CAR T cell therapy for RCC

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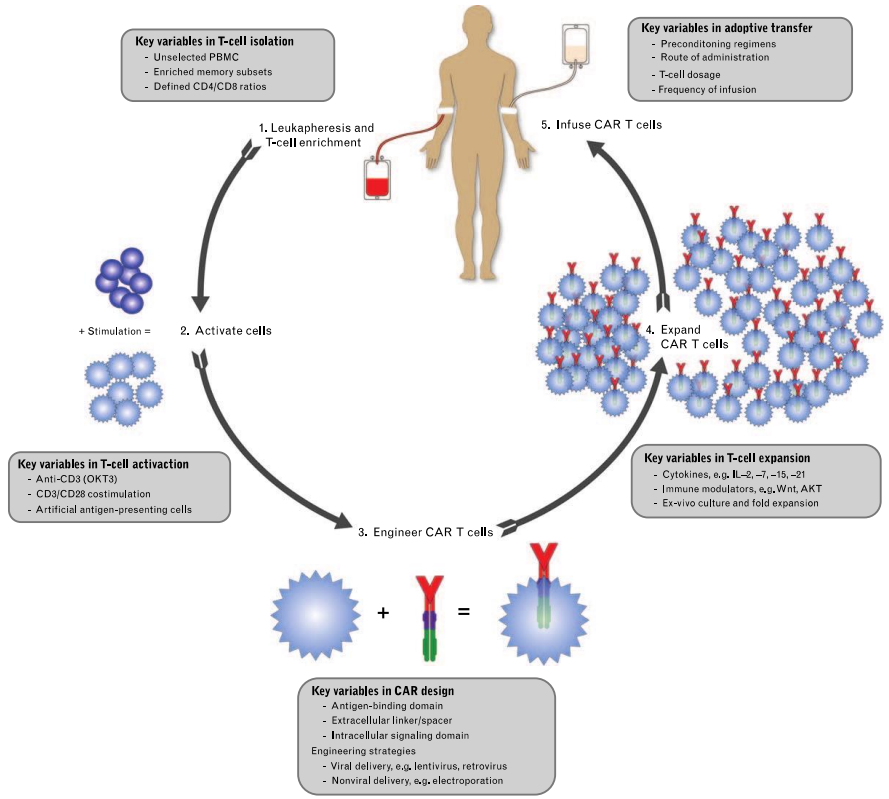
(Autologous) CAR-engineered T cells can work in prostate CA

PSMA TGFbRII ko
Narayan, Fraietta et al. Nat Med 2022

PSCA 41bb
Dorff, Priceman et al. Nat Med 2024

PSCA (BPX601) GoCAR T®
Stein, Becerra et al. Nat Comm

P-PSMA-101
Slovin, Dorff et al (subm)

