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ORIGINAL ARTICLE

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

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Abstract

Carfilzomib is an irreversible proteasome inhibitor used for the treatment of relapsed and/or refractory multiple myeloma (RRMM). We evaluated the efficacy and safety of carfilzomib in subgroups of Asian patients in the randomized phase 3 ENDEAVOR and A.R.R.O.W. trials. In ENDEAVOR, patients received carfilzomib twice-weekly (56 mg/m^2) plus dexamethasone (Kd; $n=56$) or bortezomib plus dexamethasone (Vd; $n=57$). In A.R.R.O.W., patients received carfilzomib once-weekly (70 mg/m^2, $n=30$) or twice-weekly (27 mg/m^2, $n=15$) plus dexamethasone. Median progression-free survival (PFS) among Asian patients in ENDEAVOR was longer with Kd than with Vd (14.9 versus 8.8 months; HR 0.599); the overall response rate (ORR) was 80.4% versus 70.2%. Median overall survival (Kd versus Vd) was 47.6 versus 38.8 months (HR 0.856). Median PFS among Asian patients in A.R.R.O.W. was longer for once-weekly versus twice-weekly Kd (16.0 versus 8.4 months; HR 0.628); ORR was 76.7% versus 53.3%. Rates of grade ≥ 3 adverse events were 89.1% (Kd) and 89.5% (Vd) in ENDEAVOR, and 76.6% (once-weekly Kd) versus 73.3% (twice-weekly Kd) in A.R.R.O.W. Overall, carfilzomib had a favorable benefit-risk profile across both dosing regimens [once-weekly (Kd 70 mg/m^2) and twice-weekly (Kd 56 mg/m^2)] in Asian patients with RRMM, which was consistent with the results of both parent studies.
Trial registration ClinicalTrials.gov: NCT01568866, NCT02412878.

Keywords Carfilzomib · Relapsed and/or refractory multiple myeloma · Asian population · Clinical trials

Introduction

Multiple myeloma (MM) is one of the most common hematologic malignances, with a worldwide age-standardized incidence of 2.1 cases per 100,000 persons and an age-standardized death rate of 1.5 deaths per 100,000 persons [1]. Although survival for patients with MM has improved in recent years with the introduction of immunomodulatory agents and proteasome inhibitors, treatment options for those in the setting of relapsed and/or refractory MM (RRMM) remain limited [2].

Although the age-standardized incidence of MM is lower in Asia than in the United States or Europe, the age-standardized rates are on the rise in Asia [1]. For example, the incidence of MM has increased twofold over the past decade in South Korea and Taiwan and is now one of the top three most common hematologic malignancies in South Korea [3]. As populations continue to age, it is expected that the incidence of MM will continue to increase in Asian populations [4].

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Thus, understanding the safety and efficacy of treatments for RRMM in the Asian population is important.

Proteasome inhibitors and immunomodulatory agents have become an integral part of the therapeutic landscape of RRMM and have radically transformed the treatment paradigm and improved survival over the past two decades [2, 5]. The clinical characteristics of MM in the Asian population appear similar to those in Caucasian populations, with similar cytogenetic profiles [3]. In view of disparities in access to healthcare and drugs for patients with MM across Asia [6], it is important to evaluate clinical data for Asian populations. Analyses of subgroups of Asian patients with RRMM from previous phase 3 studies evaluating daratumumab and ixazomib demonstrated efficacy and safety profiles [7, 8] that were comparable with those observed in the primary analysis populations from those studies [9, 10].

Carfilzomib is an epoxyketone proteasome inhibitor that irreversibly and selectively binds the constitutive proteasome and immunoproteasome and is used for the treatment of RRMM [11, 12].

