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

Jon Terrett, Ph.D.
CRISPR Therapeutics, Boston, MA

CRISPR THERAPEUTICS®

Disclosure Information

Jon Terrett

I have the following relevant financial relationships to disclose:

Employee of: CRISPR Therapeutics

Stockholder in: CRISPR Therapeutics

Forward-Looking Statements

The presentation and other related materials may contain a number of "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including statements regarding CRISPR Therapeutics' expectations about any or all of the following: (i) its plans and expectations for its preclinical studies, clinical trials and pipeline products and programs; (ii) the safety, efficacy and clinical progress of its various clinical programs; (iii) the status of preclinical studies and clinical trials (including, without limitation, the expected timing of data releases, announcement of additional programs and activities at clinical trial sites, and discussions with regulatory authorities) and expectations regarding the data that is being presented; (iv) the data that will be generated by ongoing and planned preclinical studies and clinical trials and the ability to use that data for the design and initiation of additional preclinical studies and clinical trials; (v) the activities under its collaborations and the expected benefits thereof; (vi) its intellectual property coverage and positions of its, its licensors and third parties as well as the status and potential outcome of proceedings involving any such intellectual property; (vii) the sufficiency of its cash resources; and (viii) the therapeutic value, development, and commercial potential of CRISPR/Cas9 gene editing technologies and therapies, including as compared to other therapies. Without limiting the foregoing, the words "believes," "anticipates," "plans," "expects" and similar expressions are intended to identify forward-looking statements. You are cautioned that forward-looking statements are inherently uncertain. Although CRISPR Therapeutics believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those projected or suggested in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: the potential for initial and preliminary data from any clinical trial and initial data from a limited number of patients not to be indicative of final trial results; the potential that clinical trial results may not be favorable; that one or more of its internal or external product candidate programs will not proceed as planned for technical, scientific or commercial reasons; that future competitive or other market factors may adversely affect the commercial potential for its product candidates; uncertainties inherent in the initiation and completion of preclinical studies and whether results from such studies will be predictive of future results of future studies or clinical trials; it may not realize the potential benefits of its collaborations; potential impacts due to the coronavirus pandemic, such as the timing and progress of clinical trials; uncertainties regarding the intellectual property protection for its technology and intellectual property belonging to third parties, and the outcome of proceedings (such as an interference, an opposition or a similar proceeding) involving all or any portion of such intellectual property; and those risks and uncertainties described under the heading "Risk Factors" in its most recent annual report on Form 10-K, quarterly report on Form 10-Q, and in any other subsequent filings made by it with the U.S. Securities and Exchange Commission, which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date they are made. CRISPR Therapeutics disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this presentation, other than to the extent required by law.

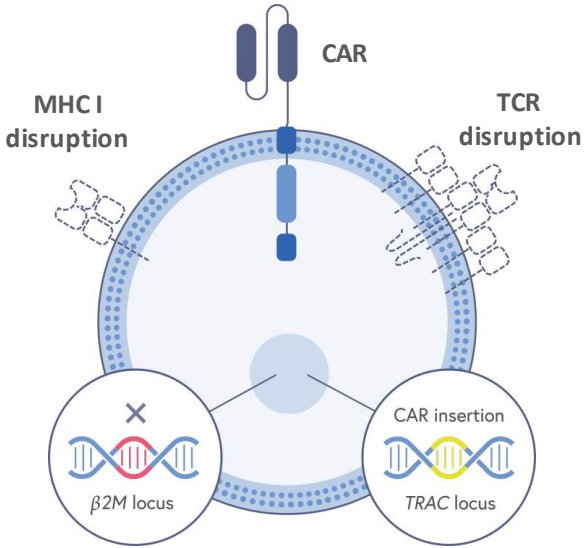
Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no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

Our Allogeneic CAR T Cells Share the Same Core Chassis

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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

