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**ANNUAL
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CTX112 and CTX131: Next-generation CRISPR/Cas9-engineered allogeneic (allo) CAR T cells incorporating novel edits that increase potency and efficacy in the treatment of lymphoid and solid tumors

Session Type: Drug Development Special Track Session

Session Title: New Drugs on the Horizon: Part 1

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Disclosure Information

Jon Terrett

I have the following relevant financial relationships to disclose:

Employee of: CRISPR Therapeutics

Stockholder in: CRISPR Therapeutics

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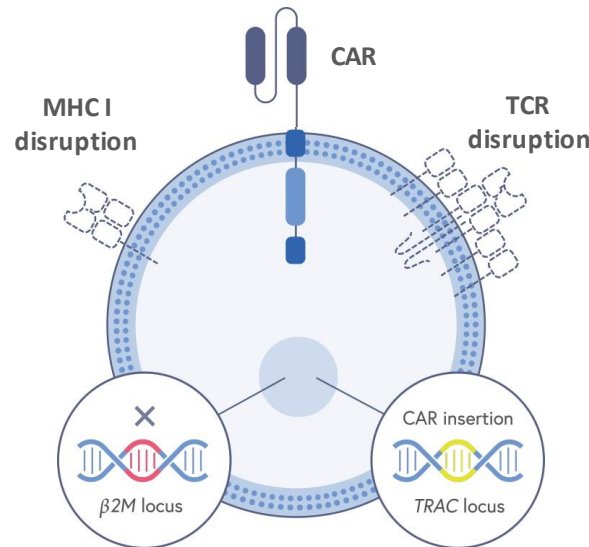
Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no interpretative value on our existing or future results.

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Our Allogeneic CAR T Cells Share the Same Core Chassis

Allogeneic CAR T chassis:

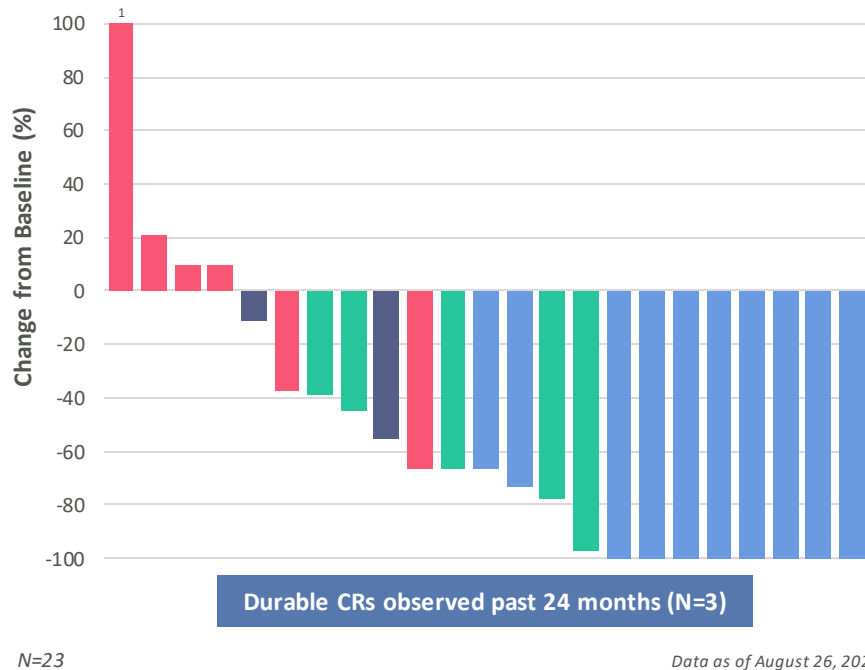
- **Improve persistence in the allo setting** via B2M knock-out to eliminate MHC I expression
- **Avoid need** for more toxic lymphodepletion regimens



