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## RESEARCH ARTICLE

# Chimeric Antigen Receptor T-cell Therapy for Acute Myeloid Leukemia

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## Abstract

Chimeric antigen receptor (CAR) T-cells targeting CD19 have drastically improved the outcomes of B-cell malignancies; however, the success has not yet extended to myeloid malignancies such as acute myeloid leukemia (AML). Main impediments in the development of CAR T therapy in AML include difficulty in identifying appropriate target antigens that are specific to myeloid leukemia stem cells while sparing the healthy hematopoietic stem progenitor cells (HSPCs). Herein, we discuss the current state of CAR T-cell therapy in AML, highlighting recent progress and limitations in clinical translation. We also discuss novel approaches in CAR T therapy development and potential strategies to enhance anti-leukemic activity while minimizing toxicity to healthy cells to make CAR T-cell therapy a viable option for patients with AML.

**Keywords:** CAR T for AML, Refractory AML, AML, Acute Myeloid Leukemia

## 1. Introduction

Acute myeloid leukemia (AML) is characterized by the clonal expansion of immature hematopoietic stem progenitor cells (HSPCs) in the bone marrow that disrupts the maturation and function of normal cells. Patients with AML generally experience an aggressive disease course with high mortality, with allogeneic hematopoietic-cell transplantation (HCT) being the only cure for most patients [1]. Recent advances in donor availability coupled with improvements in HCT modalities have allowed an increasing number of patients with AML to undergo transplant, and more than 3000 patients have received HCT in 2019 in the United States, as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), up from a 1000 patients in 2000 [2]. Although HCT has remained an important treatment option, it is associated with severe side effects such as graft-

versus-host disease (GVHD) and slow immune reconstitution. Additionally, relapse after HCT occurs in approximately 25–50% of patients with a two-year survival rate of <20% [3]. Additional safe and efficacious therapeutic options are greatly needed to improve the clinical outcomes of patients with AML.

Cancer immunotherapy has made significant strides in the treatment of hematologic malignancies (HM) in recent years. Adoptive T-cell therapy using CAR T-cells targeting CD19 have demonstrated remarkable success in the treatment of B-cell acute lymphoblastic leukemia (B-ALL) and other B-cell malignancies. The first-in-class anti-CD19 CAR T-cell product tisagenlecleucel (tisa-cel) was used in a phase II trial in 75 pediatric and young adult relapsed or refractory B-ALL patients, with 81% of patients achieving a complete remission (CR) at three months and 50% achieving event-free survival (EFS) at 12 months [4]. Another anti-CD19 CAR T-cell product, axicabtagene ciloleucel (axi-cel), was

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compared to chemoimmunotherapy followed by autologous stem-cell transplant in an international phase III trial in patients with large B-cell lymphoma refractory to or relapsed after first-line therapy; at a median follow up of 25 months, the overall response rate (ORR) was 83% in the axi-cel group and 50% in the chemoimmunotherapy group, with a 24-month EFS of 41% and 16%, respectively [5].

The successes of CAR T therapy in the treatment of B-cell malignancies have not yet translated to AML, largely due to the lack of a suitable antigen target exclusively expressed on myeloid leukemic blasts. Additionally, while B-cell ablating therapy is clinically tolerated and can be easily corrected via intravenous immunoglobulin infusion, depletion of myeloid cells leads to profound immunosuppression and high infection risk. Thus, creative solutions to overcome these barriers are urgently required to develop effective AML CAR T-cell therapy.

## 2. The current state-of-the-art CAR T therapy in AML

Currently, there are 20 clinical trials evaluating the use of CAR T therapy in AML, with only six trials in the US (Table 1). All trials are in early phases of clinical development. The most common targets for CAR T therapy in AML are CD123, CD33, and CLL1. CD123 and CD33 are present on AML leukemic blasts, although they are also expressed on healthy HSPCs.

### 2.1. Interleukin-3 receptor/CD123

Interleukin-3 receptor subunit alpha (IL-3RA or CD123), is expressed on leukemic blasts in about 80% of AML patients as well as in normal HSPCs and their progeny [6]. Aberrant CD123 expression has been shown to be a reliable marker for monitoring minimal residual disease (MRD) [7] and correlates with poor OS as well as failure to achieve a CR after induction chemotherapy [8]. Conventional CAR T-cells targeting CD123 can lead to durable remissions albeit at the cost of bone marrow aplasia and profound myelosuppression. Thus, patients are generally required to undergo subsequent HCT and must have a stem cell source available to become eligible for clinical trials. In 2015, a phase I clinical trial using a lentivirus-transduced second-generation CAR (autologous or allogeneic CD123CAR-CD28-CD3 $\zeta$ -EGFRt-expressing T lymphocytes) was initiated at the City of Hope in six CD123+ AML patients, all of whom had relapsed after HCT (*clinicaltrials.gov identifier*: NCT02159495).

