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

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Disclosures

• The COBALT™-RCC study of CTX130™ is sponsored by CRISPR Therapeutics

• Dr. Sumanta Pal is a Professor in the Department of Medical Oncology & Therapeutics Research and Co-director of the Kidney Cancer Program at City of Hope

• Dr. Pal received travel reimbursement from CRISPR Therapeutics and Ipsen
Overview

• Renal cell carcinoma (RCC) is one of the ten most common cancers, with an annual incidence of 50,000 in the US and 45,000 in the EU5\textsuperscript{1-4}
  – About 40% are primary refractory\textsuperscript{2-4}

• Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype and is often unresponsive to available therapies, including radiation, chemotherapy, and immunotherapy
  – While localized RCC can often be treated with partial or radical nephrectomy, approximately 30% of ccRCC patients will develop metastases that require systemic therapy\textsuperscript{5,6}

• CD70 is a ligand for CD27 with transient expression on activated lymphocytes and is highly expressed in ccRCC tumor samples\textsuperscript{7-10}

• CTX130 is a first-in-class, CD70-targeting allogeneic CAR T therapy being investigated in patients with advanced (metastatic or unresectable) ccRCC

CAR, chimeric antigen receptor; EU5, European Union countries with the 5 largest economies: France, Germany, Italy, Spain, and the United Kingdom.


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Role of CD70 in Immune Response and Cancer

### Physiological role of CD70\(^1,2\)
- Transient CD70 expression on activated lymphocytes as well as activated APCs (dendritic cells), and some B and NK cells
- In T cells, CD70 controls naïve and memory T-cell activation via interaction with CD27

### Role of CD70 in cancer\(^1\)
- High levels of CD70 expression have been detected in approximately 82%-85% of ccRCC samples\(^3,4\)
- Possible immunosuppressive role due to T-cell exhaustion, apoptosis, or Treg expansion

References:

APC, antigen presenting cell; ccRCC, renal cell carcinoma; NK, natural killer; Treg, regulatory T cell.
CTX130

- CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR T cell therapy with targeted disruption of the TRAC, β2M, and CD70 loci
  - Using an AAV vector, an anti-CD70 CAR cassette is specifically inserted into the TRAC locus by homology-directed repair
- CTX130 is manufactured from T cells collected from a healthy donor, which are then selected and edited before expansion and cryopreservation for off-the-shelf availability


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Five million A498 cells were injected subcutaneously into the right flank of NOG (NOD.Cg-Prkdc<sup>scid</sup>/Il2rg<sup>tm1Sug/JicTac</sup>) mice. When mean tumor size reached an average size of approximately 150 mm$^3$, mice were either left untreated (n=5) or injected intravenously with $8 \times 10^6$ CAR$^+$ CTX130 cells per mouse (n=5) or with $7.5 \times 10^6$ CAR$^+$ CD70$^+$ anti-CD70 CAR T cells (n=4) per mouse. Tumor volumes were measured twice weekly for the duration of the study. Each point represents the mean tumor volume ± standard error.

**Efficacy of CTX130 vs CD70+ anti-CD70 CAR T Cells in a Subcutaneous A498 RCC Xenograft Model**

**Efficacy and Systemic Antitumor Activity of a Single Dose of CTX130 in an A498 RCC Xenograft Model**
COBALT-RCC (NCT04438083) Clinical Trial Design

Phase 1, open-label, multicenter, international, single-arm study (NCT04438083) evaluating the safety and efficacy of CTX130, an investigational, allogeneic CAR T cell targeting CD70

**Informed consent form**

**CTX130 infusion (D +1):**

<table>
<thead>
<tr>
<th>DL1</th>
<th>DL2</th>
<th>DL3</th>
<th>DL4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3×10^7 cells</td>
<td>1×10^8 cells</td>
<td>3×10^8 cells</td>
<td>9×10^8 cells</td>
</tr>
</tbody>
</table>

Flu 30mg/m² + Cy 500mg/m² for 3 days (D −5, −4, −3)

**Primary endpoint**

- Part A (Dose Escalation): Incidence of adverse events defined as dose-limiting toxicities
- Part B (Cohort Expansion): Objective response rate per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

