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Carfilzomib plus dexamethasone in patients with relapsed and refractory multiple myeloma: A retro-prospective observational study

Maria Livia Del Giudice[1] | Alessandro Gozzetti[2] | Elisabetta Antonioli[3] | Irene Attucci[3] | Ludovica Pengue[3] | Raffaella Cassano Cassano[1] | Francesco Ghio[1] | Enrico Orciuolo[1] | Martina Simoncelli[2] | Monica Bocchia[2] | Sara Galimberti[1] | Gabriele Buda[1]

[1]Department of Clinical and Experimental Medicine, Hematology, University of Pisa, Pisa, Italy

[2]Hematology, Azienda Ospedaliera Universitaria Senese, University of Siena, Siena, Italy

[3]Hematology, Careggi Hospital, University of Florence, Florence, Italy

Correspondence
Maria Livia Del Giudice, Hematology Division, Pisa University Hospital, Via Roma, 67, 56126 PI, Pisa, Italy.
Email: mliviadelgiudice@gmail.com

Abstract

Objective: We investigate safety and efficacy in common clinical practice of the combination of carfilzomib and dexamethasone (Kd56) approved for the ENDEAVOR trial for the treatment of relapsed or refractory multiple myeloma.

Methods: We retro-prospective analyzed 75 patients in three centers in Tuscany, 48 of whom had a clinically relevant comorbidity and 50 of whom were older than 65 years, treated with a median use in the fourth line of therapy. We assessed the efficacy based on the International Myeloma Working Group criteria.

Results: The overall response rate was 60%. Median PFS was 10 months in the general cohort; in patients treated for more than 1 cycle of therapy PFS was 12 months. Quality of response to Kd56 treatment was found to positively impact PFS. Refractory status to previous line of therapy or to lenalidomide or an history of exposure to pomalidomide, seemed to have no impact on survival. We also showed a low adverse events rate, with no neuropathy events, and a relatively small number of cardiovascular events above grade 3 (10%).

Conclusion: Kd56 is an effective and well tolerated regimen in highly pretreated and elderly patients with a good safety profile.

KEYWORDS
carfilzomib, dexamethasone, multiple myeloma, real world clinical trials

1 | INTRODUCTION

Multiple myeloma (MM) is the second most frequent blood cancer, with a complex array of clinical manifestations including anemia, bone lesions, hypercalcemia, renal dysfunction, and compromised immune function.[1,2] Although MM is an incurable disease, increasingly difficult to treat with each relapse, recent years have seen a progressive improvement in patient survival.[3,4] A major role in this achievement was certainly played by proteasome inhibitors (PIs), of which bortezomib (V) is the first-in-class, initially approved in 2003 as a single agent

in patients with RRMM from the second recurrence.[5,6] PIs currently form the backbone of the treatment of MM, as they specifically target the 20S proteasome, which is central to the proliferation of malignant plasma cells[7]: as Myeloma cells are highly dependent on the proteasome to eliminate abnormal or cytotoxic proteins, they are more susceptible to PIs than nonmalignant ones.[8,9] Carfilzomib (K), a second-generation PI, was approved by FDA in 2012. It binds irreversibly and selectively the β5 subunit of the 20S immunoproteasome and inhibits the chymotrypsin-like activity,[10] indicated in RRMM as a single agent or in combination with dexamethasone or lenalidomide plus dexamethasone. In particular, the data provide support for K as a more potent PI than V, as shown in ENDEAVOR, a phase III study comparing Kd56 versus Vd, which demonstrated the efficacy of the first scheme in terms of longer OS and PFS, response rates and health-related quality of life, leading to the regulatory approval of Kd56 regimen in 2016.[11,12] The toxicity profile of carfilzomib is quite different from other available PIs; in particular, it is associated with cardiovascular effects not related to proteasome inhibition, but to the autophagy pathway and upregulation of protein phosphatase-2A activity.[13] Treatment paradigms change rapidly; however, Kd still finds a place in the latest treatment guidelines.[14,15] Despite its wide routine use, there is a lack of data in the literature on its use in practice. So, we have collected data from 75 patients treated according to the Kd56 scheme in three centers in Tuscany, to assess the impact of the evidence from the registration study in real-life settings, providing a measure of the efficacy and safety of this regimen in common clinical practice.

