Accelerating an Anthracycline-Free Future: A New Drug in Clinical Testing Offers Patients Hope for Safer, More Effective Breast Cancer Therapy Combinations

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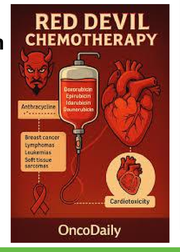
Triple Negative Breast Cancer (TNBC)

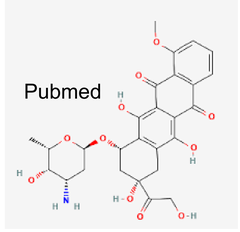
TNBC is an aggressive breast cancer subtype that affects 420,000 women worldwide and 56,000 in the US. Patients agree to intense neoadjuvant immunochemotherapy (Keynote-522), hoping to achieve a pathologic complete response (pCR), which means no cancer left at the time of surgery. Achieving pCR is strongly linked to an increase in event-free survival (EFS) and can serve as an endpoint to expedite FDA drug approvals.

Background

Doxorubicin is used in several chemotherapy regimens for many breast cancer subtypes, including triple-negative breast cancer (TNBC) and HER2-positive breast cancer before surgery (neoadjuvant). Doxorubicin can also be used in early-stage breast cancer in adjuvant therapy, after surgery, or in metastatic breast cancer. Patients refer to this drug as the "red devil." It earns this moniker not just for its harsh red color, but for its side effects: fatigue, nausea, hair loss, and, far worse, permanent heart damage. Some patients die from neoadjuvant treatment itself.

Doxorubicin



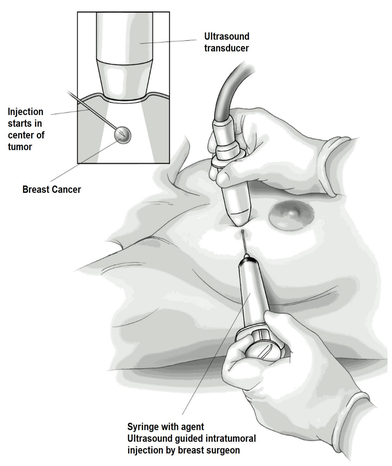


Reference
OncoDaily
June 2025

New Drug Product INT230-6

INT230-6 is a new drug consisting of two potent cytotoxic chemotherapy agents (cisplatin and vinblastine sulfate) formulated with a diffusion and cell penetration enhancer (SHAO) in a single vial. The product candidate is designed for intratumoral injection. INT230-6 kills cancer cells locally and stimulates the immune system to recognize and attack cancer systemically. The drug, after being injected into the tumor, attacks the entire tumor. Figure below shows the IT technique.

Figure 5. IT injections



Prior Clinical Results Using INT230-6

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. When the tumors were injected, patients' tumors showed high levels of necrosis and immune activation

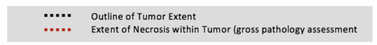


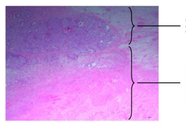
Figure 2. Tumor killing after IT

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

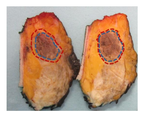


Histology: increase in tumor infiltrating lymphocytes (TILs) as well as ghost cells consistent with apoptosis

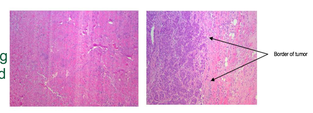


Patient #32
3.3 cm invasive ductal cancer: Grade 2, ER+PR+Her2- (13 mls) preoperatively.

Gross: 95% necrosis



Histology: sheet like necrosis going to and beyond tumor border



Ongoing INVINCIBLE-4 (SCI study 66/22)

INT230-6 is being tested in combination with neoadjuvant immunochemotherapy (NAIC). There are two cohorts. This is a randomized, open-label multicenter phase 2 clinical study to determine the clinical activity, safety, and tolerability of one or two doses of INT230-6 prior to NAIC (the Keynote 522 regimen) in patients with early-stage, operable TNBC and NAIC alone., INT230-6 in tumors ≥1.5 cm. Early results of the study are being presentation as shown below:

- **Abstract Number:** 1589
- **Presentation Number:** PS5-08-16
- **Presenation Title:** 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 Controlled Trial
- **Poster Presentation Date/Time:** Friday, December 12, 2025, 12:30 PM - 2:00 PM

