Original Study

Real-World Use of carfilzomib-lenalidomide-dexamethasone (KRd) and carfilzomib-dexamethasone (Kd) in Relapsed/Refractory Multiple Myeloma in the Asia Pacific Region: A Prospective Multicenter Observational Study

Hang Quach,[1] Kihyun Kim,[2] Raymond Siu Ming Wong,[3] Si Yun Melinda Tan,[4] Ming-Chung Wang,[5] Kopei Chang,[6] Megan Braunlin,[6] Mihaela Talpes,[6] Rani Najdi,[6] Jin Seok Kim[7]

Abstract

In this real-world study of 300 patients with RRMM from 29 sites in the Asia Pacific region, the safety and efficacy of carfilzomib in two approved regimens, carfilzomib with lenalidomide and dexamethasone (KRd) and carfilzomib with dexamethasone alone (Kd) was assessed. Both the KRd or Kd regimens were effective and well tolerated, even in patients with multiple prior lines of treatment, confirming the safety and response rates observed from clinical trials and real-world studies.

Background: Carfilzomib has demonstrated enhanced efficacy and tolerability in head-to-head clinical trials in patients with relapsed/refractory multiple myeloma (RRMM). However, real-world data on its use and outcomes in the Asia Pacific region remains limited. **Methods:** This prospective, observational, real-world study included 300 RRMM patients from 29 sites in the Asia Pacific region, who received carfilzomib between July 2019 and June 2023. Data was collected from medical records every 3 months to assess safety and efficacy of two approved regimens: carfilzomib with lenalidomide and dexamethasone (KRd) and carfilzomib with dexamethasone alone (Kd). **Results:** In KRd cohort, mean age was 62.7 years and median prior lines of therapy (LOT) was 1; in Kd cohort, mean age was 66.3 years with a median LOT of 3 (38% $\geq$ 4 LOTs). KRd achieved an overall response rate (ORR) of 81.7%, including 53.6% complete responses (CR) and 73.3% very good partial responses (VGPR). In the Kd cohort, ORR was 54.5%, with 27.2% CR and 34.8% VGPR. Median overall survival (OS) was 60.9 months with KRd and 41.6 with Kd; median time to progression (TTP) was 38.5 and 23.7 months, respectively. Grade $\geq$ 3 adverse events occurred in 18.8% (KRd) and 30.7% (Kd); treatment-related events occurred in 4.0% and 8.8%, leading to discontinuations in 1.1% and 2.6%, respectively. **Conclusion:** Carfilzomib

Abbreviations: AEs, adverse events; CR, complete response; CTCAE, common terminology criteria for adverse events; ECOPS, eastern cooperative oncology group performance status; HSCT, hematopoietic stem cell transplant; IMiD, immunomodulatory agent; Kd, carfilzomib-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; LOT, lines of treatment; mAb, monoclonal antibody; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide-dexamethasone; RDI, relative dose intensity; RRMM, relapsed/refractory multiple myeloma; SOC, system organ class; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse events; TTP, time to progression; Vd, bortezomib-dexamethasone; VGPR, very good partial response.

[1]Department of Haematology, St Vincents Hospital Melbourne and Department of Medicine, University of Melbourne, Victoria, Australia
[2]Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea
[3]Sir Y.K. Pao Centre for Cancer and Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China
[4]Department of Hematology, Singapore General Hospital, Singapore, Singapore
[5]Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital - Kaohsiung Medical Center, Kaohsiung, Taiwan
[6]Amgen Inc., Thousand Oaks, California, USA
[7]Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea

Submitted: Mar 24, 2025; Revised: Apr 29, 2025; Accepted: May 2, 2025; Epub: 7 May 2025

Address for correspondence: Professor Jin Seok Kim, MD, PhD, Division of Hematology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Yonsei University Health System, 50-1, Yonsei-Ro, Seodaemun-gu, Seoul 03722, Republic of Korea
E-mail contact: hemakim@yuhs.ac

https://doi.org/10.1016/j.clml.2025.05.001

administered as either KRd or Kd was effective and well tolerated, even in patients with multiple prior LOTs, confirming the safety and response rates observed from clinical trials and real-world studies.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 25, No. 11, e886–e898
Keywords: Relapse/refractory, Safety, Efficacy, Real-world data, Treatment

Introduction

In 2022, multiple myeloma (MM) was the third most prevalent hematologic malignancy worldwide, following non-Hodgkin lymphoma and leukemia, accounting for 187,952 new cases reported globally.[1] The incidence of MM exhibit considerable variations based on ethnicity, with Asian countries reporting the highest number of cases at 73,870, which constitutes 39.3% of the global incidence, and mortality figures at 53,795, representing 44.3% of the worldwide mortality of MM.[1-3]

Survival rates for patients with MM have substantially increased in recent decades, largely due to the introduction of new therapeutic options. The approval of multiple active agents for MM treatment, including targeted small molecule inhibitors, novel immunomodulatory agents (IMiD), proteasome inhibitors (PI), and monoclonal antibodies (mAb), has led to a wide array of potential drug combinations for both patients with newly diagnosed MM and those with relapsed MM.[4] Despite these therapeutic advancements, clinicians in the real-world face considerable challenges in providing effective care to patients with MM, such as selecting an optimal treatment regimen and managing treatment-related toxicity and complications during therapy.

Carfilzomib, a second-generation PI, irreversibly binds to the CT-L subunit of the proteasome, leading to sustained inhibition of the ubiquitin-proteasome pathway, a key mechanism for intracellular protein degradation.[5] Myeloma cells demonstrate greater sensitivity to proteasome inhibition than normal cells, making carfilzomib particularly effective in this malignancy.[5] Clinical studies have documented the efficacy of carfilzomib in adult patients with MM who have undergone at least 1 prior therapy. The ASPIRE study demonstrated that adding carfilzomib to a regimen of lenalidomide and dexamethasone (KRd) significantly improved progression-free survival (PFS) compared with lenalidomide and dexamethasone alone in patients with relapsed/refractory MM (RRMM).[6] The ENDEAVOR study demonstrated a significant improvement in PFS for RRMM patients receiving carfilzomib with dexamethasone (Kd) compared to bortezomib and dexamethasone (Vd), a first-generation PI regimen.[7]

Between 2017 and 2018, KRd and Kd were approved in Australia, Hong Kong, Singapore, South Korea, and Taiwan for patients with MM who had received 1-3 prior LOTs. However, Asian real-world data on the use of carfilzomib outside of clinical trials remain limited.[8] This study aimed to address this gap by providing regional, real-world data on carfilzomib use in Asia with a focus on regimen selection, efficacy and safety outcomes, and reasons for discontinuation of therapy. These findings will provide essential insights into carfilzomib's real-world impact and effectiveness beyond the clinical trial setting.

Methods

This was a prospective observational cohort study that collected data from serial reviews of medical records of consenting patients every 3 months. The first subject was enrolled on July 10, 2019, and the final study follow-up was completed on June 8, 2023. The study assumed that the relevant data were routinely recorded in patient charts following local clinical practices, and that the data were regularly abstracted from the charts at enrollment and at the end of the study. The study involved adult patients ($\geq$ 18 years) who were diagnosed with MM and had received at least 1 prior therapy before being treated with carfilzomib in the real-world clinical setting. Eligible patients had received at least 1 dose of carfilzomib prescribed by their physicians. The study gathered baseline data and details of MM treatment from the first dose of carfilzomib and followed patients for up to 2 years after enrollment, or until death, withdrawal of consent, loss to follow-up or study close.

The study was conducted in countries which spanned across the Asia Pacific region, including Australia, Korea, Hong Kong, Taiwan, and Singapore, and covered a variety of healthcare settings, providing a comprehensive view of carfilzomib's real-world use across different types of healthcare facilities (such as academic centers, local hospitals, and private offices). This approach enabled capture of a broad spectrum of patient experiences and treatment outcomes. The study included patients with MM whose therapy was carfilzomib-related, with a focus on the KRd and Kd regimens.

Statistical analyses employed descriptive summaries with two-sided 95% confidence intervals (CIs) estimated via the Clopper-Pearson method for binary outcomes and the Klein and Moeschberger method for time to event outcomes, with no formal hypotheses being tested. Categorical data were summarized by the number and percentage of patients in each category, with two-sided 95% CIs presented using Wilson's method where suitable. Continuous data were summarized by mean, standard deviation (SD), median, and range. Overall survival (OS) and time to progression were analyzed and summarized using the Kaplan-Meier method.

