Elotuzumab, lenalidomide, and dexamethasone as salvage therapy for patients with multiple myeloma: Italian, multicenter, retrospective clinical experience with 300 cases outside of controlled clinical trials

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ONLINE SUPPLEMENTARY CONTENTS

Elotuzumab, lenalidomide, and dexamethasone as salvage therapy for patients with multiple myeloma: Italian, multicenter, retrospective clinical experience with 300 cases outside of controlled clinical trials

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Supplementary Methods

Supplementary References

Supplementary Tables

Supplementary Figures

Methods

Databases from 40 Italian centers including all patients with RRMM treated with EloRd were established for research purposes. 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 40 databases included 300 consecutive cases of RRMM who received at least one cycle of EloRd as salvage treatment between April 2017 and April 2019. All patients were treated with EloRd according to marketing approval as follows: Elo 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 a dose of 40 mg during the week without Elo, and 36 mg on the day of Elo administration. 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 starting dose was adjusted according renal function. Elderly patients (>75 years) received d at a weekly dose of 20 mg.

Response to treatment and disease progression were evaluated according the IMWG criteria(1, 2). Responsive patients had to reach at least a partial remission (PR). In all patients on EloRd antibacterial, antiviral, and antithrombotic prophylaxis was prescribed.

The study was approved by institutional ethics committees according to the principles of the Declaration of Helsinki.

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. To account for multiple testing, a Bonferroni correction was applied. 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. In light of the etiological nature of our study, in this analysis, we introduced all variables

which significantly differed ($P<0.05$) among the three categories of response (CR + VGPR, PR + MR, and SD + PD) irrespectively of Bonferroni correction.

The analysis of PFS, measured from the initiation of EloRd treatment until death from all causes or progression or last follow-up, was performed using the Kaplan-Meier method. The analysis of time to next treatment (TTNT), measured from the initiation of EloRd treatment until start date of subsequent therapy or last follow-up visit, was also 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.

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Supplementary Table 1. Association between best response and main clinical-hematological characteristics of multiple myeloma patients treated with EloRd

Variable	CR + VGPR N (%)	PR + MR N (%)	SD + PD N (%)	P
Sex				
Female	48 (33.6)	70 (49)	25 (17.4)	0.14
Male	63 (40.1)	58 (36.9)	36 (22.8)	
Age				
≤75	61 (34.5)	78 (44.1)	38 (21.5)	0.55
>75	50 (40.7)	50 (40.7)	23 (18.7)	
CrCl mL/min				
≥60	75 (35)	95 (44.4)	44 (20.6)	0.53
<60	36 (41.9)	33 (38.4)	17 (19.8)	
β2M (mg/L)				
<3.5	42 (37.5)	47 (42)	23 (20.5)	
≥3.5 and <5.5	21 (26.3)	39 (48.8)	20 (25)	0.12
≥5.5	22 (41.5)	26 (49.1)	5 (9.4)	
Albumin (g/L)				
≥35	81 (36.3)	96 (43)	46 (20.6)	0.97
<35	26 (37.7)	28 (40.6)	15 (21.7)	
ASCT				
Yes	45 (39.1)	47 (40.9)	23 (20)	0.83
No	66 (35.7)	81 (43.8)	38 (20.5)	
Time from diagnosis to EloRd				
≥3.5 years	57 (37)	60 (39)	37 (24)	0.39
<3.5 years	54 (37)	68 (46.6)	24 (16.4)	
Prior bortezomib				
No	9 (50)	8 (44.4)	1 (5.6)	0.23
Yes	102 (36.2)	120 (42.6)	60 (21.3)	
Prior lenalidomide				
No	90 (40.5)	96 (43.2)	36 (16.2)	0.006
Yes	21 (26.9)	32 (41)	25 (32.1)	
Disease status at EloRd				
Relapse	93 (41.2)	88 (38.9)	45 (19.9)	0.026*
Refractory	18 (24.3)	40 (54.1)	16 (21.6)	
Type of relapse				
Biochemical	26 (46.4)	19 (33.9)	11 (19.6)	0.58
Symptomatic	67 (39.2)	70 (40.9)	34 (19.9)	

*Not significant after Bonferroni correction.