Potential Phase 3 INVINCIBLE TNBC Trial

If the Phase 2 INVINCIBLE-4 study shows a promising increase in pCR with INT230-6 before the KN-522 regimen, the next step would be to design a Phase 3 trial with 2 arms. The aim is a head-to-head comparison of INT230-6 with the KN-522 regimen compared to the KN-522 regimen alone. This trial would allow an interim analysis of pCR to set sample size and power for both pCR and EFS endpoints. Should the totality of the clinical data (pCR and safety) suggest that INT230-6 could replace doxorubicin from the KN-522 regimen, then a third arm could be added (INT230-6 followed by KEYNOTE-522 without doxorubicin). The three-arm randomized controlled Phase 3 study for TNBC patients could be:

1. INT230-6 followed by full KEYNOTE-522 NAIC regimen
2. INT230-6 followed by KEYNOTE-522 without doxorubicin
3. Standard KEYNOTE-522 NAIC regimen alone

The SCARLET Phase III Trial

The SCARLET phase III trial, led by the National Cancer Institute, is studying whether an anthracycline-free regimen (NeoPACT) can remove doxorubicin in early-stage TNBC. To assess whether participants with early stage TNBC randomized to receive anthracycline-free, taxane-platinum neoadjuvant chemotherapy with pembrolizumab have non-inferior breast cancer event-free survival (BC-EFS) compared to participants randomized to taxane-platinum-anthracycline neoadjuvant chemotherapy with pembrolizumab. EFS results are not expected until 2033 or 2034. Many patients are unable to wait so long, in the adjuvant or metastatic settings.

SCARLET STUDY: Patients are randomized to 1 of 2 arms; there are 953 centers in the trial, and plans to enroll >1000 patients

ARM I:
- Patients receive paclitaxel intravenously (IV), carboplatin IV, and pembrolizumab IV on study.
- Patients then receive doxorubicin IV, cyclophosphamide IV, and pembrolizumab IV on study.

ARM II:
- Patients receive docetaxel IV, carboplatin IV, and pembrolizumab IV on study.
- the trial.

Patients then undergo surgery. Patients may receive pembrolizumab after surgery. Patients may optionally undergo collection of blood samples throughout Patients are followed up every 6 months for the first 2 years and then annually until 5 years from registration.

Hypothesis for Use of INT230-6 in TNBC

Recent development showed improved pCR rates and EFS by adding pembrolizumab to neoadjuvant chemotherapy according to data of the Keynote-522 study, confirming the importance of addressing immune-regulatory mechanisms in patients with early TNBC. Still BC is known to be less immune-responsive compared to other solid tumors due to a relatively low tumor mutational burden and immune-excluded or immune-desert histological phenotypes. Accordingly, therapeutic strategies to improve immune reactivity of BC and TNBC in particular are urgently needed.

Given that INT230-6 kills cancer cells locally and stimulates the immune system to recognize and attack cancer systemically, the use of INT230-6 with the KN-522 regimen is likely to show a higher pCR rate than KN-522 alone

Prior Translational INT230-6 Results in BC

Figure 3: TILs

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

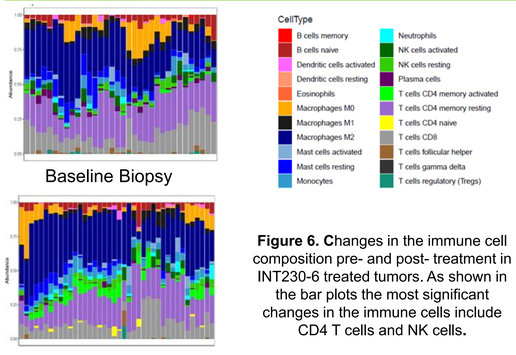


Figure 6. Changes in the immune cell composition pre- and post- treatment in INT230-6 treated tumors. As shown in the bar plots the most significant changes in the immune cells include CD4 T cells and NK cells.

Discussion of the Potential Phase 3 Trial

Pathological complete response (pCR) rate in the primary tumor (ypT0/Tis) and affected lymph nodes (ypN0) would be the primary endpoint for accelerated approval of INT230-6 with a KN-522 regimen with or without doxorubicin. Historically, the FDA has accepted pCR as a surrogate endpoint for accelerated approval. Thus, approval of INT230-6 using arm 2 via a pCR endpoint could allow the use of a neoadjuvant treatment without the red devil well in advance of the SCARLET trial's readout.

To obtain full approval, the Phase 3 study would still need to enroll a sufficient number of TNBC patients to achieve an endpoint of improved EFS. Depending on the clinical benefit, the three-arm 1:1:1 randomized study design, comparing EFS of arms 1 and 2 separately to arm 3, may also enable a faster full-approval pathway for a doxorubicin-free regimen than the Scarlett trial if arm 2 shows a statistically significant improvement in EFS rate at 3 years compared to arm 3.

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