Data were summarized for the full analysis set, which included all enrolled patients, and separately based on their treatment regimen of KRd, Kd, or other.

Results

A total of 300 patients were included from various countries in the Asia Pacific region, including Australia (n = 47), Korea (n = 198), Hong Kong (n = 17), Taiwan (n = 25), and Singapore (n = 13). These patients were enrolled in 29 sites starting in July 2019 (first patient enrolled) until study termination in June 2023 (last patient completed study). There were 176 patients who

received KRd, 114 patients who received Kd, and 10 patients who received other regimens containing carfilzomib.

The mean (SD) age at carfilzomib treatment initiation was 62.7 (8.7) years in the KRd treated patients, and 66.3 (9.6) years in the Kd treated patients (Table 1). Cytogenetic risk data were available for 72.2% of KRd and 60.5% of Kd treated patients at the time of MM diagnosis and indicated the number of patients with unfavorable or high-risk cytogenetics was 35.4% for KRd and 37.7% for Kd treated patients. The International Staging System (ISS) status available at MM diagnosis showed that 29.5% (52/176) of KRd and 26.3% (30/114) of Kd treated patients were ISS stage 3.

Approximately 46.3% of all patients had Eastern Cooperative Oncology Group performance status (ECOG PS) assessed at carfilzomib initiation. Of patients with available ECOG PS data, 95.7% (n = 89) of KRd and 95.4% (n = 42) of Kd treated patients had an ECOG PS $\leq$ 1.

Medical history was reported for 81.3% of KRd and 86.0% of Kd treated patients (Table 2). A proportion of patients presented with pre-existing cardiovascular conditions (35.8% for KRd, 51.8% for Kd treated patients), predominantly hypertension (24.4% for KRd, 32.5% for Kd treated patients).

The median time from the discontinuation of last prior treatment to the initiation of carfilzomib-containing regimens was 14.9 months for the KRd treated patients and 1.6 months for the Kd treated patients (Table 3). Patients who received KRd had a median of 1 prior LOT, while patients who received Kd were heavily pre-treated (median prior LOTs = 3); more KRd treated patients (69.3%) had 1 prior LOT compared with patients treated with Kd (16.7%). Overall, 37.7% of Kd treated patients had at least 4 prior LOTs. The proportion of patients with disease progression 1 year or more after first-line treatment initiation was higher in those treated with KRd (61.4%, n = 108) compared to those treated with Kd (52.6%, n = 60). A large proportion of patients in the study had prior exposure to bortezomib (88.1% of KRd, 89.5% of Kd). Overall, while patients with both carfilzomib regimens had a comparable proportion of patients who were treated with thalidomide (58.5% of KRd and 65.8% of Kd treated patients), more Kd treated patients had received pomalidomide or lenalidomide (19.3% and 71.9%, respectively) than KRd treated patients (0.6% and 5.1%, respectively). Previous hematopoietic stem cell transplant (HSCT) was reported for 56.8% of KRd and 50.9% of Kd treated patients. A majority of the HSCTs were autologous.

A summary of the planned carfilzomib administration, defined as the physician-prescribed regimen and dose in the first week of carfilzomib initiation, is presented in Table 4. All patients received at least 1 dose of carfilzomib. Most patients from the KRd (94.9%) and Kd (80.7%) cohorts planned to receive carfilzomib on a twice-weekly schedule, with 89.8% of KRd and 64.9% of Kd patients planned to receive dosing according to the Kyprolis (carfilzomib) Prescribing Information (20/27 mg/m^2 for KRd and 20/56 mg/m^2 for Kd).[9]

In the KRd treated patients, 75.6% of patients received an average carfilzomib dose that was at the standard dose for this regimen of 27 mg/m^2. In the Kd treated patients, only 21.0% of patents received an average carfilzomib dose at the standard dose for this regimen of 56 mg/m^2, with 70.2% of patients receiving a lower dose.

The median number of treatment cycles was 18 for the KRd treated patients and 10 for the Kd treated patients. Among patients receiving KRd, 29.5% discontinued treatment after achieving the required treatment response by completing 18 cycles as recommended by Kyprolis (carfilzomib) Prescribing Information.[9] Overall, a similar proportion of patients discontinued carfilzomib during the study observation period: 96.0% in the KRd and 92.1% in the Kd treated patients. The Kaplan-Meier estimated median time to discontinuation was 16.6 months (95% CI, 16.4-17.0) for KRd and 10.3 months (95% CI, 8.1-14.4) for Kd treatment patients. The estimated median follow-up times of 49.8 months (95% CI, 32.4-NE) for KRd and 36.9 months (95% CI, 2.9.7-NE) for Kd.

Besides achieving the required treatment response (29.5%) in the KRd treated patients, the main reason for discontinuation was disease progression (22.7%). In the Kd treated patients, disease progression was the primary reason for discontinuation in 60.5% of patients. Other reasons for carfilzomib discontinuation in KRd (34.1%) and Kd (20.2%) treated patients included the investigator's judgment of the clinical situation, challenges related to coronavirus disease 2019 (COVID-19) pandemic, and lack of insurance coverage for carfilzomib/lenalidomide.

Among patients with a response assessment as per physician criteria (Table 5), a high overall response rate (ORR) of 81.7% was seen in KRd treated patients, with 53.6% achieving a complete response (CR) or better and 73.3% achieving a very good partial response (VGPR) or better. An ORR of 54.5% was observed in Kd treated patients, with 27.2% achieving CR or better and 34.8% achieving VGPR or better.

Kaplan-Meier plots of time to progression (TTP) and overall survival were shown in Figure 1. Overall, 23.3% of KRd and 32.5% of Kd treated patients had disease progression, with a median time to progression of 38.5 months (95% CI, 35.7-not evaluable [NE]) and 23.7 months (95% CI, 19.4-37.3) for the KRd and Kd treated patients, respectively (Table 5).

The median OS was 60.9 months (95% CI, 60.9-NE) for KRd and 41.6 months (95% CI, 32.8-55.9) for Kd treated patients. Deaths were recorded for 17.6% of KRd and 48.2% of Kd treated patients. By the end of the study observation period, 73.9% of KRd treated patients (n = 130) and 43.9% of Kd treated patients (n = 50) were alive (Table 5).

The most frequently reported grade $\geq$ 3 treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE), by system organ class (SOC), are presented in Table 6. CTCAE grade $\geq$ 3 TEAEs were reported for 18.8% of KRd and 30.7% of Kd treated patients. Only 4.0% of KRd and 8.8% of Kd treated patients experienced CTCAE grade $\geq$ 3 TRAEs.

Carfilzomib discontinuation due to TEAEs occurred in 4.0% of KRd and 7.9% of Kd treated patients. However, discontinuation due to TRAEs was reported in 1.1% of KRd and 2.6% of Kd treated patients. Fatal TEAEs were reported in 4.5% of KRd and 14.0% of Kd treated patients, while fatal TRAEs were reported in 0.0% of KRd and 1.8% of Kd treated patients.

