Assessing the benefit of incorporating an anti-CD38 monoclonal antibody into second- or third-line systemic treatment for patients with relapsed/refractory multiple myeloma: results from the French real-world EMMY study

Multiple myeloma (MM) is a malignant disorder characterized by the proliferation of abnormal monoclonal plasma cells. The therapeutic management of patients with MM comprises several sequences of treatments, accompanied by cycles of response to treatments followed by eventual relapse. Over the last few decades several therapies have been developed including proteasome inhibitors (PI), immunomodulatory drugs (IMiD), bispecific antibodies, antibody-drug conjugates (ADC), and anti-CD38 monoclonal antibodies (mAb).[1] These therapies have improved outcomes. However, optimal sequencing of these treatments, either alone or combined, has not yet been established.[2] Real-world data can provide preliminary evidence to assist physicians with therapeutic decisions.

Among the emerging treatments, anti-CD38 mAb show promise in treating relapsed-refractory MM (RRMM). Evi-

Table 1. Patient characteristics at baseline, all patients, and according to whether second- or third-line treatment included an anti-CD38 mAb.

Patient characteristic	All patients N (%)	Without an anti-CD38 mAb N (%)	With an anti-CD38 mAb N (%)
Total N of patients	1,784	962	822
Age at start of treatment line, years Median (range)	72.1 (39-99.2)	73.4 (39-99.2)	71.2 (39.5-93)
Age, years <59 60-69 70-79 ≥80	 235 (13.2) 481 (27.0) 693 (38.9) 375 (21.0)	 111 (11.5) 237 (24.6) 353 (36.7) 261 (27.1)	 124 (15.1) 244 (29.7) 340 (41.4) 114 (13.9)
ECOG PS 0-1 ≥2 Missing data	 1,134 (79.6) 290 (20.4) 360/1,784 (20.2)	 574 (77.9) 163 (22.1) 22/962 (22.9)	 560 (81.5) 127 (18.5) 135/822 (16.4)
Refractory to IMiD Yes No Not determined	 595 (33.4) 1,185 (66.4) 4 (0.2)	 317 (33.0) 643 (66.8) 2 (0.2)	 278 (33.8) 542 (65.9) 2 (0.2)
ISS stage at diagnosis Stage I Stage II Stage III Missing data	 257 (25.6) 303 (30.1) 446 (44.3) 778/1,784 (43.6)	 140 (25.5) 156 (28.4) 254 (46.2) 412/962 (42.8)	 117 (25.6) 147 (32.2) 192 (42.1) 366/822 (44.5)
Cytogenetic testing Yes No Missing data	 784 (57.8) 573 (42.2) 427/1,784 (23.9)	 423 (57.5) 313 (42.5) 226/962 (23.5)	 361 (58.1) 260 (41.9) 201/822 (24.5)
Patient at high cytogenetic risk[a]	213 (27.2)	107 (25.3)	106 (29.4)
Fragility score Not fragile Fragile Missing data	 806 (53.7) 695 (46.3) 283/1,784 (15.9)	 366 (46.1) 428 (53.9) 168/962 (17.5)	 440 (62.2) 267 (37.8) 115/822 (14.0)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; IMiD: immunomodulatory drug; ISS: International Staging System; mAb: monoclonal antibody; N: number. [a]High cytogenetic risk was defined as having either a t(4 ;14) or a del(17p) genetic anomaly.

dence suggests that anti-CD38 mAb-based combination therapies improve survival outcomes in RRMM.[3] During the years studied (2017-2021), anti-CD38 mAb available for treating RRMM in France were daratumumab and isatuximab. We designed the non-interventional, multicenter, longitudinal EMMY study to collect real-world data (during an annual pre-defined 3-month period) to assess the evolution of therapeutic management of MM as new therapies emerge in France.[4,5] Patients aged 18 years or older with symptomatic MM requiring systemic treatment were eligible. Patients with non-secretory, solitary plasmacytoma, or plasma cell leukemia, and those treated in clinical trials were not eligible. Between 2017-2023, patients were annually enrolled in 73 centers during a pre-defined 3-month period. The study was conducted in accordance with the principles of the Declaration of Helsinki, and French and European laws and regulations. Ethical approval was not required. Before participating, all patients were informed about the study and of their rights concerning the use of their personal data.

