#### Check for updates

### OPEN ACCESS

EDITED BY Srinivas Devarakonda, The Ohio State University, United States

REVIEWED BY Fabio Malavasi, University of Turin, Italy Pulak Ranjan Nath, National Cancer Institute (NIH), United States

\*CORRESPONDENCE Yang Liu Vanju V7878@163.com Yanju Li Vanju Li

<sup>†</sup>These authors have contributed equally to this work

RECEIVED 18 July 2024 ACCEPTED 29 November 2024 PUBLISHED 23 December 2024

#### CITATION

Yang X, Wang F, Yuan X, Yang B, Chen J, Cheng J, Liu G, Tang D, Xu X, Wang S, He Z, Liu Y and Li Y (2024) Efficacy and safety of chimeric antigen receptor T cells targeting BCMA and GPRC5D in relapsed or refractory multiple myeloma. *Front. Immunol.* 15:1466443. doi: 10.3389/fimmu.2024.1466443

#### COPYRIGHT

© 2024 Yang, Wang, Yuan, Yang, Chen, Cheng, Liu, Tang, Xu, Wang, He, Liu and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

# Efficacy and safety of chimeric antigen receptor T cells targeting BCMA and GPRC5D in relapsed or refractory multiple myeloma

Xu Yang<sup>1†</sup>, Feiqing Wang<sup>1,2†</sup>, Xiaoshuang Yuan<sup>3†</sup>, Bo Yang<sup>1</sup>, Juan Chen<sup>1</sup>, Jinyang Cheng<sup>1</sup>, Guangyang Liu<sup>1</sup>, Dongxin Tang<sup>1</sup>, Xiao Xu<sup>4</sup>, Sanbin Wang<sup>5</sup>, Zhixu He<sup>6</sup>, Yang Liu<sup>1\*</sup> and Yanju Li<sup>3\*</sup>

<sup>1</sup>Clinical Medical Research Center, The First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, Guiyang, Guizhou, China, <sup>2</sup>Academy of Medical Engineering and Translational Medicine, Tianjin University, Tianjin, China, <sup>3</sup>Department of Hematology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China, <sup>4</sup>Fourth Medical Center, People's Liberation Army General Hospital, Beijing, China, <sup>5</sup>Department of Hematology, The 920th Hospital of Joint Logistics Support Force, Kunming, Yunnan, China, <sup>6</sup>Key Laboratory of Adult Stem Cell Translational Research, Chinese Academy of Medical Sciences, Guizhou Medical University, Guiyang, Guizhou, China

**Background:** Clinical studies have demonstrated the high efficacy of using chimeric antigen receptor (CAR)-T cells targeting B-cell maturation antigen (BCMA) and orphan G protein-coupled receptor, class C group 5 member D (GPRC5D) to treat relapsed or refractory multiple myeloma (RRMM). In this study, we compared the efficacy and safety of BCMA CAR-T-cell therapy (BCMA CAR-T) and GPRC5D CAR T-cell therapy (GPRC5D CAR-T) in patients with RRMM.

**Methods:** We retrieved and included eligible clinical trials of BCMA or GPRC5D CAR-T for RRMM patients. The primary outcomes for efficacy were overall response rate (ORR), complete response rate (CRR), minimal residual disease (MRD) negativity, and relapse rate. The primary outcomes for safety were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

**Results:** We incorporated 18 early-phase, single-arm clinical trials, which included 503 and 133 patients receiving BCMA CAR-T and GPRC5D CAR-T, respectively. For the GPRC5D CAR-T cohort, the estimated ORR, CRR, MRD negativity rate, and relapse rate were found to be 89.8% [95% confidence interval (CI), 82.8%–96.9%], 50.5% (95% CI, 38.0%–62.9%), 78.8% (95% CI, 53.0%–100%), and 26.0% (95% CI, 7.4%–44.6%), respectively. In the BCMA CAR-T group, the ORR was 76.3% (95% CI, 67.9%–84.7%), the CRR was 34.3% (95% CI, 25.9%–42.7%), the MRD negativity rate was 76.5% (95% CI, 63.1%–90.0%), and the recurrence rate was 57.3% (95% CI, 47.7%–66.9%). These values were significantly lower than those observed in the GPRC5D CAR-T cohort. Both BCMA and GPRC5D CAR-T demonstrated acceptable safety. The estimated incidence of BCMA CAR-T resulting in grade 3–5 CRS and ICANS was only 5.4% (95% CI, 2.0%–10.4%) and 3.3% (95% CI, 0.6%–8.0%), respectively. The estimated incidence of GPRC5D CAR-T resulting in grade 3–5 CRS and ICANS was only 1.6% (95% CI, 0.0%–6.5%) and 2.7% (95% CI, 0.7%–6.2%), respectively.

**Conclusion:** GPRC5D CAR-T potentially demonstrates enhanced effectiveness relative to BCMA CAR-T in treating patients with RRMM. Therefore, GPRC5D CAR-T can be regarded as the preferred therapeutic option for RRMM, particularly among patients who have undergone relapse subsequent to BCMA CAR-T treatment.

#### KEYWORDS

B-cell maturation antigen, G protein-coupled receptor, class C group 5 member D, car-T, relapsed or refractory multiple myeloma

## Introduction

Multiple myeloma (MM) is a malignant plasma cell neoplasm, constituting approximately 10% of all hematological malignancies (1, 2). Despite several therapeutic advances, MM still remains, for most patients, incurable (3). Nevertheless, with the advent of novel therapeutic agents, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 monoclonal antibodies, selective nuclear export protein inhibitors (SINEs), and T-cell-redirected bispecific antibodies, over the past decade, the survival outcomes of patients with MM have improved considerably (4-7). However, nearly all patients eventually experience relapse due to drug resistance (8). Particularly concerning are those with relapsed or refractory multiple myeloma (RRMM) and individuals presenting with high-risk cytogenetic features or extramedullary disease (EMD), who exhibit a dismal prognosis (9, 10). Consequently, there is an urgent necessity for innovative therapeutic approaches that target RRMM.

In preclinical evaluations, therapies based on chimeric antigen receptor (CAR)-T cells have demonstrated high efficacy against MM, particularly RRMM (11, 12). B-cell maturation antigen (BCMA) is consistently expressed on MM cells but is absent from normal tissues or plasma cells (13). Brudno et al. conducted the first trial on BCMA-targeted CAR-T therapy (hereinafter referred to as BCMA CAR-T) and reported a high response rate in patients with RRMM (14). Currently, idecabtagene vicleucel (ide-cel, bb2121) and ciltacabtagene autoleucel (cilta-cel) are two BCMA CAR-T modalities approved for adult RRMM patients with at least two prior lines of therapy for ide-cel and one prior line of therapy for cilta-cel, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. Nevertheless, neither modality has demonstrated sustained survival benefits in this patient population, with most patients eventually experiencing relapse (15–18).

In the realm of MM treatment, orphan G protein-coupled receptor class C group 5 member D (GPRC5D) has emerged as a promising alternative target for CAR-T cell therapy (19). This receptor is not only present in the bone marrow plasma cells of MM patients but is also expressed in MM cell lines (19, 20). We recently performed an early dose escalation trial, MCARH109, which

presents the first formally published results regarding the activity of GPRC5D-targeted CAR-T cells (hereinafter: GPRC5D CAR-T) in patients with RRMM (including those previously treated with BCMA CAR-T) (21). The results confirmed that GPRC5D is an effective immunotherapeutic target for CAR-T therapy in RRMM.

Although both BCMA CAR-T and GPRC5D CAR-T may effectively resolve RRMM, no study has compared their efficacies in these patients. Furthermore, most studies thus far have included a small sample size and lacked sufficient validation. Therefore, in this systematic review and meta-analysis, we compared the efficacies and safety of BCMA and GPRC5D CAR-T therapies in RRMM to provide a theoretical basis for the clinical treatment of the malignancy.

## **Methods**

### Data sources and search strategy

We searched several publication databases, including PubMed, ScienceDirect, Embase, and Medline, for eligible studies published until December 2023. Only clinical trials published in English and registered at Clinicaltrials.gov (NCT number) or in the Chinese Clinical Trial Registry (ChiCTR number) were included. The following English search terms were used for this search: "B-cell maturation antigen" or "BCMA"; "chimeric antigen receptor" or "CAR"; "G protein-coupled receptor, family C, group 5, member D" or "GPRCD"; "Relapse or Refractory Multiple Myeloma"; and "clinical trials." We also included eligible full articles or abstracts presented at the annual scientific meetings of the American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), and European Association of Hematology (EHA). Patient data were extracted only from the obtained articles; no additional requests for original patient data were made by any of the authors.

## Inclusion and exclusion criteria

We only included studies that (1) were published in English, (2) were clinical trials on BCMA or GPRC5D CAR-T, and (3) included

patients with RRMM regardless of their age or sex. In contrast, we excluded studies that did not (1) assess the effects of BCMA or GPRC5D CAR-T in patients with RRMM, (2) provide data required for meta-analysis (e.g., total patient number, CAR-T efficacy, and adverse reactions), or (3) use a clinical trial design (e.g., review, case report, or animal study).

### Data extraction

The literature search, abstract and full-text review, and data collection were independently performed by two authors, followed by a cross-review for data collection accuracy. The primary outcome measures were overall response rate (ORR), complete response rate (CRR), minimal residual disease (MRD) negativity, relapse rate, and CAR-T-related toxicity [i.e., cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)]. We defined ORR according to the International Myeloma Working Group criteria as the total of (strict) complete responses and (very good) partial responses (22). For each study, we collected the following information: authors, year of publication, median patient age, patient number, line of prior treatment, median follow-up duration, treatment targets, efficacy outcome measures (ORR, CRR, MRD negativity, and relapse rate), and safety outcome measures (CRS and ICANS incidence).

### Risk of bias and quality evaluation

We used the Methodological Index for Non-Randomized Studies (MINORS) scale to evaluate the methodological quality of each study (23). Since none of the studies included a control group, we only used eight MINORS items, with the maximum score for each study set at 16. We assessed the certainty of the body of evidence in the domains of risk of bias, originality, imprecision, inconsistency, and publication bias using hierarchical methods for all included studies. According to the quality of evidence recorded in the GRADE system, we used the following evidence levels: high, medium, low, and very low (24).

### Statistical analysis

Because of the diversity among the included studies, we used random-effects models to obtain outcome rates along with their 95% confidence intervals (CIs). Subgroup analyses were performed to assess differences between study groups, with proportions pooled using the random-effect models (DerSimonian–Laird). Freeman– Tukey double inverse sine transformation was used when the data did not follow a normal distribution. Interassay heterogeneity was measured using the  $I^2$  statistic (i.e., the percentage of studied variation due to heterogeneity rather than chance). All analyses were performed using R (version 4.3.2), and p < 0.05 indicated statistical significance.

## Results

### Literature search results

Our initial search yielded 707 abstracts, clinical studies, case studies, and other publications. Of these, only 19 studies were eligible (14, 21, 25–41). However, because two of these studies (40, 41) had an identical clinical trial number (NCT04674813), 18 studies were finally included. All of these studies were early-stage single-arm clinical trials. In these trials, 503 patients were administered BCMA CAR-T, while 133 received GPRC5D CAR-T. The flow of the study selection process is presented in Figure 1.

# Characteristics and MINORS grades of the included studies

Table 1 presents the clinical data from the included studies. All trials were published between 2018 and 2023, and their sample sizes ranged from 9 to 128. Of all 18 included studies, 14 and 4 focused on BCMA and GPRC5D CAR-T, respectively. In the intervention protocols, the dosage ranged from  $7.5 \times 10^5$  to  $8.0 \times 10^8$  CAR-T cells/kg.

# Response rates in RRMM patients treated with BCMA and GPRC5D CAR-T

A clinical response was evaluated in 636 patients. The pooled ORR and CRR were 79.1% (95% CI, 72.0%–86.3%; I2 = 80.9%; p < 0.01; Figure 2A) and 37.8% (95% CI, 30.1%–45.6%; I2 = 77.93%; p < 0.01; Figure 3A), respectively. In the subgroup analysis, BCMA and GPRC5D CAR-T demonstrated ORRs of 76.3% (95% CI, 67.9%–84.7%; Figure 2B) and 89.8% (95% CI, 82.8%–96.9%; Figure 2B), and CRRs of 34.3% (95% CI, 25.9%–42.7%; Figure 3B) and 50.5% (95% CI, 38.0%–62.9%; Figure 3B), respectively. Both the ORR and CRR were significantly higher for GPRC5D CAR-T than for BCMA CAR-T [p = 0.02 (Figure 2B) and 0.03 (Figure 3B), respectively].

# MRD negativity in RRMM patients treated with BCMA and GPRC5D CAR-T

In the subgroup analysis of 10 BCMA CAR-T trials, 187 of 265 patients became MRD negative; their combined MRD-negativity rate was 77.2% (95% CI, 65.8%–88.6%; I2 = 85.03%; p < 0.01; Figure 4). In the subgroup analysis of three GPRC5D CAR-T trials, 45 of 60 patients became MRD negative; their combined MRD negativity rate was 78.8% (95% CI, 53.0%–100%; Figure 4), which did not differ significantly from that for BCMA CAR-T.

# Relapse rates in RRMM patients treated with BCMA and GPRC5D CAR-T

Relapse rates were evaluated in seven BCMA CAR-T and three GPRC5D CAR-T trials. Their combined relapse rates were 57.3%



(95% CI, 47.7%–66.9%) and 26.0% (95% CI, 7.4%–44.6%), respectively (Figure 5); the between-group difference in the rates was significantly different (p < 0.01).

### ORRs in RRMM patients with EMD or highrisk cytogenetic characteristics

Only eight trials included patients with EMD and demonstrated no significant differences in the ORRs for BCMA and GPRC5D CAR-T (p = 0.95; Figure 6A). Similarly, only five studies included patients with high cytogenetic characteristics, and their ORRs for BCMA and GPRC5D CAR-T did not demonstrate significant differences (p = 0.97; Figure 6B).

# Safety in RRMM patients treated with BCMA and GPRC5D CAR-T

In total, 18 trials reported the overall CRS rate and 15 trials reported the overall ICANS rate. Additionally, 18 trials provided the severe CRS rate, and 15 trials provided the severe ICANS rate. The total CRS rate for BCMA and GPRC5D CAR-T was 75.8% (95% CI, 60.5%-88.2%), and the rate of severe (grade  $\geq$ 3) CRS was 4.4% (95% CI, 1.7%-8.2%, Figure 7A). In turn, the total ICANS rate for both BCMA and GPRC5D CAR-T was 11.5% (95% CI, 5.2%-19.7%), and the rate of severe (grade  $\geq$ 3) ICANS was 3.1% (95% CI, 1.1%-6.0%, Figure 7B).

A total of 18 trials reported the incidence of CRS caused by BCMA CAR-T and GPRC5D CAR-T. The incidence of CRS grades 1-5 caused by BCMA CAR-T was 74.2% (95% CI, 56.6%–88.5%, Figure 8A), and the incidence of severe ( $\geq$  grade 3) CRS was 5.4% (95% CI, 2.0%–10.4%, Figure 8B). For GPRC5D CAR-T, the incidence of CRS grades 1–5 caused by GPRC5D CAR-T was 81.2% (95% CI, 44%–99.7%, Figure 8A), and the incidence of severe ( $\geq$  grade 3) CRS was 1.6% (95% CI, 0.0%–6.5%, Figure 8B).

