Pharmacoepidemiological study protocol ER-9542

An Observational Cohort Study on Multiple Myeloma Patients in Finland

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1 Abstract

Rationale and background: Multiple myeloma (MM) is a progressive clonal haematologic malignancy of plasma cells. In Finland, there are approximately 350-400 new MM cases diagnosed each year, primarily amongst the elderly. The average survival time following diagnosis is 5-6 years, but prognosis varies greatly and the recent introduction of novel therapies has improved overall survival. However, the treatment and subsequent outcomes of MM in Finland are not completely understood.

Research question and objectives: The primary objective of this study is to describe the Finnish MM 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 is to identify and describe characteristics of specific subpopulations, including those who received a specific treatment selection, who have 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 will also be determined.

Study design: Descriptive retrospective study using nationwide data from the Finnish Hematology Register (FHR). The study will collect retrospective data including but not limited to information such as age, gender, co-morbidities, date of MM diagnosis, clinical status of MM, and received treatment.

Population and setting: The whole study cohort will include patients diagnosed for MM during the FHR data availability period 01 January 2010 – 31 December 2015 aged 18 years or older at the time of diagnosis. The actual study cohort will include 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, who have at least one year of potential follow-up time following start of treatment (to 31 December 2017). Characteristics of all MM patients recorded in the FHR will be described on an overall level.

Data sources: The whole cohort will be identified from the FHR. Patient data will be collected from the FHR retrospectively starting from diagnosis.

Study size: Baseline data will be collected from all new MM patients for descriptive analyses. The study size for the actual cohort will be at least 300-400 Finnish MM patients. There are approximately 1600 MM patients all together recorded at FHR.

Data analysis: Descriptive statistics of subject baseline characteristics, diagnosis, gender, age, treatment selection, and laboratory values will be provided. Continuous variables will be described by mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum. Categorical variables and continuous variables that are also categorized will be described by proportion and frequency in each category. 95% confidence intervals (CI) will be presented when appropriate. Time to event analyses will be estimated using Kaplan-Meier curves and multivariate Cox proportional hazard models where appropriate.

2 List of abbreviations

ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplant
BUN	Blood urea nitrogen
CA	Chromosomal abnormality
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence interval
CP	Cyclophosphamide + prednisone treatment
CR	Complete response
CRAB	C = calcium (elevated), R = renal failure, A = anaemia, B = bone lesions
Dg	Diagnosis
DSS	Durie-Salmon clinical staging system
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
FIMM	The Institute of Molecular Medicine Finland
FISH	Fluorescence in situ hybridization
FRCBS	Finnish Red Cross Blood Service
GPP	Good Pharmacoepidemiology Practice
IC	Informed consent
ICMJE	International Committee of Medical Journal Editors
iFISH	Interphase fluorescence in situ hybridization
IMWG	International Myeloma Working Group
ISPE	International Society for Pharmaceutical Engineering
ISS	International staging system
LDH	Lactate dehydrogenase
LenDex	Lenalomide + dexamethasone treatment
MGUS	Monoclonal gammopathy of unknown significance
MM	Multiple myeloma
MP	Melphalan + prednisone treatment

MR	Minimal response
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
PAS	Post-authorization study
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RCT	Randomized-controlled trial
RD	Lenalomide + dexamethasone treatment
R-ISS	Revised international staging system
RRMM	Relapsed/refractory multiple myeloma
SAP	Statistical analysis plan
sCR	Stringent complete response
SID	Study Identification Number
SD	Stable disease
TTNT	Time to next treatment
VCD	Bortezomib + cyclophosphamide + dexamethasone treatment
VD	Bortezomib + dexamethasone treatment
VGPR	Very good partial response
VMD	Bortezomib + melphalan + dexamethasone treatment
VRD	Bortezomib + lenalomide + dexamethasone treatment
VTD	Bortezomib + thalidomide + dexamethasone treatment
VTD-PACE	Bortezomib + thalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide treatment

3 Approvals

We have reviewed this study protocol (ER-9542 Version 2.0, dated 13 June 2019) and agree to its terms by signing it.

Principal investigator:

5 AUG 2019

Signature Date

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Medical expert Juha Lievonen (MD), Helsinki University Central Hospital

Representative of the sponsor Tatu Miettinen (MD), Takeda Finland

4 Amendments and updates

No.	Date	Section of study protocol	Amendment or update	Reason
1	13 June 2019	- Abstract - 5 Milestones - 7.2 Secondary objectives - 8.1 Study design - 8.2.3 Follow-up - 8.3.4 Treatment patterns - 8.3.5.3 Treatment selection - 8.10.1 Data source - 10 Protection of human subjects	- The actual study cohort changed to include 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. - The end of the follow-up period changed from 31 December 2015 to 31 December 2017. - "No treatment" removed from treatment selection. - References to applicable legislation updated.	Extension of the follow-up period until the end of 2017. Treatment selection redefined for accuracy. Outdated references to applicable legislation.

