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Once- versus twice-weekly carfilzomib in relapsed and refractory multiple myeloma by select patient characteristics: phase 3 A.R.R.O.W. study subgroup analysis

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Abstract

The phase 3 A.R.R.O.W. study demonstrated that treatment with once-weekly carfilzomib (70 mg/m²) and dexamethasone (once-weekly Kd70 mg/m²) improved progression-free survival compared with twice-weekly carfilzomib (27 mg/m²) and dexamethasone (twice-weekly Kd27 mg/m²) in patients with relapsed and refractory multiple myeloma (RRMM; median, 11.2 versus 7.6 months; hazard ratio [HR] = 0.69; 95% confidence interval, 0.54–0.88; *P* = 0.0029). Once-weekly dosing also improved response rates and depth of response. We performed a subgroup analysis from A.R.R.O.W. according to age (<65, 65–74, or ≥75 years), renal function (creatinine clearance <50, ≥50–<80, or ≥80 mL/min), number of prior therapies (2 or 3), and bortezomib-refractory status (yes or no). Compared with twice-weekly Kd27 mg/m², once-weekly Kd70 mg/m² reduced the risk of progression or death (HR = 0.60–0.85) and increased overall response rates in nearly all the examined subgroups, consistent with reports in the overall A.R.R.O.W. population. The safety profiles of once-weekly Kd70 mg/m² across subgroups were also generally consistent with those in the overall population. Findings from this subgroup analysis generally demonstrate a favorable benefit–risk profile of once-weekly Kd70 mg/m², further supporting once-weekly carfilzomib dosing as an appropriate treatment option for patients with RRMM, regardless of baseline patient and disease characteristics.

Introduction

Multiple myeloma (MM) is the third most common hematologic malignancy worldwide, characterized by excessive proliferation of monoclonal plasma cells^{1,2}. The development of novel anti-MM agents has expanded treatment options for MM patients and improved outcomes³. Despite recent treatment advances, MM remains incurable, with most patients relapsing and developing treatment-refractory disease¹. Relapsed and refractory MM (RRMM) represents a challenging disease to treat,

given the heterogeneity of the disease and patient population^{3–5}.

Importantly, advanced age, Eastern Cooperative Oncology Group performance status (ECOG PS), International Staging System (ISS), renal impairment, exposure to multiple lines of therapy, refractoriness to treatment, and the presence of high-risk cytogenetics have been associated with poor prognosis and shorter survival in patients with MM (including RRMM)^{6–10}. Therefore, there is a continued need to identify safe and efficacious and ultimately convenient treatments across the heterogeneous RRMM patient population. For treatments with demonstrated safety and efficacy, convenience represents an important factor for optimizing adherence and patient quality of life^{11–13}.

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Carfilzomib (K) is a second-generation proteasome inhibitor (PI) with selective, irreversible, robust, and well-tolerated activity in MM, both as single agent¹⁴ and in combination with dexamethasone (Kd) or lenalidomide plus dexamethasone (KRd) when administered as a twice-weekly infusion in patients with RRMM¹⁵. Efficacy and safety of twice-weekly carfilzomib-based therapies were previously demonstrated in the phase 3 ASPIRE and ENDEAVOR trials^{16–19}. Importantly, the treatment effect of carfilzomib was confirmed across several patient subgroups^{20–26}. The favorable benefit–risk profile of twice-weekly carfilzomib-based therapies versus standards of care (SOCs) provided an opportunity to consider the value of more convenient once-weekly carfilzomib therapy for patients with RRMM.

The randomized phase 3 A.R.R.O.W. trial (NCT02412878) was designed to evaluate a once-weekly carfilzomib dosing schedule compared with twice-weekly administration in patients with RRMM²⁷. Patients were randomly assigned to receive once-weekly carfilzomib (70 mg/m²) with dexamethasone (once-weekly Kd70-mg/m² arm) or twice-weekly carfilzomib (27 mg/m²) with dexamethasone (twice-weekly Kd27-mg/m² arm). In the prespecified interim analysis, progression-free survival (PFS) and overall response rate (ORR) were improved in the once-weekly Kd70-mg/m² arm versus the twice-weekly Kd27-mg/m² arm (median PFS: 11.2 months versus 7.6 months; hazard ratio [HR] = 0.69; 95% confidence interval (CI), 0.54–0.88; *P* = 0.0029; ORR: 62.9% versus 40.8%). A greater proportion of once-weekly Kd70 mg/m² patients achieved a very good partial response or better (≥VGPR) and complete response or better (≥CR) compared with twice-weekly Kd27 mg/m² patients (≥VGPR, 34.2% versus 13.4%; ≥CR, 7.0% versus 1.7%). Safety was generally comparable between the treatment arms²⁷. Results from A.R.R.O.W. led to the recent approval of once-weekly Kd70 mg/m² for the treatment of patients with RRMM^{15,27}. Furthermore, compared with twice-weekly Kd27 mg/m², once-weekly Kd70 mg/m² improved treatment adherence, patient satisfaction, and health-related quality of life in patients with RRMM¹³. Overall, these results support the value of once-weekly carfilzomib as an additional, more convenient treatment option for patients with RRMM. Here we report results from a pre-planned subgroup analysis of A.R.R.O.W. to evaluate treatment effects by age, renal function, number of prior therapies, bortezomib-refractory status, ISS, and ECOG PS.

Methods

Study design and participants

Full A.R.R.O.W. study design details have been published previously²⁷. Eligibility criteria included: two or three previous lines of therapy, prior exposure to a PI and

an immunomodulatory drug (IMiD), refractory to most recent therapy, measurable disease (per International Myeloma Working Group [IMWG] consensus criteria^{28,29}), ECOG PS of 0 or 1, and calculated or measured creatinine clearance (CrCL) of ≥30 mL/min. The primary endpoint of A.R.R.O.W. was PFS. Secondary endpoints included ORR, OS, and safety. The study protocol was approved by the institutional review boards or ethics committees of all participating sites, and all patients provided written informed consent.

Procedures

Patients were randomized (1:1) to receive once-weekly Kd70 mg/m² or twice-weekly Kd27 mg/m². Treatment was given in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Patients in the once-weekly Kd70-mg/m² group received carfilzomib on days 1, 8, and 15 (20 mg/m² on day 1 [cycle 1]; 70 mg/m² thereafter; 30-min intravenous infusion). Twice-weekly Kd27 mg/m² patients received carfilzomib on days 1, 2, 8, 9, 15, and 16 (20 mg/m² on days 1 and 2 during cycle 1; 27 mg/m² thereafter; 10-min intravenous infusions). All patients received dexamethasone (40 mg) on days 1, 8, 15 (all cycles), and 22 (cycles 1–9 only).