A total of 15 trials reported the incidence of ICANS caused by BCMA and GPRC5D CAR-T. The incidence of ICANS grades 1–5 caused by BCMA CAR-T was 13.6% (95% CI, 5.5%–24.5%, Figure 9A), while that of severe ( $\geq$  grade 3) ICANS was 3.3% (95% CI, 0.6%–8.0%, Figure 9B). In turn, for GPRC5D CAR-T, the incidence of ICANS grades 1-5 caused by GPRC5D CAR-T cell

Study ID	No. Studies	Age	Line of previous treatment regimen	CAR T target	Median follow- up time	ORR (%)	CRR (%)	MRD nega- tive(%)	Relapse (%)	Serious CRS(%)	Serious ICANS(%)	MINORS grade
Minakata2023 ( <mark>25</mark> )	9	54	4	BCMA	12.9 Months	89%	55.6%	66.7%	25.0%	0	0	13
Asherie 2023 (26)	20	62	6	BCMA	4.5 Months	75.0%	50.0%	40.0%	53.3%	0	0	14
Mailankody 2023 (27)	43	66.3	5	BCMA	10.2 Months	55.8%	35.3%	92.9%	54.2%	2.3%	0	13
Qu 2022 (28)	31	65	5	BCMA	9.4 Months	87.1%	45.2%	93.8%	NA	9.7%	3.2%	13
Du 2022 ( <mark>29</mark> )	49	66	4	BCMA	≥1 Months	77.6%	46.9%	42.9%	68.4%	6.1%	NA	12
Munshi 2021 ( <mark>30</mark> )	128	67	5	BCMA	13.3 Months	73.4%	32.8%	78.6%	NA	5.5%	3.1%	13
Raje 2021 (31)	33	66	7	BCMA	11.3 Months	84.8%	45.5%	83.3%	53.6%	6.1%	3.0%	13
Alsina 2020 (32)	46	62	6	BCMA	8.5 Months	54.3%	17.4%	NA	NA	4.3%	6.5%	13
An 2020 (33)	21	60	4	BCMA	182 Days	95.2%	28.6%	NA	NA	5%	NA	12
Kumar 2020 (34)	14	59	6	BCMA	4.5 months	100%	40%	91.7%	NA	0	0	12
Fu 2019 (35)	44	NA	NA	BCMA	≥1 Months	79.65	40.9%	36.4%	NA	6.8%	NA	11
Cohen 2019 (36)	25	58	5	BCMA	NA	48.0%	8%	NA	75.0%	32%	8.0%	12
Brudno 2018 (14)	26	56.5	9.5	BCMA	NA	57.7%	11.5%	NA	53.8%	37.5%	37.5%	12
Liu 2018 (37)	14	NA	NA	BCMA	≥1 Months	78.6%	50.0%	64.3%	NA	0	7.1%	11
Xia 2023 (38)	44	63	5	GPRC5D	10 Months	90.9%	63.6%	78.8%	16.7%	0	2.3%	13
Zhang 2023 (39)	10	64	5.5	GPRC5D	9 Months	100%	60.0%	100%	20.0%	0	0	13
Mailankody 2023 (27)	17	58.5	4	GPRC5D	10.1 Months	70.6%	35.3%	52.9%	50.0%	5.9%	5.9%	12
Bal 2023 (40, 41)	64	NA	NA	GPRC5D	5.9 Months	87.7%	45.2%	NA	NA	4.3%	2.9%	11

BCMA, B cell membrane antigen; GPRC5D, G protein-coupled receptor, class C group 5 member D; ORR, overall response rate; CRR, complete response rate; MRD, minimal residual lesion negative; CRS, Cytokine release syndrome; ICANS, Immune effector cell-associated neurotoxicity syndrome.

NA, not available.



therapy was 6.8% (95% CI, 2.5%–12.9%, Figure 9A), and that of severe ( $\geq$  grade 3) ICANS was 2.7% (95% CI, 0.7%–6.2%, Figure 9B). The differences in the rates of adverse events (total or severe) for BCMA and GPRC5D CAR-T were insignificant (Table 2).

design and demonstrated differences in follow-up duration (Table 3). Nevertheless, our estimated results were consistent, suggesting that they may be crucial for guiding clinical decisions and treatment.

### Risk of bias

We assessed the quality of evidence for the included studies using the GRADE system. The results thus obtained using the evidence from the GRADE system may be associated with some bias because all the included trials used a single-arm intervention

## Discussion

Clinically, the treatment of RRMM remains difficult and warrants further development (42). Cellular immunotherapy may lead to effective outcomes in patients with RRMM (43). Several recent studies have assessed the efficacy and safety of BCMA CAR-T

	Events	Total	Proportion [95% Cl]	Weight	CRR
Minakata 2023	5	9	0.556 [0.212; 0.863]	3.3%	
Asherie 2023	10	20	0.500 [0.272; 0.728]	4.9%	
Mailankody 2023	6	17	0.353 [0.142; 0.617]	4.8%	<b>_</b>
Qu 2022	14	31	0.452 [0.273; 0.640]	5.7%	
Du 2022	23	49	0.469 [0.325; 0.617]	6.4%	
Munshi 2021	42	128	0.328 [0.248; 0.417]	7.4%	
Raje 2021	15	33	0.455 [0.281; 0.636]	5.8%	
Alsina 2020	8	46	0.174 [0.078; 0.314]	6.9%	
An 2020	6	21	0.286 [0.113; 0.522]	5.4%	
Kumar 2020	6	14	0.429 [0.177; 0.711]	4.2%	
Fu 2019	18	44	0.409 [0.263; 0.568]	6.3%	
Cohen 2019	2	25	0.080 [0.010; 0.260]	7.0%	
Brudno 2018	3	26	0.115 [0.024; 0.302]	6.7%	:
Liu 2018	3 7	20 14	0.115 [0.024, 0.302]	4.2%	
Xia 2023	21	33		4.2% 5.9%	
	6		0.636 [0.451; 0.796]		
Zhang 2023 Mailankady, 2022		10 17	0.600 [0.262; 0.878] 0.353 [0.142; 0.617]	3.6%	
Mailankody 2023	6	17		4.8%	
Bal 2023	33	73	0.452 [0.335; 0.573]	6.8%	: <b>-</b>
Total (95% CI)			0.378 [0.301; 0.456]	100.0%	-
	= 0.020; Chi <sup>i</sup>	<sup>2</sup> = 77.04.	df = 17 (P < 0.01); $I^2 = 77.9$	93%	
B Study or Subgroup	Events	Total	Proportion [95% CI]	Weight	CRR
Study or	Events	Total	Proportion [95% Cl]	Weight	CRR
Study or Subgroup Endpoint:BCMA Minakata 2023	5	9	0.556 [0.212; 0.863]	3.3%	CRR
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023	5 10	9 20	0.556 [0.212; 0.863] 0.500 [0.272; 0.728]	3.3% 4.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023	5 10 6	9 20 17	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617]	3.3% 4.9% 4.8%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023	5 10	9 20	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640]	3.3% 4.9% 4.8% 5.7%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022	5 10 6 14	9 20 17 31	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617]	3.3% 4.9% 4.8%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021	5 10 6 14 23 42 15	9 20 17 31 49 128 33	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.636]	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020	5 10 6 14 23 42 15 8	9 20 17 31 49 128 33 46	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.638] 0.174 [0.078; 0.314]	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020	5 10 6 14 23 42 15 8 6	9 20 17 31 49 128 33 46 21	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.636] 0.174 [0.078; 0.314] 0.286 [0.113; 0.522]	3.3% 4.9% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020	5 10 6 14 23 42 15 8	9 20 17 31 49 128 33 46	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.638] 0.174 [0.078; 0.314]	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019	5 10 6 14 23 42 15 8 6 6 8 6 18 2	9 20 17 31 49 128 33 46 21 14 44 25	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.636] 0.174 [0.078; 0.314] 0.266 [0.113; 0.522] 0.429 [0.177; 0.711] 0.409 [0.263; 0.568] 0.080 [0.010; 0.260]	3.3% 4.9% 4.8% 5.7% 6.4% 5.8% 6.9% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018	5 10 6 14 23 42 15 8 6 6 18 2 3	9 20 17 31 49 128 33 46 21 14 44 25 26	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.800 \ [0.010; \ 0.260]\\ 0.805 \ [0.010; \ 0.260]\\ 0.802 \ [0.012; \ 0.302]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 6.3% 6.7%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018	5 10 6 14 23 42 15 8 6 6 8 6 18 2	9 20 17 31 49 128 33 46 21 14 44 25	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.080 \ [0.010; \ 0.260]\\ 0.115 \ [0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl)	5 10 6 14 23 42 15 8 6 6 18 2 3 7	9 20 17 31 49 128 33 46 21 14 44 25 26 14	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.800 \ [0.010; \ 0.260]\\ 0.805 \ [0.010; \ 0.260]\\ 0.802 \ [0.012; \ 0.302]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup>	5 10 6 14 23 42 15 8 6 6 18 2 3 7 7	9 20 17 31 49 128 33 46 21 14 44 25 26 14	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.636] 0.174 [0.078; 0.314] 0.286 [0.113; 0.522] 0.429 [0.177; 0.711] 0.409 [0.263; 0.568] 0.880 [0.010; 0.260] 0.115 [0.024; 0.302] 0.500 [0.230; 0.770] 0.343 [0.259; 0.427]	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl)	5 10 6 14 23 42 15 8 6 6 18 2 3 7 7	9 20 17 31 49 128 33 46 21 14 44 25 26 14	0.556 [0.212; 0.863] 0.500 [0.272; 0.728] 0.353 [0.142; 0.617] 0.452 [0.273; 0.640] 0.469 [0.325; 0.617] 0.328 [0.248; 0.417] 0.455 [0.281; 0.636] 0.174 [0.078; 0.314] 0.286 [0.113; 0.522] 0.429 [0.177; 0.711] 0.409 [0.263; 0.568] 0.880 [0.010; 0.260] 0.115 [0.024; 0.302] 0.500 [0.230; 0.770] 0.343 [0.259; 0.427]	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Zhang 2023	5 10 6 14 23 42 15 8 6 6 18 2 3 7 = 0.017; Ch D 21 6	9 20 17 31 49 128 33 46 21 14 44 25 26 14 $1^2 = 53.52$ 33 10	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.459 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.499 \ [0.263; \ 0.562]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.560]\\ 0.010; \ 0.260]\\ 0.115 \ [0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.600 \ [0.262; \ 0.878]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 6.7% 4.2% 78.9% 78.9% 78.9% 3.6%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Mailankody 2023	5 10 6 14 23 42 15 8 6 6 18 2 3 7 7 = 0.017; Ch D 21 6 6 6	9 20 17 31 49 128 33 46 21 14 44 25 26 14 14 26 14 14 33 10 17	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.286 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.080 \ [0.010; \ 0.260]\\ 0.105 \ [0.230; \ 0.770]\\ 0.343 \ [0.229; \ 0.427]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.600 \ [0.262; \ 0.878]\\ 0.535 \ [0.142; \ 0.617]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9% 7.1%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023	5 10 6 14 23 42 15 8 6 6 18 2 3 7 = 0.017; Ch D 21 6	9 20 17 31 49 128 33 46 21 14 44 25 26 14 $1^2 = 53.52$ 33 10	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.286 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.800 \ [0.010; \ 0.260]\\ 0.115 \ [0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.504 \ [0.259; \ 0.427]\\ 0.536 \ [0.451; \ 0.796]\\ 0.636 \ [0.451; \ 0.796]\\ 0.636 \ [0.451; \ 0.796]\\ 0.635 \ [0.142; \ 0.617]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.335; \ 0.573]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 4.2% 6.3% 7.0% 6.3% 7.0% 6.7% 4.2% 78.9% 3.6% 4.8% 6.8%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Au 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% Cl)	5 10 6 14 23 42 15 8 6 6 18 2 3 7 7 = 0.017; Ch D 21 6 6 33	9 20 17 31 49 128 33 46 21 14 25 26 14 25 26 14 $1^2 = 53.52$ 33 10 17 73	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.469 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.286 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.080 \ [0.010; \ 0.260]\\ 0.105 \ [0.230; \ 0.770]\\ 0.343 \ [0.229; \ 0.427]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.600 \ [0.262; \ 0.878]\\ 0.535 \ [0.142; \ 0.617]\\ \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9% 7.1% 5.9% 3.6% 4.8% 6.8% 21.1%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Au 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% Cl)	5 10 6 14 23 42 15 8 6 6 18 2 3 7 7 = 0.017; Ch D 21 6 6 33	9 20 17 31 49 128 33 46 21 14 25 26 14 25 26 14 $1^2 = 53.52$ 33 10 17 73	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.328 \ [0.248; \ 0.417]\\ 0.328 \ [0.248; \ 0.417]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.286 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.409 \ [0.263; \ 0.568]\\ 0.409 \ [0.263; \ 0.568]\\ 0.415 \ [0.010; \ 0.260]\\ 0.115 \ [0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.600 \ [0.262; \ 0.878]\\ 0.353 \ [0.142; \ 0.677]\\ 0.452 \ [0.335; \ 0.573]\\ 0.505 \ [0.380; \ 0.629] \end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 78.9% 7.1% 5.9% 3.6% 4.8% 6.8% 21.1%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup>	5 10 6 14 23 42 15 8 6 6 18 2 3 7 = 0.017; Ch D 21 6 6 33 = 0.007; Ch	9 20 17 31 49 128 33 46 21 14 44 25 26 14 $^{12} = 53.52$ $^{12} = 53.52$ $^{12} = 5.35$ , $^{12} = 77.04$	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.459 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.499 \ [0.263; \ 0.562]\\ 0.429 \ [0.177; \ 0.711]\\ 0.499 \ [0.263; \ 0.562]\\ 0.429 \ [0.115; \ 0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.636 \ [0.451; \ 0.796]\\ 0.505 \ [0.380; \ 0.629]\\ 0.505 \ [0.380; \ 0.629]\\ df = 3 \ (P = 0.15); \ l^2 = 43.9!\\ 0.378 \ [0.301; \ 0.456]\\ 0.601; \ l^2 = 77\end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 6.7% 4.2% 7.0% 6.7% 4.2% 5.9% 3.6% 4.8% 6.8% 21.1%	
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint:GPRC5 Xia 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup>	5 10 6 14 23 42 15 8 6 6 18 2 3 7 = 0.017; Ch D 21 6 6 33 = 0.007; Ch	9 20 17 31 49 128 33 46 21 14 44 25 26 14 $^{12} = 53.52$ $^{12} = 53.52$ $^{12} = 5.35$ , $^{12} = 77.04$	$\begin{array}{c} 0.556 \ [0.212; \ 0.863]\\ 0.500 \ [0.272; \ 0.728]\\ 0.353 \ [0.142; \ 0.617]\\ 0.452 \ [0.273; \ 0.640]\\ 0.459 \ [0.325; \ 0.617]\\ 0.328 \ [0.248; \ 0.417]\\ 0.455 \ [0.281; \ 0.636]\\ 0.174 \ [0.078; \ 0.314]\\ 0.266 \ [0.113; \ 0.522]\\ 0.429 \ [0.177; \ 0.711]\\ 0.499 \ [0.263; \ 0.562]\\ 0.429 \ [0.177; \ 0.711]\\ 0.499 \ [0.263; \ 0.562]\\ 0.429 \ [0.115; \ 0.024; \ 0.302]\\ 0.500 \ [0.230; \ 0.770]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.343 \ [0.259; \ 0.427]\\ 0.636 \ [0.451; \ 0.796]\\ 0.636 \ [0.451; \ 0.796]\\ 0.505 \ [0.380; \ 0.629]\\ 0.505 \ [0.380; \ 0.629]\\ df = 3 \ (P = 0.15); \ l^2 = 43.9!\\ 0.378 \ [0.301; \ 0.456]\\ 0.601; \ l^2 = 77\end{array}$	3.3% 4.9% 4.8% 5.7% 6.4% 7.4% 5.8% 6.9% 5.4% 4.2% 6.3% 7.0% 6.7% 4.2% 6.7% 4.2% 7.0% 6.7% 4.2% 5.9% 3.6% 4.8% 6.8% 21.1%	

in RRMM (44, 45). BCMA is considered critical for the survival of bone marrow plasma cells (46). However, MM patients with negative or low BCMA expression will still relapse after receiving BCMA-targeted CAR T-cell therapy, with problems arising from immune escape (11, 31, 36). Moreover, although considered a rare event, BCMA antigen loss may occur after anti-BCMA treatment due to biallelic deletion of the BCMA locus on chromosome 16 or reversible downregulation of BCMA expression, which prevents subsequent response to BCMA-targeted therapy (47–50). Therefore, identifying more specific or consistent MM targets may help mitigate BCMA escape-mediated recurrence. GPRC5D is a target validated for rationally designed immunotherapeutic strategies because it is preferentially expressed on plasma cells; a preclinical study demonstrated its efficacy in a BCMA escape model (19). Compared with BCMA, GPRC5D has better specificity, and its expression does not decrease with time. Furthermore, they are independently expressed and they can be single- or double-targeted to develop therapeutic drugs (51). However, the efficacy and safety of GPRC5D CAR-T in patients with RRMM warrants evaluation.

