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Subsequent CAR-T and engineered antibody for relapsed/refractory multiple myeloma following BCMA-targeted treatment: a systematic review and meta-analysis

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Abstract

Relapse following B-cell maturation antigen (BCMA)-directed therapies represents a critical challenge in relapsed/refractory multiple myeloma (R/R MM). We performed a systematic review and meta-analysis of 35 studies (n = 1,302) published between 2020 and 2025 to evaluate salvage CAR-T versus engineered antibody therapies post-BCMA exposure. The pooled overall response rate (ORR) was 60%. CAR-T therapy achieved significantly superior ORR compared to antibody-based approaches (77% vs 52%; p < 0.0001), with comparable complete response rates. While incidences of CRS and ICANS were similar, grade ≥ 3 cytopenias were more frequent with CAR-T. Notably, GPRC5D-targeted CAR-T yielded higher ORRs than BCMA-targeted constructs (86% vs 66%; p = 0.0006). Furthermore, patients with prior exposure to BCMA bispecific antibodies exhibited lower response rates compared to those with prior CAR-T exposure (71% vs 86%; p = 0.0404). In conclusion, GPRC5D CAR-T demonstrates superior efficacy to engineered antibodies in the post-BCMA setting. These findings support prioritising earlier CAR-T use and underscore the importance of antigen selection in optimising treatment sequencing.

Introduction

The robust development of immunotherapies designed to re-educate the immune system to recognise and eliminate target cells has given rise to a paradigm shift in treating patients with multiple myeloma (MM). Among the most promising and extensively studied targets is B-cell maturation antigen (BCMA), a transmembrane glycoprotein highly expressed on myeloma cells but limited to normal tissues, making it an ideal therapeutic target. BCMA-directed strategies, involving antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), and chimeric antigen receptor (CAR) -T therapies, have reshaped the therapeutic landscape of MM and are being increasingly integrated into clinical practice. Belantamab mafodotin (belamaf) is a first-in-class ADC which delivers cytotoxic payloads directly to myeloma cells. Although belamaf monotherapy failed to demonstrate a progression-free survival (PFS) advantage in the DREAMM-3 trial and was withdrawn from the market[1], recent evidence from combination regimens has revived interest and led to the approval in the UK and European Union for patients with early relapse after first-line therapy[2, 3]. Two commercial CAR-T products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), representing the most potent forms of BCMA-targeted treatment, have achieved deep and durable remissions in patients who have exhausted conventional therapies[4, 5]. In addition, BsAbs, particularly bispecific T-cell engagers, can facilitate the formation of immunological synapses and CD4 + and CD8 + T cells to proliferate, generate cytokines, and kill malignant cells in a polyclonal manner. Teclistamab and elranatamab were BCMA-directed BsAbs approved for treating adults with relapsed or refractory (R/R) MM[6, 7]. Nevertheless, about half of the patients receiving BCMA CAR-T experienced disease progression[4, 5, 8–10].

Mechanisms underlying resistance and relapse to BCMA-targeted immunotherapies have been identified, including immune escape by tumour cells, intrinsic T-cell factors, and extrinsic factors from the immunosuppressive tumour microenvironment (TME) that impede sustained immune activity[11]. Initial investigations into the mechanisms have facilitated the advancement of personalised interventions and innovative adaptive therapeutic strategies. A second BCMA-targeted treatment is thought to be a viable option for subsequent anti-myeloma therapy (sAMT); however, the sequential use of various BCMA-targeted modalities raises concerns regarding potential cross-resistance. In early-phase clinical trials[12–16], novel targets such as GPRC5D and FcRH5 have shown promising efficacy and manageable side-effect profiles, making an immunotherapy that is feasible for patients who are relapsing on BCMA-directed treatment. Meta-analyses suggest that BCMA CAR-T therapy as a third-line or later intervention achieves higher complete response (CR) rates compared with BsAb, though it is also associated with increased rates of adverse events (AE)[17, 18]. Conversely, a single-centre comparative study reported no significant differences in PFS between CAR-T and BsAb cohorts, underscoring the ongoing debate regarding the optimal sequencing of immunotherapies[19]. Given the rapidly expanding population of patients previously exposed to BCMA-targeted therapies and the current lack of evidence-based guidance regarding the choice of immunotherapy modality or antigen target, we conducted a systematic review and meta-analysis of clinical trials and real-world retrospective studies evaluating CAR-T cells and engineered antibody therapies in patients with prior BCMA-targeted treatment. The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Methods

Systematic literature search process

This systematic review was prospectively registered in PROSPERO (CRD420251083913) and conducted in accordance with PRISMA guidelines. A comprehensive literature search was performed across PubMed, Embase, Web of Science, and the Cochrane Library, covering the period from June 12, 2020, to June 12, 2025. The search strategy was developed in collaboration with a medical information specialist and independently peer-reviewed following the PRISMA-S recommendations. The search framework incorporated controlled vocabulary terms (MeSH/Emtree: “Multiple Myeloma,” “BCMA,” “Receptors”, “Chimeric Antigen”) combined with predefined free text keywords (e.g., “GPRC5D,” “FcRH5,” “bispecific antibody,” “CAR-T”). A population filter was applied to identify studies enrolling patients with relapsed/refractory multiple myeloma previously exposed to BCMA-directed therapies (e.g., “salvage therapy,” “sequential therapy,” “BCMA-exposed”). Intervention terms encompassed chimeric antigen receptor T cell therapies and engineered antibody platforms, including BsAbs and ADCs. To minimize publication bias, grey literature was systematically reviewed through manual screening of ASH, EHA (2020–2025), and ClinicalTrials.gov was queried for completed or ongoing studies lacking published results. All retrieved records were deduplicated in EndNote X9 and screened in blinded, dual-reviewer mode using Rayyan.

