Received: 25 March 2024 | Revised: 15 May 2024 | Accepted: 18 May 2024

DOI: 10.1002/hon.3290

WILEY

ORIGINAL ARTICLE

Elotuzumab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended follow-up of a multicenter, retrospective real-world experience with 321 cases outside of controlled clinical trials

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Funding information
Progetto Ricerca Finalizzata PNRR-MAD-2022-12375673, Italian Ministry of Health, Rome, Italy.

Abstract

The ELOQUENT-3 trial demonstrated the superiority of the combination of elotuzumab, pomalidomide, and dexamethasone (EloPd) in terms of efficacy and safety, compared to Pd in relapsed/refractory multiple myeloma (RRMM), who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor. The present study is an 18-month follow-up update of a previously published Italian real-life RRMM cohort of patients treated with EloPd. This revised analysis entered 319 RRMM patients accrued in 41 Italian centers. After a median follow-up of 17.7 months, 213 patients (66.4%) experienced disease progression or died. Median progression-free survival (PFS) and overall survival (OS) were 7.5 and 19.2 months, respectively.

[Correction added on 20 August 2025, after first online publication: The copyright line was changed.]

The updated multivariate analysis showed a significant reduction of PFS benefit magnitude both in advanced International Staging System (ISS) (II and III) stages and previous exposure to daratumumab cases. Instead, advanced ISS (II and III) stages and more than 2 previous lines of therapy maintained an independent prognostic impact on OS. Major adverse events included grade three-fourths neutropenia (24.9%), anemia (13.4%), lymphocytopenia (15.5%), and thrombocytopenia (10.7%), while infection rates and pneumonia were 19.3% and 8.7%, respectively. A slight increase in the incidence of neutropenia and lymphocytopenia was registered with longer follow-up. In conclusion, our real-world study still confirms that EloPd is a safe and possible therapeutic choice for RRMM. Nevertheless, novel strategies are desirable for those patients exposed to daratumumab.

KEYWORDS
dexamethasone, elotuzumab, multiple myeloma, pomalidomide, salvage therapy

1 | INTRODUCTION

In recent decades, the landscape of multiple myeloma (MM) treatment has been significantly reshaped by the introduction of various innovations, resulting in notable improvements in patient outcomes.[1,2] Among the key therapeutic strategies, proteasome inhibitors (PI) and immunomodulatory drugs (IMIDs) have emerged as cornerstone elements of the therapeutic arsenal against MM therapy.

Several trials have substantiated the efficacy of triplet and quadruplet therapeutic approaches in achieving deeper and more durable remissions, thus prolonging patients' survival, both in the setting of newly diagnosed MM and relapsed/refractory disease (relapsed/refractory multiple myeloma (RRMM)).[3] Indeed, PI and IMIDs are currently incorporated in the earlier lines of therapy, often in association with monoclonal antibodies (mAbs), while maintaining a favorable safety profile.[4] Elotuzumab (Elo) is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody designed to target signaling lymphocytic activation molecule F7 (SLAMF7).[5,6] SLAMF7, a glycoprotein expressed in myeloma cells and natural killer (NK) cells, plays a crucial role in sustaining the proliferation and survival of MM cells. Elo exerts its therapeutic effects by disrupting critical interactions necessary for the growth and maintenance of neoplastic cells, while simultaneously enhancing the activity of NK cells through reinforcement of their antibody-dependent cellular cytotoxicity (ADCC) activity.[7,8] In vitro studies have previously demonstrated that Elo's activity is enhanced when combined with IMIDs, in particular lenalidomide (R).[9] Those findings, coupled with the compelling outcomes from the pivotal phase III trial (ELOQUENT-2),[10] including RRMM patients who received Elo in combination with R and dexamethasone, alongside our real-world investigations, confirming the safety and effectiveness of the anti-SLAM7 antibody combined with an IMID in a cohort of RRMM treated outside clinical trials,[11–14] collectively have laid a robust groundwork for exploring the clinical efficacy of Elo when combined with pomalidomide (P) and dexamethasone.

P is an IMID exerting its therapeutic effects by promoting direct MM cell death and enhancing immune responses through its interaction with cereblon.[15] Both in vitro and preclinical experiments, as well as in vivo studies have underscored the potency of P, particularly in those targeting R-resistant MM cell lines. Furthermore, compelling evidence indicates that combining Elo with P pomalidomide exerts synergistic antimyeloma effects.[16]

The ELOQUENT-3 trial, a multicenter, randomized, controlled, open-label, phase II trial, aimed to investigate the efficacy and safety of Elo in combination with P and d (EloPd) versus Pd alone in RRMM patients previously treated with R and a PI.[17] After a follow-up of 45 months, the study demonstrated that the triplet improved progression-free survival (PFS).[18] Furthermore, a recent follow-up analysis confirmed the additional benefit in terms of overall survival (OS) with a lower rate of adverse events (AEs) compared to the control arm.[17]

Recently, our group performed a retrospective analysis focusing on the outcomes of heavily pre-treated MM patients who received EloPd outside of clinical trials.[18] In this current study, we have expanded upon our previous retrospective analysis[18] by undertaking an extended follow-up investigation. This extended analysis includes additional previously unpublished cases, intending to provide a more comprehensive understanding of the safety and effectiveness of EloPd therapy in heavily pre-treated MM patients within a real-world clinical setting.

