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Real-world treatment patterns and outcomes for patients with multiple myeloma in Denmark, Finland and Sweden: An analysis using linked Nordic registries

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ABSTRACT

Aim: The Health outcomes and Understanding of MyelomA multi-National Study (HUMANS) was a large-scale, retrospective study conducted across Denmark, Finland and Sweden using linked data from national registries. We describe the characteristics, treatment patterns and clinical outcomes for patients with newly diagnosed multiple myeloma (NDMM) over 2010–2018.

Methods: Patients with NDMM who received MM-specific, first-line treatments, were categorised by treatment (autologous stem cell transplantation [ASCT] or a combination chemotherapy regimen based on bortezomib, lenalidomide or melphalan-prednisolone-thalidomide).

Results: 11,023 patients received treatment over 2010–2018. Time between diagnosis and treatment was shortest in Denmark (0.9 months), then Sweden (2.9 months) and Finland (4.6 months). Around one third of patients underwent ASCT. Lenalidomide-based regimens were prescribed to 23–28% of patients in Denmark and Finland, versus 12% in Sweden. Patients receiving lenalidomide had the longest wait for treatment, from 3.2 months (Denmark) to 12.1 months (Sweden). Treatment persistence was highest among patients receiving melphalan-prednisolone-thalidomide (7–8 months) in Finland and Sweden and lowest among those receiving bortezomib (3.5 months) in Finland. Overall survival (OS) was longest among patients with ASCT (7–10 years). Among patients receiving chemotherapy, OS (from diagnosis/treatment initiation), varied between cohorts. In a sensitivity analysis excluding patients with smouldering MM, OS decreased for all; for patients receiving bortezomib or lenalidomide, OS from diagnosis was 40–49 and 27–54 months, respectively.

Conclusions: This population-based study of patients with NDMM receiving first-line MM-specific treatment, provides real-world data on treatment patterns and outcomes to complement data from randomised clinical trials.

1. Background

Multiple myeloma (MM) is the second most common haematological malignancy [1,2]. Patient survival has improved significantly in recent decades [2], related to the introduction of new drugs, changes in therapeutic strategies and autologous stem cell transplantation (ASCT) [3,4]. Nevertheless, MM remains incurable, and 5-year overall survival (OS) rates differ markedly between countries [5]. Although a range of

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treatment options are available, patients with newly diagnosed MM (NDMM) eventually relapse and become refractory to treatment, owing to multiple drug resistance [2,4,6].

Evidence underpinning decision making in MM is based predominantly on randomised clinical trial (RCT) data [7]. Although RCTs remain the gold standard for determining efficacy and safety, external validity may be limited owing to restrictive patient eligibility criteria.

Observational studies in MM have been conducted using data from registries or hospital charts [8–12]; however, analyses of larger populations are needed to understand real-world treatment patterns and outcomes, and to extend knowledge about new agents. The Health outcomes and Understanding of MyelomA multi-National Study (HUMANS) was conducted across Denmark, Finland and Sweden using national registry data providing almost complete coverage of the population. Here, we describe the characteristics, treatment patterns and clinical outcomes for patients with NDMM in Nordic countries from 2010–2018.

2. Methods

2.1. Study design

HUMANS was a population-based, longitudinal, retrospective study conducted across Denmark, Finland and Sweden (Supplementary Fig. 1). Data were obtained from national health registries between 1 January 2010 to 31 October 2018. Use of data was approved by data holders in each registry, and the ethics committee in Sweden (DNR 2017/2355–31). All patient data were pseudonymised, with no identifying information, to comply with privacy laws in each country.

2.2. Data sources

The four registry archetypes evaluated in the study were the National Patient Registry (NPR), National Prescription Registry (PDR), Cancer Registry (CR) and Cause of Death Registry (CDR). For further information on the registries, please see Abildgaard et al. 2022 [13] and Supplementary Material.

2.3. Study population

Patients first diagnosed with MM between January 2010 and December 2016 (2017 in Sweden), who initiated first-line (1 L) MM-specific therapy, were included. In Denmark, first MM diagnoses up to 2016 were identified in the NPR and CR. The NPR was used to identify patients with first MM diagnoses up to 2016 (Finland) and up to 2017 (Sweden) [13]. Patients with any other haematological cancer, or who had received any MM-specific treatment before their first MM diagnosis, were excluded. Patients were categorised into two subgroups according to their MM-specific 1 L therapy: ASCT or non-ASCT (combination therapy).

2.4. Treatments

Index treatment was defined as MM-specific 1 L therapy with the index date defined as treatment initiation and classified as ASCT or combination therapy, based on MM-specific drug regimens. If dispensing dates for drugs in combination differed, the dispensing date of the earliest MM-specific treatment was considered as the initiation date. Two treatment lines were included in the analyses, with second-line (2 L) treatment defined as a new MM-specific treatment regimen starting after 1 L treatment.

