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Real-word assessment of treatment patterns and outcomes in patients with relapsed-refractory Multiple Myeloma in an Italian haematological tertiary care centre

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Real-word assessment of treatment patterns and outcomes in patients with relapsed-refractory Multiple Myeloma in an Italian haematological tertiary care centre

Sonia Morè[1], Laura Corvatta[2], Maria Valentina Manieri[1], Attilio Olivieri[1], Massimo Offidani[1]

[1]Clinica di Ematologia Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona; [2]U.O.C. Medicina, Ospedale Profili, Fabriano, Italy

Corresponding author:

Massimo Offidani, MD

Clinica di Ematologia, Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona

Via Conca, 71, 60020 Ancona, Italy

Tel: +390715964735

Mail: massimo.offidani@ospedaliriuniti.marche.it

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Abstract

Despite significant improvements in therapeutic options, multiple myeloma (MM) patients experience a series of remissions and relapses requiring further lines of therapy (LOTs). We analysed treatment pathways, attrition rates (ARs) and refractoriness patterns across LOTs in 413 MM patients treated from 2011 and 2021. Across LOT-2 to LOT-5 ARs were 26%, 27%, 34% and 37.5%, being 50% for subsequent LOTs. In univariate analysis age >65 years, ISS II/III, >2 comorbidities, no transplant and no maintenance therapy were significantly associated with AR but regression analysis selected only age > 65 years and >2 comorbidities. Median PFS was 40.5 months, 19.5, 10.3, 6 and 4.7 from LOT-1 to LOT-5. Lenalidomide-refractory patients, among those relapsed after LOT-1, were 26% and 64.5%, respectively, in patients starting therapy <2019 *vs* ≥2021. In the two cohorts, 57.5% and 85.5% of patients relapsed after LOT-2 were lenalidomide-refractory. Among patients not relapsed from LOT-1, 80% are receiving continuous lenalidomide and could become refractory to it, whereas 91% and 51.5% of patients in LOT-2 could become potential lenalidomide- and daratumumab-refractory, respectively. In our analysis the rate of patients reaching subsequent LOTs was higher than previously reported and the increase in early refractoriness could make licensed treatments not usable or ineffective.

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Introduction

Multiple Myeloma (MM) is a very complex and heterogeneous haematological disease that in Italy is diagnosed in over 5,000 people every year[1].

Natural history of most MM patients is to receive many lines of therapy until their disease becomes refractory and incurable[2]. Nevertheless, several cross-sectional real-life studies[3-5] found a high rate of patients not achieving subsequent lines of therapy and an increasing worsening of survival outcomes line by line. However, the cross-sectional studies, by their very nature, take into account neither the changes regarding therapeutic approaches occurring over time nor the therapeutic regimens licensed in the different places.

Really, in the last decade novel drugs as proteasome inhibitors (PIs), immunomodulatory agents (IMIDs) and monoclonal antibodies (mAbs) have been licensed for using in the early relapsed/refractory Multiple Myeloma (RRMM), moving then in the newly diagnosed (NDMM) setting as continuous or maintenance therapy[4,5], increasing double- and triple-refractory patients at early relapse. These patients may be orphan of suitable treatment options in a not so far time. Currently, as demonstrated by real-life MAMMOTH[6] and LocoMMotion[7] studies, there are no standard of care (SOC) for patients exposed/refractory to PIs, IMiDs and anti-CD38 mAbs and the outcome in terms of response, duration of response (DoR) and survival is totally unsatisfactory. Nevertheless, the retrospective MAMMOTH study[6] has been conducted in the United States (USA) where drugs approval and administrative treatment modality are completely different from those in force in Italy. In contrast with MAMMOTH, the LocoMMotion study[7] prospectively enrolled MM patients in USA and in many countries of Europe where the availability of new drugs can take place at very different time due to authorization timelines for medicines pricing and reimbursement procedures at national level. So that, to have a real idea of what has happened in recent years and of the future possibilities in the treatment of MM, it is necessary to consider the data nation by nation.

The aim of this study was to assess treatment pathway and outcomes of a MM population referred to a tertiary Italian haematological centre, focusing on the attrition rate (AR) and refractoriness patterns per line of treatment.

Patients and Methods

Population, study design and assessment

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This is a retrospective observational longitudinal study describing a real-life population of MM patients referred to our centre from 2011 and 2021. All patients met the International Myeloma Working Group (IMWG) criteria for MM diagnosis[8].

The objectives of this study were treatment patterns and outcomes of relapse-refractory MM patients, attrition rate (AR) in the subsequent lines of therapy and dynamic evolution of refractoriness across the lines of therapy and over time.

The outcomes considered were Overall Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) assessed by IMWG criteria[9]. AR was defined as the rate of patients who did not receive a subsequent line of therapy, because of any reasons, out of the total of relapsed patients from the previous line of therapy. Refractoriness to the anti-myeloma agents was defined as the follow: "double-refractory" as refractory to 1 IMiD and 1 PI; "triple-refractory" as refractory to 1 IMiD, 1 PI and 1 CD38 mAb; "quad-refractory" as refractory 2 IMiDS, 1 PI and 1 CD38 mAb or 1 IMiD, 2 PIs and 1 CD38 mAb; "penta-refractory" as refractory to 2 IMiDs, 2 PIs and 1 CD38 mAb[6]. Current refractoriness status was defined that of patients already relapsed throughout the different LOTs whereas the potential refractoriness one was defined as the future refractoriness of patients exposed to agents but not yet relapsed.

