CTX112, a Next-Generation Allogeneic CRISPR-Cas9 Engineered CD19 CAR T Cell with Novel Potency Edits: Data from Phase 1 Dose Escalation Study in Patients with Relapsed or Refractory B-Cell Malignancies

Poster 4829

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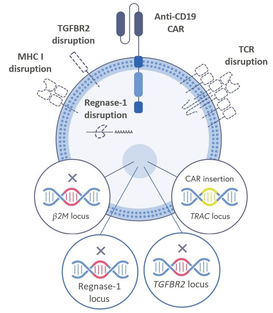
Introduction

- CRISPR/Cas9 editing allows for advanced cell engineering, which could prevent common CAR T failure modes (e.g., exhaustion, lack of expansion[1]) and result in more efficacious therapies
- Various editing strategies have been shown to improve CAR T cell effector function in nonclinical models[2,3], however whether these edits can improve clinical CAR T cell activity is unknown
- CTX112 is a next-generation CD19-directed allogeneic CAR T cell therapy with 5 edits to improve allo-immune evasion and increase CAR T cell potency
- This editing strategy was chosen based on a large scale phenotypic CRISPR screen to identify novel potency edits, and further informed by our first-generation CTX110 data, which showed durable remissions were possible in patients with large B-cell lymphoma (LBCL) without long-lived CAR T cell persistence[4]
- Here we report the results from the dose-escalation phase of the study from 12 subjects with lymphoma (3 FL, 3 MZL, 1 MCL, 5 LBCL) treated with CTX112 at doses ranging from 30 x 10^6 (Dose Level [DL] 1) to 600 x 10^6 (DL4) CAR+ T cells
- This is the first clinical demonstration that disruption of Regnase-1 and TGFβR2 can increase CAR T cell expansion, functional persistence, and potency

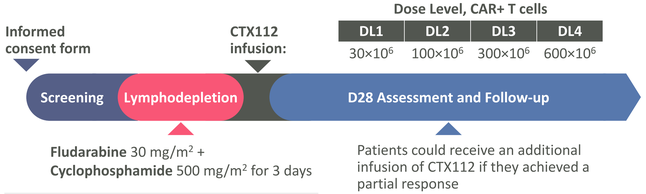
Figure 1: CTX112™ Construct



CTX112 is a second-generation allogeneic CAR T cell therapy with 5 edits:

- **TCR KO** to minimize the risk of GvHD
- **β2M KO** to eliminate MHC class I expression and mitigate host T cell-mediated clearance of CAR T cells
- **Regnase-1 KO** to remove an intrinsic "brake" on T cell function
- **TGFβR2 KO** to remove a key extrinsic "brake" on T cell anti-tumor activity
- **CAR KI** via precise insertion of CAR transgene into the TRAC locus using an AAV template

Figure 2: CRSP-ONC-006 Clinical Trial Design



This is an open-label, multicenter, Phase 1/2 study evaluating the safety and efficacy of CTX112 in subjects with relapsed or refractory B-cell malignancies (NCT05643742)

Key eligibility criteria

- Age ≥18 years
- Patient population: R/R FL grade 1-3a, MZL, MCL, CLL/SLL, DLBCL NOS, DLBCL/high grade lymphoma with MYC and BCL2 rearrangement, grade 3b FL, DLBCL arising from FL or MZL or LBCL with prior CAR T
- No prior allogeneic SCT
- No history of CNS lymphoma involvement
- Adequate organ function

Primary endpoint

- Incidence of AEs, defined as DLTs
- ORR (per Lugano 2014 criteria or iwCLL 2018 guidelines for CLL/SLL)

Secondary endpoints

- CR rate
- DOR
- OS

Allogeneic CAR T enables simplified trial design:

- Short screening timeframe
- No apheresis
- No bridging chemotherapy
- On-site availability of CAR T cell product

Table 1: Patient Demographics and Baseline Characteristics

Baseline Patient Characteristics	Total N = 12
Median Age, y (range)	62 (49-79)
Sex (Male), n (%)	8 (66.7)
ECOG PS at Screening, n (%)	
0	8 (66.7)
1	4 (33.3)
NHL Subtype, n (%)	
Follicular Lymphoma (Low Grade 1-3a)	3 (25)
Marginal Zone Lymphoma	3 (25)
Mantle Cell Lymphoma	1 (8.3)
Large B Cell Lymphoma	5 (41.7)
DLBCL NOS	2 (16.7)
Transformed Follicular Lymphoma	2 (16.7)
Transformed Marginal Lymphoma	1 (8.3)
Disease Stage (per Lugano 2014[2])	
Stage IV	8 (66.7)
Tumor Burden	
SPD > 4000 mm², n (%)	6 (50)
LDH > ULN at Baseline, n (%)	6 (50)
Prognostic Score at Baseline[3]	
Intermediate or High Risk, n (%)	9 (75)

