Study Report

P4-C2-004

DARWIN EU® - Multiple Myeloma: patient characterisation, treatments, and survival in the period 2012–2024

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Version 4.0

Authors: Guido J. van Leeuwen, Talita Duarte-Salles, Marzyeh Amini

Public

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CONTENTS

LIST OF ABBREVIATIONS **6**
1. TITLE **8**
2. DESCRIPTION OF THE STUDY TEAM **8**
3. ABSTRACT **9**
4. AMENDMENTS AND UPDATES **13**
5. MILESTONES **14**
6. RATIONALE AND BACKGROUND **14**
7. RESEARCH QUESTION AND OBJECTIVES **15**
8. RESEARCH METHODS **15**
8.1. Study design 15
Figure 1. Graphical depiction of study design. 15
8.2. Follow-up 16
8.3. Study population with inclusion and exclusion criteria 16
Table 1. Operational definitions of inclusion criteria. 17
Table 2. Operational definitions of exclusion criteria. 17
8.4. Study setting and data sources 18
Table 3. Data Sources. 18
8.5. Study period 19
8.6. Variables 19
8.6.1. Exposure 19
8.6.2. Outcome 19
8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables 20
8.7. Study size 20
8.8. Data transformation 20
8.9. Statistical methods 21
8.9.1. Patient privacy protection 21
8.9.2. Main statistical methods 21
Table 4. *TreatmentPatterns* settings. 21
Figure 2. Graphical depiction of *TreatmentPatterns* setting options. 22
8.9.3. Missing values 23
8.10. Deviations from the protocol 23
9. RESULTS **23**
9.1. Participants 23
Table 5. Study attrition of individuals included in each cohort per data source 23
9.2. Descriptive data 24
9.2.1. Demographic characteristics of cohort 1 24
Table 6. Demographics characteristics of incident multiple myeloma individuals in Cohort 1* per data source. 24
9.2.2. Comorbidities 25
Table 7. Number and % of pre-specified comorbidities among all individuals in Cohort 1 by data source at 30 to 1 days prior to index date (Objective 1). 26
9.2.3. Comedications 26
Table 8. Number and % of pre-specified medication use among individuals in Cohort 1 by data source at 30 to 1 days prior to index date and 1 to 90 days post index date (Objective 1) 28

9.3. Multiple Myeloma treatments 30
9.3.1. Demographic characteristics in Cohort 2 30
Table 9. Demographics characteristics of incident multiple myeloma individuals in Cohort 2* per data source. 30
9.3.2. Multiple myeloma treatments and treatment classes 30
Figure 3. Frequency of use of multiple myeloma treatments from 1 to 90 days after diagnosis. 33
Figure 4. Frequency of use of multiple myeloma treatments from 1 to 365 days after diagnosis. 34
Figure 5. Frequency of use of multiple myeloma treatments from 1 day to 5 years after diagnosis. 35
9.3.3. Multiple myeloma treatment sequences 35
9.3.3.1 Overall (0 to 5 years post index date) 35
Figure 8. Sunburst plot legend of treatment patterns analysis in HARMONY-MM (0 to 5 years post index date). 39
Figure 9. Sunburst plot legend of treatment patterns analysis in DK-DHR (0 to 5 years post index date) 40
Figure 10. Sunburst plot legend of treatment patterns analysis in FinOMOP-THL (0 to 5 years post index date). 41
9.3.3.2 Analysis stratified by sex (0 to 5 years post index date) 42
9.3.3.3 Analysis stratified by age group (0 to 5 years post index date) 42
9.3.3.4 Analysis stratified by stem cell transplantation (0 to 5 years post index date) 42
9.4. Survival analysis 42
9.4.1. Demographic characteristics in cohort 3 42
Table 10. Demographics characteristics of incident multiple myeloma individuals in Cohort 3* per data source. 42
9.4.2. Proportion of death 43
9.4.3. Survival probabilities 43
Table 11. Survival of multiple myeloma individuals in Cohort 3 overall and stratified by sex and age group. 45
Figure 11. Kaplan-Meier overall survival of multiple myeloma individuals by data source 47
Figure 12. Kaplan-Meier overall survival of multiple myeloma individuals stratified by sex and data source. 48
Figure 13. Kaplan-Meier overall survival of multiple myeloma individuals stratified by age categories and data source. 49

10. DISCUSSION 50
10.1. Key results 50
10.2. Strengths and limitations of the research methods 51
10.3. Interpretation 52
10.4. Generalisability 54

11. CONCLUSION 54

12. REFERENCES 55

13. ANNEXES 57
ANNEX I. Description of data sources 57
ANNEX II. Supplementary figures 66
Figure S1. Frequency of use of multiple myeloma treatment classes from 1 to 90 days after diagnosis. 66
Figure S2. Frequency of use of multiple myeloma treatment classes from 1 to 365 days after diagnosis. 67
Figure S3. Frequency of use of multiple myeloma treatment classes from 1 day to 5 years after diagnosis. 68

Figure S4. Sunburst plot of treatment patterns analysis in females in CDW Bordeaux (0 to 5 years post index date). 69
Figure S5. Sunburst plot of treatment patterns analysis in males in CDW Bordeaux (0 to 5 years post index date). 70
Figure S6. Sunburst plot of treatment patterns analysis in females in CRN (0 to 5 years post index date) 71
Figure S7. Sunburst plot of treatment patterns analysis in males in CRN (0 to 5 years post index date) 72
Figure S8. Sunburst plot of treatment patterns analysis in females in HARMONY-MM (0 to 5 years post index date). 73
Figure S9. Sunburst plot of treatment patterns analysis in males in HARMONY-MM (0 to 5 years post index date). 74
Figure S10. Sunburst plot of treatment patterns analysis in females in DK-DHR (0 to 5 years post index date). 75
Figure S11. Sunburst plot of treatment patterns analysis in males in DK-DHR (0 to 5 years post index date) 76
Figure S12. Sunburst plot of treatment patterns analysis in females in FinOMOP-THL (0 to 5 years post index date). 77
Figure S13. Sunburst plot of treatment patterns analysis in males in FinOMOP-THL (0 to 5 years post index date). 78
ANNEX III. Operational and reporting considerations 79
ANNEX IV. Concept sets/code lists 81
Table S1. Multiple Myeloma concept set/code lists. 81
Table S2. Multiple Myeloma treatment concept set/code lists. 81
ANNEX V. Glossary 83

Study title[1]	DARWIN EU® - Multiple Myeloma: patient characterisation, treatments, and survival in the period 2012–2024
Study report version	V4.0
Date	25/06/2026
EUPAS number	EUPAS1000000757
Active substance	N/A
Medicinal product	N/A
Research question and objectives	The overall objective of this study was to characterise individuals with multiple myeloma diagnosed in the period 2012–2024. The specific objectives of this study were: 1. To describe demographic and clinical characteristics of individuals with multiple myeloma at the time of diagnosis. 2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. triplets). 3. To describe sequences of treatments and treatment combinations for multiple myeloma. 4. To estimate the overall survival of incident multiple myeloma individuals during the study period (2012–2024). All results are reported by country/data source, overall and stratified by age and sex when possible.
Countries of study	Denmark, Finland, France, Germany, Spain, Norway, Sweden
Authors	Guido van Leeuwen (g.vanleeuwen@darwin-eu.org) Talita Duarte-Salles (t.duarte@darwin-eu.org) Marzyeh Amini (m.amini@darwin-eu.org)

[1]This is a routinely repeated study from P2-C1-001 with EUPAS EUPAS105033.

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ADHD	Attention Deficit Hyperactivity Disorder
ASTC	Autologous stem cell transplant
ATC	Anatomical Therapeutic Chemical
CAR	Chimeric Antigen Receptors
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CHUBX	Centre Hospitalier Universitaire de Bordeaux
COPD	Chronic obstructive pulmonary disease
CRN	Cancer Registry Norway
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DKMA	Danish Medicines Agency
EBB	Estonian Biobank
EGCUT	Estonian Genome Centre at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care (THL)
GDPR	General Data Protection Regulation
GERD	Gastro-oesophageal reflux disease
GP	General Practitioner
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IKNL	Netherlands Cancer Registry
IMASIS	Institut Municipal Assistència Sanitària Information System
IMiDs	Immunomodulatory agents
InGef RDB	InGef Research Database
IP	Inpatient
IRB	Institutional Review Board
KM	Kaplan-Meier
MGUS	Monoclonal Gammopathy of Unknown Significance
MM	Multiple Myeloma

Acronyms/terms	Description
NIPH	Norwegian Institute of Public Health
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PCT	Primary Care Teams
PI	Proteasome Inhibitors
PSMar	Parc Salut Mar
RMST	Restricted mean survival time
RxNorm	Medical prescription normalized
SIDIAP	The Information System for Research in Primary Care
SINE	Selective inhibitors of nuclear export
SNOMED	Systematized Nomenclature of Medicine
SCT	(Autologous/allogenic) Stem Cell Transplantation
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Multiple myeloma: patient characterisation, treatments, and survival in the period 2012–2024

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Guido van Leeuwen Talita Duarte-Salles Marzyeh Amini[1]	Erasmus MC
Epidemiologist/Clinical Domain Expert	Guido van Leeuwen Talita Duarte-Salles Anton Barchuk	Erasmus MC
Data Analysts/Programmers	Maarten van Kessel Ioanna Nika Ger Inberg Cesar Barboza Ross Williams	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency (DKMA)
Finnish Care Register for Health Care (FinOMOP-THL)	Tiina Wahlfors	FinOMOP
Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)	Audrey Terranova Melanie Koska Romain Griffier Antoine Barre Guillaume Verdy	Centre Hospitalier Universitaire de Bordeaux (CHUBX)
InGef Research Database (InGef RDB)	Raeleesha Norris Annika Vivirito Alexander Harms Josephine Jacob	Institute for Applied Health Research Berlin GmbH (InGef)
Cancer Registry Norway (CRN)	Anna Skog Lise Enerstvedt Espen Enerly	Norwegian Institute of Public Health (NIPH)
HARMONY - Multiple Myeloma (HARMONY-MM)	Ana Hernandez	HARMONY Alliance Foundation (HARMONY)

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.
[1]Added to the study team on 16/03/2026.

3. ABSTRACT

Title

DARWIN EU® - Multiple myeloma: patient characterisation, treatments, and survival in the period 2012–2024.

Rationale and background

Multiple myeloma is a rare type of blood cancer with an estimated overall crude and age-standardized incidence rate of 6.7 and 2.8 per 100,000 persons in 2022 in Europe, respectively.

Survival rates have improved in recent years due to advancement in disease management and the introduction of new therapies, such as immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies. However, unmet needs for new medicines remain for the individuals who do not respond to current therapies.

The rarity of multiple myeloma poses challenges across Europe in obtaining a comprehensive understanding of patient characteristics at the time of diagnosis, the different therapies administered in subsequent treatment lines, and overall survival. This study aims to address these gaps, which are important from a regulatory point of view to provide context and help understand the added value of the newest medicines under development or recently approved.

Research question and objectives

What were the demographic and clinical characteristics, treatment patterns, and overall survival of individuals diagnosed with multiple myeloma during the period 2012–2024?

The specific objectives of this study were:

1. To describe demographic and clinical characteristics of individuals with multiple myeloma at the time of diagnosis.
2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. triplets, etc.).
3. To describe sequences of treatments and treatment combinations for multiple myeloma.
4. To estimate the overall survival of incident multiple myeloma individuals during the study period (2012–2024).

All results are reported by country/data source, overall and stratified by age and sex, when possible.

Methods

Study design

Population-based cohort study.

Population

The study population included all individuals identified in the data sources between 01/01/2012 and 31/12/2024. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded.

Additional eligibility criteria were applied for each study objective: cohort 1 required at least 365 days of prior history available before date of multiple myeloma diagnosis (index date) for large-scale characterisation (objective 1); cohort 2 required a minimum follow-up time of 30 days to capture cancer treatment (objective 2) and sequences of treatment combinations (objective 3); and cohort 3 required a minimum of 1 year of potential follow-up time for the survival analyses (objective 4). The eligibility criteria

for cohort 1 were not applied to data sources with a (possible) lack of observation period prior to index data (i.e. HARMONY-MM, CRN, CDW Bordeaux).

Variables

Two main outcomes of interest were studied: i) treatments, treatment classes, and treatment combinations initiated at index date, 1 to 30, 1 to 90, 1 to 365 days, and from 1 day to 5 years post index date (objective 2), as well as ii) treatment and treatment combination patterns and sequences over time (objective 3) at 1 to 365 days, and from 1 to 5 years. For objective 2 and 3, a pre-specified list of multiple myeloma treatments and treatment classes was generated. The respective treatment combinations were defined by exposure to the treatments with a minimum number of days of overlap. Overall survival in individuals with incident multiple myeloma was also be calculated based on the registered date of death.

All comorbidities and comedications were used for large-scale patient characterisation and a list of pre-specified comorbidities and comedications was also described.

Data sources

1. Denmark, Danish Data Health Registries (DK-DHR)
2. Finland, Finnish Care Register for Health Care - THL (FinOMOP-THL)
3. France, Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)
4. Germany, InGef Research Database (InGef RDB)
5. Norway, Cancer Registry Norway (CRN)
6. Spain, HARMONY - Multiple Myeloma (HARMONY-MM)

Study size

No sample size was calculated, as this was a descriptive study where the interest was in the characteristics of all incident multiple myeloma individuals, and no specific hypothesis was tested.

Statistical analyses

Characterisation based on pre-defined comorbidities and medications, as well as large-scale characterisation, was conducted (objective 1). Age and sex at time of a multiple myeloma diagnosis was described for each cohort. Medical history was assessed for anytime and up to 365 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Medication use history was assessed for -365 to -31 days before index date, for -30 to -1 day at index date and days 1 to 30, 1 to 90, and 1 to 365 days post index date.

The number and % of individuals receiving each of a pre-specified list of multiple myeloma treatments and treatment classes (objective 2) (see **ANNEX II**) were described at index date, 1 to 30, 1 to 90, 1 to 365 days, and 1 day to 5 years post index date. Additionally, sunburst plots and Sankey diagrams were used to describe treatment and treatment combination patterns and sequences over time (objective 3) at 1 to 365 days, and 1 to 5 years.

Overall survival (objective 4) was calculated using data on time-at-risk of death from any cause and the Kaplan-Meier (KM) method. Results were reported as plots of the estimated survival curves, as well as the estimated median survival, the restricted mean survival time (RMST), and the estimated probability of survival at year 3 and 5. Follow-up for the restricted mean survival was 5 years.

For all analyses, n and % were reported. All analyses were reported by country/data source, overall and stratified by age and sex, when possible (minimum cell count reached). Additionally, sunburst plots, Sankey diagrams, and KM curves were further stratified by sex, age, and (autologous/allogenic) stem-cell transplantation (SCT).

A minimum cell counts of 5 was applied when reporting results; any smaller count were reported as "<5" and zero counts as "0".

Results

Multiple myeloma patient characterisation

We identified 1,381 to 7,545 individuals with an incident multiple myeloma diagnosis across data sources (Cohort 1) with median age ranging from 67 to 72 years that were mostly males (range 50.8% – 56.9%).

In the month before index date the most frequently recorded comorbidities were hypertension (12.0% – 44.3%), hyperlipidaemia (3.8% – 38.0%), pneumonia (2.4% – 38.9%), osteoarthritis (1.5% – 24.3%), and diabetes mellitus (3.9% – 18.5%). The least frequent comorbidities were schizophrenia, attention deficit hyperactivity disorder (ADHD), human immunodeficiency virus (HIV), Crohn's disease, and chronic liver disease.

In the month before index date the most frequently prescribed medications were agents acting on the renin-angiotensin system (2.0% – 34.3%), opioids (3.2% – 29.3%), antithrombotic agents (3.0% – 27.2%), lipid modifying agents (1.5% – 26.8%), and drugs for acid related disorders (2.7% – 24.4%).
In the three months after index date, frequently prescribed medications also encompassed antineoplastic agents (16.7% – 60.9%), antibacterials (24.8% – 55.8%), and psycholeptics (10.5% – 33.0%).

Multiple myeloma treatment characterisation

Across data sources, chemotherapies (cyclophosphamide, melphalan), proteasome inhibitors (bortezomib), glucocorticoids (dexamethasone), and immunomodulatory drugs (lenalidomide) were the most used treatment classes and treatments in the five years following multiple myeloma diagnosis. Dexamethasone (24.1% – 63.2%), cyclophosphamide (10.9% – 35.5%), bortezomib (4.9% – 67.3%), lenalidomide (13.9% – 64.4%), and melphalan (8.6% – 34.8%) were the most used treatments in the five years after multiple myeloma diagnosis. This corresponded with glucocorticoids (24.1% – 63.2%), chemotherapies (15.8% – 35.3%), proteasome inhibitors (4.9% – 67.3%), and immunomodulatory drugs (13.9% – 64.4%) as the most prescribed treatment classes.

Treatment patterns:

Due to the dependence of the *TreatmentPatterns* package on the parameterisation of the analysis settings, and the variation between the registration of treatments per data sources (i.e. duration, construction of drug exposures or episodes), results were difficult to interpret and not comparable between data sources. Across most data sources, in the 5 years after multiple myeloma diagnosis no recorded treatments in the treatment pathway analysis was the most frequent category, with the proportion of patents classified as having "no recorded treatment (None)" ranging from 46.8% in CRN to 66.2% in CDW Bordeaux. The exception was HARMONY-MM, where the proportion of individuals with no recorded treatment was only 1.7%. Generally, single-agent therapies without subsequent treatment (e.g. dexamethasone, melphalan, bortezomib, and lenalidomide) were most common in DK-DHR, FinOMOP-THL, and CDW Bordeaux. Nevertheless, HARMONY-MM differed, showing more frequent and complex sequences. Moreover, there were no clear differences in the frequency of treatments, treatment combinations, and treatment sequences when stratifying by sex or age-group.

Survival results

Mortality during follow-up ranged from 14.9% (InGef RDB) to 67.2% (CDW Bordeaux). Five-year restricted mean survival ranged from 2.7 years (CDW Bordeaux) to 4.5 years (InGef RDB). Survival probability varied substantially across data sources, with 3-year survival probability ranging from 46.0% (CDW Bordeaux) to 89.6% (InGef RDB) and 5-year survival from 28.4% (CDW Bordeaux) to 85.9% (InGef RDB). Females showed slightly higher survival than males (e.g. 5-year survival: 61.1% vs 53.8% in DK-DHR), while survival declined markedly with age, with 5-year survival exceeding 70–90% in younger individuals and ranging from 17.8% to 78.6% in those aged ≥70 years.

Discussion

In this study, we identified a total of 31,657 individuals with a new multiple myeloma diagnosis between 2012 and 2024 across Europe. In agreement with previous findings, the most frequent comorbidities in the month prior to the date of diagnosis were hypertension, hyperlipidaemia, osteoarthritis, and diabetes mellitus, while the most frequent medications were agents acting on the renin-angiotensin system, lipid modifying agents, opioids, antibacterials, and psycholeptics.

Regarding multiple myeloma treatments, in line with current guidelines, the most frequently used treatment classes were chemotherapies, proteasome inhibitors, glucocorticoids, and immunomodulatory drugs. Among the most frequent treatments were bortezomib, lenalidomide, cyclophosphamide, and dexamethasone. Nevertheless, the *TreatmentPatterns* package at this moment was not capable of reliably capturing the expected oncology treatment regimens and combinations, which made interpretation and comparison of the results not feasible. The settings and ability to capture (complex oncology) treatments need to be improved before *TreatmentPatterns* can provide reliable expected regimen and combinations results. Overall survival in this study appears broadly consistent with improvements reported over the past two decades, driven by the introduction of novel therapies, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies.

4. AMENDMENTS AND UPDATES

Amendment number	Previous approved version of the report	Date	Section of the study report	Amendment or update	Reason
1	Not applicable	06/06/2025	Not applicable	Update from initial study protocol P2-C1-001 (EUPAS105033)	This is a routine repeated study
2	Not applicable		Not applicable	HARMONY-MM removed from Survival analysis (Obj 4).	Removed due to concerns regarding incomplete mortality capture and incomplete follow-up in hospital electronic health records (EHR) data

Study deliverables	P2-C1-001 (EUPAS105033)	P4-C2-004 (current study protocol)
Study period	2012–2022	2012–2024
Data partners:[1]		
- DK-DHR (Denmark)		X
- EBB (Estonia)	X (Objective 1, 2, and 4)	
- FinOMOP-THL (Finland)		X
- CDW Bordeaux (France)	X (Objective 1, 2, 3, and 4)	X
- InGef RDB (Germany)		X (Objective 1 and 4)*
- IQVIA Germany (Germany)	X (Objective 1)	
- NCR (the Netherlands)	X (Objective 1 (only sex and age), 2, and 4)	
- HARMONY-MM (Spain)		X (Objective 1,2 and 3)
- CRN (Norway)		X
- IMASIS (Spain)	X (Objective 1, 2, and 4)	
- SIDIAP (Spain)	X (Objective 1 and 4)	
Reference study protocol	N/A	P2-C1-001 (EUPAS105033)
Changes from reference study protocol	N/A	Objective 1) the report presented only the pre-defined comorbidities and medications on time points [-30,1] and [1,90]. The other time points and large-scale characterisation were only presented in the Shiny app. Objective 2) autologous/allogenic stem cell transplantation was included as a treatment. Objective 3) sequences were defined based on combinations of treatments across first/second/third line of therapy. Stratification by time periods (2017 or earlier and 2018 or later) removed.

Study deliverables	P2-C1-001 (EUPAS105033)	P4-C2-004 (current study protocol)
		4) Follow-up for the restricted mean survival was 5 years, and the survival probabilities focused on 3- and 5-year survival. Stratification by time periods (2017 or earlier and 2018 or later) removed.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	September 2025	8 September 2026
Creation of Analytical code	September 2025	December 2025/January 2026
Execution of Analytical Code on the data	September/October 2025	January/February 2026
Draft Study Report	October/November 2025	February 2026
Final Study Report	March 2026	28 April 2026

6. RATIONALE AND BACKGROUND

Multiple myeloma (MM) is a haematologic malignancy that is characterized by the abnormal proliferation of plasma cells in the bone marrow, leading to substantial morbidity and mortality. The most common presenting signs and symptoms include anaemia, bone pain, renal impairment, fatigue, hypercalcemia, infection, and weight loss.[1] Globally, it accounts for approximately 1% of all cancer cases and 13% of haematologic malignancies. The incidence of multiple myeloma varies geographically, with higher and increasing rates in developed countries, particularly in Asia, Europe, and North America. In Europe, the crude and age-standardized incidence rates of multiple myeloma were 6.7 and 2.8 per 100,000 persons in 2022, respectively, with a higher incidence observed in males than females and a median age at diagnosis of 72 years.[2-4]

Over recent decades, survival rates for patients with multiple myeloma have improved due to advancements in disease management and the development of novel therapies, including immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies.[4] More recently, the approval of chimeric antigen receptors (CAR) T-cell therapies has introduced a promising immunotherapeutic approach for patients with advanced relapsed multiple myeloma.[5]

To date, the standard treatment for multiple myeloma is largely dependent on patient health status, underlying comorbidities, tumour stage, and age at time of diagnosis. For patients younger than 70 to 75 years who have no comorbidities, the preferred approach includes a triplet novel agent regimen, typically including an IMiD and PI in combination with glucocorticoids, followed by an autologous stem cell transplant (ASCT) and maintenance therapy with low-dose IMiD or PI. For patients ineligible for ASCT, induction therapy with novel agents followed by low-dose maintenance therapy is recommended.[4, 6] Despite these advancements, there remains an unmet need for effective new medicines in patients who do not respond to existing therapy options.

The rarity of multiple myeloma makes it challenging across Europe to obtain a comprehensive understanding of the characteristics of these patients at the time of diagnosis, the different therapies they receive in subsequent lines, and their overall survival. The goal of this study was to inform these aspects, which are important from a regulatory perspective to provide context and help understanding how new medicines may add value for patients.

7. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study was to characterise individuals with multiple myeloma diagnosed in the period 2012–2024.

The specific objectives of this study were:

1. To describe demographic and clinical characteristics of individuals with multiple myeloma at the time of diagnosis.
2. To describe multiple myeloma treatments (including combinations and regimen types, e.g. triplets, etc.).
3. To describe sequences of treatments and treatment combinations for multiple myeloma.
4. To estimate the overall survival of incident multiple myeloma individuals during the study period (2012–2024).

All results were reported by country/data source, overall and stratified by age and sex when possible.

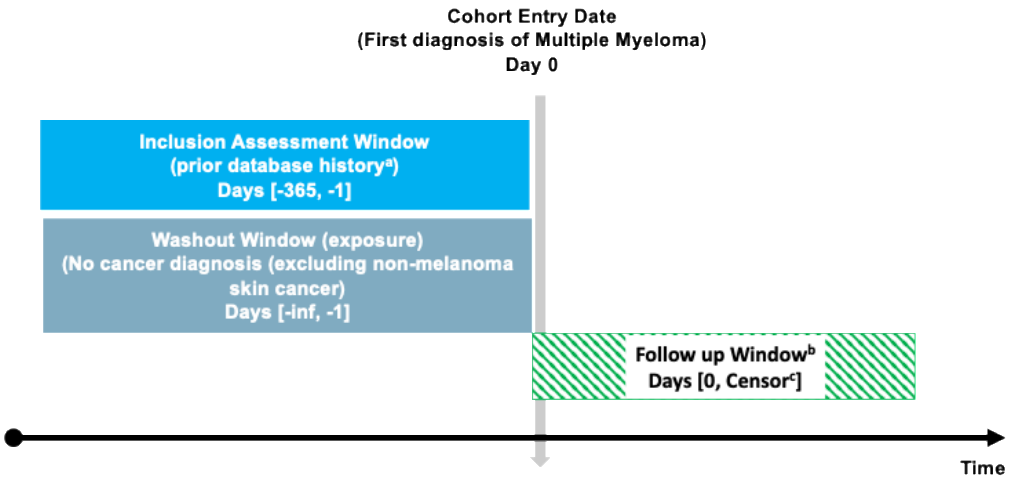
8. RESEARCH METHODS

8.1. Study design

A cohort study was conducted using routinely collected health data. The study comprised of:

- A patient-level characterisation was conducted to address objective 1, 2, 3, and 4 to characterise individuals with multiple myeloma diagnosed in the period 2012–2024.

The study design, including assessment windows, is visualized in **Figure 1**.



a. 365 days of prior database history applied for objective 1
b. Minimum follow-up of 30 days for objective 2 and 3, minimum follow-up of 365 days for objective 4
c. Earliest of: loss to follow-up, end of data availability or date of death

Figure 1. Graphical depiction of study design.

