Abstract # 3103

First-in-Human Trial of CB-010, a CRISPR-Edited Allogeneic Anti-CD19 CAR-T Cell Therapy with a PD-1 Knock Out, in Patients with Relapsed or Refractory B Cell Non-Hodgkin Lymphoma (ANTLER Study)

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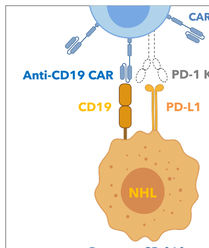
CB-010: anti-CD19 allogeneic CAR-T cell therapy

Key attributes	CB-010	Conventional allo anti-CD19 CAR-Ts
PD-1 KO for enhanced persistence of antitumor activity	✓	X
▪ Potentially better initial tumor debulking preclinically	✓	X
▪ Potentially better therapeutic index	✓	X
Site-specific insertion of CAR into TRAC locus		
▪ Eliminates random integration and reduces risk of GvHD	✓	Varies
Cas9 chRDNA editing for enhanced genomic integrity	✓	X
▪ Reduced off-target editing and genomic rearrangements	✓	X



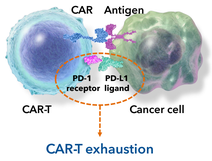
Program: CB-010
Tumor antigen: CD19
Healthy donor leukapheresis-derived T cells
Indication: r/r non-Hodgkin lymphoma (NHL)
Status: Phase 1

Source: Caribou preclinical data on file; Donohoue P, et al. Conformational control of Cas9 by CRISPR hybrid RNA-DNA guides mitigates off-target activity in T cells. (Molecular Cell Vol 81, issue 17, P3637-3649.E5, Sept 02, 2021)

CB-010: PD-1 KO designed to reduce CAR-T cell exhaustion

Conventional allogeneic CAR-T therapy

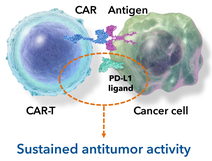
The PD-L1 ligand on cancer cells binds to the PD-1 receptor on a conventional allogeneic CAR-T, limiting the CAR-T's killing ability.



CAR-T exhaustion

CB-010 CAR-T therapy

CB-010 cells lack PD-1 receptors on their surface and, therefore, are insensitive to PD-L1 interaction. CB-010 cells are designed to maintain high antitumor activity for a longer duration.



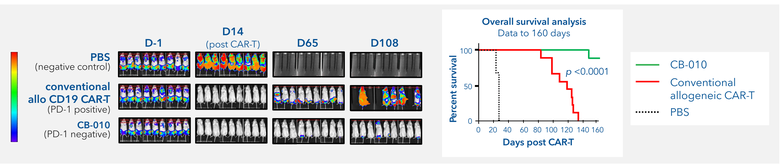
Sustained antitumor activity

CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor T-cell

Source: Caribou preclinical data on file

CB-010 maintains persistent tumor eradication longer than conventional allogeneic CAR-T cells

In preclinical studies, a single dose of CB-010 resulted in profound tumor regression of metastatic CD19+ tumor xenografts and led to a significantly more durable antitumor response vs conventional CD19-specific allogeneic CAR-Ts (expressing PD-1)



- NALM-6/PD-L1+ B-ALL tumors were established by IV engraftment for 23 days (Day -1)
- A single-dose treatment was administered by IV on Day 24 (PBS or 10^7 cells where indicated)

B-ALL, B cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; IV, intravenous; PBS, phosphate-buffered saline

Source: Caribou preclinical data on file

Acknowledgement

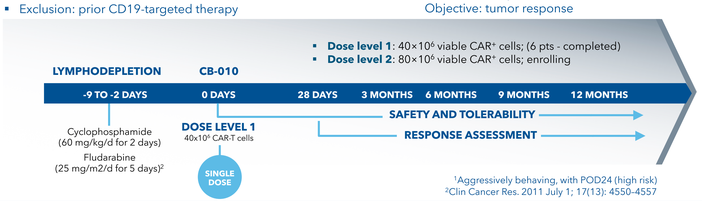
With gratitude for patients, caregivers, investigators, and research colleagues

