

Online Resource 1

Cardiovascular Adverse Events with Anti-CD38 Antibodies Added to Identical Myeloma Regimens: A Systematic Review and Meta-analysis

Cardiovascular Toxicology

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Methods S1. Information Sources, Search Strategies and Counts

ID	Source	Platform	Run (UTC)	Found	Exported
CTG1	ClinicalTrials.gov	API v2	2026-10-10T23:45:15+00:00	77	77
CTG2	ClinicalTrials.gov	API v2	2026-10-10T23:45:32+00:00	151	151
PM1	MEDLINE	PubMed via NCBI E-utilities	2026-10-10T23:54:23+00:00	1755	1755
EP1	Europe PMC	EMBL-EBI REST API (resultType=core)	2026-10-10T23:55:18+00:00	3502	3502
CL1	Cochrane CENTRAL (Issue 10 of 12, October 2026)	Cochrane Library (Wiley) Search Manager	2026-10-11T00:00Z	1490	1490
SC1	Scopus	Elsevier Scopus Advanced Search	2026-10-11T00:04:58Z	2385	2385
WS1	Web of Science Core Collection	Clarivate Web of Science Advanced Search	2026-10-11T00:04:01Z	2241	2241 (3 files: 1-1000 exported 2026-10-11T02:33Z; 1001-2000 and 2001-2241 exported 2026-10-11T10:3xZ from the same session result set, still 2,241)
EM1	Embase	Embase.com (Elsevier)	2026-10-11T10:44:01Z	6090 (Articles 5635; Clinical trials 455)	6090 (5635 articles + 455 trial records)

PubMed (MEDLINE)

PubMed / MEDLINE search strategy Review: Anti-CD38 add-on therapy and cardiovascular adverse events in multiple myeloma

#1 "Multiple Myeloma"[Mesh] OR myeloma*[tiab] OR "plasma cell neoplasm*" [tiab] OR "plasma cell myeloma"[tiab] OR plasmacytoma*[tiab]

#2 "daratumumab"[Supplementary Concept] OR daratumumab[tiab] OR darzalex[tiab] OR "HuMax-CD38"[tiab] OR "JNJ-54767414"[tiab] OR "isatuximab"[Supplementary Concept] OR isatuximab[tiab] OR sarclisa[tiab] OR "SAR650984"[tiab] OR "SAR 650984"[tiab] OR felzartamab[tiab] OR "MOR202"[tiab]

OR "MOR 202"[tiab] OR "anti-CD38"[tiab] OR "anti CD38"[tiab] OR "CD38-targeting"[tiab] OR "CD38 targeting"[tiab] OR "CD38 antibod*"[tiab] OR "CD38 monoclonal"[tiab] OR "CD38-directed"[tiab]

#3 Cochrane Highly Sensitive Search Strategy (sensitivity-maximizing, PubMed 2008 revision): randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR "phase 3"[tiab] OR "phase III"[tiab] OR "phase 2"[tiab] OR "phase II"[tiab] v0.2 additions (known-trial test missed an IKEMA subgroup report, PMID 37584290): OR "clinical trial"[pt] OR subgroup*[tiab] OR "post hoc"[tiab] OR "pooled analysis"[tiab]

#4 animals[mh] NOT humans[mh]

#5 (#1 AND #2 AND #3) NOT #4 ← MAIN SEARCH (no date or language limits)

Notes

- AE outcomes are rarely in titles/abstracts, so the main search has no outcome block.

Embase.com

Embase (Embase.com, Elsevier; RCSI subscription) — v0.2, translated from embase_ovid.txt (v0.1) and executed 2026-10-10T23:58Z. Re-run 2026-10-11T10:44Z with identical counts for every line; exported then:

#1 'multiple myeloma'/exp OR (myeloma* OR plasmacytoma* OR 'plasma cell neoplas*' OR 'plasma cell myeloma'):ti,ab,kw 168,997

#2 'daratumumab'/exp OR 'isatuximab'/exp OR (daratumumab OR darzalex OR 'humax cd38' OR 'humax-cd38' OR 'jnj 54767414' OR jnj54767414 OR isatuximab OR sarclisa OR 'sar 650984' OR sar650984 OR felzartamab OR 'mor 202' OR mor202):ti,ab,kw,tn 13,582

#3 ('anti-cd38' OR 'anti cd38' OR 'cd38-targeting' OR 'cd38 targeting' OR 'cd38 directed' OR ((cd38 OR 'cd 38') NEAR/3 (antibod* OR monoclonal OR mab))):ti,ab,kw 6,088

#4 #2 OR #3 16,119

#5 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'randomization'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'phase 3 clinical trial'/exp OR 'phase 2 clinical trial'/exp OR 'randomized controlled trial (topic)'/exp 2,053,803

#6 (random* OR placebo* OR 'open label' OR 'open-label' OR ((phase OR stage) NEAR/2 (3 OR iii OR 2 OR ii))):ti,ab,kw 3,457,504

#7 ((compar* OR versus OR vs) AND (arm OR arms OR group*)):ti,ab 4,419,979

#8 trial:ti 641,061

#9 (subgroup* OR 'post hoc' OR 'pooled analysis'):ti,ab (v0.2 addition after PubMed known-trial test) 777,190

#10 #5 OR #6 OR #7 OR #8 OR #9 7,630,587

#11 #1 AND #4 AND #10	6,124
#12 ('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp	8,670,344
#13 #11 NOT #12 ← MAIN SEARCH	6,090 (Articles 5,635; Clinical trials 455)

Notes: keep conference abstracts (no 'conference abstract' exclusion). Export BOTH the Articles and the Clinical trials tabs.

Cochrane CENTRAL

Cochrane CENTRAL (Cochrane Library, Advanced Search → Search manager). No RCT filter needed. v0.2 — executed 2026-10-11 (CENTRAL Issue 10 of 12, October 2026). Counts are as displayed by the Search Manager (whole Cochrane Library); the Trials tab for #10 = 1,490.

#1 [mh "Multiple Myeloma"]	2,662
#2 (myeloma* OR plasmacytoma* OR "plasma cell neoplasm*" OR "plasma cell myeloma"):ti,ab,kw	8,359 (v0.1 line; Cochrane warns wildcard inside quotes not applied)
#3 #1 OR #2	8,359
#4 (daratumumab OR darzalex OR "HuMax-CD38" OR "JNJ-54767414" OR isatuximab OR sarclisa OR SAR650984 OR "SAR 650984" OR felzartamab OR MOR202 OR "MOR 202" OR "anti-CD38" OR "anti CD38" OR "CD38 targeting" OR "CD38-targeting" OR "CD38 directed"):ti,ab,kw	1,618
#5 (CD38 NEAR/3 (antibod* OR monoclonal OR mAb)):ti,ab,kw	522
#6 #4 OR #5	1,637
#7 #3 AND #6	1,494
#8 (myeloma* OR plasmacytoma* OR (plasma NEXT cell NEXT neoplasm*) OR "plasma cell myeloma"):ti,ab,kw	8,363 (v0.2 correction of #2)
#9 #1 OR #8	8,363
#10 #9 AND #6 ← MAIN SEARCH (v0.2)	1,494 (Cochrane Reviews 2; Protocols 0; Trials 1,490)

Web of Science Core Collection

v0.2 — executed 2026-10-11T00:04Z.

#1 TS=(myeloma* OR plasmacytoma* OR "plasma cell neoplasm*")	118,798
#2 TS=(daratumumab OR darzalex OR "HuMax-CD38" OR isatuximab OR sarclisa OR SAR650984 OR felzartamab OR MOR202 OR "anti-CD38" OR "anti CD38" OR "CD38 targeting" OR "CD38-targeting" OR (CD38 NEAR/3 (antibod* OR monoclonal)))	6,771

#3 #1 AND #2 AND TS=(random* OR placebo OR "open-label" OR "open label" OR "phase 3" OR "phase III" OR "phase 2" OR "phase II" OR trial OR subgroup* OR "post hoc" OR "pooled analysis") 2,241 ← MAIN SEARCH (design block entered inline; v0.2 adds subgroup*/"post hoc"/"pooled analysis" after the PubMed known-trial test) Export: RIS (other reference software), Full Record, ≤1,000 per batch:

Scopus

Scopus (Elsevier) Advanced document search — v0.2, executed 2026-10-11T00:04:58Z. Design filter mirrors PubMed/WoS v0.2 (incl. subgroup*/post hoc/pooled analysis additions from the known-trial test).

