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Elotuzumab plus Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: extended 3-year follow-up of a multicenter, retrospective clinical experience with 319 cases outside of controlled clinical trials

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ABSTRACT

The combination of elotuzumab, lenalidomide, and dexamethasone (EloRd) enhanced the clinical benefit over Rd with a manageable toxicity profile in the ELOQUENT-2 trial, leading to its approval in relapsed/refractory multiple myeloma (RRMM).

The present study is a 3-year follow-up update of a previously published Italian real-life RRMM cohort of patients treated with EloRd.

This revised analysis entered 319 RRMM patients accrued in 41 Italian centers. After a median follow-up of 36 months (range 6-55), 236 patients experienced disease progression or died. Median progression-free survival (PFS) and overall survival (OS) were 18.4 and 34 months, respectively. The updated multivariate analyses showed a significant reduction of PFS and OS benefit magnitude only in cases with ISS stage III.

Major adverse events included grade 3/4 neutropenia (18.5%), anemia (15.4%), lymphocytopenia (12.5%), and thrombocytopenia (10.7%), while infection rates and pneumonia were 33.9% and 18.9%, respectively. No new safety signals with longer follow-up have been observed.

Of 319 patients, 245 (76.7%) reached at least a partial remission. A significantly lower response rate was found in patients previously exposed to lenalidomide.

In conclusion, our study confirms that EloRd is a safe and effective regimen for RRMM patients, maintaining benefits across multiple unfavorable subgroups.

INTRODUCTION

The treatment of multiple myeloma (MM) has undergone significant changes and progress in recent years, with patient life expectancy almost doubled over the past decades (1, 2). This extraordinary progress is mainly due to the extensive use in clinical practice of proteasome inhibitors (PI) and immunomodulatory drugs (IMIDS), which still represent the milestones of MM therapy. However, the outcome of patients whose diseases become refractory to PI and IMiDs remains poor, with a median overall survival (OS) of nearly one year (3). Therefore, improving the myeloma treatment armamentarium with effective novel agents has become mandatory. Hence, new agents with the ability to modulate the microenvironment or activate the immune response are often combined with the standard regimens to overcome the drug resistance phenomenon. Elotuzumab (Elo), a humanized immunoglobulin G1 immunostimulatory monoclonal antibody against signaling lymphocytic activation molecule F7 (SLAMF7), a glycoprotein expressed on myeloma cells and natural killer (NK) cells, but not on normal nonlymphoid tissues, has been increasingly included in relapsed/refractory (RR) MM (RRMM) therapeutic regimens (4). Elo showed a dual mode of action, causing activation of NK cells and myeloma cell death through antibody-dependent cellular cytotoxicity (ADCC) (5, 6).

Furthermore, the finding that lenalidomide (R) can boost the Elo capability to activate NK cells (7) further endorsed the rationale to compare the association of Elo with R and dexamethasone (EloRd) with Rd in a large Phase III trial (ELOQUENT-2) in RRMM patients (8). This trial resulted in a higher overall response rate (ORR) and more prolonged progression-free survival (PFS) for patients

allocated to the experimental arm. Moreover, comprehensive assessments at 3-(9), 4-(10), and 5-year follow-ups (11) demonstrated a sustained PFS benefit and long-term safety of EloRd. Finally, at 70.6 months of follow-up, EloRd showed a statistically significant 8.7-month improvement in OS versus Rd (12).

This trial led to the approval by the Food and Drug Administration in the USA of EloRd for RRMM patients and marketing approval in Italy in April 2017.

The research recognizing the challenges and translating clinical trial results to real-world scenarios is an appropriate scientific approach and still deserves continuous investigation. Recently, we reported data of an Italian real-life experience on EloRd as therapy for 300 RRMM patients treated outside of controlled clinical trials (13). Our real-world data confirmed the ELOQUENT-2 trial results indicating this triplet is a safe and effective regimen for RRMM patients. Reanalyzing the updated Italian real-life cohort data with an extended 3-year follow-up, we assessed the time to the next therapy (TTNT), endorsing further analyses of PFS, OS, response evaluation, and long-term safety in RRMM patients treated with EloRd outside of controlled clinical trials.

