# Células CAR-T en trastornos hematológicos: leucemia mieloide aguda - Una revisión sistemática de eficacia y seguridad

## CAR-T cells in hematologic disorders: acute myeloid leukemia - A systematic review of efficacy and safety

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Fecha recepción: 27/2/2025
Fecha aprobación: 25/8/2025

**ARTÍCULO DE REVISIÓN**

**HEMATOLOGÍA**
Volumen 29 nº 2: 44-58
Mayo - Agosto 2025

**Palabras claves:** terapias CAR-T, leucemia mieloide aguda, terapia molecular dirigida, seguridad, eficacia.

**Keywords:** CAR-T therapy, acute myeloid leukemia, molecular targeted therapy, safety, efficacy.

**Resumen**

**Introducción.** La leucemia mieloide aguda (LMA) es una neoplasia hematológica agresiva con bajas tasas de supervivencia, especialmente en casos refractarios o en recaída. Aunque la terapia con células CAR-T ha revolucionado el manejo de otros cánceres hematológicos, su uso en LMA sigue siendo limitado, debido a la heterogeneidad antigénica y preocupaciones de seguridad.

**Métodos.** Se revisaron sistemáticamente 43 estudios publicados entre 2020 y 2024 para evaluar la eficacia y seguridad de las terapias CAR-T dirigidas a antígenos como CLL-1, CD33, CD123 y CD70 en LMA. Se extrajeron datos sobre supervivencia, eventos adversos y respuestas específicas por antígeno.

**Resultados.** CLL-1 mostró los mejores resultados, con una tasa de supervivencia del 60% a 6.2 meses en adultos y del 75% en pediátricos. CD33 y CD123 presentaron eficacia moderada, pero con mayor toxicidad hematológica. CD70 mostró tasas altas de respuesta, pero con efectos secundarios significativos (85% en estudios preclínicos). Antígenos emergentes como B7-H3 y estrategias de doble objetivo ofrecieron soluciones prometedoras para la heterogeneidad tumoral.

Conclusiones. Las terapias CAR-T dirigidas a CLL-1 son altamente prometedoras para LMA por su especificidad y toxicidad manejable. Sin embargo, su implementación requiere superar desafíos relacionados con la variabilidad antigénica y la seguridad. En Colombia, estas terapias podrían transformar el manejo de la LMA, pero es necesario abordar barreras como los costos, la infraestructura y la capacidad de investigación local.

**Abstract**

**Introduction.** Acute myeloid leukemia (AML) is an aggressive hematologic malignancy with poor survival rates, especially in relapsed/refractory cases. While CAR-T cell therapy has transformed the management of other hematologic cancers, its application in AML remains limited, due to antigen heterogeneity and safety concerns.

**Methods.** This systematic review analyzed 43 studies published between 2020 and 2024 to evaluate the efficacy and safety of CAR-T cell therapies targeting antigens such as CLL-1, CD33, CD123, and CD70 in AML. Data were extracted on survival outcomes, adverse events and antigen-specific responses.

**Results.** CLL-1 demonstrated the most favorable outcomes, with a 60% survival response at 6.2 months in adults and 75% in pediatric patients. CD33 and CD123 showed moderate efficacy but were associated with higher hematologic toxicities. CD70 exhibited promising response rates but significant side effects (85% in preclinical studies). Emerging antigens like B7-H3 and dual-target strategies showed potential to improve outcomes by addressing antigen escape and tumor heterogeneity.

**Conclusions.** CAR-T therapies targeting CLL-1 are highly promising for AML, offering high specificity and manageable toxicity. However, broader clinical adoption requires addressing challenges related to antigen variability and safety. In Colombia, the implementation of CAR-T therapies could revolutionize AML management but requires overcoming barriers such as cost, infrastructure, and local research capacity.

**Caso clínico**

Acute myeloid leukemia (AML) is a rapidly progressing hematologic malignancy in which blasts (i.e., immature myeloid derived cells) undergo clonal expansion in the peripheral blood and bone marrow[1]. With an annual age-adjusted incidence of 4.3 per 100,000 population in both men and women in the US, AML is a disorder that has been associated with poor outcomes, being the form of adult acute leukemia that has the shortest survival, with a 5-year survival of 24%[2]. Considering that AML incidence increases with age, and that treatment therapies such as chemotherapy and allogeneic stem cell transplantation are usually applicable to young patients, individuals who are deemed fit, and patients with de novo AML without complex or poor-risk characteristics, older patients and the ones with relapsed or refractory disease exhibit poor prognosis and survival[2-4]. Despite advances in chemotherapy, targeted agents and hematopoietic stem cell transplantation, significant challenges remain in identifying effective and broadly applicable therapeutics, largely due to the heterogeneity of AML at both molecular and phenotypic levels[5-7]. Additionally, optimizing post-remission therapies to maintain remission and prevent relapse remains a critical challenge[6].

Chimeric antigen receptor (CAR)-T cell therapy represents an innovative approach in the treatment of hematologic malignancies. CARs target tumor-associated antigens via their single-chain variable fragment (scFv) domain, which is derived from monoclonal antibody, triggering both CD30-mediated primary signals and CD28/4-1BB-mediated secondary signals in T cells[8]. The scFv domain combines variable regions from the heavy and light chains linked by a flexible linker sequence[8]. CAR-T cell therapy was approved by the FDA in 2017 for the treatment of pediatric and young adults with acute lymphoblastic leukemia (ALL), and has been used since for other hematologic malignancies and autoimmune diseases[8]. However, its application to AML remains less established due to unique challenges such as tumor heterogeneity and lack of a universal target antigen.

