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RESEARCH

Real-world evidence of Carfilzomib, Lenalidomide and Dexamethasone (KRD) Scheme in patients with relapsed / refractory multiple myeloma

Antoni Garcia-Guiñon[1] · Paola Andrea Charry[2] · María Jimenez[3] · Josep Sarra[4] · Izarbe Delgado[1] · Laura Segura de la Torre[5] · Marta Santaliestra[6] · Marta Garcia-Pintos[7] · Yolanda Gonzalez[8] · Alicia Senin[9] · Cristina Motlló[10] · Eugènia Abella[11] · Elena Cabezudo[12] · Miquel Granell[13] · Esther Sancho[14] · María José Herranz[15] · Yasmina Seres[1] · Mercedes Gironella[3] · Juan Alfons Soler[5] · Josep Maria Marti-Tutusaus[6] · Ran Ben Azaiz[11] · Carlos Fernandez de Larrea[2]

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Abstract

Carfilzomib, lenalidomide and dexamethasone (KRd) is still a widely used treatment option for patients with relapsed / refractory multiple myeloma (RRMM). However, there is limited real-world evidence. Here we evaluated the efficacy and safety of KRd in patients with RRMM treated following the standard clinical practice of the hospitals in the Catalan region. This was a retrospective, observational study. The objective response rate (ORR) according to IMWG criteria was the primary endpoint. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). The study planned to include at least 100–150 patients. In total 194 patients were included. Median age was 64 years (range: 40–88) and 56% were male. All patients had received bortezomib. Additionally, 89 patients (46%) had received thalidomide and 29 (15%) lenalidomide. The ORR was 73% (95% CI: 66–79), with 72 patients (37%) having ≥ CR. The ORR was influenced by ISS score, number of previous treatments and exposure to lenalidomide. The median PFS was 26 months and 2-years OS rate 70%. The ISS stage and LDH levels were independent prognostic factors of survival. In conclusion, the KRd scheme led to a good effectiveness comparable safety profile to the phase III clinical trial in patients with RRMM.

Keywords Real-world · Carfilzomib, lenalidomide and dexamethasone · Relapsed/refractory multiple myeloma

✉ Antoni Garcia-Guiñon
agarciag.lleida.ics@gencat.cat

[1] Hematology Department, Hospital Universitari Arnau de Vilanova de Lleida, Av. Rovira Roure, Lleida 80 | 25198, Spain

[2] Hematology Department, Hospital Clínic and IDIBAPS, Universitat de Barcelona, Barcelona, Spain

[3] Hematology Department, Hospital Universitari Vall D'hebron, Barcelona, Spain

[4] Hematology Department, Hospital Universitari Joan XXIII- ICO Camp de Tarragona, Tarragona, Spain

[5] Hematology Department, Hospital Universitari Parc Taulí, Sabadell, Spain

[6] Hematology Department, Hospital Universitari Mútua Terrassa, Terrassa, Spain

[7] Hematology Department, Consorci Sanitari Terrassa, Terrassa, Spain

[8] Hematology Department, Hospital Universitari Josep Trueta-ICO Girona, Girona, Spain

[9] Hematology Department, Hospital Universitari Germans Trias I Pujol-ICO Can Ruti, Badalona, Spain

[10] Hematology Department, Hospital Sant Joan de Déu – Fundació Althaia, Manresa, Spain

[11] Hematology Department, Hospital del Mar, Barcelona, Spain

[12] Hematology Department, Hospital St Joan Despi-Moises Broggi-ICO-H, Sant Joan Despi, Spain

[13] Hematology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[14] Hematology Department, Hospital General de Granollers, Granollers, Spain

[15] Hematology Department, Hospital del Vendrell - Xarxa Santa Tecla, Tarragona, Spain

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy with an incidence in Europe of 4.5–6 cases per 100.000 people [1, 2]. The introduction of immunomodulatory drugs has substantially improved survival outcomes in recent years [3–11]. However, a significant proportion of patients still experience relapse or are refractory to front-line treatment. In patients with relapsed / refractory MM (RRMM), the second-line therapy should include a lenalidomide plus dexamethasone (Rd)-based regimen [12–14].

Carfilzomib, a second-in-class proteasome inhibitor in combination with lenalidomide and dexamethasone (KRd) or dexamethasone alone (Kd). are common options for patients with RRMM showing sensitivity to lenalidomide or bortezomib or those relapsing to daratumumab. The use of KRd is sustained by a higher overall response rate (ORR), 87.1% v 66.7%, and prolonged progression-free survival (PFS), 26.1 vs. 16.6 months, over Rd in the phase III ASPIRE trial, which also resulted in a benefit in overall survival (OS) [15, 16]. In the real world, retrospective series including small cohorts confirmed the feasibility and efficacy of KRd in populations of specific geographic locations, with median OS of approximately 30 months [19–22].

