Intratumoral Injections of INT230-6 Prior to Neoadjuvant Immuno-chemotherapy in Early-Stage Triple Negative Breast Cancer: Early observations from INVINCIBLE-4-SAKK 66/22 (NCT06358573), a Phase II Randomized Clinical Trial

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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 an 81.2% 5-year event-free survival (EFS) and 86.6% overall survival in early-stage TNBC patients using NAIC. The KN522 regiment 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.

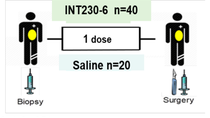
Prior Clinical Use in Local Breast Cancer

- 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

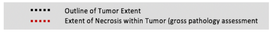


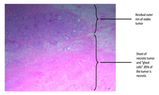
Figure 2. Tumor killing after IT

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

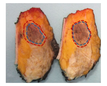


Histology: increase in tumor infiltrating lymphocytes (TILs) as well as ghost cells consistent with apoptosis

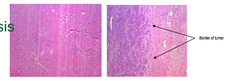


Patient #32: 3.3 cm invasive ductal cancer: Grade 2, ER+PR+Her2- (13 mls) preoperatively.

Gross: 95% necrosis



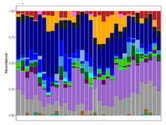
Histology: sheet like necrosis going to and beyond tumor border



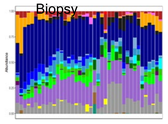
Prior Translational Results

Figure 3: TILs

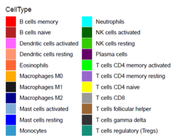
Differential immune cell composition in regions of interest within INT230-6 treated tumors



Baseline Biopsy



Surgical Resection



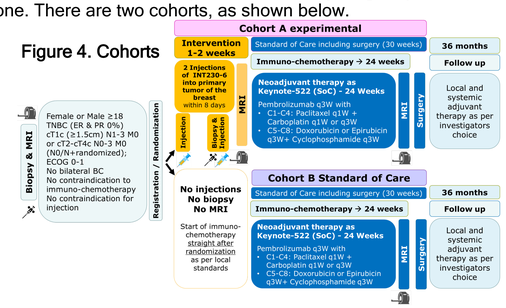
Changes in the immune cell composition pre- and post- treatment in INT230-6 treated tumors. As shown in the bar plots the most significant changes in the immune cells include CD4 T cells and NK cells.

- 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

INVICIBLE-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

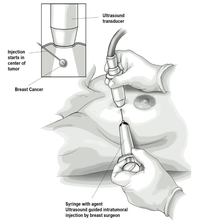


Objectives

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 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. Intratumoral injection



Endpoints and Statistics

Primary Endpoint

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

Secondary Endpoints include

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 treatment

Statistical Considerations

Null hypothesis (H0): pCR rate ≤ 0.6, Alternative hypothesis (H1): pCR rate ≥ 0.8. Type I error: 10% (one-sided), Power: 80%. This Sample size of 27 patients per cohort (including 10% dropouts).

Key Inclusion and Exclusion

Inclusion

- 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 80% ER/PgR and HER2-negative.
- Multifocal and multicentric primary tumors are allowed,
- Measurable disease in the breast with at least one lesion with a diameter ≥1.5cm that is evaluable per RECIST v1.1, visible in ultrasound and injectable.

Exclusion

- Inflammatory Breast Cancer cT4d for concurrent bilateral breast cancer
- 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.
- Concomitant treatment with any other experimental drug for recent breast cancer diagnosis in another clinical trial

Status of the Study

- Trial activation: September 2024
- 14 patients included: 7 in Cohort A and 7 in Cohort B
- 8 sites in Switzerland, 6 in France

Observations (Safety)

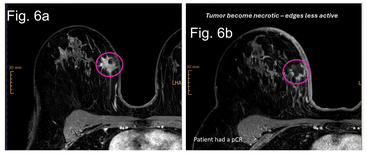
Systemic safety is favorable (per table below) as of 10 Nov 2025

		Cohort A - experimental (N=7)			Cohort B - SOC (N=7)		
SOC	Term	Grade 3	Grade 4	Overall	Grade 3	Grade 4	Overall
Blood and lymphatic system disorders	Anemia				1 (14.3%)		1 (14.3%)
	Febrile neutropenia	2 (28.6%)		2 (28.6%)	2 (28.6%)		2 (28.6%)
Ear and labyrinth disorders	Vertigo				1 (14.3%)		1 (14.3%)
General disorders and administration site conditions	Fatigue				1 (14.3%)		1 (14.3%)
	Injection site reaction	4 (57.1%)		4 (57.1%)			
Infections and infestations	Catheter related infection				1 (14.3%)		1 (14.3%)
	Infected seroma				1 (14.3%)		1 (14.3%)
	Skin infection				1 (14.3%)		1 (14.3%)
	Urinary tract infection	1 (14.3%)		1 (14.3%)			
Investigations	Alanine aminotransferase increased				1 (14.3%)		1 (14.3%)
	Creatinine increased				1 (14.3%)		1 (14.3%)
	GGT increased				1 (14.3%)		1 (14.3%)
	Neutrophil count decreased	2 (28.6%)	2 (28.6%)		1 (14.3%)	2 (28.6%)	3 (42.9%)
Metabolism and nutrition disorders	Anorexia				1 (14.3%)		1 (14.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Disease progression				1 (14.3%)		1 (14.3%)
Nervous system disorders	Guillain-Barre syndrome				1 (14.3%)		1 (14.3%)
	Immunotherapy related encephalitis					1 (14.3%)	1 (14.3%)
Renal and urinary disorders	Chronic kidney disease				2 (28.6%)		2 (28.6%)
TOTAL		7	2	9	17	3	20

A patient with 2.2 cm tumor and 1 dose showed skin irritation at the time of surgery and high levels of tumor necrosis in the MRI Fig. 6; some patients with two doses showed skin and adipose necrosis requiring more surgery. The patient with 1 dose had a pCR.

MRI Predose

Strong contrast uptake



MRI Post 1 Dose

Significant necrosis in tumor

The protocol will be modified to administer one dose at lower volumes for each tumor size; if there is tumor necrosis observed in the MRI, then only 1 dose will be given prior to the start of the NAIC

Poster presented at SABCS 2025

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