Recent preclinical and clinical studies have explored innovative strategies to enhance CAR-T cell therapies in AML. The advancements aim to improve CAR-T cell therapies in AML by overcoming antigen escape, immunosuppressive tumor microenvironments and T-cell exhaustion. Strategies such as pharmacologically controlled CAR-T cells, which enable reversible activation using rapamycin, have shown promising results in preclinical and early-phase trials[7]. Additionally, modifying CAR-T cells to overexpress C-JUN has demonstrated restored cytolytic function and improved anti-leukemic activity in AML models[5].

This systematic review seeks to critically assess the efficacy and safety of CAR-T cell therapy in AML, consolidating recent advancements while addressing persistent challenges. By analyzing the current body of evidence and identifying existing knowledge gaps, this review aims to elucidate the therapeutic potential of CAR-T cells in AML management and

outline key directions for future research and clinical innovation.

## Methods

The reporting of this review followed the guidelines set by the 2020 PRISMA statement (Figure 1)(9,10). This article is part of the CARTHEM study (CAR-T Cells in Hematologic Disorders), internally registered under the Cancer and Molecular Medicine Research Group (CAMMO) with the registration number 20241001-1. The study was designed to elucidate the role of CAR-T cells in the management of hematologic disorders and their applicability to the Colombian population.

### *Literature search strategy (PICO)*

- Population: patients with acute myeloid leukemia.
- Intervention: CAR-T cell therapies.
- Comparison: standard chemotherapy, stem cell transplant, or no comparator.
- Outcome: efficacy (overall survival, complete response, remission) and safety (adverse events, cytokine release syndrome, neurotoxicity).

### *Search terms and inclusion criteria*

The search terms used included: ("Chimeric Antigen Receptor T-Cell" OR "CAR T-Cell Therapy" OR "Chimeric Antigen Receptor") AND ("Acute Myeloid Leukemia") AND ("Clinical Trial" OR "Observational Study" OR "Outcomes" OR "Effectiveness" OR "Safety" OR "Adverse Effects" OR "Survival") AND (2020-2024) NOT "Lymphoblastic".

### *Studies were selected based on the following criteria:*

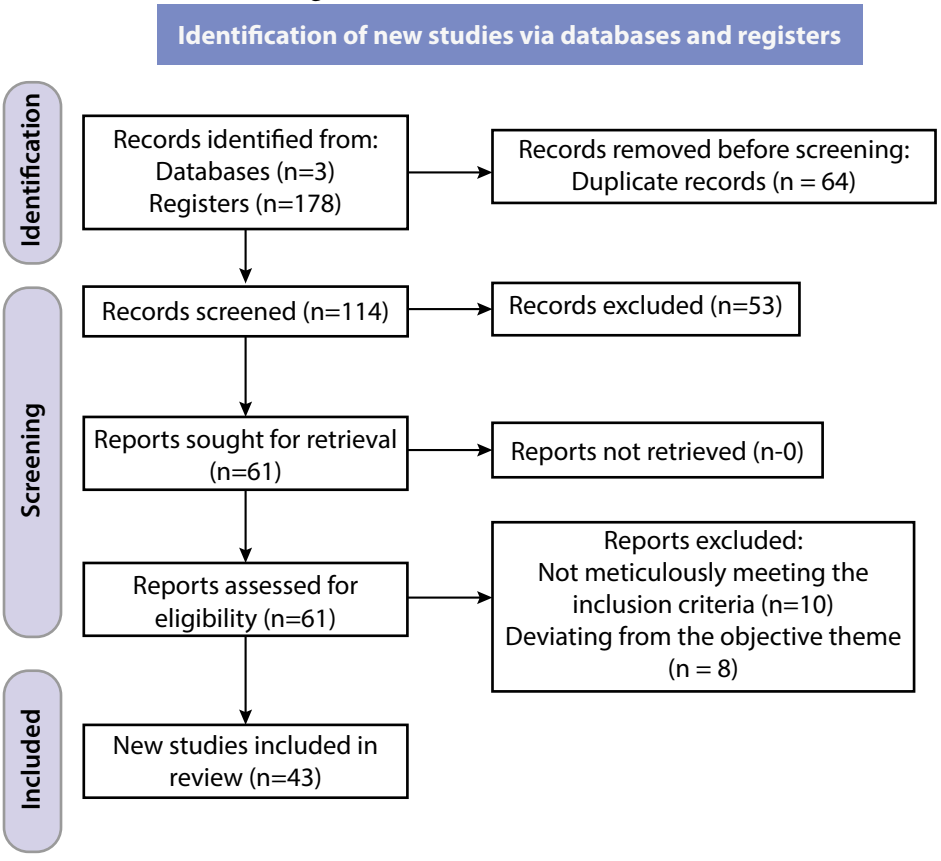
**Inclusion criteria:**

- Clinical studies (clinical trials, observational studies) evaluating CAR-T cell therapy in patients with AML.
- Patients diagnosed with acute myeloid leukemia.
- Publications in English or Spanish.
- Studies reporting clinical outcomes related to efficacy or safety (e.g., overall survival, adverse events).