Data collection and statistical analysis

Data were collected prospectively on a specific electronic data-base and revised by at least 2 expert physicians for quality check. Missing data was internally searched and treated as appropriate. Sample size was not calculated given the observational nature of the study but we payed attention to have adequate sample for any specific analysis.

The study was conducted according to Declaration of Helsinki and it was approved by Internal Review Committee which ruled that the mandatory signature of informed consent could be waived.

Categorical variables were summarized by number of observations and percentage and compared by chi-square test. Continuous variables were described by median and range and compared by Kruskall-Wallis non-parametric test. Time-dependent events (PFS, OS and time to attrition with therapy interruption as event) were analysed according to Kaplan-Meier methods and compared by log-rank test. Factors affecting AR were searched by univariate and multivariate logistic regression analysis. All analyses were conducted using SPSS statistical package (version 27).

Results

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Study population

We analysed data from 413 newly diagnosed MM patients, treated from 2011 to 2021. The patients' characteristics are summarized in Table 1. Median age was 69 years (range 30-93), ECOG PS ≥ 2 was found in 22% of patients, R-ISS stage II/III and renal failure were detected in 72% and 18% of patients respectively. One hundred and ninety-nine patients (48%) were transplant eligible. Through the lines of therapy, 105 patients (25%) have been enrolled in experimental studies. Median follow-up was 48.7 months (range 6-132 months).

Treatment summary and attrition rate

Among 413 patients who received a first line of therapy (LOT-1), 270 relapsed and 200 patients (74%) received a second line of therapy (LOT-2) (Figure 1). A second relapse occurred in 145 patients and 92 patients (63%) underwent a third line of therapy (LOT-3). Among patients experiencing a third relapse, 66% received a fourth line of therapy (LOT-4) whereas a fifth line (LOT-5) and a further line (LOT-6) were given to 62.5% and 50% of patients, respectively. As regard AR it was 26%, 27%, 34%, 37.5% from LOT-2 to LOT-5, being 50% for subsequent therapies (Figure 1). Comparing TE with NTE patients, AR was 9% *vs* 40% (p<0.0001) in LOT-2, 16.5% *vs* 59% (p<0.0001) in LOT-3 and 28 % *vs* 48 % (p=0.053) in LOT-4, respectively.

The main causes of attrition in any lines of therapy were death or poor overall status-life expectancy of the patients. In univariate analysis age > 65 years, ISS II/III ≥ 2 comorbidities, no transplant, response < VGPR and no maintenance therapy were significantly associated with AR but multivariate analysis selected only age > 65 years [OR 7.4 (3.3-16.5)] and > 2 comorbidities [OR 2.5 (1.5-5.6)] as factors affecting AR (Table 2).

We administered 31, 30, 31, 23 and 17 different treatment regimens in LOT-1, 2, 3, 4 and 5 respectively (Figure 2, SDC, Tables 1-5). The main drugs and regimens we used are pictured in the Table 3. The most frequent regimens administered as induction therapy were bortezomib, thalidomide, dexamethasone (VTD = 27%), other bortezomib-based regimens (26.7%) and lenalidomide-based combinations (19%). In LOT-2 the most frequently used treatments were bortezomib-based (29.5%) and lenalidomide-based (27%) regimens while a daratumumab-based therapy was given to 14.5% of patients. In LOT-3 patients received mainly lenalidomide- (22%), pomalidomide- (20.5%), bortezomib- and carfilzomib-based regimens with or without IMiDs (13% and 12%, respectively) whereas anti-CD38 MoAbs-based regimens were given to 14% of patients. In LOT-4 and LOT-5 pomalidomide-based regimens were the most used (22% and 32%, respectively).

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Refractoriness over time and potential refractoriness

Considering that in Italy the use of lenalidomide maintenance in patients who had undergone ASCT has been possible since 2018 and that in NDMM the applicability of daratumumab-containing regimens was allowed since the beginning of 2021, we compared refractoriness status of MM patients beginning therapy before 2019 (< 2019 cohort), in or after 2019 (≥ 2019 cohort) and in or after 2021 (≥ 2021 cohort). Among patients who relapse after induction therapy (1st relapse), the proportion of those refractory to lenalidomide was 26% in < 2019 cohort *vs* 49.5% and 64.5% in ≥ 2019 and ≥ 2021 cohorts, respectively. Double-refractory patients were 1% in the < 2019 cohort, increasing to 3% in the later cohort as well as triple-refractory patients rose from 0% to 3% in early and later cohort, respectively. As regard rates of refractoriness to daratumumab, they were 0.5% *vs* 5% *vs* 6.5% across the different cohorts (Figure 3). In patients who experienced a second relapse, rates of lenalidomide refractoriness ranged from 57.5% in the < 2019 cohort to 85.5% in the ≥ 2021 cohort whereas double- and triple-refractory patients increased from 12.5% to 43% and from 0 to 28.5%, respectively. Less than 1% (0.5%) of patients were refractory to daratumumab in the early cohort *vs* 35.5% in the later one (Figure 3). In the most recent cohort all patients (100%) with a 3rd relapse were refractory to lenalidomide and double- and triple-refractory were 87.5% and 62.5%, respectively. The rate of quad-refractory patients increased from 21.5% in the cohort ≥ 2019 to 25% in the > 2021 cohort whereas that of penta-refractory from 14.5% to 25%, respectively (Figure 3). Moreover, in the later cohort 87% of patients were refractory to daratumumab (Figure 3).

