Evolving Treatment Trends in Relapsed/Refractory Multiple Myeloma in Europe from 2016 to 2018: Analysis of a Multi-National Survey

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Background

- Recently, treatment options for RRMM have increased substantially with multiple approvals of novel agents and combinations (**Table 1**).[1–11]
  - Patients with RRMM now generally receive a range of different doublet or triplet regimens.[12]
- These approvals have made the MM treatment algorithm increasingly complex, with changes driven chiefly by access to novel agents and regimens.
- Furthermore, patient and disease characteristics have a profound impact on treatment decision-making.

Table 1. Key treatment options approved for RRMM since 2015

Agent	Regimen	Study	Median age, yrs*	US approval	US label	EU approval	EU label
Carfilzomib	KRd	ASPIRE[1]	64	July 2015	1–3 prior lines	Nov 2015	≥1 prior therapy
	Kd	ENDEAVOR[2]	65	Jan 2016	1–3 prior lines	July 2016	≥1 prior therapy
Ixazomib	IRd	TOURMALINE-MM1[3]	66	Nov 2015	≥1 prior therapy	Nov 2016	≥1 prior therapy
Daratumumab	Single-agent	SIRIUS[4]	63.5	Nov 2015	≥3 prior lines (inc. a PI and an IMiD)	May 2016	RRMM (prior therapy inc. a PI and an IMiD)
	DRd	POLLUX[5]	65	Nov 2016	≥1 prior therapy	April 2017	≥1 prior therapy
	DVd	CASTOR[6]	64	Nov 2016	≥1 prior therapy	April 2017	≥1 prior therapy
	D-Pom-dex	EQUULEUS[7]	64	June 2017	≥2 prior therapies (inc. a PI and R)	N/A	N/A
Elotuzumab	Elo-Rd	ELOQUENT-2[8]	67	Nov 2015	1–3 prior therapies	May 2016	≥1 prior therapy
	Elo-Pom-dex	ELOQUENT-3[9]	69	Nov 2018	≥2 prior therapies (inc. a PI and R)	Aug 2019	≥2 prior therapies (inc. a PI and R)
Pomalidomide	Pom-Vd	OPTIMISMM[10]	67	N/A	N/A	May 2019	≥1 prior regimen (inc. R)
(Approval prior to 2015)	Pom-dex	MM-003[11]	64	Feb 2013	≥2 prior therapies (inc. a PI and R)	Aug 2013	≥2 prior regimens (inc. V and R)

*Median age shown for investigational arm.

Objective

- To investigate the management of RRMM across Europe and understand the impact of recently approved novel regimens on real-world treatment patterns.

Methods

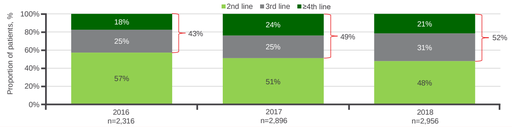
- This multi-national survey (iREAL) extracted retrospective, anonymized data from patients with RRMM treated in academic or community hospitals and practices in eight selected European countries from January 2016 to December 2018.
  - Center selection was conducted based on epidemiologic research and analysis; the patient sample was determined by considering the distribution of the treated prevalence on the healthcare providers, the regional population density, and the healthcare structure.
  - Data were analyzed overall and for Germany, Austria, and Switzerland (DACH) versus other countries (Belgium, France, Greece, Spain, and UK; non-DACH) due to differences in treatment access.
- Patients with RRMM, defined as undergoing ≥2nd-line treatment, who were receiving treatment on a regular or other type of prescription or on a named-patient program, were included.
  - Centers reported all RRMM patients treated in the reporting period retrospectively back to initial diagnosis based on data in the patients' files; treatment course data were updated and new RRMM patients were included quarterly.
  - Patients receiving treatment in clinical trials were excluded.
  - Data on prior 1st-line treatment were gathered retrospectively from patient records.
- Treatment regimens were classified according to the 'leading agent' in the combination:
  - PI-based regimens included bortezomib-based, carfilzomib-based, and ixazomib-based regimens, and could include doublets and triplets in combination with IMiDs (but not mAbs)
  - IMiD-based regimens included thalidomide-based, lenalidomide-based, and pomalidomide-based regimens that did not also include a PI or a mAb
  - mAb-based regimens included daratumumab-based and elotuzumab-based regimens, and could include single-agent use, doublets, and triplets in combination with PIs or IMiDs.
- Rates of treatment initiation due to biochemical relapse (based on M-protein level only, no symptoms) are summarized in **Figure 4**.
- Approximately one third of patients manifested an asymptomatic rather than clinical relapse.
  - The reason for the apparent decrease in rate of biochemical relapses from 2016 to 2018 in later lines of therapy is not clear.

