Safety and efficacy of BCMA CAR-T *vs*. bispecific antibodies in patients with relapsed multiple myeloma: a systematic review and meta-analysis

B-cell maturation antigen (BCMA) has emerged as a promising target in patients with relapsed multiple myeloma (MM) and the approval of two different types of T-cell engagement therapies – chimeric antigen receptor T-cell (CAR-T) therapy and bispecific antibodies (BsAb) – has revolutionized outcomes.[1] To date, two BCMA-targeting CAR-T products, idecabtagene vicleucel and ciltacabtagene autoleucel, have been approved as earlier lines of therapy, and two BsAb, teclistamab and elranatamab, for patients who have received four or more lines of therapy.[2-5]

CAR-T therapy is a one-time treatment with complex logistics, while BsAb is an "off-the-shelf" treatment given continuously.[6] Both treatments exhibit unique adverse events.[6] We performed a systematic review and meta-analysis of clinical trials evaluating the safety and efficacy of BCMA CAR-T and BsAb in patients who had received at least three prior lines of therapy.

We included clinical trials that investigated BCMA-targeting CAR-T and BsAb in patients with relapsed or refractory MM who had received three or more prior lines of therapy. An extensive literature search was performed using MEDLINE, Scopus and the Cochrane Central Register of Controlled Trial databases between inception and May 31, 2024, using the term "CAR-T" "bispecific antibodies" "BCMA" and "multiple myeloma". We also conducted a search of conference abstracts of the American Society of Clinical Oncology, American Society of Hematology, and European Hematology Association since 2010. The studies were evaluated by two independent reviewers (HV and BD) based on the following inclusion criteria: (i) BCMA CAR-T or BsAb investigated in MM clinical trials; (ii) included patients who had received three or more prior lines of therapy and had been exposed to proteosome inhibitors, immunomodulatory drugs, and/or CD38; (iii) phase I and phase II trials in which the recommended dose was confirmed, and efficacy was evaluated. The study followed PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines and was prospectively registered with the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42024549186).

A total of 2,269 articles that investigated BCMA-targeting CAR-T or BsAb in MM were identified. After careful consideration of the inclusion criteria, 23 studies involving 1,767 patients were included in our analysis (*Online Supplementary Figure S1*). The baseline characteristics of the 23 studies (26 cohorts due to different dose levels) are shown in Table 1. Overall, 14 studies investigated CAR-T (N= 604 patients) and nine were BsAb trials (N=1,163 patients).

The pooled overall response rate (ORR) was 59% (95% confidence interval [95% CI]: 55-63) in the BsAb group with moderate-high variation across the studies (I^2 42%, P=0.06). In the CAR-T group, the pooled ORR was 88% (95% CI: 72-96) with significant variation in the reported response rates across studies (I^2 75%, P<0.0.01). The meta-regression model predicting ORR showed significantly higher rates of ORR with CAR-T than with BsAb (odds ratio [OR]=3.9, 95% CI: 1.8-8.8, P<0.001). CAR-T was associated with significantly deeper responses compared to BsAB. The pooled rate of complete response and better was significantly higher with CAR-T (54%) than with BsAb (31%) (OR=2.67, 95% CI: 1.45-4.91, P=0.002) (Figure 1A). Similarly, CAR-T was associated with a higher rate of very good partial responses or better: 75% *versus* 49% for BsAb (OR=2.95, 95% CI: 1.60-5.44, P<0.001). The pooled rate of grade ≥3 adverse events was significantly higher in the CAR-T (86%) group than in the BsAb group (59%) (OR=22, 95% CI: 7.8-62, P<0.001). In terms of specific adverse events, CAR-T therapy was associated with significantly higher rates of grade ≥3 cytokine release syndrome (CRS) (5% with CAR-T *vs*. 1% with BsAb) (OR=10.6, 95% CI: 3.5-31.4, P<0.001) and immune effector cell associated neurotoxicity syndrome (ICANS) (2% with CAR-T *vs*. 1% with BsAb) (OR=4.83, 95% CI: 1.19-19.6, P=0.027) (Figure 1B, C). Additionally, CAR-T therapy was associated with higher rates of cytopenia including grade ≥3 neutropenia, anemia, leukopenia and thrombocytopenia. Despite the higher rates of adverse events associated with CAR-T therapy, the rates of overall and grade ≥3 infections were significantly lower with CAR-T than with BsAb. The pooled rate of infections of any grade was 44% in the CAR-T cohort *versus* 65% in the BsAb cohort; the pooled rate of grade ≥3 infections, was 17% in the CAR-T cohort *versus* 30% in the BsAb cohort (OR=0.48, 95% CI: 0.29-0.79, P=0.004) (Figure 1D).