5 Milestones

Milestone	Actual/Planned 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	13 November 2017
Start of data analysis	21 September 2018
End of data analysis	August 2019
Start of data permit process for extended study period	May 2019
End of data permit process for extended study period	July 2019
Start of data collection for extended study period	July 2019
End of data collection extended study period	August 2019

Start of data analysis extended study period	August 2019
End of data analysis extended study period	September 2019
Start of study reporting process	September 2019
Final report of study results	December 2019
Start of scientific reporting process	January 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. 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]. However, factors that cause MM are not fully known. MM symptoms including bone pain, bleeding, anaemia, fatigue, hypercalcaemia, renal insufficiency, and frequent infections occur as the disease advances. Treatment is usually required only after the disease has advanced. It constitutes approximately 1% of all reported cancers and it is the second most common haematologic malignancy worldwide [2]. In Finland, approximately 350 – 400 new MM cases are diagnosed each year. 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 it varies greatly depending on the patient's risk status. As MM patients are generally elderly patients, they have potentially multiple co-morbidities. Therefore, and due to factors related to the disease itself and myeloma-specific and supportive treatments, patients require frequent monitoring and hospital visits.

The overall survival (OS) in MM has improved significantly during the last decades, mainly due to developments in autologous stem cell transplants and novel drug treatments. However, despite improved treatment options, MM remains practically incurable with current therapy and it is characterized by multiple relapses. 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 [3]. 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)]) [4].

Standardized staging systems for MM help predict outcome and help physicians in some cases select appropriate therapy for patients [5]. 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 staging of MM [6]. The systems are based on key measures that describe the disease burden and assess patients' characteristics. These risk assessment scores (described in Annex 2) include parameters like serum β_2-microglobulin, albumin and lactate dehydrogenase, and the presence or absence of high-risk cytogenetic changes. The Finnish nationwide characterization of myeloma patients regarding phenotypic and genotypic features, and their effect on survival, has not been studied.

There are general treatment guidelines for myeloma [7]. The treatment guidelines are different for patients older than 65 (-70) years and younger than that. Stem cell transplant is considered the front-line treatment in younger and fit enough patients and is most often autologous (called ASCT) but may be allogenic. ASCT treatment consists of induction therapy of 3-4 cycles with a doublet or triplet therapy (primarily bortezomib + cyclophosphamide + dexamethasone OR bortezomib + dexamethasone) followed by collection of stem cells, high-dose chemotherapy, and stem cell transplantation. In some cases, a second ASCT (called a tandem transplant) may be recommended within 6 to 12 months, or upon relapse. Elderly and/or frail patients are not considered eligible for ASCT and their primary treatment options 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). The complete guidance is presented in Annex 3.

It is thought that already at the time of diagnosis, there are heterogeneous populations of tumour cells present, known as sub-clones [8]. 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 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 may have

several practical limitations. Real-life clinical practice may differ greatly from the RCTs' highly selected patient population, who are randomised to obtain pre-selected study treatments. Therefore, the risks and benefits may manifest differently in real-life clinical practice as compared to that in an RCT. In addition, RCTs are often based on a relatively small population with a short follow-up time. Observational studies based on secondary data collected in routine clinical practice may provide the opportunity to investigate large-scale 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 overall survival (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 (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 questions and objectives

There is a lack of information on real-life clinical practice, treatment patterns, and treatment outcomes in Finnish MM patients with different types and stages of the disease. The aim of this study is 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 is a descriptive study without specific a-priori hypotheses to be tested.

7.1 Primary objectives

The primary objective is to characterise the Finnish MM population and to describe the overall survival and time to next treatment on the overall level, and stratified by known patient-related prognostic factors.

Primary objective 1 is to describe the characteristics and patient journey of Finnish MM patients, including

- Demographics
- Disease characteristics
- Treatment patterns

Primary objective 2 is to evaluate OS and TTNT among MM patients, stratified by

- Patients' demographics
- Disease characteristics
- Types of treatment (major treatment regimens in the 1st, 2nd, 3rd, 4th, >4th line)
- Lines of treatment, including first-line treatment in newly diagnosed (ND) MM patients as well as later treatment lines (relapsed/refractory (RR) MM patients)

7.2 Secondary objectives

Secondary objective 1 is to identify patient, disease, and treatment-related factors that are associated with

- Treatment selection
- OS
- Duration of each treatment line
- TTNT

Secondary objective 2 is to characterise MM patient subpopulations, including those categorised as high-, standard- or low-risk according to R-ISS. Additionally, the following MM patient subpopulations will be identified and characterised:

- Patients who did not receive the following pre-specified treatments:
    - Transplant, duplet vs. triplet therapy, other
- Patients who had short durations of each treatment line

The definition of short treatment duration will be described in more detail in the statistical analysis plan (SAP). Characterisation of each of these subpopulations includes similar description as in Primary objective 1. In addition, OS and TTNT will be described in these subgroups.