Results

Patient disposition and characteristics

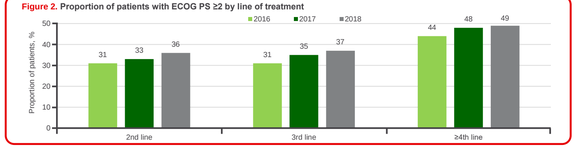
- The total number of patients included was 2,782 in 2016, 3,902 in 2017, and 4,658 in 2018, including:
  - 1,202, 1,704, and 2,047 in DACH countries (Germany: 1,024, 1,469, 1,805; Austria: 101, 124, 139; Switzerland: 77, 111, 103)
  - 1,580, 2,198, and 2,611 in non-DACH countries (Belgium: 101, 202, 268; France: 617, 820, 974; Greece: 91, 95, 76; Spain: 411, 586, 640; UK: 360, 495, 653).
- Of the patients enrolled who initiated a new treatment in 2016, 2017, and 2018, 40%, 49%, and 51%, respectively, were in 3rd line or beyond (**Figure 1**).
  - This potentially reflects the increasing availability of treatment options for RRMM and extended survival in MM.

Figure 1. Line of therapy in which RRMM patients initiated a new treatment, by year



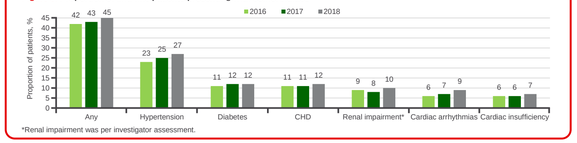
- The data revealed a real-world population that was older and with poorer PS than RCT populations, and that had a substantial comorbidity burden.
- Median age at diagnosis for patients enrolling in 2016, 2017, and 2018, was 68, 69, and 70 years, respectively.
  - 23%, 24%, and 26% of these patients were aged >75 years.
  - 58%, 57%, and 58% of patients were male.
- Median age at 2nd-, 3rd- and ≥4th-line was 71–73 years.
  - These real-world patients appear older than phase 3 RRMM RCT populations, in which median age was 64–67 years.[1–3, 5–7, 8, 10, 11]
- Approximately one third of patients had an ECOG PS ≥2 at 2nd line in 2016–2018, increasing to >40% at ≥4th line (**Figure 2**).
  - This compares to reported rates of ECOG PS 2 of 5–10% in phase 3 RRMM RCTs.[1–3]

Figure 2. Proportion of patients with ECOG PS ≥2 by line of treatment



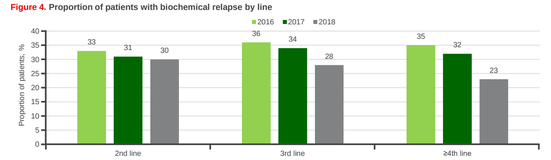
- Among 2nd-line patients, >40% presented with ≥1 treatment-dependent comorbidity in 2016–2018, including hypertension in 23–27% and renal impairment in 9–10% (**Figure 3**).
  - Comorbidity burden was similar at 3rd line and ≥4th line (data not shown).
- Cytogenetic risk was evaluated in 38%, 39%, and 42% of patients at initial diagnosis among those included in iREAL in 2016, 2017, and 2018, respectively.
  - The proportion of patients with high-risk cytogenetics, defined as del(17), t(4;14), or t(14;16), was 8%, 10%, and 10% of the total population, respectively.

Figure 3. Proportion of 2nd-line patients presenting with comorbidities



*Renal impairment was per investigator assessment.

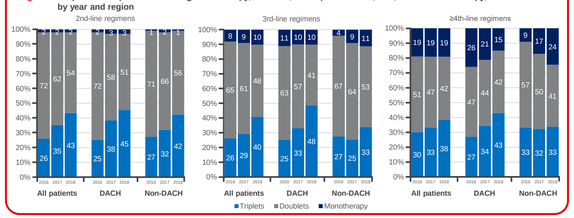
Figure 4. Proportion of patients with biochemical relapse by line



Treatment patterns

- The proportion of patients treated with triplet regimens increased in all lines of therapy from 2016 to 2018, reflecting the adoption of newly approved triplets in RRMM, particularly in DACH countries (**Figure 5**).
  - The limited adoption in non-DACH countries in later lines may be associated with delayed access and possibly limited availability of additional triplet options following relapse/refractoriness to prior regimens.

