Real-world treatment patterns and clinical outcomes in patients with relapsed/refractory multiple myeloma with 2-4 lines of treatment in the PREAMBLE registry

PS1768

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Introduction

- Most patients with multiple myeloma (MM) will eventually relapse or become refractory to available treatments, with a 5-year relative survival rate of only 59.8%[1,2]
- There are numerous treatment options for patients with relapsed/refractory MM (RRMM); however, patient populations are significantly heterogenous with variable disease and clinical characteristics as well as exposure and response to treatments, leading to challenges identifying the optimal therapy[1,2]
- Limited recent real-world data exist to determine clinical outcomes for patients with early RRMM (1–3 prior therapies)[1,2]
- Given the rapidly evolving treatment landscape, real-world evidence is warranted to better understand the unmet medical needs of patients with RRMM who received 2nd to 4th lines of therapy

Objective

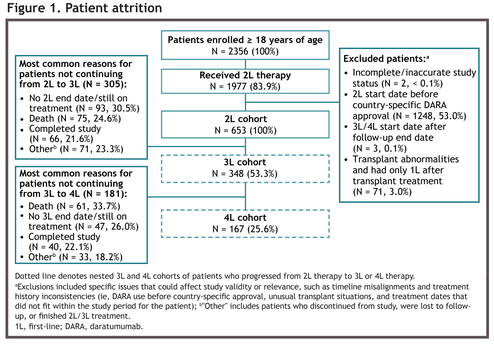
- This study aimed to describe patient characteristics, treatment patterns, and clinical outcomes in patients with RRMM who initiated second-line (2L) therapy and who went on to receive third-line (3L) or fourth-line (4L) therapy in a real-world setting

Methods

Study design

- This study included adult patients with RRMM who participated in the **P**rospective **RE**search Assessment in multiple **M**yeloma: an OB**S**ervationa**L** Evaluation (PREAMBLE) registry (NCT01838512; Jan 1, 2012, to Sep 5, 2024), and initiated 2L therapy
  - Patients who progressed to 3L or 4L were included in nested cohorts
- PREAMBLE is a global observational study that has enrolled patients with MM across Canada, France, Germany, Italy, the UK, and the USA since 2012
- Inclusion/exclusion criteria and patient attrition can be seen in **Figure 1**

Figure 1. Patient attrition



Dotted line denotes nested 3L and 4L cohorts of patients who progressed from 2L therapy to 3L or 4L therapy.
[a]Exclusions included specific issues that could affect study validity or relevance, such as timeline misalignments and treatment history inconsistencies (ie, DARA use before country-specific approval, unusual transplant situations, and treatment dates that did not fit within the study period for the patient); [b]"Other" includes patients who discontinued from study, were lost to follow-up, or finished 2L/3L treatment.
1L, first-line; DARA, daratumumab.

Variables and outcomes

- These included demographics, clinical characteristics, and treatment patterns
- Clinical outcomes included progression-free survival (PFS) and overall survival (OS)
  - PFS was defined as the time from 2L/3L/4L start date to first progression, death, or next subsequent therapy start, whichever occurred first
  - OS was defined as the time from 2L/3L/4L start date to death

Statistical analysis

- Demographics, clinical characteristics, and treatment patterns were descriptively summarized
- Kaplan–Meier methods were used to analyze PFS and OS in the 2L, 3L, and 4L cohorts and across subgroups defined by region (USA or ex-USA), age (< 75 or ≥ 75 years), race (White or Black/African American [AA]), high cytogenetic risk (yes or no), transplant status (yes or no), year of index date (< 2019 or ≥ 2019), prior treatment class exposure, and top regimens received at index date

Results

Patient characteristics

- 653 patients met the eligibility criteria and were included in the 2L cohort (**Figure 1**)
  - 348 (53.3%) and 167 (25.6%) went on to initiate 3L and 4L therapy, respectively
- Most patients who initiated 2L therapy were male (56.8%), White (70.9%), and in Europe (68.7%) (**Table 1**)