Here we report the results concerning patients with RRMM treated with second- or third-line systemic treatment between 2017-2021. We focus on describing the populations of patients treated with and without an anti-CD38 mAb (alone or in combination). Furthermore, we report the time-to-next treatment (TTNT), progression-free survival (PFS), overall survival (OS), and response to treatment in these populations. The TTNT was defined as the interval between start of treatment (second- or third-line) and the initiation of the subsequent line of treatment or death, whichever occurs first. PFS was defined as the time interval between start of treatment (second- or third-line) and either disease progression or death. OS was defined as the time interval between start of treatment (second- or third-line) and death.

Between 2017 and 2021, 1,784 patients with RRMM initiating second- or third-line systemic treatment had been enrolled in the EMMY study. Among them, 1,128 patients (63.2%) were initiating second-line treatments and 656 (36.8%) third-line treatments. The median age was 72.1 years (59.9% aged >70 years), and 79.6% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Of the 1,784 patients assessed, 822 (46.1%) had received an anti-CD38 mAb during second- or third-line systemic treatment and 962 (53.9%) had not. The baseline characteristics were similar between the two groups (Table 1).

Among the 962 patients treated without an anti CD38 mAb, in the second or third line of treatment, 95.5% received a corticosteroid, 77.1% an IMiD, 57.0% a PI, and 28.0% an alkylator. Of the 822 patients treated with an anti-CD38 mAb, 95.9% received a corticosteroid, 71.4% an IMID, 27.1% a PI, and 7.9% an alkylating agent. Most patients treated with an anti-CD38 mAb received daratumumab (88.8%) (Table 2). Among the 822 patients treated with an anti-CD38 mAb, 49 patients (6.0%) initiated their second- or third-line of treatment in 2017, 81 (9.9%) in 2018, 242 (29.4%) in 2019, 211 (25.7%) in 2020, and 239 (29.1%) in 2021.

At analysis, second- or third-line treatment was ongoing (as appropriate) in 19.2% of the patients not treated with an anti-CD38 mAb *versus* 51.2% of patients treated with

Table 2. Treatment and disease status according to whether a second- or third-line of treatment included an anti-CD38 mAb.

	Without an anti-CD38 mAb N (%)	With an anti-CD38 mAb N (%)
Total N of patients	962	822
Prior stem cell transplant		
Yes	296 (30.8)	354 (43.1)
No	666 (69.2)	468 (56.9)
2nd- or 3-line of treatment		
Corticosteroids	919 (95.5)	788 (95.9)
Anti-CD38 mAb, alone or combined	0	822 (100)
Daratumumab	0	730 (88.8)
Isatuximab	0	92 (11.2)
IMiD, alone or combined	742 (77.1)	587 (71.4)
Lenalidomide	495 (51.5)	373 (45.4)
Pomalidomide	241 (25.1)	212 (25.8)
Thalidomide	6 (0.6)	2 (0.2)
PI, alone or combined	548 (57.0)	223 (27.1)
Bortezomib	258 (26.8)	173 (21.0)
Ixazomib	121 (12.6)	4 (0.5)
Carfilzomib	169 (17.6)	46 (5.6)
Alkylators	269 (28.0)	65 (7.9)
Other cytotoxic agents	40 (4.2)	9 (1.1)
Anti-BMCA	2 (0.2)	0
Treatment combinations		
anti-CD38 mAb, alone or combined	0 (0.0)	822 (100.0)
IMiD and PI, alone or combined	367 (38.1)	0 (0.0)
IMiD, alone or combined	375 (39.0)	0 (0.0)
PI, alone or combined	181 (18.8)	0 (0.0)
Other combination	39 (4.1)	0 (0.0)
Treatment status		
Ongoing	185 (19.2)	421 (51.2)
Discontinued	777 (80.8)	401 (48.8)
Due to disease progression	475 (49.4)	288 (35.0)
Due to toxicity	140 (14.6)	41 (5.0)
Treatment protocol completed	102 (10.6)	36 (4.4)
Due to 2nd cancer	4 (0.4)	1 (0.1)
Unknown reason	56 (5.8)	35 (4.3)
Started next line of treatment	538 (55.8)	271 (33.0)
Primary refractory		
Yes	165 (17.2)	112 (13.6)
No	700 (72.9)	664 (80.8)
N/A	96 (9.9)	46 (5.6)
Missing data	2	0
Secondary refractory		
Yes	239 (25.1)	123 (15.1)
No	284 (29.9)	141 (17.3)
N/A	428 (45.0)	551 (67.6)
Missing data	11	7