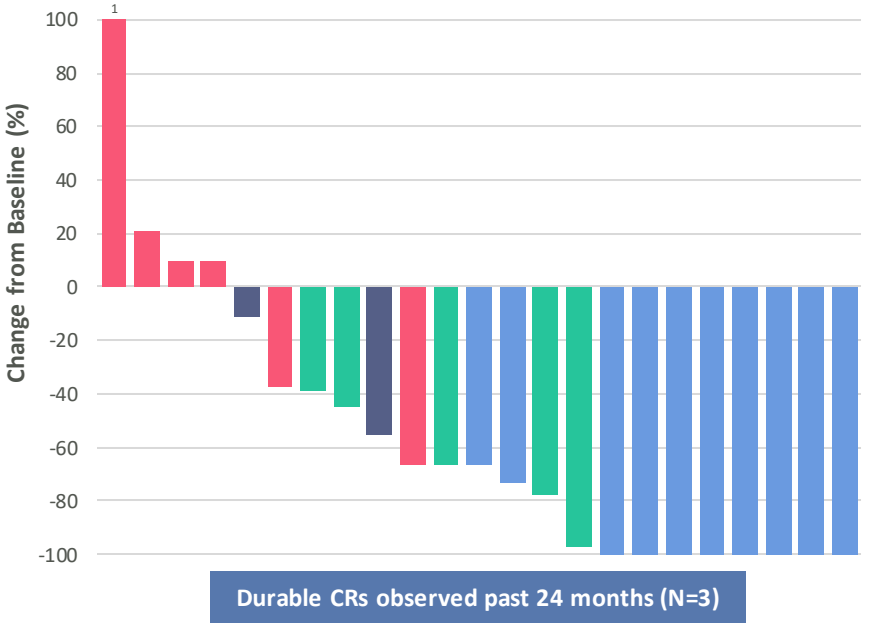


- **Reduce risk of GvHD** via TCR disruption
- **Improve consistency and safety by precise insertion** of CAR construct into *TRAC* locus without using lentivirus or retrovirus

B2M: beta-2-microglobulin; MHC I: major histocompatibility complex class I; GvHD: graft versus host disease; TRAC: T-cell receptor (TCR) alpha chain

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

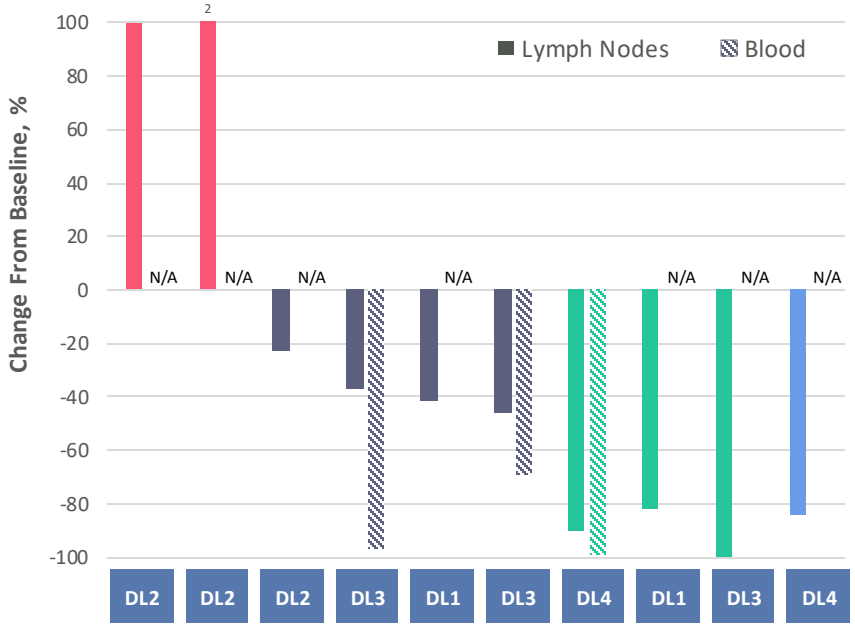
CTX110 (DL2+ with re-dosing) in Non-Hodgkin Lymphoma



