Prostate cancer is the most common cancer and the second leading cause of cancer death in men in the United States.[1] While radical prostatectomy (RP) is curative for some patients, a subset with aggressive local prostate cancer will experience a recurrence and have an increased risk of prostate cancer mortality.[2, 3] Consequently, new treatment strategies, including multimodality therapy, are warranted to improve outcomes for high-risk patients. Approximately 10-20% of localized prostate cancers harbor mutations in BRCA1/2,[4-6] which confer sensitivity to PARP inhibition.[7-9] In this proposal, we will test the efficacy of neoadjuvant olaparib on pathologic outcomes in men with aggressive local prostate cancer. We previously conducted a series of phase 2 neoadjuvant clinical trials and have developed a platform for central pathology review, standardized criteria for pathologic response, and infrastructure for tissue and imaging corelating studies.[10, 11] To better understand therapeutic vulnerabilities in BRCA1/2 mutated tumors, we will molecularly interrogate baseline biopsy and RP specimens to identify mutational profiles associated with response and resistance. In the context of curative intent treatment, non-invasive disease monitoring is critical. We will integrate multiparametric prostate MRI to enable correlation with pathologic and molecular findings. This trial will serve as a catalyst for future research endeavors, grant funding, and additional studies to more definitively test this strategy. This multidisciplinary, collaborative effort harnesses the expertise of clinical and laboratory scientists at UCSD; and if successful, may shepherd a new treatment paradigm to improve survival for men with localized aggressive prostate cancer.

Lay Abstract:

Prostate cancer is a common cancer among men in the United States. While surgery can be curative for some patients, a subset of patients will develop a recurrence after surgery and are at risk of death from prostate cancer. There is an urgent need to develop new treatments to cure more patients who have localized aggressive prostate cancer. Some prostate cancers have mutations in genes that impact DNA repair in the tumor. Tumors that have mutations in DNA repair genes, in particular BRCA1/2, are sensitive to drugs called PARP inhibitors. Olaparib is a PARP inhibitor which has been demonstrated to improve survival in men with prostate cancer that has spread throughout the body. In this study, we will test the early use of olaparib prior to surgery to see if we can kill the cancer cells in the prostate. We suspect that killing the cancer cells in the prostate will prevent the cancer from recurring. In this study, we will also look at the DNA and RNA in the tumor before and after treatment to understand if there are markers that can best predict which tumors will respond to therapy. We will also obtain prostate MRIs before and after treatment to see if we can predict from the imaging which tumors have responded to therapy. We believe that olaparib prior to surgery in patients with tumors with BRCA1/2 mutations will cure more men with aggressive local prostate cancer.