Evaluation of Pathological Complete Response (pCR) and Immunomodulatory Effects Following Intratumoral Injection of INT230-6 Prior to Neoadjuvant Immuno-chemotherapy in Early-Stage Triple Negative Breast Cancer (TNBC): A Phase II Randomized Study, the INVINCIBLE-4-SAKK 66/22 Trial. NCT06358573

Ursina Zürrer-Härdi, M.D.[1], Andreas Müller, M.D.[1], Arianna Calcinotto, Asst. Prof., Ph.D.[2], Zsuzsanna Varga, Prof., M.D.[3], Magda Marcon, P.D., M.D.[4], Olivier Tredan, M.D.[5], Katrin Gobat[6], Katrin Eckhardt, Ph.D.[6], Roch-Philippe Charles, P.D., Ph.D.[6], Razvan Andrei Popescu, M.D., FRCP[7], Thomas Schmid, M.D.[8], Lorenzo Rossi, M.D.[9], Michael Schwitter, M.D.[10], Marcus Vetter, M.D.[11], Markus Niemeyer, M.D.[12], Witzel Isabell, M.D.[13], Patsouris Anne, M.D.[14], Sylvain Ladoire, M.D.[15], Jérôme Martin-Babau, M.D.[16], Antoine Deleuze, M.D.[17], Marie Robert, M.D.[18], Lewis H. Bender[19], Markus Joerger, Prof, Ph.D., M.D.[20] for the Swiss Group for Clinical Cancer Research (SAKK)

[1]Kantonsspital Winterthur, CH, [2]Institute of Oncology Research, Bellinzona, CH, [3]Institute of Pathology and Molecular Pathology, University Hospital Zurich, CH, [4]Institute for diagnostic and Interventional Radiology, University Hospital Zurich, CH, [5]Centre Léon Bérard, Lyon, FR, [6]Swiss Group for Clinical Cancer Research (SAKK), Competence Center, Berne, CH, [7]Tumor Zentrum Aarau and Hirslanden Clinic Aarau, Aarau, CH, [8]Claraspital, Basel, CH, [9]EOC, Bellinzona, CH, [10]Kantonsspital Graubünden, Chur, CH, [11]Kantonspital Baselland, Liestal, CH, [12]Tumor- und Brust Zentrum Ostschweiz, St. Gallen, CH, [13]Universitätsspital Zürich, CH, [14]ICO Site Paul Papin, Angers, FR, [15]CGFL, Dijon, FR, [16]Hôpital Privé des Côtes d'Armor – Centre Cario-HPCA, Plérin, FR, [17]Centre Eugène Marquis, Rennes, FR, [18]ICO – Site René Gauducheau, Saint-Herblain, FR, [19]Intensity Therapeutics, Inc., Shelton, CT, USA, [20]Kantonspspital St. Gallen, CH

Background

TNBC poses significant challenges due to its aggressiveness, high relapse rates, and increased mortality. Neoadjuvant immuno-chemotherapy (NAIC) is now a common treatment for early-stage (≥T2 or N+) TNBC before surgery. NAIC aims to eliminate viable cancer in the tumor, lymph nodes and possible occult distant metastases, and shrink tumors to improve surgical outcomes and prevent disease recurrence. The Keynote-522 (KN522) study revealed a 81.2% 5-year event-free survival (EFS) and 86.6% overall survival in early-stage TNBC patients using NAIC. The KN522 regimen also improved pCR rates from 51.2% with neoadjuvant Chemotherapy to 64.8% with neoadjuvant immuno-chemotherapy. Larger tumors pose an increased risk for resulting in a non-pCR and breast cancer recurrence post-surgery. A new method with the potential to improve clinical outcome and induce immune activation pre-surgery is through novel local therapies in combination with immuno-chemotherapy that could cause increased cell death, create personalized tumor antigens and potentially increase pCR.

New Drug Product INT230-6

- INT230-6 is a novel product with a unique dual anti-cancer mechanism that achieves cancer cell apoptosis and activation of immune cells. The drug is designed specifically for the intratumoral injection (IT) into dense, fatty tumors and is comprised of cisplatin (CIS) and vinblastine (VIN) co-formulated with a cell penetration and unique tissue dispersing enhancing molecule, 8-((2-hydroxybenzoyl)amino) octanoate (SHAO).
- Previous non-clinical studies have demonstrated that INT230-6 halts cancer cell replication and induces apoptosis while maturing dendritic cells and recruiting T-cells to the tumor microenvironment.