8.2. Follow-up

Study participants were followed up from their date of first multiple myeloma diagnosis (index date) until the earliest of the following: 1) loss to follow-up, 2) end of data availability, or 3) date of death. In the survival analysis, individuals in 1) were censored at the time of loss to follow-up. Individuals in 2) were administratively censored at end of data availability.

Time to loss of follow-up might have varied by data source, but we expected that loss to follow-up was going to be minimum in cancer and population registries and assumed it happened at random.

8.3. Study population with inclusion and exclusion criteria

The study population included all individuals with a first diagnosis of multiple myeloma identified in the data source between 01/01/2012 and 31/12/2024. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded.
InGef RDB only had data available from 01/01/2015 onwards; therefore, the study period started on 01/01/2016 to allow for sufficient data source history (365 days prior to index). Moreover, CRN only has information on treatments from 01/01/2019 onwards; therefore, for the objectives regarding treatment (objective 2 and 3), the study period started on 01/01/2019.

Multiple myeloma is a malignant uncontrolled proliferation of plasma cells derived from one single clone. It can affect many organs, typically bones and calcium metabolism, kidneys, immune system, blood, and more rarely, the nervous system. Diagnosis is typically obtained after a bone marrow biopsy, where plasma cells, monoclonal kappa, or lambda light chains will be present. The most important differential diagnosis is monoclonal gammopathy of unknown significance (MGUS) or 'smouldering multiple myeloma'. For this study, cases were identified based on a record indicating a diagnosis or observation of multiple myeloma. Conditions in the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) use the Systematized Nomenclature of Medicine (SNOMED) as the standard vocabulary for diagnosis codes. A clinical description, along with a code list, is provided in **ANNEX IV.** This list was previously developed to define multiple myeloma for the DARWIN EU® study EUPAS50800 and refined in this study.

Additional eligibility criteria were applied for each study objective:

Cohort 1) for large-scale characterisation (objective 1), at least 365 days of prior history available before date of multiple myeloma diagnosis (=index date) was required. This was needed to ensure a minimum prior observation time to exclude prevalent cases and to identify individuals' characteristics (e.g. comorbidities and drug history). This criterion was not applied to data sources with a (possible) lack of observation period prior to index data (i.e. HARMONY-MM, CRN, CDW Bordeaux).

Cohort 2) for cancer treatments (objective 2) and treatment sequences (objective 3), a minimum follow-up time of 30 days after multiple myeloma diagnosis (=index date) was applied to allow time to capture treatments.

Cohort 3) for survival analysis (objective 4), a minimum of 1 year of potential follow-up time was required, i.e. the diagnosis of multiple myeloma (=index date) could not fall within the last year of data availability of the data source.

Information on the operational definitions of inclusion and exclusion criteria are described in **Table 1** and **Table 2**.

Table 1. Operational definitions of inclusion criteria.

Criterion	Details	Order of application*	Assessment window	Care Settings[1]	Applied to study populations:
Prior data source history of 1 year (objective 1)	Study participants were required to have a year of prior history observed before contributing observation time	After	1 year	IP, OP, OT	All study participants with incident multiple myeloma
Minimum 30 days follow-up (objectives 2 and 3)	Only participants with a minimum of 30 days follow-up time after a diagnosis of multiple myeloma (index date)	After	30 days	IP, OP, OT	All study participants with incident multiple myeloma
Minimum potential 1 year follow-up time (objective 4)	Only participants with a diagnosis of multiple myeloma (index date) occurring one year prior to end of data availability in the data source were included	After	1 year	IP, OP, OT	All study participants with incident multiple myeloma

[1]IP=inpatient, OP=outpatient, OT=other (claims/registry), n/a=not applicable
* = Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting "before" means that all possible study entry dates of a patient are identified, and then one or more is chosen. Selecting "after" means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient does not meet the criterion, then the patient drops out.

Table 2. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
History of cancer diagnosis	Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma or prior to the start of the study period	After diagnosis of Multiple Myeloma	Any time prior to multiple myeloma diagnosis	IP, OP, OT	SNOMED	Any	All study participants with incident multiple myeloma

[1]IP=inpatient, OP=outpatient, OT=other (claims/registry), n/a=not applicable

8.4. Study setting and data sources

This study was conducted using routinely collected data from 6 data sources in the DARWIN EU® Network of Data Partners from 6 European countries, of which 6 EU member states (**Table 3**). All data were a priori mapped to the OMOP CDM. Detailed information on the data sources used for the study are described in **Annex I**.

Table 3. Data Sources.

Country	Name of Data source	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update	Contributing to
Denmark	DK-DHR	Registry data with information on cancer diagnoses, mortality, and cancer treatment.	Registry	Registry	5.9 million	11/2024	All objectives
Finland	FinOMOP-THL	Registry data with information on cancer diagnoses, mortality, and cancer treatment.	Registry	Registry	5.6 million	10/2024	All objectives
France	CDW Bordeaux	Covers secondary care setting, database has information on cancer treatment, mortality, and other outcomes	Secondary care (in and outpatients)	EHR	0.2 million	09/2024	All objectives
Germany	InGef RDB	Covers primary and secondary care setting, database has information on cancer treatment, mortality, and other outcomes	Secondary care (in and outpatients) and primary care	Claims	7.6 million	12/2024	Objective 1 and 4
Norway	CRN	Cancer registry data with high quality information on cancer diagnoses, mortality, and cancer treatment.	Cancer Registry	Registry	0.3 million	11/2024 with histologically confirmed cancer patients until 31/12/2022	All objectives

Country	Name of Data source	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update	Contributing to
Spain	HARMONY-MM	Cancer registry data with high quality information on cancer diagnoses, mortality, and cancer treatment.	Cancer registry	Registry	100	31/03/2023	Objective 1, 2, and 3

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; HARMONY-MM=HARMONY-Multiple Myeloma; CRN=Cancer Registry Norway

8.5. Study period

The study population included all individuals with a first diagnosis of multiple myeloma identified in the data source between 01/01/2012 and 31/12/2024. Participants with a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma were excluded.
InGef RDB only had data available from 01/01/2015 onwards; therefore, the study period started on 01/01/2016 to allow for sufficient data source history (365 days prior to index). Moreover, CRN only has information on treatments from 01/01/2019 onwards; therefore, for the objectives regarding treatment (objective 2 and 3), the study period started on 01/01/2019.

8.6. Variables

8.6.1. Exposure

Not applicable

8.6.2. Outcome

Two main outcomes of interest were studied:

- **Multiple Myeloma treatments:** treatments and treatment classes initiated at index date, 1 to 30, 1 to 90, 1 to 365 days, and 1 day to 5 years post index date (Objective 2); and the sequences of treatments and treatment combinations post index date were described at 1 to 365 days, and 1 to 5 years (Objectives 3).

  Multiple Myeloma treatments included chemotherapies (melphalan, bendamustine, doxirubicin, cisplatin, cyclophosphamide, etoposide, vincristine), IMiDs (thalidomide, lenalidomide, pomalidomide), PI (bortezomib, carfilzomib, ixazomib, venetoclax), monoclonal antibodies (daratumumab, isatuximab, denosumab, elotuzumab), nuclear export inhibitor (selinexor), CAR T-cell (lisocabtagene maraleucel, idecabtagene vicleucel, brexucabtagene autoleucel, axicabtagene ciloleucel, tisagenlecleucel), glucocorticoids (dexamethasone, prednisone), bisphosphonates (zoledronate, pamidronate, clodronate, ibandronate, etidronate), others (panobinostat), and autologous/allogenic stem cell transplantation. The combination of the aforementioned treatments in the treatment of multiple myeloma was also investigated. The description of the construction of treatment combinations is described in **Section 8.9.4.** Please see **Table S2** for a list of codes to identify these treatments and treatment classes.

- **Time to death:** Overall survival in individuals with incident multiple myeloma was calculated based on the registered date of death for the latter. Individuals contributed survival time as per the follow-up described in **Section 8.9.4.**

8.6.3. Covariates, including confounders, effect modifiers, intercurrent events, and other variables

Age at multiple myeloma diagnosis was described. The following age grouping was used: 0–17; 18–44; 45–59; 60–69; 70 and over. The sex (male/ female) of study participants was also identified.

All comorbidities and comedications recorded prior and at index date were used for large-scale patient characterisation, identified as concept/code and descendants. Additionally, a list of pre-specified comorbidities and comedications was described. These included:

- Medical History: Asthma, chronic obstructive pulmonary disease (COPD), chronic liver disease, Crohn's disease, diabetes mellitus, gastro-oesophageal reflux disease (GERD), GI-bleeding, human immunodeficiency virus (HIV), hyperlipidaemia, hypertension, obesity, osteoarthritis, pneumonia, psoriasis, renal impairment, ulcerative colitis, urinary tract infection, viral hepatitis, schizophrenia, dementia, Parkinson's disease, depressive disorder, anxiety, attention deficit hyperactivity disorder (ADHD) [Neurology]. Any cancer except non-melanoma skin cancer (for quality assessment purposes, this should be 0 in our study population before index date).
- Medication use: Agents acting on the renin-angiotensin system, antibacterials for systemic use, antidepressants, antiepileptics, anti-inflammatory and antirheumatic products, antineoplastic agents, antipsoriatics, antithrombotic agents, beta-blocking agents, calcium channel blockers, diuretics, drugs for acid related disorders, drugs for obstructive airway diseases, drugs used in diabetes, immunosuppressants, lipid modifying agents, opioids, psycholeptics, psychostimulants, agents used for ADHD.
- Presence of (autologous/allogenic) stem cell transplantation (SCT) as treatment for MM (Yes/No). The definition for SCT is described in **Table S2**.

8.7. Study size

No sample size was calculated, as this was a descriptive study where the interest was in the characteristics of all incident multiple myeloma individuals, and no specific hypothesis was tested. In addition, to estimate frequencies of treatment use and survival probabilities of individuals diagnosed with multiple myeloma, already collected data was used (i.e. secondary data usage). Thus, the sample size was driven by the availability of individuals with conditions of interest.

8.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed (see **Annex III**), the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the, by default, aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Patient privacy protection

Cell suppression was applied as required by data sources to protect people's privacy. Cell counts <5 were masked.

8.9.2. Main statistical methods

R-packages

We used the R packages *CohortDiagnostics*[7] for the patient-level characterisation of demographics and clinical characteristics, *DrugExposureDiagnostics*[8], developed by DARWIN EU®, to investigate the duration of drug exposure to determine the minimum overlap used to define treatment combinations, *TreatmentPatterns*[9], developed by DARWIN EU®, for the patient-level characterisation of treatments, and *CohortSurvival*[10], developed by DARWIN EU®, for the estimation of overall survival.

Patient-level characterisation

Characterisation based on pre-defined comorbidities and large-scale patient-level characterisation was conducted (objective 1). Age and sex at time of multiple myeloma diagnosis was described for each of the generated study cohorts. The index date was the date of the multiple myeloma diagnosis for each patient. Medical history was assessed for any time, and up to 366 days before index date, for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. Medication use history was assessed for 365 to 31 days before index date, for 30 to 1 day before index date, and at index date. We also assessed medication use for 1 to 30, 1 to 90, and 1 to 365 days post index date. These time windows were defined based on the options currently available in the standard analytical tools that were used in this project. Covariates to be presented in a summary baseline characteristics table were pre-defined, as described in **Section 8.6.2**. Estimates for the other time windows and the large-scale characteristics were only presented on the Shiny app EUPAS1000000757.

The number and % of MM individuals receiving each of a pre-specified list of multiple myeloma treatments and treatment classes (objective 2, as listed in **Section 8.6.1.**), were described at index date, 1 to 30, 1 to 90, 1 to 365 days, and 1 day to 5 years post index date. Additionally, sunburst plots and Sankey diagrams were used to describe treatment and treatment combination patterns at 1 to 365 days, and 1 day to 5 years post index date (objective 3). Sankey diagrams were censured at end of treatment or end of follow-up, as described in **Section 8**. For treatments patterns, all drug durations were imputed to 30 days, meaning all drug prescriptions with a duration <30 days were imputed to be 30 days, prescriptions with durations >30 days were not imputed. A minimum overlap of 14 days was selected for treatments to be considered a combination, the full setting specifications and explanation for treatment patterns can be seen in **Table 4** and **Figure 2**.

Table 3. *TreatmentPatterns* settings.

Individual pathway setting	Description	Value
WindowStart	The start time (number of days) prior to the index date of the target cohort (i.e. cohort of patients newly diagnosed with multiple myeloma) from which treatments should be included	0 days
WindowEnd	The end time (number of days) after the index date of the target cohort (i.e. cohort of patients newly diagnosed with multiple myeloma) from which treatments should be included	0 days
StartAnchor	Start target cohort (i.e. cohort of patients newly diagnosed with multiple myeloma)	StartDate (Multiple Myeloma)

Individual pathway setting	Description	Value
EndAnchor	End of target cohort (i.e. cohort of patients newly diagnosed with multiple myeloma)	EndDate (Multiple Myeloma)
minEraDuration	Minimum time an event era (i.e. span of time an individual is exposed to a specific treatment of interest) should last to be included in the analysis	14 days
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	7 days
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	14 days
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	14 days
filterTreatments	Select which treatments should be included in pathway first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	Changes
maxPathLength	Maximum number of treatments included in pathway	10

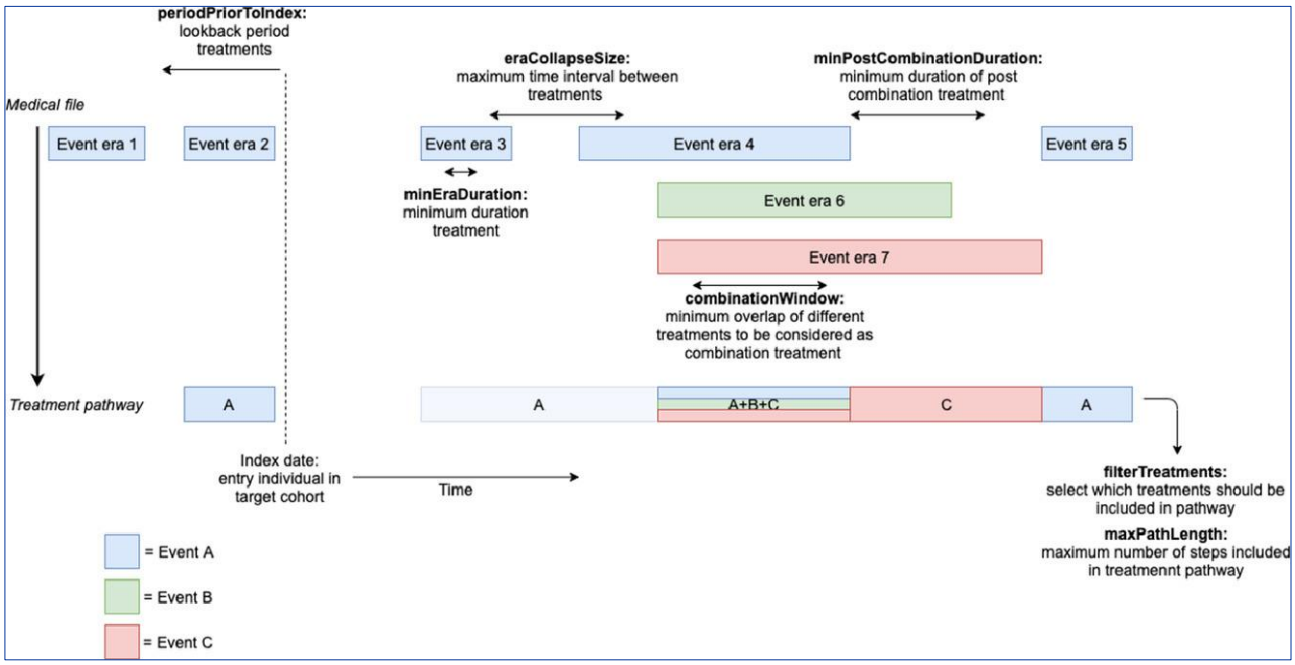


Figure 2. Graphical depiction of *TreatmentPatterns* setting options.

Overall survival (objective 4) was calculated using data on time-at-risk of death from any cause and the Kaplan-Meier (KM) method. Results were reported as plots of the estimated survival curves, as well as the estimated probability of survival at years 3 and 5. The restricted mean survival (RMST) had a follow-up of 5 years. Individuals who were lost to follow-up were censored at the time of loss of follow-up. Time to loss of follow-up might had varied by data source, but we expected that loss to follow-up to be minimum in cancer and population registries. The KM approach implicitly assumes censoring occurs at random.

For all analyses, n and % were reported. All analyses were reported by country/data source, overall and stratified by age and sex when possible (minimum cell count reached). Additionally, to capture treatments availability and survival changes over time, sunburst plots, and 3 and 5-year survival were further stratified by sex, age, and the presence of SCT (yes/no).

8.9.3. Missing values

Methods for characterisation implicitly assume missing data on patient demographic and clinical characteristics occurred completely at random.

For the objective on survival, individuals who were lost to follow-up prior to the end of the study period were non-administratively censored. The methods employed in the analyses implicitly assumed censoring occurred at random.

8.10. Deviations from the protocol

Deviation number	Protocol version	Date	Section of study protocol	Deviation	Reason
1	4.0	04/12/2025	8.9.4	*TreatmentPatterns* settings	Settings specified more clearly after discussions/meetings with EMA and advice given to EMA from clinical domain experts. Added Table 4 and Figure 2 for more clarity.

9. RESULTS

The full set of results for this study is available through an interactive web-application Shiny app at EUPAS1000000757.

9.1. Participants

The number of individuals contributing to each study objective by data source is described in **Table 5**.

Overall, there were 4,387 (DK-DHR), 5,481 (FinOMOP-THL), 1,381 (CDW Bordeaux), 8,962 (InGef RDB), 7545 (HARMONY-MM), and 5,252 (CRN) individuals with a diagnosis of multiple myeloma between 2012 and 2024, no diagnosis of other cancers (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and had at least 365 days of prior history available before the date of multiple myeloma diagnosis (Cohort 1).

From these individuals, 4,387 (DK-DHR), 5,458 (FinOMOP-THL), 1,381 (CDW Bordeaux), 8,940 (InGef RDB), 7,545 (HARMONY-MM), and 5,221 (CRN) had at least 365 days of prior history available before the date of multiple myeloma diagnosis and a minimum follow-up of 30 days (Cohort 2).

Lastly, 4,387 (DK-DHR), 5,048 (FinOMOP-THL), 1,381 (CDW Bordeaux), 4,376 (InGef RDB), 7,518 (HARMONY-MM), and 4,791 (CRN) of the individuals had at least 365 days of prior history available before the date of multiple myeloma diagnosis and a minimum of 365 days of potential follow-up time (Cohort 3).

Table 4. Study attrition of individuals included in each cohort per data source.

	DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	HARMONY-MM	CRN
Data source population	8,593,356	6,618,745	2,474,759	10,512,283	14,351	1,248,103
with a diagnosis of multiple myeloma identified in the	5,611	7,529	1,534	12,009	7,545	6,429

	DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	HARMONY-MM	CRN
data source between 01/01/2012 and 31/12/2024						
without a diagnosis of cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma	4,394	5,502	1,381	9,164	7,545	5,252
with at least 365 days of prior history available before date of multiple myeloma diagnosis **(Cohort 1)***	4,387	5,481	1,381	7,461	7,545	5,252
with a minimum follow-up time of 30 days **(Cohort 2)****	4,387	5,458	1,381	7,439	7,545	5,221
with a minimum of 1 year of potential (see Table 1, Section 8.3) follow-up time **(Cohort 3)**	4,387	5,048	1,381	7,084	7,518	4,791

*Prior history requirement of 365 days was not enforced for CDW Bordeaux, HARMONY-MM, and CRN for any of the cohorts.
**InGef RDB did not participate in Objectives 2 and 3 (Cohort 2)
DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; HARMONY-MM=HARMONY-Multiple Myeloma; CRN=Cancer Registry Norway

9.2. Descriptive data

9.2.1. Demographic characteristics of cohort 1

Table 6 describes the demographic characteristics of multiple myeloma individuals included in Cohort 1 per data source. Overall, demographic characteristics were consistent across data sources, with multiple myeloma primarily affecting older adults. The total of incident multiple myeloma individuals identified across the included data sources ranged from 1,381 individuals in CDW Bordeaux to 7,545 in HARMONY-MM (incident multiple myeloma individuals in the other data sources were DK-DHR: 4,387; FinOMOP-THL: 5,481; InGef RDB: 7,461; CRN: 5,252).

The median age of multiple myeloma individuals ranged from 67 years in HARMONY-MM to 72 years in FinOMOP-THL. Most individuals were 70 years of age or older at time of multiple myeloma diagnosis, with a proportion of cases ranging from 43.4% in HARMONY-MM to 58.7% in FinOMOP-THL, followed by those aged 60 – 69 years (ranging from 24.1% in InGef RDB to 32.0% in HARMONY-MM). Individuals younger than 45 years were rare (<4% in all data sources).

The proportion of females was lower than the proportion of males in all data sources, ranging from 42.9% in InGef RDB to 49.2% in FinOMOP-THL.

Table 5. Demographics characteristics of incident multiple myeloma individuals in Cohort 1* per data source.

		DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	HARMONY-MM	CRN
Number of individuals		4,387	5,481	1,381	7,461	7,545	5,252
Age (in years), median [IQR]		71 [63 – 78]	72 [64 – 79]	70 [62 – 79]	69 [59 – 78]	67 [60 – 75]	71 [63 – 79]

		DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	HARMONY-MM	CRN
Age (in years), mean (SD)		69.7 (10.9)	71.0 (11.4)	70.1 (12.0)	68.3 (12.3)	66.8 (10.9)	70.2 (11.8)
Age (in years) , range (min – max)		24 – 97	5 – 101	23 – 97	7 – 101	28 – 96	26 – 101
Age group (in years), N (%)	0 – 17	0 (0.0)	6 (0.1)	0 (0.0)	<5	0 (0.0)	0 (0.0)
	18 – 44	72 (1.6)	105 (1.9)	22 (1.6)	227 (3.0)	221 (2.9)	112 (2.1)
	45 – 59	748 (17.1)	692 (12.6)	234 (16.9)	1,653 (22.2)	1,638 (21.7)	851 (16.2)
	60 – 69	1,151 (26.2)	1,459 (26.6)	409 (29.6)	1,862 (25.0)	2,415 (32.0)	1,376 (26.2)
	≥70	2,416 (55.1)	3,219 (58.7)	716 (51.9)	3,717 (49.8)	3,271 (43.4)	2,913 (55.5)
Sex, N (%)	Female	1,896 (43.2)	2,698 (49.2)	655 (47.4)	3,204 (42.9)	3,207 (42.5)	2,265 (43.1)
	Male	2,491 (56.8)	2,783 (50.8)	726 (52.6)	4,257 (57.1)	4,338 (57.5)	2,987 (56.9)

*Cohort 1: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2024. Prior history requirement was not enforced for CDW Bordeaux, HARMONY-MM, and CRN.
DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; HARMONY-MM=HARMONY-Multiple Myeloma; CRN=Cancer Registry Norway; IQR=Interquartile range; SD=standard deviation; N=number of subjects; min=minimum; max=maximum; <5=less than five individuals

9.2.2. Comorbidities

Table 7 reports the frequency of the list of pre-specified conditions for each data source for 30 to 1 day prior to index date.

The frequency of these pre-specified conditions within other time windows, including any time up to 365 days before index date, for 365 to 31 days before index date, and at index date, are presented in the Shiny app at EUPAS1000000757. Due to the nature of their data source, HARMONY-MM and CRN do not have information on comorbidities prior to index date, which is why they are not present in **Table 7**, and the results are zero in the Shiny app at EUPAS1000000757.

In the 30 day period before index date, the five most frequent comorbidities were hypertension (ranging from 12.0% in CDW Bordeaux to 44.3% in FinOMOP-THL), hyperlipidaemia (ranging from 3.8% in CDW Bordeaux to 38.0% in DK-DHR), pneumonia (ranging from 2.4% in CDW Bordeaux to 38.9% in DK-DHR), osteoarthritis (ranging from 1.5% in CDW Bordeaux to 24.3% in FinOMOP-THL), and diabetes mellitus (from 3.9% in CDW Bordeaux to 18.5% in FinOMOP-THL).

The least frequent comorbidities were schizophrenia, ADHD, HIV, Crohn's disease, and chronic liver disease, which were all below 2% or censored in all data sources.

Table 6. Number and % of pre-specified comorbidities among all individuals in Cohort 1 by data source at 30 to 1 days prior to index date (Objective 1).

	DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB
Anxiety	317 (7.2)	220 (4.0)	23 (2.1)	137 (1.8)
Asthma	720 (16.4)	469 (8.6)	11 (1.0)	160 (2.1)
Attention deficit hyperactivity disorder (ADHD)	9 (0.2)	<5	0 (0.0)	<5
Chronic liver disease	28 (0.6)	51 (0.9)	<5	87 (1.2)
COPD	415 (9.5)	216 (3.9)	15 (1.4)	310 (4.2)
Crohn´s disease	26 (0.6)	22 (0.4)	<5	23 (0.3)
Dementia	46 (1.0)	250 (4.6)	13 (1.2)	112 (1.5)
Depressive disorder	773 (17.6)	280 (5.1)	10 (0.9)	346 (4.6)
Diabetes mellitus	530 (12.1)	1.014 (18.5)	43 (3.9)	692 (9.3)
Gastro-oesophageal reflux disease (GERD)	96 (2.2)	160 (2.9)	9 (0.8)	58 (0.8)
Gastrointestinal haemorrhage	241 (5.5)	159 (2.9)	12 (1.1)	190 (2.5)
HIV	<5	<5	<5	<5
Hyperlipidaemia	1,668 (38.0)	976 (17.8)	42 (3.8)	1,047 (14.0)
Hypertension	1,894 (43.2)	2,430 (44.3)	132 (12.0)	2,436 (32.6)
Malignancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Obesity	293 (6.7)	199 (3.6)	30 (2.7)	514 (6.9)
Osteoarthritis	892 (20.3)	1,331 (24.3)	16 (1.5)	615 (8.2)
Parkinson disease	54 (1.2)	52 (1.0)	6 (0.5)	43 (0.8)
Pneumonia	1,706 (38.9)	769 (14.0)	26 (2.4)	402 (5.4)
Psoriasis	302 (6.9)	74 (1.4)	<5	26 (0.3)
Renal impairment	518 (11.8)	705 (12.9)	79 (7.2)	974 (13.1)
Schizophrenia	19 (0.4)	31 (0.6)	0 (0.0)	18 (0.2)
Ulcerative colitis	53 (1.2)	51 (0.9)	0 (0.0)	25 (0.3)
Urinary tract infection	941 (21.4)	293 (5.4)	12 (1.1)	432 (5.8)
Viral hepatitis	8 (0.2)	10 (0.2)	<5	16 (0.2)

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; <5=less than five individuals

9.2.3. Comedications

Table 8 reports the frequency of the list of pre-specified medications for each data source for 30 to 1 day prior to index date and 1 to 90 days post index date.

