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ORIGINAL RESEARCH

A Real-World Analysis of Patients with Triple Class Exposed Multiple Myeloma in Italy: Epidemiology Estimates, Treatment Pattern and Economic Burden

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ABSTRACT

OBJECTIVES: This research aimed to provide updated epidemiological estimates of multiple myeloma (MM) in Italy and to characterize the clinical journey, treatment patterns, and economic burden focusing specifically on the subset of patients who have been exposed to all three major therapeutic classes: proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies (triple-class exposed, TCE).

METHODS: A retrospective analysis was conducted using Italian healthcare administrative databases covering 12 million individuals. The research included (i) an epidemiological analysis of MM prevalence and incidence, and (ii) a longitudinal analysis of TCE patients identified between January 2017 and June 2023. Inclusion criteria required exposure to the three major MM drug classes. Healthcare resource utilization (HCRU) and direct costs from the Italian National Health Service perspective were assessed at one-year follow-up.

RESULTS: As of August 2022, MM incidence was 9/100,000 and prevalence 40.9/100,000; TCE prevalence was estimated at 4.1/100,000, projecting to 2,557 TCE patients in Italy. From 6,102 MM patients, 894 were identified as TCE; 887 had sufficient follow-up for inclusion. TCE patients had a mean age of 67 years and a mild comorbidity burden (Charlson Index = 0.7). Among 309 recent TCE cases (2022–2023), 35.6% became TCE in first-line therapy and 46.5% in second-line. HCRU analysis (n=461) showed high service use, with annual per-patient costs averaging €119,899—88% attributable to MM-related drugs.

CONCLUSIONS: This real-world analysis highlights a growing population of TCE MM patients in Italy, with increasing exposure to combination therapies earlier in treatment. The findings underscore the substantial clinical and economic burden posed by this population, reinforcing the need for novel therapeutic options to improve outcomes and manage costs within the healthcare system.

Keywords

Anti-CD38 monoclonal antibodies; Direct healthcare costs; Epidemiology estimates; Immunomodulatory drugs; Multiple myeloma; Proteasome inhibitors; Real-world evidence; Triple class-exposed patients

INTRODUCTION

Multiple myeloma (MM) is a malignant neoplasm characterised by abnormal clonal proliferation of plasma cells; if left undiagnosed, MM can lead to specific end-organ damage [1].

MM accounts for nearly 2% of all cancers and 10% of onco-haematological disorders [2] with a notable global impact. In 2022, approximately 188,000 new cases were diagnosed worldwide, leading to an estimated 121,000 deaths [3]. MM affects predominantly the elderly population with a median age at onset of around 70 years, is more common in males than females (1.4:1) and in black populations than white (2:1) [4,5]. Projections indicate a substantial rise in MM cases and associated deaths by 2045, primarily attributed to population aging and growth [3]. Epidemiological data provided by the Italian Association of Cancer Registries (AIRTUM) reported a variable incidence of MM across different regions, but anyhow higher than the European average [6].

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Although MM remains an incurable disease, in view of its frequent recurrence after transient remission [7], the treatment landscape of MM has largely benefited over the years from the introduction of novel drugs that have increased patient survival [8,9]. Immunomodulatory (IMID) agents and proteasome inhibitors still represent a mainstay of MM therapy, and are used in early lines of treatment (in both transplant-eligible and non-transplant-eligible patients), as well as in advanced lines [10]. However, despite such undeniable advances, a substantial number of patients still experience relapsed or refractory MM, characterized by weaker and less durable drug response when progressing to successive lines of therapy [11]. In patients who become refractory to both proteasome inhibitors and immunomodulatory drugs, monoclonal antibodies directed against the CD38 antigen (anti-CD38 mAb), a transmembrane glycoprotein highly expressed by MM cells, have further improved clinical outcomes in terms of progression-free survival and overall survival [12-15].

Deeper and more sustained responses with an adequate safety profile have been achieved in MM treated with the use of triplet combinations of IMID agents (thalidomide lenalidomide and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, ixazomib) and anti-CD38 monoclonal antibodies (daratumumab, isatuximab, elotuzumab) [12-18]. However, real-world data from five European countries, including Italy, revealed that triple-class exposed (TCE) MM patients receiving therapy with IMID, proteasome inhibitors, anti-CD38 mAbs, had a more complex clinical status with a subsequent higher degree of healthcare resource utilization compared to non-tri-exposed patients [19]. Hence, TCE MM have an unmet need for more effective therapies to reduce disease burden.

