Patients with metastatic breast cancer (BC) start their treatment with heavy tumor burden, resulting in high numbers of BC cells (BCCs) acquiring drug resistance. The resistant BCCs adopt a property of immaturity that are referred as cancer stem cells (CSCs). These stem cells are the source of further metastasis and account for the short period of remission. Unfortunately, due to health disparity in the metropolitan regions such as Newark where the population is predominantly black, there is little to no preventive care. Thus, patients are diagnosed with late-stage metastatic disease. Compound with this disparity is the increased number of patients with triple negative BC. However, regardless of hormone status, there is a preponderance of late stage diagnosis and short remission. We propose a treatment that can be given to patients, regardless of their hormone status with the following long-term goal: develop a safe treatment that combines standard care to eliminate lingering chemoresistant BCCs that prolong remission, which could be lifetime. We have two immediate goals: i) To predict tumor recurrence early with identified markers; ii) To repurpose drugs to eliminate resistant BCCs.

Our research studies support our proposed plan. We recently published studies showing the FDA-approved drug, bortezomib, could make CSCs chemosensitive and it is now proposed as one of two drugs for the additional treatment. The other drug is low dose carboplatin that will synergize with bortezomib. Specifically, bortezomib will shift the residual CSCs into dividing cells thereby making them accessible to carboplatin, resulting in cell death.

Our scientific evidence indicated that although epigenetic drugs such as azacytidine can benefit patients with leukemias, in the case of BC, azacytidine will make the cancer worse, which is in line with failed Phase II clinical trial for BC patients treated with azacytidine. Bortezomib alone will fail because once it acted on the cells and allow them to divide, the BCCs can use properties of tissues and return to CSCs. Thus, the treatment will need to include both drugs, bortezomib and carboplatin. Importantly, the reduced tumor burden will permit the use of low dose carboplatin to minimize side effects.

A strength of this study is our plan to identify markers that predict early drug resistance so the treatment will prevent return of the cancer to metastatic disease. We plan to identify how changes in the DNA of resistant BCCs during and after treatment can inform the oncologists that patients could have a short time of remission and additional treatment (identified in this study) should be employed. We have a strong team including statistician, scientists and advocates to ensure the success of this proposal.

Hypothesis: Standard treatment for metastatic BC increases blood CSCs with changes in their DNA that will predict chemoresistance. These resistant CSCs can be eliminated with bortezomib and low dose carboplatin.

AIM 1 will enroll 40 patients with Stages 1/II and III/IV. During and after treatment, 1-2 green top tubes of blood will be studied to test the hypothesis stated above. We will examine the BCCs for immature/CSCs; drug resistance; assay to show how resistant BCCs accumulate in the body. AIM 2 will test bortezomib and/or carboplatin and then examine for cell death. Overall, the findings, combined with patient outcome, will identify how drug resistance and cancer recurrence can occur early and also for the basis of a larger study. We plan after year 1 or towards the end of year 2 to submit an IND for a clinical trial.