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Research Article

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Real-world treatment patterns, healthcare resource use and disease burden in patients with multiple myeloma in Europe

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Aim: To investigate treatment patterns, healthcare resource utilization and disease burden in patients with multiple myeloma (MM). **Methods:** Point-in-time survey of physicians and their patients presenting in a real-world clinical setting, collected across Europe between May and November 2021. **Results:** In total, 173 physicians provided data for 2179 patients with MM. Treatments received became more diverse as line of therapy increased, dictated by previous treatment choices. Overall, 25% of all patients were tri-exposed, and experienced a higher degree of healthcare resource utilization, disease burden and impairment than non-tri-exposed patients. **Conclusion:** The treatment landscape in MM is complex and evolving. There is an unmet need for more effective therapies to reduce disease burden, particularly in tri-exposed patients.

Plain language summary: There are many new treatments available for patients with multiple myeloma. While outcomes such as survival, symptoms and health problems experienced have improved, patients still continue to relapse and fall ill again. This means their current treatment stops working and they have to change to a new treatment to prevent their disease from developing further. Patients who have received three different types of treatment are classed as being 'tri-exposed', and they experience greater problems with their health. To better understand this course of events, we used information from a survey of doctors and their patients with multiple myeloma across Europe in 2021. We looked at patient's symptoms, the treatments they received, how and when they accessed healthcare (including hospital visits and tests) and the overall difficulties experienced due to their illness. We found that patients were broadly treated according to the most recent European guidelines, although differences were seen between countries. When patients had to switch therapy, the type of treatment received next depended on what they had previously been prescribed, meaning that treatment choices became increasingly complicated. Overall, 25% of patients in our study were classed as tri-exposed, and had more hospitalisations, required more hospital tests, had greater health problems and experienced more difficulties at work than those who were not tri-exposed. Despite recent developments in the treatment of multiple myeloma, there is still a need for more effective therapies. This is especially true for patients who are tri-exposed, who have limited treatment options and experienced greater health problems.

Tweetable abstract: Despite improvements in the treatment of multiple myeloma, patients still experience symptoms and disease burden, all of which impact on healthcare resource use. Patients who are tri-exposed also have limited treatment options.

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Future Medicine

Multiple myeloma (MM) is a clonal plasma cell neoplasm, which accounts for approximately 10% of hematological malignancies globally [1]. The Global Cancer Observatory estimated that around 50,918 new cases of MM and about 32,495 deaths due to MM occurred in Europe in 2020 [2,3].

MM is an incurable disease, however the introduction of more effective therapies has improved outcomes over the past decade. The European Society for Medical Oncology (ESMO) treatment guidelines for MM were initially updated in 2017 [4] and then further updated in 2021 [5], to take into account the increasing number of treatment options available following updated clinical trial data and approval of therapies across the treatment pathway. The introduction of these new agents and continuing research into new therapeutic approaches for relapsed/refractory MM (RRMM) have coincided with a marked increase in survival globally [6]. A retrospective claim-based cohort study in the USA found a 35% decrease in the risk of death among patients diagnosed with MM in 2011–2014 compared with 2006–2010 [7].

The ultimate aim of treatment remains to improve survival and reduce symptomatic burden and quality of life for patients with MM, who also tend to be older in age. The disease impacts multiple locations in the body, resulting in symptoms such as bone pain and fractures, anaemia, fatigue and weight loss. Physicians use myeloma defining events, which include the CRAB criteria (hypercalcemia, renal insufficiency, anemia and bone abnormalities) [1], or the presence of one or more biomarkers of malignancy (clonal bone marrow plasma cells ≥60%, serum free light chain [FLC] ratio of 100 or higher, provided involved FLC level is 100 mg/l or higher, or more than one focal lesion on imaging) to identify symptoms, aid diagnosis and assess severity of MM [8]. However, despite the range of treatment combinations now available, many patients continue to relapse and become resistant to conventional therapies. Survival rates are poor in certain patient groups, such as those with high-risk disease or in those who have undergone multiple lines of prior therapy. Patients who have previously received three therapy classes, i.e. at least one immunomodulatory drug (IMiD®; lenalidomide, thalidomide or pomalidomide), at least one protease inhibitor (PI; bortezomib, carfilzomib or ixazomib) and at least one anti-cluster of differentiation 38 (CD38) antibody (daratumumab or isatuximab) are defined as being tri-exposed, and poor clinical outcomes are particularly evident in this patient group. The MAMMOTH study investigated patients with MM refractory to an anti-CD38 antibody, a subset of patients who had tri-exposed disease, finding poor prognosis in terms of progression-free survival and overall survival in this patient group [9]. The ongoing prospective observational LocoMMotion study is also investigating tri-exposed patients with RRMM and recent data confirmed poor outcomes of these patients, in particular overall response rate and treatment-related adverse events [10].

While these studies indicated considerable unmet need in the tri-exposed patient population, data from real-world studies, highlighting real-world treatment pathways, areas of concern and unmet need which are not addressed in clinical trials, are lacking. Given the evolving and complex treatment landscape in MM, we investigated current treatment patterns, healthcare resource utilization (HCRU) and disease burden (both health-related quality of life [HRQoL] and patient-reported outcomes) in patients with MM from real-world practice settings in Europe, focusing particularly on patients with tri-exposed MM.

Methods

Study design

Data were drawn from the Adelphi Real World MM Disease Specific Programme (DSP™). DSPs are large, independent, multinational point-in-time surveys of physicians and their patients presenting in a real-world clinical setting. The data analysed for this study were collected from five European countries (EU5: France, Germany, Italy, Spain and the UK) between May and November 2021. A complete description of the DSP survey methodology has been previously published and validated [11–13].

A geographically diverse sample of physicians were recruited to participate in the survey by local fieldwork agents. Physicians were eligible to participate if they were a haematologist or haem-oncologist that was personally responsible for treatment decisions and management of patients with RRMM.

Patients were eligible for inclusion if, at data collection, they were over the age of 18 years at diagnosis of MM, had a physician-confirmed diagnosis of MM, were receiving an active drug treatment of their MM and were not participating in a clinical trial, or receiving best supportive care only for their MM.

Physician participation was financially incentivised, with reimbursement upon survey completion according to fair market research rates. Patients were not compensated for participation.

Ethics & consent

Using a checkbox, patients provided informed consent to take part in the survey. Data were collected in such a way that patients and physicians could not be identified directly. Physician and patient data were pseudo-anonymised. A code was assigned when data were collected. Upon receipt by Adelphi Real World, data were pseudo-anonymised again to mitigate against tracing them back to the individual. Data were aggregated before being shared with the subscriber and/or for publication.

The DSP survey was submitted to the Pearl Institutional Review Board (study protocol number: #21-ADRW-103). Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such did not require ethics committee approval [14]. In addition, the survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 [15].

Physician-reported data

To investigate treatment patterns across lines of therapy (LOT) representative of real-world clinical practice, recruited physicians were instructed to complete an electronic patient record form for the next eight consecutively consulting patients in alignment with the following quota, two patients on each of the following LOT: first-line (1L) or second-line (2L), third-line (3L), fourth-line and beyond (4L+), and previous receipt of a PI, IMID and CD38-targeted drug (tri-exposed) irrespective of LOT.

The patient record form contained detailed questions on patient demographic and clinical characteristics, capturing disease severity, symptomatic burden, HCRU, as well as full treatment history, related to the patient's MM. Completion of the patient record form was undertaken through consultation of existing patient clinical records, as well as the judgement and diagnostic skills of the respondent physician at the time of data collection. No additional tests, treatments or investigations were performed as part of the survey.

Patient-reported data

Each patient for whom the physician completed a patient record form was invited to voluntarily complete a patient-reported questionnaire (either a pen-and-paper version or an online version), and upon agreement provided their informed consent to participate. The patient-reported questionnaire contained detailed questions on their current symptomatic burden and other patient-reported outcomes (PRO). All patient-reported questionnaires were completed by the patient independently from their physician.

A number of validated PRO instruments were used to assess HRQoL. The EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) utility score and Visual Analogue Scale (VAS) assessed general HRQoL [16], with a difference of 0.10 in the EQ-5D-5L utility score and a difference of 8 on the EQ-5D VAS considered clinically meaningful [17]. The European Organisation for Research and Treatment of Cancer Quality of Life Core-30 Questionnaire version 3 (EORTC QLQ-C30) assessed cancer-specific HRQoL [18,19], with a difference of 5 for individual symptoms and 10 for global health status considered clinically meaningful in patients with MM [20]. The European Organisation for Research and Treatment of Cancer Quality of Life of Myeloma Patients 20-item questionnaire (EORTC QLQ-MY20) assessed myeloma-specific HRQoL [21,22], with minimally important differences across different domains defined as previously published [23].