The results of different time windows, for 365 to 31 days before index date, index date, 1 to 30 days post index, and 1 to 365 days post index, are presented in the Shiny app at EUPAS1000000757. Due to the nature of their data source, HARMONY-MM and CRN do not have information on medications prior to index date and after index date, only on antineoplastic agents and immunosuppressants.

In the 30 day period before index date, the five most frequent medications were agents acting on the renin-angiotensin system (ranging from 2.0% in CDW Bordeaux to 34.3% in DK-DHR), opioids (ranging from 3.2%

in CDW Bordeaux to 29.3% in DK-DHR), antithrombotic agents (ranging from 3.0% in CDW Bordeaux to 27.2% in DK-DHR), lipid modifying agents modifying (ranging from 1.5% in CDW Bordeaux to 26.8% in DK-DHR), and drugs for acid related disorders (ranging from 2.7% in CDW Bordeaux to 24.4% in DK-DHR). The least frequent medications were antipsoriatics and psychostimulants, which were below 1% or censored in all data sources

In general, the most frequent medications in the three months after index date mostly aligned with the most frequent medications in the month before index (i.e. agents acting on the renin-angiotensin system, drugs for acid related disorders, opioids, and antithrombotic agents). Additionally, within this time window, frequent medication encompassed antineoplastic agents (ranging from 16.7% in FinOMOP-THL to 60.9% in DK-DHR), antibacterials (ranging from 24.8% in CDW Bordeaux to 55.8% in FinOMOP-THL), and psycholeptics (ranging from 10.5% in InGef RDB to 33.0% in FinOMOP-THL).

Table 7. Number and % of pre-specified medication use among individuals in Cohort 1 by data source at 30 to 1 days prior to index date and 1 to 90 days post index date (Objective 1).

	DK-DHR		FinOMOP-THL		CDW Bordeaux		InGef RDB		HARMONY-MM		CRN	
	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]
Agents acting on the renin-angiotensin system	1,505 (34.3)	1,603 (36.6)	656 (12.0)	1,136 (20.7)	22 (2.0)	176 (12.7)	2,102 (28.2)	3,207 (43.0)	N/A	N/A	N/A	N/A
Antibacterials	648 (14.8)	1,306 (29.8)	826 (15.1)	3,058 (55.8)	18 (1.6)	43 (24.8)	881 (11.8)	2,720 (36.5)	N/A	N/A	N/A	N/A
Antidepressants	377 (8.6)	535 (12.2)	328 (6.0)	611 (11.2)	13 (1.2)	119 (8.6)	485 (6.5)	901 (12.1)	N/A	N/A	N/A	N/A
Antiepileptics	289 (6.6)	456 (10.4)	284 (5.2)	621 (11.3)	<5	35 (2.5)	331 (4.4)	754 (10.1)	N/A	N/A	N/A	N/A
Anti-inflammatory drugs	922 (21.0)	756 (17.3)	1,218 (22.2)	1,269 (23.2)	8 (0.7)	50 (3.6)	1,348 (18.1)	1,956 (25.2)	N/A	N/A	N/A	N/A
Antineoplastic agents	133 (3.0)	2,668 (60.9)	64 (1.2)	915 (16.7)	7 (0.6)	553 (40.0)	264 (3.5)	2,089 (28.0)	N/A	3,282 (43.6)	N/A	1,433 (28.7)
Antipsoriatics	6 (0.1)	6 (0.1)	<5	5 (0.1)	0 (0.0)	<5	17 (0.2)	18 (0.2)	N/A	N/A	N/A	N/A
Antithrombotic agents	1,195 (27.2)	1,581 (36.1)	661 (12.1)	2,140 (39.0)	33 (3.0)	447 (32.4)	1,005 (13.5)	2,352 (31.5)	N/A	N/A	N/A	N/A
Beta blocking agents	690 (15.7)	925 (21.1)	602 (11.0)	1,275 (23.3)	25 (2.3)	191 (13.8)	1,557 (20.9)	2,439 (32.7)	N/A	N/A	N/A	N/A
Calcium channel blockers	957 (21.8)	1.127 (25.7)	420 (7.7)	938 (17.1)	17 (1.5)	170 (12.3)	847 (11.4)	1,497 (20.1)	N/A	N/A	N/A	N/A
Diuretics	886 (20.2)	1,543 (35.2)	537 (9.8)	1,481 (27.0)	25 (2.3)	213 (15.4)	1,105 (14.8)	2,088 (28.0)	N/A	N/A	N/A	N/A
Drugs for acid related disorders	1,072 (24.4)	1,695 (38.7)	966 (17.6)	3,022 (55.1)	30 (2.7)	351 (25.4)	1,492 (20.0)	3,575 (47.9)	N/A	N/A	N/A	N/A
Drugs for obstructive airway diseases	469 (10.7)	574 (13.1)	413 (7.5)	801 (14.6)	<5	89 (6.4)	617 (8.3)	1,160 (15.5)	N/A	N/A	N/A	N/A

	DK-DHR		FinOMOP-THL		CDW Bordeaux		InGef RDB		HARMONY-MM		CRN	
	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]	[-30, -1]	[1, 90]
Drugs used in diabetes	372 (8.5)	433 (9.9)	322 (5.9)	769 (14.0)	10 (0.9)	107 (7.7)	687 (9.2)	968 (13.0)	N/A	N/A	N/A	N/A
Immunosuppressants	73 (1.7)	1,086 (24.8)	46 (0.8)	861 (15.7)	5 (0.5)	205 (14.8)	241 (3.2)	1,146 (15.4)	N/A	1,211 (16.1)	N/A	1,317 (26.4)
Lipid modifying agents modifying	1,175 (26.8)	1,248 (28.5)	428 (7.8)	801 (14.6)	16 (1.5)	130 (9.4)	953 (12.8)	1,581 (21.2)	N/A	N/A	N/A	N/A
Opioids	1,285 (29.3)	1,964 (44.8)	1,523 (27.8)	2,656 (48.5)	35 (3.2)	333 (24.1)	1,037 (13.9)	2,267 (30.4)	N/A	N/A	N/A	N/A
Psycholeptics	387 (8.8)	992 (22.6)	651 (11.9)	1,810 (33.0)	33 (3.0)	355 (25.7)	320 (4.3)	780 (10.5)	N/A	N/A	N/A	N/A
Psychostimulants	9 (0.2)	10 (0.2)	0 (0.0)	<5	10 (0.9)	56 (4.1)	6 (0.1)	7 (0.1)	N/A	N/A	N/A	N/A

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; HARMONY-MM=HARMONY-Multiple Myeloma; CRN=Cancer Registry Norway.
N/A=not available (due to nature of the data source); <5=less than five individuals

9.3. Multiple Myeloma treatments

9.3.1. Demographic characteristics in Cohort 2

Table 9 describes the demographic characteristics of multiple myeloma individuals included in Cohort 2 per data source. InGef RDB was excluded from the multiple myeloma treatment (classes) characterisation and the treatment patterns analysis due to the absence of complete data on multiple myeloma treatments. Overall, demographic characteristics were consistent with Cohort 1. Only FinOMOP-THL (5,458) and CRN (5,221) had a slightly lower number of individuals compared to Cohort 1. Nevertheless, median and mean age, age range, age groups and sex distribution remained unchanged.

Table 8. Demographics characteristics of incident multiple myeloma individuals in Cohort 2* per data source.

		DK-DHR	FinOMOP-THL	CDW Bordeaux	HARMONY-MM	CRN
Number of individuals		4,387	5,458	1,381	7,545	5,221
Age (in years), median [IQR]		71 [63 – 78]	72 [64 – 79]	70 [62 – 79]	67 [60 – 75]	71 [63 – 79]
Age (in years), mean (SD)		69.7 (10.9)	71.0 (11.4)	70.1 (12.0)	66.8 (10.9)	70.2 (11.8)
Age (in years), range (min – max)		24 – 97	5 – 101	23 – 97	28 – 96	26 – 101
Age group, N (%)	0 – 17	0 (0.0)	6 (0.11)	0 (0.0)	0 (0.0)	0 (0.0)
	18 – 44	72 (1.6)	105 (1.9)	22 (1.6)	221 (2.9)	112 (2.2)
	45 – 59	748 (17.1)	690 (12.6)	234 (16.9)	1,638 (21.7)	848 (16.2)
	60 – 69	1,151 (26.2)	1,454 (26.6)	409 (29.6)	2,415 (32.0)	1,370 (26.2)
	≥70	2,416 (55.1)	3,203 (58.7)	716 (51.9)	3,271 (43.4)	2,891 (55.4)
Sex, N (%)	Female	1,896 (43.2)	2,682 (49.1)	655 (47.4)	3,207 (42.5)	2,249 (43.1)
	Male	2,491 (56.8)	2,776 (50.9)	726 (52.6)	4,338 (57.5)	2,972 (56.9)

* Cohort 2: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis between 01/01/2012 and 31/12/2024 and a minimum follow-up of 30 days after index date.
DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; HARMONY-MM=HARMONY-Multiple Myeloma; CRN=Cancer Registry Norway; IQR= Interquartile range; SD=standard deviation; N=number of subjects; min=minimum; max=maximum; <5=less than five individuals

9.3.2. Multiple myeloma treatments and treatment classes

Figures 3–5 show the frequency of use of captured multiple myeloma treatments for 1 to 90 days, 1 to 365 days, and 1 to 5 years post index date, while **Figures S1–3** show the frequency of use of captured multiple myeloma treatment classes for the same time points.

The results of different time windows, for index date, and 1 to 30 days post index, and all time points stratified by sex or age-group, are presented in the Shiny app at EUPAS1000000757. There were no clear

differences in the frequency of use of multiple myeloma treatments when stratified by sex or age-group, except for the age-group 0 to 17, where there were zero treatments. The most frequently prescribed treatments stratified by age-group or sex did not differ from the overall results.

Of the 34 pre-specified multiple myeloma treatments, 6 were not found in any of the participating data sources during the study period. These included: all CAR T-cell treatments (axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, tisagenlecleucel), bisphosphonate (etidronate).

In general, chemotherapies (cyclophosphamide, melphalan), proteasome inhibitors (bortezomib), glucocorticoids (dexamethasone), and immunomodulatory drugs (lenalidomide) were the most captured treatment classes and treatments across any time window post diagnosis (**Figures 3–5** and **Figures S1–3**). Moreover, as expected, a higher proportion of individuals were treated when looking at 365 days and 5 years following diagnosis as compared to the 1 to 90 days post-diagnosis time window. In CRN, the proportion of individuals with a record of use of proteasome inhibitors increased from 50.7% in the first 90 days, to 56.7% in the first 365 days, and 60.3% in the 5 years post multiple myeloma diagnosis. In FinOMOP-THL, these proportions were 13.6% (0 – 90 days), 33.5% (0 – 365 days), and 46.9% (0 – 5 years), for treatment with immunomodulatory drugs, respectively. In DK-DHR, the proportion of individuals with recorded use of chemotherapies were 20.0% (0 – 90 days), 30.1% (0 – 365 days), and 35.3% (0 – 5 years), respectively.

Within 90-days post multiple myeloma diagnosis

In the first 90 days post multiple myeloma diagnosis (**Figure S1**), generally the most frequently prescribed **class** of treatments were proteasome inhibitors (range 3.3% (FinOMOP-THL) – 55.6% (DK-DHR)), glucocorticoids (range 7.1% (DK-DHR) – 46.3% (FinOMOP-THL)), immunomodulatory drugs (range 8.1% (CDW Bordeaux) – 50.0% (CRN)), bisphosphonates (range 4.3% (FinOMOP-THL) – 26.6% (DK-DHR)), and chemotherapies (range 4.5% (CRN) – 23.5% (HARMONY-MM)). The least frequently prescribed class of treatments were monoclonal antibodies (range 1.2% (HARMONY-MM) – 4.6% (CRN)).

The most frequently prescribed **treatments** in the first 90 days post multiple myeloma diagnosis (**Figure 3**), were bortezomib (range 3.3% (FinOMOP-THL) – 55.6% (DK-DHR)), dexamethasone (range 7.1% (DK-DHR) – 46.3% (FinOMOP-THL)), lenalidomide (range 8.1% (CDW Bordeaux) – 50.0% (CRN)), and cyclophosphamide (range 4.3% (CDW Bordeaux) – 23.5% (HARMONY-MM), and melphalan (range 2.4% (CRN) – 18.8% (CDW Bordeaux)). The least frequently prescribed treatments were thalidomide (range 1.2% (FinOMOP-THL) – 5.6% (CDW Bordeaux)), denosumab (range 2.8% (DK-DHR) – 8.1% (FinOMOP-THL)), and pamidronic acid (range 0.9% (FinOMOP-THL) – 7.5% (DK-DHR)). Treatments with very low frequency (<1%) were not individually reported and were considered rare. These included, for example, carfilzomib, cisplatin, clodronic acid, and pomalidomide.

Within 365-days post multiple myeloma diagnosis

Compared to the first 90 days, there were no substantial differences in frequently prescribed treatments and classes in the first 365 days post multiple myeloma diagnosis (**Figure 4** and **Figure S2**). The most frequently prescribed **class** of treatments were still glucocorticoids (range 11.9% (DK-DHR) – 54.4% (FinOMOP-THL)), proteasome inhibitors (range 4.1% (FinOMOP-THL) – 60.2% (DK-DHR)), immunomodulatory drugs (range 10.0% (CDW Bordeaux) – 56.7% (CRN)), bisphosphonates (range 7.6% (FinOMOP-THL) – 40.2% (DK-DHR)), and chemotherapies (range 10.4% (FinOMOP-THL) – 27.9% (CDW Bordeaux)). The least frequently prescribed class of treatments were still monoclonal antibodies (range 2.6% (HARMONY-MM) – 9.0% (CRN)).

The most frequently prescribed treatments in the first 365 days post multiple myeloma diagnosis were similar compared to the first 90 days, namely dexamethasone (range 11.9% (DK-DHR) – 54.4% (FinOMOP-THL)), cyclophosphamide (range 10.4% (FinOMOP-THL) – 27.2% (DK-DHR)), bortezomib (range 4.1%

(FinOMOP-THL) – 60.2% (DK-DHR)), lenalidomide (range 10.0% (CDW Bordeaux) – 56.7% (CRN)), and melphalan (range 8.0% (HARMONY-MM) – 30.1% (DK-DHR)). The least frequently prescribed class of treatments were still thalidomide (range 2.2% (FinOMOP-THL) – 8.5% (HARMONY-MM)), pamidronic acid (range 1.6% (FinOMOP-THL) – 13.9% (DK-DHR)), denosumab (range 4.6% (DK-DHR) – 12.0% (FinOMOP-THL)), and carfilzomib (range 0.2% (FinOMOP-THL) – 4.1% (CRN)). Treatments with very low frequency (<1%) in this time window were not individually reported and were considered rare. These included, for example, bendamustine, cisplatin, elotuzumab, etoposide, and vincristine.

Within 5-year post multiple myeloma diagnosis

Lastly, compared to the first 90 and 365 days, there were no differences in the most frequently prescribed treatments and classes in the first 5 years post multiple myeloma diagnosis (**Figure 5** and **Figure S3**). The most frequently prescribed class of treatments were glucocorticoids (range 24.1% (DK-DHR) – 63.2% (FinOMOP-THL)), chemotherapies (range 15.8% (FinOMOP-THL) – 35.3% (DK-DHR)), proteasome inhibitors (range 4.9% (FinOMOP-THL) – 67.3% (DK-DHR)), immunomodulatory drugs (range 13.9% (CDW Bordeaux) – 64.4% (CRN)), and bisphosphonates (range 7.9% (CDW Bordeaux) – 51.7% (DK-DHR)). Despite increased use, the least frequently prescribed class of treatments were still monoclonal antibodies (range 0.1% (FinOMOP-THL) – 28.8% (DK-DHR)).

The most frequently prescribed treatments in the first 5 years post multiple myeloma diagnosis were still dexamethasone (range 24.1% (DK-DHR) – 63.2% (FinOMOP-THL)), cyclophosphamide (range 10.9% (CDW Bordeaux) – 35.3% (DK-DHR)), bortezomib (range 4.9% (FinOMOP-THL) – 67.3% (DK-DHR)), and lenalidomide (range 13.9% (CDW Bordeaux) – 64.4% (CRN)), and melphalan (range 8.6% (HARMONY-MM) – 34.8% (DK-DHR)). The least frequently prescribed class of treatments were now bendamustine (range 0.3% (HARMONY-MM) – 1.6% (CDW Bordeaux)), elotuzumab (range 0.4% (HARMONY-MM) – 1.1% (DK-DHR)), etoposide (range 0.2% (CRN) – 1.0% (DK-DHR)).

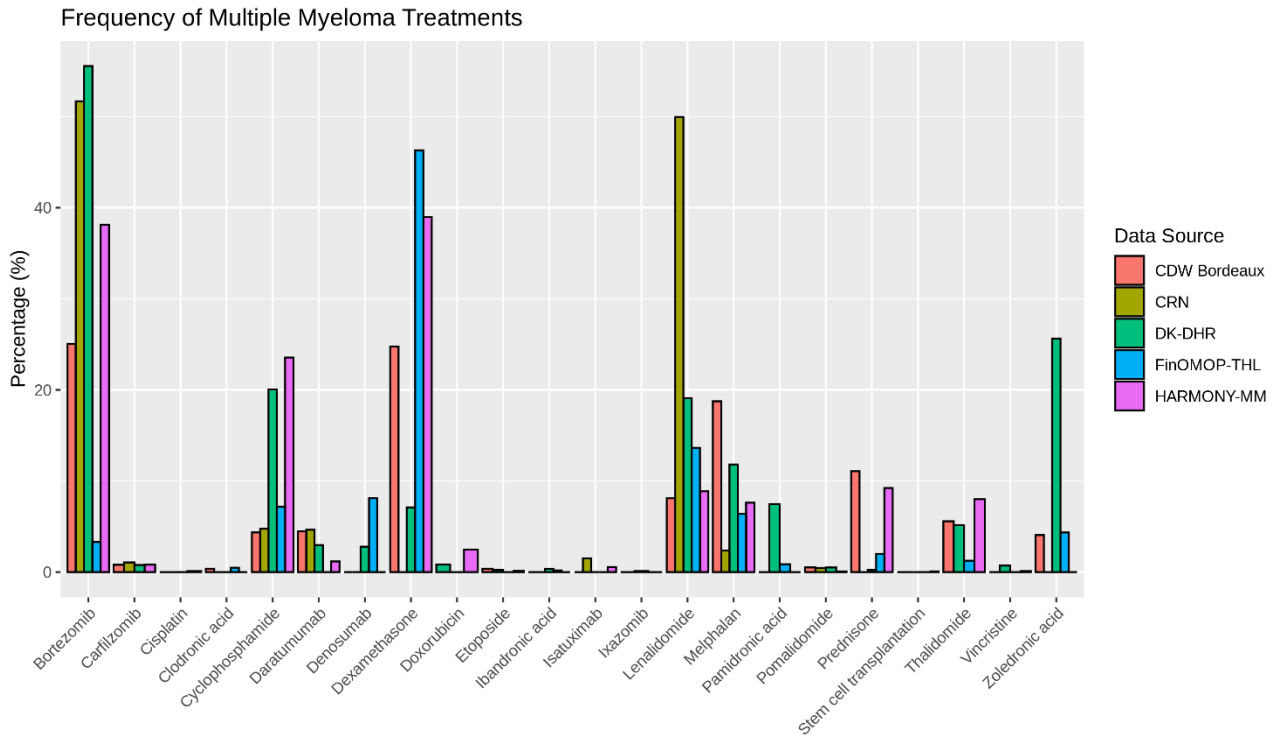


Figure 3. Frequency of use of multiple myeloma treatments from 1 to 90 days after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

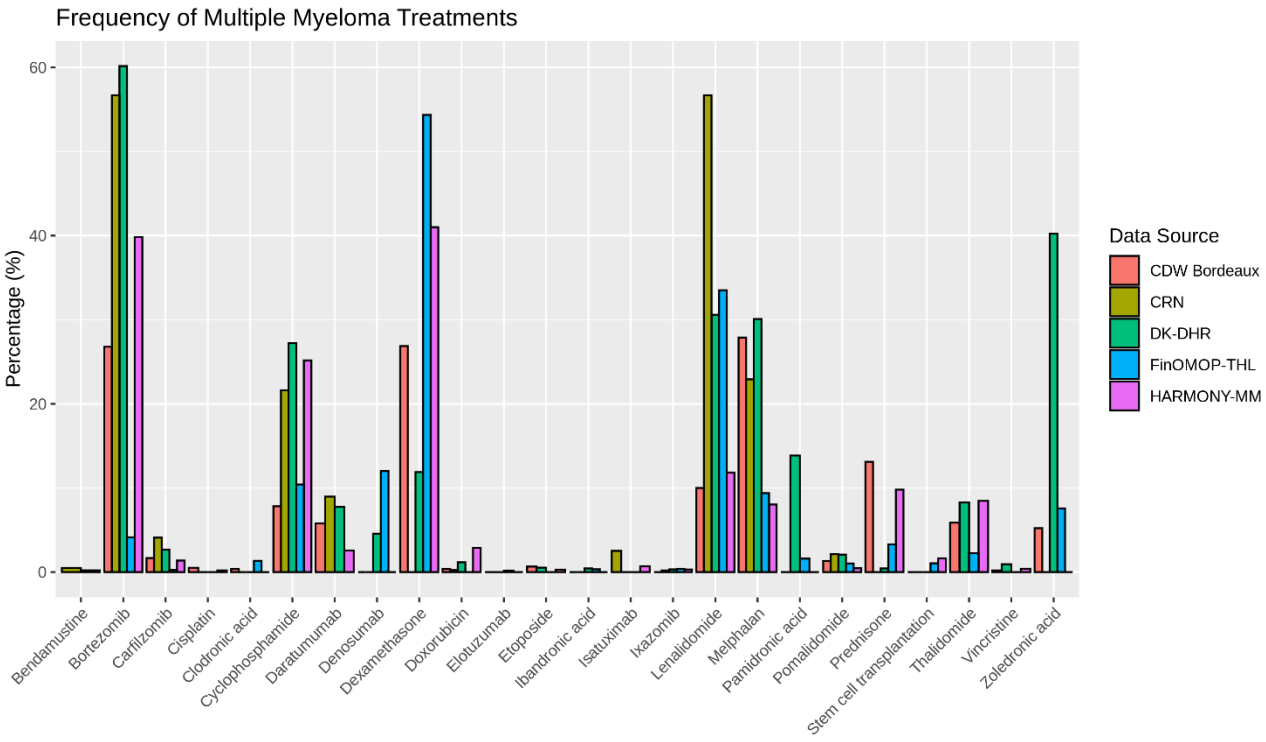


Figure 4. Frequency of use of multiple myeloma treatments from 1 to 365 days after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

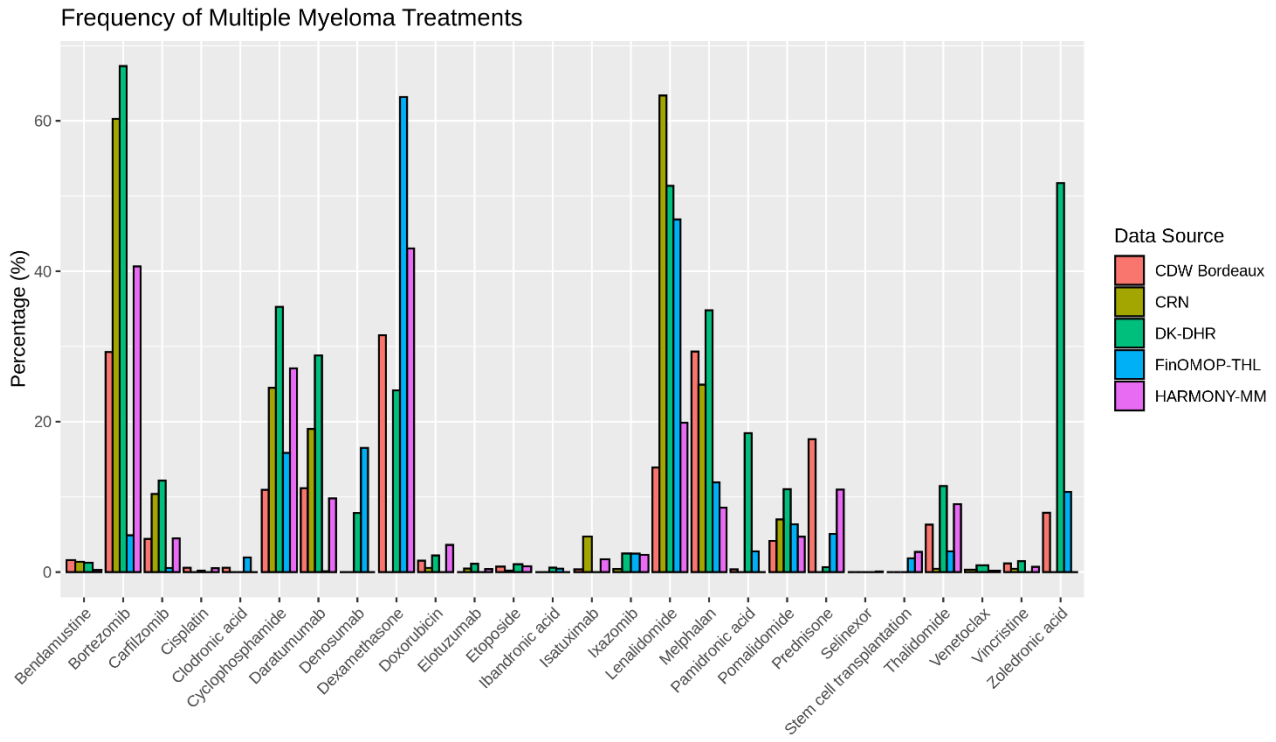


Figure 5. Frequency of use of multiple myeloma treatments from 1 day to 5 years after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

9.3.3. Multiple myeloma treatment sequences

Figures 6–10 depict the sunburst plots of treatment patterns analysis in all data sources in the 5 years after multiple myeloma diagnosis.

The results for the first year after diagnosis are presented in the Shiny app at EUPAS1000000757.

