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Multiple Myeloma Treatment in Real-world Clinical Practice: Results of a Prospective, Multinational, Noninterventional Study

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Abstract

Multiple myeloma (MM) remains an incurable disease, with little information available on its management in real-world clinical practice. The results of the present prospective, noninterventional observational study revealed great diversity in the treatment regimens used to treat MM. Our results also provide data to inform health economic, pharmacoepidemiologic, and outcomes research, providing a framework for the design of protocols to improve the outcomes of patients with MM.

Poster presented at the 57th Annual Meeting of the American Society of Hematology, December 5-8, 2015, Orlando, FL. Additional presentations of prefinal data were given at the 2014 and 2015 European Hematology Association annual meetings, 2014 European School of Haematology annual meeting, and 2013 and 2015 International Myeloma Workshops.

The full list of EMMOS investigators is provided in the Supplemental Appendix (available in the online version).

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Background: The present prospective, multinational, noninterventional study aimed to document and describe real-world treatment regimens and disease progression in multiple myeloma (MM) patients. **Patients and Methods:** Adult patients initiating any new MM therapy from October 2010 to October 2012 were eligible. A multistage patient/site recruitment model was applied to minimize the selection bias; enrollment was stratified by country, region, and practice type. The patient medical and disease features, treatment history, and remission status were recorded at baseline, and prospective data on treatment, efficacy, and safety were collected electronically every 3 months. **Results:** A total of 2358 patients were enrolled. Of these patients, 775 and 1583 did and did not undergo stem cell transplantation (SCT) at any time during treatment, respectively. Of the patients in the SCT and non-SCT groups, 49%, 21%, 14%, and 15% and 57%, 20%, 12% and 10% were enrolled at treatment line 1, 2, 3, and $\geq$ 4, respectively. In the SCT and non-SCT groups, 45% and 54% of the patients had received bortezomib-based therapy without thalidomide/lenalidomide, 12% and 18% had received thalidomide/lenalidomide-based therapy without bortezomib, and 30% and 4% had received bortezomib plus thalidomide/lenalidomide-based therapy as frontline treatment, respectively. The corresponding proportions of SCT and non-SCT patients in lines 2, 3, and $\geq$ 4 were 45% and 37%, 30% and 37%, and 12% and 3%, 33% and 27%, 35% and 32%, and 8% and 2%, and 27% and 27%, 27% and 23%, and 6% and 4%, respectively. In the SCT and non-SCT patients, the overall response rate was 86% to 97% and 64% to 85% in line 1, 74% to 78% and 59% to 68% in line 2, 55% to 83% and 48% to 60% in line 3, and 49% to 65% and 36% and 45% in line 4, respectively, for regimens that included bortezomib and/or thalidomide/lenalidomide. **Conclusion:** The results of our prospective study have revealed great diversity in the treatment regimens used to manage MM in real-life practice. This diversity was linked to factors such as novel agent accessibility and evolving treatment recommendations. Our results provide insight into associated clinical benefits.

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Keywords: Bortezomib, Global, Observational study, Routine practice, Stem cell transplantation

Introduction

Multiple myeloma (MM) is a common hematologic malignancy, with an annual incidence of ~86,000 cases worldwide (6.6 cases/100,000 persons annually).[1,2] Survival outcomes have improved markedly in recent years owing to advances in our understanding of MM disease biology, earlier detection, and improved treatment strategies.[3] The introduction of novel agents, such as bortezomib, thalidomide, and lenalidomide, has contributed considerably to these improved outcomes.[3-5] However, despite these advances, MM remains an incurable disease that typically follows a variable, chronically relapsing course.[6] Thus, many patients will require multiple lines of therapy.[4,5,7]

The treatment landscape in MM is rapidly evolving. In 2010, the main novel agents approved for use were bortezomib, lenalidomide (after $\geq$ 1 previous line), and thalidomide. Since then, 6 novel agents (ie, pomalidomide, carfilzomib, panobinostat, daratumumab, ixazomib, elotuzumab) have been approved, and the indications for both bortezomib and lenalidomide have been expanded. Although the focus on the development of new therapies in clinical trials is strong, limited real-world data are available on the treatment of MM from a broad regional perspective.[8-13] Therefore, the noninterventional, multinational Europe, Middle East and Africa Multiple Myeloma Observational Study (EMMOS; ClinicalTrials.gov identifier, NCT01241396) was initiated in 2010 to capture real-world data from multiple countries regarding MM treatment practices and outcomes at different stages of the disease. Numerous types of treatment centers were included in the EMMOS to provide robust data regarding MM therapy in the real world.

Patients and Methods

Patients and Study Design

The present study was a prospective, noninterventional, multicenter, observational study performed to document the use of different treatment protocols and resource usage for MM in routine clinical practice. Adult patients initiating any new therapy for MM from October 2010 to October 2012 were consecutively enrolled in the EMMOS registry, regardless of the therapy type or treatment line at enrollment. Patients who were starting an investigational drug at screening and patients who had received a new line of therapy during the study if that new line was a part of a clinical study were excluded. To minimize the selection bias, a multistage site/patient recruitment model was applied. Enrollment occurred at sites across Europe, the Middle East, and Africa and was stratified by country, region, and practice type (academic, local, private, or regional). The number of sites selected per country was proportional to the overall population estimate of MM prevalence in each country using the GLOBOCAN 2002 data.[14,15] Each site had an enrollment target to ensure that a representative number of patients from each geographic location and practice type were enrolled. A full list of the EMMOS investigators can be found in the Supplemental Appendix (available in the online version).

Because the present study was a noninterventional study, patient participation had no effect on their treatment course, and all therapy-related questions were decided by the treating physician. The appropriate independent ethics committees and institutional review boards of all participating countries approved the present study, which was conducted in accordance with the Declaration of

Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements. An advisory board oversaw the conduct of the study and monitored the data on an ongoing basis. All the patients provided written informed consent.

Objectives and Assessments

The primary objective of the EMMOS was to document and describe current treatment regimens and disease progression in patients with MM. The secondary objectives involved understanding the MM patient population included in the present study (evaluation of patient demographic data and disease characteristics), and the extent to which the results of clinical trials can be applied to the wider MM patient community. Additional objectives included documenting and comparing the usage, effectiveness, and safety profiles of the current MM treatment regimens.

The primary efficacy endpoint was the best response to each line of treatment (defined as the greatest level of response achieved with a treatment line). The responses were assessed and recorded after each cycle by the treating physician; no predefined response criteria were mandated. The other efficacy endpoints included time-to-event analyses, such as the time to next treatment (TTNT; starting from the beginning of the previous treatment), treatment-free interval (TFI; starting from the end of the previous treatment), and the treatment-free ratio (TFR; ratio of TFI to the duration of the line preceding the TFI). The TFR, calculated as TFI/(TTNT − TFI), was used to evaluate the treatment-free time, considering the duration of the preceding treatment. A greater TFR indicates that the patient spent more time treatment free than being treated, which might result in improved quality of life. Overall survival was also assessed; however, these data were not sufficiently mature at the study end and were not included in the present report.

Data Collection

At enrollment in the study (baseline), retrospective data (including patient demographic data and disease features, MM treatment history, and remission status) were captured by a review of the patients' medical records (Supplemental Table 1; available in the online version). During the prospective phase of the study, the data regarding MM treatments and adverse events (AEs) were captured electronically every 3 months, except for serious AEs, which were reported within 24 hours of knowledge of the event. The responses were captured as close to the start of each cycle as possible, at the investigator's discretion. Data collection ended 2 years after the last patient was enrolled.

Statistical Analysis

Because the study was observational, no formal statistical hypotheses were tested. The target sample size was 2665 patients, which represents ≥ 5% of the applicable population of patients with MM treated within the participating countries. The data were analyzed in the full set (defined as all patients meeting the inclusion and exclusion criteria who had received ≥ 1 prospective line of treatment) and according to whether the patients had undergone stem cell transplantation (SCT) during any prospective or retrospective line of treatment (SCT vs. non-SCT patients). In addition, for the outcomes, the patient data were analyzed stratified by the treatment received (thalidomide- or lenalidomide-based regimen, no bortezomib; bortezomib plus thalidomide/lenalidomide-based regimen; bortezomib-based regimen, no thalidomide/lenalidomide; other, no bortezomib or thalidomide/lenalidomide). In each group (SCT vs. non-SCT), the treatment line number was counted from diagnosis rather than from entry into the study. The data were summarized descriptively, except where stated; time-to-event endpoints were analyzed using the Kaplan-Meier method.

