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Adjusted comparison between elotuzumab and carfilzomib in combination with lenalidomide and dexamethasone as salvage therapy for multiple myeloma patients

Fortunato Morabito[1,2] | Elena Zamagni[3,4] | Concetta Conticello[5] | Vincenzo Pavone[6] | Salvatore Palmieri[7] | Sara Bringhen[8] | Monica Galli[9] | Silvia Mangiacavalli[10] | Daniele Derudas[11] | Elena Rossi[12] | Roberto Ria[13] | Lucio Catalano[14] | Paola Tacchetti[3] | Giuseppe Mele[15] | Iolanda Donatella Vincelli[16] | Enrica Antonia Martino[17] | Ernesto Vigna[17] | Cirino Botta[17] | Antonella Bruzzese[17] | Anna Mele[6] | Lucia Pantani[3] | Serena Rocchi[3,4] | Bruno Garibaldi[5] | Nicola Cascavilla[18] | Stelvio Ballanti[19] | Giovanni Tripepi[20] | Ferdinando Frigeri[21] | Antonetta Pia Falcone[18] | Clotilde Cangialosi[22] | Giovanni Reddiconto[23] | Giuliana Farina[21] | Marialucia Barone[24] | Ilaria Rizzello[3,4] | Pellegrino Musto[25] | Valerio De Stefano[12] | Maurizio Musso[26] | Maria Teresa Petrucci[27] | Massimo Offidani[28] | Antonino Neri[29] | Nicola Di Renzo[23] | Francesco Di Raimondo[5] | Mario Boccadoro[8] | Michele Cavo[3,4] | Massimo Gentile[17]

[1]Biothecnology Research Unit, AO of Cosenza, Cosenza, Italy

[2]Hematology and Bone Marrow Transplant Unit, Hemato-Oncology Department, Augusta Victoria Hospital, East Jerusalem, Israel

[3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

[4]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

[5]Division of Hematology, Azienda Policlinico-OVE, University of Catania, Catania, Italy

[6]Department of Hematology and Bone Marrow Transplant, Hospital Card. G. Panico, Tricase (LE), Italy

[7]Hematology Unit, Ospedale Cardarelli, Napoli, Italy

[8]Division of Hematology, University of Torino, AOU Città della Salute e della Scienza di Torino, Torino, Italy

[9]Hematology and Bone Marrow Transplant Unit, Azienda Socio-Sanitaria Territoriale-Papa Giovanni XXIII, Bergamo, Italy

[10]Hematology Division, Department of Hematology-Oncology, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy

[11]Department of Hematology, Businco Hospital, Cagliari, Italy

[12]Istituto di Ematologia, Università Cattolica, Fondazione Policlinico Gemelli IRCCS, Roma, Italy

[13]Department of Biomedical Science, University of Bari "Aldo Moro" Medical School, Internal Medicine "G. Baccelli", Policlinico, Bari, Italy

[14]AUOP "Federico II", Naples, Italy

[15]Department of Hematology, Hospital Perrino, Brindisi, Italy

[16]Hematology Unit, Department of Hemato-Oncology and Radiotherapy, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

[17]Hematology Unit AO of Cosenza, Cosenza, Italy

[18]Department of Hematology and Bone Marrow Transplant, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

[19]Institute of Haematology and Stem Cell transplantation, Ospedale Santa Maria della Misericordia, University of Perugia, Perugia, Italy

[20]Nephrology Center of National Research Institute of Biomedicine and Molecular Immunology, Reggio Calabria, Italy

[21]UOC Ematologia a Indirizzo Oncologico, AORN "Sant'Anna e San Sebastiano", Caserta, Italy

[22]U.O.C. Ematologia A. O. Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy

[23]Department of Hematology, Hospital Vito Fazzi, Lecce, Italy

[24]Onco-Hematology, "Tortora" Hospital, Pagani, Italy

[25]Hematology Section, University of Bari, Italy

[26]U.O.C. OncoEmatologia e TMO, Dipartimento Oncologico, La Maddalena, Palermo, Italy

[27]Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Rome, Italy

[28]Hematology Unit, AOU Ospedali Riuniti di Ancona, Ancona, Italy

[29]Hematology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy

Correspondence
Fortunato Morabito, Biotechnology Research Unit, AO of Cosenza, Contrada San Nicola, 87100 Cosenza, Italy.
Email: f.morabito53@gmail.com

Massimo Gentile, Hematology Unit, AO of Cosenza, Italy; 87100 Cosenza, Italy; viale della Repubblica snc.
Email:massim.gentile@tiscali.it

Abstract

The lack of a randomized trial comparing carfilzomib (K) *versus* elotuzumab (Elo) associated with lenalidomide and dexamethasone (Rd) prompted us to assess the relative usefulness of one triplet over the other. Five independent retrospective cohorts of 883 relapsed/refractory multiple myeloma (RRMM) patients, including 300 EloRd and 583 KRd cases, outside clinical trials, entered this non-randomized comparison. KRd cohort accounted for a higher incidence of younger patients, cases with ≥3 lines of therapy, already exposed to lenalidomide, International Staging System (ISS) stage III, and abnormal lactic dehydrogenase (LDH) level compared with EloRd cohort. Moreover, cytogenetic risk categories, detected in roughly one-third of cases, were equally distributed between the two therapy arms. The probability of CR+VGPR response was significantly higher in KRd (n = 314, 53.9%) than in EloRd patients (n = 111, 37.0%). Likewise, the cumulative incidence function of CR+VGPR, taking into account the competitive risk of death, was significantly higher in KRd arm patients than those in the EloRd arm (p = .003). Moreover, KRd treatment significantly reduced the progression or death risk by 46% in an adjusted multivariate analysis (HR: 0.54, 95% CI 0.42–0.69, p < .0001). Finally, in an adjusted illness-progression/death model, the effect of KRd *versus* EloRd was of higher magnitude among those who achieved CR+VGPR (−39% hazard ratio reduction, p = .02) than among those who achieved < VGPR (−29% hazard ratio reduction, p = .007). With limitations characteristic to any retrospective analysis, this current clinical practice study's overall results demonstrated potential benefits of KRd therapy compared with EloRd. This observation may help the daily clinical practice.

