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

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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**[1-4]
  - **About 40% are primary refractory**[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[5,6]
- **CD70** is a ligand for CD27 with transient expression on activated lymphocytes and is **highly expressed in ccRCC tumor samples**[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.

References: 1. Rini BI et al. *N Engl J Med* 2019;380:1116-1127. 2. SEER*Explorer. https://nccrexplorer.ccdi.cancer.gov/. 3. Global Cancer Observatory. https://gco.iarc.fr/. 4. Powles T, et al. *Lancet Oncol*. 2020;21:1563-1573. 5. Frank I, et al. *J Urol*. 2002;168:2395-400. 6. Patard JJ, et al. *J Clin Oncol*. 2004;22:3316-22. 7. Wajant H. *Expert Opin Ther Targets*. 2016;20:959-973. 8. Hintzen RQ, et al. *Int Immunol*. 1994;6:477-480. 9. Lens SM, et al. *Immunology*. 1997;90:38-45. 10. Benhamouda H,et al. *Clin Cancer Res*. Sep 6:CCR-22-0905. doi: 10.1158/1078-0432.CCR-22-0905. Online ahead of print.

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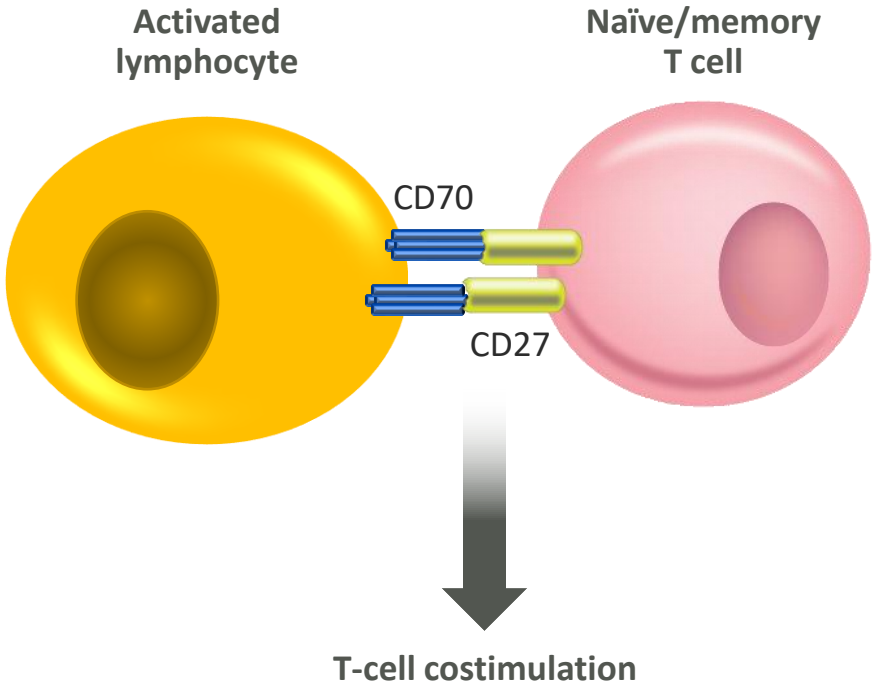
Role of CD70 in Immune Response and Cancer