In the ENDEAVOR study, patients with RRMM who had received 1–3 previous lines of therapy were treated with either twice-weekly carfilzomib (56 mg/m^2) plus dexamethasone (20 mg; Kd) or bortezomib (1.3 mg/m^2) plus dexamethasone (20 mg; Vd) [13, 14]. Both median progression-free survival [PFS; 18.7 versus 9.4 months; hazard ratio (HR) 0.53; 95% CI 0.44–0.65; $P < 0.0001$] and median overall survival (OS; 47.6 versus 40.0 months; HR 0.79; 95% CI 0.65–0.96; $P = 0.010$) were improved with Kd versus Vd [13, 14]. In the A.R.R.O.W. study, patients with RRMM who had received 2–3 previous lines of therapy, and who were refractory to the most recent line of therapy, were treated with either once-weekly (70 mg/m^2) or twice-weekly (27 mg/m^2) carfilzomib in combination with dexamethasone [15]. The median (95% CI) PFS was 11.2 (8.6–13.0) months in the once-weekly carfilzomib group versus 7.6 (5.8–9.2) months in the twice-weekly carfilzomib group (HR 0.69; 95% CI 0.54–0.88; $P = 0.003$); OS data were not yet mature at the time of the primary analysis [15].

The purpose of this subgroup analysis was to evaluate the safety and efficacy of carfilzomib in Asian patients from the ENDEAVOR and A.R.R.O.W. trials.

Materials and methods

Patients

Both the ENDEAVOR (ClinicalTrials.gov identifier: NCT01568866) and A.R.R.O.W. (ClinicalTrials.gov identifier: NCT02412878) trials have been previously reported and described in detail elsewhere [13–15]. Briefly, in the ENDEAVOR study, adult patients with RRMM who had received 1–3 prior treatments and had at least a partial response to ≥ 1 previous treatment were eligible for enrollment [13]. Prior treatments could include carfilzomib or bortezomib as long as the patients had at least a partial response to these treatments before relapse or progression (e.g., became refractory to therapy), the carfilzomib or bortezomib treatment was not discontinued because of toxic effects, and patients had a ≥ 6-month proteasome inhibitor treatment-free interval before enrollment. Patients were excluded if they had grade 2 (with pain), grade 3, or grade 4 peripheral neuropathy within 14 days before randomization; myocardial infarction within 4 months before randomization; or New York Heart Association class III or IV heart failure.

In the A.R.R.O.W. study, adult patients with RRMM who had received 2–3 prior therapies, who were refractory to their most recent therapy, and who had prior exposure to a proteasome inhibitor (excluding carfilzomib or oprozomib) and an immunomodulatory agent were eligible for inclusion [15]. Patients were excluded if they had grade ≥ 3 neuropathy within 14 days before randomization, myocardial infarction within 6 months before randomization, or New York Heart Association class III or IV heart failure.

In both trials, the study protocols were approved by institutional review boards or ethics committees at each participating institution; all patients provided written informed consent [13, 15].

Study design

Both ENDEAVOR and A.R.R.O.W. were phase 3, open-label, multicenter studies, with patients randomized to treatment arms using a central interactive voice and web response system [13, 15].

In the ENDEAVOR study, patients were randomized 1:1 to receive twice-weekly Kd (carfilzomib 20 mg/m^2 on days 1 and 2 of cycle 1, 56 mg/m^2 thereafter; dexamethasone 20 mg) or Vd (bortezomib 1.3 mg/m^2; dexamethasone 20 mg) [13]. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent [13]. Dose reductions were permitted to manage toxicity according to protocol-specific guidance [13].

In the A.R.R.O.W. study, patients were randomized 1:1 to receive once-weekly carfilzomib (20 mg/m^2 on day 1 of cycle 1, 70 mg/m^2 thereafter) or twice-weekly carfilzomib (20 mg/m^2 on days 1 and 2 of cycle 1, 27 mg/m^2 thereafter) in combination with dexamethasone (40 mg) [15]. Similar to the ENDEAVOR study, treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent [15]. Carfilzomib and dexamethasone dose reductions were also allowable for the management of toxicity, following specified dose-modification guidelines [15].

Assessments

Asian patients from both the ENDEAVOR and A.R.R.O.W. studies were included in this post hoc subgroup analysis. For ENDEAVOR, the data cutoff date of November 10, 2014 from the primary interim analysis was used to assess response rates and PFS [13]. Analysis for OS and safety from the ENDEAVOR study was conducted using data from a second interim analysis cutoff (January 3, 2017) [14]. Response rates, PFS, and safety for A.R.R.O.W. were all from the primary analysis with a data cutoff of June 15, 2017 [15].

