CATER-MRD: Capecitabine for Targeted Eradication of aRising ctDNA Molecular Residual Disease in ER+/HER2-negative Breast Cancer

Mitchell J. Elliott[1], Eitan Amir[1], Michelle B. Nadler[1], Meredith Li[1], Celeste Yu[2], Michelle Audoin[3], Girish Putcha[4], Wendy Levin[4], Sofia Birkeälv[4], Nuria Segui[4], Karen Howarth[4], Hal K. Berman[5], Carol Townsley[6], Melinda Wu[6], Lillian L. Siu[1], Philippe L. Bedard[1], David W. Cescon[1]

1. Division of Medical Oncology & Hematology, Department of Medicine, Princess Margaret Cancer Centre and University of Toronto, Toronto, Canada 2. Cancer Genomics Program, Princess Margaret Cancer Centre, Toronto, Canada 3. Patient Partner, Toronto, Canada 4. SAGA Dx, Morrisville, NC, USA 5. Department of Pathology and Laboratory Medicine, University Health Network, Toronto, Canada 6. Department of Family Medicine, Women's College Hospital, Toronto, Canada

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INTRODUCTION

- Routine post-treatment surveillance remains limited, as prior studies using legacy imaging and therapeutic modalities demonstrated no survival advantage to earlier detection of recurrence.[1,2]
- Despite modern therapies and biomarkers, many high-risk ER+/HER2- patients still develop distant metastatic relapse years after treatment.[1]
- Circulating tumor DNA (ctDNA) enables highly sensitive detection of molecular residual disease (MRD), often preceding clinical recurrence by months to years.
- Tumor-informed ctDNA assays that interrogate patient-specific genomic variants provide excellent clinical sensitivity and specificity for MRD detection.[2]
- ctDNA-positive, imaging-negative patients currently have no evidence-based interventions, representing a major unmet need.
- Capecitabine, a 5-FU prodrug with a mechanism distinct from endocrine therapy and CDK4/6 inhibitors, provides potential non cross-resistant antitumor activity.[3,4]
- Capecitabine is an effective and well-tolerated therapy for metastatic ER+/HER2- breast cancer, including endocrine-resistant disease.
- Metronomic low-dose capecitabine in combination with endocrine therapy is active in the 1L metastatic setting[5], and offers continuous exposure, anti-angiogenic and immunomodulatory effects, and good tolerability, well suited for the MRD setting.
- The CATER MRD trial evaluates whether metronomic capecitabine can clear ctDNA and inform future MRD-guided treatment strategies.

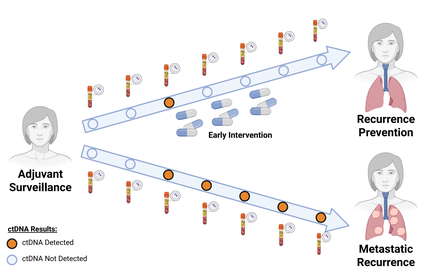

Figure 1. Conceptual Framework for ctDNA-guided Early Intervention to Prevent Metastatic Recurrence. During routine adjuvant surveillance, rising or recurrent ctDNA signals the presence of molecular residual disease (MRD) prior to radiographic detection. Early therapeutic intervention at the point of ctDNA detection has the potential to eliminate MRD and shift the clinical trajectory from metastatic recurrence toward recurrence prevention.