Clinicaltrials.gov: NCT#04637763

CB-010 ANTLER Phase 1 trial design

Patients with aggressive disease
- **r/r B-NHL** (DLBCL, HGBL, tFL, PMBCL, FL[1], MZL, MCL)
- ≥ 2 prior lines of chemoimmunotherapy
- Exclusion: prior CD19-targeted therapy

Part A: 3+3 dose escalation
Objective: safety, determine MTD, RP2D
Part B: dose expansion
Objective: tumor response



[1]Aggressively behaving, with POD24 (high risk)
[2]Clin Cancer Res. 2011 July 1; 17(13): 4550-4557

Baseline and disease characteristics

Cohort 1 (N=6)	
Median age (range), years	65 (62-68)
Male, n (%)	5 (83)
ECOG performance status, n (%)	
0	5 (83)
1	1 (17)
Time since first diagnosis, years	
Median (range)	6.0 (0.7-16)
Non-Hodgkin lymphoma subtype	
DLBCL	2
FL[1]	2
MCL	1
PMBCL	1
CD19+ disease, n (%)	6 (100)
Prior systemic therapies, median number (range)[2]	3 (2-8)

[1]Aggressively behaving, with POD24 (high risk)
[2]Patients are CD19 auto CAR-T naïve

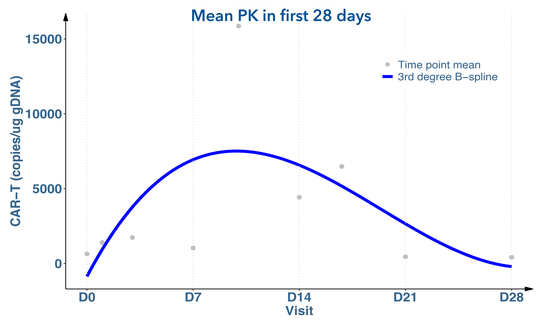
Treatment emergent adverse events (TEAEs)

Cohort 1 (N=6)	Any Grade[1] N (%)	Grade ≥ 3 N (%)	Related[2] Grade ≥ 3 N (%)
Total number of TEAEs	**137**	**39**	**17**
Patients with TEAEs	**6 (100)**	**5 (83)**	**4 (67)**
Neutropenia/neutrophil count decreased	5 (83)	5 (83)	1 (17)
Thrombocytopenia/platelet count decreased	4 (67)	4 (67)	3 (50)
Anemia	4 (67)	2 (33)	-
White blood cell count decreased	3 (50)	3 (50)	3 (50)
Lymphocyte count decreased	3 (50)	2 (33)	1 (17)
Lactate dehydrogenase (LDH) increased	2 (33)	1 (17)	1 (17)
Cytokine release syndrome (CRS)	2 (33)	-	-
Blood creatinine increased	2 (33)	-	-
Fatigue	2 (33)	-	-
Hypoalbuminemia	2 (33)	-	-
Hypocalcemia	2 (33)	-	-
Hyponatremia	2 (33)	-	-
ICANS	1 (17)	1 (17)	1 (17)
Febrile neutropenia	1 (17)	1 (17)	-
Syncope	1 (17)	1 (17)	-

[1]All TEAEs in at least 2 patients of any grade or a TEAE in at least 1 patient of Grade ≥ 3 are included.
[2]Related TEAEs include TEAEs with a relationship to CB-010 of "probably related" or "related" as evaluated by investigator.
Data cutoff date 13 May 2022

Kinetics of CB-010

(N=6)



AEs of special interest

Event	Cohort 1 (N=6)
CRS[1], n (%)	
Any grade	2 (33)
Grade 1	2 (33)
Grade ≥ 2	0 (0)
Median days to onset, days (range)	4 (1-7)
Median duration of events, days (range)	8 (7-8)

[1]1 CRS required treatment. Patient received tocilizumab (8mg x 2) and antibiotics and was hospitalized.

