Systematic literature review and meta-analysis of clinical trials of fourth line or higher treatment for relapsed/refractory multiple myeloma patients

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BACKGROUND

- Treatment options for relapsed/refractory multiple myeloma (RRMM) have expanded, with the approvals of novel chimeric antigen receptor T-cell (CAR T-cell) therapies and bispecific antibodies (BsAb).[1] However, the clinical burden remains high, particularly for heavily pretreated patients.
- This systematic literature review and meta-analysis was conducted to synthesize outcomes from clinical trials evaluating fourth line or higher (4L+) treatment regimens.

METHODS

Systematic literature review

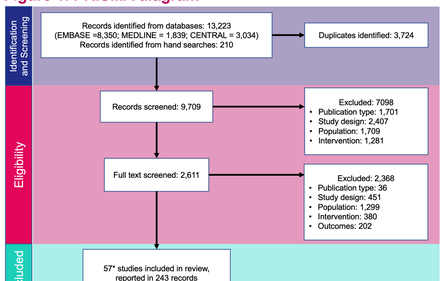
- Searches using Embase, MEDLINE, and CENTRAL were conducted (January 2012-March 2024), and publications from key conferences were hand-searched.
- Clinical trials of 4L+ RRMM patients were eligible for inclusion. Studies of which ≥80% of patients were 4L+ were included.
- Eligible interventions were those listed in the National Comprehensive Cancer Network (NCCN) treatment guidelines, given at the recommended phase II dose.
- Regimens with a same class substitution were eligible (i.e., lenalidomide replaced by thalidomide in a triplet).
- The systematic review protocol was prospectively registered with PROSPERO (CRD42023446880)

Meta-analyses

- Evidence was stratified by treatment class: CAR T-cell, BsAb, and Other.
- Dichotomous outcomes were meta-analyzed using a generalized linear mixed model with random-effects.[2]
- Survival outcomes were evaluated using Kaplan-Meier curves that were reconstructed from pseudo individual patient data. Bayesian meta-analyses were conducted using survival function parameters fitted to the curves.[3]

RESULTS

Figure 1. PRISMA diagram



**Of the 57 trials included, 5 were excluded from the analyses due to belantamab mafodotin no longer being approved, 4 were excluded as they were in prior-BCMA exposed patients only, and 14 were trials in earlier line populations that reported only minimal subgroup data for fourth line or higher patients, and did not report on the outcomes presented here*

- A total of 13,223 records were identified by the searches (**Figure 1**).
- Of these, 243 records reporting on 57 trials were eligible for inclusion.
- 34 unique trials were included in the analysis
- The remaining trials were not relevant for the current analysis as they either reported interventions not of interest (n=5), were in prior BCMA exposed patients (n=4) or did not report outcomes included in this analyses (n=14).

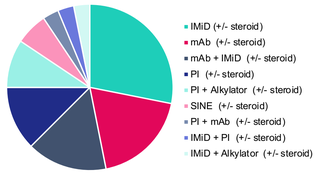
RESULTS *(CONTINUED)*

Table 1. CAR T-cell and BsAb treatments

Intervention	Study	Treatment class	N	Median follow up (months, range)
Cilta-cel	CARTIFAN-1	CAR T-cell	48	26.4 (18 – NR)
	CARTITUDE-1	CAR T-cell	97	33.4 (1.4 – 45.2)
Ide-cel	CRB-401	CAR T-cell	62	18.1 (1.5 – 44.5
	KarMMa	CAR T-cell	128	28.1 (24.1 – 34.4)
	KarMMa-3	CAR T-cell	176	18.6 (0.4 – 35.4)
Elranatamab	MagnetisMM-3 Cohort A	BsAb	123	17.6 (0.2 – 31.1)
Teclistamab	MajesTEC-1	BsAb	165	23 (NR)
Talquetabmab	MonumenTAL-1	BsAb	288	18.8 (NR)

CAR T-cell and BsAb trials in prior BCMA sub-populations were not included in the primary analysis set. BsAb: Bispecific antibodies; CAR T-cell: chimeric antigen receptor T-cell; Cilta-cel: ciltacabtagene autoleucel; Ide-cel: idecabtagene vicleucal; NR: Not reported.

