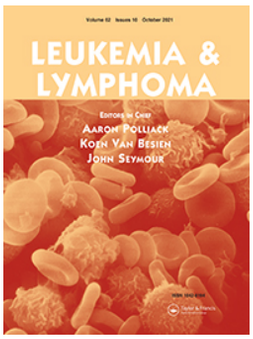

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ORIGINAL ARTICLE

Real-world analysis of patient characteristics, treatment outcomes, and healthcare resource utilization across Europe in patients with newly diagnosed multiple myeloma ineligible for stem cell transplantation who received lenalidomide- or bortezomib-based regimens

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ABSTRACT

We aimed to compare real-world outcomes, resource use, and costs for patients with newly diagnosed multiple myeloma (NDMM) treated with continuous first-line (1 L) lenalidomide or fixed bortezomib in Europe. We performed a multicenter, retrospective, observational chart review of transplant-ineligible NDMM patients across 7 countries. Of 453 eligible patients, 220 received 1 L lenalidomide-based regimens; 105 (47.7%) received second-line (2 L) treatment, of which 50 (47.6%) received 2 L bortezomib. 233 patients received 1 L bortezomib-based regimens; 142 (60.9%) had 2 L treatment, of which 104 (73.2%) received 2 L lenalidomide. Patients receiving 1 L lenalidomide-based regimens had better progression-free survival than patients receiving 1 L bortezomib-based regimens ($p = .002$) and a longer time to 2 L or third-line treatment (both $p < .05$). Total treatment-associated monthly costs for patients receiving 1 L lenalidomide-based regimens ($n = 171$, €2,268.55) were significantly greater than for 1 L bortezomib-based regimens ($n = 188$, €1,724.77) ($p < .001$) over the follow-up period (median, 38.7 months).

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Lenalidomide; bortezomib; multiple myeloma; transplant-ineligible; healthcare resource utilization; real world

Introduction

Multiple myeloma (MM) accounts for approximately 1.8% of all malignancies [1] and is the second most common hematological malignancy in Europe, with an estimated incidence of 6 per 100,000 people [2]. Outcomes for patients with MM have recently improved due to several therapeutic advances [3].

The FIRST trial investigated the efficacy and safety of lenalidomide and dexamethasone (continuous Rd; given until disease progression), Rd (fixed 18-month duration), and melphalan, prednisone, and thalidomide (MPT; given for 18 months) in patients with newly diagnosed MM (NDMM) [4]. Continuous Rd was associated with fewer treatment-related adverse events and extended progression-free survival (PFS) and overall survival (OS) compared with a fixed 18-month course of MPT [4–5]. Based on these data, lenalidomide received approval from the European Medicines Agency (EMA) in February 2015 for use in transplant-ineligible adults with NDMM [6].

The VISTA trial evaluated the efficacy of bortezomib with melphalan and prednisone in transplant-ineligible patients with NDMM and concluded that it was effective and well-tolerated [7]. Bortezomib received approval from the EMA in 2004 [8].

The European Hematology Association (EHA)-European Society for Medical Oncology (ESMO) guidelines recommend lenalidomide-based and bortezomib-based regimens as first-line (1 L) treatment options for transplant-ineligible patients with NDMM [9].

The use of these therapies for transplant-ineligible patients has improved clinical outcomes and increased the number of treatment options [4,5,9], but to our knowledge, there are no data that directly compare clinical characteristics, treatment outcomes (e.g. PFS), and healthcare resource utilization (HCRU) for transplant-ineligible patients in 1 L settings in Europe. The aim of this study was to examine real-world treatment

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outcomes and HCRU of transplant-ineligible patients with NDMM in Europe receiving 1 L treatment with continuous lenalidomide or fixed bortezomib.

Materials and methods

Study design

A multicenter, retrospective, observational chart review was performed for transplant-ineligible patients with NDMM who received lenalidomide or bortezomib as part of 1 L treatment. The study was conducted in 7 European countries (Austria, Belgium, France, Germany, Italy, the Netherlands, and Spain). No country-specific analyses were planned. An index period of June 1, 2015 to November 30, 2016 was used for all countries. Data were extracted retrospectively, at a single point in time, from eligible patient medical records from the index date until the most recent event, allowing at least a 24-month follow-up period by the start of data collection.

Eligible physicians were invited to complete electronic case record forms (eCRFs) for up to 10 patients who met the study inclusion and exclusion criteria. Eligible patients were identified by physicians in a consecutive manner from the index date (defined as the date of 1 L treatment initiation with either lenalidomide or bortezomib).

Study population

Eligible physicians were hematologists or hematologist-oncologists; spent $\geq$50% of their time in clinical practice and were responsible for treatment and management of patients with MM; treated and managed $\geq$2 transplant-ineligible patients with NDMM weekly; actively prescribed both lenalidomide and bortezomib during the index period; and were able to provide data for $\geq$3 patients per cohort (1 L lenalidomide and 1 L bortezomib).

Participating patients were aged >18 years; were diagnosed with NDMM; were transplant-ineligible; had a minimum of 24 months of follow-up data or complete data to the end date (i.e. death); received either continuous lenalidomide or fixed bortezomib as part of 1 L treatment for NDMM between June 1, 2015 and November 30, 2016; and completed $\geq$1 cycle of 1 L treatment with either drug. Patients participating in a clinical trial (including receiving 1 L treatment as part of a clinical trial) and those receiving combination therapy at 1 L that consisted of 2 targeted treatments (e.g. proteasome inhibitor [PI] + immunomodulatory drug, or 2 immunomodulatory agents) were excluded.