Among patients who did not relapse after LOT-1 and are receiving continuous therapy, the potential refractoriness to lenalidomide is 80% whereas those to daratumumab and daratumumab plus lenalidomide are 34.5% and 20.5%, respectively. Moreover, a rate of 15.5% of patients could become double refractory and 11% triple-refractory. In patients who are receiving a LOT-2 after a 1st relapse and have not been experienced a further relapse, the potential refractoriness to lenalidomide is 91%, to daratumumab 51.5% and to daratumumab plus lenalidomide 45.5%. Moreover, 45% and 33% of patients could become double- and triple-refractory, respectively (Figure 4).

Activity and efficacy

The best responses obtained with regimens used across LOT-1 to LOT-5 are summarized in the Table 3.

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Considering the whole study population, in transplant eligible (TE) OS at 5 and 10 years were 80% and 55%, respectively, whereas they were 55% and 23% in non-transplant eligible (NTE) ones (Figure 5).

Median PFS was 40.5 months in LOT-1, 19.5 in LOT-2, 10.3 in LOT-3, 6 in LOT- 4 and 4.7 in LOT-5 (Figure 6), whereas median OS was 83, 38.3, 24, 12.2 and 10.5 months, respectively.

In the 37 double refractory patients, median PFS and OS were 6.7 and 15.5 months, respectively. Depending on whether patients received a subsequent therapy or palliative care, median PFS was 8.1 *vs* 2.8 months, respectively (p=0.005) while median OS was 20 *vs* 7 months for the two groups, respectively (p=0.017). In patients treated with an anti-CD38 mAb- or carfilzomib-based regimens, median PFS was 9.5 months compared to 4.7 months in patients receiving other treatments (p=0.063) as well as median OS was 20.3 *vs* 12.3 months, respectively (p=0.03). As regard response to treatment in double refractory patients, median PFS was 9.9 *vs* 3.9 months in patients achieving ≥ PR *vs* < PR (p=0.012) and median OS was 20 *vs* 15.1 months, respectively (p=0.054). Depending on whether patients became double refractory within the first 2 lines of therapy or afterwards, median PFS and OS were 8 *vs* 5.5 months (p=0.78) and 19 *vs* 8 months (p=0.057), respectively.

Comparing double refractory patients according to age, those aged ≤ 65 years had a median PFS of 8 *vs* 4.7 months for patients younger (p=0.55) whereas median OS was 15 *vs* 16 months, respectively (p=0.87).

The 19 triple refractory patients had a median PFS of 3.9 months and a median OS of 5.2 months. Median PFS was 4.9 *vs* 3.2 months in patients receiving either a subsequent therapy or palliative care, after becoming refractory (p=0.123). Median OS was 9 *vs* 3.3 months respectively (p= 0.013). Patients obtaining at least a partial remission had a median PFS of 6.8 *vs* 3.4 months, compared to those not responding (p=0.017). Median OS was 13.3 *vs* 3.9 months, respectively (p=0.05). Depending on whether patients became triple refractory within the third lines of therapy or afterwards, median OS was 5.2 *vs* 4.5 months, respectively.

Twenty-two patients became daratumumab-refractory in first, second or third line of therapy. Regardless of the timing of refractoriness, median PFS was 3.5 months and median OS was 4.5 months. Patients who received a subsequent line of therapy had a median PFS of 6.8 months *vs* 1.5 months of patients treated with palliative care (p=0.003). Median OS was 16 *vs* 3 months in the two groups, respectively (p=0.001).

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Discussion

At this moment, natural history of MM is characterized by the alternation of remission and relapse phases that become progressively shorter. Our study confirms that, currently, more than 50% of TE transplant eligible patients with MM survived 10 years and that 5-yrs OS of NTE patients is more than 50%.

Driven by the observation of our real life data that seemed profoundly different from those reported by Raab et al[3] in a European cross-sectional study, our analysis aimed to assess whether this impression was true. Considering the initial study population, we also observed a progressive reduction in the percentage of patients reaching subsequent treatment lines but, taking into account the number of relapsed patients, the rate of patients who received therapy at the time of each relapse was very higher. AR was found to be nearly constant across LOT-2 to LOT-3 (nearly a quarter of patients), it increased to one third of patients in LOT-4 and LOT-5 and reaching 50% in subsequent LOTs. The increasing of AR with each successive LOT has been reported by Fonseca et al[10] in a study using three US patient-level databases covering the period 2000-2018. However, in our NTE patient population we found a not negligible lower AR for LOT-2, being 57% in the US study and 40% in our one probably related to more effective frontline treatments we used both in TE and NTE patients. Really, for TE patients, ARs across LOT-1 to LOT-3 ranged from 9%-28% *vs* 21%-37% reported by Fonseca et al. These data seem to support that early use of very effective and well tolerated therapies could reduce ARs in MM patients.

Retrospective studies conducted in Europe showed a great heterogeneity nation by nation regarding treatment patterns due to local guidelines recommendations or limitations in reimbursement. In the Weisel et al study, TE patients received VTD regimen in a range of 1% to 65% from Germany to Italy[11] as well as another European retrospective observational study,[12] showed a real difference in treatment patterns of NTE patients across 4 European countries. Taking extreme heterogeneity of the real-world practice in Europe into account, it seemed to us more suitable and useful to analyse treatment patterns within a single country.

