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Elotuzumab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma: a multicenter, retrospective real-world experience with 200 cases outside of controlled clinical trials

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M.G., E.V., F.D.R., A.N., F.M., and P.M. designed the study; M.G. and F.M. performed statistical analysis; S.P., M.Ga., D.D., R.M., R.D.P., R.Z., E.A.M., A.B., S.M., E.Z., C.C., M.M., C.C., C.Ce., G.M., N.D.R., M.O., G.T., G.M.C., A.R., R.R., G.U., G.B., G.P., A.P., D.V., M.B., F.A., V.A., A.A., R.F., V.B., B.R., E.C., A.G., R.Ri, N.S., E.F., G.B., D.N., and M.T.P. analyzed and interpreted data. M.G., E.V., F.D.R., A.N., F.M., and P.M. wrote the manuscript; all authors gave final approval.

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

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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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ABSTRACT

In the ELOQUENT-3 trial, the combination of elotuzumab, pomalidomide and dexamethasone (EloPd) proved a superior clinical benefit over Pd with a manageable toxicity profile, leading to its approval in relapsed/refractory multiple myeloma (RRMM), who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI).

We report here a real-world experience of 200 RRMMs treated with EloPd in 35 Italian centers outside of clinical trials. In our dataset, the median number of prior lines of therapy was 2, with 51% of cases undergoing autologous stem cell transplant (ASCT) and 73% exposed to daratumumab.

After a median follow-up of 9 months, 126 patients stopped EloPd, most of them (88.9%) because of disease progression. The overall response rate (ORR) was 55.4%, in line with the pivotal trial results. Regarding adverse events, our cohort experienced a toxicity profile similar to the ELOQUENT-3 trial, with no significant differences between younger (<70 years) and older patients. The median progression-free survival (PFS) was 7 months, shorter than that observed in the ELOQUENT-3, probably due to the different clinical characteristics of the two cohorts. Interestingly, the ISS stage III (HR:2.55) was associated with worse PFS. Finally, our series's median overall survival (OS) was shorter than that observed in the ELOQUENT-3 trial (17.5 *versus* 29.8 months). In conclusion, our real-world study confirms EloPd as a safe and possible therapeutic choice for RRMM who received at least two prior therapies, including lenalidomide and a PI.

ARTICLE SUMMARY

Here, we present the outcome of 200 MM patients heavily pre-treated who received EloPd outside of clinical trials to evaluate the safety and efficacy of this combination in a real-world setting.

Our real-world data fairly confirmed that EloPd is a safe and possible therapeutic choice for RRMM patients and the previous daratumumab exposure did not negatively impact the efficacy of the EloPd triplet regimen.

INTRODUCTION

The treatment landscape of multiple myeloma (MM) has dramatically changed over the years due to the introduction of several new drugs which improved MM patients' survival (1, 2). Nowadays, proteasome inhibitors (PI) and immunomodulatory drugs (IMIDS) still represent the fundamental backbones of MM therapy. However, given the encouraging results from clinical trials, especially among double-refractory MM patients, a new class of drugs, the monoclonal antibodies (mAbs), are now used with PI and IMIDs and are incorporated in the earlier lines of therapies (3). The use of triplets in clinical practice allows for deeper and more sustained responses with an acceptable safety profile (3). Elotuzumab (Elo) is a humanized immunoglobulin G1 immunostimulatory monoclonal antibody which is directed against signaling lymphocytic activation molecule F7 (SLAMF7) (4). SLAMF7 is a glycoprotein expressed on myeloma cells and natural killer (NK) cells, which promotes MM cell proliferation and survival (5). The mechanisms of action prevent the interactions that allow the growth and sustenance of neoplastic cells. Moreover, Elo stimulates NK cells by strengthening their antibody-dependent cellular cytotoxicity (ADCC) activity (6, 7). This phenomenon is amplified when Elo is combined with lenalidomide (R) as found in vitro models (8). It was hypothesized that a similar effect would be observed in patients with RRMM. Indeed, based on the results from the phase III trial (ELOQUENT-2), Elo was first approved by the FDA in November 2015 and by the EMA in January 2016 in combination with R and dexamethasone (d) for the treatment of MM patients who received at least one prior line of therapy (9). Our group confirmed the safety and efficacy of this combination in a cohort of RRMM treated outside clinical trials (10-13).

Like R, Pomalidomide (P) is an IMID determining direct MM cell death and immune-enhancing effects via binding to cereblon (14). However, compared to R, P demonstrated a more potent anti-neoplastic activity towards R-resistant MM cell lines *in vitro* and preclinical *in vivo* studies. Moreover, it was shown that combining Elo with pomalidomide exerts synergistic antimyeloma effects (15). These results lay the groundwork for an *in vivo* combination. ELOQUENT-3, a multicenter, randomized, controlled, open-label, phase II trial, investigated the efficacy and safety

of Elo in combination with P and d (EloPd) compared to Pd alone in the setting of RRMM previously treated with lenalidomide and a PI (16). After a follow-up of 45 months, the study still demonstrates that the triplet improved progression-free survival (PFS) and overall survival (OS) with a lower rate of adverse events (AEs) compared to the control arm (17).

Here, we present the outcome of 200 heavily pre-treated MM patients who received EloPd outside of clinical trials to evaluate the safety and efficacy [response evaluation, PFS, OS, the time to the next therapy (TTNT)] of this combination in a real-world setting.