The impact of MM on patient day-to-day functioning and impairment was quantified using the Work Productivity and Activity Impairment (WPAI) questionnaire [24].

Data analysis

Analysis was primarily conducted using descriptive bivariate analysis. Descriptive analyses of key measures, including demographics, clinical characteristics, treatment characteristics and patterns, were undertaken. The mean and standard deviation (SD), or the median and interquartile range (IQR), are cited for continuous variables where appropriate, with counts and percentages listed for categorical variables.

All analyses were conducted in Stata v17 [25]. Statistical testing was performed where appropriate, with significance defined as $p < 0.05$. No formal sample size was defined in advance, as the DSP survey was not hypothesis driven. Missing data were not imputed; therefore, the base of patients for analysis could vary from variable to variable and is reported separately for each analysis.

Results

Study population

A total of 173 physicians (France n = 41, Germany n = 20, Italy n = 40, Spain n = 39, UK n = 33) participated in the survey. Of these physicians, 108 were haematologists and 65 were haem-oncologists, with 91 (53%) based in an academic/comprehensive cancer care setting and 82 (47%) based in a non-academic/general community practice setting. In total, physicians provided data for 2179 patients (France n = 483, Germany n = 421, Italy n = 449, Spain n = 411, UK n = 415), of whom 449 (21%) patients completed the voluntary patient-reported questionnaires.

Patient demographics & clinical characteristics

Patient demographics and clinical characteristics are presented in Table 1, and a detailed overview of patient characteristics by country can be found in Supplementary Table 1. Patients were predominately male (58%) and white (93%), with a mean (SD) age of 70.3 (9.36) years. There was little difference observed in patient ages between countries, which ranged from a mean (SD) in Italy of 68.6 (11.07) years to 72.1 (9.07) years in France. Of all patients, 73% were retired, with 13% unemployed, retired or on long-term sick leave due to their MM (ranging from 8% in the UK to 21% in Spain). The number of patients working full-/part time ranged from 22% in Italy to 3% in Germany.

At data collection, 71% of all patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1 and 61% had stage III MM (Table 1). Of all patients that received biomarker testing with a known result (n = 623, 29%), 39% had high cytogenetic risk and 27% had an inconclusive risk (i.e., no known mutations tested for were identified by the biomarker test). The median (IQR) time since diagnosis was 41.9 (19.4–67.2) months. Of all patients, 25% were tri-exposed at time of data collection and 10% were tri-refractory.

In total, n = 547 patients were tri-exposed and n = 1632 patients were non-tri-exposed. Overall, patients who were tri-exposed had similar demographics to non-tri-exposed patients (Table 1). However, the tri-exposed patient sample had a higher rate of being on long-term sick leave, retired or unemployed due to their MM compared with non-tri-exposed patients (18 vs 11%; p = 0.0004). In particular, a higher proportion of tri-exposed versus non-tri-exposed patients was retired as a result of their MM (9 vs 4%; p = 0.0034). In addition, tri-exposed patients had a significantly longer mean (SD) time since diagnosis compared with non-tri-exposed patients (62.8 [38.38] months vs 43.2 [38.59] months; $p < 0.0001$) and had a significantly higher mean (SD) number of prior treatment lines (2.8 [0.76] vs 1.8 [0.79]; $p < 0.0001$; Table 1).

At two time points (both at time of initiation of patients' current LOT, and at time of data collection), tri-exposed patients typically presented with a higher International Staging System disease stage compared with non-tri-exposed patients (Stage III: 66 vs 58%; p = 0.0258 and 67 vs 59%; p = 0.0174, respectively; Table 1). A lower proportion of tri-exposed patients had an ECOG score of 0–1 at time of data collection than non-tri-exposed patients (65 vs 73%; p = 0.0006), and a significantly higher proportion of tri-exposed patients experienced bone lesions compared with non-tri-exposed patients (73 vs 61%; $p < 0.0001$). There was a significant difference in cytogenetic risk (p = 0.0002) between tri-exposed and non-tri-exposed patients, with high risk being more prevalent in the tri-exposed patient group (51 vs 34%) in comparison to non-tri-exposed patient group (Table 1).

Physician-reported symptomatic burden

Physician-reported symptomatic burden at data collection was compared between tri-exposed (n = 547) and non-tri-exposed (n = 1632) patients. A lower proportion of patients who were tri-exposed were asymptomatic, compared with those who were non-tri-exposed (5 vs 10%; p = 0.0001; Figure 1A).

The same observations were made for concomitant conditions reported, with tri-exposed patients experiencing a higher number of conditions compared with non-tri-exposed patients. Additionally, a higher proportion of tri-exposed patients were experiencing some concomitant conditions related to CRAB criteria (anaemia, 31 vs 23%; p = 0.0003; bone lesions; 73 vs 61%; $p < 0.0001$) compared with non-tri-exposed patients. Tri-exposed versus non-tri-exposed patients also experienced more neurological/psychological conditions (27 vs 19%; p = 0.0003; Figure 1B). A lower proportion of patients who were tri-exposed did not suffer from a concomitant condition in comparison with non-tri-exposed patients (19 vs 23%; p = 0.0432; Figure 1B).

Treatment patterns

Treatment class and regimen received are shown in Figure 2A and B, stratified by LOT and tri-exposure status, respectively. Patients on 1L (n = 401) mainly received bortezomib- (58%),

Table 1. Patient demographics and clinical characteristics.

	Total (n = 2179)	Tri-exposed (n = 547)	Non-tri-exposed (n = 1632)	p-values
Age, years				
Mean (SD)	70.3 (9.36)	69.7 (9.14)	70.5 (9.42)	0.0695 (TT)
Median (IQR)	72.0 (65.0, 77.0)	71.0 (64.0, 77.0)	72.0 (65.0, 77.0)	
Sex, n (%)				
Male	1255 (58)	304 (56)	951 (58)	0.2719 (FE)
Female	924 (42)	243 (44)	681 (42)	
Ethnicity, n (%)				
White	2025 (93)	507 (93)	1518 (93)	0.5908 (CH)
Asian (Indian subcontinent)	19 (1)	5 (1)	14 (1)	
Asian (Other)	2 (<1)	0 (0)	2 (<1)	
Hispanic/Latino	38 (2)	9 (2)	29 (2)	
Middle Eastern	14 (1)	5 (1)	9 (1)	
Mixed Race	7 (<1)	4 (1)	3 (<1)	
Afro-Caribbean	57 (3)	14 (3)	43 (2)	
South-East Asian	14 (1)	3 (1)	11 (1)	
Other	3 (<1)	0 (0)	3 (<1)	
Employment status, n (%)				
Working full-time	166 (8)	34 (6)	132 (8)	0.0838 (CH)
Working part-time	73 (3)	24 (4)	49 (3)	
Unemployed	59 (3)	16 (3)	43 (3)	
On long-term sick leave	126 (6)	42 (8)	84 (5)	
Retired	1,597 (73)	385 (70)	1,212 (74)	
Homemaker	152 (7)	44 (8)	108 (7)	
Furloughed/Government work scheme	6 (0)	2 (0)	4 (0)	
On long-term sick leave/retired/unemployed due to their MM, n (%)				
	n = 1696	n = 424	n = 1272	0.0004† (FE)
Yes	216 (13)	76 (18)	140 (11)	
No	1480 (87)	348 (82)	1132 (89)	
Of retired patients, number who retired due to their MM, n (%)				
	n = 1516	n = 367	n = 1149	0.0034† (FE)
Yes	83 (5)	32 (9)	51 (4)	
No	1433 (95)	335 (91)	1098 (96)	
Number of previous lines received				
	n = 1778	n = 547	n = 1231	<0.0001† (TT)
Mean (SD)	2.1 (0.91)	2.8 (0.76)	1.8 (0.79)	
Median (IQR)	2.0 (1.0, 3.0)	3.0 (2.0, 3.0)	2.0 (1.0, 2.0)	
Current LOT, n (%)				
	n = 2,179	n = 547	n = 1,632	<0.0001† (MW)
1	401 (18)	n/a	401 (25)	
2	508 (23)	n/a	508 (31)	
3	637 (29)	182 (33)	455 (28)	
4	555 (25)	296 (54)	259 (16)	
5+	78 (4)	69 (13)	9 (1)	
Mean (SD)	2.7 (1.17)	3.8 (0.76)	2.4 (1.04)	<0.0001† (TT)
Median (IQR)	3.0 (2.0, 4.0)	4.0 (3.0, 4.0)	2.0 (2.0, 3.0)	

†Indicates significant p-values.
‡Cytogenetic risk – high risk was detection of any of the following: Del17p, t(14;16), t(14;20), Del(1p), or detected both Del17p and t(4;14); intermediate risk was detected t(4;14); low risk was detection of either t(11;14) or t(6;14).
§Tri-refractoriness was calculated out of tri-exposed patients.
All variables defined at time of data collection unless stated otherwise.
p-values are reported for comparison between tri-exposed and non-tri-exposed patients.
"Don't know", "Not specified" and "Unknown" responses were not included in the statistical analysis.
CH: Chi-squared test; ECOG: Eastern Cooperative Oncology Group; FE: Fisher's exact test; ISS: International Staging System; IQR: Interquartile range; LOT: Line of therapy; MM: Multiple myeloma; MW: Mann-Whitney U test; n/a: Not applicable; SD: Standard deviation; TT: t-test.

