# PHARMACOEPIDEMIOLOGICAL STUDY REPORT
# ER-9542

## An Observational Cohort Study on Multiple Myeloma Patients in Finland


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## Study information

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| **Joint PASS** | No |
| **Research question and objectives** | The primary objective of this study was to describe the Finnish multiple myeloma patient population, treatment patterns, and treatment outcomes with different types and stages of the disease, and to stratify by known patient-related prognostic factors. The secondary objective was to identify and describe characteristics of specific subpopulations, including those who received a specific treatment selection, who had short treatment durations, as well as risk-stratified subpopulations. Where possible, the effect of transplant, duplet/triplet therapies, treatment duration, and risk-stratification on overall survival (OS) and time to next treatment (TTNT) outcomes was also determined. |
| **Country(-ies) of study** | Finland |
| **Author** | Giorgi Tskhvarashvili, Camilla Bengtsson, Katja Hakkarainen, and Alisa Kopilow |

## Marketing authorisation holder(s)

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# 1 Abstract


**Title**

An Observational Cohort Study on Multiple Myeloma Patients in Finland

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**Keywords**

Multiple myeloma, retrospective, treatment patterns, Finnish Hematology Register

**Rationale and background**

In Finland, the average survival time following a multiple myeloma (MM) diagnosis is 5-6 years, but novel therapies have improved overall survival (OS). However, the treatment and subsequent outcomes of MM in Finland are not completely understood.

**Research question and objectives**

The primary objective was to characterize the Finnish MM population and to describe the OS and time to next treatment (TTNT) both overall and stratified by known patient-related prognostic factors.

*Primary objective 1* described the characteristics and patient journey of Finnish MM patients, including patient characteristics, disease characteristics, and treatment patterns, in each treatment line. Patient characteristics included gender, age, and co-morbidities. Disease characteristics included CRAB (calcium (elevated), renal failure, anaemia, bone lesions) components, fluorescence *in situ* hybridization (FISH) findings, the serum M-protein type, and risk classification according to the Revised International Staging System (R-ISS). Treatment patterns included identifying the treatment regimens, bone marrow transplant status, and treatment type (single, duplet, triplet therapy). Overall response rate (ORR) per treatment line was summarized per treatment.

*Primary objective 2* evaluated OS and TTNT per treatment line among MM patients, stratified by patient characteristics, disease characteristics, and by three treatment patterns, including treatment regimen, bone marrow transplant status, and treatment type.

*Secondary objective 1* identified patient, disease, and treatment-related factors that were associated with OS, TTNT, and treatment selection.

*Secondary objective 2* characterized subpopulations of MM patients in each treatment line, including those categorized as high-, standard-, or low-risk according to R-ISS. Additionally, the following MM patient subpopulations were characterized: patients who did not receive the following pre-specified treatments: autologous bone marrow transplant, allogeneic bone marrow transplant, duplet therapy and triplet therapy; and patients who had short durations of each treatment line. Characterization of each of these subpopulations included a similar description as stated in Primary objective 1.

**Study design**
Retrospective observational cohort study using data from the nationwide Finnish Hematology Register (FHR).

**Setting**
The whole study cohort included MM patients (aged >18 years) diagnosed 01 January 2010 – 31 December 2015 in the Helsinki and Uusimaa Hospital District. The main analyses were conducted on the actual cohort of patients who were treated for MM between 01 January 2010 – 31 December 2016 and therefore had at least one year of potential follow-up time

**Subjects and study size, including dropouts**
In total, 225 patients were included in the whole cohort, and 224 in the actual cohort of patients receiving treatment.

**Variables and data sources**
Data was collected from the FHR. Descriptive variables included patient and disease characteristics, as well as treatment patterns. Outcome variables included overall response rate (ORR), OS, TTNT, and treatment selection variables.

**Statistical analysis of the actual cohort**
*Primary objective 1.* Patients and disease characteristics as well treatment patterns were described at diagnosis and at the start of each treatment line. Disease characteristics were also described at the end of follow-up, however, FISH findings, CRAB components, and disease stage (ISS and R-ISS) were available only at diagnosis. Continuous variables were described by mean, standard deviation (Std dev), median, $25^{th}$ and $75^{th}$ percentiles, and minimum and maximum values. Categorical variables were described by proportion and frequency in each category. If any value was missing, the number of missing values was presented. ORR per treatment line was summarized together with 90% confidence intervals (CI), using the Clopper-Pearson method.

*Primary objective 2.* OS was described by the Kaplan-Meier estimator and TTNT by the Aalen-Johansen estimator treating death as a competing risk. OS and TTNT were stratified by different patient characteristics, disease characteristics and treatment patterns. These time-to-event outcomes were derived based on the Kaplan-Meier or Aalen-Johansen estimator data: the proportion of censoring, the number of events and number of censorings were reported.

*Secondary objective 1.* Factors associated with OS and TTNT were identified using a multivariate Cox regression model. In addition, to produce crude estimates for individual variables, stratified incidence rates were calculated with regard to patient, disease characteristics and treatment regimens.

*Secondary objective 2.* The subpopulations were described similarly as defined in Primary Objective 1. Specifically, baseline and disease characteristics were tabulated for all the subgroups.

**Results**

*Primary objective 1.* In total, 224 MM patients in the Helsinki and Uusimaa Hospital District region were treated in line 1 with 36 patients remaining after treatment line 4. Across the treatment lines, more than 50% were men and the median age was 68 years. The most common co-morbidity was hypertension. The most prevalent CRAB components were lytic bone lesions and anaemia, across the treatment lines. Of high-risk FISH findings, del(17p13) was most common across the treatment lines, as was the serum M-protein type IgG. More than 50% had the standard R-ISS risk classification. Novel therapy (Bor/Dxm, Bor/Dxm+AutoHSCT HD-mel, Bor/Cpm/Dxm, Bor/Cpm/Dxm+AutoHSCT HD-mel, Mel/Pred/Tal (MPT), Tal/Dxm) accounted for 63.4% of treatment regimens in line 1, with the highest frequency of Bor/Dxm (19.2%). The frequency of these regimens was lower in the subsequent treatment lines. In treatment lines >4, Len/Dxm (11.36%) and treatment regimens other than the ten most common ones were the most frequent (55.68%). In treatment line 1, 47 patients (20.98%) received a single autologous haematological stem cell transplant (AutoHSCT). In total, 81 patients (36%) received AutoHSCT. Duplet or triplet therapy was more frequent than single therapy across all treatment lines. The ORR decreased from 60.71% in treatment line 1 to 19.32% in treatment lines >4.

*Primary objective 2.* Across the treatment lines, the median OS lowered from 62.36 months to 12.00, whereas median TTNT appeared higher from 8.54 months to 18.82 in subsequent treatment lines. The median OS was longer for women in the first treatment line, but from the second treatment line onwards, median OS was longer for men. The median OS was longer in younger age groups, especially in the first two treatment lines. The older age groups had longer median TTNT in first treatment line. Patients with CRAB components had a shorter median OS and TTNT for all treatment lines. Overall, the median OS and TTNT was longer for the patients with high-risk FISH findings than for patients with non-high-risk FISH findings, for all treatment lines. Patients with the standard R-ISS risk classification had a longer median OS and TTNT in treatment line 1 than those with high R-ISS risk. Patients treated with an AutoHSCT in the treatment lines 1-3 appeared to have a longer median OS and TTNT than those without the AutoHSCT treatment. Finally, for patients with triplet therapy, the median OS and TTNT in the first treatment line appeared longer than in the strata of patients with duplet or single therapy.

*Secondary objective 1.* Patients having CRAB components hypercalcemia and anaemia at diagnosis was associated with a lower OS and a higher risk of earlier proceeding to the next treatment in the first treatment line. Further, being treated with various treatment regimens other than the 10 most common ones decreased the risk for death in the treatment lines 2-3 and was associated with a lower risk of proceeding to the next treatment in treatment lines 1-4, compared with the reference treatment regimen Bor/Cpm/Dxm. Of factors associated with treatment selection, being in treatment lines 3 and 4 was associated with higher odds of duplet therapy, and lower odds of triplet therapy, compared to being in treatment line 1. Further, patients with the CRAB component hypercalcemia at diagnosis had higher odds to be treated with duplet therapy compared to the patients without hypercalcemia. Having the FISH findings del(1p32 or 1p36) or gain(1q) was associated with lower odds of duplet therapy, while the same findings were associated with higher odds of the triplet therapy. Due to small number of patients, no patient, disease, and treatment-related factors were associated with OS and TTNT across all treatment lines.

*Secondary objective 2.* In all analyses of this objective, the number of patients was small. According to the R-ISS classification, in treatment line 1 the mean age in the low R-ISS risk group was lower compared with standard and high-risk R-ISS groups. On the contrary, the mean age decreased over the treatment lines in the high-risk R-ISS subpopulation. In the high-risk R-ISS group, the CRAB components and high-risk FISH findings appeared largely more prevalent than in the lower risk subpopulations throughout all treatment lines. Among the sub-groups without specific treatments, patient and disease characteristics did not differ substantially between subpopulations without autologous/allogeneic bone marrow transplant or duplet/triplet therapy. Among patients with short treatment duration, the mean age of patients increased slightly with each successive treatment line, ranging from 67.8 to 70.0. Further, a substantial percentage of patients had no diagnosed co-morbidities, particularly for patients in treatment line 4 onwards who had a short duration of treatment in lines 3-4. Across all treatment lines of patients with short treatment durations, lytic bone lesions and anaemia appeared to be the most common CRAB components; most patients did not have high risk cytogenetic FISH findings, and most patients had the standard R-ISS risk classification.

**Conclusion**

*Primary objective 1.* The study confirms that MM occurs relatively late in life and equally among men and women, but that the proportion of male patients increased with the treatment lines. The disease characteristics at diagnosis were largely consistent with previously reported characteristics in other populations, with lytic bone lesions and anaemia being the most common CRAB components, del(17p13) being the most common FISH finding, most patients having the standard risk classification and the serum M-protein type IgG. Interestingly, the proportion of patients with the low ISS classification was lower than normally observed in RCTs, indicating that MM patients are in a worse condition in the real-life clinical practice. Furthermore, the treatment pattern showed that clinical practice in Finland between 2010 and 2017 broadly reflected the Finnish guidelines for MM treatment. The finding that the ORR, regardless of treatment, was the best in the first treatment line and then decreased in subsequent lines was expected, as moving to subsequent treatment lines indicates lack of adequate response as the disease progresses. Similarly, it was expected that the best ORRs of 50% or more were observed for novel therapies.

*Primary objective 2.* In this study, median OS in Finland was, in general, longer than in the previous studies. Further, the median TTNT was also shortest in the first treatment line, compared to later treatment lines, as a result of a need-based optimization of the therapy in the first treatment line, which generally leads to progression to the second treatment line in the data. In addition, patients with CRAB components presented a shorter median of OS and a shorter median TTNT than those without. Also, patients with FISH finding del(17p13) had the shorter survival in this study than without del(17p13). Further, patients with the standard R-ISS risk classification had a longer median OS and TTNT, than those with high R-ISS risk, as expected, considering that low risk patients are more likely to have a positive treatment response. Nevertheless, this study also concluded that the median OS and TTNT was longer for patients treated with the single AutoHSCT, compared to no transplant, as expected. Further, the median OS and TTNT for the triplet treatment was longer than duplet, which could indicate that patients were treated according to the treatment guidelines. However, this could also be due to duplet treatments being given generally to older patients and patients in worse health conditions. Further, the effect of

treatments on the prognosis is extremely difficult to estimate, because of treatment choice bias, and other confounding factors that may have a large effect.

*Secondary objective 1.* The CRAB components at diagnosis, hypercalcemia and anaemia, were associated with an increased risk of death and faster progression to the next treatment in the first treatment line (shorter TTNT) among Finnish MM patients. Having the high-risk FISH findings del(17p13) or t(14,16) were associated with an increased risk of proceeding to the next treatment in the treatment line 1. Further, patients with standard or high R-ISS risk classification also had a higher risk of proceeding to the next treatment in the treatment lines 2, compared to patients with low R-ISS risk classification.

*Secondary objective 2.* In all subpopulations the number of observations was low, especially in the high-risk population. Thus, no firm conclusions could be made based on the results for this objective.

**Marketing Authorisation Holder(s)**
Not Applicable

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# 2 List of abbreviations

| | |
|---|---|
| ANC | Absolute neutrophil count |
| AutoHSCT | Autologous haematological stem cell transplant |
| BUN | Blood urea nitrogen |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CR | Complete response |
| CRAB | C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions |
| CI | Confidence interval |
| CT | Computed tomography |
| Dg | Diagnosis |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| EU PAS | European register of non-interventional post-authorisation studies |
| FHR | Finnish Hematology Register |
| FSH | Finnish Society of Hematology |
| FISH | Fluorescence *in situ* hybridization |
| GPP | Good Pharmacoepidemiology Practice |
| HR | Hazard ratio |
| HUS | Helsingin ja Uudenmaan sairaanhoitopiiri (eng. Helsinki and Uusimaa Hospital District) |
| IG | Immunoglobulin |
| IMWG | International Myeloma Working Group |
| IR | Incidence ratio |
| ISPE | International Society for Pharmaceutical Engineering |
| ISS | International staging system |
| LDH | Lactate dehydrogenase |
| MGUS | Monoclonal gammopathy of unknown significance |
| MM | Multiple myeloma |
| MR | Minimal response |

| | |
|---|---|
| MRD | Minimal residual disease |
| MRI | Magnetic resonance imaging |
| NDMM | Newly diagnosed multiple myeloma |
| OR | Odds ratio |
| ORR | Overall response rate |
| OS | Overall survival |
| PAS | Post-authorization study |
| PD | Progressive disease |
| PET | Positron emission tomography |
| PR | Partial response |
| RCT | Randomized-controlled trial |
| R-ISS | Revised international staging system |
| RRMM | Relapsed/refractory multiple myeloma |
| SAP | Statistical analysis plan |
| sCR | Stringent complete response |
| SD | Stable disease |
| TTNT | Time to next treatment |
| VGPR | Very good partial response |

## Treatments

| | |
|---|---|
| B | Bendamustine |
| Bor/V | Bortezomib |
| Cis | Cisplatin |
| Cpm/C | Cyclophosphamide |
| D | Daratumumab *(D in triplets DXX)* |
| Dox | Doxorubicin |
| DR-PACE | Cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide |
| Dxm/D | Dexamethasone |
| Eto | Etoposide |
| HD-mel | High-dose melphalan |
| IMiD | Immunomodulatory drugs |
| K | Carfilzomib |

| | |
|---|---|
| Len/R | Lenalidomide |
| Mel/M | Melphalan |
| MP | Melphalan + prednisone |
| MPT | Melphalan + prednisone + thalidomide |
| N | Ixazomib |
| P | Pomalidomide |
| Pred/P | Prednisone *(P, when in MP and CP)* |
| RD | Lenalidomide + dexamethasone |
| Tal/T | Thalidomide |
| VCD | Bortezomib + cyclophosphamide + dexamethasone |
| VelDex | Bortezomib + dexamethasone |
| VMP | Bortezomib + melphalan + prednisone |
| VRD | Bortezomib + lenalidomide + dexamethasone |

# 3 Investigators and approvals

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**We have reviewed this pharmacoepidemiological study report (ER-9542 Version 1.0, dated 29 May 2020) and confirm it by signing it.**

DocuSigned by Katja Hakkarainen
Katja Hakkarainen | I approve this document June 29, 2020 | 4:02:30 AM PDT — June 29, 2020
Signature — Date
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**EPID Research Oy**

Katja Hakkarainen, PhD

DocuSigned by Juha Lievonen
Juha Lievonen | Hyväksyn tämän asiakirjan kesäkuuta 26, 2020 | 2:36:54 AM PDT — kesäkuuta 26, 2020
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Juha Lievonen, MD

25.6.2020
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**Takeda Oy**

Tatu Miettinen, MD

# 4 Other responsible parties

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**Sponsor project lead:** Tatu Miettinen

**Steering committee:** Principal investigator Katja Hakkarainen (PhD), EPID Research
Medical expert Juha Lievonen (MD), Helsinki University Central Hospital
Representative of the sponsor Tatu Miettinen (MD), Takeda Finland

# 5 Milestones

| Milestone | Actual date |
|---|---|
| Registration in the EU PAS register | 01 September 2017 |
| Start of data permit process | 12 September 2017 |
| End of data permit process | 20 April 2018 |
| Start of data collection | 18 June 2018 |
| End of data collection | 12 November 2018 |
| Start of data analysis | 13 November 2018 |
| End of data analysis | 29 March 2019 |
| Start of data permit process for extended study period | 20 August 2019 |
| End of data permit process for extended study period | 1 October 2019 |
| Start of data collection for extended study period | 2 October 2019 |
| End of data collection extended study period | 16 October 2019 |
| Start of data analysis extended study period | 17 October 2019 |
| End of data analysis extended study period | 21 January 2020 |
| Start of study reporting process | 21 January 2020 |
| Final report of study results | 29 May 2020 |
| Start of scientific reporting process | Estim. Q3 2020 |

# 6 Rationale and background

Multiple myeloma (MM) is a clonal haematologic malignancy of plasma cells that is characterized by accumulation of these malignant plasma cells in the bone marrow which interfere with the production of healthy blood cells. The development of MM results from early genetic aberrations that lead to monoclonal gammopathy of unknown significance (MGUS), and further genetic changes that may lead to smouldering myeloma and, potentially, to the progression to active myeloma (1). While the factors that cause MM are not fully known, risk factors include increasing age, family history, sex, and race. MM symptoms including bone pain, bleeding, anaemia, fatigue, hypercalcaemia, renal insufficiency, and frequent infections that occur as the disease advances. Treatment is usually required only after the disease has advanced. MM constitutes approximately 1% of all reported cancers and is the second most common haematologic malignancy worldwide (2). Globally, 159,985 new cases of MM have been estimated annually, and in Finland, more than 450 new cases (n=471), using 2018 estimates sourced from the International Agency for Research on Cancer (IARC)) (3). The median age at diagnosis is close to 70 years of age, and the average survival with the disease is estimated to be 5-6 years, but varies greatly depending on the patient's risk status. As MM patients are generally elderly, they likely have multiple co-morbidities. Therefore, due to factors related to the disease itself and myeloma-specific and supportive treatments, MM patients require frequent monitoring and hospital visits in order to manage their disease.

The overall survival (OS) in MM has improved significantly during the last decades, mainly due to developments in autologous haematological stem cell transplants (AutoHSCT) and novel drug treatments. However, despite improved treatment options, MM remains practically incurable with current therapy and is characterized by multiple relapses and disease-related complications, such as frequent infections, reduced kidney function, and anaemia. It typically recurs with a more aggressive disease course after each remission, resulting in shorter duration of response with each successive line of therapy and eventually treatment-refractory disease (4). Patients may have several phenotypic characteristics, such as tumour burden, co-morbidities, age, or other general conditions that influence treatment decisions. In addition, there are genotypic factors that affect prognosis and treatment responses. These high-risk biomarkers include cytogenetic abnormalities (defined as deletion 17p [del(17p)], translocation [t(4;14)], and/or translocation [t(14;16)]) (5).

Standardized staging systems for MM help predict outcomes and may aid physicians in some cases select appropriate therapy for patients (6). The International Staging System (ISS), which has recently been updated to the revised (R)-ISS by the International Myeloma Working Group (IMWG), is commonly used for the staging of MM (7). The staging systems are based on key measures that describe the disease burden and assess patients' characteristics. These risk assessment scores (described in Annex 2. ISS and R-ISS) include parameters like serum β2-microglobulin, albumin, and lactate dehydrogenase (LDH), and the presence or absence of high-risk cytogenetic changes. Based on the values of these parameters, both the ISS and R-ISS consist of three stages (I-III). The Finnish nationwide characterization of myeloma patients regarding phenotypic and genotypic features and their effect on survival has not been studied.

National treatment guidelines for myeloma in Finland have been developed (8). Stem cell transplantation is considered the front-line treatment in younger (≤70-75 years) and fit patients and is most often autologous (called AutoHSCT), but it may also be allogenic. AutoHSCT treatment consists of induction therapy of 4 cycles with a triplet therapy (primarily bortezomib + cyclophosphamide + dexamethasone OR bortezomib + thalidomide + dexamethasone) followed by a collection of stem cells, high-dose chemotherapy, and stem cell transplantation. In some cases, a second AutoHSCT may be recommended within 6 months (called a tandem transplant), or upon relapse. Elderly or frail patients are not considered eligible for AutoHSCT. Primary treatment options for these patients include bortezomib + melphalan + prednisone for 8-9 nine cycles (or 12 months) OR lenalidomide + dexamethasone for 18 months or until progression OR bortezomib + dexamethasone for 8-9 nine cycles (or 12 months).

It is thought that at the time of diagnosis, there are heterogeneous populations of tumour cells already present, known as sub-clones (9). It is not known how myeloma treatments and different treatment combinations and their sequences modify the drug-sensitivity and/or the resistance of myeloma cell clones. Therefore, it is interesting to study whether initial or early line therapies have a significant effect on later treatment responses and survival.

Evidence of the safety and efficacy of new treatments is usually based on phase III randomized-controlled trials (RCTs). Despite being the gold standard for providing evidence on treatments' causal effects on patient outcomes, RCTs have several practical limitations. Real-life clinical practice may differ greatly from the RCTs' highly selected patient population, who are randomized to obtain pre-selected study treatments. Therefore, the risks and benefits of a treatment may manifest differently in real-world settings as compared to those in an RCT. In addition, RCTs are often based on a relatively small population with short follow-up time. Observational studies based on secondary data collected in routine clinical practice provide the opportunity to investigate larger populations with long-term follow-up.

In Finland, it is not completely known how MM patients are treated in real-life clinical settings. In addition, the prevalence of various risk factors and the effect of a patient's risk status on treatment, e.g. on type, duration, and outcomes such as OS and time to next treatment (TTNT), have not been sufficiently reported in Finland. In order to evaluate the effectiveness of new MM treatments in real-life clinical practice, it may not be possible to find suitable comparators shortly after the new treatment has entered the market. Historical comparators may then serve as alternative references. Moreover, the need for real-world evidence for new improved treatment options might be highlighted in certain MM patient subgroups. For example, there might be subgroups who have not been able to receive certain conventional therapies due to their condition or who have had the need to discontinue or modify the dose of therapy due to the (unsuitable) nature of the therapy. To be able to evaluate how such subgroups could benefit from new treatment options, it is important to identify these subgroups and to evaluate the outcomes under current and past treatment options.

# 7 Research question and objectives

There is a lack of information on real-life clinical practice, treatment patterns, and treatment outcomes in Finnish MM patients, specifically in patients with different types and stages of the disease. This study aimed to provide a representative description of MM patients' characteristics, treatment patterns, and treatment outcomes in Finland. The results of this study can be used as a historical reference when evaluating the changing MM treatment landscape. This was a descriptive study without specific a-priori hypotheses to be tested.

## 7.1 Primary objectives

The primary objective was to characterize the Finnish MM population and to describe the OS and TTNT both overall and stratified by known patient-related prognostic factors.

**Primary objective 1** described the characteristics and patient journey of Finnish MM patients, including:

- Patient characteristics
- Disease characteristics
- Treatment patterns

**Primary objective 2** evaluated OS and TTNT per treatment line among MM patients, stratified by:

- Patient characteristics
- Disease characteristics, including myeloma type per major treatment regimen
- Treatment patterns, including
    - Treatment regimen (major treatment regimens in the 1$^{st}$, 2$^{nd}$, 3$^{rd}$, 4$^{th}$, >4$^{th}$ line)
    - Bone marrow transplant status
    - Treatment type (single, duplet, triplet)

## 7.2 Secondary objectives

**Secondary objective 1** identified patient, disease, and treatment-related factors that are associated with:

- OS
- TTNT
- Treatment selection

**Secondary objective 2** characterized MM patient subpopulations, including those categorized as high-, standard-, or low-risk according to R-ISS. Additionally, the following MM patient subpopulations were identified and characterized:

- Patients who did not receive the following pre-specified treatments:
    - Autologous bone marrow transplant
    - Allogeneic bone marrow transplant
    - Duplet therapy
    - Triplet therapy

- Patients who had short durations of each treatment line

Characterization of each of these subpopulations included a similar description as in Primary objective 1. In addition, OS and TTNT were described in these subgroups.

# 8 Amendments and updates

| Number | Date | Section | Amendment or update | Reason |
|---|---|---|---|---|
| NA | NA | NA | NA | This is the first version. |

# 9 Research methods

## 9.1 Study design

This was a retrospective observational cohort study using the Finnish Hematology Register (FHR) as the data source. The study included:

1) Patients diagnosed with MM during the period 01 January 2010 – 31 December 2015 and aged 18 years or older at diagnosis (i.e. the whole study cohort).

2) Patients diagnosed with MM during the period 01 January 2010 – 31 December 2015 and treated for MM during the period 01 January 2010 – 31 December 2016 and aged 18 years or older at diagnosis. This actual study cohort included only patients for whom at least one treatment initiation date could be identified during the period 01 January 2010 - 31 December 2016 and who had a minimum of one year of potential follow-up time (until 31 December 2017).

Parameters such as age, gender, co-morbidities, date of MM diagnosis, disease status, received treatments, the start of treatments and lines of treatment were collected.

A schematic representation of the study design (for each MM patient) is provided in Figure 1.

## 9.2 Setting

The study retrospectively collected data from the FHR. The whole study cohort consisted of patients with MM diagnosis during the period of 1st January 2010 – 31st December 2015. The main analyses were conducted on the actual cohort of 224 patients who were treated for MM and thereby had hat least one year of potential follow-up time.

For each patient, the whole study cohort entry date was defined as the date of the MM diagnosis based on ICD-10 or, if available, ICD-O codes. If the patient had ICD-O code indicating MM, respective date was used in order to exclude preceding plasmacytoma or smoldering Myeloma diagnosis. The actual study cohort entry date was defined as the first MM treatment initiation in the FHR. MM treatments were indicated by diagnoses of treatment variable from FHR, with additional information from ICD-O code when available.

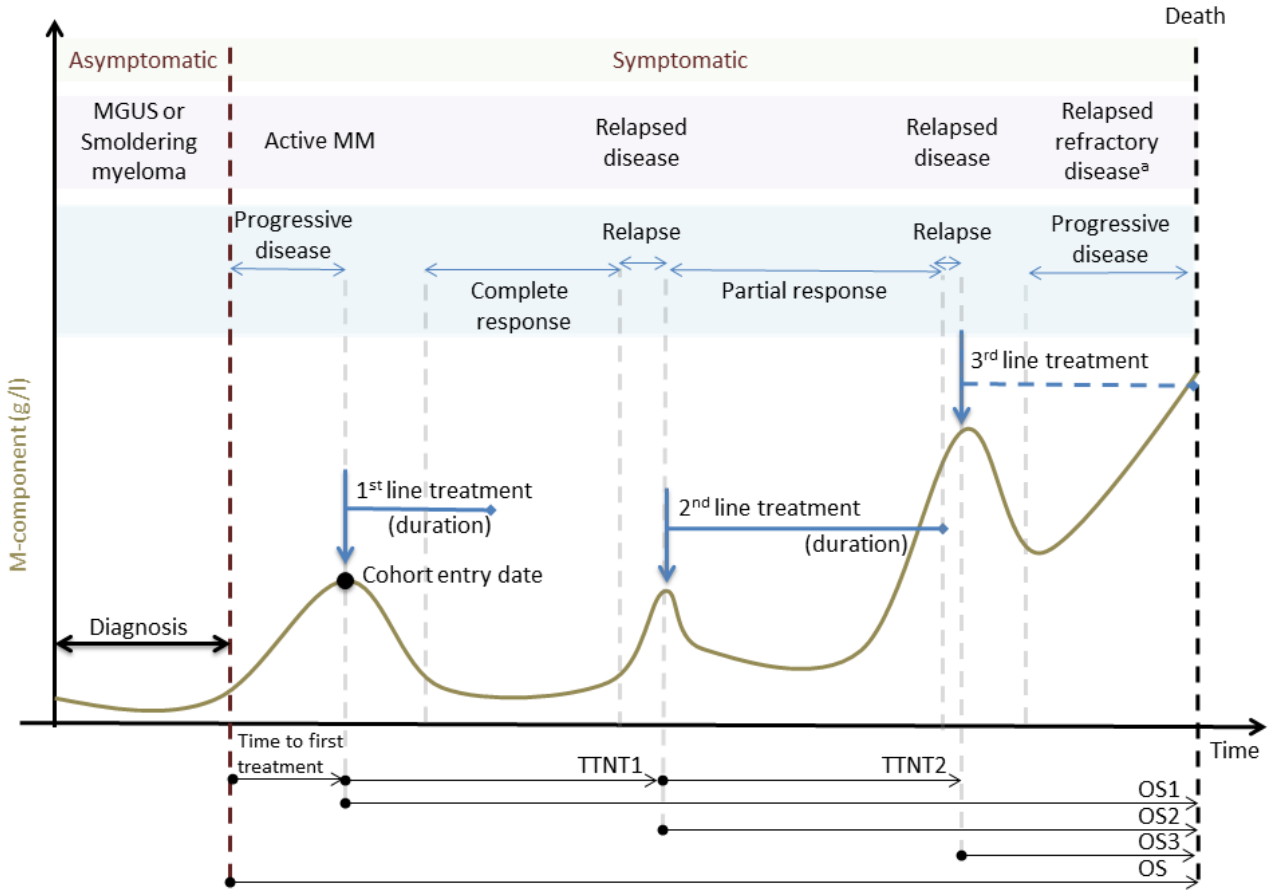


**Figure 1. Schematic representation of the study for a single multiple myeloma patient**

MM, multiple myeloma; MGUs, monoclonal gammopathy of unknown significance; OS, overall survival; TTNT, time to next treatment. The figure shows several patient and treatment-related characteristics as a function of time, starting from the date of MM diagnosis until death. Specifically, the M-component amount (g/L) is shown with the light brown curve, start of symptoms with a vertical dashed brown line and time of death with a vertical dashed black line. Depending on the patient, date of diagnosis can occur at any time over an interval and is indicated with a black horizontal arrow. At the top of the figure, type of myeloma is presented as being asymptomatic vs. symptomatic, and more specifically as being either MGUS, active MM, relapsed, or relapsed refractory[a]. Dates of different disease statuses are indicated with blue horizontal arrows (status start/end). Treatment line start (1st, 2nd, 3rd) is shown with a vertical arrow and the duration of each treatment line with a horizontal blue line. The cohort entry date is indicated by a black dot at the start of the first line of treatment. Outcomes (OS, TTNT) are illustrated at the bottom of the figure with black arrows.
[a] Refractory only applies to the major treatment regimens.

