear evidence, the guideline recommendations for the cN+ → ycN0 patients differ strongly. The current ESMO guidelines state that (1) SLNB may be carried out in selected cases, and, if negative, further axillary surgery may be avoided and (2) the FNR of SLNB alone can be improved by marking the biopsied positive node(s) to verify the removal. In Germany, the S3 guideline (last version: 2019) recommends ALND in patients with initial nodal involvement. In contrast, the German Working Group Gynecological Oncology (AGO) changed their recommendations in 2019 and endorsed TAD as technique of choice for this patient subgroup. In several European countries (Sweden, Norway, Finland) ALND is still considered standard of care for these patients. In others, such as Italy, most patients receive SLNB alone without marking and removing the target lymph node. In the current NCCN guidelines the TAD is considered an optional technique. A prospective analysis comparing different techniques regarding feasibility, safety, morbidity and surgical effort is urgently needed. Due to high complexity and discordant recommendations, a randomized trial comparing different techniques is hardly feasible and therefore would not clarify currently open issues within a reasonable timeframe.

Based on the lack of sufficient evidence and discrepancies between different national and institutional standards, the EUBREAST study group ([www.eubreast.com](http://www.eubreast.com)) decided to initiate a prospective cohort study as an international project that aims at comparatively evaluating data on axillary staging after NACT.

## **Study design**

European prospective cohort study

## **Study aims**

### Primary study aims:

- Evaluation of the 5-year invasive disease-free survival (iDFS) in cN+ → ycN0 patients treated with different axillary staging techniques (ALND, TAD, SLNB, TLNB)

- Evaluation of the 3-year axillary recurrence rate in cN+ → ycN0 patients treated with different axillary staging techniques (ALND, TAD, SLNB, TLNB)
- Evaluation of quality of life and arm morbidity in patients treated with different axillary staging techniques

Secondary study aims:

- Evaluation of the feasibility of different forms of axillary staging techniques regarding:
  - Detection rate of the SLNB
  - Detection rate of the TLN
  - Detection rate of the SLN + TLN
- Evaluation of the success rate of nodal staging using different axillary staging techniques
- Evaluation of the number of removed lymph nodes using different axillary staging techniques and their correlation to complications, arm morbidity and quality of life
- Evaluation of the operating time as a surrogate parameter for surgical resources
- Evaluation of the rate of patients with positive nodes according to the technique used (as a surrogate parameter for the FNR)
- Evaluation of factors (marking technique) associated with successful detection of the TLN
- Evaluation of the impact of experience of centers on the success rates of TAD
- Evaluation of surgical standards of care in different European countries
- Evaluation of treatment decisions in case of ypN+ status following NACT (ALND vs. radiation therapy)
- Evaluation of iDFS in patients with ypN+ status who received ALND or radiation therapy or both
- Analysis of factors contributing to a decreased quality of life and subjective symptoms of arm morbidity, i.e. baseline quality of life and sense of coherence, extent of axillary surgery and other locoregional and systemic therapies received
- Evaluation of economic resources required for different forms of axillary staging techniques (material costs, operative time etc.)

## **Inclusion and exclusion criteria**

### Inclusion criteria

- Signed informed consent form
- Primary invasive breast cancer (confirmed by core biopsy)
- cN+ (confirmed by core biopsy/fine needle aspiration or presence of highly suspicious axillary node[s] on imaging)
- In case a minimally invasive biopsy of axillary lymph node(s) has been performed and yielded a negative or inconclusive result, patients may be included if the final classification after imaging-pathology-correlation is cN+
- cT1-cT4c
- Scheduled for neoadjuvant systemic therapy
- Female / male patients  $\geq$  18 years old

### Exclusion criteria

- Distant metastasis
- Recurrent breast cancer
- Inflammatory breast cancer
- Extramammary breast cancer
- Bilateral breast cancer
- History of invasive breast cancer, DCIS or any other invasive cancer
- Confirmed or suspected supraclavicular lymph node metastasis
- Confirmed or suspected parasternal lymph node metastasis
- Axillary surgery before NACT (e.g. SLNB or nodal sampling)
- Pregnancy
- Less than 4 cycles of NACT administered
- Patients not suitable for surgical treatment

## **Registration and therapy**

All patients with histologically confirmed invasive breast cancer and suspicious ipsilateral axillary lymph node(s) on ultrasound and/or clinical examination should be informed about the possible participation in the AXSANA study. The inclusion and exclusion criteria are verified by the investigator and written informed consent is obtained from the patient. The pretherapeutic evaluation of the suspicious node is conducted using core biopsy or fine needle aspiration.

Surgical treatment, pathological assessment and postoperative locoregional and systemic therapy should be conducted according to institutional and national standards. Since the AXSANA study is a non-interventional trial, the study sites do not deviate from their own institutional protocol at any timepoint.