BMCA: B-cell maturation antigen; IMiD: immunomodulatory drug; mAb: monoclonal antibody; N: number; N/A: not applicable; PI: proteasome inhibitor.

an anti-CD38 mAb. Most (80.8%) of the patients treated without an anti-CD38 mAb had discontinued their second or third line of treatment due to disease progression (49.4%), toxicity (14.6%), or completion of the treatment protocol (10.6%). In contrast, most of the 401 patients (48.8%) treated with an anti-CD38 mAb, had discontinued their second- or third-line treatment due to disease progression (35.0%), toxicity (5.5%), or completion of the treatment protocol (4.4%). Overall, 538 patients (55.8%) of the patients without an anti-CD38 mAb had initiated the subsequent treatment line *versus* 271 (33.0%) of those with an anti-CD38 mAb (Table 2).

At analysis, the median follow-up was 21.0 months (Interquartile Range: 10.4-35.7). The median TTNT, PFS, and OS, as well as the annual TTNT, PS, and OS rates were increased in patients treated with second- or third-line anti-CD38 mAb (*Online Supplementary Table S1*). Median TTNT was 29.8 months (95% Confidence Interval [CI]: 25.4-33.9) in patients with an anti CD38 mAb *versus* 15.9 months (95% CI: 14.3-17.7) in those not treated with an anti-CD38 mAb (Figure 1A). Median PFS was 26.3 months (95% CI: 22.7-29.7) in patients treated with an anti-CD38 mAb *versus* 14.5 months (95% CI: 13.5-16.5) in those not treated with an anti-CD38 mAb (Figure 1B). Median OS was not reached in patients treated with an anti-CD38 mAb *versus* 46.1 months (95% CI: 39.2-54.8) in those not treated with an anti-CD38 mAb (Figure 1C).

In our study, 57.8% of patients had cytogenetic data. Of these, 27.2% had a high cytogenetic risk. Interestingly, the ICARIA-MM study found that adding the anti-CD38 mAb isatuximab to pomalidomide and dexamethasone benefited all patients with RRMM (in terms of response and PFS), irrespective of the cytogenetic risk.[6] To interpret our results, it is important to consider the timing of approvals and availability of the anti-CD38 mAb daratumumab and isatuximab for treating patients with RRMM in France. In Europe, daratumumab first received a conditional marketing authorization for treating adults with RRMM on the 20th of May 2016, while isatuximab was only approved by the EMA on the 30th of May 2020 for treating adults with RRMM.[3,7] Consequently, in our study, most of the patients treated with an anti-CD38 mAb received daratumumab, with only 11.2% receiving isatuximab. Moreover, the use of an anti-CD38 mAb-based regimen for patients with RRMM gradually increased during the period under study: 49 patients in 2017, 81 in 2018, 242 in 2019, 211 in 2020, and 239 in 2021.

