Once-Weekly Versus Twice-Weekly Carfilzomib Dosing in Patients With Relapsed and Refractory Multiple Myeloma (A.R.R.O.W.): Efficacy and Safety Analyzed by Age Group

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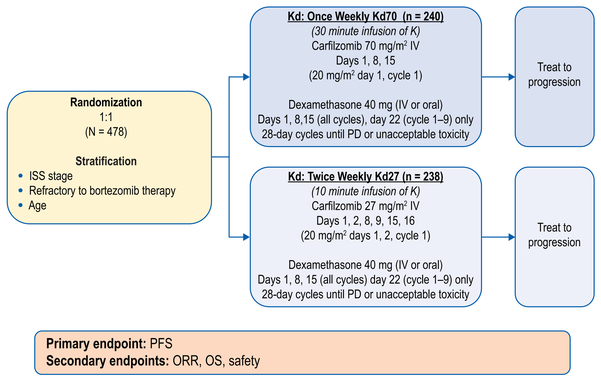
INTRODUCTION

- Carfilzomib is a second-generation proteasome inhibitor that selectively binds the constitutive proteasome and immunoproteasome
- Twice-weekly carfilzomib (K) is approved as a single agent and as combination therapy with lenalidomide and dexamethasone at a K dose of 27 mg/m^2 or with dexamethasone alone at a K dose of 56 mg/m^2 for the treatment of relapsed and/or refractory multiple myeloma (RRMM)[1]
  - In addition, once-weekly carfilzomib at 70 mg/m^2 plus dexamethasone (Kd70) was recently approved for the treatment of RRMM based on results of the randomized phase 3 study A.R.R.O.W. (NCT02412878)[1]
- The primary analysis of the A.R.R.O.W. study showed improved efficacy with Kd once-weekly (70 mg/m^2) compared with twice-weekly (27 mg/m^2) dosing[2]
  - Median PFS was 11.2 months (once-weekly Kd70) versus 7.6 months (twice-weekly Kd27) (HR, 0.69; 95% CI, 0.54–0.83; 2-sided P = 0.0029)
  - Overall response rate was 62.9% vs 40.8% (OR, 2.49; 2-sided P < 0.0001)
  - Importantly, the safety profile was comparable between the two treatment groups[2]
- Patients with multiple myeloma are typically 65 years of age or older at diagnosis
- Elderly patients are often more challenging to treat as they tend to be more frail, have more comorbidities, and are at higher risk of complications[3]
- There is a continued need to identify treatments that are effective, safe, and convenient for RRMM patients across age groups
- This subgroup analysis of the A.R.R.O.W. study investigated the impact of age on the efficacy and safety of once-weekly Kd70 versus twice-weekly Kd27 in RRMM

PATIENTS AND METHODS

- A.R.R.O.W. is a randomized, open-label phase 3 study
- Adult patients with RRMM who had received 2–3 prior lines of therapy and who were refractory to the most recent line were included
- Patients were randomized 1:1 to receive carfilzomib once-weekly (70 mg/m^2) or twice-weekly (27 mg/m^2) plus weekly dexamethasone (40 mg) in 28-day cycles (**Figure 1**)
- Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death
- Endpoints were analyzed according to age group (< 65 versus ≥ 65 years, < 75 versus ≥ 75 years) in this analysis; comparisons were not adjusted for multiplicity

Figure 1. A.R.R.O.W. Study Design



IMWG-URC = International Myeloma Working Group–Uniform Response Criteria; ISS = International Staging System; IV = intravenous; Kd = carfilzomib and dexamethasone; ORR = overall response rate; OS = overall survival, PD = disease progression; PFS = progression-free survival.

RESULTS

- Of the 478 patients enrolled in A.R.R.O.W., 208 (43.5%) were < 65 years, 270 (56.5%) were ≥ 65 years, 400 (83.7%) were < 75 years, and 78 (16.3%) were ≥ 75 years
- Baseline demographics and disease characteristics were generally balanced between treatment groups for each age group with the exception of the following (**Table 1**):
  - Among patients ≥ 65 years of age, a higher proportion were refractory to lenalidomide in the once-weekly Kd70 arm compared with the twice-weekly Kd27 arm
  - A higher proportion of patients in the once-weekly Kd70 arm were refractory to bortezomib in the ≥ 65 and < 75 years age subgroups, and a higher proportion of patients in the twice-weekly Kd27 arm were refractory to bortezomib in the ≥ 75 years age subgroup

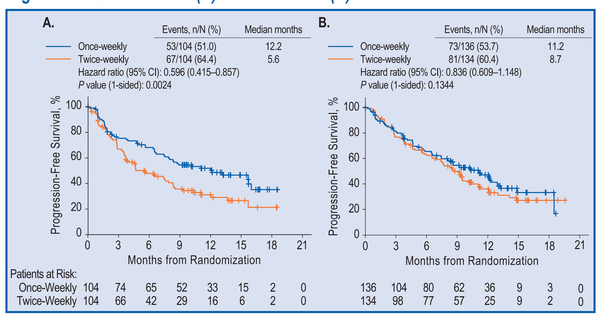
Table 1. Baseline Demographics and Disease Characteristics

