The PLUMB Study: a **P**rospective study of **L**ob**U**lar **M**etastatic **B**reast cancer using serial circulating tumor DNA to measure disease response

Public/Lay Abstract

Metastatic breast cancer can be classified by its tumor receptor subtype, including the status of hormone receptors (HR) and amplification of the human epidermal growth factor receptor-2 (HER2). Additionally, metastatic breast cancer can also be classified by its histologic growth pattern, with the two most common types being invasive ductal carcinoma and invasive lobular carcinoma (ILC). This study focuses on patients with metastatic invasive lobular carcinoma (mILC), a unique and understudied type of metastatic breast cancer. Historically, mILC has been treated the same as other breast cancer types. But in recent years, there is a new appreciation for significant differences in tumor biology. Patients with mILC are less likely to enroll in clinical trials, experience shorter overall survival, and suffer from a lack of subtype specific research and data. There is a huge need to improve our treatment for patients with mILC, which represent 20% of all HR positive HER2 negative metastatic breast cancer cases.

One of the major problems facing patients with mILC is that imaging tests (including computed tomography and positron emission tomography, or CT and PET scans) do not detect mILC tumors as well as other tumor types. This occurs because mILC is missing a protein that normally allows cells to stick to one another, the adhesion protein E-cadherin. Because of this, mILC tumors grow in a diffuse pattern that can be difficult to see and measure on imaging. Additionally, mILC tends to metastasize in a different pattern than other types of breast cancer, with metastases often involving the gastrointestinal tract and lining of the abdominal cavity in addition to other sites. The metastases from mILC often form fluid around organs, which is considered “unmeasurable” on scans. The inability to accurately detect tumor progression leads to uncertainty regarding whether treatment is working or not, and importantly, limits patient participation in clinical trials. Most metastatic breast cancer trials require that a patient has “measurable” disease so that an objective assessment can be made regarding whether treatment is effective.

To address this problem, we will test whether a blood-based liquid biopsy approach can provide an accurate biomarker for serially monitoring disease status in mILC. We will prospectively enroll 40 patients with mILC from 4 centers in the United States. We will show that changes in liquid biopsy correlate with the clinical assessment of disease status. This type of serial monitoring will result in a biomarker that can be used for treatment decisions, earlier intervention, and as a surrogate endpoint in clinical trials. Specifically, we will evaluate an ultrasensitive assay that detects circulating tumor DNA (ctDNA) or “minimal residual disease” (MRD) in the blood. We will measure this 2-4 times per year for 2 years, and determine what change in MRD correlates with tumor progression. Additionally, we will explore a novel assay that detects tumor-derived orphan non-coding RNA (oncRNA) in the blood.

The findings from this study have the potential to change treatment for those with mILC and improve outcomes. If an MRD assay can detect progression before scans do, this could allow for earlier intervention that may improve overall survival. Additionally, showing that MRD assays correlate with the findings of scans means that patients may not need to undergo imaging as frequently, which will reduce radiation exposure. Importantly, upon completion of this study, we will continue to leverage the study infrastructure to conduct addition research on mILC. The results from this study will allow us to compete for additional funding and conduct interventional treatment and imaging trials across the study platform. This will have a major impact on outcomes for those living with mILC.