Supplementary Contents

34   Supplementary Figure S1: Detailed Search Strategy

1. exp antibody, bispecific/ and exp immunotherapy/ and exp myeloma, adoptive/

2. (bispecific* or BITE* or trispecific*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

3. (teclistamab or abbv-383 or elranatamab or linvoseltamab or REGN5458 or pavurutamab or AMG701 or talquetamab or cevostamab or RG6234 or BFCR4350A).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]

4. 2 and (1 or 3)

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36   Detailed Search Strategy

37   Studies were identified via the OVID platform of PUBMED, MEDLINE, EMBASE and
38   Cochrane to identify relevant articles, translatable to English, between inception and
39   February 10, 2023 using the following terms; antibody, bispecific, immunotherapy, myeloma,
40   adaptive, teclistamab, abbv-383, elranatamab, linvoseltamab, REGN5458, pavurutamab,
41   AMG701, talquetamab, cevostamab, RG6234, BFCR4350A. The comprehensive search
42   strategy is included below. Manual searches of article reference lists were performed.
43   Manual searches of recent international conference presentations for additional data
44   (American Society of Haematology; 2020, 2021, 2022 and American Society of Clinical
45   Oncology; 2020, 2021, 2022) were performed.

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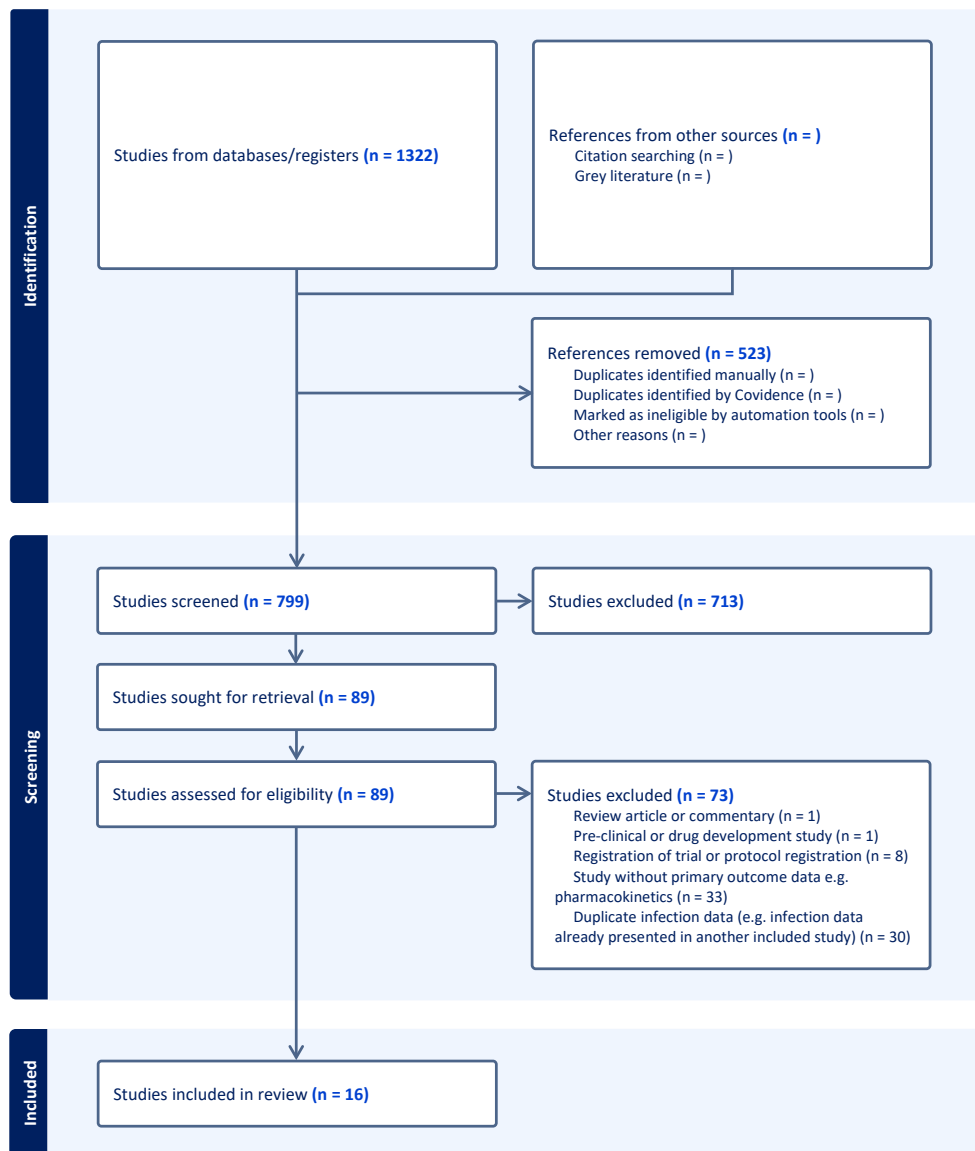52

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63   Supplementary Table S1 - Extracted Variables

Patient information	- Median age - Triple- refractory disease - Penta- refractory disease - Prior transplant
Treatment complications	- Cytokine release syndrome (all grade, Grade ≥ 3) - ICANS (all grade, Grade ≥ 3) - Neutropenia (all grade, Grade ≥ 3) - Hypogammaglobulinaemia (all grade, Grade ≥ 3)
Infection Outcomes	- All-grade infections - Grade ≥ 3 infections - Grade ≥ 5 infections - Microbiologically confirmed infections - Bacterial infections - Viral infections - Fungal infections

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Supplementary Figure S2 – PRISMA flow-chart of extracted document

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89   Supplementary Table S2 – Complications of treatment according to bispecific target

	BCMA-bispecific (%, 95CI)	Non-BCMA-bispecific
Grade ≥3 Neutropenia	44 (29 – 59)	55 (42 – 68)
Grade ≥3 CRS	1 (0 – 1)	2 (1 – 3)
All-grade ICANS	6 (2 – 10)	19 (2 – 37)
Received Steroids	12 (7 – 18)	21 (5 – 38)

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117 Supplementary Table S3 – S3a: Fatal infections recorded in clinical trials, S3b: Causative
118 pathogens by microbiological classification.