N=23

Data as of August 26, 2021

CTX130 in Cutaneous T-Cell Lymphoma



N=11

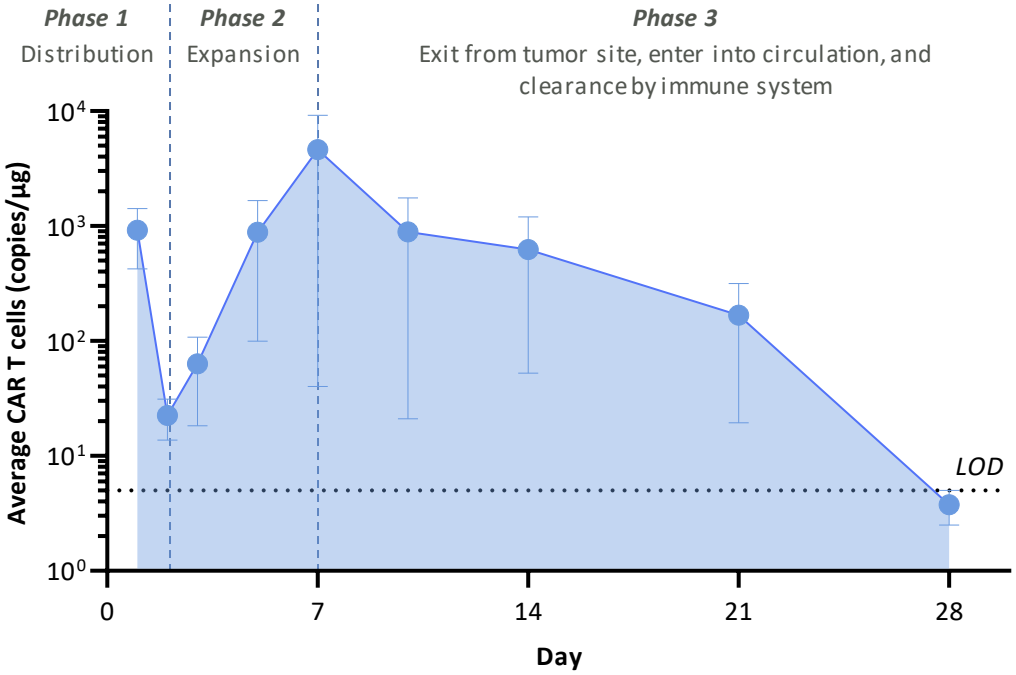
Data as of April 26, 2022

CR PR SD PD

(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)



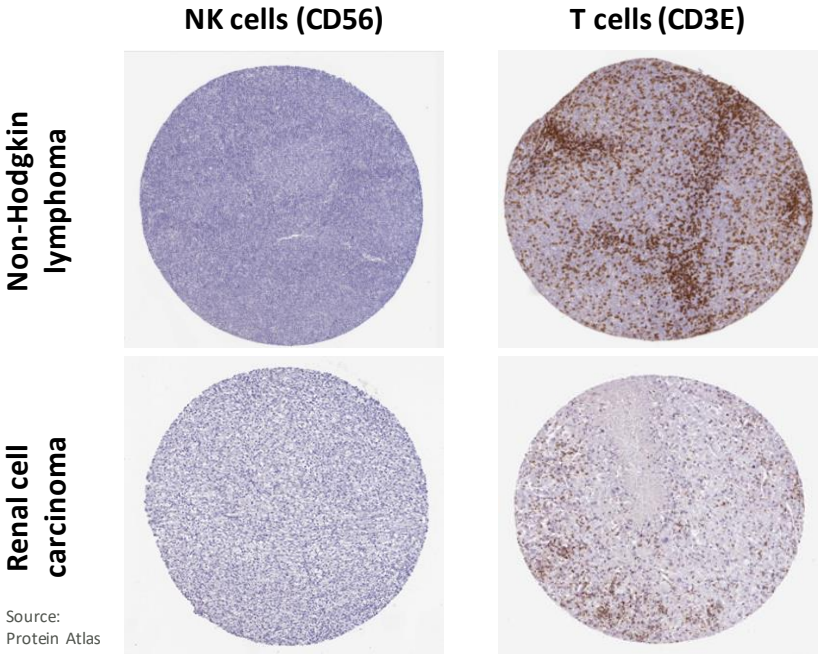
Durable remissions do not require long lived CAR T cell persistence, i.e., >28 days

