

# A first-in-human Phase 1, multicenter, open-label study of CB-012, a next-generation CRISPR-edited allogeneic anti-CLL-1 CAR-T cell therapy for adults with relapsed/refractory acute myeloid leukemia (AMpLify)

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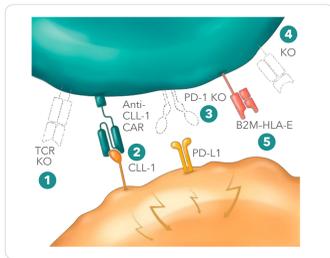
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## Background

- In acute myeloid leukemia (AML), a challenge in the development of CAR-T cell therapies has been the limitation of suitable target antigens since many are also expressed on hematopoietic stem cells and progenitor cells (HSPCs)
- C-type lectin-like molecule-1 (CLL-1) has emerged as an attractive therapeutic target due to its expression on AML mature blasts and leukemic stem cells and its absence on HSPCs<sup>1</sup>
- CB-012 is an allogeneic CAR-T cell therapy that targets CLL-1
- In murine xenograft models of AML, CB-012 significantly reduced tumor burden and increased the survival of mice bearing CLL-1<sup>+</sup> tumors<sup>2</sup>

<sup>1</sup> Daver N, et al. *Leukemia*, 2021;35(7):1843-1863. <https://doi.org/10.1038/s41375-021-01253-x>.  
<sup>2</sup> Francica B, et al. 2024 American Association for Cancer Research Annual Meeting, April 9, 2024; San Diego, CA. Abstract 6323. <https://investor.cariboubio.com/static-files/3066bbc8d-d94f-461a-847d-1d426c76e8f>.

## CB-012: anti-CLL-1 allogeneic CAR-T cell therapy with a PD-1 knockout and immune cloaking



### Armored with 5 genome edits

- TRAC gene knockout (KO)**
  - Eliminates TCR expression, reduces GvHD risk
- Human anti-CLL-1 CAR site-specifically inserted into TRAC gene**
  - Eliminates random integration, targets tumor antigen
- PD-1 KO for enhanced antitumor activity**
  - Potentially better therapeutic index via initial tumor debulking
- B2M gene KO**
  - Reduces HLA class I presentation and T cell-mediated rejection
- B2M-HLA-E-peptide fusion site-specifically inserted into B2M gene**
  - Blunts NK cell-mediated rejection

1<sup>st</sup> CAR-T cell with **checkpoint inhibition and immune cloaking** (PD-1 KO, B2M KO + B2M-HLA-E-peptide fusion) to enter the clinic\*

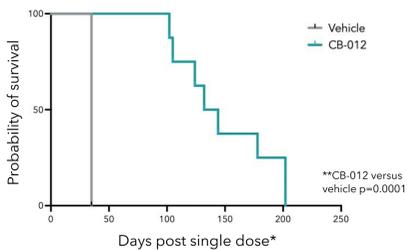
Cas12a chRDNA editing for reduced off-target editing and **enhanced insertion rates**

Potent, fully human **anti-CLL-1 scFv** with a CD28 costimulatory domain

\* To company's knowledge  
<sup>†</sup> Anti-CLL-1-specific scFv exclusively licensed from Memorial Sloan Kettering Cancer Center for allogeneic cell therapies

## CB-012 significantly reduced tumor burden and increased overall survival in preclinical studies

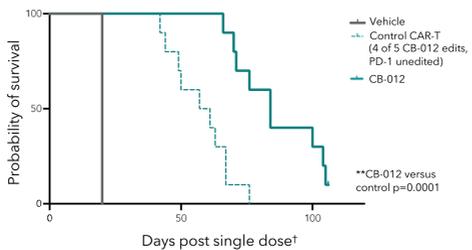
### Overall survival analysis



Single dose of CB-012 **significantly reduced tumor burden** over a longer duration compared to vehicle treatment in an AML xenograft model