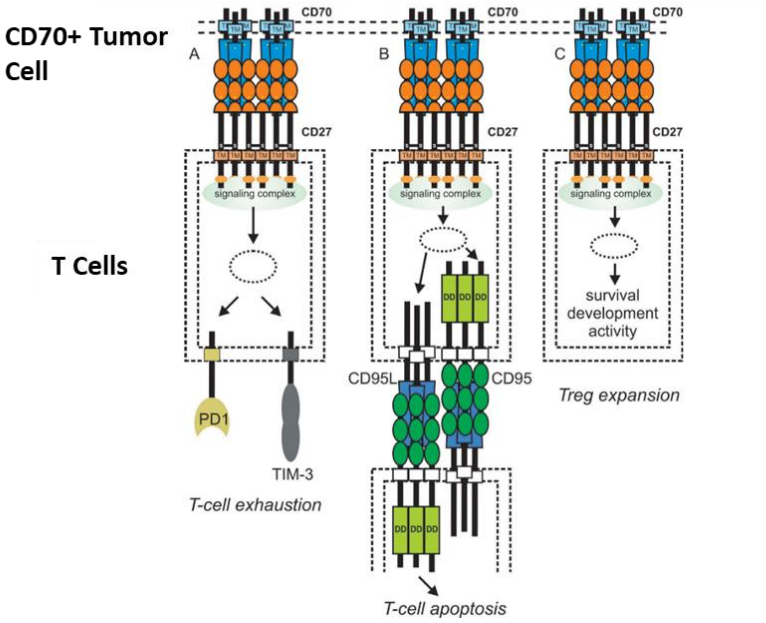


Priceman, et al. Curr Opin Oncol 2015

RCC targets: CD70, CA9 – mostly ALLO constructs in development

Role of CD70 in Cancer

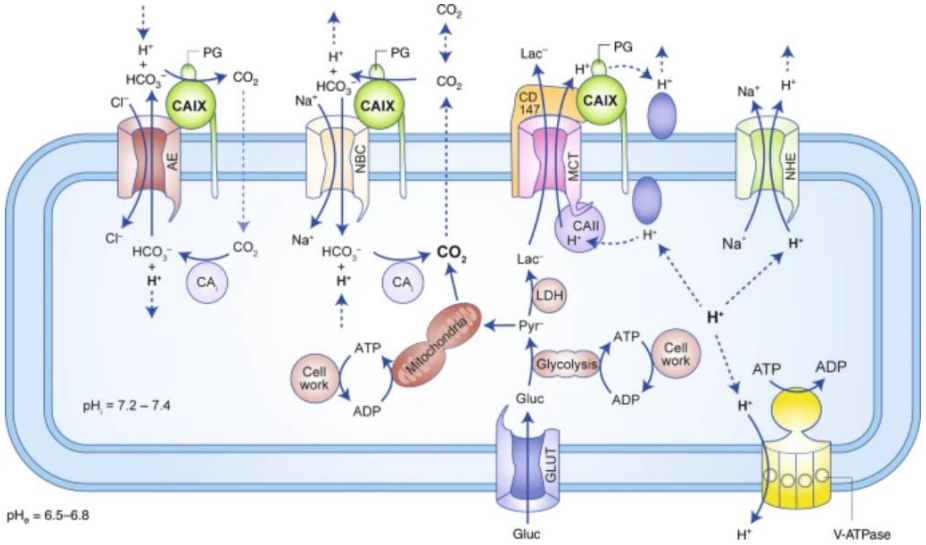
- Elevated CD70 expression on RCC, lymphomas, AML and other solid tumors
- Possible immunosuppressive role via CD27 due to T cell exhaustion, apoptosis or T reg expansion



Wajant H. Exp Op Ther Target 2016; 959-973

Role of CA IX in Cancer

- Create gradient to facilitate migration of cancer cells



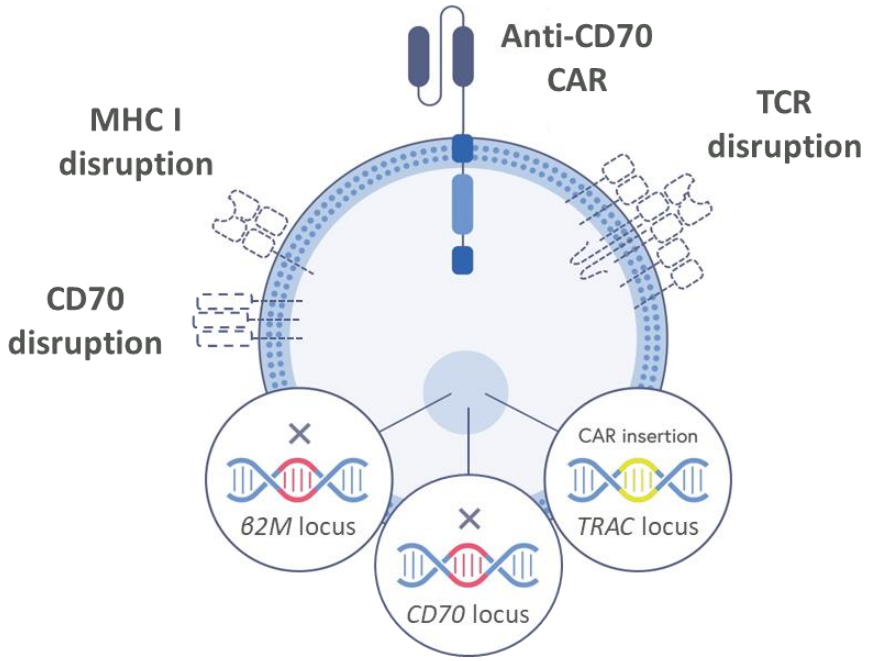
Becker JM Br J Cancer 2020; 122:157-67

City of Hope

CTX130: Anti-CD70 Allogeneic CAR-T

- **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.

