Reasons for treatment discontinuation in multiple myeloma: insights from the PREAMBLE registry

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Objective

- This study aimed to understand reasons for treatment discontinuation in patients with MM

Conclusions

- The reasons for MM treatment discontinuation observed in this study underscore persistent challenges in continuing treatment, despite the availability of multiple regimens and modalities across the disease spectrum
- Analysis of free-text comments highlighted the complexity of decision-making around ending treatment in patients with MM
  - Factors such as disease biology, quality of life, and overall health and wellbeing influence the treatment pathway, prompting re-evaluation of what constitutes treatment completion in the context of therapeutic goals
- While exposure to multiple treatment classes increased with each subsequent LOT, discontinuation data suggested that toxicity remained stable across LOTs; however, as treatment options become more limited with each progression, patients tend to exhibit greater tolerance and higher attrition rates, which may affect observed toxicity rates
- These results emphasize the need for more tolerable and effective treatments to improve adherence and long-term outcomes for patients with MM; further research on the real-world impact of treatment discontinuation is warranted to guide treatment strategies and improve outcomes

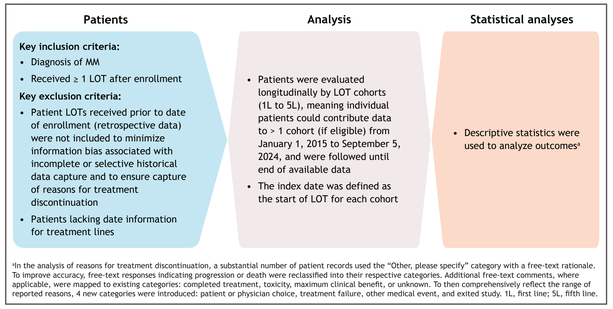
Introduction

- Despite treatment advances, patients with multiple myeloma (MM) continue to experience shorter overall survival compared with the general population, highlighting a persistent unmet need[1]
- Though many treatment options and modalities for MM exist, they remain insufficient due to a heterogenous population, prior treatment exposure, and disease biology[2]
- As patients progress through lines of therapy (LOT), attrition increases due to factors such as cumulative toxicities, treatment-resistant disease, and patient frailty
- In real-world practice, treatment-limiting toxicities are a common reason for discontinuing therapy, even when there is no evidence of disease progression[3]; however, most available data on the frequency and impact of these toxicities come from clinical trials, with limited information published from routine clinical settings

Methods

- This prospective, observational cohort study used data from the PREAMBLE registry (NCT01838512) to assess demographic and clinical characteristics, treatment patterns, and rates and reasons for treatment discontinuation in patients with MM (**Figure 1**)

Figure 1. Study design



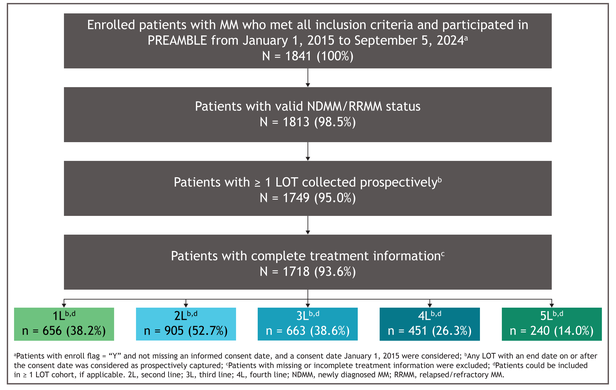
[a]In the analysis of reasons for treatment discontinuation, a substantial number of patient records used the "Other, please specify" category with a free-text rationale. To improve accuracy, free-text responses indicating progression or death were reclassified into their respective categories. Additional free-text comments, where applicable, were mapped to existing categories: completed treatment, toxicity, maximum clinical benefit, or unknown. To then comprehensively reflect the range of reported reasons, 4 new categories were introduced: patient or physician choice, treatment failure, other medical event, and exited study. 1L, first line; 5L, fifth line.