- 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

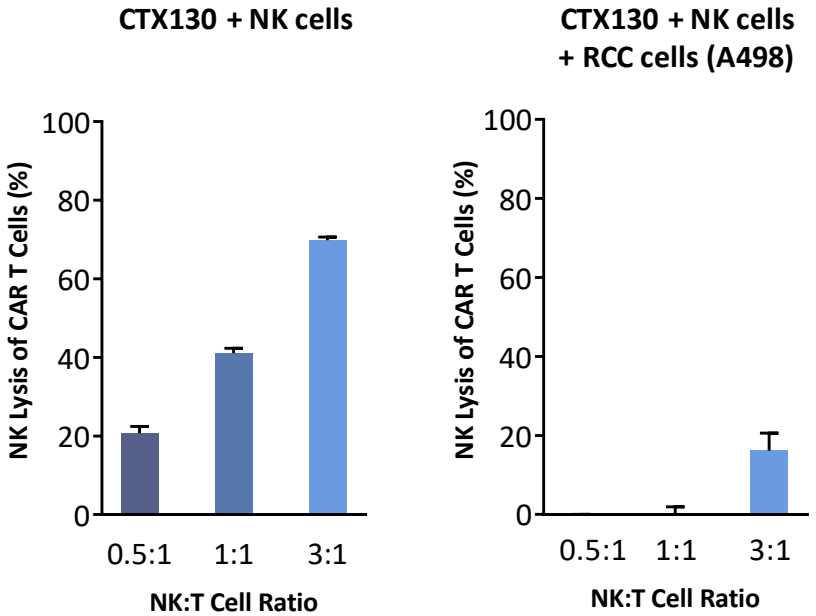
Patient NK Cells Unlikely to Limit Allogeneic CAR T Function at the Tumor Site

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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



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



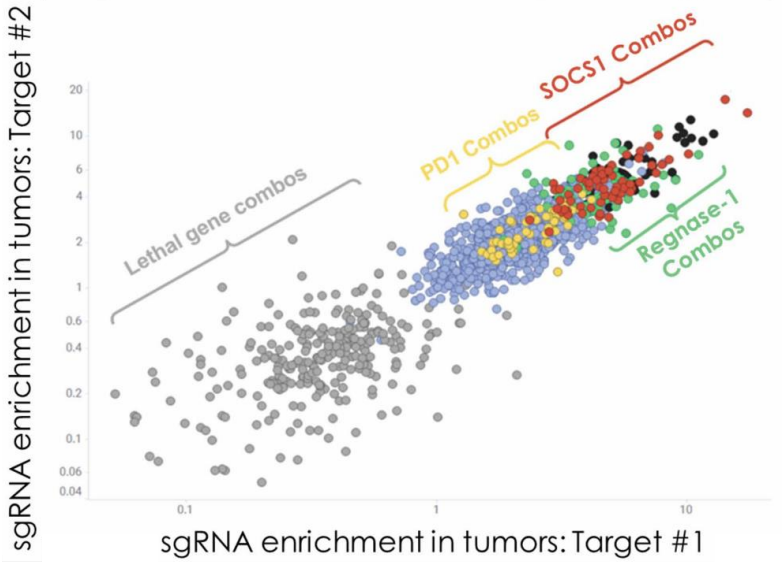
Immune evasion edits beyond B2M KO may not improve antitumor activity

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

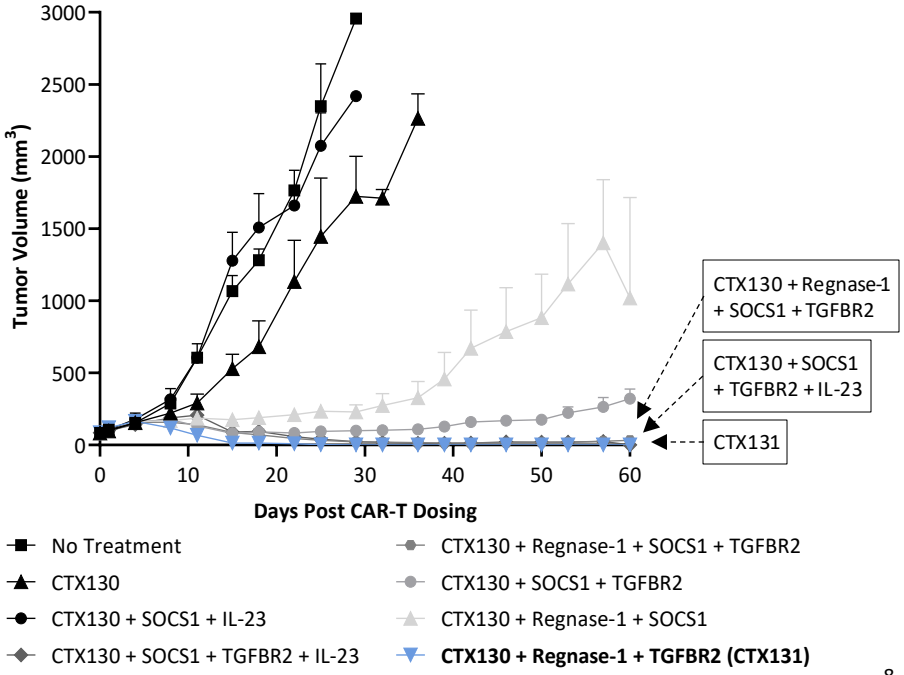
CRISPR Screening Revealed the Most Synergistic Potency Edit Combinations

