A phase II single-arm, open-label trial of T-DM1 (*ado-trastuzumab emtansine*) And Neratinib for HER2+ Breast Cancer with Molecular Residual Disease (KAN-HER2 MRD)

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INTRODUCTION

- Standard treatment of high risk HER2-positive early breast cancer includes preoperative chemotherapy in combination with trastuzumab (+/-pertuzumab), followed by adjuvant T-DM1 for patients with residual disease at the time of surgery. Despite this, some patients subsequently experience recurrence.[1,2]
- Ongoing randomized studies are investigating whether further escalation of therapy in patients with residual disease can improve outcomes. Precisely identifying those who will not be cured by standard treatment could reduce the financial and clinical toxicity of treatment escalation.
- The detection of circulating tumor DNA (ctDNA) in the adjuvant period is strongly associated with relapse and can further stratify patients with residual disease.[3,4]
- The emerging strategy of ctDNA-based detection of molecular residual disease (MRD) could enable the development of individualized curative treatments for "recurrence interception".
- The RaDaR® assay (NeoGenomics) is a tumor-informed assay that uses deep sequencing to detect ctDNA with high sensitivity and specificity for up to 48 tumor-specific variants.
- Preclinical and clinical evidence suggests that Neratinib, an irreversible inhibitor of the HER2 tyrosine kinase, may be effective in combination with standard T-DM1.[5,6]
- A recommended phase II dose of T-DM1 (3.6 mg/kg) and Neratinib (160 mg/d) was identified in the NSABP FB-10 study.[7]

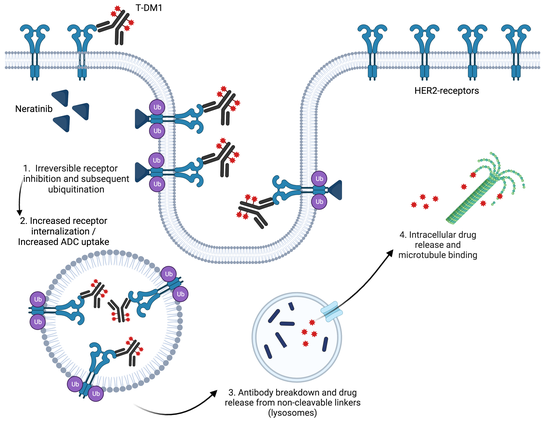

Figure 1. Proposed mechanism of T-DM1 and Neratinib synergy. Irreversible HER2 receptor inhibition increases receptor shuttling and ADC uptake, increasing cellular concentration of emtansine. Ub: ubiquitination of HER2 receptors. Adapted from Li et. al., Cancer Discovery 2020

KAN-HER2 MRD Study Design

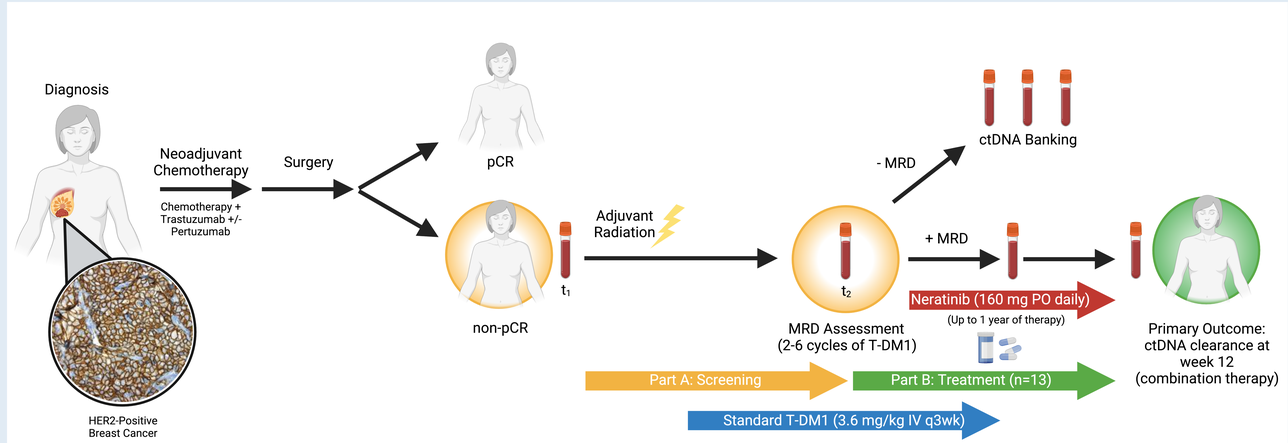

Figure 2. Overall Study Design and Schema. The study consists of two parts. **Part A: MRD screening**, will enroll patients who did not achieve a pCR following standard neoadjuvant therapy for HER2-positive breast cancer, who are planned to receive T-DM1. Tissue and blood will be collected. MRD/ctDNA will be assessed with the clinical NeoGenomics RaDaR assay. A blood sample following 2-6 cycles of T-DM1 will constitute the eligibility sample for the **Interventional / Treatment Phase, Part B:** Participants with MRD/ctDNA detected by RaDaR will be enrolled in the interventional phase where Neratinib (160 mg/day) will be added to standard T-DM1.

ENDPOINTS

Primary objective:

1. Evaluate clearance of ctDNA at week 12 with the addition of Neratinib to T-DM1.

Secondary objectives:

1. Identify correlates of ctDNA MRD+* in the screened population (RCB, tumor genomics, ER, patient-related factors, imaging features etc.).
2. Characterize changes in ctDNA detected post-operatively, upon switch to T-DM1.
3. Describe clinical outcomes for MRD+* patients treated with escalated strategy, including invasive disease free survival (iDFS).
4. Describe clinical outcomes, including iDFS for non-pCR patients *without* detectable MRD+*.
5. Describe the toxicities of the combination of Neratinib and T-DM1 in the study population.

*MRD+ = detection of ctDNA as per RaDaR assay

KAN-HER2 MRD is the first trial to use a highly sensitive ctDNA assay to guide escalation of adjuvant systemic therapy in HER2-positive early breast cancer.

ELIGIBILITY

Part A (Screening Phase):

- Adult patients with histologically confirmed (by local assessment with ASCO/CAP criteria), resected HER2-positive stage I-III breast cancer, with residual invasive disease (non-pCR) following neoadjuvant trastuzumab (+/- pertuzumab)-based chemotherapy
- No clinical and/or radiological evidence of metastases or disease recurrence
- Good performance status and adequate organ function
- No contraindications to T-DM1 or Neratinib
- Tumor tissue (diagnostic biopsy or surgical resection) available for exome sequencing, as required for RaDaR

Part B (Interventional / Treatment Phase):

- Participants of Screening Phase (Part A) with ctDNA detected (positive test by RaDaR) during the eligibility period (following initiation of T-DM1)
- Previous Therapy:
  - Received 2-6 cycles of T-DM1 in the adjuvant setting (prior to eligibility MRD timepoint, *t2*)
  - Adjuvant radiation permitted (minimum 14 day washout required)
  - No prior Neratinib or other HER2 tyrosine kinase inhibitors
- No clinical and/or radiological evidence of metastases or disease recurrence
- Good performance status and adequate organ function
- No contraindications to T-DM1 or Neratinib

STUDY INFORMATION

Status: Active and Recruiting

Clinicaltrials.gov Identifier: NCT05388149

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