The reported data on treatments, response, safety, and efficacy were from the prospective phase of the study, defined as the period from baseline to patient withdrawal or completion of the study. An MM treatment regimen was defined as ≥ 1 antineoplastic agent, glucocorticoid, or other medication prescribed for MM tumor reduction. A line of treatment was defined as ≥ 1 cycle of a planned MM treatment regimen and could include ≥ 1 planned cycle of single-agent or combination therapy or a sequence of combination therapy administered in a planned schedule (eg, induction therapy followed by high-dose chemotherapy/SCT and maintenance).[16] We grouped treatments within a given line as follows: (1) treatment received during a line was defined according to the regimen received in cycle 1 of that line; and (2) because it was possible to receive multiple drug combinations within a single treatment line, the line grouping was also categorized according to the drugs received at any time during that line (eg, during induction, high-dose chemotherapy, and maintenance). The first method sought to better identify the treatments received during induction, rather than sequentially within a given line; the second method was used for the analyses of efficacy and safety.

Results

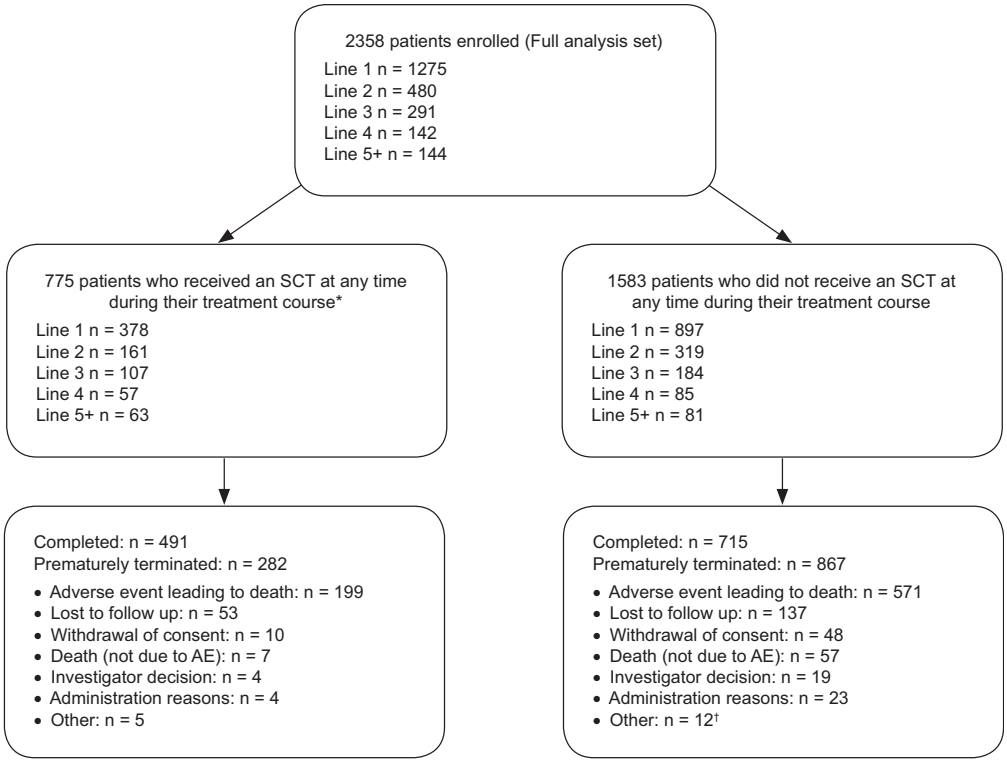
Patients

From October 2010 to October 2012, 2358 patients from 22 countries across Europe, the Middle East, and Africa were enrolled (Figure 1). The target enrollment of 2665 patients was not met owing to the high number of interventional studies initiated during this period and the exclusion of patients enrolled in such from the EMMOS registry. Most patients were enrolled in academic (43.7%) or regional (29.1%) study sites, and most were enrolled at sites in Europe. Of the 2358 patients, 51% were male and 43.4% were aged > 65 years at diagnosis (Table 1), in line with epidemiologic expectations.

A total of 775 patients (33%) underwent SCT within 1 of their treatment lines (SCT group) and 1583 (67%) did not (non-SCT group; Table 1). The number of evaluable patients in the SCT and non-SCT groups stratified by line of therapy at study entry is listed in Table 1. The median duration of study participation was 27.7 months (interquartile range [IQR], 19.7-32.8 months) in the SCT group and 24.5 months (IQR, 11.8-30.3 months) in the non-SCT group. The final data collection was on November 26, 2014.

As expected, the patients in the SCT group were younger at diagnosis than those in the non-SCT group (90.3% of the SCT patients were aged ≤ 65 years compared with 40.1% of the non-SCT patients). A lower percentage of SCT patients had International Staging System (ISS) stage III disease at baseline compared with the non-SCT population (34.6% vs. 44.3%, respectively). The proportion of patients with a history of bone lesions (71.5% vs. 67.5%) and the proportion of patients requiring dialysis (12.7% vs. 17.5%) in the SCT and non-SCT groups, respectively, were in line with current expectations for the MM population.[17] Cytogenetic

Figure 1 Patient Disposition and Enrollment Stratified By Country and Site Type. *Patients Who Underwent Stem Cell Transplantation (SCT) Within This Line: Line 1, n = 299; Line 2, n = 133; Line 3, n = 76; Line 4, n = 21; Line 5+, n = 29. †Included 1 Patient Who Was Withdrawn From the Study Because of an Undocumented Screen Failure



	Sites, n (%)	Patients per site, n (%)
All sites	234	2358
By site type		
Academic	95 (40.6)	1031 (43.7)
Regional	72 (30.8)	687 (29.1)
Local	27 (11.5)	266 (11.2)
Private	40 (17.1)	374 (15.9)
By country		
Italy	48 (20.5)	467 (19.8)
Germany	43 (18.4)	360 (15.3)
Ukraine	21 (9.0)	212 (9.0)
Spain	25 (10.7)	208 (8.8)
Russia	19 (8.1)	206 (8.7)
Poland	16 (6.8)	182 (7.7)
France	15 (6.4)	155 (6.6)
Turkey	10 (4.3)	126 (5.3)
Algeria	6 (2.6)	81 (3.4)
Greece	4 (1.7)	53 (2.2)
Israel	5 (2.1)	47 (2.0)
Latvia	1 (< 1)	44 (1.9)
Hungary	4 (1.7)	35 (1.5)
South Africa	4 (1.7)	31 (1.3)
Estonia	2 (< 1)	28 (1.2)
Lithuania	2 (< 1)	24 (1.0)
Macedonia	1 (< 1)	23 (1.0)
Austria	2 (< 1)	20 (< 1)
Portugal	2 (< 1)	19 (< 1)
Denmark	2 (< 1)	14 (< 1)
Croatia	1 (< 1)	13 (< 1)
Slovenia	1 (< 1)	10 (< 1)

Table 1 Patient Demographics and Disease Characteristics at Baseline

Variable	SCT Received		All Patients (n = 2358)
	Yes (n = 775)	No (n = 1583)	
Gender			
Male	447 (58)	764 (48)	1211 (51)
Female	328 (42)	819 (52)	1147 (49)
Age at diagnosis, y			
Median	57	68	63
IQR	51-62	60-74	56-71
Range	25-74	32-91	25-91
Aged > 65 y at diagnosis, y (%)	75 (9.7)	949 (60)	1024 (43)
Age at study entry, y			
Median	59	70	65
IQR	53-64	61-75	58-73
Range	28-79	33-91	28-91
Age ≤ 65 y at study entry, %			
Overall	80	36	NA
Treatment line at study entry			
1	87	36	
2	76	33	
3	72	35	
≥ 4	71	39	
Disease stage at study entry[a]			
ISS stage only	187 (24.1)	313 (19.7)	500 (21)
Durie-Salmon stage only	302 (40.8)	799 (51.9)	1101 (48)
ISS, Durie-Salmon stage	192 (25.9)	333 (21.6)	525 (22)
Not available	60 (8.1)	94 (6.1)	154 (7)
Missing	34 (4.3)	44 (2.7)	78 (3)
ISS stage at study entry[a]	379	646	1025
I	119 (31.4)	135 (20.9)	254 (25)
II	129 (34.0)	225 (34.8)	354 (35)
III	131 (34.6)	286 (44.3)	417 (41)
II/III stratified by therapy line at study entry[b]			NA
1	68	80	
2	71	81	
3	60	81	
≥ 4	71	74	
Durie-Salmon disease stage at study entry[a]	494	1132	1626
1	51 (10.3)	91 (8.0)	142 (9)
2	101 (20.4)	301 (26.6)	402 (25)
3	342 (69.2)	740 (65.4)	1082 (67)
2/3 stratified by therapy line at study entry[c]			
1	90	91	NA
2	92	90	NA
3	85	95	NA
≥ 4	92	91	NA
Cytogenetics[a]	337 (43.6)	333 (21.0)	670 (28)
High risk	60 (17.8)	45 (13.5)	110 (15)
Del17p	30 (8.9)	25 (7.5)	55 (8)
t(4;14)	30 (8.9)	20 (6.0)	50 (7)
Del13	75 (22.3)	55 (16.5)	130 (19)