In vivo murine T cell screen identified gene edit combinations that boost potency against solid tumors[1]



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

Example of select combos in H1975 lung cancer xenograft model

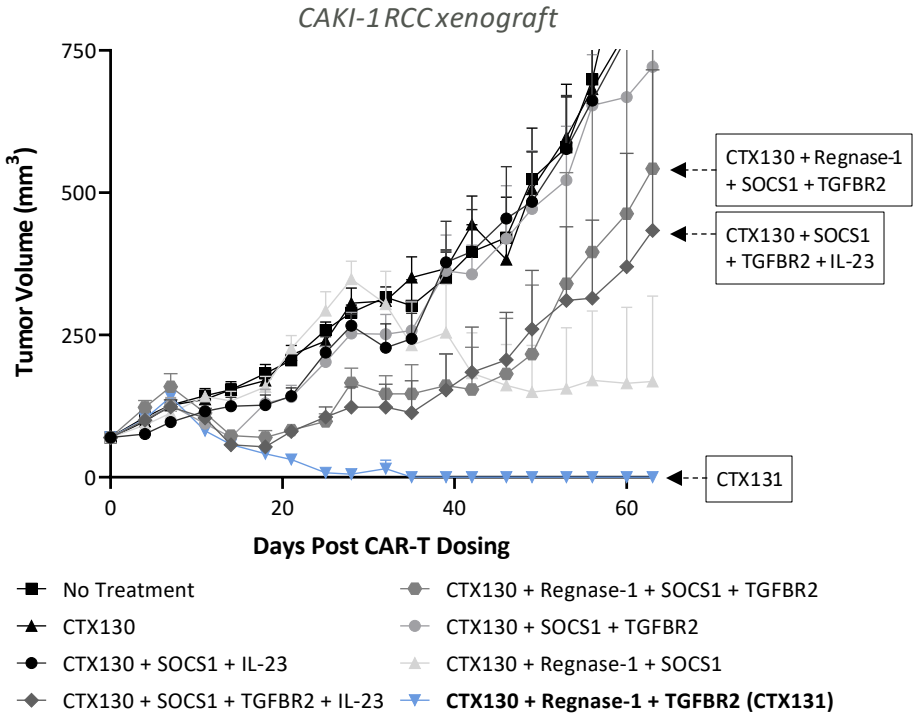


(1) Wrocklage et. al. KSQ Therapeutics, Presented at Society for Immunotherapy of Cancer, 2021

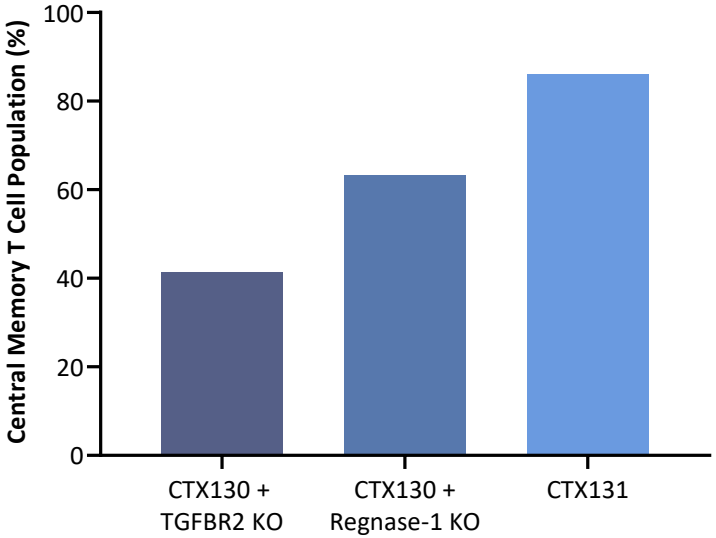
Regnase-1 + TGFBR2 Double KO Consistently Outperformed Other Combinations

