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# Preclinical Analysis of CB-010, an Allogeneic anti-CD19 CAR-T Cell Therapy with a PD-1 Knockout, for the Treatment of Patients with Refractory Systemic Lupus Erythematosus (SLE)

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## BACKGROUND

Autologous CD19-directed CAR-T cell therapy has been shown to effectively target aberrant B cells leading to durable clinical responses in SLE patients (*Müller 2024; Wang 2024*). However, autologous CAR-T cell therapy is characterized by logistical complexities of apheresis and long manufacturing periods, which may be accompanied by extended periods of immunosuppressive washout. CB-010 is an anti-CD19 allogeneic CAR-T cell therapy derived from healthy donor T cells and engineered with a Cas9 CRISPR hybrid RNA-DNA (chRDNA) genome-editing technology. Here we describe CB-010 preclinical data, CB-010 clinical data in lymphoma patients from an ongoing phase 1 clinical trial (ANTLER), and a phase 1 clinical trial design (GALLOP) in lupus nephritis (LN) and extrarenal lupus (ERL) patients.

## WHY CB-010 FOR LUPUS?

- CB-010 is a **readily available** off-the-shelf therapy
- CB-010 uses **FMC63 scFv** with a 4-1BB costimulatory domain
- **Precision genome editing** via chRDNA technology is used in CB-010 to reduce risk of off-target editing
- From clinical data in lymphoma (N=46), **CB-010 was generally well tolerated with encouraging efficacy,** and B cell aplasia was on par with published data

## CB-010 PRECLINICAL RESULTS

### CB-010 demonstrates targeted B cell cytotoxicity in SLE patient-derived co-cultures

- Autoreactive B cells play a pivotal role in the pathogenesis of SLE.
- Therapeutic approaches that target the B cell repertoire are novel strategies being pursued in the field of B cell-dependent autoimmune disease.
- The potential of CB-010 to target and deplete B cells in SLE patient-derived peripheral blood mono-nuclear cell (PBMC) samples was examined.
- Increasing numbers of CB-010 co-cultured with SLE PBMCs demonstrated a concentration-dependent specific lysis of B cells without affecting non-B cell populations.
- **CB-010 exhibited robust targeted B cell cytotoxicity across multiple patient-derived samples *in vitro*.**

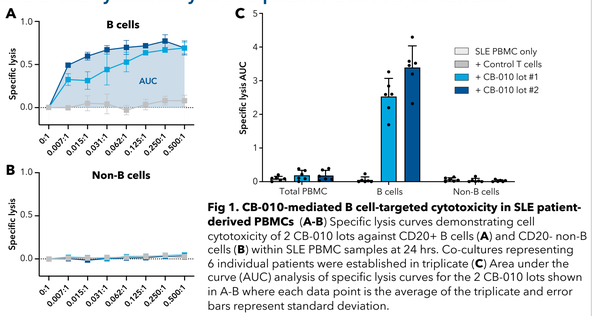
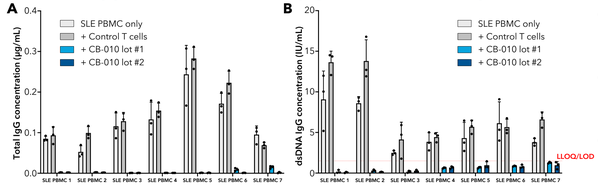



**Fig 1. CB-010-mediated B cell-targeted cytotoxicity in SLE patient-derived PBMCs** (**A-B**) Specific lysis curves demonstrating cell cytotoxicity of 2 CB-010 lots against CD20+ B cells (**A**) and CD20- non-B cells (**B**) within SLE PBMC samples at 24 hrs. Co-cultures representing 6 individual patients were established in triplicate (**C**). Area under the curve (AUC) analysis of specific lysis curves for the 2 CB-010 lots shown in A-B where each data point is the average of the triplicate and error bars represent standard deviation.