Patients received lymphodepleting therapy consisting of cyclophosphamide and fludarabine followed by CAR T-cell infusion. Although final results have not been published, preliminary results suggested that two of those patients had achieved a CR with bridge to second HCT, one patient continued to remain in MRD-negative remission with good engraftment and 100% donor chimerism at 5.4 months post infusion [9]. Two additional patients had blast reduction. All toxicities were manageable and there were no dose-limiting toxicities.

In an attempt to avoid complete myeloablation and mitigate other side effects, researchers at the University of Pennsylvania developed sequential infusions of “biodegradable T cells” that were incorporated with anti-CD123 CAR to diminish CAR T-cell persistence *in vivo* and reduce the risk of myeloablation (*clinicaltrials.gov identifier*: NCT02623582). Five patients with relapsed AML received the RNA CART123 product. Unfortunately, although there was a biological effect as manifested by fever and cytokine release syndrome (CRS) in all patients, CD123+ leukemic blasts persisted in the bone marrow and all patients had disease progression within one month post CAR T-cell infusion [10]. Additional efforts employing lentivirus-transduced CART123 followed by CAR T-cell depletion with alemtuzumab and a rescue HCT are currently underway.

### 2.2. Myeloid lineage cell surface antigen CD33

CD33 is highly expressed on myeloid lineage including myeloid progenitors and mature myeloid cells [11]. Gemtuzumab ozogamicin is an anti CD33 indicated for the treatment of AML. A CD33-CAR T construct using CD28 costimulatory domain was found to exert potent inhibition of leukemia proliferation in AML cell line in patient-derived xenograft models [12]. Based on results of this study, a clinical grade lentivirus-transduced CD33-redirected CAR T-cells therapy is currently ongoing in a phase I/II clinical trial for children and young adults with relapsed/refractory (R/R) AML at multiple locations across the United States (*clinicaltrials.gov identifier*: NCT03971799). It is expected that treatment will induce profound myeloablation such that a rescue HCT will be necessary to restore normal hematopoiesis.

### 2.3. C-type lectin-like molecule-1/CLL1

C-type lectin-like molecule-1, also known as CLL1, is an ideal candidate for AML CAR T-cell therapy as it is highly expressed on leukemic stem cells while being absent on granulocyte-

Table 1. Current clinical trials of chimeric antigen receptor (CAR) T-cell therapies.

CAR T-cell antigen target	Trial number (status)	Disease subtype (age)	Location	Strategies to mitigate toxicity
Anti-CD123	NCT04678336 (Recruiting)	R/R AML (1–29)	Children's Hospital of Philadelphia, PA, USA	Patients with marrow aplasia at D28 ± 5 undergo allo-SCT; patients must have a stem cell donor available
	NCT02159495 (Recruiting)	R/R AML ( ≥ 12) R/R BPDCN ( ≥ 12)	City of Hope Medical Center, California, USA	Using truncated EGFR in CAR construct to eliminate persistence of CAR T-cells; patients must have a stem cell source available
	NCT03190278 (Recruiting)	R/R AML (18–65)	Multiple locations in the USA	T-cell receptor knockout to reduce risk of GVHD; patients must have a stem cell source available
	NCT03766126 (Active, not recruiting)	R/R AML ( ≥ 18)	University of Pennsylvania, PA, USA	Fractionated dosing; patients with marrow aplasia at D28 ± 5 undergo allo-SCT; must have a stem cell donor available
	NCT04230265 (Recruiting)	R/R AML ( ≥ 18)	Universitätsklinikum Carl Gustav Carus Dresden, Sachsen, Germany (multiple locations)	Combination of a universal CAR T-cell with a recombinant anti-body derivative (TM123)
	NCT04014881 (Recruiting) NCT03556982 (Unknown)	R/R AML (18–70) R/R AML (14–75)	Wuhan Union Hospital, China The Affiliated Hospital of the Chinese Academy of Military Medical Sciences, Beijing, China	Escalated dosing Not stated
	NCT03114670 (Unknown)	AML relapsed after allo-SCT ( ≥ 18)	Affiliated Hospital to Academy of Military Medical Sciences, Beijing, China	Not stated
	NCT03796390 (Unknown)	R/R AML (2–65)	Hebei Senlang Biotechnology Inc., Ltd., Hebei, China	Not stated
Anti-CD123/CLL1	NCT03631576 (Unknown)	R/R AML (<70)	Fujian Medical University, Fujian, China	Not stated
Anti-CD33	NCT03971799 (Recruiting)	R/R AML (1–35)	Multiple locations in the USA	Escalated dosing; patients proceed to allo-SCT or alternative therapy as clinically applicable
	NCT01864902 (Unknown)	R/R AML (5–90)	Chinese PLA General Hospital, Beijing, China	Not stated
	NCT02799680 (Unknown)	R/R AML (>50)	The Affiliated Hospital of the Chinese Academy of Military Medical Sciences, Beijing, China	Not stated
Anti-CLL1	NCT04789408 (Recruiting)	R/R or secondary AML ( ≥ 18)	Multiple locations in the USA	Escalated dosing; patients must have a stem cell donor available for potential allo-SCT
	NCT04884984 (Recruiting)	R/R AML (6–65)	The First Affiliated Hospital of Soochow University, Suzhou, China	Escalated dosing
	NCT04923919 (Recruiting)	R/R AML (2–75)	920th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Kunming, Yunnan, China	Not stated