Subgroups

Patients in the intention-to-treat (ITT) population were grouped according to age (<65, 65–74, or ≥75 years), renal function (baseline CrCL <50, ≥50 to <80, or ≥80 mL/min), prior lines of therapy (2 or 3), bortezomib-refractory status (yes or no), ECOG PS (0 or 1), and ISS stage (stages 1 and 2 or stage 3). Within 21 days prior to randomization, adequate bone marrow and organ function assessments were performed at a central laboratory. Renal function was calculated using the Cockcroft and Gault formula as follows: [(140 – Age) × Mass (kg)]/(72 × Creatinine (mg/dL)); results were multiplied by 0.85 for female patients. Patients were considered refractory to bortezomib if (A) they were non-responsive to any regimen containing bortezomib (i.e., best overall response was stable or progressive disease) or (B) disease progression occurred within 60 days of bortezomib treatment discontinuation²⁷. Here we report analyses of PFS, ORR, and safety in these prespecified subgroups. OS was not included because this data was not mature at the time of the interim analysis.

Assessments

PFS, ORR, and best overall response were assessed in the ITT population. Response and disease progression were evaluated from the time of randomization in accordance with the IMWG Uniform Response Criteria^{28,29}. Safety was assessed in all patients who received at least one dose of carfilzomib or dexamethasone.

Statistical analyses

Median PFS was estimated using the Kaplan–Meier method. HRs and corresponding 95% CIs were estimated using an unstratified Cox proportional hazards model. Comparisons between treatment arms were evaluated using an unstratified log-rank test. The Clopper–Pearson method was used to estimate 95% CIs for ORR. Mantel–Haenszel unadjusted estimates were used to estimate the odds ratio (OR) and corresponding 95% CI. Comparisons between treatment arms were evaluated using Fisher exact test. Reported *P* values are one sided and unadjusted for multiple comparisons.

Data sharing

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

Results

Patient enrollment

The cutoff date for the pre-planned interim analysis was June 15, 2017²⁷. Within the ITT population (*N* = 478), 240 patients received once-weekly Kd70 mg/m² and 238 received twice-weekly Kd27 mg/m². Baseline characteristics were generally balanced between treatment arms across subgroups. Select characteristics with ≥10% difference between treatment arms are shown in Supplementary Tables 1–4.

Efficacy

Age

In total, 208 patients (43.5%) were aged <65 years (once-weekly Kd70 mg/m², *n* = 104; twice-weekly Kd27 mg/m², *n* = 104), 192 patients (40.2%) were aged 65–74 years (*n* = 90; *n* = 102), and 78 (16.3%) patients were aged ≥75 years (*n* = 46; *n* = 32). The median PFS in patients aged <65 years was longer in the once-weekly Kd70-mg/m² arm compared with the twice-weekly Kd27-mg/m² group (12.2 versus 5.6 months; HR = 0.60; 95% CI, 0.42–0.86; *P* = 0.0024; Fig. 1). Among patients aged 65–74 and ≥75 years, median PFS (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) was 9.2 versus 8.4 months (HR = 0.84; 95% CI, 0.58–1.23; *P* = 0.1866) and 12.2 versus 9.5 months (HR = 0.80; 95% CI, 0.43–1.48; *P* = 0.2385), respectively.

Response by age is shown in Table 1. ORR was improved with once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m² for all age subgroups. ORRs (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) were 64.4% versus 34.6% (OR, 3.42; 95% CI, 1.94–6.05) in patients aged <65 years, 60.0% versus 42.2% (OR, 2.06; 95% CI, 1.16–3.66) in patients aged 65–74 years, and 65.2% versus 56.3% (OR, 1.46; 95% CI, 0.58–3.68) in patients aged ≥75 years. Regardless of age, a higher

proportion of patients treated with once-weekly Kd70 mg/m² achieved a ≥VGPR and a ≥CR versus twice-weekly Kd27 mg/m² (Table 1).

Renal function

Eighty-five (17.8%) patients had baseline CrCL <50 mL/min (once-weekly Kd70 mg/m², *n* = 50; twice-weekly Kd27 mg/m², *n* = 35), 202 (42.3%) patients had baseline CrCL ≥50 to <80 mL/min (*n* = 91; *n* = 111), and 190 (39.7%) patients had baseline CrCL ≥80 mL/min (*n* = 99; *n* = 91). Median PFS (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) was 10.3 versus 8.7 months (HR = 0.85; 95% CI, 0.48–1.53; *P* = 0.2931) in patients with CrCL <50 mL/min, 12.4 versus 7.6 months (HR = 0.64; 95% CI, 0.44–0.94; *P* = 0.0112) in patients with CrCL ≥50 to <80 mL/min, and 8.6 versus 7.5 months (HR = 0.71; 95% CI, 0.49–1.02; *P* = 0.0305) in patients with CrCL ≥80 mL/min (Fig. 1).

ORR was improved with once-weekly Kd70 mg/m² across all renal function subgroups (Table 1). The ORRs for once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m² were 50.0% versus 40.0% (OR, 1.50; 95% CI, 0.63–3.60) in patients with CrCL <50 mL/min, 65.9% versus 39.6% (OR, 2.95; 95% CI, 1.66–5.25) in patients with CrCL ≥50 to <80 mL/min, and 66.7% versus 42.9% (OR, 2.67; 95% CI, 1.48–4.81) in patients with CrCL ≥80 mL/min. A greater proportion of once-weekly Kd70-mg/m² patients achieved ≥VGPR and ≥CR versus twice-weekly Kd27 mg/m² across all renal function subgroups (Table 1).

Prior lines of therapy

Within the ITT population, 241 (50.4%) patients received two prior therapies (once-weekly Kd70 mg/m², *n* = 116; twice-weekly Kd27 mg/m², *n* = 125) and 237 (49.6%) patients received three prior therapies (*n* = 124; *n* = 113). Median PFS was comparable or better in patients treated with once-weekly Kd70 mg/m² vs twice-weekly Kd27 mg/m² according to prior number of therapies. Median PFS (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) was 12.1 versus 7.6 months (HR = 0.61; 95% CI, 0.43–0.86; *P* = 0.0023) in the two prior therapies subgroup and 8.9 versus 7.9 months (HR = 0.82; 95% CI, 0.59–1.15; *P* = 0.1244) in the three prior therapy subgroup (Fig. 2).

ORRs for once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m² were 62.9% versus 40.8% (OR, 2.46; 95% CI, 1.47–4.14) in the two prior line subgroup and 62.9% versus 40.7% (OR, 2.47; 95% CI, 1.46–4.17) in the three prior line subgroup, respectively. Patients treated with once-weekly Kd70 mg/m² achieved higher rates of ≥VGPR and ≥CR versus those treated with twice-weekly Kd27 mg/m² regardless of the number of prior lines of therapy (Table 2).

