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CRISPR-edited Allogeneic Anti-CD19 CAR-T Cell Therapy with PD-1 Knockout Induces Prolonged Complete Response in Relapsed/Refractory Follicular Lymphoma Patient: Case Report from CB-010 ANTLER Trial

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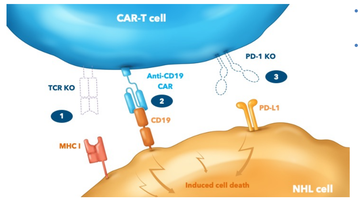
Aggressive follicular lymphoma disease overview

1. Follicular lymphoma (FL) is a B-cell lymphoproliferative disorder of transformed follicular center B cells
2. Subsets of FL patients have a clinically **variable course,** experience multiple relapses, transform to a more aggressive histology, or observe early disease progression
3. Early FL relapse, defined as recurrence or progression of disease within 24 months of front-line therapy (POD24), occurs in **~20%** of FL patients who receive first-line chemoimmunotherapy
4. POD24, an aggressively behaving FL, is associated with poor outcomes:
   - **5-year OS for early progressors ranges from 34-50%,** compared to 90% for those FL patients without early disease recurrence
   - **Early progression is a robust indicator of poor survival** as validated in a pooled analysis of patients with FL (N>5,000, from 13 prospective clinical trials)
   - Predictors of early progression or death includes male gender, poor performance status (PS), high FLIPI score, and elevated baseline B2M level

Casulo C, et al. Blood 2022;139:1684-1693; B2M: β2 microglobulin, FLIPI: Follicular Lymphoma International Prognostic Index; OS: overall survival

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



- CB-010 is an allogeneic anti-CD19 CAR-T cell therapy derived from healthy donor T cells
- A next-generation CRISPR-Cas9 technology (chRDNA) 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

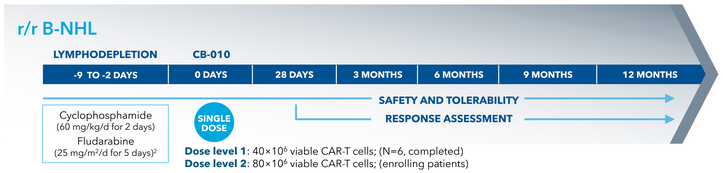
CAR: chimeric antigen receptor, KO: knockout, CD: cluster of differentiation, chRDNA: CRISPR hybrid RNA-DNA, CRISPR: clustered regularly interspaced short palindromic repeats, PD-1: programmed cell death protein 1, TCR: T cell receptor, *TRAC*: T cell receptor alpha constant gene

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



B-NHL: B cell non-Hodgkin lymphoma, CAR: chimeric antigen receptor, CD: cluster of differentiation, FL: follicular lymphoma, MTD: maximum tolerated dose, PET: positron emission tomography, POD24: progression of disease within 2 years, r/r: relapsed/ refractory, RP2D: recommended Phase 2 dose, tFL: transformed FL

[1] Aggressively behaving, with POD24 (high risk)
[2] Rosenberg SA, et al. Clin Cancer Res. 2011;17(13): 4550-4557
Clinicaltrials.gov NCT#04637763.

Patient case presentation

Patient demographics

Age	Sex	Race	Ethnicity	Height	Weight	BMI	BSA
66	Male	White	Not Hispanic or Latino	180.34 cm	82.64 kg	25.4	2.0347

Medical history and disease characteristics

Tumor subtype	**Follicular Lymphoma (FL)**
Stage	**IV**
Years since diagnosis	**8**
Prior lines anti-cancer therapy	**8**

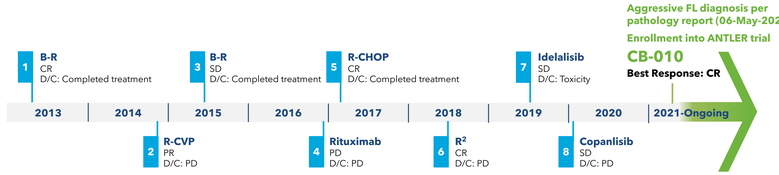
Relevant past medical history:
- *C. difficile* infection (Jan-Feb 2020)
- Acute kidney injury (Sep 2020)
- Varicella zoster virus reactivation (Apr 2021)