City of Hope

Patient Demographics and Baseline Characteristics

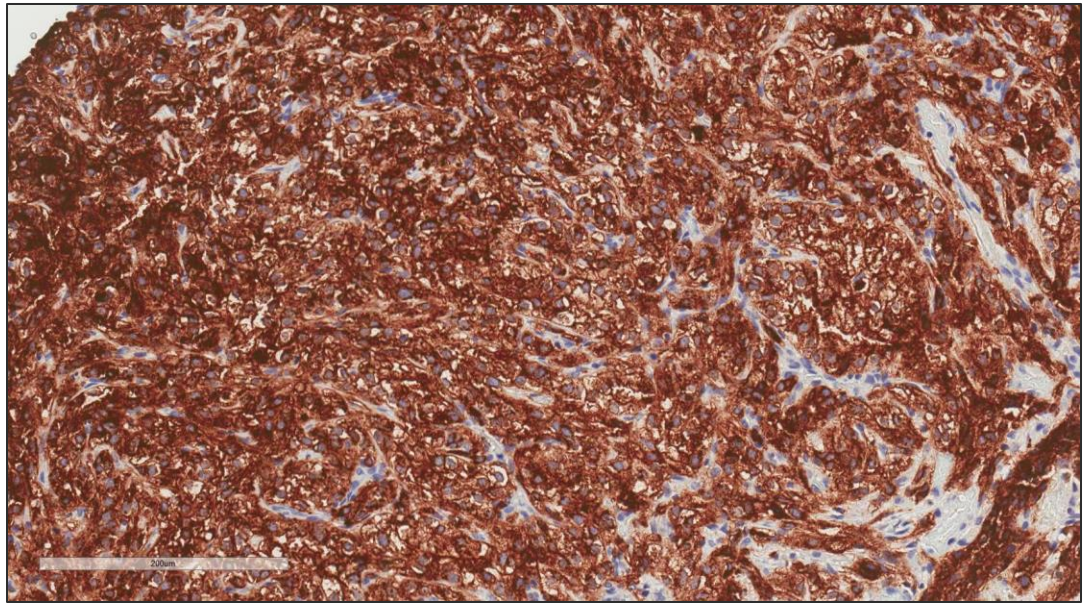
	DL1 (3×10^7 cells) $N = 3$	DL2 (1×10^8 cells) $N = 3$	DL3 (3×10^8 cells) $N = 6$	DL4 (9×10^8 cells) $N = 4$	Total $N = 16$
Median age, y (range)	59.0 (58-64)	60.0 (54-65)	61.0 (53-73)	70.0 (66-77)	63.0 (53-77)
Sex at birth, male, *n* (%)	3 (100.0)	3 (100.0)	6 (100.0)	2 (50.0)	14 (87.5)
Metastatic disease, *n* (%)	3 (100.0)	3 (100.0)	6 (100.0)	4 (100.0)	16 (100.0)
Prior anticancer therapies, *n* (%)					
Systemic therapy	3 (100.0)	3 (100.0)	6 (100.0)	4 (100.0)	16 (100.0)
Radiotherapy	1 (33.3)	2 (66.7)	4 (66.7)	4 (100.0)	11 (68.8)
Surgery	3 (100.0)	3 (100.0)	5 (83.3)	4 (100.0)	15 (93.8)
Median prior lines of systemic therapy, *n* (range)	2 (1-3)	3 (2-4)	3 (1-5)	3 (2-6)	3 (1-6)
Median time from diagnosis, y (range)	3.4 (2.5-6.3)	2.7 (0.7-3.3)	5.1 (2.5-6.3)	10.5 (5.1-24.0)	4.9 (0.7-24.0)
IMDC category at screening, *n* (%)					
Favorable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intermediate	3 (100.0)	3 (100.0)	3 (50.0)	1 (25.0)	10 (62.5)
Poor	0 (0.0)	0 (0.0)	3 (50.0)	3 (75.0)	6 (37.5)
eGFR <60 mL/min/1.73 m^2, *n* (%)	2 (66.7)	1 (33.0)	1 (16.7)	2 (50.0)	6 (37.5)

Abbreviations: DL, dose level; eGFR, estimated glomerular filtration rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Pal SK et al. Cancer Discov 2024; 14:1176-89

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

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.

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

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)**

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.

- 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

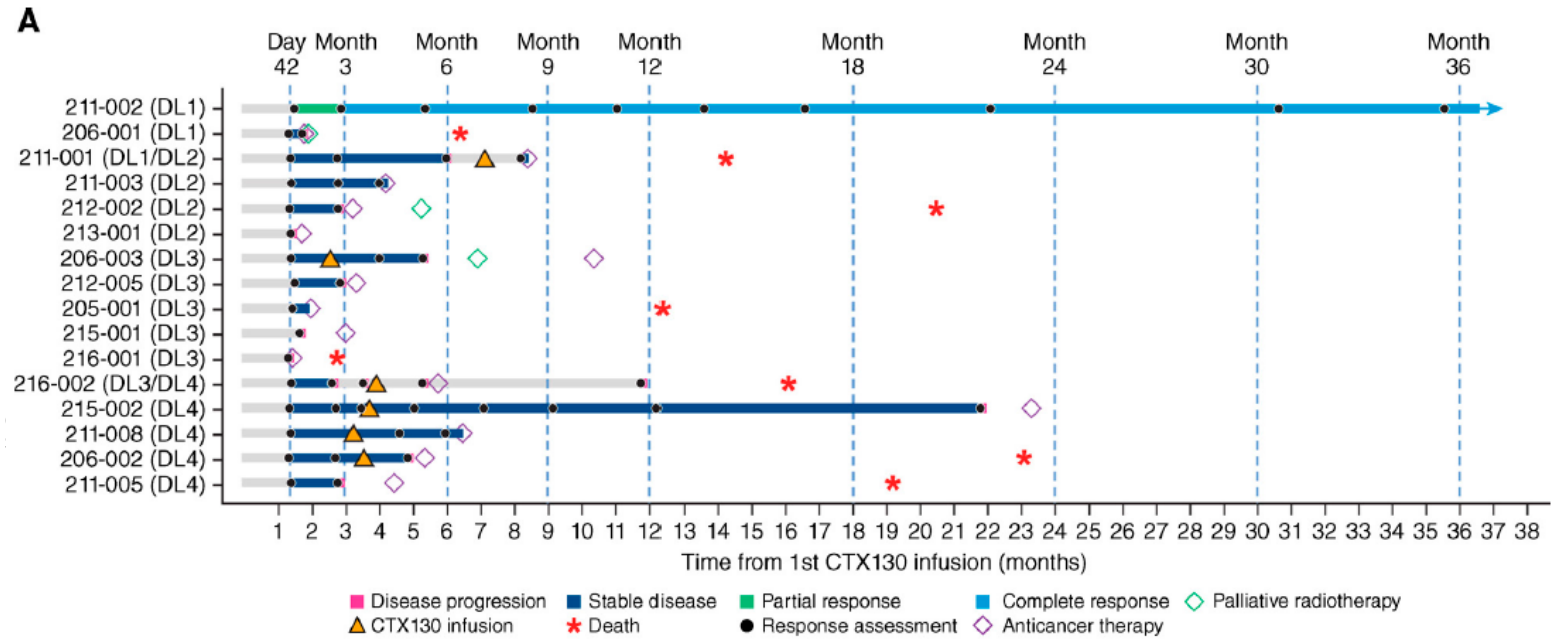
Presented at the SITC 37th Annual Meeting. Nov 10, 2022