Results

Patient flow and patient characteristics

- Patient flow diagram is shown in **Figure 2**, and patient characteristics are shown in **Table 1**

Figure 2. Patient flow diagram

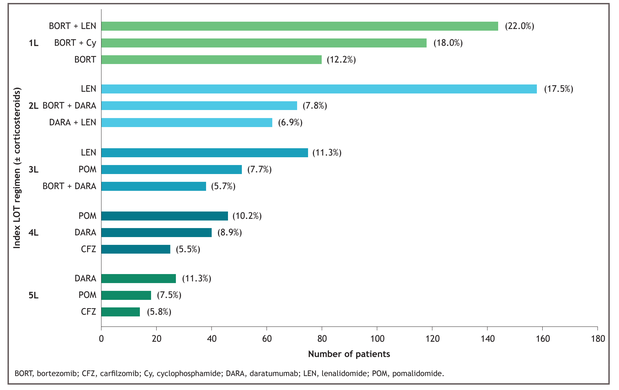


[a]Patients with enroll flag = "Y" and not missing an informed consent date, and a consent date January 1, 2015 were considered; [b]Any LOT with an end date on or after the consent date was considered as prospectively captured; [c]Patients with missing or incomplete treatment information were excluded; [d]Patients could be included in ≥ 1 LOT cohort, if applicable. 2L, second line; 3L, third line; 4L, fourth line; NDMM, newly diagnosed MM; RRMM, relapsed/refractory MM.

Treatment patterns

- Patients in the US were generally more likely to receive immunomodulatory drug (IMiD®) agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs) and become double-class and triple-class exposed earlier than patients in ex-US (**Table 2**)
- Patients in ex-US had higher exposure to alkylating agent-based therapies (**Table 2**)
- The most common index LOT regimens ± corticosteroids are shown in **Figure 3**
  - The most common treatment regimens were BORT and LEN (22.0%) at 1L, LEN (17.5%) at 2L, LEN (11.3%) at 3L, POM (10.2%) at 4L, and DARA (11.3%) at 5L

Figure 3. Most common index-line regimens (± corticosteroids)



BORT, bortezomib; CFZ, carfilzomib; Cy, cyclophosphamide; DARA, daratumumab; LEN, lenalidomide; POM, pomalidomide.

Reasons for treatment discontinuation

- Reasons for treatment discontinuation are shown in **Table 3**
- The proportion of patients discontinuing treatment due to death or disease progression increased with later LOTs, and fewer patients in later LOTs discontinued due to treatment completion/maximum clinical benefit
- During reclassification of the free text "Other, please specify" responses, 189 comments were reviewed. Of these, 65 were reassigned to existing registry categories, 110 were redistributed into 4 newly created categories, and 14 remained under "Other" due to their infrequent occurrence or unclear wording
  - For example, "other medical event" encompassed comments such as "complications with comorbidity" and "operation"; "toxicity" encompassed comments such as "adverse event" and "thrombocytopenia"; and "patient or physician choice" included "patient request" and "doctor's decision"
- Following recategorization, completed treatment increased in 1L, with no differences in later LOTs for treatment completion as a reason for treatment discontinuation
- While discontinuation due to toxicity was generally stable across LOTs, the proportion of patients experiencing toxicity increased following recategorization; progression remained unchanged as a reason for treatment discontinuation across LOTs

