Frequency and Impact of Retreatment in Relapsed Refractory Multiple Myeloma: Real-World Survey Conducted in 5 European Countries (France, Germany, Italy, Spain, and the United Kingdom)

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BACKGROUND

- Multiple myeloma (MM) accounts for ≈10% of all haematological cancers[1]
  - The annual estimated incidence in Europe is 4.5 to 6.0/100,000[2]
- Recent approval of multiple new agents with various mechanisms of action have helped to improve patient disease management. However, MM remains incurable[1,3]
  - Approval and use of regimens containing proteasome inhibitors (PI), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs) in first-line (1L) treatment for MM has improved patient outcomes[1,4-6]
  - However, over time, patients become refractory to any one or combination of the recommended 1L agents, including bortezomib (BORT), lenalidomide (LEN), or daratumumab (DARA), and report poor outcomes[2,7]
- Patients with relapsed or refractory MM (RRMM) often receive multiple lines of therapy (LOTs); deciding which agents and/or combinations to use for patients who relapse in the context of a rapidly evolving treatment landscape can be challenging[1,3]
- Multiple factors, including patient and physician preferences, geography and access to different MM treatments may impact which regimens are used or re-used during the patient journey[8-10]
- Valuable insights into the complexities of regimen choices from real-world data on retreatment patterns and clinical practices can help inform patients' treatment options as their disease progresses

OBJECTIVES

- To describe the real-world treatment patterns of patients with RRMM in France, Germany, Italy, Spain, and the United Kingdom (UK), with a focus on:
  - Retreatment patterns
  - Time-to-event outcomes
  - Physician retreatment decision-making

METHODS

- Real-world data on both physician and patient treatment experiences were obtained from the Adelphi MM Disease Specific Programme™ (DSP),[11-13] a point-in-time survey of haematologists and haemato-oncologists
- The DSP survey was conducted from May to November 2021 in France, Germany, Italy, Spain, and the UK
- Online patient record forms were completed by physicians for 8 consecutive consulting patients with MM
  - A quota of ≥2 patients for each LOT and for the triple-class exposed (PI/IMiD/anti-CD38 mAb) cohort were recruited
  - Physicians selected from 5 reasons (focusing on physician experience, patient needs, insurance, and guidelines) for prescribing treatment at each LOT received
- At the time of data collection and historically (back to MM diagnosis), descriptive information on demographics, MM retreatment patterns, and physician decision making were collated and analyzed by LOT since diagnosis
  - The base of patients could differ from variable to variable because missing data were not imputed
  - No statistical comparisons were made; all analyses were descriptive in nature
- Limitation: only patients seeking care for MM and actively on treatment were included; therefore, results may not be representative of the full MM population

Key physician eligibility criteria	Key patient eligibility criteria
▪ Specialty in haematology or haem-oncology	▪ ≥18 years old
▪ ≥6 patients with RRMM seen per month	▪ Confirmed medical diagnosis of MM
▪ Personally responsible for prescribing decisions for patients with MM	▪ Undergoing active systemic drug treatment for MM
▪ Agreed to adhere to all survey rules and responsibilities	▪ Not involved in a clinical trial
	▪ Not receiving only best supportive care

RESULTS

Patient demographics and clinical characteristics

- A total of 256 physicians provided data for 1778 patients with RRMM who received ≥ 2 LOTs; 29%, 36%, and 31% received 2, 3, and 4 LOTs, respectively
- Across countries, patient demographics and clinical characteristics were generally similar (**Table 1**)
  - France had a high percentage of patients with International Staging System stage III disease
  - Germany had a low percentage of patients who underwent stem cell transplant (SCT) at 1L induction therapy