Table 1 Continued

Variable	SCT Received		All Patients (n = 2358)
	Yes (n = 775)	No (n = 1583)	
Other	108 (32.0)	120 (36.0)	228 (34)
Normal (no specific findings)	146 (43.3)	157 (47.1)	303 (45)
Baseline laboratory evaluations[d]			2332
Serum β_2M, mg/L	NA	NA	1445 (62.0)
< 3.5	NA	NA	550 (38.1)
3.5 to < 5.5	NA	NA	375 (26.0)
≥ 5.5	NA	NA	520 (36.0)
Serum LDH, U/L	NA	NA	1714 (73.5)
< 300	NA	NA	1143 (66.7)
≥ 300	NA	NA	571 (33.3)
MM-related medical history at study entry[a]			
History of bone lesion	554 (71.5)	1068 (67.5)	1622 (69)
History of bone lesion stratified by line at study entry, %			
1	66	64	NA
2	74	72	NA
3	77	75	NA
≥ 4	80	70	NA
Severe renal impairment	102 (13.2)	292 (18.4)	394 (17)
Dialysis dependent	13 (12.7)	51 (17.5)	64 (16)
History of heart failure	52 (6.7)	280 (17.7)	332 (14)
MM treatment line at study entry			
1	378 (49)	897 (57)	1275 (55)
2	161 (21)	319 (20)	480 (21)
3	107 (14)	184 (12)	291 (12)
4	57 (7)	85 (5)	142 (6)
≥ 5	63 (8)	81 (5)	144 (6)
Missing[e]	9	17	26

Data presented as n (%), with all percentages calculated using the total number minus any missing values.
Abbreviations: β_2M = β_2-microglobulin; Del = deletion; IQR = interquartile range; ISS = International Staging System; LDH = lactate dehydrogenase; MM = multiple myeloma; SCT = stem cell transplantation; t = translocation.
[a]Percentages determined from number of patients with Durie-Salmon stage or number of patients with cytogenetic data.
[b]Percentages calculated from number of patients with available staging data (SCT: line 1, n = 225; line 2, n = 66; line 3, n = 35; line ≥ 4, n = 48; total, n = 374; non-SCT: line 1, n = 412; line 2, n = 118; line 3, n = 56; line ≥ 4, n = 54; total, n = 640).
[c]Percentages calculated from number of patients with available staging data (SCT: line 1, n = 233; line 2, n = 96; line 3, n = 75; line ≥ 4, n = 83; total, n = 487; non-SCT: line 1, n = 641; line 2, n = 220; line 3, n = 138; line ≥ 4, n = 120; total, n = 1119).
[d]Baseline β_2M and LDH summarized for the full analysis set as the number and percentage of patients with an MM treatment line at baseline (± 75 days) and available results; the percentages for the categories within β_2M and LDH were calculated using the number of subjects with available results.
[e]Missing patients did not receive treatment at study entry (within the 75-day baseline window) because of the following: treatment planned but not received, observation only (protocol deviation), or start date missing and imputed date therefore outside the baseline window.

abnormalities assessed by metaphase karyotype and fluorescence in situ hybridization were evaluated in 670 of 2358 patients (28%) overall. These assessments were performed significantly more frequently in the SCT than in the non-SCT patients (337 [43.5%] and 333 [21.0%] patients, respectively). Approximately one half of the patients in the SCT and non-SCT groups were previously untreated at study entry.

MM Therapies

Frontline Therapy. Of the 380 patients who underwent SCT after study enrollment, 299 (79%) received it as a component of their first-line therapy, and 81 underwent SCT-based therapy only in salvage lines (Table 2). Of the 299 frontline SCT patients, most received autologous SCT (97%), and most had a single transplant (81%; Table 2). The most common induction therapies for patients with frontline SCT (cycle 1 regimens) were VTD (bortezomib, thalidomide, dexamethasone; n = 95), VD (bortezomib, dexamethasone; n = 56), VCD (bortezomib, cyclophosphamide, dexamethasone; n = 49), vincristine, doxorubicin, bortezomib, dexamethasone (n = 26), and CDT (cyclophosphamide, dexamethasone, thalidomide; n = 26).

During their first cycle, most patients in the overall SCT population received a bortezomib-based regimen without thalidomide/lenalidomide (n = 170; 45%) or a bortezomib plus thalidomide/lenalidomide-based regimen (n = 114; 30%; Table 2). In total, 159 SCT patients (42%) received a bortezomib plus thalidomide/

Table 2 Frontline Therapy for SCT and Non-SCT Patients Recorded During Prospective Data Collection Phase[a]

Treatment	SCT Patients (n = 380)	Non-SCT Patients (n = 906)
Regimens received during cycle 1 of frontline therapy		
Thalidomide/lenalidomide-based, no bortezomib	46 (12.1)	160 (17.7)
MPT	0 (0)	68 (7.5)
CDT	34 (8.9)	56 (6.2)
Bortezomib plus thalidomide/lenalidomide-based	114 (30.0)	34 (3.8)
VTD	100 (26.3)	28 (3.1)
VRD	5 (1.3)	2 (0.2)
Bortezomib-based, no thalidomide/lenalidomide	170 (44.7)	491 (54.2)
VD	70 (18.4)	122 (13.5)
VCD	56 (14.7)	61 (6.7)
VMP	3 (0.8)	218 (24.1)
Other, no bortezomib or thalidomide/lenalidomide	50 (13.2)	221 (24.4)
MP	0	65 (7.2)
Vincristine, doxorubicin, dexamethasone	29 (7.6)	37 (4.1)
Regimens received at any point during frontline therapy		
Thalidomide/lenalidomide-based, no bortezomib	53 (13.9)	177 (19.5)
Bortezomib plus thalidomide/lenalidomide-based	159 (41.8)	61 (6.7)
Bortezomib-based, no thalidomide/lenalidomide	131 (34.5)	478 (52.8)
Other, no bortezomib or thalidomide/lenalidomide	37 (9.7)	190 (21.0)
Agents received during frontline therapy, n		
Median	4	3
IQR	3-5	3-3
Range	1-10	1-7
Treatment duration, mo		
Median	7.5	6.4
IQR	4.4-13.9	3.0-10.6
Range	0.1-132.5	0.03-51.9
SCT within frontline therapy[b]		
Any SCT	299	NA
Autologous	291 (97.3)	NA
Allogeneic	8 (2.7)	NA
SCTs		NA
1	242 (80.9)	NA
2	57 (19.1)	NA

For cycle 1 regimens, any combination for ≥ 10% of patients in SCT or non-SCT group was provided, with ≥ 2 regimens (most frequent) for each grouping.
Abbreviations: C = cyclophosphamide; D = dexamethasone; IQR = interquartile range; M = melphalan; P = methylprednisolone/prednisolone/prednisone; R = lenalidomide; SCT = stem cell transplantation; T = thalidomide; V = bortezomib.
[a]For example, among the patients who entered the study at the point of receiving their first therapy line.
[b]SCT was counted once per separate date recorded; a patient could have undergone > 1 (overall if in different lines and per line as a planned tandem transplant) during the study period.

lenalidomide-based regimen at any point during their frontline regimen and 131 (35%) received a bortezomib-based regimen without thalidomide/lenalidomide (Table 2). Thus, of the 170 patients who initiated cycle 1 with a bortezomib-based regimen that did not include thalidomide/lenalidomide, 39 (23%) subsequently received thalidomide/lenalidomide in later cycles of their frontline therapy. Of those patients who initiated cycle 1 with an "other" regimen (not containing bortezomib or thalidomide/lenalidomide), 13 (26%) received bortezomib (n = 6) or thalidomide/lenalidomide (n = 7) during subsequent cycles of frontline therapy. The patients were treated for a median of 7.5 months (IQR, 4.4-13.9 months).

In the non-SCT population, more than one half of patients received a frontline bortezomib-based regimen without thalidomide/lenalidomide during their first cycle (54%) and 24% of patients received a combination of "other" agents (Table 2). The most common combinations in the non-SCT group were VMP (bortezomib, melphalan, prednisone) and VD. More than one half of the patients received bortezomib at any time during their frontline therapy (59%), including 53% who received a bortezomib-based regimen without thalidomide/lenalidomide (Table 2). Of those patients who received a bortezomib-based regimen without thalidomide/lenalidomide during cycle 1, 13 subsequently received thalidomide/lenalidomide in later cycles of their frontline therapy as maintenance. Of those patients

who initiated cycle 1 with an "other" regimen, 31 were later treated with either bortezomib (n = 14) or thalidomide/lenalidomide (n = 17). Patients were treated in the frontline for a median of 6.4 months (IQR, 3.0-10.6 months).

Because the patient numbers were insufficient to analyze the data for frontline regimens per country, the data from countries classified as having a high or low 60-year-old life expectancy using the World Health Organization's Global Health Observatory data, with the patients grouped according to age (≤ 65 years vs. > 65 years) in the SCT and non-SCT populations are listed in Supplemental Table 2 (available in the online version).