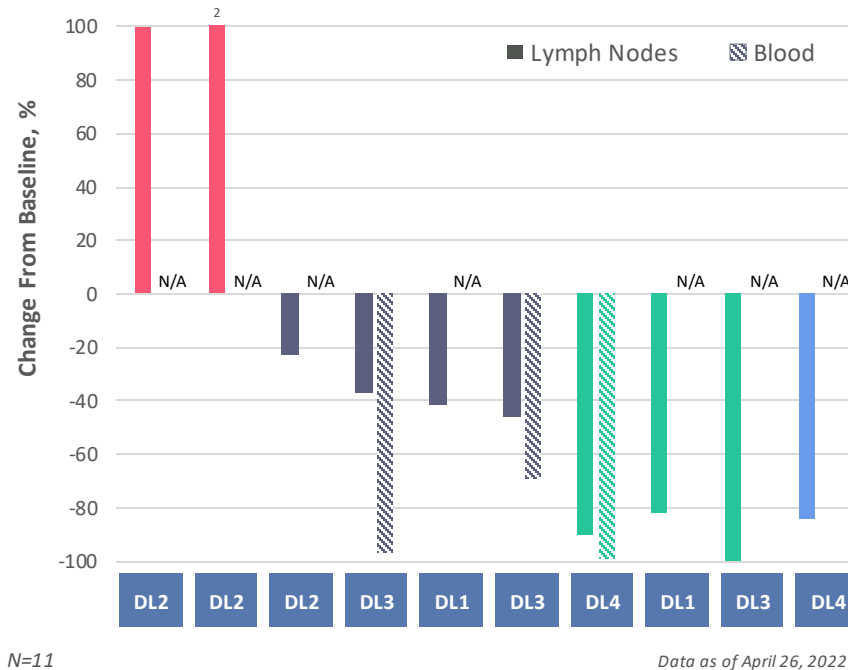
- **Reduce risk of GvHD** via TCR disruption
- **Improve consistency and safety by precise insertion** of CAR construct into *TRAC* locus without using lentivirus or retrovirus

CTX110 and CTX130 Allogeneic CAR T Cells Produced Deep Reductions in Tumor Burden

CTX110 (DL2+ with re-dosing) in Non-Hodgkin Lymphoma



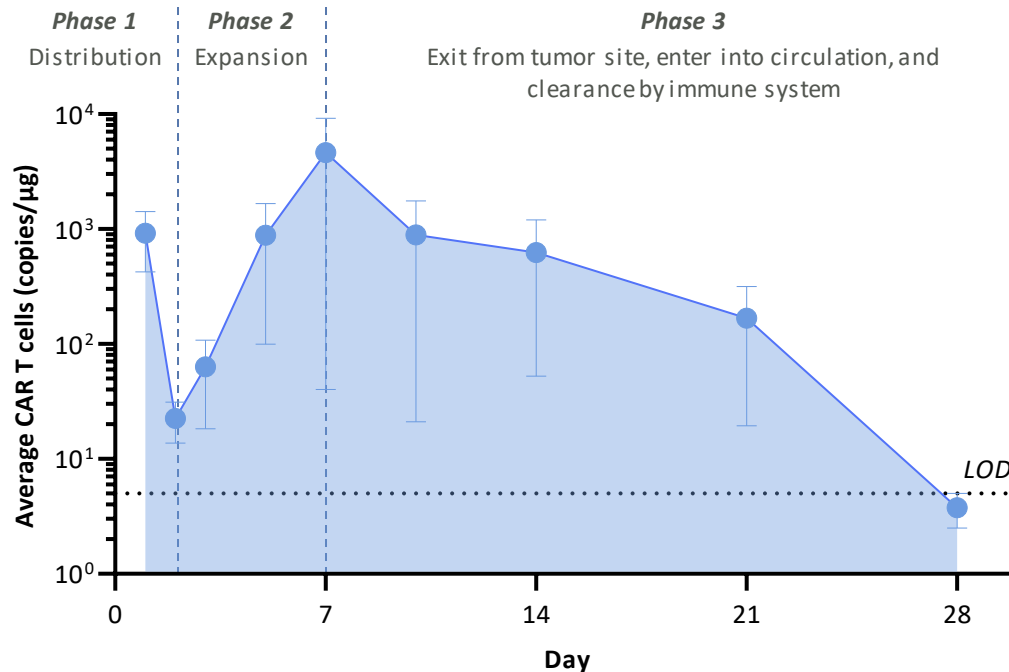
CTX130 in Cutaneous T-Cell Lymphoma



(1) Value extends beyond top of axis (215%); (2) Value extends beyond top of axis (111%)

Allo CAR T Cells Show Classic “Tri-phasic” PK

Mean of CTX130 pharmacokinetics (n=5 DL4 subjects, first infusions only)



