A Phase 1, Multiple-Dose Study to Evaluate the Safety and Tolerability of XmAb®819 in Patients With Relapsed or Refractory Clear Cell Renal Cell Carcinoma

Sumanta Kumar Pal,[1] Pavlos Masouel,[2] Sreeni Yalamanchili,[3] Huajiang Li,[3] Jitendra Kanodia,[3] Raphael Clynes,[3] Zequn (Tony) Tang,[3] Benjamin Garmezy[4]

[1]Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Xencor, Inc., Monrovia, CA; [4]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN

Study Overview

This is a Phase 1, first-in-human study of XmAb819 in patients with relapsed or refractory clear cell RCC (ccRCC)

Part A, dose escalation

- **Estimated to enroll up to 54 patients; will establish a priming dose, step-up priming dose(s), cohort limit dose, and the dosing schedule in patients with ccRCC**

Part B, dose expansion

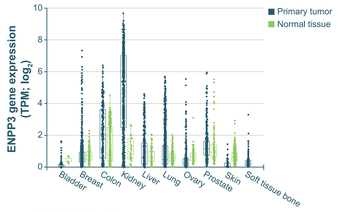
- **Will enroll in 2 stages, with a total sample size of up to 41 patients**
- **Stage 1 will enroll a total of 13 patients**
- **If there are ≥ 1 responses in stage 1, stage 2 will accrue up to 28 additional patients**

Patient enrollment is currently ongoing, and ~12 sites in the United States will participate

Background and Preclinical Evidence

- Ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3) is differentially expressed in RCC as measured by bulk RNA sequencing and immunohistochemistry (**Figure 1**)

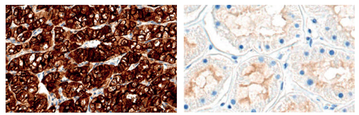
Figure 1. ENPP3 differential expression



TPM, transcripts per million.

- The expression of ENPP3 in normal human tissues is generally low and localized apically in the tubules of the kidney cortex, fallopian epithelium, endometrium, gastrointestinal epithelium, parotid gland, and thymic cortex[1] (**Figure 2**)

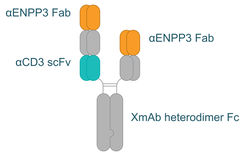
Figure 2. ENPP3 expression in ccRCC and normal kidney tissue



ccRCC **Score 3+** | Kidney **Score 1+**

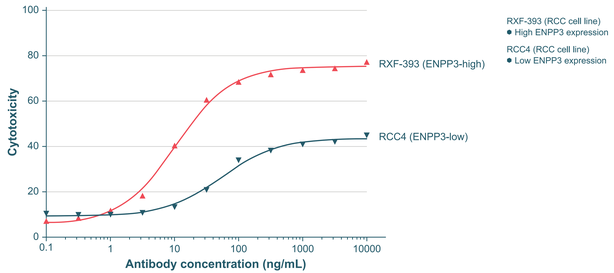
- XmAb819 is a humanized, anti-ENPP3 x anti-CD3 bispecific antibody that directs T-cell–mediated cytotoxicity (**Figure 3**)

Figure 3. XmAb819: 2+1 ENPP3 x CD3



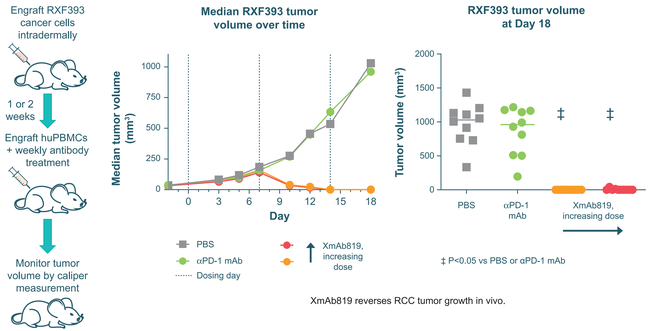
- The XmAb 2+1 format antibody provides avid tumor targeting and selectivity (**Figure 4, Figure 5**)
- This is a Phase 1, first-in-human study of XmAb819 in patients with relapsed or refractory ccRCC
- Patient enrollment is currently ongoing, and ~12 sites in the United States will participate

Figure 4. In vitro cell killing assay by redirected T cells after 48 hours



Bivalent 2+1 format promotes preferential killing of ENPP3-high target cells.