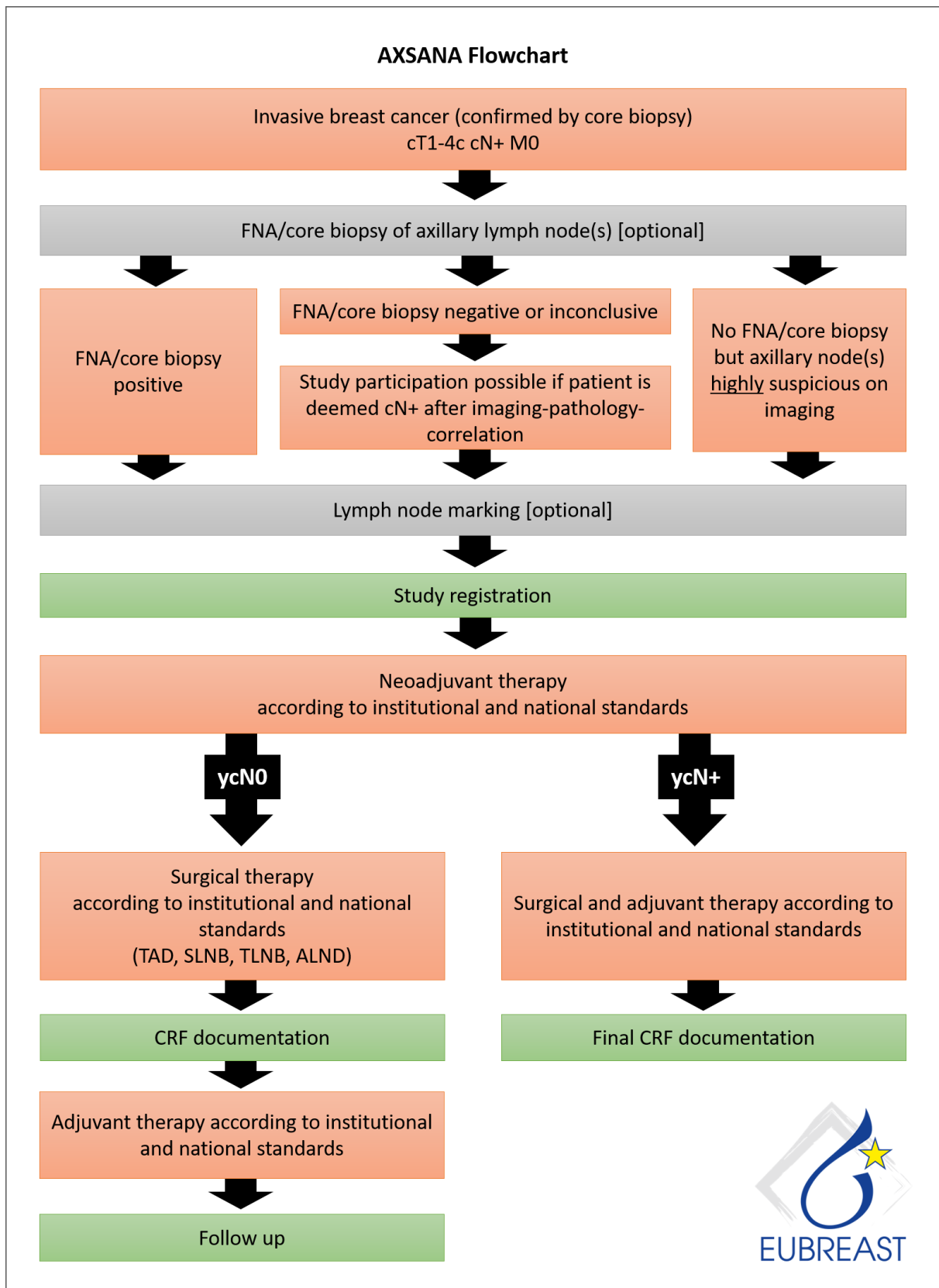
Tissue from the axilla must be clearly identified as SLN, TLN or non-SLN. In case the SLN and the TLN are the same node, this must be documented.

The follow up on patient status is conducted yearly during the first 5 years after surgery. The follow up on arm morbidity and quality of life is conducted at baseline (i.e. between 4 weeks before surgery and the day of surgery) and after 1, 3 and 5 years.

### **Evaluation of the quality of life**

The quality of life is to be evaluated using standardized forms that are included in the CRF:

- EORTC QLQ-C 30
- EORTC QLQ BR 23
- Lymph ICF
- Sense of coherence (SoC)
- Three questions concerning training activity and smoking



## **Data management and analysis**

Data management and analysis are conducted by the EUBREAST study group and its affiliates. All patients who fulfill inclusion criteria should be recorded in the study identification list that remains at the study site. For further analysis pseudonymized data are either filled in the CRF by the study site and forwarded to the Klinikum Esslingen, Germany for inclusion in the electronic database or transmitted directly by the study site via eCRF. Are the data insufficient for evaluation of predefined study aims, the center will be requested to provide further pseudonymized surgical and pathological details.