TITLE-ABS-KEY(myeloma* OR plasmacytoma* OR "plasma cell neoplasm*" OR "plasma cell myeloma") AND TITLE-ABS-KEY(daratumumab OR darzalex OR "HuMax-CD38" OR isatuximab OR sarclisa OR sar650984 OR felzartamab OR mor202 OR "anti-CD38" OR "anti CD38" OR "CD38 targeting" OR "CD38-targeting" OR "CD38-directed" OR (cd38 W/3 (antibod* OR monoclonal OR mab))) AND TITLE-ABS-KEY(random* OR placebo OR "open label" OR "open-label" OR "phase 3" OR "phase III" OR "phase 2" OR "phase II" OR trial OR subgroup* OR "post hoc" OR "pooled analysis")

Result: 2,385 documents (Documents tab). Export: Select all → RIS, all information fields (citation, bibliographical, abstract & keywords)

Europe PMC

Europe PMC (EMBL-EBI REST API, <https://www.ebi.ac.uk/europepmc/webservices/rest/search>), v0.2, run 2026-10-11 by script. Supplementary source (preprints, non-MEDLINE records). No design filter: Europe PMC has no MeSH subheading field, so the PubMed HSSS cannot be reproduced; the myeloma AND anti-CD38 set is small enough to screen after deduplication against PubMed.

#A (myeloma) (TITLE_ABS:(myeloma* OR plasmacytoma* OR "plasma cell neoplasm" OR "plasma cell neoplasms" OR "plasma cell myeloma") OR MESH_HEADING:"Multiple Myeloma")

#B (anti-CD38) (TITLE_ABS:(daratumumab OR darzalex OR "HuMax-CD38" OR "JNJ-54767414" OR isatuximab OR sarclisa OR SAR650984 OR "SAR 650984" OR felzartamab OR MOR202 OR "MOR 202" OR "anti-CD38" OR "anti CD38" OR "CD38-targeting" OR "CD38 targeting" OR "CD38-directed") OR (TITLE_ABS:CD38 AND TITLE_ABS:(antibody OR antibodies OR monoclonal)) OR CHEM:daratumumab OR CHEM:isatuximab)

#C (design; tested, NOT applied) (TITLE_ABS:(random* OR placebo OR randomly OR trial OR groups OR "phase 3" OR "phase III" OR "phase 2" OR "phase II" OR subgroup* OR "post hoc" OR "pooled analysis") OR PUB_TYPE:"Randomized Controlled Trial" OR PUB_TYPE:"Clinical Trial" OR PUB_TYPE:"Controlled Clinical Trial") MAIN = #A AND #B (resultType=core, all sources incl. preprints; no date/language limits) Test counts 2026-10-11: A&B&C = 1065; A&B&C non-MEDLINE = 69; A&B&C preprints = 22.

ClinicalTrials.gov (API v2)

ClinicalTrials.gov API v2 (<https://clinicaltrials.gov/api/v2/studies>), run by script on 2026-10-11 (UTC times in the JSON files)

CTG1 (with results): query.cond = multiple myeloma query.intr = daratumumab OR isatuximab OR felzartamab OR MOR202 OR "anti-CD38" OR SAR650984 OR TAK-079 OR mezagitamab filter.advanced = AREA[StudyType]INTERVENTIONAL AND AREA[HasResults]true CTG2 (randomized, any status, results or not): same

query.cond / query.intr filter.advanced = AREA[StudyType]INTERVENTIONAL AND AREA[DesignAllocation]RANDOMIZED Targeted lookups: GEM2017FIT -> NCT03742297; KMM1910 -> NCT04277845 (VRd vs Rd, no anti-CD38: not relevant).

Regulatory documents: EMA product pages for Darzalex, Sarclisa and Kyprolis (all English assessment reports, variation/extension assessment reports, CHMP opinions and procedural documents) and FDA Drugs@FDA reviews (BLA 761036, 761113, 761145) were downloaded on 11 October 2026; the ledger with SHA-256 checksums is available from the authors.

Two reviewers independently screened the titles and abstracts of all deduplicated records and assessed full texts. Two reviewers extracted data, a third checked the extractions and a fourth resolved discrepancies; risk of bias was assessed by one reviewer, checked by a second, with disagreements resolved by a third. Reports were linked at the trial level using trial names and registry identifiers. The list of unavailable reports is available from the authors.

Methods S2. Risk-of-Bias Conventions (RoB 2, Harms Outcomes)

Applying RoB 2 to cardiac harms in this review

Risk of bias for the primary cardiac harms outcomes was assessed using RoB 2 for the effect of assignment to intervention. One reviewer completed the assessments and a second reviewer checked them. Disagreements were resolved by a third reviewer. Domain and overall judgments were classified as low risk, some concerns or high risk. The following conventions guided assessment of cardiac harms.

Domain	Convention for this review
D1 Randomization	Assess sequence generation, allocation concealment and baseline balance using trial-specific sources. Industry sponsorship or phase 3 status alone does not establish low risk.
D2 Deviations (effect of assignment)	Open-label is expected. Low if deviations were not imbalanced and the safety population is used consistently.
D3 Missing outcome data	Determine whether outcomes continued to be collected after treatment stopped and whether missing observation differs by arm. Unequal treatment duration and missing follow-up require separate consideration. Approximate person-time cannot correct or validate missing outcome observation.
D4 Measurement	Open-label with investigator-reported AEs. Antibody arms have more frequent visits (weekly infusions early), so more vitals and ECGs. Some concerns for hypertension and AF, unless protocol-mandated cardiac monitoring was identical in both arms. Low for fatal events and clearly objective serious events (e.g. hospitalised cardiac failure).
D5 Selective reporting	Consider availability of all defined terms, reporting thresholds and changes to grouping definitions. Complete registry tables reduce threshold-related omission but do not establish that outcome definitions were fixed before data inspection.

Table S1. PRISMA 2020 Checklist

Item	Checklist item	Location	Status
1	Title	Title	reported
2	Abstract (PRISMA 2020 for Abstracts)	Abstract	reported
3	Rationale	Introduction ¶1-2	reported
4	Objectives	Introduction, final paragraph; Abstract	reported
5	Eligibility criteria	Materials and methods: Inclusion and exclusion criteria	reported
6	Information sources	Materials and methods: Information sources and search strategy; Methods S1	reported
7	Search strategy	Methods S1 (full strategies for all databases/registers)	reported
8	Selection process	Materials and methods: Study selection; Methods S1	reported
9	Data collection process	Materials and methods: Data extraction; Table S2 (arm map)	reported
10a	Data items - outcomes	Materials and methods: Outcomes; Table 1; Table S9	reported
10b	Data items - other variables	Table 2; Table S6 (characteristics extracted)	reported
11	Study risk of bias assessment	Materials and methods: Risk of bias; Methods S2	reported
12	Effect measures	Materials and methods: Statistical analysis	reported
13a	Synthesis - eligibility for each synthesis	Materials and methods: Inclusion criteria; Outcomes (first vs second randomisations; sensitivity-only populations)	reported
13b	Synthesis - data preparation	Materials and methods: Outcomes (composite bounds, layers, double-zero handling)	reported
13c	Synthesis - tabulation/display	Figures 2-5; Table 3	reported
13d	Synthesis - methods and rationale	Materials and methods: Statistical analysis	reported

Item	Checklist item	Location	Status
13e	Synthesis - heterogeneity exploration	Materials and methods: Statistical analysis (subgroups)	reported
13f	Synthesis - sensitivity analyses	Materials and methods: Statistical analysis (sensitivity analyses)	reported
14	Reporting bias assessment	Materials and methods: Statistical analysis (Egger- and Peters-type tests)	reported
15	Certainty assessment	Materials and methods: Certainty of evidence; Table 3	reported
16a	Study selection - results/flow	Results; Figure 1	reported
16b	Study selection - excluded studies	Table S4 (excluded, ongoing, awaiting, eligible-no-data trials with reasons)	reported
17	Study characteristics	Table 2; Results: Study/Patient characteristics	reported
18	Risk of bias in studies	Results: Risk of bias; Table S5	reported
19	Results of individual studies	Figures 2–5; Tables S12–S14	reported for registry outcomes
20a	Syntheses - characteristics/RoB summary	Results: Risk of bias; Patient characteristics	reported
20b	Syntheses - results	Results: outcome subsections	reported
20c	Syntheses - heterogeneity investigations	Results: Sensitivity and subgroup analyses; Table S8	reported
20d	Syntheses - sensitivity analyses	Results: Sensitivity and subgroup analyses; Table S7	reported
21	Reporting biases	Results: Sensitivity and subgroup analyses (small-study tests)	reported
22	Certainty of evidence	Table 3; Results: Outcomes more frequent with anti-CD38 therapy	reported
23a	Discussion - interpretation	Discussion ¶1-4	reported
23b	Discussion - evidence limitations	Study limitations	reported
23c	Discussion - review process limitations	Study limitations	reported