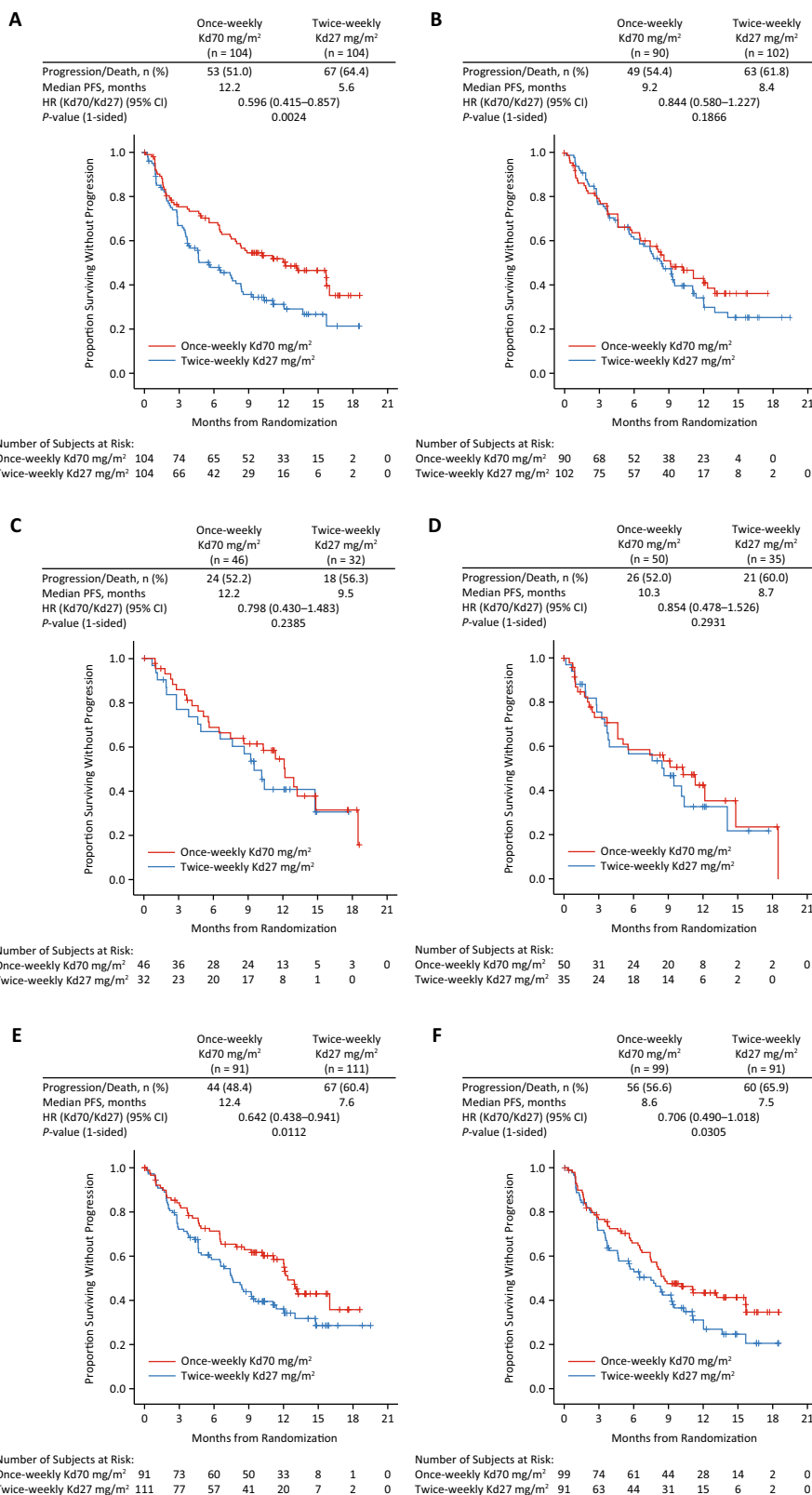


Fig. 1 Kaplan–Meier curves for progression-free survival by subgroups' age and renal function. **a** <65 years, **b** 65–74 years, **c** ≥75 years, **d** creatinine clearance (CrCL) <50 mL/min, **e** CrCL ≥50–<80 mL/min, **f** CrCL ≥80 mL/min.

Table 1 Response rates by age and renal function subgroups.

Subgroup	Baseline creatinine clearance											
	<65 years		65–74 years		≥75 years		<50 mL/min		≥50–<80 mL/min		≥80 mL/min	
	Once-weekly Kd70 mg/m ² (n = 104)	Twice-weekly Kd27 mg/m ² (n = 104)	Once-weekly Kd70 mg/m ² (n = 90)	Twice-weekly Kd27 mg/m ² (n = 102)	Once-weekly Kd70 mg/m ² (n = 46)	Twice-weekly Kd27 mg/m ² (n = 32)	Once-weekly Kd70 mg/m ² (n = 50)	Twice-weekly Kd27 mg/m ² (n = 35)	Once-weekly Kd70 mg/m ² (n = 91)	Twice-weekly Kd27 mg/m ² (n = 111)	Once-weekly Kd70 mg/m ² (n = 99)	Twice-weekly Kd27 mg/m ² (n = 91)
Best overall response, n (%)	0	0	2 (2.2)	0	0	0	1 (2.0)	0	2 (2.2)	0	1 (1.0)	0
sCR	2 (1.9)	4 (3.8)	5 (5.6)	0	1 (2.2)	0	1 (2.0)	0	5 (5.5)	1 (0.9)	7 (7.1)	3 (3.3)
CR	7 (6.7)	8 (7.7)	19 (21.1)	13 (12.7)	15 (32.6)	7 (21.9)	11 (22.0)	7 (20.0)	24 (26.4)	11 (9.9)	30 (30.3)	10 (11.0)
VGPR	31 (29.8)	27 (26.0)	28 (31.1)	30 (29.4)	14 (30.4)	11 (34.4)	12 (24.0)	7 (20.0)	29 (31.9)	32 (28.8)	28 (28.3)	26 (28.6)
PR	27 (26.0)	36 (34.6)	54 (60.0)	43 (42.2)	30 (65.2)	18 (56.3)	25 (50.0)	14 (40.0)	60 (65.9)	44 (39.6)	66 (66.7)	39 (42.9)
ORR, n (%)	67 (64.4)	3420 (1.935–6.045)	2.058 (1.156–3.663)	1.458 (0.578–3.678)	1.458 (0.578–3.678)	1.458 (0.578–3.678)	1.500 (0.626–3.596)	2.947 (1.656–5.246)	2.947 (1.656–5.246)	2.947 (1.656–5.246)	2.947 (1.656–5.246)	2.947 (1.656–5.246)
OR (95% CI)	3.420 (1.935–6.045)											
P value	<0.0001	0.0073	0.0073	0.2412	0.2412	0.1929	0.0001	0.0006	0.0006	0.0006	0.0006	0.0006

CI confidence interval, CR complete response, Kd27 carfilzomib (27 mg/m²) with dexamethasone, Kd70 carfilzomib (70 mg/m²) with dexamethasone, OR odds ratio, ORR overall response rate, PR partial response, sCR stringent complete response, VGPR very good partial response.

