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RESEARCH ARTICLE

Real-life effectiveness of carfilzomib in patients with relapsed multiple myeloma receiving treatment in the context of early access: The CARMYN study

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Abstract

The real-life retrospective observational study CARMYN aimed at investigating the long-term efficacy and safety of carfilzomib in combination with dexamethasone and lenalidomide (KRd, 159 patients). These patients (62% in first and 38% in second relapse, median age 62 yo) were treated between 02/2014 and 02/2017. Most had been pre-exposed to bortezomib (98.2%) and to an IMID (75.4%). At the time of collection, 90% had permanently discontinued carfilzomib. Data collection was conducted from January to July 2021 in 27 participating sites, after a median of 39 months follow-up. For patients treated with KRd, an overall response rate of 78.4% translated

in a median progression free survival (PFS) of 24.0 months (95% CI 18.8–27.6) and a median overall survival (OS) of 51.1 months (95% CI 41.3–not reached). Results were poorer but difficult to interpret in the small cohort of Kd recipients. The study is one of the longest real-life studies of carfilzomib treatment in patients in first or second relapse. CARMYN confirmed the real-life long-term efficacy of carfilzomib in combination with lenalidomide and dexamethasone with results similar to those of clinical trials. The KRd regimen is thus an option to consider for late relapses in the current context of MM management.

KEYWORDS
carfilzomib, effectiveness, real-life evidence, refractory relapsing multiple myeloma

1 | INTRODUCTION

The past decade has seen major advances in the management of symptomatic multiple myeloma (MM), notably with the advent of proteasome inhibitors, immunomodulators, and anti-CD38 monoclonal antibodies (mAbs) [1–4]. However, disease recurrence remains inevitable and response rates decrease with each subsequent relapse. The disease ultimately becomes refractory to most treatments, may extend to extramedullary sites and additional cytogenetic abnormalities emerge, negatively impacting the prognosis.

Carfilzomib is a second-generation proteasome inhibitor indicated for the treatment of refractory/relapsed MM (RRMM). In the phase 3 ASPIRE study [5], the combination of carfilzomib with lenalidomide and dexamethasone (KRd) resulted in significantly longer median progression free survival (PFS) and overall survival (OS) than in the control arm of lenalidomide and dexamethasone (Rd), without additional toxicity. In the phase 3 ENDEAVOR trial [6], a regimen of carfilzomib and dexamethasone (Kd) was compared to bortezomib and dexamethasone (Vd). Again, the experimental arm of Kd yielded better PFS and OS, without excess toxicity.

Following these studies, carfilzomib was made available in France via a two-stage "early access" program. From February 2014 to March 2016 a nominative authorization of temporary use (nATU) was available from the French Agency for drug security (ANSM, Agence Nationale de Sécurité du Médicament et des produits de santé). It was followed, from March 2016 to February 2017 by a compassionate program. After that, carfilzomib received marketing authorization. During these periods of compassionate availability, ultimately, more than 1000 patients with RRMM could receive carfilzomib at any stage of relapsing disease.

Here, data from a multicenter retrospective study (CARMYN) are reported, collected from patients who benefited from the French early access programs for a first or a second relapse.

2 | PATIENTS AND METHODS

2.1 | Study design

CARMYN was an observational, retrospective, noninterventional, multicenter study conducted in France for patients with RRMM who received carfilzomib combined with dexamethasone (Kd) or with lenalidomide and dexamethasone (KRd) in real-life conditions during the early access programs.

To be eligible, adult patients had to have received Kd or KRd after one or two lines of chemotherapy (first or second relapse) within the framework of the French nATU or compassionate programs. The decision to treat with Kd or KRd was at the discretion of the medical team. Patient management was performed according to standard of care at each site, making CARMYN a real-life study.

Patients identified using early access lists and chemotherapy software were informed about the collection and computerization of their data for research purpose. Thirty-five sites, both university and general hospitals, agreed to participate. Ultimately, 27 actively enrolled patients in the study.