PATIENTS AND METHODS

Patients

For the aim of this retrospective analysis, updated data from 41 Italian centers of a previously published retrospective cohort of RRMM patients treated with EloRd (13) were collected. The databases contained clinical information such as age, sex, date of diagnosis, laboratory parameters, treatment history, and date of last follow-up or death abstracted from clinical records at the time of inclusion and updated on an ongoing basis. The 41 databases included 319 consecutive patients with RRMM who received at least one cycle of EloRd as salvage treatment between April 2017 and December 2020. All patients were treated with EloRd according to marketing approval as previously described (13). Specifically, Elo was given at 10 mg/kg i.v. on days 1, 8, 15, and 22 during the first two cycles and then on days 1 and 15 of each following cycle, R 25 mg on days 1 to 21 of each cycle

and d at the dose of 40 mg during the week without Elo, and 36 mg on the day of Elo administration. All patients received premedication with diphenhydramine (25 to 50 mg) or its equivalent, ranitidine (50 mg) or its equivalent, and acetaminophen (650 to 1000 mg) or its equivalent 30 to 90 minutes before the Elo infusion. Lenalidomide's starting dose was adjusted according to renal function. Elderly patients (>75 years) received d at a weekly dose of 20 mg. All patients received antibacterial, antiviral, and antithrombotic prophylaxis during treatment.

The time-to-event endpoints were PFS, OS, TTNT. Safety profile and response evaluation entered the purposes of the study.

Response to treatment and disease progression were evaluated according to the IMWG criteria (14, 15). Responsive patients had to reach at least a partial remission (PR).

Institutional Ethics Committees approved the study according to the principles of the Declaration of Helsinki.

Statistical analysis

For categorical variables, statistical comparisons were performed using two-way tables for the Fisher's exact test and multi-way tables for the Pearson's Chi-square test. Multivariate ordinal regression analysis was used to examine the effects of potential confounders on the association between the best response and several variables that were statistically significant on univariate analysis by Pearson chi-square or Fisher's exact test. The analysis of PFS, measured from the initiation of RRMM EloRd treatment until death from any cause or progression or last follow-up, of TTNT, measured from the initiation of RRMM EloRd treatment to earliest start date of subsequent therapy or last follow-up, and of OS, measured from the initiation of RRMM EloRd treatment until death from any cause or last follow-up, were performed using the Kaplan-Meier method. Statistical significance of associations between individual variables and survival was calculated using the log-rank test. The prognostic impact for the outcome variable was investigated by univariate and multiple Cox regression analysis. Results are expressed as hazard ratios (HR) and 95% confidence intervals

(CI). A value of P<0.05 was considered significant. Data analysis was performed by STATA for Windows v.9 and SPSS Statistics v.21.

RESULTS

Patients

Overall, 319 RRMM patients treated with EloRd between April 2017 and December 2020 in 41 Italian centers entered this study. Baseline characteristics are shown in Table 1. At the beginning of EloRd, according to International Staging System (ISS), the disease status was available only for 255 patients; 22% of patients had advanced disease (ISS stage III), 38.8% were in ISS stage I, 39.2% in ISS stage II.

Approximately one-fourth of patients (24.5%) had refractory disease to the previous line of therapy, while symptomatic relapse was observed in 179 patients (56.1%) and a biochemical relapse in 62 (19.4%). Before EloRd, 198 patients (62.1%) had received only 1 line of therapy, over one-third (38.6%) underwent autologous stem cell transplant (ASCT), while 27% of patients were exposed to lenalidomide. Approximately half of the patients (49.5%) started EloRd less than 3.5 years from the first diagnosis of MM. FISH analysis data were available in 66 patients. Fifty-five (83.3%) patients presented favorable cytogenetic abnormalities, while 11 patients (16.7%) where categorized as high risk, harboring one of the following aberrations: t(4;14), t(14;16) and del(17p). Thirty-eight patients with mild renal impairment received R at the starting dose of 10 mg, while 24 with severe renal impairment at the starting dose of 15 mg every other day; 133 elderly patients (>75 years) received d at a weekly dose of 20 mg.

