759 **ADPORT-601 (TT-10–101): FIRST-IN-HUMAN STUDY OF ADENOSINE 2A (A2A) AND ADENOSINE 2B (A2B) RECEPTOR ANTAGONISTS IN PARTICIPANTS WITH SELECTED ADVANCED SOLID TUMORS**

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Background Despite significant advances in immunotherapy, novel approaches to promoting immune response and overcoming immunosuppressive pathways are needed. Hypoxic tumors possess high levels of extracellular adenosine within the tumor microenvironment, suppressing innate and adaptive immune responses by binding the adenosine receptors A2AR and A2BR. Clinical trials with other adenosine targeting agents have demonstrated the potential of adenosine regulation and have suggested that biomarkers can be used to select for tumors that are more heavily dependent on this pathway. TT-10 (PORT-6) and TT-4 (PORT-7) are novel, potent and selective antagonists of A2AR and A2BR, respectively. Preclinical studies further demonstrate that TT-10 exhibits high-affinity receptor binding with a long dissociation rate ($t_{1/2}$ >10 hours) and is characterized by very slow displacement in the presence of super-physiologic concentrations of adenosine. Both agents have shown monotherapy activity in traditionally non-immunogenic tumor mouse models (4T-1) and immunogenic models (CT-26). Optimizing inhibition of A2AR and A2BR separately and in combination provides an opportunity to dissect the role of each signaling pathway in the tumor microenvironment.

Methods ADPORT-601 is a multi-center Ph1 study, designed to evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of TT-10 (A2A) in participants with selected advanced solid tumors. A separate arm will test TT-4 (A2B) with the same endpoints. The goal is to implement a companion diagnostic to enrich for patients who have increased levels of the A2A and/or A2B receptors. Dose escalation will utilize a 3+3 design. Ph1b will be initiated once the recommended Ph2 doses have been established and will include expansion cohorts for each drug as monotherapy, as well as the 2 drugs combined at the optimal doses, and with other immunotherapy agents. A robust biomarker program, including multi-omic single cell analyses, will be incorporated via an innovative collaboration with Cancer Research Institute, MD Anderson and University of California San Francisco.

Key inclusion criteria for the TT-10 Ph1 cohort include metastatic castration-resistant prostate cancer, non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), or renal cell carcinoma that is refractory to standard therapy. The TT-4 Ph1 cohort will enroll patients with colorectal cancer, NSCLC, endometrial cancer or ovarian cancer that is refractory to standard therapy. The Ph1 primary endpoint is safety of TT-10 alone, TT-4 alone, or both in combination. Secondary endpoints include Objective Response Rate, Duration of Response, and Progression-Free Survival. Longitudinal blood and tissue samples will be collected.

Trial Registration Clinicaltrials.gov: NCT04969315

Ethics Approval This study has been approved by the Advarra IRB.

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