Non-relapse mortality (NRM) was reported in 12 CAR-T studies and seven BsAb studies. The pooled cumulative incidences of NRM were 6% (95% CI: 3-11) with CAR-T and 9% (95% CI: 5-13) with BsAb. The meta-regression model predicting NRM showed no significant difference in NRM rates with CAR-T compared to BsAb (OR=0.76, 95% CI: 0.35-1.65, P=0.48). The causes of NRM were reviewed and it was found that infection was the most common cause of death in both groups (14 in the CAR-T group and 45 in the BsAb cohort). CRS (N=4) and ICANS (N=1) deaths were associated with CAR-T but not with BsAb (*Online Supplementary Figure S2A, B*).

Progression-free survival (PFS) rates at 12 months were reported in three CAR-T trials and five BsAb trials and calculated from Kaplan-Meier plots in seven CAR-T and three BsAb trials. At 12 months, there was no difference in the PFS rates between the groups (73% for CAR-T and 67% for BsAb) (hazard ratio=0.81, 95% CI: 0.40-1.62, *P*=0.51)

The risk of bias of included studies was evaluated using MINORS (Methodological Index for Non-Randomized Studies), which showed that all the studies were moderate to good quality (*Online Supplementary Table S1*).

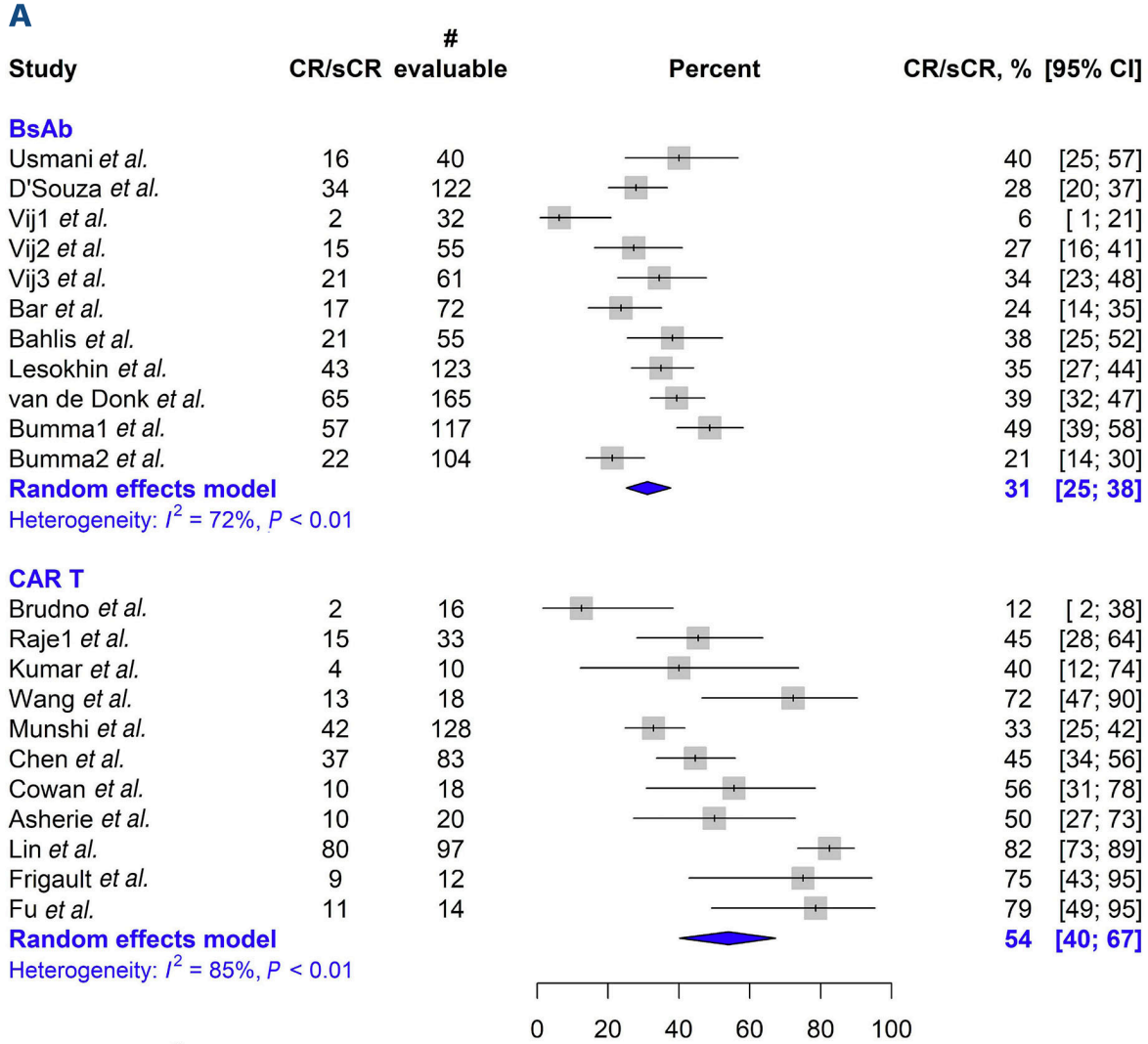
A total of eight studies (4 with CAR-T and 4 with BsAb) were included in the sensitivity analysis (*Online Supplementary Figure S1*). Compared to BsAb, CAR-T therapy was associated with significantly higher rates of overall response, complete response or better, and very good partial response or better. CAR-T was, however, associated with higher grades of CRS,