METHODS

Patients

Data from a retrospective cohort of RRMM patients treated with EloPd in 35 Italian centers were collected for the purpose of this retrospective analysis. The databases contained clinical information such as age, gender, 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 35 databases included 200 consecutive patients with RRMM who received at least one cycle of EloPd as salvage treatment between October 2020 and December 2022. All patients were treated with EloPd according to marketing approval as previously described (16,17). Specifically, Elo 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, P 4 mg orally once daily on days 1 to 21 of each cycle, and d at the dose of 40 mg (or 20 mg in patients age older than 75 years) once weekly, except on days of Elo administration, when patients received both oral (28 mg [or 8 mg in patients age older than 75 years]) and intravenous (8 mg) d.

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 Elo infusion.

All patients received antibacterial, antiviral, and antithrombotic prophylaxis during treatment. EloPd was administered in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent.

The time-to-event endpoints were PFS, OS, and time to next treatment (TTNT). Safety profile and response evaluation were provided for the purposes of the study.

Response to treatment and disease progression were evaluated according to the International Myeloma Working Group (IMWG) criteria (18, 19). Responsive patients had to reach at least 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 Fis'er'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, measured from the initiation of RRMM EloPd treatment until death from any cause or progression or last follow-up, of TTNT, measured from the initiation of RRMM EloPd treatment to the earliest start date of subsequent therapy or last follow-up, and of OS, measured from the initiation of RRMM EloPd treatment until death from any cause or last follow-up, were performed using the Kaplan-Meier method. 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 $P<0.05$ was considered significant. Data analysis was performed by STATA for Windows v.9 and SPSS Statistics v.21.

RESULTS

Patients

Overall, 200 RRMM patients treated with EloPd between October 2020 and December 2022 in 35 Italian centers entered this study. Baseline characteristics are shown in Table 1. At the EloPd start, 26.5% of patients were in stage III according to the International Staging System (ISS), 30.5% were in ISS stage I, and 43% were in ISS stage II. Seventy-six cases (38%) had refractory disease to the previous line of therapy, a symptomatic relapse was observed in 94 patients (47%) and a biochemical relapse in 30 (15%); almost all cases (97.5%) were lenalidomide-refractory. Fifty-one (25.5%) patients showed mild renal impairment, while in 17 (8.5%) patients kidney function was severely compromised. Before EloPd, 101 patients (50.5%) had received 2 lines of therapy, approximately half of the patients (51%) underwent autologous stem cell transplant (ASCT), while roughly three-quarters (73%) of patients were exposed to daratumumab. All 146 daratumumab-exposed patients were refractory to daratumumab. One hundred and eleven patients received EloPd immediately after a daratumumab-containing regimen, while 35 patients between a daratumumab-containing regimen and EloPd received other schedules of therapy. FISH analysis data were available in 80 patients. Forty-three (53.8%) patients presented favorable cytogenetic abnormalities, while 37 patients (46.2%) were categorized as high risk, harboring one of the following aberrations: t(4;14), t(14;16) and del(17p).

Response Evaluation

At the last follow-up, 193/200 patients were evaluable for response (7 cases have not yet completed the first cycle of therapy). Out of 193 patients, 107 (55.4%) reached at least partial remission (≥PR). More in detail, 6 (3.1%) achieved a complete remission (CR), 39 (20.2%) a very good partial response (VGPR), and 62 (32.1%) a PR. The median time to response was 1.8 months.

A statistically higher ORR was accounted for patients who did not undergo ASCT (63.3% *versus* 47.8%, P=0.032) (Table 2), while a trend towards statistical significance was observed in cases with

ISS stage I (stage I=66.1%, stage II=54.9%, and stage III=44.2%; P=0.068), in those treated at biochemical relapse (biochemical relapse=75.9%, symptomatic relapse=52.8%, refractory disease=50.7; P=0.054) and in those older (>70 years=48.8% and ≤70 years =36.4%; P=0.08) (Table 2). Gender, creatinine clearance, lactate dehydrogenase (LDH) value, number of prior lines of therapy, and previous daratumumab exposure did not impact the probability of achieving a response to EloPd (Table 2). No differences in terms of ORR were observed between cases receiving EloPd immediately after a daratumumab-containing regimen and who received other schedules of therapy between a daratumumab-containing regimen and EloPd (ORR: 55% vs 43%; P=0.42).

Progression-free survival

After a median follow-up of 9 months (range 1-26), 121 patients (60.5%) out of 200 experienced disease progression or died. The total number of deaths was 79 (39.5%). Median PFS was 7 months (95% CI, 5.8–8.2 months), and the 1-year probability of PFS was 33.6% (Figure 1A). Univariable analyses showed that ISS stage II (HR=1.61, 95% CI 1.03-2.54; P=0.039), ISS stage III (HR=2.9, 95% CI 1.77-4.75; P<0.0001), previous ASCT (HR=1.43, 95% CI 1.05-2.05; P=0.05), previous daratumumab exposure (HR=1.72, 95% CI 1.14-2.59; P=0.01) (Supplementary Figure 1A), symptomatic relapse (HR=2.02, 95% CI 1.13-3.63; P=0.018) and refractory disease at EloPd start (HR=1.86, 95% CI 1.02-3.37; P=0.041) were associated with a significantly lower PFS (Table 3).

No differences in terms of PFS were observed between cases receiving EloPd immediately after a daratumumab-containing regimen and those who received other schedules of therapy between a daratumumab-containing regimen and EloPd (HR= 1.34, 95% CI 0.83-2.16; P=0.23).