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

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 TGFBR2 KO Address Both Intrinsic and Extrinsic "Brakes" on T Cell Activity

Regnase-1 and TFGBR2 KO work synergistically to increase effector function in the presence of TME inhibitory signals like TGF-β while maintaining memory cell functional attributes

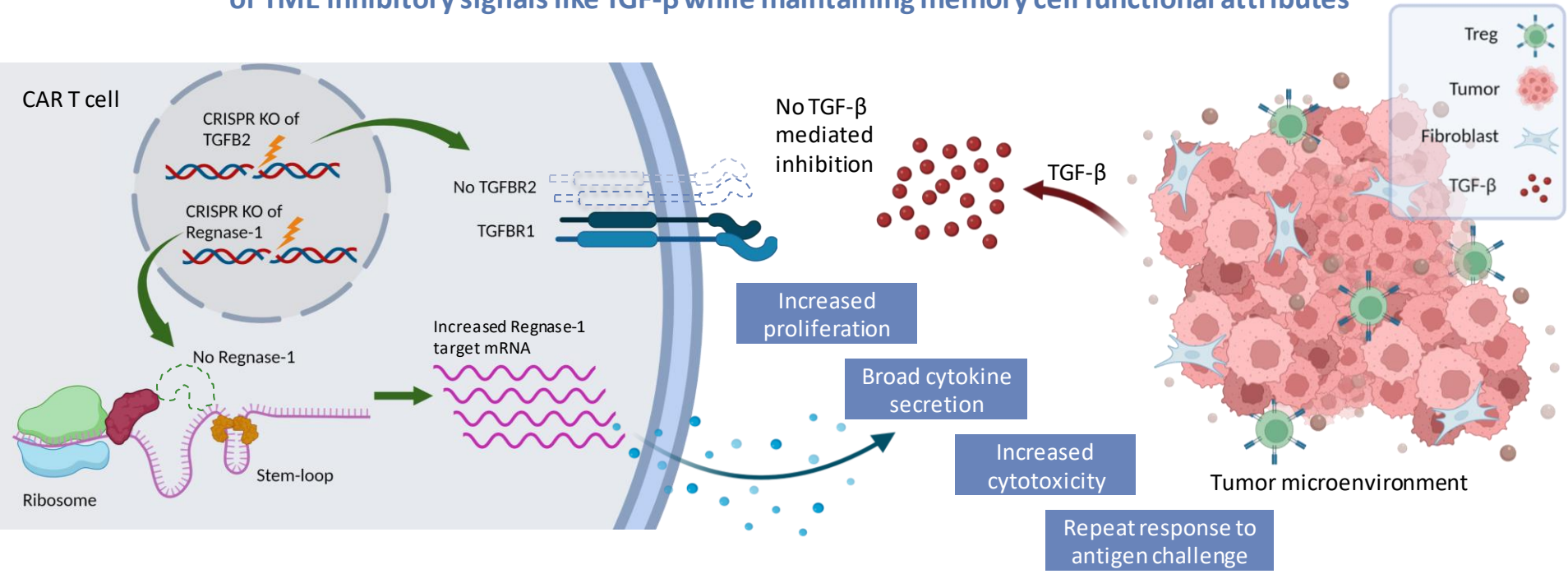
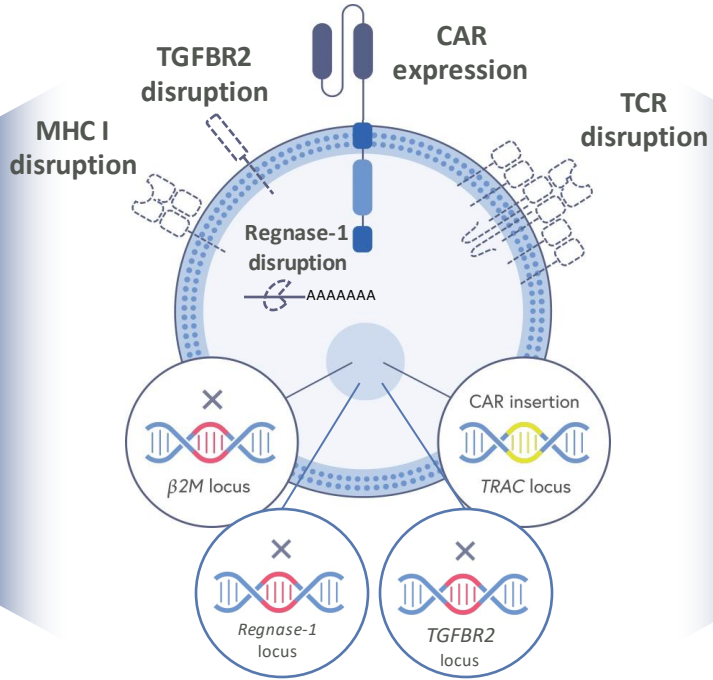


