Evolution of multiple myeloma treatment practices in Europe from 2014 to 2016

Marc S. Raab,[1] Leah Fink,[2] Paul Schoen,[3] Sebastian Gonzalez-McQuire,[3] Alain Flinois,[2] Michele Cavo,[4] Maria-Victoria Mateos,[5] Kwee Yong[6]

[1]Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany

[2]Kantar Health, Montrouge, France

[3]Amgen (Europe) GmbH, Zug, Switzerland

[4]"Seragnoli" Institute of Haematology and Medical Oncology, Bologna University School of Medicine, Bologna, Italy

[5]Haematology Service, University Hospital, Salamanca, Salamanca, Spain

[6]Department of Haematology, University College London, London, UK

Short title: Multiple myeloma: changes in practice patterns across Europe

Target journal: British Journal of Haematology

Corresponding author: Dr. med. Marc-Steffen Raab

Full Address of corresponding author: Department of Medicine V, University Hospital Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

Email: marc.raab@med.uni-heidelberg.de

Tel: +49 6221 42 1450

Letter

Word count: 1108

References: 8

Tables/figures: 1/1

Supplementary tables/figures: 4/1

Keywords

European chart review, multiple myeloma, observational, practice patterns, real-world.

The number of treatments for multiple myeloma (MM) has expanded since the approval of bortezomib and lenalidomide. Patients are increasingly receiving multiple lines of therapy, leading to improvements in survival (Sengsayadeth *et al,* 2017; Torimoto *et al,* 2015).

In 2014, we conducted a chart review to describe real-world treatment patterns and outcomes for MM in Europe (Raab *et al,* 2016). The range of available treatments has continued to expand, with carfilzomib, daratumumab, elotuzumab, ixazomib and panobinostat now approved in the relapsed setting (Moreau 2017) and lenalidomide approved at first line for patients not eligible for stem cell transplant (SCT) (Celgene International Sàrl 2015). This 2-year period has also seen wider reimbursement of pomalidomide and bortezomib.

Considering recent developments, we performed a follow-up study to capture current practice in 2016; an exploratory objective was to compare the findings with those from 2014. The five European countries in which the 2016 study was conducted (France, Germany, Italy, Spain and the UK) were also included in the 2014 study, and methodology was similar (Raab *et al,* 2016; Yong *et al,* 2016). Both studies comprised cross-sectional and retrospective analyses. In the cross-sectional analysis, physicians completed a questionnaire on patient characteristics and current treatment for all patients with symptomatic MM seen during a 2–4-week period. In 2014, the retrospective analysis included all patients who had completed a first, second, third or later line of treatment in the 3 months before inclusion; in 2016, it included all patients who had progressed after first-, second- or third-line treatment or who had died in the 3 months before inclusion.

Cross-sectional data were obtained on 7328 and 7709 patients in the 2014 and 2016 studies, respectively, making these among the largest real-world data sets of patients treated for MM. Patient characteristics were broadly similar in both studies (Table I). The incident population was slightly older in 2016 than 2014; the proportion of patients aged over 75 years at diagnosis was 33% in 2016 compared with 25% in 2014.

From 2014 to 2016, the most recent treatment line shifted towards first line (45% vs 51%; Supplementary Figure 1). The proportion of patients receiving active treatment increased from 46% in 2014 to 55% in 2016. Correspondingly, there was a reduction in the proportion of patients who were not currently being treated or had never been treated. When analysed by country, there were notable increases in overall rates of active treatment in Spain and the UK in 2016, bringing them into line with treatment rates for the other countries (Table I).

Higher active first-line treatment rates in 2016 compared with 2014 may result from increased use of maintenance therapy or continuous therapy in elderly patients. Availability of drugs with better toxicity profiles facilitates the treatment of elderly patients, while improvements in supportive care can increase patient fitness for treatment and enable timely delivery of protocols (Diamond *et al*, 2017).