\* Orthotopic engraftment of HL-60 CLL-1-expressing AML model in NSG mice  
<sup>†</sup> Orthotopic engraftment of U937 CLL-1- and PD-L1-expressing cell line in NSG mice

### Overall survival analysis



Single dose of CB-012 **significantly reduced tumor burden** over a longer duration compared to control CAR-T cells in an AML xenograft model

## CB-012 AMpLify Phase 1 trial design

### Dose escalation underway

- Patients with r/r AML**
- Relapsed or refractory or MRD+ AML patients who have received 1 to 3 prior lines of therapy
  - Patients with prior allo or auto SCT are allowed
  - Exclusions: prior CAR-T cell therapy and/or CLL-1-targeted therapy

#### Part A: 3+3 dose escalation

- Objective: safety, determine MTD/RDE

#### Part B: dose expansion

- Objective: antitumor response, determine RP2D, safety



NCT06128044

\* Additional follow-up scheduled for months 13-24 at longer intervals

Contact: [clinicaltrials@cariboubio.com](mailto:clinicaltrials@cariboubio.com)

## AMpLify trial objectives

### Dose Escalation (Phase 1, Part A)

#### Primary Objectives:

- Safety and tolerability of CB-012 therapy in patients with r/r AML (de novo or secondary)
- MTD and/or RDE

#### Secondary Objectives:

- PK/PD of CB-012
- Preliminary antitumor activity of CB-012 in patients with r/r or MRD-positive AML

### Dose Expansion (Phase 1, Part B)

#### Primary Objectives:

- Antitumor response of CB-012 in patients with r/r or MRD-positive AML

#### Secondary Objectives:

- Efficacy of CB-012 in patients with r/r or MRD-positive AML
- Safety and tolerability of CB-012 therapy in patients with r/r or MRD-positive AML
- PK/PD of CB-012

## AMpLify key inclusion criteria

- r/r AML that failed standard treatment or MRD-positive AML with lack of effective treatment options plus any of the following criteria:
  - Relapsed AML\*
  - Refractory AML, defined as having not achieved a first CR after 2 cycles of intensive induction chemotherapy<sup>†</sup>
  - MRD-positive AML in CR after prior relapse, regardless of risk criteria\*
  - MRD-positive AML in first CR\*
- Nonproliferative disease
- Suitable candidate for allogeneic SCT with an identified donor
- ≤ 3 prior lines of therapy and ≤ 2 allogeneic SCTs

- ECOG performance status of 0 or 1

#### Clinical laboratory values during screening:

- AST and ALT ≤ 3.0 × ULN
- Total bilirubin ≤ 2.0 × ULN<sup>‡</sup>
- Creatinine clearance ≥ 45 mL/min/1.73 m<sup>2</sup>

\* Per European LeukemiaNet 2022

<sup>†</sup> Such as 7 + 3 or 5 + 2 or similar regimen, 1 cycle of FLAG-Ida or CLIA or CLAG-M or similar purine analogue containing induction, or 2 cycles combining venetoclax with either a hypomethylating agent or low-dose cytarabine

<sup>‡</sup> Except in patients with congenital hyperbilirubinemia (e.g., Gilbert syndrome)

