# Clinical Outcomes Associated With Anti-CD38 Retreatment in Relapsed/Refractory Multiple Myeloma: A Review of the Literature

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This targeted literature review suggests that anti-CD38 retreatment produces only limited clinical benefit and highlights an unmet need for new treatment options for anti-CD38-exposed patients with RRMM

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## Aims

- This targeted literature review aimed to explore the clinical effectiveness of retreatment with anti-CD38 agents in patients with relapsed/refractory multiple myeloma (RRMM)

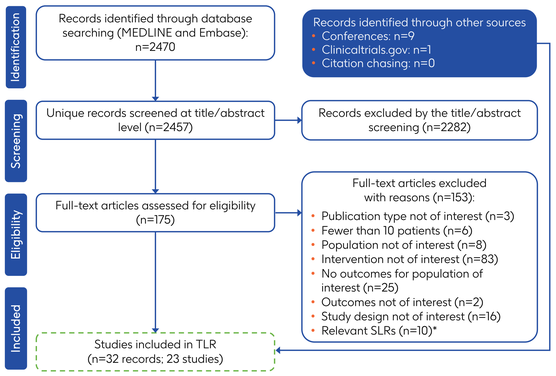
## Study design

- The following sources were searched for records published in English
  - Embase, MEDLINE, and MEDLINE In-Process (database inception–July 10, 2023)
  - Conference proceedings from American Association for Cancer Research, American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, and European Society for Medical Oncology (2016–August 21, 2023)
  - Clinicaltrials.gov
- Publications were screened using the predefined Population, Intervention, Comparison, Outcomes, Study design (PICOS) criteria. To be eligible for inclusion in the review, publications must have reported observational/interventional studies that assessed clinical outcomes (progression-free survival [PFS], overall survival [OS], or overall response rate [ORR]) of anti-CD38-based retreatment in adults with RRMM
- Data were extracted from eligible publications by one reviewer, then validated by a second reviewer. The extracted evidence was assessed using narrative synthesis

## Results

- The search and screening process identified 32 records that met eligibility criteria (**Figure 1**). These publications collectively reported on 23 unique studies of varying population size, median follow-up, and patient clinical characteristics (**Table 1**); 6 of the studies were clinical trials (2 randomized controlled trials [RCTs] and 4 single-arm studies), and 17 were real-world evidence studies (RWE), of which 1 was prospective
- Most studies evaluated retreatment with daratumumab, but 2 RCTs reported results for isatuximab following previous daratumumab therapy

Figure 1: **PRISMA diagram for identified studies**




*Relevant SLRs were used for citation identification but were not included in this review to avoid double-counting data cited in both primary study records and the published SLRs

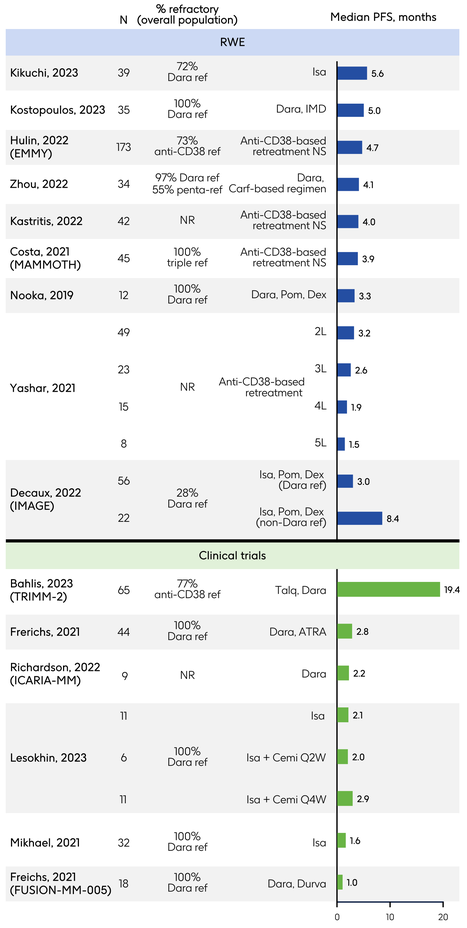
Table 1: **Summary of identified publications**