Item	Checklist item	Location	Status
23d	Discussion - implications	Discussion: Clinical implications; Conclusions	reported
24a	Registration	Materials and methods, first paragraph; PROSPERO CRD420261543288 (registered 17 October 2026), main-text reference 15	reported
24b	Protocol access	PROSPERO CRD420261543288 (main-text reference 15): https://www.crd.york.ac.uk/PROSPERO/view/CRD420261543288	reported
24c	Amendments	Methods; Table S3; original and current term maps available from the authors	reported
25	Support	Title page and Statements and Declarations: Funding	reported
26	Competing interests	Title page and Statements and Declarations: Competing interests	reported
27	Availability of data, code and materials	Data and code availability	reported

Table S2. Mapping of ClinicalTrials.gov Result Groups to Comparison Arms

Comparison	NCT	Group	Registry group title	Role	Notes
MAIA	NCT02252172	EG001	Daratumumab + Lenalidomide + Dexamethasone (DRd)	intervention	Registry group = randomised arm (safety population)
MAIA	NCT02252172	EG000	Lenalidomide + Dexamethasone (Rd)	control	
ALCYONE	NCT02195479	EG001	Daratumumab, Velcade, Melphalan and Prednisone (D-VMP)	intervention	
ALCYONE	NCT02195479	EG000	Velcade, Melphalan and Prednisone (VMP)	control	
CEPHEUS	NCT03652064	EG001	Arm B: Daratumumab-bortezomib-lenalidomide-dexamethasone (D-VRd)	intervention	
CEPHEUS	NCT03652064	EG000	Arm A: Bortezomib-lenalidomide-dexamethasone (VRd)	control	
PERSEUS	NCT03710603	EG001	Daratumumab + VRd (D-VRd)	intervention	
PERSEUS	NCT03710603	EG000	Velcade Lenalidomide Dexamethasone (VRd)	control	
CASSIOPEIA_P1	NCT02541383	EG001	DVTd - Part 1	intervention	Registry AE description: Part 1 groups contain TEAEs to Part 1 treatment only (before rando 2 or subsequent therapy)
CASSIOPEIA_P1	NCT02541383	EG000	VTd - Part 1	control	as above
CASSIOPEIA_P2	NCT02541383	EG003	VTd-DARA - Part 2	intervention	Part 2 DARA = EG003 + EG005 (summed across part-1 strata); AE window: rando 2 to 30 d after last dose (differs from OBS window of 2 y + 30 d) - note for RoB/D4
CASSIOPEIA_P2	NCT02541383	EG005	DVTd-DARA - Part 2	intervention	as above
CASSIOPEIA_P2	NCT02541383	EG002	VTd-OBS - Part 2	control	Part 2 OBS = EG002 + EG004
CASSIOPEIA_P2	NCT02541383	EG004	DVTd-OBS - Part 2	control	as above
GRIFFIN	NCT02874742	EG001	Randomized: Daratumumab+RVd (D-RVd)	intervention	EG002 safety run-in (non-randomised) excluded
GRIFFIN	NCT02874742	EG000	Randomized: Lenalidomide+Bortezomib+Dexamethasone (RVd)	control	
GRIFFIN	NCT02874742	EG002	Safety Run-in: D-RVd	exclude	non-randomised safety run-in
AURIGA	NCT03901963	EG000	Daratumumab + Lenalidomide	intervention	
AURIGA	NCT03901963	EG001	Lenalidomide	control	
CASTOR	NCT02136134	EG001	Daratumumab + Bortezomib and Dexamethasone (DVd)	intervention	
CASTOR	NCT02136134	EG000	Bortezomib + Dexamethasone (Vd)	control	
CASTOR	NCT02136134	EG002	Switch From Vd to Daratumumab Monotherapy	exclude	post-progression crossover to daratumumab monotherapy (not randomised treatment)
POLLUX	NCT02076009	EG001	Daratumumab, Lenalidomide, Low-dose Dexamethasone (DRd)	intervention	
POLLUX	NCT02076009	EG000	Lenalidomide, Low-dose Dexamethasone (Rd)	control	

Comparison	NCT	Group	Registry group title	Role	Notes
CANDOR	NCT03158688	EG001	KdD - Carfilzomib, Dexamethasone and Daratumumab	intervention	
CANDOR	NCT03158688	EG000	Kd - Carfilzomib and Dexamethasone	control	
APOLLO	NCT03180736	EG001	Daratumumab+Pomalidomide+Dexamethasone	intervention	EG001 (n=149) = randomised D-Pd arm; EG002 (SC n=142) and EG003 (IV n=7) are subsets of EG001 and are NOT added (would double count)
APOLLO	NCT03180736	EG000	Pomalidomide+Dexamethasone	control	
APOLLO	NCT03180736	EG002	Daratumumab (SC)+Pomalidomide+Dexamethasone	exclude	subset of EG001
APOLLO	NCT03180736	EG003	Daratumumab (IV)+Pomalidomide+Dexamethasone	exclude	subset of EG001
IKEMA	NCT03275285	EG001	Isatuximab + Carfilzomib + Dexamethasone (IKd)	intervention	
IKEMA	NCT03275285	EG000	Carfilzomib + Dexamethasone (Kd)	control	
ICARIA	NCT02990338	EG001	IPd (Isatuximab + Pomalidomide + Dexamethasone)	intervention	
ICARIA	NCT02990338	EG000	Pd (Pomalidomide + Dexamethasone)	control	
ANDROMEDA	NCT03201965	EG002	Daratumumab Plus CyBorD	intervention	sensitivity only (E5); EG000 run-in excluded
ANDROMEDA	NCT03201965	EG001	CyBorD	control	sensitivity only (E5)
ANDROMEDA	NCT03201965	EG000	Run-In: Daratumumab Plus CyBorD	exclude	non-randomised safety run-in
AQUILA	NCT03301220	EG001	Arm B: Daratumumab SC	intervention	sensitivity only (E5); comparator active monitoring
AQUILA	NCT03301220	EG000	Arm A: Active Monitoring (ACTM)	control	sensitivity only (E5)
LYNX	NCT03871829	EG001	Arm B: Dara-SC in Combination With Kd (DKd)	intervention	
LYNX	NCT03871829	EG000	Arm A: Carfilzomib+Dexamethasone (Kd)	control	

Table S3. Extension of the MedDRA Preferred-Term Lists

Change	Timing	Handling
MedDRA preferred-term lists extended with terms used in ClinicalTrials.gov tables but not anticipated in the original lists (marked * in Table S9); for cardiac failure: cardiopulmonary failure, cardiovascular insufficiency, heart failure (CTCAE term). Broad lists made supersets of narrow lists.	After registry counts had been generated	Results with the original term lists reported as a post hoc sensitivity analysis (Table S7); The updated overlap analyses are reported in Tables S12–S14.