Supplementary Figures legend

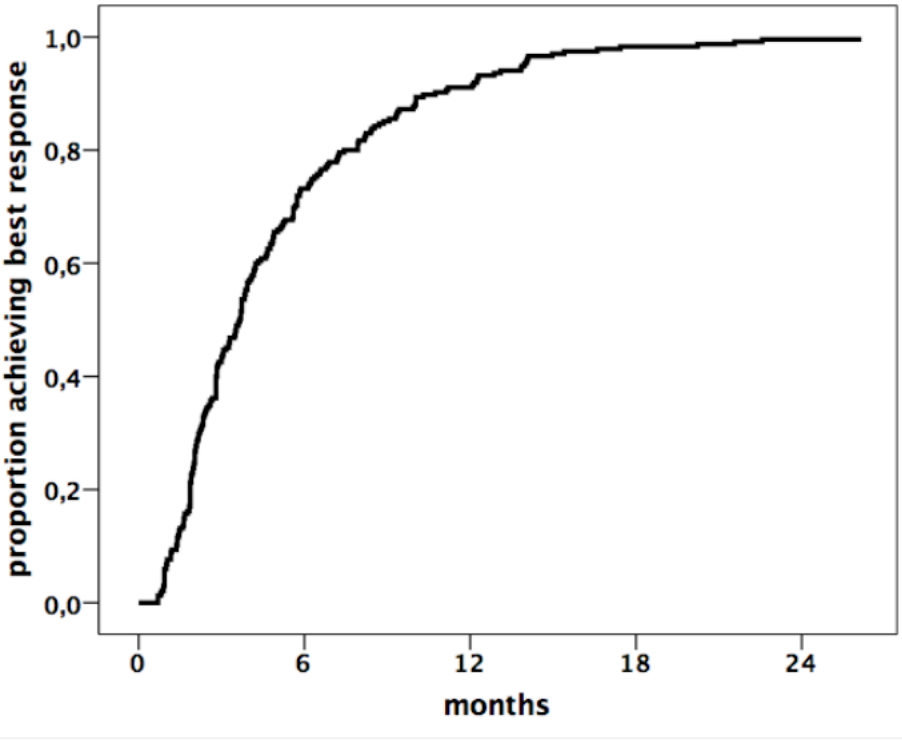
Supplementary Figure 1. Time to achieve best response.

Supplementary Figure 2. Progression-free survival by cytogenetic risk.

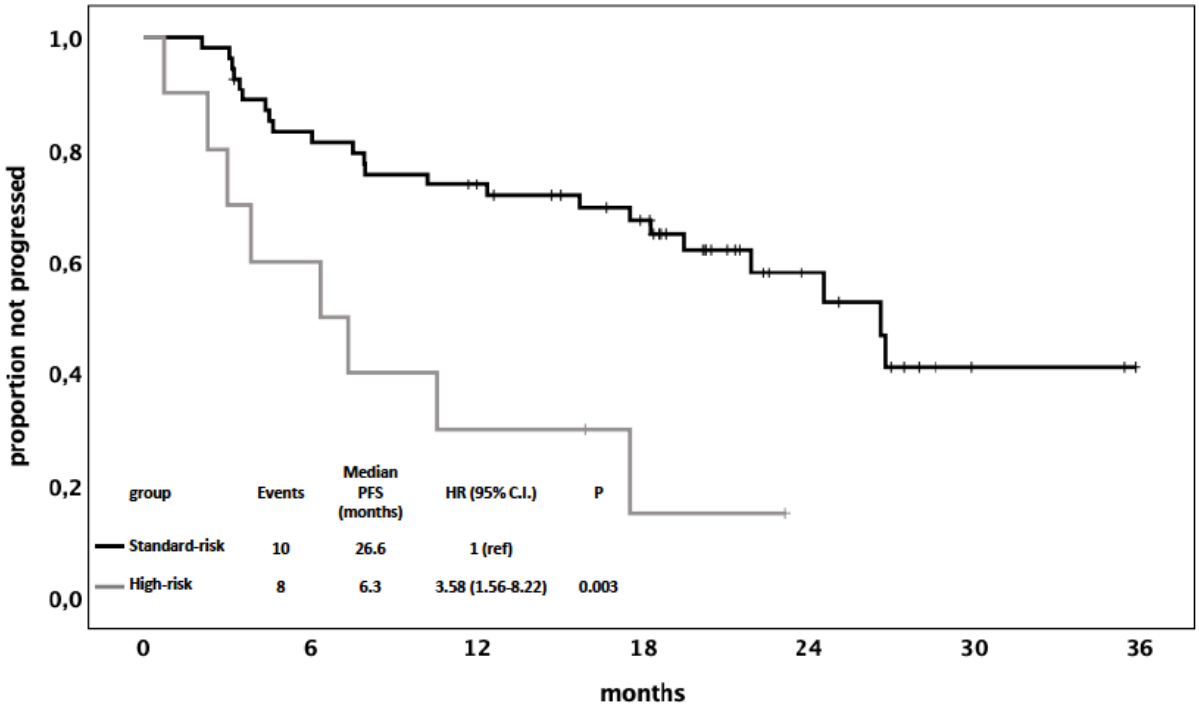
Supplementary Figure 3. Progression-free survival by tumor response to EloRd.