2 | METHODS

2.1 | Patients

For the aim of this retrospective analysis, we gathered updated clinical data from a previously published retrospective cohort of RRMM patients who were treated with EloPd across 41 Italian centers. After the last follow-up,[18] we have integrated an additional 121 previously unpublished cases into our analysis. Consequently, the combined databases from these 41 centers now encompass a total of 321 consecutive patients with RRMM who received at least one cycle of EloPd as salvage treatment between October 2020 and December 2023.

The databases contained clinical information including age, gender, date of diagnosis, laboratory parameters, such as isotype of paraprotein, renal function, International Staging System (ISS) and lactate dehydrogenase (LDH) value, and treatment history, including number and type of previous therapies. Last follow-up or death extracted from clinical records were also registered. All patients were treated with EloPd according to marketing approval as previously described.[19] Elotuzumab was given at 10 mg/kg i.v. on days 1, 8, 15, and 22 during the first two cycles and at a dose of 20 mg/kg once daily on day 1 of each following cycle, pomalidomide 4 mg orally once daily on days 1 to 21 of each cycle, and dexamethasone at the dose of 40 mg once weekly. Patients aged older than 75 years received a reduced dosage of steroids (20 mg of dexamethasone) once a week. EloPd was administered in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent.

From 30 to 90 min before elotuzumab infusion, all patients underwent premedication with diphenhydramine (25–50 mg) or its equivalent, ranitidine (50 mg) or its equivalent, and acetaminophen (650–1000 mg) or its equivalent. Moreover, all patients received antibacterial, antiviral, and antithrombotic prophylaxis during treatment.

The primary endpoints of our analysis encompassed PFS, OS, time to next treatment (TTNT), and assessment of safety profile. Additionally, response evaluations were conducted according to the International Myeloma Working Group (IMWG) criteria.[20] Treatment response and disease progression were evaluated based on these criteria, with patients deemed responsive if they achieved at least partial remission (PR).

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

2.2 | Statistical analysis

For categorical variables, statistical comparisons were performed using two-way tables for Fisher's exact test and multi-way tables for Pearson's Chi-square test. Multivariable 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 univariable analysis by Pearson chi-square or Fisher's exact test. The analyses of PFS, TTNT, and OS, were performed using the Kaplan-Meier method. PFS was calculated from the initiation of EloPd treatment until either death from any cause, disease progression, or the last follow-up. TTNT was measured from the initiation of treatment until the earliest start date of subsequent therapy or the last follow-up. OS was determined from the initiation of EloPd treatment until either death from any cause or the last follow-up. The statistical significance of associations between individual variables and survival was calculated using the log-rank test. The prognostic impact of the outcome variable was investigated by univariable and multiple Cox regression analysis. Results are expressed as hazard ratios (HR) and 95% confidence intervals (CI). A value of $p \leq 0.05$ was considered significant. Data analysis was performed by STATA for Windows v.9 and SPSS Statistics v.21.

3 | RESULTS

3.1 | Patients

The study enrolled a total of 321 RRMM patients who received EloPd between October 2020 and December 2023 across 41 Italian centers. Baseline characteristics are summarized in Table 1. Upon initiation of EloPd, the majority of patients were aged over 70 years. About 24% of cases were classified as stage III according to the ISS, while 36.1% were in ISS stage I and 39.9% were in ISS stage II. Among the 130 cases with available fluorescence in situ hybridization (FISH) analyses, high-risk cytogenetic lesions, such as t,[4,14] t,[14,16] and del (17p), were observed in 55 cases. Approximately one-third of patients had renal impairment, with a creatinine clearance of less than 60 mL/min. At the beginning of EloPd treatment, 33.6% of patients experienced refractory disease, while the remaining 66.4% had relapsed disease. The majority of patients (57%) had undergone 2 previous lines of therapy, with over 16% having received 4 or more lines of treatment before initiating EloPd. Notably, nearly 77% of cases had been exposed to daratumumab. All 247 daratumumab-exposed patients were refractory to daratumumab. One hundred and seventy-eight patients received EloPd immediately after a daratumumab-containing regimen, while 69 patients between a daratumumab-containing regimen and EloPd received other schedules of therapy. Almost all were refractory to lenalidomide.