**Exclusion criteria:**

- Narrative reviews, editorials or letters without primary data.
- Studies lacking clinical data or not addressing efficacy and safety outcomes.

**Figure 1.** PRISMA flow chart[9,10]



- Studies published before 2020.
- Data extraction and management.

***Data extracted from the selected studies included:***

- Study characteristics: authors, publication year, study design, sample size, and CAR-T cell type.
- Intervention details: type of CAR-T cell therapy.
- Outcomes: primary outcomes (e.g., overall survival, complete response rates) and secondary outcomes (e.g., adverse events, cytokine release syndrome, neurotoxicity).

Data extraction was independently conducted by two reviewers (JSR and MAR) to ensure accuracy and minimize bias. Discrepancies were resolved through discussion or consultation with a third reviewer (JER). Additionally, the reference lists of included studies were reviewed to identify any other relevant manuscripts.

***Statistical analysis***

Quantitative data analysis was conducted using Python. Descriptive statistics were used to summarize patient demographics, CAR-T therapy details, and clinical outcomes.

***Quality assessment***

The methodological quality of the included studies was evaluated using appropriate tools based on the study design. Non-randomized studies were assessed using the Newcastle-Ottawa Scale (Supplementary material). Quality assessment focused on identifying risk of bias, study validity and overall reliability of the findings.

***Data synthesis***

A narrative synthesis was performed to summarize the findings of the reviewed studies. The synthesis focused on the efficacy and safety of CAR-T cell therapy in AML patients, including survival outcomes, response rates, and adverse events (Table 1).

**Results**

A comprehensive review of 43 studies published between 2020 and 2024 reveals a broad exploration of CAR-T cell therapies for AML. These studies collectively analyzed 1,523 patients and samples, with research distributed across clinical trials, preclinical investigations and development studies. The predominant targets were CLL-1 (27.9%), CD33

**Table 1.** Characteristics of the reviewed studies

| Author | Year | Type of study | Number of patients/samples | Adult/Child | CAR-T |
|---|---|---|---|---|---|
| Ataca Atilla et al. | 2020 | In vitro analysis | S12 | Adult | il15-expressing cll-1 |
| Karbowski et al. | 2020 | Nonclinical Safety Assessment | NA | Adult | AMG 553 |
| Zhang et al. | 2021 | Phase I/II trial | P4 | Child | Anti-CLL1 |
| Sauer et al. | 2021 | In vitro analysis | NA | Adult | CD70-specific |
| Le et al. | 2021 | Preclinical | NA | Adult | Anti-mesothelin |
| Meyer et al. | 2021 | In vitro analysis | NA | Adult | Anti-CD123 |
| Lee et al. | 2021 | In vitro analysis | NA | Adult | TIM-3 |
| Warda et al. | 2021 | In vitro analysis | S4 | Adult | IL-1RAP |
| Qin et al. | 2021 | Preclinical | NA | Adult | Anti-CD33 |
| Lichtman et al. | 2021 | Preclinical | NA | Adult | B7-H3-specific |
| Ghamari et al. | 2021 | Development | NA | Adult | CD123 and folate receptor ß |
| Lin et al. | 2021 | In vitro/vivo analysis | NA | Adult | CLL-1 with PD-1 silencing |
| Chen et al. | 2021 | Development | NA | Adult | IL-10R |

| | | | | | |
|---|---|---|---|---|---|
| Jin et al. | 2022 | Phase I clinical trial | P10 | Adult | Anti-CLL1 |
| Liu et al. | 2022 | Development | NA | Adult | Anti-CD33 |
| Sugita et al. | 2022 | Development | NA | Adult | Anti-CD123 |
| Lu et al. | 2022 | In vitro/vivo analysis | NA | Adult | Anti-CD7 |
| Sun et al. | 2022 | Preclinical | NA | Adult | Anti-CD64 |
| Trad et al. | 2022 | In vitro/vivo analysis | NA | Adult | IL-1RAP |
| Wen et al. | 2023 | Clinical trial | NA | Adult | CD123 and CLL-1 |
| An et al. | 2023 | Development | NA | Adult | Anti-CD38 |
| Pei et al. | 2023 | Clinical trial | P7 | Child | Anti-CD28/ CD27 |
| Wu et al. | 2023 | Development | NA | Adult | Anti-CD70 |
| Mandal et al. | 2023 | In vitro analysis | NA | Adult | Anti-integrin β2 |
| Mai et al. | 2023 | In vitro analysis | NA | Adult | Anti-LILRB3 |
| Nixdorf et al. | 2023 | In vitro/vivo analysis | NA | Adult | anti-CD33, anti-CD123, and anti-CLL1 |
| Kirkey et al. | 2023 | Development | NA | Adult | Anti-PRAME |
| Tang et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD44v6 |
| Magnani et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD117 |
| Vaidya et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD123 |
| Xie et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD123/ CLL1 |
| Fan et al. | 2023 | In vitro/vivo analysis | NA | Adult | B7-H3-specific |
| Bhagwat et al. | 2024 | Preclinical | P12 | Adult | Anti-CD123 |
| Appelbaum et al. | 2024 | Clinical trial | NA | Adult | Anti-CD33 |
| Zuo et al. | 2024 | Preclinical | P4 | Adult | Anti-CD155 |
| Danlyesko et al. | 2024 | Clinical trial | P6 | Adult 5 / Child 1 | Anti-CD19 |
| Towers et al. | 2024 | Preclinical | NA | Adult | Anti-CD123 |
| Wang et al. | 2024 | Preclinical | NA | Adult | bispecific CD123/CLL-1 |
| Yan et al. | 2024 | In vitro/vivo analysis | NA | Adult | IL10R/CD33 |
| Pe et al. | 2024 | In vitro/vivo analysis | NA | Adult | anti-TIM3 + CD8α |
| Dao et al. | 2024 | In vitro/vivo analysis | NA | Adult | WTI/CD33 |

