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*Review Article*

# Chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL: a systematic review and meta-analysis

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**Abstract:** Objectives: Chronic lymphocytic leukemia (CLL) is a hematologic malignancy characterized by the excessive production of lymphocytes in the bone marrow. One of the emerging therapeutic strategies for CLL is chimeric antigen receptor (CAR) T-cell therapy, wherein T-cells are genetically modified to recognize and target cancer cells more effectively. The present study aims to systematically compare the therapeutic impact of high-dose versus low-dose status of CAR T-cell therapy targeting CD19 (CART-19) in patients with relapsed or refractory CLL. Methods: To identify relevant studies, a comprehensive literature search was conducted in PubMed, Scopus, and Web of Science databases up to April 2023. The primary outcome measures included treatment response rates, assessed as complete response (CR) and partial response (PR), and toxicity, as indicated by the incidence of cytokine release syndrome (CRS). Additionally, sensitivity and bias analyses were performed to evaluate the robustness of the findings. Results: Four randomized controlled trials (RCTs) comprising 89 patients with relapsed or refractory CLL met the inclusion criteria. Comparison of treatment response rates between high-dose and low-dose CART-19 therapy demonstrated a significantly higher complete and partial response rate in the high-dose group (SMD [95% CI]: 1.02 [0.10, 1.94]; P<0.05). However, no significant association was observed between CTL019 dosage and the incidence of CRS (P>0.05). Conclusion: This meta-analysis suggests that high-dose CART-19 is associated with improved response rates and survival outcomes in patients with CLL compared to low-dose therapy. However, due to variability in study results, further large-scale, well-designed trials are required to establish the optimal therapeutic dosing strategy for CART-19 therapy in CLL.

**Keywords:** Chronic lymphocytic leukemia, chimeric antigen receptor, CAR T-cell therapy, CART-19, dose-response relationship, treatment efficacy, toxicity, cytokine release syndrome

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## Introduction

Chronic lymphocytic leukemia (CLL) is the most prevalent leukemia among adults, affecting an estimated 200,000 individuals in the United States, with approximately 4,410 deaths annually. It accounts for 1.1% of all newly diagnosed cancers in the U.S., with a median age at diagnosis of 70 years and a male-to-female ratio of 1.7:1. In 2022, approximately 20,160 new cases of CLL were expected in the U.S. The five-year survival rate is 90%, while the ten-year survival rate is estimated at 82% [1]. The progression of CLL varies significantly, with 70-80% of patients being asymptomatic at diagnosis, and some never requiring treatment. The disease's natural history depends on molecular factors, with time to first treatment ranging from months to decades [2, 3].

CLL is often incidentally diagnosed during routine blood testing, with unexplained lymphocytosis as a hallmark finding. Among symptomatic patients, 50% present with lymphadenopathy, while 20-50% develop splenomegaly or hepatomegaly. Constitutional "B symptoms" such as unintentional weight loss (>10% over 6 months), fever, and night sweats are reported in 5-10% of cases [4]. Additionally, complications include autoimmune hemolytic anemia (≤10%) and immune thrombocytopenia (≤2%). Given its impact on humoral immunity, frequent infections, particularly affecting the respiratory tract, occur in up to 10% of patients [5, 6]. Diagnosis is typically confirmed using peripheral blood flow cytometry, with a requirement of $\geq 5 \times 10^9$/L monoclonal B cells for a definitive CLL diagnosis [7-9].

CLL is characterized by the accumulation of dysfunctional, monoclonal B lymphocytes, which exhibit an aberrant immunophenotype, including CD5, CD23, and CD19 positivity, alongside dim expression of CD20, CD22, and CD79b [10]. A major driver of CLL pathogenesis is the overexpression of B-cell lymphoma 2 (BCL2), which inhibits apoptosis and promotes clonal expansion [11]. The B-cell receptor (BCR) signaling pathway is constitutively active, contributing to proliferation and survival [12, 13]. Immunoglobulin heavy chain variable region (IGHV) mutational status is a critical prognostic factor, with unmutated IGHV (≤2% deviation from germline) being associated with more aggressive disease [14-16]. Additionally, CLL is marked by impaired humoral and cellular immune responses, increasing susceptibility to infections, and reducing vaccine efficacy [17].

First-line treatment for CLL includes Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib or the BCL2 inhibitor named venetoclax [18, 19]. In relapsed or refractory CLL, non-covalent BTK inhibitors such as pirtobrutinib have demonstrated response rates >70%, while phosphoinositide 3-kinase (PI3K) inhibitors, including idelalisib and duvelisib, remain alternative options [20, 21]. Chimeric antigen receptor T-cell (CAR-T) therapy has shown a 45% complete response rate, and allogeneic hematopoietic cell transplantation remains the only curative option [22]. The status of CAR T-cell therapy targeting CD19 (CART-19) in CLL remains an area of ongoing investigation, with emerging data on its efficacy yet to be fully established.

