Poster 4629

CTX110 Allogeneic CRISPR-Cas9–Engineered CAR T Cells in Patients (Pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL): Results From the Phase 1 Dose Escalation CARBON Study

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Introduction

- Outcomes for patients with R/R B-cell malignancies are historically poor. However, the use of auto CAR T-cell therapy has produced complete and durable responses[1-5]
- Owing to the aggressive nature of R/R LBCL, some patients experience disease progression while waiting for auto CAR T-cell manufacture and infusion and may be ineligible to receive cells once available[6-9]
  - Among patients who are eligible for auto CAR T cell therapy, less than 30% go on to receive CAR T-cell therapy[10-13]
- Allo CAR T-cell therapies that produce durable remissions in patients with R/R LBCL may offer advantages over auto CAR T products such as the potential for immediate "off-the-shelf" availability, no required leukapheresis, potential for an improved safety profile, and the option for additional infusions[6,14]
- We designed a phase 1 study to evaluate the safety and efficacy of CTX110, an allogeneic CD19-directed CAR T cell therapy in patients with R/R LBCL and report here results from the dose-escalation phase of the study

Figure 1: CTX110™ Construct

- Investigational allogeneic anti-CD19 CAR T cell therapy
- Modified using CRISPR/Cas9 editing designed to disrupt the endogenous TRAC locus to remove TCR expression and disrupt β2M
  - Disruption of the TCR minimizes risk of GvHD
  - Disruption of β2M eliminates MHC class I expression to mitigate host T-cell-mediated clearance of CTX110
- Anti-CD19 CAR transgene construct is precisely inserted into the TRAC locus using an AAV vector

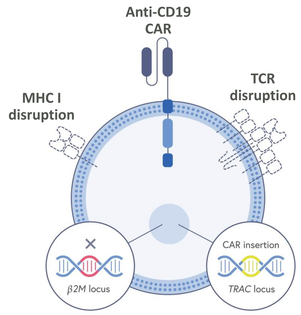
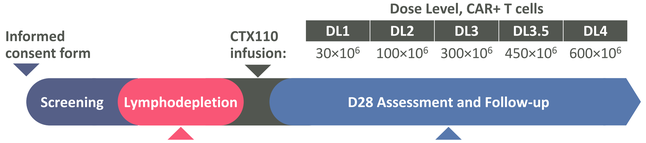


Figure 2: CARBON™ (NCT04035434) Clinical Trial Design



This is an open-label, multicenter, Phase 1 study evaluating the safety and efficacy of CTX110 in subjects with relapsed or refractory B-cell malignancies (NCT04035434)

Key eligibility criteria
- Age ≥18 years
- R/R DLBCL NOS, double- or triple-hit DLBCL, or transformed or grade 3b FL, as evidenced by ≥2 lines of prior therapy
- No prior allogeneic SCT or treatment with CAR-T therapy
- No history of CNS lymphoma involvement
- No minimum CBC requirements

Primary endpoint
- Incidence AEs, defined as DLTs
- ORR (per Lugano 2014 criteria)

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

	DL1 N=3	DL2 N=3*	DL3 N=6	DL3.5 N=6	DL4 N=14	Total N=32
Median age, y (range)	52 (50-61)	64 (58-74)	69 (62-74)	67.5 (25-74)	64 (35-75)	**64 (25-75)**
Female, n (%)	1 (33.3)	1 (33.3)	4 (66.7)	2 (33.3)	2 (14.3)	**10 (31.3)**
ECOG PS at screening, n (%)						
0	2 (66.7)	1 (33.3)	2 (33.3)	4 (66.7)	4 (28.6)	**13 (40.6)**
1	1 (33.3)	2 (66.7)	4 (66.7)	2 (33.3)	10 (71.4)	**19 (59.4)**
Refractory disease, n (%)	3 (100)	3 (100)	2 (33.3)	1 (16.7)	8 (57.1)	**17 (53.1)**
Prior anticancer therapies						
Median prior therapies, n (range)	2 (2-8)	3 (2-3)	2 (2-4)	2.5 (2-10)	2.5 (2-10)	**2 (2-10)**
≥3 prior therapies, n (%)	1 (33.3)	2 (66.7)	2 (33.3)	3 (50)	7 (50)	**15 (46.9)**
Prior stem cell transplant, n (%)	0	0	3 (50)	4 (66.7)	4 (28.6)	**11 (34.4)**
NHL subtype, n (%)						
DLBCL, NOS	1 (33.3)	2 (66.7)	2 (33.3)	4 (66.7)	8 (57.1)	**17 (53.1)**
HGLBCL w MYC/BCL2 and/or BCL6 rearr.	0	1 (33.3)	1 (16.7)	1 (16.7)	2 (14.3)	**5 (15.6)**
Transformed FL	1 (33.3)	0	2 (33.3)	1 (16.7)	3 (21.4)	**7 (21.9)**
Grade 3b FL	0	0	0	0	1 (7.1)	**1 (3.1)**
Other†	1 (33.3)	0	1 (16.7)	0	0	**2 (6.2)**
Baseline SPD >50 cm², n (%)	1 (33.3)	1 (33.3)	2 (33.3)	1 (16.7)	6 (42.9)	**11 (34.4)**
Baseline LDH > ULN, n (%)	1 (33.3)	2 (66.7)	2 (33.3)	5 (83.3)	7 (50)	**17 (53.1)**