Patients in the whole study cohort were described at diagnosis, without follow-up. Patients in the actual study cohort were followed-up starting from the first treatment initiation date recorded in the FHR during the study period. Follow-up was continued until the first of the following events occurred: death or end of the study or follow-up period (31 December 2017).

## 9.3 Subjects

**Inclusion criteria:**

- MM diagnosis recorded in the FHR during the period of 1st January 2010 – 31st December 2015,
- Age 18 years or older at the time of MM diagnosis.

**Exclusion criteria:**

- Multiple haematological diagnoses in the FHR for which the treatments cannot be differentiated.

All individuals meeting the above inclusion criteria and none of the exclusion criteria were included for descriptive analyses (e.g. whole study cohort). Data recordings related to treatment were required for some analyses, and therefore only individuals for whom such records were available in the register (i.e. actual study cohort) were included in those analyses. It was expected that data recordings in the FHR were not selective and that the study population represented the general MM patient population in Finland.

## 9.4 Variables

The following data were retrieved from the FHR from the date of diagnosis (Dg), from the start of treatment, and/or at the start of follow-up as indicated when available for the actual cohort (refer to Section 6 of the SAP 2.0 for further details).

### 9.4.1 Patient characteristics

Variables concerning patient characteristics were available only at the date of diagnosis.

- **Demographic characteristics**
  - Year of birth, categorized as detailed in the SAP 2.0.
  - Gender
  - Year of MM diagnosis, categorized as detailed in the SAP 2.0.
  - Age at diagnosis, continuous and categorized as detailed in the SAP 2.0.
- **Known co-morbidities**, as detailed in the SAP 2.0.

### 9.4.2 Disease characteristics

1. **Available only at diagnosis:**
   - **Calcium (elevated), Renal failure, Anaemia, Bone lesions (CRAB) components**
     - Hypercalcemia
     - Renal dysfunction
     - Anaemia
     - Lytic bone lesions

   The variables on the CRAB components were defined in two ways: 1) using the original dichotomous FHR variable (yes/no/unknown), and 2) combining the dichotomous variable with laboratory values, if the dichotomous FHR variable was unknown, using the following definitions according to the IMWG (5):
     - Hypercalcaemia was defined as serum calcium >11.5 mg/dL (none observed in the data) or 2.5 mmol/L.
     - Renal dysfunction is defined as having a creatinine clearance of <40 mL per minute, or serum creatinine >2 mg/dL (177 µmol/L) (10).
     - Anaemia is defined as a haemoglobin value <100 g/L

- Bone lesions including one or more osteolytic lesions found on skeletal radiography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-CT (PET-CT)

- **Fluorescence *in situ* hybridization (FISH) findings**, (and/or)
  - High risk cytogenetics (yes, no, or unknown)
    - Deletion [del(17p)]
    - Translocation [t(4;14)]
    - Translocation [t(14;16)]
  - Non-high risk cytogenetics (yes, no, or unknown)
    - Translocation [t(14;20)]
    - Gain of 1q [gain(1q)]
    - Deletion 1p32 or 1p36 [1p32 or 1p36)]
  - The following other cytogenetics (yes, no, or unknown)
    - Deletion [del(13q) / -13]
    - Gain of 9 [+9]
    - Gain of 11 [+11]
    - Gain of 5 [+5]
    - Gain of 15 [+15]
    - Translocation [t(11;14)]
    - FISH: other abnormality (e.g. [t(6:14)], other chromosome 6 aberration)
  - FISH: no findings (yes, no, or unknown)
- **Disease stage**
  - ISS stage (FHR)
    - According to the ISS, using the original dichotomous FHR variable (1, 2, 3, or unknown)
  - ISS stage (Lab)
    - According to the ISS, combining the dichotomous FHR variable with laboratory values. If the dichotomous FHR variable was unknown, defining ISS stage according to the serum beta2-microglubulin and serum albumin values, as detailed in the SAP 2.0.
  - R-ISS stage (7)
    - According to the R-ISS risk classification, categorized as 1 (low), 2 (standard), 3 (high), or unknown, as detailed in Annex 2. ISS and R-ISS.

2. **Available at diagnosis and/or for each treatment line:**
   - **Myeloma type per major treatment regimen** (14 categories, see Section 9.4.4 Treatment patterns). Possible categories were: naïve, sensitive, or refractory, per major regimen. The categorization was updated at the start of each treatment line, if a new value was recorded.
   - **Disease status** (Diagnosis (Dg), stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD), clinical relapse, exitus, or not available (NA))
     - Relapse was defined using the variable clinical relapse.

- **M-component:**
  - Serum M-protein type (no findings, not tested, immunoglobulin (Ig) IgA, IgG, IgD, or IgM)
  - Serum M-protein concentration (continuous in g/L)
- **Urine M-protein type** (no findings, not tested, IgA, IgG, IgD, or IgM)
  - Urine M-protein concentration (continuous in g/Day)
  - Serum light chain type (no finding, not tested, Kappa, Lambda, or unknown)
  - Serum Kappa free light chain (FLC) (continuous in mg/L)
  - Serum Lambda FLC (continuous in mg/L)
- **Clinical haematology**:
  - Absolute neutrophil count (ANC) (continuous in E9/L)
  - Haemoglobin (continuous in g/L)
  - Platelet count (thrombocytes) (continuous in E9/L)
  - Creatinine (estimated glomerular filtration rate [eGFR] calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula) (continuous in µmol/*L*)
  - LDH (continuous in U/L)
- **Bone marrow aspirate and/or biopsy results** (and/or):
  - Percentage of plasma cells in bone marrow aspirates (continuous in percentage)
  - Percentage of plasma cells in bone marrow trephine biopsies (continuous in percentage)
  - Percentage of MM cells of total (continuous in percentage)
  - Percentage of MM cells of plasma cells (continuous in percentage)
- **Early progression** (yes, no, or unknown), defined as "yes" if the time from diagnosis to first disease progression was among the 25% of patients with the shortest 25% time to progression, among the patients for which disease progression was available. For this definition, disease progression was defined as any of the following disease statuses as recorded in the FHR: PD, or clinical relapse. If both variables used to define disease progression were missing then early progression was defined as unknown.

### 9.4.3 Follow-up variables

- Date of last follow-up
- Patient status at the date of last follow-up or end of the data collection period (until 31 December 2017)
- Date of death (where available)

### 9.4.4 Treatment patterns

Variables concerning treatment patterns as available during follow-up for the actual cohort:

- **Line of treatment** (1st, 2nd, 3rd, 4th, ….) was defined as one or more cycles of a treatment program planned by a treating physician. Treatment lines were numbered successively, starting with the first treatment line, second treatment line, and

further, as recorded in the FHR. In a sensitivity analysis, an alternative definition the treatment line variable was applied (see 9.9.4).

- **Treatment regimen**: Drugs and/or therapies that the treatment line consisted of, as recorded in FHR. The treatments were categorized into **major treatment regimens**, defined as detailed in Annex 3. Categorization of individual therapies into major regimens. If a treatment was given at least 10 times over all patients and lines, the treatment formed separate major regimen, otherwise the treatment was categorised as other, this resulted in the following treatment regimens:
    - Bortezomib, cyclophosphamide, and dexamethasone (Bor/Cpm/Dxm)
    - Bortezomib, cyclophosphamide, and dexamethasone with autologous haematopoietic stem cell transplant and high-dose melphalan (Bor/Cpm/Dxm+AutoHSCT (HD-mel))
    - Bortezomib and dexamethasone (Bor/Dxm)
    - Bortezomib and dexamethasone with autologous haematopoietic stem cell transplant and high-dose melphalan (Bor/Dxm+AutoHSCT (HD-mel))
    - Bortezomib, dexamethasone, and lenalidomide Bor/Dxm/Len
    - Bortezomib, dexamethasone, and lenalidomide with autologous haematopoietic stem cell transplant and high-dose melphalan (Bor/Dxm/Len+AutoHSCT (HD-mel))
    - Bortezomib, melphalan, and prednisone (Bor/Mel/Pred (VMP))
    - Cyclophosphamide and prednisone (Cpm/Pred)
    - Cisplatin, cyclophosphamide, dexamethasone, doxorubicin, etoposide, and lenalidomide (DR-PACE (Cis/Cpm/Dxm/Dox/Eto/Len))
    - Lenalidomide and dexamethasone (Len/Dxm)
    - Melphalan and prednisone (Mel/Pred (MP))
    - Melphalan, prednisone and thalidomide (Mel/Pred/Tal (MPT))
    - Thalidomide and dexamethasone (Tal/Dxm)
    - Other regimens
- **Bone marrow transplant status**:
    - Autologous bone marrow transplant (no, yes (single)) was defined as recorded in the FHR
    - Allogeneic bone marrow transplant (no, yes (single)) was defined as recorded in the FHR
- **Treatment type** (single therapy, duplet therapy, triplet therapy, or other) was determined based on the number of treatment regimens in each treatment line. Treatment type was determined as "other" if it could not be specified as single, duplet or triplet: if the treatment regimen had more than three drugs, the treatment line had several treatment regimens (e.g. both single and duplet) or combination therapy (e.g., DR-PACE).
- **Treatment line start year** (2010, 2011, …, 2017)
- **Treatment duration** (months) of treatment regimens in each treatment line. Mobilizations and bone marrow transplants were ignored, also radiation therapy, dexamethasone pulses and under 17 days dexamethasone treatments unless no systemic treatments in line.

- **Time to treatment line discontinuation** (months) was calculated as the number of months from the initiation to last discontinuation record in the respective treatment line, where applicable.
- **Treatment line duration** was defined as the length of time (months) from the start of a treatment line to the end of that treatment line (discontinuation or start of new treatment line). In cases where a treatment line had been discontinued, the time from the initiation to the last discontinuation record in the treatment line was considered as the duration of treatment line. If any treatments were recorded after the last discontinuation record, the line was not considered as discontinued. When discontinuation was not recorded and exclusively start of a new treatment line was recorded, the TTNT (see Section 9.4.5) was equal to treatment line duration.

### 9.4.5 Outcome variables

The outcomes of the study, to address the objectives, are summarized in Table 1.

**Table 1. Summary of the outcomes of the study to address the study objectives**

| Study objective for which outcome variables applied | Outcomes in the study, to address the objective |
|---|---|
| Primary objective 1: described the characteristics and patient journey of Finnish MM patients | ORR |
| Primary objective 2: estimated OS and TTNT per treatment line among MM patients, including stratifications | OS<br>TTNT |
| Secondary objective 1: identified patient, disease, and treatment-related factors that are associated with:<br>• OS<br>• TTNT<br>• Treatment selection | OS<br>TTNT<br>Treatment selection:<br>• Single therapy<br>• Duplet therapy<br>• Triplet therapy<br>• Bone marrow transplant status:<br>  • Autologous bone marrow transplant: single<br>  • Allogeneic bone marrow transplant: single<br>• Major treatment regimens, by category |

MM, multiple myeloma; OS, overall survival; ORR, overall response rate; TTNT, time to next treatment.

- **Overall response rate (ORR)**, defined as the proportion of patients in the actual cohort who had at least a partial response to treatment (sCR, CR, VGPR, PR) recorded at least once within a line of treatment. ORR was calculated stratified by major treatment regimens (Section 9.4.4). This way ORR measured if the best response within the treatment line was at least partial response, given that a particular major treatment regimen was applied within that treatment line.
- **Overall survival (OS)**, defined as the time (months) from actual cohort entry until death (from first MM treatment initiation to death; this outcome was referred to as OS1). In addition, 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 ($2^{nd}$, $3^{rd}$, $4^{th}$, $5^{th}$ lines of treatment; outcomes named OS2, OS3, OS4, OS5) until death. All patients alive at the end of study period ($31^{st}$ December 2017) were censored at that timepoint.
- **Time to next treatment (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.

- **Treatment selection**, defined as an outcome for assigning specific treatments to patients at the beginning of a treatment line. The following treatment selections were analysed as outcomes, as defined above (Section 9.4.4)
    - Treatment type
        - Single therapy
        - Duplet therapy
        - Triplet therapy
    - Bone marrow transplant status
        - Autologous bone marrow transplant: single
        - Allogeneic bone marrow transplant: single
    - Major treatment regimens, categorized as described in Annex 3. Categorization of individual therapies into major regimens.

### 9.4.6 Other definitions

For secondary objective 2, additional subpopulations were formed based on variables **short treatment line duration** (yes, no), which was defined as "yes" per treatment line if the duration of the treatment line was among the shortest 25% of all corresponding treatment line durations, and "no" otherwise.

## 9.5 Data sources and measurement

Data from the FHR on MM patients with recordings were used. The FHR is owned by the Finnish Society of Hematology (FSH). The FHR is a national, population-based register founded in January 2010. Information concerning the treatment and treatment responses of patients with haematological disorders are included in this register, starting from the time of diagnosis and during follow-up. Patients must provide informed consent for their data to be recorded into the register and to be used for research purposes.

The FHR data have been collected from the electronic medical records and are managed by an ICT services company, Granitics Ltd. The FHR is responsible for collecting data from the electronic medical records into the database maintained by Granitics. Contract research organization EPID Research Oy received the study data from Granitics and was responsible for data processing and analyses. EPID Research also performed quality assurance for the received data. Finalization of the analysis dataset occurred when EPID Research had performed the quality assurance procedures and resolved all potential issues with either Granitics, FHR, or both. The final statistical analyses started after the database lock.

EPID Research used R language in data processing, creating the analysis database, and statistical analyses (11). All study data, source code of data management, and data analyses will be retained for inspection purposes for five years after the end of the study. The study may be inspected by the sponsor's independent representatives, steering committee, or by competent authorities.

Data was checked for any errors or anomalies during the analysis dataset building process. All steps and modifications applied during the analysis dataset building process were documented. The data management was Quality Control checked and documented as described in the quality control section (see Section 9.10).

## 9.6 Bias

The potential biases and efforts to assess and address potential sources of bias are described in Section 11.2 Limitations.

## 9.7 Study size

The population size for the whole study cohort was estimated to be approximately 1600 MM patients, while the population size for the actual study cohort was planned to be approximately 300-400 patients. As this was primarily a descriptive study, this population size was considered sufficient at the time of initiating the study.

## 9.8 Data transformation

A few decisions worth noting were made in terms of how treatments were handled in the analysis set. If a treatment line had several consecutive records of systemic treatments (i.e. drugs and drug combinations), repetitive treatments were combined as one, even if mobilization, bone marrow transplant, radiation therapy or dexamethasone pulse therapy occurred between records. A new start date was based on the first one of those consecutive records, and the new end date was the end date of the last one of those consecutive records.

Further, the definition of the systemic treatment in each treatment line was depending on the type of change. If a component of a treatment (drug combination) was dropped, the initial treatment was assumed to be continued as "intention to treat", however if one or several drugs were initiated, treatment was recorded as a new treatment in the same treatment line. For example, if the treatment line consisted of two treatments Drug1/Drug2/Drug3 and Drug1/Drug3, Drug1/Drug2/Drug3 was recorded for that treatment line. But if the treatments were Drug1/Drug2 and Drug1/Drug2/Drug3 then Drug1/Drug2+Drug1/Drug2/Drug3 was recorded.

In terms of major treatment regimens, pretreatments (i.e., procedures done to prepare for a specific treatment) were ignored unless no systemic treatment was present in a treatment line. Mobilizations were considered as preceding treatment of autologous bone marrow transplant, and therefore ignored as major treatment regimens.

Finally, co-morbidities as well as CRAB, FISH, ISS and R-ISS variables could be defined exclusively at diagnosis using the latest FHR record before or at the cohort entry date, and no follow up measures were available in the dataset. If a value was calculated using laboratory data, the value at the cohort entry date was used.

## 9.9 Statistical methods

### 9.9.1 Main summary measures

Summaries describing all included patients both in the whole and actual cohorts were created. Continuous variables were described by mean, standard deviation (Std dev), median, 25th and 75th percentiles, and minimum and maximum values. Categorical variables were described by proportion and frequency in each category. If any value was missing, the number of missing values was presented.

### 9.9.2 Main statistical methods

#### 9.9.2.1 Primary objective 1

- Patient characteristics

Variables on patient characteristics (Section 9.4.1) were described at diagnosis for the whole cohort. For the actual cohort, these variables were described at diagnosis and repeated at the start of each treatment line (from 1st to 4th separately and lines >4 combined for patients having the corresponding treatment line).

- Disease characteristics

Variables on disease characteristics (Section 9.4.2) were described at diagnosis for the whole cohort. For the actual cohort, disease characteristics were described at diagnosis, at the start of each treatment line, and at the end of follow-up. However, disease characteristic variables on FISH findings, CRAB components, disease stage (ISS and R-ISS) were available only at diagnosis, and thus the same for all treatment lines of the same patient. For the other variables on disease characteristics the latest value before or at the start of the treatment line was reported. In the reporting at the end of follow-up, the last status/result was used.

- Follow-up variables

Patient status at the end of follow-up (Section 9.4.3) and duration of follow-up (time from actual cohort entry to the date of the last follow-up in months) were described for the actual study cohort.

- Treatment patterns

Treatment patterns (Section 9.4.4), were reported for the actual cohort by treatment line (until 4th line and for >4th lines) and overall, i.e., irrespective of treatment line. At each treatment line, the number and proportion of patients in the categories of each treatment pattern variable was reported:

  - Treatment regimen
  - Bone marrow transplant statuses (Autologous and Allogeneic)
  - Treatment type
  - Treatment line start year

Furthermore, the continuous treatment pattern variables were summarized by treatment line:

  - Treatment duration
  - Time to treatment line discontinuation
  - Treatment line duration

ORR per treatment line was summarized per treatment, bone marrow transplant statuses, and treatment type together with 90% confidence intervals (CI) that were calculated using the Clopper-Pearson method. When calculating the CIs for line >4$^{th}$ and for the total column, the independence of observations was assumed, although there might exist multiple observations from one patient.

#### 9.9.2.2 Primary objective 2

- Description of OS and TTNT

OS was analyzed for treatment lines 1 to 5. In TTNT analyses lines 1, 2, 3, 4 and >4 were used. OS (including OS1, OS2, OS3, OS4, OS5) was described with the Kaplan-Meier estimator and TTNT (including TTNT1, TTNT2, TTNT3, TTNT4, TTNT>4) per treatment line was described with the Aalen-Johansen estimator treating death as a competing risk. OS and TTNT were described for the actual study cohort population stratified by patient characteristics (Section 9.4.1), disease characteristics (Section 9.4.2), and treatment patterns (Section 9.4.4) for the following variables:

- Treatment regimen: Major treatment regimens, categorized as detailed in Annex 3. Categorization of individual therapies into major regimens.
- Bone marrow transplant statuses, categorized as in Section 9.4.4
- Treatment type: single therapy, duplet therapy, triplet therapy, or other
- Age category at diagnosis: 37-50 years: 51-60 years, 61-70 years, 71-80 years, or >80 years
- The CRAB components: hypercalcemia, renal dysfunction, anaemia, and lytic bone lesions, defined exclusively using the dichotomous variable in the FHR. The components were categorized as yes, no, or unknown.
- Disease stage according to the R-ISS risk classification: 1 (low), 2 (standard), or 3 (high)
- FISH findings:
  - High risk cytogenetics
    - Deletion [del(17p)]
    - Translocation [t(4;14)]
    - Translocation [t(14;16)]
  - Non-high risk cytogenetics (yes)
    - Translocation [t(14;20)]
    - Gain 1q [gain(1q)]
    - Deletion 1p32 or 1p36 [1p32 or 1p36)]

  The FISH findings were categorized as yes, no, or unknown.
- Myeloma type (naïve, sensitive) per major treatment regimen
- Early progression: yes, no, unknown

These time-to-event outcomes were also summarized by the relevant statistics derived based on the Kaplan-Meier or Aalen-Johansen estimator data: the proportion of censoring, the number of events and number of censorings were reported. Stratifications by patient characteristics, disease characteristics, and treatment patterns were also reported.

Each of the outcomes TTNT1, TTNT2, TTNT3, TTNT4 were analyzed as a separate outcome. In the analysis of TTNT>4, all TTNT outcomes for treatment lines 5 or higher were treated as a

single outcome where risk time began at 0 at the start of each treatment line and covariates were time-varying with status updated at the start of each treatment line. In the OS1, OS2, OS3, OS4, and OS5 analyses covariate status at the start of treatment line 1, 2, 3, 4, or 5 were used, respectively.

#### 9.9.2.3 Secondary objective 1

- Factors associated with TTNT and OS

Factors associated with OS (including OS1, OS2, OS3, OS4, OS5) and TTNT (including TTNT1, TTNT2, TTNT3, TTNT4, TTNT>4) were identified using a multivariate Cox regression model (adjusted results). In addition, to produce crude estimates for individual variables, stratified incidence rates were calculated with regard to the variables described below. The following variables were included as stratifying variables in incidence rate analysis and also in all Cox models:

- Treatment regimen: Major treatment regimens, categorised as in Section 9.4.4 and with Bor/Cpm/Dxm as reference.
- Gender: male (reference), or female
- Age category at diagnosis: 37-50 years (reference): 51-60 years, 61-70 years, 71-80 years, or >80 years
- The CRAB components: hypercalcemia, renal dysfunction, anaemia, and lytic bone lesions, defined exclusively using the dichotomous variable in the FHR. The components were categorized as yes, no (reference), or unknown.
- Disease stage according to the R-ISS risk classification: 1 (low, reference), 2 (standard), or 3 (high)
- FISH findings:
  - High risk cytogenetics
    - Deletion [del(17p)]
    - Translocation [t(4;14)]
    - Translocation [t(14;16)]
  - Non-high risk cytogenetics (yes)
    - Translocation [t(14;20)]
    - Gain 1q [gain(1q)]
    - Deletion 1p32 or 1p36 [1p32 or 1p36)]

  The FISH findings were categorized as yes, no (reference), or unknown.

In addition, the following additional patient characteristics, disease characteristics, and treatment patterns were used in the stratified incidence rate analyses and added into the Cox model one at a time:

- Year of follow-up start (based on the date of start of each treatment line): 2010 (reference), 2011, 2012, …, 2017
- Short treatment line duration (in the previous line of treatment, for OS>1 and TTNT >1): yes, no (reference), or unknown
- Bone marrow transplant status, categorized as in Section 9.4.4
- Early progression: yes, no (reference), unknown
- Treatment type (single (reference), duplet, triplet therapy); This variable replaced existing variable: *Treatment: Major treatment regiments* (see 9.9.5).

In the analysis of TTNT>4 the observations were assumed to be independent, although there might exist multiple lines from one patient.
In the analysis of TTNT competing risks were not taken into account and deaths were treated with censoring.

- Treatment selection

In the treatment selection analyses, the following binary treatment selection outcome variables were used

- Single therapy
- Duplet therapy
- Triplet therapy
- Bone marrow transplant status: single autologous bone marrow transplant
- Bone marrow transplant status: single allogeneic bone marrow transplant
- Major treatment regimens, by category according to Annex 3. Categorization of individual therapies into major regimens.

These binary outcome variables that indicated if a patient received the specified treatment at the start of the treatment line or not (1 meaning that the patient received the treatment and 0 that the patient did not receive the specified treatment). Thereafter, factors associated with treatment selection were identified using a multivariate mixed effects logistic regression model treating patient ID as a random effect and the following variables as fixed effects:

- Treatment line, as defined in Section 9.4.4 and with the first treatment line as reference
- Gender (Section 9.4.1): male (reference), or female
- Age category at diagnosis (Section 9.4.1): 37-50 years (37 to <51 years) (reference): 51-60 years (51 to <61 years), 61-70 years (61 to <71 years), 71-80 years (71 to <81 years), or >80 years (81 years or more)
- The CRAB components (Section 9.4.2): hypercalcemia, renal dysfunction, anaemia, and lytic bone lesions, defined exclusively using the dichotomous variable in the FHR. The components were categorized as yes, no (reference), or unknown.
- Disease stage according to the R-ISS risk classification (Section 9.4.2): 1 (low, reference), 2 (standard), or 3 (high)
- FISH findings:
  - High risk cytogenetics
    - Deletion [del(17p)]
    - Translocation [t(4;14)]
    - Translocation [t(14;16)]
  - Non-high risk cytogenetics (yes)
    - Translocation [t(14;20)]
    - Gain 1q [gain(1q)]
    - Deletion 1p32 or 1p36 [1p32 or 1p36)]

  The FISH findings were categorized as yes, no (reference), or unknown.
- Early progression: yes, no (reference), or unknown

### 9.9.2.4 Secondary objective 2

Patients at low-, standard-, and high-risk were identified at diagnosis and divided into groups based on the R-ISS categorization (Annex 2. ISS and R-ISS); This generated 3 subgroups. Patients who did not receive the following pre-specified treatments: allogeneic bone marrow transplant, autologous bone marrow transplant, duplet or triplet therapies as the 1st, 2nd, 3rd, 4th, >4th line treatment were identified and followed-up at the start of each treatment line (1st, 2nd, 3rd, 4th, >4th line); This generated 4 subgroups per treatment line, 20 in total. Patients with short treatment line duration were defined at the end of a treatment line (short duration of 1st line treatment, short duration of 2nd line treatment, …, short duration of 4th treatment line) and followed-up after the end of the treatment line with short duration; this generated 1 subgroup per treatment line, 4 in total.

After identifying the above subpopulations, they were described similarly as defined in Primary Objective 1. Specifically, baseline and disease characteristics were tabulated for all the subgroups. Kaplan-Meier and Aalen-Johansen estimators stratified by R-ISS, transplant statuses, and single/duplet/triplet therapy were made as part of the primary objective. Therefore, additional Kaplan-Meier and Aalen-Johansen analysis were done only for those having short previous treatment line duration.

**Table 2. Summary of the subpopulations for objective 2.**

| | **Subpopulations of varying disease status, according to the R-ISS risk classification** | **Subpopulations without specific treatments** | **Subpopulations of short treatment durations** |
|---|---|---|---|
| Subpopulations names | • Low (1) R-ISS risk classification<br>• Standard (2) R-ISS risk classification<br>• High (3) R-ISS risk classification | • Without autologous bone marrow transplant in treatment line 1<br>• Without allogeneic bone marrow transplant in treatment line 1<br>• Without duplet therapy in treatment line 1<br>• Without triplet therapy in treatment line 1<br><br>• Without autologous bone marrow transplant in treatment line 2<br>• Without allogeneic bone marrow transplant in treatment line 2<br>• Without duplet therapy in treatment line 2<br>• Without triplet therapy in treatment line 2<br><br>• Without autologous bone marrow transplant in treatment line 3<br>• Without allogeneic bone marrow transplant in treatment line 3<br>• Without duplet therapy in treatment line 3<br>• Without triplet therapy in treatment line 3<br><br>• Without autologous bone marrow transplant in treatment line 4<br>• Without allogeneic bone marrow transplant in treatment line 4<br>• Without duplet therapy in treatment line 4<br>• Without triplet therapy in treatment line 4<br>• Without autologous bone marrow transplant in treatment line 5 | • Short duration of 1st line treatment<br>• Short duration of 2nd line treatment<br>• Short duration of 3rd treatment line Short duration of 4th treatment line |

| | | | |
|---|---|---|---|
| | | • Without allogeneic bone marrow transplant in treatment line 5<br>• Without duplet therapy in treatment line 5<br>• Without triplet therapy in treatment line 5 | |
| **Total number of subpopulations** | **3** | **20** | **4** |

R-ISS, revised international staging system for multiple myeloma

### 9.9.3 Missing values

If a given variable was totally or systematically missing from a database, it was excluded from the analyses. If a variable was missing for only some of the patients or arbitrarily missing, a missing data category was added and used in the analyses. As specified in more detail in Section 9.4, an unknown category was used for each categorical study variable. If continuous variables had missing observations, a category "not applicable (NA)" was used.

According to the SAP, a sensitivity analysis was planned to be conducted without variables with a high proportion of missingness in the models (see Section 9.9.4). However, no variable had a high proportion of missingness.

When a variable was missing from the database, equivalent information was derived from other available variables, if possible. Specifically, when the treatment end date was missing, it was imputed according to following steps:

1. Treatment end date was set to be the date before the start of next treatment (or period without treatment) in the same treatment line. Starts of a therapy that may be in parallel with other treatment were ignored (e.g. radiation therapy).
2. If still missing, treatment end date was the death date, if treatment was in the last line and line ended at death before end of follow-up.
3. If still missing, treatment end date was the date before start of next line, if next line occurred.

