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Real-world treatment patterns in patients initiating third-line therapy for relapsed or refractory multiple myeloma in Germany, Italy, the United Kingdom, France, and Spain

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Abstract

Objectives: To retrospectively analyze real-world treatment patterns in patients with relapsed/refractory multiple myeloma (RRMM) who initiated third-line treatment in Europe.

Methods: German and Italian administrative claims data were sourced from the German AOK PLUS health insurance fund and Italian local health units (2016–2020). Data for the United Kingdom (UK), France, and Spain were sourced from medical chart reviews (MCRs) from 2016 to 2018 (historical) and 2019 to 2021 (new) using electronic case report forms.

Results: Across all countries, immunomodulatory imide drug (IMiD)-based regimens were prominent in the third-line setting. From 2016 to 2020, lenalidomide-dexamethasone was most common in Italy (18.0%) and Germany (12.7%). From 2019 to 2021, the most common regimen was ixazomib-lenalidomide-dexamethasone (67.5%) in the UK, pomalidomide-dexamethasone (17.1%) in France, and daratumumab-bortezomib-dexamethasone (15.0%) in Spain.

In the historical data (2016–2018), third-line lenalidomide- and pomalidomide-dexamethasone doublet use across the UK (>47%), France (>46%), and Spain (>33%) was high. From historical to new, triplet use increased in Spain (>19% to >60%) as did anti-CD38 agent use in France (15.1% to 51.9%) and Spain (19.7% to 42.1%).

Conclusions: From 2016 to 2021, third-line regimens were mostly IMiD based. The MCR data demonstrated evolving treatment choices from 2016 to 2018 and 2019 to 2021, providing insights into uptake of novel agents and current RRMM European clinical practice.

KEYWORDS
costs, Europe, health outcomes, healthcare resource utilization, multiple myeloma, relapsed/refractory, third-line treatment patterns, treatment outcomes, treatment sequence

Novelty statements

What is the new aspect of your work?

Analysis of real-world patient data from Germany, Italy, the United Kingdom, France, and Spain demonstrated evolving treatment choices in relapsed or refractory multiple myeloma from 2016 to 2018 and 2019 to 2021, providing insights into uptake of novel agents and current European clinical practice.

What is the central finding of your work?

From 2016 to 2021, third-line regimens were mostly IMiD based, and the medical chart reviews data demonstrated evolving treatment choices from 2016 to 2018 and 2019 to 2021.

What is (or could be) the specific clinical relevance of your work?

Results provide insights into the uptake of novel agents and current relapsed or refractory multiple myeloma European clinical practice and will help inform later-line treatment decisions.

1 | INTRODUCTION

Multiple myeloma (MM) is a malignancy of plasma cells characterized by end-organ damage and debilitating symptoms, including bone pain, anemia, fatigue, weakness, and weight loss.[1–3] With the expansion of available antimyeloma agents, choosing an optimal treatment sequence to maximize clinical benefit in later lines of therapy (LOTs), especially after triple-class exposure (immunomodulatory imide drugs [IMiDs], proteasome inhibitors [PIs], and monoclonal antibodies [mAbs]), remains a challenge.[4,5] Treatment strategies for newly diagnosed and relapsed/refractory disease generally involve regimens containing combinations of IMiDs, PIs, mAbs, and corticosteroids.[6–8] More recently, B-cell maturation antigen-targeting agents (e.g., belantamab mafodotin, teclistamab, idecabtagene vicleucel, and ciltacabtagene autoleucel) have emerged as candidates in the treatment landscape, in addition to talquetamab, a bispecific antibody targeting GPRC5D on myeloma cells and CD3 on T cells.[4,8–10]

These advances in MM therapy have led to significant improvements in survival.[11–13] Nevertheless, few patients obtain long-term disease control, and most eventually relapse and progress through multiple LOTs. Patients with MM also have highly individualized disease courses; treatment of relapsed/refractory MM (RRMM) remains challenging, with no consensus on how to best treat these patients.[10,14,15]

European guidelines for subsequent therapy largely depend on whether patients have disease that is refractory or remains sensitive to any agent in a prior regimen.[4,16] Because of the vast number of treatment options, treatment patterns in Europe vary from country to country and even region to region and become more heterogeneous in later lines[14,15]; other factors include differences in drug availability and access, physician and/or patient preferences, and individual patient characteristics.[10]

Clinical trials are often used to inform treatment guidelines, but they may not be representative of data observed in real-world (RW) clinical practice.[9,17–19] As clinical trials enroll patients who meet specific inclusion criteria, significant proportions of patients may be excluded. For example, data from the Connect MM Registry indicated that 40% of patients enrolled in the registry were not eligible for inclusion in randomized controlled trials.[20] Given the multiple available treatment options and the ability of clinicians to choose diverse combinations for patients, it is important to understand the RW treatment landscape and how treatment choices may impact LOTs. Real-world evidence (RWE) on treatment patterns can complement clinical trial data and provide valuable insights to help identify and address unmet medical needs, especially among individuals typically excluded from clinical trials.[16]

Continued study of RW treatment patterns and burden of disease remains important in patients with RRMM to help guide physician decision-making. This is particularly important in the third-line (3L) setting and subsequent lines because treatment patterns are more heterogeneous, and most patients have already been triple class exposed.[5,14,15]

This study focuses on an analysis of administrative claims data as well as data from a medical chart review (MCR) to describe RW baseline characteristics and treatment patterns of patients with RRMM initiating 3L therapy in Germany, Italy, the United Kingdom (UK), France, and Spain. An estimate of all-cause and MM-related healthcare resource utilization (HCRU) and costs in Germany and Italy is also described.

2 | METHODS

2.1 | Study design and patient population

This retrospective, noninterventional, cohort study used a longitudinal design to evaluate and describe the following primary objectives: RW treatment patterns (Germany, Italy, the UK, Spain, and France) and HCRU and costs (Germany and Italy) for patients initiating 3L treatment for RRMM. This study did not aim to statistically compare results across countries.

2.1.1 | Germany and Italy

Administrative claims data were analyzed for Germany and Italy. For Germany, data from the German health insurance fund AOK PLUS were used, which contained anonymized records of approximately 3.4 million insured people with >10 years of coverage from the regions of Saxony and Thuringia. The database included information on prescriptions, diagnoses (inpatient/outpatient), primary care and outpatient specialist visits, and surgeries as well as related costs in the inpatient and outpatient settings. For Italy, data from the local health unit (LHU) databases were used, which covered >12 million people across the country and included information on prescriptions, diagnoses in the inpatient setting, specialist visits, and procedures as well as associated costs of inpatient and observable outpatient settings.

The claims data measurement window for Germany and Italy was from January 1, 2010, to December 31, 2020 (Figure 1A). Patients were included if they initiated 3L treatment between January 1, 2016, and December 31, 2020 (inclusion period). Within this study period, the index date was the date at which 3L therapy was initiated, defined as the first prescription of MM-related treatment as part of 3L therapy. Treatment patterns were described for adult patients (age ≥ 18 -years at the index date) with RRMM who initiated 3L therapy within the defined study period.

For analysis of HCRU and costs, patients initiating 3L therapy in Germany and Italy from January 1, 2016, to December 31, 2019, were selected, allowing for ≥12 months of follow-up. Patients were followed up until death, loss to follow-up, or end of the study period. Patients were also observed in the 12 months before the index date for reporting of baseline characteristics.

