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Carfilzomib in Relapsed or Refractory Multiple Myeloma: Frailty Subgroup Analysis From Phase 3 ASPIRE and ENDEAVOR – Facon T, et al.

Safety And Efficacy of Once-Weekly Carfilzomib Dosing in Frail Patients: A Subgroup Analysis From the Phase 3 A.R.R.O.W. Study – Mateos M-V, et al.

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Real-World Use of the Triplet Regimen Carfilzomib, Lenalidomide and Dexamethasone (KRd) in Patients with Relapsed Multiple Myeloma: A Sub-group Interim Analysis from a Prospective Observational Study – Leleu X, et al.

AMGEN Oncology

Carfilzomib in Relapsed or Refractory Multiple Myeloma: Frailty Subgroup Analysis From Phase 3 ASPIRE and ENDEAVOR

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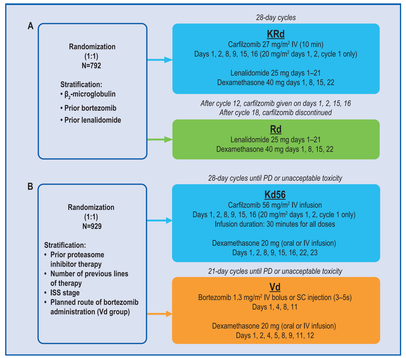
INTRODUCTION

- Carfilzomib is an irreversible proteasome inhibitor that has been approved in combination with dexamethasone or lenalidomide plus dexamethasone (KRd) for the treatment of relapsed or refractory multiple myeloma (MM)[1] based on the phase 3 ASPIRE and ENDEAVOR studies
  - ASPIRE (KRd vs lenalidomide plus dexamethasone, Rd) and ENDEAVOR (carfilzomib [56 mg/m^2] plus dexamethasone [Kd56] vs bortezomib plus dexamethasone, Vd) demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) with carfilzomib-based regimens over the comparator arms[2–5]
- In post hoc analyses of ASPIRE and ENDEAVOR, survival benefits with the respective carfilzomib-containing regimens were maintained, regardless of patient age[6,7]
- The elderly population can vary widely in fitness level, with frail patients having an increased risk for poor clinical outcomes, given their physiological deficits and vulnerability to stressors[8]
- Proper assessment of MM patients' frailty status is critical for appropriate treatment administration.[9] For a comprehensive fitness measure, the International Myeloma Working Group (IMWG) developed a frailty index based on age, comorbidities, and cognitive/physical conditions[10,11]
- In this post hoc analysis, we assessed the efficacy and safety of frail patients in the ASPIRE and ENDEAVOR studies

METHODS

- Both ASPIRE (NCT01080391) and ENDEAVOR (NCT01568866) were phase 3, randomized, open-label trials that enrolled adult patients with relapsed or refractory MM treated with 1–3 prior lines of therapy[2,3] **(Figure 1)**
  - The primary endpoint of ASPIRE and ENDEAVOR was PFS; secondary endpoints included OS, overall response rate (ORR), and safety[2,3]
- In this post hoc analysis, PFS, OS, ORR, and safety were assessed by treatment arm and frailty score
- Patients were categorized into 3 groups according to frailty status (fit, intermediate, or frail) using a proxy algorithm based on the IMWG frailty index.[10,11] This algorithm was based on patient age, a modified Charlson Comorbidity Index (CCI) derived from medical history, and Eastern Cooperative Oncology Group performance status (ECOG PS)
  - The IMWG frailty index used Activities of Daily Living (ADL) and Instrumental ADL (IADL) scales to assess functional status. The proxy algorithm used ECOG PS in lieu of these scales, as ADL data were not collected for ASPIRE or ENDEAVOR
  - The proxy algorithm was based on frailty scores derived separately for age, modified CCI, and ECOG PS, as follows:
    - Age: score=0 if <75 years, score=1 if 75–80 years, score=2 if >80 years
    - Modified CCI: score=0 if modified CCI≤1, score=1 if modified CCI>1
    - ECOG PS: score=0 if ECOG PS=0, score=1 if ECOG PS=1, score=2 if ECOG PS≥2
  - Patients with frailty score sums of 0, 1, or ≥2 were classified as fit, intermediate, or frail, respectively

Figure 1. Study designs for (A) ASPIRE and (B) ENDEAVOR



ISS, International Staging System; IV, intravenous; Kd56, carfilzomib (56 mg/m2) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; PD, progressive disease; Rd, lenalidomide and dexamethasone; SC, subcutaneous; Vd, bortezomib and dexamethasone.

RESULTS

Patients

- Baseline age, modified CCI, and ECOG PS, as well as frailty status scores, were generally balanced between treatment arms in ASPIRE and ENDEAVOR **(Table 1)**

Table 1. Frailty scores in ASPIRE and ENDEAVOR (ITT population)

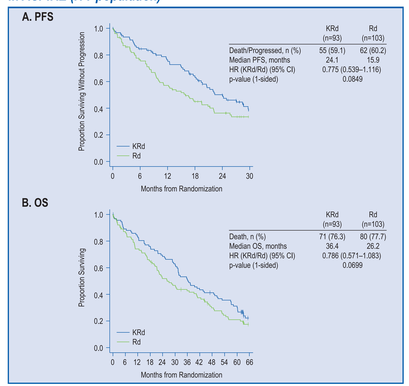
	ASPIRE		ENDEAVOR	
	KRd n=396	Rd n=396	Kd56 n=464	Vd n=465
Age group, years, n (%)				
<75	353 (89)	343 (87)	387 (83)	399 (86)
75–80	33 (8)	42 (11)	60 (13)	52 (11)
>80	10 (3)	11 (3)	17 (4)	14 (3)
Modified CCI score, n (%)				
≤1	280 (71)	258 (65)	225 (48)	230 (49)
>1	77 (19)	97 (24)	221 (48)	222 (48)
Missing[a]	39 (10)	41 (10)	18 (4)	13 (3)
ECOG PS at baseline, n (%)				
0	165 (42)	175 (44)	221 (48)	232 (50)
1	191 (48)	186 (47)	210 (45)	203 (44)
≥2	40 (10)	35 (9)	33 (7)	30 (6)
Frailty score, n (%)				
0 (Fit)	**115 (29)**	**114 (29)**	**110 (24)**	**121 (26)**
1 (Intermediate)	**149 (38)**	**138 (35)**	**168 (36)**	**169 (36)**
≥2 (Frail)	**93 (23)**	**103 (26)**	**168 (36)**	**162 (35)**
Missing[a]	**39 (10)**	**41 (10)**	**18 (4)**	**13 (3)**

CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; Kd56, carfilzomib (56 mg/m²) and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone.
[a]No medical history available.

ASPIRE efficacy and safety of frail patients

- Median PFS with KRd vs Rd in frail patients was 24.1 vs 15.9 months (hazard ratio [HR] 0.78; 95% confidence interval [CI], 0.54–1.12) **(Figure 2A)**
- Median OS with KRd vs Rd in frail patients was 36.4 vs 26.2 months (HR 0.79; 95% CI, 0.57–1.08) **(Figure 2B)**
- Efficacy outcomes by frailty status in ASPIRE are summarized in **Table 2**

Figure 2. Kaplan–Meier curves for PFS and OS in the frail subgroup in ASPIRE (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; KRd, carfilzomib, lenalidomide, and dexamethasone; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.
The curve was truncated at the time point when only 10 patients (KRd and Rd combined) were at risk.