To our knowledge, this is the first systematic review and metaanalysis comparing BCMA and GPRC5D CAR-T outcomes in



patients with RRMM. BCMA-targeted CAR-T cell therapy has shown effectiveness in RRMM patients, but there are problems of relapse and antigen escape in patients who are BCMA-negative or have a low expression (52). As a target of immunotherapy, GPRC5D has shown potential efficacy in BCMA escape models, and its expression has better specificity and persistence (19, 53). Our subgroup analysis also showed that GPRC5D CAR-T had a higher MRD negative rate (78.8%) than BCMA CAR-T (76.5%). As

Study or Subgroup	Events	Total	Proportion [95% CI]	Weight	Relapse
Endpoint:BCMA					:
Minakata 2023	2	8	0.250 [0.032; 0.651]	8.1%	
Asherie 2023	8	15	0.533 [0.266; 0.787]	9.3%	
Mailankody 2023	13	24	0.542 [0.328; 0.744]	10.7%	
Du 2022	26	38	0.684 [0.513; 0.825]	12.1%	
Raje 2021	15	28	0.536 [0.339; 0.725]	11.1%	
Cohen 2019	9	12	0.750 [0.428; 0.945]	9.5%	
Brudno 2018	7	13	0.538 [0.251; 0.808]	8.8%	
Total (95% CI)			0.573 [0.477; 0.669]	69.6%	
Heterogeneity: Tau <sup>2</sup> =	0.004; Chi <sup>2</sup>	<sup>2</sup> = 8.99, 0	$df = 6 (P = 0.17); I^2 = 33.249$	6	
Endpoint:GPRC5D					
Xia 2023	5	30	0.167 [0.056; 0.347]	12.4%	
Zhang 2023	2	10	0.200 [0.025; 0.556]	9.4%	
Mailankody 2023	6	12	0.500 [0.211; 0.789]	8.5%	
Total (95% CI)			0.260 [0.074; 0.446]	30.4%	
Heterogeneity: Tau <sup>2</sup> =	0.015; Chi <sup>2</sup>	<sup>2</sup> = 4.4, df	= 2 (P = 0.11); I <sup>2</sup> = 54.56%		
Total (95% CI)			0.471 [0.341; 0.601]	100.0%	
Heterogeneity: Tau <sup>2</sup> =	0.031; Chi <sup>2</sup>	<sup>2</sup> = 40.91,	df = 9 (P < 0.01); $I^2$ = 78.00		
Test for subgroup diffe	rences: Ch	$i^2 = 8.60$ .	df = 1 (P < 0.01)		0 0.2 0.4 0.6 0.8

Study or		EMD		o EMD			
Subgroup	Events	Total	Events	Total	Weight	RR [95% CI]	Risk Ratio
Endpoint:BCMA							
Mailankody 2023	4	5	13	19	5.4%	1.169 [0.685; 1.995]	<del></del>
Qu 2022	1	3	15	25	0.6%	0.556 [0.109; 2.841] -	
Du 2022	7	11	31	38	6.9%	0.780 [0.487; 1.250]	<b>_</b>
Munshi 2021	36	50	59	78	33.7%	0.952 [0.769; 1.179]	-
Raje 2021	8	9	20	24	18.0%	1.067 [0.796; 1.429]	_ <b></b>
Cohen 2019	4	7	8	18	2.3%	1.286 [0.564; 2.930]	
Total (95% CI)		85		202	66.9%	0.983 [0.845; 1.144]	+
Heterogeneity: Tau <sup>2</sup>	= 0; Chi <sup>2</sup> = 2	.59, df =	5 (P = 0.76)	l <sup>2</sup> = 0%			
Endpoint:GPRC5	D						
Xia 2023	10	11	20	22	29.4%	1.000 [0.795; 1.257]	<b></b>
Mailankody 2023	5	8	7	9	3.8%	0.804 [0.424; 1.525]	<b>_</b>
Total (95% CI)		19		31	33.1%	0.976 [0.786; 1.210]	+
Heterogeneity: Tau <sup>2</sup>	= 0; Chi <sup>2</sup> = 0	4, df = 1	(P = 0.53);	<sup>2</sup> = 0%		10 / al	
Total (95% CI)		104		233	100.0%	0 981 [0 866: 1 110]	4
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> Test for subgroup diff					<b>100.0%</b> %	0.981 [0.866; 1.110]	0.2 0.5 1 2 5
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff	erences: Ch	99, df =		(1 <sup>2</sup> = 0.00 0.95)			
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff	erences: Ch	99, df = i <sup>2</sup> = 0.00, gh risk	df = 1 (P = Standa	(1 <sup>2</sup> = 0.00 0.95)		0.981 [0.866; 1.110] RR [95% CI]	0.2 0.5 1 2 5
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or	erences: Ch	99, df = i <sup>2</sup> = 0.00, gh risk	df = 1 (P = Standa	1 <sup>2</sup> = 0.00 0.95)	%		
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff S Study or Subgroup	erences: Ch	99, df = i <sup>2</sup> = 0.00, gh risk	df = 1 (P = Standa	1 <sup>2</sup> = 0.00 0.95)	%		
Heterogeneity: Tau <sup>2</sup> Test for subgroup dif Study or Subgroup Endpoint: BCMA	ferences: Ch Hi Events	99, df = <sup>-</sup> i <sup>2</sup> = 0.00, gh risk Total	df = 1 (P = Standa Events	1 <sup>2</sup> = 0.00 0.95) ard risk Total	% Weight	RR [95% CI]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff Study or Subgroup Endpoint: BCMA Mailankody 2023	ferences: Ch Hi Events	99, df = i <sup>2</sup> = 0.00, gh risk Total	df = 1 (P = Standa Events	1 <sup>2</sup> = 0.00 0.95) rd risk Total	Weight 6.2%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff <b>Subgroup</b> Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021	erences: Ch Hi Events 6 16	99, df = <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21	df = 1 (P = Standa Events	1 <sup>2</sup> = 0.00 0.95) <b>Ird risk</b> <b>Total</b> 16 28 66	% Weight 6.2% 17.7% 34.1%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff <b>Subgroup</b> Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021 Raje 2021	Ferences: Ch Hi Events 6 16 32	99, df = <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21 45	df = 1 (P = <b>Standa</b> <b>Events</b> 11 22 53	1 <sup>2</sup> = 0.00 0.95) <b>rd risk</b> <b>Total</b> 16 28 66 18	% Weight 6.2% 17.7% 34.1% 15.8%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105] 0.776 [0.561; 1.075]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or Subgroup Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021	Hi Events 6 16 32 11	99, df = <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21 45 15 89	df = 1 (P = <b>Standa</b> <b>Events</b> 11 22 53 17	1 <sup>2</sup> = 0.00 0.95) <b>rd risk</b> <b>Total</b> 16 28 66 18 128	% Weight 6.2% 17.7% 34.1%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or Subgroup Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021 Raje 2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup>	ierences: Ch Hi Events 6 16 32 11 = 0; Chi <sup>2</sup> = 1	99, df = <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21 45 15 89	df = 1 (P = <b>Standa</b> <b>Events</b> 11 22 53 17	1 <sup>2</sup> = 0.00 0.95) <b>rd risk</b> <b>Total</b> 16 28 66 18 128	% Weight 6.2% 17.7% 34.1% 15.8%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105] 0.776 [0.561; 1.075]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or Subgroup Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021 Raje 2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint: GPRC5	ierences: Ch Hi Events 6 16 32 11 = 0; Chi <sup>2</sup> = 1 D	99, df = ' 2' = 0.00, yh risk Total 8 21 45 15 89 9 56, df = -	df = 1 (P = Standa Events 11 22 53 17 3 (P = 0.67)	1 <sup>2</sup> = 0.00 0.95) <b>rd risk</b> <b>Total</b> 16 28 66 18 128 128 1 <sup>2</sup> = 0%	% Weight 6.2% 17.7% 34.1% 15.8% 73.8%	RR [95% CI] 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105] 0.776 [0.561; 1.075] 0.895 [0.770; 1.041]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or Subgroup Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021 Raje 2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup>	ierences: Ch Hi Events 6 16 32 11 = 0; Chi <sup>2</sup> = 1	99, df = <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21 45 15 89	df = 1 (P = <b>Standa</b> <b>Events</b> 11 22 53 17	1 <sup>2</sup> = 0.00 0.95) <b>rd risk</b> <b>Total</b> 16 28 66 18 128	% Weight 6.2% 17.7% 34.1% 15.8%	<b>RR [95% CI]</b> 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105] 0.776 [0.561; 1.075]	
Heterogeneity: Tau <sup>2</sup> Test for subgroup diff B Study or Subgroup Endpoint: BCMA Mailankody 2023 Du 2022 Munshi 2021 Raje 2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> Endpoint: GPRC5	ierences: Ch Hi Events 6 16 32 11 = 0; Chi <sup>2</sup> = 1 D 11	99, df = ' i <sup>2</sup> = 0.00, <b>gh risk</b> <b>Total</b> 8 21 45 15 89 9 9 556, df = 13 102	df = 1 (P = <b>Standa</b> <b>Events</b> 11 22 53 17 3 (P = 0.67) 19	I <sup>2</sup> = 0.00 0.95) ard risk Total 16 28 66 18 128 66 18 128 20 20 148	% Weight 6.2% 17.7% 34.1% 15.8% 73.8% 26.2% 100.0%	RR [95% CI] 1.091 [0.649; 1.833] 0.970 [0.713; 1.319] 0.886 [0.710; 1.105] 0.776 [0.561; 1.075] 0.895 [0.770; 1.041]	

mentioned above, GPRC5D has BCMA-independent expression on plasma cells, ensuring continued expression even after BCMA relapse. Studies have shown that the largest population of CD138<sup>+</sup> cells express both BCMA and GPRC5D. However, GPRC5D expression is dominant and an independent expression pattern targeting a second antigen (GPRC5D) may increase the frequency, depth, and/or duration of response in patients with BCMA-low or -negative MM plasma cells (13, 19). Our study showed in turn a significantly higher CRR for GPRC5D CAR-T (50.5% vs. 34.3%) than BCMA CAR-T when treating RRMM. GPRC5D is a c7-transmembrane receptor protein that is, unlike BCMA, not easily shed in serum. Thus, targeting GPRC5D is less likely to cause an "antigen-sinking" effect that would reduce subsequent CAR-T efficacy (54, 55). Similarly, in our subgroup analysis, GPRC5D CAR-T achieved a significantly higher ORR (89.8%) than BCMA CAR-T (76.3%).

Studies have reported that BCMA CAR-T does not yield stable survival in patients with MM, with most patients eventually demonstrating relapse (8–11). In this study, the combined relapse rate of BCMA CAR-T was high (57.3%), whereas that of GPRC5D CAR-T was much lower (26.0%)—suggesting that GPRC5D CAR-T is associated with lower rates of relapse in patients with RRMM. High-risk cytogenetic characteristics and EMD are risk factors for poor MM prognosis (4, 56). When comparing the efficacy of BCMA

