# THE COBALT-LYM STUDY OF CTX130: A PHASE 1 DOSE ESCALATION STUDY OF CD70-TARGETED ALLOGENEIC CRISPR-CAS9–ENGINEERED CAR T CELLS IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) T-CELL MALIGNANCIES

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# Disclosures

- The COBALT™ – LYM study of CTX130™ is sponsored by CRISPR Therapeutics
- Dr. Swaminathan P. Iyer is a Professor, Lead of the T Cell Lymphoma Program, Department of Lymphoma/Myeloma, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center
- Dr. Iyer receives research support from CRISPR Therapeutics, Merck, Seagen, Rhizen, Acrotech, Legend, Innate Pharma, Astra Zeneca, Dren Bio, Yingli, and Secura Bio; participates in scientific advisory boards for Seagen, Yingli, and Secura Bio; and participates in Biocure's and Targeted Oncology's speaker bureaus as a speaker

# Overview

- **PTCL and CTCL are complex diseases with significant unmet need and limited approved systemic therapies.** Few therapies effectively treat all disease compartments (lymph nodes, skin, blood) or achieve meaningful CR rates. For patients with R/R PTCL and transformed CTCL, median OS is 1-2.5 and <5 years, respectively[1-5]
- **CTX130™ is a first-in-class, CD70-targeting allogeneic CAR T therapy that represents the first potential cell therapy for TCL patients.** Allogeneic cellular therapy approaches for TCL have greater potential to meet the unmet need in this patient population given the patients' own T cells are not suitable for autologous manufacturing[6]
- **CD70** is a ligand for CD27 with transient expression on activated lymphocytes and is **highly expressed in many TCLs**[7-10]
- **Preliminary data from dose escalation of CTX130 shows promising efficacy,** including a 70% ORR and a 30% CR rate at DL≥3 (≥3x$10^8$ cells), with an acceptable safety profile

CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; ORR, overall response rate; OS, overall survival; PTCL, peripheral T cell lymphoma; R/R, relapsed/refractory; TCL, T cell lymphoma.

**References:** 1. Fleischer LC, et al. *J Hematol Oncol*. 2019;12:141. 2. Toki H, et al. *Jpn J Clin Oncol*. 1986;16:41-48.3. Lansigan F, et al. *Acta Hematol.* 2020;143:40-50. 4. Scarisbrick JJ, et al. *J Clin Oncol*. 2015;33:3766-3733. 5. Lansigan F, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20:744-748. 6. Alcantara M, et al. Leukemia. 2018; 32, 2307–2315. 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. Marques-Piubelli M, et al. *Histopathology*. 2022 Apr 26. doi: 10.1111/his.14670. Online ahead of print.

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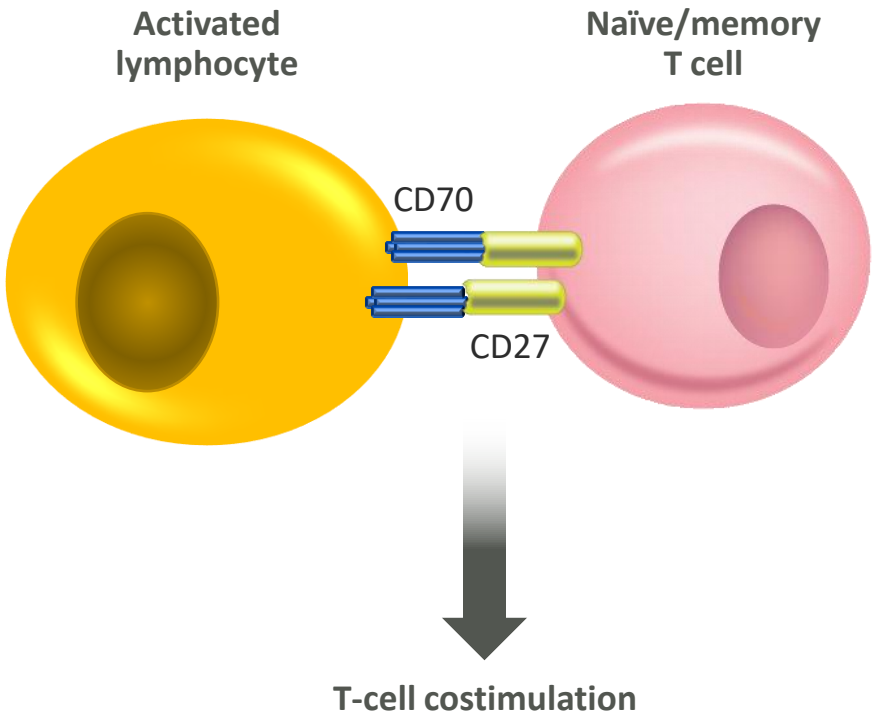
# Role of CD70 in Immune Response and Cancer