CART-19 therapy is an advanced immunotherapeutic approach in which T-cells are genetically modified to enhance their ability to recognize and eliminate cancer cells. Recent studies indicate that CAR T-cell therapy demonstrates superior efficacy compared to conventional treatments previously utilized [23]. This therapy functions similarly to an active drug, meaning that rather than acting solely at a localized target, CAR T-cells actively seek out, bind to, and eliminate cancer cells [24].

While CART-19 therapy has shown promise in CLL, determining the optimal dosage remains a challenge. Higher doses may enhance antitumor activity but are associated with increased toxicity, particularly cytokine release syndrome (CRS) and neurotoxicity. Conversely, lower doses may reduce these risks but could compromise therapeutic efficacy. Given the lack of a standardized dosing protocol, this systematic review and meta-analysis aim to provide the first comprehensive comparison of high-dose versus low-dose CART-19 in relapsed and refractory CLL, evaluating both treatment response and safety outcomes.

## Material and method

### *Study aim and design*

This study aims to evaluate the efficacy of high-dose versus low-dose CART-19 in patients with

**Table 1.** The search strategy of the included databases

| Database | Search strategy | Additional filters |
|---|---|---|
| PubMed | ((“Receptors, Chimeric Antigen”[Mesh]) OR (“Receptors, Antigen, T-Cell”[Mesh])) AND (“Antigens, CD19”[Mesh]) AND (“Leukemia, Lymphocytic, Chronic, B-Cell”[Mesh]) | English, April 28th, 2023 |
| Scopus | (TITLE-ABS-KEY(Chimeric antigen receptor-modified t-cells)) AND (TITLE-ABS-KEY(CD19)) AND ((TITLE-ABS-KEY(CLL) OR TITLE-ABS-KEY(Chronic lymphocytic leukemia))) | English, April 28th, 2023 |
| Web of Science | 1: chimeric Antigen receptor-modified T-cell (All Fields)<br>2: CD19 (All Fields)<br>3: CLL (All Fields) OR Chronic lymphocytic leukemia (All Fields)<br>4: #1 AND #2 AND #3<br>5: #1 AND #2 AND #3<br>6: #1 AND #2 AND #3 | English, April 30th, 2023 |

relapsed or refractory CLL. A standardized checklist was used to guide the study design, screening process, and data selection. The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor. The research protocol was registered on the Open Science Framework (OSF) and can be accessed at https://osf.io/j5d9x.

*Search strategy*

A systematic literature search was performed across PubMed, Scopus, and Web of Science up to April 2023. Advanced search techniques, including Boolean operators and database-specific tags, were applied to refine search results (**Table 1**). The search strategy incorporated key terms related to chimeric antigen receptor (CAR) T-cell therapy, CD19, chronic lymphocytic leukemia (CLL), B-cell malignancies, and immunotherapy to ensure comprehensive coverage of relevant literature. The selection process was conducted in two phases: (1) Study retrieval, where potentially relevant studies were identified based on titles, abstracts, and keywords, and (2) Screening and selection, in which three independent reviewers assessed the titles and abstracts after duplicate removal. Studies meeting the inclusion criteria were shortlisted for full-text review and final inclusion in the analysis.

*Inclusion and exclusion criteria*

Studies were eligible for inclusion if they included observational and interventional studies that examined the response to CART-19 therapy in relapsed or refractory CLL patients, comparing high-dose versus low-dose administration. Exclusion criteria included review articles, case reports, case series, letters to the editor, and conference abstracts or posters, as these did not provide primary data relevant to treatment efficacy.

*Quality assessment*

The methodological quality of the included studies was assessed using the critical appraisal checklist provided by the Joanna Briggs Institute (JBI) (https://jbi.global/critical-appraisal-tools) (**Figure 2**). Full-text articles meeting the inclusion criteria were independently reviewed for quality by two researchers (M.R & R.K). Any disagreements with the reviewer were resolved through discussion to reach a consensus (M.A.K). A standardized data extraction sheet was then developed to systematically collect relevant study details, including authors’ names, study location, study design, sample size, participant demographics (age and gender), treatment protocols, follow-up duration, and key outcomes related to treatment response and toxicity.

*Statistical analysis*

This meta-analysis evaluated the efficacy of high-dose versus low-dose CART-19 in patients with relapsed or refractory CLL. Data analysis was conducted using Stata version 13.1 (Stata Corp, College Station, TX, USA). The results were reported as standardized mean difference (SMD) with 95% confidence intervals (CI) and visualized in a forest plot. Heterogeneity among studies was assessed using the $I^2$ sta-