Outcome measures

The following data were collected and analyzed for each patient: patient and clinical characteristics, including demographics; time since diagnosis; MM staging at 1 L; Eastern Cooperative Oncology Group (ECOG) performance status at 1 L; comorbidities at 1 L; cytogenetics, fluorescence *in situ* hybridization (FISH), and molecular testing; calcium, renal, anemia, and bone (CRAB) criteria; bone lesions at diagnosis; treatment characteristics, including full treatment details for 1 L and any subsequent lines of treatment (administration frequency or number of cycles were not captured); health outcomes, including time to progression (time from start of treatment to date of progression), time to next treatment (TTNT; time from start of treatment to start of next treatment – included as a proxy measure of progression), response rate, and time to death (if applicable); and HCRU outcomes, including hospitalizations (including reason), additional supportive treatments, healthcare professional (HCP) visits, and monitoring tests. Only patients who had full data within an HCRU category were included in the analysis for that category.

Statistical methods

For all study objectives, standard descriptive statistics were used to describe outcomes. Numerical variables are presented as means, medians, and standard deviations (SD); categorical variables are presented as frequency and percentage of patients per category.

All statistical comparisons were between patients who received 1 L lenalidomide and or 1 L bortezomib. Bivariate tests were used to assess baseline clinical characteristics; the test used depended on the variable type.

Health outcomes (PFS, time to second-line treatment [TT2T], and time to third-line treatment [TT3T]) for patients who received lenalidomide and bortezomib were compared using the Kaplan–Meier (KM) estimator, a non-parametric statistic used to estimate the time to an event when incomplete observations are available [10]. A log-rank test was used to test for differences between treatment cohorts.

All analyses were performed using STATA v16.1.

HCRU usage and costing analysis

HCRU data were collected for each treatment line. Dates of occurrence were not abstracted for each resource. For the main analyses, data were pooled across the entire follow-up period. HCRU was

calculated as means per month per usage type to account for potential varying treatment durations. Patients with complete resource use data for an HCRU category were included in the HCRU analysis for that category.

Units were calculated per month for all patients; results are presented as HCRU units per patient per month (PPPM). If a supportive treatment or therapy was used but the total number of cycles or courses was unknown, a value of 1 was used, as it was known that the value was not zero. The same assumption was applied to HCP visits if it was known that a patient visited an HCP but the number of visits was unknown.

To estimate drug usage costs, unit costs were applied to targeted treatment (i.e. PIs, immunomodulatory agents, monoclonal antibodies) usage data only. Tariffs from the French health service perspective were sourced and applied to the targeted treatment usage data of all patients, across markets when conducting this analysis. The French costs selected *a priori* as drug costs (i.e. net) were expected to be the most transparently available, ensuring that a realistic estimate of treatment costs was derived across markets. A sensitivity analysis was conducted using targeted treatment costs sourced and applied from the other 6 markets to explore the robustness of any identified differences between treatment cohorts.

Costing assumptions

For all targeted treatments, a per mg per day cost was derived. As the number of cycles was not abstracted from the medical record, standard drug cycles were assumed based on EMA and US Food and Drug Administration (FDA) product labels and recommended dosages were used to derive this cost. When a standard cycle length was not available, a 28-day cycle was assumed. If regimen dosages differed by weight and body surface area, the mean weight and body surface area for the overall sample were used to derive the cost. If recommended dosages were not available for an observed treatment regimen, the lowest available cost for a similar regimen was assumed. For any treatments available in single-use vials, no vial sharing was assumed.

Ethics

The study was conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) and Guidelines for Good Pharmacoepidemiology Practices (GPP). The protocol was approved by a centralized Institutional Review Board (IRB) for methodological approval. Patient informed consent was not required for this study as all data were retrospective, aggregated, and anonymized.

Results

Physician and patient characteristics

Overall, 63 physicians across 7 European countries completed eCRFs for 453 patients (Austria: 41 patients; Belgium: 44; France: 104; Germany: 81; Italy: 51; the Netherlands; 44; Spain: 88). Physicians were mostly hematologists ($n = 34$; 54%). Physicians saw an average of 25 patients with MM per week.

A summary of the main patient and clinical characteristics is in Table 1. Of 453 patients assessed, 273 (60%) were male, and the median age at diagnosis was 74 (interquartile range [IQR], 69–78) years. At 1 L treatment initiation, 394 (87.0%) patients had International Staging System (ISS) stage II or III MM, and ECOG performance status was good (0 or 1) for 291 (64.2%) patients. Baseline patient and clinical characteristics were similar between patients who received 1 L lenalidomide and 1 L bortezomib. The proportion of patients with renal insufficiency (RI) by CRAB criteria was similar for those receiving 1 L lenalidomide and 1 L bortezomib (34.0% vs 36.1%, respectively; $p = .67$). Cytogenetics were similar for both cohorts. The median time to initiate 1 L treatment from diagnosis was 12.5 days and was similar for lenalidomide (11 days) and bortezomib patients (13 days) (Table 1).

Treatment patterns

Median follow-up time was 38.7 months (IQR, 32.5–44.9), with similar follow-up times observed for 1 L lenalidomide (median, 36.9 months; IQR, 31.8–44.6) and 1 L bortezomib patients (median, 39.9 months; IQR, 33.3–45.0). All patients initiated $\geq$1 line of treatment, with the mean number of treatment lines being 1.7 (SD, 0.7) (Table 1).

