Abstract 7025

A CRISPR-edited allogeneic anti-CD19 CAR-T cell therapy with a PD-1 knockout (CB-010) in patients with relapsed/refractory B cell non-Hodgkin lymphoma (r/r B-NHL): Updated phase 1 results from the ANTLER clinical trial

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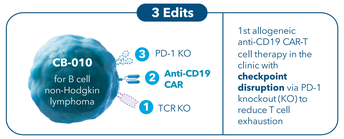
BACKGROUND

- Recent advances in autologous CAR-T cell therapies have brought clinically meaningful benefit to patients with r/r B-NHL. However, treatment delays remain a significant challenge due to the need for leukapheresis, manufacturing time, and production failure
- Despite availability of autologous CAR-T cell therapies in the 2L LBCL setting, the following reasons were considered by investigators when enrolling patients to the ANTLER clinical trial: rapidly progressing disease, insurance rejection, not wanting to go through apheresis, preference for an off-the-shelf therapy and/or electing not to receive bridging therapy while waiting for their autologous CAR-T cells to be manufactured
- CB-010 is a CD19-targeted allogeneic CAR-T cell therapy engineered with a PD-1 knockout employing a 4-1BB costimulatory domain. It is manufactured using Cas9 CRISPR hybrid RNA-DNA (chRDNA) technology, which allows for 3 precise genome edits:
  1. knockout of the *TRAC* gene to eliminate T cell receptor expression
  2. site-specific insertion of a CD19-targeted CAR expression cassette into the *TRAC* locus
  3. knockout of *PDCD1*, the gene encoding PD-1



METHODS

Figure 1. ANTLER clinical trial design

Part A: 3+3 dose escalation - completed (N=16)
- Eligibility: aggressive r/r B-NHL[1] with ≥2 prior lines of chemoimmunotherapy or primary refractory
- Exclusion: prior CD19-targeted therapy

Part B: dose expansion - enrolling
- Eligibility: 2nd line LBCL[2]
- Exclusion: prior CD19-targeted therapy
- Objective: tumor response, RP2D

r/r B-NHL
Lymphodepletion | **CB-010**

-9 to -3 DAYS | DAY 0 | 28 DAYS | 3 MONTHS | 6 MONTHS | 9 MONTHS | 12 MONTHS

Cyclophosphamide (60 mg/kg/d for 2 days) followed by Fludarabine (25 mg/m²/d for 5 days)[3]

SINGLE DOSE

Safety and tolerability
Response assessment

Dose level 1: 40x10⁶ CAR-T cells (N=8, completed[4])
Dose level 2: 80x10⁶ CAR-T cells (N=5, completed[4])
Dose level 3: 120x10⁶ CAR-T cells (N=3, completed)
Dose expansion: 30[th] patient dosed; 80x10⁶ CAR-T cells selected as RP2D
Will enroll ~20 patients at RP2D to prospectively evaluate partial (≥4) HLA matching, DSA screening

NCT04637763
[1] Subtypes include: DLBCL, HGBL, tFL, PMBCL, FL (aggressively behaving with POD24 (high risk)), and MZL
[2] LBCL subtypes include: DLBCL NOS, HGBL, transformed DLBCL from FL or MZL, and PMBCL
[3] Clin Cancer Res. 2011 July 1; 17(13): 4550-4557. doi:10.1158/1078-0432.CCR-11-0116
[4] Includes 2 backfill patients at dose level 1 and 2 backfill patients at dose level 2

Key trial endpoints

Primary endpoints

Dose escalation (Part A):
- DLTs, AEs, and SAEs

Dose expansion (Part B):
- ORR

Secondary and exploratory endpoints

Dose escalation (Part A):
- Concentrations of CB-010 and lymphocyte subsets in blood, persistence of CB-010 in blood, ORR, and PFS

Dose expansion (Part B):
- DOR, disease control rate, PFS, levels of CB-010 and lymphocyte subsets in blood
- Incidence of AEs and SAEs

STUDY POPULATION

- Overall, 46 patients with r/r B-NHL were treated with CB-010 in Parts A and B and had reached at least 28 days post CB-010 infusion as of the data cutoff date of April 1, 2024
- Of these, 40 patients had LBCL; 34 patients with LBCL received CB-010 as second-line treatment (2L LBCL)
- Median patient age was 65 years (range 21-82) with 10 (21.7%) patients ≥70 years old (Table 1)
- Median time since first diagnosis was 10.6 months (range 2.9-196.4)
- Median prior lines of therapy was 1 (range 1-8)

