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ORIGINAL ARTICLE

Outcomes and prognostic indicators in daratumumab-refractory multiple myeloma: a multicenter real-world study of elotuzumab, pomalidomide, and dexamethasone in 247 patients

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Available online 7 January 2025

Background: Daratumumab-refractory multiple myeloma (Dara-R MM) presents a significant treatment challenge. This study aimed to evaluate the efficacy and survival outcomes of elotuzumab, pomalidomide, and dexamethasone (EloPd) in a large, real-world cohort of patients with Dara-R MM, with particular focus on progression-free survival (PFS) and overall survival (OS).

Materials and methods: This retrospective analysis included 247 Dara-R MM patients treated with EloPd. All patients were also refractory to lenalidomide, with 51.4% to a proteasome inhibitor, thus classified as triple-class refractory (TCR). Survival risk-scoring systems for PFS (progression-free risk score-PRS_{DaraR}) and OS (survival risk score-SRS_{DaraR}) were developed to stratify patients based on their risk profiles.

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Results: The overall response rate was 52.6%, with a median PFS and OS of 6.6 and 17.0 months, respectively. The International Staging System (ISS) stages II and III, low hemoglobin (Hb) levels, the last therapy being daratumumab, and symptomatic relapse were identified as significant independent predictors of shorter PFS in multivariable analysis. In addition to advanced ISS stages, low Hb levels (<10.6 g/dl), symptomatic relapse, and refractory disease exhibited an independent negative impact on OS. Importantly, no significant differences in both PFS and OS were observed between TCR and non-TCR patients. Based on these multivariable analyses, we developed PRS_{DaraR} and SRS_{DaraR} according to the magnitude of the hazard ratio. In PRS_{DaraR}, 10.1% were low-risk, 41.3% intermediate, 43.3% high, and 5.3% very high-risk. The 12-month PFS probabilities were 86.3% (low), 67.6% (intermediate), 52.9% (high), and 31.8% (very high). For SRS_{DaraR}, 6.1% were low-risk, 47.8% intermediate, 19.4% high, and 26.7% very high. The 12-month OS probabilities were 90.9% (low), 75.7% (intermediate), 55.9% (high), and 32.6% (very high).
Conclusions: This study supports EloPd as an effective treatment option in Dara-R MM patients, providing valuable disease control and acting as a potential bridge to newer therapies, such as CAR-T and bispecific antibodies.
Key words: elotuzumab, pomalidomide, dexamethasone, daratumumab-refractory, multiple myeloma

INTRODUCTION

The therapeutic landscape for multiple myeloma (MM) has significantly evolved over recent years, offering a broader array of treatment options tailored to both patient and disease characteristics, which has ultimately improved prognosis.[1-3] However, despite these advancements, most patients with MM will eventually experience relapse or refractoriness (RRMM), necessitating additional treatment. With each subsequent relapse, there is increased drug resistance and shorter remission durations due to accumulating genomic and epigenetic alterations.[4] While the management of first-line therapy is now well defined and successfully improved since the growing availability of newer triplets and quadruplets, managing patients who progress after or become refractory to specific drugs is more complex. This requires careful consideration of patient characteristics, disease progression rates, prior treatment efficacy, and tolerance. In particular, the growing population of patients acquiring daratumumab resistance (Dara-R) presents a significant therapeutic challenge.

The MAMMOTH study set an important benchmark for evaluating emerging therapies aimed at improving outcomes for MM patients refractory to anti-CD38 monoclonal antibodies, such as daratumumab and isatuximab, especially those classified as penta-refractory.[5] The findings from this study revealed a concerning median overall survival (OS) of <9 months for the entire cohort and 6 months for penta-refractory patients, highlighting the poor prognosis for this patient population, especially since CD38-targeted therapies have been increasingly used in earlier lines of treatment.[5] Additionally, approximately one-third of the patients responded to subsequent therapies, with a median progression-free survival (PFS) of only 3.4 months. Carfilzomib- and alkylator-based combinations showed the most promising results, achieving a response rate of 47% and a median PFS of 5.7 months.[5]

Building on these findings, a recent retrospective study evaluated the efficacy of the ixazomib, lenalidomide, and dexamethasone (IxaRd) regimen in 43 patients with RRMM previously exposed or refractory to daratumumab.[6] With an overall response rate (ORR) of 39.5% and a median PFS of 4.56 months, the outcomes were comparable to other salvage regimens used in this setting.