2.2 | Study objectives

The primary objective of CARMYN was to assess the effectiveness of carfilzomib with PFS as endpoint. PFS was defined as the time from the date of the first dose of carfilzomib to the date of disease progression or death, whichever occurred first. Other endpoint measures included OS, time to next treatment (TTNT), time to treatment discontinuation (TTD), and response rates (RRs). The latter were assessed as a complete response (CR), very good partial response (VGPR), partial response (PR), and stable disease (SD). The overall response rate (ORR) was calculated by combining CR, VGPR, and PR, as assessed by investigators. Safety objectives included the occurrence of treatment-related adverse events (AEs) documented in medical files, including AEs and serious AEs (SAEs).

2.3 | Data collection

Medical chart data were collected from the initiation of carfilzomib therapy until death or the day of data collection, to assess survivals. Subsequent therapies were also documented. Whenever available, Eastern Cooperative Oncology Group performance status (ECOG) and International Staging System (ISS) were also recorded.

Data collection was conducted from January to July 2021, yielding a median follow-up of 39 months. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, of the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practice, and in compliance with the General Data Protection Regulation. The protocol was approved by the Local Ethical Committee of the General Hospital of Le Mans on August 20, 2020.

2.4 | Statistical analyses

Baseline patient characteristics, responses, and safety data are summarized using descriptive statistics. Qualitative data are presented as numbers and percentages. Quantitative data are presented as mean and standard deviation or median and interquartile range. Missing data were not replaced.

Time-to-event analyses were used to estimate TTD, TTNT, PFS, and OS, using the Kaplan–Meier method. The Greenwood formula was used to estimate 95% confidence intervals (CIs). Patients still alive with no disease progression at the end of the study were censored at the date of last assessment. For TTNT, patients were also censored at the date of death. Patients without assessment of response or progression at the database lock were excluded from analyses that used these data.

ORR, TTD, TTNT, PFS, and OS were assessed for the KRd population, according to lines of treatment (L2 or L3), age (<75- or ≥75-year-old) and previous autologous stem cell transplantation (ASCT).

It was expected to collect data from 175 KRd patients. Results of the final analysis are presented.

Statistical analyses were conducted using statistical analysis system (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

3.1 | Patients

A total of 171 patients initiated a carfilzomib-based regimen for a first or second relapse at participating sites during the early access program. Among them, only 12 received Kd, while 159 were treated with KRd. Characteristics of both groups are reported in Table 1. Half (52%) of the patients were men, their median age was 62 years, 47.2% had comorbidities, and 13% had an ECOG of 2 or more. Most patients were less than 75-year-old. At baseline, the median time since MM diagnosis was 27 months and most patients (66.7%) had only received one line of prior therapy. In these previous lines, nearly all patients had been exposed to bortezomib (98.2%). Thalidomide or lenalidomide had also been prescribed to 75.4% of the patients. Only two patients had received anti-CD38 mAb, consistent with the period of inclusion.

Only the larger group of patients treated with KRd is detailed below.

TABLE 1 Patient demographics and disease characteristics.