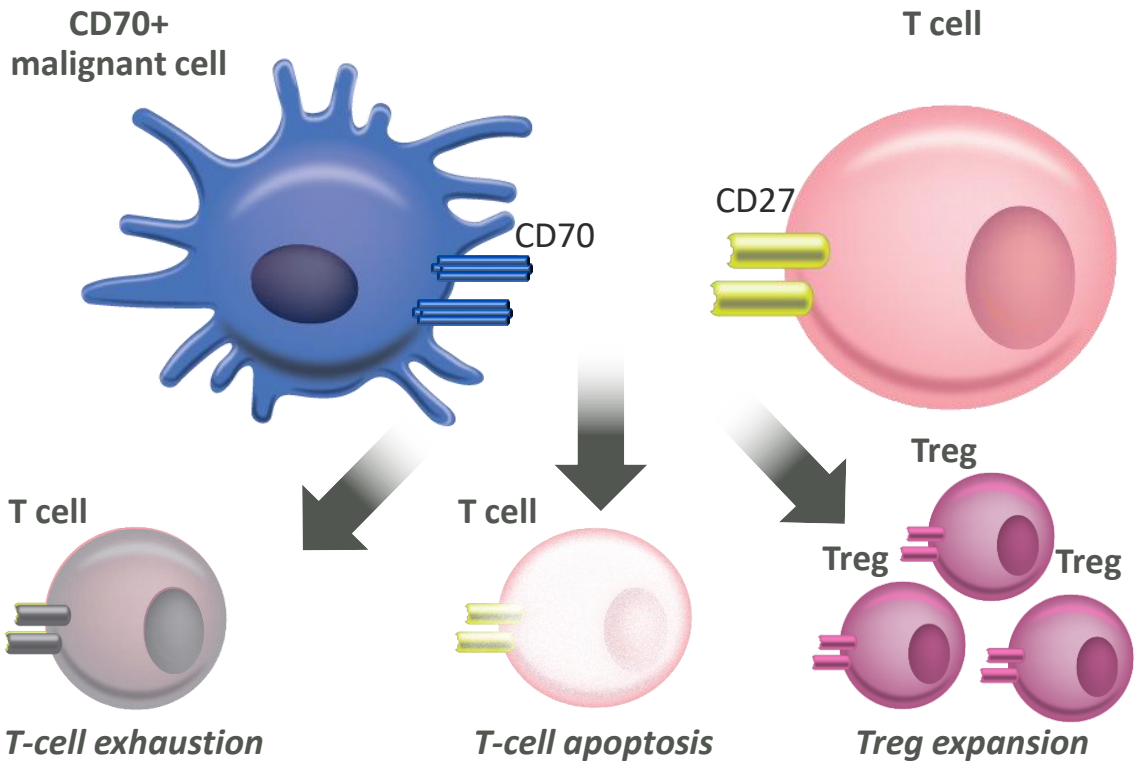
## Physiological role of CD70[1]

- Transient CD70 expression on activated lymphocytes
- Controls naïve and memory T-cell activation via interaction with CD27




## Role of CD70 in cancer[1]

- Increased CD70 expression has been **detected in certain cancers, including 85% of TCL samples** with a median surface expression of 40%[2]
- Possible immunosuppressive role due to T-cell exhaustion, apoptosis, or Treg expansion




TCL, T cell lymphoma; Treg, regulatory T cell.

**References:** 1. Wajant H. *Expert Opin Ther Targets*. 2016;20:959-973. 2. Marques-Piubelli M, et al. *Histopathology*. 2022 Apr 26. doi: 10.1111/his.14670. Online ahead of print.

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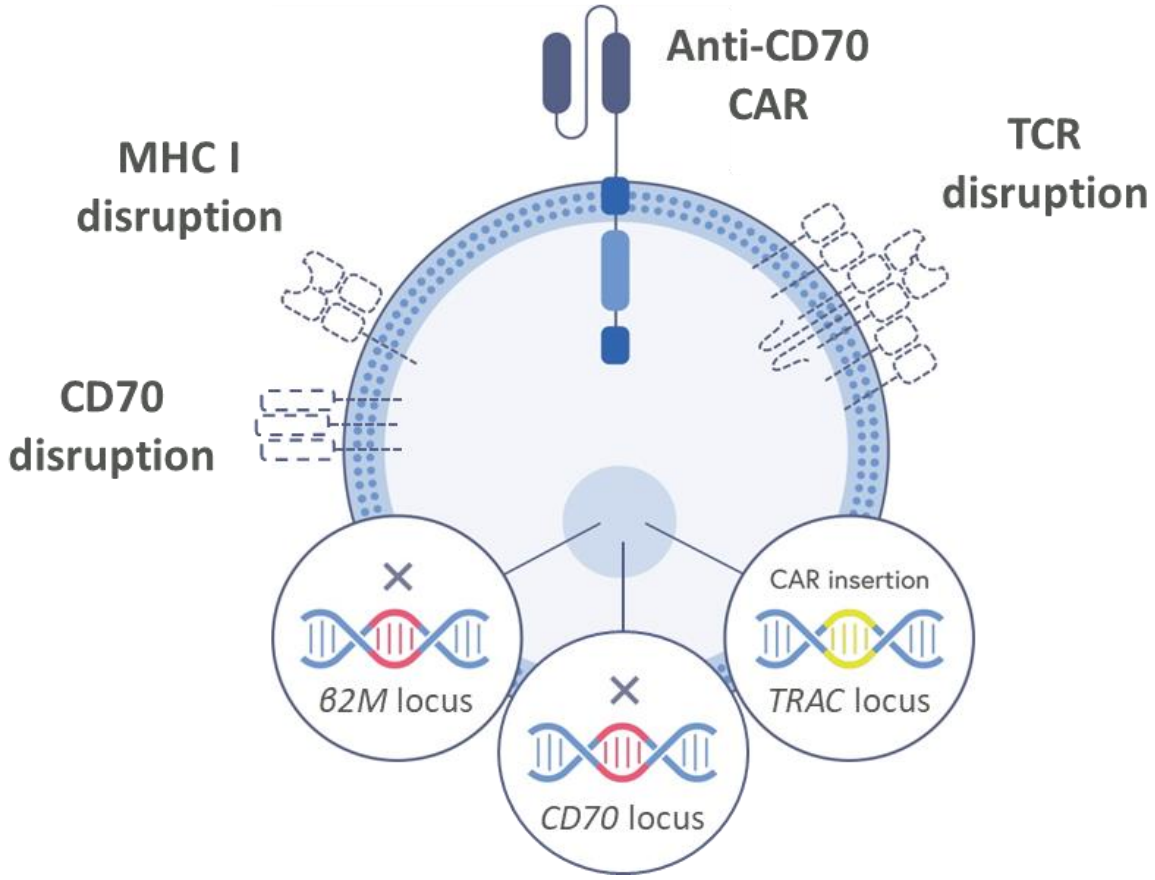
# CTX130

- **Autologous approaches continue to be challenging** due to the poor function of donor T cells, potential for fratricide, and risk of infusing transduced malignant CAR T cells into patients
- **CTX130 is an investigational allogeneic, CRISPR/Cas9 gene-edited, anti-CD70 CAR T cell therapy** with TRAC, β2M, and CD70 disruptions
  - An **anti-CD70 CAR cassette is site-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