8 Research methods

8.1 Study design

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

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 will include only patients for whom at least one treatment initiation date can be identified and who have a minimum of one year of potential follow-up time (to 31 December 2017).

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

8.2 Population and setting

8.2.1 Subject selection

The FHR includes approximately 1600 MM patients, but it is estimated that data are comprehensively recorded for at least 300-400 patients. Main analyses are conducted on the actual cohort with complete records and at least one year of potential follow-up time. Descriptive and sensitivity analyses will be performed on the whole MM cohort.

8.2.1.1 Inclusion criteria

- MM diagnosis recorded in the FHR
- Age 18 years or older at the time of MM diagnosis

8.2.1.2 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 will be included for descriptive analyses (e.g. whole study cohort). Data recordings related to treatment are required for some analyses and therefore only individuals for which such records are available in the register (i.e. actual study cohort) will be included in those analyses. The analyses will be described in more detail in the SAP. It is expected that data recordings in the FHR are not selective and that the study population represents the general MM patient population in Finland.

8.2.2 Cohort entry date

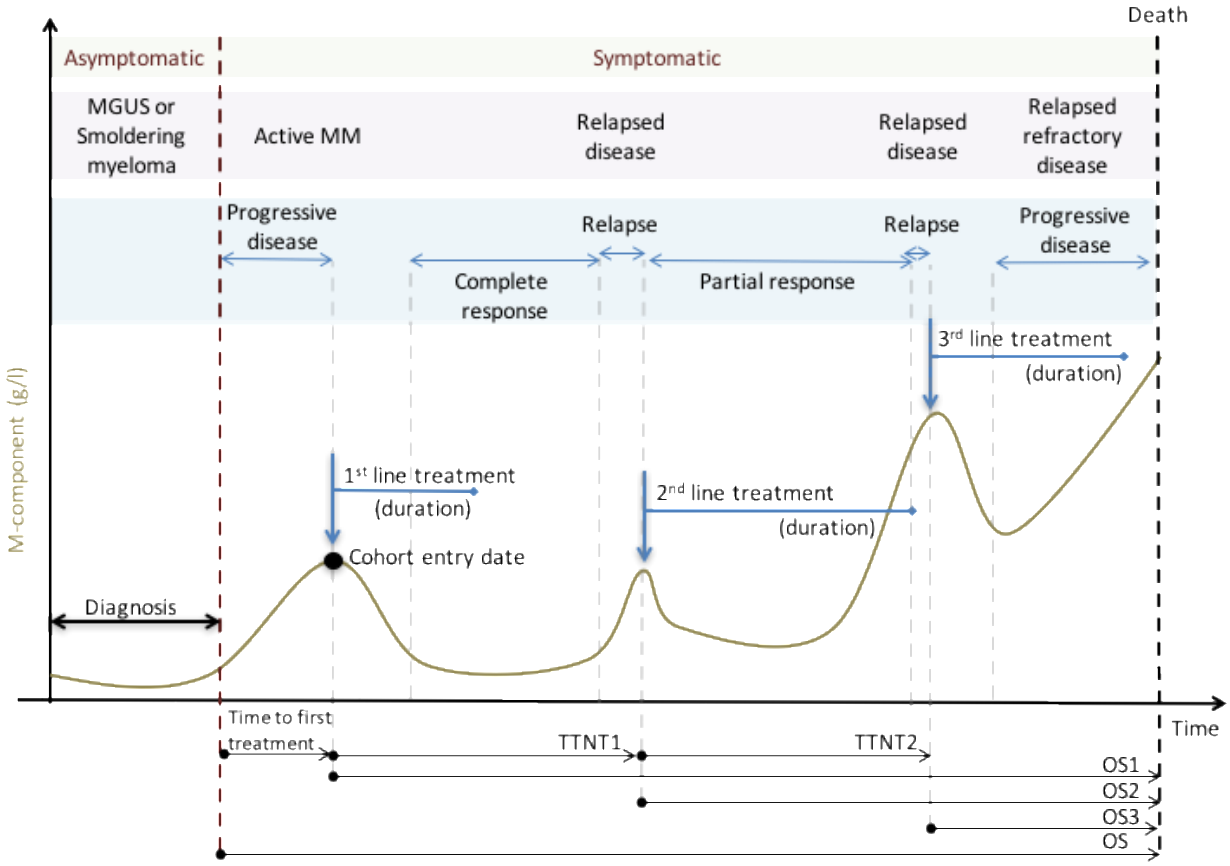
For each patient, the whole study cohort entry date is defined as date of MM diagnosis. The actual study cohort entry date is defined as the first MM treatment initiation in the FHR.