CATER-MRD Study Design

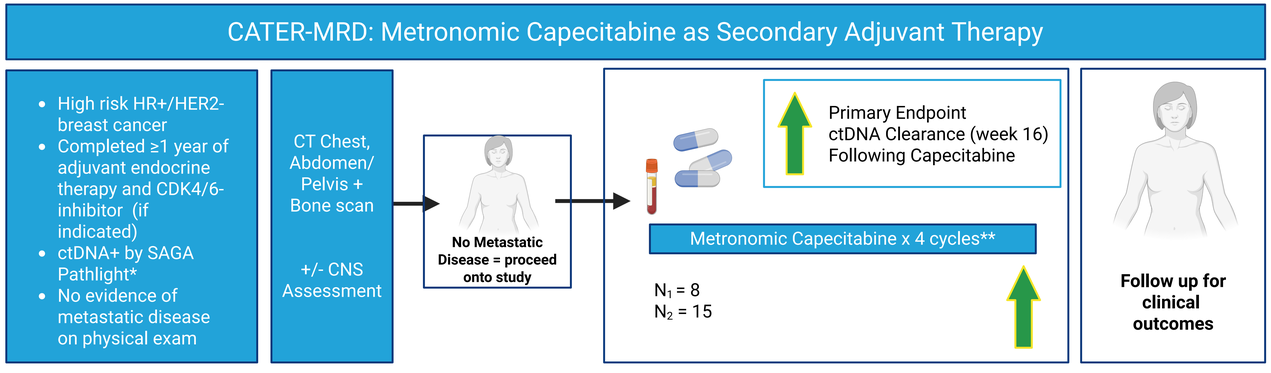

Figure 2. Schema of the CATER-MRD Phase II Trial. This single-arm Phase II study enrolls patients with resected ER+/HER2- stage I–III breast cancer who have received guideline-directed adjuvant endocrine therapy (and CDK4/6 inhibition when indicated) and have ctDNA-detected molecular residual disease (MRD) by the SAGA Pathlight assay. After confirming absence of radiographically detectable metastatic disease, participants receive metronomic capecitabine (500 mg TID) for 12 months. The primary endpoint is week-16 ctDNA clearance, evaluated using a Simon two-stage design ($N_1 = 8$; $N_2 = 15$). Patients are monitored for safety, ctDNA dynamics, and clinical outcomes.

OBJECTIVES

Primary Objective:
Evaluate week-16 clearance of ctDNA using the Pathlight™ assay with the use of metronomic capecitabine in patients with MRD despite standard adjuvant therapy for ER+/HER2-negative breast cancer.

Secondary Objectives:

1. Describe clinical outcomes for MRD+ patients treated with this escalated strategy, including distant recurrence free survival (DRFS), overall survival (OS).
2. Describe the toxicities of metronomic capecitabine in this study population.
3. Characterize dynamic changes and kinetics in ctDNA for MRD+ individuals enrolled in the trial.
4. Describe patient-reported outcomes (PROs)

Exploratory Objectives:

1. Explore the clinical utility of novel liquid biopsy methods.
2. Explore the relationship between genomic/epigenomic features of cancers with MRD and observed ctDNA dynamics upon adjuvant therapy initiation.
3. Characterize the genomic and epigenetic features of treatment-resistant ER+/HER2- breast cancer.

ENROLMENT

- Male or female patients ≥ 18 years of age with histologically confirmed (by local assessment with ASCO/CAP criteria), resected ER-positive/HER2-negative stage I-III breast cancer
- Evidence of MRD (positive test by the Pathlight assay) despite standard adjuvant therapy
- No contraindications to capecitabine (including absence of DPYD variants that in the opinion of the investigator are a contraindication to metronomic capecitabine)
- No clinical or radiographic evidence of recurrent or metastatic disease
- Previous Therapy requirements:
  - Received at least 24 months of adjuvant endocrine therapy, including 6 months of an aromatase inhibitor
  - Received at least 12 months of adjuvant CDK4/6i if indicated, unless not tolerated or declined
- ECOG performance status of 0-1.

STATISTICAL DESIGN

This Simon two-stage Phase II trial evaluates week-16 ctDNA clearance with metronomic capecitabine (P_0=0.10, P_1=0.40; α=0.05; 80% power). Eight patients are enrolled in Stage 1; if ≤1 has clearance of ctDNA, the study ends for futility. If criteria are met, a total of 13 evaluable patients are accrued, with the regimen deemed ineffective if ≤3 clear ctDNA by week 16. Up to 15 patients will be enrolled to account for dropouts, with follow-up every 3 months in year 1 and every 6 months in years 2-3.

CATER MRD is a Phase II study testing metronomic capecitabine as secondary adjuvant therapy for patients with ER+/HER2- breast cancer who have ctDNA-detected molecular residual disease.

STUDY INFORMATION

Status: Active and Recruiting

Lead Site:

- Princess Margaret Cancer Centre, Toronto, Canada [Open]

Clinicaltrials.gov Identifier: NCT05196087

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