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Treatment Patterns in Patients with Refractory/Relapsed Multiple Myeloma in Germany Between 2016 and 2018

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BACKGROUND

- The refractory/relapsed multiple myeloma (RRMM) treatment landscape has increased in complexity in recent years due to the availability of novel agents
  - Bortezomib (V) and lenalidomide (R) are both considered standard of care 1st-line (1L) treatments (before and after stem-cell transplantation [SCT]) for patients with MM
  - Novel proteasome inhibitors (e.g. carfilzomib [K] and ixazomib [I]) and monoclonal antibodies (e.g. daratumumab [D] and elotuzumab [E]) are considered standard of care in the 2nd-line (2L) RRMM setting, with pomalidomide (P) generally retained for use after second relapse (3rd-line treatment and beyond [3L+])
- Based on these advances in the management of MM, treatment guidelines have been established by national and international expert committees.1,2 However, it is unclear if novel agents are already being implemented in routine clinical practice3
- Therefore, the purpose of this analysis was to evaluate the treatment landscape in RRMM over the past 3 years in real-world clinical practice in Germany

METHODS

- In this non-interventional study, we retrospectively analyzed data from a German longitudinal database, TherapyMonitor, for patients receiving 2L treatment and beyond for RRMM between January 1, 2016 and December 31, 2018
- TherapyMonitor is a database comprising anonymized data on the course of therapy in MM, derived from a representative sample of treatment centers in Germany (university and non-university hospitals, and office-based hematology practices)
  - Centers in the TherapyMonitor database were identified through searches of publicly accessible platforms for centers treating MM. The final sample of 98 centers was distributed across institution types (university hospital: 11%; non-university-based hospital: 36%; office-based practice: 52%), reflecting the distribution of patients being treated for MM in Germany4
  - Data on the 2,367 patients' entire treatment history of RRMM were retrospectively included in the database and updated quarterly
- To be eligible for inclusion in this analysis, patients needed to: have a diagnosis of MM according to the International Classification of Diseases, Tenth Revision, Clinical Modification Diagnosis Code C90.0: MM; have initiated treatment with one of the specified agents (K, V, R, P, I, D, or E) during the reporting period (2016–2018); and have received at least one line of MM therapy prior to treatment during the reporting period. The final sample comprises 2020 patients

Objectives and Analyses

- The primary objective was to describe patient demographics and clinical characteristics (collected at initiation of most recent line of therapy), and treatment details, by line of therapy (2L and 3L+)
- Treatment patterns were described until the censor date (December 31, 2018). Data were analyzed overall, by treatment line, by most recent treatment, and by year of treatment initiation (2016, 2017, or 2018)
  - 1L treatment use was assessed by looking at the treatment prior to 2L therapy
- The secondary objective was to describe treatment duration for patients receiving novel regimens
- D isease and patient characteristics were measured at the time of the latest treatment line
- Frailty score was calculated based on the methods of Facon et al 2019 using the patient's age, Eastern Cooperative Oncology Group performance status and their modified Charlson Comorbidity Index (CCI) score5
- Treatment duration was estimated using the Kaplan-Meier method, including both ongoing and completed treatment regimens until censor date. Median durations were reported (where reached)

RESULTS

Patient Characteristics

- Of the entire study population of 2020 patients with RRMM, 973 (48%) patients had reached 3L+ treatment by the censor date (December 31, 2018)
- Patient demographics and disease characteristics are shown in Table 1
  - Overall, 15% of patients received SCT in 1L

Table 1. Patient Demographics and Clinical Characteristics Collected at Initiation of Most Recent Treatment