Patients who underwent ASCT were identified by NPR International Classification of Diseases 10th revision and medical procedure codes. For the combination therapy subgroup, patients were classified and identified according to their specific chemotherapy regimen (Supplementary table 1). In Denmark, the melphalan-prednisolone-thalidomide (MPT) arm was excluded from the analysis due to inconsistent reporting for patients receiving 1 L MPT treatment.

2.5. Treatment persistence

Treatment persistence was defined as the number of days/months that a treatment was taken (from first dose/first day, to the last day of the last dispensed dose or discontinuation), permitting a grace period of 60 days. A treatment break was recorded if a patient had not been dispensed treatment for a given period but, subsequently, re-initiated the same treatment. If the treatment break between current dispensing and end of the previous dispensing was within the 60-day grace period, consecutive treatment periods were merged. If the patient re-initiated the same treatment after the grace period, a 2 L treatment of that drug was considered to have started. In Denmark, dispensed package or dose information was unavailable; therefore, defined daily dose (DDD) was used for persistence analysis, and defined as the number of days after the last dispensation, which counts towards treatment length. A DDD of 28 days was assumed for lenalidomide (LEN) and 7 for bortezomib (BTZ).

As BTZ is typically administered in a hospital setting, and these data are not captured by the PDR, 1 L treatment persistence could not be determined for BTZ in Sweden. A proxy outpatient pattern, including procedure code analysis, was used to identify patients who may have been prescribed BTZ in Finland. MPT 1 L treatment persistence could not be assessed in Denmark given the complexity of classifying whether patients were receiving 1 L melphalan or thalidomide monotherapy or concomitant melphalan-thalidomide or MPT treatment.

2.6. Study outcomes

OS was evaluated from MM diagnosis to death and from initiation of 1 L therapy to death. Patients were censored at the date of loss to follow-up or study end, whichever came first. Time to next treatment (TTNT) was defined as the time from initiation of 1 L to that of 2 L treatment.

2.7. Data analyses

Descriptive statistics included categorical variables that were summarised using frequency and percentages in each category. Unless otherwise specified, these were based on the full analysis set, and continuous variables. Kaplan-Meier curves were used to examine time-to-event analyses for treatment persistence of 1 L agents, OS and TTNT. Analyses included observed events and censored observations for each time-to-event outcome.

Data robustness was assessed via sensitivity analyses: for treatment persistence, a more restrictive 42-day grace period was permitted; for OS, treatment initiation within 3 months of diagnosis to identify true 1 L patients without previous smouldering MM (SMM); for considering two MM-specific treatments as the same treatment line or as combination treatment, a more restrictive 14-day overlap period was agreed.

Data were stratified according to index treatment group and country. Analyses were performed using SAS v9.3 or higher (SAS Institute, Cary, NC, USA), Stata v11 or higher (StataCorp, College Station, TX, USA) and R v3.1.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) or higher.

3. Results

3.1. Patient characteristics

Overall, 25,326 patients were identified across Denmark, Finland and Sweden; 11,023 (43.5%) were treated over the study period. Around one third of patients received ASCT as 1 L treatment ($n = 2924$; Table 1); in Sweden, patients with any other haematological cancer record in the CR, at least two other haematological cancer records in the NPR or only one MM diagnosis recorded in the NPR, were excluded from the initial

Table 1
Study population identified from Denmark, Finland and Sweden according to 1 L treatment regimen.

	Denmark	Finland	Sweden
Raw dataset, *N* (C90.0 in NPR/CR)	5244	6559	13523
Treated patients, *N* (in 2010–2016/2018 timeframe)	3680	1987	5356
Final analysis set,[a] *N*	2451	1585	4823
Treatment regimen, *n* (%)			
ASCT	887 (36.2)	470 (29.9)	1567 (32.5)
Non-ASCT	1564 (63.8)	1102 (70.1)	2946 (67.5)
BTZ based	838 (53.5)	559 (50.7)	629 (21.3)
LEN based	356 (22.7)	306 (27.7)	356 (12.1)
MPT	102 (6.5)	64 (5.8)	411 (14.0)
Other	631 (40.3)	380 (34.5)	1550 (52.6)

Abbreviations: 1 L, first line; ASCT, autologous stem cell transplantation; BTZ, bortezomib; CR, cancer registry; LEN, lenalidomide; MPT, melphalan-prednisolone-thalidomide; NPR, national patient registry.
[a] BTZ and LEN groups are not mutually exclusive, as some patients receive a BTZ/LEN/dexamethasone regimen.

data set.