### 9.9.4 Sensitivity analyses

The representativeness of the actual study cohort in the FHR was investigated by presenting baseline summary statistics of the whole study cohort. These baseline statistics on patient and disease characteristics were described to be evaluated against the actual study cohort. The SAP 2.0 detailed statistical test for the comparison between the cohorts. However, as the discrepancy between the cohorts was 1 person (see Section 10.1), no comparative analyses were performed.

In a sensitivity analysis, the treatment line definition was re-defined. In case disease progression (PD or relapse) was followed by a new therapy, a change of the line of treatment was defined even if not recorded originally in the FHR. The re-defined line of treatment variable was compared to the original FHR-recorded one by counting the number of occasions in which the FHR recorded treatment line variable was updated. According to the SAP 2.0, the main outcome analyses would have been repeated if the number of treatment lines would have increased by >10%. However, as the increase was 8.35% (see Section 10.9) the analyses were not repeated.

Finally, the SAP 2.0 detailed sensitivity analyses to explore the effect of missingness, by excluding variables with a high proportion (>50% of patients) of missingness from the statistical models, as described in Section 9.9.3. As no variable had missing values in >50% patients, these sensitivity analyses were not performed (see Section 10.9).

### 9.9.5 Amendments to the statistical analysis plan

Statistical analyses deviating from SAP 2.0 are defined in Table 3.

**Table 3. Statistical analyses deviating from SAP 2.0.**

| No. | Section of SAP 2.0 | Deviation from SAP 2.0 | Reason |
|---|---|---|---|
| 1 | 3.2, 8.3 | For secondary objective 1, treatment line duration was omitted as an outcome. | The recording of treatment discontinuation was considered too incomplete. |
| 2 | 5.3 | MM diagnosis based on ICD-10 or, if available, ICD-O codes. | Clarification of definition, additional check of appropriate diagnosis. |
| 3 | 5.2, 6.4, 8.5, 8.6, 12 | Sensitivity analyses (regression) excluding variables with high proportion of missingness were not performed. | Conditions for sensitivity analyses were not fulfilled. |
| 4 | 5.2, 6.4, 8.5, 8.6, 12 | Sensitivity analyses comparing the actual and whole study cohort were not performed. | Difference between actual and whole study cohort was only one patient. |
| 5 | 6.2 | Calcium level was used instead of corrected serum calcium. | Feedback from medical expert at FHR. |
| 6 | 6.2 | Relapse defined according to variable "clinical relapse". | Variable "relapse" was not recorded in the data. |
| 7 | Multiple | The included patients represented only one hospital region, HUS. | Data was considered complete only in this region by the data holder. |

## 9.10 Quality control

The study was conducted according to the protocol. All revisions to the protocol were approved by the principal investigator, sponsor, and co-authors of the study. All changes to the protocol were properly documented as protocol amendments and when necessary such protocol amendments were delivered to FHR.

The study protocol was written by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct (12) and the Guideline for Good Pharmacoepidemiology Practices (GPP) (13) by the International Society for Pharmacoepidemiology (ISPE). The study protocol, as well as results, will be published in the European register of non-interventional post-authorisation studies (EU PAS) register maintained by the European Medicines Agency (EMA).

All study data, source code of data management, and data analyses will be retained for five years after the end of the study and then destroyed. As the register holder of the study register, EPID Research is responsible for archiving and destroying the data. Secure archives will be maintained for the orderly storage and retrieval of all study related material on the EPID Research server. An index shall be prepared to identify the archived contents and their locations. Access to the archives will be controlled and limited to authorized personnel only.

Due to the study type (register study using administrative databases) on-site monitoring was not performed.

# 10 Results

The below section highlights key findings based on primary and secondary objectives 1 and 2. Full results are presented in Annex 4 Results Report.

## 10.1 Participants

In total, 225 patients were included in the whole study cohort, and 224 patients in the actual study cohort (
Figure 2). The mean time of follow-up for the actual cohort was 40.6 months (SD 22.6) and 123 (54.9%) were alive at the end of the study period (31 December 2017) (Results Report Table 5; Annex 4).

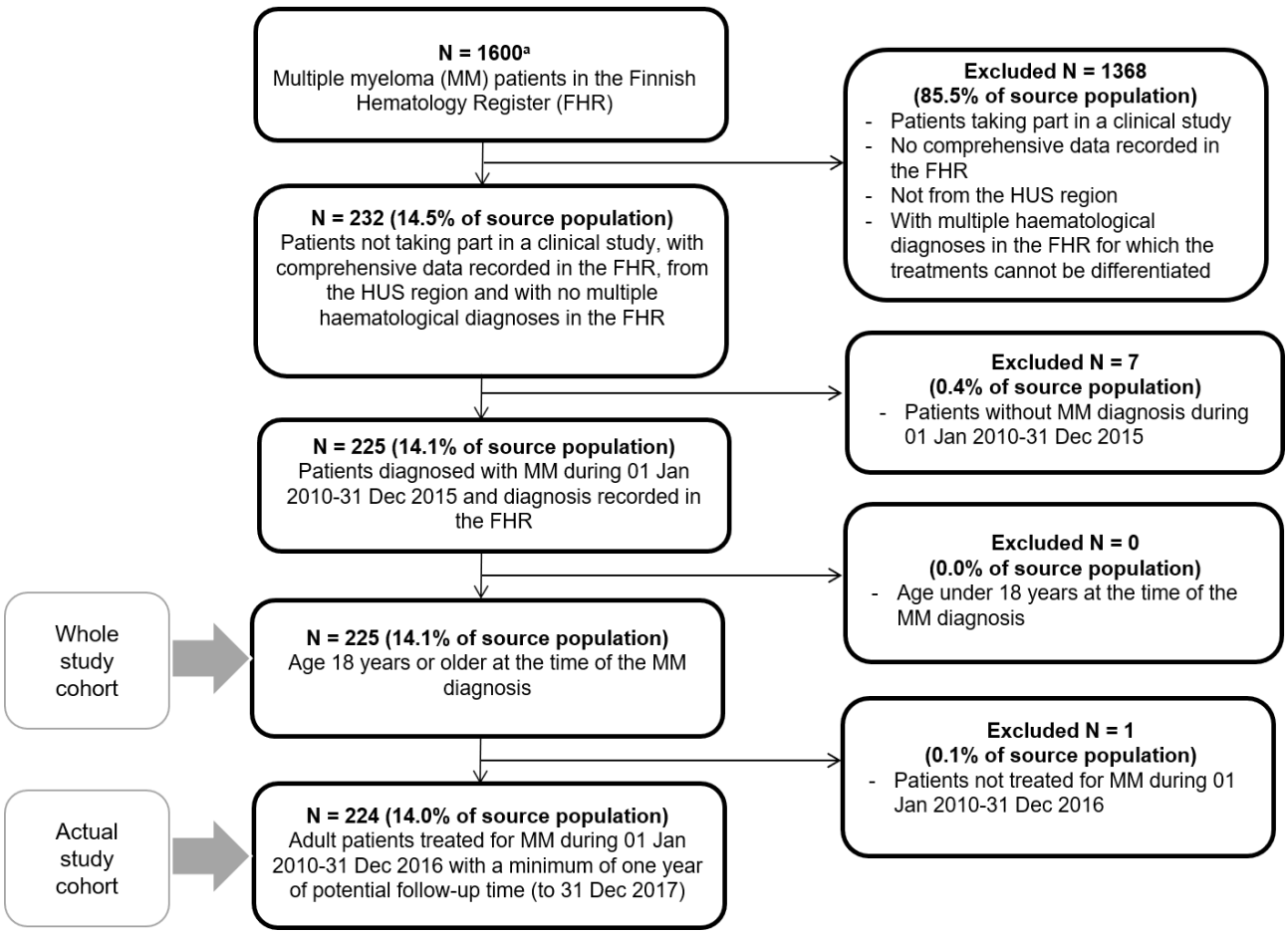


**Figure 2. Flow diagram of MM patients included in the whole and actual study cohorts.**

FHR, Finnish Hematology Register; HUS, Helsingin ja Uudenmaan sairaanhoitopiiri (eng. Helsinki and Uusimaa Hospital District); MM, multiple myeloma.
[a] Based on an estimate

## 10.2 Primary objective 1: Descriptive characteristics and patient journey of Finnish MM patients

### 10.2.1 Patient characteristics

In the whole study cohort (n=225), 52.4% of MM patients were male (Table 4). The mean age at diagnosis was 66.9 years (SD 9.0 years) with the highest frequency of MM diagnosis in the age group 61-70 years (41.3%). The most common co-morbidity in the whole study cohort was hypertension followed by dyslipidaemia, diabetes I/II, history of other cancers, moderate lung disease and arrythmia. In total, 28.9% of the population had no other co-morbidities at diagnosis. Other co-morbidities with a prevalence of less than 5% and further demographic characteristics in the whole study cohort are presented in the Results Report Table 1 (Annex 4).

**Table 4. Selected patient characteristics at MM diagnosis in the whole study cohort (n=225)**

| Patient characteristics[a] | Summary statistics |
|---|---|
| **Demographic characteristics** | |
| **Gender, n (%)** | |
| Male | 118 (52.4%) |
| Female | 107 (47.6%) |
| **Age in years** | |
| 37-50, n (%) | 13 (5.8%) |
| 51-60, n (%) | 37 (16.4%) |
| 61-70, n (%) | 93 (41.3%) |
| 71-80, n (%) | 75 (33.0%) |
| >80, n (%) | 7 (3.1%) |
| Range (min,max) | (37.0, 87.4) |
| Mean (SD) | 66.9 (9.0) |
| Median (Q1,Q3) | 67.7 (62.3, 73.2) |
| **Most frequent co-morbidities[b], n (%)** | |
| Hypertension | 95 (42.2%) |
| Dyslipidaemia | 51 (22.7%) |
| Arrhythmia | 14 (6.2%) |
| Lung disease (moderate) | 18 (8.0%) |
| Diabetes (I/II) | 27 (12.0%) |
| History of other cancers | 20 (8.9%) |
| No other co-morbidities diagnosed | 65 (28.9%) |

MM, multiple myeloma; SD, standard deviation.
Source: Annex 4 – Table 1.
[a] At the time of MM diagnosis.
[b] Co-morbidities at MM diagnosis with a prevalence of 5% or more.

Selected patient characteristics of the actual study cohort (n=224), by treatment line, are presented in Table 5. From treatment line 1 to lines >4, the number of patients decreased from 224 to 36. The proportion of male patients increased from 52.7% in treatment line 1 to 64.8% in treatments lines >4, while the median age ranged 67.7-68.4 years. Across all treatment lines, hypertension was the most common co-morbidity, while 29.0-39.8% of patients had no other co-morbidities at the time of MM diagnosis. All patient characteristics of the actual cohort, per treatment line, are described in the Results Report Table 2 (Annex 4).

**Table 5. Selected patient characteristics in the actual study cohort (n=224), per treatment line**

| Patient characteristics[a] | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Patients / lines, n** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** |
| **Demographic characteristics** | | | | | |
| **Gender, 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) |
| **Most frequent co-morbidities[b], n (%)** | | | | | |
| Hypertension | 95 (42.4%) | 74 (40.4%) | 52 (39.4%) | 21 (30.9%) | 24 (27.3%) |
| Dyslipidaemia | 51 (22.8%) | 43 (23.5%) | 30 (22.7%) | 15 (22.1%) | 21 (23.9%) |
| Arrhythmia | 14 (6.2%) | 10 (5.5%) | 7 (5.3%) | 2 (2.9%) | 0 (0.0%) |
| Lung disease (moderate) | 18 (8.0%) | 17 (9.3%) | 12 (9.1%) | 6 (8.8%) | 8 (9.1%) |
| Diabetes (I/II) | 27 (12.1%) | 23 (12.6%) | 17 (12.9%) | 6 (8.8%) | 4 (4.5%) |
| History of other cancers | 20 (8.9%) | 19 (10.4%) | 14 (10.6%) | 4 (5.9%) | 12 (13.6%) |
| No other co-morbidities diagnosed | 65 (29.0%) | 54 (29.5%) | 42 (31.8%) | 25 (36.8%) | 35 (39.8%) |

BMI, body mass index; MM, multiple myeloma; SD, standard deviation.
Source: Annex 4 – Table 2.
[a] Patient characteristics, including age and the presence of co-morbidities, are defined at the time of MM diagnosis. However, the descriptive statistics differ by treatment line, because the descriptive statistics describes these characteristics (at diagnosis) for the MM patients left in each treatment line.
[b] Co-morbidities at MM diagnosis with a prevalence of 5% or more in at least one treatment line.

### 10.2.2 Disease characteristics

The disease characteristics of whole study cohort at MM diagnosis (n=225) and the actual cohort (n=224), by treatment line, are presented in the Results Report Table 3 and Table 4 (Annex 4). Across all treatment lines, the most common **CRAB component** was lytic bone lesions followed by anaemia (Table 6). The distribution of the CRAB components appeared similar between the treatment lines with the exception of a declining pattern for renal dysfunction. Of the **high risk cytogenetic findings**, FISH del(17p13) was the most frequent, with 8.3-11.4% of patients in treatment lines 1->4 having the finding. Of the **non-high risk cytogenetic findings**, gain(1q) was the most common in all treatment lines. For **other cytogenetics,** approximately 7% of patients in treatment lines 1-4 had the finding t(11;14). According to the ISS risk classification, for patients in all treatment lines the standard risk classification was the most common (ranging from 41.5% in line 1 to 46.6% in treatment lines >4); although the percentage of the high-risk classification increased from 29.5% in line 1 to 36.8% in line 4. Less than 10% of patients in all treatment lines had an MM with the low **R-ISS risk classification**, while most patients in all treatment lines (>50%) had an MM with the standard risk classification. For **serum M-protein type**, IgG was the most common with 48.9-55.2% of patients in treatment lines 1->4 having the finding; IgD was the least common (less than 1% of patients in treatment lines 1-3 and no patients in treatment lines 4+); across treatment lines, between 16.4% and 22.7% of patients had no findings. In all treatment lines, 15.9-22.7% of patients had an MM with **early**

**progression**; however, early progression was unknown in 29.5% in treatment line 1 although this percentage decreased in subsequent treatment lines (1.1% in lines >4).

**Table 6. Selected disease characteristics in the actual study cohort (n=224), per treatment line**

| Disease characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Patients / lines, n** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** |
| **CRAB component[a,b], n (%)** | | | | | |
| Hypercalcemia | 35 (15.6%) | 31 (16.9%) | 24 (18.2%) | 17 (25.0%) | 11 (12.5%) |
| Anaemia | 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%) |
| **FISH findings[a], n (%)** | | | | | |
| **High risk cytogenetics** | | | | | |
| del(17p13) | 22 (9.8%) | 18 (9.8%) | 11 (8.3%) | 7 (10.3%) | 10 (11.4%) |
| t(4;14) | 10 (4.5%) | 9 (4.9%) | 6 (4.5%) | 5 (7.4%) | 6 (6.8%) |
| t(14;16) | 8 (3.6%) | 8 (4.4%) | 6 (4.5%) | 3 (4.4%) | 6 (6.8%) |
| **Non-high risk cytogenetics** | | | | | |
| t(14;20) | 1 (0.4%) | 1 (0.5%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| 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%) |
| **Other cytogenetics** | | | | | |
| t(11;14) | 16 (7.1%) | 13 (7.1%) | 10 (7.6%) | 5 (7.4%) | 1 (1.1%) |
| **Disease status according to the ISS risk classification[a,b], n (%)** | | | | | |
| Low (1) | 38 (17.0%) | 28 (15.3%) | 18 (13.6%) | 7 (10.3%) | 20 (22.7%) |
| Standard (2) | 93 (41.5%) | 78 (42.6%) | 55 (41.7%) | 29 (42.6%) | 41 (46.6%) |
| High (3) | 66 (29.5%) | 56 (30.6%) | 46 (34.8%) | 25 (36.8%) | 20 (22.7%) |
| Unknown | 27 (12.1%) | 21 (11.5%) | 13 (9.8%) | 7 (10.3%) | 7 (8.0%) |
| **Disease status according to the R-ISS risk classification[a], n (%)** | | | | | |
| Low (1) | 18 (8.0%) | 11 (6.0%) | 6 (4.5%) | 4 (5.9%) | 7 (8.0%) |
| Standard (2) | 121 (54.0%) | 103 (56.3%) | 79 (59.8%) | 39 (57.4%) | 55 (62.5%) |
| High (3) | 27 (12.1%) | 21 (11.5%) | 16 (12.1%) | 9 (13.2%) | 7 (8.0%) |
| Unknown | 58 (25.9%) | 48 (26.2%) | 31 (23.5%) | 16 (23.5%) | 19 (21.6%) |
| **Serum M-protein type, n (%)** | | | | | |
| No findings | 41 (18.3%) | 30 (16.4%) | 22 (16.7%) | 12 (17.6%) | 20 (22.7%) |
| Not tested | 4 (1.8%) | 3 (1.6%) | 2 (1.5%) | 1 (1.5%) | 2 (2.3%) |
| IgA | 57 (25.4%) | 47 (25.7%) | 35 (26.5%) | 19 (27.9%) | 23 (26.1%) |
| IgD | 2 (0.9%) | 1 (0.5%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| IgG | 119 (53.1%) | 101 (55.2%) | 71 (53.8%) | 36 (52.9%) | 43 (48.9%) |
| Unknown | 1 (0.4%) | 1 (0.5%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| **Early progression[c], n (%)** | | | | | |
| Yes | 40 (17.9%) | 38 (20.8%) | 30 (22.7%) | 14 (20.6%) | 14 (15.9%) |
| No | 118 (52.7%) | 113 (61.7%) | 94 (71.2%) | 53 (77.9%) | 73 (83.0%) |
| Unknown | 66 (29.5%) | 32 (17.5%) | 8 (6.1%) | 1 (1.5%) | 1 (1.1%) |

CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; ISS, international staging system; OS, overall survival; R-ISS, revised international staging system for multiple myeloma.
Source: Annex 4 – Table 4.
[a] Patient characteristics are defined at the time of MM diagnosis. However, the percentage of patients differ by treatment line, because the percentage of patients with these characteristics (at diagnosis) is among the MM patients left in each treatment line.
[b] FHR variables.
[c] At the start of each treatment line.

### 10.2.3 Treatment patterns

Table 7 displays selected treatment patterns by treatment line. The full description of all treatment patterns is presented in the Results Report Table 6 (Annex 4). The most common **treatment regimens** in line 1 were Bor/Dxm (19.20%), Bor/Cpm/Dxm (17.41%) and other regimens (20.98%). Treatment with both Bor/Dxm and Bor/Cpm/Dxm was lower at all other subsequent treatment lines. At treatment lines >4, Len/Dxm (11.36%) and other regimens (55.68%) were the most frequent. Concerning the **bone marrow transplant status**, 20.98% of patients in the treatment line 1 received a single autologous bone marrow transplant, while only 5 patients (2.23%) received a single allogeneic bone marrow transplant. The proportion of patients with either type of bone marrow transplant treatment appeared to decline in the subsequent treatment lines. Of **treatment types**, the duplet or triplet treatment were more common than single treatment across all treatment lines. The mean **treatment line duration** decreased from 11.65 and 11.98 months in lines 1 and 2, respectively, to 4.48 months in lines>4. Similarly, the median line duration was 5.05 and 6.66 months in lines 1 and 2, respectively, and decreased to 3.21 months in line >4.

**Table 7. Selected treatment patterns in the actual study cohort (n=224), per treatment line**

| Treatment pattern variable[a] | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 | Total |
|---|---|---|---|---|---|---|
| **Patients / lines, n** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** | **224 / 695** |
| **Treatment regimen, n lines (%)** | | | | | | |
| Bor/Cpm/Dxm | 39 (17.41%) | 9 (4.92%) | 2 (1.52%) | 3 (4.41%) | 3 (3.41%) | 56 (8.06%) |
| Bor/Cpm/Dxm+AutoHSCT (HD-mel) | 22 (9.82%) | 0 (0.00%) | 1 (0.76%) | 0 (0.00%) | 0 (0.00%) | 23 (3.31%) |
| Bor/Dxm | 43 (19.20%) | 14 (7.65%) | 17 (12.88%) | 4 (5.88%) | 8 (9.09%) | 86 (12.37%) |
| Bor/Dxm+AutoHSCT (HD-mel) | 12 (5.36%) | 5 (2.73%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 17 (2.45%) |
| Bor/Dxm/Len | 0 (0.00%) | 27 (14.75%) | 21 (15.91%) | 3 (4.41%) | 7 (7.95%) | 58 (8.35%) |
| Bor/Dxm/Len+AutoHSCT (HD-mel) | 0 (0.00%) | 11 (6.01%) | 0 (0.00%) | 1 (1.47%) | 0 (0.00%) | 12 (1.73%) |
| Bor/Mel/Pred (VMP) | 17 (7.59%) | 21 (11.48%) | 4 (3.03%) | 0 (0.00%) | 4 (4.55%) | 46 (6.62%) |
| Cpm/Pred | 4 (1.79%) | 7 (3.83%) | 5 (3.79%) | 10 (14.71%) | 1 (1.14%) | 27 (3.88%) |
| DR-PACE (Cis/Cpm/Dxm/Dox/Eto/Len) | 0 (0.00%) | 3 (1.64%) | 4 (3.03%) | 3 (4.41%) | 5 (5.68%) | 15 (2.16%) |
| Len/Dxm | 0 (0.00%) | 34 (18.58%) | 35 (26.52%) | 16 (23.53%) | 10 (11.36%) | 95 (13.67%) |
| Mel/Pred (MP) | 14 (6.25%) | 14 (7.65%) | 5 (3.79%) | 4 (5.88%) | 1 (1.14%) | 38 (5.47%) |
| Mel/Pred/Tal (MPT) | 12 (5.36%) | 2 (1.09%) | 1 (0.76%) | 0 (0.00%) | 0 (0.00%) | 15 (2.16%) |
| Tal/Dxm | 14 (6.25%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 14 (2.01%) |
| Other regimens | 47 (20.98%) | 36 (19.67%) | 37 (28.03%) | 24 (35.29%) | 49 (55.68%) | 193 (27.77%) |
| **Bone marrow transplant status, n lines (%)** | | | | | | |
| Single[b] autologous bone marrow transplant | 47 (20.98%) | 29 (15.85%) | 4 (3.03%) | 1 (1.47%) | 0 (0.00%) | 81 (11.65%) |
| Single[b] allogeneic bone marrow transplant | 5 (2.23%) | 4 (2.19%) | 1 (0.76%) | 1 (1.47%) | 0 (0.00%) | 11 (1.58%) |
| **Treatment type, n lines (%)** | | | | | | |
| Single | 2 (0.89%) | 0 (0.00%) | 12 (9.09%) | 8 (11.76%) | 11 (12.50%) | 33 (4.75%) |
| Duplet | 92 (41.07%) | 85 (46.45%) | 68 (51.52%) | 38 (55.88%) | 32 (36.36%) | 315 (45.32%) |
| Triplet | 94 (41.96%) | 75 (40.98%) | 37 (28.03%) | 13 (19.12%) | 25 (28.41%) | 244 (35.11%) |
| Other[c] | 36 (16.07%) | 23 (12.57%) | 15 (11.36%) | 9 (13.24%) | 20 (22.73%) | 103 (14.82%) |
| **Treatment line duration (months)[d], n lines (%)** | | | | | | |
| NA | 35 (15.62%) | 45 (24.59%) | 56 (42.42%) | 27 (39.71%) | 31 (35.23%) | 194 (27.91%) |
| Range (min,max) | (0.07, 72.92) | (0.07, 71.05) | (0.10, 32.43) | (0.69, 35.38) | (0.10, 15.90) | (0.07, 72.92) |
| Mean (SD) | 11.65 (14.56) | 11.98 (12.89) | 7.92 (7.63) | 7.46 (8.12) | 4.48 (3.91) | 10.02(12.15) |
| Median (Q1,Q3) | 5.05 (2.66, 15.21) | 6.66 (2.51, 18.52) | 5.90 (2.88, 11.05) | 3.77 (2.52, 9.15) | 3.21 (1.93, 6.03) | 5.08 (2.49, 12.75) |

AutoHSCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; Cis, cisplatin; Cpm, cyclophosphamide; Dox, doxorubicin; DR-PACE, cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide; Dxm, dexamethasone; Eto, etoposide; HD-mel, high-dose melphalan; Len, lenalidomide; Mel, melphalan; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; NA, not available; Tal, thalidomide; Pred, prednisone; VMP, bortezomib + melphalan + prednisone.

Source: Annex 4 – Table 6.

[a] At the start of each treatment line.

[b] No tandem bone marrow transplants were observed. Thus, the single transplants represent all bone marrow transplants.

[c] Treatment type was *other* if it could not be specified as Single, Duplet or Triplet: if the treatment had more than three drugs, treatment line had several treatments (e.g. single and duplet) or combination therapy (e.g. DR-PACE).
[d] Treatment line duration is the time from treatment line start to discontinuation or start of next treatment line.

### 10.2.4 Overall response rate

The ORR of any treatment across all treatment lines was 43.17% (90% CI 40.03-46.35). The ORR, regardless of the received treatment, was 60.71% (90% CI 55.04-66.17 ) in treatment line 1, 44.26% (90% CI 38.05-50.61) in treatment line 2, 34.09% (90% CI 27.25-41.48) in treatment line 3, 30.88% (90% CI 21.72-41.35) in treatment line 4, and 19.32% (90% CI 12.70-27.56) in treatment line >4 (not shown). The overall response rate (ORR) for the varying **treatment regimens** reached 50% or more for the following therapies: Bor/Cpm/Dxm, Bor/Cpm/Dxm+AutoHSCT (HD-mel), Bor/Dxm, Bor/Dxm+AutoHSCT (HD-mel), Bor/Dxm/Len+AutoHSCT (HD-mel), Bor/Mel/Pred (VMP), and Mel/Pred/Tal (MPT) with the highest response for Bor/Cpm/Dxm+AutoHSCT (HD-mel) (69.57%) (Table 8). Overall response for **bone marrow transplant status** was 62.96% for single autologous transplants and less than 30% (27.27%) for allogeneic. Of **treatment types**, single treatment yielded the lowest response rate (6.06%) as compared to duplet, triple and other treatment types which ranged between 40% and 52% ORR. The full results of overall response rates are found in the Results Report Table 7 (Annex 4).

**Table 8. Overall response rates by therapy pattern variables**

| Treatment pattern variable | Total treatment lines | |
|---|---|---|
| | n/N (%) | 90% CI |
| **Treatment** | | |
| Any | 300/695 (43.17%) | [40.03%,46.35%] |
| Bor/Cpm/Dxm | 28/56 (50.00%) | [38.33%, 61.67%] |
| Bor/Cpm/Dxm+AutoHSCT (HD-mel) | 16/23 (69.57%) | [50.36%, 84.75%] |
| Bor/Dxm | 47/86 (54.65%) | [45.22%, 63.83%] |
| Bor/Dxm+AutoHSCT (HD-mel) | 9/17 (52.94%) | [31.08%, 73.99%] |
| Bor/Dxm/Len | 23/58 (39.66%) | [28.83%, 51.30%] |
| Bor/Dxm/Len+AutoHSCT (HD-mel) | 7/12 (58.33%) | [31.52%, 81.90%] |
| Bor/Mel/Pred (VMP) | 24/46 (52.17%) | [39.15%, 64.98%] |
| Cpm/Pred | 10/27 (37.04%) | [21.66%, 54.66%] |
| DR-PACE (Cis/Cpm/Dxm/Dox/Eto/Len) | 7/15 (46.67%) | [24.37%, 70.00%] |
| Len/Dxm | 29/95 (30.53%) | [22.78%, 39.21%] |
| Mel/Pred (MP) | 13/38 (34.21%) | [21.56%, 48.80%] |
| Mel/Pred/Tal (MPT) | 9/15 (60.00%) | [35.96%, 80.91%] |
| Tal/Dxm | 6/14 (42.86%) | [20.61%, 67.50%] |
| Other | 72/193 (37.31%) | [31.50%, 43.41%] |
| **Bone marrow transplant status, n (%)** | | |
| Single[a] autologous bone marrow transplant | 51/81 (62.96%) | [53.27%, 71.93%] |
| Single[a] allogeneic bone marrow transplant | 3/11 (27.27%) | [7.88%, 56.44%] |
| **Treatment type** | | |
| Single | 2/33 (6.06%) | [1.09%, 17.87%] |
| Duplet | 128/315 (40.63%) | [36.00%, 45.40%] |
| Triplet | 116/244 (47.54%) | [42.12%, 53.01%] |
| Other | 54/103 (52.43%) | [43.88%, 60.87%] |

AutoHSCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; CI, confidence interval; Cis, cisplatin; Cpm, cyclophosphamide; Dox, doxorubicin; DR-PACE, cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide; Dxm, dexamethasone; Eto, etoposide; HD-mel, high-dose melphalan; Len, lenalidomide; Mel, melphalan; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; Tal, thalidomide; Pred, prednisone; VMP, bortezomib + melphalan + prednisone.

Source: Annex 4 – Table 7.

[a] No tandem bone marrow transplants were observed. Thus, the single transplants represent all bone marrow transplants.

Note: The 90% confidence interval is presented for the proportion, calculated using the Clopper-Pearson method. When calculating confidence intervals for Total treatment lines, independence of observations is assumed, although there might be multiple observations from a patient.

