Public/Lay Abstract:

Triple negative breast cancer (TNBC) is the term used to describe breast cancers that lack estrogen- and progesterone-receptor expression and do not overexpress human epidermal growth factor receptor 2 (HER2). Metastatic TNBC, where the cancer has spread to another part of the body, has a highly aggressive clinical course with shorter average survival compared to patients with other subtypes of metastatic breast cancer, representing a clinically unmet need.

The natural history of TNBC is to become resistant to chemotherapy and patients with this type of breast cancer have a poor survival. The most common genetic alterations in TNBC is a mutations in a gene called *TP53*. At the moment, a drug that directly target TP53 mutated breast cancer does not exist and novel approaches for the treatment of metastatic TNBC are needed to improve clinical outcomes.

Dr. Antonio Giordano is a physician-scientist at MUSC, who cares for patients with breast cancer and is a co-investigator in multiple clinical trials for metastatic breast cancer. Dr. Giordano has spent the past three years in the laboratory to seek to identify new therapies for the most aggressive and difficult to treat metastatic breast cancers, TNBC. They were able to identify a protein called polo-like kinase 1 (PLK1) with an important role for growth and survival of breast cancer cells with mutations in the *TP53* gene. In his laboratory they found that preclinical models of HER2-negative breast cancer with TP53 mutations responded very well when treated with a PLK1 inhibitor, called onvansertib, in combination with taxane (such as paclitaxel), chemotherapeutic drug utilized for the treatment of metastatic breast cancer. Specifically, cell lines with TP53 mutation were strongly inhibited when treated with onvansertib plus paclitaxel. Conversely, in cell lines with normal TP53, onvansertib plus paclitaxel did not show synergy. Moreover, in a mouse model of TNBC with TP53 mutation, the combination onvansertib plus paclitaxel was significantly superior to single agent treatments.

In this proposal we will test for the first time in humans the safety and preliminary efficacy of onvansertib in combination with nab-paclitaxel in patients with HER2-negative metastatic breast cancer. Onvansertib (also known as PCM-075 and NMS-1286937, and produced by Trovagene Oncology, San Diego, CA) is a PLK1 inhibitor that can be administered by mouth. The primary goal of this study is to define the safety and tolerability of different doses of onvansertib used in combination with intravenous nab-paclitaxel and to determine the optimal dose of the combination in patients with metastatic HER2-negative breast cancer. We will also evaluate whether any association exists between the response to treatment and *TP53* gene mutation status. The study will be conducted at the Hollings Cancer Center at MUSC in Charleston, SC. Our cancer center is the only National Cancer Institute designated cancer center in the state of South Carolina, and has all the facilities and infrastructures to conduct phase 1 clinical trials.

The integration of tumor DNA analysis with clinical data may improve our knowledge of the mechanisms of resistance to chemotherapy in breast cancer. In addition, data generated from our study may trigger the development of novel treatment strategies for patients with TP53 gene mutations, with the ultimate goal of reducing mortality in this patient population.