Bortezomib-refractory status

Within the ITT population, 201 (42.1%) patients were bortezomib refractory (once-weekly Kd70 mg/m², n = 111; twice-weekly Kd27 mg/m², n = 90) and 277 (57.9%) patients were not bortezomib refractory (n = 129; n = 148). Median PFS (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) was 10.3 versus 7.4 months (HR = 0.73; 95% CI, 0.51–1.05; P = 0.0440) in patients with disease refractory to bortezomib and 12.1 versus 7.7 months (HR = 0.70; 95% CI, 0.51–0.96; P = 0.0124) in patients with disease not refractory to bortezomib (Fig. 2). Twice-weekly Kd27 mg/m² had similar median PFS outcomes, irrespective of disease sensitivity to bortezomib.

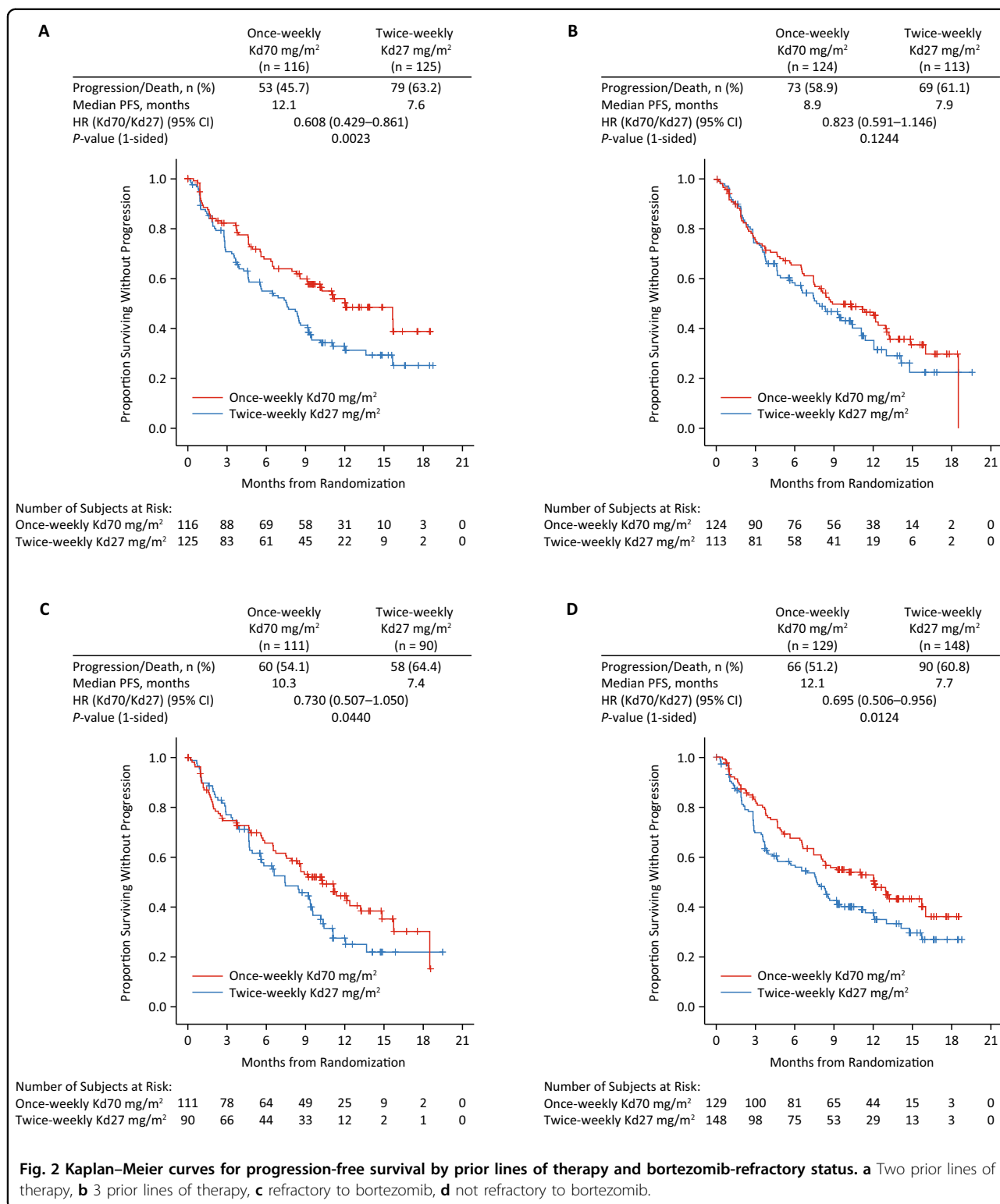
Patients treated with once-weekly Kd70 mg/m² demonstrated higher response rates compared with those treated with twice-weekly Kd27 mg/m² across subgroups based on disease sensitivity to bortezomib. ORRs (once-weekly Kd70 mg/m² versus twice-weekly Kd27 mg/m²) were 57.7% versus 42.2% (OR, 1.86; 95% CI, 1.06–3.27) in patients with bortezomib-refractory disease and 67.4% versus 39.9% (OR, 3.13; 95% CI, 1.91–5.12) in patients with disease not refractory to bortezomib. Regardless of bortezomib-refractory status, a greater proportion of once-weekly Kd70-mg/m² patients achieved ≥VGPR and ≥CR versus twice-weekly Kd27-mg/m² patients (Table 2).

Safety

Age

The median number of cycles patients received carfilzomib (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 11 and 6 cycles in patients aged <65 years, 9 and 9 cycles in patients aged 65–74 years, and 10 and 10 cycles in patients aged ≥75 years, respectively. Median carfilzomib treatment duration was higher in the once-weekly Kd70-mg/m² treatment arm relative to the twice-weekly Kd27-mg/m² treatment arm in patients aged <65 years (41.1 and 21.3 weeks, respectively); median treatment duration was 33.1 and 34.9 weeks in patients aged 65–74 years, and 40.1 and 37.3 weeks in patients aged ≥75 years, respectively. Treatment-emergent adverse events (TEAEs) by age are shown in Table 3. The incidence of grade ≥3 TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 59.2% and 56.3% (<65 years), 68.9% and 63.4% (65–74 years), and 84.4% and 74.2% (≥75 years), respectively. Rates of grade ≥3 cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) were 1.0% and 5.8%, 5.6% and 2.0%, and 2.2% and 6.5% in these age subgroups, respectively.

TEAEs leading to carfilzomib discontinuation (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) occurred at rates of 6.8% and 13.6% (<65 years), 16.7% and 7.9% (65–74 years), and 17.8% and 16.1% (≥75 years); rates of TEAEs leading to dexamethasone discontinuation were 8.7% and 13.6%, 18.9% and 7.9%, and 20.0% and



16.1%, respectively. Incidence of fatal TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 9.7% and 8.7% (<65 years), 11.1% and 5.0% (65–74 years), and 4.4% and 12.9% (≥75 years).

Renal function

TEAEs by renal function are shown in Table 3. Rates of grade ≥3 TEAEs by baseline CrCL (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) were 77.6% and

Table 2 Response rates by prior lines of therapy and bortezomib-refractory status subgroups.