In both the ENDEAVOR and A.R.R.O.W. studies, data from central laboratories have been key for assessing efficacy endpoints [13, 15]. Response and disease progression were determined using International Myeloma Working Group–Uniform Response Criteria. PFS was defined as the time from randomization until disease progression or death, and OS was defined as the time from randomization to death. Overall response was defined as the proportion of patients who achieved partial response or better, very good partial response, complete response, or stringent complete response.

For assessment of safety and tolerability, data on adverse events (AEs) were collected from the time of signing informed consent up to 30 days after the last dose of study treatment; AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using Common Terminology Criteria for Adverse Events version 4.03 for both ENDEAVOR and A.R.R.O.W. [13, 15]. Select AEs of interest for this analysis (hypertension, cardiac failure, acute renal failure, peripheral neuropathy) were reported as standardized MedDRA query narrow grouped terms.

Statistical analyses of data from ENDEAVOR and A.R.R.O.W.

In this analysis, median PFS and OS were summarized using the Kaplan–Meier method, and HRs were estimated using a Cox proportional hazards model. Overall response rate (ORR) for each subgroup was calculated and the associated 95% CI was estimated using the Clopper–Pearson method. Odds ratio for response of the treatment group versus control group was calculated, as was the associated 95% CI using the Wald normal approximation method.

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

Results

Patients

Overall, 113 Asian patients were included in the analysis from the ENDEAVOR study (Kd 56 mg/m^2, $n=56$; Vd, $n=57$), and 45 patients were included from A.R.R.O.W. (once-weekly Kd 70 mg/m^2, $n=30$; twice-weekly Kd 27 mg/m^2, $n=15$). Baseline demographics and disease characteristics are presented in Table 1. Most Asian patients enrolled in ENDEAVOR were male ($n=62$, 55%), and patients had a median age of 63 years at baseline. Overall, 55% ($n=31$) of patients in the Kd group and 65% ($n=37$) in the Vd group had received prior treatment with bortezomib, and 9% ($n=5$) and 7% ($n=4$), respectively, were refractory to bortezomib. Additionally, 34% ($n=19$) in the Kd group and 28% ($n=16$) in the Vd group had received prior treatment with lenalidomide, and 23% ($n=13$) and 21% ($n=12$), respectively, were refractory. Asian patients enrolled in A.R.R.O.W. were also primarily male (56%, $n=25$), and patients had a median age of 67 years. All patients had received prior treatment with bortezomib ($n=45$, 100%), and 40% of patients in each of the once-weekly ($n=12$) and twice-weekly ($n=6$) treatment groups were refractory to bortezomib. Additionally, 97% ($n=29$) of patients in the once-weekly group and 87% ($n=13$) in the twice-weekly group had received prior treatment with lenalidomide, and 80% ($n=24$) and 87% ($n=13$) of patients in each treatment group, respectively, were refractory to lenalidomide.

Asian patients included in this subgroup analysis from ENDEAVOR were enrolled from Japan ($n=44$), Taiwan ($n=24$), Singapore ($n=20$), Republic of Korea ($n=16$), Thailand ($n=5$), and other countries ($n=4$). Asian patients included in this subgroup analysis from A.R.R.O.W. were enrolled from Japan ($n=40$) and Canada ($n=5$).

Efficacy

For the ENDEAVOR study, median PFS was 14.9 months in the Kd group compared with 8.8 months in the Vd group (HR 0.599; 95% CI 0.309–1.161; Fig. 1a). Median (95% CI) follow-up for PFS in ENDEAVOR was 8.4 (5.7–9.3) months in the Kd group and 8.4 (5.6–9.2) months in the Vd group. In the A.R.R.O.W. study, median PFS in the once-weekly group was 16.0 months compared with 8.4 months in the twice-weekly group (HR 0.628; 95% CI 0.267–1.473; Fig. 1b). Median (95% CI) follow-up for PFS in A.R.R.O.W. was 14.9 (13.3–15.8) months in the once-weekly group and 14.8 (12.1–17.7) months in the twice-weekly group. In ENDEAVOR,