Notably, in the Cox multivariable analysis, only advanced ISS stage (III) maintained an independent prognostic impact on PFS (HR=2.55, 95% CI 1.54-4.24; P<0.0001) (Table 3). Conversely, ISS stage II (HR=1.53, 95% CI 0.97-2.44; P=0.69), previous ASCT (HR=1.35, 95% CI 0.93-1.96; P=0.31), previous daratumumab exposure (HR=1.35, 95% CI 0.9-2.08; P=0.17),

symptomatic relapse (HR=1.69, 95% CI 0.94-3.05; P=0.008) and refractory disease at EloPd start (HR=1.49, 95% CI 0.81-2.73; P=0.2) lost their independent predictive value on PFS.

Overall survival

Median OS was 17.5 months (95% CI 28-40.2), and the 1-year probability of OS was 57.9% (95% CI, 12–23.2 months) (Figure 1B). Univariable analyses showed that ISS III (HR=2.46, 95% CI 1.35-4.48; P=0.003), previous daratumumab exposure (HR=1.87, 95% CI 1.1-3.19; P=0.02) (Supplementary Figure 1B), symptomatic relapse (HR=2.83, 95% CI 1.19-6.7; P=0.018) and refractory disease at EloPd beginning (HR=2.56, 95% CI 1.07-6.12; P=0.034) were associated with a significantly shorter OS (Table 3). No differences in terms of OS were observed between cases receiving EloPd immediately after a daratumumab-containing regimen and those who received other schedules of therapy between a daratumumab-containing regimen and EloPd (HR= 1.19; 0.7-2.01; P=0.53).

Notably, in the Cox multivariable analysis, advanced ISS stage (III) (HR=1.87, 95% CI 1.16-3.02; P=0.01), symptomatic relapse (HR=2.5, 95% CI 1.06-6.0; P=0.04) and refractory disease at EloPd beginning (HR=2.4, 95% CI 1.04-5.5; P=0.05) maintained an independent prognostic impact on the survival outcome (Table 4). In contrast, previous daratumumab exposure lost its independent prognostic significance on OS (HR=1.68, 95% CI 0.98-2.88; P=0.06).

Time to next treatment and subsequent therapy

After discontinuation of EloPd therapy, 71 patients (35.5%) received subsequent treatment. Median TTNT was 8.1 months (95% CI 6.7-9.4), with a 1-year re-treating probability of 37.5% (Figure 1C). The type of subsequent treatment is shown in Table 5. Overall, 20 different salvage therapy regimens were used after EloPd discontinuation or failure. Roughly one-third of patients (24 cases) received Belantamab alone (23 cases) or in combination with Isatuximab (1), 24 patients (33.8%) a PI-containing regimen (14 patients Carfilzomib-based, 6 Bortezomib-based and 4 Ixazomib-based

regimens), while 13 patients (18.3%) received an anti-CD38 containing regimen (10 cases Daratumumab-based and 3 Isatuximab-based regimens). Finally, 10 patients (14.1%) received a subsequent chemotherapeutic regimen (6 cases were treated with a cyclophosphamide-based regimen, 3 with bendamustine, and 1 with melphalan).

Safety

At the last database update, the median number of EloPd courses administered was 5 (range 1–20). A total of 126 (62.5%) patients withdrew EloPd treatment at the cut-off date, mainly due to disease progression (112 cases). Of the remaining cases, 9 patients discontinued therapy for toxicity (6 infections and 3 pomalidomide-related severe skin rash) and 5 for therapy-unrelated deaths. Infusion reactions occurred at first administration of Elo in 11 patients (5.5%, all grades 1-2) and were promptly resolved in all patients (no discontinuation reported). Major adverse events (AEs) are depicted in Table 6 and include grade 3/4 neutropenia (21.5%), anemia (11%), lymphocytopenia (9.5%), and thrombocytopenia (9.5%), while infection rates and pneumonia were roughly 14% and 6.5%, respectively. Furthermore, the rate of AEs was not significantly different between patients aged less or more than 70 years (data not shown).

Outcome analysis by cytogenetic risk

Data on cytogenetic abnormalities were available in only 40% of cases (80/200). However, the analytical weight for the prognosis of this biomarker, also emphasized by the revised ISS (R-ISS) (20), prompted us to carry out an ancillary analysis, conscious that the relatively low incidence of accessible cases could bias the statistical accuracy. When comparing each other, the main characteristics of the group with cytogenetic information differed from the remaining cases only for a lower rate of patients with creatinine clearance <60 mL/min (Supplementary Table 1).

No difference in ORR was observed between the high-risk and the standard-risk group (54.1 versus 53.7%; P=0.97). The two subgroups showed a non-statistically different PFS (1-year PFS; high-risk

group *versus* standard-risk: 28.4% *versus* 44.7%; HR 1.34, 95% CI 0.77-2.34; P=0.29) (Supplementary Figure 2A), while a trend towards statistical significance in terms of OS was observed in standard-risk patients (1-year OS; high-risk group versus standard-risk: 50.1 versus 75.1%; HR 2, 95% CI 0.94-4.29; P=0.07) (Supplementary Figure 2B).

DISCUSSION

Elo, as monotherapy, was first evaluated in a phase 1, dose-finding study, which demonstrated the safety and tolerability of the drug at either 10 mg/kg or 20 mg/kg, but, at the same time, the absence of response, especially in the setting of heavily pre-treated patients (21). Given the enhanced antimyeloma activity in combination with other drugs within preclinical studies, Elo was tested in association with Rd (EloRd) in a phase 2 study showing better efficacy of the triplet in the setting of relapsed-refractory patients (22). Those results were subsequently confirmed by phase 3 ELOQUENT-2 (23) and remain robust at a follow-up of 70 months (24).

