REVIEW
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Efficacy and safety of CAR-T cells in multiple myeloma: a systematic literature review

Juan Pablo Alzate-Granados[1*], Gloria Ibis Tirado[2], Carlos Camargo[3]

[1]Faculty of Medicine, National University of Colombia, Bogotá 111321, Colombia.
[2]Faculty of Medicine, University Foundation of Health Sciences, Bogotá 110111, Colombia.
[3]Hemato-Oncology, Cobos Clinic, Cali 760033, Colombia.

[*]**Correspondence to:** Juan Pablo Alzate-Granados, Faculty of Medicine, National University of Colombia, Carrera 45 No. 26–85, Bogotá 111321, Colombia. E-mail: jpalzategr@unal.edu.co.

Abstract

Relapsed/refractory multiple myeloma (RRMM) remains a life-threatening disease despite the availability of novel agents. We systematically searched MEDLINE, EMBASE, CENTRAL, LILACS, and ClinicalTrials.gov through 30 July 2025 for clinical trials of chimeric antigen receptor T-cell (CAR-T) therapy in adults with RRMM. Two reviewers independently extracted data, assessed risk of bias, and conducted a random-effects meta-analysis of proportions. Forty studies (n = 2,650), including two phase III randomized controlled trials, met the inclusion criteria. The pooled overall response rate was 94% (95% CI, 93–96%). In pivotal trials, median progression-free survival ranged from 9 to 15 months, and 12-month overall survival was 78–88%. Treatment-related toxicities were frequent: any-grade cytokine-release syndrome occurred in 89% of patients (grade ≥ 3 in 9%), and immune effector cell-associated neurotoxicity syndrome in 18% (grade ≥ 3 in 4%). These findings indicate that B-cell maturation antigen (BCMA)-directed CAR-T therapy induces high response rates and clinically meaningful remissions in heavily pretreated RRMM, but adverse events remain substantial and require vigilant monitoring. Longer follow-up to define durability and late effects, as well as cost-effectiveness analyses, are warranted to clarify the role of CAR-T in routine practice.

Keywords: CAR-T cell therapy; multiple myeloma; B-cell maturation antigen; treatment efficacy; treatment safety

Author contributions

Alzate-Granados JP conceived the study, defined the research question, and designed the review and meta-analysis framework. Camargo C contributed to the clinical design and refined inclusion/exclusion criteria. Tirado GI and Alzate-Granados JP led the database searches. Tirado GI and Camargo C independently screened titles/abstracts, assessed full texts, and extracted study-level data. Alzate-Granados JP conducted statistical analyses and generated pooled estimates. Alzate-Granados JP and Tirado GI drafted the manuscript. Camargo C provided critical revisions, particularly regarding clinical implications and safety interpretation. All authors contributed to editing and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

RRMM, relapsed/refractory multiple myeloma; MM, multiple myeloma; CAR-T, chimeric-antigen-receptor T cell; BCMA, B-cell maturation antigen; ORR, overall response rate; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity; CR, complete response; sCR, stringent complete response; PFS, progression-free survival; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; PVd, pomalidomide, bortezomib, and dexamethasone; DPd, daratumumab, pomalidomide, and dexamethasone; DOR, median duration of response; TEAEs, treatment-emergent adverse events; AEs, adverse events; CI, confidence interval; HR, hazard ratio; CD, cluster of differentiation; NKG2D, natural killer group 2, member D; MRD, minimal residual disease; MCARH, modified chimeric antigen receptor human; GPRC5D, protein-coupled receptor class C group 5 member D; CTL, cytotoxic T lymphocytes; OS, overall survival; PR, partial response; VGPR, very good partial response; DL, dose level; DPBS, Dulbecco's phosphate-buffered saline.

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Introduction

Multiple myeloma (MM) is a hematologic malignancy that originates from the clonal proliferation of plasma cells in the bone marrow, representing the second most frequent hematologic malignancy [1]. In most cases, these abnormal cells produce monoclonal proteins, leading to a series of severe complications, including renal failure, hypercalcemia, anemia, and osteolytic lesions that increase the risk of pathological fractures [2]. Over the past few decades, the treatment of MM has evolved considerably due to the introduction of new therapeutic agents, such as proteasome inhibitors (e.g., bortezomib), immunomodulators (such as lenalidomide and pomalidomide), and monoclonal antibodies [3]. These treatments have significantly improved response rates and overall survival in this population. However, despite these advances, a large proportion of patients eventually develop resistance to these therapies. The prognosis worsens as resistance to more therapies develops; thus, patients who are refractory to three therapeutic lines have a median overall survival of 9.2 months, and for those who are penta-refractory, the median is only 5.6 months [1]. This underscores the critical need to develop and implement innovative therapies that can overcome resistance and provide durable responses in patients with MM [4, 5].

Chimeric Antigen Receptor T-cell (CAR-T) therapy has emerged as an innovative and promising therapeutic strategy in the treatment of hematologic malignancies, particularly in refractory leukemias and lymphomas [6]. CAR-T therapy involves the genetic reprogramming of the patient's autologous T cells to express a chimeric receptor that combines an antigen recognition domain (a single chain that fuses the variable region of the heavy chain and the light chain) with a transmembrane portion and finally an intracellular signaling domain [7, 8]. This chimeric receptor allows the modified T cells to recognize and destroy tumor cells that express the specific antigen. In the context of MM, the most widely used CAR-T cells target the B-cell maturation antigen (BCMA), a protein highly expressed in MM cells and with low representation in healthy tissues. The results of this therapy have been promising in clinical studies [9–11]. These data suggest that BCMA-targeted CAR-T therapy has the potential to transform MM treatment, providing a viable therapeutic option for patients with refractory or relapsed disease.

Despite the encouraging results of preliminary studies, evidence on the long-term efficacy and safety of CAR-T therapy in MM remains limited. Many studies conducted to date have included a small number of patients and have had short-term follow-up, leaving several critical questions unanswered [12]. These include the durability of the response to CAR-T therapy, long-term toxicity profiles, and best practices for managing the side effects associated with the treatment [13–15]. Furthermore, there is considerable variability in CAR-T cell manufacturing and administration protocols across different studies, complicating direct comparison of results and hindering therapy standardization [16–18]. This systematic review aims to synthesize the available literature on the use of CAR-T in MM, providing a comprehensive and up-to-date overview of the current state of knowledge and highlighting areas that require further research.

The purpose of this review is to provide a thorough synthesis of the current evidence on CAR-T therapy in relapsed/refractory multiple myeloma (RRMM), identifying response and toxicity patterns as well as areas that require further investigation. We hope that our findings will inform clinical practice and guide future studies to optimize the use of CAR-T in this disease.

Methods

Study type

The study is a systematic review of clinical trials. The systematic review and meta-analysis were registered in PROSPERO (https://www.crd.york.ac.uk/prospero/), with the registration number CRD42024592655.

Selection criteria

Types of studies. Clinical trials of any phase (I, II, III, or IV) evaluating CAR-T cell therapy in patients with MM were included.