Table 1. Patient demographics and disease characteristics

Patient and disease characteristics	All treated (N=46)	Dose escalation (N=16)	Dose expansion (N=30)
Age, years, median (range)	65.0 (21-82)	66.0 (55-82)	63.0 (21-78)
Men, n (%)	36 (78.3)	14 (87.5)	22 (73.3)
ECOG performance status, n (%)			
0	21 (45.7)	6 (37.5)	15 (50.0)
1	25 (54.3)	10 (62.5)	15 (50.0)
Months from diagnosis, median (range)	10.6 (2.9-196.4)	29.0 (2.9-196.4)	9.5 (4.9-79.6)
NHL subtype, n (%)			
LBCL			
DLBCL	26 (56.5)	7 (43.8)	19 (63.3)
HGBL	8 (17.4)	2 (12.5)	6 (20.0)
tFL	4 (8.7)	0	4 (13.3)
PMBCL	2 (4.3)	1 (6.3)	1 (3.3)
Other B-NHL			
MCL	3 (6.5)	3 (18.8)	0
FL	2 (4.3)	2 (12.5)	0
MZL	1 (2.2)	1 (6.3)	0
Prior systemic therapies, median (range)	1 (1-8)	2 (1-8)	1 (1-1)
IPI score at screening, n (%)[1]			
0 or 1	11 (23.9)	4 (25.0)	7 (23.3)
2	8 (17.4)	2 (12.5)	6 (20.0)
≥3	18 (39.1)	3 (18.8)	15 (50.0)
Maximum lesion diameter ≥7.5 cm, n (%)	10 (21.7)	3 (18.8)	7 (23.3)
Baseline LDH, U/L, median (range)	216 (126-1799)	202 (126-710)	233.5 (140-1799)
Baseline LDH > ULN, n (%)	23 (50.0)	5 (31.3)	18 (60.0)
LDH >2 x ULN, n (%)	7 (15.2)	1 (6.3)	6 (20.0)

[1] IPI scores were not recorded for all patients

CB-010 TREATMENT AND RP2D

- Median time from confirmed eligibility to the start of lymphodepletion was 2 days (range 0-12)
  - Median time from confirmation of eligibility to CB-010 infusion (including lymphodepletion) was 11 days (range 9-21)
- As of the cutoff date, 2 patients have completed the study in CR (defined as 24 months post CB-010 infusion), 16 are ongoing, and 28 have discontinued, including 5 who died and 23 who experienced disease progression
- Based on the review and analysis of safety, efficacy, and PK data, **80×10⁶ CAR-T cells** has been selected as the RP2D for CB-010
  - The safety profile was similar across dose levels
  - There was no significant difference in cytopenia recovery across dose levels
  - The 80×10⁶ CAR-T cell dose showed improved efficacy in 2L LBCL patients relative to the 40×10⁶ and 120×10⁶ CAR-T cell doses (Figure 2)
  - CB-010 PK profile was independent of dose level

Table 2. Dose for all treated patients

Study phase	CAR-T cell dose			Total (N=46)
	40×10⁶ CAR⁺ T cells (N=14)	80×10⁶ CAR⁺ T cells (N=23)	120×10⁶ CAR⁺ T cells (N=9)	
Dose escalation	8	5	3	16
Dose expansion	6	18	6	30

SAFETY AND TOLERABILITY

Table 3. Treatment-emergent adverse events in ≥20% of all patients

System organ class, n (%) Preferred term, n (%)	All treated (N=46)		LBCL subgroup (N=40)		2L LBCL RP2D subgroup (N=20)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	46 (100)	41 (89.1)	40 (100)	35 (87.5)	20 (100)	18 (90.0)
Thrombocytopenia	30 (65.2)	29 (63.0)	26 (65.0)	25 (62.5)	12 (60.0)	11 (55.0)
Anemia	27 (58.7)	24 (52.2)	24 (60.0)	22 (55.0)	13 (65.0)	11 (55.0)
Neutropenia	22 (47.8)	19 (41.3)	18 (45.0)	15 (37.5)	10 (50.0)	8 (40.0)
White blood cell count decreased	15 (32.6)	14 (30.4)	14 (35.0)	13 (32.5)	9 (45.0)	8 (40.0)
CRS	26 (56.5)	0	23 (57.5)	0	13 (65.0)	0
Infections	22 (47.8)	10 (21.7)	19 (47.5)	8 (20.0)	9 (45.0)	6 (30.0)
Hypokalemia	11 (23.9)	0	9 (22.5)	0	4 (20.0)	0
Pyrexia	11 (23.9)	0	10 (25.0)	0	2 (10.0)	0
ICANS	10 (21.7)	3 (6.5)	8 (20.0)	2 (5.0)	5 (25.0)	1 (5.0)
Diarrhea	10 (21.7)	0	7 (17.5)	0	3 (15.0)	0