Several recent studies focused on the growing issue of refractoriness across lines of therapy, limiting further therapeutic options.[8,9,15]. In our study, aimed to examine refractoriness pattern and its change throughout years, we found that 64.5% of patients in first relapse, in or after 2021, were refractory to lenalidomide. However, 80% of our patients are receiving continuous lenalidomide-based frontline treatment, so, potentially, only 20% of patients could be able to receive lenalidomide in LOT-2. Until recently, in Italy, only PVd (pomalidomide, bortezomib, dexamethasone) regimen[18] has been

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approved for this population whereas among triplets including Kd and anti CD-38 mAbs, potentially bridging the gap of IMiDs-free regimens in RRMM, only Isa-Kd (isatuximab, carfilzomib, dexamethasone) triplet[13] has been approved, whereas Daratumumab-Kd has been not[14].

Moreover, we observed an increase rate of patients refractory to anti-CD38 and, particularly, near 10% of patients already relapsed from LOT-1 are nowadays anti-CD38 plus lenalidomide-refractory. However, nearly 20% of patients are receiving a frontline anti-CD38 plus lenalidomide-based regimen and nearly one third (34.5%) an anti-CD38-based treatment. These patients could become a new hard unmet medical need considering that retreatment with anti-CD38 mAbs seems to be not effective[15] and there are no approved regimens tested for this population in first relapse in Italy. To be underlined as a distinguishing Italian feature is that the rate of double-refractory patients who relapse after induction therapy is negligible since VRd regimen has been recently approved only for NTE patients and its use is very low in Italy[16], as confirmed also by our experience.

Among patients who experienced a second relapse and underwent a LOT-3 more recently, near one third were double- or anti-CD38-refractory but these latter could potentially become more than 50% in a short time. In these patients, using pomalidomide combinations is the rule although deciding which partner to combine with it represents a real challenge[17,18]. Moreover, other drugs/regimens with alternative mechanism of action are not available in Italy.[19,20,21,22,23]

The matter gets even more challenging moving to LOT-4 where 62.5% of patients in the most recent our cohort are triple-refractory. These patients could be the ideal candidates to anti-BCMA therapies but, in Italy, both CAR-T cell therapies and bispecific antibodies have not yet been approved, so currently treatment of the fourth line of therapy is the most important unmet medical need in Italy and, as proof of this, 23 different regimens were used in our population. Overall, in LOT-5 we used 16 alternative combinations before the belantamab-mafodotin approval[24].

The finding of PFS and OS decreasing through subsequent LOTs, observed by Yong et al and Verelst et al in European real-life studies[25,26], was confirmed in our experience, yet. Nevertheless, PFS and OS of our patients were considerably longer than those reported above due to availability of more effective therapies across the multiple LOTs such as anti-CD38 mAb- or carfilzomib-containing regimens.

On the contrary, median PFS (4.9 months) and OS (9 months) we observed in triple-refractory patients were comparable with those reported in the retrospective US MAMMOTH[8] and prospective multinational LocoMMotion[9] studies. These results demonstrate that current real-life treatments of

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triple-refractory MM are not well established and ineffective paving the way for the use of drugs with new mechanisms of action.

Our experience shows that AR is very lower than previously described; therefore, new drugs experimentation in the later lines of therapy should be continued. Despite our data demonstrated a significant improvement in the recent years, treatment of multi-refractory MM patients remains a challenge. Upgrades of outcomes will risk be frustrated by the rising of refractoriness in even earlier lines of therapy, due to the earlier and earlier approval of new drugs or regimens. A significant step forward would be the availability of new treatments that have been approved for specific population of refractory patients rather than for specific lines of therapy.

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Disclosures

SM: Honoraria from Amgen, Janssen

LC: Honoraria from Celgene, Janssen, Amgen;

Table 3 Treatments and response rates across subsequent lines of therapy

AO: non conflict of interest

MO: Honoraria from and Advisor for AbbVie, Amgen, BMS, Celgene, GSK, Janssen, Roche, Sanofi, Takeda

Author Contributions

Study design: MO, SM; LC, MVM; Statistics: MO; Data management: MO, SM; LC, MVM; Analysis of data: MO, SM, LC, MVM; Manuscript writing: MO, SM; LC, MVM; Reading, comments and approval of manuscript: All authors

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Table 1. Baseline characteristics

Characteristics	N = 413
Median age (range), years	69 (30-93)
≤ 65 years (%)	162 (39)
≤ 75 years (%)	293 (71)
>75 years (%)	120 (29)
Male, n (%)	200 (48)
ECOG score, n (%)	
0	182 (44)
1	141 (34)
2	74 (18)
3	16 (4)
ISS stage, n (%)	
I	153 (37)
II	149 (36)
III	111 (27)
R-ISS stage, n (%)	
I	102 (25)
II	247 (60)
III	50 (12)
Not evaluable	14 (3)
Renal failure, n (%)	76 (18)
Comorbidities, n (%)	
0	80 (19)
≤ 2	178 (43)
> 2	119 (29)
Not evaluable	36 (9)
Isotype, n (%)	
IgG	220 (53)
IgA	98 (24)
IgD	1 (0.3)
Light chain only	89 (21.5)
Non-secretor	5 (1.2)
ASCT, n (%)	171 (41)
Follow-up, median (range), months	48.7 (6-140)

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Table 2. Univariate and multivariate analyses for Attrition Rate

	Univariate analysis OR	**p**	**Multivariate Analysis OR (95% CI)**	**p**
Age > 65 years	6.5	0.001	7.4 (3.3-16.5)	<0.001
Comorbidities ≥ 2	3.4	0.024	2.5 (1.5-5.6)	0.01
ISS stage II/III	1.5	0.054	-	
Response < VGPR	2.1	0.047	-	
No transplant	2.5	0.032	-	
No maintenance	2.7	0.043	-	