Of 453 patients, 247 (54.5%) received $\geq$2 lines of treatment and only 49 (10.8%) received $\geq$3 lines within the follow-up period. A smaller proportion of 1 L lenalidomide patients went on to 2 L and third-line (3 L) treatment versus 1 L bortezomib patients ($p = .001$) (Table 1). Treatments received at 1 L, 2 L, and 3 L are summarized in Table 2. The 2 L treatments for patients who received 1 L bortezomib and 1 L lenalidomide are displayed in a Sankey plot (Figure 1).

Table 1. Patient demographics and clinical characteristics.

Characteristic	Overall ($n = 453$)	1L LEN-based ($n = 220$)	1L BORT-based ($n = 233$)	p value[a]
Median age at diagnosis (IQR), years	74 (69–78)	74 (69–79)	73 (69–78)	.64
Male, *n* (%)	273 (60)	142 (64.6)	131 (56.2)	.08
BMI, kg/m^2	$n = 410$	$n = 199$	$n = 211$	
Median (IQR)	25.2 (23.3–27.5)	25.4 (23.4–27.8)	25.0 (23.3–27.1)	.33
Number of lines of treatment at data abstraction, *n* (%)	$n = 453$	$n = 220$	$n = 233$	.001
1	206 (45.47)	115 (52.27)	91 (39.06)	
2	198 (43.71)	89 (40.45)	109 (46.78)	
3	48 (10.60)	15 (6.82)	33 (14.16)	
4	1 (0.22)	1 (0.45)	0 (0.00)	
Mean number of lines	1.7	1.6	1.8	
ECOG PS at 1L treatment initiation, *n* (%)	$n = 453$	$n = 220$	$n = 233$	.44
0	70 (15.5)	34 (15.5)	36 (15.5)	
1	221 (48.8)	103 (46.8)	118 (50.6)	
2	129 (28.5)	64 (29.1)	65 (27.9)	
3	31 (6.8)	18 (8.2)	13 (5.6)	
4	2 (0.4)	1 (0.5)	1 (0.4)	
ISS stage at 1L treatment initiation, *n* (%)	$n = 453$	$n = 220$	$n = 233$	.05
Smoldering	4 (0.9)	2 (0.9)	2 (0.9)	
I	34 (7.5)	23 (10.5)	11 (4.7)	
II	140 (30.9)	70 (31.8)	70 (30.0)	
III	254 (56.1)	115 (52.3)	139 (60.0)	
Unknown or missing	21 (4.6)	10 (4.5)	11 (4.7)	
Cytogenetics, *n* (%)	$n = 409$	$n = 195$	$n = 214$	
Normal	167 (41)	75 (38.5)	92 (43.0)	.37
del(17p)	41 (10)	21 (10.8)	20 (9.4)	.74
t(4;14)	62 (15)	27 (13.9)	35 (16.4)	.49
t(14;16)	34 (8)	16 (8.2)	18 (8.4)	1
t(14;20)	12 (3)	8 (4.1)	4 (1.9)	.24
t(11;14)	33 (8)	20 (10.3)	13 (6.1)	.15
t(6;14)	18 (4)	9 (4.6)	9 (4.2)	1
1q+	17 (4)	8 (4.1)	9 (4.2)	1
Abnormalities chromosome 13	27 (7)	11 (5.6)	16 (7.5)	.55
Hyperdiploid	20 (5)	9 (4.6)	11 (5.1)	.82
No cytogenetic testing undertaken	44 (10)	25 (12.8)	19 (8.9)	
CRAB criteria, *n* (%)	$n = 393$	$n = 188$	$n = 205$	
Hypercalcemia	121 (31)	54 (28.72)	67 (32.68)	.44
Renal insufficiency	138 (35)	64 (34.04)	74 (36.10)	.67
Anemia	294 (75)	149 (79.26)	145 (70.73)	.06
Bone lesions	231 (59)	112 (59.57)	119 (58.05)	.83
Time to initiate 1L treatment from diagnosis (days)	$n = 432$	$n = 210$	$n = 222$	
Median (IQR)	12.5 (3.0–36.5)	11 (2.0–53.0)	13 (3.0–33.0)	.05
Treatment follow-up time	$n = 453$	$n = 220$	$n = 233$	
Median (IQR)	38.7 (32.5–44.9)	36.9 (31.8–44.6)	39.9 (33.3–45.0)	.06

[a]p value comparison is between patients who received 1 L LEN-based regimens vs. patients who received 1 L BORT-based regimens.
1L: first-line; BORT: bortezomib; BMI, body mass index; CRAB: calcium, renal, anemia, and bone; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; ISS: International Staging System; LEN: lenalidomide.

Overview of 1 L treatment regimens

Patients were stratified by 1 L lenalidomide- or bortezomib-based treatment. Of 453 patients, 220 (48.6%) received lenalidomide at 1 L and 233 (51.4%) received bortezomib (76.4% subcutaneously, 23.6% intravenously) (Table 2). The most common 1 L lenalidomide-based regimen was Rd ($n = 194$; 88.2%) per the indication, while 15 (6.8%) patients received lenalidomide + prednisone (RP). The most common 1 L bortezomib-based regimen was bortezomib + melphalan + prednisone (VMP) ($n = 83$; 35%) per the indication, followed by bortezomib + low- or high-dose dexamethasone (VD) ($n = 82$; 35%) and bortezomib + cyclophosphamide + dexamethasone (VCd) ($n = 32$; 13%). Overall, 33% of patients received treatment that included chemotherapy at 1 L; cyclophosphamide and melphalan were the most frequently used chemotherapies. Consistent with the approved label, a higher proportion of bortezomib-treated patients received chemotherapy at 1 L. Overall, 97% of patients received a corticosteroid at 1 L.