Table 2. Efficacy outcomes by frailty status in ASPIRE

	Fit		Intermediate		Frail	
	KRd n=115	Rd n=114	KRd n=149	Rd n=138	KRd n=93	Rd n=103
Median PFS, months	31.4	18.9	29.6	18.5	24.1	15.9
HR (95% CI)	0.70 (0.49–1.01)		0.70 (0.50–0.96)		0.78 (0.54–1.12)	
Median OS, months	55.6	43.3	48.3	47.9	36.4	26.2
HR (95% CI)	0.71 (0.51–0.99)		0.94 (0.70–1.27)		0.79 (0.57–1.08)	
Best overall response, n (%)						
Stringent complete response	17 (15)	6 (5)	19 (13)	6 (4)	13 (14)	2 (2)
Complete response	22 (19)	5 (4)	29 (19)	6 (4)	16 (17)	6 (6)
Very good partial response	44 (38)	43 (38)	61 (41)	39 (28)	35 (38)	28 (27)
Partial response	21 (18)	32 (28)	23 (15)	35 (25)	14 (15)	30 (29)
ORR, % (95% CI)	90 (84–95)	75 (67–83)	89 (82–93)	62 (54–70)	84 (75–91)	64 (54–73)

CI, confidence interval; HR, hazard ratio; KRd, carfilzomib, lenalidomide, and dexamethasone; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and dexamethasone.

- In the frail subgroup, grade ≥3 TEAEs occurred in 93% of KRd-treated and 94% of Rd-treated patients
- TEAEs leading to treatment discontinuation occurred in 37% of KRd-treated and 43% of Rd-treated patients classified as frail
- Rates of treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, TEAEs of interest, and treatment-related AEs (TRAEs) leading to treatment discontinuation across frailty subgroups in ASPIRE are summarized in **Table 3**

Table 3. Adverse events by frailty status in ASPIRE (safety population)

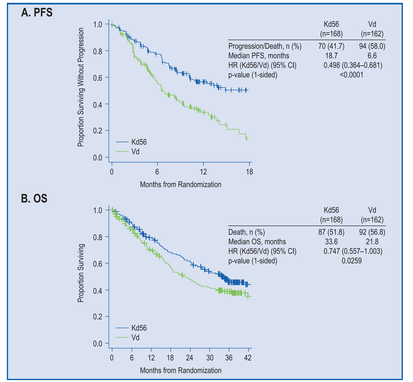
	Fit		Intermediate		Frail	
	KRd n=115	Rd n=114	KRd n=147	Rd n=135	KRd n=92	Rd n=100
Any-grade TEAE, n (%)	114 (99)	113 (99)	145 (99)	129 (96)	91 (99)	100 (100)
Grade ≥3 TEAE, n (%)	102 (89)	96 (84)	130 (88)	107 (79)	86 (93)	94 (94)
Grade ≥3 TEAEs of interest, n (%)[a]						
Peripheral neuropathy	4 (3)	1 (1)	4 (3)	6 (4)	2 (2)	5 (5)
Acute renal failure	5 (4)	3 (3)	5 (3)	4 (3)	3 (3)	6 (6)
Cardiac failure	5 (4)	2 (2)	3 (2)	5 (4)	9 (10)	1 (1)
Ischemic heart disease	4 (3)	3 (3)	4 (3)	2 (1)	7 (8)	4 (4)
Pulmonary hypertension	0	0	1 (1)	1 (1)	1 (1)	0
TEAEs leading to treatment discontinuation, n (%)	38 (33)	34 (30)	53 (36)	31 (23)	34 (37)	43 (43)
TEAEs of interest leading to carfilzomib/lenalidomide discontinuation, n (%)[a]						
Peripheral neuropathy	2 (2)	0	0	3 (2)	0	1 (1)
Acute renal failure	0	1 (1)	0	0	2 (2)	3 (3)
Cardiac failure	0	0	0	2 (1)	2 (2)	1 (1)
Ischemic heart disease	1 (1)	3 (3)	2 (1)	0	3 (3)	0
Pulmonary hypertension	0	0	0	0	0	0
TRAEs leading to treatment discontinuation, n (%)	27 (23)	22 (19)	35 (24)	23 (17)	17 (18)	27 (27)

AE, adverse event; KRd, carfilzomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; Vd, bortezomib and dexamethasone.
[a]Standardized MedDRA Query, narrow scope.

ENDEAVOR efficacy and safety by frailty status

- Median PFS with Kd56 versus Vd in frail patients was 18.7 vs 6.6 months (HR 0.50; 95% CI, 0.36–0.68) **(Figure 3A)**
- Median OS with Kd56 vs Vd in frail patients was 33.6 vs 21.8 months (HR 0.75; 95% CI, 0.56–1.00) **(Figure 3B)**
- Efficacy outcomes by frailty status in ENDEAVOR are summarized in **Table 4**
- In the frail subgroup, grade ≥3 TEAEs occurred in 85% of Kd56-treated and 79% of Vd-treated patients
- TEAEs leading to treatment discontinuation occurred in 33% of Kd56-treated and 30% of Vd-treated patients classified as frail
- Rates of TEAEs, TEAEs leading to treatment discontinuation, TEAEs of interest, and TRAEs leading to treatment discontinuation in ENDEAVOR are summarized in **Table 5**

Figure 3. Kaplan–Meier curves for PFS and OS in the frail subgroup in ENDEAVOR (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd56, carfilzomib (56 mg/m²) and dexamethasone; OS, overall survival; PFS, progression-free survival; Vd, bortezomib and dexamethasone.
The curve was truncated at the time point when only 10 patients (Kd56 and Vd combined) were at risk.

Table 4. Efficacy outcomes by frailty status in ENDEAVOR

	Fit		Intermediate		Frail	
	Kd56 n=110	Vd n=121	Kd56 n=168	Vd n=169	Kd56 n=168	Vd n=162
Median PFS, months	NE	12.1	16.8	9.9	18.7	6.6
HR (95% CI)	0.51 (0.33–0.79)		0.54 (0.39–0.75)		0.50 (0.36–0.68)	
Median OS, months	NE	42.2	NE	41.9	33.6	21.8
HR (95% CI)	0.65 (0.40–1.06)		0.89 (0.64–1.24)		0.75 (0.56–1.00)	
Best overall response, n (%)						
Stringent complete response	2 (2)	4 (3)	5 (3)	2 (1)	1 (1)	3 (2)
Complete response	18 (16)	5 (4)	18 (11)	7 (4)	9 (5)	7 (4)
Very good partial response	39 (35)	25 (21)	72 (43)	44 (26)	77 (46)	32 (20)
Partial response	27 (25)	50 (41)	34 (20)	58 (34)	40 (24)	45 (28)
Overall response rate, % (95% CI)	78 (69–86)	70 (61–78)	77 (70–83)	66 (58–73)	76 (69–82)	54 (46–62)