Recently, data from the ELOQUENT-3 trial showed as the addition of Elo to Pd allowed to achieve a significant clinical improvement, in terms of PFS and OS, over Pd with a manageable toxicity profile in the treatment of RRMM patients who received at least two prior therapies, including R and PI (16,17). Furthermore, the addition of Elo to Pd did not negatively impact on health-related quality of life of MM patients (25). Based on these results FDA approved EloPd for this setting of MM patients.

We, herein, described an Italian real-world experience on EloPd. To the best of our knowledge, our survey is the first real-world EloPd series.

Real-world profiles are rarely fully represented in randomized clinical trials, and this caveat further complicates treatment decision-making. In this regard, aging is a critical factor in MM patients' treatment management because of its association with frailty, increased comorbidities, poor tolerability, and a higher risk of complications (26). In our series, approximately one-third of patients were aged ≥75 years and 8.5% showed severe renal impairment (creatinine clearance <30

mL/min). In comparison, in the registration trial, elderly patients were 21.7%, while a creatinine clearance <45 mL/min was an exclusion criterion.

The ELOQUENT-3 trial (16), and its update (17), showed the safety of this triplet drug regimen. Although some caution should be considered for the retrospective nature of the present study, our real-world cohort documented similar AEs profiles, except for a slightly higher incidence of neutropenia, possibly due to the differences mentioned above in terms of age and cases with severe renal impairment. Nevertheless, the incidence of infections was comparable (16). Of note, no significant differences in terms of AEs incidence were documented between younger (<70 years) and elderly patients.

The ORR of our real-world cohort was comparable with that of the ELOQUENT-3 trial (55.4% *versus* 53%), with a similar number of patients reaching good quality responses (16), although it must be taken into consideration the different clinical features of patients included in the two series (i.e., the median number of previous lines of therapies, 3 in the ELOQUENT-3 trial and 2 in our retrospective series, see Table 7). Interestingly, the only cases that showed a significantly lower response rate were those who had undergone previous ASCT. Conversely, a trend towards the statistical significance of a higher response rate was observed in cases with low ISS stage and those treated in biochemical relapse. These findings should also be considered an additional concern when choosing EloPd treatment.

Moreover, the median time to achieve the best response was similar to that of the ELOQUENT-3 trial (16), precisely 1.8 months *versus* 2 months.

PFS predictors should also be considered to reduce the chance to progress. In our series, the estimated median PFS was 7 months, shorter than the 10.3 months observed in the ELOQUENT-3 trial (16). This relatively poorer clinical outcome is possibly due to the difference in baseline characteristics of patients between real-world data and clinical trials (Table 7). Specifically, our cohort accounted for a higher rate of advanced stage ISS (III) (26.5% *versus* 11.7%) and a not

negligible rate of patients with high-risk cytogenetics (46.2% *versus* 10%) (Table 7), having both categories a poor prognosis.

A multivariable model revealed only the stage III ISS as an independent indicator predictive of shorter PFS.

In our series, the median OS was shorter than that observed in the ELOQUENT-3 trial (17.5 *versus* 29.8 months) (17). Nevertheless, OS results should be considered somewhat immature due to the relatively short follow-up. Anyway, the difference in baseline patient characteristics between real-world data and the clinical trial could also have negatively impacted survival (Table 7).

Again, at multivariable analysis, advanced ISS stage (III) showed an independent prognostic impact on the OS together with disease status at EloPd beginning.

In our cohort, PFS and OS were similar in both age groups (i.e., < and >70 years), showing a good safety profile of EloPd even when used in an elderly cohort (57% of our EloPd cohort), whose treatment is challenging since generally associated with frailty, increased comorbidities, poor tolerability, and higher risk of complications (26).

There are two key reasons why the information on patients exposed to daratumumab is not trivial. First of all, the data are lacking in the ELOQUENT-3 trial. Secondly, daratumumab-based therapy is currently the standard of care for most MM patients, both in the first- and in the second-line, allowing the evaluation of the impact of previous daratumumab exposure on the EloPd efficacy in the real-world setting. Nevertheless, in our experience, daratumumab exposure neither impacted the probability of achieving a response nor the outcome indicators in RRMM patients treated with EloPd.

The IMWG consensus recommends using ISS and cytogenetic abnormalities to analyse OS risk stratification (27). Unfortunately, cytogenetic analysis is rarely performed in a real-world setting. Although we were conscious that the relatively low number of accessible cases (approximately 40%) might lead to incorrect statistical interpretation, the FISH prognostic importance, highlighted by the R-ISS (20), motivated us to conduct an additional investigation. In this respect, high-risk

patients, defined as poor cytogenetics (t[4;14], t[14;16], or del[17p]), did not show a significantly shorter PFS and OS, although the low number of cases did not allow of analyzing the independent prognostic value of this parameter in a multivariable analysis.

Among the study's strengths, we highlight that the number of patients enrolled in our real-world study is more than three times the cohort of patients enrolled in the EloPd arm (n=60). In addition, taking into account the growing rate of patients receiving anti-CD38 MoAb in the early phase of treatment, data on the efficacy of EloPd in patients previously exposed to daratumumab represent an additional value coming from our retrospective observation, since it is currently missing in the randomized clinical trial. Conversely, among the weaknesses, the relatively short follow-up time to draw definitive conclusions about OS and the well-known biases associated with the study's retrospective nature must be mentioned.

In conclusion, our real-world data fairly confirmed the results obtained in the ELOQUENT-3 controlled clinical trial (16,17). EloPd is a safe and possible therapeutic choice for RRMM patients who received at least two prior therapies, including R and PI. Notably, the previous daratumumab exposure did not negatively impact the efficacy of the EloPd triplet regimen.