Progression-free survival

After a median follow-up of 36 months (range 6-55), 236 patients out of 319 experienced disease progression or died. The total number of deaths was 179. Median PFS was 18.4 months (95% CI, 15.5–21.4), and the 3-year probability of PFS was 28% (Figure 1). Univariate analyses showed that ISS stage III (HR=1.44, 95% CI 1.01-2.17; P=0.05), previous exposure to lenalidomide (HR=1.43, 95% CI 1.1-1.85; P=0.001) and >1 previous line of therapy (HR=1.22, 95% CI 1.09-1.91; P=0.007) were associated with a significantly lower PFS (Table 3). Notably, in the Cox multivariate analysis only advanced ISS stage (III) maintained an independent prognostic impact on PFS (HR=1.52, 95% CI 1.04-2.23; P=0.03) (Table 2).

Overall survival

Median OS was 34 months (95% CI 28-40.2), and the 3-year probability of OS was 48% (Figure 2). Univariate analyses showed that ISS III (HR=1.85, 95% CI 1.2-2.83; P=0.005), symptomatic relapse (HR=1.59, 95% CI 1.03-2.44; P=0.035) and a refractory disease at EloRd beginning (HR=1.63, 95% CI 1.01-2.63; P=0.047) were associated with a significantly shorter OS (Table 3). Notably, in the Cox multivariate analysis, only advanced ISS stage (III) maintained an independent prognostic impact on the survival outcome (HR=1.85, 95% CI 1.19-2.87; P=0.006) (Table 3).

Time to next treatment and subsequent therapy

After discontinuation of EloRd therapy, half of the patients received subsequent treatment. Median TTNT was 25.7 months (95% CI 21.3-30.9), with a 3-year re-treating probability of 41.2% (Figure 3). The type of subsequent treatment is shown in Table 4. Overall, 18 different salvage therapy regimens were used after EloRd discontinuation or failure. Over one-third of patients (57 cases) received pomalidomide plus dexamethasone, 26 patients (16.2%) daratumumab associated with bortezomib and dexamethasone (DVd regimen), while 24 patients (15%) received daratumumab as monotherapy. Seven patients received as subsequent therapy lenalidomide-based regimen, 3 of them

(1.9%) in combination with daratumumab and dexamethasone, 2 (1.2%) in combination with carfilzomib and dexamethasone, and 2 (1.2%) in combination with ixazomib and dexamethasone.

Safety and Response Evaluation

At the last database update, the median number of EloRd courses administered was 14 (range 1–60). A total of 254 (79.6%) patients withdrew EloRd treatment at the cut-off date, mainly due to disease progression (189 cases). Of the remaining cases, 32 patients discontinued therapy for toxicity (23 infections, 5 cardiovascular disorders, 2 lenalidomide-related severe skin rash, 1 dexamethasone-related psychosis, and 1 lenalidomide-related hepatotoxicity), 17 for therapy-unrelated deaths, 2 for secondary malignancies (1 acute myeloid leukemia and 1 ovarian cancer), while 2 cases to undergoing ASCT. Finally, 5 patients withdrew therapy for medical decisions and 7 for removal of informed consent. Infusion reactions occurred in 20 patients (6.3%, all grade 1-2) and were promptly resolved in all patients (no discontinuation reported). Major adverse events (AEs) are depicted in Table 5 and included grade 3/4 neutropenia (18.5%), anemia (15.4%), lymphocytopenia (12.5%), and thrombocytopenia (10.7%), while infection rates and pneumonia were roughly 33.9% and 18.9%, respectively. Furthermore, the rate of AEs was not significantly different between patients aged less or more than 75 years (data not shown).

Out of 319 patients 245 (76.7%) reached at least a partial remission (>PR). More in details, 24 (7.5%) achieved a complete remission (CR), 92 (28.8%) a very good partial response (VGPR), and 129 (40.4%) a PR.

In patients who have previously received 2 or more therapy lines, ORR was 70.2% vs 80.8%, P=0.03. Similarly, a lower ORR was also accounted for in those previously exposed to lenalidomide (65.1% vs. 81.1%, P=0.003) (Table 6). Multivariate ordinal regression analysis showed prior lenalidomide exposure as the unique variable adversely and independently associated with the best response (HR 2.18, 95% CI 1–4.7, P=0.05). Supplementary Table 1 shows the baseline characteristics of the 86 lenalidomide-exposed patients, whose main characteristics matched with those of the entire EloRd

cohort. All cases received a minimum of 2 lines of therapies, while none of the lenalidomide-exposed patients received the drug just before EloRd.