Table 1. Patient demographics and clinical characteristics

Characteristics	2L (N = 653)	3L (N = 348)	4L (N = 167)
Age at index date,[a] median (IQR), years	71 (64-77)	72 (65-78)	71 (64-77)
Sex, n (%)			
Male	371 (56.8)	197 (56.6)	92 (55.1)
Female	282 (43.2)	151 (43.4)	75 (44.9)
Race, n (%)			
White	463 (70.9)	241 (69.3)	119 (71.3)
Black/AA	44 (6.7)	22 (6.3)	8 (4.8)
Asian	4 (0.6)	2 (0.6)	0
Other	5 (0.8)	2 (0.6)	1 (0.6)
Missing/not reported	137 (21.0)	81 (23.3)	39 (23.4)
Ethnicity, n (%)			
Not Hispanic/Latino	315 (48.2)	163 (46.8)	79 (47.3)
Hispanic/Latino	11 (1.7)	4 (1.1)	2 (1.2)
Missing/not reported	327 (50.1)	181 (52.0)	86 (51.5)
Region, n (%)			
USA	204 (31.2)	112 (32.2)	55 (32.9)
France	93 (14.2)	55 (15.8)	25 (15.0)
Germany	158 (24.2)	79 (22.7)	42 (25.1)
Italy	56 (8.6)	27 (7.8)	15 (9.0)
UK	142 (21.7)	75 (21.6)	30 (18.0)
Length of follow-up, median (range), months	25.9 (0.03-84.3)	15.7 (0.1-73.7)	10.3 (0.3-56.5)
Time from diagnosis to index date,[a] median (range), months	20.8 (1.1-345.7)	30.0 (3.3-348.9)	36.5 (5.5-351.7)
Year of index date,[a] n (%)			
2016	2 (0.3)	0	0
2017	109 (16.7)	24 (6.9)	3 (1.8)
2018	130 (19.9)	57 (16.4)	18 (10.8)
2019	157 (24.0)	74 (21.3)	26 (15.6)
2020	98 (15.0)	67 (19.3)	41 (24.6)
2021	42 (6.4)	43 (12.4)	29 (17.4)
2022	36 (5.5)	31 (8.9)	14 (8.4)
2023	48 (7.4)	33 (9.5)	25 (15.0)
2024	31 (4.7)	19 (5.5)	11 (6.6)
ISS stage at study entry, n (%)			
I	92 (14.1)	45 (12.9)	25 (15.0)
II	116 (17.8)	59 (17.0)	22 (13.2)
III	144 (22.1)	77 (22.1)	35 (21.0)
Unknown/missing	301 (46.1)	167 (48.0)	85 (50.9)
Cytogenetics,n (%)			
Abnormal[b]	200 (30.6)	112 (32.2)	61 (36.5)
Normal	128 (19.6)	68 (19.5)	35 (21.0)
Unknown/missing	325 (49.8)	168 (48.3)	71 (42.5)
CCI assessed at index date,[a] n (%)	228 (34.9)	124 (35.6)	66 (39.5)
CCI at index date,[a] n (%)			
2	117 (51.3)	66 (53.2)	33 (50.0)
3	47 (20.6)	19 (15.3)	9 (13.6)
4	28 (12.3)	17 (13.7)	9 (13.6)
≥ 5	36 (15.8)	22 (17.7)	15 (22.7)

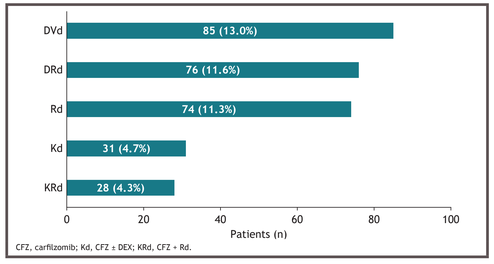
[a]Index date was defined as the start date of each line of therapy; [b]abnormal cytogenetics was defined as presence of any one of the following: t(4;14), t(14;16), del(17p), 17p/53p, IGH translocation, 1Q+, amplification 1q21.
CCI, Charlson Comorbidity Index; del, deletion; IGH, immunoglobulin heavy chain; IQR, interquartile range; ISS, International Staging System.

- Median time from diagnosis to index date was 20.8 months (2L), 30.0 months (3L), and 36.5 months (4L)
- The median length of follow-up was 25.9 months (2L), 15.7 months (3L), and 10.3 months (4L)
- Across the 3 cohorts, about 50% of patients had a CCI of 2 on index date
  - Proportionally more patients had CCI ≥ 5 in later lines compared with 2L

Treatment patterns

- The most common index regimen (± dexamethasone [DEX]) at 2L was DARA + bortezomib (BORT; DVd) (13.0%), followed by DARA + lenalidomide (LEN; DRd) (11.6%) and LEN (Rd) (11.3%) (**Figure 2**); by region, this was:
  - USA: DARA + pomalidomide (POM; DPd) (10.8%), DRd (8.3%), and DVd (7.8%)
  - Ex-USA: DVd (15.4%), Rd (15.1%), and DRd (13.1%)

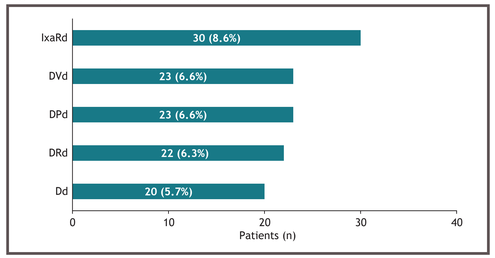
Figure 2. Top 5 regimens at 2L (N = 653)



CFZ, carfilzomib; Kd, CFZ ± DEX; KRd, CFZ + Rd.