TABLE 1 Baseline demographic and clinical characteristics of patients

Characteristic (75 patients)[a]	At diagnosis	At Kd start
Female; male	37 (49.3); 38 (50.6)	
Median years, range	64, 38–78	70, 43–83
Distribution ≤65; >65	39 (52); 36 (48)	25 (33.3); 50 (66.7)
ISS		
I	37 (49.3)	
II	12 (16)	
III	16 (21.3)	
No information	10 (13.4)	
R-ISS		
I	17 (22.6)	
II	26 (34.7)	
III	6 (8)	
No information	26 (34.7)	
M-protein		
IgG κ	31 (41.3)	
IgG λ	17 (22.7)	
IgA κ	6 (8)	
IgA λ	6 (8)	
κ	8 (10.7)	
λ	5 (6.7)	
IgD λ	1 (1.3)	
Nonsecretory disease	1 (1.3)	
Serum creatinine		
<2 mg/dL	56 (74.7)	69 (92)
≥2 mg/dL	10 (13.3)	6 (8)
No information	9 (12)	0 (0)
Extra medullary disease		10 (13.4)
Cytogenetic risk group established by FISH		
High risk	11 (14.7)	
Standard risk	36 (48)	
No information	28 (37.3)	
Underwent ASCT (single or tandem)	37 (49)	
Induction therapy		
Three-drug V-based VTD; VMP; VCD; VRD	29 (38.7); 23 (31); 4 (5.3); 1 (1.3); 1 (1.3)	
Other VD; TD; RD; DAV; DaraRD; TMyD	7 (9.3); 4 (5.3); 2 (2.6); 2 (2.6); 1 (1.3); 1 (1.3)	
No information	1 (1.3)	

[a]Data are median (range) or number (%). The high risk group consisted of patients with the genetic subtypes t(4;14), t(4;16), and 17p deletion. The standard risk group consisted of patients without the genetic subtypes t (4;14), t(4;16), and 17p deletion.

Abbreviations: ASCT, autologous stem cell transplantation; DaraRd, daratumumab plus lenalidomide-dexamethasone; DAV, doxorubicin plus vincristine-dexamethasone; FISH, fluorescence in situ hybridation analysis; ISS, International Staging System; RD, lenalidomide plus dexamethasone; R-ISS, Revised Multiple Myeloma International Staging System; TD, thalidomide plus dexamethasone; TMyD, thalidomide, liposomal doxorubicine and dexamethasone; V, bortezomib; VCD, cyclophosphamide plus bortezomib-dexamethasone; VD, bortezomib plus dexamethasone; VMP, bortezomib plus melphalan-prednisone; VRD, bortezomib plus lenalidomide-dexamethasone; VTD, bortezomib plus thalidomide-dexamethasone.

2 | METHODS

Patients with RRMM, who had shown relapse, disease refractoriness or drug intolerance during the previous line of therapy, treated with Kd56 starting between 2017 and 2021 in three sites (Florence, Pisa and Siena University Hospitals) were retro-prospectively analyzed. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee (CEAVNO). All patients provided written informed consent. Patients received K as an IV infusion over 30 min on days 1, 2, 8, 9, 15, 16 of 28-day cycles at the planned dose of 20 mg/m^2 on days 1 and 2 of cycle 1, followed

by 56 mg/m^2 at subsequent administration; they also received dexamethasone orally or IV (40 mg weekly or 20 mg for patient older than 75 years of age) on days 1, 2, 8, 9, 15, 16, 22 and 23. Treatment was permanently discontinued when withdrawal of patient consent, disease progression or unacceptable adverse effects occurred. Treatment deferral, dose reduction or additional supportive therapies were performed in the judgment of physicians to manage adverse events or disease features. Thromboprophylaxis was considered on the basis of individual risk/benefit assessment and usually performed with low molecular weight heparin or aspirin, according to IMWG recommendations.[16] Myeloid and erythroid growth factors, anti-infectious prophylaxis, treatments for adverse events, and other supportive therapies were based on physicians' decisions. Demographic characteristics, including prior medical history, MM features (including M-protein subtype, extramedullary disease, cytogenetics, ISS and R-ISS), prior treatment needed, comorbidities and renal function were collected at diagnosis and at beginning of Kd56 treatment. Cytogenetic analysis was assessed by interphase fluorescence in situ hybridization in order to identify high-risk alterations according to the International Myeloma Working Group (IMWG) 2014 Consensus Criteria.[17] Response and progression were assessed according to IMWG criteria.[18] Relapse was defined as disease progression in patients who achieved at least a partial response in previous treatment; refractoriness was defined as disease progression without ever achieving a measurable disease response during previous treatment or within 60 days after treatment. The severity of adverse events was assessed according to version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events.