Outcome analysis by cytogenetic risk

Unfortunately, data on cytogenetic abnormalities were available in only one-fifth of cases (66/319, 20.7%). However, the analytical weight for prognosis of this biomarker, also emphasized by the revised ISS (R-ISS) (16), prompted us to carry out nevertheless an ancillary analysis, conscious that the relatively low incidence of accessible cases could bias the statistical accuracy. However, the main characteristics of the group with cytogenetic information did not differ from the remaining cases (Supplementary Table 2). The ORR was lower in the high-risk than the standard-risk group, but the difference did not reach a statistical significance (85.5 versus 63.6%; P=0.087). Standard-risk cases showed a significant longer PFS than high-risk (3-year PFS: 40.2% vs 0%; HR 3.04, 95% CI 1.46-6.3; P=0.003). Kaplan-Meier curves of OS showed a significantly better prognosis in standard-risk patients (3-year OS: 61.2 versus 13.6%; HR 4.98, 95% CI 2.16-11.5; P<0.0001).

DISCUSSION

Nowadays, the pharmacological scenario of RRMM is constantly changing, crowded with new drugs, i.e., novel proteasome inhibitors (ixazomib and carfilzomib), IMiDs (pomalidomide), monoclonal antibodies (daratumumab, isatuximab, and elotuzumab), and other biological drugs (17). Therefore, choosing the best treatment in this setting is very complicated in clinical practice.

The present paper described a 3-year follow-up of an Italian real-life experience on EloRd, a worldwide-approved combination regimen for RRMM. To our knowledge, our survey is one of the most extensive real-life EloRd series in terms of the number of patients evaluated.

Extend follow-up of our cohort of RRMM treated with EloRd in a real-life setting showed that this triplet maintains its efficacy. Our 3-year PFS was similar to that reported in the extended 4-year follow-up of the ELOQUENT-2 trial (18), 28 versus 27%, respectively. While, the 3-year OS

probability of our cohort was inferior to that reported in the original trial (48 versus 60%, respectively) (19). These results may probably correlate with the difference of baseline characteristics of patients between real-life data and clinical trials.

Real-life profiles are rarely fully represented in randomized clinical trials, and this caveat further complicates treatment decision-making. Mostly, lenalidomide-exposed cases were excluded adequately from randomized phase 3 trials testing the backbone Rd versus Rd plus a third agent (8, 20-22). Thus, the precise effect of the EloRd combination in patients with the lenalidomide-exposed disease is unknown based on clinical trial results. This hard-to-treat subgroup of patients should most likely lead to suboptimal results; thus, these regimens should intuitively be avoided in this setting. Indeed, the main difference between our real-life cohort and that enrolled in the ELOQUENT-2 trial was the higher rate of patients previously exposed to lenalidomide (27 versus 5%) (8). As expected, a significantly lower incidence of cases achieving a PR or better was accounted for in lenalidomide-exposed compared to lenalidomide-naïve patients (65.1 versus 81.1%). Moreover, prior lenalidomide exposure remained the unique variable adversely and independently associated with the best response at multivariate ordinal regression analysis, confirming our previous result (13).

Thus, although we demonstrated that PFS and OS survival benefits were not adversely affected by prior lenalidomide exposure in this specific real-life case profile, it remains a concern when choosing EloRd treatment, suggesting the need for more effective combinations (17). Nowadays, the combination of elotuzumab, pomalidomide, and dexamethasone, approved for the treatment of RRMM who have received at least two prior therapies, may represent a validated alternative therapeutic strategy for those cases relapsed after or refractory to lenalidomide (23). Nevertheless, the treatment of lenalidomide-refractory patients remains an unmet clinical need and should be addressed in additional clinical trials.

The final evaluation of the ELOQUENT-2 trial validates a significant OS improvement of EloRd over Rd through several clinically relevant clusters comprising ISS stage III disease (18). However, the median OS of the entire cohort of patients treated with EloRd was 48.3 months, while the median

OS observed in the ISS stage III disease setting was 21.7 months (18), thus envisaging its negative prognostic role. Accordingly, high-risk ISS is still an issue in our real-world EloRd-treated patients since it remains the unique factor independently associated with a worse OS.