2.1.2 | The UK, France, and Spain

Patient data from MCRs in the UK, France, and Spain were collected by TriNetX Oncology GmbH and its affiliated company, CancerDataNet GmbH.

The overall dataset was accrued from January 1, 2016, to June 1, 2021, and comprised historical data (2016–2018; obtained from a prior RW multinational survey, the TherapyMonitor Multiple Myeloma project)[15] as well as new data (2019–2021) specifically collected for this study (Figure 1B). Electronic case report forms (eCRFs) were used to capture a patient's full treatment history from initial diagnosis to all subsequent LOTs until the end of the study period, loss to follow-up, or death.[15]

The index date was the start of 3L therapy, defined as the earliest date of treatment initiation with an agent in the 3L therapy regimen documented in the MCR. For describing treatment patterns in the historical data cohort, adult patients (age ≥ 18 years at the index date) with MM who initiated 3L therapy from January 1, 2016, to December 31, 2018, were selected. For the new data cohort, patients who initiated 3L therapy from January 1, 2019, to June 30, 2020, were selected and followed up for a minimum of 12 months until June 1, 2021. To achieve target patient numbers for the new data cohort, an additional inclusion period was implemented to include patients who initiated 3L therapy from June 30, 2020, to June 1, 2021. These patients were followed up for a minimum of 12 months until June 1, 2022. For both inclusion periods, patients were followed up until death, loss to follow-up, or the end of the respective study period.

Key inclusion and exclusion criteria for patient selection for both the administrative claims and MCR data are presented in Table S1.

2.2 | Algorithm for defining LOTs in Germany and Italy

LOTs were not directly available in the claims data from Germany and Italy since neither dataset captured physician recommendations or treatment plans. Thus, an algorithm based on existing guidelines for determining LOTs in patients with MM was used and refined with input from clinical experts from Germany, Italy, and the UK to accurately reflect clinical practice (Figures S1 and S2).[21,22]

2.3 | Study variables

Baseline characteristics, including sex, age, Charlson Comorbidity Index (CCI), International Staging System stage (MCR data only), CRAB criteria for end-organ damage comprising hypercalcemia (C), renal dysfunction (R), anemia (A), and bone disease (B) (MCR data only), comorbidities (Germany), time since diagnosis, and prior therapy, were described at the start of 3L therapy (index date) or during a 12-month pre-index period. Baseline comorbidities were identified based on inpatient (Germany and Italy) and confirmed outpatient (Germany) diagnoses. In the MCR data, comorbidities were limited to those relevant at the time of MM treatment decision. Only comorbidities for Germany are reported due to probable underestimation in other countries caused by missing outpatient diagnoses (Italy) or underreporting (MCR countries).

Treatment pattern variables included 3L therapy regimens and prior and subsequent LOTs, which were identified using the algorithm based on prescription and medication procedure dates (Germany/Italy) or the completed eCRFs (the UK/France/Spain).

HCRU and costs were reported as per patient per month (PPPM) for the administrative claims data (Germany/Italy) in the 12-month period before the start of 3L therapy (baseline period), from the start of 3L therapy to the start of fourth-line (4L) therapy (pre-progression period), and from the start of 4L therapy until the end of the follow-up period, loss to follow-up, or death (post-progression period).

HCRU variables included hospitalizations during the observational period, outpatient visits to general practitioners (GPs) or specialists (for Italy, only specialist outpatient visits were analyzed, as data from GPs were not available), and rehabilitation stays. Costs for hospitalizations (based on diagnosis-related group *International Classification of Diseases*, *Tenth* or *Ninth Revision* codes), outpatient specialist visits, outpatient prescriptions (MM related), emergency department (ED) visits leading to a