The median age of patients at first MM diagnosis was 69–70 years (60–61 years for patients who underwent ASCT compared with 70–74 years for those receiving BTZ or LEN). Median age at treatment initiation was 61–62 years (ASCT) and 72–76 years (BTZ) (Table 2). Patients who received other chemotherapy regimens in the 1 L setting were older at diagnosis (median 75–77 years) and at treatment initiation (median 76–78 years) than those who received BTZ or LEN in the 1 L setting.

The time between diagnosis and treatment varied across countries (Denmark: 0.9; Sweden: 2.9; Finland: 4.6 months). When individual chemotherapy agents were considered ($n = 5625$), BTZ-based regimens were most frequently prescribed as 1 L treatment in Denmark and Finland, with ~50% of patients receiving this regimen. In Sweden, only 21% of patients received a BTZ-based regimen in the 1 L setting. Patients receiving 1 L LEN had the longest wait for treatment (Sweden: 12.1; Finland: 8.1; Denmark: 3.2 months). Conversely, BTZ treatment was initiated after < 1 month in Denmark and Sweden, but 3.4 months in Finland. Patients receiving MPT-based regimens (Finland and Sweden), generally received treatment within < 2 months. These results should be interpreted with caution owing to the use of prescription dispensing as a proxy for BTZ treatment in Finland and Sweden.

3.2. Treatment persistence

Due to limitations with drug registration, treatment persistence could not be ascertained for MPT in Denmark and BTZ in Sweden. Overall, treatment persistence was highest among patients treated 1 L with MPT in Finland (8.1 months) and Sweden (7.4 months) (Table 3). Treatment persistence was lowest among patients receiving 1 L BTZ

Table 2
Patient demographic and disease characteristics for the Denmark, Finland and Sweden cohorts.

Denmark	All patients[a] *N* = 2451	ASCT *n* = 887	Bortezomib *n* = 838	Lenalidomide *n* = 102	MPT	Other *n* = 631
Median age at first MM Dx (Q1, Q3), years	69 (62, 76)	60 (54, 65)	72 (67, 77)	74 (70, 82)	–	76 (72, 82)
Median age at TI (Q1, Q3), years	70 (63, 77)	62 (56, 66)	73 (68, 78)	76 (71, 82)	–	77 (72, 82)
Sex, *n* (%)					–	
Female	1060 (43.2)	380 (42.8)	339 (40.5)	50 (49.0)		294 (46.6)
Male	1391 (56.8)	507 (57.2)	499 (59.5)	52 (51.0)		337 (53.4)
Median time MM Dx to TI (Q1, Q3), months	0.9 (0.4, 5.4)	0.8 (0.4, 16.3)	0.7 (0.3, 1.6)	3.2 (0.9, 16.7)	–	–
Median time MGUS Dx to TI (Q1, Q3), months	59.1 (20.5, 109.0)	65.1 (31.5, 109.8)	50.4 (16.7, 103.8)	47.3 (16.9, 98.1)	–	–
Median time MGUS to MM Dx (Q1, Q3), months	41.6 (1.3, 88.5)	41.6 (11.9, 78.2)	50.2 (5.6, 86.0)	10.9 (0.5, 45.1)	–	–
No MGUS Dx, *n* (%)	2354 (96.0)	859 (96.8)	803 (95.8)	94 (92.2)	–	–

Finland	All patients[a] *N* = 1585	ASCT *n* = 470	Bortezomib *n* = 559	Lenalidomide *n* = 306	MPT *n* = 64	Other *n* = 380
Median age at first MM Dx (Q1, Q3), years	69.9 (62.7, 76.7)	61.0 (55.8, 64.9)	71.3 (66.7, 76.0)	70.5 (65.8, 74.5)	76.7 (73.2, 79.3)	77.5 (72.3, 81.7)
Median age at TI (Q1, Q3), years	71.0 (63.6, 77.3)	62.1 (56.6, 65.7)	72.3 (67.9, 76.7)	72.1 (67.2, 76.3)	77.8 (73.3, 79.6)	78.1 (73.0, 82.4)
Sex, *n* (%)						
Female	797 (50.3)	228 (48.5)	279 (49.9)	130 (42.5)	32 (50.0)	208 (54.7)
Male	788 (49.7)	242 (51.5)	280 (50.1)	176 (57.5)	32 (50.0)	172 (45.3)
Median time MM Dx to TI (Q1, Q3), months	4.6 (1.7, 9.7)	6.2 (4.6, 9.3)	3.4 (0.9, 11.4)	8.1 (3.7, 30.7)	1.7 (1.0, 3.9)	–
Median time MGUS Dx to TI (Q1, Q3), months	16.9 (5.3, 52.6)	12.2 (6.5, 30.3)	18.9 (2.8, 54.1)	34.8 (5.7, 58.4)	10.3 (6.3, 42.8)	–
Median time MGUS to MM Dx (Q1, Q3), months	2.7 (0.5, 19.3)	1.9 (0.6, 13.6)	2.3 (0.5, 14.4)	3.5 (0.5, 22.1)	0.8 (0.3, 34.6)	–
No MGUS Dx, *n* (%)	1365 (86.1)	414 (88.1)	488 (87.3)	268 (87.6)	57 (89.1)	–