	< 65 years		≥ 65 years		< 75 years		≥ 75 years	
	Once-weekly Kd70 (n = 104)	Twice-weekly Kd27 (n = 104)	Once-weekly Kd70 (n = 136)	Twice-weekly Kd27 (n = 134)	Once-weekly Kd70 (n = 194)	Twice-weekly Kd27 (n = 206)	Once weekly Kd70 (n = 46)	Twice-weekly Kd27 (n = 32)
Mean (SD) age, y	56.5 (6.3)	56.9 (6.0)	72.4 (4.9)	71.1 (4.5)	62.5 (8.2)	62.9 (7.7)	78.1 (2.5)	77.4 (2.3)
Sex, n (%)								
Male	65 (62.5)	60 (57.7)	67 (49.3)	68 (50.7)	113 (58.2)	114 (55.3)	19 (41.3)	14 (43.8)
Female	39 (37.5)	44 (42.3)	69 (50.7)	66 (49.3)	81 (41.8)	92 (44.7)	27 (58.7)	18 (56.3)
ECOG performance status, n (%)								
0	59 (56.7)	62 (59.6)	59 (43.4)	56 (41.8)	99 (51.0)	109 (52.9)	19 (41.3)	9 (28.1)
1	45 (43.3)	42 (40.4)	76 (55.9)	78 (58.2)	94 (48.5)	97 (47.1)	27 (58.7)	23 (71.9)
2	0	0	1 (0.7)	0	1 (0.5)	0	0	0
ISS stage at baseline, n (%)								
Stage 1	51 (49.0)	53 (51.0)	43 (31.6)	46 (34.3)	82 (43.3)	87 (42.2)	12 (26.1)	12 (37.5)
Stage 2	34 (32.7)	32 (30.8)	46 (33.8)	49 (36.6)	61 (31.4)	71 (34.5)	19 (41.3)	10 (31.3)
Stage 3	18 (17.3)	18 (17.3)	45 (33.1)	36 (26.9)	49 (25.3)	44 (21.4)	14 (30.4)	10 (31.3)
Missing	0	0	2 (1.5)	2 (1.5)	1 (0.5)	2 (1.0)	1 (2.2)	0
Creatinine clearance (mL/min), n (%)								
< 30	0	0	2 (1.5)	1 (0.7)	2 (1.0)	0	0	1 (3.1)
30 to < 50	6 (5.8)	9 (8.7)	42 (30.9)	25 (18.7)	22 (11.3)	21 (10.2)	26 (56.5)	13 (40.6)
50 to < 80	25 (24.0)	29 (27.9)	66 (48.5)	82 (61.2)	74 (38.1)	96 (46.6)	17 (37.0)	15 (46.9)
≥ 80	73 (70.2)	66 (63.5)	26 (19.1)	25 (18.7)	96 (49.5)	88 (42.7)	3 (6.5)	3 (9.4)
Missing	0	0	0	1 (0.7)	0	1 (0.5)	0	0
Cytogenetic risk by FISH, n (%)								
High risk	23 (22.1)	26 (25.0)	11 (8.1)	21 (15.7)	30 (15.5)	46 (22.3)	4 (8.7)	1 (3.1)
Standard risk	18 (17.3)	24 (23.1)	29 (21.3)	29 (21.6)	41 (21.1)	42 (20.4)	6 (13.0)	11 (34.4)
Unknown	63 (60.6)	54 (51.9)	96 (70.6)	84 (62.7)	123 (63.4)	118 (57.3)	36 (78.3)	20 (62.5)
Prior lines of therapy, n (%)								
2	56 (53.8)	50 (48.1)	60 (44.1)	75 (56.0)	99 (51.0)	106 (51.5)	17 (37.0)	19 (59.4)
3	48 (46.2)	53 (51.0)	76 (55.9)	59 (44.0)	95 (49.0)	99 (48.1)	29 (63.0)	13 (40.6)
> 3	0	1 (1.0)	0	0	0	1 (0.5)	0	0
Refractory to bortezomib, n (%)								
Yes	43 (41.3)	36 (34.6)	68 (50.0)	54 (40.3)	86 (44.3)	69 (33.5)	25 (54.3)	21 (65.6)
No	59 (56.7)	68 (65.4)	66 (48.5)	79 (59.0)	106 (54.6)	136 (66.0)	19 (41.3)	11 (34.4)
Refractory to lenalidomide, n (%)								
Yes	76 (73.1)	76 (73.1)	110 (80.9)	94 (70.1)	145 (74.7)	152 (73.8)	41 (89.1)	18 (56.3)
No	10 (9.6)	11 (10.6)	11 (8.1)	13 (9.7)	18 (9.3)	20 (9.7)	3 (6.5)	4 (12.5)

ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; ISS = International Staging System.

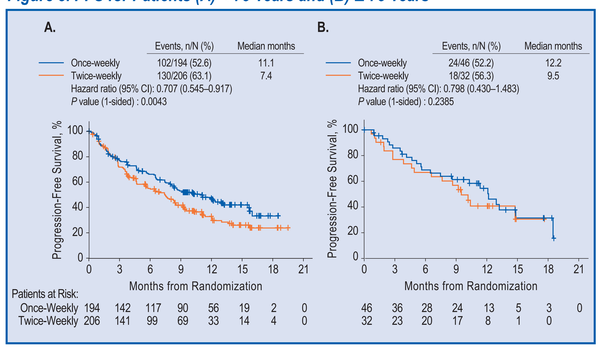
- Median PFS was prolonged with once-weekly Kd70 (12.2 months) versus twice-weekly Kd27 (5.6 months) treatment in for patients < 65 years (HR, 0.60; 95% CI, 0.42–0.86; P = 0.002) and for patients ≥ 65 years (11.2 versus 8.7 months; HR, 0.84; 95% CI, 0.61–1.15; P = 0.13; **Figure 2**; interaction between age groups and treatment, P = 0.11)

