A Phase 1B, Nonrandomized Trial Investigating Docetaxel Combined with Cirmtuzumab in Patients with Metastatic Castration Resistant Prostate Cancer

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Scientific Abstract:

Genomic studies of patients with advanced prostate cancer have demonstrated that somatic mutations in genes that regulate the Wnt signaling pathway (WSP) are enriched in 20% of patients. Wnt signaling is critical for cancer stem cell renewal, cell proliferation, and differentiation. Noncanonical WSP activation is mediated through tyrosine protein kinases including ROR1 and ROR2 which are activated by WNT5A, WSP activation has been associated with inferior outcomes to androgen signaling inhibitors and activation of the non-canonical pathway via WNT5A has been implicated in anti-androgen resistance. Despite these initial studies, the broader clinical significance of WSP alterations in prostate cancer has not been fully characterized and attempts to therapeutically target the WSP has been limited. Cirmtuzumab, a ROR1-binding monoclonal antibody, is a compelling novel agent with the potential for efficacy in patients with advanced castration resistant prostate cancer (CRPC). We hypothesize that cirmtuzumab combined with standard of care docetaxel will be 1) tolerable and safe, 2) result in early antitumor activity, and 3) may demonstrate a signal of enhanced efficacy in patients with WSP activation. We will investigate these hypotheses in the context of a phase 1b trial of cirmtuzumab combined with docetaxel in patients with metastatic CRPC. Additionally, we propose baseline, on-treatment, and progression tumor sampling with metastatic CRPC. Additionally, we propose baseline, on-treatment, and progression tumor sampling and serial blood collection to investigate mechanisms of response and resistance to therapy. This project has broad applicability to advance our understanding of the clinical significance of WSP alterations and advance treatments to improve the outcomes of men with lethal prostate cancer.

Lay Abstract:

Metastatic castration resistant prostate cancer (CRPC) is a lethal disease that claims 30,000 lives annually in the U.S. Although current approved drugs will slow the growth of metastatic CRPC, development of drug resistance—and cancer progression—is inevitable. It is therefore imperative to develop new treatments to improve survival. As we learn more about the factors driving progression of metastatic prostate cancer, we have discovered that the Wnt signaling pathway is activated in these patients. The Wnt pathway possibly confers resistance to standard drug treatments, including hormone therapy and chemotherapy. Prior attempts to target this pathway have been unsuccessful. Cirmtuzumab, a ROR1-binding monoclonal antibody which inhibits the Wnt pathway, is a compelling new drug with the potential to treat CRPC by blocking Wnt activity. Cirmtuzumab was developed at UCSD by Drs. Kipps, Jamieson, and Carson. Studies are underway in chronic lymphocytic leukemia and breast cancer. We hypothesize that the addition of cirmtuzumab to docetaxel, a chemotherapy drug, will be safe and effective for patients with metastatic CRPC. To test this hypothesis for the first time, we propose a clinical trial of cirmtuzumab combined with docetaxel in men with prostate cancer. To better understand mechanisms of drug resistance, and which patients might benefit most from cirmtuzumab, we will perform molecular analyses of cancer tissue and blood samples throughout the study. This multidisciplinary, collaborative effort harnesses the expertise of clinical and laboratory scientists at
UCSD; and if successful, may reveal a new and unique drug to improve survival for patients with CRPC.