Table 1 Patient Demographics and Patient Disease Characteristics

	KRd (N = 176)	Kd (N = 114)	Other[f] (N = 10)	Total (N = 300)
Country, n (%)				
Australia	4 (2.3)	40 (35.1)	3 (30.0)	47 (15.7)
Hong Kong	5 (2.8)	12 (10.5)	0 (0.0)	198 (66.0)
Korea	157 (89.2)	41 (36.0)	0 (0.0)	17 (5.7)
Singapore	2 (1.1)	6 (5.3)	5 (50.0)	25 (8.3)
Taiwan	8 (4.5)	15 (13.2)	2 (20.0)	13 (4.3)
Sex, n (%)				
Male	104 (59.1)	62 (54.4)	4 (40.0)	170 (56.7)
Female	72 (40.9)	52 (45.6)	6 (60.0)	130 (43.3)
Age at multiple myeloma diagnosis (years)				
Mean (SD)	59.5 (9.3)	61.7 (10.1)	61.0 (9.6)	60.4 (9.6)
Age at carfilzomib initiation (years)				
Mean (SD)	62.7 (8.7)	66.3 (9.6)	64.7 (9.9)	64.1 (9.2)
Cytogenetic status at multiple myeloma diagnosis				
Patients with cytogenetic risk reported,[a] n (%)	127 (72.2)	69 (60.5)	5 (50.0)	201 (67.0)
High/unfavorable	45 (35.4)	26 (37.7)	2 (40.0)	73 (36.3)
Intermediate	19 (15.0)	4 (5.8)	0 (0.0)	23 (11.4)
Normal/favorable	51 (40.2)	23 (33.3)	2 (40.0)	76 (37.8)
Unknown/not done	12 (9.4)	16 (23.2)	1 (20.0)	29 (14.5)
Cytogenetic profile, n (%)				
At least 1 abnormality[b]	75 (58.6)	33 (47.8)	4 (80.0)	112 (55.4)
High risk (IMWG)[c]	39 (30.5)	22 (31.9)	2 (40.0)	63 (31.2)
Del(13)	24 (22.6)	16 (30.2)	2 (66.7)	42 (25.9)
t(11;14)	17 (18.7)	7 (15.2)	1 (33.3)	25 (17.9)
Chromosome 1 abnormalities	39 (36.4)	18 (33.3)	2 (50.0)	59 (35.8)
t(4;14)	27 (23.5)	13 (21.7)	1 (25.0)	41 (22.9)
Del(17p)	17 (11.5)	8 (13.8)	0 (0.0)	25 (11.2)
t(14;16)	12 (10.8)	6 (10.5)	1 (25.0)	19 (11.0)
t(6;14)	1 (2.2)	0 (0.0)	0 (0.0)	1 (1.1)
t(14;20)	1 (1.6)	1 (2.3)	0 (0.0)	2 (1.8)
Disease characteristics at carfilzomib initiation				
Time since diagnosis to C1D1 (months)				
Median (min, max)	30.30 (1.1, 243.4)	47.50 (1.0, 219.9)	30.45 (12.0, 107.3)	36.15 (1.0, 243.4)
ISS stage at diagnosis,[a] n (%)				
I	52 (29.5)	15 (13.2)	3 (30.0)	70 (23.3)
II	43 (24.4)	31 (27.2)	2 (20.0)	76 (25.3)
III	52 (29.5)	30 (26.3)	2 (20.0)	84 (28.0)
Unknown	29 (16.5)	38 (33.3)	3 (30.0)	70 (23.3)
ECOG PS at carfilzomib initiation,[b] n (%)				
Patients with ECOG PS reported, n (%)	93 (52.8)	44 (38.6)	2 (20.0)	139 (46.3)
0	44 (47.3)	24 (54.5)	1 (50.0)	69 (49.6)
1	45 (48.4)	18 (40.9)	0 (0.0)	63 (45.3)
2	3 (3.2)	1 (2.3)	1 (50.0)	5 (3.6)
3	1 (1.1)	1 (2.3)	0 (0.0)	2 (1.4)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Derived frailty score (Palumbo) at carfilzomib initiation,[d,e] n (%)				
Patients with frailty score	67 (38.1)	52 (45.6)	0 (0)	119 (39.7)
Fit	50 (28.4)	35 (30.7)	0 (0.0)	85 (28.3)
Intermediate	16 (9.1)	15 (13.2)	0 (0.0)	31 (10.3)
Frail	1 (0.6)	2 (1.8)	0 (0.0)	3 (1.0)

Abbreviations: C1D1 = cycle 1 day 1; ECOG PS = Eastern Cooperative Oncology Group Performance status; IMWG = International Myeloma Working Group; ISS = International Staging System; Kd = carflizmob with dexamethasone; KRd = carfilzomib with lenalidomide and dexamethasone; max = maximum; min = minimum; SD = standard deviation.
[a] Percentage is relative to the number of patients with reported data.
[b] Percentage is relative to the number of patients with cytogenetics reported.
[c] del(17p), t(4;14), t(14;16).
[d] Percentage is relative to the number of patients with data.
[e] Derived from age, ECOG PS, and comorbidities (Palumbo et al. 2015, Facon et al. 2015).
[f] The remaining patients (n = 10) received other carfilzomib-based triplets, mainly carfilzomib + cyclophosphamide + dexamethasone (KCyd), carfilzomib + pomalidomide + dexamethasone (KPd), or carfilzomib + daratumumab + dexamethasone (Kd-Dara).

Table 2 Summary of Medical History

	KRd (N = 176) n (%)	Kd (N = 114) n (%)	Other (N = 10) n (%)
Patients reporting medical history	143 (81.3)	98 (86.0)	9 (90.0)
Patients with pre-existing CV conditions	63 (35.8)	59 (51.8)	6 (60.0)
Vascular disorders	48 (27.3)	46 (40.4)	2 (20.0)
Deep vein thrombosis	4 (2.3)	6 (5.3)	0 (0.0)
Hypertension	43 (24.4)	37 (32.5)	2 (20.0)
Surgical and medical procedures	5 (2.8)	15 (13.2)	1 (10.0)
Metabolism and nutrition disorders	24 (13.6)	35 (30.7)	5 (50.0)
Diabetes mellitus	12 (6.8)	9 (7.9)	0 (0.0)
Hyperlipidaemia	6 (3.4)	8 (7.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	39 (22.2)	24 (21.1)	2 (20.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	14 (8.0)	13 (11.4)	1 (10.0)
Nervous system disorders	22 (12.5)	14 (12.3)	1 (10.0)
Gastrointestinal disorders	34 (19.3)	21 (18.4)	0 (0.0)
Cardiac disorders	11 (6.3)	16 (14.0)	3 (30.0)
Atrial fibrillation	4 (2.3)	2 (1.8)	0 (0.0)
Angina pectoris	2 (1.1)	2 (1.8)	0 (0.0)
Cardiac failure	2 (1.1)	2 (1.8)	0 (0.0)
Cardiac amyloidosis	2 (1.1)	0 (0.0)	0 (0.0)
Infections and infestations	31 (17.6)	15 (13.2)	3 (30.0)
Respiratory, thoracic and mediastinal disorders	16 (9.1)	14 (12.3)	0 (0.0)
Renal and urinary disorders	18 (10.2)	13 (11.4)	1 (10.0)
Chronic kidney disease	11 (6.3)	4 (3.5)	1 (10.0)
Acute kidney injury	2 (1.1)	2 (1.8)	0 (0.0)

Medical and surgical history were coded using MedDRA version 26.0.
Abbreviations: CV = cardiovascular; Kd = carfilzomib with dexamethasone; KRd = carfilzomib with lenalidomide and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities.

The most frequently reported TEAEs categorized by system organ class (SOC) are presented in Table 6. Among KRd treated patients (vs. Kd), the most frequently reported events by SOC were infections and infestations (5.7% vs. 9.6%); benign, malignant and unspecified neoplasms (3.4% vs .7.9%); general disorders and administration site conditions (2.3% vs. 6.1%); and then gastrointestinal disorders (2.3%) in KRd but respiratory, thoracic and mediastinal disorders in Kd (2.6%).

TRAEs categorized by SOC are also summarized in Table 6. Among KRd treated patients, the most frequently reported TRAEs were infections and infestations (1.1%), general disorders and administration site conditions (1.1%), and cardiac disorders (1.1%). Among Kd treated patients, the most frequently reported TRAEs were infections and infestations (3.5%), general disorders and administration site conditions (2.6%), respiratory, thoracic and mediastinal disorders (2.6%) and cardiac disorders (1.8%).

The management of cardiotoxicity is summarized in Table 6. Among KRd treated patients (vs. Kd), 9.1% (vs. 17.5%) were receiving treatment for hypertension at carfilzomib initiation, with 24.4% (vs. 27.2%) initiating antihypertensive therapy after initiating carfilzomib. Two patients receiving KRd (1.1%) were taking heart failure treatment at initiation of carfilzomib, with 15 (8.5%) starting heart failure treatment after carfilzomib initiation. Among Kd treated patients, 4 patients (3.5%) were using heart failure treatment at time of carfilzomib initiation, with 15 (13.2%) starting heart failure treatment after carfilzomib initiation. Among patients who experienced cardiovascular toxicity (such as, hypertension, cardiac failure, or ischemic heart disease), 0.0% (0/5) of affected KRd treated patients and 16.7% (1/6) of affected Kd treated patients had a subsequent carfilzomib dose reduction. MM therapy was withheld in 60.0% (3/5) of affected KRd treated patients and 33.3% (2/6) of affected Kd treated patients.

