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Original Article

Descriptive analysis of multiple myeloma patients in a real-world setting from the Finnish Hematology Registry

Giorgi Tskhvarashvili[1], Katja M Hakkarainen[2,3], Riho Klement[4,5], Pia Vattulainen[6], Tatu Miettinen[7,8], Saku Torvinen[9], Juha Lievonen[10]

[1]Global Database Studies, IQVIA, Tallinn, Estonia; [2]Global Database Studies, IQVIA, Mölndal, Sweden; [3]Epidemiology and Real-World Science, RWE Scientific Affairs, Parexel International, Gothenburg, Sweden; [4]Global Database Studies, IQVIA, Tartu, Estonia; [5]Aastat Estonia OÜ, Tallinn, Estonia; [6]Global Database Studies, IQVIA, Espoo, Finland; [7]Takeda Finland Oy, Helsinki, Finland; [8]Medaffcon Oy, Espoo, Finland; [9]MedEngine Oy, Helsinki, Finland; [10]Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

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Abstract: Objective: Evidence on multiple myeloma (MM) in the real-world settings (RWS) is scarce. Our study describes patient characteristics, treatment patterns, the overall response rate (ORR), overall survival (OS), and time to next treatment line (TTNT) in MM patients in RWS in Finland. Materials and methods: This observational cohort study included patients with MM who were ≥18 years of age from the Finnish Hematology Registry. The patients from Helsinki and Uusimaa districts had been diagnosed with MM during 2010-2015 and followed up until 2017. Results: This study included 224 patients with a median age of 67.7 years. Of note, 60% of the patients <70 years of age had received autologous hematological stem-cell transplantation (HSCT), while no patient ≥70 years of age had been treated with HSCT. For first-line treatment, the ORR was 81.9%, the median TTNT 8.5 months, and the median duration of treatment 3.2 months. Median OS was 62.4 months for all patients and 48.2 months for patients with high-risk cytogenetics [del(17p), t(4;14), t(4;16), t(4;20)]. Conclusion: This study reflects myeloma treatment practice in Finland in the era when bortezomib and lenalidomide were still regarded as "novel" treatments. Although first-line TTNT was short, the OS was comparable with other RWS studies. This reflects the need to change the first-line treatment due to both toxicity and the suboptimal response seen in real-world practice. Further, the shorter OS among patients with high-risk cytogenetics highlights the need for identifying such patients and improving their treatment paradigms as early as possible.

Keywords: Multiple myeloma, epidemiology, response rate, survival, registry, Finland

Introduction

Multiple myeloma (MM), a clonal hematologic malignancy of plasma cells, accounts for approximately 1% of all reported cancers and is the second most common hematologic malignancy worldwide [1]. Globally, 160,000 new cases of MM are detected annually, and in Finland, the International Agency for Research on Cancer [2] estimated approximately 400 new cases in 2018. MM remains incurable with current therapies and patients have multiple relapses throughout the course of their disease. Typically, the disease becomes more aggressive upon relapse, with the duration of response becoming shorter with each successive line of therapy, eventually not responding to the treatments available (refractory disease) [3]. MM mainly affects elderly (median age 70 years) individuals, and male patients are more likely to develop the disease than female patients [4]. Genotypic factors and clinical manifestations affect the prognosis and treatment response. These high-risk biomarkers include cytogenetic abnormalities (defined as deletion 17p [del(17p)], translocation [t(4;14)], and/or translocation [t(14;16)]) [5]. The most typical clinical manifestations of MM include hypercalcemia, renal failure, anemia, and bone disease (CRAB) [6]. Based on previous studies conducted among MM populations and cytogenic findings according to fluorescence in situ hybridization (FISH), del(17p13) is the most common high-risk cytogenetic marker in all treatment lines [7,

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8]. Further, lytic bone lesions and anemia are the most common CRAB components, regardless of the treatment line [9-13].

The national treatment guidelines in Finland (2017) [14] specify hematological stem-cell transplantation (HSCT) as a front-line treatment in patients ≤70-75 years of age. HSCT is most commonly autologous (autoHSCT), but may also be allogeneic in few patients [15]. As elderly or frail patients are not considered eligible for autoHSCT, a combination of treatments such as bortezomib, melphalan and prednisone for 8-9 cycles (or 12 months) are used. Lenalidomide with dexamethasone was reimbursed as a first-line treatment in Finland for transplant-ineligible patients in 2016.

Overall survival (OS) in MM patients has improved significantly during the last decade, mainly due to developments in HSCT and novel drug treatments [16]. Despite improved treatment options, their safety and efficacy, when based on randomized controlled trials (RCTs), may not be generalizable to real-world settings (RWS). In previous observational studies [17], the median OS in RWS was noted to be only 37-48 months in the first-line setting. Although a few observational studies on MM in RWS have investigated patient characteristics, treatment patterns, overall response rate (ORR), OS, and time to next treatment line (TTNT) [9-11, 17-26], prior studies in Finland [9, 27] do not include a comprehensive characterization of MM patients (e.g., cytogenetic findings).

The objective of the present observational cohort study was to describe patient characteristics, treatment patterns, and the ORR in MM patients in Finland by treatment line. An additional objective was to describe the OS and TTNT by treatment line and OS by the selected patient characteristics.

Materials and methods

This retrospective observational cohort study used the Finnish Hematology Registry (FHR) as a data source. The study included patients diagnosed with MM between 1 January 2010-31 December 2015, aged ≥18 years at diagnosis, for whom at least one treatment initiation date could be identified during the period 1 January 2010-31 December 2016 and who had a minimum of 1 year (until 31 December 2017) of follow-up. Patients were excluded if they had multiple hematological diagnoses for which treatments could not be differentiated. This study only included patients from Finland's largest hospital districts, Helsinki and Uusimaa (HUS), with a population of 1.7 million, representing 30% of the population in Finland. The inclusion and exclusion criteria are detailed in **Figure 1**.

The patients were followed up from the first treatment initiation date (index date) recorded in the FHR during the study period. Follow-up was continued until death or the end of the follow-up period (31 December 2017), whichever occurred first.

MM diagnosis was based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: C90.0) [20] or, if available, the International Classification of Diseases for Oncology (ICD-O: 9732) [21] codes. The corresponding dates of diagnoses were used to define the study cohort entry date. When available, the date of the ICD-O code was used to exclude preceding plasmacytoma diagnoses.

Patient characteristics

Variables related to patient characteristics are defined in Supplementary Table 1. Demographic characteristics included sex and age at diagnosis. Disease characteristics included cytogenic findings, according to FISH and CRAB definitions.

Treatment patterns, overall response rate, overall survival, and time to the next treatment line

Collected treatment data included treatment duration, treatment with autoHSCT, and any other novel or conventional MM treatment during follow-up. ORR was defined as the percentage of cohort patients with at least a partial response, as recorded at least once within a treatment line using the International Myeloma Working Group criteria. OS was defined as the time (months) from MM treatment initiation in each treatment line to death. TTNT was defined as the length of time (in months) between the start of a treatment line and the start of the next treatment line. Full definitions used in the study are available in Supplementary Table 1.

