

## **PUBLIC/LAY ABSTRACT:**

Breast cancer brain metastases (spread of breast cancer to the brain) is a devastating complication of breast cancer which can significantly disrupt daily life. Unfortunately, up to half of patients with HER2+ metastatic breast cancer will develop brain metastases, often despite control of cancer in other parts of the body. The vast majority of these patients will ultimately die of related complications, and better treatments are urgently needed.

Some successful treatments for breast cancer brain metastases do exist. Surgery and/or radiation therapy have been used to treat brain metastases for many years. While these treatments often provide immediate relief, their long-term benefit is limited as brain tumors recur in most patients. Further, patients treated with brain surgery and/or radiation may suffer from significant side effects related to treatment. Recently, it has been demonstrated that treating patients with a combination of the anti-HER2 treatments tucatinib (Tukysa) and trastuzumab (Herceptin) with the oral chemotherapy capecitabine (Xeloda) is effective in treating breast cancer brain metastases. However, in patients with brain metastases that were uncontrolled (not previously treated or previously treated and regrowing), the combination treatment did not provide long-term control of brain metastases (median time before cancer worsening in the brain < 10 months), and the oral chemotherapy capecitabine (Xeloda) was associated with significant side effects.

Immune therapy has resulted in a significant improvement of outcomes in many different cancers. In laboratory experiments, it has been shown that combining anti-HER2 treatment with immune therapy can improve cancer control in HER2+ breast cancer. In this study, we propose to combine the anti-HER2 treatments tucatinib (Tukysa) and trastuzumab (Herceptin) with the immune promoting drug pembrolizumab (Keytruda) in patients with HER2+ breast cancer brain metastases which are uncontrolled (new and untreated or previously treated and regrowing) with the goal of controlling cancer in the brain. Responses seen with immune therapy tend to be durable, and it is hoped that this combination will result in long-lasting control of brain metastases.

In addition to developing successful treatment strategies for patients with advanced cancer, it is important to identify patients who might respond to such treatments. In this study, we propose to evaluate laboratory markers in stored breast tumors, metastatic tumors outside of the brain, and blood from patients enrolled in the study to best identify patients who might experience cancer control in the brain with the proposed combination.

Ultimately, we hope that the proposed study will identify a chemotherapy-free treatment that will improve outcomes for patients with HER2+ breast cancer brain metastases as well as advance our understanding of using immune therapy in the treatment of HER2+ breast cancer and cancer that has spread to the brain.