3.2 | Progression-free survival

After a median follow-up of 17.7 months (range 15.2–20.3), 213 out of 321 patients (66.4%) experienced disease progression or died, with 138 deaths recorded (43%). The median PFS was 7.5 months (95% CI, 6.0–8.9 months), and the 18-month probability of PFS was 24.7% (Figure 1A). Univariable analyses revealed that ISS stage II (HR = 1.67, 95% CI 1.21–2.31; $p = 0.002$), ISS stage III (HR = 2.35, 95% CI 1.62–3.39; $p < 0.0001$), and previous daratumumab exposure (HR = 1.73, 95% CI 1.23–2.42; $p = 0.001$) were significantly associated with shorter PFS (Table S1, Figure 1B,C & D).

Both advanced ISS II/III stage (HR = 2.21, 95% CI 1.52–3.2; $p < 0.0001$ and previous exposure to the anti-CD38 monoclonal antibody (HR = 1.62, 95% CI 1.15–2.27; P 0.005) maintained an independent prognostic impact on PFS in the Cox multivariable analysis (Table S1).

3.3 | Overall survival

The median OS was 19.2 months (95% CI 14.9–23.6), with an 18-month probability of OS of 51.7% (Figure 2A). Univariable analyses

TABLE 1 Main characteristics of patients at baseline.

	No. of patients (%)
Age, (years)	
<70	138 (43)
≥70	183 (57)
Sex	
Male	177 (55.1)
Female	144 (44.9)
Paraproteins (isotype)	
Immunoglobulin G	184 (57.3)
Immunoglobulin A	73 (22.7)
Immunoglobulin D	3 (0.9)
Immunoglobulin M	3 (0.9)
Light chain only	58 (18.1)
Creatinine clearance (mL/min)	
≥60	216 (67.3)
<60	105 (32.7)
International staging system	
I	116 (36.1)
II	128 (39.9)
III	77 (24)
LDH	
Normal	233 (72.6)
Elevated	88 (27.4)
Previous lines of therapy	
2	183 (57)
3	85 (26.5)
≥4	53 (16.5)
Previous autologous stem cell transplantation	
No	161 (50.2)
Yes	160 (49.8)
Previous daratumumab	
No	74 (23.1)
Yes	247 (76.9)
Lenalidomide refractory	
No	13 (4)
Yes	308 (96)
Disease status	
Relapsed disease	213 (66.4)
Refractory disease	108 (33.6)
FISH analysis available (n = 130)	
Standard risk	75 (57.7)
High risk	55 (42.3)

showed that ISS II (HR = 1.57, 95% CI 1.02–2.41; $p = 0.04$) and ISS III (HR = 3.1, 95% CI 1.97–4.88; $p < 0.0001$) negatively affected OS (Table S2, Figure 2B & C). Moreover, having undergone more than 2 previous lines of therapy was significantly correlated with shorter OS (HR = 1.45, 95% CI 1.04–2.02; $p = 0.02$) (Table S2, Figure 2B & D). The above-mentioned clinical features maintained an independent prognostic impact on the survival outcome (Table S2). Notably, previous exposure to daratumumab lost its independent prognostic significance on OS (HR = 1.4, 95% CI 0.91–1.8; $p = 0.15$).

3.4 | Time to next treatment and subsequent therapy

Following the discontinuation of EloPd therapy, 131 patients (40.8%) proceeded to undergo subsequent treatment. The median TTNT was 8.1 months (95% CI 6.9–9.3), with an 18-month re-treating probability of 24% (Figure S1). The type of subsequent treatment is detailed in Table 2. In total, 25 different salvage treatment strategies were utilized post-EloPd discontinuation or failure. The most common salvage treatment was a belantamab-based regimen, with 53 cases utilizing this approach, 52 of which as a single drug and one in combination with isatuximab. Additionally, 39 patients (27.6%) received a PI-based regimen, with 26 patients opting for a carfilzomib-based regimen, 6 for a bortezomib-based and 7 for ixazomib-based regimens. Furthermore, 20 patients (14.1%) received an anti-CD38-containing regimen, including 13 cases of daratumumab-based and 7 isatuximab-based regimens. Furthermore, 10 patients (7%) were treated with bispecific antibodies, including 6 cases of teclistamab, 3 of talquetamab, and 1 of forintamig. Finally, 19 patients (13.4%) received subsequent chemotherapeutic regimens, with 15 patients treated with a cyclophosphamide-based regimen, 3 with bendamustine, and 1 with melphalan.