- The most common index regimen (± DEX) at 3L was ixazomib (IXA) + LEN (IxaRd) (8.6%), followed by DVd (6.6%) and DARA + POM (6.6%) (**Figure 3**); by region, this was:
  - USA: DPd (12.5%), DARA + DEX (Dd) (8.9%), DRd (8.0%), and CFZ + POM (8.0%)
  - Ex-USA: IxaRd (10.6%), DVd (6.8%), Rd (6.8%), and POM + DEX (6.8%)

Figure 3. Top 5 regimens at 3L (N = 348)



- Patient exposure to all drug classes increased with later lines (**Table 2**)
  - 41.2% and 79.8% of patients were LEN-exposed or BORT-exposed in 1L, respectively
  - Only 5.8% of patients were DARA-exposed in 1L
  - A higher proportion of patients in the USA had prior LEN exposure before initiating 2L/3L therapy (78% at 2L, 88% at 3L) than patients in ex-USA (24% at 2L, 63% at 3L)

Table 2. Systemic therapies prior to start of 2L/3L/4L

	2L			3L			4L		
	All (N = 653)	USA (n = 204)	Ex-USA (n = 449)	All (N = 348)	USA (n = 112)	Ex-USA (n = 236)	All (N = 167)	USA (n = 55)	Ex-USA (n = 112)
Treatment exposure prior to index date, n (%)									
IMiD® agents	383 (59)	160 (78)	223 (50)	299 (86)	101 (90)	198 (84)	158 (95)	55 (100)	103 (92)
LEN	269 (41)	159 (78)	110 (24)	247 (71)	99 (88)	148 (63)	151 (90)	55 (100)	96 (86)
POM	4 (1)	1 (<1)	3 (1)	37 (11)	26 (23)	11 (5)	60 (36)	33 (60)	27 (24)
THAL	116 (18)	0	116 (26)	79 (23)	2 (2)	77 (33)	31 (19)	1 (2)	30 (27)
Proteasome inhibitors	556 (85)	178 (87)	378 (84)	336 (97)	106 (95)	230 (98)	164 (98)	54 (98)	110 (98)
BORT	521 (80)	156 (77)	365 (81)	316 (91)	96 (86)	220 (93)	161 (96)	52 (95)	109 (97)
CFZ	33 (5)	24 (12)	9 (2)	78 (22)	34 (30)	44 (19)	72 (43)	32 (58)	40 (36)
IXA	13 (2)	8 (4)	5 (1)	25 (7)	14 (13)	11 (5)	27 (16)	10 (18)	17 (15)
Anti-CD38 mAbs	39 (6)	6 (3)	33 (7)	125 (36)	44 (39)	81 (34)	106 (64)	39 (71)	67 (60)
DARA	38 (6)	6 (3)	32 (7)	123 (35)	44 (39)	79 (34)	100 (60)	39 (71)	61 (54)
ISA	1 (<1)	0	1 (<1)	2 (1)	0	2 (1)	6 (4)	0	6 (5)
Triple-class exposed[a]	15 (2)	2 (1)	13 (3)	100 (29)	37 (33)	63 (27)	96 (58)	38 (69)	58 (52)
Treatment refractoriness prior to index date, n (%)									
LEN	82 (13)	52 (26)	30 (7)	107 (31)	38 (34)	69 (29)	71 (43)	23 (42)	48 (43)
BORT	141 (22)	43 (21)	98 (22)	120 (35)	35 (31)	85 (36)	81 (49)	22 (40)	59 (53)
DARA	32 (5)	6 (3)	26 (6)	111 (32)	43 (38)	68 (29)	90 (54)	38 (69)	52 (46)

[a]Defined as prior exposure to an IMiD agent, a proteasome inhibitor, and an anti-CD38 mAb.
IMiD, immunomodulatory drug; ISA, isatuximab; mAb, monoclonal antibody, THAL, thalidomide.