We observed a median PFS of 26.3 months in patients treated with an anti-CD38 mAb. While the median OS in patients treated with an anti-CB38 has not yet been reached (but will exceed the 46.1 months in patients not treated with an anti-CD38 mAb). Our results are consistent with those previously reported.[8] The median PFS and OS of 582 patients in the Canadian Myeloma Research Group Database that received daratumumab-based therapies was 23.5 months and 49.1 months, respectively, with daratumumab-based therapies as the second-line.[8] The median PFS and OS decreased with daratumumab use in further lines, and was 12.8 months and 43.0 months, respectively, in the third-line and 7.0 months and 20.5 months, respec-

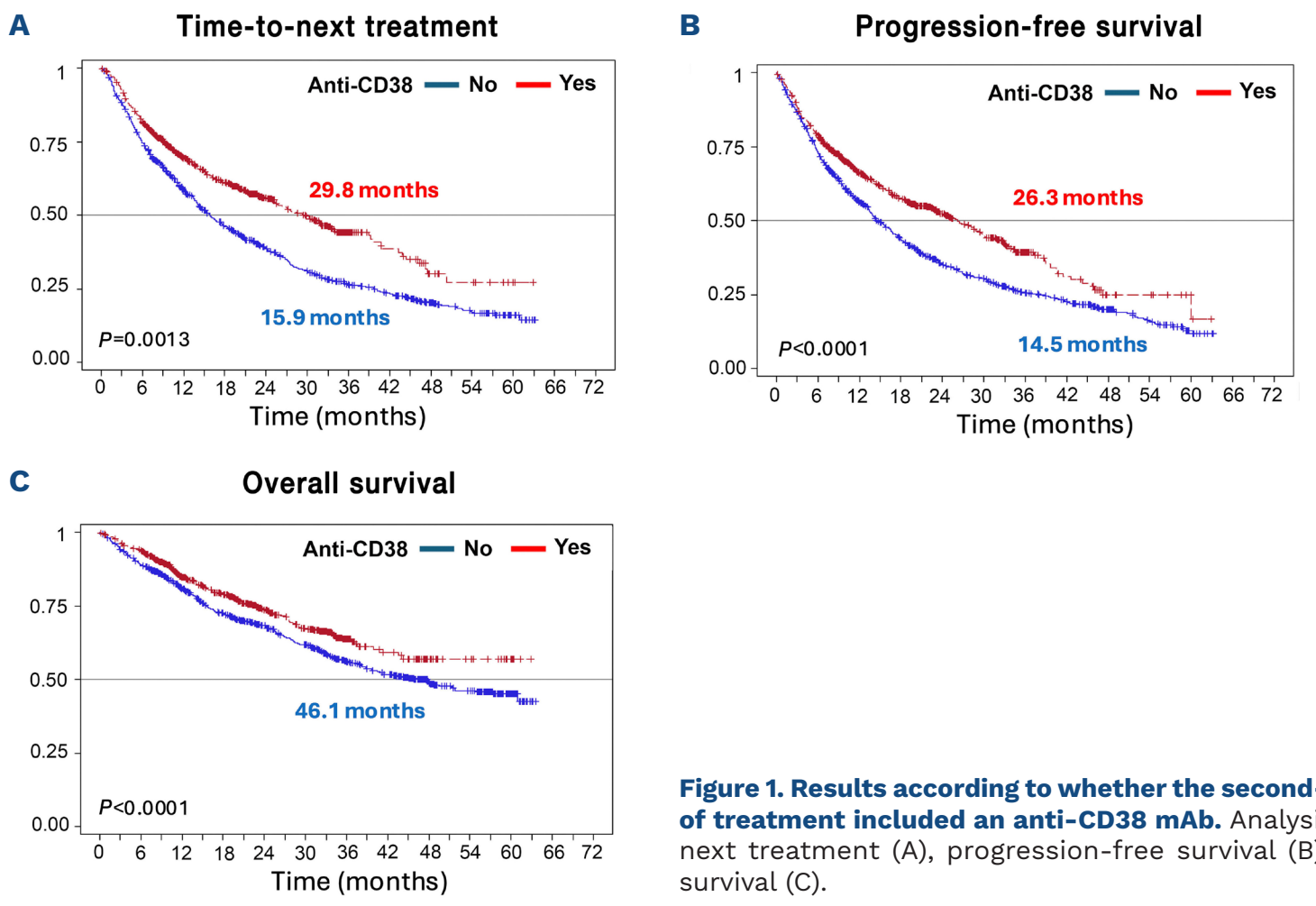

Figure 1. Results according to whether the second- or third-line of treatment included an anti-CD38 mAb. Analysis of time-to-next treatment (A), progression-free survival (B), and overall survival (C).

tively, in the fourth and subsequent lines. Median PFS and OS were extended when daratumumab was combined with bortezomib, lenalidomide, or pomalidomide (compared to monotherapy). Also, several recent systematic reviews and/or meta-analyses have shown that anti-CD38 mAb (alone or combined) significantly extend survival outcomes in patients with RRMM.[9,10]

Currently, there are several emerging therapies that will transform the therapeutic landscape of RRMM. These include chimeric antigen receptor (CAR) T-cell therapies, bispecific antibodies, and ADC.[1,11] Furthermore, now that daratumumab and isatuximab have been approved in patients newly diagnosed with MM, anti-CD38 mAb will be used earlier during MM evolution.[12-15]

This study, as with all real-world studies, has limitations. In this case, the data collected depended on the completeness, accuracy, and frequency of the data entered in the medical files.

However, our results show that incorporating an anti-CD38 mAb into second- or third-line systemic treatment for patients with RRMM extends median TTNT, PFS, and OS.