Table 1. Characteristics of clinical trial records.

Authors and trial identifier	Phase	Regimen	N of pts	Median age years	Median prior LOT	Previous AutoSCT %	ISS stage III %	HRC %	EMD %	Refractory %
Chimeric antigen receptor T-cell therapies										
Raje1 *et al.*	I	bb2121	33	60	7	97	NR	45	27	64
Mailankody *et al.*	I	ALLO-715	43	64	5	91	18.6	37.2	20.9	100
Wang *et al.*	I	CT103A	18	53.5	4	33	0	38.9	27.8	NR
Cowan *et al.*	I	FCARH143	18	65	10	89	NR	55	28	NR
Asherie *et al.*	I	HBI0101	20	62	6	85	10	50	30	100
Cornell *et al.*	I	KITE-585	17	56	5.5	94	24	12	NR	100
Brudno *et al.*	-	CAR-BCMA T-cell	16	-	9.5	90	NR	40	NR	63
Lin *et al.*	I/II	ciltacabtagene autoleucel	97	61	6	NR	NR	23.7	13.4	99
Raje2 *et al.*	I	bb21217	72	63	6	NR	NR	NR	NR	100
Munshi *et al.*	II	bb2121	128	61	6	94	16	35	39	100
Kumar *et al.*	Ib/II	CT053	14	59	6	NR	NR	64	36	100
Frigault *et al.*	I	CART-ddBCMA	12	69	5	58	NR	90	58	NR
Fu et al.	I	Zevorcabtagene autoleucel	14	54	6	78.6	14.3	50	14.3	NR
Chen *et al.*	II	Zevorcabtagene autoleucel	102	59.5	4	23.5	38.2	45	6.9	100
Bispecific antibody treatments										
Usmani *et al.*	I	Teclistamab	157	63	6	85	21	33	13	90
D'Souza *et al.*	I	ABBV-383	124	68	5	81	31	18	NR	87
Vij1 *et al.*	I - 20 mg	ABBV-383	32	68	5	NR	31	-	22	NR
Vij2 *et al.*	I - 40 mg	ABBV-383	55	69	4	NR	25	-	27	NR
Vij3 *et al.*	I - 60 mg	ABBV-383	61	68	4	NR	28	-	25	NR
Bar *et al.*	I	Alnuctumab	73	64	4	NR	NR	NR	NR	96
Madan *et al.*	I	HPN217	97	70	6	68	NR	NR	NR	NR
Bumma1 *et al.*	II - 200 mg	Linvoseltamab	117	70	5	66	17.9	39.3	16.2	85.5
Bumma2 *et al.*	II - 50 mg	Linvoseltamab	104	65	6	79.8	23.1	26.9	16.3	89.4
Bahlis *et al.*	I	Elranatamab	55	64	5	69.1	20	29.1	30.9	89.1
Lesokhin *et al.*	II	Elranatamab	123	68	5	70.7	15.4	25.2	31.7	95.9
van de Donk *et al.*	I/II	Teclistamab	165	64	5	81.8	12	25.7	17	90