The purpose of this study was to evaluate the efficacy and safety of KRd in patients with RRMM treated following the standard clinical practice of the hospitals in the Catalan region (Spain).

Methods

Study design and patients

This was a retrospective, multicenter, observational study sponsored by the Grup per l'estudi del mieloma múltiple i l'amiloïdosi de Catalunya (GEMMAC) and performed at 15 centers in the catalan region (Spain; Supplementary Table 1). The study sought to describe the efficacy and safety of the KRd scheme in patients with RRMM treated according to the standard clinical practice.

Eligible patients were ≥ 18 years of age, male or female, with a diagnosis of MM, and at least one prior treatment with a documented disease progression as defined by IMWG criteria [23]. The KRd scheme was assigned and administered according to the standard clinical practice. Patients who received KRd in the context of a clinical trial or those who were treatment-naive before KRd were not eligible.

The study was conducted in accordance with the principles of the declaration of Helsinki, the International Council for Harmonisation Guidelines for Good Clinical Practice and the local regulations. The study protocol was approved by the institutional review board (IRB) of Hospital Arnau de Vilanova on May 8th, 2020 (Ref: CEIC 2256; 6/2020) and all participating sites. All alive patients provided written informed consent. The data from dead patients was collected with the exemption of informed consent, which was previously approved by the IRB to avoid a bias in the sample consequence of excluding patients with worse prognosis who died before study initiation.

Objectives

The primary objective was the ORR of the KRd scheme according to IMWG criteria, including all patients who achieve a stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) [23]. Secondary objectives included: to describe the demographic parameters and baseline characteristics of patients with RRMM treated with KRd; to analyze the PFS to KRd and OS of the population; to analyze the effectiveness of the treatment in specific patient groups, including those with extramedullary disease and renal impairment; and to analyze the safety profile associated with the KRd scheme. The PFS was defined as the time from the first dose of KRd to progression or death, whichever was first. The OS was defined as the time from the first dose of KRd to death.

Assessments

All the information was collected retrospectively from the patient medical records in the eCRF. The study recorded sociodemographic data, including sex, age and data of diagnosis; pathological characteristics and pathological history, including hypertension, cardiopathies, diabetes mellitus (DM); clinical parameters including, hemoglobin, creatinine, albumin, B2-microglobulin, lactate dehydrogenase (LDH) and cytogenetic risk; and previous treatments with detail of the scheme, start date, end date and best response obtained; KRd treatment-associated endpoints, including the scheme used, treatment start and end dates, best response obtained and date of response, progression date, dose modifications; and the last status of the patient, including last contact date, and date and cause of death, if applicable.

The disease was staged according to the International Staging System (ISS) and the revised version (R-ISS) [24]. The cytogenetic risk evaluation by fluorescence in situ hybridization (FISH) analysis was collected and, for the purpose of this study, high risk profile was defined as the presence of one of the following cytogenetic abnormalities:

del17, t(4;14) or t(14,16). Extramedullary disease was defined as the presence of plasmacytoma.

The response to treatment was measured taking into consideration the quantification of the monoclonal protein (serum and urine protein electrophoresis and immunofixation, serum free light chain), bone marrow examination, evaluation of extramedullary plasmacytomas, and radiological imaging assessment.

Safety assessments included the collection of all adverse events (AEs) causally related to KRd treatment regardless of their severity and paying special attention to AEs classically attributed to KRd such as hypertension, cardiotoxicity, gastrointestinal events, hepatotoxicity, hematologic toxicity, peripheral neuropathy, renal toxicity, thromboembolic events, and infections.

Statistical analysis

No formal sample size calculations were performed. It was estimated that the inclusion of approximately 100–150 patients was feasible based on the prevalence of RRMM [25]. To prevent selection bias, patients were consecutively included.

The efficacy and safety were evaluated in all enrolled patients (full analysis set). Descriptive statistics were used for baseline characteristics, efficacy and safety outcomes. Exact two-sided 95% CIs or full range (i.e. min-max) were included as applicable. Time-to-event endpoints were summarized using the Kaplan–Meier method and Cox regression to obtain HR and CIs. Patients without documented progression or death were censored at the last date of tumor evaluation for PFS assessment and at the last date of follow-up for OS.