OR = Odds Ratio; CI = confidence interval; VGPR = very good partial remission; ISS= International Staging System

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Table 3 Treatments and response rates across subsequent lines of therapy

Line of therapy	**LOT-1**	**LOT-2**	**LOT-3**	**LOT-4**	**LOT-5**
Number of patients	413	200	92	45	25
Regimen, n (%)					
Thalidomide-based	34 (8)	4 (2)	4 (4)	2 (4)	4 (16)
Lenalidomide-based	77 (19)	54 (27)	20 (22)	2 (4)	
Pomalidomide-based		4 (2)	19 (20.5)	10 (22)	8 (32)
Bortezomib-based	105 (25.5)	50 (25)	11 (12)	2 (4)	2 (8)
Carfilzomib-based	17 (4)	10 (5)	5 (5.5)	5 (11)	1 (4)
Ixazomib-based	4 (1)	2 (1)		1 (2)	
Bortezomib + Thalidomide-based	113 (27)	8 (4)			
Bortezomib + Lenalidomide-based	5 (1.2)	1 (0.5)	1 (1)		
Carfilzomib + Lenalidomide-based	16 (3.5)	7 (3.5)	6 (6.5)		
Elotuzumab-based	5 (1.2)	18 (9)	3 (3)	1 (2)	1 (4)
Daratumumab-based	23 (5.5)	29 (14.5)	10 (11)	3 (7)	3 (12)
Isatuximab-based	6 (1.5)		3 (3)	2 (4)	
Venetoclax-based		2 (1)	3 (3)		
Belantamab Mafodotin			1 (1)	2 (4)	1 (4)
Other	8 (2)	11 (5.5)	6 (6.5)	15 (33)	5 (20)
Lenalidomide maintenance	90 (22)				
ORR (≥ PR), n (%)	85	70	52	31.5	9.5
CR, n (%)	37	25	16.5	8	0

ORR = overall response rate; CR = complete response

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Figure legends

Figure 1. Flow-chart of the study cohort

Figure 2. Treatment patterns during various lines of therapy

Figure 3. Refractoriness across lines of therapy (A) Refractoriness after LOT-1 (B) Refractoriness after LOT-2 (C) Refractoriness after LOT-3

Figure 4. Potential refractoriness in LOT-1 (A) and in LOT-2 (B)

Figure 5. Progression free survival in the whole population (A) and in transplant and not-transplant eligible patients (B); overall survival in the whole population (C) and in transplant and not transplant eligible patients (D)

Figure 6. PFS of the study population across different lines of therapy

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Abbreviations

Fig. 1. AR: Attrition Rate

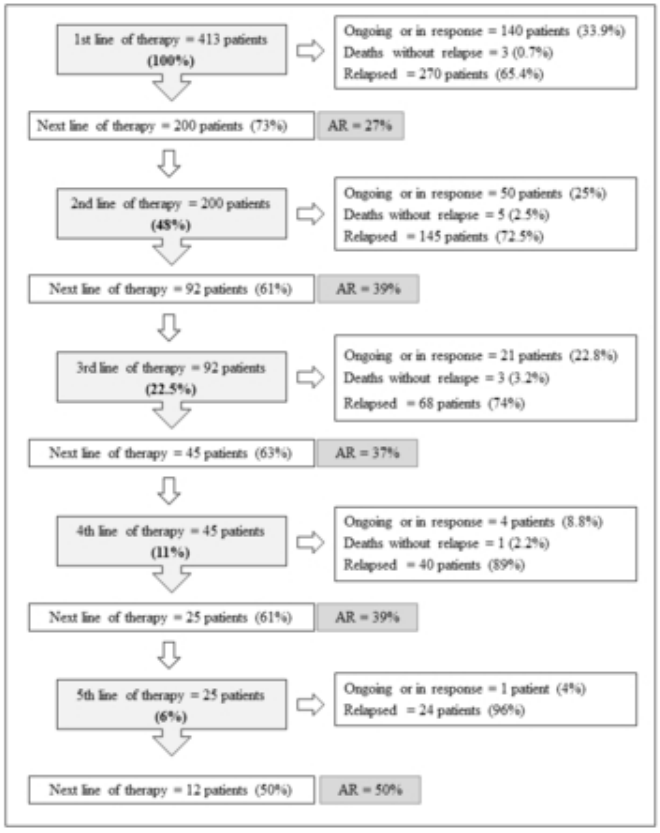
Fig. 2. CHT: chemotherapy, IMID: Immunomodulatory drugs, PI: Proteasome Inhibitors