Figure created using BioRender

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**



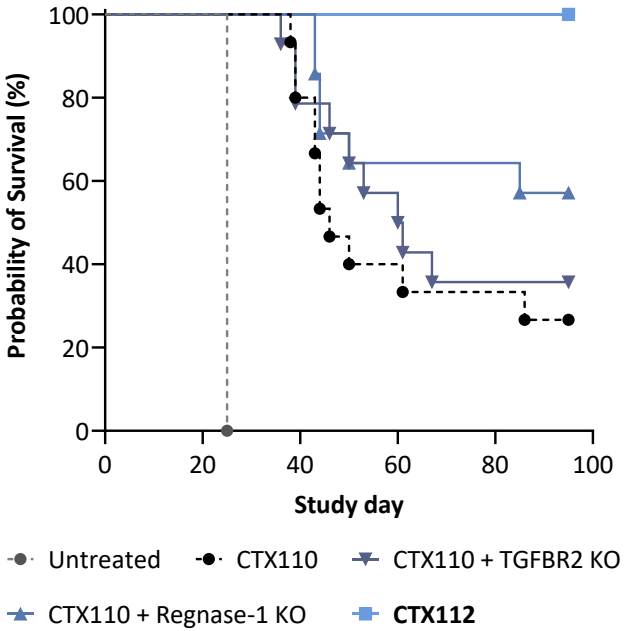
- **TGFBR2 KO:** Removes key extrinsic "brake" on T cell anti-tumor activity
- **Reduces TME inhibition of multiple CAR-T cell functions**

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

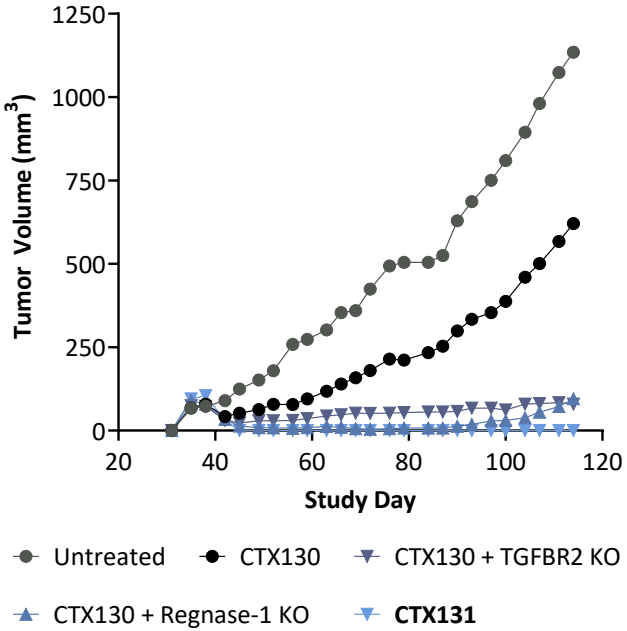
Prolonged Survival and Consistent Tumor Reduction Observed in CD19+ and CD70+ Malignancies *In Vivo*

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

CTX112 extends survival in Nalm6-Luc mice



CTX131 eliminates tumors in tumor rechallenge with ACHN (RCC)