Table 1 Baseline demographics and disease and treatment characteristics

	ENDEAVOR		A.R.R.O.W.	
	Kd ($n=56$)	Vd ($n=57$)	Once-weekly Kd ($n=30$)	Twice-weekly Kd ($n=15$)
Median (range) age, years	63.5 (36–82)	62.0 (44–86)	68.0 (45–80)	65.0 (35–79)
Men, *n* (%)	31 (55.4)	31 (54.4)	17 (56.7)	8 (53.3)
ECOG performance status, *n* (%)				
0	35 (62.5)	31 (54.4)	16 (53.3)	9 (60.0)
1	20 (35.7)	23 (40.4)	14 (46.7)	6 (40.0)
2	1 (1.8)	3 (5.3)	0	0
ISS stage, *n* (%)				
1	30 (53.6)	33 (57.9)	16 (53.3)	13 (86.7)
2	16 (28.6)	16 (28.1)	8 (26.7)	1 (6.7)
3	10 (17.9)	8 (14.0)	6 (20.0)	1 (6.7)
Cytogenetics, *n* (%)				
High risk[a]	13 (23.2)	15 (26.3)	6 (20.0)	4 (26.7)
Standard risk	33 (58.9)	36 (63.2)	6 (20.0)	3 (20.0)
Missing/unknown	10 (17.9)	6 (10.5)	18 (60.0)	8 (53.3)
Creatinine clearance				
Mean (SD)	66.0 (29.2)	67.9 (26.7)	67.4 (24.5)	72.6 (15.8)
< 30 mL/min, *n* (%)	7 (12.5)	5 (8.8)	1 (3.3)	0
30 to < 50 mL/min, *n* (%)	11 (19.6)	11 (19.3)	6 (20.0)	2 (13.3)
50 to < 80 mL/min, *n* (%)	20 (35.7)	19 (33.3)	16 (53.3)	9 (60.0)
≥ 80 mL/min, *n* (%)	18 (32.1)	22 (38.6)	7 (23.3)	4 (26.7)
Previous treatment, *n* (%)				
Bortezomib	31 (55.4)	37 (64.9)	30 (100)	15 (100)
Lenalidomide	19 (33.9)	16 (28.1)	29 (96.7)	13 (86.7)
Refractory to bortezomib, *n* (%)	5 (8.9)	4 (7.0)	12 (40.0)	6 (40.0)
Refractory to lenalidomide, *n* (%)	13 (23.2)	12 (21.1)	24 (80.0)	13 (86.7)

ECOG Eastern Cooperative Oncology Group, *ISS* International Staging System

[a]High-risk patients had genetic subtypes *t*(4; 14), *t*(14;16), or del(17p)