Subgroup	Events	Total	Proportion [95% CI]	Weight	CRS
Endpoint:1-5					
Minakata 2023	9	9	1.000 [0.664; 1.000]	0.7%	
Asherie 2023 Mailankody 2023	18 24	20 43	0.900 [0.683; 0.988] 0.558 [0.399; 0.709]	1.6% 3.5%	
Qu 2022	29	31	0.935 [0.786; 0.992]	2.5%	
Du 2022	17	49	0.347 [0.217; 0.496]	3.9%	
Munshi 2021	107	128	0.836 [0.760; 0.895]	10.3%	
Raje 2021	25	33	0.758 [0.577; 0.889]	2.6%	
Alsina 2020	31	46	0.674 [0.520; 0.805]	3.7%	
An 2020	20	21	0.952 [0.762; 0.999]	1.7%	
Kumar 2020 Fu 2019	12 10	14 44	0.857 [0.572; 0.982] 0.227 [0.115; 0.378]	1.1% 3.5%	
Cohen 2019	22	25	0.880 [0.688; 0.975]	2.0%	
Brudno 2018	15	16	0.938 [0.698; 0.998]	1.3%	
Liu 2018	1	14	0.071 [0.002; 0.339]	1.1%	
Xia 2023	10	33	0.303 [0.156; 0.487]	2.6%	
Zhang 2023	10	10	1.000 [0.692; 1.000]	0.8%	
Mailankody 2023	15	17	0.882 [0.636; 0.985]	1.4%	
Bal 2023 Total (95% CI)	59	70	0.843 [0.736; 0.919] 0.758 [0.605; 0.882]	5.6%	
	0.116: Chi <sup>2</sup>	$^{2} = 216.6$	df = 17 (P < 0.01); I <sup>2</sup> = 92.	15%	
Endpoint:3-5					
Minakata 2023	0	9	0.000 [0.000; 0.336]	0.7%	<b>•</b> ;
Asherie 2023	0	20	0.000 [0.000; 0.168]	1.6%	• E
Mailankody 2023	1	43	0.023 [0.001; 0.123]	3.5%	
Qu 2022 Du 2022	3	31 49	0.097 [0.020; 0.258]	2.5%	
Du 2022 Munshi 2021	3 7	49 128	0.061 [0.013; 0.169] 0.055 [0.022; 0.109]	3.9% 10.3%	
Raie 2021	2	33	0.055 [0.022; 0.109]	2.6%	
Alsina 2020	2	46	0.043 [0.005; 0.148]	3.7%	
An 2020	1	21	0.048 [0.001; 0.238]	1.7%	
Kumar 2020	0	14	0.000 [0.000; 0.232]	1.1%	<b>↓</b>
Fu 2019	3	44	0.068 [0.014; 0.187]	3.5%	
Cohen 2019	8	25	0.320 [0.149; 0.535]	2.0%	
Brudno 2018	6	16	0.375 [0.152; 0.646]	1.3%	
Liu 2018	0	14	0.000 [0.000; 0.232]	1.1%	• · · · · · · · · · · · · · · · · · · ·
Xia 2023	0	33	0.000 [0.000; 0.106]	2.6%	<b>1</b>
Zhang 2023	0	10	0.000 [0.000; 0.308]	0.8%	
Mailankody 2023 Bal 2023	1	17 70	0.059 [0.001; 0.287] 0.043 [0.009; 0.120]	1.4% 5.6%	
				0.070	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe	0.257; Chi	<sup>2</sup> = 1054.8	0.044 [0.017; 0.082] df = 17 (P < 0.01); l <sup>2</sup> = 65. 0.348 [0.199; 0.515] 55, df = 35 (P < 0.01); l <sup>2</sup> = 5 2, df = 1 (P < 0.01)		0 0.2 0.4 0.6 0.8 1
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or	0.257; Chi	<sup>2</sup> = 1054.8	df = 17 (P < 0.01); I <sup>2</sup> = 65. <b>0.348 [0.199; 0.515]</b> 55, df = 35 (P < 0.01); I <sup>2</sup> = 6 c, df = 1 (P < 0.01)	 96.68%	0 0.2 0.4 0.6 0.8 1
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup	0.257; Chi <sup>i</sup> erences: Ch	<sup>2</sup> = 1054.8 ii <sup>2</sup> = 82.12	. df = 17 (P < 0.01); I <sup>2</sup> = 65. 0.348 [0.199; 0.515] 55, df = 35 (P < 0.01); I <sup>2</sup> = 9		
Heterogeneity: Tau <sup>2</sup> = Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1–5	0.257; Chi <sup>i</sup> erences: Ch	<sup>2</sup> = 1054.8 ii <sup>2</sup> = 82.12 Total	df = 17 ( $\hat{P} < 0.01$ ); $\hat{P} = 65$ . <b>0.348 [0.199; 0.515]</b> 55, df = 35 ( $P < 0.01$ ); $\hat{P} = 6$ <b>25</b> , df = 1 ( $P < 0.01$ ); $\hat{P} = 6$ <b>Proportion [95% CI]</b>	 66.68% Weight	
Heterogeneity: Tau <sup>2</sup> = Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1–5 Minakata 2023	e 0.257; Chi <sup>a</sup> erences: Ch <b>Events</b> 1	<sup>2</sup> = 1054.5 ii <sup>2</sup> = 82.12 <b>Total</b> 9	$df = 17 (\vec{P} < 0.01); \vec{P} = \vec{0}s.$ $0.348 [0.199; 0.615]$ $5s. d = 35 (P < 0.01); \vec{P} = c$ $d = 1 (P < 0.01)$ Proportion [95% CI] 0.111 [0.003; 0.482]	 96.68%	
Heterogeneity: Tau <sup>2</sup> = Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1–5 Minakata 2023 Asherie 2023	e 0.257; Chi <sup>i</sup> erences: Ch Events	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43	df = 17 ( $\hat{P} < 0.01$ ); $\hat{P} = 65$ . <b>0.348 [0.199; 0.515]</b> 55, df = 35 ( $P < 0.01$ ); $\hat{P} = 6$ <b>25</b> , df = 1 ( $P < 0.01$ ); $\hat{P} = 6$ <b>Proportion [95% CI]</b>	 66.68% Weight 0.9% 2.0% 4.2%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Vialiankody 2023 Ju 2022	e 0.257; Chi <sup>*</sup> erences: Ch Events 1 0 6 1	<sup>2</sup> = 1054.5 <sup>12</sup> = 82.12 <b>Total</b> 9 20 43 31	$df = 17 (\vec{P} < 0.01); \vec{P} = \vec{0}s.$ <b>0.348 [0.199; 0.515]</b> 55, df = 35 (P < 0.01); \vec{P} = \vec{0}s. <b>Proportion [95% C1]</b> <b>0.111 [0.003; 0.482]</b> 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.002 [0.000; 0.016]	 Weight 0.9% 2.0% 4.2% 3.0%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Qui 2022 Munshi 2021	0.257; Chi <sup>a</sup> erences: Ch Events 1 0 6 1 33	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.515] 55. df = 35 (P < 0.01); P = 6 t, df = 1 (P < 0.01) Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.258 [0.185; 0.343]	 66.68% Weight 0.9% 2.0% 4.2% 3.0% 12.5%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Mallankody 2023 Qu 2022 Munshi 2021	0.257; Chi <sup>1</sup> erences: Ch Events 1 0 6 1 33 14	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33	$df = 17 (\vec{P} < 0.01); \vec{P} = \vec{0}s.$ $0.348 [0.199; 0.515]$ $55, df = 35 (\vec{P} < 0.01); \vec{P} = \vec{0}s.$ $df = 1 (\vec{P} < 0.01)$ Proportion [95% CI] $0.111 [0.003; 0.482]$ $0.000 [0.000; 0.168]$ $0.140 [0.053; 0.279]$ $0.032 [0.001; 0.167]$ $0.232 [0.010; 1.015]$ $0.424 [0.255; 0.608]$		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Gu 2022 Munshi 2021 Raje 2021 Alsina 2020	0.257; Chi <sup>a</sup> erences: Ch Events 1 0 6 1 33	<sup>2</sup> = 1054.5 1 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128	$\begin{array}{c} dt = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s.\\ 0.348 \; [0.199;\; 0.515]\\ 55.\; dt = 35 \; (P < 0.01); \; \vec{P} = \vec{0}s.\\ t \; dt = 1 \; (P < 0.01) \end{array}$	 66.68% Weight 0.9% 2.0% 4.2% 3.0% 12.5%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Mulankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Kumar 2020	0.257; Chi <sup>*</sup> erences: Ch Events 1 0 6 1 33 14 10 0 0	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14	$ \begin{array}{l} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199}; \textbf{0.515}] \\ \textbf{55}, \; df = 36 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{c}, \; df = 1 \; (P < 0.01) \\ \end{array} $		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Mailankody 2023 Gu 2022 Munshi 2021 Raje 2021 Ajsina 2020 Kumar 2020 Cohen 2019	0.257; Chi <sup>*</sup> erences: Ch Events 1 0 6 1 33 14 10	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46	$\begin{array}{c} dt = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199}; \textbf{0.515}] \\ \textbf{5}. \; dt = 35 \; (\textbf{P} < 0.01); \; \vec{P} = cs. \\ \textbf{0}. \; \textbf{0} = 1 \; (\textbf{P} < 0.01) \\ \end{array}$		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Mailankody 2023 Gu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018	0.257; Chi <sup>1</sup> erences: Ch Events 1 0 6 1 3 3 14 10 0 8 6 1	<sup>2</sup> = 1054.8 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.515] 55. df = 35 (P < 0.01); P = 65. df = 1 (P < 0.01) Proportion [95% C1] 0.111 [0.003; 0.482] 0.000 [0.000; 0.186] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.608] 0.217 [0.109; 0.364] 0.037 [0.0149; 0.533] 0.375 [0.152; 0.646] 0.077 [0.002; 0.339]		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = <b>Est for subgroup diffe</b> <b>B</b> <b>Study or</b> <b>Subgroup</b> Endpoint:1-5 Minakata 2023 Asherie 2023 Munshi 2021 Raje 2021 Alisina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 33 3 14 10 0 8 6 1 2	<sup>2</sup> = 1054.5 j <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.615] 55. df = 35 (P < 0.01); P = 65. (, df = 1 (P < 0.01) Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.145; 0.343] 0.424 [0.255; 0.609] 0.217 [0.102; 0.341] 0.000 [0.000; 0.252] 0.320 [0.149; 0.535] 0.375 [0.152; 0.646] 0.071 [0.002; 0.339] 0.061 [0.007; 0.202]		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 33 14 10 0 8 6 1 1 2 0	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.515] 55, df = 35 (P < 0.01); P = 65. e, df = 1 (P < 0.01) Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.606] 0.217 [0.109; 0.364] 0.000 [0.000; 0.232] 0.320 [0.146; 0.535] 0.375 [0.152; 0.646] 0.071 [0.007; 0.202] 0.000 [0.000; 0.302]	Weight 0.9% 2.0% 4.2% 3.0% 12.5% 3.2% 1.4% 3.2% 1.4% 3.2%	
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe <b>B</b> <b>Study or</b> <b>Subgroup</b> Endpoint:1-5 Minakata 2023 Asherie 2023 Ausiana 2020 Kumar 2020 Kumar 2020 Cohen 2019 Erudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 2 0 1	<sup>2</sup> = 1054.5 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10 17	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.615] 55. df = 35 (P < 0.01); P = 65. (a = 1 (P < 0.01) Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.608] 0.217 [0.105; 0.355] 0.032 [0.100; 0.232] 0.330 [0.148; 0.355] 0.375 [0.152; 0.646] 0.071 [0.000; 0.232] 0.001 [0.000; 0.232] 0.001 [0.000; 0.232] 0.001 [0.000; 0.233] 0.061 [0.000; 0.236] 0.059 [0.000; 0.268]	Weight 0.9% 2.0% 3.0% 12.5% 1.4% 2.4% 1.6% 1.6% 1.6% 1.0% 1.7%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Mailankody 2023 Munahi 2021 Raje 2021 Alsina 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Zhang 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 33 14 10 0 8 6 1 1 2 0	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10	df = 17 (P < 0.01); P = 65. 0.348 [0.199; 0.515] 55, df = 35 (P < 0.01); P = 65. e, df = 1 (P < 0.01) Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.606] 0.217 [0.109; 0.364] 0.000 [0.000; 0.232] 0.320 [0.146; 0.535] 0.375 [0.152; 0.646] 0.071 [0.007; 0.202] 0.000 [0.000; 0.302]	Weight 0.9% 2.0% 4.2% 3.0% 12.5% 3.2% 1.4% 3.2% 1.4% 3.2%	
Heterogeneity: Tau <sup>2</sup> = <b>Total</b> (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Ausian 2021 Raje 2021 Alsina 2020 Kumar 2020 Kumar 2020 Cohen 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI)	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 2 0 1 8	<sup>2</sup> = 1054.5 j <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10 17 73	$df = 17 (\vec{P} < 0.01); \vec{P} = \vec{0}s.$ 0.348 [0.199; 0.515] 55, df = 35 (P < 0.01); \vec{P} = \vec{0}s. Proportion [95% CI] Proportion [95% CI] 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.608] 0.217 [0.109; 0.364] 0.000 [0.000; 0.232] 0.320 [0.149; 0.535] 0.376 [0.152; 0.646] 0.071 [0.002; 0.339] 0.061 [0.007; 0.202] 0.000 [0.000; 0.384] 0.000 [0.000; 0.238] 0.059 [0.001; 0.287] 0.110 [0.049; 0.205]	Weight 0.9% 2.0% 3.0% 12.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2	
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Ausiana 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Stal 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 2 0 1 8	<sup>2</sup> = 1054.5 j <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10 17 73	df = 17 ( $\hat{P} < 0.01$ ); $\hat{P} = \hat{O}$ . <b>0.348 [0.199; 0.615]</b> 55. df = 35 ( $P < 0.01$ ); $\hat{P} = \hat{O}$ . <b>proportion [95% CI]</b> <b>Proportion [95% CI]</b> 0.111 [0.003; 0.482] 0.000 [0.000; 0.168] 0.140 [0.053; 0.279] 0.032 [0.001; 0.167] 0.258 [0.185; 0.343] 0.424 [0.255; 0.608] 0.217 [0.198; 0.343] 0.424 [0.255; 0.608] 0.375 [0.152; 0.646] 0.071 [0.102; 0.339] 0.061 [0.007; 0.202] 0.000 [0.000; 0.285] 0.059 [0.001; 0.285] 0.110 [0.049; 0.205] 0.1110 [0.049; 0.205] 0.1110 [0.049; 0.205] 0.1110 [0.049; 0.205]	Weight 0.9% 2.0% 3.0% 12.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4.5% 1.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2.4% 2	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Zhang 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5	0.257; Chi <sup>i</sup> rences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 1 8 0.040; Chi <sup>i</sup>	<sup>2</sup> = 1054.5 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 16 17 73 <sup>2</sup> = 72.35.	$ \begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{55}, df = 36 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{c}, df = 1 \ (P < 0.01) \\ \end{array} $	Weight 0.9% 2.0% 4.2% 3.2% 4.5% 1.4% 2.4% 1.4% 3.2% 1.4% 3.2% 5.2%	
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1–5 Minakata 2023 Asherie 2023 Ausiana 2020 Kumar 2020 Kumar 2020 Kumar 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Mailan	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 33 14 10 0 8 6 1 1 2 0 0 1 8 8 0.040; Chi <sup>2</sup> 0	<sup>2</sup> = 1054.4 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 33 34 128 33 46 14 25 16 14 33 10 17 73 2 = 72.35	$\begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}s. d = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}s. d = 53 \ (P < 0.01); \ \vec{P} = c \\ \textbf{0}, \ df = 1 \ (P < 0.01) \\ \end{array}$		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Munshi 2021 Mushi 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Minakata 2023 Asherie 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 0 1 8 0.040; Chi <sup>2</sup> 0 0 0	<ul> <li><sup>2</sup> = 1054.4</li> <li><sup>2</sup> = 82.12</li> <li>Total</li> <li>9</li> <li>20</li> <li>43</li> <li>33</li> <li>46</li> <li>14</li> <li>33</li> <li>46</li> <li>14</li> <li>33</li> <li>10</li> <li>17</li> <li>73</li> <li>2<sup>2</sup> = 72.35.</li> <li>9</li> <li>20</li> </ul>	$ \begin{array}{c} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199}; \textbf{0.515}] \\ \textbf{55}, df = 35 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{0} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{D} < 0.03; \; 0.482] \\ \textbf{0}, 000 \; [0.000; \; 0.168] \\ \textbf{0}, 140 \; [0.053; \; 0.279] \\ \textbf{0}, 242 \; [0.255; \; 0.608] \\ \textbf{0}, 271 \; [0.109; \; 0.364] \\ \textbf{0}, 000 \; [0.000; \; 0.232] \\ \textbf{0}, 320 \; [0.149; \; 0.535] \\ \textbf{0}, 375 \; [0.152; \; 0.646] \\ \textbf{0}, 071 \; [0.002; \; 0.339] \\ \textbf{0}, 061 \; [0.007; \; 0.202] \\ \textbf{0}, 000 \; [0.000; \; 0.237] \\ \textbf{0}, 110 \; [0.645; \; 0.137] \\ \textbf{df} = 14 \; (\vec{P} < 0.01); \; \vec{F} = \vec{0} \\ \textbf{0}, 000 \; [0.000; \; 0.336] \\ \textbf{0}, $		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Munshi 2021 Raje 2021 Asima 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Mailankody 2023	0.257; Chi <sup>2</sup> erences: Ch <b>Events</b> 1 0 6 1 1 3 3 14 10 0 6 1 1 3 3 14 10 0 6 1 1 3 3 14 10 0 6 1 1 3 3 14 10 0 6 1 1 3 3 11 0 0 6 1 1 3 3 1 1 0 0 6 1 1 3 3 1 1 0 0 6 1 1 3 3 1 1 0 0 6 1 1 3 3 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	<sup>2</sup> = 1064.4 <sup>2</sup> = 22.12 Total          9       20         31       128         33       46         14       25         16       14         17       73         9       20.39         9       20.40         9       20.40         9       20.40         9       20.40         9       20.40         9       20.40         9       20.40         9       20.40         43       43	$\begin{array}{c} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [0.199; \; 0.615] \\ \textbf{5}s. df = 35 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{5}s. df = 35 \; (P < 0.01); \; \vec{P} = cs. \\ \textbf{0}s. df = 1 \; (P < 0.01) \\ \hline \end{array}$		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup EndpoInt:1-5 Minakata 2023 Asherie 2023 Mulainkody 2023 Ou 2022 Munshi 2021 Akisna 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Chaliankody 2023 Bai 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = EndpoInt:3-5 Minakata 2023 Maibankody 2023	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 0 1 8 0.040; Chi <sup>2</sup> 0 0 0	<ul> <li><sup>2</sup> = 1054.4</li> <li><sup>2</sup> = 82.12</li> <li>Total</li> <li>9</li> <li>20</li> <li>43</li> <li>33</li> <li>46</li> <li>14</li> <li>33</li> <li>46</li> <li>14</li> <li>33</li> <li>10</li> <li>17</li> <li>73</li> <li>2<sup>2</sup> = 72.35.