*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3.
†1 patient enrolled in DL1 had Richter's transformation of CLL, and 1 patient in DL3 had both grade 3b FL and germinal center B-cell-like DLBCL.

- As of Oct 6, 2022, 34 patients with LBCL were enrolled for dose escalation and 32 received CTX110. Only 2 enrolled patients did not receive CTX110 due to intercurrent infections (COVID-19 and pneumonia)
- Median time from enrollment to the beginning of lymphodepleting chemotherapy (LDC) was 2 days

Table 2: CTX110 Demonstrated Encouraging Efficacy at Dose Level ≥3

Cell dose (CAR+ T cells)	DL1 N=3	DL2 N=3*	DL3 N=6	DL3.5 N=6	DL4 N=14	≥1 Infusion at DL≥3 N=27
ORR, n (%)	0	1 (33.3)	4 (66.7)	4 (66.7)	9 (64.3)	**18 (66.7)**
CR	0	1 (33.3)	2 (33.3)	4 (66.7)	4 (28.6)	**11 (40.7)**
PR	0	0	2 (33.3)	0	5 (35.7)	**7 (25.9)**

*1 patient received two CTX110 infusions with the first infusion at DL2 and the second at DL3.

- Among patients who received ≥1 infusion of CTX110 at doses of ≥300 x 10^6 CAR T cells (DL ≥3; N=27):
  - **Best ORR and CR rates were 66.7% (18/27) and 40.7% (11/27), respectively**
  - 6-mo CR rate was 19% (5/27)
  - Three patients have achieved and maintained ongoing CR for more than 24 months**
  - For the 13 patients who received a second infusion of ≥300 x 10^6 CAR T cells, CAR T cell expansion was observed in all patients, with no change in the overall safety profile

** 2 patients were in CR for more than 24 months at the time of the data cutoff; 3 patients were in CR for over 24 months at the date of the presentation.

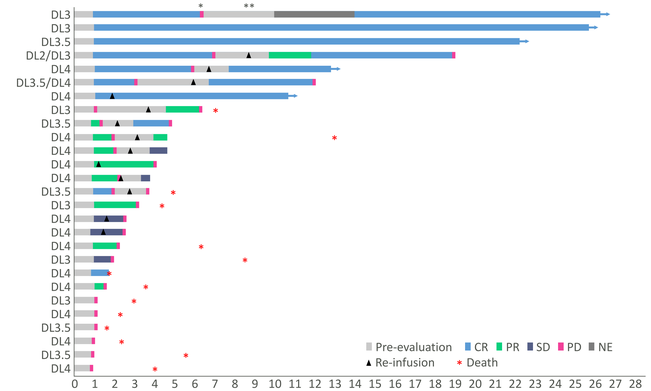
Table 3: Adverse Events of Interest, N (%)

	DL1 30x10^6 N=3		DL2 100x10^6 N=3		DL3 300x10^6 N=6		DL3.5 450x10^6 N=6		DL4 600x10^6 N=14		Total N=32	
	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	Gr 1-2	Gr ≥3
CRS	1 (33.3)	0	2 (66.7)	0	2 (33.3)	0	3 (50)	0	10 (71.4)	0	**18 (56.3)**	**0**
ICANS	0	0	1 (33.3)	0	0	0	0	0	0	2 (14.3)	**1 (3.1)**	**2 (6.2)**
GvHD	0	0	0	0	0	0	0	0	0	0	**0**	**0**
Infections	0	1 (33.3)	0	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (7.1)	2 (14.3)	**4 (12.5)**	**4 (12.5)**