The present analysis was undertaken to provide an updated scenario in Italy on the epidemiology of MM and to describe the population of TCE MM patients, focusing on their therapeutic journey, and the resulting economic burden from the perspective of the National Health Service (NHS).

MATERIAL AND METHODS

Data source

An observational analysis was conducted using data extrapolated from the administrative flows of Italian healthcare entities (Local Health Units, LHUs), covering about 12 million health-assisted individuals. Specifically, the following databases were used for the analysis: beneficiaries' database for data on patients' demographics; pharmaceutical database for data on drug prescriptions reimbursed by the Italian NHS, including the Anatomical-Therapeutic Chemical (ATC) code, and prescription date; hospitalization database, for data on discharge diagnoses at any level classified according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and date of diagnosis; outpatient diagnostic tests and specialist visits database, for data on the type and date of provisions of diagnostic tests, procedures and specialist visits; exemption database for data on date and type of active exemption.

Approval has been obtained from the ethics committees of the involved LHUs. The dataset used consists solely of anonymized data.

Study design

The research consisted of two different designs: (a) an epidemiological evaluation to assess the prevalence and incidence of MM patients at a defined date, considering the entire period of data availability within the administrative flows of each LHU; (b) a longitudinal analysis in which TCE patients were included in a defined period and then observed in both the pre- and post-inclusion period in order to determine the treatment lines with the related healthcare consumption and costs for the NHS (costs calculated in the post-inclusion period only).

Study population

Inclusion criteria

Patients with MM were identified by the presence of at least one of the following criteria: (i) hospital discharge diagnosis (at any level) for MM (ICD-9 code: 203.0); (ii) at least 1 prescription for drugs specifically indicated for MM (used as a proxy for diagnosis), i.e. daratumumab (ATC codes L01XC24, L01FC01), elotuzumab (ATC codes L01XC23, L01FX08), isatuximab (ATC codes L01XC38, L01FC02), ixazomib (ATC codes L01XX50, L01XG03), carfilzomib (ATC codes L01XX45, L01XG02), belantamab mafodotin (ATC code L01FX15); (iii) specific exemption code for MM (code 048.203.0). Among patients identified with MM,

those who had at least 3 drugs (in combination or consequential) each belonging to one of the classes IMID, proteasome inhibitors and anti-CD38 mAbs or belantamab mafodotin were defined as TCE patients.

Exclusion criteria

Given that from January 2023, daratumumab was authorized as a second indication and reimbursability for light-chain amyloidosis, the patients with a successive prescription of daratumumab and a hospitalization diagnosis for light-chain amyloidosis (ICD-9-CM code 277.3) or exemption code RCG130 were excluded. In addition, all TCE MM patients with less than 1 year of data availability prior to inclusion were excluded from the longitudinal analysis.

Epidemiological analysis

The epidemiological analyses were carried out considering the inclusion criteria throughout the entire period of data availability of the LHUs (that were not necessarily the same across each LHU).

Prevalence as of August 2022 was calculated as the number of patients identified from the start of data availability in the LHUs alive as of 31 August 2022 per 100,000 people.

The incidence in August 2022 was calculated from 1 September 2021 to 31 August 2022 as the number of new cases per 100,000 alive subjects on 31 August 2022.

Longitudinal analysis

Patients were identified as MM considering the entire period of data availability; among them, patients who became TCE during the inclusion period between January 2017 and June 2023 were included. The index-date corresponded to the date when the patient became TCE. All patients had at least one year of data availability prior to the index-date (characterization period), while the follow-up was the timespan from the index-date (included) until the end of data availability or death of the patient, whichever came first.

Baseline characteristics

For all patients included in the analysis, demographic characteristics, namely age and sex distribution, were collected at index-date. Patient's clinical status was evaluated during the characterization period by means of the Charlson Comorbidity Index (CCI) [20]. In this analysis, a modified version of the CCI, not accounting for oncological conditions, was used.