Figure 5. Proportions of patients receiving monotherapy, doublets, and triplets as 2nd-, 3rd-, and ≥4th-line therapy, by year and region



- The proportions of patients treated with PI-based regimens as 2nd-, 3rd-, and ≥4th-line therapy increased from 2016 to 2018 (**Figure 6**), as did the use of daratumumab-based regimens (**Figure 7**).
  - The increased use of PI-based regimens was driven by increased/earlier use of the novel PIs carfilzomib and ixazomib.
  - These trends were more obvious in DACH, highlighting the impact of earlier access to modern treatment in these countries.

Figure 6. Proportions of patients receiving PI-based treatment as 2nd-, 3rd-, and ≥4th-line therapy, by year and region

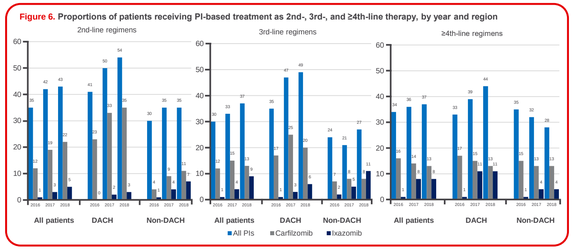
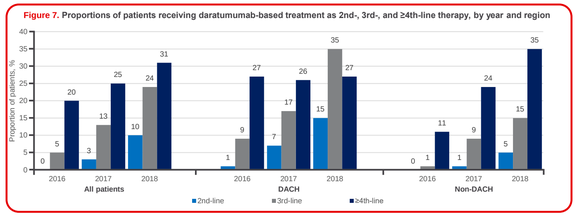


Figure 7. Proportions of patients receiving daratumumab-based treatment as 2nd-, 3rd-, and ≥4th-line therapy, by year and region



- Proportions of patients receiving specific key novel treatment regimens are summarized in **Table 2**.

Table 2. Change in rates of use of key novel treatment regimens in Europe, 2016 to 2018

Regimen, %*	2nd-line therapy			3rd-line therapy			4th-line therapy		
	2016	2017	2018	2016	2017	2018	2016	2017	2018
Carfilzomib-based triplets (KRd)	7.9	11.4	12.7	6.3	4.9	3.7	6.2	4.3	4.7
Carfilzomib-based doublets (Kd)	4.3	7.7	9.0	5.4	10.5	9.6	9.9	9.8	8.4
Ixazomib-based (IRd)	0.5	3.0	5.1	1.5	3.9	8.9	0.9	8.2	8.2
DRd	0.2	2.2	5.9	0	2.7	6.0	0.2	2.3	3.6
DVd	0	0.5	2.3	0	1.6	6.8	0.6	2.3	4.7
Dd	0.1	0.6	1.2	4.7	8.0	10.1	19.3	20.5	21.6
Elo-based	0.6	2.0	1.9	1.6	2.4	3.4	1.1	3.2	3.3
Pom-based	1.0	1.0	0.7	25.5	21.3	20.7	22.2	15.6	16.5

*% of treated patients with regimen data.

- The progression-free period (time from start of one line to start of next line) decreased with increasing number of relapses (**Table 3**).
  - Further investigation is needed to clarify these trends over time.

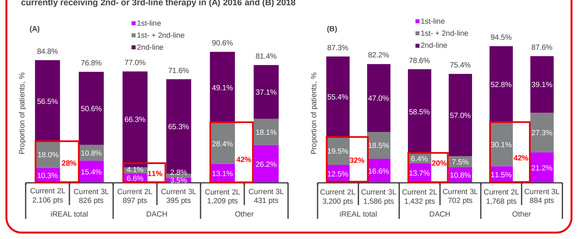
Table 3. Median time from start of one line of therapy to start of subsequent line, by year

Treatment period		2016	2017	2018
Start of 1st-line (including SCT) to start of 2nd-line treatment	N	802	1034	1144
	Median progression-free period, months (range)	35 (0–198)	35 (0–198)	34 (0–210)
Start of 1st-line (no SCT) to start of 2nd-line treatment	N	1814	2649	3298
	Median progression-free period, months (range)	17 (0.5–380)	14 (0.5–380)	15 (0.7–380)
Start of 2nd-line to start of 3rd-line treatment	N	1250	1210	668
	Median progression-free period, months (range)	16 (0.4–96)	14 (0.5–96)	13 (0.5–96)
Start of 3rd-line to start of 4th-line treatment	N	507	574	331
	Median progression-free period, months (range)	11 (0.5–71)	9 (0.6–71)	9 (0.9–67)