Supplementary Figure 4. Kaplan-Meier curve of time to next treatment of the entire cohort.

Supplementary Figure 5. Kaplan-Meier curve of overall survival of the entire cohort.



Supplementary Figure 1.



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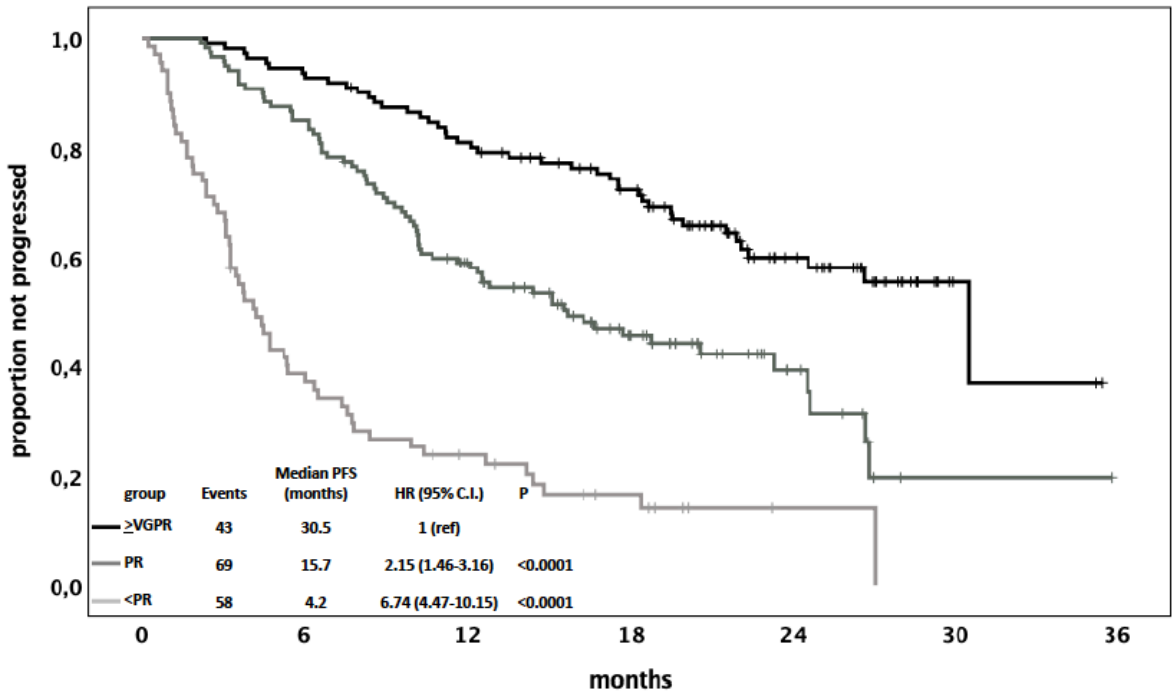