Number of lines of therapy

Lines of therapy were investigated throughout the entire period before and after inclusion. The identification of the line of therapy considered either the presence of autologous stem cell transplant (ASCT) identified by ICD-9-CM procedure codes 41.01, 41.04, 41.07, 41.09, or the presence of the following treatment regimens:

- DaraVTD: daratumumab/bortezomib/thalidomide/dexamethasone (4-week cycles);
- DaraVMp: daratumumab/bortezomib/melphalan/prednisone (6-week cycles);
- DaraRd: daratumumab/lenalidomide/dexamethasone (4-week cycles);
- VMp: bortezomib/melphalan/prednisone (6-week cycles);
- VRd: bortezomib/lenalidomide/dexamethasone (3-week cycles);
- VTd: bortezomib/thalidomide/dexamethasone (4-week cycles);
- PomVd: pomalidomide/bortezomib/dexamethasone (3-week cycles);
- IxaRd: ixazomib/lenalidomide/dexamethasone (4-week cycles);
- EloRd: elotuzumab/lenalidomide/dexamethasone (4-week cycles);
- KRd: carfilzomib/lenalidomide/dexamethasone (4-week cycles);
- DaraVd: daratumumab/bortezomib/dexamethasone (6-week cycles);
- EloPd: elotuzumab/pomalidomide/dexamethasone (4-week cycles);
- DaraKd: daratumumab/carfilzomib/dexamethasone (4-week cycles);
- IsaKd: isatuximab/carfilzomib/dexamethasone (4-week cycles);
- VTd: bortezomib/thalidomide/dexamethasone (4-week cycles);
- VCd: bortezomib/cyclophosphamide/dexamethasone (3-week cycles);
- VRd: bortezomib/lenalidomide/dexamethasone (3-week cycles);
- Rd: lenalidomide/dexamethasone (4-week cycles);
- Kd: carfilzomib/dexamethasone (4-week cycles).

Lenalidomide (R), melphalan (M), venetoclax (Ven), belantamab mafodotin (patients on the latter drug were considered as baseline fourth-line patients) were deemed as monotherapy regimens.

Patients were divided according to their eligibility for ASCT. For eligible patients, the induction phase prior to ASCT and the subsequent maintenance with lenalidomide were counted as single-line. In contrast, for patients not undergoing ASCT, treatment lines were identified exclusively based on the sequence of drug regimens over time, without applying ASCT-specific grouping rule.

To evaluate combination regimens, the prescriptions of the different drugs were searched over a time interval equal to the duration of the cycle plus an additional week to allow flexibility between prescriptions. In the event of a regimen without dexamethasone, it was brought back to the defined treatment regimen (dexamethasone was only mandatory to discriminate between R and Rd).

Since some prednisone prescriptions were found among the combinations of regimens with dexamethasone, prednisone was not considered in the definition of the combination regimens.

Healthcare resource consumption and related direct costs for the Italian NHS

HCRU was analysed at 1-year follow-up, in terms of all drugs and MM-related drugs, hospitalizations, and outpatient specialist services (laboratory tests, specialist visits, diagnostic procedures). The resulting direct costs sustained by the Italian NHS were calculated as follows: ex-factory price net of the confidential discount for LHUs for the drugs related to MM or other causes; single hospitalisation rate derived directly from the regionally assigned Diagnosis Related Groups (DRG) for all-cause hospitalisations and regional tariff nomenclator for outpatient services. Data were reported in Euros (€) as mean healthcare cost per patient during the first year of follow-up.

Statistical analysis

A descriptive statistical analysis was conducted on continuous variables, reported as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables expressed as numbers and percentages. According to "Opinion 05/2014 on Anonymization Techniques" drafted by the "European Commission Article 29 Working Party", the results of subgroups consisting of less than 3 patients were not disclosed, as potentially attributable to single individuals and reported as NI (not issuable). In cost analysis, outliers (values above more than 3 times the SD) were excluded. All the analyses have been performed using STATA SE version 17.0 (StataCorp LLC, College Station, TX, USA).