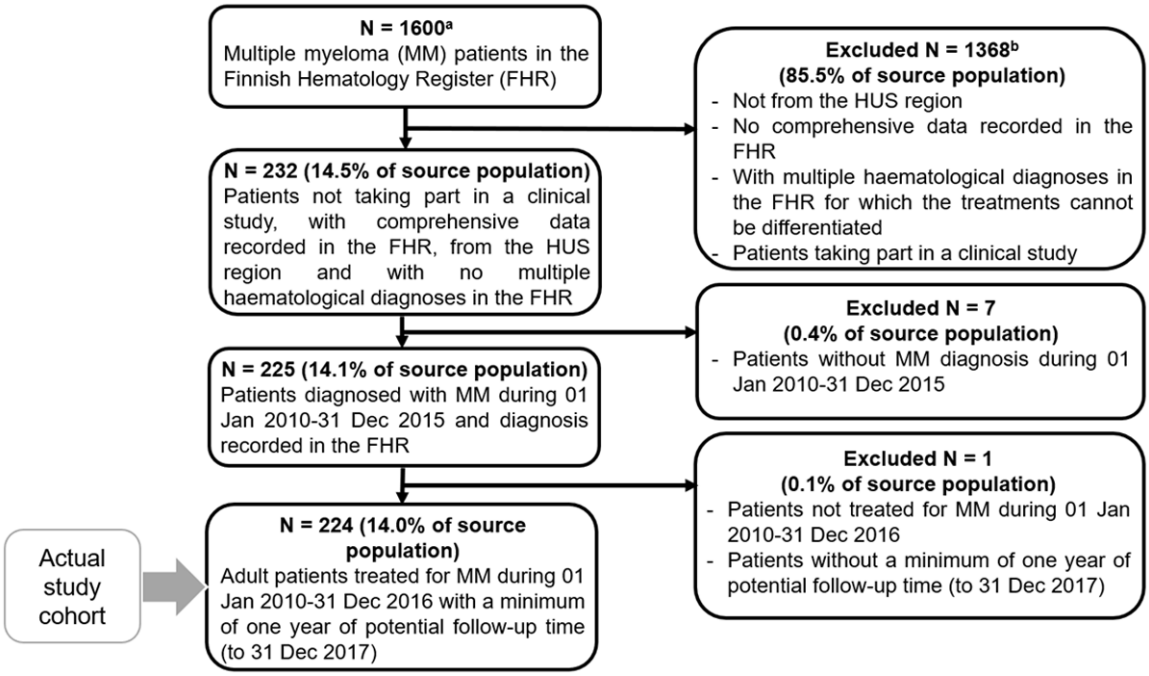

Figure 1. Flow diagram of multiple myeloma patients included in study cohort. Abbreviations: FHR, Finnish Hematology Registry; HUS, Helsingin ja Uudenmaan sairaanhoitopiiri (Eng. Helsinki and Uusimaa Hospital Districts); MM, multiple myeloma; N, number of patients. [a]Based on an estimate. [b]The number of patients excluded for the listed reasons was unknown. However, most patients were excluded due to not being from the HUS region (estimated 70% of the excluded), while a few patients were anticipated to be excluded due to participating in a clinical study.

Statistical analysis

All analyses were descriptive. The number and percentage of patients with each known characteristic were stratified by treatment line. For treatment pattern variables, the number and percentage were described for all patients and by treatment line. Treatment with autoHSCT or any other MM treatment was stratified by age categories, while the treatment duration was stratified by treatment line.

The ORR was reported as a percentage, along with the corresponding 90% confidence interval (CI), using the Clopper-Pearson method [22]. ORR was stratified by treatment line and described in subgroups by treatment regimen and HSCT status. Observational independence was assumed when calculating the 90% CI for the all the treatment lines, although multiple observations per patient were possible.

The median OS was reported descriptively, including the 90% CI for the median, examined via the Kaplan-Meier (KM) estimator, and reporting the number and proportion of patients censored at risk and with events. The median TTNT was also reported descriptively, including the 90% CI for the median, examined via the Aalen-Johansen estimator, including death as a competing risk, and reporting the number and proportion of patients censored at risk, with events, and who died. The OS was stratified by treatment line, patient characteristics, and FISH findings. Stratification variables and subgroups are defined in Supplementary Table 1. Missing data are classified as "unknown". R software 3.5.0 was used for all analyses [23].

Ethics

This study was performed in accordance with the Declaration of Helsinki and in compliance with national laws. Ethical approval was obtained from the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital districts [24]. All patients included in the FHR provided informed consent prior to participating in studies using FHR data. The study was conducted per protocol, with analyses preplanned prior to data access [25].

Results

In total, 224 patients were included in this study (**Figure 1**). The mean time of follow-up

Table 1. Patient characteristics at multiple myeloma diagnosis by treatment line (N=224 patients)

Patient characteristics	Line 1	Line 2	Line 3	Line 4	Line >4
Patients/lines, n/N	224 patients/224 lines	183 patients/183 lines	132 patients/132 lines	68 patients/68 lines	36 patients/88 lines
Demographic characteristics[a]					
Sex, n (%)					
Male	118 (52.7)	96 (52.5)	71 (53.8)	39 (57.4)	57 (64.8)
Female	106 (47.3)	87 (47.5)	61 (46.2)	29 (42.6)	31 (35.2)
Age in years					
37-50, n (%)	13 (5.8)	9 (4.9)	5 (3.8)	2 (2.9)	4 (4.5)
51-60, n (%)	37 (16.5)	32 (17.5)	22 (16.7)	11 (16.2)	20 (22.7)
61-70, n (%)	93 (41.5)	74 (40.4)	52 (39.4)	25 (36.8)	30 (34.1)
71-80, n (%)	74 (33.0)	64 (35.0)	51 (38.6)	29 (42.6)	32 (36.4)
>80, n (%)	7 (3.1)	4 (2.2)	2 (1.5)	1 (1.5)	2 (2.3)
Range (min-max)	(37.0-87.4)	(45.2-86.0)	(49.1-82.6)	(49.1-81.6)	(49.1-81.6)
Mean (SD)	66.8 (9.0)	67.0 (8.5)	67.6 (7.9)	67.9 (7.9)	66.3 (8.4)
Median (Q1-Q3)	67.7 (62.3-73.2)	67.7 (62.0-72.9)	68.3 (62.6-73.4)	69.3 (63.2-73.5)	68.4 (60.1-73.2)
FISH findings, n (%)					
High-risk cytogenetics[b]	37 (16.5)	32 (17.5)	21 (15.9)	12 (17.6)	18 (20.5)
del(17p13)	22 (9.8)	18 (9.8)	11 (8.3)	7 (10.3)	10 (11.4)
t(14;20)	1 (0.4)	1 (0.5)	1 (0.8)	0 (0.0)	0 (0.0)
t(14;16)	8 (3.6)	8 (4.4)	6 (4.5)	3 (4.4)	6 (6.8)
t(4;14)	10 (4.5)	9 (4.9)	6 (4.5)	5 (7.4)	6 (6.8)
Intermediate-risk cytogenetics[c]	24 (10.7)	21 (11.5)	17 (12.9)	9 (13.2)	14 (15.9)
gain(1q)	39 (17.4)	34 (18.6)	26 (19.7)	14 (20.6)	19 (21.6)
del(1p32 or 1p36)	6 (2.7)	5 (2.7)	5 (3.8)	3 (4.4)	2 (2.3)
Standard-risk cytogenetics[d]	163 (72.8)	130 (71.0)	94 (71.2)	47 (69.1)	56 (63.6)
t(11;14)	16 (7.1)	13 (7.1)	10 (7.6)	5 (7.4)	1 (1.1)
del(13q)	66 (29.5)	50 (27.3)	39 (29.5)	23 (33.8)	35 (39.8)
Any other or no abnormality[e]	51 (22.8)	36 (19.7)	21 (15.9)	7 (10.3)	13 (14.8)
CRAB component, n (%)					
Hypercalcemia	35 (15.6)	31 (16.9)	24 (18.2)	17 (25.0)	11 (12.5)
Anemia	106 (47.3)	93 (50.8)	71 (53.8)	40 (58.8)	55 (62.5)
Renal dysfunction	58 (25.9)	45 (24.6)	31 (23.5)	16 (23.5)	6 (6.8)
Lytic bone lesions	156 (69.6)	128 (69.9)	93 (70.5)	49 (72.1)	57 (64.8)
Unknown	21 (9.4)	18 (9.8)	12 (9.1)	7 (10.3)	11 (12.5)