## 10.3 Primary objective 2: Description of overall survival (OS)

### 10.3.1 Among all MM patients with treatment (actual study cohort)

Among the 224 MM patients in the actual cohort, the median OS in treatment line 1 was 62.36 months (90% CI 54.89-73.54) (Table 9). The median OS decreased in all subsequent treatment lines. Patients on lines 4 and 5 had the lowest median OS with 18.07 and 12.00 months, respectively. OS in all treatment lines is also presented graphically in the Kaplan-Meier curves in Figure 3.

**Table 9. Median overall survival (OS) in treatment lines 1-5 among MM patients (n=224)**

| Variable | Line 1 | Line 2 | Line 3 | Line 4 | Line 5 |
|---|---|---|---|---|---|
| **Total** | | | | | |
| N at risk | 224 (100.00%) | 183 (100.00%) | 132 (100.00%) | 68 (100.00%) | 36 (100.00%) |
| N with event | 101 (45.09%) | 92 (50.27%) | 79 (59.85%) | 50 (73.53%) | 28 (77.78%) |
| N censored | 123 (54.91%) | 91 (49.73%) | 53 (40.15%) | 18 (26.47%) | 8 (22.22%) |
| Q1, months (90% CI) | 29.93 (23.38, 37.67) | 16.16 (13.08, 22.07) | 8.46 (4.52, 11.21) | 4.75 (3.61, 10.46) | 6.03 (3.41, 10.66) |
| Median, months (90% CI) | 62.36 (54.89, 73.54) | 40.82 (35.18, 52.26) | 23.38 (17.44, 29.15) | 18.07 (12.62, 22.26) | 12.00 (10.43, 16.43) |
| Q3, months (90% CI) | n.r (76.98, n.r) | 71.25 (71.05, n.r) | 44.69 (33.93, n.r) | 25.57 (24.23, 41.70) | 20.89 (15.80, n.r) |

CI, confidence interval; MM, multiple myeloma.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.
Source: Annex 4 – Table 8.

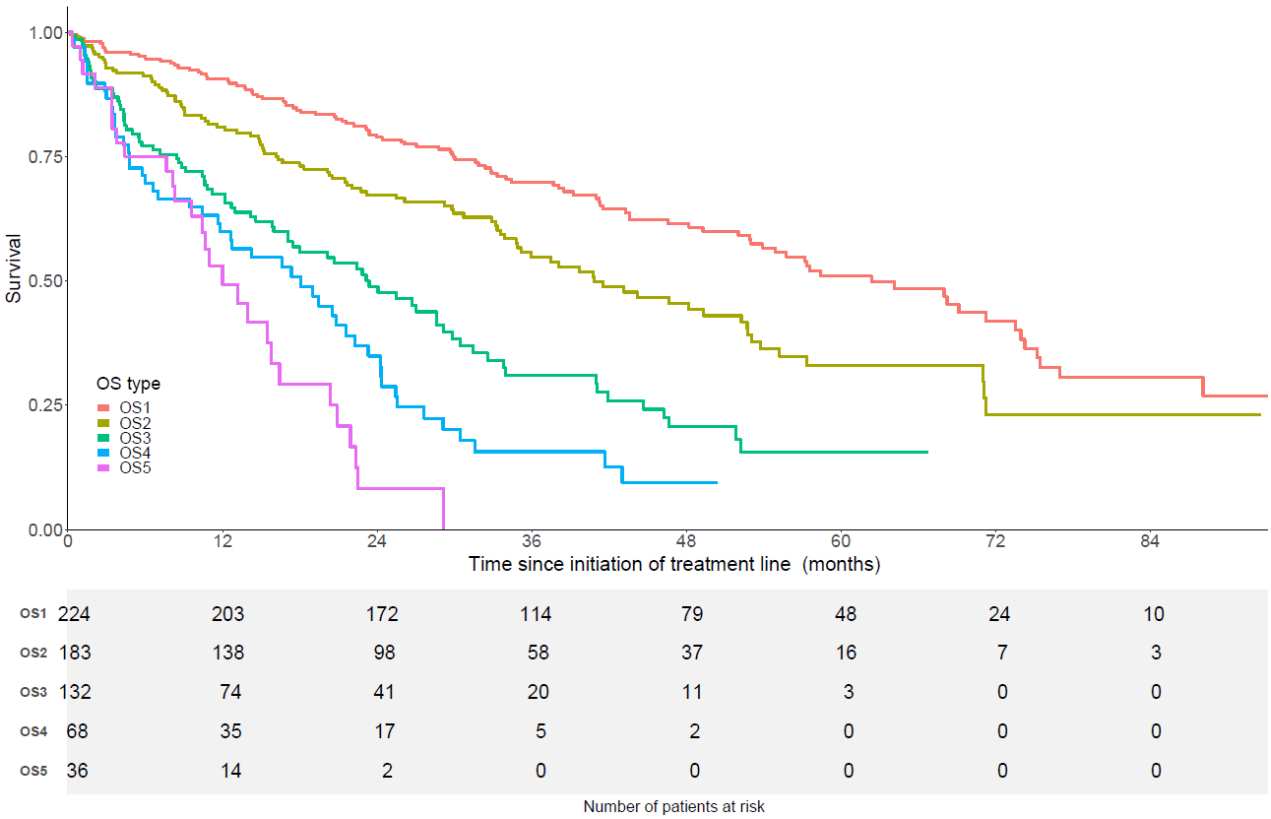


**Figure 3. Kaplan-Meier curves for overall survival (OS) in treatment lines 1-5 among MM patients**
Source: Annex 4 – Figure 1
OS, overall survival.

## 10.3.2 Stratified by demographic characteristics

The results on the OS stratified by all demographic characteristics are described in the Result Report Table 8 (Annex 4) and summarized below in Table 10. When OS was stratified by demographic characteristics, female patients had longer OS in the first treatment line than male patients (median OS 64.16 and 57.18 months, respectively). However, the OS for men improved and was higher relative to women in all subsequent treatment lines. Overall, the OS appeared longer in the strata of younger age compared to older age. In general, the low number of patients per strata limited meaningful interpretation on differing patterns between the strata and treatment lines.

The Kaplan-Meier curves for OS in the treatment lines, stratified by demographic characteristics, are presented in the Result Report Figures 7-8 (OS1), 36-37 (OS2), 69-70 (OS3), 102-103 (OS4), and 132-133 (OS5) (Annex 4).

**Table 10. Median overall survival (OS) stratified by selected demographic characteristics, all treatment lines**

| Strata by demographic characteristics | Median OS in months (90% CI) | | | | |
|---|---|---|---|---|---|
| | Line 1 | Line 2 | Line 3 | Line 4 | Line 5 |
| **Patients / lines, n[a]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 36** |
| **Gender[b]** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Male | 57.18 (52.03, 71.28) | 43.15 (37.48, 52.72) | 26.72 (20.13, 33.93) | 20.82 (17.34, 25.44) | 13.93 (9.61, 20.89) |
| Female | 64.16 (58.39, n.r) | 40.82 (33.18, n.r) | 17.97 (12.98, 28.59) | 12.62 (6.62, 23.31) | 10.98 (8.30, n.r) |
| **Age group, in years[b]** | | | | | |
| 37-50 | n.r (37.67, n.r) | n.r (33.90, n.r) | n.r (28.62, n.r) | 32.87 (20.82, n.r) | 13.93 (n.r, n.r) |
| 51-60 | 76.98 (57.34, n.r) | 52.26 (33.31, n.r) | 17.97 (11.21, n.r) | 12.72 (11.80, n.r) | 15.48 (8.16, n.r) |
| 61-70 | 73.54 (58.39, n.r) | 43.15 (35.93, 71.08) | 29.84 (14.59, 33.80) | 16.59 (6.98, 30.46) | 12.00 (4.43, n.r) |
| 71-80 | 52.03 (41.54, 57.57) | 35.18 (29.80, 46.62) | 20.69 (15.97, 26.72) | 19.02 (6.03, 23.31) | 10.98 (7.64, 20.89) |
| >80 | 29.93 (23.97, n.r) | 24.31 (21.67, n.r) | n.r (n.r, n.r) | n.r (n.r, n.r) | n.r (n.r, n.r) |

CI, confidence interval; OS, overall survival.
Source: Annex 4 – Table 8.
[a] Total per treatment line, n per strata are available in Annex 4.
[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declined.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

### 10.3.3 Stratified by disease characteristics

The results on the OS stratified by all disease characteristics are described in the Result Report Table 8 (Annex 4), and summarized below in Table 11. In general, the low number of patients and events per stratum resulted in wide, overlapping CIs for the OS, which limited the ability to detect patterns between the strata, especially after treatment line 1.

In the treatment line 1, the median OS appeared shorter in the strata of the patients with the **CRAB components** *hypercalcemia* or *renal dysfunction* than in the strata of patients with *anaemia* or *lytic bone lesions*, although the CIs were wide (Table 11). In the strata of patients with **high risk or non-high risk FISH findings**, the median OS in treatment line 1 appeared the longest among patients with the high risk FISH finding del(17p13) (48.20 months). In the stratum of patients with the standard **R-ISS risk classification** for MM, the median OS in the treatment line 1 (62.36 months) appeared longer than in the stratum of patients with the high R-ISS risk classification (32.79 months). The median OS in the treatment line 1 was more than 50 months shorter in the stratum of patients with **early progression** compared to patients without (15.80 and 68.00 months, respectively).

The Kaplan-Meier curves for OS in the treatment lines, stratified by disease characteristics, are presented in the Result Report Figures 9-33 (OS1), 38-62 (OS2), 71-95 (OS3), 104-128 (OS4), and 134-158 (OS5) (Annex 4).

**Table 11. Median overall survival (OS) stratified by selected disease characteristics, in all treatment lines**

| Strata by disease characteristics | Median OS in months (90% CI) | | | | |
|---|---|---|---|---|---|
| | **Line 1** | **Line 2** | **Line 3** | **Line 4** | **Line 5** |
| **Patients / lines, n[a]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 36** |
| **CRAB component[b]** | | | | | |
| Hypercalcemia | 32.79 (21.57-64.16) | 29.21 (20.26-40.82) | 11.21 (8.59-26.72) | 6.62 (3.70-17.34) | 10.66 (1.15-n.r) |
| Renal dysfunction | 43.28 (31.87-n.r) | 30.72 (23.18-n.r) | 17.97 (9.15-33.93) | 4.87 (3.61-n.r) | 6.26 (1.15-n.r) |

| | | | | | |
|---|---|---|---|---|---|
| Anaemia | 52.92 (39.21-64.16) | 34.79 (29.93-41.54) | 17.97 (12.98-29.84) | 12.72 (6.98-23.31) | 10.98 (8.16-15.80) |
| Lytic bone lesions | 58.39 (52.03-75.21) | 40.79 (34.79-52.75) | 22.85 (15.97-28.59) | 16.59 (11.80-22.26) | 10.98 (9.61-15.80) |
| **FISH findings[b]** | | | | | |
| **High risk cytogenetics** | | | | | |
| del(17p13) | 48.20 (32.85-n.r) | 33.31 (20.26-n.r) | 20.69 (15.87-n.r) | 12.72 (11.80-n.r) | 8.30 (8.16-n.r) |
| t(4;14) | 29.95 (20.82-n.r) | 14.89 (12.16-n.r) | 12.20 (8.59-n.r) | 11.80 (6.62-n.r) | 8.16 (3.41-n.r) |
| t(14;16) | 38.10 (18.07-n.r) | 34.79 (14.95-n.r) | 28.59 (12.98-n.r) | 25.44 (11.64-n.r) | 16.66 (10.98-n.r) |
| **Non-high risk cytogenetics** | | | | | |
| t(14;20) | 12.49 (n.r-n.r) | 11.57 (n.r-n.r) | 1.74 (n.r-n.r) | - | - |
| gain(1q) | 39.21 (38.10-n.r) | 33.31 (23.18-39.67) | 23.38 (11.21-33.80) | 11.64 (6.03-25.57) | 10.82 (3.41-n.r) |
| del(1p32 or 1p36) | n.r (20.82-n.r) | n.r (12.16-n.r) | n.r (5.51-n.r) | n.r (1.31-n.r) | n.r (n.r-n.r) |
| **Disease status according to the R-ISS risk classification[b]** | | | | | |
| Low (1) | n.r (n.r-n.r) | 52.26 (29.80-n.r) | 25.48 (4.33-n.r) | 21.57 (3.38-n.r) | 20.39 (0.36-n.r) |
| Standard (2) | 62.36 (55.77-73.54) | 40.79 (35.18-52.75) | 22.85 (15.97-33.80) | 19.44 (11.80-27.64) | 13.18 (8.30-16.43) |
| High (3) | 32.79 (18.07-75.21) | 20.26 (14.95-n.r) | 12.98 (8.46-29.84) | 12.62 (3.70-n.r) | 6.93 (1.15-n.r) |
| **Early progression[c]** | | | | | |
| Yes | 15.80 (13.08, 34.39) | 10.89 (8.75-21.67) | 8.46 (4.36-23.15) | 11.64 (3.70-30.46) | 13.93 (13.18-n.r) |
| No | 68.00 (57.18-73.97) | 40.82 (35.18-52.26) | 26.72 (20.69-31.44) | 19.44 (12.72-24.23) | 10.98 (9.61-16.43) |

CI, confidence interval; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; OS, overall survival; R-ISS, revised international staging system for multiple myeloma.
Source: Annex 4 – Table 8.
[a] Total per treatment line, n per strata are available in Annex 4.
[b] At the time of MM diagnosis.
[c] At the start of each treatment line.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

### 10.3.4 Stratified by treatment patterns

The results on the OS stratified by all treatment pattern variables are described in the Result Report Table 8 (Annex 4) and summarized below in Table 12. Similar to the previous stratified results presented in Sections 10.3.2 and 10.3.3, the low number of patients and events in the strata of the **treatment regimens** hindered the detection of patterns in the strata.

In the strata by **bone marrow transplant status**, patients treated with a single autologous transplant in the treatment lines 1-3 appeared to have a longer median OS than those without the treatment (Table 12), although the possibility to detect differences between the strata was limited by the low numbers of patients per strata especially in the later treatment lines . In the stratum of patients with triplet **treatment type**, the median OS in the first treatment line appeared longer than in the stratum of patients with duplet treatment (68.00 and 55.77, respectively); single treatment had the lowest median OS compared to all treatment types (12.33 months). In treatment lines 4 and 5, median OS in the in strata of duplet therapy had the highest OS compared to all other treatment types.

The Kaplan-Meier curves for the OS in the treatment lines, stratified by the treatment pattern variables, are presented in the Result Report Figures 3-6 (OS1), 32-35 (OS2), 65-68 (OS3), 98-101 (OS4), and 130-131 (OS5) (Annex 4).

**Table 12. Median overall survival (OS) stratified by selected treatment pattern variables, in all treatment lines**

| Strata by selected treatment pattern variables[a] | Median OS in months (90% CI) | | | | |
|---|---|---|---|---|---|
| | Line 1 | Line 2 | Line 3 | Line 4 | Line 5 |
| **Patients / lines, n[b]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 36** |
| **Bone marrow transplant status** | | | | | |
| Autologous bone marrow transplant | | | | | |
| Single[c] | 76.98 (64.16, n.r) | 71.08 (71.05, n.r) | 46.66 (10.62, n.r) | 18.07 (n.r, n.r) | - |
| No | 57.18 (48.20, 69.15) | 35.18 (33.18, 44.20) | 23.15 (17.44, 28.62) | 19.02 (11.80, 23.31) | 12.00 (10.43, 16.43) |
| Allogeneic bone marrow transplant | | | | | |
| Single[c] | n.r (32.85, n.r) | n.r (n.r, n.r) | 15.87 (n.r, n.r) | n.r (n.r, n.r) | - |
| No | 62.36 (54.89, 73.54) | 40.79 (34.89, 52.26) | 23.38 (17.97, 29.15) | 18.07 (11.80, 22.26) | 12.00 (10.43, 16.43) |
| **Treatment type** | | | | | |
| Single | 12.33 (0.23, n.r) | - | 41.02 (17.08, n.r) | 3.61 (1.51, n.r) | 9.43 (1.15, n.r) |
| Duplet | 55.77 (41.31, 73.54) | 40.79 (33.31, 52.75) | 26.72 (23.15, 33.93) | 23.31 (17.34, 25.57) | 16.43 (10.98, n.r) |
| Triplet | 68.00 (62.36, n.r) | 38.10 (33.90, 71.25) | 20.69 (17.44, 29.84) | 16.59 (10.46, n.r) | 10.66 (9.61, 21.93) |
| Other[d] | 71.28 (31.64, n.r) | 46.62 (39.67, n.r) | 5.51 (4.03, 10.62) | 11.80 (4.75, n.r) | 3.80 (3.41, n.r) |

CI, confidence interval; OS, overall survival.
Source: Annex 4 – Table 8.
[a] At the start of each treatment line.
[b] Total per treatment line, n per strata are available in Annex 4.
[c] No tandem bone marrow transplants were observed. Thus, the single transplants represent all bone marrow transplants.
[d] Treatment type was *other* if it could not be specified as Single, Duplet or Triplet: if the treatment had more than three drugs, treatment line had several treatments (e.g. single and duplet) or combination therapy (e.g. DR-PACE).
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

## 10.4 Primary objective 2: Description of time to next treatment (TTNT)

### 10.4.1 Among all MM patients with treatment (actual study cohort)

The median TTNT for treatment line 1 among the 224 MM patients was 8.54 months (90% CI 6.07-12.75) (Table 13). Overall, the median TTNT appeared longer in duration for the subsequent treatment lines, with the exception of treatment line >4 which was similar to median TNNT in the first treatment line (8.59 months, 90% CI 6.20-14.66). However, the wide CIs hindered meaningful interpretation of differences between the treatment lines. The Aalen-Johansen curves for the TTNT per treatment line are presented in Figure 4.

**Table 13. Median time to next treatment (TTNT) for treatment lines 1 - >4 among MM patients**

| Variable | Line 1 | Line 2 | Line 3 | Line 4 | Line >4[a] |
|---|---|---|---|---|---|
| **Total** | | | | | |
| N at risk | 224 (100.00%) | 183 (100.00%) | 132 (100.00%) | 68 (100.00%) | 88 (100.00%) |
| N with event | 183 (81.70%) | 133 (72.68%) | 68 (51.52%) | 37 (54.41%) | 52 (59.09%) |
| N censored | 32 (14.29%) | 38 (20.77%) | 35 (26.52%) | 10 (14.71%) | 8 (9.09%) |
| N died | 9 (4.02%) | 12 (6.56%) | 29 (21.97%) | 21 (30.88%) | 28 (31.82%) |

| | | | | | |
|---|---|---|---|---|---|
| Q1, months (90% CI) | 3.31 (2.95, 3.77) | 4.82 (3.51, 6.20) | 5.64 (3.90, 7.80) | 3.64 (3.02, 6.89) | 2.82 (2.07, 3.77) |
| Median, months (90% CI) | 8.54 (6.07, 12.75) | 16.03 (10.59, 20.46) | 15.61 (11.84, 32.00) | 18.82 (10.79, n.r) | 8.59 (6.20, 14.66) |
| Q3, months (90% CI) | 34.43 (26.13, 44.46) | 38.82 (30.75, 43.93) | n.r (n.r, n.r) | n.r (n.r, n.r) | n.r (n.r, n.r) |

CI, confidence interval; MM, multiple myeloma.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.
Source: Annex 4 – Table 9.
[a] For treatment line >4 the confidence interval was calculated assuming that all (subsequent) treatment lines are independent of each other.

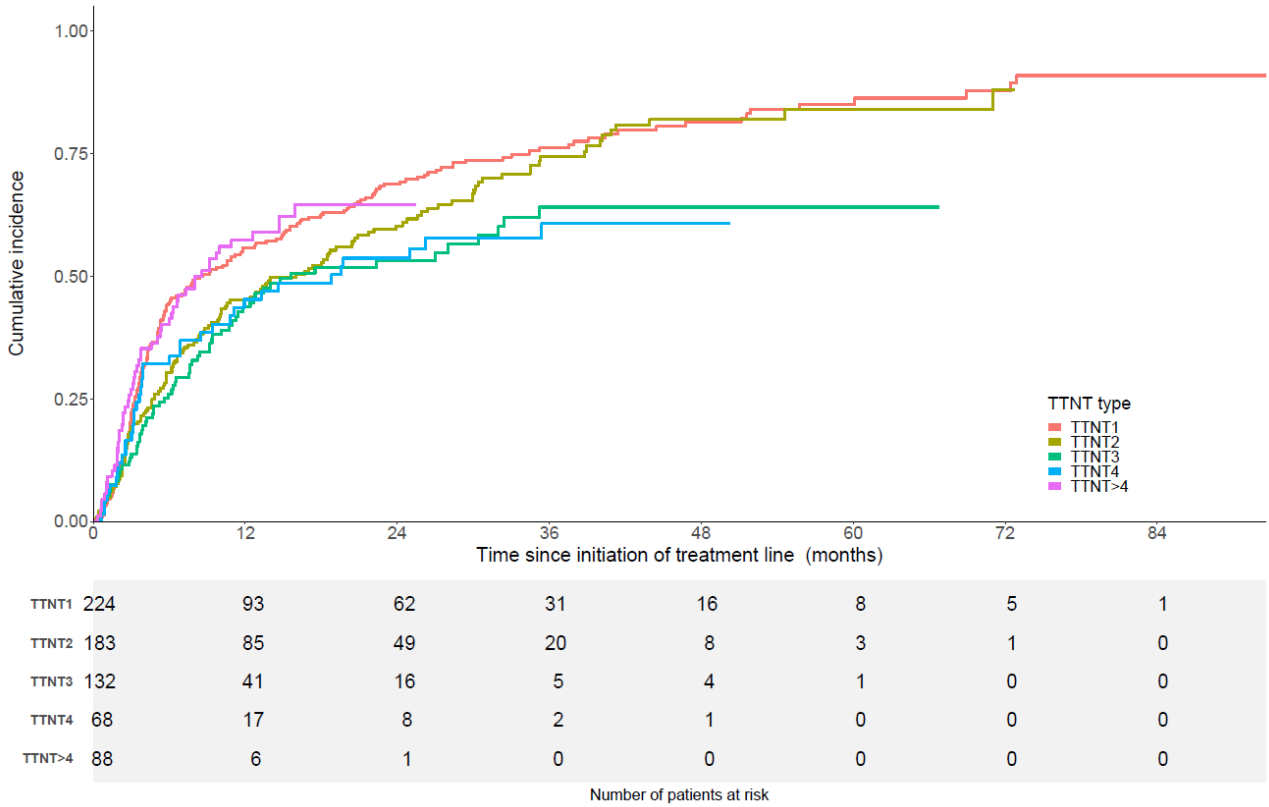


**Figure 4 Aalen-Johansen curves for time to next treatment (TTNT) for treatment lines 1 - >4 among MM patients**
Source: Annex 4 – Figure 159
TTNT, Time to next treatment

## 10.4.2 Stratified by demographic characteristics

The results on the TTNT stratified by all demographic characteristics are described in the Result Report Table 9 (Annex 4) and summarized below in Table 14. The median TTNT in treatment line 1 appeared shorter for women compared to men (7.25 and 10.56 months, respectively) (Table 14). However, male patients' median TTNT was lower in duration relative to female patients in treatment lines 2 and 3. In treatment line 1, patients in the highest age group (>80 years) had the longest TTNT, compared to the youngest patients (ages 37-50), with a duration of 46.79 and 3.77 months, respectively. In the subsequent treatment lines, the low numbers of patients and events limited the possibility to detect patterns in the median TTNT.

The Aalen-Johansen curves on the TTNT in the treatment lines, stratified by demographic characteristics, are presented in the Result Report Figures 165-166 (TTNT1), 194-195 (TTNT2), 227-228 (TTNT3), 260-261 (TTNT4), 290-291 (TTNT>4) (Annex 4).

**Table 14. Median time to next treatment (TTNT) stratified by selected demographic characteristics, in all treatment lines**

| Strata by demographic | Median TTNT in months (90% CI) |
|---|---|

| characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Patients / lines, n[a]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** |
| **Gender[b]** | | | | | |
| Male | 10.56 (6.13, 15.54) | 16.03 (10.79, 22.16) | 14.00 (11.25, 32.00) | 11.93 (6.03, 26.23) | 9.21 (6.30, 15.90) |
| Female | 7.25 (5.28, 12.75) | 17.02 (9.34, 25.61) | 27.02 (10.75, n.r) | n.r (14.59, n.r) | 6.00 (3.44, n.r) |
| **Age group, in years[b]** | | | | | |
| 37-50 | 3.77 (2.95, n.r) | 20.85 (5.28, n.r) | n.r (7.80, n.r) | 25.90 (6.89, n.r) | 5.69 (2.03, n.r) |
| 51-60 | 11.84 (5.15, 22.16) | 9.93 (5.61, 40.16) | 22.36 (10.13, n.r) | 19.74 (3.64, n.r) | 7.66 (2.36, n.r) |
| 61-70 | 7.84 (5.80, 15.54) | 24.79 (17.02, 29.93) | 28.00 (9.44, n.r) | 19.57 (6.03, n.r) | 8.59 (4.59, n.r) |
| 71-80 | 9.02 (5.51, 13.64) | 12.39 (8.79, 16.72) | 13.44 (10.98, 35.25) | 14.59 (9.41, n.r) | 12.59 (6.20, n.r) |
| >80 | 46.79 (9.74, n.r) | 15.20 (3.15, n.r) | 8.23 (n.r, n.r) | 8.49 (n.r, n.r) | 5.38 (n.r, n.r) |

CI, confidence interval; TTNT, time to next treatment.
Source: Annex 4 – Table 9.
[a] Total per treatment line, n per strata are available in Annex 4.
[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declined.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

### 10.4.3 Stratified by disease characteristics

The results on the TTNT stratified by all disease characteristics are described in the Result Report Table 9 (Annex 4) and summarized below in Table 15. In general, the low number of patients and events per stratum resulted in wide, overlapping CIs for the TTNT, which hindered the detections of patterns between the strata, especially after the treatment line 1.

In the strata of patients with **CRAB components**, the median TTNT in treatment line 1 was 5.74-9.49 months (Table 15), and appeared generally longer in the subsequent treatment lines, although the CIs were wide. In the strata of patients with **high risk or non-high risk FISH findings**, the median TTNT in the treatment line 1 appeared the longest among patients with the high risk FISH findings del(17p13) and t(4;14), 8.07 and 14.89 months, respectively. In the stratum of patients by **R-ISS risk classification** for MM, the median TTNT in the treatment line 1 appeared the longest for patients with the low risk classification (29.44 months), and the shortest for those with the standard risk classification (9.21 months). The median TTNT in treatment lines 1 to 3 appeared shorter in the stratum of patients with **early progression** than for those without.

The Aalen-Johansen curves on the TTNT in the treatment lines, stratified by disease characteristics, are presented in the Result Report Figures 167-188 (TTNT1), 196-221 (TTNT2), 229-254 (TTNT3), 262-286 (TTNT4), 292-316 (TTNT>4) (Annex 4).

**Table 15. Median time to next treatment (TTNT) stratified by selected disease characteristics, in all treatment lines**

| Strata by disease characteristics | Median TTNT in months (90% CI) | | | | |
|---|---|---|---|---|---|
| | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
| **Patients / lines, n[a]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** |
| **CRAB component[b]** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Hypercalcemia | 5.74 (4.26-11.80) | 11.79 (6.66-18.69) | 8.43 (5.25-14.75) | n.r (10.79-n.r) | n.r (8.59-n.r) |
| Renal dysfunction | 8.93 (5.08-15.21) | 13.34 (8.72-24.79) | 32.00 (7.61-n.r) | n.r (n.r-n.r) | n.r (5.38-n.r) |
| Anaemia | 5.80 (5.05-11.21) | 10.79 (8.79-18.16) | 12.79 (10.98-28.00) | 16.70 (8.49-35.38) | 9.21 (6.00-n.r) |
| Lytic bone lesions | 9.49 (6.13-12.75) | 13.18 (9.93-19.15) | 13.44 (10.13-32.43) | 19.57 (11.15-n.r) | 8.59 (5.28-12.59) |
| **FISH findings[b]** | | | | | |
| **High risk cytogenetics** | | | | | |
| del(17p13) | 8.07 (4.36-21.48) | 25.93 (18.00-n.r) | 7.61 (5.25-n.r) | 11.15 (2.56-n.r) | 7.80 (3.28-n.r) |
| t(4;14) | 14.89 (5.31-n.r) | 6.66 (2.69-n.r) | 4.20 (1.97-n.r) | 3.64 (3.21-n.r) | 6.11 (1.70-n.r) |
| t(14;16) | 3.21 (3.02-n.r) | 14.11 (6.20-n.r) | 15.61 (3.02-n.r) | 14.59 (3.11-n.r) | 8.89 (2.82-n.r) |
| **Non-high risk cytogenetics** | | | | | |
| t(14;20) | 0.92 (n.r-n.r) | 9.84 (n.r-n.r) | n.r (n.r-n.r) | - | - |
| gain(1q) | 5.64 (3.57-20.16) | 8.20 (5.77-19.15) | 7.61 (4.75-n.r) | 10.74 (3.21-n.r) | 6.69 (3.21-n.r) |
| del(1p32 or 1p36) | 3.21 (2.62-n.r) | 6.20 (5.15-n.r) | 14.75 (5.64-n.r) | n.r (1.08-n.r) | 8.59 (n.r-n.r) |
| **Disease status according to the R-ISS risk classification[b]** | | | | | |
| Low (1) | 29.44 (9.25-n.r) | 28.30 (10.10-n.r) | 13.13 (1.34-n.r) | 3.46 (0.69-n.r) | 15.90 (3.77-n.r) |
| Standard (2) | 5.97 (5.28-11.84) | 12.79 (8.30-18.16) | 17.51 (11.44-n.r) | 19.74 (10.79-35.38) | 7.31 (5.38-12.59) |
| High (3) | 9.21 (3.84-21.48) | 9.84 (4.82-23.90) | 10.75 (5.25-n.r) | 18.82 (3.84-n.r) | n.r (1.87-n.r) |
| **Early progression[c]** | | | | | |
| Yes | 4.31 (3.57-5.31) | 6.38 (5.15-10.59) | 8.43 (6.56-n.r) | n.r (11.93-n.r) | 7.16 (4.59-n.r) |
| No | 13.23 (10.56-16.43) | 12.82 (9.93-18.52) | 14.75 (11.25-28.00) | 13.31 (6.89-35.38) | 8.59 (6.00-14.66) |
| Unknown | n.r (6.07-n.r) | n.r (n.r-n.r) | n.r (n.r-n.r) | 19.74 (n.r-n.r) | n.r (n.r-n.r) |

CI, confidence interval; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; R-ISS, revised international staging system for multiple myeloma.
Source: Annex 4 – Table 9.
[a] Total per treatment line, n per strata are available in Annex 4.
[b] At the time of MM diagnosis.
[c] At the start of each treatment line.
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

### 10.4.4 Stratified by treatment patterns

The results on the TTNT stratified by all treatment pattern variables are described in the Result Report Table 9 (Annex 4) and summarized below in Table 16. By large, the low number of patients and events in the strata of the treatment patterns hindered the detection of differences in the strata.