Salvage Therapies. In the SCT population, of the patients with data collected prospectively for treatment lines 2, 3, or ≥ 4 (first, second, or later salvage, respectively), 45%, 33%, and 27% had received a bortezomib-based regimen without thalidomide/lenalidomide during that line, 12%, 8%, and 6% had received a bortezomib plus thalidomide/lenalidomide-based regimen, 30%, 35%, and 27% had received a thalidomide/lenalidomide-based regimen without bortezomib, and 13%, 24%, and 40% had received an "other" regimen, respectively (Table 3). The most common combination in lines 2, 3, and ≥ 4 was RD (lenalidomide, dexamethasone; 20%, 21%, and 13%, respectively; Table 3).

In the non-SCT group, 37% of the patients received a bortezomib-based regimen without thalidomide/lenalidomide and 37% received a thalidomide/lenalidomide-based regimen without bortezomib in their second-line treatment, with only 3% receiving a second-line regimen containing both types of agents (Table 3). In lines 3 and ≥ 4, 32% and 23%, respectively, received a thalidomide/lenalidomide-based regimen without bortezomib, and 39% and 46%, respectively, were treated with a combination of "other" agents. The frequently observed other salvage regimens in lines 2, 3, and ≥ 4 included MP (melphalan plus methylprednisolone or prednisolone or prednisone; Table 3).

Data for salvage regimens from countries with either a high or low 60-year-old life expectancy for both SCT and non-SCT populations are listed in Supplemental Table 3 (available in the online version).

Treatment Response

Frontline Therapy. In the SCT group, the best overall response rate (ORR) at any time during frontline therapy was > 85% for patients receiving bortezomib and/or thalidomide/lenalidomide, including ≥ 50% rates of a very good partial response (VGPR) or better (Table 4). The ORR for patients receiving other therapies was 71% and the VGPR or better rate was 29%. In the non-SCT population, the ORR was 80%, with 40% of the patients achieving a VGPR or better. For patients treated with a thalidomide/lenalidomide-based regimen without bortezomib, the ORR and VGPR or better rate was 64% and 24%, respectively (Table 4). In those patients receiving other combinations, the ORR was 51%, with only 10% achieving a VGPR or better.

Salvage Therapy. In the SCT group, the ORR for patients receiving a bortezomib plus thalidomide/lenalidomide-based regimen was 78%, 83%, 60%, and 33% for treatment lines 2, 3, 4, and ≥ 5, respectively. Similar data were observed across the other regimen groups (Table 4). For treatment lines 2, 3, 4, and ≥ 5 in the non-SCT group, the ORR was 68%, 60%, 45%, and 35%, respectively, for patients treated with a bortezomib plus thalidomide/lenalidomide-based regimen. Again, the data for the other regimen groups were largely similar (Table 4). As seen with the frontline regimens, the ORRs for the SCT group were greater than those for the non-SCT population through line 4; however, in later lines (≥ 5), the ORRs were similar overall in the SCT and non-SCT groups.

Efficacy: Time-to-event Endpoints

Frontline Therapy. The patients in the SCT group who received a thalidomide-based regimen, a bortezomib plus thalidomide-based regimen, a bortezomib-based regimen without thalidomide/lenalidomide, or 'other' regimens had a median TTNT of 29.4, 38.4, 23.6, and 5.7 months and a median TFI of 14.6, 28.5, 16.5, and 1.7 months, respectively (Table 5). The TFR appeared greater for regimens typically not using a maintenance component or a treat-to-progression approach, such as the 'other' category, which was primarily vincristine, doxorubicin, dexamethasone induction in this setting. Both the median TTNT and the median TFI were shortest in this subgroup.

In the non-SCT population, the median TTNT for the patients treated with a thalidomide-based regimen, a bortezomib plus thalidomide-based regimen, a bortezomib-based regimen without thalidomide/lenalidomide, or 'other' regimens was 17.7, 18.5, 22.0, and 13.3 months, respectively (Table 5). The median TFI for the patients who received a thalidomide-based regimen, a bortezomib plus thalidomide-based regimen, or a bortezomib-based regimen without thalidomide/lenalidomide was 3.71, 6.11, and 11.2 months, respectively. For the patients treated with 'other' regimens, the median TFI was only 2.7 months, corresponding to a TFR of 0.91.

Salvage Therapy. In the SCT population, the patients who received a bortezomib plus thalidomide-based regimen had a TTNT of 34.4 and 14.1 months in treatment lines 2 and 3, respectively (Table 5). In lines 2, 3, 4, and ≥ 5, the patients treated with a thalidomide-based regimen without bortezomib had a TTNT of 17.7, not evaluable, 13.7, and 4.7 months, respectively. The corresponding TTNT for patients receiving lenalidomide-based regimens without bortezomib was 19.3, 22.6, 22.7, and 35.8 months. The corresponding TTNT for patients receiving 'other' regimens was 17.2, 13.2, 7.4, and 10.4 months (Table 5). The TFR decreased with each subsequent line, suggesting that patients were increasingly in need of continuing with treatment as they received subsequent lines of therapy. In the non-SCT group, a similar pattern of declining TTNT and TFI with subsequent lines was observed (Table 5). The TFR also decreased with each subsequent line of therapy.

Safety

In the SCT group, 77% of patients who had received a bortezomib-based regimen without thalidomide/lenalidomide recorded ≥ 1 treatment-emergent AE (Supplemental Table 4; available in the online version). Similar rates were observed for patients who received bortezomib plus thalidomide- or lenalidomide-based regimens (83% and 82%, respectively). Serious AEs were recorded in 21%, 16%, and

Table 3 Salvage Therapies for SCT and Non-SCT Patients Recorded During Prospective Data Collection Phase[a] and Based on Agents Received During Cycle 1 of Each Line

Treatment	SCT Patients (n = 395)			Non-SCT Patients (n = 677)		
	Line 2 (n = 345)	Line 3 (n = 288)	Line ≥ 4 (n = 486)	Line 2 (n = 805)	Line 3 (n = 590)	Line ≥ 4 (n = 935)
Regimens received during cycle 1 of each salvage therapy line						
Thalidomide/lenalidomide-based, no bortezomib	103 (29.9)	101 (35.1)	131 (27.0)	295 (36.6)	189 (32.0)	215 (23.0)
Bortezomib plus thalidomide/lenalidomide-based	41 (11.9)	23 (8.0)	30 (6.2)	20 (2.5)	13 (2.2)	34 (3.6)
Bortezomib-based, no thalidomide/lenalidomide	156 (45.2)	95 (33.0)	132 (27.2)	296 (36.8)	158 (26.8)	255 (27.3)
Other, no bortezomib or thalidomide/lenalidomide	45 (13.0)	69 (24.0)	193 (39.7)	194 (24.1)	230 (39.0)	431 (46.1)
Most prevalent combinations						
First	RD: 69 (20.0)	RD: 61 (21.2)	RD: 63 (13.0)	RD: 163 (20.2)	RD: 100 (16.9)	VD: 92 (9.8)
Second	VD: 65 (18.8)	VCD: 25 (8.7)	VD: 38 (7.8)	VD: 140 (17.4)	VD: 57 (9.7)	RD: 71 (7.6)
Third	VCD: 43 (12.5)	ADV: 11 (3.8)	VCD: 31 (6.4)	VMP: 44 (5.5)	MP: 39 (6.6)	MP: 50 (5.4)
Fourth	VTD: 25 (7.2)	VRD: 9 (3.1)	CD: 19 (3.9)	VCD: 40 (5.0)	VCD: 32 (5.4)	VCD: 47 (5.0)
Treatment duration, mo						
Median	4.4	3.7	3.5	4.6	3.9	3.0
IQR	2.3-8.8	1.6-7.0	1.1-7.2	2.3-8.2	1.6-7.9	1.0-6.6
Range	0.03-37.1	0.03-32.1	0.03-50.9[b]	0.03-44.0	0.03-46.9	0.03-36.1[b]
SCT within each line of salvage therapy						
Any SCT	133	76	50	NA	NA	NA
Autologous	126 (94.7)	66 (86.8)	42 (84)	NA	NA	NA
Allogeneic	7 (5.3)	10 (13.2)	8 (16)	NA	NA	NA
SCTs[c]				NA	NA	NA
1	123 (92.5)	71 (93.4)	47 (94)	NA	NA	NA
2	10 (7.5)	5 (6.6)	3 (6)	NA	NA	NA

Most prevalent treatment combinations (counted in ≥ 50 lines within each therapy line) for prospective MM treatment lines during the first cycle in SCT or non-SCT group shown stratified by treatment line; SCTs were counted only once per separate date recorded; thus, a patient could have undergone > 1 SCT (overall and per line) during the study period.
Abbreviations: A = doxorubicin; C = cyclophosphamide; D = dexamethasone; M = melphalan; MM = multiple myeloma; P = methylprednisolone/prednisolone/prednisone; R = lenalidomide; SCT = stem cell transplantation; T = thalidomide; V = bortezomib.
[a]For example, if a patient entered the study to begin treatment line 3, these data included the treatment regimens received by the patient at line 3 (and any subsequent lines) but not the information collected retrospectively for previous treatment (line 1, line 2) before study enrollment.
[b]Data for treatment line 4 only.
[c]Tandem SCT.

