558 CTX130 ALLOGENEIC CRISPR-CAS9–ENGINEERED CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS IN PATIENTS WITH ADVANCED CLEAR CELL RENAL CELL CARCINOMA: RESULTS FROM THE PHASE 1 COBALT-RCC STUDY

[1]Sumanta Pal*, [2]Ben Tran, [3]John Haanen, [4]Michael Hurwitz, [5]Adrian Sacher, [6]Neeraj Agarwal, [7]Nizar Tannir, [1]Elizabeth Budde, [2]Simon Harrison, [3]Sebastian Klobuch, [6]Sagar Patel, [8]Mary Lee Dequeant, [9]Verena Karsten, [8]Kaitlyn Cohen, [8]Ellen Gurary, [8]Henia Dar, [8]Anna Ma, [8]Anjali Sharma, [7]Samer Srour. *[1]City of Hope Comprehensive Cancer Center, Duarte, CA, United States; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Netherlands Cancer Institute, Amsterdam, Netherlands; [4]Yale School of Medicine, New Haven, CT, United States; [5]Princess Margaret Cancer Centre, Toronto, Canada; [6]University of Utah, Salt Lake City, UT, United States; [7]The University of Texas, Houston, TX, United States; [8]CRISPR Therapeutics, Boston, MA, United States; [9]Formerly CRISPR Therapeutics, Boston, MA, United States*

Background Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal tumors. Patients with ccRCC who fail checkpoint inhibitors (CPIs) and tyrosine kinase inhibitors (TKIs) have a poor prognosis. Preclinical studies identified substantial expression of CD70 in ccRCC tumor samples. Here, we report results from the Phase 1 dose-escalation study of CTX130™, a CD70-targeting allogeneic CAR T cell therapy in patients with ccRCC.

Methods COBALT-RCC (NCT04438083) is a Phase 1, open-label, multicenter, global study evaluating safety and efficacy of CTX130 in patients ≥18y with advanced (unresectable or metastatic), relapsed, or refractory (R/R) ccRCC and prior exposure to both CPIs and TKIs. Patients received standard lymphodepleting chemotherapy with fludarabine 30mg/m2 and cyclophosphamide 500mg/m2 for 3 days, followed by CTX130 infusion.

Results As of May 2, 2022, 14 patients with a median age of 64.5y (range, 54-77) were treated with CTX130. All patients had stage IV disease, and received a median of 3 (range, 1-6) prior treatments. Six patients had documented refractory disease at study entry. Median CD70 expression level on the tumors was 100% (range, 1-100%). Patients received CTX130 at dose levels (DLs) ranging from $3x10^7$ to $9x10^8$ CAR T cells. Overall, expansion occurred across all DLs. An emerging relationship between higher CAR T exposure and disease control was observed. CTX130 had an acceptable safety profile; there were no dose-limiting toxicities across all DLs. Seven (50%) patients experienced grade (Gr) 1-2 cytokine release syndrome (CRS); there was no Gr≥3 CRS. Three patients experienced serious adverse events (SAEs) related to CTX130; all were episodes of CRS. Three patients had SAEs of infections, all unrelated to CTX130, including a Gr5 pneumonia with Gr4 dyspnea resulting in death. No patients experienced immune effector cell associated neurotoxicity syndrome, graft versus host disease, or hemophagocytic lymphohistiocytosis. One patient (7.7%) had a durable complete remission (CR) maintained at 18+ months and 9 (69.2%) patients had stable disease (SD) with 4 patients (30.8%) in SD at 4 months. The disease control rate (CR + partial response + SD) was 76.9%.

Conclusions This first-in-human clinical trial exploring CD70 CAR T-cell therapy in ccRCC showed an excellent safety profile with no unexpected on-target off-tumor toxicities and encouraging antitumor activity. To our knowledge, this durable CR is the first to be achieved with allogeneic CAR T cell therapy in patients with R/R solid tumors and represents a proof-of-concept for further exploration of CD70-targeted CAR T cells in ccRCC and other CD70+ malignancies.

Trial Registration This study is registered at www.ClinicalTrials.gov. NCT04438083

Ethics Approval The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH Guidelines for GCP and applicable regulatory requirements. This study was approved by all participating Institutional Review Boards (IRBs). The Ethics Committee/IRB Approval Numbers/IDs for each participating institution are as follows: City of Hope (189473), Huntsman Cancer Institute (00133621), MD Anderson Cancer Center (2020-0151), Yale Cancer Center (20202730), Princess Margaret Cancer Centre (20-5071), Netherlands Cancer Institute (METC20.1170/M20CTX), and Peter MacCallum Cancer Centre (20/16). All participants provided informed consent before taking part in the study.

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