(continued on next page)

Table 1. (continued)

CAR T-cell antigen target	Trial number (status)	Disease subtype (age)	Location	Strategies to mitigate toxicity
Anti-CD38	NCT04351022 (Recruiting)	R/R AML (6–65)	The First Affiliated Hospital of Soochow University, Suzhou, China	Escalated dosing
Anti-CD19	NCT03896854 (Unknown)	R/R AML (6–65)	The First Affiliated Hospital of Soochow University, Suzhou, China	Escalated dosing
Anti-FLT3	NCT05023707 (Recruiting)	R/R AML (16–65)	The First Affiliated Hospital of Soochow University, Suzhou, China	Not stated
Anti-CD276	NCT04692948 (Recruiting)	R/R AML (18–70)	Anhui Provincial Hospital, Hefei, Anhui, China	Not stated

Information abstracted from [www.clinicaltrials.gov](http://www.clinicaltrials.gov) using search terms “acute myeloid leukemia” and “CAR T” on 2/10/2022. R/R AML: relapsed/refractory acute myeloid leukemia; BPD/CN: blastic plasmacytoid dendritic cell neoplasm; allo-SCT: allogeneic hematopoietic-cell transplantation; EGFRt: truncated epidermal growth factor receptor; mAb: monoclonal antibody; TCR: T-cell receptor; KO: knockout; GVHD: graft-versus-host-disease; TM: target molecule.

macrophage progenitors [13]. CLL1-specific CAR in combination with 4-1BB and CD28 signaling domains have been developed with strong anti-leukemic activity in a patient-derived xenograft model of AML. Although CLL1+ myeloid progenitor cells and mature myeloid cells were eliminated by CLL-1 CAR T-cells, normal HSPCs were spared, allowing full myeloid recovery once CAR T activity diminishes [14]. An autologous, gene-edited CAR T-cell therapy that targets CLL-1 recently began accruing R/R *de novo* or secondary AML patients at multiple locations across the United States (*clinicaltrials.gov* identifier: NCT04789408).

#### 2.4. CD38

CD38 is another candidate antigen target as it is expressed on most AML and multiple myeloma cells, but not on normal HSPCs. A clinical trial using anti-CD38 CAR T-cells in six AML patients who relapsed after HCT was recently published (*clinicaltrials.gov* identifier: NCT04351022), where four patients achieved a CR or CR with incomplete count recovery (CRi) and full donor chimerism at four weeks after initial infusion. Remission lasted for a median of 6.4 (range 3.9–8.7) months, with median OS of 7.9 months for this small cohort. One patient relapsed 3.9 months after the first anti-CD38 CAR T-cell infusion but achieved remission after repeated CAR T-cell treatment. All patients experienced clinically manageable side effects, with grade I-II CRS in most of the patients [15].

### 3. Novel approaches of CAR T-cell therapy in AML

A number of other immunotherapeutic strategies have been developed in AML including targeting natural killer group 2D (NKG2D) ligands, compound CARs targeting dual antigen targets, rapidly switchable CARs, recombinant bispecific CARs, and utilizing genetically modified allografts followed by CAR T-cell therapy.