Table 1. Patient demographics and clinical characteristics (cont.).

	Total (n = 2179)	Tri-exposed (n = 547)	Non-tri-exposed (n = 1632)	p-values
ISS stage of MM at initiation of most recent treatment, n (%)				
	n = 2039	n = 517	n = 1522	0.0258† (MW)
Stage I	245 (12)	69 (13)	176 (12)	
Stage II	564 (28)	108 (21)	456 (30)	
Stage III	1230 (60)	340 (66)	890 (58)	
ISS stage of MM at time of data collection, n (%)				
	n = 1903	n = 482	n = 1421	0.0174† (MW)
Stage I	225 (12)	60 (12)	165 (12)	
Stage II	517 (27)	101 (21)	416 (29)	
Stage III	1161 (61)	321 (67)	840 (59)	
ECOG scores, n (%)				
	n = 2178	n = 547	n = 1631	0.0006† (MW)
0–1	1539 (71)	355 (65)	1184 (73)	
2+	638 (29)	192 (35)	446 (27)	
Mean (SD)	1.2 (0.82)	1.3 (0.88)	1.1 (0.8)	<0.0001† (TT)
Median (IQR)	1 (1.0, 2.0)	1 (1.0, 2.0)	1 (1.0, 2.0)	
Time since diagnosis, months				
	n = 2,037	n = 506	n = 1,531	<0.0001† (TT)
Mean (SD)	48.0 (38.38)	62.8 (33.73)	43.2 (38.59)	
Median (IQR)	41.9 (19.4, 67.2)	54.6 (40.3, 79.7)	35.1 (10.3, 63.4)	
Cytogenetic risk‡, n (%)				
	n = 623	n = 188	n = 435	0.0002† (MW)
High risk	244 (39)	95 (51)	149 (34)	
Intermediate risk	125 (20)	34 (18)	91 (21)	
Low risk	84 (13)	20 (11)	64 (15)	
Inconclusive risk	170 (27)	39 (21)	131 (30)	
Tri-refractoriness§, n (%)				
	n = 2179	n = 547	n = 1632	n/a
Tri-refractory	226 (10)	226 (41)	n/a	
Non-tri-refractory	313 (14)	313 (57)	n/a	
Outcome unknown	8 (<1)	8 (1)	n/a	
Bone lesions identified, n (%)				
	n = 2125	n = 536	n = 1589	<0.0001† (FE)
Yes	1,366 (64)	392 (73)	974 (61)	
No	759 (36)	144 (27)	615 (39)	
Bone lesions first identified, n (%)				
	n = 1,290	n = 368	n = 922	0.4162 (CH)
Prior to initial diagnosis	237 (18.37)	75 (20.38)	162 (17.57)	
At initial diagnosis	1047 (81.16)	292 (79.35)	755 (81.89)	
After initial diagnosis	6 (0.47)	1 (0.27)	5 (0.54)	

†Indicates significant p-values.
‡Cytogenetic risk – high risk was detection of any of the following: Del17p, t(14;16), t(14;20), Del(1p), or detected both Del17p and t(4;14); intermediate risk was detected t(4;14); low risk was detection of either t(11;14) or t(6;14).
§Tri-refractoriness was calculated out of tri-exposed patients.
All variables defined at time of data collection unless stated otherwise.
p-values are reported for comparison between tri-exposed and non-tri-exposed patients.
"Don't know", "Not specified" and "Unknown" responses were not included in the statistical analysis.
CH: Chi-squared test; ECOG: Eastern Cooperative Oncology Group; FE: Fisher's exact test; ISS: International Staging System; IQR: Interquartile range; LOT: Line of therapy; MM: Multiple myeloma; MW: Mann-Whitney U test; n/a: Not applicable; SD: Standard deviation; TT: t-test.