Durable remissions do not require long lived CAR T cell persistence, i.e., >28 days

- CAR T cells produce rapid responses: tumor regression in the first week after infusion and radiographic CRs at D28
- Allogeneic CAR T cells do not routinely persist beyond 28 days

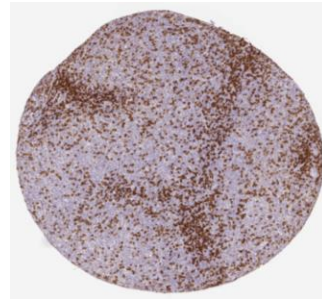
Patient NK Cells Unlikely to Limit Allogeneic CAR T Function at the Tumor Site

Tumor samples stained for NK and T cells show absence of NK cells at the tumor site

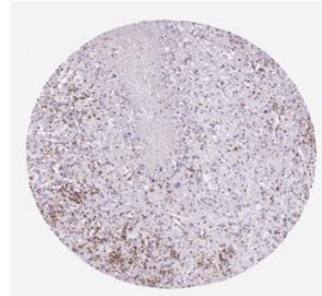
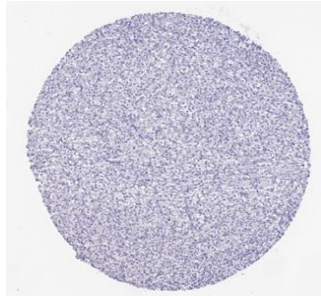
NK cells (CD56)

T cells (CD3E)

Non-Hodgkin lymphoma



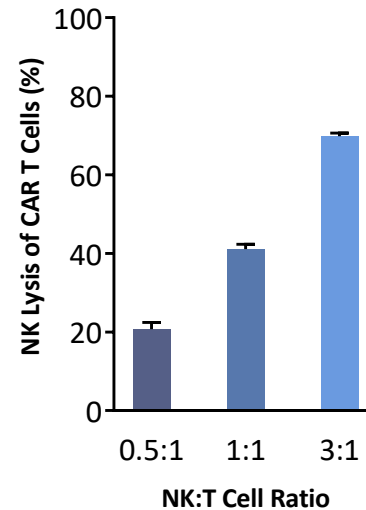
Renal cell carcinoma



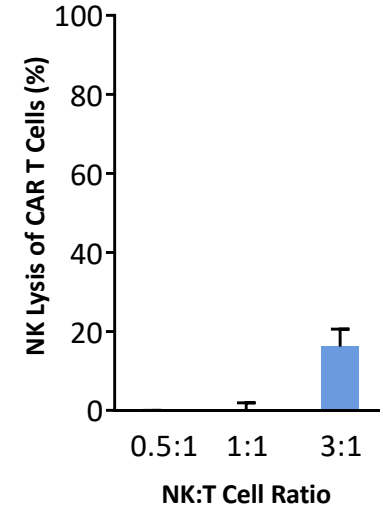
Source:
Protein Atlas

CAR T expansion and activity following target cell engagement far outpaces NK killing capacity *in vitro*

CTX130 + NK cells



CTX130 + NK cells + RCC cells (A498)

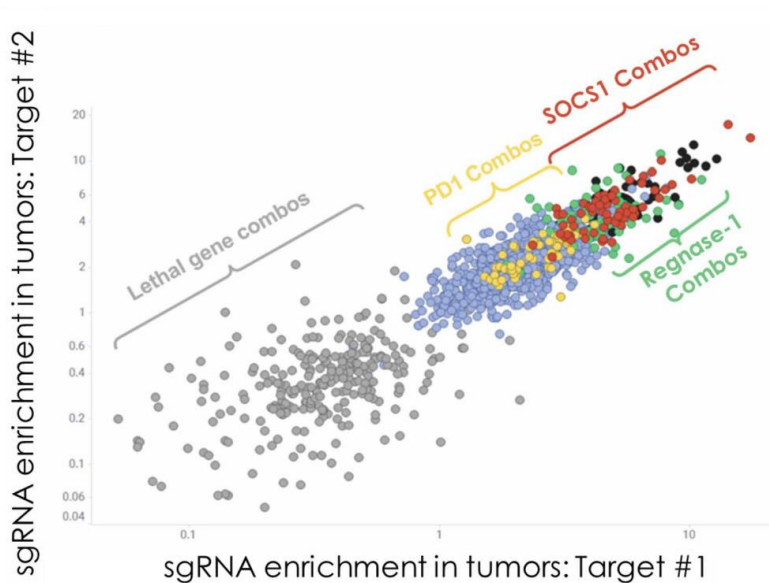


Learnings from CTX110 and CTX130 Support Development of Next-Generation Candidates