Table 1. Patient Demographics and Clinical Characteristics by Country

		Total (n=1778)	France (n=377)	Germany (n=339)	Italy (n=388)	Spain (n=333)	UK (n=341)
	Median age, years (IQR)	72 (66-77)	74 (69-78)	71 (67-74)	71 (64-77)	73 (66-79)	72 (65-77)
	Male, n (%)	999 (56)	190 (50)	206 (61)	220 (57)	184 (55)	199 (58)
	Stage at data collection, n %						
	I	167 (9)	16 (4)	33 (10)	45 (12)	44 (13)	29 (9)
	II	408 (23)	59 (16)	119 (35)	78 (20)	91 (27)	61 (18)
	III	970 (55)	270 (72)	161 (47)	221 (57)	148 (44)	170 (50)
	Unknown/not assessed	233 (13)	32 (8)	26 (8)	44 (11)	50 (15)	81 (24)
	ECOG PS at data collection, n (%)						
	0	298 (17)	50 (13)	21 (6)	74 (19)	64 (19)	89 (26)
	1	904 (51)	217 (58)	177 (52)	168 (43)	163 (49)	179 (52)
	2	446 (25)	83 (22)	112 (33)	104 (27)	79 (24)	68 (20)
	3	117 (7)	24 (6)	29 (9)	37 (10)	22 (7)	5 (1)
	4	12 (1)	3 (1)	0	5 (1)	4 (1)	0
	Unknown/not assessed	1 (<1)	0	0	0	1 (<1)	0
	SCT, n (%)						
	Eligible	216 (12)	39 (10)	36 (11)	42 (11)	63 (19)	36 (11)
	Received SCT	533 (30)	118 (31)	81 (24)	105 (27)	135 (41)	94 (28)
	Received SCT at 1L[a]	481 (90)	110 (93)	56 (69)	100 (95)	125 (93)	90 (96)
	Autologous[b]	475 (99)	110 (100)	55 (98)	98 (98)	124 (99)	88 (98)
	Allogeneic[b]	6 (1)	0	1 (2)	2 (2)	1 (1)	2 (2)
	Lines of therapy, n (%)[c]						
	2	508 (29)	141 (37)	70 (21)	138 (36)	87 (26)	72 (21)
	3	637 (36)	124 (33)	157 (46)	119 (31)	114 (34)	123 (36)
	4	555 (31)	96 (25)	108 (32)	115 (30)	112 (34)	124 (36)
	≥5	78 (4)	16 (4)	4 (1)	16 (4)	20 (6)	22 (6)

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SCT, stem cell transplant.
[a] Percentage based on patients who received SCT. [b] Percentage based on patients who received SCT at 1L. [c] Patient numbers by lines of therapy are mutually exclusive.

1L treatment regimens

- PI and/or IMiD agents were common 1L treatments across all 5 countries (**Table 2**)
  - PI only use was 42% and IMiD only use was 13%
    - Patients in Germany (48%) had the highest use of PIs only in 1L, whereas those in the UK (28%) reported the highest use of IMiDs only
  - 39% of patients were double-class (PI/IMiD or PI/anti-CD38 mAb or IMiD/anti-CD38 mAb) treated in 1L
  - Anti-CD38 mAb use was generally low across countries; however, Germany had the highest proportion of patients that were triple-class (PI/IMiD/anti-CD38 mAb) treated in 1L
- Across all 5 countries BORT (80%) and LEN (25%) were the most common 1L agents; use of DARA (5%) in 1L was low

Retreatment regimens

- Retreatment with IMiDs or PIs was seen in 70% and 62% of patients across all countries, respectively (**Figure 1**)
  - The overall pattern of retreatment was generally similar across countries, except in Germany where retreatment with a PI was more common than retreatment with an IMiD
- LEN (21%) and BORT (29%) were common retreatment agents, but their use varied by country
  - LEN retreatment rates were low in the UK (10%) and Spain (11%) and high in Germany (35%) (**Figure 2A**)
  - Most BORT retreatment was seen in second-line (2L), but it varied by country with some countries (Italy and Spain) having more BORT retreatment in third-line (3L) (**Figure 2B**)
  - Patients in the UK had a low rate of BORT retreatment in 3L and fourth-line (4L) (**Figure 2B**)
- Retreatment with anti-CD38 mAbs was low in general (**Figure 1**)
  - DARA retreatment was 3% in 4L and infrequently observed in earlier lines (1% each) (**Figure 2C**)

Table 2. Use of Select 1L Treatments by Country

1L treatment, n (%)		Total (n=1778)	France (n=377)	Germany (n=339)	Italy (n=388)	Spain (n=333)	UK (n=341)
Key agent class[a]	PI	746 (42)	153 (41)	163 (48)	157 (40)	155 (47)	118 (35)
	IMiD	235 (13)	50 (13)	35 (10)	31 (8)	25 (8)	94 (28)
	PI/IMiD	648 (36)	151 (40)	93 (27)	163 (42)	123 (37)	118 (35)
	PI/anti-CD38 mAb	14 (1)	1 (<1)	5 (1)	2 (1)	6 (2)	0
	IMiD/anti-CD38 mAb	34 (2)	13 (3)	4 (1)	17 (4)	0	0
	Triple class[b]	41 (2)	6 (2)	14 (4)	7 (2)	7 (2)	7 (2)
Key agent	BORT	1430 (80)	309 (82)	262 (77)	326 (84)	291 (87)	242 (71)
	LEN	445 (25)	137 (36)	132 (39)	72 (19)	66 (20)	38 (11)
	DARA	89 (5)	20 (5)	23 (7)	26 (7)	13 (4)	7 (2)

[a] Class received at 1L induction therapy. [b] PI + IMiD + anti-CD38 mAb.

