Real-world outcomes in relapsed/refractory multiple myeloma: retreatment versus no retreatment with an anti-CD38 monoclonal antibody in the 2L and 3L in patients from the Flatiron Health database

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Maria Nieto,[1,2] Katie Gravagna,[3] Jiaqi Fang,[3] Yu-Hsuan Shih,[3] Christian Gentili,[4] Gabriela Hernandez-Rivera,[4] Ying Qiu,[3] Paulo Maciag[3]

[1]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA; [2]R.J. Zuckerberg Cancer Center, Lake Success, NY, USA; [3]Bristol Myers Squibb, Princeton, NJ, USA; [4]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland

Introduction

- A growing number of patients with multiple myeloma (MM) receive anti-CD38 monoclonal antibodies (mAbs) in early lines of treatment (LOTs)
  - Optimal strategies following early relapse after anti-CD38 mAb exposure remain unclear
  - Prior studies suggest that retreatment with daratumumab (DARA) may yield comparable progression-free survival (PFS) and overall survival (OS),[1-3] even in patients with MM refractory to DARA
  - However, these studies had methodological challenges such as small sample size and the use of older data that no longer reflect the current MM treatment landscape
- As the number of patients who are anti-CD38 mAb-naive decreases, even in early LOTs, being able to understand characteristics and outcomes of patients who are and who are not retreated with an anti-CD38 mAb is critical for informing best clinical practice

Objective

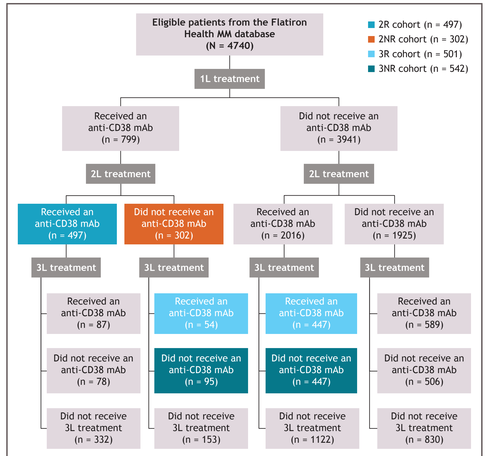
- To describe the demographic and clinical characteristics, treatment patterns, and clinical outcomes (PFS and OS) of patients with relapsed/refractory MM (RRMM) who were retreated or were not retreated with an anti-CD38 mAb in the second line (2L) or third line (3L) of treatment

Methods

Study design

- This is a retrospective observational study of US patients with RRMM included in the Flatiron Health MM database, an electronic health record database that has enrolled patients across 280 clinics
- The study period was from January 1, 2011 to December 30, 2024
- Eligible patients were ≥ 18 years of age at index date, diagnosed with MM, had received ≥ 2 documented LOTs, so as to be considered RRMM, including an anti-CD38 mAb
- Patients were excluded if they had received any 2L treatment before May 7, 2018, the date of approval of DARA as first-line (1L) treatment in combination with lenalidomide (LEN) and dexamethasone for patients with newly diagnosed MM who are ineligible for autologous stem cell transplant

Figure 1. Study cohorts



In this real-world analysis of patients in the US, 40.6% of patients who received 2L treatment and 22.0% of patients who received 3L treatment were anti-CD38 naive.

- Patients were assigned to 4 cohorts: received an anti-CD38 mAb in the 1L and were retreated (2R) or not retreated (2NR) in the 2L; or received an anti-CD38 mAb in the 1L or 2L and were retreated (3R) or not retreated (3NR) in the 3L (**Figure 1**)
- The index date was the start date of the 2L (2R and 2NR cohorts) or 3L (3R and 3NR cohorts) treatment

Variables and outcomes

- Study variables included demographics, clinical characteristics, and treatment patterns
- MM was considered refractory to a drug if patients experienced disease progression (PD) during treatment or ≤ 60 days after the treatment end date, whichever occurred first
- Clinical outcomes included PFS and OS
  - PFS was defined as the time from index date until PD, death, or start of the next subsequent treatment, whichever occurred first
  - OS was defined as the time from index date to death
- A sensitivity analysis was conducted to investigate the PFS of patients in the 3R cohort who received treatment with an anti-CD38 mAb sequentially in 2L and 3L