- Efficacy and PK data from CTX110 and CTX130 indicate that **durable remissions do not require long-lived CAR T cell persistence**
- NK cells not observed in significant numbers at tumor sites, **suggesting that increased immune evasion will have limited impact on antitumor activity**
- In contrast, internal and external data (e.g., Mai, et al. 2023) suggest that **edits to enhance T cell function have the potential to improve efficacy**
- As a result, our next-generation strategy focuses on **improving CAR T potency**
- Through systematic CRISPR screening, we identified **two synergistic potency edits** that we have incorporated into our next-generation CTX112 and CTX131 programs

CRISPR Screening Revealed the Most Synergistic Potency Edit Combinations

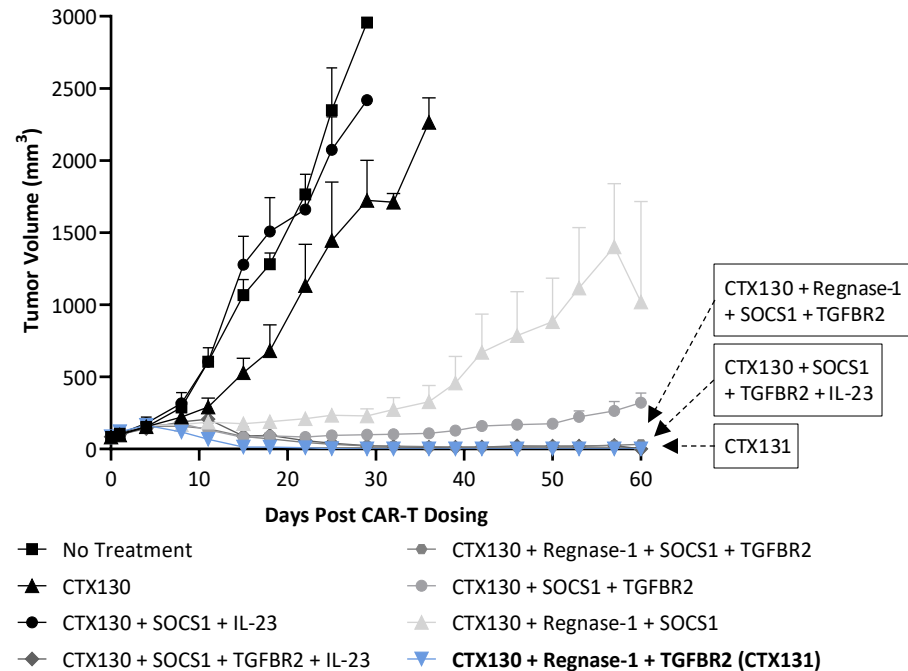
In vivo murine T cell screen identified gene edit combinations that boost potency against solid tumors¹



(1) Wrocklage et. al. KSQ Therapeutics, Presented at Society for Immunotherapy of Cancer, 2021

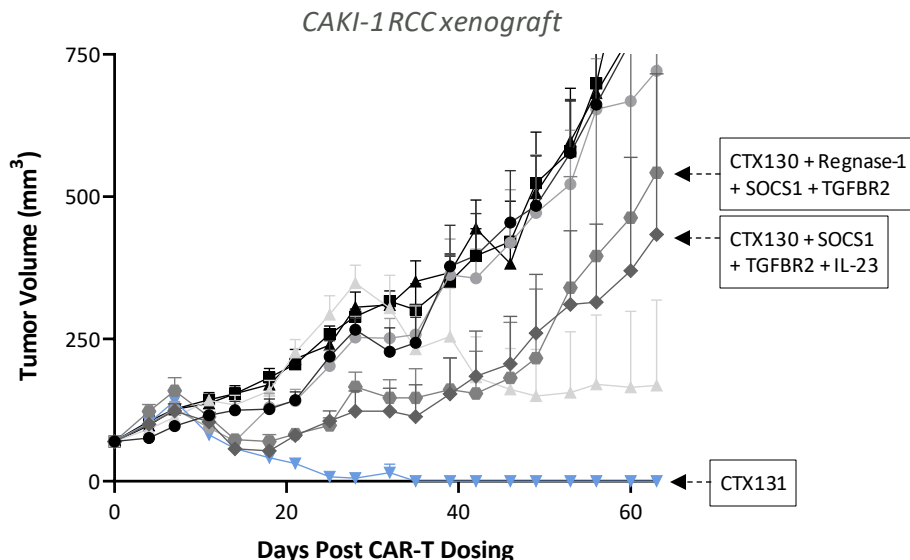
Comprehensive empirical evaluation of >50 edit combinations performed *in vivo*