KEYWORDS
carfilzomib, dexamethasone, elotuzumab, lenalidomide, multiple myeloma, salvage therapy

1 | INTRODUCTION

The therapeutic algorithm of multiple myeloma (MM) patients has noticeably changed in the last few years, becoming increasingly complex in choosing the subsequent best therapy for relapsed and refractory MM (RRMM) patients.[1–5] In this setting, optimal treatment selection warrants unique concerns associated with the patient- and disease-related factors.[3–5] Nevertheless, the triplet regimens characterize the new standard of care for RRMM since they produce more profound responses and result in prolonged progression-free survival (PFS) compared with doublet therapies.[6,7] Irrespective of the more recent combinations,[8–11] the endorsement in favor of

Significance statement

- In this current study, we weighed the relative usefulness of EloRd over KRd, comparing a multicenter retrospective EloRd cohort with four multicenter retrospective KRd cohorts, all including RRMM cases treated outside of clinical trials.
- This current clinical practice study's overall results demonstrate that KRd therapy offers a superior outcome than EloRd.

a 3-drug regimen was first due to the introduction in the current clinical practice of immunomodulatory drugs (IMiDs)-based protocols, that is, lenalidomide and dexamethasone (Rd) associated with carfilzomib, (KRd),[12,13] elotuzumab (EloRd),[14,15] or daratumumab.[8,9] The effectiveness of combinations having Rd as backbone seems also connected to the mechanism of action of IMiDs that have immunomodulatory effects through the induction of NK cell activation and boosted ADCC activity.[16] Today, one of the most effective combinations available in the setting of RRMM remains daratumumab in combination with Rd.[8,9] Nevertheless, the approval of daratumumab for previously untreated MM patients will lead to a renewed use of KRd and EloRd as second-line therapy.

Phase III randomized trials unquestionably represent the optimal approach to generate clinical evidence. In this respect, KRd significantly improved RRMM patients' outcomes, reducing the risk of disease progression or death by 31% and increasing roughly 9 months the median PFS compared with Rd.[12] Similarly, the addition of elotuzumab to Rd reduced the risk of progression by 30%, with a gain of 4.5 progression-free months compared with the control arm.[14]

In this current study, in the lack of a randomized KRd vs. EloRd trial, and with the well-known limitations and susceptibility to the bias of real-life suggestions,[17] we weighed the relative usefulness of one triplet over the other, comparing a multicenter retrospective EloRd cohort[18] with four multicenter retrospective KRd cohorts,[19–22] all including RRMM cases treated outside of clinical trials. This current clinical practice study's overall results demonstrate that KRd therapy offers a superior outcome than EloRd.

2 | MATERIALS AND METHODS

2.1 | Patients

2.1.1 | Elotuzumab, lenalidomide, dexamethasone, and Carfilzomib, lenalidomide, dexamethasone cohorts

Five independent retrospective cohorts of RRMM patients included in previous papers[18–22] entered this study. In these five cohorts, all consecutive RRMM patients who received at least one cycle of KRd or EloRd as salvage treatment treated outside of clinical trials with KRd or EloRd regimens after marketing approval have been enclosed. All the databases of the five cohorts contained clinical information such as age, sex, date of diagnosis, laboratory parameters, treatment history, and date of last follow-up or death abstracted from clinical records at the time of inclusion and updated on an ongoing basis. In all five cohorts, PFS was calculated from the time of therapy start until the date of progression, relapse, death, or the date the patient was last known to be in remission. OS was calculated from the time of therapy start until the date of death for any cause or the date the patient was last known to be alive. The five databases were merged in a single meta-database. Three extra unpublished cases were also added. A CONSORT (Consolidated Standards of Reporting Trials) diagram encompassing the enrollment phases of the five real-world cohorts is depicted in Figure S1.

EloRd patients were treated according to marketing approval: Elo 10 mg/kg i.v. on days 1, 8, 15, and 22 during the first two cycles and then on days 1 and 15 of each following cycle, R 25 mg on days 1 to 21 of each cycle and d at a dose of 40 mg during the week without Elo, and 36 mg on the day of Elo administration. Patients received premedication with diphenhydramine (25 to 50 mg) or its equivalent, ranitidine (50 mg) or its equivalent, and acetaminophen (650 to 1000 mg) or its equivalent 30 to 90 min before the Elo infusion. Lenalidomide's starting dose was adjusted according to renal function. Elderly patients (>75 years) received d at a weekly dose of 20 mg.[18]

KRd cases were treated according to the ASPIRE schedule as previously described.[2-4] All patients received intravenous K at the standard dose (20 mg/m^2 the first two infusions, then 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16), in association with dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23, and lenalidomide 25 mg orally on days 1–21 of each 28-day cycle. After twelve cycles, K was reduced (days 1, 2, 15, and 16) and prolonged beyond 18 cycles at the physician's discretion.[19–22]

In all five cohorts (EloRd and KRd), the dose of each drug was adjusted according to drug recommendations in case of specific pre-existing comorbidities. In cases of specific predefined hematological and non-hematological toxic events, drugs' dosages were reduced, according to the manufacturers' recommendations and medical choice. Treatment was discontinued in cases of disease progression, unacceptable adverse events, or consent withdrawal.

The study was approved by institutional ethics committees according to the principles of the Declaration of Helsinki. The main demographic and clinical characteristics of patients according to KRd and EloRd treatment are given in Table 1.

2.2 | Statistical analysis

Data are expressed as absolute numbers, and percentages and between-groups comparisons were performed by the chi-Squared test. The incidence of CR+VPGR response over time between the two study arms was investigated by the cumulative incidence function taking into account the competitive risk of death.