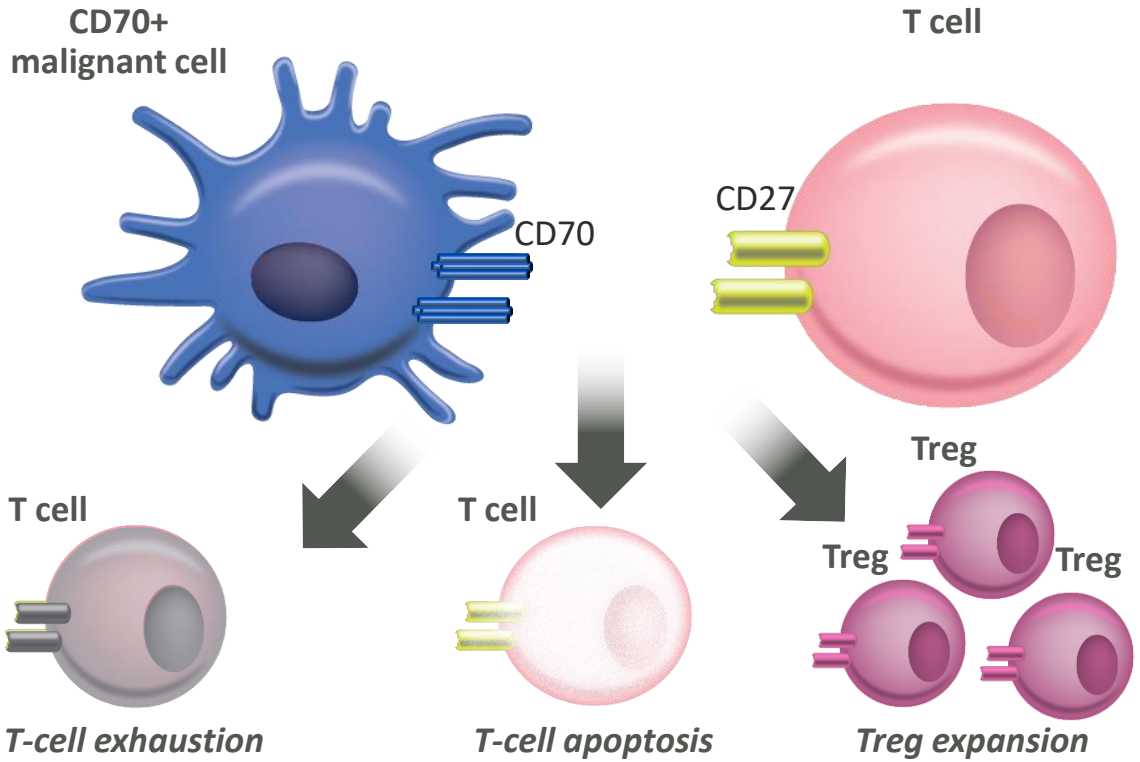
Physiological role of CD70[1,2]

- 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



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

References: 1. Wajant H. *Expert Opin Ther Targets*. 2016;20:959-973. 2. Buchan SL, et al. *Blood.* 2018;131:39-48. 3. Karnik S, et al. AACR 2020. Poster P6595. 4. Benhamouda H,et al. *Clin Cancer Res*. Sep 6:CCR-22-0905. doi: 10.1158/1078-0432.CCR-22-0905. Online ahead of print.

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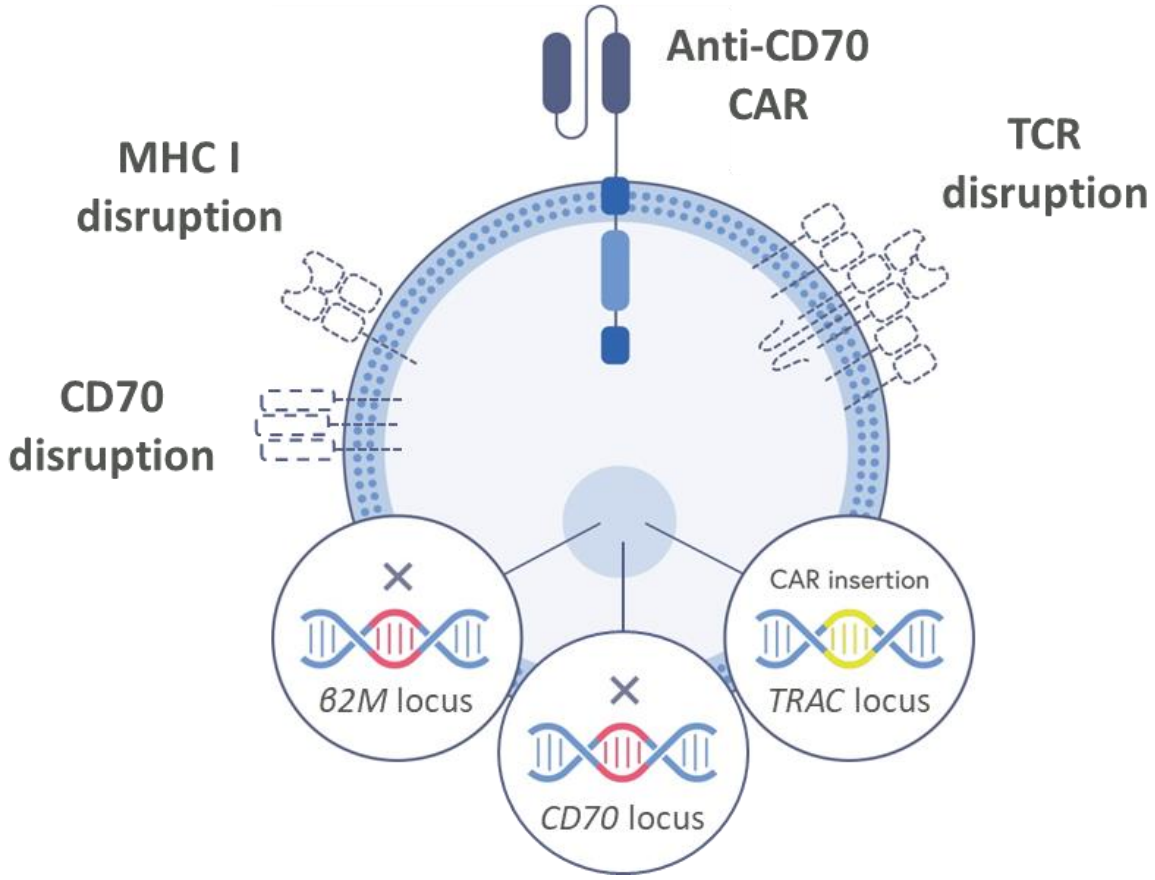
CTX130