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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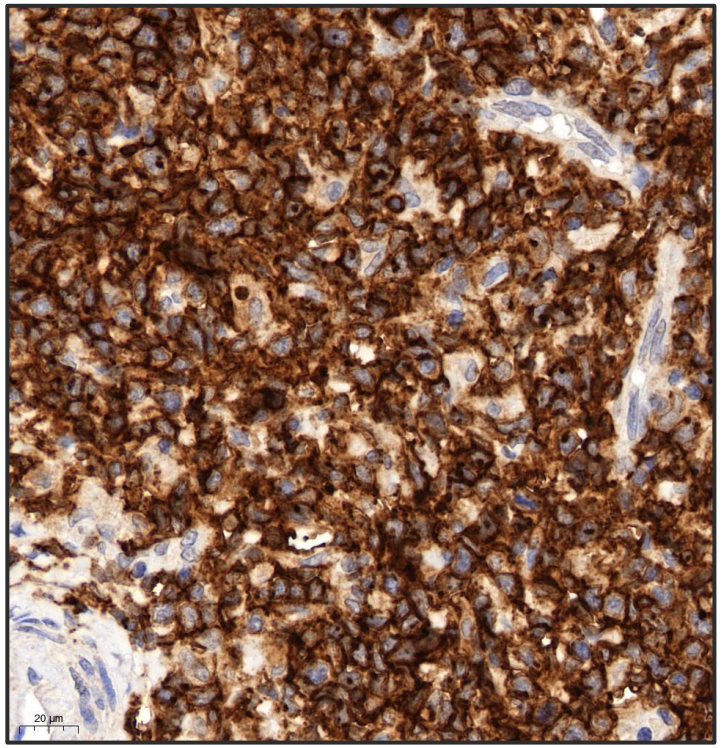
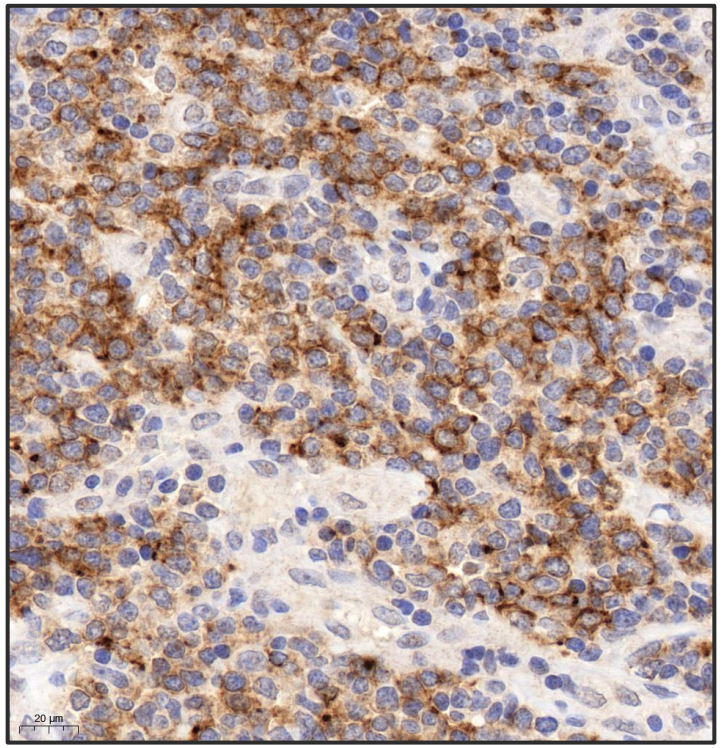
# CTX130 – Preclinical Data