All statistical tests were considered two-tailed, and results with $p < 0.05$ were considered statistically significant. All statistical analyses were performed using the R software (Version 4.3.1 [2023]. RStudio: Integrated Development Environment for R. Posit Software, PBC, Boston, MA, US). Figures and tables were generated using RStudio (Version 1.2.5033 2009–2019 RStudio, Inc., Boston, MA, US).

Table 1 Patient characteristics

Characteristic		*N* = 194
Median age; years (min - max)		64 (40–88)
Sex; *n* (%)	Male	109 (56)
	Female	85 (44)
Disease stage ISS; *n* (%)	Stage I	57 (29)
	Stage II	64 (33)
	Stage III	64 (33)
	Unknown	9 (5)
Disease stage R-ISS; *n* (%)	Stage I	22 (11)
	Stage II	95 (49)
	Stage III	30 (15)
	Unknown	47 (24.2)
Cytogenetic risk; *n* (%)	Standard risk	75 (39)
	High risk *	39 (20)
	Not evaluated	80 (41)
Previous treatment lines; *n* (%)	1	153 (79)
	2	27 (14)
	≥ 3	14 (7)
Previous treatment type; *n* (%) [#]	Proteasome inhibitor	194 (100)
	Thalidomide	89 (46)
	Lenalidomide	29 (15)
	Monoclonal antibody	12 (6)
Previous ASCT; *n* (%)	Yes	79 (41)
	No	115 (59)
Extramedullary disease; *n* (%)	Yes	55 (28)
	No	139 (72)
Creatinine clearance; *n* (%)	≥ 60 ml/min/1,73m^2	150 (77)
	< 60 ml/min/1,73m^2	41 (22)
	Not evaluated	3 (1)
Hemoglobin; *n* (%)	≥ 10 g/dL	154 (79)
	< 10 g/dL	36 (19)
	Not evaluated	3 (2)
Lactate dehydrogenase; *n* (%)	Normal	123 (63)
	> ULN	47 (24)
	Not evaluated	24 (13)

ASCT autologous stem cell transplant, *CrCl* creatinine clearance, *IMID* Immunomodulatory drug, *ISS* International Staging System, *R* lenalidomide treatment, *R-ISS* Revised International Staging System, *T* Thalidomide treatment, *ULN* upper limit normal

*del17, t(4;14) or t(14,16)

[#]patients may have received more than one treatment option, either as single agent or combination

Results

Patient characteristics

A total of 194 patients diagnosed with MM between January 2007 and June 2022 were included. The median age was 62 years (full range: 40–88), 56% were male and 33% had stage III disease according to the ISS (Table 1). The cytogenetic risk was assessed in 114 patients (58.8%), with 39 patients (20%) having high risk. All patients received bortezomib prior to the start of the KRd scheme. Additionally, 89 patients (46%) had received thalidomide and 29 (15%) lenalidomide. The median time from initial diagnosis to the start of the KRd scheme was 33 months (full range: 1–129). Seventy-nine patients (41%) received a previous ASCT.