8.2.3 Follow-up

Patients in the actual study cohort will be followed-up starting from the first treatment initiation date recorded in the FHR during the study period. Follow-up will continue until the first of the following events occur: death, loss to follow-up, or end of the study or follow-up period (31 December 2017).

8.2.4 Schematic presentation of a study patient

Figure 1. Schematic presentation of the study for a single MM patient. 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. 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.



8.3 Variables

The following data will be collected from the FHR, from diagnosis (Dg), from the start of treatment, and/or from the time of follow-up as indicated when available for the actual cohort.

8.3.1 Patients' demographics

Variables concerning patient demographics are available only at diagnosis.

- Year of birth
- Gender
- Date of MM diagnosis
- Age at diagnosis
- Known co-morbidities

8.3.2 Disease characteristics

8.3.2.1 Available only at diagnosis

- Calcium (elevated), Renal failure, Anaemia, Bone lesions (CRAB)
  - Hypercalcaemia
  - Renal dysfunction
  - Anaemia
  - Lytic bone lesions
- Fluorescence in situ hybridization (FISH), including (and/or)
  - High risk cytogenics, e.g.
    - Deletion 17p [del(17p)]
    - Translocation [t(4;14)]
    - Translocation [t(14;16)]
  - Non-high risk cytogenics, e.g.
    - Translocation [t(14;20)]
    - Gain 1q [gain(1q21)]
    - Deletion 1p32 [del(1p32)]

8.3.2.2 Available at diagnosis and/or for each treatment line

- Myeloma type (e.g. smouldering, MGUS, or active MM)
- Disease stage (ISS/R-ISS)
- Risk classification, according to the R-ISS in Annex 2 (high-, standard-, or low-risk)
- 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, relapse from CR, relapse from minimal residual disease (MRD) negative, exitus)
- M-component, including:
  - Concentration and type (serum and urine): g/L and IgA/IgG/IgD/IgM
  - Concentration and type of light chain (serum): K, L
- Clinical haematology, including:
  - Absolute neutrophil count (ANC)
  - Haemoglobin
  - Platelet count
  - Creatinine (eGFR to be calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula)
  - Lactate dehydrogenase (LDH)
- Bone lesions

- Bone marrow aspirate and/or biopsy results, including (and/or):
    - Percentage of plasma cells in bone marrow aspirates
    - Percentage of plasma cells in bone marrow trephine biopsies
    - Percentage of MM cells of total cells and of plasma cells (flow cytometry)

8.3.3 Follow-up variables

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

8.3.4 Treatment patterns

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

- Line of treatment (1st, 2nd, 3rd, 4th, >4 lines of treatment)
- Treatment, such as:
    - Transplant (single/tandem) vs. no transplant
    - Duplet vs triplet therapy
    - Other
- Number of cycles per treatment line
- Date of start of each treatment
- Date of end of each treatment
- Time to discontinuation of each treatment, where applicable

8.3.5 Outcomes

8.3.5.1 OS

OS is defined as time from actual cohort entry until death. In addition, OS among those who have received treatment lines 1, 2, 3, 4, >4, will be defined as time from first having the treatment in question (1st, 2nd, 3rd, 4th, >4 lines of treatment) until death.

8.3.5.2 TTNT

The time to next treatment (TTNT1, TTNT2, and further) is defined as the length of time between the start of a treatment line to the start of the next treatment line. Specifically, TTNT1 is 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 is the length of time between the start of the second treatment line to the start of the third treatment line, and so on.

8.3.5.3 Treatment selection

Treatment selection is defined as single transplant, tandem transplant, duplet therapy, triplet therapy, or other. All available treatments will be described and later categorised into selected treatment groups in the SAP.

8.3.5.4 Treatment duration

The duration of treatment is defined as the length of time (month) from the start of a treatment line to the end of that treatment line. In cases where treatment has been discontinued, the time from the initiation to discontinuation of the treatment will be calculated.

8.3.5.5 Overall response rate

The overall response rate (ORR) is defined as the proportion of patients in the actual cohort who have at least a partial response to treatment, and will be calculated per treatment regimen within a line of treatment.