CI, confidence interval; HR, hazard ratio; Kd56, carfilzomib (56 mg/m2) and dexamethasone; NE, not estimable; OS, overall survival; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

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DISCLOSURES

TF served as a consultant or advisor for Janssen, Celgene, Amgen, Takeda, Karyopharm, and Oncopeptides, and served on speakers' bureaus for Janssen, Celgene, and Takeda. RN served as a consultant for Celgene, Amgen, Takeda, Janssen, and BMS. KW received honoraria from Amgen, Celgene, BMS, Janssen, and Takeda; received research funding from Amgen, Celgene, Janssen, and Sanofi; and served as a consultant for Amgen, Adaptive Biotech, Sanofi, Celgene, BMS, Juno, Janssen, and Sanofi. SB served as a consultant for Takeda, received honoraria from Amgen, Takeda, Janssen, Celgene, and Bristol; and served as a member on the board of directors/advisory committees of Janssen and Celgene. PJH served as a member on the advisory committees (without honoraria) of Amgen, Celgene, Janssen, Novartis, and Takeda, and received registration and travel costs from Celgene to EHA 2016. MO, ZY, ZK, JB, and KM are employees of and own stock in Amgen, Inc. DS received honoraria and consulting or advisory role fees for Celgene, Amgen, Merck, Janssen, BMS, Takeda, and Karyopharm; participated in speakers' bureaus for Celgene, Amgen, Merck, Janssen, BMS, and Takeda; and received research funding from Celgene.

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Table 5. Adverse events by frailty status in ENDEAVOR (safety population)

	Fit		Intermediate		Frail	
	Kd56 n=110	Vd n=119	Kd56 n=167	Vd n=165	Kd56 n=168	Vd n=159
Any-grade TEAE, n (%)	110 (100)	118 (99)	164 (98)	163 (99)	168 (100)	157 (99)
Grade ≥3 TEAE, n (%)	91 (83)	76 (64)	135 (81)	117 (71)	142 (85)	125 (79)
Grade ≥3 TEAEs of interest, n (%)[a]						
Peripheral neuropathy	3 (3)	12 (10)	3 (2)	17 (10)	4 (2)	15 (9)
Acute renal failure	4 (4)	2 (2)	7 (4)	6 (4)	15 (9)	7 (4)
Cardiac failure	4 (4)	2 (2)	8 (5)	0	15 (9)	7 (4)
Ischemic heart disease	2 (2)	1 (1)	1 (1)	0	8 (5)	6 (4)
Pulmonary hypertension	3 (3)	0	1 (1)	0	0	1 (1)
TEAEs leading to treatment discontinuation, n (%)	29 (26)	34 (29)	45 (27)	36 (22)	55 (33)	48 (30)
TEAEs of interest leading to carfilzomib/bortezomib discontinuation, n (%)[a]						
Peripheral neuropathy	1 (1)	12 (10)	1 (1)	13 (8)	0	15 (9)
Acute renal failure	2 (2)	1 (1)	3 (2)	1 (1)	1 (1)	0
Cardiac failure	2 (2)	1 (1)	7 (4)	1 (1)	7 (4)	2 (1)
Ischemic heart disease	0	0	1 (1)	0	3 (2)	3 (2)
Pulmonary hypertension	1 (1)	0	1 (1)	0	1 (1)	1 (1)
TRAEs leading to treatment discontinuation, n (%)	23 (21)	32 (27)	25 (15)	28 (17)	35 (21)	34 (21)

AE, adverse event; Kd56, carfilzomib (56 mg/m²) and dexamethasone; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; Vd, bortezomib and dexamethasone.
[a]Standardized MedDRA Query, narrow scope.

LIMITATIONS

- A limitation of this analysis was that the frailty score was retrospectively determined according to baseline data provided for the ASPIRE and ENDEAVOR trials; therefore, the frailty score was derived using a proxy algorithm that differed from the IMWG frailty index
  - The use of ECOG PS in the proxy algorithm may have increased the number of patients classified as frail, as ECOG PS is strongly influenced by the disease itself and may not directly reflect patient frailty
  - However, other studies have used PS in lieu of ADL and IADL scales to examine the effect of treatment by frailty status[12,13]

CONCLUSIONS

- In this post hoc analysis of ASPIRE and ENDEAVOR, carfilzomib-containing regimens consistently improved clinical outcomes compared with controls for frail patients, as defined by the proxy algorithm for frailty status
- Safety profiles for frail patients were generally consistent with those observed in the overall ASPIRE and ENDEAVOR populations
  - In both ASPIRE and ENDEAVOR, among frail patients, rates of cardiac failure were higher with carfilzomib-containing regimens compared with controls; however, treatment discontinuations related to cardiac AEs were relatively low
- Overall, the results support the use of carfilzomib-based therapies (KRd or Kd56) as treatment options for frail patients with relapsed or refractory MM as assessed by the proxy algorithm

Safety and Efficacy of Once-Weekly Carfilzomib Dosing in Frail Patients: A Subgroup Analysis From the Phase 3 A.R.R.O.W. Study

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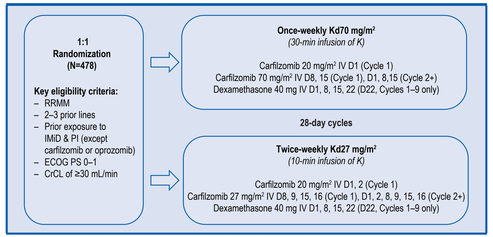
INTRODUCTION

- The fitness of elderly patients with multiple myeloma (MM) can range from frail to fit, and assessment of frailty status is important for optimal treatment selection and accurate prognosis[1,2]
  - The International Myeloma Working Group (IMWG) frailty index, which is based on age, comorbidities (assessed by the Charlson Comorbidity Index [CCI]), and cognitive/physical conditions (assessed by the Activities of Daily Living [ADL] and Instrumental ADL [IADL] scales), was developed to appraise the frailty status of patients with MM[3,4]
- The randomized phase 3 A.R.R.O.W. trial demonstrated superior progression-free survival (PFS) with once-weekly carfilzomib (70 mg/m^2) plus dexamethasone (Kd70 mg/m^2) vs twice-weekly carfilzomib (27 mg/m^2) plus dexamethasone (Kd27 mg/m^2) in relapsed and refractory MM (RRMM).[5] These findings supported the approval in the United States of once-weekly Kd70 mg/m^2 for the treatment of relapsed or refractory MM (1–3 prior therapy lines)[6]
  - In a subgroup analysis within A.R.R.O.W., hazard ratios (HRs) for PFS favored the once-weekly Kd70 mg/m^2 group over the twice-weekly Kd27 mg/m^2 group in patients, regardless of age (<65 years: HR 0.60 [95% confidence interval (CI), 0.42–0.86]; ≥65 years, HR 0.84 [95% CI, 0.61–1.15])[5]
- Here, we assessed post hoc patient efficacy and safety outcomes by frailty status in patients receiving once-weekly Kd70 mg/m^2 from the A.R.R.O.W. trial