Efficacy

- 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



Pal SK et al. Cancer Discov 2024; 14:1176-89

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

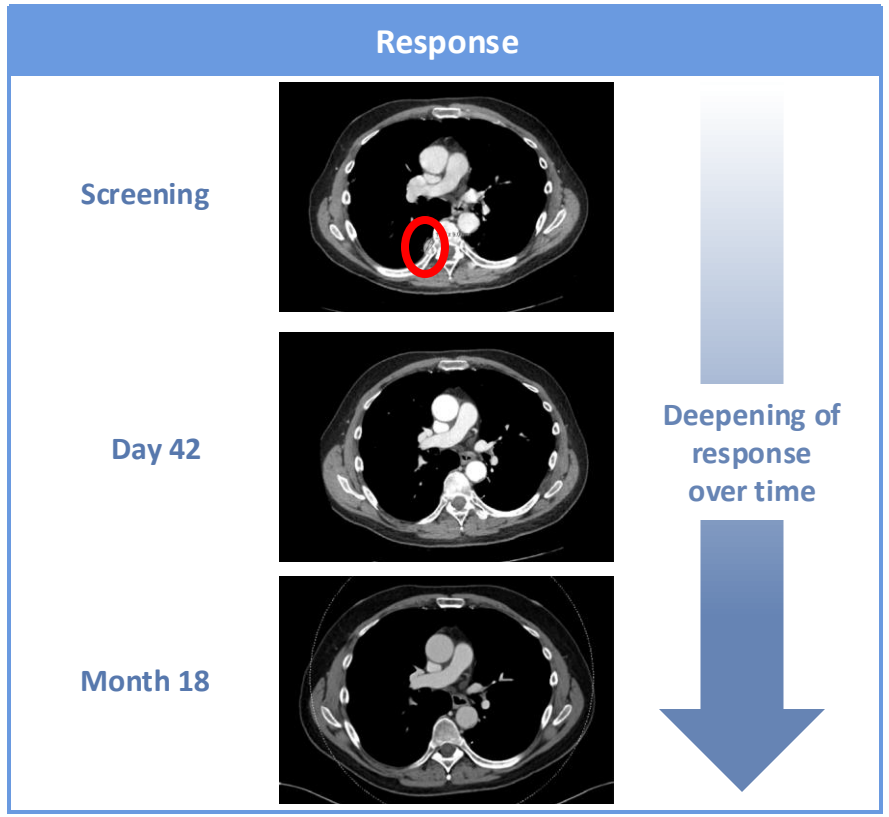
Efficacy

- 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

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

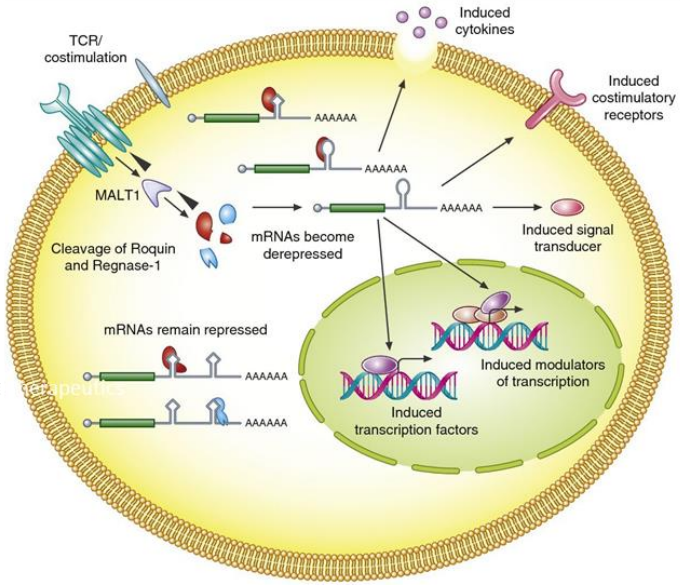


Data cutoff date: 02 May 2022

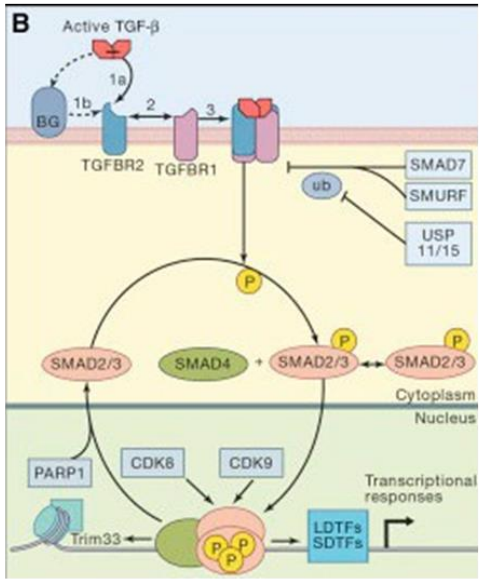
Presented at the SITC 37th Annual Meeting. Nov 10, 2022

Phase I Study: CTX131 (Additional edits to Regnase-1 & TGFRB2)

Regnase-1 KO: *removes intrinsic "brake" on T cell function*



TGFBR2 KO: *removes key extrinsic "brake" on T cell anti-tumor activity*

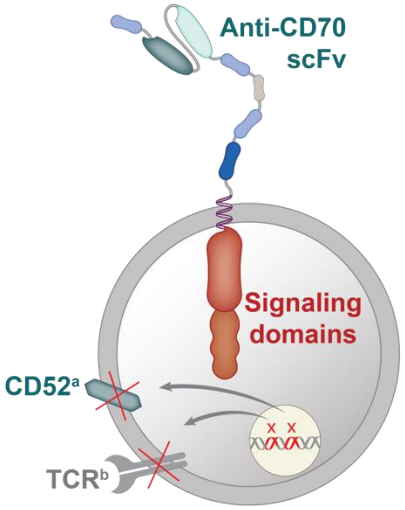


Sources: Jeltsch & Heissmeyer. Curr Opin Immunol. 2016 Apr;39:127-35; Batlle & Massague. Immunity. 2019 Apr 16;50(4):924-940