### CB-010 suppresses autoantibody generation in SLE patient-derived co-cultures




- The effect of CB-010 activity was examined on the generation of anti-dsDNA auto- antibodies in co-cultures with SLE patient-derived PBMCs.
- Robust depletion of B cells through CB-010 activity was hypothesized to result in suppression of autoantibody generation by pathogenic B cells *in vitro*.
- **CB-010 suppressed total IgG and anti-dsDNA auto-antibody generation by SLE patient-derived PBMCs *in vitro*.**

**Fig 2. CB-010-mediated suppression of total IgG and anti-dsDNA antibody production from SLE patient-derived PBMCs** CB-010 CAR-T cells were co-cultured with SLE patient-derived PBMCs. Co-cultures were established for 7 days in media supplemented with 1µM of the B cell stimulant ODN 2006 (a Class B CpG oligo-nucleotide and TLR9 agonist). Supernatants were subsequently harvested for analysis of total IgG (**A**) or anti-dsDNA IgG by ELISA (**B**). Seven individual patient sample co-cultures were established in triplicate. Each data point represents a single replicate. LLOQ/LOD for Total IgG ELISA 0.008 µg/mL.

## CB-010 PRECLINICAL RESULTS (continued)

### CB-010 treatment specifically targets the B cell compartment in humanized mouse models of hematopoiesis

- B cell depleting activity of CB-010 in murine pharmacological models was examined.
- A humanized hematopoietic system from cord blood-derived CD34+ hematopoietic stems cells (HSCs) in NOG-EXL mice was established.
- When these animals were treated with CB-010, in the absence of lymphodepletion, we observe significant and extended depletion of the B cell compartment. In contrast, non-B cell subsets, including the T cell compartment, remain intact.
- **CB-010 activity specifically promoted extended B cell depletion in humanized mouse models**

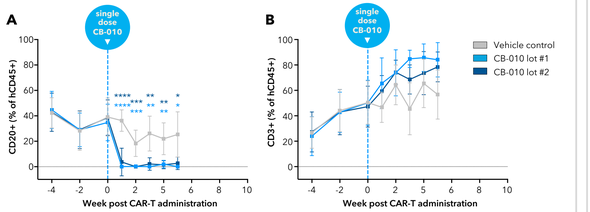



**Fig 3. CB-010-mediated B cell aplasia in humanized mouse models** NOG-EXL mice were engrafted with human CD34+ HSCs via tail vein injection. At 16 weeks post engraftment, animals were dosed intravenously with $1\times10^7$ CB-010 CAR+ T cells per animal. In-life sampling of peripheral blood was analyzed via flow cytometry every two weeks prior to CAR-T administration and every week post CAR-T administration. Human CD19+ cells as a percentage of total human CD45+ cells are plotted indicating B cell dynamics (**A**). Human CD3+ cells as a percentage of total human CD45+ cells are plotted indicating T cell dynamics (**B**). Significance determined by unpaired T test. *p < 0.05, **p< 0.01, ***p < 0.001, ****p< 0.0001.

## DEEP B CELL DEPLETION OBSERVED WITH CB-010 IN LYMPHOMA PATIENTS (ANTLER TRIAL)

### CB-010 treatment results in extended B cell aplasia coupled with rapid recovery of NK and T cells in lymphoma patients

- In the ANTLER trial, an ongoing Phase 1 study of the safety, tolerability, and efficacy of CB-010 in patients with lymphoma, a single dose of CB-010 results in deep depletion of B cells and extended B cell aplasia combined with rapid recovery of NK and T cells following lymphodepletion.
- Following administration, CB-010 specifically targets B cells, resulting in extended B cell aplasia for ~114 days. While, on average, B cells recovered to baseline levels by ~268 days, patient T cells and NK cells rapidly recovered within 3 weeks post lymphodepletion regimen.
- **CB-010 treatment promoted deep B cell depletion with extended B cell aplasia while preserving T cell and NK cell recovery**