Figure 1. Proportion of Patients Retreated With a PI, IMiD, or Anti-CD38 mAb by Country

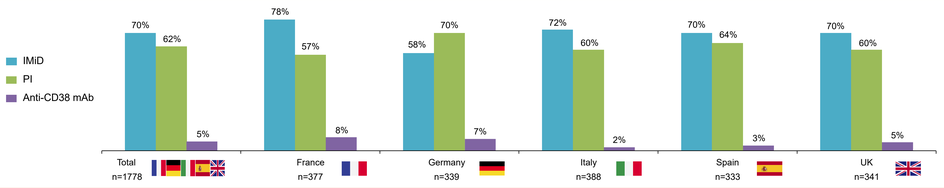


Figure 2A. Proportion of Patients Retreated With LEN by LOT and Country

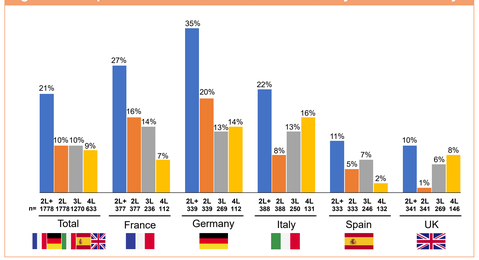


Figure 2B. Proportion of Patients Retreated With BORT by LOT and Country

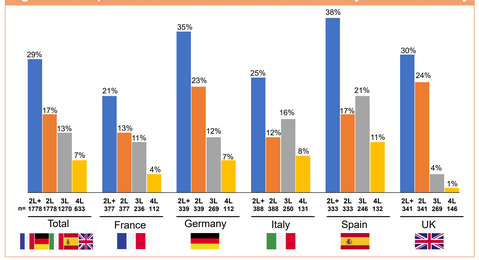
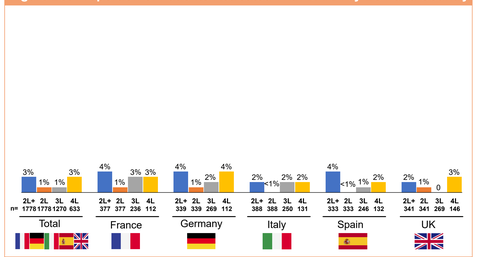


Figure 2C. Proportion of Patients Retreated With DARA by LOT and Country



Physician reasons for starting and stopping retreatment with the same agent

- Following treatment guidelines was a main reason for choosing retreatment with BORT or LEN across LOTs (**Table 3**)
  - Other key reasons for retreatment with these agents were health insurance coverage of medication costs and the physician's personal experience or familiarity
  - Health insurance coverage was a key reason for DARA retreatment in 2L and 4L
- Disease progression was the primary reason for stopping retreatment, regardless of agent and LOT

Table 3. Selected Physician Reasons for Prescribing and Stopping Retreatment with BORT, LEN, or DARA by LOT[a]

	Retreatment with BORT			Retreatment with LEN			Retreatment with DARA		
	2L	3L	4L	2L	3L	4L	2L	3L	4L
Prescribing treatment, n (%)	n=309	n=164	n=43	n=180	n=129	n=59	n=10	n=18	n=17
Guidelines	168 (54)	98 (60)	21 (49)	91 (51)	62 (48)	35 (59)	2 (20)	9 (50)	7 (41)
Cost of treatment covered by health insurance	117 (38)	60 (37)	16 (37)	65 (36)	52 (40)	10 (17)	5 (50)	5 (28)	8 (47)
Personal experience/familiarity	114 (37)	66 (40)	20 (47)	75 (42)	49 (38)	27 (46)	3 (30)	8 (44)	3 (18)
Stopping treatment, n (%)	n=237	n=88	n=12	n=120	n=64	n=7	n=1	n=9	n=0
Disease progression/relapse	155 (65)	65 (74)	10 (83)	81 (68)	45 (70)	6 (86)	1 (100)	5 (56)	–
Patient refractory to treatment	11 (5)	8 (9)	2 (17)	7 (6)	7 (11)	–	–	1 (11)	–
Patient experienced toxicity/AE	3 (1)	7 (8)	–	5 (4)	1 (2)	–	–	2 (22)	–
Frequency of administration	16 (7)	1 (1)	–	7 (6)	1 (2)	–	–	–	–
Patient request	4 (2)	5 (6)	–	11 (9)	5 (8)	1 (14)	–	–	–
Poor compliance to therapy care	6 (3)	2 (2)	–	5 (4)	5 (8)	–	–	1 (11)	–