Abbreviations: CRAB, C, calcium (elevated), R, renal failure, A, anemia, B, bone lesions; FISH, fluorescence in situ hybridization; MM, multiple myeloma; n/N, number of patients/treatment lines; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile. [a]Defined at the time of MM diagnosis. [b]At least one high-risk FISH finding. FISH findings are defined exclusively at diagnosis because it is not clinical practice in Finland to follow-up cytogenetics after diagnosis. However, the descriptive results differ by treatment line because the results describe these characteristics (at diagnosis) for the MM patients left in each treatment line. [c]At least one intermediate-risk FISH finding; no high-risk FISH findings. [d]Any other FISH finding, excluding high-risk and intermediate-risk FISH findings. [e]Includes any other FISH findings not listed above, and "no FISH findings" category (also when FISH was not tested), and excludes high-risk and intermediate-risk cytogenetics.

Table 2. Treatment patterns by age group: patients treated with autologous hematopoietic stem-cell transplant or any multiple myeloma treatment during follow-up (N=224 patients in total)

Age at start of treatment line 1	Number of patients, n	Patients who had autoHSCT during follow-up, n (%)	Patients with any MM treatment during follow-up, n (%)
<66 years	94	58 (61.7)	94 (100.0)
66-69 years	40	23 (57.5)	40 (100.0)
Total under 70 years	134	81 (60.4)	134 (100.0)
≥70 years	90	0 (0)	90 (100.0)
Total	224	81 (36.2)	224 (100.0)

Abbreviations: AutoHSCT, autologous hematopoietic stem-cell transplant; MM, multiple myeloma; n, number of patients.

Table 3. Treatment patterns: treatment duration by treatment line and in total for all treatment lines (N=224 multiple myeloma patients in treatment line 1)

Treatment duration variable[a]	Line 1	Line 2	Line 3	Line 4	Line >4	Total
Patients/lines, n/N	224/224	183/183	132/132	68/68	36/88	224/695
Unknown, n (%)	0 (0.0)	7 (3.8)	13 (9.8)	4 (5.9)	5 (5.7)	29 (4.2)
Range, in months (min-max)	(0.1-44.1)	(0.0[b]-36.8)	(0.1-42.5)	(0.1-26.2)	(0.0-15.3)	(0.0-44.1)
Mean, in months (SD)	4.6 (4.9)	6.5 (7.5)	6.5 (8.1)	6.1 (6.5)	3.5 (3.6)	5.5 (6.4)
Median, in months (Q1-Q3)	3.2 (2.2-5.6)	4.4 (1.8-7.5)	3.6 (1.3-8.1)	3.4 (1.3-9.4)	2.3 (0.9-5.0)	3.4 (1.7-6.9)

Abbreviations: n/N, number of patients/treatment lines; SD, standard deviation; Q1, 1st quartile; Q3, 3rd quartile. [a]At the start of each treatment line. [b]Includes e.g., one day of treatment as this is in months.

was 40.6 months (standard deviation [SD] 22.6), and 54.9% of the patients were alive at the end of the study period (i.e., 31 December 2017) (**Table 1**). Of the 224 patients in treatment line 1, 183 patients progressed to treatment line 2, and 41 did not have more lines due to death or end of follow-up; furthermore, 132 patients progressed to line 3, 68 to line 4, and 36 to line 5.

Patient characteristics

In total, 52.7% of the MM patients were male (**Table 1**). The median age at diagnosis was 67.7 (Q1-Q3: 62.3-73.2) years, with 41.5% being diagnosed at 61-70 years of age and the youngest patient being diagnosed at 37 years of age. In treatment line 1, 16.5% of the patients had at least one high-risk cytogenetic finding, while 10.7% had at least one intermediate-risk finding without high-risk cytogenetic findings. Most patients (72.8%) had standard-risk cytogenetic findings, without high or intermediate-risk findings. Lytic bone lesions (69.6%) were the most common CRAB feature, followed by anemia (47.3%), at the time of diagnosis.

Treatment patterns

Of note, 36.2% of patients were treated with autoHSCT across all treatment lines (**Table 2**), with 60.4% of patients being <70 years of age and receiving an autoHSCT, while no patients ≥70 years of age received autoHSCT. The median treatment duration in treatment line 1 was 3.2 months (Q1-Q3: 2.2-5.6 months) and 3.4 months (Q1-Q3: 1.7-6.9 months) for the total cohort, including all treatment lines. Overall, the medians ranged from 2.3 to 4.4 months across treatment lines (**Table 3**).

Overall response rate

The ORR of any treatment across all treatment lines was 64.5% (90% CI: 61.1-67.7%) (**Table 4**). The ORR, regardless of the treatment received, was 81.9% (90% CI: 76.8-86.3%) in line 1 and declined gradually in later treatment lines to 24.7% (90% CI: 16.6-34.3%) in line >4. For conventional therapies, the ORR across all treatment lines was 50.0%-57.1%, while the response across all treatment lines was 53.8%-79.5% for novel therapies without HSCT and reached 91.7%-100.0% for novel therapies with HSCT (Supplementary Table 2). When HSCT status was considered, the ORR in total was 98.8% (90% CI: 94.2-99.9%) for single autologous transplants.