The median time to treatment discontinuation (treatment start date to treatment end date) was 22.1 and 10.2 months for patients who received 1 L lenalidomide and 1 L bortezomib, respectively.

Overview of subsequent 2 L treatment regimens

Overall, 247 (54.5%) patients received 2 L treatment during the follow-up period (Figure 1, Table 2). Of the 220 patients who received 1 L lenalidomide, 105 (47.7%) received 2 L treatment, of which 50 (47.6%) received 2 L bortezomib; the most common

Table 2. Overview of treatments received at 1 L, 2 L and 3 L.

	1L			2L			3L		
Treatment, *n* (%)	Overall (*N* = 453)	1L LEN (*n* = 220)	1L BORT (*n* = 233)	Overall (*n* = 247)	1L LEN (*n* = 105)	1L BORT (*n* = 142)	Overall (*n* = 49)	1L LEN (*n* = 16)	1L BORT (*n* = 33)
Targeted treatment									
Lenalidomide	220 (48.57)	220 (100.00)	0 (0.00)	126 (51.01)	22 (20.95)	104 (73.24)	9 (18.37)	1 (6.25)	8 (24.24)
IV bortezomib	55 (12.14)	0 (0.00)	55 (23.61)	11 (4.45)	6 (5.71)	5 (3.52)	2 (4.08)	0 (0.00)	2 (6.06)
SC bortezomib	178 (39.29)	0 (0.00)	178 (76.39)	46 (18.62)	44 (41.90)	2 (1.41)	11 (22.45)	11 (68.75)	0 (0.00)
Daratumumab	–	–	–	28 (11.34)	10 (9.52)	18 (12.68)	19 (38.78)	7 (43.75)	12 (36.36)
Pomalidomide	–	–	–	12 (4.86)	6 (5.71)	6 (4.23)	14 (28.57)	5 (31.25)	9 (27.27)
Thalidomide	–	–	–	9 (3.64)	3 (2.86)	6 (4.23)	2 (4.08)	1 (6.25)	1 (3.03)
Elotuzumab	–	–	–	8 (3.24)	7 (6.67)	1 (0.70)	–	–	–
Carfilzomib	–	–	–	59 (23.89)	29 (27.62)	30 (21.13)	5 (10.20)	1 (6.25)	4 (12.12)
Ixazomib	–	–	–	20 (8.10)	1 (0.95)	19 (13.38)	3 (6.12)	2 (12.50)	1 (3.03)
Chemotherapy									
Bendamustine	3 (0.66)	2 (0.91)	1 (0.43)	2 (0.81)	1 (0.95)	1 (0.70)	1 (2.04)	0 (0.00)	1 (3.03)
Cisplatin	1 (0.22)	0 (0.00)	1 (0.43)	1 (0.40)	1 (0.95)	0 (0.00)	–	–	–
IV cyclophosphamide	19 (4.19)	4 (1.82)	15 (6.44)	4 (1.62)	2 (1.90)	2 (1.41)	–	–	–
Oral cyclophosphamide	20 (4.42)	3 (1.36)	17 (7.30)	8 (3.24)	6 (5.71)	2 (1.41)	1 (2.04)	0 (0.00)	1 (3.03)
Doxorubicin	4 (0.88)	0 (0.00)	4 (1.72)	2 (0.81)	1 (0.95)	1 (0.70)	–	–	–
Oral idarubicin	1 (0.22)	0 (0.00)	1 (0.43)	1 (0.40)	0 (0.00)	1 (0.70)	–	–	–
Liposomal doxorubicin	2 (0.44)	0 (0.00)	2 (0.86)	–	–	–	–	–	–
IV melphalan	8 (1.77)	0 (0.00)	8 (3.43)	1 (0.40)	1 (0.95)	0 (0.00)	1 (2.04)	1 (6.25)	0 (0.00)
Oral melphalan	94 (20.75)	1 (0.45)	93 (39.91)	12 (4.86)	12 (11.43)	0 (0.00)	2 (4.08)	2 (12.5)	0 (0.00)
Panobinostat	–	–	–	–	–	–	2 (4.08)	0 (0.00)	2 (6.06)
Corticosteroid									
High-dose dexamethasone	142 (31.35)	65 (29.55)	77 (33.05)	87 (35.22)	37 (35.24)	50 (35.21)	14 (28.57)	3 (18.75)	11 (33.33)
Low-dose dexamethasone	191 (42.16)	130 (59.09)	61 (26.18)	115 (46.56)	43 (40.95)	72 (50.70)	20 (40.82)	7 (43.75)	13 (39.39)
Prednisone	110 (24.28)	18 (8.18)	92 (39.48)	37 (14.98)	19 (18.10)	18 (12.68)	6 (12.24)	1 (6.25)	5 (15.15)
Other	1 (0.22)	1 (0.45)	0 (0.00)	–	–	–	1 (2.04)	1 (6.25)	0 (0.00)

1 L: first-line; 2 L: second-line; 3 L: third-line; BORT: bortezomib; IV, intravenous; LEN: lenalidomide; SC, subcutaneous.