Types of participants. Participants were adults (≥ 18 years) diagnosed with RRMM.

Types of interventions. The intervention of interest was the administration of CAR-T cell therapy, with no restrictions on the specific type of CAR-T (e.g., targeting different antigens such as BCMA, CD19, etc.).

Types of outcomes.

Primary outcomes:

1. Overall response rate (ORR).
2. Cytokine release syndrome (CRS).

Secondary outcomes:

1. Stringent complete response (sCR).
2. Progression-free survival (PFS).
3. Overall survival (OS).
4. CAR-T cell expansion.
5. Patient-reported quality of life.
6. Adverse events.
7. Hematologic toxicity.
8. Other outcomes reported by the studies.

Search methods for identifying studies

Electronic searches. Extensive searches were conducted in the following electronic databases from their inception until July 2024: MEDLINE (via PubMed), EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, and ClinicalTrials.gov.

A combination of controlled vocabulary terms (MeSH, Emtree) and free-text terms was used, tailored to each database. The general search strategy is presented below: ("Chimeric Antigen Receptor T-Cell Immunotherapy" [MeSH Terms] OR CAR-T [Text Word]) AND ("Multiple Myeloma" [MeSH Terms] OR myeloma [Text Word]).

An additional targeted search was performed on 30 July 2025 (MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov) to capture reports published between 1 August 2024 and 30 July 2025.

Other resource searches. In addition to electronic searches, the references of included studies and relevant reviews were screened to identify additional studies. Clinical trial registries were also searched, including the WHO International Clinical Trials Registry Platform and the EU Clinical Trials Register.

Data collection and analysis

Study selection. Two independent reviewers blindly assessed the titles and abstracts of all studies identified in the searches. Potentially relevant studies were evaluated in full text to determine eligibility. Disagreements were resolved through discussion or consultation with a third reviewer.

Disagreements were resolved by consensus; persistent discrepancies were adjudicated by a third reviewer (JPA).

Data extraction and management. A specific data extraction form was designed. Two reviewers independently extracted the following data from each study:

1. General study information (authors, year of publication, country).
2. Participant characteristics (age, sex, disease status).
3. Intervention details (type of CAR-T, dose, treatment regimen).
4. Primary and secondary outcomes.
5. Statistical data (effect measures, confidence intervals, *P*-values).

Assessment of studies with critical appraisal tools for epidemiological design. Randomised controlled trials (RCTs) were appraised with the Cochrane RoB 2 tool, while single-arm or non-randomised studies were assessed with ROBINS-I.

Plan for quantitative and qualitative synthesis of the review. A meta-analysis of proportions was conducted to quantitatively synthesize the results of the included clinical trials. A random-effects model was used to account for heterogeneity between studies and provide more conservative effect estimates.

Heterogeneity was explored with Cochran's Q ($P < 0.10$) in

addition to I^2. A DerSimonian-Laird random-effects model was chosen a priori to accommodate clinical diversity among constructs and patient populations, even when statistical heterogeneity was low ($I^2 \approx 0\%$).

The meta-analysis results were presented as forest plots, showing combined proportions and their 95% confidence intervals for primary and secondary outcomes.

Results

Search results

Figure 1 shows the PRISMA flow diagram depicting the study selection process. A total of 170 records were identified from databases. After removing duplicates (n = 32), 138 records were screened, and 75 were excluded for not meeting the inclusion criteria. Fifty-five full reports were assessed for eligibility, and 46 studies were included in the systematic review.

CAR-T design strategies across included studies

Four distinct design categories were identified across 46 trials. (1) Autologous, single-target BCMA constructs (n = 28); (2) Autologous, non-BCMA targets such as GPRC5D or FCRH5 (n = 4); (3) Autologous dual/bispecific CARs (e.g., BCMA/CD19, BCMA/GPRC5D) designed to mitigate single-antigen escape (n = 6); and (4) Allogeneic, gene-edited BCMA CAR-T cells (n = 6; e.g., ALLO-715, PBCMA-ALLO1) with rapid off-the-shelf availability. To ensure consistency with the Efficacy section, constructs are referred to by product/research code and their explicit antigen target(s) at first mention.

Efficacy/effectiveness results

The systematic review included 40 studies that evaluated the efficacy of various CAR-T therapies in patients with RRMM. A qualitative synthesis of the interventions used and the reported efficacy outcomes is presented below (Table 1). For clarity and consistency with the design taxonomy above, we list the principal constructs together with their antigen target(s): BM38 (BCMA + CD38); CT103A (BCMA); LCAR-B38M (biepitopic BCMA); JNJ-68284528/ciltacabtagene autoleucel (cilta-cel, dual-epitope BCMA); bb2121/idecabtagene vicleucel (ide-cel, BCMA); ARI0002h (BCMA); C-CAR088 (BCMA); CART-BCMA and CART-ddBCMA (BCMA); MCARH109/BMS-986393 and OriCAR-017 (GPRC5D); dual-target BCMA/CD19 platforms; bispecific BCMA/GPRC5D platforms; and ALLO-715/PBCMA-ALLO1 (allogeneic BCMA).

In terms of efficacy, studies demonstrated significant ORR and complete response (CR) rates. For instance, Mei et al. reported an ORR of 87% and a sCR of 52% with BM38 (BCMA + CD38), while Wang et al., with CT103A (BCMA), showed an ORR of 88.9% and a CR of 44%. Zhao et al., with LCAR-B38M (biepitopic BCMA), achieved an ORR of 88% and a CR of 68% [19–21]. Other studies also reported promising results: in Zhang et al., the responses with JNJ-68284528/cilta-cel (dual-epitope BCMA) were 98.3% and 70.7% for ORR and CR, respectively. Li et al., with bb2121/ide-cel (BCMA), reported an ORR of 90%, which was later evaluated in a Phase 3 trial published in NEJM in 2023 [22, 23].

In terms of PFS, medians varied between studies, with periods of 11.8 months in Mei et al., 9 months in Yan et al., and 15 months in Zhang et al. [19, 22, 24]. Some studies did not reach the median PFS during follow-up, such as Wang et al., indicating a potentially durable benefit [20, 23].