Discussion

KRd and Kd were the most utilized regimens in this real-world study. Only 3.3% (10 of 300) of our study patients received a carfilzomib-based regimen other than KRd or Kd, such as carfilzomib + cyclophosphamide + dexamethasone (KCyd), carfilzomib + pomalidomide + dexamethasone (KPd), or carfilzomib + daratumumab + dexamethasone (Kd-Dara). This study reports that both the Kd and KRd regimens were safe and effective in patients with RRMM and aligns with the known safety profile of carfilzomib in the phase 3 randomized controlled trials, ENDEAVOR (Kd vs. Vd) [7] and ASPIRE (KRd vs. Rd).[6] Importantly, our study also sheds light on some differences between the patient selection and outcomes of the two carfilzomib regimens in the real-world settings.

This study used data from medical records and suggested that MM assessment in Asia is thorough with documented ISS stage available for 76.7% of patients and documented cytogenetic risk for 67% of patients at first diagnosis. Documented ECOG PS was available for 46.3% of patients who initiated carfilzomib. These findings

Table 3 Prior Treatment History and Prior Therapy

	KRd (N = 176)	Kd (N = 114)	Other (N = 10)	Total (N = 300)
Time since last prior treatment discontinuation to C1D1 (months)				
Median (min, max)	14.90 (0.0, 128.6)	1.60 (0.0, 94.4)	1.35 (0.0, 31.6)	4.90 (0.0, 128.6)
Number of lines of prior treatment—n (%)				
1	122 (69.3)	19 (16.7)	2 (20.0)	143 (47.7)
2	37 (21.0)	20 (17.5)	1 (10.0)	58 (19.3)
3	13 (7.4)	32 (28.1)	3 (30.0)	48 (16.0)
4 or more	4 (2.3)	43 (37.7)	4 (40.0)	51 (17.0)
Median (min, max)	1 (1, 6)	3 (1, 12)	3 (1, 7)	2 (1, 12)
Time to progression after first-line treatment initiation—n (%)				
Progression less than 1 year	38 (21.6)	21 (18.4)	2 (20.0)	61 (20.3)
Progression 1 year or more	108 (61.4)	60 (52.6)	6 (60.0)	174 (58.0)
Did not relapse/progress	29 (16.5)	32 (28.1)	2 (20.0)	63 (21.0)
Unknown	1 (0.6)	1 (0.9)	0 (0.0)	2 (0.7)
Prior therapy—n (%)				
Proteasome inhibitor	156 (88.6)	105 (92.1)	10 (100.0)	271 (90.3)
Bortezomib	155 (88.1)	102 (89.5)	10 (100.0)	267 (89.0)
Ixazomib	4 (2.3)	7 (6.1)	1 (10.0)	12 (4.0)
Carfilzomib	0 (0.0)	3 (2.6)	0 (0.0)	3 (1.0)
IMiD	104 (59.1)	105 (92.1)	7 (70.0)	216 (72.0)
Thalidomide	103 (58.5)	75 (65.8)	4 (40.0)	182 (60.7)
Pomalidomide	1 (0.6)	22 (19.3)	2 (20.0)	25 (8.3)
Lenalidomide	9 (5.1)	82 (71.9)	7 (70.0)	98 (32.7)
Chemotherapy	109 (61.9)	84 (73.7)	9 (90.0)	202 (67.3)
Monoclonal antibody	5 (2.8)	7 (6.1)	2 (20.0)	14 (4.7)
Daratumumab	5 (2.8)	7 (6.1)	2 (20.0)	14 (4.7)
Elotuzumab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Isatuximab	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panobinostat	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (1.7)	0 (0.0)	0 (0.0)	3 (1.0)
Previous hematopoietic stem cell transplant	100 (56.8)	58 (50.9)	8 (80.0)	166 (55.3)
Previously treated for MM in a clinical trial	48 (27.3)	28 (24.6)	0 (0.0)	76 (25.3)
Previous radiotherapy for MM	21 (11.9)	20 (17.5)	0 (0.0)	41 (13.7)

Abbreviations: C1D1 = cycle 1 day 1; Kd = carfilzomib with dexamethasone; KRd = carfilzomib with lenalidomide and dexamethasone; IMiD = immunomodulatory drug; max = maximum; min = minimum; MM = multiple myeloma.

aligned with carfilzomib real-world studies from Europe (with data on ISS in 35.1%-81%, cytogenetic risk in 18.1%-38%, and ECOG PS in 70.8% of patients).[10,11] In the real-world setting, variability in physician-recorded responses and incomplete cytogenetic data limit direct comparisons between regimens and may constrain the generalizability of our findings to the broader RRMM population.

In this study, the initial mean age at MM diagnosis was 60.4 years. In the KRd treated patients, the mean age of starting carfilzomib was 62.7 years, which is lower than the 66.3 years observed with the Kd treated patients. A similar trend is observed in real-world data from Europe where patients with RRMM initiated KRd at an median age of 63 years and Kd at an median age of 68 years.[10,11] Although the median ages of carfilzomib patients with RRMM was around 64-65 years in ENDEAVOR and ASPIRE,[6,7] our real-world study observed that KRd was given to younger patients compared with those receiving Kd. Additionally, KRd treated patients had fewer prior LOTs and concomitant health issues, such as heart problems, when compared with Kd. Although the KRd regimen appears to have high ORR and CR rates, the inclusion of lenalidomide may impact the tolerability for some patients, such as older patients, heavily pretreated patients, or those with renal impairment or thrombosis due to its cumulative side effects.

Our real-world study revealed that in Asia, carfilzomib was often administered later in the treatment sequence for RRMM. This trend was especially notable for the Kd regimen. In contrast to the randomized controlled trials ASPIRE and ENDEAVOR, which enrolled patients with 1–3 prior lines of therapy (LOTs), 69.3% of the KRd treated patients in our study had received only 1 prior

Table 4 Summary of Carfilzomib Administration and Discontinuation

	KRd (N = 176)	Kd (N = 114)
Planned twice weekly schedule, n (%)	167 (94.9)	92 (80.7)
20/27 mg/m^2	158 (89.8)	9 (7.9)
20/56 mg/m^2	5 (2.8)	74 (64.9)
Other	4 (2.3)	9 (7.9)
20/36 mg/m^2	1 (0.6)	1 (0.9)
≤ 27 mg/m^2	3 (1.7)	1 (0.9)
Not classified	0 (0.0)	7 (6.1)
Patients who received 20 mg/m^2 at the first dose of carfilzomib, n (%)	165 (93.8)	95 (83.3)
Average dose per administration (mg/m^2),[a] overall		
Mean (SD)	27.75 (5.57)	47.17 (10.79)
Median (min, max)	26.84 (20.0, 68.1)	51.92 (17.3, 68.6)
Average dose per administration group,[b] overall		
Below standard dose[c], n (%)	20 (11.4)	80 (70.2)
At standard dose[d], n (%)	133 (75.6)	24 (21.0)
Above standard dose[e], n (%)	23 (13.0)	10 (8.8)
Average number of doses of carfilzomib administered per cycle, all administrations[f]		
Mean (SD)	5.31 (0.79)	5.00 (1.23)
Number of cycles patient received carfilzomib		
Mean (SD)	14.9 (5.5)	12.0 (10.2)
Median (min, max)	18.0 (1, 31)	10.0 (1, 53)
Patients who are continuing carfilzomib, n (%)	7 (4.0)	9 (7.9)
Patients who discontinued carfilzomib, n (%)	169 (96.0)	105 (92.1)
Disease progression/refractory n (%)	40 (22.7)	69 (60.5)
Required level of treatment response reached[g] n (%)	52 (29.5)	0 (0.0)
Patient request n (%)	5 (2.8)	7 (6.1)
Transplant n (%)	4 (2.3)	0 (0.0)
Adverse event n (%)	4 (2.3)	4 (3.5)
Death n (%)	3 (1.7)	2 (1.8)
Loss to follow-up n (%)	1 (0.6)	0 (0.0)
Noncompliance n (%)	0 (0.0)	0 (0.0)
Other[h] n (%)	60 (34.1)	23 (20.2)
Kaplan-Meier median estimate of time to carfilzomib discontinuation, months (95% CI)	16.6 (16.4-17.0)	10.3 (8.1-14.4)
Median follow-up,[i] months (95% CI)	49.8 (32.4-NE)	36.9 (29.7-NE)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; Kd = carfilzomib with dexamethasone; KRd = carfilzomib with lenalidomide and dexamethasone; max = maximum; min = minimum; SD = standard deviation.
[a] Average dose per administration was calculated as the cumulative dose received divided by the number of doses administered.
[b] Total dose received divided by the number of doses administered.
[c] KRd ≤ 26; Kd: ≤ 55.
[d] KRd: > 26 and < 28; Kd: > 55 and < 57.
[e] KRd: ≥ 28; Kd ≥ 57.
[f] Total number of doses administered divided by the number of cycles in which at least 1 dose of carfilzomib was administered.
[g] Patients completed 18 cycles of KRd regimen suggested in the carfilzomib label.
[h] Other reasons, which were not found in medical records, included investigator's decision to the clinical situation, COVID-19 pandemic, limited insurance coverage for carfilzomib/lenalidomide etc.
[i] Estimated using the reverse Kaplan-Meier method (Schemper and Smith, 1996).