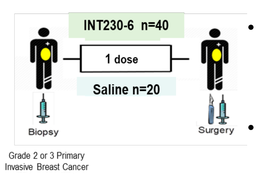
Prior Clinical Use in Local Breast Cancer

- Arnaout et al. conducted a randomized, phase 2 neoadjuvant window-of-opportunity trial using IT INT230-6 that, evaluated clinical and biological effects in patients with early-stage operable breast cancer (the INVINCIBLE trial, NCT04781725).
- 91 women with newly diagnosed operable early-stage intermediate or high-grade T1-T2 invasive breast cancers randomly allocated (2:1) prior to resection to intratumoral injections of INT230-6 vs no treatment or saline sham.
- This study had two parts

Part I (N=29) was a randomized trial comparing 1-3 doses of INT230-6 injected weekly vs no treatment prior to surgery to evaluate safety, feasibility, and optimal drug dosing.

PART II was a double-blinded randomized trial of 60 patients where patients received **one** dose of intratumoral dose of INT230-6 vs saline sham injection (2:1).

Figure 1. Part II cohorts



Prior Clinical Results

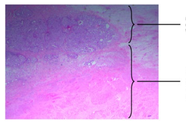
Outline of Tumor Extent
Extent of Necrosis within Tumor (gross pathology assessment

Figure 2. Tumor killing after IT

Patient #14: 3.9 cm invasive ductal cancer: Grade 3, ER+PR+Her2+; 2 intratumoral injections (7.4 and 14.8mls) preoperatively.

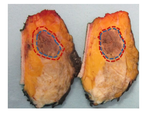
Gross Pathology: 85% necrosis

Histology: increase in tumor infiltrating lymphocytes (TILs) as well as ghost cells consistent with apoptosis

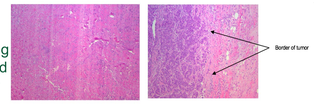


Patient #32
3.3 cm invasive ductal cancer: Grade 2, ER+PR+Her2- (13 mls) preoperatively.

Gross: >95% necrosis



Histology: sheet like necrosis going to and beyond tumor border



Prior Translational Results

Figure 3: TILs

Differential immune cell composition in regions of interest within INT230-6 treated tumors

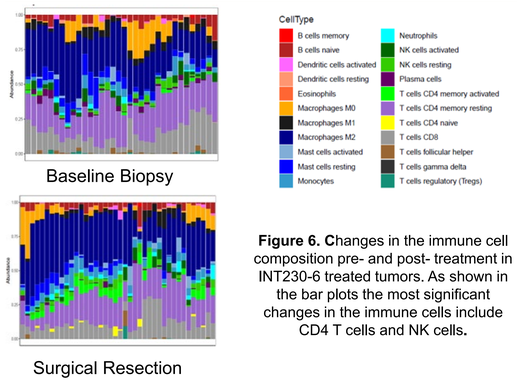


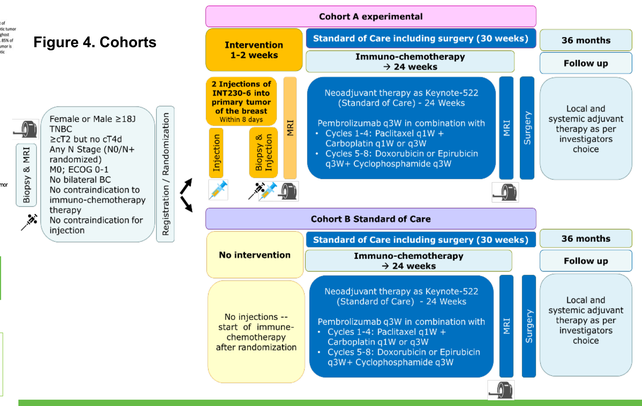
Figure 6. Changes in the immune cell composition pre- and post- treatment in INT230-6 treated tumors. As shown in the bar plots the most significant changes in the immune cells include CD4 T cells and NK cells.