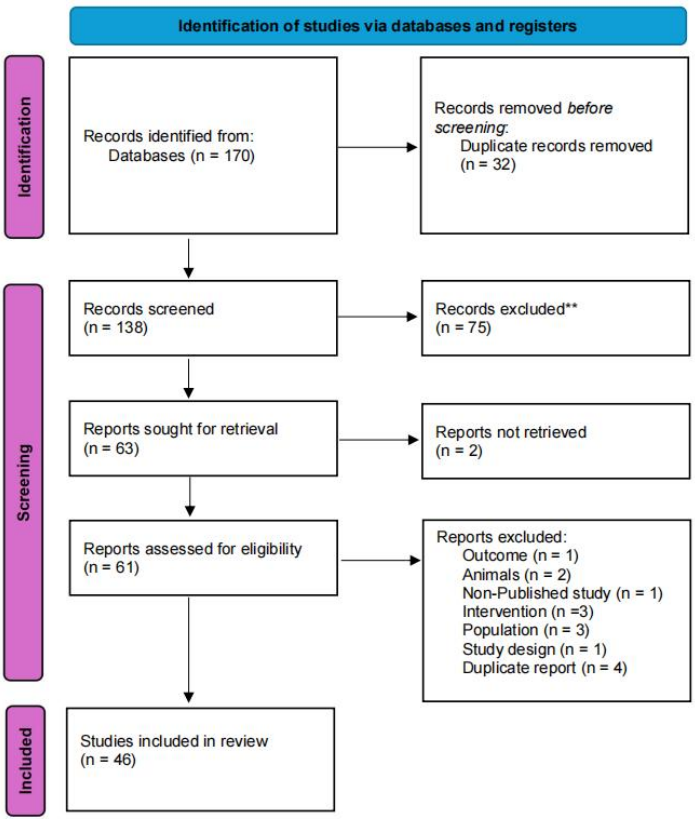

Figure 1 PRISMA flow diagram

Table 1 Efficacy/effectiveness results

Author, Year	Design	N	Intervention	Target	Efficacy/effectiveness	Results
Asherie, 2023 [25]	Phase I clinical trial	20	HBI0101	BCMA	ORR, CR/sCR, PFS, OS	ORR: 75%; CR/sCR: 50%, PFS: 160 days, OS: 308 days
Baumeister, 2019 [26]	Phase I clinical trial	12	NKG2D-CAR T cells	NKG2D-ligands	Objective tumor response, PFS	No objective tumor responses observed; disease stability in some patients.
Berdeja, 2021 [27]	Phase I/II clinical trial	97	Cilta-cel	BCMA	ORR	ORR: 97% (94/97), sCR: 65 (67%)
Hu, 2022 [28]	Phase I clinical trial	99	BCMA CAR-T cells	BCMA	ORR (CR, VGPR, PR)	ORR: 95.8% (CR: 53, VGPR: 15, PR: 23)
Chen, 2021 [29]	Phase I clinical trial	7	CAR T-cells targeting BCMA and CD19	BCMA + CD19	sCR, MRD-negative remission	Scr: 6/7; all evaluated MRD-negative post-infusion
Cohen, 2019 [30]	Phase I clinical trial	25	CART-BCMA	BCMA	ORR (PR or better)	Cohort 1: 44%; Cohort 2: 20%; Cohort 3: 64%
Cowan, 2023 [31]	Phase I clinical trial	18	BCMA CAR-T + crenigacestat	BCMA	OR, CR, sCR, VGPR, PR	ORR: 89% (16/18); CR: 11% (2/18); sCR: 44% (8/18); VGPR: 22% (4/18); PR: 11% (2/18)
Du, 2022 [32]	Phase I/II clinical trial	49	HDS269B CAR-T	BCMA	ORR, PFS, OS	ORR: 77%, PFS: 10 mo, OS: 29 mo
Frigault, 2023 [33]	Phase I clinical trial	13	CART-ddBCMA	BCMA	CR/sCR	CR/sCR: 75% (9/12)
Garfall, 2018 [34]	Phase I clinical trial	10	CTL019 (anti-CD19)	CD19	PFS	PFS after ASCT + CTL019 longer in 2/10 vs prior ASCT (479 vs 181 days; 249 vs 127 days)
Hillengass, 2024 [35]	Phase II clinical trial	39	Cilta-cel	BCMA	ORR, PFS, MRD	ORR: 95% (Cohort A), 100% (Cohort B); 24-mo PFS: 75% (A), 73% (B); MRD negativity in most evaluable patients
Li, 2021 [23]	Phase I clinical trial	30	Anti-BCMA CAR-T	BCMA	ORR, PFS, OS	ORR: 90%, PFS: 5.2 mo, OS: 14.0 mo
Li, 2022 [36]	Phase I/II clinical trial	54	Anti-BCMA/CD19 CAR-T	BCMA + CD19	ORR	ORR: 95%
Mailankody, 2022 [37]	Phase I clinical trial	17	MCARH109	GPRC5D	Clinical response (PR or better)	71% overall; 58% at 25–150 $\times 10^6$ cells
Mailankody, 2023 [38]	Phase I clinical trial	43	ALLO–715	BCMA (allogeneic)	ORR	ORR: 55.8% responded; 34.9% ≥ VGPR
Manjunath, 2021 [39]	Phase I clinical trial	25	CART-BCMA	BCMA	PR or better	Group A: 54%, Group B: 38%, Group C: 50%
Martin, 2022 [40]	Phase I/II clinical trial	78	Cilta-cel	BCMA	HRQOL (EORTC QLQ-C30)	Improved global health: +8.0, physical: +4.6, emotional: +1.9; reduced pain: –14.1, fatigue: –15.4
Mei, 2021 [19]	Phase I clinical trial	23	BM38 CAR-T	BCMA + CD38	ORR, sCR	ORR: 87%, sCR: 52%
Minakata, 2023 [41]	Phase I/II clinical trial	9	Ide-cel, bb2121	BCMA	ORR, sCR, DOR, PFS, OS	ORR: 89%, sCR: 56%; 6-mo PFS: 88%, 12-mo PFS: 75%; 6-mo OS: 89%, 12-mo OS: 78%
Munshi, 2021 [42]	Phase II clinical trial	128	Ide-cel/bb2121	BCMA	ORR	73% (94/128)
Oliver-Caldés, 2023 [17]	Phase I clinical trial	30	ARI0002h	BCMA	ORR at 100 days	ORR: 100% (15 CR, 9 VGPR, 6 PR)
Qu, 2022 [43]	Phase I clinical trial	31	C-CAR088	BCMA	ORR, PFS	ORR: 96.4%; 12-mo PFS: 69.5% (95% CI: 51.6–93.6)
Raje, 2019 [4]	Phase I clinical trial	33	bb2121	BCMA	ORR	ORR: 85%
Ri, 2022 [44]	Phase I/II clinical trial	9	Cilta-cel	BCMA	ORR; ≥ VGPR	ORR: 100%; ≥ VGPR: 87.5%
Shao, 2021 [45]	Phase I/II clinical trial	37	BCMA-targeted CAR-T	BCMA	ORR	97% response; CR: 59%, VGPR: 29%, PR 11%
Shi, 2022 [46]	Phase I clinical trial	10	Anti-CD19 and anti-BCMA CAR-T + len maintenance	BCMA + CD19	ORR	ORR: 100%; sCR: 90%, CR: 10%
Shi, 2024 [47]	Phase I/II clinical trial	50	BC19 CAR-T cells	BCMA + CD19	ORR, PFS, OS	ORR: 92%, PFS: 19.7 mo, OS: 19.7 mo

Table 1 Efficacy/effectiveness results (*continued*)