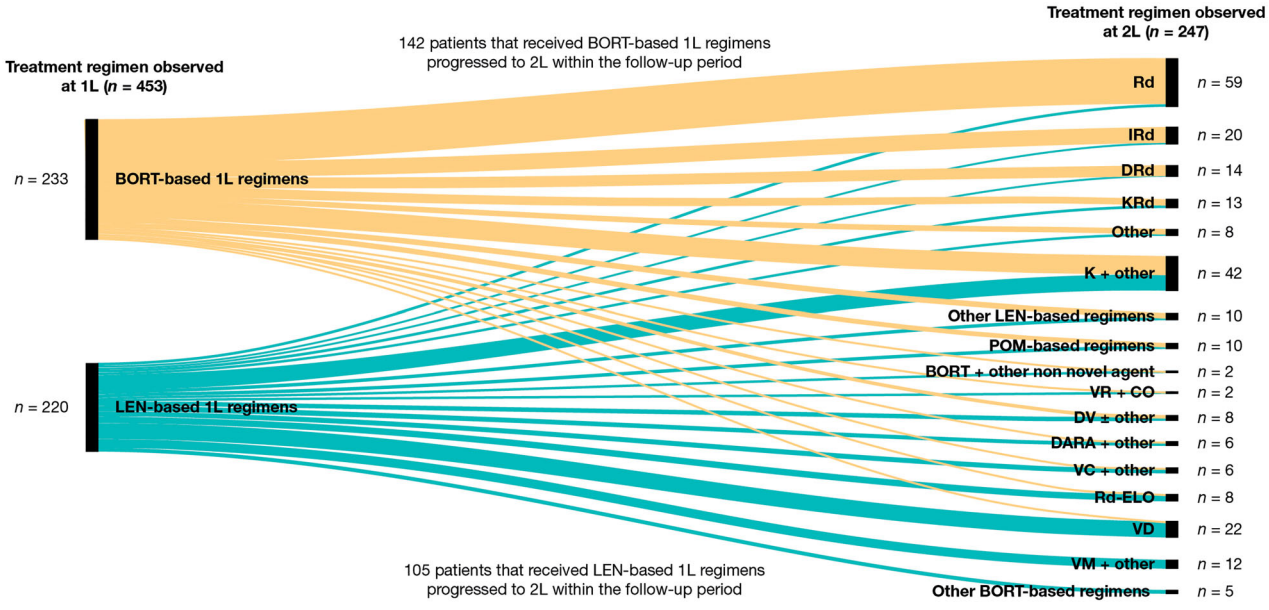


Figure 1. 2 L treatment regimens for patients who received 1 L LEN or 1 L BORT. 1 L: first line; 2 L: second line; BORT: bortezomib; CO: corticosteroid; DARA: daratumumab; DRd: DARA + Rd; DV: DARA + BORT; ELO: elotuzumab; IRd: ixazomib + Rd; K: carfilzomib; KRd: carfilzomib + Rd; LEN: lenalidomide; POM: pomalidomide; Rd: LEN + dexamethasone; VC: BORT + corticosteroid; VD: BORT + dexamethasone; VM: BORT + melphalan; VR: BORT + lenalidomide.

bortezomib-based combinations were VD (*n* = 21; 20%) and VMP (*n* = 11; 10%).

Of 233 patients who received 1 L bortezomib, 142 (60.9%) received 2 L treatment, of which 104 (73.2%) received 2 L lenalidomide. Forty-four (31%) patients received lenalidomide with another targeted agent (i.e. a PI, immunomodulatory agent, or monoclonal antibody); the most common regimens were ixazomib + Rd (IRd) (*n* = 19; 13%), daratumumab + Rd (DRd) (*n* = 13; 9%), and carfilzomib + Rd (KRd) (*n* = 9;

6%). Fifty-six (39%) patients received lenalidomide per the indication (Rd) at 2 L.

A total of 239 (97%) patients received a treatment regimen containing a corticosteroid and 50 (20%) patients received chemotherapy at 2 L.

Overview of subsequent 3 L treatment regimens

During the follow-up period, 49 (11%) patients received 3 L treatment (Table 2). As the median follow-up period was 38.7 months (IQR, 32.5–44.9), only a limited number of patients were expected to progress to 3 L during this study. Of 220 patients who received 1 L lenalidomide, 16 (7%) received 3 L treatment, of whom 11 (68.8%) received a bortezomib-based regimen at 3 L. The combinations received were variable, with 13 different treatment combinations observed. Bortezomib + daratumumab ± corticosteroid was the most common regimen observed.

Of the 233 patients who received 1 L bortezomib, 33 (14%) patients had 3 L treatment. Daratumumab- (36%), pomalidomide- (27.3%), and lenalidomide- (24%) based regimens were most frequently used.

At 3 L, all patients received a targeted agent; 82% of patients received a corticosteroid and 33% received chemotherapy.