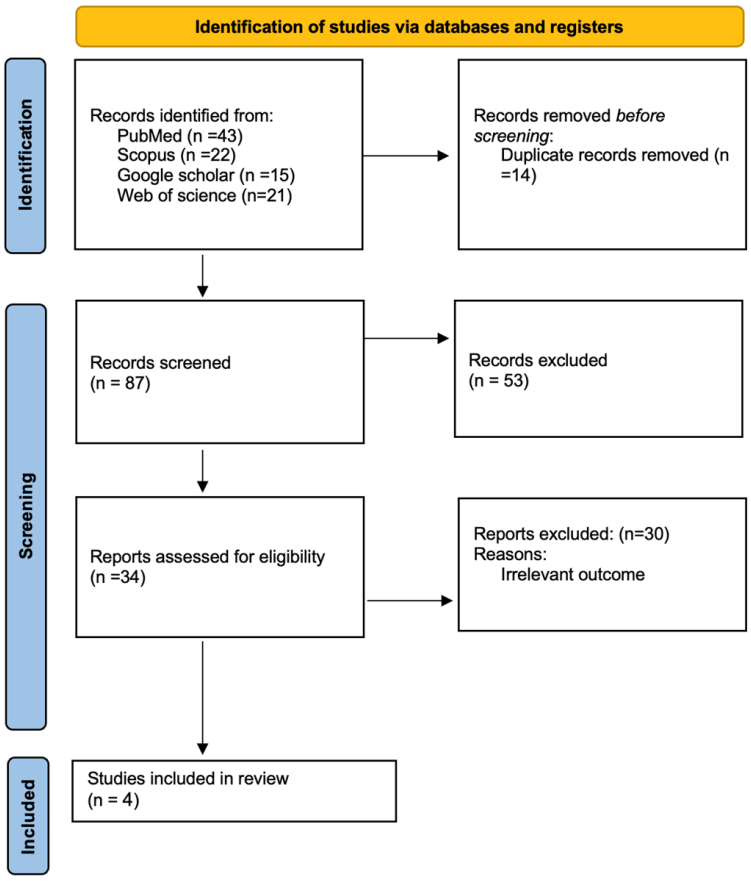


**Figure 1.** PRISMA 2020 flow diagram. Flowchart depicting the study selection process for the systematic review and meta-analysis. A total of 101 records were identified from PubMed, Scopus, Google Scholar, and Web of Science. After the removal of 14 duplicate records, 87 studies were screened based on title and abstract. Following the exclusion of 53 studies due to irrelevance, 34 full-text articles were assessed for eligibility. Of these, 30 were excluded for not meeting the inclusion criteria. Ultimately, 4 studies were included in the final systematic review and meta-analysis.

tistic, with a random-effects model applied when significant heterogeneity was detected ($I^2$>50%). To evaluate the robustness of findings, sensitivity analysis was performed by sequentially excluding individual studies and repeating the meta-analysis. Additionally, potential publication bias was examined through funnel plot asymmetry and Egger's regression analysis.

## Results

A systematic literature search was conducted in PubMed, Scopus, and Web of Science, yielding a total of 101 articles. After removing 14 duplicate records, 34 studies remained following title and abstract screening. Subsequently, 4 studies met the full-text eligibility criteria and were included in the final review, while the remaining studies were excluded due to irrelevance (**Figure 1**).

This systematic review and meta-analysis incorporated four randomized controlled trials (RCTs) involving 89 participants with relapsed or refractory CLL in the active disease stage. All trials were conducted in the United States, specifically in Philadelphia and New York. The follow-up period ranged from one month to two years, with participants' ages varying between 54 and 76 years; approximately 30% of the cohort was female. Lymphodepleting regimens were administered before T-cell infusion in all RCTs, commonly using regimens such as Fludarabine/Cyclophosphamide, Pentostatin/Cyclophosphamide, or Bendamustine.

The included trials evaluated response parameters, including complete response (CR), partial response (PR), and overall response rate (ORR), comparing high-dose infusion ($5 \times 10^8$) versus low-dose infusion ($5 \times 10^7$) of CART-19. The safety profile of CART-19 therapy was assessed in all trials, with CRS being the most frequently reported adverse event. **Table 2** presents the detailed characteristics of the included studies.

A pooled analysis of four RCTs demonstrated a statistically significant improvement in complete and partial response rates in patients receiving high-dose CAR-T19 therapy compared to those in the low-dose group (SMD [95% CI]: 1.02 [0.10, 1.94]; $P$<0.05, **Figure 3**). Importantly, no heterogeneity was detected among the included studies ($I^2$=0.00%). In contrast, the incidence of cytokine release syndrome (CRS) did not differ significantly between the high-dose and low-dose groups (SMD [95%


**Figure 2.** Quality assessment of the included studies.

CAR-19 treatment remains a subject of ongoing debate among researchers. This systematic review aimed to assess the efficacy and safety of high-dose ($5 \times 10^8$ cells) and low-dose ($5 \times 10^7$ cells) of CART-19 therapy in patients with relapsed or refractory CLL. A comprehensive literature search was conducted to identify relevant clinical trials evaluating CART-19 in this patient population. The review included four RCTs with a total of 89 participants. The findings indicate that patients receiving high-dose CART-19 exhibited a higher rate of complete or partial remission compared to those receiving low-dose CART-19. Moreover, the incidence of CRS did not differ significantly between the two dosage groups, suggesting comparable safety profiles.

CI]: 0.21 [-0.78, 1.20]; *P*>0.05, **Figure 4**), with similarly low heterogeneity ($I^2$=0.00%).