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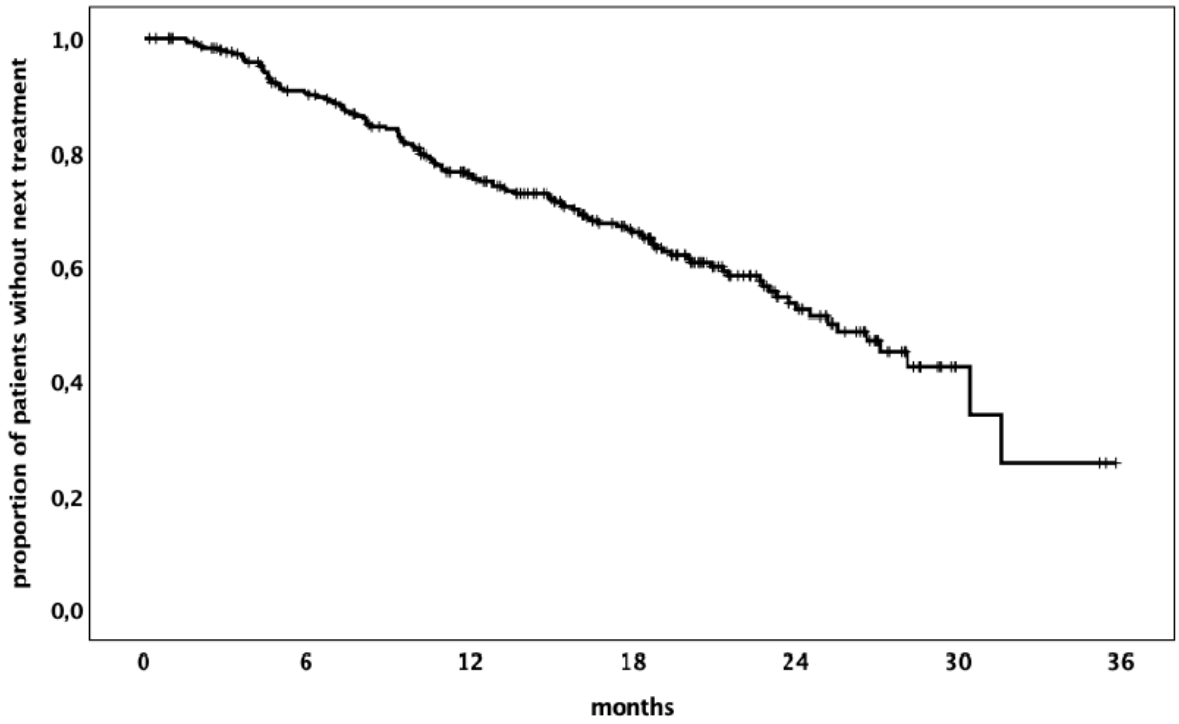

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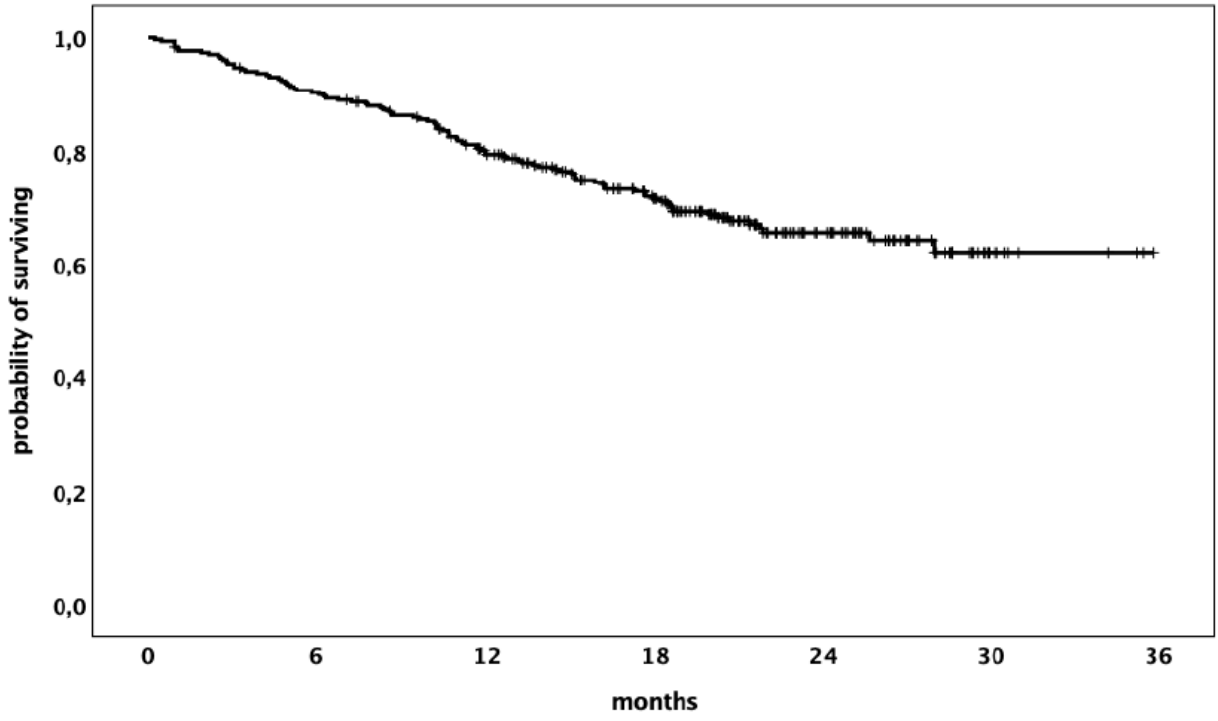

Supplementary Figure 5.