	Kd group (*N* = 12)	KRd group (*N* = 159)
Median age at treatment initiation years (IQR)	62.5 (59–68)	62.0 (56–59)
Male sex, *n* (%)	8 (66.7)	81 (50.0)
Comorbidities[a], *n* (%)	9 (75.0)	75 (47.2)
Median time since diagnosis, months	*n* = 12	*n* = 155
	27.0	34.5
ECOG at KRd initiation, *n* (%)	*n* = 10	*n* = 138
0	5 (50.0)	56 (40.6)
1	4 (40.0)	64 (46.4)
≥2	1 (10.0)	18 (13.0)
M protein type (*n*%)		
IgG	8 (66.7)	97 (61.0)
IgA	3 (25.0)	29 (18.2)
None	1 (8.3)	22 (13.8)
Other	0 (0.0)	6 (3.7)
Not determined	0 (0.0)	5 (3.1)
ISS disease staging at diagnosis, *n* (%)	*n* = 8	*n* = 93
Stage I	0 (0)	21 (22.6)
Stage II	4 (50)	34 (36.6)
Stage III	4 (50)	38 (40.8)
Median clearance, mL/min	*n* = 10	*n* = 115
	71.8	80.8
Number of previous lines, *n* (%)	*n* = 12	*n* = 159
1	0 (0)	106 (66.7)
2	12 (100)	53 (33.3)
Previous therapy, *n* (%)	*n* = 12	*n* = 159
Bortezomib	11 (91.7)	157 (98.7)
Lenalidomide	11 (91.7)	51 (32.1)
Pomalidomide	2 (16.7)	9 (5.7)
Thalidomide	4 (33.3)	89 (56.0)
Anti-CD38 mAb	0 (0.0)	2 (1.3)
Alkylating agents	11 (917)	139 (87.4)
Previous ACST, *n* (%)	6 (50.0)	92 (57.9)

Abbreviation: IQR, interquartile range.

[a]Including diabetes, arterial hypertension, moderate to end-stage renal failure, other tumors, and other relevant comorbidities.

3.2 | KRd therapy

The treatment schedule planned twelve cycles of 3 weeks comprising two doses of carfilzomib per week (20 mg/m^2 cycle 1, then 27 mg/m^2) associated with 40 mg dexamethasone once per week and lenalidomide 25 mg from day (d) 1 to d21. Table 2 details the dose modifications. Very few patients had temporary interruptions (*n* = 10).

At the time of data collection, 142 of 159 patients had permanently discontinued treatment with carfilzomib. The reason was known

TABLE 2 Treatment schedules and posology changes.

	KRd patients, *N* = 159 N (%)
Line of treatment	
Second line	106 (66.7)
Third line	53 (33.3)
Carfilzomib	
Planned schedule 20 then 40 mg/m^2, twice weekly	112 (70.9)
56 mg/m^2 after cycle 1	39 (24.7)
Other	7 (4.4%
Lenalidomide	
25 mg/d, d1-21	140 (88.1)
Other (lower dosage)	19 (11.9)
Dexamethasone	
40 mg/d, d1,8,15,22	128 (81.0)
20 mg/d, d 1–2, 8–9, 15–16, 22–23	22 (13.9)
Other (lower dosage)	8 (5.1)

for 125 of them and it was mostly disease progression (60.8%) or AEs (17.6%). For 17.6% of the patients, the planned treatment duration had been achieved. Withdrawal and deaths were the reason for treatment cessation in six and eight cases respectively. The median estimated treatment duration was 12.7 months (95% CI 10.5–16.2) (Table 3).

The median TTNT was 23.8 months (95% CI 19.7–27.4). The most frequently prescribed next treatments were pomalidomide-based combinations (58.5% of L3 post-KRd L2, 52.8% of L4 post-KRd L3) or anti-CD38 mAb (44.3% of L3 post-KRd L2, 44.4% of L4 post-KRd L3).

Responses were available for 125 patients. The ORR was 78.4% for this population. None of the patients reached CR, but there were 59.2% of VGPR and 19.2% PR, while five patients remained in SD and 22 progressed.

The median PFS was 24.0 months (95% CI 18.8–27.6). There was no difference in PFS when the cohort was stratified by line of treatment (Figure 1), age (75 yo threshold) nor previous ASCT. Overall, 88 deaths were recorded, mostly due to progression of the MM. The median OS was 51.1 months (95% CI 41.3–not reached). No difference either was linked to the line of treatment (Figure 2), age nor previous ASCT.

