A Phase 1, Multiple-Dose Study to Evaluate the Safety and Tolerability of XmAb®819 (ENPP3 x CD3) in Subjects with Relapsed or Refractory Clear Cell Renal Cell Carcinoma (RCC)

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Background Despite multiple advances in the treatment of metastatic RCC based on VEGF-directed therapies and immune checkpoint inhibitors (ICIs), few patients are ultimately cured. Therapies exploiting novel targets are greatly needed. A detailed antigen screen identified ENPP3 (Ectonucleotide pyrophosphatase/phosphodiesterase family member 3) as having consistent high expression in RCC (among other histologies), and low expression in adjacent normal tissue. ENPP3 is a transmembrane ectoenzyme, thought to be involved in hydrolysis of extracellular nucleotides. XmAb819 is an affinity-tuned 2+1 (high-avidity bivalent ENPP3 binding with low-avidity monovalent CD3 binding) bispecific antibody that was engineered for preferential engagement of high ENPP3-expressing cancer cells relative to low ENPP3-expressing normal cells, with the goal of preferentially inducing T-cell-mediated killing of the cancer cells. In addition, the expression of ENPP3 in healthy human tissues is generally low and typically localized apically which is likely to make it inaccessible to XmAb819 and/or T cells.

Methods This is a US based, multicenter, open-label, multiple-dose study designed in 2 parts with up to 95 participants: Part A dose escalation, to establish a priming dose, step-up priming dose(s), a cohort limit dose, and the dosing schedule; and Part B dose expansion, to further evaluate safety and tolerability, as well as provide an initial evaluation of efficacy for the relevant dose regimens established in Part A. The primary objectives are safety and tolerability, and to identify the doses and schedule for expansion. XmAb819 will be administered weekly by IV dosing on Day 1 of each priming dose(s) and Days 1, 8, and 15 for the cohort limit dose of each 21-day cycle. All eligible subjects will have relapsed or refractory RCC and have undergone disease progression on standard-of-care therapies including combination of immune checkpoint inhibitors followed by targeted therapies or immune checkpoint inhibitors plus anti-vascular endothelial growth factor agents in combination or sequentially.

Enrollment has been initiated.

Trial Registration NCT05433142. Research Sponsor: Xencor, Inc.

Ethics Approval This study was approved wg IRB; IRB Tracking Number 20221085.