3.5 | Safety and response evaluation

At the time of the last database update, the median number of EloPd courses administered was 6 (range 1–34). A total of 225 patients (70.1%) withdrew from EloPd treatment by the cut-off date. The main cause for discontinuation was disease progression observed in 196 cases. Among the remaining cases, 14 patients discontinued therapy due to toxicity, including 11 infections and 4 cases of P-related severe skin rash. Additionally, 7 patients ceased treatment due to therapy-unrelated deaths. Infusion reactions were observed in 15 patients (4.7%), all of which occurred during the initial administration of Elo. Among these, 8 patients experienced grade 1 reactions, while 7 patients had grade 2 reactions. The infusion reactions were promptly resolved in all patients, and no discontinuation due to infusion reactions was reported.

Major AEs are depicted in Table 3 and include grade three-fourths neutropenia (24.9%), anemia (13.4%), lymphocytopenia

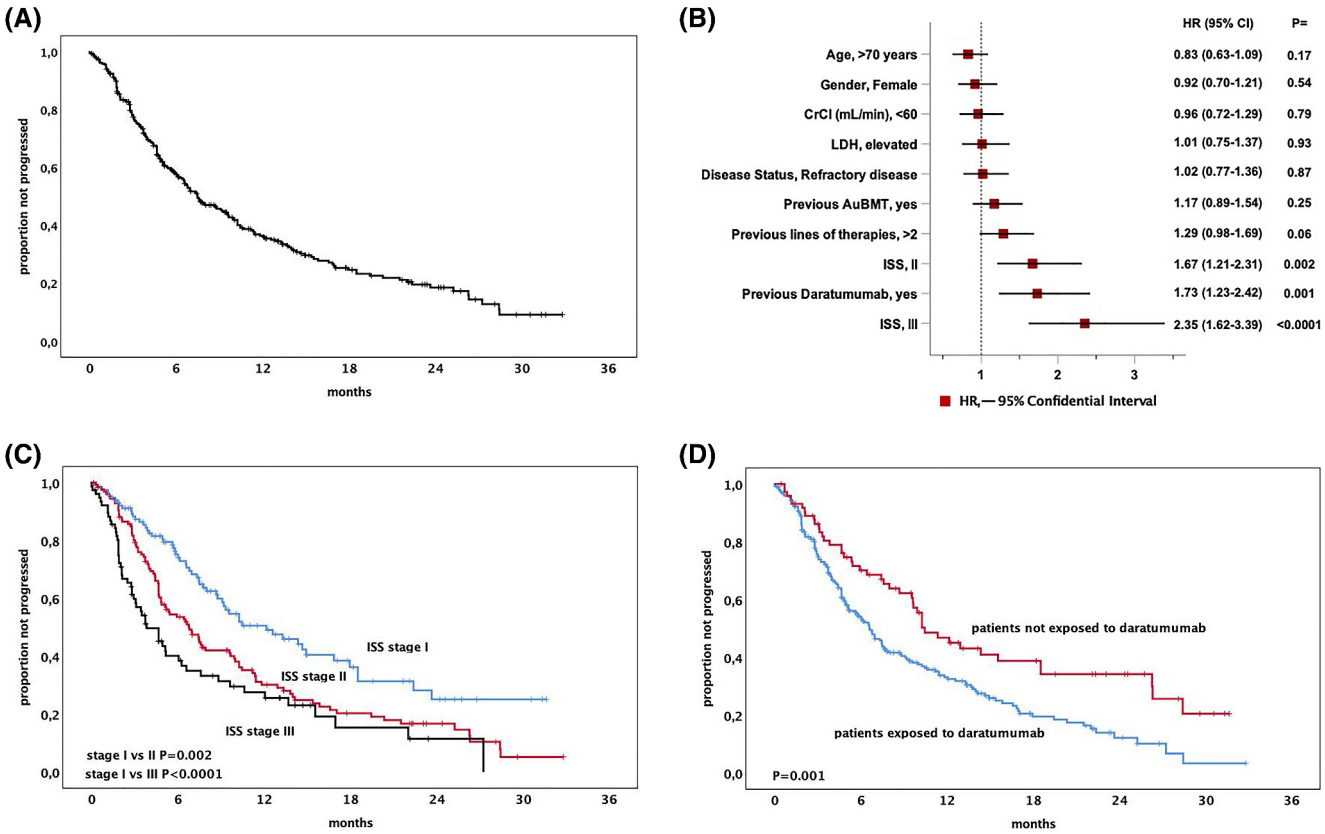

FIGURE 1 Progresssion free survival. (A) Kaplan Meier curve of progression-free survival (PFS) for all 321 relapsed/refractory multiple myeloma (RRMM) patients treated with EloPd. (B) Results of an analysis of PFS in subgroups defined according to baseline characteristics. (C) Kaplan Meier curve of PFS according International Staging System (ISS) stage. (D) Kaplan Meier curve of PFS according Daratumamb exposure.