Availability of next generation and new-in-class novel agents has diversified prescriptions in the relapsed setting such that patterns of care were more varied in 2016 than in 2014, especially in later lines (Supplementary Tables I–IV). At first line (Supplementary Table I), there was increased use of bortezomib–based regimens in 2016, particularly in the UK (59% vs 30%, respectively), reflecting the reimbursement of bortezomib at first line during this period. There was also increased use of bortezomib in combination with thalidomide, particularly in France (32% vs 18%, respectively), Spain (15% vs 8%) and the UK (15% vs 1%). Of patients who received SCTs, most (78%) received bortezomib at first line in 2016 (40% in combination with thalidomide). In all countries except Italy, use of lenalidomide as first-line treatment increased by more than two-fold in 2016 compared with 2014 (Supplementary Table I). There was also decreased use of thalidomide (UK and France) and of melphalan plus prednisone (Spain and Germany) in 2016.

At second line (Supplementary Table II), use of bortezomib was generally lower in 2016 than in 2014 (Germany: 9% vs 20%; Italy: 12% vs 27%; Spain: 14% vs 32%; UK: 54% vs 62%); this likely reflects the increased use of bortezomib at first line. There was also increased use of second-generation agents and monoclonal antibodies (e.g. carfilzomib, pomalidomide, daratumumab), especially following relapse after SCT.

At third line (Supplementary Table III), use of lenalidomide was lower in 2016 than in 2014 (except in combination with novel agents) in all countries except Spain. This is likely to be because of its increased use at first line, and the increased use of pomalidomide in later lines. In 2016, there was also reduced use of bendamustine (France, Germany and Spain) and

reduced use of bortezomib (Germany), but new use of carfilzomib (Germany and Spain) and daratumumab (Germany).

At fourth line and beyond (Supplementary Table IV), patients had more diverse treatment patterns in 2016 than in 2014, reflecting the introduction of novel treatments such as daratumumab and wider access to pomalidomide.

Reimbursement varies across Europe and, consequently, heterogeneous treatment patterns have evolved in the countries studied. While there was some uniformity across countries in early lines of treatment, strategies diverge at later lines as local reimbursement impacts availability of novel treatments. Notably, Germany supports an early access scheme that makes novel agents available soon after approval.

Retrospective analysis of treatment sequencing for patients who received bortezomib at first line showed that first- to third-line treatment typically incorporated bortezomib in 2016, followed by lenalidomide and then pomalidomide; this was similar to 2014, except for an increased use of pomalidomide at third line (Figure 1).

It was not possible to assess changes in patient outcomes between 2014 and 2016; however, a retrospective study assessing real-world trends in MM survival and treatment costs between 2000 and 2014 in the United States of America found that a greater proportion of patients survived for 2 years after diagnosis in 2012 (87.1%) than in 2006 (69.9%). Importantly, patients receiving novel therapies had better outcomes than those managed with non-novel agents. Although there are concerns regarding the economic impact of novel therapies, real-world data show that, while the total cost of MM treatment increased from 2000 to 2014, the relative contribution of drug costs has remained stable since 2009, despite the availability of novel therapies (Fonseca *et al*, 2016).

This collation of data from five European countries contributes to our understanding of how recent advances in treatment of MM are impacting clinical practice; it also highlights the value of conducting repeated analyses using consistent methodology to understand the changing treatment patterns in MM. The MM landscape will continue to evolve with the approval of new agents and widening reimbursement; therefore, continued monitoring of treatment patterns will be required to understand how these changes impact patient care.

Conflicts of Interest Disclosures

Marc S. Raab has received research support from Amgen and Novartis, and honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen and Novartis.
Leah Fink and Alain Flinois are employees of Kantar Health, who received funding from Amgen to conduct this research.
Paul Schoen and Sebastian Gonzalez-McQuire are Amgen employees and hold Amgen stock.
Michele Cavo has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda.
Maria-Victoria Mateos has received honoraria from Amgen, Celgene, Janssen and Takeda, derived from lectures and participation in advisory boards.
Kwee Yong has received honoraria from Amgen, Celgene, Janssen, Sanofi and Takeda, and research funding from Amgen, Celgene and Janssen, and was a consultant for Autolus.