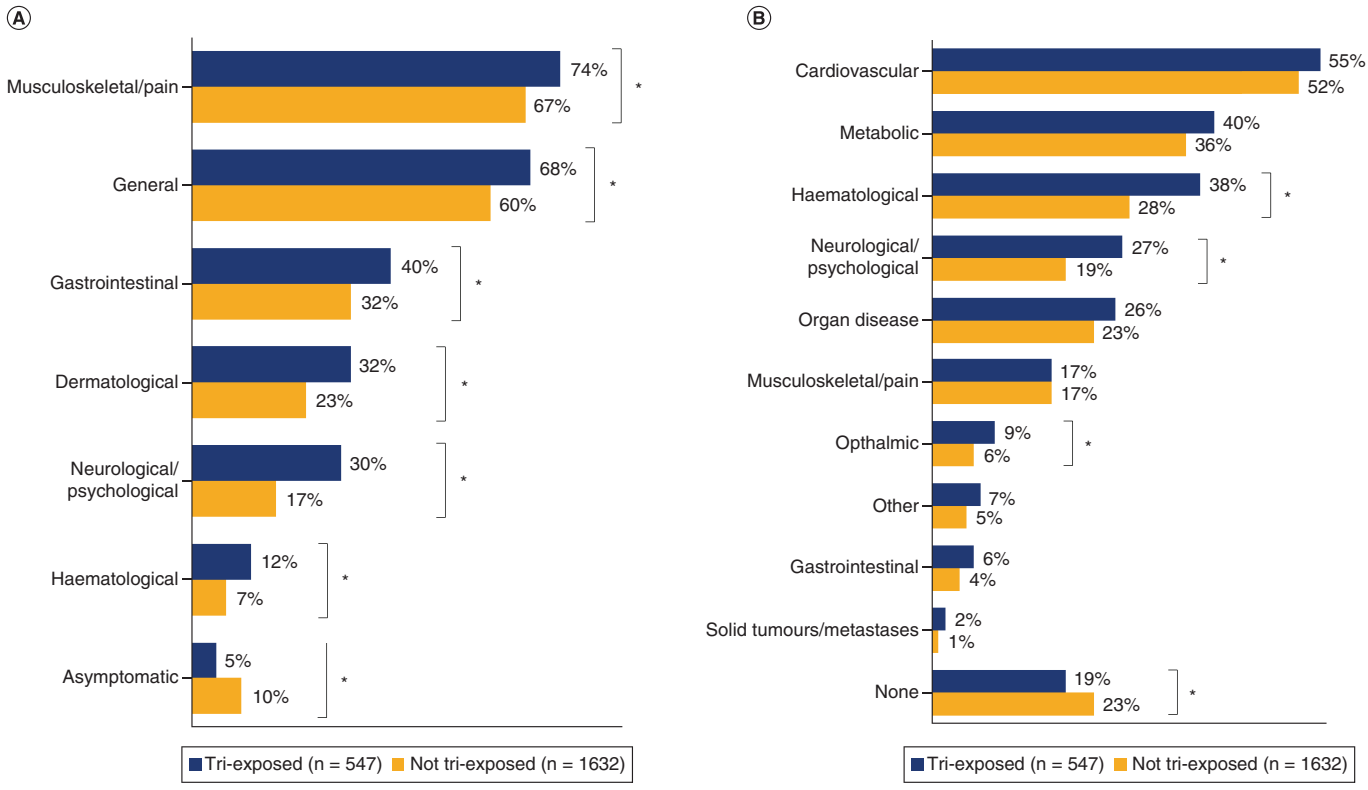

Figure 1. Physician-reported symptomatic burden. (A) Physician-reported symptomatic burden experienced by tri-exposed versus non-tri-exposed patients. **(B)** Physician-reported concomitant conditions experienced by tri-exposed versus non-tri-exposed patients.
*Indicates significant p-values.
'Musculoskeletal/pain' included: bone pain, bone fractures, lower back pain, middle back pain, rib pain, hip pain and abdominal pain.
'General' included: weight loss, shortness of breath, fatigue, cough/sore throat, fever, headaches, blurred vision, dizziness/poor balance, increased thirst, increased or decreased urination, oedema, restlessness and impotence.
'Gastrointestinal' included: indigestion, nausea, vomiting, early satiety, loss of appetite and constipation.
'Dermatological' included: pallor/pale skin and pruritus/itchy skin.
'Neurological/psychological' included: tingling of hands or feet, numbness and confusion.
'hematological' included: bleeding and bruising.
'Cardiovascular' included: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hypertension and prior stroke/Transient Ischaemic Attack (TIA).
'Metabolic' included: diabetes without chronic complications, diabetes with chronic complications, hyperlipidaemia and obesity.
'hematological' included: anaemia, thrombocytopenia, neutropenia, leukopenia and hypercalcaemia.
'Neurological/psychological' included: hemiplegia or paraplegia, dementia, depression, anxiety and peripheral neuropathy.
'Organ disease' included: mild renal disease, moderate or severe renal disease, mild liver disease and moderate or severe liver disease.
'Musculoskeletal/pain' included: rheumatologic disease, osteoarthritis, osteoporosis, osteonecrosis and connective tissue disease.
'Ophthalmic' included: blurred vision, dry eye, macular degeneration and cataracts.
'Other' included: amyloidosis, chronic pulmonary disease and AIDS/HIV.
'Gastrointestinal' included: upper gastrointestinal problems and peptic ulcer disease.
'Solid tumours/metastases' included: tumour without metastasis and metastatic solid tumour.

daratumumab- (24%) or lenalidomide-based regimens (15%). The most frequently used 1L regimens were VRd (bortezomib/lenalidomide/dexamethasone) and VTd (bortezomib/thalidomide/dexamethasone; both 18%). The top five regimens (VRd, VTd, DRd [daratumumab/lenalidomide/dexamethasone], Rd [lenalidomide/dexamethasone], VCd [bortezomib/cyclophosphamide/dexamethasone]) accounted for 66% of all patients receiving 1L at the time of data collection.

Patterns between countries varied greatly (Supplementary Figure 1). VTd was mostly used in Italy (57% of all 1L regimens) and the UK (36%), and to a lesser extent in Spain (15%). VRd was most frequently used in Spain at 1L (44%). At 1L, France and Germany had the highest use of daratumumab-based regimens (48% in France, 28% in Germany).

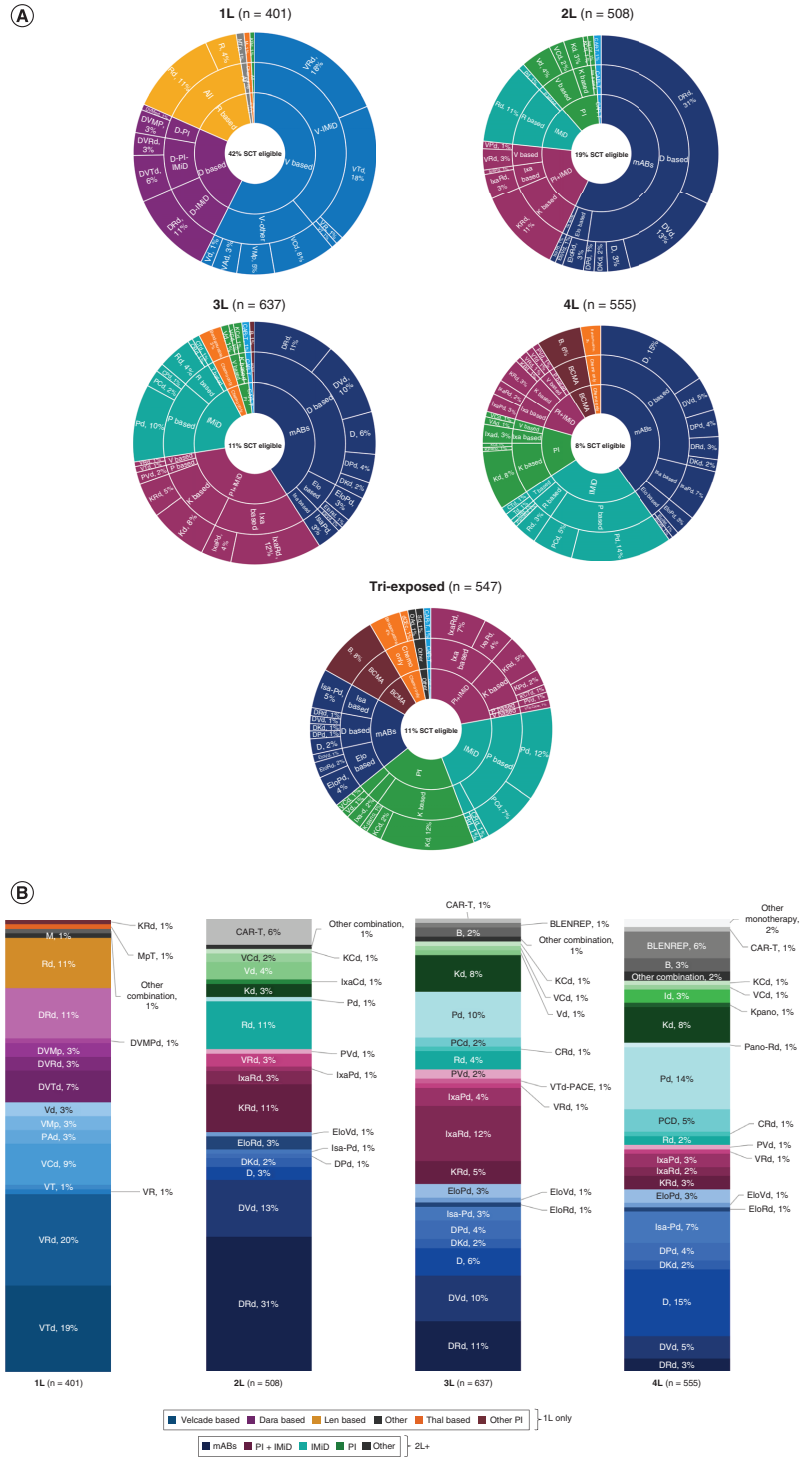

Figure 2. Treatment class and regimens received at data collection. (A) Treatment class and regimens received at data collection, by line of therapy and tri-exposed status*. **(B)** Regimens received at data collection by line of therapy. *X-based regimen was any regimen containing that drug.
1L: 1st line; 2L: 2nd line; 3L: 3rd line; 4L: 4th line; A: Doxorubicin; BCMA: B-cell maturation antigen; B: Belantamab mefodotin; CAR-T: Chimeric Antigen Receptor T-Cell; C: Cyclophosphamide; c: Cisplatin; D: Daratumumab; d: Dexamethasone; E: Etoposide; Elo: Elotuzumumab; IMiD: Immunomodulatory drug; Isa: Isatuximab; Ixa: Ixazomib; K: Carfilzomib; L: Line of therapy; mABs: Monoclonal antibodies; M: Melphalan; O: Vincristine; Pano: Panobinostat; PI: Proteasome inhibitor; P: Pomalidomide; p: Prednisone; Pano: Panobinostat; S: Selinexor (SINE); SCT: Stem cell transplant; R: Lenalidomide; T: Thalidomide; V: Bortezomib.

In 2L (n = 508 patients), daratumumab-based regimens were most frequently used (50%), led by DRd (31%) and DVd (daratumumab/bortezomib/dexamethasone; 13%). DRd was predominantly used in France (40%) and Italy (44%), but rarely in the UK (3%) where patients most frequently received DVd (35%). Other frequently used regimens were KRd (carfilzomib/lenalidomide/dexamethasone; 11%) and Rd (11%).

In 3L (n = 637 patients), patients started to receive more diverse regimens, with equally frequent use of IxaRd (ixazomib/lenalidomide/dexamethasone), DRd, DVd and Pd (pomalidomide/dexamethasone; 10–12% each). Overall, 41 unique treatment regimens were used. Large differences between countries were observed. While France, Germany, Italy and Spain still had significant anti-CD38-based regimen use (42–53%), in the UK IxaRd was primarily used (44%).

In 4L (n = 555 patients), 36% of patients were treated with anti-CD38 regimens, compared with 51% of patients at 2L.) In the UK, 54% of patents received a daratumumab or isatuximab-based regimen, led by 29% daratumumab monotherapy use. The breadth of different regimens used continued to grow in 4L with 42 unique treatment regimens and the top five regimens only accounting for 50% of all regimens. The use of B-cell maturation antigen targeting regimens was observed for the first time (6%). Nine different treatment regimens accounted for <1% each of the total. Overall, 58% of patients at 4L were tri-exposed.