PFS was calculated from therapy time to disease progression or death (event) or last follow-up (censoring). OS was calculated from the time of therapy start until the date of death for any cause or the date the patient was last known to be alive. The relationship between risk factors and the outcome variable was investigated by univariate and multiple Cox regression analysis. Univariate Cox regression analyses preliminarily investigated the effect of study arms on PFS. On univariate Cox regression analyses, tested covariates for progression or death included allocation arm (KRd *versus* EloRd) as well as the line of therapy, prior lenalidomide exposure, disease status at the start of therapy, the exposure to previous autologous bone marrow transplantation (ASCT), International Staging System (ISS), quality

TABLE 1 Clinical features of patients treated with carfilzomib, lenalidomide, dexamethasone (KRd), and elotuzumab, lenalidomide, dexamethasone (EloRd)

Features	KRd (N = 583) (%)	EloRd (N = 300) (%)	*p*-value
Age, years			
≤65	305 (52.3)	66 (22.0)	**<.0001**
>65	278 (47.7)	234 (78.0)	
Gender			
Female	295 (50.6)	157 (52.3)	.7
Male	288 (49.4)	143 (47.7)	
Line of therapy			
2nd	287 (49.2)	186 (62.0)	**<.0001**
3rd	129 (22.1)	70 (23.3)	
>3rd	167 (28.6)	44 (14.7)	
Prior Lenalidomide			
No	372 (63.8)	222 (74.0)	**.002**
Yes	211 (36.2)	78 (26.0)	
Disease status at therapy			
Relapse	415 (71.2)	226 (75.3)	.2
Refractory	168 (28.8)	74 (24.7)	
ASCT			
Yes	260 (44.6)	115 (38.3)	.075
No	323 (55.4)	185 (61.7)	
ISS			
I	214 (36.7)	91 (30.3)	**.001***
II	153 (26.2)	95 (31.7)	
III	176 (30.2)	52 (17.3)	
Missing	40 (6.9)	62 (20.7)	
Time from diagnosis, years			
>3.5	292 (50.1)	151 (50.3)	.94
<3.5	291 (49.9)	149 (49.7)	
LDH serum levels			
Normal	200 (34.3)	152 (50.7)	**.004***
Abnormal	266 (45.6)	130 (43.3)	
Missing	117 (20.1)	18 (6)	
Cytogenetic risk			
Standard risk	170 (29.2)	54 (18)	.13*
High risk	56 (9.6)	10 (3.3)	
Missing	357 (61.2)	236 (78.7)	

Abbreviations: ASCT, autologous stem cell transplantation; ISS, international staging system.

*The between-groups *p*-value was calculated only in patients with available data (patients with missing data were excluded). For the missing data category, only the absolute number is reported. The bold values indicate a *p*-value less than 0.05 that is statistically significant.

TABLE 2 Association between best response and main clinical-hematological characteristics of multiple myeloma patients treated with EloRd and KRd

Variables	CR +VGPR *N* (%)	<VGPR *N* (%)	*p*-value
Therapy			
KRd	314 (53.9)	269 (46.1)	**<.0001**
EloRd	111 (37.0)	189 (63.0)	
Age, years			
<65	193 (52.0)	178 (48.0)	**.049**
≥65	232 (45.3)	280 (54.7)	
ISS			
I	158 (51.8)	147 (48.2)	**.043**
II	105 (42.3)	143 (57.7)	
III	119 (52.2)	109 (47.8)	
Line of therapy			
2nd	255 (53.9)	218 (46.1)	**<.0001**
3rd	95 (47.7)	104 (52.3)	
>3rd	75 (35.5)	136 (64.5)	
ASCT			
Yes	184 (49.1)	191 (50.9)	.58
No	241 (47.4)	267 (52.6)	
Time from diagnosis to therapy			
>3.5 years	214 (48.3)	229 (51.7)	.92
<3.5 years	211 (48.0)	229 (52.0)	
Prior lenalidomide			
No	302 (50.8)	292 (49.2)	**.021**
Yes	123 (42.6)	166 (57.4)	
Disease status at the start of therapy			
Relapse	321 (50.1)	320 (49.9)	.06
Refractory	104 (43.0)	138 (57.0)	
LDH serum levels			
Normal	150 (42.6)	202 (57.4)	**.003**
Abnormal	212 (53.5)	184 (46.5)	
Cytogenetic risk			
Standard risk	127 (56.7)	97 (43.3)	**.007**
High risk	25 (37.9)	41 (62.1)	

Abbreviations: ASCT, autologous stem cell transplantation; ISS, international staging system; LDH, lactic dehydrogenase. The bold values indicate a *p*-value less than 0.05 that is statistically significant.

of response, time since diagnosis, lactic dehydrogenase (LDH), and cytogenetic abnormalities. All univariate correlates of progression/death and all variables, which significantly differed between the two study arms ($p < .05$), were simultaneously introduced into the same multiple Cox regression model. In Cox models, data were expressed as hazard ratio, 95% confidence interval (CI), and *p*-value.

To model the effect of KRd *versus* EloRd taking into account the intermediate endpoint of response (CR+VGPR vs.< VGPR) and data adjustment for confounders (ie, age, time from diagnosis, prior lenalidomide exposure, ISS, the line of therapy, and disease status at salvage therapy) significantly associated with progression-free survival and for all the variables which resulted differently distributed between the two groups at study inception (ie, AUBMT), an illness-progression/death model was fitted.[23,24] In this model, the primary

measures of interest are the pathway-specific hazard ratios. Three pathways were considered: pathway 1 going from baseline to progression/death in patients with <VGPR, pathway 2 going from baseline to response (CR+VGPR *versus* < VGPR), and pathway 3 going from baseline to progression/death after a CR+VGPR response. In this analysis, data were expressed as HR, 95% CI, and P-value. All analyses were performed by SPSS for Windows Version 22, Chicago, Illinois, USA, and STATA 16 for Window, Texas, USA.