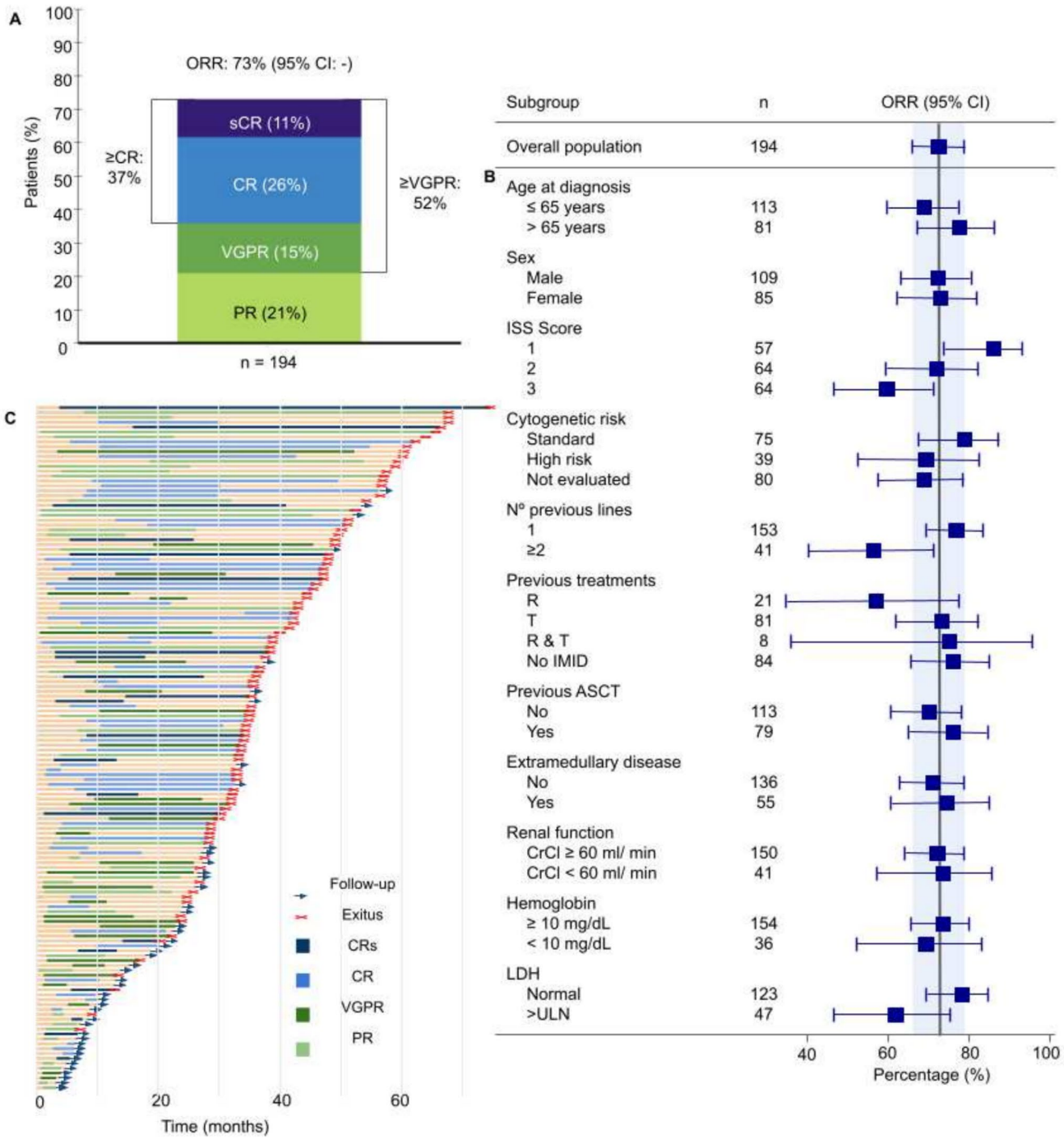

Fig. 1 Response rates to KRd. **A** Stacked bar graph illustrating the rate of sCR, CR, VGPR and PR in 194 patients included. **B** Forest plot illustrating with blue squares the ORR in patients subgroups. Whiskers indicate 95% CIs. **C** Swimmer plot showing responses over time in 141 patients who had a response to KRd scheme. Abbreviations: CR: complete response; CrCl: creatinine clearance; IMID: Immunomodulatory drug; ISS: International Staging System; LDH: lactate dehydrogenase; ORR: objective response rate; PR: partial response; R: lenalidomide treatment; sCR: stringent complete response; T: Thalidomide treatment; VGPR: very good partial response

Efficacy

The KRd scheme showed an ORR of 73% (95% CI: 66–79) (Fig. 1a). A CR or better (≥ CR) was achieved in 72 patients (37%), and a VGPR or better in 101 (52%). ORRs were higher in patients with ISS stage 1 (86%, 95% CI: 73–93) (Fig. 1b). Response rates were maintained across subgroups, including elderly, patients with high