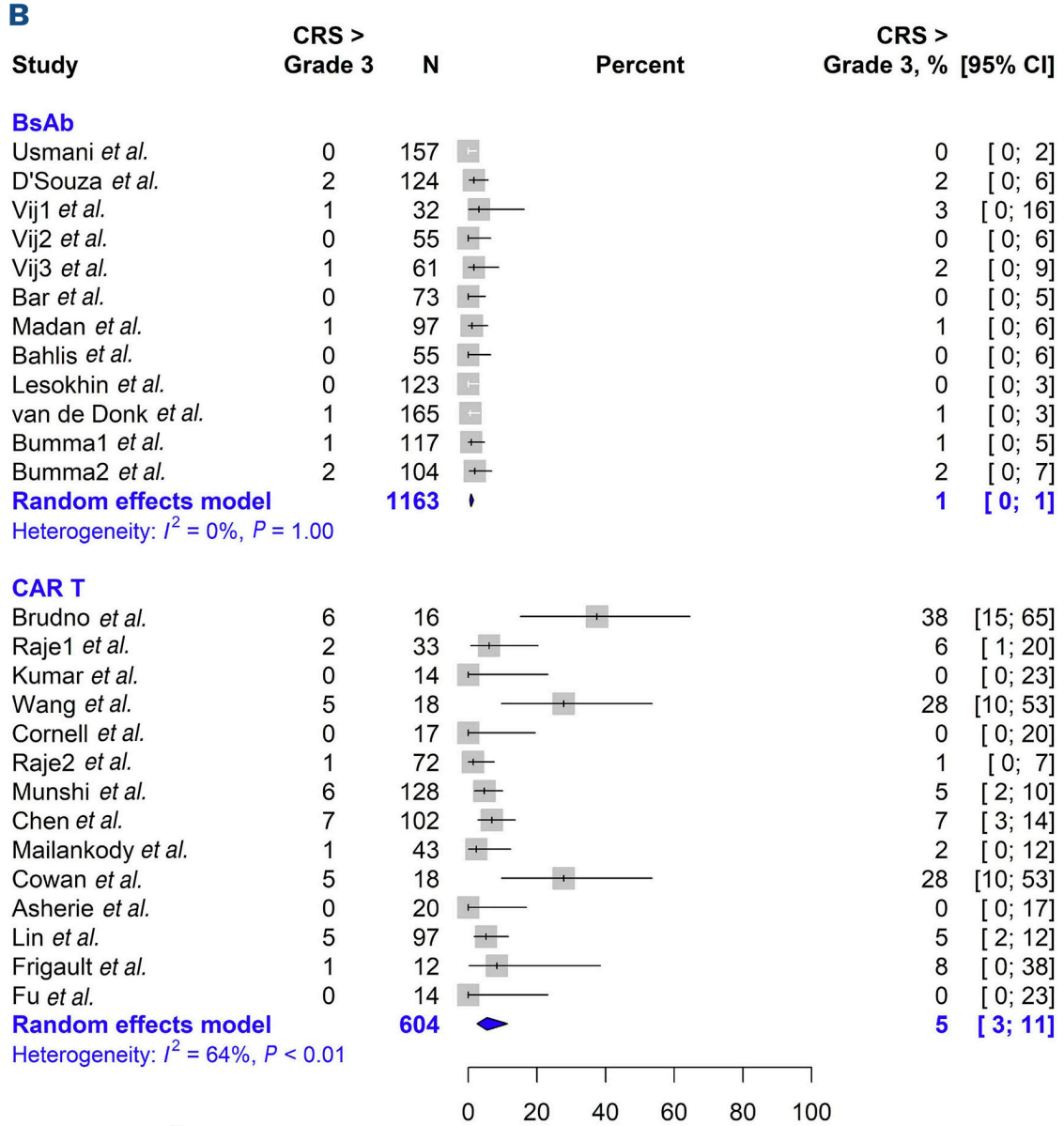
References listed in the *Online Supplementary Material*. Data for the different dose cohorts in the studies by Vij *et al.* and Bumma *et al.* are presented separately. Pts: patients; LOT: lines of therapy; AutoSCT: autologous stem cell transplantation; ISS: International Staging System; HRC: high-risk cytogenetics; EMD: extramedullary disease; NR: not reported.