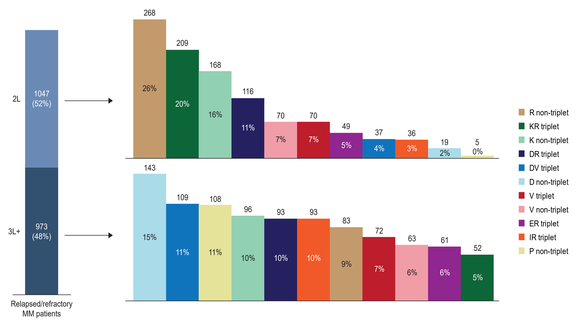
	Most recent line of treatment		
	2L (n=1047)	3L+ (n=973)	Total (n=2020)
Age, median (range) – years	70 (42–92)	71 (32–94)	71 (32–94)
Age category, n (%) – years			
≤65	243 (23.2)	192 (19.7)	435 (21.5)
66–75	579 (55.3)	515 (52.9)	1094 (54.2)
>75	225 (21.5)	266 (27.3)	491 (24.3)
Sex, n (%) – male	590 (56.4)	602 (61.9)	1192 (59.0)
ISS stage, n (%)			
I or II	247 (23.6)	142 (14.6)	389 (19.3)
III	592 (56.5)	604 (62.1)	1196 (59.2)
Unknown/NA	208 (19.9)	227 (23.3)	435 (21.5)
ECOG PS, n (%)			
0 or 1	594 (56.7)	492 (50.6)	1086 (53.8)
2–4	422 (40.3)	439 (45.1)	861 (42.6)
Unknown/NA	31 (3.0)	42 (4.3)	73 (3.6)
Modified CCI score, n (%)			
0	463 (44.2)	433 (44.5)	896 (44.4)
1	229 (21.9)	221 (22.7)	450 (22.3)
2–4	316 (30.2)	285 (29.3)	601 (29.8)
≥5	23 (2.2)	22 (2.3)	45 (2.2)
Unknown/NA	16 (1.5)	12 (1.2)	28 (1.4)
Frailt y, n (%)			
Frail	611 (58.4)	609 (62.6)	1220 (60.4)
Not frail	420 (40.1)	351 (36.1)	771 (38.2)
Unknown/NA	16 (1.5)	13 (1.3)	29 (1.4)
SCT, n (%) – received in 1L	150 (14.3)	160 (16.4)	310 (15.3)

1L, 1st-line therapy; 2L, 2nd-line therapy; 3L+, 3rd-line therapy and beyond; CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; NA, not available; SCT, stem-cell transplantation

Treatment Distribution

- Regarding the patients' most recent treatment line across the study period, in 2L patients (n=1047) R non-triplet (26%) was the most common treatment regimen, with 20% and 11% of patients receiving KR and DR triplets, respectively. In 3L+ patients (n=973), the most common treatments were D-based regimens (35% [15% were non-triplet, 11% were DV triplet, and 10% were DR triplet]) (Figure 1)
- Overall, 634/1047 (61%) 2L patients and 647/973 (66%) of 3L+ patients received treatment with a novel agent
  - Novel triplet regimens were preferred in 2L (447/634 [71%]) and 3L+ (408/647 [63%]); non-triplet use comprised 29% of 2L and 37% of 3L+ novel agent-containing regimens
- In patients who were most recently receiving 2L treatment, the most frequent prior regimens were V triplets/non-triplets (45%/19%) and R non-triplets (15%) (Figure 2), in accordance with clinical guidelines2
  - The low frequency of R non-triplet use is likely because such regimens were only approved for 1L use in non-SCT-eligible patients in 2015 and for post-SCT maintenance therapy in 2017
- In 3L+ patients, the most frequent prior treatments were R non-triplets (27%) and K non-triplets (16%)
  - Of the patients currently receiving 3L+ treatment, 51% had received a prior immunomodulatory drug-based regimen as either their 2L (36%) or 1L (15%) treatment

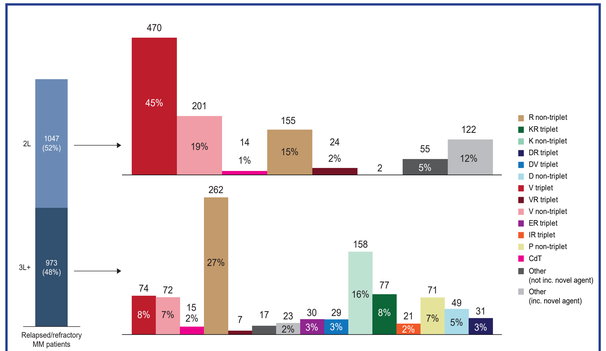
Figure 1. Distribution of 2L and 3L+ Regimens in Patients[a] with Relapsed/Refractory MM



[a]555 patients were excluded as they had been assigned to a specific regimen group

D, daratumumab; E, elotuzumab; I, ixazomib; K, carfilzomib; MM, multiple myeloma; P, pomalidomide; R, lenalidomide; V, bortezomib