Statistical analysis

- Demographics, clinical characteristics, and treatment patterns were summarized descriptively
- Kaplan-Meier methods were used to analyze PFS and OS in each cohort and across subgroups defined by: age at index date, anti-CD38 mAb refractory status prior to index date, time between anti-CD38 mAb retreatment (for patients who were retreated), transplant status prior to index date, simplified frailty score (frail and non-frail), and whether patients were considered high risk

Results

Patient characteristics

- Of the 4740 eligible patients with RRMM from the Flatiron Health MM database, 1567 were included in the study: 497 in the 2R, 302 in the 2NR, 501 in the 3R, and 542 in the 3NR cohorts (cohorts were not mutually exclusive)
  - Of the 4740 eligible patients, 799 (16.9%) received an anti-CD38 mAb-containing regimen in the 1L, 2513 (53.0%) in the 2L, and 1177 (24.8%) in the 3L
- The index date for most patients (87.1%, 78.8%, 72.1%, and 61.3% in the 2R, 2NR, 3R, and 3NR cohorts, respectively) was from 2022 through 2025; around 40% and 30% of the patients in the 2L and 3L cohorts, respectively, had their index date in the past 2 years (2024 and 2025)
- Across all cohorts, patients had comparable demographics (**Table 1**)

Table 1. Patient demographics

Demographic, n (%)	2R cohort (n = 497)	2NR cohort (n = 302)	3R cohort (n = 501)	3NR cohort (n = 542)
Age at index				
< 75 years	356 (71.6)	224 (74.2)	332 (66.3)	379 (69.9)
≥ 75 years	141 (28.4)	78 (25.8)	169 (33.7)	163 (30.1)
Sex				
Female	248 (49.9)	134 (44.4)	215 (42.9)	244 (45.0)
Male	249 (50.1)	168 (55.6)	286 (57.1)	298 (55.0)
Race				
White	303 (61.0)	186 (61.6)	311 (62.1)	317 (58.5)
Black/African American	99 (19.9)	47 (15.6)	88 (17.6)	96 (17.7)
Asian	11 (2.2)	5 (1.7)	13 (2.6)	17 (3.1)
Other	42 (8.5)	17 (5.6)	39 (7.8)	40 (7.4)
Unknown	42 (8.5)	47 (15.6)	50 (10.0)	72 (13.3)
Ethnicity				
Hispanic/Latino	38 (7.6)	32 (10.6)	34 (6.8)	47 (8.7)
Non-Hispanic/Non-Latino	365 (73.4)	218 (72.2)	382 (76.2)	403 (74.4)
Unknown	94 (18.9)	52 (17.2)	85 (17.0)	92 (17.0)

Clinical characteristics

- Clinical characteristics were similar across the 4 cohorts except for transplant status (**Table 2**), where 23.3% of patients in the 2R cohort received a transplant prior to index versus 34.4% in the 2NR cohort
- The median time from diagnosis to index was longer in the 3L versus 2L cohorts and in the cohorts who were not retreated compared with the cohorts who were retreated (**Table 2**)
- For the 2R and 3R cohorts, 93.4% and 86.8% of patients, respectively had < 3 months between their first and second anti-CD38 mAb exposures (**Table 3**)