2.1 | Statistical analysis

Categorical data were described by absolute and relative frequency, continuous data by median and range. Progression-free survival (PFS) was defined as the time interval from therapy initiation to observed disease progression, relapse, or death from any cause. Overall survival (OS) was defined as the time interval from therapy initiation to death. Kaplan–Meier methodology was used to summarize distributions; the log-rank test was used to evaluate the differences between curves. Hazard ratio with CI 95% was expressed too. Significance was fixed at .05.

3 | RESULTS

3.1 | Patient characteristics

The analysis includes a total of 75 patients (37 women and 38 men) with RRMM, treated with carfilzomib and dexamethasone as the approved schedule. Table 1 shows the patients' baseline characteristics. Median age of all patients at the time of diagnosis was 64 years old (range, 38–78), when 36 patients (48%) were 65 years old or older. Among the patients, 16 (21%) had International Staging System (ISS) stage III myeloma. Furthermore, 37 patients had received a previous autologous stem cell transplant (single or double). Eleven patients carried high-risk cytogenetic lesions; 10 patients carried an extramedullary disease; 17 (22%) had achieved a complete response after induction therapy. At the time of treatment with Kd56, 48 patients

TABLE 2 Comorbidities summary

Comorbidities	No. (%)
≥2	21 (28)
≥1	48 (64)
Cardiovascular	26 (34.6)
No information	1 (1.3)
Hypertension	22
Thromboembolic event, of which PE	11, 4
Endocrine disorders, of which DM	8, 5
Renal/urinary disorders	10
Secondary solid cancer	6
Arrhythmias, CAD, heart failure	3, 1, 1
Liver disease	4
Secondary blood cancer	4
Dyslipidemia	3
GI disease	3
Chronic lung disease	2
Eye disorders	2
Skin disorders	2
Other	7

Abbreviations: CAD coronary acute disease; DM, diabetes mellitus; GI, gastro-intestinal; PE, pulmonary embolism.

TABLE 3 Novel agents background

Category	No. (%)	No. (%)
IMiDs	Lenalidomide	Pomalidomide
	63 (84)	23 (31)
	Of which refractory	Of which refractory
	44 (70)	16 (70)
PIs	Bortezomib	Ixazomib
	71 (95)	3 (4)
moAbs	Daratumumab	Elotuzumab
	18 (24)	2 (3)
	Daratumumab refractory	
	9 (50)	
Last line of treatment refractory	41 (54.6)	
	Including lenalidomide	Including PIs
	17 (41.4)	8 (19.5)

Abbreviations: IMiDs, immunomodulatory drugs; moAbs, monoclonal antibody; PIs, proteasome inhibitors.

(64% of the entire cohort) had at least one clinically relevant comorbidity, as summarized in Table 2. A large number of patients had already been treated with lenalidomide (84%), with 70% of these defined as Lenalidomide refractory, or with pomalidomide (31%), of which most were also refractory (70%), as shown in Table 3 which summarizes the treatment history of patients with the newer drugs. We included in the analysis any patient that received at least one course of the regimen. The median use of Kd56 was as the fourth line of therapy (with a median of three previous lines of therapy, range 1–8). Patients received a median of 8 cycles of treatment. At the Kd56 beginning, the main part of the cohort was 65 years old or older (66.7%). Fifty-one patients received Kd56 at the recommended dosage; dose reduction was required in 23 patients (with a 25% K-dose reduction in one patient from the first administration of Kd56 for the starting characteristics and with a permanent 50% dose reduction for 16 patients from the cycle following the occurrence of an adverse event; for six patients there are not available details on the amount of dose reduction). Based on the immediately preceding line of therapy, patients were considered relapsed (34) or refractory (41). Efficacy and safety profile were assessed throughout.