</li> <li>9</li> <li>20</li> </ul>	$ \begin{array}{c} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199}; \textbf{0.515}] \\ \textbf{55}, df = 35 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{P} < 0.01); \; \vec{0} = \vec{0}s. \\ \textbf{0}, df = 1 \; (\vec{D} < 0.03; \; 0.482] \\ \textbf{0}, 000 \; [0.000; \; 0.168] \\ \textbf{0}, 140 \; [0.053; \; 0.279] \\ \textbf{0}, 242 \; [0.255; \; 0.608] \\ \textbf{0}, 271 \; [0.109; \; 0.364] \\ \textbf{0}, 000 \; [0.000; \; 0.232] \\ \textbf{0}, 320 \; [0.149; \; 0.535] \\ \textbf{0}, 375 \; [0.152; \; 0.646] \\ \textbf{0}, 071 \; [0.002; \; 0.339] \\ \textbf{0}, 061 \; [0.007; \; 0.202] \\ \textbf{0}, 000 \; [0.000; \; 0.237] \\ \textbf{0}, 110 \; [0.645; \; 0.137] \\ \textbf{df} = 14 \; (\vec{P} < 0.01); \; \vec{F} = \vec{0} \\ \textbf{0}, 000 \; [0.000; \; 0.336] \\ \textbf{0}, $		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Qui 2022 Munshi 2021 Raje 2021 Asima 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Bal 2023 Cotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Endpoint:3-5 Endpoint:3-2 Mailankody 2023 Qui 2023 Mailankody 2023 Qui 2023 Mailankody 2023 Qui 2023 Mailankody 2023 Qui 2023 Mailankody 2023 Qui 2024 Munshi 2021	0.257; Chi <sup>2</sup> erences: Ch 1 0 6 1 3 3 14 10 0 8 6 1 1 2 0 0 1 8 0.040; Chi <sup>2</sup> 0 0 0 1	<sup>2</sup> = 1054.1 <b>Total</b> 9 20 43 31 128 33 46 14 25 46 14 33 10 17 73 9 20 43 33 10 7 7 3 9 20 43 33 10 128 128 128 128 128 128 128 128	$ \begin{array}{c} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199}; \textbf{0.615}] \\ \textbf{55}, \; df = 35 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{D} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{D} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{0} = \vec{0}s. \\ \textbf{0}, \; df = 16 \; (D < 0.05; \; 0.279] \\ \textbf{0}, \; df = 16 \; (D < 0.05; \; 0.279] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.328] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.326] \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = 60 \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = 60 \\ \textbf{0}, \; df = 16 \; (P < 0.01); \; \vec{P} = 60 \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D < 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.336] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.366] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.366] \\ \textbf{0}, \; df = 16 \; (D \; 0.00; \; 0.366] \\ \textbf{0}$		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:15 Minakata 2023 Asherie 2023 Asherie 2023 Munshi 2021 Raje 2021 Akina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Mailankody 2023 Bal 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Akina 2020	0.257; Chi <sup>j</sup> erences: Ch 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 0 1 8 8 0.040; Chi <sup>j</sup> 0 0 0 1 1 8 8 0.040; Ch <sup>j</sup>	<sup>2</sup> = 1054.4 <sup>2</sup> = 22.12 <b>Total</b> 9 20 43 43 43 14 128 33 46 14 25 16 14 14 25 16 17 3 10 77 3 9 20 20 43 43 43 43 45 128 128 128 128 128 128 128 128	$\begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, df = 3 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}, df = 3 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \ \vec{P} = \vec{0} \ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \ \vec{P} = \vec{0} \\ \vec{P} = \vec{0} \ \vec{P}$		
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = <b>East for subgroup diffe</b> <b>B</b> <b>Study or</b> <b>Subgroup</b> Endpoint:1-5 Minakata 2023 Asherie 2023 Munshi 2021 Raje 2021 Alisina 2020 Cohen 2019 Erudno 2018 Liu 2018 Xia 2023 Zhang 2023 Bailankody 2023 Bailankody 2023 Bailankody 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alisina 2020 Kaje 2021 Alisina 2020 Kaje 2021 Alisina 2020 Kimar 2020 State 2023 State 2024 State 2025 State 2025	0.257; Chi <sup>2</sup> erences: Chi 1 0 6 1 3 3 14 10 0 8 6 1 1 2 0 0 1 8 0.040; Chi <sup>2</sup> 0 0 1 8 0.040; Chi <sup>2</sup>	<sup>2</sup> = 1054.1 <b>Total</b> 9 9 20 43 31 128 33 34 6 14 25 16 14 33 10 17 73 9 20 43 31 17 73 9 20 43 31 17 82 12 18 18 19 10 10 10 10 10 10 10 10 10 10	$ \begin{array}{c} df = 17 \; (\vec{P} < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0.348} \; [\textbf{0.199; 0.615]} \\ \textbf{55, df = 35 \; (P < 0.01); \; \vec{P} = \vec{0}s. \\ \textbf{0, 01}; \; \vec{P} = \vec{0}, \\ \textbf{0, 01}; \; \vec{P} = \vec{0}, \\ \textbf{0, 01}; \; \vec{P} = \vec{0}, \\ \textbf{0, 01}; \; \vec{0} = \vec{0}, \\ \textbf{0, 00}; \; \vec{0} = \vec{0}, \\ \textbf{0, 00}; \; \vec{0} = \vec{0}, \\ \textbf{0, 01}; \; \vec{0} = \vec{0}, \\ \textbf{0, 01}; \; \vec{0} = \vec{0}, \\ \textbf{0, 00}; \; \vec{0} = \vec{0}, \\ \textbf{0, 01}; \; \vec{0} = \vec{0}, \\ \vec{0} = $		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Qui 2022 Munshi 2021 Raje 2021 Asisna 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Cohen 2019 Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Endpoint:3-5 Minakata 2023 Asherie 2023 Asherie 2023 Mailankody 2023 Qui 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Kumar 2020 Kumar 2020 Cohen 2019	0.257; Chi <sup>j</sup> erences: Ch 1 0 6 1 1 33 3 14 10 0 8 6 1 1 2 0 0 1 8 8 0.040; Chi <sup>j</sup> 0 0 0 1 4 4 1 3 0 0 2	<sup>2</sup> = 1054.1 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 10 17 7 2 2 2 2 2 2 2 3 3 3 14 2 5 2 5 2 12 3 3 3 3 14 2 5 2 5 2 12 5 2 12 5 2 12 5 2 12 5 2 12 5 2 12 5 2 12 5 5 12 12 5 5 12 12 12 12 12 12 12 12 12 12	$\begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, df = 3 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}, df = 3 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01) \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0} \\ \textbf{7}, df = 1 \ df $	0.9% 2.0% 4.2% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 2.0% 3.2% 4.2% 3.0% 1.2.5% 3.2% 4.2% 3.0% 1.2.5% 3.2% 4.2% 4.2% 4.2% 4.2% 3.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4	
Heterogeneity: Tau <sup>2</sup> = <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Munshi 2021 Raje 2021 Atisina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Minakata 2023 Asherie 2023 Mailankody 2024 Mailankody 2024 Mai	0.257; Chi <sup>2</sup> prences: Ch <b>Events</b> 1 0 6 1 3 3 14 10 0 8 6 1 2 0 1 8 0.040; Chi <sup>2</sup> 0 1 8 0.040; Chi <sup>2</sup> 0 1 4 1 0 6 1 2 0 0 1 4 1 0 6 1 1 4 1 0 6 1 1 2 0 0 0 6 1 1 4 1 0 6 1 1 4 1 0 6 1 1 4 1 0 0 6 1 1 4 1 0 0 0 0 1 1 4 1 0 0 0 0 1 1 4 1 0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 1 1 1 1 1 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	<sup>2</sup> = 1054.1 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 17 73 9 20 43 31 17 73 9 20 43 31 17 73 9 20 43 31 14 25 16 16 16 16 16 16 16 16 16 16	$ \begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{55}, df = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \ (P < 0.01) \\ \end{array} $	Weight 0.9% 2.0% 4.2% 3.2% 3.2% 2.4% 1.4% 3.2% 3.2% 1.4% 3.2% 3.2% 1.4% 3.2% 3.2% 1.7% 7.1% 0.9% 2.0% 4.2% 3.0% 4.2% 3.0% 4.2% 3.2% 5.2% 1.4% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2% 5.2	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1–5 Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Qu 2023 Mailankody 2023 Qu 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2011 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Brudno 2018 Liu 2018	0.257; Chi <sup>i</sup> erences: Ch 1 0 6 1 1 33 3 14 10 0 8 6 1 1 2 0 1 8 8 0.040; Ch <sup>i</sup> 0 0 0 0 0 0 1 4 1 3 0 0 1 1 8 8 0 1 1 8 8 0 0 1 1 8 8 0 0 1 1 8 8 0 0 1 1 1 3 3 1 1 4 1 1 2 0 1 1 1 1 3 3 1 1 1 1 1 1 1 1 1 1 1 1 1	2 = 1054.1 P 9 20 43 31 128 33 46 14 33 10 17 7 20 43 33 11 128 33 46 14 25 128 33 11 128 33 11 128 33 11 128 33 11 128 12 12 12 12 12 12 12 12 12 12	$\begin{array}{c} dt = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, dt = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}, dt = 1 \ (P < 0.01) \\ \hline \end{array}$		
Heterogeneity: Tau <sup>2</sup> = <b>Total</b> (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Asherie 2023 Qu 2022 Munshi 2021 Raje 2021 Atsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Cotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Minakata 2023 Asherie 2023 Asherie 2023 Munshi 2021 Asiana 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2014 Asiana 2020 Asherie 2023 Dustal 2021 Asiana 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023	0.257; Chi <sup>2</sup> prences: Ch <b>Events</b> 1 0 6 1 3 3 14 10 0 8 6 1 2 0 1 8 0.040; Chi <sup>2</sup> 0 1 8 0.040; Chi <sup>2</sup> 0 1 4 1 0 6 1 2 0 0 1 4 1 0 6 1 1 4 1 0 6 1 1 2 0 0 0 6 1 1 4 1 0 6 1 1 4 1 0 6 1 1 4 1 0 0 6 1 1 4 1 0 0 0 0 1 1 4 1 0 0 0 0 1 1 4 1 0 0 0 0 1 1 1 1 1 1 1 1 0 0 0 0 1 1 1 1 1 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 1 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	<sup>2</sup> = 1054.1 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 17 73 9 20 43 31 17 73 9 20 43 31 17 73 9 20 43 31 14 25 16 16 16 16 16 16 16 16 16 16	$ \begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0, 199; 0, 615] \\ \textbf{55}, df = 35 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0}, df = 1 \ (\vec{P} < 0.01) \\ \end{array} $	Weight 0.9% 2.0% 4.2% 3.2% 1.4% 2.6% 1.4% 3.2% 1.4% 3.2% 1.7% 2.0% 4.2% 3.0% 1.7% 2.0% 4.2% 3.2% 1.7% 2.0% 4.2% 3.2% 1.4% 3.2% 4.2% 3.2% 1.4% 3.2% 4.2% 3.2% 1.4% 3.2% 4.2% 3.2% 1.4% 3.2% 3.2%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:15 Minakata 2023 Asherie 2023 Asherie 2023 Munshi 2021 Raje 2021 Akina 2020 Kumar 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:35 Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Asherie 2023 Munshi 2021 Raje 2021 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023	0.257; Chi <sup>2</sup> prences: Ch 1 0 6 1 3 3 14 10 0 8 6 1 1 2 0 1 8 0.040; Chi <sup>2</sup> 0 1 8 0.040; Chi <sup>2</sup> 1 8 0 0 1 1 8 0 0 1 1 8 0 0 6 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	2 = 1054.1 Total 9 20 43 31 128 9 20 43 31 128 33 46 14 25 16 17 73 9 20 43 33 14 25 16 17 73 9 20 43 33 14 25 16 16 17 16 16 16 16 16 16 16 16 16 16	$\begin{array}{c} dt = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.515] \\ \textbf{5}, d = 35 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0}, ds \ [0, 199; 0.515] \\ \textbf{0}, ds \ [0, 199; 0.515] \\ \textbf{0}, ds \ [0, 100; 0.016] \\ \textbf{0}, ds \ [0, 100; 0.036] \\ \textbf{0}, ds \ [0, 100; 0.036] \\ \textbf{0}, ds \ [0, 000; 0.000; 0.003] \\ \textbf{0}, ds \ [0, 000; 0.000; 0.036] \\ \textbf{0}, ds \ [0, 000; 0.036] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.287] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.287] \\ \textbf{0}, ds \ [0, 001; 0.287] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.156] \\ \textbf{0}, ds \ [0, 001; 0.283] \\ \textbf{0}, ds \ [0, 000; 0.385] \\ \textbf{0}, ds \ [0, 001; 0.285] \\ \textbf{0}, ds \ [0, 000; 0.385] \\ \textbf{0}, ds \ [0, 000; 0$		
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:15 Minakata 2023 Asherie 2023 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Mailankody 2023 Munshi 2021 Raje 2021 Asherie 2023 Mailankody 2023 Mallankody 2023 Mallankody 2023 Mallankody 2023 Mallankody 2023 Munshi 2021 Raje 2021 Asherie 2023 Mallankody 2023 M	0.257; Chi <sup>i</sup> erences: Ch 1 1 0 6 1 1 33 3 14 10 0 8 6 1 1 2 0 1 8 0 0 0 0 0 0 0 0 1 4 1 3 0 0 0 0 0 0 1 1 8 0 0 0 1 1 8 0 0 0 0 1 1 1 3 3 1 1 4 1 0 0 0 0 1 1 1 3 3 1 1 4 1 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	<sup>2</sup> = 1054.1 <sup>2</sup> = 82.12 <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 33 31 128 33 31 128 33 31 128 33 31 128 33 14 128 33 10 128 128 12 128 12 128 12 128 128	$\begin{array}{c} dt = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, dt = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}, dt = 1 \ (P < 0.01) \\ \hline \end{array}$		
Heterogeneity: Tau <sup>2</sup> = <b>Total</b> (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Ausian 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Stal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Miniakata 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Munahi 2021 Raje 2021 Asherie 2023 Asherie 2023 Munahi 2021 Raje 2021 Asherie 2023 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Zhang 2023 Cohen 2019 Bal 2023 Zhang 2023 Chen 2019 Bal 2023 Chen 2019 Bal 2023 Chen 2019 Stal (95% CI)	0.257; Chi <sup>i</sup> prences: Chi 1 0 6 1 3 3 14 10 0 8 6 1 1 2 0 1 1 8 0.040; Chi <sup>i</sup> 0 0 1 1 8 0.040; Chi <sup>i</sup> 1 3 0 0 1 1 3 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 1	2 = 1054.1 <b>Total</b> 9 20 43 31 33 46 14 25 16 14 25 16 17 73 9 20 43 33 14 25 16 17 73 21 22 33 33 46 14 25 16 17 20 43 10 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 20 43 20 20 43 20 20 43 20 20 43 20 20 43 20 20 20 20 20 20 20 20 20 20	$ \begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0,199; 0,615] \\ \textbf{5}; \ df = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0}; \ df = 1 \ (P < 0.01) \\ \end{array} $	Weight 0.9% 2.0% 4.2% 3.2% 1.4% 2.4% 1.4% 3.2% 1.7% 2.0% 4.5% 1.7% 2.0% 4.2% 3.0% 1.7% 2.0% 4.2% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 1.7% 1.4% 3.2% 1.4% 1.7% 1.4% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.7% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.7% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.7% 1.4%	
Heterogeneity: Tau <sup>2</sup> = <b>Total</b> (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:1-5 Minakata 2023 Asherie 2023 Ausian 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Kumari 2020 Stal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:3-5 Miniakata 2023 Asherie 2023 Asherie 2023 Asherie 2023 Asherie 2023 Munahi 2021 Raje 2021 Asherie 2023 Asherie 2023 Munahi 2021 Raje 2021 Asherie 2023 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Zhang 2023 Mailankody 2023 Zhang 2023 Cohen 2019 Bal 2023 Zhang 2023 Chen 2019 Bal 2023 Chen 2019 Bal 2023 Chen 2019 Stal (95% CI)	0.257; Chi <sup>i</sup> prences: Chi 1 0 6 1 3 3 14 10 0 8 6 1 1 2 0 1 1 8 0.040; Chi <sup>i</sup> 0 0 1 1 8 0.040; Chi <sup>i</sup> 1 3 0 0 1 1 3 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 2 0 0 1 1 1 1	2 = 1054.1 <b>Total</b> 9 20 43 31 33 46 14 25 16 14 25 16 17 73 9 20 43 33 14 25 16 17 73 21 22 33 33 46 14 25 16 17 20 43 10 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 43 20 20 43 20 20 43 20 20 43 20 20 43 20 20 43 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} dt = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, dt = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{5}, dt = 1 \ (P < 0.01) \\ \hline \end{array}$	Weight 0.9% 2.0% 4.2% 3.2% 1.4% 2.4% 1.4% 3.2% 1.7% 2.0% 4.5% 1.7% 2.0% 4.2% 3.0% 1.7% 2.0% 4.2% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 1.7% 1.4% 3.2% 1.4% 1.7% 1.4% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.4% 1.7% 1.4% 1.7% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.7% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.4% 1.7% 1.4%	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:15 Minakata 2023 Asherie 2023 Asherie 2023 Munshi 2021 Raje 2021 Akina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Mailankody 2023 Total (95% CI)	0.257; Chi <sup>2</sup> prences: Ch 1 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 0 0 0 1 4 1 3 0 0 0 0 0 1 4 1 3 0 0 1 2 0 0 0 0 0 1 1 3 0 0 0 0 0 0 1 1 3 0 0 0 0	2 = 1054.1 9 20 43 128 33 46 14 25 16 14 33 30 17 73 9 20 43 11 28 33 46 14 25 16 14 33 31 17 25 16 14 17 33 10 17 73 72 25 25 25 25 25 25 25 25 25 2	$ \begin{array}{c} dt = 17 \ (\vec{P} < 0.01); \ \vec{F} = \vec{0}s. \\ \textbf{0.348} \ [0.199; 0.615] \\ \textbf{5}, dt = 35 \ (\vec{P} < 0.01); \ \vec{F} = \vec{0}s. \\ \textbf{0}, dt = 1 \ (\vec{P} < 0.01) \\ \hline \end{array} $	0.9% 2.0% 4.2% 3.2% 4.5% 1.4% 2.4% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.6% 1.5% 4.5% 4.5% 4.5% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 3.2% 1.4% 3.2% 3.2% 3.2% 3.2% 3.2% 3.2% 3.2% 3.2	
Heterogeneity: Tau <sup>2</sup> = Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:15 Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Akina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:35 Minakata 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Asherie 2023 Mailankody 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Asherie 2023 Mailankody 2023 Qu 2022 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Xia 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Total (95% CI)	0.257; Chi <sup>2</sup> prences: Ch 1 1 0 6 1 1 33 14 10 0 8 6 1 1 2 0 0 0 0 1 4 1 3 0 0 0 0 0 1 4 1 3 0 0 1 2 0 0 0 0 0 1 1 3 0 0 0 0 0 0 1 1 3 0 0 0 0	2 = 1054.1 9 20 43 128 33 46 14 25 16 14 33 30 17 73 9 20 43 11 28 33 46 14 25 16 14 33 31 17 25 16 14 17 33 10 17 73 72 25 25 25 25 25 25 25 25 25 2	$ \begin{array}{c} df = 17 \ (\vec{P} < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0.348} \ [0,199; 0,615] \\ \textbf{5}; \ df = 35 \ (P < 0.01); \ \vec{P} = \vec{0}s. \\ \textbf{0}; \ df = 1 \ (P < 0.01) \\ \end{array} $	0.9% 2.0% 4.2% 3.2% 4.5% 1.4% 2.4% 1.4% 3.2% 1.4% 3.2% 1.4% 3.2% 1.0% 1.7% 7.1% 7.1% 7.1%	