## AMpLify key exclusion criteria

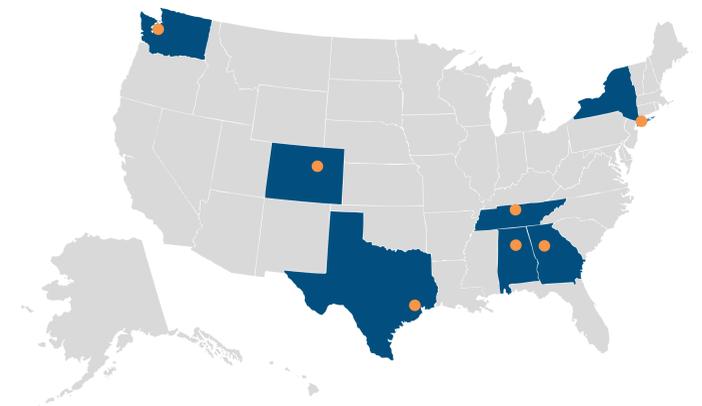
- Prior treatment with CAR-T cell therapy directed at any target
- Prior treatment with any CLL-1-directed agent
- Acute promyelocytic leukemia
- Rapidly progressive disease
- Metabolically inactive or isolated extramedullary disease
- Diagnosed with or treated for invasive malignancy other than AML, except for malignancy treated with curative intent and with no known active disease present for > 1 year before enrollment
- Prior antitumor therapy received within 14 days (some exceptions are allowed)

#### Received any of the following:

- Allogeneic SCT within 100 days before lymphodepletion
- Any drug used for GvHD treatment ≤ 4 weeks before CB-012 infusion
- Donor lymphocyte infusion < 30 days prior to lymphodepletion
- Autologous SCT < 6 weeks before lymphodepletion
- Known active CNS involvement or clinical signs of meningeal involvement
- Clinically significant stroke or seizure < 6 months of signing informed consent form
- Seropositive for HIV; active HBV/HCV infection
- Presence of donor-specific (product-specific) anti-HLA antibodies

## AMpLify participating sites

7 active sites
<b>Alabama</b> University of Alabama at Birmingham
<b>Colorado</b> Colorado Blood Cancer Institute
<b>Georgia</b> Blood & Marrow Transplant Group of Georgia (Northside)
<b>New York</b> Memorial Sloan Kettering Cancer Center
<b>Tennessee</b> TriStar Bone Marrow Transplant
<b>Texas</b> MD Anderson Cancer Center
<b>Washington</b> Fred Hutchinson Cancer Center
<b>Additional sites planned</b>



## AMpLify Phase 1 clinical trial summary

- Allogeneic CAR-T cell therapy is an investigational treatment that may address the unmet needs of r/r AML patients
- CB-012 is an allogeneic anti-CLL-1 CAR-T cell therapy derived from healthy donor T cells and engineered using Cas12a chRDNA technology
- To our knowledge, CB-012 is the first allogeneic CAR-T cell therapy being studied in a clinical trial for r/r AML that is designed to improve antitumor activity through:
  - Checkpoint disruption via PD-1 knockout to reduce T cell exhaustion *and*
  - An immune cloaking strategy with a B2M knockout and insertion of a B2M-HLA-E fusion protein to blunt immune-mediated rejection
- AMpLify is a Phase 1 first-in-human trial investigating the safety and efficacy of CB-012 as a single infusion in patients with r/r AML at clinical sites across the United States

**Patient enrollment is ongoing in dose escalation of the AMpLify trial**

### ABBREVIATIONS

ALT: alanine aminotransferase; AML: acute myeloid leukemia; AST: aspartate aminotransferase; B2M: β2-microglobulin; CAR: chimeric antigen receptor; chRDNA: CRISPR hybrid RNA-DNA; CLAG-M: cladribine, cytarabine, granulocyte colony-stimulating factor, mitoxantrone; CLIA: cladribine, idarubicin, cytarabine; CLL-1: C-type lectin-like molecule-1; CNS: central nervous system; CR: complete remission; ECOG: Eastern Cooperative Oncology Group; FLAG-Ida: fludarabine, cytarabine, granulocyte colony-stimulating factor, idarubicin; GvHD: graft-versus-host disease; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; HSPCs: hematopoietic stem cells and progenitor cells; KO: knockout; MRD: measurable residual disease; MTD: maximum tolerated dose; NK: natural killer; PD: pharmacodynamics; PK: pharmacokinetics; RDE: recommended dose for expansion; RP2D: recommended Phase 2 dose; r/r: relapsed/refractory; SCT: stem cell transplantation; TCR: T cell receptor; ULN: upper limit of normal.

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