Of the strata by **treatment regimens**, patients treated with various treatment combinations appeared to have prolonged TTNT in treatment line 1, compared with Bor/Cpm/Dxm (Result Report Table 9 (Annex 4)). Of the strata by **bone marrow transplant status**, patients who received a single autologous bone marrow transplant also appeared to have prolonged TTNT, compared to not being treated with an autologous transplant (Table 16). Due to low numbers, median TNNT for patients who received an allogeneic transplant are not reported in the table below. In the stratum of patients with triplet **treatment type**, the median TTNT in the first treatment line appeared longer than in the stratum of patients with duplet treatment (12.79

versus 5.08 months, respectively). However, by treatment line 3, median TNNT is relatively longer in duplet treatment compared to triplet treatment for all successive treatment lines.

The Aalen-Johansen curves on the TTNT in the treatment lines, stratified by the treatment pattern variables, are presented in the Result Report Figures 161-164 (TTNT1), 190-193 (TTNT2), 223-226 (TTNT3), 256-259 (TTNT4), 288-289 (TTNT>4) (Annex 4).

**Table 16. Median time to next treatment (TTNT) stratified by selected treatment pattern variables, all treatment lines**

| Strata by selected treatment pattern variables[a] | Median TTNT in months (90% CI) | | | | |
|---|---|---|---|---|---|
| | **Line 1** | **Line 2** | **Line 3** | **Line 4** | **Line >4** |
| **Patients / lines, n[b]** | **224 / 224** | **183 / 183** | **132 / 132** | **68 / 68** | **36 / 88** |
| **Bone marrow transplant status** | | | | | |
| Autologous bone marrow transplant | | | | | |
| Single[c] | 37.97 (32.36, 51.61) | 30.07 (28.30, n.r) | 18.56 (7.64, n.r) | 11.93 (n.r, n.r) | -[d] |
| No | 5.28 (4.36, 6.07) | 10.46 (8.39, 16.72) | 15.61 (11.44, 35.25) | 19.57 (9.41, n.r) | 8.59 (6.20, 14.66) |
| Allogeneic bone marrow transplant | | | | | |
| Single[c] | n.r (22.16, n.r) | n.r (n.r, n.r) | n.r (n.r, n.r) | n.r (n.r, n.r) | -[d] |
| No | 7.84 (5.80, 11.67) | 13.87 (10.10, 19.15) | 15.61 (11.44, 32.00) | 18.82 (9.41, 35.38) | 8.59 (6.20, 14.66) |
| **Treatment type** | | | | | |
| Single | 7.02 (7.02, n.r) | -[d] | 13.44 (12.39, n.r) | n.r (n.r, n.r) | n.r (7.31, n.r) |
| Duplet | 5.08 (4.26, 5.97) | 13.97 (8.72, 25.93) | 27.02 (11.84, n.r) | 14.59 (8.49, 35.38) | 8.59 (5.28, 15.90) |
| Triplet | 12.79 (8.66, 18.13) | 18.16 (12.39, 20.66) | 10.13 (5.25, 28.00) | 11.93 (3.41, n.r) | 6.62 (4.59, n.r) |
| Other[e] | 15.30 (9.21, 24.23) | 13.87 (10.00, 40.00) | n.r (7.64, n.r) | 11.15 (3.84, n.r) | 5.72 (2.52, n.r) |

CI, confidence interval; OS, overall survival.
Source: Annex 4 – Table 9.
[a] At the start of each treatment line.
[b] Total per treatment line, n per strata are available in Annex 4.
[c] No tandem bone marrow transplants were observed. Thus, the single transplants represent all bone marrow transplants.
[d] No patients in this subgroup.
[e] Treatment type was *other* if it could not be specified as Single, Duplet or Triplet: if the treatment had more than three drugs, treatment line had several treatments (e.g. single and duplet) or combination therapy (e.g. DR-PACE).
n.r. - the Kaplan-Meier estimate or its lower/upper confidence bound did not reach the quantile.

## 10.5 Secondary objective 1: Factors associated with overall survival (OS)

The crude IRs for OS by all factors and the associations of all factors to OS, per treatment line, are presented in the Results Report Tables 10-14 (IRs) and Tables 20-24 (hazard ratios (HRs), associated factors) (Annex 4). Table 17 displays the results for the factors that were statistically associated with the OS (90% CI for the HR not overlapping 1.00) in at least one treatment line.

**Patient characteristics** age and gender were not associated with OS in any treatment line, apart from female patients having a higher risk of death compared to men in treatment line 4 (HR 3.08).

Of **disease characteristics**, patients with the CRAB component hypercalcemia had a higher risk of death compared to patients without in treatment lines 1 and 4 (HR 1.98 and HR 3.68, respectively). Patients with the CRAB component anaemia in treatment lines 1 and 5 had higher risk than patients without, although due to low numbers the CI in treatment line 5 is very wide (HR 1.56 and HR 33.59, respectively). Patients with the high risk **FISH finding** del(17p13) had a lower risk of death in treatment line 4 (HR 0.13), but an increased risk of death in treatment line 5 (HR 12.50), the CI again being wide in treatment line 5. Having the high risk FISH finding FISH t(4;14) was also associated with higher risk of death for patients in the treatment line 2 (HR 2.78).

Concerning **treatment characteristics,** being treated with various other treatment regimens demonstrated a protective effect for death in the treatment lines 2-3 (HRs ranging between 0.04 and 0.36), compared with the reference treatment regimen Bor/Cpm/Dxm.

**Table 17. Crude incidence rates (IR) per 1000 person-years (PY) for the overall survival (OS) and factors[a] associated OS, in treatment lines 1-5**

| Factors[a] | OS at treatment line 1 (OS1) | | OS at treatment line 2 (OS2) | | OS at treatment line 3 (OS3) | | OS at treatment line 4 (OS4) | | OS at treatment line 5 (OS5) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI)* | Crude IR (90% CI) | Adjusted HR (90% CI)* | Crude IR (90% CI) | Adjusted HR (90% CI)* | Crude IR (90% CI) | Adjusted HR (90% CI)* |
| Total IR | 133.01 (112.93-156.66) | - | 203.23 (171.20-241.25) | - | 383.46 (318.67-461.41) | - | 569.48 (451.28-718.62) | - | 819.8 (600.77-1118.68) | - |
| **Patient characteristics** | | | | | | | | | | |
| Female (ref: male) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 673.30 (470.25-964.0) | 3.08 (1.42-6.71) | -[a] | -[a] |
| **Disease characteristics** | | | | | | | | | | |
| CRAB component: Hypercalcemia (ref: no) | 239.41 (169.90-337.3) | 1.98 (1.24-3.15) | -[a] | -[a] | -[a] | -[a] | 1020.66 (657.60-1584.16) | 3.68 (1.54-8.75) | -[a] | -[a] |
| CRAB component: Anaemia (ref: no) | 180.06 (145.86-222.2) | 1.56 (1.01-2.40) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 888.23 (609.04-1295.42) | 39.59 (2.35-667.7) |
| FISH: High risk cytogenetic del(17p13) (ref: no) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 741.88 (379.05-1451.99) | 0.13 (0.02-0.75) | 1129.93 (496.45-2571.74) | 12.50 (1.08-144.3) |
| FISH: High risk cytogenetic t(4;14) (ref: no) | -[a] | -[a] | 751.32 (403.48-1399.3) | 2.78 (1.05-7.36) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| **Treatment patterns** | | | | | | | | | | |
| Bor/Dxm (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | 137.83 (88.81-213.9) | 0.09 (0.02-0.37) | -[a] | -[a] | -[a] | -[a] |
| Bor/Dxm+AutoHSCT (HD-mel) (ref: Bor/Cpm/Dxm) | -[a] | -[a] | 30.08 (5.81-155.8) | 0.04 (0.01-0.30) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Bor/Dxm/Len (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | 365.04 (227.05-586.8) | 0.10 (0.02-0.44) | -[a] | -[a] | -[a] | -[a] |
| Bor/Mel/Pred (VMP) (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | 391.69 (122.41-1253.32) | 0.13 (0.02-0.92) | -[a] | -[a] | -[a] | -[a] |
| Cpm/Pred (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | 235.72 (73.67- | 0.06 (0.01-0.35) | -[a] | -[a] | -[a] | -[a] |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 754.2) | | | | | |
| Other treatment regimens (ref: Bor/Cpm/Dxm) | -[a] | -[a] | 137.83 (88.81-213.9) | 0.36 (0.14-0.96) | 501.08 (360. 1-696.2) | 0.15 (0.04-0.64) | -[a] | -[a] | -[a] | -[a] |

AutoHSCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; CI, confidence interval; Cpm, cyclophosphamide; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; Dxm, dexamethasone; FISH, fluorescence in situ hybridization; HD-mel, high-dose melphalan; HR, hazard ratio; IR, incidence ratio; Mel, melphalan; MM, multiple myeloma; Pred, prednisone; OS, overall survival; VMP, bortezomib + melphalan + prednisone.

Source: Annex 4 – Tables 10-14 (IRs) and Tables 20-24 (associated factors).

[a] The results on the crude IRs and the associations of patient factors are presented exclusively for factors associated with OS in the Cox regression models in at least one treatment line are presented. The results for all factors are available in Annex 4 – Tables 10-14 (IRs) and Tables 20-24 (associated factors).

Note: The crude incidence rates were relatively high due to the median follow-up time being less than a year. In OS analysis, the higher the treatment line, the higher rate values were expected.

## 10.6 Secondary objective 1: Factors associated with time to next treatment (TTNT)

The crude IRs for TTNT by all factors and the associations of all factors to the TTNT, per treatment line, are presented in the Results Report Tables 10-14 (IRs) and Tables 25-29 (HRs, associated factors) (Annex 4). Table 18 below displays the results for the factors that were statistically associated (90% CI for the HR not overlapping 1.00) with the TTNT in at least one treatment line.

**The patient characteristic** gender was not associated with TTNT in any treatment line (not presented in Table 18). Further, age was not significantly associated with TTNT in treatment lines 1-3 and 5, but in the treatment line 4, the risk of proceeding to the next treatment was higher for patients aged 61-70 (HR 21.86) years or >80 years (HR 88.10) compared to those aged 37-50 years. However, the confidence intervals for the association were wide, likely due to the small number of patients in higher treatment lines.

Of **disease characteristics**, having the CRAB component anaemia was associated with an increased risk of proceeding to the next treatment in the treatment lines 1 (HR 1.94), 3 (HR 2.00), and 4 (HR 5.82). Having the CRAB component renal dysfunction was associated with a lower risk of proceeding to the next treatment in the treatment line 4 (HR 0.2). Having the high-risk FISH findings del(17p13) or t(14,16) were associated with an increased risk of proceeding to the next treatment in the treatment line 1 (HRs 1.78 and 3.75, respectively). Patients with standard or high R-ISS risk classification also had a higher risk of proceeding to the next treatment in the treatment lines 2 (HRs 2.30 and 3.19, respectively) and 5 (HRs 4.89 and 15.02, respectively), compared to patients with low R-ISS risk classification. In the treatment line 3, however, patients with R-ISS risk classifications standard, high or unknown had a lower risk of proceeding to the next treatment (HRs ranging 0.18-0.31).

Of **treatment characteristics**, various treatment regimens were associated with a lower risk of proceeding to the next treatment in treatment lines 1-4 (HRs between 0.09 and 0.33). However, being treated with Mel/Pred (MP) in the treatment line 4 was associated with an increased risk of proceeding to the next treatment (HR 14.17).

**Table 18. Crude incidence rates per 1000 person-years (PY) for the time-to-next treatment (TTNT) and factors[a] associated TTNT (HRs), in treatment lines 1-5.**

| Factors[a] | Time-to-next treatment at treatment line 1 (TTNT1) | | Time-to-next treatment at treatment line 2 (TTNT2) | | Time-to-next treatment at treatment line 3 (TTNT3) | | Time-to-next treatment at treatment line 4 (TTNT4) | | Time-to-next treatment at treatment line 5 (TTNT5) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) |
| Total IR | 596.8 (528.47-673.96) | - | 540.59 (468.73-623.46) | - | 575.2 (471.18-702.17) | - | 696.36 (531.37-912.58) | - | 1522.48 (1211.97-1912.56) | - |
| **Patient characteristics** | | | | | | | | | | |
| Age at diagnosis: 61-70 years (ref. 37-50 years) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 764.86 (484.68-1207.0) | 21.86 (1.34-356.6) | -[a] | -[a] |
| Age at diagnosis: >80 years (ref. 37-50 years) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 1410.23 (272.23-7305.3) | 88.10 (2.02-3834.72) | -[a] | -[a] |
| **Disease characteristics** | | | | | | | | | | |
| CRAB component: Hypercalcemia (ref: no) | 921.22 (685.59-1237.84) | 1.72 (1.16-2.55) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| CRAB component: Hypercalcemia unknown (ref: no) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 925.27 (406.53-2105.93) | 7.82 (1.02-59.76) | -[a] | -[a] |
| CRAB component: Anaemia (ref: no) | 754.51 (636.20-894.8) | 1.94 (1.40-2.68) | -[a] | -[a] | 753.05 (580.60-976.7) | 2.00 (1.06-3.75) | 881.26 (638.28-1216.75) | 5.82 (1.62-20.85) | -[a] | -[a] |
| CRAB component: Renal dysfunction (ref: no) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 346.21 (152.11-787.98) | 0.20 (0.05-0.85) | -[a] | -[a] |
| FISH: High risk cytogenetic del(17p13) (ref: no) | 715.94 (485.85-1055.00) | 1.78 (1.08-2.95) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| FISH: High risk cytogenetic t(14,16) (ref: no) | 1953.21 (1091.91-3493.89) | 3.75 (1.85-7.62) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| R-ISS risk classification: Standard (2) (ref: low) | -[a] | -[a] | (620.07 515.91-745.2) | 2.30 (1.05-5.02) | 530.41 (407.59-690.2) | 0.31 (0.10-0.97) | -[a] | -[a] | 1653.85 (1242.06-2202.16) | 4.89 (1.08-22.21) |
| R-ISS risk classification: High (3) (ref: low) | -[a] | -[a] | 830.23 (550.32- | 3.19 (1.16- | 820.79 (474.37- | 0.19 (0.04- | -[a] | -[a] | 1399.43 (541.40- | 15.02 (1.43- |

| Factors[a] | Time-to-next treatment at treatment line 1 (TTNT1) | | Time-to-next treatment at treatment line 2 (TTNT2) | | Time-to-next treatment at treatment line 3 (TTNT3) | | Time-to-next treatment at treatment line 4 (TTNT4) | | Time-to-next treatment at treatment line 5 (TTNT5) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) | Crude IR (90% CI) | Adjusted HR (90% CI) |
| | | | 1252.53) | 8.77) | 1420.19) | 0.88) | | | 3617.27) | 157.7) |
| R-ISS risk classification: Unknown (ref: low) | -[a] | -[a] | -[a] | -[a] | 554.67 (367.66-836.8) | 0.18 (0.05-0.60) | -[a] | -[a] | -[a] | -[a] |
| **Treatment patterns** | | | | | | | | | | |
| Bor/Cpm/Dxm+AutoHSCT (HD-mel) (ref: Bor/Cpm/Dxm) | 258.13 (168.81-394.7) | 0.18 (0.10-0.32) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Bor/Dxm+AutoHSCT (HD-mel) (ref: Bor/Cpm/Dxm) | 90.59 (39.80-206.1) | 0.09 (0.04-0.18) | 254.62 (111.87-579.5) | 0.24 (0.07-0.76) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Bor/Dxm/Len+AutoHSCT (HD-mel) (ref: Bor/Cpm/Dxm) | -[a] | -[a] | 232.07 (124.63-432.1) | 0.19 (0.07-0.55) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Bor/Mel/Pred (VMP) (ref: Bor/Cpm/Dxm) | -[a] | -[a] | 414.02 (270.76-633.0) | 0.27 (0.11-0.67) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Cpm/Pred (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 308.14 (119.21-796.49) | 0.09 (0.01-0.71) | -[a] | -[a] |
| Mel/Pred (MP) (ref: Bor/Cpm/Dxm) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 5003.42 (2198.33 11387.88) | 14.17 (1.40-142.9) | -[a] | -[a] |
| Mel/Pred/Tal (MPT) (ref: Bor/Cpm/Dxm) | 551.25 (342.87-886.2) | 0.30 (0.15-0.60) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Other treatment Regimens (ref: Bor/Cpm/Dxm) | 424.04 (319.82-562.2) | 0.24, (0.16-0.38) | 420.35 (302.51-584.0) | 0.33 (0.14-0.76) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |

AutoHSCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; CI, confidence interval; Cpm, cyclophosphamide; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; Dxm, dexamethasone; FISH, fluorescence in situ hybridization; HD-mel, high-dose melphalan; HR, hazard ratio; IR, incidence ratio; Mel, melphalan; MM, multiple myeloma; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; Tal, thalidomide; Pred, prednisone; VMP, bortezomib + melphalan + prednisone.
Source: Annex 4 – Tables 10-14 (IRs) and Tables 25-29 (associated factors)
[a] The results on the crude IRs and the associations of factors are presented exclusively for factors associated with TTNT in the Cox regression models in at least one treatment line. The results for all factors are available in Annex 4 – Tables 10-14 (IRs) and Tables 25-29 (associated factors).
Note: The crude incidence rates were relatively high due to the event under investigation (start of the next treatment line) being non-rare and the median follow-up time being less than a year.

## 10.7 Secondary objective 1: Factors associated with treatment selection

The associations of all factors to all treatment selection outcomes are presented in the Results Report Tables 30-48 (Annex 4). Factors that were associated with at least one outcome on treatment type or transplant status are summarized in Table 19. Table 20 presents the results for the factors that were statistically associated with at least one treatment regimen outcome.

As shown in Table 19, for outcomes related to **treatment type**, being in treatment lines 3 and 4 were associated with higher odds of duplet therapy (ORs 1.53 and 1.86, respectively), compared to being in treatment line 1. In addition, patients with CRAB component hypercalcemia at diagnosis had higher odds to be treated with **duplet therapy** (OR 1.71), compared to the patients without hypercalcemia at diagnosis. In contrast, patients with the FISH findings t(4;14), gain(1q), or del(1p32 or 1p36) at diagnosis had lower odds to be treated with duplet therapy (ORs between 0.11-0.64), compared to the patients without such findings. Patients in treatment lines 3, 4 or >4 had lower odds to be treated with **triplet therapy**, compared to patients in treatment line 1. In contrast, patients with the FISH findings gain(1q) or del(1p32 or 1p36) at diagnosis had higher odds of being treated with triplet therapy (ORs 4.18 and 1.63, respectively). The model on single therapy did not converge (mostly due to the small sample size).

Of outcomes on **transplant status**, the odds of being treated with a **single autologous bone marrow transplant** were higher in the older age groups (51-60 and 61-70 years at diagnosis), compared to the youngest age group (37-50 years) (ORs 4.06 and 3.82, respectively). In contrast, the odds of being treated with a single autologous bone marrow transplant were lower for patients with early progression (OR 0.45) and also on treatment lines 3 (OR 0.12) or 4 (OR 0.06), compared to treatment line 1. Being treated with a single allogeneic bone marrow transplant was not significantly associated with any factors, thus not presented in Table 19.

**Table 19. Factors[a] associated with treatment type and transplant status, in multivariate logistic regression**

| Associated factors | OR (90% CI) for each selection of treatment | | | |
|---|---|---|---|---|
| | Single therapy[b] | Duplet therapy | Triplet therapy | Single autologous bone marrow transplants |
| Early progression: Yes (ref: no) | -[a] | -[a] | -[a] | 0.45 (0.22-0.93) |
| Early progression: Unknown (ref: no) | 20.56 (3.12-135.64) | -[a] | -[a] | 2.13 (1.23-3.71) |
| Treatment line 3 (ref: Treatment line 1) | -[a] | 1.53 (1.03-2.26) | 0.54 (0.36-0.81) | 0.12 (0.05-0.29) |
| Treatment line 4 (ref: Treatment line 1) | -[a] | 1.86 (1.12-3.08) | 0.33 (0.19-0.59) | 0.06 (0.01-0.32) |
| Treatment line >4 (ref: Treatment line 1) | -[a] | -[a] | 0.56 (0.34-0.91) | -[a] |
| CRAB component: Hypercalcemia (ref: no) | -[a] | 1.71 (1.09-2.70) | -[a] | -[a] |
| FISH: High risk cytogenetic t(4;14) at diagnosis (ref: no) | -[a] | 0.38 (0.16-0.92) | -[a] | -[a] |
| FISH: Non-high risk cytogenetic del(1p32 or 1p36) (ref: no) | -[a] | 0.11 (0.03-0.41) | 4.18 (1.79-9.76) | -[a] |
| FISH: Non-high risk cytogenetic gain(1q) (ref: no) | -[a] | 0.64 (0.41-0.98) | 1.63 (1.11-2.39) | -[a] |
| Age at diagnosis: 51-60 years (ref: 37-50 years) | -[a] | -[a] | -[a] | 4.06 (1.25-13.21) |
| Age at diagnosis: 61-70 years (ref: 37-50 years) | -[a] | -[a] | -[a] | 3.82 (1.20-12.16) |
| Age at diagnosis: >80 years (ref: 37-50 years) | -[a] | -[a] | 0.12 (0.02-0.77) | -[a] |

CI, confidence interval; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; odds ratio, OR.
Source: Annex 4 – Tables 30-33
[a] The results are presented exclusively for factors associated with at least one outcome on treatment type or transplant status in the logistic regression models. The results for all factors are available in Annex 4 – Tables 30-33.
[b] The model did not converge mostly due to small sample sizes.

As shown in **Table 20**, for **treatment regimen outcomes**, having the non-high risk FISH finding del(1p32 or 1p36) at diagnosis was associated with higher odds of being treated with **VCD** (OR 5.23). In contrast, being treated in treatment line >4 or being in the oldest age category lowered the odds of treatment with VCD (ORs 0.18 and 0.30, respectively). The odds of being treated with **VCD+AutoHSCT** was higher for patients with the non-high risk FISH finding gain(1q) at diagnosis (OR 4.23) and lower for patients with the CRAB component anaemia at diagnosis (OR 0.23). The odds of selecting **VelDex** as the treatment was higher for patients with early progression, the CRAB component hypercalcemia, or the high-risk FISH finding t(14;16) at diagnosis (ORs between 1.94-2.85). However, being in treatment lines 2, 4, or >4 was associated with lower odds of having **VelDex** as the treatment (ORs between 0.24-0.43), compared to treatment line 1. Patients with early progression had higher odds for **VRD** and **Tal/Dxm** treatment compared to patients without early progression (OR 1.95 and 4.29 respectively). For the selection of **DR-PACE** treatment, having the non-high risk FISH finding del(1p32 or 1p36) at diagnosis was associated with increased the odds of the treatment.

For the treatment regimen outcomes **single therapy**, **VRD + AutoHSCT**, **VMP**, **Cpm/Pred**, **DR-PACE, RD**, **MP**, **Mel/Pred/Tal (MPT)** and **Tal/Dxm** the model did not converge (mostly due to the small sample size).

Additional factors associated with treatment selection outcomes are presented in the Results Report Tables 49-106 (Annex 4).

**Table 20. Factors[a] associated with major treatment regimens, in multivariate logistic regression**

| Associated factors | | OR (90% CI) for each selection of treatment | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | VCD | VCD +AutoHSCT | VelDex | VelDex + AutoHSCT[b] | VRD | VRD + AutoHSCT[b] | VMP[b] | Cpm/Pred[b] | DR-PACE[b] | RD[b] | MP[b] | Mel/Pred/Tal (MPT)[b] | Tal/Dxm[b] |
| Early progression: Yes (ref: no) | -[a] | -[a] | -[a] | -[a] | 1.95 (1.08-3.52) | -[a] | -[a] | -[a] | -[a] | 0.41 (0.22-0.76) | -[a] | -[a] | 4.29 (1.14-16.14) |
| Early progression: Unknown (ref: no) | -[a] | -[a] | -[a] | 3.62 (1.36-9.66) | -[a] | -[a] | 2.13 (1.01-4.49) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| Treatment line: 2 (ref: Treatment line: 1) | -[a] | -[a] | 0.33 (0.19-0.57) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 0.14 (0.04-0.54) | -[a] |
| Treatment line: 3 (ref: Treatment line: 1) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 0.36 (0.13-0.96) | -[a] | -[a] | -[a] | -[a] | 0.08 (0.01-0.46) | -[a] |
| Treatment line: 4 (ref: Treatment line: 1) | -[a] | -[a] | 0.24 (0.09-0.60) | -[a] | -[a] | -[a] | -[a] | 8.61 (2.96-25.08) | -[a] | -[a] | -[a] | -[a] | -[a] |
| Treatment line: >4 (ref: Treatment line: 1) | 0.18 (0.06-0.52) | -[a] | 0.43 (0.21-0.90) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 0.13 (0.02-0.74) | -[a] | -[a] |
| CRAB component Hypercalcemia (ref: no) | -[a] | -[a] | 1.94 (1.08-3.47) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 3.25 (1.46-7.21) | -[a] | -[a] |
| CRAB component Anaemia (ref: no) | -[a] | 0.23 (0.07-0.75) | -[a] | -[a] | -[a] | 14.35 (1.83-112.35) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| CRAB component Lytic bone lesions (ref: no) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 2.03 (1.28-3.23) |
| R-ISS risk classification at diagnosis: Unknown (ref: low) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | 0.49 (0.25-0.97) |
| FISH t(14;16) at diagnosis (ref: no) | -[a] | -[a] | 2.85 (1.15-7.04) | -[a] | -[a] | -[a] | 5.38 (1.53-18.87) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |
| FISH gain(1q) at diagnosis (ref: no) | -[a] | 4.23 (1.38-13.00) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| FISH del(1p32 or 1p36) at diagnosis (ref: no) | 5.23 (1.71-15.99) | -[a] | -[a] | | -[a] | -[a] | -[a] | -[a] | 10.25 (1.27-82.50) | -[a] | -[a] | -[a] | -[a] |
| Age at diagnosis category (years): 71-80 (ref: 37-50 years) | 0.30 (0.10-0.92) | -[a] | -[a] | | -[a] | -[a] | 10.46 (1.65-66.44) | -[a] | -[a] | -[a] | -[a] | -[a] | -[a] |

AutoHSCT, autologous haematopoietic stem cell transplant; Bor, bortezomib; CI, confidence interval; Cis, cisplatin; Cpm, cyclophosphamide; CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; Dox, doxorubicin; DR-PACE, cisplatin + cyclophosphamide + dexamethasone + doxorubicin + etoposide + lenalidomide; Dxm, dexamethasone; Eto, etoposide; FISH, fluorescence in situ hybridization HD-mel, high-dose melphalan; Len, lenalidomide; Mel, melphalan; MP, melphalan + prednisone; MPT, melphalan + prednisone + thalidomide; OR, odds ratio; Pred, prednisone; RD, lenalidomide + dexamethasone; R-ISS, revised international staging system for multiple myeloma; Tal, thalidomide; VCD, bortezomib + cyclophosphamide + dexamethasone; VelDex, bortezomib + dexamethasone; VMP, bortezomib + melphalan + prednisone; VRD, bortezomib + lenalidomide + dexamethasone.

Source: Annex 4 – Tables 35-48

[a] The results are presented exclusively for factors associated with at least one treatment regimen outcome. The results for all factors are available in Annex 4 – Tables 35-48.

[b] The model did not converge.

## 10.8 Secondary objective 2: Characteristics of MM patient subpopulations

In general, several of the subpopulations had few patients overall, which led to even fewer patients in the subpopulation having a specific characteristic. This is especially apparent in the latter treatment lines, as patient numbers decrease with each successive treatment line. Due to this low number of observations for specific characteristics, no firm conclusions were attainable.