8.4 Other definitions

- Newly diagnosed multiple myeloma (NDMM) is defined as those patients who have active, measurable MM and have initiated no more than the first line of treatment. Definitions of other patient populations according to the IMWG, including RRMM, can be found in Annex 4.
- CRAB components are defined below according to the IMWG [4]:
    - Hypercalcaemia is defined as corrected serum calcium > 11.5 mg/dL 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).
    - Anaemia is defined as a haemoglobin value < 100 g/L, or > 20 g/L below the lowest limit of normal
    - Bone lesions including one or more osteolytic lesions found on skeletal radiography, CT, Magnetic Resonance Imaging (MRI), or PET-CT
- Overall response to treatment is defined as any of the following disease statuses as recorded in the FHR: PR, VGPR, CR, or sCR. In the case of missing data, partial or complete response to treatment will be defined as not having SD nor disease progression.
- Disease progression is defined as any of the following disease statuses as recorded in the FHR: PD or clinical relapse. In the case of missing data, disease progression is defined according to the IMWG criteria as indicated in Annex 5.
- Relapse is defined as any of the following disease statuses as recorded in the FHR: Relapse from CR, or relapse from MRD negative.
- Line of treatment is defined as one or more cycles of a treatment program. Treatment lines are numbered successively, starting with first treatment line, second treatment line, and further. Where available, they are defined numerically using the line of treatment variable recorded in the register. If not available in this way, each new treatment line is defined as a drug regimen that starts following disease progression. In the case of transplantation, tandem transplantation is defined as two transplantations within 6 months, whereas multiple single transplants are defined as two transplantations separated by at least a 12-months interval.

8.5 Data sources

Data from FHR on MM patients with recordings will be 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 (IC) for their data to be recorded into the register and to be available for research purposes. The FHR includes approximately 1600 MM patients, but it is estimated that currently data including treatment are recorded for at least 300-400 patients.

8.6 Study size

The population size for the whole study cohort is approximately 1600 MM patients, while the population size for the actual study cohort is approximately 300-400 patients. As this is primarily a descriptive study, this

population size is considered sufficient. The MM population in FHR is also considered to be a representative sample of the complete MM population in Finland.

8.7 Data management

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 will receive the study data from Granitics and is responsible for data processing and analyses. EPID Research will also perform quality assurance for the received data. Database lock will occur when EPID Research has performed the quality assurance procedures and resolved all potential issues with either Granitics, FHR, or both. The final statistical analyses will start after the database lock.

EPID Research will use R language [9] in data processing, creating the analysis database, and in statistical analyses. All study data, source code of data management, and data analyses are kept for inspection 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.

Access to the study data cannot be given to any third parties, nor may the study data be used for other purposes than prescribed in this protocol. All requests to use the study data for other purposes than those mentioned in this study protocol must be subjected to appropriate data permit processes.

8.8 Data analysis

The principles of the statistical analysis are outlined below. A more detailed SAP will be written separately before any data is being transferred to EPID Research. In the descriptive analyses, continuous variables will be described by mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum and maximum. Categorical variables and continuous variables that are also categorised will be described by proportion and frequency in each category. 95% confidence intervals (CIs) will be presented when appropriate.

Potential confounders and effect modifiers

In the analysis of OS and TTNT outcome variables the potential confounding variables include but are not limited to:

- Age, gender, CRAB, ISS-/R-ISS-stage, FISH-test results, type of MM, early progression

8.8.1 Primary objective 1

Patient demographics and disease characteristics will be described separately by the relevant summary statistics at diagnosis, for the whole study cohort and for the actual study cohort.

Treatment patterns and where relevant, disease characteristics, will be described at cohort entry for the actual study cohort and during follow-up. During follow-up, variables will be described at the start and end of each treatment line as relevant and available from the data source.

For the general description, the follow-up variables will be described at the end of follow-up.

8.8.2 Primary objective 2

OS and TTNT (including TTNT1, TTNT2, and further) will be described with the Kaplan-Meier estimator in the actual study cohort population and stratified by patients' demographic factors, disease characteristics, and

types and lines of treatment. These time-to-event outcomes will also be summarized by the relevant statistics among uncensored events. In addition, the proportion of censoring will be reported.

In the analyses of time-to-event outcomes there might be potential immortal time bias in case IC was requested after the start of follow-up. Hence, for each patient the time periods prior to the request of IC will not be considered as a risk-time and will be left-censored. The same will apply in the analyses of the secondary objectives as well.

8.8.3 Secondary objective 1

Factors associated with treatment duration (TTNT) and OS will be identified using a multivariate Cox regression model. The previously defined potential confounders and effect modifiers will be included in all models. In addition, additional demographic variables, disease characteristics, and treatment patterns will be added into the models using a variable selection procedure. The detailed variable selection procedure will be defined in the SAP.

In the treatment selection analyses, a specified treatment type will be defined as a binary outcome variable that indicates 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 will be identified using a multivariate logistic model in a similar manner as described for TTNT and OS / Cox model above.

8.8.4 Secondary objective 2

Patients at low-, standard-, and high-risk will be identified at diagnosis and divided into groups based on the ISS/R-ISS categorisation (shown in Annex 2). Patients who did not receive the pre-specified treatments (e.g. transplant, duplet or triplet therapies) as the 1^{st}, 2^{nd}, 3^{rd}, 4^{th}, $>4^{th}$ line treatment will be identified and followed-up at the start of each treatment line (1^{st}, 2^{nd}, 3^{rd}, 4^{th}, $>4^{th}$ line). Patients with short treatment duration will be defined at the end of a treatment line (short duration of 1^{st} line treatment, short duration of 2^{nd} line treatment and so on) and followed-up after the end of the treatment line with short duration.