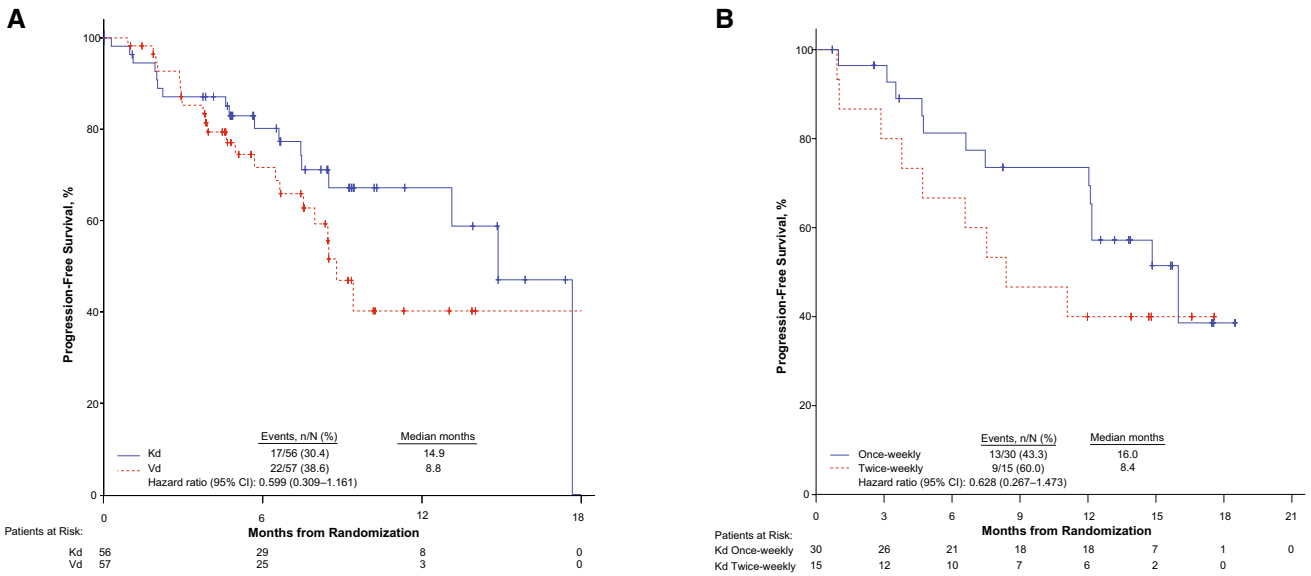

Fig. 1 Progression-free survival curves from **a** ENDEAVOR and **b** A.R.R.O.W. studies

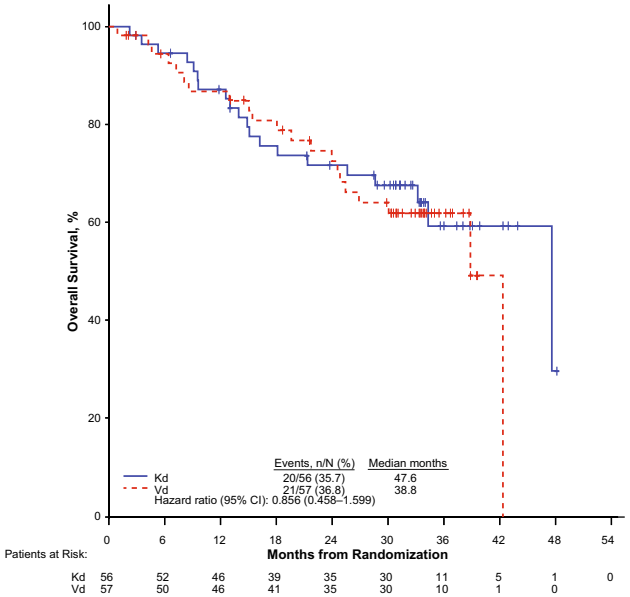

Fig. 2 Overall survival curve from ENDEAVOR study

median OS was 47.6 months in the Kd group compared with 38.8 months in the Vd group (HR 0.856; 95% CI 0.458–1.599; Fig. 2). Median (95% CI) follow-up for OS in ENDEAVOR was 33.5 (31.3–35.6) months in the Kd group and 33.6 (31.1–34.7) months in the Vd group. OS data from A.R.R.O.W. were not yet mature at the time of this analysis.

For patients in the ENDEAVOR study, 45 (80.4%) patients in the Kd group and 40 (70.2%) in the Vd group achieved an overall response [odds ratio (OR) 1.739; 95% CI 0.729–4.149]. Thirty-five (62.5%) patients in the Kd group and 14 (24.6%) patients in the Vd group achieved a very good partial response or better. For patients in A.R.R.O.W., 23 (76.7%) patients in the once-weekly group and 8 (53.3%) patients in the twice-weekly group achieved an overall response (OR, 2.875; 95% CI 0.767–10.772; Fig. 3). Fourteen (46.7%) patients and 4 (26.7%) patients in the once-weekly and twice-weekly groups, respectively, achieved a very good partial response or better.

Safety

An AE of any grade was reported by 54 (98.2%) patients in the Kd group and 57 (100%) patients in the Vd group in the ENDEAVOR study, and a grade ≥ 3 AE occurred in 49 (89.1%) patients in the Kd group and 51 (89.5%) patients in the Vd group (Table 2). Serious AEs were reported in