(15.5%), and thrombocytopenia (9.3%). The infection rate was roughly 19.3%, with pneumonia reported in 8.7% of cases. Furthermore, the rate of AEs was not significantly different between patients aged less than or more than 70 years (data not shown).

At the last follow-up, a response evaluation was conducted for all patients. Fifty-five percent of cases (174 patients) reached at least PR (≥PR) (Table 4). In particular, 2 patients (0.6%) achieved a stringent complete remission, 9 patients (2.8%) attained a CR, 55 patients (17.1%) achieved a very good partial response (VGPR), and 108 patients (33.6%) obtained a PR. The median time to best response was 2 months.

The extended follow-up did not confirm a statistically significant difference in the ORR accounted for between patients who underwent autologous stem cell transplantation and those who did not (59% versus 49.4%, $p = 0.08$) (Table S3). Additionally, factors such as gender, creatinine clearance, LDH value, number of prior lines of therapy, and previous daratumumab exposure did not impact the probability of achieving a response to EloPd (Table S3).

3.6 | Outcome analysis by cytogenetic risk

Data on cytogenetic abnormalities were available in only 40.5% of cases (130 out of 321). Despite this limitation, the prognostic significance of this biomarker, as emphasized by the revised ISS (revised ISS (R-ISS)),[21] prompted us to conduct an ancillary analysis, acknowledging the potential bias introduced by the relatively low incidence of accessible cases. Notably, when comparing the group with cytogenetic information to the remaining cases, it was observed that a higher proportion of patients in the former group had received only 2 previous lines of therapy (63.8% versus 52.4%, $p = 0.04$) (Table S4).

No difference in ORR was observed between the high-risk and standard-risk groups (52.7% versus 57.3%; $p = 0.6$). Moreover, the two subgroups exhibited statistically non-significant differences in PFS (18-month PFS; high-risk group versus standard-risk: 20.9% versus 37.3%; HR 1.37, 95% CI 0.89–2.11; $p = 0.15$) (Figure S2), as well as in OS (18-month OS; high-risk group versus standard-risk: 53.2% versus 65.9%; HR 1.3, 95% CI 0.75–2.27; $p = 0.35$) (Figure S3).

4 | DISCUSSION

In contemporary medical practice, the therapeutic repertoire of RRMM is continuously evolving. Alongside established PIs and IMIDs, emerging modalities such as chimeric antigen receptor (CAR) T-cell therapies,[22] bispecific antibodies,[23] and monoclonal antibodies,[24] represent a transformative shift, fundamentally reshaping treatment