30% of patients who had received a bortezomib-based regimen without thalidomide/lenalidomide, a bortezomib plus thalidomide-based regimen, or a bortezomib plus lenalidomide-based regimen, respectively (Supplemental Table 4; available in the online version). Similar rates were also observed in non-SCT patients in these treatment groups, although the numbers were small in some cases. The rates of AEs were lower for patients who had received regimens without bortezomib, thalidomide, or lenalidomide (43% in the SCT and 53% in the non-SCT patients; Supplemental Table 4; available in the online version). In the SCT group, the incidence of peripheral neuropathy (PN) or peripheral sensory neuropathy (PSN) in those regimens without bortezomib (all lines) was < 5%. For patients receiving a bortezomib-based regimen with thalidomide, with lenalidomide, or without thalidomide/lenalidomide, the corresponding rates were 12.9% (PN; PSN 10.8%), 6.3% (PSN), and 5% (PN; PSN 6.2%), respectively. In the non-SCT group, a similar pattern was observed. The incidence of PN (or PSN) for patients receiving a bortezomib-based regimen with thalidomide, with lenalidomide, or without thalidomide/lenalidomide were < 5% (PN), 7.0% (PSN), and 6.6% (PN; PSN 6.0%), respectively. However, the incidence of PN for patients receiving thalidomide without bortezomib was 9.7%. Owing to the cumulative dose-related nature of both bortezomib-induced and thalidomide-induced PN and the absence of data on the duration of treatment for individual regimens, it is possible that the PN rates were affected by the treatment durations used for different regimens in different settings, and these data should be interpreted accordingly.

Discussion

To the best of our knowledge, the results from the EMMOS provide the first comprehensive information on the baseline characteristics and treatment of patients with MM treated in multiple countries across Europe, the Middle East, and Africa. This real-world evidence, which differs, by definition, from the evidence obtained through clinical trials, permits an evaluation of the safety and efficacy of MM treatments in daily practice compared with those reported from controlled clinical trials and allows for interpretation on the generalizability of results obtained from such trials compared with those achievable in routine practice. As a prospective, multinational registry, the EMMOS also provides an opportunity to evaluate real-

Table 4 Best Response for SCT and Non-SCT Patients Stratified by Treatment Line and Type (at Any Point in Line) in Prospective Study Phase (Patients With Available Response Data)

Response	SCT Patients			Non-SCT Patients		
	Patients, n	OR	VGPR or Better	Patients, n	OR	VGPR or Better
Line 1						
Thalidomide/lenalidomide-based, no bortezomib	48	45 (94)	29 (60)	140	90 (64)	34 (24)
Bortezomib plus thalidomide/lenalidomide-based	119	115 (97)	92 (77)	40	34 (85)	21 (53)
Bortezomib-based, no thalidomide/lenalidomide	111	95 (86)	57 (51)	380	302 (79)	148 (39)
Other, no bortezomib or thalidomide/lenalidomide	28	20 (71)	8 (29)	153	78 (51)	15 (10)
Line 2						
Thalidomide/lenalidomide-based, no bortezomib	69	52 (75)	25 (36)	223	132 (59)	61 (27)
Bortezomib plus thalidomide/lenalidomide-based	40	31 (78)	22 (55)	22	15 (68)	7 (32)
Bortezomib-based, no thalidomide/lenalidomide	117	87 (74)	54 (46)	233	153 (66)	67 (29)
Other, no bortezomib or thalidomide/lenalidomide	28	20 (71)	15 (54)	146	74 (51)	18 (12)
Line 3						
Thalidomide/lenalidomide-based, no bortezomib	74	41 (55)	19 (26)	134	64 (48)	23 (17)
Bortezomib plus thalidomide/lenalidomide-based	18	15 (83)	9 (50)	20	12 (60)	4 (20)
Bortezomib-based, no thalidomide/lenalidomide	66	38 (58)	22 (33)	116	66 (57)	30 (26)
Other, no bortezomib or thalidomide/lenalidomide	41	22 (54)	11 (27)	176	72 (41)	20 (11)
Line 4						
Thalidomide/lenalidomide-based, no bortezomib	37	24 (65)	9 (24)	76	27 (36)	9 (12)
Bortezomib plus thalidomide/lenalidomide-based	10	6 (60)	1 (10)	11	5 (45)	3 (27)
Bortezomib-based, no thalidomide/lenalidomide	45	22 (49)	14 (31)	89	39 (44)	16 (18)
Other, no bortezomib or thalidomide/lenalidomide	38	10 (26)	7 (18)	116	33 (28)	4 (3)
Line $\geq$ 5						
Thalidomide/lenalidomide-based, no bortezomib	46	20 (43)	8 (17)	96	39 (41)	13 (14)
Bortezomib plus thalidomide/lenalidomide-based	12	4 (33)	4 (33)	17	6 (35)	2 (12)
Bortezomib-based, no thalidomide/lenalidomide	55	23 (42)	8 (15)	111	39 (35)	4 (4)
Other, no bortezomib or thalidomide/lenalidomide	83	24 (29)	12 (15)	196	37 (19)	5 (3)

Percentages calculated from total number per type of therapy, excluding any missing or not evaluable patients.
Abbreviations: OR = overall response; SCT = stem cell transplantation; VGPR = very good partial response.

world data on MM that are robust and reliable. The findings from this large, multinational, multisite analysis provide important evidence to add to the increasing number of reports from analyses of MM treatment in the real-world setting.[8-13]

The reliability of the EMMOS registry is supported by the baseline demographic data and clinical characteristics of the study cohort, which were as expected for a MM population. For example, almost 80% of patients with MM have been reported to have radiologic evidence of skeletal involvement.[18] In our study, ~70% of patients reported a history of bone lesions at study entry. Equally, MM is well known as a disease that predominantly occurs in an older population.[10] In the non-SCT group in the EMMOS, the median age at study entry was 70 years, with that in the SCT group slightly younger at 59 years, as expected, given that younger age can be a key factor in determining SCT eligibility.[10] Nevertheless, we acknowledge that a reporting bias might be present toward patients who were younger or fitter at diagnosis owing to the inclusion of patients who had received multiple previous lines of therapy—older or more frail patients might not have survived long enough to receive several lines of treatment. In contrast, a slight reporting bias might have been present owing to the omission from the EMMOS of patients already enrolled in the large number of prospective studies taking place concurrently, who potentially might have been younger and/or fitter than the nonclinical trial population eligible for the EMMOS.

In terms of treatment, data from the EMMOS have shown that bortezomib was the most commonly used backbone agent in the frontline setting, with 75% and 58% of SCT and non-SCT patients receiving a bortezomib-based regimen with or without thalidomide/lenalidomide. Patients in the SCT group were more likely to receive a frontline combination of VTD than were their counterparts in the non-SCT group (30% vs. 4%, respectively). In contrast, the VMP regimen was more commonplace in the latter group (1% vs. 24%), reflecting the different standard-of-care regimens in these settings in Europe. In the salvage setting, the use of bortezomib-based and thalidomide/lenalidomide-based regimens appeared similar, with the exception of second-line therapy for SCT patients. In both the SCT and the non-SCT groups, the receipt of 'other' treatments and the diversity of combinations within this category were increasingly common in later lines, suggesting a lack of overall consensus for the best treatment practices in advanced disease. These findings also reflect the limited treatment options at the time of the EMMOS, with many patients "exhausting" their bortezomib- and/or

Table 5 Time-to-event Endpoints for SCT and Non-SCT Patients Stratified By Treatment Line and Type Received at Any Point During Line[a]