S3a	Target	Grade 5 Infections	Bacterial pathogen	Fungal Pathogen	Viral Pathogen
Wong et al., 2022	BCMA	0	0	0	0
D'Souza et al., 2022	BCMA	8	1	0	7
Topp et al., 2020	BCMA	2	NR	NR	NR
Harrison et al., 2020	BCMA	2	2	0	0
Raje et al., 2022	BCMA	1	NR	NR	NR
Bumma et al., 2022	BCMA	10	NR	NR	NR
Bahlis et al., 2022	BCMA	6	--	--	2
Moreau et al., 2022	BCMA	15	2	0	13
Abdallah et al., 2022	BCMA + albumin	NR	NR	NR	NR
Grosicki et al., 2022	BCMA +CD38	8	NR	NR	NR
Rodriguez-Otero et al., 2022	BCMA +CD38	1	1	0	0
Searle et al., 2022	BCMA +CD38 + IMID	1	0	0	1
Trudel et al., 2021	FcRH5	0	0	0	0
Carlos-Stella et al., 2022	GPR5CD	2	NR	NR	NR
Chari et al., 2022	GPR5CD	2	1	--	--
van de Donk et al., 2022	GPR5CD + CD38	0	0	0	0

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S3b	Bacterial pathogen	Fungal Pathogen	Viral Pathogen
Causative pathogen of a fatal infection	Sepsis NOS (N = 3) *Strep pneumoniae* (N = 1) *Pseudomonas* (N = 2) Bacterial pneumonia (N =1)		COVID-19 (N = 21) PML (N = 1) CMV (N =1) Adenovirus FHF(N=1)

120 NOS = not otherwise specified, PML = progressive multifocal leukoencephalopathy, FHF = fulminant hepatic failure

121 Supplementary Table S4 – Infection outcomes reported by observational studies of bispecific
122 treated patients.

Author / Year	Mohan et al., 2022[25]	Sim et al., 2022[26,27]	Lancman et al., 2022[28]	Hoeynck et al., 2022[29]
Study Design	Observational	Observational	Observational	Observational
Product	NR	NR	NR	NR
Target	BCMA	NR	BCMA	BCMA
Participants (N)	36	39	37	29
Median age (years)	66.5	62	66	64
Prior therapy (median)	6	6	7	6
Penta-class refractory	NR	NR	NR	45%
Median follow-up	8.5 months	5.1 months	424 months[1]	10.3 months
Grade ≥ 3 CRS	0%	NR[2]	NR	NR
Grade ≥ 3 ICANS	0%	NR[3]	NR	NR
Steroid exposure	0%	NR	NR	NR
Tocilizumab exposure	28.6%	NR	NR	NR
Grade ≥ 3 neutropenia	NR		NR	NR
Hypogammaglobulinaemia	80%[4]	87%	100%[5]	59%[6]
Median time to infection onset	49 days	79 days[7]	114 days[8]	278 days[9]
Infection incidence for observation period (all-patients)	0.69 events / patients	2.8 events / patient	3.3 events / patient-year	1.4 events / patient
Patients with All Grade Infections	41%	90%	100%	36%
Patients with Grade ≥ 3 infection	38%	41%	38%	NR
Patients with Grade 5 infections	6%	8%	5%	NR
Infection events requiring hospitalisation	60%	57%	NR	NR
Average hospital LOS	4.8 days	4 days	NR	NR
Infection events requiring ICU admission	NR	4%	NR	NR
Total Infection Events	25	111	118	39
Microbiologically confirmed infection	23	33	118	25
Bacterial infections	13	15	51	12
Gram negative bacteria	6	12	NR	NR
Gram positive bacteria	4	3	NR	NR
Viral infections	10	22	54	13
Respiratory virus (e.g. COVID-19, adenovirus, rhinovirus)	NR	68%	NR	NR
Viral reactivation (e.g. CMV, HSV, BK virus)	NR	32%	22%[10]	NR
Fungal infections	NR	0	13[11]	0

123 NR = not reported

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[1] Cumulative treatment months
[2] 72% all-grade CRS
[3] 5% all-grade ICANS
[4] With baseline hypogammaglobujlinaemia; no post-treatment data reported
[5] Of the 70% of patients with disease response
[6] Received IVIG supplementation

[7] Microbiologically confirmed infections
[8] Grade 3 – 5 infections
[9] Grade 3 – 5 infections
[10] CMV reactivation rate in cohort 22%
[11] No further breakdown of fungal pathogen provided

124　　Supplementary Table S5 – Joanna Brigg's Institute assessment of study bias.

	Criteria 1: Reflective sample	Criteria 2: Appropriate recruitment	Criteria 3: Detailed setting	Criteria 4: Sufficient coverage	Criteria 5: Definition of infection	Criteria 6: Measurement of infection	Criteria 7: Statistical analysis	Criteria 8: Follow-up
Wong et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
D'Souza et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Topp et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Harrison et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Trudel et al., 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raje 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Bahlis 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grosicki 2022	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Bumma et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carlos-Stella et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chari et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
van de Donk et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Moreau et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rodriguez-Otero et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Searle et al 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Abdallah et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mohan et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sim et al., 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lancman et al., 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Hoeynck et al., 2022	Yes	Yes	No	Yes	Yes	No	Yes	Yes

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