Prior Therapy Exposure	Total N = 12
Median Prior Therapies, n (range)	3 (1-7)
≥ 3 Prior Therapies, n (%)	8 (66.7)
Primary Refractory Disease	
All Histologies[1], n (%)	7 (58)
Early Relapse to Frontline Therapy[2], n (%)	9 (75)
Median Time Since Diagnosis (yrs), n (range)	3.25 (0.5-18)
BOR to last therapy	
SD/PD, n (%)	5 (42)
PR/CR, n (%)	7 (58)

Study population is enriched for heavily pre-treated patients with high-risk features

1) Primary refractory defined as absence of CR after first line of NHL treatment.
2) Early relapse for LBCL defined as progression <12M from start of 1L chemoimmunotherapy; or progression <24 mo from start of front-line chemoimmunotherapy for FL, MZL and MCL (i.e., POD24)
3) IPI Scoring: Low = 0-1, Intermediate = 2-3, High = 4-5; FLIPI Scoring: Low = 0 or 1, Intermediate = 2; High = 3-5; MIPI Scoring: Low = 0-3, Intermediate = 4-5, High = 6-11; MZL-IPI Scoring: Low = 0, Intermediate = 1–2, High = 3-5

- As of Aug 26, 2024, all 12 patients with NHL that were enrolled in dose escalation received CTX112
- Median time from enrollment to the beginning of lymphodepleting chemotherapy (LDC) was 2 days

Table 2 : CTX112 Produced Responses Across All Dose Levels

Cell dose (CAR+ T cells)	DL1 30x10^6 N=3	DL2 100x10^6 N=3	DL3 300x10^6 N=3	DL4 600x10^6 N=3	Total N=12
ORR, n (%)	2 (67)	2 (67)	2 (67)	2 (67)	8 (67)
CR	1 (33)	2 (67)	1 (33)	2 (67)*	6 (50)
PR	1 (33)	0	1 (33)	0	2 (17)

*1 patient received two CTX112 infusions at DL4 with an initial PR followed by conversion to CR

- **Best ORR and CR rates were 67% (8/12) and 50% (6/12), respectively**
  - 6-mo response rate was 36% (4/11)
  - Patient treated at DL1 in ongoing remission at 1+ year
- Objective and complete responses seen at all dose levels and in patients with different NHL subtypes (e.g., FL, MZL, MCL and LBCL)
- Objective and complete responses seen in patients with primary refractory disease and high baseline tumor burden (SPD > 4000 mm²)

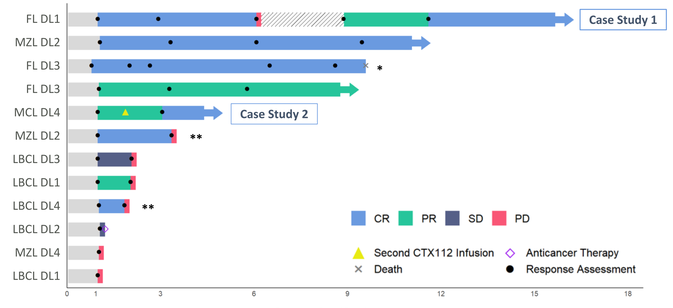
Table 3: Adverse Events of Interest, N (%)

	DL1 30x10^6 N=3		DL2 100x10^6 N=3		DL3 300x10^6 N=3		DL4 600x10^6 N=3		Total N=12	
	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 (33)	0	2 (67)	0	1 (33)	0	3 (100)	0	7 (58)	0
ICANS	0	0	1 (33)	0	1 (33)	0	2 (67)	0	4 (33)	0
Infections	1 (33)	0	0	0	2 (67)	0	2 (67)	0	5 (42)	0

*All events listed in table are treatment-emergent adverse events

- CTX112 demonstrated a tolerable safety profile across all dose levels
- No unforeseen toxicity with Regnase-1 or TGFβR2 edits
- There were no infusion reactions, HLH or GvHD with CTX112
- Cytopenias were a common adverse event; all G3+ cytopenias resolved to Gr 2 or better within 1 month of CTX112 infusion

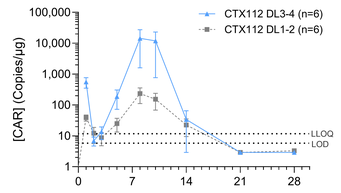
Figure 3: Ongoing Responses in Patients with Poor Prognostic Factors



* Patient had a pre-existing lung lesion biopsied 1 month after CTX112 and found to be mucinous adenocarcinoma of the lung. Patient died of complications secondary to lung cancer progression and treatment. Patient was PET and MRD negative for lymphoma at last assessment (9 months).
** 2 patients relapsed with significantly lower disease burden than baseline and were subsequently followed for 3+ months without receiving any additional anti-cancer therapy at the time of data cut

Figure 4: Pharmacokinetics

A. AUC and C_{max} increased at higher CTX112 CAR+ cell dose



B. AUC and C_{max} significantly increased with same dose (300M) of CTX112 vs. CTX110

	CTX110 DL3 (n=5)	CTX112 DL3 (n=3)	Fold-increase
Mean AUC	13,830	133,701	9.7x
Mean C_{max}	3,773	26,235	7.0x