A small proportion of patients (n = 78) were receiving fifth-line treatment and beyond (5L+) at the point of data collection. Of these patients, belantamab mafodotin was the most common treatment received (15%), followed by Pd (10%). The top five regimens accounted for 46% of all patients receiving 5L+ at the time of data collection.

Across all LOT, triplets were mostly used with an increasing range of unique regimens observed (1L: 23 – 4L: 42). The extent to which each treatment class was used at each line also differed (Supplementary Figure 2). The share of tri-exposed patients increased with each LOT, from 0% of patients on 2L to 88% of patients on 5L+ at data collection. In tri-exposed patients, the most frequently used treatment after initial tri-exposure was Pd (12%), driven by high use in the UK (20%) and Italy (16%). Similarly high usage was observed for Kd (carfilzomib/dexamethasone; 12%), driven by high use in Spain (21%). Furthermore, there was increased use of belantamab mafodotin and other regimens including chemotherapy combinations.

With respect to other treatment modalities, at the time of data collection 26% of patients had previously received a stem cell transplant (SCT), while 18% of patients were currently deemed to be eligible for SCT. At data collection, fewer tri-exposed patients (n = 547) were considered to be SCT eligible compared with all non-tri-exposed patients (n = 1632; 11 versus 20%; $p < 0.0001$). Furthermore, of all patients, only 22% had ever received radiotherapy and 4% had received surgery at any time during their treatment history for MM.

Figure 3 shows the retreatment rates by LOT and tri-exposure status. Retreatment with the same treatment class was common (range for IMiDs and PIs: 51–57%), although retreatment with the same treatment agent was infrequent (range for bortezomib, ixazomib, carfilzomib, lenalidomide, thalidomide and pomalidomide: 24–<1%). Overall, across all LOT, the agents that patients were most frequently retreated with were bortezomib (24%) and lenalidomide (17%). Of patients who were retreated with the same treatment class, retreatment rates of lenalidomide ($p < 0.0001$), thalidomide ($p = 0.0029$), bortezomib ($p < 0.0001$) and carfilzomib ($p = 0.0009$) increased with each successive LOT. The share for retreatment with the same agent at 4L was 12%, compared with 9% at 3L and 5% at 2L. Across all LOTs, 11% of tri-exposed patients were retreated compared with 8% of non-tri-exposed patients. The rates of retreatment at 4L were 17% in Germany followed by Italy (13%), France (11%), Spain (10%) and the UK (8%). While these differences were observed between countries across all LOT, retreatment in tri-exposed patients was similar across countries (range 9–12%; Supplementary Figure 3).

Healthcare resource utilization

Differences in HCRU in the past 12 months prior to data collection were evaluated between tri-exposed (n = 547) and non-tri-exposed patients (n = 1632), and are summarised in Table 2. Of all patients, regardless of tri-exposure status, with at least one inpatient hospitalisation in the last 12 month prior to data collection (n = 407), the majority had one inpatient hospitalisation (66%). Compared with the other countries, this rate was the highest in Germany (90%; $p = 0.0299$) and the lowest in the UK (55%; $p = 0.1297$; Supplementary Table 2). The median (IQR) nights spent in hospital over the past 12 months was 7.0 (4.5–10.0). Only 3% of patients were treated in intensive care units. When focusing on tri-exposed versus non-tri-exposed patients, a significant difference is observed between the number of inpatient hospitalisations, with a higher proportion of tri-exposed patients having >3 inpatient hospitalisations compared with non-tri-exposed patients (13 vs 7%; $p = 0.008$); however, when the mean (SD) number of outpatient visits within the past 4 weeks (prior to data collection) was analysed, there

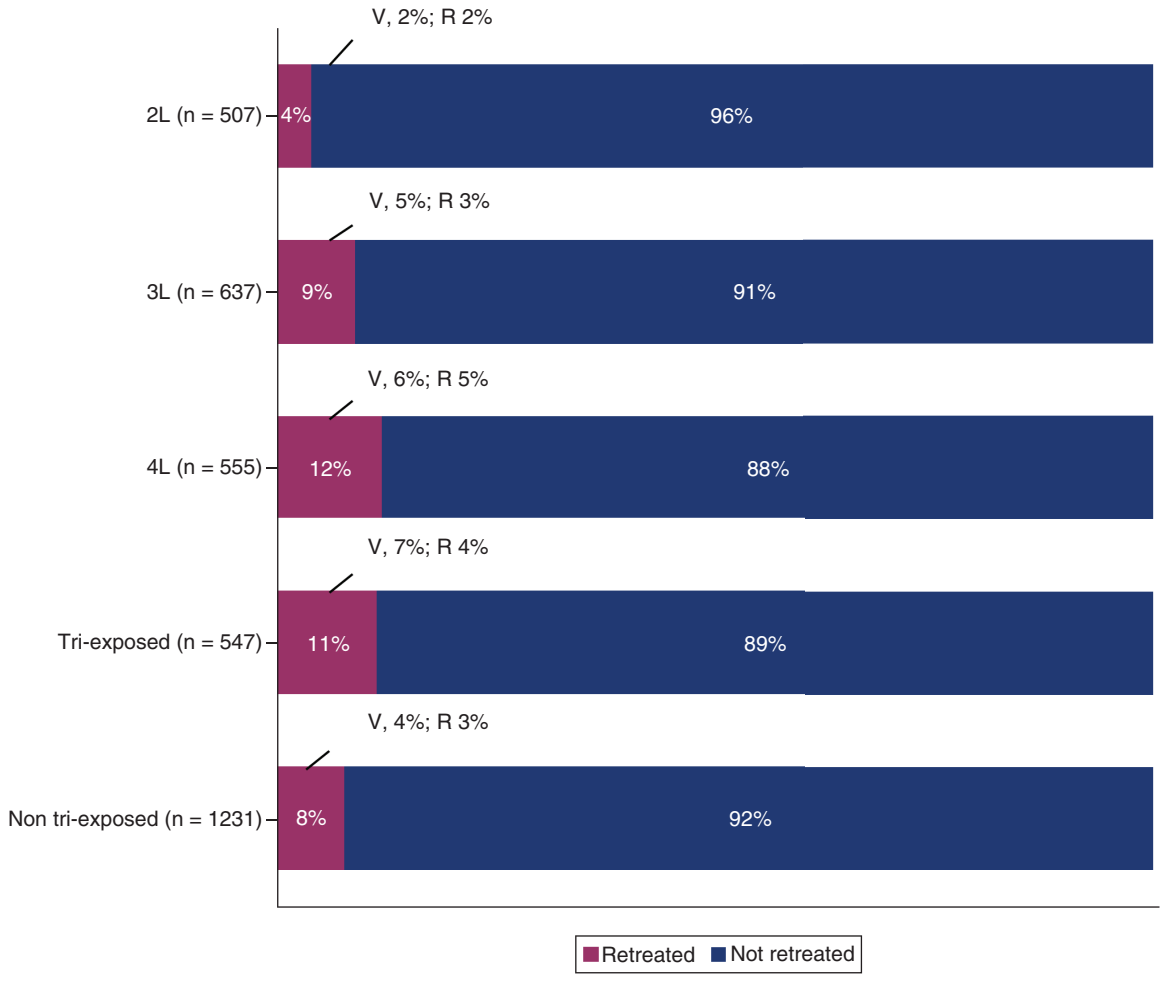

Figure 3. Retreatment by line of therapy and tri-exposure status. Retreatment of thalidomide, pomalidomide, carfilzomib and ixazomib were <1%. Retreatment included reuse of drug in any combination or as a single agent. Non-tri-exposed included patients 2L+. Tri-exposed included patients 3L+; there were no 2L tri-exposed patients at data collection.
LOT: Line of therapy; R: Lenalidomide; V: Bortezomib; 2L: Second line; 3L: Third line; 4L: Fourth line.

was no statistically significant difference between the two groups (2.7 [2.8] vs 3.0 [3.0]; p = 0.1504). Over the five most recent hospitalisations, there was little difference in the proportion of patients admitted to hospital for an emergency (tri-exposed; 62%, non tri-exposed; 57%; p = 0.3972). For both tri-exposed and non-tri-exposed patients, the majority of recent outpatient visits were for receiving drug treatment (87 vs 89%; p = 0.6023) or for tests/scans (26 and 27%; p = 0.6516). Tri-exposed patients also had a higher mean (SD) number of times seen by a healthcare professional (12.1 [8.4] vs 10.0 [7.3]; p < 0.0001) within the past 12 months.