LOT, whereas 65.8% of the Kd treated patients had received 3 or more prior LOTs. These findings were aligned with other real-world studies, such as the studies in Europe, wherein 32% of KRd treated patients and 53.8% of Kd treated patients had received 3 or more prior LOTs;[11,12] and the KRd study in Korea with 27% having received 4 or more prior LOTs.[13] In the Asian countries included in our study, factors such as National Health Insurance reimbursement criteria, treatment affordability, and the recent introduction of anti-CD38 monoclonal antibodies may have influenced the use of carfilzomib in different lines of MM treatment sequence.

The long interval (14.9 months) between the end of the last treatment and the start of the KRd regimen, compared to the short interval (1.9 months) for the Kd regimen reflects their roles in a typical myeloma treatment journey. Patients selected for KRd were usually

Table 5 Summary of Best Overall Response, Time to Progression, and OS

	KRd	Kd	Other
Best Overall Response			
Patients with a response assessment (response assessment analysis set), n (%)	142 (80.7)	66 (57.9)	9 (90.0)
ORR,[a] n (%)	116 (81.7)	36 (54.5)	4 (44.4)
Best overall response of ≥ CR, n (%)	76 (53.6)	18 (27.2)	1 (11.1)
Best overall response of ≥ VGPR, n (%)	104 (73.3)	23 (34.8)	2 (22.2)
sCR	15 (10.6)	3 (4.5)	1 (11.1)
CR	61 (43.0)	15 (22.7)	0 (0.0)
VGPR	28 (19.7)	5 (7.6)	1 (11.1)
PR	12 (8.5)	13 (19.7)	2 (22.2)
MR	1 (0.7)	1 (1.5)	0 (0.0)
Stable disease	11 (7.7)	7 (10.6)	1 (11.1)
PD	11 (7.7)	22 (33.3)	4 (44.5)
NE	3 (2.1)	0 (0.0)	0 (0.0)
ORR in patients with 1 prior line of treatment n/N (%)	90/102 (88.2)	7/12 (58.3)	-
ORR in patients with 2 prior lines of treatment n/N (%)	20/30 (66.7)	6/9 (66.7)	-
ORR in patients with 3 prior lines of treatment n/N (%)	4/7 (57.1)	8/17 (47.1)	-
ORR in patients with ≥ 4 prior lines of treatment n/N (%)	2/3 (66.7)	15/28 (53.6)	
Time to progression			
Patient status, n (%)			
Events[a]	41 (23.3)	37 (32.5)	6 (60.0)
Censored	135 (76.7)	77 (67.5)	4 (40.0)
Time to progression (KM) (months)[c]			
Median (95% CI)	38.5 (35.7-NE)	23.7 (19.4-37.3)	19.2 (2.4-NE)
Overall survival[b]			
Patient status, n (%)			
Death	31 (17.6)	55 (48.2)	5 (50.0)
Censored	145 (82.4)	59 (51.8)	5 (50.0)
Alive	130 (73.9)	50 (43.9)	4 (40.0)
Withdrawal consent	3 (1.7)	2 (1.8)	0 (0.0)
Lost to follow-up	12 (6.8)	7 (6.1)	1 (10.0)
OS (months)[c]			
Median (95% CI)	60.9 (60.9-NE)	41.6 (32.8-55.9)	NE (0.6-NE)

[a] An event is defined as disease progression during the observational period. Time to progression was calculated in months as: (date of disease progression or censoring - first carfilzomib dose date + 1)/30.4. Patients without myeloma response assessment were censored to C1D1; patients without disease progression were censored to the date of last myeloma response assessment; patients with withdrawal of consent before disease progression were censored to the date of last myeloma response assessment before withdrawal of consent.
[b] OS was defined as the time from the first dose of carfilzomib in the first cycle to the date of death due to any cause: OS in months = (death date - first carfilzomib dose date + 1)/30.4. Patients who were alive, withdrew consent, or were lost to follow-up were censored at their last known alive date. The observational period was defined as the period from the first dose of carfilzomib to the end of study. If patients received subsequent antimyeloma treatment before the end of study, the observation period was defined as the period from the first dose of carfilzomib until the first dose of subsequent antimyeloma therapy after discontinuation of carfilzomib.
[c] Time was calculated from carfilzomib initiation to disease progression. Medians were estimated using the Kaplan-Meier method. 95% CIs for medians and percentiles were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.Abbreviations: C1D1 = cycle 1 day 1; CI = confidence interval; CR = complete response; Kd = carfilzomib with dexamethasone; KM = Kaplan-Meier; KRd = carfilzomib with lenalidomide and dexamethasone; MR = minimal response; NE = not evaluable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PR = partial response; sCR = stringent complete response; VGPR = very good partial response.

in an earlier line of therapy, often after a successful, durable response to frontline induction ± transplant. When their first regimen lost effect, the disease often progressed slowly enough to allow a prolonged "treatment-free" or maintenance phase before KRd was begun. By contrast, most Kd recipients were heavily pre-treated and had relapsed multiple times. In this setting, disease biology is usually more aggressive and prior options have shorter remissions, so clinicians move almost immediately from one regimen to the next. Hence, once the previous therapy failed, patients needed prompt initiation of Kd to regain disease control.

This study reported the planned and received carfilzomib dose in 2 regimens, KRd (K standard twice-weekly dose of 27 mg/m^2) and Kd (K standard twice-weekly dose of 56 mg/m^2). The median carfilzomib dose for KRd was 26.84 mg/m^2, and most KRd treated patients (75.6%) received the recommended dose. The median carfilzomib dose for Kd was 51.92 mg/m^2, but less than a quarter of Kd treated patients (21.0%) received the standard Kd dose, with most patients receiving lower than the suggested Kd dose. In real-world settings, the carfilzomib dose in the Kd regimen was often reduced, possibly due to factors such as the frailty of patients

Table 6 Summary of Treatment-Emergent, Treatment-Related Adverse Events and Management of Cardiovascular Issues