Author, Year	Design	N	Intervention	Target	Efficacy/effectiveness	Results
Singh, 2021 [48]	Phase I clinical trial	33	Iide-cel; bb2121	BCMA	Response (serum M-protein reduction)	450-million dose is most effective (higher response, fewer relapses)
Wang, 2021 [20]	Phase I clinical trial	18	CT103A	BCMA	ORR	ORR: 100%
Wang, 2022 [49]	Phase I clinical trial	25	BCMA-targeted CAR-T	BCMA	CAR-T expansion	Greater expansion with DPBS vs X-VIVO15
Xia, 2023 [50]	Phase II clinical trial	33	Anti-GPRC5D CAR-T	GPRC5D	ORR	ORR: 91% (30/33)
Xu, 2019 [51]	Phase I clinical trial	17	LCAR-B38M	BCMA	ORR	ORR: 88.20%
Yan, 2019 [24]	Phase II clinical trial	21	Humanized anti-CD19 and murine anti-BCMA CAR-T	BCMA + CD19	Proportion of overall response	95% (20/21), including 43% sCR
Zhang, 2021 [22]	Phase I clinical trial	61	Anti-BCMA CAR-T	BCMA	ORR, CR	ORR: 98.3%, CR: 70.3%
Zhang, 2023 [52]	Phase I clinical trial	12	OriCAR–017	GPRC5D	ORR, sCR	sCR: 60%, VGPR: 40%
Zhao, 2018 [21]	Phase I clinical trial	57	LCAR-B38M	BCMA	ORR	ORR: 88% (95% CI, 76–95)
Zhao, 2022 [53]	Phase I clinical trial	74	LCAR-B38M	BCMA	ORR, PFS, DOR, OS	ORR: 87.8%; median PFS: 18.0 mo; median DOR: 23.3 mo; 24 mo OS: 63.4%
Zweegman, 2023 [54]	Phase II clinical trial	19	Cilta-cel	BCMA	ORR, PFS	ORR: 100%; 12-mo PFS: 90%
Jagannath, 2025 [55]	Ph Ib/II follow-up	97	Cilta-cel	BCMA	PFS, OS	5-year PFS: 33%; median OS: 60.7 mo
Sidana, 2025 [56]	Real-world cohort	255	Cilta-cel	BCMA	mORR, PFS	mORR: 88%; 12-mo PFS: 71%
Ailawadhi, 2024 [57]	Ph III KarMMa–3 final	386	Ide-cel	BCMA	mPFS	mPFS: 13.8 vs 4.5 mo (HR 0.48)
Bal, 2024 [58]	Ph I	79	BMS (GPRC5D)	GPRC5D	ORR, CR	ORR: 96%, CR: 75%
Yao, 2025 [59]	Ph I	9	Bispecific BCMA/GPRC5D CAR	BCMA + GPRC5D	ORR, sCR	ORR: 78%, sCR: 33%
Dholaria, 2025 [60]	Ph I	27	PBCMA-ALLO1 (allogeneic)	BCMA	ORR	ORR: 67% (Arm C)

The "Target" column lists antigen targets only (e.g., BCMA, CD19, GPRC5D). Structural domains frequently reported in manuscripts – CD8α (hinge/transmembrane), CD28 or CD137/4-1BB (co-stimulatory), and CD3-ζ (signaling) – are not antigen targets. BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; CR/sCR, complete response/stringent complete response; CTL, cytotoxic T lymphocytes; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GPRC5D, protein-coupled receptor class C group 5 member D; HRQOL, health-related quality of life; CI, confidence interval; MCARH, modified chimeric antigen receptor human; MRD, minimal residual disease; NKG2D, natural killer group 2, member D; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete respons; VGPR, very good partial response; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel.

Figure 2 includes 19 studies that evaluated ORR in patients with MM treated with CAR-T therapies. The studies varied in the number of participants and the specific CAR-T therapy used. The results of each study are summarized below, along with the overall analysis. The studies by Mei et al., Zhao et al., and Li et al. reported ORRs of 0.87 (95% CI: 0.68–0.95), 0.88 (95% CI: 0.77–0.94), and 0.90 (95% CI: 0.74–0.97), respectively [19, 21, 23]. Other studies, such as Mailankody et al., presented an ORR of 0.56 (95% CI: 0.41–0.70), while Raje et al. reported an ORR of 0.85 (95% CI: 0.69–0.93) [4, 38]. Xia et al. and Shi et al. showed ORRs of 0.91 (95% CI: 0.76–0.97) and 0.92 (95% CI: 0.81–0.97), respectively [47, 50]. One of the studies with the most weight in the analysis was Berdeja et al., with an ORR of 0.97 (95% CI: 0.91–0.99), contributing 21.72% of the total weight [27]. Other relevant studies include Shao et al. (ORR 0.97; 95% CI: 0.86–1.00) and Zhang et al. (ORR 0.98; 95% CI: 0.91–1.00), the latter representing 25.38% of the total weight [22, 45]. The meta-analysis showed a combined ORR of 0.94 (95% CI: 0.93–0.96), indicating high effectiveness of CAR-T therapies in treating patients with MM. The heterogeneity index (I^2) was 0.00%, suggesting low variability between studies.

Safety

In terms of safety, several key outcomes were reported, mainly related to CRS and other adverse events (Table 2).

CRS incidence was a common finding in most studies; however, it was mostly reported as grade 1–2. Mei et al. reported that 82.6% of patients treated with BM38 CAR-T experienced CRS, predominantly grade 1–2 [19]. Yan et al. found that 61.9% of patients receiving anti-CD19 and anti-BCMA CAR-T combination therapy presented CRS, mainly grade 1–2 [24]. Wang et al., with CT103A, observed CRS in 70.6% of patients, also grade 1–2 [20]. Zhang et al. documented a high incidence of CRS in 96.7% of patients treated with LCAR-B38M, with 16.7% experiencing grade 3 [22]. Similarly, Li et al. reported CRS in 96.7% of patients treated with anti-BCMA CAR-T, mostly grade 1–2 [23].

Other studies also reported consistent CRS and adverse event

results. Zhang et al., with JNJ-68284528, found CRS in 90% of patients, though with a low incidence of severe cases [22].

In addition to CRS, other significant adverse events were reported. Mei et al. and Yan et al. documented cases of neurotoxicity, although to a lesser extent compared to CRS [19, 24]. For example, Mei et al. reported neurotoxicity in 13% of patients, while Yan et al. observed it in 19% of cases [19, 24]. Li et al. reported a neurotoxicity incidence of 16.7%, with no severe cases [23].

Figure 3 presents the results of 23 studies that evaluated the frequency of grade I/II CRS in patients with MM treated with CAR-T therapies. The studies varied in the number of participants and the specific CAR-T therapy used. The results of each study are summarized below, along with the overall analysis.

The studies by Mei et al., Yan et al., and Wang et al. reported grade I/II CRS frequencies of 0.87 (95% CI: 0.68–0.95), 0.90 (95% CI: 0.71–0.97), and 0.72 (95% CI: 0.49–0.88), respectively [19, 20, 24]. Other studies, such as Zhao et al., presented a frequency of 0.89 (95% CI: 0.79–0.95), while Raje et al. reported a frequency of 0.76 (95% CI: 0.59–0.87) [4, 21]. Xia et al. and Cohen et al. showed frequencies of 0.76 (95% CI: 0.59–0.87) and 0.88 (95% CI: 0.70–0.96), respectively [30, 50].