The International Myeloma Working Group (IMWG) consensus recommends using ISS and cytogenetic abnormalities to analyze OS risk stratification (24). Disappointingly, the cytogenetic analysis is not routinely performed in a real-world scenario. However, the FISH prognostic relevance, also emphasized by the R-ISS (16), encouraged us to perform an extra analysis, aware that the fairly low incidence of accessible cases (roughly 21%) could mislead statistical interpretation. In this respect, high-risk patients, defined as poor cytogenetics (t[4;14], t[14;16], or del[17p]), showed a significantly shorter PFS and OS. Nevertheless, the low number of cases does not allow analyzing the independent prognostic value of this parameter in a multivariate analysis.

The OS was independent to age, demonstrating that EloRd is a safe and effective strategy for elderly patients, showing no difference in terms of AE when compared to younger patients. Nevertheless, elderly patients (41% of our population) represent a challenge in treating MM because of its association with frailty, increased comorbidities, poor tolerability, and higher risk of complications (25).

Notably, an anticipated EloRd treatment in MM patients with asymptomatic biochemical relapse failed to improve PFS in our series.

In a post hoc analysis of ELOQUENT-2, the time from diagnosis to EloRd and the number of prior lines of therapy demonstrated a significant impact in the PFS, with the benefit observed in patients further from diagnosis and in those who had received only 1 line of treatment before EloRd (18). Noteworthy, differently from our previous report (13), patients with a short disease history and already exposed to more than 1 line of prior therapies were no longer more prone to progress. Conversely, ISS stage III was the only risk factor negatively and independently associated with PFS in the present updated analysis. Possible explanations of this result could be related to a longer follow-up and the introduction of the ISS variable instead of each single score component (13).

The depth of response, which represents a precocious and noteworthy indicator of long-term effectiveness, was similar in our series to the ELOQUENT-2 trial (ORR 76.7 versus 79%; CR rate 7.5 versus 4%) (8).

Concerning the safety profile, our findings were similar to those reported in the ELOQUENT-2, with a modestly lower rate of anemia and neutropenia (8). The most common non-hematological AEs were infections with an incidence of 33.7 versus 35% in the ELOQUENT-2 trial, followed by pneumonia (16.3 versus 15%) and diarrhea (7.3 versus 8%) (8). No new safety signals with longer follow-up have been observed.

In conclusion, our study confirms the finding from the updated ELOQUENT-2 trial, showing that the EloRd clinical benefits were maintained across multiple predefined subgroups generally associated with poorer outcomes, including patients with multiple prior lines of therapy, older patients, and those refractory to their most recent treatment. Our study demonstrated EloRd as a safe and effective regimen for RRMM patients, mainly if used in low-risk ISS cases. This regimen represents one example of five triple schedules that have received high-level evidence and uniform consensus as a preferred treatment regimen for patients with RRMM.

For the next future, the synergic potential of new drugs and drug combinations with currently approved agents will be crucial in their integration into established MM backbone algorithms.

Contributions: A.B., M.G., A.N., V.D.S., F.D.R., M.T.P., M.O., P.M., M.B., M.C., and F.M. designed the study, analyzed and interpreted data, and wrote the manuscript; M.G., G.T., and F.M. performed statistical analysis; D.D., M.G., E.A.M., C.B., S.R., C.C., C.Ca., N.G., S.M., G.F., E.A., A.L., M.B., E.R., R.R., R.Z., N.D.R., G.M., G.Ma., G.P., G.Pa., N.C., C.C., A.B., C.Cr., G.U., P.C., E.V., F.M., E.I., D.V., N.S., A.Bo., L.C., R.S., M.M., S.B., D.G., A.G., B.G., A.P., F.F., U.C., S.B., E.Z., F.P., and S.P. provided the patients and collected clinical data; and all authors gave final approval for the manuscript.