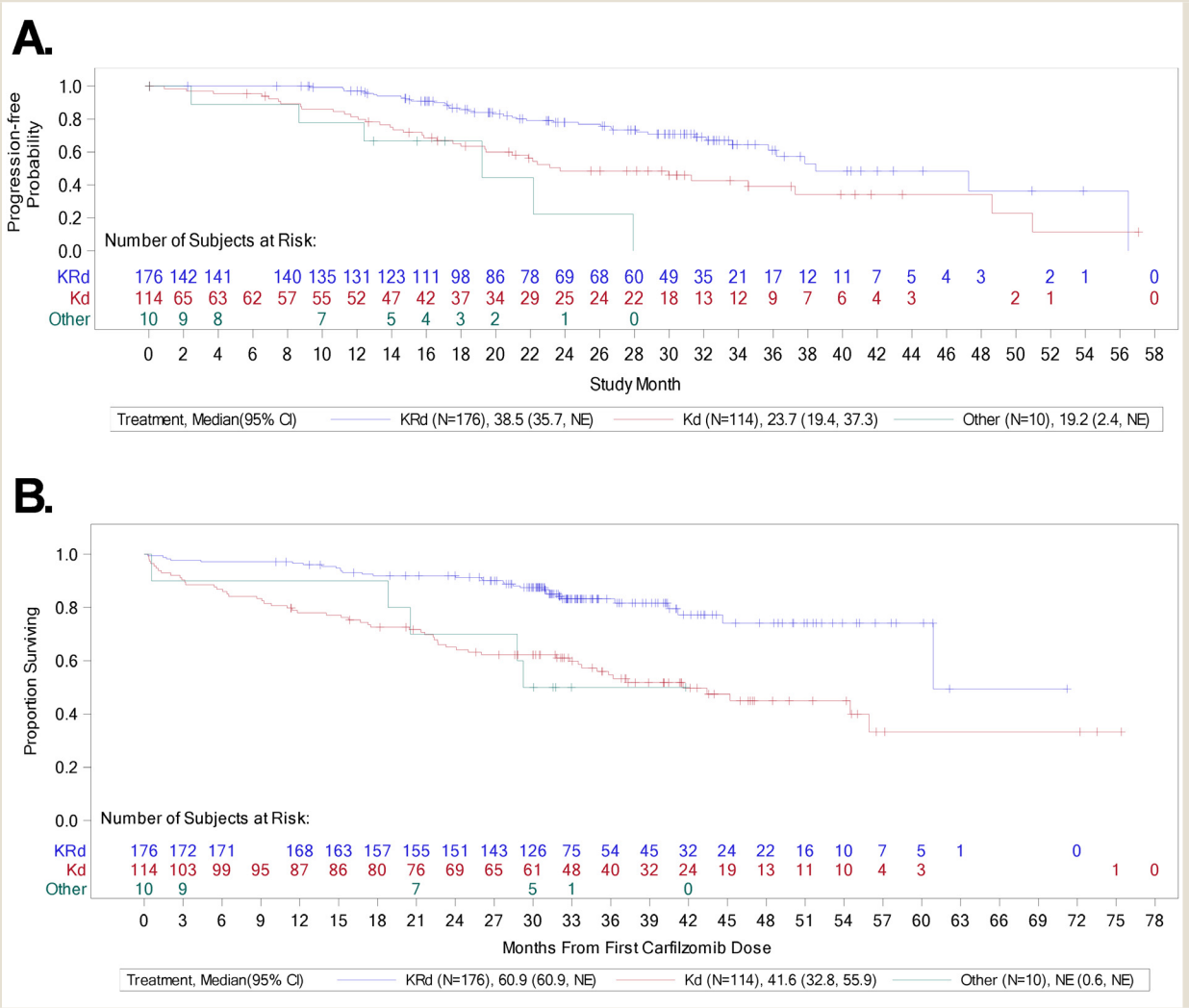
	KRd (N = 176), n (%)	Kd (N = 114), n (%)	Other (N = 10), n (%)
TEAEs			
Number of patients reporting grade ≥ 3 TEAEs	33 (18.8)	35 (30.7)	2 (20.0)
Leading to discontinuation of carfilzomib	7 (4.0)	9 (7.9)	1 (10.0)
Leading to blood transfusion	1 (0.6)	1 (0.9)	0 (0.0)
Leading to a dose reduction of carfilzomib	1 (0.6)	3 (2.6)	0 (0.0)
Fatal adverse events	8 (4.5)	16 (14.0)	1 (10.0)
System organ class in preferred term of TEAEs			
Infections and infestations	10 (5.7)	11 (9.6)	2 (20.0)
Neoplasms benign, malignant and unspecified (Including cysts and polyps)	6 (3.4)	9 (7.9)	1 (10.0)
General disorders and administration site conditions	4 (2.3)	7 (6.1)	0 (0.0)
Gastrointestinal disorders	4 (2.3)	2 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (1.7)	3 (2.6)	0 (0.0)
Cardiac disorders	3 (1.7)	2 (1.8)	0 (0.0)
Hepatobiliary disorders	3 (1.7)	1 (0.9)	0 (0.0)
Blood and lymphatic system disorders	2 (1.1)	2 (1.8)	0 (0.0)
Nervous system disorders	0 (0.0)	4 (3.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	3 (2.6)	0 (0.0)
Renal and urinary disorders	2 (1.1)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	1 (0.6)	1 (0.9)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	2 (1.8)	0 (0.0)
Vascular disorders	1 (0.6)	0 (0.0)	0 (0.0)
TRAEs			
Number of patients reporting grade ≥ 3 TRAEs	7 (4.0)	10 (8.8)	2 (20.0)
Leading to discontinuation of carfilzomib	2 (1.1)	3 (2.6)	1 (10.0)
Leading to blood transfusion	0 (0.0)	1 (0.9)	0 (0.0)
Leading to a dose reduction of carfilzomib	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	2 (1.8)	1 (10.0)
System Organ Class in Preferred Term of TRAEs			
Infections and infestations	2 (1.1)	4 (3.5)	1 (10.0)
General disorders and administration site conditions	2 (1.1)	3 (2.6)	0 (0.0)
Cardiac disorders	2 (1.1)	2 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	3 (2.6)	0 (0.0)
Gastrointestinal disorders	1 (0.6)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.9)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (0.9)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (10.0)
Management of cardiovascular issues			
Hypertension management			
Taking antihypertensive treatment at carfilzomib regimen initiation	16 (9.1)	20 (17.5)	0 (0.0)
Initiation of antihypertensive treatment after carfilzomib regimen initiation	43 (24.4)	31 (27.2)	2 (20.0)
Dose increase of existing antihypertensive treatment	4 (2.3)	9 (7.9)	0 (0.0)
Initiation of antihypertensive treatment or dose increase of existing antihypertensive treatment	44 (25.0)	31 (27.2)	2 (20.0)
Heart failure treatment			
Taking heart failure treatment at carfilzomib regimen initiation	2 (1.1)	4 (3.5)	0 (0.0)
Initiation of heart failure treatment after carfilzomib regimen initiation	15 (8.5)	15 (13.2)	0 (0.0)
Dose increase of existing heart failure treatment	2 (1.1)	4 (3.5)	0 (0.0)
Initiation of heart failure treatment or dose increase of existing heart failure treatment	15 (8.5)	16 (14.0)	0 (0.0)
Number of patients who have experienced ≥ 1 cardiovascular toxicity[a]	5 (2.8)	6 (5.3)	0 (0.0)
Dose reduction of carfilzomib due to cardiotoxicity[a], n/N (%)[b]	0 (0.0)	1/6 (16.7)	0 (-)
Dose reduction of multiple myeloma treatment due to cardiotoxicity[a], n/N (%)[b]	0 (0.0)	1/6 (16.7)	0 (-)
Multiple myeloma treatment withheld due to cardiotoxicity[a], n/N (%)[b]	3/5 (60.0)	2/6 (33.3)	0 (-)

Adverse events were coded using MedDRA version 26.0. TEAEs are events with an onset after the administration of the first dose of carfilzomib and up to the earliest of end of study or 30 days after the last dose of carfilzomib. Multiple myeloma treatment included carfilzomib, dexamethasone, and lenalidomide.

[a] Cardiovascular toxicity was defined as a patient who experienced at least 1 TEAE from the following MedDRA search strategies: criteria 1: hypertension (PT); criteria 2: cardiac failure (SMQN); criteria 3: Ischaemic heart disease (SMQB); criteria 4: cardiovascular event determined by physician.

[b] Percentage was relative to the number of patients who experienced at least 1 cardiovascular toxicity.Abbreviations: Kd = carfilzomib with dexamethasone; KRd = carfilzomib with lenalidomide and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TRAE = treatment-related treatment emergent adverse event.

Figure 1 Kaplan-Meier plot of (A) Time to progression and (B) Overall survival.