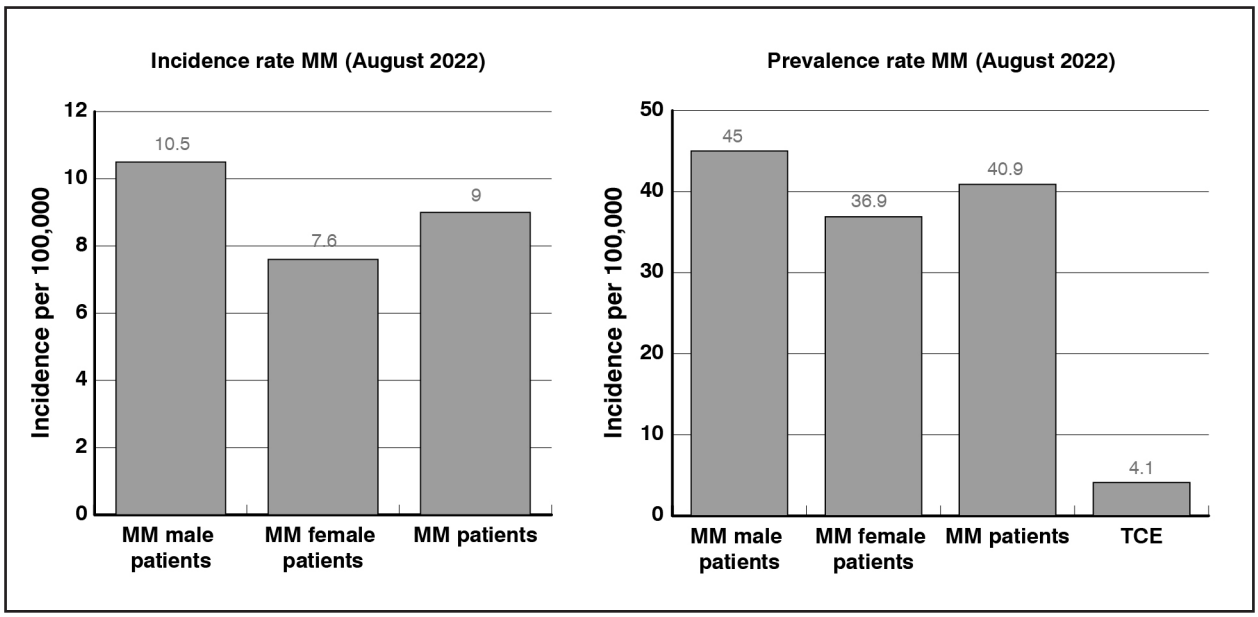


Figure 1. *Incidence of MM and prevalence of MM and TCE as of August 2022. By projecting the prevalence at 31st August 2022 on Italian population, we could estimate around 2,557 patients currently living with RRMM*
MM: multiple myeloma; RRMM: relapsed refractory; TCE: triple-class exposed

RESULTS

Epidemiology estimates

As of August 2022, the estimated annual incidence of new MM cases was 9/100,000 (10.5/100,000 men, 7.6/100,000 women) and the prevalence in August 2022 was 40.9/100,000 (45.0/100,000 in men, 36.9/100,000 in women). The prevalence of TCE was 4.1/100,000 inhabitants, which projected to the entire Italian population, corresponded to an estimate of 2,557 TCE patients as of 31 August 2022 (Figure 1).

Between January 2017 and June 2023, from a total sample of 12 million citizens, 6,102 patients with MM were extrapolated (none through the exemption code). Among them, 894 patients identified as TCE, 887 (99.2%) with at least one year of data availability prior to index-date were included. The distribution by year of inclusion shows an increasing trend of TCE patients over time (Table I).

The demographic and clinical characteristics of the included TCE MM patients are shown in Table II. The proportion of male sex was 53.7% and the mean age was 67 years. The modified CCI with the exclusion of the weight of cancer averaged 0.7, suggestive of a mild comorbidity profile. Among the 887 TCE patients included, 247 (27.8%) resulted to be eligible for ASCT: these patients had a mean age of 59.2 years, and the largest majority (98%) were aged below 70 years. However, the proportion of patients eligible for ASCT may be affected by the period of data availability, in the event that ASCT was performed before or after the period analysed.

Then, in order to identify the line of therapy, considering the different guidelines over the years, and to compare a more recent period and a past period, two sub-cohorts of patients were analysed: one included the 309 patients enrolled in the years between 2022 and 2023, the other included 339 patients enrolled between 2017 and 2021 with at least 3 years of data available prior to inclusion and 2 years after inclusion.