Clinical outcomes

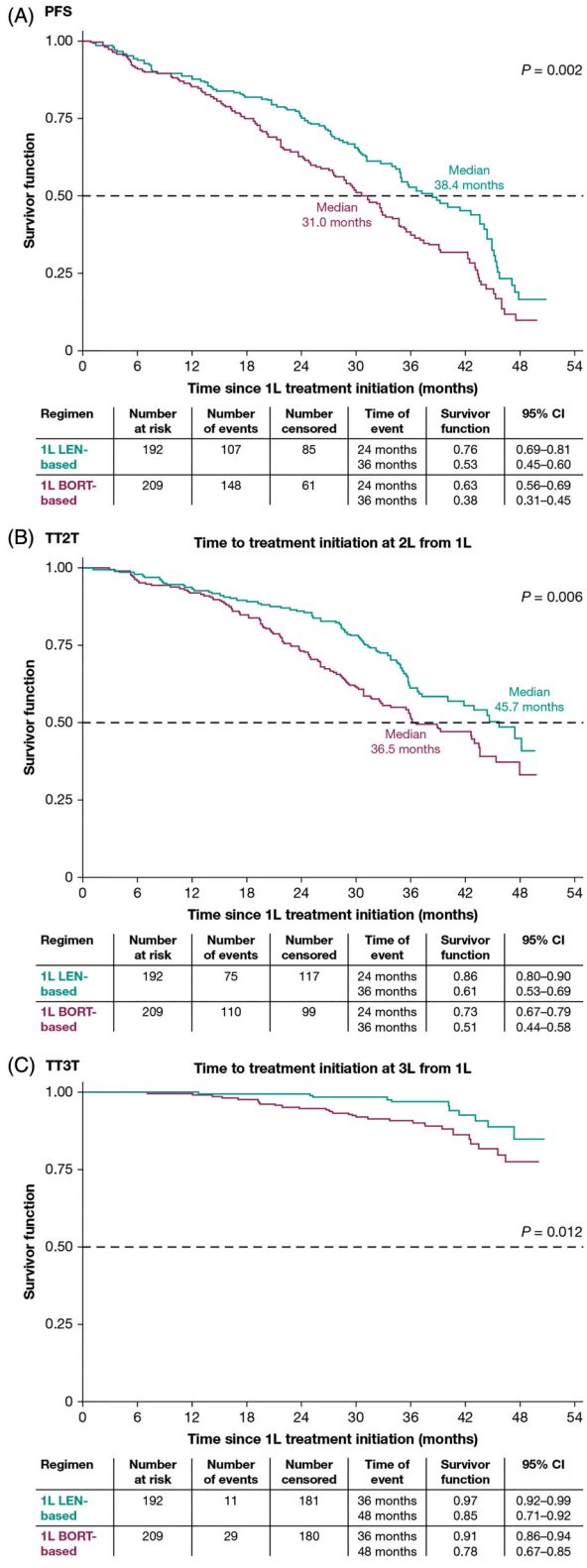
PFS

A significantly longer PFS ($p = .002$) was estimated for 1 L lenalidomide versus 1 L bortezomib patients (median, 38.4 vs 31.0 months, respectively; (Figure 2(A)). KM estimates indicated that a smaller proportion of 1 L lenalidomide patients would experience disease progression at 24 and 36 months than 1 L bortezomib patients (24% vs 37% and 47% vs 62%, respectively) (Figure 2(A)).

TTNT

A significantly longer TT2T ($p = .006$) was estimated by KM for 1 L lenalidomide versus 1 L bortezomib patients (median, 45.7 vs 36.5 months, respectively). Compared with bortezomib-based regimens, KM analyses estimated that a smaller proportion of patients who received lenalidomide-based regimens at 1 L would start 2 L at 24 months (14% vs 27%) and 36 months (39% vs 49%) after 1 L initiation (Figure 2(B)).

A significantly longer ($p = .012$) TT3T was estimated by KM for 1 L lenalidomide than for 1 L bortezomib patients. Median TT3T could not be estimated for either cohort, as few patients received 3 L treatment



Regimen	Number at risk	Number of events	Number censored	Time of event	Survivor function	95% CI
1L LEN-based	192	107	85	24 months 36 months	0.76 0.53	0.69–0.81 0.45–0.60
1L BORT-based	209	148	61	24 months 36 months	0.63 0.38	0.56–0.69 0.31–0.45

Regimen	Number at risk	Number of events	Number censored	Time of event	Survivor function	95% CI
1L LEN-based	192	75	117	24 months 36 months	0.86 0.61	0.80–0.90 0.53–0.69
1L BORT-based	209	110	99	24 months 36 months	0.73 0.51	0.67–0.79 0.44–0.58

Regimen	Number at risk	Number of events	Number censored	Time of event	Survivor function	95% CI
1L LEN-based	192	11	181	36 months 48 months	0.97 0.85	0.92–0.99 0.71–0.92
1L BORT-based	209	29	180	36 months 48 months	0.91 0.78	0.86–0.94 0.67–0.85

Figure 2. Clinical outcomes (A) PFS, (B) TT2T, and (C) TT3T for patients who received 1 L LEN or 1 L BORT. 1 L: first line; 2 L: second line; 3 L: third line; BORT: bortezomib; CI, confidence interval; LEN: lenalidomide; PFS: progression-free survival; TT2T: time to 2 L treatment; TT3T: time to 3 L treatment. Only patients with data variables recorded were included in this analysis.

Table 3. Comparison of HCRU and targeted treatment costs across the follow-up period for patients who received lenalidomide or bortezomib at 1L.