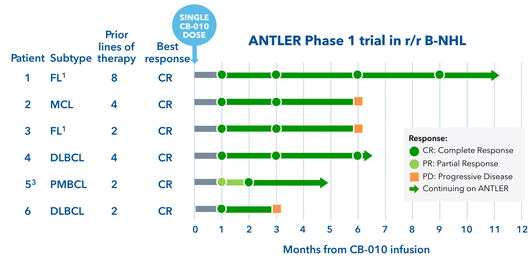
Event	Cohort 1 (N=6)
ICANS[2], n (%)	
Any grade	1 (17)
Grade 3	1 (17)
Grade ≥ 4	0 (0)
Time to onset, days	8
Duration of event, days	<2 (~39 hrs)

[2]Patient received dexamethasone (10mg x 2 and 20mg x 4) and was hospitalized.

Event	Cohort 1 (N=6)
Infections[3], n (%)	
Any grade	2 (33)
Grade 1	0 (0)
Grade 2	1 (17)
Grade 3	1 (17)
Median days to onset, (range)	8.5 (2-140)
Median duration of events, days (range)	5 (1-56)

[3]Grade 3, pre-CB-010 infusion. Grade 2, post-CB-010 infusion. None were related to CB-010.

CB-010: preliminary efficacy



- 6 patients treated with a single infusion at dose level 1 (40x10⁶ CAR-T cells)
- 6 patients evaluable for efficacy[2]
  - 100% CR (6/6, best response)
  - 40% CR (2/5) at 6 months
- 9 months was longest measured CR
- Responses measured by investigator assessment and independent radiologist

[1]Aggressively behaving, with POD24 (high risk)
[2]As of 13 May 2022 data cutoff date, data collection ongoing, efficacy based on Lugano criteria
[3]Patient 5's 3-month PET-CT conducted on day 63 post-CB-010 infusion as per investigator's discretion

FL: follicular lymphoma
MCL: mantle cell lymphoma
DLBCL: diffuse large B cell lymphoma
PMBCL: primary mediastinal large B cell lymphoma

Case study from ANTLER Phase 1 trial

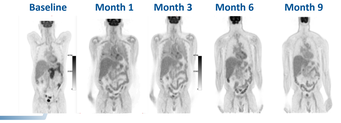
Patient #1

Age: 66
Gender: M
BMI: 25.4

Original prognosis

Tumor subtype: FL (aggressively behaving + POD24)
Stage: IV
Years since diagnosis: 8
Lines of prior therapy: 8
History: multiple relapses and progressive disease, then enrolled on ANTLER trial

PET-CT scans evaluated by investigator assessment and independent radiologist



After CB-010 dose level 1 treatment

- Days since CB-010 infusion: 329
- Best ORR: confirmed CR from Day 28 post-infusion to Month 9
- Tolerability: Grade ≥ 3 related AE: 1
- Status: continuing on study

Conclusions

- In ANTLER Phase 1 study, CB-010, an allogeneic CD19-directed CAR-T cell therapy with a PD-1 KO, demonstrated promising preliminary safety and efficacy in patients with r/r B-NHL at dose level 1
- CB-010 was generally well tolerated
  - 1 Grade 3 ICANS was observed that resolved in 39 hours
  - No Grade ≥ 2 CRS, no GvHD, and no Grade 5 AEs were observed
- At the initial dose level of 40×10⁶ CAR-T cells, best response of 100% CR rate (6/6) with 6-month CR rate of 40% (2/5) was observed by investigator as well as independent radiologist assessment
- Enrolling patients at dose level 2 of 80×10⁶ CAR-T cells

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