Overall survival

Among the 224 MM patients, the median OS in treatment line 1 was 62.4 months (90% CI:

Table 4. Overall response rate for any treatment by treatment line and in total for all treatment lines (N=224 multiple myeloma patients in treatment line 1)

Treatment line (number of all treatment lines)[a]	n/N	ORR % (90% CI)
1 (224)	163/199	81.9 (76.8-86.3)
2 (183)	116/162	71.6 (65.2-77.4)
3 (132)	66/106	62.3 (53.9-70.1)
4 (68)	25/62	40.3 (29.8-51.6)
>4 (88)	18/73	24.7 (16.6-34.3)
Total (695)	388/602	64.5 (61.1-67.7)

Abbreviations: CI, confidence interval; n/N, number of patients/the number of lines with existing disease status records. [a]Including treatment lines with missing disease status, which were excluded from the denominator.

54.9-73.5 months) (**Table 5**), while in lines 4 and 5, the median OS was 18.1 and 12.0 months, respectively. The KM curves illustrated the pattern of shorter OS in later treatment lines (**Figure 2**).

Among patients with FISH findings, the descriptive median OS in treatment line 1 seemed longer among patients with standard-risk FISH findings (68.0 months) than among patients with intermediate-risk (62.4 months) or high-risk (48.2 months) cytogenic findings (**Table 5**). The pattern of shorter OS for patients with high-risk FISH findings was also detected in the KM curves (**Figure 3**).

Time to the next treatment line

Among the 224 MM patients, the median TTNT in treatment line 1 was 8.5 months (90% CI: 6.1-12.8) (**Table 6**), while in subsequent treatment lines, the median TTNT was longer. The Aalen-Johansen curves visualized the longer TTNT in later treatment lines (**Figure 4**).

Discussion

The demographics and characteristics of MM patients in this cohort study are well aligned with those of previous studies in Finland [9] and elsewhere [10, 11, 13, 17-19, 26, 28]. The findings from the FISH analysis in a small proportion of patients (16%-20%) with high-risk cytogenetic findings versus those with standard-risk cytogenetic findings are also in accordance with previous reviews by Rajan et al. [7] and Corre et al. [8], as well as the findings of an American study conducted among patients with smoldering myeloma (of whom nearly half developed MM) [29] and an RCT in Finland [15]. Compared with previous studies, fewer patients in this study had intermediate-risk FISH findings, probably due to differing risk categorizations of FISH. Further, the results from FISH at the beginning of the study period were not fully comparable with those after 2012, since the use of plasma-cell selection (CD138 selection) for FISH testing was introduced to the study population in 2013.

Our study demonstrated that physicians in Finland were adherent to treatment guidelines during the study period [14], and based on the results, most MM patients were <70 years of age. However, no patients ≥70 years of age were treated with autoHSCT.

However, the short median treatment durations of approximately 2-4 months in all lines indicate that finding a suitable treatment for MM patients can be a challenge. Such short treatment durations can be explained by the switching of treatments due to inadequate response or treatment-related toxicities [14]. Moreover, the longer mean treatment durations versus medians could be due to outlier patients. The treatment duration is, however, expected to be longer than the study period because maintenance treatment has become increasingly common. The results regarding short treatment durations demonstrate the challenge of finding a suitable treatment for MM patients and warrant more effective treatments.

The ORR, regardless of treatment, was the best in treatment line 1 and expectedly decreased in subsequent lines, which indicates a lack of adequate response as the disease progressed. The high ORR among patients who received HSCT (98.8%) and complete response after first-line treatment versus patients who did not receive HSCT were also aligned with the results of another European study by Szabo et al. [28].

By and large, our results regarding OS were comparable with other RWS studies [7, 9, 17, 18, 30]. However, the median OS of 62.4 months in treatment line 1 among these patients with MM from Finland was longer compared with that observed in other countries

Table 5. Median overall survival by treatment line and stratified by FISH findings (N=224 multiple myeloma patients in treatment line 1)

Variable	Line 1	Line 2	Line 3	Line 4	Line 5
Number of patients at risk, n (%)	224 (100.0)	183 (100.0)	132 (100.0)	68 (100.0)	36 (100.0)
Number of patients with event, n (%)	101 (45.1)	92 (50.3)	79 (59.8)	50 (73.5)	28 (77.8)
Number of patients censored, n (%)	123 (54.9)	91 (49.7)	53 (40.2)	18 (26.5)	8 (22.2)
Q1 OS, months (90% CI)	29.9 (23.4-37.7)	16.2 (13.1-22.1)	8.5 (4.5-11.2)	4.8 (3.6-10.5)	6.0 (3.4-10.7)
Median OS, months (90% CI)	62.4 (54.9-73.5)	40.8 (35.2-52.3)	23.4 (17.4-29.1)	18.1 (12.6-22.3)	12.0 (10.4-16.4)
Q3 OS, months (90% CI)	NA (77.0-NA)	71.2 (71.0-NA)	44.7 (33.9-NA)	25.6 (24.2-41.7)	20.9 (15.8-NA)
Stratified[a] by FISH findings	Line 1	Line 2	Line 3	Line 4	Line 5
FISH findings[b]					
High-risk cytogenetics[c], median OS in months (90% CI)	48.2 (32.8-NA)	29.2 (16.2-53.7)	18.0 (13.0-29.8)	12.7 (11.6-25.4)	9.5 (8.2-NA)
Intermediate-risk cytogenetics[d], median OS in months (90% CI)	62.4 (39.2-NA)	39.7 (35.2-NA)	30.4 (27.0-NA)	23.8 (6.0-NA)	16.4 (2.1-NA)
Standard-risk cytogenetics[e], median OS in months (90% CI)	68.0 (57.3-75.5)	46.6 (40.8-53.1)	23.1 (16.0-31.4)	18.1 (10.5-24.3)	13.9 (10.4-20.9)

Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization; n, number of patients; NA, not available, as the Kaplan-Meier (KM) estimate or its lower/upper confidence bound did not reach the quantile; OS, overall survival; Q1, 1st quartile; Q3, 3rd quartile. [a]Patient characteristics at MM diagnosis in the study cohort are available in **Table 1**. [b]At the time of MM diagnosis. [c]At least one high-risk FISH finding. [d]At least one intermediate-risk FISH finding; no high-risk FISH findings. [e]Includes any other FISH finding, and "No FISH findings" category (also when FISH was not tested), and excludes high-risk and intermediate-risk cytogenetics.