### 10.8.1 Subpopulations of varying disease status, according to the R-ISS risk classification

#### 10.8.1.1 Patient characteristics

The full results on patient characteristics in the three subpopulations by the R-ISS risk classification are presented in the Results Report Tables 107-109 (Annex 4) and are summarized below in Table 21.

In the subpopulations of low or high R-ISS risk classification, most patients in all treatment lines were **male**, apart from exactly 50.0% of the high risk subpopulation in line 3 (Table 21). The distribution between female and male patients was more equal in the subpopulation of the standard risk classification.

In the subpopulation with low R-ISS risk classification at the time of MM diagnosis and among those who were in the first treatment line, the mean **age** at diagnosis was 60.4 years (SD 10.6 years) (Table 21), and typically increased in the subsequent treatment lines with a maximum mean age of 68.1 in treatment lines >4. When the R-ISS risk classification at MM diagnosis was standard, the mean age at diagnosis ranged between 66.6 and 69.4 years across the treatment lines. In the subpopulation with the high risk classification, the mean age at diagnosis was 66.6 years (SD 7.2 year) in the first treatment line and exhibited a pattern of an decreasing mean age towards the latter treatment lines (age 61.1 (SD 5.2) in lines >4).

Regardless of the R-ISS risk classification, **hypertension** was among the most common co-morbidities in all treatment lines (Table 21), apart from the subpopulation with the low R-ISS risk classification in treatment lines 3, 4, and >4, in which the total number of patients was low. In the subpopulation with standard risk classification, the proportion of patients with **no other co-morbidities** across the treatment lines seemed to be lower than in low- or high-risk population.

**Table 21. Selected patient characteristics, by treatment line, in subpopulations of varying disease status according to the R-ISS risk classification**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Low (1) R-ISS risk classification[a]** | | | | | |
| ***Patients / lines, n*** | 18 / 18 | 11 / 11 | 6 / 6 | 4 / 4 | 3 / 7 |
| ***Demographic characteristics[a]*** | | | | | |
| Male, n (%) | 11 (61.1%) | 6 (54.5%) | 4 (66.7%) | 3 (75.0%) | 7 (100.0%) |
| Age in years, mean (SD) | 60.4 (10.6) | 61.9 (9.9) | 66.6 (9.1) | 64.8 (10.4) | 68.1 (12.0) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 5 (27.8%) | 3 (27.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| No other co-morbidities diagnosed, n (%) | 7 (38.9%) | 3 (27.3%) | 2 (33.3%) | 2 (50.0%) | 3 (42.9%) |
| **Standard (2) R-ISS risk classification[a]** | | | | | |
| ***Patients / lines, n*** | 121 / 121 | 103 / 103 | 79 / 79 | 39 / 39 | 22 / 55 |
| ***Demographic characteristics[a]*** | | | | | |
| Male, n (%) | 59 (48.8%) | 51 (49.5%) | 40 (50.6%) | 21 (53.8%) | 30 (54.5%) |
| Age in years, mean (SD) | 67.2 (8.6) | 67.4 (8.3) | 68.1 (7.7) | 69.4 (7.2) | 66.6 (7.7) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 69 (57.0%) | 62 (60.2%) | 46 (58.2%) | 26 (66.7%) | 39 (70.9%) |
| No other co-morbidities diagnosed, n (%) | 32 (26.4%) | 29 (28.2%) | 22 (27.8%) | 13 (33.3%) | 23 (41.8%) |
| **High (3) R-ISS risk classification[a]** | | | | | |
| ***Demographic characteristics[a]*** | | | | | |
| ***Patients / lines, n*** | 27 / 27 | 21 / 21 | 16 / 16 | 9 / 9 | 4 / 7 |
| Male, n (%) | 17 (63.0%) | 12 (57.1%) | 8 (50.0%) | 5 (55.6%) | 5 (71.4%) |
| Age in years, mean (SD) | 66.6 (7.2) | 65.4 (6.9) | 64.5 (7.6) | 63.1 (6.5) | 61.1 (5.2) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 11 (40.7%) | 7 (33.3%) | 5 (31.2%) | 2 (22.2%) | 2 (28.6%) |
| No other co-morbidities diagnosed, n (%) | 10 (37.0%) | 9 (42.9%) | 7 (43.8%) | 4 (44.4%) | 4 (57.1%) |

SD, standard deviation; R-ISS, revised international staging system for multiple myeloma.
Source: Annex 4 – Tables 107-109.
[a] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declines.
[b] The table presents the most frequent co-morbidity hypertension in the actual study population, hypertension, and the category no other co-morbidities diagnosed.

### 10.8.1.2 Disease characteristics

The full results on disease characteristics according to the R-ISS risk classification are presented in the Results Report Tables 134-136 (Annex 4) and are summarized below in Table 22.

For patients with low and standard R-ISS risk classification, over 70% of patients in treatment line 1 had the **CRAB component** lytic bone lesions, and more than half of patients with high risk classification (55.6%). In the subpopulation of the high risk classification, the CRAB components appeared largely more prevalent than in the lower risk subpopulations, e.g., 85% of patients on first-line treatment and 100% of patients on fourth-line or higher had anaemia. The distribution of the CRAB components in the other subpopulations appeared similar in the subsequent treatment lines.

In patients with the standard classification, less than 10% of patients in the treatment line 1 had high risk cytogenetic FISH finding del(17p13), t(4;14), or t(14;16). In the subpopulation with

high R-ISS risk classification, the high risk cytogenetic FISH findings were more frequent: 22.2% of patients in treatment line 1 had del(17p13), 18.5% t(4;14), and 22.2% t(14;16).

**Table 22. Selected disease characteristics, by treatment line, in subpopulations of varying disease status according to the R-ISS risk classification**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Low (1) R-ISS risk classification[a]** | | | | | |
| ***Patients / lines, n*** | 18 / 18 | 11 / 11 | 6 / 6 | 4 / 4 | 3 / 7 |
| ***CRAB component[a,b]*** | | | | | |
| Hypercalcemia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Renal dysfunction | 1 (5.6%) | 1 (9.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Anaemia | 1 (5.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Lytic bone lesions | 14 (77.8%) | 14 (77.8%) | 7 (63.6%) | 3 (50.0%) | 1 (25.0%) |
| ***High risk cytogenetics FISH findings[a]*** | | | | | |
| del(17p13) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| t(4;14) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| t(14;16) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[a]*** | | | | | |
| t(14;20) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 2 (11.1%) | 2 (18.2%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) |
| del(1p32 or 1p36) | 1 (5.6%) | 1 (9.1%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) |
| **Standard (2) R-ISS risk classification[a]** | | | | | |
| ***Patients / lines, n*** | 121 / 121 | 103 / 103 | 79 / 79 | 39 / 39 | 22 / 55 |
| ***CRAB component[a]*** | | | | | |
| Hypercalcemia | 21 (17.4%) | 19 (18.4%) | 15 (19.0%) | 9 (23.1%) | 8 (14.5%) |
| Renal dysfunction | 27 (22.3%) | 22 (21.4%) | 16 (20.3%) | 9 (23.1%) | 3 (5.5%) |
| Anaemia | 60 (49.6%) | 54 (52.4%) | 42 (53.2%) | 24 (61.5%) | 40 (72.7%) |
| Lytic bone lesions | 86 (71.1%) | 75 (72.8%) | 59 (74.7%) | 28 (71.8%) | 41 (74.5%) |
| ***High risk cytogenetics FISH findings[a]*** | | | | | |
| del(17p13) | 12 (9.9%) | 10 (9.7%) | 5 (6.3%) | 2 (5.1%) | 5 (9.1%) |
| t(4;14) | 5 (4.1%) | 4 (3.9%) | 2 (2.5%) | 2 (5.1%) | 4 (7.3%) |
| t(14;16) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[a]*** | | | | | |
| t(14;20) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 21 (17.4%) | 17 (16.5%) | 13 (16.5%) | 7 (17.9%) | 13 (23.6%) |
| del(1p32 or 1p36) | 2 (1.7%) | 1 (1.0%) | 1 (1.3%) | 1 (2.6%) | 2 (3.6%) |
| **High (3) R-ISS risk classification[a]** | | | | | |
| ***Patients / lines, n*** | 27 / 27 | 21 / 21 | 16 / 16 | 9 / 9 | 4 / 7 |
| ***CRAB component[a]*** | | | | | |
| Hypercalcemia | 8 (29.6%) | 7 (33.3%) | 5 (31.2%) | 5(55.6%) | 3(42.9%) |
| Renal dysfunction | 19 (70.4%) | 13 (61.9%) | 9 (56.2%) | 5(55.6%) | 3(42.9%) |
| Anaemia | 23 (85.2%) | 18 (85.7%) | 15 (93.8%) | 9(100.0%) | 7(100.0%) |
| Lytic bone lesions | 15 (55.6%) | 13 (61.9%) | 11 (68.8%) | 7(77.8%) | 7(100.0%) |
| ***High risk cytogenetics FISH findings[a]*** | | | | | |
| del(17p13) | 6 (22.2%) | 5 (23.8%) | 4 (25.0%) | 4 (44.4%) | 4 (57.1%) |
| t(4;14) | 5 (18.5%) | 5 (23.8%) | 4 (25.0%) | 3 (33.3%) | 2 (28.6%) |
| t(14;16) | 6 (22.2%) | 6 (28.6%) | 4 (25.0%) | 1 (11.1%) | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[a]*** | | | | | |
| t(14;20) | 1 (3.7%) | 1 (4.8%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 11 (40.7%) | 11 (52.4%) | 9 (56.2%) | 5 (55.6%) | 3 (42.9%) |
| del(1p32 or 1p36) | 2 (7.4%) | 2 (9.5%) | 2 (12.5%) | 1 (11.1%) | 0 (0.0%) |

standard deviation; R-ISS, revised international staging system for multiple myeloma.

Source: Annex 4 – Tables 134-136.
[a] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declines.
[b] FHR variables.

## 10.8.2 Subpopulations without specific treatments

### 10.8.2.1 Patient characteristics

The full results on patient characteristics of the subpopulations who did not receive the four pre-specified treatments, autologous bone marrow transplant, allogeneic bone marrow transplant, duplet therapy or triplet therapy, in the different treatment lines are presented in the Results Report Tables 110-129 (Annex 4).

Table 23 summarizes the patient characteristics in the subpopulations of patients who did not receive the four pre-specified treatments of interest in the first treatment line: autologous bone marrow transplant, allogeneic bone marrow transplant, duplet therapy or triplet therapy. In all of these four subpopulations and across the treatment lines, the majority of patients were male and the mean age ranged 66.3-68.9 years. In all treatment lines of these subpopulations, hypertension was among the most common co-morbidities, and 23.1 to 54.3% of patients had no diagnosed other co-morbidities. The proportion of patients with no other co-morbidities, across the treatment lines, appeared slightly higher in the subpopulation without duplet therapy in treatment line 1, compared to the subpopulations without the other treatments of interest in treatment line 1.

In the four subpopulations without the specific treatments, the patient characteristics from treatment line 2 onwards were largely consistent with the treatment line 1 (Results Report Tables 110-129; Annex 4). In these subpopulations and across the treatment lines, most patients were also male, the mean age was approximately 66-69 years, hypertension was among the most common co-morbidities, and from a quarter to half of patients had no other co-morbidities.

**Table 23. Selected patient characteristics, by treatment line, in subpopulations without specified treatments in treatment line 1**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Without autologous bone marrow transplant[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 177 / 177 | 156 / 156 | 113 / 113 | 58 / 58 | 29 / 68 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | 95 (53.7%) | 83 (53.2%) | 61 (54.0%) | 33 (56.9%) | 41 (60.3%) |
| Age in years, mean (SD) | 68.0 (9.5) | 67.9 (8.7) | 68.6 (7.9) | 68.9 (7.9) | 68.3 (8.1) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 77 (43.5%) | 66 (42.3%) | 47 (41.6%) | 19 (32.8%) | 22 (32.4%) |
| No other co-morbidities diagnosed, n (%) | 46 (26.0%) | 41 (26.3%) | 31 (27.4%) | 19 (32.8%) | 17 (25.0%) |
| **Without allogeneic bone marrow transplant[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 219 / 219 | 181 / 181 | 130 / 130 | 67 / 67 | 35 / 86 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | 114 (52.1%) | 95 (52.5%) | 70 (53.8%) | 39 (58.2%) | 57 (66.3%) |
| Age in years, mean (SD) | 67.3 (8.6) | 67.2 (8.4) | 67.9 (7.7) | 68.2 (7.7) | 66.6 (8.2) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 95 (43.4%) | 74 (40.9%) | 52 (40.0%) | 21 (31.3%) | 24 (27.9%) |
| No other co-morbidities diagnosed, n (%) | 61 (27.9%) | 52 (28.7%) | 40 (30.8%) | 24 (35.8%) | 33 (38.4%) |
| **Without duplet therapy[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 132 / 132 | 109 / 109 | 74 / 74 | 36 / 36 | 20 / 46 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | 71 (53.8%) | 58 (53.2%) | 41 (55.4%) | 22 (61.1%) | 30 (65.2%) |
| Age in years, mean (SD) | 66.7 (9.2) | 67.0 (8.3) | 68.3 (8.0) | 68.1 (8.1) | 66.8 (9.0) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 54 (40.9%) | 44 (40.4%) | 31 (41.9%) | 11 (30.6%) | 15 (32.6%) |
| No other co-morbidities diagnosed, n (%) | 43 (32.6%) | 36 (33.0%) | 27 (36.5%) | 15 (41.7%) | 25 (54.3%) |
| **Without triplet therapy[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 130 / 130 | 103 / 103 | 78 / 78 | 41 / 41 | 20 / 53 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | 71 (54.6%) | 57 (55.3%) | 43 (55.1%) | 23 (56.1%) | 35 (66.0%) |
| Age in years, mean (SD) | 67.5 (8.9) | 67.4 (8.5) | 67.1 (8.0) | 68.0 (7.9) | 66.3 (8.0) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | 62 (47.7%) | 44 (42.7%) | 31 (39.7%) | 14 (34.1%) | 16 (30.2%) |
| No other co-morbidities diagnosed, n (%) | 30 (23.1%) | 26 (25.2%) | 22 (28.2%) | 13 (31.7%) | 14 (26.4%) |

CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; SD, standard deviation.

Source: Annex 4 – Tables 110, 111, 120, and 125.

[a] At the start of the treatment line.

[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declines.

[c] The table presents the most frequent co-morbidity in the actual study population, hypertension, and the category no other co-morbidities diagnosed.

### 10.8.2.3 Disease characteristics

The full results on disease characteristics of the subpopulations who did not receive the four pre-specified treatments, autologous bone marrow transplant, allogeneic bone marrow transplant, duplet therapy or triplet therapy, in the different treatment lines are presented in the Results Report Tables 137-156 (Annex 4).

Table 24 summarizes the disease characteristics in these subpopulations of patients who did not receive the treatments of interest in the first treatment line: autologous bone marrow transplant, allogeneic bone marrow transplant, duplet therapy or triplet therapy. In these subpopulations of patients, the **CRAB component** lytic bone lesions was the most frequent (>70% of patients) followed by anaemia (>40 %). The distribution of the CRAB components in the subpopulations appeared similar in the subsequent treatment lines.

Less than 10% of patients in treatment line 1 had a high risk finding del(17p13), t(4;14), or t(14;16), with a similar pattern found in the subsequent treatment lines.

In all the four subpopulations, less than 11% of patients in treatment line 1 had an MM with the low R-ISS risk classification, while most patients (>50%) had an MM with the standard risk classification. The distribution of the R-ISS risk classification in these subpopulations appeared similar in the subsequent treatment lines.

In the four subpopulations without the specific treatments, the disease characteristics from treatment line 2 onwards were largely consistent with the treatment line 1 (Results Report Tables 137-156; Annex 4). In these subpopulations and across the treatment lines, lytic bone lesions was the most frequent CRAB component, high risk cytogenetic FISH finding were relatively uncommon (>10%, with few exceptions), and most patients (>50%) had an MM with the standard risk classification.

**Table 24. Selected disease characteristics, by treatment line, in subpopulations without specified treatments in treatment line 1**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Without autologous bone marrow transplant[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 177 / 177 | 156 / 156 | 113 / 113 | 58 / 58 | 29 / 68 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | 27 (15.3%) | 24 (15.4%) | 19 (16.8%) | 14 (24.1%) | 7 (10.3%) |
| Renal dysfunction | 46 (26.0%) | 39 (25.0%) | 28 (24.8%) | 15 (25.9%) | 6 (8.8%) |
| Anaemia | 85 (48.0%) | 79 (50.6%) | 61 (54.0%) | 36 (62.1%) | 45 (66.2%) |
| Lytic bone lesions | 122 (68.9%) | 109 (69.9%) | 78 (69.0%) | 40 (69.0%) | 37 (54.4%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | 17 (9.6%) | 14 (9.0%) | 8 (7.1%) | 4 (6.9%) | 5 (7.4%) |
| t(4;14) | 5 (2.8%) | 5 (3.2%) | 3 (2.7%) | 3 (5.2%) | 2 (2.9%) |
| t(14;16) | 7 (4.0%) | 7 (4.5%) | 5 (4.4%) | 3 (5.2%) | 6 (8.8%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | 1 (0.6%) | 1 (0.6%) | 1 (0.9%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 28 (15.8%) | 26 (16.7%) | 20 (17.7%) | 10 (17.2%) | 14 (20.6%) |
| del(1p32 or 1p36) | 6 (3.4%) | 5 (3.2%) | 5 (4.4%) | 3 (5.2%) | 2 (2.9%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | 11 (6.2%) | 8 (5.1%) | 5 (4.4%) | 3 (5.2%) | 7 (10.3%) |
| Standard (2) | 98 (55.4%) | 90 (57.7%) | 69 (61.1%) | 34 (58.6%) | 41 (60.3%) |
| High (3) | 20 (11.3%) | 16 (10.3%) | 12 (10.6%) | 7 (12.1%) | 3 (4.4%) |
| **Without allogeneic bone marrow transplant[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 219 / 219 | 181 / 181 | 130 / 130 | 67 / 67 | 35 / 86 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | 35 (16.0%) | 31 (17.1%) | 24 (18.5%) | 17 (25.4%) | 11 (12.8%) |
| Renal dysfunction | 57 (26.0%) | 44 (24.3%) | 30 (23.1%) | 16 (23.9%) | 6 (7.0%) |
| Anaemia | 105 (47.9%) | 92 (50.8%) | 70 (53.8%) | 39 (58.2%) | 53 (61.6%) |
| Lytic bone lesions | 151 (68.9%) | 126 (69.6%) | 91 (70.0%) | 48 (71.6%) | 55 (64.0%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | 20 (9.1%) | 17 (9.4%) | 10 (7.7%) | 6 (9.0%) | 8 (9.3%) |
| t(4;14) | 8 (3.7%) | 7 (3.9%) | 4 (3.1%) | 4 (6.0%) | 4 (4.7%) |
| t(14;16) | 8 (3.7%) | 8 (4.4%) | 6 (4.6%) | 3 (4.5%) | 6 (7.0%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | 1 (0.5%) | 1 (0.6%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 38 (17.4%) | 33 (18.2%) | 25 (19.2%) | 14 (20.9%) | 19 (22.1%) |
| del(1p32 or 1p36) | 6 (2.7%) | 5 (2.8%) | 5 (3.8%) | 3 (4.5%) | 2 (2.3%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | 16 (7.3%) | 11 (6.1%) | 6 (4.6%) | 4 (6.0%) | 7 (8.1%) |
| Standard (2) | 119 (54.3%) | 102 (56.4%) | 78 (60.0%) | 38 (56.7%) | 53 (61.6%) |
| High (3) | 26 (11.9%) | 20 (11.0%) | 15 (11.5%) | 9 (13.4%) | 7 (8.1%) |
| **Without duplet therapy[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 132 / 132 | 109 / 109 | 74 / 74 | 36 / 36 | 20 / 46 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | 16 (12.1%) | 15 (13.8%) | 12 (16.2%) | 9 (25.0%) | 7 (15.2%) |

| | | | | | |
|---|---|---|---|---|---|
| Renal dysfunction | 28 (21.2%) | 23 (21.1%) | 17 (23.0%) | 9 (25.0%) | 3 (6.5%) |
| Anaemia | 54 (40.9%) | 49 (45.0%) | 35 (47.3%) | 18 (50.0%) | 25 (54.3%) |
| Lytic bone lesions | 99 (75.0%) | 81 (74.3%) | 56 (75.7%) | 30 (83.3%) | 39 (84.8%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | 17 (12.9%) | 14 (12.8%) | 7 (9.5%) | 5 (13.9%) | 8 (17.4%) |
| t(4;14) | 8 (6.1%) | 8 (7.3%) | 5 (6.8%) | 4 (11.1%) | 6 (13.0%) |
| t(14;16) | 2 (1.5%) | 2 (1.8%) | 1 (1.4%) | 1 (2.8%) | 2 (4.3%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 28 (21.2%) | 26 (23.9%) | 18 (24.3%) | 10 (27.8%) | 11 (23.9%) |
| del(1p32 or 1p36) | 5 (3.8%) | 4 (3.7%) | 4 (5.4%) | 3 (8.3%) | 2 (4.3%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | 14 (10.6%) | 8 (7.3%) | 4 (5.4%) | 3 (8.3%) | 5 (10.9%) |
| Standard (2) | 73 (55.3%) | 61 (56.0%) | 46 (62.2%) | 23 (63.9%) | 36 (78.3%) |
| High (3) | 10 (7.6%) | 9 (8.3%) | 5 (6.8%) | 3 (8.3%) | 2 (4.3%) |
| **Without triplet therapy[a] in treatment line 1** | | | | | |
| ***Patients / lines, n*** | 130 / 130 | 103 / 103 | 78 / 78 | 41 / 41 | 20 / 53 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | 25 (19.2%) | 21 (20.4%) | 16 (20.5%) | 10 (24.4%) | 4 (7.5%) |
| Renal dysfunction | 41 (31.5%) | 30 (29.1%) | 21 (26.9%) | 11 (26.8%) | 5 (9.4%) |
| Anaemia | 70 (53.8%) | 59 (57.3%) | 48 (61.5%) | 29 (70.7%) | 41 (77.4%) |
| Lytic bone lesions | 89 (68.5%) | 71 (68.9%) | 54 (69.2%) | 28 (68.3%) | 29 (54.7%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | 9 (6.9%) | 8 (7.8%) | 5 (6.4%) | 3 (7.3%) | 2 (3.8%) |
| t(4;14) | 4 (3.1%) | 3 (2.9%) | 2 (2.6%) | 1 (2.4%) | 0 (0.0%) |
| t(14;16) | 7 (5.4%) | 7 (6.8%) | 5 (6.4%) | 2 (4.9%) | 4 (7.5%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | 1 (0.8%) | 1 (1.0%) | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | 17 (13.1%) | 13 (12.6%) | 11 (14.1%) | 6 (14.6%) | 11 (20.8%) |
| del(1p32 or 1p36) | 1 (0.8%) | 1 (1.0%) | 1 (1.3%) | 0 (0.0%) | 0 (0.0%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | 7 (5.4%) | 4 (3.9%) | 2 (2.6%) | 1 (2.4%) | 2 (3.8%) |
| Standard (2) | 68 (52.3%) | 57 (55.3%) | 43 (55.1%) | 21 (51.2%) | 30 (56.6%) |
| High (3) | 21 (16.2%) | 16 (15.5%) | 13 (16.7%) | 7 (17.1%) | 5 (9.4%) |

CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; SD, standard deviation; R-ISS, revised international staging system for multiple myeloma.

Source: Annex 4 – Tables 137, 138, 147 and 152.

[a] At the start of the treatment line.

[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declines.

[c] FHR variables.

## 10.8.3 Subpopulation of short treatment durations

### 10.8.3.1 Patient characteristics

The full results on patient characteristics in subpopulations with short treatment durations (defined as when the treatment line is among the shortest 25% of all corresponding treatment line durations)

are presented in the Results Report Tables 130-133 (Annex 4) and selected results are summarized below in Table 25.

The **number of patients** included in the subpopulation with short treatment durations in the first line decreased from 41 (line 2) to 9 patients (line >4), while the percentage of **male** patients increased in subsequent treatment lines (51.5% in line 2; 64.3% in treatment lines >4). The mean age of patients increased slightly with each successive treatment line, ranging from 67.8 to 70.0.

A substantial percentage of patients with short treatment durations had **no diagnosed co-morbidities**, particularly for patients in treatment line 4 who had a short duration of 3rd line treatment (46.7%) and patients on treatment lines >4 with previous short treatment durations in line 2 or 3 (61.5% and 87.5%, respectively). For patients who did have co-morbidities, **hypertension** was the most common co-morbidity across all treatment lines (ranging from 30.8% to 50% of patients) for the subpopulations with short treatment durations in line 1 or 2. Only for subpopulations with short durations in later treatment lines (3rd or 4th) was the percentage of hypertension low (ranging from 9.1-13.3% in treatment lines 4 or >4).

**Table 25. Selected patient characteristics, by treatment line, in subpopulations of short treatment durations**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Short duration of 1st line treatment[a]** | | | | | |
| ***Patients / lines, n*** | N/A | 41 / 41 | 31 / 31 | 18 / 18 | 9 / 14 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | N/A | 21 (51.2%) | 15 (48.4%) | 11 (61.1%) | 9 (64.3%) |
| Age in years, mean (SD) | N/A | 67.8 (9.4) | 68.4 (7.7) | 69.4 (7.6) | 70.0 (4.7) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | N/A | 18 (43.9%) | 12 (38.7%) | 7 (38.9%) | 7 (50.0%) |
| No other co-morbidities diagnosed, n (%) | N/A | 9 (22.0%) | 7 (22.6%) | 4 (22.2%) | 3 (21.4%) |
| **Short duration of 2nd line treatment[a]** | | | | | |
| ***Patients / lines, n*** | N/A | N/A | 31 / 31 | 15 / 15 | 7 / 13 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | N/A | N/A | 13 (41.9%) | 7 (46.7%) | 9 (69.2%) |
| Age in years, mean (SD) | N/A | N/A | 66.7 (7.5) | 67.7 (6.5) | 66.7 (6.0) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | N/A | N/A | 14 (45.2%) | 5 (33.3%) | 4 (30.8%) |
| No other co-morbidities diagnosed, n (%) | N/A | N/A | 9 (29.0%) | 6 (40.0%) | 8 (61.5%) |
| **Short duration of 3rd line treatment[a]** | | | | | |
| ***Patients / lines, n*** | N/A | N/A | N/A | 15 / 15 | 8 / 16 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | N/A | N/A | N/A | 8 (53.3%) | 9 (56.2%) |
| Age in years, mean (SD) | N/A | N/A | N/A | 67.6 (6.5) | 67.0 (6.8) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | N/A | N/A | N/A | 2 (13.3%) | 1 (6.2%) |
| No other co-morbidities diagnosed, n (%) | N/A | N/A | N/A | 7 (46.7%) | 14 (87.5%) |

| | | | | | |
|---|---|---|---|---|---|
| **Short duration of 4th line treatment[a]** | | | | | |
| ***Patients / lines, n*** | N/A | N/A | N/A | N/A | 9 / 33 |
| ***Demographic characteristics[b]*** | | | | | |
| Male, n (%) | N/A | N/A | N/A | N/A | 20 (60.6%) |
| Age in years, mean (SD) | N/A | N/A | N/A | N/A | 66.0 (7.6) |
| ***Most frequent co-morbidities[a,b]*** | | | | | |
| Hypertension, n (%) | N/A | N/A | N/A | N/A | 3 (9.1%) |
| No other co-morbidities diagnosed, n (%) | N/A | N/A | N/A | N/A | 17 (51.5%) |

CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; N/A, not applicable; SD, standard deviation.
Source: Annex 4 – Tables 130-133.
[a] Short previous treatment line duration, followed-up after the end of the treatment line with short duration.
[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declined.
[c] The table presents the most frequent co-morbidity hypertension in the actual study population, hypertension, and the category no other co-morbidities diagnosed.

### 10.8.3.2 Disease characteristics

The full results on disease characteristics in subpopulations with short treatment durations are presented in the Results Report Tables 157-160 (Annex 4) and selected results are summarized below in Table 26.

In these subpopulations of patients, the **CRAB component** lytic bone lesions and anaemia were the most common. The distribution of the CRAB components in the subpopulations appeared fairly similar in the subsequent treatment lines, and for all four subgroups with short durations in previous treatment lines. However, due to low numbers in higher treatment lines a clear pattern was not distinguishable.

Less than 10% of these patients had high risk cytogenetic FISH finding del(17p13), t(4;14), or t(14;16); The exceptions were for patients with a short duration of 2nd or 3rd line treatment for del(17p13) (range: 16.1-37.5%) and t(4;14) for patients with a short duration in 3rd line (13.3% and 25.0% for patients on 4th and >4, respectively).

For **non-high risk cytogenetics FISH findings** the most frequent finding among patients was gain(1q), ranging from 11.1 to 19.4% for patients on treatment lines 2-4 who had a short 1st line treatment duration. There were none or a limited number of other non-high risk findings, t(14;20) and del(1p32 or 1p36), consistent across treatment lines and subpopulations.

In all of the four subpopulations, most patients had an MM with the standard **R-ISS risk classification**, while only 0-2 patients were classified as low risk (regardless of subpopulation) in all treatment lines except lines >4 (n=4).