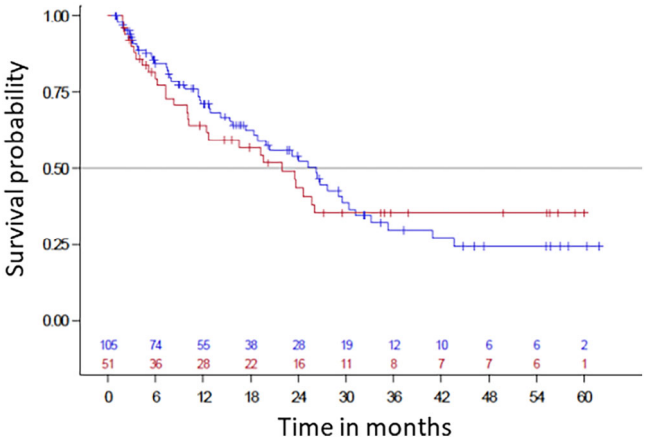

FIGURE 1 Progression free survival (PFS). Patients treated in second (blue) or third (red) line of therapy.

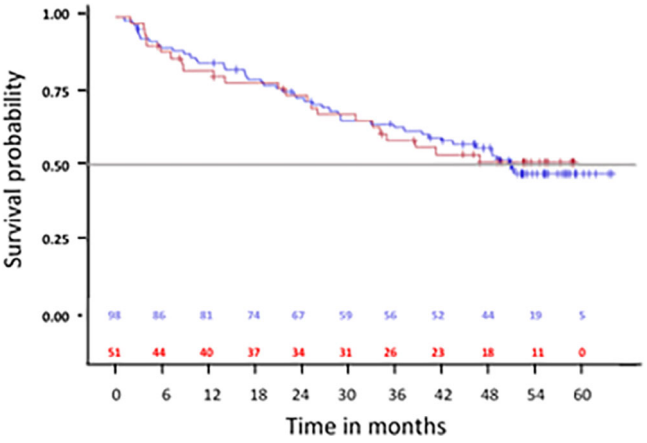

FIGURE 2 Overall survival (OS). Patients treated in second (blue) or third (red) line of therapy.

3.3 | Safety

Overall, 31 of 159 patients (19.5%) had at least one AE of any grade with a median of 1 (range 1–3). This accounted for 46 AEs in total. For 6 of these patients (3.8%), the AE was reported as serious in the medical chart. The most frequently reported AEs were hematological (thrombocytopenia, neutropenia, anemia, cytopenia), digestive (nausea, diarrhea), and general (fatigue, asthenia). One case of heart failure was considered SAE.

TABLE 3 Survival parameters.

	Median months, (95%CI)	24 months % (95%CI)	48 months % (95%CI)
Duration of treatment (TTD)	12.7 (10.5–16.2)	29.1 (21.9–36.4)	9.1 (4.4–13.9)
Time to next treatment (TTNT)	23.8 (19.7–27.4)	47.1 (38.8–55.4)	24.9 (17.4–32.3)
Progression free survival (PFS)	24.0 (18.8–27.6)	49.1 (39.9–58.3)	28.6 (19.0–38.3)
Overall survival (OS)	51.1 (41.3–NR)	73 (65.7–80.2)	54.3 (45.9–62.6)

Abbreviation: NR, not reached.

4 | DISCUSSION

The retrospective CARMYN study presented here confirmed the long-term effectiveness of a KRd regimen for RRMM patients in 2nd or 3rd line, in real-life settings.

The 78.4% ORR rate and 59.2% of VGPR are consistent with data reported in the literature ranging for the latter between 50 and 70% [5, 7–9]. No patient reached CR, which is probably explained by the routine practice since there is no need to distinguish VGPR and CR for treatment adaptation in real life and bone marrow aspiration is seldom performed. An interesting feature is the rather long TNTT, longer than the median treatment duration, indicating that some patients survive off therapy after a KRd regimen.