METHODS

- A.R.R.O.W. (NCT02412878) was a phase 3, randomized, open-label trial that enrolled eligible adult patients with RRMM (patients had received 2–3 prior lines of therapy)[5] **(Figure 1)**
- The primary endpoint of A.R.R.O.W. was PFS; secondary endpoints included overall response rate (ORR) and safety[5]
- In this post hoc analysis, PFS, ORR, and safety were assessed by treatment arm and frailty score
- Using a proxy algorithm based on the IMWG frailty index, patients were categorized into fit, intermediate, or frail groups.[3,4] As ADL data were not collected for A.R.R.O.W., this algorithm used Eastern Cooperative Oncology Group performance status (ECOG PS) for functional status in lieu of ADL and IADL scales; a modified CCI based on medical history was used for comorbidities
  - The proxy algorithm was based on the sum of age (score=0 if <75 years, score=1 if 75–80 years, score=2 if >80 years), modified CCI (score=0 if modified CCI≤1, score=1 if modified CCI>1), and ECOG PS (score=0 if ECOG PS=0, score=1 if ECOG PS=1, score=2 if ECOG PS ≥2) scores
  - Patients were classified as fit, intermediate, or frail if they had frailty score sums of 0, 1, or ≥2, respectively
  - A limitation of the proxy algorithm is that ECOG PS is strongly influenced by the disease itself and may not be a direct reflection of patient frailty; thus, the use of this scale may have biased the classification of patients toward a frail status
    - However, the approach of using PS in lieu of ADL and IADL scales has also been used in other studies to assess the effect of treatment by frailty status[7,8]
- Efficacy analyses were conducted in the intent-to-treat population
- Safety analyses were based on the safety population, which included all patients who received ≥1 treatment dose

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; PI, proteasome inhibitor; RRMM, relapsed and refractory multiple myeloma.

RESULTS

Patients

- Baseline characteristics used by the proxy algorithm for frailty (age, modified CCI, ECOG PS) as well as overall frailty scores were generally balanced between treatment arms **(Table 1)**

Table 1. Frailty scores in A.R.R.O.W.

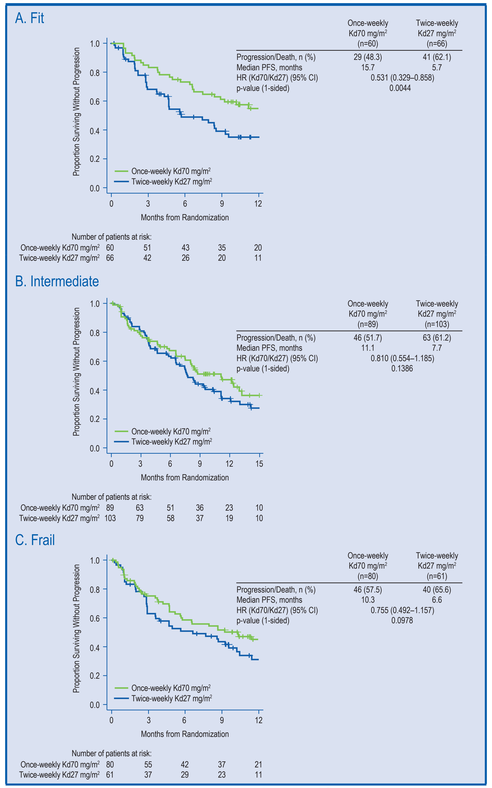
	Once-weekly Kd70 mg/m^2 (n=240)	Twice-weekly Kd27 mg/m^2 (n=238)
Age group, years, n (%)		
<75	194 (81)	206 (87)
75–80	35 (15)	29 (12)
>80	11 (5)	3 (1)
Modified CCI score, n (%)		
≤1	124 (52)	138 (58)
>1	105 (44)	92 (39)
Missing	11 (5)	8 (3)
ECOG PS, n (%)		
0	118 (49)	118 (50)
1	121 (50)	120 (50)
≥2	1 (0.4)	0
Frailty score, n (%)		
0 (Fit)	**60 (25)**	**66 (28)**
1 (Intermediate)	**89 (37)**	**103 (43)**
≥2 (Frail)	**80 (33)**	**61 (26)**
Missing	**11 (5)**	**8 (3)**

CCI, Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group performance status; Kd27, carfilzomib (27 mg/m^2) and dexamethasone; Kd70, carfilzomib (70 mg/m^2) and dexamethasone.

Efficacy by frailty status

- Median PFS with once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 in the fit, intermediate, and frail groups was 15.7 vs 5.7 months (HR 0.53; 95% CI, 0.33–0.86), 11.1 vs 7.7 months (HR 0.81; 95% CI, 0.55–1.19), and 10.3 vs 6.6 months (HR 0.76; 95% CI, 0.49–1.16), respectively **(Figure 2)**

Figure 2. Kaplan–Meier curves for PFS by frailty status (ITT population)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd27, carfilzomib (27 mg/m^2) and dexamethasone; Kd70, carfilzomib (70 mg/m^2) and dexamethasone; PFS, progression-free survival.
The curves were truncated at the time point when only 10 patients (once-weekly Kd70 mg/m^2 and twice-weekly Kd27 mg/m^2 combined) were at risk.

- ORRs with once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 in the fit, intermediate, and frail groups were 67% vs 29%, 64% vs 48%, and 56% vs 41%, respectively **(Table 2)**
  - Rates of complete response or better with once-weekly Kd70 mg/m^2 vs twice-weekly Kd27 mg/m^2 in the fit, intermediate, and frail groups, respectively, were 10% vs 3%, 8% vs 2%, and 4% vs 0%

Table 2. Efficacy outcomes by frailty status (ITT population)

	Fit		Intermediate		Frail	
	Once-weekly Kd70 mg/m^2, n=60	Twice-weekly Kd27 mg/m^2, n=66	Once-weekly Kd70 mg/m^2, n=89	Twice-weekly Kd27 mg/m^2, n=103	Once-weekly Kd70 mg/m^2, n=80	Twice-weekly Kd27 mg/m^2, n=61
Median PFS, months	15.7	5.7	11.1	7.7	10.3	6.6
HR (95% CI)	0.53 (0.33–0.86)		0.81 (0.55–1.19)		0.76 (0.49–1.16)	
Best overall response, n (%)						
CR+	6 (10)	2 (3)	7 (8)	2 (2)	3 (4)	0
VGPR+	24 (40)	6 (9)	30 (34)	16 (16)	23 (29)	9 (15)
ORR, % (95% CI)	67 (53–78)	29 (18–41)	64 (53–74)	48 (38–58)	56 (45–67)	41 (29–54)

CI, confidence interval; CR+, complete response or better; HR, hazard ratio; ITT, intent-to-treat; Kd27, carfilzomib (27 mg/m^2) and dexamethasone; Kd70, carfilzomib (70 mg/m^2) and dexamethasone; ORR, overall response rate; PFS, progression-free survival; VGPR+, very good partial response or better.