3 | RESULTS

3.1 | Patients' characteristics and distribution between arms

Overall, 883 cases entered into the study. Three hundred cases were treated with EloRd and 583 with KRd. Table 1 summarizes the demographic data and the incidence of the potential prognostic indicators in the two therapy arms. At the start of therapy, the median age was 67 years (range 33–91), with 512 patients (58%) over 65 years, with a significantly higher prevalence detected into the EloRd cohort (78.0% versus 47.7%). The median number of previous therapies was 1 (range 1–11): 473 (53.6%), 199 (22.5%), and 211 (23.9%) received respectively 1, 2, and ≥3 previous lines of therapies, with a significantly higher proportion of cases with ≥3 lines identified in the KRd group. Similarly, the proteasome inhibitor group accounted for a significantly higher rate of patients already exposed to lenalidomide, with ISS stage III, and abnormal LDH levels. A trend toward an increased number of prior ASCT in the KRd cluster was also found (Table 1). Cases with refractoriness to the last treatment and time from diagnosis longer than 3.5 years were equally distributed between the two therapy arms.

3.2 | Effectiveness of KRd versus EloRd on the number of cases reaching CR or VGPR

At the last databases update, the median number of cycles administered was 12 (range, 1–43) and 10 (range, 1–36) for EloRd and KRd groups, respectively. A total of 425 cases achieved quality responses (ie, CR+VGPR), 314 (53.9%), and 111 (37%) patients in the KRd and EloRd, respectively (Table 2), with an overall median time from therapy initiation to ≥VGPR of 6.1 months for KRd and 6.6 months for EloRd. The cumulative incidence function of CR+VGPR, taking into account the competitive risk of death, was significantly higher ($p = 0.003$) in patients of the KRd arm than in those of the EloRd arm, and this was true over the whole study period (Figure 1). Accordingly, in an unadjusted analysis, the hazard ratio of CR+VGPR was 31% higher (HR: 1.31, 95% CI: 1.06–1.63, $p = .01$) in patients of the KRd arm than in those of the EloRd arm (Figure 2–unadjusted model), and such an effect did not change (HR: 1.28, 95% CI: 1.00–1.64, $p = .05$) after data adjustment for a series of potential confounders, that is, age, time from diagnosis, prior lenalidomide exposure, ISS, the line

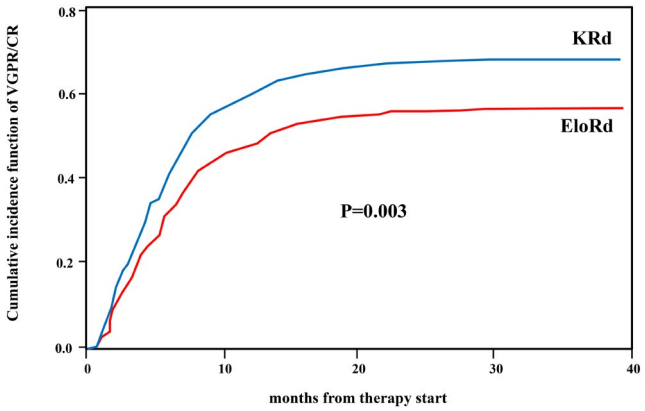


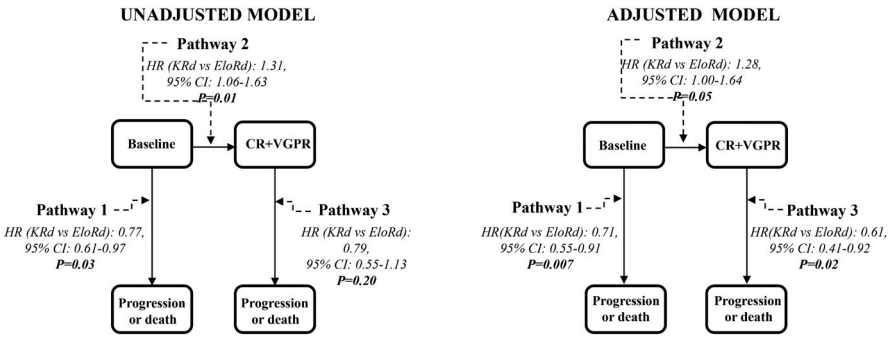
FIGURE 1 Cumulative incidence function of complete response plus very good partial response over time. The two curves were derived by a competitive risk analysis taking into account death

of therapy, and disease status at salvage therapy, which resulted significantly associated with PFS (see below) and for all the variables which resulted differently distributed between the two groups at study inception (ie, ASCT) (Figure 2—adjusted model). A face-to-face comparison between patients with CR+VGPR *versus* those with <VGPR is reported in Table 2.

3.3 | Effectiveness of KRd versus EloRd on progression-free survival

After a median follow-up of 17 months (EloRd = 16 months; KRd = 18 months) since therapy started, 423 patients had progressed or died. Among them, 253 events belong to the KRd and 170 to the EloRd group. Kaplan-Meier curves of PFS showed a significantly longer PFS in patients treated with KRd (Figure 3). Accordingly, an unadjusted Cox analysis performed in both pooled cohorts showed that KRd was significantly more effective than EloRd for reducing the risk of disease progression or death (2-year PFS 49.3% vs 41.2%; HR = 0.77, 95% CI: 0.63–0.93, $p = .007$, see Table 4). To minimize the problem of confounding, we adjusted the relationship between allocation therapy (KRd *versus* EloRd) and disease progression for all the variables which resulted differently distributed between the two cohorts at study inception as described in Table 1 (age, line of therapy, prior lenalidomide, ISS, and LDH), as well as for all variables significantly associated with PFS at Cox univariate analysis, as described in Table 4 (therapy, age, time from diagnosis to therapy, prior lenalidomide, ISS, and disease status at the start of therapy).

