A phase II single-arm, open-label trial of T-DM1 (ado-trastuzumab emtansine) And Neratinib for HER2+ Breast Cancer with Molar 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

● 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.

● The emerging strategy of ctDNA-based detection of molecular residual disease (MRD) could enable the development of individualized supportive 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-DM1.1,4

● A recommended phase II dose of TDM1 (2.6 mg/kg) and Neratinib (160 mg/d) was identified in the NSABP FB-10 study.1

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 (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.

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.