Sweden	All patients[a] *N* = 4494	ASCT *n* = 1567	Bortezomib *n* = 610	Lenalidomide *n* = 356	MPT *n* = 411	Other *n* = 1550
Median age at first MM Dx (Q1, Q3), years	70.0 (62.0, 78.0)	60.0 (53.0, 64.0)	73.0 (68.0, 78.0)	72.0 (68.0, 77.0)	75.0 (71.0, 79.0)	77.0 (72.0, 83.0)
Median age at TI (Q1, Q3), years	71.0 (63.0, 79.0)	61 (54.0, 65.0)	73 (69.0, 78.0)	74.5 (70.0, 79.0)	76.0 (72.0, 80.0)	78.0 (73.0, 83.0)
Sex, *n* (%)						
Female	1915 (42.6)	585 (37.3)	270 (44.3)	151 (42.4)	182 (44.3)	727 (46.9)
Male	2579 (57.4)	982 (62.7)	340 (55.7)	205 (57.6)	229 (55.7)	823 (53.1)
Median time MM Dx to TI (Q1, Q3), months	2.9 (0.8, 7.0)	3.9 (3.1, 6.9)	0.9 (0.2, 3.1)	12.1 (2.1, 31.5)	0.8 (0.3, 2.8)	–
Median time MGUS Dx to TI (Q1, Q3), months	19.5 (3.4, 67.2)	18.8 (5.0, 66.2)	14.3 (1.6, 64.2)	58.9 (16.1, 111.6)	12.3 (1.2, 51.1)	–
Median time MGUS to MM Dx (Q1, Q3), months	1.4 (0.00, 45.8)	0.6 (0, 40.2)	1.1 (0, 54.8)	20.5 (0.4, 74.2)	1.3 (0.0, 35.9)	–
No MGUS Dx, n (%)	3662 (81.5)	1346 (85.9)	499 (81.8)	286 (80.3)	326 (79.3)	–

Abbreviations: ASCT, autologous stem cell transplantation; Dx, diagnosis; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MPT, melphalan-prednisolone-thalidomide; Q, quartile; TI, treatment initiation.
[a] Treatment subgroups (ASCT, bortezomib, lenalidomide, MPT, other) do not total 2451 as these are not mutually exclusive groups.

Table 3
Treatment persistence (months) with BTZ, LEN and MPT based on the primary (all patients) and sensitivity (patients who initiated treatment within 3 months of diagnosis) analyses.

	Denmark	Finland	Sweden
Primary analysis, median (95% CI), months			
BTZ cohort	4.4 (4.0–4.6)	3.5 (2.9–4.1)	–
LEN cohort	7.3 (4.7–10.1)	5.9 (5.1–6.5)	6.1 (5.5–7.0)
MPT cohort	–	8.1 (6.4–9.4)	7.4 (6.6–7.9)
Sensitivity analysis, median (95% CI), months			
BTZ cohort	4.5 (4.1–4.9)	3.8 (2.8–4.4)	–
LEN cohort	9.6 (6.7–14.7)	6.7 (4.5–8.2)	5.9 (5.0–7.8)
MPT cohort	–	8.5 (6.5–9.6)	7.6 (6.9–8.5)

Abbreviations: BTZ, bortezomib; CI, confidence interval; LEN, lenalidomide; MPT, melphalan-prednisolone-thalidomide.

compared with MPT and LEN (Finland: 3.5; Denmark: 4.4 months). In Finland, treatment persistence was shorter with BTZ compared with MPT (3.5 versus 8.1 months, respectively). Including data from patients who initiated treatment within 3 months of diagnosis (sensitivity analysis) had a minor effect on treatment persistence (Table 3). An additional sensitivity analysis with a 42-day grace period and exclusion of patients initiating treatment within 3 months of diagnosis, had a minor impact on the results.