Safety by frailty status

- Rates of treatment-emergent adverse events (TEAEs), grade ≥3 TEAEs of interest, and TEAEs leading to carfilzomib discontinuation are summarized in **Table 3**

Table 3. Adverse events by frailty status (safety population)

	Fit		Intermediate		Frail	
	Once-weekly Kd70 mg/m^2, n=60	Twice-weekly Kd27 mg/m^2, n=66	Once-weekly Kd70 mg/m^2, n=88	Twice-weekly Kd27 mg/m^2, n=101	Once-weekly Kd70 mg/m^2, n=79	Twice-weekly Kd27 mg/m^2, n=60
Any-grade TEAE, n (%)	57 (95)	66 (100)	81 (92)	96 (95)	78 (99)	60 (100)
Grade ≥3 TEAEs, n (%)	33 (55)	41 (62)	60 (68)	58 (57)	64 (81)	42 (70)
Grade ≥3 TEAEs of interest, n (%)[a]						
Peripheral neuropathy	0	1 (2)	0	0	0	0
Acute renal failure	0	3 (5)	6 (7)	6 (6)	3 (4)	4 (7)
Cardiac failure	1 (2)	1 (2)	3 (3)	3 (3)	3 (4)	5 (8)
Ischemic heart disease	1 (2)	0	0	1 (1)	0	1 (2)
Pulmonary hypertension	0	0	0	0	0	1 (2)
TEAEs leading to carfilzomib discontinuation, n (%)	2 (3)	5 (8)	11 (13)	11 (11)	16 (20)	11 (18)

Kd27, carfilzomib (27 mg/m^2) and dexamethasone; Kd70, carfilzomib (70 mg/m^2) and dexamethasone; TEAE, treatment-emergent adverse event.
[a]Standardized MedDRA Query, narrow scope.

- In the once-weekly Kd70 mg/m^2 and twice-weekly Kd27 mg/m^2 arms, respectively, grade ≥3 TEAEs occurred in 55% and 62% of patients classified as fit, 68% and 57% of patients classified as intermediate, and 81% and 70% of patients classified as frail
- In the once-weekly Kd70 mg/m^2 and twice-weekly Kd27 mg/m^2 arms, respectively, TEAEs leading to carfilzomib discontinuation occurred in 3% and 8% of patients classified as fit, 13% and 11% of patients classified as intermediate, and 20% and 18% of patients classified as frail

CONCLUSIONS

- In this post hoc analysis of A.R.R.O.W., both fit and frail patients experienced improved and clinically meaningful PFS benefit with once-weekly Kd70 mg/m^2 as compared to twice-weekly Kd27 mg/m^2, while maintaining a favorable benefit-risk profile
- The safety profile across frailty subgroups was similar to that of the overall population of A.R.R.O.W. with no observed new safety signals
- As expected, the greatest PFS benefit was observed in fit patients
- These results support the use of once-weekly Kd70 mg/m^2 as a treatment option for both fit and frail patients with RRMM

ACKNOWLEDGMENTS

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DISCLOSURES

MVM received honoraria from Celgene, Janssen, Takeda, Amgen, and AbbVie. HL served as a consultant or advisor for PharmaMer; served on speakers' bureaus for Takeda, Amgen, BMS, Janssen, and Celgene; and received research funding from Takeda and Amgen. SK reports non-paid consulting and advisory board roles for AbbVie, Celgene, Janssen, Kite Pharma, Merck, and Takeda. CR received honoraria from, and had travel/accommodations/expenses paid for by, Celgene and BMS. MH, AG, and JB are employees of, and own stock in, Amgen, Inc. MD received honoraria from Celgene, BMS, Janssen, Takeda, and Amgen.

PF612 Once-Weekly (70 mg/m^2) Versus Twice-Weekly (56 mg/m^2) Dosing of Carfilzomib in Combination With Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma: A Post Hoc Analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 Trials

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INTRODUCTION

- Carfilzomib, a selective second-generation proteasome inhibitor, is approved for the treatment of relapsed and/or refractory multiple myeloma (RRMM) in combination with dexamethasone (Kd)
- The Kd combination is used in two dosing schedules based on results from two randomized-controlled phase 3 studies, A.R.R.O.W. and ENDEAVOR:
  - Once-weekly administration of carfilzomib 70 mg/m^2 with dexamethasone (Kd70 QW)
  - Twice-weekly administration of carfilzomib 56 mg/m^2 with dexamethasone (Kd56 BIW)
- Kd70 QW and Kd56 BIW have not been compared head-to-head in a randomized clinical trial
- The purpose of this analysis was to compare the efficacy and safety profiles of Kd70 QW versus Kd56 BIW. We performed a post hoc cross-trial comparison using data from the following three clinical trials of patients with RRMM who received the Kd regimen: A.R.R.O.W., CHAMPION-1, and ENDEAVOR[1-3]

METHODS

Patient Selection

- Post hoc cross-trial comparisons were performed using pooled data from patients who received Kd70 QW in A.R.R.O.W. and CHAMPION-1 and Kd56 BIW in ENDEAVOR
  - A.R.R.O.W.: phase 3 randomized trial comparing Kd70 QW with carfilzomib administered twice weekly at 27 mg/m^2 and Kd in patients with RRMM with 2–3 prior therapies and refractory to the most recent therapy (ClinicalTrials.gov identifier: NCT02412878)
  - CHAMPION-1: phase1/2 dose-finding study of once-weekly carfilzomib in combination with Kd in patients with RRMM with 1–3 prior lines of therapy (excluding patients with prior carfilzomib therapy) (NCT01677858)
  - ENDEAVOR: phase 3 head-to-head comparison study of Kd56 BIW or bortezomib in patients with RRMM with 1–3 prior lines of therapy (patients with prior bortezomib or carfilzomib treatment were eligible if partial response to treatment was achieved, there were no tolerability issues, and they had a ≥ 6-month interval without proteasome inhibitor treatment before enrollment) (NCT01568866)
- To control for variances in eligibility criteria across studies, side-by-side analyses were conducted in subgroups of patients from each trial who had received 2–3 prior lines of therapy and were non-refractory to bortezomib
  - Kd70 QW subgroup, n = 146; Kd56 BIW subgroup, n = 217

Outcomes

- Endpoints included overall response rate (ORR), progression-free survival (PFS), and safety

Statistical Analysis

- ORR exact 95% confidence intervals (CI) were determined based on binomial distribution
- PFS medians were estimated using the Kaplan-Meier method. The log-log transformation method by Klein and Moeschberger was used to estimate 95% CIs for PFS medians. Median PFS follow-up time was estimated using the reverse Kaplan-Meier method
- ORR and PFS were also independently estimated with multivariate regression modeling of all 808 patients with 1–3 prior lines of therapy who received Kd70 QW in A.R.R.O.W. and CHAMPION-1 (n = 344) compared with those who received Kd56 BIW in ENDEAVOR (n = 464)
  - Covariates adjusted for in the models included age, International Staging System (ISS) stage, bortezomib-refractory status, lenalidomide-refractory status, and the number of prior therapies

RESULTS

- Baseline characteristics of Kd70 QW and Kd56 BIW subgroups were generally similar (**Table 1**), though differences were noted in the proportion of patients with prior treatment with bortezomib or lenalidomide and lenalidomide-refractory patients

Table 1. Baseline Patient Characteristics of Kd70 QW and Kd56 BIW Subgroups (Patients With 2–3 Prior Lines of Therapy and Not Refractory to Prior Bortezomib)