Example of select combos in H1975 lung cancer xenograft model

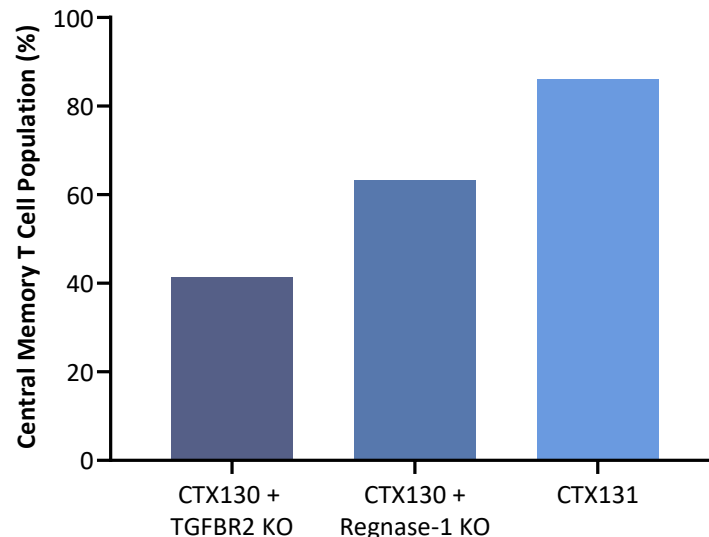


Regnase-1 + TGFBR2 Double KO Consistently Outperformed Other Combinations

Regnase-1 + TGFBR2 KO proved the most potent combo across multiple different tumor models and antigens



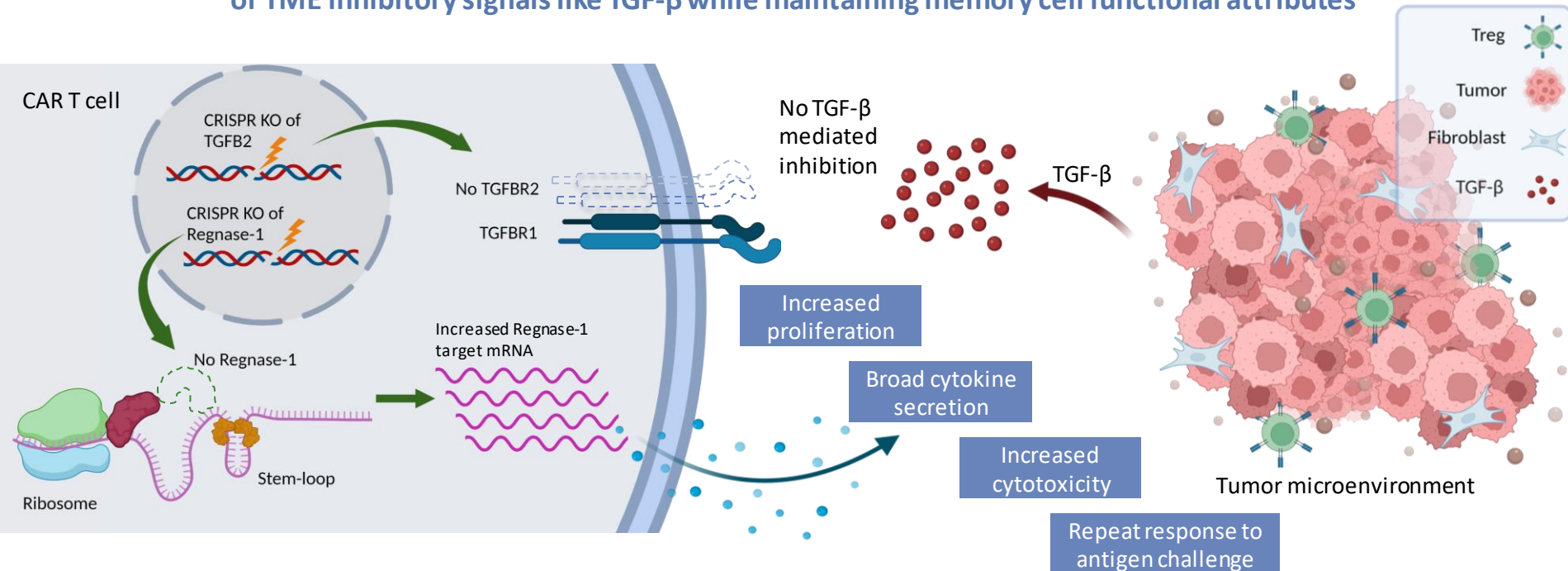
T_{CM} phenotype maintained longer with Regnase-1 + TGFBR2 double KO