- Addition of Regnase-1 and TGFβR2 results in higher CAR T cell expansion and functional persistence without increased LD chemotherapy doses

Figure 5: Case Studies

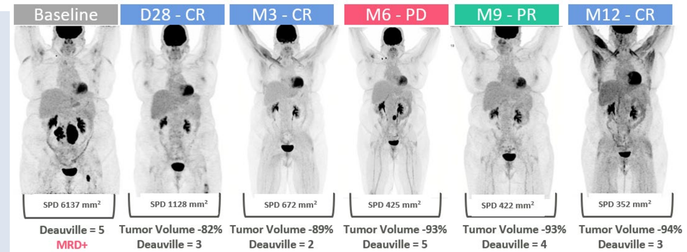
1

Patient Characteristics

- 54-year-old female
- Stage IV, Grade 3 FL
- PR to R-CHOP; POD24
- Single infusion of CTX112 at DL1

Safety and Efficacy Data

- G1 CRS at D8; resolved w/ 1 dose tocilizumab
- Radiological CR at D28 and M3
- Relapse at M6; watch and wait with **no additional anti-cancer Tx**
- PR at M9, CR ongoing at M12+



Deauville = 5 MRD+ | Tumor Volume -82% Deauville = 3 | Tumor Volume -89% Deauville = 2 | Tumor Volume -93% Deauville = 5 MRD+ | Tumor Volume -93% Deauville = 4 MRD- | Tumor Volume -94% Deauville = 3 MRD-

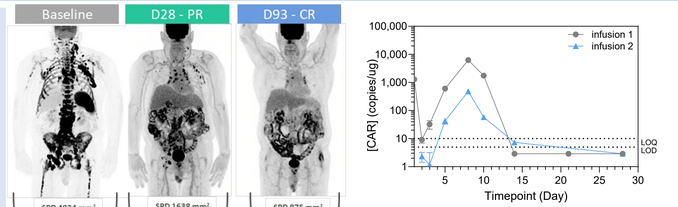
2

Patient Characteristics

- 76-year-old male
- Stage IV MCL; blastoid, TP53+
- 3 prior lines (R-CHOP, BTKi); POD24
- Extensive hypermetabolic LDA with 80% bone marrow involvement
- Two infusions of CTX112 at DL4

Safety and Efficacy Data

- PR after first dose with significant reduction in tumor burden
- **Conversion to CR with 2nd infusion**
- CTX112 was well tolerated (transient Gr1 CRS and Gr1 ICANS)



80% BM Involvement D1: CTX112 DL4 | Tumor Volume -67% <5% BM Involvement D56: CTX112 DL4 | Tumor Volume -82% 0% BM Involvement

- Expansion observed infusion proportional to tumor burden after second; no signs of allo-immune sensitization/rejection

Conclusions

- In a r/r NHL patient population with poor prognostic factors (e.g., 50% bulky disease, 58% primary refractory, 75% early relapse to frontline therapy), CTX112 showed a 67% overall response rate and 50% complete response rate during dose escalation
- CAR T cell expansion increased with dose escalation
- Responses and PK data suggest that additional edits in Regnase-1 and TGFβR2 confer greater potency to CTX112 compared to CTX110
- CTX112 demonstrated an acceptable safety profile and no Grade ≥ 3 CRS, ICANS or infections
- CTX112 is administered with a standard LDC regimen, in contrast to higher intensity regimens reported for other allogeneic CAR T therapies
- CTX112 will continue to be evaluated in an expansion phase of the study

References

1. Shah NN, et al. *Nat Rev Clin Oncol*. 2019 Jun;16(6):372-385.
2. Mai D, et al. *PNAS*. 2023; Mar 21;120(12):e2218632120
3. Kloss, CC, et al. *Mol. Ther*. 2018; 26:1855–1866.
4. McGuirk JP, et al. *Blood* 2022; 140, 10303-10306

Acknowledgements

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Abbreviations: AE, adverse events; allo, allogeneic; auto, autologous; AUC, area under the curve; β2M, β2 microglobulin; BOR, best overall response; CAR, chimeric antigen receptor; CBC, complete blood count; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CR, complete response; CRS, cytokine release syndrome; DL, dose level; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; FL, follicular lymphoma; Gr, grade; GvHD, graft versus host disease; ICANS, immune effector cell associated neurotoxicity syndrome; KI, knock-in; LBCL, large B-cell lymphoma; LDA, lymphadenopathy; LDC, lymphodepleting chemotherapy; LDH, lactate dehydrogenase; LLOQ, lower limit of quantification; LOD, limit of detection; MCL, mantle cell lymphoma; MHC, major histocompatibility complex; MRD, minimal residual disease; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PD, progressive disease; POD24, progression of disease within 24 months; PR, partial response; PS, performance status; R/R, relapsed/refractory; SCT, stem cell transplant; SD, stable disease; SPD, sum of the product of perpendicular diameters; TCR, T-cell receptor; TLS, tumor lysis syndrome; ULN, upper limit of normal