Table 2. Clinical characteristics

Characteristics	2R cohort (n = 497)	2NR cohort (n = 302)	3R cohort (n = 501)	3NR cohort (n = 542)
ISS stage, n (%)				
I	88 (17.7)	45 (14.9)	94 (18.8)	114 (21.0)
II	99 (19.9)	60 (19.9)	112 (22.4)	118 (21.8)
III	112 (22.5)	73 (24.2)	111 (22.2)	125 (23.1)
Unknown	198 (39.8)	124 (41.1)	184 (36.7)	185 (34.1)
ECOG PS, n (%)				
0	119 (23.9)	89 (29.5)	142 (28.3)	140 (25.8)
1	193 (38.8)	87 (28.8)	201 (40.1)	207 (38.2)
2	54 (10.9)	38 (12.6)	69 (13.8)	70 (12.9)
3	16 (3.2)	9 (3.0)	17 (3.4)	13 (2.4)
4	2 (0.4)	0	0	0
Unknown	113 (22.7)	79 (26.2)	72 (14.4)	112 (20.7)
Transplant prior to index, n (%)				
≥ 1	116 (23.3)	104 (34.4)	198 (39.5)	241 (44.5)
None	381 (76.7)	198 (65.6)	303 (60.5)	301 (55.5)
High-risk cytogenetics, n (%)				
High	94 (18.9)	79 (26.2)	92 (18.4)	129 (23.8)
Low	190 (38.2)	91 (30.1)	195 (38.9)	159 (29.3)
Uncertain	213 (42.9)	132 (43.7)	214 (42.7)	254 (46.9)
CCI score, median (IQR)	0 (2)	0 (2)	1 (3)	1 (3)
Simplified frailty score,[a] n (%)				
Frail	188 (37.8)	99 (32.8)	232 (46.3)	219 (40.4)
Non-frail	196 (39.4)	124 (41.1)	197 (39.3)	211 (38.9)
Unknown	113 (22.7)	79 (26.2)	72 (14.4)	112 (20.7)
Time from diagnosis to index, median (IQR), months	9.6 (14.0)	14.6 (22.2)	29.9 (36.2)	34.2 (40.7)
Duration of index therapy, median (IQR), months	7.2 (12.7)	4.8 (9.3)	7.4 (11.9)	4.0 (8.8)
Anti-CD38 mAb refractory status, n (%)	81 (16.3)	53 (17.5)	111 (22.2)	157 (29.0)

[a]Frailty was defined using a simplified frailty score based on age, CCI, and ECOG PS. Each variable was assigned a categorical score (age [years]: ≤ 75 = 0, 76-80 = 1, > 80 = 2; CCI score: ≤ 1 = 0, > 1 = 1; ECOG PS: 0 = 0, 1 = 1, ≥ 2 = 2) and the total frailty score was calculated as the sum of these component scores. Total scores of 0 or 1 were classified as "Non-frail" and ≥ 2 as "Frail". Patients with missing data on ≥ 1 variable were reported as "Unknown". CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile ratio; ISS, International Staging System.

Table 3. Time between the first and second exposure to an anti-CD38 mAb

n (%)	2R cohort (n = 497)	3R cohort (n = 501)
< 3 months	464 (93.4)	435 (86.8)
≥ 3 to < 6 months	27 (5.4)	28 (5.6)
≥ 6 to < 12 months	1 (0.2)	21 (4.2)
≥ 12 months	5 (1.0)	17 (3.4)

Treatment exposure and refractoriness

- Treatment exposure prior to the index date by anti-CD38 mAb refractory status was similar across the 2L and 3L (**Table 4**)
- Anti-CD38 mAb refractory status prior to the index date was higher in the 3L compared with the 2L (**Table 5**)
- Index regimens consisted mostly of various combinations of PIs, IMiD agents, and anti-CD38 mAbs and there was no standard index regimen (**Table 6**)
- Patients received treatment with an anti-CD38 mAb as induction or maintenance for a median of 6.3-8.9 months across the 4 cohorts (**Table 6**)