Subgroup	Prior lines of therapy				Bortezomib-refractory status			
	2 prior lines		3 prior lines		Refractory to bortezomib		Not refractory to bortezomib	
	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)	Once-weekly Kd70 mg/m ² (n = 111)	Twice-weekly Kd27 mg/m ² (n = 90)	Once-weekly Kd70 mg/m ² (n = 129)	Twice-weekly Kd27 mg/m ² (n = 148)
Best overall response, n (%)								
sCR	1 (0.9)	0	3 (2.4)	0	0	0	4 (3.1)	0
CR	10 (8.6)	4 (3.2)	3 (2.4)	0	7 (6.3)	2 (2.2)	6 (4.7)	2 (1.4)
VGPR	32 (27.6)	14 (11.2)	33 (26.6)	14 (12.4)	23 (20.7)	4 (4.4)	42 (32.6)	24 (16.2)
PR	30 (25.9)	33 (26.4)	39 (31.5)	32 (28.3)	34 (30.6)	32 (35.6)	35 (27.1)	33 (22.3)
ORR, n (%)	73 (62.9)	51 (40.8)	78 (62.9)	46 (40.7)	64 (57.7)	38 (42.2)	87 (67.4)	59 (39.9)
OR (95% CI)	2.463 (1.466–4.139)		2.470 (1.464–4.167)		1.863 (1.061–3.271)		3.125 (1.907–5.120)	
P value	0.0004		0.0004		0.0169		<0.0001	

CI confidence interval, CR complete response, Kd27 carfilzomib (27 mg/m²) with dexamethasone, Kd70 carfilzomib (70 mg/m²) with dexamethasone, OR odds ratio, ORR overall response rate, PR partial response, sCR stringent complete response, VGPR very good partial response.

70.6% (CrCL < 50 mL/min), 71.1% and 61.5% (CrCL ≥ 50 to <80 mL/min), and 59.6% and 59.3% (CrCL ≥ 80 mL/min). The incidence of grade ≥3 cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 2.0% and 5.9%, 6.7% and 3.7%, and 0% and 4.4% in these renal function subgroups, respectively.

TEAEs leading to carfilzomib discontinuation (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) occurred at rates of 28.6% and 14.7% (CrCL < 50 mL/min), 14.4% and 11.0% (CrCL ≥ 50 to <80 mL/min), and 3.0% and 11.0% (CrCL ≥ 80 mL/min); rates of TEAEs leading to dexamethasone discontinuation were 30.6% and 14.7%, 16.7% and 11.0%, and 5.1% and 11.0%, respectively. Incidence of fatal TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 18.4% and 17.6% (CrCL < 50 mL/min), 6.7% and 4.6% (CrCL ≥ 50 to <80 mL/min), and 7.1% and 7.7% (CrCL ≥ 80 mL/min).

Prior lines of therapy

TEAEs by prior lines of therapy are shown in Table 4. The incidence of grade ≥3 TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 59.1% and 65.0% (2 prior lines) and 75.6% and 58.0% (3 prior lines). The incidence of grade ≥3 cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 2.6% and 2.4% (2 prior lines) and 3.3% and 6.3% (3 prior lines).

TEAEs leading to carfilzomib discontinuation (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) occurred at rates of 13.0% and 9.8% (2 prior lines) and 12.2% and 13.4% (3 prior lines); rates of TEAEs leading to dexamethasone discontinuation were 16.5% and 9.8% (2 prior lines) and 13.0% and 13.4% (3 prior lines). The

incidence of fatal TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) was 8.7% and 6.5% (2 prior lines) and 9.8% and 8.9% (3 prior lines).

Bortezomib-refractory status

Rates of TEAEs by bortezomib-refractory status are shown in Table 4. Frequencies of grade ≥3 TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) were 68.2% and 61.8% (refractory to bortezomib) and 67.2% and 61.6% (not refractory to bortezomib). The frequencies of grade ≥3 cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) by bortezomib-refractory status were 4.5% and 6.7% (refractory to bortezomib) and 1.6% and 2.7% (not refractory to bortezomib).

TEAEs leading to carfilzomib discontinuation (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) occurred at rates of 14.5% and 10.1% (refractory to bortezomib) and 10.9% and 12.3% (not refractory to bortezomib); frequencies of TEAEs leading to dexamethasone discontinuation were 14.5% and 10.1% (refractory to bortezomib) and 14.8% and 12.3% (not refractory to bortezomib). Rates of fatal TEAEs (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) were 6.4% and 7.9% (refractory to bortezomib) and 11.7% and 7.5% (not refractory to bortezomib).

ECOG PS and ISS stage

Rates of grade ≥3 TEAEs of interest are shown in Supplementary Table 5. The incidence of grade ≥3 cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) by ECOG PS was 1.7% and 2.6% (ECOG PS of 0) and 4.2% and 5.9% (ECOG PS of 1). The rates of grade ≥3

Table 3 Safety in once-weekly Kd70-mg/m² versus twice-weekly Kd27-mg/m² treatment arms by age and renal function subgroups.