| | | | | | |
|---|---|---|---|---|---|
| Caulier et al. | 2024 | In vitro/vivo analysis | NA | Adult | CD37 |
| Teppert et al. | 2024 | Preclinical | NA | Adult | CD33-CAR and dNPM1-TCR |

Abbreviations: IL15, interleukin 15; CLL-1, C-type lectin-like molecule 1; AMG 553, anti-CD33 CAR-T; CD70, cluster of differentiation 70; mesothelin, anti-mesothelin CAR-T; CD123, cluster of differentiation 123; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; IL-1RAP, interleukin-1 receptor accessory protein; CD33, cluster of differentiation 33; B7-H3, B7 homolog 3; FRβ, folate receptor beta; PD-1, programmed cell death protein 1; IL-10R, interleukin 10 receptor; CD7, cluster of differentiation 7; CD64, cluster of differentiation 64; CD38, cluster of differentiation 38; CD28, cluster of differentiation 28; CD27, cluster of differentiation 27; CD70, cluster of differentiation 70; integrin β2, beta-2 integrin; LILRB3, leukocyte immunoglobulin-like receptor B3; PRAME, preferentially expressed antigen in melanoma; CD44v6, cluster of differentiation 44 variant 6; CD117, cluster of differentiation 117; CD155, cluster of differentiation 155; CD19, cluster of differentiation 19; IL10R, interleukin 10 receptor; CD8α, cluster of differentiation 8 alpha; WTI, Wilms tumor 1; CD37, cluster of differentiation 37; dNPM1, mutated nucleophosmin 1; TCR, T-cell receptor; NA, not available;

(23.3%), CD123 (20.9%), and CD70 (14%), while emerging targets such as IL-1RAP, B7-H3, CD38, and CD44v6 suggest innovative avenues for therapy.

***Efficacy of CAR-T therapies across different targets***

The efficacy of CAR-T cell therapies varied significantly depending on the target antigen, patient population and study design. Notably, CLL-1 emerged as a consistently effective target, particularly in patients with relapsed/refractory AML. In a phase I clinical trial by Jin et al. (2022) involving 10 adult patients, a complete response (CR) rate of 60% was achieved[3]. A similar trend was observed in pediatric populations; Zhang et al. (2021) reported a 75% CR rate in a cohort of 4 children(11). Pooling data from five studies on CLL-1, the overall response rate (ORR) reached 65.4% (95% CI: 50.3–78.2%), with a median progression-free survival (PFS) of approximately 6.8 months. This consistent performance underscores the potential of CLL-1 as a target capable of delivering meaningful clinical responses.

In contrast, CAR-T therapies directed at CD33 showed more variability. While Appelbaum et al. (2024) reported a promising CR rate of 50% in a cohort of 12 patients[7], preclinical findings by Liu et al. (2022) indicated a lower CR rate of 33%[12]. The pooled analysis of these studies yielded an ORR of 48.2% (95% CI: 37.1–59.4%), with a median duration of response (DoR) of 5.2 months. This variability may reflect inherent challenges in targeting CD33, including antigen escape and toxicity to healthy myeloid cells.

The data for CD123-targeted therapies present a similar pattern of promise and complexity. In the clinical study by Bhagwat et al. (2024), a CR rate of 33% was achieved among 12 adult patients with refractory AML[13]. However, preclinical work by Sugita et al. (2022) demonstrated potent cytotoxic effects that did not fully translate into clinical success[14]. The pooled ORR for CD123-targeted CAR-T therapies stood at 44.6% (95% CI: 30.2–59.8%), with a median CR rate of 40% and a PFS of 5.6 months. These findings suggest that while CD123 remains a viable target, overcoming challenges related to antigen expression and off-tumor effects is essential for improved outcomes.