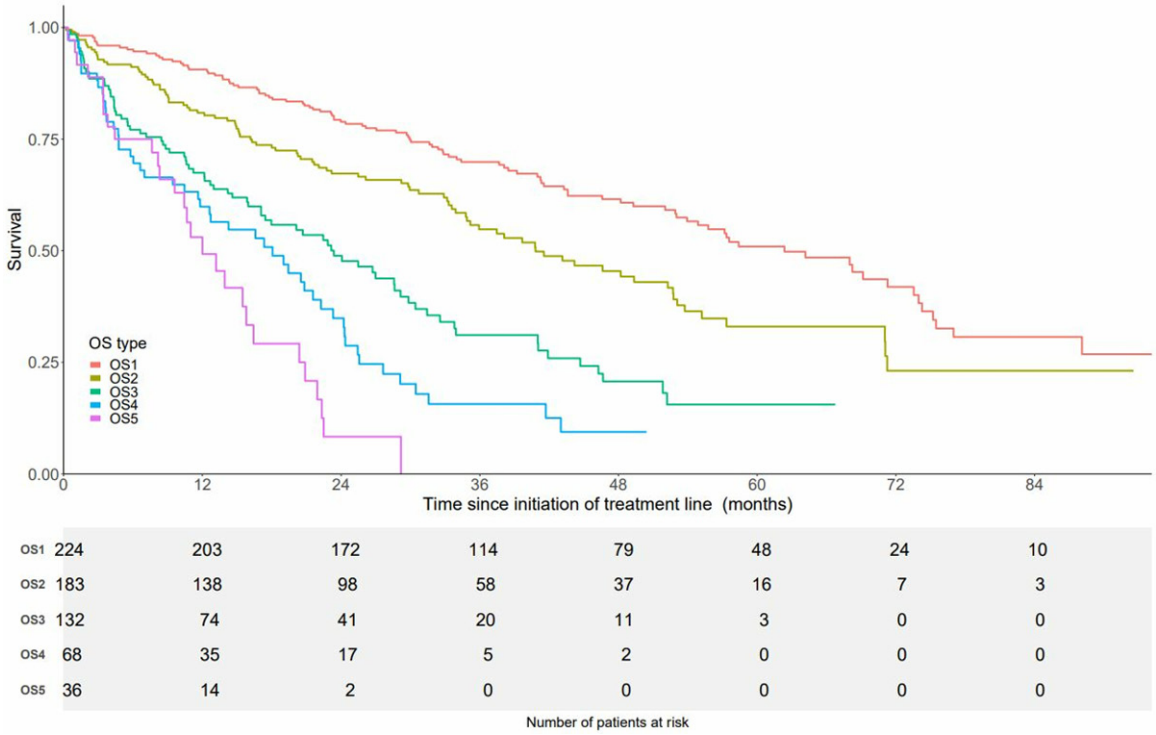

Figure 2. Kaplan-Meier curves for overall survival (OS[a]) in treatment lines 1-5 among multiple myeloma patients. Abbreviation: OS, overall survival. [a]OS1 refers to overall survival in treatment line 1, OS2 in treatment line 2, etc.

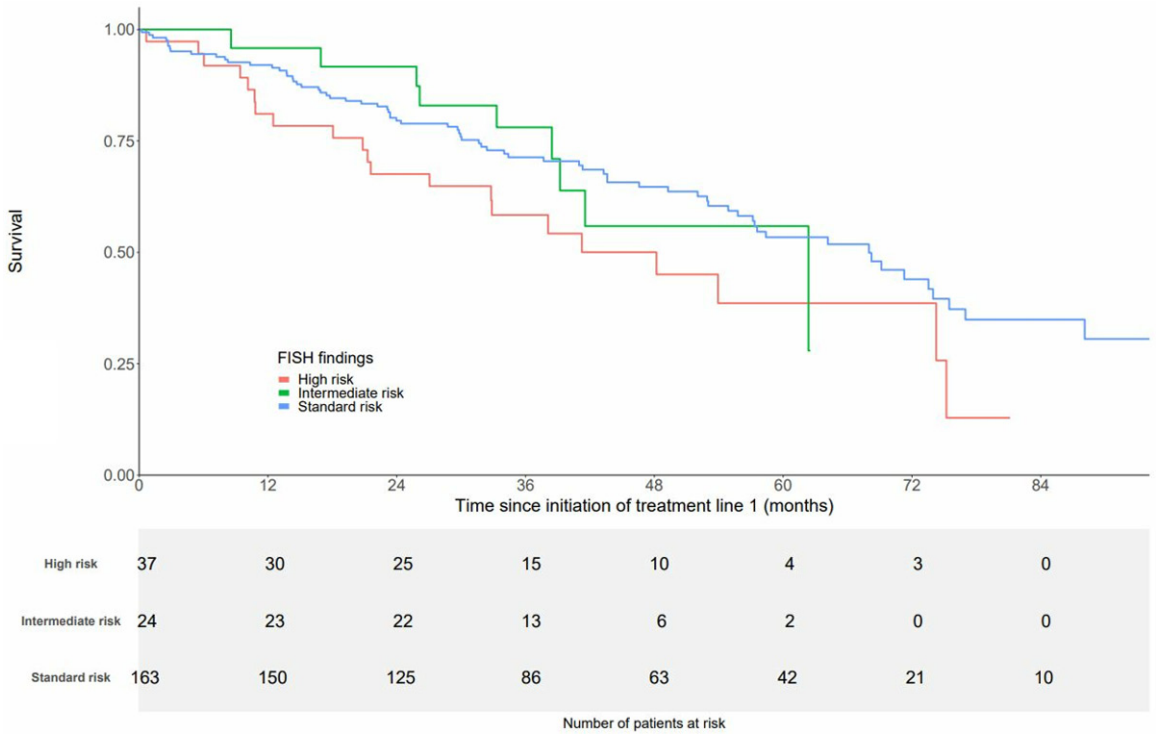

Figure 3. Kaplan-Meier curves for overall survival in treatment line by FISH risk (high, intermediate, standard) category among multiple myeloma patients (N=224 patients in treatment line 1). Abbreviation: FISH, fluorescence in situ hybridization.

Table 6. Median time to next treatment by treatment line (N=224 multiple myeloma patients in treatment line 1)

Variable	Line 1	Line 2	Line 3	Line 4	Line >4[a]
Number of patients at risk, n (%)	224 (100.0%)	183 (100.0%)	132 (100.0%)	68 (100.0%)	88 (100.0%)
Number of patients with event, n (%)	183 (81.7%)	133 (72.7%)	68 (51.5%)	37 (54.4%)	52 (59.1%)
Number of patients censored, n (%)	32 (14.3%)	38 (20.8%)	35 (26.5%)	10 (14.7%)	8 (9.1%)
Number of patients died, n (%)	9 (4.0%)	12 (6.6%)	29 (22.0%)	21 (30.9%)	28 (31.8%)
Q1 TTNT, months (90% CI)	3.3 (3.0, 3.8)	4.8 (3.5, 6.2)	5.6 (3.9, 7.8)	3.6 (3.0, 6.9)	2.8 (2.1, 3.8)
Median TTNT, months (90% CI)	8.5 (6.1, 12.8)	16.0 (10.6, 20.5)	15.6 (11.9, 32.0)	18.8 (10.8, NA)	8.6 (6.2, 14.7)
Q3 TTNT, months (90% CI)	34.4 (26.1, 44.5)	38.8 (30.8, 43.9)	NA	NA	NA

CI, confidence interval; MM, multiple myeloma; NA, the Aalen-Johansen estimate or its lower/upper confidence bound did not reach the quantile.
[a]For treatment line >4, the confidence interval was calculated assuming that all (subsequent) treatment lines are independent of each other.