(A) KRd = carfilzomib + lenalidomide + dexamethasone; Kd = carfilzomib + dexamethasone; Other = carfilzomib + other agents; C1 D1 = Cycle 1 Day 1. The full analysis set is defined as all patients enrolled in the study, where 11 deceased patients enrolled prior to waiver of informed consent approval are excluded. An event is defined as disease progression during observational period. Time to progression is calculated in months as: (Date of disease progression or censoring - First carfilzomib dose date + 1)/30.4. Patients without myeloma response assessment will be censored to C1 D1; subjects without disease progression will be censored to date of last myeloma response assessment; subjects with withdrawal of consent before disease progression will be censored to date of last myeloma response assessment before withdrawal of consent. The observational period is defined as the period from the first dose of carfilzomib until end of study. If patients have received subsequent anti-myeloma treatment before end of study, the observation period is defined as the period from the first dose of carfilzomib until the first dose of subsequent anti-myeloma therapy after discontinuation of carfizomib. (B) KRd = carfilzomib + lenalidomide + dexamethasone; Kd = carfilzomib + dexamethasone; Other = carfilzomib + other agents; OS = Overall Survival. The full analysis set is defined as all patients enrolled in the study, where 11 deceased patients enrolled prior to waiver of informed consent approval are excluded. The survival curves in this plot and the median OS are derived by Kaplan-Meier method.

with MM in later LOTs, cardiovascular risks, and treatment costs. Additionally, the adoption of a once-weekly dosing schedule, which involves administering carfilzomib on Days 1, 8, and 15 of a 28-day cycle—compared to the traditional twice-weekly schedule on Days 1, 2, 8, 9, 15, and 16—also influenced overall dose exposure. While the weekly schedule results in an increased range of doses, it does not necessarily affect the median dose. This shift to a weekly regimen is intended to enhance convenience, reduce the burden of frequent clinic visits, and potentially improve tolerability, especially in more vulnerable patient populations.

When our study opened in mid-2019, the approved carfilzomib options in the participating countries were the twice-weekly KRd and Kd schedules listed in the local Kyprolis (carfilzomib) Prescribing Information. Since then, the therapeutic landscape has expanded: once-weekly Kd (70 mg/m^2) and new triplets such as KPd, Kd-Dara, and Isa-Kd (isatuximab + carfilzomib + dexam-

ethasone) have become choices, and several centers are testing intermediate-dose Kd or novel partners (eg, bendamustine, next-generation immunotherapies) to improve tolerability in frail, heavily pre-treated patients. Accordingly, a study launched today would likely capture a different and even more diverse set of real-world treatment patterns and outcomes.

The observation period lasted until > 90% of patients stopped carfilzomib treatment. KRd had an estimated median (Kaplan-Meier) time to discontinuation of 16.6 months, which is comparable to the 18-month recommended treatment (18 cycles) according to the Kyprolis (carfilzomib) Prescribing Information.[9] Kd had an estimated median time to discontinuation of 10.3 months, which is comparable to the median PFS of 14.9 months from an Asian subgroup analysis of the ENDEAVOR trial.[14] Among KRd treated patients, 29.5% discontinued carfilzomib after achieving the required level of treatment response, indicating strong adherence to treatment protocols of completing 18 cycles in clinical practice. KRd regimens, which is known for its tolerability and efficacy, might contribute to patients completing planned cycles without progression or discontinuation due to adverse events. Discontinuation reasons were obtained from medical records in our study. All instances of carfilzomib discontinuation not specified in medical records, were categorized as "Other" reasons (34.1% for KRd, 20.2% for Kd treated patients). Some of these reasons included the COVID-19 pandemic, investigator's judgment, and financial limitations affecting treatment continuation.

In this real-world setting, the response assessment analysis set represents a subset of patients with recorded or evaluable response data. This subset is smaller than the full analysis set, reflecting practical challenges in capturing complete data in real-world practice. Factors such as patients being lost to follow-up, incomplete documentation, or variability in data collection protocols contribute to the gap between the full analysis set and the response assessment set. We recognize that the difference between the full set and the response assessment set may raise concerns about bias. Of the patients with a response assessment per physician criteria, KRd treated patients had a high ORR of 81.7%, with CR in 53.6% and VGPR in 73.3% of treated patients. The ASPIRE trial compared KRd with Rd (lenalidomide and dexamethasone alone) in patients with RRMM who had received 1-3 prior treatments. The response rate for KRd treated patients in our study was consistent with observations in the ASPIRE trial (ORR, 87.1%; CR, 31.8%), and the real-world KRd studies from Italy (ORR, 83%; CR, 21%), and Korea (ORR, 73%; CR, 27%). [6,12,13]

Among the Kd treated patients in our study, ORR was 54.5%, with CR in 27.2% and VGPR in 34.8% of treated patients. This response rate was similar to that in the Kd real-world study in Europe (ORR, 68.8%; CR, 13.2%; and VGPR, 43.6%) but slightly lower than reported for the Asian subgroup analysis of the phase 3 ENDEAVOR trial (ORR, 80.4%; and VGPR, 62.5%). [11,14] Unlike clinical trials wherein patients must adhere to the prescribed dosing schedule, in real-world settings (like our study) deviations from the approved dosing and regimen may impact the observed efficacy. In this study, most of Kd treated patients (37.7%) had 4 or more prior LOTs, in contrast to ENDEAVOR, where half of patients in the Kd arm had received 1 prior LOT and half had received 2-3 prior LOTs.[14]

In real-life settings, disease progression may not be immediately detected due to the absence of regular clinical tests and protocol-defined follow-ups. Likewise, death may be underreported due to factors such as loss to follow-up, occurrences outside hospital settings, misattribution to other causes, and other reporting limitations. These data may be incomplete or missing from medical records and some patients may be lost to follow-up. The survival of patients may be extended by the subsequent newly approved and emerging MM therapies. The comparison of TTP and OS data of real-world studies to those of phase 3 randomized controlled trials should be interpreted with caution. With this in mind, the present study had a median TTP of 38.5 months for KRd treated patients and 23.7 months for Kd treated patients. The median OS was 60.9 months for patients receiving KRd patients and 41.6 months for the Kd treated patients. These results were comparable to the findings of the ASPIRE (KRd: PFS, 26.3 months; OS, 48.3 months and the ENDEAVOR (Kd: PFS, 18.7 months; OS, 47.6 months) trials.[6,7,15,16]

In our study, the KRd regimen demonstrated outcomes consistent with those observed in confirmatory trials, showing comparable time to progression and OS. In real-world clinical practice, KRd is widely regarded as a standard second-line treatment option for cases that are not refractory to a first-line lenalidomide-containing regimen. Further research is needed to explore the outcomes of transplant-eligible patients who received KRd as a second-line therapy following upfront autologous transplantation. Such studies could provide valuable insights into the potential benefits of second-line lenalidomide-based combination therapy compared to lenalidomide maintenance therapy alone after transplantation. In contrast, the Kd regimen was generally used in later lines of therapy but delivered notable OS results. Clinically, the Kd regimen is frequently selected for third- or fourth-line treatment settings, particularly in patients without prior exposure to carfilzomib.

In our real-world study, a significant proportion of patients presented with pre-existing cardiovascular conditions at the initiation of carfilzomib treatment, reflecting the challenges of managing heavily pretreated and often older populations with multiple comorbidities. Hypertension was the most prevalent condition, particularly among patients receiving Kd, emphasizing the need for careful cardiovascular monitoring in this subgroup. The low rate of cardiac TRAEs leading to carfilzomib discontinuation in this study is particularly notable given the relatively high prevalence of pre-existing cardiovascular conditions among participants (35.8% in KRd and 51.8% in Kd). Despite a substantial proportion of patients requiring treatment for hypertension or heart failure before or after carfilzomib initiation, dose reductions and treatment discontinuations due to cardiovascular AEs were rare. Although the number of patients is limited, no KRd treated patients with cardiovascular toxicity had a carfilzomib dose reduction, and only 16.7% of affected Kd treated patients required one. These findings reinforce the overall cardiac safety profile of carfilzomib in a real-world setting.

TEAEs were observed more frequently in Kd treated patients compared to those on KRd, aligning with the higher prevalence of underlying health issues in the Kd cohort. TEAEs were more

common and grade ≥ 3 events higher in the Kd cohort, consistent with Kd treated patients having heavier prior therapy burden and greater comorbidity. Notably, infections and tumors emerged as the most common adverse events among KRd treated patients, while Kd treated patients also experienced issues related to blood disorders and general health problems. Despite these adverse events, TRAEs were relatively uncommon, with only a small percentage of patients discontinuing carfilzomib. This suggests that carfilzomib overall safety profile remains consistent with findings from clinical trials. These results showed the importance of tailoring regimens like KRd and Kd based on patient-specific factors, such as age, comorbidities, and treatment history, to maximize efficacy while minimizing adverse effects.