## CD70 surface expression on clinical samples of TCL as measured by immunohistochemistry

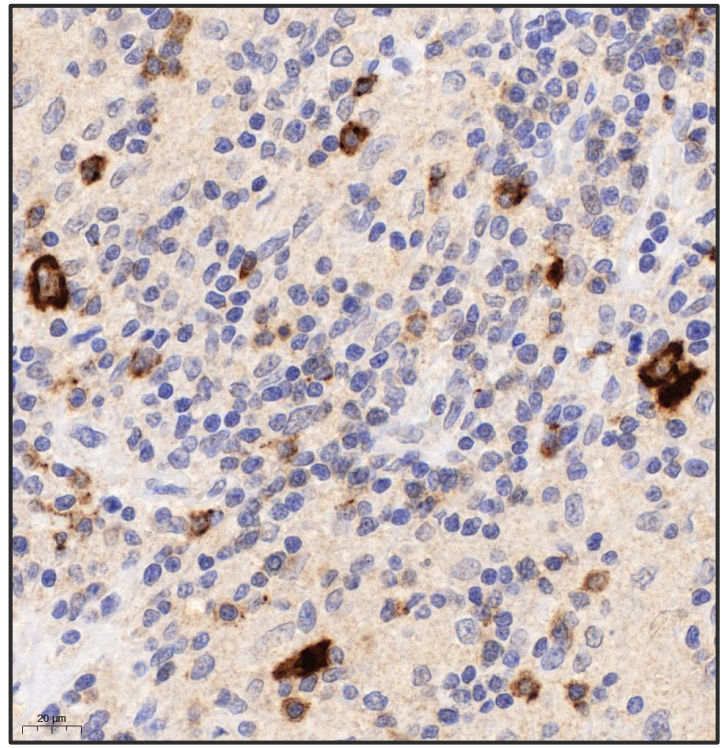
**High**




**Moderate**




**Low**




**Reference:** Karnik S, et al.. Poster presented at American Association for Cancer Research 2020.

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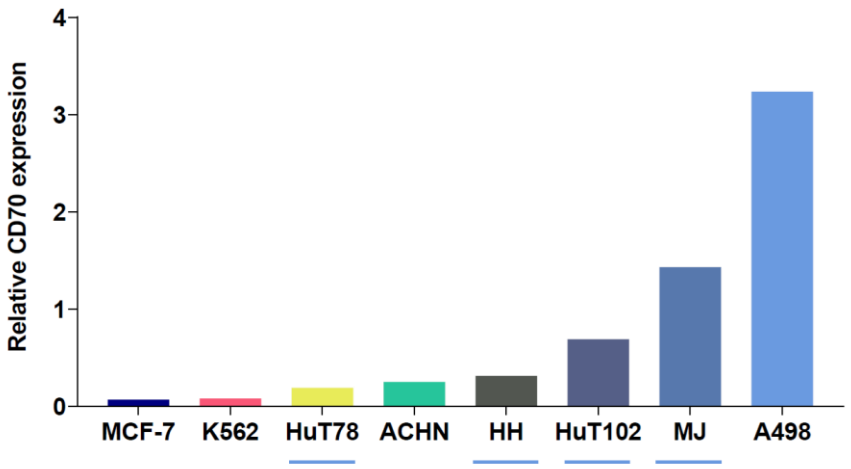
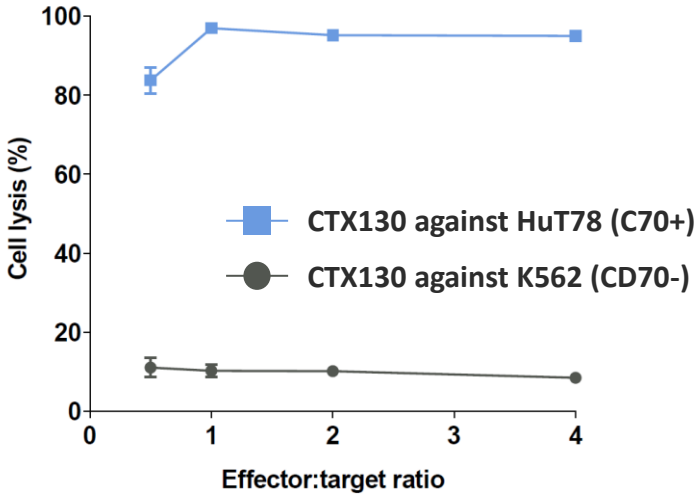
# CTX130 – Preclinical Data

## CD70 expression by flow cytometry in TCL and RCC cancer cell lines



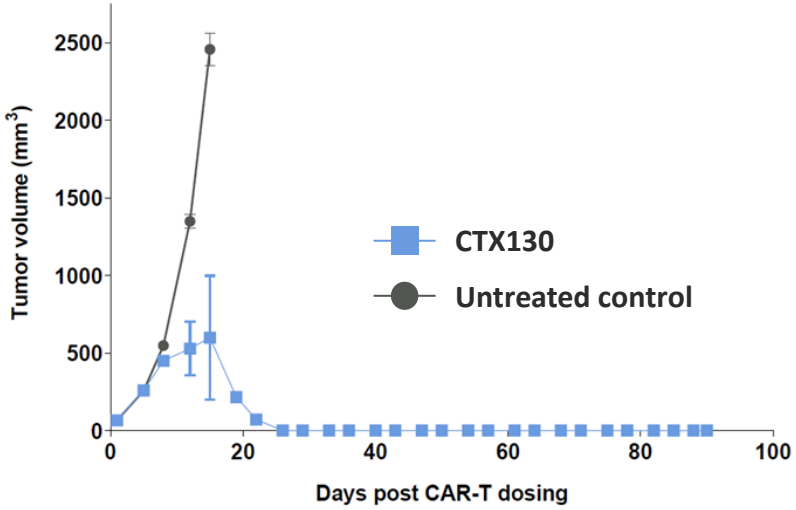

Consistent with the IHC data, TCL cell lines HuT78, HH, HuT102 and MJ (blue lines) show a range of CD70 expression from low/medium to high. RCC cell lines A498 and ACHN show high and low expression, respectively. MCF-7 and K562 are CD70-negative cell lines shown as negative controls

## *In vitro* cytotoxicity against CD70+ but not CD70- cell lines




CTX130 was co-cultured with HuT78 or K562 cells for 24 hours at a range of T-cell:tumor cell ratios. CTX130 showed high cytotoxicity against CD70-expressing cells, even the low expressing HuT78 cell line, but not against CD70-negative cells (K562)

## *In vivo* efficacy against an established HuT78 xenograft tumor model of Sézary Syndrome




3x10$^6$ HuT78 cells were injected subcutaneously into the right flank of NSG mice. When mean tumor size reached an average size of ~66 mm$^3$, mice were either left untreated or injected intravenously with 8.6x10$^6$ CTX130 cells per mouse (N=5 per group)

IHC, immunohistochemistry; RCC, renal cell carcinoma; TCL, T-cell lymphoma

**Reference:** Karnik S, et al.. Poster presented at American Association for Cancer Research 2020.

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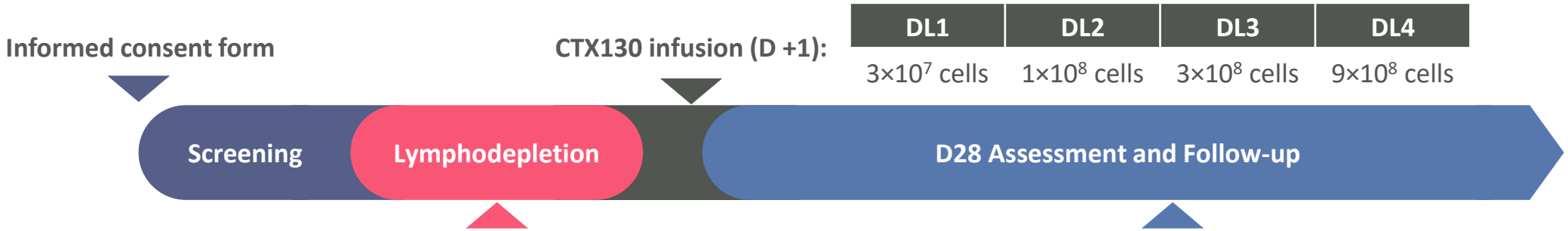
# COBALT-LYM (NCT04502446) Clinical Trial Design

***Phase 1, open-label, multicenter, international, single-arm study (NCT04502446) evaluating the safety and efficacy of CTX130, an investigational, allogeneic CAR-T cell targeting CD70***




*2nd course of CTX130 can be administered with LD after*:

1. Loss of CR within the first 2 years after initial infusion
2. PR, SD, or PD with clinical benefit as determined by the investigator

**Key inclusion criteria**

- Age ≥18 years
- Confirmed diagnosis of a **CD70+ (≥10% of cells)** T-cell malignancy
- ECOG performance status of 0−1
- Adequate renal, liver, cardiac, and pulmonary organ function
- **Platelets >25,000/mm³** and **absolute neutrophil count >500/mm³**

**Key exclusion criteria**

- Prior allogeneic SCT
- Prior treatment with any anti-CD70 agents
- History of certain CNS, cardiac, or pulmonary conditions

**Primary endpoint**

- Part A (Dose Escalation): Incidence of adverse events
- Part B (Cohort Expansion): Objective response rate*

**Secondary endpoints**

- Progression-free survival
- Overall survival

*As assessed by Lugano response criteria for PTCL, International Society for Cutaneous Lymphoma Response Criteria for CTCL.
CNS, central nervous system; CR, complete response; CTCL, cutaneous T cell lymphoma; D: day; LD, lymphodepletion; PD, progressive disease; PR, partial response; PTCL, peripheral, T cell lymphoma; SCT, stem cell transplant; SD, stable disease.

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# Patient Demographics and Pharmacokinetics

*Data cutoff date: 26 April 2022*

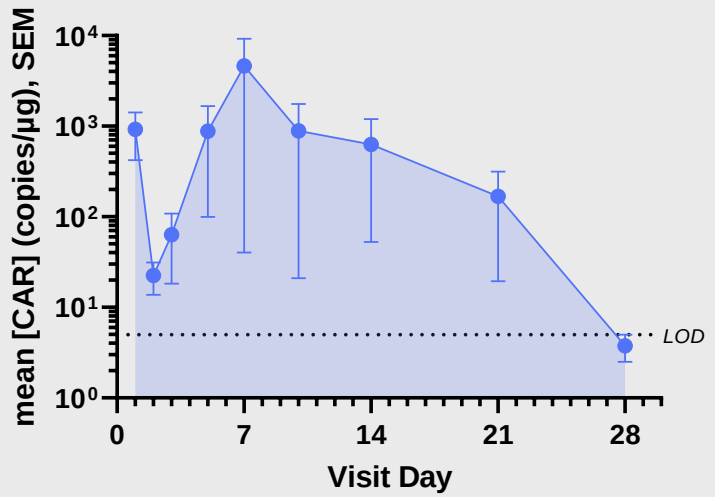
## Patient characteristics, *All Dose Levels n = 18*

| | |
|---|---|
| **Age**, median years (range) | 65 (39 – 78) |
| **ECOG PS at screening,** n (%) | |
| 0 | 8 (44) |
| 1 | 10 (56) |
| **Prior lines of therapy,** median n (range) | 4 (1 – 8) |
| **TCL subtype,** n (%) | |
| *PTCL* | 8 (44) |
| AITL | 3 (17) |
| ALCL | 1 (6) |
| ATLL | 3 (17) |
| PTCL - NOS | 1 (6) |
| CTCL (MF, SS, tMF) | 10 (56) |
| **Skin involvement,** n (%) | 12 (67) |
| **Blood involvement,** n (%) | 6 (33) |
| **Bone marrow involvement,** n (%) | 4 (22) |
| **CD70 expression level,** median % (range) | 90 (20 – 100) |
| **Second CTX130 infusion received,** n (%) | 5 (28) |

## Pharmacokinetics, *All Dose Levels n = 18*

| | |
|---|---|
| **Peak expansion concentration ($C_{max}$)*†,** geometric mean copies/µg (range) | 80.9 (<4.9 – 61,349.8) |
| **Time to peak expansion ($T_{max}$)†,** median days (range) | 8.5 (5 – 14) |

**Peak expansion concentration ($C_{max}$)*† at DL4,** n=5[1]




* For summary statistics of $C_{max}$, values below the limit of detection (LOD) were imputed as half the LOD and values below the limit of quantification (LOQ) were imputed as (LOQ+LOD)/2. † From Screening to D28 post infusion.
[1] Includes first infusions only

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# Safety

*Data cutoff date: 26 April 2022*

## Adverse Events of Interest, N (%)

| | DL1 $3x10^7$ N=4 | | DL2 $1x10^8$ N=4 | | DL3 $3x10^8$ N=5 | | DL4 $9x10^8$ N=5 | | DL≥3 N=10 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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** | 1 (25) | - | 1 (25) | - | 4 (80) | - | 4 (80) | - | **8 (80)** | **-** |
| **ICANS** | - | - | - | - | 3 (60) | - | - | - | **3 (30)** | **-** |
| **GvHD** | - | - | - | - | - | - | - | - | **-** | **-** |
| **Infections** | 2 (50) | 1 (25) | - | 1 (25) | 2 (40) | 1 (20) | 1 (20) | 1 (20) | **3 (30)** | **2 (20)** |

- Acceptable safety profile across all DLs: no DLTs or instances of TLS with LDC or CTX130
- Treatment-emergent (TE) SAEs occurred in 10/18 (56%) patients and included Gr ≥3 infections (n=4, 22%), Gr 1-2 tumor hemorrhage, Gr ≥3 syncope, Gr ≥3 presyncope, Gr ≥3 HLH, Gr ≥3 drug eruption, and Gr 1-2 ligament sprain (n=1 each, 6%). With exception of one Gr 3 infection, all other TE SAEs were not found to be related to CTX130.
- There was a sudden death in 1 patient with William's syndrome in the context of a lung infection, deemed unrelated to CTX130
- Three cancers were diagnosed in patients with CTCL post treatment: 1 patient had EBV-associated lymphoma which resolved and a squamous cell carcinoma, 1 patient had invasive ductal breast carcinoma which was resected and cured. These were deemed unrelated to CTX130

All events listed in table are treatment-emergent adverse events.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; EBV, Epstein-Barr virus; Gr, grade; GvHD, graft versus host disease; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell associated neurotoxicity syndrome; LDC, lymphodepleting chemotherapy; SAE, serious adverse events; TLS, tumor lysis syndrome.