Study selection

Studies were eligible for inclusion if they met all of the following criteria: (1) Prospective clinical trials or retrospective observational studies; (2) Enrolled patients with R/R MM, defined according to IMWG criteria; (3) Included patients previously treated with at least one BCMA-directed agent (CAR-T cells, BsAbs, or ADC), while allowing prior exposure to non-BCMA targeted therapies; (4) Reported at least one prespecified clinical outcome, including CR rate,

overall response rate (ORR), very good partial response (VGPR) rate, partial response (PR) rate, cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), or haematologic toxicities. Studies were excluded if they met any of the following criteria: (1) No documented prior exposure to BCMA-targeted therapy; (2) Employed combination regimens involving ≥ 2 immune-based therapeutics (e.g., dual target CAR-T constructs, BsAbs plus ADC, or BsAbs combined with proteasome inhibitors or corticosteroids as multi-agent immunotherapy dominated regimens); (3) Did not provide sufficient data to assess efficacy or safety outcomes.

Data extraction and quality assessment

Two investigators (Qiaolin Liu and Yun Kang) independently extracted data from all eligible studies using a standardized template. Duplicate reports originating from the same study centre were manually identified and removed to avoid redundancy. Key parameters included trial identifiers (name, registration number), publication details (journal, year, first author), and clinical profiles (median age, median prior treatment lines, high-risk cytogenetic profile, penta-refractory MM). Additional parameters were extracted: The Revised International Staging System (R-ISS) stage III proportion, and extramedullary disease. Efficacy endpoints included CR, VGPR rate, PR rate, ORR and mPFS. Safety outcomes contained CRS, ICANS, infection, anaemia, thrombocytopenia and neutropenia incidence.

Methodological quality and risk of bias were assessed using the Methodological Index for Non-Randomised Studies (MINORS)[20], with independent scoring by QLL and YK. Discrepancies were resolved through consensus or third-party adjudication. Publication bias was evaluated using Begg's test (two-tailed $P < 0.05$ indicating significance). Data extraction and bias assessment workflows followed PRISMA guidelines to ensure reproducibility.

Statistical analysis

The primary outcome measure for this meta-analysis was the ORR. Secondary outcomes included the CR, VGPR rate, CRS-related AEs, severe CRS (grade 3 or higher), ICANS, severe ICANS (grade 3 or higher), and the incidence of anaemia, thrombocytopenia, and neutropenia. Given the predominance of single-arm studies, a random-effects model was implemented to synthesize pooled estimates for all outcomes, with corresponding 95% confidence intervals (CIs) and P values, using the restricted maximum likelihood method. Heterogeneity was quantified using the I^2 statistic.

Subgroup analyses were conducted using the Q statistic to evaluate outcomes stratified by treatment type (e.g., CAR-T therapy, BsAbs). To investigate heterogeneity within the CAR-T group, studies were further grouped by product type. Meta-regression analysis was performed to identify potential confounders influencing ORR, including the types of product, extramedullary disease, high-risk cytogenetic abnormalities, median age, median prior lines of therapy, and penta-refractory MM. Continuous variables (e.g., median age) were analysed via weighted regression, while categorical variables were assessed using the Mann-Whitney U test to compare proportions between subgroups. Sensitivity analysis was conducted using a leave-one-out approach, iteratively excluding individual studies to assess their impact on pooled effect sizes (Figure S1). All statistical tests were two-sided, with $P < 0.05$ considered significant. Analyses were performed in R Studio (version 2023.12.1) using the meta and metafor packages. Data visualization was generated using forest plots and funnel plots to evaluate publication bias.

Results

Literature search

From an initial database query of 5273 records, 2844 studies were selected for full-text review following deduplication and title/abstract screening. Consistent with predefined exclusion criteria, 35 studies comprising 1302 patients (CAR-T cells: n = 13; engineered antibody therapies: n = 22) were ultimately included in the quantitative pooled analysis (Fig. 1).

Baseline Study Characteristics

Baseline characteristics of the 35 included studies are summarized in supplement Table 1. All studies were published between 2021 and 2025. Engineered antibody therapies trials evaluated teclistamab (n = 9)[21–29], talquetamab (n = 4)[30–33], cevostamab (n = 2)[16, 34], RO7297089 (n = 1)[35], modakafusp alfa (n = 1)[36], belamaf (n = 1)[37], elranatamab (n = 2)[38, 39], linvoseltamab (n = 1)[40], and RG6234 (n = 1)[41], while CAR-T cell therapy trials (n = 13) investigated commercial products (n = 4)[9, 42–44], and those still in clinical trials (n = 9)[12, 45–52]. Most patients had undergone multiple prior lines of systemic therapy and presented with highly-invasive disease.

Table 1
Additional characteristics of the included trials

Product	Target	Types	Register No.	Study design	MINOR	Total pts	ORR, %	Overall survival	With BCM
									No. of BCMA-exposed pts
Modakafusp Alfa	CD38	immunocytokine	NCT03215030	prospective	16	146	120mg: 32 240mg: 41	120mg: 4.1mos 240mg: 5.3mos	66
Teclistamab	BCMA	BsAb	/	retrospective	14	123	59	8.7mos	45
Teclistamab	BCMA	BsAb	NCT03145181 NCT04557098	prospective	16	40	/	/	40
Teclistamab	BCMA	BsAb	/	retrospective	14	22	/	/	22
Teclistamab	BCMA	BsAb	/	retrospective	14	110	62	6-month PFS rate 52%, 6-month OS rate 80%	38
Teclistamab	BCMA	BsAb	/	retrospective	14	22	/	/	22
Teclistamab	BCMA	BsAb	/	retrospective	14	164	BCMA-naive: 68	BCMA-naive:9.7 mos/NR	60
Teclistamab	BCMA	BsAb	/	retrospective	14	210	all: 67	all:6-month PFS 53%	84
							BCMA-naive: 74	BCMA-naive:6-month PFS 63%	
Teclistamab	BCMA	BsAb	/	retrospective	14	106	66	5.4mos/NR	56
Teclistamab	BCMA	BsAb	/	retrospective	14	33	46	OS: 17.7 weeks	20
Elranatamab	BCMA	BsAb	NCT03269136 NCT04649359 NCT05014412	retrospective	14	86	/	/	86
Elranatamab	BCMA	BsAb	/	retrospective	14	34	53	/	26

