Phase I pilot of pegylated liposomal doxorubicin, CD40 agonist antibody CDX-1140, and Flt3 ligand CDX-301 in advanced HER2-negative breast cancer

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Background

- Metastatic breast cancers have shown limited responses to immune checkpoint blockade (ICB).
- Breast cancer is associated with defects in antigen presentation which may contribute to resistance to ICB[1]. Flt3 ligand (Flt3L) is a growth factor that increases differentiation of DC1 dendritic cells (DCs), critical mediators of antigen presentation. CD40 agonist (CD40a) activates all 3 classes of antigen presenting cells - DCs, B cells, and macrophages – and promote favorable tertiary lymphoid structures[2].
- Anthracycline chemotherapy has been shown to promote immunogenic cell death and enhance responses in combination with immunotherapy in breast cancer clinical trials (TONIC, KEYNOTE-522)[3]. Pegylated liposomal doxorubicin (PLD; Doxil) is the most commonly used anthracycline in metastatic breast cancer.
- We hypothesize that triplet therapy of PLD chemotherapy + Flt3L + CD40a will enhance anti-tumor immunity and improve cancer control, leading to improved long-term outcomes [Fig 1].
- We previously demonstrated synergy when CD40a and Flt3L are combined with pegylated liposomal doxorubicin in pre-clinical models of breast cancer[4]. This novel triplet significantly outperformed PLD as well as other monotherapy and doublet combinations [Fig 2].

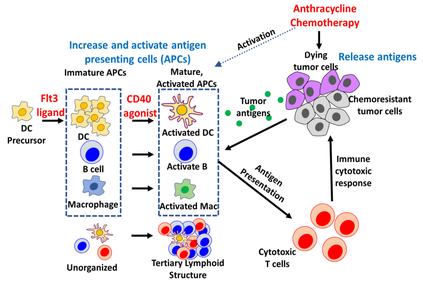


Figure 1. Rationale for Triplet Combination

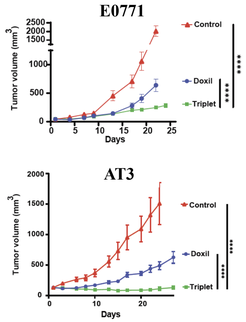


Figure 2. Addition of CD40a and Flt3L enhances tumor control in pre-clinical breast cancer models

Objectives

Primary Objective:

- To determine the safety and tolerability of the drug combination of CD40 agonist CDX-1140, Flt3L CDX-301, and PLD in patients with unresectable or metastatic HER2- breast cancer and specify recommended phase 2 dose for the combination.

Secondary Objectives:

- To assess anti-tumor immune response due to CDX-1140, CDX-301, and chemotherapy.
- To assess anti-tumor immune response due to CDX-1140, CDX-301, and chemotherapy compared to chemotherapy alone.
- To assess median progression free survival by RECIST v1.1 after treatment with CDX-1140, CDX-301, and PLD chemotherapy.
- To determine best overall response rate by RECIST v1.1 after treatment with CDX-1140, CDX-301, and PLD.
- To determine duration of response by RECIST v1.1 after treatment with CDX-1140, CDX-301, and PLD.
- To determine clinical benefit rate by RECIST v1.1 after treatment with CDX-1140, CDX-301, and PLD.

Exploratory Objectives:

- To identify biomarkers of response to CDX-1140, CDX-301, and PLD chemotherapy.
- To identify potential mechanisms of resistance to CDX-1140, CDX-301, and PLD chemotherapy.
- To identify overall survival in patients with unresectable or metastatic HER2 negative breast cancer treated with CDX-1140, CDX-301, and PLD chemotherapy.
- To determine responses in patients treated beyond progression (as determined by RECIST v1.1) using iRECIST.

Study Design

- This is a single arm phase I pilot study of PLD, CDX-1140 (CD40a), and CDX-301 (Flt3L) combination therapy in patients with metastatic or unresectable locally advanced HER2-negative breast cancer (NCT05029999).
- Of note, the trial originally opened to TNBC only but was expanded with recent amendment to all HER2- breast cancers.
- There is a safety run-in followed by dose expansion to a total of 30 evaluable patients.