Nowadays, several clinical trials are exploring the efficacy of elotuzumab in association with other anti-myeloma drugs such as Iberdomide (CC-220) (28), Isatuximab (29) and Belantamab (30) in the setting of relapsed-refractory MM patients.

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Table 1. Main characteristics of patients at baseline.

	No. of patients (%)
Age, (years)	
<70	86 (43)
≥70	114 (57)
Sex	
Male	108 (54)
Female	92 (46)
Paraproteins (isotype)	
Immunoglobulin G	121 (60.5)
Immunoglobulin A	44 (22)
Immunoglobulin D	3 (1.5)
Immunoglobulin M	2 (1)
Light chain only	30 (15)
Creatinine clearance (mL/min)	
≥60	132 (66)
<60	68 (34)
International staging system	
I	61 (30.5)
II	86 (43)
III	53 (26.5)
LDH	
Normal	142 (71)
Elevated	58 (29)
Previous lines of therapy	
2	101 (50.5)
3	57 (28.5)
≥4	42 (21)
Previous autologous stem cell transplantation	
No	99 (49.5)
Yes	101 (50.5)
Previous daratumumab	
No	54 (27)
Yes	146 (73)
Lenalidomide refractory	
No	5 (2.5)
Yes	195 (97.5)
Disease status	
Biochemical relapse	30 (15)
Symptomatic relapse	94 (47)
Refractory to last treatment	76 (38)
FISH analysis available (n= 80)	
Standard Risk	43 (53.8)
High Risk	37 (46.2)

Table 2. Association between overall response rate and main clinical-hematological characteristics of multiple myeloma patients treated with EloPd (N=193)

Variable	≥PR N (%)	<PR N (%)	P-value
Age			
≤70	39 (36.4)	68 (63.6)	
>70	42 (48.8)	44 (51.2)	0.08
Sex			
Female	50 (56.8)	38 (43.2)	
Male	57 (54.3)	48 (45.7)	0.72
Creatinine clearance (mL/min)			
≥60	67 (62.6)	59 (68.6)	
<60	40 (37.4)	27 (31.4)	0.38
International staging system			
I	39 (66.1)	20 (33.9)	
II	45 (54.9)	37 (45.1)	0.068
III	23 (44.2)	29 (55.8)	
LDH			
Normal	72 (52.6)	65 (47.4)	
Elevated	35 (62.5)	21 (37.5)	0.2
Previous lines of therapy			
2	59 (60.2)	39 (39,8)	
>2	48 (50.5)	47 (49.5)	0.17
Previous autologous stem cell transplantation			
No	62 (63.3)	36 (36.7)	
Yes	44 (47.8)	48 (52.2)	**0.032**
Previous daratumumab			
No	31 (60.8)	20 (39.2)	
Yes	76 (53.5)	66 (46.5)	0.37
Disease status			
Biochemical relapse	22 (75.9)	7 (24.1)	
Symptomatic relapse	47 (52.8)	42 (47.2)	0.054
Refractory to last treatment	38 (50.7)	37 (49.3)	

Table 3. Univariable and multivariable analyses of PFS.

		Univariable analysis			Multivariable analysis	
	N	PFS @12 months	HR (%95 CI)	P-value	HR (%95 CI)	P-value
Age, (years)						
≤70	86	27.9				
>70	114	39.2	0.72 (0.5-1.03)	0.75		
Gender						
Male	108	34.7				
Female	92	34.2	1.05 (0.74-1.49)	0.79		
Creatinine clearance (mL/min)						
≥60	132	31.2				
<60	68	41.3	0.9 (0.62-1.32)	0.6		
International staging system						
I	61	50.4				
II	86	30.2	1.61 (1.03-2.54)	**0.039**	1.53 (0.97-2.44)	0.69
III	53	24.2	2.9 (1.77-4.75)	**<0.0001**	2.55 (1.54-4.24)	**<0.0001**
LDH						
Normal	142	33.7				
Elevated	58	33.1	0.99 (0.67-1.45)	0.95		
Previous lines of therapy						
2	101	39.6				
>2	99	28.6	1.33 (0.93-1.9)	0.11		
Previous autologous stem cell transplantation						
No	99	41.1				
Yes	101	25.4	1.43 (1.05-2.05)	**0.05**	1.35 (0.93-1.96)	0.31
Previous daratumumab						
No	54	46.9				
Yes	146	29.2	1.72 (1.14-2.59)	**0.01**	1.35 (0.9-2.08)	0.17
Disease status						
Biochemical relapse	30	57.3				
Symptomatic relapse	94	29.1	2.02 (1.13-3.63)	**0.018**	1.69 (0.94-3.05)	0.08
Refractory to last treatment	76	31.2	1.86 (1.02-3.37)	**0.041**	1.49 (0.81-2.73)	0.2

Table 4. Univariable and multivariable analyses of OS.