After identifying the above subpopulations, they will be described similarly as described in Primary objective 1. OS, TTNT (including TTNT1, TTNT2, and further) will be described with the Kaplan-Meier estimator in these subpopulations.

8.8.5 Sensitivity analyses

The representativeness of the actual study cohort in the FHR will be investigated by presenting baseline summary statistics of the whole study cohort. These baseline statistics will be compared with the actual study cohort. Comparisons will concentrate on demographic variables and disease characteristics as available in the whole study cohort.

As described in Section 8.4, PD is recorded in the FHR and missing data will be completed according to the IMWG criteria. The number of original PD events recorded in the FHR and the number of PD events found only using the IMWG criteria will be reported.

As described in Section 8.4, for patients whose treatment line is not recorded in the FHR, the start of each treatment line will be defined as a drug regimen following disease progression. In a sensitivity analysis, treatment line will be defined in the latter way for all patients and compared to the original treatment line recorded in the FHR.

Sensitivity analyses will be performed by excluding variables with a high proportion of missingness from statistical models, as described in Section 8.8.7.

8.8.6 Statistical analysis plan

EPID Research will produce a separate SAP including detailed description of statistical analyses and the corresponding outputs before undertaking the analyses.

8.8.7 Missing data

If a given variable is totally or systematically missing from a database, it is excluded from the analyses. If a variable is missing for only some of the patients or arbitrarily missing, a missing data category will be added and used in the analyses. However, in case a variable with a high proportion of missingness is included in an analysis, a sensitivity analysis will be conducted without having that variable in the model. If a variable is missing from the database but equivalent information can be inferred using available variables, this will be specified and performed.

8.9 Quality control

The study will be conducted as specified in this protocol. All revisions to the protocol must be approved by the principal investigator, sponsor, and co-authors of the study. All changes to the protocol shall be properly documented as protocol amendments and when necessary such protocol amendments are delivered to FHR.

The study protocol has been written by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct [10] and the Guideline for Good Pharmacoepidemiology Practices (GPP) [11] by the International Society for Pharmacoepidemiology (ISPE). The study protocol and as well as results will be published in EU PAS register maintained by 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 of 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 authorised personnel only.

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

8.10 Limitations of the research methods

8.10.1 Data source

This study is based on data collected from the FHR, which covers the whole of Finland and has an accuracy considered appropriate for scientific research. It is expected that the majority of all MM diagnoses have been recorded but that comprehensive coverage is available for approximately 25% of the recorded MM diagnoses and may differ based on region. However, it must be considered that data is recorded by different individuals and therefore there may be variability within variables for which there is no clear clinical definition. In some cases, some data may be missing from individual patients but this may be verified based on other existing variables.

Data which would be relevant for the objectives of this study but are completely missing overall from the FHR include:

- Treating hospital district (for determining distance between place of residence and treating hospital)
- History data (prior to date of diagnosis)
- Reason for loss to follow-up
- Reason for treatment discontinuation

Data relevant to the objectives of this study that may be incompletely recorded in the FHR include:

- Line of treatment
- Date of end of treatment
- LDH

For the incompletely recorded data, other variables may be used to supplement the missing information.

Since as date of end of treatment and clear denotation of progression is likely missing from the register, progression-free survival (PFS) cannot be calculated. In this case, TTNT will be used instead.

As the study period ends in 31 December 2017 the reporting delay of the FHR will not affect study outcomes.

8.10.2 Selection bias and study power

This study will also characterize treatment selection. Treatment selection may be based on age or existing medical factors and therefore co-morbidities will be analysed. Similarly, due to confounding by indication it may not be possible to compare the efficacy of different treatments.

This is a small retrospective study with expected data recorded for at least 300-400 MM patients in the actual study cohort. This is sufficient for descriptive analyses but may in some cases result in limited study power when comparing different groups.

Risk-stratification using the R-ISS is based in part on FISH results. FISH results from before 2011-2012 are not fully comparable with those after 2012. Therefore, it may not be possible to compare risk-stratified groups of patients from before and after 2012.

8.10.3 Immortal time bias

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

9 Informed consent

Since this is a retrospective analysis on data obtained from the FHR, using epidemiological methods for analysis based on data selected from the abovementioned sources, the patients will not be asked for their IC for this specific study. However, the FHR asks patients for their IC before any patient data is entered into the FHR. This IC indicates that data from the register may be used for collaborative research projects with national study groups and commercial organisations.

10 Protection of human subjects

This is a fully register-based study. The study does not affect the treatment of the patients, and the patients will not be contacted in any phase of the study. The study is conducted by following the ENCePP code of conduct [10] as well as the Guidelines for GPP [11].