Authors

Thomas Chalopin,[1] Cyrille Hulin,[2] Bruno Royer,[3] Jean-Noel Bastie,[4] Arthur Bobin,[5] Karim Belhadj Merzoug,[6] Margaret Macro,[7] Lionel Karlin,[8] Caroline Jacquet,[9] Mohamad Mohty,[10] Laurent Frenzel,[11] Cécile Sonntag,[12] Jean Fontan,[13] Sophie Rigaudeau,[14] Murielle Roussel,[15] Laurence Sanhes,[16] Driss Chaoui,[17] Laure Vincent,[18] Hubert Orfeuvre,[19] Malek Bouketouche,[20] Ronan Garlantezec,[21] Olivier Decaux[22] and Aurore Perrot[23]

[1]Service d'Hématologie et Thérapie Cellulaire, Centre Hospitalier Universitaire (CHU) Tours, Hôpital Bretonneau, Tours; [2]Service d'Hématologie, Hôpital Haut Lévêque, Pessac; [3]Service d'Hématologie, Hôpital Saint-Louis, Paris; [4]Hématologie Clinique, CHU Dijon Bourgogne, Dijon; [5]Service d'Hématologie, Hôpital Poitiers, Poitiers; [6]Unité Fonctionnelle Hémopathies Lymphoïdes, CHU Henri Mondor, Créteil; [7]Service d'Hématologie, Hôpital Caen, Caen; [8]Service d'Hématologie, Hôpital Lyon, Lyon; [9]CHU de Nancy, Vandoeuvre les Nancy; [10]Sorbonne University, Saint-Anne Hospital (AP-HP), INSERM UMRS-938, Paris; [11]Service d'Hématologie , Hôpital Necker, Paris; [12]Hôpital Hautepierre, Strasbourg; [13]Service d'Hématologie, Centre Hospitalier Régional Universitaire Jean Minjoz, Besançon; [14]Service d'Hématologie, Centre Hospitalier de Versailles André Mignot, Le Chesnay; [15]Hématologie Clinique, CHU de Limoges, Hospital Dupuytren, Limoges; [16]Centre Hospitalier Perpignan, Perpignan; [17]Hôpital Victor Dupouy, Argenteuil; [18]Département d'Hématologie Clinique, Hôpital Saint Eloi, CHU de Montpellier; [19]Hôpital de Fleyriat, Bourg en Bresse; [20]Centre Hospitalier Saint-Quentin, Saint Quentin; [21]Santé Publique et Épidémiologie, CHU de Rennes, Rennes; [22]Service d'Hématologie, Hôpital Rennes, Rennes and [23]Service d'Hématologie, Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France.