- The most common grade ≥3 TEAEs were thrombocytopenia (63.0%), anemia (52.2%), and neutropenia (41.3%) (Table 3)
  - 37 out of 46 patients (80%) recovered from cytopenias to grade ≤2 by day 35 post CB-010 infusion
- GvHD was not observed in any patients
- TEAEs associated with CB-010 are shown in Table 4
  - Median time to ICANS onset was 7.5 days (range 6-34), and median duration was 2 days (range 1-27)
  - Median time to CRS onset was 3 days (range 0-22), and median duration was 3 days (range 1-19)
- Five patients died due to AEs following CB-010 infusion, one of which was possibly related to CB-010 per investigator
  - This death was due to complications of a bladder perforation in the context of a BK virus hemorrhagic cystitis

Table 4. Notable treatment-emergent adverse events

TEAE, n (%)	All treated (N=46)	
	Any grade	Grade ≥3
Cytopenias[1]	38 (82.6)	38 (82.6)
CRS	26 (56.5)	0
Infections	22 (47.8)	10 (21.7)
ICANS	10 (21.7)	3 (6.5)[2]
HLH	1 (2.2)	0
GvHD	0	0

[1] Includes TEAE records with preferred terms neutropenia, neutrophil count decreased, thrombocytopenia, platelet count decreased, and anemia
[2] 2 grade 3 events, 1 grade 4 event, 0 grade 5 events; all events resolved with supportive care

EFFICACY

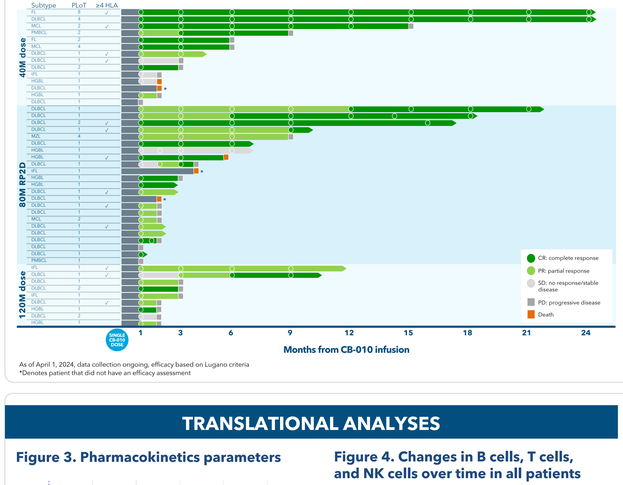
- Median overall follow-up at the time of data cutoff was 6.0 months (range 1-27), 16.8 months (range 2-27) for Part A and 3.7 months (range 1-11) for Part B
- For all patients infused, ORR was 76.1% (Table 5)
- 21 (45.7%) patients achieved a CR as best response
- Median time to CR was 28 days (range 28-357) for all patients and all subgroups
- Median duration of CR was 6.7 months for all patients and the LBCL subgroup
- Median duration of CR was not reached in the 2L LBCL RP2D subgroup

Table 5. Preliminary efficacy

	All treated (N=46)	LBCL subgroup (N=40)	2L LBCL RP2D subgroup (N=20)
ORR, n (%)	35 (76.1)	29 (72.5)	15 (75.0)
DOR, months, median (range)	5.0 (0.7-23.0+)	2.1 (0.7-23.0+)	4.8 (0.7-19.8+)
CR rate, n (%)	21 (45.7)	17 (42.5)	10 (50.0)
Duration of CR, months, median (range)	6.7 (0.6-23.0+)	6.7 (0.6-23.0+)	NR (0.6-12.2+)
Follow-up time for CR, months, median (range)	12.2 (0.0-23.0)	9.0 (0.0-23.0)	5.2 (0.0-12.2)
Time to first CR, days, median (range)	28 (28-357)	28 (28, 357)	28 (28-357)
PR rate, n (%)	14 (30.4)	12 (30.0)	5 (25.0)

+ denotes censored observation

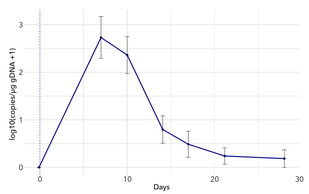
Figure 2. Efficacy outcomes in all patients by CB-010 dose (N=46)



As of April 1, 2024, data collection ongoing, efficacy based on Lugano criteria
*Denotes patient that did not have an efficacy assessment

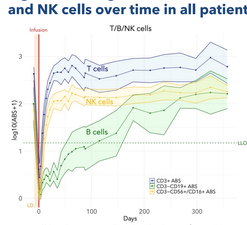
TRANSLATIONAL ANALYSES

Figure 3. Pharmacokinetics parameters



- Peak expansion (C_{max}) of CB-010 occurred between days 7 and 10 post infusion
- Persistence of CB-010 was observed up to approximately 30 days based on ddPCR assay
- No relationship between CB-010 dose and exposure was observed