Authorship Contributions

Marc S. Raab, Leah Fink, Paul Schoen, Sebastian Gonzalez-McQuire and Alain Flinois designed the research study. Leah Fink, Paul Schoen, Sebastian Gonzalez-McQuire and Alain Flinois performed the research. Michele Cavo, Maria-Victoria Mateos, Kwee Yong, Marc S. Raab, Leah Fink, Paul Schoen, Sebastian Gonzalez-McQuire and Alain Flinois analysed and interpreted the data. All authors critically revised the manuscript. All authors approved the final version of the manuscript for submission.

Acknowledgements

Medical writing support, funded by Amgen (Europe) GmbH, was provided by Kelly Soady PhD from Oxford PharmaGenesis, Oxford, UK.

References

Celgene International Sàrl (2015) REVLIMID® (Lenalidomide) approved by the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Press release 20 February Available at: http://ir.celgene.com/releasedetail.cfm?releaseid=897381. [Accessed on 19 September 2017]

Diamond, E., Lahoud, O.B. & Landau, H. (2017) Managing multiple myeloma in elderly patients. *Leuk Lymphoma,* 10.1080/10428194.10422017.11365859.

Fonseca, R., Abouzaid, S., Bonafede, M., Cai, Q., Parikh, K., Cosler, L. & Richardson, P. (2016) Trends in overall survival and costs of multiple myeloma, 2000–2014. *Leukemia,* **31,** 1915.

Moreau, P. (2017) How I treat: New agents in myeloma. *Blood,* **10.1182/blood-2017-05-743203**.

Raab, M.S., Cavo, M., Delforge, M., Driessen, C., Fink, L., Flinois, A., Gonzalez-McQuire, S., Safaei, R., Karlin, L., Mateos, M.V., Schoen, P. & Yong, K. (2016) Multiple myeloma: practice patterns across Europe. *Br J Haematol,* **175,** 66–76.

Sengsayadeth, S., Malard, F., Savani, B.N., Garderet, L. & Mohty, M. (2017) Posttransplant maintenance therapy in multiple myeloma: the changing landscape. *Blood Cancer J,* **7,** e545.

Torimoto, Y., Shindo, M., Ikuta, K. & Kohgo, Y. (2015) Current therapeutic strategies for multiple myeloma. *Int J Clin Oncol,* **20,** 423–430.

Yong, K., Delforge, M., Driessen, C., Fink, L., Flinois, A., Gonzalez-McQuire, S., Safaei, R., Karlin, L., Mateos, M.V., Raab, M.S., Schoen, P. & Cavo, M. (2016) Multiple myeloma: patient outcomes in real-world practice. *Br J Haematol,* **175,** 252–264.

Table I. Key patient and treatment characteristics included in the cross-sectional chart review.