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

- CTX110 demonstrated a tolerable safety profile across all dose levels
- There were no infusion reactions with CTX110
- All cases of ICANS were considered related to CTX110 and all CRS events were related or possibly related
- Gr ≥3 infections occurred in 4/32 patients (12.5%) including 1 patient who died with HHV6 encephalitis. 1 infection was considered possibly related to CTX110
- There were 7 patients who experienced serious adverse events that were attributed to CTX110; these included CRS, ICANS, and febrile neutropenia

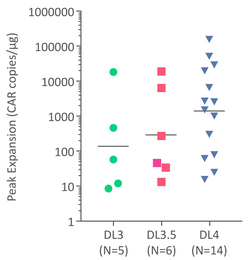
Figure 3: Durable Responses Occurred at Clinically Active Doses



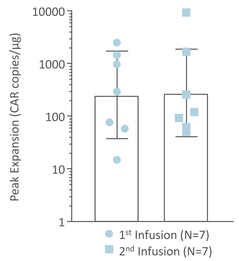
*PET CT identified a single new small FDG-avid node located in the left upper arm. The lesion was completely excised. The patient remained clinically well and required no subsequent anti cancer therapy including no steroids, no radiotherapy and no chemotherapy.
** On the Month 9 scan, the PET CT identified unspecific localized small FDG uptake in the right upper arm. The patient did not have subsequent surgery nor anti cancer therapy, and the lesion spontaneously resolved.

Figure 5: Pharmacokinetics

A. Observed peak expansion CTX110 levels following 1st Infusion by dose

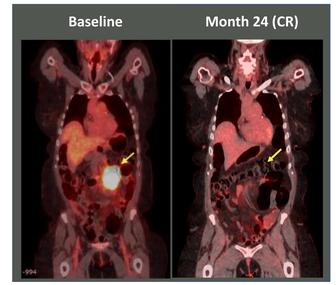


B. Peak expansion of CTX110 in subjects following 1st and 2nd infusions



- Dose-dependent increase in observed peak expansion (CAR T copies/µg) among patients receiving CTX110 at DL≥3 (**Figure 5A**)
- Expansion observed after second infusion (**Figure 5B**)

Figure 4: Case Study



Patient characteristics
- 62-year-old female diagnosed with DLBCL
- Relapsed following 2 prior lines of therapy, including autologous SCT
- Treated with single infusion of CTX110 at DL3 (300x10^6 CAR+ T cells)

Safety and efficacy data
- CR at Day 28 after a single dose with no tumor visible
- No CRS, ICANS, or infections
- CR ongoing at 24+ months

Conclusions

- In a heavily pre-treated patient population with R/R LBCL (46.9% with 3 or more prior lines of therapy), CTX110 at DL≥3 or higher resulted in **clinically meaningful ORR, CR rate, and durable remissions**, accompanied by a **favorable safety profile** during dose escalation
- Nearly half of all patients who achieved a CR maintained this response for at least 6 months
- CTX110 offers a potential off-the-shelf and feasible treatment option for patients and the **median time from enrollment to LDC was just 2 days**; median time from enrollment to infusion of CTX110 was 7 days. Only 2 enrolled patients were unable to receive CTX110
- Administration of a second CTX110 infusion was well tolerated and CAR T cells expanded following the second infusion
- CTX110 will continue to be evaluated in an expansion phase of the study

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CARBON (NCT04035434) Study Sites

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Abbreviations: AE, adverse event; allo, allogeneic; auto, autologous; β2M, β2 microglobulin; 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; HGLBCL, high-grade large B-cell lymphoma; HHV6, human herpesvirus 6; ICANS, immune effector cell associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; LDC, lymphodepleting chemotherapy; LDH, lactate dehydrogenase; LLOQ, lower limit of quantification; LOD, limit of detection; MHC, major histocompatibility complex; NHL, non-Hodgkin's lymphoma; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PD, progressive disease; PR, partial response; PS, performance status; R/R, relapsed/refractory; SCT, stem cell transplant; SD, stable disease; SPD, sum of the perpendicular diameters; TCR, T-cell receptor; TLS, tumor lysis syndrome; ULN, upper limit of normal; y, years.