The number of tests received in the past 12 months (prior to data collection, where data was available) was investigated (Figure 4; Supplementary Figure 4, split by country). Tri-exposed patients had a higher mean (SD) number of times each test was conducted (97.5 [46.0–166.5] vs 73.0 [32.0–130.0]; p < 0.0001) compared with non-tri-exposed patients. Tri-exposed patients (n = 518) had a higher median (IQR) number of complete blood counts (11.5 [8.75] vs 9.4 [6.97]; p < 0.0001) and biochemistry tests conducted (10.6 [7.45] vs 8.9 [6.12]; p < 0.0001) compared with non-tri-exposed patients (n = 1565). Of all patients, only 2% received care from professional caregivers with a median (IQR) time spent of 15.0 (10.0–20.0) hours per week. In total, 31% of patients received care from non-professional caregivers (i.e., family or friends), with a median (IQR) time spent of 20.0 (10.0–41.0) hours per week. No significant differences in caregiving requirements were observed between tri-exposed versus non-tri-exposed patients.

Table 2. Healthcare resource utilization[†].

	Total (n = 2179)	Tri-exposed (n = 547)	Non-tri-exposed (n = 1632)	p-values
Number of inpatient hospitalisations in the 12 months prior to data collection, n (%)				
	n = 407	n = 143	n = 264	0.008[†] (MW)
1	269 (66)	83 (58)	186 (70)	
2	102 (25)	42 (29)	60 (23)	
3+	36 (9)	18 (13)	18 (7)	
Mean (SD)	1.6 (1.5)	1.7 (1.3)	1.5 (1.6)	0.2373 (TT)
Median (IQR)	1 (1.00, 2.00)	1 (1.00, 2.00)	1 (1.00, 2.00)	
Reported reasons for inpatient hospitalizations, n (%)				
To treat a complication	236 (58)	96 (67)	140 (53)	0.0063[‡] (FE)
For surgery	19 (5)	6 (4)	13 (5)	0.8108 (FE)
Receiving CAR-T therapy	19 (5)	10 (7)	9 (3)	0.138 (FE)
Receiving a SCT	32 (8)	3 (2)	29 (11)	0.0009[‡] (FE)
Other	125 (31)	35 (24)	90 (34)	0.0555 (FE)
Patient admitted through the emergency room, n (%)				
	n = 404	n = 142	n = 262	0.3972 (FE)
Yes	238 (58.9)	88 (62.0)	150 (57.3)	
No	166 (41.1)	54 (38.0)	112 (42.7)	
Number of nights spent in hospital in the 12 months prior to data collection				
	n = 362	n = 131	n = 231	0.9809 (TT)
Mean (SD)	8.2 (6.3)	8.3 (6.2)	8.2 (6.3)	
Median (IQR)	7.0 (4.5, 10.0)	6.5 (5.0, 10.0)	7.0 (4.0, 10.0)	
Patient treated in intensive care units, n (%)				
	n = 407	n = 143	n = 264	1 (FE)
Yes	11 (3)	4 (3)	7 (3)	
No	396 (97)	139 (97)	257 (97)	
Number of outpatient visits in the 4 weeks prior to data collection, n (%)				
	n = 1227	n = 294	n = 933	0.6028 (MW)
1	486 (40)	116 (40)	370 (40)	
2	330 (27)	87 (30)	243 (26)	
3+	411 (33)	91 (30)	320 (34)	
Mean (SD)	2.9 (3.0)	2.7 (2.8)	3.0 (3.0)	0.1504 (TT)
Median (IQR)	2 (1.00, 4.00)	2 (1.00, 3.00)	2 (1.00, 4.00)	
Reported reasons for outpatient visits in the 4 weeks prior to data collection, n (%)				
	n = 1227	n = 294	n = 933	
Tests/scans	331 (27)	76 (26)	255 (27)	0.6516 (FE)
Receiving drug treatment	1084 (88)	257 (87)	827 (89)	0.6023 (FE)
Receiving radiotherapy	11 (1)	2 (1)	9 (1)	1 (FE)
Rehabilitation/physiotherapy	18 (1)	4 (1)	14 (2)	1 (FE)
Other	37 (3)	11 (4)	26 (3)	0.434 (FE)
Number of times patient has seen a healthcare professional in the last 12 months prior to data collection				
	n = 2179	n = 547	n = 1632	<0.0001[‡] (TT)
Mean (SD)	10.5 (7.6)	12.1 (8.4)	10.0 (7.3)	
Median (IQR)	9 (6.00, 12.00)	11 (6.00, 14.00)	8 (5.00, 12.00)	
Caregiver required, n (%)				
	n = 1915	n = 461	n = 1454	0.1676 (FE)
Yes	716 (37)	185 (40)	531 (37)	
No	1199 (63)	276 (60)	923 (63)	

[†]Base sizes differ due to availability of data.
[‡]Indicates significant p-values.
p-values are reported for comparison between tri-exposed and non-tri-exposed patients.
CAR-T: Chimeric Antigen Receptor T-cell therapy; CH: Chi-squared test; FE: Fisher's exact test; IQR: Interquartile range; MW: Mann-Whitney U test; SCT: Stem cell transplant; SD: Standard deviation; TT: t-test.

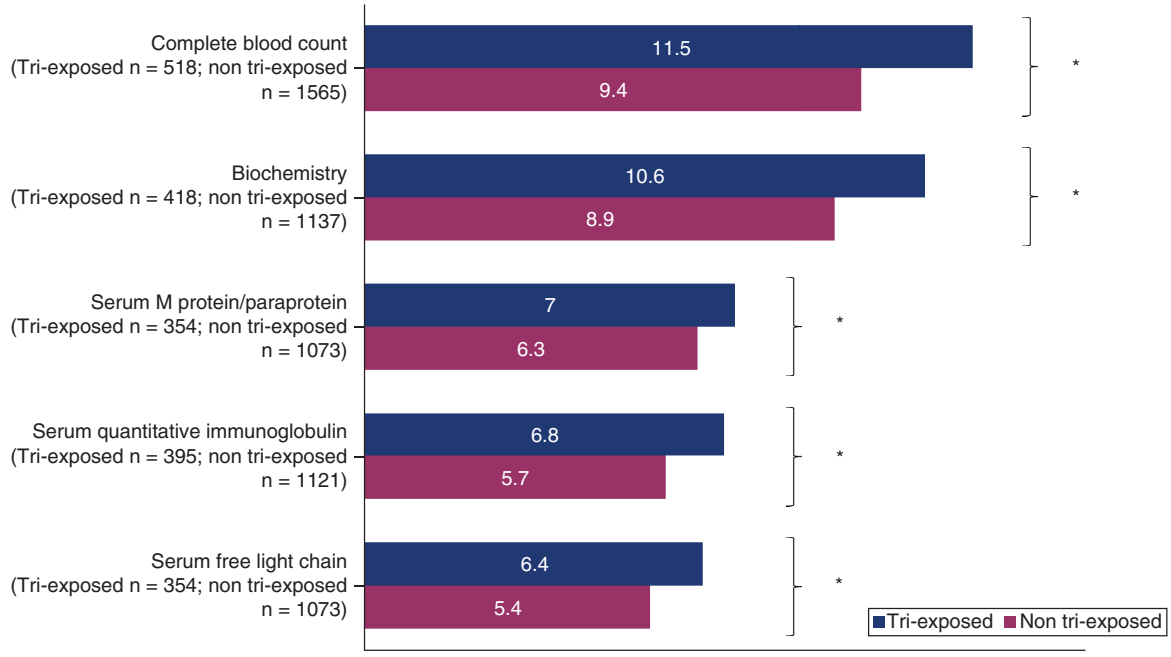

Figure 4. Mean number of tests conducted in the 12 months prior to data collection, stratified by tri-exposure status.
*Indicates statistically significant p-value.
M: Myeloma.

Patient-reported burden of disease

Patient-reported outcomes (PRO) are reported in Table 3. As completion of the patient-reported questionnaire was voluntary, patient demographics and characteristics were compared between those who completed a patient-reported questionnaire (n = 449) and those who did not (n = 1730), in order to understand the representativeness of the patient sample. Overall, the rate of tri-exposure was similar in both groups (24% for questionnaire completers vs 25% for questionnaire non-completers; p = 0.5022). At data collection, a higher proportion of questionnaire completers versus non-completers was 3L (35 vs 28%; p = 0.0136) and had stage II MM (33 vs 21%; p = 0.0007), and a lower proportion of questionnaire completers versus non-completers were stage III at data collection (47 vs 55%; p = 0.0007). A lower proportion of questionnaire non-completers had an ECOG score of 0 versus questionnaire completers (13 vs 20%; p = 0.0010).