Table S4. Trials Not Contributing to the Main Meta-Analysis, With Reasons

Trial	Category	Rationale	Source
Daratumumab graft purging (ISRCTN40735896)	Awaiting classification	Daratumumab graft purging before ASCT; registry text does not establish whether mobilisation/transplant backbone is identical; no results found	trial registry record (ISRCTN40735896)
Melphalan ± daratumumab conditioning (ChiCTR2100052302)	Awaiting classification	High-dose melphalan +/- daratumumab conditioning (would meet I2); registry status unknown and no results found	trial registry record (ChiCTR2100052302)
Vejle DRd vs Rd (NCT02419118)	Awaiting classification	DRd vs Rd translational study, completed with N=4; no results in registry or literature found	ClinicalTrials.gov NCT02419118
ANDROMEDA	E5 (AL amyloidosis / smoldering myeloma): sensitivity analysis only	AL amyloidosis (E5): sensitivity analysis only (registered eligibility criteria)	ClinicalTrials.gov NCT03201965; EMA II/0043 assessment report
AQUILA	E5 (AL amyloidosis / smoldering myeloma): sensitivity analysis only	Smoldering myeloma (E5): sensitivity analysis only (registered eligibility criteria)	ClinicalTrials.gov NCT03301220; EMA II/0077 assessment report
ADVANCE	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT04268498; conference abstracts
AGMT MM-4	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT04891809; conference abstract
AMaRC 03-16	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	PMID 38739707 abstract; ACTRN12617000202369 (trial registry record)
Felzartamab-Rd vs Rd (TJ202001MMY301)	Eligible; not pooled	No complete registry serious-AE table. Publication reports individual AF/cardiac-failure terms and severity grades without complete composite coverage; retained descriptively in Table S11.	PMID 42822478 abstract; ClinicalTrials.gov NCT03952091
GMMG-HD7	Eligible; not pooled	No complete registry serious-AE table. Publication reports grade 3–4 cardiac disorders, which differs from the serious-event registry composite; retained descriptively in Table S11.	ClinicalTrials.gov NCT03617731; EMA Sarclisa II/0035 assessment report
IMROZ	Eligible; not pooled	No complete registry serious-AE table. The EMA report supplies thresholded AF and cardiac-disorder data, with incomplete coverage of the protocol composites; retained descriptively in Table S11.	ClinicalTrials.gov NCT03319667; EMA Sarclisa II/0030 assessment report
IsKia (EMN24)	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT04483739; PMID 41942646 abstract
LEPUS	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT03234972; PMID 34108127 abstract
OCTANS	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT03217812; PMID 37024420 abstract
PREDATOR (MRD and BR cohorts)	Eligible; not pooled	No usable per-arm counts for the defined cardiac outcomes in the retrieved sources.	ClinicalTrials.gov NCT03697655; PMID 41704058 abstract; conference abstract

Trial	Category	Rationale	Source
IFM2017-03	Excluded (E2)	Dexamethasone stopped after 2 cycles in the daratumumab arm but continued until progression in the control arm (dexamethasone-sparing design, not a label-mandated premedication adjustment); backbones differ	ClinicalTrials.gov NCT03993912; PMID 41038184 abstract
Isaxomib combinations (NCT01415882), arms D vs E	Excluded (E2)	Arm E (ICd + daratumumab) cyclophosphamide cycles 1-12 vs arm D (ICd) cycles 1-18: backbone duration differs; the publication describes the D vs E comparison as indirect	ClinicalTrials.gov NCT01415882; PMID 42315418 abstract
Isatuximab during ASCT (NCT05346809)	Excluded (E5)	Mixed population (myeloma, non-Hodgkin and Hodgkin lymphoma; N=8); no myeloma-only per-arm data; not a prespecified sensitivity population	ClinicalTrials.gov NCT05346809; conference abstract
DETER-SMM (EAA173)	Ongoing (no results)	Smouldering myeloma (E5; sensitivity candidate,); recruiting, no results	ClinicalTrials.gov NCT03937635
DRAMMATIC	Ongoing (no results)	Meets I1-I3 (R vs D-R maintenance, first randomisation) but no results reported (registry: active, not recruiting; only design abstracts)	ClinicalTrials.gov NCT04071457; conference abstract
GMMG-HD9/DSMM XVIII maintenance	Ongoing (no results)	Iberdomide vs iberdomide + isatuximab maintenance meets I2; no results (active, not recruiting)	ClinicalTrials.gov NCT06216158
ITHACA	Ongoing (no results)	Smouldering myeloma (E5; sensitivity candidate,); randomised part has no results (published abstracts are the safety run-in)	ClinicalTrials.gov NCT04270409; conference abstract
Isa-VRd vs VRd, high-risk TIE (ChiCTR2600116772)	Ongoing (no results)	Isa-VRd vs VRd, high-risk TIE (ChiCTR2600116772, registered 2026); no results; may be the same trial as NCT07334535	trial registry record (ICTRP)
Isa-VRd vs VRd, high-risk TIE (NCT07334535)	Ongoing (no results)	Isa-VRd then Isa-VR vs VRd then VR; not yet recruiting	ClinicalTrials.gov NCT07334535
MagnetisMM-5	Ongoing (no results)	Arm A elranatamab vs arm B elranatamab + daratumumab meets I2; no randomised results reported (recruiting; part 1 safety lead-in is non-randomised)	ClinicalTrials.gov NCT05020236; conference abstract
RADAR (UK-MRA Myeloma XV)	Ongoing (no results)	Post-ASCT randomisations add isatuximab to identical backbones (high-risk RBorD+R vs RBorIsaD+RIsa; standard-risk MRD+ arms); no randomised results reported	PMID 36396306 (protocol paper) abstract; conference abstract

Previously known trials excluded before full-text stage (design): MajesTEC-3, BENEFIT, CCTG MY13 (E1); COLUMBA, IRAKLIA (E3); NCT03829371 (E4). Pooled analyses excluded as E7 are available from the authors.

Table S5. Risk of Bias (RoB 2) for Serious AF/Flutter and Cardiac Failure (Registry Data)

Comparison	Outcome	D1 Randomization	D2 Deviations	D3 Missing data	D4 Measurement	D5 Selection	Overall
ALCYONE	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
ALCYONE	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
ANDROMEDA	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
ANDROMEDA	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
APOLLO	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
APOLLO	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
AQUILA	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
AQUILA	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
AURIGA	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
AURIGA	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
CANDOR	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
CANDOR	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
CASSIOPEIA_P1	af_flutter	Some concerns	Low	Low	Some concerns	Low	Some concerns
CASSIOPEIA_P1	cardiac_failure	Some concerns	Low	Low	Low	Low	Some concerns
CASSIOPEIA_P2	af_flutter	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
CASSIOPEIA_P2	cardiac_failure	Some concerns	Low	Some concerns	Low	Low	Some concerns
CASTOR	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
CASTOR	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
CEPHEUS	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
CEPHEUS	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
GRIFFIN	af_flutter	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
GRIFFIN	cardiac_failure	Some concerns	Low	Some concerns	Low	Low	Some concerns
ICARIA	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
ICARIA	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
IKEMA	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
IKEMA	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns
LYNX	af_flutter	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
LYNX	cardiac_failure	Some concerns	Low	Some concerns	Low	Low	Some concerns
MAIA	af_flutter	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns

Comparison	Outcome	D1 Randomization	D2 Deviations	D3 Missing data	D4 Measurement	D5 Selection	Overall
MAIA	cardiac_failure	Some concerns	Low	Some concerns	Low	Low	Some concerns
PERSEUS	af_flutter	Some concerns	Low	Some concerns	Some concerns	Low	Some concerns
PERSEUS	cardiac_failure	Some concerns	Low	Some concerns	Low	Low	Some concerns
POLLUX	af_flutter	Low	Low	Some concerns	Some concerns	Low	Some concerns
POLLUX	cardiac_failure	Low	Low	Some concerns	Low	Low	Some concerns

Table S5 contains 34 outcome-specific assessments: 28 for the 14 main registry trials and six for ANDROMEDA, AQUILA and the second CASSIOPEIA randomization. All were rated as some concerns.

Table S6. Additional Trial Characteristics and Treatment Exposure

Comparison	Age (registry)	Median tx, mo (anti-CD38)	Median tx, mo (control)	CTCAE	Cut-off	Locators
MAIA	74.1 (mean)	47.5	22.6	NA	2021-10-21	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results text (safety population) / Control duration: Results text / Cutoff: Results text
ALCYONE	71.4 (mean)	14.74	11.99	NA (4 (eligibility text))	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: p.52 Patient exposure / Control duration: p.52 / CTCAE: p.24
CEPHEUS	70 (median)	56.3	34.3	NA (5 (eligibility text))	2024-05-07	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results text / Extended Data Table 1 / Control duration: Results text / Cutoff: Methods/Results / CTCAE: Methods
PERSEUS	58.4 (mean)	45.7	42.2	NA	2023-08-01	ClinicalTrials.gov AE and baseline tables; Intervention duration: Table S2 p.23 / Control duration: Table S2 p.23 / Cutoff: Results p.7
CASSIOPEIA_P1	56.6 (mean)	8.9	8.7	NA	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: p.49 Patient exposure / Control duration: p.49
GRIFFIN	58.2 (mean)	32.5	27.5	4.03	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: p.51 / Control duration: p.51 / CTCAE: Methods
GEM2017FIT	NA	NA	NA	NA	NA	NA
AURIGA	61 (mean)	30.7	20.6	NA	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results text (supplemental Table 1) / Control duration: Results text
CASTOR	63.4 (mean)	NA	NA	NA	NA	CT.gov Adverse Events module (seriousNumAtRisk of mapped groups; timeFrame; frequencyThreshold) / CT.gov Baseline Characteristics: Age, Continuous (total column)
POLLUX	64.4 (mean)	NA	NA	NA	NA	CT.gov Adverse Events module (seriousNumAtRisk of mapped groups; timeFrame; frequencyThreshold) / CT.gov Baseline Characteristics: Age, Continuous (total column)
CANDOR	63.4 (mean)	18.2	9.2	4.03	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results text: 79 weeks / Control duration: Results text: 40 weeks / CTCAE: Methods
APOLLO	66.0 (mean)	11.5	6.6	4.03	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: p.53 Patient exposure / Control duration: p.53 / CTCAE: p.60 table footnote
IKEMA	63.1 (mean)	21.7	14.3	4.03	2022-01-14	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results text: 94.0 weeks / Control duration: Results text: 61.9 weeks / Cutoff: Results text / CTCAE: Methods
ICARIA	65.9 (mean)	9.5	5.5	NA	NA	ClinicalTrials.gov AE and baseline tables; Intervention duration: p.93: 41 weeks / Control duration: p.93: 24 weeks