Please note that due to the dependence of the *TreatmentPatterns* package on the parameterisation of the analysis settings, and the variation between the registration of treatments per data sources (i.e. duration, construction of drug exposures or episodes), results were difficult to interpret and not comparable between data sources.

9.3.3.1 Overall (0 to 5 years post index date)

Across most data sources, in the 5 years after multiple myeloma diagnosis, no recorded treatments in the treatment pathway analysis was the most frequent category, with the proportion of patients classified as having “no recorded treatment (None)” ranging from 42.1% in CRN to 66.5% in CDW Bordeaux. The exception was HARMONY-MM, where the proportion of individuals with no recorded treatment was only 1.7%. Stem cell transplantation was only observed in HARMONY-MM and FinOMOP-THL. Generally, single-agent therapies without subsequent treatment (e.g. dexamethasone, melphalan, bortezomib, and lenalidomide) were most common in DK-DHR, FinOMOP-THL, and CDW Bordeaux. Nevertheless, HARMONY-MM differed, showing more frequent and complex sequences.

In the individuals with recorded treatments in CDW Bordeaux, the most common treatment was melphalan without subsequent treatments (48.5%), followed by the combination of bortezomib+melphalan+prednisone (8.1%), and dexamethasone (6.6%), all without subsequent

treatment(s). Other observed treatments included the combination of bortezomib+dexamethasone (6.3%), prednisone (5.1%), lenalidomide (4.2%), bortezomib+cyclophosphamide+dexamethasone (3.0%), and daratumumab (3.0%), all without subsequent treatment. The full picture of overall treatment sequences is shown as a sunburst plot in **Figure 6.**

In CRN, the most commonly observed treatment was individuals who were treated with lenalidomide without a subsequent treatment (23.6%), followed by the combination of bortezomib+lenalidomide with subsequent lenalidomide (12.4%), bortezomib without a subsequent treatment (9.2%), and the combination of bortezomib+lenalidomide with subsequent bortezomib (6.1%). Other treatments that were captured but less frequent were carfilzomib without subsequent treatment (1.8%), and isatuximab (1.3%). A full picture of overall treatment sequences is shown as a sunburst plot in **Figure 7.**

In HARMONY-MM, the most common treatments were the combinations of cyclophosphamide+dexamethasone+lenalidomide (29.3%), cyclophosphamide+dexamethasone+thalidomide (29.1%), and bortezomib+cyclophosphamide+dexamethasone (22.0%), all without subsequent treatments. There were some combinations of more than three treatments in HARMONY-MM. For example, the combination of dexamethasone+lenalidomide+melphalan+prednisone (2.3%) and the combination of bortezomib+dexamethasone+lenalidomide+melphalan+prednisone (0.7%). The most common treatment sequence was the combination of bortezomib+dexamethasone+thalidomide with subsequent daratumumab+dexamethasone+lenalidomide (0.9%), followed by the combination of bortezomib+cyclophosphamide+dexamethasone with subsequent daratumumab+dexamethasone+lenalidomide (0.6%). The full picture of overall treatment sequences is shown as a sunburst plot in **Figure 8.**

In DK-DHR, the most commonly recorded treatments among individuals were dexamethasone (25.2%), bortezomib (20.9%), zoledronic acid (13.7%), and lenalidomide (6.3%), all without subsequent treatments. Thalidomide (3.7%), denosumab (3.3%), and melphalan (3.3%) were also commonly observed without subsequent treatment. Among combination therapies, the most frequent were bortezomib+cyclophosphamide (4.1%), followed by bortezomib+lenalidomide (1.5%) and bortezomib+melphalan (1.3%), all without subsequent treatments. Treatment sequences were infrequent; the most common sequences were bortezomib with subsequent lenalidomide (2.2%) and the combination of bortezomib+lenalidomide with subsequent bortezomib (1.1%), and bortezomib+melphalan with subsequent bortezomib (1.1%). The full picture of overall treatment sequences is shown as a sunburst plot in **Figure 9.**

In FinOMOP-THL, the most common treatment was dexamethasone without subsequent treatments (27.6%), followed by the dexamethasone with subsequent lenalidomide (9.4%), and the combination of dexamethasone+lenalidomide (5.4%). Other frequent treatments were denosumab (4.7%), melphalan (3.4%), cyclophosphamide (3.2%), and lenalidomide (2.9%) all without subsequent treatment. Lastly, another relatively frequent treatment sequence was dexamethasone with a subsequent combination of dexamethasone+lenalidomide with subsequent lenalidomide (3.4%). The full picture of overall treatment sequences is shown as a sunburst plot in **Figure 10.**

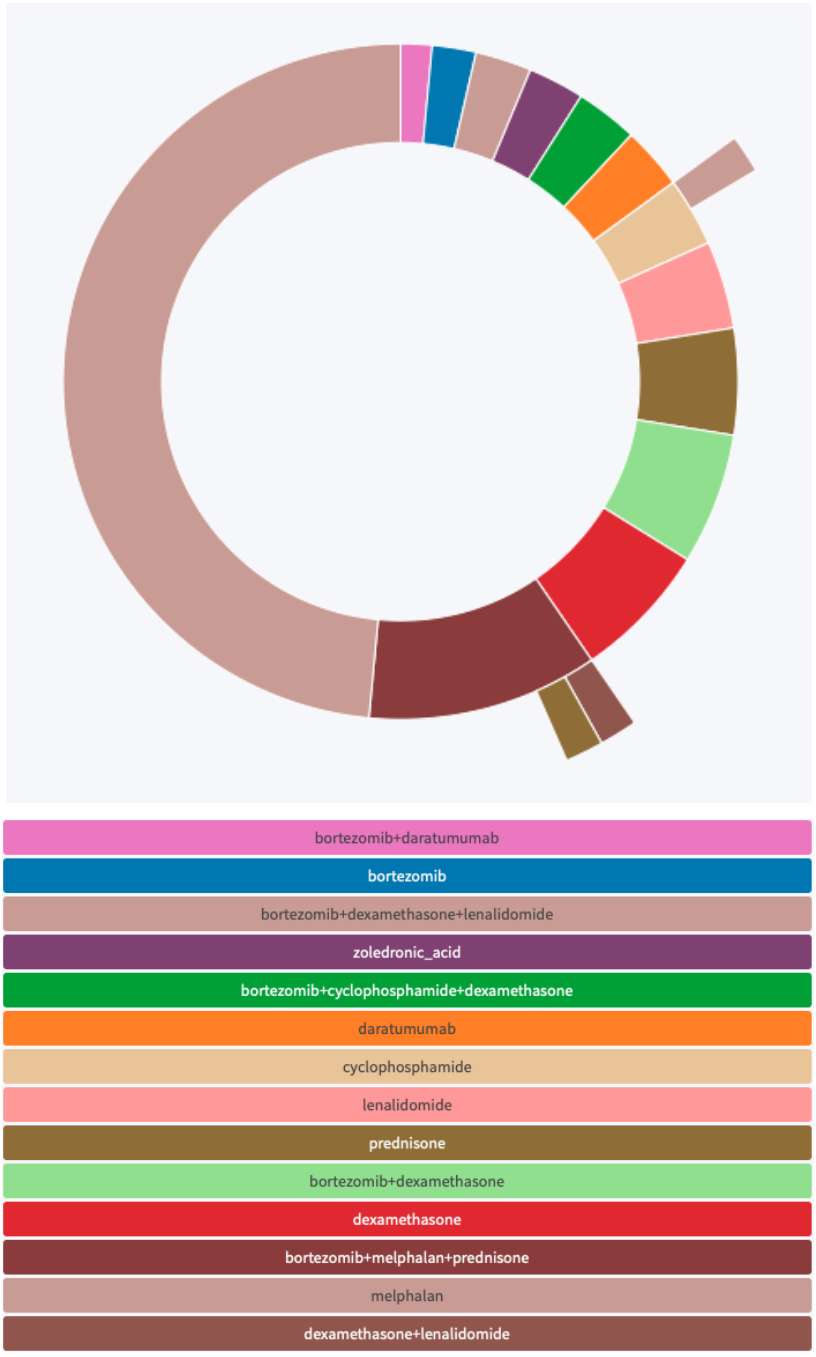


Figure 6. Sunburst plot of treatment patterns analysis in CDW Bordeaux (0 to 5 years post index date).

CDW Bordeaux=Clinical Data Warehouse of Bordeaux

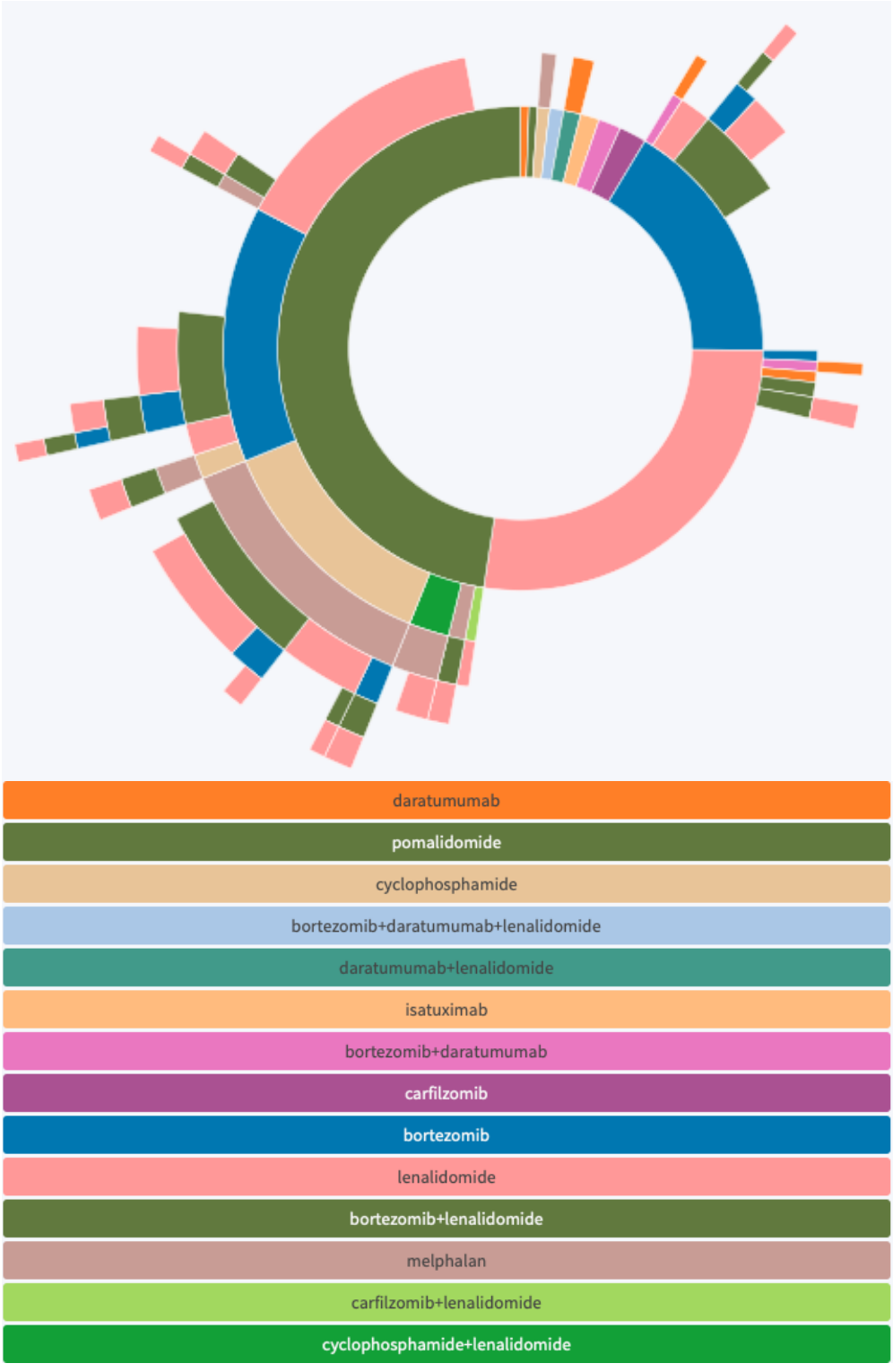


Figure 7. Sunburst plot of treatment patterns analysis in CRN (0 to 5 years post index date).

CRN=Cancer Registry Norway

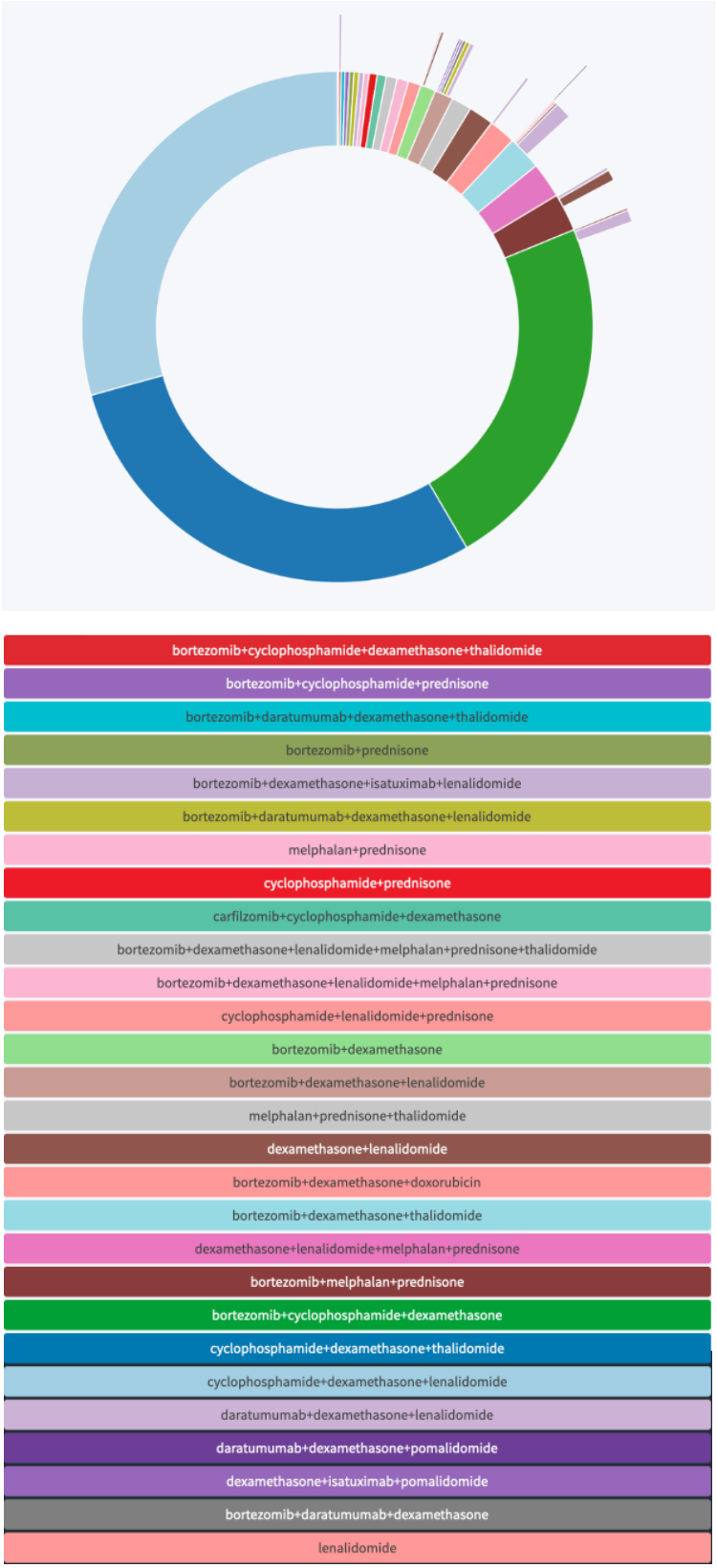


Figure 8. Sunburst plot legend of treatment patterns analysis in HARMONY-MM (0 to 5 years post index date).

HARMONY-MM=HARMONY-Multiple Myeloma

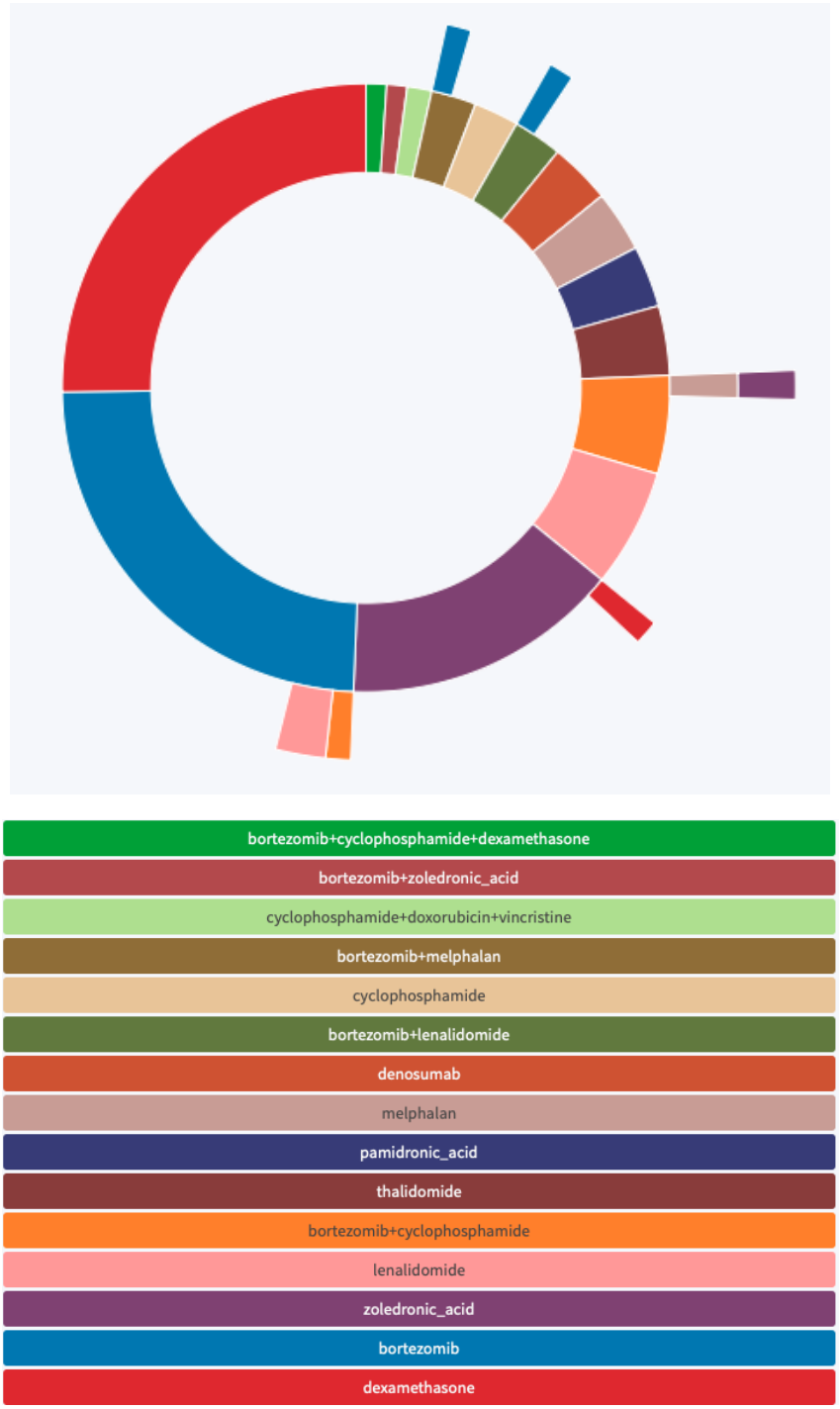


Figure 9. Sunburst plot legend of treatment patterns analysis in DK-DHR (0 to 5 years post index date).

DK-DHR=Danish Data Health Registries

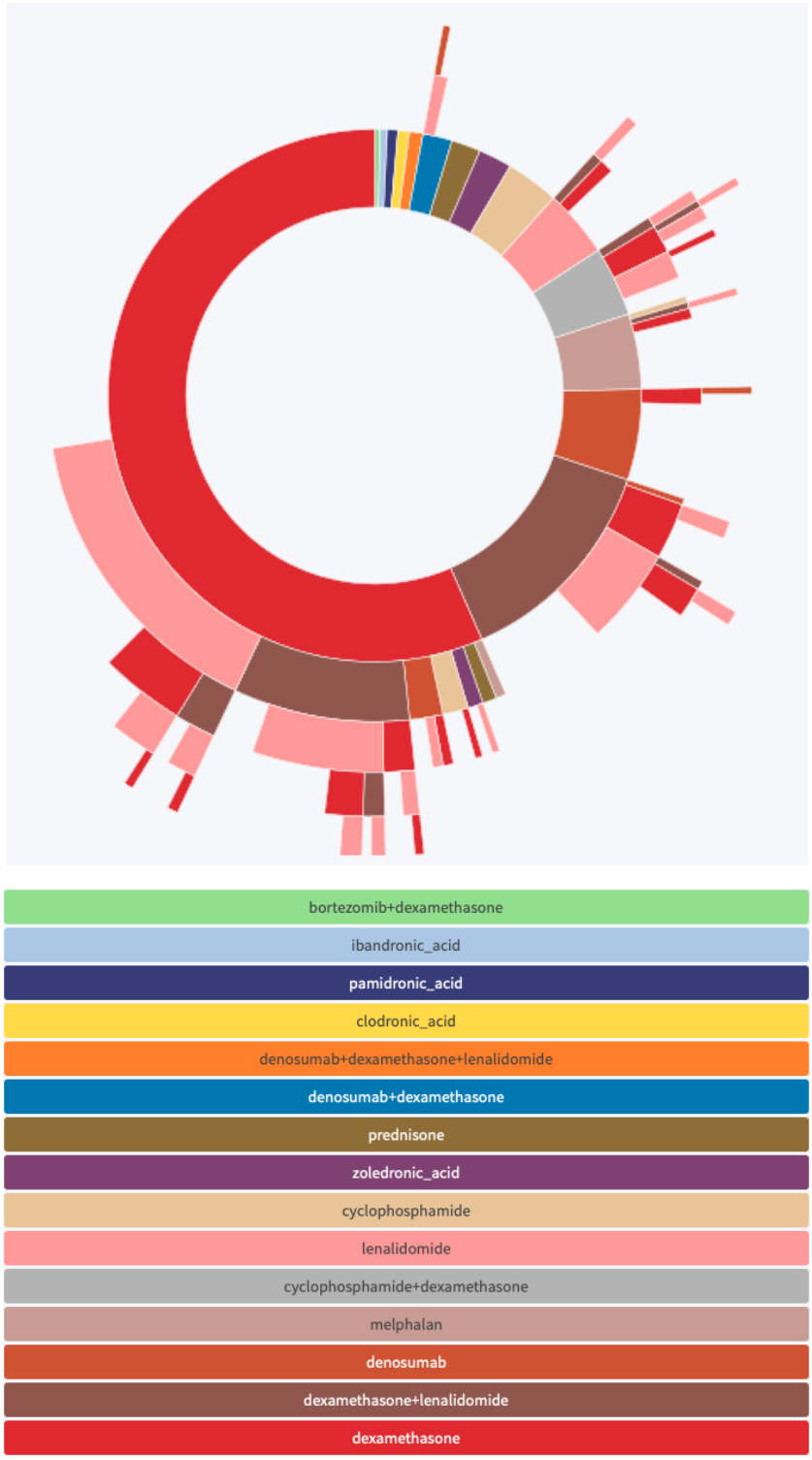


Figure 10. Sunburst plot legend of treatment patterns analysis in FinOMOP-THL (0 to 5 years post index date).

FinOMOP-THL=Finnish Care Register for Health Care - THL

9.3.3.2 Analysis stratified by sex (0 to 5 years post index date)

Figures S4–S13 show the sunburst plots of treatment patterns analysis in the first 5 years after multiple myeloma diagnosis per data source stratified by sex.

When stratified by sex there was no clear difference between females and males in the most common treatments. Across most data sources, in both females and males, no recorded treatments in the treatment pathway analysis was the most frequent category. Moreover, comparable to the overall analysis, single-agent therapies without subsequent treatment (e.g. dexamethasone, melphalan, bortezomib, and lenalidomide) were most common in DK-DHR, FinOMOP-THL, and CDW Bordeaux, while HARMONY-MM differed, showing more frequent and complex sequences.

Only in DK-DHR was one clear difference found, namely that no females treated with lenalidomide while in males there were.

9.3.3.3 Analysis stratified by age group (0 to 5 years post index date)

Similar to the stratification by sex, the treatment pathway analysis stratified by age group did not show clear differences between age groups and compared to the overall analysis. Moreover, none of data sources had any individuals in the age group 0 to 17, and only CDW Bordeaux and HARMONY-MM had any individuals in the age group of 17–44, with CDW Bordeaux only having 6 (untreated) individuals. Lastly, in CRN, there were no individuals in the age group 44 to 59 at all.

9.3.3.4 Analysis stratified by stem cell transplantation (0 to 5 years post index date)

There were only two data sources where stem cell transplantation as a treatment was recorded, namely FinOMOP-THL and HARMONY-MM. There were 6 individuals in FinOMOP-THL with only stem cell transplantation (STC) and no individuals with STC as part of their sequence or combination. In HARMONY-MM, there were a total of 85 individuals with STC. Among the individuals with STC in HARMONY-MM, the most common treatment was the combination of bortezomib+dexamethasone+thalidomide followed by STC (32 individuals (37.7%)), followed by only STC without subsequent treatment (24 individuals (28.2%)). The other treatments present in HARMONY-MM were the combination of bortezomib+dexamethasone+lenalidomide followed by STC (15 individuals (17.7%)) and the combination of bortezomib+cylcophospamide+dexamethasone followed by STC (14 individuals (16.5%)).

9.4. Survival analysis

9.4.1. Demographic characteristics in cohort 3

Table 10 describes the demographic characteristics of multiple myeloma individuals included in Cohort 3 per data source. HARMONY-MM was excluded from the survival analyses due to concerns regarding incomplete mortality capture and incomplete follow-up in hospital electronic health records (EHR) data, which resulted in atypical survival patterns and limited comparability with other data sources.

Overall, demographic characteristics were consistent with Cohort 1 and 2. FinOMOP-THL (5,048), InGef RDB (7,084), and CRN (4,791) had a slightly lower number of individuals compared to Cohort 2. Nevertheless, median and mean age, age range, age groups, and sex distribution remained unchanged.

Table 9. Demographics characteristics of incident multiple myeloma individuals in Cohort 3* per data source.

		DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	CRN
Number of individuals		4,387	5,048	1,381	7,084	4,791
Age (in years), median [IQR]		71 [63 – 78]	72 [64 – 79]	70 [62 – 79]	70 [59 – 78]	71 [63 – 79]

		DK-DHR	FinOMOP-THL	CDW Bordeaux	InGef RDB	CRN
Age (in years), mean (SD)		69.7 (10.9)	71.0 (11.5)	70.1 (12.0)	68.4 (12.3)	70.2 (11.8)
Age (in years), range (min – max)		24 – 97	5 – 101	23 – 97	7 – 101	26 – 101
Age group, N (%)	0 – 17	0 (0.0)	6 (0.1)	0 (0.0)	<5	0 (0.0)
	18 – 44	72 (1.6)	97 (1.9)	2 (1.6)	217 (3.1)	101 (2.1)
	45 – 59	748 (17.1)	642 (12.7)	234 (16.9)	1,566 (22.1)	774 (16.2)
	60 – 69	1,151 (26.2)	1,360 (26.9)	409 (29.6)	1,740 (24.6)	1,282 (26.8)
	≥70	2,416 (55.1)	2,943 (58.3)	716 (51.9)	3,559 (50.2)	2,634 (55.0)
Sex, N (%)	Female	1,896 (43.2)	2,477 (49.1)	655 (47.4)	3,038 (42.9)	2,087 (43.6)
	Male	2,491 (56.8)	2,571 (50.9)	726 (52.6)	4,046 (57.1)	2,704 (56.4)

*Cohort 3: individuals with a first diagnosis of multiple myeloma, with no history of other cancer (any, excluding non-melanoma skin cancer) any time prior to the diagnosis of multiple myeloma, and with at least 365 days of prior history available before date of multiple myeloma diagnosis (except for hospital data sources CRN and CDW-Bordeaux) between 01/01/2012 and 31/12/2024 and a minimum of 1 year potential follow-up.
DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway.

9.4.2. Proportion of death

Across data sources, the proportion of deaths during follow-up ranged from 13.7% in InGef RDB to 67.2% in CDW Bordeaux. Intermediate death proportions were observed in FinOMOP-THL (56.8%), DK-DHR (49.6%), and CRN (48.1%) (**Table 11**).

Median overall survival varied across data sources. The shortest median survival was observed in CDW Bordeaux (2.7 years), while longer median survival estimates were reported in FinOMOP-THL (4.7 years), CRN (6.0 years), and DK-DHR (6.2 years). Median survival was not reached in InGef RDB (**Table 11**).

9.4.3. Survival probabilities

Survival of multiple myeloma individuals in Cohort 3 overall and stratified by sex and age group is presented in **Table 11**. RMST at 5 years varied across data sources. The highest RMST estimates were observed in InGef RDB (4.6 years) and DK-DHR (3.7 years), followed by CRN (3.7 years), FinOMOP-THL (3.4 years), and CDW Bordeaux (2.7 years). Across all data sources, RMST was marginally but consistently higher in females than males (**Table 11**).

Overall survival probabilities also differed across data sources. At 3 years, survival ranged from 46.0% in CDW Bordeaux to 89.6% in InGef RDB, while 5-year survival ranged from 28.4% to 85.9%, respectively. Intermediate estimates were observed in DK-DHR (70.7% and 56.9%), CRN (69.1% and 56.1%), and FinOMOP-THL (62.6% and 48.6%) at 3 and 5 years, respectively. Overall, survival outcomes were more favourable in InGef RDB and less favourable in CDW Bordeaux (**Table 11**). **Figure 11** shows the Kaplan-Meier overall survival curves for each data source.

When stratified by sex, females generally showed slightly higher survival probabilities than males across most data sources, although differences were modest. For example, in DK-DHR, 3- and 5-year survival were 74.2% and 61.1% in females compared with 68.0% and 53.8% in males. Similarly, in FinOMOP-THL, survival was 64.9% and 51.2% in females versus 60.4% and 46.2% in males at 3 and 5 years, respectively. In CRN, survival was similar between sexes (3-year: 68.4% vs 69.7%; 5-year: 55.8% vs 56.4% for females and males, respectively) (**Table 11**). **Figure 12** shows the Kaplan-Meier survival curves stratified by sex.

Survival outcomes varied markedly by age. Younger individuals (18–44 and 45–59 years) had substantially higher survival probabilities, with 5-year survival often exceeding 70–90% across data sources. In contrast, individuals aged ≥70 years had considerably lower survival, with 5-year survival ranging from approximately 17.8% in CDW Bordeaux to 78.6% in InGef RDB. A clear gradient was observed, with survival decreasing progressively with increasing age across all data sources (**Table 11**). **Figure 13** shows the Kaplan-Meier survival curves stratified by age group.

Table 10. Survival of multiple myeloma individuals in Cohort 3 overall and stratified by sex and age group.

Data source	Population subgroups	Cases (N)	Events (N)	Median survival (years)**	Restricted mean survival (years)*	3-year survival probability % (95%CI)	5-year survival probability % (95%CI)
DK-DHR	Overall	4,381	2,175 (49.6%)	6.2	3.7	70.7 (69.4–72.1)	56.9 (55.4–58.6)
	Female	1,893	865 (45.7%)	7.0	3.9	74.2 (72.3–76.3)	61.1 (58.7–63.5)
	Male	2,488	1,310 (52.7%)	5.6	3.6	68.0 (66.2–69.9)	53.8 (51.7–56.0)
	0–17 years	0	NA	NA	NA	NA	NA
	18–44 years	72	14 (19.4%)	NA	4.5	88.5 (81.4–96.4)	85.0 (76.8–94.1)
	45–59 years	746	197 (26.4%)	NA	4.5	88.1 (85.8–90.5)	80.9 (77.9–84.0)
	60–69 years	1,151	459 (39.9%)	8.8	4.1	79.3 (76.9–81.7)	67.9 (65.0–70.9)
	>=70 years	2,412	1,505 (62.4%)	4.1	3.3	60.7 (58.8–62.7)	43.1 (41.0–45.4)
FinOMOP-THL	Overall	5,048	2,867 (56.8%)	4.7	3.4	62.6 (61.2–64.0)	48.6 (47.2–50.2)
	Female	2,477	1,383 (55.8%)	5.2	3.5	64.9 (63.0–66.9)	51.2 (49.1–53.4)
	Male	2,571	1,484 (57.7%)	4.3	3.3	60.4 (58.4–62.3)	46.2 (44.1–48.3)
	0–17 years	6	0 (0.0%)	NA	NA	100.0 (100.0–100.0)	100.0 (100.0–100.0)
	18–44 years	97	18 (18.6%)	NA	4.6	89.2 (83.1–95.8)	83.6 (76.0–92.0)
	45–59 years	642	191 (29.8%)	NA	4.3	84.3 (81.4–87.2)	75.2 (71.7–78.9)
	60–69 years	1,360	626 (46.0%)	7.3	4.0	74.7 (72.3–77.1)	64.7 (62.1–67.5)
	>=70 years	2,943	2,032 (69.0%)	3.1	2.9	51.2 (49.4–53.1)	33.6 (31.7–35.5)
CDW Bordeaux	Overall	1,378	926 (67.2%)	2.7	2.7	46.0 (43.0–49.1)	28.4 (25.6–31.4)
	Female	654	438 (67.0%)	2.7	2.7	44.2 (40.0–48.9)	29.8 (25.8–34.3)
	Male	724	488 (67.4%)	2.8	2.7	47.4 (43.5–51.8)	27.2 (23.5–31.3)
	0–17 years	0	NA	NA	NA	NA	NA
	18–44 years	22	7 (31.8%)	NA	4.0	71.1 (50.7–99.7)	71.1 (50.7–99.7)

Data source	Population subgroups	Cases (N)	Events (N)	Median survival (years)**	Restricted mean survival (years)*	3-year survival probability % (95%CI)	5-year survival probability % (95%CI)
	45–59 years	234	109 (46.6%)	4.9	3.6	69.4 (62.6–76.9)	49.1 (41.6–58.1)
	60–69 years	408	248 (60.8%)	3.1	3.0	51.2 (45.8–57.3)	36.4 (31.0–42.6)
	>=70 years	714	562 (78.7%)	2.0	2.3	35.9 (32.1–40.0)	17.8 (14.8–21.3)
InGef RDB	Overall	7,083	968 (13.7%)	NA	4.6	89.6 (88.9–90.4)	85.9 (85.0–86.9)
	Female	3,038	403 (13.3%)	NA	4.6	89.8 (88.7–91.0)	86.4 (85.0–87.8)
	Male	4,045	565 (14.0%)	NA	4.6	89.5 (88.5–90.6)	85.6 (84.3–86.9)
	0–17 years	0	NA	NA	NA	NA	NA
	18–44 years	217	<5	NA	NA	NA	NA
	45–59 years	1,566	91 (5.8%)	NA	4.8	95.9 (94.9–96.9)	94.8 (93.6–96.0)
	60–69 years	1,740	181 (10.4%)	NA	4.7	91.5 (90.1–93.0)	89.3 (87.6–91.0)
	>=70 years	3,558	692 (19.4%)	NA	4.4	84.9 (83.6–86.2)	78.6 (77.0–80.3)
CRN	Overall	4,545	2,186 (48.1%)	6.0	3.7	69.1 (67.7–70.5)	56.1 (54.5–57.8)
	Female	1,975	947 (47.9%)	6.1	3.6	68.4 (66.3–70.5)	55.8 (53.4–58.3)
	Male	2,570	1,239 (48.2%)	5.9	3.7	69.7 (67.9–71.6)	56.4 (54.3–58.6)
	0–17 years	0	NA	NA	NA	NA	NA
	18–44 years	100	28 (28.0%)	NA	4.3	81.6 (74.1–90.0)	80.4 (72.6–89.0)
	45–59 years	764	201 (26.3%)	NA	4.4	86.1 (83.5–88.6)	78.5 (75.4–81.8)
	60–69 years	1,259	463 (36.8%)	8.5	4.2	80.9 (78.6–83.1)	70.2 (67.4–73.0)
	>=70 years	2,422	1,494 (61.7%)	3.8	3.1	57.0 (55.0–59.1)	40.0 (37.9–42.4)

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; N/A=not available; CI=confidence interval; <5=less than 5 events, results will be censored
*=restricted mean survival follow-up 5 years

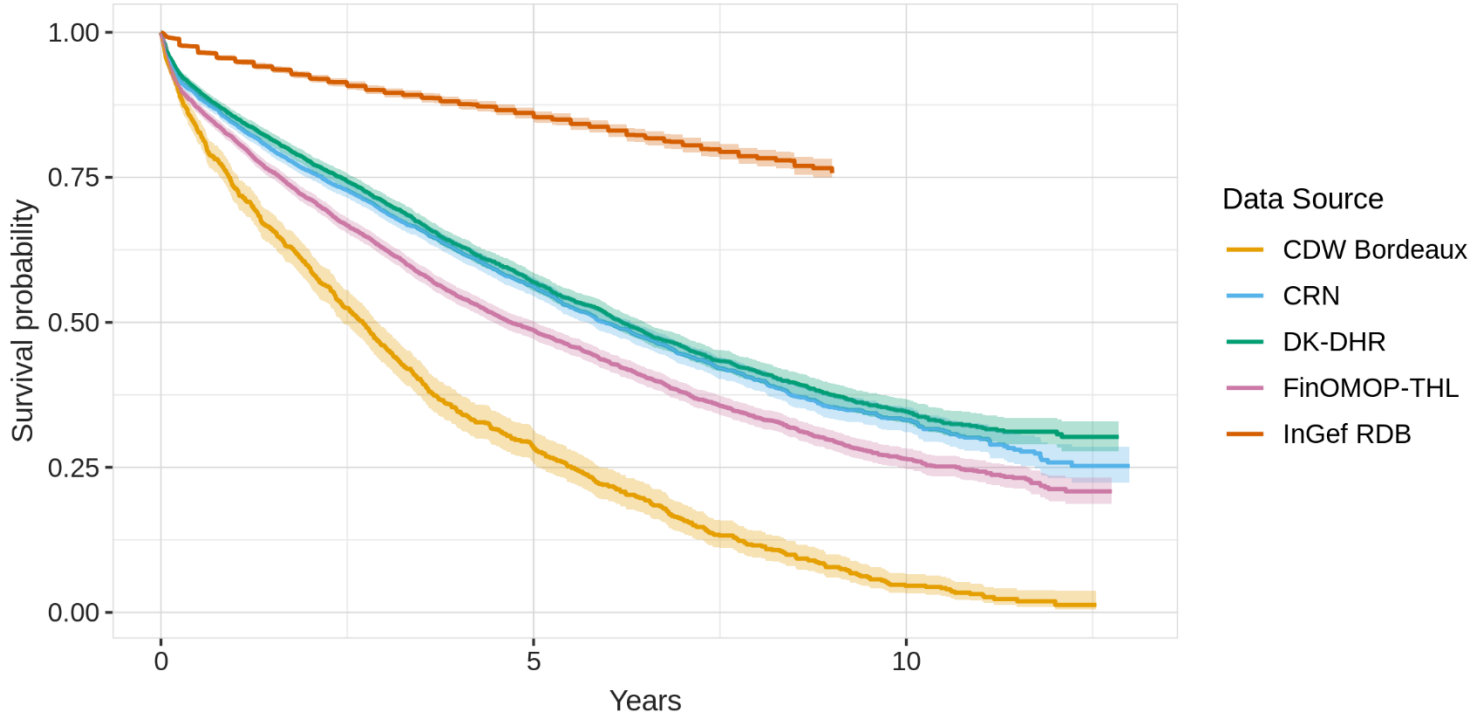


Figure 11. Kaplan-Meier overall survival of multiple myeloma individuals by data source.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway

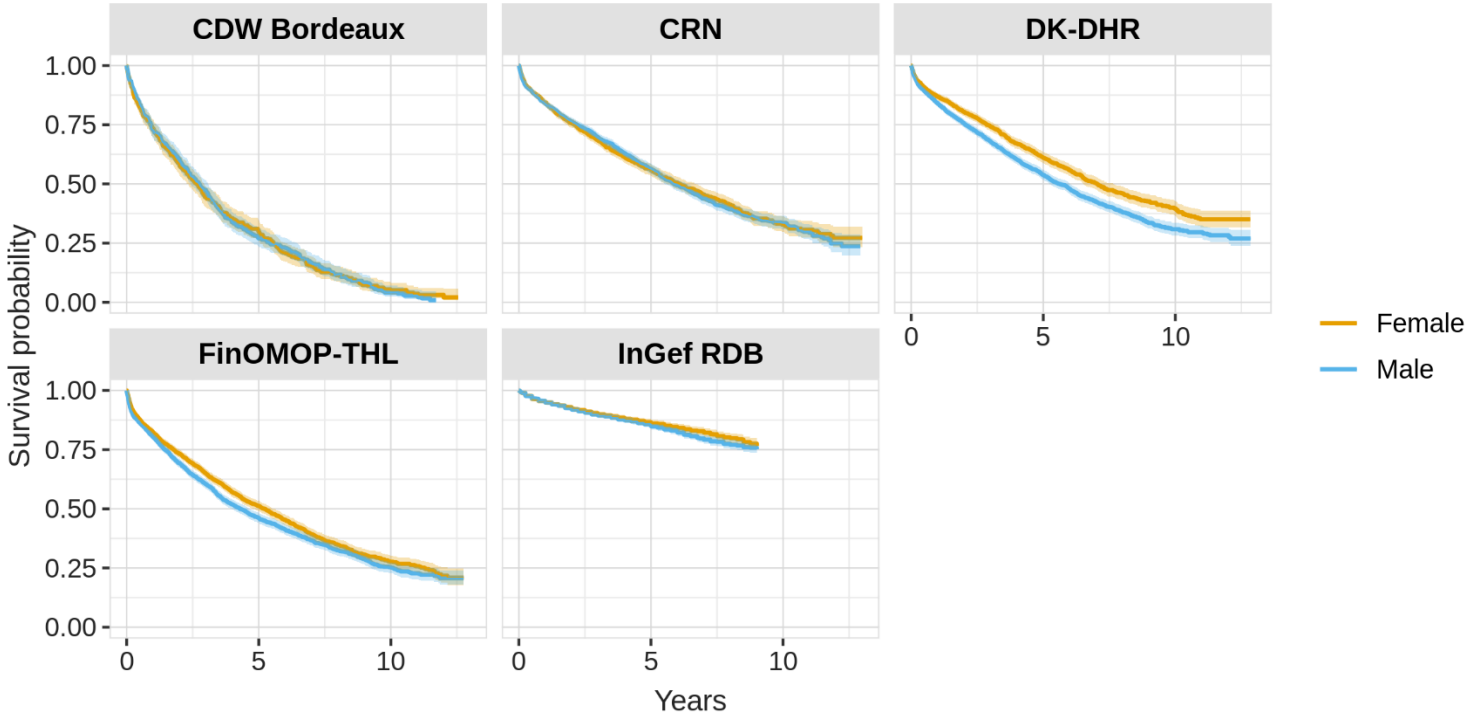


Figure 12. Kaplan-Meier overall survival of multiple myeloma individuals stratified by sex and data source.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway

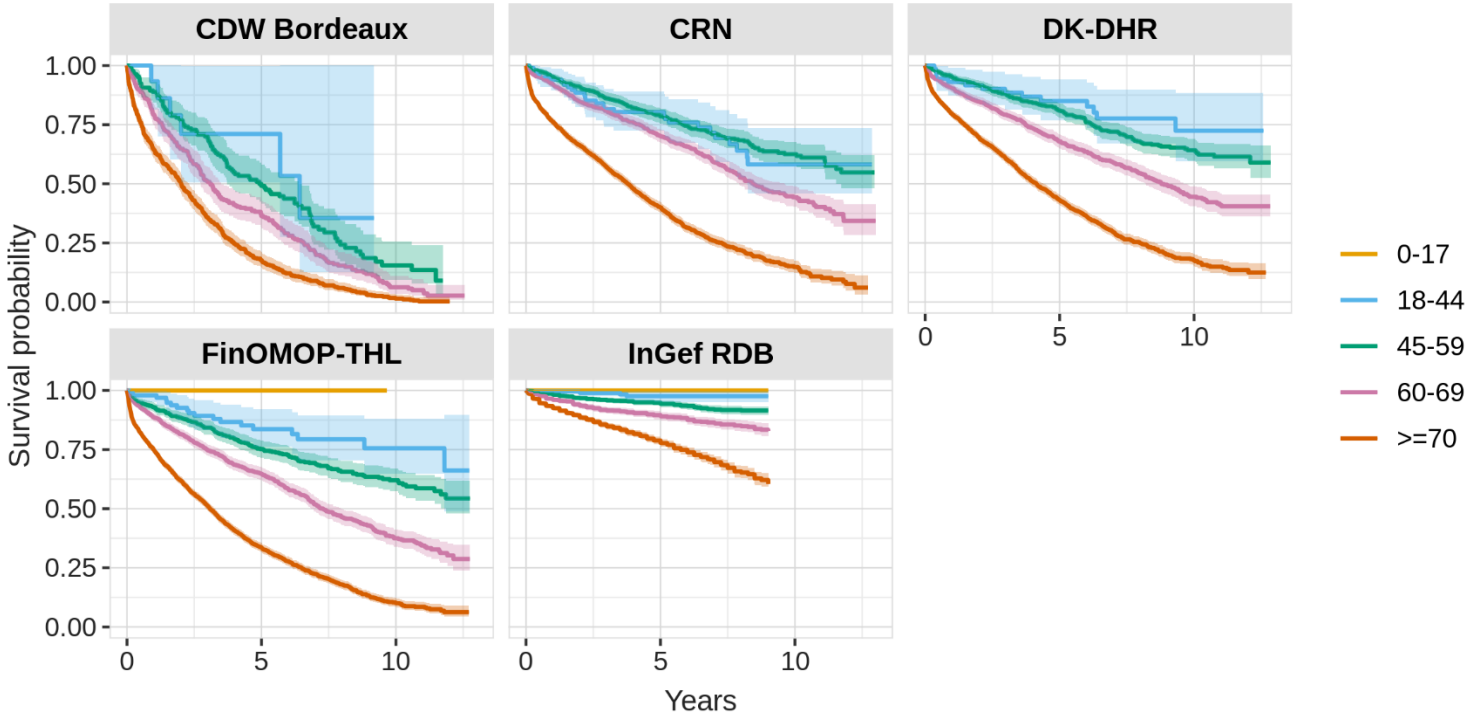


Figure 13. Kaplan-Meier overall survival of multiple myeloma individuals stratified by age categories and data source.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway.

10. DISCUSSION

10.1. Key results

In this study, we identified individuals newly diagnosed with multiple myeloma from 2012 and 2024 in 6 data sources from 6 countries (DK-DHR [Denmark], FinOMOP-THL [Finland], CDW Bordeaux [France], InGef RDB [Germany], HARMONY-MM [Spain], and CRN [Norway]).

Multiple myeloma patient characterisation
We identified 1,381 to 7,545 individuals with an incident multiple myeloma diagnosis (Cohort 1), with median age ranging from 67 to 72 years. Most individuals were 70 years of age or older (range 43.4% – 58.7%) and were mostly males (range 50.8% – 56.9%).

In the month before index date, the most frequent comorbidities were hypertension (12.0% – 44.3%), hyperlipidaemia (3.8% – 38.0%), pneumonia (2.4% – 38.9%), osteoarthritis (1.5% – 24.3%), and diabetes mellitus (3.9% – 18.5%). The least frequent comorbidities were schizophrenia, ADHD, HIV, Crohn's disease, and chronic liver disease.

In the month before index date the most frequently prescribed medications were agents acting on the renin-angiotensin system (2.0% – 34.3%), opioids (3.2% – 29.3%), antithrombotic agents (3.0% – 27.2%), lipid modifying agents (1.5% – 26.8%), and drugs for acid related disorders (2.7% – 24.4%).
The most frequently prescribed medications in the three months after index date aligned with the most frequent medications in the month before index. Additionally, within this time window, frequently prescribed medications also encompassed antineoplastic agents (16.7% – 60.9%), antibacterials (24.8% – 55.8%), and psycholeptics (10.5% – 33.0%). The least frequent medications were antipsoriatics and psychostimulants.

Multiple myeloma treatment characterisation
Across data sources, chemotherapies (cyclophosphamide, melphalan), proteasome inhibitors (bortezomib), glucocorticoids (dexamethasone), and immunomodulatory drugs (lenalidomide) were the most used treatment classes and treatments in the five years as after multiple myeloma diagnosis. Dexamethasone (24.1% – 63.2%), cyclophosphamide (10.9% – 35.5%), bortezomib (4.9% – 67.3%), lenalidomide (13.9% – 64.4%), and melphalan (8.6% – 34.8%) were the most used treatments in the five years after multiple myeloma diagnosis. Corresponding with glucocorticoids (24.1% – 63.2%), chemotherapies (15.8% – 35.3%), proteasome inhibitors (4.9% – 67.3%), and immunomodulatory drugs (13.9% – 64.4%) being the most prescribed treatment classes.

Treatment patterns:

Across most data sources, in the 5 years after multiple myeloma diagnosis, no recorded treatments in the treatment pathway analysis was the most frequent category, with the proportion of patents classified as having "no recorded treatment (None)" ranging from 42.2% in CRN to 65.1% in CDW Bordeaux. The exception was HARMONY-MM, where the proportion of individuals with no recorded treatment was only 1.7%. Generally, single-agent therapies without subsequent treatment (e.g. dexamethasone, melphalan, bortezomib, and lenalidomide) were most common in DK-DHR, FinOMOP-THL, and CDW Bordeaux. Nevertheless, HARMONY-MM differed, showing more frequent and complex sequences. Moreover, there were no clear differences in the frequency of treatments, treatment combinations, and treatment sequences when stratifying by sex or age-group. None of data sources had any individuals in the age group 0 to 17, and only CDW Bordeaux and HARMONY-MM had any individuals in the age group of 17–44. Stratification by stem cell transplantation did not provide meaningful results, due to low number of individuals, and were only observed as a treatment in HARMONY-MM and FinOMOP-THL.

Survival analysis:
Across data sources, 1,381 to 5,481 incident multiple myeloma individuals (Cohort 3) were identified,

median age ranged from 69 to 72 years, and most individuals were aged ≥70 years (48.8% – 58.7%), and were mostly males (50.8% – 56.9%).

The proportion of deaths during follow-up varied from 13.7% in InGef RDB to 67.2% in CDW Bordeaux, with intermediate values in FinOMOP-THL (56.8%), DK-DHR (49.6%), and CRN (48.1%). Median overall survival ranged from 2.7 years in CDW Bordeaux to 6.2 years in DK-DHR (4.7 years in FinOMOP-THL; 6.0 years in CRN) and was not reached in InGef RDB. Restricted mean survival time at 5 years ranged from 2.7 years in CDW Bordeaux to 4.5 years in InGef RDB (3.7 years in DK-DHR; 3.7 years in CRN; 3.4 years in FinOMOP-THL). Survival probabilities varied substantially, with 3-year survival ranging from 46.0% (CDW Bordeaux) to 89.6% (InGef RDB) and 5-year survival from 28.4% (CDW Bordeaux) to 85.9% (InGef RDB) (e.g. DK-DHR: 70.7% and 56.9%; CRN: 69.1% and 56.1%; FinOMOP-THL: 62.6% and 48.6%). Females generally showed slightly higher survival than males (e.g. 5-year CDW Bordeaux: 29.8% vs 27.2% DK-DHR: 61.1% vs 53.8%; FinOMOP-THL: 51.2% vs 46.2%; CRN: 56.2% vs 56.6%; InGef RDB: 86.4% vs 85.6%). Survival declined markedly with age, with 5-year survival exceeding 70–90% in younger individuals (e.g. up to 94.8% in InGef RDB, 80.9% in DK-DHR) and ranging from 17.8% to 78.6% among those aged ≥70 years.

10.2. Strengths and limitations of the research methods

This study was based on routinely collected healthcare data; therefore, data quality issues needed to be considered. In particular, the identification of multiple myeloma individuals and the recording of comorbidities may have varied across data sources. While relatively few false positives were expected, false negatives were more likely, especially in data sources without patient-level linkage to secondary care data. Nevertheless, data sources from or linked to cancer registries (e.g. CRN) were considered to contain high-quality data on cancer diagnoses.

The recording of events used for patient characterisation may also have varied across data sources. In addition, in data sources containing information on cancer treatment, the recording of treatment use may have been incomplete. This limitation was particularly relevant for newly introduced therapies, such as CAR T-cell treatments, which may not have been fully mapped to the OMOP Common Data Model. Stem cell transplantation, for example, was only present in FinOMOP-THL and HARMONY-MM, with very low numbers. This made any analysis or stratification by ASTC difficult and did not provide meaningful results.