Figure 2. PFS for Patients (A) < 65 Years and (B) ≥ 65 Years



- Median PFS was also longer in the once-weekly Kd70 (11.1 months) versus twice-weekly Kd27 group (7.4 months) for patients < 75 years (HR, 0.71; 95 % CI, 0.55–0.92; P = 0.004) and for those ≥ 75 years (12.2 versus 9.5 months; HR, 0.80; 95% CI, 0.43–1.48; P = 0.24; **Figure 3**; interaction between age groups and treatment, P = 0.57)

Figure 3. PFS for Patients (A) < 75 Years and (B) ≥ 75 Years



- ORR was improved with once-weekly Kd70 versus twice-weekly Kd27 treatment for all patient age groups (**Table 2**)
- Across all age subgroups, a greater proportion of patients treated with once-weekly Kd70 achieved high quality responses (≥ VGPR) compared with those treated with twice-weekly Kd27 (**Table 2**)

Table 2. Overall Response Rate

	< 65 years		≥ 65 years		< 75 years		≥ 75 years	
	Once-weekly Kd70 (n = 104)	Twice-weekly Kd27 (n = 104)	Once-weekly Kd70 (n = 136)	Twice-weekly Kd27 (n = 134)	Once-weekly Kd70 (n = 194)	Twice-weekly Kd27 (n = 206)	Once weekly Kd70 (n = 46)	Twice-weekly Kd27 (n = 32)
ORR (95% CI), %	64.4 (54.4–73.6)	34.6 (25.6–44.6)	61.8 (53.0–70.0)	45.5 (36.9–54.3)	62.4 (55.1–69.2)	38.3 (31.7–45.4)	65.2 (49.8–78.6)	56.3 (37.7–73.6)
OR (95% CI)	3.42 (1.94–6.05)		1.93 (1.19–3.14)		2.67 (1.78–3.99)		1.46 (0.58–3.68)	
P value	<0.0001		0.0051		<0.0001		0.2412	
Best overall response, n (%)								
sCR	2 (1.9)	0	2 (1.5)	0	4 (2.1)	0	0	0
CR	7 (6.7)	4 (3.8)	6 (4.4)	0	12 (6.2)	4 (1.9)	1 (2.2)	0
VGPR	31 (29.8)	8 (7.7)	34 (25.0)	20 (14.9)	50 (25.8)	21 (10.2)	15 (32.6)	7 (21.9)
PR	27 (26.0)	24 (23.1)	42 (30.9)	41 (30.6)	55 (28.4)	54 (26.2)	14 (30.4)	11 (34.4)

CR = complete response; ORR = overall response rate; OR = odds ratio; sCR = stringent complete response; PR = partial response; VGPR = very good partial response.

- Carfilzomib treatment duration was longer in the once-weekly Kd70 group versus the twice-weekly Kd27 group in all evaluated age subgroups (**Table 3**)

Table 3. Duration of Treatment

	< 65 years		≥ 65 years		< 75 years		≥ 75 years	
	Once-weekly Kd70 (n = 104)	Twice-weekly Kd27 (n = 104)	Once-weekly Kd70 (n = 136)	Twice-weekly Kd27 (n = 134)	Once-weekly Kd70 (n = 194)	Twice-weekly Kd27 (n = 206)	Once weekly Kd70 (n = 46)	Twice-weekly Kd27 (n = 32)
Carfilzomib treatment duration, median (range)	41.1 (0.1–82.4)	21.3 (0.3–81.3)	37.1 (0.1–84.1)	35.5 (0.1–84.3)	37.9 (0.1–82.4)	26.4 (0.1–84.3)	40.1 (1.1–84.1)	37.3 (2.1–78.4)
Carfilzomib cycles received, median (range)	11.0 (1–21)	6.0 (1–21)	10.0 (1–22)	9.0 (1–22)	10.0 (1–21)	7.0 (1–22)	10.0 (1–22)	10.0 (1–20)

- Overall safety was generally comparable across age groups
  - Importantly, the incidence of grade ≥ 3 cardiovascular events was similar or numerically lower with once-weekly Kd70 versus the twice-weekly Kd27 regimen across age subgroups (**Table 4**)
  - Treatment-emergent fatal AEs occurred in 19 (9.2%) patients < 65 years, 21 (7.9%) patients ≥ 65 years, 34 (8.6%) patients < 75 years, and 6 (7.9%) patients ≥ 75 years (**Table 4**)

Table 4. AE Overview and AEs of Interest (Safety Population)

