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

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revision of the manuscript for important intellectual content: Szabo, Mohan, Narra, Pasquini, Akhtar and Dhakal; Statistical analysis: Szabo; Study supervision: Dhakal

Conflicts of Interest

B.D has received research funding from Janssen, BMS, Sanofi, Arcellx, Carsgen, C4 therapeutics, Pfizer. He has received honorarium from Janssen, BMS, Pfizer, Genentech, Arcellx, Kite, Karyopharm and Sanofi.

Data availability

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

Code availability

All analyses were performed in R version 4.3.1 using the meta and metafor packages. Data sheets were created using the Microsoft Excel. The underlying R code for the present study can be found in the Supplementary information.

B-cell maturation antigen (BCMA) has emerged as a promising target in these patients, 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 therapy products, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) in earlier lines, and two BsAbs, teclistamab (Tec) and elranatamab (Elra), have been approved for patients with four or more lines of therapy.[2-5]

CAR-T is a one-time treatment with complex logistics, while BsAb is an "off-the-shelf" therapy requiring continuous treatment.[6] Both treatments exhibit unique adverse events (AEs).[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 with at least three prior lines of therapy (LOT).

We included clinical trials that investigated BCMA targeting CAR-T and BsAb in RRMM patients with three or more prior LOT. An extensive literature search was performed using MEDLINE, Scopus and the Cochrane Central Register of Controlled Trial databases between inception and May 31st, 2024, using the term “CAR-T” “bispecific antibodies” “BCMA” and “multiple myeloma”. We conducted a search of conference abstracts from since 2010 of the American Society of Clinical Oncology, American Society of Hematology, and European Hematology Association. The studies were evaluated by two independent reviewers (H.V and B.D) based on the following inclusion criteria: a) BCMA CAR-T or BsAb investigated in MM clinical trials; b) included patients with 3 or more prior LOT and exposed to PI, IMID and/or CD38; c) phase I and phase II trials where the recommended dose was confirmed, and efficacy was evaluated.

The study followed PRISMA guidelines and was prospectively registered to the PROSPERO database (CRD42024549186).

A total of 2,269 articles were identified that investigated BCMA targeting CAR-T or BsAb in multiple myeloma. A total of 23 studies involving 1,767 patients were included after careful

consideration of the inclusion criteria (**Supplemental Figure 1).** 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) and 9 were BsAb trials (N= 1,163).

The pooled overall response rate (ORR) was 59% (95% CI, 55-63) in the BsAb group with moderate-high variation across the studies (I^2 42%, p=0.06). In the CART 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 compared to BsAb (Odds ratio, OR 3.9, 95% CI 1.8-8.8, p<0.001). CAR-T was associated with significantly higher depth of response compared to BsAB. The pooled complete response and better (≥CR) rates was significantly higher with CAR-T (54%) compared to BsAb (31%) (OR 2.67, 95% CI 1.45-4.91; p=0.002) (**Figure 1A**)**.** Similarly, CAR-T was associated with higher very good partial response rates or better, ≥VGPR; 75% vs. 49% respectively (OR 2.95, 95% CI 1.60-5.44; p<0.001).

The pooled grade 3 and higher AEs were significantly higher in the CAR-T (86%) group vs BsAb group (59%) (OR 22, 95% CI 7.8-62; p <0.001)**.** In terms of specific AEs, CAR-T was associated with significantly higher rates of grade ≥3 cytokine release syndrome (CRS) (5%) vs. BsAb (1%) (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) respectively (**Figure 1B and 1C**). Additionally, CAR-T was also associated with higher rates of cytopenia including grade ≥3 neutropenia, anemia, leucopenia and thrombocytopenia**.** Despite the higher rates of AEs associated with CAR-T, the rates of overall and grade ≥3 infections were significantly lower with CAR-T compared to BsAb. The pooled rate of infections of any grade was 44% in the CAR-T cohort vs. 65% in the BsAb cohort**,** and for grade ≥ 3 infections, was 17% in the CAR-T cohort vs. 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 7 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 revealed that infection was the most common cause of death for both groups (14 in the CAR-T group and 45 in the BsAb cohort). CRS (4) and ICANS (1) deaths were associated with CAR-T but not with BsAb **(Supplemental Figure 2A and 2B).**

Progression free survival (PFS) rates 12-month time points were reported in 3 CAR-T trials and 5 BsAb trials and calculated based on Kaplan-Meier plots in 7 CAR-T and 3 BsAb trials. The pooled 12-month PFS was 0.67 for CAR-T and BsAb respectively. At 12 months, there was no difference in the PFS rates between the groups (73% for CAR-T and 67% for BsAb, hazard ratio, HR 0.81, 95% CI 0.40-1.62, p=0.51)

The risk of bias of included studies using MINORS shows all the studies were moderate to good quality **(Supplemental Table 1**)**.**

A total of 8 studies (CAR-T=4 and BsAb=4) were included in the sensitivity analysis (**Supplemental Figure 1).** CAR-T was associated with significantly higher ORR, ≥CR and ≥ VGPR rates when compared to BsAb. Additionally, CAR-T was also associated with higher grades of CRS, ICANS and cytopenia but comparable NRM and 12-month PFS rates.