A recent retrospective study evaluated the efficacy and tolerability of selinexor-based regimens in 62 patients with RRMM previously exposed or refractory to an anti-CD38 monoclonal antibody, including selinexor-bortezomib-dexamethasone (XVd), selinexor-pomalidomide-dexamethasone (XPd), and selinexor-carfilzomib-dexamethasone (XKd) regimens.[7] To note, 53 out of the 62 patients (85%) were Dara-R. This study showed that these selinexor-based combinations offer an effective and well-tolerated therapeutic option and could help address the unmet clinical need in this subset of high-risk patients. Emerging strategies utilizing CAR-T therapies targeting B-cell maturation antigen (BCMA), such as idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), as well as bispecific antibodies like teclistamab, have demonstrated significant efficacy, yielding high response rates and durable remissions even in this hard-to-treat patient population. Ide-cel and cilta-cel have achieved impressive ORR ranging from 73% to 97%. In the pivotal phase I/II MajesTEC-1 trial, teclistamab achieved a noteworthy ORR of 63% and a median PFS of 11.3 months in a cohort of 165 patients, 77.6% of whom were TCR.[8] Elotuzumab, in combination with pomalidomide and dexamethasone (EloPd), represents another viable therapeutic option for RRMM patients, demonstrating efficacy in both clinical trials[8,9] and real-world settings.[10,11] In a phase II clinical trial specifically enrolling Dara-R patients, this regimen achieved a response rate of 35% and a median PFS of 3.7 months.[12] Despite the heavily pretreated nature of the cohort, which included 73% triple-class refractory (TCR) patients, the median OS was an encouraging 56.7 months. These findings suggest that even with limited PFS, EloPd can provide a meaningful survival benefit, making it an additional valuable option for patients with limited therapeutic alternatives.

While the phase II study formally assessed EloPd in Dara-R MM patients,[12] our current study offers further insights from a large, multicenter, retrospective real-world analysis of EloPd efficacy in 247 Dara-R MM cases. This study aims to provide an additional real-world perspective on the effectiveness and prognosis of EloPd in this challenging patient population.

MATERIALS AND METHODS

Patients

For this retrospective analysis, clinical data were extracted from the medical records of RRMM patients and compiled into a centralized database. This database included information such as age, sex, date of diagnosis, laboratory parameters, treatment history, and the date of last follow-up or death. Data collection began at the time of patient inclusion and was continually updated.

This analysis was conducted on a cohort of 247 consecutive RRMM patients treated with the EloPd regimen across 51 centers in Italy. All patients were refractory to Dara-R and received at least one cycle of EloPd, as previously described.[9,10] TCR patients were defined as those who were refractory to an anti-CD38 monoclonal antibody, a proteasome inhibitor (PI), and an immunomodulatory drug. During treatment, all patients received prophylactic antibacterial, antiviral, and antithrombotic therapy. The primary endpoints of this analysis were PFS and OS. Treatment response and disease progression were assessed according to the International Myeloma Working Group criteria,[13] with patients classified as responsive if they achieved at least a partial response (PR). Refractory myeloma was defined as disease that does not respond to primary or salvage therapy or progresses within 60 days of the last therapy. Biochemical relapse was characterized by an increase in serum and/or urine monoclonal protein alone, whereas clinical relapse referred to relapse accompanied by progression-related features, including CRAB symptoms, i.e. hypercalcemia (C), renal failure (R), anemia (A), and bone disease (B).

The study protocol was reviewed and approved by the institutional ethics committees of all participating centers, in accordance with the principles of the Declaration of Helsinki. During treatment, all patients received prophylactic antibacterial, antiviral, and antithrombotic therapies, following each center's policy.

Statistical analysis

Categorical variables were compared using two-way tables with Fisher's exact test and multi-way tables with Pearson's chi-square test.

The Kaplan–Meier method was used to analyze PFS and OS, measured from the initiation of RRMM EloPd treatment until, respectively, death from any cause or progression or last follow-up, the earliest start date of subsequent therapy or last follow-up, and death from any cause or last follow-up. The predictive cut-off value of hemoglobin (Hb) levels (optimal threshold as identified by the Youden index) for discriminating patients who progressed or died of any cause among those without these outcomes was identified by the receiver operating characteristic (ROC) curve analysis.

The optimal cut-off corresponds to the Hb threshold that maximizes the difference between true positives (sensitivity) and false positives (1-specificity) for predicting the occurrence of these outcomes.