	< 65 years		≥ 65 years		< 75 years		≥ 75 years	
	Once-weekly Kd70 (n = 103)	Twice-weekly Kd27 (n = 103)	Once-weekly Kd70 (n = 135)	Twice-weekly Kd27 (n = 132)	Once-weekly Kd70 (n = 193)	Twice-weekly Kd27 (n = 204)	Once weekly Kd70 (n = 45)	Twice-weekly Kd27 (n = 31)
TEAEs, n (%)	95 (92.2)	100 (97.1)	132 (97.8)	129 (97.7)	182 (94.3)	198 (97.1)	45 (100.0)	31 (100.0)
Grade ≥3 TEAEs, n (%)	61 (59.2)	58 (56.3)	100 (74.1)	87 (65.9)	123 (63.7)	122 (59.8)	38 (84.4)	23 (74.2)
Grade ≥3 TEAEs of interest, n (%)								
Peripheral neuropathy	0	1 (1.0)	0	0	0	1 (0.5)	0	0
Acute renal failure	2 (1.9)	5 (4.9)	7 (5.2)	8 (6.1)	9 (4.7)	13 (6.4)	0	0
Acute kidney injury	1 (1.0)	3 (2.9)	7 (5.2)	5 (3.8)	8 (4.1)	8 (3.9)	0	0
Cardiac failure	1 (1.0)	6 (5.8)	6 (4.4)	4 (3.0)	6 (3.1)	8 (3.9)	1 (2.2)	2 (6.5)
Ischemic heart disease	1 (1.0)	0	1 (0.7)	2 (1.5)	1 (0.5)	1 (0.5)	1 (2.2)	1 (3.2)
Hypertension	4 (3.9)	2 (1.9)	10 (7.4)	11 (8.3)	8 (4.1)	9 (4.4)	6 (13.3)	4 (12.9)
Anemia	0	0	0	0	0	0	0	0
Thrombocytopenia	8 (7.8)	9 (8.7)	9 (6.7)	7 (5.3)	14 (7.3)	15 (7.4)	3 (6.7)	1 (3.2)
Neutropenia	7 (6.8)	10 (9.7)	7 (5.2)	6 (4.5)	10 (5.2)	14 (6.9)	4 (8.9)	2 (6.5)
TEAEs leading to carfilzomib discontinuation,* n (%)	7 (6.8)	14 (13.6)	23 (17.0)	13 (9.8)	22 (11.4)	22 (10.8)	8 (17.8)	5 (16.1)
TEAEs leading to dexamethasone discontinuation, n (%)	9 (8.7)	14 (13.6)	26 (19.3)	13 (9.8)	26 (13.5)	22 (10.8)	9 (20.0)	5 (16.1)
Fatal TEAEs, n (%)	10 (9.7)	9 (8.7)	12 (8.9)	9 (6.8)	20 (10.4)	14 (6.9)	2 (4.4)	4 (12.9)

*AEs leading to discontinuation of carfilzomib and dexamethasone were calculated from the efficacy population.
AE = adverse event; TEAE = treatment-emergent adverse event.

CONCLUSIONS

- Once-weekly Kd70 improved PFS and ORR for all age groups compared with twice-weekly Kd27
- Median treatment duration in the once-weekly Kd70 arm was comparable across age groups
- Improved clinical outcomes in elderly patients (≥ 75 years) treated with once-weekly Kd70 are consistent with findings in the phase 3 ENDEAVOR study[4]
- The incidence of grade ≥ 3 AEs for once-weekly Kd70 was comparable to that of twice-weekly Kd27 across age groups, and the safety profile according to age was generally consistent with the safety profile in the overall A.R.R.O.W. population
  - Of note, the rate of grade ≥ 3 cardiac failure was numerically lower with once-weekly Kd70 compared with twice-weekly Kd27 in elderly patients despite the higher dose of carfilzomib treatment
- Overall, once-weekly Kd70 is efficacious and safe across all age subgroups, including elderly patients who are traditionally more challenging to treat
- Based on the notable efficacy and favorable safety of once-weekly Kd, this dosing regimen should be considered as convenient carfilzomib treatment option for patients with RRMM irrespective of age

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DISCLOSURES

- MD has received honoraria from and served on advisory boards for Takeda, Celgene, Amgen, Janssen, and Bristol-Myers Squibb
- RN has received research grants from and served as a consultant for Celgene, Amgen, Takeda, Bristol-Myers Squibb, and Janssen
- PM has received honoraria from and served as a consultant for Amgen, Celgene, Takeda, Janssen, Bristol-Myers Squibb, Novartis, Millennium, and Onyx Pharmaceuticals
- DS has received honoraria from and served as a consultant for Celgene, Amgen, Merck, Janssen, Bristol-Myers Squibb, Takeda, and Karyopharm; has served on speakers bureaus for Celgene, Amgen, Merck, Janssen, Bristol-Myers Squibb, and Takeda; and has received research funding from Celgene
- RH has received honoraria and grants from Amgen, Janssen, Bristol-Myers Squibb, Takeda, Celgene, and Novartis
- M-VM has received honoraria from Amgen, Celgene, Takeda, and Janssen; and consulting or advisory role fees from Amgen, Celgene, Takeda, Janssen, AbbVie and GlaxoSmithKline
- MC has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda
- MH has received employment and stock from Amgen Inc
- AZ-K has received employment and stock from Amgen Inc
- KW has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda; has served on advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen, Juno, Sanofi, and Takeda; and has received institutional research funding from Amgen, Celgene, Sanofi, and Janssen

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Efficacy and Safety of Once-weekly vs Twice-weekly Carfilzomib Plus Dexamethasone: Subgroup Analysis of the Phase 3 A.R.R.O.W. Study (NCT02412878) by Prior Lines

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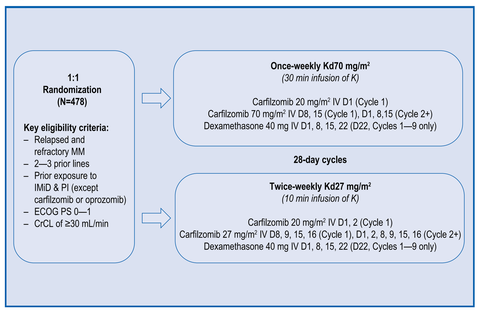
INTRODUCTION