The current approach to treatment selection in patients who are eligible for both 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 important to note that the responses reported in the CAR-T trials included “as

treated” population only and not the intent to treat population 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 could likely be the fact that the chosen time point is less than or equivalent to median PFS for the majority of both CAR and BsAbs. It is important to note that there was significant heterogeneity in PFS within both 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 between the two cohorts. Given the high risk for immune-mediated toxicity seen with CAR-T therapy, BsAb are often preferred for patients perceived to be at high risk for poor treatment tolerance.[7] Consistent with the existing literature, we observed higher pooled rates of CRS, ICANS and cytopenia with CAR-T compared to 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 rates of grade ≥3 infections were almost twice as high in the BsAb cohort compared to 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 between the two cohorts. In a prior meta-analysis looking at the CAR-T products, half of all NRM deaths were also due to infections whether 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 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] Cardio-respiratory failure and second primary cancers remain important causes of deaths as reported in prior studies.[8,12]

Several limitations 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 both CAR-T and BsAb.

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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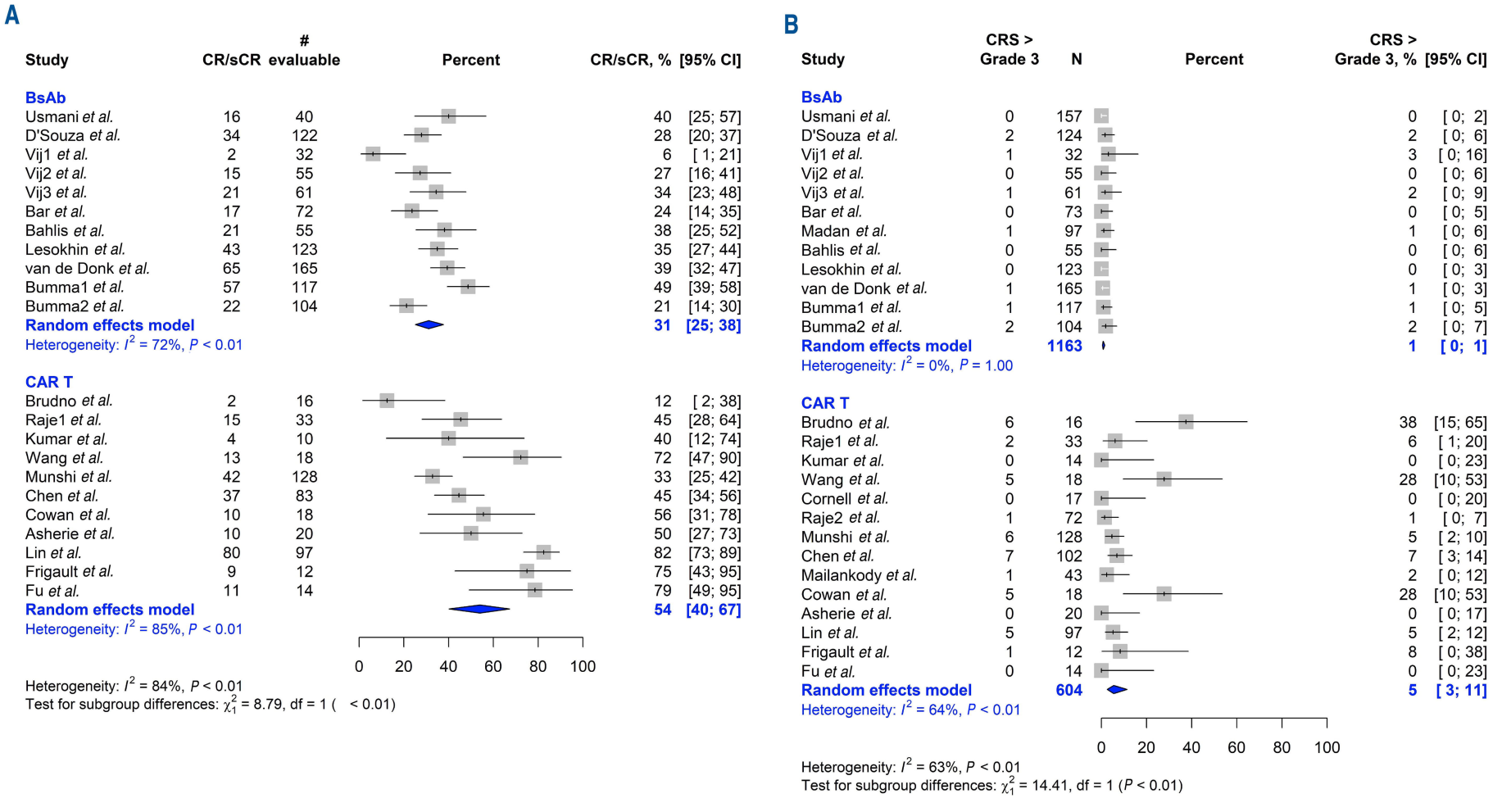
Table 1: Characteristics of Clinical Trial Records