TABLE 4 Summary of response details to carfilzomib plus dexamethasone treatment

Category[a]	No.	%
ORR	45	60
CRR	3	4
CR	3	4
VGPR	12	16
PR	30	40
MR	7	9.3
SD	7	9.3
PD	12	16
No information	3	1.4

[a]Category of response on the basis of International Myeloma Working Group (IMWG) criteria.
Abbreviations: CR, complete response; CRR, complete response rate; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

3.2 | Efficacy

On data cut off (January 10, 2022), median survival from initial diagnosis was 64 months. Treatment response rate (ORR), including all patients with a partial response or better, was observed to be 60%, with 12 patients who achieved a very good partial response and 3 patients achieving a complete response. More details regarding the responses to treatment are shown in Table 4. Among patients with refractory myeloma (41), 23 achieved PR or better (ORR 56%); in the relapsed myeloma group (made up of the remaining 34 patients) 22 achieved a PR at least (64%). Seven patients out of 11 who harbored a high-risk cytogenetic lesion achieved at least a partial response. At least a partial response was also observed in 49% (37 of 57) patients treated with Kd56 up to the fourth line, and in 44% (8 of 18) of those treated in subsequent lines up to the ninth. PFS in the entire cohort of 75 patients was 10 months; in patients treated with more than one course of therapy (64 patients) was 12 months. Quality of response had an influence on PFS (median PFS in patients who achieved at least VGPR was 16 months, 14 months in patients who achieved PR and 8 months in patient who achieved a MR), as shown

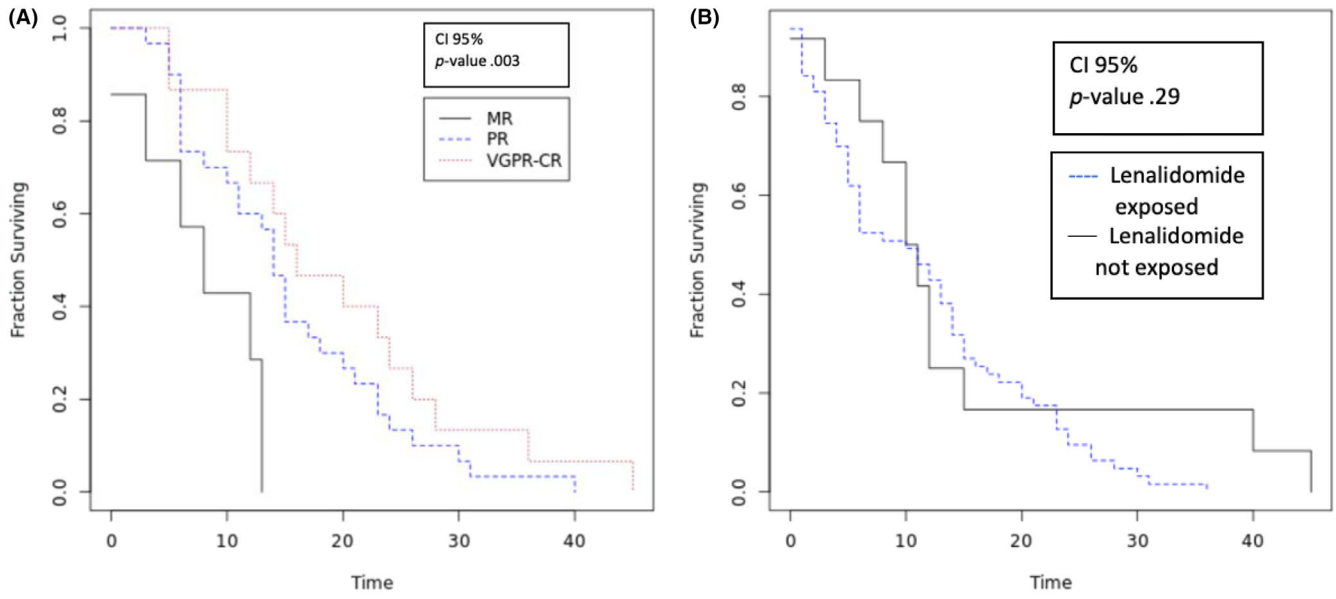

FIGURE 1 Median progression free survival (PFS) subgroup analyses, according to response quality to Kd56 treatment (A) and to previous lenalidomide exposure (B)