- Carfilzomib, a selective, second-generation proteasome inhibitor, was originally approved for the treatment of relapsed or refractory multiple myeloma (MM) as a twice-weekly, intravenous infusion
- A more convenient, once-weekly carfilzomib dosing schedule was evaluated in the randomized, phase 3 A.R.R.O.W. study.[1] The results of this trial supported the recent approval in the United States of once-weekly carfilzomib (70 mg/m^2) in combination with dexamethasone (once-weekly Kd70 mg/m^2) for the treatment of patients with relapsed or refractory MM[2]
  - In the primary analysis, once-weekly Kd70 mg/m^2 extended median progression-free survival (PFS; primary endpoint) by 3.6 months compared with twice-weekly carfilzomib (27 mg/m^2) in combination with dexamethasone (twice-weekly Kd27 mg/m^2; 11.2 vs 7.6 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.54–0.88; two-sided *P*=0.0029) and demonstrated a superior overall response rate (ORR) of 62.9% vs 40.8%[1]
- The number and type of prior therapies may affect the efficacy of subsequent therapies.[3–5] Furthermore, as continuous treatment with lenalidomide has become a new standard of care in initial MM therapy,[6,7] there is an additional need to identify active regimens to treat patients exposed to lenalidomide
- We conducted a subgroup analysis of once-weekly Kd70 mg/m^2 versus twice-weekly Kd27 mg/m^2 by number of prior lines of therapy and prior lenalidomide exposure in patients with relapsed and refractory MM (RRMM) who enrolled in the A.R.R.O.W. study

METHODS

- A.R.R.O.W. was a randomized, multi-center, open-label, phase 3 study. Eligible patients included adults with RRMM who received 2 or 3 prior lines of therapy, including an immunomodulatory agent and proteasome inhibitor (except for carfilzomib and oprozomib), had a partial response to ≥1 prior line of therapy, and were refractory to their most recent therapy **(Figure 1)**
- Patients were randomized 1:1 to receive once-weekly Kd70 mg/m^2 or twice-weekly Kd27 mg/m^2 until disease progression, unacceptable toxicity, or withdrawal of consent
- PFS, ORR, and safety were evaluated in subgroups according to number of prior lines of therapy (2 vs 3) and prior lenalidomide exposure (yes vs no)
- Disease progression and response were assessed by the sponsor using the validated Response Computational Assessment Tool based on the International Myeloma Working Group Uniform Response Criteria[8,9]
- Comparisons of PFS and ORR between treatment arms of each subgroup were performed using an unstratified log-rank test and a Fisher exact test, respectively
- Safety outcomes were evaluated in all patients who received ≥1 dose of carfilzomib or dexamethasone

Figure 1. A.R.R.O.W. Study Design



CrCL, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMiD, immunomodulatory agent; IV, intravenous; K, carfilzomib; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone; MM, multiple myeloma; PI, proteasome inhibitor.

RESULTS

- Within the intent-to-treat population (N=478), 241 (50.4%) patients received 2 prior lines of therapy (once-weekly Kd70 mg/m^2, n=116; twice-weekly Kd27 mg/m^2, n=125) and 237 (49.6%) patients received 3 prior lines of therapy (once-weekly Kd70 mg/m^2, n=124; twice-weekly Kd27 mg/m^2, n=113) **(Table 1)**
- A total of 401 (83.9%) patients had prior exposure to lenalidomide (once-weekly Kd70 mg/m^2, n=207; twice-weekly Kd27 mg/m^2; n=194) **(Table 1)**
- Baseline characteristics were generally balanced between subgroups; in the 3 prior lines of therapy subgroup, the proportion of patients aged ≥75 years was higher in the once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 treatment arm (23.4% vs 11.5%; **Table 1**)