- **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**

CTX130 Construct



AAV, adeno-associated virus; β2M, β2-microglobulin; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.

Reference: Dequeant M-L, et al. CD70 knockout: A novel approach to augment CAR-T cell function. Poster presented at American Association for Cancer Research 2021. April 10-15 and May 17-21, 2021.

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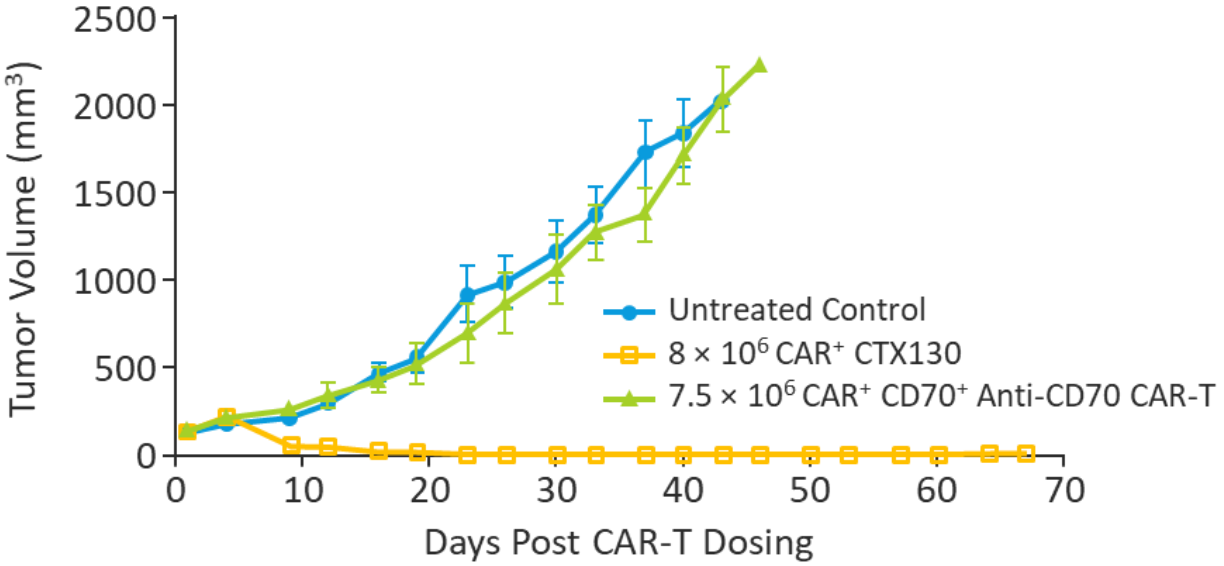
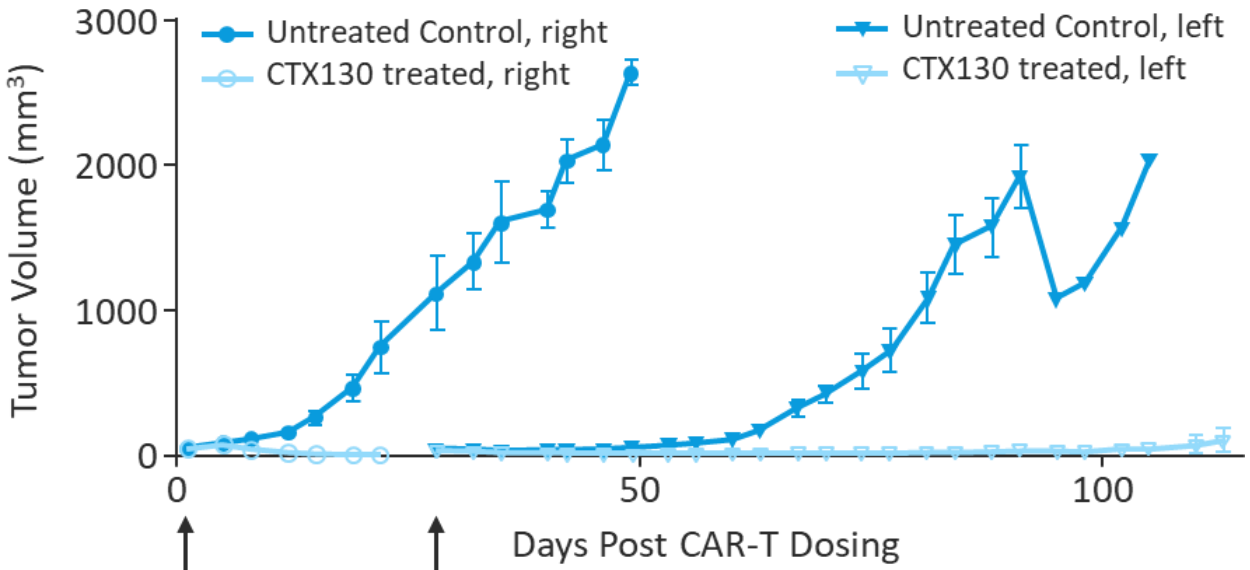
CTX130 Demonstrated Encouraging Efficacy in a Renal Cell Carcinoma Xenograft Model