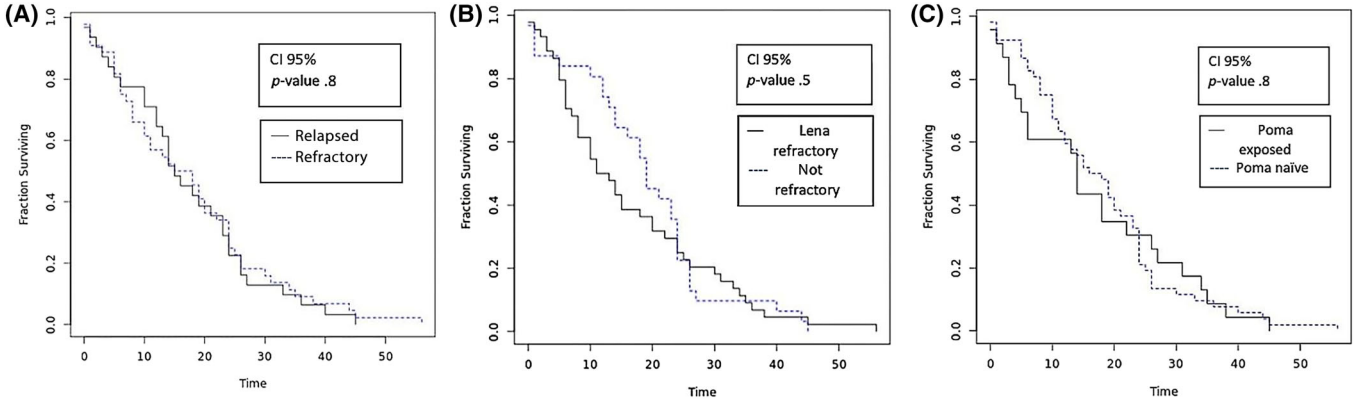

FIGURE 2 Overall survival (OS) subgroup analyses, according to refractory or relapsed status to previous therapy exposure (A), lenalidomide refractoriness (B), pomalidomide exposure (C). Lena, lenalidomide; Poma, pomalidomide

TABLE 5 Summary of the most reported non hematologic adverse events

AEs	G 1–2	G 3–4
Abdominal pain	1	
Acute kidney injury		4
Acute pulmonary edema		1
Bronchial infection	2	
Cholangitis		1
Cholesterol high		1
Conduction disorder	1	
Cough	1	
Creatinine increased	4	1
Diarrhea	4	1
Diastolic dysfunction	1	
Dizziness	1	
Dyspnea	2	
Fever	7	
Flu like symptoms	1	
Generalized edema	4	
Headache	1	
Heart failure	5	2
Hyperglycemia	1	
Hypertension	2	8
Pneumonia (of which COVID19)	2 (1)	4 (1)
Myalgia	1	
Nausea	2	
Otitis	1	
Palpitations	2	
Pericardial effusion		1
Periodontal disease		1
Pharyngitis	1	
Phlebitis	1	
Phlebitis infective	1	
Rash maculo-papular	2	1
Renal colic	1	
Sepsis		2
Shingles	1	
Skin infections	1	
Skin ulceration	1	3
Stroke		1
Supraventricular tachycardia	1	
Syncope		1
Thromboembolic event		1
Urinary tract infections	2	1
Urinary tract obstruction	2	1
Urostomy site bleeding	1	
Wound infections	1	