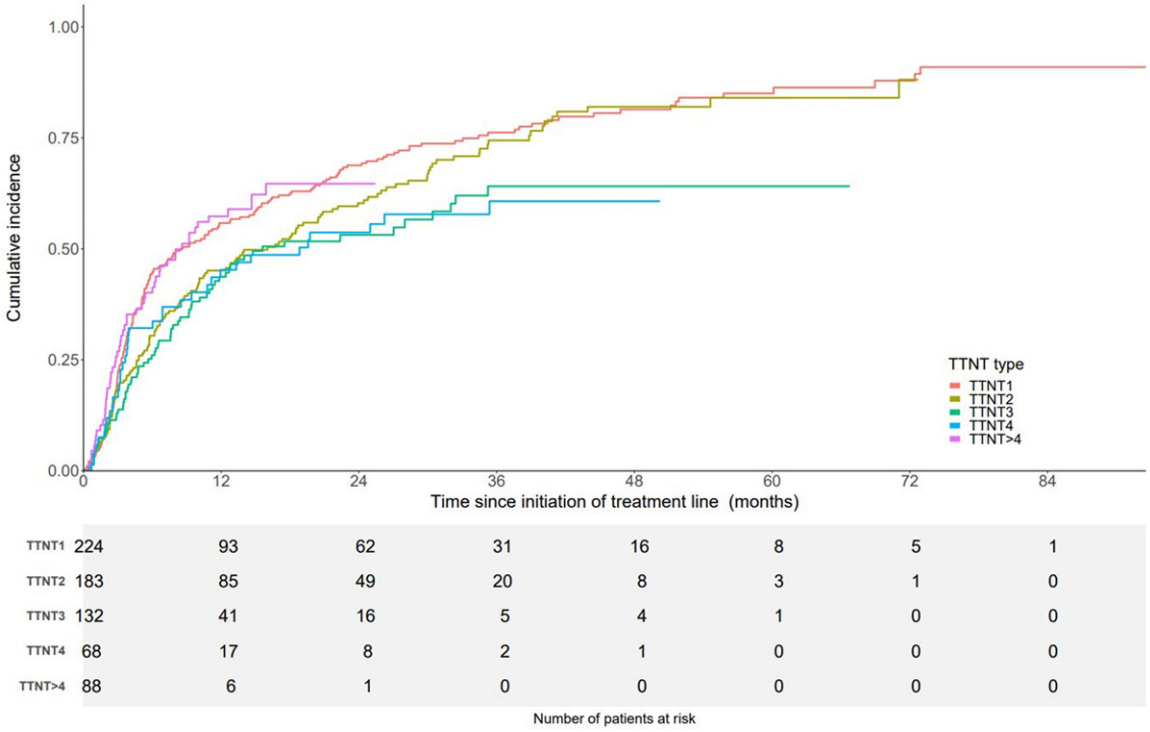

Figure 4. Aalen-Johansen curves for time to next treatment line (TTNT) in treatment lines 1-4 and >4 among multiple myeloma (MM) patients. Abbreviation: TTNT, Time to next treatment line.

[18, 30] and previous results in Finland using the same registry [9]. In addition, the results from the most recent nationwide MM study, where all MM patients were included regardless of whether they received treatment, concur with this observation [27]. In a Dutch observational study, the median treatment line 1 OS was 37.5 months (95% CI: 34.8-41.8 months) [17], and in a Czech study, it was 47.5 months (95% CI: 43.1-52.0 months) [18]. The better OS in our study could be due to more advanced treatments being available in Finland during the study period. Moreover, the median OS was likely to improve given the relatively young study population compared with MM patients in general in Finland [31].

The descriptive OS was inferior among patients from Finland with high-risk cytogenic findings, which was expected and consistent with clinical trial results [32]. The finding highlights the need for detecting patients with high-risk cytogenic findings as early as possible to improve their treatment paradigms.

Since progression-free survival can be hard to interpret in RWS, we opted to look for the TTNT. It was interesting to find that the TTNT in the first-line was shorter than in later lines. We do not have comprehensive data about why the therapy was changed. However, we believe that in first-line therapy, the treatment is more often changed due to toxicity (e.g., neuropathy) or suboptimal response and less often due to progression, leaving the first progression often to the second line.

Our study used data from the FHR, which included approximately 90% of MM patients from Finland's largest hospital districts (HUS). Data from the FHR are considered appropriate for scientific research [9, 15, 27]. The FHR is a national registry wherein information concerning the treatment and treatment response of patients with hematological disorders is included, starting from the time of diagnosis and during follow-up. As the validity of the MM diagnosis and the date of death is high, defining the study population or death as an outcome was not a source of misclassification in the study. The long, robust patient follow-up also ensured the generation of sufficient information to address the study's objectives. Finally, this observational study reflected real-world clinical practice, complementing the results of RCTs. Written consent was needed from the patients to participate in the registry, thus creating a bias toward patients who survived longer and, thus, had more opportunities to be recruited into the registry. For this analysis, we only included patients with comprehensive data (including cytogenetics) in the registry. However, cytogenetics was not always checked in elderly patients during this period. This may be a reason why patients >80 years of age (only 3%) were clearly underrepresented in our study.

The limitation of the study included the relatively low number of patients, especially after treatment line 1, resulting in overlapping CIs. As the small study size hindered performing comparative analyses, the absence of formal comparisons with adjustment for confounders will be considered in the interpretation. An additional limitation was that the MM patients included in the study represented the capital region, HUS, and were therefore younger than typical MM patients in Finland [31]. The treatment pattern results are hence interpreted considering that hospital-administered therapies were probably more common in the HUS region than other regions that are distant from hospitals. As is typical for real-word data, the results were also limited by missing data, including CRAB components (see "unknown" category in **Table 1**). In addition, the significant changes to the treatment landscape since 2015 have likely changed the progression-free survival and ORR values in this analysis [33-35]. Further studies with more recent data are needed to study ORR, OS, and TTNT comprehensively.

Finally, although the study population represented a relatively small country and region, the findings are by and large considered generalizable to other real-world populations, as patients with MM from Finland and their treatment modalities are not anticipated to markedly deviate from those in other Western countries.

This study reflects myeloma treatment practice in Finland in the era when bortezomib and lenalidomide were still regarded as "novel" treatments. Although the median 62-month OS was relatively long in the first-line of therapy, the OS was comparable with other RWS studies. The shorter OS in patients with high-risk cytogenetics highlights the need for identifying such patients to improve their treatment paradigms as early as possible. Further, the median TTNT was shortest in the first treatment line, compared with later treatment lines, which is likely because of a need-based optimization of therapy in the first treatment line, and generally progressed to the second treatment line.