The statistical significance of associations between individual variables and survival outcomes was calculated using the log-rank test. The prognostic impact of the outcome variable was further investigated by univariable and multivariable Cox regression analysis, with results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We derived a survival risk score for PFS (PFS_{DaraR}) and OS (SRS_{DaraR}) based on the HRs. HRs were exploited giving 1 point for HRs ranging from 1.1 to 1.9, 2 points for HRs 2.0-2.9, etc. A value of $P \leq 0.05$ was considered statistically significant. Data analysis was carried out by STATA for Windows v.9 and SPSS Statistics v.21.

RESULTS

Patient characteristics

This retrospective cohort included 247 Dara-R MM patients. The baseline characteristics of the entire cohort of 247 Dara-R MM patients are summarized in Table 1. The majority of patients initiating EloPd were aged $\geq$70 years, with a predominance of males, and most had creatinine clearance (CrCl) $\geq$60 ml/min. The distribution across the International Staging System (ISS) stages I-III was relatively balanced, and 72.9% of patients exhibited normal lactate dehydrogenase (LDH) levels. Regarding treatment history, 54.3% of patients had received two prior lines of therapy, 47.4% had undergone a prior autologous stem cell transplant (ASCT), and 72.1% of cases showed refractoriness to daratumumab immediately before EloPd treatment. Beyond daratumumab refractoriness, all patients were also refractory to lenalidomide, and 127 (51.4%) were refractory to a PI, categorizing nearly half of the cohort as TCR. At EloPd initiation, 51.4% of patients were in symptomatic relapse, while 32.8% had refractory disease. FISH analysis, carried out at EloPd start, available for 99 patients, showed that 45.5% of cases had high-risk cytogenetic features.

Response evaluation

At the last follow-up, all 247 patients were assessable for response. A total of 130 patients (52.6%) achieved at least a PR, including 2 patients (0.8%) achieving a stringent complete response (sCR), 7 (2.8%) a CR, 38 (15.4%) a very good PR, and 83 (33.6%) a PR.

Age, sex, number of prior lines of therapy, previous ASCT, MM status at EloPd initiation (i.e. biochemical relapse versus symptomatic relapse versus refractory to last treatment), PI refractory, CrCl, ISS, LDH levels, and timing of EloPd administration (after daratumumab-containing regimen compared with those who received other therapies between anti-CD38 monoclonal antibody and EloPd) did not significantly impact the likelihood of achieving at least a PR to EloPd (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104084).

Progression-free survival

After a median follow-up of 8.9 months (interquartile range 4.31-15.6 months), 169 patients (68.4%) experienced

Table 1. Main characteristics of patients at elotuzumab, pomalidomide, and dexamethasone initiation

	Patients, *n* (%)
Age (years)	
<70	109 (44.1)
≥70	138 (55.9)
Sex	
Male	138 (55.9)
Female	109 (44.1)
Paraproteins (isotype)	
Immunoglobulin G	141 (57.1)
Immunoglobulin A	57 (23.1)
Immunoglobulin D	1 (0.4)
Immunoglobulin M	2 (0.8)
Light chain only	46 (18.6)
Creatinine clearance (ml/min)	
≥60	169 (68.4)
<60	78 (31.6)
International Staging System	
I	88 (35.6)
II	96 (38.9)
III	63 (25.5)
Hb g/l, median (IQR)	11.4 (10.1-11.7)
LDH	
Normal	180 (72.9)
Elevated	67 (27.1)
Previous lines of therapy	
2	134 (54.3)
3	64 (25.9)
≥4	49 (19.8)
Previous autologous stem cell transplantation	
No	130 (52.6)
Yes	117 (47.4)
Daratumumab refractory	
Yes	247 (100)
No	0 (0)
Daratumumab as the last therapy	
Yes	178 (72.1)
No	69 (27.9)
Lenalidomide refractory	
Yes	247 (100)
No	0 (0)
Proteasome inhibitor refractory	
Yes	127 (51.4)
No	120 (48.6)
Disease status	
Biochemical relapse	39 (15.8)
Symptomatic relapse	127 (51.4)
Refractory disease	81 (32.8)
Cytogenetic analysis ($n = 99$)	
Standard risk	54 (21.9)
High risk	45 (18.2)

IQR, interquartile range; LDH, lactate dehydrogenase.

disease progression or death. The median PFS was 6.6 months (95% CI 5.5-7.8 months), and a 12-month PFS probability of 33.2% (Figure 1A).