Year of inclusion	TCE patients, n (%)
2017	4 (0.5)
2018	73 (8.2)
2019	138 (15.6)
2020	189 (21.3)
2021	174 (19.6)
2022	257 (29.0)
January-June 2023	52 (5.9)

Table I. *TCE patients by year of inclusion*
TCE: triple-class exposed

	Patients with TCE (n=887)
Male sex, n (%)	476 (53.7)
Age at inclusion (years), mean (±SD)	67.0 (±9.6)
CCI, mean (±SD)	0.7 (±1.2)
• 0, n (%)	538 (60.7)
• 1, n (%)	243 (27.4)
• ≥2, n (%)	106 (12.0)
Patients eligible for ASCT, n (%)	247 (27.8)
Follow-up (years), mean (±SD)	1.0 (±1.2)

Table II. *Demographic and clinical characteristics of patients with MM included*
ASCT: autologous stem cell transplantation; CCI: Charlson Comorbidity Index; SD: standard deviation; TCE: triple-class exposed

	Patients with MM included in 2022-2023 (n=309)
Male sex, n (%)	167 (54.0)
Age at inclusion (years), mean (±SD)	66.2 (±10.2)
CCI, mean (±SD)	0.7 (±1.4)
• 0, n (%)	196 (63.4)
• 1, n (%)	71 (23.0)
• ≥2, n (%)	42 (13.6)
Patients eligible for ASCT, n (%)[1]	172 (55.6)
Follow-up (years), mean (±SD)	7.3 (±2.5)

Table III. *Demographic and clinical characteristics of the subset of 309 patients with MM included in the years 2022-2023*
[1] The number of eligible for ASCT also included 85 patients who received first-line induction treatment with DaraVTd but not transplanted yet due to the short follow-up
ASCT: autologous stem cell transplantation; CCI: Charlson Comorbidity Index; MM: multiple myeloma; SD: standard deviation

Patients included in the years 2022-2023

The characteristics of the subset of 309 patients included in the years 2022-2023 are depicted in Table III. The proportion of male sex was 54.0% and the mean age was 66.2 years, the CCI averaged 0.7, and 55.6% were eligible for ASCT.

Considering 172 patients with ASCT, 108 (62.8%) became TCE in first-line therapy, 40 (23.3%) in second-line and 20 (11.6%) in third-line (Table IVA). This subset also included the 85 patients who received first-line induction treatment with DaraVTd but had not received ASCT yet due to short follow-up. Of the 131 patients without ASCT, no patients became TCE during first-line therapy, 101 (77.1%) became TCE during second-line therapy, and 24 (18.3%) during third-line (Table IVB). Considering the 309 patients included in 2022-2023 (Table 4C), most of them were identified as second-line TCE (n=141, 46.5%), followed by

	A. Patients with ASCT (n=172)[1]	B. Patients without ASCT (n=131)	C. Total patients (n=309)[2]
TCE at first-line, n (%)	108 (62.8)	0 (0.0)	108(35.6)
TCE at second-line, n (%)	40 (23.3)	101 (77.1)	141 (46.5)
TCE at third-line, n (%)	20 (11.6)	24 (18.3)	44 (14.5)
TCE at fourth-line, n (%)	4 (2.3)	6 (4.6)	10 (3.3)

Table IV. *Treatment lines in TCE patients with available classification included in the years 2022-2023: (A) with ASCT (n=172), (B) without ASCT (n=131) and (C) total (n=309)*

[1] The number of eligible for ASCT also included 85 patients who received first-line induction treatment with DaraVTd but not transplanted yet due to the short follow-up