- While most patients who received DVd, DRd, Rd, or Kd as their 2L therapy had prior exposure to BORT, BORT-refractory status ranged from 7.1% for DVd to 31.1% for Rd (**Table 3**)
- 43.5% of patients treated with 2L DVd and 48.4% receiving 2L Kd had prior exposure to LEN, whereas only 21.1% of those receiving 2L DRd and none of those receiving 2L Rd had prior exposure to LEN; additionally, patients who received 2L DRd and Rd were predominantly not refractory to LEN (**Table 3**)

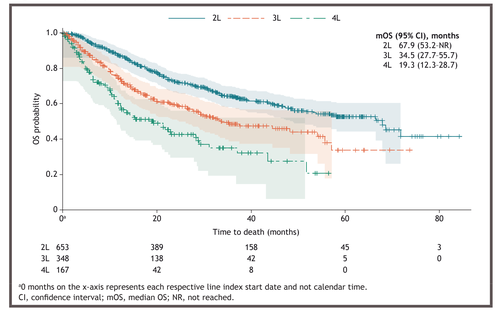
Table 3. Systemic therapies at 2L by regimens received

	DVd (N = 85)	DRd (N = 76)	Rd (N = 74)	Kd (N = 31)
Treatment exposure prior to index date, n (%)				
IMiD agents	61 (71.8)	25 (32.9)	12 (16.2)	16 (51.6)
LEN	37 (43.5)	16 (21.1)	0	15 (48.4)
POM	0	0	0	0
THAL	24 (28.2)	9 (11.8)	12 (16.2)	3 (9.7)
Proteasome inhibitors	62 (72.9)	70 (92.1)	72 (97.3)	27 (87.1)
BORT	56 (65.9)	68 (89.5)	70 (94.6)	25 (80.6)
CFZ	4 (4.7)	2 (2.6)	1 (1.4)	0
IXA	3 (3.5)	0	1 (1.4)	2 (6.5)
Anti-CD38 mAbs	2 (2.4)	2 (2.6)	4 (5.4)	2 (6.5)
DARA	2 (2.4)	2 (2.6)	4 (5.4)	1 (3.2)
ISA	0	0	0	1 (3.2)
Triple-class exposed	0	1 (1.3)	2 (2.7)	0
Treatment refractoriness prior to index date, n (%)				
LEN	9 (10.6)	3 (3.9)	0	5 (16.1)
BORT	6 (7.1)	19 (25.0)	23 (31.1)	7 (22.6)
DARA	2 (2.4)	1 (1.3)	4 (5.4)	1 (3.2)

Outcomes

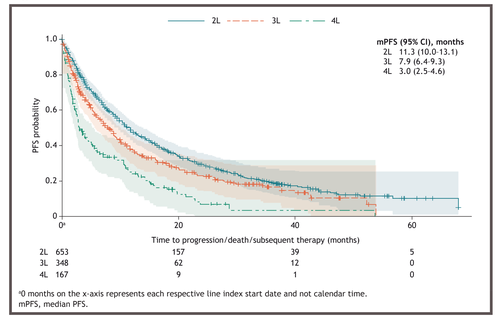
- Survival outcomes were worse in patients receiving later-line therapy (**Figures 4** and **5**)
  - 2L: mOS was 67.9 months and mPFS was 11.3 months
  - 3L: mOS was 34.5 months and mPFS was 7.9 months
  - 4L: mOS was 19.3 months and mPFS was 3.0 months

Figure 4. Kaplan-Meier estimate of OS from the 2L/3L/4L start date



[a]0 months on the x-axis represents each respective line index start date and not calendar time.
CI, confidence interval; mOS, median OS; NR, not reached.

Figure 5. Kaplan-Meier estimate of PFS from the 2L/3L/4L start date



[a]0 months on the x-axis represents each respective line index start date and not calendar time.
mPFS, median PFS.

- Survival outcomes varied based on exposure to prior therapies (**Table 4**)
  - Patients who had received LEN, BORT, and anti-CD38 mAbs as part of their 1L regimen had numerically shorter 2L mPFS compared with those who had not received these agents prior to 2L
  - Patients who were triple-class exposed prior to initiating 3L had numerically shorter 3L mPFS and mOS compared with those who were not triple-class exposed
- In patients who received 2L therapy, mPFS was 13.2, 19.5, 10.6, and 4.9 months for those who received DVd, DRd, Rd, and Kd, respectively (**Table 4**)
- For patients on 3L therapy who received IxaRd, mPFS was 20.0 months (not shown)