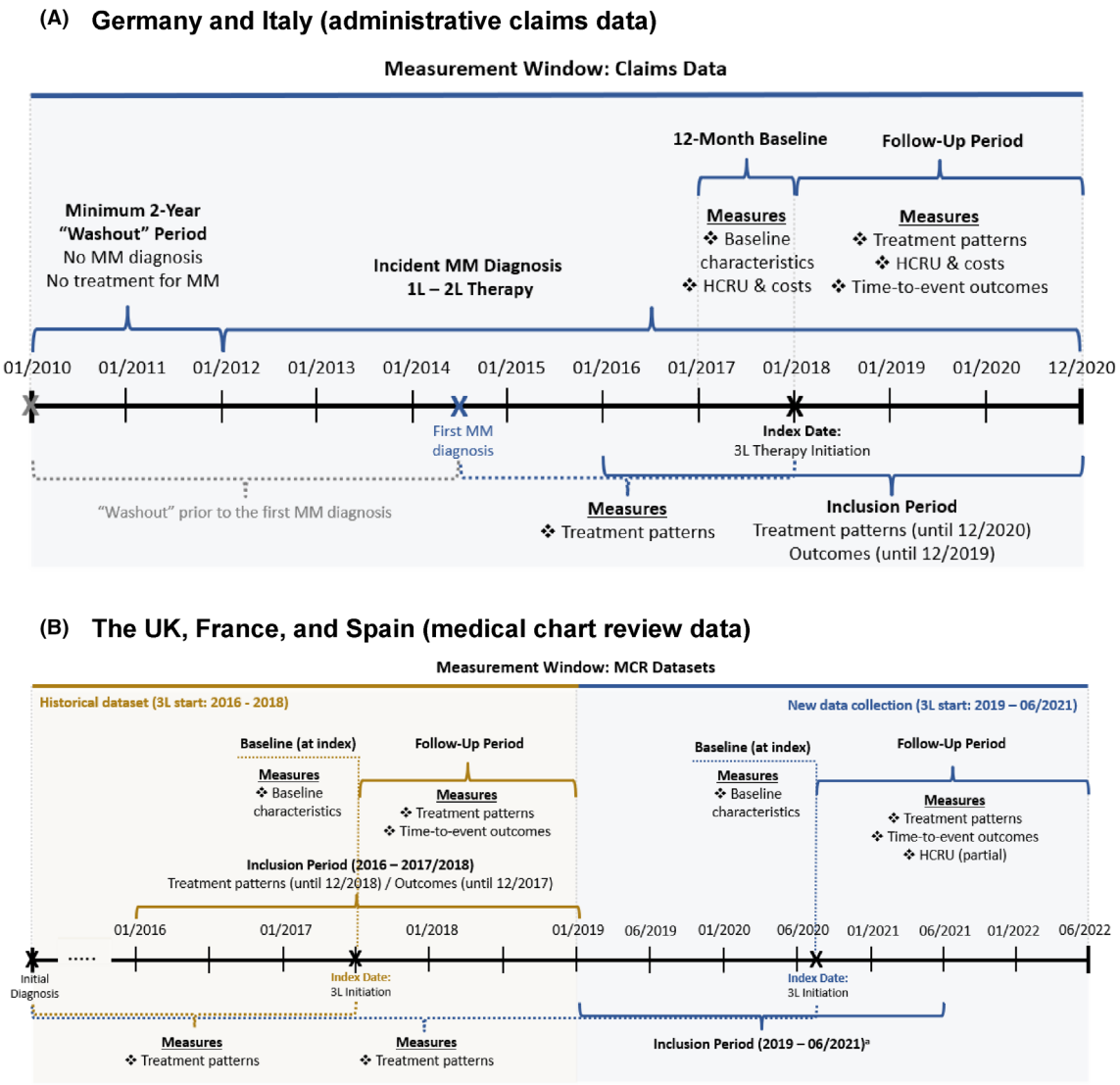

FIGURE 1 Study design scheme for the Germany and Italy claims (A) and the UK, France, and Spain medical chart review (B) datasets. (A) Patients with an incident MM diagnosis, defined as a patient with no prior MM diagnosis or treatment for MM in a minimum 2-year washout period, were identified within the period between January 1, 2010, and December 31, 2020. For the treatment patterns cohort, adult patients (age ≥ 18 years at the index date) with MM initiating 3L therapy from January 1, 2016, to December 31, 2020, were selected. For the outcomes cohort (including analysis of HCRU and costs), patients initiating 3L therapy in Germany and Italy from January 1, 2016, to December 31, 2019, were selected, permitting a 12-month follow-up until the earliest of December 31, 2020 (end of study period), loss to follow-up, or death. Patients were also observed in the 12 months prior (baseline) to the index date. (B) The study population included patients initiating 3L therapy in an initial (historical) and a subsequent (new) inclusion period. The historical data included patients initiating 3L therapy from January 1, 2016, to December 31, 2017 (outcomes cohort), or December 31, 2018 (treatment patterns cohort). • The historical data, extracted from a prior RW analysis of data accrued in a multinational survey (TherapyMonitor Multiple Myeloma project), were collected quarterly from 2016 to 2018 from medical care centers and clinical sites, including university and community hospitals, and specialized cancer clinics. Centers documented all patients with RRMM treated in the reporting period retrospectively back to initial diagnosis based on data in the patients' files. Only patients newly diagnosed with RRMM were included over the course of the year and were subsequently followed up quarterly. Data on prior 1L treatment were gathered retrospectively from patient records. • The new data (treatment patterns cohort and outcomes cohort) included patients initiating 3L therapy between January 01, 2019, and June 30, 2020, who were followed up for a minimum of 12 months until June 1, 2021. To achieve target patient numbers in the new data, an additional inclusion period was implemented to accommodate patients initiating 3L therapy from June 30, 2020, to June 1, 2021, and were followed up for a minimum of 12 months until June 1, 2022. For both inclusion periods, patients were followed up until death, loss to follow-up, or the end of the respective study period. Treatment lines of the study population were fully documented by physicians from end of the study period to initial diagnosis for MM. 1L, first line; 2L, second line; 3L, third line; HCRU, healthcare resource utilization; MCR, medical chart review; MM, multiple myeloma; RRMM, relapsed or refractory multiple myeloma; RW, real world. [a]For simplification, inclusion period I and inclusion period II for the new data are shown combined. Note that for inclusion period I, the follow-up period occurred until June 2021.

hospital admission (Germany only), and rehabilitation stays (Germany only) were included. Total direct costs for Germany included inpatient hospitalization costs, costs of GP visits, costs of outpatient specialist visits, MM-related prescriptions, and costs of rehabilitation stays. Total direct costs for Italy included inpatient hospitalization costs, costs of outpatient visits/services (specialists, unspecified specialty) and MM-related prescriptions.

2.4 | Data analysis

Descriptive statistics were used to report patient characteristics and MM treatment patterns by country. HCRU and costs were reported for Germany and Italy only.

Categorical variables were reported as frequencies and percentages, along with corresponding sample sizes. Continuous variables were summarized using mean, standard deviation, median, range (min-max), and interquartile range values. Data were analyzed with R version 4.1.3.[23] German claims data were analyzed under the formal agreement and legal basis of §75, Tenth Book of the Social Code. Accordingly, no informed consent or ethical approval from an institutional review board was required. Italian claims data were analyzed with the approval of the local ethics committee of each LHU. The analysis was conducted by Clicon Srl Società Benefit. Clicon Srl Società Benefit developed a retrospective observational study, approved by each LHU's Institutional Review Boards included in the study, according to the Agenzia Italiana del Farmaco Determination of 20 March 2008 "Guidelines for the classification and conduct of observational studies on drugs." Clicon Srl Società Benefit received only anonymized data from LHU, which remain the body entitled to data treatment, and for this reason, informed consent is not required. MCR data were collected in accordance with legal and ethical regulations of the individual countries.

3 | RESULTS

3.1 | Patient demographic and clinical characteristics in Germany and Italy (2016–2020) and the UK, France, and Spain (2016–2021 [combined data])

Patients who met selection criteria (Table S1) from Germany ($n = 276$), Italy ($n = 289$), the UK ($n = 401$), France ($n = 527$), and Spain ($n = 372$) were analyzed (Table 1). The median age at index date (initiation of 3L treatment) ranged from 70 (Spain) to 75 years (Germany), and the median time since first MM diagnosis to start of 3L therapy was shortest in Italy (2.1 years) and longest in France (4.9 years). The distribution of patients by type of center is presented for the UK, Spain, and France in Table S2.

Data on comorbidities and associated burden were robustly collected only in Germany (median CCI, 6).

3.2 | Prior treatment exposure in patients initiating third-line treatment in Germany and Italy (2016–2020) and the UK, France, and Spain (2016–2018 [historical data] and 2019–2021 [new data])

Across all countries, PI- and IMiD-based regimens were most commonly used in first-line (1L) and/or second-line (2L) treatment, with bortezomib (BTZ) as the PI of choice and lenalidomide (LEN) as the IMiD of choice in all countries except the UK, in which thalidomide (Tha) was more frequently selected (77.3% vs. 21.9% for LEN) (Table 1; Table S3). By 3L, the proportion of double class-exposed (PI and IMiD) patients was 52.2% (Germany), 33.2% (Italy), 66.1% (the UK), 78.6% (France), and 68.8% (Spain). Prior exposure to anti-CD38 mAbs (daratumumab [DAR]) was low in Germany (10.9%), Italy (4.5%), France (2.8%), and Spain (9.1%) but notably higher in the UK (30.9%). Prevalence of prior stem cell transplant (SCT) was lower in Germany (27.2%) and Italy (14.9%) but was 41.9%, 44.2%, and 40.6% in the UK, France, and Spain. Prior use of 1L triplet combinations was more frequent (>60%) in the UK, France, and Spain, while non-triplet regimens (vs. triplet) were more common in Germany and Italy in both the 1L (>38% vs. >25%) and 2L (>50% vs. >8%) settings (Table S3).

3.3 | Third-line treatment patterns

IMiDs were the most common agent class used in 3L treatment settings across all countries over the time periods studied (Figure 2). IMiD use in Germany (55.8%) and Italy (64.4%) was primarily driven by LEN (48.9% and 45.3%, respectively). The most frequently used IMiD was LEN (historical, 78.4%; new, 74.6%) in the UK and pomalidomide (POM; historical, 45.2%; new, 49.6%) in France. In Spain, LEN was the most used IMiD historically (36.0%), but POM was most common in the new MCR data (30.1%). PI use in the 3L setting was common in the UK (new, 71.1%), Spain (new, 50.4%), and Germany (44.6%), with DAR also commonly used in Spain (new, 42.1%), France (new, 38.0%), and Germany (29.0%) in this setting (Figure 2).