Subgroup	Baseline creatinine clearance											
	Age		65–74 years		≥75 years		<50 mL/min		≥50–<80 mL/min		≥80 mL/min	
	Once-weekly Kd70 mg/m ² (n = 103)	Twice-weekly Kd27 mg/m ² (n = 103)	Once-weekly Kd70 mg/m ² (n = 90)	Twice-weekly Kd27 mg/m ² (n = 101)	Once-weekly Kd70 mg/m ² (n = 45)	Twice-weekly Kd27 mg/m ² (n = 31)	Once-weekly Kd70 mg/m ² (n = 49)	Twice-weekly Kd27 mg/m ² (n = 34)	Once-weekly Kd70 mg/m ² (n = 90)	Twice-weekly Kd27 mg/m ² (n = 109)	Once-weekly Kd70 mg/m ² (n = 99)	Twice-weekly Kd27 mg/m ² (n = 91)
Any grade TEAEs, n (%)	95 (92.2)	100 (97.1)	87 (96.7)	98 (97.0)	45 (100.0)	31 (100.0)	47 (95.9)	33 (97.1)	89 (98.9)	106 (97.2)	91 (91.9)	89 (97.8)
Grade ≥3 TEAEs, n (%)	61 (59.2)	58 (56.3)	62 (68.9)	64 (63.4)	38 (84.4)	23 (74.2)	38 (77.6)	24 (70.6)	64 (71.1)	67 (61.5)	59 (59.6)	54 (59.3)
Grade ≥3 TEAEs of interest, n (%)												
Peripheral neuropathy	0	1 (1.0)	0	0	0	0	0	0	0	1 (0.9)	0	0
Acute renal failure	2 (1.9)	5 (4.9)	7 (7.8)	8 (7.9)	0	0	5 (10.2)	2 (5.9)	3 (3.3)	7 (6.4)	1 (1.0)	4 (4.4)
Acute kidney injury	1 (1.0)	3 (2.9)	7 (7.8)	5 (5.0)	0	0	4 (8.2)	0	3 (3.3)	5 (4.6)	1 (1.0)	3 (3.3)
Cardiac failure	1 (1.0)	6 (5.8)	5 (5.6)	2 (2.0)	1 (2.2)	2 (6.5)	1 (2.0)	2 (5.9)	6 (6.7)	4 (3.7)	0	4 (4.4)
Ischemic heart disease	1 (1.0)	0	0	1 (1.0)	1 (2.2)	1 (3.2)	1 (2.0)	1 (2.9)	0	0	1 (1.0)	1 (1.1)
Pulmonary hypertension	0	1 (1.0)	0	0	0	0	0	1 (2.9)	0	0	0	0
Hypertension	4 (3.9)	2 (1.9)	4 (4.4)	7 (6.9)	6 (13.3)	4 (12.9)	5 (10.2)	2 (5.9)	5 (5.6)	8 (7.3)	4 (4.0)	3 (3.3)
Anemia	17 (16.5)	23 (22.3)	15 (16.7)	18 (17.8)	10 (22.2)	1 (3.2)	16 (32.7)	9 (26.5)	14 (15.6)	19 (17.4)	12 (12.1)	14 (15.4)
Thrombocytopenia	8 (7.8)	9 (8.7)	6 (6.7)	6 (5.9)	3 (6.7)	1 (3.2)	5 (10.2)	3 (8.8)	5 (5.6)	6 (5.5)	7 (7.1)	7 (7.7)
Neutropenia	7 (6.8)	10 (9.7)	3 (3.3)	4 (4.0)	4 (8.9)	2 (6.5)	4 (8.2)	2 (5.9)	6 (6.7)	5 (4.6)	4 (4.0)	9 (9.9)
TEAEs leading to carfilzomib discontinuation, n (%)	7 (6.8)	14 (13.6)	15 (16.7)	8 (7.9)	8 (17.8)	5 (16.1)	14 (28.6)	5 (14.7)	13 (14.4)	12 (11.0)	3 (3.0)	10 (11.0)
TEAEs leading to dexamethasone discontinuation, n (%)	9 (8.7)	14 (13.6)	17 (18.9)	8 (7.9)	9 (20.0)	5 (16.1)	15 (30.6)	5 (14.7)	15 (16.7)	12 (11.0)	5 (5.1)	10 (11.0)
TEAEs leading to death, n (%)	10 (9.7)	9 (8.7)	10 (11.1)	5 (5.0)	2 (4.4)	4 (12.9)	9 (18.4)	6 (17.6)	6 (6.7)	5 (4.6)	7 (7.1)	7 (7.7)

TEAEs are defined as any adverse event with an onset date from the first dose through 30 days after the last dose of any study drug.

Adverse events were coded using MedDRA version 20.0 and graded using NCI-CTCAE (version 4.03).

Subjects were counted only once for each search strategy and each preferred term.

Adverse events (peripheral neuropathy, cardiac failure, ischemic heart disease, and pulmonary hypertension) are listed as SMO, narrow scope or preferred terms (acute kidney injury, anemia, thrombocytopenia, and neutropenia).

Kd27 carfilzomib (27 mg/m²) with dexamethasone, Kd70 carfilzomib (70 mg/m²) with dexamethasone, MedDRA Medical Dictionary for Regulatory Activities, NCI-CTCAE National Cancer Institute–Common Terminology Criteria for Adverse Events, SMO Standardized MedDRA Queries, TEAE treatment-emergent adverse event.

Table 4 Safety in once-weekly Kd70-mg/m² versus twice-weekly Kd27-mg/m² treatment arms by prior lines of therapy and bortezomib-refractory status subgroups.

Subgroup	Prior lines of therapy				Bortezomib-refractory status			
	2 prior lines		3 prior lines		Refractory to bortezomib		Not refractory to bortezomib	
	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)	Once-weekly Kd70 mg/m ² (n = 110)	Twice-weekly Kd27 mg/m ² (n = 89)	Once-weekly Kd70 mg/m ² (n = 128)	Twice-weekly Kd27 mg/m ² (n = 146)
Any grade TEAEs, n (%)	107 (93.0)	121 (98.4)	120 (97.6)	108 (96.4)	104 (94.5)	88 (98.9)	123 (96.1)	141 (96.6)
Grade ≥3 TEAEs, n (%)	68 (59.1)	80 (65.0)	93 (75.6)	65 (58.0)	75 (68.2)	55 (61.8)	86 (67.2)	90 (61.6)
Grade ≥3 TEAEs of interest, n (%)								
Peripheral neuropathy	0	0	0	1 (0.9)	0	0	0	1 (0.7)
Acute renal failure	3 (2.6)	6 (4.9)	6 (4.9)	7 (6.3)	4 (3.6)	3 (3.4)	5 (3.9)	10 (6.8)
Acute kidney injury	3 (2.6)	6 (4.9)	5 (4.1)	2 (1.8)	3 (2.7)	2 (2.2)	5 (3.9)	6 (4.1)
Cardiac failure	3 (2.6)	3 (2.4)	4 (3.3)	7 (6.3)	5 (4.5)	6 (6.7)	2 (1.6)	4 (2.7)
Ischemic heart disease	2 (1.7)	0	0	2 (1.8)	1 (0.9)	1 (1.1)	1 (0.8)	1 (0.7)
Pulmonary hypertension	0	0	0	1 (0.9)	0	1 (1.1)	0	0
Hypertension	3 (2.6)	8 (6.5)	11 (8.9)	5 (4.5)	6 (5.5)	7 (7.9)	8 (6.3)	6 (4.1)
Anemia	16 (13.9)	19 (15.4)	26 (21.1)	23 (20.5)	24 (21.8)	16 (18.0)	18 (14.1)	26 (17.8)
Thrombocytopenia	7 (6.1)	9 (7.3)	10 (8.1)	7 (6.3)	10 (9.1)	7 (7.9)	7 (5.5)	9 (6.2)
Neutropenia	5 (4.3)	10 (8.1)	9 (7.3)	6 (5.4)	7 (6.4)	7 (7.9)	7 (5.5)	9 (6.2)
TEAEs leading to carfilzomib discontinuation, n (%)	15 (13.0)	12 (9.8)	15 (12.2)	15 (13.4)	16 (14.5)	9 (10.1)	14 (10.9)	18 (12.3)
TEAEs leading to dexamethasone discontinuation, n (%)	19 (16.5)	12 (9.8)	16 (13.0)	15 (13.4)	16 (14.5)	9 (10.1)	19 (14.8)	18 (12.3)
TEAEs leading to death, n (%)	10 (8.7)	8 (6.5)	12 (9.8)	10 (8.9)	7 (6.4)	7 (7.9)	15 (11.7)	11 (7.5)

TEAEs are defined as any adverse event with an onset date from the first dose through 30 days after the last dose of any study drug. Adverse events were coded using MedDRA version 20.0 and graded using NCI-CTCAE (version 4.03). Subjects were counted only once for each search strategy and each preferred term. Adverse events (peripheral neuropathy, cardiac failure, ischemic heart disease, and pulmonary hypertension) are listed as SMQ, narrow scope or preferred terms (acute kidney injury, anemia, thrombocytopenia, and neutropenia). Kd27 carfilzomib (27 mg/m²) with dexamethasone, Kd70 carfilzomib (70 mg/m²) with dexamethasone, MedDRA Medical Dictionary for Regulatory Activities, NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events, SMQ Standardized MedDRA Queries, TEAE treatment-emergent adverse event.

cardiac failure (once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m²) by ISS stage were 2.3% and 4.0% (ISS stages 1 and 2) and 4.8% and 3.7% (ISS stage 3).