Comparison	Age (registry)	Median tx, mo (anti-CD38)	Median tx, mo (control)	CTCAE	Cut-off	Locators
LYNX	67 (mean)	8.8	8.1	NA	2022-08-15	ClinicalTrials.gov AE and baseline tables; Intervention duration: Results: Treatment exposure / Control duration: Results: Treatment exposure / Cutoff: Results

NA = not reported in the sources examined. Durations reported in weeks were converted to months ($\text{weeks} \times 12/52$).

Trial counts and denominators in the model tables describe all available comparisons, including double-zero trials; these trials do not contribute to MH ratio pooling. Interpretation of model outputs: all intervals and tests for reconstructed composites are nominal working-model quantities. They do not account for within-participant overlap between preferred terms. Tables S12–S14 give the added source counts and overlap scenarios.

Table S7. Primary Outcomes, Approximate Exposure and Sensitivity Analyses

Analysis	Label	Model	k	Events/N (anti-CD38 vs control)	Estimate (nominal 95% CI)	Heterogeneity
P_af_flutter	primary	MH	14	64/3344 vs 42/3134	RR 1.44 (0.97–2.13)	I ² = 49%
P_af_flutter	primary	GLMM binomial-normal UM.FS	14	64/3344 vs 42/3134	OR 1.85 (0.94–3.63)	I ² = 44%; τ^2 = 0.57
P_af_flutter_exposure	secondary	MH incidence rate ratio	12	52/2818 vs 39/2616	IRR 0.79 (0.52–1.20)	
P_af_flutter_exposure	secondary	Poisson GLMM UM.FS	12	52/2818 vs 39/2616	IRR 1.05 (0.50–2.23)	I ² = 47%; τ^2 = 0.63
P_af_flutter_S_broad	sensitivity	MH	14	72/3344 vs 48/3134	RR 1.42 (0.98–2.05)	I ² = 43%
P_af_flutter_S_broad	sensitivity	GLMM binomial-normal UM.FS	14	72/3344 vs 48/3134	OR 1.79 (0.97–3.31)	I ² = 44%; τ^2 = 0.48
P_af_flutter_S_lowerbound	sensitivity	MH	14	57/3344 vs 38/3134	RR 1.43 (0.94–2.15)	I ² = 40%
P_af_flutter_S_lowerbound	sensitivity	GLMM binomial-normal UM.FS	14	57/3344 vs 38/3134	OR 1.74 (0.91–3.34)	I ² = 38%; τ^2 = 0.47
P_af_flutter_S_no_phase2	sensitivity	MH	12	63/3202 vs 41/2989	RR 1.45 (0.98–2.15)	I ² = 49%
P_af_flutter_S_no_phase2	sensitivity	GLMM binomial-normal UM.FS	12	63/3202 vs 41/2989	OR 1.91 (0.94–3.87)	I ² = 48%; τ^2 = 0.59
P_af_flutter_S_no_regional	sensitivity	MH	14	64/3344 vs 42/3134	RR 1.44 (0.97–2.13)	I ² = 49%
P_af_flutter_S_no_regional	sensitivity	GLMM binomial-normal UM.FS	14	64/3344 vs 42/3134	OR 1.85 (0.94–3.63)	I ² = 44%; τ^2 = 0.57
P_af_flutter_S_plus_AL_SMM	sensitivity	MH	16	73/3730 vs 44/3518	RR 1.58 (1.08–2.29)	I ² = 49%
P_af_flutter_S_plus_AL_SMM	sensitivity	GLMM binomial-normal UM.FS	16	73/3730 vs 44/3518	OR 2.02 (1.07–3.80)	I ² = 42%; τ^2 = 0.54
P_cardiac_failure	primary	MH	14	56/3344 vs 56/3134	RR 0.88 (0.61–1.27)	I ² = 17%
P_cardiac_failure	primary	GLMM binomial-normal UM.FS	14	56/3344 vs 56/3134	OR 0.92 (0.56–1.53)	I ² = 33%; τ^2 = 0.24
P_cardiac_failure_exposure	secondary	MH incidence rate ratio	12	42/2818 vs 53/2616	IRR 0.44 (0.29–0.66)	
P_cardiac_failure_exposure	secondary	Poisson GLMM UM.FS	12	42/2818 vs 53/2616	IRR 0.44 (0.27–0.70)	I ² = 9%; τ^2 = 0.04
P_cardiac_failure_S_broad	sensitivity	MH	14	87/3344 vs 69/3134	RR 1.10 (0.81–1.50)	I ² = 25%
P_cardiac_failure_S_broad	sensitivity	GLMM binomial-normal UM.FS	14	87/3344 vs 69/3134	OR 1.11 (0.73–1.69)	I ² = 30%; τ^2 = 0.16
P_cardiac_failure_S_lowerbound	sensitivity	MH	14	30/3344 vs 40/3134	RR 0.66 (0.41–1.06)	I ² = 0%
P_cardiac_failure_S_lowerbound	sensitivity	GLMM binomial-normal UM.FS	14	30/3344 vs 40/3134	OR 0.65 (0.40–1.06)	I ² = 0%; τ^2 = 0.00
P_cardiac_failure_S_no_phase2	sensitivity	MH	12	56/3202 vs 53/2989	RR 0.93 (0.64–1.34)	I ² = 18%
P_cardiac_failure_S_no_phase2	sensitivity	GLMM binomial-normal UM.FS	12	56/3202 vs 53/2989	OR 1.00 (0.60–1.67)	I ² = 33%; τ^2 = 0.22
P_cardiac_failure_S_no_regional	sensitivity	MH	14	56/3344 vs 56/3134	RR 0.88 (0.61–1.27)	I ² = 17%
P_cardiac_failure_S_no_regional	sensitivity	GLMM binomial-normal UM.FS	14	56/3344 vs 56/3134	OR 0.92 (0.56–1.53)	I ² = 33%; τ^2 = 0.24
P_cardiac_failure_S_plus_AL_SMM	sensitivity	MH	16	73/3730 vs 68/3518	RR 0.97 (0.70–1.34)	I ² = 21%

Analysis	Label	Model	k	Events/N (anti-CD38 vs control)	Estimate (nominal 95% CI)	Heterogeneity
P_cardiac_failure_S_plus_AL_SMM	sensitivity	GLMM binomial-normal UM.FS	16	73/3730 vs 68/3518	OR 0.97 (0.62–1.52)	I ² = 32%; τ^2 = 0.21
P_af_flutter_S_AFonly	sensitivity	MH	14	56/3344 vs 38/3134	RR 1.40 (0.93–2.12)	I ² = 40%
P_af_flutter_S_AFonly	sensitivity	GLMM binomial-normal UM.FS	14	56/3344 vs 38/3134	OR 1.68 (0.87–3.22)	I ² = 39%; τ^2 = 0.47

Post hoc (PH_ptmap_v0.2), pre-amendment term map: af_flutter MH RR 1.44 (0.97-2.13); cardiac_failure MH RR 0.81 (0.56-1.18).