3.3. Clinical outcomes

As 2 L treatment is administered predominantly in the hospital setting, the TTNT analysis was conducted for Denmark only, where such treatment is recorded reliably [14]. TTNT was shorter for patients receiving BTZ (15.3 months) compared with those receiving LEN (16.9 months) (Table 4). There was a high degree of variability for the two OS timeframes (Table 4, Figures 1 and 2), irrespective of the type of treatment. Across all countries, OS from diagnosis was longest for patients who underwent ASCT (main analysis: 93–117 months; sensitivity analysis: 72–99 months).

Patients receiving LEN-based regimens generally survived longer than those receiving BTZ treatments; however, there was more variability in OS (both timeframes) among patients receiving LEN. For patients receiving BTZ, OS from diagnosis was 53–58 months (sensitivity analysis: 40–49 months) and for LEN, 62–78 months (sensitivity analysis: 27–55 months). Across treatments, sensitivity analyses confirmed that, when patients with longer time intervals between diagnosis and treatment were excluded, OS was similar, decreasing across all cohorts, consistent with the exclusion of patients with SMM (Table 4).

4. Discussion

As the prognosis for patients with MM has improved, it is important to review treatments to clarify the most beneficial regimens and identify shortfalls in existing therapy. As RCTs have strict eligibility criteria, large population studies, representing heterogeneous patient cohorts and daily clinical practice, are needed to provide insight. To our knowledge, this was the first large-scale, observational study to describe regional differences in the real-world management of patients with MM across Nordic countries.

The accuracy, reliability and registration of MM data have been discussed [13]. Danish registries are the most comprehensive overall, particularly related to treatment patterns, whereas Finnish and Swedish registries provide less complete data for non-solid versus solid tumours [15,16]. In Denmark, integration of the CR with the NPR provides highly reliable coverage for MM. Maret-Ouda *et al.* [17] reported on the potential for combining Nordic data registries, and concluded that these can be combined with high validity and statistical strength. Laugesen *et al.* [18] reported that similarities between and within Nordic registries (e.g. welfare state models) permit researchers to obtain large quantities of linked patient population data with long-term ($\geq$10 years) follow-up.

Our study population of $>$ 11,000 patients who initiated 1 L treatment for NDMM within the study period resulted in a final data set of 8859 patients with $>$ 10 years' follow-up, representing an important resource for gaining insight into clinical characteristics, treatment patterns and outcomes for patients with MM.

Patient characteristics were largely consistent with those described previously; patients undergoing ASCT were generally younger at diagnosis than those receiving combination chemotherapy [4,19], in line with international clinical guidelines for MM [20,21].

Clinical guidelines recommend treating patients with NDMM within 3 months of diagnosis; however, a delay to treatment was found in our study, with patients receiving 1 L treatment waiting longest. Such delays for LEN, particularly in Sweden, could be explained by a proportion of patients with SMM receiving LEN, patient uncertainty/refusal and long waiting times. Nevertheless, while measures were implemented to ensure that no non-registered treatments would distort the analysis, it is possible that some patients receiving LEN were 2 L patients.

There was variation in treatment persistence between countries, possibly related to differences in reporting methods, speed of treatment [8] and drug availability or access [22,23]. Nevertheless, using a

Table 4
TTNT and OS in the different treatment cohorts across countries based on the primary (all patients) and sensitivity (patients who initiated treatment <3 months of diagnosis) analyses.

	Denmark		Finland		Sweden	
	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis	Primary analysis	Sensitivity analysis
Bortezomib cohort						
TTNT	15.3 (14.0 –16.8)	–	–	–	–	–
OS from diagnosis	52.9 (46.2–58.2)	40.7 (37.6–47.4)	57.6 (47.7–66.8)	42.1 (37.0–58.9)	54.8 (50.4–64.0)	49.3 (42.6–54.8)
OS from 1 L therapy	41.5 (37.8–47.4)	40.0 (37.0–47.3)	38.3 (34.2–44.7)	41.7 (37.2–61.3)	48.7 (42.3–53.6)	48.1 (41.6–54.5)
Lenalidomide cohort						
TTNT	16.9 (12.4–22.0)	–	–	–	–	–
OS from diagnosis	69.3 (54.7–108.4)	54.7 (37.1–NA)	61.5 (52.1–79.1)	27.3 (19.7–NA)	77.9 (63.4–105.2)	35.0 (21.1–56.0)
OS from 1 L therapy	39.7 (35.8–53.4)	53.4 (36.1–NA)	31.7 (26.1–38.6)	26.4 (18.1–NA)	37.5 (31.8–44.6)	32.2 (20.1–53.3)
MPT cohort						
TTNT	–	–	–	–	–	–
OS from diagnosis	–	–	61.1 (42.7–73.5)	48.0 (37.1–61.1)	49.4 (43.9–55.8)	41.5 (38.6–48.1)
OS from 1 L therapy	–	–	54.7 (38.1–68.3)	47.3 (35.1–60.7)	43.9 (39.4–49.8)	41.1 (38.3–48.1)
ASCT cohort						
OS from diagnosis	117.2 (104.2–133.8)	99.3 (88.1–NA)	92.6 (83.0–113.1)	72.4 (NA)	107.4 (98.5–116.2)	84.9 (74.7–92.0)

