HIRSLANDEN

SAKK - SWISS GROUP FOR
CLINICAL CANCER RESEARCH

CTU Hirslanden
Klinik Hirslanden
Witellikerstrasse 40
8032 Zürich
Phone: +41 387 95 45
ClinicalTrialUnit@hirslanden.ch

TRIAL OVERVIEW VISION I

Sponsor:	Hirslanden AG
Trial Title:	Intelligent Vacuum assisted biopsy Immediately before Surgery as an Intra- or pre-Operative surrogate for patient response to Neoadjuvant chemotherapy for breast cancer (VISION I). A multicenter prospective feasibility trial
Short Title / Trial ID:	pCR prediction by I-VAB after NAC
Protocol Version and Date:	Version 2.1, 18.05.2022
Trial registration:	The trial has been registered at www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at www.kofam.ch.
Trial category and Rationale:	Clinical trial with health intervention. The health-intervention is a routine procedure in Switzerland and in the EU. According to the Swiss HRA and its corresponding Ordinance ClinO on clinical trials, this trial is classified as category A.
Clinical Phase:	N/A
Background and Rationale:	Neoadjuvant chemotherapy (NAC), initially indicated to downstage tumors to achieve the option of breast conserving surgery, has lately become common practice in the primary treatment of breast cancer. The use of modern NAC regimens leads to a complete pathologic remission (pCR) of the tumor in more than 50% in aggressive tumor types. In general, it is difficult to predict pCR in the absence of invasive surgical techniques, as it depends on several factors such as biological subtype, the used chemotherapy regimen and anatomic stage. The most common imaging methods beside clinical examination are breast ultrasound, mammography and breast magnetic resonance imaging (MRI). As NAC induces different response patterns, radiologic imaging is not sufficiently accurate in predicting residual disease. Because of this uncertainty, surgery (and the standardized assessment of resected tissue) is so far the only valid option to either ascertain complete response or to remove the complete residual disease. Vacuum-assisted biopsy (VAB) with the possibility of obtaining tissue of the former tumor center could contribute more reliably to detect any residual tumor or respectively, rule out residual disease. Ultrasound (US) or mammographically (MG) guided VAB will be used in this trial in order to detect residual tumor lesions in patients with radiological complete response (rCR) after NAC.

	We have learned from similar previous trials that VAB alone fails to accurately predict pCR in the breast. More promising results have been shown using a combination of multiple clinical, radiological and pathological variables (including VAB)- these variables have been trained and validated to predict pCR using standard machine learning (ML) tools. This more advanced ML-algorithm which includes the result from VAB is termed intelligent VAB (I-VAB). In this trial we aim to prospectively evaluate the diagnostic accuracy of I-VAB using the full pathologic specimen evaluation obtained after open surgery as the gold standard to detect residual tissue.
Objective(s):	The main objective of the trial is to determine the diagnostic accuracy of I-VAB in determining pCR compared to open surgery.
Endpoints:	The primary endpoint of the trial is: • Sensitivity of I-VAB to predict pCR (breast) Secondary endpoints of the trial are: • Sensitivity of the I-VAB to predict pCR in the breast and axilla • Specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) of I-VAB to predict pCR (breast) • Sensitivity of “representative” VAB to predict pCR (breast) • Adverse events (AE) Explorative endpoints of the trial are: • Estimation of the differences in sensitivity between VAB (breast) and I-VAB (breast) per center • Estimation of the generalizability of the I-VAB (breast) and of the I-VAB (axilla) • Sensitivity of the I-VAB retrained on the combined VISION and RESPONDER data (for both breast and breast + axilla separately).
Trial design:	Multicenter, prospective, single arm, feasibility trial

Inclusion / Exclusion criteria:	Inclusion criteria 1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures 2. Unifocal, histologically confirmed invasive breast cancer with IHC luminal B (with or without overexpression or amplification of the HER2 receptor) and all ER negative (ER < 10%) breast cancers Notes: - Multifocal lesions are allowed if they fit into the following definition of satellite lesions: Every tumor close to the main tumor within a distance ≤ the shortest diameter of the main tumor (measured on MRI) (see Appendix 1) - Surrounding non-mass enhancement (NME) next to the primary cancer **and ≤ 2 cm in size** is considered as unifocal breast cancer independently of histologically confirmed or not as ductal carcinoma in situ (DCIS) 3. Initial tumor size larger than 1 and less than 5 cm (cT1c to cT2), any N, M0 4. Clipping of the primary tumor center prior to the start of neo-adjuvant chemotherapy 5. Neoadjuvant chemotherapy resulting in a radiological complete response or near complete response on MR-Imaging (confirmed within 28 days before or on registration) as described in the trial specific MR-Imaging instructions (available on the welcome page of the study specific SecuTrial link (hirslanden.ch/vision)) Notes: - Bilateral breast cancer is allowed, however in case of full remission in both sides, one side will be selected by the investigator for the trial intervention - NAC is administered in accordance with the standard guidelines for the respective tumor subtypes 6. Former tumor bed must be accessible for biopsy 7. Female or male aged ≥ 18 years 8. Adequate condition for breast cancer surgery 9. Patients with a previously treated malignancy are eligible, when the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low Exclusion criteria 1. Metastatic breast cancer 2. Multifocal/Multicentric breast cancer *- Surrounding NME next to the primary cancer and **> 2cm in size** respectively extending to more than 2 cm (measured from the border of the primary cancer), which is either histologically confirmed as DCIS or suspicious of DCIS is considered as unifocal cancer with extensive intraductal component (EIC). This constellation unifocal cancer + EIC is **not** allowed.* 3. Inflammatory breast cancer 4. Luminal-A types of breast cancers (ER ≥ 10% and PgR ≥ 10 % and G1 or 2, and/or Ki-67 ≤ 20%, HER2 negative) or low risk if assessed by a validated genomic prognostic test (e.g. Mammaprint,