Figure 2. Distribution of Prior Treatments for Patients with Relapsed/Refractory MM Currently Receiving 2L or 3L+ Treatment

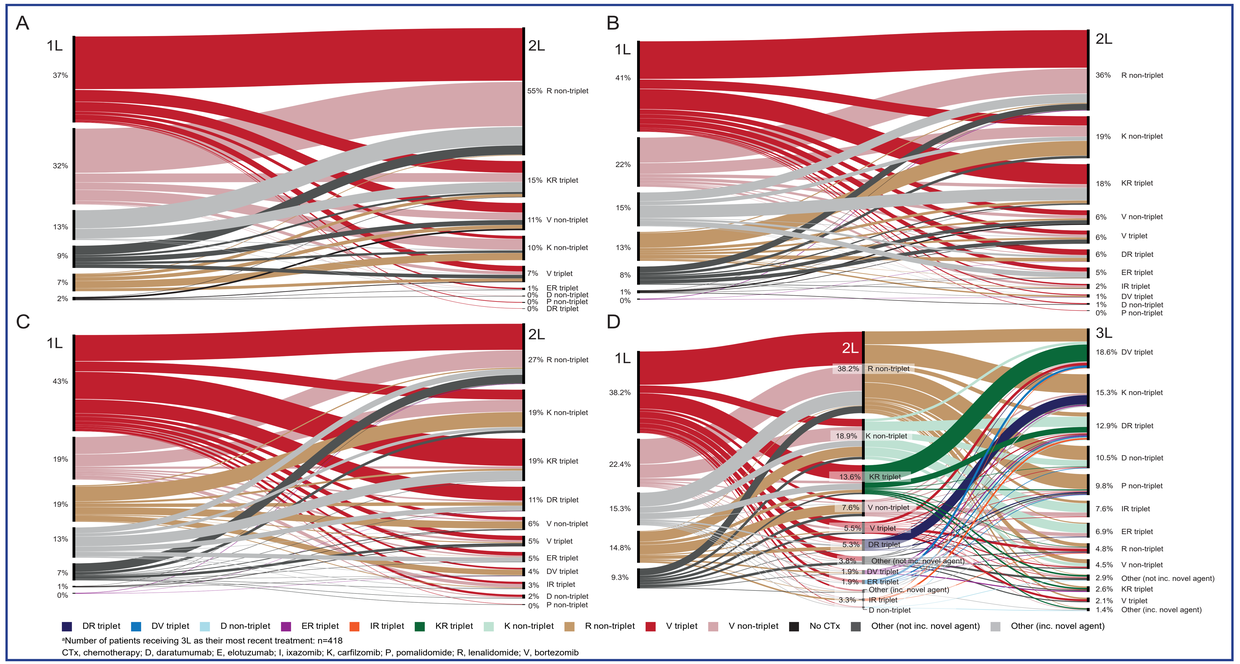


CdT, cyclophosphamide, dexamethasone and thalidomide; D, daratumumab; E, elotuzumab; I, ixazomib; K, carfilzomib; MM, multiple myeloma; P, pomalidomide; R, lenalidomide; V, bortezomib

Treatment Patterns and Sequence Over Time

- Regarding trends over time and considering all treatments, V triplet was the most frequently used regimen prior to 2L (ranging from 37% of regimens in 2016 to 43% in 2018) in-line with clinical guidelines (Figures 3A–C)
  - Over the same time period, V non-triplet use decreased from 32% in 2016 to 19% in 2018 and R non-triplet use more than doubled (from 7% to 19%), suggesting that R non-triplets have increasingly started to replace V non-triplets since their approval in 2015
- R non-triplets were the leading 2L regimen in 2016 comprising 55% of regimens. Following approval of 2L K-based regimens in November 2015 and approval of E-, D-, and I-based regimens during 2016–2017, 2L use of novel agents increased and R non-triplet use halved (to 27% in 2018)
- Patients receiving K- or D-based triplets at 2L predominantly received V triplet regimens at 1L
- Most 2L patients receiving non-triplet regimens also received V or R non-triplets at 1L
- The complete sequence of therapies prior to 3L+ and 2L in 2018 is shown in Figure 3D. These data suggest that most current 3L+ patients had already been treated with a novel agent during prior (2L) therapy