The study with the most weight in the analysis was Berdeja et al., with a grade I/II CRS frequency of 0.95 (95% CI: 0.88–0.98), contributing 13.16% of the total weight [27]. Other relevant studies include Zhang et al., with a frequency of 0.98 (95% CI: 0.91–1.00), and Martin, 2022, with a frequency of 0.96 (95% CI: 0.88–0.98), representing 25.09% and 10.70% of the total weight of the analysis, respectively [22, 40].

The meta-analysis showed a combined grade I/II CRS frequency of 0.89 (95% CI: 0.88–0.91), indicating that most patients experienced mild to moderate CRS. The heterogeneity index (I^2) was 0.00%, suggesting low variability between the included studies.

Phase III clinical trials

Table 3 presents the efficacy and safety results of two phase III clinical trials.

Efficacy. The Sidiqi et al. study included 208 patients treated with cilta-cel, targeting BCMA, compared to pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) in lenalidomide-refractory MM patients [61]. The efficacy measure was PFS, showing a hazard ratio (HR) of 0.26 with statistical significance ($P < 0.0001$), indicating a significant reduction in the risk of disease progression or death in the intervention group.

On the other hand, the Rodriguez-Otero et al. study included 386 patients treated with ide-cel, also targeting BCMA, compared with five standard regimens [62]. PFS was the efficacy measure, showing an HR for disease progression or death of 0.49 (95% CI: 0.38–0.65; $P < 0.001$), indicating a significant reduction in the risk of progression or death compared to standard regimens.

Safety. In terms of safety, Sidiqi et al. reported that CRS occurred in 76% of patients, with only 1% experiencing grade 3 [61]. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 5% of patients at any grade, with no grade 3/4 cases. Other neurotoxicities were observed in 17% of patients at any grade, including cranial nerve paralysis (9%), peripheral neuropathy (3%), and one case of grade 1 movement/neurocognitive-related adverse events.

In the Rodriguez-Otero et al. study, CRS was reported in 93% of patients, with 11 patients (5%) experiencing grade 3 or higher CRS, and two patients (1%) dying due to CRS [62]. Neurotoxicity occurred in 15% of patients at any grade, with 3% being grade 3 or higher.

High-grade toxicity and other adverse events. Across 32 studies reporting granulometry, grade ≥ 3 CRS occurred in 9% (range 0–17%) and grade ≥ 3 ICANS in 4% (0–12%). Prolonged cytopenia > 60 days was documented in 42% of idecel and 37% of ciltacel recipients. Serious infections (≥ grade 3) were reported in 23% overall, most frequently viral reactivations. Two cases of therapy-related myeloid neoplasm emerged beyond 24 months. No treatment-related mortality exceeded 2% in contemporary protocols employing early tocilizumab and corticosteroid escalation.

Duration of response, overall survival, and CAR-T persistence. Median duration of response (DOR) exceeded 18 months for ciltacel and 11 months for ide-cel (Table 4). Five-year follow-up of LCARB38M demonstrated a 23.3-month median DOR and 63.4% 24-month OS. CAR-transgene persistence was detectable at ≥ 12 months in 61% of CT103A-treated patients but < 28 days for the allogeneic product ALLO-715, consistent with lower long-term activity. Longer persistence correlated qualitatively with PFS plateaus, although causal inference is limited in single-arm data.

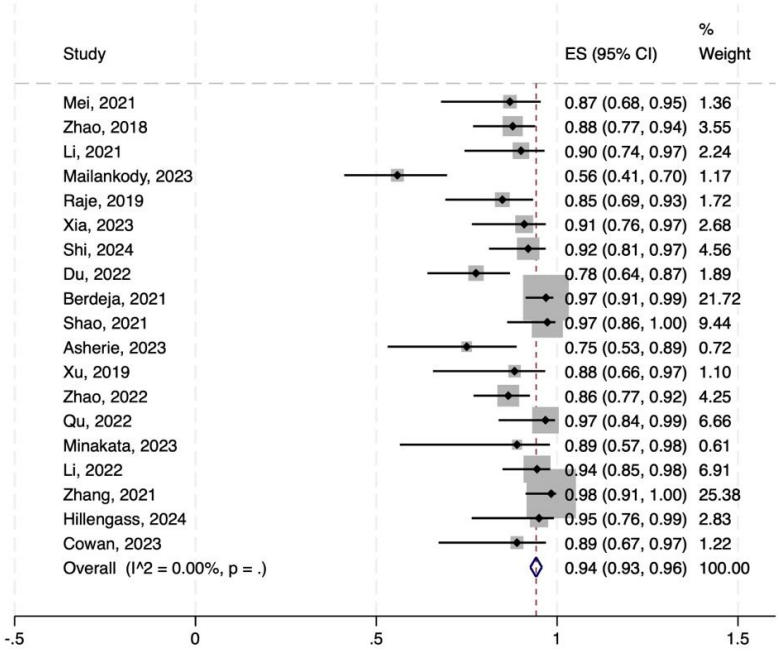

Figure 2 Meta-analysis of ORR proportions.
This *P*-value corresponds to a high level of heterogeneity. ORR, overall response rate; CI, confidence interval; ES, effect size.