The 24-month median PFS observed is in the same range as in similar retrospective cohorts [7–9] and marginally shorter than the 26.3 months of the ASPIRE trial [5]. These results were not impacted by the line of therapy, age nor previous ASCT. The long follow-up available resulted in an estimated PFS rate at 48 months of 28.6%.

The median OS of 51.1 months observed here in the CARMYN study is also quite remarkable, 79 patients being still alive and the upper limit of 95% CI not reached. Of note, this real-life study shows similar median OS than the ASPIRE study (48.3 months) [5]. Comparison with other reports from the literature confirms the better outcome of KRd patients in CARMYN, or cannot be performed because of shorter follow-ups.

These good results could be explained by the differences in the characteristics of the populations treated with KRd, but globally, patients of the CARMYN study are similar to those of the pivotal study in terms of age, ECOG and renal function. Less patients had initiated treatment after the first relapse in the ASPIRE study but no difference in outcome was related to the line of treatment in CARMYN. In comparable real-life studies, the differences were a longer time since diagnosis (3–5 years vs. almost 3 years here) and slightly more patients with previous ACST or in third line of treatment. Yet, again, these parameters did not affect outcomes in CARMYN. The ISS stage was predominantly II or III, which suggests that CARMYN concerned predominantly younger patients with an intermediate or poor prognosis.

The limitations of CARMYN are those associated with retrospective observational studies. The selection of centers and patients may have limited the representativeness of the sample, although it is a balanced mixture of University and general hospitals. Patient selection biases also were minimized because eligible patients were identified using comprehensive and standardized data sources. These patients received carfilzomib in the framework of compassionate programs, and physicians may have selected specific at-risk patient profiles that would benefit from these programs. However, patient characteristics were similar to those reported in published studies. Estimates of progression or response to treatment were based on investigator judgment and may not have been as robust as those in clinical trials. This nevertheless seems unlikely considering that the results of this study were close to those of ASPIRE and other cohort studies.

CARMYN is one of the longest follow-up real-life studies of carfilzomib in L2 and L3 patients, interestingly yielding similar outcomes as clinical trials. Of note, very little AEs and SAEs were reported, confirming the safety of the KRd combination. Although new treatment schedules keep appearing for MM patients, this study brings more evidence of the feasibility and safety of this salvage therapy that can still be considered in real life for relapsing patients, yet probably after more previous lines of treatment.

AUTHOR CONTRIBUTIONS

KL, XL, CT, MH, AP, SS, RLC, AT, DC, SD, OB, RB, ACR, OD, AP, as investigators, included and followed patients. KL, AP, OD, NT participated in the review and interpretation of analyses and the exploitation of results. KL, OD, AP, NT, RG, CJ, and ER participated in protocol design, analyses review and interpretation, and results exploitation. All authors approved the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

KL received honoraria from AbbVie, AstraZeneca, Beigene, Iqone, Janssen, Novartis and Takeda. XL is a consultant and received honoraria from Amgen, Merck, BMS, GSK, Janssen, Oncopeptide, Takeda, Roche, Novartis, AbbVie, Sanofi, Gilead, Pfizer, Harpoon Therapeutic, Regeneron and Iteos. CT received adboards and honoraria from AMGEN. RLC received honoraria from Abbvie, Gilead, Takeda and Janssen.DC received honoraria from Roche. AP received honoraria from Abbvie, Amgen, BMS, Janssen, Pfizer, Sanofi & Takeda. The other authors declare no financial interests.

DATA AVAILABILITY STATEMENT

Data from this study can be made available upon reasonable request to the corresponding author.

ETHICS STATEMENT

As mentioned in the manuscript, the CARMYN study was approved by the Ethical Committee of the General Hospital of Le Mans.

PATIENT CONSENT STATEMENT

All patients provided informed consent when enrolled in the compassionate program.

CLINICAL TRIAL REGISTRATION

CARMYN was a retrospective analysis of patients included in the compassionate program of French Health Authorities, which was not a trial.

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