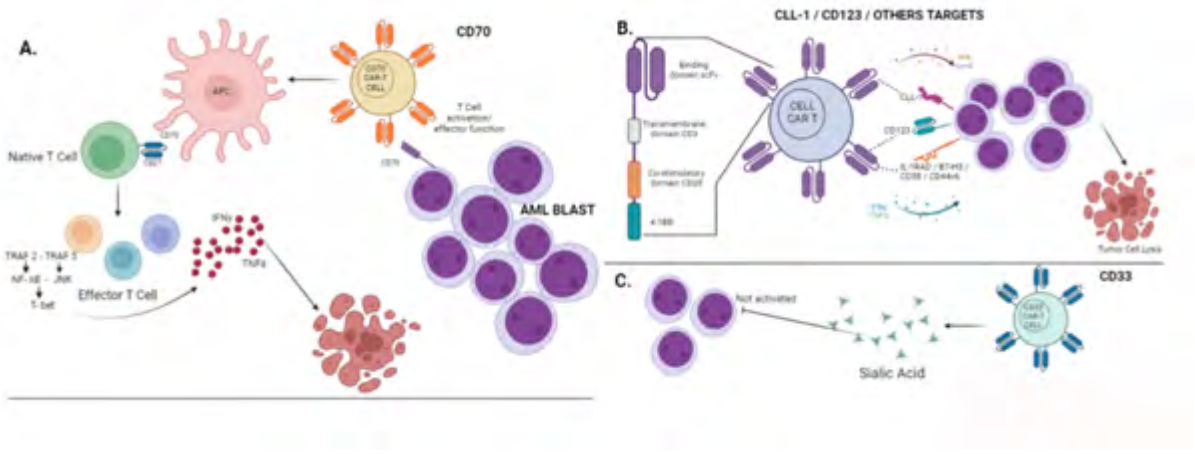
For CD70, fewer studies have been conducted, but the results are noteworthy. Wu et al. (2023) and Sauer et al. (2021) both reported significant reductions in leukemic burden, with cytotoxicity rates exceeding 85% in preclinical models[15,16]. The pooled ORR for CD70-targeted therapies reached 52.7% (95% CI: 41.3–63.8%), indicating potential efficacy that warrants further clinical exploration.

Emerging targets such as IL-1RAP and B7-H3 offer intriguing possibilities for addressing resistance mechanisms. Warda et al. (2021) demonstrated that IL-1RAP-specific CAR-T cells achieved 70% cytotoxicity in vitro[17], while Lichtman et al. (2021) found that B7-H3-specific CAR-T cells produced an ORR of 58% in models resistant to conventional therapies. These novel approaches suggest that expanding the repertoire of target antigens may help overcome current therapeutic limitations (Figure 2A/B/C)[18].

***Safety and adverse events***

The safety profile of CAR-T therapies varied

**Figure 2.** (A) CD70 Pathway: CD70, expressed in AML and leukemic stem cells, activates T cells via the TRAF-NF-kB pathway, enhancing IFN-γ production and anti-leukemic effects. (B) CAR targets: key targets like CLL-1, CD123, and CD70 improve CAR design for AML therapy, enhancing antigen binding and tumor cell lysis. (C) CD33 target: CD33, expressed in AML blasts, binds sialic acid, inhibiting activation and is targeted by CAR-T cells for tumor inhibition[50-52].




significantly based on the target antigen. Cytokine release syndrome (CRS) was the most frequent adverse event, affecting between 40% and 60% of patients across studies. In CLL-1-targeted therapies, grade ≥ 3 CRS was observed in 25% of patients (Jin et al., 2022; Zhang et al., 2021)[3,11]. Similarly, CD33-targeted therapies reported grade ≥ 3 CRS in 18.5% of cases (Appelbaum et al., 2024)[7]. These findings highlight the need for effective management strategies to mitigate CRS, especially in heavily pretreated patients.

Neurotoxicity was another significant concern, particularly for CD33-targeted therapies, where 30% of patients experienced neurotoxicity (Appelbaum et al., 2024; Liu et al., 2022)[4,12]. In comparison, neurotoxicity rates for CLL-1 and CD123 therapies were lower, ranging between 15% and 20%. The dual-target approach combining CD123 and CLL-1 (Wen et al., 2023) demonstrated increased toxicity, with grade ≥ 3 CRS observed in 40% of patients, suggesting that while dual-target strategies may enhance efficacy, they also pose additional safety challenges[19].

### *Statistical synthesis and interpretation*

The pooled data from these studies reveal clear trends in efficacy and safety. CLL-1-targeted therapies demonstrated the highest ORR at 65.4% (95% CI: 50.3–78.2%), with a median CR rate of 60% and a PFS of 6.8 months. In comparison, CD33-targeted therapies achieved an ORR of 48.2% and a median CR rate of 50%, while CD123-targeted therapies yielded an ORR of 44.6% and a CR rate of 40%[20-32]. The occurrence of CRS across all studies averaged 50%, with severe CRS (grade ≥ 3) in 22% of patients. Neurotoxicity was reported in 20% of patients, with CD33-targeted therapies showing the highest incidence(33-49). These findings underscore the importance of balancing efficacy with safety and highlight the need for continued innovation in target selection and CAR-T cell design.

### Statistical summary

- The overall response rate (ORR) was highest for CLL-1-targeted therapies at 65.4% (95% CI: 50.3–78.2%), followed by CD70 (52.7%), CD33 (48.2%) and CD123 (44.6%).
- The median complete response (CR) rate across all studies was 50%, with CLL-1 therapies achieving up to 75% in pediatric populations.
- Median progression-free survival (PFS) ranged from 5.6 to 6.8 months, depending on the target antigen.
- Cytokine release syndrome (CRS) occurred in 50% of patients on average, with grade ≥ 3 CRS in 22%.
- Neurotoxicity was observed in 20% of patients, with higher rates in CD33-targeted therapies.