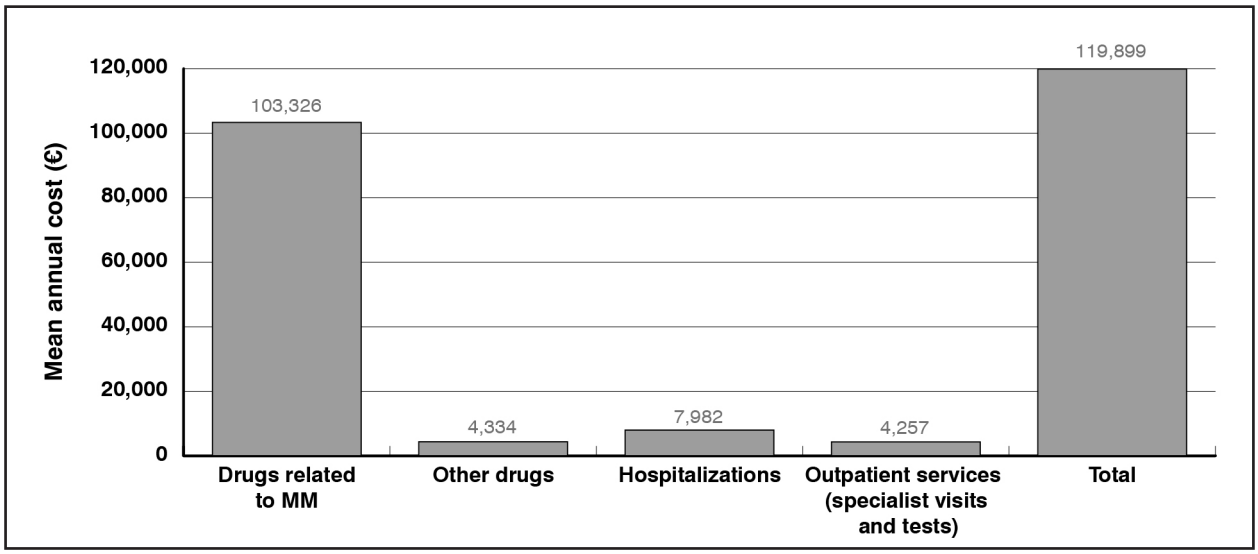
[2] For 6 patients, the number of lines could not be assigned with certainty

ASCT: autologous stem cell transplantation; TCE: triple-class exposed

Type of healthcare service	Mean (±SD)	Median (IQR)
N. of all drug prescriptions	62.1 (±21.4)	61 (26)
N. of MM-related drug prescriptions	28.6 (±11.2)	28 (13)
N. of other drug prescriptions	33.5 (±16.2)	32 (21)
N. of hospitalizations	1.0 (±1.3)	1 (1)
N. of outpatient specialist services	29.9 (±23.3)	28 (27)

Table V. *Annual HCRU per TCE patient at 1-year follow-up*

IQR: interquartile range; MM: multiple myeloma; SD: standard deviation; TCE: triple-class exposed



Cost per patient at 1-year follow-up (€)	Mean (±SD)	Median (IQR)
Drugs	107,661 (±47,516)	107,041 (66,260)
Drugs related to MM	103,326 (±47,619)	103,046 (68,504)
Other drugs	4,334 (±6,008)	2,141 (3,914)
Hospitalizations	7,982 (±18,132)	0 (6,307)
Outpatient services (specialist visits and tests)	4,257 (±5,463)	2,521 (4,824)
Total	119,899 (±47,434)	118,181 (66,320)

Figure 2. *Annual cost per TCE patient at 1-year follow-up*

first-line (n=108, 35.6%%) and third-line (n=44, 14.5%) and fourth-line (n=10, 3.3%) for total 303 patients. The number of lines could not be assigned with certainty for 6 patients. In addition, 17 patients (5.5%) had at least one other line after becoming TCE (proxy for refractory patients). In particular, 12 patients were eligible for ASCT, and 5 patients were not eligible for ASCT.

HCRU and direct costs

Resource consumption and average costs per TCE patient per year were assessed in 461 patients with at least 1-year follow-up. Concerning HCRU, there was an average number of 62 drugs per year, of which 29 were related to MM and 33 to other causes, one hospitalisation per year and 29 outpatient specialist services per year (Table V).

The average annual cost per patient was €119,899, of which €103,326 related to drugs for MM, that represented the most expensive item, followed by the cost for hospitalisations (€7,982), other drugs (€4,334) and outpatient services (€4,257) (Figure 2).

DISCUSSION

This analysis reported an updated estimate of the epidemiology of MM in Italy and described the current therapeutic management of the TCE MM population with the resulting economic impact for the NHS.