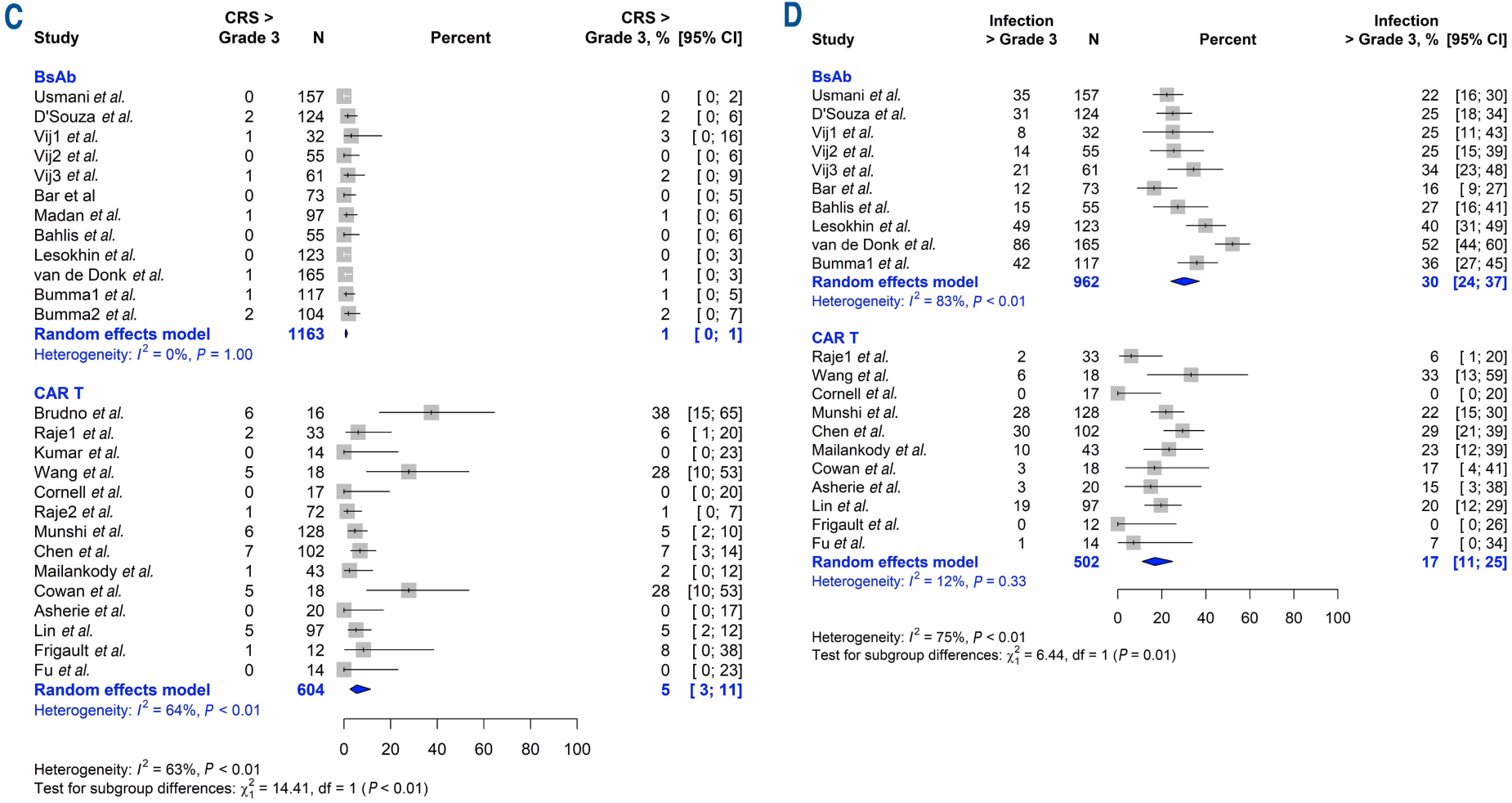
Authors (trial identifier)	Phase	Regimen	No	Median age	Median prior LOT	Previous AutoSCT	ISS Stage III %	HRC	EMD	Refractoriness
Raje1 et al	Phase 1	bb2121	33	60	7	97%	NR	45%	27%	64%
Mailankody et al	Phase 1	ALLO-715	43	64	5	91%	18.60 %	37.20 %	20.90 %	100.00%
Wang et al	Phase 1	CT103A	18	53.5	4	33%	0.00%	38.90 %	27.80 %	NR
Cowan et al	Phase 1	FCARH143	18	65	10	89%	NR	55%	28%	NR
Asherie et al	Phase 1	HBI0101	20	62	6	85%	10%	50%	30%	100%
Cornell et al	Phase 1	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	Phase 1/2	ciltacabtagene autoleucel	97	61	6	NR	NR	23.70 %	13.40 %	99%
Raje2 et al	Phase 1	bb21217	72	63	6	NR	NR	NR	NR	100%
Munshi et al	Phase 2	bb2121	128	61	6	94%	16%	35%	39%	100%
Kumar et al	Phase 1b/2	CT053	14	59	6	NR	NR	64%	36.00 %	100%
Frigault et al	Phase -1	CART-ddBCMA	12	69	5	58%	NR	90%	58%	NR
Fu et al	Phase 1	Zevorcabtagene autoleucel	14	54	6	78.60%	14.30 %	50%	14.30 %	NR
Chen et al	Phase 2	Zevorcabtagene autoleucel	102	59.5	4	23.50%	38.20 %	45%	6.90%	100%
Usmani et al	Phase 1	Teclistamab	157	63	6	85%	21%	33%	13%	90%
D'Souza et al	Phase 1	ABBV-383	124	68	5	81%	31%	18%	NR	87%
Vij1 et al	Phase 1 - 20mg	ABBV-383	32	68	5	NR	31%		22%	NR
Vij2 et al	Phase 1 - 40mg	ABBV-383	55	69	4	NR	25%		27%	NR
Vij3 et al	Phase 1 - 60mg	ABBV-383	61	68	4	NR	28%		25%	NR