**Secondary endpoints**

- Best overall response
- Progression-free survival
- Overall survival

**Key inclusion criteria**

- Age ≥18 years and body weight ≥42 kg
- Unresectable or metastatic RCC with clear cell differentiation
- Prior exposure to both check point and VEGF inhibitor and documented progression after adequate exposure
- Karnofsky performance status (KPS) ≥80%
- Adequate renal, liver, cardiac, and pulmonary organ function

**Key exclusion criteria**

- Prior treatment with any anti-CD70 targeting agents
- Prior treatment with any CAR T cells or any other modified T or natural killer (NK) cells
- History of certain central nervous system (CNS), cardiac or pulmonary conditions
- Prior solid organ transplantation or bone marrow transplant

CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; D, day; DL, dose level; RCC, renal cell carcinoma.

Presented at the SITC 37th Annual Meeting. Nov 10, 2022
## Patient Demographics and Baseline Characteristics

*Presented at the SITC 37th Annual Meeting. Nov 10, 2022*

**Data cutoff date: 02 May 2022**

<table>
<thead>
<tr>
<th></th>
<th>DL1 3x10^7 N=3</th>
<th>DL2 1x10^8 N=3</th>
<th>DL3 3x10^8 N=4</th>
<th>DL4 9x10^8 N=4</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>59 (58-64)</td>
<td>60 (54-65)</td>
<td>64.5 (59-73)</td>
<td>70 (66-77)</td>
<td>64.5 (54-77)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>2 (50)</td>
<td>12 (85.7)</td>
</tr>
<tr>
<td><strong>Stage IV at enrollment, n (%)</strong></td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>14 (100)</td>
</tr>
<tr>
<td><strong>Metastatic disease, n (%)</strong></td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>14 (100)</td>
</tr>
<tr>
<td><strong>Prior anticancer therapies, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>3 (75)</td>
<td>3 (75)</td>
<td>9 (64.3)</td>
</tr>
<tr>
<td>Surgery</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (75)</td>
<td>4 (100)</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td><strong>IMDC risk category at screening, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>1 (25)</td>
<td>1 (25)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>3 (75)</td>
<td>3 (75)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td><strong>eGFR &lt;60 mL/min/1.73m^2, n (%)</strong></td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td><strong>Median time from diagnosis, y (range)</strong></td>
<td>3.4 (2.5-6.3)</td>
<td>2.7 (0.7-3.3)</td>
<td>5.1 (2.5-5.6)</td>
<td>10.5 (5.1-24.0)</td>
<td>4.9 (0.7-24.0)</td>
</tr>
<tr>
<td><strong>SoD for target lesions, mm (range)</strong></td>
<td>73 (12-141)</td>
<td>51 (45-122)</td>
<td>61 (47-135)</td>
<td>88 (40-135)</td>
<td>64 (12-141)</td>
</tr>
</tbody>
</table>

DL, dose level; eGFR, estimated glomerular filtration rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SoD, sum of diameters.
CD70 Expression in ccRCC Clinical Samples

- CD70 expression was assessed by IHC in tumor samples
  - Median CD70 expression level (range, n=12): 100% (1-100)
  - Mean CD70 expression was >75%

IHC, immunohistochemistry; ccRCC, clear cell renal cell carcinoma.
## Safety

**Adverse Events of Interest, N (%)**

<table>
<thead>
<tr>
<th></th>
<th>DL1 3x10⁷ N=3</th>
<th>DL2 1x10⁸ N=3</th>
<th>DL3 3x10⁸ N=4</th>
<th>DL4 9x10⁸ N=4</th>
<th>Total N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr 1-2</td>
<td>–</td>
<td>–</td>
<td>3 (75)</td>
<td>–</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Gr ≥3</td>
<td>–</td>
<td>–</td>
<td>4 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CRS</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>ICANS</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GvHD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infections*</td>
<td>–</td>
<td>–</td>
<td>1 (33)</td>
<td>1 (25)</td>
<td>2 (14.3)</td>
</tr>
</tbody>
</table>

- 7 (50%) patients had Gr 1-2 CRS; no Gr ≥3 CRS events. 3 patients had SAEs related to CTX130; all were CRS events
  - Median time to CRS onset was 1 day with a median duration of 2 days
- No ICANS or GvHD
- 3 patients had SAEs of infections; all unrelated to CTX130, including Gr 5 pneumonia with Gr 4 dyspnea resulting in death
- No instances of TLS, infusion reactions, HLH, or secondary malignancies
- Acceptable safety profile across all DLs and no DLTs

*Includes COVID-19, pneumonia, enterocolitis, and urinary tract infections.