Patient Characteristics	Kd70 QW A.R.R.O.W. + CHAMPION-1 (n = 146)	Kd56 BIW ENDEAVOR (n = 217)
Sex		
Male	79 (54.1)	112 (51.6)
Female	67 (45.9)	105 (48.4)
Age group, years		
Mean (SD)	64.9 (9.7)	63.9 (9.7)
< 65	68 (46.6)	112 (51.6)
65 to < 75	53 (36.3)	74 (34.1)
≥ 75	25 (17.1)	31 (14.3)
ISS stage		
1	65 (44.5)	97 (44.7)
2 and 3	80 (54.8)	120 (55.3)
Missing	1 (0.7)	0
Total number of prior regimens		
2	84 (57.5)	148 (68.2)
3	62 (42.5)	69 (31.8)
Prior treatment with bortezomib	139 (95.2)	139 (64.1)
Prior treatment with lenalidomide	128 (87.7)	117 (53.9)
Refractory to lenalidomide	116 (79.5)	83 (38.2)
ECOG performance status		
0	73 (50.0)	104 (47.9)
1–2	73 (50.0)	113 (52.1)
Creatinine clearance,[a] mL/min		
Mean (SD)	83.1 (37.9)	79.1 (33.9)
Median (range)	76.7 (27.6–257.7)	75.0 (14.0–182.0)

Data are n (%) unless specified otherwise.
[a]Creatinine clearance was calculated using the Cockcroft-Gault formula.
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone; SD, standard deviation.

- ORR (**Table 2**) was comparable between Kd70 QW and Kd56 BIW subgroups in the side-by-side analyses
  - ORR was 69.9% for Kd70 QW (95% CI, 61.7–77.2) and 72.4% for Kd56 BIW (95% CI, 65.9–78.2)
  - Complete response or better was achieved in 8.2% of patients who received Kd70 QW and 13.3% of patients who received Kd56 BIW

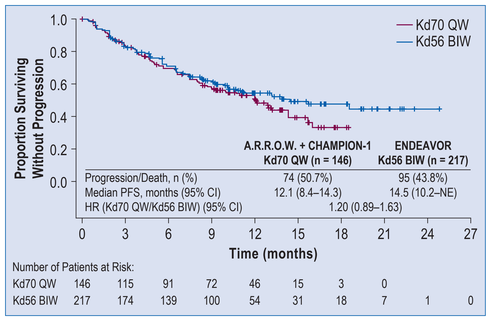
Table 2. Overall Response Rate of Kd70 QW and Kd56 BIW Subgroups (Patients With 2–3 Prior Lines of Therapy and Not Refractory to Prior Bortezomib)

	Kd70 QW A.R.R.O.W. + CHAMPION-1 (n = 146)	Kd56 BIW ENDEAVOR (n = 217)
Best overall response, n (%)		
Stringent complete response	4 (2.7)	2 (0.9)
Complete response	8 (5.5)	27 (12.4)
Very good partial response	50 (34.2)	72 (33.2)
Partial response	40 (27.4)	55 (25.3)
Overall response rate (95% CI)	69.9 (61.7–77.2)	72.4 (65.9–78.2)

CI, confidence interval; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone.

- Median PFS (**Figure 1**) was 12.1 months (95% CI, 8.4–14.3) for Kd70 QW and 14.5 months (95% CI, 10.2–not evaluable) for Kd56 BIW in the side-by-side comparison
  - Median PFS follow-up time was 12.9 months (95% CI, 11.4–13.8) for Kd70 QW and 11.2 months (95% CI, 10.2–13.0) for Kd56 BIW

Figure 1. PFS of Kd70 QW and Kd56 BIW Subgroups (Patients With 2–3 Prior Lines of Therapy and Not Refractory to Prior Bortezomib)



CI, confidence interval; HR, hazard ratio; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone; NE, not evaluable; PFS, progression-free survival.

- Median treatment exposure time was 38.1 weeks (range, 0.1–82.4) for the Kd70 QW subgroup and 40.3 weeks (range, 0.3–210.0) for the Kd56 BIW subgroup
- In the side-by-side safety analysis (**Table 3**), the rate of grade ≥ 3 AEs was 67.6% for Kd70 QW and 85.3% for Kd56 BIW
- The frequencies of grade ≥ 3 AEs of interest in Kd70 QW and Kd56 BIW subgroups, respectively, were 1.4% and 5.1% for cardiac failure, 3.4% and 6.0% for acute renal failure, 2.1% and 2.3% for embolic and thrombotic events, and 5.5% and 15.7% for hypertension

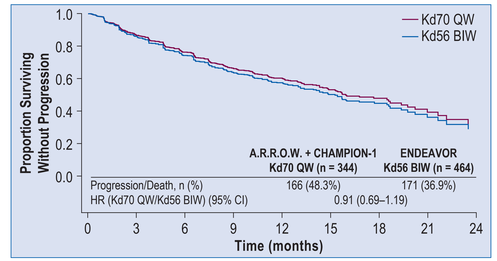
Table 3. Adverse Events in Kd70 QW and Kd56 BIW Subgroups (Patients With 2–3 Prior Lines of Therapy and Not Refractory to Prior Bortezomib)

	Kd70 QW A.R.R.O.W. + CHAMPION-1 (n = 145)	Kd56 BIW ENDEAVOR (n = 217)
All treatment-emergent adverse events, n (%)	140 (96.6)	217 (100.0)
Grade ≥ 3	98 (67.6)	185 (85.3)
Serious adverse events	57 (39.3)	141 (65.0)
Cardiac failure[a]	2 (1.4)	19 (8.8)
Grade ≥ 3	2 (1.4)	11 (5.1)
Acute renal failure[a]	9 (6.2)	22 (10.1)
Grade ≥ 3	5 (3.4)	13 (6.0)
Embolic and thrombotic events, venous[a]	5 (3.4)	23 (10.6)
Grade ≥ 3	3 (2.1)	5 (2.3)
Hypertension[a]	27 (18.6)	69 (31.8)
Grade ≥ 3	8 (5.5)	34 (15.7)

[a]Standardized MedDRA Queries Narrow terms.
Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone; MedDRA, Medical Dictionary for Regulatory Activities.

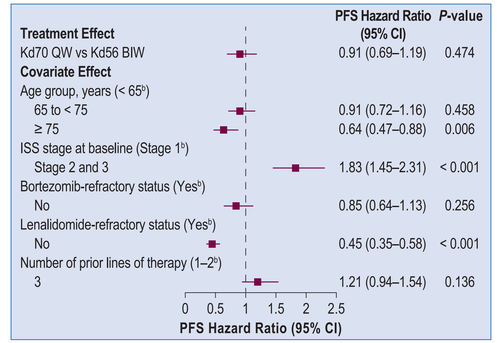
- Multivariate regression analyses were performed on all 808 patients receiving Kd70 QW or Kd56 BIW across the three trials. For Kd70 QW versus Kd56 BIW:
  - The estimated PFS hazard ratio was 0.91 (95% CI, 0.69–1.19; *P* = 0.474) (**Figure 2** and **Figure 3**)
  - The estimated ORR odds ratio was 1.12 (95% CI, 0.74–1.69; *P* = 0.609) (**Figure 4**)
  - Regression modeling identified ISS stage (Stage 2 and 3) and lenalidomide-refractory status (Yes) as significant prognostic factors of worse PFS and ORR