A

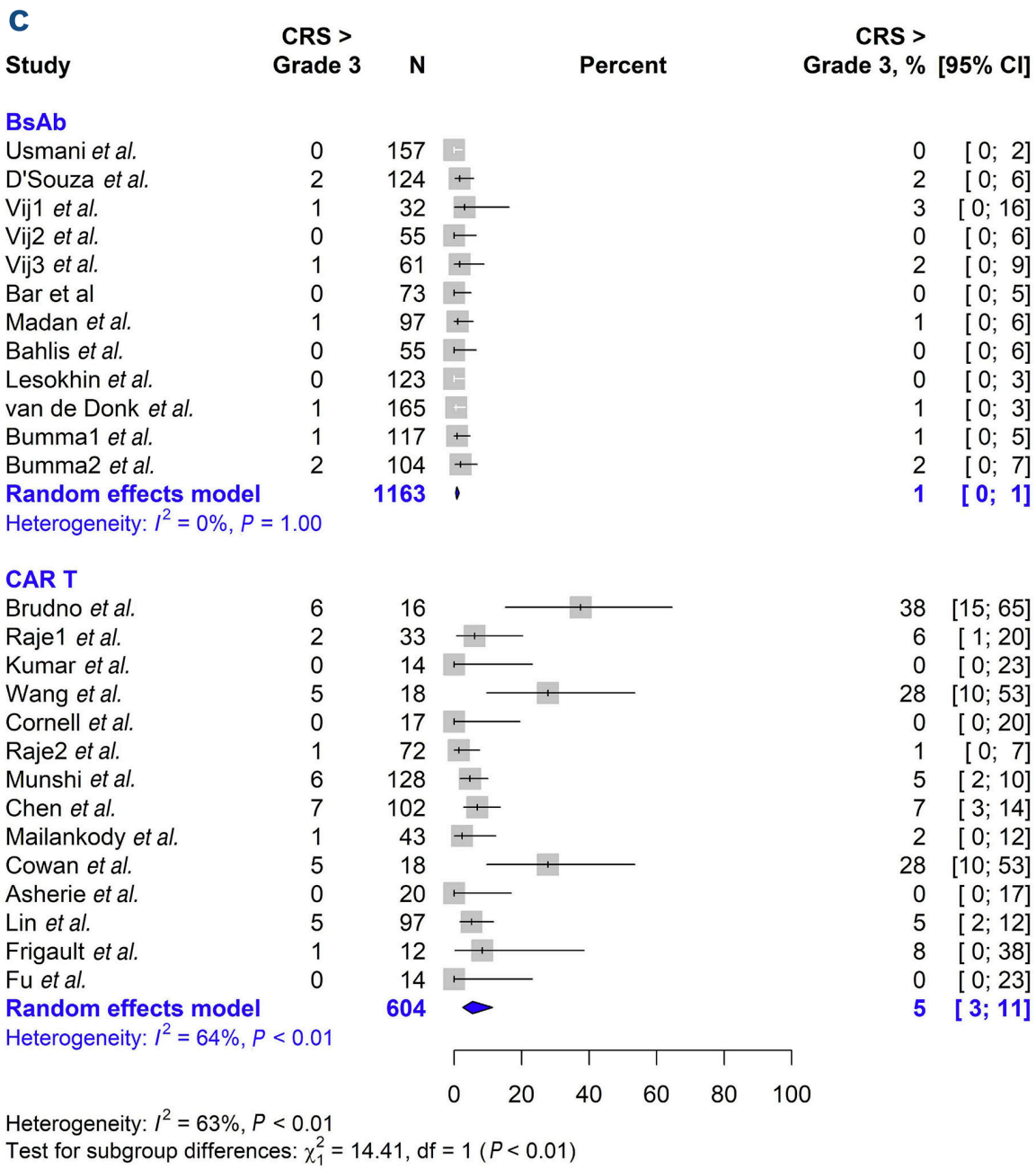


Heterogeneity: I^2 = 84%, P < 0.01
Test for subgroup differences: χ^2_1 = 8.79, df = 1 (< 0.01)

B



Heterogeneity: I^2 = 63%, P < 0.01
Test for subgroup differences: χ^2_1 = 14.41, df = 1 (P < 0.01)