Table 1. Patient demographics and clinical characteristics

Characteristic	1L (n = 656)	2L (n = 905)	3L (n = 663)	4L (n = 451)	5L (n = 240)
Age,[a] median (IQR), years	69 (14)	70 (14)	70 (13)	70 (13)	69 (13)
< 70 years, n (%)	355 (54.1)	419 (46.3)	306 (46.2)	217 (48.1)	127 (52.9)
≥ 70 years, n (%)	300 (45.7)	484 (53.5)	355 (53.5)	232 (51.4)	112 (46.7)
Sex, n (%)					
Female	289 (44.1)	384 (42.4)	293 (44.2)	197 (43.7)	100 (41.7)
Male	366 (55.8)	519 (57.3)	368 (55.5)	252 (55.9)	139 (57.9)
Missing	1 (0.2)	2 (0.2)	2 (0.3)	2 (0.4)	1 (0.4)
Race, n (%)					
White	516 (78.7)	666 (73.6)	474 (71.5)	329 (72.9)	184 (76.7)
Black/African American	73 (11.1)	62 (6.9)	50 (7.5)	29 (6.4)	15 (6.3)
American Indian/Alaska Native	0	1 (0.1)	1 (0.2)	0	0
Asian	3 (0.5)	4 (0.4)	4 (0.6)	5 (1.1)	4 (1.7)
Native Hawaiian/other Pacific Islander	1 (0.2)	0	0	0	0
Other[b]	4 (0.6)	9 (1.0)	5 (0.8)	4 (0.9)	1 (0.4)
Missing	59 (9.0)	163 (18.0)	129 (19.5)	84 (18.6)	36 (15.0)
Geography, n (%)					
US	331 (50.5)	275 (30.4)	190 (28.7)	128 (28.4)	71 (29.6)
Ex-US[c]	325 (49.5)	630 (69.6)	473 (71.3)	323 (71.6)	169 (70.4)
Length of follow-up from index, median (IQR), months	40.5 (40.4)	28.3 (26.3)	17.8 (25.5)	12.4 (20.4)	10.9 (15.3)
Disease status at enrollment, n (%)					
Refractory	0	88 (9.7)	75 (11.3)	62 (13.7)	40 (16.7)
Relapsed	0	456 (50.4)	394 (59.4)	287 (63.6)	153 (63.8)
Unknown RRMM	0	2 (0.2)	3 (0.5)	5 (1.1)	3 (1.3)
NDMM	656 (100)	359 (39.7)	191 (28.8)	97 (21.5)	44 (18.3)
ISS stage,[d] n (%)					
Stage I	121 (18.4)	137 (15.1)	106 (16.0)	65 (14.4)	41 (17.1)
Stage II	161 (24.5)	172 (19.0)	114 (17.2)	54 (12.0)	29 (12.1)
Stage III	135 (20.6)	204 (22.5)	140 (21.1)	102 (22.6)	59 (24.6)
Unknown	236 (36.0)	389 (43.0)	300 (45.2)	226 (50.1)	109 (45.4)
Missing	3 (0.5)	3 (0.3)	3 (0.5)	4 (0.9)	2 (0.8)
Stem cell transplant prior to index, n (%)					
No	656 (100)	713 (78.8)	397 (59.9)	212 (47.0)	95 (39.6)
Yes	0	192 (21.2)	266 (40.1)	239 (53.0)	145 (60.4)
Single	0	176 (91.7)	226 (85.0)	187 (78.2)	106 (73.1)
Multiple	0	16 (8.3)	40 (15.0)	52 (21.8)	39 (26.9)
Autologous	0	189 (98.4)	263 (98.9)	238 (99.6)	144 (99.3)
Allogeneic	0	4 (2.1)	5 (1.9)	7 (2.9)	3 (2.1)
Risk stratification,[e] n (%)					
High risk	148 (22.6)	160 (17.7)	128 (19.3)	92 (20.4)	55 (22.9)
Time from initial MM diagnosis to index, median (IQR), months	0.6 (0.9)	20.2 (33.5)	35.3 (38.2)	47.9 (43.8)	55.6 (45.6)

Percentages may not total 100% due to rounding. [a]Patients with missing birth dates were excluded from the age calculation; [b]Other includes Caribbean, Hispanic, or not specified; [c]Including Canada, France, Germany, Italy, and the UK; [d]ISS stage is captured as the closest to diagnosis; [e]The presence of any of the following features were considered high risk: R-ISS III, t(4;14), t(14;16), t(14;20), del(17p), 17p/53p. Ex-US, excluding US; IQR, interquartile ratio; ISS, International Staging System; R-ISS, revised-ISS.