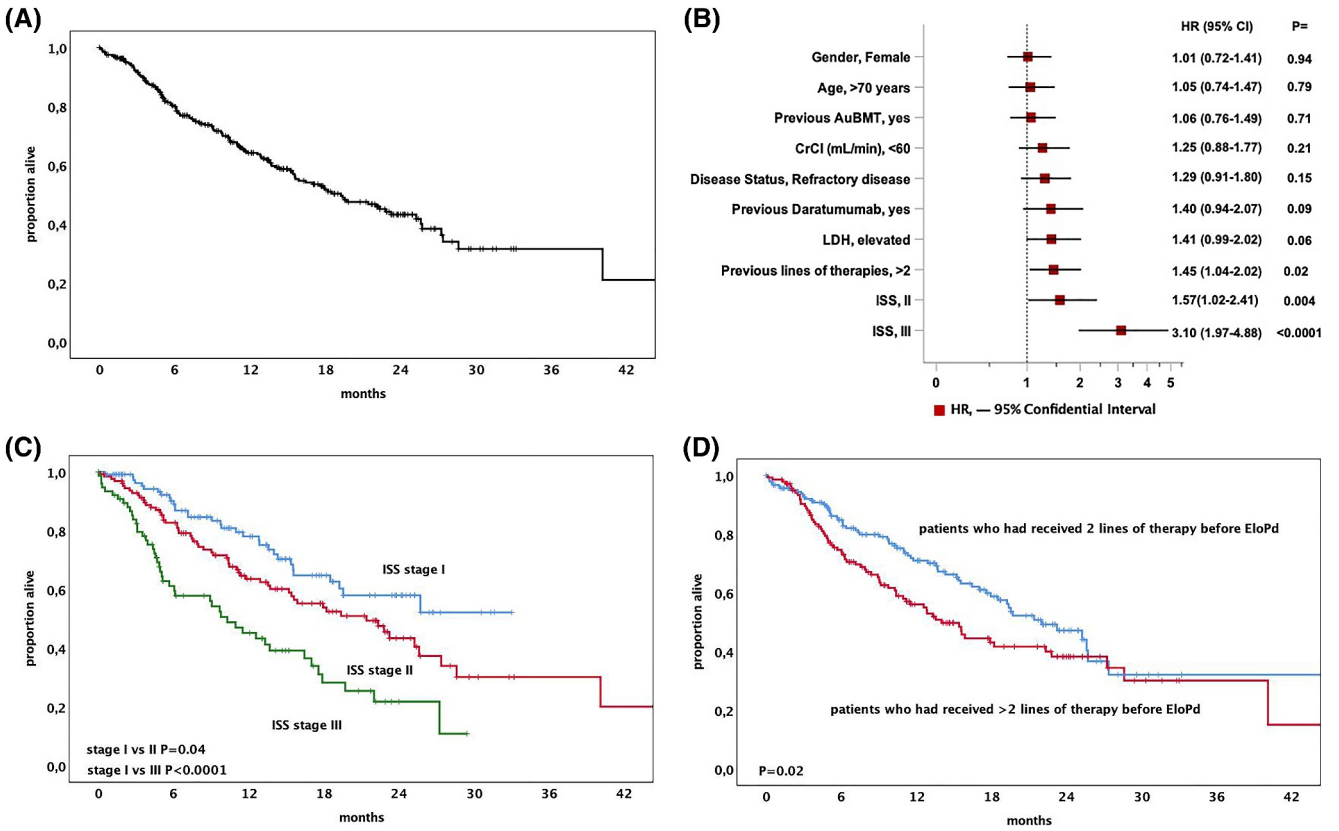

FIGURE 2 Overall survival (OS). (A) Kaplan Meier curve of OS for all 321 relapsed/refractory multiple myeloma (RRMM) patients treated with EloPd. (B) Results of an analysis of OS in subgroups defined according to baseline characteristics. (C) Kaplan Meier curve of progression-free survival (PFS) according International Staging System (ISS) stage. (D) Kaplan Meier curve of PFS according to the number of previous lines of therapy before EloPd (2 vs. > 2).

strategies for MM patients. Within clinical settings, patients who have received two prior lines of therapy may derive benefit from two distinct P-based regimens, each in association with a monoclonal antibody, EloPd and isatuximab-Pd (IsaPd). The triplet regimen including daratumumab, P, and d (DaraPd), has recently garnered approval from the Food and Drug Administration and European Medicines Agency for this patient subset, as well as for those who have received a single line of therapy incorporating a PI and R and have become refractory to R.

The present study described an Italian cohort of RRMM patients treated with EloPd, featuring an extended follow-up period and encompassing a larger cohort size. To our knowledge, this retrospective analysis is the most comprehensive real-world assessment of EloPd to date, boasting a notably heightened enrollment count. The extended follow-up duration of our cohort of patients treated with EloPd in a real-life setting corroborates the findings of our previous analysis.[18] The median PFS of 7.5 months, ascertained in the current study, aligns consistently with our previous investigation,[18] but is inferior to that observed in the registered trial ELOQUENT-3 (10.3 months).[17] Likewise, OS remained inferior to that reported in the original trial (19.2 months versus 29.8 months),[17] slightly longer than OS emerged from our previous analysis.[18] The observed disparities in outcomes may be attributable to variations in the baseline characteristics of the patient populations between our real-world cohort and those enrolled in the ELOQUENT-3 trial (Table S5). Indeed, our cohort exhibited a greater prevalence of cases aged 75 years or older, along with a higher incidence of severe renal impairment (creatinine clearance <30 mL/min), advanced ISS stage, high-risk cytogenetics, and prior exposure to daratumumab. This latter variable, not addressed in the ELOQUENT-3 trial, which did not include patients undergoing daratumumab, unsurprisingly retained independent and significant predictive value for PFS, in addition to ISS stages II-III. Notably, the shorter follow-up failed to provide evidence to support the detrimental effect of daratumumab on PFS in our previous study.[18] Recently, it has been elucidated that relapsed MM patients treated with daratumumab, lenalidomide, and dexamethasone (Dara-Rd) exhibited pronounced depletion of CD38 + NK cells, along with persistent manifestation of T cell exhaustion, and reduced depletion of regulatory T cells.[25] Elotuzumab, which targets signaling lymphocytic activation molecule family member 7 (SLAMF7), displays its therapeutic activity against MM cells via two mechanisms: firstly, through NK cell-mediated ADCC targeting SLAMF7-expressing MM cells, and secondly through direct activation of NK cells.[5] It is conceivable that the observed adverse effect on PFS in our patient cohort previously exposed to daratumumab treatment could be attributed to the

TABLE 2 Salvage therapy regimens after EloPd.