Values are months, median (95% CI).
Abbreviations: 1 L, first line; ASCT, autologous stem cell transplantation; CI, confidence interval; MM, multiple myeloma; MPT, melphalan-prednisolone-thalidomide; NA, not available (median predicted patient survival not reached for the higher 95% CI within the timeframe of study follow-up); OS, overall survival; TTNT, time to next treatment.

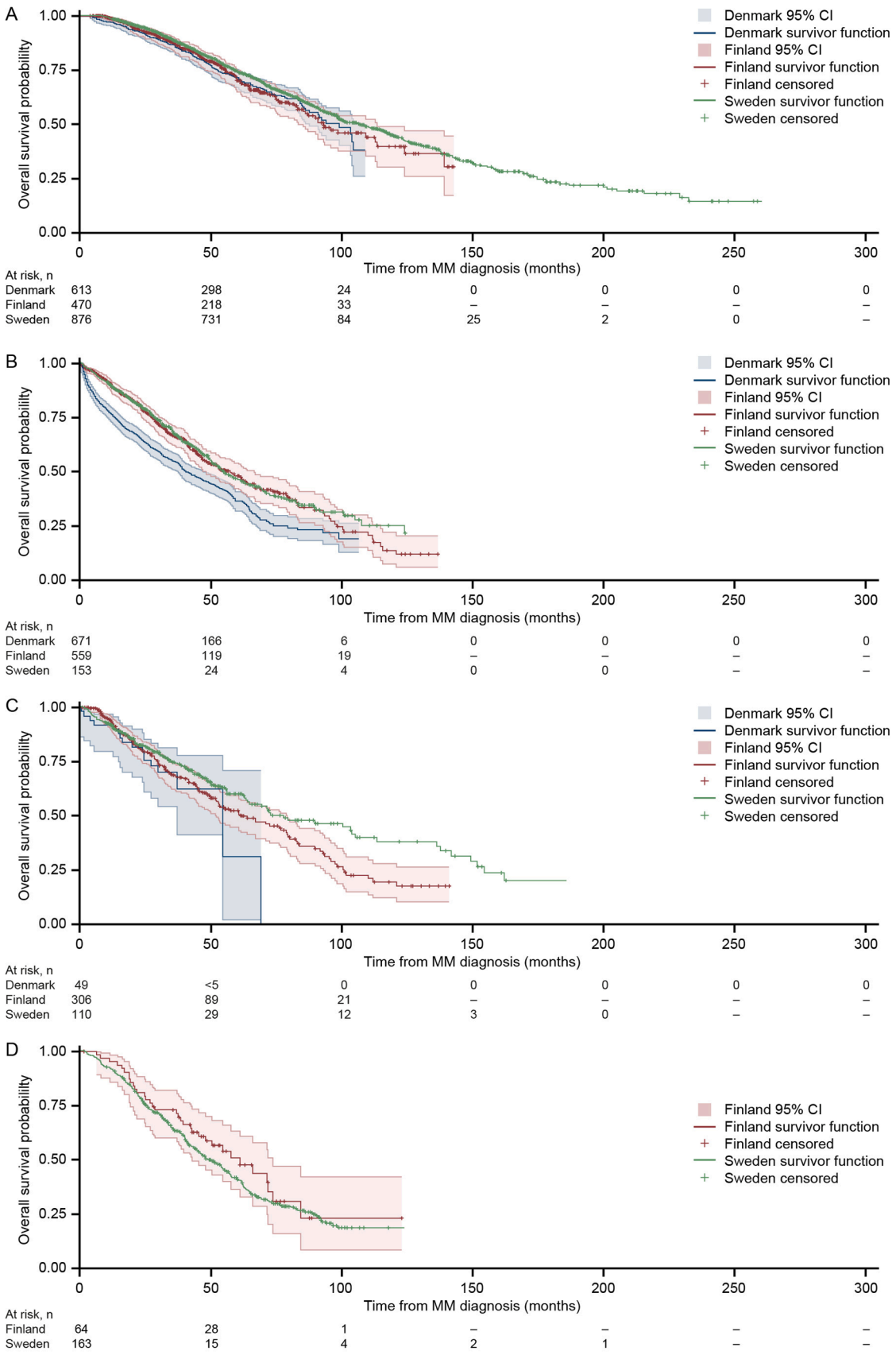

Fig. 1. Overall survival from diagnosis among patients receiving **A)** ASCT, **B)** BTZ, **C)** LEN and **D)** MPT in Denmark, Finland and Sweden. Abbreviations: ASCT, autologous stem cell transplantation; BTZ, bortezomib; CI, confidence interval; LEN, lenalidomide; MM, multiple myeloma; MPT, melphalan-prednisolone-thalidomide.