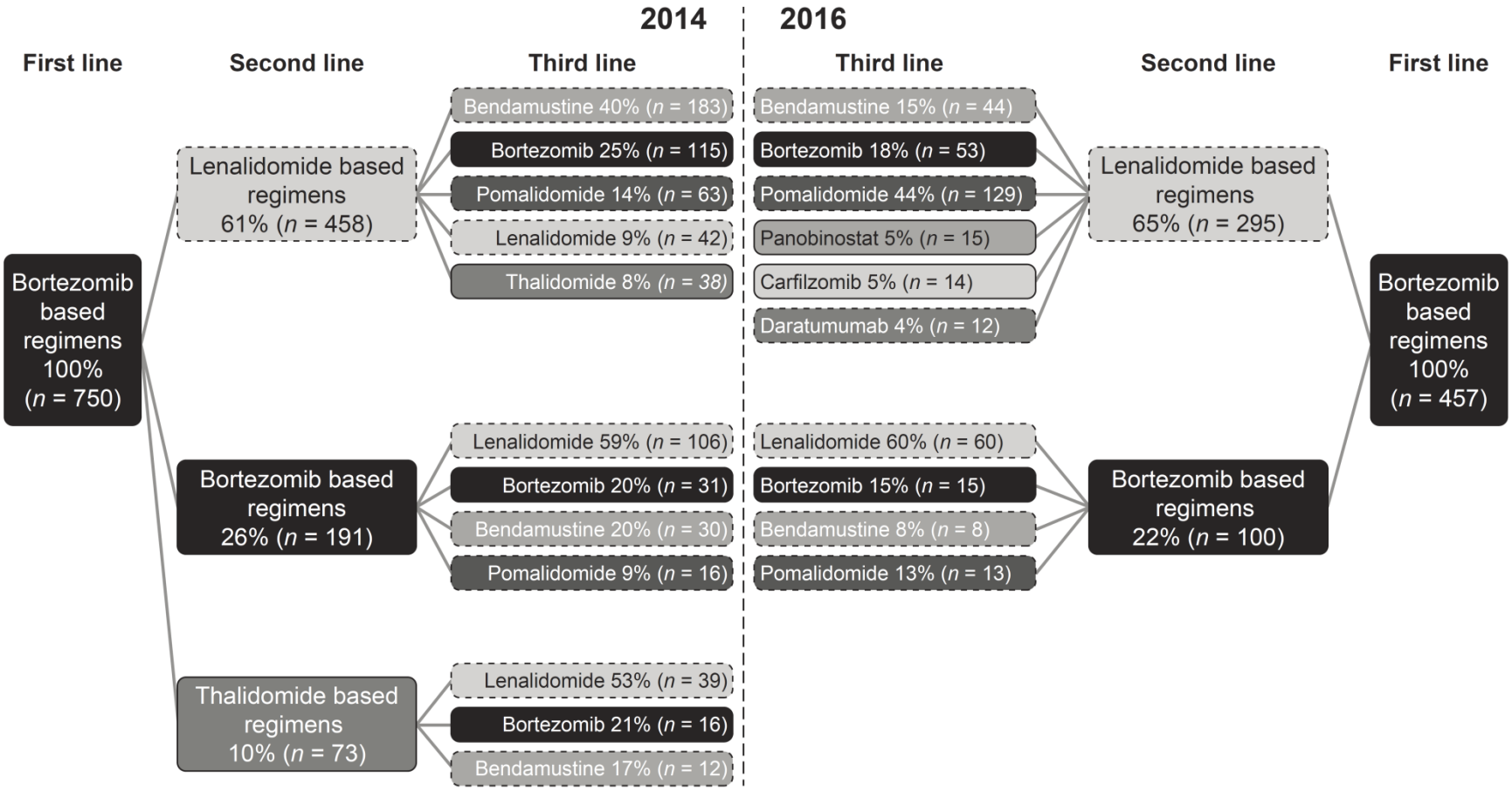
	EU5		France		Germany		Italy		Spain		UK	
	2014 (*n* = 7328)	2016 (*n* = 7709)	2014 (*n* = 1770)	2016 (*n* = 1639)	2014 (*n* = 1817)	2016 (*n* = 1894)	2014 (*n* = 1710)	2016 (*n* = 1716)	2014 (*n* = 1007)	2016 (*n* = 1376)	2014 (*n* = 1024)	2016 (*n* = 1084)
Sex (%)												
Male	54	51*	52	51	52	54	53	51	58	50*	57	51*
Female	46	49†	47	48	48	46	48	49	42	50†	43	49†
Age at time of inclusion (%)												
< 65 years	38	34*	37	34	39	35	38	33*	43	33*	38	38
65–75 years	36	35	33	35	39	37	35	36	39	34	41	31*
> 75 years	27	31†	30	31	22	28†	27	31†	19	33†	21	32†
ISS at diagnosis (%)												
I	23	23	19	23†	24	23	23	25	26	27	24	19*
II	37	35*	29	27	29	35†	44	34*	51	42*	43	47
III	37	43†	49	50	35	41†	30	41†	24	31†	33	35
Unknown	4	< 1	3	< 1	12	0	3	1	0	0	< 1	0
Median time since diagnosis (months)	25	27	33	30	23	21	27	29	15	28	23	23
Receiving active treatment, by line (%)												
First line	94	92	97	96	92	91	97	92	85	93	94	89
Second line	61	63	74	65	66	62	59	61	41	62	49	64
Third line	40	46	50	47	45	50	35	41	4	33	43	52
Fourth line	19	20	28	25	20	20	15	17	1	13	17	22

