STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Dr. med. Walter P. Weber Chief Breast Surgery Service University Hospital Basel
Study Title	Axillary radiotherapy or axillary lymph node dissection in patients with clinically node-positive breast cancer undergoing upfront tailored axillary surgery: An international, randomized superiority trial
Short Title / Study ID	OPBC-10/ NOAX
Protocol Version and Date	v1.1, 04 August 2025
Study Registration	The trial will be registered at https://clinicaltrials.gov and Human Research Switzerland https://www.humanforschung-schweiz.ch/.
Study Category and Rationale	Other Clinical trial with health intervention. The health-intervention is tailored axillary surgery a personalized, situation-dependent approach to axillary management combined with axillary radiotherapy. According to the Swiss HRA and its corresponding Ordinance on clinical trials (ClinO), this trial is classified as category B.
Background and Rationale	Despite major morbidity, axillary lymph node dissection (ALND) is standard of care in patients with clinically node positive breast cancer (cN+ BC) who undergo upfront surgery, which is frequently indicated in case of luminal biology. Tailored axillary surgery (TAS) was shown to selectively target positive nodes, thereby removing significantly more nodes than sentinel lymph node biopsy (SLNB), but less nodes than ALND. Therefore, it is currently unclear if TAS in combination with axillary radiotherapy (ART) exposes the axilla to less harm compared to ALND. It is hypothesized that patient's quality of life (QoL) and morbidity can be improved by replacing ALND with the combination of TAS and ART in patients undergoing upfront surgery. The main goal of the proposed NOAX trial is to investigate if in patients with clinically node positive breast cancer undergoing upfront surgery, treatment with TAS and ART is superior to ALND in terms of QoL and lymphedema.
Risk / Benefit Assessment	The potential risk associated with trial participation is that TAS followed by ART may be inferior to ALND in terms of oncologic safety, resulting in an increased risk of recurrence. The potential benefit is that TAS followed by ART may be equally effective in terms of oncologic safety, but superior in terms of morbidity, thereby improving patients' QoL and lymphedema.
Objective(s) *(continued on the next page)*	Primary objective: Evaluate the impact of TAS combined with ART compared to ALND on the arm-specific quality of life and the incidence of lymphedema in patients with clinically node-positive breast cancer undergoing upfront surgery.

Objective(s) *(continuation)*	<u>Secondary objectives</u> Evaluate the impact of TAS combined with ART compared to ALND at different timepoints on: • Quality of life • Shoulder range of motion • The incidence and nature of surgical complications • Oncological outcomes Radiotherapy-related toxicity
Endpoint(s)	<u>Co-primary endpoints:</u> • Change in arm-specific quality of life from baseline to 24 months post-randomization, measured by the ARM subscale of the FACT-B+4 questionnaire. • Incidence of lymphedema within 24 months following randomization, based on standardized arm volume measurements. <u>Secondary endpoints:</u> • Changes in quality of life, measured by the FACT-B+4 and Lymph-ICF questionnaires at different timepoints. • Range of shoulder motion, assessed by goniometry at different timepoints. • Incidence and severity of surgical complications, including pain, abnormal sensation, seroma, brachial plexopathy, hemorrhage and site infections. • Incidence and severity of radiotherapy-related adverse events, including both acute and late toxicities. • Oncological outcomes, including local, regional, and distant recurrence rates and disease and recurrence free survival.
Study Design	International, multicenter, randomized controlled, superiority trial comparing TAS and ART (experimental group) to ALND (control group) in terms of arm-related QoL and occurrence of lymphedema two years after randomization (co-primary endpoints).
Inclusion- / Exclusion Criteria *(continued on the next page)*	<u>Inclusion criteria at screening:</u> • Written informed consent according to ICH/GCP regulations prior to any trial specific procedures. • Patients ≥ 18 years of age. • Node-positive breast cancer (histologically or cytologically proven both in primary tumor and in lymph node) AJCC/UICC stage II-III (all molecular subtypes allowed). • Node-positivity detected by imaging and non-palpable (iN+) and confirmed by pathology. • Node-positivity palpable (cN1-3) and confirmed by pathology. • Occult breast cancer is allowed, if biopsy-proven axillary lymphatic metastasis is present.

Inclusion- / Exclusion Criteria *(continuation)*	• Eligible for primary ALND or SLN procedure and either: - Newly diagnosed. - Isolated in-breast recurrence or second ipsilateral breast cancer after previous breast conserving surgery and sentinel procedure and at least 3 years disease free and no prior axillary dissection or axillary RT. • Upfront surgery setting. • Most suspicious axillary lymph node clipped. *(If clipping is not part of the routine, this should be done after consent of the patient as a study procedure.)* • Ability to complete the QoL questionnaires. • WHO performance status 0-2 (see Appendix 1). • Adequate condition for general anesthesia, breast cancer surgery and radiotherapy. • Adult patients (≥18 years of age). • Women of child-bearing potential are using effective contraception (condom, diaphragm, intrauterine device), are not pregnant or lactating and agree not to become pregnant during trial treatment (until end of RT) and thereafter during the time recommended by the guidelines – also for adjuvant systemic therapies. A negative pregnancy test before registration is required for all women of child-bearing potential. • Men agree not to father a child during trial treatment and for 6 months afterward. <u>Exclusion criteria at screening:</u> • Stage IV breast cancer. • Clinical N3c breast cancer without axillary disease (clinical N3a and clinical N3b are allowed). • Clinical N2b breast cancer (clinical N2a is allowed). • Contralateral breast cancer within 3 years. • Prior axillary surgery (except prior sentinel node procedure in case of in-breast recurrence). • Prior regional radiotherapy. • Neoadjuvant treatment with the exception of bridging therapy given for less than 3 months. • History of hematologic or primary solid tumor malignancy, unless in remission for at least 3 years from pre-registration with the exception of adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer. • Any other serious underlying medical, psychiatric, psychological, familial or geographical condition, which in the judgment of the investigator may interfere with the planned staging, treatment and follow-up, affect patient compliance or place the patient at high risk from treatment-related complications.