Salvage therapy regimen	No of cases (%)
Ab drug-coniugates	53 (37.5)
Belantamab	52 (36.8)
Belantamab-Isa	1 (0.7)
Bispecific antibodies	10 (7)
Teclistamab	6 (4.2)
Talquetamab	3 (2.1)
Forintamig	1 (0.7)
Anti-CD38 containing regimens	20 (14.1)[a]
DVd	6 (4.2)
Dara	3 (2.1)
DRd	4 (2.8)
IsaKd	7 (4.9)
PI containing regimens	39 (27.6)
Kd	19 (13.4)
KRd	3 (2.1)
K-Ctx-d	3 (2.1)
K-Mezigdomide	1 (0.7)
Vd	1 (0.7)
Vd-Venetoclax	1 (0.7)
Vd-PACE	1 (0.7)
Vd-Eftozanermin	1 (0.7)
VMP	1 (0.7)
V-Ctx-d	1 (0.7)
Ixa-rd	5 (3.5)
Ixa-Ctx	2 (1.4)
Other therapies	19 (13.4)
Bendamustine	3 (2.1)
Ctx	14 (9.9)
Ctx + Caelyx + d	1 (0.7)
Melphalan	1 (0.7)

[a]Considering the patient treated with Belantamab-isatuximab: 21 (14.8%).

Abbreviations: Ctx + Caelyx + d, cyclophosphamide; caelyx, dexamethasone; Ctx, cyclophosphamide; Dara, daratumumab; DRd, daratumumab; lenalidomide, dexamethasone; DVd, daratumumab; bortezomib, dexamethasone; Isa, isatuximab; IsaKd, isatuximab; carfilzomib, dexamethasone; Ixa-Ctx, ixazomib cyclophosphamide; IxaRd, ixazomib; lenalidomide, dexamethasone; K-Ctx-d; carfilzomib cyclophosphamide, dexamethasone; Kd, carfilzomib; dexamethasone; KRd; carfilzomib, lenalidomide; dexamethasone; PIs, proteasome inhibitors; Vd, bortezomib; dexamethasone; Vd-PACE; bortezomib, dexamethasone; cisplatin, doxorubicin; cyclophosphamide, etoposide; VMP, bortezomib, melphalan, prednisone.

TABLE 3 Incidence of serious adverse events.

Grade 3/4 adverse events	EloPd ($N = 321$) No of cases (%)
Hematological toxicities	
Lymphocytopenia	50 (15.5)
Anemia	43 (13.4)
Thrombocytopenia	30 (9.3)
Neutropenia	80 (24.9)
Non-hematological toxicities	
Infections	62 (19.3)
Pneumonia	28 (8.7)
Gastrointestinal toxicity	15 (4.7)

immunological alterations induced by the anti-CD38 antibody. As a counterproof, the PFS curve observed in patients who did not receive daratumumab closely resembles that depicted in ELOQUENT-3, suggesting a significant finding with potential implications for clinical practice. Indeed, given the growing utilization of daratumumab in earlier lines of therapy, it is unusual to encounter patients in the third line who have not been exposed to the anti-CD38 monoclonal antibody in either the first or second line of treatment. Thus, patients receiving the EloPd regimen after two prior lines of therapy, which includes daratumumab, currently represent an unmet clinical need.

Once again, in the multivariable analysis ISS stages II-III showed independent prognostic value on OS, alongside the number of previous lines of therapy exceeding two. Nevertheless, it is noteworthy that the ELOQUENT-3 cohort comprised a higher rate of heavily pretreated patients compared to our retrospective cohort (median previous lines of therapy 3 versus 2). In our series age (i.e., <70 years and ≥70 years) did not appear to impact PFS and OS, indicating that the EloPd regimen maintains a favorable safety profile, even among elderly individuals who are often burdened by comorbidities and at elevated risk of developing complications.

The ORR observed in our real-world cohort was comparable with that reported in the ELOQUENT-3 trial[17] (55% versus 53%), encompassing patients who achieved high-quality responses. Additionally, the median time to best response was consistent between both studies, occurring at 2 months.

In our previous report,[18] with the limit of its retrospective nature, we documented a comparable rate of AEs between the real-world cohort and the registered study.[17] However, we registered an increased incidence of neutropenia and lymphocytopenia in the current analysis. This finding may be explained by the extended follow-up, a higher number of cases included, and the real-world setting of our research. Nevertheless, the occurrence of infections remained still comparable to that reported in the registered study.[17]

The IMWG consensus recommends employing ISS and cytogenetic abnormalities for assessing risk stratification in OS.[26]

TABLE 4 Treatment response.

Response category	EloPd (*N* = 321)
Overall response rate- no (%)	174 (55)
Best overall response- no (%)	
Stringent complete response	2 (0.6)
Complete response	9 (2.8)
Very good partial response	55 (17.1)
Combined response[a]	
Partial response	108 (33.6)
Minor response	30 (9.3)
Stable disease	89 (27.7)
Progressive disease	28 (8.7)

[a]Combined response was defined as VGPR or better.