Table 2. Treatment patterns by region, agent, and class

Prior treatment exposure by agent and class,[a] n (%)	US				Ex-US			
	2L (n = 277)	3L (n = 191)	4L (n = 129)	5L (n = 71)	2L (n = 628)	3L (n = 472)	4L (n = 322)	5L (n = 169)
IMiD agents	204 (73.6)	167 (87.4)	126 (97.7)	71 (100)	287 (45.7)	384 (81.4)	295 (91.6)	167 (98.8)
PIs	242 (87.4)	181 (94.8)	128 (99.2)	69 (97.2)	502 (79.9)	448 (94.9)	308 (95.7)	167 (98.8)
Anti-CD38 mAbs	6 (2.2)	46 (24.1)	49 (38.0)	36 (50.7)	19 (3.0)	65 (13.8)	77 (23.9)	60 (35.5)
Alkylating agent-based therapies	40 (14.4)	69 (36.1)	50 (38.8)	36 (50.7)	349 (55.6)	356 (75.4)	276 (85.7)	154 (91.1)
BCMA therapies								
CAR T cell therapy	0	0	0	0	0	0	0	0
TCE	0	0	0	0	0	0	0	1 (0.6)
ADC	0	0	1 (0.8)	2 (2.8)	0	0	0	3 (1.8)
Other[b]	0	7 (3.7)	9 (7.0)	6 (8.5)	0	21 (4.4)	26 (8.1)	19 (11.2)
Double-class exposure								
IMiD agent + PI	171 (61.7)	157 (82.2)	125 (96.9)	69 (97.2)	178 (28.3)	361 (76.5)	281 (87.3)	165 (97.6)
IMiD agent + anti-CD38 mAb	3 (1.1)	43 (22.5)	49 (38.0)	36 (50.7)	12 (1.9)	53 (11.2)	70 (21.7)	59 (34.9)
PI + anti-CD38 mAb	5 (1.8)	43 (22.5)	48 (37.2)	36 (50.7)	13 (2.1)	63 (13.3)	76 (23.6)	60 (35.5)
Triple-class exposure	2 (0.7)	40 (20.9)	48 (37.2)	36 (50.7)	8 (1.3)	51 (10.8)	69 (21.4)	59 (34.9)

[a]Regimens are ± corticosteroids; [b]Other was defined as patients who were exposed to drugs not listed in the table. ADC, antibody drug conjugate; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; TCE, T cell engager.

Table 3. Reasons for treatment discontinuation

Reasons for treatment discontinuation, n (%)	1L (n = 656)	2L (n = 905)	3L (n = 663)	4L (n = 451)	5L (n = 240)
Death	76 (11.6)	133 (14.7)	123 (18.6)	109 (24.2)	55 (22.9)
Disease progression[a]	58 (8.8)	149 (16.5)	151 (22.8)	110 (24.4)	57 (23.8)
Completed treatment[a]	161 (24.5)	85 (9.4)	47 (7.1)	15 (3.3)	10 (4.2)
Toxicity[a]	59 (9.0)	76 (8.4)	47 (7.1)	26 (5.8)	24 (10.0)
Maximum clinical benefit	61 (9.3)	65 (7.2)	33 (5.0)	18 (4.0)	11 (4.6)
Patient or physician choice[b]	8 (1.2)	17 (1.9)	13 (2.0)	8 (1.8)	1 (0.4)
Treatment failure[b]	6 (0.9)	5 (0.6)	7 (1.1)	1 (0.2)	3 (1.3)
Other medical event[b]	4 (0.6)	3 (0.3)	6 (0.9)	1 (0.2)	1 (0.4)
Exited study[b]	2 (0.3)	16 (1.8)	10 (1.5)	7 (1.6)	5 (2.1)
Other	2 (0.3)	5 (0.6)	2 (0.3)	2 (0.4)	3 (1.3)
Unknown[c]	219 (33.4)	351 (38.8)	224 (33.8)	154 (34.1)	70 (29.2)

[a]Original categories from which reasons for treatment discontinuation were recategorized; [b]Categories created following recategorization of the "Other, please specify" free text; [c]Unknown is defined as not reported, unknown treatment end, loss to follow-up, or still on treatment.

References

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2. Richter J, et al. *Blood* 2022;140(suppl 1):4338-4340.
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