Product	Target	Types	Register No.	Study design	MINOR	Total pts	ORR, %	Overall survival	With BCM
									No. of BCMA-exposed pts
Linvoseltamab	BCMA	BsAb	NCT03761108	prospective	16	117	200 mg: 71 50 mg: 48	200mg: NR/31.4mos	10
RO7297089	BCMA	BsAb	NCT04434469	prospective	16	27	7	/	5
Talquetamab	GPRC5D	BsAb	NCT03399799 NCT04634552	prospective	16	537	0.4 mg/kg:74 0.8 mg/kg:69	0.4 mg/kg:7.5mos/NR 0.8 mg/kg:11.2mos/NR	78
Talquetamab	GPRC5D	BsAb	/	retrospective	14	68	71	4.9mos/NR	63
Talquetamab	GPRC5D	BsAb	/	retrospective	14	55	BCMA-naive: 68	BCMA-naive:0.67 mos/NR	24
Talquetamab	GPRC5D	BsAb	/	retrospective	14	138	65	6.4mos/NR	71
RG6234	GPRC5D	BsAb	NCT04557150	prospective	16	105	IV: 71 SC: 60	/	18
Cevostamab	FcRH5	BsAb	NCT03275103	prospective	16	167	BCMA-naive: 61	/	96
Cevostamab	FcRH5	BsAb	NCT05535244	prospective	16	42	CAR-T:73, ADC:60, BsAb:10	/	42
Belantamab mafodotin	BCMA	ADC	/	retrospective	14	82	43	3.8mos/17.2mos	18
HRC0202	BCMA	CAR-T	NCT04003168	prospective	16	7	/	9mos	7
cilta-cel	BCMA	CAR-T	NCT04133636	prospective	16	20	/	9.1mos	20
ide-cel and cilta-cel	BCMA	CAR-T	/	retrospective	14	36	/	9.6mos	36
HBI0101	BCMA	CAR-T	NCT04720313	prospective	16	50	90	10.6mos	12
ide-cel	BCMA	CAR-T	NCT03361748	prospective	16	821	73	8.8mos	123

Product	Target	Types	Register No.	Study design	MINOR	Total pts	ORR, %	Overall survival	With BCM
									No. of BCMA-exposed pts
Equecabtagene Autoleucel	BCMA	CAR-T	ChiCTR2000033946	prospective	16	101	96	/	12
P-BCMA-ALLO1	BCMA	CAR-T	NCT04960579	prospective	16	5	/	/	5
anti-GPRC5D CAR T	GPRC5D	CAR-T	ChiCTR2100048888	prospective	16	37	/	4.5mos	37
CC-95266	GPRC5D	CAR-T	NCT06297226	prospective	16	84	87	14.5 mos	38
OriCAR-017	GPRC5D	CAR-T	NCT05016778	prospective	16	10	100	11.4 mos	5
DM91	GPRC5D	CAR-T	NCT05739188	prospective	16	7	86	/	3
MCARH109	GPRC5D	CAR-T	NCT04674813	prospective	16	17	71	150×10^6group 7.8mos	10
CT071	GPRC5D	CAR-T	NCT05838131	prospective	16	17	94	/	4

No.= number. Pts= patients. ORR = overall response rate. PFS = progression-free survival. OS = overall survival. CAR = chimeric antigen receptor. BsAb = bisp conjugates. Mos=months. SC=subcutaneous. IV=intravenous.

Overall, the included studies demonstrated robust quality as evaluated by the MINORS scale (Table 1)[20]. Publication bias was formally assessed using Begg's and Egger's tests. Significant publication bias was detected across evaluated endpoints: response rate (Begg's test $P = 0.50$; Egger's test $P < 0.05$) with graphical confirmation in Figure S2A.

Comparative Efficacy and Safety Outcomes

Efficacy of CAR-T vs. Engineered Antibody Therapies

The aggregate pooled CR was 27% (95% CI 0.19–0.36). No significant difference in CR was observed between the CAR-T cell group (30%, 95% CI 0.16–0.43) and engineered antibody therapies group (26%, 95% CI 0.16–0.37, Fig. 2A). The overall pooled proportion of ORR was 60% (95% CI 0.53–0.67). There was a significant difference in ORR between CAR-T group and the engineered antibody therapies group ($P < 0.01$); 77% (95% CI 0.69–0.85) in the CAR-T group and 52% (95% CI 0.44–0.59) in the engineered antibody therapies group (Fig. 2B). Subgroup analysis stratified by CAR-T regimen and products revealed that heterogeneity primarily originated from diversity in product types. In Table 1, the median PFS period for the CAR-T group is longer than that of the antibody group. Moreover, we performed a meta-analysis of the mPFS between the CAR-T group (n = 1) and the antibody group (n = 5), revealing a median PFS of 8.9 months and 3.62 months, respectively (Figure S2B, $P = 0.1174$).