Fig. 3. Dara+L: daratumumab plus lenalidomide

Fig. 4. Dara+L: daratumumab plus lenalidomide

Fig. 5. TE: transplant eligible; NTE: not transplant eligible

Figure 1 Flow-chart of the study cohort



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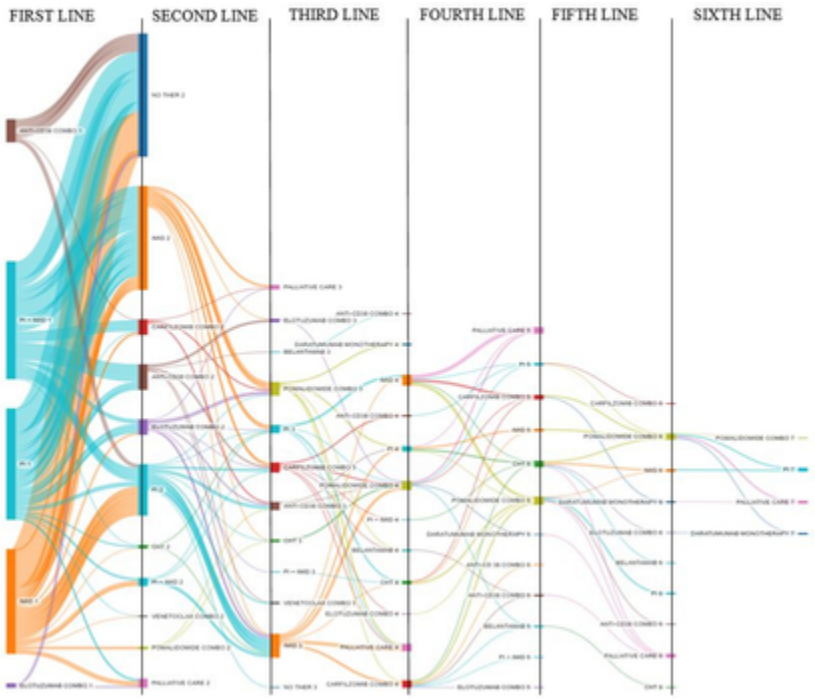

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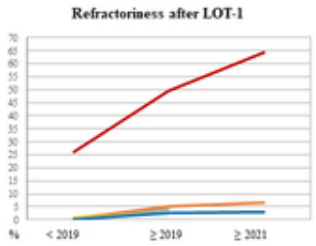
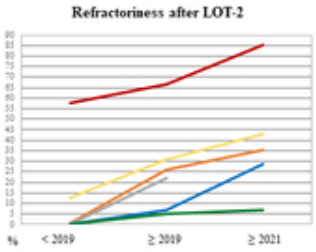
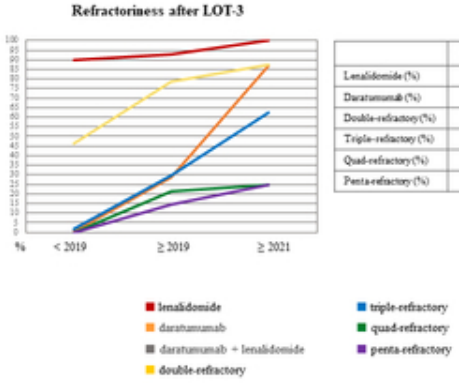


	< 2019	≥ 2019	≥ 2021
Lenalidomide (%)	26	49.5	64.5
Daratumumab (%)	0.5	5	6.5
Lenalidomide + daratumumab (%)	0	4	
Double-refractory (%)	1	2.5	3
Triple-refractory (%)	0	2.5	3



	< 2019	≥ 2019	≥ 2021
Lenalidomide (%)	57.5	66.5	85.5
Daratumumab (%)	0.5	26	35.5
Lenalidomide + daratumumab (%)	0	22	
Double-refractory (%)	12.5	31	43
Triple-refractory (%)	0	7	28.5
Quad-refractory (%)	0	5	7



	< 2019	≥ 2019	≥ 2021
Lenalidomide (%)	90	93	100
Daratumumab (%)	0.5	28.5	87
Double-refractory (%)	46.5	78.5	87.5
Triple-refractory (%)	2	29.5	62.5
Quad-refractory (%)	0	21.5	25
Penta-refractory (%)	0	14.5	25

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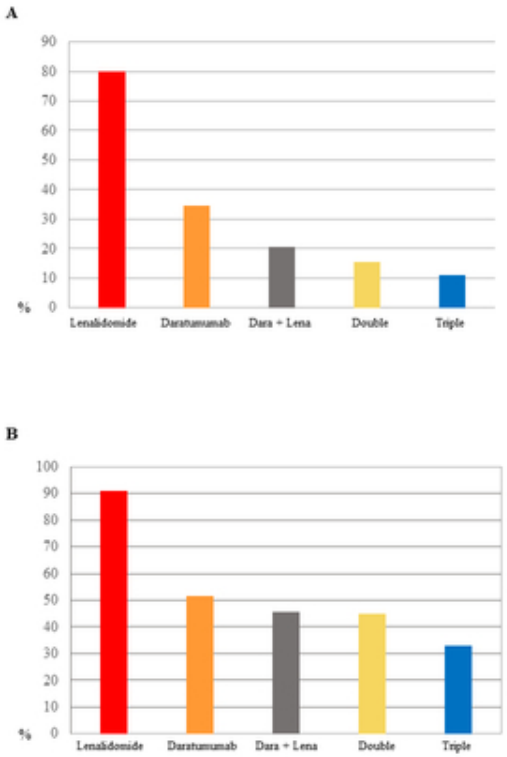

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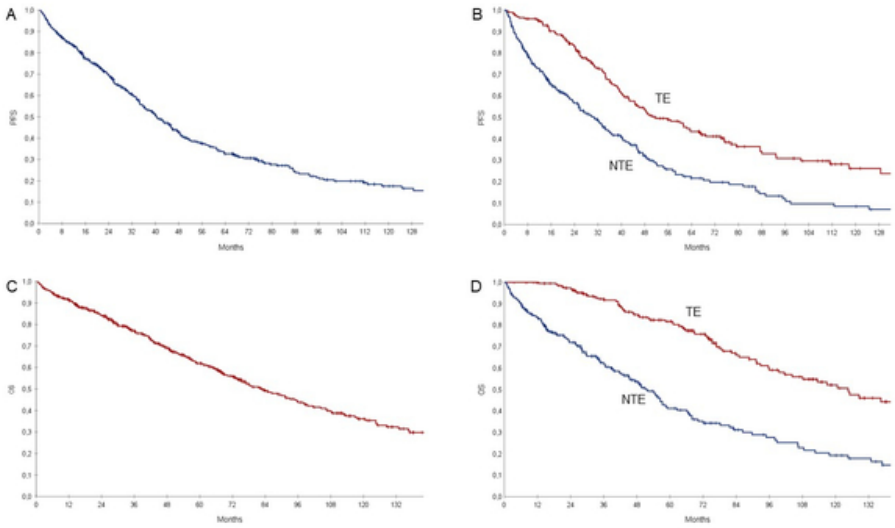