FIGURE 7

Forest plots of CRS and ICANS incidence stratified by severity. (A) Combined estimates for all CRS (1–5) and severity (3–5) grades. (B) Combined estimates for all ICANS (1–5) and severity (3–5) grades.

and GPRC5D CAR-T in patients with and without these adverse prognostic factors, no differences in ORR were noted between patients for either of the modalities. This suggests that both GPRC5D CAR-T and BCMA CAR-T can alleviate the poor outcomes associated with high-risk karyotypes in MM patients. BCMA is highly expressed in myeloma cells but shows limited expression in normal tissues and B cells. GPRC5D is highly expressed on the surface of myeloma cells, while its expression in normal tissues is limited to the hair follicle region. It has been reported that GPRC5D-targeted CAR-T cell therapy can cause a

Subgroup	Events	Total	Proportion [95% CI]	Weight	CRS(1-5)
Endpoint:BCMA					
Minakata 2023	9	9	1.000 [0.664; 1.000]	1.4%	
Asherie 2023	18	20	0.900 [0.683; 0.988]	3.2%	
Mailankody 2023	24	43	0.558 [0.399; 0.709]	6.9%	
Qu 2022	29	31	0.935 [0.786; 0.992]	5.0%	
Du 2022	17	49	0.347 [0.217; 0.496]	7.9%	
Munshi 2021	107	128	0.836 [0.760; 0.895]	20.5%	- <b></b>
Raje 2021	25	33	0.758 [0.577; 0.889]	5.3%	<b>_</b>
Alsina 2020	31	46	0.674 [0.520; 0.805]	7.4%	
An 2020	20	21	0.952 [0.762; 0.999]	3.4%	
Kumar 2020	12	14	0.857 [0.572; 0.982]	2.2%	
Fu 2019	10	44	0.227 [0.115; 0.378]	7.1%	
Cohen 2019	22	25	0.880 [0.688; 0.975]	4.0%	
Brudno 2018	15	16	0.938 [0.698; 0.998]	2.6%	
Liu 2018	1	14	0.071 [0.002; 0.339]	2.2%	
Total (95% CI)	= 0 116 <sup>.</sup> Chi <sup>2</sup>	$^{2} = 170.4$	<b>0.742 [0.566; 0.885]</b> 2, df = 13 (P < 0.01); l <sup>2</sup> = 92		:
Endpoint:GPRC5	D 10	33	0.303 [0.156; 0.487]	E 29/	
Xia 2023 Zhang 2023	10	10	1.000 [0.692; 1.000]	5.3% 1.6%	:
Zhang 2023 Mailankody 2023	10	10	0.882 [0.636; 0.985]	2.7%	
Bal 2023	59	70	0.843 [0.736; 0.919]	11.2%	:
Total (95% CI)	59	70	0.812 [0.440; 0.997]	11.2 %	
	= 0.152; Chi <sup>2</sup>	$^{2} = 45.2$	$df = 3 (P < 0.01); I^2 = 93.36^{\circ}$	%	
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> Test for subgroup diff			<b>0.758 [0.605; 0.882]</b> 0, df = 17 (P < 0.01); l <sup>2</sup> = 92	 2.15%	0 0.2 0.4 0.6 0.8
B Study or					
	Events	Total	Proportion [95% Cl]	Weight	CRS(3-5)
Study or Subgroup Endpoint:BCMA					CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023	0	9	0.000 [0.000; 0.336]	1.4%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023	0	9 20	0.000 [0.000; 0.336] 0.000 [0.000; 0.168]	1.4% 3.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023	0 0 1	9 20 43	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123]	1.4% 3.2% 6.9%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022	0 0 1 3	9 20 43 31	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258]	1.4% 3.2% 6.9% 5.0%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022	0 0 1 3 3	9 20 43 31 49	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169]	1.4% 3.2% 6.9% 5.0% 7.9%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Gu 2022 Du 2022 Munshi 2021	0 0 1 3 3 7	9 20 43 31 49 128	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021	0 0 1 3 7 2	9 20 43 31 49 128 33	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020	0 0 1 3 3 7 2 2	9 20 43 31 49 128 33 46	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.065 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020	0 0 1 3 7 2 2 2 1	9 20 43 31 49 128 33 46 21	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148] 0.048 [0.001; 0.238]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 3.4%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020	0 1 3 7 2 2 1 0	9 20 43 31 49 128 33 46 21 14	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148] 0.048 [0.001; 0.238]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 3.4% 2.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Alsina 2020 Alsina 2020 Kumar 2020 Fu 2019	0 1 3 7 2 2 1 0 3	9 20 43 31 49 128 33 46 21 14 44	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.065 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.007; 0.202] 0.043 [0.000; 0.238] 0.000 [0.000; 0.232] 0.068 [0.014; 0.187]	1.4% 3.2% 6.9% 5.0% 20.5% 5.3% 7.4% 3.4% 2.2% 7.1%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019	0 0 1 3 7 2 2 1 0 3 8	9 20 43 31 49 128 33 46 21 14 44 25	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.055 [0.022; 0.109] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148] 0.048 [0.001; 0.238] 0.048 [0.001; 0.238] 0.068 [0.014; 0.187] 0.320 [0.149; 0.535]	1.4% 3.2% 6.9% 5.0% 7.9% 5.3% 7.4% 3.4% 2.2% 7.1% 4.0%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018	0 1 3 7 2 2 1 0 3 8 6	9 20 43 31 49 128 33 46 21 14 44 25 16	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.007; 0.202] 0.043 [0.001; 0.238] 0.0048 [0.014; 0.187] 0.300 [0.149; 0.535] 0.375 [0.152; 0.646]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 3.4% 2.2% 7.1% 4.0% 2.6%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018	0 0 1 3 7 2 2 1 0 3 8	9 20 43 31 49 128 33 46 21 14 44 25	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.061 [0.007; 0.202] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148] 0.048 [0.001; 0.238] 0.000 [0.000; 0.232] 0.068 [0.014; 0.187] 0.375 [0.152; 0.646] 0.000 [0.000; 0.232]	1.4% 3.2% 6.9% 5.0% 7.9% 5.3% 7.4% 3.4% 2.2% 7.1% 4.0%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl)	0 1 3 7 2 2 1 0 3 8 6 0	9 20 43 31 49 128 33 46 21 14 44 25 16 14	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.007; 0.202] 0.043 [0.001; 0.238] 0.048 [0.011; 0.1387] 0.320 [0.149; 0.535] 0.375 [0.152; 0.646] 0.000 [0.000; 0.232]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 7.4% 3.4% 2.2% 7.1% 4.0% 2.6% 2.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% Cl)	0 1 3 7 2 2 1 0 3 8 6 0	9 20 43 31 49 128 33 46 21 14 44 25 16 14	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.061 [0.007; 0.202] 0.061 [0.007; 0.202] 0.043 [0.005; 0.148] 0.048 [0.001; 0.238] 0.000 [0.000; 0.232] 0.068 [0.014; 0.187] 0.375 [0.152; 0.646] 0.000 [0.000; 0.232]	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 7.4% 3.4% 2.2% 7.1% 4.0% 2.6% 2.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 Alsina 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> •	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 = 0.023; Chi <sup>2</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14	0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.023 [0.001; 0.123] 0.097 [0.020; 0.258] 0.061 [0.013; 0.169] 0.055 [0.022; 0.109] 0.061 [0.007; 0.202] 0.043 [0.001; 0.238] 0.048 [0.001; 0.238] 0.048 [0.014; 0.187] 0.320 [0.149; 0.535] 0.375 [0.152; 0.646] 0.005 [0.020; 0.104] 0.054 [0.020; 0.104] 0.054 [0.020; 0.104] .df = 13 (P < 0.01); l <sup>2</sup> = 67.	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 7.1% 4.0% 2.6% 2.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Asina 2020 An 2020 Fu 2019 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> + Endpoint:GPRC5I	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 = 0.023; Chi <sup>2</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 5 6 33	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.061 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.001; \ 0.238 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.106 \right] \\ \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 5.3% 7.4% 2.2% 7.1% 2.6% 2.2% 2.6% 2.2% 5.3%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Diau (95% Cl) Heterogeneity: Tau <sup>2</sup> - Endpoint:GPRC51 Xia 2023	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 = 0.023; Chi <sup>3</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.228 \right] \\ 0.061 \left[ 0.007; \ 0.202 \right] \\ 0.061 \left[ 0.000; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.305 \left[ 0.022; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.308 \right] \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 7.4% 3.4% 3.4% 2.2% 7.1% 4.0% 2.6% 2.2% 32%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> + Endpoint:GPRC5I Xia 2023 Mailankody 2023	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 = 0.023; Chi <sup>3</sup>	9 20 43 31 49 128 33 46 21 14 25 16 14 25 16 14 25 33 10 17	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.037 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.068 \left[ 0.014; \ 0.187 \right] \\ 0.320 \left[ 0.149; \ 0.135 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ .df = 13 \left( P < 0.01 \right) \left  {}^2 = 67. \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 7.1% 2.2% 7.1% 2.6% 2.2% 5.3% 1.6% 2.7%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> - Endpoint:GPRC5I Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 = 0.023; Chi <sup>3</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.061 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.001; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.006 \left[ 0.014; \ 0.187 \right] \\ 0.325 \left[ 0.142; \ 0.535 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.106 \right] \\ 0.055 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.106 \right] \\ 0.000 \left[ 0.000; \ 0.308 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.058 \left[ 0.020; \ 0.120 \right] \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 7.4% 3.4% 3.4% 2.2% 7.1% 4.0% 2.6% 2.2% 32%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Cohen 2019 Brudno 2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> s Endpoint:GPRC5I Xia 2023 Mailankody 2023 Bal 2023 Total (95% Cl)	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 0 0 1 3	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10 17 70	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.065 \left[ 0.022; \ 0.109 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.065 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.005; \ 0.238 \right] \\ 0.048 \left[ 0.011; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.320 \left[ 0.149; \ 0.535 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.055 \left[ 0.000; \ 0.106 \right] \\ 0.000 \left[ 0.000; \ 0.106 \right] \\ 0.005 \left[ 0.000; \ 0.106 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.043 \left[ 0.009; \ 0.065 \right] \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 2.6% 2.2% 2.6% 2.2% 2.6% 2.2% 5.3% 1.6% 2.7% 1.6%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Cohen 2019 Brudno 2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> s Endpoint:GPRC5I Xia 2023 Mailankody 2023 Bal 2023 Total (95% Cl)	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 0 0 1 3	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10 17 70	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.061 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.001; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.006 \left[ 0.014; \ 0.187 \right] \\ 0.325 \left[ 0.142; \ 0.535 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.106 \right] \\ 0.055 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.106 \right] \\ 0.000 \left[ 0.000; \ 0.308 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.058 \left[ 0.020; \ 0.120 \right] \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 2.6% 2.2% 2.6% 2.2% 2.6% 2.2% 5.3% 1.6% 2.7% 1.6%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> + Endpoint:GPRC5I Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> +	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 0 0 1 3	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10 17 70	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.250 \right] \\ 0.043 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.007; \ 0.202 \right] \\ 0.043 \left[ 0.000; \ 0.232 \right] \\ 0.006 \left[ 0.014; \ 0.187 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.300 \left[ 0.000; \ 0.232 \right] \\ 0.064 \left[ 0.001; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.005 \left[ 0.000; \ 0.232 \right] \\ 0.005 \left[ 0.000; \ 0.232 \right] \\ 0.055 \left[ 0.000; \ 0.308 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.043 \left[ 0.009; \ 0.065 \right] \\ 0.041 \left[ 0.000; \ 0.065 \right] \\ df = 3 \left( P = 0.14 \right); \  ^2 = 44.71 \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 2.6% 2.2% 2.6% 2.2% 2.6% 2.2% 5.3% 1.6% 2.7% 1.6%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> - Endpoint:GPRC5I Xia 2023 Mailankody 2023 Bal 2023 Total (95% CI)	0 0 1 3 3 7 2 2 1 0 3 8 6 0 0 0 1 3 = 0.023; Chi <sup>2</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14 25 16 14 33 10 17 70 2 = 5.43, 1	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.651 \left[ 0.013; \ 0.169 \right] \\ 0.655 \left[ 0.022; \ 0.109 \right] \\ 0.655 \left[ 0.022; \ 0.109 \right] \\ 0.048 \left[ 0.010; \ 0.238 \right] \\ 0.048 \left[ 0.010; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.320 \left[ 0.149; \ 0.535 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.000 \left[ 0.000; \ 0.106 \right] \\ 0.000 \left[ 0.000; \ 0.106 \right] \\ 0.000 \left[ 0.000; \ 0.106 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.043 \left[ 0.000; \ 0.120 \right] \\ 0.045 \left[ 0.000; \ 0.065 \right] \\ df = 3 \left( P = 0.14 \right); \  ^2 = 44.71 \\ 0.044 \left[ 0.017; \ 0.082 \right] \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 7.1% 4.0% 2.6% 2.2% 32% 5.3% 1.6% 2.7% 11.2%	CRS(3-5)
Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Du 2022 Munshi 2021 Raje 2021 Alsina 2020 An 2020 Kumar 2020 Fu 2019 Cohen 2019 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> - Endpoint:GPRC5I Xia 2023 Mailankody 2023 Bal 2023 Total (95% CI)	0 0 1 3 3 7 2 2 1 0 3 8 6 0 = 0.023; Chi <sup>2</sup> D 0 1 3 = 0.008; Chi <sup>2</sup>	9 20 43 31 49 128 33 46 21 14 44 25 16 14 14 25 33 10 17 70 2 = 5.43, -	$\begin{array}{c} 0.000 \left[ 0.000; \ 0.336 \right] \\ 0.000 \left[ 0.000; \ 0.168 \right] \\ 0.023 \left[ 0.001; \ 0.123 \right] \\ 0.097 \left[ 0.020; \ 0.258 \right] \\ 0.061 \left[ 0.013; \ 0.169 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.055 \left[ 0.022; \ 0.109 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.048 \left[ 0.001; \ 0.238 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.375 \left[ 0.152; \ 0.646 \right] \\ 0.000 \left[ 0.000; \ 0.232 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.054 \left[ 0.020; \ 0.104 \right] \\ 0.055 \left[ 0.020; \ 0.104 \right] \\ 0.056 \left[ 0.000; \ 0.232 \right] \\ 0.056 \left[ 0.000; \ 0.308 \right] \\ 0.059 \left[ 0.001; \ 0.287 \right] \\ 0.043 \left[ 0.009; \ 0.106 \right] \\ 0.043 \left[ 0.009; \ 0.106 \right] \\ 0.044 \left[ 0.017; \ 0.082 \right] \\ df = 17 \left( P < 0.01 \right)  ^2 = 65. \end{array}$	1.4% 3.2% 6.9% 5.0% 7.9% 20.5% 5.3% 7.4% 2.2% 7.1% 4.0% 2.6% 2.2% 32% 5.3% 1.6% 2.7% 11.2%	CRS(3-5)

low degree of skin and nail toxicity and oral adverse events, while cerebellar toxicity has been reported in only two MM cases (19, 20). The adverse reactions caused by CAR-T cell therapy are mainly CRS and ICANS, and there is little literature data on the incidence of other adverse reactions caused by GPRC5D CAR-T. Therefore, CRS and ICANS were analyzed in this study to evaluate the safety of the two cell therapies. Studies have shown that due to the short extracellular domain, epitopes exposed by GPRC5D for T cell redirection agents may be closer to the plasma membrane. This in turn promotes tighter immune synapses between T cells and target cells, which may confer more significant cytotoxicity (20, 57). This study also found that GPRC5D CAR-T caused a higher incidence of CRS grades 1-5 than BCMA CAR-T (81.2% vs.

74.2%), although in the subgroup analysis, this difference was not statistically significant. In contrast, a significantly lower incidence of ICANS grades 1-5 (6.8% vs. 13.6%), ICANS grades 3-5 (2.7% vs. 3.3%), and CRS grades 3-5 (1.6% vs. 5.4%) was observed for GPRC5D CAR-T compared to BCMA CAR-T. Therefore, the incidence of CRS and ICANS grades 3-5 in both cell therapies is acceptable.