Bar et al	Phase 1	Alnuctumab	73	64	4	NR	NR	NR	NR	96%
Madan et al	Phase I	HPN217	97	70	6	68%	NR	NR	NR	NR
Bumma1 et al	Phase 2 - 200mg	Linvoseltamab	117	70	5	66%	17.90 %	39.30 %	16.20 %	85.50%
Bumma2 et al	Phase 2 - 50mg	Linvoseltamab	104	65	6	79.80%	23.10 %	26.90 %	16.30 %	89.40%
Bahlis et al	Phase 1	Elranatamab	55	64	5	69.10%	20%	29.10 %	30.90 %	89.10%
Lesokhin et al	Phase 2	Elranatamab	123	68	5	70.70%	15.40 %	25.20 %	31.70 %	95.90%
van de Donk et al	Phase 1-2	Teclistamab	165	64	5	81.80%	12%	25.70 %	17%	90%

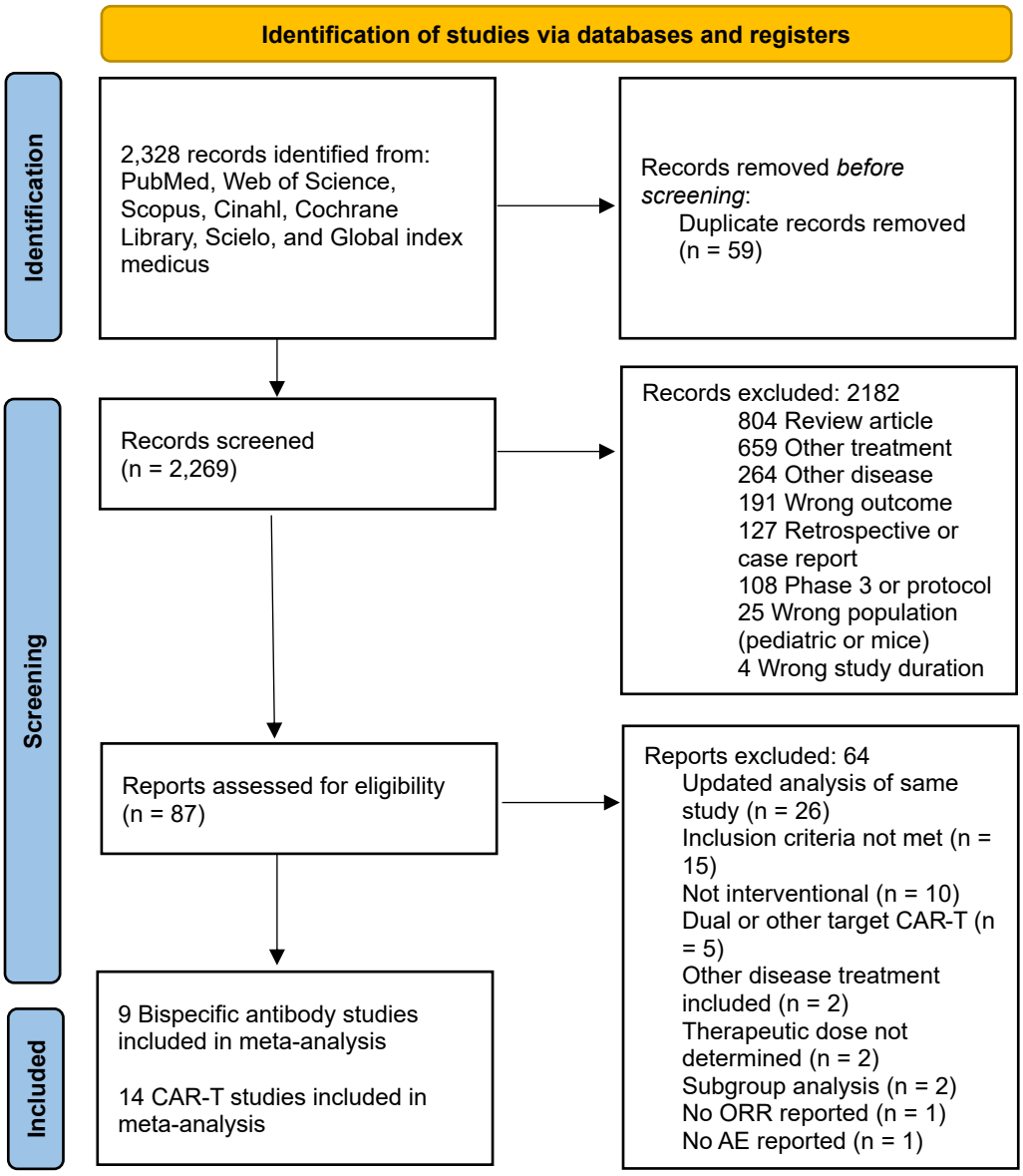
LOT: Lines of therapy, AutoSCT: Autologous stem cell transplantation; ISS: International Staging System; HRC: High risk cytogenetics; EMD: Extramedullary disease; NR: Not reported