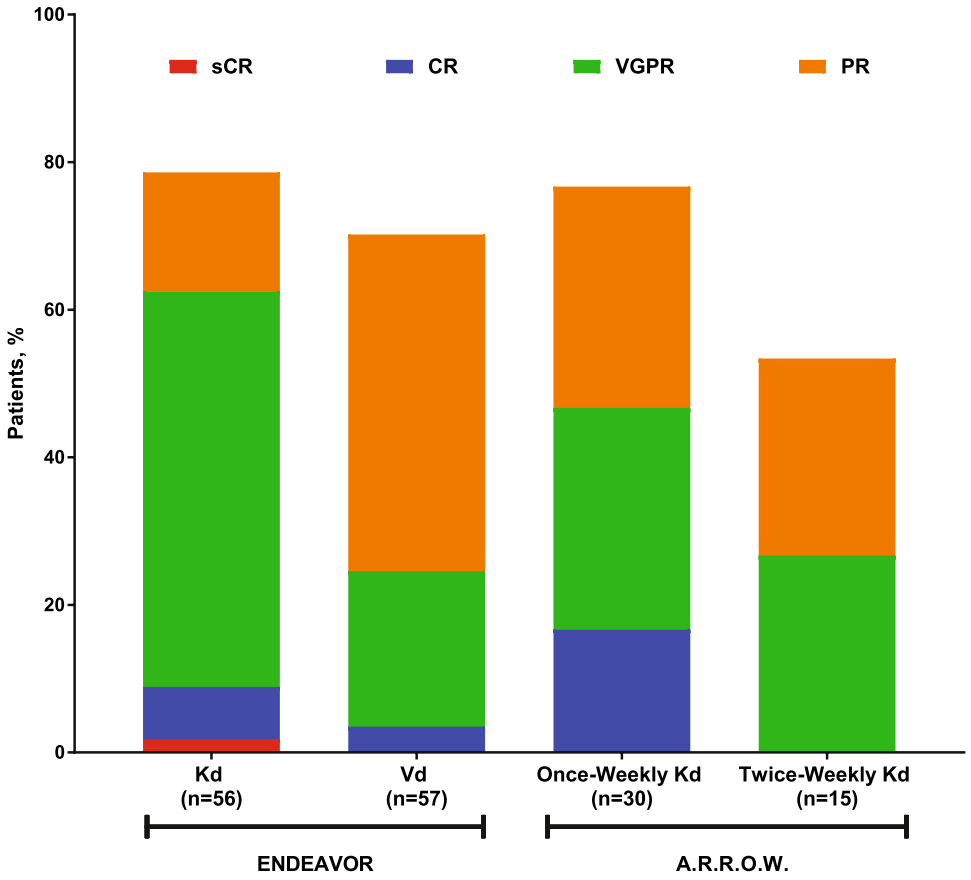

Fig. 3 Best overall responses. *CR* complete response, *PR* partial response, *sCR* stringent complete response, *VGPR* very good partial response

Table 2 Summary of AEs

	ENDEAVOR		A.R.R.O.W.	
	Kd ($n=55$)	Vd ($n=57$)	Once-weekly Kd ($n=30$)	Twice-weekly Kd ($n=15$)
Patients with any grade AE, *n* (%)	54 (98.2)	57 (100)	30 (100)	15 (100)
Grade ≥ 3 AEs	49 (89.1)	51 (89.5)	23 (76.7)	11 (73.3)
Serious AEs	34 (61.8)	25 (43.9)	18 (60.0)	4 (26.7)
Fatal AEs	2 (3.6)	1 (1.8)	2 (6.7)	0
AEs leading to discontinuation of carfilzomib or bortezomib, *n* (%)	15 (27.3)	10 (17.5)	9 (30.0)	2 (13.3)
AEs leading to dose reduction of carfilzomib or bortezomib, *n* (%)	22 (40.0)	35 (61.4)	6 (20.0)	1 (6.7)
Grade ≥ 3 AEs of interest, *n* (%)				
Hypertension	15 (27.3)	2 (3.5)	4 (13.3)	2 (13.3)
Cardiac failure	6 (10.9)	0	4 (13.3)	1 (6.7)
Acute renal failure	2 (3.6)	1 (1.8)	2 (6.7)	1 (6.7)
Peripheral neuropathy	0	7 (12.3)	0	0

AE adverse event

34 (61.8%) patients in the Kd group and 25 (43.9%) in the Vd group. Overall, 15 (27.3%) patients in the Kd group and 10 (17.5%) patients in the Vd group had AEs leading to discontinuation of carfilzomib or bortezomib, respectively. AEs leading to dose reduction of carfilzomib or bortezomib occurred in 22 (40.0%) patients in the Kd group and 35 (61.4%) patients in the Vd group. Median length of treatment exposure was 49.0 weeks for carfilzomib and 25.4 weeks for bortezomib. Grade ≥ 3 hypertension occurred in 15 (27.3%) Kd patients and 2 (3.5%) Vd patients; other grade ≥ 3 AEs of interest (Kd, Vd) were cardiac failure (10.9%, 0%), acute renal failure (3.6%, 1.8%), and peripheral neuropathy (0%, 12.3%).