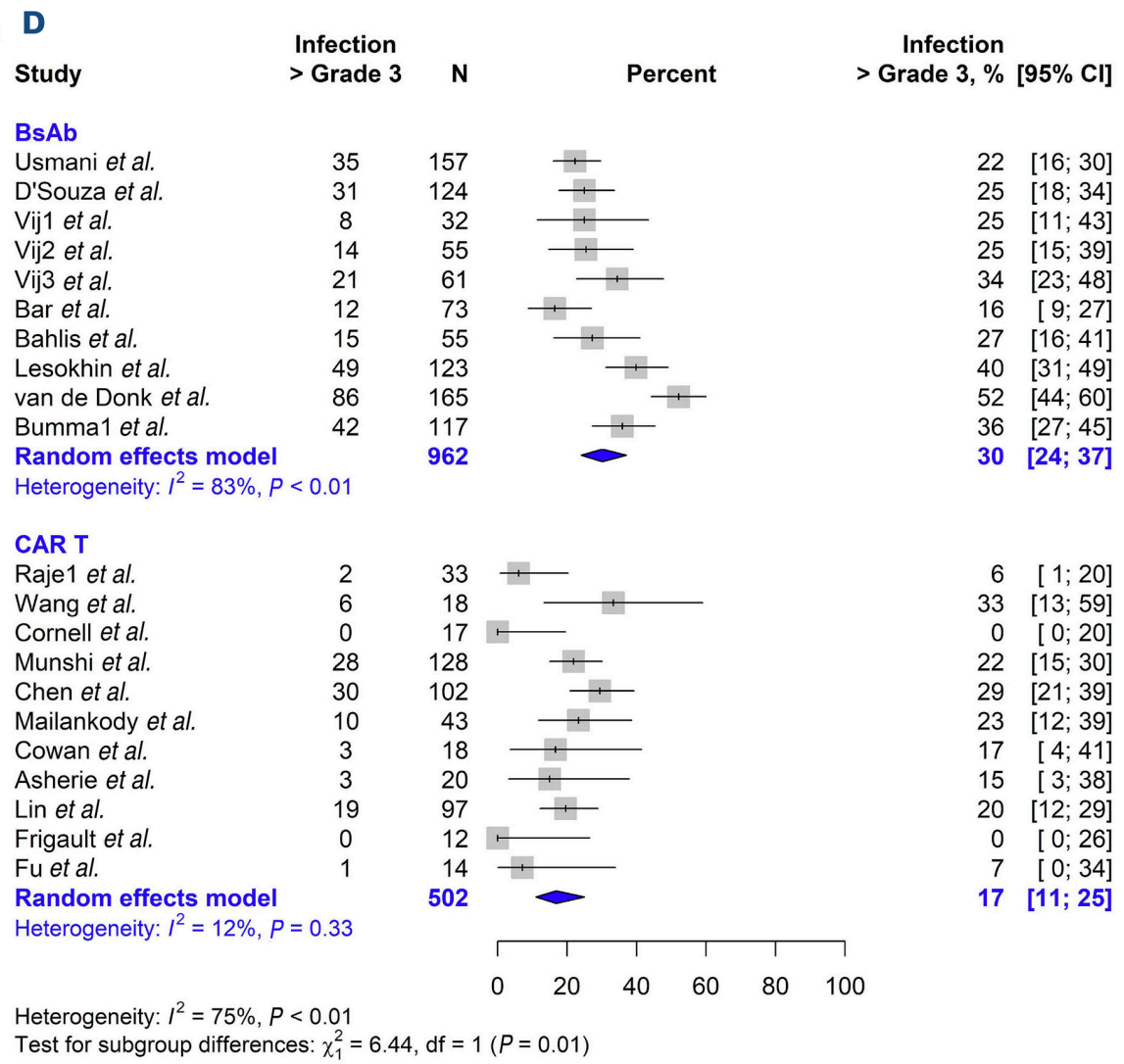


Figure 1. Forest plot illustrating safety and efficacy of chimeric antigen receptor T-cell therapy and bispecific antibodies. (A-D) Rates and 95% confidence intervals of complete response or better (A), grade ≥3 cytokine release syndrome (B), immune effector cell associated neurotoxicity syndrome (C) and infections (D) using a random-effect model between trials involving chimeric antigen receptor T-cell therapy or bispecific antibodies. The *P* value for the comparison of subgroups was derived from a two-sided test for subgroup differences (random-effect model). Heterogeneity measures including I^2 are depicted (I^2 between 50% and 75% indicates moderate-to-high study heterogeneity). BsAb: bispecific antibodies; CR: complete response; sCR: stringent complete response; 95% CI: 95% confidence interval; CAR T: chimeric antigen receptor T-cell therapy; d.f., degree of freedom; CRS: cytokine release syndrome; ICANS: immune effector cell associated neurotoxicity syndrome.