Our epidemiological findings align with existing literature in Italy, despite variability across studies due to differences in geographical areas, observation periods, and potential occupational risk factors [21-23]. A comparison of our estimates with those of the AIRTUM registry is not directly feasible, because of some disparities in the timeframe and in the disease setting. The AIRTUM data for the period from 1998 to 2002 reported an incidence rate of new yearly cases of 9.5 per 100,000 males and 8.1 per 100,000 females [24]. A successive AIRTUM report described a higher numbers incidence rate of rare lymphoid diseases, included MM, in Italy compared to the other European countries, but without estimates of the incidence of MM alone [6]. The latest report on cancer numbers in Italy of the Italian Association of Medical Oncology (AIOM) estimated around 3,530-3,590 new MM cases during 2024, calculated through the observed trend of the period 2013-2017 [25]. The prevalence rate of MM found in the present analysis in August 2022 was 40.9/100,000 (45.0/100,000 in men, 36.9/100,000 in women), so it resulted to be higher with respect to previous data from the Lombardy region (31/100,000) [26]. These discordant results might be explicated by the geographical disparities and the different data sources, as the study in Lombardy used a representative regional registry and the databases of National Cancer Institute in Milan [26].

A recent study in Italy by Mina et al. estimated 33,734 prevalent MM patients in 2020, suggesting that by 2027, treated patients are expected to grow from 28,499 to 35,074. One main reason beyond this rising projections lies in the introduction of lenalidomide and mAb therapies in earlier lines of therapy which led to longer survival and a higher proportion of patients receiving these drugs as first-line therapies [21]. In this analysis we observed an outstanding rise in the proportion of TCE (i.e. IMID, proteasome inhibitors, and anti-CD38 mAbs) from January 2017 to June 2023. Overall, the literature confirmed an increasing TCE proportions over time, with some differences related to the specific patient cohorts, countries, observation period, and healthcare settings examined. Real-world data from US databases reported that around one-third of MM patients identified before 2019 were TCE [27,28]. A successive analysis in Canada on 1,835 patients showed that 79% TCE MM were treated after 2020, 27% were >75 years old and 39% received a subsequent line of therapy [29].

The LocoMMotion study represents the first observational real-world analysis of TCE patients from European countries and the US. Most of the patients resulted to be triple-class refractory, after a median of four prior lines of therapy. Moreover, these patients received 92 treatments, each of them unique to the single patient, suggesting a lack of a standard of care options for heavily pretreated TCE MM patients [30], and strongly supporting the need for novel treatments. This view was further corroborated by the results of the ITEMISE study, a Delphi-like survey administrated to hematologists from August to October 2020 across Canada and nine European countries including Italy. The interviewed clinicians estimated that approximately 55% of patients would receive active treatment after TCE, equivalent to fourth-line treatment onward since diagnosis. The wide range of combination regimens confirm the lack of a shared approach and highlight a substantial clinical unmet need [31].

Considering the therapeutic sequences in patients with or without ASCT during the period 2022-2023, nearly two-thirds of MM patients with ASCT became TCE in first-line therapy, while none of the patients without ASCT became TCE during first-line therapy and about 77% became TCE during second-line. Regarding this markedly different therapeutic approach, it should considered that no first-line regimen including all three major drug classes is currently approved for transplant-ineligible MM patients in Italy. This regulatory constraint likely explains why none of the patients without ASCT became TCE during first-line therapy in our cohort. However, this scenario is expected to evolve with the upcoming availa-

bility of IsaVRd and DaraVRd for transplant-ineligible patients. Once implemented, these regimens may lead to a substantial increase in the proportion of non-transplant candidates who become TCE already in the first line of therapy. So far, first-line treatment strategies for transplant-ineligible MM patients have progressively included various combination therapies [32]. Historically, doublet regimens such as lenalidomide plus dexamethasone (Rd) have been commonly used, but more recent clinical trials have demonstrated improved outcomes with triplet regimens, leading to their increased adoption in this patient population [33]. In Italy, a study by Boccadoro and colleagues investigated the utilization of single agents and drug combinations in MM across treatment successive lines in the period 2021-2023, through a survey was administered to 15 centres of the Italian Working Group of the European Myeloma Network (EMN). The responders estimated approximately 890 new yearly diagnoses of MM. Among the transplant-eligible in 2021, the panel calculated that 66% were expected to receive a first line therapy with bortezomib-thalidomide-dexamethasone (VTD) and 32% of patients with daratumumab-bortezomib-thalidomide-dexamethasone (DVTd). For 2023, the experts forecasted a 15% decrease of VTD and a marked increase of DVTd (81%). Besides, the second and third-line lenalidomide-based combinations were deemed to decline over time and replaced by a 3-fold increase (from 7% to 23%) of pomalidomide-based regimens. These data describe the everchanging therapeutic management of MM patients, and reveal how with the availability of new drugs and combinations, the currently used options are expected to lose market share in favour of the most recent therapies, especially in later lines of therapy [34].

