Abstract TPS6586

2024 ASCO ANNUAL MEETING

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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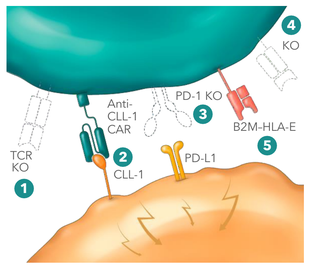
Background

- 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[1]
- 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$^+$ tumors[2]

[1] Daver N, et al. *Leukemia*, 2021;35(7):1843-1863. https://doi.org/10.1038/s41375-021-01253-x.
[2] 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/306bbc8d-d94f-461a-847d-1d426cf76e8f.

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



Armored with 5 genome edits

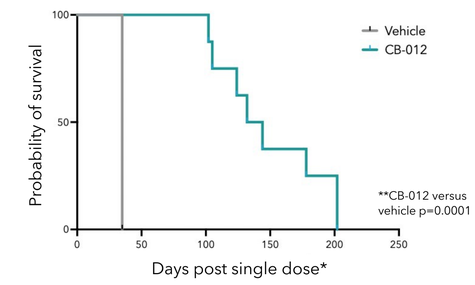
1. ***TRAC* gene knockout (KO)**
   • Eliminates TCR expression, reduces GvHD risk
2. **Human anti-CLL-1 CAR site-specifically inserted into *TRAC* gene**
   • Eliminates random integration, targets tumor antigen
3. **PD-1 KO for enhanced antitumor activity**
   • Potentially better therapeutic index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

- 1st 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
† Anti-CLL-1-specific scFv exclusively licensed from Memorial Sloan Kettering Cancer Center for allogeneic cell therapies

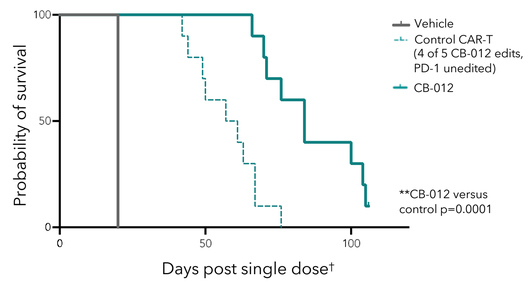
CB-012 significantly reduced tumor burden and increased overall survival in preclinical studies

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

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

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

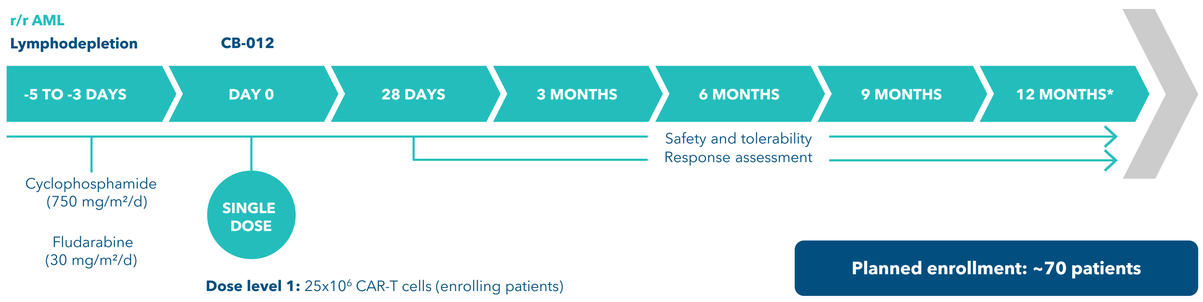
CB-012 AMpLify Phase 1 trial design

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



Dose level 1: 25x10^6 CAR-T cells (enrolling patients)

Planned enrollment: ~70 patients

NCT06128044

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

Contact: 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†
  - 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‡
  - Creatinine clearance ≥ 45 mL/min/1.73 m^2

* Per European LeukemiaNet 2022
† 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
‡ Except in patients with congenital hyperbilirubinemia (e.g., Gilbert syndrome)

AMpLify key exclusion criteria

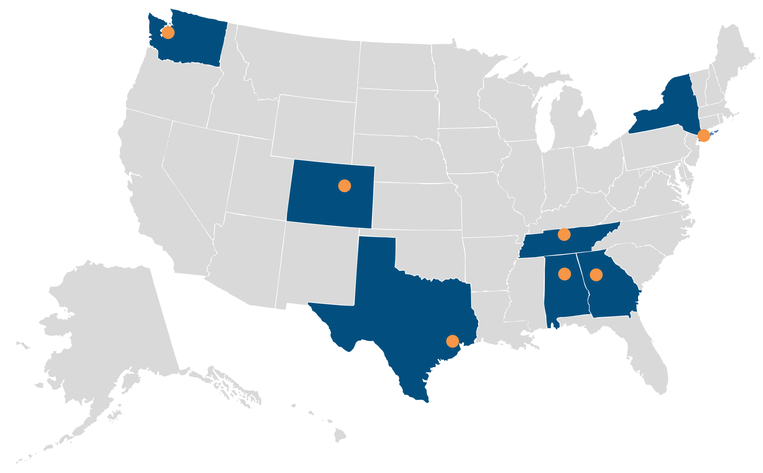
- Prior treatment with CAR-T cell therapy directed at any target
- Prior treatment with any CLL-1–directed agent
- Acute promyelocytic leukemia
- Rapidly progressive disease
- Metabolically inactive or isolated extramedullary disease
- Diagnosed with or treated for invasive malignancy other than AML, 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

Alabama	University of Alabama at Birmingham
Colorado	Colorado Blood Cancer Institute
Georgia	Blood & Marrow Transplant Group of Georgia (Northside)
New York	Memorial Sloan Kettering Cancer Center
Tennessee	TriStar Bone Marrow Transplant
Texas	MD Anderson Cancer Center
Washington	Fred Hutchinson Cancer Center

Additional sites planned



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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