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



Five million A498 cells were injected subcutaneously into the right flank of NOG (NOD.*Cg-Prkdc*^{scid}*Il2rg*^{tm1Sug}/JicTac) 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 x 10^6 CAR$^+$ CTX130 cells per mouse (n=5) or with 7.5 x 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 and Systemic Antitumor Activity of a Single Dose of CTX130 in an A498 RCC Xenograft Model



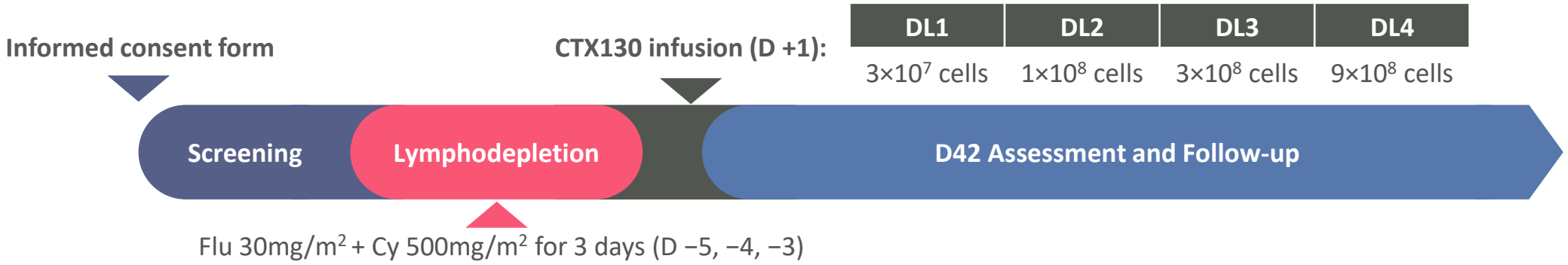
Day 1: Right flank: animals with average tumor volume of 50 mm^3 were randomized and left untreated (solid circle) or treated with 7 × 10^6 CAR$^+$ CTX130 cells (open circle).