We excluded from this analysis LDH and cytogenetic risk due to the significant number of missing values. As previously stated, ASCT, which showed a different, although at borderline significance ($p = .075$), distribution between the two cohorts (Table 1), was also added to the analysis. After simultaneously introducing variables evaluable at the start of therapy as covariates into the same model, multiple Cox regression confirmed the protective effect of KRd *versus* EloRd in terms of risk of disease progression or death



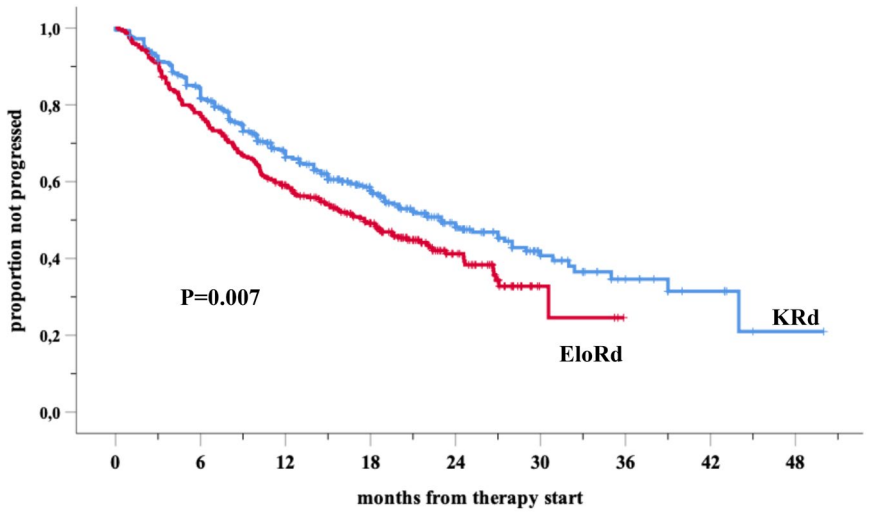
Pathway 1: effect of KRd versus EloRd on PFS in patients with <VGPR

Pathway 2: effect of KRd versus EloRd on CR+VGPR

Pathway 3: effect of KRd versus EloRd on PFS in patients with CR+VGPR

FIGURE 2 Unadjusted (left panel) and adjusted (right panel) illness-progression/death models by confounders significantly associated with progression-free survival. In the adjusted model (right panel), we included all variables significant at Cox univariate analysis for progression-free survival (see Table 4). Pathway 1 refers to the effect of KRd vs. EloRd on progression-free survival (ie, progression or death) in those patients who had less than very good partial response (VGPR), whereas pathway 3 refers to the effect of KRd vs. EloRd on progression-free survival in those patients who had CR+VGPR response. Of course, pathway 3 is preceded by pathway 2, which reflects the effect of KRd *versus* EloRd on patients' response (ie, the achievement of CR+VGPR)

FIGURE 3 Progression-free survival of the retrospective relapsed/refractory (RR) multiple myeloma patients grouped by therapy arm



No. of pts at risk									
KRd	583	467	308	182	86	34	14	6	1
EloRd	300	231	168	112	44	3	1	0	0

independently of a series of potential confounders achievable at the start of therapy (HR = 0.54, 95% CI 0.42–0.69, $p < .0001$) (Table 4). Notably, ISS stage II and III, time from diagnosis ≤3.5 years, and more than 3 lines of therapy were also adversely associated with a higher risk to experience an event (Table 4). Of interest, age failed to be independently associated with PFS ($p = .70$), even when it was added as a continuous variable into the model (data not shown).

3.4 | Illness-progression/death model

To model the effect of KRd *versus* EloRd taking into account the intermediate endpoint of response (CR+VGPR vs. <VGPR) and data adjustment for previously described confounders, an illness-progression/death model was fitted. In this model, three pathways were considered (Figure 2): pathway 1 going from baseline to progression/death in patients with <VGPR, pathway 2 going from baseline to response (CR+VGPR vs. <VGPR), and pathway 3 going from baseline to progression/death after a CR+VGPR response.

In an unadjusted illness-progression/death model (Figure 2), among those who achieved <VGPR (pathway 1), patients in the KRd arm had a lower risk of progression/death (−33%, $p = .03$) as compared to those in the EloRd arm. In patients with CR+VGPR (pathway 3), the HR of progression/death was 21% lower in KRd than in EloRd treated patients on crude analysis, but such an effect did not achieve the statistical significance ($p = .20$). Remarkably, after data adjustment for potential confounders (Figure 2- adjusted model), a significantly higher benefit for progression/death of KRd *versus* EloRd was found either in patients who achieved <VGPR ($p = .007$, pathway 1) or in those who achieved CR+VGPR ($p = .02$, pathway 3) (Figure 2).

Of note, the effect of KRd *versus* EloRd benefit was of higher magnitude among those who achieved CR+VGPR (−39%, $p = .02$) than among those who achieved <VGPR (−29%, $p = .007$).

3.5 | Outcome analysis by cytogenetic risk and LDH serum level

Regrettably, LDH serum levels and data on cytogenetic abnormalities were available in 748/883 cases (84.7%) and 290/883 cases (32.8%), respectively. However, the prognostic relevance of both biomarkers highlighted by the revised ISS (R-ISS)[25] prompted us to carry out a supplementary analysis, conscious that the relatively low number of available cases would have reduced the statistical power.

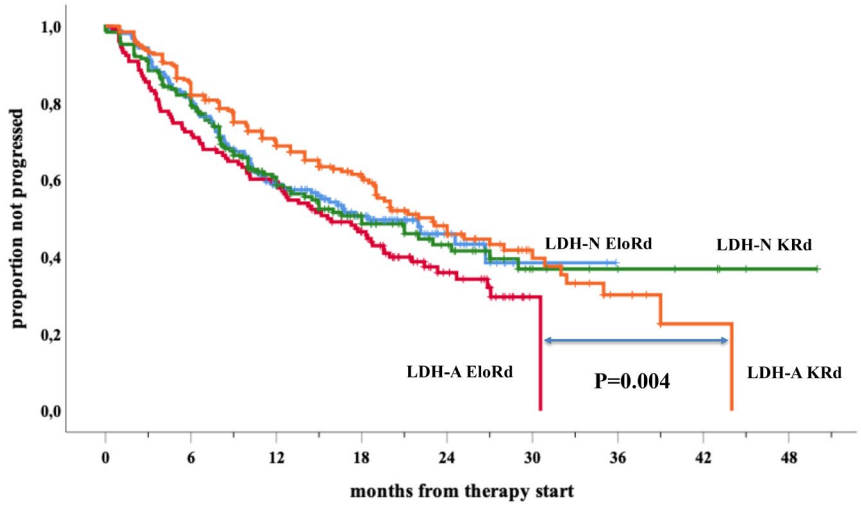
The percentages of cases with abnormal LDH levels (calculated in a complete case analysis) were 57.1% (266/466 cases) and 46.1% (130/282 cases) in the KRd and EloRd group, respectively ($p = .004$). Unexpectedly, the incidence of CR+VGPR was significantly higher in the abnormal LDH group (Table 2). Noteworthy, the percentage of high-quality response was 61.8% (161/260 cases) among abnormal LDH level cases treated with KRd, and 40.4% (53/131 cases) in the EloRd group (Table 3). Finally, as described in Table 4, LDH did not retain a significant impact on PFS in the entire cohort ($p = .76$). However, a significant superior KRd performance was accounted for in the abnormal LDH cases (2-year PFS 48.2% vs. 36.2%; HR 0.66, 95% CI 0.492–0.88, $p = 0.004$), while the two triplets showed overlapped PFS curves in the group of patients with average LDH serum level (Figure 4).