Leave-one-out (MH RR):

Outcome	Comparison omitted	RR (nominal 95% CI)
af_flutter	ALCYONE	1.36 (0.91–2.04)
af_flutter	APOLLO	1.44 (0.97–2.13)
af_flutter	AURIGA	1.42 (0.96–2.10)
af_flutter	CANDOR	1.37 (0.92–2.05)
af_flutter	CASSIOPEIA_P1	1.70 (1.12–2.57)
af_flutter	CASTOR	1.30 (0.87–1.94)
af_flutter	CEPHEUS	1.53 (1.00–2.34)
af_flutter	GRIFFIN	1.42 (0.96–2.10)
af_flutter	ICARIA	1.40 (0.94–2.09)
af_flutter	IKEMA	1.38 (0.93–2.05)
af_flutter	LYNX	1.48 (1.00–2.19)
af_flutter	MAIA	1.97 (1.21–3.21)
af_flutter	PERSEUS	1.27 (0.84–1.91)
af_flutter	POLLUX	1.40 (0.93–2.10)
cardiac_failure	ALCYONE	0.88 (0.59–1.30)
cardiac_failure	APOLLO	0.88 (0.61–1.27)
cardiac_failure	AURIGA	0.88 (0.61–1.27)
cardiac_failure	CANDOR	0.95 (0.64–1.41)
cardiac_failure	CASSIOPEIA_P1	0.92 (0.63–1.35)
cardiac_failure	CASTOR	0.84 (0.58–1.23)
cardiac_failure	CEPHEUS	0.86 (0.59–1.25)

Outcome	Comparison omitted	RR (nominal 95% CI)
cardiac_failure	GRIFFIN	0.88 (0.61–1.27)
cardiac_failure	ICARIA	0.88 (0.61–1.27)
cardiac_failure	IKEMA	0.86 (0.58–1.26)
cardiac_failure	LYNX	0.93 (0.64–1.34)
cardiac_failure	MAIA	1.05 (0.69–1.59)
cardiac_failure	PERSEUS	0.86 (0.59–1.25)
cardiac_failure	POLLUX	0.72 (0.49–1.07)

Table S8. Original Subgroup Analyses (Primary Outcomes)

Outcome	Variable	Level	k	MH RR (nominal 95% CI)	P for interaction
af_flutter	setting_group	NDMM-TE	3	1.33 (0.56-3.15)	
af_flutter	setting_group	NDMM-TIE	3	0.97 (0.57-1.64)	
af_flutter	setting_group	RRMM	7	3.46 (1.40-8.54)	
af_flutter	setting_group	TEST FOR SUBGROUP DIFFERENCES	14		0.347
af_flutter	backbone_class	IMiD	5	1.04 (0.59-1.86)	
af_flutter	backbone_class	PI	5	4.43 (1.51-12.99)	
af_flutter	backbone_class	PI+IMiD	4	1.18 (0.61-2.28)	
af_flutter	backbone_class	TEST FOR SUBGROUP DIFFERENCES	14		0.174
af_flutter	carfilzomib	no	11	1.35 (0.90-2.02)	
af_flutter	carfilzomib	yes	3	3.04 (0.62-14.92)	
af_flutter	carfilzomib	TEST FOR SUBGROUP DIFFERENCES	14		0.642
af_flutter	antibody	daratumumab	12	1.34 (0.90-2.01)	
af_flutter	antibody	isatuximab	2	5.36 (0.60-48.14)	
af_flutter	antibody	TEST FOR SUBGROUP DIFFERENCES	14		0.338
af_flutter	route	IV	7	1.20 (0.75-1.93)	
af_flutter	route	SC	5	1.78 (0.83-3.83)	
af_flutter	route	TEST FOR SUBGROUP DIFFERENCES	12		0.887
af_flutter	treatment_design_group	continuous	12	1.67 (1.10-2.53)	
af_flutter	treatment_design_group	fixed	2	0.29 (0.06-1.38)	
af_flutter	treatment_design_group	TEST FOR SUBGROUP DIFFERENCES	14		0.058
af_flutter	ctcae_group	unknown	8	1.25 (0.79-1.97)	
af_flutter	ctcae_group	v4.x	6	2.04 (0.96-4.34)	
af_flutter	ctcae_group	TEST FOR SUBGROUP DIFFERENCES	14		0.456
cardiac_failure	setting_group	NDMM-TE	3	0.75 (0.26-2.15)	
cardiac_failure	setting_group	NDMM-TIE	3	0.69 (0.40-1.22)	
cardiac_failure	setting_group	RRMM	7	1.17 (0.67-2.03)	
cardiac_failure	setting_group	TEST FOR SUBGROUP DIFFERENCES	14		0.647

Outcome	Variable	Level	k	MH RR (nominal 95% CI)	P for interaction
cardiac_failure	backbone_class	IMiD	5	1.00 (0.54-1.84)	
cardiac_failure	backbone_class	PI	5	0.79 (0.46-1.35)	
cardiac_failure	backbone_class	PI+IMiD	4	0.90 (0.39-2.12)	
cardiac_failure	backbone_class	TEST FOR SUBGROUP DIFFERENCES	14		0.732
cardiac_failure	carfilzomib	no	11	1.00 (0.65-1.54)	
cardiac_failure	carfilzomib	yes	3	0.61 (0.30-1.25)	
cardiac_failure	carfilzomib	TEST FOR SUBGROUP DIFFERENCES	14		0.240
cardiac_failure	antibody	daratumumab	12	0.85 (0.58-1.26)	
cardiac_failure	antibody	isatuximab	2	1.08 (0.39-3.00)	
cardiac_failure	antibody	TEST FOR SUBGROUP DIFFERENCES	14		0.800
cardiac_failure	route	IV	7	0.85 (0.56-1.30)	
cardiac_failure	route	SC	5	0.87 (0.32-2.38)	
cardiac_failure	route	TEST FOR SUBGROUP DIFFERENCES	12		0.819
cardiac_failure	treatment_design_group	continuous	12	0.92 (0.63-1.35)	
cardiac_failure	treatment_design_group	fixed	2	0.50 (0.13-2.00)	
cardiac_failure	treatment_design_group	TEST FOR SUBGROUP DIFFERENCES	14		0.448
cardiac_failure	ctcae_group	unknown	8	0.91 (0.55-1.48)	
cardiac_failure	ctcae_group	v4.x	6	0.85 (0.49-1.47)	
cardiac_failure	ctcae_group	TEST FOR SUBGROUP DIFFERENCES	14		0.796

Subgroup levels with fewer than 2 comparisons are not estimated. Route analysed within daratumumab trials only. All composite model intervals and P values are working quantities conditional on reconstructed counts; they do not incorporate within-person term dependence.

Table S9. MedDRA Preferred-Term Map (After Amendments A005/A005a)

Outcome	Definition	Preferred terms
af	narrow	Atrial fibrillation
af_flutter	narrow	Atrial fibrillation; Atrial flutter
af_flutter	broad	Atrial tachycardia; Supraventricular tachycardia; Supraventricular tachyarrhythmia; Atrial fibrillation; Atrial flutter; Arrhythmia supraventricular*
cardiac_failure	narrow	Cardiac failure; Cardiac failure congestive; Cardiac failure acute; Cardiac failure chronic; Acute left ventricular failure; Left ventricular failure; Right ventricular failure; Cardiogenic shock; Cardiac failure high output; Cardiopulmonary failure*; Cardiovascular insufficiency*; Heart failure*
cardiac_failure	broad	Cardiac failure; Cardiac failure congestive; Cardiac failure acute; Cardiac failure chronic; Acute left ventricular failure; Left ventricular failure; Right ventricular failure; Cardiogenic shock; Cardiac failure high output; Ejection fraction decreased; Left ventricular dysfunction; Cardiomyopathy; Cardiomyopathy congestive; Pulmonary oedema; Acute pulmonary oedema; Cardiopulmonary failure*; Cardiovascular insufficiency*; Diastolic dysfunction*; Heart failure*; Hypertrophic cardiomyopathy*; Stress cardiomyopathy*; Systolic dysfunction*
any_cardiac	narrow	SOC:Cardiac disorders
ihd	narrow	Myocardial infarction; Acute myocardial infarction; Acute coronary syndrome; Angina pectoris; Angina unstable; Coronary artery disease; Coronary artery occlusion; Coronary artery stenosis; Myocardial ischaemia; Arteriosclerosis coronary artery*; Coronary artery insufficiency*; Microvascular coronary artery disease*
ihd	broad	Myocardial infarction; Acute myocardial infarction; Acute coronary syndrome; Angina pectoris; Angina unstable; Coronary artery disease; Coronary artery occlusion; Coronary artery stenosis; Myocardial ischaemia; Troponin increased; Troponin I increased; Troponin T increased; Arteriosclerosis coronary artery*; Arteriospasm coronary*; Coronary artery insufficiency*; Microvascular coronary artery disease*
hypertension	narrow	Hypertension; Hypertensive crisis; Hypertensive emergency; Hypertensive urgency
hypertension	broad	Hypertension; Hypertensive crisis; Hypertensive emergency; Hypertensive urgency; Blood pressure increased; Hypertensive heart disease*
other_arrhythmia	narrow	Ventricular tachycardia; Ventricular fibrillation; Supraventricular tachycardia; Atrioventricular block complete; Atrioventricular block second degree; Bradycardia; Sinus bradycardia; Sick sinus syndrome; Sinus node dysfunction; Arrhythmia; Atrioventricular block*; Bradyarrhythmia*; Ventricular arrhythmia*
other_arrhythmia	broad	Ventricular tachycardia; Ventricular fibrillation; Supraventricular tachycardia; Atrioventricular block complete; Atrioventricular block second degree; Bradycardia; Sinus bradycardia; Sick sinus syndrome; Sinus node dysfunction; Arrhythmia; Tachycardia; Sinus tachycardia; Palpitations; Atrioventricular block*; Bradyarrhythmia*; Extrasystoles*; Paroxysmal arrhythmia*; Sinus arrhythmia*; Ventricular arrhythmia*; Ventricular extrasystoles*
vte	narrow	Deep vein thrombosis; Pulmonary embolism; Venous thrombosis; Venous thrombosis limb; Jugular vein thrombosis; Portal vein thrombosis; Embolism venous; Pulmonary artery thrombosis*; Pulmonary thrombosis*; Subclavian vein thrombosis*; Vena cava thrombosis*
vte	broad	Deep vein thrombosis; Pulmonary embolism; Venous thrombosis; Venous thrombosis limb; Jugular vein thrombosis; Portal vein thrombosis; Embolism venous; Thrombosis; Device related thrombosis; Embolism*; Pulmonary artery thrombosis*; Pulmonary thrombosis*; Retinal vein thrombosis*; Subclavian vein thrombosis*; Thromboembolic event*; Thrombophlebitis*; Vena cava thrombosis*
ate	narrow	Myocardial infarction; Acute myocardial infarction; Ischaemic stroke; Cerebrovascular accident; Cerebral infarction; Transient