The univariable and multivariable analyses for PFS highlighted several critical factors influencing patient PFS (Table 2). At univariable analysis, parameters associated with poorer PFS were ISS II and III stages (HR ISS II versus I, HR 1.64, 95% CI 1.14-2.37, $P = 0.008$ ISS III versus I, HR 2.01, 95% CI 1.33-3.04, $P < 0.001$), daratumumab not given as the last therapy before the EloPd salvage (HR 1.55, 95% CI 1.11-2.16, $P = 0.009$), and symptomatic relapse at EloPd start (symptomatic versus biochemical relapse HR 1.63, 95% CI 1.03-2.59, $P = 0.039$). Patients with Hb < 9.5 g/l, a value detected by ROC curve analysis (Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2024.104084), had nearly double the risk of disease progression in univariable analysis (HR 1.89, $P < 0.001$). In contrast, factors such as age, sex, CrCl, LDH levels, PI refractoriness, and prior ASCT do not significantly alter the PFS risk in this analysis, as well as cytogenetic analysis carried out in the 99 available cases.

In the Cox multivariable analysis (Table 2), the influence of the ISS remains independently associated with PFS, with stage II and stage III patients exhibiting, respectively, a significant 1.66- and 1.88-fold increase in the risk of progression compared with those in stage I. Moreover, having undergone other therapeutic regimens after daratumumab therapy continues to be a significantly independent factor associated with PFS, with 1.5 times the risk of progressing for patients who were not treated with EloPd soon after the anti-CD38 monoclonal antibody therapy. The risk associated with symptomatic relapse persisted, showing 1.6 times the risk of biochemical relapse. The increased risk associated with lower Hb levels dropped to a 1.4-fold rise in progression risk, nevertheless showing a *P* value close to significance ($P = 0.075$).

Overall survival

The median OS in this cohort was 17.0 months (95% CI 13.7-20.4 months), with a 12-month OS probability of 61.6% (Figure 1B). Table 3 shows univariable and multivariable analyses of prognostic factors influencing OS.

Hb < 10.6 g/l, as determined by ROC analysis (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2024.104084), emerged as a strong predictor of reduced OS, with patients demonstrating a threefold increase in the risk of mortality in the univariable analysis. This effect remained significant in the multivariable analysis, where low Hb continued to be associated with a 2.26-fold higher risk of death, reinforcing the importance of anemia as an independent prognostic factor. This Hb cut-off demonstrated a high specificity (94%) for identifying patients who survived, although its sensitivity for identifying patients who died was relatively low (24%).

The ISS also maintained its relevance as a critical determinant of OS. Specifically, patients in stage III had a threefold increase in the risk of death compared with those in stage I, and this association persisted in the multivariable model, with a 2.39-fold increased risk of death. Additionally, patients presenting with symptomatic relapse exhibited a 3.62-fold increased risk of death in the univariable analysis, with this elevated risk remaining significant in the multivariable model (HR 3.08, $P = 0.006$). Refractory disease was similarly associated with a 2.36-fold increase in mortality risk ($P = 0.04$). The potential influence of daratumumab exposure before EloPd salvage therapy showed borderline significance in the univariable analysis (HR 1.50, $P = 0.057$), but this association was not retained in the multivariable model (HR 1.21, $P = 0.41$).