Table 4. Treatment exposure by anti-CD38 mAb refractory status prior to index

	2R cohort (n = 497)		2NR cohort (n = 302)		3R cohort (n = 501)		3NR cohort (n = 542)	
	Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status	
n (%)	Yes (n = 81)	No (n = 416)	Yes (n = 53)	No (n = 249)	Yes (n = 111)	No (n = 390)	Yes (n = 157)	No (n = 385)
IMiD® agents	51 (63.0)	269 (64.7)	38 (71.7)	178 (71.5)	92 (82.9)	337 (86.4)	143 (91.1)	333 (86.5)
LEN	50 (98.0)	252 (93.7)	36 (94.7)	152 (85.4)	91 (98.9)	312 (92.6)	139 (97.2)	294 (88.3)
POM	1 (2.0)	13 (4.8)	1 (2.6)	27 (15.2)	17 (18.5)	88 (26.1)	51 (35.7)	124 (37.2)
THAL	0	4 (1.5)	1 (2.6)	0	0	5 (1.5)	1 (0.7)	3 (0.9)
PIs	54 (66.7)	293 (70.4)	37 (69.8)	181 (72.7)	106 (95.5)	349 (89.5)	152 (96.8)	351 (91.2)
BORT	54 (100)	280 (95.6)	37 (100)	154 (85.1)	100 (94.3)	324 (92.8)	146 (96.1)	296 (84.3)
CFZ	0	12 (4.1)	1 (2.7)	26 (14.4)	24 (22.6)	63 (18.1)	36 (23.7)	103 (29.3)
IXA	0	3 (1.0)	0	4 (2.2)	5 (4.7)	14 (4.0)	3 (2.0)	14 (4.0)
Anti-CD38 mAbs	81 (100)	416 (100)	53 (100)	249 (100)	111 (100)	390 (100)	157 (100)	385 (100)
DARA	81 (100)	413 (99.3)	53 (100)	247 (99.2)	109 (98.2)	383 (98.2)	156 (99.4)	375 (97.4)
ISA	0	3 (0.7)	0	2 (0.8)	2 (1.8)	7 (1.8)	1 (0.6)	10 (2.6)
Alkylating agent-based therapies	14 (17.3)	42 (10.1)	10 (18.9)	17 (6.8)	28 (25.2)	76 (19.5)	23 (14.6)	62 (16.1)
Cyclophosphamide	14 (100)	41 (97.6)	10 (100)	15 (88.2)	26 (92.9)	74 (97.4)	23 (100)	60 (96.8)
Triple-class exposed	32 (39.5)	187 (45.0)	26 (49.1)	122 (49.0)	87 (78.4)	299 (76.7)	138 (87.9)	301 (78.2)

BORT, bortezomib; CFZ, carfilzomib; IMiD, immunomodulatory imide drug; ISA, isatuximab; IXA, ixazomib; PI, proteasome inhibitor; POM, pomalidomide; THAL, thalidomide.

Table 5. Treatment refractoriness prior to index

n (%)	2R cohort (n = 497)	2NR cohort (n = 302)	3R cohort (n = 501)	3NR cohort (n = 542)
IMiD agents	43 (8.7)	35 (11.6)	115 (23.0)	147 (27.1)
LEN	42 (8.5)	33 (10.9)	111 (22.2)	127 (23.4)
POM	1 (0.2)	1 (0.3)	16 (3.2)	43 (7.9)
PIs	48 (9.7)	37 (12.3)	102 (20.4)	118 (21.8)
BORT	48 (9.7)	37 (12.3)	82 (16.4)	99 (18.3)
CFZ	0	0	19 (3.8)	29 (5.4)
Anti-CD38 mAbs	81 (16.3)	53 (17.5)	111 (22.2)	157 (29.0)
DARA	81 (16.3)	53 (17.5)	109 (21.8)	156 (28.8)
Triple-class refractory	24 (4.8)	19 (6.3)	33 (6.6)	55 (10.1)