Lenalidomide-dexamethasone (LEN-d) was the most common regimen in Germany (12.7%) and Italy (18.0%). The most common regimens in the UK were ixazomib-LEN-d (IXA-LEN-d; new, 67.5%) and LEN-d (historical, 36.3%) (Table 2). POM-based regimens were preferentially used in France, and POM-d was most common in both the historical (33.9%) and new (17.1%) data. In Spain, LEN-d (19.7%) and DAR-BTZ-d (15.0%) were the most common historical and new regimens, respectively.

From 2016 to 2018 (historical), LEN- and POM-based 3L regimens were frequent, with a high use of LEN-d and POM-d across the UK (>47%), France (>46%), and Spain (>33%). From historical to new (2019–2021), there was a rise in triplet regimen use (with the sharpest increase in Spain [>19% to >60%]), an overall increase in anti-CD38

TABLE 1 Baseline and treatment characteristics in patients with RRMM who initiated 3L treatment from 2016 to 2020 (Germany and Italy) and 2016 to 2021 (historical and new combined for the UK, France, and Spain).

	Germany ($n = 276$)	Italy ($n = 289$)	UK ($n = 401$)	France ($n = 527$)	Spain ($n = 372$)
Sex, *n* (%)					
Female	137 (49.6)	148 (51.2)	212 (52.9)	242 (45.9)	172 (46.2)
Age groups at index date, *n* (%)					
<65 years	69 (25.0)	66 (22.8)	123 (30.7)	129 (24.5)	107 (28.8)
65–74 years	65 (23.6)	90 (31.1)	124 (30.9)	182 (34.5)	155 (41.7)
≥75 years	142 (51.4)	133 (46.0)	154 (38.4)	216 (41.0)	110 (29.6)
Median age at index date (range), years	75 (33–91)	73 (39–95)	71 (42–88)	72 (36–93)	70 (36–102)
Median time since diagnosis (range), years[a]	2.7 (0.4–7.4)	2.1 (0.3–6.7)	3.4 (0.4–15.3)	4.9 (0.2–20.2)	3.8 (0.3–27)
Charlson Comorbidity Index score					
Median (range)	6 (2–16)	–	–	–	–
Select comorbidities, *n* (%)[b]					
Cardiovascular disease	153 (55.4)	–	–	–	–
Renal disease	149 (54.0)	–	–	–	–
Ocular diseases	132 (47.8)	–	–	–	–
Congestive heart failure	113 (40.9)	–	–	–	–
Diabetes mellitus	102 (37.0)	–	–	–	–
Polyneuropathy	72 (26.1)	–	–	–	–
Chronic pulmonary disease	65 (23.6)	–	–	–	–
Extramedullary disease	8 (2.9)	–	–	–	–
ISS stage, *n* (%)					
I	NA	NA	11 (2.7)	33 (6.3)	68 (18.3)
II	NA	NA	18 (4.5)	83 (15.7)	94 (25.3)
III	NA	NA	94 (23.4)	43 (8.2)	115 (30.9)
Unknown	NA	NA	278 (69.3)	368 (69.8)	95 (25.5)
CRAB criteria, *n* (%)[c]					
Hypercalcemia (C)	NA	NA	91 (22.7)	57 (10.8)	58 (15.6)
Renal dysfunction (R)	NA	NA	54 (13.5)	49 (9.3)	73 (19.6)
Anemia (A)	NA	NA	187 (46.6)	157 (29.8)	183 (49.2)
Bone disease (B)	NA	NA	100 (24.9)	156 (29.6)	172 (46.2)
Unknown	NA	NA	78 (19.5)	202 (38.3)	67 (18.0)
M-protein type, *n* (%)					
IgG	NA	NA	208 (51.9)	310 (58.8)	197 (53.0)
Non-IgG	NA	NA	107 (26.7)	107 (20.3)	113 (30.4)
Unknown	NA	NA	86 (21.4)	110 (20.9)	62 (16.7)
Prior MM treatments in 1L or 2L, *n* (%)[d]					
PI	264 (95.7)	151 (52.2)	392 (97.8)	467 (88.6)	348 (93.5)
Bortezomib	261 (94.6)	143 (49.5)	385 (96.0)	464 (88.0)	347 (93.3)
Carfilzomib	39 (14.1)	15 (5.2)	7 (1.7)	34 (6.5)	29 (7.8)
Ixazomib	4 (1.4)	≤3	28 (7.0)	19 (3.6)	3 (0.8)
IMiD	154 (55.8)	213 (73.7)	374 (93.3)	488 (92.6)	307 (82.5)
Lenalidomide	148 (53.6)	162 (56.1)	88 (21.9)	442 (83.9)	271 (72.8)
Pomalidomide	8 (2.9)	9 (3.1)	1 (0.2)	9 (1.7)	3 (0.8)
Thalidomide	≤3	79 (27.3)	310 (77.3)	249 (47.2)	94 (25.3)
Anti-CD38 mAb	30 (10.9)	13 (4.5)	124 (30.9)	15 (2.8)	34 (9.1)
Daratumumab	30 (10.9)	13 (4.5)	124 (30.9)	15 (2.8)	34 (9.1)

TABLE 1 (Continued)

	Germany ($n = 276$)	Italy ($n = 289$)	UK ($n = 401$)	France ($n = 527$)	Spain ($n = 372$)
LEN + PI exposed and POM naive	135 (48.9)	61 (21.1)	84 (20.9)	377 (71.5)	250 (67.2)
Double-class exposed[e]	144 (52.2)	96 (33.2)	265 (66.1)	414 (78.6)	256 (68.8)
Triple-class exposed[e]	15 (5.4)	8 (2.8)	112 (27.9)	15 (2.8)	32 (8.6)
Stem cell transplant	75 (27.2)	43 (14.9)	168 (41.9)	233 (44.2)	151 (40.6)

Abbreviations: 1L, first line; 2L, second line; 3L, third line; IgG, immunoglobulin G; IMiD, immunomodulatory imide drug; ISS, International Staging System; LEN, lenalidomide; mAb, monoclonal antibody; MM, multiple myeloma; NA, not available; PI, proteasome inhibitor; POM, pomalidomide; RRMM, relapsed or refractory multiple myeloma.

[a]For Spain, one patient with a missing date of initial diagnosis was excluded from analysis; for France, one patient with an implausible date of first diagnosis was excluded from analysis.

[b]Only Germany reliably captured comorbidity data. As such, data for the other countries are not shown.

[c]More than one criterion can be fulfilled per patient. Unknown refers to unknown entries across all criteria.

[d]Excluding maintenance.

[e]Categories are mutually exclusive. Defined as exposure to two (double; IMiD and PI) or three (triple; IMiD, PI, and anti-CD38 mAb) agent classes.