Figure 3. Sequence of Treatments Prior to 2L in A) 2016, B) 2017, and C) 2018, and D) Sequence of Treatments Prior to 3L[a], in 2018



[a]Number of patients receiving 3L as their most recent treatment: n=418

CTx, chemotherapy; D, daratumumab; E, elotuzumab; I, ixazomib; K, carfilzomib; P, pomalidomide; R, lenalidomide; V, bortezomib

Treatment Duration – All Treatments

- Overall, D or E triplet and KR triplet regimens were associated with the longest treatment durations compared with the other regimens identified in the study (Table 2); median durations had not yet been achieved with D- and E-triplets (62% of patients were still on treatment). Among non-triplet regimens, K reached the longest treatment duration

Table 2. Kaplan-Meier Estimates of Treatment Duration

Regimen	Overall n (% who had completed treatment)	Treatment duration 2L+ – months, KM estimated (median, 95% CI)
K non-triplet	535 (70)	9.6 (8.3–10.9)
KR triplet	411 (55)	12.8 (11.0–14.6)
R or P non-triplet	1088 (78)	8.3 (7.7–8.9)
V or I triplet	434 (71)	5.9 (5.3–6.5)
V non-triplet	262 (81)	5.6 (5.4–5.8)
D non-triplet	308 (77)	5.2 (4.8–5.5)
D or E triplet	592 (38)	13.1 (11.3–14.6)

CI, confidence interval; D, daratumumab; E, elotuzumab; I, ixazomib; K, carfilzomib; KM, Kaplan-Meier; P, pomalidomide; R, lenalidomide; V, bortezomib

DISCUSSION

- This analysis helps us to understand the real-world usage of novel MM agents in Germany over a 3-year time period
  - As the analysis only includes data until December 2018, it does not reflect the latest changes in the German treatment landscape; e.g. changes in 1L treatment and approval of triplet combinations without R, are not taken into account
  - Frailty is significantly associated with reduced overall survival in patients with MM.6 These new therapies were implemented in a real-world population of predominantly frail elderly patients (most were >65 years, almost one-quarter were >75 years old). Although this is older than the patients included in the trials that led to the approval of these drugs7–11 and also older than the patients included in a previous real-world study conducted in Europe11,12 outcomes were similar in terms of treatment duration.13-15 Interestingly, some clinical studies have shown that novel treatments for RRMM can positively impact patient quality of life16
  - After R non-triplets became available for 1L use in non-SCT eligible patients in 2015, there was a shift in the use of R non-triplets from 2L to 1L, replacing 1L V non-triplets and resulting in greater use of 2L novel non-triplets in this analysis
  - Most 3L+ patients (76%) received treatment with a novel agent-containing regimen, with 49% receiving triplet therapy. Similarly, many patients receiving 2L R non-triplets received 3L+ novel agent-based triplet therapy, suggesting that novel agent-based triplet therapy is sufficiently tolerable for this highly pretreated, mostly frail population
  - There have already been advances in the RRMM treatment landscape; notably, 48% of those included in this analysis reached 3L+ by the censor date

LIMITATIONS

- Some variables were missing for CCI score and frailty calculations
- The differences in launch date/availability in the German market over the 3 years were not taken into account (not all agents were available in 2016)
- This sample should be representative of patients with RRMM in Germany, as all the key types of treatment center were included and contributed data

CONCLUSIONS

- Multiple approvals of novel agents for the treatment of RRMM in Europe resulted in changes in the treatment landscape, with a more immediate impact observed in countries with earlier access to the new drugs
- In this population of patients with RRMM, we found increased use of R non-triplets and decreased use of V non-triplets prior to 2L between 2016 and 2018
- Patients receiving 1L non-triplets generally received 2L non-triplet treatment; those receiving 1L triplets generally also received 2L triplet treatment
- 2L D-based and K-based regimen use increased between 2016 and 2018
- 3L+ patients were mostly R-pretreated due to the high use of 2L R-based triplets and increasing use of 1L R non-triplets
- Antibody-based triplet regimens and K-based triplet and non-triplet regimens were associated with the most prolonged treatment durations
- Germany may serve as an example for the adoption of novel treatments as these data demonstrate that all agents for the treatment of RRMM approved since 2015 have been incorporated into clinical practice

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