EPID Research will receive pseudonymised data including study identification numbers (SIDs) only. EPID Research employees have undertaken professional secrecy and are aware of their concern with the local legislation: Act on the Openness of Government Activities 621/1999 (based on which the data can be received from the original register holders). The study register is formed on the basis of the Data Protection Act (1050/2018). The implications of the General Data Protection Regulation (EU) 2016/679 on the national legislations, during the course of the study, will be considered.

The sponsor will not have access to the patient level data at any time of the study. Sponsor’s representation in the steering committee does not repeal this principle.

The protocol will be subjected to the Ethics Committee of the Hospital District of Helsinki and Uusimaa for review and approval. Register notification of the forming study register will be sent to the Office of the Data Protection Ombudsman.

11 Management and reporting of adverse events/adverse reactions

The nature of this non-interventional study does not meet the criteria for adverse event reporting [12].

12 Plans for disseminating and communicating study results

The principal investigator together with the co-investigators will write a study report. This report will be delivered to the sponsor and members of the steering committee.

Within three months following the final study report, at minimum an abstract of the study findings will be provided through the EU PAS register. According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

Based on the study report, the principal investigator and co-investigators with co-authors (members of the steering committee and possible other contributors approved by the steering committee) will prepare (a) scientific manuscript(s) for academic publication. The steering committee decides the publication forums.

The sponsor is entitled to view the final results prior to submission for publication. The sponsor also has the right to comment the results and interpretations thereof. This must be done without unjustifiably delaying the publication. In this particular study the commenting time for the sponsor during the review rounds is agreed to be maximum of one month. Possible changes in the presentations must be based on scientific reasons only. The steering committee is free not to take the comments of the sponsor into account.

The principal investigator and the sponsor are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE. There it is stated that each author should have participated sufficiently in the work to take public responsibility for the content [13]. These conditions apply equally to external investigators and to employees of the sponsor.

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Annex 1. List of stand alone documents

- ENCePP checklist for study protocols.

Annex 2. ISS and R-ISS

ISS for MM

Stage	Criteria	Median survival, months
I	• Serum β_2-microglobulin <3.5 mg/L • Serum albumin ≥3.5 g/dL	62
II	Not fitting stage I or III	44
III	• Serum β_2-microglobulin ≥5.5 mg/L	29

There are two categories of stage II: serum β_2-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum β_2-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.
Source: [14]