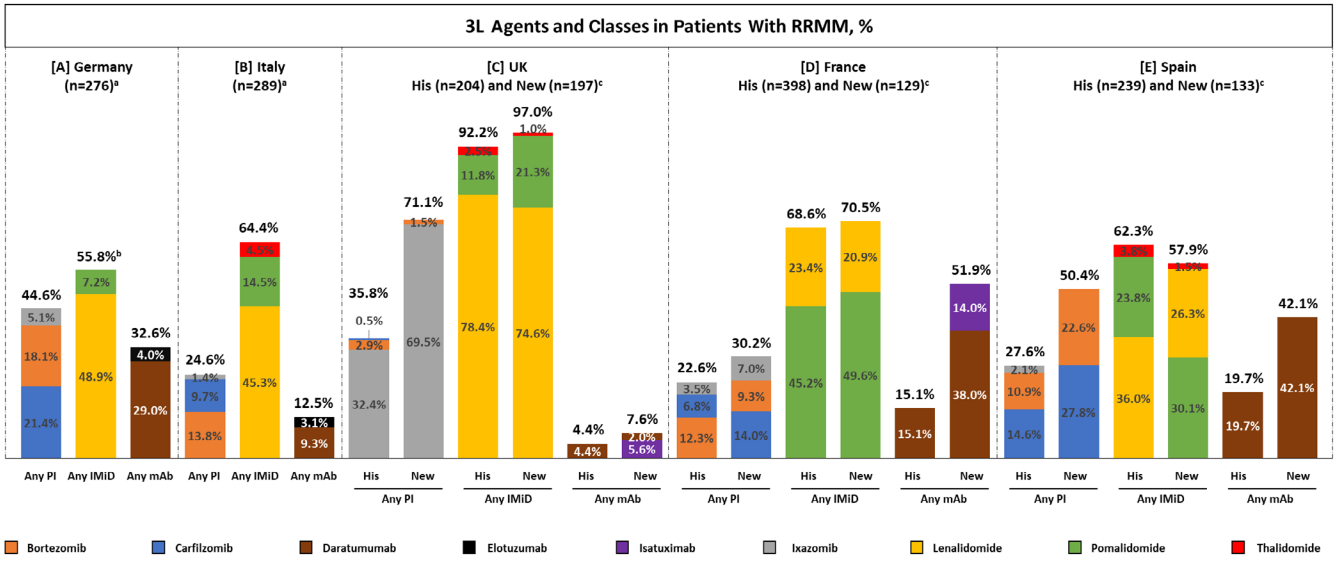

FIGURE 2 3L treatments in patients with RRMM in Germany and Italy (2016–2020) and the UK, France, and Spain (2016–2018 [historical] and 2019–2021 [new]) by agent and class. 3L, third line; His, historical; IMiD, immunomodulatory imide drug; mAb, monoclonal antibody; PI, proteasome inhibitor; RRMM, relapsed or refractory multiple myeloma. [a]Agents used in any combination or monotherapy are listed. [b]Fewer than three patients used thalidomide; percentage could not be calculated. [c]Agents used in any combination or monotherapy are listed and include agents as part of any therapeutic measure in the line (e.g., induction, high-dose consolidation, stem cell mobilization, maintenance/consolidation, if applicable).

agent use (France [15.1% to 51.9%]; Spain [19.7% to 42.1%]), and reduced variability in types of regimens used in the UK, with the top two regimens (IXA-LEN-d and POM-d) used by >80% of patients (Figure 2 and Table 2).

3.4 | Treatment sequence from first to fourth line in Germany and Italy (2016–2020) and the UK, France, and Spain (2016–2021 [combined data])

In Germany, BTZ-containing regimens were the most commonly used 1L treatments (Figure 3A). Following a BTZ-based 1L regimen, patients typically received a LEN-based 2L regimen. Most patients who received a LEN-based 2L regimen proceeded to receive a PI- and/or DAR-based 3L regimen. Increased heterogeneity was observed in 3L treatments, but LEN (19.9%) remained a common regimen. Overall, DAR was the most common 4L treatment (19.5%).

In Italy, 1L regimens were primarily melphalan (MEL) based (Figure 3B). Following 1L treatment, most patients subsequently received LEN in 2L, followed by LEN or POM in 3L. Of the patients who received LEN in 3L, a large proportion received LEN again in 4L.

In the UK historical data, 1L regimens were predominantly Tha-cyclophosphamide (CTX; 47.1%) or BTZ-Tha (21.1%) (Figure 3C).

TABLE 2 Most common 3L treatment regimens in patients with RRMM in Germany and Italy (2016–2020) and the UK, France, and Spain (2016–2018 [historical] and 2019–2021 [new]).

Most common 3L treatment regimens (≥10 patients), *n* (%)[a]															
Germany ($n = 276$)[b]		Italy ($n = 289$)[b]		UK ($n = 401$)[c]				France ($n = 527$)[c]				Spain ($n = 372$)[c]			
				His ($n = 204$)		New ($n = 197$)		His ($n = 398$)		New ($n = 129$)		His ($n = 239$)		New ($n = 133$)	
LEN-d	35 (12.7)	LEN-d	52 (18.0)	LEN-d	74 (36.3)	IXA-LEN-d	133 (67.5)	POM-d	135 (33.9)	POM-d	22 (17.1)	LEN-d	47 (19.7)	DAR-BTZ-d	20 (15.0)
CFZ-LEN (±d)[d]	27 (9.8)	POM (±d)[d]	35 (12.1)	IXA-LEN-d	64 (31.4)	POM-d	29 (14.7)	LEN-d	50 (12.6)	ISA-POM-d	16 (12.4)	POM-d	34 (14.2)	POM-CTX-d	19 (14.3)
CFZ-d	22 (8.0)	LEN	27 (9.3)	POM-d	22 (10.8)	LEN-d	12 (6.1)	POM-CTX-d	27 (6.8)	DAR-d	14 (10.9)	DAR	25 (10.5)	DAR-LEN-d	15 (11.3)
DAR-LEN (±d)[d]	22 (8.0)	MEL + steroids	27 (9.3)	CTX-LEN-d	15 (7.4)	ISA-POM-d	11 (5.6)	DAR-d	22 (5.5)	DAR-LEN-d	14 (10.9)	POM-CTX-d	18 (7.5)	CFZ-LEN-d	14 (10.5)
LEN	18 (6.5)	DAR-LEN (±d)[d]	15 (5.2)					CFZ-LEN-d	19 (4.8)			CFZ	11 (4.6)	POM-d	14 (10.5)
DAR-BTZ (±d)[d]	18 (6.5)	CFZ-LEN (±d)[d]	11 (3.8)					DAR	17 (4.3)			CFZ-LEN-d	11 (4.6)	CFZ-d	10 (7.5)
DAR	11 (4.0)	LEN + steroids[e]	10 (3.4)					BTZ-CTX-d	15 (3.8)			CFZ-d	10 (4.2)	DAR	10 (7.5)
POM (±d)[d]	11 (4.0)							BEN	13 (3.3)						
BTZ-d	10 (3.6)							BTZ-BEN-d	13 (3.3)						
								DAR-POM-d	12 (3.0)						
								BTZ-d	11 (2.8)						
								IXA-LEN-d	11 (2.8)						
								BEN-d	10 (2.5)						

Abbreviations: 3L, third line; BEN, bendamustine; BEN-d, bendamustine-dexamethasone; BTZ, bortezomib; BTZ-BEN-d, bortezomib-bendamustine-dexamethasone; BTZ-CTX-d, bortezomib-cyclophosphamide-dexamethasone; BTZ-d, bortezomib-dexamethasone; CFZ, carfilzomib; CFZ-d, carfilzomib-dexamethasone; CFZ-LEN-d; carfilzomib-lenalidomide-dexamethasone; CTX-LEN-d, cyclophosphamide-lenalidomide-dexamethasone; d, dexamethasone; DAR, daratumumab; DAR-BTZ-d, daratumumab-bortezomib-dexamethasone; DAR-d, daratumumab-dexamethasone; DAR-LEN-d, daratumumab-lenalidomide-dexamethasone; DAR-POM-d, daratumumab-pomalidomide-dexamethasone; His, historical; ISA, isatuximab; ISA-POM-d, isatuximab-pomalidomide-dexamethasone; IXA-LEN-d, ixazomib-lenalidomide-dexamethasone; LEN, lenalidomide; LEN-d, lenalidomide-dexamethasone; MEL, melphalan; POM, pomalidomide; POM-CTX-d, pomalidomide-cyclophosphamide-dexamethasone; POM-d, pomalidomide-dexamethasone; RRMM, relapsed or refractory multiple myeloma.