- Results in T2 to T4 tumors showed significant necrosis in 74% of subjects at the time of surgery, with some patients having >95% tumor necrosis following a single IT administration of INT230-6.
- Gene expression analysis showed a significant difference between baseline biopsies and surgical specimens. Pathway analysis identified genes associated with TCR signaling, B-cell and T-cell activation, with increasing effects in post-treatment samples (SABCS 2023 #PS16-03).
- The INVINCIBLE WOO study demonstrated pathologic and immune priming effects of intratumoral cytotoxicity with INT230-6 in traditional immune quiescent breast cancers, with a treatment that is safe and well tolerated
- In INT230-6 treated patients, significant differential gene expression was present and identified genes were associated with T cell activation, lymphocyte activation and inflammatory response
- Treatment with INT230-6 not only resulted in an increase in CD4 T cells and NK cells within the tumor, but there were associated changes in the diversity of T cell repertoire

INVINCIBLE-4 SAKK 66/22 Design

This is a randomized, open-label multicenter phase 2 clinical study to determine the clinical activity, safety, and tolerability of INT230-6 in combination with NAIC in patients with early-stage, operable TNBC and NAIC alone. There are two cohorts, as shown below.

Figure 4. Cohorts

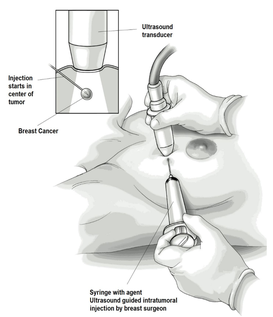


Objectives

The primary objective of this study is to determine the clinical activity of IT INT230-6 in combination with NAIC in patients with early TNBC having tumor T2 to T4c or NAIC alone. The primary endpoint is pCR in the primary tumor (ypT0/Tis) and affected lymph nodes (ypN0)

The secondary objectives of this study are to determine the safety of intratumoral INT230-6 in patients with early TNBC, and to determine translational aspects of its mechanism-of-action.

Figure 5. IT injections



Endpoints

Primary Endpoint

- Pathological complete response (pCR) rate in the primary tumor (ypT0/Tis) and affected lymph nodes (ypN0).

Secondary Endpoints

- pCR rate (invasive and in-situ, only invasive, respectively) in the breast
- pCR rate in lymph nodes
- Pattern of non pCR
- Radiological response according to RECIST v1.1
- Radiological tumor response using two perpendicular diameters
- EFS
- Conversion of intention for mastectomy to BCS or ALND to SLND or TAS after neoadjuvant therapy

Key Inclusion Criteria

- Newly diagnosed, previously untreated, locally advanced non-metastatic TNBC stage cT2-4c N0-3 M0 per American Joint Committee on Cancer (AJCC) version 8 defining TNBC as 0% ER/PgR and HER2-negative.
- Multifocal and multicentric primary tumors are allowed, with the most advanced T stage being used for eligibility. In case of multifocal or multicentric disease, TNBC needs to be confirmed for each focus.
- Patients have to have measurable disease in the breast with at least one lesion with a diameter ≥2cm that is evaluable per RECIST v1.1, visible in ultrasound and injectable.
- Patients are either male or female with age ≥ 18 years,
- ECOG performance status <2,
- Adequate bone marrow function, hepatic and renal function.

Key exclusion Criteria

- Inflammatory Breast Cancer cT4d
- Prior chemotherapy, targeted therapy, radiation therapy or anti-PD-L1 agent for previous breast cancer or Ductal Carcinoma in Situ (DCIS) on the same side.
- Concurrent bilateral breast cancer
- Concomitant treatment with any other experimental drug for recent breast cancer diagnosis in another clinical trial.
- Known history of human immunodeficiency virus (HIV) or active chronic hepatitis C or hepatitis B virus infection or any uncontrolled active systemic infection requiring intravenous (iv) antimicrobial treatment.
- Active autoimmune disease that required systemic treatment in past 2 years
- History of (non-infectious) pneumonitis and tuberculosis.
- Known history of allogeneic organ or stem cell transplant.
- Diagnosis of immunodeficiency, concomitant or prior use of immunosuppressive medication within 7 days before registration.
- Concomitant anticoagulation with warfarin or equivalent vitamin K antagonist, direct thrombin inhibitors or platelet inhibitors/antiplatelet agents that cannot be stopped 24 hours before the administration of IMP.
- Known hypersensitivity to trial drug or to any component of the trial drug.

Statistical Analysis

The sample size calculation for both cohorts is determined based on a single-stage phase II single-arm clinical trial design according to A'Hern. The hypothesis for the trial is as follows:

Null hypothesis (H0): pCR rate ≤ 0.6, Alternative hypothesis (H1): pCR rate ≥ 0.8. The specified parameters for the sample size calculation are: Type I error: 10% (one-sided), Power: 80%. This leads to a sample size of 27 patients per cohort (including 10% dropouts). The accrual duration is expected to be 12 months, and the trial therapy per patient will be eight months. The duration of follow-up is 36 months.

Funding provided by Intensity Therapeutics, Inc.