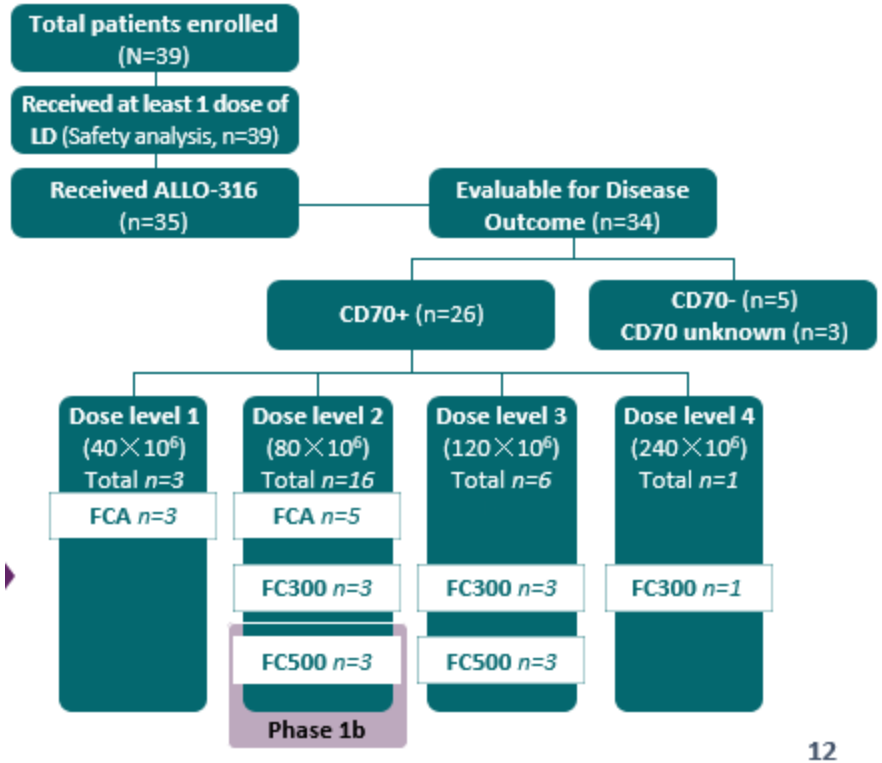
City of Hope

ALLO-316: Allogenic CAR for ccRCC

- **investigational allogeneic CD70 CAR T cell product**
-
  - Healthy donor-derived, HLA-unmatched, and off-the-shelf product
  - **Designed to recognize and kill both CD70+ tumor cells and CD70+ host T cells that cause allo-rejection**



ALLO-316



12

Baseline Characteristics: Patients Were Heavily Pretreated and

Characteristic	All Patients (N=39)
Median age (range), years	60 (35-70)
Gender: male/female, %	90/10
ECOG PS: 0/1, %	56/44
Disease stage IV, n (%)	38 (97)
Previous nephrectomy, n (%)	32 (82)
CD70 Positive, m (%) High TPS (≥50), n/m (%) Low TPS (<50), n/m (%) **CD70 Negative or Unknown, n (%)**	31 (79) 24 (77) 7 (23) 8 (21)
Median time since original diagnosis (range), months	43 (12-216)
IMDC category at screening Favorable risk Intermediate risk Poor risk	 13 (33) 20 (51) 4 (10)