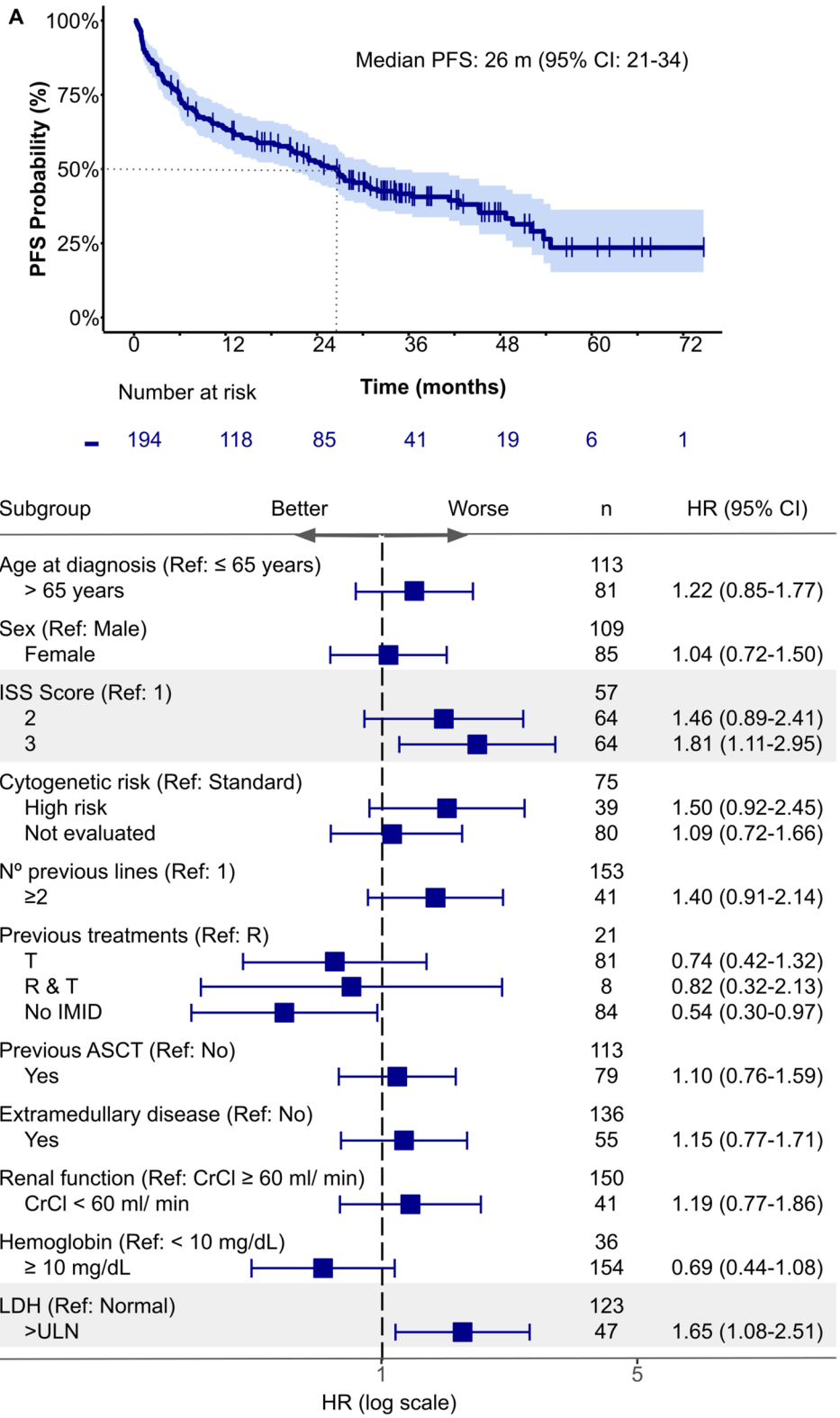

Fig. 2 PFS with KRd scheme in the real-world. **A** PFS in the overall population (blue line) with its 95% CI (blue shaded area). The dotted line indicates the 50% PFS probability. **B** Forest plot showing the correlation of baseline patients characteristics and PFS. Blue squares represent the hazard ratio of the subgroup with respect to the reference (ref) subgroup and whiskers indicate 95% CIs. Characteristics and values with white background correspond to the univariable analysis. The characteristics which show highest correlation with PFS in the univariable preliminary analysis are used to construct a multivariable model (shown with a grey background within the forest plot). Abbreviations: ASCT: autologous stem cell transplant; CrCl: creatinine clearance; IMID: Immunomodulatory drug; ISS: International Staging System; LDH: lactate dehydrogenase; PFS: progression-free survival; R: lenalidomide treatment; Ref: reference group; T: Thalidomide treatment

cytogenetic risk, presence of extramedullary disease, renal impairment or hemoglobin levels. Previous progression to R or receiving ≥ 2 previous lines correlated with worse response rates, with an ORR of 57% (95% CI: 34–77) and 56% (95% CI: 40–71), respectively. The best responses were achieved after a median time of 6 months (95% CI: 5–8) and maintained for a median of 19 months (95% CI: 15–24) (Fig. 1c).

After a median follow-up of 32 months (full range: 1–75), the median PFS was 26 months (95% CI: 21–34), with a 12-m PFS rate of 64% (95% CI 57–71) (Fig. 2a). The PFS was maintained for patients with 1 or 2 previous treatment lines, showing a median PFS of 27 months (95% CI: 22–32) and 25 months (95% CI: 10–40), respectively. Patients with ≥ 3 prior lines showed a limited PFS with a median of 4 months (95% CI: 0–8). The ISS score (HR = 1,81, 95% CI:

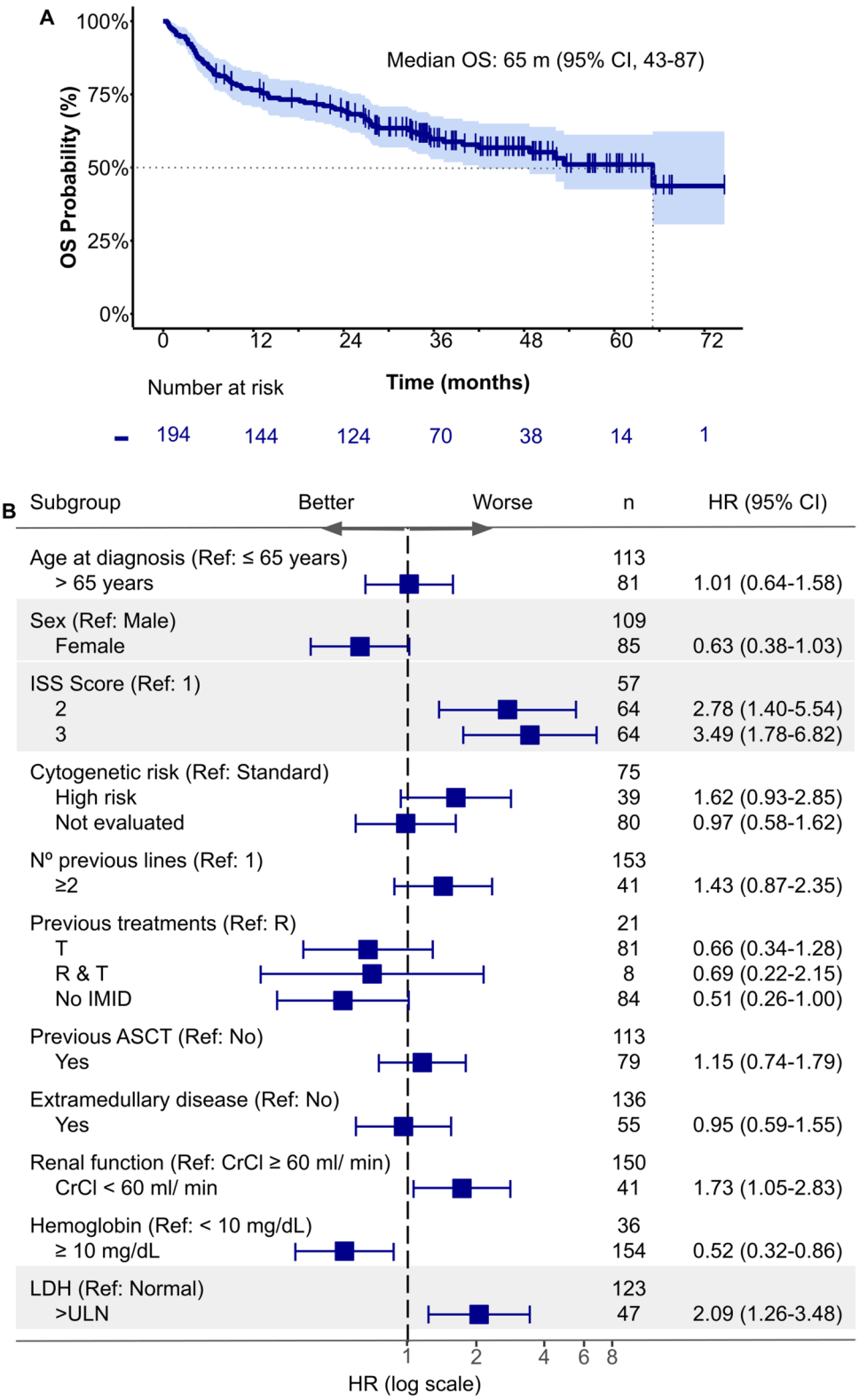

Fig. 3 OS with KRd scheme in the real-world. **A** OS in the overall population (blue line) with its 95% CI (blue shaded area). The dotted line indicates the 50% OS probability. **B** Forest plot showing the correlation of baseline patients characteristics and OS. Blue squares represent the hazard ratio of the subgroup with respect to the reference (ref) subgroup and whiskers indicate 95% CIs. Characteristics and values with white background correspond to the univariable analysis. The characteristics which show highest correlation with OS in the univariable preliminary analysis are used to construct a multivariable model (shown with a grey background within the forest plot). Abbreviations: ASCT: autologous stem cell transplant; CrCl: creatinine clearance; IMID: Immunomodulatory drug; ISS: International Staging System; LDH: lactate dehydrogenase; OS: overall survival; R: lenalidomide treatment; Ref: reference group; T: Thalidomide treatment

1.81–2.95 for stage 1 vs. 3) and LDH levels (HR = 1,65, 95% CI: 1.08–2.51) showed a significant correlation with the probability of PD or death at multivariable analysis (Fig. 2b and supplementary Figs. 1,2,3,4).