Fifth line or later	2	4	3	8	2	5	1	1	0	2	2	3
Current line of treatment (%)												
First line	45	44	38	40	40	47†	49	43	66	48*	42	42
Induction	34	34	30	35†	28	37†	30	31	55	34*	36	32
Maintenance	11	10*	8	5*	12	10	19	14*	11	14	6	9
Second line	26	27	29	26	27	25	24	28	25	30†	26	26
Third line	18	19	19	19	18	19	19	18	9	16†	23	22
Fourth line	9	8	11	10	13	7*	7	8	1	6†	8	9
Fifth line	2	3†	4	5	2	2	1	1	0	1	1	2
Transplant status (%)												
SCT complete		40		39		38		44		37		38
SCT planned		6		3		7		5		5		9
No SCT		55		58		55		50		57		53

ISS, International Staging System; SCT, stem cell transplant.

*Lower than 2014 value ($P < 0.05$). †Higher than 2014 value ($P < 0.05$).

Fig 1. Treatment sequencing for patients with symptomatic multiple myeloma who received a bortezomib-based regimen at first line in 2014 and 2016.



Note that treatment sequencing shows first-, second- and third-line treaments only for patients who received bortezomib-based regimens at first line.

Supplementary figures and tables.

Supplementary Table I. Treatment patterns (first-line induction regimens) in 2014 and 2016 (percentage of patients).

	EU5		France		Germany		Italy		Spain		UK	
Treatment	2014 (*n* = 1145)	2016 (*n* = 1429)	2014 (*n* = 258)	2016 (*n* = 284)	2014 (*n* = 206)	2016 (*n* = 382)	2014 (*n* = 233)	2016 (*n* = 264)	2014 (*n* = 298)	2016 (*n* = 233)	2014 (*n* = 124)	2016 (*n* = 170)
Bortezomib-based	57	66†	60	77†	64	58	73	80	65	75†	30	59†
Bortezomib (excluding thalidomide and lenalidomide	42	44	38	43	62	56	37	44	55	53	29	43†
Bortezomib + thalidomide	13	20†	18	32†	<1	1	37	36	8	15†	1	15†
Bortezomib + lenalidomide	2	2	4	2	1	2	0	1	1	7†	<1	1
Lenalidomide (excluding bortezomib)	5	11	3	10†	6	16†	3	2	3	8†	4	11†
Thalidomide (excluding bortezomib)	20	7*	24	7*	5	3	9	4*	0	<1	60	20*
Melphalan + prednisone	9	4*	6	4	6	2*	10	6	22	6*	4	4
Daratumumab	< 1	4	0	1	0	4	<1	<1	0	1	0	0
Bendamustine	2	3	2	<1	9	10	0	2	2	3	0	<1
Carfilzomib	< 1	2	0	<1	0	1	0	<1	0	2	0	0
Ixazomib	< 1	1	0	0	0	0	0	1	0	0	0	0
Pomalidomide	< 1	< 1	1	<1	<1	1	<1	1	0	1	1	0
Elotuzumab	< 1	< 1	0	0	0	1	0	0	0	0	0	0
Other	6	4	4	<1	10	5*	4	5	9	5	2	5

*Lower than 2014 value ($P < 0.05$). †Higher than 2014 value ($P < 0.05$).

Supplementary Table II. Treatment patterns (second-line) in 2014 and 2016 (percentage of patients).