Figure 1: Forest plot illustrating safety and efficacy of CAR-T and bispecific antibodies. 1A complete response or better; 1B ≥grade 3 cytokine release syndrome, 1C immune effector cell associated neurotoxicity syndrome and 1D infections rates and 95% CIs using a random-effect model between CAR-T and BsAb trials. The P value for the comparison of subgroups was derived from a two-sided test for subgroup differences (random-effect model). Heterogeneity measures including I2 are depicted (I2 between 50% and 75% indicates moderate-to-high study heterogeneity). d.f., degree of freedom.


A
Study
CR/sCR
evaluable
Percent
CR/sCR, % [95% CI]
BsAb
Usmani et al. 16 40 40 [25; 57]
D'Souza et al. 34 122 28 [20; 37]
Vij1 et al. 2 32 6 [1; 21]
Vij2 et al. 15 55 27 [16; 41]
Vij3 et al. 21 61 34 [23; 48]
Bar et al. 17 72 24 [14; 35]
Bahlis et al. 21 55 38 [25; 52]
Lesokhin et al. 43 123 35 [27; 44]
van de Donk et al. 65 165 39 [32; 47]
Bumma1 et al. 57 117 49 [39; 58]
Bumma2 et al. 22 104 21 [14; 30]
Random effects model 31 [25; 38]
Heterogeneity: I^2 = 72%, P < 0.01
CAR T
Brudno et al. 2 16 12 [2; 38]
Raje1 et al. 15 33 45 [28; 64]
Kumar et al. 4 10 40 [12; 74]
Wang et al. 13 18 72 [47; 90]
Munshi et al. 42 128 33 [25; 42]
Chen et al. 37 83 45 [34; 56]
Cowan et al. 10 18 56 [31; 78]
Asherie et al. 10 20 50 [27; 73]
Lin et al. 80 97 82 [73; 89]
Frigault et al. 9 12 75 [43; 95]
Fu et al. 11 14 79 [49; 95]
Random effects model 54 [40; 67]
Heterogeneity: I^2 = 85%, P < 0.01
0 20 40 60 80 100
Heterogeneity: I^2 = 84%, P < 0.01
Test for subgroup differences: χ^2_1 = 8.79, df = 1 (< 0.01)
B
Study
CRS > Grade 3
N
Percent
CRS > Grade 3, % [95% CI]
BsAb
Usmani et al. 0 157 0 [0; 2]
D'Souza et al. 2 124 2 [0; 6]
Vij1 et al. 1 32 3 [0; 16]
Vij2 et al. 0 55 0 [0; 6]
Vij3 et al. 1 61 2 [0; 9]
Bar et al. 0 73 0 [0; 5]
Madan et al. 1 97 1 [0; 6]
Bahlis et al. 0 55 0 [0; 6]
Lesokhin et al. 0 123 0 [0; 3]
van de Donk et al. 1 165 1 [0; 3]
Bumma1 et al. 1 117 1 [0; 5]
Bumma2 et al. 2 104 2 [0; 7]
Random effects model 1163 1 [0; 1]
Heterogeneity: I^2 = 0%, P = 1.00
CAR T
Brudno et al. 6 16 38 [15; 65]
Raje1 et al. 2 33 6 [1; 20]
Kumar et al. 0 14 0 [0; 23]
Wang et al. 5 18 28 [10; 53]
Cornell et al. 0 17 0 [0; 20]
Raje2 et al. 1 72 1 [0; 7]
Munshi et al. 6 128 5 [2; 10]
Chen et al. 7 102 7 [3; 14]
Mailankody et al. 1 43 2 [0; 12]
Cowan et al. 5 18 28 [10; 53]
Asherie et al. 0 20 0 [0; 17]
Lin et al. 5 97 5 [2; 12]
Frigault et al. 1 12 8 [0; 38]
Fu et al. 0 14 0 [0; 23]
Random effects model 604 5 [3; 11]
Heterogeneity: I^2 = 64%, P < 0.01
0 20 40 60 80 100
Heterogeneity: I^2 = 63%, P < 0.01
Test for subgroup differences: χ^2_1 = 14.41, df = 1 (P < 0.01)