Cytogenetic abnormalities were detected by fluorescence in situ hybridization on highly purified bone marrow plasma cells. The analysis distinguished high-risk [including t(4;14), t(14;16) and del(17p)] and standard-risk (all the remaining) cases. Risk categories were equally distributed between the two therapy arms (Table 1). However, the rate of CR+VGPR was lower in the high-risk compared with the standard-risk group (Table 2). Notably, while a superimposable percentage of CR+VGPR was accounted in both therapy arms in the high-risk cytogenetic group [KRd 21/56 cases (38.2%) *versus* EloRD 4/10 cases (40%)], cases treated with KRd showed a higher incidence of CR+VGPR among standard-risk cases [KRd 100/170 (59.6) *versus* EloRd 27/54 (50%)] (Table 3).

As expected, patients with a high-risk cytogenetic group showed a 2.6 higher risk of disease progression or death than the standard-risk cluster at univariate analysis (2-year PFS 53.6% vs. 23.5%; HR 2.6, 95% CI 1.82–3.79). However, KRd failed to show any significant superiority over EloRd in both standard (2-year PFS 51.9% vs 52.7%; HR = 1.1, 95% CI 0.72–1.85, $p = 0.6$) and high (2-year PFS 25.9% vs 15%; HR = 0.74, 95% CI 0.34–1.60, $p = 0.45$) cytogenetic risk groups at Cox univariate analysis. The Kaplan-Meier curve of PFS by cytogenetic risk and therapy arm endorse this finding (Figure 5). In a multiple Cox analysis, adjusting also for cytogenetic risk, patients on treatment with KRd had a 29% lower risk of progression/death (HR 0.71, 95% CI 0.43–1.20) as compared to those treated with EloRd, but this association failed to reach the statistical significance ($p = .17$) possibly due to the relatively low sample size ($n = 290$). Also, when we adjusted the relationship between the two study arms and PFS for age and prior lenalidomide treatment, the results did not change (standard, HR: 0.91, 95% CI 0.55.- 1.52, $p = .7$; high, HR: 1.35, 95% CI 0.55–3.1, $p = .5$).

3.6 | Overall survival

An unadjusted analysis showed no significant differences between KRd and EloRd when OS was considered (2-year OS 38% vs. 34.1%; HR = 1.10, 95% CI 0.83–1.37, $p = .61$), even after data adjustment



No. of pts at risk

LDH-N KRd	200	155	89	49	27	10	7	5	1
LDH-A KRd	266	211	143	85	43	19	6	1	0
LDH-N EloRd	152	122	81	50	17	1	1	0	0
LDH-A EloRd	130	94	76	52	21	1	0	0	0

FIGURE 4 Kaplan-Meier curve of progression-free survival after clustering cases by LDH serum level (normal, N *versus* abnormal A) and therapy arm

TABLE 3 Relationship between response and cytogenetic risk and LDH level, both gathered by therapy arm

		CR +VGPR N (%)	<VGPR N (%)	*p*-value		CR+VGPR *N* (%)	<VGPR *N* (%)	*p*-value
Therapy arm	Cytogenetic risk				LDH serum level			
KRd	Standard	100 (59.6)	70 (40.4)	**.036***	Normal	93 (48.7)	98 (51.3)	**<.0001***
	High	21 (38.2)	35 (61.8)		Abnormal	161 (61.9)	99 (38.1)	
EloRd	Standard	27 (50.0)	27 (50.0)		Normal	52 (32.9)	106 (67.1)	
	High	4 (40.0)	6 (60.0)		Abnormal	53 (40.5)	78 (59.5)	

Abbreviations: CR, complete response; VGPR, very good partial response.

*The P-values refer to the comparison of the joint distribution of Cytogenetic risk, as well as LDH serum level, and treatment allocation between the two groups of patients (CR +VGPR vs. <VGPR). Four groups were considered. For cytogenetic, patients at standard risk on KRd; patients at high risk on KRd; patients at standard risk on EloRd; patients at high risk on EloRd. For LDH serum level, patients with normal LDH on KRd; patients with abnormal LDH on KRd; patients with normal LDH on EloRd; patients with abnormal LDH on EloRd. The distribution of these risk categories was compared between patients with CR +VGPR and <VGPR. The bold values indicate a *p*-value less than 0.05 that is statistically significant.

for age and prior lenalidomide exposure (HR 1.02, 95% CI 0.66–1.56; $p = .9$).

4 | DISCUSSION

Randomized phase 3 trials remain the standard to cost-effectively inform the best therapy among arms for several well-known reasons, that is, adjustment by randomization and pre-declared and well-defined endpoints. KRd and EloRd, when compared with Rd, undoubtedly prolonged both PFS and OS in RRMM patients.[13,26] Moreover, in both trials, the triplets significantly impacted survival.[13,26] Nevertheless, no randomized study compared these two triplets. However, in the absence of efficacy data produced by randomized clinical trials, effectiveness suggestions could be recovered from the real-world setting.