Figure 5. RXF-393 xenograft tumor model in NSG mice with PBMC effector cells



‡ P<0.05 vs PBS or αPD-1 mAb

XmAb819 reverses RCC tumor growth in vivo.

αPD-1, anti-programmed death-1 antibody; huPBMC, human peripheral blood mononuclear cell; mAb, monoclonal antibody; NSG, NOD *scid* gamma; PBS, phosphate-buffered saline.

Study Design

- This study has a novel trial design with dose escalation, priming dose, step-up doses determined by biomarkers, and intracohort dose escalation
- XmAb819 is administered as an IV infusion on Days 1, 8, and 15 each 21-day cycle (**Figure 6**)
  - Dosing includes a priming dose on Day 1 followed by higher weekly step-up doses to reach a cohort limit dose
- Imaging is performed at screening, every 6 weeks from the day of the first priming dose, and at end of treatment (EOT)
- Samples are collected for evaluation of PK and pharmacodynamics in peripheral blood (T-cell activation and proliferation, cytokines) at multiple time points throughout treatment
- Tumor biopsies are performed at screening and between 1 and 3 weeks after first dose

Primary Objectives

- To assess the safety and tolerability of XmAb819 in patients with relapsed or refractory ccRCC
- To identify the minimum safe and biologically effective dose, the recommended dose, and the schedule for expansion of XmAb819

Secondary Objectives

- To characterize the pharmacokinetics (PK) of XmAb819 when administered as monotherapy
- To assess the immunogenicity of XmAb819 when administered as monotherapy
- To preliminarily assess antitumor activity of XmAb819 by objective response rate, progression-free survival, duration of response, and overall survival per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Exploratory Objectives

- To assess the incidence, timing, and severity of cytokine release syndrome
- To characterize the biological activity of XmAb819 by assessment of immune cell frequencies and markers of activation and exhaustion in peripheral blood by flow cytometry or similar bioanalytical methods
- To explore associations between baseline tumor ENPP3 expression and clinical response

Key Inclusion Criteria

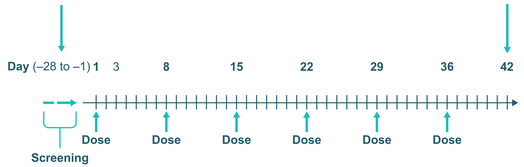
- Patients must have measurable disease by RECIST v1.1 as assessed by the local site investigator or radiology department
- Patients who have relapsed and refractory ccRCC and have undergone disease progression on standard-of-care therapies
- All patients in part A (dose escalation) must have adequate archival tumor sample, except for patients who consent to having a fresh tumor biopsy
- All patients in part B (dose expansion) must have a tumor lesion that can be biopsied at acceptable risk in the judgment of the investigator

Key Exclusion Criteria

- Prior treatment with an investigational anti-ENPP3/CD203c therapy
- History of serious allergic or anaphylactic/hypersensitivity reaction to mAb therapy
- Have known active central nervous system metastases and/or carcinomatous meningitis
- Active known autoimmune disease
- Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy
- Patient is pregnant, breastfeeding, or planning to become pregnant while enrolled in the study, up to the end-of-study visit
- Laboratory tests indicating inadequate organ function

Figure 6. Radiographic tumor assessment

Radiographic tumor evaluation (as determined by the investigator) will be performed by CT/MRI at baseline (within 14 days prior to the first dose of study drug), every 6 weeks (± 3 days) from the day of the first priming dose, and at EOT.



CT, computed tomography; MRI, magnetic resonance imaging.

Reference

1. Doñate F, et al. *Clin Cancer Res*. 2016;22:1989-1999.

Acknowledgments

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