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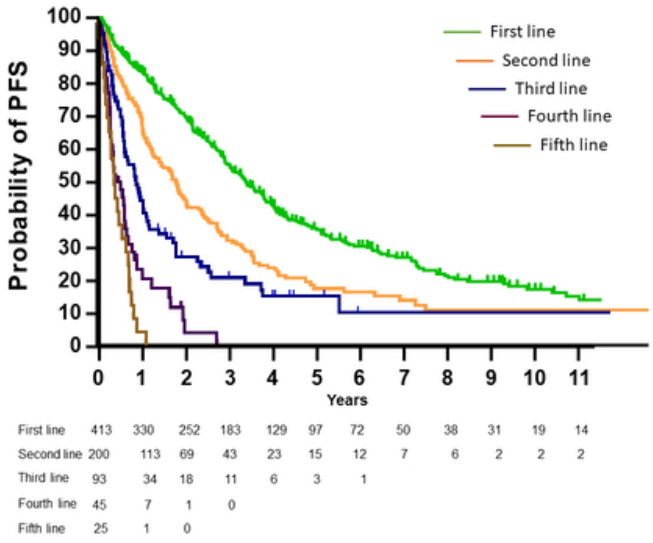

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Table S1 Regimens administered in LOT-1

Regimens	**n (%)**
Bortezomib-thalidomide-dexamethasone	99 (24)
Lenalidomide-dexamethasone	62 (15)
Bortezomib-melphalan-prednisone	56 (13.6)
Cyclophosphamide-bortezomib-dexamethasone	33 (8)
Thalidomide-dexamethasone	17 (4.1)
Carfilzomib-lenalidomide-dexamethasone	16 (3.9)
Bortezomib-prednisone	12 (2.9)
Carfilzomib-cyclophosphamide-dexamethasone	12 (2.9)
Bortezomib-melphalan-prednisone-thalidomide	12 (2.9)
Thalidomide-liposomal doxorubicin-dexamethasone	11 (2.7)
Daratumumab-bortezomib-cyclophosphamide-dexamethasone	8 (1.8)
Cyclophosphamide-lenalidomide-dexamethasone	7 (1.7)
Daratumumab-lenalidomide-dexamethasone	7 (1.7)
Elotuzumab-lenalidomide-dexamethasone	5 (1.2)
Carfilzomib-melphalan-dexamethasone	5 (1.2)
Melphalan-prednisone-lenalidomide	5 (1.2)
Melphalan-prednisone-thalidomide	5 (1.2)
Bortezomib-lenalidomide-dexamethasone	5 (1.2)
Daratumumab-bortezomib-lenalidomide-dexamethasone	5 (1.2)
Cyclophosphamide-prednisone	5 (1.2)
Bortezomib-doxorubicin-dexamethasone	4 (1)
Isatuximab-bortezomib-lenalidomide-dexamethasone	4 (1)
Cyclophosphamide-dexamethasone	3 (0.7)
Cyclophosphamide-lenalidomide-prednisone	3 (0.7)
Ixazomib-dexamethasone	3 (0.7)
Daratumumab-bortezomib-melphalan-prednisone	2 (0.5)
Thalidomide-liposomal doxorubicin-bortezomib-dexamethasone	2 (0.5)
Isatuximab-carfilzomib-lenalidomide-dexamethasone	2 (0.5)
Cyclophosphamide-thalidomide-dexamethasone	1 (0.2)
Ixazomib-cyclophosphamide-dexamethasone	1 (0.2)
Daratumumab-bortezomib-thalidomide-dexamethasone	1 (0.2)

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Table S2 Regimens administered in LOT-2

Regimens	**n (%)**
Lenalidomide-dexamethasone	36 (18)
Daratumumab-lenalidomide-dexamethasone	23 (11.5)
Cyclophosphamide-bortezomib-dexamethasone	19 (9.5)
Cyclophosphamide-lenalidomide-dexamethasone	18 (9)
Bortezomib-dexamethasone	16 (8)
Elotuzumab-lenalidomide-dexamethasone	14 (7)
Bendamustine-bortezomib-dexamethasone	9 (4.5)
Cyclophosphamide-dexamethasone	8 (4)
Carfilzomib-lenalidomide-dexamethasone	7 (3.5)
Carfilzomib-dexamethasone	6 (3)
Thalidomide-liposomal doxorubicin-bortezomib-dexamethasone	5 (2.5)
Daratumumab-bortezomib-dexamethasone	5 (2.5)
Pomalidomide-bortezomib-dexamethasone	4 (2)
Elotuzumab-bortezomib-dexamethasone	4 (2)
Carfilzomib-cyclophosphamide-dexamethasone	4 (2)
Bortezomib-doxorubicin-dexamethasone	3 (1.5)
Bortezomib-thalidomide-dexamethasone	3 (1.5)
Thalidomide-dexamethasone	2 (1)
Cyclophosphamide-prednisone	2 (1)
Bortezomib-melphalan-prednisone	2 (1)
Venetoclax-bortezomib-dexamethasone	2 (1)
Ixazomib-lenalidomide-dexamethasone	2 (1)
Melphalan-prednisone	1 (0.5)
Melphalan-prednisone-thalidomide	1 (0.5)
Cyclophosphamide-thalidomide-dexamethasone	1 (0.5)
Etoposide-vincristine-doxorubicin-dexamethasone	1 (0.5)
Bortezomib-lenalidomide-dexamethasone	1 (0.5)
Daratumumab-pomalidomide-dexamethasone	1 (0.5)