Figure 2: Other interventions



- The analysis set included 5 trials of CAR T-cell therapies, 3 BsAb trials (**Table 1**), and 26 trials of 'Other' treatments (**Figure 2**).
- All the CAR T-cell and BsAb trials, except for MonumenTAL-1, were of BCMA-targeting therapies.
- Publication dates for CAR T-cell ranged from 2021-2023, BsAb from 2022-2024 and Other from 2012-2024

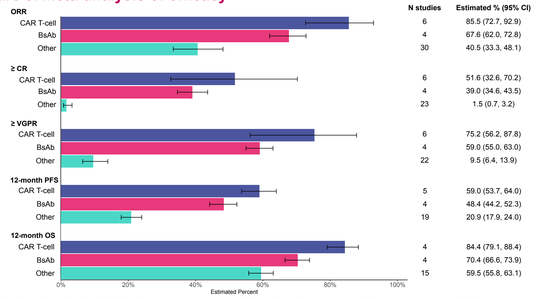
Table 2. Meta-analysis of patient characteristics

		CAR T-cell		BsAb		Other	
		N studies*	Estimate (95% CI)	N studies*	Estimate (95%CI)	N studies*	Estimate (95% CI)
Age, median years		5	61.8 (60.7, 62.9)	6	66.5 (64.8, 68.1)	15	64.8 (63.9, 65.7)
Male, %		6	60.7 (56.2, 64.9)	4	56.4 (52.3, 60.4)	25	57.0 (55.0, 58.4)
Race, %	White	2	79.2 (73.2, 84.1)	4	82.0 (74.9, 87.4)	16	86.0 (79.4, 90.4)
	Black	2	9.9 (3.5, 24.8)	4	11.3 (8.3, 15.2)	15	7.0 (4.2, 12.9)
Prior LOT, meadian		5	5.3 (4.5, 6.2)	4	5.0 (4.8, 5.2)	16	5.0 (4.4, 5.5)
High risk cytogenetics, %		5	41.3 (27.5, 56.7)	4	26.7 (23.2, 30.6)	21	37.0 (29.2, 44.7)
Extramedullary disease, %		6	25.8 (16.2, 38.7)	4	23.9 (19.0, 29.4)	13	21.0 (15.6, 27.5)
ISS III, %		2	15.9 (10.8, 22.7)	3	18.3 (13.3, 24.6)	14	44.5 (34.3, 55.1)
R-ISS III, %		4	15.5 (12.0, 19.9)	--	--	--	--
Prior ASCT, %		6	86.4 (70.2, 94.5)	--	--	12	82.0 (72.9, 88.7)
Refractory status, %	IMiD	4	95.4 (87.0, 98.5)	2	94.3 (89.8, 96.9)	11	95.0 (73.9, 99.3)
	PI	4	85.8 (79.6, 90.4)	2	92.7 (80.6, 97.5)	11	90.0 (67.1, 97.3)
	Anti-CD38 mAb	4	95.5 (92.9, 97.1)	2	93.6 (86.2, 97.2)	11	35.0 (0.7, 97.6)
	Triple-class	6	71.8 (50.5, 86.4)	3	84.6 (60.0, 95.2)	14	33.0 (3.7, 85.9)
	Penta	3	29.9 (18.0, 45.3)	4	31.1 (25.3, 37.7)	13	10.0 (2.4, 31.8)

**Includes study treatment arms or study subgroups (e.g. dose); ASCT: autologous stem-cell transplant; BsAb: bispecific antibodies; CAR T-cell: chimeric antigen receptor T-cell; CI: confidence interval; IMiD: immunomodulatory agent; ISS: International Staging System; LOT: line of therapy; mAb: monoclonal antibody; PI: proteasome inhibitor.*

- Age, sex, race, and extramedullary disease were similar between classes (**Table 2**).
- The proportion of patients with high-risk cytogenetics was lower for BsAb trials compared to both CAR T-cell and Other, whilst the proportion of patients with an International Staging System stage of III was higher in Other compared to CAR T-cell and BsAb.
- Triple-class refractory status was much lower in the 'Other' interventions, likely driven by the lower proportion of these patients who were refractory to anti-CD38 monoclonal antibodies. Similarly, there were fewer penta-refractory patients in the Other category.