Modern therapeutic evolution has substantially increased patients' frequency of achieving CR, with a clear relationship between the depth of response and PFS in recent phase III studies in MM.[27] In our cohort, KRd demonstrated a higher chance of attaining a quality response than EloRd. Moreover, the cumulative incidence function of CR+VGPR, taking into account the competitive risk of death, was significantly higher in the KRd than EloRd arms. Accordingly, the hazard ratio of best response was 31% higher in patients of the KRd arm than in those of the EloRd arm, and such an effect remained substantially unchanged also after data adjustment for a series of potential confounders (+28%).

KRd performed significantly better than EloRd for lowering the risk of disease progression or death. Nevertheless, this crude analysis poses a drawback of confounding due to the study's non-randomized nature, which precludes the possibility of claiming a more significant KRd benefit *versus* EloRd. This superior protective effect was also maintained after adjustment for a series of possible confounders achievable at the start of therapy. Of note, the adjusted effect of KRd versus EloRd for PFS was of higher magnitude (−46% risk reduction) as compared to the crude (unadjusted) estimate (−23% risk reduction). Notably, the advanced ISS stage, a short time from diagnosis, and more than 3 lines of therapy still represent unique concerns in managing RRMM patients undergoing KRd or EloRD therapy in this real-world setting.[5]

Given that disease progression and death usually consist of intermediary events that may alter the progression to an endpoint, an illness-death model analysis was performed.[23,24] In our study, we applied such a technique because standard statistical methods for time to event analyses, such as the Kaplan-Meier curves and the Cox regression, do not allow to take into account the potential effect of response (CR+VGPR vs. <VGPR) on the effectiveness of the two drugs on PFS. In other words, the Kaplan-Meier analysis and the standard Cox regression method only allow to adjust for baseline effect modifiers and not for effect modifiers occurring longitudinally.

In this model, individuals start without a condition and may eventually experience an intermediate event (eg, a response), which modifies the pathway from the baseline status to the final endpoint. In an unadjusted illness-progression/death model, among those who achieved <VGPR, patients in the KRd arm have a significantly lower risk of progression/death ($p = .03$) as compared to those in the EloRd arm, whereas no such significant effect was found in those who achieved CR+VGPR ($p = .20$). However, data adjustment for potential confounders in the illness-progression/death model revealed that the effect of KRd *versus* EloRd was of higher magnitude among those who achieved CR+VGPR (−39%, $p = .02$) than among those who achieved <VGPR (−29%, $p = .007$).

Herein, we demonstrated a superior protective effect of KRd vs. EloRd in terms of risk of disease progression or death independently of several confounders attainable at the start of therapy. Unfortunately, this first part of our analysis presents some limitations.

First, age is a critical issue in the therapy choice process for MM patients owing to its relationship with frailty, increased comorbidities, reduced tolerability, and a higher risk of side effects; thus, elderly patients comprise a heterogeneous group with variable fitness status.[28] In our cohort, age failed to be independently associated with PFS, even when it was added as a continuous variable into the model. However, the use of age only should be considered

unsatisfactory, and an adequate assessment of fitness status before treatment is crucially important. Nevertheless, the fact that age is not an independent predictor of PFS in our analysis could be reasonably linked to optimal therapy choice by measuring fitness status based on physician clinical experience. In this respect, the EloRd cohort included a significantly higher number of patients older than 65 years. This choice may be due to previous reports on carfilzomib-related cardiovascular adverse events,[29] which have likely influenced the choice of KRd for younger patients in clinical practice. Accordingly, 87.3% (210/242) and 81.6% (235/288) of cases were treated with KRd in the ≤ 60 and >60 ≤70 age groups, respectively. This percentage decreased to 45.3% (131/289), to drop to 12% (6/64) in cases over the age of 80, indicating a careful choice by physicians. Nevertheless, KRd appears to be more effective than EloRd, maintaining its superiority over EloRd if the choice is compatible with the age and the frailty level (especially cardiac) of patients.

Second, a low percentage of the cytogenetic report was available in our study since we tend to evaluate it at diagnosis, mainly in research centers.[30] Although KRd and EloRd equally performed in both standard and high cytogenetic risk groups, even after adjustment by multivariate analysis, the low number of cases did not allow for drawing definitive conclusions. Moreover, we cannot compare the two trials, and our analysis directly for several reasons, including the discrepancy of FISH analysis and cutoffs utilized in the different studies, the median PFS in the ASPIRE KRd *versus* the ELOQUENT-2 EloRd were reasonably similar in patients with both standard-risk (29.6 *versus* 28.6 months) and with high-risk cytogenetics (23.1 *versus* 18.5 months).[31,32]

Third, although in the multivariate analysis we adjusted for a series of major potential confounders (such as age, time from diagnosis to therapy, prior Lenalidomide, ISS, line of therapy, and disease status at the start of therapy), the possibility of residual confounding due to unmeasured confounders cannot be excluded.

A specific remark deserves LDH serum level, another relevant biomarker in the R-ISS.[25] Notably, KRd performed better than EloRd in the abnormal LDH group, reducing the risk of progression or death by 44%, while the two triplets are equivalent in the group of patients with normal LDH serum levels.

Finally, no significant difference was observed between KRd and EloRd arms when OS was measured. However, one triplet's superiority over the other in OS has still to be entirely ascertained after a longer follow-up.