		Univariable analysis			Multivariable analysis	
	N	OS @ 12 months	HR (%95 CI)	P-value	HR (%95 CI)	P-value
Age, (years)						
≤70	86	51.8				
>70	114	62.4	0.77 (0.49-1.21)	0.26		
Gender						
Male	108	61.1				
Female	92	54.4	1.17 (0.75-1.83)	0.48		
Creatinine clearance (mL/min)						
≥60	132	59.1				
<60	68	55.1	1.02 (0.64-1.64)	0.91		
International staging system						
I	61	72.9				
II	86	56.9	1.24 (0.7-2.22)	0.46		
III	53	42.9	2.46 (1.35-4.48)	**0.003**	1.87 (1.16-3.02)	**0.01**
LDH						
Normal	142	59.7				
Elevated	58	53.4	1.31 (0.82-2.1)	0.26		
Previous lines of therapy						
2	101	64.5				
>2	99	50.8	1.43 (0.91-2.22)	0.12		
Previous autologous stem cell transplantation						
No	99	59.3				
Yes	101	56.1	1.25 (0.8-1.96)	0.33		
Previous daratumumab						
No	54	69.7				
Yes	146	50.6	1.87 (1.1-3.19)	**0.02**	1.68 (0.98-2.88)	0.06
Disease status						
Biochemical relapse	30	81				
Symptomatic relapse	94	55.1	2.83 (1.19-6.7)	**0.018**	2.5 (1.06-6.0)	**0.04**
Refractory to last treatment	76	51.8	2.56 (1.07-6.12)	**0.034**	2.4 (1.04-5.5)	**0.05**

Table 5. Salvage therapy regimens after EloPd.

Salvage therapy regimen	No of cases (%)
Ab drug-coniugates	**24 (33.8)**
Belantamab	23 (32.4)
Belantamab-Isa	1 (1.4)
Anti-CD38 containing regimens	**13 (18.3)***
DVd	5 (7)
Dara	3 (4.2)
DRd	2 (2.8)
IsaKd	3 (4.2)
PI containing regimens	**24 (33.8)**
Kd	12 (16.9)
KRd	2 (2.8)
K-Ctx-d	1 (1.4)
Vd	1 (1.4)
Vd-Venetoclax	1 (1.4)
Vd-PACE	1 (1.4)
Vd-Eftozanermin	1 (1.4)
VMP	1 (1.4)
Ixa-Rd	2 (2.8)
Ixa-Ctx	2 (2.8)
Other therapies	**10 (14.1)**
Bendamustine	3 (4.2)
Ctx	5 (7)
Ctx+Caelyx+d	1 (1.4)
Melphalan	1 (1.4)

***Considering the patient treated with Belantamab-isatuximab: 14 (19.7%).**

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

Table 6. Incidence of serious adverse events

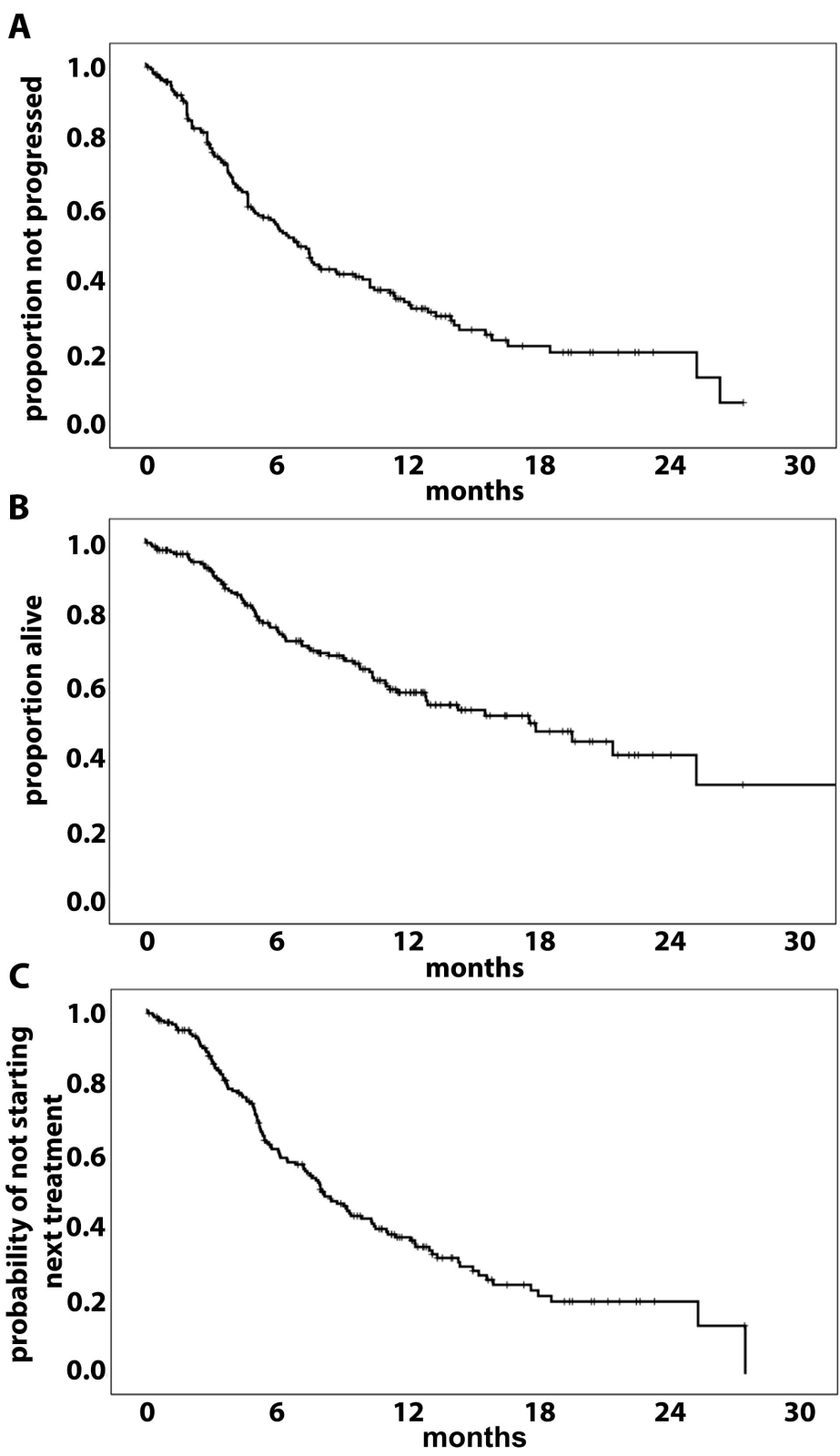
	EloRd (N=200)
Grade 3/4 adverse events	**No of cases (%)**
Hematological toxicities	
Lymphocytopenia	19 (9.5)
Anemia	22 (11)
Thrombocytopenia	19 (9.5)
Neutropenia	43 (21.5)
Non-hematological toxicities	
Infections	28 (14)
Pneumonia	13 (6.5)
Gastrointestinal toxicity	8 (4)

Table 7. Comparison of characteristics at baseline between the cohort of patients treated with EloPd in real-world and those enrolled in the Eloquent-3 clinical trial.