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Disclosure of conflict of interest

KMH is an employee of Parexel International; however, during the study and manuscript development, she was an employee of IQVIA. GT and PV are employees of IQVIA, which performs commissioned pharmacoepidemiological studies for several pharmaceutical compa-

nies. RK is an employee of Aastat Estonia OÜ; however, during the study and manuscript development, he was an employee of IQVIA. TM is an employee of Takeda Oy, Finland. ST is an employee of MedEngine Oy; however, during the study and manuscript development, he was an employee of Takeda Oy, Finland. JL is an employee of Helsinki University Hospital Comprehensive Cancer Center and the University of Helsinki, Finland.

Address correspondence to: Juha Lievonen, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland. E-mail: Juha.Lievonen@hus.fi

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Supplementary Table 1. Variable definitions

Patient characteristics	Definition/categorisation	Use as a stratification variable or as subgroup
Demographic characteristics		
Sex	At the time of MM diagnosis; Categorised: male/female; mutually exclusive categories.	Yes, KM curves for OS
Age	At the time of MM diagnosis, in years; Continuous and categorised: 37-50/51-60/61-70/71-80/>80; Yes or no for all of the categories, that are mutually exclusive.	Yes, for treatment patterns "*Treated with AutoHSCT during follow-up*" and "*Any MM treatment during follow-up*"; Strata: <66/66-69/≥70 years, and also reported as total under 70 years
Disease characteristics		
FISH findings	At the time of MM diagnosis; fluorescence in situ hybridisation (FISH) findings, Categorised (and/or): ● High risk: ○ del(17p13) ○ t(14;20) ○ t(14;16) ○ t(4;14) ● Intermediate risk: ○ gain(1q) ○ del(1p32 or 1p36) ● Standard risk: ○ t(11;14) ○ del(13q) ○ Other abnormality* *Includes any other FISH findings not listed above, also "No FISH findings", and excluding high, and intermediate-risk cytogenetics. The categories are mutually exclusive.	Yes, for OS, only the high-risk (at least one high-risk FISH finding), intermediate-risk (at least one intermediate-risk FISH finding, no high-risk FISH findings), or standard-risk cytogenetics (Includes any other FISH finding, also "No FISH findings" category (also when FISH was not tested), and excludes high-risk and intermediate-risk cytogenetics)
CRAB component	At the time of MM diagnosis; Categorised: hypercalcaemia/anaemia/renal dysfunction/lytic bone lesions/unknown. The variables on the CRAB components were defined in 2 ways: 1) using the original dichotomous FHR variable (yes/no/unknown), and 2) combining the variable with laboratory values, if the FHR variable was unknown, using the following definitions according to the IMWG (34)MM was defined by the presence of end-organ damage, specifically hypercalcemia, renal failure, anemia, and bone lesions (CRAB features: Yes, no, or unknown for all of the categories, which are not mutually exclusive (apart from "unknown" excludes the other categories).	No
Treatment patterns	**Definition/categorisation**	
Treatment with AutoHSCT during follow-up	Any record of autoHSCT during follow-up; Yes or no, mutually exclusive categories.	No
Any MM treatment during follow-up	Record of any MM treatment during follow-up; Yes or no, mutually exclusive categories.	No
Treatment duration	Treatment duration (months) of treatment regimens in each treatment line. Mobilizations and haematological stem-cell transplants were ignored, also radiation therapy, dexamethasone pulses and under 17 days dexamethasone treatments unless no systemic treatments in line; Continuous.	No
Overall response rate (ORR)	**Definition/categorisation**	
	ORR was defined as the percentage (%) of patients in the cohort who had at least a partial response to treatment (stringent complete response, complete response, very good partial response, partial response) recorded at least once within a line of treatment. The ORR measured if the best response within the treatment line was at least partial response. If there was no disease status recorded during a treatment line, it was recorded as missing.	No

Overall survival (OS)	Definition/categorisation	
	The OS was defined as the time (months) from the MM treatment initiation in each treatment line to death. In the treatment line 1, the OS was referred to as OS1. OS among those who had received treatment lines 2, 3, 4, 5, was defined as the time from first having the treatment line in question (2nd, 3rd, 4th, 5th lines of treatment; outcomes named OS2, OS3, OS4, OS5) until death. All patients alive at the end of study period (31 December 2017) were censored at that timepoint.	No
Time to next treatment line (TTNT)	**Definition/categorisation**	
	The TTNT for each treatment line (TTNT1, TTNT2, and further) was defined as the length of time (months) between the start of a treatment line to the start of the next treatment line. Specifically, TTNT1 was defined as the length of time between the start of the first treatment line (following diagnosis) to the start of the second treatment line, TTNT2 was the length of time between the start of the second treatment line to the start of the third treatment line, and so on. In the analysis of TTNT competing risks were not taken into account and deaths were treated with censoring.	No
Stratification variables	**Definition/categorisation**	
Stratification: Treatment lines	Treatment lines were defined as one or more cycles of a treatment programme planned by a treating physician. Treatment lines were numbered successively, starting with the treatment line 1, second treatment line, and further, as recorded in the FHR: Categorised: 1/2/3/4/>4*; Yes or no for all of the categories. *>4 is categorised later by IQVIA. FHR had all lines individually.	Yes, for ● Patient characteristics ● Treatment pattern "*Treatment duration*" ● ORR ● OS
Subgroups: Treatment regimen	Drugs and/or therapies that the treatment line consisted of, as recorded in the FHR, categorised based on observed treatments in the data: ● Bortezomib + cyclophosphamide + dexamethasone (VCD). ● Bortezomib + cyclophosphamide + dexamethasone (VCD) + AutoHSCT (HD-mel). ● Bortezomib + dexamethasone (VelDex) (VelDex). ● Bortezomib + dexamethasone (VelDex) + AutoHSCT (HD-mel). ● Bortezomib + lenalidomide + dexamethasone (VRD). ● Bortezomib + lenalidomide + dexamethasone (VRD) + AutoHSCT (HD-mel). ● Bortezomib + melphalan + prednisone (VMP). ● Cyclophosphamide + prednisone (CP)*. ● Cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide (DR-PACE). ● Lenalidomide + dexamethasone (RD). ● Melphalan + prednisone (MP)*. ● Melphalan + prednisone + thalidomide (MPT). ● Thalidomide + dexamethasone. ● Other (including treatments that were observed less than 10 times in the data). Yes or no for all categories, mutually exclusive categories. Treatment regimens marked with an asterisk (*) are conventional therapies, others were considered novel therapies.	Yes, for ORR
Subgroups: HSCT status	As recorded in the FHR*: Categorised: ● AutoHSCT (autologous): no/yes (single). Yes or no for all categories, mutually exclusive categories. *For consistency, bone marrow transplant was categorised later by IQVIA as haematological stem-cell transplantation (HSCT) in the manuscript.	Yes, for ORR

Abbreviations: AutoHSCT, autologous haematological stem-cell transplantation; CRAB, C, calcium (elevated), R, renal failure, A, anaemia, B, bone lesions; CT, computed tomography; FHR, Finnish Haematology Registry; FISH, fluorescence in situ hybridisation; IMWG, International Myeloma Working Group; KM, Kaplan-Meier; MM, multiple myeloma; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography.

