TRIALS-IN-PROGRESS – ABSTRACT #4257

A First-in-Human Phase 1, Multicenter, Open-label Trial of CB-010, a Next-Generation CRISPR-Edited Allogeneic Anti-CD19 CAR-T Cell Therapy with a PD-1 Knockout, in Patients with Relapsed/Refractory B cell Non-Hodgkin Lymphoma (ANTLER Trial)

S. O'BRIEN[1], L. NASTOUPIL[2], J. ESSELL[3], L. DSOUZA[2], D. HART[3], E. MATSUDA[1], T. SATTERFIELD-LEDBETTER[4], T. NESHEIWAT[5], A. HAMMAD[5], F. DAVI[5], S. CHUNG[5], S. ASIM SHAMSI[5], M. BRYAN[5], J. SKOBLE[5], E. GARNER[5], S. KANNER[5], S. RIZVI[5], and H. HOLMES[4]

1. Department of Hematology and Oncology, University of California Irvine, Irvine, CA 2. Lymphoma/Myeloma, UT MD Anderson Cancer Center, Houston, TX 3. Oncology Hematology Care, Cincinnati, OH 4. Oncology, Texas Oncology/Baylor Sammons Cancer Center, Dallas, TX 5. Caribou Biosciences, Inc., Berkeley, CA

INTRODUCTION

T cells are an integral part of the immune system and have been harvested from the peripheral blood of healthy donors and modified to express chimeric antigen receptors (CARs). Chimeric antigen receptor T (CAR-T) cells bind to specific antigens on malignant cells and induce cell death

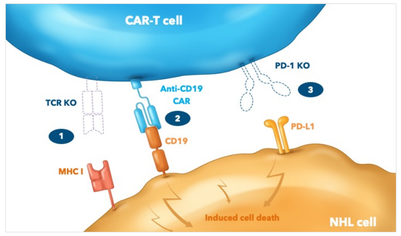
Autologous CAR-T cell therapies have shown clinical benefit[1,2,3], but may present barriers for some patients due to insufficiencies in the patient's own T cells as well as in the manufacturing process

Allogeneic CAR-T cell therapies may offer a significant benefit to patients who are:

- refractory to or relapsed on prior systemic anti-cancer therapies
- ineligible for autologous CAR-T cell therapies
- at risk for manufacturing failure of their own T cells
- at risk of disease progression while on bridging therapy

CB-010 includes a PD-1 KO designed to improve persistence of antitumor activity

- CB-010 is an allogeneic anti-CD19 CAR-T cell therapy with a 4-1BB costimulatory domain that is derived from healthy donor T cells
- A next-generation CRISPR-Cas9 (chRDNA) technology developed at Caribou that **significantly reduces off-target editing** was implemented to generate 3 genome edits in the manufacture of CB-010:



1. Knockout of the *TRAC* gene to eliminate TCR expression to reduce the risk of graft-versus-host disease (GvHD)
2. Site-specific insertion of a CD19-specific CAR into the *TRAC* locus
3. Knockout of the gene encoding PD-1, designed to limit premature CAR-T cell exhaustion and enhance antitumor activity

ANTLER phase 1 trial design

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

ANTLER key trial endpoints

Primary Endpoints:

Dose Escalation (Part A):

- Incidence of AEs and SAEs*, incidence of AEs defined as DLT**

Dose Expansion (Part B):

- Objective response rate (CR+PR)

Secondary Endpoints:

Dose Escalation (Part A):

- Objective response rate (CR+PR), duration of response, disease control rate, best objective response
- Progression-free survival, overall survival

Dose Expansion (Part B):

- Duration of response, disease control rate, progression-free survival, overall survival
- Incidence of AEs and SAEs*

*CTCAE v5.0 and CRS, ICANS, GvHD grading criteria **DLT assessment period is 28 days after CB-010 infusion

ANTLER key inclusion criteria

- Age 18 or older at the time of informed consent
- ECOG performance status of 0 or 1
- Measurable disease as per Lugano 2014 criteria
- Multiple subtypes of B-NHL: DLBCL, HGBL, tFL, PMBCL, MCL, FL*,5, and MZL*
- ≥2 prior lines of systemic chemoimmunotherapy

