

A PHASE II RANDOMIZED WINDOW OF OPPORTUNITY TRIAL EVALUATING CYTOTOXIC AND IMMUNOMODULATORY EFFECTS OF INTRATUMORAL INT230-6 (CISPLATIN, VINBLASTINE) IN EARLY STAGE BREAST CANCER: THE INVINCIBLE TRIAL

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Background The majority of breast cancers are considered immunological quiescent and are therefore minimally responsive to immunotherapies. Local therapies that induce cell death and expose tumor antigens and potentially increase responsiveness to immunotherapies. We conducted a randomized, phase 2 presurgical window-of-opportunity trial with intratumoral (IT) INT230-6 (composed of a dispersion enhancer molecule (SHAO) in solution with drug agents vinblastine and cisplatin) designed to cause tumor necrosis by dispersion throughout the tumor and diffusion into cancer cells. The objective of the trial is to understand the effect of IT cytotoxic chemotherapy on the immune response within the tumor, microenvironment and blood in patients who are awaiting surgery for breast cancer.

Methods Women awaiting surgery for newly diagnosed intermediate or high-grade T1-T2 invasive breast cancers were recruited to the trial. Part I of the study randomized patients to 1-3 doses of INT230-6 injected weekly versus no treatment prior to surgery (2:1, open label) to evaluate safety, feasibility, and optimal drug dosing. Part II was a double-blinded randomized (2:1) trial where patients received one dose of INT230-6 versus saline injection. The primary objective was to assess the degree of tumor necrosis and to perform targeted sequencing and proteomic profiling in tumor samples from injected patients.

Results The study screened 95 patients, of which 87 enrolled. Mean age was 60 (range 40-77 yrs) and tumor size was 1.5-4.3 cm (mean = 2.4cm). The majority of the cancers were ductal histology (82%) and hormone (estrogen and/or progesterone) receptor positive (81%). The most common (>10%) AEs were injection site pain, injection site reaction and nausea/vomiting. INT230-6 induced up to 95% tumor necrosis in varying breast cancer subtypes and histologies, including invasive lobular carcinoma. Gene expression analysis showed significant differential gene expression between the baseline biopsy and surgical specimens. Pathway analysis identified genes associated with TCR signaling, B cells, T cells, chemokine signaling and NF- κ B signaling were significantly changed in the post treatment samples. There was a relative increase in CD4 and CD8 T cells and B and NK cells within the tumor and in the tumor microenvironment.

Conclusions This window of opportunity clinical trial demonstrates that INT230-6 injection is a novel and simple method to convert traditionally immune quiescent breast cancers into immunogenic tumors with minimal adverse effects and good tolerability. The results indicate a future potential for INT230-6 as an immunotherapeutic option in early stage breast cancer.

Trial Registration Phase 2 presurgical Window-Of-Opportunity trial for intratumoral (IT) INT230-6 (comprising VINblastine (VIN) Cisplatin (VIN)) evaluating clinical and BioLogical Effects in patients with early-stage operable Breast Cancer (the

INVINCIBLE trial- <https://clinicaltrials.gov/ct2/show/NCT04781725>).

Ethics Approval Ethics approval has been obtained at the Ottawa Hospital Research Institute 1.2 OHSN-REB Protocol Number: 20210002-01H.

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