When PROs were analysed by tri-exposure status (Table 3), tri-exposed patients had significantly and clinically worse mean (SD) EORTC functioning scores including physical functioning (59.2 [24.70] vs 66.6 [22.00]; p = 0.0037), role functioning (51.4 [29.74] vs 59.4 [25.41]; p = 0.0069) and cognitive functioning (68.1 [25.56] vs 73.9 [23.41]; p = 0.0319) in comparison to non-tri-exposed patients [20]. No significant changes across the other EORTC functioning domains (global, emotional and social domains) were observed between the two groups. Tri-exposed patients also had significantly and clinically worse mean (SD) EORTC symptomology scores including fatigue (49.8 [22.60] vs 43.3 [21.30]; p = 0.0071), nausea and vomiting (20.8 [23.88] vs 15.7 [20.64]; p = 0.0334), pain (47.0 [25.49] vs 40.9 [24.99]; p = 0.0281), dyspnoea (35.8 [28.99] vs 25.3 [26.78]; p = 0.0006), constipation (23.5 [29.21] vs 16.4 [22.48]; p = 0.0089) and diarrhoea (16.3 [23.22] vs 10.6 [19.18]; p = 0.0118) in comparison to non-tri-exposed patients [20]. No other significant changes were observed across the other EORTC symptom domains (insomnia, appetite loss and financial difficulties) between the two groups. Tri-exposed patients had significantly more disease symptoms (34.0 [20.93] vs 27.8 [19.60]; p = 0.0059) and side effects of treatments (26.7 [21.11] vs 21.3 [18.20]; p = 0.0133) in comparison to non-tri-exposed patients; however, these were not clinically different. Tri-exposed versus non-tri-exposed patients reported higher percentage of activity impairment due to their MM (55% [20.24] vs 47.8% [20.84]; p = 0.0019), as quantified by WPAI scores.

Table 3. Patient-reported outcomes.

	All (n = 449)	Tri-exposed (n = 107)	Non-tri-exposed (n = 342)	p-values
EQ-5D-5L, mean (SD)				
	n = 441	n = 104	n = 337	
EQ-5D-5L	0.82 (0.19)	0.77 (0.24)	0.84 (0.18)	0.0022† (TT)
EQ-5D VAS	60.35 (17.08)	57.40 (18.67)	61.26 (16.49)	0.0439† (TT)
EORTC-QLQ-C30 Functional scores, mean (SD)				
	n = 441	n = 105	n = 336	
Global health status	52.95 (16.67)	50.95 (17.42)	53.57 (16.41)	0.1602 (TT)
	n = 444	n = 106	n = 338	
Physical functioning	64.85 (22.86)	59.25 (24.70)	66.61 (22.00)	0.0037†‡ (TT)
Role functioning	57.51 (26.69)	51.42 (29.74)	59.42 (25.41)	0.0069†‡ (TT)
	n = 441	n = 104	n = 337	
Emotional functioning	62.84 (23.56)	62.61 (23.74)	62.92 (23.53)	0.9069 (TT)
Cognitive functioning	72.52 (24.03)	68.11 (25.56)	73.89 (23.41)	0.0319†‡ (TT)
	n = 438	n = 105	n = 333	
Social functioning	64.76 (26.18)	61.27 (27.20)	65.87 (25.79)	0.1169 (TT)
EORTC-QLQ-C30 Symptom scores, mean (SD)				
	n = 445	n = 106	n = 339	
Fatigue	44.83 (21.77)	49.79 (22.60)	43.28 (21.30)	0.0071† (TT)
Pain	42.32 (25.22)	47.01 (25.49)	40.86 (24.99)	0.0281†‡ (TT)
Dyspnoea	27.79 (27.66)	35.85 (28.99)	25.27 (26.78)	0.0006†‡ (TT)
	n = 443	n = 105	n = 338	
Nausea and vomiting	16.89 (21.53)	20.79 (23.88)	15.68 (20.64)	0.0334†‡ (TT)
	n = 444	n = 106	n = 338	
Insomnia	33.03 (26.87)	36.16 (29.14)	32.05 (26.09)	0.1695 (TT)
	n = 442	n = 104	n = 338	
Appetite loss	32.43 (26.83)	35.58 (29.11)	31.46 (26.06)	0.1714 (TT)
	n = 439	n = 105	n = 334	
Constipation	18.07 (24.41)	23.49 (29.21)	16.37 (22.48)	0.0089†‡ (TT)
	n = 440	n = 104	n = 336	
Diarrhoea	11.97 (20.33)	16.35 (23.22)	10.62 (19.18)	0.0118†‡ (TT)
	n = 433	n = 104	n = 329	
Financial difficulties	18.63 (24.99)	19.23 (24.44)	18.44 (25.19)	0.7788 (TT)
EORTC-QLQ-MY20 Symptom scores, mean (SD)				
	n = 425	n = 104	n = 321	
Body image	70.2 (27.77)	66.67 (29.01)	71.34 (27.30)	0.136 (TT)
	n = 436	n = 105	n = 331	
Future perspective	55.96 (21.57)	55.24 (22.83)	56.19 (21.19)	0.6931 (TT)
EORTC-QLQ-MY20 Functional scores, mean (SD)				
	n = 441	n = 104	n = 337	
Disease symptoms	29.28 (20.07)	34.01 (20.93)	27.83 (19.60)	0.0059† (TT)
	n = 440	n = 105	n = 335	
Side effects of treatment	22.85 (19.08)	27.37 (21.11)	21.43 (18.20)	0.0052† (TT)
WPAI, mean (SD)				
	n = 21	n = 7	n = 14	
% work time missed due to problem	30.46 (35.72)	23.59 (32.68)	33.89 (37.85)	0.5472 (TT)
	n = 19	n = 7	n = 12	

†Indicates significant p-values.
‡Indicates clinically significant differences.
For the EORTC, a higher functional score represents better functioning, whereas a higher symptom score represents worse symptoms.
p-values are reported for comparison between tri-exposed and non-tri-exposed patients.
EORTC-QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: EuroQol-5D; SD: Standard deviation; TT: T-test; VAS: Visual Analogue Scale WPAI: Work Productivity and Activity Impairment.

Table 3. Patient-reported outcomes (cont.).

	All (n = 449)	Tri-exposed (n = 107)	Non-tri-exposed (n = 342)	p-values
% impairment while working due to problem	37.37 (26.63)	42.86 (26.90)	34.17 (27.12)	0.5084 (TT)
% overall work impairment due to problem	46.35 (33.59)	50.91 (33.53)	43.69 (34.82)	0.6642 (TT)
	n = 437	n = 105	n = 332	
% activity impairment due to problem	49.54 (20.90)	55.05 (20.24)	47.8 (20.84)	0.0019† (TT)

†Indicates significant p-values.
‡Indicates clinically significant differences.
For the EORTC, a higher functional score represents better functioning, whereas a higher symptom score represents worse symptoms.
p-values are reported for comparison between tri-exposed and non-tri-exposed patients.
EORTC-QLQ: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D: EuroQol-5D; SD: Standard deviation; TT: T-test; VAS: Visual Analogue Scale WPAI: Work Productivity and Activity Impairment.

Discussion

This study investigated current treatment patterns, HCRU and disease burden in patients with MM presenting in a real-world clinical setting across Europe. Differences in treatment class and regimen received were observed as LOT increased and regimens became more diverse, possibly dictated by previous treatment choices at earlier LOT. We also observed that patients with tri-exposed MM experienced significantly and clinically worse HCRU and disease burden, as demonstrated *via* HRQoL and PRO measurements, than those who were non-tri-exposed.

The 2021 ESMO guidance was published around 3 months before the data was collected (May–November 2021), therefore we investigated how treatment regimen received at point of data collection compared with both the 2017 [4] and 2021 [5] guidelines. While the results observed in this analysis broadly align with both sets of guidance, some differences were observed. Both VMP (bortezomib/melphalan/prednisone; 5%) and MTP (melphalan/thalidomide/prednisone; 1%) were listed in the 2017 ESMO guidelines for use at 1L [4], but were not cited in the top five regiments observed in this analysis. DVTD is listed in the 2021 ESMO guidelines for use at 1L as a first option, but did not feature in the top five treatment regiments prescribed at 1L (5%) in our analysis [5], possibly due to it only having been approved relatively recently before the guidelines were updated. The 2021 guidelines for 2L treatment are stratified depending on what was previously prescribed, with DRd, DVd and KRd all listed as appropriate 2L choices depending on previous treatment regimen and whether the patient was sensitive or refractory to a particular class of therapy [5]. This was reflected by our results; as treatment lines progressed, we saw divergence in prescribed regimens, which were dependent on previously prescribed treatments. Our analysis indicated that retreatment with the same treatment class was common; however, retreatment with the same treatment agent was infrequent. Overall, 41 unique treatment regimens were used at 3L and 42 unique regimens at 4L, with the top five regimens at 4L accounting for only 50% of all regimens.