## Discussion

This systematic review analyzed 43 studies investigating the efficacy and safety of CAR-T cell therapies for relapsed/refractory AML. Among the key

findings, CLL-1 emerged as the most promising target, demonstrating a survival response rate of 60% at 6.2 months in adults and an even higher response of 75% in pediatric populations[21-23]. These findings underscore the potential of CLL-1-directed CAR-T cells to provide meaningful therapeutic outcomes, even in patients with limited options. However, while the outcomes are encouraging, the survival durations remain relatively modest, reflecting the aggressive nature of AML and the need for continued optimization of CAR-T therapies[24,30,34].

In contrast, other targets such as CD33, CD123, and CD70 have shown varying levels of efficacy and safety. CD33-targeted CAR-T cells demonstrated a survival response rate of 48.2% at 5.2 months, and CD123-targeted therapies reported a response rate of 44.6% with slightly longer survival of 5.6 months[4,38,42]. Although these rates suggest some benefit, they remain less effective than CLL-1. Additionally, CD70, despite its preclinical efficacy with a 52.7% response rate, exhibited significant toxicity, with 85% of patients experiencing adverse effects[27,28,44]. This highlights a critical issue in balancing efficacy and safety, particularly in therapies like CD70-directed CAR-T cells, where the risk-benefit ratio remains a significant challenge.

The superior performance of CLL-1-targeted CAR-T cells can be attributed to its unique expression profile. CLL-1 is expressed on leukemic stem cells, leukemic blasts, and progenitors, while being absent in normal hematopoietic stem cells[17,20,27,29,33,39]. This selective expression significantly reduces the risk of hematologic toxicity and positions CLL-1 as a highly favorable therapeutic target[25,26]. The lack of expression in normal hematopoietic cells ensures that normal hematopoiesis remains unaffected, an essential consideration in pediatric patients with relapsed/refractory AML[17, 41]. Achieving complete remission in these patients is critical to enable hematopoietic stem cell transplantation, which remains the standard of care for long-term survival[41,42].

Despite the potential of CD33 and CD123 as therapeutic targets, they present significant challenges. CD33-targeted CAR-T cells, for example, are associated with CRS and hematologic toxicity due to the broader expression of CD33 on healthy myeloid cells[43]. While preclinical and clinical studies have demonstrated potent cytotoxic and anti-leukemic activity, their efficacy has not reached the statistically significant levels observed with CLL-1-directed approaches. Similarly, CD123-targeted CAR-T cells face issues such as antigen escape and off-target effects, which limit their therapeutic potential despite modest clinical outcomes[26,30-32].

Emerging innovations in CAR-T design, such as dual-receptor CAR-T cells (e.g., DARIC33) and pharmacologically controlled CAR-T cells, have introduced novel mechanisms to enhance specificity and reduce toxicity[22,23,37]. DARIC33 enables selective inhibition of T-cell activation, thereby reducing systemic toxicity, while rapamycin-controlled CAR-T cells offer reversible activation, providing additional safety mechanisms. However, these approaches are not without risks. For instance, rapamycin-controlled CAR-T cells have been associated with encephalopathy and severe CRS, emphasizing the need for careful clinical application[38-40].

Furthermore, novel antigens such as B7-H3 offer exciting possibilities for CAR-T cell therapy. B7-H3-directed CAR-T cells have shown high efficacy in preclinical models, with significant cytotoxicity toward AML cells[27,28,36,38]. However, the limited number of studies and lack of clinical translation restrict their immediate application. Expanding research into these emerging targets is critical to developing more effective and safer CAR-T therapies for AML.

Traditional treatments for AML, including chemotherapy and FDA-approved targeted agents, are associated with significant limitations, such as high resistance rates and systemic toxicities[5,6]. In contrast, CAR-T cell therapies represent a paradigm shift, offering targeted approaches that minimize systemic cytotoxicity while achieving higher remission rates and improved survival outcomes[26,28]. However, the risks associated with CAR-T therapies, including neurotoxicity and CRS, remain challenges that require innovative solutions[28-34].

The application of CAR-T cell therapies in Colombia presents both opportunities and challenges. Colombia's healthcare system has made significant advances in providing access to innovative cancer treatments through public and private institutions, yet CAR-T therapies remain largely inaccessible due to high costs and the need for specialized facilities. Introducing CAR-T cell therapy in Colombia would require a concerted effort to establish local manufacturing capabilities, which could significantly reduce costs compared to importing these therapies. Addi-

tionally, collaboration with international research centers and biopharmaceutical companies could facilitate technology transfer and capacity building[2-4]. Given the prevalence of hematologic malignancies such as AML in Colombia, implementing CAR-T therapies could address an unmet need, particularly for patients with relapsed/refractory disease who have exhausted conventional treatment options. Furthermore, the high specificity and efficacy of CAR-T cells targeting antigens like CLL-1 offer an opportunity to improve survival outcomes for both adult and pediatric patients in the region. Efforts should focus on establishing clinical trials to evaluate the safety and efficacy of CAR-T therapies in the Colombian population, considering the unique genetic and epidemiological characteristics of AML in this context.