Table 2 Safety results

Author, Year	Target	Safety	Result
Asherie, 2023 [25]	BCMA	CRS, neurotoxicity, neutropenia, lymphopenia, thrombocytopenia, anemia	Grade 1–2 CRS: 90%, Grade 3–4 CRS: 0%, Any grade neurotoxicity: 0%, Grade 3–4 neutropenia: 100%, Grade 3–4 lymphopenia: 100%, Grade 3–4 thrombocytopenia: 60%, Grade 3–4 anemia: 65%
Baumeister, 2019 [26]	NKG2D and CD3-ζ	Adverse events ≥ Grade 3, autoimmune reactions	26 adverse events ≥ Grade 3, none attributed to NKG2D CAR-T cells. No severe autoimmune reactions observed.
Berdeja, 2021 [27]	BCMA and CD3-ζ	CRS, neurotoxicity	CRS: 95% (92 of 97 patients), experienced CRS, 21% (20 of 97 patients)
Hu, 2022 [28]	BCMA	CRS	CRS: 97% of patients (96/99), grades 1–2: 52.1%, grade 3: 43.8%, grade 4: 4.1%
Chen, 2021 [29]	BCMA, CD19, and CD3-ζ	CRS, hematological toxicities	CRS: 6 patients (1 patient with grade 3, managed with tocilizumab); common hematological toxicities were leukopenia (6 patients), anemia (3 patients), and thrombocytopenia (3 patients)
Cohen, 2019 [30]	BCMA and CD3-ζ	CRS, neurotoxicity	CRS: 88% (Grade 3–4: 32%), Neurotoxicity: 32% (Grade 3–4: 12%)
Cowan, 2023 [31]	BCMA	Grade 3 or higher non-hematological adverse events	Hypophosphatemia: 78% (14/18); Fatigue: 61% (11/18); Hypocalcemia: 50% (9/18); Hypertension: 39% (7/18)
Du, 2022 [32]	BCMA, CD137, and CD3-ζ	CRS, neurological toxicity, infections, febrile neutropenia	CRS: 34.69% (Grade 1–2: 28.57%, Grade 3: 6.12%), Neurological toxicity: 0%, Infections: 28.57% (pulmonary infection), Febrile neutropenia: 100% (leukopenia)
Frigault, 2023 [33]	CD8a and CD3-ζ	TEAEs, CRS, ICANS	100% of patients experienced Grade 3 or 4 TEAEs, CRS occurred in all patients (1 case of Grade 3 CRS in DL2), ICANS in 2 patients (1 in DL1 and 1 in DL2)
Garfall, 2018 [34]	CD19	Adverse events ≥ Grade 3	Several adverse events ≥ Grade 3, most attributed to high-dose melphalan.
Hillengass, 2024 [35]	BCMA	TEAEs, neurotoxicity	Grade 3/4 hematological TEAEs: leukopenia, lymphopenia, and thrombocytopenia in Cohort A; Neurotoxicity in Cohort B (26%)
Li, 2021 [23]	BCMA	CRS, hematological toxicities	CRS: 96.7% (80% Grade 1–2, 16.7% Grade 3), Hematological toxicities: 100%
Li, 2022 [36]	BCMA and CD19	PHT	Severe neutropenia: 52%, Severe anemia: 30%, Severe thrombocytopenia: 31%
Mailankody, 2022 [37]	GPRC5D and CD3-ζ	CRS, ICANS, cerebellar disorders	CRS: 88%; Grade 4 ICANS in 1 patient; Grade 3 cerebellar disorder in 2 patients
Mailankody, 2023 [38]	BCMA	Adverse events ≥ Grade 3	88% of patients experienced adverse events ≥ Grade 3
Manjunath, 2021 [39]	BCMA and CD3-ζ	Grade 4 hematological toxicity, Grade 3–4 neurotoxicity, Grade 3–4 CRS	Hematological toxicity: 25% (Group C); Neurotoxicity: 25% (Group C); CRS: 25% (Group C)
Martin, 2022 [40]	BCMA	CRS	CRS: 95%, median onset at 7 days, median duration 4 days
Mei, 2021 [19]	BCMA and CD38	CRS, hematological toxicities	CRS: 87%, Neutropenia: 96%, Leukopenia: 87%, Anemia: 43%, Thrombocytopenia: 61%
Minakata, 2023 [41]	BCMA	Adverse events of special interest, CRS, and neurotoxicity	Grade 3/4 cytopenia in all patients, Grade 1/2 CRS in 100% of patients, 11% Grade 2 neurotoxicity
Munshi, 2021 [42]	BCMA	Cytokine release syndrome, neurotoxicity, hematological toxicity	CRS: 84% (107 of 128 patients), Neurotoxicity: 18% (23 of 128 patients), Neutropenia: 91% (117 of 128 patients), Anemia: 70% (89 of 128 patients), Thrombocytopenia: 63% (81 of 128 patients)
Oliver-Caldés, 2023 [17]	BCMA	CRS and neurotoxic events	CRS in 80% of patients (all Grade 1–2), no neurotoxic events observed
Qu, 2022 [43]	BCMA	TEAEs, CRS, ICANS	CRS: 93.5%, Grade 3 CRS: 9.7%, Grade 1 ICANS: 3.2%
Raje, 2019 [4]	BCMA and CD137	Hematological toxicities, cytokine release syndrome, neurological toxicities, and infections	Neutropenia: 85%, Leukopenia: 58%, Anemia: 45%, Thrombocytopenia: 45%, CRS: 76%, Neurological toxicities: 42%, Infections: 42%
Ri, 2022 [44]	BCMA and CD3-ζ	Grade 3 or 4 AEs, CRS	Grade 3 or 4 AEs: 88.9%, CRS: 88.9%
Shao, 2021 [45]	BCMA	Incidence of CRS and coagulation dysfunction	CRS: 100%; 91% developed at least one abnormal coagulation parameter

Table 2 Safety results (*continued*)

Author, Year	Target	Safety	Result
Shi, 2022 [46]	BCMA and CD19	CRS	100% of patients: 50% Grade 1, 50% Grade 2
Shi, 2024 [47]	BCMA and CD19	CRS, neurotoxic events	Grade 3 or higher CRS: 8%, Grade 1 neurotoxic events: 4%
Wang, 2021 [48]	CD8a and CD3- ζ	CRS	70.6% of patients experienced Grade 1 or 2 CRS
Wang, 2022 [49]	BCMA	$CD14^+$ expression in CAR-T cells	Reduced manufacturing failures using DPBS (14.3% failures with X-VIVO15 vs 0% with DPBS)
Xia, 2023 [50]	GPRC5D, CD8a, and CD3- ζ	Incidence and severity of CRS and neurotoxicities	CRS: 76% (all Grade 1 or 2), Neurotoxicities: 9%
Xu, 2019 [51]	BCMA and CD3- ζ	CRS	10 cases of mild CRS, 6 severe but manageable CRS, one death from severe toxic reaction
Yan, 2019 [24]	BCMA and CD19	CRS, hematological toxicities	CRS: 90%, Neutropenia: 86%, Anemia: 62%, Thrombocytopenia: 62%
Zhang, 2021 [22]	BCMA and CD3- ζ	CRS	CRS in 60 of 61 patients (98.4%); Grades 1–2: 33 cases, Grade 3: 23 cases, Grade 4: 4 cases
Zhang, 2023 [52]	GPRC5D	CRS, hematological toxicity	100% CRS: 90% Grade 1, 10% Grade 2, 100% neutropenia, 90% thrombocytopenia, 90% leukopenia, 70% anemia
Zhao, 2018 [21]	BCMA	CRS	CRS: 90%
Zhao, 2022 [53]	BCMA	AEs, CRS	Grade ≥ 3 AEs: 60.8%, CRS: 91.9% (Grade ≥ 3: 9.5%)
Zweegman, 2023 [54]	BCMA	CRS, ICANS	CRS: 84.2% (Grade 4 in 1 patient), ICANS: 1 patient (Grade 1)
Jagannath, 2025 [55]	BCMA	CRS, ICANS	CRS: 4%, ICANS: 2%
Sidana, 2025 [56]	BCMA	CRS, ICANS	CRS: 6%, ICANS: 3%
Ailawadhi, 2024 [57]	BCMA	CRS, ICANS	CRS: 0%, ICANS: 2%
Bal, 2024 [58]	GPRC5D	CRS, ICANS	CRS: 3%, ICANS: 0%
Yao, 2025 [59]	Dual	CRS, ICANS	CRS: 11%, ICANS: 0%
Dholaria, 2025 [60]	BMCA	CRS, ICANS	CRS: 0%, ICANS: 0%

AEs, adverse events; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; CRS, cytokine release syndrome; DL, dose level; DPBS, Dulbecco's phosphate-buffered saline; GPRC5D, G protein-coupled receptor, class C, group 5, member D; ICANS, immune effector cell-associated neurotoxicity syndrome; MCARH, modified chimeric antigen receptor human; NKG2D, natural killer group 2, member D; PHT, prolonged hematologic toxicity; sCR, stringent complete response; TEAEs, treatment-emergent adverse events; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel.