Variable	SCT Patients				Non-SCT Patients			
	Line, n/N (%)	Median TTNT, mo (95% CI)	Median TFI, mo (95% CI)	TFR	Line, n/N (%)	Median TTNT, mo (95% CI)	Median TFI, mo (95% CI)	TFR
Line 1[b]								
Thalidomide-based	26/51 (51)	29.4 (15.51-NE)	14.6 (0.99-NE)	1.55	89/158 (56)	17.7 (15.1-22.1)	3.71 (2.30-5.13)	0.71
Bortezomib plus lenalidomide-based	6/27 (22)	NE (NE-NE)	NE (NE-NE)	0.67	4/19 (21)	NE (NE-NE)	16.4 (0.07-16.4)	0.35
Bortezomib plus thalidomide-based	42/124 (34)	38.4 (38.4-NE)	28.5 (17.9-34.2)	1.68	18/35 (51)	18.5 (8.28-31.4)	6.11 (1.38-24.2)	1.56
Bortezomib-based, no thalidomide/ lenalidomide	69/125 (55)	23.6 (21.5-37.6)	16.5 (15.4-23.0)	2.52	236/450 (52)	22.0 (20.0-24.2)	11.2 (10.0-13.8)	1.71
Other,[c] no bortezomib or thalidomide/ lenalidomide	25/32 (78)	5.7 (2.6-9.7)	1.7 (1.0-2.7)	2.80	102/167 (61)	13.3 (9.5-17.1)	2.7 (1.7-5.5)	0.91
Line 2[d]								
Thalidomide-based	10/19 (53)	17.7 (10.3-NE)	11.8 (0.13-NE)	2.29	42/80 (53)	15.2 (10.5-23.6)	2.96 (1.22-7.49)	0.72
Lenalidomide-based	39/80 (49)	19.3 (13.2-36.1)	2.37 (1.25-5.09)	0.56	64/182 (35)	27.1 (17.6-NE)	7.23 (2.53-14.5)	0.64
Bortezomib plus lenalidomide-based	8/18 (44)	21.3 (5.62-NE)	5.29 (0.76-NE)	0.89	3/8 (38)	20.1 (10.7-NE)	14.8 (0.33-14.8)	0.49
Bortezomib plus thalidomide-based	12/31 (39)	34.4 (13.9-NE)	19.4 (10.3-NE)	2.36	13/18 (72)	9.86 (5.42-14.9)	1.22 (0.49-2.86)	0.80
Bortezomib-based, no thalidomide/ lenalidomide	83/138 (60)	14.7 (10.5-19.1)	7.7 (4.6-11.7)	2.82	151/260 (58)	13.6 (11.2-14.9)	6.3 (4.6-8.1)	1.62
Other,[c] no bortezomib or thalidomide/ lenalidomide	12/26 (46)	17.2 (8.2-NE)	7.8 (1.3-NE)	2.28	79/141 (56)	15.4 (10.5-18.2)	4.3 (2.5-6.7)	1.26
Line 3								
Thalidomide-based	5/14 (36)	NE (NE-NE)	NE (NE-NE)	0.92	24/50 (48)	11.6 (6.90-NE)	4.27 (0.92-8.71)	0.75
Lenalidomide-based	28/79 (35)	22.6 (18.2-NE)	4.44 (1.91-NE)	0.80	43/105 (41)	21.1 (13.0-26.0)	3.78 (1.61-7.66)	0.52
Bortezomib plus lenalidomide-based	4/12 (33)	NE (NE-NE)	NE (NE-NE)	1.32	5/10 (50)	36.1 (3.81-36.1)	7.89 (0.07-24.0)	0.78
Bortezomib plus thalidomide-based	6/11 (55)	14.1 (5.95-22.8)	6.74 (0.26-21.0)	1.72	6/11 (55)	8.16 (1.54-NE)	2.66 (0.20-4.11)	0.39
Bortezomib-based, no thalidomide/ lenalidomide	46/79 (58)	14.2 (9.4-19.5)	7.3 (4.0-12.6)	2.17	71/129 (55)	13.8 (9.7-17.1)	6.1 (3.3-9.9)	1.86
Other,[c] no bortezomib or thalidomide/ lenalidomide	17/39 (44)	13.2 (11.0-NE)	9.6 (2.2-NE)	1.97	102/174 (59)	12.0 (9.5-14.8)	3.4 (2.6-4.6)	1.08
Line 4[e]								
Thalidomide-based	4/7 (57)	13.7 (3.94-NE)	1.05 (0.30-NE)	0.79	14/30 (47)	13.3 (9.23-NE)	6.74 (0.39-NE)	0.77
Lenalidomide-based	19/44 (43)	22.7 (14.8-28.9)	2.07 (1.28-12.1)	0.38	19/50 (38)	15.7 (10.5-27.0)	1.87 (1.38-4.70)	0.38
Bortezomib-based, no thalidomide/ lenalidomide	23/47 (49)	15.9 (9.0-26.7)	7.1 (2.3-20.4)	1.53	62/92 (67)	10.0 (7.6-12.3)	4.3 (2.5-5.3)	1.22
Other,[c] no bortezomib or thalidomide/ lenalidomide	23/36 (64)	7.4 (5.1-10.8)	2.2 (1.0-3.7)	1.26	46/105 (44)	10.1 (8.5-15.9)	2.6 (1.9-7.1)	0.74

Table 5 Continued

Variable	SCT Patients				Non-SCT Patients			
	Line, n/N (%)	Median TTNT, mo (95% CI)	Median TFI, mo (95% CI)	TFR	Line, n/N (%)	Median TTNT, mo (95% CI)	Median TFI, mo (95% CI)	TFR
Line 5[f]								
Thalidomide-based	7/15 (47)	4.70 (3.68-NE)	1.18 (0.07-NE)	0.96	33/47 (70)	7.23 (5.22-10.1)	1.18 (0.76-2.56)	0.58
Lenalidomide-based	18/43 (42)	35.8 (13.3-35.8)	1.18 (0.30-10.9)	0.38	23/50 (46)	12.6 (11.2-19.4)	2.33 (1.54-4.99)	0.58
Bortezomib plus lenalidomide-based	6/9 (67)	8.25 (1.77-NE)	1.05 (0.03-NE)	2.75	2/11 (18)	NE (NE-NE)	NE (NE-NE)	0.52
Bortezomib-based, no thalidomide/lenalidomide	32/57 (56)	9.6 (7.1-11.5)	3.0 (1.7-5.5)	1.10	58/110 (53)	10.4 (8.5-12.9)	3.7 (1.8-4.9)	0.71
Other,[c] no bortezomib or thalidomide/lenalidomide	32/70 (46)	10.4 (6.7-14.3)	1.7 (1.3-5.4)	0.56	70/153 (46)	9.3 (7.7-12.3)	3.0 (2.4-4.4)	0.78

Abbreviations: CI = confidence interval; n/N = number of patients within treatment line with subsequent treatment/total number of patients with treatment line during prospective study phase; NE = not evaluable; R = lenalidomide; SCT = stem cell transplantation; T = thalidomide; TFI = treatment-free interval; TFR = treatment-free ratio; TTNT = time to next treatment.

[a]Data presented for treatment lines with > 30 days' duration.

[b]Patient numbers for line 1, lenalidomide-based regimen: 1 and 7; line 1, thalidomide/lenalidomide-based regimen, no bortezomib: 0 and 0; line 1, bortezomib plus thalidomide/lenalidomide-based regimen: 8 and 2; thus, these data were excluded.

[c]Most regimens were ADO (Adriamycin, dexamethasone, Oncovin).

[d]Patient numbers for line 2, thalidomide/lenalidomide-based regimen, no bortezomib: 1 and 1; line 2, bortezomib plus thalidomide/lenalidomide-based regimen: 3 and 0; thus, these data were excluded.

[e]Patient numbers for line 4, bortezomib plus lenalidomide-based regimen: 8 and 6; line 4, bortezomib plus thalidomide-based regimen: 6 and 8; thus, these data were excluded.

[f]Patient numbers for line ≥ 5, bortezomib plus thalidomide-based regimen: 9 and 3; thus, these data were excluded.

thalidomide/lenalidomide-based options within their first few lines of therapy. With the introduction of multiple new drugs, a consensus of treatment sequences for MM now seems even more remote, and choosing the best available therapy might be compromised by the restrictions of drug access in multiple national settings. This variation with subsequent lines of therapy is supported by an analysis of MM practice patterns across Europe conducted in 2014. Although bortezomib-containing combinations were identified as the most commonly used induction regimen, with lenalidomide the most frequently used agent in lines 2 and 3,[10] greater variation was seen in later lines, just as seen in the present study. Also, these findings from the EMMOS and other European real-world studies are not likely to be reflective of real-world practice in the United States. In addition, specific centers of excellence might also have their own treatment protocols, for example, to define risk stratification and treatment sequencing. Furthermore, the increased number of regimens and approved agents for MM treatment is very likely to have altered the current data with respect to the frequency of use of different backbone agents in different treatment settings.

Regarding the specific treatment combinations, although still an option in the relevant guidelines at the time of data collection,[19,20] regimens such as MP have been thought to have been generally superseded in routine clinical practice. However, our data showed that several patients were still receiving them, most notably as first- and second-line therapy for patients not selected or not eligible for SCT. However, this might reflect the timeline of approvals during the EMMOS data collection, because combinations such as VMP and MPT (melphalan, prednisolone, thalidomide) were still somewhat new at study start, resulting in cost and/or access barriers in some countries. The current guidelines recommend 4 bortezomib-based regimens with/without thalidomide/lenalidomide (VMP, VCD, VTD, VRD [bortezomib, lenalidomide, dexamethasone]) and 2 non−bortezomib-based regimens (RD [lenalidomide, dexamethasone] and MPT) as frontline therapy.[21]

In general, patients in the SCT group had greater ORRs, with a greater proportion achieving a VGPR or better compared with those in the non-SCT group. For example, patients receiving frontline therapies incorporating thalidomide/lenalidomide, with or without bortezomib, had an ORR of 97% and 94%, respectively, in line with previously reported rates in phase III clinical trials.[22] High ORRs were also observed with both frontline and salvage bortezomib-containing lines across the SCT and non-SCT groups. The VGPR or better rates observed with frontline bortezomib in the SCT population were similar to the rates reported with bortezomib-based induction therapy in SCT-eligible patients in randomized phase III clinical trials,[23-25] with the caveat that the trials used standardized and stringent response criteria. In general, however, the ORRs for each type of regimen decreased with each subsequent therapy line. In the SCT population, bortezomib plus thalidomide/lenalidomide regimens resulted in the numerically greatest ORRs through line 3; however, in later lines ($\geq$ 5), the ORRs for all types of bortezomib- or thalidomide/lenalidomide-based therapies were within 10% of each other.