(continued on the next page) **Inclusion- / Exclusion Criteria** *(continuation)*	<u>Exclusion criteria at randomization (intraoperatively):</u> • Absence of clip in the specimen radiography. • Palpable disease left behind in the axilla after TAS. • No SLN identified in the axilla.
Number of Participants with Rationale	1060 patients (530 per treatment arm), about 765 of whom were/will be included into the TAXIS trial by December 2025 and about 295 additional patients to be recruited within the NOAX trial. The exact numbers will be determined, when TAXIS accrual is completed. For rationale see statistical consideration.
Study Intervention (I) – all patients	<u>Surgery:</u> Tailored Axillary Surgery (TAS) includes the sentinel lymph node (SLN) procedure, radiographic confirmation of the removal of previously marked lymph nodes (clip removal), and the targeted excision of palpably suspicious lymph nodes. <u>Radiotherapy:</u> All patients receive adjuvant breast irradiation following breast-conserving surgery, along with extended regional lymph node irradiation. In Arm A (control group), the axilla is excluded from the radiation field, whereas in Arm B (intervention group), the axilla is included.
Study Intervention (II)	<u>Arm B (experimental), Radiotherapy:</u> Axillary radiotherapy (ART).
Control Intervention	<u>Arm A (control), Surgery:</u> ALND – current standard of care, with the intention to remove the entire soft tissue within the anatomical borders of the axilla.
Study procedures	• Pre-treatment assessments include breast/axilla imaging, clinical exams, QoL questionnaire, pregnancy test, arm measurements, and shoulder mobility. • Clipping of the most suspicious lymph node prior to surgery, in case this is not part of the clinical routine. • Randomization: - Arm A (Control): TAS + ALND + breast/chest wall irradiation excluding the axilla. - Arm B (Investigational): TAS + breast/chest wall and axillary irradiation. • Assessment of surgical characteristics occur one and 4 weeks after surgery including surgical complications and AE monitoring • Radiotherapy assessments occur before, at the end of, and 3 weeks post-treatment, including symptom-guided exams and AE monitoring. • Follow-up: (I) Interventional phase (up to 24 months): QoL, lymphedema, shoulder mobility, oncologic outcomes, and complications including related (S)AEs.

	(II) Observational phase (3–10 years after randomization): QoL, lymphedema, shoulder mobility, oncologic outcomes, and long term complications.
Study Duration and Schedule	First patient in: Q1/2026 Last patient in: Q4/2027 Treatment of last patient: Q2/2028 Primary endpoint analysis: Q2/2029 Last patient last visit: Q4/2037 Study report and manuscript: Q2/2038
Investigator(s)	Please refer to the separate document "OPBC-10/NOAX participating sites and investigators" for the complete contact list of investigators.
Study Center(s)	An international, multicenter trial is planned, with over 32 participating sites across approximately ten countries, including CH, DE, AT, HR, GR, IT, KR, AR, CA, and the USA.
Statistical Considerations	Sample size calculations using PASS 2024 are based on two co-primary endpoints: Change in the FACT-B ARM subscale and incidence of lymphedema at two years. A 2-point difference in the ARM subscale was defined as the minimal clinically important difference. Assuming a standard deviation of 3.5 points, a 5% significance level, a power of 90%, and a 10% dropout rate, calculations indicate that 148 patients are required. Lymphedema incidence was estimated at 12% after ALND, with a 50% reduction when ALND is omitted. Using a 5% significance level, a power of 90%, and a 10% dropout rate, calculations estimate that 1060 patients (530 per arm) are needed. These sample size calculations ensure adequate power to detect clinically meaningful differences in both quality of life and lymphedema outcomes.
Data privacy	Trial and participant data and samples will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the study. On the electronic Case Report Form (eCRF) and other study specific documents, participants are only identified by a unique participant number; therefore, coded data and samples will be used for the trial analysis.
Ethical consideration	The NOAX study addresses an important clinical question on axillary surgery de-escalation in patients with breast cancer in the upfront surgery setting, aiming to lower morbidity without compromising cancer control. Risks are limited to standard surgical and radiotherapy complications, with careful monitoring to protect patient safety. Potential benefits include improved quality of life through reduced incidence of lymphedema and less surgical morbidity.
GCP Statement	This trial will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.