AE, adverse event.
[a] In the total population.

Patient outcomes by LOT

- No clear trends were observed with BORT or LEN retreatment for median duration of treatment (mDOT) and median time to next treatment (mTTNT) (**Table 4**)
- The number of patients retreated with DARA in 2L or 3L was small; however, there may be a trend for mDOT and mTTNT to be shorter in DARA-retreated patients

Table 4. mDOT and mTTNT Outcomes in the Total Population

	BORT		LEN		DARA	
	Retreatment	No retreatment	Retreatment	No retreatment	Retreatment	No retreatment
mDOT[a]						
2L (n=1067)	n=183	n=884	n=90	n=977	n=2	n=1065
%	17	83	8	92	<1	>99
Months	7.2	11.3	10.9	10.7	6.6	10.8
3L (n=551)	n=83	n=468	n=57	n=494	n=9	n=542
%	15	85	10	90	2	98
Months	10.8	10.5	10.0	10.8	4.0	10.8
4L (n=92)	n=12	n=80	n=8	n=84	n=0	n=92
%	13	87	9	91	0	100
Months	7.9	7.0	9.7	6.6	–	7.0
mTTNT (start of listed line to start of next line)[b]						
2L (n=1069)	n=188	n=881	n=91	n=978	n=1	n=1068
%	18	82	9	91	<1	>99
Months	16.1	16.4	15.0	16.5	4.4	16.4
3L (n=540)	n=81	n=459	n=58	n=482	n=9	n=531
%	15	85	11	89	2	98
Months	16.0	14.3	16.8	14.0	4.0	14.6
4L (n=68)	n=11	n=57	n=6	n=62	n=0	n=68
%	16	84	9	91	0	100
Months	13.3	11.7	12.9	11.8	–	11.9

[a] Includes patients with known LOT start and end date. [b] Includes patients with known start date of listed line and next line.

CONCLUSIONS

- In this analysis of 1778 patients who received ≥ 2 LOTs for RRMM treatment, most patients were retreated with an IMiD or a PI in 2L and 3L therapy
  - Patients in France, Italy, Spain, and the UK were more likely to be retreated with an IMiD, whereas in Germany retreatment with a PI was more often observed
- Retreatment with BORT and LEN was common in 2L and 3L
  - Patients in France and Italy were more likely to have retreatment with LEN, whereas those in Spain and the UK were observed more often to have BORT retreatment
  - In Germany, retreatment of patients with LEN or BORT was similar
  - Overall, DARA retreatment rates were low, which may be reflective of its more recent (2018) approval for 1L use, leaving little opportunity to retreat with DARA
- Although sample sizes were limited, some trends in the time-to-event outcomes may exist, suggesting some retreatment options may be suboptimal in a real-world setting
- The variation in retreatment patterns between countries was more prominent with LEN-based regimens compared with others
- When choosing to retreat with BORT or LEN, most physicians cited "following treatment guidelines" as a common reason; but health insurance coverage appeared to have influenced retreatments with DARA
- Disease progression was cited as the primary reason for stopping a retreatment regimen, regardless of agent and/or LOT
- These real-world data on retreatment patterns implies there is a need for novel treatments for RRMM with new mechanisms of action

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SP, TdE, and PFW are employees of GSK.

Abbreviations
1L, first line; 2L, second line; 3L, third line; 4L, fourth line; AE, adverse event; BORT, bortezomib; DARA, daratumumab; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory drug; IQR, interquartile range; LEN, lenalidomide; LOT, line of therapy; mAb, monoclonal antibody; mDOT, median duration of treatment; MM, multiple myeloma; mTTNT, median time to next treatment; PI, proteasome inhibitor; RRMM, relapsed refractory multiple myeloma; SCT, stem cell transplant.

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