Conflict-of-interest disclosure:
Nothing to disclose

Figures legend

Figure 1. Kaplan Meier curve of PFS for all 319 RRMM patients treated with EloRd

Figure 2. Kaplan Meier curve of OS for all 319 RRMM patients treated with EloRd

Figure 3. Kaplan Meier curve of TTNT for all 319 RRMM patients treated with EloRd

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Table 1. Main characteristics of patients at baseline

	No. of patients (%)
Age, (years)	
<75	186 (58.3)
≥75	133 (41.7)
Sex	
Male	164 (51.4)
Female	155 (48.6)
Paraproteins (isotype)	
Immunoglobulin G	199 (62.4)
Immunoglobulin A	59 (18.5)
Immunoglobulin D	3 (0.9)
Light chain only	56 (17.6)
Non-secretory	2 (0.6)
Creatinine clearance (mL/min)	
≥60	229 (71.8)
<60	90 (28.2)
Stage ISS, (%) (n=255)	
I	99 (38.8)
II	100 (39.2)
III	56 (22)
Number of previous lines of therapy	
1	198 (62.1)
2	73 (22.9)
3	22 (6.9)
≥4	26 (8.1)
Previous ASCT	
No	196 (61.4)
Yes	123 (38.6)
Previous therapies	
Bortezomib	301 (94.4)
Lenalidomide	86 (27)
Disease status	
Biochemical relapse	62 (19.4)
Symptomatic relapse	179 (56.1)
Refractory to last treatment	78 (24.5)
Time from diagnosis to EloRd treatment (years)	
≥3.5	161 (50.5)
<3.5	158 (49.5)
FISH analysis available (n= 66)	
Standard Risk	55 (83.3)
High Risk	11 (16.7)

Table 2 Univariate and multivariate analyses of PFS.

		Univariate analysis			Multivariate analysis	
	N	PFS @ 36 months	HR (%95 CI)	P-value	HR (%95 CI)	P-value
Age, (years)						
≤75	186	26.2				
>75	133	30.8	1.03 (0.79 -1.33)	0.82		
Gender						
Female	155	29.5				
Male	164	26.4	0.94 (0.73 – 1.21)	0.63		
CrCl mL/min						
>60	229	28.9				
<60	90	26	1.14 (0.86 – 1.51)	0.35		
ISS (N=255)						
I	99	26.7				
II	100	26.8	1.19 (0.86-1.65)	0.28		
III	56	22.2	1.44 (1.01-2-17)	**0.05**	1.52 (1.04-2.23)	**0.03**
Lines of therapy						
1	198	31.4				
>1	121	22.8	1.43(1.1-1.85)	**0.007**	1.22 (0.82-1.8)	0.32
Previous ASCT						
No	123	25.4				
Yes	196	29.8	0.97 (0.75-1.26)	0.83		
Previous lenalidomide						
No	233	30.4				
Yes	86	21.9	1.44 (1.09-1.91)	**0.001**	1.24 (0.82-1.88)	0.31
Disease status at EloRd						
Biochemical relapse	62	30.8				
Symptomatic relapse	179	25.9	1.19 (0.85-1.67)	0.3		
Refractory to last treatment	78	31.1	1.17 (0.79-1.74)	0.42		
Time from diagnosis to EloRd						
>3.5 years	161	26.6				
<3.5 years	158	30.2	1.07 (0.83 -1.38)	0.62		

Table 3. Univariate and multivariate analyses of OS.

		Univariate analysis			Multivariate analysis	
	N	OS @ 36 months	HR (%95 CI)	P-value	HR (%95 CI)	P-value
Age, (years)						
≤75	186	49.1				
>75	133	46.6	1.06 (0.79-1.43)	0.69		
Gender						
Female	155	51.3				
Male	164	44.1	1.13 (0.85-1.52)	0.41		
CrCl mL/min						
>60	229	49.9				
<60	90	43.2	1.23 (0.89-1.69)	0.21		
ISS (N=255)						
I	99	54.7				
II	100	44.5	1.44 (0.99-2.1)	0.06		
III	56	37.7	1.85 (1.2-2.83)	**0.005**	1.85 (1.19-2.87)	**0.006**
Lines of therapy						
1	198	49.8				
>1	121	45.2	1.31 (0.97-1.75)	0.08		
Previous ASCT						
No	123	52.7				
Yes	196	45.1	1.21 (0.89-1.65)	0.21		
Previous lenalidomide						
No	233	50.6				
Yes	86	41.1	1.34 (0.97-1.84)	0.08		
Disease status at EloRd						
Biochemical relapse	62	61.1				
Symptomatic relapse	179	44.5	1.59 (1.03-2.44)	**0.035**	1.4 (0.89-2.2)	0.15
Refractory to last treatment	78	46.1	1.63 (1.01-2.63)	**0.047**	1.28 (0.76-2.14)	0.36
Time from diagnosis to EloRd						
>3.5 years	161	53.1				
<3.5 years	158	42.9	1.24 (0.92-1.66)	0.16		

Table 4. Salvage therapy regimens after EloRd.