Outcome	Definition	Preferred terms
		ischaemic attack; Peripheral arterial occlusive disease; Arterial thrombosis; Embolism arterial; Basal ganglia infarction*; Brain stem infarction*; Brain stem stroke*; Cerebellar infarction*; Cerebellar stroke*; Cerebral ischaemia*; Embolic cerebral infarction*; Embolic stroke*; Femoral artery embolism*; Ischaemic cerebral infarction*; Peripheral artery thrombosis*; Peripheral ischaemia*; Retinal artery embolism*; Vertebrobasilar stroke*
ate	broad	Atrial thrombosis*; Stroke*; Myocardial infarction*; Acute myocardial infarction*; Ischaemic stroke*; Cerebrovascular accident*; Cerebral infarction*; Transient ischaemic attack*; Peripheral arterial occlusive disease*; Arterial thrombosis*; Embolism arterial*; Basal ganglia infarction*; Brain stem infarction*; Brain stem stroke*; Cerebellar infarction*; Cerebellar stroke*; Cerebral ischaemia*; Embolic cerebral infarction*; Embolic stroke*; Femoral artery embolism*; Ischaemic cerebral infarction*; Peripheral artery thrombosis*; Peripheral ischaemia*; Retinal artery embolism*; Vertebrobasilar stroke*

*Terms added to the original map. Both map versions are available from the authors; historical approval metadata are not used to establish prospective specification.

Table S10. Secondary Outcomes (Registry Serious and Non-Serious Layers)

Analysis	Label	Model	k	Events/N (anti-CD38 vs control)	Estimate (nominal 95% CI)	Heterogeneity
S_any_cardiac_L1	secondary	MH	14	285/3344 vs 194/3134	RR 1.33 (1.12–1.58)	I ² = 57%
S_any_cardiac_L1	secondary	GLMM binomial-normal UM.FS	14	285/3344 vs 194/3134	OR 1.48 (1.08–2.02)	I ² = 51%; τ^2 = 0.16
S_ihd_L1	secondary	MH	14	90/3344 vs 51/3134	RR 1.56 (1.11–2.18)	I ² = 0%
S_ihd_L1	secondary	GLMM binomial-normal UM.FS	14	90/3344 vs 51/3134	OR 1.58 (1.11–2.25)	I ² = 0%; τ^2 = 0.00
S_hypertension_L1	secondary	MH	14	17/3344 vs 9/3134	RR 1.44 (0.68–3.08)	I ² = 29%
S_hypertension_L1	secondary	GLMM binomial-normal UM.FS	14	17/3344 vs 9/3134	OR 1.63 (0.60–4.39)	I ² = 20%; τ^2 = 0.42
S_other_arrhythmia_L1	secondary	MH	14	23/3344 vs 14/3134	RR 1.60 (0.82–3.12)	I ² = 13%
S_other_arrhythmia_L1	secondary	GLMM binomial-normal UM.FS	14	23/3344 vs 14/3134	OR 1.71 (0.77–3.80)	I ² = 10%; τ^2 = 0.15
S_vte_L1	secondary	MH	14	103/3344 vs 113/3134	RR 0.85 (0.65–1.10)	I ² = 0%
S_vte_L1	secondary	GLMM binomial-normal UM.FS	14	103/3344 vs 113/3134	OR 0.84 (0.62–1.14)	I ² = 12%; τ^2 = 0.04
S_ate_L1	secondary	MH	14	98/3344 vs 67/3134	RR 1.37 (1.01–1.86)	I ² = 29%
S_ate_L1	secondary	GLMM binomial-normal UM.FS	14	98/3344 vs 67/3134	OR 1.49 (0.99–2.24)	I ² = 24%; τ^2 = 0.14
S_af_flutter_L2	secondary	MH	7	95/1537 vs 71/1544	RR 1.34 (1.00–1.81)	I ² = 59%
S_af_flutter_L2	secondary	GLMM binomial-normal UM.FS	7	95/1537 vs 71/1544	OR 1.65 (0.91–2.97)	I ² = 57%; τ^2 = 0.31
S_cardiac_failure_L3_any_grade	secondary	MH	2	19/196 vs 17/197	RR 1.12 (0.60–2.10)	I ² = 4%
S_cardiac_failure_L3_any_grade	secondary	GLMM binomial-normal UM.FS	2	19/196 vs 17/197	OR 1.14 (0.57–2.26)	I ² = 0%; τ^2 = 0.00
S_hypertension_L2	secondary	MH	13	522/3195 vs 264/2984	RR 1.64 (1.43–1.88)	I ² = 65%
S_hypertension_L2	secondary	GLMM binomial-normal UM.FS	13	522/3195 vs 264/2984	OR 1.85 (1.43–2.40)	I ² = 56%; τ^2 = 0.12
S_other_arrhythmia_L2	secondary	MH	2	10/195 vs 14/200	RR 0.73 (0.33–1.61)	I ² = 54%
S_other_arrhythmia_L2	secondary	GLMM binomial-normal UM.FS	2	10/195 vs 14/200	OR 0.72 (0.28–1.89)	I ² = 4%; τ^2 = 0.02
S_vte_L2	secondary	MH	5	57/933 vs 64/882	RR 0.85 (0.60–1.20)	I ² = 0%
S_vte_L2	secondary	GLMM binomial-normal UM.FS	5	57/933 vs 64/882	OR 0.84 (0.58–1.22)	I ² = 0%; τ^2 = 0.00

L2 = ClinicalTrials.gov non-serious ("other") AE table, truncated at a reporting threshold; trials in which no term of an outcome appeared were treated as missing, not zero.