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# Efficacy

*Data cutoff date: 26 April 2022*

**Best overall response,** n (%)

| Cell dose (CAR+ T cells) | DL1 $3x10^7$ N=4 | DL2 $1x10^8$ N=4 | DL3 $3x10^8$ N=5 | DL4 $9x10^8$ N=5 | DL≥3 N=10 |
|---|---|---|---|---|---|
| **Overall Response Rate (ORR)** | 2 (50) | 0 | 3 (60) | 4 (80) | **7 (70)** |
| **CR** | 1 (25) | 0 | 2 (40)* | 1 (20) | **3 (30)** |
| **PR** | 1 (25) | 0 | 1 (20) | 3 (60) | **4 (40)** |
| **Disease Control Rate (DCR = CR + PR + SD)** | 3 (75) | 1 (25) | 5 (100) | 4 (80) | **9 (90)** |

| | PTCL | | CTCL | |
|---|---|---|---|---|
| | DL≥3 N=5 | Total N=8 | DL≥3 N=5 | Total N=10 |
| **ORR** | 4 (80) | 5 (63) | 3 (60) | 4 (40) |
| **CR** | 2 (40) | 3 (38) | 1 (20) | 1 (10) |
| **PR** | 2 (40) | 2 (25) | 2 (40) | 3 (30) |
| **DCR** | 4 (80) | 5 (63) | 5 (100) | 8 (80) |

*1 patient in DL3 who initially achieved a PR was re-infused at DL4 following a change to SD and achieved a CR at DL4.
CAR, chimeric antigen receptor; CR, complete response; CTCL, cutaneous T cell lymphoma; DCR, disease control rate; DL, dose level; ORR, overall response rate; PR, partial response; PTCL, peripheral T cell lymphoma; SD, stable disease.

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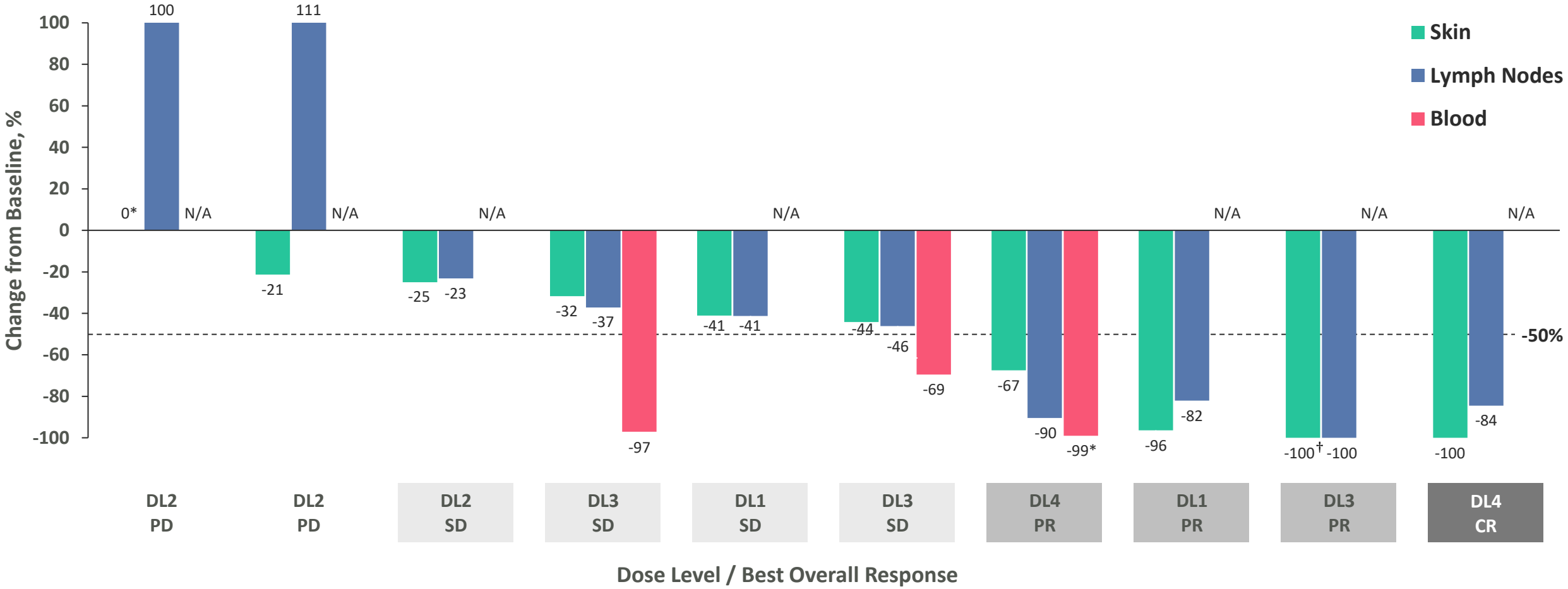
# CTCL Responses Observed Across All Compartments




*Day 7 assessment; †Initially unconfirmed CR, later confirmed to be PR by mSWAT and biopsy.
CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PR, partial response; SD, stable disease.