Salvage therapy regimen	No of cases (%)
Anti-CD38 containing regimens	**57 (35.6)**
DVd	26 (16.2)
Dara	24 (15)
Dara-pom-dex	4 (2.5)
DRd	3 (1.9)
Pom containing regimens	**62 (38.7)***
Pom-dex	57 (35.6)
Pom-Ctx-dex	3 (1.9)
PVd	2 (1.2)
PIs containing regimens	**31 (19.1)**
Kd	19 (11.9)
KRd	2 (1.2)
IxaRd	2 (1.2)
PAD	2 (1.2)
VMP	2 (1.2)
Ixa	1 (0.6)
Ixa-Ctx	1 (0.6)
BVd	1 (0.6)
VCD	1 (0.6)
Other therapies	**9 (5.6)**
Ctx	7 (4.4)
Melflufen	1 (0.6)
Radiotherapy	1 (0.6)

***Considering the 4 patients treated with Dara-pom-dex: 66 (41.2%).**

Legend: DVd= daratumumab, bortezomib, dexamethasone; Dara= daratumumab; Dara-pom-dex= daratumumab, pomalidomide, dexamethasone; DRd= daratumumab, lenalidomide, dexamethasone; Pom-dex= pomalidomide, dexamethasone; Pom-Ctx-dex= pomalidomide, cyclophosphamide, dexamethasone; PVd= pomalidomide, bortezomib, dexamethasone; PIs= proteasome inhibitors; Kd= Carfilzomib, dexamethasone; KRd= carfilzomib, lenalidomide, dexamethasone; IxaRd= ixazomib, lenalidomide, dexamethasone; PAD= bortezomib, doxorubicin, dexamethasone; VMP= bortezomib, melphalan, prednisone; Ixa= ixazomib; Ixa-CTX= ixazomib, cyclophosphamide; BVd= bendamustine, bortezomib, dexamethasone; VCD= bortezomib, cyclophosphamide, dexamethasone; CTX= cyclophosphamide.

Table 5. Incidence of serious adverse events

	EloRd (N=319)
Grade 3/4 adverse events	**No of cases (%)**
Hematological toxicities	
Lymphocytopenia	40 (12.5)
Anemia	49 (15.4)
Thrombocytopenia	34 (10.7)
Neutropenia	59 (18.5)
Non-hematological toxicities	
Infections	108 (33.9)
Pneumonia	60 (18.8)
Fatigue	66 (20.7)
Diarrhea	24 (7.5)

Table 6. Association between overall response rate and main clinical-hematological characteristics of multiple myeloma patients treated with EloRd

Variable	>PR N (%)	<PR N (%)	P-value
Age			
≤75	138 (74.2)	74 (25.8)	NS
>75	107 (80.5)	26 (19.5)	
Sex			
Female	122 (78.7)	33 (21.3)	NS
Male	123 (75)	41 (25)	
CrCl mL/min			
≥60	174 (76)	55 (24)	NS
<60	71 (78.9)	19 (21.1)	
ISS (n=255)			
I	76 (76.8)	23 (23.2)	
II	73 (73)	27 (27)	NS
III	49 (87.5)	7 (12.5)	
Number of previous lines of therapy			
<1	160 (80.8)	38 (19,2)	0.03
>1	85 (70.2)	36 (29.8)	
ASCT			
Yes	93 (75.6)	30 (24.4)	NS
No	152 (77.6)	44 (22.4)	
Prior lenalidomide			
No	189 (81.1)	44 (18.9)	0.003
Yes	56 (65.1)	30 (34.9)	
Disease status at EloRd			
Biochemical relapse	48 (77.4)	14 (22.6)	NS
Symptomatic relapse	140 (78.2)	39 (21.8)	
Refractory to last treatment	57 (73.1)	21 (26.9)	
Time from diagnosis to EloRd			
>3.5 years	117 (72.7)	44 (27.3)	NS
<3.5 years	128 (81)	30 (19)