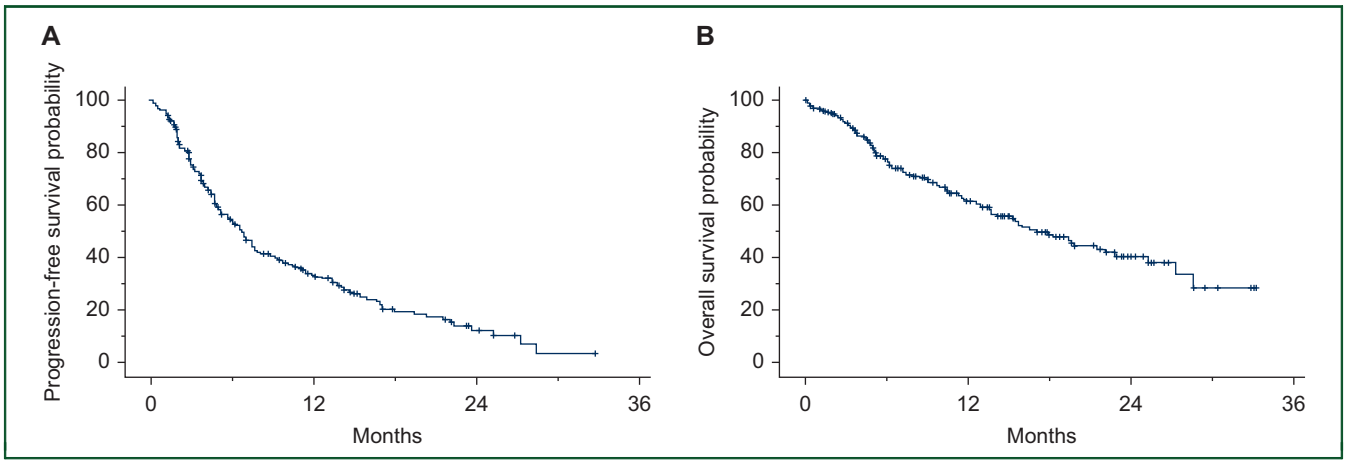

Figure 1. Outcomes of the entire cohort.
Progression-free survival (A), and overall survival (B) of the retrospective cohort of 247 daratumumab-refractory multiple myeloma patients treated with elotuzumab pomalidomide and dexamethasone.

Other variables, such as age, sex, CrCl, prior ASCT, the number of previous therapy lines, and PI refractoriness did not significantly influence OS in the univariable analysis. Although elevated LDH was a significant factor in the univariable model (HR 1.65, $P = 0.016$), it did not maintain statistical significance in the multivariable model (HR 1.37, $P = 0.14$), suggesting that its impact on OS may be confounded by other variables (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104084).

Prognostic survival scoring systems

Based on the identified prognostic models, we developed a risk-scoring system for PFS and OS, termed PRS_{DaraR} and SRS_{DaraR}, respectively. The scores were calculated by assigning points according to the magnitude of the HR: 1 point for HRs between 1.1 and 1.9, 2 points for HRs from 2.0 to 2.9, and so on. Each patient's score was calculated by summing the points corresponding to their risk factors (Table 3). This resulted in a prognostic scale ranging from 0 (no risk factors) to a maximum of 3 for PFS and 7 for OS (Table 3). For PRS_{DaraR}, four distinct risk categories were established: low-risk (score 0), intermediate-risk (score 1), high-risk (score 2), and very high-risk (score 3) (Figure 2A). In this cohort, 25 patients (10.1%) were classified as low-risk, 102 (41.3%) as intermediate-risk, 107 (43.3%) as high-risk, and 13 (5.3%) as very high-risk.

The 12-month PFS probability for these groups was 86.3% for the low-risk, 67.6% for the intermediate-risk, 52.9% for the high-risk, and 31.8% for the very-high-risk groups (Figure 2A). Unlike the low-risk group, which did not reach the median PFS, the estimated median PFS for intermediate-, high-, and very-high-risk groups were 22.8 months (95% CI 13.4-32.2 months), 12.8 months (95% CI 7.8-17.9 months), and 8.9 months (95% CI 2.3-15.5 months), respectively.

For SRS_{DaraR}, visual inspection of the Kaplan—Meier curves of the seven-level risk score (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.104084) suggested clustering of cases with scores of 2-4 and those with scores of 6-7, leading to the generation of four risk categories: low risk (score 0), intermediate risk (scores 2-4), high risk (score 5), and very high risk (scores 6-7) (Figure 2B). In this cohort, 15 patients (6.1%) were classified as low risk, 118 (47.8%) as intermediate risk, 48 (19.4%) as high risk, and 66 (26.7%) as very high risk.

Similarly to PRS_{DaraR}, the low-risk group of SRS_{DaraR} did not reach the median timeline, while the estimated median OS were 25.3, 13.7, and 6.3 months for the low-, intermediate-, high-, and very-high-risk scores, respectively (Figure 2B). The 12-month OS probabilities were 90.9% for the low-risk (HR = 1, reference category), 75.7% for the intermediate-risk, 55.9% for the high-risk, and the 32.6% for the very-high-risk groups.

Similar to PRS_{DaraR}, the low-risk group did not reach the median OS. The estimated median OS for the intermediate-, high-, and very-high-risk groups were 25.3 months, 13.7 months, and 6.3 months, respectively. The 12-month OS probabilities were 90.9% for the low-risk, 75.7% for the intermediate-risk, 55.9% for the high-risk, and 32.6% for the very-high-risk groups (Figure 2B).

