**Lay Description of Important Outcomes**

There is an unmet urgent need to identify effective treatments for patients with breast cancer brain metastasis (BCBM), a major clinical challenge; BCBM constitutes approximately 10-30% of metastatic breast cancer cases and associated with poor prognosis of 8.7 months of survival. The poor prognosis is attributed to the fact that we still do not fully understand the factors driving breast cancer cells to the brain, the biology of brain metastases, and the lack of drugs that effectively penetrate the blood-brain barrier (BBB) and blood-tumor barrier (BTB).

The goal of our study is therefore set to identify novel treatment strategies that can be used to effectively treat women with established BCBM without unwanted toxicity and side effects. To achieve our study goal, we proposed to generate preclinical evidence to support future clinical utility of ketoconazole (KCZ), an antifungal drug already approved by the FDA for other diseases and/or being evaluated in multiple types of cancers including metastatic breast cancer. Based on cilinicaltrials.gov, there are about 60 active clinical trials using KCZ for treating cancer patients, including our clinical trial entitled “Ketoconazole before surgery in treating patients with recurrent glioma or breast cancer brain metastases” (NCT03796273).

If proven effective in our preclinical studies, KCZ in combination with surgery or radiation therapy can be moved to Phase I/II trials relatively quickly at the University of Texas Memorial Hermann Cancer Center. To improve KCZ’s safety profile, we created a novel analog WF 229A that could be a safer derivative of KCZ that has no impact on liver or adrenal functions. According to our mouse study, both compounds did not reach toxicity threshold at the highest dose of 300 mg/Kg suggesting their safety. Specifically, our preclinical animal study showed that both KCZ and WF-229A are safe without liver, renal or cardiac toxicities at the highest dose of 300 mg/Kg. While KCZ elevates ACTH suggesting its adverse effect of adrenal deficiency, WF-229A doesn’t inhibit cortisone synthesis and appears to be a safer analog of KCZ.

Based on the results of this mouse study, both KCZ and WF-229A are warranted for further investigations for BCBM. More than 80% of the women with metastatic triple-negative and HER2-positive breast cancers plus >85% of BCBM patients could benefit from the treatments. KCZ could be further validated in Phase I/I trials within a relatively short period of time and conducted by an experienced breast oncologist. The promising derivative WF-229A could be further tested in human patients after approval for Investigational New Drug.