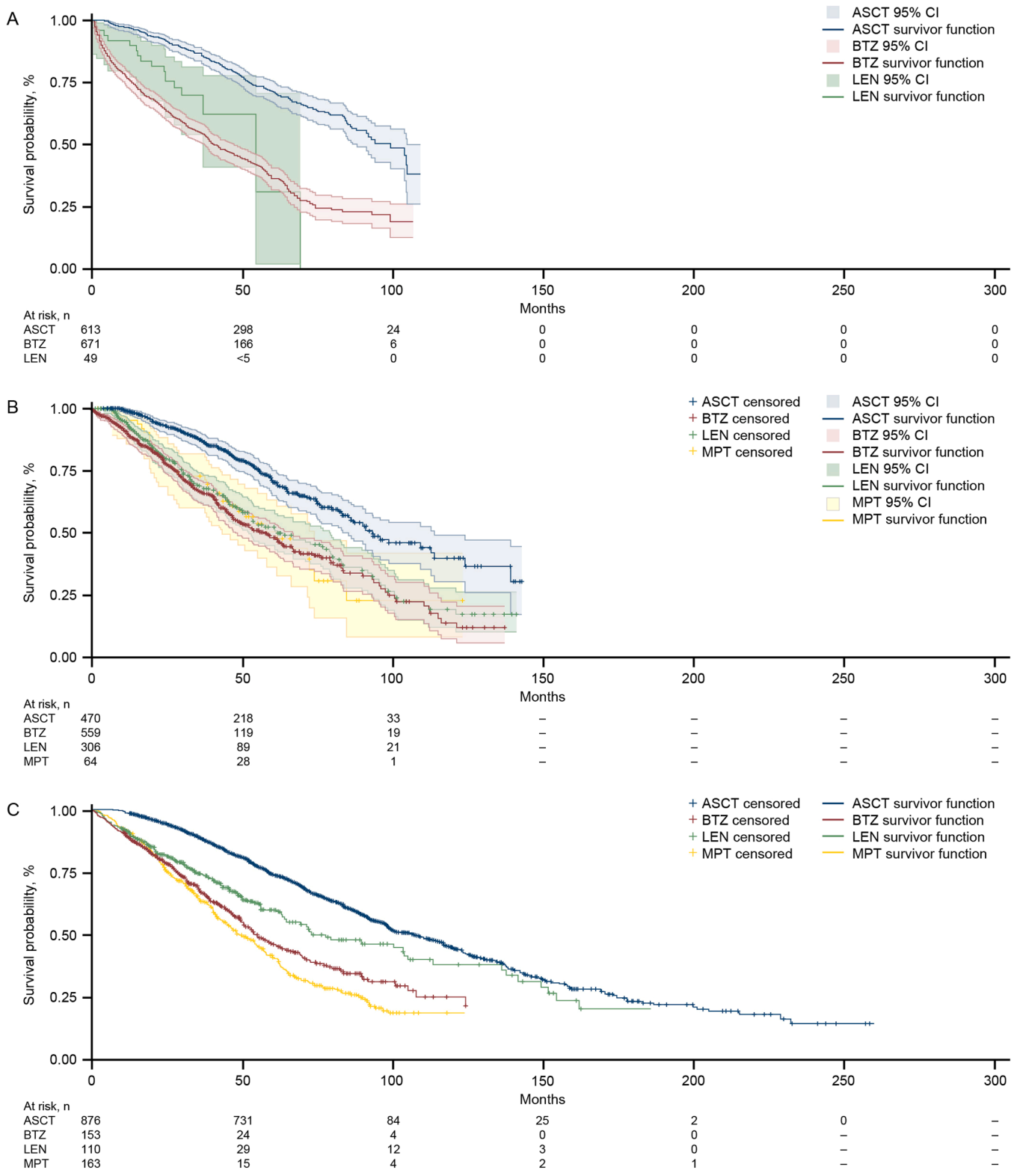

Fig. 2. Overall survival from diagnosis among patients in A) Denmark, B) Finland and C) Sweden receiving ASCT, BTZ, LEN and MPT. Abbreviations: ASCT, autologous stem cell transplantation; BTZ, bortezomib; CI, confidence interval; LEN, lenalidomide; MPT, melphalan-prednisolone-thalidomide.

sensitivity analysis with a more restrictive 42-day grace period and excluding patients initiating treatment within 3 months of diagnosis showed only a marginal effect on the results, suggesting that the study methods were robust. Indeed, previous real-world studies reported the median duration of 1 L therapy to be approximately 6–9.9 months [8, 24]; however, these did not describe the median duration of treatment with individual therapies. While clinical guidelines recommend a longer duration for the regimens than was observed here, early discontinuation of MM treatment may be related to side effects. Patients receiving BTZ had a shorter treatment duration than those receiving LEN or MPT, which is expected based on regimen differences.