	1L LEN		1L BORT		
HCRU category	*N*	Mean (SD)	*N*	Mean (SD)	*p* value
Supportive treatments[a]	170	0.968 (1.322)	177	0.943 (1.209)	.856
Supportive therapies[b]	184	0.041 (0.086)	196	0.049 (0.131)	.295
Hospitalizations (inpatient admissions)[c]	162	0.238 (0.387)	176	0.256 (0.478)	.662
HCP visits	184	0.487 (0.474)	196	0.545 (0.513)	.053
Monitoring tests conducted	184	2.573 (3.026)	196	2.787 (3.496)	.313
Targeted treatment costs	*N*	PPPM mean (SD), €	*N*	PPPM mean (SD), €	*p* value
Full follow-up period	171	2,268.55 (1,132.70)	188	1,724.77 (1,222.97)	.001
1L	186	2,205.61 (1,089.87)	202	1,203.38 (949.64)	<.001
2L	83	2,665.49 (2,833.59)	117	3,863.07 (2,752.83)	.012

[a]Includes analgesics, antibiotics, anticoagulants, anti-emetics, antifungals, antivirals, bisphosphonates, denosumab, erythropoiesis-stimulating agents, laxatives and proton pump inhibitors.
[b]Includes dialysis, blood transfusion, plasmapheresis and radiotherapy.
[c]Does not include drug administration visits needed for BORT.
1 L: first-line; 2 L: second-line; BORT: bortezomib; €: Euro; HCP: healthcare professional; HCRU: healthcare resource utilization; LEN: lenalidomide; PPPM: per patient per month; SD: standard deviation.

Table 4. Treatment-associated costs across the follow-up period.

	Treatment costs, €[a]						
	Overall (*N* = 359)		1L LEN (*n* = 171)		1L BORT (*n* = 188)		Difference[b]
Tariff, €	Mean	SD	Mean	SD	Mean	SD	
Austria	5,925.2	4,236.4	8,328.0	4,274.8	3,815.6	2,853.5	–4,512.3*
Belgium	2,410.7	1,733.2	3,236.7	1,672.0	1,685.6	1,436.2	–1,551.1*
France	1,979.0	1,212.3	2,268.5	1,132.7	1,724.8	1,223.0	–5,43.8*
Germany	4,393.3	2,576.9	5,225.4	2,558.5	3,662.7	2,362.7	–1,562.7*
Italy	5,438.5	3,172.2	6,240.6	3,043.8	4,734.4	3,115.1	–1,506.2*
Netherlands	3,477.0	2,049.4	4,043.5	1,982.9	2,979.7	1,976.7	–1,063.8*
Spain	3,390.7	2,027.5	3,945.9	1,942.3	2,903.3	1,974.8	–1,042.6*

[a]For markets where specific drug tariffs were not able to be sourced, the lowest tariff across the other markets for that drug was used.
[b]Difference is the mean value in the 1 L BORT column minus the mean value in the 1 L LEN column.
*Statistically significant difference observed ($p < .001$).
1 L: first-line; BORT: bortezomib; €: Euro; LEN: lenalidomide; SD: standard deviation.

during the follow-up period. Compared with bortezomib-based regimens, KM estimates predicted that a smaller proportion of patients who received lenalidomide-based regimens at 1 L would start 3 L at 36 months (3% vs 9%) and 48 months (15% vs 22%) after 1 L initiation (Figure 2(C)).

HCRU

No significant differences were observed between cohorts regarding the use of supportive treatments or supportive therapies, hospitalizations, HCP visits, and monitoring tests conducted (Table 3). HCRU related to treatment administration may be underestimated, as drug administration visits were not explicitly captured in this study.

HCRU and treatment-associated costs

Overall, 359 patients had full treatment-related data across the follow-up period and were included in the cost analysis. The total treatment-associated costs PPPM were significantly higher ($p < .001$) for patients receiving 1 L lenalidomide-based regimens ($n = 171$; €2,268.55) versus 1 L bortezomib-based regimens ($n = 188$; €1,724.77) (Table 3).

To explore where the differences in treatment-associated PPPM costs occurred, costs at 1 L and 2 L were compared between cohorts. At 1 L, bortezomib patients had significantly lower targeted treatment-associated PPPM costs than lenalidomide patients (€1,203.38 vs €2,205.61, respectively). 1 L bortezomib patients who received 2 L treatment had significantly higher targeted treatment-associated PPPM costs at 2 L than 1 L lenalidomide patients who received 2 L treatment (€3,863.07 vs €2,665.49, respectively) (Table 3).

Treatment costs for 1 L lenalidomide patients were significantly higher than for 1 L bortezomib patients regardless of the tariff applied. The sensitivity analysis demonstrated that the French tariff analysis provided the lowest overall mean cost (€) across the 7 countries and the lowest total difference between the 2 treatment groups. The Austrian tariff represented the highest overall cost and the largest difference between the 2 treatment groups (Table 4).

Discussion

This study provides insights into real-world treatment patterns, clinical outcomes, and HCRU for patients with NDMM treated with continuous lenalidomide and fixed bortezomib regimens across 7 European countries.

Our data show that in 1 L, most lenalidomide was prescribed per the label (i.e. as Rd), while bortezomib was commonly prescribed without melphalan. This may indicate that clinicians prefer a regimen without melphalan to manage toxicity, and may explain differences in PFS and TTNT. We also found that physicians prescribed lenalidomide and bortezomib to a similar proportion of patients with RI at 1 L, suggesting they are equally confident of the safety and efficacy of lenalidomide-based regimens for patients with myeloma-related RI. While the specific dosage of lenalidomide prescribed to patients with renal impairment (RI) has not been captured in this analysis, several studies have shown lenalidomide-based regimens to be efficacious and safe for patients with myeloma-related RI [11–13].