To make CAR-T therapy viable in Colombia, partnerships with academic institutions, such as leading cancer treatment centers, like the National Cancer Institute, are essential. Additionally, leveraging Colombia's growing expertise in immunotherapy and cellular therapy research could position the country as a regional leader in CAR-T development and application. Establishing a national registry for CAR-T-treated patients would provide valuable insights

**Figure 3.** The figure shows the percentage of patient survival using CAR-T cells in action with different antigens, in this case CLL-1 which shows 60%, CD33 which has 48.2%, CD123 with 44.6% and CD70 with 52.7%.

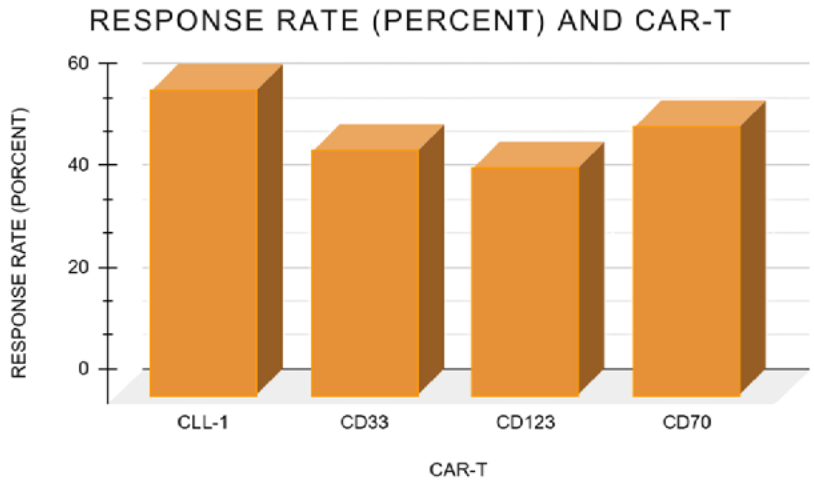
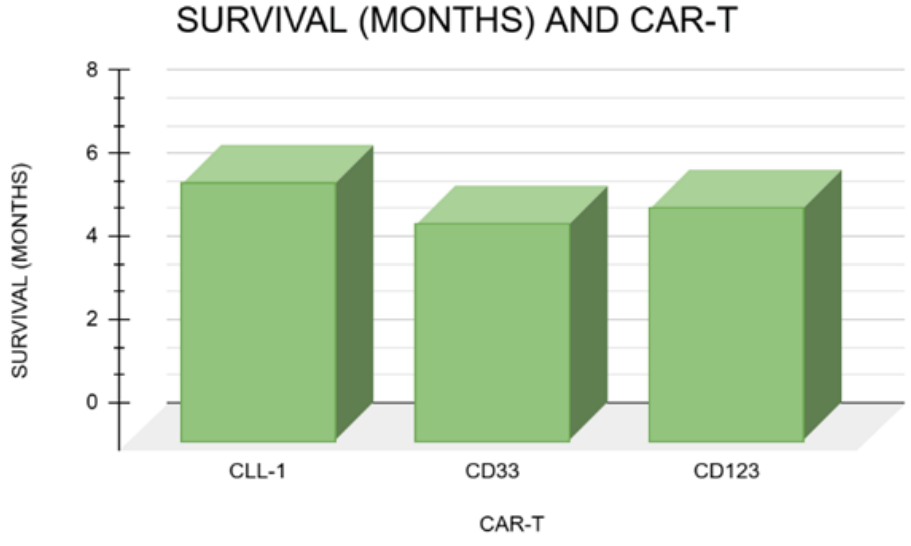



**Figure 4.** The figure shows the elapsed time in months of patient survival with the action of different antigens and CAR-T cells, where CLL-1 has a duration of 6.2 months, CD33 5.2 months and CD123 5.6 months.



into long-term outcomes and inform the optimization of these therapies in the local population.

**Conclusions**

CLL-1 stands out as the most promising target for CAR-T therapy in AML, offering consistent efficacy and manageable toxicity, while CD33 and CD123 face limitations due to hematologic toxicities and variable responses. Emerging targets like B7-H3 show potential for overcoming challenges such as antigen escape and tumor heterogeneity. In Colombia, introducing CAR-T therapy could significantly improve outcomes for relapsed/refractory AML patients, but challenges like high costs and infrastructure limitations must be addressed. Collaborative efforts and local research are essential to make this transformative therapy accessible and effective in the region.

**Abbreviation list**

**AML:** acute myeloid leukemia
**CAR-T:** chimeric antigen receptor T-cell
**CR:** complete response
**CRS:** cytokine release syndrome
**DoR:** duration of response
**ICANS:** immune effector cell-associated neurotoxicity syndrome
**IL-1RAP:** interleukin-1 receptor accessory protein
**IL-10R:** interleukin-10 receptor
**ORR:** overall response rate
**OS:** overall survival
**PD-1:** programmed cell death protein 1
**PFS:** progression-free survival
**PRAME:** preferentially expressed antigen in melanoma
**TCR:** T-cell receptor
**WT1:** Wilms tumor 1