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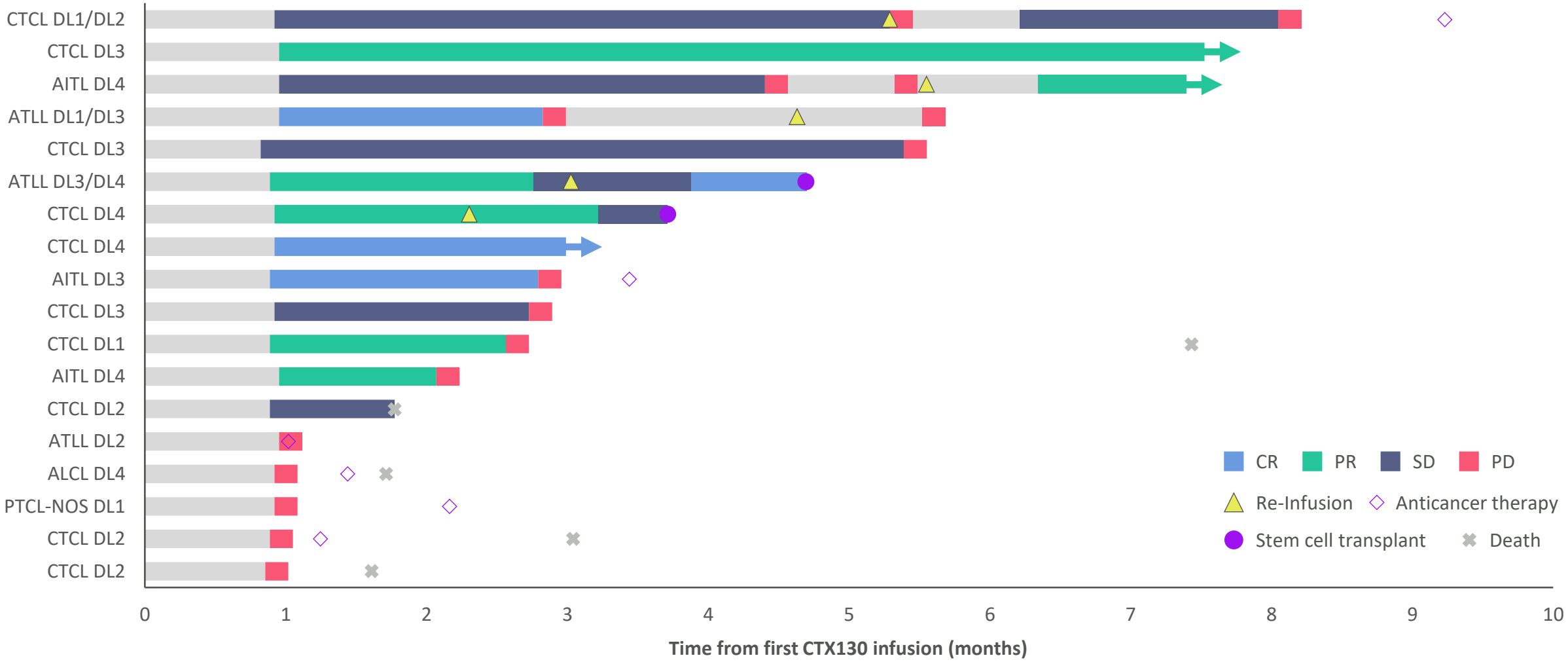
# Efficacy (continued)




AITL, angioimmunoblastic T cell lymphoma; ALCL, anaplastic large cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; CR, complete response; CTCL, cutaneous T cell lymphoma; DL, dose level; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T cell lymphoma not otherwise specified; SD, stable disease

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*Case Study*

# Complete Response with Single-Infusion of CTX130

## Subject Overview

### Patient profile

- 47-year-old male with stage IVA2 transformed mycosis fungoides (tMF)
- 5 prior lines of therapy
- Refractory after last treatment with brentuximab vedotin
- CD70+ expression: 100% at baseline

### Efficacy

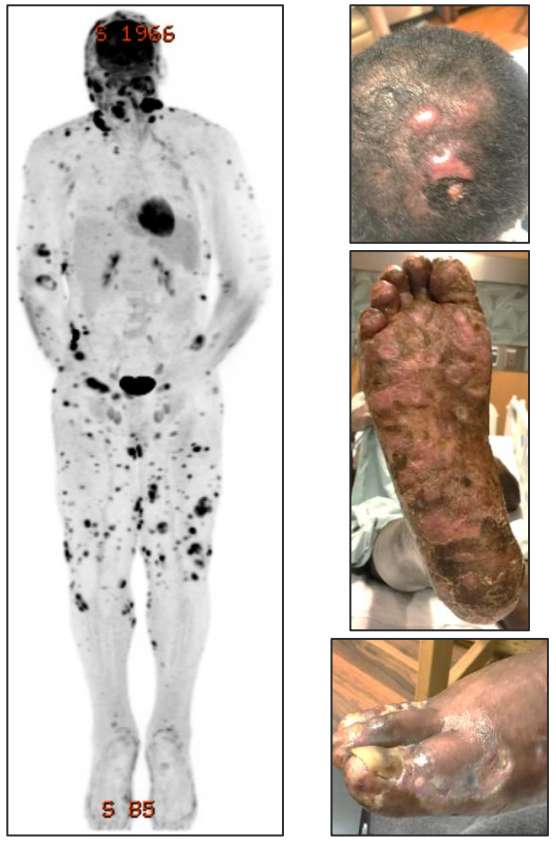
- CR at D28 after a single infusion of $9x10^8$ CAR+ T cells
- Remains in CR at Month 3

### Safety

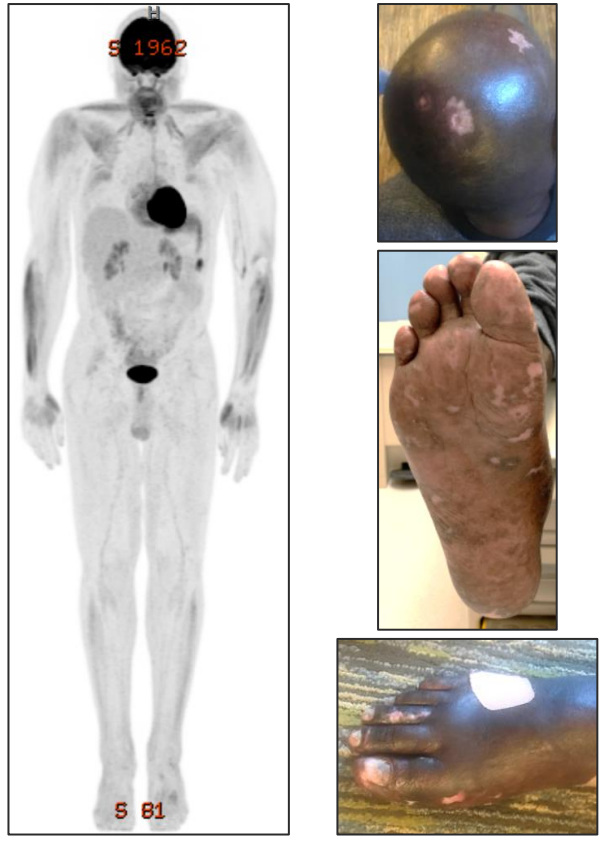
- Gr 3 anemia (D3) & Gr 3 neutropenia (D4)
- All other AEs were Gr 1

## Response

**Pre-Treatment | mSWAT = 84.74**




**Post-CTX130 (D18 skin, D28 PET) | mSWAT = 0**




AE, adverse event; CAR, chimeric antigen receptor; CR, complete response; D, day; DL, dose level; Gr, grade; mSWAT; modified severity weight assessment tool.