Safety Profile: CAR-T vs. Engineered Antibody Therapies

In the analysis related to AEs, CAR-T therapy was associated with a higher incidence of AEs. The incidence rate of CRS was in the CAR-T group (67%) compared with the engineered antibody therapies group (69%) Figure S3A. Grade ≥ 3 CRS occurred in 3% of patients in the CAR-T group and 1% in the engineered antibody therapies group ($P > 0.05$) Figure S3B. The incidence rate of ICANS was in the CAR-T group (10%) compared with the engineered antibody therapies group (8%) Figure S3C. The incidence rate of grade ≥ 3 ICANS was 1% in the CAR-T group and 2% in the engineered antibody therapies group Figure S3D. About haematologic adverse effect, the incidence rate of neutropenia was 87% in the CAR-T group and 57% in the engineered antibody therapies group (Fig. 3A, $P = 0.0674$). The incidence rate of anaemia was 67% in the CAR-T group and 56% in the engineered antibody therapies group (Fig. 3C, $P = 0.0552$). The incidence rate of thrombocytopenia was 85% in the CAR-T group and 42% in the engineered antibody therapies group (Fig. 3E, $P < 0.01$). Intergroup disparities were observed in the occurrence of haematologic adverse events of grade 3 or higher, notably with neutropenia at an incidence of 79% (95% CI 0.70–0.89) in the CAR-T group and 47% (95% CI 0.34–0.59) for the engineered antibody therapies group (Fig. 3B, $P < 0.01$). Similarly, the rate of anaemia of grade 3 or higher was markedly higher in the CAR-T group with 60% (95% CI 0.47–0.72) while 38% (95% CI 0.28–0.47) within the engineered antibody therapies group (Fig. 3D, $P < 0.01$). The rate of thrombocytopenia of grade 3 or higher was markedly higher in the CAR-T group with 65% (95% CI 0.53–0.77) and 29% (95% CI 0.22–0.36) within the engineered antibody therapies group (Fig. 3F, $P < 0.01$). The rate of grade ≥ 3 infections was higher with CAR-T therapy (22%; 95% CI 0.10–0.38) than with engineered antibodies (37%; 95% CI 0.23–0.50), although the difference was not statistically significant (Figure S4, $P = 0.114$). Given the limited number of studies, these results require further validation.

Meta-Regression Insights and Clinical Implications

To explore potential sources of heterogeneity, we conducted mixed-effects meta-regression analyses incorporating key moderators, including patient demographics, disease characteristics, and methodological variables (Table 2). This approach enabled simultaneous evaluation of heterogeneity determinants while adjusting for relevant covariates. In univariate meta-regression, treatment therapeutics emerged as a significant moderator of ORR, with GPRC5D-directed CAR-T therapy demonstrating superior efficacy compared with teclistamab (P < 0.001). For FcRH5-targeted BsAbs, cevostamab demonstrated a significantly lower ORR compared with teclistamab (P = 0.004). In contrast, for GPRC5D-targeted BsAbs, talquetamab achieved a significantly higher ORR than teclistamab (P = 0.03). Subgroup analyses based on therapeutic targets further supported these findings. ORR was higher in GPRC5D CAR-T (86%; 95% CI 0.79–0.93) than in BCMA CAR-T (66%; 95% CI 0.58–0.75) (Fig. 4A, P < 0.001). Among antibody-based therapies, ORR varied by target: 52% (95% CI 0.43–0.61) for BCMA-directed agents, 63% (95% CI 0.56–0.69) for GPRC5D-directed agents, and 44% (95% CI 0.16–0.71) for FcRH5-directed agents (Fig. 4B, P < 0.001). Talquetamab also demonstrated higher ORR than teclistamab (65% [95% CI 0.59–0.71] vs. 53% [95% CI 0.48–0.58], P = 0.0037) (Fig. 4C). Prior BCMA-directed exposure influenced CAR-T outcomes: ORR was higher in patients previously treated with BCMA CAR-T (86%; 95% CI 0.77–0.94) than in those exposed to BCMA BsAbs (71%; 95% CI 0.61–0.82) (Fig. 4D, P = 0.04). In contrast, prior exposure type did not significantly affect outcomes among patients receiving BsAbs (Fig. 4E, P = 0.664). In the CAR-T subgroup, ORR was 65% (95% CI 0.55–0.76) for commercial products and 84% (95% CI 0.77–0.90) for investigational CAR-T therapies (Figure S5A, P < 0.01). In engineered antibody therapies group, ORR was 57% (95% CI 0.50–0.64) for commercial products and 36% (95% CI 0.18–0.54) for CAR-T therapies in trials (Figure S5B, P = 0.0031).

Table 2
Univariate meta-regression analysis to explore the factors that affect the overall response rate

Variables	Coefficient	SE	95% CI	P
commercial CAR-T	0.444	0.253	(0.949–2.562)	0.08
GPRC5D CAR-T	1.517	0.332	(2.378–8.746)	**< 0.001**
BCMA CAR-T	0.747	0.489	(0.809–5.509)	0.127
Cevostamab	-0.802	0.278	(0.260–0.773)	**0.004**
Talquetamab	0.486	0.224	(1.048–2.522)	**0.03**
Extramedullary disease	-0.021	0.013	(0.954–1.005)	0.114
High-risk cytogenetic profile	0.002	0.046	(0.916–1.096)	0.965
R-ISS stage III	-0.044	0.073	(0.830–1.103)	0.543
Median age (years)	-0.088	0.073	(0.794–1.057)	0.228
Median prior lines of therapy	-0.258	0.223	(0.499–1.195)	0.246
Penta refractory MM	-0.021	0.023	(0.936–1.023)	0.343

CAR= chimeric antigen receptor. R-ISS = The Revised International Staging System. MM = multiple myeloma. SE=standard error. CI=confidence interval.

Discussion

Clinical trials and real-world data on CAR-T and engineered antibody therapy have shown promising results as sAMT for patients who first achieve remission preceding relapse. Individuals who experience relapse on BCMA-targeted therapy frequently exhibit resistance to standard regimens and necessitate the development of innovative therapeutic agents. The optimal strategy for sequential immunotherapies remains elusive. To address this gap, we conducted the first systematic review and meta-analysis comparing the outcomes of 1,302 R/R MM patients with prior exposure to BCMA-targeted therapy who subsequently received CAR-T or engineered antibody therapies.