*Publication bias*

Publication bias was assessed in the comparison of high-dose versus low-dose CART-19 therapy in relapsed CLL. The funnel plot revealed asymmetry (**Figure 5**), raising concerns about potential bias. However, Begg's test (P=1.00) and Egger's test (P=0.78) indicated no statistically significant publication bias.

*Outlier detection and sensitivity analysis*

An L'Abbé plot was constructed to assess patient remission rates between high-dose and low-dose groups, revealing no outlier studies (**Figure 6**). Sensitivity analysis was conducted by systematically removing individual studies and reassessing the pooled results. The findings demonstrated that no single study significantly influenced the overall effect size, confirming the robustness and stability of the results.

## Discussion

CAR T-cell therapy has demonstrated promising outcomes in the treatment of relapsed and refractory CLL. However, the optimal dosage of

Our findings suggests a potential advantage of high-dose CART-19 therapy over low-dose therapy in achieving complete or partial remission in relapsed or refractory CLL, although differences favored the high-dose group, they did not reach statistical significance in all studies. Porter et al., in two separate studies conducted in 2013 [25] and 2014 [26], reported higher response rates in the high-dose groups, with 6 out of 13 (46.2%) and 7 out of 19 (36.8%) patients achieving remission, respectively, compared to 3 out of 13 (23.1%) and 2 out of 13 (15.4%) in the low-dose groups. In contrast, Porter et al. [27] and Frey et al. [28] did not observe a substantial difference, reporting response rates of 6 out of 11 (54.5%) vs. 4 out of 13 (30.8%) and 2 out of 4 (50%) vs. 2 out of 4 (50%) for high-dose and low-dose groups, respectively.

While these findings suggest a potential benefit of high-dose CART-19 therapy, the lack of statistical significance and the variability in response rates across studies indicate that dosing may not be the sole determinant of therapeutic efficacy. Factors such as patient-specific immune responses, disease burden, and prior treatments may contribute to the observed differences. Additionally, the absence of

**Table 2.** Baseline characteristics of the included studies

| Author (Year) | Country | Study design | Duration of follow up (months) | Participants | Age (years) | Sex % (female) | Side effects | Response |
|---|---|---|---|---|---|---|---|---|
| Porter et al. (2013) [25] | USA | RCT | 3 (1.3-5) | Total (n=10)<br>• HD[1]: 4<br>• LD[2]: 6 | 63 (59-76) | 30% | • CRS (n=7)<br>• HD: 3<br>• LD: 4 | • Overall: 2 CR, 2 PR<br>• HD: 2 (CR or PR)<br>• LD: 2 (CR or PR) |
| Porter et al. (2014) [26] | USA | RCT | 7.3 (1-16) | Total (n=23)<br>• HD: 11<br>• LD: 12 | 62 (54-76) | 33% | • CRS (n=13)<br>• HD: 6<br>• LD: 7 | • Overall: 5 CR, 4 PR (3/9 later progressed)<br>• HD: 6 (CR or PR)<br>• LD: 3 (CR or PR) |
| Frey et al. (2020) [28] | USA | RCT | 31.5 (2-75) | Total (n=32)<br>• HD: 19<br>• LD: 13 | 61.3 (48.8-76.1) | 22% | • HD: 5 pts with infection, 1 pt with second malignancy, 5 pts with CRS<br>• LD: 4 pts with infection, 3 pts with CRS | • Overall: 9 CR, 5 PR, 15 PD, 2 Died<br>• HD: 7 CR, 3 PR, 7 PD, 1 Died<br>• LD: 2 CR, 2 PR, 8 PD, 1 Died |
| Porter et al. (2016) [27] | USA | RCT | 9 (1-34) | Total (n=24)<br>• HD: 11<br>• LD: 13 | 62 | NM | CRS (numbers not specified by dosage) | • Overall: 5 CR, 5 PR<br>• HD: 4 CR, 2 PR<br>• LD: 1 CR, 3 PR |

Abbreviations: RCT, Randomized Controlled Trial; HD, High Dose; LD, Low Dose; CR, Complete Response; PR, Partial Response; CRS, Cytokine Release Syndrome; PD, Progressive Disease; NM, Not Mentioned. [1]HD: single dose of $5 \times 10^8$ CART-19. [2]LD: single dose of $5 \times 10^7$ CART-19.