TABLE 4 Univariate and multivariate Cox regression analyses of progression-free survival in the entire cohort of patients treated with carfilzomib, lenalidomide, dexamethasone (KRd), or elotuzumab, lenalidomide, and dexamethasone (EloRd)

		Univariate analyses		Multivariate analyses	
Variables		**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Therapy	EloRd	1	**.007**	**1**	**<.0001**
	KRd	0.77 (0.63–0.93)		**0.54 (0.42–0.69)**	
Age, years	<65	1	**.013**	1	.7
	≥65	1.28 (1.05–1.37)		1.05 (0.82–1.34)	
Gender	Female	1	.21	–	
	Male	1.13 (0.93–1.36)			
ASCT	No	1	.22	–	
	Yes	1.13 (0.93 –1.37)			
Time from diagnosis to therapy	≥3.5	1	**.003**	**1**	**.001**
	<3.5	1.33 (1.10–1.62)		**1.59 (1.22–2.08)**	
Prior Lenalidomide	No	1	**.001**	1	.064
	Yes	1.40 (1.15–1.70)		1.27 (0.99–1.63)	
ISS	I	1	**.003**	1	.14
	II	1.46 (1.13–1.87)	**<.0001**	1.24 (0.93–1.64)	**.004**
	III	1.89 (1.47–2.42)		**1.53 (1.14–2.04)**	
Line of therapy	2nd	1	.22	1	.78
	3rd	0.93 (0.73–1.21)	**<.0001**	1.05 (0.76–1.44)	**<.0001**
	>3rd	1.87 (1.51–2.33)		**2.17 (1.55–3.03)**	
Disease status at the start of therapy	Relapsed	1	**.006**	1	.25
	Refractory	1.33 (1.09–1.63)		1.15 (0.9–1.47)	
LDH serum levels	Normal	1	.76	–	
	Abnormal	0.96 (0.79–1.19)			

Abbreviations: ASCT, autologous stem cell transplantation; CI, confidence interval; HR, hazards ratio; ISS, international staging system. The bold values indicate a *p*-value less than 0.05 that is statistically significant.

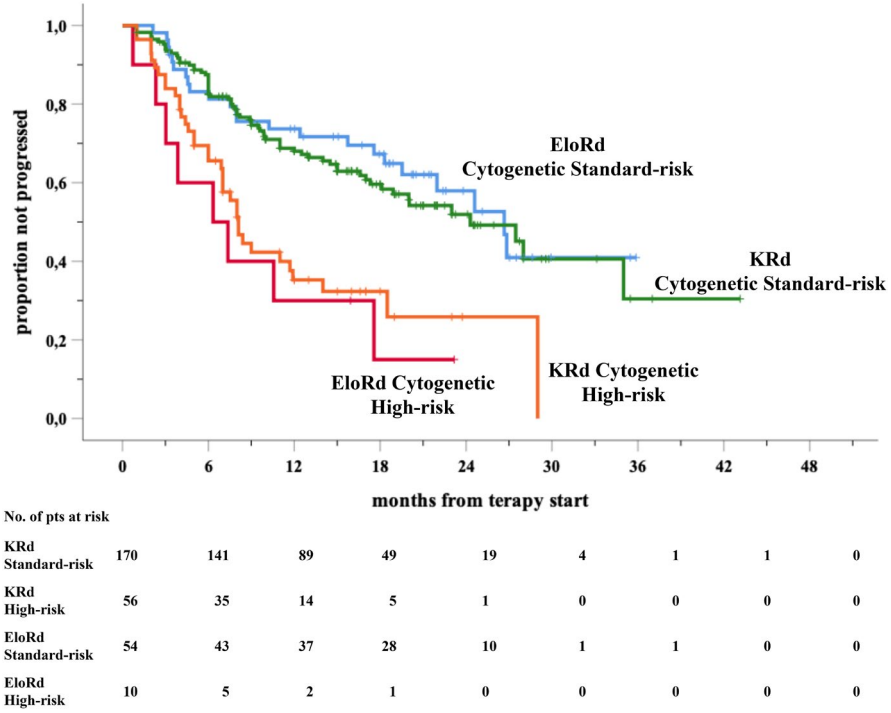


FIGURE 5 Kaplan-Meier curve of progression-free survival according to cytogenetic risk and therapy arm

No. of pts at risk

KRd Standard-risk	170	141	89	49	19	4	1	1	0
KRd High-risk	56	35	14	5	1	0	0	0	0
EloRd Standard-risk	54	43	37	28	10	1	1	0	0
EloRd High-risk	10	5	2	1	0	0	0	0	0

Although this retrospective analysis has shown that KRd is superior to EloRd as rescue therapy for patients with RR multiple myeloma, the interest in EloRd remains for old patients and cases with potential cardiac problems. Moreover, Elo has been recently renewed by the Eloquent-3 study. In particular, Elo showed significant clinical efficacy in the subgroup of Len-refractory patients when combined with pomalidomide and dexamethasone.

In conclusion, although our analysis presents some constraints, that is, the unavailability or limited availability of additional hypothetical confounders as well as the potential for coding errors inherent to any retrospective analysis, the overall results of this current clinical practice study demonstrate that KRd therapy provides a superior PFS compared with EloRd. Based on this study's results and the literature's data,[12–15] we endeavored to provide additional recommendations (see Figure S2), which may help the daily clinical practice, mainly in the lack of randomized trials comparing the two schedules.

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CONFLICT OF INTEREST

P.T. received honoraria from Bristol-Myers Squibb, Takeda, Janssen, Celgene, and Amgen. L.P. received honoraria from Celgene, Takeda, Janssen, and Amgen. E.Z. has received a speaker honorarium from Bristol-Myers Squibb, Takeda, Janssen, Celgene, and Amgen. M.C. has received a speaker honorarium from Adaptive Biotechnology, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Takeda, AbbVie, and GlaxoSmithKline, and he is a member of committee of these Company. C.C., F.D.R., A.R., U.M., and V.L. received honoraria from Amgen. C.C., F.D.R., and A.R. received honoraria from Celgene.

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M.G., E.Z., C.C., V.P., S.P., S.B., V.D.S., F.D.R., M.M., M.T.P., M.O., P.M., A.N., M.B., M.C., and F.M. designed the study, analyzed and interpreted data, and wrote the manuscript. M.G., G.T., and F.M. performed statistical analysis; D.D., Mo.G., C.B., S.M., E.R., R.R., L.C., P.T., G.M., I.D.V., E.A.M., E.V., A.B., A.M., L.P., S.R., B.G., N.C., S.B., F.F., A.P.F., Cl. C., G.R., G.F., M.B., N.D.R., and I.R. provided the patients and collected clinical data. And all authors gave final approval for the manuscript.

DATA AVAILABILITY STATEMENT

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

ORCID

Fortunato Morabito https://orcid.org/0000-0002-2585-7073
Cirino Botta https://orcid.org/0000-0002-1522-4504

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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