Our study revealed some variation in OS between countries. The

marked differences in OS reported from diagnosis or from treatment initiation can be explained by patients waiting longer between diagnosis and treatment initiation also having longer OS given the inclusion of patients with SMM. In the sensitivity analysis excluding patients with a longer wait (i.e. patients with SMM), OS rates decreased for all. In each country, patients who received ASCT had longer OS than those receiving chemotherapy. Previous OS data have generally been extrapolated from RCTs, providing longer estimates than in our study [25–27].

A retrospective chart review suggested OS and progression-free survival benefits for patients with NDMM receiving 1 L LEN-based regimens, compared with those receiving 1 L BTZ-based regimens in Europe [28]. Despite this, the comparative efficacy of 1 L LEN versus BTZ in patients with MM must be interpreted with caution as physician treatment choices were not accounted for in the current study or by Zamagni *et al.* [28].

A strength of our study was that it was, in principle, unbiased, providing representative real-world data and clinically meaningful insights into MM characteristics, treatment patterns and outcomes. While registries are well established in epidemiological research, data used in our analyses were not collected for this purpose and we had no control over data quality, although this was checked by the registry holders and study investigators through exploratory analyses. There were limitations attributed to the data sources; for example, baseline patient characteristics such as disease stage or risk status could not be evaluated from these registries, although it is acknowledged that these can have a large impact on patient outcomes. In addition, proxies were used for hospital-registered drugs (BTZ) in Finland and Sweden. Furthermore, the registries do not routinely collect relevant disease-specific outcomes, such as progression-free survival, although TTNT is commonly used as a clinically meaningful endpoint for patients with incurable malignancies [29]. Nevertheless, TTNT may not be reliable across Finland and Sweden, as 2 L treatment is often administered in hospitals or clinics and would not be picked up in the study. Additionally, registration methods/diagnostic habits/procedure codes may have differed across the regions/countries. We advise caution in applying our data to other geographical regions, which may have different clinical practices and/or healthcare systems. In particular, countries such as the United States do not operate universal and tax-funded healthcare systems as seen in the Nordic countries. This may have an impact on access to specific treatment regimens and could affect how long oncologists are able to keep patients on expensive treatments [18].

In conclusion, this large-scale, observational study using data from national patient registries across Denmark, Finland and Sweden provided real-world evidence relating to patient profiles, treatment patterns and clinical outcomes of the NDMM population receiving 1 L treatments.

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Authors' contributions

Niels Abildgaard: Overall study design, plan for collection and interpretation of data in Denmark, primary investigator for Denmark, interpretation of data across all countries. **Pekka Anttila**, **Anders Waage**, **Markus Hansson**: Conception and design of the study, data analysis and interpretation. **Katrine Hass Rubin**: Data management, analyses of the Danish data. **Sigurd Ørstavik**: Conception and design of the study, supervision of data collection, data analysis and interpretation. **Nawal Bent-Ennakhil**, **François Gavini**: Input into the study analyses, reviewed the study results. **Yuanjun Ma**: Data analysis and interpretation. **Jonatan Freilich**: Overall study design, primary investigator for Sweden, coordinated data access in Finland and Denmark, oversight of the analysis in all countries. All authors: Writing, reviewing, editing, and accountability for the work.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: N Abildgaard has received research grants from Amgen, Bristol Myers Squibb, Celgene, Janssen, and Takeda; consulting fees from Bristol Myers Squibb, Celgene, Janssen, Novartis, and Takeda. P Anttila has received consulting fees from Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Novartis, Sanofi, and Takeda; travel grants from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Mundipharma, Novartis, Roche, Sanofi Genzyme, and Teva. A Waage has received consulting fees from Janssen and Takeda. J Freilich and Y Ma are employees of Parexel and received funding from Takeda for conducting study analyses. N Bent-Ennakhil and S Ørstavik are employees of Takeda. M Hansson has received lecture fees or participated in advisory board meetings for Amgen, Bristol Myers Squibb, Celgene, Janssen, Sanofi, Shire and Takeda. All remaining authors have declared no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113921.

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