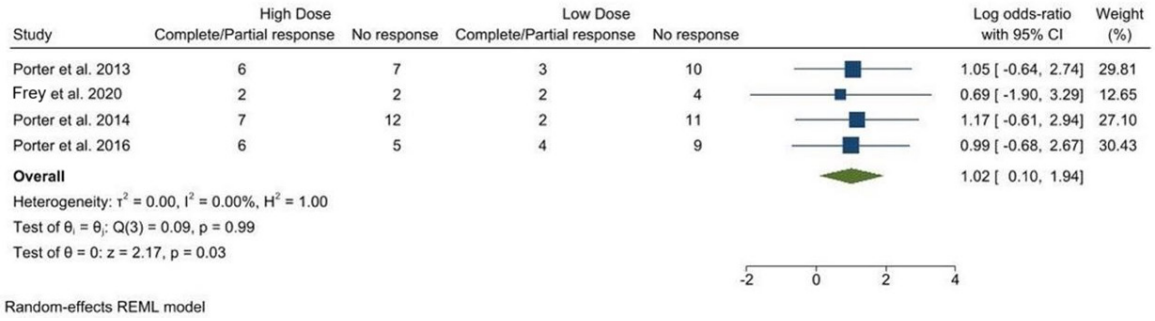


**Figure 3.** Forest plot comparing complete/partial response between low-dose and high-dose CAR-T19 treatment.

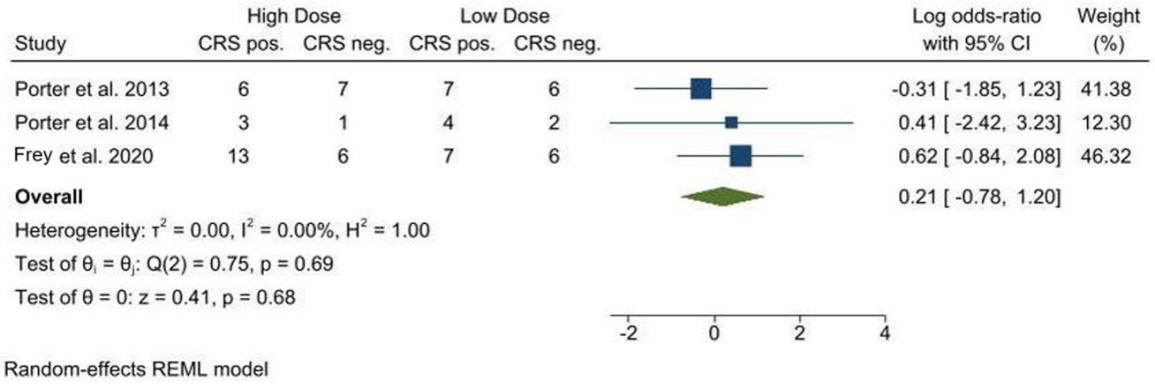


**Figure 4.** Forest plot comparing cytokine release syndrome (CRS) between low-dose and high-dose CAR-T19 treatment.

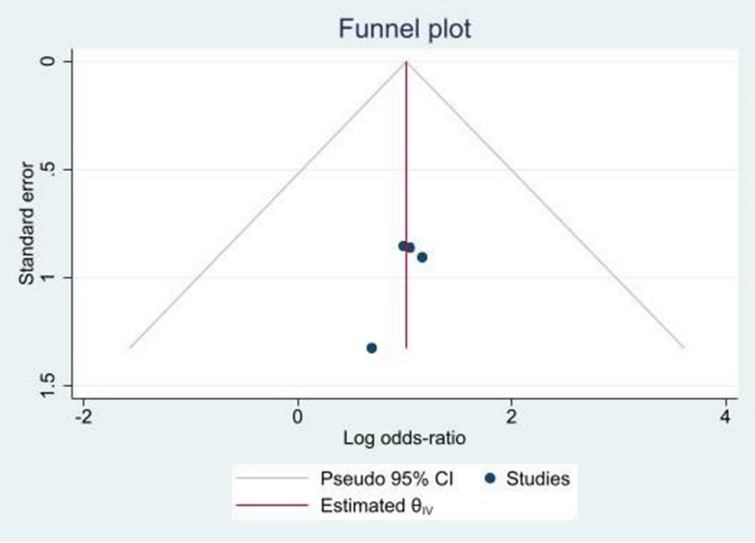


**Figure 5.** Assessment of publication bias in the included studies.

heterogeneity among the included studies ($I^2$=0.00%) suggests methodological consistency, yet the relatively small sample sizes limit the generalizability of the findings. Given the marginal statistical significance (P=0.03) and wide confidence intervals, further well-powered, multi-center clinical trials with longer follow-up periods are necessary to establish a definitive dosing strategy for CART-19 therapy in relapsed or refractory CLL.

Over the past few decades, cell-based immunotherapy has emerged as a promising strategy for treating malignant diseases. This approach utilizes patient-derived immune cells, which are expanded in vitro and genetically modified to enhance their ability to identify and eliminate tumor cells [29]. Several T cell-based therapeutic modalities have been developed for malignancies, including tumor-infiltrating lymphocytes (TILs), T-cell receptor (TCR)-engineered T cells, and CAR T-cells [29, 30]. Among these,