**Table 26. Selected disease characteristics, by treatment line, in subpopulations of short treatment durations**

| Patient characteristics | Line 1 | Line 2 | Line 3 | Line 4 | Line >4 |
|---|---|---|---|---|---|
| **Short duration of 1st line** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **treatment[a]** | | | | | |
| ***Patients / lines, n*** | NA | 41 / 41 | 31 / 31 | 18 / 18 | 9 / 14 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | NA | 9 (22.0%) | 8 (25.8%) | 7 (38.9%) | 6 (42.9%) |
| Renal dysfunction | NA | 13 (31.7%) | 8 (25.8%) | 4 (22.2%) | 0 (0.0%) |
| Anaemia | NA | 27 (65.9%) | 22 (71.0%) | 16 (88.9%) | 14 (100.0%) |
| Lytic bone lesions | NA | 27 (65.9%) | 20 (64.5%) | 11 (61.1%) | 6 (42.9%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | NA | 3 (7.3%) | 2 (6.5%) | 1 (5.6%) | 0 (0.0%) |
| t(4;14) | NA | 1 (2.4%) | 1 (3.2%) | 1 (5.6%) | 0 (0.0%) |
| t(14;16) | NA | 2 (4.9%) | 2 (6.5%) | 0 (0.0%) | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | NA | | | | |
| t(14;20) | NA | 1 (2.4%) | 1 (3.2%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | NA | 6 (14.6%) | 6 (19.4%) | 2 (11.1%) | 0 (0.0%) |
| del(1p32 or 1p36) | NA | 3 (7.3%) | 3 (9.7%) | 2 (11.1%) | 2 (14.3%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | NA | 1 (2.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Standard (2) | NA | 25 (61.0%) | 20 (64.5%) | 12 (66.7%) | 12 (85.7%) |
| High (3) | NA | 5 (12.2%) | 5 (16.1%) | 2 (11.1%) | 0 (0.0%) |
| **Short duration of 2nd line treatment[a]** | | | | | |
| ***Patients / lines, n*** | NA | NA | 31 / 31 | 15 / 15 | 7 / 13 |
| ***CRAB component[b,c]*** | | | | | |
| Hypercalcemia | NA | NA | 6 (19.4%) | 3 (20.0%) | 0 (0.0%) |
| Renal dysfunction | NA | NA | 8 (25.8%) | 4 (26.7%) | 0 (0.0%) |
| Anaemia | NA | NA | 14 (45.2%) | 7 (46.7%) | 7 (53.8%) |
| Lytic bone lesions | NA | NA | 24 (77.4%) | 9 (60.0%) | 11 (84.6%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | NA | NA | 5 (16.1%) | 3 (20.0%) | 4 (30.8%) |
| t(4;14) | NA | NA | 2 (6.5%) | 1 (6.7%) | 0 (0.0%) |
| t(14;16) | NA | NA | 1 (3.2%) | 1 (6.7%) | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | NA | NA | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | NA | NA | 8 (25.8%) | 3 (20.0%) | 1 (7.7%) |
| del(1p32 or 1p36) | NA | NA | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | NA | NA | 1 (3.2%) | 1 (6.7%) | 1 (7.7%) |
| Standard (2) | NA | NA | 21 (67.7%) | 8 (53.3%) | 10 (76.9%) |
| High (3) | NA | NA | 5 (16.1%) | 3 (20.0%) | 0 (0.0%) |
| **Short duration of 3rd line treatment[a]** | | | | | |
| ***Patients / lines, n*** | NA | NA | NA | 15 / 15 | 8 / 16 |
| ***CRAB component[b,c]*** | NA | | | | |
| Hypercalcemia | NA | NA | NA | 3 (20.0%) | 3 (18.8%) |
| Renal dysfunction | NA | NA | NA | 2 (13.3%) | 1 (6.2%) |
| Anaemia | NA | NA | NA | 7 (46.7%) | 6 (37.5%) |
| Lytic bone lesions | NA | NA | NA | 10 (66.7%) | 14 (87.5%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | NA | NA | NA | 3 (20.0%) | 6 (37.5%) |
| t(4;14) | NA | NA | NA | 2 (13.3%) | 4 (25.0%) |

| | | | | | |
|---|---|---|---|---|---|
| t(14;16) | NA | NA | NA | 1 (6.7%) | 0(0.0%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | NA | NA | NA | 0 (0.0%) | 0 (0.0%) |
| gain(1q) | NA | NA | NA | 6 (40.0%) | 4 (25.0%) |
| del(1p32 or 1p36) | NA | NA | NA | 0 (0.0%) | 0 (0.0%) |
| ***Disease status according to the R-ISS risk classification[b]*** | NA | | | | |
| Low (1) | NA | NA | NA | 2 (13.3%) | 1 (6.2%) |
| Standard (2) | NA | NA | NA | 9 (60.0%) | 9 (56.2%) |
| High (3) | NA | NA | NA | 2 (13.3%) | 0 (0.0%) |
| **Short duration of 4th line treatment[a]** | | | | | |
| ***Patients / lines, n*** | NA | NA | NA | NA | 9 / 33 |
| ***CRAB component[b,c]*** | NA | | | | |
| Hypercalcemia | NA | NA | NA | NA | 4 (12.1%) |
| Renal dysfunction | NA | NA | NA | NA | 0 (0.0%) |
| Anaemia | NA | NA | NA | NA | 16 (48.5%) |
| Lytic bone lesions | NA | NA | NA | NA | 18 (54.5%) |
| ***High risk cytogenetics FISH findings[b]*** | | | | | |
| del(17p13) | NA | NA | NA | NA | 2 (6.1%) |
| t(4;14) | NA | NA | NA | NA | 2 (6.1%) |
| t(14;16) | NA | NA | NA | NA | 0 (0.0%) |
| ***Non-high risk cytogenetics FISH findings[b]*** | | | | | |
| t(14;20) | NA | NA | NA | NA | 0 (0.0%) |
| gain(1q) | NA | NA | NA | NA | 9 (27.3%) |
| del(1p32 or 1p36) | NA | NA | NA | NA | 2 (6.1%) |
| ***Disease status according to the R-ISS risk classification[b]*** | | | | | |
| Low (1) | NA | NA | NA | NA | 4 (12.1%) |
| Standard (2) | NA | NA | NA | NA | 20 (60.6%) |
| High (3) | NA | NA | NA | NA | 2 (6.1%) |

CRAB, C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions; FISH, fluorescence in situ hybridization; NA, Not applicable; SD, standard deviation; R-ISS, revised international staging system for multiple myeloma.
Source: Annex 4 – Tables 157-160.
[a] Short previous treatment line duration, followed-up after the end of the treatment line with short duration.
[b] At the time of diagnosis. The frequency varies in treatment lines, because the subpopulation left in the treatment lines declined.
[c] FHR variables.

### 10.8.4 Overall survival (OS) and time to next treatment (TTNT) in subpopulations of short treatment line duration

The Kaplan-Meier curves for the OS in the subpopulations of short treatment line duration, per treatment line, are presented in Results Report Figures 317-320 (Annex 4). The Aalen-Johansen curves on the TTNT in the subpopulations, per treatment line, are presented in the Result Report Figures 321-324.

## 10.9 Other analyses

When the treatment line definition was re-defined, the increase in the number of treatment lines was 8.35% (Results Report Table 161, Annex 4). As the frequency did not reach the pre-specified threshold of 10% (Section 9.9.4), the analyses were not performed.

## 10.10 Adverse events/adverse reactions

The nature of this non-interventional study did not meet the criteria for adverse event reporting.

# 11 Discussion

## 11.1 Key results

### 11.1.1 Primary objective 1

*Patient characteristics.* In this register-based cohort study, 224 MM patients were treated in line 1 with 36 patients left after the treatment line 4. The proportion of male patients increased with the treatment lines (52.7% in treatment line 1; 64.8% in treatments lines >4) and the median age of 67.7 years in the first treatment line remained similar in later treatment lines. Hypertension was the most common co-morbidity, while 29.0% (treatment line 1) and 39.8% (treatment lines >4) of patients had no other co-morbidities.

*Disease characteristics*. The most common CRAB component was lytic bone lesions followed by anaemia, while the high-risk FISH del(17p13) and the non-high-risk gain(1q) were the most common FISH findings. Less than 10% of patients had low R-ISS risk classification, while most patients (>50%) had an MM with the standard risk classification. A larger proportion of patients were classified as high-risk based on the ISS classification as compared to classification according to R-ISS. IgG was the most common M-protein type (53.1%), and IgD the least common (<1%). In all treatment lines, 17.9% (treatment line 1) to 15.9% (treatment lines>4) of patients had an MM with early progression, however the variable was missing for almost 30% of the patients.

*Treatment pattern.* Novel therapy (Bor/Dxm, Bor/Dxm+AutoHSCT HD-mel, Bor/Cpm/Dxm, Bor/Cpm/Dxm+AutoHSCT HD-mel, Mel/Pred/Tal (MPT), Tal/Dxm) accounted for 64.5% of treatment regimens in line 1, with the highest frequency of Bor/Dxm (19.2%). The frequency of these regimens was lower in the subsequent treatment lines. In treatment lines >4, Len/Dxm (11.36%) and other regimens (55.68%) were the most frequent. Single autologous was the most common bone marrow transplant type in treatment line 1 (20.98%) but very rare after treatment line 2. In total 81 patients (36%) received this treatment. Furthermore, of the treatment type, duplet or triplet treatment were most common in all treatment lines (83% in line1; 65% in lines >4). The median treatment line duration decreased from 5.05 months in treatment line 1 to 3.21 months in lines>4, whereas the mean duration decreased from almost a year in line 1, to less than 5 months in lines >4.

*Overall response rate (ORR).* The ORR was 32.17% (90% CI 40.03-46.35). The ORR, regardless of treatment, was the best in the first treatment line and steadily declined over treatment lines. Novel therapies (Bor/Cpm/Dxm, Bor/Dxm, Bor/Mel/Pred (VMP), Mel/Pred/Tal (MPT)) reached the best ORR of 50% or more, especially in combination with AutoHSCT, with the highest response for Bor/Cpm/Dxm+AutoHSCT (HD-mel) (69.57%). Regarding bone marrow transplants, the ORR for single autologous transplants was superior to for allogeneic transplants. Of treatment types, single treatment achieved a lower ORR as compared to duplet, triple, and other therapy.

### 11.1.2 Primary objective 2: Description of overall survival (OS)

*Among all MM patients with treatment.* The median OS in the first treatment line was longer (62.36 months) than in subsequent lines.

*Stratified by patient characteristics.* The median OS was longer for men (except in the first treatment line) and in younger age groups (especially in the first two treatment lines).

*Stratified by disease characteristics.* Patients with the CRAB components had a shorter median OS in all treatment lines, than without. The median OS in the first treatment line was the longest among patients with the high-risk FISH finding del(17p13). Patients with the standard R-ISS risk classification had a longer OS in treatment line 1 than those with high R-ISS risk. Patients with early progression had a shorter median OS for all treatment lines.

*Stratified by treatment patterns.* Patients treated with a single autologous transplant in the treatment lines 1-3 had longer median OS than those without the single autologous treatment. Patients with triplet therapy appeared to have a longer median OS in the first treatment line, than patients with single or duplet therapy.

### 11.1.3 Primary objective 2: Description of time to next treatment (TTNT)

*Among all MM patients with treatment.* The median TTNT was 8.54 months in the first treatment line and appeared longer in the subsequent treatment lines.

*Stratified by demographic characteristics.* The median TTNT appeared longer for male patients in treatment line 1, than female patients. The median TTNT also appeared longer for the patients in the highest age group (>80 years), compared to the youngest patients (ages 37-50).

*Stratified by disease characteristics.* For patients with the CRAB components, the median TTNT for the first treatment line was shorter than for those without, with a pattern of longer TTNT of all components in the second and third treatment lines. In treatment line 1 and 2, patients with the low R-ISS risk classification, the median TTNT was the longest, while patients with the standard R-ISS risk classification, demonstrated shortest median TTNT in the first treatment line.

*Stratified by treatment patterns, across treatment lines.* Patients treated with various therapies had a prolonged TTNT in line 1, compared to Bor/Cpm/Dxm. The median TTNT for single autologous bone marrow transplant was considerably higher in first treatment line, compared to no transplant. For patients with triplet therapy, the median of TTNT was longer in line 1.

### 11.1.4 Secondary objective 1: Factors associated with overall survival (OS)

*Patient and disease characteristics and treatment patterns.* In the multivariate analyses on factors associated with OS, no patient, disease, or treatment-related characteristics were consistently

associated with OS in all the treatment lines. Further, the low number of events and patients having specific characteristics led to relatively unstable regression models and commonly a low precision (wide CI) of the HRs. Nonetheless, having the CRAB components hypercalcemia with HR 1.72 (90% CI 1.16-2.55) and anaemia with HR 1.94 (90% CI 1.40-2.68) at diagnosis were associated with an inferior OS in some treatment lines, while having the high-risk FISH finding del(17p13) was associated with improved OS in treatment line 4 but inferior OS in line 5. Being treated with various other treatment regimens decreased the risk for death in the treatment lines 2-3, compared with the reference treatment regimen Bor/Cpm/Dxm.

### 11.1.5 Secondary objective 1: Factors associated with time to next treatment (TTNT)

*Patient and disease characteristics and treatment patterns.* Having the CRAB component hypercalcemia with HR 1.72 (90% CI 1.16-2.55) and anaemia with HR 1.94 (90% CI 1.40-2.68) at diagnosis were associated with an increased risk of proceeding to the next treatment in the first treatment line. The high-risk FISH findings del(17p13) or t(14,16) were associated with an increased risk of proceeding to the next treatment in the treatment line 1. Patients with the standard or high R-ISS risk classification had in several treatment lines a higher risk of proceeding to the next treatment, compared to patients with low R-ISS risk classification. Being treated with the various treatment regimens were generally associated with a lower risk of proceeding to the next treatment, compared to Bor/Cpm/Dxm.

### 11.1.6 Secondary objective 1: Factors associated with treatment selection

Multivariate analyses on factors associated with treatment selection outcomes were also limited by the low number of events and patients having specific characteristics. However, factors associated with being treated with duplet therapy included being in treatment lines 3 and 4 compared to line 1, and having the CRAB component hypercalcemia at diagnosis, while having the FISH findings t(4;14), gain(1q), or del(1p32 or 1p36) decreased the odds to be treated with duplet therapy. The odds of treatment with triplet therapy was decreased in later treatment lines, compared to the treatment line 1, while the FISH findings gain(1q) or del(1p32 or 1p36) at diagnosis increased the odds of being treated with triplet therapy. The odds of being treated with a single autologous bone marrow transplant were higher in older age, compared to the younger, and the odds were lower for patients with early progression and also in treatment lines 3-4, compared to line 1. Factors associated with increased odds of being treated with the specific individual treatment regimens included the CRAB component hypercalcemia (regimens: VelDex, MP), the high-risk FISH finding t(14;16) (regimens: VelDex and VMP), the non-high risk FISH findings del(1p32 or 1p36) (regimens: DR-PACE) or gain(1q) (regimens: VCD +AutoHSCT), early progression (regimens: VelDex and VRD). The odds of treatment with the individual regimens was decreased for patients with the CRAB component anaemia (regimens: VCD +AutoHSCT) and for patients treated in lines 2, 4, or >4 compared to treatment line 1 (regimens: VelDex).

### 11.1.7 Secondary objective 2: Subpopulations

In all analyses of this objective, the number of patients were small.

*Subpopulations of varying disease status, according to the R-ISS risk classification.* The mean age was the lowest in the subpopulation with low R-ISS risk classification. In the subpopulations of low and standard risk classification, the mean age appeared to increase with subsequent treatment lines, while the mean age decreased over the treatment lines in the high-risk R-ISS subpopulation. In all R-ISS subpopulations, hypertension was among the most common co-morbidities. In the high-risk R-ISS group, the CRAB components and high-risk FISH findings appeared largely more prevalent than in the lower risk subpopulations, throughout all treatment lines. In the subpopulations with standard risk classification, the proportion of patients with **no other co-morbidities** across the treatment lines seemed to be lower than in low or high-risk populations.

*Subpopulations without specific treatments.* The patient and disease characteristics, across the treatment lines, did not differ substantially between subpopulations without autologous/allogeneic bone marrow transplant or duplet/triplet therapy, or in comparison with the entire cohort.

*Subpopulations of short treatment duration.* Among patients with short treatment duration, the mean age of patients increased slightly with each successive treatment line, ranging from 67.8 to 70.0 in all subpopulations. A substantial percentage of patients with short treatment duration had no diagnosed co-morbidities particularly for patients in treatment line 4 onwards who had a short duration of treatment in line 3 or 4. Across all treatment lines of patients with short treatment durations, lytic bone lesions and anaemia appeared the most common CRAB components, most patients did not have high risk cytogenetic FISH findings, and most patients had the standard R-ISS risk classification.

## 11.2 Limitations

Overall, in many analyses after treatment line 1 the subgroups were small which hindered the ability to draw firm conclusions from these results.

### 11.2.1 Selection bias

This study used data from the FHR which included approximately 90% of MM patients of one large hospital region, members of the HUS. The included patients in this study may not be fully representative of the target population of all MM patients in Finland, because the source data represents patients only residing in an urban region. Thus, hospital-administrated therapies may be more common in the HUS region than in rural areas, because prescribers may favor oral therapies when the distance to the nearest hospital is longer than in suburban or urban areas. Accordingly, the potential selection bias was considered valid for the interpretation of the results related to treatment patterns. Otherwise, the patient cases in the hospital were considered representative of the rest of country; for example, the OS is identical for MM patients in HUS compared to all MM patients in Finland (as confirmed via personal communication with the register holder).

As detailed in the study protocol and the SAP 2.0, the representativeness of the actual study cohort (those who initiated 1st line treatment), against the whole study cohort (all patients diagnosed with MM), was intended to be investigated through formally comparing the characteristics of both sets of patients. This analysis could not, however, be performed, because the whole study cohort only differed from the actual cohort by one patient. This was related to the fact that the data holder restricted the patient population (i.e. dataset), for secondary use, to only those patients with comprehensive data available in the FHR in the beginning of the study. In the absence of a formal comparison to the whole FHR population, the results of this study were interpreted with the understanding that the study population may to some extent differ from all MM patients in Finland, even beyond area of residence discussed above.

Selection bias from identifying the study population (via a MM diagnosis) was not considered a concern in the study, because the validity of the MM diagnosis in the FHR is considered high. All included patients had ICD-10 and/or ICD-O code for MM. Although a few included patients may have had an invalid MM diagnosis, that would be unlikely to significantly impact the results.

### 11.2.2 Data source and information bias

The use of the FHR as the data source enabled the inclusion of a wider range of variables, compared to exclusively using the national cancer register. Data from the FHR is considered of appropriate quality for scientific research, and has been used in prior studies (14–16). Typical to studies based on data collected from routine clinical practice, however, this study was limited to the quality of data and availability of the variables in the FHR. As the date of end of treatment and clear denotation of progression was known to be missing in the register, TTNT was calculated instead of progression-free survival. Further, data is recorded to FHR by different individuals in the hospital, potentially leading to inconsistency within variables where there is no clear clinical definition (e.g. a lack of standardization of data entries). In terms of data availability, the following information was considered relevant for the objectives of this study but are unavailable in the FHR: historical data prior to MM diagnosis, reason for loss to follow-up, and reason for treatment discontinuation.

Moreover, partially missing data was anticipated to occur for some variables, which was addressed by reporting the missing values descriptively as a separate "unknown" or "not available (NA)" category. Of all variables included in the analyses, only three contained >20% of missingness in the whole study cohort: R-ISS stage (26.2%), urine M-protein type (43.6%), and early progression (29.5%). The study did not systematically record separate urine M-protein type. Usually only light chains are detected, and only kappa or lambda are recorded (and not the listed IgA, IgG etc. heavy chains). While the variables R-ISS stage and early progression were included in the model-based regression analyses, urine M-protein type was only included in summary statistics and not as a covariate in any of the models. As detailed in the SAP 2.0, in the case that a variable contained >50% missing values, sensitivity analyses would be conducted to address any bias stemming from a high proportion of missingness in the variable. As no variables met this condition, the sensitivity analyses excluding such variables from the regression models were not

performed. Thus, the impact of the partial missingness on the results was considered relatively minimal. Describing the missingness and handling missing data in the models by the inclusion of a separate "unknown" category for those below the threshold level of missingness was deemed sufficient. Further, treatment pattern variables had unexpectedly small differences between treatment lines; the limitation could be also considered due to the difficulty of assigning and evaluating each treatment line, as the recording of treatment lines in FHR may be inconsistent.

Of the outcome variables, no information bias for survival (death) was considered to occur. The TTNT and treatment pattern variables may be limited due to the matters detailed above.

As the variables defining the end of follow-up did not include information on emigration from the HUS to another region in Finland or abroad, some patients may have been included in the follow-up even though they in fact no longer contributed to the study cohort. This could have led to patients being misclassified in the study as not having outcome events (e.g. death, change in treatments), if their events in fact occurred and were registered in another region. Further, since any patient who may have emigrated were not censored at the last observation, there may be minor impact on the total time at risk (increase) in the survival models. However, this misclassification was unlikely to impact the results of the study, as severely ill patients are generally less likely to migrate when being actively treated and monitored for their chronic condition.

Concerning other variables, measures for CRAB components and ISS were presented in two versions in the descriptive tables: the original FHR variables and a combination of the FHR variables and relevant laboratory values, including FISH measures (R-ISS). In the descriptive results, the frequency of the variables with the laboratory values was higher than without, informing that the variable definitions were sensitive to the used definition. It was also noted in the FHR that FISH results from before 2011-2012 are not fully comparable with those after 2012. It should also be noted that in HUS FISH has been used in 2010-15 more broadly than in other parts of Finland. The recommendation was to only take FISH from patients eligible for transplant, but in HUS it was sometimes also taken from non-eligible patients. Accordingly, the results of this study were interpreted considering possible misclassification of these variables, especially acknowledging that the main definition for the CRAB components was the one without the laboratory values, which was also used in the further analyses.

Furthermore, at diagnosis the proportion of patients without co-morbidities was relatively high and it was therefore expected that patients who were healthier in the beginning also received more treatment lines. However, information on co-morbidities that emerged after diagnosis was not recorded and the potential effect of other conditions than MM after diagnosis on subsequent treatments could not be analysed.

Finally, there was information on whether an AutoHSCT was actually performed, but not if it was planned. In some cases, a planned AutoHSCT might not have been achieved, e.g., due to illnesses, unsuccessful mobilization of stem cells, or if the disease was completely refractory. It

is to be noted however, that in the present day only a small minority have such a refractory disease that they cannot reach AutoHSCT, and over 90% of stem cell mobilizations are successful.

It is also to be noted that the total number of AutoHSCT could be overestimated in the results. There were no records of tandem transplants, but there might be patients who received a transplant with sufficient time between the individual transplants for them not be classified as tandem. These patients therefore would be represented twice in the data.

The sensitivity analysis on the definition of treatment line (see Section 9.9.4) indicate that the results of this study were not sensitive when the treatment line was re-defined.

### 11.2.3 Confounding

In the regression analyses concerning factors associated with the OS, TTNT, and treatment patterns, the models were adjusted for pre-defined other variables by introducing them all at once to the model. However, because the available data was limited by partial missingness and/or full unavailability of some relevant variables, such as historical data prior to diagnosis as previously noted in Section 11.2.2, residual confounding likely remained.

Further, due to anticipated confounding by indication, and also the small study size, definite conclusions on the effectiveness of treatments cannot be drawn from this study.

### 11.2.4 Immortal time bias

In case the informed consent of patients was requested after diagnosis, the time period from diagnosis to the date of informed consent is the immortal time. The immortal time was handled in survival analyses as left-censoring.

### 11.2.5 Study size

At the time of initiating the study, at least 300-400 patients with data on treatments were estimated to be available. However, population size of the whole cohort was 225 patient and the actual cohort was 224 patients. The small study size was considered sufficient for main descriptive analyses including all the 224 patients. However, the small study size decreased the precision of all results, and limited meaningful interpretations from the stratified descriptive analyses, from the regression models on associated factors, and from the descriptive analyses in subpopulations. Further, the fact that few patients remained in the later treatment lines, especially fourth-line treatment (n=68) or higher (n=36), decreased the precision and limited the interpretation of results presented by treatment line.

## 11.3 Interpretation

### 11.3.1 Primary Objective 1: Descriptive characteristics and patient journey of Finnish MM patients

#### 11.3.1.1 Patients characteristics

The results that the gender distribution of the MM patients were almost equal and the median age was approximately 67 years at treatment line 1 are largely in accordance with both another Finnish study using the same register (17) as well as other demographic descriptions of the MM population in Sweden (18) the US (19,20), the UK (21), Denmark (22), the Netherlands (23) the Czech Republic (24) and in Latin America (25). Across the treatment lines, the median age was almost constant which has also been reported by Verelst et al (23). The reason why the proportion of men increased across the treatment lines might be because women are generally older when they are diagnosed and might not survive until the later treatment lines. The most common co-morbidity in all treatment lines in the current study, hypertension, reflected the general disease burden in Finland (26). Although co-morbidities of MM patients are scarcely described in previous research, American observational studies have described hypertension, diabetes, and cardiovascular diseases as among the most common co-morbidities of MM patients on first line treatment (20,27), similar to the findings of this study. In addition, the high proportion of patients no co-morbidities across the treatment lines indicates that these patients, who were healthier in the beginning, also received more treatment lines.

#### 11.3.1.2 Disease characteristics

Lytic bone lesions and anaemia were the most common CRAB components, regardless of the treatment line, which is in line with disease characteristics in other MM populations (17,18,20,21,28). However, when the CRAB components were defined using laboratory values, the frequency of each component was higher, especially for hypercalcemia. This not only demonstrates that hypercalcemia is frequent in Finnish MM patients, similar to prior research (21), but also that the variable definitions were sensitive to whether laboratory values were considered in the definition. Further, the results on the frequency of MM patients with the CRAB components should be interpreted with caution considering that the CRAB components were missing for approximately 10% of the Finnish MM patients.

The FISH del(17p13) being the most common high-risk cytogenetic marker in all treatment lines is in accordance with a review by Rajan et al (29) and with findings of an American study on patients with smoldering myeloma (of which approximately half develops MM) (30). The result of the current study that a similar proportion of patients (8-11%) had the FISH del(17p13) finding in all treatment lines at diagnosis, however, differs from previous research, which has described deletions involving chromosome 17p to occur later in the disease course (29). There were no missing FISH values, but the discrepancy may be caused by incomplete recoding of FISH findings in the FHR, as described in Section 11.2.2 Particularly the FISH results before 2011-2012 were

not fully comparable with those after 2012, since there were no plasma cell selection (CD138 selection) in HUS before FISH analyses before 2013 forward.

The majority of patients across the treatment lines (54-62%) had a standard R-ISS classification which is in line with other studies (20), although the previous studies used the ISS risk classification. In addition, the low ISS classification was lower than what is normally observed in randomized controlled trials (7). In the current study, the proportion of ISS high-risk group was larger as compared to the proportion of R-ISS high-risk classification, which might be explained by the higher proportion of missing values for the R-ISS classification. The fact that the R-ISS risk classification was missing for a substantial proportion patients (26.2%), similar to other studies (20), hinders firm conclusions on the distribution of the risk classification among Finnish MM patients. It could also be the case that those in the missing category were in the poor condition, and thus it was not considered important to perform tests on these patients. Furthermore, the high proportion of M-protein type IgG is in line with a previously reported over 50% prevalence of the IgG among MM patients (30–32). The finding that 15.9-22.7% of patients in all treatment lines had MM with early progression shall be interpreted with caution, because close to 30% of patients had the early progression variable missing, which limits drawing definite conclusions on early progression.

#### 11.3.1.3 Treatment patterns

Treatment guidelines for MM are relatively recent in Finland, as the 2017 guidelines (8), summarized in Figure 5, were the first formally published national guidelines. Prior to this, general guidelines were published and modified as needed by the FHR online (in www.hematology.fi). These earlier guidelines are no longer available, so comparison of the treatment patterns between 2010 and 2016 to the corresponding guidelines is not possible. Even still, the results from this study show that clinical practice in Finland between 2010 and 2017 broadly reflected the Finnish guidelines for MM treatment in 2017 (8). The observed major regimens were ones specified in the treatment guidelines, with the exception of DR-PACE, Mel/Pred/Tal and Tal/Dxm.