Discussion

In this pre-planned subgroup analysis of the A.R.R.O.W. study, patients were evaluated by age, renal function, prior lines of therapy, bortezomib-refractory status, ECOG PS, and ISS stage. These factors have demonstrated prognostic significance in RRMM^{6–10} and are important considerations when selecting therapy. Across nearly all examined subgroups in A.R.R.O.W., once-weekly administration of carfilzomib at the higher 70-mg/m² dose in combination with dexamethasone was associated with longer median PFS and higher ORR compared with twice-weekly administration of carfilzomib at the 27-mg/m² dose in combination with dexamethasone. These findings are consistent with those in the overall population²⁷. Part of the observed benefit in patients receiving once-weekly Kd70 mg/m² in A.R.R.O.W. is likely due to the higher dose of carfilzomib administered in this treatment arm. Furthermore, patient-reported outcomes analysis reinforced that the higher 70-mg/m² carfilzomib dose is convenient and provided more favorable health-related quality of life than the 27-mg/m² carfilzomib dose¹³. Adherence to therapy might have improved for patients treated with once-weekly Kd70 mg/m² due to the more convenient weekly carfilzomib dosing schedule, which could have translated to improved clinical outcomes.

Elderly patients with MM are a challenging population to treat, in part due to higher chemotherapy toxicities³⁰ and comorbidity burden^{31,32}. In ENDEAVOR and ASPIRE, analyses of twice-weekly carfilzomib-based therapies by age demonstrated consistent improvements in PFS and OS compared with the control treatment arms across all subgroups^{20,21}. In A.R.R.O.W., once-weekly Kd70 mg/m² improved PFS and ORR for all age subgroups versus twice-weekly Kd27 mg/m². Compared with the two older-age subgroups, patients in the younger subgroup (aged <65 years) received a greater median number of cycles of treatment in the once-weekly Kd70 mg/m² arm than in the twice-weekly Kd27 mg/m² arm. Since patients aged <65 years stayed on treatment longer with once-weekly Kd70 mg/m² compared with twice-weekly Kd27 mg/m² relative to the older-age subgroups, the younger-age patients receiving once-weekly Kd70 mg/m² were able to derive a greater PFS benefit.

The safety profile for once-weekly Kd70 mg/m² was generally comparable to twice-weekly Kd27 mg/m² across all assessed age subgroups. In patients aged <65 years, the shorter median duration of carfilzomib administration in the twice-weekly Kd27 mg/m² arm (21.3 weeks) compared to once-weekly Kd70 mg/m² (41.1 weeks) may be partially explained by the higher incidence of disease

progression or death in the twice-weekly Kd27-mg/m² arm (64.4%) compared to the once-weekly Kd70-mg/m² arm (51.0%) (Fig. 1a). In patients aged ≥75 years, the higher incidence of grade ≥3 TEAEs in the once-weekly Kd70-mg/m² group (84.4%) compared to those in the twice-weekly Kd27-mg/m² group (74.2%) may be due to the higher proportion of patients with baseline CrCL 30–<50 mL/min (56.5% versus 40.6%). Overall, once-weekly Kd70 mg/m² was effective and well tolerated in patients with RRMM regardless of age. The improved convenience of the once-weekly dosing schedule could be important for elderly patients with restricted mobility or for those who are working.

Impaired renal function is a common clinicopathological feature of MM that has been associated with worse prognosis and survival in patients⁸. Furthermore, drug dosing can be complicated by renal impairment, which can increase or worsen AEs³³. In a subgroup analysis of ENDEAVOR, twice-weekly Kd56 therapy demonstrated clinically meaningful improvements in PFS and OS across renal subgroups, including severe renal impairment, compared with bortezomib-based therapy²⁶. Our results show that patients administered once-weekly Kd70 mg/m² had longer median PFS and higher response rates compared with twice-weekly Kd27 mg/m² across all renal function subgroups, including patients with baseline CrCL <50 mL/min.

In patients with baseline CrCL <80 mL/min, rates of grade ≥3 TEAEs and TEAEs leading to treatment discontinuation were greater in the once-weekly Kd70-mg/m² group compared to the twice-weekly Kd27-mg/m² group. Specifically in patients with CrCL <50 mL/min, the incidence of TEAEs leading to carfilzomib treatment discontinuation was 28.6% for once-weekly Kd70 mg/m² compared with 14.7% for twice-weekly Kd27 mg/m². Similar rates of grade ≥3 heart failure, hypertension, and acute kidney injury were reported for once-weekly Kd70 mg/m² and twice-weekly Kd27 mg/m² within each renal subgroup. Overall, once-weekly Kd70 mg/m² had a favorable benefit–risk profile relative to twice-weekly Kd27 mg/m² in patients with baseline CrCL ≥50 mL/min. In patients with decreased renal function (CrCL <50 mL/min), the once-weekly Kd70-mg/m² regimen improved PFS and response rates compared with the twice-weekly Kd27-mg/m² regimen; however, a higher rate of AEs leading to carfilzomib treatment discontinuation was observed with once-weekly Kd70 mg/m². Taken together, once-weekly Kd70 mg/m² demonstrates benefit over twice-weekly Kd27 mg/m², although to a lesser extent in patients with CrCL <50 mL/min.

Previously treated patients with RRMM are a challenging population to treat, as the disease has been reported to become less sensitive or refractory to certain therapies with each successive line of treatment^{6,34}. Previous

subgroup reports from ASPIRE²² and ENDEAVOR²³ demonstrated improved PFS and ORR of twice-weekly carfilzomib-based regimens compared to recent SOCs, regardless of the number of prior therapies patients had received before enrollment. Consistent with previous reports^{22,23}, a greater benefit was observed in patients with fewer previous therapies, suggesting that carfilzomib efficacy (administered once- or twice-weekly) can be optimized by earlier administration in the disease course for patients with RRMM.

The safety profiles for the prior lines subgroups were generally consistent with those reported for the overall population. In patients previously treated with three lines of therapy, the incidence of grade ≥ 3 TEAEs was greater in the once-weekly Kd70-mg/m² treatment arm (75.6%) compared with the twice-weekly Kd27-mg/m² arm (58.0%). This may be partially due to the higher proportion of patients aged 75–84 years (22.6% versus 11.5%) in the once-weekly Kd70-mg/m² treatment arm. Importantly, the incidence of grade ≥ 3 cardiac failure was $< 7\%$ across treatment arms and was lower for once-weekly Kd70 mg/m² (2.6%–3.3%), and no additional toxicities were found. This subgroup analysis confirmed that once-weekly treatment with carfilzomib (70 mg/m²) plus dexamethasone is safe, feasible, and superior to twice-weekly carfilzomib (27 mg/m²) plus dexamethasone, regardless of the number of prior therapies.