  Note: ≥1 prior line of chemoimmunotherapy for primary refractory disease

*Aggressively behaving FL and MZL

ANTLER key exclusion criteria

- Prior therapy with an anti-CD19 targeted agent
- Active acute or chronic GvHD requiring therapy
- Clinically significant active infection

  Note: Patients receiving IV antibiotics or having received IV antibiotics within 7 days of enrollment are excluded (prophylactic antibiotics, antivirals or antifungals are permitted)
- Prior allogeneic stem cell transplant
- Prior autologous stem cell transplant within 8 weeks of informed consent
- Prior or current lymphomatous CNS involvement or leptomeningeal disease
- Clinically significant CNS dysfunction
- Radiation therapy within 10 days prior to lymphodepletion start date

ANTLER trial participating sites*

ARIZONA
Honor Health Cancer Institute (Scottsdale)

CALIFORNIA
University of California Irvine (Irvine)
University of California San Diego (La Jolla)

NEW JERSEY
Atlantic Health (Morristown)

OHIO
Oncology Hematology Care (Cincinnati)
Ohio State University (Columbus)

TEXAS
Baylor Sammons Cancer Center (Dallas)
MD Anderson Cancer Center (Houston)

UTAH
Huntsman Cancer Institute (Salt Lake City)

*NCT#04637763 on clinicaltrials.gov

ANTLER trial summary

- Allogeneic CAR-T cell therapy is an investigational treatment that may address the unmet needs of r/r B-NHL patients with aggressive disease
- CB-010 is a next-generation CRISPR-edited allogeneic CD19-directed CAR-T cell therapy with a PD-1 KO that is being evaluated in the ANTLER trial
- ANTLER is a phase 1 first-in-human trial investigating the safety and efficacy of CB-010 as a single infusion in patients with r/r B-NHL patients at clinical sites across the United States
- Multiple subtypes of B-NHL patients who are eligible for enrollment in the ANTLER trial are: DLBCL, HGBL, tFL, PMBCL, MCL, FL*,5, and MZL*

Patient enrollment is ongoing in the dose escalation phase of the ANTLER trial

*Aggressively behaving FL and MZL

References

1. **Neelapu S et al.** Axicabtagene ciloleucel CAR T cell therapy in refractory large B cell lymphoma. *N Engl J Med 2017; 377:2531-2544*
2. **Schuster S et al.** Tisagenlecleucel in adult relapsed or refractory diffuse large B cell lymphoma. *N Engl J Med 2017; 380:45-56*
3. **Abramson S et al.** Lisocabtagene maraleucel for patients with relapsed or refractory large B cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet 2020;396(10254):839-852*
4. **Rosenberg S et al.** Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin Cancer Res 2011;17(13):4550-4557*
5. **Casulo C et al.** Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. *Blood 2022;139(11):1684-1693*

Abbreviations

AE: adverse event
B-NHL: B cell non-Hodgkin lymphoma
CAR: chimeric antigen receptor
CAR-T: chimeric antigen receptor T cell
CD: cluster of differentiation
chRDNA: CRISPR hybrid RNA-DNA
CNS: central nervous system
CR: complete response
CRS: cytokine release syndrome
CRISPR: clustered regularly interspaced short palindromic repeats
DLBCL: diffuse large B cell lymphoma
DLT: dose limiting toxicity
ECOG: Eastern Cooperative Oncology Group
FL: follicular lymphoma
GvHD: graft-vs-host disease
HGBL: high grade B cell lymphoma
ICANS: immune effector cell-associated neurotoxicity syndrome
KO: knockout
MCL: mantle cell lymphoma
MTD: maximum tolerated dose
MZL: marginal zone lymphoma
PD-1: programmed cell death protein 1
PMBCL: primary mediastinal B cell lymphoma
POD24: progression of disease within 2 years
PR: partial response
r/r: relapsed/refractory
RP2D: recommended Phase 2 dose
SAE: serious adverse event
TCR: T cell receptor
tFL: transformed follicular lymphoma
TRAC: T-cell receptor alpha constant

CORRESPONDING AUTHOR: Susan O'Brien, M.D. (obrien@hs.uci.edu)
Professor of Medicine at the Chao Family Comprehensive Cancer Center, University of California Irvine

American Society of Hematology Annual Meeting
Aggressive Lymphomas - Prospective Therapeutic Trials (Poster III)
December 12, 2022 - New Orleans, LA