Table S11. Publication and Regulatory Data

Comparison	Outcome	Layer	Severity	Bound	Events anti-CD38	N	Events control	N	Source	Locator
IMROZ	af	L3	any_grade	exact	21	263	16	181	EMA Sarclisa EMEA/H/C/004977/II/0030 assessment report (IMROZ, EFC12522)	Table 23 p.64 (TEAEs >=5%, patient-years analysis)
IMROZ	af_flutter	L3	any_grade	lower	21	263	16	181	EMA Sarclisa EMEA/H/C/004977/II/0030 assessment report (IMROZ, EFC12522)	Table 23 p.64
IMROZ	any_cardiac	L3	any_grade	exact	59	263	42	181	EMA Sarclisa EMEA/H/C/004977/II/0030 assessment report (IMROZ, EFC12522)	Table 23 p.64; text p.72
IMROZ	af	L3	serious	exact	8	263	8	181	EMA Sarclisa EMEA/H/C/004977/II/0030 assessment report (IMROZ, EFC12522)	Table 24 p.65 (treatment-emergent SAEs >=2%)
IMROZ	cardiac_failure	L3	serious	lower	1	263	6	181	EMA Sarclisa EMEA/H/C/004977/II/0030 assessment report (IMROZ, EFC12522)	Table 24 p.65
GEM2017FIT	cardiac_failure	L3	any_grade	exact	16	153	12	154	Mateos MV et al. Lancet Haematol 2025 (GEM2017FIT; PMID 40769684)	Table 3 (Haematological and non-haematological toxicities), row Cardiac failure, sum of grade 1-2, 3, 4, 5 columns
GEM2017FIT	cardiac_failure	L3	grade3plus	exact	8	153	3	154	Mateos MV et al. Lancet Haematol 2025 (GEM2017FIT; PMID 40769684)	Table 3, Cardiac failure grade 3+4+5
GEM2017FIT	hypertension	L3	any_grade	exact	17	153	31	154	Mateos MV et al. Lancet Haematol 2025 (GEM2017FIT; PMID 40769684)	Table 3, Hypertension, sum of grade columns
GEM2017FIT	hypertension	L3	grade3plus	exact	3	153	8	154	Mateos MV et al. Lancet Haematol 2025 (GEM2017FIT; PMID 40769684)	Table 3, Hypertension grade 3+4+5
FELZ_RD	af	L3	any_grade	exact	3	192	1	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3 (TEAEs, safety analysis set), Atrial fibrillation, sum of grade columns
FELZ_RD	af_flutter	L3	any_grade	lower	3	192	1	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3, Atrial fibrillation (atrial flutter not listed)
FELZ_RD	af	L3	grade3plus	exact	1	192	0	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3, Atrial fibrillation grade 3+4+5
FELZ_RD	cardiac_failure	L3	any_grade	lower	4	192	1	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3, Cardiac failure (single PT; other cardiac-failure PTs not listed)
FELZ_RD	cardiac_failure	L3	grade3plus	lower	2	192	1	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3, Cardiac failure grade 3+4+5
FELZ_RD	hypertension	L3	any_grade	lower	6	192	3	97	Felzartamab phase 3 (TJ202001MMY301), Lancet Haematol 2026 (PMID 42822478)	Table 3, Hypertension (single PT)
LYNX	cardiac_failure	L3	any_grade	exact	3	43	5	43	LYNX, Leuk Lymphoma 2025 (PMID 41041907)	Results text, safety: cardiac failure most common cardiac event
LYNX	any_cardiac	L3	any_grade	exact	5	43	5	43	LYNX, Leuk Lymphoma 2025 (PMID 41041907)	Results text, safety: patients with >=1 cardiac event

Comparison	Outcome	Layer	Severity	Bound	Events anti-CD38	N	Events control	N	Source	Locator
HD7_P1	any_cardiac	L3	grade3plus	exact	13	330	5	328	Goldschmidt H et al. Lancet Haematol 2022 (GMMG-HD7 part 1; PMID 36328040)	Table 2, Cardiac disorders (SOC), grade 3 or 4 column
PERSEUS	af	L3	serious	exact	9	351	2	347	Sonneveld P et al. N Engl J Med 2024 supplementary appendix (PMID 38084760)	Appendix Table S4 (serious adverse events), Atrial fibrillation

Methods S3. Source Reconstruction and Composite Overlap

Registry result tables were processed using the arm map and outcome definitions, with safety denominators taken from the mapped event groups. The resulting counts were checked against the source tables and analysis dataset. A separate computational reconstruction reproduced all 224 first-randomization outcome/definition rows. CASSIOPEIA part 2 was analyzed separately. Source URLs, record update dates and SHA-256 checksums are available from the authors.

For each trial and arm, L is the largest single-term participant count and U is the sum of term counts capped at the arm denominator. The number of unique participants with the composite lies between L and U, subject to source completeness. The MH point calculation increases with each intervention count and decreases with each control count. Its feasible extremes therefore use intervention L/control U and intervention U/control L. These are deterministic ranges over possible overlap patterns, not confidence intervals. They do not incorporate sampling error or identify the actual overlap. Ordinary binomial model intervals applied to reconstructed composites are retained as nominal reference intervals only.

Ischemic single-term analyses were added on 17 October 2026 as exploratory checks. They use participants affected by one preferred term, which avoids overlap across different terms within that endpoint. No individual term establishes the complete clinical composite. Multiple single-term analyses were descriptive and were not treated as independent confirmatory tests.

Table S12. Ischemic Counts by Trial and Composite Construction

Trial	Safety N anti-CD38/control	Largest term anti-CD38/control	Summed terms anti-CD38/control
MAIA	364/365	3/5	15/14
ALCYONE	346/354	5/1	10/2
CEPHEUS	197/195	3/2	8/4
PERSEUS	351/347	3/4	9/4
CASSIOPEIA_P1	536/538	1/1	3/2
GRIFFIN	99/102	0/1	0/1
AURIGA	96/98	1/0	1/0
CASTOR	243/237	2/2	6/2
POLLUX	283/281	3/4	8/8
CANDOR	308/153	4/2	15/6
APOLLO	149/150	1/1	1/1
IKEMA	177/122	2/2	6/4
ICARIA	152/149	3/2	7/3
LYNX	43/43	1/0	1/0

Totals: 32/27 using the largest term within each trial arm; 90/51 using summed terms. Denominators: 3,344/3,134. Different arms may have different largest terms. Neither construction identifies unique affected participants. Preferred-term components and all trial/outcome counts are available from the authors.

Table S13. Exploratory Individual-Term Analyses

Preferred term	Affected anti-CD38	Affected control	MH RR (95% CI)
Acute Coronary Syndrome	12	10	1.07 (0.47–2.48)
Acute Myocardial Infarction	23	10	2.00 (0.96–4.17)
Angina Pectoris	13	6	1.84 (0.73–4.68)
Angina Unstable	3	2	1.49 (0.25–9.03)
Arteriosclerosis Coronary Artery	3	1	2.10 (0.29–15.31)
Atrial fibrillation	56	38	1.40 (0.93–2.12)
Cardiac failure	26	39	0.58 (0.35–0.95)
Coronary Artery Disease	9	2	4.33 (0.92–20.48)
Coronary Artery Insufficiency	0	2	No finite two-sided estimate
Coronary Artery Occlusion	1	0	No finite two-sided estimate
Coronary Artery Stenosis	4	0	No finite two-sided estimate
Microvascular coronary artery disease	1	0	No finite two-sided estimate
Myocardial Infarction	15	17	0.82 (0.41–1.65)
Myocardial Ischaemia	6	1	4.66 (0.46–47.63)

Each term was evaluated across the same 14 first-randomization registry trials. A term absent from a complete serious-event table was counted as zero. These are individual preferred terms, not complete composites. No continuity correction was applied to pooled calculations. Cases with an empty arm-wide numerator do not yield a finite two-sided interval by this calculation. Nominal single-term intervals are not adjusted for multiple comparisons.

Table S14. Composite Overlap Scenarios

Outcome	Summed terms ratio (nominal CI)	Largest terms ratio (nominal CI)	Feasible MH point-ratio range
af_flutter	1.44 (0.97–2.13)	1.43 (0.94–2.15)	1.29–1.59
cardiac_failure	0.88 (0.61–1.27)	0.66 (0.41–1.06)	0.47–1.24
any_cardiac	1.33 (1.12–1.58)	0.96 (0.67–1.36)	0.29–4.32
ihd	1.56 (1.11–2.18)	1.08 (0.65–1.79)	0.56–2.98
hypertension	1.44 (0.68–3.08)	1.56 (0.66–3.69)	1.20–1.89
other_arrhythmia	1.60 (0.82–3.12)	1.67 (0.69–4.04)	0.95–2.79
vte	0.85 (0.65–1.10)	0.88 (0.64–1.21)	0.59–1.26
ate	1.37 (1.01–1.86)	1.34 (0.80–2.23)	0.50–3.66

The final column is not a confidence interval. It varies the unknown overlap independently between arms within each trial, without sampling uncertainty. The first two columns show nominal working-model intervals conditional on each construction; they are not overlap-adjusted intervals for unique-patient risk.

Table S15. CASSIOPEIA Maintenance Randomization, Reported Separately

Outcome	N anti-CD38/control	Largest-term count	Summed-term count
af_flutter	440/444	3/1	3/2
cardiac_failure	440/444	0/1	0/1

This second randomization reuses participants from CASSIOPEIA part 1. It is not added to the 14 first-randomization comparisons. No pooled 15-comparison estimate combining both randomizations is presented.