Unfortunately, cytogenetic analysis is rarely performed in a real-world setting. In our study number of cases with FISH analysis available was 130/321 (40.5% of the entire population). Despite being aware of the relatively limited number of accessible cases, given the well-balanced clinical and biological characteristics between patients with available FISH and those without, we may assume that observed data are representative of the entire population. Despite the prognostic relevance of cytogenetic abnormalities indicated by R-ISS,[26] this biomarker did not significantly impact treatment response or survival outcomes in our cohort. Larger studies are needed to confirm these observations and understand their implications for risk stratification and treatment decisions.

In conclusion, our analysis reaffirms the safety and efficacy of EloPd as a therapeutic option for RRMM patients who have received at least two prior treatment regimens, including R and a PI, within the real-world clinical setting. However, with extended follow-up, we observed that patients previously exposed to daratumumab may not derive optimal benefit from this triplet, highlighting an unmet clinical need in this subset of patients. Consequently, new therapeutic strategies are mandatory. Promising approaches include CAR T-cell therapies,[22] such as idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), the bispecific antibody teclistamab,[23] and anti-BCMA antibody-drug conjugate belantamab mafodotin 24. Moreover, ongoing clinical trials are exploring the efficacy of combining elotuzumab with other anti-myeloma drugs such as iberdomide (CC-220),[27] isatuximab,[28] and belantamab[29] in the setting of relapsed-refractory MM patients.

AUTHOR CONTRIBUTIONS

Enrica Antonia Martino, Massimo Gentile, Francesco Di Raimondo, Antonino Neri, Fortunato Morabito, and Pellegrino Musto designed the study; Massimo Gentile and Fortunato Morabito performed statistical analysis; Salvatore Palmieri, Monica Galli, Daniele Derudas, Roberto Mina, Roberta Della Pepa, Renato Zambello, Ernesto Vigna, Antonella Bruzzese, Silvia Mangiacavalli, Elena Zamagni, Catello Califano, Maurizio Musso, Concetta Conticello, Claudio Cerchione, Giuseppe Mele, Nicola Di Renzo, Massimo Offidani, Giuseppe Tarantini, Gloria Margiotta Casaluci, Angela Rago, Roberto Ria, Giuseppina Uccello, Gregorio Barilà, Gaetano Palumbo, Loredana Pettine, Iolanda Donatella Vincelli, Marino Brunori, Fabrizio Accardi, Valeria Amico, Angela Amendola, Raffaele Fontana, Velia Bongarzoni, Bernardo Rossini, Emilia Cotzia, Alessandro Gozzetti, Rita Rizzi, Nicola Sgherza, Giovanni Reddiconto, Antonio Maroccia, Luca Franceschini, Giuseppe Bertuglia, Davide Nappi, Emiliano Barbieri, Barbara Gamberi and Maria Teresa Petrucci analyzed and interpreted data. Massimo Gentile, Ernesto Vigna, Francesco Di Raimondo, Antonino Neri, Fortunato Morabito, and Pellegrino Musto wrote the manuscript; all authors gave final approval.

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ACKNOWLEDGMENTS

The present study is supported in part by Progetto Ricerca Finalizzata PNRR-MAD-2022-12375673 (Next Generation EU, M6/C2_CALL 2022), Italian Ministry of Health, Rome, Italy.

CONFLICT OF INTEREST STATEMENT

EZ has received honoraria and has served as advisory board member for Janssen, Bristol Myers Squibb, Sanofi, Amgen, GlaxoSmithKline, Pfizer, Oncopeptides, and Menarini-Stemline; RZ has served on the advisory for Bristol, Janssen, Sanofi, Takeda, Amgen, and GSK; SM has received honoraria from Bristol-Myers Squibb, Sanofi, AMGEN, GSK Takeda, and Janssen; has served on the advisory boards for Sanofi, Takeda, Bristol-Myers Squibb and Janssen; AG has received honoraria from Janssen, Amgen, Pfizer, and Takeda; MTP has received honoraria from Bristol-Myers Squibb, Sanofi, AMGEN, GSK, Takeda and Janssen; has served on the advisory boards for Celgene-Bristol-Myers Squibb, Sanofi, AMGEN, Sanofi, GSK, Takeda, Roche, Karyopharm and Janssen; received support for attending meetings and/or travel from Janssen, Celgene-Bristol-Myers Squibb, AMGEN, Sanofi and Takeda.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee at all participating hospitals. It adhered to the Declaration of Helsinki and the Good Clinical Practice guidelines.

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PEER REVIEW

The peer review history for this article is available at. https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/hon.3290.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Martino EA, Palmieri S, Galli M, et al. Elotuzumab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of a multicenter, retrospective real-world experience with 321 cases outside of controlled clinical trials. *Hematol Oncol*. 2024;e3290. https://doi.org/10.1002/hon.3290