In terms of the time-to-event outcomes, patients in the SCT group had longer TTNT and TFI after frontline therapy than did their counterparts in the non-SCT group, with a higher TFR in the SCT group, suggesting that these patients were spending relatively less time "on treatment." However, in subsequent lines, these differences were

generally much less pronounced. In the SCT and non-SCT groups, the TFR generally decreased with each subsequent line, suggesting that patients were increasingly continuing treatment as they received subsequent lines of therapy.[26] Those patients receiving 'other' regimens, however, had longer TTNT and TFI with second-line treatment compared with frontline, which, although shorter in subsequent lines, stayed largely greater than that seen in frontline. Overall, the median treatment duration decreased in the SCT and non-SCT groups with each subsequent line of therapy.

Because the EMMOS was a registry-based study, a number of limitations should be considered. The data were limited by the information available from the treating physicians as a part of routine clinical practice; thus, parameters such as minimal residual disease were not collected, and the rate of cytogenetic evaluation was limited. It was also not possible to clearly determine the intentions underlying the treatment choices. This is also linked to the fact that comparisons between different regimen types must be interpreted with caution, because the allocation of patients to a particular intervention were not randomized and, thus, could have influenced the outcomes. Additionally, regimens or agents could have been used in different combinations and in different treatment approaches within or between lines of therapy and in different treatment contexts (eg, as maintenance after autologous SCT); thus, caution should be used in the interpretation of the findings between the broad-based categories of regimens. Moreover, no standardized response criteria were used across the sites, and no uniform requirement for confirmation of a complete response by bone marrow analysis was included, making comparisons of response less reliable. Also, the collection of safety data was limited by comparisons with clinical trial protocols, restricting the interpretation of these data. Finally, owing to the timeframe of the EMMOS, with the final data collected in 2014, the recent rapid developments in MM treatment options and assessment techniques could not be reflected or incorporated. For example, the proteasome inhibitors carfilzomib and ixazomib have been approved for the treatment of relapsed/refractory MM,[27,28] and the histone deacetylase inhibitor, panobinostat, and the monoclonal antibodies daratumumab and elotuzumab have also been approved.[29,30]

These factors do not diminish the usefulness of our data but merely clarify the parameters of applicability. With the continued approval of new agents, the information presented in the present study can be expected to evolve, pointing to future changes in the treatment paradigm and likely further improvements in patient outcomes. It will be interesting to see, in subsequent evaluations, how quickly recently approved agents actually become integrated into standard real-world treatment practices. Access to novel agents varies greatly from country to country, with factors such as affordability, local guidelines and restrictions, and regulatory decisions or delays all affecting treatment availability. The need for robust health economic evaluations, in addition to efficacy and safety data, has become increasingly important in this respect.

Conclusion

These prospective real-world data highlight the large diversity of treatments used to manage MM in normal practice. This was an unexpected finding that was likely linked to various factors, including study duration, the large number of sites and countries involved and their differing access to treatments, the diversity of patients included in the registry, the approval and introduction of new novel agents during the study period, and changes in treatment recommendations over time. The results also provide insights into the real-world clinical benefits that can be achieved with both SCT and systemic treatment regimens in MM, with efficacy similar to that seen in controlled clinical trials. Taken together, these data provide a framework toward the design of future protocols aiming to improve the outcomes in MM.

Clinical Practice Points

- MM, although treatable, remains an incurable disease, with a dearth of evidence on how this disease is treated in real-world clinical practice.
- Despite the availability of an increasing number of agents to treat MM, objective, detailed knowledge is lacking on the natural history of patients with MM at different stages of disease and on treatment selection, dose, duration of therapy, outcomes, and how practices vary from country to country.
- The present prospective, noninterventional observational study found huge diversity in the treatment regimens used in everyday clinical practice for MM.
- The present study has also described the efficacy and provided insights into treatment tolerability of patients with MM in geographically diverse real-world settings.
- The present study has provided representative and descriptive data to allow for health economic, pharmacoepidemiologic, and outcomes research.
- These results provide a framework toward the design of future protocols aiming to improve the outcomes of patients with MM and identify imbalances in regional treatment strategies.

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Disclosure

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Supplemental Data

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Supplemental Appendix

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Supplemental Table 1 Summary of Data Collection

Data Collection
Retrospective
Demographic data and baseline disease characteristics
Physical examination
Treatment
All previous MM therapies, including start/stop dates
Rationale for treatment of MM-related complications
Concomitant medications
Effectiveness
Outcomes
Medical resource usage and health economics
Resource usage
Prospective
Demographic data and baseline disease characteristics
Sociodemographic data
Disease
Diagnosis history
Comorbidities
Disease severity
Current disease status
Treatment
Current MM treatment, including participating physician's rationale for treatment choice
Certain concomitant medications
Effectiveness
Response, including criteria used for assessment
Time-to-event endpoints
Medical resource usage and health economics
Resource usage and HRQL
Safety
All ADRs and AE (serious and not serious) in prospective phase; ADRs related to bortezomib only in retrospective phase
Reason for early withdrawal from the study (where applicable)

Abbreviations: ADR = adverse drug reaction; AE = adverse event; HRQL = health-related quality of life; MM = multiple myeloma.

Supplemental Table 2 Frontline Therapy for SCT and Non-SCT Patients Stratified by High Versus Low 60-year Life Expectancy and Age ≤ 65 Versus > 65 years Recorded During Prospective Data Collection Phase[a] and Based on Therapies Received During Cycle 1

Regimen	SCT Patients			Non-SCT Patients (n = 906)
	Frontline (n = 299)	Not Frontline (n = 81)	Total (n = 380)	
All patients				
Thalidomide/lenalidomide-based, no bortezomib	32 (10.7)	14 (17.3)	46 (12.1)	160 (17.7)
Bortezomib plus thalidomide/lenalidomide-based	108 (36.1)	6 (7.4)	114 (30.0)	34 (3.8)
Bortezomib-based, no thalidomide/lenalidomide	141 (47.2)	29 (35.8)	170 (44.7)	491 (54.2)
Other, no bortezomib or thalidomide/lenalidomide	18 (6.0)	32 (39.5)	50 (13.2)	221 (24.4)
High 60-y life expectancy countries[b]				
Patients, n	210	30	240	489
Thalidomide/lenalidomide-based, no bortezomib	2 (1.0)	0	2 (0.8)	47 (9.6)
Bortezomib plus thalidomide/lenalidomide-based	97 (46.2)	4 (13.3)	101 (42.1)	24 (4.9)
Bortezomib-based, no thalidomide/lenalidomide	107 (51.0)	23 (76.7)	130 (54.2)	379 (77.5)
Other, no bortezomib or thalidomide/lenalidomide	4 (1.9)	3 (10.0)	7 (2.9)	39 (8.0)
Low 60-y life expectancy countries[c]				
Patients, n	89	51	140	417
Thalidomide/lenalidomide-based, no bortezomib	30 (33.7)	14 (27.5)	44 (31.4)	113 (27.1)
Bortezomib plus thalidomide/lenalidomide-based	11 (12.4)	2 (3.9)	13 (9.3)	10 (2.4)
Bortezomib-based, no thalidomide/lenalidomide	34 (38.2)	6 (11.8)	40 (28.6)	112 (26.9)
Other, no bortezomib or thalidomide/lenalidomide	14 (15.7)	29 (56.9)	43 (30.7)	182 (43.6)
Patients aged ≤ 65 y				
Patients, n	262	77	339	337
Thalidomide/lenalidomide-based, no bortezomib	31 (11.8)	13 (16.9)	44 (13.0)	67 (19.9)
Bortezomib plus thalidomide/lenalidomide-based	93 (35.5)	6 (7.8)	99 (29.2)	25 (7.4)
Bortezomib-based, no thalidomide/lenalidomide	121 (46.2)	27 (35.1)	148 (43.7)	124 (36.8)
Other, no bortezomib or thalidomide/lenalidomide	17 (6.5)	31 (40.3)	48 (14.2)	121 (35.9)
Patients aged > 65 y				
Patients, n	37	4	41	569
Thalidomide/lenalidomide-based, no bortezomib	1 (2.7)	1 (25)	2 (4.9)	93 (16.3)
Bortezomib plus thalidomide/lenalidomide-based	15 (40.5)	0	15 (36.6)	9 (1.6)
Bortezomib-based, no thalidomide/lenalidomide	20 (54.1)	2 (50)	22 (53.7)	367 (64.5)
Other, no bortezomib or thalidomide/lenalidomide	1 (2.7)	1 (25)	2 (4.8)	100 (17.6)

Data presented as n (%); all percentages calculated from respective numbers within high or low 60-year life expectancy group.
Abbreviation: SCT = stem cell transplantation.
[a]For example, among patients who entered the study at the point of receiving their first treatment line.
[b]Austria, France, Germany, Greece, Israel, Italy, Portugal, and Spain.
[c]Algeria, Croatia, Denmark, Estonia, Hungary, Latvia, Lithuania, Macedonia, Poland, Russia, Slovenia, South-Africa, Turkey, and Ukraine.