C
Study
CRS > Grade 3
N
Percent
CRS > Grade 3, % [95% CI]
BsAb
Usmani et al. 0 157 0 [0; 2]
D'Souza et al. 2 124 2 [0; 6]
Vij1 et al. 1 32 3 [0; 16]
Vij2 et al. 0 55 0 [0; 6]
Vij3 et al. 1 61 2 [0; 9]
Bar et al 0 73 0 [0; 5]
Madan et al. 1 97 1 [0; 6]
Bahlis et al. 0 55 0 [0; 6]
Lesokhin et al. 0 123 0 [0; 3]
van de Donk et al. 1 165 1 [0; 3]
Bumma1 et al. 1 117 1 [0; 5]
Bumma2 et al. 2 104 2 [0; 7]
Random effects model 1163 1 [0; 1]
Heterogeneity: I^2 = 0%, P = 1.00
CAR T
Brudno et al. 6 16 38 [15; 65]
Raje1 et al. 2 33 6 [1; 20]
Kumar et al. 0 14 0 [0; 23]
Wang et al. 5 18 28 [10; 53]
Cornell et al. 0 17 0 [0; 20]
Raje2 et al. 1 72 1 [0; 7]
Munshi et al. 6 128 5 [2; 10]
Chen et al. 7 102 7 [3; 14]
Mailankody et al. 1 43 2 [0; 12]
Cowan et al. 5 18 28 [10; 53]
Asherie et al. 0 20 0 [0; 17]
Lin et al. 5 97 5 [2; 12]
Frigault et al. 1 12 8 [0; 38]
Fu et al. 0 14 0 [0; 23]
Random effects model 604 5 [3; 11]
Heterogeneity: I^2 = 64%, P < 0.01
0 20 40 60 80 100
Heterogeneity: I^2 = 63%, P < 0.01
Test for subgroup differences: χ^2_1 = 14.41, df = 1 (P < 0.01)
D
Study
Infection > Grade 3
N
Percent
Infection > Grade 3, % [95% CI]
BsAb
Usmani et al. 35 157 22 [16; 30]
D'Souza et al. 31 124 25 [18; 34]
Vij1 et al. 8 32 25 [11; 43]
Vij2 et al. 14 55 25 [15; 39]
Vij3 et al. 21 61 34 [23; 48]
Bar et al. 12 73 16 [9; 27]
Bahlis et al. 15 55 27 [16; 41]
Lesokhin et al. 49 123 40 [31; 49]
van de Donk et al. 86 165 52 [44; 60]
Bumma1 et al. 42 117 36 [27; 45]
Random effects model 962 30 [24; 37]
Heterogeneity: I^2 = 83%, P < 0.01
CAR T
Raje1 et al. 2 33 6 [1; 20]
Wang et al. 6 18 33 [13; 59]
Cornell et al. 0 17 0 [0; 20]
Munshi et al. 28 128 22 [15; 30]
Chen et al. 30 102 29 [21; 39]
Mailankody et al. 10 43 23 [12; 39]
Cowan et al. 3 18 17 [4; 41]
Asherie et al. 3 20 15 [3; 38]
Lin et al. 19 97 20 [12; 29]
Frigault et al. 0 12 0 [0; 26]
Fu et al. 1 14 7 [0; 34]
Random effects model 502 17 [11; 25]
Heterogeneity: I^2 = 12%, P = 0.33
0 20 40 60 80 100
Heterogeneity: I^2 = 75%, P < 0.01
Test for subgroup differences: χ^2_1 = 6.44, df = 1 (P = 0.01)