Treatment patterns analysis

Due to the dependence of the *TreatmentPatterns* package on the parameterisation of the analysis settings, and the variation between the registration of treatments per data sources (i.e. duration, construction of drug exposures or episodes), results were difficult to interpret and not comparable between data sources. As a results of the settings, most of the results did not provide logical sequences and expected combinations (based on guidelines) of treatments. For example, most data sources only had single-agent therapies without subsequent treatments, and a combination of bortezomib+dexamethasone+lenalidomide+melphalan+prednisone+thalidomide was seen in HARMONY-MM. Moreover, the duration of treatments differed between data sources, for example, all treatments in CDW Bordeaux had a duration of 1 day, while all durations in InGef RDB were 30 days. Therefore, we imputed all treatments lower than 30 days to be 30 days. In future studies it would be beneficial to not have to impute durations and to define the *TreatmentPatterns* settings, after thorough testing, separately per data source. Having a tailor-made setting per data source, as well as data sources mapping the actual regimens to a single concept, would likely improve the quality and usability of the *TreatmentPatterns* results. Furthermore, there was a discrepancy between the number of individuals and treatments in the multiple myeloma treatment characterisation (objective 2) and the *TreatmentPatterns* results. In *TreatmentPatterns*, many individuals were excluded due to the absence of treatment registrations, and certain treatments were also absent in treatment patterns, as they were part of sequences and combinations that were not present in more than 5 individuals and were therefore censored. Lastly, due to the aforementioned limitations in event recording and the *TreatmentPatterns* package, there was no clear

information on the lines of therapy. To conclude, even with extensive testing and tailor-made settings per data source, it might be that *TreatmentPatterns* is currently not well enough equipped to provide meaningful results for complex oncology treatment regimens such as the multiple myeloma treatments.

Data source-specific limitations:

CRN:

No information on cancer medication use was only available from 2019 onwards; therefore, detailed records of treatments and treatment sequences were limited to the period from 2019 onwards. Furthermore, no data were available on non-cancer-related comorbidities or comedications.

DK-DHR:

Only histologically validated cancer records were available from 1 January 1995 to 31 December 2022; therefore, for survival analyses, individuals diagnosed within this period could only be followed up until 31 December 2024.

InGef RDB:

The analyses of treatment patterns (objectives 2 and 3) were not conducted, as treatment information was limited to outpatient prescriptions at the ingredient level. Inpatient treatments were captured using procedure codes, which generally described the type of chemotherapy without specifying individual drug components, limiting the identification of treatment combinations. Furthermore, not all mortality data in InGef RDB was complete up until the end of 2024, and date of death is registered to the end of the quarter, which both have impact on the survival analysis results and therefore does not seem complete fit for purpose.

CDW Bordeaux:

CDW Bordeaux indicated that they might not have captured all treatments, since individuals are also treated in a specialised cancer centre that is not directly linked to their hospital data warehouse, and thus the treatments administered there are not captured in their data source. Moreover, another CDW Bordeaux limitation could be that they only capture hospital data. It is possibly that only individuals in more severe conditions that require hospitalisation are recorded in the data, impacting the survival analysis.

HARMONY-MM:

HARMONY-MM were removed from the survival analysis (objective 4), because the follow-up and information on mortality data was not complete, which led to unreliable results.

10.3. Interpretation

In this study, we identified a total of 31,657 individuals with a new multiple myeloma diagnosis between 2012 and 2024 across 6 data sources. In line with previous studies, we show that multiple myeloma individuals are more often men and older than 70 years of age.[3, 4, 11] Previous studies and statistics have shown that there are approximately 40,000 to 50,000 individuals diagnosed with multiple myeloma in Europe annually; however, these numbers are difficult to compare to the numbers in this study, as this study does not encompass all countries in Europe, and the study period spans more than one year.[12, 13]

Across all data sources, the most frequent comorbidities prior to index date were hypertension, osteoarthritis, hyperlipidaemia, and diabetes mellitus, which are known to be some of the most prevalent comorbidities in the general population, especially older individuals.[14-18]

In this study, the most frequent comedications prior to index date align with the most common comorbidities, as agents acting on renin-angiotensin system, lipid modifying agents, and opioids are often used in hypertension, hyperlipidaemia, and osteoarthritis. Moreover, in the three months after diagnosis,

the use antineoplastic agents, antibacterials, and psycholeptics increased greatly. This seems in concordance with the situation of a newly diagnosed multiple myeloma patient, with increased infection risk, and also increased psychiatric symptoms in new individuals.[19, 20].

In this study, the most common treatment classes and treatments following diagnosis were chemotherapies (cyclophosphamide, melphalan), proteasome inhibitors (bortezomib), glucocorticoids (dexamethasone), and immunomodulatory drugs (lenalidomide). This is in line with the recommendations in the guidelines for multiple myeloma individuals.[4] These results are in agreement with the previous DARWIN EU® study into multiple myeloma, performed in data sources from Estonia, France, Germany, the Netherlands, and Spain. That study also showed that chemotherapies, glucocorticoids, and proteasome inhibitors were among the most frequently used treatments.[21]

In the treatment patterns analysis, generally single-agent therapies without subsequent treatment (e.g. dexamethasone, melphalan, bortezomib, and lenalidomide) were the most common treatments recorded in almost all data sources. The exception was HARMONY-MM, which had treatment combinations as the most frequently used treatments, namely cyclophosphamide+dexamethasone+lenalidomide, cyclophosphamide+dexamethasone+thalidomide, and bortezomib+cyclophosphamide+dexamethasone. All of the most common treatment (combinations) consist of treatments which are recommended to be part of first line therapy according to the guidelines.[4] Nevertheless, in HARMONY-MM, only the combination of bortezomib+cyclophosphamide+dexamethasone is mentioned exactly in the guidelines.[4] The absence of more expected combinations (based on guidelines) across all data sources is likely the result of the variation in treatment registration across data sources and the limitations of the *TreatmentPatterns* package, especially with more complex cancer regimens, which currently seem to be at high risk of bias. Aiming for more standardisation in duration among data sources and specific settings per separate data source could be part of the solution to better capturing combinations and sequences. Other methods, such as the OHDSI *Artemis* package, could also provide assistance in capturing the treatment regimen from the data sources.[22]

Overall survival in this study appears broadly consistent with improvements reported over the past two decades, driven by the introduction of novel therapies, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. Population-based studies have shown that 5-year survival for multiple myeloma has increased from approximately 30% in the early 2000s to over 50–60% in more recent cohorts.[23-25] The 5-year survival ranged from 28.4% (CDW Bordeaux) to 85.9% (InGef RDB), which is in line with the current survival 5 year survival estimates rates of around 60% for multiple myeloma and the overall survival estimates of the Global Cancer Observatory, and also largely in agreement with the 5-year survival range in the previous DARWIN EU® study (49% to 78%).[21, 26-28]

Consistent with prior evidence and the numbers in the previous DARWIN EU® study, females demonstrated slightly better survival compared to males.[21] This modest survival advantage has been reported in several studies and may be related to differences in comorbidity burden, treatment patterns, or biological factors, although the underlying mechanisms remain incompletely understood.[29]

A strong age gradient in survival was observed, with markedly poorer outcomes in individuals aged ≥70 years. This finding aligns with previous literature showing that older individuals have reduced survival due to frailty, higher comorbidity burden, and lower likelihood of receiving intensive treatments such as stem cell transplantation Stem Cell Transplantation.[30, 31] In contrast, younger individuals exhibited substantially higher survival, reflecting better treatment tolerance and access to more aggressive therapeutic strategies.

Lastly, there was quite some heterogeneity in the results of the survival analysis between data sources. This does not seem to reflect the actual difference in survival of multiple myeloma individuals across the different countries, but rather the differences in data source and setting. For example, CDW Bordeaux only has hospital data, and possibly more severe individuals require hospitalisation are captured and therefore

have a lower survival. Moreover, in InGef RDB there was a higher survival probability than other data sources, which might have been a result of some incomplete data until the end of 2024 and the exact date of death not being available, but set to the end of the quarter.

10.4. Generalisability

This study included 6 data sources across several European countries, including HARMONY-MM, which is a multi-country data source, covering different data source types, such as cancer registries, hospital data, and administrative claims, and capturing complementary aspects of the healthcare pathway.

While the findings may be broadly representative of multiple myeloma individuals in the included settings, they should not be fully generalised to all European countries or regions outside Europe. Differences in population characteristics, healthcare systems, access to treatments, and adoption of novel therapies, as well as variation in data capture and completeness, may lead to heterogeneity across data sources and limit generalisability.

11. CONCLUSION

In this study, we identified a total of 31,657 individuals with a new multiple myeloma diagnosis between 2012 and 2024 across Europe. In agreement with previous findings, the most frequent comorbidities in the month prior to the date of diagnosis were hypertension, hyperlipidaemia, osteoarthritis, and diabetes mellitus, while the most frequent medications were agents acting on the renin-angiotensin system, lipid modifying agents, opioids, antibacterials, and psycholeptics.

Regarding multiple myeloma treatments, in line with current guidelines the most frequently used treatment classes were chemotherapies, proteasome inhibitors, glucocorticoids, and immunomodulatory drugs. Among the most frequent treatments were bortezomib, lenalidomide, cyclophosphamide, and dexamethasone. Nevertheless, the *TreatmentPatterns* package at this moment is not capable of reliably capturing the expected oncology treatment regimens and combinations, which made interpretation and comparison of the results not feasible. The settings and ability to capture (complex oncology) treatments need to be improved before *TreatmentPatterns* can provide reliable expected regimen and combinations results. Overall survival in this study appears broadly consistent with improvements reported over the past two decades, driven by the introduction of novel therapies, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies.

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13. ANNEXES

ANNEX I. Description of data sources

Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data Analytics Centre (DAC)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content /source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have unique identifiers used to link datasets.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g. non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.

#	Section	Description
12	Limitations	DK-DHR has the following limitations, which may be relevant confounders for certain complex Darwin EU studies: - We lack information on key socio-economic status (SES) factors, such as occupation, education, and income. These variables may be important for analysis in some studies. - We only have complete data on lifestyle factors (such as smoking status and weight) for pregnant women. - We have no information on patient contacts in primary care (visits to the GP). Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy. Stillborn children will not have any records in our CDM. This means that e.g. birth length of stillborns is not recorded.
13	Main references	Schmidt M, Schmidt SAJ,Adelborg K,Sundbøll J,Laugesen K,Ehrenstein V,Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finnish Care Register for Health Care-THL (FinOMOP-THL)

#	Section	Description
1	Data source identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	Finnish Institute for Health and Welfare (THL) The Department of Data and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – General Practioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and other (specify). THL maintains health registers that cover both public and private, primary, and specialised inpatient, urgent and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the Care Register for Health Care (TerveysHilmo) has covered both public outpatient and inpatient specialized care and private inpatient care. Since 2009, the Finnish National Vaccination Register has covered all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good to complete from 2020 onwards. Since 2011, the Register of Primary Health Care Visits (AvoHilmo) has covered public primary care. Since 2020, the register has also covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register. The register itself covers all laboratory confirmations for around 70 specific microbes from 1995 onwards, but only COVID-19 has currently been mapped to the CDM. The CDM also includes prescription records from multiple different sources. Both Care Register for Health Care and Register of Primary Health Care Visits contain very basic prescription data recorded during health care encounters that include just the ATC-code and trade name of medication. More comprehensive prescription data from Kanta Prescription Centre, maintained by Social Insurance Institution of Finland (Kela), has been integrated into the CDM since its 2024 release. The Kanta Prescription records are based electronic prescriptions, which were adopted by most public health care providers in 2010 and by most private providers by 2017.

#	Section	Description
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL (Kela in the case of Kanta Prescription Centre).
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates.
7	Data content /source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ICPC-2, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveydenhuollon erikoisalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (data source specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	All drug records in the CDM are currently based on prescriptions. Kanta Prescription Centre also includes information on drug dispensings, but these have not currently been converted into OMOP CDM. Depending on the type of the medication, a single prescription can be for up to two years dosage of the drug. This means a patient can have up to two-year breaks between observations while actively using the drug. Observation of a prescription also does not mean that the patient necessarily bought or used the medication. The CDM does not currently have meaningful end dates or days of supply for drug exposure. This information is not available for Care Register for Health Care or Register of Primary Health Care Visits, and for Kanta Prescription Centre it is only available in unstructured, free-form format that has not been converted into OMOP CDM. The source system for prescription drug data is only available to the DP until Dec-2023, therefore drug_exposure records from this source are only available in that time range. Not all private health care records are covered for the CDM's entire follow-up time from 2011 onwards. For Register of Primary Health Care Visits and Finnish National Vaccination Register, records from private health care have been available from 2020 onwards. For Kanta Prescription Centre, the coverage of private health care records has been good from 2017 onwards. The inclusion of private health care mainly presents itself as an increase in the number of observations, meaning that it has to be accounted for when interpreting any time series data from the CDM.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveyden ja hyvinvoinnin laitos (2019):
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187;https://catalogues.ema.europa.eu/data-source/1111191 Website: https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions;https://www.kanta.fi/en/research-and-knowledge-management

Clinical Data Warehouse of Bordeaux (CDW Bordeaux)

#	Section	Description
1	Data source identification and country	CDW Bordeaux (Clinical Data Warehouse of Bordeaux University Hospital) Nouvelle-Aquitaine, France
2	Data partner information section	CHU DE BORDEAUX - DIRECTION GENERALE Gironde / Nouvelle-Aquitaine
3	Coverage and timespan	Data collection since: 2005 Extent: Regional. It covers the population of Bordeaux metropolitan area, and possibly beyond, as the health care centre for referrals and expertise for the Nouvelle Aquitaine region. The database contains data from 2005 onwards.
4	Healthcare setting / type of data	Secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and claims data. The database currently captures information about patient demographics, visit details, conditions, procedures, drugs, measurements, and mortality.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Inpatient hospital billing systems, and Biobank. The integrated data is extracted from the hospital production information system via a real-time research database. The data is then processed and quality controlled by a team dedicated to maintaining the database. Internal evaluations were carried out to ensure consistency between the research database and the patient bedside software.
6	General representativeness	This is the 6th largest metropolitan area in France, and CHUBX is the largest hospital in the region. More than 75% of the patients administered to Bordeaux university hospital reside in the Gironde departments, with almost 50% coming directly from the Bordeaux metropolitan area. The hospital also captures additional cases from Nouvelle-Aquitaine region.
7	Data content /source coding	Diagnosis source data is coded in ICD-10 terminology. Procedures are coded in CCAM (French terminology). Laboratory measurements are coded in local terminology and partially mapped to LOINC. Drugs are coded through a local terminology and then mapped to UCD (French terminology), as well as ATC codes.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. We use the hospital's unique identifier to generate the patient identifier in OMOP. If two identities are merged at the hospital, the merge is taken into account in the CDW. An automatic (hourly) detection of suspected duplicated identities has been implemented at the hospital since 2020, with merging of duplicated identities by a specialized team. Identities since 2015 were processed retrospectively. Thus, the rate of identity duplication in the database is low, especially since 2015.
9	Quality control (data source specific)	- The integrated data comes from the hospital production information system through a real-time replicated database. Consistency evaluations between the replicated database and the production system are performed by the technical team in charge of maintaining the replicated database. - In the same way, consistency checks are performed between the replicated database and the data integrated into the i2b2 CDW. In addition, dashboards enable monitoring the data integrated into the i2B2 CDW, in particular by controlling the amount of data available over time, and its evolution, according to the various data sources. - An internal evaluation was carried out to ensure the consistency between the data integrated into i2b2 and the data available in the software used at the patient's bedside. In addition, many use cases were performed on the i2b2 CDW, with return to the patient chart and comparison of the data integrated into i2b2 and the data available in the care file.
10	Linkage	Death certificates (without the cause of death).

#	Section	Description
11	Vital status	The database is linked to the French death registry.
12	Limitations	CDW Bordeaux is limited to events captured in the hospital setting and thus does not include patient events not treated by the hospital (e.g. rare cancers). Patient events that are not included in CDW Bordeaux are rare disease treatments or specialist events that occur outside of CHUBX.
13	Main references	Cossin S, Diouf S,Griffier R,Le Barrois d'Orgeval P,Diallo G,Jouhet V "Linkage of Hospital Records and Death Certificates by a Search Engine and Machine Learning." JAMIA open (2021): 33709061
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111112 Website: https://www.chu-bordeaux.fr/

InGef Research Database (InGef RDB)

#	Section	Description
1	Database Identification and country	InGef Research Database (InGef RDB) Germany (DE)
2	Data partner information section	InGef – Institute for Applied Health Research Berlin GmbH InGef is a research service provider within the German statutory health insurance system.
3	Coverage and timespan	The Research Database contains approximately 10.5 million insured persons from 50 of the 94 statutory health insurances in Germany (as of Oct 2025). All individuals in the research database are included in the OMOP CDM. Due to data protection laws for personal data in Germany, only the last 10 years of data are available in the RDB and thus in the OMOP CDM.
4	Healthcare setting / type of data	In general, the data in the RDB reflects most of the health services paid for by statutory health insurances. In the OMOP CDM, the health services are reduced to primary and secondary care. This means that treatments by GPs and specialists (e.g. paediatricians), prescription medicines dispensed by pharmacies, hospital inpatient and outpatient care, as well as information about all insured individuals are included. The following data elements are presented in the OMOP CDM: demographic information, diagnoses, procedures, dispensing drugs and advanced therapy medicinal products, vaccinations, pregnancy data (via diagnoses and procedures) and contraception.
5	Data collection process	In Germany, data exchange between medical service providers and statutory health insurances is organized via central data collection centers. In addition to receiving and forwarding data, these centers also store data and provide access to third parties under strict regulations in data warehouses. The RDB contains selected, condensed and anonymized information from one of these data warehouses. Data sovereignty remains with the individual health insurance companies.
6	General representativeness	The RDB covers about 11% of the German population and is comparable to the German population in terms of the distribution of age and sex. Most health insurances that contribute to the RDB have nationwide coverage, meaning that the database covers all regions of Germany. Since almost all services covered by statutory health insurances are specified in national legislation, healthcare provision all over Germany is well represented in the RDB. Additionally, in Germany it is very common to stay with the same health insurance throughout life, which results in a good longitudinal coverage over the entire period of 10 years.
7	Data content /source coding	The coding in the research database complies with national classification and coding rules in Germany. Diagnoses are coded according to ICD-10-GM. Inpatient and outpatient surgeries or procedures are recorded as OPS codes (German classification of Operations and Procedures). The dispensing of drugs in pharmacies is recorded using the PZN (pharmaceutical registration number). For drugs that miss a PZN-to-

#	Section	Description
		RxNorm mapping, the ATC code is used instead. In some cases, dispensed drugs can be coded using OPS codes (e.g. in hospitals) or EBM codes (fee schedule for outpatient treatments).
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network.
9	Quality control (database specific)	The data transmitted by healthcare providers complies with the standardized requirements and formats of the Association of Statutory Health Insurances (GKV-SV). Before being imported into the research database, the data elements are checked for data format, completeness and plausibility. After each update of the research database, various counts are compared with the previous update to verify completeness. Due to the anonymity of the database, direct validation of the data (e.g. using medical records as the gold standard) is not possible.
10	Linkage	Due to the anonymization of the source data, linkage is not possible.
11	Vital status	The date of death is recorded as the last day of the quarter in which the death occurred (i.e. 30/31st of Mar/Jun/Sept/Dec) as reported to the health insurance (no linkage to death registry). The cause of death is not available.
12	Limitations	Ambulatory diagnoses and procedures are summarised in the source on a quarterly basis. Both are mapped to the observation table with the date set to the last day of the respective quarter (i.e. 30/31st of Mar/Jun/Sept/Dec) and the concept “History of event within 3 months” (observation_concept_id 1340222), with the actual diagnosis or procedure concept_id recorded in the field “value_as_concept_id”. There is no vocabulary for the German pharmaceutical product codes (PZN). A direct source-to-standard-mapping has been done manually by InGef but is incomplete. The drug exposure duration is unknown. Following OMOP conventions, the end date is always set to dispensing date + 29. Outpatient and inpatient procedures are recorded as OPS codes (German Procedure Classification), for which the vocabulary is incomplete.
13	Main references	Andersohn F, Walker J "Characteristics and external validity of the German Health Risk Institute (HRI) Database." Pharmacoepidemiology and drug safety (2016): PMID 26530279 | doi: 10.1002/pds.3895 Ludwig M, Enders D, Basedow F, Walker J, Jacob J: Sampling strategy, characteristics and representativeness of the InGef research database. Public Health 2022. doi: 10.1016/j.puhe.2022.02.013
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111207 Website: https://www.ingef.de/en/

Cancer Registry Norway (CRN)

#	Section	Description
1	Data source identification and country	CRN (Cancer Registry Norway) Norway
2	Data partner information section	Norwegian Institute of Public Health Cancer Registry of Norway
3	Coverage and timespan	Data collection since: 1953 Extent: Nation-wide. The catchment area is all of Norway. The approximate population is around 5.6 Million. The

#	Section	Description
		cancer-specific clinical registries have collected nationwide data since the mid-2010s and are continuously updated.
4	Healthcare setting / type of data	Secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnoses, pathology, lab reports, clinical notifications, deaths, procedures, measurements, drug prescription, and dispensing. The CRN also includes data from various clinical cancer registries for specific cancer types, providing extended information on diagnosis, treatment and follow-up. For example, there are clinical registries for lung, breast, gynecological (ovarian, cervical), prostate, melanoma, sarcoma, and other cancers, which supplement the main incidence registry.
5	Data collection process	Registries. Sources of information for the cancer registry are: clinical notifications from hospitals and specialists (public and private), pathology reports from pathology departments (public and private), radiation therapy and SACT-information from hospitals, data from the Norwegian Patient Registry, the Population Registry and the Cause of Death Registry, and PREM and PROM from patients. The data sources send data to the Cancer Registry, mainly in electronic form. Data is received and pre-processed before they are further enriched and processed by the data controllers, following a standard SOP for data quality checks. In addition, strict quality assessment procedures are carried out to manually evaluate the quality of the information regarding general statistics and cancer-specific domain data.
6	General representativeness	The Cancer Registry of Norway is a population-based cancer registry covering the entire Norwegian population. Registration of cancer patients in the CRN is mandatory in Norway, with no possibility for opt-out. The registry therefore includes all cancer patients (including premalignant cases and some benign tumors of the CNS) and provides a comprehensive representation of the national cancer population.
7	Data content /source coding	ICD03 and ICD10 are used for topography/morphology/disease of the cancer diagnosis. Some examples of other used classifications are ISUP, ECOG, TNM and SNOMED. The cancer registry also has extensive in-house classifications developed through over 70 years of cancer registration. Drugs prescriptions and dispensing is recorded with ATC codes, indications for the prescriptions are recorded with ICD10 codes. All information on the content of the CRN can be found in our online metadata-catalogue at https://metadata.kreftregisteret.no
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. All patients have 11-digit unique national identifiers for identification and linkage.
9	Quality control (data source specific)	The CRN follows a strict quality assurance regime, including validation of all incoming data and a rule engine that enforces international, national, and internal standards uniformly. Manual checks are performed for specific cancer types to identify unlikely data, such as melanoma cases with tumour diameters exceeding 2 cm. Data quality is documented in scientific articles and annual statistics, including metrics like morphological verification rate, estimated completeness, proportion of cases identified only via death certificates, and male-to-female ratios.
10	Linkage	Every citizen has a unique personal identifier, and via this identifier, patients can be linked to other national data sources.
11	Vital status	Vital status is regularly updated in the Cancer Registry of Norway through linkage with the National Population Register. Information on cause for death is obtained from the Cause of death Registry through linkage.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.