	Endopredict, Oncotype or Nanostring) 5. Distinct radiological sign of residual disease in the breast after neo-adjuvant chemotherapy in MRI 6. Intra-/peritumoral microcalcifications larger than 2 cm at time of diagnosis 7. Any local therapy (irradiation or surgery) to the currently treated breast prior to the trial intervention 8. Contraindication for MRI 9. Any other serious underlying medical, psychiatric, psychological, familial or geographical condition, which in the judgment of the investigator may interfere with the planned staging, trial intervention and follow-up, affect patient compliance or place the patient at high risk from trial intervention-related complications
Measurements and procedures:	The trial intervention consists of a diagnostic interventional procedure, US-guided or mammographically guided VAB post-NAC, prior to the standard breast surgery. In patients scheduled for NAC, the center of the tumor will be marked with a clip under US-guidance as part of site standard operating procedure. NAC is administered in accordance with the standard guidelines for the respective tumor subtypes. After completion of NAC, a final MRI will be performed to evaluate the radiological response. Patients with either rCR or near-rCR on MRI are allowed to enter the study and will undergo US-guided VAB, provided the clip was sonographically detectable during prior examination. If the clip cannot be visualized in ultrasound, investigators will use stereotactic guidance (mammography). The VAB has to be performed either concurrently to the surgical excision of the tumor bed or up to 1 week before surgery. Only qualified surgeons or radiologists are allowed to perform or supervise the VAB. Following VAB, conventional surgery is performed, either in the form of breast conserving surgery or mastectomy. Results obtained from the pathologist for both tissue samples will be compared to determine whether VAB can reliably predict pCR in patients who have undergone NAC. **Evaluations before registration** Mammography at time of diagnosis, histological confirmation of breast cancer, staging according to local standards, clip-control by US, breast MRI (at diagnosis) **Evaluations within 4 weeks before or at registration** Medical history, vital signs (weight and height), mammography (limited to the clipped/affected breast), clinical examination of the breast and the axilla, preoperative breast US and clip-control, breast MRI (post-NAC) **Evaluations at trial intervention** Adverse events **Evaluations in the follow-up phase** Clinical examination of the breast and the axilla, adverse events

IMP / Intervention:	VAB post-NAC followed by surgery (breast conserving surgery or mastectomy)
Control Intervention (if applicable):	Surgery is performed according to institutional routine practice in all patients. This is a feasibility trial.
Number of Participants with Rationale:	It is planned to enroll a total of 420 patients in the trial. See statistical considerations for rationale.
Trial Duration:	Start of the trial: Q2 2020 End of accrual: Q2 2025 End of trial treatment: Q2 2025 Follow-up for 14 days after the conservative breast surgery or mastectomy Trial termination (last patient last visit): Q2 2025
Schedule:	First-Participant-In: Q2 2020 Last-Participant-Out: Q2 2025
Coordinating Investigator:	PD Dr. med. Christoph Tausch Brust-Zentrum, Zürich Phone: +41 44 533 81 01 c.tausch@brust-zentrum.ch
Investigator(s):	The Investigator List can be downloaded from the welcome page of the study specific SecuTrial link (hirslanden.ch/vision) and is listed in Appendix 2
Trial Site(s):	International and multicenter with 32 participating sites foreseen (Current status: Switzerland: 18; Germany 3; Austria: 5
Statistical Considerations:	The sample size is based on the primary endpoint sensitivity. With a typeI error of 5% and a power of 80%, 179 patients in the primary full analysis set (PFAS) with non pCR in surgical specimen will be needed to show that the sensitivity is higher than 0.9. Consequently, a total of 358 patients in PFAS have to be recruited to get the required number of patients with non pCR in surgical specimen. To account for patients who were excluded from the PFAS, the number of patients need to be accrued will be increased to 420. The number of patients excluded from the PFAS will be regularly checked from the time point where the accrual of 358 patients is reached and if necessary the sample size will be adjusted. One interim analysis for efficacy is foreseen after 210 patients are recruited and have their follow-up assessment. The primary endpoint will be analyzed based on the PFAS and other efficacy endpoints will be analyzed based on the FAS.
GCP Statement:	This trial will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.