	EU5		France		Germany		Italy		Spain		UK	
Treatment	2014 (*n* = 892)	2016 (*n* = 1115)	2014 (*n* = 249)	2016 (*n* = 238)	2014 (*n* = 168)	2016 (*n* = 261)	2014 (*n* = 186)	2016 (*n* = 242)	2014 (*n* = 100)	2016 (*n* = 202)	2014 (*n* = 100)	2016 (*n* = 141)
Lenalidomide (excluding triplets)	57	59	78	79	61	50*	61	79†	59	63	20	25
Bortezomib-based	27	19*	13	11	20	9*	27	12*	32	14*	62	54
Bortezomib (excluding triplets)	24	16*	11	5*	20	8*	25	11*	23	7*	59	50
Bortezomib + thalidomide	1	1	1	1	0	<1	1	1	8	4	1	2
Bortezomib + lenalidomide	1	2	2	5	<1	1	1	<1	0	3	3	2
Carfilzomib	<1	6†	0	2	0	16	0	<1	0	7	0	0
Pomalidomide	<1	5†	1	3	0	3	0	1	0	2	0	11
Bendamustine (excluding triplets)	3	3	3	<1*	7	12	2	1	0	0	0	1
Thalidomide (excluding triplets)	7	2*	4	2	6	<1*	3	2	5	3	13	4*
Melphalan + prednisone	2	1	1	1	2	1	2	2	1	1	0	1
Daratumumab	<1	1†	0	0	0	4	0	0	0	2	0	0
Ixazomib	<1	1	0	0	0	1	0	0	0	1	0	1
Elotuzumab	<1	1	0	0	0	3	0	0	0	1	0	0
Panobinostat	0	<1	0	<1	0	<1	0	0	0	0	0	0
Other	4	3	1	1	3	2	4	3	0	0	5	3

*Lower than 2014 value ($P < 0.05$). †Higher than 2014 value ($P < 0.05$).

Supplementary Table III. Treatment patterns (third-line) in 2014 and 2016 (percentage of patients).

	EU5		France		Germany		Italy		Spain		UK	
Treatment	2014 (*n* = 619)	2016 (*n* = 797)	2014 (*n* = 165)	2016 (*n* = 179)	2014 (*n* = 130)	2016 (*n* = 195)	2014 (*n* = 146)	2016 (*n* = 157)	2014 (*n* = 48)	2016 (*n* = 107)	2014 (*n* = 90)	2016 (*n* = 123)
Lenalidomide (excluding triplets)	51	34*	42	14*	32	19*	57	41*	18	29	86	73*
Pomalidomide	12	32†	21	60†	15	25†	6	26†	16	20	1	14†
Bortezomib-based	12	9	9	11	15	3*	17	14	23	17	7	4
Bortezomib (excluding triplets)	11	7*	9	7	14	3*	15	14	20	11	7	2
Bortezomib + thalidomide	<1	<1	0	0	0	0	<1	<1	0	3	0	1
Bortezomib + lenalidomide	1	2	<1	4	1	0	2	0	2	3	0	1
Bendamustine	14	7*	19	7*	25	15*	7	4	24	2*	3	3
Carfilzomib	<1	6†	0	3	0	11	0	3	0	10	1	0
Daratumumab	<1	3†	0	1	0	12	0	1	0	3	0	0
Panobinostat	0	2	0	0	0	8	0	0	0	2	0	2
Melphalan + prednisone	1	1	0	1	2	1	4	2	4	1	0	1
Thalidomide (excluding triplets)	4	1*	7	0	2	2	5	3	0	3	2	0
Elotuzumab	1	1	0	0	<1	1*	0	0	0	1	0	0
Ixazomib	0	1	0	0	0	2	0	0	0	0	0	1
Other	5	4	2	3	9	3	4	7	17	13	1	3