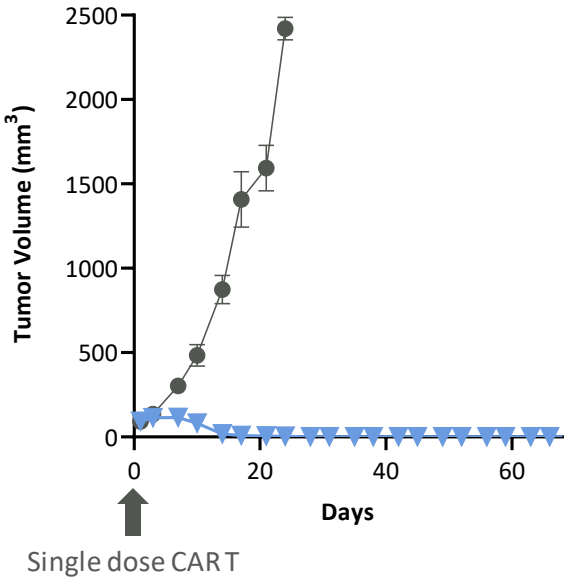


Regnase-1 + TGFBR2 double KO outperforms either KO alone regardless of CAR construct or cancer model

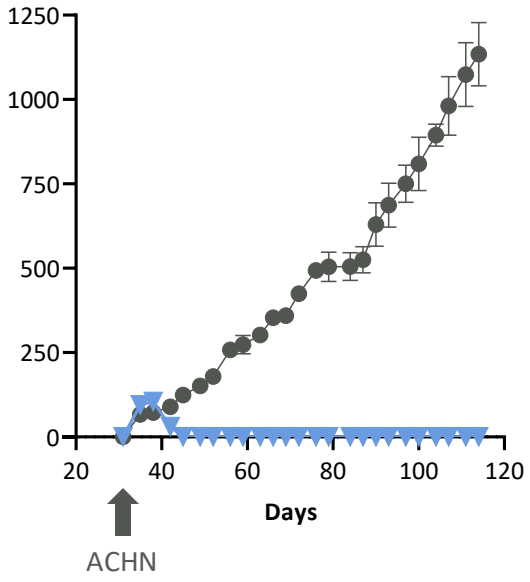
A Single Dose of CTX131 Eliminates 3 Different Tumor Models in Succession Without Loss of Function

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

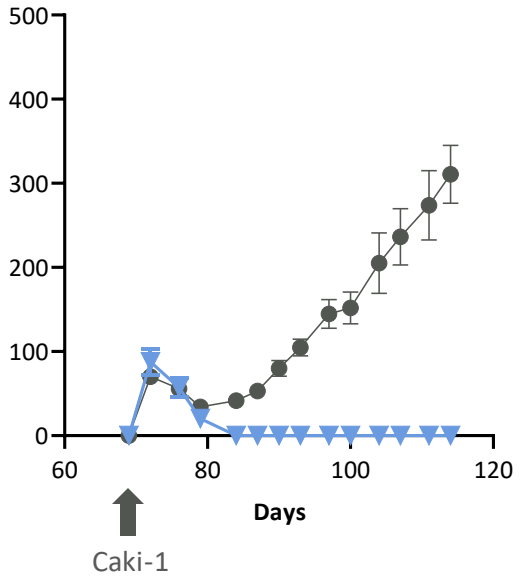
Tumor 1: *NCI-H1975 (Lung)*



Tumor 2: *Rechallenge 1 with ACHN (RCC)*

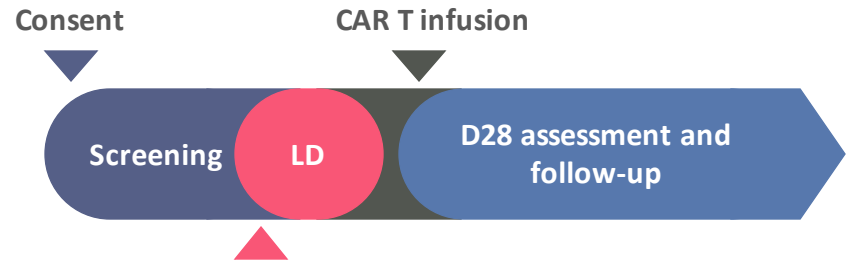


Tumor 3: *Rechallenge 2 with Caki-1 (RCC)*



Untreated CTX131

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



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

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

- 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!