Characteristic	All Patients (N=39)
Median lines of prior therapy (range)	3 (1-8)
Prior Therapies, n(%) Anti–PD-1 therapy Anti–PD-L1 therapy Anti–CTLA-4 therapy Belzutifan Cabozantinib ≥1 TKI ≥2 TKIs ≥3 TKIs	 39 (100) 1 (3) 25 (64) 5 (13) 31 (79) 39 (100) 23 (59) 11 (28)
Progressive disease despite anti–CTLA-4, anti–PD-1, TKI, and belzutifan, n (%)	3 (8)
Median time from enrollment to lymphodepletion, days (range)	5 (1-10)

Data cutoff: October 14, 2024.

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; ECOG PS, Eastern Cooperative Oncology performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TPS, tumor proportion score; TKI, tyrosine kinase inhibitor.

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Safety Profile (All Patients and the Expansion Cohort)

AEs, n (%)	All Patients (N=39)		DL2 FC500 (n=11)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
CRS	24 (62)	1 (3)	8 (73)	0
Fatigue	23 (59)	1 (3)	2 (18)	0
Neutropenia	22 (56)	20 (51)	7 (64)	7 (64)
Anemia	20 (51)	13 (33)	7 (64)	5 (46)
Nausea	20 (51)	0	3 (27)	0
Thrombocytopenia	18 (46)	10 (26)	7 (64)	3 (27)
Pyrexia	16 (41)	2 (5)	4 (36)	0

AEs of Special Interest	Any Grades	Grade ≥3	Any Grades	Grade ≥3
Infection Viral Infections	24 (62) 13 (33)	12 (31) 2 (5)	5 (46) 2 (18)	2 (18) 0
Neurotoxicity Headache	17 (44) 8 (21)	3 (8) 0	4 (36) 2 (18)	0 0
ICANS	3 (8)	0	3 (27)	0
IEC-HS	5 (13)	1 (3)	2 (18)	0
Graft-vs-host disease	0	0	0	0

- DLTs were seen in 2 patients, both of whom received DL2 (80×10^6 CAR cells) FCA
  - DLTs were autoimmune hepatitis (patient also had COVID) and cardiogenic shock related to multi-organ failure (n=1 each)
- Other related fatal AEs:
  - Failure-to-thrive (Grade 5) at 15 months in a patient with stable disease
  - Sepsis (Grade 5)

Data cutoff: October 14, 2024.
AE, adverse event; CRS, cytokine release syndrome; DL, dose level; DLT, dose-limiting toxicity; FCA, fludarabine, cyclophosphamide, and ALLO-647; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; ICANS, immune effector cell-associated neurotoxicity syndrome; IEC-HS, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome.

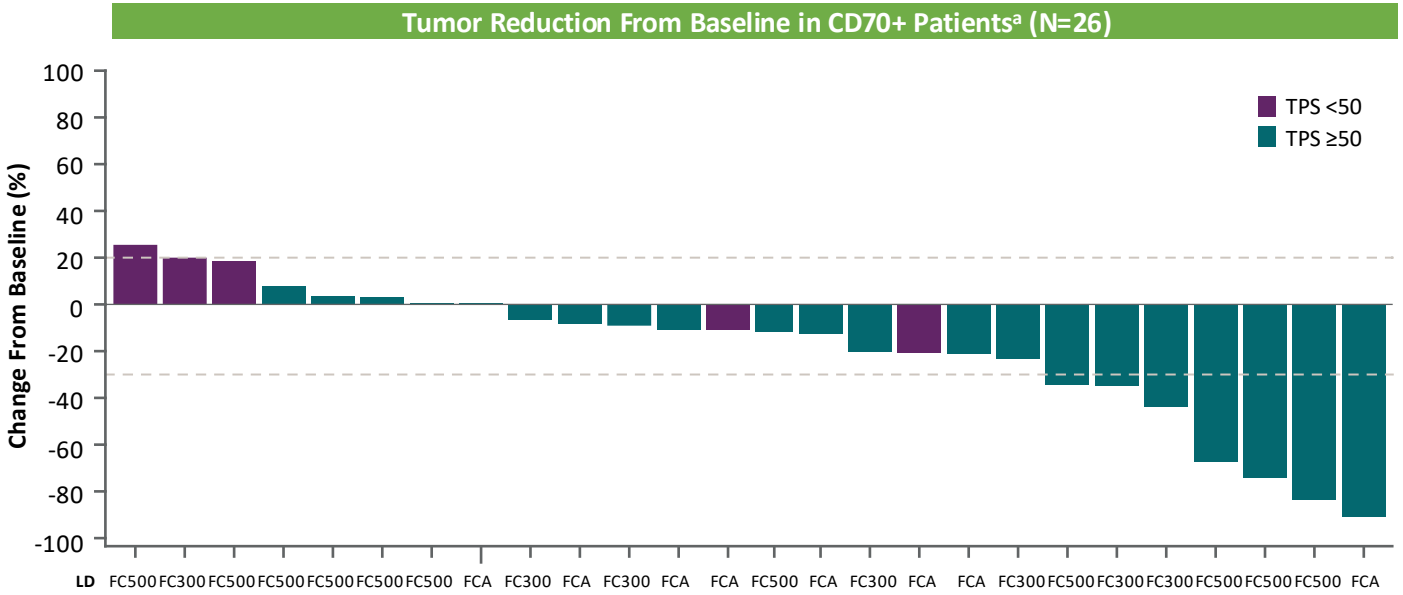
Response Rates Based on CD70 Expression and Standard Lymphodepletion