Figure 2. Multiple Cox Regression Analysis Results of Progression-Free Survival of Kd70 QW and Kd56 BIW[a]



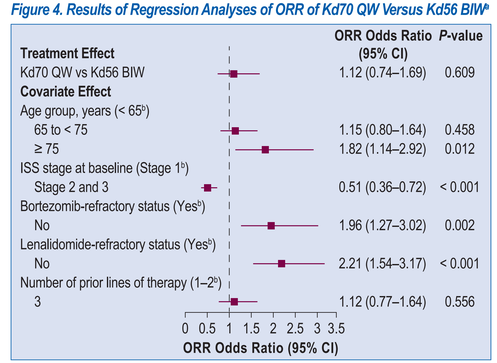
[a]In all 808 patients with observed data receiving Kd70 QW in the A.R.R.O.W. (n = 240) and CHAMPION-1 (n = 104) trials and Kd56 BIW in the ENDEAVOR (n = 464) trial. Direct-adjusted survival curves derived from the Cox regression model with treatment group, age, ISS stage, bortezomib-refractory status, lenalidomide-refractory status, and the number of prior lines of therapy as covariates.
CI, confidence interval; HR, hazard ratio; ISS, International Staging System; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone.

Figure 3. Results of Regression Analyses of PFS of Kd70 QW Versus Kd56 BIW[a]



[a]In all 808 patients with observed data receiving Kd70 QW in the A.R.R.O.W. (n = 240) and CHAMPION-1 (n = 104) trials and Kd56 BIW in the ENDEAVOR (n = 464) trial. Includes treatment group, age, ISS stage, bortezomib-refractory status, lenalidomide-refractory status, and number of prior lines of therapy as covariates. [b]Reference group (hazard ratio = 1.0).
CI, confidence interval; ISS, International Staging System; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone; PFS, progression-free survival.

Figure 4. Results of Regression Analyses of ORR of Kd70 QW Versus Kd56 BIW[a]



[a]In all 808 patients with observed data receiving Kd70 QW in the A.R.R.O.W. (n = 240) and CHAMPION-1 (n = 104) trials and Kd56 BIW in the ENDEAVOR (n = 464) trial. Includes treatment group, age, ISS stage, bortezomib-refractory status, lenalidomide-refractory status, and number of prior lines of therapy as covariates. [b]Reference group (odds ratio = 1.0).
CI, confidence interval; ISS, International Staging System; Kd56 BIW, twice-weekly carfilzomib 56 mg/m^2 with dexamethasone; Kd70 QW, once-weekly carfilzomib 70 mg/m^2 with dexamethasone; ORR, overall response rate.

CONCLUSIONS

- **ORR and PFS were comparable with Kd70 QW and Kd56 BIW dosing schedules in side-by-side analyses of subgroups of patients who received 2–3 lines of prior therapy and were not refractory to prior bortezomib**
- **In multivariate regression modeling of all patients who received Kd70 QW or Kd56 BIW, results showed no significant difference in ORR and PFS between the two dosing regimens, further supporting that they have comparable efficacy**
- **Kd70 QW led to a lower rate of overall grade ≥ 3 AEs, serious AEs, and several grade ≥ 3 AEs of interest (cardiac failure, acute renal failure, and hypertension) compared with Kd56 BIW in subgroups of patients who received 2–3 lines of prior therapy and were not refractory to prior bortezomib, despite having comparable median treatment exposure times**
- **Caution must be applied during the design of cross-trial comparisons to mitigate confounding by numerous factors (eg, study design, disease and patient heterogeneity, disease- and treatment-related factors), which have the potential to influence trial outcomes and cross-trial comparisons.[4,5] These factors were carefully considered in this post hoc cross-trial comparison and the analyses were designed to minimize the risk of influence from confounding factors**
  - **Side-by-side analyses were conducted in subgroups of patients who received 2–3 lines of prior therapy and were not refractory to prior bortezomib**
  - **Age, ISS stage, bortezomib-refractory status, lenalidomide-refractory status, and number of prior lines of therapy were adjusted for in regression models for all patients with 1–3 prior lines of therapy in the three studies**
- **Overall, Kd70 QW represents a convenient treatment schedule with a favorable benefit-risk profile for the treatment of RRMM**

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DISCLOSURES

Philippe Moreau reports consultancy for and honoraria from Amgen, Celgene, Takeda, Janssen, Bristol-Myers Squibb, Novartis, Millennium, and Onyx Pharmaceuticals.
A. Keith Stewart reports consultancy for Amgen, Bristol-Myers Squibb, Celgene, Takeda, Roche, Seattle Genetics, Janssen, and Ono, and research funding from Amgen, Celgene, Roche, and Seattle Genetics.
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David Siegel reports consultancy for and honoraria from Celgene, Amgen, Merck, Janssen, Bristol-Myers Squibb, Takeda, and Karyopharm Therapeutics; speakers' bureaus for Celgene, Amgen, Merck, Janssen, Bristol-Myers Squibb, and Takeda; and research funding from Celgene.
Thierry Facon reports consultancy for Amgen, Celgene, Janssen, Karyopharm Therapeutics, Oncopeptides, Sanofi, and Takeda, and speakers' bureaus for Janssen, Takeda, and Celgene.
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Real-World Use of the Triplet Regimen Carfilzomib, Lenalidomide and Dexamethasone (KRd) in Patients with Relapsed Multiple Myeloma: A Sub-group Interim Analysis from a Prospective Observational Study

PF616

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BACKGROUND

- Results of a first interim analysis from a large observational study (NCT03091127)[1] describing the usage of carfilzomib-based regimens in patients with relapsed multiple myeloma (MM) showed that patients who received carfilzomib, lenalidomide (Len) and dexamethasone (KRd) are younger and receive carfilzomib in earlier lines than patients treated with carfilzomib and dexamethasone alone[2]

AIM

- To further characterize the KRd patient population, describe carfilzomib use in accordance to the EU label,[3] and the benefit-risk profile of KRd in this real-world setting

METHODS

- This prospective cohort study recruited adults who received ≥1 prior line of MM treatment and ≥1 dose of a carfilzomib combination regimen in routine clinical practice[1,2]
- Prior to carfilzomib initiation, medical history from diagnosis and patient characteristics were collected
- For the efficacy and safety analyses, patients were followed until 30 days after final carfilzomib administration or until 18 months after initiation, whichever was earlier
- All adverse events (AEs) of grade 3 or above (Gr3+) including serious adverse events (SAEs) were collected
- Investigators reported whether they conducted disease response assessments according to International Myeloma Working Group (IMWG) criteria or other methods
- Duration of carfilzomib treatment from the first dose of carfilzomib to the last dose of carfilzomib was estimated using reverse Kaplan-Meier (KM) methodology.[4] For patients who have not discontinued carfilzomib, time was censored at their last recorded dose date
- Patients were classified as Len-refractory if they met at least one of the following criteria: a) Best response to any regimen containing Len was either stable or progressive disease; b) Reason the drug was stopped is progression; c) Date of relapse/progression was after the start date and ≤60 days after the stop date of the drug
- The cut-off date for this second planned interim analysis was 22 October 2018

RESULTS

- Of 293 patients enrolled between 14 March 2017 and 22 October 2018 across 10 participating countries in EU and Israel, 178 (60.8%) patients received KRd
- Median study observation time was 8.5 months