#	Section	Description
13	Main references	Larsen IK, Småstuen M,Johannesen TB,Langmark F,Parkin DM,Bray F,Møller B "Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness." European journal of cancer (Oxford, England : 1990) (2009): 19091545
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111128 Website: https://www.kreftregisteret.no/en/

HARMONY-Multiple Myeloma (HARMONY-MM)

#	Section	Description
1	Data source identification and country	HARMONY Platform (HARMONY Big Data Platform)
2	Data partner information section	HARMONY Alliance Foundation Executive Office
3	Coverage and timespan	Data collection since: 2018 Extent: Other. The HARMONY Big Data Platform does not have a defined catchment area as it is composed of separate sources from all over the world.
4	Healthcare setting / type of data	Other (specify). The included data depends on the data source and covers at least inpatient hospital care.
5	Data collection process	Inpatient hospital electronic health records, and Registries. The data sets are provided by HARMONY Alliance Partners and Associated Members. The anonymous patient data sets at the Big Data Platform are collected securely following all legal and ethical requirements.
6	General representativeness	HARMONY is a network has a worldwide coverage for patients with haematological malignancies, with most cases from Europe. For more details on coverage see https://harmony-alliance.eu/collaborative-research/#network to check on the Data Partners and the diseases where they have contributed records.
7	Data content /source coding	HARMONY includes standard disease classifications such as the European Group for Immunological Characterization of Acute Leukemia (EGIL), World Health Organization (WHO) classifications of the myeloid neoplasms, response criteria like International Working Group (IWG) response criteria in myelodysplasia, European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia or Ann Arbor-Cotswolds response criteria for NHL, QoL questionaries, among others.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In HARMONY each patient has a unique ID within the platform. However, if the data from the same patient is shared by two organisations (a hospital and a national registry, for example), it would be registered twice with a different identifier. HARMONY is working on approaches to check the baseline information recorded for each patient in order to detect these potential "duplicates". This is a work in progress and still requires testing and validation.
9	Quality control (data source specific)	Each data source, before being mapped into OMOP, is evaluated in two stages: 1) In the first stage, the completeness and type of data supplied it is evaluated. It considers the technical requirements for data sources, the variables representing the required data for the specific HM and research project, and the pre-defined minimum essential data requirements. The original data sources must comply with the technical and clinical requirements of data format, including information about the fields, and data catalogues and scales employed. 2) In the second stage, it is verified that the individual files can be read and contain the fields as described in the data dictionary, that fields are respectful of the indicated data type, categorical

#	Section	Description
		values match the description, rows with null values are imported correctly, date fields are reasonable, and there is a correct distribution of value of key fields. During these quality checks data are returned to the data provider if they are of insufficient quality.
10	Linkage	No linkage possible.
11	Vital status	Depending on the original source of data, the death record comes from the hospital or national registry.
12	Limitations	As the HARMONY Platform combines data from multiple partners that can each have a different capture system. This makes the data, also within one malignancy, very heterogneous; per partner the variables collected can be different, as well as the time period covered. Time period covered is study-specific and not all data sources are updated with new information.
13	Main references	Sobas MA, Turki AT,Ramiro AV,Hernández-Sánchez A,Elicegui JM,González T,Melchor RA,Abáigar M,Tur L,Dall'Olio D,Sträng E,Tettero JM,Castellani G,Benner A,Döhner K,Thiede C,Metzeler KH,Haferlach T,Damm F,Ayala R,Martínez-López J,Mills KI,Sierra J,Lehmann S,Porta MGD,Mayer J,Reinhardt D,Medina RV,Schulze-Rath R,Barbus M,Hernández-Rivas JM,Huntly BJP,Ossenkoppele G,Döhner H,Bullinger L "Outcomes with intensive treatment for acute myeloid leukemia: an analysis of two decades of data from the HARMONY Alliance." Haematologica (2025): 39506894
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111137 Website: https://www.harmony-alliance.eu/

ANNEX II. Supplementary figures

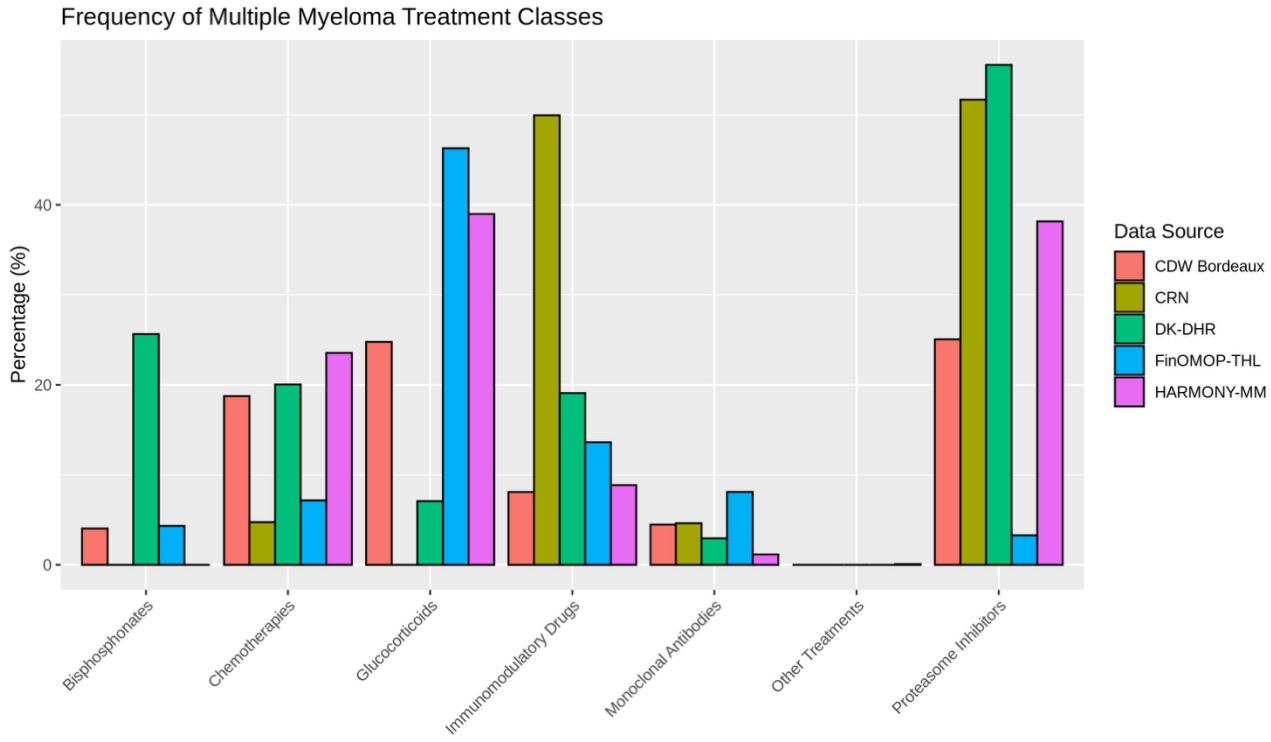


Figure S1. Frequency of use of multiple myeloma treatment classes from 1 to 90 days after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

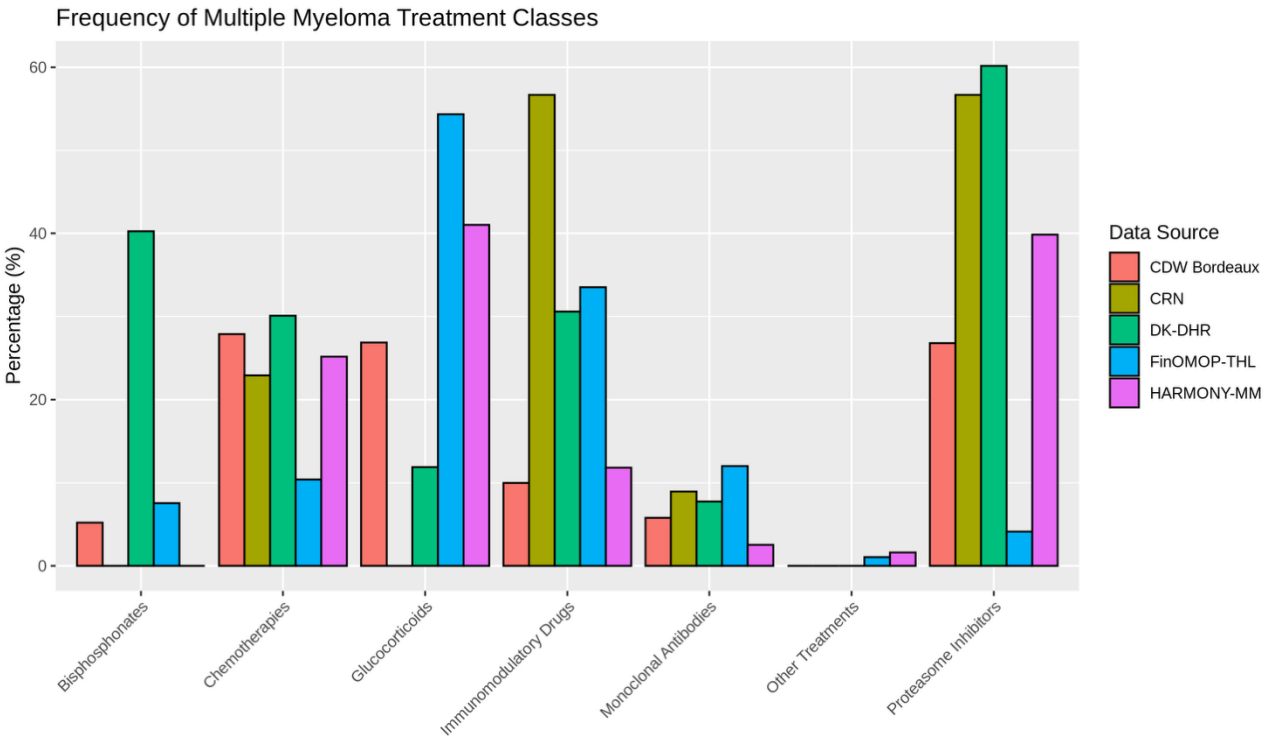


Figure S2. Frequency of use of multiple myeloma treatment classes from 1 to 365 days after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

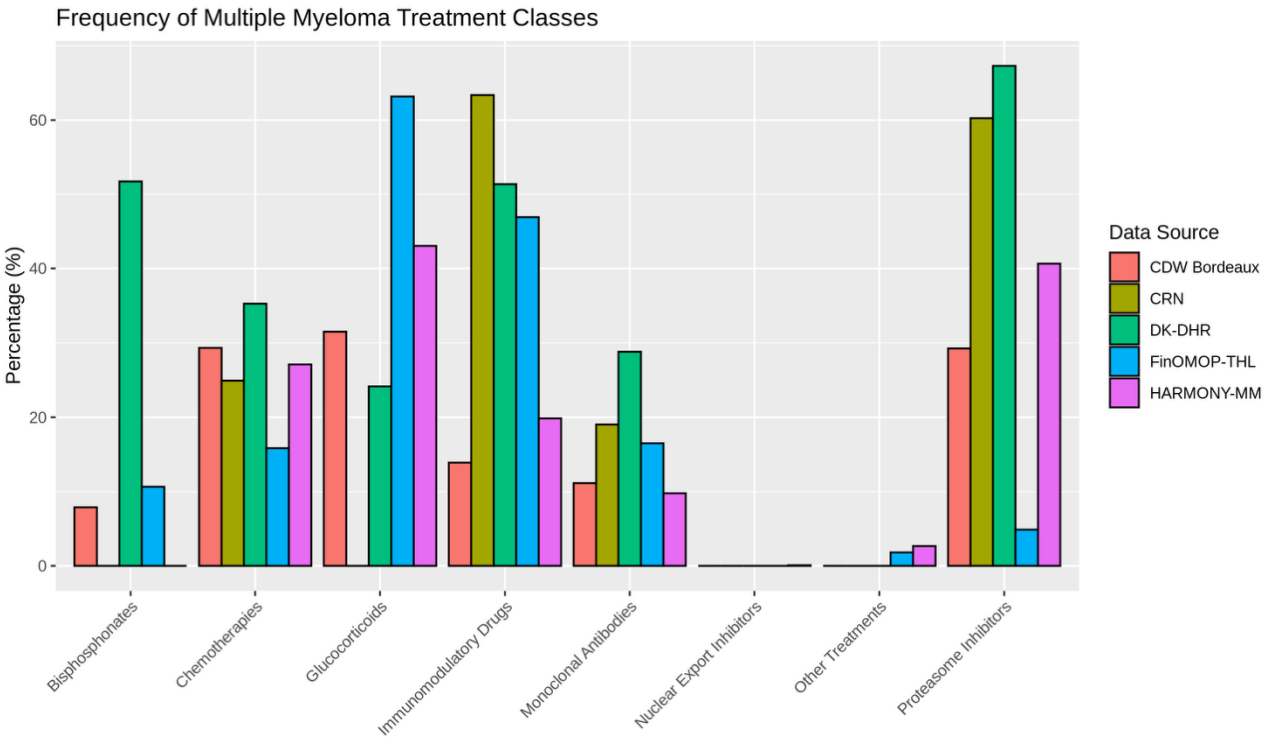


Figure S3. Frequency of use of multiple myeloma treatment classes from 1 day to 5 years after diagnosis.

DK-DHR=Danish Data Health Registries; FinOMOP-THL=Finnish Care Register for Health Care - THL; CDW Bordeaux=Clinical Data Warehouse of Bordeaux; InGef RDB=InGef Research Database; CRN=Cancer Registry Norway; HARMONY-MM=HARMONY-Multiple Myeloma

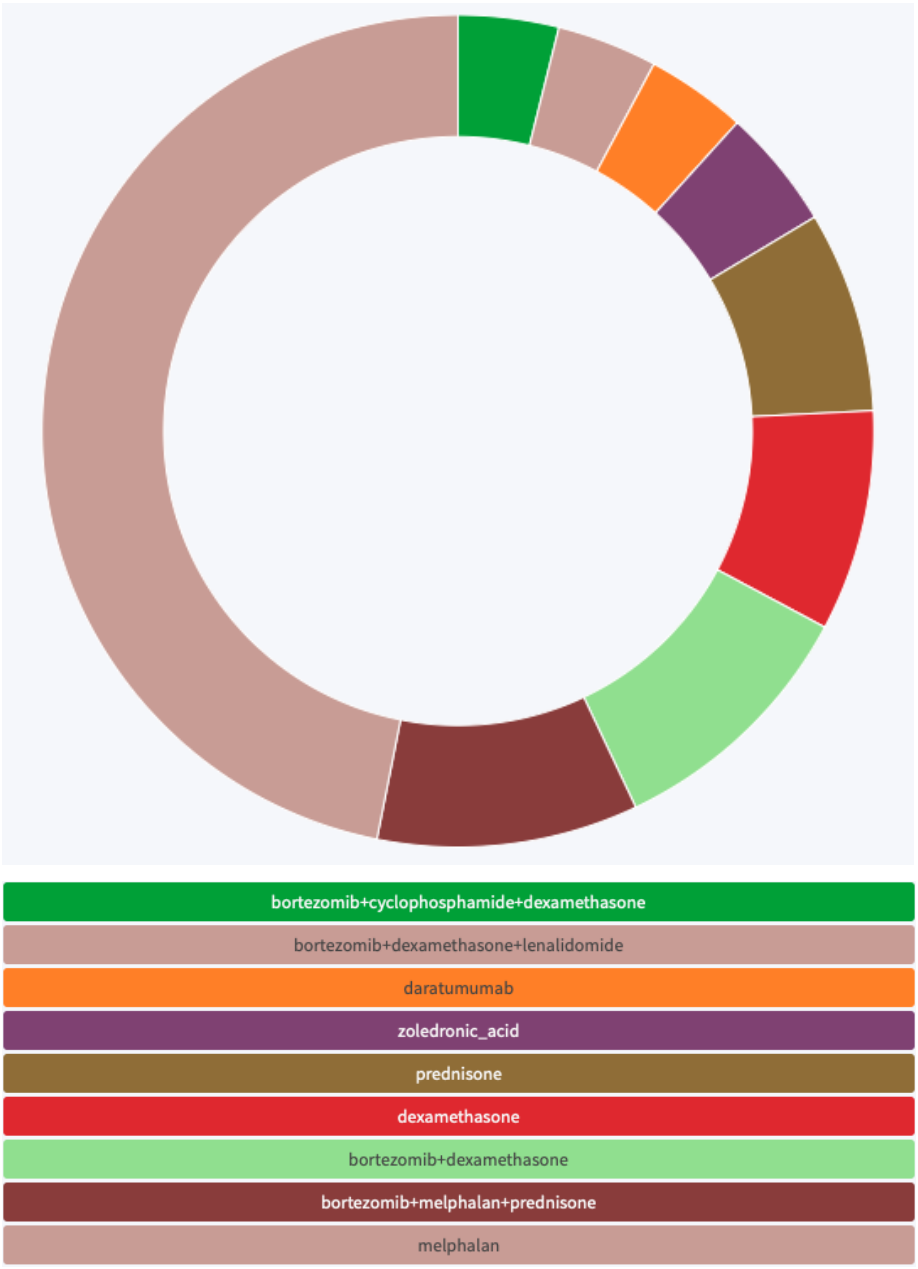


Figure S4. Sunburst plot of treatment patterns analysis in females in CDW Bordeaux (0 to 5 years post index date).

CDW Bordeaux=Clinical Data Warehouse of Bordeaux

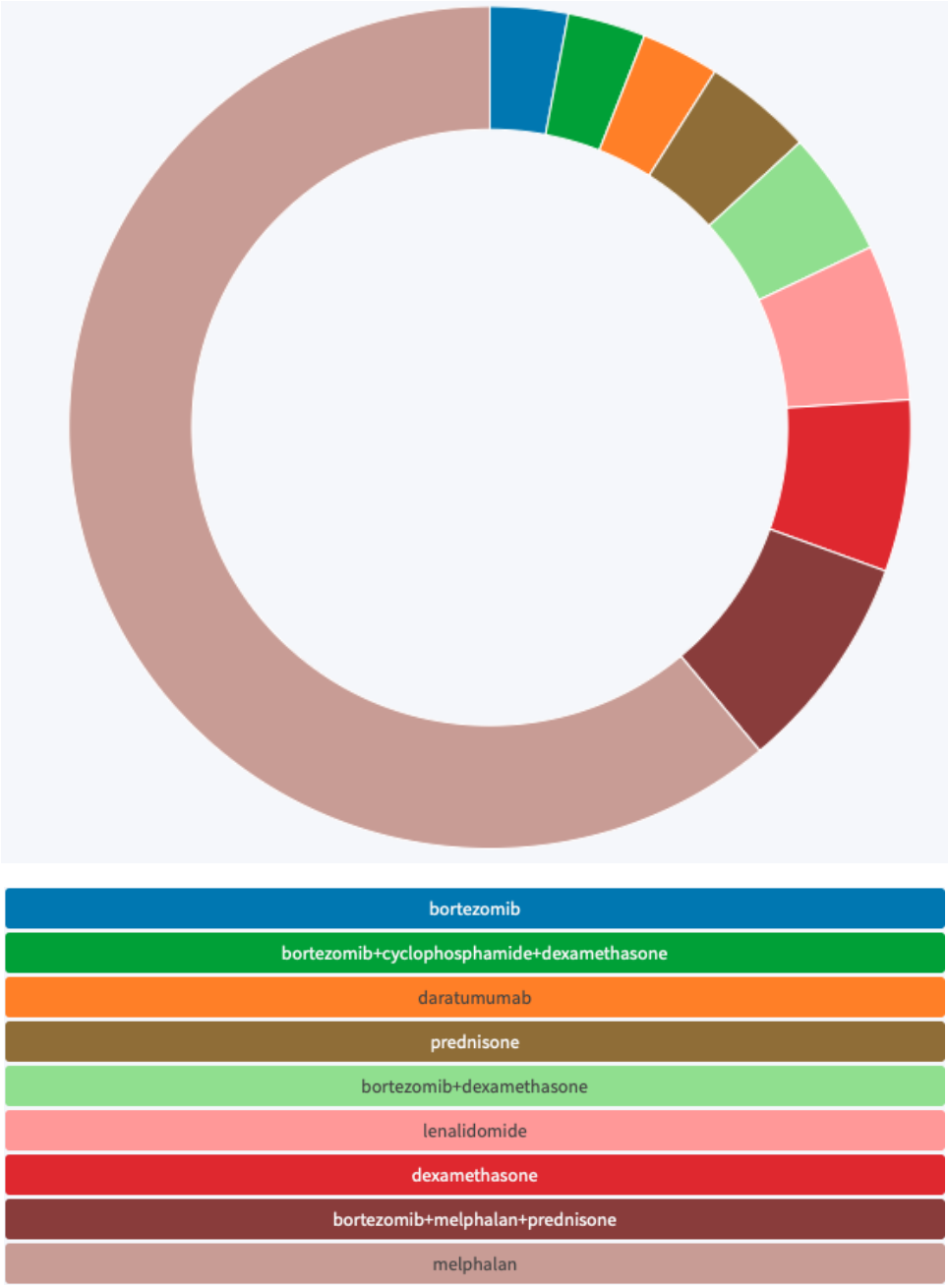


Figure S5. Sunburst plot of treatment patterns analysis in males in CDW Bordeaux (0 to 5 years post index date).

CDW Bordeaux=Clinical Data Warehouse of Bordeaux

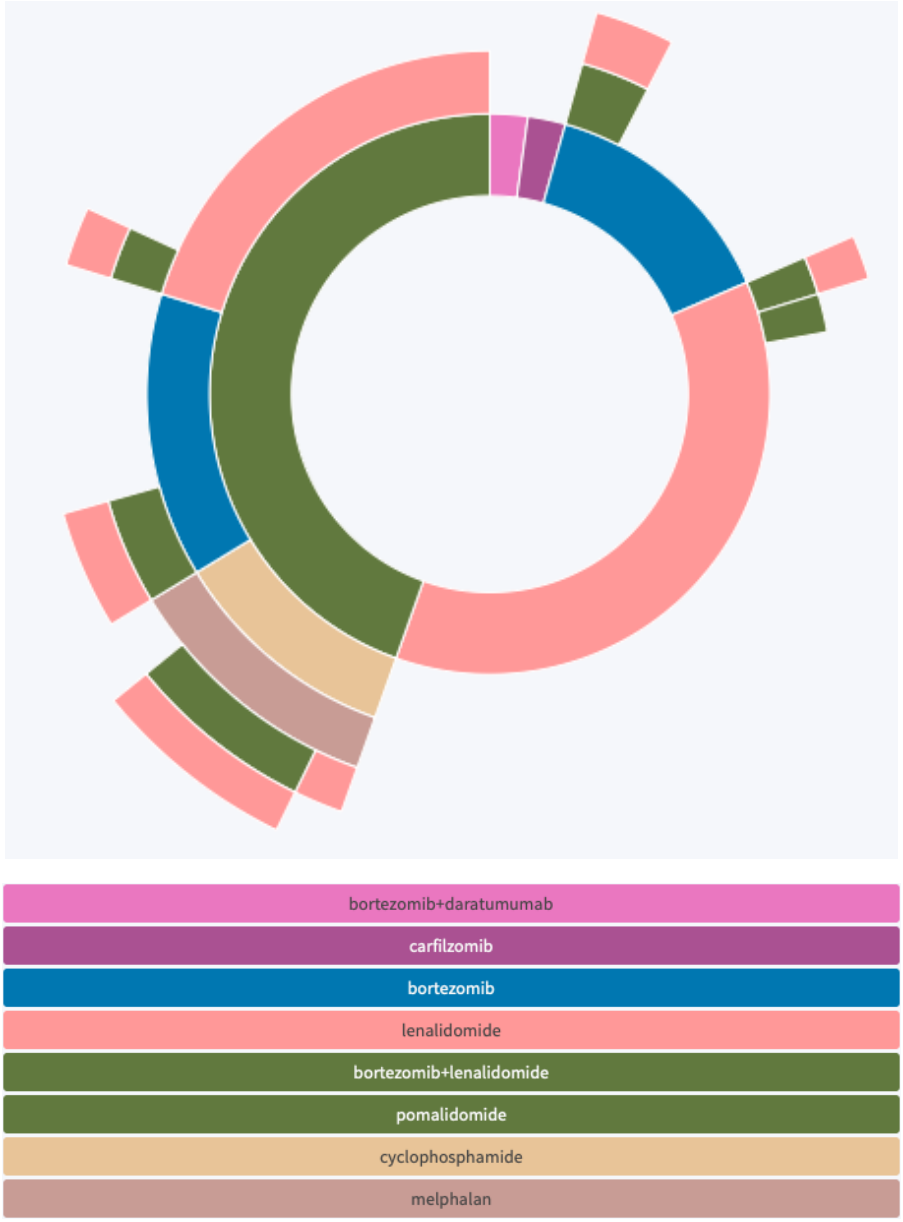


Figure S6. Sunburst plot of treatment patterns analysis in females in CRN (0 to 5 years post index date).

CRN=Cancer Registry Norway

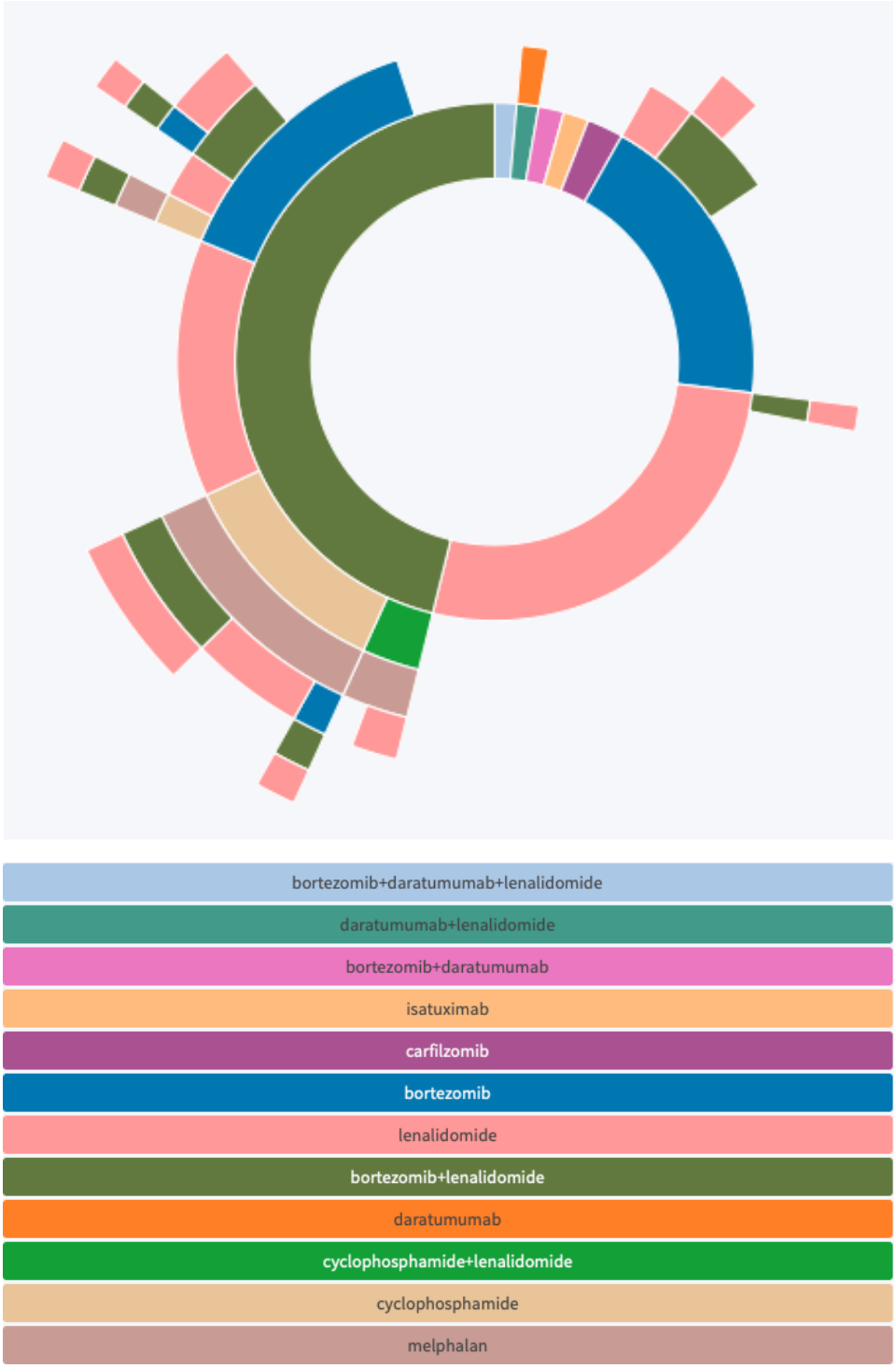


Figure S7. Sunburst plot of treatment patterns analysis in males in CRN (0 to 5 years post index date).