In summary, our results indicated that GPRC5D CAR-T can induce a substantial response in patients with RRMM. However, research on GPRC5D CAR-T for RRMM is in its early stages, hence further studies elucidating its mechanisms are warranted. In particular, phase 2 and 3 clinical trials are required to focus on the efficacy and safety of GPRC5D CAR-T in specific subgroups to

Subgroup	Events	Total	Proportion [95% CI]	Weight		ICAN	S(1-5)		
Endpoint:BCMA									
Minakata 2023	1	9	0.111 [0.003; 0.482]	1.8%	<u> </u>				
Asherie 2023	0	20	0.000 [0.000; 0.168]	3.9%					
Mailankody 2023	6	43	0.140 [0.053; 0.279]	8.4%		-			
Qu 2022	1	31	0.032 [0.001; 0.167]	6.1%	· · · · ·				
Munshi 2021	23	128	0.180 [0.117; 0.257]	25.0%					
Raje 2021	14	33	0.424 [0.255; 0.608]	6.4%					
Alsina 2020	10	46	0.217 [0.109; 0.364]	9.0%	-				
Kumar 2020	0	14	0.000 [0.000; 0.232]	2.7%					
Cohen 2019	8	25	0.320 [0.149; 0.535]	4.9%	:	-	_		
Brudno 2018	6	16	0.375 [0.152; 0.646]	3.1%	· · · · · · · · · · · · · · · · · · ·				
Liu 2018	1	14	0.071 [0.002; 0.339]	2.7%					
Total (95% CI)			0.136 [0.055; 0.245]						
Heterogeneity: Tau <sup>2</sup> =	= 0.046; Chi	<sup>2</sup> = 51.66,	df = 10 (P < 0.01); l <sup>2</sup> = 80.	64%	-				
	_								
Endpoint:GPRC5				o					
Xia 2023	2	33	0.061 [0.007; 0.202]	6.4%					
Zhang 2023	0	10	0.000 [0.000; 0.308]	2.0%		_			
Mailankody 2023	1	17	0.059 [0.001; 0.287]	3.3%		-			
Bal 2023	8	73	0.110 [0.049; 0.205]	14.3%					
Total (95% CI)		2	<b>0.068 [0.025; 0.129]</b> df = 3 (P = 0.23); I <sup>2</sup> = 30.38		· ·				
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe			<b>0.110 [0.051; 0.189]</b> df = 14 (P < 0.01); I <sup>2</sup> = 77. df = 1 (P = 0.20)	79%	0 0.2	0.4	0.6	0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or	erences: Ch	i <sup>2</sup> = 1.63,	df = 14 (P < 0.01); l <sup>2</sup> = 77. df = 1 (P = 0.20)		0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup			df = 14 (P < 0.01); l <sup>2</sup> = 77.	79% Weight	0 0.2	I 0.4 ICANS		0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe B Study or Subgroup Endpoint:BCMA	erences: Ch	i <sup>2</sup> = 1.63, <b>Total</b>	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI]	Weight	0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe <b>B</b> <b>Study or</b> <b>Subgroup</b> Endpoint:BCMA Minakata 2023	erences: Ch Events 0	i <sup>2</sup> = 1.63, <b>Total</b> 9	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336]	Weight	0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe <b>B</b> <b>Study or</b> <b>Subgroup</b> Endpoint:BCMA Minakata 2023 Asherie 2023	Events 0 0	i <sup>2</sup> = 1.63, <b>Total</b> 9 20	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% C]] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168]	Weight 1.8% 3.9%	0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023	Events 0 0 0	i <sup>2</sup> = 1.63, <b>Total</b> 9 20 43	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082]	Weight 1.8% 3.9% 8.4%	0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022	Events 0 0 0 1	9 20 43 31	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.167]	<b>Weight</b> 1.8% 3.9% 8.4% 6.1%	0 0.2			0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021	Events 0 0 0	i <sup>2</sup> = 1.63, <b>Total</b> 9 20 43	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.032 [0.001; 0.167] 0.031 [0.009; 0.078]	Weight 1.8% 3.9% 8.4% 6.1% 25.0%	0 0.2			и 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022	Events 0 0 0 1 4	9 20 43 31 128	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.167]	<b>Weight</b> 1.8% 3.9% 8.4% 6.1%				и 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diffe <b>Study or</b> <b>Subgroup</b> Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021	Events 0 0 1 4 1	9 20 43 31 128 33	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% Ci] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.167] 0.031 [0.009; 0.078] 0.030 [0.001; 0.158]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4%	0 0.2			и 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020	erences: Ch Events 0 0 0 1 4 1 3	9 20 43 31 128 33 46	df = 14 (P < 0.01); l <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.167] 0.031 [0.009; 0.078] 0.030 [0.001; 0.158]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0%	0 0.2			1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018	Events 0 0 0 1 4 1 3 0 2 6	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16	df = 14 (P < 0.01); I <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.168] 0.030 [0.001; 0.158] 0.065 [0.014; 0.179] 0.080 [0.010; 0.260] 0.375 [0.152; 0.646]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019	Events 0 0 1 4 1 3 0 2	9 20 43 31 128 33 46 14 25	df = 14 (P < 0.01);   <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% C]] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.168] 0.032 [0.001; 0.167] 0.031 [0.009; 0.078] 0.030 [0.001; 0.158] 0.056 [0.014; 0.179] 0.000 [0.000; 0.232] 0.080 [0.010; 0.260]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9%				и 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI)	Events 0 0 1 4 1 3 0 2 6 1	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14	df = 14 (P < 0.01); I <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.168] 0.031 [0.009; 0.078] 0.030 [0.001; 0.167] 0.035 [0.014; 0.179] 0.030 [0.000; 0.232] 0.080 [0.010; 0.260] 0.375 [0.152; 0.646] 0.071 [0.002; 0.339] 0.033 [0.006; 0.080]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI)	Events 0 0 1 4 1 3 0 2 6 1	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14	df = 14 (P < 0.01); I <sup>2</sup> = 77. df = 1 (P = 0.20) Proportion [95% CI] 0.000 [0.000; 0.336] 0.000 [0.000; 0.168] 0.000 [0.000; 0.082] 0.032 [0.001; 0.167] 0.031 [0.009; 0.078] 0.035 [0.014; 0.179] 0.000 [0.000; 0.232] 0.80 [0.010; 0.260] 0.375 [0.152; 0.646] 0.071 [0.002; 0.339]	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRC50	events 0 0 0 1 4 1 3 0 2 6 1 1 5 0 0 0 0 0 0 0 0 1 4 1 3 0 2 6 1 1 5 1 1 5 1 5 1 1 1 5 1 1 1 1 1 1 1 1 1 1 1 1 1	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 14 25 14	$ \begin{array}{l} \text{df} = 14 \; (P < 0.01);   ^2 = 77. \\ \text{df} = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{l} \textbf{Proportion} \; [95\% \; CI] \\ \hline \\ \textbf{0.000} \; [0.000; \; 0.336] \\ \textbf{0.000} \; [0.000; \; 0.336] \\ \textbf{0.000} \; [0.000; \; 0.032] \\ \textbf{0.032} \; [0.001; \; 0.168] \\ \textbf{0.032} \; [0.001; \; 0.167] \\ \textbf{0.031} \; [0.009; \; 0.078] \\ \textbf{0.030} \; [0.001; \; 0.158] \\ \textbf{0.000} \; [0.000; \; 0.232] \\ \textbf{0.080} \; [0.010; \; 0.260] \\ \textbf{0.375} \; [0.152; \; 0.646] \\ \textbf{0.071} \; [0.022; \; 0.339] \\ \textbf{0.033} \; [0.006; \; 0.080] \\ \textbf{df} = 10 \; (P < 0.01); \;  ^2 = 64.5 \\ \end{array} $	Weight 1.8% 3.9% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRC50	Events 0 0 0 1 4 1 3 0 2 6 1 0 0 1 1 4 1 3 0 2 6 1 1 0 1 0 1 0 1 0 1 0 1 0 0 1 0 0 0 0	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 16 14 25 16 33 33	$ \begin{array}{l} df = 14 \; (P < 0.01);   ^2 = 77. \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{l} \hline Proportion \; [95\% \; CI] \\ \hline \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.168] \\ 0.031 \; [0.009; \; 0.078] \\ 0.031 \; [0.009; \; 0.078] \\ 0.035 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.080 \; [0.010; \; 0.260] \\ 0.375 \; [0.152; \; 0.646] \\ 0.071 \; [0.002; \; 0.339] \\ 0.033 \; [0.006; \; 0.080] \\ df = 10 \; (P < 0.01); \;  ^2 = 64.5 \\ \hline \\ 0.030 \; [0.001; \; 0.158] \\ \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 6.4%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRC5IT Xia 2023	Events           0           0           0           1           4           1           3           0           2           6           1           0           0           1           0           1           0           1           0           1           0	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 16 14 25 16 14 25 16 14 25 16 14 25 16 14 16 16 16 16 16 16 16 16 16 16	$ \begin{array}{c} df = 14 \; (P < 0.01);   ^2 = 77; \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.168] \\ 0.031 \; [0.009; \; 0.078] \\ 0.033 \; [0.009; \; 0.078] \\ 0.030 \; [0.000; \; 0.232] \\ 0.035 \; [0.010; \; 0.260] \\ 0.375 \; [0.152; \; 0.646] \\ 0.071 \; [0.002; \; 0.339] \\ 0.033 \; [0.006; \; 0.080] \\ df = 10 \; (P < 0.01);  1^2 = 64.5 \\ 0.030 \; [0.000; \; 0.308] \\ 0.030 \; [0.000; \; 0.308] \\ \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 6.4% 2.7% 6.4% 2.0%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Muilankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRCSI Xia 2023 Zhang 2023	events           0           0           0           0           1           3           0           2           6           1           0           0           1           3           0           2           6           1           0           1           0           1           0           1	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 <sup>2</sup> = 28.56, 33 10 17	$ \begin{array}{c} df = 14 \; (P < 0.01);   ^2 = 77; \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.68] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.167] \\ 0.031 \; [0.009; \; 0.078] \\ 0.030 \; [0.001; \; 0.168] \\ 0.065 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.080 \; [0.010; \; 0.260] \\ 0.071 \; [0.020; \; 0.339] \\ 0.033 \; [0.006; \; 0.080] \\ df = 10 \; (P < 0.01);   ^2 = 64.5 \\ 0.030 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.050 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.050 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 38% 6.4% 2.0% 3.3%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRC5IT Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023	Events           0           0           0           1           4           1           3           0           2           6           1           0           0           1           0           1           0           1           0           1           0	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 16 14 25 16 14 25 16 14 25 16 14 25 16 14 16 16 16 16 16 16 16 16 16 16	$ \begin{array}{c} df = 14 \; (P < 0.01);   ^2 = 77. \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.01; \; 0.168] \\ 0.032 \; [0.001; \; 0.167] \\ 0.031 \; [0.009; \; 0.078] \\ 0.030 \; [0.001; \; 0.158] \\ 0.005 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.037 \; [0.152; \; 0.646] \\ 0.071 \; [0.002; \; 0.339] \\ 0.033 \; [0.006; \; 0.080] \\ df = 10 \; (P < 0.01); \; P = 64.9 \\ \hline \\ \begin{array}{c} 0.030 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.033 \; [0.000; \; 0.308] \\ 0.059 \; [0.001; \; 0.287] \\ 0.027 \; [0.003; \; 0.095] \\ \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 6.4% 2.7% 6.4% 2.0%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Muilankody 2023 Qu 2022 Munshi 2021 Alsina 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRCSI Xia 2023 Zhang 2023	erences: Ch           Events           0           0           0           1           4           1           2           6           1           0           2           6           1           0           2           6           1           2           1           2           1           2	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 17 18 19 20 20 20 20 20 20 20 20 20 20	$ \begin{array}{c} df = 14 \; (P < 0.01);   ^2 = 77; \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.168] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.167] \\ 0.031 \; [0.009; \; 0.078] \\ 0.030 \; [0.001; \; 0.158] \\ 0.065 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.080 \; [0.010; \; 0.260] \\ 0.375 \; [0.152; \; 0.646] \\ 0.071 \; [0.002; \; 0.339] \\ 0.033 \; [0.006; \; 0.80] \\ df = 10 \; (P < 0.01); \; l^2 = 64.5 \\ \hline \\ \begin{array}{c} 0.030 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.059 \; [0.001; \; 0.287] \\ 0.027 \; [0.003; \; 0.095] \\ 0.027 \; [0.007; \; 0.062] \\ \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 38% 6.4% 2.0% 3.3%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Qu 2022 Munshi 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Liu 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRCSI Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	erences: Ch           Events           0           0           0           1           4           1           2           6           1           0           2           6           1           0           2           6           1           2           1           2           1           2	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 17 18 19 20 20 20 20 20 20 20 20 20 20	$ \begin{array}{c} df = 14 \; (P < 0.01);  l^2 = 77; \\ df = 1 \; (P = 0.20) \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.168] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.168] \\ 0.030 \; [0.001; \; 0.158] \\ 0.065 \; [0.014; \; 0.179] \\ 0.030 \; [0.001; \; 0.158] \\ 0.065 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.080 \; [0.010; \; 0.260] \\ 0.071 \; [0.022; \; 0.339] \\ 0.033 \; [0.006; \; 0.080] \\ df = 10 \; (P < 0.01);  l^2 = 64.5 \\ \hline \\ \begin{array}{c} 0.030 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.059 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.059 \; [0.001; \; 0.158] \\ 0.027 \; [0.003; \; 0.095] \\ 0.027 \; [0.007; \; 0.062] \\ 3 \; (P = 0.67);  l^2 = 0\% \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 38% 6.4% 2.0% 3.3%				1 0.8	
Heterogeneity: Tau <sup>2</sup> = Test for subgroup diff B Study or Subgroup Endpoint:BCMA Minakata 2023 Asherie 2023 Mailankody 2023 Qu 2022 Munshi 2021 Raje 2021 Alsina 2020 Kumar 2020 Cohen 2019 Brudno 2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Endpoint:GPRC5I Xia 2023 Zhang 2023 Mailankody 2023 Bal 2023 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	erences: Ch           Events           0           0           0           1           4           1           3           0           2           6           1           2           1           2           1           2           0: Chi <sup>2</sup> = 1	<sup>1</sup> <sup>2</sup> = 1.63, <b>Total</b> 9 20 43 31 128 33 46 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 14 25 16 16 16 16 25 16 16 16 16 16 16 16 16 16 16	$ \begin{array}{c} df = 14 \; (P < 0.01);   ^2 = 77; \\ df = 1 \; (P = 0.20) \\ \end{array} \\ \hline \\ \begin{array}{c} Proportion \; [95\% \; CI] \\ \hline \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.336] \\ 0.000 \; [0.000; \; 0.168] \\ 0.000 \; [0.000; \; 0.082] \\ 0.032 \; [0.001; \; 0.167] \\ 0.031 \; [0.009; \; 0.078] \\ 0.030 \; [0.001; \; 0.158] \\ 0.065 \; [0.014; \; 0.179] \\ 0.000 \; [0.000; \; 0.232] \\ 0.080 \; [0.010; \; 0.260] \\ 0.375 \; [0.152; \; 0.646] \\ 0.071 \; [0.002; \; 0.339] \\ 0.033 \; [0.006; \; 0.80] \\ df = 10 \; (P < 0.01); \; l^2 = 64.5 \\ \hline \\ \begin{array}{c} 0.030 \; [0.001; \; 0.158] \\ 0.000 \; [0.000; \; 0.308] \\ 0.059 \; [0.001; \; 0.287] \\ 0.027 \; [0.003; \; 0.095] \\ 0.027 \; [0.007; \; 0.062] \\ \end{array} $	Weight 1.8% 3.9% 8.4% 6.1% 25.0% 6.4% 9.0% 2.7% 4.9% 3.1% 2.7% 4.9% 3.1% 2.7% 4.9% 3.1% 2.7% 4.9% 3.1% 2.7% 4.9% 3.1%				1 0.8	

### TABLE 2 Meta-regression CRS and ICANS.

Model	Predictor Variable	Estimate	SE	Z-Value	p-Value
All CRS (1-5 class)	Intercept CAR Target BCMA (vs. GPRC5D)	1.0886 0.1592	0.0784 0.1628	13.8799 0.9776	<0.0001 0.328
Serious CRS (3-5 class)	Intercept CAR Target BCMA (vs. GPRC5D)	0.2354 -0.1138	0.0452 0.0972	5.2104 -1.1706	<0.0001 0.2418
All ICANS (1-5 class)	Intercept CAR Target BCMA (vs. GPRC5D)	0.1519 -0.0921	0.0416 0.0730	3.6485 -1.2625	0.0003 0.2068

(Continued)

#### TABLE 2 Continued

Model	Predictor Variable	Estimate	SE	Z-Value	p-Value
Serious ICANS(3-5 class)	Intercept CAR Target BCMA (vs. GPRC5D)	0.1827 -0.0228	0.0455 0.0884	4.0165 -0.2581	<0.0001 0.7963

SE, standard error.