in Figure 1A. Lenalidomide exposition that occurred in the main part of the cohort, on the other hand, seemed to have no influence of PFS (median PFS in patients exposed to lenalidomide was 10 months), versus 10.5 months in patients not lenalidomide exposed (Figure 1B). In lenalidomide-refractory patients treated for more than 1 cycle of Kd56 (38 out of 44), median PFS was 12 months. In all lenalidomide-refractory patients in the analysis (i.e., including the six patients treated with only 1 cycle), median PFS was 6 months. OS in general cohort of patients was 15 months; cardiovascular toxicity or other reported AEs seemed to not impact the OS (the group of patients with cardiovascular event reported or at least one adverse event reported have median OS of 19 and 18.5 months, respectively). In our population, refractory or relapsed status to the immediately preceding line of therapy, refractoriness to lenalidomide, and exposure to pomalidomide were also found to have no influence on OS (as summarized in Figure 2). In patients treated with more than 1 cycle of therapy, median OS was 19 months.

TABLE 6 Summary of the grade 3 and 4 hematologic adverse events

AEs	G 3–4
Anemia	8
Neutropenia	4
Thrombocytopenia	9
Nos	1

Abbreviation: Nos, not otherwise specified.

3.3 | Adverse events

In the entire cohort of 75 patients, 19 of them experienced at least one infectious episode during treatment, 19 one cardiovascular event and 30 another event of any grade (details of the frequency of events and their severity are given in Table 5). Sixteen patients reported at least one grade 3 or 4 hematological adverse event (details in Table 6). No patient experienced neuropathy. The rate of thromboembolic events was very low. During the treatment, a reduction in the pharmacological dose administered was necessary in 23 patients; however, only in five patients this was dictated by the occurrence of cardiovascular toxicity (in one patient also associated with acute renal injury). In five patients the PI dose was reduced based on persistent and significant alterations in CBC (mainly thrombocytopenia). two patients needed the reduction of the steroid dose only, due to the persistent tampering of glycemic homeostasis. As a precautionary measure, one patient with increased baseline serum troponin received carfilzomib from the 1st cycle at 75% of its planned dose; however, in this patient, a cardiotoxic event never appeared during the treatment, nor a worsening of the laboratory value up to the end of chemotherapy treatment.

4 | DISCUSSION

Multiple Myeloma remains an incurable disease, even though rapidly changing therapeutic paradigms and, above all, new pharmacological molecules, are opening new horizons. However, relapses still represent the natural history of the disease and may appear increasingly difficult to treat because they occur after exposure to a growing number of newer drugs. Kd56 regimen still has a place in recent therapy indications. Despite its widespread use, very limited data are available in the literature on the use of the Kd56 regimen in RRMM from real clinical practice.[19,20] To our knowledge, our study, designed as retro-prospective study, is one of the largest available on this subject to date.

The results we have described, although inferior, are comparable in terms of survival and response rate to those obtained in the registration study or in more recent clinical trials using Kd56 as a control arm (in ENDEAVOR, Kd arm registered mPFS 18.7 months with ORR 77%, while in CANDOR mPFS was 15.8 months and ORR was 75%).[12,21] In particular this was described despite the different characteristics of the patients enrolled, with our population that was undoubtedly unchosen, heavily pretreated with about half of our population having clinically relevant comorbidities and a significant proportion of patients with renal failure, specifically with previous exposition to IMIDS (we described treatment data in this population up to the ninth line of therapy, while both ENDEAVOR and CANDOR enrolled patients who had received a maximum of 1–3 lines of previous therapy) and more elderly (in ENDEAVOR and in CANDOR only 52% and 50% of the population respectively was over 65 years old, compared with 67% in our case series). For these reasons, we consider the results significant. This statement also follows from the evaluation of the lenalidomide-exposed patients, with a median PFS of 10 months, and from data on lenalidomide-refractory patients. For the latter, in fact, the results in terms of PFS are consistent with the findings from randomized clinical trials (lenalidomide-refractory patients treated with Kd at the second or third relapse had a median PFS of 8.8 months[22]) and from real world,[23] in a population considered to be at high risk (for which, even when treated with different regimens, the reported median PFS is about 9 months) and which still represents an unmet medical need to date.[24] We also consider the studied scheme to be valid considering the risk profile. When compared to the registration study, dose reduction for adverse events occurred at a slightly different rate (23% vs. 30%); in no case we reported neuropathy, which was the most expected adverse event for first-generation PI. In addition, we noticed that serious non-hematological events were a minority of all recorded events (32%), with a small part of these related to the carfilzomib cardiotoxicity profile. Furthermore, in our analysis we looked at some issues representing some of the crucial questions of the RRMM, that, despite improvements in the care of patients with myeloma, remain unanswered: the clinical impact of the refractoriness to previous treatment, the clinical impact of the exposure to newer molecules (with particular reference to IMiDs and monoclonal antibodies) and the clinical impact of the refractoriness to lenalidomide, which is increasingly used in the early stages of the disease, and the current lack of guidelines that can concretely steer toward one or the other regimen in lenalidomide-refractory patients.[24] According to the current definition, our population was almost equally divided between relapsed and refractory; furthermore, a very large rate of our patients had already been exposed to lenalidomide and a large proportion also to pomalidomide, with high percentage of refractoriness to these molecules. We were pleasantly impressed that none of these characteristics seemed to have a significant impact on the survival of our population: we considered this to be very important because, on the one hand, the current attitude in the treatment of patients with multiple myeloma is continuous treatment whenever possible, which makes the patients almost always refractory to the drugs with which they are treated, and, on the other hand, because today the appropriate therapeutic sequencing cannot disregard the use of IMiDs. This finding supports the choice of Kd56, which is also a treatment that can be easily administered in an outpatient setting and within a short time frame. We therefore believe that Kd56 has its place in the current scenario especially in cases where lenalidomide is not indicated, for example, due to a history of previous exposure or intolerance. In addition, the dose of carfilzomib used in