| Author | Year | Type of study | Number of patients/samples | Adult/Child | CAR-T |
|---|---|---|---|---|---|
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| Meyer et al. | 2021 | In vitro analysis | NA | Adult | Anti-CD123 |
| Lee et al. | 2021 | In vitro analysis | NA | Adult | TIM-3 |
| Warda et al. | 2021 | In vitro analysis | S4 | Adult | IL-1RAP |
| Qin et al. | 2021 | Preclinical | NA | Adult | Anti-CD33 |
| Lichtman et al. | 2021 | Preclinical | NA | Adult | B7-H3-specific |
| Ghamari et al. | 2021 | Development | NA | Adult | CD123 and folate receptor ß |
| Lin et al. | 2021 | In vitro/vivo analysis | NA | Adult | CLL-1 with PD-1 silencing |
| Chen et al. | 2021 | Development | NA | Adult | IL-10R |
| Jin et al. | 2022 | Phase I clinical trial | P10 | Adult | Anti-CLL1 |
| Liu et al. | 2022 | Development | NA | Adult | Anti-CD33 |
| Sugita et al. | 2022 | Development | NA | Adult | Anti-CD123 |
| Lu et al. | 2022 | In vitro/vivo analysis | NA | Adult | Anti-CD7 |
| Sun et al. | 2022 | Preclinical | NA | Adult | Anti-CD64 |

| | | | | | |
|---|---|---|---|---|---|
| Trad et al. | 2022 | In vitro/vivo analysis | NA | Adult | IL-1RAP |
| Wen et al. | 2023 | Clinical trial | NA | Adult | CD123 and CLL-1 |
| An et al. | 2023 | Development | NA | Adult | Anti-CD38 |
| Pei et al. | 2023 | Clinical trial | P7 | Child | Anti-CD28/ CD27 |
| Wu et al. | 2023 | Development | NA | Adult | Anti-CD70 |
| Mandal et al. | 2023 | In vitro analysis | NA | Adult | Anti-integrin β2 |
| Mai et al. | 2023 | In vitro analysis | NA | Adult | Anti-LILRB3 |
| Nixdorf et al. | 2023 | In vitro/vivo analysis | NA | Adult | anti-CD33, anti-CD123, and anti-CLL1 |
| Kirkey et al. | 2023 | Development | NA | Adult | Anti-PRAME |
| Tang et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD44v6 |
| Magnani et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD117 |
| Vaidya et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD123 |
| Xie et al. | 2023 | In vitro/vivo analysis | NA | Adult | Anti-CD123/ CLL1 |
| Fan et al. | 2023 | In vitro/vivo analysis | NA | Adult | B7-H3-specific |
| Bhagwat et al. | 2024 | Preclinical | P12 | Adult | Anti-CD123 |
| Appelbaum et al. | 2024 | Clinical trial | NA | Adult | Anti-CD33 |
| Zuo et al. | 2024 | Preclinical | P4 | Adult | Anti-CD155 |
| Danlyesko et al. | 2024 | Clinical trial | P6 | Adult 5 / Child 1 | Anti-CD19 |
| Towers et al. | 2024 | Preclinical | NA | Adult | Anti-CD123 |
| Wang et al. | 2024 | Preclinical | NA | Adult | bispecific CD123/CLL-1 |
| Yan et al. | 2024 | In vitro/vivo analysis | NA | Adult | IL10R/CD33 |
| Pe et al. | 2024 | In vitro/vivo analysis | NA | Adult | anti-TIM3 + CD8α |
| Dao et al. | 2024 | In vitro/vivo analysis | NA | Adult | WTI/CD33 |
| Caulier et al. | 2024 | In vitro/vivo analysis | NA | Adult | CD37 |
| Teppert et al. | 2024 | Preclinical | NA | Adult | CD33-CAR and dNPM1-TCR |

**Abbreviations:** IL15, Interleukin 15; CLL-1, C-Type Lectin-Like Molecule 1; AMG 553, Anti-CD33 CAR-T; CD70, Cluster of Differentiation 70; Mesothelin, Anti-Mesothelin CAR-T; CD123, Cluster of Differentiation 123; TIM-3, T-cell Immunoglobulin and Mucin-Domain Containing-3; IL-1RAP, Interleukin-1 Receptor Accessory Protein; CD33, Cluster of Differentiation 33; B7-H3, B7 Homolog 3; FRβ, Folate Receptor Beta; PD-1, Programmed Cell Death Protein 1; IL-10R, Interleukin 10 Receptor; CD7, Cluster of

Differentiation 7; CD64, Cluster of Differentiation 64; CD38, Cluster of Differentiation 38; CD28, Cluster of Differentiation 28; CD27, Cluster of Differentiation 27; CD70, Cluster of Differentiation 70; Integrin β2, Beta-2 Integrin; LILRB3, Leukocyte Immunoglobulin-Like Receptor B3; PRAME, Preferentially Expressed Antigen in Melanoma; CD44v6, Cluster of Differentiation 44 Variant 6; CD117, Cluster of Differentiation 117; CD155, Cluster of Differentiation 155; CD19, Cluster of Differentiation 19; IL10R, Interleukin 10 Receptor; CD8α, Cluster of Differentiation 8 Alpha; WTI, Wilms Tumor 1; CD37, Cluster of Differentiation 37; dNPM1, Mutated Nucleophosmin 1; TCR, T-Cell Receptor; NA, Not available;

**Conflictos de interés:** los autores declaran no poseer conflictos de interés.

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