Public/Lay Abstract

Treating metastatic breast cancer is a challenge, especially when the cancer subtype does not have available biomarkers for targeted therapeutics. Mutation of p53 occurs in 80% of triple negative, and 75% of Her2+ breast cancer cases. As such, metastatic breast cancer could be well targeted by addressing the mutant p53 biomarker. Our work focuses on developing the biomarkers of mutant p53 and high levels of the DNA repair protein poly-ADP ribose Polymerase (PARP1) in breast cancer cells as a dual target. We discovered that triple negative breast cancers (TNBC) with mutant p53 are sensitive to treatment with a combination of the PARP inhibitor talazoparib plus the chemotherapeutic agent temozolomide. Our published, and preliminary data strongly indicate that using mutant p53 and high PARP as dual biomarkers will help to generate a new targetable pathway for breast cancers that previously had no available targeted treatments. Talazoparib was approved, based on the EMBRACA trial, for the treatment of patients with BRCA1/2 mutant breast cancers. Temozolomide has shown promise at reducing brain metastases. Our preliminary data demonstrated that using the two agents in combination, in a mouse model, reduced mutant p53 expressing TNBC circulating tumor cells. This proposal aims to expand on our preliminary data to test, and validate the ability to **target metastatic breast cancer using the mutant p53-PARP biomarkers for treatment with metronomic low dose temozolomide treatment in combination with the PARP inhibitor talazoparib.**

We will use a metastasis permissive mouse model with human patient derived metastatic breast cancers that express mutant p53. This preclinical model will be used to determine if metronomic low dose treatment with the PARP inhibitor talazoparib plus temozolomide can be used to stop progression and prevent metastases from forming in mice. We will determine if such treatments reduce brain and lung metastases and prolong survival in the metastasis permissive animals. Temozolomide is able to cross the blood-brain barrier. As such, temozolomide has a higher potential to block brain metastasis than cyclophosphamide. We hypothesize that metronomic low dose temozolomide plus talazoparib will be more effective at extending mouse lifespan than metronomic low dose cyclophosphamide plus talazoparib.

Aim 1: Determine if the mutant p53-PARP axis cooperates to allow metronomic low dose temozolomide plus talazoparib treatment to reduce circulating tumor cells and metastases. We will evaluate the treatment response by the reduction in metastases and circulating tumor cell numbers. Animals will be treated with low daily dose temozolomide in combination with talazoparib and compared to the successful higher dosing using the metastasis permissive mouse model.

Aim 2: Determine if increased survival can be achieved by targeting the mutant p53-PARP axis with metronomic low dose temozolomide plus talazoparib. This will be compared to low dose cyclophosphamide treatment plus talazoparib. We will determine if talazoparib plus temozolomide treatment induced reductions of circulating tumor cells are directly correlated with lifespan extension.

We propose that low dose temozolomide treatment in combination with talazoparib will target the mutant p53-PARP axis and will be more effective than high dose chemotherapy treatments at increasing survival. This is because the low dose metronomic treatments are expected to cause fewer side effects including fatigue, anemia, infection, and appetite changes that lead to weight loss.