## **Statistical considerations**

The analysis will be conducted using descriptive statistics.

## **Funding**

The study will be supported by the AGO-B (study group of the German Working Group Gynecological Oncology), the AWOgyn (the German Working Group for Reconstructive Surgery in Oncology-Gynecology) and a grant from the Claudia von Schilling Foundation for Breast Cancer Research. Further grants may be applied for.

## **Target accrual**

3000 patients

## **Study duration**

10 years (5 years of enrollment and 5 years follow up)

## Amendments

<p>Amendment 1 (26.10.2020)</p>	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• “cN+ (confirmed by core biopsy or fine needle aspiration)” changed to: “cN+ (confirmed by core biopsy/fine needle aspiration or presence of highly suspicious axillary node[s] on imaging)”</li> <li>• Added: “In case a minimally invasive biopsy of axillary lymph node(s) has been performed and yielded a negative or inconclusive result, patients may be included if the final classification after imaging-pathology-correlation is cN+”</li> <li>• „cT1-3“ changed to „cT1-cT4c“</li> </ul> <p>The following exclusion criteria have been added:</p> <ul style="list-style-type: none"> <li>• Bilateral breast cancer</li> <li>• History of invasive breast cancer, DCIS or any other invasive cancer</li> <li>• Confirmed or suspected supraclavicular lymph node metastasis</li> <li>• Confirmed or suspected parasternal lymph node metastasis</li> <li>• Axillary surgery before NACT (e.g. SLNB or nodal sampling)</li> </ul> <p>Evaluation of the quality of life: “Three questions concerning training activity and smoking” added</p> <p>AXSANA Flowchart changed according to new inclusion and exclusion criteria</p> <p>Funding: “Further grants may be applied for” added</p> <p>Target accrual added</p> <p>Study duration added</p>
-------------------------------------	---



## References

1. Kühn T, Klauss W, Darsow M, Regele S, Flock F, Maiterth C, Dahlbender R, Wendt I, Kreienberg R. Long-term morbidity following axillary dissection in breast cancer patients – clinical assessment, significance for life quality and the impact of demographic, oncologic and therapeutic factors. *Breast Cancer Res Treat* 2000; 64(3):275-286
2. Diagnosis and Treatment of Patients with early and advanced Breast Cancer. Published by AGO Breast Committee (represented by: Wolfgang Janni) of the German Working Group Gynecological Oncology 2019
3. German S3 guideline on breast cancer. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.1, 2018 AWMF Registernummer: 032-045OL, <http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/> (accessed: Dec 11th 2019)
4. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer, Version 3.2019 – September 6, 2019, accessed: Dec 27<sup>th</sup> 2019, [www.nccn.org](http://www.nccn.org)
5. Cardoso F, Kyriakides S, Ohno S et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2019; 30: 1194–1220, 2019 doi:10.1093/annonc/mdz173
6. Boughey J, Suman V, Mittendorf E et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013;310(14):1455-1461
7. Kuehn T, Bauerfeind I, Fehm T et al. Sentinel-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicenter cohort study. *Lancet Oncol* 2013;14(7):609-618
8. Caudle AS, Wang WT, Krishnamurthy S et al. Improved Axillary Evaluation after Neoadjuvant Chemotherapy for Patients with Node-Positive Breast Cancer using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection. *J Clin Oncol* 2016; 34:1072-8
9. Untch M, Jackisch C, Schneeweiss A et al. NAB – Paclitaxel Improves Disease Free Survival in Early Breast Cancer: GBG 69 – GeparSepto. *J Clin Oncol* 2019 doi: 10.1200/JCO.18.01842
10. Boughey J, McCall L, Ballman K et al. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant

chemotherapy for breast cancer: findings from ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg* 2014;260(4):608-614

11. Wong SM, Weiss A, Mittendorf EA, King TA, Golshan M. Surgical Management of the Axilla in Clinically Node-Positive Patients Receiving Neoadjuvant Chemotherapy: A National Cancer Database Analysis. *Ann Surg Oncol* 2019; Jul24. Doi:10.1245/s10434-019-07583
12. Hartmann S, Reimer T, Gerber B et al. Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic treatment. *Eur J Surg Oncol* 2018; 34:1072-78
13. Siso C, Torres J, Esgueva-Colmenarejo A et al. Intraoperative Ultrasound-Guided Excision of Axillary Clip with Neoadjuvant Therapy (IRINA Trial). *Ann Surg Oncol* 2018; 25:784-91
14. Banyas-Paluchowski M, Gruber IV, Hartkopf A et al. Axillary ultrasound for prediction of response to neoadjuvant therapy in the context of surgical strategies to axillary dissection in primary breast cancer: a systematic review of the current literature. *Arch Gyn Obstet* 2020, DOI: 10.1007/s00404-019-05428-x