While some of the differences and trends in treatment patterns observed in this analysis may be due to the timing of ESMO guidance and survey recruitment window, there may also be a difference between treatments being approved and included in the guidelines, and being made available and reimbursed in different countries. We did observe differences in treatment patterns between countries (as further detailed in Supplementary Figure 1), likely due to factors surrounding reimbursement and local guidance, as well as preferred treatment scheduling regimens across different LOT. These differences between countries were particularly evident at 3L+; treatment regimens became more diverse, and were dictated by previous treatment choices at earlier LOT. All of this demonstrates the complexity of treatment regimens available for the treatment of MM as patients progress from one LOT to the next.

Previous studies have shown that improved treatment response was associated with lower costs and reduced hospitalisations [26]. Another study indicated that total healthcare costs were the lowest in patients with MM at 1L than in patients at more advanced LOTs [27]. This was confirmed in our analysis, which indicated that over the past 12 months prior to data collection, tri-exposed patients experienced more inpatient hospitalisations, and required more hospital and diagnostic tests, than non-tri-exposed patients. Importantly, our data showed that 79% of recent outpatient visits for both tri-exposed and non-tri-exposed patients were for receiving drug treatment, indicating the burden of treatment experienced by patients with MM, regardless of tri-exposure status or LOT. Selection of treatment regimens that prolong time to disease progression could not only improve HRQoL but also reduce the overall economic burden of MM [27], with a further study indicating that mean cost per month was the lowest in

patients achieving a very good partial response or better [28]. Improved treatment outcomes may reduce the overall HCRU and related costs of care in patients with MM.

As the management of MM continues to evolve and survival outcomes improve, consideration of PROs and the assessment of HRQoL in the evaluation of treatment efficacy from the patient perspective is becoming increasingly important given the high symptomatic burden of MM [29]. We observed that a higher proportion of tri-exposed patients experienced symptomatic burden, in particular concomitant conditions related to CRAB criteria, compared with non-tri-exposed patients, as well as a higher degree of disease burden and impairment, as illustrated by EQ-5D-5L, EQ-5D VAS, EORTC QLQ-C30, EORTC QLQ-MY20 and WPAI scores, with many of these differences also considered clinically meaningful [17,20,23]. Our results correspond with previous studies which have shown that patients with MM have impaired HRQoL, which deteriorates with increasing LOT and at later stage of disease [30–33]. A recent systematic review found the available PRO evidence base was predominately derived from clinical trials and that reporting of results made it difficult to describe prevalence, severity or patterns of symptoms and HRQoL issues [34], hence the emerging importance of PROs and evidence derived from real-world studies. Assessment of PROs in future studies will help to better inform clinical decision-making for patients with MM [35].

Given the unmet need in the MM patient population, several recent clinical studies on novel therapies not investigated in this study have been performed or are currently underway. These include, but are not limited to, the DREAMM-2 [36,37], STORM [38,39], HORIZON [40], KarMMa [41], CARTITUDE-1 [42], MajesTEC-1 studies [43] and Talquetamab studies [43]. These trials, conducted in selected tri-exposed patients with RRMM, have demonstrated success in achieving treatment response and extending progression-free and overall survival with acceptable toxicity profiles. Given the approval and increasing access of many new treatments for tri-exposed MM, further real-world analyses looking into their uptake and use, as well as HCRU and patient-reported outcomes, are needed.

The DSP methodology (from which the data collected was used for analysis in this study) has a number of strengths and limitations. Patients who visit their physician more frequently may be more severely affected than those with mild disease, who do not consult their physician as frequently. While minimal inclusion criteria for the survey governed the selection of the participating physicians, participation was influenced by willingness to complete the survey. The point-in-time design of the methodology prevented any conclusions about causal relationships; however, identification of significant associations was possible. As the survey excluded patients who had moved onto best supportive care or passed away, patient-reported outcomes could be overstated, particularly for patients at later LOT. As SCT eligibility was only captured at time of data collection, it was not possible to determine if the patient was eligible for a SCT previously but did not proceed to receive an SCT. Similarly, as patients were alive at the time of data capture, this resulted in an artificial inflation of time from treatment initiation, as patients who may have died following initiation were not captured.

Despite such limitations, real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials. Patients included in clinical trials, due to the presence of specific inclusion criteria, often do not reflect the general patient population, rather a subset of patients who still have a good performance status, good organ function, blood cell count and a disease that can wait to be treated for the duration of the screening period. Physicians were asked to provide data for a consecutive series of patients aligning to a pre-defined quota, to mitigate against selection bias, with this analysis reporting on a relatively large sample of patients treated at different LOT in a real-world setting across Europe. While recall bias is a common limitation of surveys, our data were collected at the time of each patient's appointment, which was expected to reduce this likelihood. In addition, physicians had access to patient medical records for data extraction. The data presented are therefore representative of current clinical practice at the time the survey was conducted.

Conclusion

In summary, we demonstrate the complexity of the evolving treatment landscape for patients with MM. As LOT increased, treatment regimens became more diverse, with tri-exposed patients having increasingly limited therapy options at later LOT. Patients who were tri-exposed reported clinically significant worse symptomatic disease burden, impairment and HRQoL compared with those who were non-tri-exposed. There is a clear unmet need for more effective therapies to reduce the disease burden experienced by patients with MM, in particular in those who are tri-exposed. This study provides a useful reference point of current real-world clinical practice. Given the development of new therapeutic options for the tri-exposed MM population, further work in this area should be done to keep up to date with the changing landscape.

Summary points

- The treatment landscape in multiple myeloma (MM) is complex and evolving, with a range of treatment options available across the treatment pathway.
- This real-world point-in-time survey investigated current treatment patterns, healthcare resource utilization and disease burden in patients with MM across Europe between May–November 2021.
- Physicians reported details on patient demographic and clinical characteristics, including disease severity, symptomatic burden, treatment history and healthcare resource utilization. Patients voluntarily reported on their current symptomatic burden and other health-related quality of life outcomes.
- Overall, 173 physicians provided data for 2179 patients with MM, of whom 449 (21%) completed the voluntary patient-reported questionnaire.
- In total, 25% of patients were tri-exposed at data collection, with the proportion of tri-exposed patients increasing with each line of therapy (LOT), from 0% of patients on second-line to 88% of patients on fifth-line and beyond.
- Differences in treatment class and regimen received were observed as LOT increased and regimens became more diverse, dictated by previous treatment choices at earlier LOT. Retreatment with the same treatment class was common, however, retreatment with the same treatment agent was infrequent. Differences in treatment patterns were observed between countries.
- Tri-exposed patients experienced more inpatient hospitalisations (11 vs 8; $p < 0.0001$), and required more hospital and diagnostic tests, than non-tri-exposed patients.
- Tri-exposed patients had a higher rate of being either on long-term sick leave, retired or unemployed due to their MM versus non-tri-exposed patients, while a higher proportion of tri-exposed versus non-tri-exposed patients experienced symptomatic burden, in particular concomitant conditions related to hypercalcemia, renal dysfunction, anemia and bone involvement criteria.
- Tri-exposed patients reported a higher degree of disease burden and impairment versus non-tri-exposed patients, as defined across a range of tools, with many differences in scores considered clinically meaningful. These same patient-reported outcome scores also worsened at later LOT.
- This study demonstrated the complexity of the treatment landscape in patients with MM. There is an unmet need for more effective therapies to reduce disease burden in patients with MM, in particular in patients who are tri-exposed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0021

Author contributions

All authors were involved in conception or design, or analysis and interpretation of data; drafting and revising the article; providing intellectual content of critical importance to the work described; and final approval of the version to be published, and therefore meet the criteria for authorship in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines. In addition, all named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Financial & competing interests disclosure

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Ethical conduct of research

Using a checkbox, patients provided informed consent to take part in the survey. Data were collected in such a way that patients and physicians could not be identified directly. Physician and patient data were pseudo-anonymised. A code was assigned when data were collected. Upon receipt by ARW, data were pseudo-anonymised again to mitigate against tracing them back to the individual. Data were aggregated before being shared with the subscriber and/or for publication.

The DSP survey was submitted to the Pearl Institutional Review Board (study protocol number: #21-ADRW-103). Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines and as such did not require ethics committee approval. In addition, the survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996, and Health Information Technology for Economic and Clinical Health Act legislation.

Data sharing statement

All data i.e. methodology, materials, data and data analysis, that support the findings of this study are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Amanda Ribbands; amanda.ribbands@adelphigroup.com.

Open access

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