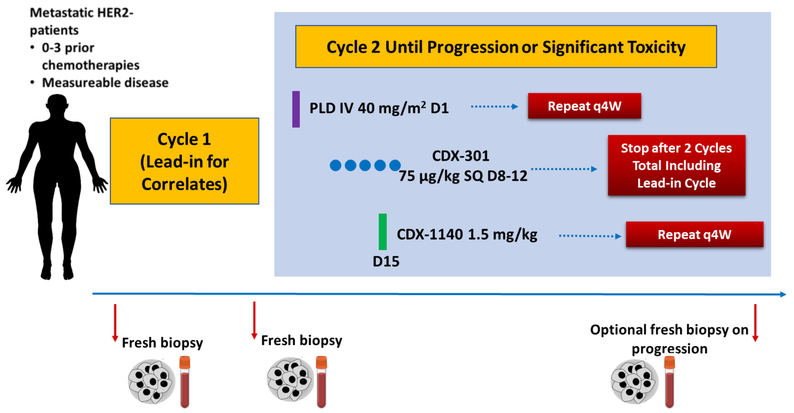


Figure 3. Study Schema

- To complement the clinical signal, we have designed the trial to have a randomized cycle 1 lead-in prior to all patients receiving full triplet therapy with fresh tissue biopsies before and after the lead-in treatment to understand mechanisms of response and resistance. **Cohort B of immunotherapy only closed as of 2/2/24.

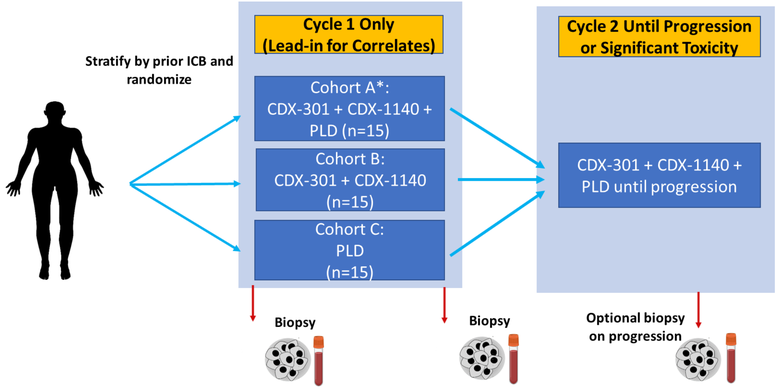


Figure 4. Design for Correlative Analysis to Understand Mechanism of Action

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Unresectable Stage III or Stage IV HER2 negative breast cancer (TNBC or hormone receptor positive).
- For TNBC patients, subject is in first to 4th line setting of treatment for metastatic or unresectable disease and have received 0 to 3 prior regimens for metastatic or unresectable disease.
- For hormone receptor positive breast cancer patients, subjects must have received prior cyclin dependent kinase inhibitor in the metastatic setting. They may have received up to 3 prior lines of chemotherapy and/or antibody drug conjugates for metastatic or unresectable disease.
- Among TNBC patients enrolled in the first line treatment setting, subjects must have either already received PD-1 or PD-L1 blockade in neoadjuvant or adjuvant setting or not be eligible for FDA approved standard of care chemotherapy and anti-PD-1/PD-L1 combination therapy as alternative to this clinical trial.
- Provision of consent for pre-treatment and on-treatment biopsies suitable for correlative studies. This may exclude many lung lesions and small lesions.

Key Exclusion Criteria:

- Prior progression while on anthracycline based therapy or within 6 months of completing neoadjuvant or adjuvant anthracycline.
- Receipt of cellular therapies within 12 weeks (or 2 weeks if patient experienced disease progression on the prior treatment).
- History of (non-infectious) pneumonitis or has current pneumonitis. This includes asymptomatic infiltrates on screening chest CT scan that are suggestive of an inflammatory process (i.e. grade 1 pneumonitis).

Study Updates

- Actively Recruiting Sites:
  - UT Southwestern Medical Center, Dallas, TX
  - Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
  - University of Chicago, Chicago, IL
  - UT San Antonio, San Antonio, TX
  - University of North Carolina, Chapel Hill, NC
- The study opened to enrollment 04-20-2022.
- As of November 20th, 2025, 25 evaluable patients have been enrolled.

References

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