Table 6. Top 5 index regimens and first anti-CD38 mAb exposure

	2R cohort (n = 497)	2NR cohort (n = 302)	3R cohort (n = 501)	3NR cohort (n = 542)
Most common index regimens, n (%)				
BORT	-	14 (4.6)	-	-
BORT + DARA + LEN	53 (10.7)	-	-	-
CFZ	-	-	-	46 (8.5)
CFZ + cyclophosphamide	-	-	-	37 (6.8)
CFZ + DARA	35 (7.0)	-	57 (11.4)	-
CFZ + DARA + LEN	28 (5.6)	-	-	-
CFZ + LEN	-	12 (4.0)	-	-
CFZ + POM	-	41 (13.6)	-	59 (10.9)
Investigational drug	-	27 (8.9)	-	-
DARA	-	-	25 (5.0)	-
DARA + ISA	-	-	23 (4.6)	-
DARA + LEN	38 (7.6)	-	41 (8.2)	-
DARA + POM	39 (7.8)	-	92 (18.4)	-
ELO + POM	-	12 (4.0)	-	33 (6.1)
POM	-	-	-	29 (5.4)
Time to next treatment, median (95% CI), months	7.4 (6.4-8.1)	9.5 (8.5-10.3)	8.3 (7.1-9.3)	8.4 (7.7-9.8)
Type of the first treatment with an anti-CD38 mAb, n (%)				
Induction	90 (18.1)	61 (20.2)	60 (12.0)	59 (10.9)
Maintenance	47 (9.5)	14 (4.6)	66 (13.2)	22 (4.1)
Duration of the first treatment with an anti-CD38 mAb, median (IQR), months	6.3 (8.0)	7.2 (11.5)	7.8 (10.8)	8.9 (13.3)

CI, confidence interval; ELO, elotuzumab.

Table 7. OS and PFS by cohort and anti-CD38 mAb refractory status

	2R cohort (n = 497)		2NR cohort (n = 302)		3R cohort (n = 501)		3NR cohort (n = 542)	
	Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status		Anti-CD38 mAb refractory status	
Median (95% CI), months	Yes (n = 81)	No (n = 416)	Yes (n = 53)	No (n = 249)	Yes (n = 111)	No (n = 390)	Yes (n = 157)	No (n = 385)
OS	NR (19.8-NR)	NR (NR-NR)	16.8 (8.6-NR)	39.8 (30.0-59.4)	46.1 (21.9-NR)	58.0 (50.5-76.8)	15.2 (10.3-20.5)	36.0 (29.2-51.8)
PFS	5.6 (3.9-7.2)	20.4 (13.5-33.6)	3.7 (2.8-5.4)	8.5 (7.1-11.9)	6.0 (4.4-10.4)	10.2 (8.5-11.6)	4.2 (3.2-5.8)	7.8 (6.4-9.3)

OS and PFS

- Median OS was not reached (NR) in the 2R cohort; within the 2NR, 3R, and 3NR cohorts, patients with RRMM not refractory to an anti-CD38 mAb had a higher median OS than patients who were refractory (**Table 7**)
- Similarly, across the 4 cohorts and within the same cohort, patients with RRMM not refractory to an anti-CD38 mAb had a higher median PFS than patients who were refractory (**Table 7**)
  - In patients with RRMM refractory to an anti-CD38 mAb, the median PFS was higher in the 2R and 3R cohorts compared with the 2NR and 3NR cohorts
- Patients in the 3R cohort who received treatment with an anti-CD38 mAb sequentially in 2L and 3L had a median PFS of 10.1 months (95% CI, 8.1-11.1), which is similar to the median PFS of all patients in the 3R cohort

Conclusions

- Treatment with anti-CD38 mAbs has become increasingly common in patients with RRMM in early stages of treatment
- In this study, patients with RRMM refractory to an anti-CD38 mAb had a much shorter PFS compared with patients with RRMM who were not refractory, both in the retreated and non-retreated cohorts
- In this real-world study, 83.7% and 77.8% of patients who received 2L and 3L retreatment with an anti-CD38 mAb, respectively, were sensitive to anti-CD38 mAbs and experienced a numerically longer PFS compared with patients who were not retreated; therefore, exposure to may not be a barrier to retreatment with an anti-CD38 mAb
- A limitation of this study is the strict definition of refractoriness used which may result in the number of patients with MM refractory to an anti-CD38 mAb being underestimated
- These findings support consideration of retreatment with an anti-CD38 mAb in patients with RRMM and highlight the need for individualized treatment strategies as anti-CD38 mAb exposure becomes more common in earlier LOTs

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