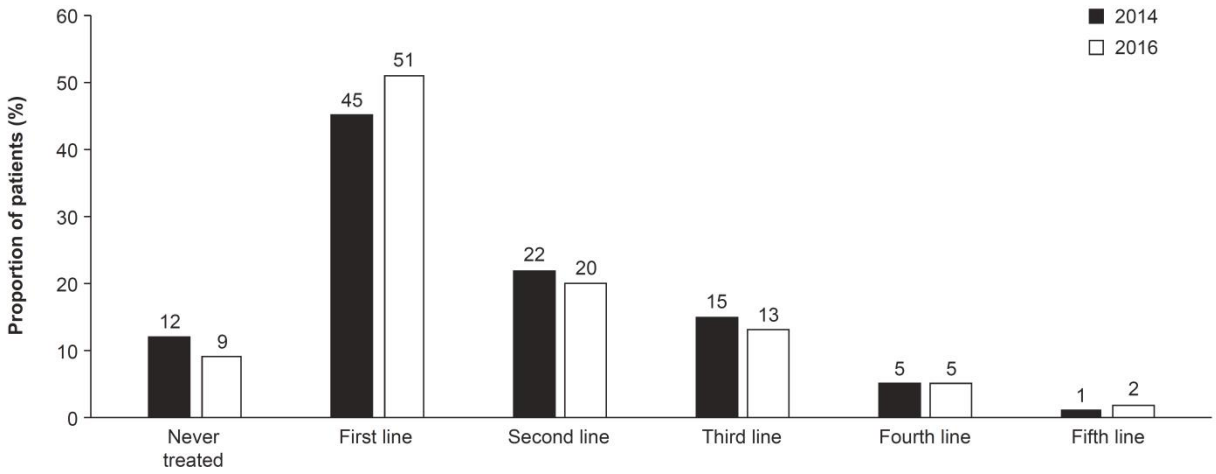
*Lower than 2014 value ($P < 0.05$). †Higher than 2014 value ($P < 0.05$).

Supplementary Table IV. Treatment patterns (fourth-line plus) in 2014 and 2016 (percentage of patients).

	EU5		France		Germany		Italy		Spain		UK	
Treatment	2014 (*n* = 356)	2016 (*n* = 463)	2014 (*n* = 125)	2016 (*n* = 143)	2014 (*n* = 106)	2016 (*n* = 99)	2014 (*n* = 64)	2016 (*n* = 76)	2014 (*n* = 3)	2016 (*n* = 50)	2014 (*n* = 38)	2016 (*n* = 56)
Pomalidomide	36	32	49	40	33	22	8	30†	0	32	29	32
Daratumumab	0	12	0	16	0	24	0	3	0	6	0	4
Carfilzomib	1	9†	<1	7	1	10†	1	5	0	23	0	6
Bendamustine (excluding triplets)	12	9	13	8	13	16	12	3	0	1	7	12
Lenalidomide (excluding triplets)	23	11*	20	7*	25	6*	23	21	0	10	35	21
Bortezomib-based	11	6*	10	3	13	3*	16	21	79	6*	5	5
Bortezomib (excluding triplets)	10	6	8	3	13	3*	16	20	29	6	2	4
Bortezomib + thalidomide	1	<1	2	0	<1	0	0	1	21	1	2	0
Bortezomib + lenalidomide	<1	<1	<1	<1	1	0	0	<1	29	0	0	1
Panobinostat	0	6	0	3	0	3	0	0	0	2	0	14
Melphalan + prednisone	2	2	<1	2	1	1	7	3	0	3	2	0
Elotuzumab	0	2	0	0	0	7	0	0	0	4	0	0
Ixazomib	0	1	0	1	0	3	0	0	0	0	0	2
Thalidomide (excluding triplets)	7	<1*	1	0	8	1*	6	1	7	0	20	1*
Other	10	10	7	14	6	4	26	15	14	13	3	2

*Lower than 2014 value ($P < 0.05$). †Higher than 2014 value ($P < 0.05$).

Supplementary Fig 1. Most recent line of treatment



Patients were receiving active treatment or having a treatment-free interval after each treatment line.

$P < 0.05$ for differences between 2014 and 2016, except for fourth line.