Last disease progression observed April 2021 after receiving copanlisib

Aggressive FL diagnosed per pathology report in May 2021 and subsequently enrolled in ANTLER trial with CD19+ disease

BMI: body mass index, BSA: body surface area, CD: cluster of differentiation

8 systemic anti-cancer lines of therapy prior to CB-010

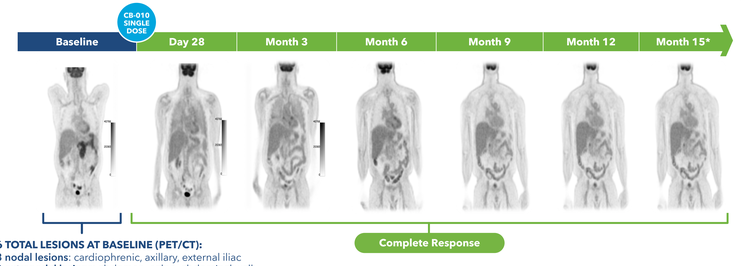


CR: complete response, SD: stable disease, D/C: discontinuation, FL: follicular lymphoma, LoT: lines of therapy, PD: progressive disease, PR: partial response, B-R: bendamustine and rituximab, R²: rituximab and lenalidomide, R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine, and prednisone
Top line is best response, lower line is reason for D/C

Patient timeline on ANTLER trial

CR: complete response *Cyclophosphamide (60 mg/kg/d for 2 days); Fludarabine (25 mg/m²/d for 5 days)

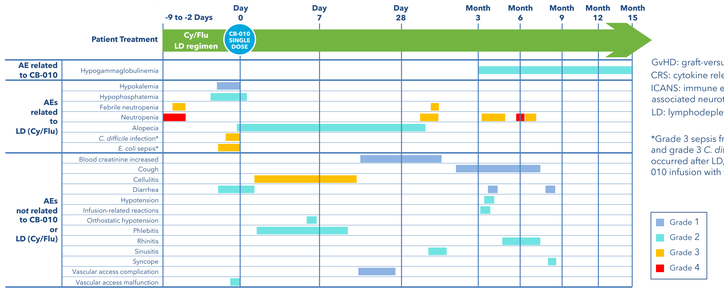
Patient efficacy: CR ongoing through month 15



6 TOTAL LESIONS AT BASELINE (PET/CT):
3 nodal lesions: cardiophrenic, axillary, external iliac
3 extranodal lesions: abdomen, colon, abdominal wall

CR: complete response, CT: computed tomography, PET: positron emission tomography * As of September 1, 2022; Month 15 PET scan was conducted as part of an unscheduled visit

Patient safety: No GvHD, CRS, or ICANS observed



GvHD: graft-versus-host disease
CRS: cytokine release syndrome
ICANS: immune effector cell-associated neurotoxicity syndrome
LD: lymphodepletion

*Grade 3 sepsis from *E. coli* infection and grade 3 *C. difficile* infection occurred after LD, but prior to CB-010 infusion with full recovery

Discussion

- In the ANTLER phase 1 trial, CB-010, an allogeneic CD19-directed CAR-T cell therapy with a PD-1 KO, demonstrated promising safety and efficacy in r/r B-NHL patients at the initial dose level (N=6)
- CB-010 was generally well tolerated
  - One case of Grade 3 ICANS observed that resolved in 39 hours
  - No Grade ≥ 2 CRS observed
  - No GvHD and no Grade 5 AEs observed
- At the initial dose level of 40x10⁶ CAR-T cells, a 100% CR rate (6/6) was observed as best response by the investigator and independent radiologist assessment. At 6 months, 3/6 patients remained in CR
- This case presentation of a heavily pre-treated, aggressive FL patient with POD24 demonstrated that durable CRs are achievable after CB-010 administration
  - This patient remains on trial in CR with a duration of response through **month 15**

AE: adverse event
B-NHL: B-cell non-Hodgkin lymphoma
CAR: chimeric antigen receptor
CD: cluster of differentiation
CR: complete response
CRS: cytokine release syndrome
GvHD: graft-versus-host disease
ICANS: immune effector cell-associated neurotoxicity syndrome
KO: knockout
PD-1: programmed cell death protein 1
PET: positron emission tomography
POD24: progression of disease within 2 years
r/r: relapsed/refractory

Patient enrollment is ongoing at the next dose level of CB-010 at 80x10⁶ CAR-T cells

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