Our findings indicate that CAR-T therapy induced more favourable response rates than engineered antibody treatment. These benefits, however, were accompanied by a higher incidence of severe haematologic toxicities, including neutropenia, anaemia, and thrombocytopenia. The rates of ICANS and CRS were comparable between CAR-T and engineered antibody therapies, suggesting that neurotoxicity and cytokine-driven toxicities are not disproportionately increased with either treatment approach. Our analysis revealed that GPRC5D represents a more advantageous subsequent target than BCMA, as GPRC5D CAR-T products demonstrate higher response rates, even in the early stages of development. Nevertheless, there was insufficient evidence concerning whether patients underwent BCMA-directed therapy as salvage treatment immediately following a prior BCMA-directed therapy. The interval between targeted therapy may be considered an important consideration for conducting subsequent treatment. In the BsAb cohort, target antigen correlates with efficacy; across 13 studies evaluating talquetamab and teclistamab, talquetamab consistently yielded superior response rates. Meta-regression analyses further confirmed that GPRC5D CAR-T therapy (P < 0.001) and talquetamab (P = 0.03) maintained superior response rates even after adjusting for confounders such as prior treatment intensity and target selection. However, cevostamab was found to be an adverse factor (P = 0.004). Furthermore, patients with prior CAR-T therapy exhibited a higher overall response rate upon subsequent immunotherapy compared to those previously treated with bispecific, implying that BsAb exposure was a risk factor for regaining remission.

Previous BsAb exposure has been responsible for hindering the effectiveness of subsequent T-cell-redirected therapies. In the CAMMA 2 trial of cevostamab for patients previously exposed to BCMA-targeted treatment, the ORR for the group with a prior BsAb was 10%, which was significantly lower than that for the cohort with a prior ADC (60%) or CAR-T therapy (73%)[34]. In the MonumenTAL-1 study of talquetamab, patients with exposure to BCMA CAR-T achieved better ORR compared to those with exposure to BsAb, with rates of 74% versus 58%, respectively[30]. However, patients who had BsAb as the immediate previous line of therapy had an ORR of 29%, but those who received BsAb prior to the final line of therapy had an ORR of 68%[53]. It suggests that the impact

of BsAb on the immune system may diminish over time. In terms of CAR-T therapy, the mPFS for the prior BCMA BsAbs was 2.8 months in the real-world experience of SOC ide-cel, whereas the median PFS were not reached for the prior CAR-T and 9.0 months for no prior BCMA treatment[43]. A multi-centre study in Germany pointed out that patients with double exposure to teclistamab talquetamab experienced a median PFS of 4.4 months following commercial BCMA CAR-T across all exposure groups[54]. Our analysis revealed no significant difference in PFS between the CAR-T group and the engineered antibody group; however, given to the scarcity of analysable studies, further research providing survival-related data is necessary to substantiate this conclusion. The sequence of CAR-T therapy and BsAb may affect the therapeutic benefit, since T-cell exhaustion caused by exposure to several BsAb treatments may be a contributing factor to poor efficacy outcomes. These observations underline the need to carefully consider treatment sequencing, as different T-cell–engaging modalities may exert distinct influences on the efficacy of subsequent immunotherapies.

The divergent outcomes of CAR-T therapies and engineered antibody therapies as sAMT could be partially attributed to multiple factors. Among engineered antibody therapies, BsAb stood out. BsAbs require repeated administration and function by redirecting preexisting T cells to eliminate malignant cells, of which the response is highly dependent on the endogenous T-cell repertoire[55]. Impaired cytotoxicity of BsAbs has been associated with an increased proportion of T cells expressing exhaustion markers, as well as expansion of regulatory T cells (Tregs)[56]. Likewise, exhausted-like T-cell clones within the bone marrow have been implicated in primary resistance or early relapse in patients receiving BCMA-CD3 BsAbs[56]. While the composition of the T-cell compartment at the time of leukapheresis also influences CAR-T efficacy[57], the genetic engineering and ex vivo expansion processes equip CAR-T cells with enhanced receptor signalling capacity, robust proliferative potential, and sustained immune surveillance that is independent of MHC restriction. These properties may reduce the effects of patient heterogeneity on T-cell fitness. The efficiency of allogeneic off-the-shelf CAR-T products as salvage therapies further shows the potential to address host T-cell variability[47]. In addition to mechanistic differences, treatment accessibility and timing may also contribute to the observed efficacy differences between the two approaches. CAR-T therapy involves personalised manufacturing and lymphodepleting treatment before infusion, whereas BsAbs are “off-the-shelf” and can be administered rapidly, which is advantageous in aggressive disease. However, in the long term, CAR-T continues to exhibit more profound and persistent responses, thereby emphasizing its importance as a more potent therapeutic option[18]. On the other hand, the higher incidence of severe haematological toxicity in CAR-T therapies have been related to the myelotoxicity of conditioning chemotherapy[58]. Moreover, delayed haematopoietic recovery after CAR-T infusion was linked to reduced niche function and elevated inflammation-related cytokines in bone marrow, which can damage haematopoietic stem cells and impair long-term bone marrow reconstitution[59].

In addition to the availability of immunotherapy modalities, several tumour-associated factors account for the target selection after BCMA treatment in the context. Poor PFS after initial BCMA-targeted therapy correlates with specific baseline characteristics, including high-risk cytogenetics, R-ISS stage III disease, extramedullary disease, poor performance status, and elevated metabolic tumour volume (MTV)[60, 61]. Indeed, outcomes with SOC ide-cel and cilta-cel pointed out that prior BCMA-targeted therapy had a negative impact on PFS[62, 63]. Nonetheless, BCMA-negative relapse following CAR-T therapy, driven by genomic loss or mutation, has been reported infrequently[64, 65].

Biallelic loss of TNFRSF17 (which encodes BCMA) at relapse has been shown to down-regulate BCMA expression and drive the expansion of dominant myeloma clones. Among patients who initially responded to CAR-T but later relapsed, monoallelic and biallelic BCMA losses were detected in 12% and 6%, respectively—compared with 4% at baseline[66]. Building on this, emerging evidence also suggests that high MTV combined with low pretreatment soluble BCMA levels may indicate plasma cell populations with absent or down-regulated BCMA expression, potentially conferring a higher risk of antigen-negative relapse[61]. Even though antigen escape might not be the main cause of relapse, the therapeutic pressure of previous BCMA-targeted therapy could render subsequent BCMA-directed treatments less effective. GPRC5D is an alternative target of sAMT, which is identified in over 50% of CD138 + MM cells in more than 65% of patient samples, and has a complementary distribution pattern to BCMA expression across patient samples[67]. MCARH109, a GPRC5D CAR-T with a human B-cell-derived scFv, has shown clinical responses at all dose levels in patients with prior BCMA-targeted CAR-T therapies, which were slightly higher than those without BCMA treatment exposure (ORR 75% vs 71%; CR 37.5% vs 35%)[12]. Similarly, OriCAR-017, a bi-epitopic GPRC5D CAR-T, achieved an ORR of 100% and a sCR rate of 40% among five patients with prior BCMA CAR-T therapy, including two who relapsed with BCMA-negative disease[14]. These results collectively emphasize the potential of GPRC5D as a prospective therapeutic target in the future and establish the capacity to circumvent resistance mechanisms that restrict the efficacy of repeated BCMA-directed strategies.