All patients in the A.R.R.O.W. study reported an AE of any grade; grade ≥ 3 AEs were reported in 23 (76.7%) patients in the once-weekly group and 11 (73.3%) patients in the twice-weekly group. Serious AEs were reported in 18 (60.0%) patients in the once-weekly group and 4 (26.7%) in the twice-weekly group. A total of 9 (30%) patients in the once-weekly group and 2 (13%) in the twice-weekly group had AEs leading to discontinuation of carfilzomib. AEs leading to dose reduction of carfilzomib occurred in 6 (20.0%) patients in the once-weekly group and 1 (6.7%) patient in the twice-weekly group. Grade ≥ 3 hypertension occurred in 4 (13.3%) patients in the once-weekly group and 2 (13.3%) patients in the twice-weekly group, grade ≥ 3 cardiac failure occurred in 4 (13.3%) patients in the once-weekly group and 1 (6.7%) patient in the twice-weekly group, and grade ≥ 3 peripheral neuropathy occurred in 0 patients (0%) in either treatment group.

Discussion

In the ENDEAVOR study, treatment with twice-weekly Kd (56 mg/m^2) resulted in improved PFS and ORR compared with treatment with Vd among Asian patients. The incidences of grade ≥ 3 AEs were similar between Kd (56 mg/m^2) and Vd treatment arms. In the A.R.R.O.W. study, treatment with once-weekly Kd (70 mg/m^2) resulted in improved PFS and ORR compared with twice-weekly Kd (27 mg/m^2) in Asian patients, and incidences of grade ≥ 3 AEs were similar between treatment arms. The results reported here demonstrate that carfilzomib (administered either once or twice weekly) in combination with dexamethasone has a favorable risk–benefit profile in Asian patients with RRMM that is consistent with the overall patient population and has acceptable toxicity.

The trends in improvements in PFS and OS versus Vd were similar to those observed for the overall population in the ENDEAVOR study [13, 14], and the incidences of AEs overall, grade ≥ 3 AEs, and serious AEs in the Asian subgroup and in the total population in the ENDEAVOR study were generally comparable, although rates of grade ≥ 3 AEs were slightly higher among Asian patients than in the total population [14]. Additionally, the rates of grade ≥ 3 hypertension and cardiac failure among Asian patients were higher with Kd (56 mg/m^2) versus Vd (1.3 mg/m^2).

The trend for improvement in PFS seen in Asian patients with once-weekly (70 mg/m^2) versus twice-weekly Kd (27 mg/m^2) was consistent with that observed in the full analysis population in the A.R.R.O.W. study [15]. The incidences of AEs overall, grade ≥ 3 AEs, and serious AEs in the Asian subgroup were slightly higher than the incidence of overall AEs, grade ≥ 3 AEs, and serious AEs for the total

population in the A.R.R.O.W. study [15]. Among Asian patients in A.R.R.O.W., the incidence of grade ≥ 3 AEs was comparable between the once-weekly and twice-weekly arms; however, higher rates of serious AEs and of AEs leading to carfilzomib discontinuation or dose reduction were reported for once-weekly Kd. Moreover, in A.R.R.O.W., the rates of grade ≥ 3 cardiac failure in patients treated with once-weekly and twice-weekly Kd (70 mg/m^2; 27 mg/m^2) were higher among Asian patients compared with the overall population [15].