Kd56 is higher than that in use with the KRd drug triplet (27 mg/m^2 vs. 56 mg/m^2 in Kd56) and this is important because second-generation PI efficacy is dose-dependent.

Furthermore, by extension, the security data we have collected support the combinations (being investigated in the IKEMA and CANDOR trials) with anti-CD38 monoclonal antibodies, which involve an identical dose of carfilzomib as Kd56 and provided significant enthusiasm for new triplets using the combination of drugs that have potent single-agent activity and low overlapping toxicity.

In the landscape of myeloma, treatments are currently polarized on triplet regimens.[25,26] However, we know that the choice of the right treatment is largely dependent on patient fitness and underlying health status. This study wants to make its contribution to support the use of this regimen for all cases in which the use of multidrug regimens does not appear to be indicated, in view of the fact that nowadays MM relapses occur in patients who are increasingly pretreated with the newest molecules and older, due to the improvement in life expectancy. We underlined the previous exposition to novel agents because the literature is currently lacking on this aspect, especially in patient refractory to IMIDS. Real world studies such as ours support the choice of the clinician, who often faces a very heterogeneous and hard-to-manage population, of which the studies available in literature are often unrepresentative. This study has potential limitations that warrant consideration, including the retrospective design, with the lack of a control arm to confirm the efficacy and the safety of the regimen, and the risk of underestimating adverse events. Given a relatively small sample size these results should be interpreted with caution. Future analyses in the light of patients' clinical status and disease evolution may also be useful and further prospective studies on a larger population would improve the quality of the investigation.

5 | CONCLUSION

These results confirm that the current routine clinical practice use of Kd56 as salvage treatment of RRMM patients, where multidrug regimens cannot be administered, is supported by safety and efficacy data, also for lenalidomide refractory patients and patients already exposed to newer molecules, which represent an unmet clinical need.

AUTHOR CONTRIBUTIONS

Conceptualization: Gabriele Buda; *Investigation and data curation*: Enrico Orciuolo, Francesco Ghio, Irene Attucci, Ludovica Pengue, Maria Livia Del Giudice, Martina Simoncelli, and Raffaella Cassano Cassano; *Writing—original draft preparation*: Maria Livia Del Giudice; *Visualization*: Alessandro Gozzetti, Elisabetta Antonioli, and Gabriele Buda; *Supervision*: Sara Galimberti; *Writing—review and editing*: Gabriele Buda; *Project administration*: Sara Galimberti, Monica Bocchia, and Gabriele Buda. Authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

ORCID

Maria Livia Del Giudice https://orcid.org/0000-0003-4291-8875
Gabriele Buda https://orcid.org/0000-0002-5240-5611

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