DISCUSSION

The study provides a detailed evaluation of the effectiveness of EloPd therapy in a large real-world cohort of 247 patients with Dara-R MM. Our findings corroborate and are consistent with previous clinical trial data,[12] reinforcing the therapeutic potential of EloPd in this heavily pretreated and challenging patient population. The observed ORR of 52.6% and the median PFS of 6.6 months exceeded those reported in the smaller trial (ORR 35%, PFS 3.7 months).[12] This discrepancy may be attributed to the broader and less heavily pretreated population in our real-world setting, compared with the more stringently selected trial participants. In contrast, the trial's median OS for both pomalidomide-exposed (45.5 months) and -unexposed cases (56.7 months) was substantially longer than the 17.0 months observed in our cohort. This difference is likely

Table 2. Univariable and multivariable analysis for progression-free survival

	N	Univariable		Multivariable	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)					
≤70	109	1	1		
>70	138	0.89 (0.66-1.20)	0.45		
Sex					
Female	109	1			
Male	138	0.93 (0.68-1.26)	0.65		
CrCl ml/min					
≥60	169	1			
<60	78	0.92 (0.66-1.29)	0.65		
LDH					
Normal	180	1			
Elevated	67	1.24 (0.88-1.75)	0.21		
Hb (g/l)					
≥9.5	202	1			
<9.5	45	1.89 (1.32-2.70)	**<0.001**	1.43 (0.96-2.13)	0.075
International Staging System					
I	88	1			
II	96	1.64 (1.14-2.37)	**0.008**	1.66 (1.15-2.42)	**0.007**
III	63	2.01 (1.33-3.04)	**<0.001**	1.82 (1.17-2.84)	**0.008**
Previous lines of therapy					
2	134	1			
>2	113	1.08 (0.80-1.47)	0.61		
Previous ASCT					
No	117	1			
Yes	130	1.01 (0.75-1.37)	0.92		
Daratumumab as last therapy					
Yes	178	1			
No	69	1.55 (1.11-2.16)	**0.009**	1.51 (1.06-2.17)	**0.023**
Proteasome inhibitor refractory					
No	120	1			
Yes	127	1.21 (0.9-1.65)	0.2		
Disease status					
Biochemical relapse	39	1			
Symptomatic relapse	127	1.63 (1.03-2.59)	**0.039**	1.63 (1.02-2.59)	**0.041**
Refractory to last treatment	81	1.35 (0.83-2.19)	0.23		
Cytogenetic analysis ($n = 99$)					
Standard risk	54	1			
High risk	45	1.03 (0.64-1.69)	0.87		

Bold values denote statistical significance at the $P < 0.05$ level.
ASCT, autologous stem cell transplant; CI, confidence interval; CrCl, creatinine clearance; Hb, hemoglobin; LDH, lactate dehydrogenase.

multifactorial, with trial patients potentially benefiting from more rigorous selection criteria, fewer comorbidities, and superior baseline health status. Moreover, clinical trials provide enhanced monitoring and management of adverse events, which may further contribute to improved OS. It is also plausible that the structured environment of clinical trials, which facilitates the use of subsequent therapies, contributed to the extended survival outcomes observed. In this respect, in our real-world study, only 7% of patients had received bispecific antibodies.[10,11]

Table 3. Prognostic survival scoring systems

Progression risk score for daratumumab-refractory patients (PRS_{DaraR})	
Prognostic factors	Points
ISS II-III	1
Daratumumab at last therapy	1
Symptomatic relapse	1
Low-risk: score 0; intermediate-risk: score 1; high-risk: score 2; very high-risk: score 3	
Survival risk score for daratumumab-refractory patients (SRS_{DaraR})	
Prognostic factors	Points
Hb <10.6 g/dl	2
ISS II-III	2
Symptomatic relapse	3
Refractory disease	2
Low-risk: score 0; intermediate-risk: scores 2-4; high-risk: score 5; very high-risk: scores 6-7	

Hb, hemoglobin; ISS, International Staging System.

The IxaRd regimen[6] used in daratumumab-exposed patients showed an ORR of 39.5%, suggesting that EloPd may be slightly more effective at inducing responses in this heavily pretreated population. Additionally, the median PFS for IxaRd was 4.56 months, again shorter than that of our EloPd cohort.