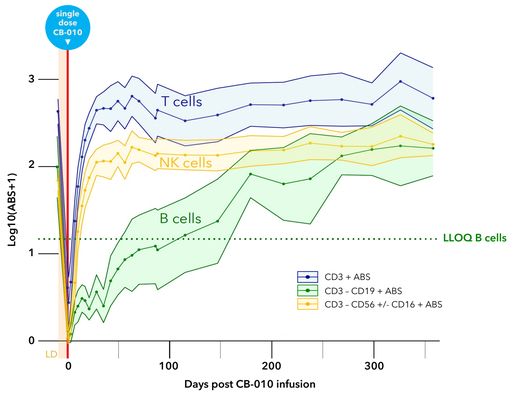



**Fig 4. Impact of CB-010 treatment on the recovery of patient T, B, and NK cells.** Absolute cellular counts determined by flow cytometry using the cell surface markers indicated in the legend. ANTLER Phase 1 clinical trial as of April 1, 2024 cutoff date (N=46). Mean of the data plotted with Standard Error as ribbons.

## CB-010 PARTIAL HLA MATCHING IN LYMPHOMA PATIENTS (ANTLER TRIAL)

### Partial donor-to-patient HLA matching is associated with enhanced expansion and persistence of CB-010 CAR-T cells in lymphoma patients

- In the ANTLER trial, the relationship between the pharmacokinetics of CB-010 CAR-T cells in peripheral blood and the donor-to-patient HLA matching status of patient to drug product were examined in a retrospective analysis.
- A panel of 12 class I and class II alleles were analyzed and used to group patients by having a match of ≥4 alleles, 2-3 alleles, or fewer than 2 alleles.
- **Higher numbers of HLA matched alleles demonstrated more expansion and persistence of CB-010 CAR-T cells**

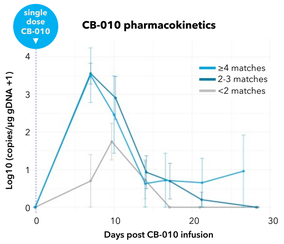



**Fig 5. Partial HLA matching impact on CB-010 PK**
Mean values represented by dots with standard error shown; values below LLOQ converted to 0; visits up to D28 shown; D0 values represent pre-infusion level set to 0. N=35 total number of patients included in PK analysis based on samples analyzed as of data cutoff of April 1, 2024.

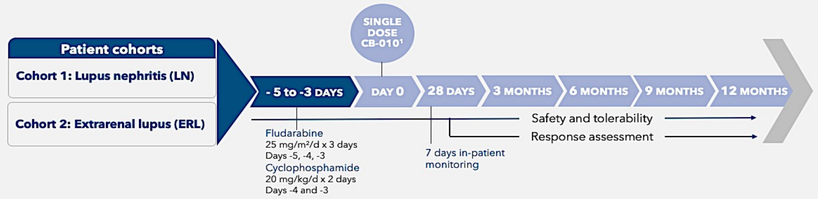
## CB-010 PHASE 1 TRIAL DESIGN IN LUPUS PATIENTS (GALLOP TRIAL)

**Study objectives and treatment**

- Primary endpoint: Safety and tolerability
- Secondary endpoint: Pharmacokinetics
- Exploratory endpoint: Pharmacodynamics and efficacy
- Single dose of CB-010[1] following lymphodepletion

**Eligibility**

- Cohort 1: Class III/IV glomerulonephritis, 24 h uPCR ≥ 0.8 mg/mg
- Cohort 2: SLEDAI-2K ≥ 8
- Refractory to glucocorticoids, and at least 2 immunosuppressive therapies
- Excludes active CNS involvement
- Partial HLA matching and absence of baseline donor-specific antibody (DSAs)




HLA: human leukocyte antigen; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; uPCR: urine protein creatinine ratio
[1] CB-010 dose of $80\times10^6$ CAR-T cells

## CONCLUSIONS

- CB-010 is an off-the-shelf anti-CD19 CAR-T cell therapy with the potential to target autoantibody producing B cells that contribute to pathogenesis of SLE.
- In the ANTLER Phase 1 trial in lymphoma patients, CB-010 led to deep B cell depletion, extended B cell aplasia, and was generally well tolerated with encouraging efficacy (N=46).
- CB-010 will be evaluated in the GALLOP Phase 1 trial for patients with lupus nephritis and extrarenal lupus.



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