	Real-world study % of patients	**Eloquent-3 trial % of patients**
Age, (years)		
≥75	33.5	21.7
Creatinine clearance (mL/min)		
<45	20	0
<30	8.5	0
International staging system		
III	26.5	11.7
LDH		
Elevated	29	23.3
Median previous lines of therapy (range)	2 (2-9)	3 (2-8)
Previous autologous stem cell transplantation	50	51.7
Prior daratumumab exposure	73	0
Lenalidomide refractory	97.5	90
FISH analysis		
High Risk	46.2	10

Figures legend

Figure 1. Kaplan Meier curves for all 200 RRMM patients treated with EloPd. **Panel A**. Kaplan Meier curve of PFS; **Panel B**. Kaplan Meier curve of OS; **Panel C.** Kaplan Meier curve of TTNT.


A
proportion not progressed
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
months
B
proportion alive
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
months
C
probability of not starting next treatment
1.0
0.8
0.6
0.4
0.2
0.0
0
6
12
18
24
30
months

SUPPLEMENTARY APPENDIX CONTENTS

Elotuzumab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma: a multicenter, retrospective real-world experience with 200 cases outside of controlled clinical trials

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Supplementary Table

Supplementary Figure Legends

Supplementary Figures

Supplementary Table 1. Main characteristics of patients at EloPd initiation according to FISH analysis availability.

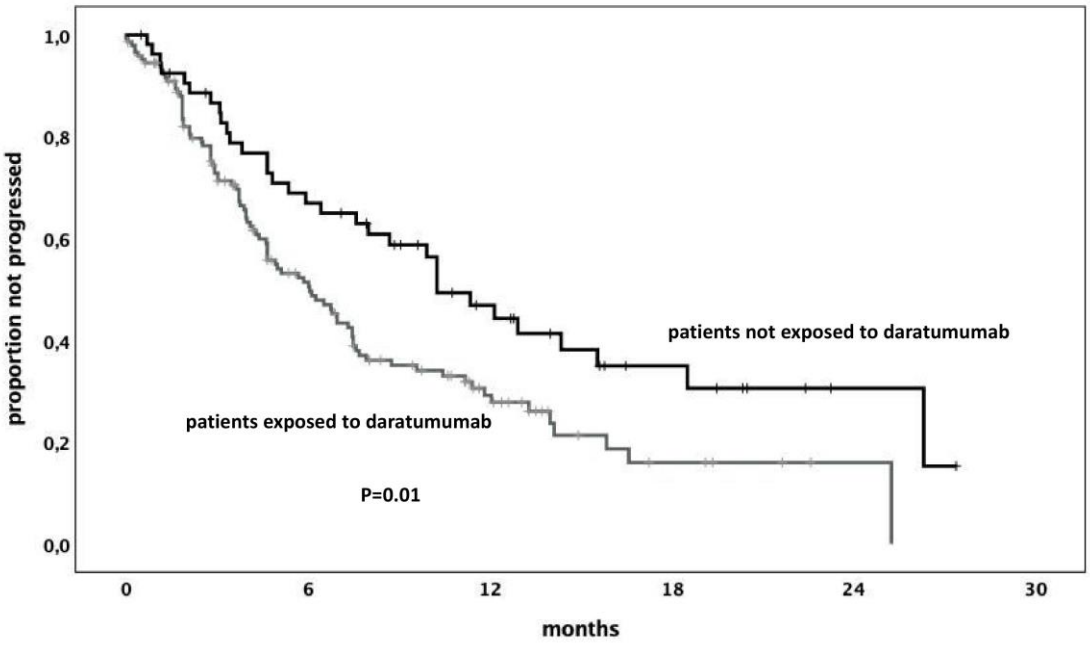
	No. of cases without FISH analysis available (%)	No. of cases with FISH analysis available (%)	P value
Age, (years)			
<70	54 (40)	32 (45)	0.48
≥70	66 (60)	48 (55)	
Sex			
Male	62 (51.7)	46 (57.5)	0.59
Female	58 (48.3)	34 (42.5)	
Paraproteins (isotype)			
Immunoglobulin G	71 (59.2)	50 (62.5)	
Immunoglobulin A	28 (23.3)	16 (20)	
Immunoglobulin D	1 (0.8)	2 (2.5)	0.63
Immunoglobulin M	2 (1.7)	0	
Light chain only	18 (15)	12 (15)	
Creatinine clearance (mL/min)			
≥60	72 (60)	60 (75)	**0.03**
<60	48 (40)	20 (25)	
Stage ISS, (%) (n=255)			
I	35 (39.2)	26 (32.5)	
II	52 (43.3)	34 (42.5)	0.86
III	33 (27.5)	20 (25)	
LDH			
Normal	85 (70.8)	57 (71.3)	0.95
Elevated	35 (29.2)	23 (28.7)	
Previous lines of therapy			
2	46 (57.5)	55 (45.8)	0.11
>2	34 (42.5)	65 (54.2)	
Previous ASCT			
No	60 (50)	41 (51.2)	0.86
Yes	60 (50)	39 (48.8)	
Previous daratumumab			
No	30 (25)	24 (30)	0.43
Yes	90 (75)	56 (70)	
Disease status			
Biochemical relapse	14 (11.7)	16 (20)	
Symptomatic relapse	63 (52.5)	31 (38.8)	0.1
Refractory to last treatment	43 (35.8)	33 (41.2)	

