TITLE: Safety and Feasibility of Intraprostatic Injection of CAN-2409 or Placebo followed by Valacyclovir in Patients on Active Surveillance for Prostate Cancer (ULYSSES Trial)

AUTHORS: Scott Eggener[1], Steven Sukin[2], Miguel A. Mercado[2], David Cahn[3], Stephen J. Savage[4], Bryan Mehlhaff[5], Ralph Miller[6], Christopher Pieczonka[7], Michael G. Chang[8], Inger Rosner[9], Roohollah Sharifi[10], Justin D. Buie[11], María Lucía Silva Polanco[11], Marcos Rafael Ramírez-Márquez[11], Andrea G. Manzanera[11], Laura K. Aguilar[11], Estuardo Aguilar-Cordova[11], Ricardo Castillejos[12], Guillermo Feria-Bernal[12]

[1]University of Chicago, Chicago, IL, [2]Texas Urology Specialists, Tomball, TX, [3]Colorado Urology, Golden, CO, [4]Ralph H. Johnson VA Medical Center, Charleston, SC, [5]Oregon Urology Institute, Springfield, OR, [6]Allegheny Health Network, Pittsburgh, PA, [7]Associated Medical Professionals, Syracuse, NY, [8]Hunter Holmes McGuire VA Medical Center, Richmond, VA, [9]Walter Reed National Military Medical Center, Bethesda, MD, [10]Jesse Brown VA Medical Center, Chicago, IL, [11]Candel Therapeutics, Inc., Needham, MA, [12]Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubiran, Mexico

PRESENTING AUTHOR: Scott Eggener, seggener@surgery.bsd.uchicago.edu

INTRODUCTION AND OVERALL GOAL: A randomized, placebo-controlled, blinded phase 2 clinical trial of intra-prostatic oncolytic viral immunotherapy in patients on active surveillance for localized prostate cancer has completed enrollment. We report the overall feasibility and safety of intra-prostatic injection of CAN-2409 or placebo, each followed by valacyclovir. Blinded follow up for efficacy endpoints is ongoing.

SPECIFIC AIMS OF PRESENTATION: Describe the mechanism of action for CAN-2409 + valacyclovir and report the blinded safety and feasibility data.

BACKGROUND: CAN-2409 is a replication-deficient adenovirus that delivers HSV thymidine kinase to cancer cells. This results in local conversion of orally administered valacyclovir into a toxic metabolite. Previous phase 1/2 clinical trials suggested intra-tumoral treatment with CAN-2409 followed by valacyclovir is well tolerated with PSA and pathologic responses across a wide-dose range. Previous preclinical and clinical studies in various indications, including prostate cancer, showed immunogenic cell death at the site of the injected tumor, followed by CD8+ T cell response at the site of the injected tumor and in distant uninjected metastases. Prostate cancer is well suited for this approach since it is immunologically 'cold' and easily accessible for injection. Patients with localized prostate cancer are often placed on active surveillance to monitor disease but approximately 25-30% of patients on active surveillance convert to radical treatment within 2-3 years based on tumor progression. CAN-2409 + valacyclovir is being evaluated to prevent or delay tumor progression. We report feasibility and blinded safety data.

METHODS: A phase 2 randomized, placebo-controlled, blinded clinical trial will evaluate the hypothesis that two courses of intra-prostatic CAN-2409 injection + oral valacyclovir (active treatment) is safe and can improve oncologic outcomes compared to a placebo injection + oral valacyclovir (control). Patients with early stage prostate cancer on active surveillance were randomized 2:1 (treatment:control). Transrectal ultrasound guided injections of 0.5 ml were delivered with a 22G needle in the outpatient setting to each of the 4 prostate quadrants and repeated 2-3 weeks later. The dose of CAN-2409 was $5x10^{11}$ vector particles per course in a total of 2 ml. Valacyclovir was administered at a dose of 2 grams three times per day for 14 days starting the day after each injection.

RESULTS: From May 2016 to May 2019, 187 patients were enrolled and treated at 22 centers. Median age was 65 years (range 40-81) with 21% Hispanic and 10% African-American. NCCN risk category at diagnosis was low in 71%, intermediate in 28%, and high in 1%. From the 362 intraprostatic injections (175 patients received 2 injections, 12 patients received 1 injection), three (0.8%) were hospitalized for infection and recovered. The most frequent adverse events (>=5%) were gastrointestinal events (diarrhea, nausea) of grade 1-2 in 21% of patients, general disorders (flu-like symptoms, fever, chills, fatigue, malaise) of grade 1-2 in 57% of patients and grade 3 in 1% of patients, headache of grade 1-2 in 13% of patients, and genitourinary events (urinary tract infection, hematuria, urinary tract pain, frequency or urgency) of grade 1-2 in 26% of patients and

grade 3 in 1%. The most frequent laboratory abnormalities (>=5%) were elevated AST/ALT of grade 1-2 in 17% and grade 3 in 1%, elevated alkaline phosphatase of grade 1-2 in 5%, hyperbilirubinemia of grade 1-2 in 5%, elevated creatinine of grade 1-2 in 15% and grade 3-4 in 2% and grade 1 anemia in 8%.

CONCLUSIONS: Intraprostatic injections of either placebo or CAN-2409 followed by oral valacyclovir in men with prostate cancer on active surveillance are feasible and well tolerated without unexpected adverse events. Cancer-specific efficacy endpoints will be evaluated after unblinding. If effective, implementation of this therapeutic modality appears to be straightforward and safe.