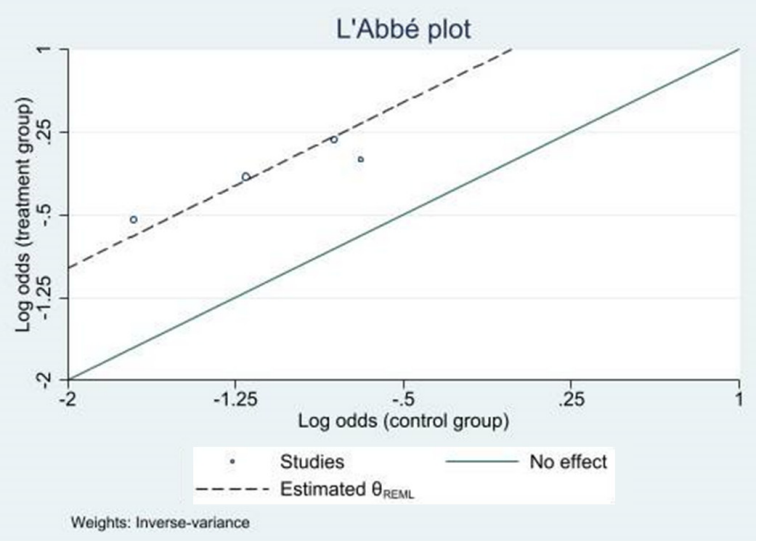


**Figure 6.** Outlier detection in the included studies.

CAR T-cell therapy has demonstrated superior and more sustained clinical responses compared to TIL and TCR-modified T-cell therapies [30, 31]. CAR T-cells are genetically engineered lymphocytes equipped with synthetic receptors that facilitate the recognition and destruction of tumor cells expressing the target antigen. These receptors, known as CARs (chimeric antigen receptors), are artificial constructs that include a single-chain variable fragment (ScFv) of an antibody for antigen recognition and an intracellular T-cell activation domain [32].

While CAR T-cell therapy has shown promising results, it may also be associated with adverse effects, including cytokine release syndrome (CRS) and neurological complications such as headaches, ataxia, and tremors [33, 34]. CRS emerged as the predominant adverse reaction observed in hematologic cancer research involving CAR-T cell therapy. CRS is a systemic inflammatory response triggered by various factors, including infections and certain immunotherapies. It is notably associated with CAR T-cell treatments, where rapid activation of T cells leads to the release of pro-inflammatory cytokines. Clinically, CRS presents with symptoms ranging from fever and fatigue to more severe manifestations like hypotension and multi-organ dysfunction [35]. This side effect, which is distinctive and frequently severe, was commonly documented in the studies. Nevertheless, our data analysis did not reveal any correlation between this unfortunate occurrence and doses of CART-19, and the incidence of CART-19 doses of CRS was not significant in these two groups.

This systematic review and meta-analysis is the first to comprehensively evaluate the effects of high-dose and low-dose CART-19 therapy in relapsed and refractory CLL, directly comparing their impact on partial remission, complete remission, and cytokine release syndrome. By synthesizing data from multiple studies, this analysis offers valuable insights into the potential benefits of high-dose CART-19 therapy, suggesting that it may be associated with higher response rates and improved survival outcomes compared to low-dose therapy. Furthermore, including multiple randomized trials enhances the robustness of the findings, contributing to a more comprehensive understanding of dosing strategies in CART-19 therapy.

Despite its strengths, this review has several limitations. The variability in study outcomes highlights the need for further research to determine the optimal dosage of CART-19, particularly considering the balance between efficacy and toxicity, such as CRS and neurotoxicity. Additionally, the small number of included studies limits the statistical power and generalizability of the findings. The lack of large-scale, multi-center trials with diverse patient populations restricts the applicability of the results across different racial and geographical groups. Therefore, further methodologically rigorous RCTs with larger sample sizes and extended follow-up periods are necessary to validate these findings and establish more definitive dosing guidelines for CART-19 therapy in relapsed and refractory CLL.

## Conclusion

This systematic review and meta-analysis assessed the efficacy and safety of high-dose and low-dose CART-19 therapy in patients with

relapsed and refractory CLL. The findings suggest that high-dose CART-19 may be associated with higher response rates and improved survival outcomes compared to low-dose therapy. However, the observed differences were not consistently significant across studies, and the variability in results underscores the need for further investigation. Given the limited number of included studies and small sample sizes, additional well-designed, large-scale RCTs are necessary to establish the optimal CART-19 dosage while ensuring a balance between therapeutic efficacy and safety. Expanding research to include diverse populations and longer follow-up periods will further enhance the generalizability and clinical applicability of these findings.

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## Disclosure of conflict of interest

None.

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## References

[1] Baliakas P, Espinet B, Mellink C, Jarosova M, Athanasiadou A, Ghia P, Kater AP, Oscier D, Haferlach C and Stamatopoulos K. Cytogenetics in chronic lymphocytic leukemia: ERIC perspectives and recommendations. Hemasphere 2022; 6: e707.

[2] Condoluci A, Terzi di Bergamo L, Langerbeins P, Hoechstetter MA, Herling CD, De Paoli L, Delgado J, Rabe KG, Gentile M, Doubek M, Mauro FR, Chiodin G, Mattsson M, Bahlo J, Cutrona G, Kotaskova J, Deambrogi C, Smedby KE, Spina V, Bruscaggin A, Wu W, Moia R, Bianchi E, Gerber B, Zucca E, Gillessen S, Ghielmini M, Cavalli F, Stussi G, Hess MA, Baumann TS, Neri A, Ferrarini M, Rosenquist R, Forconi F, Foà R, Pospisilova S, Morabito F, Stilgenbauer S, Döhner H, Parikh SA, Wierda WG, Montserrat E, Gaidano G, Hallek M and Rossi D. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. Blood 2020; 135: 1859-1869.