This meta-analysis acknowledges several inherent constraints. As a single-arm trial synthesis, the investigation lacked the capacity to assess patient-level variables comprehensively. Additionally, the limited cohort size may restrict broader applicability. Notably, while significant intergroup heterogeneity was detected through multiple outcome measures, subsequent stratification analyses were not pursued to elucidate these variations. Despite these methodological drawbacks, our rigorous inclusion protocols and advanced statistical approaches validated the therapeutic advantages of T cell-mediated interventions for R/R MM. The systematic methodology employing stringent selection criteria and robust analytic frameworks maintained scientific validity despite the acknowledged limitations.

In summary, our study demonstrated superior therapeutic potential of CAR-T therapy as a subsequent intervention for patients relapsing after prior BCMA-directed treatments, though with elevated AEs. Furthermore, the vast majority of AEs are manageable. Future studies should focus on refining patient selection, optimising sequential therapy strategies, and exploring alternative antigen targets such as GPRC5D and FcRH5 to overcome resistance and further improve clinical outcomes in this high-risk population. Treatment selection necessitates strict integration of individualized patient profiles, incorporating molecular biomarkers, prior therapy responses, and comorbidities guided by precision oncology principles (NCCN Guidelines v3.2023).

Abbreviations

relapsed/refractory multiple myeloma (R/R MM); cytokine release syndrome (CRS); immune effector cell - associated neurotoxicity syndrome (ICANS); multiple myeloma (MM); antibody-drug conjugates (ADCs); bispecific antibodies (BsAbs); chimeric antigen receptor (CAR); Belantamab mafodotin (belamaf) ; progression-free survival (PFS); idecabtagene vicleucel (ide-cel); ciltacabtagene autoleucel (cilta-cel); immunosuppressive tumour microenvironment (TME);

subsequent anti-myeloma therapy (sAMT); complete response (CR); adverse events (AE); overall response rate (ORR); very good partial response (VGPR); partial response (PR) ; Revised International Staging System (R-ISS); Methodological Index for Non-Randomised Studies (MINORS); confidence intervals (CIs); metabolic tumour volume (MTV).

Declarations

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Contributors MH and KY designed the study. KY and LQL screened studies, interpreted data, performed statistical analysis, and wrote the manuscript. LQL, KY performed the literature search. MH, KY and SCY verified extracted data and contributed to manuscript revision. All authors approved the final version of the manuscript and takes full responsibility for the decision to submit for publication.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

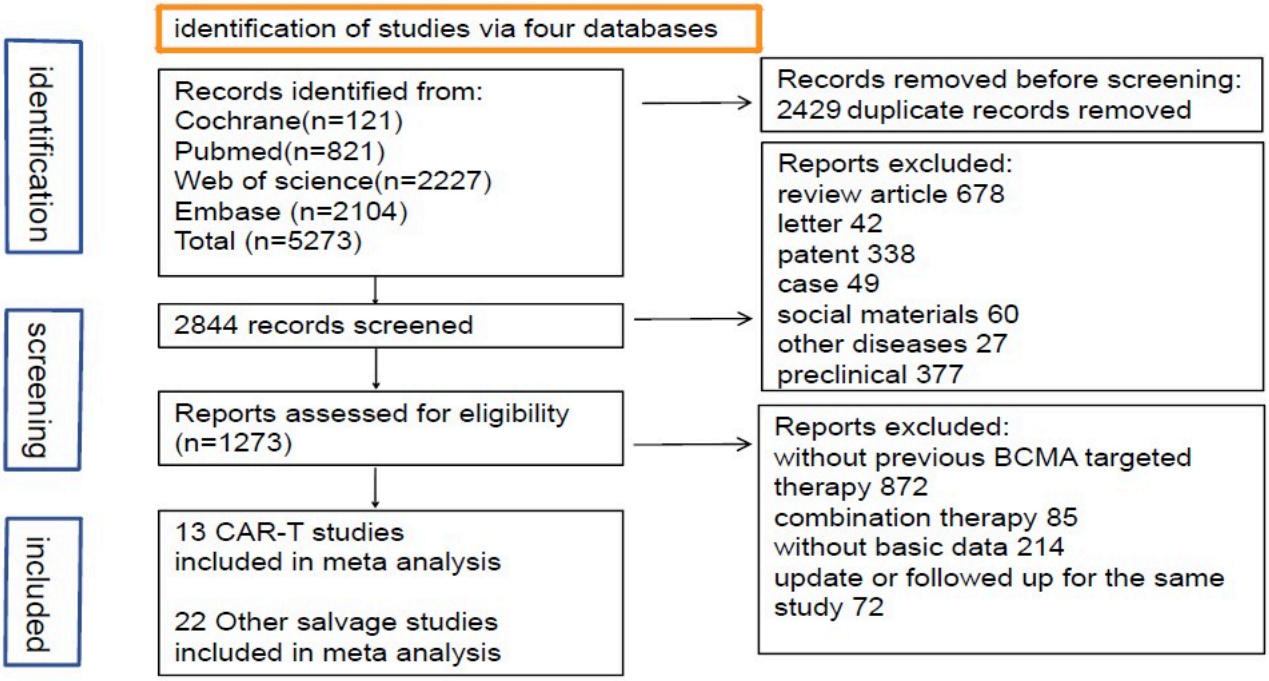


Figure 1

Trial selection flow diagram.