| Study | Publication | Anti-CD38-based retreatment regimen* | Median follow-up duration (range), months | Median (range) prior LOTs | % refractory (overall population) |
|---|---|---|---|---|---|
| **Observational study** | | | | | |
| *Retrospective* | Abdallah, 2023[1] | Dara-based therapy | 19.5 (10.3–25.9) | NR | 100% Dara ref |
| *Retrospective* | Atrash, 2021[2] | Dara | NR | NR | NR |
| *Retrospective* | Girvan, 2022[3] | Dara-based therapy | NR | NR | 100% Dara ref |
| EMMY *Prospective* | Hulin, 2022[4] | Anti-CD38-based retreatment NS | NR | NR | 73% anti-CD38 ref |
| IMAGE *Retrospective* | Decaux, 2022[5] | Isa + Pom + Dex: Dara ref vs Dara non-ref | 14.2 (NR) | NR | 28% Dara ref |
| *Retrospective* | Kastritis, 2022[6] | Anti-CD38-based retreatment NS | NR | 2 (1–10) | NR |
| *Retrospective* | Kikuchi, 2023[7] | Isa | 8.7 (0.1–25) | 4 (1–8) | 72% Dara ref |
| *Retrospective* | Kostopoulos, 2023[8]<br>Fotiou, 2021[9]<br>Fotiou, 2020[10] | Dara + IMD | NR | 3 (1–16)<br>NR | 100% Dara ref<br>NR |
| *Retrospective* | Leblanc, 2022[11] | Anti-CD38-based retreatment NS | 21 (NR) | 4 (2–10) | NR |
| MAMMOTH *Retrospective* | Gandhi, 2019[12] | Dara-based therapy | 10.6 (1.9–42.3) | 5 (2–17) | 100% anti-CD38 ref |
| | Costa, 2021[13] | | NR | 5 (3–17) | 100% triple ref |
| *Retrospective* | Nooka, 2019[14] | Dara + Pom + Dex | 41 (NR) | 6.5 (3–13) | 100% Dara ref |
| *Retrospective* | Nooka, 2016[15] | Dara + Pom + Dex | Dara and Pom naïve: 14 months<br>Dara and Pom ref: 5 months<br>Dara ref: 3 months | Dara and Pom naive: 3 (1–7)<br>Dara and Pom ref: 6.5 (3–13)<br>Dara ref: 6 (3–13) | NR |
| *Retrospective* | Regidor, 2021[16] | Ven + Bor + Dara + Dex | NR | 7 (2–16) | NR |
| *Retrospective* | Szabo, 2022[17]<br>Szabo, 2021[18] | Dara | 9.2 (1.8–17.6)‡ | 3 (0–15) | NR |
| *Retrospective* | Reyes, 2022[19] | Anti-CD38-based retreatment NS | 21.3 (NR) | 7 (1–14) | NR |
| *Retrospective* | Yashar, 2021[20] | Anti-CD38-based retreatment NS | NR | NR | NR |
| *Retrospective* | Zhou, 2020[21] | Pom + Bor + Dox + Dex + Dara | NR | 4 (1–10) | 100% penta-ref |
| *Retrospective* | Zhou, 2022[22] | Dara, Carf-based regimen | NR | 5 (2–12) | 97% Dara ref 55% penta-ref |
| **RCT** | | | | | |
| ICARIA-MM *Phase 3* | Richardson, 2022[23,24]<br>Perrot, 2021[25]<br>Richardson, 2021[26] | Dara† | 35.3 (33.5–37.4)‡ | 3 (2–4)‡ | NR |
| *NCT03194867 Phase 1/2* | Lesokhin, 2023[27] | Isa | 10.0 (8.5–10.9)§ | >3 | 100% Dara ref |
| **Single-arm trial** | | | | | |
| TRIMM-2 *Phase 1* | Bahlis, 2023[28] | Dara + Talq | 11.5 (1.0–27.3) | >3 | 77% anti-CD38 ref |
| *NCT02751255 Phase 1/2* | Frerichs, 2021[29] | Dara + ATRA | NR | 5 (3–12) | 100% Dara ref |
| FUSION-MM-005 *Phase 2* | Frerichs, 2021[30]<br>Clinicaltrials.gov[31] | Dara + Durva | 2.9 (0.13–5.8) | 5 (5–16) | 100% Dara ref |
| *NCT02514668 Phase 1/2* | Mikhael, 2021[32] | Isa | 1.9 (0.8–17) | 7 (2–14) | 100% Dara ref |

*Only anti-CD38-based regimens used for retreatment are shown; therefore, subgroup details are presented for some studies. †Detailed here is the subgroup analysis of patients treated with Dara after receiving Isa + Pom + Dex or Pom + Dex. ‡Median (IQR). §Median (95% CI)