Bortezomib is a common component of frontline therapies, and there is a need for effective salvage options in patients whose disease becomes refractory to this agent. The ASPIRE trial previously reported improved PFS and OS in bortezomib-refractory patients treated with twice-weekly KRd versus Rd^{18,22}. In A.R.R.O.W., patients treated with once-weekly Kd70 mg/m² demonstrated longer median PFS and higher ORRs versus those treated with twice-weekly Kd27 mg/m², regardless of disease sensitivity to bortezomib. In both treatment arms, absolute PFS durations and response rates were lower in patients with bortezomib-refractory disease compared with bortezomib-sensitive disease. This is consistent with the existence of some cross-resistance between the two PIs^{35,36}. Taken together with ASPIRE, these results support the benefit of carfilzomib-based therapy for patients with disease refractory to bortezomib.

Safety profiles by bortezomib-refractory status were comparable to the overall population²⁷. Once-weekly Kd70 mg/m² demonstrated improved efficacy with a similar safety profile compared to twice-weekly Kd27 mg/m², regardless of bortezomib-refractory status. As continuous treatment with lenalidomide has become a new SOC in frontline MM^{37,38}, there is a need for active regimens to treat patients who have relapsed or become refractory to lenalidomide. In the A.R.R.O.W. trial, 401 (83.9%) patients had prior lenalidomide exposure and 356

(74.5%) were refractory to any prior lenalidomide²⁷. Although lenalidomide-exposed and lenalidomide-refractory patient subgroups were not evaluated in this study, analyses from these subgroups are underway and will be presented in a separate paper.

ECOG PS (0–5) and ISS stages (1–3) are prognostic factors used to assess patients with MM^{39,40}, with higher values associated with worse prognosis and greater susceptibility to AEs. In our study, grade ≥ 3 TEAEs, including cardiac TEAEs, were comparable across treatment arms, regardless of ECOG PS (0 or 1) or ISS stage (stage 1 and 2 or stage 3). Once-weekly Kd70 mg/m², therefore, represents a tolerable therapeutic option in RRMM patients with advanced disease and functional impairment.

Limitations of this subgroup analysis of A.R.R.O.W. include the open-label trial design and the small numbers of patients in subgroups. In addition, the control group in our study was administered twice-weekly carfilzomib at a dose of 27 mg/m² in combination with dexamethasone; the currently approved dose of carfilzomib in combination with dexamethasone is 56 mg/m² (based on ENDEAVOR^{15,16}), which was not yet approved during the enrollment period of the A.R.R.O.W. study. Nevertheless, findings from this study warrant further investigation.

Clinical practice guidelines from the National Comprehensive Cancer Network, American Society of Oncology, and Cancer Care Ontario recommend doublet and triplet regimens as treatment options for patients with previously treated MM^{41,42}. In randomized trials, carfilzomib- and daratumumab-based triplets have improved PFS, ORR, and/or OS in relapsed and/or refractory MM patients relative to doublet therapies; however, triplet therapies were also associated with higher rates of toxicity in these studies^{17,18,43–46}. Therefore, patients with lower tolerance for increased toxicity, higher comorbidity burden, and/or frail status may not be suited for triplet therapies⁴². Comparisons of once-weekly Kd70 mg/m² with currently available data from triplet combination studies are challenging, given differences in patient population (e.g., prior therapy, sensitivity to IMiDs and/or PIs, baseline creatinine clearance) and stratification of subgroups^{17,20,22,43–47}. Future studies evaluating the efficacy and safety of once-weekly Kd70 mg/m² dosing relative to recommended triplet salvage regimens may further highlight the potential utility of once-weekly Kd70 mg/m² in the RRMM treatment armamentarium.

Conclusions

In this pre-planned subgroup analysis of the A.R.R.O.W. study, PFS and ORR were consistently improved in the once-weekly carfilzomib treatment arm at the higher 70-mg/m² dose compared with the twice-weekly carfilzomib treatment arm at the 27-mg/m² dose across several

important baseline patient and disease characteristics. The safety profiles of once-weekly Kd70 mg/m² in each patient subgroup were generally consistent with that in the overall population²⁷. Overall, this subgroup analysis of A.R.R.O.W. supports the favorable benefit–risk profile of once-weekly Kd70 mg/m² and the use of this regimen as a safe, effective, and convenient treatment option for patients with RRMM, regardless of age, prior lines of therapy, and bortezomib-refractory status.

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Author contributions

All authors participated in manuscript writing and approved the final version of the manuscript. Conception and design of study: P.M. and M.-V.M. Acquisition of data: M.A.D., P.M., M.-V.M., and M.C. Statistical analysis: M.H. Analysis and interpretation of data: All authors.

Conflict of interest

M.A.D. has received consulting fees and honoraria from Amgen, Bristol-Myers Squibb (BMS), Takeda, Celgene, and Janssen. R.N. has received consulting fees and research funding from Takeda, Celgene, BMS, Amgen, and Janssen. K.W. has received honoraria from Amgen, BMS, Celgene, Janssen, Novartis, and Takeda; consulting fees from Amgen, Adaptive, BMS, Celgene, Janssen, Takeda, Sanofi, and Juno; and research funding from Amgen, Celgene, Sanofi, and Janssen. D.S.S. has received consulting fees from Takeda, Karyopharm, Merck, Celgene, Janssen, BMS, and Amgen; honoraria from Takeda, Karyopharm, Merck, Celgene, Janssen, BMS, Novartis, and Amgen; served on speakers' bureaus for Takeda, Merck, Celgene, Janssen, BMS, Novartis, and Amgen; and has received research funding from Celgene. R.H. has received consulting fees, honoraria, and research funding from Amgen, Takeda, Celgene, Janssen, AbbVie, Novartis, PharmaMar, and BMS. M.-V.M. has received consulting fees from and served on Board of Directors/advisory committees for AbbVie, Amgen, GlaxoSmithKline, Takeda, Janssen, and Celgene and honoraria from Amgen, Takeda, Janssen, and Celgene. M.C. has received honoraria from and served on Board of Directors/advisory committees for AbbVie, BMS, Takeda, GlaxoSmithKline, Adaptive Biotechnologies, Janssen, Celgene, and Amgen and served on speakers' bureaus for and received research funding from Janssen and Celgene. M.H. and A.Z.-K. are employees of, and own stock in, Amgen. P.M. has received honoraria from, and served on Board of Directors/advisory committees for, Amgen, Celgene, Janssen, Takeda, and AbbVie and served on speakers' bureaus for Amgen, Celgene, Janssen, and AbbVie.

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