[a]Only regimens administered to ≥10 patients have been shown. Regimens administered to fewer than five patients were subsumed as Other/unknown.

[b]Regimens often included dexamethasone or another steroid. Based on the algorithm used to define therapy lines in claims data, we observed a tendency for particular agents such as lenalidomide or pomalidomide in 3L classified as monotherapy. After discussion with clinical experts, it was confirmed that such agents are most frequently prescribed together with dexamethasone and that the regimens should be counted as such.

[c]All regimens described include induction regimens. A subset of patients may have additionally received other types of therapy across different lines if applicable (consolidation, maintenance, high-dose/stem cell mobilization).

[d]Regimens with and without dexamethasone combined.

[e]Represents lenalidomide + prednisone ($n = 5$) and lenalidomide + prednisone + dexamethasone ($n = 5$).

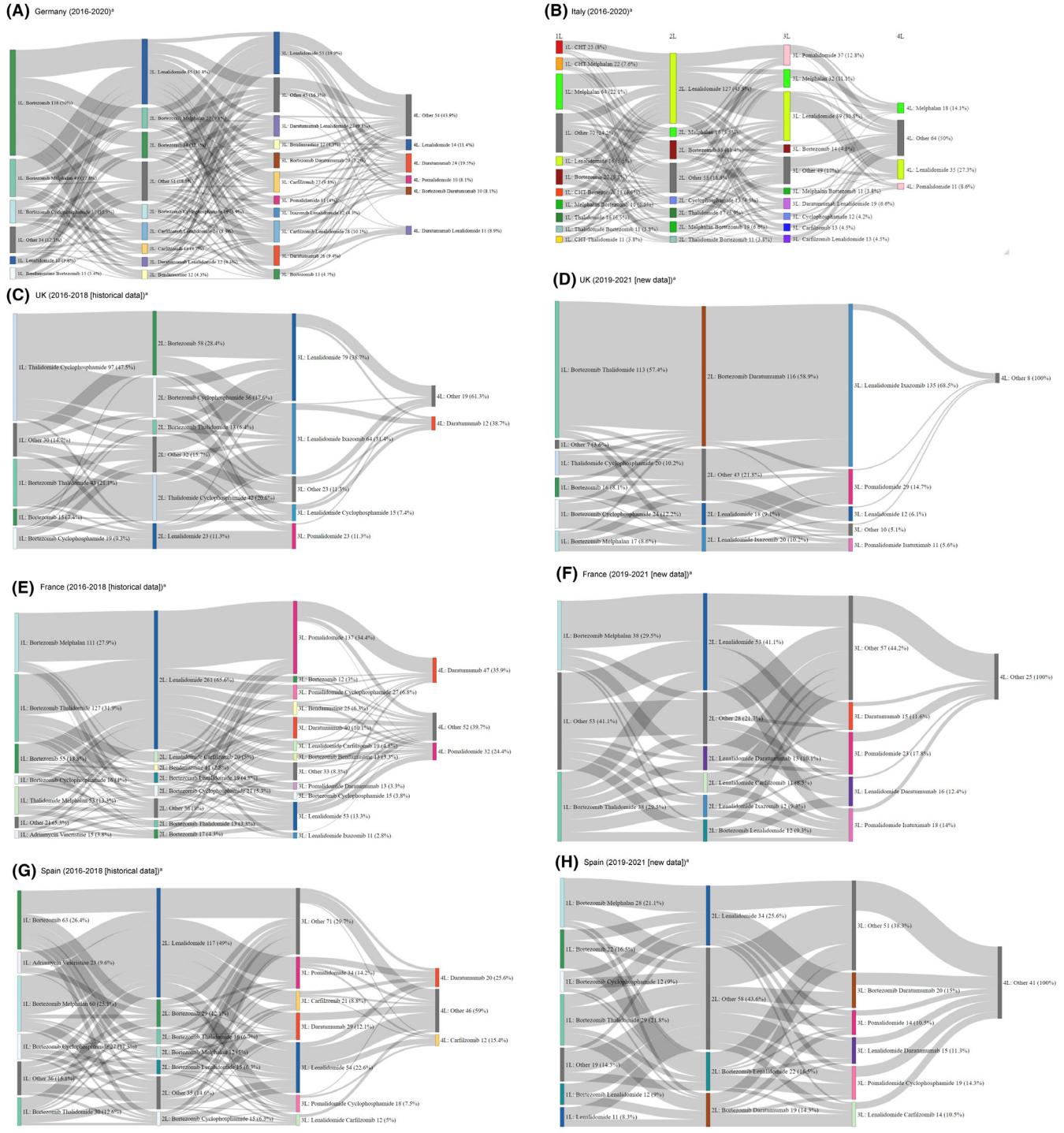

FIGURE 3 Sequence of treatment observed in 1L to 4L in patients with RRMM initiating 3L treatment in Germany and Italy (2016–2020) and the UK, France, and Spain (combined, 2016–2018 [historical] and 2019–2021 [new]). 1L, first line; 2L, second line; 3L, third line; 4L, fourth line; CHT[b], inpatient chemotherapy; RRMM, relapsed or refractory multiple myeloma. [a]Steroids are not taken into account (i.e., regimens may or may not include steroids). [b]CHT are inpatient therapies classified on generic inpatient procedure code for a chemotherapy and further details about the specific agent are not available. Regimens with numbers <10 are grouped as "Other."

Among patients who received BTZ-Tha in 1L, most received Tha-CTX in 2L. Among the patients who received 1L Tha-CTX, most were treated with a BTZ-based regimen in 2L. Most patients who received Tha-CTX in 2L subsequently received LEN-IXA in 3L. Overall, LEN was the most common 3L regimen used (38.7%). Most patients who received a BTZ-based regimen in 2L subsequently received a LEN-based regimen in 3L. Treatment with a POM-based regimen in 3L was common for patients who previously received a LEN-based regimen in 2L. In the UK new data, the most common treatment sequence was 1L BTZ-Tha (57.4%) to 2L BTZ-DAR (58.9%) to 3L

LEN-IXA (67.5%), with approximately half of patients receiving this sequence (Figure 3D). Compared with historical data, 1L and 2L use of CTX was lower in the new dataset, with increased 2L use of BTZ-DAR observed. In the 3L setting, LEN-IXA use was prominent in the new dataset. Overall, the new data featured less variety of treatment sequences compared with historical data.