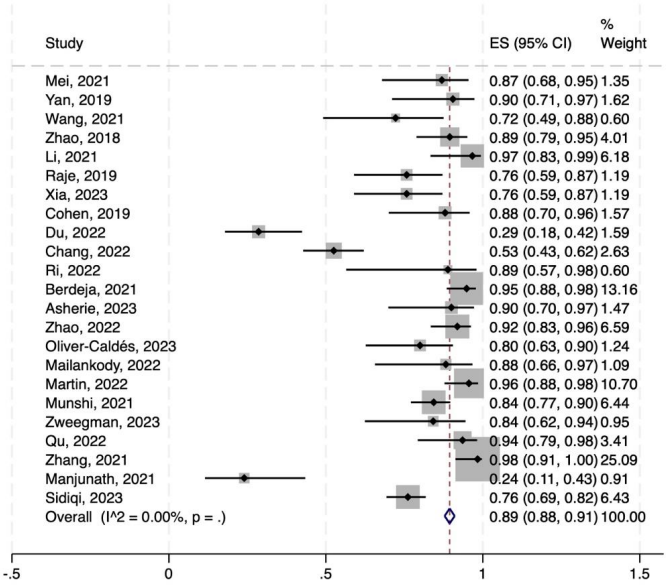

Figure 3 Meta-analysis of grade I/II CRS.
This *P*-value corresponds to a high level of heterogeneity. CRS, cytokine release syndrome; CI, confidence interval; ES, effect size.

Table 3 Efficacy/effectiveness and safety results in phase III clinical trials

Author, Year	Sample size	Intervention	Target	Comparator	Efficacy	Comparison of intervention and comparator	Safety	Safety in the intervention
Sidiqi, 2023 [61]	208	Cilta-cel	BCMA	PVd or DPd	PFS	HR: 0.26; $P < 0.0001$	CRS, ICANS	CRS: 76% any grade, 1% Grade 3; ICANS: 5% any grade, 0% Grade 3/4; Other neurotoxicities: 17% any grade, 2% Grade 3/4 (including cranial nerve paralysis 9%, peripheral neuropathy 3%, and one case of Grade 1 movement/neurocognitive-related AE)
Rodriguez-Otero, 2023 [62]	386	Ide-cel	BCMA	Standard regimens (five different regimens)	PFS	HR for disease progression or death: 0.49 (95% CI, 0.38 to 0.65; $P < 0.001$)	Grade 3 or 4 adverse events	CRS: 93%
San-Miguel, 2024 [63]	419	Cilta-cel	BMCA	SOC	Overall survival	30mo OS 76.4% vs 63.8% (HR 0.55)	CRS, ICANS	≥ G3 CRS: 1%, ICANS: 0%
Ailawadhi, 2024 [57]	386	Ide-cel	BMCA	SOC	mPFS	mPFS 13.3 vs 4.4 mo (HR 0.49)	CRS, ICANS	≥ G3 CRS: 0%, ICANS: 2%

BCMA, B-cell maturation antigen; PVd, pomalidomide, bortezomib, and dexametasone; DPd, daratumumab, pomalidomide, and dexametasone; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CRS, citoquine release syndrome; Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; SOC, standard of care.

Table 4 Infusion schedule, target dose, and in-vivo persistence

Product	Infusion schedule	Target dose	Reported in vivo persistence*
Cilta-cel	Single	0.75×10^6 CAR$^+$ cells/kg	Median 277 days
Ide-cel	Single	150×10^6 to 450×10^6 cells	Median 4.2 months
CT103A	Single	1.0×10^6 cells/kg	Detectable ≥ 12 months (61%)
LCAR-B38M	3 split (20/30/50%)	0.5×10^6 cells/kg	Median 8 months
ALLO–715	Single	320×10^6 cells	< 28 days

*Persistence assessed by CAR-transgene PCR where reported. Cilta-cel, ciltacabtagene autoleucel; Ide-cel, idecabtagene vicleucel; CAR, chimeric-antigen-receptor.

Updated evidence published August 2024 – July 2025

Six additional studies met the original eligibility criteria. Five focused on BCMA-directed products and one on the GPRC5D epitope. Notably, the 5-year follow-up of CARTITUDE-1 confirmed a 33% PFS rate and a median OS of 60.7 months after a single infusion of cilta-cel in triple-class–exposed patients. A 16-centre US real-world series (n = 255) reproduced high efficacy (ORR 88%, 12-month PFS 71%) with acceptable grade ≥ 3 CRS (6%). The final KarMMa3 analysis (median follow-up 30.9 months) showed ide-cel maintained a PFS advantage vs standard regimens (HR 0.48) without new safety signals. Two first-in-human platforms – GPRC5D-targeted BMS986393 (ORR 96%, CR 75%) and a bispecific BCMA/GPRC5D CAR (ORR 78%) – demonstrated potent activity, while the fully allogeneic product P-BCMA-ALLO1 yielded an early ORR of 67% with no ≥ grade 3 CRS.

Factors influencing efficacy outcomes. Descriptive subgroup synthesis suggested higher ORR for dual-target or bispecific constructs (median 96%) compared with singletarget BCMA (median 87%). Autologous products with 4-1BB costimulation trended toward longer median PFS than CD28-based designs (12 vs 9 months). Responses were attenuated in cohorts with high-risk cytogenetics or ≥ 5 prior lines (pooled ORR 82%). Conditioning with fludarabine/cyclophosphamide was associated with greater in vivo expansion, echoing published pharmacokinetic models. These exploratory signals did not warrant additional metaregression.

Risk of bias assessment. The risk of bias assessment for Phase III clinical trials, specifically in the studies by Sidiqi et al. and Rodriguez-Otero et al., revealed significant differences [61, 62]. The former had "some concerns" in the domains of randomization process, effect of assignment to intervention, and selective outcome reporting, and was assessed as "high risk" for outcome measurement. In contrast, Rodriguez-Otero et al. showed "low risk" in all evaluated domains [62]. Both studies adequately managed missing outcome data, being classified as "low risk" in this aspect. Overall, the global risk was considered "some concerns" for Sidiqi et al., and "low risk" for Rodriguez-Otero et al. [61, 62]. These results suggest that the findings of Rodriguez-Otero et al. (2023) may be more robust and less susceptible to bias than those of San Miguel et al. (2023) (Table 5).