The analysis of the economic burden of TCE MM patients showed that 86% of the total healthcare costs were related to the expenses for medications for MM. These findings are not surprising considering that most MM patients can relapse or become refractory to treatment, and have to progress through several lines of therapy, which in turn require the use of multiple MM drug classes. Our economic analysis aligns with studies conducted overseas, although evidence remains limited in Europe. Data from US adults with MM extrapolated from the MarketScan and Medicare databases between January 2009 and February 2021 included TCE patients with at least one subsequent line of therapy after January 2017. The results showed that during an average follow-up of 20.9 months, 90.7% ($655,524 per patient) of the total all-cause healthcare costs were related to MM management, of which around 66.0% were expenses for MM drugs and infusions [35]. A more recent research examined 5,395 Medicare patients with relapsed or refractory MM TCE between January 2016 and 30 June 2019. The results confirmed that drug combinations to treat MM were the largest cost driver [28]. Data from the real clinical practice in Italy were made available by the Adelphi Real World MM Disease Specific Programme (DPS), based on large multinational surveys administered to physicians and their patients in five European countries (France, Germany, Italy, Spain and the UK) from May to November 2021. The surveys were focused on treatment patterns, HCRU and disease burden in MM patients. The results revealed that the treatments received became progressively more variable along with the later lines of therapy, depending on the previous treatment choices. About one-quarter of all patients were TCE, and their management implied a higher degree of HCRU and disease burden [19].

This study provides one of the first comprehensive, real-world overviews of TCE MM patients across multiple Italian regions, combining epidemiological estimates with detailed analysis of treatment patterns and healthcare resource use. The large population base (12 million individuals), robust longitudinal design, and integration of multiple healthcare administrative databases lend strong generalizability to the findings and offer valuable insights into national clinical practice and economic burden.

On the other hand, some limitations of this analysis must be acknowledged. First, the retrospective nature of the study and reliance on administrative claims data limit the availability of detailed clinical variables such as disease staging, cytogenetic risk profile, and response to therapy. Proxy measures were used to identify MM and TCE status, which may have led to potential misclassification or underestimation. Indeed, certain conditions like the diseases included in CCI, the eligibility to ASCT, the recognition of TCE MM status itself could be only identified using proxy for diagnosis, like hospitalization codes, exemption code and ATC codes for drug prescriptions, so some patients might have been missed. Secondly, it was not possible to identify the high-risk myeloma because cytogenetic abnormalities cannot be extrapolated from the administrative databases. Likewise, occupational risk factors, like the exposure to specific pesticides in agricultural work [23], could not be evaluated since this data are not traceable using the administrative flows. Moreover, the results are reported in an aggregated form, without discriminating the epidemiological estimates by region, even though MM numbers are known to be variable across geographical areas [21-23, 26]. Finally,

as newer combinations such as IsaVRd and DaraVRd become available, the treatment landscape, particularly for transplant-ineligible patients, is expected to shift, requiring ongoing updates to maintain relevance.

In conclusion, the present analysis confirmed the increasing numbers of TCE MM patients in Italy, and indicated a shift of attitude of prescribing more effective combination therapies in earlier lines of therapy, especially in patients with ASCT eligibility. Consistent with evidence from other counties, the use of complex medication regimes resulted in a significant economic burden from the NHS perspective. Taken together, these data from the real clinical practice in Italy suggest that, despite the evolving treatment landscape in MM, further efforts are still required to reduce disease and economic burden of the disease.

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Conflict of interest

VP, SM, and MC are employees of CliCon, which has received project funding by Pfizer for the conduct of the study.
RDV is an employee of Pfizer Italia, which funded the conduction of this study.
LDE is owner of CliCon, which has received project funding by Pfizer for the conduct of the study.

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