Table 1. Patient Baseline Demographic and Clinical Characteristics

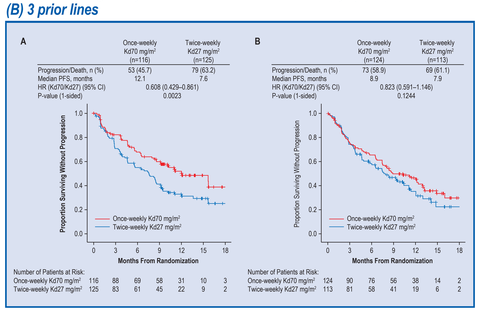
	2 prior lines		3 prior lines[a]	
	Once-weekly Kd70 mg/m^2 (n=116)	Twice-weekly Kd27 mg/m^2 (n=125)	Once-weekly Kd70 mg/m^2 (n=124)	Twice-weekly Kd27 mg/m^2 (n=113)
Age, median years (range)	65 (40–83)	66 (35–83)	69 (39–85)	65 (40–83)
Age (years), n (%)				
<75	99 (85.3)	106 (84.8)	95 (76.6)	100 (88.5)
≥75	17 (14.7)	19 (15.2)	29 (23.4)	13 (11.5)
Sex, n (%)				
Male	65 (56.0)	67 (53.6)	67 (54.0)	61 (54.0)
Female	51 (44.0)	58 (46.4)	57 (46.0)	52 (46.0)
ECOG PS, n (%)[b]				
0	58 (50.0)	66 (52.8)	60 (48.4)	52 (46.0)
1	57 (49.1)	59 (47.2)	64 (51.6)	61 (54.0)
ISS stage at baseline, n (%)				
Stage I	54 (46.6)	58 (46.4)	40 (32.3)	41 (36.3)
Stage II	36 (31.0)	40 (32.0)	44 (35.5)	41 (36.3)
Stage III	23 (19.8)	24 (19.2)	40 (32.3)	30 (26.5)
Missing	2 (1.7)	2 (1.6)	0	0
Risk group as determined by FISH, n (%)[c]				
High risk	21 (18.1)	25 (20.0)	13 (10.5)	22 (19.5)
Standard risk	19 (16.4)	37 (29.6)	28 (22.6)	16 (14.2)
Unknown	76 (65.5)	63 (50.4)	83 (66.9)	75 (66.4)
Baseline CrCL (mL/min), n (%)				
<30	2 (1.7)	1 (0.8)	0	0
30 to <50	21 (18.1)	14 (11.2)	27 (21.8)	20 (17.7)
50 to <80	39 (33.6)	59 (47.2)	52 (41.9)	52 (46.0)
≥80	54 (46.6)	50 (40.0)	45 (36.3)	41 (36.3)
Missing	0	1 (0.8)	0	0
β_2 microglobulin (mg/L), n (%)				
<3.5	61 (52.6)	61 (48.8)	46 (37.1)	45 (39.8)
≥3.5	52 (44.8)	61 (48.8)	78 (62.9)	67 (59.3)
Missing	3 (2.6)	3 (2.4)	0	1 (0.9)
Previous transplant, n (%)	76 (65.5)	80 (64.0)	70 (56.5)	77 (68.1)
Previous treatment, n (%)				
Bortezomib	114 (98.3)	124 (99.2)	122 (98.4)	113 (100.0)
Lenalidomide	93 (80.2)	94 (75.2)	114 (91.9)	100 (88.5)
Thalidomide	53 (45.7)	58 (46.4)	66 (53.2)	61 (54.0)
Refractory to any previous bortezomib, n (%)[d]	45 (38.8)	43 (34.4)	66 (53.2)	47 (41.6)
Refractory to any previous lenalidomide, n (%)	85 (73.3)	79 (63.2)	101 (81.5)	91 (80.5)
Refractory to any previous thalidomide, n (%)	16 (13.8)	20 (16.0)	23 (18.5)	29 (25.7)

[a]One patient received 4 prior therapies.
[b]One patient in the once-weekly Kd70 mg/m^2 treatment arm with 2 prior therapies had an ECOG PS of 2.
[c]Genetic abnormalities t(4; 14), t(14;16), and del(17p) are in the high risk group while standard risk patients did not have these genetic subtypes; based on historical FISH data.
[d]Patients were classified as refractory to any previous bortezomib if they were non-responsive to any bortezomib-containing regimen (i.e. BOR was stable or progressive disease) or had disease progression on treatment or within 60 days of bortezomib discontinuation.
BOR, best overall response; CrCL, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridization; ISS, International Staging System; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone.

Efficacy

- The cutoff date for this analysis of A.R.R.O.W. was June 15, 2017; the median follow-up time for PFS was 12.6 months and 12.0 months in the once-weekly Kd70 mg/m^2 and twice-weekly Kd27 mg/m^2 treatment arms, respectively
- Median PFS (once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2) for patients with 2 prior lines of therapy was 12.1 months vs 7.6 months (HR, 0.61; 95% CI, 0.43–0.86) and 8.9 months vs 7.9 months for patients with 3 prior lines of therapy (HR, 0.82; 95% CI, 0.59–1.15) **(Table 2, Figure 2)**
- ORRs for once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 were 62.9% vs 40.8% (odds ratio [OR], 2.46; 95% CI, 1.47–4.14) in patients with 2 prior lines of therapy and 62.9% vs 40.7% (OR, 2.47; 95% CI, 1.46–4.17) in patients with 3 prior lines of therapy **(Table 2)**
  - A greater proportion of once-weekly Kd70 mg/m^2 patients achieved a complete response or better compared with twice-weekly Kd27 mg/m^2, regardless of number of prior lines of therapy (2 prior lines, 9.5% vs 3.2%; 3 prior lines, 4.8% vs 0%)
- In patients with prior lenalidomide exposure, median PFS (once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2) was 11.1 months vs 7.4 months (HR, 0.72; 95% CI, 0.56–0.94) and not estimable vs 9.4 months (HR, 0.63; 95% CI, 0.33–1.21) in patients without prior lenalidomide exposure **(Figure 3)**
- ORRs (once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2) were 62.3% vs 39.2% (OR, 2.57; 95% CI, 1.72–3.84) in patients with prior lenalidomide exposure and 66.7% vs 47.7% (OR, 2.19; 95% CI, 0.86–5.58) in patients without prior lenalidomide exposure

Figure 2. Kaplan–Meier PFS Curves for Once-weekly Kd70 mg/m^2 vs Twice-weekly Kd27 mg/m^2 by Number of Prior Lines of Therapy: (A) 2 prior lines (B) 3 prior lines



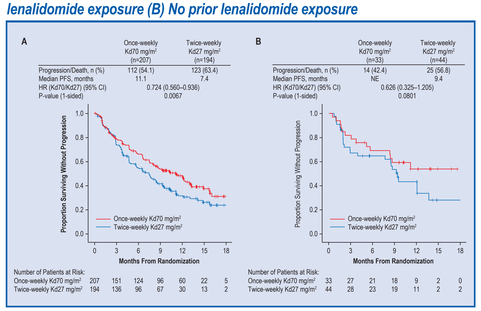
CI, confidence interval; HR, hazard ratio; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone; PFS, progression-free survival.