Supplementary Table 2. Overall response rate for treatment regiments and hematological stem-cell transplant status, by treatment line and in total for all treatment lines (N=224 patients in treatment line 1)

Treatment regimen	Line 1 (224 lines)		Line 2 (183 lines)		Line 3 (132 lines)		Line 4 (68 lines)		Line >4 (88 lines)		Total (695 lines)	
	n/N	% (90% CI)	n/N	% (90% CI)	n/N	% (90% CI)	n/N	% (90% CI)	n/N	% (90% CI)	n/N	% (90% CI)
Conventional therapies												
Cyclophosphamide + prednisone (CP)	3/4	75.0 (24.9-98.7)	5/7	71.4 (34.1-94.7)	2/3	66.7 (13.5-98.3)	2/9	22.2 (4.1-55.0)	0/1	0.0 (0.0-95.0)	12/24	50.0 (31.9-68.1)
Melphalan + prednisone (MP)	8/10	80.0 (49.3-96.3)	7/10	70.0 (39.3-91.3)	1/3	33.3 (1.7-86.5)	0/4	0.0 (0.0-52.7)	0/1	0.0 (0.0-95.0)	16/28	57.1 (40.0-73.1)
Novel therapies without haematological stem-cell transplantation (HSCT)												
Bortezomib + cyclophosphamide + dexamethasone (VCD)	23/30	76.7 (60.6-88.5)	5/7	71.4 (34.1-94.7)	0/2	0.0 (0.0-77.6)	0/3	0.0 (0.0-63.2)	1/2	50.0 (2.5-97.5)	29/44	65.9 (52.5-77.7)
Bortezomib + dexamethasone (VelDex)	28/38	73.7 (59.5-85.0)	4/12	33.3 (12.3-60.9)	11/15	73.3 (48.9-90.3)	2/4	50.0 (9.8-90.2)	3/5	60.0 (18.9-92.4)	48/74	64.9 (54.7-74.1)
Bortezomib + lenalidomide + dexamethasone (VRD)	0/0	NA (NA-NA)	16/23	69.6 (50.4-84.8)	13/16	81.2 (58.3-94.7)	2/2	100.0 (22.4-100.0)	1/7	14.3 (0.7-52.1)	32/48	66.7 (53.9-77.8)
Bortezomib + melphalan + prednisone (VMP)	14/16	87.5 (65.6-97.7)	13/16	81.2 (58.3-94.7)	2/4	50.0 (9.8-90.2)	0/0	NA (NA-NA)	2/3	66.7 (13.5-98.3)	31/39	79.5 (66.0-89.4)
Cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide (DR-PACE)	0/0	NA (NA-NA)	1/2	50.0 (2.5-97.5)	2/4	50.0 (9.8-90.2)	2/3	66.6 (13.5-98.3)	2/4	50.0 (9.8-90.2)	7/13	53.8 (28.7-77.6)
Lenalidomide + dexamethasone (RD)	0/0	NA (NA-NA)	21/33	63.6 (47.8-77.5)	18/25	72.0 (53.8-86.1)	10/15	66.7 (42.3-85.8)	2/9	22.2 (4.1-55.0)	51/82	62.2 (52.5-71.2)
Melphalan + prednisone + thalidomide (MPT)	7/11	63.6 (35.0-86.5)	2/2	100.0 (22.4-100.0)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	9/15	60.0 (36.0-80.9)
Thalidomide + dexamethasone	6/14	42.9 (20.6-67.5)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	9/13	69.2 (42.7-88.7)
Novel therapies with haematological stem-cell transplantation (HSCT)												
Bortezomib + cyclophosphamide + dexamethasone (VCD) + AutoHSCT (HD-mel)	21/21	100.0 (86.7-100.0)	0/0	NA (NA-NA)	1/1	100.0 (5.0-100.0)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	22/22	100.0 (87.3-100.0)
Bortezomib + dexamethasone (VelDex) + AutoHSCT (HD-mel)	12/12	100.0 (77.9-100.0)	5/5	100.0 (54.9-100.0)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	0/0	NA (NA-NA)	17/17	100.0 (83.8-100.0)
Bortezomib + lenalidomide + dexamethasone (VRD) + AutoHSCT (HD-mel)	0/0	NA (NA-NA)	10/11	90.9 (63.6-99.5)	0/0	NA (NA-NA)	1/1	100.0 (5.0-100.0)	0/0	NA (NA-NA)	11/12	91.7 (66.1-99.6)
Other therapies												
Other	41/45	91.1 (80.8-96.9)	27/34	79.4 (64.8-89.9)	16/33	48.5 (33.3-63.9)	6/21	28.6 (13.2-48.7)	7/41	17.1 (8.3-29.7)	97/174	55.7 (49.2-62.1)
Haematological stem-cell transplantation (HSCT) transplant status												
AutoHSCT: No	117/153	76.5 (70.1-82.0)	88/133	66.2 (58.8-73.0)	62/102	60.8 (52.2-68.9)	24/61	39.3 (28.8-50.7)	18/73	24.7 (16.6-34.3)	309/522	59.2 (55.5-62.8)
AutoHSCT: Single[a]	46/46	100.0 (93.7-100.0)	28/29	96.6 (84.7-99.8)	4/4	100.0 (47.3-100.0)	1/1	100.0 (5.0-100.0)	0/0	NA (NA-NA)	79/80	98.8 (94.2-99.9)
AlloHSCT: No	158/194	81.4 (76.2-85.9)	112/158	70.9 (64.4-76.8)	65/105	61.9 (53.5-69.8)	24/61	39.3 (28.8-50.7)	18/73	24.7 (16.6-34.3)	377/591	63.8 (60.4-67.1)
AlloHSCT: Single[a]	5/5	100.0 (54.9-100.0)	4/4	100.0 (47.3-100.0)	1/1	100.0 (5.0-100.0)	1/1	100.0 (5.0-100.0)	0/0	NA (NA-NA)	11/11	100.0 (76.2-100.0)

Abbreviations: AlloHSCT, allogeneic haematological stem-cell transplantation; AutoHSCT, autologous haematopoietic stem-cell transplant; CI, confidence interval; HD-mel, high-dose melphalan; HSCT, haematological stem-cell transplantation; Len, lenalidomide; Mel, melphalan; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; NA, not applicable; n/N, patients with response/the number of lines with existing disease status records. [a]No tandem hematological stem-cell transplants were observed. Thus, the single transplants represent all haematological stem-cell transplants.