

Public/Lay Abstract

Up to half of patients with metastatic HER2-positive breast cancer, more than one-quarter of patients with metastatic triple-negative breast cancer, and 10-15% of patients with metastatic, estrogen receptor (ER)-positive breast cancer will develop brain metastases (spread of breast cancer to the brain). Because of the essential role of the brain in everyday functioning and quality of life, a diagnosis of brain metastases can be devastating.

In recent years, we and others have conducted clinical trials to test targeted treatments in breast cancer patients with brain metastases. On a positive note, we have identified several regimens which lead to control of brain metastases in a subset of patients, and some of these regimens are already being used in clinical practice. For example, we developed the regimen of neratinib + capecitabine and demonstrated that approximately half of patients with HER2-positive breast cancer will experience initial shrinkage of their brain metastases with this treatment. However, not all patients respond, and in patients who do respond, treatment resistance (with associated re-worsening/progression of cancer) almost always subsequently occurs. Very little is understood at this time about how brain metastases become resistant to treatment, whether by acquiring new genetic changes, or by escaping the immune system.

One major barrier to progress has been the difficulty in studying what happens when brain metastases become resistant to treatment, in large part because of their inaccessibility to tissue biopsies. However, the development of highly sensitive assays to detect and study cell-free DNA, shed by cancer cells into the circulation, may now allow for less invasive methods to track and study this resistance in patients with brain metastases. In addition, advances in technology now allow us to move beyond simply quantifying broad categories of immune cells in the tumor microenvironment, towards detailed assays that can uncover how immune cell specificity may differ in brain metastases versus other locations of breast cancer.

We propose a multi-part project to study tissue- and blood specimens collected from patients with breast cancer brain metastases in order to understand the basis of treatment resistance. First, we will test how well “blood biopsies” (ie blood samples analyzed for circulating fragments of DNA released by cancer cells) match on a genetic level with brain metastases collected from the same patient. Second, we will evaluate blood biopsy samples collected in breast cancer patients with brain metastases before and after HER2-targeted treatments (tucatinib or neratinib) for tumor DNA sequences, in order to identify changes that appear upon the development of treatment resistance. Finally, because we hypothesize that not all resistance occurs through tumor mutations, we will broaden our view, and compare the diversity of the immune response surrounding breast cancer brain metastases versus metastases in other locations (e.g. liver, lung, bone, lymph nodes).

Together, we hope that our research will allow us to design and prioritize more targeted and effective treatments to improve quality of life, functional outcomes and survival in patients with brain metastases from breast cancer.