Treatment History, Patient/Disease Characteristics

- At KRd initiation, median age was 64 years and 9.6% were ≥75 years. KRd patients had a median (range) of 1 prior line of therapy (1, 8)
- In the KRd arm of ASPIRE phase 3 trial, median age was 64 years; KRd patients had received a median (range) of 2 prior lines of therapy (1,3)[5]
- Nearly all (97.8%) patients had an ECOG status 0-2 (Table 1)

Table 1. Patient and Disease Characteristics

Characteristics at diagnosis	KRd Cohort (N=178)
Patients with cytogenetic risk recorded, n (%):[a]	**55 (30.9)**
High / unfavorable	25 (45.5)[b]
Intermediate	4 (7.3)[b]
Normal	26 (47.3)[b]
Patients with frailty score recorded, n (%):[a]	**98 (55.1)**
Fit	67 (68.4)[b]
Intermediate	21 (21.4)[b]
Frail	10 (10.2)[b]
Characteristics at carfilzomib initiation	
Age, median years (min, max)	**64 (32, 87)**
Patients with calculated ISS stage, n (%): [a,c]	**53 (29.8)**
I	22 (41.5)[b]
II	16 (30.2)[b]
III	15 (28.3)[b]
Patients with ECOG status reported, n (%):[a]	**90 (50.6)**
0–1	82 (91.1)[b]
2	6 (6.7)[b]
3–4	2 (2.2)[b]
Number of prior lines of therapy, n (%):	
1	105 (59.0)
2	36 (20.2)
3	19 (10.7)
4 or more	18 (10.1)
Patients with available renal lab values, n (%):[d]	**85 (47.8)**
Renal insufficiency	7 (8.2)[b]
Patients with available LDH values, n (%):	**123 (69.1)**
Patients with LDH ≥ULN,[e] n (%)	39 (31.7)[b]

[a]Assessed by the physician; [b]% based on number non-missing; [c]Calculated from collected lab values; [d]Defined as serum creatinine >177 µmol/L; [e]Defined as above upper limit of normal according to local range, or ≥240 U/l in absence of a local range; ECOG status, Eastern Cooperative Oncology Group Performance status; ISS, International staging system; KRd, carfilzomib in combination with lenalidomide and dexamethasone; LDH, Lactate dehydrogenase; N/A, not available or not applicable; ULN, upper limit of normal

- Among 98 patients assessed for frailty at diagnosis, 32% were intermediate (int) or frail. Median age was similar between frail/int and fit patients (65 vs 64 at KRd initiation)
- Hypertension (HT, 28.7%), diabetes (12.4%), cardiac disorder (10.1%), and renal disorder (4.5%) were reported in medical history
- Median time since last prior treatment discontinuation was 16.9, 4.6, and 1.1 months for patients with 1, 2, or ≥3 prior lines, respectively
- Over half (63%) of KRd patients had a previous hematopoietic stem cell transplant (HSCT)
- Among patients at first relapse, nearly all (90%) received frontline bortezomib and 44% an IMiD of which 74% were exposed to thalidomide and 37% to Len
- In total, 21.9% of KRd patients were defined as Len-refractory. This included 12.8% (n=5) patients in 1st relapse, 28.2% (n=11) in 3rd line and 60.0% (n=23) in 4th line and beyond

Efficacy and Treatment Duration

- Among 142 evaluable patients, the best overall response rate (ORR) was obtained within a median time of 3.6 months and was high irrespective of the number of prior lines of therapy
- Complete response or better (CR+), or very good partial response or better (VGPR+) was achieved by 22% and 61% of patients, respectively. More patients achieved CR+ in earlier lines (Table 2)

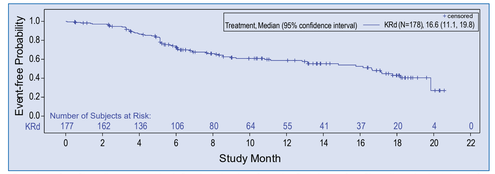
Table 2. Response among Evaluable KRd Patients, by Prior Line of Therapy

	1 n = 84	2 n = 27	≥3 n = 31	Overall n = 142
Best overall response rate (ORR),[a] %	77.4	88.9	80.6	80.3
(95% Confidence interval)	(67.0, 85.8)	(70.8, 97.6)	(62.5, 92.5)	(72.8, 86.5)
Best overall response of VGPR or better, %	65.5	66.6	45.2	61.3
Complete response or better (sCR/CR)	26.2	22.2	12.9	22.5
Very good partial response (VGPR)	39.3	44.4	32.3	38.7
Partial response (PR)	11.9	22.2	35.5	19.0

[a]The overall response rate (ORR) is defined as the proportion of patients who have a best overall response of PR or better, i.e. sCR, CR, VGPR, or PR

- ORR (including CR+) in frail/int patients was 78.6% (14.3%) vs 86.0% (26.3%) in fit patients
- For all patients receiving KRd, the KM median estimate of treatment duration was 16.6 months (95% confidence interval: 11.1, 19.8) (Figure 1)
- The KM median follow-up time was 15.9 months

Figure 1. Kaplan-Meier Plot of Duration of Carfilzomib Treatment for KRd Patients



Duration of carfilzomib treatment is defined as the time from the first dose of carfilzomib to the last dose of carfilzomib. For patients who have not discontinued carfilzomib, time is censored at their last recorded dose date

Carfilzomib Utilisation

- Nearly all (97%) patients had a planned KRd dosing schedule per EU label (twice weekly carfilzomib 20/27 mg/m^2)[3]
- Irrespective of the number of prior lines, patients received on average 95% of the total expected dose (95.9%, 95.1% and 91.6% for 1, 2 and ≥3 prior lines, respectively)
- The average % expected dose received by both frail/int and fit patients was high and similar: 97% vs 96%, respectively
- Out of 175 patients starting a twice-weekly schedule, 9.0% switched to once-weekly
- In practice, more delays (n=80 [44.9%]) than reductions (25 [14.0%]) of carfilzomib dose were used

Carfilzomib Discontinuation and Safety

- Among 74 patients discontinuing carfilzomib the main reasons were disease progression/ refractoriness (25.7%), desired level of response reached (20.3%), or an AE (17.6%)
- Salvage HSCT was planned for 29.7% of patients discontinuing carfilzomib and Len
- One-third (34.3%) of KRd patientts reported Gr3+ AEs, including HT (3.4%) and cardiac failure (0.6%) and 5 fatal events occurred.
- Blood disorders (12.4%) such as anemia and neutropenia, and infections (11.2%) were the most frequent events reported

CONCLUSIONS

- **Patients receiving KRd in real-world were consistent with those in the KRd arm of the pivotal ASPIRE trial[4] in terms of age and prior lines of therapy**
- **Additionally, KRd is shown to be used in practice in frail patients and was effective**
- **Carfilzomib was appropriately prescribed per EU label and could be maintained for long durations leading to high overall response rates and deep responses**
- **The magnitude of response (CR/sCR) was greater for KRd patients in earlier lines**
- **KRd benefit-risk profile is consistent with efficacy and safety data from ASPIRE trial**

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