Treatment sequencing

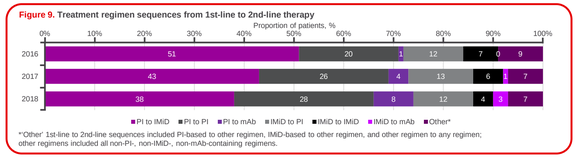
- From 2016 to 2018, prior IMiD exposure among patients receiving 2nd-line therapy increased from 28% to 32% overall, including from 11% to 20% in DACH (**Figure 8**).
  - This may be associated with the approval of Rd as frontline therapy in Europe in February 2015 and the approval of lenalidomide as post-ASCT maintenance therapy in Europe in February 2017.
  - Among patients receiving 3rd-line therapy, there was an increase in prior IMiD exposure from 77% to 82% in all countries, reflecting the uptake of novel triplet combinations.
  - Rates of prior IMiD exposure appeared higher in non-DACH versus DACH, associated with a higher rate of frontline thalidomide use in certain non-DACH countries.
- Most patients were IMiD-exposed or IMiD-refractory at ≥4th line (data not shown).

Figure 8. Prior and current treatment with IMiDs as induction or maintenance in 1st- and/or 2nd-line therapy among patients currently receiving 2nd- or 3rd-line therapy in (A) 2016 and (B) 2018



- The rate of PI-based treatment as 1st-line therapy was 74%, 74%, and 75% in 2016, 2017, and 2018, respectively.
- Among these patients (**Figure 9**):
  - Any PI-based to any IMiD-containing therapy was the most common treatment sequence in all years
  - Any PI-based to any PI-based therapy use increased from 20% in 2016 to 28% in 2018
  - Any PI-based to any mAb-based therapy use also increased from 1% to 8%.

Figure 9. Treatment regimen sequences from 1st-line to 2nd-line therapy



*'Other' 1st-line to 2nd-line sequences included PI-based to other regimen, IMiD-based to other regimen, and other regimen to any regimen; other regimens included all non-PI-, non-IMiD-, non-mAb-containing regimens.

Drivers of treatment selection

- The frequencies of key disease, patient, and treatment journey characteristics among all patients and among patients receiving select key regimens for 2nd-line and ≥3rd-line therapy in 2018 are summarized in **Table 4** and **Table 5**, respectively.
- Among patients receiving IMiD-based therapies in subsequent lines, the rates of prior IMiD treatment were significantly lower than in the overall population.
  - Conversely, the rates of prior PI exposure were lower than average among patients receiving Kd and DVd at 2nd line, and higher than average among patients receiving Rd-based therapies at 2nd line.
- At 2nd line, the proportions of patients with ISS Stage III disease were higher among those receiving KRd, Kd, DRd, and DVd but lower among those receiving Dd, IRd, and R/Rd.
  - Conversely, the proportion of patients having a prior biochemical relapse was higher among patients subsequently receiving IRd.
- The groups receiving KRd and DRd included higher proportions of younger and fitter patients.
  - However, there was a lower-than-average rate of cardiac comorbidities in those patients receiving KRd.
- Of note, at 3rd line the treatment choices are also driven by access to novel-agent-based regimens in the prior 2nd-line setting.

Table 4. Patient/disease and treatment journey characteristics (%) among patients in 2018 receiving specific 2nd-line regimens

Characteristic	Any regimen*	KRd	Kd	DRd	DVd	Dd	IRd	R/Rd
Age <70 years	38.7	46.8	41.3	49.2	37.5	46.2	39.9	32.1
ECOG PS ≤1	64.6	77.5	32.6	70.9	66.7	71.8	63.8	61.8
Cardiac comorbidities	36.2	20.0	60.4	25.4	33.3	38.5	35.6	38.3
ISS Stage III	42.1	52.8	60.4	54.0	61.1	25.6	27.0	32.2
High-risk cytogenetics†	10.8	13.1	5.9	5.3	6.9	7.7	14.1	8.4
Prior SCT	22.7	28.9	10.8	30.2	20.8	30.8	25.8	17.8
Prior PI treatment	77.0	95.8	56.9	87.3	34.7	89.7	89.0	82.5
Prior IMiD treatment	16.8	3.2	37.8	11.1	62.5	7.7	9.2	8.2
Initiated in university hospital	40.4	18.5	13.9	14.3	18.1	28.2	41.7	49.6
Biochemical relapse	30.2	25.2	35.1	23.8	34.7	35.9	44.2	28.5
Biochemical and symptomatic relapse	54.1	62.0	47.6	55.0	43.1	30.8	48.5	56.7
Symptomatic relapse	14.6	10.6	16.3	21.2	20.8	30.8	6.1	13.9