[3] Brieghel C, Galle V, Agius R, da Cunha-Bang C, Andersen MA, Vlummens P, Mattsson M, Rosenquist R, Smedby KE, Herling CD, Bahlo J, Hallek M, Lundgren JD, Offner F and Niemann CU. Identifying patients with chronic lymphocytic leukemia without need of treatment: End of endless watch and wait? Eur J Haematol 2022; 108: 369-378.

[4] Abrisqueta P, Pereira A, Rozman C, Aymerich M, Giné E, Moreno C, Muntañola A, Rozman M, Villamor N, Hodgson K, Campo E, Bosch F and Montserrat E. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clínic of Barcelona experience. Blood 2009; 114: 2044-50.

[5] Nabhan C and Rosen ST. Chronic lymphocytic leukemia: a clinical review. JAMA 2014; 312: 2265-76.

[6] Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN and Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975; 46: 219-34.

[7] Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, Hillmen P, Keating M, Montserrat E, Chiorazzi N, Stilgenbauer S, Rai KR, Byrd JC, Eichhorst B, O'Brien S, Robak T, Seymour JF and Kipps TJ. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018; 131: 2745-2760.

[8] Jain N, Wierda WG and O'Brien S. Chronic lymphocytic leukaemia. Lancet 2024; 404: 694-706.

[9] Hallek M and Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. Am J Hematol 2021; 96: 1679-1705.

[10] Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, Bhagat G, Borges AM, Boyer D, Calaminici M, Chadburn A, Chan JKC, Cheuk W, Chng WJ, Choi JK, Chuang SS, Coupland SE, Czader M, Dave SS, de Jong D, Du MQ, Elenitoba-Johnson KS, Ferry J, Geyer J, Gratzinger D, Guitart J, Gujral S, Harris M, Harrison CJ, Hartmann S, Hochhaus A, Jansen PM, Karube K, Kempf W, Khoury J, Kimura H, Klapper W, Kovach AE, Kumar S, Lazar AJ, Lazzi S, Leoncini L, Leung N, Leventaki V, Li XQ, Lim MS, Liu WP, Louissaint A Jr, Marcogliese A, Medeiros LJ, Michal M, Miranda RN, Mitteldorf C, Montes-Moreno S, Morice W, Nardi V, Naresh KN, Natkunam Y, Ng SB, Oschlies I, Ott G, Parrens M, Pulitzer M, Rajkumar SV, Rawstron AC, Rech K, Rosenwald A, Said J, Sarkozy C, Sayed S, Saygin C, Schuh A, Sewell W, Siebert R, Sohani AR, Tooze R, Traverse-Glehen A,

Vega F, Vergier B, Wechalekar AD, Wood B, Xerri L and Xiao W. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia 2022; 36: 1720-1748.

[11] Zhang S and Kipps TJ. The pathogenesis of chronic lymphocytic leukemia. Annu Rev Pathol 2014; 9: 103-18.

[12] Burger JA. Treatment of chronic lymphocytic leukemia. N Engl J Med 2020; 383: 460-473.

[13] García-Muñoz R, Roldan Galiacho V and Llorente L. Immunological aspects in chronic lymphocytic leukemia (CLL) development. Ann Hematol 2012; 91: 981-96.

[14] Modepalli S and Hattangadi SM. Novel use for selective inhibitors of nuclear export in β-thalassemia: block of HSP70 export from the nucleus via exportin Xpo1 improves ineffective erythropoiesis. Haematologica 2020; 105: 2188-2189.

[15] Bosch F and Dalla-Favera R. Chronic lymphocytic leukaemia: from genetics to treatment. Nat Rev Clin Oncol 2019; 16: 684-701.

[16] Crombie J and Davids MS. IGHV mutational status testing in chronic lymphocytic leukemia. Am J Hematol 2017; 92: 1393-1397.

[17] Shadman M, Liu C, Eakle K, Hiew HJ, Biondo JML, Ghia P and Mato AR. COVID-19 vaccination response and its practical application in patients with chronic lymphocytic leukemia. Hemasphere 2022; 7: e811.

[18] Moreno C, Greil R, Demirkan F, Tedeschi A, Anz B, Larratt L, Simkovic M, Samoilova O, Novak J, Ben-Yehuda D, Strugov V, Gill D, Gribben JG, Hsu E, Lih CJ, Zhou C, Clow F, James DF, Styles L and Flinn IW. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20: 43-56.

[19] Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, Jelinek DF, Braggio E, Leis JF, Zhang CC, Coutre SE, Barr PM, Cashen AF, Mato AR, Singh AK, Mullane MP, Little RF, Erba H, Stone RM, Litzow M and Tallman M. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med 2019; 381: 432-443.