CRN=Cancer Registry Norway

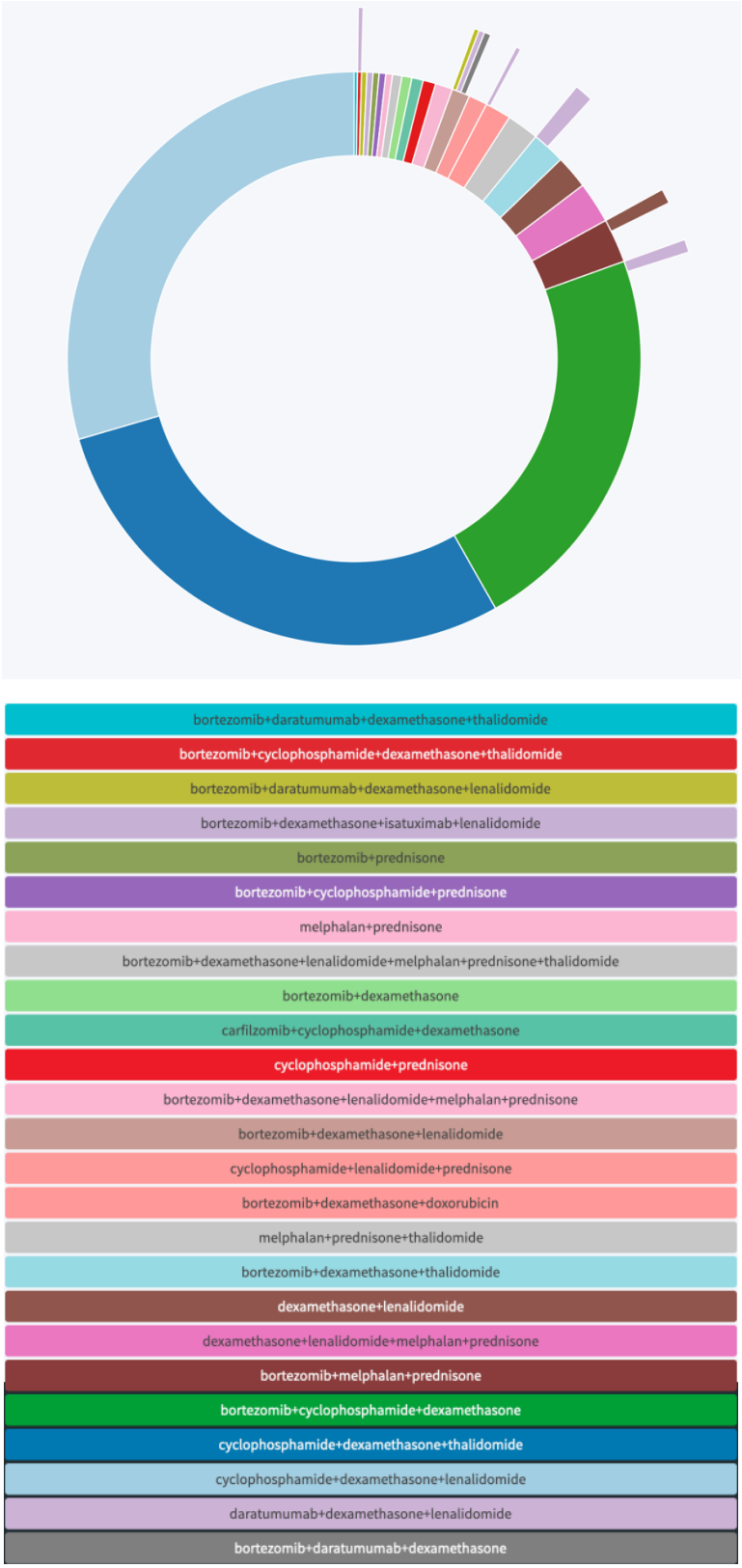


Figure S8. Sunburst plot of treatment patterns analysis in females in HARMONY-MM (0 to 5 years post index date).

HARMONY-MM=HARMONY-Multiple Myeloma

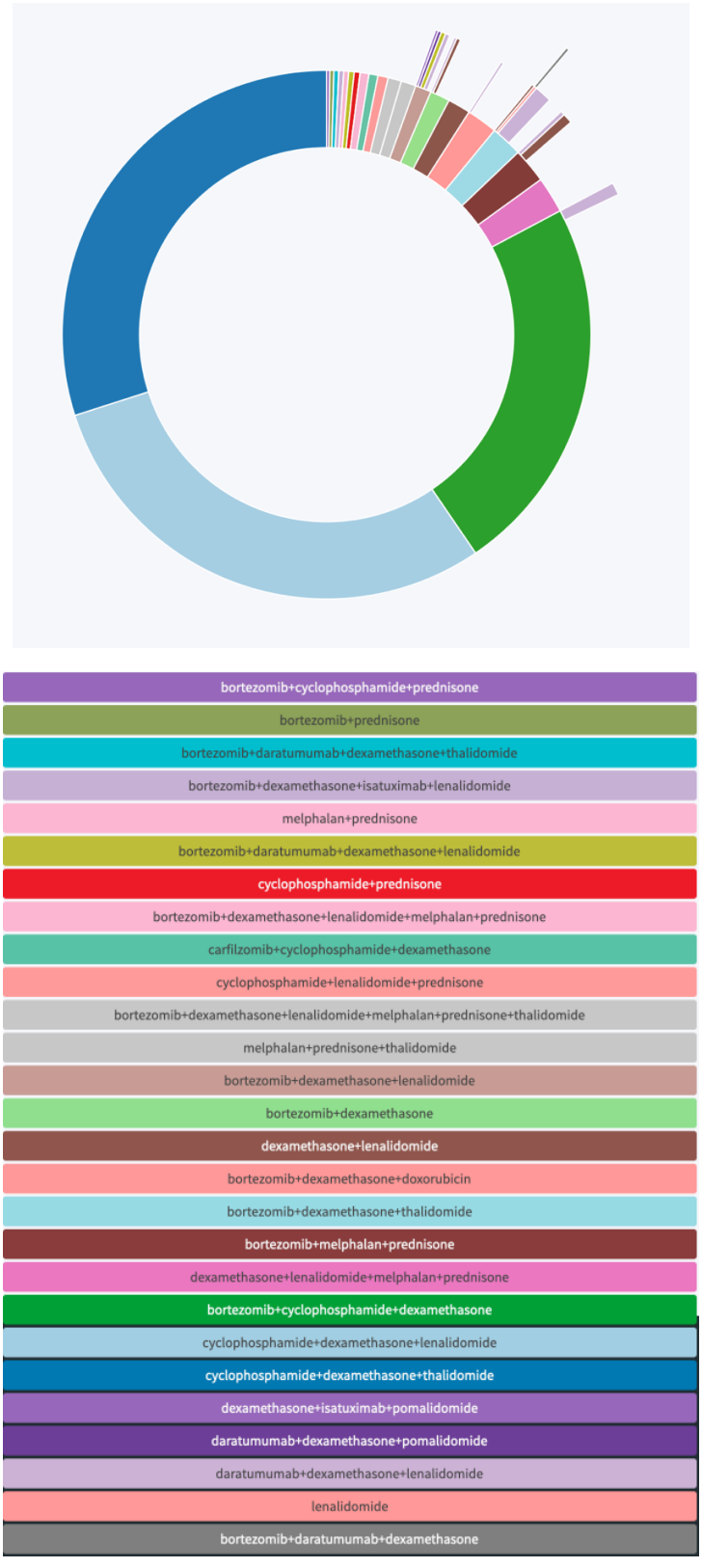


Figure S9. Sunburst plot of treatment patterns analysis in males in HARMONY-MM (0 to 5 years post index date).

HARMONY-MM=HARMONY-Multiple Myeloma

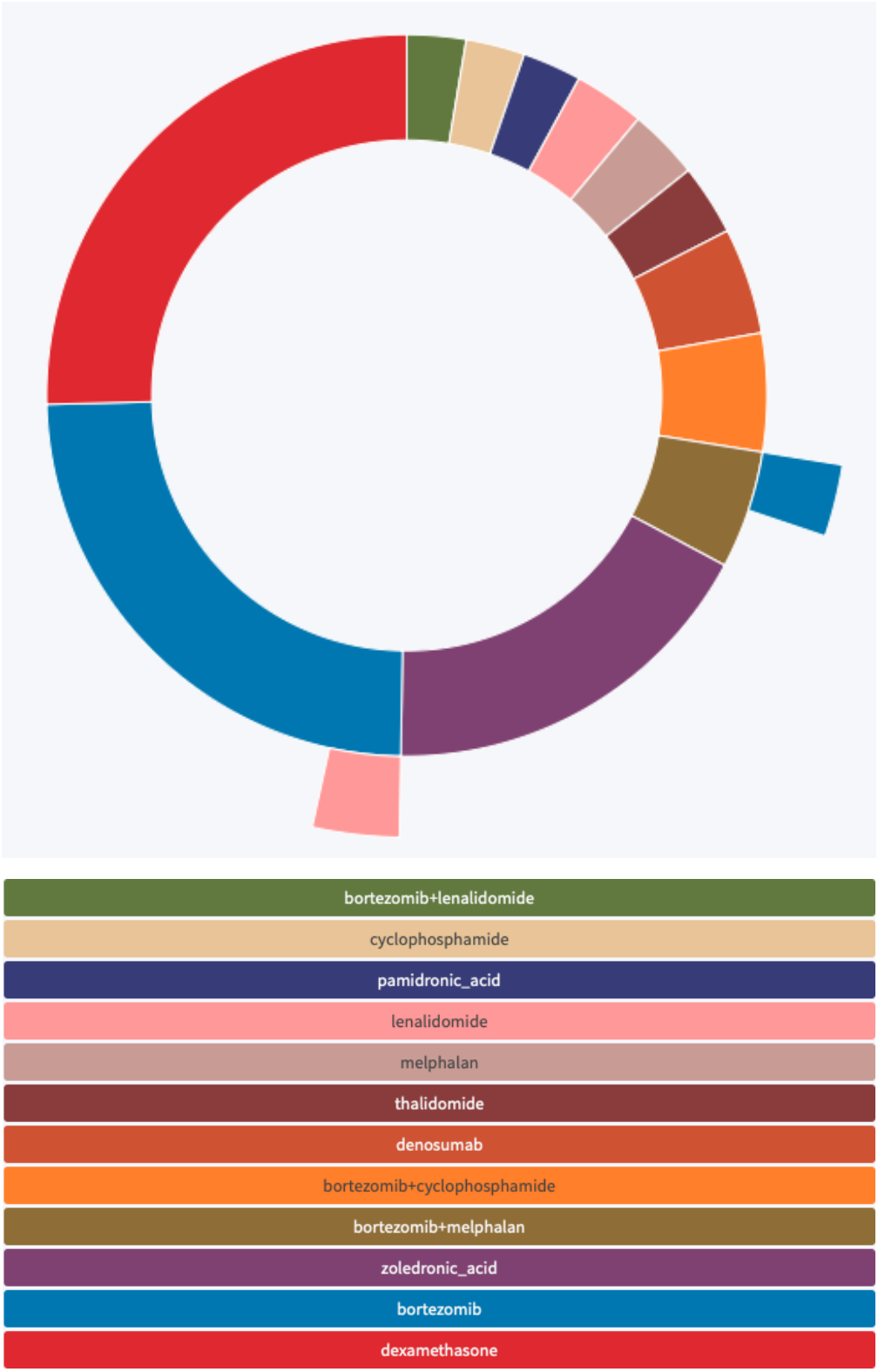


Figure S10. Sunburst plot of treatment patterns analysis in females in DK-DHR (0 to 5 years post index date).

DK-DHR=Danish Data Health Registries

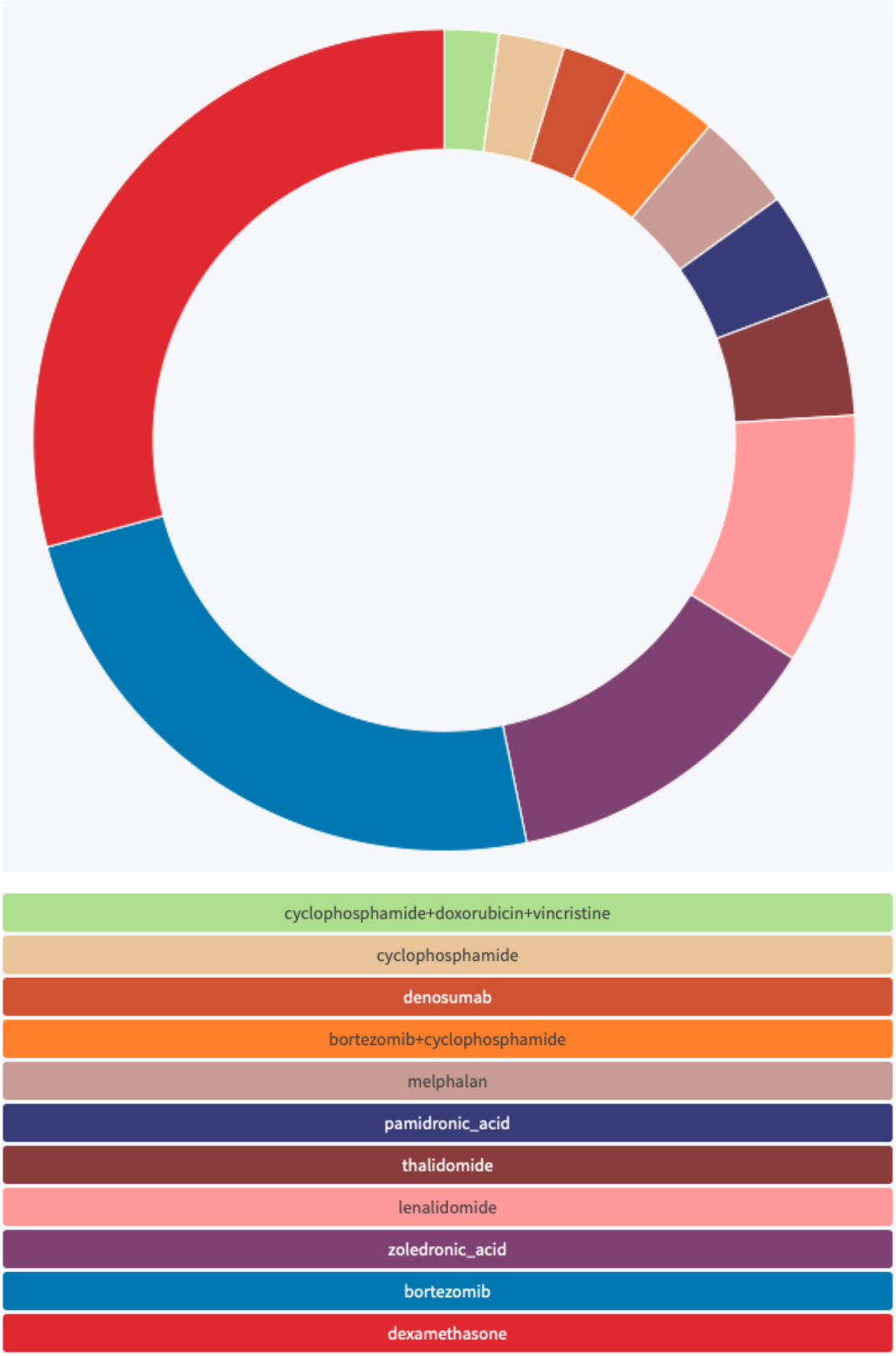


Figure S11. Sunburst plot of treatment patterns analysis in males in DK-DHR (0 to 5 years post index date).

DK-DHR=Danish Data Health Registries

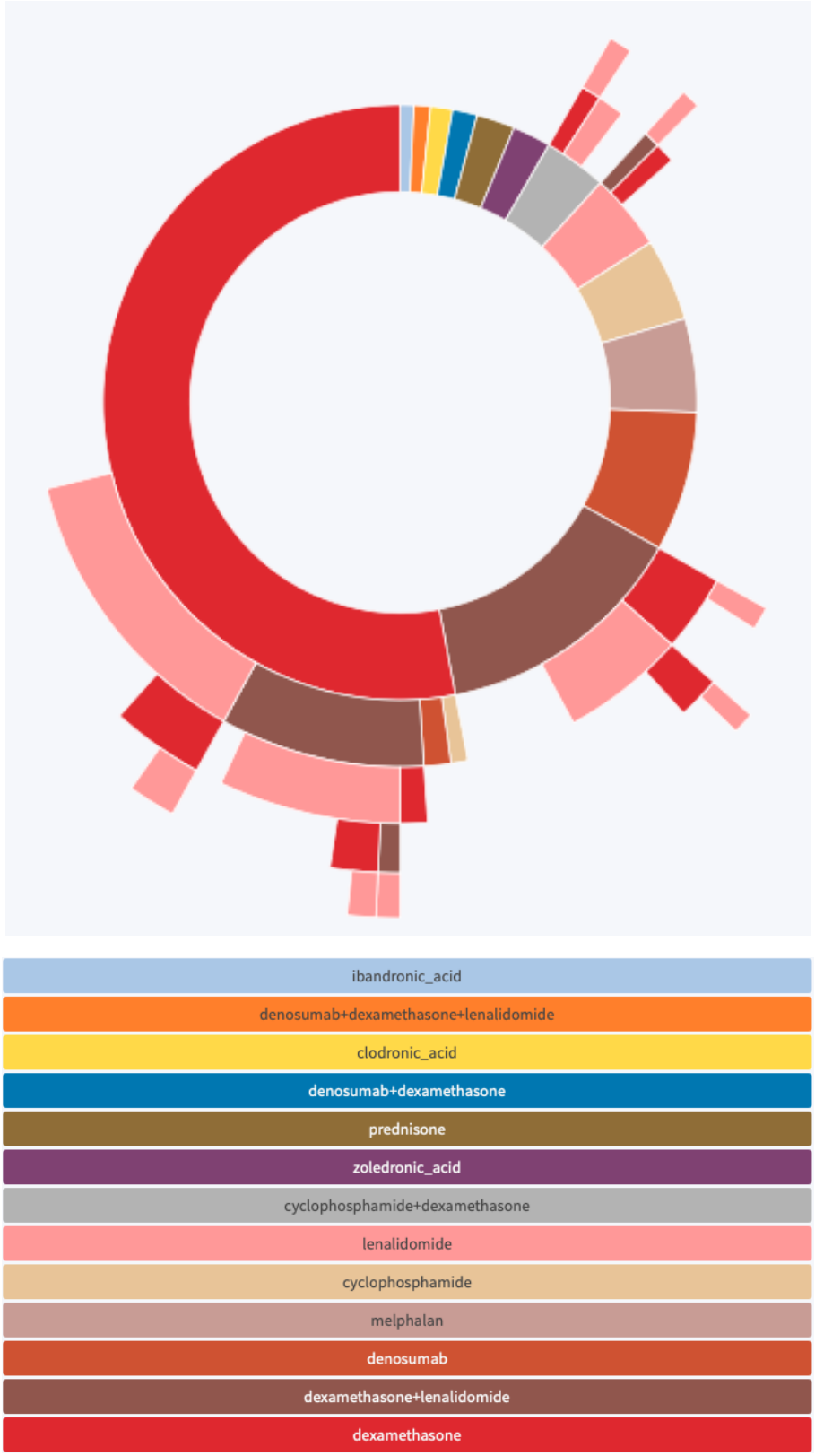


Figure S12. Sunburst plot of treatment patterns analysis in females in FinOMOP-THL (0 to 5 years post index date).

FinOMOP-THL=Finnish Care Register for Health Care - THL

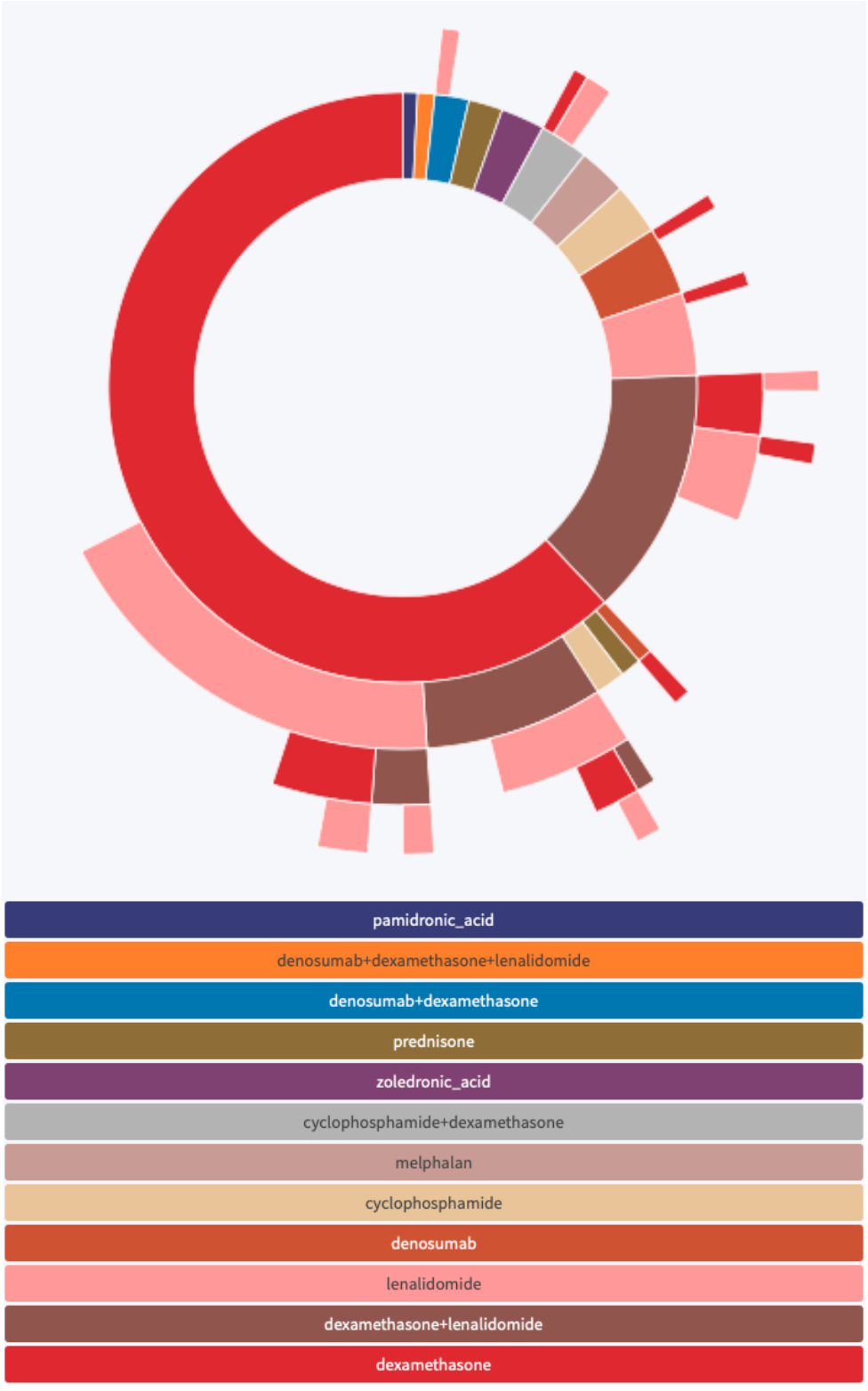


Figure S13. Sunburst plot of treatment patterns analysis in males in FinOMOP-THL (0 to 5 years post index date).

FinOMOP-THL=Finnish Care Register for Health Care - THL

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing individual data and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

Data storage and protection

For this study, personal data from individuals in various EU member states were processed, using information collected from national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence* to estimate Incidence and Prevalence, *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the cohort by indication. These packages will include numerous automated unit tests to ensure the validity of

the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

ANNEX IV. Concept sets/code lists

Table S1. Multiple Myeloma concept set/code lists.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Multiple Myeloma	Bone marrow: myeloma cells Multiple Myeloma Multiple solitary plasmacytomas Myeloma kidney Myeloma-associated amyloidosis Plasma cell myeloma/plasmacytoma	4043447 437233 4214660 4137433 4019477 4163558	4224628 37209514 3168489 436059 4043713 42538151 760936 764229	SNOMED SNOMED SNOMED SNOMED SNOMED SNOMED

Table S2. Multiple Myeloma treatment concept set/code lists.

Concept name	Class	ATC code	Ingredient Concept ID	Include descendants	Exclude Concept ID
Melphalan	Chemotherapies	L01AA03	21601392	Yes	N/A
Bendamustine	Chemotherapies	L01AA09	21601397	Yes	N/A
Doxorubicin	Chemotherapies	L01DB01	21603732	Yes	N/A
Cisplatin	Chemotherapies	L01XA01	21603748	Yes	N/A
Cyclophosphamide	Chemotherapies	L01AA01	21601390	Yes	N/A
Etoposide	Chemotherapies	L01CB01	21603718	Yes	N/A
Vincristine	Chemotherapies	L01CA02	21601448	Yes	N/A
Thalidomide	IMiDs	L04AX02	21603928	Yes	N/A
Lenalidomide	IMiDs	L04AX04	21603930	Yes	N/A
Pomalidomide	IMiDs	L04AX06	43534824	Yes	N/A
Bortezomib	PI	L01XX32	21603804	Yes	N/A
Carfilzomib	PI	L01XG02	947958	Yes	N/A
Ixazomib	PI	L01XG03	947997	Yes	N/A
Venetoclax	PI	L01XX52	1123676	Yes	N/A
Daratumumab	Monoclonal antibodies	L01XC24	1123898	Yes	N/A
Isatuximab	Monoclonal antibodies	L01XC38	947956	Yes	N/A
Denosumab	Monoclonal antibodies	M05BX04	21604169	Yes	N/A
Elotuzumab	Monoclonal antibodies	L01XC23	1123776	Yes	N/A
Selinexor	Nuclear export inhibitor	L01XX66	715834	Yes	N/A
Lisocabtagene maraleucel	CAR T-cell	L01XX88	739860	Yes	N/A

Concept name	Class	ATC code	Ingredient Concept ID	Include descendants	Exclude Concept ID
Idecabtagene vicleucel	CAR T-cell	L01XL07	36026872	Yes	N/A
Brexucabtagene autoleucel	CAR T-cell	L01XL06	37002393	Yes	N/A
Axicabtagene ciloleucel	CAR T-cell	L01XX70	947849	Yes	N/A
Tisagenlecleucel	CAR T-cell	L01XX71	947930	Yes	N/A
Dexamethasone	Glucocorticoids	H02AB02	21602730	Yes	N/A
Prednisone	Glucocorticoids	H02AB07	21602735	Yes	N/A
Zoledronic acid	Bisphosphonates	M05BA08	21604156	Yes	N/A
Pamidronic acid	Bisphosphonates	M05BA03	21604151	Yes	N/A
Clodronic acid	Bisphosphonates	M05BA02	21604150	Yes	N/A
Ibandronic acid	Bisphosphonates	M05BA06	21604154	Yes	N/A
Etidronate	Bisphosphonates	M05BA01	21604149	Yes	N/A
Panobinostat	Other treatments	L01XH03	947750	Yes	N/A
Autologous/Allogenic Stem cell Transplantation	Other treatments	N/A	4028623 46272967 46271079 1243851	Yes	45890494 41229202108458

IMiDs=Immunomodulatory drugs; PI=proteasome inhibitors; N/A=not applicable

ANNEX V. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of Real-World Data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing Real-World Data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in Real-World Evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific Real-World study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.