Nevertheless, one of the key limitations of the use of the IxaRd combination in the subset of our cohort's patients may be represented by the fact that all our cases were lenalidomide refractory. The interesting PFS observed with EloPd could be strategically utilized as a bridge to novel therapies, such as CAR-T-cell therapy[14] and bispecific antibodies.[15,16] By providing effective disease control in the short-to-medium term, EloPd may help stabilize patients

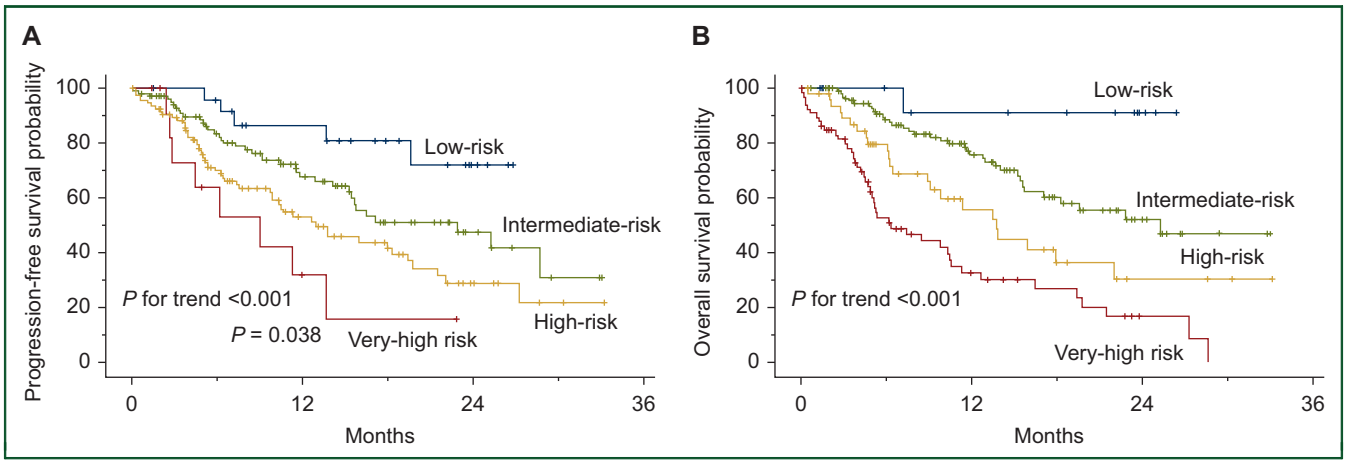

Figure 2. Outcomes according prognostic model.
Progression-free survival risk model (PSR_{DaraR}, A) and overall survival risk model (SSR_{DaraR}, B) of the retrospective cohort of 247 daratumumab-refractory multiple myeloma patients treated with elotuzumab pomalidomide and dexamethasone.

and extend their eligibility for these cutting-edge treatments, which are often more accessible after bridging therapies that maintain disease suppression. This approach could optimize the timing of more advanced therapeutic options, allowing patients to benefit from the latest advancements in MM treatment. In addition, elotuzumab, working through the induction of natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity of SLAMF7-expressing myeloma cells,[17] while less convenient, brings the benefit of pomalidomide's immune-enhancing effects, which might help overcome the NK-cell depletion and exhaustion caused by prior daratumumab exposure.[18] This trade-off between good tolerance and potential immunological benefit is an important factor when choosing between these regimens. There are at least two alternative strategies, selinexorVd (XVd) and PVd, that could represent valid therapeutic options in Dara-R cases, especially for patients who are not PI inhibitor refractory. However, it is important to note that in pivotal trials the subset of Dara-R patients was either underrepresented in XVd or not included in the PVd cohort at all.[19,20] Despite this, recent retrospective data investigating the efficacy and safety of selinexor-based regimens in anti-CD38-exposed patients—85% of whom were Dara-R—have demonstrated promising outcomes. Specifically, 16 patients treated with the XVd regimen achieved an ORR of 56.3%, with a median PFS of 6.7 months.[21]

Our analysis indicates that specific patient characteristics at EloPd initiation significantly influence survival outcomes. One of the most remarkable results is the strong and consistent impact of Hb levels, an indirect marker of medullary plamocytosis and/or renal failure, on OS. While low Hb (cut-off 9.5 g/l) was a significant predictor of poorer outcomes in the PFS univariable analysis, its significance diminished in the multivariable model, becoming only borderline significant. In contrast, for OS, the effect of low Hb, although at a different cut-off (10.6 g/l), was profound and highly significant in both the univariable and multivariable analyses. This suggests that while low Hb might not immediately accelerate disease progression, it plays a much larger role in long-term patient survival, likely reflecting its broader impact on overall health, treatment tolerance, and disease resilience. Anemia is often associated with systemic weakness and increased susceptibility to complications, which may explain its stronger association with OS.