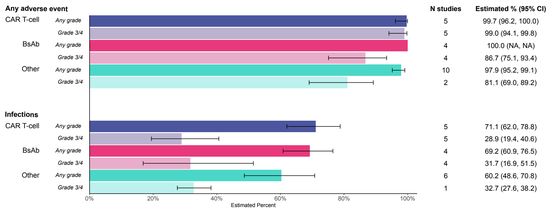
Figure 3. Meta-analysis of efficacy



BsAb: bispecific antibodies; CAR T-cell: chimeric antigen receptor T-cell; CI: confidence interval; CR: complete response; ORR: overall response rate; VGPR: very good partial response;

- Across all included efficacy outcomes, estimates were highest for CAR T-cell, followed by BsAb (**Figure 3**).
- The ≥ VGPR and ≥ CR rate for Other interventions were very low, at 9.5% and 1.5%, respectively.
- The estimated OS and PFS at 12 months was highest in CAR T-cell with 84.4% and 59.0%.

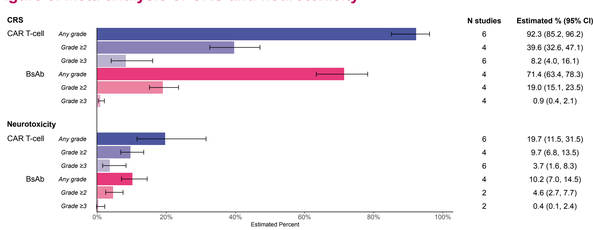
Figure 4. Meta-analysis of Any Adverse Event and Infections



Grade 3/4 events were not reported by maximum grade, so patients who progressed to Grade 5 are included in the count. For Other interventions, these events were often reported as Grade ≥3, so have not been included in the figure to avoid making assumptions about the equivalence of Grade 3/4 and Grade ≥3. Confidence intervals for Any Adverse Events for BsAb were not available as all trials reported 100% rate. BsAb: bispecific antibodies; CAR T-cell: chimeric antigen receptor T-cell; CI: confidence interval

- The rate of Any Grade Adverse Events was high and comparable across classes (**Figure 4**), ranging from 86.7% to 99.7%.
- The rates of Grade 3/4 Infections were highest in BsAb and Other, but were comparable across classes, ranging from 28.9% to 32.7%.
- For Other interventions, Any Adverse Events and Infections were more often reported as Grade ≥3 than as Grade 3/4, hence the small number of studies included. Additional analyses showed Grade ≥3 Any Adverse Events and Infections for Other interventions were 73.0% (85% CI: 63.3, 81.0 across 10 studies) and 25.7% (95% CI: 17.6, 35.9 across 5 studies) respectively.
- Any Grade CRS was estimated 92.3% and 71.4% for CAR T-cell and BsAb, with the majority being Grade 1 for both classes (**Figure 5**). Neurotoxicity was low across CAR T-cell and BsAb classes (18.7% and 10.2%) with a small proportion being Grade ≥3. It was not possible to conduct analyses of recurrence or duration of these Adverse Events.

Figure 5. Meta-analysis of CRS and neurotoxicity



BsAb: bispecific antibodies; CAR T-cell: chimeric antigen receptor t-cell; CI: confidence interval. Neurotoxicity estimates included one study that reported immune effector cell-associated neurotoxicity syndrome (ICANS).

- The overall rate of Grade 5 events for CAR T-cell and BsAb trials, where reported, ranged from 7.0% to 16.7%.

Limitations

- There was inconsistency in the reporting of Any Adverse Events and Infections, with some studies reporting Grade 3/4 to include those who progressed to Grade 5 and some reporting by maximum grade. To avoid assumptions, only those reported as Grade 3/4 have been included for this analysis.
- Due to limited data availability, the analyses of safety outcomes attributes such as time of onset, duration, and recurrence were not possible; these variables are likely influenced by the different administration schedules (one-time vs continuous) of the therapy classes. The FDA Drug Labels for the BsAbs included here report CRS recurrence in 13% to 33% of patients, suggesting that incidence alone does not provide adequate information for a comparative assessment.

CONCLUSIONS

- This study offers a comprehensive and up-to-date synthesis of clinical trial outcomes for recommended interventions in 4L+ treatments for RRMM.
- Results of this systematic literature review and meta-analysis indicate that both CAR T-cell therapies and BsAbs yielded superior outcomes compared to 'Other' therapies in clinical trials, with CAR T-cell therapies showing the best outcomes.
- While the CRS rate was highest with the CAR T-cell therapies, the CAR T-cell therapy benefit vs risk remains favorable due to its one-time treatment compared to agents requiring ongoing therapy which may result in recurring and repeated toxicities.
- Efficacy outcomes are improving with more recently approved interventions, however, there remains an unmet need for durable therapies, treatment free intervals, and an improved safety profile for this 4L+ RRMM patient population.

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DISCLOSURES

Contact: Krina Patel, KPatel1@mdanderson.org
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