Table 4. Kaplan-Meier estimates of PFS and OS for 2L and 3L cohorts by subgroup

	2L cohort			3L cohort		
Subgroup	n	mPFS (95% CI), months	mOS (95% CI), months	n	mPFS (95% CI), months	mOS (95% CI), months
Region						
USA	204	8.7 (6.6-10.6)	NR (39.1-NR)	112	6.0 (5.0-8.3)	33.0 (19.8-NR)
Ex-USA	449	12.9 (11.1-15.1)	66.5 (49.2-NR)	236	9.0 (6.9-11.0)	44.6 (27.7-55.7)
Age						
< 75 years	429	10.8 (9.2-14.5)	71.8 (66.5-NR)	219	8.3 (5.6-10.0)	48.3 (29.8-NR)
≥ 75 years	224	12.0 (9.7-13.6)	45.0 (30.2-NR)	129	7.9 (5.9-10.2)	26.2 (14.5-37.6)
High cytogenetic risk						
Yes	128	8.8 (6.2-10.9)	49.0 (30.4-NR)	71	5.6 (3.4-9.3)	24.7 (15.1-44.6)
No	525	12.1 (10.6-14.8)	67.9 (53.9-NR)	277	8.7 (6.9-10.2)	48.3 (29.2-57.1)
2L or 3L start date						
Before 2019	241	10.5 (7.9-14.3)	66.5 (44.8-NR)	81	6.7 (3.8-10.0)	29.8 (16.4-55.7)
On or after 2019	412	12.0 (10.2-14.0)	NR (51.5-NR)	267	8.7 (6.0-10.2)	37.6 (27.5-NR)
≥ 1 transplant prior to 2L or 3L						
Yes	156	10.9 (8.3-17.5)	68.6 (48.3-NR)	129	8.7 (5.4-10.0)	44.6 (24.7-55.7)
No	497	11.7 (9.8-13.2)	67.9 (49.0-NR)	219	7.4 (5.8-10.0)	31.3 (24.4-NR)
Race						
White	463	10.9 (9.7-13.2)	58.2 (44.8-NR)	241	6.9 (5.6-8.8)	30.2 (20.3-54.2)
Black/AA	44	7.9 (6.0-17.0)	NR (30.9-NR)	22	8.3 (2.8-27.6)	NR (16.0-NR)
Prior LEN exposure						
Yes	269	10.5 (7.9-13.1)	NR (45.0-NR)	247	6.0 (5.0-7.4)	27.7 (18.6-35.3)
No	384	12.0 (10.2-14.3)	66.5 (49.2-NR)	101	16.4 (9.1-22.8)	55.7 (37.6-NR)
Prior BORT exposure						
Yes	521	10.8 (9.2-12.6)	66.5 (48.3-NR)	316	8.5 (6.7-10.0)	34.5 (27.5-57.1)
No	132	13.2 (10.2-18.0)	NR (57.0-NR)	32	4.2 (2.5-10.2)	28.8 (12.5-55.7)
Prior anti-CD38 mAb exposure						
Yes	39	6.0 (2.5-9.7)	NR (16.0-NR)	125	7.8 (5.4-9.4)	33.4 (16.7-NR)
No	641	12.0 (10.5-14.1)	67.9 (53.2-NR)	223	8.5 (6.0-11.0)	37.6 (26.7-55.7)
Triple-class exposed						
Yes	15	3.0 (1.0-NR)	16.3 (4.1-NR)	100	6.4 (5.0-9.0)	18.6 (14.4-35.3)
No	638	11.6 (10.2-13.6)	67.9 (53.9-NR)	248	8.8 (6.7-11.0)	48.3 (29.8-57.1)
Top 4 regimens at 2L						
DVd	85	13.2 (10.2-16.2)	NR (44.0-NR)	-	-	-
DRd	76	19.5 (9.8-28.8)	NR (37.7-NR)	-	-	-
Rd	74	10.6 (7.4-17.9)	53.9 (24.3-NR)	-	-	-
Kd	31	4.9 (2.4-8.7)	22.2 (14.1-47.0)	-	-	-

Limitations

- Data may not be representative of patients outside of the PREAMBLE registry
- Capture of data from patient history prior to PREAMBLE enrollment for patients with RRMM may contribute to measurement bias
  - Functional high-risk data (ie, early relapse to 1L treatment) was not captured and could therefore not be analyzed
- The data are descriptive in nature

Conclusions

- There is no clear standard of care for patients with early RRMM in real-world clinical practice
- Prior therapies may impact the clinical outcomes of subsequent therapies
  - Future studies are needed to confirm this by adjusting for confounders
- Poor 2L and 3L PFS outcomes emphasize the existing unmet needs in patients with early RRMM and the demand for new treatment options
- This study highlights the importance of identifying unmet need and prior exposures in real-world patients, who represent a different and more generalizable population than patients enrolled in clinical trials

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