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Table S3 Regimens administered in LOT-3

Regimens	**n (%)**
Pomalidomide-dexamethasone	15 (16.3)
Lenalidomide-dexamethasone	10 (10.8)
Cyclophosphamide-lenalidomide-dexamethasone	9 (9.7)
Bortezomib-dexamethasone	7 (7.6)
Daratumumab-lenalidomide-dexamethasone	7 (7.6)
Carfilzomib-lenalidomide-dexamethasone	6 (6.5)
Carfilzomib-bendamustine-dexamethasone	4 (4.3)
Isatuximab-pomalidomide-dexamethasone	3 (3.2)
Bendamustine-bortezomib-dexamethasone	2 (2.1)
Melphalan-thalidomide-dexamethasone	2 (2.1)
Thalidomide-dexamethasone	2 (2.1)
Vincristine-doxorubicin-dexamethasone	2 (2.1)
Cyclophosphamide-pomalidomide-dexamethasone	2 (2.1)
Venetoclax-bortezomib-dexamethasone	2 (2.1)
Daratumumab-bortezomib-dexamethasone	2 (2.1)
Elotuzumab-pomalidomide-dexamethasone	2 (2.1)
Carfilzomib-pomalidomide-dexamethasone	2 (2.1)
Bortezomib-lenalidomide-dexamethasone	1 (1)
Cyclophosphamide-bortezomib-dexamethasone	1 (1)
Elotuzumab-bortezomib-dexamethasone	1 (1)
Melphalan-lenalidomide-prednisone	1 (1)
Bortezomib-doxorubicin-dexamethasone	1 (1)
Daratumumab-pomalidomide-dexamethasone	1 (1)
Carfilzomib-dexamethasone	1 (1)
Venetoclax-dexamethasone	1 (1)
Belantamab mafodotin	1 (1)
Cyclophosphamide-dexamethasone	1 (1)
Cyclophosphamide	1 (1)
Melphalan	1 (1)
Metronomic	1 (1)

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Table S4 Regimens administered in LOT-4

Regimens	**n (%)**
Pomalidomide-dexamethasone	8 (17.8)
Cyclophosphamide-dexamethasone	6 (13.3)
Carfilzomib-dexamethasone	3 (6.7)
Bendamustine	3 (6.7)
Metronomic	3 (6.7)
Carfilzomib-bendamustine-dexamethasone	2 (4.4)
Daratumumab	2 (4.4)
Belantamab-mafodotin	2 (4.4)
Isatuximab-pomalidomide-dexamethasone	2 (4.4)
Bendamustine-bortezomib-dexamethasone	1 (2.2)
Cyclophosphamide-lenalidomide-dexamethasone	1 (2.2)
Melphalan	1 (2.2)
Thalidomide-dexamethasone	1 (2.2)
Lenalidomide-dexamethasone	1 (2.2)
Bortezomib-dexamethasone	1 (2.2)
Bendamustine-thalidomide-dexamethasone	1 (2.2)
Vincristine-doxorubicin-dexamethasone	1 (2.2)
Elotuzumab-pomalidomide-dexamethasone	1 (2.2)
Daratumumab-lenalidomide-dexamethasone	1 (2.2)
Ixazomib-lenalidomide-dexamethasone	1 (2.2)
Pomalidomide-bortezomib-dexamethasone	1 (2.2)
Pomalidomide-cyclophosphamide-dexamethasone	1 (2.2)
Prednisone	1 (2.2)

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Table S5 Regimens administered in LOT-5

Regimens	**n (%)**
Pomalidomide-dexamethasone	7 (28)
Daratumumab	2 (8)
Melphalan	2 (8)
Cyclophosphamide-bortezomib-dexamethasone	1 (4)
Bortezomib-dexamethasone	1 (4)
Carfilzomib-bendamustine-dexamethasone	1 (4)
Elotuzumab-lenalidomde-dexamethasone	1 (4)
Daratumumab-bortezomib-dexamethasone	1 (4)
Belantamab-mafodotin	1 (4)
Cyclophosphamide-pomalidomide-dexamethasone	1 (4)
Cyclophosphamide-thalidomide-dexamethasone	1 (4)
Cyclophosphamide-dexamethasone	1 (4)
Bendamustine-thalidomide-dexamethasone	1 (4)
Melphalan-prednisone-thalidomide	1 (4)
Thalidomide-dexamethasone	1 (4)
Vincristine-doxorubicin-dexamethasone	1 (4)
Prednisone	1 (4)

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Patient consent statement: *IRB ruled that the mandatory signature of informed consent could be waived*

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Clinical trial registration (including trial number): *n/a*

MO performed the research design, analysed and interpreted data, drafting and revising paper

SM, LC, MVM acquired and interpreted data, drafting the paper

AO critically revised paper

All the Authors approved the submitted final version

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