Supplementary Figures legend

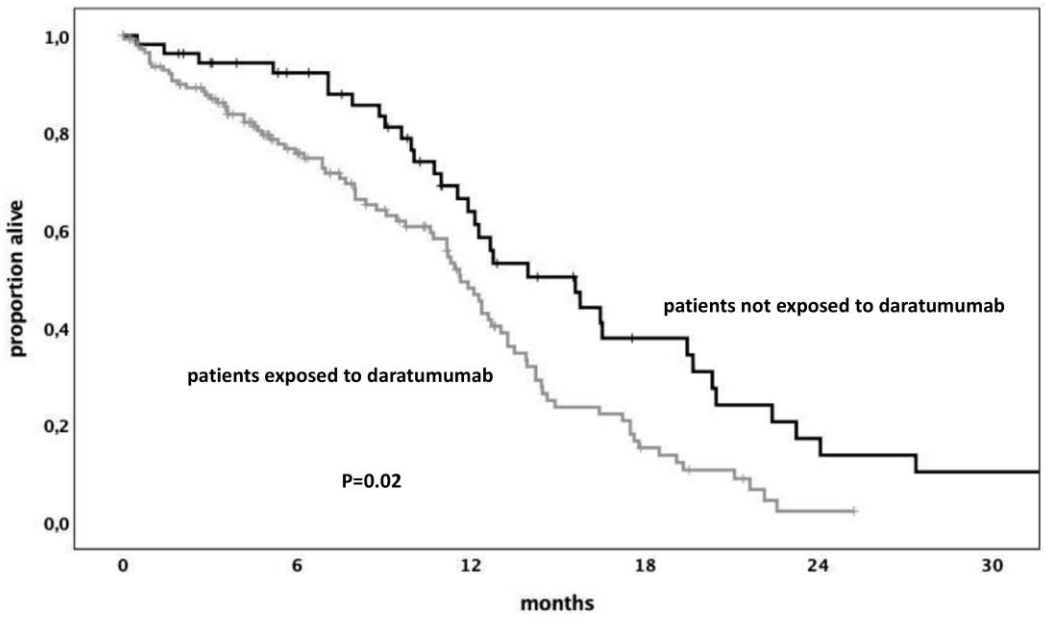
Supplementary Figure 1. Kaplan Meier curves for RRMM patients treated with EloPd according to daratumumab exposure. **Panel A**. Kaplan Meier curve of PFS**. Panel B.** Kaplan Meier curve of OS.

Supplementary Figure 2. Kaplan Meier curves for RRMM patients treated with EloPd according to FISH risk. **Panel A**. Kaplan Meier curve of PFS**. Panel B.** Kaplan Meier curve of OS.

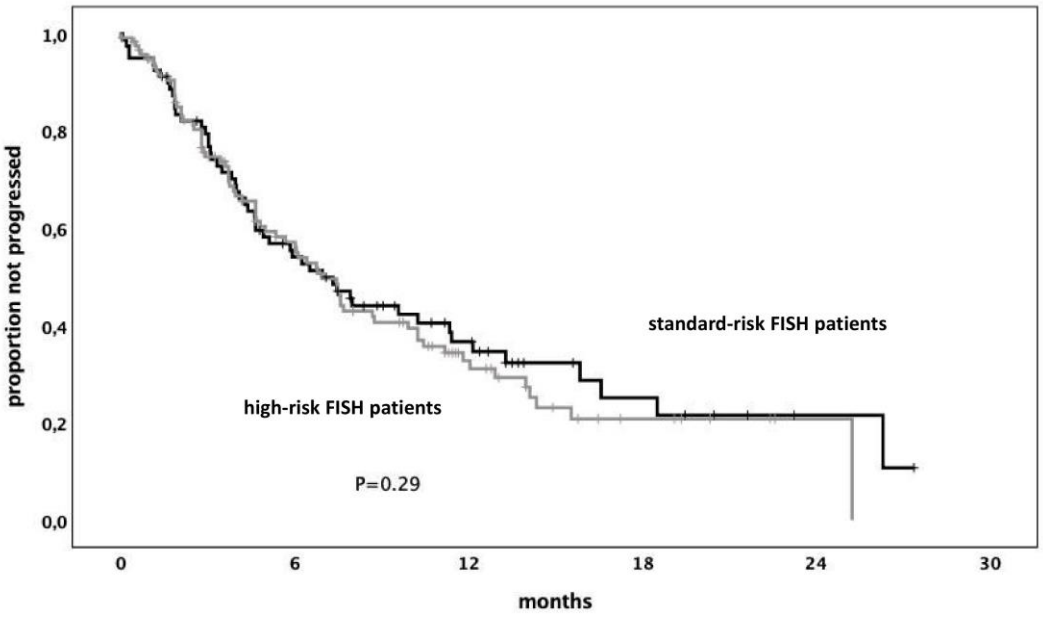
Supplementary Figure 1A



Supplementary Figure 1B



Supplementary Figure 2A



Supplementary Figure 2B