Table 2. Efficacy outcomes by prior lines of therapy

	2 prior lines		3 prior lines	
	Once-weekly Kd70 mg/m^2 (n=116)	Twice-weekly Kd27 mg/m^2 (n=125)	Once-weekly Kd70 mg/m^2 (n=124)	Twice-weekly Kd27 mg/m^2 (n=113)
Best overall response, n (%)				
Complete response or better	11 (9.5)	4 (3.2)	6 (4.8)	0
Very good partial response	32 (27.6)	14 (11.2)	33 (26.6)	14 (12.4)
Partial response	30 (25.9)	33 (26.4)	39 (31.5)	32 (28.3)
ORR, % (95% CI)	62.9 (53.5–71.7)	40.8 (32.1–49.9)	62.9 (53.8–71.4)	40.7 (31.6–50.4)
OR for once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 (95% CI)	2.463 (1.466–4.139)		2.470 (1.464–4.167)	
Median DOR, months (95% CI)	15.0 (14.8–NE)	14.8 (7.8–NE)	13.0 (11.1–NE)	13.2 (9.2–NE)

CI, confidence interval; DOR, duration of response; HR, hazard ratio; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone; NE, not estimable; OR, odds ratio; ORR, overall response rate.

Figure 3. Kaplan–Meier PFS Curves for Once-weekly Kd70 mg/m^2 vs Twice-weekly Kd27 mg/m^2 by Prior Lenalidomide Exposure: (A) Prior lenalidomide exposure (B) No prior lenalidomide exposure



CI, confidence interval; HR, hazard ratio; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone; NE, not estimable; PFS, progression-free survival.

Table 3. Incidence of treatment-emergent adverse events by number of prior lines of therapy

	2 prior lines		3 prior lines	
	Once-weekly Kd70 mg/m^2 (n=115)	Twice-weekly Kd27 mg/m^2 (n=123)	Once-weekly Kd70 mg/m^2 (n=123)	Twice-weekly Kd27 mg/m^2 (n=112)
Any-grade TEAEs, n (%)	107 (93.0)	121 (98.4)	120 (97.6)	108 (96.4)
Grade ≥3 TEAEs, n (%)	68 (59.1)	80 (65.0)	93 (75.6)	65 (58.0)
Most common grade ≥3 TEAEs, n (%)[a]				
Anemia	16 (13.9)	19 (15.4)	26 (21.1)	23 (20.5)
Pneumonia	12 (10.4)	7 (5.7)	12 (9.8)	9 (8.0)
Thrombocytopenia	7 (6.1)	9 (7.3)	10 (8.1)	7 (6.3)
Neutropenia	5 (4.3)	10 (8.1)	9 (7.3)	6 (5.4)
Hypertension	3 (2.6)	8 (6.5)	10 (8.1)	4 (3.6)
Platelet count decreased	2 (1.7)	8 (6.5)	8 (6.5)	4 (3.6)
Acute kidney injury	3 (2.6)	6 (4.9)	5 (4.1)	2 (1.8)
Fatigue	4 (3.5)	1 (0.8)	7 (5.7)	4 (3.6)
Cataract	2 (1.7)	4 (3.3)	5 (4.1)	2 (1.8)
Plasma cell myeloma	3 (2.6)	4 (3.3)	1 (0.8)	4 (3.6)
Hypercalcemia	2 (1.7)	4 (3.3)	1 (0.8)	2 (1.8)
Hyperglycemia	2 (1.7)	4 (3.3)	2 (1.6)	1 (0.9)
Sepsis	4 (3.5)	0	2 (1.6)	3 (2.7)
Tumor lysis syndrome	3 (2.6)	1 (0.8)	4 (3.3)	1 (0.9)
Neutrophil count decreased	3 (2.6)	1 (0.8)	4 (3.3)	0
Gamma-glutamyltransferase increased	1 (0.9)	1 (0.8)	4 (3.3)	0
Pyrexia	1 (0.9)	4 (3.3)	1 (0.8)	0
Septic shock	1 (0.9)	1 (0.8)	4 (3.3)	0
Syncope	1 (0.9)	1 (0.8)	4 (3.3)	0
Renal failure	0	0	1 (0.8)	4 (3.6)
Hyponatremia	0	0	4 (3.3)	0
Grade ≥3 TEAEs of interest, n (%)[b]				
Hypertension	3 (2.6)	8 (6.5)	11 (8.9)	5 (4.5)
Acute renal failure	3 (2.6)	6 (4.9)	6 (4.9)	7 (6.3)
Cardiac failure	3 (2.6)	3 (2.4)	4 (3.3)	7 (6.3)
Ischemic heart disease	2 (1.7)	0	0	2 (1.8)
TEAEs leading to carfilzomib discontinuation, n (%)	15 (13.0)	12 (9.8)	15 (12.2)	15 (13.4)
TEAEs leading to death, n (%)[c]	6 (5.2)	4 (3.3)	10 (8.1)	6 (5.4)

TEAEs were defined as any AE with an onset date from the first dose through 30 days after the last dose of any study drug. Patients were counted only once for each preferred term.
[a]Preferred terms occurring in ≥3% of patients in any subgroup.
[b]SMQN.
[c]Plasma cell myeloma and disease progression (preferred terms) were excluded.
AE, adverse event; Kd27, carfilzomib (27 mg/m^2) plus dexamethasone; Kd70, carfilzomib (70 mg/m^2) plus dexamethasone; SMQN, Standardized Medical Dictionary for Regulatory Activities Query, narrow scope; TEAE, treatment-emergent adverse event.