CRS, cytokine release syndrome; DLT, dose-limiting toxicity; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; LDC, lymphodepleting chemotherapy; SAE, serious adverse event; TLS, tumor lysis syndrome.
### Efficacy

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>DL1 3x10^7 N=3</th>
<th>DL2 1x10^8 N=3</th>
<th>DL3 3x10^8 N=4</th>
<th>DL4 9x10^8 N=3</th>
<th>Total N=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2 (67)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>3 (100)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Disease Control Rate (DCR = CR + PR + SD)</td>
<td>3 (100)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>3 (100)</td>
<td>10 (77)</td>
</tr>
</tbody>
</table>

- One patient achieved PR, which then deepened to CR by month 3; he has maintained CR through his most recent visit at month 18
- 4 patients (31%) were in SD at 4 months
- Typical PK seen with peak time to expansion at a median of D10 and peak concentration of ~3500 copies/μg
- Encouraging results underscore the potential of further increasing potency

CR, complete response; DCR, disease control rate; D, day; DL, dose level; ORR, overall response rate; PK, pharmacokinetics; PR, partial response; SD, stable disease.

Data cutoff date: 02 May 2022

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Efficacy (continued)

Data cutoff date: 02 May 2022

DL, dose level.

Subjects

Time From 1st CTX130 Infusion (months)

- Disease progression
- Stable disease
- Partial response
- Complete response
- Ongoing
- Reinfusion
- Death
- Response assessment
- Anti-cancer therapy
- Palliative radiotherapy

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Subject Overview

Patient profile
- 64-year-old male with clear cell RCC diagnosed in 2017
- 1 prior line of therapy with cabozantinib and atezolizumab
- After PR to previous therapy, patient relapsed with lesions in the lung and pleura
- CD70+ expression: 100% at baseline

Efficacy
- PR at D42 after a single infusion of 3x10^7 CAR+ T cells
- CR at M3 and remains in CR at M18

Safety
- Only Gr 1-2 adverse events
- No AEs considered related to CTX130

Response

<table>
<thead>
<tr>
<th>Time</th>
<th>Description</th>
<th>Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Deepening of response over time</td>
<td>![Images]</td>
</tr>
<tr>
<td>Day 42</td>
<td></td>
<td>![Images]</td>
</tr>
<tr>
<td>Month 18</td>
<td></td>
<td>![Images]</td>
</tr>
</tbody>
</table>

Data cutoff date: 02 May 2022

AE, adverse event; CAR, chimeric antigen receptor; CR, complete response; D, day; DL, dose level; Gr, grade; M, month; PR, partial response.
Conclusions

- This first-in-human clinical trial exploring CD70 CAR T-cell therapy in ccRCC showed a tolerant safety profile with no unexpected on-target off-tumor toxicities and encouraging antitumor activity.

- To our knowledge, this durable complete response (CR) is the first to be achieved with allogeneic CAR T cell therapy in patients with R/R solid tumors.

- CTX130 achieved a 77% DCR in a heavily pretreated RCC patient population. The longest duration of SD achieved was observed for 7.8 months and ongoing. During periods of SD, patients did not receive any other anticancer therapies.

- CTX130 represents a proof-of-concept for further exploration of CD70-targeted CAR T cells in ccRCC and other CD70+ malignancies.

- CTX130 is being developed with second-generation edits (CTX131™) containing disruption of regnase-1 and TGFβR2 which when edited together, increase potency at least 10X in preclinical models. Clinical studies are planned for 2023.
Acknowledgments

• Thank you to all the patients, families and investigators involved with the COBALT-RCC Study
• This study was sponsored by CRISPR Therapeutics