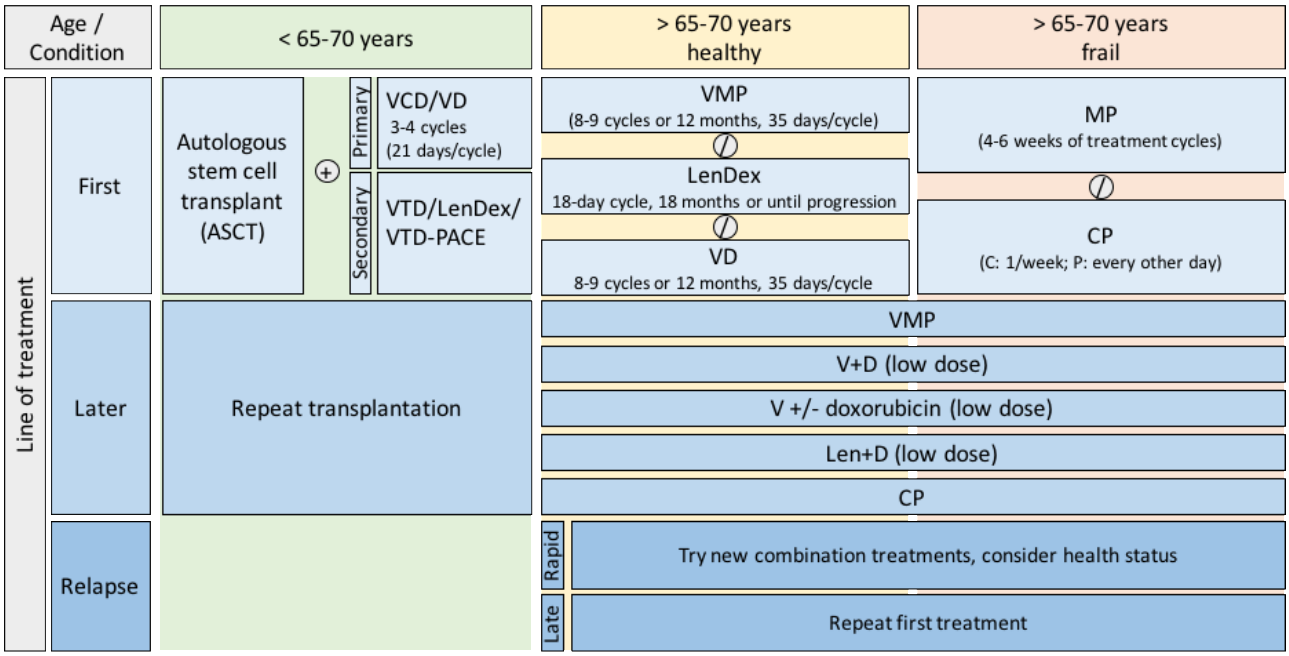
Revised-ISS for MM

Stage	Criteria	5-year PFS rate, %	5-year OS rate, %	Median OS, months
I	• Original ISS stage I; and • Standard-risk* CAs by iFISH; and • Normal LDH	55%	82%	Not reached
II	Not fitting stage I or III	36%	62%	83
III	• Original ISS stage III; and • High-risk* CAs by iFISH; and/or • 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: [6]

Annex 3. Finnish national guidelines for MM treatment

Figure 2. Finnish national guidelines for MM treatment, divided along the type by patient age and along the side by line of treatment.



The following abbreviations are used above: VCD, bortezomib + cyclophosphamide + dexamethasone; VD, bortezomib + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone; LenDex, lenalidomide + dexamethasone; VTD-PACE, bortezomib + lenalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide; VMP, bortezomib + melphalan + prednisone; MP, melphalan + prednisone; CP, cyclophosphamide + prednisone; V, bortezomib; D, dexamethasone.
Source: [7]

Annex 4. Definitions of patient populations

IMWG definitions of MM patient populations.

Category	Definition
Primary refractory multiple myeloma	Non-responsive patients who have never achieved MR or better with no significant change in M-component concentration and no evidence of clinical progression
Refractory multiple myeloma	Non-responsive while on primary or salvage* therapy or progress within 60 days of last therapy
Relapsed multiple myeloma	Previously-treated myeloma that progresses and requires the initation of salvage* therapy but does not meet criteria for either primary refractory MM or RRMM
Relapsed and refractory multiple myeloma (RRMM)	Non-responsive while on salvage* therapy, or progress within 60 days of last therapy in patients who have achieved MR or better at some point previously before, then progress in their disease course

Where possible, additional qualifiers that describe the specific population, for example “relapsed and refractory to immunomodulatory therapy”, should be included.

*Salvage, or rescue, therapy is a form of treatment provided to patients who have relapse following ASCT, with primary progressive disease following ASCT, or who are ineligible for ASCT following initial induction therapy.

Source: [16]

Annex 5. Definitions of disease status

IMWG definitions of disease status.

Disease status	Definition
CR*	• Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • < 5% plasma cells in bone marrow
sCR	• CR as defined, and • Normal free light chain ratio, and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
VGPR*	• Serum and urine M-component detectable by immunofixation but not on electroporesis, or • ≥ 90% reduction in serum M-component and urine M-component < 100 mg/24 h
PR	• ≥ 50% reduction of serum M-component and ≥ 90% reduction in 24-h urine M-component or to < 200 mg/24 h • Where M-component and serum free light assay not measurable, ≥ 50% reduction in bone marrow plasma cells (provided baseline percentage ≥ 30%) • If present at baseline, also ≥ 50% reduction in the size of soft tissue plasmacytomas
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD**	• Increase of ≥ 25% from baseline in serum M-component (absolute increase ≥ 0.5 g/dL) • Increase of ≥ 25% from baseline in urine M-component (absolute increase ≥ 200 mg/24 h) • For those with measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels must have absolute increase > 10 mg/dL • Absolute bone marrow plasma cell percentage ≥ 10% • Definite development of new bone lesions, soft tissue plasmacytomas, or increase in size of existing bone lesions, soft tissue plasmacytomas • Development of hypercalcaemia attributed solely to multiple myeloma
MR†	• ≥ 25% but ≤ 49% reduction of serum M-component, and • Reduction in 24-h urine M-component by 50-89%, and • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas, and • No increase in size or number of lytic bone lesions
Clinical relapse	• Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI, or other imaging, and/or • Definite increase in the size of existing plasmacytomas or bone lesions, as defined as a 50% and at least 1 cm increase as measured serially by the sum of products of the cross-diameters of the measurable lesion, and/or • Hypercalcaemia (> 11.5 mg/dL; > 2.875 mM/L) • Decrease in haemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL, and/or • Rise in serum creatinine by ≥ 2 mg/dL (≥ 177 mM/L) • Hyperviscosity

*For CR and VGPR in patients for whom the only measurable disease is by serum free light chain levels, CR indicates a normal free light chain ration (0.26 to 1.65) in addition to other critera. VGPR requires a > 90% decrease in the difference between involved and uninvolved free light chain levels.

**For PD, bone marrow criteria are only to be used for those patients without measurable disease by M-component and free light chain levels. Baseline is considered to be the lowest response value and does not need to be a confirmed value.

†For patients with RRMM

Source: [16]