Transplant-ineligible patients with NDMM who received 1 L lenalidomide had significantly better clinical outcomes, including longer PFS ($p = .002$), TT2T ($p = .006$), and TT3T ($p = .012$), compared with patients treated with 1 L bortezomib. Our results are similar to those from a recent US claims database study, which suggested that lenalidomide-based treatment regimens are associated with a longer TTNT versus Vd [14].

Although HCRU costs were higher for 1 L lenalidomide in our study, these were associated with longer PFS, TT2T, and TT3T. This could potentially reduce the number of lines of treatment that patients receive, alleviating their treatment burden.

The difference in treatment costs that was observed may be explained in part by the longer TT2T for lenalidomide patients. Lenalidomide is given until progression, whereas bortezomib is given for a fixed period. Consistent with the label recommendations, we observed that the time to treatment discontinuation at 1 L was significantly longer for lenalidomide than for bortezomib, which is recommended to only be given in up to 9 × 6-week cycles. Dosing until progression for lenalidomide produced cost differences but also resulted in improved outcomes.

Patients who received 1 L bortezomib were likely to receive lenalidomide at later lines, and many of the lenalidomide-based treatment regimens observed at 2 L involved >1 targeted agent. Therefore, targeted treatment costs at 2 L were higher for 1 L bortezomib patients than for those who received 1 L lenalidomide.

Drug costs have previously been shown to be the main contributor to total HCRU costs associated with MM [15]. By delaying progression and 2 L treatment initiation, the use and associated cost, of combination regimens (such as doublet and triplet regimens) can be reduced. At 2 L and 3 L, multiple targeted agents may be used in combination. In a changing treatment landscape, triplet therapy may become the standard of care at 1 L, as the addition of bortezomib to Rd [16], and daratumumab in combination with VD or Rd, improves OS and PFS [9]. As quadruplet regimens are shown to improve OS and PFS in patients with NDMM [17], 1 L costs could increase further.

Few studies have looked at cost patterns for transplant-ineligible patients with NDMM. A US claims data study demonstrated that 1 L lenalidomide patients had lower mean monthly costs in the first 3 years after initiating 1 L treatment versus 1 L bortezomib [18]. Treatment administration was the biggest cost contributor for bortezomib, where bortezomib patients accrued greater costs in the outpatient setting. Costs declined steadily over time within a line of treatment and therefore cost reductions may be expected by increasing time to 2 L. In another study, transplant-ineligible patients with NDMM who received 1 L lenalidomide had a greater TT2T (used as a proxy for progression) and lower costs per month [19]. In addition to HCRU benefits, treatment at home has been reported as a preferred option for patients with cancer [20] and oral treatments could have more relevance, for example in the current COVID-19 pandemic [21].

Given the 2 L cost findings of the current study, it is plausible that if a longer follow-up period was observed, overall treatment costs may have been more similar between cohorts. The costs associated with drug administration were not captured in this study. As bortezomib is likely to be administered in the outpatient setting with HCP support, whereas lenalidomide is an oral treatment, the overall cost difference observed in this study may be lower if treatment administration costs were included.

This study was conducted at multiple sites and countries and is reflective of real-world practice due to the limited screening criteria. However, some limitations should be noted. Only physicians who actively prescribed both lenalidomide and bortezomib during the predefined index period were included. To mitigate this, physicians were recruited from different regions and practices. A lack of treatment administration cost data is a limitation of this study, and while HCRU data were captured for each line of treatment, we were unable to specify the exact time of intense resource use. Many months may include zero usage and will wash out intense usage around key events,

such as disease progression. Median PFS values were based on KM estimations using medical record data and may differ from those reported in randomized trials.

This study addresses a gap in the literature by using real-world evidence to compare health outcomes and treatment costs of transplant-ineligible patients with NDMM who received initial 1 L treatment with either lenalidomide or bortezomib. When compared with 1 L bortezomib patients, 1 L lenalidomide patients had significantly longer median PFS, and significantly fewer patients progressed to 2 L and 3 L within the follow-up period. Although the costs over the follow-up period for 1 L lenalidomide patients were significantly greater than those of 1 L bortezomib patients, the majority of 1 L bortezomib patients received lenalidomide at 2 L and often in combination with other targeted agents; a longer follow-up period could inform whether currently observed cost differences would remain constant or vary.

Disclosure statement

EZ received honoraria from Amgen, Celgene (BMS), Janssen, Sanofi, and Takeda; participated on an advisory board for Amgen, Celgene (BMS), Janssen, and Sanofi; and participated on a speakers bureau for Amgen, Celgene (BMS), Janssen, Sanofi, and Takeda. SD is an employee of and has equity interests in BMS. AG is a former employee of Adelphi Real World. AM is an employee of Adelphi Real World. MR received honoraria from Amgen, Celgene (BMS), Janssen, and Takeda; and received travel fees from Amgen, Celgene (BMS), Janssen, Sanofi, and Takeda.

Author contributions

All authors contributed to and approved the manuscript, the authors are fully responsible for all content and editorial decisions for this manuscript. Editorial assistance was provided by Lynne Cairns, PhD, of Excerpta Medica, funded by Bristol Myers Squibb.

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