In France historical data, BTZ-based regimens were common in 1L, including combinations with Tha or MEL (Figure 3E); 2L treatment was predominantly LEN based, followed mainly by POM- or DAR-based regimens in 3L. DAR (35.9%) or POM (24.4%) was common in the 4L setting. In the new cohort, similar treatment sequences were observed favoring 1L BTZ in combination with Tha or MEL, LEN-based regimens in 2L, and POM-based regimens in 3L (Figure 3F).

In Spain historical data, 1L regimens were primarily BTZ based, most commonly as BTZ (26.4%) and BTZ-MEL (25.1%) (Figure 3G), followed by LEN in 2L. Patients who received LEN-based regimens in 2L typically received DAR- or POM-based regimens in 3L. Among patients advancing to 4L, DAR-based regimens were common. In Spain new data, 1L regimens continued to be primarily BTZ based, as BTZ-Tha (21.8%) and BTZ-MEL (21.8%). In Spain new data, LEN (25.6%) in 2L was the most common; however, there was high variation in 3L regimens (Figure 3H).

3.5 | Retreatment patterns

Claims and new MCR data showed that 83.3% (Italy), 93.2% (the UK), 92.3% (France), and 83.1% (Spain) of patients treated with an IMiD during 3L treatment had prior exposure to the same agent class, compared with only 42.9% in Germany (Table S4). Among those who received a PI in 3L, 97.6% (Germany), 76.1% (Italy), 100% (the UK), 92.3% (France), and 97.0% (Spain) had prior exposure to the same agent class. Retreatment with a mAb in 3L was very low in Germany (14.4%), Italy (19.4%), the UK (0%), France (3.0%), and Spain (3.6%). Most 3L patients had prior exposure to the same agent class (IMiD, PI, or mAb) in an earlier treatment line (Germany, 60.1%; Italy, 82.0%; the UK, 98.0%; France, 82.2%; Spain, 82.7%).

3.6 | Healthcare resource utilization and costs (Germany and Italy)

A high proportion of patients from the Germany (>72%; >61% MM related) and Italy (>53%; >43% MM related) cohorts had one or more inpatient hospitalizations across the baseline, pre-progression, and post-progression periods (Table S5). The highest mean number of hospitalizations PPPM was observed in the post-progression period in Germany (0.24; 0.19 MM related) and baseline period in Italy (0.14; 0.11 MM related). The median (interquartile range) length of hospitalization in the pre-progression and post-progression periods was 7 (3–14) and 6 days (2–13) in Germany and 19 (7–91) and 17 days (10–101) in Italy. This difference between countries was likely due to differences in their respective healthcare structures and patient and symptom variation.

Most patients (>94% in both countries) had one or more outpatient specialist visits, with the mean number of visits ranging from 1.4 (pre-progression, Germany) to 1.9 (baseline, Italy) visits per patient month. There were >62% of German and >38% of Italian patients with one or more MM-related outpatient specialist visit across all periods (baseline and pre-progression and post-progression), with means ranging from 0.2 (pre-progression, Germany) to 0.9 (post-progression, Italy) visits PPPM. In Germany, >51% of all-cause patient HCRU and >33% of MM-related patient HCRU had one or more ED admissions. Mean visits per patient month ranged from 0.09 (baseline) to 0.16 (post-progression) for all-cause and 0.05 (baseline) to 0.10 (post-progression) for MM-related ED admissions. ED admissions were not specified in the Italy claims data.

Overall, total direct costs increased across periods (with time) and were highly driven by prescription costs required for MM (Table S6). Mean total direct costs per patient month ranged from €2731.35 (baseline) to €6917.00 (4L+) and €2654.25 (baseline) to €4141.41 (4L+) in Germany and Italy.

4 | DISCUSSION

This multicountry retrospective analysis of administrative claims data from Germany and Italy and MCR data from the UK, France, and Spain provides a perspective of RW treatment patterns in patients with RRMM initiating 3L treatment in Europe. Treatments reflect clinical practice at the time, with some newer treatment options (e.g., DAR) likely underrepresented in initial LOTs compared with the current treatment paradigm (Table S7 details the European approvals of key treatment options). While this study was not designed to facilitate direct comparisons across countries, certain trends were observed.

Patients ≥65 years of age comprised the majority of patients initiating 3L treatment, reflecting an older MM population (particularly in Germany and Italy, where nearly 50% of patients in both countries were ≥75 years of age). PIs and IMiDs, primarily BTZ and LEN, respectively, predominated 1L and 2L treatment regimens for patients initiating 3L treatment. Most patients in Germany, the UK, France, and Spain were previously exposed to PIs, whereas prior use of IMiDs vs. other agents was more prominent in Italy and France. More than half of the patients in Germany, the UK, France, and Spain were exposed to IMiDs and PIs by the time they started a 3L treatment regimen, while about a third in Italy were exposed to IMiDs and PIs. Except for in the UK, generally very few patients had prior exposure to an anti-CD38 antibody, potentially because this treatment option was not yet available during the pre-index inclusion period or was introduced later (2019–2021). The proportion of patients with prior SCT was high in the UK, France, and Spain; the low occurrence in Germany and Italy may reflect stricter regional- or country-specific guidance on SCT suitability for older patients; for example, in

Germany, high-dose treatment and SCT are recommended in 1L for healthy patients <65 years of age.

IMiD-based regimens were prominent in the 3L, with LEN generally being the most frequently used. However, POM was most common in France (historical [2016–2018] and new [2019–2021]) and Spain (new). When PIs were used, BTZ and carfilzomib (CFZ) were the most common agents in Germany, Italy, France, and Spain. In the UK, IXA (an oral agent) was preferentially used and may reflect the adjustment of UK clinical practices during the COVID-19 pandemic to prefer oral drugs vs. injected agents, which likely helped to minimize the need for clinic visits and allowed for patient self-administration. Delays between EMA authorization of agents and reimbursement approval is evident in the UK with National Institute for Health and Care Excellence (NICE) approval of LEN in newly diagnosed MM not received until 2019.[24]

Use of mAbs, often as DAR, was common in Germany and increased between 2019 and 2021 in France and Spain. The use of DAR was especially low in the UK, which was likely due to its country-specific approval in 2L and 4L only.[25–27] In Germany, agents are reimbursable and available immediately following regulatory authorization, which may explain why novel treatment use is observed earlier in Germany.[28] In France, recently authorized therapies are less readily accessible; however, some may be granted "Temporary Authorization for Use" (ATU) prior to Health Technology Assessment or commission/reimbursement decisions.[29] In Spain, there are also delays between EMA approval of agents and reimbursement approval; for DAR, this was 22 months. Additionally, there is variability between regions/hospitals subsequently granting approval for prescriptions, which for DAR has been reported as ranging from a median of 5 to 36 months.[30]

DAR and CFZ were the second and third most common 3L agents in Germany. These observations align with a recent retrospective chart review of treatment patterns at multiple centers across Germany between May 2017 and June 2018.[28] In Italy, POM was the second most common 3L agent and <10% of patients used CFZ or DAR, reflecting a delayed uptake of the latter agents in the 3L in clinical practice. Furthermore, CFZ is not typically used for older/frail patients in Italy. Use of conventional chemotherapies (CHTs) (MEL based and Tha based) in Italy could potentially be due to lower drug costs, fewer toxicity concerns, or lack of alternative approved options, particularly in the context of small community hospitals or centers. In Italy, Tha is not typically given to patients with RRMM in the 3L; however, because of its favorable toxicity profile, it may be given during end stages of the disease.

