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

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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\(^{TM}\) 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\(\geq\)3 (\(\geq\)3x10\(^8\) cells), with an acceptable safety profile

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**References:**


*Presented at the European Hematology Association Annual Meeting. 11 June 2022*
Role of CD70 in Immune Response and Cancer

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

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

References:

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

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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**

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β2M, β2-microglobulin; CAR, chimeric antigen receptor; MHC, major histocompatibility complex; TCR, T-cell receptor; TRAC, T-cell receptor alpha constant.
CTX130 – Preclinical Data

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

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.

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).

3x10⁶ HuT78 cells were injected subcutaneously into the right flank of NSG mice. When mean tumor size reached an average size of ~66 mm³, mice were either left untreated or injected intravenously with 8.6x10⁶ CTX130 cells per mouse (N=5 per group).

**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**

**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

*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.

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

**Secondary endpoints**
- Progression-free survival
- Overall survival

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# Patient Demographics and Pharmacokinetics

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median years (range)</strong></td>
<td>65 (39 – 78)</td>
</tr>
<tr>
<td><strong>ECOG PS at screening, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (44)</td>
</tr>
<tr>
<td>1</td>
<td>10 (56)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy, median n (range)</strong></td>
<td>4 (1 – 8)</td>
</tr>
<tr>
<td><strong>TCL subtype, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>PTCL</td>
<td>8 (44)</td>
</tr>
<tr>
<td>AITL</td>
<td>3 (17)</td>
</tr>
<tr>
<td>ALCCL</td>
<td>1 (6)</td>
</tr>
<tr>
<td>ATLL</td>
<td>3 (17)</td>
</tr>
<tr>
<td>PTCL - NOS</td>
<td>1 (6)</td>
</tr>
<tr>
<td>CTCL (MF, SS, tMF)</td>
<td>10 (56)</td>
</tr>
<tr>
<td><strong>Skin involvement, n (%)</strong></td>
<td>12 (67)</td>
</tr>
<tr>
<td><strong>Blood involvement, n (%)</strong></td>
<td>6 (33)</td>
</tr>
<tr>
<td><strong>Bone marrow involvement, n (%)</strong></td>
<td>4 (22)</td>
</tr>
<tr>
<td><strong>CD70 expression level, median % (range)</strong></td>
<td>90 (20 – 100)</td>
</tr>
<tr>
<td><strong>Second CTX130 infusion received, n (%)</strong></td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak expansion concentration (C_{max})</strong></td>
<td>80.9</td>
</tr>
<tr>
<td>geometric mean copies/μg (range)</td>
<td>(&lt;4.9 – 61,349.8)</td>
</tr>
<tr>
<td><strong>Time to peak expansion (T_{max})</strong></td>
<td>8.5 (5 – 14)</td>
</tr>
</tbody>
</table>

## Patient Demographics and Pharmacokinetics

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* 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.

† Includes first infusions only
**Safety**

Data cutoff date: 26 April 2022

### Adverse Events of Interest, N (%)

<table>
<thead>
<tr>
<th></th>
<th>DL1 3x10^7 N=4</th>
<th>DL2 1x10^8 N=4</th>
<th>DL3 3x10^8 N=5</th>
<th>DL4 9x10^8 N=5</th>
<th>DL≥3 N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1-2</td>
<td>Gr ≥3</td>
<td>Gr 1-2</td>
<td>Gr ≥3</td>
<td>Gr 1-2</td>
</tr>
<tr>
<td>CRS</td>
<td>1 (25)</td>
<td>-</td>
<td>1 (25)</td>
<td>-</td>
<td>4 (80)</td>
</tr>
<tr>
<td>ICANS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (60)</td>
</tr>
<tr>
<td>GvHD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infections</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>-</td>
<td>1 (25)</td>
<td>2 (40)</td>
</tr>
</tbody>
</table>

- **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

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

<table>
<thead>
<tr>
<th>Cell dose (CAR+ T cells)</th>
<th>DL1 3x10⁷ N=4</th>
<th>DL2 1x10⁸ N=4</th>
<th>DL3 3x10⁸ N=5</th>
<th>DL4 9x10⁸ N=5</th>
<th>DL≥3 N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate (ORR)</td>
<td>2 (50)</td>
<td>0</td>
<td>3 (60)</td>
<td>4 (80)</td>
<td>7 (70)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (40)*</td>
<td>1 (20)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (20)</td>
<td>3 (60)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Disease Control Rate (DCR = CR + PR + SD)</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>5 (100)</td>
<td>4 (80)</td>
<td>9 (90)</td>
</tr>
</tbody>
</table>

Data cutoff date: 26 April 2022

*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)

- CTCL DL1/DL2
- CTCL DL3
- AITL DL4
- ATLL DL1/DL3
- CTCL DL3
- ATLL DL3/DL4
- CTCL DL4
- AITL DL3
- CTCL DL3
- CTCL DL1
- AITL DL4
- CTCL DL2
- ATLL DL2
- ALCCL DL4
- PTCL-NOS DL1
- CTCL DL2
- CTCL DL2

Time from first CTX130 infusion (months)

- CR (Complete Response)
- PR (Partial Response)
- SD (Stable Disease)
- PD (Progressive Disease)
- Re-Infusion
- Anticancer therapy
- Stem cell transplant
- Death

AITL, angioimmunoblastic T cell lymphoma; ALCCL, 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 $9 \times 10^8$ CAR+ T cells
- Remains in CR at Month 3

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

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 1\textsuperscript{st} infusion of 3x10\textsuperscript{8} CAR+ T cells and SD at Month 3
- CR at D28 after 2\textsuperscript{nd} infusion with 9x10\textsuperscript{8} CAR+ T cells

Safety
- Gr 4 neutropenia (D8 post 1\textsuperscript{st} infusion, D5 post 2\textsuperscript{nd} infusion)
- All other AEs Gr 1-2

Response

<table>
<thead>
<tr>
<th>1\textsuperscript{st} Infusion (DL3)</th>
<th>D28 Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC chart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2\textsuperscript{nd} Infusion (DL4)</th>
<th>D28 Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC chart</td>
<td></td>
</tr>
</tbody>
</table>

Bone marrow | Skin
---|---
Before 1\textsuperscript{st} infusion | 25% ATLL with aberrant CD25+ | mSWAT = 3.6
After 2\textsuperscript{nd} 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** (≥3x10^8 cells)

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