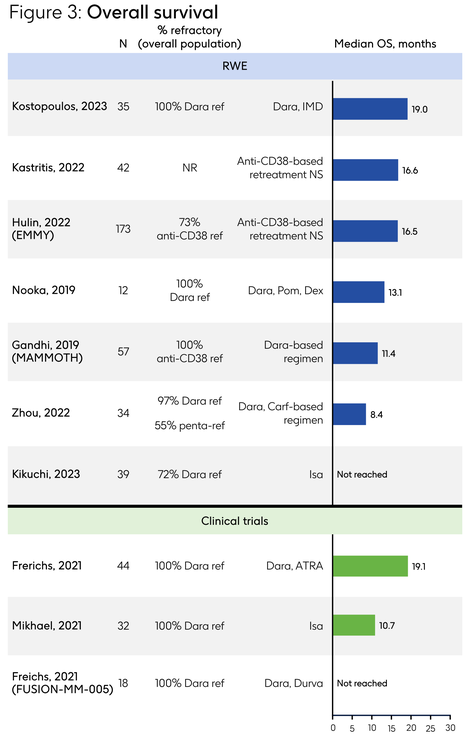
- PFS was reported in 9 RWE, and the median ranged from 1.5 months (95% CI not reported [NR]) to 8.4 months (95% CI 2.8–not estimable [NE]) (**Figure 2**); the longest median PFS was reported in the IMAGE RWE in patients exposed to but not refractory to daratumumab, while those refractory had a median PFS of 3.0 months (95% CI 2.4–4.8)
  - PFS was shorter in RWE with >95% anti-CD38-refractory patients (3.3 months [95% CI 0–6.93] to 5 months [95% CI 1.5–8.4])
- PFS was reported in 6 clinical trials, and the median was <3 months in all of these studies except for TRIMM-2, where a novel therapy, talquetamab, was used in addition to daratumumab (median PFS 19.4 months)

Figure 2: **Progression-free survival**




- Across the 7 RWE that reported OS with anti-CD38-based retreatment, the median ranged from 8.4 months (95% CI 6.7–10.0) to 19 months (95% CI 13.5–24.5) (**Figure 3**)
- In the 3 clinical trials that reported OS, the median ranged from 10.7 months (95% CI 8.0–19.0) to 19.1 months (95% CI 15.0–23.1)

Figure 3: **Overall survival**




- ORR was reported in 13 RWE and ranged from 25–90%
  - An ORR of <50% with anti-CD38 retreatment was reported in 8 of the 13 RWE (62%)
  - ORR was generally lower in RWE that had populations with more prior lines of therapy and those with higher proportions of anti-CD38-refractory patients
  - The 90% ORR was reported among a subgroup of 10 penta-refractory patients who were treated with pomalidomide, bortezomib, doxorubicin, dexamethasone, and daratumumab. Most of these patients had a stem cell transplant in a previous line
- Across the 6 clinical trials, ORR varied from 0% (FUSION-MM-005, Lesokhin, 2023, and Mikhael, 2021) to 75% (TRIMM-2). High variability in ORR may be related to differences in study populations (eg, presence of extramedullary disease)
  - The 75% ORR was reported with the unlicensed talquetamab + daratumumab combination, and this ORR is similar to that associated with talquetamab monotherapy in RRMM[33]

## Background

- Multiple myeloma (MM) is an incurable and debilitating hematologic malignancy characterized by uncontrolled proliferation of clonal plasma cells[34]
- MM treatment has significantly improved with the introduction of novel therapies; however, most patients relapse and require multiple lines of therapy[35]
- With the availability of first-line daratumumab + lenalidomide + dexamethasone (MAIA regimen)[36] and daratumumab + bortezomib + lenalidomide + dexamethasone (PERSEUS regimen),[37] the proportion of patients who are refractory to anti-CD38 agents at second line of therapy is likely to increase
- There is a need to evaluate the clinical utility of retreatment with an anti-CD38 monoclonal antibody in patients who are refractory to such therapy, as a recent study of daratumumab retreatment in daratumumab-exposed patients was stopped early following futility analysis[38]

## Conclusions

Multiple studies have evaluated anti-CD38 retreatment in RRMM, with highly variable patient populations and outcomes

The RWE and clinical trial data available suggest that anti-CD38-retreated patients experience limited clinical benefit and highlight the need for new treatment options

With the anticipated increase in uptake of the daratumumab-based MAIA and PERSEUS regimens for first line use, there will be a need for alternative second-line therapies that are effective in anti-CD38-treated patients

## Abbreviations

#L, line #; ATRA, all-trans retinoic acid; Bor, bortezomib; Carf, carfilzomib; Cemi, cemiplimab; CI, confidence interval; Dara, daratumumab; Dex, dexamethasone; Dox, doxorubicin; Durva, durvalumab; IMD, immunomodulatory drug; IQR, interquartile range; Isa, isatuximab; LOT, line of therapy; MM, multiple myeloma; NE, not estimable; NR, not reported; NS, not specified; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pom, pomalidomide; Q#W, every # weeks; ref, refractory; RRMM, relapsed/refractory multiple myeloma; RWE, real-world evidence studies; SLR, systematic literature review; Talq, talquetamab; TLR, targeted literature review; Ven, venetoclax

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**SM**, **NB**, **MP**, and **JB** are employees of GSK and hold stocks/shares in GSK. **II**, **AP**, and **JC** are employees of Evidera



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