#### 3.1. NKG2D-CAR T-cell therapy

NKG2D ligands represent a promising target in AML therapy as they are widely expressed in a wide range of malignancies but absent or poorly expressed on healthy cells. Researchers at the Dana-Farber Cancer Institute conducted a phase I study to evaluate the safety and tolerability of NKG2D-CAR in patients with AML and other HM [16]. Seven patients with R/R AML were recruited. There were no objective tumor responses observed at low cell dose with limited persistence of the CART



population; however, there was an improvement in hematologic parameters in one of two subjects at higher dose levels. Additionally, the NKG2D-CAR killing activity can be further enhanced via pharmacologic histone deacetylase (HDAC) inhibition without affecting healthy cells [17]. This study showed that NKG2D-CAR T-cell therapy combined with HDAC-inhibitors represents a potential approach to achieve anti-leukemic efficacy in AML.

### 3.2. Compound CARs targeting dual antigen targets

A dual anti-CLL CAR linked to an anti-CD33 CAR on the surface of a T-cell was developed and tested in multiple AML cell lines with potent anti-leukemic activity. This compound was tested in a first-in-human phase I dose escalation study in R/R AML patients [18]. One patient achieved MRD-negative CR on day 19 post CAR T-cell infusion with total myeloid ablation in the bone marrow and subsequently underwent non-myeloablative HCT. Results for other patients enrolled in this clinical trial have not been reported.

### 3.3. Universal, rapidly switchable CAR T-cell therapy

A novel rapidly switchable 2-component, next-generation CAR T-cell product using a universal CAR T-cell in combination with a recombinant antibody derivative called targeting module directed against CD123 (TM123), was developed and used to treat three R/R AML patients in a phase 1 trial (*clinicaltrials.gov* identifier: NCT04230265) with encouraging early results [19]. Two patients achieved a CRi and one patient had partial remission (PR) as the best response. The half-life of TM123 is no more than 30 minutes, thereby eliminating potential toxicity associated with persistence of CAR T-cells and obviating the need for subsequent HCT, but does require continuous intravenous infusion for 24 days and repeated administration. There were no dose-limiting toxicities and the adverse events were generally mild.

### 3.4. Recombinant bispecific and split CAR

Researchers at the University of Pennsylvania developed a system to identify tumor-specific antibodies to preferentially bind specific target antigens that are highly expressed in AML cells, thereby eliminating leukemic cells in preclinical models [20]. A bispecific CAR targeting both CD13 and TIM3 was developed to effectively eradicate CD13 + TIM3+ leukemic cells, while reducing the

impact on CD13+ healthy normal cells. This enables targeting of previously unrecognized surface antigens, which expands the ability to generate functional CARs in AML and other cancers [21]. This approach is yet to be tested in clinical trials but represents a highly attractive approach to harness the immunotherapeutic power of T-cell therapy while sparing the toxicities to normal HSPCs and myeloid progenitors.

### 3.5. Genetic inactivation of CD33 in HSPCs

Since targeting tumor-specific antigens is a major hurdle to the development of CAR T-cell therapy for AML, it may be possible to avoid destruction of normal hematopoiesis by deleting certain antigens from the normal HSPCs and enabling the CAR T-cells to specifically target leukemic cells. Indeed, one study showed that autologous CD33 knockout (KO) bone marrow transplantation in animal models was resistant to CD33+ CAR T-cells and enabled anti-tumor activity while sparing the normal cells [22]. Additionally, CD33-deficient myeloid cells were fully functional, suggesting CD33 may not be essential for normal cellular function and development. However, occult functional deficits in CD33 KO myeloid cells cannot be excluded, thus the clinical implications of translating this approach to humans are not yet clear.

## 4. Conclusions

Results from ongoing trials in CAR T-cell therapy are eagerly awaited and will be crucial for understanding the role of this treatment option in the management of AML patients. Continued progress in identifying novel immunotherapeutic targets as well as gene-modifying approaches appears to be a promising strategy in preclinical models, although its extensibility to humans remains limited. Safe and tolerable CAR T-cells without significant toxicity such as those of myeloablation are urgently needed. Together with established HCT, CAR T-cell therapy has the potential to change therapeutic outcomes of patients with AML.

### Conflict of interest

The authors declare no conflict of interest with the contents of the manuscript.

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