Day 25: Left flank: new control group (solid triangle) or CTX130 treated group (open triangle) inoculated with tumor cells.

CAR, chimeric antigen receptor; RCC, renal cell carcinoma.

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



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

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

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

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Patient Demographics and Baseline Characteristics

Data cutoff date: 02 May 2022

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

DL, dose level; eGFR, estimated glomerular filtration rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SoD, sum of diameters.

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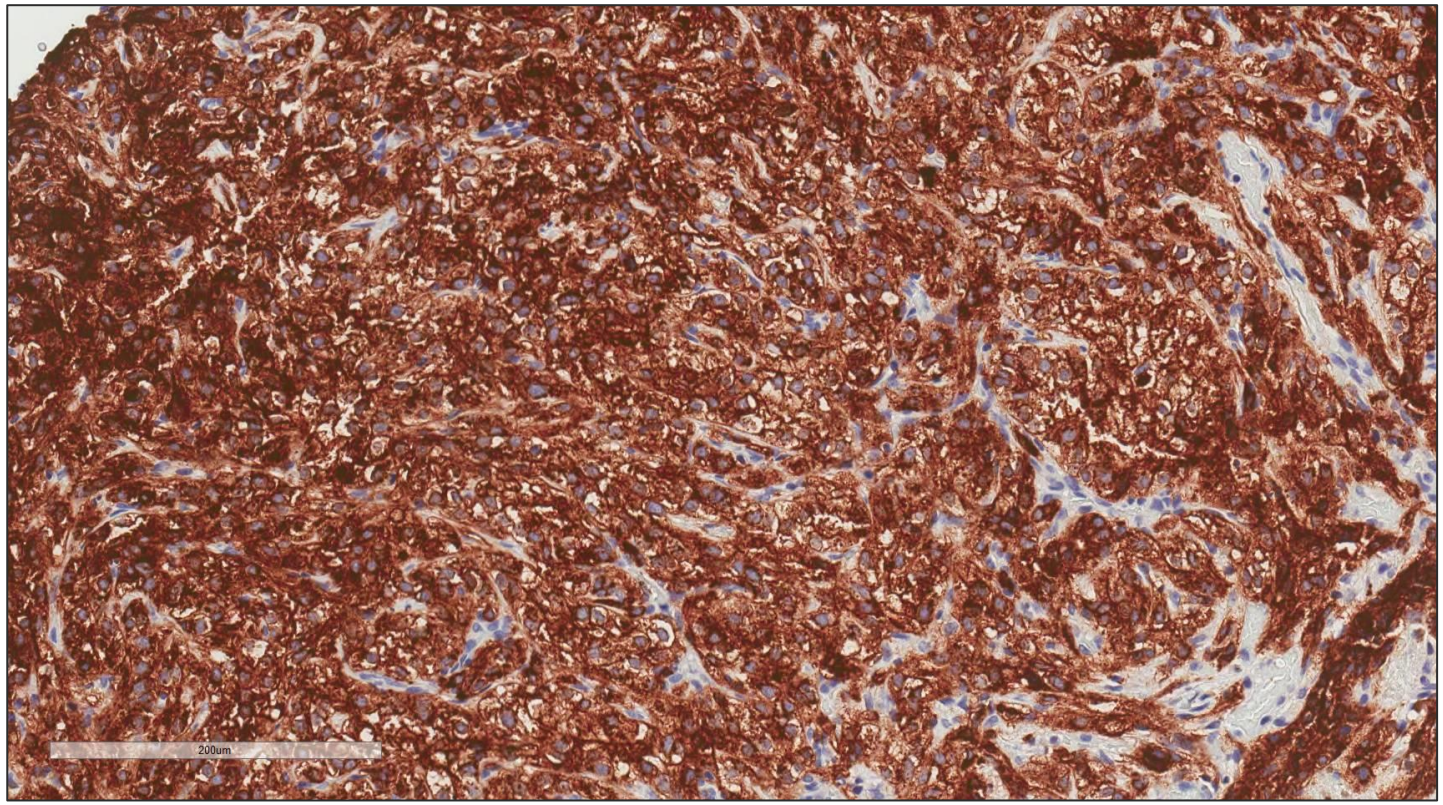
CD70 Expression in ccRCC Clinical Samples



- 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.