In both studies, the incidences of cardiac failure appeared slightly higher among the Asian subgroups compared with the overall populations; however, these comparisons should be interpreted with caution because of the small sample size of the Asian subgroups for each trial. Additionally, although no fatal cardiac events were reported among Asian patients in either of these studies, careful attention should be given to cardiovascular events during the treatment period. Potential risks for developing cardiac events should be identified before treatment (i.e., advanced age, pre-existing cardiac failure, history of recent myocardial infarction, conduction abnormalities, angina, arrhythmias uncontrolled by medications) [11, 12], and any risk-mitigation measures available should be taken (i.e., optimize management of hypertension, consult cardiologist) [11, 12, 16]. During treatment, careful monitoring of blood pressure and fluid intake and monitoring for any signs of active cardiac failure (i.e., dyspnea, cough/wheezing, edema, chest pain, fatigue/weakness, confusion/impaired thinking, nausea/lack of appetite, high heart rate, sudden weight change) are recommended [11, 12]. It is recommended to stop or withhold carfilzomib therapy for grade ≥ 3 cardiac events, for any instance of pulmonary hypertension, or for a hypertensive crisis, until the events are resolved or returned to baseline [11, 12, 16]. When restarting carfilzomib therapy, a reduction of dose level based on risk–benefit assessment should be considered [11, 12, 16].

In previous studies, carfilzomib has been evaluated in Asian patients as a single agent, in combination with low-dose dexamethasone, and in combination with dexamethasone and lenalidomide [17–20]. In 1 phase 1/2 single-agent study in Japanese patients, the ORR was 22.5%, median PFS was 5.1 months, and median OS was not reached at the time of data cutoff for those treated with carfilzomib 20/27 mg/m^2 [17]. Grade ≥ 3 hypertension, congestive heart failure, and dyspnea were reported in 8.0%, 0%, and 0% of patients, respectively [17]. In another phase 1 Japanese study of carfilzomib 20/45 or 20/56 mg/m^2 administered in combination with 4 or 8 mg of dexamethasone, respectively, the ORR for the 20/56 mg/m^2 cohort was 50.0%. PFS ranged from 29 to 573 + days, and OS ranged from 116 to 574 + days (+ indicated time when data were censored). No grade ≥ 3 hypertension, cardiac failure, dyspnea, or acute renal failure events were reported [18]. Furthermore, in a subsequent phase 1 study of once-weekly carfilzomib 20/70 mg/m^2 administered to Japanese patients in conjunction with oral or intravenous dexamethasone 40 mg, the ORR was 83.3%; PFS ranged from 1 to 603 + days; and OS ranged from 463 to 603 + days [19]. No grade ≥ 3 hypertension, cardiac failure, dyspnea, or acute renal failure events were reported; however, two patients discontinued treatment because of thrombotic microangiopathy and thrombotic thrombocytopenic purpura, respectively [19]. Both patients were treated with plasmapheresis and recovered from these conditions [19]. Moreover, in another phase 1 study, carfilzomib 20/27 mg/m^2 administered in combination with lenalidomide (25 mg) and dexamethasone (40 mg) following the treatment regimen used in the ASPIRE study [21] resulted in an ORR of 88.5% in Japanese patients; however, the median PFS and OS could not be estimated because of the short follow-up period at time of analysis [20]. One patient experienced grade 2 congestive cardiac failure; no grade ≥ 3 hypertension, cardiac failure, dyspnea, or acute renal failure events were reported [20].

Overall, the ORRs observed for Asian patients in this analysis of the ENDEAVOR and A.R.R.O.W. studies were comparable with, or superior to, those seen in these analyses with carfilzomib alone or in combination with either low-dose dexamethasone or dexamethasone plus lenalidomide in previous studies [17–20].

In summary, results from ENDEAVOR indicated that among Asian patients, outcomes were improved with Kd (56 mg/m^2) compared with Vd, with an acceptable safety profile. Similarly, results from A.R.R.O.W. indicated that once-weekly Kd (70 mg/m^2) improved efficacy outcomes compared with twice-weekly Kd (27 mg/m^2) in Asian patients, with comparable safety profiles. Asian patients receiving carfilzomib should be carefully monitored for cardiotoxicity. Overall, Kd therapy demonstrated a favorable benefit-risk profile across different dosing regimens (both once-weekly and twice-weekly) in two large phase 3 trials among Asian patients with RRMM.

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Compliance with ethical standards

Conflict of interest MAD reports receiving honoraria and consulting and/or advisory role fees from Celgene, Janssen, Amgen Inc., Novartis, and Takeda, and research funding from Genesis Pharma. PM reports receiving honoraria from and advisory board participation

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