Maintenance of memory cell properties allows for greater expansion and anti-tumor activity

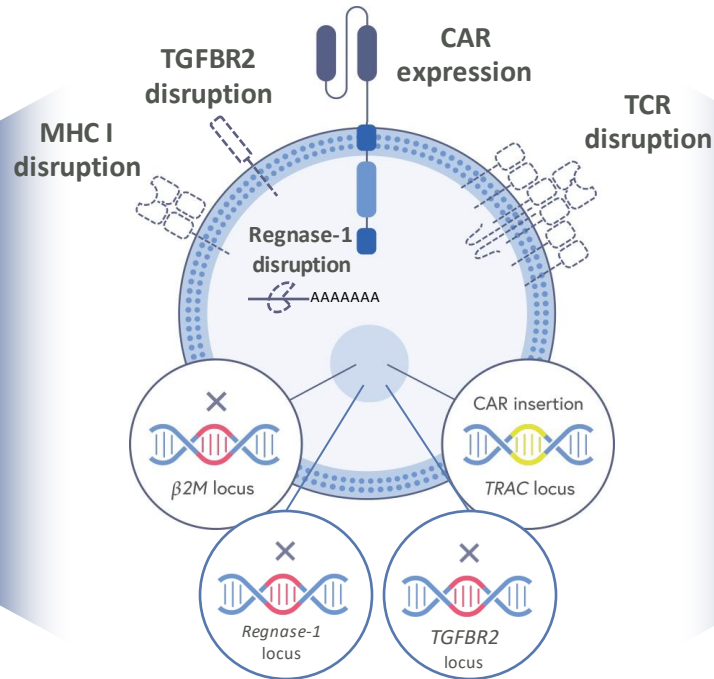
Regnase-1 and TGFB2 KO Address Both Intrinsic and Extrinsic “Brakes” on T Cell Activity

Regnase-1 and TGFB2 KO work synergistically to increase effector function in the presence of TME inhibitory signals like TGF- β while maintaining memory cell functional attributes



Next-Gen Allogeneic CAR-T Candidates Build on Core Chassis

Generation 2.0 allogeneic CAR T chassis:



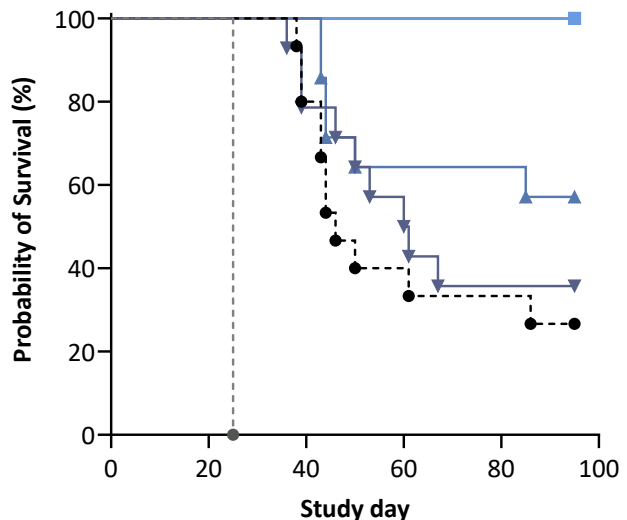
- **Regnase-1:** Removes intrinsic “brake” on T cell function
- **Increases functional persistence, cytokine secretion and sensitivity, effector function on tumors**