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Safety

Data cutoff date: 02 May 2022

Adverse Events of Interest, N (%)

	DL1 $3x10^7$ N=3		DL2 $1x10^8$ N=3		DL3 $3x10^8$ N=4		DL4 $9x10^8$ N=4		Total N=14	
	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3	Gr 1-2	Gr ≥3
CRS	–	–	–	–	3 (75)	–	4 (100)	–	**7 (50)**	–
ICANS	–	–	–	–	–	–	–	–	–	–
GvHD	–	–	–	–	–	–	–	–	–	–
Infections*	–	–	–	1 (33)	1 (25)	1 (25)	1 (25)	–	**2 (14.3)**	**2 (14.3)**

- 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

All events listed in table are treatment-emergent adverse events.
*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.

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Efficacy

Data cutoff date: 02 May 2022

Best overall response, n (%)

	DL1 $3x10^7$ N=3	DL2 $1x10^8$ N=3	DL3 $3x10^8$ N=4	DL4 $9x10^8$ N=3	Total N=13
Overall Response Rate	1 (33)	0	0	0	**1 (8)**
Stable Disease	2 (67)	2 (67)	2 (50)	3 (100)	**9 (69)**
Disease Control Rate (DCR = CR + PR + SD)	3 (100)	2 (67)	2 (50)	3 (100)	**10 (77)**

- 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.

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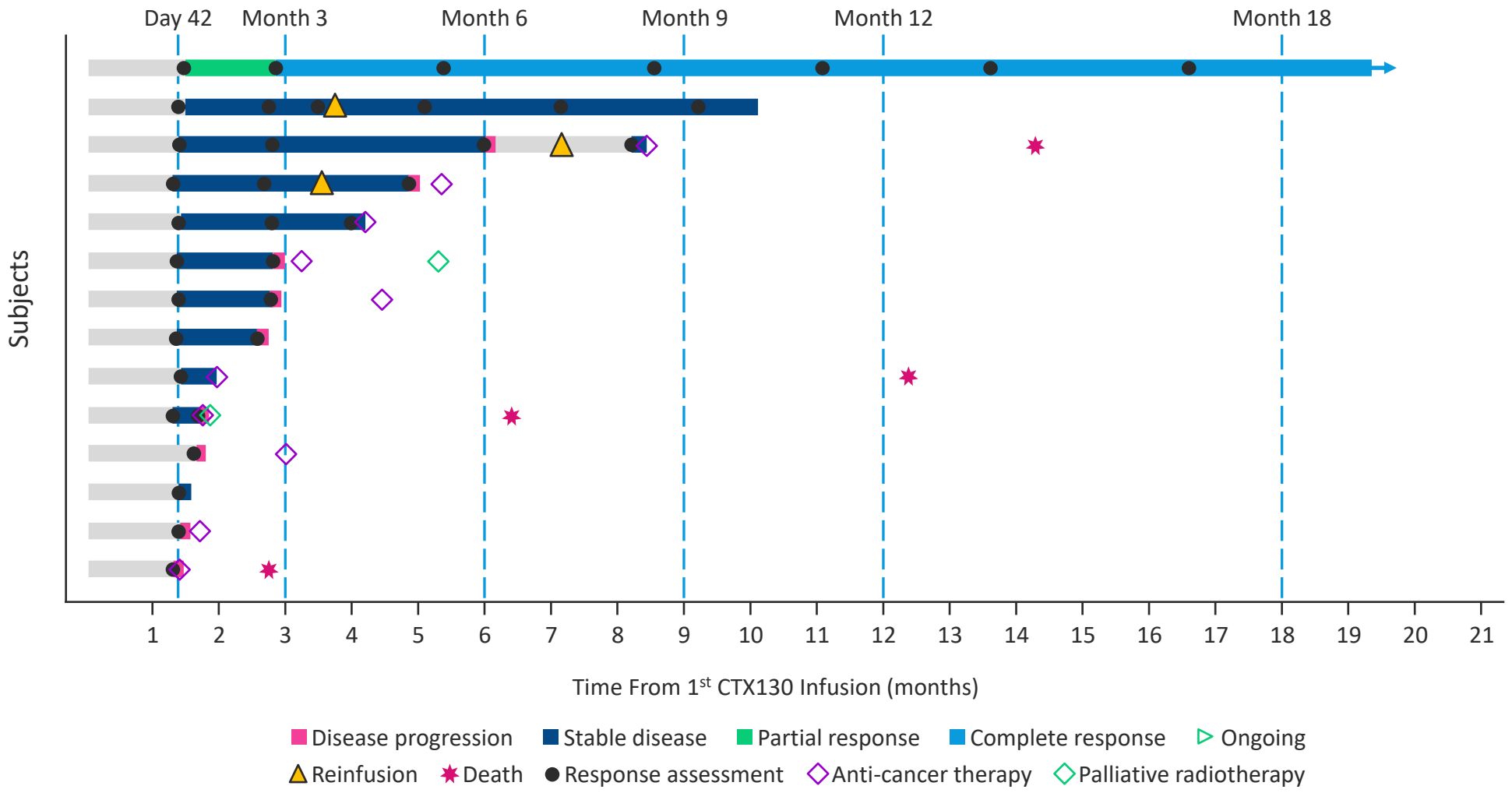
Efficacy (continued)