ICANS and cytopenia but comparable NRM and 12-month PFS rates.

The current approach to treatment selection in patients who are eligible for both CAR-T and BsAb is driven by multiple factors, including product efficacy, patient fitness, disease dynamics and logistical capabilities.[7] It is important to note that there was significant heterogeneity in response rates within the CAR-T cohort, consistent with the known differences in outcomes seen with different CAR-T products.[3] In contrast, there was no significant heterogeneity in response within the BsAb cohort. It is also important to note that the responses reported in the CAR-T trials are for "as treated" populations only and not intent-to-treat populations, which could affect the overall responses. Despite the superior responses in the CAR-T cohort, there was no significant difference in 12-month PFS between the CAR-T and BsAb cohorts. This lack of difference is likely to be due to the fact that the chosen timepoint is less than or equivalent to the median PFS for the majority of patients treated with either CAR-T or BsAb. It should also be noted that there was significant heterogeneity in PFS within both the CAR-T and BsAb cohorts. As a result, while these results suggest that both treatment modalities have the ability to induce durable responses, they do not account for the impact of individual products on outcomes.

One of the key findings of our study was the comparable NRM of patients in the two cohorts. Given the high risk of immune-mediated toxicity seen with CAR-T therapy, BsAb are often preferred for patients perceived to be at high risk of tolerating treatment poorly.[7] Consistent with the existing literature, we observed higher pooled rates of CRS, ICANS and cytopenia with CAR-T than with BsAb. The pooled rates of grade ≥3 CRS and ICANS with BsAb was around 1% with no significant heterogeneity among studies. In contrast, there was a higher rate of infections in the BsAb cohort. The pooled rate of grade ≥3 infections in the BsAb cohort was almost double that in the CAR-T cohort (30% *vs*. 17%). Importantly, infections were the most common cause of death in both cohorts, and the increased risk of infections with BsAb therapy resulted in comparable rates of NRM in the two cohorts. In a prior meta-analysis looking at CAR-T products, half of all NRM deaths were also due to infections independently of whether the patients were treated in trials or as a standard of care.[8] It is important to highlight that many infection-related deaths in both cohorts were related to coronavirus disease 2019 (COVID19) infection as these trials were conducted early in the COVID19 pandemic.[4,9] In addition, these findings preceded recommendations for more widespread use of intravenous immunoglobulin and anti-infective prophylaxis.[10,11] Cardiorespiratory failure and second primary cancers remain important causes of deaths, as reported in prior studies.[8,12]

Several limitations of our analysis should be noted. First, the studies included in this meta-analysis were predominantly phase I and II trials, and the results should be interpreted with caution in the absence of direct, randomized comparisons between CAR-T and BsAb therapies. Additionally, the heterogeneity of the studies, particularly in terms of patient populations and follow-up durations, may have influenced the pooled estimates. Finally, being a study-level meta-analysis we were not able to investigate patient-level confounders. We excluded non-BCMA studies as only BCMA agents are approved for use in both CAR-T and BsAb therapies.

Despite these limitations, in this meta-analysis we demonstrate that CAR-T therapy is associated with superior responses albeit with higher rates of immune-mediated toxicity.

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Contributions

HV acquired, analyzed or interpreted data, and drafted the manuscript. OA acquired, analyzed or interpreted data, drafted the manuscript, and critically revised it for intellectual content. AS acquired, analyzed or interpreted data, conducted the statistical analysis, and critically revised the manuscript for important intellectual content. MM, AD'S, RN and MP critically revised the manuscript for intellectual content. BD conceived and designed the study, acquired, analyzed or interpreted data, drafted the manuscript, critically revised it for intellectual content, and supervised the study. He had full access to all of the data in the

study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data-sharing statement
All data needed to evaluate the conclusions in the paper are present in the paper and/or *Online Supplementary Information*. Data from primary studies are publicly available within the databases and the search algorithms are described in the *Online Supplementary Information* (MEDLINE, Scopus and Cochrane). In case of further questions, please contact the corresponding author.

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