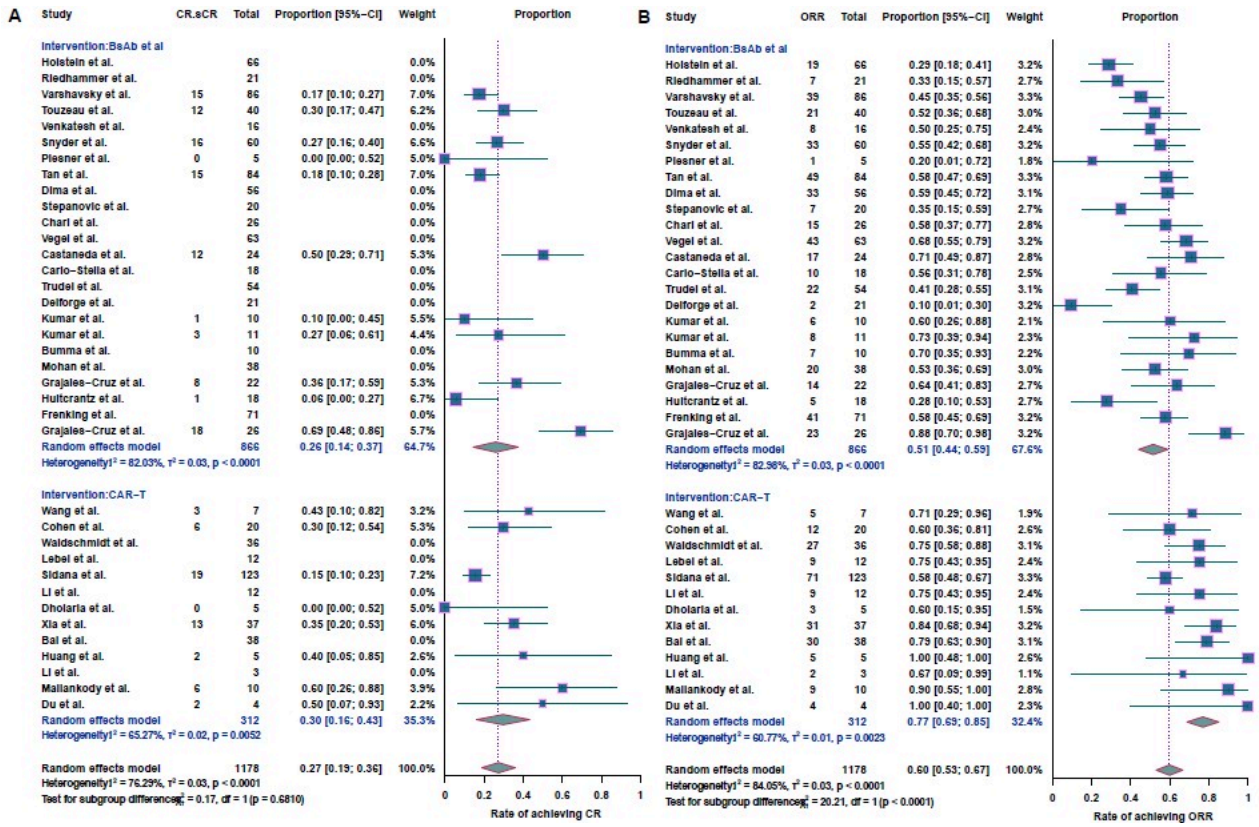


Figure 2

Forest plot of the efficacy on CAR-T and engineered antibody therapies. (A) Complete response (CR) rate; (B) overall response rate. CAR, chimeric antigen receptor.