	Patients Evaluable for Disease Outcomes (N=34)				
	CD70 Positive (N=26)				CD70 Negative or Unknown (n=8)
	All (N=26)	FCA only (n= 8)	FC only (n=18)	DL-2[a] FC500 (Phase 1b) (n=8)	
Best overall response,[b] n/N (%)	7/26 (27)	1/8 (13)	6/18 (33)	3/8 (38)	0/8 (0)
High TPS (≥50)	7/21 (33)	1/6 (17)	6/15 (40)	3/6 (50)	—
Low TPS (<50)	0/5 (0)	0/2 (0)	0/3 (0)	0/2 (0)	—
Confirmed ORR,[c] n/N (%)	5/26 (19)	1/8 (13)	4/18 (22)	2/8 (25)	0/8 (0)
High TPS (≥50)	5/21 (24)	1/6 (17)	4/15 (27)	2/6 (33)	—
Low TPS (<50)	0/5 (0)	0/2 (0)	0/3 (0)	0/2 (0)	—

- 2 of 8 (25%) patients who received DL2 FC500 showed durable responses ongoing at ≥4 months
- Responses were seen in patients who did not receive ALLO-647–containing lymphodepletion

Data cutoff: October 14, 2024.
[a] 80×10^6 dose of CD70 CAR+ cells (DL2). [b] Best overall response across visits did not require confirmation for CR/PR or minimum duration for SD. [c] Confirmed best overall response of CR/PR required confirmation at the subsequent visit.
CR, complete response; DL-2, dose level 2; FCA, fludarabine and cyclophosphamide; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; ORR, overall response rate; PR, partial response; TPS, tumor proportion score.

Tumor Reduction With TPS ≥50



- Of the patients with TPS ≥50:
  - 76% (16/21) experienced a tumor burden reduction
  - 33% (7/21) had >30% reduction

Data cutoff: October 14, 2024.

[a] Fresh biopsies were not required; responses were observed in patients deemed CD70+ with fresh and archival tissues.

FC300, fludarabine 30 mg/m² and cyclophosphamide 300 mg/m²; FC500, fludarabine 30 mg/m² and cyclophosphamide 500 mg/m²; FCA, fludarabine, cyclophosphamide, and ALLO-647; LD, lymphodepletion; TPS, tumor proportion score.

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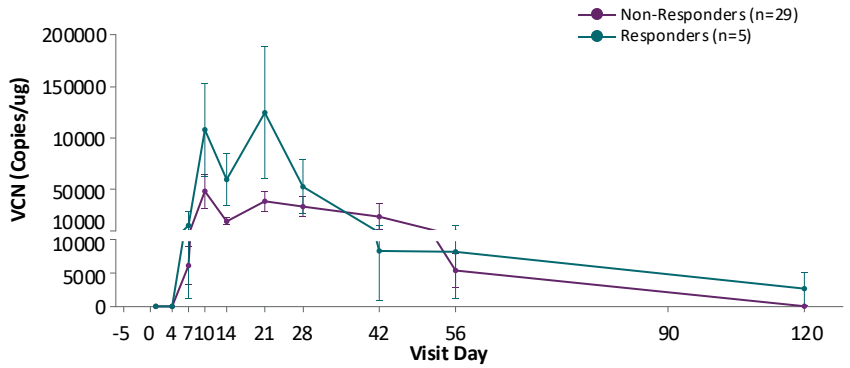
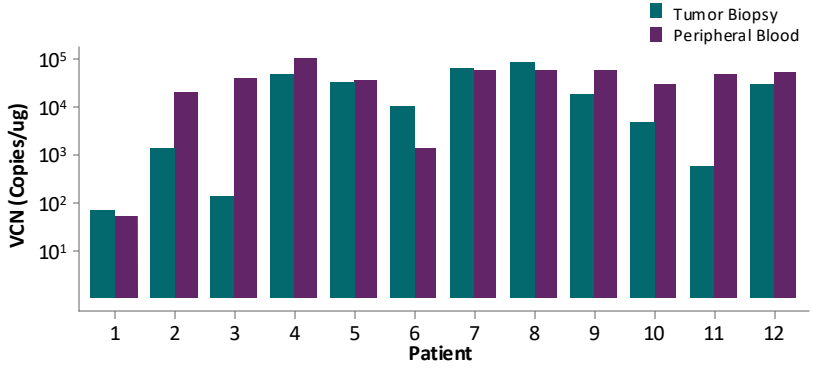
Highly Active ALLO-316 CAR

- Robust CAR T cell expansion and persistence were observed, which was superior in responders relative to non-responders
- The high VCN levels observed in the tumor samples demonstrates the extensive infiltration of ALLO-316 cells

VCN Over Time by Best Confirmed Overall Response



Tumor Biopsy and Day 10 Blood VCN



Data cutoff: October 14, 2024.
CAR, chimeric antigen receptor; VCN, vector copy number.