Data cutoff date: 02 May 2022



DL, dose level.

Case Study

Complete Response with Single-Infusion of CTX130

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

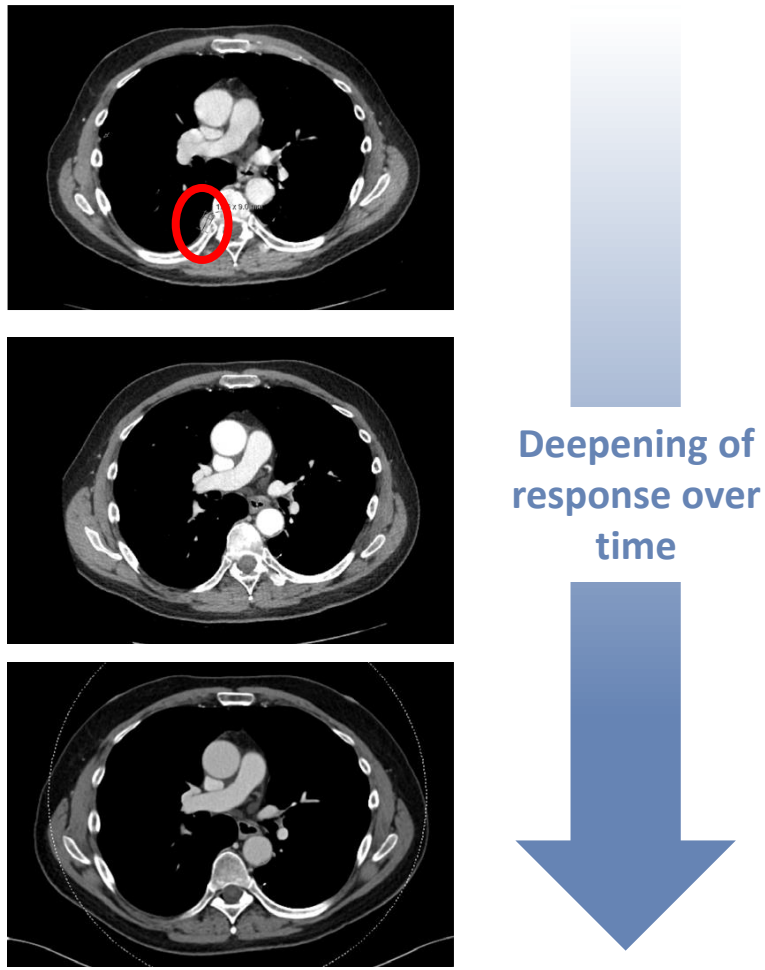
Efficacy

- 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



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

Data cutoff date: 02 May 2022

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Conclusions

- This first-in-human clinical trial exploring CD70 CAR T-cell therapy in ccRCC showed a **tolerable 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

CAR, chimeric antigen receptor; ccRCC, clear cell renal cell carcinoma; CR, complete response; DCR, disease control rate; DL, dose level; R/R, relapsed/refractory; SD, stable disease; TGFβR2, transforming growth factor beta receptor 2.

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Acknowledgments

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- This study was sponsored by CRISPR Therapeutics

COBALT-RCC (NCT04438083) Study Sites