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*Case Study*

# Complete Response at D28 After Re-Infusion

## Subject Overview

### Patient profile

- 54-year-old female with stage IV ATLL, with skin involvement
- 2 prior lines of therapy
- Refractory after last treatment with IFNα-b, zidovudine
- CD70+ expression: 100% (skin), 1% (lymph nodes) at baseline

### Efficacy

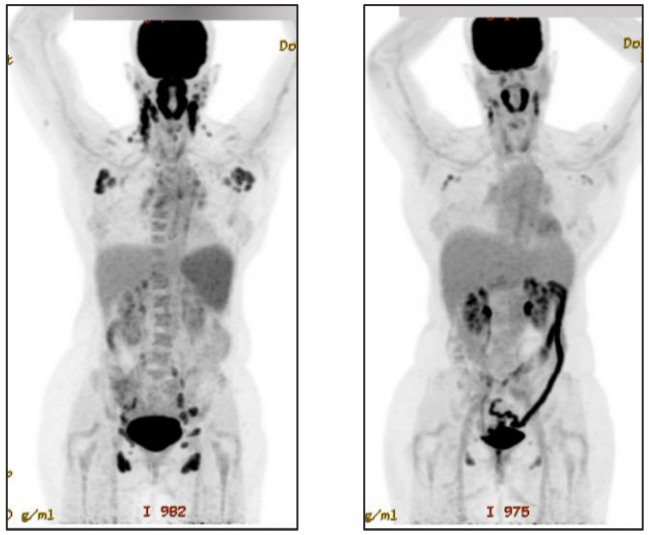
- PR at D28 after 1st infusion of $3x10^8$ CAR+ T cells and SD at Month 3
- CR at D28 after 2nd infusion with $9x10^8$ CAR+ T cells

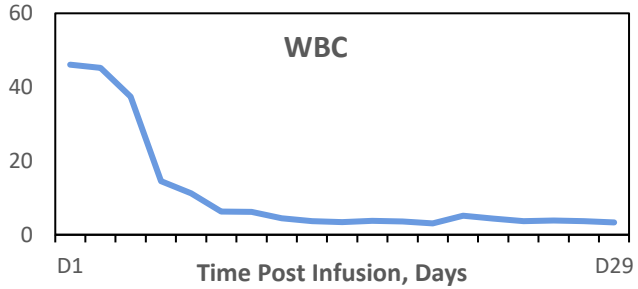
### Safety

- Gr 4 neutropenia (D8 post 1st infusion, D5 post 2nd infusion)
- All other AEs Gr 1-2

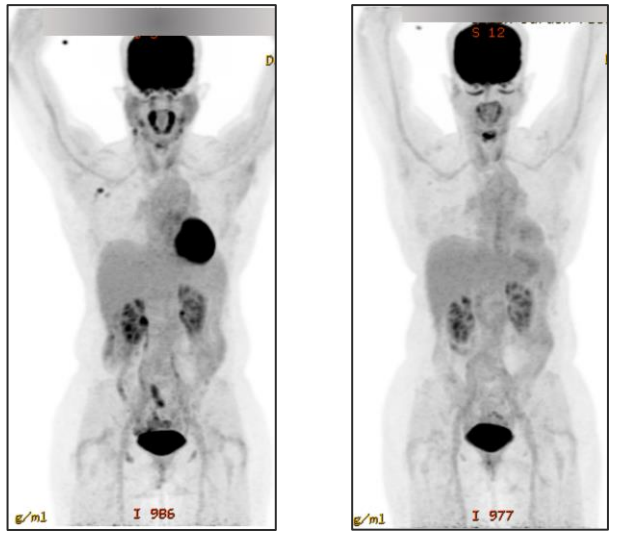
## Response

**1st Infusion (DL3)** **D28 Assessment**






**2nd Infusion (DL4)** **D28 Assessment**



| | Bone marrow | Skin |
|---|---|---|
| **Before 1st infusion** | 25% ATLL with aberrant CD25+ | mSWAT = 3.6 |
| **After 2nd infusion** | 1.3% aberrant cells, 0.1% of total | mSWAT = 0 |

AE, adverse event; ATLL, adult T-cell leukemia/lymphoma; CAR, chimeric antigen receptor; CR, complete response; D, day; DL, dose level; Gr, grade; IFN, interferon; mSWAT; modified severity weight assessment tool; PR, partial response; SD, stable disease.

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# Conclusions

- **Relapsed / refractory T cell lymphoma patients, including those with large cell transformation, have limited options and poor prognosis;** there are few therapies which effectively treat multiple disease compartments (lymph nodes, skin, blood)

- **CTX130 is the first allogeneic CAR T directed against the novel target CD70 to demonstrate preliminary findings of encouraging efficacy and a tolerable safety profile.** Although median CD70 expression amongst patients with relapsed / refractory T cell lymphoma was 90%, responses were observed across all levels of CD70 expression

- In the first-in-human COBALT-LYM trial, **CTX130 has demonstrated an acceptable safety profile in heavily pretreated patients** with relapsed / refractory T cell lymphomas

- Of the initial 18 TCL patients presented here today, none had achieved a CR in their previous line of therapy. By comparison, we have observed **clinically meaningful responses with CTX130, including a 70% ORR and 30% CR rate at DL≥3** ($\geq 3x10^8$ cells)

- **CTX130 represents a potentially best-in-class cell therapy treatment for T cell lymphoma patients**

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# Acknowledgments


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


**COBALT-LYM (NCT04502446) Study Sites**

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