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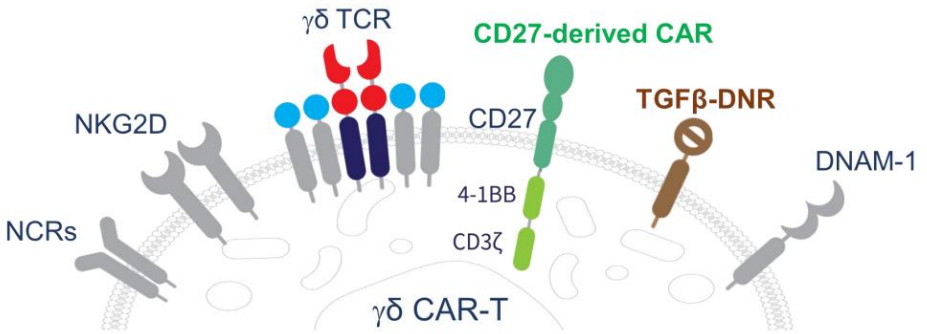
Now Enrolling at COH: ADI-270

- ADI-270 is an investigational, allogeneic, CD70-targeting (CD27 receptor-based) Vδ1 γδ CAR T cell product expressing a dominant negative form of the TGFβ receptor II (dnTGFβRII) to provide resistance against the immunosuppressive tumor microenvironment
- γδ T cells are ideal for an allogeneic cell therapy

  - TCR recognizes MHC-independent antigens (avoids risk of graft versus host disease without the need for gene editing)



Beckermann SITC 2024; slide courtesy of S. Pal

Now Enrolling at COH: AB2100 (autologous PSMA+ CA9+ CAR T)

AB-2100 Phase 1/2, Open-label, Multicenter Study Design

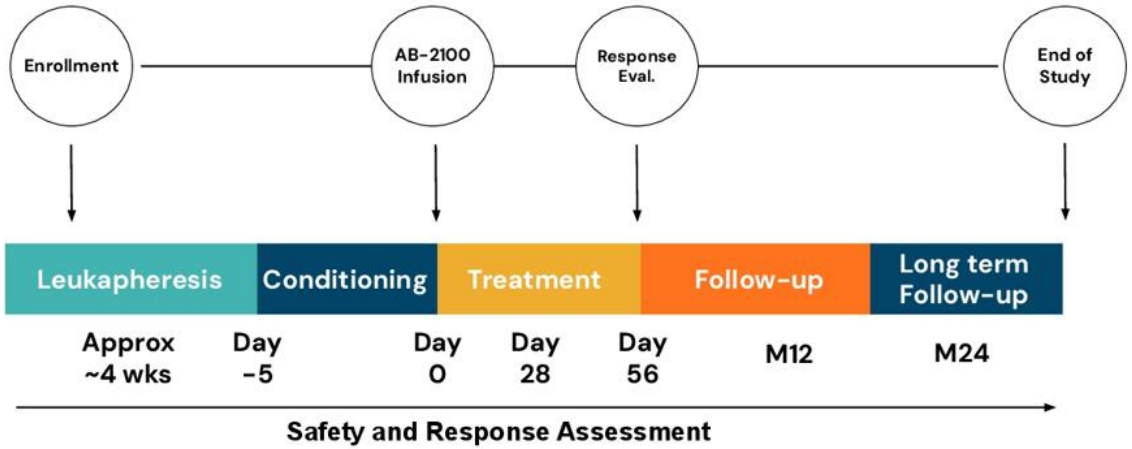
A

Population:
- Advanced/metastatic clear cell renal cell carcinoma (ccRCC) after immune checkpoint inhibitor and VEGF-targeted therapy
- No initial selection for PSMA/CA9

Design:
- Phase 1:
  - 3+3 design, backfill
  - Without conditioning may be explored

Status:
- Open

B



Retreatment with AB-2100 available for subjects meeting criteria.

Up to 3 dose levels may be evaluated.

Conditioning Regimen (Day -5, -4, -3)
- Fludarabine (Flu) 30 mg/m^2
- Cyclophosphamide (Cy) 300 mg/m^2

Scarfo ASCO GU 2024; slide courtesy of S. Pal

CONCLUSIONS: CAR T for RCC (and other GU cancers)

"Lymphodepletion" is actually tumor immune microenvironment modulation

- and IS necessary for CAR T expansion/ function

CD70, CAIX promising targets for immunotherapy for RCC

Allo "off the shelf" approach has activity

- ?Unique to CD70 target