

## Public/Lay Abstract

Metastatic breast cancer (MBC) is a deadly disease with limited treatment options. Most MBCs carry genetic alterations (mutations) in the tumor suppressor gene called p53, which ordinarily is critically important to preventing normal cells from becoming cancerous cells. It is also now known that such alterations in p53 drive cancer progression and spread (metastasis), not only by affecting the cells of the target tissue or organ, but also by promoting the accumulation of other host cells that suppress the immune response within the tumor site known as the tumor microenvironment (TME). At present, there are no effective treatment options for p53-mutant MBC. We developed a novel therapeutic strategy for selectively killing p53-mutant tumors that takes advantage of their unique DNA repair processes. Our data demonstrated that this novel anti-mutant-p53 regimen effectively blocked tumor growth and metastasis in p53-mutant MBC models without adverse effects. Based on our work, this new anti-mutant-p53 strategy is now being tested in the *first-in-human* Phase I clinical trial for advanced colorectal cancer (CRC). Our preliminary results showed good tolerance to this treatment in the first eight patients. Immunotherapy with agents called immune checkpoint inhibitors (ICIs) has provided new prospects for cancer patients. However, ICI therapy showed low response rates in MBC. Our new data suggest that our anti-mutant-p53 regimen may decrease these immune suppressive cells in the TME and thus may improve responses to ICI therapy. The current study will test the hypothesis that our novel anti-mutant-p53 regimen can stimulate antitumor immune responses and improve ICI efficacy by acting on both the tumor cells themselves and the recruited immune suppressive populations in p53-mutant MBC models. The proposal includes two specific aims: Aim 1 will delineate the impact of our anti-mutant-p53 regimen on the various immune cell populations within the TME, specifically how the therapy reshapes the immune landscape from a suppressive to an activating state. Aim 2 will test this anti-mutant-p53 treatment in combination with ICI agents in p53-mutant MBC. This work matters for numerous patients with advanced BC, such as MBC which is presently incurable. The results of this work can lead to more effective treatment options for the majority of MBC. Excitingly, our new therapeutic strategy can be quickly translated into clinical trials, as all components are already approved for cancer treatment but never been combined, to the best of our knowledge.