Safety

- Median carfilzomib treatment duration was 36.1 weeks (once-weekly Kd70 mg/m^2) and 32.3 weeks (twice-weekly Kd27 mg/m^2) in patients with 2 prior lines of therapy and 38.1 weeks (once-weekly Kd70 mg/m^2) and 27.7 weeks (twice-weekly Kd27 mg/m^2) in patients with 3 prior lines of therapy
- Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 59.1% (once-weekly Kd70 mg/m^2) and 65.0% (twice-weekly Kd27 mg/m^2) of patients who received 2 prior lines of therapy and 75.6% (once-weekly Kd70 mg/m^2) and 58.0% (twice-weekly Kd27 mg/m^2) of patients who received 3 prior lines of therapy **(Table 3)**; no grade ≥3 TEAEs (preferred term) had ≥5% difference in incidence between treatment arms
  - In patients treated with 3 prior lines of therapy, the higher incidence of grade ≥3 TEAEs in the once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 treatment arms may have been due to the higher proportion of patients aged 75–84 years (22.6% vs 11.5%) and/or the longer duration of carfilzomib treatment (median, 38.1 vs 27.7 weeks) in the once-weekly Kd70 mg/m^2 group
  - Rates of grade ≥3 TEAEs of interest (hypertension, acute renal failure, cardiac failure, and ischemic heart disease) are shown in **Table 3**
- Grade ≥3 TEAEs occurred in 69.3% (once-weekly Kd70 mg/m^2) and 60.2% (twice-weekly Kd27 mg/m^2) of patients with prior lenalidomide exposure and 57.6% (once-weekly Kd70 mg/m^2) and 68.2% (twice-weekly Kd27 mg/m^2) of patients without prior lenalidomide exposure

CONCLUSIONS

- **The results from this subgroup analysis of the A.R.R.O.W. study indicate that convenient once-weekly Kd70 mg/m^2 dosing has a better benefit-risk profile than twice-weekly Kd27 mg/m^2 dosing, regardless of the number of prior lines of therapy or prior lenalidomide exposure**
- **ORRs in the once-weekly Kd70 mg/m^2 arm were higher than those in the twice-weekly Kd27 mg/m^2 arm for patients with 2 prior lines of therapy (62.9% vs 40.8%; OR, 2.46) and 3 prior lines of therapy (62.9% vs 40.7%; OR, 2.47)**
- **Once-weekly Kd70 mg/m^2 extended median PFS by 4.5 months in patients with 2 prior therapies (12.1 vs 7.6 months; HR, 0.61) and by 1.0 month in patients with 3 prior therapies (8.9 vs 7.9 months; HR, 0.82); once-weekly Kd70 mg/m^2 also demonstrated superior efficacy compared to twice-weekly Kd27 mg/m^2, regardless of prior exposure to lenalidomide**
- **Consistent with previous reports,[3,4] patients with fewer prior therapies achieved a greater benefit with carfilzomib therapy (once- or twice-weekly), suggesting carfilzomib efficacy can be optimized by earlier administration in the disease course for patients with RRMM**
- **Safety profiles were generally consistent with those reported in the overall population**
  - **Importantly, the incidence of grade ≥3 cardiac failure was <7% across treatment arms and was lower for once-weekly Kd70 mg/m^2 (2.6%–3.3%)**
  - **No additional toxicities were found**
- **This subgroup analysis further confirmed the positive results from A.R.R.O.W. of using the more convenient once-weekly carfilzomib (70 mg/m^2) dosing schedule compared to twice-weekly carfilzomib (27 mg/m^2)**

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DISCLOSURES

PM has received honoraria and consulting fees from Amgen, Celgene, Janssen, Takeda, BMS, Novartis, Millennium, and Onyx. **AKS** has received consulting fees from Amgen, BMS, Celgene, Takeda, Roche, Seattle Genetics, Janssen, and Onc; received research funding from Amgen, Celgene, Roche, and Seattle Genetics. **AL** has received consulting fees from Celgene; received research funding from Celgene and Amgen. **MD** has receiving consulting fees from Janssen, Celgene, Amgen, Novartis, and Takeda; received research funding from Genesis Pharma. **MC** has received honoraria and membership on an entity's Board of Directors or has served on advisory committees for AbbVie, GlaxoSmithKline, BMS, Adaptive Biotechnologies, Takeda, Janssen, Celgene, and Amgen; has served on speakers bureau for Janssen and Celgene; has received research funding from Janssen and Celgene. **SA** has received consulting fees from Celgene, Takeda, Amgen, and Janssen; has received research funding from Pharmacyclics. **KI, MH,** and **AZ-K** are employees of, and own stock in, Amgen. **M-VM** has received honoraria from Celgene, Janssen, Takeda, and Amgen; received consulting fees from Amgen, GSK, Celgene, Janssen, Takeda, and Abbvie; has membership on Board of Directors or has served on advisory committees for Celgene, Janssen, Takeda, Amgen, GlaxoSmithKline, and AbbVie.

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