The study is not without limitations. The data were collected from 5 different countries with different reimbursement policies and access to MM treatment, which may affect the generalizability of the findings. Additionally, variability in medical records and common clinical practices in real-world settings could have influenced the consistency and completeness of the data. This study also had a broader eligibility criteria compared to clinical trials, which may contribute to differences in observed outcomes. We agree that, as an observational study, our analysis is vulnerable to selection bias. Because the KRd and Kd treated patients differed substantially at baseline, any comparison between the regimens is descriptive only, not inferential and reflects the inherent limitations of real-world, non-randomized data. Despite these limitations, the study provides valuable information regarding carfilzomib treatment practices and outcomes of Asian populations and emphasizes the need for customized treatment approaches for this group. The study also adds to the growing evidence that supports the safe and effective use of carfilzomib in the real-world treatment of RRMM, especially in the Asian Pacific region. One notable difference from clinical trials is the use of carfilzomib in later LOTs in Asia, often in a more challenging disease state. Moreover, the study showed real-world challenges, such as insurance coverage, tolerability issues, and patient conditions, which can affect treatment decisions and dosing regimens. These findings could help patients, prescribers, and payers in understanding the real-world use of the drug, including adherence to prescribed dosing and scheduling, a comprehensive overview of treatment patterns, and the practical use of carfilzomib beyond the controlled environment of clinical trials.

Conclusions

This real-world study offers a comprehensive view of how carfilzomib is used in real-world settings for patients with RRMM in the Asia Pacific region. This study reviewed medical records across 5 countries to provide valuable insights into the diversity of MM disease and its treatment patterns. Despite baseline differences, KRd was linked to fewer high-grade TRAEs and lower risks of progression and death than Kd, supporting KRd as the preferred second-line regimen for lenalidomide-sensitive, fit patients. Kd still has a role in later-line or lenalidomide-refractory settings, but less intensive dosing schedules deserve evaluation. Prospective studies that integrate frailty indices and biomarker-based risk stratification are needed to refine patient selection and optimise real-world carfilzomib use.

Efficacy outcomes observed in this real-world study were largely comparable to those reported in clinical trials and other real-world studies, confirming carfilzomib as an effective treatment option for RRMM. While differences in demographics and prior LOTs between the KRd and Kd regimens were noted, these differences were consistent with those seen in trials such as ASPIRE and ENDEAVOR, supporting the notion that carfilzomib performs similarly in real-world practice. This study also showed that the safety profile of carfilzomib in both the KRd and Kd regimens aligns with the known safety profile established in key clinical trials; no new safety concerns were identified.

In summary, this study contributes to the understanding of carfilzomib's real-world use, confirming both its safety and effectiveness in the Asia Pacific patients. These findings have important implications for optimizing the use of carfilzomib in the treatment of RRMM in clinical practice.

Data Sharing Statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at: https://www.amgen.com/science/clinical-trials/clinical-data-transparency-practices.

Clinical Practice Points

- Efficacy of Carfilzomib Regimens: KRd (Carfilzomib + Lenalidomide + Dexamethasone) demonstrated a higher overall response rate (ORR) of 81.7% compared to Kd (Carfilzomib + Dexamethasone) with an ORR of 54.5%. Median overall survival (OS) was significantly longer for KRd at 60.9 months versus 41.6 months for Kd. KRd showed higher complete response (CR) and very good partial response (VGPR) rates compared to Kd.
- Patient Demographics: Patients receiving KRd were younger and had fewer prior lines of treatment (LOTs) compared to those on Kd. KRd was typically used as a second-line treatment, while Kd was often employed in later treatment lines.
- Safety Profile: Fewer severe treatment-emergent adverse events (TEAEs) were reported in KRd (18.8%) compared to Kd (30.7%). The rates of treatment-related adverse events (TRAEs) leading to discontinuation were low: 1.1% for KRd and 2.6% for Kd. Cardiovascular toxicities, primarily hypertension, were manageable with adjustments in antihypertensive therapy.
- Clinical Considerations: KRd is recommended for younger, fitter patients, especially in second-line settings. Kd is suited for heavily pretreated patients or those unable to tolerate lenalidomide.
- Management of Adverse Events: Most adverse events were infections, hypertension, and cardiovascular complications, which were manageable with appropriate interventions. Dose adjustments and supportive care were essential in managing toxicity and maintaining treatment efficacy.

CRediT authorship contribution statement

Hang Quach: Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Kihyun Kim:** Writing – review & editing, Data curation. **Raymond Siu Ming Wong:** Writing – review &

editing, Data curation. **Si Yun Melinda Tan:** Writing – review & editing, Data curation. **Ming-Chung Wang:** Writing – review & editing, Data curation. **Kopei Chang:** Writing – review & editing, Writing – original draft, Project administration. **Megan Braunlin:** Writing – review & editing, Conceptualization. **Mihaela Talpes:** Writing – review & editing, Validation, Methodology, Formal analysis. **Rani Najdi:** Writing – review & editing, Validation, Supervision, Conceptualization. **Jin Seok Kim:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Acknowledgments

The authors extend their heartfelt gratitude to the patients and their families, whose participation and support made this study possible. We are deeply appreciative of the dedicated staff at the participating study sites, as well as the invaluable contributions of the research nurses and data coordinators who ensured the smooth conduct of this study. We gratefully acknowledge all the support provided by Amgen Inc., whose resources and expertise were instrumental in enabling this work. Special thanks go to the team for their statistical analysis, operational support, and assistance in study reporting. Finally, we thank all individuals who provided thoughtful comments and suggestions that enriched the quality of this research. This work was funded and supported by Amgen Inc. Amgen was involved in the study design, data collection, analysis, and interpretation, as well as in the writing of the report and the decision to submit the article for publication.

References

1. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer, 2024. https://gco.iarc.who.int/today. Accessed: July 2, 2024.
2. Michels TC, Petersen KE. Multiple myeloma: diagnosis and treatment. *Am Fam Physician*. 2017;95:373–383.
3. Huang J, Chan SC, Lok V, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. *Lancet Haematol*. 2022;9:e670–e677. doi:10.1016/S2352-3026(22)00165-X.
4. Padala SA, Barsouk A, Barsouk A, et al. Epidemiology, staging, and management of multiple myeloma. *Med Sci (Basel)*. 2021;9:3. doi:10.3390/medsci9010003.
5. Crawford LJ, Walker B, Irvine AE. Proteasome inhibitors in cancer therapy. *J Cell Commun Signal*. 2011;5:101–110. doi:10.1007/s12079-011-0121-7.
6. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2015;372:142–152. doi:10.1056/NEJMoa1411321.
7. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17:27–38. doi:10.1016/S1470-2045(15)00464-7.
8. Kim K, Lee JH, Kim JS, et al. Clinical profiles of multiple myeloma in Asia-An Asian Myeloma network study. *Am J Hematol*. 2014;89:751–756. doi:10.1002/ajh.23731.
9. Amgen Inc. Kyprolis® (carfilzomib) prescribing information. U.S. Food and Drug Administration; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202714s034lbl.pdf. Revised 2022. Accessed July 02, 2024.
10. Leleu X, Katodritou E, Kuehr T, et al. Real-world use of carfilzomib combined with lenalidomide and dexamethasone in patients with multiple myeloma in Europe and Israel. *EJ Haem*. 2023;4:174–183. doi:10.1002/jha2.595.
11. Terpos E, Zambello R, Leleu X, et al. Real-world use and effectiveness of carfilzomib plus dexamethasone in relapsed/refractory multiple myeloma in Europe. *Cancers (Basel)*. 2022;14:5311. doi:10.3390/cancers14215311.
12. Rocchi S, Tacchetti P, Pantani L, et al. A real-world efficacy and safety analysis of combined carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory multiple myeloma. *Hematol Oncol*. 2021;39:41–50. doi:10.1002/hon.2820.
13. Lee JH, Park Y, Kang KW, et al. Carfilzomib in addition to lenalidomide and dexamethasone in Asian patients with RRMM outside of a clinical trial. *Ann Hematol*. 2021;100:2051–2059. doi:10.1007/s00277-021-04407-0.
14. Dimopoulos MA, Moreau P, Iida S, et al. Outcomes for Asian patients with multiple myeloma receiving once- or twice-weekly carfilzomib-based therapy: a subgroup analysis of the randomized phase 3 ENDEAVOR and A.R.R.O.W. Trials. *Int J Hematol*. 2019;110:466–473. doi:10.1007/s12185-019-02704-z.
15. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18:1327–1337. doi:10.1016/S1470-2045(17)30578-8.
16. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36:728–734. doi:10.1200/JCO.2017.76.5032.