Correspondence:
T. Chalopin - t.chalopin@chu-tours.fr

https://doi.org/10.3324/haematol.2025.287954

Received: April 4, 2025.
Accepted: August 20, 2025.
Early view: August 28, 2025.

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Disclosures

No conflicts of interest to disclose.

Contributions

TC wrote the manuscript. OD and CH supervised the project. MM and LV revised the manuscript. All authors approved the final version of the manuscript for publication.

Acknowledgments

The authors would like to thank Trevor Stanbury (Pro-Pens) for medical writing services.

Funding

The EMMY study was funded by the "Intergroupe Francophone du Myelome (IFM)" (https://www.myelome.fr/), with the support of a consortium of pharmaceutical companies.

Data-sharing statement

The data assessed in this manuscript will be made available upon reasonable request.

References

1. Omer MH, Shafqat A, Ahmad O, Alkattan K, Yaqinuddin A, Damlaj M. Bispecific antibodies in hematological malignancies: a scoping review. Cancers (Basel). 2023;15(18):4550.
2. Fonseca R, Facon T, Hashim M, et al. Impact of treatment sequencing on overall survival in patients with transplant-ineligible newly diagnosed myeloma. Oncologist. 2023;28(5):e263-e269.
3. Michaleas S, Penninga E, Hovgaard D, et al. EMA review of daratumumab (Darzalex) for the treatment of adult patients newly diagnosed with multiple myeloma. Oncologist. 2020;25(12):1067-1074.
4. Decaux O, Garlantézec R, Belhadj-Merzoug K, et al. The EMMY longitudinal, cohort study: real-world data to describe multiple myeloma management and outcomes as more therapeutic options emerge. Clin Hematol Int. 2024;6(3):22-27.
5. Chalopin T, Macro M, Decaux O, et al. Real-life management of

patients aged 80 years old and over with multiple myeloma: results of the EMMY cohort. Clin Lymphoma Myeloma Leuk. 2025;25(2):e103-e109.e1.
6. Harrison SJ, Perrot A, Alegre A, et al. Subgroup analysis of ICARIA-MM study in relapsed/refractory multiple myeloma patients with high-risk cytogenetics. Br J Haematol. 2021;194(1):120-131.
7. Delgado J, Zienowicz M, van Hennik PB, et al. EMA review of isatuximab in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma. Oncologist. 2021;26(11):983-987.
8. LeBlanc R, Mian H, Reece D, et al. Outcomes of daratumumab in the treatment of multiple myeloma: a retrospective cohort study from the Canadian Myeloma Research Group Database. Br J Haematol. 2022;198(1):93-102.
9. Ye L, Zhou F, Cheng D, et al. Efficacy and safety of anti-CD38 monoclonal antibodies in patients with relapsed/refractory multiple myeloma: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials. Front Oncol. 2023;13:1240318.
10. Moraes FCA, Sano VKT, Lôbo AOM, et al. Efficacy and safety of anti-CD38 monoclonal antibodies in patients with relapsed or refractory multiple myeloma: a meta-analysis of randomized clinical trials. J Pers Med. 2024;14(4):360.
11. Tacchetti P, Talarico M, Barbato S, et al. Antibody-drug conjugates, bispecific antibodies and CAR-T cells therapy in multiple myeloma. Expert Rev Anticancer Ther. 2024;24(6):379-395.
12. Moreau P, Hulin C, Perrot A, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial. Lancet Oncol. 2024;25(8):1003-1014.
13. Facon T, Moreau P, Weisel K, et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. Leukemia. 2025;39(4):942-950.
14. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390(4):301-313.
15. Facon T, Dimopoulos MA, Leleu XP, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;391(17):1597-1609.