- **TGFBR2 KO:** Removes key extrinsic “brake” on T cell anti-tumor activity
- **Reduces TME inhibition of multiple CAR-T cell functions**

CTX112 and CTX131, our next-gen CD19 and CD70 targeting therapies, contain these additional edits (CTX131 also contains a CD70 locus knockout) – details in patent ID US 11,497,773

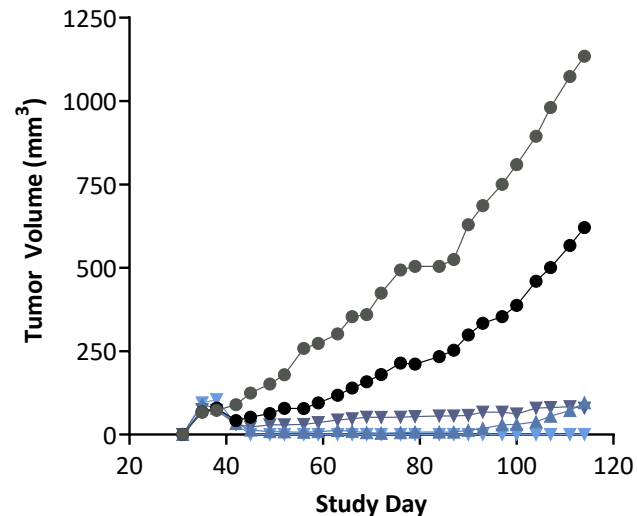
Prolonged Survival and Consistent Tumor Reduction Observed in CD19+ and CD70+ Malignancies *In Vivo*

CTX112 extends survival in Nalm6-Luc mice



● Untreated ● CTX110 ▾ CTX110 + TGFBR2 KO
 ▲ CTX110 + Regnase-1 KO ■ CTX112

CTX131 eliminates tumors in tumor rechallenge with ACHN (RCC)

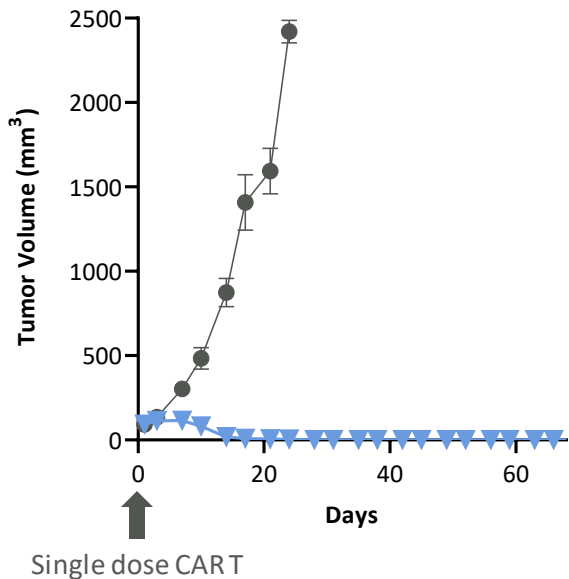


● Untreated ● CTX130 ▾ CTX130 + TGFBR2 KO
 ▲ CTX130 + Regnase-1 KO ▾ CTX131

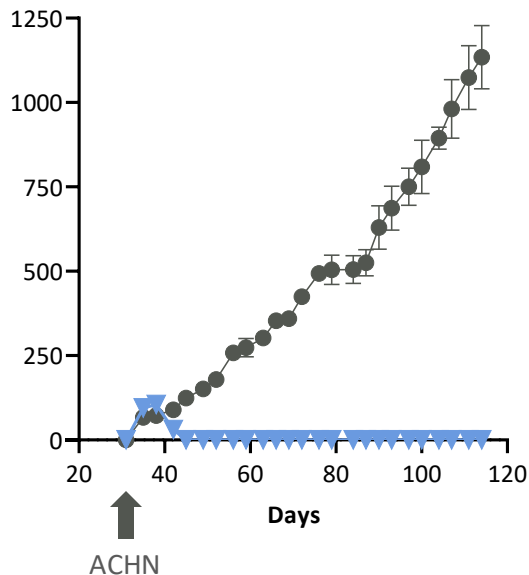
Regnase-1 + TGFBR2 double KO outperforms either KO alone regardless of CAR construct or cancer model