Figure 4. Changes in B cells, T cells, and NK cells over time in all patients



- B cell levels remained under the limit of quantitation of the assay for over 100 days on average, supporting specific targeting of B cells by CB-010
- B cells recover to normal levels by ~260 days
- T cells and NK cells recovered approximately 3 weeks after completion of lymphodepletion

HLA AND ASSOCIATION WITH PFS

- Patients who received CB-010 manufactured from a donor with at least 4 matched HLA alleles achieved longer PFS

Figure 5. Progression-free survival by level of HLA matching in all treated patients (N=46)

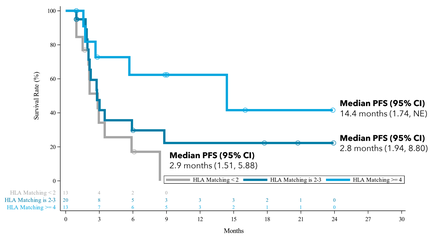
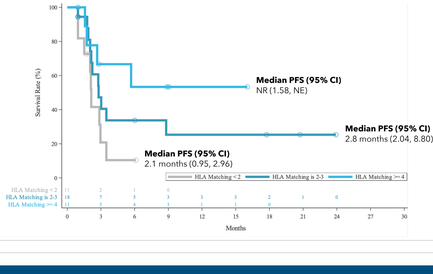


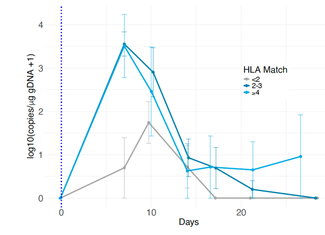
Figure 6. Progression-free survival by level of HLA matching in patients with LBCL (N=40)



IMPACT OF HLA ON CB-010 PK

- Expansion and persistence of CB-010 were impacted by the level of HLA matching

Figure 7. PK by HLA match level



CONCLUSIONS

- In this first-in-human Phase 1 trial in patients (N=46) with aggressive forms of r/r B-NHL, CB-010 demonstrated encouraging safety and antitumor activity
  - No GvHD, no grade ≥3 CRS, 6.5% of patients experienced grade ≥3 ICANS
  - Cytopenia recovery to grade ≤2 occurred in 80% of patients by day 35 after CB-010 infusion
  - For all patients infused, ORR was 76.1%, and 45.7% of patients achieved a CR as best response
- The RP2D has been determined to be 80x10⁶ CAR-T cells
- The off-the-shelf availability of CB-010 allowed for lymphodepletion to begin a median of 2 days after confirmation of eligibility
- Higher HLA matching is associated with improved PFS in these data, and approximately 20 additional 2L LBCL patients with partial HLA matching (≥4 alleles) will be enrolled

ABBREVIATIONS
2L LBCL: patients with large B cell lymphoma receiving second-line treatment; **2L LBCL RP2D**: patients in the 2L LBCL subgroup who received 80x10⁶ CAR-T cells; **AEs**: adverse events; **AESIs**: adverse events of special interest; **B-NHL**: B cell non-Hodgkin lymphoma; **CAR**: chimeric antigen receptor; **chRDNA**: CRISPR hybrid RNA-DNA; **CI**: confidence interval; **CR**: complete response; **CRS**: cytokine release syndrome; **ddPCR**: droplet digital polymerase chain reaction; **DLBCL**: diffuse large B cell lymphoma; **DLTs**: dose-limiting toxicities; **DOR**: duration of response; **DSA**: donor-specific antibodies; **ECOG**: Eastern Cooperative Oncology Group; **FL**: follicular lymphoma, aggressively behaving with POD24 (high risk); **GvHD**: graft-versus-host disease; **HGBL**: high-grade B cell lymphoma; **HLA**: human leukocyte antigen; **HLH**: hemophagocytic lymphohistiocytosis; **ICANS**: immune effector cell-associated neurotoxicity syndrome; **IPI**: International Prognostic Index; **KO**: knockout; **LBCL**: large B cell lymphoma; **LDH**: lactate dehydrogenase; **LLOQ**: lower limit of quantification; **MCL**: mantle cell lymphoma; **MZL**: marginal zone lymphoma; **NE**: not estimable; **NK**: natural killer; **NOS**: not otherwise specified; **NR**: not reached; **ORR**: overall response rate; **PD**: progressive disease; **PFS**: progression-free survival; **PK**: pharmacokinetics; **PLoT**, prior lines of therapy; **PMBCL**: primary mediastinal large B cell lymphoma; **POD24**: progression of disease within 24 months; **PR**: partial response; **RP2D**: recommended Phase 2 dose; **r/r**: relapsed/refractory; **SAEs**: serious adverse events; **SD**: stable disease; **TCR**: T cell receptor; **TEAEs**: treatment-emergent adverse events; **tFL**: transformed follicular lymphoma; **ULN**: upper limit of normal

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