[20] Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, Fakhri B, Eyre TA, Lamanna N, Patel MR, Alencar A, Lech-Maranda E, Wierda WG, Coombs CC, Gerson JN, Ghia P, Le Gouill S, Lewis DJ, Sundaram S, Cohen JB, Flinn IW, Tam CS, Barve MA, Kuss B, Taylor J, Abdel-Wahab O, Schuster SJ, Palomba ML, Lewis KL, Roeker LE, Davids MS, Tan XN, Fenske TS, Wallin J, Tsai DE, Ku NC, Zhu E, Chen J, Yin M, Nair B, Ebata K, Marella N, Brown JR and Wang M. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet 2021; 397: 892-901.

[21] Wang E, Mi X, Thompson MC, Montoya S, Notti RQ, Afaghani J, Durham BH, Penson A, Witkowski MT, Lu SX, Bourcier J, Hogg SJ, Erickson C, Cui D, Cho H, Singer M, Totiger TM, Chaudhry S, Geyer M, Alencar A, Linley AJ, Palomba ML, Coombs CC, Park JH, Zelenetz A, Roeker L, Rosendahl M, Tsai DE, Ebata K, Brandhuber B, Hyman DM, Aifantis I, Mato A, Taylor J and Abdel-Wahab O. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med 2022; 386: 735-743.

[22] Siddiqi T, Soumerai JD, Dorritie KA, Stephens DM, Riedell PA, Arnason J, Kipps TJ, Gillenwater HH, Gong L, Yang L, Ogasawara K, Thorpe J and Wierda WG. Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. Blood 2022; 139: 1794-1806.

[23] Lemal R and Tournilhac O. State-of-the-art for CAR T-cell therapy for chronic lymphocytic leukemia in 2019. J Immunother Cancer 2019; 7: 202.

[24] Fraietta JA, Lacey SF, Orlando EJ, Pruteanu-Malinici I, Gohil M, Lundh S, Boesteanu AC, Wang Y, O'Connor RS, Hwang WT, Pequignot E, Ambrose DE, Zhang C, Wilcox N, Bedoya F, Dorfmeier C, Chen F, Tian L, Parakandi H, Gupta M, Young RM, Johnson FB, Kulikovskaya I, Liu L, Xu J, Kassim SH, Davis MM, Levine BL, Frey NV, Siegel DL, Huang AC, Wherry EJ, Bitter H, Brogdon JL, Porter DL, June CH and Melenhorst JJ. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018; 24: 563-571.

[25] Porter DL, Kalos M, Frey NV, Grupp SA, Loren AW, Jemision C, Gilmore J, McConville H, Capobianchi J, Lledo L, Chew A, Shen A, Wood PA, Litchman M, Zheng Z, Levine BL and June CH. Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL. Blood 2013; 122: 873.

[26] Porter DL, Frey NV, Melenhorst JJ, Hwang WT, Lacey SF, Shaw P, Chew A, Grupp SA, Capobianchi J, Gilmore J, Kalos M, Litchman M, Lledo L, Loren AW, Mahnke Y, Marcucci KT, Mcconville H, Shen A, Wood PA, Zheng Z, Levine BL and June CH. Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL. Blood 2014; 124: 1982.

[27] Porter DL, Frey NV, Melenhorst JJ, Hwang WT, Lacey SF, Shaw PA, Chew A, Marcucci K, Gill S,

Loren AW, Mato AR, Schuster SJ, Lledo L, McConville H, Gilmore J, Capobianchi J, Kalos MD, Grupp SA, Levine BL and June CH. Randomized, phase II dose optimization study of chimeric antigen receptor (CAR) modified T cells directed against CD19 in patients (pts) with relapsed, refractory (R/R) CLL. Journal of Clinical Oncology; 2016.

[28] Frey NV, Gill S, Hexner EO, Schuster S, Nasta S, Loren A, Svoboda J, Stadtmauer E, Landsburg DJ, Mato A, Levine BL, Lacey SF, Melenhorst JJ, Veloso E, Gaymon A, Pequignot E, Shan X, Hwang WT, June CH and Porter DL. Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia. J Clin Oncol 2020; 38: 2862-2871.

[29] Barrett DM, Grupp SA and June CH. Chimeric antigen receptor- and TCR-modified T cells enter main street and wall street. J Immunol 2015; 195: 755-61.

[30] Fujiwara H. Adoptive immunotherapy for hematological malignancies using T cells gene-modified to express tumor antigen-specific receptors. Pharmaceuticals (Basel) 2014; 7: 1049-68.

[31] Chmielewski M, Hombach AA and Abken H. Antigen-specific T-cell activation independently of the MHC: chimeric antigen receptor-redirected T cells. Front Immunol 2013; 4: 371.

[32] Srivastava S and Riddell SR. Engineering CAR-T cells: design concepts. Trends Immunol 2015; 36: 494-502.

[33] American Cancer Society. CAR T-cell therapy and its side effects. Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html.

[34] National Cancer Institute. CAR T cells: engineering patients' immune cells to treat their cancers. Available from: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells.

[35] Freeman CL, Morschhauser F, Sehn L, Dixon M, Houghton R, Lamy T, Fingerle-Rowson G, Wassner-Fritsch E, Gribben JG, Hallek M, Salles G and Cartron G. Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions. Blood 2015; 126: 2646-9.