Historical MCR data (2016–2018) from the UK, France, and Spain were generally consistent with formerly published RWE for European countries, such as more frequent use of DAR- and POM-based regimens in the 3L in France and Spain but not the UK.[31] In the new MCR data (2019–2021), 3L regimens broadly reflected treatment guidelines from the European Society for Medical Oncology at the time of data collection (such as greater use of DAR-based combinations), with country-specific differences.[32] For instance, treatment regimens were generally standardized in the UK, possibly reflecting a restricted set of regimens reimbursed within the National Health Service.

Retreatment with PIs or IMiDs in 3L was common in all countries (including historical and new MCR data) but very low with mAbs. Specifically, retreatment with BTZ was common, with a large proportion of patients treated with BTZ in 3L having previously been treated with BTZ in 1L or 2L (range, 66.7% [the UK] to 96.2% [Spain, historical]). This discrepancy could reflect how clinical practice has evolved from 2014 to 2021. The 2021 European Hematology Association and European Society for Medical Oncology guidelines were updated to recommend DAR combinations in 1L with the quadruplet DAR-BTZ-Tha-d (Dara-VTD) as the new standard of care for induction therapy.[4] In 2L we also see a shift in recommendation favoring the use of triplet regimens over doublet.[4] These recommendations of early-line use of triplet and quadruplet therapies may explain the retreatment patterns in 3L where earlier use of major agent classes may necessitate retreatment with the same class of agent used in previous lines.

Comorbidity burden was difficult to assess due to inconsistent data availability across all countries, but the best capture of an overall comorbidity profile was observed in the German claims data, which recorded diagnoses in the different healthcare settings. As such, patients in Germany were frequently reported to have comorbidities, with cardiovascular disease and renal impairment being the most common. These conditions are expected for patients with MM, particularly given their advanced age.[33]

Costs in 3L+ were largely driven by prescription medications, followed by hospitalizations costs. Lower hospitalization costs in Italy vs. Germany may be due to differences in disease management and health system resource allocation as well as variances in patients and symptoms.

4.1 | Strengths and limitations

Since LOTs were not explicitly captured in the claims data, an algorithm based on prescription and procedure codes to classify treatment lines was used, which may have led to misclassification of later LOTs where standard of care is not well established. Regional differences in RW treatment strategies for MM may have existed, limiting the generalizability of the results to the overall national populations. Nevertheless, due to largely uniform healthcare regulations, data entry requirements, and access to health resources, the treatment of patients was not expected to be significantly different across regions within the same country.

In the UK, France, and Spain, where data were acquired from MCRs, missing or implausible entries were possible despite having data monitoring and query steps in place. Historical data were not collected under the same protocol, causing potential minor misalignments to this study that may not be represented in the dataset. Comorbidity data were limited, as treating specialists typically did not have complete information on the overall health profile of a patient unless it was directly relevant and necessary for determining MM treatment decisions. Collectable data were limited to information in patient charts accessible to the reporting center, leading to limited HCRU and costs data. While healthcare structure research was

performed to identify a representative sample, site-specific bias in large treatment centers may have resulted in the selection of patients who were not always fully representative of the treated MM population in each country and subsequently may not have reflected the complete spectrum of treatment patterns in RW clinical practice. For Germany, data were collected from only one sickness fund of the German statutory health insurance. However, all statutory health insurance sickness funds, which cover around 90% of the German population, largely provide the same services stipulated by national regulations, thus minimizing potential bias in the study.

Finally, eligibility criteria required patients to have initiated 3L therapy, thus reflecting a population that survived prior LOTs, leading to survivor bias in the study's MM population by default. Therefore, the interpretation of results in 1L/2L should not be generalized to overall 1L/2L MM patient populations.

5 | CONCLUSIONS

This study provides extensive RW information on clinical practice patterns, HCRU, and costs in patients with RRMM initiating 3L treatment in Europe, which adds to existing RWE for 3L treatment patterns and sequencing. These findings will help inform later-line treatment decisions, primarily for a population with continued unmet needs. From 2016 to 2021, 3L regimens were predominantly IMiD based, which was consistent with prior European studies and treatment guidelines at the time of data collection. The MCR data demonstrated evolving trends from 2016 to 2018 and 2019 to 2021 in the 3L setting, with a clear shift toward triplet combinations and increased anti-CD38 mAb use, presenting insights into recent RRMM clinical practice in Europe. Based on these trends, multiagent combinations with mAbs (triplets and quadruplets) are likely to predominate in the treatment landscape in the future. Furthermore, treatment patterns across all countries in this setting were heterogeneous, and physicians may look to consider those of other countries into their treatment choice decision-making. Finally, the high level of retreatment indicates a clear unmet need for agents with newer mechanisms of action, which may impact sequencing in later lines. Future studies comparing EU data to the US and other regions such as Asia-Pacific to see trends and/or differences in treatment patterns may also be informative.

AUTHOR CONTRIBUTIONS

Conceptualization: Moritz Lehne, K. Martin Kortüm, Karthik Ramasamy, Elena Zamagni, Tim d'Estrubé, Evi Zhuleku, Maya Hanna, Marco Ghiani, Sue Perera. *Formal analysis*: Moritz Lehne, Evi Zhuleku. *Writing—original draft preparation*: Moritz Lehne, K. Martin Kortüm, Karthik Ramasamy, Elena Zamagni, Tim d'Estrubé, Evi Zhuleku, Maya Hanna, Soham Shukla, Marco Ghiani, Ulf Maywald, Thomas Wilke, Lenka Kellermann, Sue Perera. *Writing—review and editing*: All authors. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

ML and EZh are employees of Cytel Inc. KMK has no conflicts of interest. KR received grants funding from Janssen, Amgen, Takeda, GSK, and Celgene/BMS; received honoraria from Janssen, Adaptive Biotech, Amgen, Takeda, AbbVie, Oncopeptides, Celgene/BMS, Pfizer, and GSK; and served as advisor for Janssen, Adaptive Biotech, Amgen, Takeda, AbbVie, Oncopeptides, Celgene/BMS, Pfizer, and GSK. EZa received honoraria from Janssen, BMS, Amgen, Sanofi, GSK, Roche, and Pfizer; and participated in advisory boards for Janssen, BMS, Amgen, Sanofi, GSK, Roche, and Pfizer. MG is a staff member of IPAM e.V. UM has no conflicts of interest to declare, except those potentially related to his employer, AOK PLUS (data provider). TW is a staff member of IPAM e.V.; and has received honoraria from GSK, Novo Nordisk, AbbVie, Merck, BMS, LEO Pharma, Bayer, and Boehringer Ingelheim. LK received grants from BMS, Celgene, Janssen, McKinsey, Stemline/Menarini, Sanofi, GSK, Seagen, Merck-Serono KG Darmstadt, and Oncopeptides. TdE, MH, and SS are employees of GSK. SP was an employee of GSK during the study and is now an employee of Moderna, Inc.

DATA AVAILABILITY STATEMENT

Patient-level data used for this study cannot be made publicly available in accordance with the local laws and policies of the participating institutions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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