Supplemental Table 3 Salvage Therapies for SCT and Non-SCT Patients Stratified by Countries With High Versus Low 60-year Life Expectancy Recorded During prospective Data Collection Phase[a] and Based on Therapies Received During Cycle 1

Treatment	SCT Patients (n = 395)					Non-SCT Patients (n = 677)			
	Line 2 (n = 345)	SCT in Line[b] (n = 133)	Line 3 (n = 288)	SCT in Line[b] (n = 74)	Line ≥ 4 (n = 458)	SCT in Line[b] (n = 49)	Line 2 (n = 805)	Line 3 (n = 590)	Line ≥ 4 (n = 481)
High 60-y life expectancy countries[c]									
Patients, n	198	62	178	38	297	22	405	266	101
Thalidomide/lenalidomide-based, no bortezomib	71 (35.9)	20 (32.3)	70 (39.3)	9 (23.7)	78 (26.3)	1 (4.5)	8 (2.0)	112 (42.1)	23 (22.8)
Bortezomib plus thalidomide/lenalidomide-based	23 (11.6)	8 (12.9)	15 (8.4)	9 (23.7)	15 (5.1)	2 (9.1)	7 (1.7)	2 (0.8)	5 (5.0)
Bortezomib-based, no thalidomide/lenalidomide	80 (40.4)	20 (32.3)	60 (33.7)	10 (26.3)	81 (27.3)	9 (40.9)	140 (34.6)	71 (26.7)	32 (31.7)
Other, no bortezomib or thalidomide/lenalidomide	24 (12.1)	13 (21.0)	33 (18.5)	10 (26.3)	123 (41.4)	10 (45.5)	61 (15.1)	81 (30.5)	41 (40.6)
Low 60-y life expectancy countries[d]									
Patients, n	147	71	110	36	158	27	400	324	380
Thalidomide/lenalidomide-based, no bortezomib	32 (21.8)	15 (21.1)	31 (28.2)	5 (13.9)	45 (28.5)	4 (14.8)	98 (24.5)	77 (23.8)	82 (25.3)
Bortezomib plus thalidomide/lenalidomide-based	18 (12.2)	10 (14.1)	8 (7.3)	2 (5.6)	13 (8.2)	2 (7.4)	13 (3.3)	11 (3.4)	15 (4.6)
Bortezomib-based, no thalidomide/lenalidomide	76 (51.7)	37 (52.1)	35 (31.8)	14 (38.9)	41 (25.9)	4 (14.8)	156 (39.0)	87 (26.9)	99 (30.6)
Other, no bortezomib or thalidomide/lenalidomide	21 (14.3)	9 (12.7)	36 (32.7)	15 (41.7)	59 (37.3)	17 (63.0)	133 (33.3)	149 (46.0)	184 (56.8)

Data presented as n (%); all percentages calculated from respective numbers within high or low 60-year life expectancy group.
Abbreviation: SCT = stem cell transplantation.
[a]For example, if a patient entered the study at the time of beginning line 3 of therapy, these data include the treatment regimens received by the patient at line 3 (and any subsequent lines), but not the information collected retrospectively on prior treatment (line 1, line 2) before study enrollment.
[b]"Line 2, SCT in Line" column contains data for all patients; "Line 3 SCT in Line" and "Line ≥ 4, SCT in Line" columns contain data only for patients aged < 65 years.
[c]Austria, France, Germany, Greece, Israel, Italy, Portugal, and Spain.
[d]Algeria, Croatia, Denmark, Estonia, Hungary, Latvia, Lithuania, Macedonia, Poland, Russia, Slovenia, South Africa, Turkey, and Ukraine.

Supplemental Table 4 Line-emergent AEs in SCT and Non-SCT Patients Stratified by Therapy Type

Variable	SCT Patients				Non-SCT Patients			
	Patients, n	Any AE	SAE	AEs Leading to Death	Patients, n	Any AE	SAE	AE Leading to Death
Line 1								
Bortezomib-based, no thalidomide/lenalidomide	131	101 (77.1)	27 (20.6)	0	478	374 (78.2)	145 (30.3)	34 (7.1)
Bortezomib plus thalidomide-based	124	103 (83.1)	20 (16.1)	0	40	32 (80.0)	16 (40.0)	8 (20.0)
Bortezomib plus lenalidomide-based	27	22 (81.5)	8 (29.6)	1 (3.7)	19	17 (89.5)	6 (31.6)	1 (5.3)
Thalidomide/lenalidomide-based, no bortezomib	1	1 (100)	1 (100)	0	0	0	0	0
Other, no bortezomib or thalidomide/lenalidomide	37	16 (43.2)	3 (8.1)	0	190	101 (53.2)	39 (20.5)	13 (6.8)
Line 2								
Bortezomib-based, no thalidomide/lenalidomide	148	95 (64.2)	30 (20.3)	12 (8.1)	290	171 (59.0)	68 (23.4)	21 (7.2)
Bortezomib plus thalidomide-based	31	23 (74.2)	1 (3.2)	0	21	9 (42.9)	5 (23.8)	2 (9.5)
Bortezomib plus lenalidomide-based	18	12 (66.7)	6 (33.3)	1 (5.6)	8	6 (75.0)	3 (37.5)	0
Thalidomide/lenalidomide-based, no bortezomib	1	1 (100)	1 (100)	0	1	1 (100)	0	0
Other, no bortezomib or thalidomide/lenalidomide	42	17 (40.5)	8 (19.0)	2 (4.8)	186	94 (50.5)	34 (18.3)	14 (7.5)
Line 3								
Bortezomib-based, no thalidomide/lenalidomide	91	49 (53.8)	16 (17.6)	9 (9.9)	151	76 (50.3)	33 (21.9)	18 (11.9)
Bortezomib plus thalidomide-based	13	9 (69.2)	4 (30.8)	3 (23.1)	11	4 (36.4)	1 (9.1)	1 (9.1)
Bortezomib plus lenalidomide-based	15	10 (66.7)	5 (33.3)	1 (6.7)	10	8 (80.0)	7 (70.0)	2 (20.0)
Thalidomide/lenalidomide-based, no bortezomib	1	1 (100)	1 (100)	1 (100)	0	0	0	0
Other, no bortezomib or thalidomide/lenalidomide	66	28 (42.4)	14 (21.2)	5 (7.6)	227	117 (51.5)	46 (20.3)	22 (9.7)
Line 4								
Bortezomib-based, no thalidomide/lenalidomide	57	39 (68.4)	17 (29.8)	8 (14.0)	111	67 (60.4)	29 (26.1)	9 (8.1)
Bortezomib plus thalidomide-based	7	4 (57.1)	0	0	9	9 (100)	4 (44.4)	2 (22.2)
Bortezomib plus lenalidomide-based	9	4 (44.4)	0	0	7	3 (42.9)	0	0
Thalidomide/lenalidomide-based, no bortezomib	0	0	0	0	1	1 (100)	0	0
Other, no bortezomib or thalidomide/lenalidomide	61	29 (47.5)	16 (26.2)	9 (14.8)	163	78 (47.9)	40 (24.5)	24 (14.7)
Line $\geq$ 5								
Bortezomib-based, no thalidomide/lenalidomide	72	46 (63.9)	26 (36.1)	14 (19.4)	143	68 (47.6)	32 (22.4)	20 (14.0)
Bortezomib plus thalidomide-based	11	9 (81.8)	5 (45.5)	3 (27.3)	9	5 (55.6)	4 (44.4)	2 (22.2)
Bortezomib plus lenalidomide-based	11	8 (72.7)	3 (27.3)	2 (18.2)	13	6 (46.2)	3 (23.1)	2 (15.4)
Thalidomide/lenalidomide-based, no bortezomib	0	0	0	0	0	0	0	0
Other, no bortezomib or thalidomide/lenalidomide	125	72 (57.6)	48 (38.4)	28 (22.4)	259	128 (49.4)	71 (27.4)	31 (12.0)

Data presented as n (%).
Abbreviations: AE = adverse event; SAE = serious adverse event; SCT = stem cell transplantation.