Supplementary Online Content

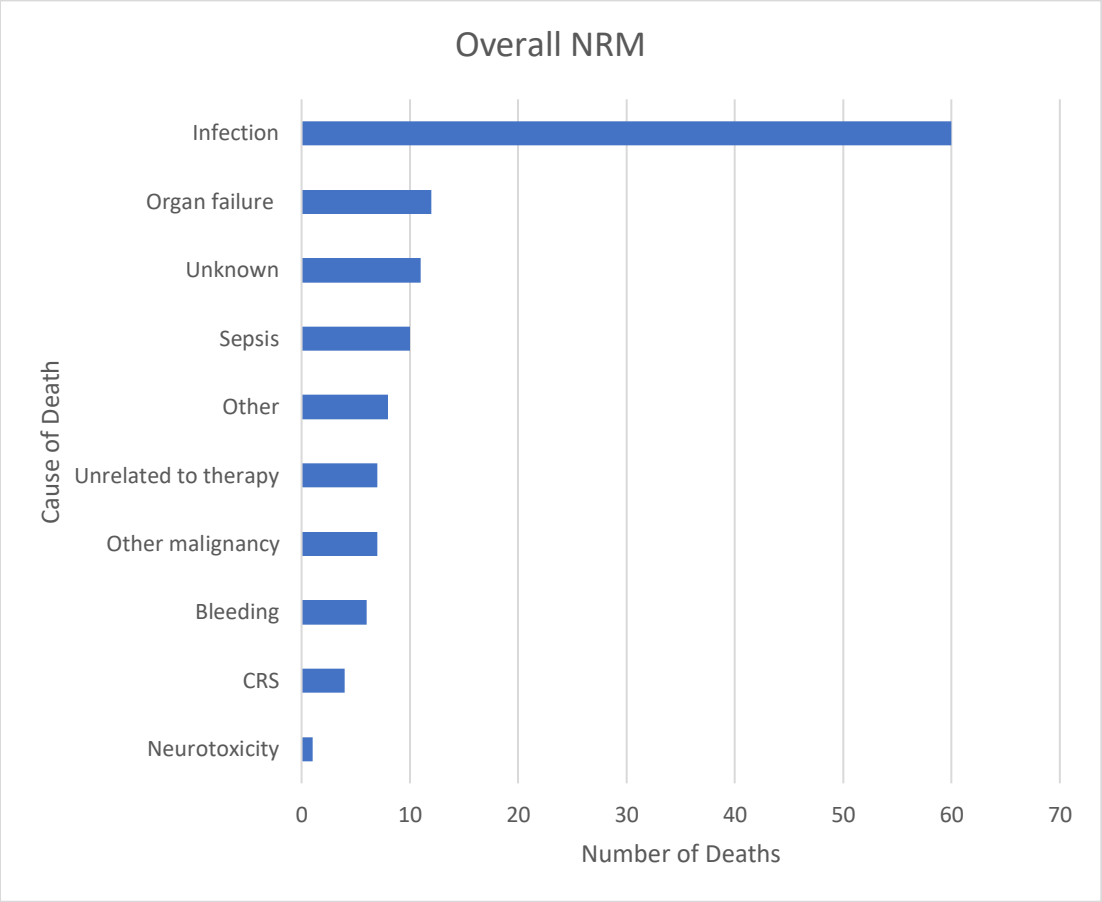


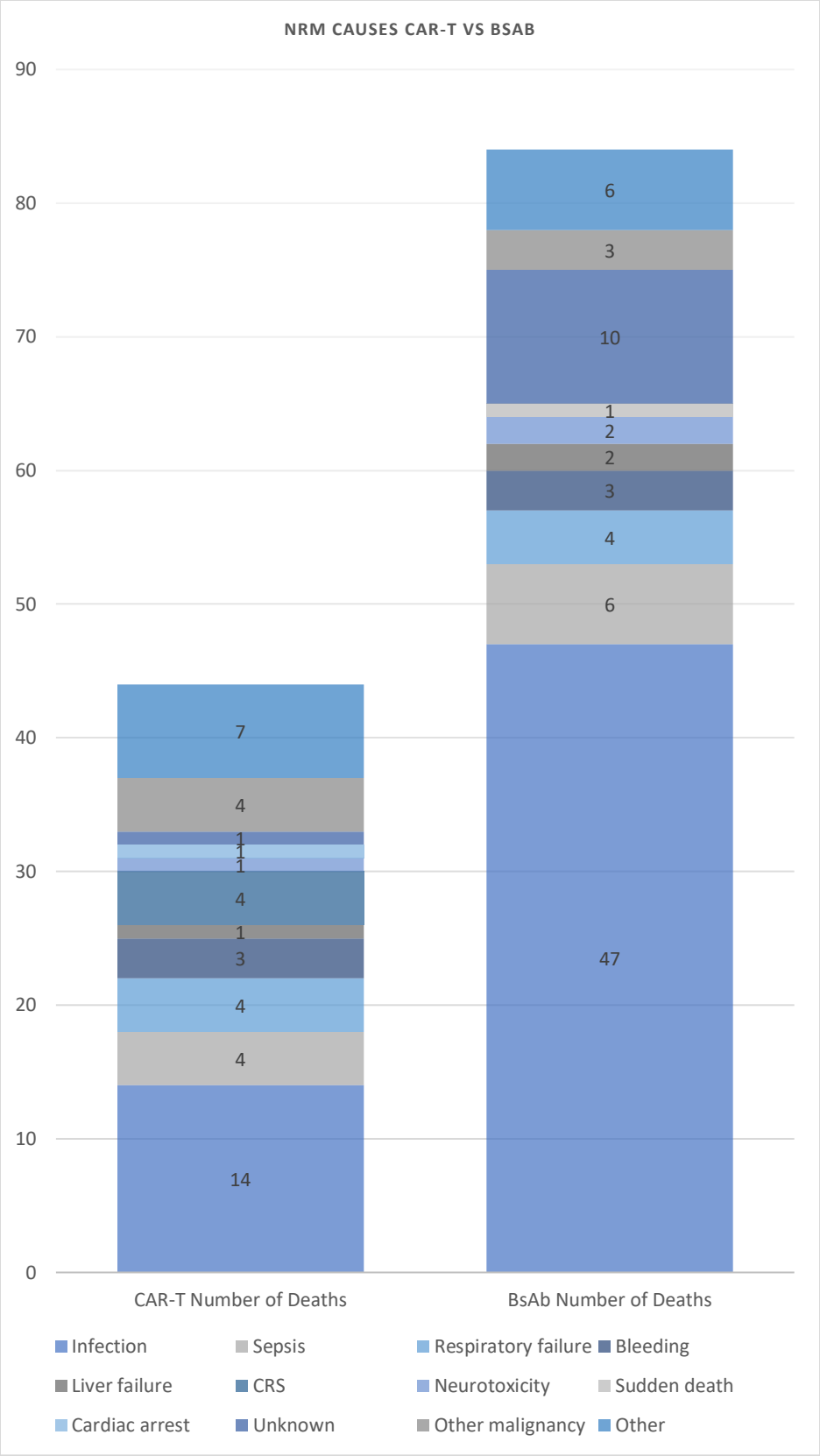
Supplemental Figure 1: Study retrieval and identification for meta-analysis. Flow diagram displaying the process for study inclusion and exclusion in the systematic review and meta-analysis of CAR-T and BsAb following the PRISMA guidelines

Trials included in the sensitivity analysis

CAR-T: Frigault et. al; Lin et. al; Munshi et. al and Raje et. al

BsAb: Lekoshin et. al; van de Donk et. Al; Bumma 1 and 2 et. al




NRM CAUSES CAR-T VS BSAB
90
80
70
60
50
40
30
20
10
0
7
4
1
1
1
4
1
3
4
4
14
6
3
10
1
2
2
3
4
6
47
CAR-T Number of Deaths
BsAb Number of Deaths
Infection
Sepsis
Respiratory failure
Bleeding
Liver failure
CRS
Neurotoxicity
Sudden death
Cardiac arrest
Unknown
Other malignancy
Other

Supplemental Figure 2: Bar chart displaying the causes of death among the entire study cohort (A). Comparison of the causes of non-relapse deaths by CAR-T and BsAb (B).

Supplemental Table 1: Risk of bias of included studies using the methodological index for non-randomized studies (MINORS)

	Raje1 et al	Mailankody et al	Wang et al	Cowan et al	Asherie et al	Cornell et al	Brudno et al	Lin et al	Raje2 et al	Munshi et al	Kumar et al	Frigault et al	Fu et al	Chen et al		Usmani et al	D'Souza et al	Vij et al	Bar et al	Madan et al	Bumma et al	Bahlis et al	Lesokhin et al	van de Donk et al