Risk of bias in early-phase and single-arm studies. Thirty-eight non-randomised trials were appraised with ROBINS-I (Table 6). Most showed a moderate overall risk owing to confounding (absence of control) and selective outcome reporting; three first-in-human studies were judged serious because of incomplete safety follow-up. No study reached a low risk rating across all seven domains.

Table 5 Risk of bias assessment for phase III clinical trials

Domain	Randomization process	Effect of assignment to intervention	Missing outcome data	Outcome measurement	Selection of reported results	Overall risk
Sidiqi, 2023 [61]	Some concerns	Some concerns	Low risk	High risk	Some concerns	Some concerns
Rodriguez-Otero, 2023 [62]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
San-Miguel, 2024 [63]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ailawadhi, 2024 [57]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns

Table 6 ROBINS-I risk-of-bias summary for the 38 non-randomised/early-phase studies

ROBINS-I domain	Low risk n (%)	Moderate risk n (%)	Serious risk n (%)
Confounding	0 (0%)	35 (92%)	3 (8%)
Selection of participants	10 (26%)	25 (66%)	3 (8%)
Classification of interventions	32 (84%)	6 (16%)	0 (0%)
Deviations from intended interventions	30 (79%)	8 (21%)	0 (0%)
Missing data	34 (89%)	4 (11%)	0 (0%)
Measurement of outcomes	24 (63%)	11 (29%)	3 (8%)
Selection of reported results	22 (58%)	13 (34%)	3 (8%)
Overall judgment	0 (0%)	35 (92%)	3 (8%)

Discussion

This study provides a comprehensive systematic review of the efficacy and safety of CAR-T cell therapies in patients with RRMM. Through the analysis of 40 clinical studies, our findings indicate that CAR-T therapy targeting BCMA and other antigens has shown significantly high ORR and CR in a population with high refractoriness and short survival. Specifically, some studies reported ORRs exceeding 90%, highlighting the potential of this therapy to achieve robust responses. Additionally, notable improvements in PFS and OS were observed compared to standard treatments. For example, the median PFS in the Phase 3 study by Rodriguez-Otero was 13.3 months, while in the anti-CD38-resistant population, a median PFS of 3.4 months was reported in the Mammoth study [1]. The incidence of adverse events, such as CRS and neurotoxicity, was very high, with almost all patients developing adverse events; however, most were grade 1–2. Safety remains a significant concern, affecting the long-term tolerability of these therapies.

When comparing this therapeutic strategy with bispecific antibodies, which are more accessible in Latin America, we found that Teclistamab in the MajesTEC1 study achieved an ORR of 65% and CR in 39.4%, similar to real-world data with this molecule [64, 65]. Notably, 77% of patients in this trial were triple-refractory, and 30% were penta-refractory. However, Frigault et al. report that in a population where all patients were at least triple-refractory, an ORR of 100% and CR of 76% was achieved [33]. These results are remarkable in a population with median survivals not exceeding 10 months. In our setting, the use of bispecific antibodies is more feasible, as they do not require extensive infrastructure, and the acquisition time is much shorter. Nonetheless, the potential advantages of CAR-T cell therapy in terms of effectiveness cannot be denied.

Moreover, the duration of response and improvements in PFS and OS observed in our analysis are consistent with previous studies. Zhao et al. reported a median PFS of 15 months with LCAR-B38M therapy, underscoring the durability of response in patients treated with CAR-T [21]. In the Rodriguez-Otero study, the median PFS was 13.3 months (65% triple-refractory), similar to that achieved with Teclistamab, which had a median PFS of 11.3 months in a comparable population [64, 65].

Regarding safety, there is variability in the reported toxicity profiles. For instance, Zhang et al. reported a high incidence of CRS (96.7%) with 16.7% of severe cases in patients treated with LCAR-B38M, whereas other studies, such as Oliver-Caldés et al., indicated lower rates of severe adverse events, finding a CRS incidence of 80%, all grade 1–2, with no neurotoxic events observed [17, 22]. These differences may be attributed to variations in CAR-T manufacturing and administration protocols, as well as the demographic and clinical characteristics of the patient cohorts studied. Furthermore, heterogeneity in the assessment and reporting of adverse events complicates direct comparison between studies, highlighting the need for standardization in CAR-T clinical trials.

One of the main limitations of our review is the heterogeneity among the included studies, particularly regarding the different types of CAR-T used and varying treatment regimens. Additionally, many of the studies analyzed have small sample sizes and short-term follow-up, which may affect the generalizability of the results. Another limitation is the variability in the evaluation and reporting of adverse events, which makes direct comparison between studies difficult.

However, a significant strength of this study is the systematic and comprehensive approach to synthesizing the available evidence, providing an integrated view of the current state of knowledge on CAR-T therapies in the treatment of MM. Moreover, the use of a meta-analysis of proportions has allowed for a robust combination of data from multiple studies, offering more precise estimates of the efficacy and safety of these therapies.

The findings of our review have important implications for clinical practice and future research. In clinical practice, CAR-T therapies targeting BCMA and other antigens should be considered a highly effective option in patients with RRMM, particularly in those refractory to multiple therapies. However, close monitoring of patients for potential adverse events, such as CRS and neurotoxicity, is crucial, and standardized protocols for managing these side effects should be developed. The social conditions in Latin America currently limit access to CAR-T cell therapy, making the use of bispecifics a tool already in use in some countries in the region.

The maturation of BCMA-CAR-T programmes – exemplified by 5-year CARTITUDE1 data – signals a plausible curative plateau for a subset of RRMM patients. Early-line integration (CARTITUDE-4, KarMMa-3) is already redefining standard care in first relapse, and health economic modelling suggests that frontloaded cost may be offset by durable remissions. Beyond MM, my view is that the next strategic inflection points will come from: (i) allogeneic “off-the-shelf” platforms that cut vein-to-vein time to < 72 h, using TALEN- or CRISPR-edited donor T cells; (ii) dual-target or logicgated CARs (e.g., BCMA/GPRC5D) to prevent single-antigen escape; (iii) armoured

CARs secreting cytokine or checkpoint-blocking payloads to sustain activity in solid-tumour stroma; and (iv) controlled-activation technologies (mRNA, ON-switch receptors) to mitigate late neuro-toxicities. Parallel expansion into autoimmune diseases – lupus, myasthenia – illustrates the broader translational horizon for engineered T cells. To realise these prospects, harmonised long-term registries and real-world pharmacovigilance are essential complements to conventional trials.

In terms of research, additional studies with larger sample sizes and long-term follow-up are needed to evaluate the durability of response and long-term toxicity profiles of CAR-T therapies. Future research should also focus on optimizing CAR-T cell manufacturing and administration protocols to reduce costs, variability in outcomes, and improve standardization of these therapies.

Conclusion

In conclusion, our systematic review demonstrates that CAR-T cell therapies, especially those targeting BCMA, are highly effective in the treatment of RRMM, showing significantly improved response rates and survival. However, the incidence of severe adverse events underscores the need for careful patient monitoring and management. Additional studies are required to confirm these findings and optimize the use of these innovative therapies in clinical practice.

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