Colored cells denote significant positive (green) or negative (red) difference from values for 'any regimen' (p<0.05, multivariate analysis).
*Not all regimens included in 'any regimen' are represented in the table.
†Presence of del17, t(4;14), or t(14;16).

Table 5. Patient/disease and treatment journey characteristics (%) among patients in 2018 receiving specific ≥3rd-line regimens

Characteristic	Any regimen*	KRd	Kd	DRd	DVd	Dd	IRd	R/Rd
Age <70 years	38.6	57.9	43.5	41.7	39.7	37.3	40.0	33.6
ECOG PS ≤1	58.3	72.9	46.4	62.1	65.4	51.7	57.8	76.0
Cardiac comorbidities	34.0	27.1	41.0	31.8	35.9	33.3	31.1	32.6
ISS stage III	39.6	28.0	52.3	53.8	57.7	39.1	46.2	25.7
High-risk cytogenetics†	9.9	12.1	15.1	3.0	8.3	12.6	12.4	7.2
Prior SCT	34.4	58.9	30.5	27.3	23.7	36.5	40.0	37.2
Prior PI treatment	93.7	94.4	83.3	99.2	95.5	96.3	97.3	92.4
Prior IMiD treatment	72.6	60.7	79.1	42.4	62.8	80.6	75.1	59.2
Initiated in university hospital	39.7	42.1	39.7	25.8	21.2	41.5	45.3	52.6
Biochemical relapse	26.3	29.9	20.5	15.9	23.7	20.5	35.6	32.9
Biochemical and symptomatic relapse	52.3	56.1	56.5	47.0	46.2	60.1	47.6	43.1
Symptomatic relapse	19.4	12.1	20.9	30.3	28.8	17.1	14.7	23.4

Colored cells denote significant positive (green) or negative (red) difference from values for 'any regimen' (p<0.05, multivariate analysis).
*Not all regimens included in 'any regimen' are represented in the table.
†Presence of del17, t(4;14), or t(14;16).

Conclusions

- Multiple drug approvals for RRMM in Europe have resulted in marked changes in the treatment algorithm, with a more immediate impact in countries with earlier access to new treatment options.
- Multiple decision drivers – such as age, fitness, comorbidities, and prior treatment – are associated with the use of different novel regimens as 2nd-line and 3rd-line therapy.
  - Results from RCTs are taken into consideration when making treatment choices and regimens are implemented in real-world practice across patients of all ages and levels of performance status.
- The increasing range of treatment options has resulted in patients receiving more lines of therapy for RRMM, highlighting the need for cautious planning of treatment sequencing to optimize the use of available combinations according to patient characteristics and disease factors.

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Abbreviations

ASCT, autologous stem cell transplantation; CHD, congestive heart disease; DACH, Germany, Austria, and Switzerland; Dd, daratumumab-dexamethasone; D-Pom-dex, daratumumab-pomalidomide-dexamethasone; DRd, daratumumab-lenalidomide-dexamethasone; DVd, daratumumab-bortezomib-dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; Elo, elotuzumab; Elo-Pom-dex, elotuzumab-pomalidomide-dexamethasone; Elo-Rd, elotuzumab-lenalidomide-dexamethasone; IMiD, immunomodulatory drug; IRd, ixazomib-lenalidomide-dexamethasone; ISS, International Staging System; Kd, carfilzomib-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; L, line; mAb, monoclonal antibody; MM, multiple myeloma; N/A, not applicable; non-DACH, Belgium, France, Greece, Spain, and UK; PI, proteasome inhibitor; Pom, pomalidomide; Pom-dex, pomalidomide-dexamethasone; Pom-Vd, pomalidomide-bortezomib-dexamethasone; PS, performance status; Pts, patients; R, lenalidomide; RCT, randomized controlled trial; Rd, lenalidomide-dexamethasone; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplantation; V, bortezomib.

Disclosures

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