More advanced ISS stages were linked to higher risks of progression and death. In multivariate analysis exploring the impact on PFS, ISS stages II and III were associated with significantly shorter times to progression, and this effect was mirrored in the OS analysis, where patients in stage III had a markedly higher risk of death. This consistency underscores the role of ISS as a crucial determinant of disease trajectory and survival, with advanced stages indicating a more aggressive and less manageable disease course. This finding is consistent with our previous study, highlighting the prognostic importance of advanced disease stage in RRMM patients.[22]

An important distinction was made between patients who received EloPd immediately after daratumumab and those who had other therapies in between before starting EloPd. For PFS, patients who had other therapies in between daratumumab and EloPd exhibited a higher risk of progression, as opposed to those who received EloPd directly after daratumumab (HR 1.55, $P = 0.009$). Importantly, we also found that patients who received EloPd immediately after daratumumab therapy showed a trend toward better OS ($P = 0.057$), lacking statistical significance after adjustment for other confounders in the multivariable model, indicating that while the timing between therapies influences PFS, it does not have as strong an impact on long-term survival. This latter finding aligns with previous results.[12]

Our findings could appear to be a paradox, in light of the time required for NK-cell recovery. Regardless of the immunomodulatory properties of pomalidomide likely

https://doi.org/10.1016/j.esmoop.2024.104084

playing a crucial role in enhancing NK-cell function and promoting immune reconstitution after daratumumab therapy, this observation may be explained by the results of our study that patients receiving EloPd directly after daratumumab had a significantly lower number of lines of prior therapies [median 2 (range 2-5) versus 3 (range 2-9), $P < 0.001$], indicating a less heavily pretreated and potentially less resistant cohort. This less extensive treatment history coupled with the aforementioned crucial role of pomalidomide in enhancing NK-cell function could mitigate the impact of daratumumab-induced NK-cell depletion,[17] ultimately allowing for more effective immune system recovery.

Additionally, patients with biochemical relapse were more likely to experience better outcomes and may benefit from this triplet regimen. In contrast, those with symptomatic relapse or refractory disease may require alternative therapeutic strategies, such as bispecific antibodies or CAR-T-cell therapies. Interestingly, other well-known prognostic indicators did not appear to significantly influence survival analysis, underscoring the complexity of RRMM treatment and the multifactorial nature of patient responses to therapy.

Nearly half of our cohort were TCR, i.e. resistant to daratumumab, lenalidomide, and a PI. However, there were no significant differences in PFS or OS between TCR and non-TCR patients, suggesting that EloPd's efficacy may be independent of prior triple refractoriness. These data are similar to those reported by Parrondo et al.[13] Nevertheless, promising results have been observed in newer approaches, such as bispecific antibodies and CAR-T therapies, though they come with challenges like cytokine release syndrome and immune effector cell-associated neurotoxicity.[22]

The prognostic scoring systems developed in this study, PRS_{DaraR} for PFS and SRS_{DaraR} for OS, provide valuable tools for stratifying patients based on their risk profiles. However, external validation is still needed to confirm their broader applicability. These systems, which take into account clinical factors extensively available such as Hb levels, ISS stage, as well as different prior treatment histories in different combinations, enable clinicians to predict outcomes more accurately and tailor treatment strategies accordingly. Notably, patients in the low-risk groups for both PFS and OS exhibited markedly better survival probabilities, with 12-month OS rates exceeding 90%. Conversely, those in the very-high-risk groups had significantly poorer outcomes, emphasizing the importance of early identification and aggressive management of high-risk patients.

In conclusion, this real-world analysis of the unselected Dara-R MM population contributes further to provide evidence of the actual treatment scenario of RRMM, suggesting that EloPd represents a meaningful option in the emerging setting of Dara-R disease. The modest PFS and OS outcomes may reflect the difficulty in treating this patient population. However, the improved efficacy across lower-risk subgroups makes EloPd an essential part of the therapeutic arsenal. Given that other therapeutic options such as CAR-T-cell therapy[14] or bispecific antibodies[15,16] may not be immediately accessible to all patients, EloPd remains an accessible and effective choice for many also in terms of a 'bridge to subsequent therapy' approach.

Future research should focus on optimizing combination regimens and investigating new therapeutic modalities to address the unmet needs of Dara-R MM patients, while further elucidating the mechanisms underlying daratumumab resistance.[23-25]

FUNDING

This work was partially supported by the Italian Ministry of Health—Ricerca Corrente Annual Program 2025 (no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

Data are available upon reasonable request and submission of a research project proposal to the corresponding authors.

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