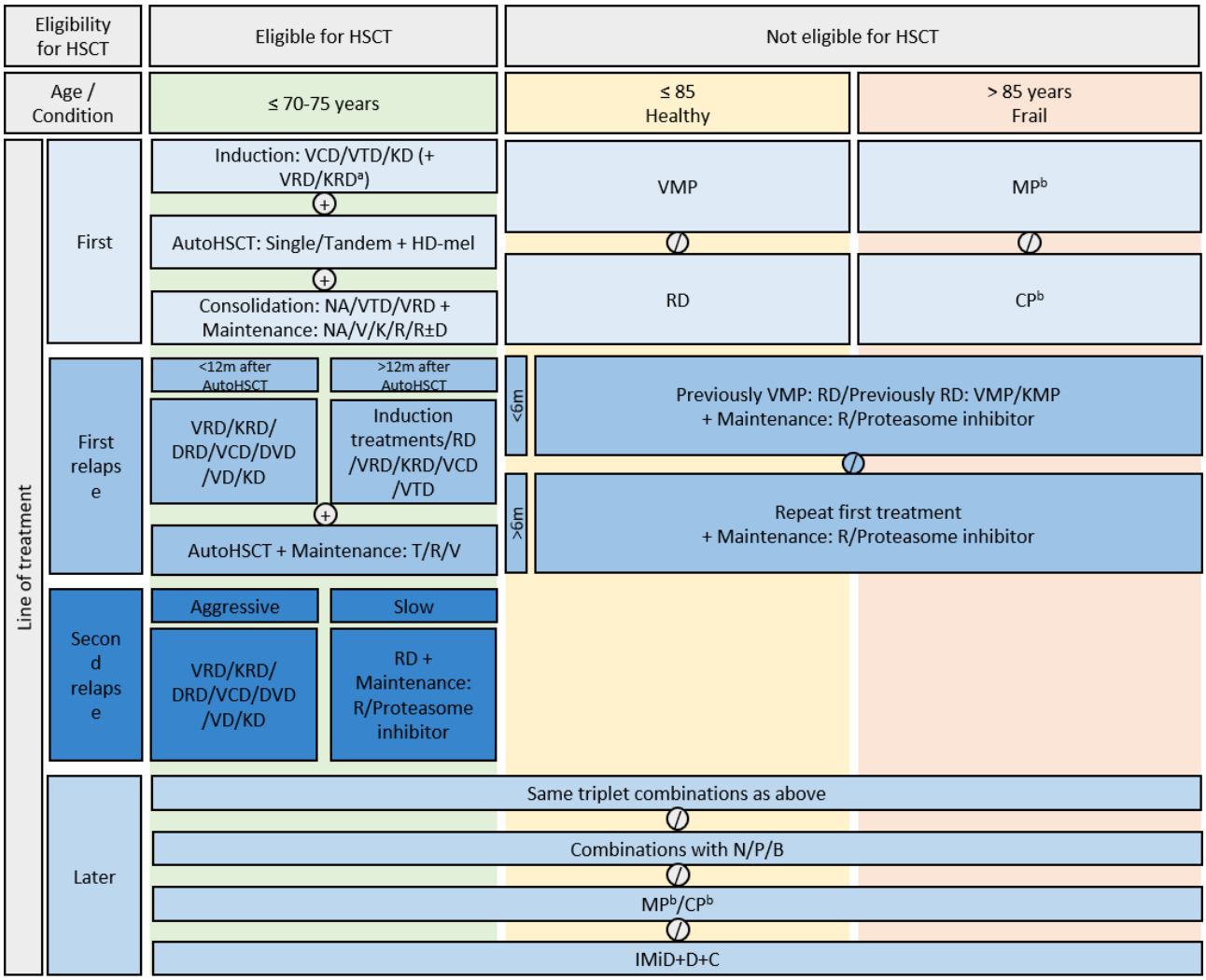


**Figure 5. Summary of the treatment guidelines for Multiple Myeloma in Finland in 2017.**

AutoHSCT, autologous haematopoietic stem cell transplant; B, bendamustine; C, cyclophosphamide; D, daratumumab (in triplets DXX), D, dexamethasone (in other cases); HD-mel, high-dose melphalan; IMiD, immunomodulatory drugs; K, carfilzomib; M, melphalan; N, ixazomib; NA, no treatment; P, pomalidomide; P, prednisone (with M or C); R, lenalidomide; T, thalidomide; V, bortezomib.

[a]VRD/KRD recommended as second line if adequate response not reached with VCD/VTD/KD.

[b]Conventional treatment, other treatments included in this figure are considered novel.

In line with the treatment guidelines from 2017 (8), in this study Bor/Cpm/Dxm was most commonly used in the first treatment line, Bor/Dxm/Len was only observed from the second treatment line onwards, and Bor/Mel/Pred was observed mostly in the first and second treatment lines. Additionally, Cpm/Pred was observed throughout the treatment lines, which reflects the recommendation on use in the first line and in later treatment lines during relapses for frail patients. Len/Dxm was also observed in all treatment lines from the second line onwards, in line with the recommendation of use in all treatment lines and among various patient populations. Mel/Pred was observed in first and second line, consistent with the recommendation of use in the first line in patients over 85 and/or frail patients. In total, treatments including bortezomib

accounted for 32.81%, lenalomide for 13.67%, and a combination of these therapies for 10.08% of all major treatment regimens in the study.

Further in line with the treatment guidelines, regimens containing AutoHSCT were observed mostly in the first and second treatment lines, with only two observations in the subsequent treatment lines. Bor/Dxm/Len+AutoHSCT (HD-mel) was mostly used in treatment line 2, as specified in the treatment guidelines (in patients with progressive or stable disease after the first two induction cycles). The higher proportion of single autologous (20.98%) than allogeneic (2.23%) bone marrow transplant in treatment line 1 was also expected, as autologous transplants are recommended over allogeneic.

Furthermore, duplet or triplet treatment were more common than single treatment across all treatment lines in this study, which is in line with the treatment guidelines from 2017, as single treatment was only recommended in maintenance therapy. Over 40% of patients received triplet therapy, similar to a study conducted in the US (20).

Finally, as the treatment landscape of MM is highly complex, it was expected that the category Other was the largest group of treatment regimens both in each line and in total.

Discrepancies to the 2017 treatment guidelines were also observed. As mentioned, DR-PACE, Mel/Pred/Tal and Tal/Dxm were identified as major treatment regimens in this study, but are not included in the treatment guidelines. This is most likely reflected in the low number of observations for each of these treatments. The low number of observations was expected for DR-PACE, which is generally used in patients who have not received an adequate treatment response with any other treatment. Mel/Pred/Tal is generally used as a first line treatment (21), as also observed in this study. Finally, Tal/Dxm was recommended as an induction therapy for patients eligible for stem cell transplants at the beginning of the study period (2010). This is reflected in the fact that the treatment was only observed in the first line.

Bor/Dxm is recommended to be used in the first relapse after HSCT, as well as in later relapses for patients eligible for HSCT if triplet treatments are not tolerated. However, in the current study this combination was most commonly used in the first treatment line, and in fact was the most common first line regimen after Other regimens. This can be explained by the fact that Bor/Dxm was recommended as the primary induction therapy for patients eligible for stem cell transplants in previous treatment guidelines.

The relatively short median treatment line durations, from approximately 5 months in line 1 to 3 months in lines >4, indicate that finding a suitable treatment for MM patients is challenging. Especially with regards to the treatment line 1, the short duration could be explained by the switching of treatments due to inadequate response in patients' therapy, as also recommended in the treatment guidelines (8). Moreover, the difference in the median and mean treatment durations, with longer means than medians, reveal that some outlier patients had very long treatment durations.

#### 11.3.1.4 Overall response rate

The finding that the ORR, regardless of treatment, was the best in the first treatment line and then decreased in subsequent lines was expected, as moving to subsequent treatment lines indicates lack of adequate response as the disease progresses. Similarly, it was expected that the best ORRs of 50% or more were observed for novel therapies (Bor/Cpm/Dxm, Bor/Dxm, Bor/Mel/Pred (VMP), Mel/Pred/Tal (MPT)) especially in combination with AutoHSCT (Bor/Cpm/Dxm+AutoHSCT (HD-mel), Bor/Dxm+AutoHSCT (HD-mel), Bor/Dxm/Len+AutoHSCT (HD-mel)). This is also aligned with another European study, where the ORR [≥ partial response] for patients who received heavy treatments in combination with stem cell transplants were significantly more likely to have a complete response in first line than patients who did not receive stem cell transplants (22). Furthermore, as expected for conventional therapies, Mel/Pred and Cpm/Pred had low ORRs (34.21% and 37.04%, respectively).

Many of the findings in the ORRs were also expected considering the treatment guidelines (8). The treatments with the best ORRs of 50% or more (mentioned above) are coincidentally first line treatments recommended for fit patients, with the exception of Bor/Dxm and Bor/Dxm+AutoHSCT (HD-mel). Likewise, the relatively lower ORRs (58.33%) for Bor/Dxm/Len+AutoHSCT (HD-mel) than for Bor/Cpm/Dxm+AutoHSCT (HD-mel) (69.57%) was also expected, as the combination is given to patients who did not achieve adequate response to the first induction regimen.

It was also expected that Len/Dex had a low ORR (30.53%), considering this duplet therapy is used for relapses according to the treatment guidelines (8). The ORR for Len/Dex also decreased in the later treatment lines, with ORRs of 25-50% in lines 2-4 but only 10% at >4 treatment lines. The same was observed for another treatment used in relapses, Bor/Dxm/Len (39.66%).

Interestingly, the ORR of 46% for DR-PACE was higher than expected. This treatment is only given to patients who are refractory to all other treatments, and still showed an ORR comparable to novel treatment combinations in a similar situation. However, it is to be noted that the number of patients was low.

Single autologous transplants yielded more than double ORR than allogeneic transplants, which is in line with the fact that autologous transplants are recommended (8). However, the use of allogeneic transplants still plays a role in the MM treatment, and it is suggested that it might have a curative potential especially in high-risk patients (33). Finally, considering that single therapy is only recommended when treatment combinations are contraindicated, single treatment expectedly yielded the lowest ORR (6.06%) as compared to duplet, triple and other therapies with ORRs ranging between 40% and 52%.

### 11.3.2 Primary objective 2: Description of overall survival (OS)

#### 11.3.2.1 Among MM patients with treatment

The decline in the OS in the current study, from 62.36 months in the first to 23.38 months in the third treatment line, is in accordance with both a Dutch registry-based observational study PHAROS (23) and a retrospective Czech study (24). However, the median OS in the current study in Finland was, in general, longer than in the previous studies. In the Dutch study the median OS was 37.5 months (95% CI 34.8-41.8 months) for the first treatment line and 13.9 months (95% CI 10.5-6.6 months) for the third treatment line; in the Czech study 47.5 months (95% CI 43.1-52.0 months) for the first and 13.2 months (95% CI 11.3-15.2 months) for the third treatment line. The improved OS in the current study could be due to the more advanced treatments being available in Finland during the study period. While the median OS was approximately 20 months longer in first compared to second treatment line, it was also observed that the median treatment line duration was only 5 months in treatment line 1. This reveals that the first line treatment prolonged the OS despite the unexpectedly short first line treatment duration, while the short first line treatment duration may originate from switching treatments due to inadequate response in patients' therapy (see Section 10.3.4). Nonetheless, this study demonstrated that the median OS of Finnish MM patients was relatively long compared to other countries, and that the OS expectedly declined as the patients progressed to further treatment lines.

#### 11.3.2.2 Stratified

Comparable to the findings of this study on MM patients in Finland, an American study also found in the OS to differ between male and female patients, where the descriptive median for OS was a slightly longer for women (8.5 months, 95% CI 5.8-13.0 vs. 7.5 months, 95% CI 5.4-9.0) (19). The longer median OS among younger MM patients in the current study, especially in the early treatment lines, was similar to the results from PHAROS (23) and the American observational study (19). Although the low number of patients and events limit drawing definite conclusions on differing patterns between the strata and treatment lines, the results of this study indicate that the OS differs by the demographic characteristics gender and age.

The shorter median OS for patients with CRAB components found in this study was in line with other research which found that patients with hypercalcemia and anaemia also presented a shorter median of OS (34). In addition, patients with FISH finding del(17p13) had the shorter survival in this study than without del(17p13), similar to a clinical trial (35), which found shorter median OS for patients with del(17p13) than without (26.7 months vs. 48.5 months, respectively). Moreover, the pattern of decreasing median OS in the strata of MM patients who had a higher R-ISS risk classification at diagnosis is in accordance with observational study PHAROS (23), where across all treatment lines, patients with stage 2 (standard) disease at diagnosis had a longer median OS than those diagnosed with stage 3 (high) (37.5 months and 30.3 months, respectively, at the first treatment line). However, the median OS for R-ISS was generally higher among the Finnish MM patients than in the previous study (23), potentially due to an advanced treatment

being available in Finland during the study period, or due to a differing risk classification in the previous study.

The finding of this study that patients with early progression had a markedly inferior OS in treatment line 1 was expected and clinically plausible, considering that the nature of an aggressive disease is typically characterized early after diagnosis and the prognosis of the patients is poorer than others. Early progression also influences the treatment choice.

Among Finnish MM parents in the current study, patients treated with a single autologous transplant in the treatment lines 1-3 had longer median OS than those without the single autologous treatment, similar to a previous Finnish study which also concluded that the median OS was longer for patients treated with the AutoHSCT (17). The finding that the median OS in the first treatment line appeared longer for patients with triplet therapy was expected, considering that triplet therapies are likely to have more positive treatment outcomes and the recipients of triplet therapies may be healthier than patients contraindicated for triplet therapies.

Although the low number of patients and events limited the interpretation of patterns between the strata and treatment lines, the results of this study support previous evidence that the median OS is shorter in the strata of MM patients with the CRAB components, higher R-ISS risk classification, or early progression.

### 11.3.3 Primary objective 2: Description of time to next treatment (TTNT)

#### 11.3.3.1 Among MM patients with treatment

The median TNNT was likely shortest in the first treatment line, compared to later treatment lines, because in the first treatment line the therapy is typically optimized as soon as a need is detected, which leads to progression to the second treatment line in the data. Moreover, the longer median TTNT than treatment line duration could be due to definitions of TTNT and treatment line duration (see Section 9.4.4), indicating that MM patients did not have treatment for some period time after finishing a treatment in the current line and before starting the new treatment. Another reason could be due to a large proportion of patients who only get the first line treatment and either die or do not tolerate the medication, which might result in that the second treatment line was a selective option.

#### 11.3.3.2 Stratified

Although the median TTNT appeared longer among men and the oldest patients, the low numbers of patients and events limited the possibility to draw definite conclusions on patterns in the median TTNT for demographic characteristics.

The result of this study that the strata of patients with the CRAB components (hypercalcemia, renal dysfunction, anaemia, and lytic bone lesions) had a shorter the median TTNT than those without is in accordance with another retrospective study in Iran (34), in which patients with hypercalcemia and anaemia demonstrated shorter median progression-free survival (PFS).

Overall, TTNT and PFS could be considered comparable, as the main difference between TTNT and PFS is that TTNT does not include deaths. The longest median TTNT among patients with the low R-ISS risk classification, in treatment line 1 and 2, was expected considering that low risk patients are more likely to have a positive treatment response.

In the strata of patients treated with various novel treatment combinations, such as thalidomide, lenalidomide and bortezomib, the descriptive median TTNT appeared longer than in the stratum of patients treated with the novel therapy Bor/Cpm/Dxm. This finding is in accordance with another real-world study carried out in Finland (17). In this study, the median TTNT was longer for patients who received novel therapy compared to conventional therapy, similar to a clinical trial (36), where combination therapy demonstrated a longer median TTNT compared to monotherapy.

### 11.3.4 Secondary objective 1: Factors associated with overall survival (OS)

The CRAB components hypercalcemia and anaemia at diagnosis were associated with increased risk of death among Finnish MM patients, in line with previous prospective observational cohort studies performed in the US (20) and in other regions including Latin America and Asia (25). In addition, in this study, FISH finding t(4;14) and del(17p13) at diagnosis presented an increased risk for death at second and fifth treatment lines, respectively, in accordance with other studies (12,13). An American prospective observational cohort study (20) also demonstrated an increased risk of death with the high-risk FISH findings del(17p) or t(4;14). In addition, the FISH finding del(17p) was described as an independent risk factor for OS in a clinical trial conducted in China (37).

Previous studies have also identified factors increasing the risk of death, which were not assessed in the current study, including history of diabetes, low serum creatinine, and low platelet count (21). Thus, further investigating these factors could be considered in future studies.

The models did have limitations especially due to the small study size. The 224 patients were considered sufficient for main descriptive analyses; however, the small study size decreased the precision of all results, and limited meaningful interpretations.

### 11.3.5 Secondary objective 1: Factors associated with time to next treatment (TTNT)

The CRAB components hypercalcemia and anaemia at diagnosis were associated with the increased risk of rapidly proceeding to the next treatment in the first treatment line, similar to another study, where hypercalcemia was associated with increased risk of first PFS (34). Further, the FISH finding del(17p13) was a risk factor for shorter TTNT, with for the first treatment line is in correlation with another clinical trial, where del(17p13) also demonstrated an increased risk for shorter PFS (35). In addition, in this study, R-ISS stage was also associated with the increased risk of proceeding to the next treatment for the standard and high stage, compared to low R-ISS stage, in line with a previous clinical trial demonstrating an increased risk for PFS at stages II and

III, compared to the stage I (35). The increased risk of proceeding to the next treatment among MM patients with FISH finding del(17p13) or standard and high R-ISS stage in the current study compared to clinical trials could be due to the study design or could be related to the wider range of CIs. Further, the main difference between TTNT and PFS is that TTNT does not include deaths (38).

The finding of the current study that various treatments in combination with AutoHSCT were associated with an improved TTNT, compared to Bor/Cpm/Dxm, is in accordance with the findings of a recent clinical trial (31).

### 11.3.6 Secondary objective 1: Factors associated with treatment selection

Based on the results of this study, being treated in lines 3 and 4 was associated with treatment type, namely the patients in lines 3 and 4 demonstrated higher odds of receiving duplet therapy (ORs 1.53 and 1.86, respectively), compared to being in treatment line 1. Further, the CRAB component hypercalcemia was also associated with higher odds (OR 1.71) of the duplet therapy. Additionally, the odds of triplet therapy were lower for the treatment line 3 and 4 (ORs 0.54 and 0.33, respectively), compared to treatment line 1. The reason for these findings could be that hypercalcemia often leads to acute kidney insufficiency, after which patients are often treated with Bor/Dxm (duplet therapy) until creatinine levels decrease, when switching to Bor/Cpm/Dxm treatment (triplet therapy) can be considered.

Other factors associated with treatment selection in this study are not further discussed in this section, due to the lack of comparable prior studies and the small study size resulting in unstable regression models. In general, treatment selection is mostly affected by treatment guidelines which is further discussed in Section 11.3.1.3. Some factors associated with treatment selection lacked clinical plausibility and were thereby probably obtained by chance, such as patients with the FISH findings t(4;14), gain(1q), or del(1p32 or 1p36) at diagnosis having lower odds to be treated with duplet therapy, compared to the patients without such findings.

### 11.3.7 Secondary objective 2: Subpopulations of varying disease status, according to the R-ISS risk classification

In all subpopulations according to the R-ISS risk, the number of observations was low, especially in the high-risk population (especially after treatment line 2). Thus, no firm conclusions could be made on any patterns across the treatment lines.

#### 11.3.7.1 Patients characteristics

The patient characteristics in all of the subpopulations of varying R-ISS classification by large reflected the findings for the entire study cohort as well as previous descriptions of MM patients of varying risk classifications (17–25) as well as the entire study cohort. The observed differences in patient characteristics by risk classification were expected and clinically plausible, including patients with low risk classification being younger.

#### 11.3.7.2 Disease characteristics

Lytic bone lesion and anaemia were the most common CRAB components in all sub-groups which is in line with the findings in the entire cohort and with observations in other studies (17,18,20,21,28). However, no previous studies have described the components in different R-ISS risk groups. The largely higher prevalence of the CRAB components (including hypercalcemia) in the high-risk group was expected since the patients in this group experience a more severe stage of disease (21). In addition, it was expected that the lytic bone lesions were the most prevalent CRAB in the lowest R-ISS risk group as it indicates a good prognosis.

As expected, in the subpopulation with lowest R-ISS risk classification, no patients had high risk cytogenetic FISH findings in any treatment line. Similarly, in the subpopulation of patients with high R-ISS risk classification, the high-risk cytogenetic FISH findings were relatively common across the different treatment lines. This also coheres with the disease severity among these patients (29,30).

### 11.3.8 Secondary objective 2: Subpopulations without specific treatments

#### 11.3.8.1 Patients characteristics

In general, the patient characteristics of the different subpopulations with no specific treatments were in line with the entire MM patient cohort and with previous literature on baseline characteristics (17–25), indicating that no discrimination of treatment occurred in Finland due to the characteristics of the patients.

#### 11.3.8.2 Disease characteristics

The results that the distribution of the selected disease characteristics (CRAB components, FISH findings, R-ISS risk) generally did not differ in the subpopulations with no specific treatments (autologous/allogeneic bone marrow transplant or duplet/triplet therapy), compared to the entire MM patient cohort and previous descriptions of MM patients (17,18,20,21,28–30), indicate that other factors, such as treatment guidelines, determine the treatment choice.

### 11.3.9 Secondary objective 2: Subpopulation of short treatment durations

In general, the number of patients included in these sub-group analyses was low, which prevented the ability to draw major conclusions about patients with short treatment durations.

#### 11.3.9.1 Patients characteristics

The patient characteristics of the subpopulation with short treatment duration did not by large differ from the entire MM patient cohort and or patient characteristics described in the literature (17–25). However, the observed substantial percentage of patients who had no diagnosed co-morbidities, particularly for patients in treatment line 4 and lines >4, indicates that healthier patients had shorter treatment lines and also reached later treatment lines.

#### 11.3.9.2 Disease characteristics

In the subpopulations with short treatment durations, the distribution of the selected disease characteristics (CRAB components, FISH findings, R-ISS risk), regardless of treatment line, did not largely differ from the entire MM patient cohort and previous descriptions of MM patients (17,18,20,21,28–30). However, the proportion of patients with the standard R-ISS risk classification was higher among the patients with short treatment durations, than among patients overall (especially in treatment line 2 and 3). The finding could be explained by quicker treatment optimization of healthier patients, when changes in the therapy have been documented in the data as the start of the next treatment line, which in turn leads to shorter treatment durations.

### 11.3.10 Overall survival (OS) and time to next treatment (TTNT) in subpopulations of short treatment line duration

In the analysis of the OS in the subpopulations of short treatment line duration, per treatment line, the number of patients were low especially in the OS3-5 groups and the TTNT3 to >TTNT4, and therefore no interpretations could be made from the results of these analyses.

## 11.4 Generalizability

Although this study included MM patients exclusively from the HUS region, the results from this MM population in the FHR are considered generalizable to the total MM population in Finland. Further, the results can be considered generalizable in other countries with similar demographics and healthcare systems as in Finland, such as other Nordic countries.

# 12 Conclusion

This observational cohort study used Finnish registry data to characterize an MM population and to describe the OS and TTNT, both overall and stratified by known patient-related prognostic factors. The patient journeys were described over several treatment lines, but the small number of observations in many subgroups limits the ability to draw firm conclusions after the first treatment line.

*Primary objective 1.* The study confirms that MM occurs relatively late in life and equally among men and women, but that the proportion of male patients increased with the treatment lines. In accordance to other studies, the findings also suggest that MM patients suffer from several co-morbidities. The disease characteristics at diagnosis were largely consistent with previously reported findings in other populations, with lytic bone lesions and anaemia being the most common CRAB components, del(17p13) being the most common FISH finding, most patients having the standard risk classification and the serum M-protein type IgG. However, the results should be interpreted considering the relatively high proportion of missing values for CRAB components, and especially R-ISS risk classification. Interestingly, the proportion of patients with the low ISS classification was lower than normally observed in RCTs, indicating that MM patients are in a worse condition in real world. The observed treatment patterns showed that clinical practice in Finland between 2010 and 2017 broadly reflected the Finnish guidelines for MM treatment, where novel treatments including bortezomib, lenalomide, and a combination of these therapies accounted for more than half of all major treatment regimens. Further, the higher proportion of single autologous compared to allogeneic bone marrow transplant in treatment line 1 was also expected, as autologous transplants are recommended over allogeneic per the national guidelines. The finding that the ORR, regardless of treatment, was the best in the first treatment line and then decreased in subsequent lines was expected, as moving to subsequent treatment lines indicates a lack of adequate response as the disease progresses. Similarly, it was expected that the best ORRs of 50% or more were observed for novel therapies.

*Primary objective 2.* The observed decline in the median OS across treatment lines (from 62.36 months in the first to 23.38 months in the third treatment line) was in accordance with findings from other studies. However, the median OS in the current study in Finland was, in general, longer than in the previously reported results. Further, the median TTNT was also shortest in the first treatment line, compared to later treatment lines, as a result of a need-based optimization of the therapy in the first treatment line, which generally leads to progression to the second treatment line in the data. Furthermore, the median for OS was slightly longer for women and in younger age groups in the first treatment line. In contrast, the median TTNT appeared longer among men and in the oldest patients. In addition, patients with CRAB components presented a shorter median OS and TTNT than those without. Also, patients with FISH finding del(17p13) had the shorter survival in this study than without del(17p13). Further, patients with the standard R-ISS risk classification had a longer median OS and TTNT, than those with high R-ISS risk, as expected, considering that low risk patients are more likely to have a positive treatment response. Another finding of this study demonstrated that patients with early progression had a markedly

inferior OS in treatment line 1. Nevertheless, this study also concluded that the median OS and TTNT was longer for patients treated with the single AutoHSCT, compared to no transplant, as expected. Further, the median OS and TTNT for the triplet treatment was longer than duplet, which could indicate that patients were treated according to the treatment guidelines. However, this could also be due to duplet treatments being given generally to older patients and patients in worse health conditions. Further, the effect of treatments on the prognosis is extremely difficult to estimate, because of treatment choice bias, and other confounding factors that may have a large effect.

*Secondary objective 1.* Although, the CRAB components at diagnosis, hypercalcemia and anaemia, were associated with an increased risk of death and faster progression to the next treatment in the first treatment line (shorter TTNT) among Finnish MM patients. Having the high-risk FISH findings del(17p13) or t(14,16) were associated with an increased risk of proceeding to the next treatment in the treatment line 1. Further, patients with standard or high R-ISS risk classification also had a higher risk of proceeding to the next treatment in the treatment lines 2, compared to patients with low R-ISS risk classification.

*Secondary objective 2.* In all subpopulations the number of observations was low, especially in the high-risk population. Thus, no firm conclusions could be made on the analysis of this objective.

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# Appendices

## Annex 1. List of stand-alone documents

| Number | Document reference number | Date | Title |
|---|---|---|---|
| 1 | 1 | 13 June 2019 | Protocol 2.0 |
| 2 | 2 | 16 October 2019 | Statistical Analysis Plan (SAP) 2.0 |

## Annex 2. ISS and R-ISS

**ISS for MM**

| Stage | Criteria | Median survival, months |
|---|---|---|
| I | • Serum $\beta_2$-microglobulin <3.5 mg/L<br>• Serum albumin ≥3.5 g/dL | 62 |
| II | Not fitting stage I or III | 44 |
| III | • Serum $\beta_2$-microglobulin ≥5.5 mg/L | 29 |

There are two categories of stage II: serum $\beta_2$-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum $\beta_2$microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.
Source: (32)

**Revised-ISS for MM**

| Stage | Criteria | 5-year PFS rate, % | 5-year OS rate, % | Median OS, months |
|---|---|---|---|---|
| I | • Original ISS stage I; and<br>• Standard-risk* CAs by iFISH; and<br>• Normal LDH | 55% | 82% | Not reached |
| II | Not fitting stage I or III | 36% | 62% | 83 |
| III | • Original ISS stage III; and<br>• High-risk* CAs by iFISH; and/or<br>• High LDH | 24% | 40% | 43 |

*High-risk chromosomal abnormalities (CAs) include the presence of deletion [del(17p)] and/or translocation [t(4;14)] and/or translocation [t(14;16)], whereas all other CAs are considered standard-risk.
Source: (7)

# Annex 3. Categorization of individual therapies into major regimens.

Major treatment regimen in this study referred to an individual therapy or a combination of several therapies that are commonly given to MM patients. Since MM treatment is complex and the number of patients receiving different individual therapies and combinations of therapies is not known, major treatment regimens were based on observed data. As this was a purely descriptive study without pre-specified hypotheses, the categorization of therapies into major treatment regimens mainly served a descriptive purpose.

Therapy categorization procedure were done as follows. First, the number of different therapies / combinations of therapies per line were summarized in a frequency table of which a template is given below. Mobilizations were ignored, also the treatments that could be considered as supportive or preceding treatments: radiation therapy, dexamethasone pulses and under 17 days dexamethasone treatments unless they were the only treatments in line. If one or several drugs of the original therapy were discontinued during line, therapy was recorded using the drug selection that was originally given. Allogeneic bone marrow transplants were categorized as AlloHSCT regardless of treatment given with them (e.g. AlloHSCT (Treo/Flu)) and in case autologous bone marrow transplant treatment specification was missing, melphalan treatment was reported: AutoHSCT (HD-Mel). Similar or exactly same therapies with sufficient number of treatment occasions (10 or more treatment occasions) were treated as individual major treatment regimens. The rest were combined into a general class "others".

| **Therapy (Named therapies below are fictious examples)** | **Number of treatment occasions (treatment lines)** |
|---|---|
| **Bortezomib – Cyclophosphamide – Dexamethasone (VCD)** | N |
| **Bortezomib – Cyclophosphamide – Dexamethasone (VCD) + AutoHSCT Melphalan** | |
| **Bortezomib – Talidomide – Dexamethasone (VTD)** | N |
| **Carfilzomib – Dexamethasone (KD)** | N |
| **Bortezomib – Lenalidomide – Dexamethasone (VRD) + AlloHSCT** | N |
| **Carfilzomib – Lenalidomide – Dexamethasone (KRD)** | N |
| **Bortezomib – Dexamethasone (VelDex)** | N |
| **Daratumumab – Bortezomib – Dexamethasone (DVD)** | N |
| **Lenalidomide – Dexamethasone (Len-Dex)** | N |
| **Bortezomib – Melphalan – Prednison (VMP)** | N |
| **Lenalidomide – Dexamethasone (RD)** | N |
| **Melphalan – Prednisone (MP)** | N |
| **Cyclophosphamide – Prednisone (CP)** | N |
| **Bortezomib** | N |
| **Carfilzomib** | N |

## Annex 4. Results Report

The full results are presented in the Results Report attached.