#### TABLE 3 Grade recommendations.

						Domains			<b>F</b>	
Outcome	Group	No. Studies	No. Patients	ROB	Imprecision	Inconsistency	Indirectness	Publication Bias	Estimate [95% CI]	Quality of Evidence
ORR	BCMA GPRC5D	14 4	503 133	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.763[0. 678-0.847] 0.898[0.828-0.969]	Low
CRR	BCMA GPRC5D	14 4	503 133	Serious	Moderate	Non-serious	Non-serious	Non-Serious	0.343[0.259-0.427] 0.505[0.380-0.629]	Low
MRD	BCMA GPR5D	10 3	205 60	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.765[0.631-0.900] 0.788[0.530-1.000]	Low
Relapse	BCMA GPR5D	7 3	138 52	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.573[0.477-0.669] 0.260[0.074-0.446]	Low
EMD	BCMA GPRC5D	6 2	287 50	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.983[0.845-1.144] 0.976 [0.786-1.210]	Low
High-risk	BCMA GPRC5D	4 1	217 33	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.814 [0.700-0.906] 0.044[0.017-0.082]	Low
CRS	Total Servre	17 18	622 636	Serious	Moderate	Non-serious	Non-serious	Non-Serious	0.054[0.020-0.104] 0.016[0.000-0.064]	Low
ICANS	Total Servre	13 15	522 552	Serious	Moderate	Non-serious	Non-serious	Non-serious	0.104[0.042-0.190] 0.031[0.011-0.060]	Low

BCMA, B cell membrane antigen; GPRC5D, G protein-coupled receptor, class C group 5 member D; ORR, overall response rate; CRR, complete response rate; MRD, minimal residual lesion negative; EMD, extramedullary disease; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ROB, risk of bias.

guide its applicability for individualized treatments. In the current study, we minimized the effects of heterogeneity by using a randomeffects model and evaluated the quality of evidence using the GRADE system. Because most of the included trials on GPRC5D CAR-T used a short follow-up duration and because many clinical trials on GPRC5D CAR-T are ongoing, we did not analyze overall and progression-free survival.

# Conclusions

In patients with RRMM, GPRC5D-targeted CAR-T cell therapy may demonstrate superior efficacy compared to BCMA-targeted CAR-T cell therapy. Consequently, GPRC5D could represent a more promising alternative therapeutic target for RRMM patients, particularly those who have experienced relapse following BCMA CAR-T treatment. Beyond offering new avenues for future research, our findings may assist healthcare professionals in making evidence-based clinical decisions and providing optimal treatment options for individuals with RRMM.

# Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Author contributions

XYa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. FW: Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XYu: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. BY: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft, Uriting – review & editing. BY: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. JC: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. JC: Conceptualization, Data curation, Investigation, Methodology,

10.3389/fimmu.2024.1466443

Software, Writing – original draft. GL: Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft. DT: Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft. XX: Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft. SW: Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft. ZH: Formal analysis, Resources, Supervision, Validation, Visualization, Writing – original draft. YjL: Formal acquisition, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. YL: Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. YL: Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. YL: Funding acquisition, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

# Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (grant number 82160519); the Natural Science Foundation of Guizhou Province (grant number QianKeHe Basics - ZK(2023) Key 042, Qiankehe Cooperation Platform talents(2021)

## References

 Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* (2014) 15:e538–48. doi: 10.1016/S1470-2045(14)70442-5

2. Rajkumar SV, Kumar S. Multiple myeloma current treatment algorithms. *Blood Cancer J.* (2020) 10:94. doi: 10.1038/s41408-020-00359-2

3. Leow CCY, Low MSY. Targeted therapies for multiple myeloma. J Pers Med. (2021) 11:334. doi: 10.3390/jpm11050334

4. Röllig C, Knop S, Bornhäuser M. Multiple myeloma. Lancet. (2015) 385:2197–208. doi: 10.1016/S0140-6736(14)60493-1

5. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol.* (2014) 32:587–600. doi: 10.1200/JCO.2013.48.7934

6. Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG \$0777): a randomised, open-label, phase 3 trial. *Lancet.* (2017) 389:519–27. doi: 10.1016/S0140-6736(16)31594-X

7. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med.* (2014) 371:906–17. doi: 10.1056/NEJMoa1402551

8. Hatjiharissi P. The progress in multiple myeloma. *Hell J Nucl Med.* (2023) 26:30–5.

 Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. (2017) 31:2443–8. doi: 10.1038/leu.2017.138

10. Touzeau C, Moreau P. How I treat extramedullary myeloma. Blood. (2016) 127:971–6. doi: 10.1182/blood-2015-07-635383

11. Bruno B, Wäsch R, Engelhardt M, Gay F, Giaccone L, D'Agostino M, et al. European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma. *Haematologica*. (2021) 106:2054–65. doi: 10.3324/haematol.2020.276402

12. Gagelmann N, Riecken K, Wolschke C, Berger C, Ayuk FA, Fehse B, et al. Development of CAR-T cell therapies for multiple myeloma. *Leukemia*. (2020) 34:2317–32. doi: 10.1038/s41375-020-0930-x

13. Brudno JN, Maric I, Hartman SD, Rose JJ, Wang M, Lam N, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen

Postdoctoral Station - 007); the Research Project of Education Department of Guizhou Province (grant number QianJiaoJi (2023)037); the Subject Excellent Reserve Talent Project (grant number gyfyxkrc-2023-14). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## **Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

receptor cause remissions of poor-prognosis relapsed multiple myeloma. J Clin Oncol. (2018) 36:2267–80. doi: 10.1200/JCO.2018.77.8084

14. Ho M, Zanwar S, Paludo J. Chimeric antigen receptor T-cell therapy in hematologic Malignancies: successes, challenges, and opportunities. *Eur J Haematol.* (2024) 112:197–210. doi: 10.1111/ejh.v112.2

15. Chong EA, Ruella M, Schuster SJ, Lymphoma Program Investigators at the University of Pennsylvania. Five-year outcomes for refractory B-cell lymphomas with CAR T-cell therapy. *N Engl J Med.* (2021) 384:673–4. doi: 10.1056/NEJMc2030164

16. Park JH, Rivière I, Gonen M, Wang X, Sénéchal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med.* (2018) 378:449–59. doi: 10.1056/NEJMoa1709919

17. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* (2017) 377:2531–44. doi: 10.1056/NEJMoa1707447

18. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* (2018) 378:439–48. doi: 10.1056/NEJMoa1709866

19. Smith EL, Harrington K, Staehr M, Masakayan R, Jones J, Long TJ, et al. GPRC5D is a target for the immunotherapy of multiple myeloma with rationally designed CAR T cells. *Sci Transl Med.* (2019) 11:eaau7746. doi: 10.1126/scitranslmed.aau7746

20. Pillarisetti K, Edavettal S, Mendonça M, Li Y, Tornetta M, Babich A, et al. A Tcell-redirecting bispecific G-protein-coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma. *Blood.* (2020) 135:1232–43. doi: 10.1182/ blood.2019003342

21. Mailankody S, Devlin SM, Landa J, Nath K, Diamonte C, Carstens EJ, et al. GPRC5D-targeted CAR T cells for myeloma. *N Engl J Med.* (2022) 387:1196–206. doi: 10.1056/NEJM0a2209900

22. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol.* (2016) 17:e328–46. doi: 10.1016/S1470-2045(16)30206-6

23. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* (2003) 73:712–6. doi: 10.1046/j.1445-2197.2003.02748.x

24. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines. Rating the quality of evidence-study limitations (risk of bias). *J Clin Epidemiol.* (2011) 64:407–15. doi: 10.1016/j.jclinepi.2010.07.017

25. Minakata D, Ishida T, Ando K, Suzuki R, Tanaka J, Hagiwara S, et al. Phase 2 results of idecabtagene vicleucel (ide-cel, bb2121) in Japanese patients with relapsed and refractory multiple myeloma. *Int J Hematol.* (2023) 117:729–37. doi: 10.1007/s12185-023-03538-6

26. Asherie N, Kfir-Erenfeld S, Avni B, Assayag M, Dubnikov T, Zalcman N, et al. Development and manufacture of novel locally produced anti-BCMA CAR T cells for the treatment of relapsed/refractory multiple myeloma: results from a phase I clinical trial. *Haematologica*. (2023) 108:1827–39. doi: 10.3324/haematol.2022.281628

27. Mailankody S, Matous JV, Chhabra S, Liedtke M, Sidana S, Oluwole OO, et al. Allogeneic BCMA-targeting CAR T cells in relapsed/refractory multiple myeloma: phase 1 UNIVERSAL trial interim results. *Nat Med.* (2023) 29:422–9. doi: 10.1038/ s41591-022-02182-7

28. Qu X, An G, Sui W, Wang T, Zhang X, Yang J, et al. Phase 1 study of C-CAR088, a novel humanized anti-BCMA CAR T-cell therapy in relapsed/refractory multiple myeloma. J Immunother Cancer. (2022) 10:e005145. doi: 10.1136/jitc-2022-005145

29. Du J, Wei R, Jiang S, Jiang H, Li L, Qiang W, et al. CAR-T cell therapy targeting B cell maturation antigen is effective for relapsed/refractory multiple myeloma, including cases with poor performance status. *Am J Hematol.* (2022) 97:933–41. doi: 10.1002/ajh.26583

30. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med.* (2021) 384:705–16. doi: 10.1056/NEJMoa2024850

31. Raje N, Berdeja J, Lin Y, Siegel D, Jagannath S, Madduri D, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med.* (2019) 380:1726–37. doi: 10.1056/NEJMoa1817226

32. Alsina M, Shah N, Raje NS, Jagannath S, Madduri D, Kaufman JL, et al. Updated results from the phase I CRB-402 study of anti-Bcma CAR-T cell therapy bb21217 in patients with relapsed and refractory multiple myeloma: correlation of expansion and duration of response with T cell phenotypes. *Blood.* (2020) 136:25–6. doi: 10.1182/blood-2020-140410

33. An G, Sui W, Wang T, Qu X, Zhang X, Yang J, et al. An anti-Bcma CAR T-cell therapy (C-CAR088) shows promising safety and efficacy profile in relapsed or refractory multiple myeloma. *Blood.* (2020) 136:29–30. doi: 10.1182/blood-2020-138734

34. Kumar SK, Baz RC, Orlowski RZ, Anderson LD, Ma H, Shrewsbury A, et al. Results from lummicar-2: a phase 1b/2 study of fully human B-cell maturation antigenspecific CAR T cells (CT053) in patients with relapsed and/or refractory multiple myeloma. *Blood.* (2020) 136:28–9. doi: 10.1182/blood-2020-139802

35. Fu W, Du J, Jiang H, Cheng Z, Wei R, Yu K, et al. Efficacy and safety of CAR-T therapy with safety switch targeting bcma for patients with relapsed/refractory multiple myeloma in a phase 1 clinical study. *Blood.* (2019) 134:3154. doi: 10.1182/blood-2019-127608

36. Cohen AD, Garfall AL, Stadtmauer EA, Melenhorst JJ, Lacey SF, Lancaster E, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest. (2019) 129:2210–21. doi: 10.1172/JCI126397

37. Liu Y, Chen Z, Fang H, Wei R, Yu K, Jiang S, et al. Durable remission achieved from Bcma-directed CAR-T therapy against relapsed or refractory multiple myeloma. *Blood.* (2018) 132:956. doi: 10.1182/blood-2018-99-112786

38. Xia J, Li H, Yan Z, Zhou D, Wang Y, Qi Y, et al. Anti-G protein-coupled receptor, Class C Group 5 member D chimeric antigen receptor T cells in patients with relapsed or refractory multiple myeloma: a single-arm, Phase II trial. *J Clin Oncol.* (2023) 41:2583–93. doi: 10.1200/JCO.22.01824

39. Zhang M, Wei G, Zhou L, Zhou J, Chen S, Zhang W, et al. GPRC5D CAR T cells (OriCAR-017) in patients with relapsed or refractory multiple myeloma (POLARIS): a first-in-human, single-centre, single-arm, phase 1 trial. *Lancet Haematol.* (2023) 10: e107–16. doi: 10.1016/S2352-3026(22)00372-6

40. Bal S, Htut M, Nadeem O, Anderson LD, Koçoğlu H, Gregory T, et al. BMS-986393 (CC-95266), a G protein-coupled receptor class c group 5 member D (GPRC5D)-targeted chimeric antigen receptor(CAR)T-cell therapy for relapsed/ refractory multiple myeloma (RRMM): updated results from a phase 1 study. *Blood.* (2023) 142:Abstract 219. doi: 10.1182/blood-2023-181857 41. Bal S, Htut M, Nadeem O, Anderson Jr.LD, Koçoğlu H, Gregory T, et al. BMS-986393 (CC-95266), a G protein-coupled receptor class C group5 member D (GPRC5D)-targeted CAR T-cell therapy for relapsed/refractory multiple myeloma (RRMM): results from a phase 1 study. *Blood*. (2023) 142:219. doi: 10.1182/blood-2023-181857

42. Parikh RH, Lonial S. Chimeric antigen receptor T-cell therapy in multiple myeloma: a comprehensive review of current data and implications for clinical practice. *CA Cancer J Clin.* (2023) 73:275–85. doi: 10.3322/caac.21771

43. Rodriguez-Otero P, San-Miguel JF. Cellular therapy for multiple myeloma: what's now and what's next. *Hematol Am Soc Hematol Educ Program.* (2022) 2022:180–9. doi: 10.1182/hematology.2022000396

44. Zhang L, Shen X, Yu W, Li J, Zhang J, Zhang R, et al. Comprehensive metaanalysis of anti-BCMA chimeric antigen receptor T-cell therapy in relapsed or refractory multiple myeloma. *Ann Med.* (2021) 53:1547–59. doi: 10.1080/ 07853890.2021.1970218

45. Gagelmann N, Ayuk F, Atanackovic D, Kröger N. B cell maturation antigenspecific chimeric antigen receptor T cells for relapsed or refractory multiple myeloma: a meta-analysis. *Eur J Haematol.* (2020) 104:318–27. doi: 10.1111/ejh.v104.4

46. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. *J Exp Med.* (2004) 199:91–8. doi: 10.1084/jem.20031330

47. Martin N, Thompson E, Dell'Aringa J, Paiva B, Munshi N, San Miguel J, et al. Correlation of tumor BCMA expression with response and acquired resistance to idecabtagene vicleucel in the KarMMa study in relapsed and refractory multiple myeloma. (2020).

48. Da Vià MC, Dietrich O, Truger M, Arampatzi P, Duell J, Heidemeier A, et al. Homozygous BCMA gene deletion in response to anti-BCMA CAR T cells in a patient with multiple myeloma. *Nat Med.* (2021) 27:616–9. doi: 10.1038/s41591-021-01245-5

49. Samur MK, Fulciniti M, Aktas Samur A, Bazarbachi AH, Tai YT, Prabhala R, et al. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. *Nat Commun.* (2021) 12:868. doi: 10.1038/s41467-021-21177-5

50. Zhou X, Rasche L, Kortüm KM, Mersi J, Einsele H. BCMA loss in the epoch of novel immunotherapy for multiple myeloma: from biology to clinical practice. *Haematologica*. (2023) 108:958–68. doi: 10.3324/haematol.2020.266841

51. Del Giudice ML, Galimberti S, Buda G. Beyond BCMA, why GPRC5D could be the right way: treatment strategies with immunotherapy at relapse after anti-BCMA agents. *Cancer Immunol Immunother*. (2023) 72:3931–7. doi: 10.1007/s00262-023-03559-4

52. Atamaniuk J, Gleiss A, Porpaczy E, Kainz B, Grunt TW, Raderer M, et al. Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma. *Eur J Clin Investig.* (2012) 42:953–60. doi: 10.1111/j.1365-2362.2012.02679.x

53. Goldsmith R, Cornax I, Ma JY, Yao X, Peng P, Carreira V. Normal human tissue expression of G protein-coupled receptor class C group 5 member D (GPRC5D), a promising novel target for multiple myeloma, is restricted to plasma cells and hard keratinized tissue. *Clin Lymphoma Myeloma Leuk*. (2021) 21:S91. doi: 10.1111/j.1365-2362.2012.02679.x

54. Sanchez E, Li M, Kitto A, Li J, Wang CS, Kirk DT, et al. Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. *Br J Haematol.* (2012) 158:727–38. doi: 10.1111/j.1365-2141.2012.09241.x

55. Laurent SA, Hoffmann FS, Kuhn PH, Cheng Q, Chu Y, Schmidt-Supprian M, et al. [amp]]gamma;-secretase directly sheds the survival receptor BCMA from plasma cells. *Nat Commun.* (2015) 6:7333. doi: 10.1038/ncomms8333

56. Bhutani M, Foureau DM, Atrash S, Voorhees PM, Usmani SZ. Extramedullary multiple myeloma. *Leukemia*. (2020) 34:1–20. doi: 10.1038/s41375-019-0660-0

57. Li J, Stagg NJ, Johnston J, Harris MJ, Menzies SA, DiCara D, et al. Membraneproximal epitope facilitates efficient T cell synapse formation by anti-FcRH5/CD3 and is a requirement for myeloma cell killing. *Cancer Cell*. (2017) 31:383–95. doi: 10.1016/ j.ccell.2017.02.001