The 12-m and 24-m OS rates were 77% (95% CI: 71–83) and 70% (95% CI: 63–76), respectively (Fig. 3a). The median OS was 65 months (95% CI, 43–87). In total, 77 patients (39%) died throughout the study period; 62 patients (32%) due to PD, 4 patients (2%) due to infection and 1 patient developed pulmonary neoplasm. Survival was independent of age, cytogenetic risk, presence of extramedullary disease, prior treatments or ASCT. In the multivariable analysis, ISS staging (HR = 3.49, 95% CI: 1.78–6.82 for stage 1 vs. 3) and LDH levels (HR = 2.09 95% CI: 1.26–3.48) were independent prognostic factors of survival (Fig. 3b and supplementary Figs. 1, 2, 3, 4).

KRd with stem cell transplantation (SCT) intention

The KRd scheme was administered prior to SCT in 44 patients (23%). The ORR in this patient subgroup was 89% (95% CI: 76–95). A CR or better (≥ CR) was achieved in 13 patients (30%), and a VGPR or better in 18 (41%). The median PFS was 52 months (95% CI: 49-NR) and the 24-m OS rate was 93% (95% CI: 86–100) (Supplementary Fig. 5).

Safety

Treatment-emergent AEs were reported in 137 patients (71%), and grade ≥ 3 in 73 (38%). Hematologic toxicities were the most common events, including anemia (35%), leukopenia (33%), and thrombocytopenia (29%), being most of them grade ≥ 3 (29%, 22% and 22%, respectively) (Fig. 4 and supplementary Table 2). Two patients died due to hematologic toxicities, due to thrombopenia and leukopenia. Infections were reported in 59 patients (31%), 18% being grade ≥ 3 and only one having a fatal outcome. Renal toxicities with grade 3–4 consisted of 2 patients who experienced acute kidney failure, 2 with thrombotic microangiopathy and 1 with nephritis. Peripheral neuropathy was reported in 9 patients (5%). The frequency of gastrointestinal events was low, including diarrhea (9%), and the incidence of dyspnea, pyrexia and peripheral edema was below 3%.

At data cutoff, 158 patients (81%) had discontinued the treatment with KRd, 71 patients (37%) due to disease progression, 43 (22%) underwent subsequent ASCT or alloSCT, 32 (16%) due to toxicities, 7 (4%) due to death, and 5 (3%) due to the appearance of secondary malignancies. The most frequent toxicities leading to treatment discontinuation were hematological (4%), cardiac (4%), cutaneous (3%), infectious (3%), renal (1%) and vascular (1%).

Discussion

The GEMMAC-KRd study is the first to report the use of KRd in the real-world population in Spain. The KRd scheme achieved an outstanding effectiveness with an ORR of 73% and 30% of patients having a CR or better. However, the ORR was below the ASPIRE trial (87.1%) [16]

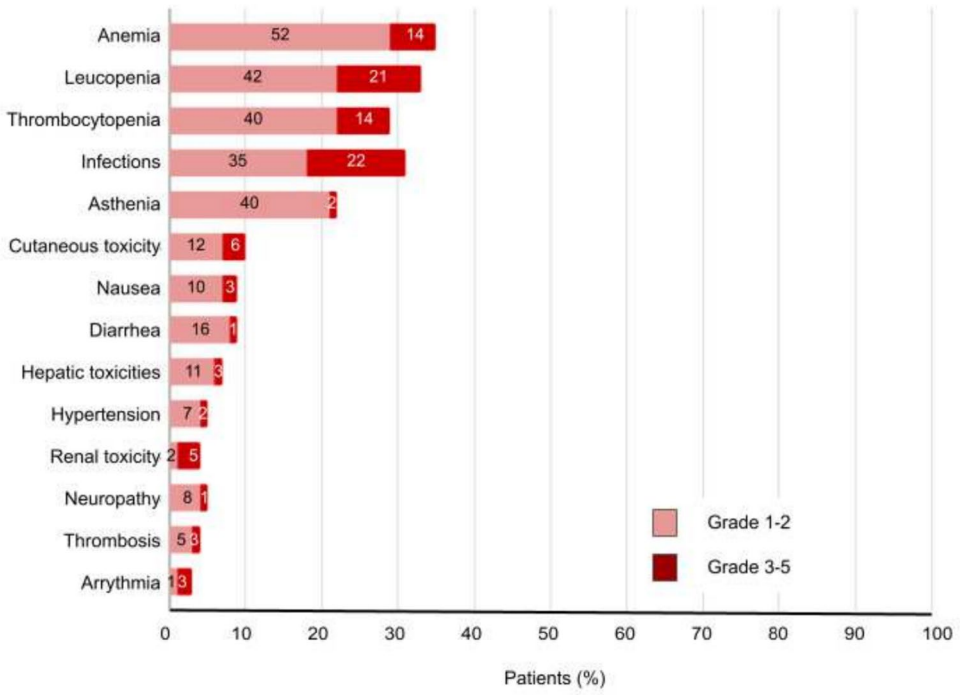

Fig. 4 Treatment-emergent adverse events with KRd in the real-world. The bar shows the percentage of patients with events grade 1-2 (light red) and grade 3-5 (dark red). The numbers within the bars show the number of patients who experienced the corresponding adverse event