1. A clearly stated aim	2	2	2	2	2	2	1	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	1	2	1	1	1	1	1	1	2	1	2	1	1		2	2	1	1	2	1	1	1	1
3. Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	1	1	1	1	0	0	1	1	2	1	2	2	1		1	1	1	1	1	2	1	1	1
6. Follow-up period appropriate to the aim of the study	2	2	2	2	1	2	1	1	1	2	1	2	2	1		1	2	1	1	1	1	2	2	2
7. Loss of follow-up less than 5%	2	2	2	2	2	2	2	2	2	2	2	2	2	2		2	2	2	2	2	2	1	2	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0
Item 9-12 only for comparative studies																								
9. Adequate control group																		0			0			
10.Contemporary groups																		2			2			
11. Baseline equivalence of groups																		1			1			
12. Adequate statistical analyses																		2			2			
TOTAL MINORS score	12	12	13	12	11	11	9	11	11	14	11	14	13	11		12	13	11	11	12	12	11	12	12
Maximum possible score	16	16	16	16	16	16	16	16	16	16	16	16	16	16		16	16	24	16	16	24	16	16	16

Legend	
Good quality	
Moderate quality	
Poor quality	

Trials included in the sensitivity analysis

CAR-T: Frigault et. al; Lin et. al; Munshi et. al and Raje et. al

BsAb: Lekoshin et. al; van de Donk et. Al; Bumma 1 and 2 et. al

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