A Single Dose of CTX131 Eliminates 3 Different Tumor Models in Succession Without Loss of Function

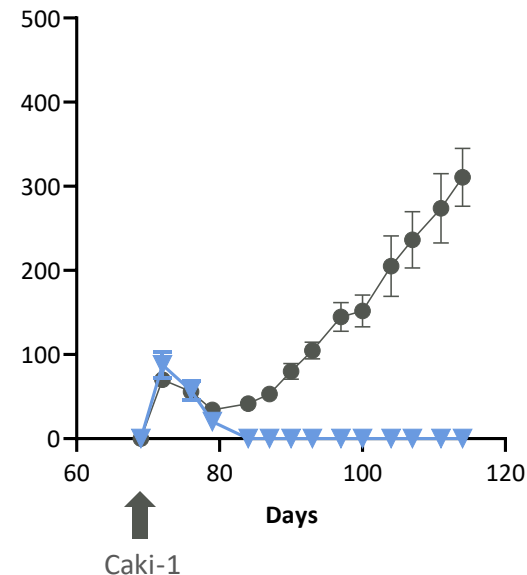
Tumor 1: NCI-H1975 (Lung)



Tumor 2: Rechallenge 1 with ACHN (RCC)

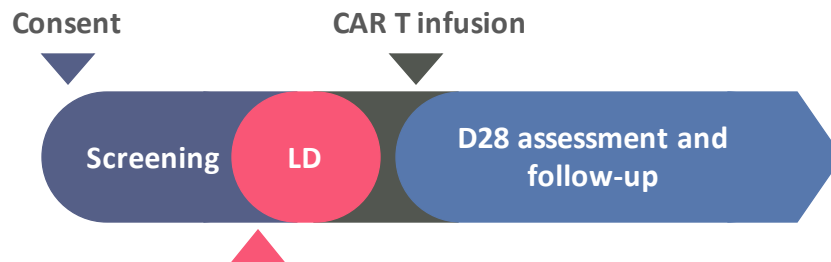


Tumor 3: Rechallenge 2 with Caki-1 (RCC)



● Untreated ▼ CTX131

Trials for CTX112 and CTX131 Follow Similar Protocols as Our CARBON and COBALT Trials



Standard lymphodepletion regimen of
Flu 30mg/m² + Cy 500mg/m² for 3 days

Candidate	NTC	Trial Name
CTX110	NCT04035434	A Safety and Efficacy Study Evaluating CTX110 in Subjects With Relapsed or Refractory B-Cell Malignancies (CARBON)
CTX112	NCT05643742	A Safety and Efficacy Study Evaluating CTX112 in Subjects With Relapsed or Refractory B-Cell Malignancies
CTX130	NCT04502446	A Safety and Efficacy Study Evaluating CTX130 in Subjects With Relapsed or Refractory T or B Cell Malignancies (COBALT-LYM)
CTX131	NCT05795595	A Safety and Efficacy Study Evaluating CTX131 in Adult Subjects With Relapsed or Refractory Solid Tumors

Preclinical Data of Our Next-Gen Allo CAR T Candidates Supports Development for Hard-to-Treat Cancers

- Clinical data with CTX110 and CTX130 demonstrate that **allogeneic CAR T efficacy and durable remissions do not require intense immune suppression or long-lived CAR T persistence**
- Regnase-1 + TGFBR2 double KO **increases cell killing and functional persistence, provides resistance to environmental suppression, and preserves memory functions to enhance anti-tumor activity**
- Furthermore, the robustness and proliferation capacity of CAR T cells bearing these edits **simplifies manufacturing and increases production capacity**
- Addition of these next-generation edits to our core chassis could enable allogeneic CAR T **use in the most challenging patients and toughest indications, including solid tumors**
- We have advanced this next-generation **CAR T chassis into the clinic with CTX112 and CTX131 for CD19+ and CD70+ malignancies, respectively**

Acknowledgments

Thank you to all the patients, families and investigators involved in our clinical trials!