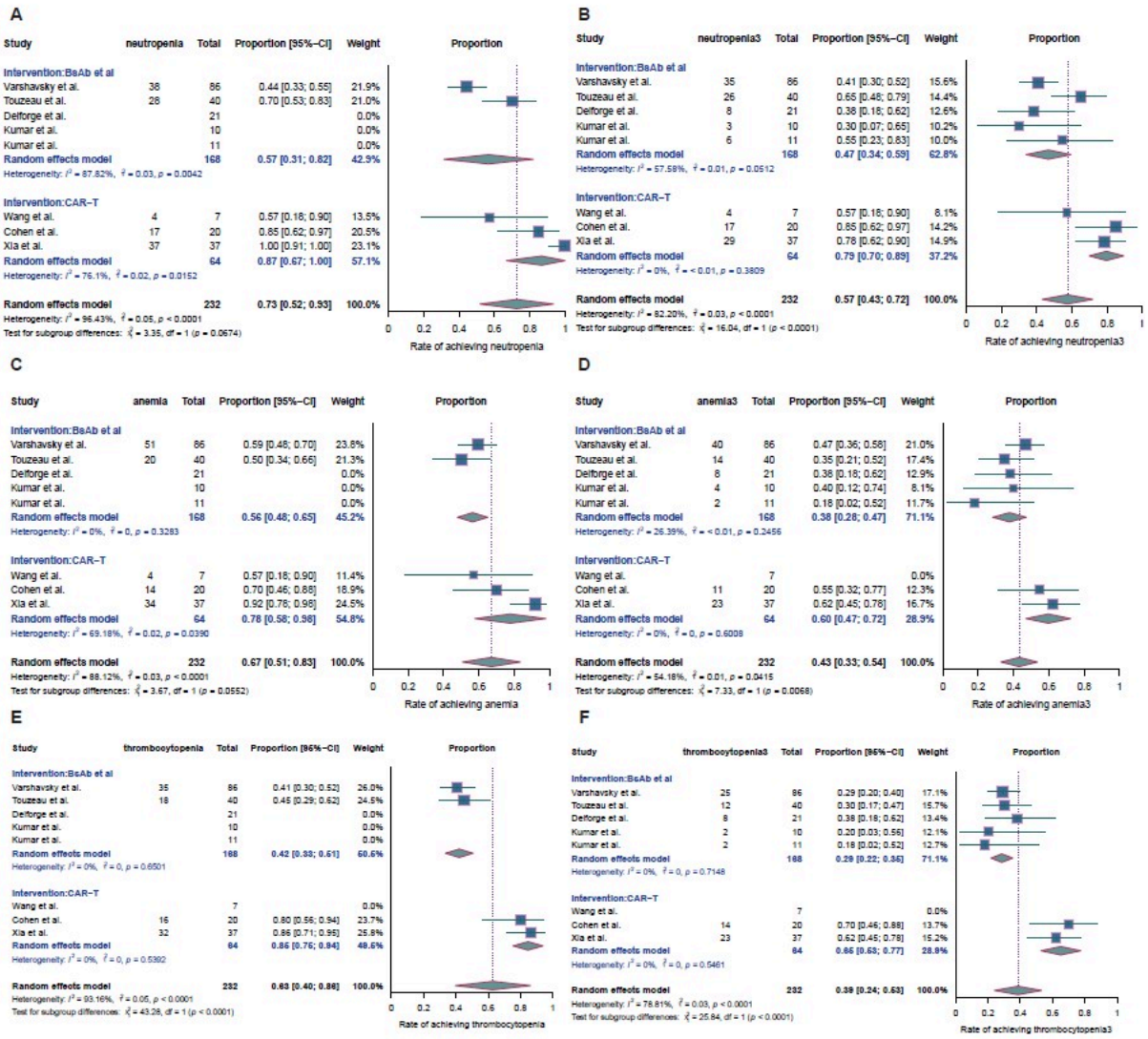


Figure 3

Forest plot of the adverse events rate on CAR-T and engineered antibody therapies. (A) neutropenia; (B) neutropenia (grade ≥3); (C) anaemia; (D) anaemia (grade ≥3); (E) thrombocytopenia; (F) thrombocytopenia (grade ≥3). CAR, chimeric antigen receptor.

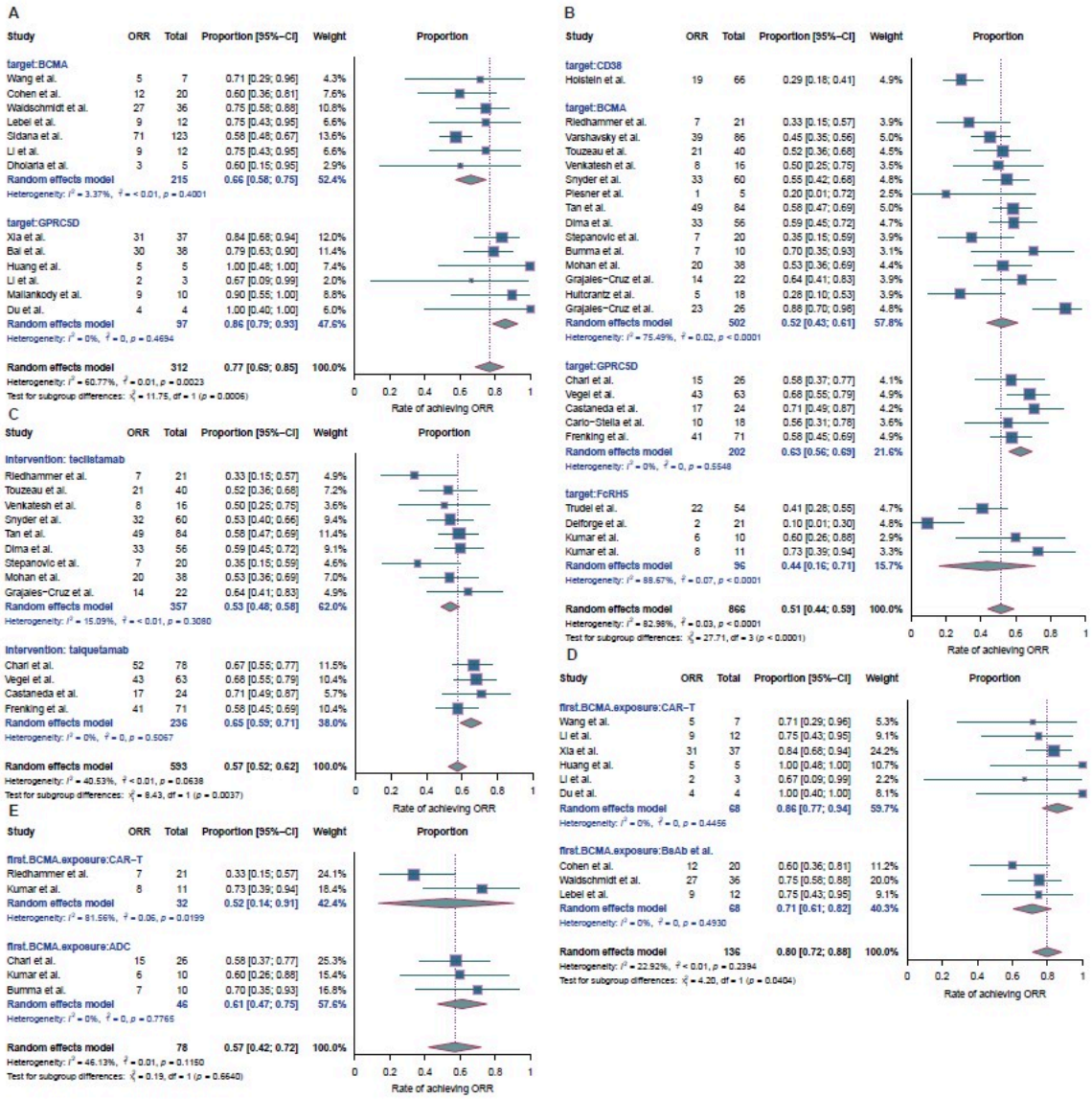


Figure 4

Forest plot of the overall response rate in different subgroup. (A) different targets in CAR-T group; (B) different targets in engineered antibody group; (C) teclistamab and talquetamab; (D) different types of BCMA exposure in CAR-T group; (E) different types of BCMA exposure in engineered antibody group. CAR, chimeric antigen receptor.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigures.docx
- Table12.docx