(supplementary Table 3 contains literature review with main outcomes with KRd). This may be partially explained by the higher rate of patients with high cytogenetic risk (20% vs. 12.1%), and the fact that all patients in our cohort had progressed to V and a substantial number had progressed also to R. For instance, previous R was associated with a negative impact on ORR, similar to patients with V resistance [19–22]. The KRd scheme is still a good option for patients with renal impairment in our cohort, achieving an ORR rate of 73%. The ORR was also independent of previous ASCT, sex or age. The population of patients who received KRd in the real-world in the Catalan region had a comparable age when compared to the ASPIRE trial [16]. Only 21% of patients received > 1 treatment lines compared to 53.3% in the clinical trial, which may be suggestive of better prognosis.

The survival outcomes were in line with the previous experience with KRd scheme, with a median PFS of 26 months and 2-years OS rate of 70% [15, 16]. Only combination schemes including daratumumab and elotuzumab have been associated with an equivalent survival outcome [12, 13]. Therefore, KRd is still a very valid second-line treatment. The ISS stage and LDH levels were the main independent prognostic factors of survival, highlighting the relevance of their monitoring for patient risk stratification and therapeutic decision making. Females were also correlated with better OS at univariable analysis, in line with a broad epidemiologic study addressing sex-based differences in patients with MM [26]. Survival outcomes were independent of cytogenetic risk, the number of previous lines and extramedullary disease.

Patients relapsing to ASCT may also benefit from KRd treatment according to our data [27]. Additionally, KRd should be also proposed when an intensification treatment with salvage SCT is planned [28].

Our study demonstrated an acceptable safety profile for KRd in the real-world, with a low discontinuation rate (16%), which was comparable to that in patients with RRMM from previous clinical trials with KRd scheme [15, 16, 23, 29] and previous real-world evidence with KRd [19–22] (supplementary Table 3). Discontinuation rates were also comparable to other second-line treatment options [12–14]. The most common toxicities were hematological and infections, showing a similar frequency than previous reports [15–22, 29, 30]. The incidence of high-grade AEs was comparable to that of K-based triplets. Surprisingly, the incidence of cardiovascular AEs such as hypertension (5%), thrombosis (4%) and arrhythmias (3%), dyspnea and renal toxicities were below previous reports [15–22, 29–31].

However, the underreporting inherent to retrospective studies could not be discarded.

The main limitation was the lack of a parallel control group and the retrospective nature of the study. No formal sample size calculations were performed. Selection bias was mitigated through systematic sequential inclusion of patients.

In conclusion, the KRd scheme led to an effectiveness comparable to the phase III clinical trials in patients with RRMM, despite the inclusion of patients with higher risk (renal impairment or high cytogenetic risk) and might be a good treatment option for second or third treatment lines regardless of age or renal functioning, and especially for patients progressing to T-based schemes. Furthermore, our results show that KRd could be a bridge therapy to SCT.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-025-06240-1.

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Author contributions Conception and design: A G-G. Acquisition of data (enrolled and managed patients) analysis and interpretation of data and manuscript writing / review: All authors; including AG-G, PAC, MJ, JS, ID, LSdlT, MS, MG-P, YG, AS, CM, EA, EC, MG, ES, MJH, YS, MG, JAS, JMM-T, RBA, CFdL.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request (equivalent purposes to those for which the patients grant their consent to use the data). Requests will be considered on a case-by-case basis in a timely manner. Data will be provided anonymized, with no personal identifiable data.

Declarations

Competing interests CFL: Advisory boards: Janssen, BMS, Amgen, Pfizer, Sanofi, Beigene, GSK, Roche, Menarini; Honoraria: Amgen, Janssen, BMS, GSK, Sanofi, Pfizer, Beigene; Grants: BMS, Janssen, Amgen, GSK.EC: Advisory boards and honoraria: Janssen, Sanofi, GSK, Menarini, Amgen.CM: Advisory boards: Sanofi.YG: Janssen and Sanofi.The remaining co-authors have no competing interests.

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