VANDERBILT-INGRAM CANCER CENTER



NCI Designated Comprehensive Cancer Center

A randomized clinical trial comparing ctDNA-directed therapy change with standard of care in patients with metastatic triple negative breast cancer

Jessica M. Sharpe, MD, PhD,[1] Caroline Brothers, APRN,[1] Ben H. Park, MD, PhD, [1] Vandana G. Abramson, MD[1]

[1] Division of Hematology and Oncology, Vanderbilt University Medical Center

San Antonio Breast Cancer Symposium ®
December 9-12, 2025

Presentation ID: PS5-07-09

BACKGROUND

- Triple negative breast cancer (TNBC) has high rates of early recurrence and death from metastatic disease.
- The standard of care first line treatment for most patients with metastatic TNBC is cytotoxic chemotherapy, with a smaller subset with CPS scores ≥ 10 eligible for combination pembrolizumab and chemotherapy[1].
- Sacituzumab govitecan (SG) is an anti-Trop-2 antibody-drug conjugate (ADC) currently approved for 2nd or 3rd line therapy in patients with mTNBC and shows higher ORR than chemotherapy in the metastatic setting[2].
- Circulating tumor DNA (ctDNA) levels have been shown to correlate with both systemic cancer burden and response to local and systemic treatment.
- The current standard to assess disease progression or response is CT scan imaging after 2-3 months of chemotherapy. There is an urgent need to identify markers of response and progression earlier to avoid toxicity from regimens that are not working.
- Preliminary data shows ctDNA mean variant allele frequency (VAF) directly correlates with tumor burden[3]. Quantitatively measuring ctDNA to guide therapeutic decisions is a promising, but still untested, strategy.

HYPOTHESIS & OBJECTIVES

Hypothesis:
- Patients with metastatic TNBC who do not have a ≥ 50% decrease in ctDNA mean VAFs two weeks after starting chemotherapy will benefit from an early change to SG.
- Switching to SG less than one month after starting an ineffective first-line therapy will improve outcomes compared to the traditional approach of using staging scans every 3 months to guide treatment changes.

Objectives:
- *Primary:* Assess whether using ctDNA to guide early changes in therapy compared to SOC assessment can prolong PFS in patients with metastatic TNBC.
- *Secondary:* Assess ORR, PFS2, and OS in the ctDNA-guided treatment arm compared to the SOC arm.
- *Exploratory:* Assess primary and secondary objectives in study population patients with particular clonal mutational profiles.

PATIENT SELECTION

Key Inclusion Criteria:
- Patients ≥ 18 years old with metastatic TNBC
- CPS <10 or otherwise not eligible for immune checkpoint inhibitors
- Measurable disease according to RECIST v1.1
- ECOG performance status ≤ 2
- No prior chemotherapy regimens for metastatic disease
- Adequate hematologic, hepatic, and renal function.

Key Exclusion Criteria:
- Major surgical procedure within 4 weeks prior to randomization
- Known brain metastases, leptomeningeal disease, or spinal cord compression that has not been definitively treated
- Uncontrolled cancer-related pain
- Uncontrolled hypercalcemia

STUDY DESIGN

Design: Randomized (1:1) two arm clinical trial

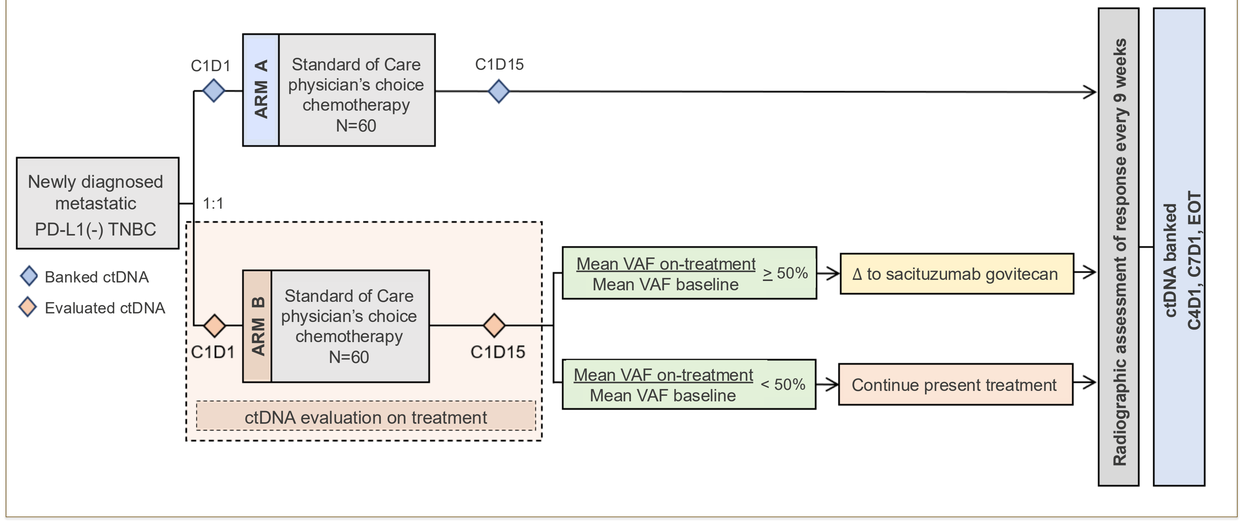
Target Population: Patients with metastatic TNBC not eligible for immunotherapy who have not received prior treatment for metastatic disease

Randomization:
- Patients will be randomized according to a permuted block scheme
- First 3 patients will be placed on Arm B to ensure reporting is efficient and accurate prior to starting randomization.

Sample Size and Power:
- The study will have 80% power to detect a 2-month improvement of PFS between the two study arms with one-sided type I error of 10%.
- Goal: Randomize 120 patients over 24 months

ClinicalTrials.gov Number: NCT05770531

STUDY SCHEMA



ENDPOINTS

Primary Endpoint:
- PFS

Secondary Endpoints:
- Overall response rate (ORR) by RECIST v1.1 criteria
- PFS2
- Overall survival (OS)

Exploratory Endpoints:
- Evaluate for unique predictive values of ctDNA-defined clones identified through the blood-based analysis.
- Assess primary and secondary objectives based on ctDNA-defined clonal mutational profile.
- Correlate changes in ctDNA with standard imaging.

ACKNOWLEDGEMENTS:
Funding – This research was supported by Guardant Health and the Vanderbilt SPORE.
This presentation is the intellectual property of the author/presenter. Contact jessica.m.sharpe@vumc.org for permission to reprint and/or distribute.

STUDY PROGRESS

Enrollment opened: August 4, 2023 at Vanderbilt University Medical Center
- 14 patients enrolled as of November 16, 2025
- Of note, with recent updates from TROPION-Breast02 and ASCENT-03 showing improved PFS with the ADCs SG and datopotamab deruxtecan-dlnk, this study will close early once those agents are approved in the first-line setting for mTNBC.

Contact information: Vandana Abramson, MD at vandana.abramson@vumc.org

REFERENCES

1. Cortes J, *et al*: Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* 396:1817-1828, 2020.
2. Bardia A, *et al*: Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. *New England Journal of Medicine* 384:1529-1541, 2021.
3. Parsons HA, *et al*: Individualized Molecular Analyses Guide Efforts (IMAGE): A Prospective Study of Molecular Profiling of Tissue and Blood in Metastatic Triple Negative Breast Cancer. Clin Cancer Res, 2016.